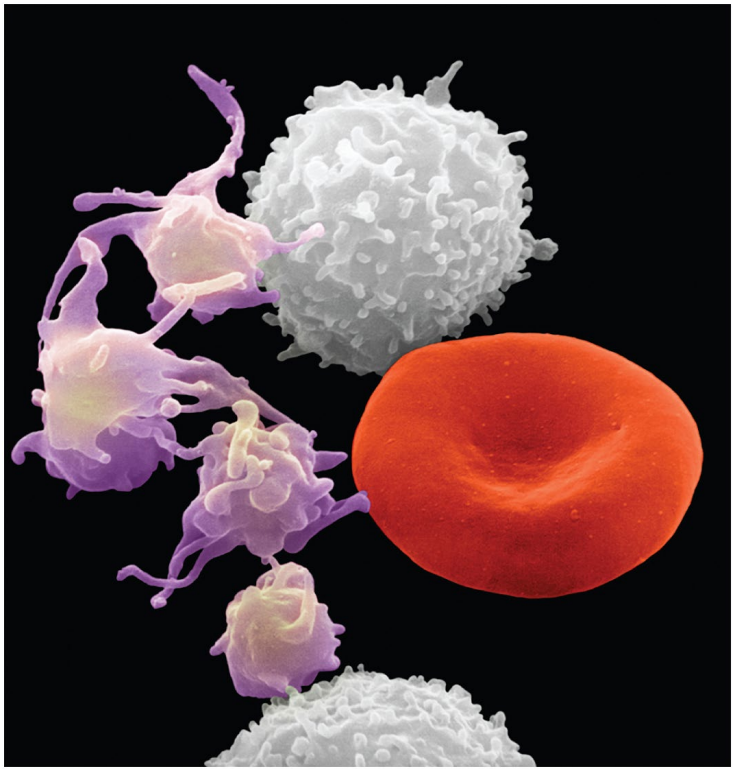
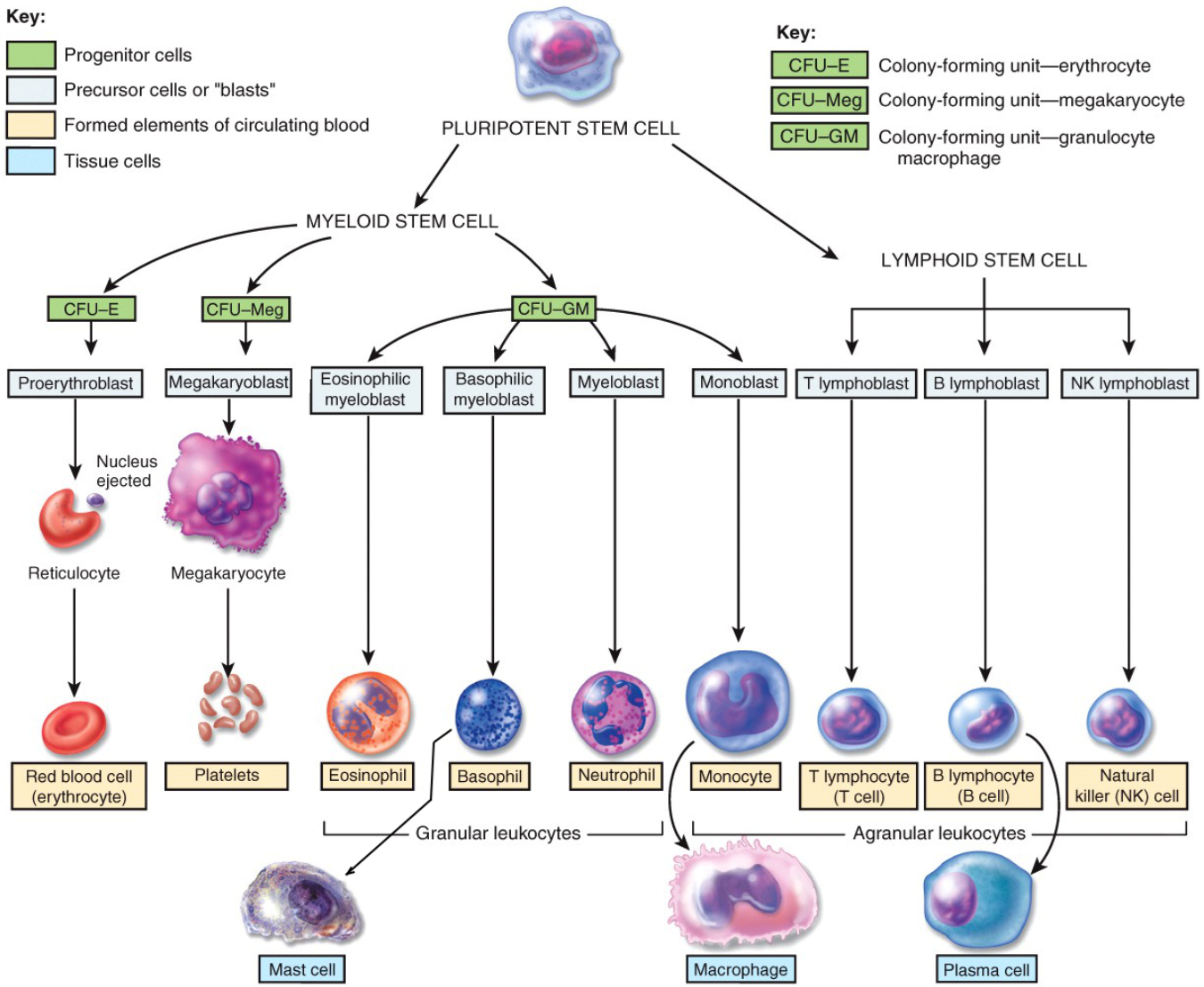
Chapter 18.3

The Structure and Function of the Formed Elements



Nine Formed Elements Plus Mast Cells, Macrophage, and Plasma Cells
(A more accurate count is *12!)*



Make a flash card for each formed element!

Erythrocytes (Red Blood Corpuscle)

Disc-shaped corpuscle with thick rim

Mature RBC is "not a cell" // it is a "corpuscle"

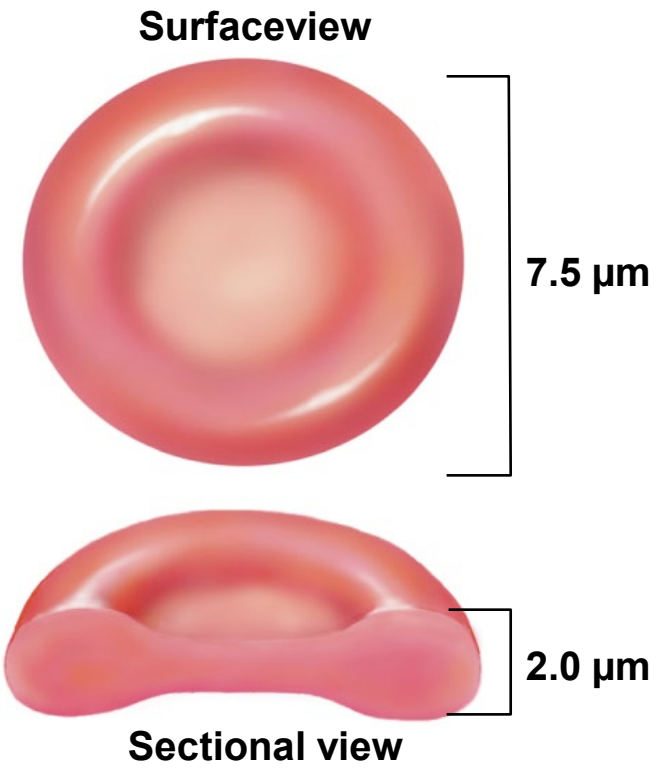
7.5 μM diameter and 2.0 μm thick at rim

Loss of 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

Mature RBC is a corpuscle full of hemoglobin. This molecule carries oxygen from the lungs to the cells throughout the body.



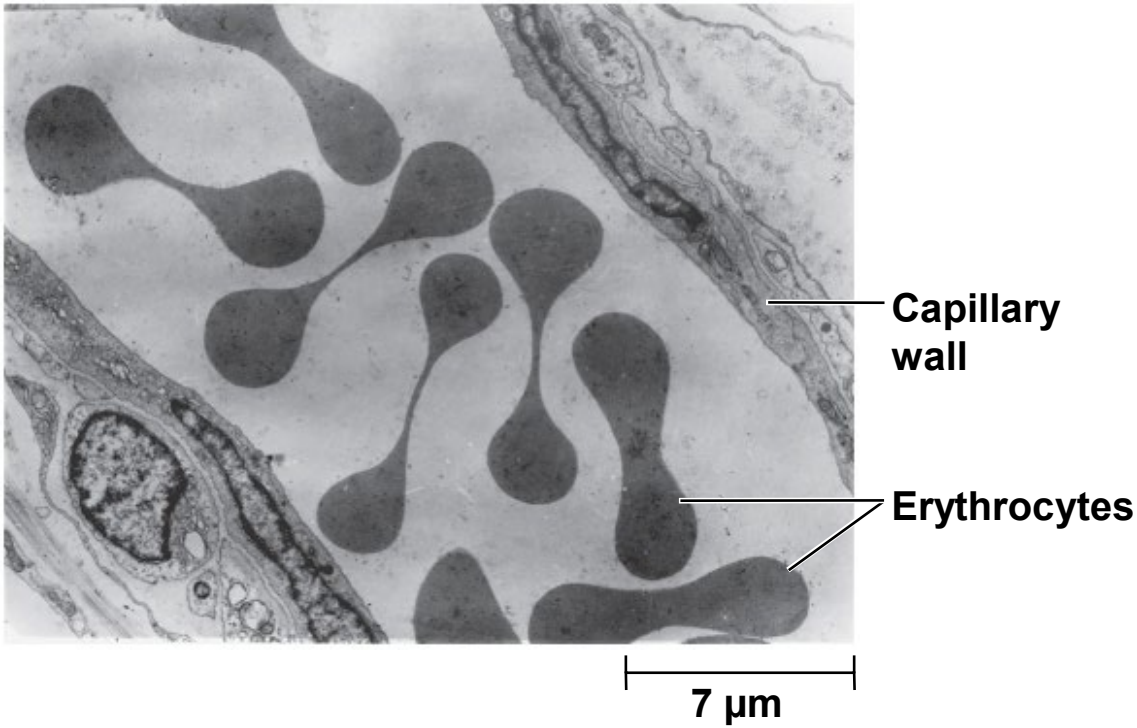
Erythrocytes

What is the diameter of a continuous capillary? (7.5 micrometers)

Why is this significance?

RBC go through capillaries "single file"

Principal function /// carry oxygen from lungs to cellular tissues of body



Most of the carbon dioxide transported as bicarbonate in plasma from tissue to lungs

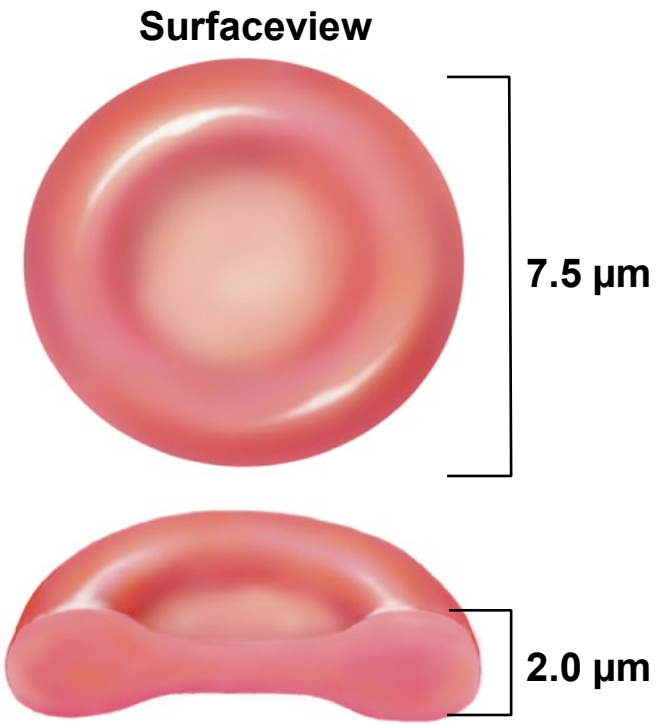
Insufficient RBC function may result in necrosis within 4 – 5 minutes due to lack of oxygen

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

Do RBC Have a Resting Membrane Potential?

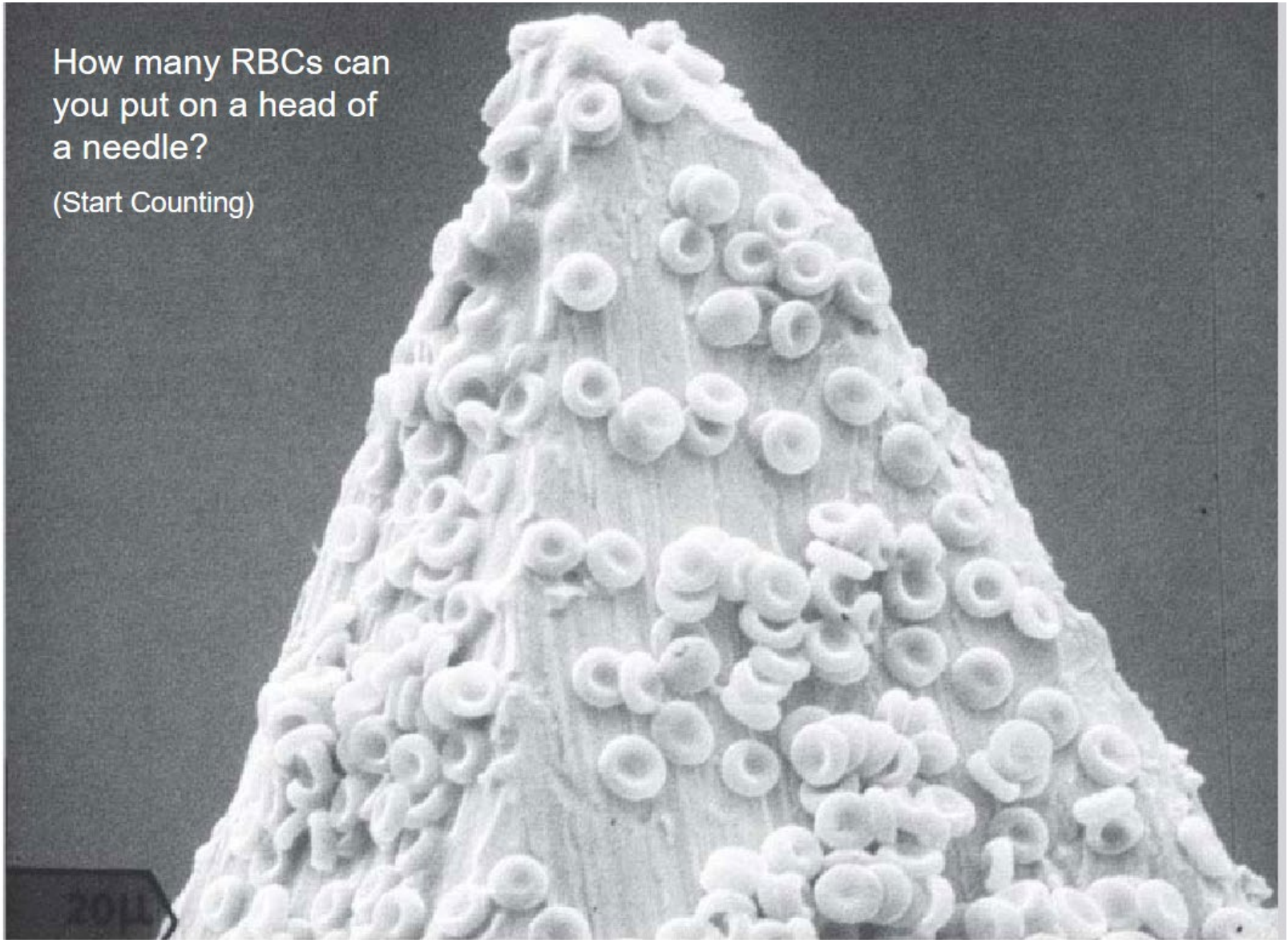
Yes, red blood cells (RBCs) have a resting membrane potential. However, it is relatively modest compared to excitable cells, typically around -10 mV.

It is determined differently than in most other cells. Unlike many other cells where potassium channels primarily dictate the resting potential, in RBCs, the resting membrane potential is largely dictated by the movement of anions, such as bicarbonate.



This anion-driven potential is essential for the optimal transport of carbon and maintaining the cell's function.

While a membrane potential exists, RBCs are not considered "excitable" like neurons or muscle cells. They do not have a significant resting potential that undergoes large, rapid changes as in an action potential.


How many RBCs can you put on a head of a needle?
(Start Counting)

(a) RBC shape

Blood type determined by special type of transmembrane glycoproteins called "antigens"

Glycoproteins located on outer face of plasma membrane

Two type of antigens // A antigen & B antigen

Four major blood types: A, B, AB, O // These antigen form the ABO Blood Type System

There are many other RBC blood antigens that create different blood types // ABO is the most problematic in medicine

The Rh Factor is another RBC plasma antigen (antigen D) which is also closely monitored.

