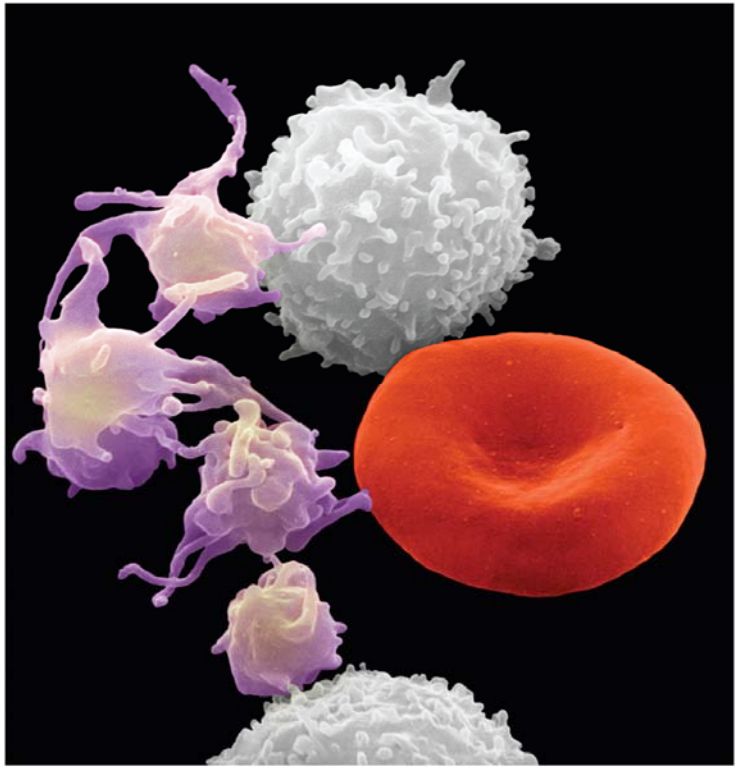
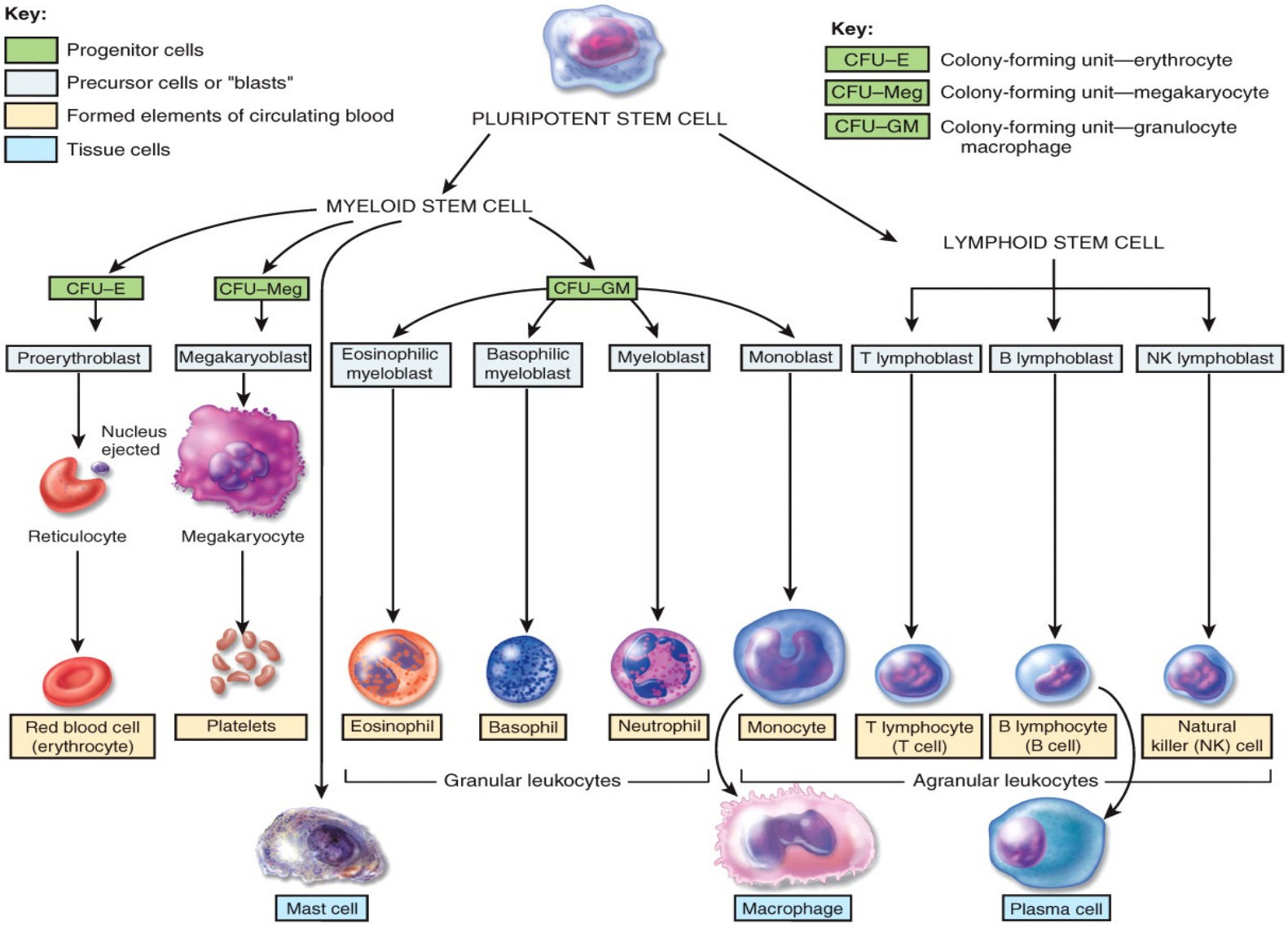
Chapter 19

Structure and Function of the Nine Formed Elements

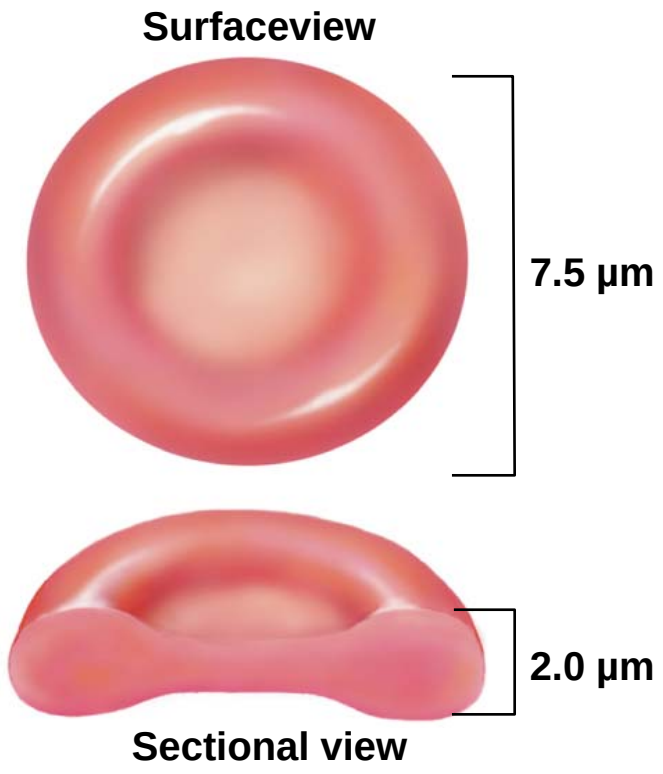


The Nine Formed Elements



Erythrocytes or RBC

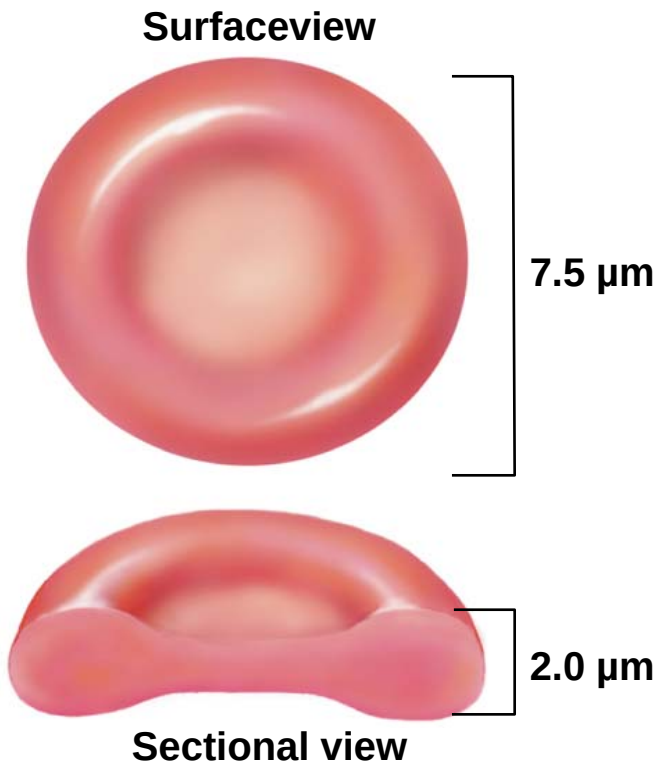
- disc-shaped cell with thick rim
  - 7.5 μM diameter and 2.0 μm thick at rim
  - lose nearly all organelles during development
    - lack mitochondria // must use anaerobic fermentation to produce ATP
    - lack of nucleus and DNA // no protein synthesis or mitosis



