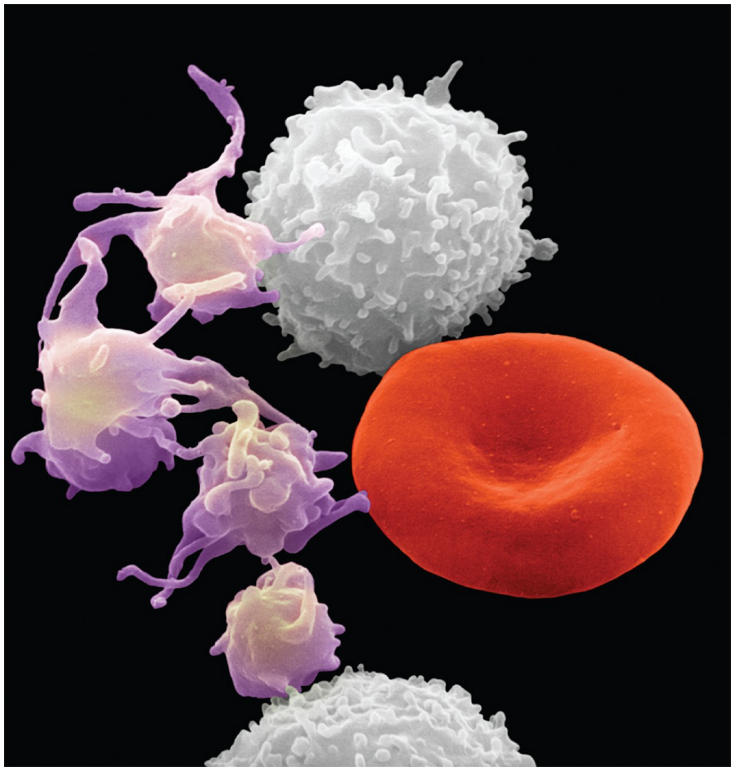
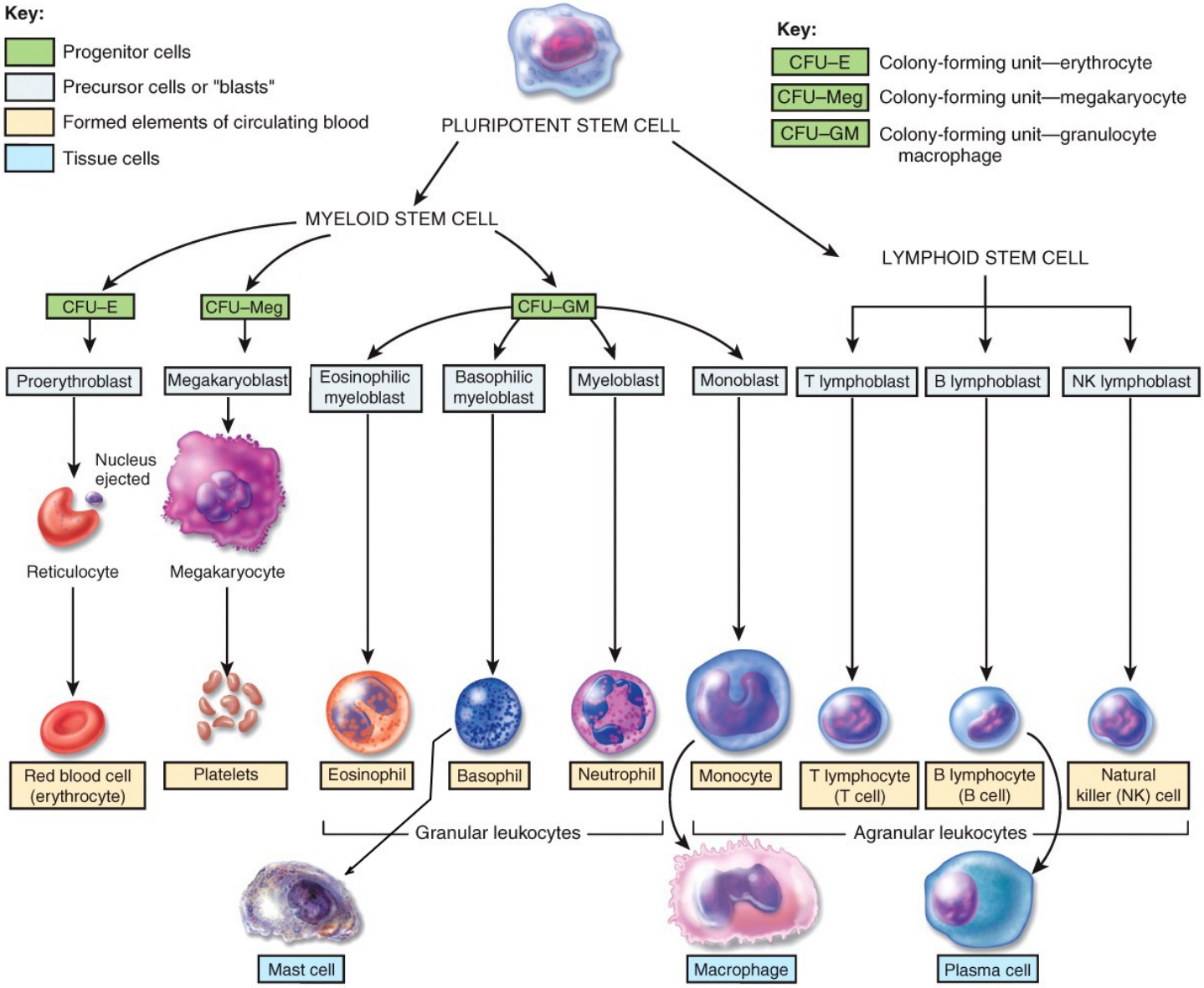
Chapter 18.3

The Structure and Function of the Formed Elements



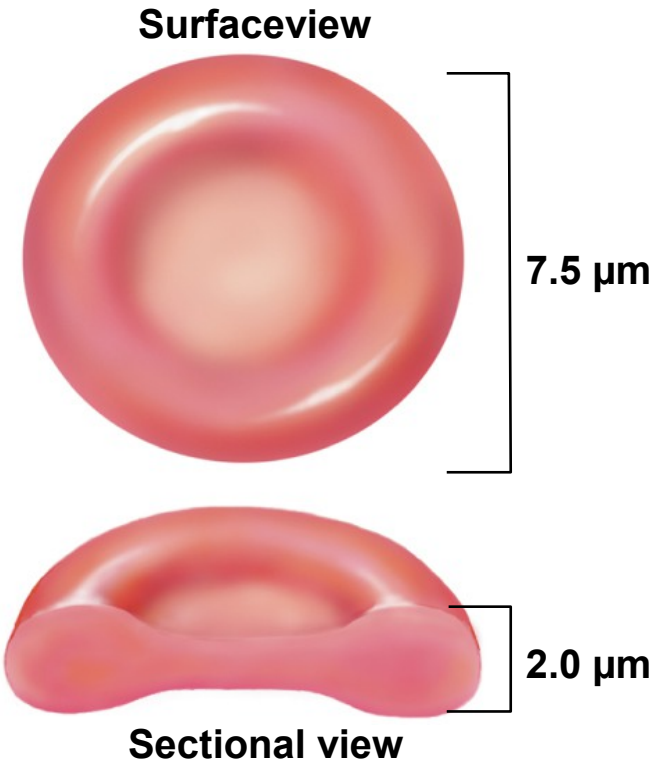
Nine Formed Elements Plus Mast Cells, Macrophage, and Plasma Cells
(*There are actually 12!*)



Make a flash card for each formed element!

Erythrocytes or RBC

- Disc-shaped cell with thick rim
  - Mature RBC is “not a cell” // it is a “corpuscle”
  - 7.5 μM diameter and 2.0 μm thick at rim
  - loses all organelles during development before it is released into blood as mature RBC
    - lack mitochondria // must use anaerobic fermentation to produce ATP
    - no nucleus and no DNA // therefore, no protein synthesis or mitosis



Blood type determined by special type of transmembane glycoprotein called an "antigen"

Glycoproteins located on outer face of plasma membrane

Two type of antigens // A antigen & B antigen

Four major blood types: A, B, AB, O // the ABO System

There are many other RBC systems used to type blood // ABO is the most problematic in medicine

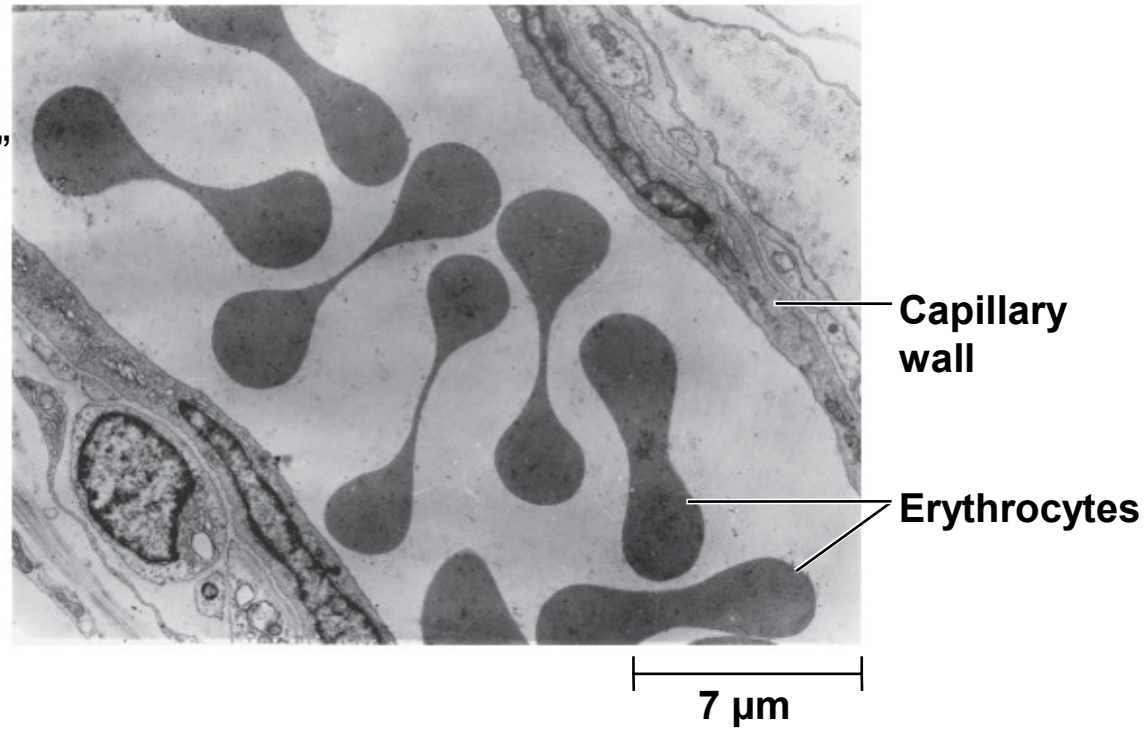
Erythrocytes or RBC

- 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 (test benchmark 1%)

Erythrocytes

RBC go through capillaries “single file”

Capillary diameter benchmark = 7.5 micrometers



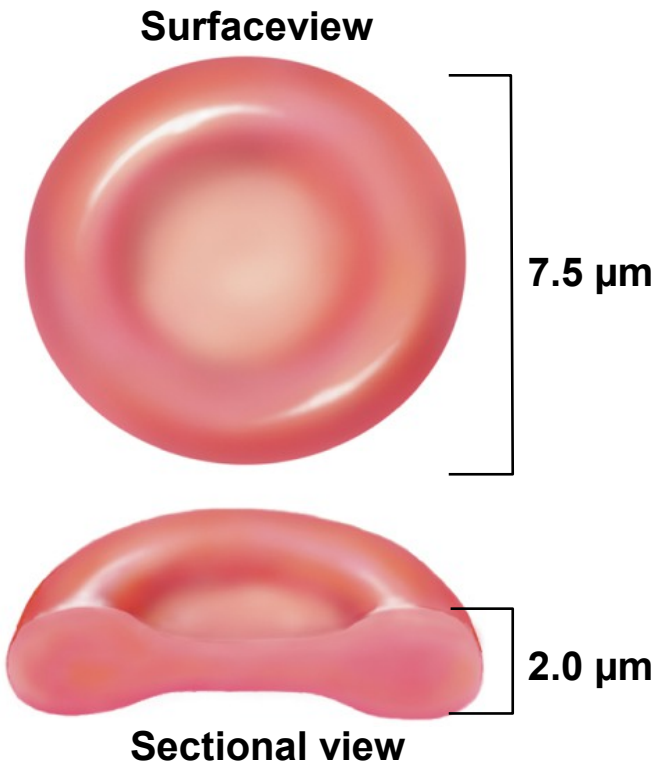
- **Principal function** /// carry oxygen from lungs to cellular tissues of body /// Note most of the carbon dioxide transported as bicarbonate in plasma from tissue to lungs

- Insufficient RBC function may result in necrosis within 4 – 5 minutes due to lack of oxygen and too much CO_2

- What is the difference between ischemia, infarction, necrosis, and apoptosis?

Erythrocytes or RBC

- Important cytoskeletal proteins
  - spectrin
  - actin
  - give RBC membrane durability and resilience
  - provide ability for RBC to stretch, bend, and not rupture as they squeeze through small capillaries
  - as RBC age spectrin and actin break down and RBC can not replace these molecules. Now the membrane is “brittle”.
  - Why can't the RBC replace these molecules?