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 (erythroblast) = erythrocyte colony forming unit // has receptors for erythropoietin (EPO) from kidneys

Erythroblasts (normoblast) multiply and synthesize hemoglobin

As erythroblast mature, they discard their nucleus, other organelles, and the last organelle to be discarded is the endoplasmic reticulum. The final stage of development for a RBC is called a reticulocyte

Reticulocytes are named for their fine network of endoplasmic reticulum still in cytoplasm // 0.5 to 1.5% of circulating RBCs are reticulocytes (test benchmark 1%)

Erythrocytes or RBC

What is the fluid mosaic model of the plasma membrane? (Chapter 3!)

Important cytoskeletal proteins are spectrin & actin

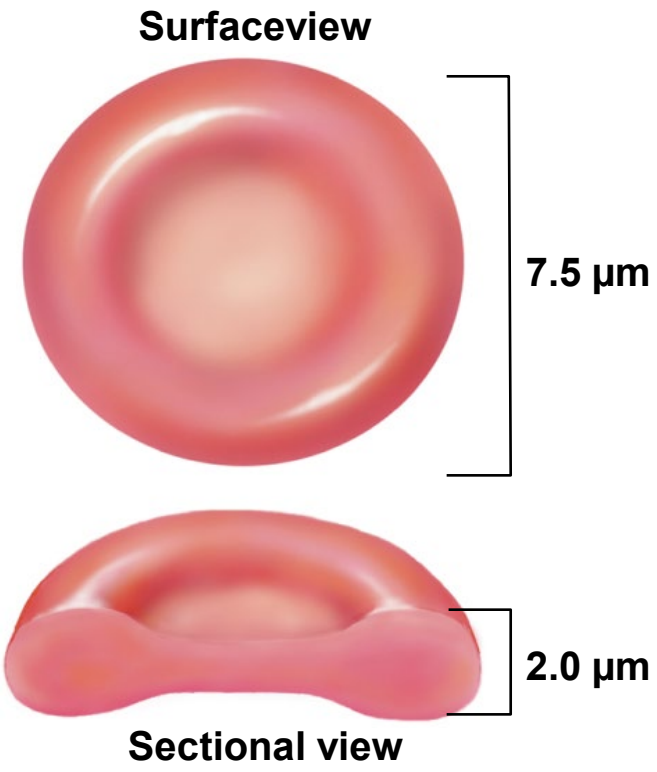
These proteins give RBC membrane durability and resilience (flexibility)

Allow RBC to stretch, bend, and not rupture as they squeeze through small capillaries

As RBC age the spectrin and actin proteins break down. The RBC can not replace these molecules.

Now RBC membrane becomes “brittle”.

Why can't the RBC replace these molecules?



Hemoglobin (Hb) Structure

Each Hb molecule consists of four globular proteins

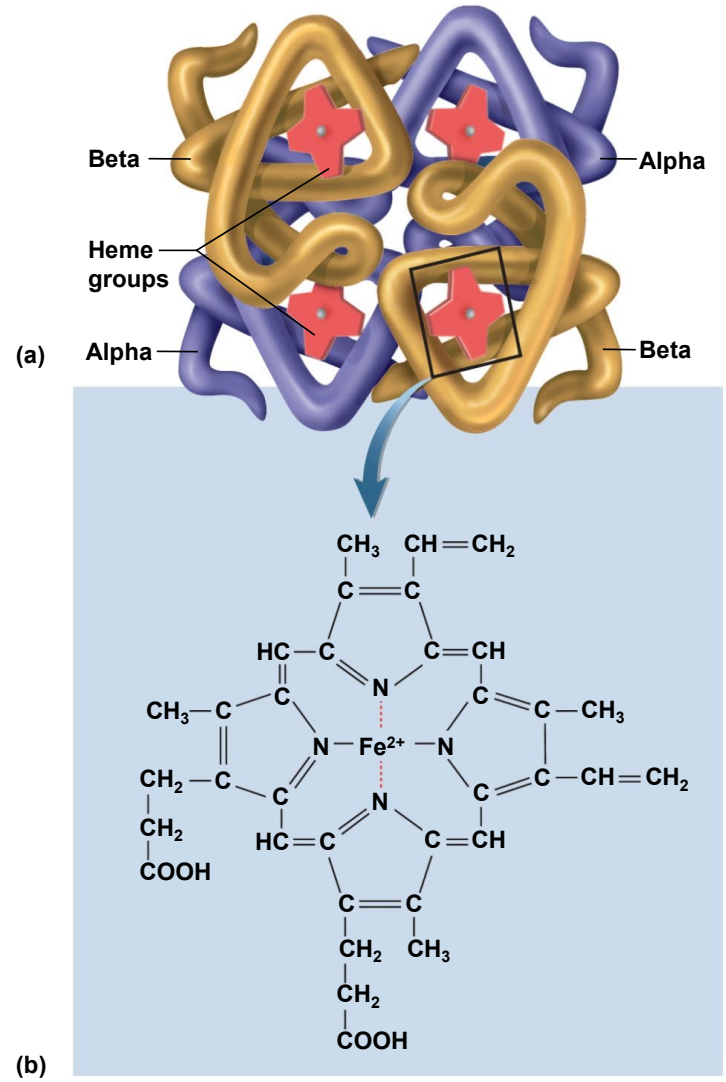
At core of each globular protein there is a heme group

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

A hemoglobin molecules 100% saturated carries four O2 molecules



Hemoglobin (Hb) Structure

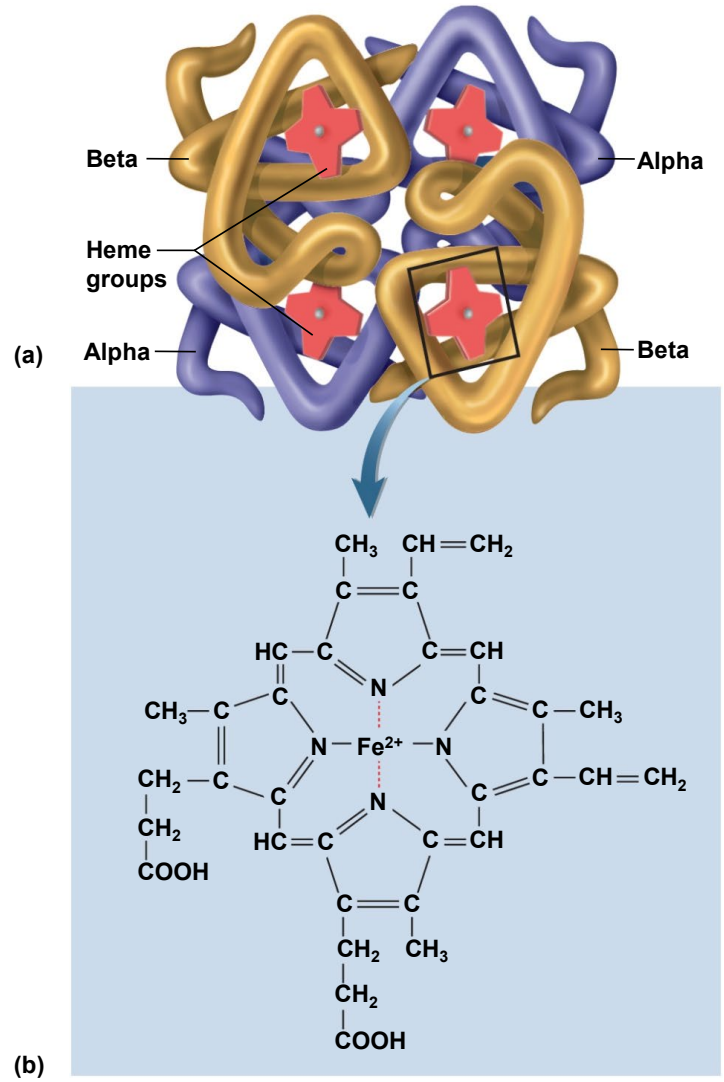
About the globin molecules

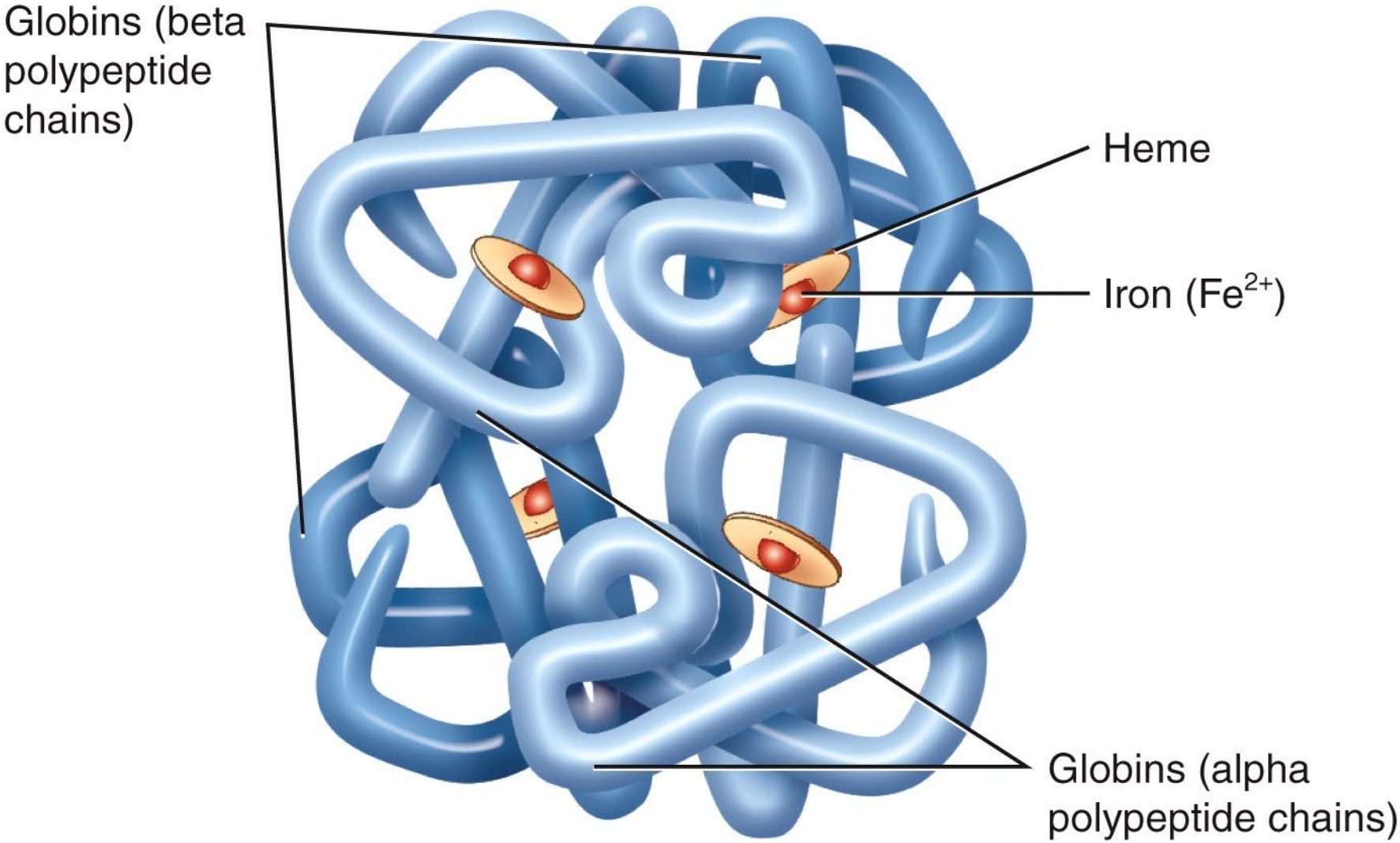
Two alpha and two beta chains

5% CO_2 in blood is bound to globin moiety

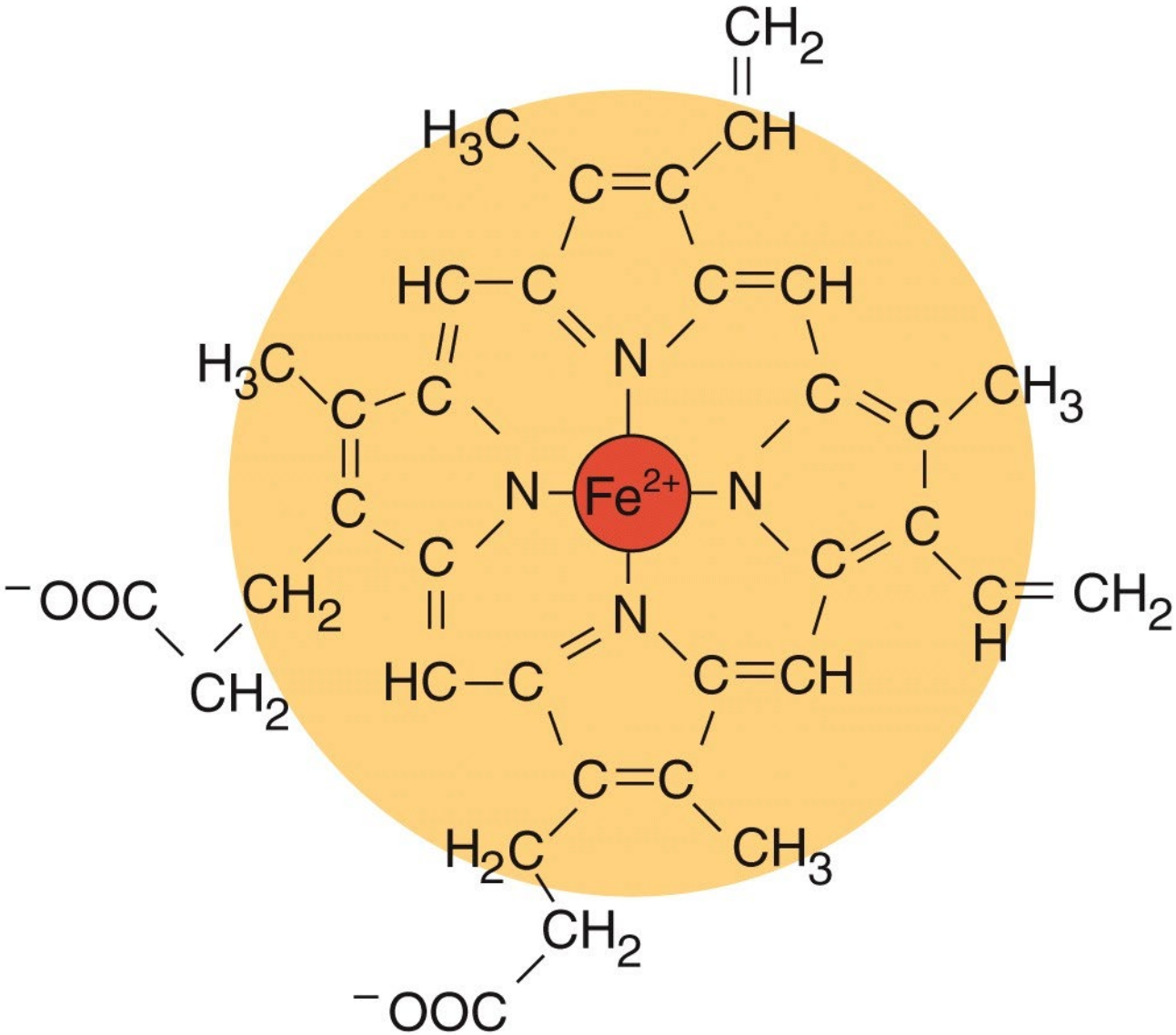
There are two types of hemoglobin in a typical life cycle. /// Adult vs. fetal Hemoglobin

Which form do you think has a greater affinity for oxygen? Why?





(b) Hemoglobin molecule



(c) Iron-containing heme

How many oxygen molecules carried by hemoglobin molecule?

Erythrocytes Death and Disposal

The spleen is called the “graveyard” for old RBC.

