# BLOOD PHYSIOLOGY

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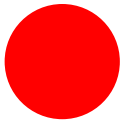
- Functions of Blood
- Composition of Blood
- Hematopoiesis
- Erythrocytes
- Leukocytes
- Thrombocytes
- Hemostasis
- Blood Grouping
- Blood Disorders

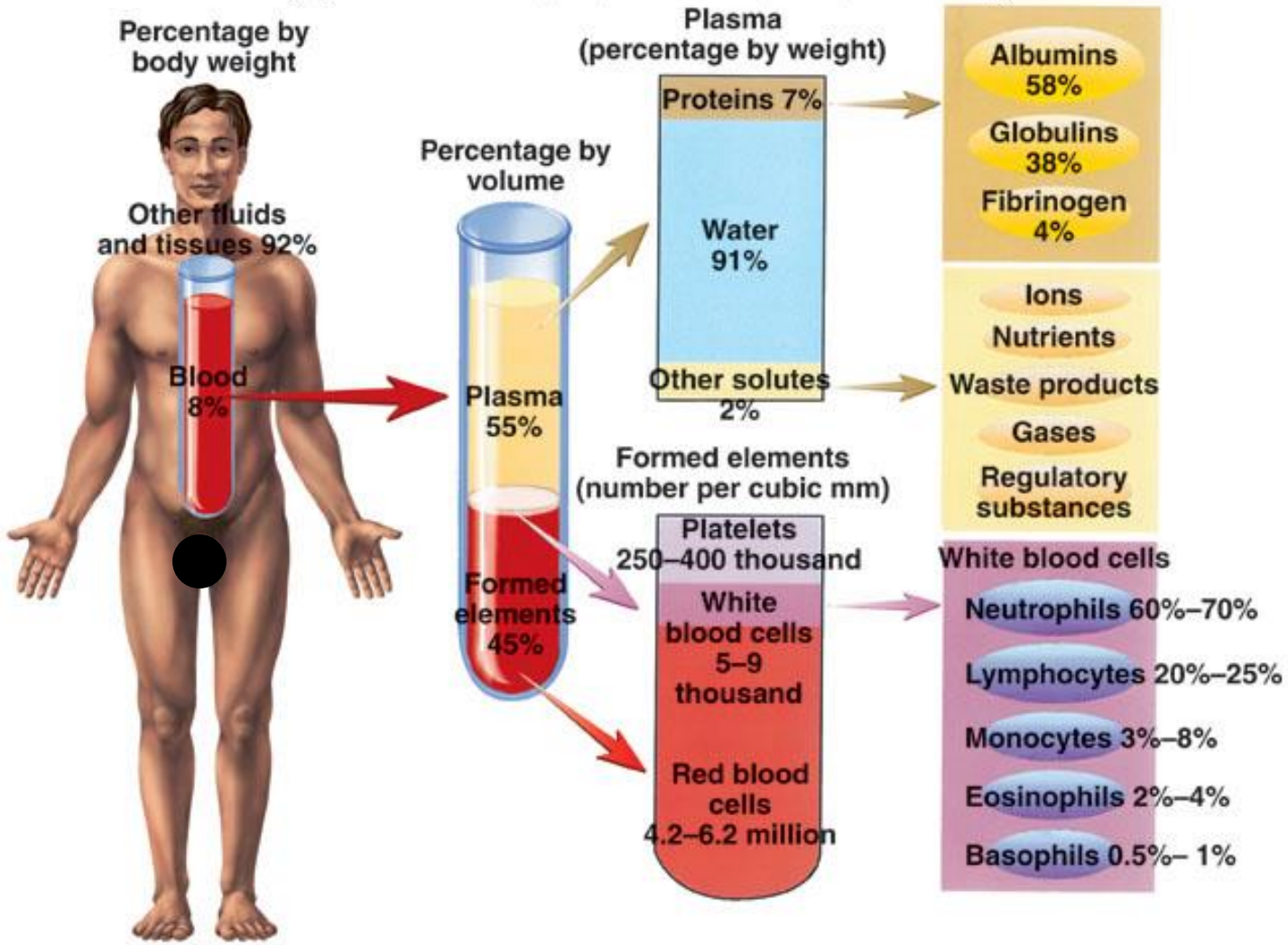
# Functions of Blood

- Transport of:
  - Gases, nutrients, waste products
  - Processed molecules
  - Regulatory molecules
- Regulation of pH and osmosis
- Maintenance of body temperature
- Protection against foreign substances
- Clot formation



# Composition of Blood





# Plasma

- Liquid part of blood
  - Pale yellow made up of 91% water, 9% other
- Colloid: Liquid containing suspended substances that don't settle out
  - Albumin: Important in regulation of water movement between tissues and blood
  - Globulins: Immune system or transport molecules
  - Fibrinogen: Responsible for formation of blood clots