(a) RBC shape

Erythrocytes or RBC

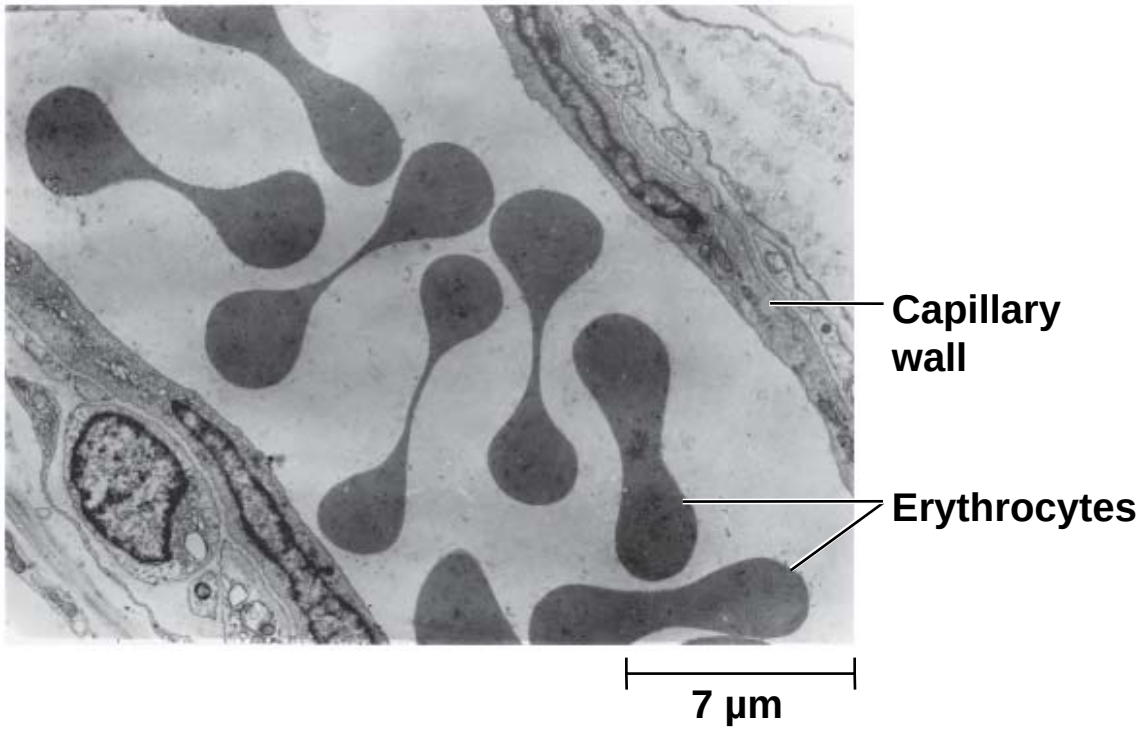
- blood type determined by surface glycoprotein and glycolipids on surface of plasma membrane
- cytoskeletal proteins = spectrin and actin
  - give RBC membrane <u>durability and resilience</u>
  - provide stretch and bend as squeeze through small capillaries
  - Can not be replaced because RBC lack organelles of protein sysnthesis



Erythrocytes or RBC

- 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

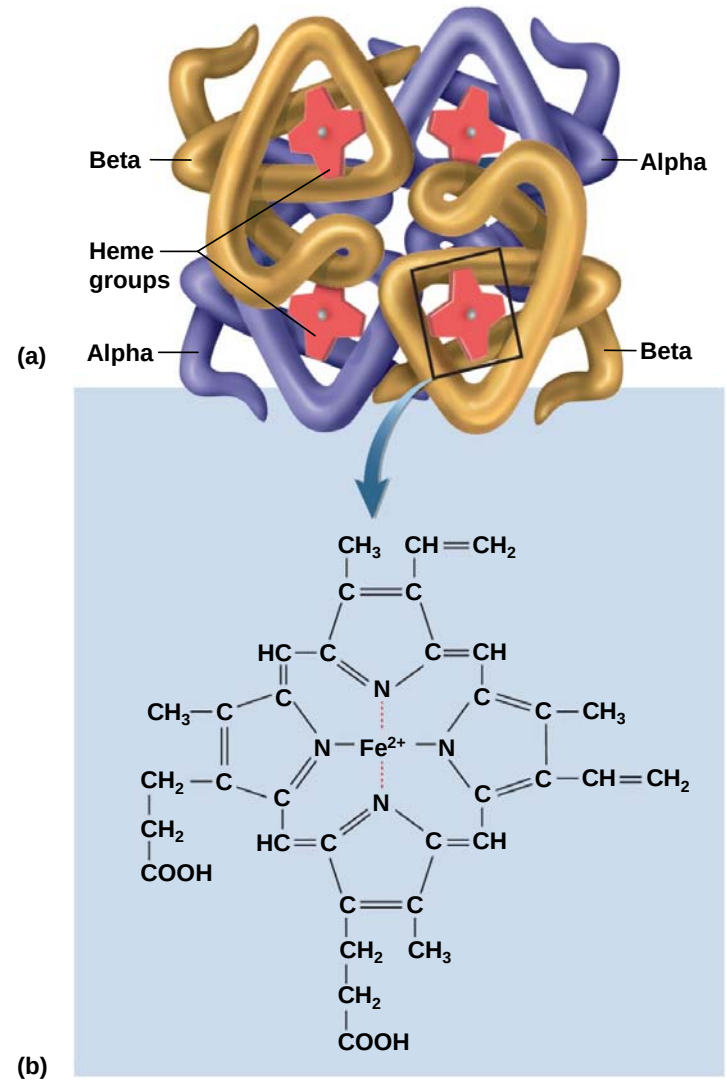
Erythrocytes



- **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

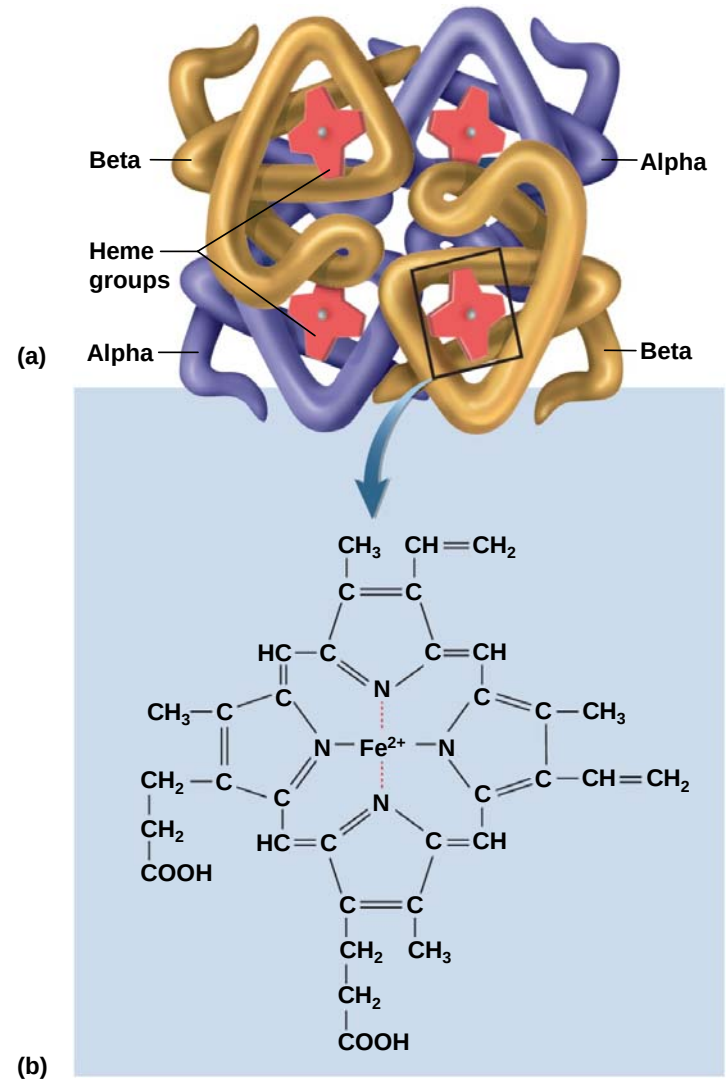
Hemoglobin (Hb) Structure

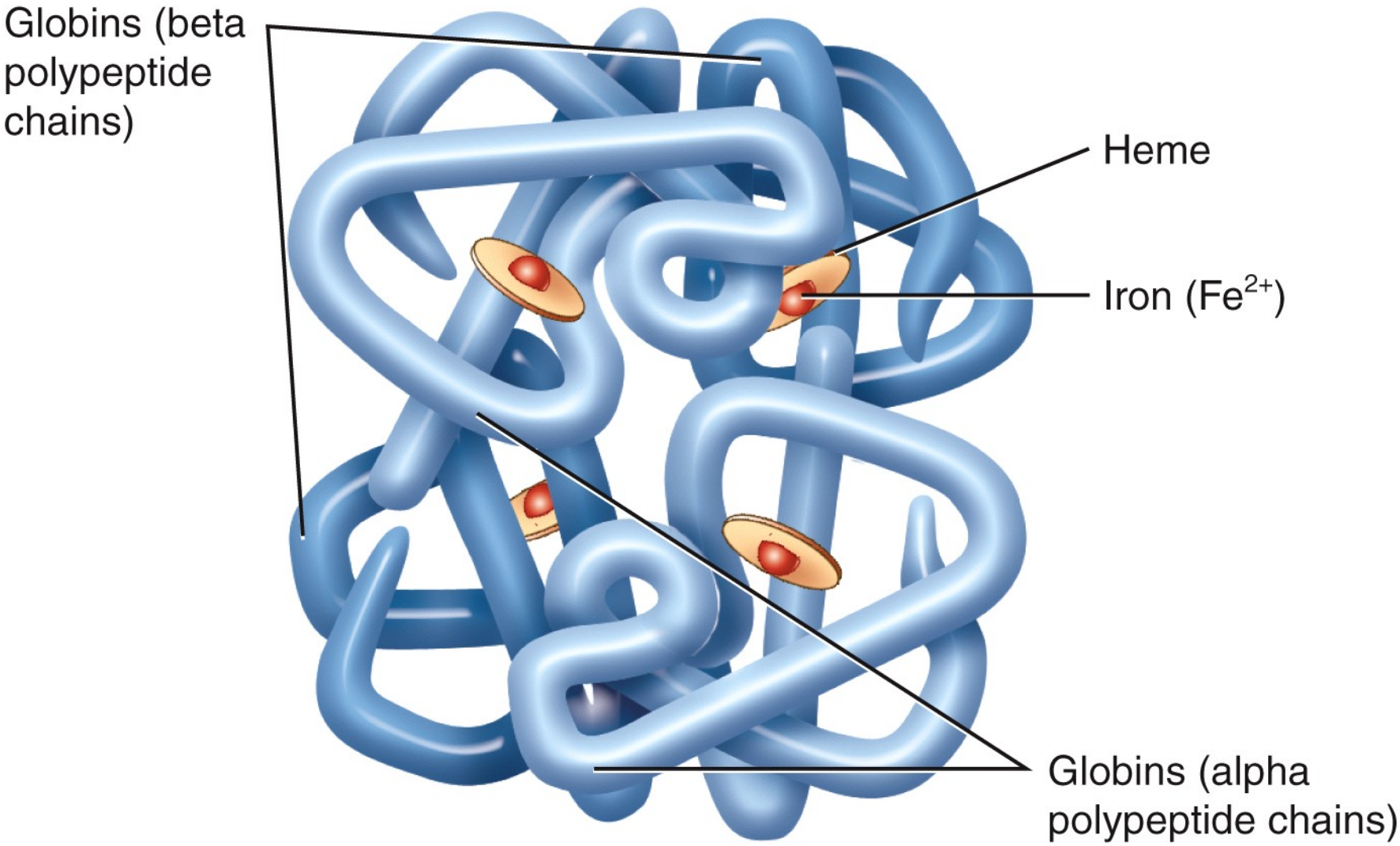
- each Hb molecule consists of:
  - globular proteins // four chains per hemoglobin molecule
  - heme groups
- about the heme groups
  - The heme is a nitrogen ring structure which holds an iron atom
  - Iron atom binds O_2 // the ferrous ion (Fe^{2+}) at its center