Old brittle RBCs lyse in the narrow spleen capillaries (2 micrometer) /// this occurs with RBC 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
- globin molecules hydrolyzed into amino acids
- iron removed from heme to be recycled
- Iron transported to liver for storage

Erythrocytes Death and Disposal

Nitrogen concentrations in the blood are toxic. // each heme molecule in hemoglobin hold four nitrogen atom (total of 16), and this becomes is a problem as RBC are recycled in the spleen

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

> kidneys pick up bilirubin and 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)

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

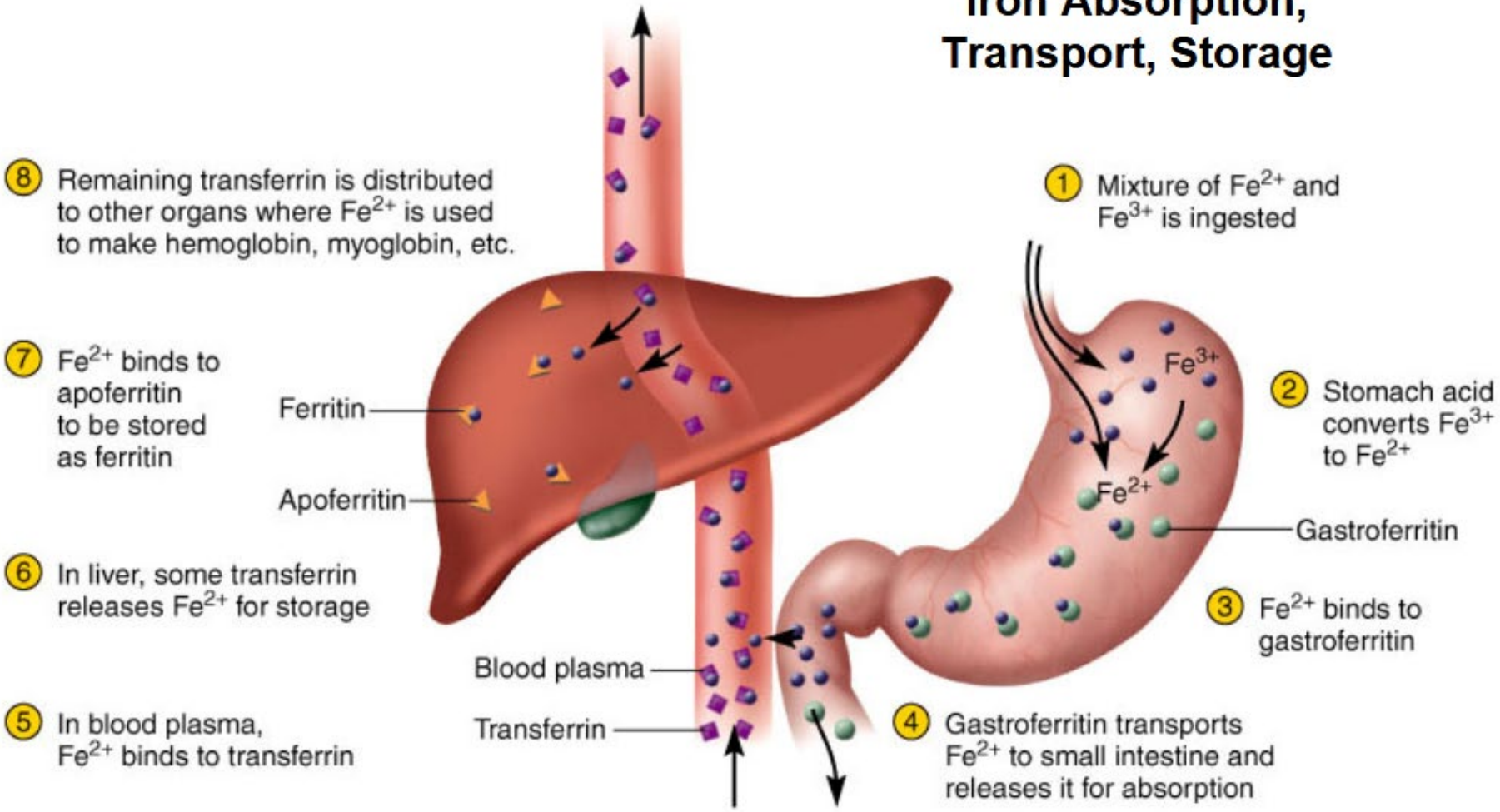
Iron lost daily through urine, feces, and bleeding //
men 0.9 mg/day VS women 1.7 mg/day

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+}

Iron Absorption, Transport, Storage



Dietary Iron: ferric (Fe3+) / ferrous (Fe2+)

Stomach acid converts ferric to ferrous, the only form of iron that can be absorbed.

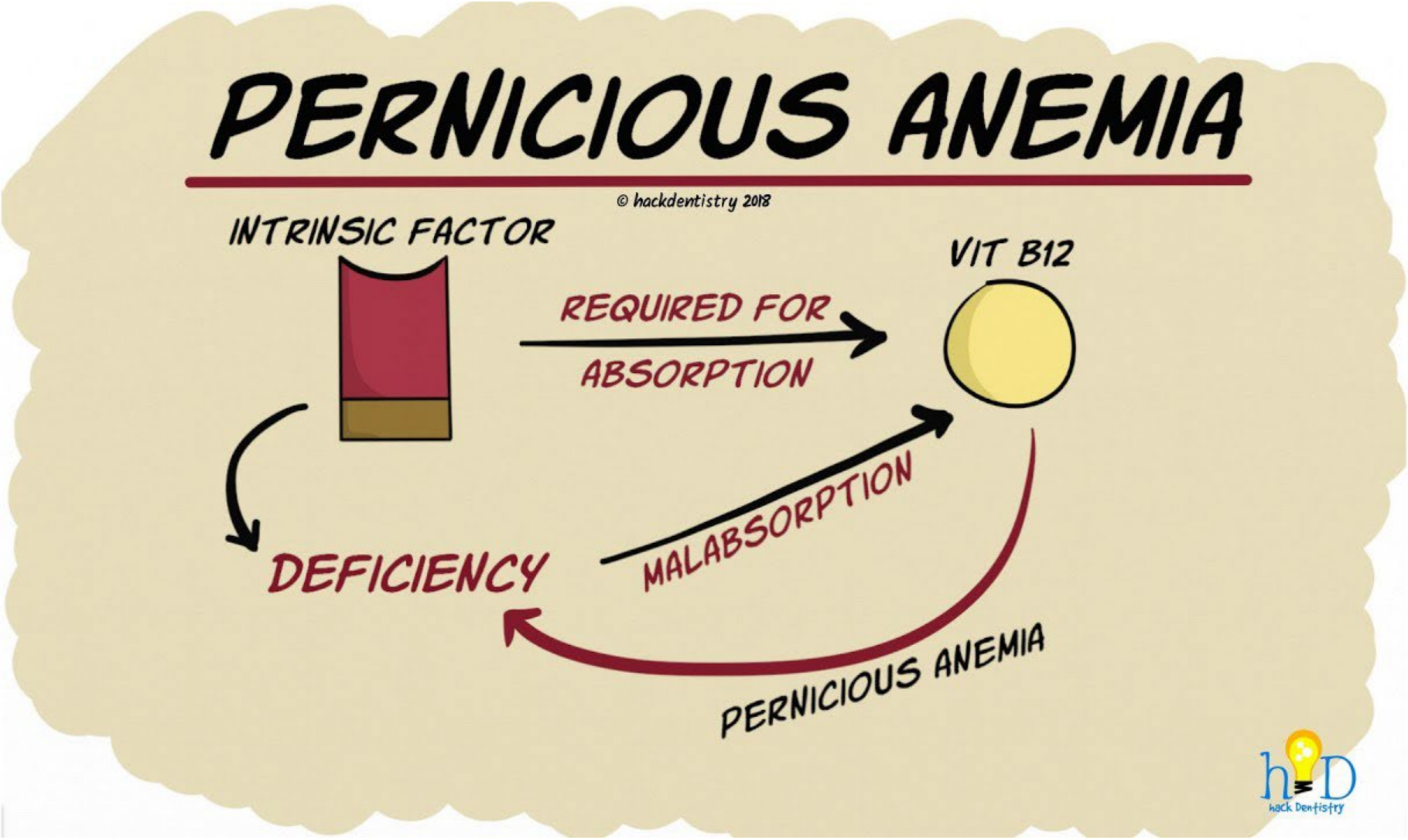
Other Nutritional Needs for Erythropoiesis

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 produce intrinsic factor /// this is required to absorb Vit B12 /// no B12 = pernicious anemia

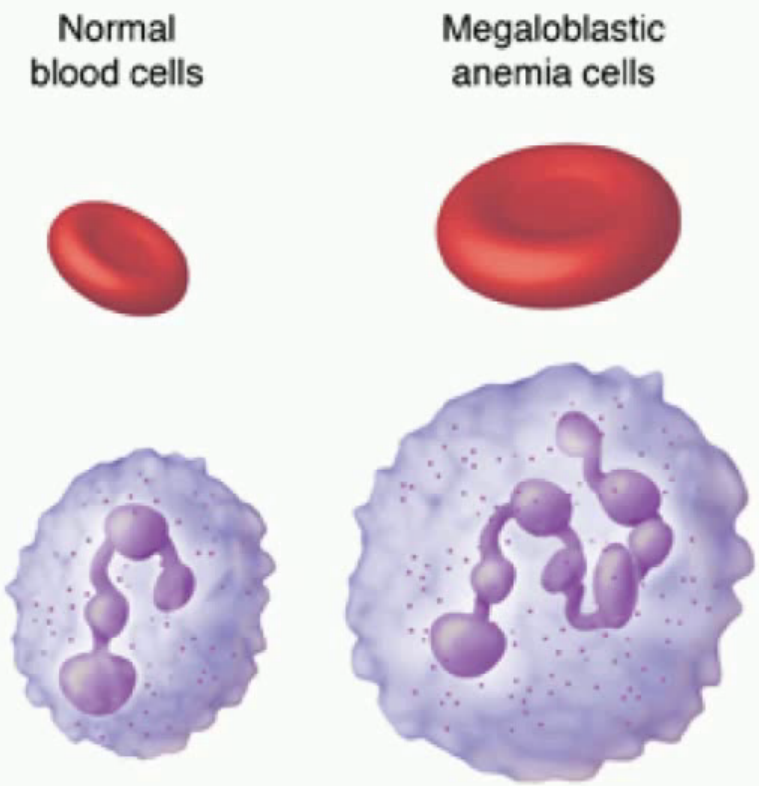
Vitamin C

Copper // cofactor for enzymes synthesizing hemoglobin // copper is transported in the blood by an alpha globulin called ceruloplasmin



The only essential function of the stomach is the production of intrinsic factor. It is needed to absorb Vit B12 . Vit B12 is required to make functional RBC.

pernicious anemia



Megaloblastic anemia caused by vitamin B12 deficiency. The red blood cells are large, immature, and nucleated, and do not function well. It is caused by impaired absorption of vitamin B12 due to the lack of intrinsic factor in the gastric mucosa.

Regulating Erythrocyte Homeostasis

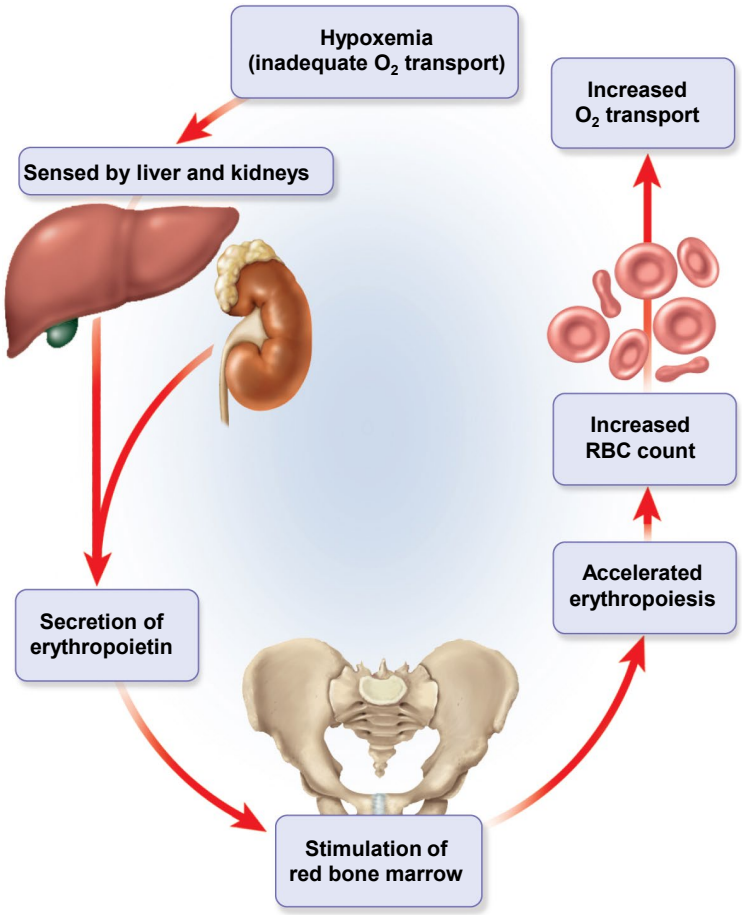
Negative feedback regulation // drop in RBC count causes hypoxemia

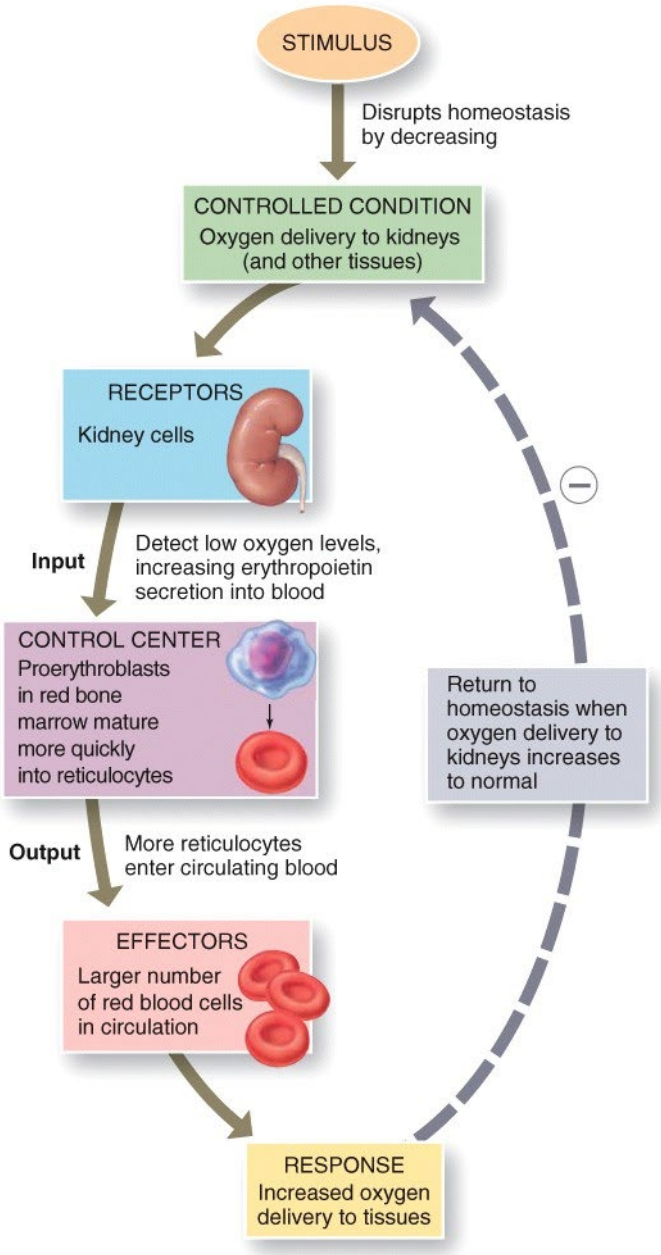
This is stimulus for kidneys to secrete erythropoietin // the hormone that stimulates bone marrow to make new RBC

RBC count increases in 3 - 5 days

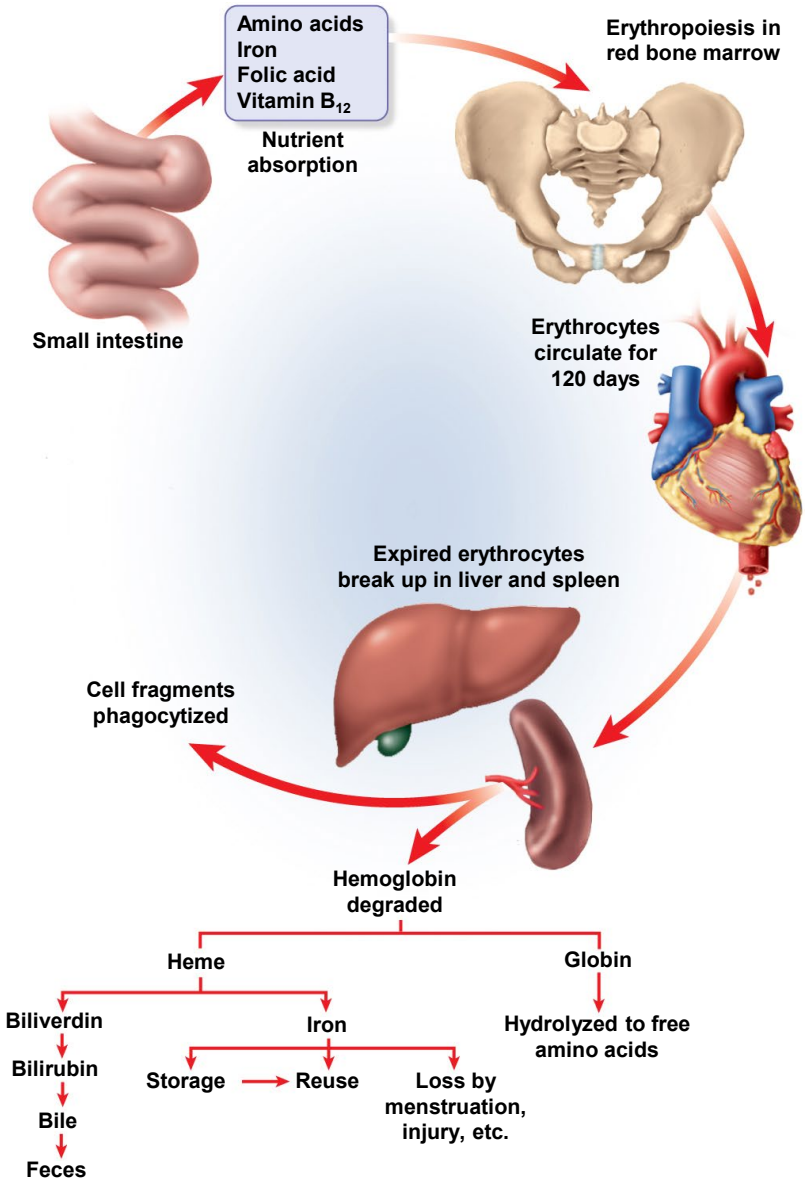
Stimuli to release erythropoietin and increase erythropoiesis

