Hemopoiesis:
Erythropoiesis & Leukopoiesis
(b) Blood smear (thin film of blood spread on a glass slide)
Hemopoiesis

- **hemopoiesis** = the production of blood, especially its formed elements

- hemopoietic tissues produce blood cells
  - yolk sac produces stem cells for first blood cells // colonize fetal bone marrow, liver, spleen and thymus
  - liver stops producing blood cells at birth
  - spleen remains involved with lymphocyte production after birth

- adult daily production
  - 400 billion platelets
  - 200 billion RBCs
  - 10 billion WBCs
Hemopoiesis

- Red bone marrow produces all seven formed elements

- **pluripotent stem cells (PPSC)** // formally called hemocytoblasts or hemopoietic stem cells // PPSC generate specific type of stem cells for each cell type

- **colony forming units** – specialized stem cells only producing one class of formed element of blood

- **myeloid hemopoiesis** – blood formation in the red bone marrow

- **lymphoid hemopoiesis** – blood formation in the lymphatic organs
Erythrocytes (RBCs)

- disc-shaped cell with thick rim
  - 7.5 \( \mu \text{M} \) diameter and 2.0 \( \mu \text{m} \) thick at rim
  - lose nearly all organelles during development

- lack mitochondria /// must use anaerobic fermentation to produce ATP

- lack of nucleus and DNA /// no protein synthesis or mitosis
Surface view

Sectioned view

(a) RBC shape

7.5 μm
Erythrocytes (RBCs)

- Blood type determined by surface glycophorin and glycolipids on surface of plasma membrane
- Cytoskeletal proteins = spectrin and actin
  - Give RBC membrane durability and resilience
  - Provide stretch and bend as they squeeze through small capillaries
  - Cannot be replaced because RBC lack organelles of protein synthesis
Erythrocytes (RBCs)

- 2.5 million RBCs are produced per second
- average lifespan of about 120 days
- development takes 3-5 days
  - reduction in cell size, increase in cell number, synthesis of hemoglobin and loss of nucleus
- first committed cell - erythrocyte colony forming unit // has receptors for erythropoietin (EPO) from kidneys
- erythroblasts (normoblast) multiply and synthesize hemoglobin
- As erythroblast mature they discard their nucleus and become a reticulocyte
  - named for fine network of endoplasmic reticulum still in cytoplasm // 0.5 to 1.5% of circulating RBCs are reticulocytes
Erythropoiesis

Pluripotent stem cell → Colony-forming unit (CFU) → Precursor cells → Mature cell

Erythrocyte CFU → Erythroblast → Reticulocyte → Erythrocyte

3 to 5 days to complete
Erythrocytes / Red Blood Corpuscles

- **principal function**
  - carry oxygen from lungs to cellular tissues of body
  - Note most of the carbon dioxide transported as bicarbonate in plasma from tissue to lungs
- insufficient RBC function may result in necrosis within 4 – 5 minutes due to lack of oxygen and too much CO2
Hemoglobin (Hb) Structure

• each Hb molecule consists of:
  – globular proteins // four chains per hemoglobin molecule
  – heme groups

• about the heme groups
  – The heme is a nitrogen ring structure which holds an iron atom
  – Iron atom binds O₂ // the ferrous ion (Fe²⁺) at its center
Hemoglobin (Hb) Structure

• About the globin molecules
  – two alpha and two beta chains
  – 5% CO₂ in blood is bound to globin moiety

• adult vs. fetal have different type of hemoglobin
  – Which form has the greatest affinity for oxygen?
  – Why?

(a) 

(b)
Factors That Influence O2 Transport

- **hematocrit** (packed cell volume) // men 42-52% cells; women 37-48% cells

- **RBC count** // men 4.6-6.2 million/μL; women 4-2-5.4 million/μL

- **hemoglobin concentration** of whole blood // men 13-18g/dL; women 12-16g/dL

- Note: values are lower in women
  - androgens stimulate RBC production
  - women have periodic menstrual losses
  - hematocrit is inversely proportional to percentage of body fat
Nutritional Needs for Erythropoiesis

- iron - key nutritional requirement
  - lost daily through urine, feces, and bleeding // men 0.9 mg/day and women 1.7 mg/day
  - low absorption rate of iron requires consumption of 5-20 mg/day

- dietary iron: can be either ferric (Fe$^{3+}$) and ferrous (Fe$^{2+}$) / ferric can not be absorbed

- stomach acid converts Fe$^{3+}$ to absorbable Fe$^{2+}$
Nutritional Needs for Erythropoiesis

- Vitamin $B_{12}$ and folic acid
  - These essential nutrients are required for rapid cell division and DNA synthesis
  - Necessary to produce formed elements // extreme mitosis

- Vitamin C

- Copper // cofactors for enzymes synthesizing hemoglobin // copper is transported in the blood by an alpha globulin called ceruloplasmin
Erythrocyte Homeostasis

- **negative feedback regulation**
  - drop in RBC count causes **hypoxemia** // stimulus for kidneys
  - kidney produces **erythropoietin** // hormone // stimulates bone marrow
  - RBC count increases in 3 - 4 days