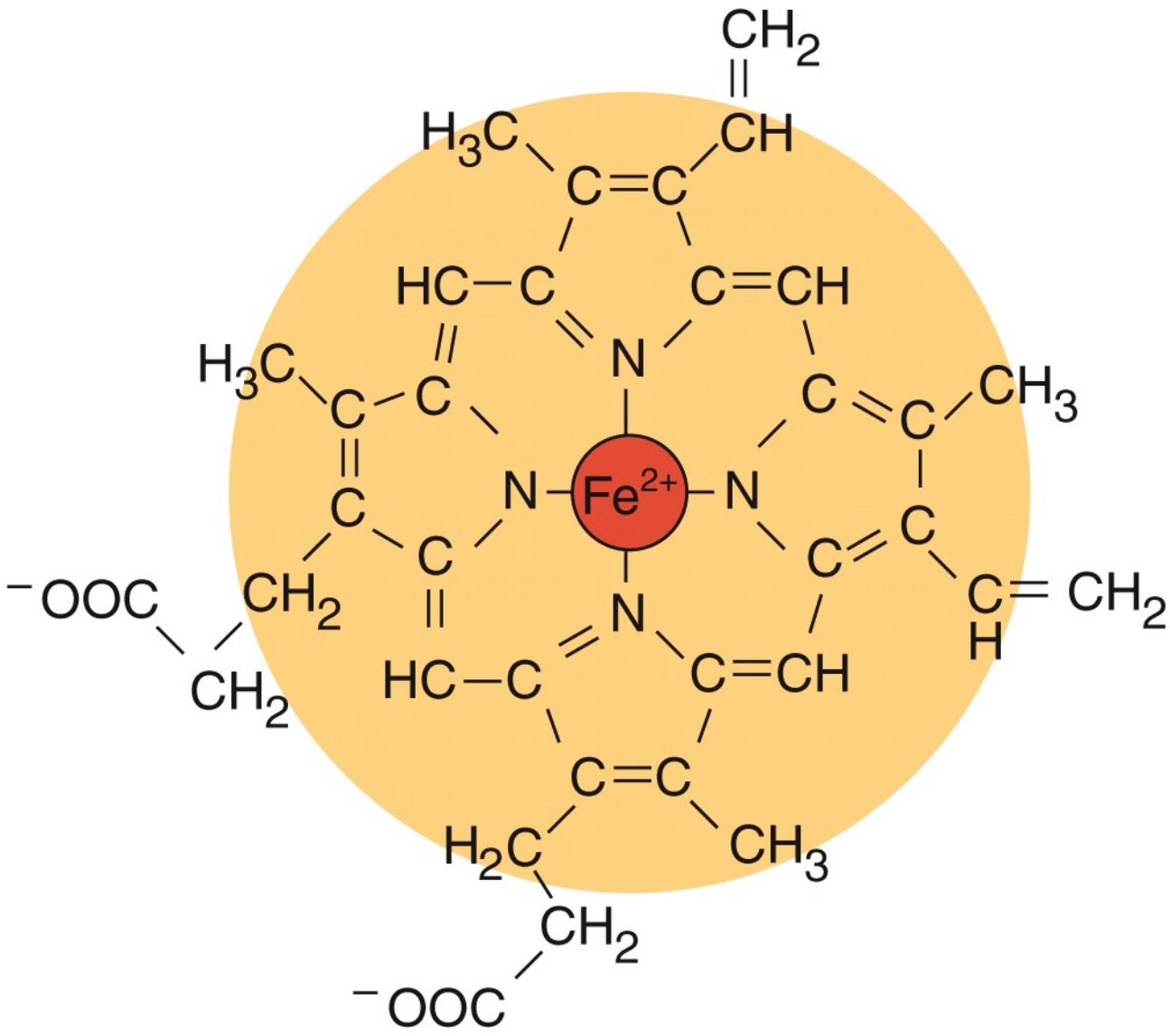
Hemoglobin (Hb) Structure

- About the globin molecules
  - two alpha and two beta chains
  - 5% CO_2 in blood is bound to globin moiety
- <u>adult vs. fetal have different type of hemoglobin</u>
  - Which form has the greatest affinity for oxygen?
  - Why?





(b) Hemoglobin molecule



(c) Iron-containing heme

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

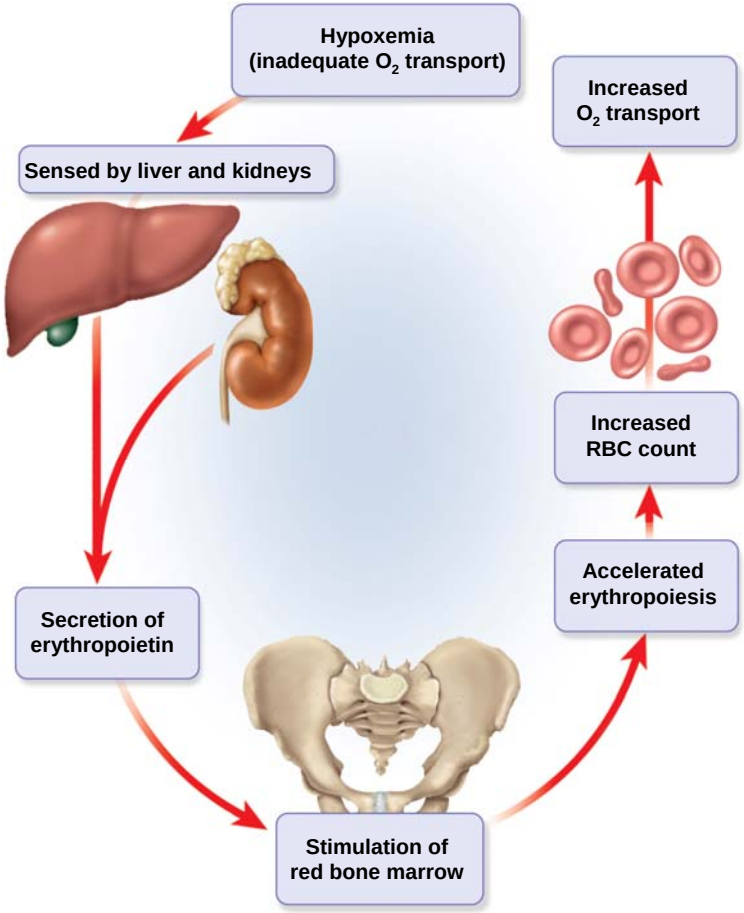
- Iron - key nutritional requirement
  - lost daily through urine, feces, and bleeding // men 0.9 mg/day and women 1.7 mg/day
  - low absorption rate of iron requires consumption of 5-20 mg/day
    - dietary iron: can be either ferric (Fe^{3+}) and ferrous (Fe^{2+}) / ferric can not be absorbed
    - stomach acid converts Fe^{3+} to absorbable Fe^{2+}

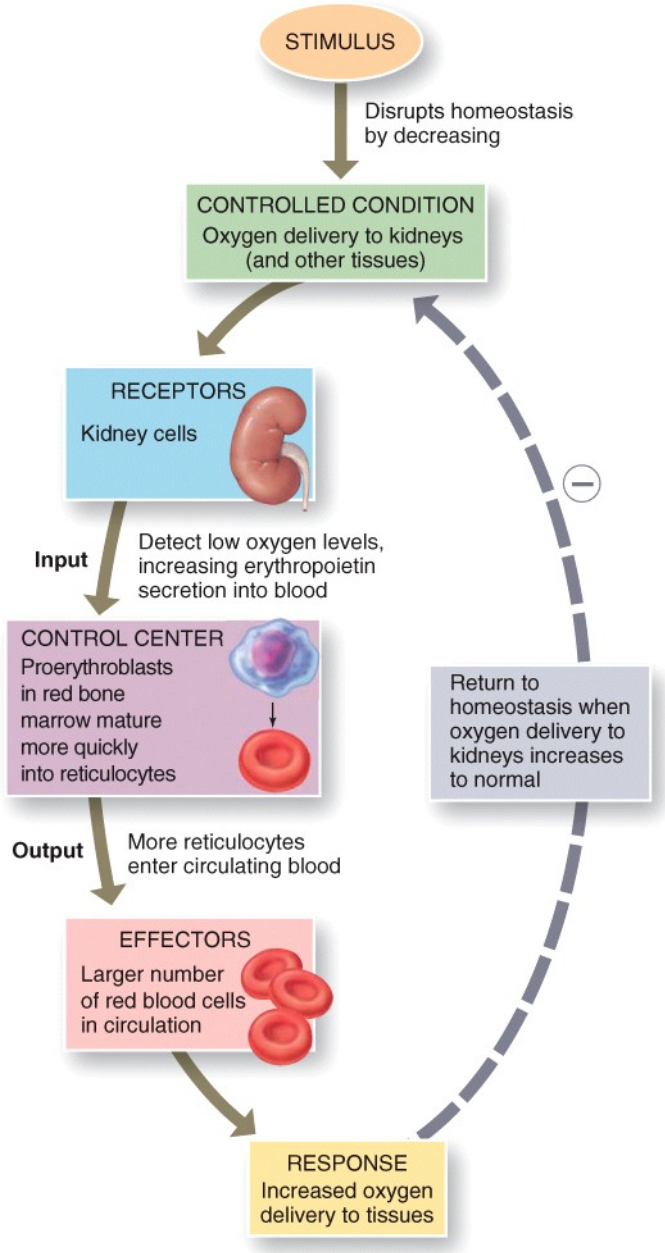
Nutritional Needs for Erythropoiesis

- Vitamin B_{12} and folic acid
  - These essential nutrients are required for rapid cell division and DNA synthesis
  - Necessary to produce formed elements // promote extreme mitosis
  - Parietal cells of intestinal crypts must produce intrinsic factor in order to absorb Vit B12 (no B12 - pernicious anemia may occur)
- Vitamin C
- Copper // cofactors for enzymes synthesizing hemoglobin // copper is transported in the blood by an alpha globulin called ceruloplasmin