Erythrocytes Death and Disposal

- RBCs lyse in the narrow capillaries (2 micrometer) found in the spleen /// called the graveyard for RBC /// occurs with older than 120 days RBC

- What two factors explain why RBC rupture? (Two reasons: size of spleen capillaries and loss of key proteins)

- <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 to be recycled**

Erythrocytes Death and Disposal

Some nitrogen molecules in high concentrations in the blood Are toxic. // the heme molecule of hemoglobin is a problem as RBC are recycled

- heme pigment converted to biliverdin (green)
- biliverdin converted to bilirubin (yellow)
- released into blood plasma

> kidneys excrete - as yellow urine

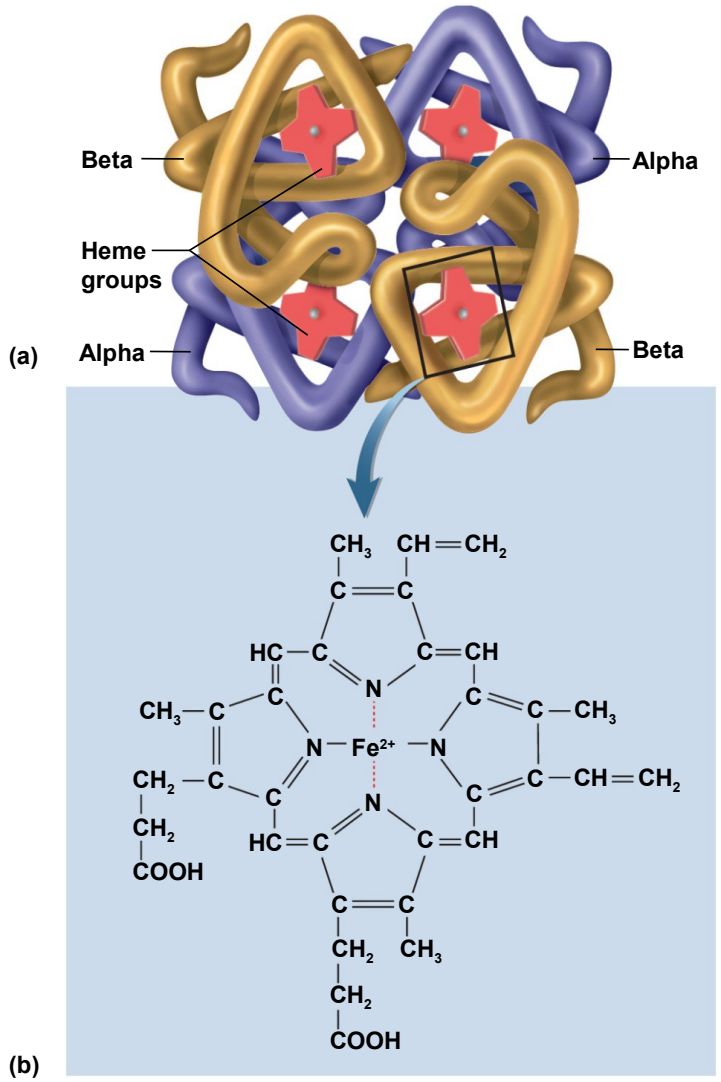
> liver removes bilirubin and secretes into bile

- concentrated in gall bladder
- released into small intestine
- bacteria in large intestine create urobilinogen // has a brown pigment (This is why the feces is brown)

Hemoglobin (Hb) Structure

- Each Hb molecule consists of:
  - Four globular proteins per hemoglobin molecule
  - At core of each globular protein = heme groups

- About the heme groups
  - The heme is a nitrogen ring structure which holds an iron atom // nitrogen potential problem
  - Iron atom binds O_2 // the ferrous ion (Fe^{2+}) is at heme's center



Hemoglobin (Hb) Structure

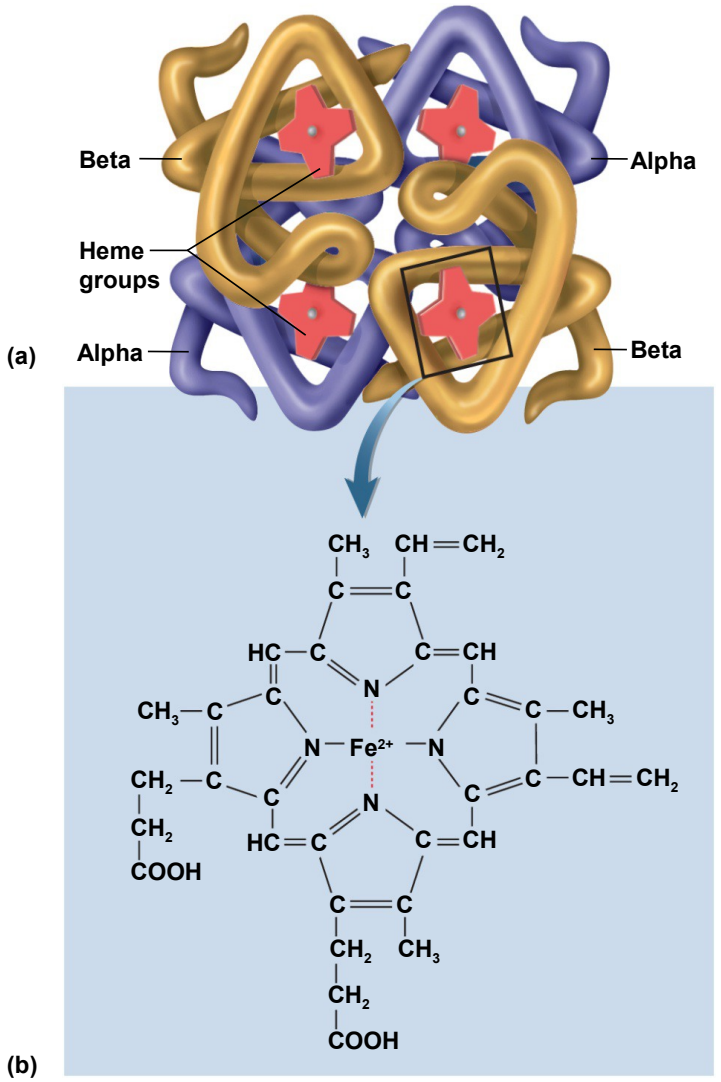
About the globin molecules

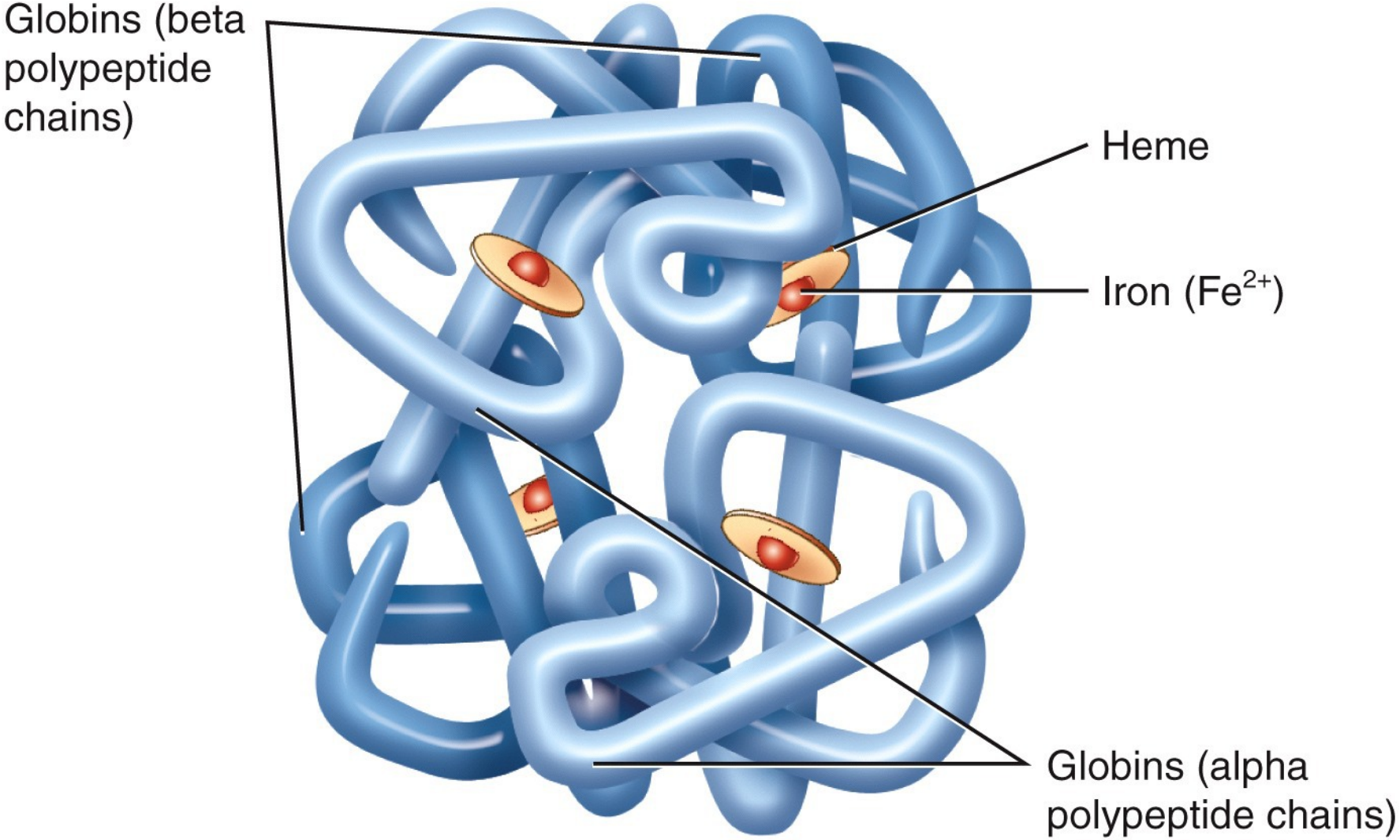
two alpha and two beta chains

5% CO_2 in blood is bound to globin moiety

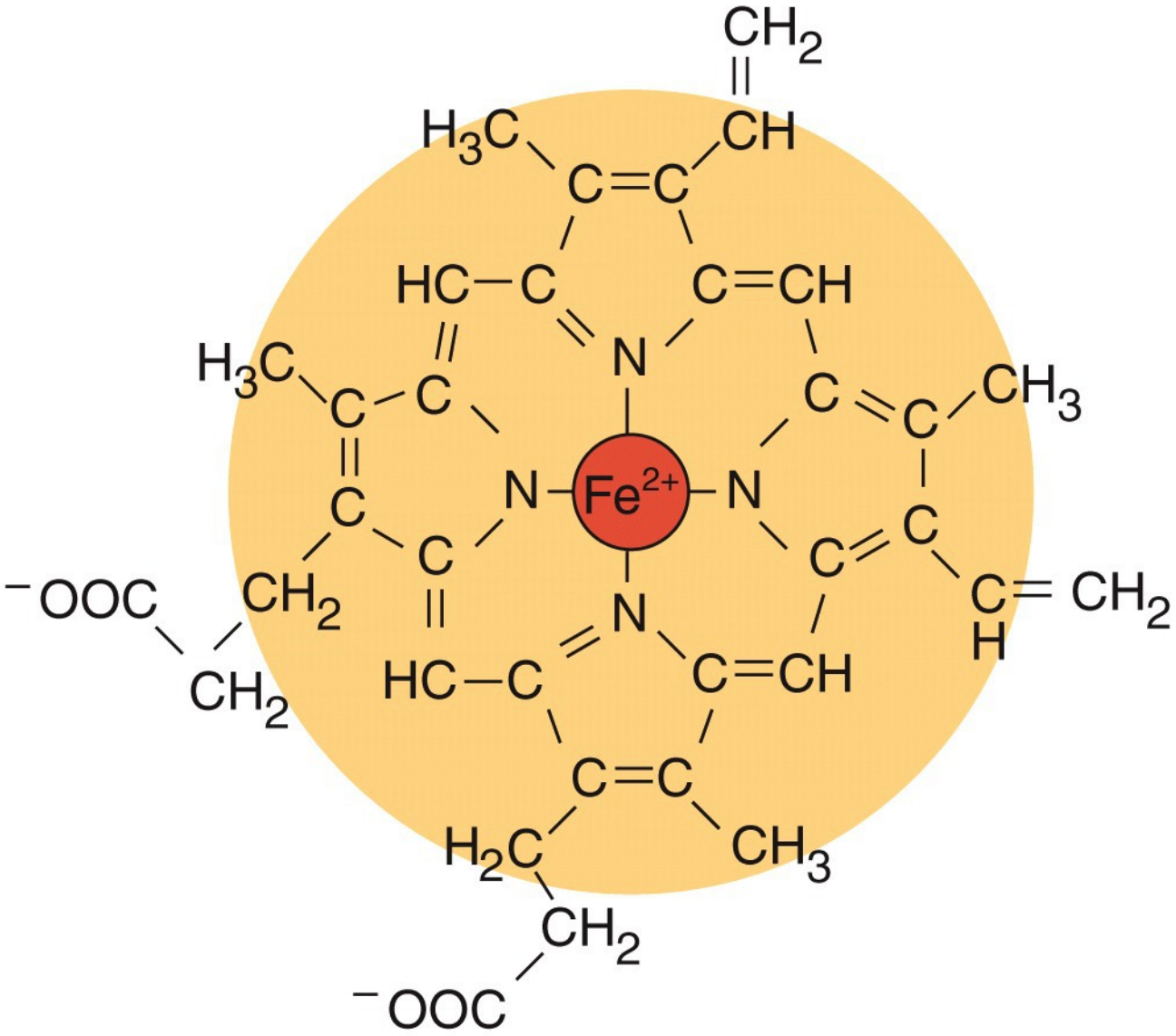
Adult vs. fetal hemoglobin have different type of hemoglobin

Which form has the greater affinity for oxygen? Why?