- **stimulus to increase erythropoiesis**
  - low levels $O_2$ (hypoxemia)
  - high altitude
  - increase in exercise
  - loss of lung tissue as in emphysema
Erythrocytes Death and Disposal

- RBCs lyse in the narrow (2 micrometer) capillaries in **spleen // graveyard for old RBC**

- **High concentration of macrophages in spleen // resident phagocytes**
  - digest and recycle membranes
  - separate heme from globin
    - **globins** hydrolyzed into **amino acids**
    - **iron** removed from **heme**
Erythrocytes Death and Disposal

- Need to eliminate nitrogen atoms of the heme molecule
  - heme pigment converted to biliverdin (green)
  - biliverdin converted to bilirubin (yellow)
  - released into blood plasma (kidneys excrete - yellow urine)
  - liver removes bilirubin and secretes into bile
    - concentrated in gall bladder: released into small intestine; bacteria create urobilinogen (brown feces)
Erythrocytes Recycle/Disposal

Amino acids
Iron
Folic acid
Vitamin B₁₂

Nutrient absorption

Small intestine

Erythrocytes circulate for 120 days

Erythropoiesis in red bone marrow

Expired erythrocytes break up in liver and spleen

Cell fragments phagocytized

Hemoglobin degraded

Heme

Iron

Biliverdin

Bilirubin

Bile

Feces

Uneaten heme and bilirubin:

Storage → Reuse

Loss by menstruation, injury, etc.

Hydrolyzed to free amino acids

Folic acid

Nutrient absorption
Erythrocyte Disorder

• polycythemia = an excess of RBCs
  – primary polycythemia (polycythemia vera) // cancer of erythropoietic cell line in red bone marrow // RBC count as high as 11 million/μL; hematocrit 80% // note – erythropoietin low concentration in blood
  – secondary polycythemia // from dehydration, emphysema, high altitude, or physical conditioning // RBC count up to 8 million/μL // note – erythropoietin high concentration in blood

• dangers associated with polycythemia
  – increased blood volume
  – pressure, viscosity
  – can lead to embolism
  – stroke
  – Increase in blood viscosity
  – heart failure
Anemia

- Not able to supply oxygen to tissue

- Causes fall into three categories
  - Inadequate erythropoiesis (or hemoglobin production)
  - Hemorrhagic anemia
  - Hemolytic anemia

- Iron-deficiency anemia

- Pernicious anemia  //  Vitamin B12 deficiency (vitamin usually present in diet / meat)
  - Problem often lack of intrinsic factor  //  required to carry B12 across mucosa / stomach glands fail to produce intrinsic factor

- Sickle cell anemia

- Hypoplastic anemia or aplastic anemia
Anemia

• Three potential consequences:
  – Hypoxia // oxygen deprivation / low energy / severe result in necrosis
  – Reduced blood osmolarity // edema
  – Reduced blood viscosity
    • little blood resistance
    • heart beats faster
    • may lead to low blood volume and viscosity to lead to low blood pressure
    • leads to cardiac failure
Chapter 19

Leukopoiesis
Leukocytes (WBCs)

- least abundant of all the formed elements // 5,000 to 10,000 WBCs/μL

- Primary function = protect against infectious microorganisms and other pathogens

- WBCs have conspicuous nucleus

- spend only a few hours in the blood stream before migrating out of blood and into connective tissue (i.e. reticuloendothelial system)

- retain their organelles for protein synthesis

- All WBC have granules but some cells don’t stain!
Leukocytes (WBCs)

- All WBC have granules but some cells don’t stain! (cont.)
  - All WBCs have lysosomes called nonspecific (azurophilic) granules
  - Inconspicuous so cytoplasm looks clear
  - Granulocytes have specific granules that contain enzymes and other chemicals employed in defense against pathogens
Leukocyte Life Cycle

- Leukopoiesis – production of white blood cells
  - Pluripotent stem cells – (PPSCs)
    - Myeloblasts – form neutrophils, eosinophils, basophils
    - Monoblasts - form monocytes
    - Lymphoblasts give rise to all forms of lymphocytes
  - Red bone marrow produce, stores and releases all granulocytes, monocytes (agranulocyte)
- B cells // a type of lymphocyte // born in red bone marrow, matures and released from RB marrow
- T lymphocytes born in red bone marrow but complete development in thymus
Leukopoiesis
Key:
- Progenitor cells
- Precursor cells or "blasts"
- Formed elements of circulating blood
- Tissue cells

PLURIPOTENT STEM CELL

MYELOID STEM CELL

CFU-E
Proerythroblast
Nucleus ejected
Reticulocyte
Red blood cell (erythrocyte)

CFU-Meg
Megakaryoblast
Megakaryocyte
Platelets

CFU-GM
Eosinophilic myeloblast
Basophilic myeloblast
Myeloblast
Granular leukocytes
Mast cell