Regulating 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



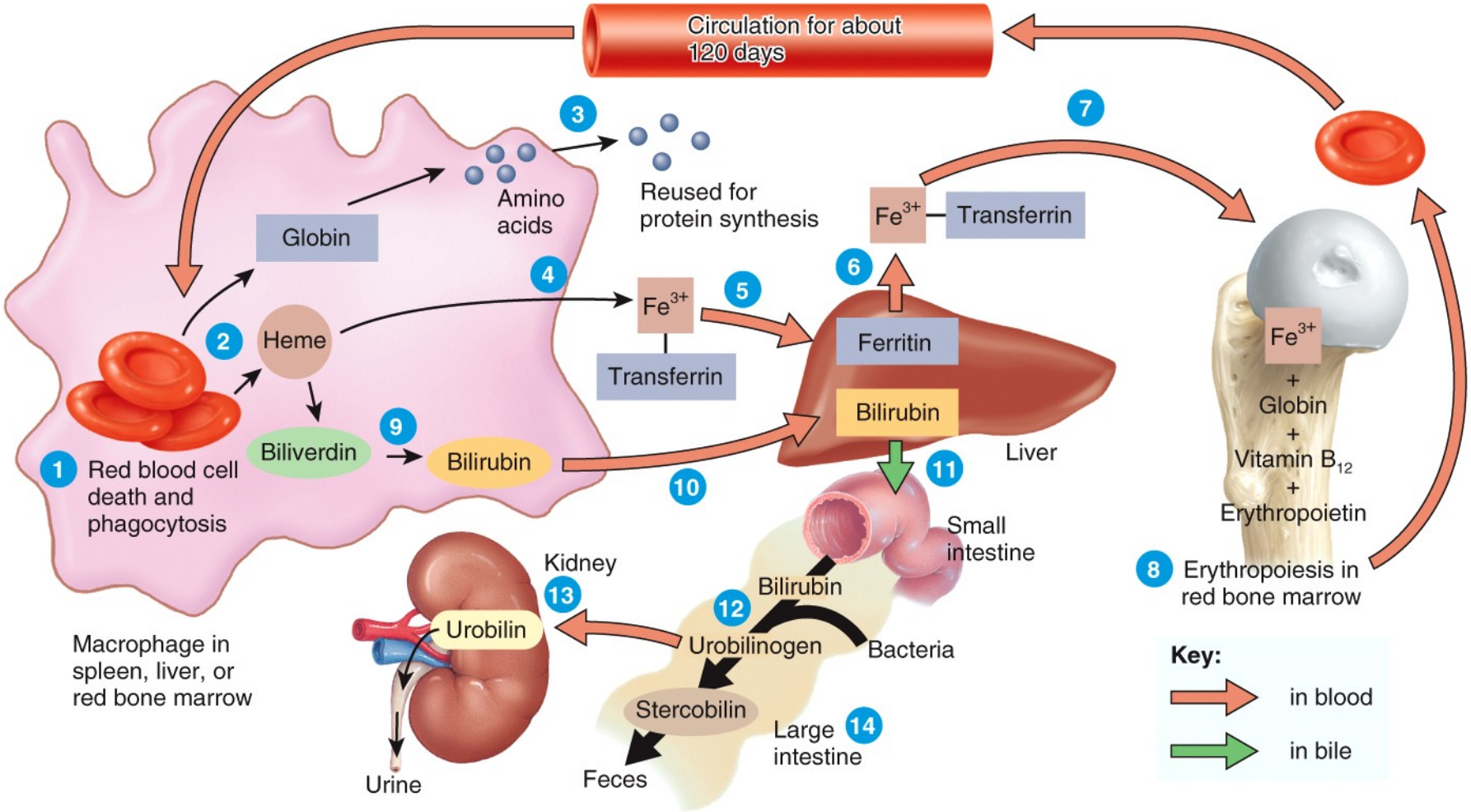

STIMULUS
Disrupts homeostasis by decreasing
CONTROLLED CONDITION
Oxygen delivery to kidneys (and other tissues)
RECEPTORS
Kidney cells
Input
Detect low oxygen levels, increasing erythropoietin secretion into blood
CONTROL CENTER
Proerythroblasts in red bone marrow mature more quickly into reticulocytes
Output
More reticulocytes enter circulating blood
EFFECTORS
Larger number of red blood cells in circulation
RESPONSE
Increased oxygen delivery to tissues
Return to homeostasis when oxygen delivery to kidneys increases to normal

Erythrocytes Death and Disposal

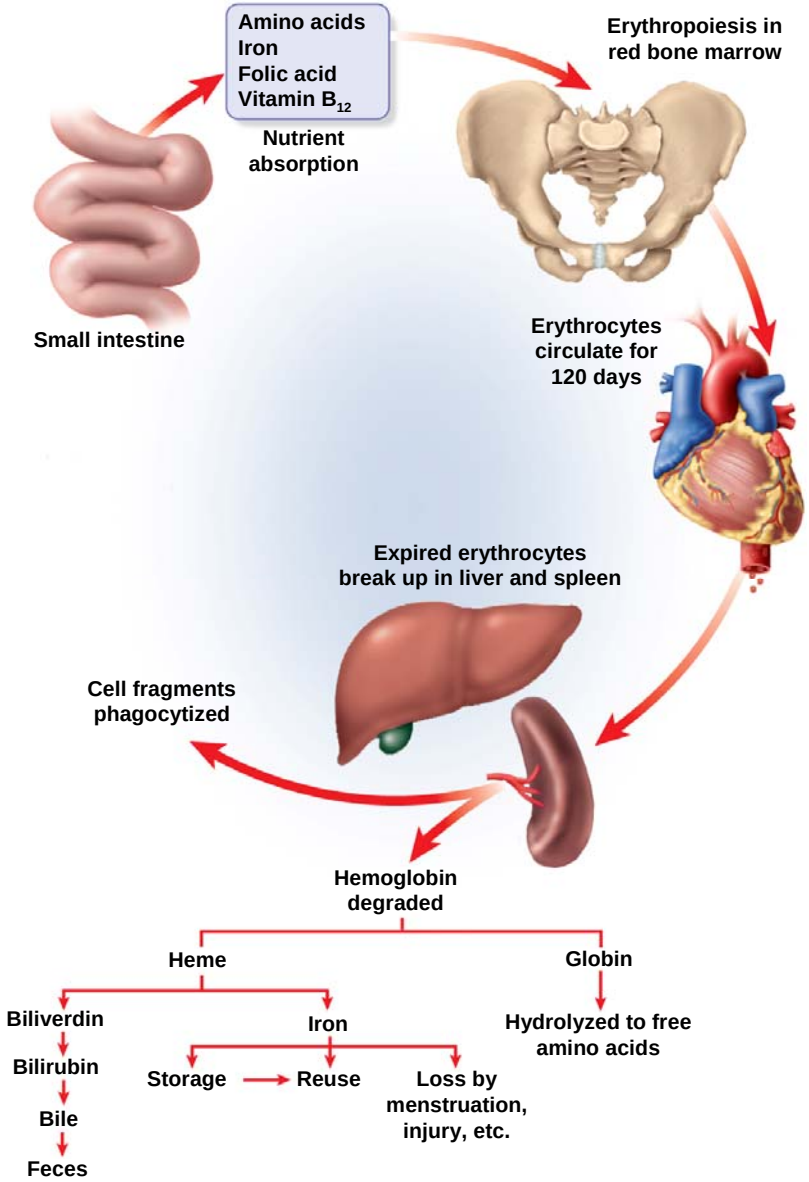
- RBCs lyse in the narrow (2 micrometer) capillaries found in the **spleen = graveyard for old RBC**
- <u>High concentration of macrophages in spleen // resident phagocytes</u>
  - digest and recycle membranes
  - separate heme from globin
    - **globins** hydrolyzed into **amino acids**
    - **iron** removed from **heme**

Erythrocytes Death and Disposal

- Need to eliminate nitrogen from 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)


Circulation for about 120 days
1 Red blood cell death and phagocytosis
2
Heme
Globin
Amino acids
3
Reused for protein synthesis
4
Biliverdin
9
Bilirubin
Fe3+
Transferrin
5
10
Ferritin
Bilirubin
Liver
6
Fe3+
Transferrin
7
Fe3+
+
Globin
+
Vitamin B12
+
Erythropoietin
8 Erythropoiesis in red bone marrow
11
Small intestine
Bilirubin
12
Urobilinogen
Bacteria
Stercobilin
Large intestine
14
Feces
Kidney
13
Urobilin
Urine
Macrophage in spleen, liver, or red bone marrow
Key:
in blood
in bile

Erythrocytes Recycle/Disposal



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
- Three main categories
  - Inadequate erythropoiesis (or failure to produce functional hemoglobin – e.g. sickle cell anemia)
  - Hemorrhagic anemia
  - Hemolytic anemia