(b) Hemoglobin molecule



(c) Iron-containing heme

How many oxygen molecules carried by hemoglobin molecule?

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
- Hematocrit value is lower in women (Why?)
  - male androgens stimulate more RBC production
  - women have periodic menstrual losses
  - hematocrit is inversely proportional to percentage of body fat

Nutritional Needs for Erythropoiesis

- Iron – most important nutritional requirement
  - Iron lost daily through urine, feces, and bleeding // men 0.9 mg/day VS 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 Fe^{2+}

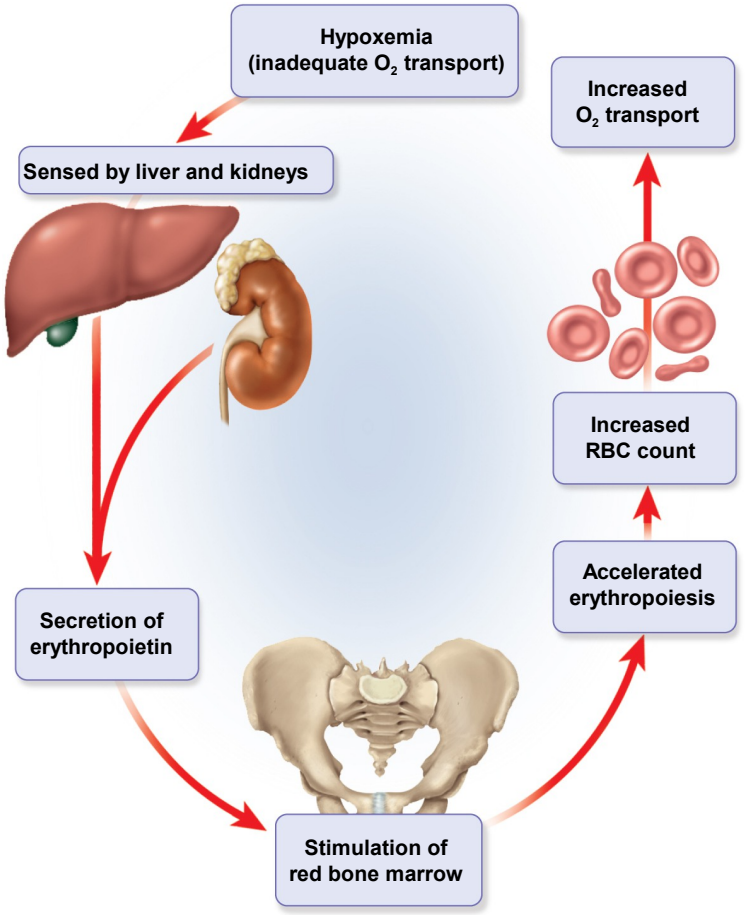
Nutritional Needs for Erythropoiesis

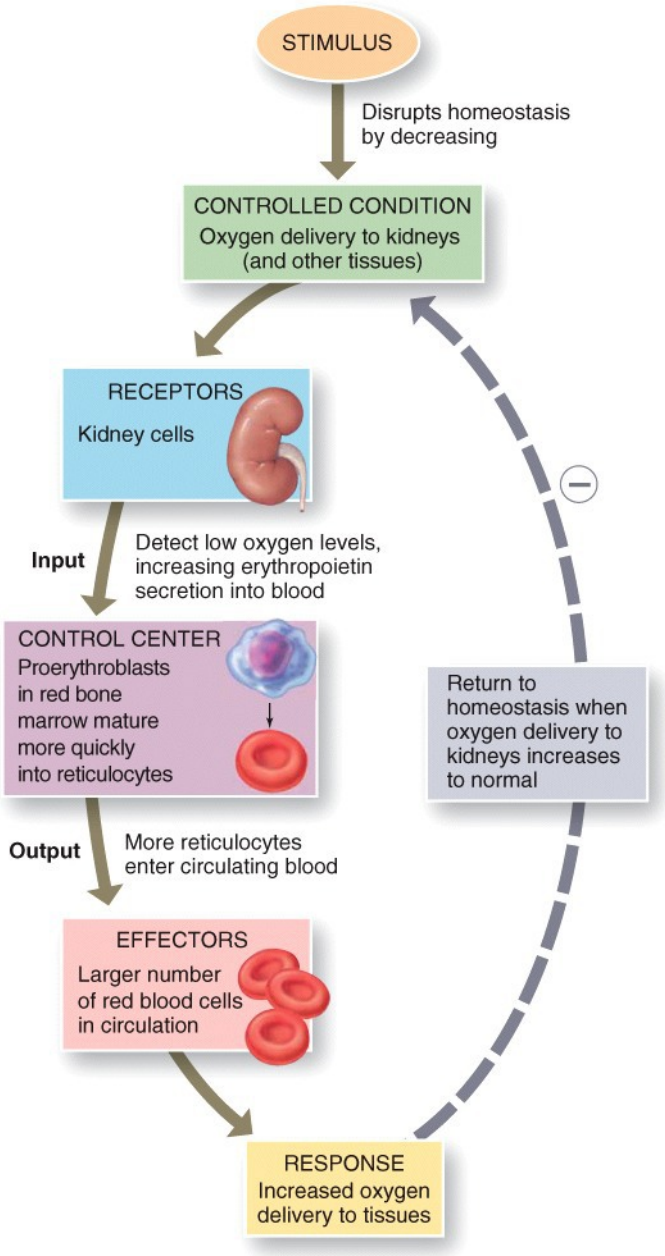
- Vitamin B_{12} and folic acid
  - These essential nutrients are required for rapid cell division and DNA synthesis (What does essential mean?)
  - Necessary to produce formed elements // promote extreme mitosis
  - Parietal cells of intestinal crypts must produce intrinsic factor to absorb Vit B12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

Regulating Erythrocyte Homeostasis

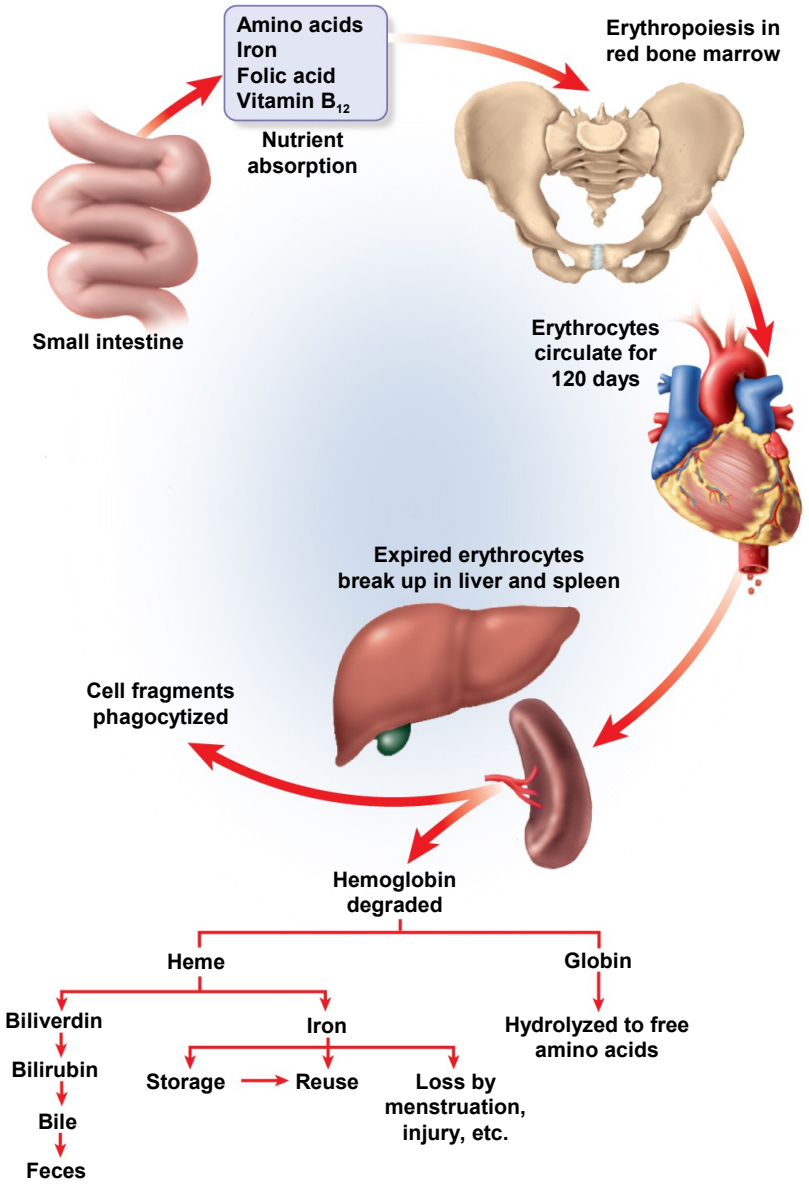
- Negative feedback regulation
  - drop in RBC count causes hypoxemia // stimulus for kidneys
  - kidney produces erythropoietin // hormone // stimulates bone marrow
  - RBC count increases in 3 - 5 days

- Stimulus to increase erythropoiesis
  - low levels O_2 (hypoxemia)
  - high altitude
  - increase in exercise
  - loss of lung tissue as in emphysema

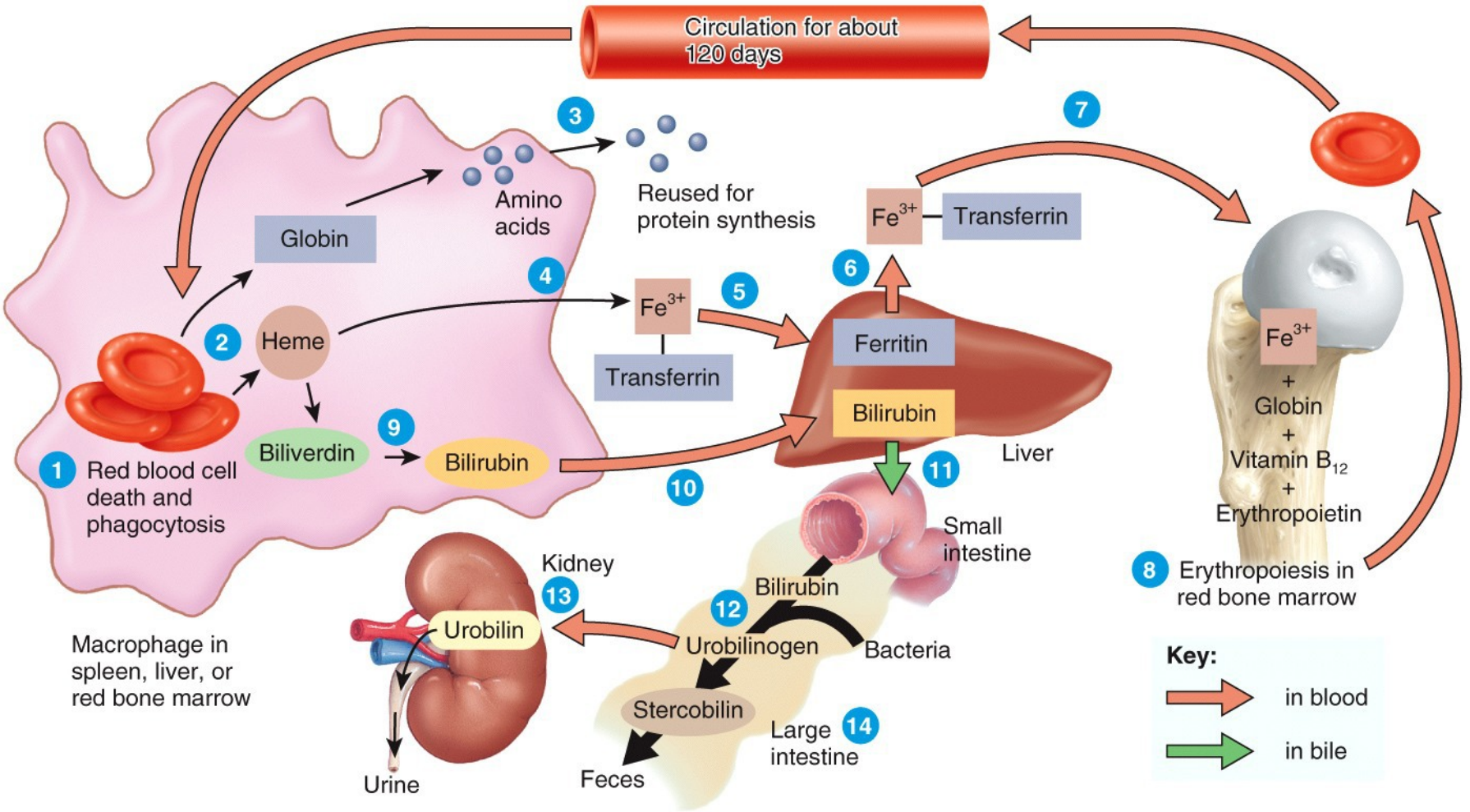



STIMULUS
Disrupts homeostasis by decreasing
CONTROLLED CONDITION
Oxygen delivery to kidneys (and other tissues)
RECEPTORS
Kidney cells
Input
Detect low oxygen levels, increasing erythropoietin secretion into blood
CONTROL CENTER
Proerythroblasts in red bone marrow mature more quickly into reticulocytes
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 Component Recycle & Disposal



