Anemia: Impaired Production of RBCs
Introduction

What is impaired production?

- All of the following anemias are due to impaired production of RBCs
  - Results in decreased production
Iron Deficiency Anemia
Etiology of IDA

- Simply
  - It is inadequate stores of iron for hemoglobin
- Worldwide most common anemia
- Etiology: the cause of the disease

*** Review “Iron” slides from Section 1: Lecture - Lifecycle & Physiology of RBCs
The development of iron deficiency anemia

Adapted from Suominies P, Punnonen K, Rajamäki A et al: Serum transferrin receptor and transferrin receptor—ferritin index identify healthy subjects with subclinical iron deficits. Blood 1998; 92:2934–2939, reprinted with permission. Copyright © 2003, Elsevier Science (USA). All rights reserved.
Iron Deficiency Anemia

- Numerous individuals may be iron deficient while appearing normal
- Symptoms do not appear until stage 3
- Abnormal CBC results do not appear until stage 3
Screening

- CBC
  - Hypochromic, microcytic anemia
  - Hgb decreases
  - Elevated RDW
Iron deficiency anemia (microcytic, hypochromic)
Anemia of Chronic Disease (ACD)
Chronic inflammation may be a better term because inflammation appears to be the unifying factor among the conditions.

- Anemia associated with chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), tuberculosis (TB), HIV, malignancies, chronic urinary tract infection.
Pathogenesis

- Paradox of ACD
  - Iron is abundant in the body stores yet...
  - Serum iron is low *(sideropenia)*
    - Resulting in:
      - Erythropoeisis is iron deficient therefore decreased production
Pathogenesis

What causes the sideropenia?

1. **Increased hepcidin**
   - Hepcidin is produced in response to inflammatory cytokines
   - Produced by hepatocytes to regulate body iron levels, particularly the absorption of iron in the intestine and release of iron from macrophages
Mild anemia
  ◦ Hgb usually 9–11 g/dL

Blood Picture
  ◦ Normochromic, normocytic
    • Can be hypochromic, microcytic in long-standing cases (about 1/3 of patients)
  ◦ RDW is usually normal
  ◦ Retics – normal or decreased
Iron Studies

- Ferritin – normal to increased
- Serum iron – decreased
- TIBC – decreased
- % transferrin saturation – decreased

- Serum ferritin useful in distinguishing from IDA
Sideroblastic Anemias
Sideroblastic Anemia

- **Group** of anemias in which heme synthesis is impaired
- Diseases that interfere with the production of adequate amounts of heme produces anemia
  - Iron is abundant
Lead poisoning is a significant public health concern
  ◦ Lead poisoning also known as plumbism
How are people exposed to lead?
  ◦ Adults work with leaded compounds (inhalation)
  ◦ Children and adults living in older homes due to lead based paint (produced prior to 1978)
Lead Poisoning

- Children & lead poisoning
  - Eat paint chips
  - Toddlers and crawling infants getting lead paint dust on hands during renovations and then placing hands in mouth
Blood Picture

- Usually normochromic, normocytic anemia
  - Can be microcytic, hypochromic with chronic exposure
- RDW normal
- Basophilic stippling (lead retards breakdown of RNA)
- Pappenheimer bodies or siderotic granules (iron deposits)
Excess iron appears in the mitochondria of developing RBCs forming a ring around the nucleus called ringed sideroblasts.

Bone marrow
Megaloblastic Anemias
Etiology of Megaloblastic Anemia

- Deficiency of vitamin B12 (cobalamin)
- Deficiency of folic acid (folate)
When either folic acid or vitamin B12 is missing DNA synthesis will be impaired

Because vitamin B12 and folic acid are vitamins necessary as coenzymes for nucleic acid synthesis
Laboratory Diagnosis of Megaloblastic Anemia

Blood Picture

- Normochromic, macrocytic anemia
  - MCV commonly greater than 120 fL
  - MCHC normal because Hgb production unaffected
- Pancytopenia
- Elevated RDW
- Oval macrocytes
- Hypersegmented neutrophils
Laboratory Diagnosis of Megaloblastic Anemia

- Blood Picture
  - Poikilocytosis
    - Dacryocytes, schistocytes, microspherocytes
  - Nucleated RBCs, Howell–Jolly bodies, basophilic stippling and cabot rings may be present

- Retic count is low
  - Cells die during division in bm never enter pb
To Determine Cause of Megaloblastic Anemia

- Necessary to determine cause for treatment
  - Is it vitamin B12 deficiency?
  - What is causing the deficiency?
  - Is it pernicious anemia?
  - Is it folic acid deficiency?
  - What is causing the deficiency?
Pernicious Anemia (PA) is a form of megaloblastic anemia
- Most common megaloblastic anemia
- Due to deficiency of vitamin B12
- Specific cause of this deficiency
  - Autoimmune destruction of IF secreting gastric cells—causes a loss of IF
- Feature of the autoimmune response to PA is the production of antibodies to IF
Pathogenesis of Aplastic Anemia