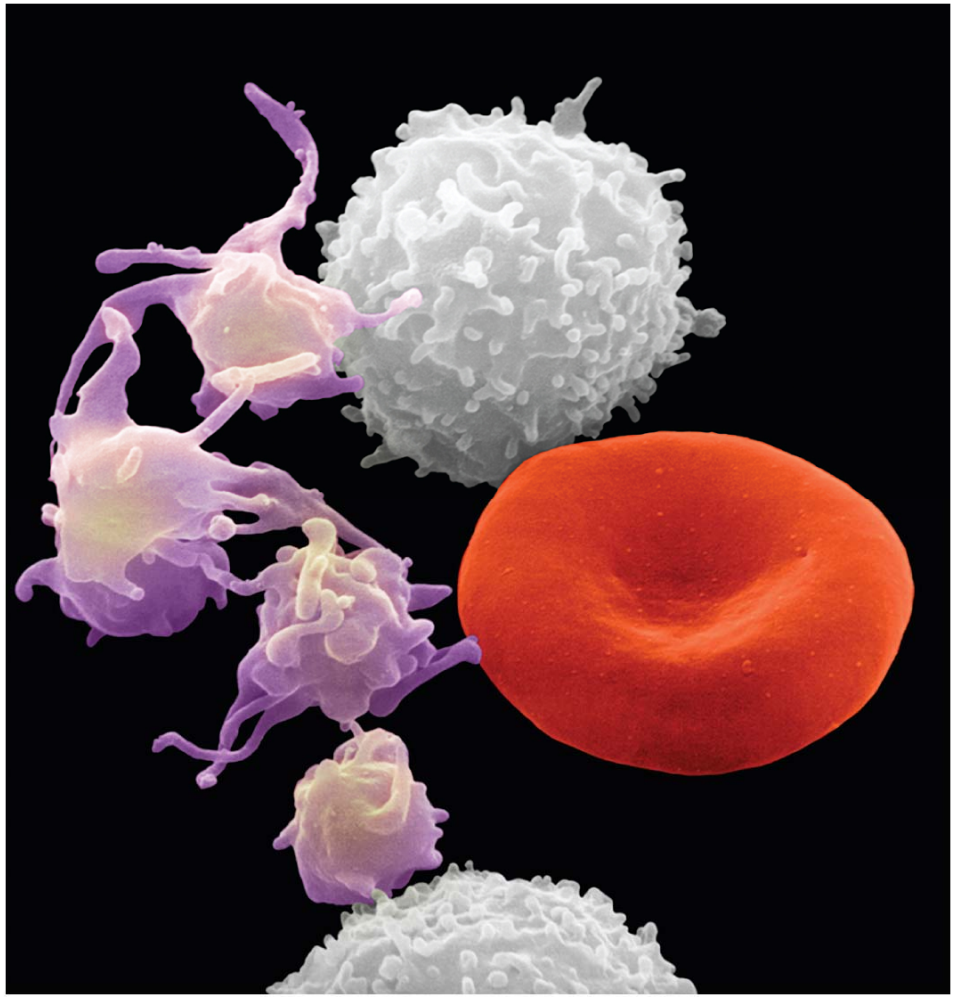
Anemia Types

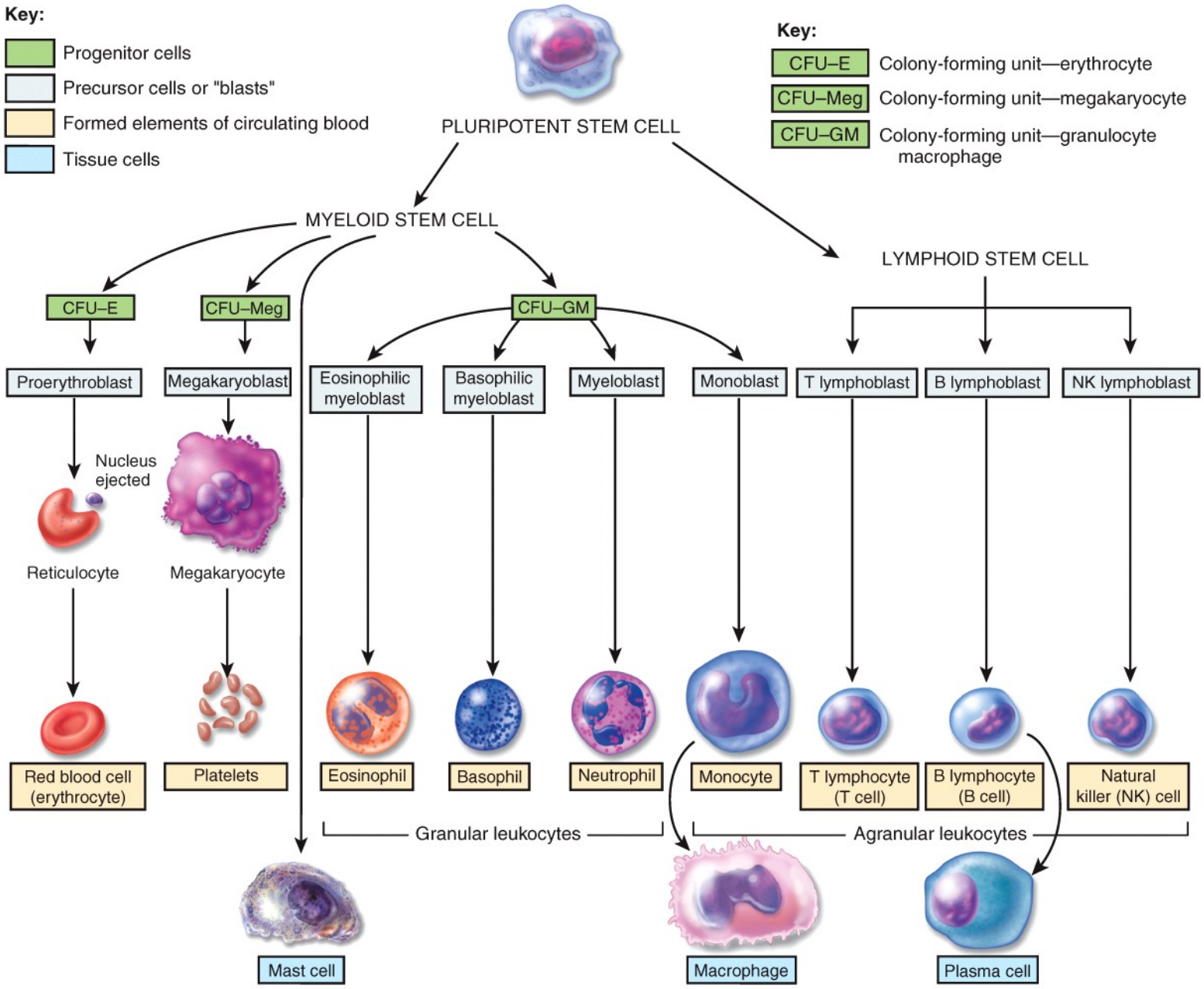
- Iron-deficiency anemia
- Pernicious anemia
  - Problem often lack of intrinsic factor // required to carry B12 across mucosa / stomach glands fail to produce intrinsic factor
  - Vitamin B12 deficiency (vitamin usually present in diet / meat)
- Sickle cell anemia
- Hypoplastic anemia
- Aplastic anemia

Anemia

- Three potential consequences:
  - Hypoxia // oxygen deprivation / low energy / if severe result in necrosis
  - Reduced blood osmolarity // causes 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

Leukocytes (WBC)




Key:
Progenitor cells
Precursor cells or "blasts"
Formed elements of circulating blood
Tissue cells
Key:
CFU–E Colony-forming unit—erythrocyte
CFU–Meg Colony-forming unit—megakaryocyte
CFU–GM Colony-forming unit—granulocyte macrophage
PLURIPOTENT STEM CELL
MYELOID STEM CELL
LYMPHOID STEM CELL
CFU–E
CFU–Meg
CFU–GM
Proerythroblast
Megakaryoblast
Eosinophilic myeloblast
Basophilic myeloblast
Myeloblast
Monoblast
T lymphoblast
B lymphoblast
NK lymphoblast
Nucleus ejected
Reticulocyte
Megakaryocyte
Red blood cell (erythrocyte)
Platelets
Eosinophil
Basophil
Neutrophil
Monocyte
T lymphocyte (T cell)
B lymphocyte (B cell)
Natural killer (NK) cell
Granular leukocytes
Agranular leukocytes
Mast cell
Macrophage
Plasma cell

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 in their cytoplasm but some cell's granules don't stain!
  - all WBCs have **lysosomes** called nonspecific (azurophilic) granules /// these don't stain so called inconspicuous (cytoplasm looks clear) known as the agranulocytes
  - the granulocytes have **specific granules** that stain // contain enzymes and other chemicals employed in defense against pathogens

Types of Leukocytes

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

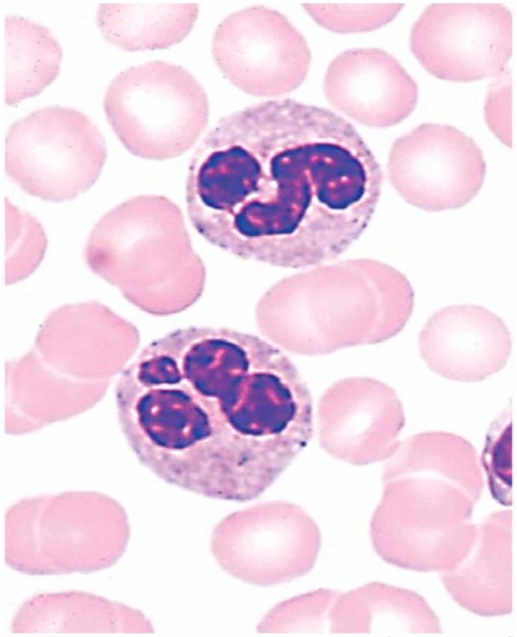
  ← The "NEB"

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

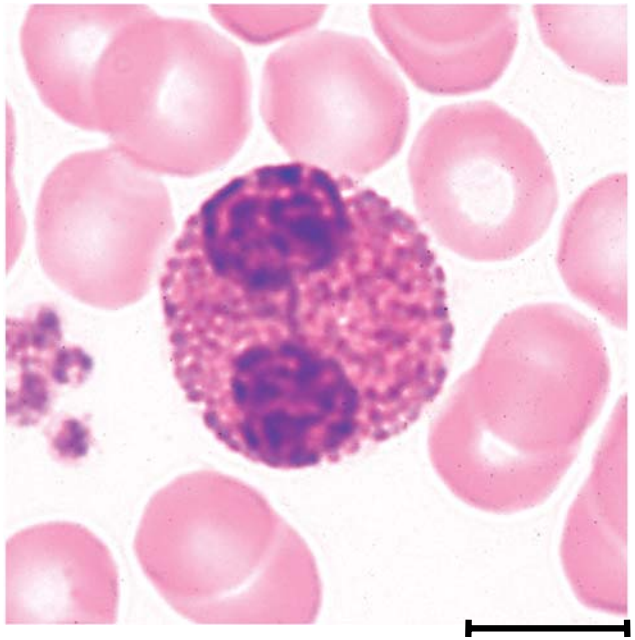
  ← The "LM"