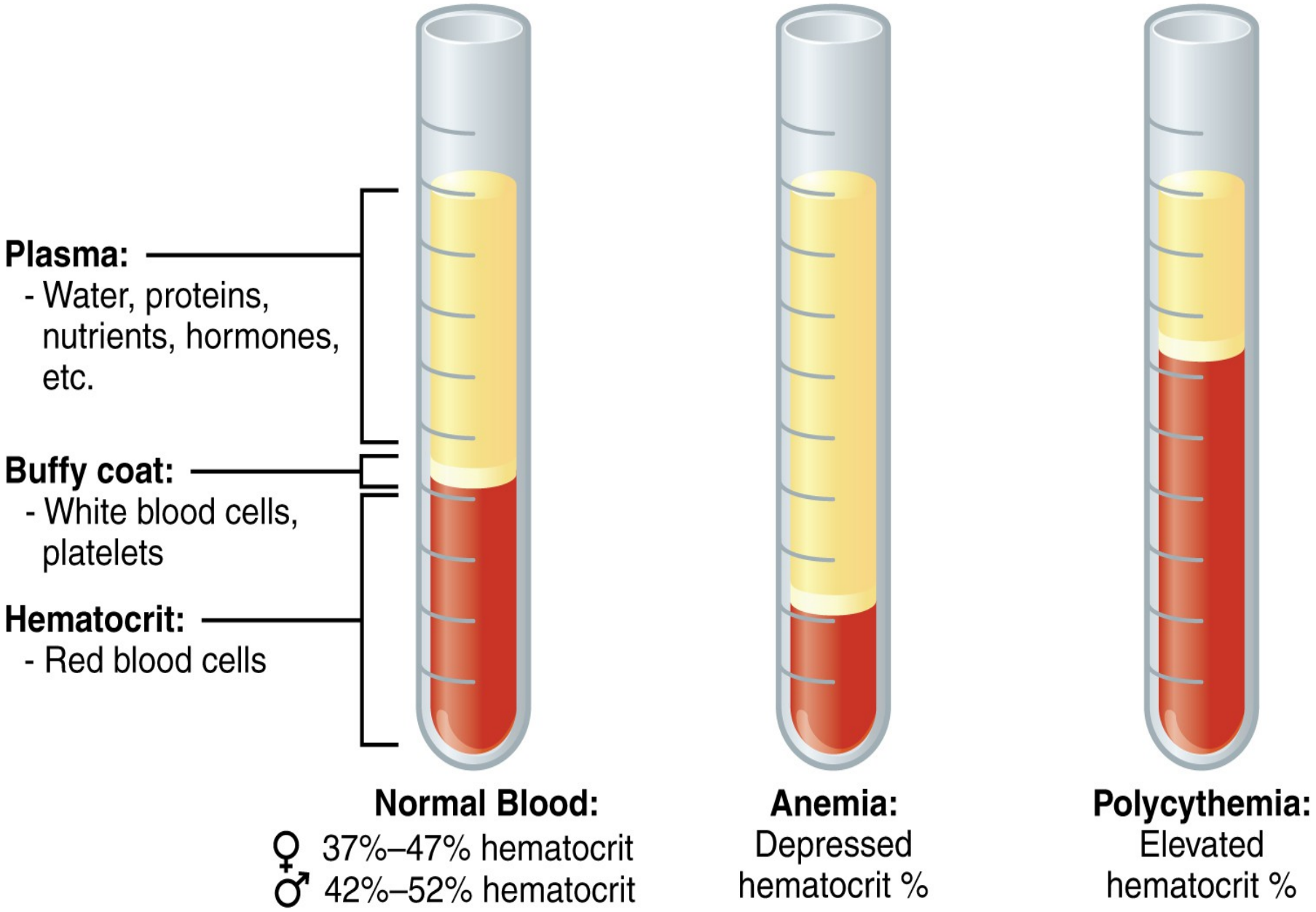
Erythrocytes Component Recycle & Disposal



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%
    - erythropoietin low concentration in blood
  - secondary polycythemia // from dehydration, emphysema, high altitude, or physical conditioning
    - RBC count up to 8 million/μL
    - erythropoietin high concentration in blood

What happens when you have too many RBC?


Plasma:
- Water, proteins, nutrients, hormones, etc.
Buffy coat:
- White blood cells, platelets
Hematocrit:
- Red blood cells
Normal Blood:
♀ 37%–47% hematocrit
♂ 42%–52% hematocrit
Anemia:
Depressed hematocrit %
Polycythemia:
Elevated hematocrit %

Dangers Associated with Polycythemia

- increased blood volume
- increase blood pressure
- increased viscosity
- can lead to embolism
- stroke
- heart failure

Anemia

- Anemia is a condition when you lack enough healthy red blood cells to carry adequate oxygen to your body's tissues. Low hemoglobin may be a factor causing anemia. This condition will make you feel tired and weak.

- Factors leading to anemia:

  - Inadequate erythropoiesis (or failure to produce functional hemoglobin – e.g. sickle cell anemia)

  - Hemorrhagic anemia /// major blood vessel ruptures

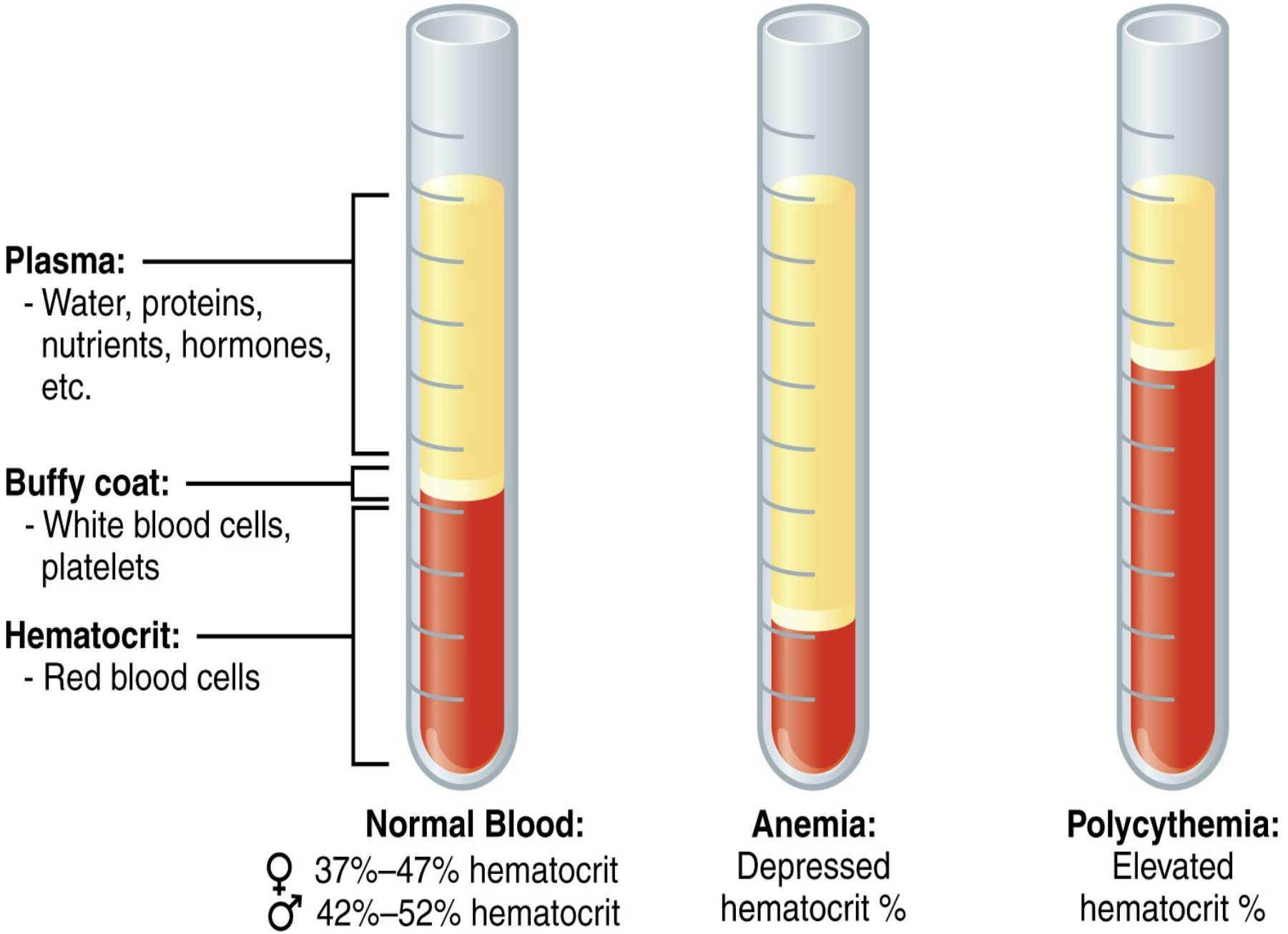
  - Hemolytic anemia /// e.g. malaria

Anemia

- Consequences:
  - Hypoxia // oxygen deprivation in tissue // 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, low viscosity, and leads to low blood pressure
    - cause cardiac failure

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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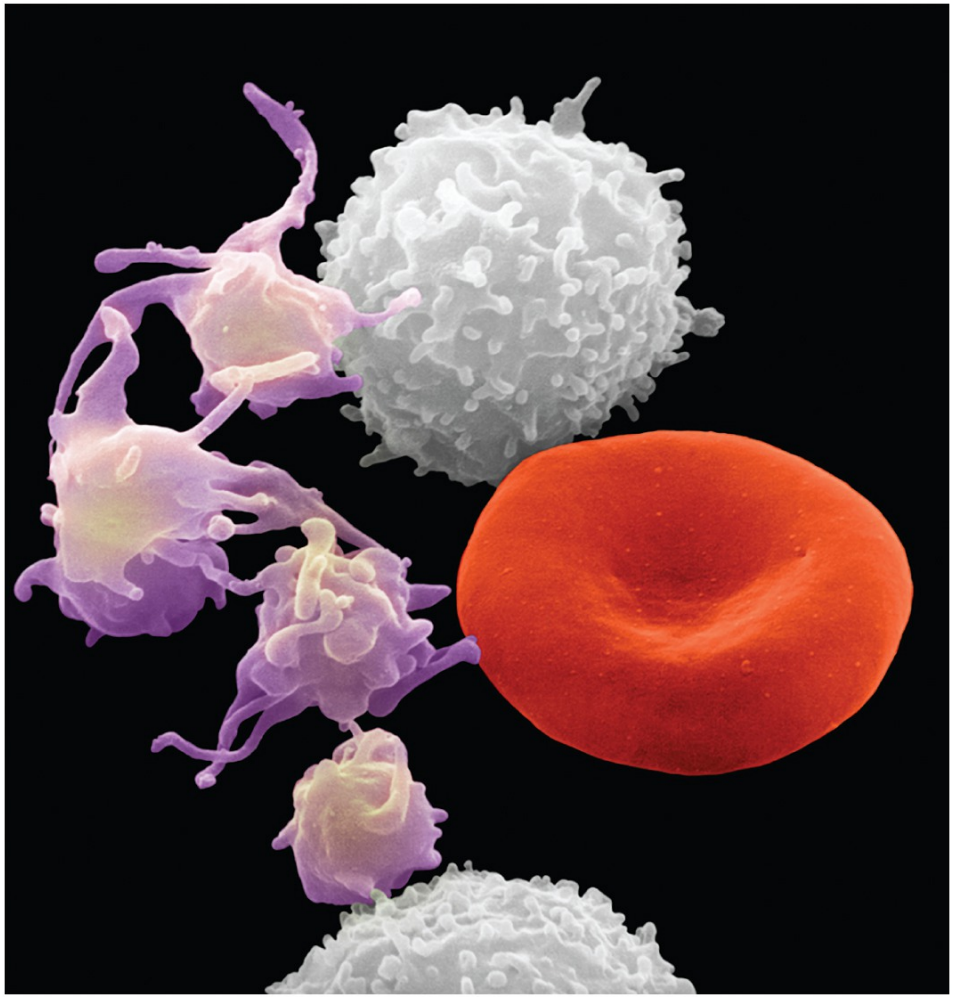
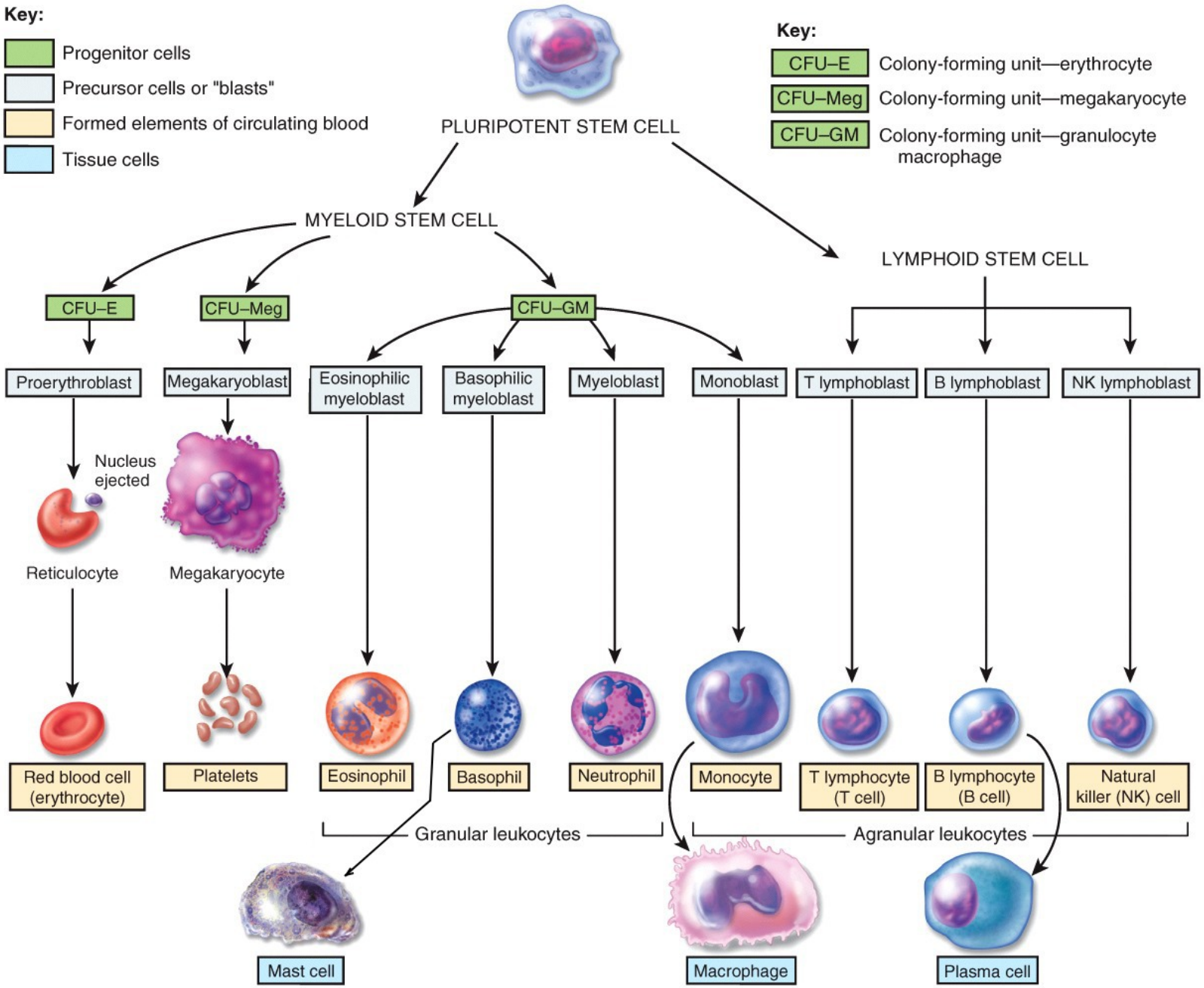
Leukocytes (WBC)