# Formed Elements

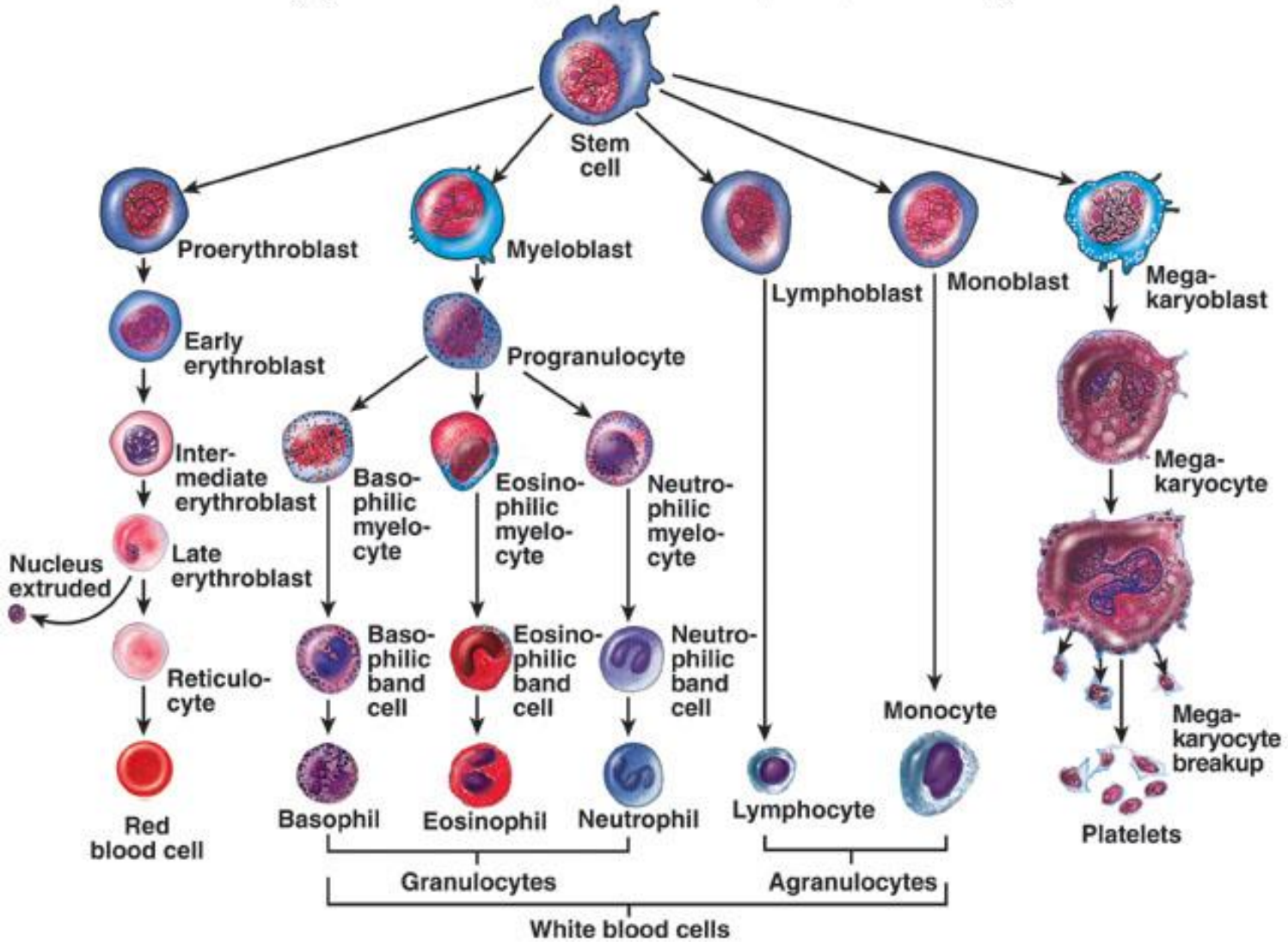
- Red blood cells (erythrocytes)
- White blood cells (leukocytes)
  - Granulocytes
    - Neutrophils
    - Eosinophils
    - Basophils
  - Agranulocytes
    - Lymphocytes
    - Monocytes
- Platelets (thrombocytes)

# Production of Formed Elements

- Hematopoiesis or hemopoiesis: Process of blood cell production
- Stem cells: All formed elements derived from single population
  - Proerythroblasts: Develop into red blood cells
  - Myeloblasts: Develop into basophils, neutrophils, eosinophils
  - Lymphoblasts: Develop into lymphocytes
  - Monoblasts: Develop into monocytes
  - Megakaryoblasts: Develop into platelets