- Bone marrow failure due to depletion of bm cells and replacement of bm with fat
  - Hypocellular
- Results in
  - Bone marrow no longer producing an adequate number of precursor blood cells = pancytopenia
Pathophysiological Classification of Anemias

BLOOD LOSS
- Chronic
- Acute

IMPAIRED PRODUCTION
- IDA, Chronic disease, Sideroblastic, Megaloblastic, Aplastic, Others

INCREASED DESTRUCTION
- Hereditary
- Acquired
  - Non-immune
    - Diseases, burns, organisms, etc
  - Immune
    - Paroxysmal nocturnal hemoglobinuria

DEFECTS IN HEMOGLOBIN
- Hemoglobinopathies
  - SCA, Hgb C, Hgb SC, Hgb E Others
- Thalassemia
  - Beta
    - Major, Minor, Intermedia
  - Alpha
    - Trait, Hgb H, Hydrops

MEMBRANE DEFECTS
- HS
- HE

ENZYME DEFECTS
- Pyruvate Kinase Def.
- G6PD

DRUG-INDUCED
- Warm, Cold, Paroxysmal Cold Hemoglobinuria

HDN
- Transfusion reaction
Anemias of Increased Destruction of RBCs
Is
Hemolytic Anemias
Outline for Hemolytic Anemias

I. Introduction to hemolytic anemias

II. Hereditary hemolytic anemias
   • Membrane Defects
   • Enzyme Defects

III. Acquired hemolytic anemias
   • Non–immune
   • Immune
   • Membrane Defects
Term **hemolytic anemia** refers to conditions in which there is **increased destruction of RBCs** causing the bm to respond by accelerating production

- Erythropoiesis is normal, the lifespan of RBCs is greatly decreased
- Hemolytic anemia occurs when RBC survival is so short that anemia develops despite a vigorous erythropoietic response
What Is a Hemolytic Anemia?

- Hemolytic anemia is a disorder in which the red blood cells are destroyed faster than the bone marrow can produce them.
- Group of normocytic, normochromic anemias in which the erythrocyte is prematurely destroyed
- Premature destruction is referred to as hemolysis
Hemolysis is the premature destruction of RBCs

2 locations of hemolysis
- Extravascular
- Intravascular
Extravascular hemolysis: the rbc is destroyed outside the blood vessels (spleen, liver, bone marrow)
- In extravascular hemolysis RBCs are phagocytized by macrophages in the spleen and liver
- Extravascular hemolysis is characterized by spherocytes
Intravascular hemolysis: the destruction of defective RBCs as they circulate
- In intravascular hemolysis RBCs lyse in the circulation releasing hemoglobin into the plasma.
- The fragmented RBCs are called schistocytes

***Destruction can occur both intravascularly and extravascularly
Hereditary Hemolytic Anemias

Outline

- Membrane Defects
  - Hereditary Spherocytosis (extravascular hemolysis)
  - Hereditary Elliptocytosis (extravascular hemolysis)

- Enzyme Defects
  - G6PD Deficiency (extravascular hemolysis)
  - Pyruvate Kinase Deficiency (extravascular hemolysis)

- Globin Defects
  - Hemoglobinopathies
  - Thalassemias
Laboratory Diagnosis of HS

- Normochromic, normocytic
- Anemia may be present (mild)
- Moderate to many spherocytes
- Elevated MCHC (due to slight dehydration of these cells)
- Reticulocytosis (usually more than 8%)
- Increased osmotic fragility
  - Confirmatory test
III. Acquired Hemolytic Anemias
Acquired Hemolytic Anemias Outline

- Non-Immune hemolytic anemias
  - Diseases
  - Intracellular organisms
  - Chemicals, venoms and drugs
  - Burns

- Immune hemolytic anemias
  - Autoimmune
    1. Warm autoimmune hemolytic anemia
    2. Cold autoimmune hemolytic anemia
    3. Paroxysmal cold hemoglobinuria
Hemoglobinopathies and Thalassemias
What is a Hemoglobinopathy?

- Clinical diseases that result from a genetically determined abnormality of the structure or synthesis of the hemoglobin molecule

- The abnormality is associated with the globin chains; the heme portion of the molecule is normal
What is a Hemoglobinopathy?

