Hematopoiesis
Anemia

Composition of the Blood

1. red blood cells (RBC's or erythrocytes)
2. white blood cells (or leukocytes)
3. platelets (or thrombocytes)
4. plasma
Hematopoiesis

- Production and Development of Blood Cells
- Pluripotent Stem Cell
  - Continuous Self-Replication
  - Gives Rise to All Blood Cell Lines
- Growth Factors (Cytokines) - Promote Differentiation Into Mature Blood Elements

Anemia

**Definition** - Decreased RBC mass
**Working Definition** - Decreased Red Blood Cell Count
Hemoglobin
Hematocrit
Red Blood Cell

- Hemoglobin (Hgb) - Direct Measurement (g/dl)
- Hematocrit (Hct) -
  - Packed RBC Volume (PV) - Manual “Spun” Hematocrit (%)
  - Automated Counters Calculate Based on RBC Number and Size

Red Blood Cell Indices

- Mean Corpuscular Volume (MCV) - Average Size of the RBCs
- Mean Cell Hemoglobin (MCH) - Hgb/RBC
- Mean Cell Hemoglobin Concentration (MCHC) - Hgb/Hct
- Red Blood Cell Distribution Width (RDW) - Index of Size Variation
Types of Anaemia

- anaemia of B12 deficiency
- anaemia of chronic disease
- anaemia of folate deficiency
- drug-induced immune haemolytic anaemia
- haemolytic anaemia
- haemolytic anaemia due to g6pd deficiency
- idiopathic aplastic anaemia
- idiopathic autoimmune haemolytic anaemia
- immune haemolytic anaemia
- iron deficiency anaemia
- megaloblastic anaemia
- pernicious anaemia
- secondary aplastic anaemia
- sickle cell anaemia

Mechanisms of Anemia

Production Disorders:

- Hematopoietic Cell Damage
  - Drugs, Radiation, Infections, Toxins
- Factor Deficiency
  - Iron (Heme Synthesis)
  - Vitamin $B_{12}$ (DNA Synthesis)
  - Folate (DNA Synthesis)
Mechanisms of Anemia

**Survival Disorders:**
- Blood Loss - External or Internal
- Red blood Cell Destruction - Hemolytic Anemias

**Anemia**

**Manifestations - Cause & Chronicity**

**Nonspecific Signs and Symptoms**
- Weakness, Malaise, Fatigue
- CNS hypoxia - Headaches, Faintness, Dimness of Vision
- Skin Pallor, Thinning and Inelasticity
- Nail Britleness
- Angina Pectoralis (if ASCVD)
Production Disorder - Iron Deficiency

- Most Common Nutritional Deficiency
- Required in Hemoglobin Synthesis
  \[ \text{Heme} + \text{Globin Chains} = \text{Hemoglobin} \]
- Occurs in RBC Cytoplasm ⇒
  Hypochromic Microcytic Anemia

Iron Metabolism

- Iron is Absorbed Primarily in \textbf{Duodenum}
  - 25% of Heme-Bound Iron (Red Meat)
  - 1-2% of Non-Heme Iron
- Body \textbf{Losses} of Iron are \textbf{Limited}
  - 1-2 mg/Day By Epithelial Cell Shedding
- \textbf{Mucosal Block} - Maintains Balance
Transferrin

- Transport Protein For Iron In Blood
- Fully Saturated Transferrin = TIBC
  300 - 350ug/dl Fe
- Normal Transferrin - 1/3 Filled With Iron
  100 - 120ug/dl Fe (Serum Iron)

Iron Storage

Ferritin - Protein Iron Complex
  *Found In All Tissues
  *BM, Liver (Transferrin)
  *Spleen (RBC Breakdown)

Hemosiderin - Breakdown Product of Ferritin
Development of Iron Deficiency

- Depletion of Stores
  - ↓ Serum Ferritin
  - ↓ Stainable BM Iron

  ↑ Transferrin (↑ TIBC)

  ↓ Serum Fe

  ↓ Transferrin Saturation

- ↓ Hemoglobin, Myoglobin, Fe Proteins

Iron Deficiency Anemia Laboratory Findings

- Hypochromic Microcytic Anemia
  (↓ RBC Count, ↓ MCV)

- ↓ Serum Ferritin Levels

- ↓ Transferrin Saturation
  (↓ Serum Fe, ↑ Transferrin)
Causes of Iron Deficiency

- External Blood Loss - Most Common
  Female Genital Tract
  Gastrointestinal Tract
- ↑↑ Demand - Infancy, Pregnancy
- Dietary Deficiency - Rare
  (Vegetarian Diets)
- Intestinal Malabsorption Syndrome

Iron Deficiency Clinical Manifestations

- Anemia - Non-Specific Findings
- Koilonychia
- Plummer-Vinson Syndrome
  - Hypochromic Microcytic Anemia
  - Atrophic Glossitis
  - Esophageal Webs (Dysphagia)
Production Disorder - Vitamin $B_{12}$ or Folate Deficiency