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

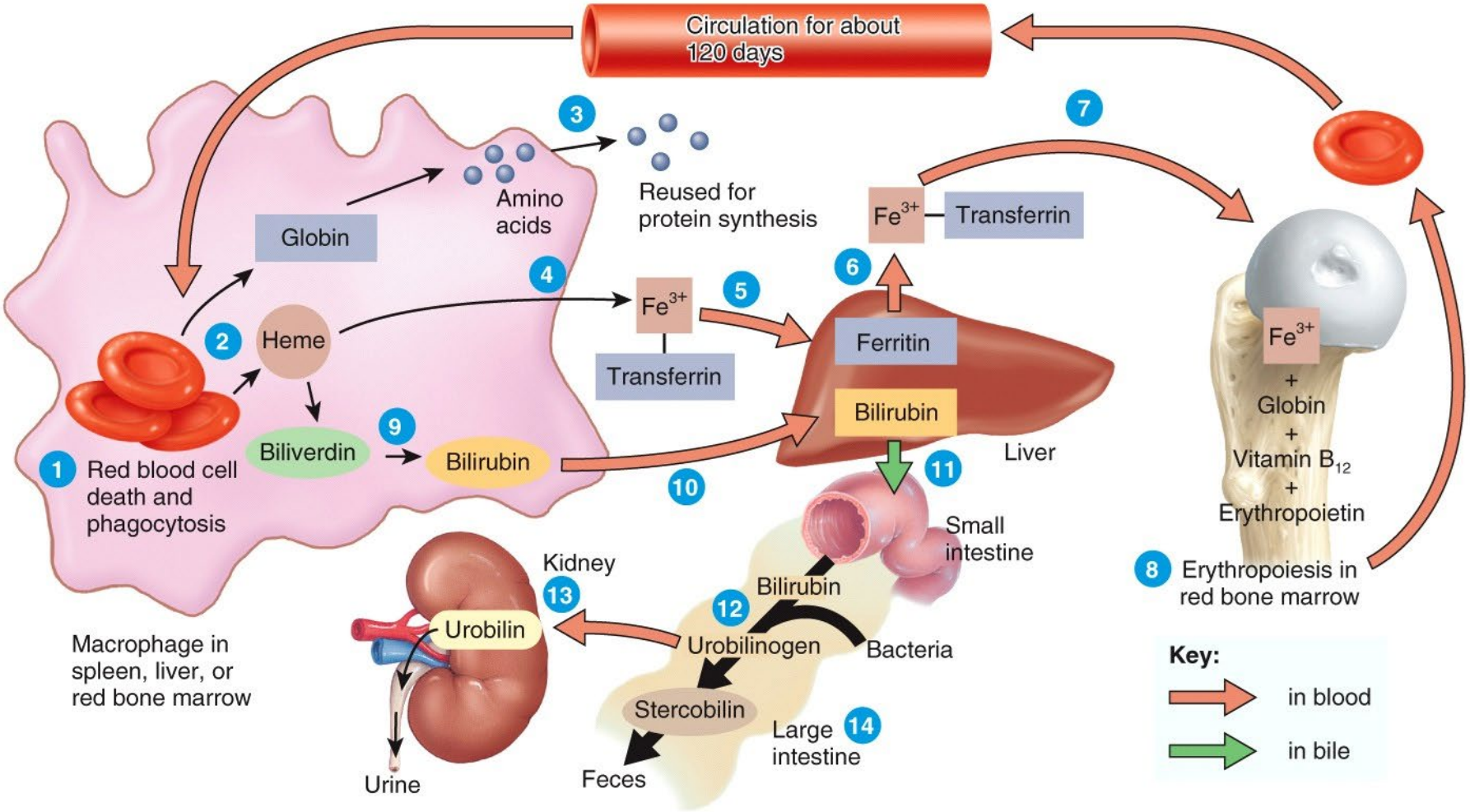



STIMULUS
Disrupts homeostasis by decreasing
CONTROLLED CONDITION
Oxygen delivery to kidneys (and other tissues)
RECEPTORS
Kidney cells
Input
Detect low oxygen levels, increasing erythropoietin secretion into blood
CONTROL CENTER
Proerythroblasts in red bone marrow mature more quickly into reticulocytes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

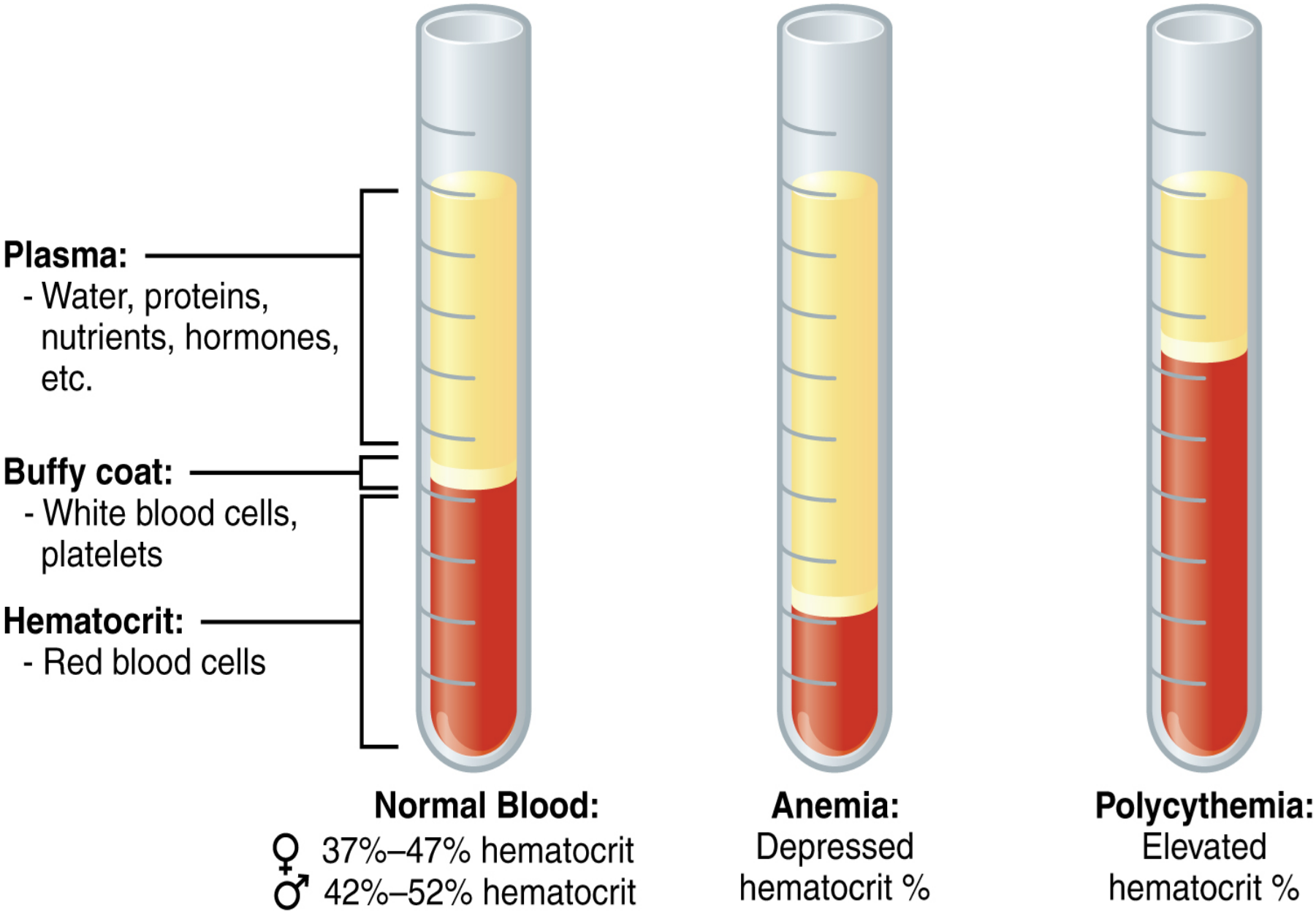
Polycythemia = an excess of RBCs

Primary polycythemia (polycythemia vera) // cancer of erythropoietic cell line in red bone marrow

RBC count maybe as high as 11 million/μL /// with a hematocrit as high as 80% // but erythropoietin has a low concentration in blood

Secondary polycythemia // from dehydration, emphysema, high altitude, or physical conditioning /// RBC count up to 8 million/μL /// but erythropoietin high concentration in blood

What happens to viscosity 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 do not have enough healthy red blood cells to carry adequate oxygen to your body's tissues.

This condition will make you feel tired and weak.

Factors leading to anemia:

Inadequate erythropoiesis (or failure to produce functional hemoglobin (eg. sickle cell anemia)

Hemorrhagic anemia /// major blood vessel ruptures

Hemolytic anemia /// e.g. malaria

Anemia

What are the consequences associated with anemia?

Hypoxia // oxygen deprivation in tissue // low energy / severe cases will result in tissue necrosis

Reduced blood osmolarity // this then causes edema

Reduced blood viscosity

- little blood resistance // heart beats faster
- low blood volume, low viscosity
- cause low blood pressure
- may cause cardiac failure

Anemia Types

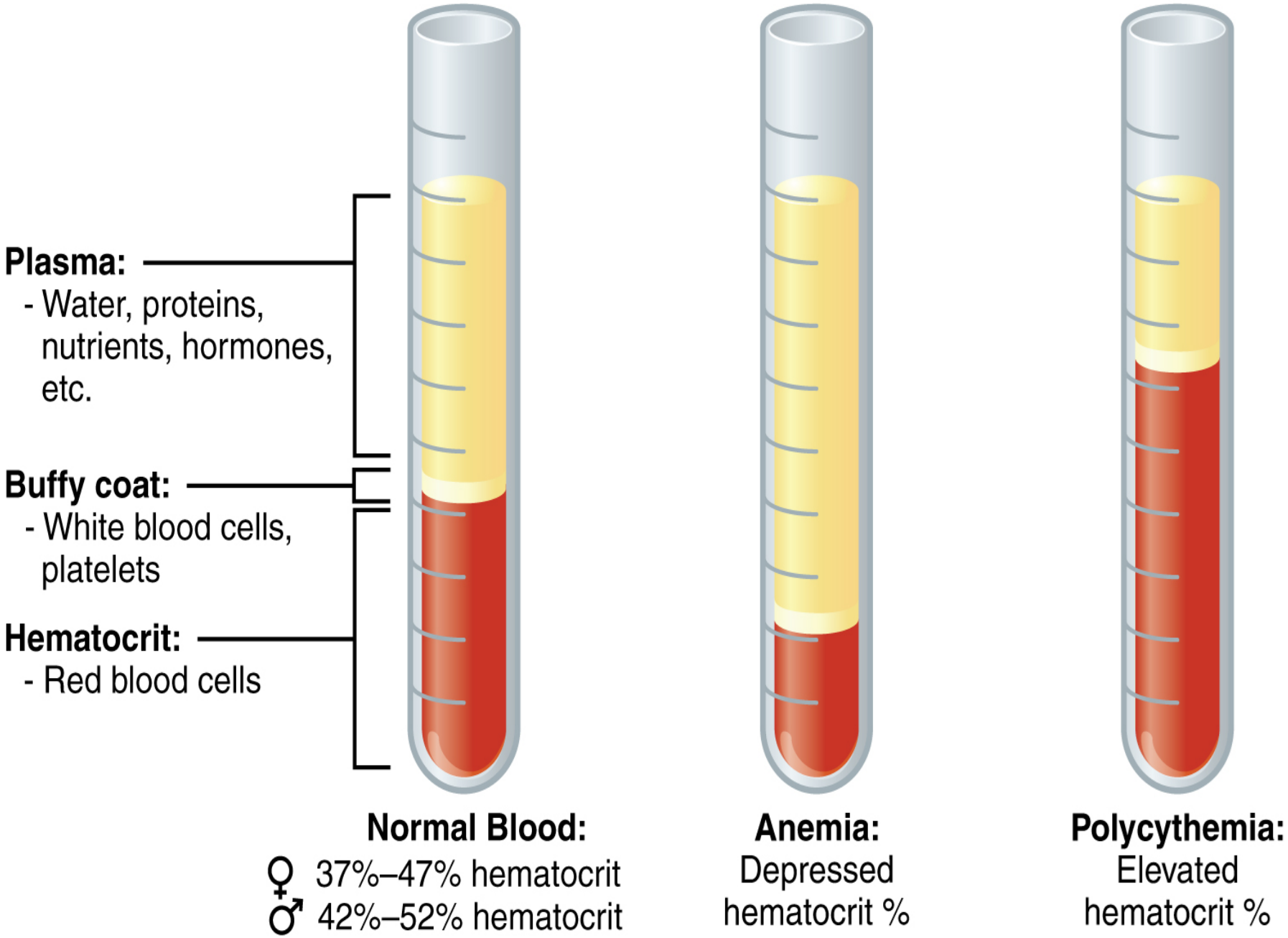
Iron-deficiency anemia

Pernicious anemia // Problem is 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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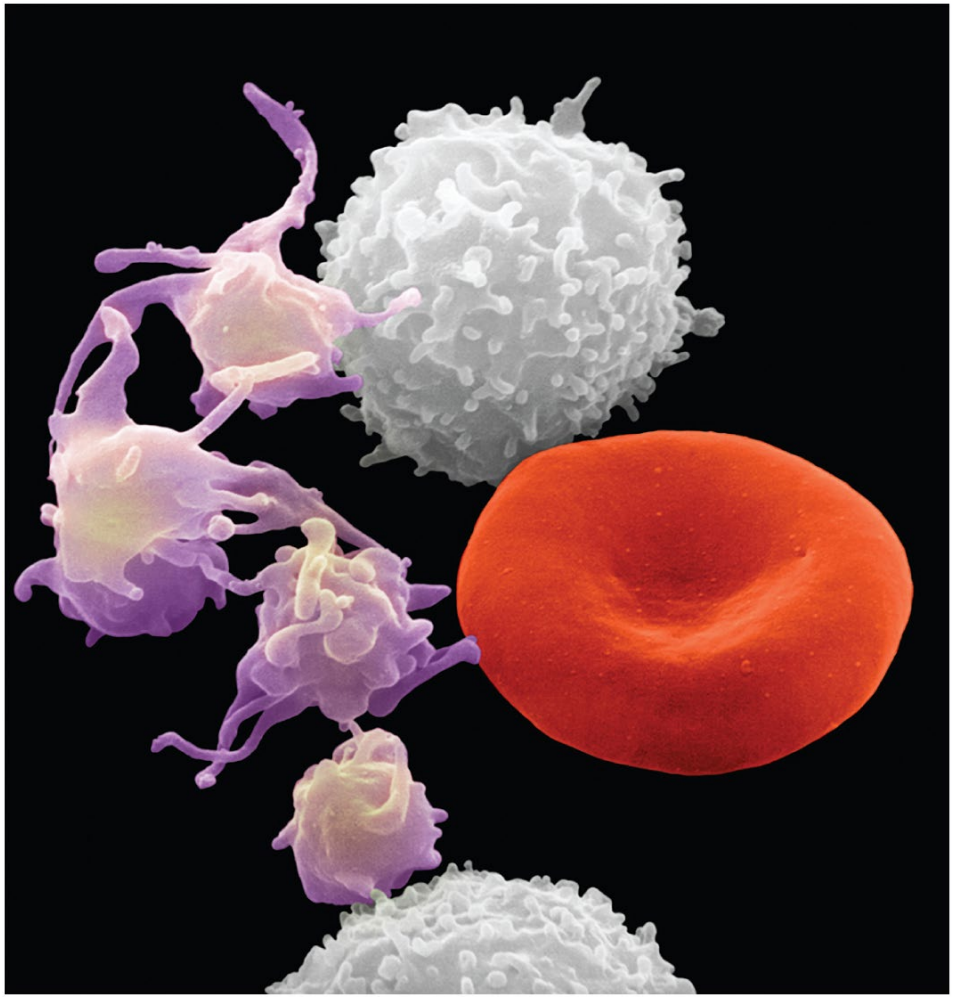
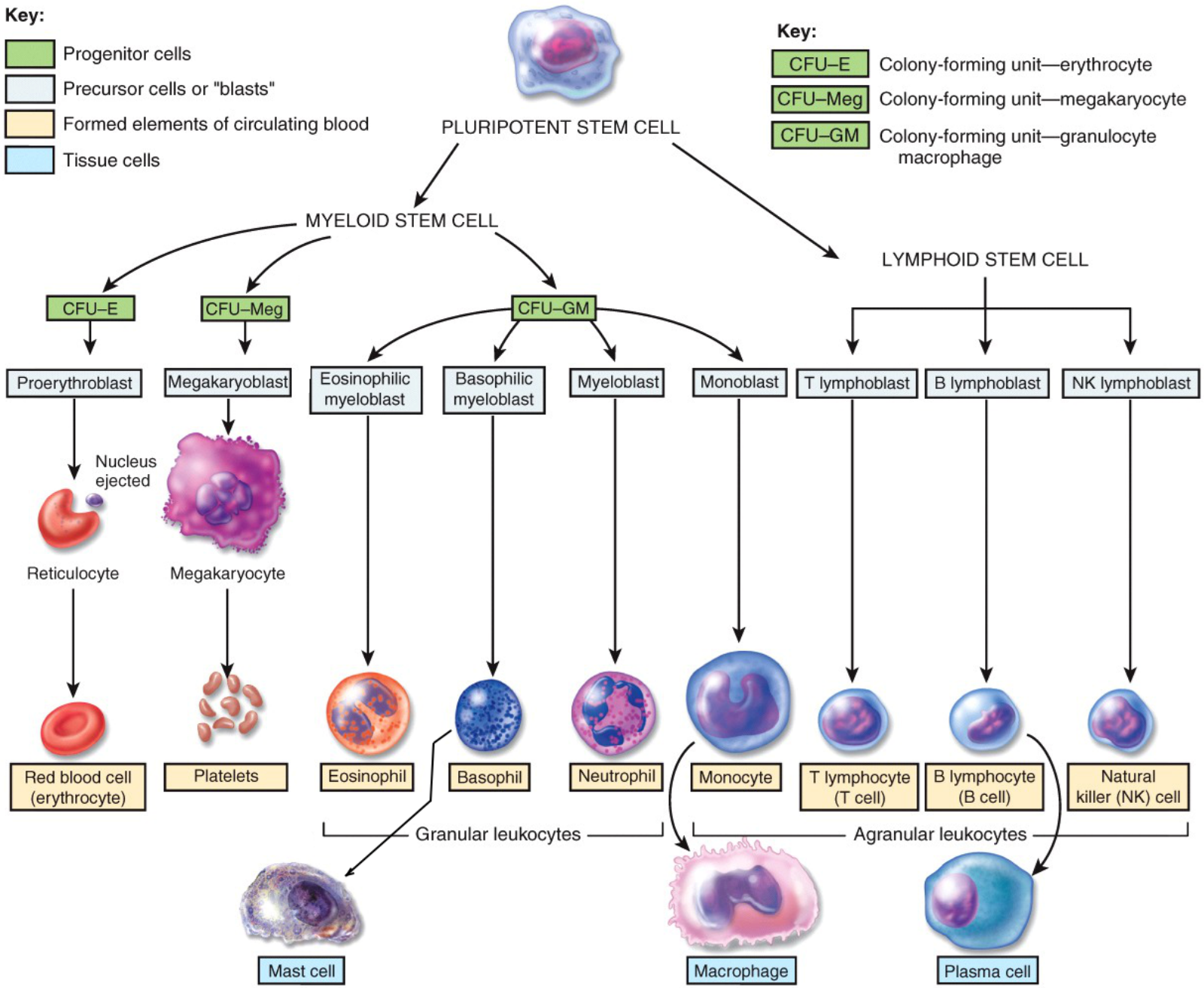
Leukocytes (WBC)



