Anemia

- Reduction below normal in oxygen carrying capacity of the blood.
- Caused by a variety of disorders.

- FA is one of the inherited anemias that leads to bone marrow failure leading to a low RBC count.
- FA is diagnosed with the help of blood tests.
- FA is treated with bone marrow transplants.
HEMATOPOIESIS
Blood Cell Formation

• DEFINITION
The process of formation and development of the various types of blood cells and other formed elements (platelets).
Hematopoiesis

- In the adult, all blood cell formation (red blood cells, white blood cells and platelets) occurs in the Red Bone Marrow or myeloid tissue.
• In adults, red bone marrow is primarily found in bones of the
  – Axial skeleton
  – Pelvic and pectoral girdles
  – Proximal epiphyses of the humerus and femur.
Samples can be taken from the bone marrow, smeared in a single cell layer on a slide, and stained. The resulting BONE MARROW SMEAR contains a sampling of stem cells and many blood cells in immature stages of development.
Hematopoiesis begins with a stem cell known as the **hemocytoblast**.
• Red Blood Cell (RBC) synthesis is known as *Erythropoiesis*.

• In erythropoiesis, the hemocytoblast goes through a series of morphological changes culminating in the formation of a cell full of hemoglobin.
Erythropoietin (EPO)

- EPO
  - produced and released by the kidneys under low oxygen conditions.
  - stimulates increased rate of cell division in erythroblasts and the stem cell that produce erythroblasts.
  - Speeds up maturation of RBCs
ERYTHROPOIESIS:

- Once the erythropoietin stimulates the red bone marrow to begin manufacturing RBCs, a series of events occurs.
- Cell size decreases
- The nucleus becomes condensed (and is eventually discarded)
ERYTHROPOESIS
the making of Red Blood Cells (RBCs)

- Cytoplasm stains *basophilic* (purple)
- then becomes more *acidophilic* (pink)
- As cells mature, they slowly fill with hemoglobin until they are bright red *reticulocytes*
- Only mature erythrocytes are released into the peripheral blood
• Note the RBC precursors
ERYTHROPOIESIS  Note RBC precursors

Is this smear from bone marrow or peripheral blood? Why?
This NORMOBLAST is caught in the act of expelling its nucleus.

These cells are termed: “normoblast” while nucleated “erythrocyte” when anucleate.

Only mature, anucleate cells are normally released into the blood, so too many NORMOBLASTS or “BLASTS” found in a blood smear may indicate cancer: usually a leukemia or lymphoma.

In fact, many early blood cancers are found in early, asymptomatic stages during “routine” blood work!
Appearance and size of normal erythrocytes (RBCs)

The diameter of an RBC (about 7 mL) is often used as a reference to estimate the size of other cells on a blood smear.
The life cycle of a red blood cell.

- **a** – Kidneys respond to low oxygen concentration in the blood by releasing erythropoietin.

- **b** – Erythropoietin travels to the red bone marrow and stimulates an increase in the production of RBC in the bone marrow.

- **c and d** – RBCs mature and then squeeze through blood vessel membranes to enter circulation.

- **e** – The heart and lungs work to supply continuous movement and oxygenation of RBCs.

- **f** – Damaged or old RBCs are destroyed primarily by the spleen.
NORMAL vs. ANEMIA

NORMAL
There are about 5 million rbc per cubic mm.

ANEMIA
Too few (<38%) is anemia

POLYCYTHEMIA
(not shown)
Too many > 55%
White Blood Cells aka Leukocytes

- All WBCs contain nuclei and organelles.
- WBCs help defend the body against invasion by pathogens. They also remove toxins, wastes, and abnormal/damaged cells.
- Far, fewer WBCs than the RBCs in circulation.
- At any given time, most of the body's WBCs are found in the connective tissue proper or in the organs of the lymphatic system. They use the blood primarily for transportation.
- Characteristics of circulating WBCs:
  - Capable of amoeboid movement. This allows WBCs to converge on pathogens and sites of injury.
  - They can migrate out of the bloodstream by squeezing between endothelial cells - this process is known as diapedesis.
Types of WBCs

Classified as to whether or not they contain granules that take up Wright's stain and are visible with the light microscope.

• Granulocytes
  – Contain visible stained granules
  – Includes:
    • Basophils
    • Eosinophils
    • Neutrophils.