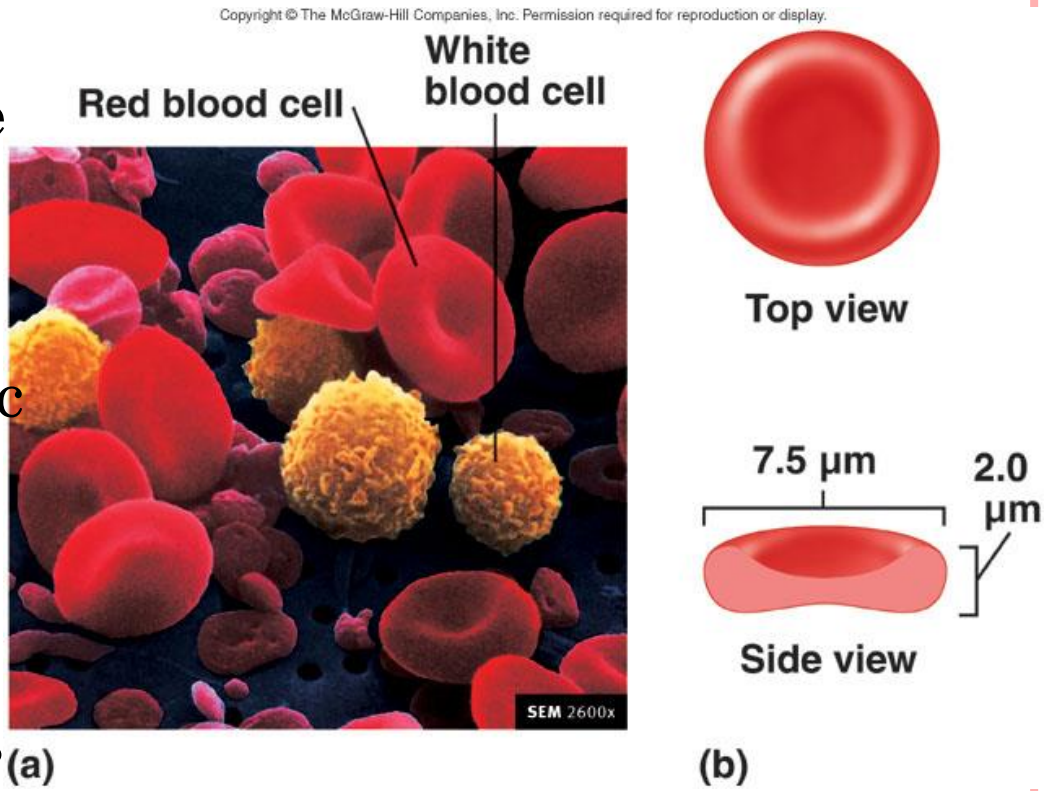
# HEMATOPOIESIS





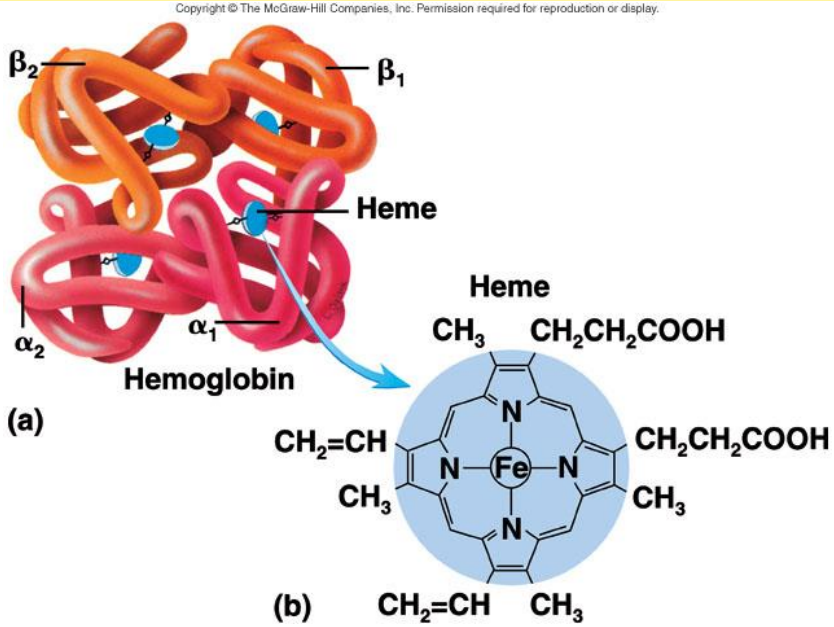
# ERYTHROCYTES

- Structure
  - Biconcave, anucleate
- Components
  - Hemoglobin
  - Lipids, ATP, carbonic anhydrase
- Function
  - Transport oxygen from lungs to tissues and carbon dioxide from tissues to lungs



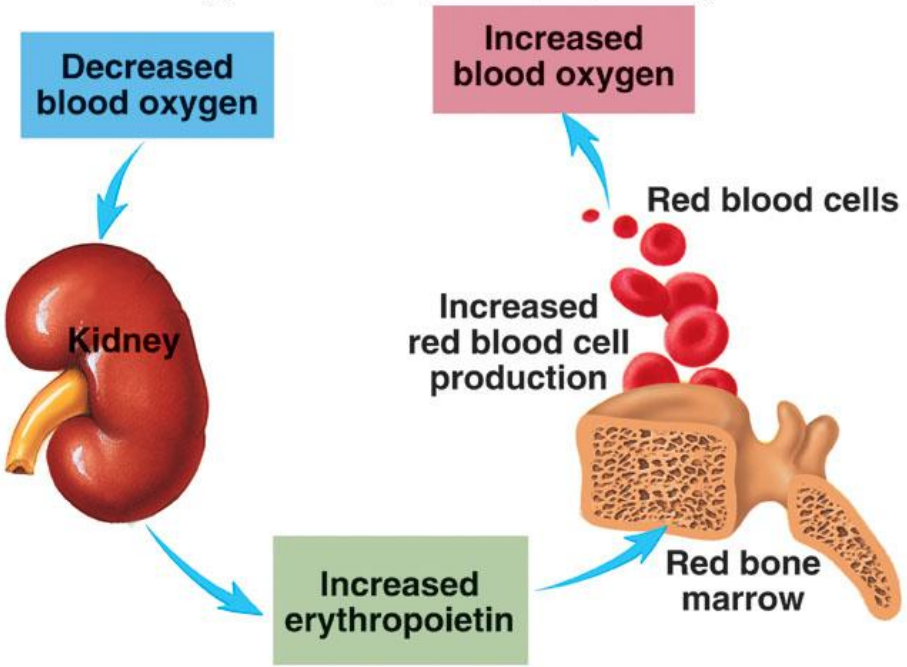
# HEMOGLOBIN






- Consists of:
  - 4 globin molecules: Transport carbon dioxide (carbonic anhydrase involved), nitric oxide
  - 4 heme molecules: Transport oxygen
    - Iron is required for oxygen transport