LYMPHOID STEM CELL

Monoblast
Monocyte
Agranular leukocytes
Macrophage
Plasma cell

T lymphoblast
T lymphocyte (T cell)

B lymphoblast
B lymphocyte (B cell)

NK lymphoblast
Natural killer (NK) cell

Key:
- CFU-E: Colony-forming unit—erythrocyte
- CFU-Meg: Colony-forming unit—megakaryocyte
- CFU-GM: Colony-forming unit—granulocyte macrophage
Types of Leukocytes

• Granulocytes // these cells stain // known as the “NEBs”
  – neutrophils (60-70
  – eosinophils (2-4%)
  – basophils (<1%)

• Agranulocytes // these don’t stain
  – lymphocytes (25-33%)
  – monocytes (3-8%)

• How to remember WBC ranking = Never let monkeys eat bananas
Granulocytes

- Neutrophils
- Eosinophil
- Basophil
Agranulocytes
Granulocyte Functions

• Neutrophils

  – 60-70% of WBC

  – Also known as polymorphonuclear leukocytes

  – Barely visible granules in cytoplasm // 3 to 5 lobed nucleus

  – First WBC to arrive during inflammation

  – increased numbers in **bacterial infections** / neutrophilia – increase 5x

  – phagocytosis of bacteria / phagosomes kill bacteria

  – release antimicrobial chemicals // called the “**respiratory burst**” – like a nuclear bomb! // hypochlorite – hydrogen peroxide – free radicals
Granulocyte Functions (The NEBs)

• Eosinophils

  – 2-4% // large rosy-orange granules, bi-lobed nucleus
  
  – increased numbers in parasitic infections

  – Increase numbers in collagen diseases, allergies, diseases of spleen and CNS

  – engulf antigen-antibody complexes, allergens, and inflammatory chemicals

  – also able to deliver a respiratory burst // release enzymes to destroy large parasites // parasite tagged by E class antibodies
Granulocyte Functions

- **Basophils**
  - <1% // large, abundant, violet granules (obscure a large S-shaped nucleus)
  - Emigrate from blood to tissue // Change into a **mast cells**
    (acquire surface receptors = E class antibodies produced by plasma cells upon “first exposure” / able to release histamine and heparin after first exposure and subsequent exposures
  - increased numbers in chicken pox, sinusitis, diabetes
  - **histamine** (vasodilator) // speeds flow of blood to an injured area
  - secrete **heparin** (anticoagulant) // promotes the mobility of other WBCs in the area
Agranulocyte Functions

Lymphocytes

- 25-33% // variable amounts of bluish cytoplasm (scanty to abundant); ovoid/round, uniform dark violet nucleus

- increased numbers in diverse infections and immune responses

- T lymphocytes able to destroy cells (cancer, foreign, and virally infected cells) // cellular immunity

- “present” antigens to activate other immune cells

- coordinate actions of other immune cells // cytokines = messenger molecules

- B lymphocytes secrete antibodies and provide immune memory // humeral immunity
Agranulocyte Functions

Monocytes

- 3-8% // largest WBC; ovoid, kidney or horseshoe shaped nucleus

- increased numbers in viral infections and inflammation // produce and secrete cytokines

- leave bloodstream and transform into macrophages (i.e. big eater)

- phagocytize pathogens and debris // the "garbage collector"

- “present” antigens to activate other immune cells // antigen presenting cells (APCs)
Diapedis: Leukocytes Emigrate into Tissue Spaces

- Circulating WBCs do not stay in bloodstream
  - Granulocytes (NEB) leave in 8 hours and live 5 days longer
  - Monocytes leave in 20 hours, transform into macrophages and live for several years
  - Lymphocytes provide long-term immunity // live for decades // continuously recycled from blood to tissue fluid to lymphatic system and back into the blood
Leukocyte Disorders

- **leukopenia** - low WBC count below 5000/μL
  - causes: radiation, poisons, infectious disease
  - effects: elevated risk of infection

- **leukocytosis** - high WBC count above 10,000/μL
  - causes: infection, allergy and disease
  - differential WBC count – identifies what percentage of the total WBC count consist of each type of leukocyte
Leukocyte Disorders

- Leukemia - cancer of hemopoietic tissue that usually produces an extraordinary high number of circulating leukocytes and their precursors
  - myeloid leukemia – uncontrolled granulocyte production
  - lymphoid leukemia - uncontrolled lymphocyte or monocyte production
  - acute leukemia – appears suddenly, progresses rapidly, death within months
  - chronic leukemia – undetected for months, survival time three years
- effects - normal cell percentages disrupted; impaired clotting; opportunistic infections
Normal and Leukemic Blood

(a) Platelets
(b) Monocyte
Neutrophils
Lymphocyte
Erythrocytes

(a) Platelets
(b) Monocyte
Neutrophils
Lymphocyte
Erythrocytes

75 µm
Complete Blood Count

- Hematocrit
- Hemoglobin concentration
- Total count for RBCs, reticulocytes, WBCs, and platelets
- Differential WBC count
- RBC size and hemoglobin concentration per RBC