Make a flash card for each formed element!


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!

Some WBCs have **lysosomes** called nonspecific (azurophilic) granules /// these don't stain /// 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 // remember "NEBs"

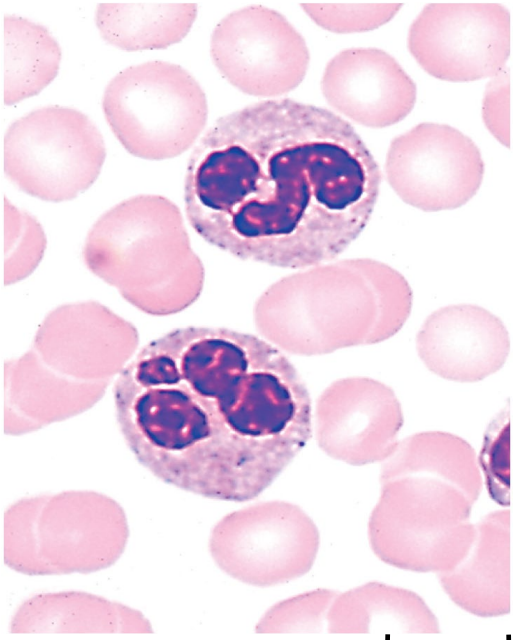
–neutrophils (60-70%)
–eosinophils (2-4%) ← "NEB"
–basophils (<1%)

Agranulocytes // these don't stain

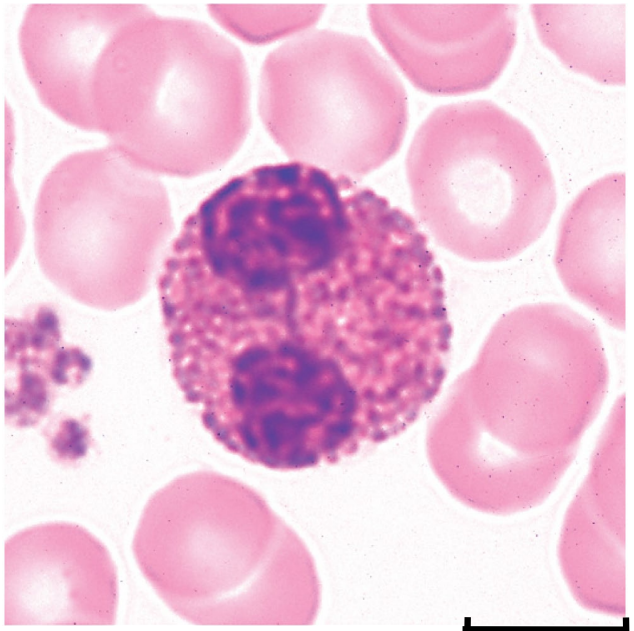
–lymphocytes (25-33%)
–monocytes (3-8%) ← "LM"

How to remember WBC ranking. Never let monkeys eat bananas

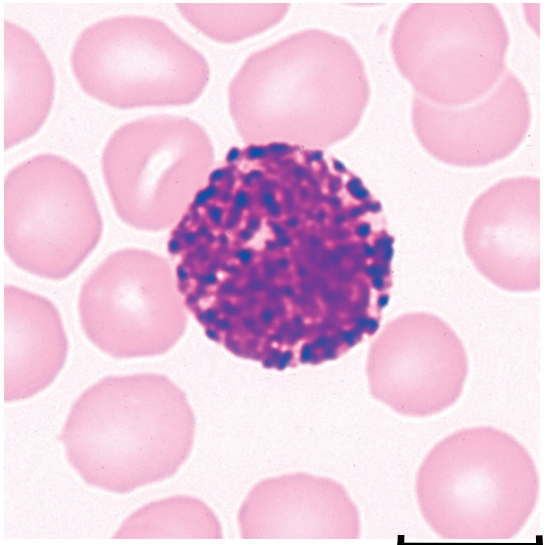
Granulocytes



Neutrophils 10 µm



Eosinophil 10 µm



Basophil 10 µm

Agranulocytes

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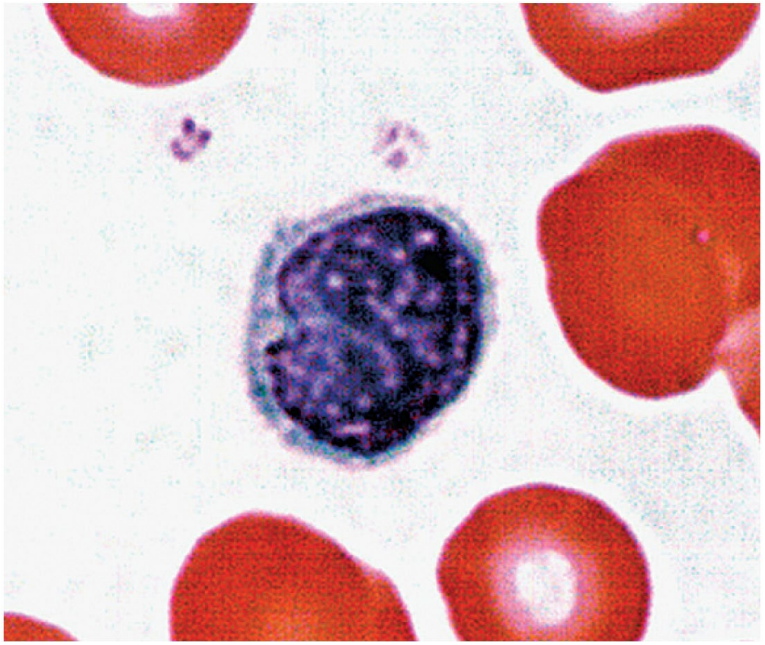
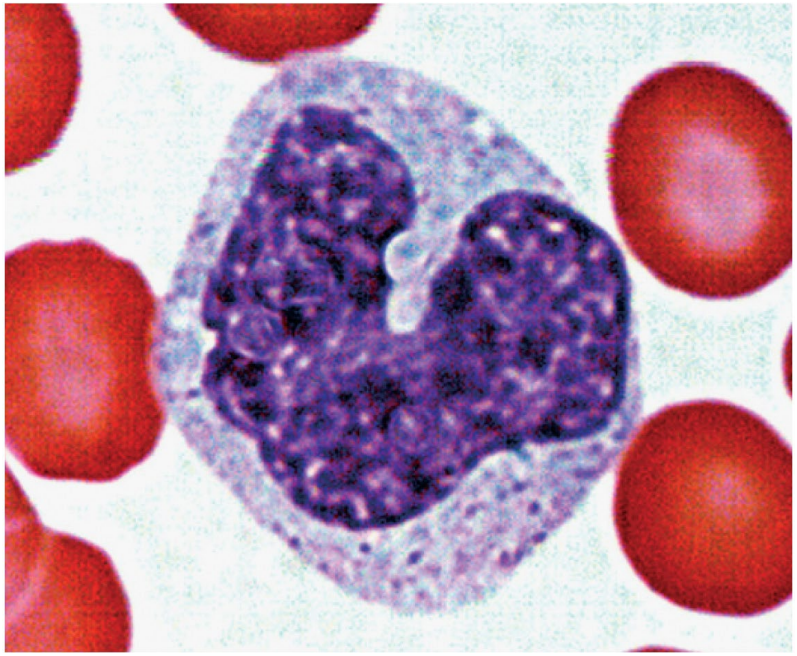


Lymphocyte

10 µm



Monocyte

10 µm

Make Flash Cards for These Cells

Red Blood Corpuscles
Neutrophils
Eosinophils
Basophils
Mast Cells
Monocytes
Macrophage
T Cell
B Cells
Plasma Cells / Megakaryocytes
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 radicals

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 = enzyme).

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

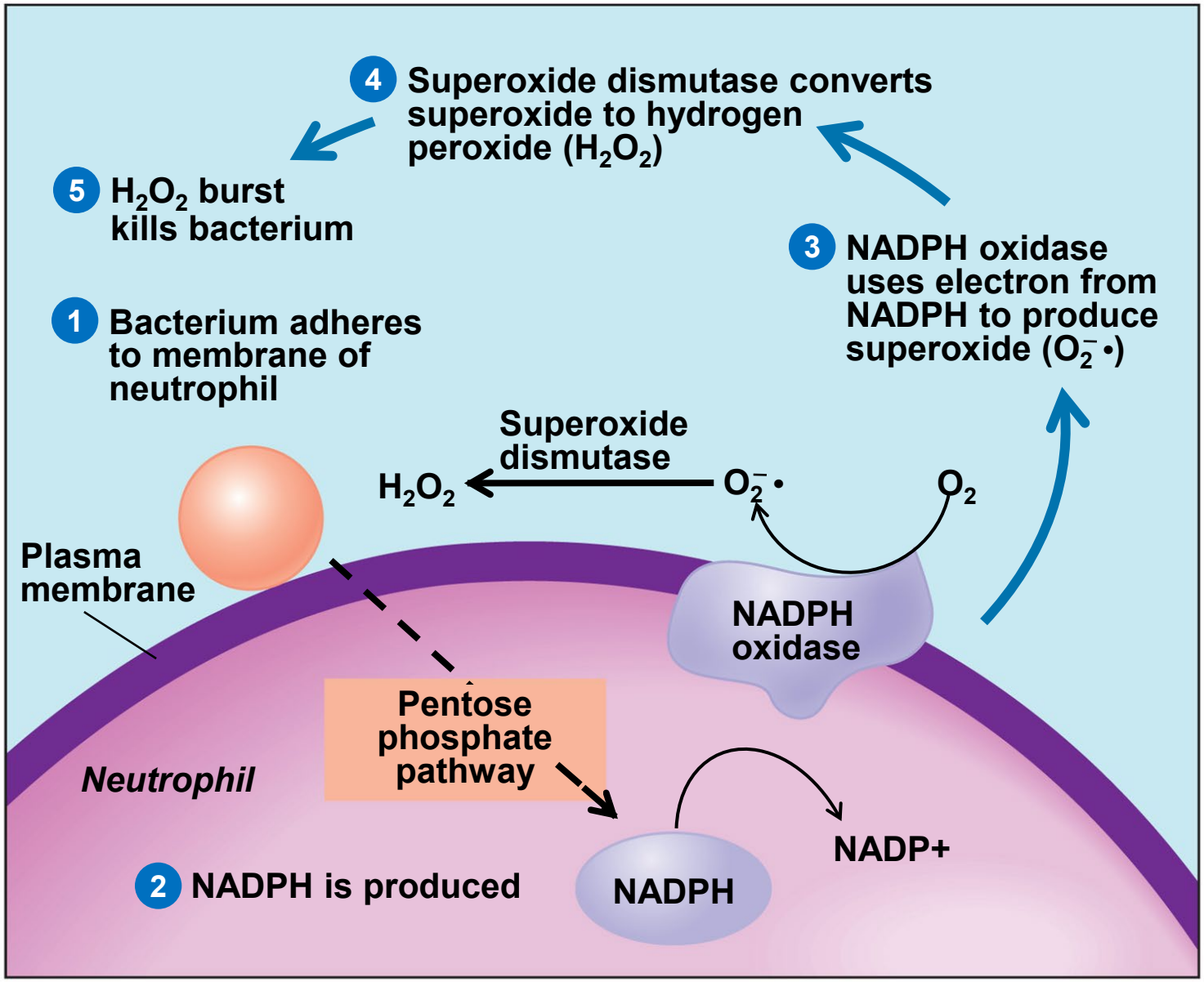
HOCl has a significant role as an antimicrobial agent but may also kill host cells.

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

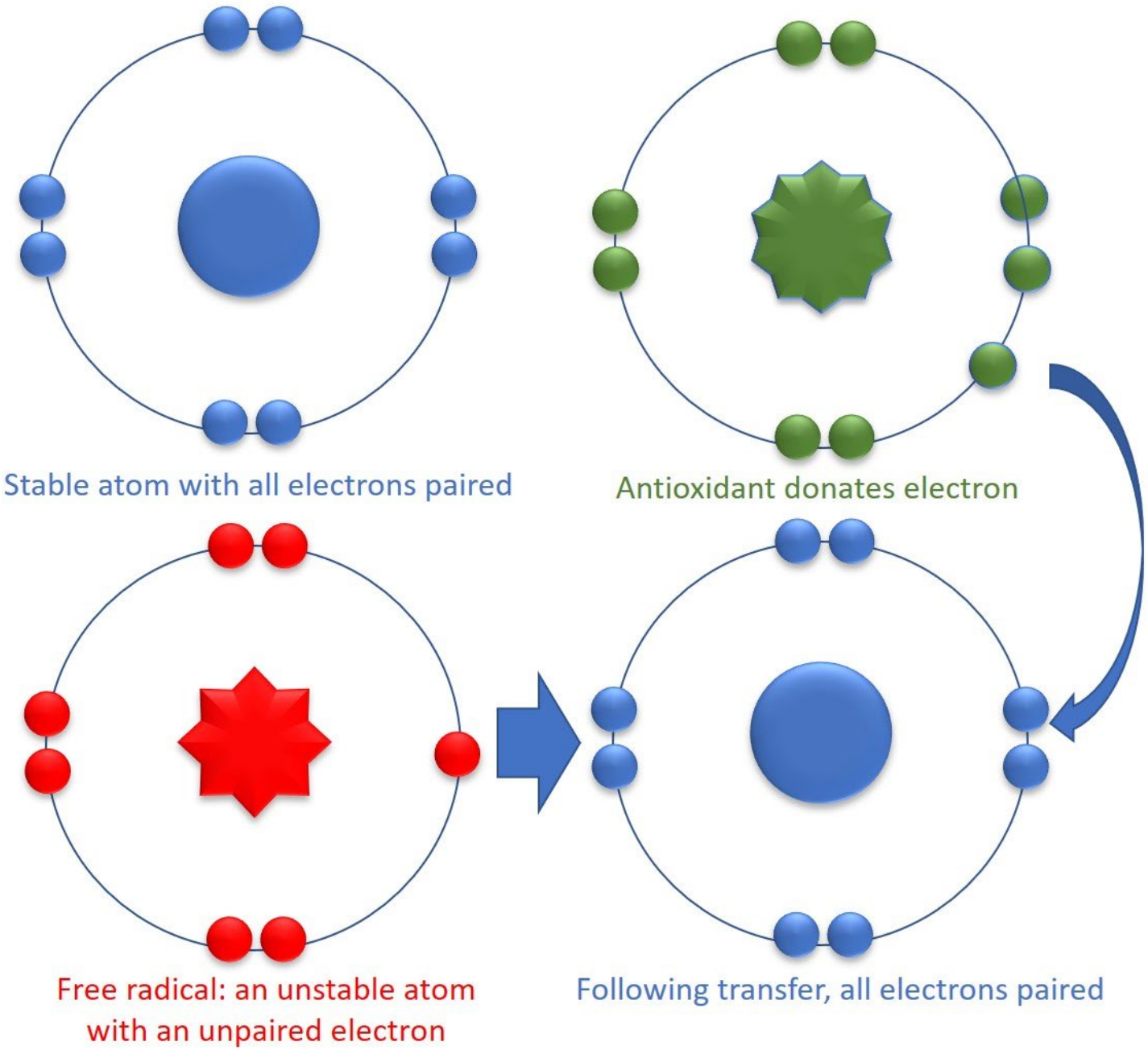
This is part of the “respiratory burst” mechanism to eliminate the bacterial infection.