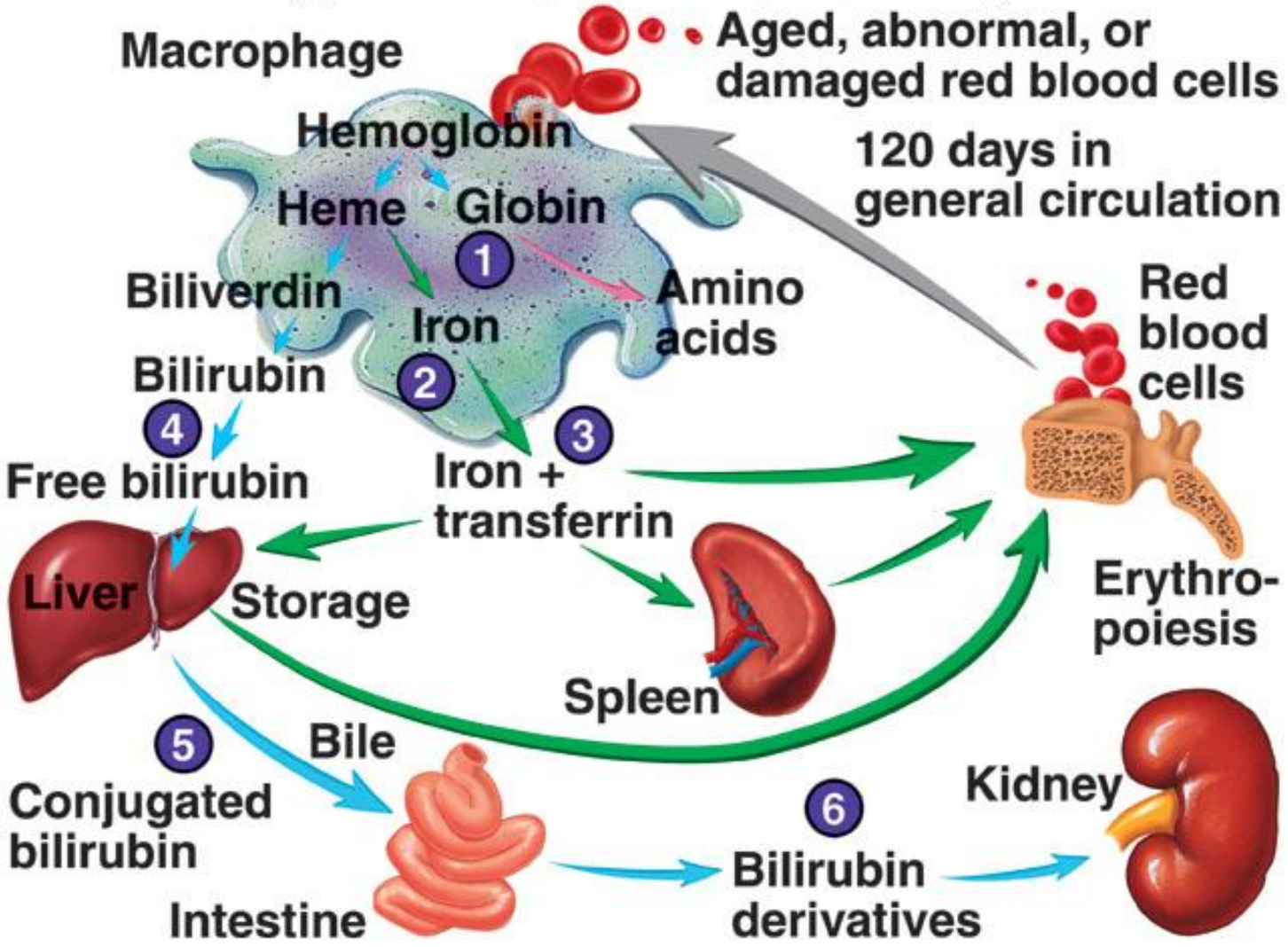
# ERYTHROPOIESIS




- Production of red blood cells
  - Stem cells ➡ proerythroblasts ➡ early erythroblasts ➡ intermediate ➡ late ➡ reticulocytes
- Erythropoietin: Hormone to stimulate RBC production

# Hemoglobin Breakdown



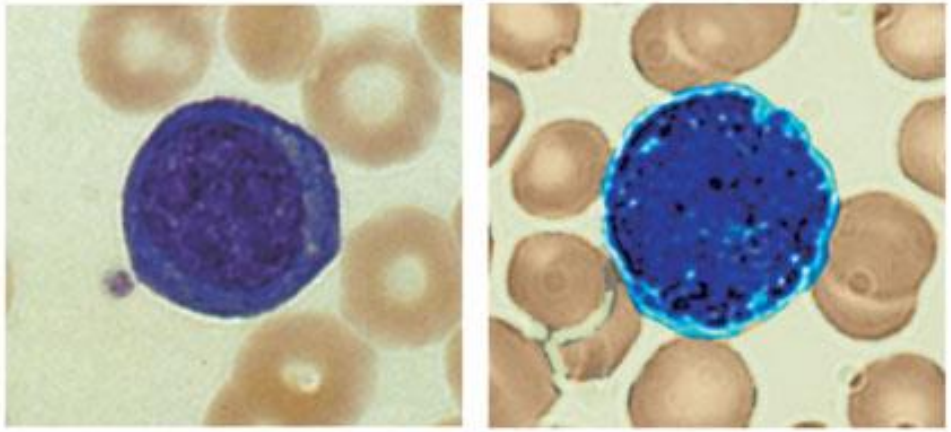


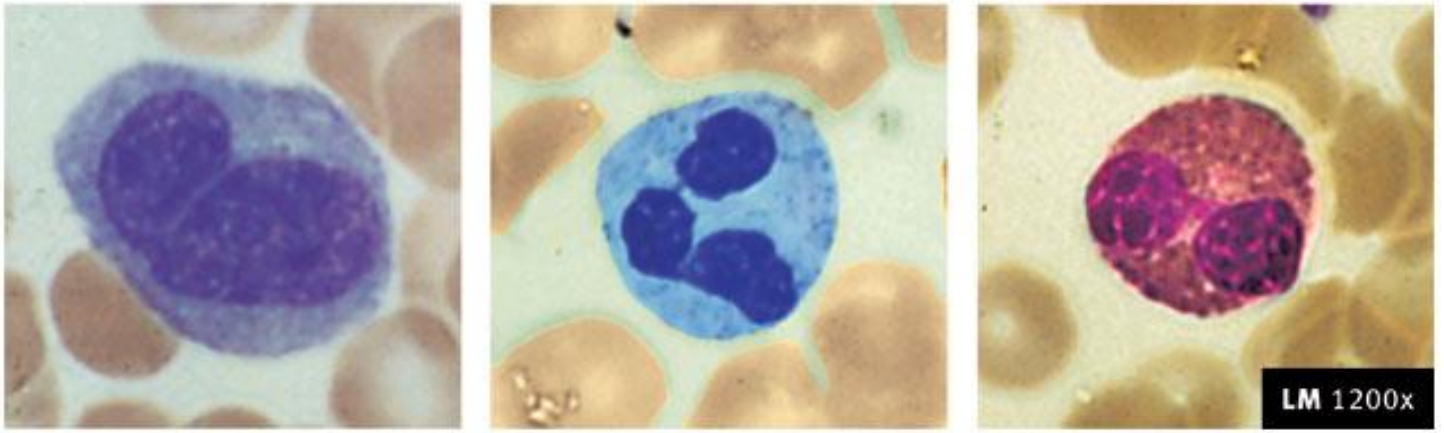
# LEUKOCYTES

- Protect body against microorganisms and remove dead cells and debris
- Types
  - Neutrophils: Most common; phagocytic cells destroy bacteria (60%)
  - Eosinophils: Detoxify chemicals; reduce inflammation (4%)
  - Basophils: Alergic reactions; Release histamine, heparin increase inflam. response (1%)
  - Lymphocytes: Immunity 2 types; b & t Cell types. IgG-infection, IgM-microbes, IgA-Resp & GI, IgE- Alergy, IgD-immune response
  - Monocytes: Become macrophages