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)

- WBC least abundant of all the formed elements in blood
- 5,000 to 10,000 WBCs/μL (mostly neutrophils in blood)
- Primary function = protect against infectious microorganisms and other pathogens
- WBCs have conspicuous nucleus
- WBC spend only a few hours in the blood stream before migrating out of blood and into the reticuloendothelial system (i.e. connective tissue) and interstitial spaces
- Retain their organelles for protein synthesis // unlike RBC WBC are alive!

Leukocytes (WBCs)

- All WBC have granules in their cytoplasm but some WBC'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 LM

  - the granulocytes have **specific granules** that stain // contain enzymes and other chemicals employed in defense against pathogens // the NEB

Types of Leukocytes

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

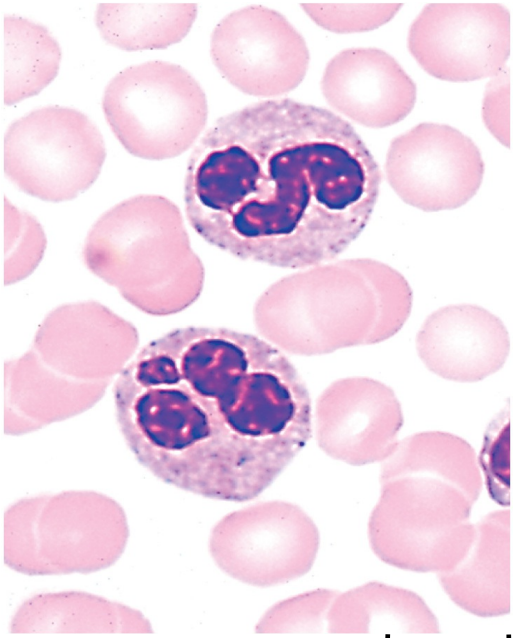
  ← "NEB"

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

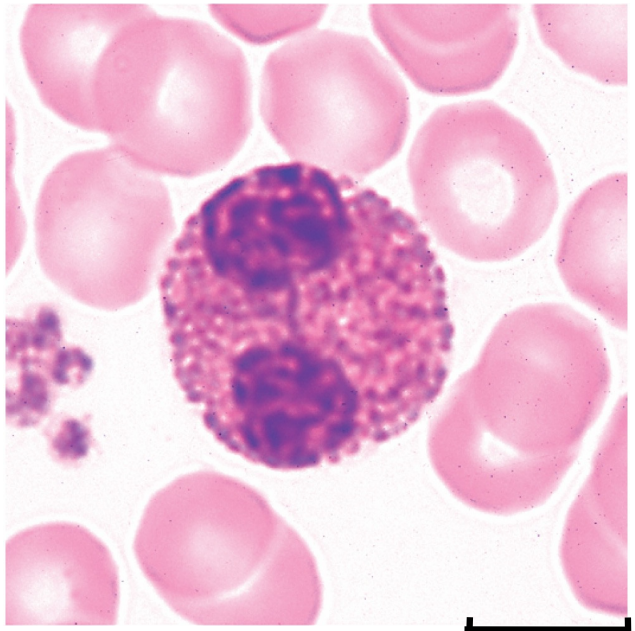
  ← "LM"

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

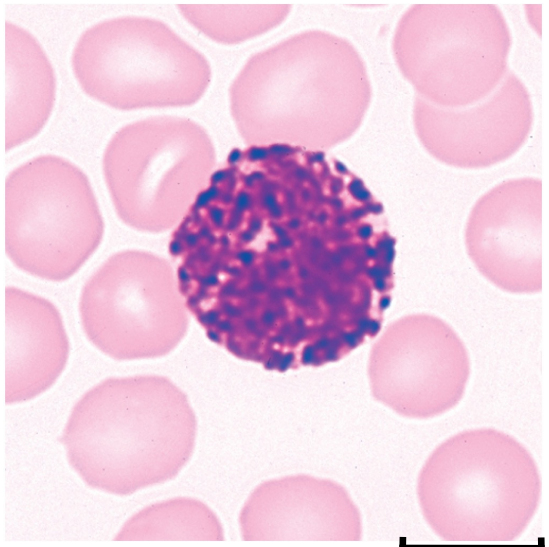
Granulocytes



Neutrophils

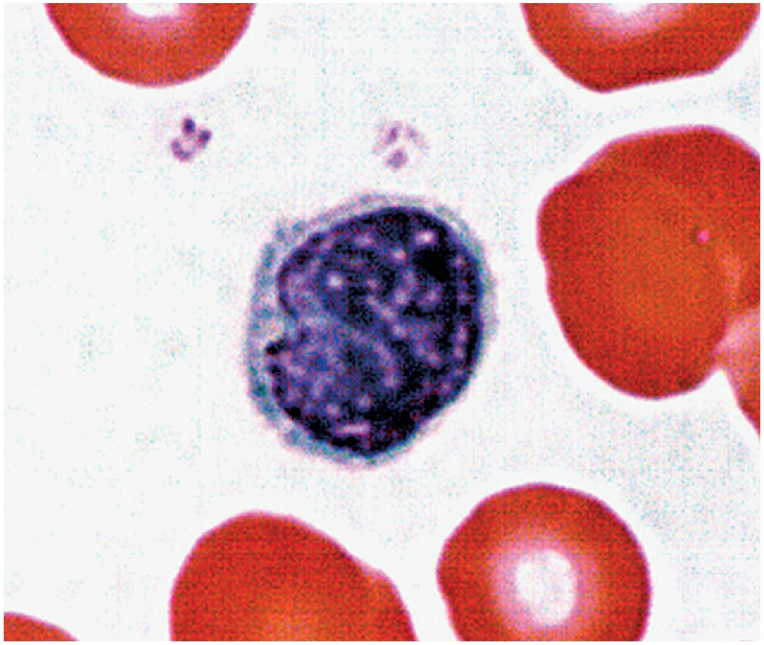


Eosinophil



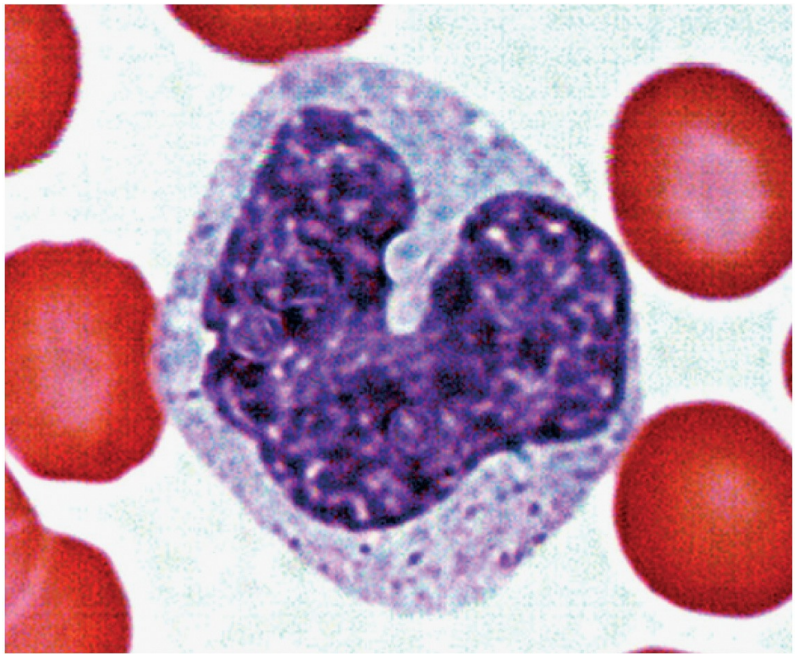
Basophil

Agranulocytes



Lymphocyte

10 µm



Monocyte

10 µm

Make Flash Cards for These Cells

Red Blood Corpuscles
Neutrophils
Eosinophils
Basophils
Mast Cells
Monocytes
Marcorphage
T Cell
B Cells
Plasma Cells
Natural Killer Cells

Function of theses corpuscles is essential information for C18 Blood and C21 Immunity (Assume 20/100 points on Unit 3 Exam)

Granulocyte Functions

- **Neutrophils**
  - 60-70% of WBC circulating in blood are neutrophils
  - also known as polymorphonuclear leukocytes // barely visible granules in cytoplasm // 3 to 5 lobed nucleus
  - increased their numbers after **bacterial infections** / neutrophilia – increase 5x /// (5,000 to 25,000) // neutrophilia
  - phagocytosis of bacteria in blood / neutrophils phagosomes kill bacteria
  - Migrate across capillaries into interstitial space / first WBC to arrive after inflammation initiated
  - release antimicrobial chemicals // called the **"respiratory burst"** – like a nuclear bomb in the immediate area! // neutrophils release deadly chemicals - hypoclorite, hydrogen peroxide, free radiacals
    - If you can not eliminate the bacteria then the bacteria will likely eliminate you!

Granulocyte Functions

- **Neutrophils**

  During neutrophil activation, the primary granules release myeloperoxidase (MPO).

  MPO uses hydrogen peroxide (HOOH) and chloride to produce hypochlorous acid (HOCl).