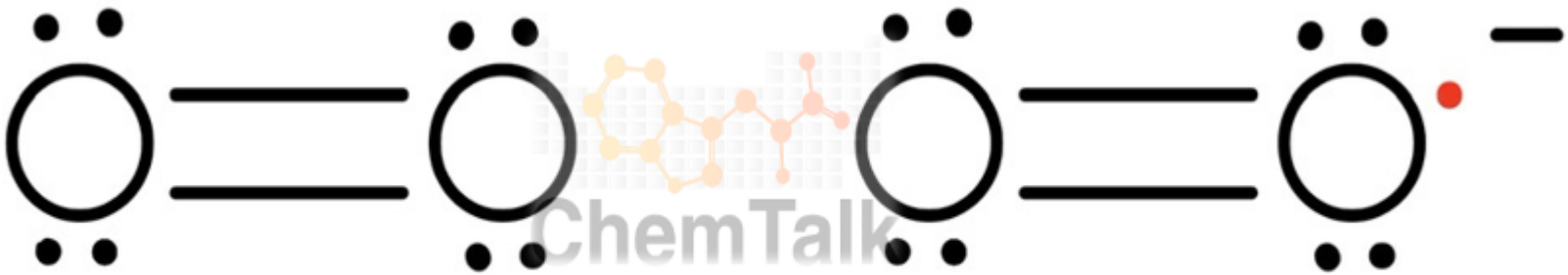
Eosinophils also have this ability and use it to kill parasites.

Oxidative Burst (Respiratory Burst)



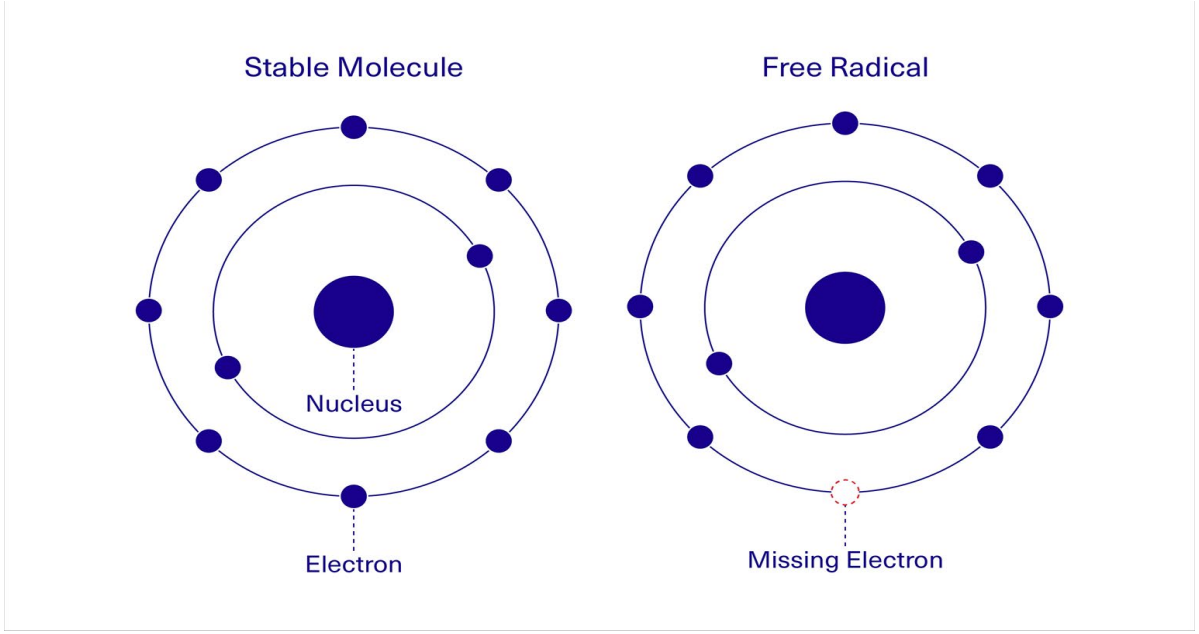
Free radicals, reactive oxygen species and antioxidants





Oxygen molecule (O_2)

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



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**

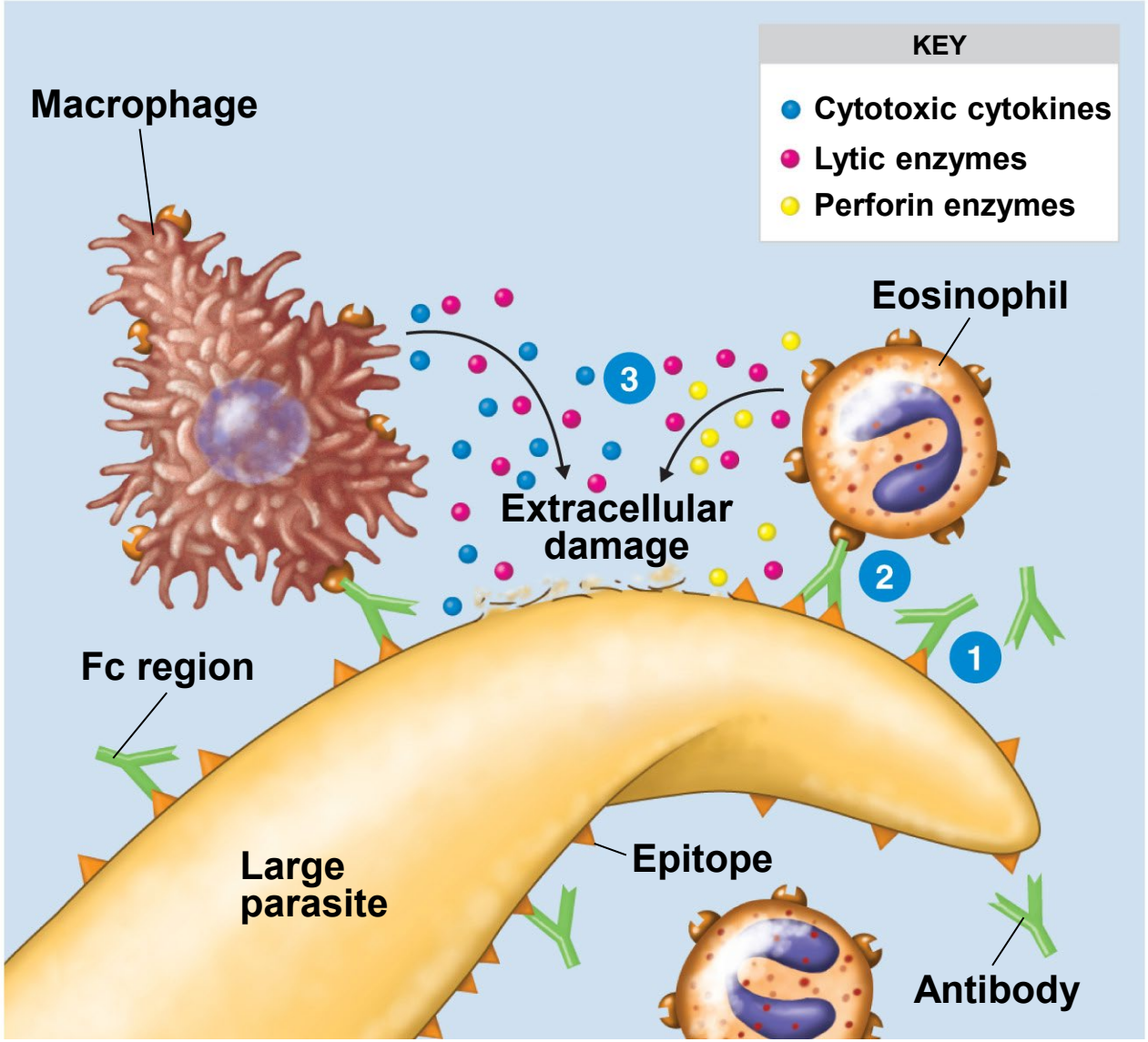
Phagocytosis of **antigen-antibody complexes**

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

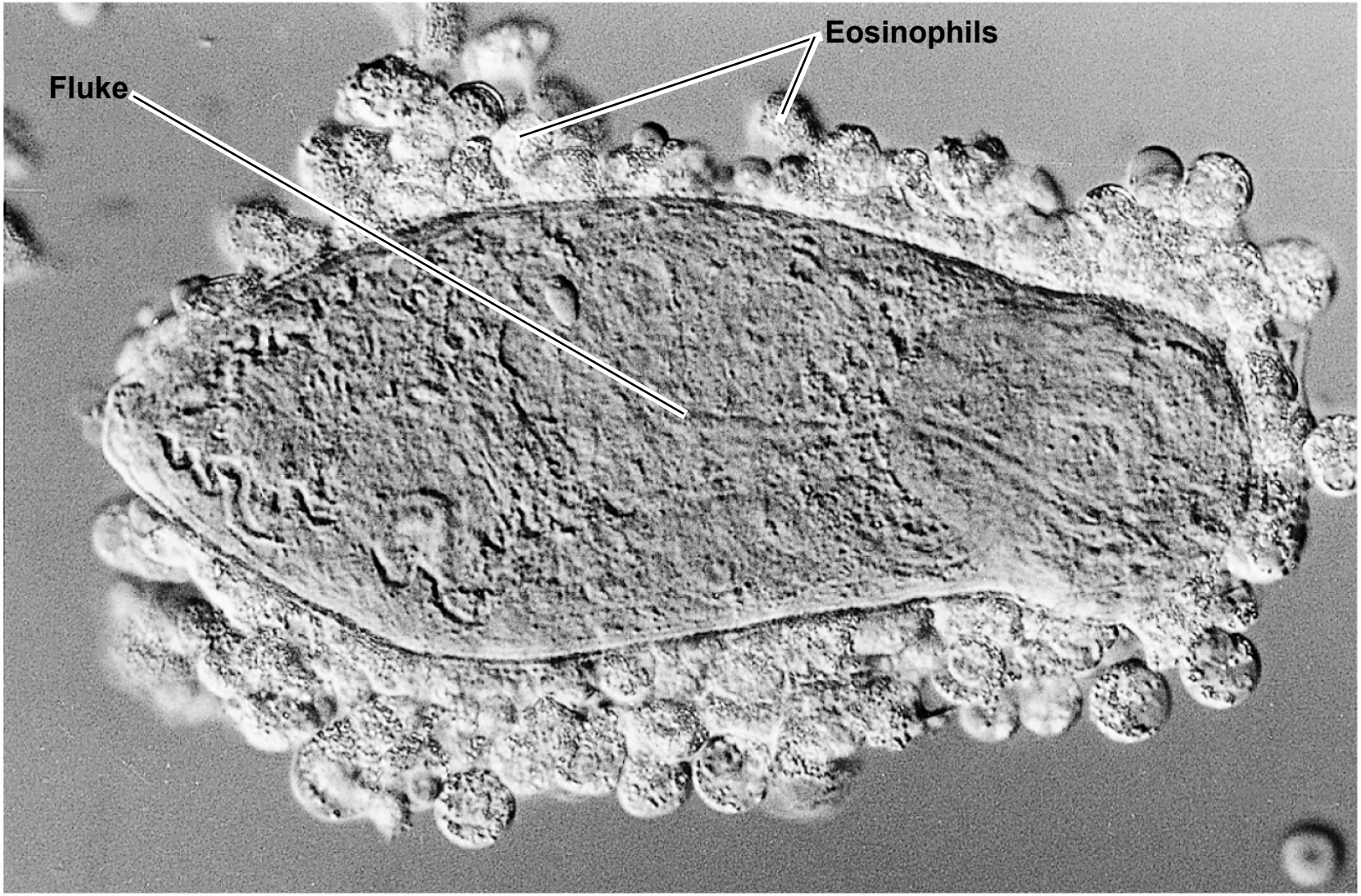
Highly concentrated in the mucous membranes (Why?)

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

Basophils 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

Antibodies render bacterial harmless and tag them for destruction

IgE will also attach to basophils' plasma membrane as a 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

This antibody now becomes a surface receptor for similar first exposure antigen!

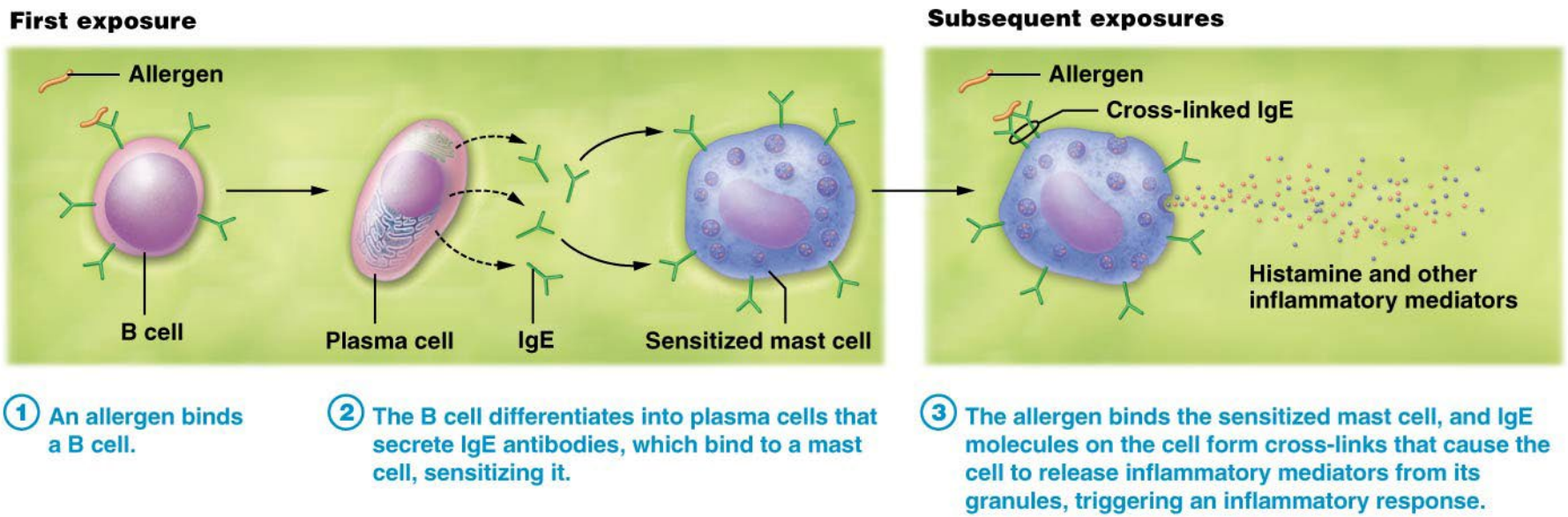
After second exposure to similar antigen, --- mast cells release histamine and heparin

Histamine (vasodilator) // speeds flow of blood to an injured area

Heparin (anticoagulant) // promotes the mobility of other WBCs in the area // lack of clotting allows other WBC to enter area

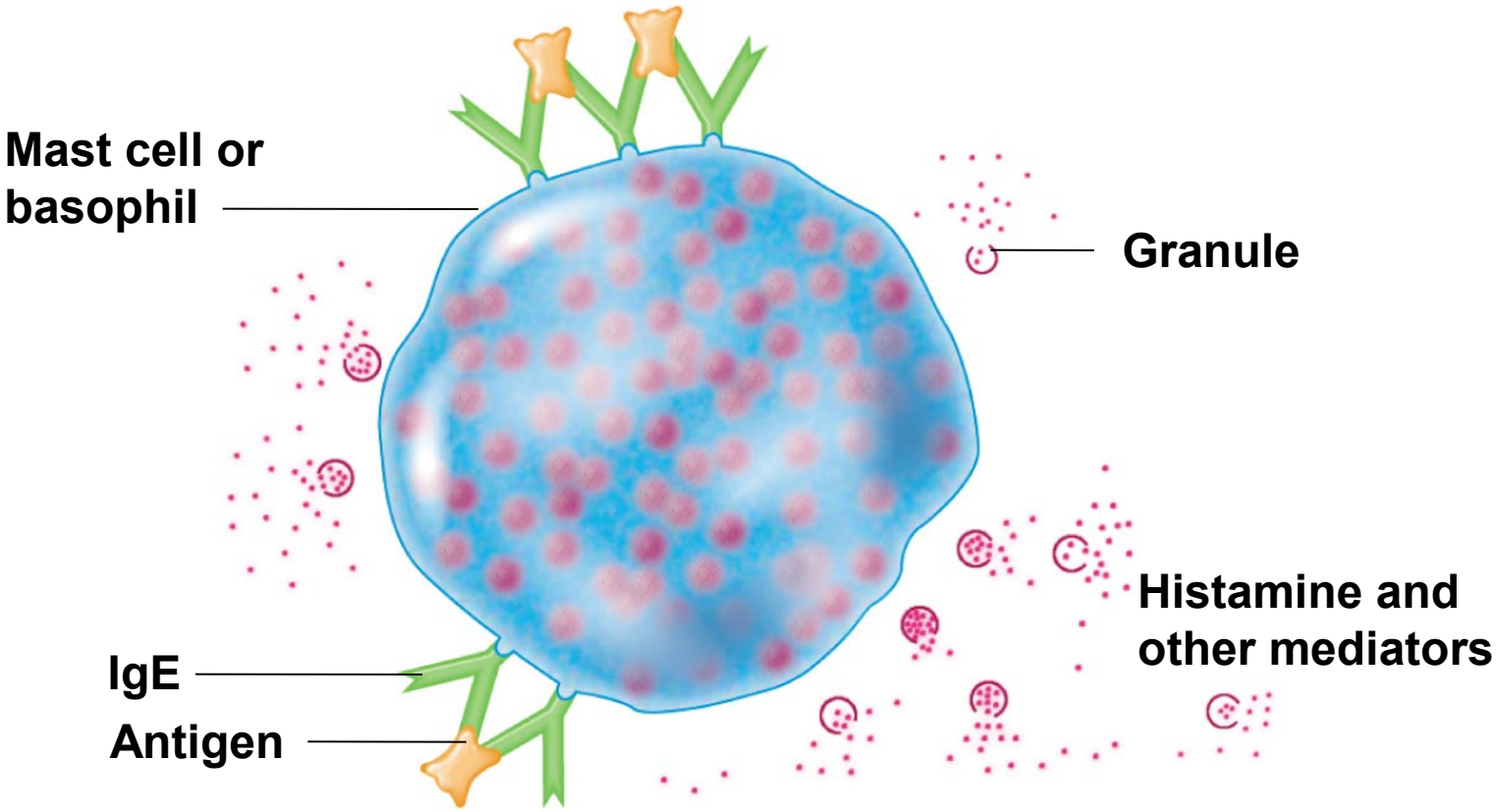
Basophils Become Mast Cells After They Acquire IgE "Receptors"

(Type I hypersensitivity response.)