• Agranulocytes
  – Do not contain stained visible granules.
    » Lymphocytes
    » Monocytes.
The stem cell is the same or similar to that for erythropoiesis
GRANULOCYTOPOIESIS
The cells in these three lines of development can be readily identified by the presence of pronounced cytoplasmic granules, and by the gradual lobulation of the nucleus.
BONE MARROW

GRANULOCYTIC PRECURSORS

A. Band or “stab” cell

B. Neutrophil
Granulocytes
in peripheral blood

- Named for prominent “granules” in the cytoplasm
- Individually named according to the way the granules stain
  - Eosinophils- have large red granules
  - Basophils- have large blue-purple granules that nearly obscure the nucleus
  - Neutrophils- stain neutrally. Cytoplasm is often “purplish” but the granules are not nearly as prominent as those in Basophils.

Let’s meet them now as they would appear in a peripheral blood smear.........
EOSINOPHIL

Fairly infrequent in blood, making up 1-6% of WBCs

- Large, red, dense granules
- Nucleus is usually bi-lobed

What is the diameter of this eosinophil?
  - About 14µm
  - 2 x 7µm RBCs

The granules of eosinophils contain (among other things) HISTAMINE.
When EOSINOPHILS encounter something you are allergic to (pollen, cat dander) they release their granules into the blood and you have a “histamine reaction”: itchy, runny eyes and nose.

A common class of drugs called ANTI-HISTAMINES fight this reaction.
BASOPHILS

Good luck finding this one in your blood smear today!...

They make up <1% of lymphocytes (WBCs)

Have very large, very dark blue-purple granules

The nucleus is S-shaped, but is usually obscured by granules

Slightly smaller than as Eosinophils and Neutrophils

Granules contain heparin and vasoactive compounds.

Like eosinophils, BASOPHILS participate in allergic reactions. But unlike eosinophils, BASOPHILS are involved in the most severe allergic reactions (like bee or wasp stings) that may be deadly if left untreated.
• Migrate to injury sites and discharge the contents of their granules:
  – Histamine
    • Vasodilator
    • Increases capillary permeability.
  – Heparin
    • An anticoagulant.
  – These 2 chemicals enhance the local inflammation initiated by mast cells and attract other WBCs.
• Lifespan is not certain.
**NEUTROPHIL**

MOST prevalent granulocyte in the peripheral smear

approx 40-75% of leukocytes

- About 12µm in diameter
- Distinctive multi-lobed or “sausage link” nucleus
- Fine granules with a neutral stain
  - similar in color to RBCs
  - not “obscuring” nucleus

Neutrophils
The neutrophil (indicated by black arrow) in the image to the right has phagocytosed bacterial microorganisms (blue rods indicated by thin red arrows) into its cytoplasm.
Monocytopoiesis and Lymphocytopoiesis

Development of the **agranular leukocytes** is difficult to follow at the light microscopic level.
Monocytes
• 2-8% of circulating WBCs.
• 2x as big as an RBC.
• Notched nucleus is large & kidney-shaped.
• Stays in circulation for about 24hrs before an entering peripheral tissues to become a tissue macrophage.
• Lifespan can be up to several months.
Lymphocytes

- 20-30% of circulating WBCs.
- Slightly larger than RBCs.
- In blood smears, you typically only see a thin halo of cytoplasm around a relatively large nucleus.
- Continuously migrate from the bloodstream into the peripheral tissues and back into the bloodstream.
- Most are in other connective tissues and in lymphatic organs.
- Circulating blood contains 2 main classes of lymphocytes:
  - *T Lymphocytes*: Defend against foreign cells and tissues and coordinate the immune response.
  - *B Lymphocytes*: Produce and distribute antibodies - proteins that attack foreign molecules.
- Lifespan of hours to years.
PLATELETS aka THROMBOCYTES