Megaloblastic Anemias
- Impaired DNA Synthesis (Nucleus)
- Function - Transfer of Carbon Groups
- Affects All Rapidly Dividing Cells
  - Mouth - Atrophic Glossitis
  - GI tract - Intestinal Malabsorption

Megaloblastic Anemia
Peripheral Blood
- RBCs - Large Oval Macroovalocytes
  - MCV > 100$\mu^3$
- Anemia Due To Ineffective Hematopoiesis
  - Autohemolysis of Megaloblasts (Circulating Large RBCs Destroyed)
- Hypersegmented Neutrophils
- Thrombocytopenia, Neutropenia (Severe)
Vitamin $\text{B}_{12}$ Deficiency - Cause

Western World - Pernicious Anemia
- Autoimmune Disorder
  - Autoantibodies to IF and Parietal Cells
  - Chronic Atrophic Gastritis
  - Achlorhydria - Absent HCL
- ↑ Incidence of Other Autoimmune Disorders

Vitamin $\text{B}_{12}$ Deficiency

Additional Causes:
- Inadequate Diet - Rare (>20yr Stores)
  - Foods Containing Animal Protein
  - Microorganisms Synthesize
  - Stored in Liver, Reabsorbed in Bile
- Gastrectomy, Ileal Resection
- Malabsorption States, Gastric Atrophy
- Diphyllobothrium Latum - Fish Tapeworm
Megaloblastic Anemia - Bone Marrow

**Nuclear-Cytoplasmic Asynchrony:**
- Erythroid Series (Hallmark Changes)
  - Megaloblasts
  - Erythroid Hyperplasia
- Myeloid Series
- Megakaryocytic Series - (Infrequent)

**Vitamin B\textsubscript{12} Deficiency**
- Clinical - Similar to Folate Deficiency But Demyelinating Neurologic Disorder
  - Affects Both Sensory and Motor Tracts
  - Lack of Correlation With Anemia
- Parenteral B\textsubscript{12} - Improves Anemia,
  +/- Resolution of Neurologic Symptoms
- Caution! Anemia of B\textsubscript{12} Deficiency Also Improves With Folate Supplementation
Vitamin B$_{12}$ Deficiency

**Laboratory Findings:**
- Low Serum Vitamin B$_{12}$ Levels
- Normal RBC Folate Levels
- Abnormal Schilling Test - Impaired Absorption of Radioactive Vitamin B$_{12}$ Correctable by Addition of IF
- Anti-Intrinsic Factor Antibodies (Anti-Parietal Antibodies Less Sensitive)

Causes of Folate Deficiency

- Dietary Deprivation
  - Widely Distributed in Foods (Uncooked Vegetables, Fruits, Liver)
  - Limited Body Stores (Wks-Months)
  - Chronic Alcoholics, Elderly, Indigent
- Malabsorption (Upper 1/3 Intestine)
  - Intestinal Disease (Sprue, Celiac Dx)
  - Chronic Drugs (Dilantin)
Folate Deficiency

- Increased Requirements - Pregnancy
- Impaired Utilization - Folic Acid Antagonists (Chemotherapy Drugs)

Laboratory Findings:
- Red Blood Cell Folate - Reflects Tissue Content of Folate Throughout Body
- Serum Folate - Levels Fluctuate Based on Recent Intake, Do Not Reflect Stores

Anemia of Chronic Disease

- Normochromic Normocytic Anemia (or Hypochromic Microcytic)
- Chronic Disorders (Inflammation or Tissue Necrosis)
  - Chronic Microbial Illnesses
  - Chronic Immune Disorders
  - Neoplasms
- Often ↓ TIBC, ↑ Ferritin
Anemia of Chronic Disease

Defect

- IL-1
- TNF α
- γ IFN

Storage Iron

Erythroid Precursors
(Insufficient Erythropoietin)

Hematopoietic Cell Damage
Aplastic Anemia

Bone Marrow Aplasia (Lack of Cells)
- Failure of Multipotent Stem Cell
  - T-cell Mediated Suppression or
  - Genetic Damage
- Bone Marrow - Markedly Hypocellular
- Peripheral Blood - Pancytopenia
- Normochromic Normocytic RBCs
Aplastic Anemia

Causes of Stem Cell Failure
- Idiopathic (>50%) - Poor Prognosis Especially If < 40 Years Old
- Whole Body Irradiation
- Viral Infections - Most Common After Non-A/Non-B Hepatitis
- Chemical Agents and Drugs - Reversible and Non-Reversible

Myelophthisic Anemia

BM Replacement ⇒ BM failure:
- Metastatic Carcinoma Most Common
- Destruction By Non-Neoplastic Process is Less Common i.e. Fibrosis, Infection
- Peripheral Blood Cytopenias, Immature Circulating Cells