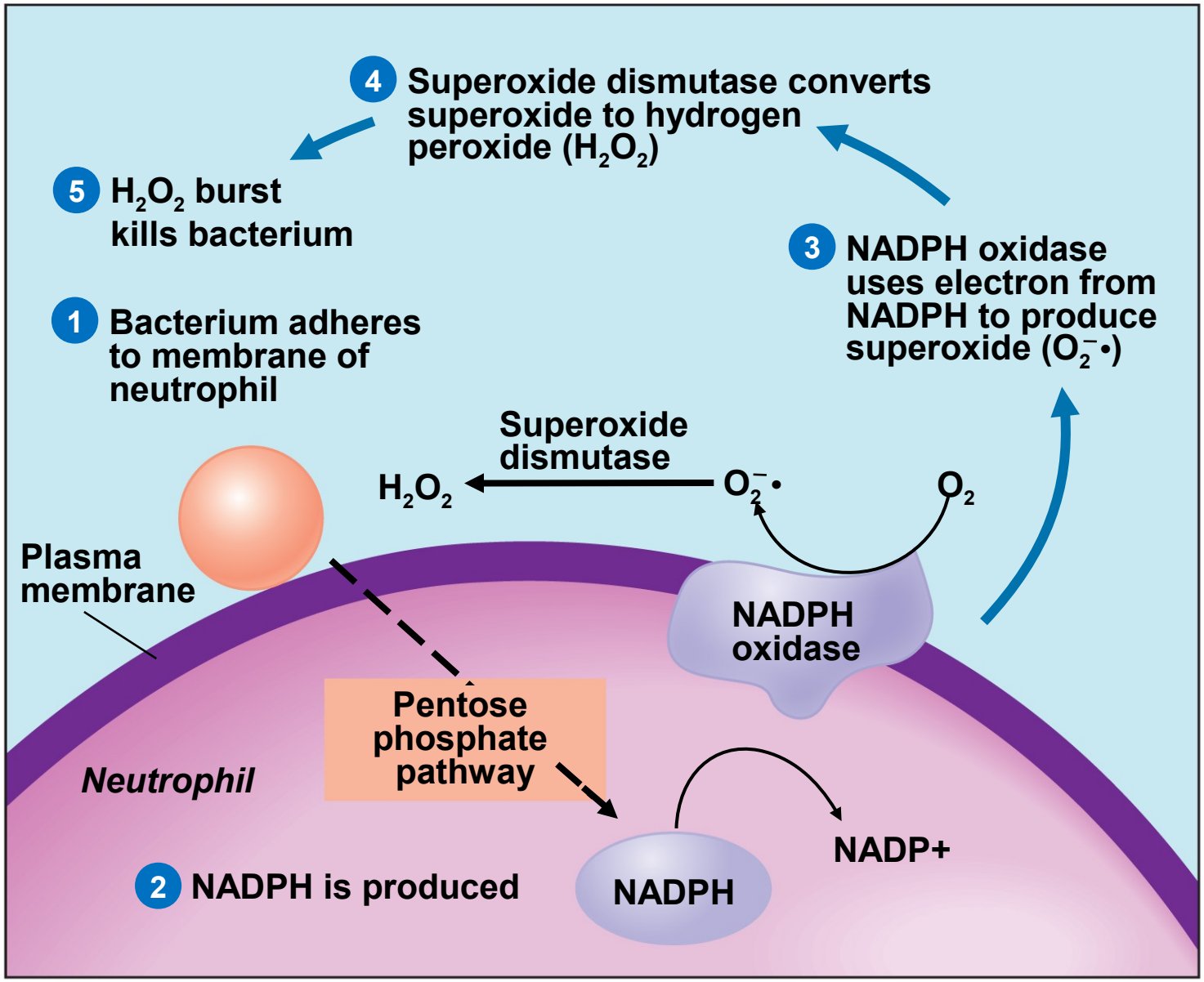
  HOCl has a significant role as an antimicrobial agent and has deleterious effects on host cells.

  The molecule has a slight green color, which you may notice if you force the puss out of the inflammatory wound on the skin.

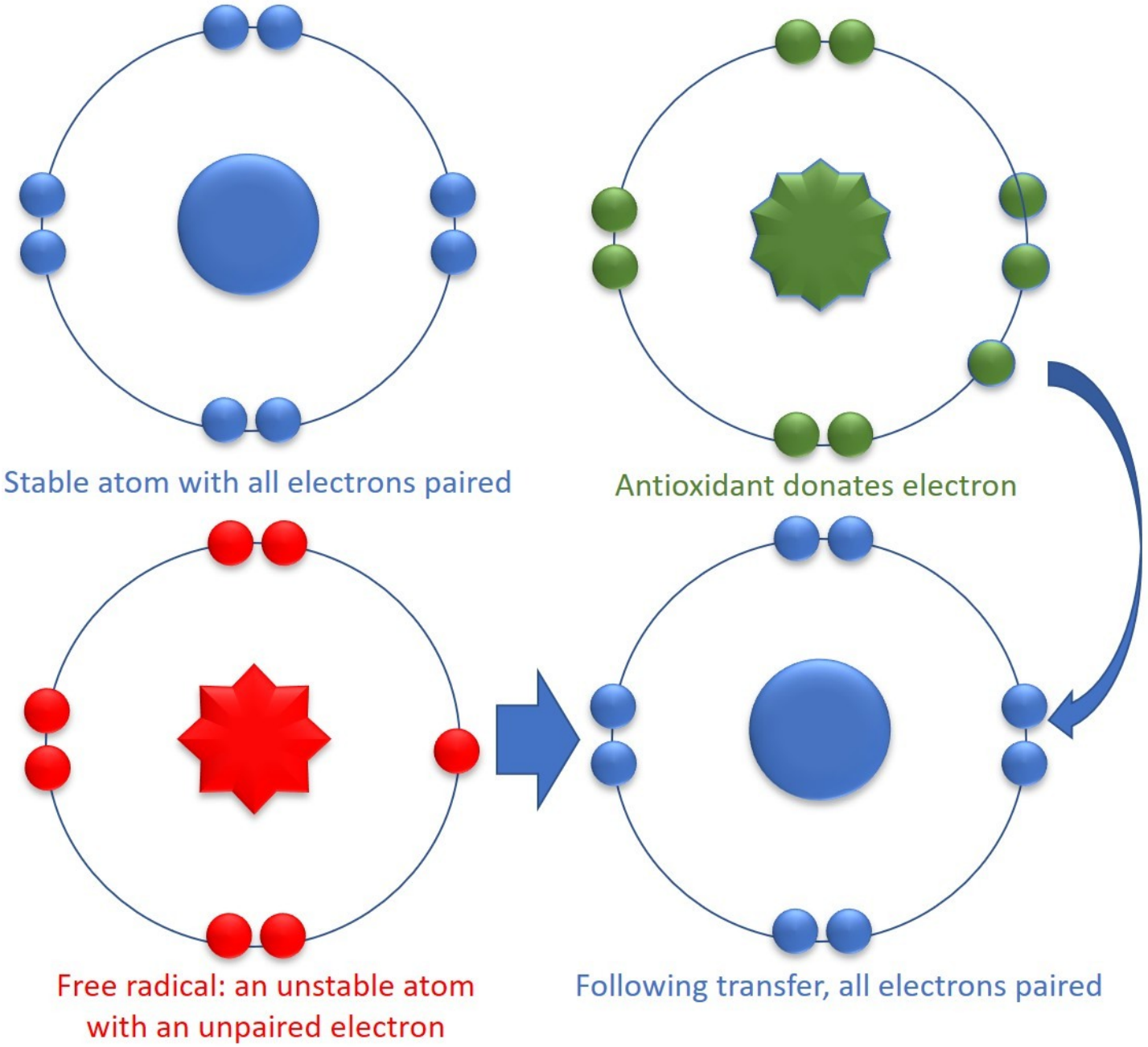
  This is part of the “respiratory burst” mechanism to eliminate the bacterial infection.

  Eosinophils also have this ability and use it to kill parasites.

Oxidative Burst (Respiratory Burst)

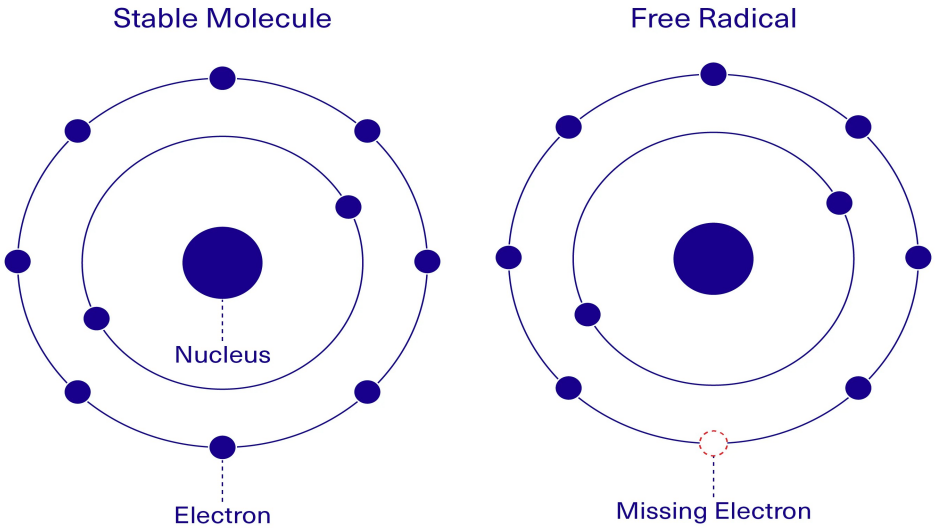


Free radicals, reactive oxygen species and antioxidants



Oxygen molecule (O_2)

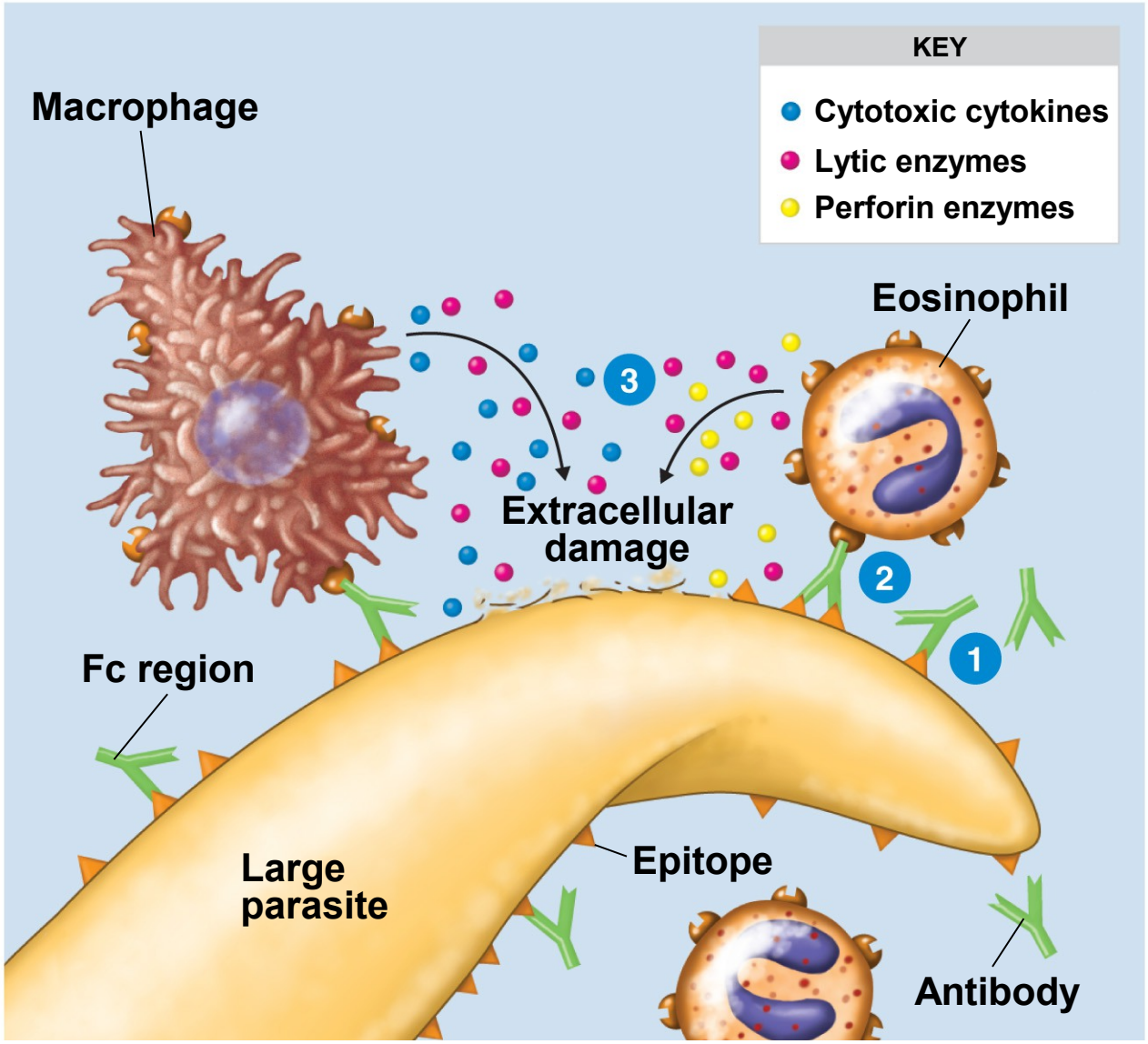
Free-radical: Superoxide anion ($O_2^{\bullet -}$)