- Disc-shaped, plasma membrane-enclosed fragments of cytoplasm that form by breaking off of larger cells called megakaryocytes.
- Function to seal small tears in blood vessels instrumental in blood clotting
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Erythrocyte</th>
<th>Lymphocyte</th>
<th>Neutrophil</th>
<th>Eosinophil</th>
<th>Basophil</th>
<th>Monocyte</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>6.7 – 7.7 µm</td>
<td>6 – 15 µm</td>
<td>12 – 14 µm</td>
<td>12 – 17 µm</td>
<td>14 – 16 µm</td>
<td>16 – 20 µm</td>
<td>1.5 – 3.5 µm</td>
</tr>
<tr>
<td>Number per litre</td>
<td>3.9 – 6.5 x 10^{12}</td>
<td>0 – 0.1 x 10^{9}</td>
<td>2 – 7.5 x 10^{9}</td>
<td>1.3 – 3.5 x 10^{9}</td>
<td>0 – 0.44 x 10^{9}</td>
<td>0.2 – 0.8 x 10^{9}</td>
<td>150 – 400 x 10^{9}</td>
</tr>
<tr>
<td>Differential leucocyte count</td>
<td>—</td>
<td>20 – 50 %</td>
<td>40 – 75 %</td>
<td>1 – 6 %</td>
<td>&lt; 1 %</td>
<td>2 – 10 %</td>
<td>—</td>
</tr>
<tr>
<td>Duration of development</td>
<td>5 – 7 days</td>
<td>1 – 2 days</td>
<td>6 – 9 days</td>
<td>6 – 9 days</td>
<td>3 – 7 days</td>
<td>2 – 3 days</td>
<td>4 – 5 days</td>
</tr>
<tr>
<td>Lifespan of mature cell</td>
<td>120 days</td>
<td>?</td>
<td>6 hours to a few days</td>
<td>8 – 12 days</td>
<td>?</td>
<td>Months to years</td>
<td>8 – 12 days</td>
</tr>
</tbody>
</table>
Let’s practice Name the cell

- Basophil
- Eosinophil
- Neutrophil
- Band/Stab Neutrophil
- Lymphocyte
- Platelet
- Monocyte
- Neutrophil
- Basophil
Disorders of the Blood

• Disorders of Erythrocytes
  – Polycythemia
  – Anemia
  – Sickle Cell disease

• Disorders of Leukocyte production
  – Leukemia

• Disorders of Platelets
  – Thrombocytopenia
Polycythemia

- “Many blood cells” - abnormal excess of erythrocytes in the blood
- Can result from a cancer of bone marrow that generates too many erythrocytes.
- Increase in blood viscosity, blocks blood flow through small vessels.
- Treated by dilution (remove some blood and replace with sterile saline or blood transfusion.)
Anemia

• Condition in which erythrocyte levels or hemoglobin concentrations are low
• Results in an abnormally low oxygen carrying capacity.
• *Why would an anemic person be intolerant of exercise?*
• There are several types of anemia that we're concerned with:
Anemia

Aplastic
• Results from destruction of red bone marrow by bacterial toxins, drugs or radiation. Impacts all blood cells, leading to clotting difficulties and immune problems.

Iron-Deficiency
• What role does iron play in oxygen transport?
• Can be secondary to hemorrhagic anemia (blood loss) or due to inadequate iron intake or absorption.

Pernicious
• Can be caused by inadequate intake or absorption of vitamin B12.
• The stomach lining produces a chemical called intrinsic factor which is necessary for the absorption of ingested vitamin B12. It is often a lack of intrinsic factor that causes pernicious anemia.
Anemia

Sickle-Cell

• A mutation in the gene for the beta chain of Hb results in an abnormal hemoglobin called HbS.
• Under low-oxygen conditions, the beta chains link together and become stiff rods - this gives the RBC a sickle shape.
• Sickled RBCs can then block and clog small blood vessels.
Aplastic Anemia

• Caused by failure of the bone marrow leading to a low RBC count.
Leukocytosis

• White blood cell count above 10,000 (normal range 4000-10,000)
• Usually due to an increase in one of the five types of WBCs
• Given the name of the cell that shows the primary increase
  – Neutrophilic = neutrophilia
  – Lymphocytic = lymphocytosis
  – Eosinophilic = eosinophilia
  – Monocytic = monocytosis
  – Basophilic = basophilia
Case #2 Neutrophilia
Eosinophilia
Pancytopenia

• A shortage of all types of blood cells, including RBCs and WBCs as well as platelets.
Leukemia

- A form of cancer - uncontrolled proliferation of a leukocyte-forming cell line in the bone marrow.
- The cancer takes over bone marrow and leukocytes flood the into the blood stream.
- Classified by the cell line involved
  - Lymphoblastic – from immature lymphocytes
  - Myeloblastic – from immature cells of the myeloid line
Thrombocytethemia/Thrombocytopenia
Anemia

Hemorrhagic
• Results from blood loss (which will of course include RBC loss).
• Can be acute (from a stab wound perhaps) or chronic (due to an undiagnosed bleeding ulcer perhaps).

Hemolytic
• RBCs rupture (lyse) prematurely.
• Can be due to Hb abnormalities, mismatched blood transfusion, parasitic or bacterial infection, or as an autoimmune condition.