- The globin abnormality can either be a qualitative defect in the globin chain (structural abnormality)
  - Resulting in a hemoglobinopathy

- Or the abnormality can be due to a quantitative defect in globin synthesis
  - Resulting in thalassemia
Hemoglobin Mutation

- Hemoglobin Mutation
  - A single nucleotide change that results in:
    - Deletion
    - Substitution
    - Insertion
  Of Amino Acids
Confirmatory Testing

- **Hgb electrophoresis?**
  - Method of identifying hemoglobins based on differences in their electrical charges
    - Hemoglobin carries an electrical charge
    - The type (net positive, net negative) and strength of charge depend upon both the amino acid sequence hemoglobin molecule and the pH of the surrounding medium
Laboratory Findings

- Normocytic, normochromic anemia
- Reticulocytosis
- Target cells
- Few sickle cells
- Hemoglobin SC crystals
III. Introduction to Thalassemias
Leads to
- Imbalanced globin chain synthesis
- Decreased production of normal hemoglobin
- Synthesis of abnormal hemoglobins
- Ineffective erythropoiesis
- Chronic hemolysis

Alpha Thalassemia

Beta Thalassemia:
- Minor, Intermedia and Major
- Which is transfusion dependent?
Introduction to Leukocyte Neoplasms
What are Leukocyte Neoplasms?

- Leukemia
- Lymphoma
- Myeloproliferative Disorders
- Lymphoproliferative Disorders
- Myelodysplastic syndromes
Leukemia is divided into 4 categories
- Myelogenous or lymphocytic
  - Each of which can be acute or chronic

<table>
<thead>
<tr>
<th>Acute lymphocytic leukemia</th>
<th>Chronic Lymphocytic Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myelogenous leukemia</td>
<td>Chronic myelogenous leukemia</td>
</tr>
</tbody>
</table>
## Acute vs Chronic

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Age</td>
<td>All</td>
<td>Adults (usually)</td>
</tr>
<tr>
<td>Death</td>
<td>Months</td>
<td>Years</td>
</tr>
<tr>
<td>WBC count</td>
<td>↑, Normal, ↓</td>
<td>Elevated</td>
</tr>
<tr>
<td>Cells seen</td>
<td>Blasts (immature)</td>
<td>Mature</td>
</tr>
</tbody>
</table>
How is Classification Determined?

- CBC
- Cytochemistry
- BM
- Flow Cytometry
- Cytogenetics
- Molecular
Classification

- Fab
  - Cytochemical Stains
  - ALL 1–3: AML M0–7
- WHO
  - Genetic abnormalities: Translocations
  - Dysplasia
  - Therapy–related
Cytochemical Stains

- Myeloperoxidase Stain
- Sudan Black B stain
- Esterases
- Peroidic Acid–Schiff Stain (PAS)
- Leukocyte alkaline phosphatase (LAP)
- Tartrate–Resistant Acid phosphatase (TRAP)
Leukocyte Neoplasms: Myeloproliferative Disorders
Include

- CML and CML Variants
- PV (Polycythemia Vera)
- ET (Essential Thrombocythemia)
- CIMF (Chronic Idiopathic Myelofibrosis)
What are Myeloproliferative Disorders?

- Abbreviated MPD
- Myeloproliferative disorders or diseases
  - Includes leukemias and disorders
    - Leukemias are malignant
    - Majority of MPDs are not leukemias
    - MPDs are not clearly malignant but are characterized by neoplastic proliferation of hematopoietic precursors
What are Myeloproliferative Disorders?

- Result in expansion and excessive production and overaccumulation of blood cells
- Causes – mutations
  - Commonly idiopathic
What are Myeloproliferative Disorders?

- Characterized by
  - **Panhypercellularity (panmyelosis)**
    - Increase in all blood cells of bone marrow and blood
    - Results in erythrocytosis, granulocytosis, thrombocytosis in pb
  - **Trilineage cell involvement** (erythrocytic, granulocytic, thrombocytic) is characteristic, one cell line is usually more prominently affected
    - Classification is based on the affected cell line
Leukocyte Neoplasms: Lymphoproliferative Disorders
Includes

- Prolymphocytic Leukemia
- CLL
- Hairy Cell Leukemia
- Hodgkins and Non Hodgkins Lymphomas
  - Which has Reed–Sternberg cells in the lymph nodes?
- Plasma Cell Disorders
  - Multiple myeloma
  - Waldenstrom’s macroglobulinemia
Myelodysplastic Syndromes
What are myelodysplastic syndromes?

- Stem cell disorder characterized by one or more peripheral blood pancytopenia and prominent cellular maturation abnormalities (dyspoiesis or dysplasia) in the bone marrow.
- Hematologic disorders characterized by progressive cytopenias in the peripheral blood, reflecting defects in erythroid, myeloid or megakaryocytic maturation.
MDS and Preleukemia

- MDS is also known as **preleukemia**
  - Because of the predisposition of MDS to terminate in leukemia, the term preleukemia is commonly used to describe these disorders
    - Usually acute myeloid leukemia
Peripheral Blood

- Erythroid Findings:
  - Anemia (hgb usually less than 10)
  - Usually macrocytic, less often normocytic
  - Oval macrocytes
  - Basophilic stippling, Howell–Jolly boides
  - Nucleated RBCs
  - Poikilocytosis and anisocytosis
Peripheral Blood

- Thrombocyte Findings:
  - Thrombocytopenia or thrombocytosis
  - Giant platelets
  - Hypogranulation of platelets
  - Presence of micromegakaryocytes