Eosinophils

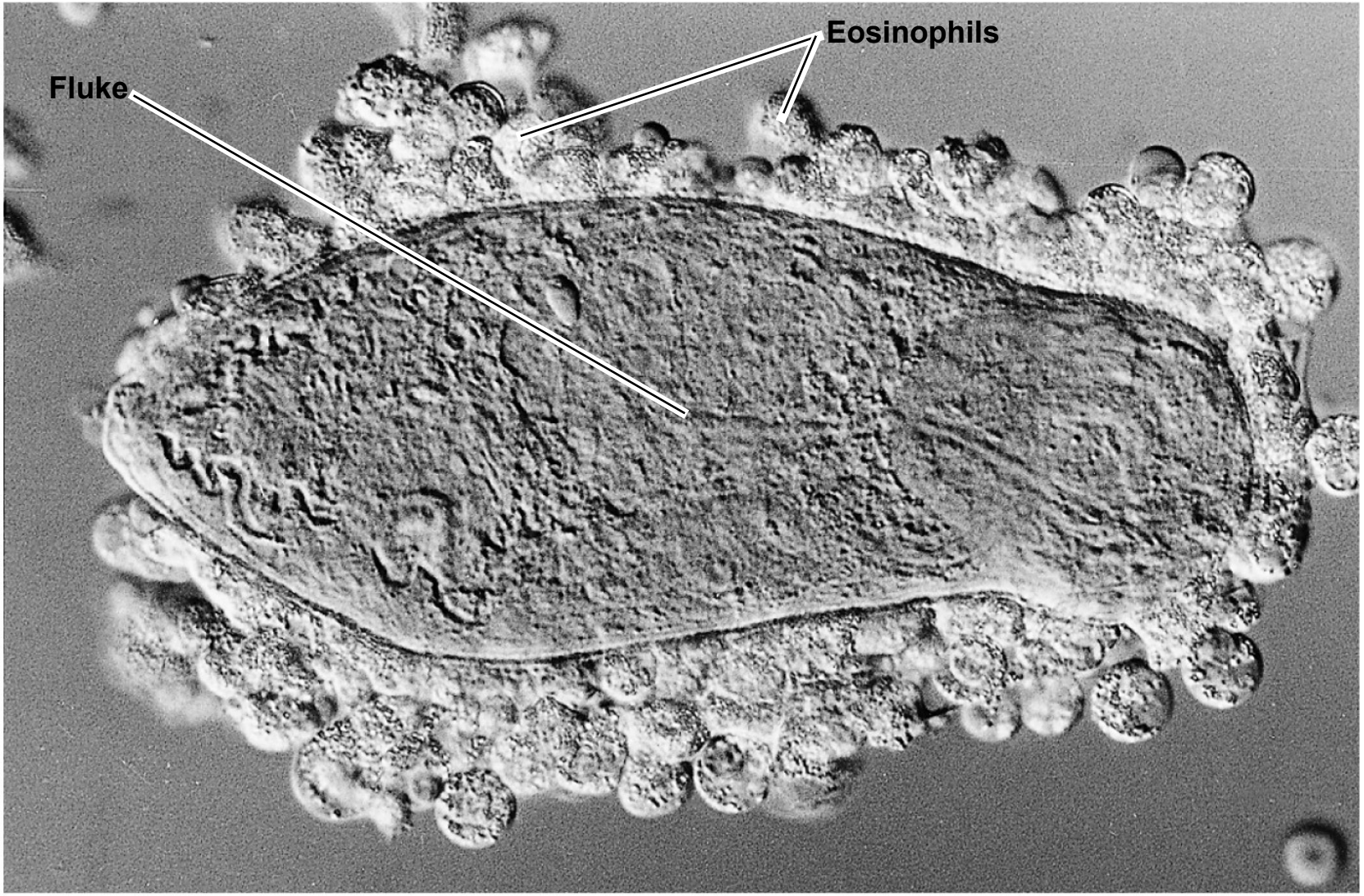
- 2-4% // large rosy-orange granules, bi-lobe nucleus
- stand guard against **parasites**, **allergens** (allergy causing agents), and other pathogens
- kill tapeworms and roundworms by producing super-oxide, hydrogen peroxide, and toxic proteins
- promote action of **basophils** and **mast cells**
- phagocytosis of **antigen-antibody complexes**
- **produces a respiratory burst!**
- limit action of **histamine** and other inflammatory chemicals /// see an increase in numbers with collagen diseases, allergies, diseases of spleen and CNS
- Highly concentrated in the mucous membranes (Why?)

Eosinophil antibody-dependent cell-mediated cytotoxicity



Organisms, such as many parasites, 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

Basophils

Less than 1% of WBC // large, abundant granules, violet granules (obscure a large S-shaped nucleus)

Basophils circulate in blood // called mast cells after they migrate into tissues

Emigrate from blood to tissue // Morph into a **mast cells**

acquire surface receptors = E class antibodies (IgE) made by plasma cells after first exposure to foreign antigen

IgE directly render bacterial harmless and tag them for Destruction /// IgE also attached to basophils as surface receptor

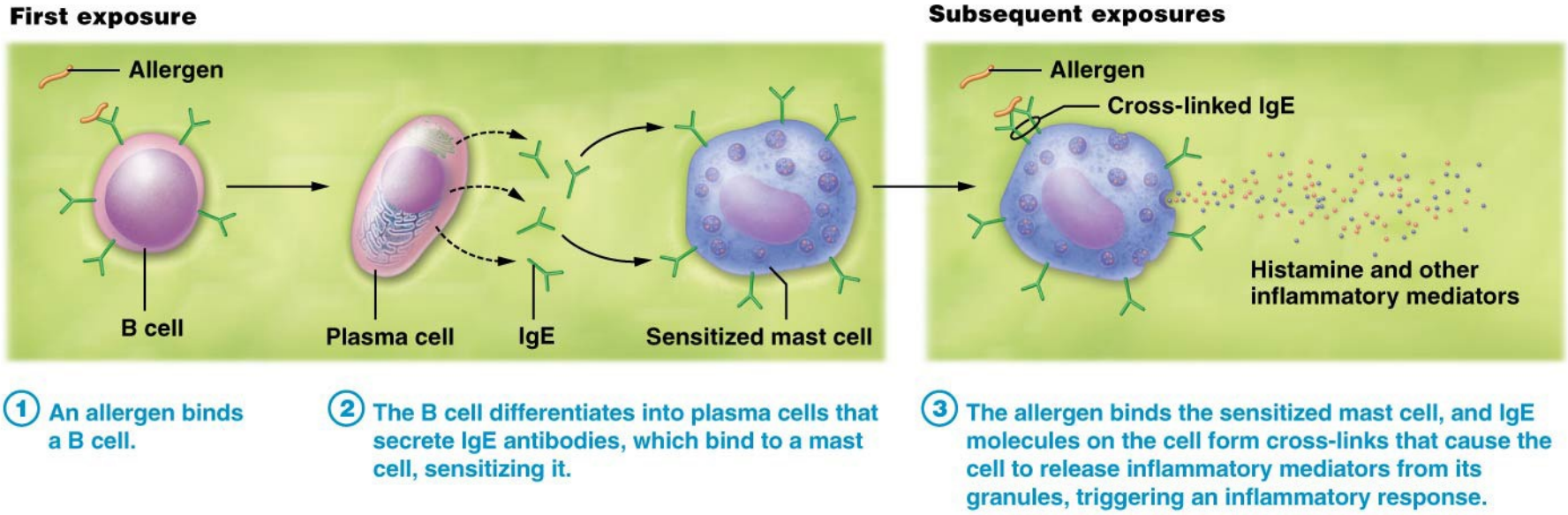
If same bacteria re-enters body, bacteria antigen hits IgE receptor and basophils initiates an immune response..

Basophils to Mast Cells

- First exposure to specific antigen places Ig-E into mast cell's plasma membrane
- after second exposure to similar antigen, --- mast cells release histamine and heparin
- **histamine** (vasodilator) // speeds flow of blood to an injured area
- secrete **heparin** (anticoagulant) // promotes the mobility of other WBCs in the area // lack of clotting allows other WBC to enter area

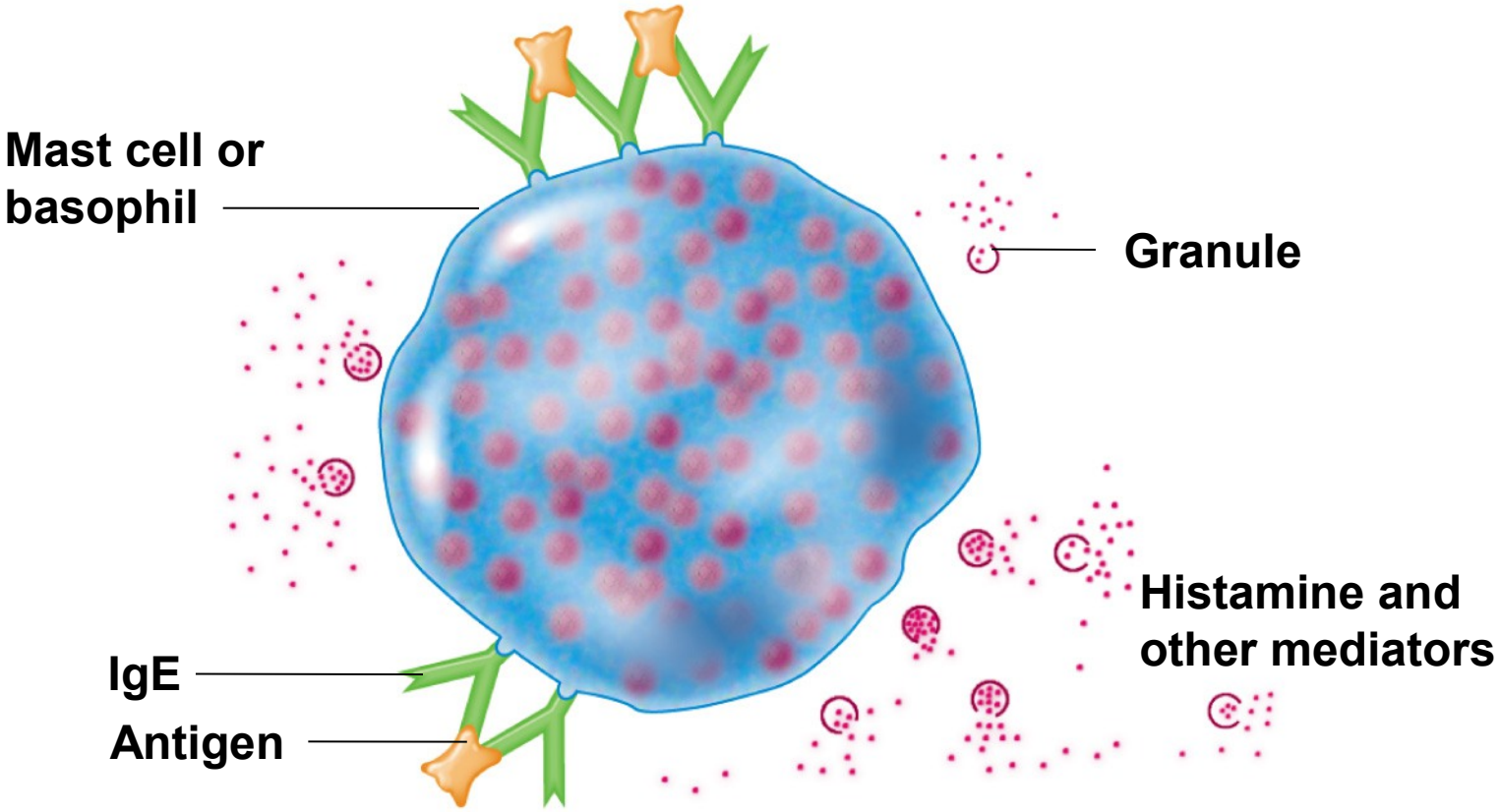
Basophils Become Mast Cells After They Acquire IgE "Receptors"

(Type I hypersensitivity response.)



Note: Basophils are in the blood / Mast cells are attached to collagen fibers within connective tissue.

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.

Monocytes Morph Into Macrophage and Dendrictic Cells

Monocytes

3-8% // largest WBC; ovoid, kidney or horseshoe shaped nucleus // monocytes are in the blood

increased numbers in viral infections and inflammation

produce and secrete **cytokines** = group of molecules which regulate immune responses

Monocytes may differentiate into two different cell lines

- Dendtrictic cells – WBC found in stratum spinosum and at mucosa surfaces // phagocytotic and antigen presenting cell

- Marcrophage – see next slide

Monocytes Morph Into Macrophage and Dendrictic Cells

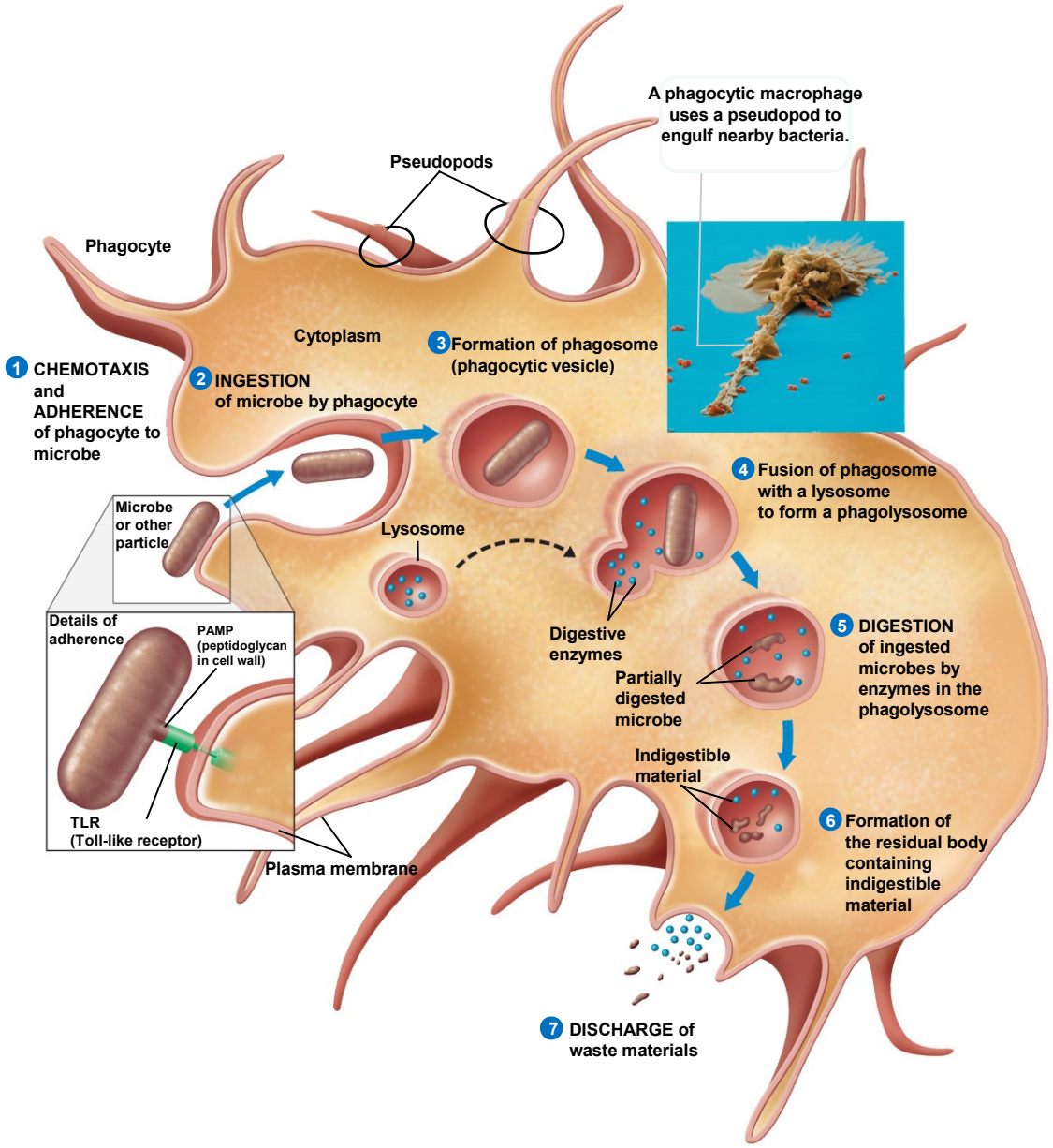
After monocytes leave bloodstream, monocytes transform into **macrophages** (i.e. big eater)

macrophage are active in phagocytosis // engulfing pathogens and debris

the **"garbage collector"** and "garbage disposal" system // recycle macromolecules