Note: Basophils are in the blood / When basophils migrate into tissue space then they are called mast cells and mast cells attached to collagen fibers of the 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 // capture bacteria and deliver them to lymph nodes / antigen present cell
- Macrophage cells - phagocytotic and antigen presenting cell

Monocytes Morph Into Macrophage and Dendrictic Cells

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

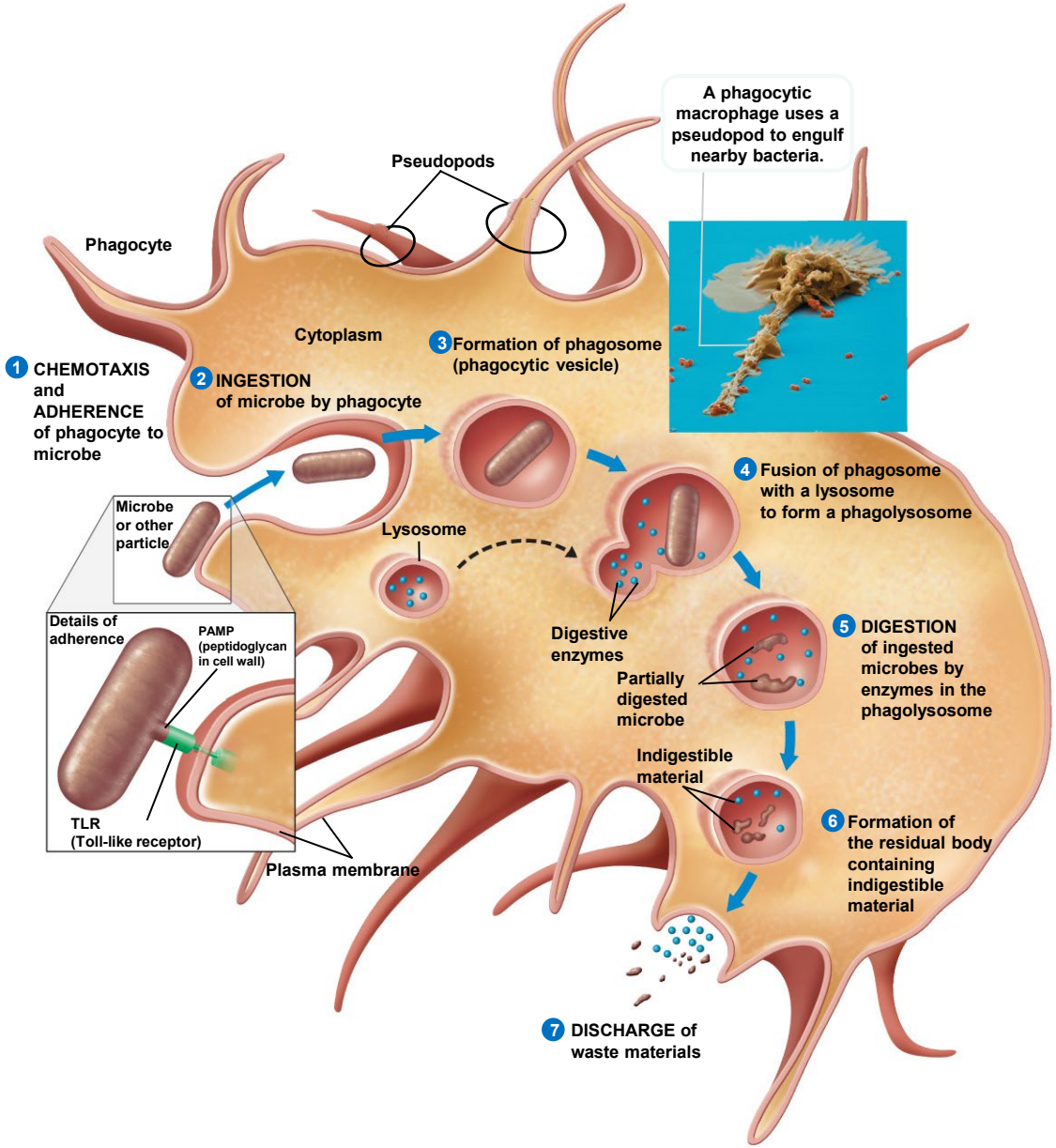
Macrophage are active in phagocytosis // engulfing pathogens and debris // 25% of their cell volume daily

Nicknamed the **"garbage collector"** // the cells "garbage disposal" system // recycle macromolecules

Also "present antigens" to activate immune cells

Macrophage are **antigen presenting cells** (APCs)

The Phases of Phagocytosis.



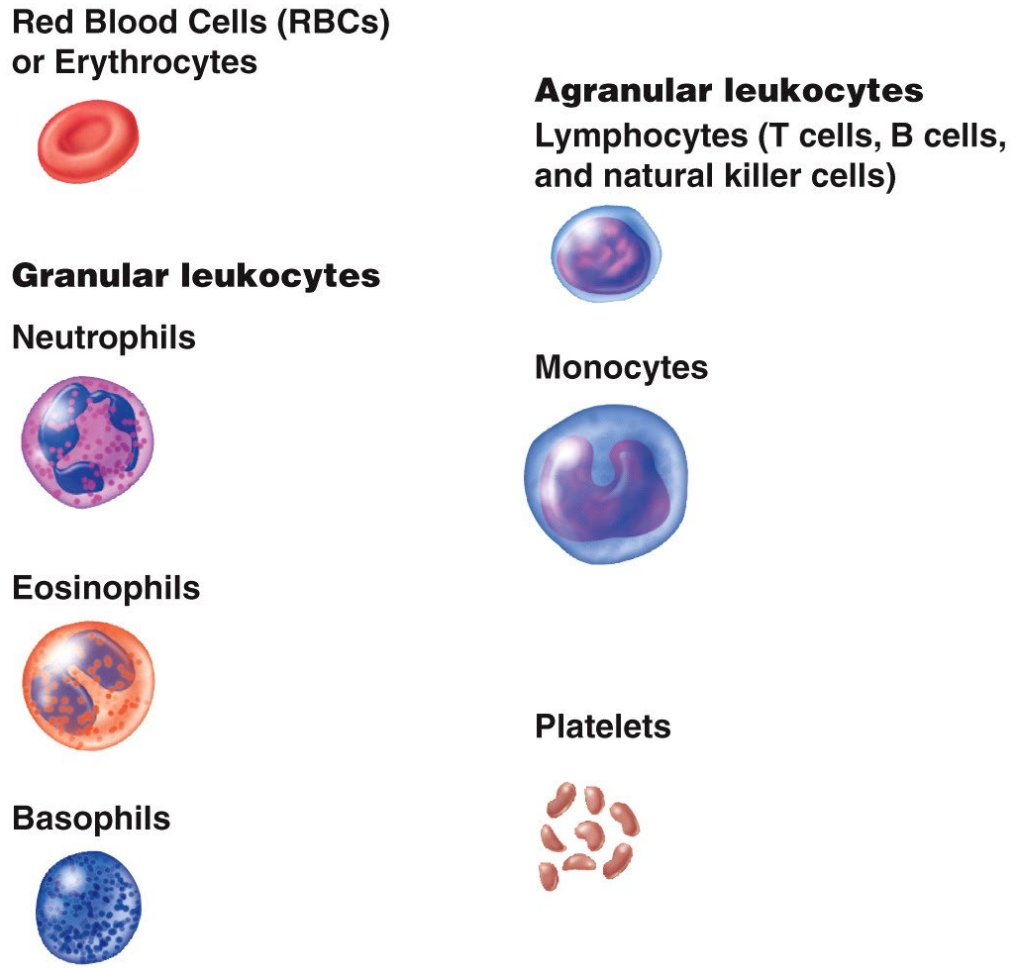
Platelets

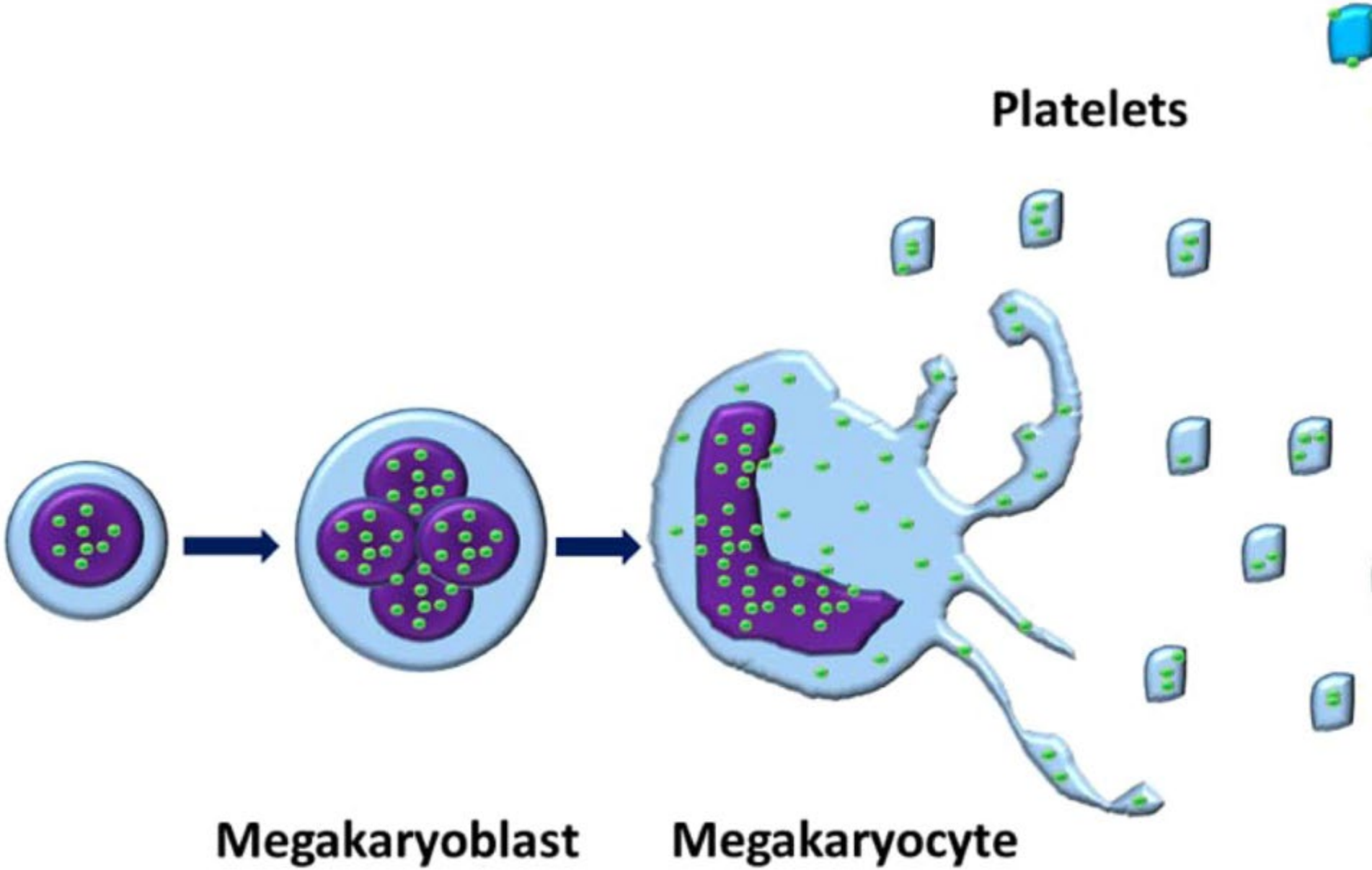
Platelets are part of the myeloid tissue but not a cell.

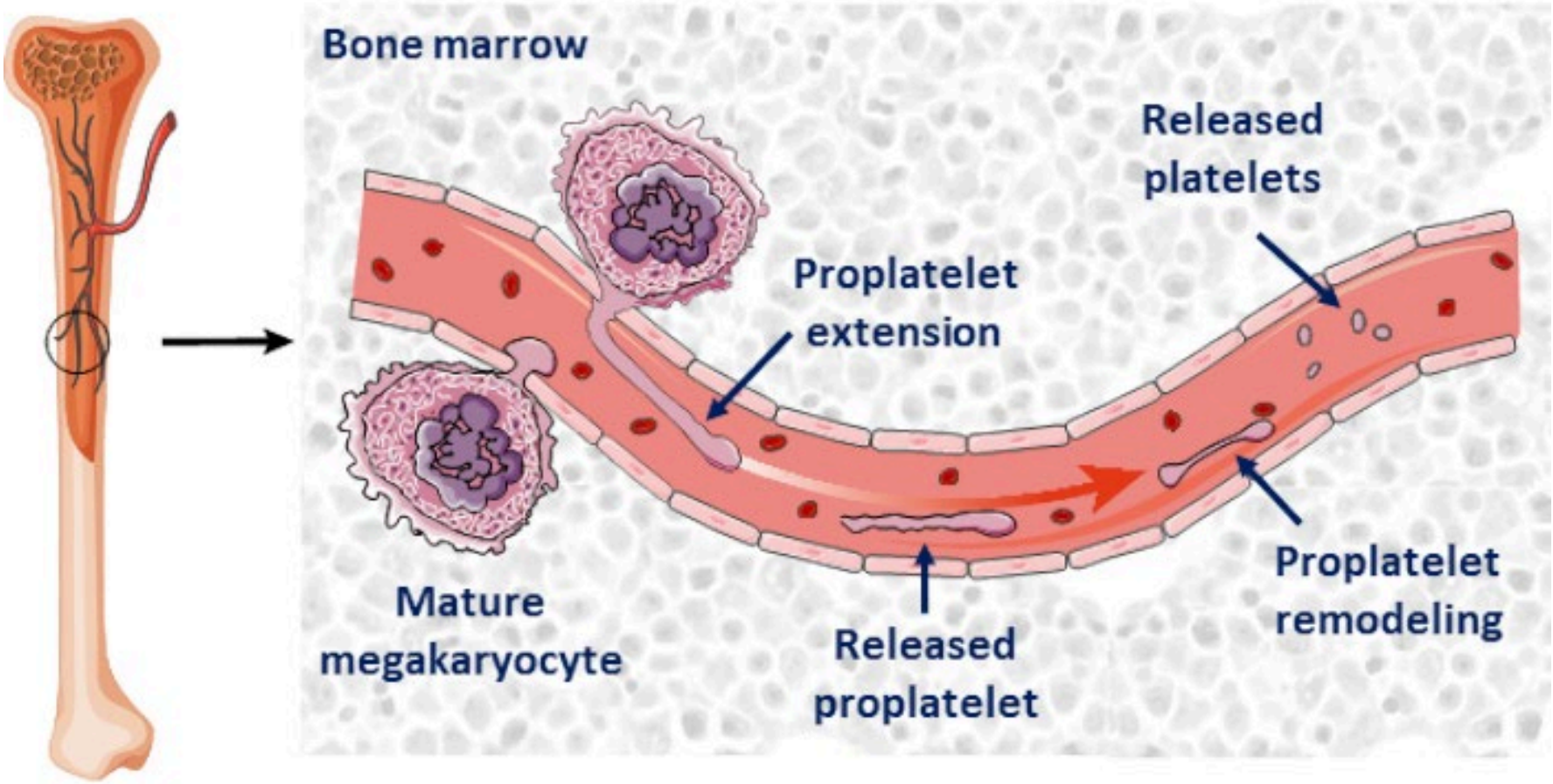
Platelets contain cytoplasm surrounded by the plasma membrane of megakaryocytes as small packets are pinched off