- How to remember WBC ranking = Never let monkeys eat bananas

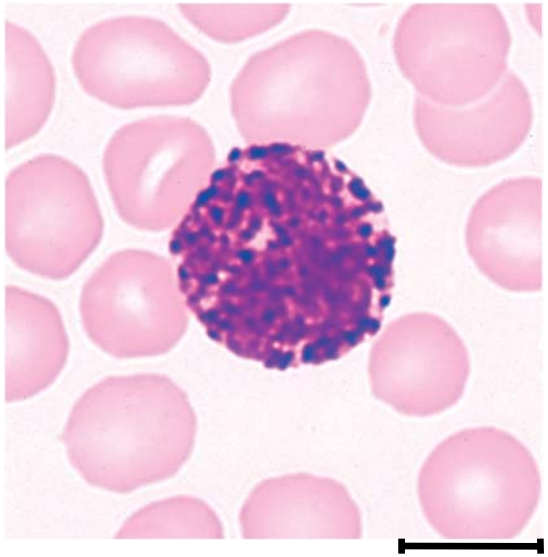
Granulocytes



Neutrophils 10 µm

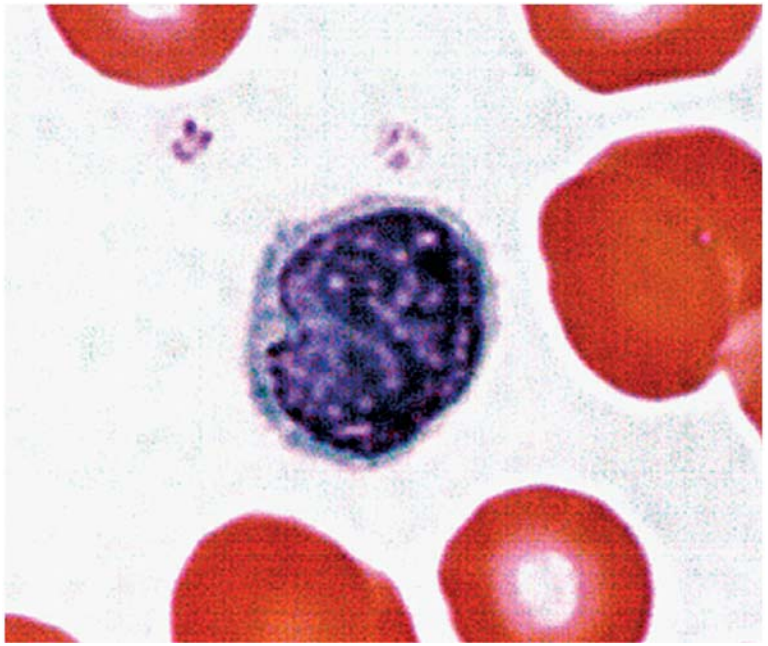


Eosinophil 10 µm



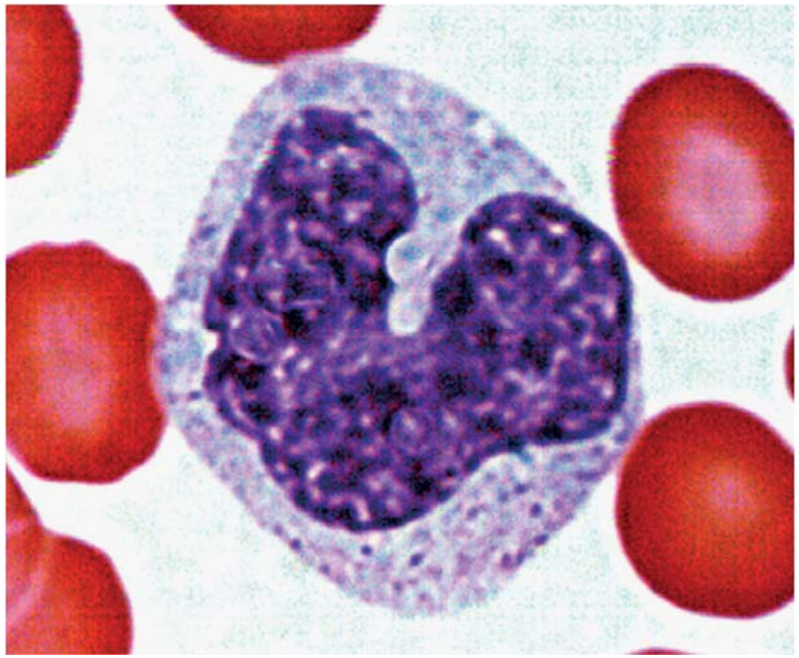
Basophil 10 µm

Agranulocytes



Lymphocyte

10 µm



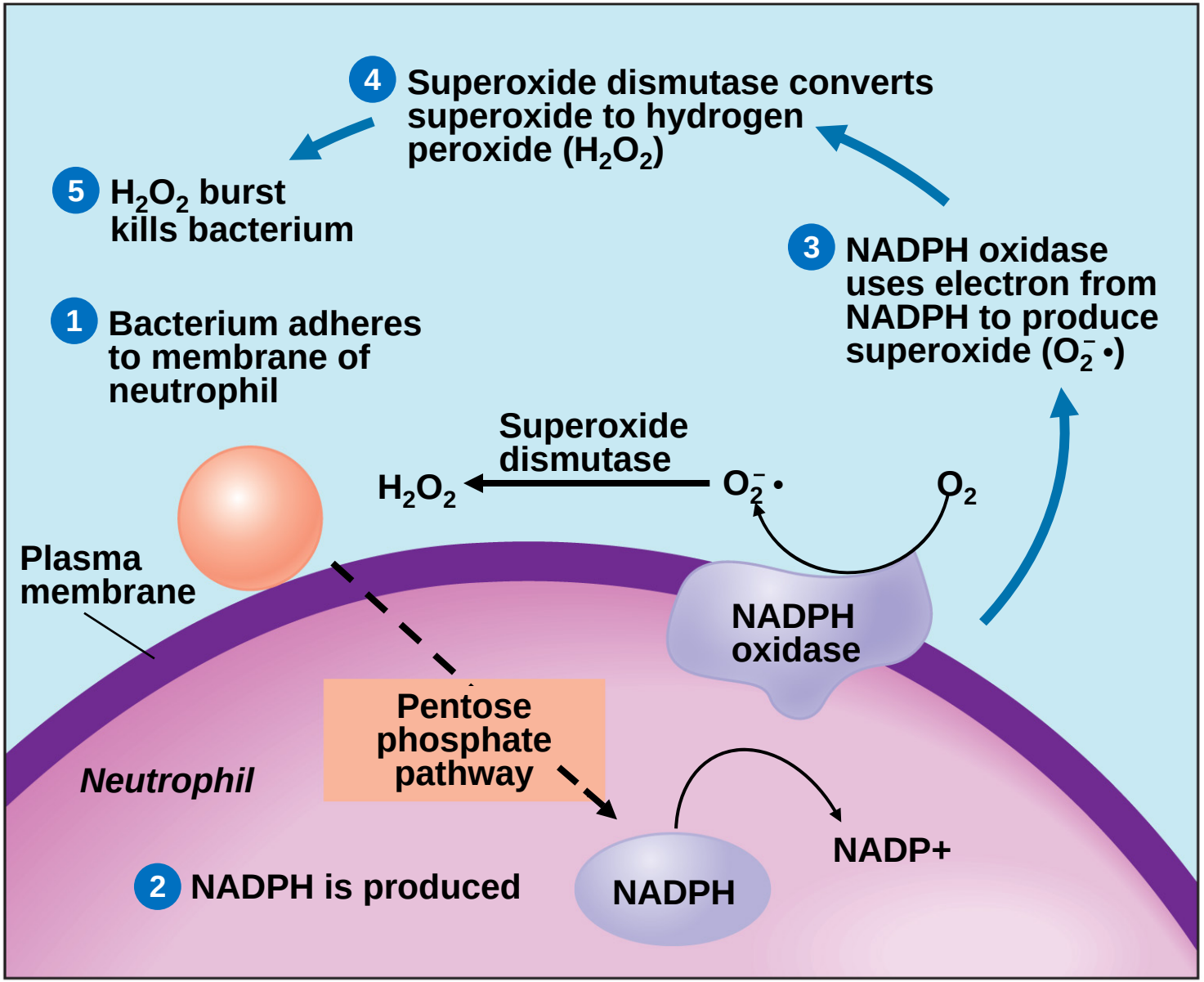
Monocyte

10 µm

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! // hypoclorite – hydrogen peroxide – free radiacals

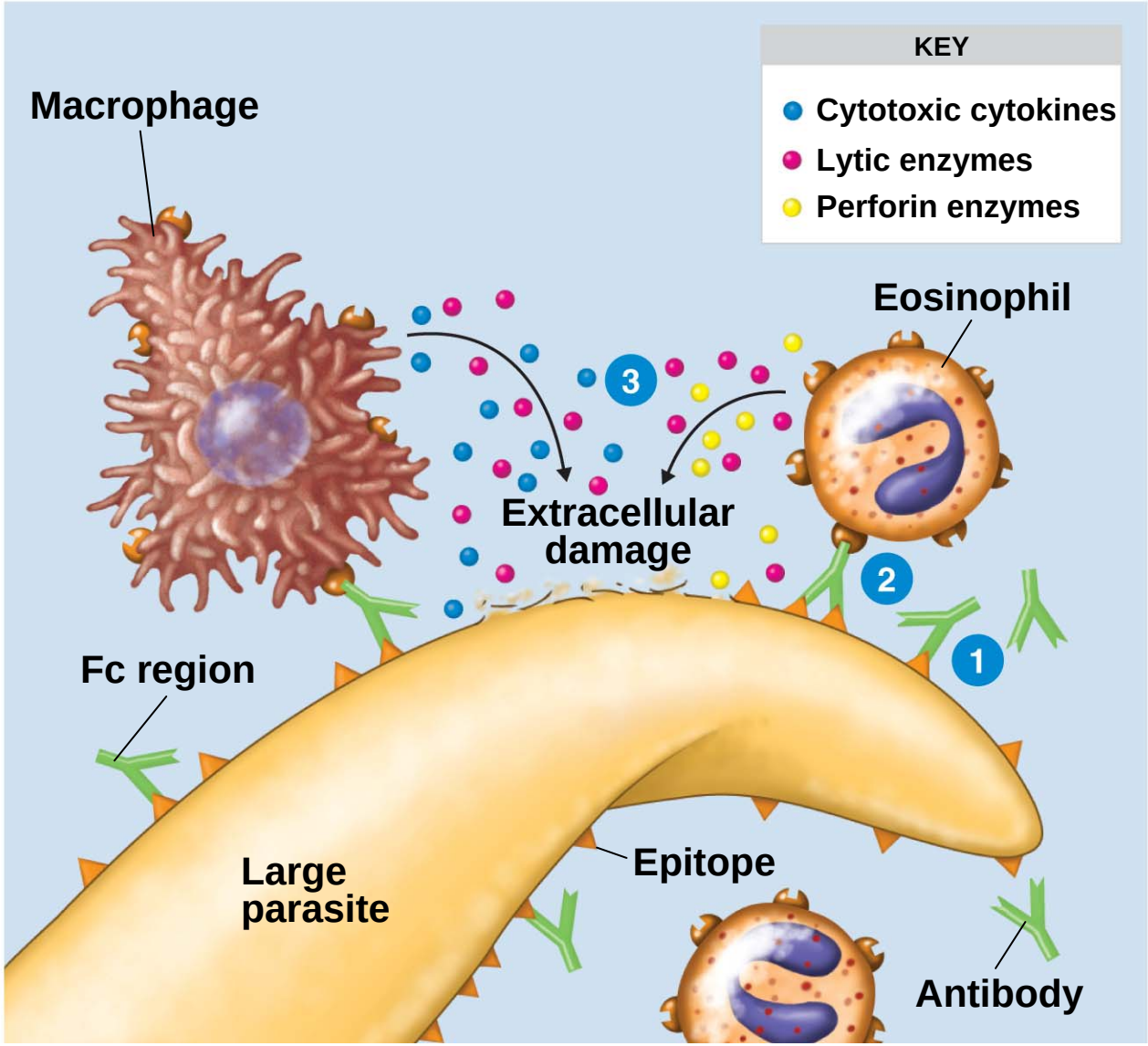
Oxidative Burst (The Respiratory)