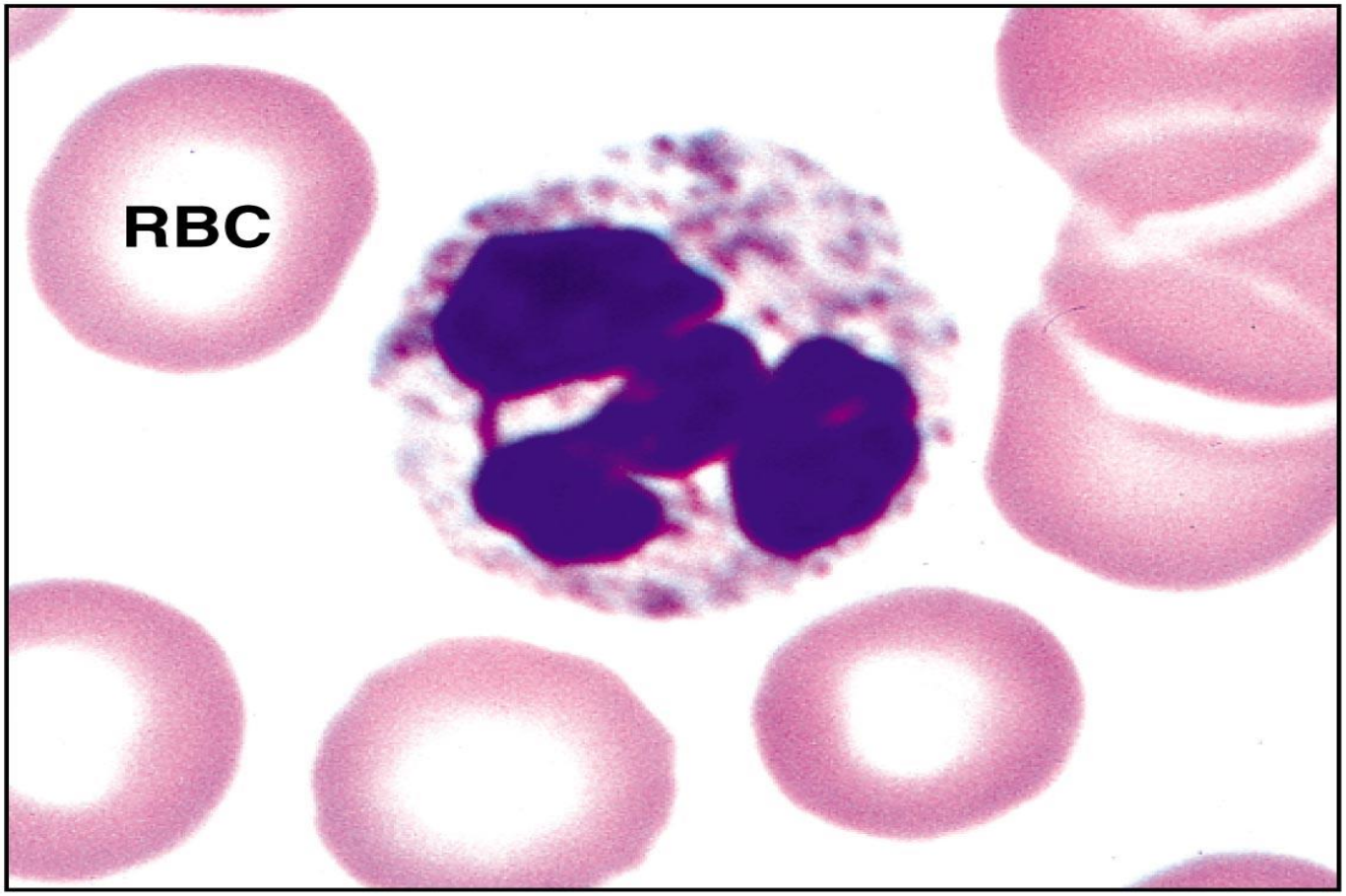
# LEUKOCYTES





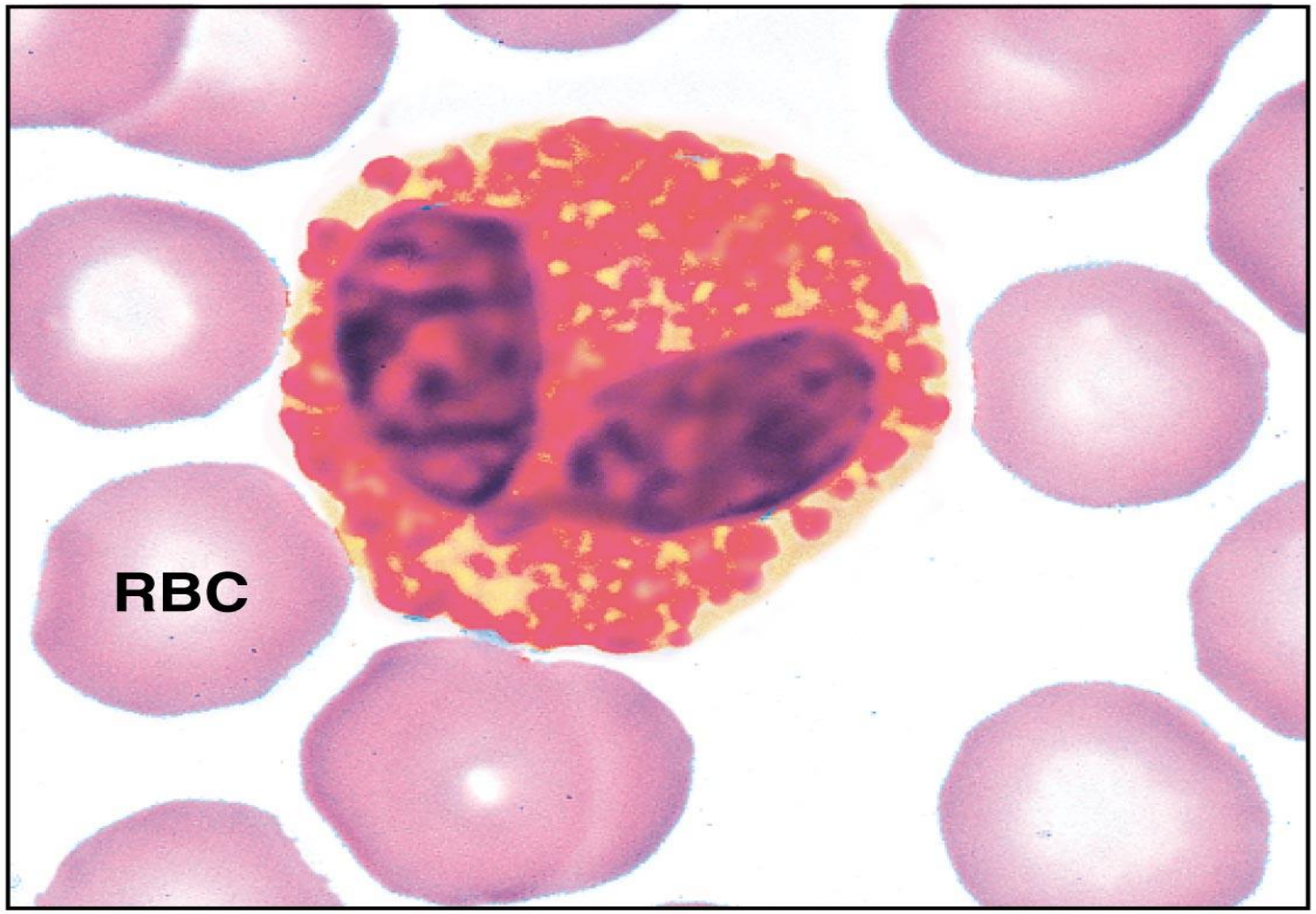


# LEUKOCYTES



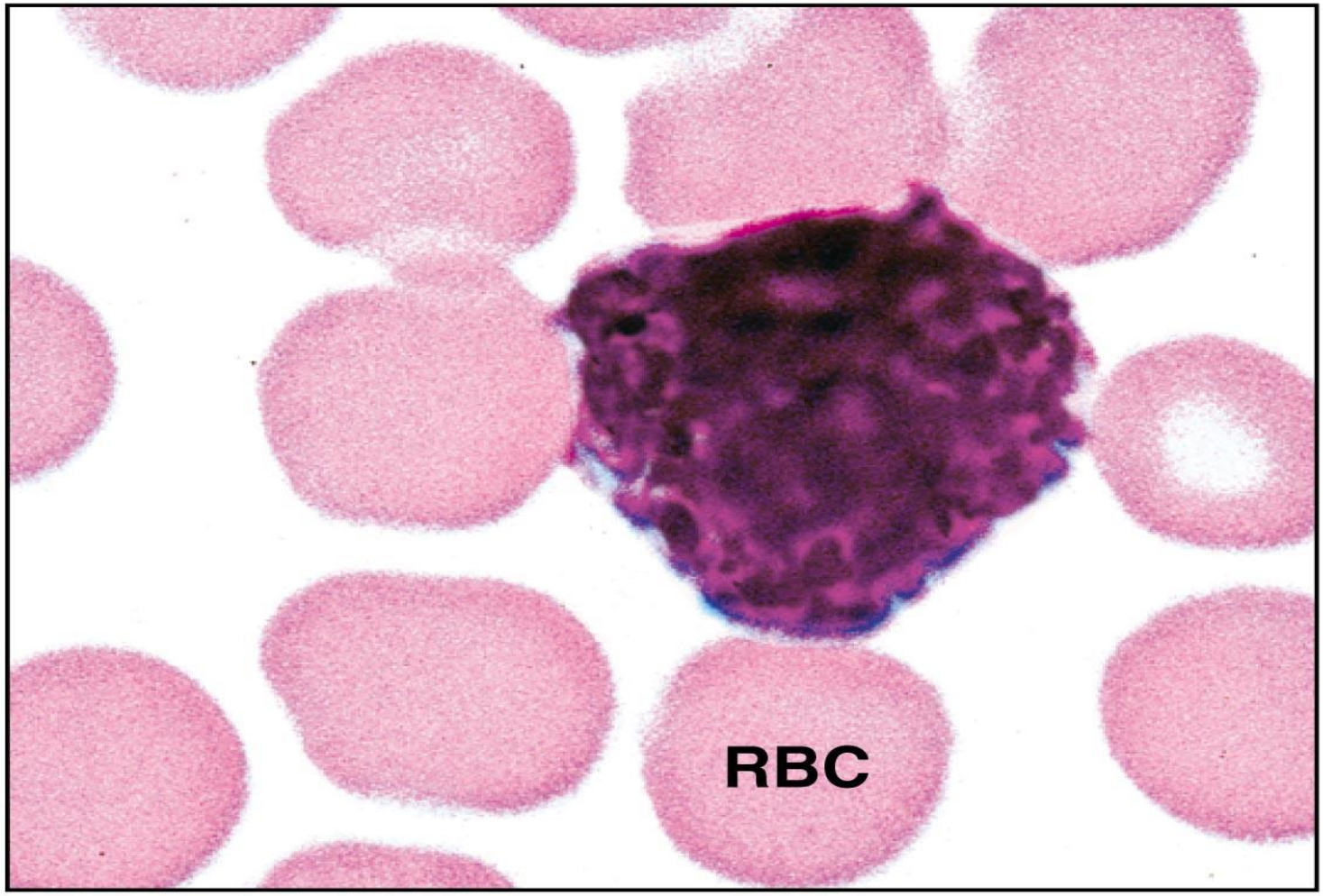

(a) Neutrophil

# LEUKOCYTES



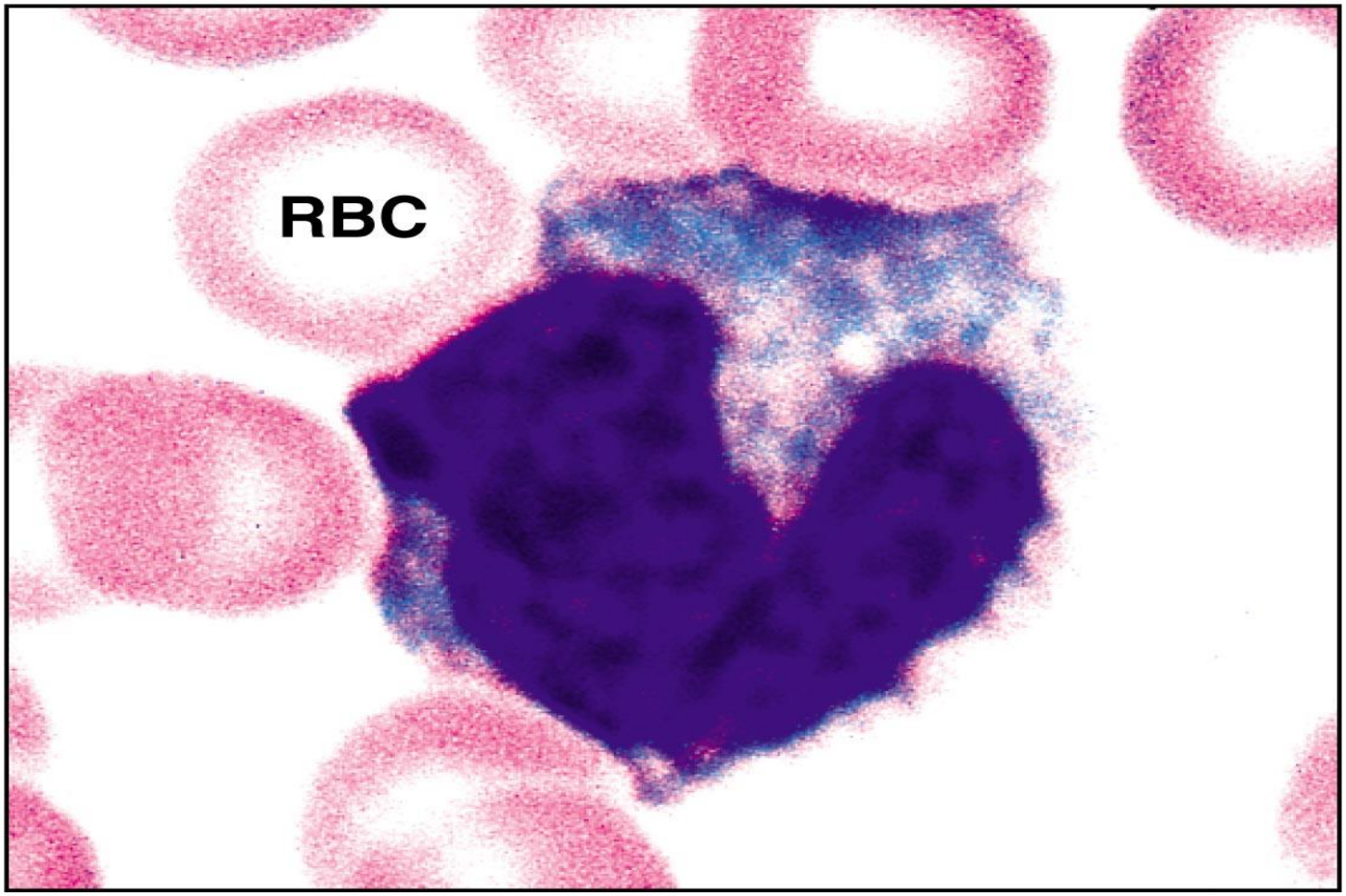