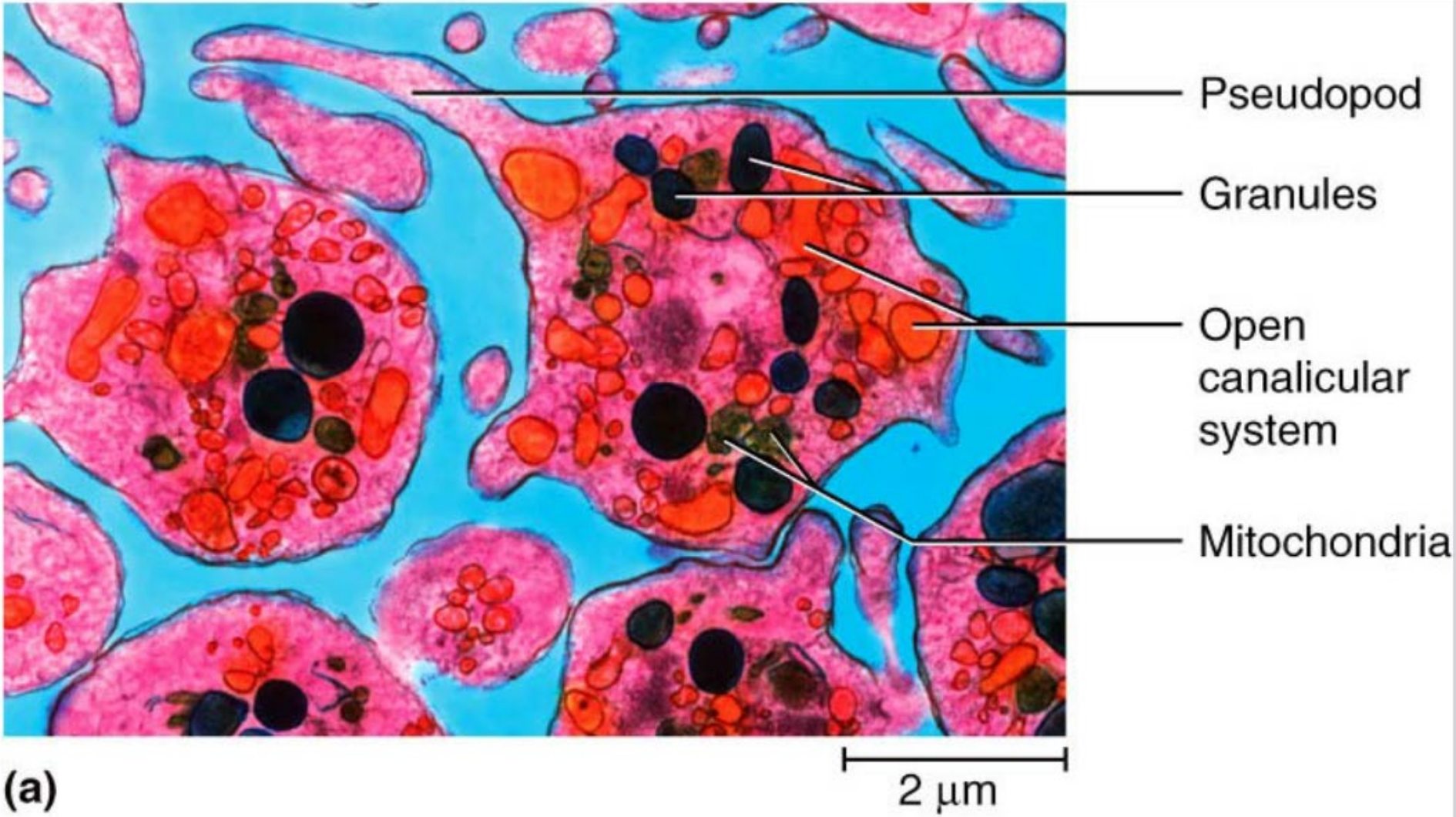
Megakaryocytes are only found in the red bone marrow.

Platelets play a critical role in hemostasis. We will cover the structure and function of platelets when we cover hemostasis.




Platelets
Megakaryoblast
Megakaryocyte


Bone marrow
Released platelets
Proplatelet extension
Mature megakaryocyte
Released proplatelet
Proplatelet remodeling



Transmission Electron Micrograph (TEM) of platelets. Within a platelet plug the platelet "streams" its plasma membranes as pseudopods. These pseudopods reach out and "grab" fibrin strands then pull back. This "tightens" the platelet plug and helps to stop the bleeding. After this happens, in a superficial wound, you can see an almost clear fluid (serum) being forced out of the platelet plug.

The Agranulocyte (T, B, NK)

Lymphocyte T cells (cytotoxic and helper)

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 (cTc) come from the lymphocyte cell line

cTc 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 and B cells

The Agranulocyte (T, B, NK)

Lymphocyte B cells

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

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

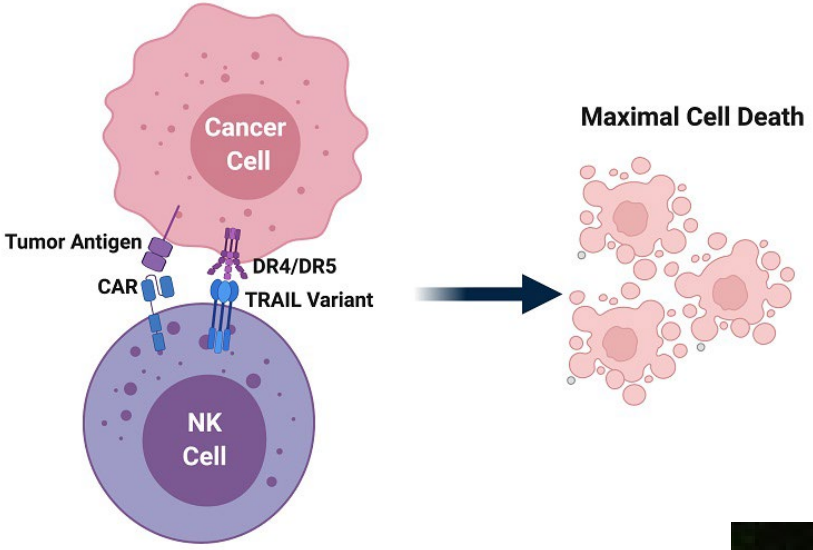
NK cells circulate in the blood and may move throughout the tissue spaces

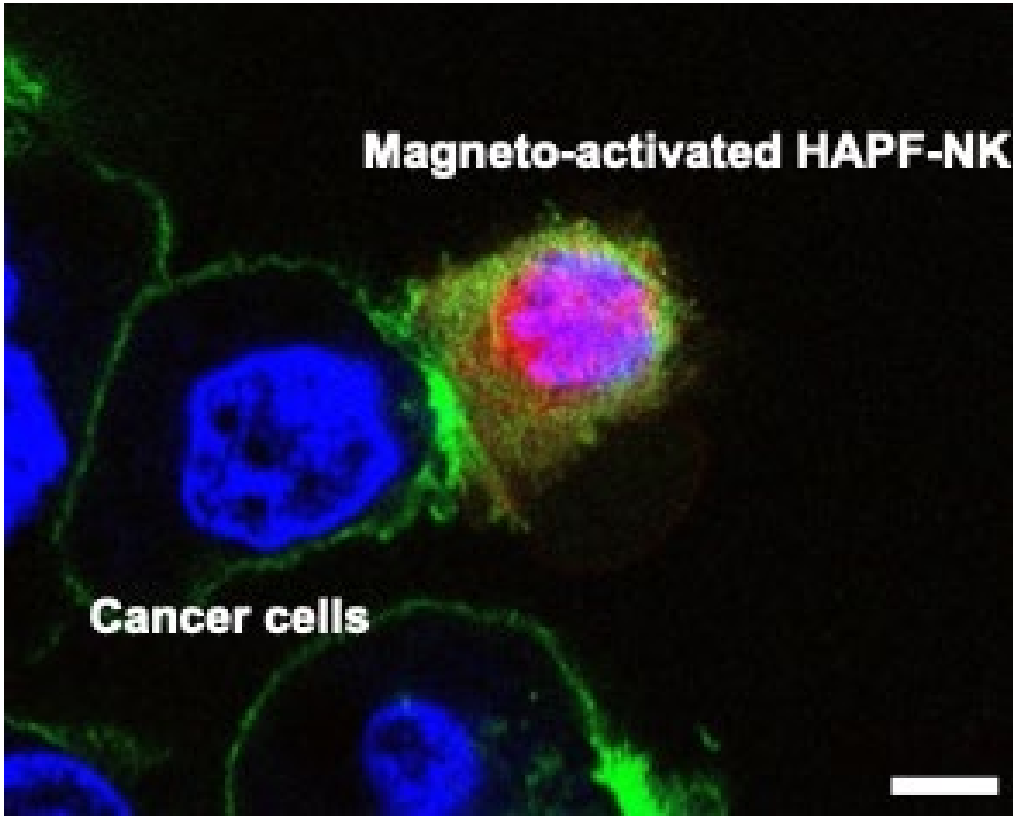
NK cells do not have to be activated

NK cells are responsible for “immune surveillance”

NK cells kill host cells infected with either cancer or virus

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


Cancer Cell
Tumor Antigen
CAR
DR4/DR5
TRAIL Variant
NK Cell
Maximal Cell Death


Magneto-activated HAPF-NK
Cancer cells

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

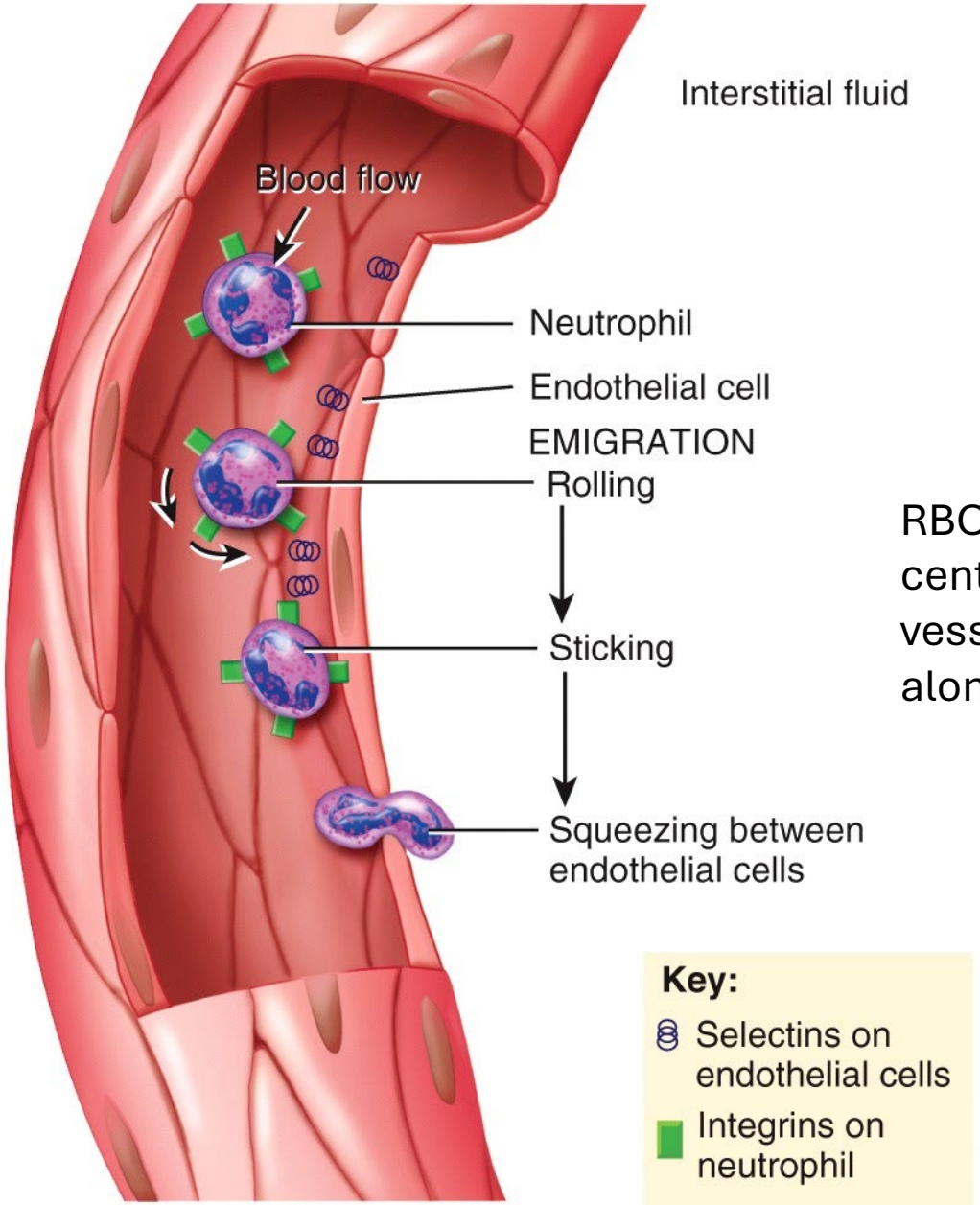
Stopped WBC stop then squeeze between endothelial cells to enter tissue space // called diapedeses

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

This is how neutrophil emigrate into interstitial space.



RBC circulate in the center of the blood vessel. Neutrophils roll along the endothelium.

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 extraordinarily high number of circulating leukocytes and their precursors

Myeloid leukemia – uncontrolled granulocyte production

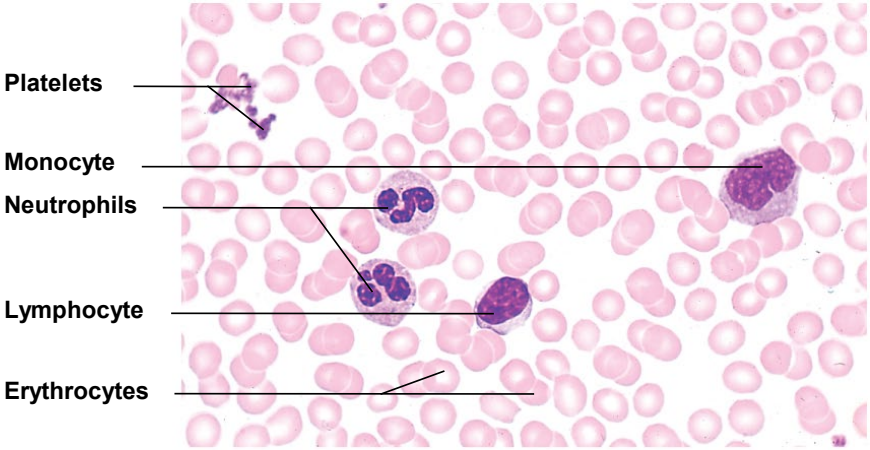
Lymphoid leukemia - uncontrolled lymphocyte or monocyte production

Acute leukemia – appears suddenly, progresses rapidly, death within months

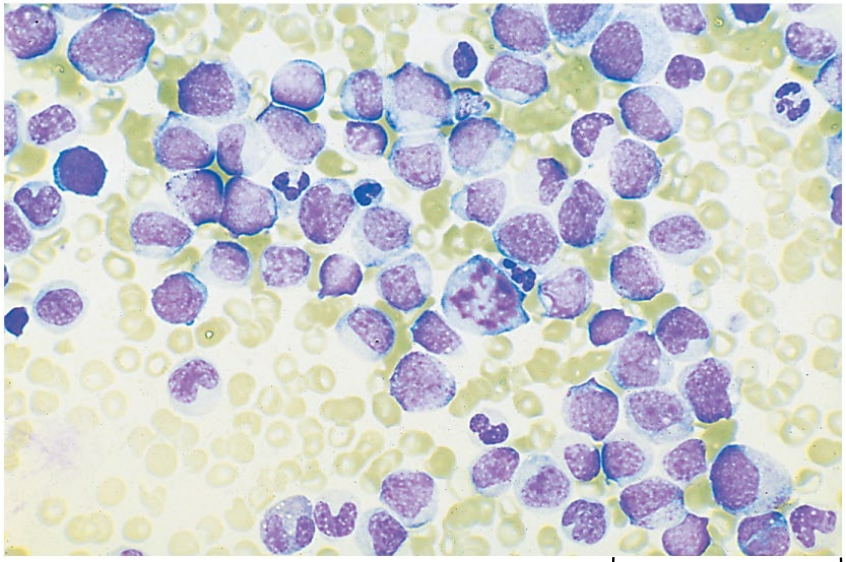
Chronic leukemia –undetected for months, survival time three years

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