Eosinophils

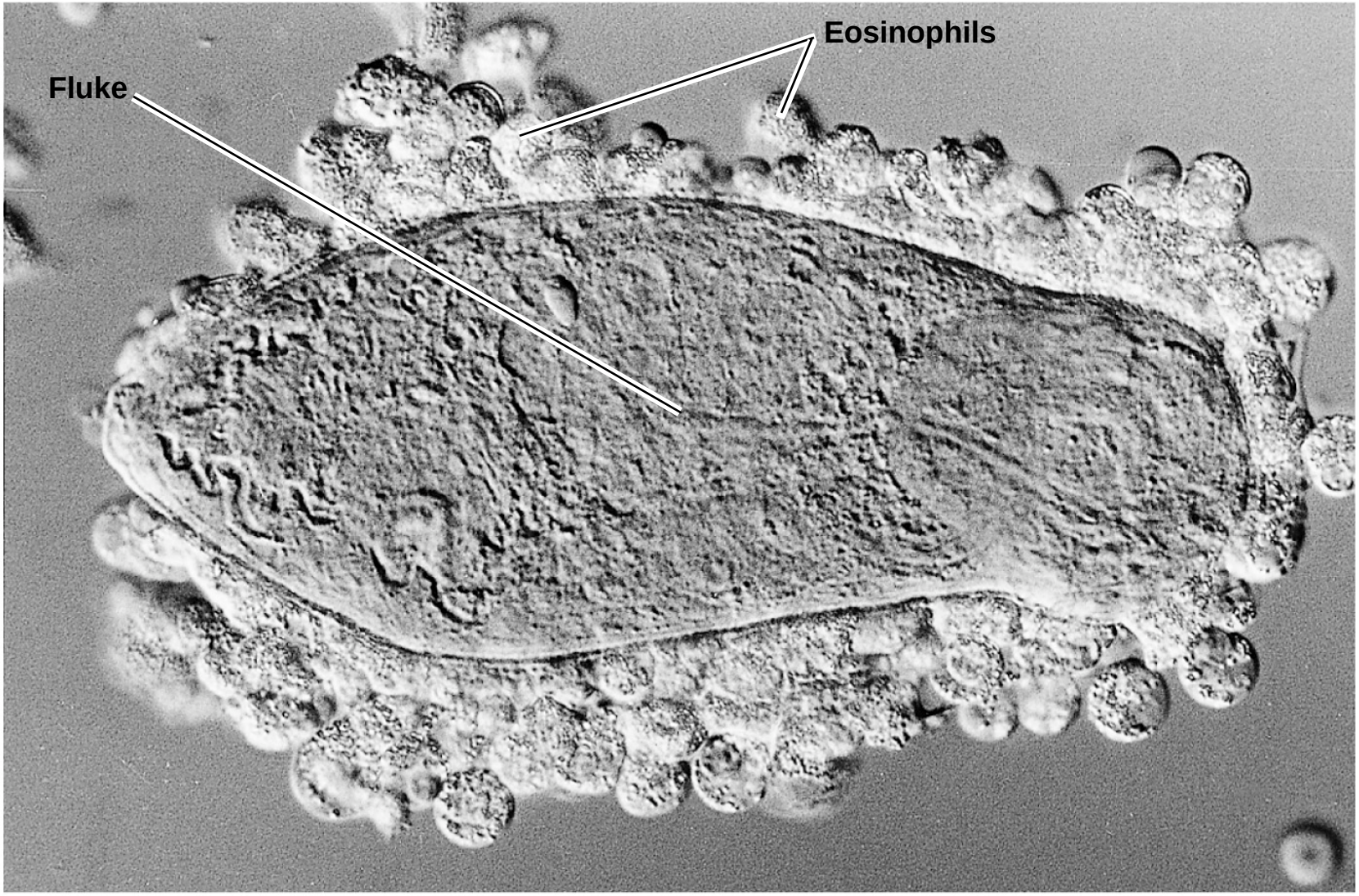
- found especially in the mucous membranes
- 2-4% // large rosy-orange granules, bi-lobe nucleus
- stand guard against **parasites**, **allergens** (allergy causing agents), and other pathogens
- kill tapeworms and roundworms by producing superoxide, hydrogen peroxide, and toxic proteins
- promote action of **basophils** and **mast cells**
- phagocytize **antigen-antibody complexes**
- limit action of **histamine** and other inflammatory chemicals
- Increase numbers in collagen diseases, allergies, diseases of spleen and CNS

Antibody-dependent cell-mediated cytotoxicity (ADCC).



Organisms, such as many parasites, that are too large for ingestion by phagocytic cells must be attacked externally.

Antibody-dependent cell-mediated cytotoxicity (ADCC).



(b) **Eosinophils adhering to the larval stage of a parasitic fluke.**

SEM

20 μm

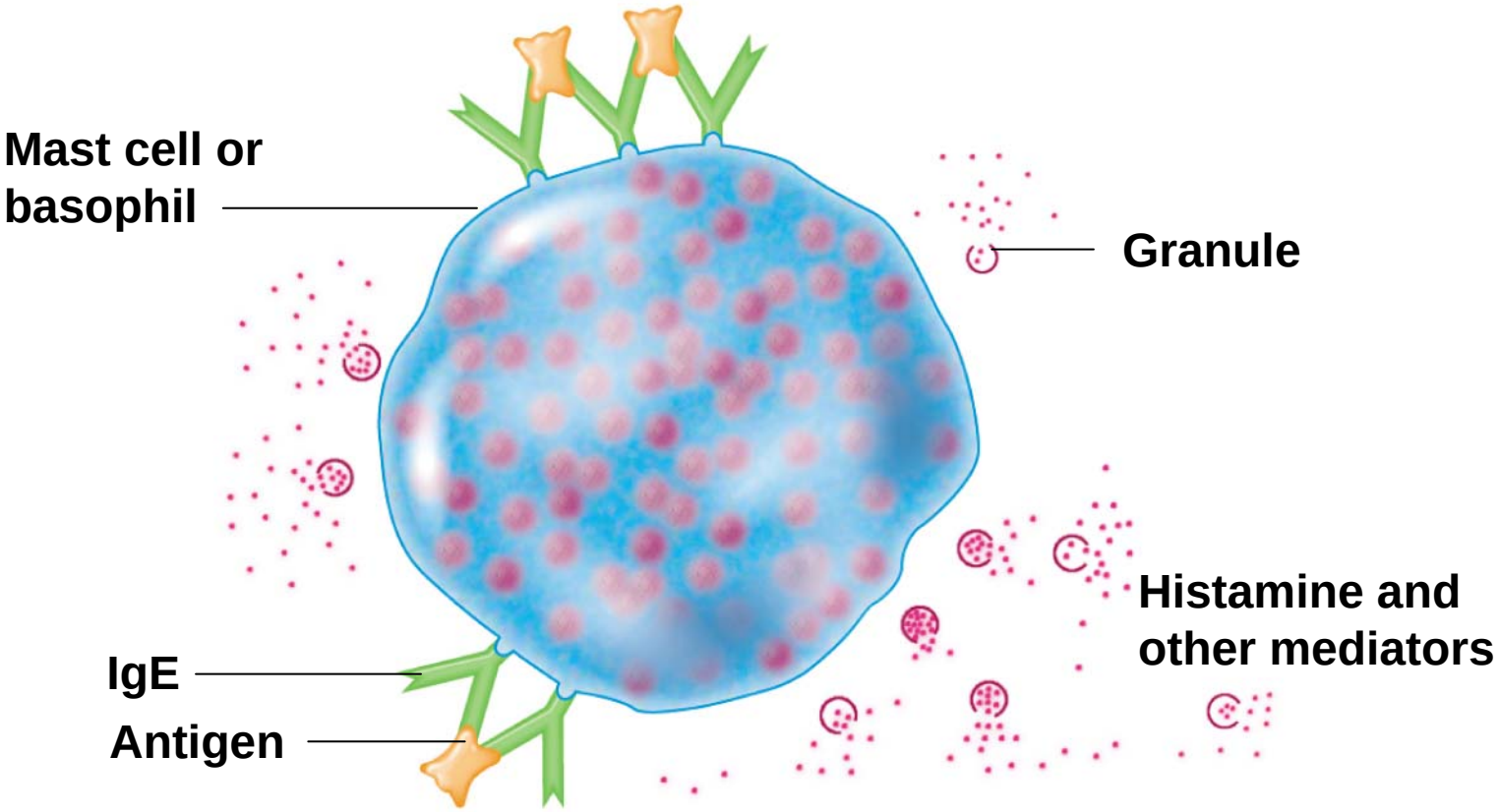
Granulocyte // Basophils

- <1% // large, abundant, violet granules (obscure a large S-shaped nucleus)
- Basophils in blood // called mast cells in tissue
- Emigrate from blood to tissue // Change into a **mast cells**
- acquire surface receptors = E class antibodies
- IgE produced by plasma cells upon “first exposure” // then attached to basophils as surface receptor

Granulocyte // Basophils to Mast Cells

- Upon second exposure foreign antigen cause mast cells to release histamine and heparin
- 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

The mechanism of anaphylaxis mediated by mast cell.



IgE antibodies, produced in response to an antigen, coat mast cells and basophils. When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell undergoes degranulation and releases histamine and other mediators.