(b) Eosinophil

# LEUKOCYTES



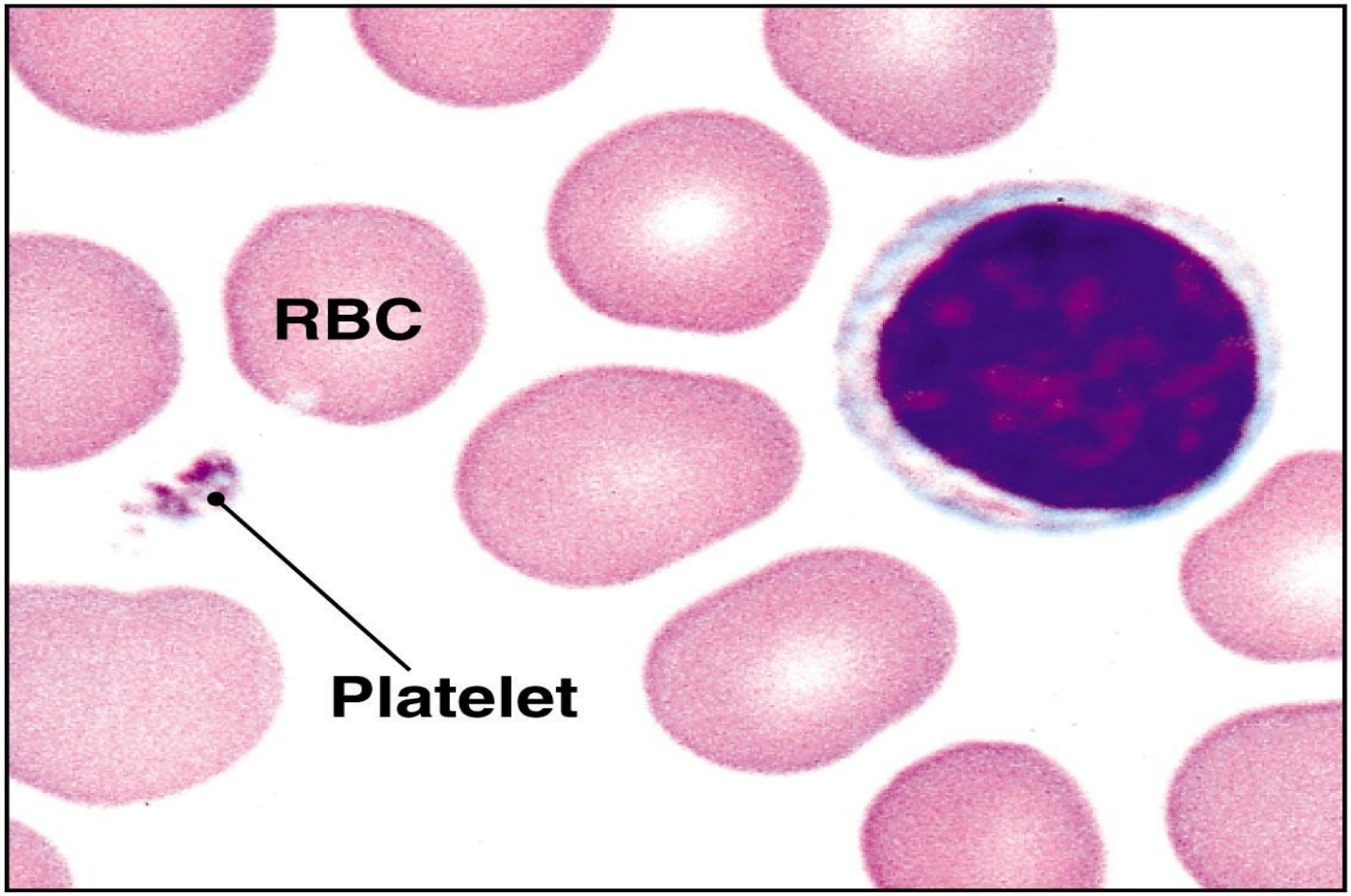

(c) Basophil

# LEUKOCYTES




(d) Monocyte

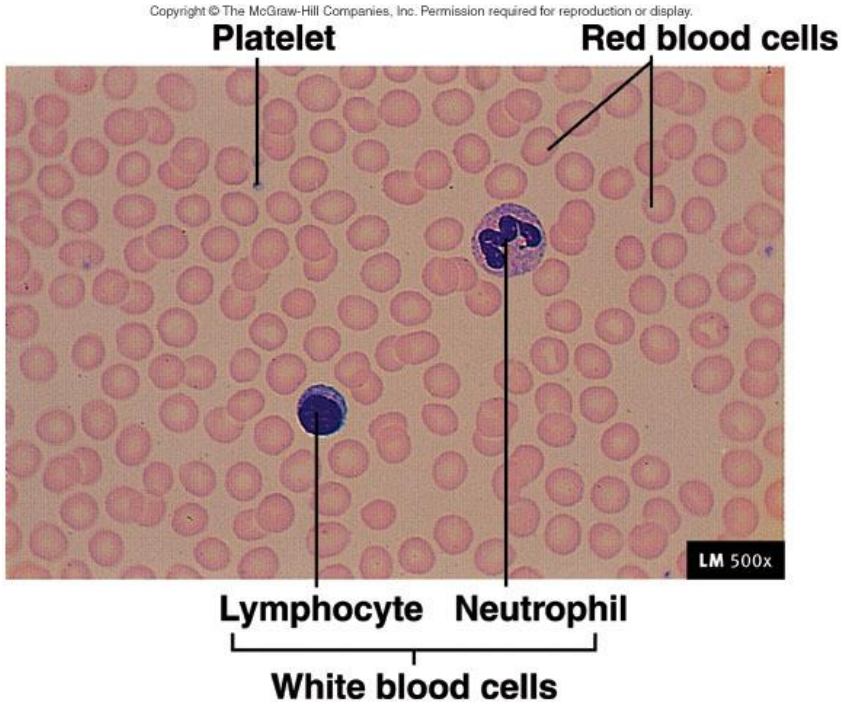
# LEUKOCYTES




(e) Lymphocyte