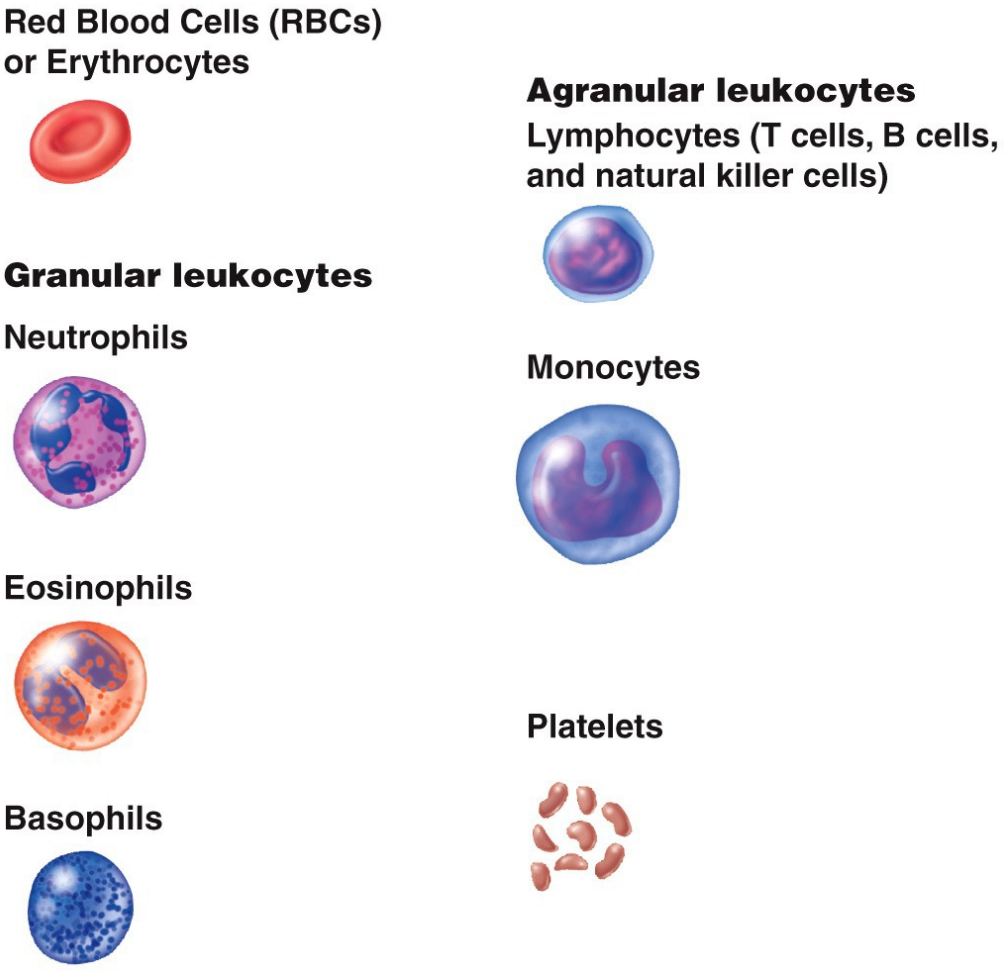
also "present" antigens to activate other immune cells // macrophage called **antigen presenting cells** (APCs)

The Phases of Phagocytosis.



What About Platelets

- Platelets are part of the myeloid tissue but not a cell.
- Platelets contain cytoplasm surrounded by the plasma membrane of megakaryocytes as small packets are pinched off
- Megakaryocytes are only found in the red bone marrow.
- Platelets play a critical role in hemostasis. We will cover the structure and function of platelets when we cover hemostasis.



The Agranulocyte (T, B, NK)

Lymphocyte T cells

- 25-33% // variable amounts of bluish cytoplasm (scanty to abundant); ovoid/round, uniform dark violet nucleus
- increased numbers in infections and immune responses
- **Cytotoix T cells come from the lymphocyte cell line**
- **only WBC** able to “specifically kill cells” infected with cancer, foreign bacteria, and virus) // adaptive immunity is a type of cellular immunity
- To activate cytotoxic T cells a foreign antigen must be presented to “educated cT-cells
- Helper T cells coordinate actions of other immune cells // use cytokines = messenger molecules // used to activate cT-cells

The Agranulocyte (T, B, NK)

LymphocyteB cells

B cells morph into plasma cells when they are activated by foreign actigen

Plasma cells make antibodies

Antibodies do not kill pathogen

Antibodies render pathogens harmless and tag them for destruction

Before plasma cell may become “fully activated” they need to receive cytokines from activated Helper T cells

The B cell make plasma cell and plasma cells provide humoral immunity

The Agranulocyte (T, B, NK)

Lymphocyte NK cells

Natural killer cells (NK) also come from the lymphocyte cell line

NK cells circulate in the blood and may move throughout the tissue spaces

NK cells do not have to be activated

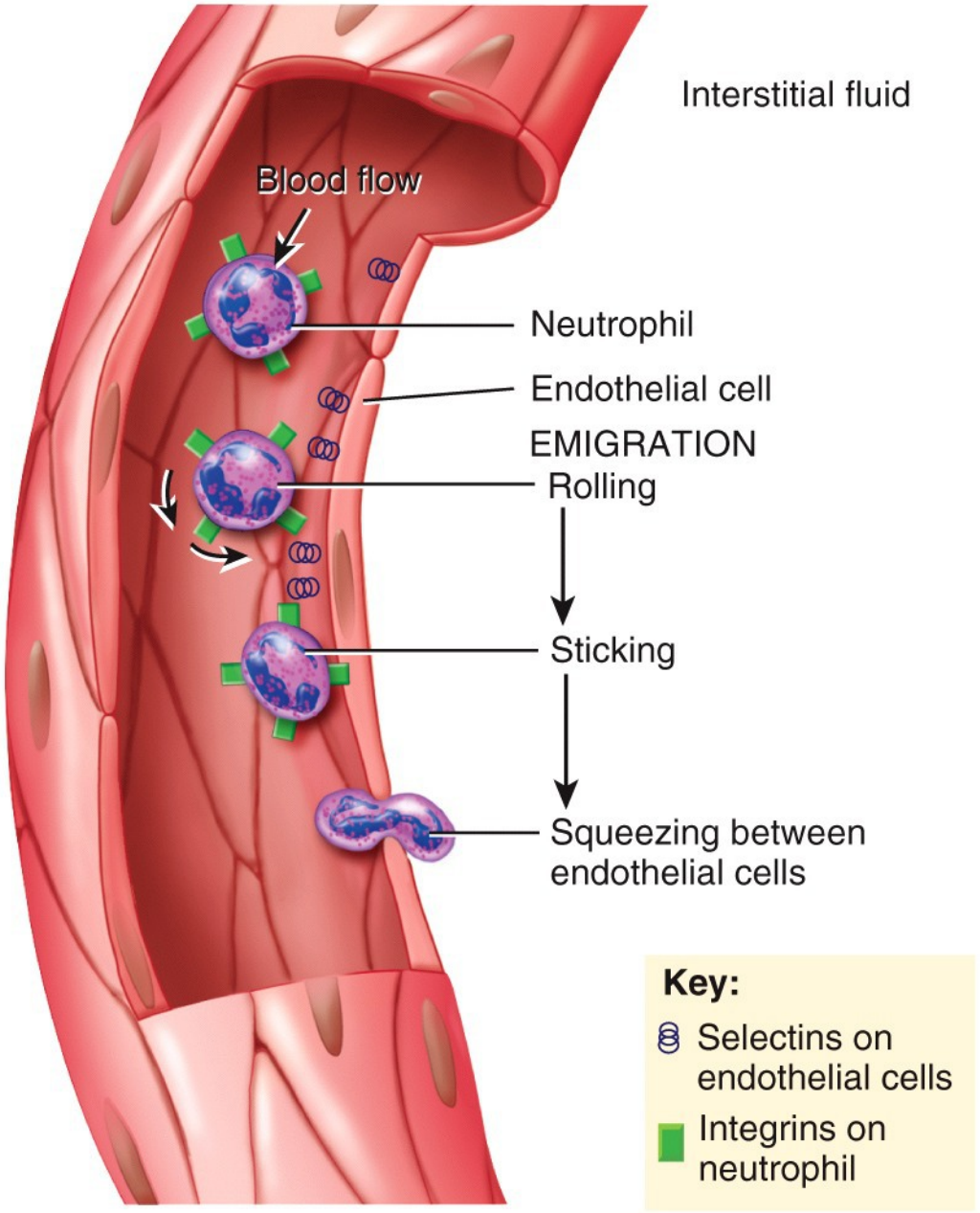
NK cells are responsible for “immune surveillance”

NK cells are able to directly kill host cells infected with either cancer or virus

When NK identifies infected cell it give the infected cell the “kiss of death”

How Leukocytes Emigrate into Tissue Spaces

- Circulating WBCs do not stay in bloodstream
  - In area of inflammation, inner face of blood vessels lined by endothelial cells become “sticky” // WBC rolling along inner surface adhere to and stop on inside of blood vessel // called margination
  - Stopped WBC stop then squeeze between endothelial cells to enter tissue space // called diapedis
  - 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


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

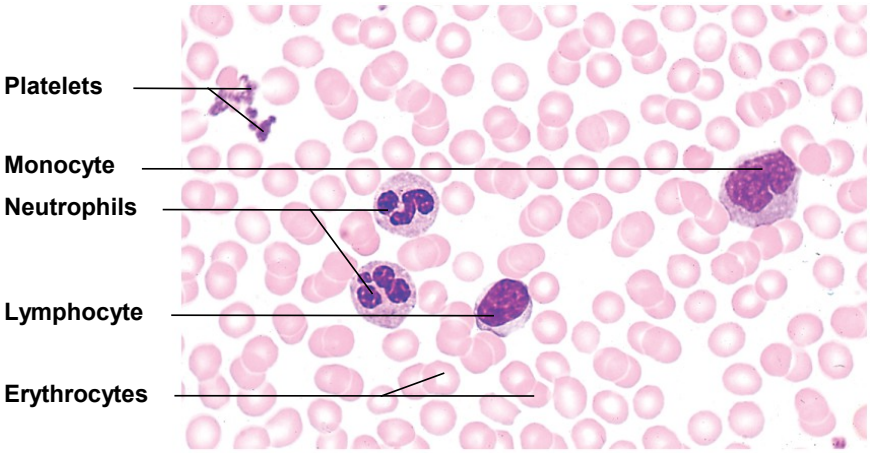
Leukocyte Disorders

- **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

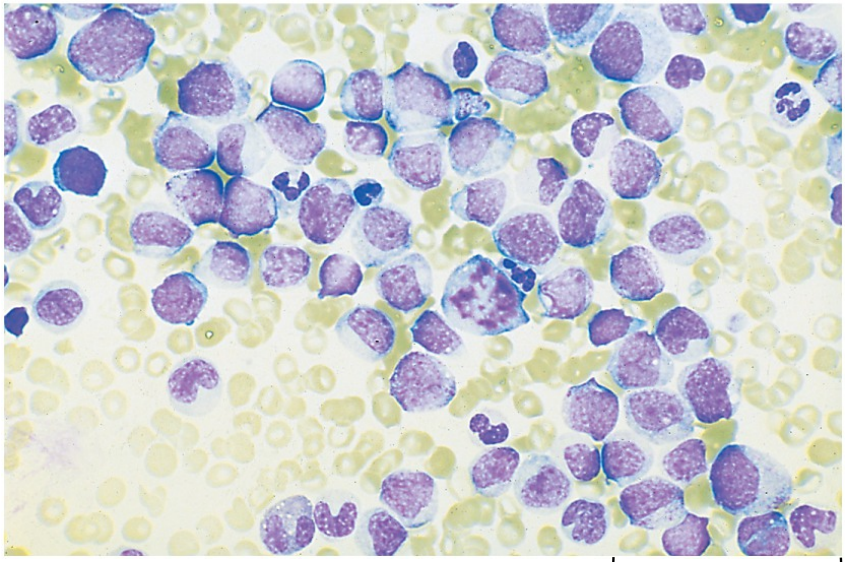
Leukocyte Disorders

- 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)

Complete Blood Count

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