Agranulocyte Function

Lymphocytes (T cells / B cells / NK cells)

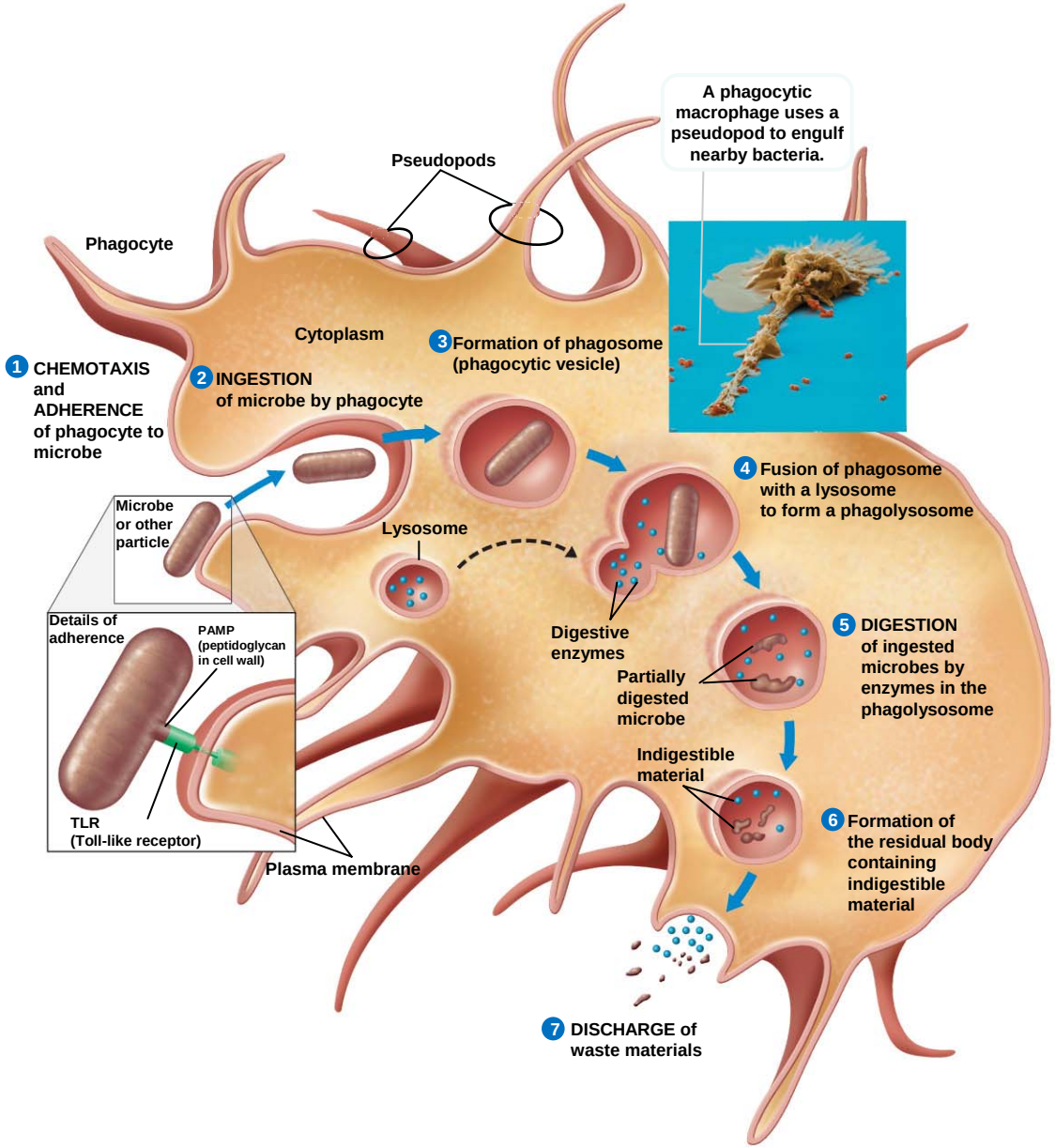
- 25-33% // variable amounts of bluish cytoplasm (scanty to abundant); ovoid/round, uniform dark violet nucleus
- increased numbers in diverse infections and immune responses
- **T lymphocytes** able to destroy cells (cancer, foreign, and virally infected cells) // cellular immunity
- “present” antigens 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 Function

Monocytes

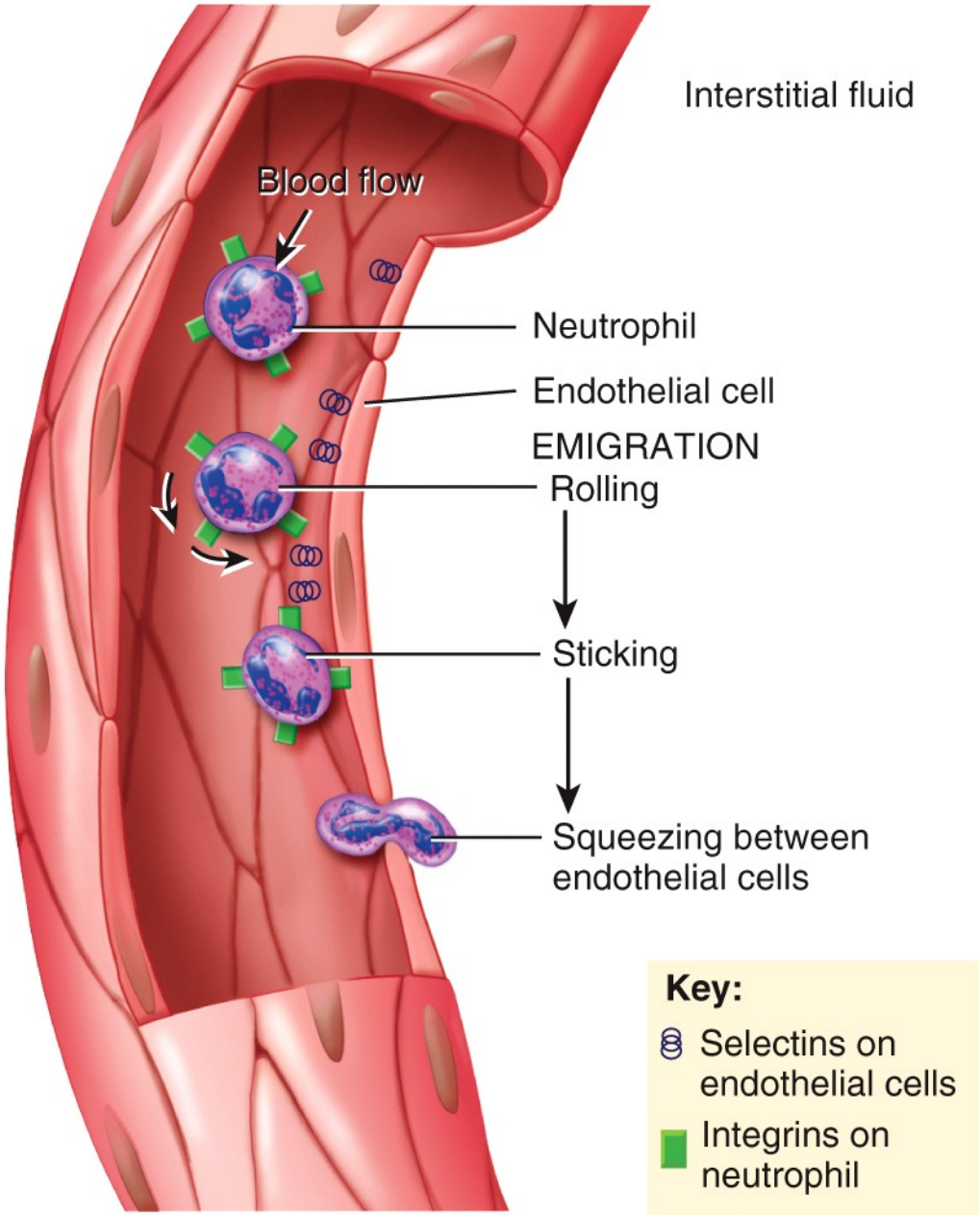
- 3-8% // largest WBC; ovoid, kidney or horseshoe shaped nucleus
- increased numbers in viral infections and inflammation
- produce and secrete **cytokines** = group of molecules which regulate immune response
- leave bloodstream and transform into **macrophages** (i.e. big eater)
- phagocytize pathogens and debris // the “garbage collector”
- “present” antigens to activate other immune cells // **antigen presenting cells** (APCs)

The Phases of Phagocytosis.



Diapedis: How Leukocytes Emigrate into Tissue Spaces

- Circulating WBCs do not stay in bloodstream
  - Area of inflammation causes endothelial cells outer face to become “sticky” – results in margination
  - Granulocytes (NEB) leave in 8 hours and <u>live 5 days longer</u>
  - Monocytes leave in 20 hours, transform into macrophages and <u>live for several years</u>
  - Lymphocytes provide long-term immunity // <u>live for decades</u> // continuously recycled from blood to tissue fluid to lymphatic system and back into the blood


Interstitial fluid
Blood flow
Neutrophil
Endothelial cell
EMIGRATION
Rolling
Sticking
Squeezing between endothelial cells
Key:
Selectins on endothelial cells
Integrins on neutrophil

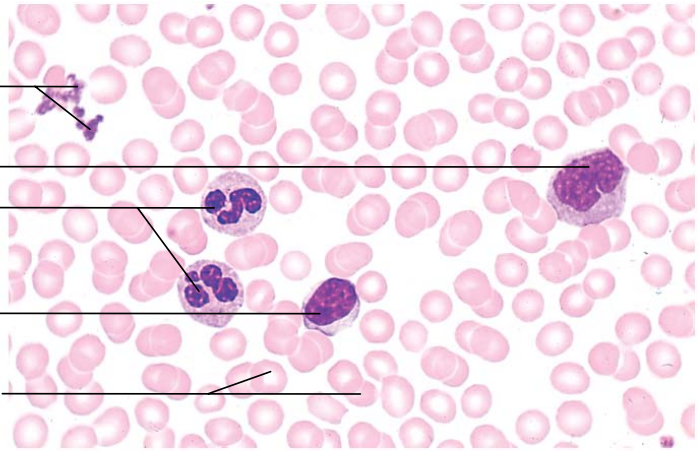
Leukocyte Disorders

- **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

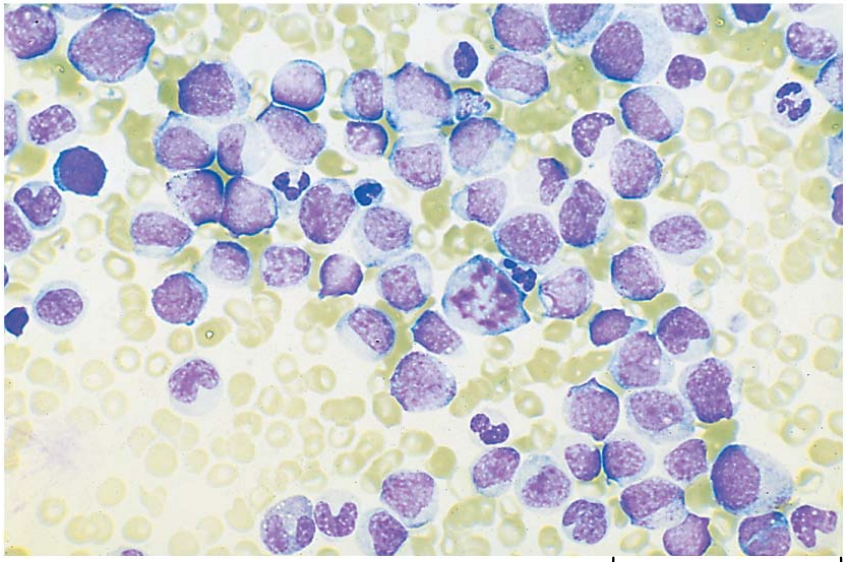
Leukocyte Disorders

- 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)



(b)

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