# Thrombocytes

- Cell fragments pinched off from megakaryocytes in red bone marrow
- Important in preventing blood loss
  - Platelet plugs
  - Promoting formation and contraction of clots

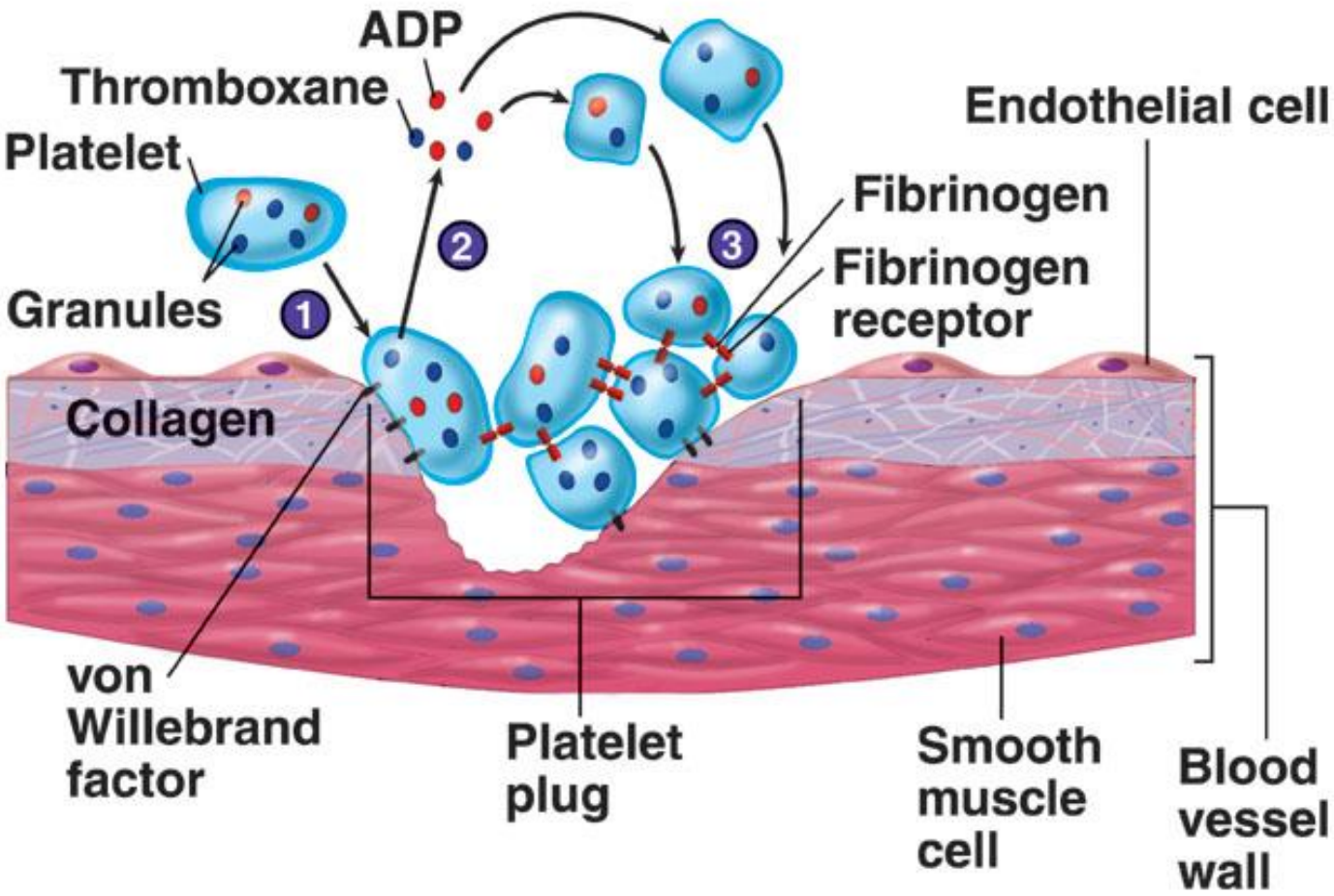


# HEMOSTASIS

- Arrest of bleeding
- Events preventing excessive blood loss
  - Vascular spasm: Vasoconstriction of damaged blood vessels
  - Platelet plug formation
  - Coagulation or blood clotting

# Platelet Plug Formation

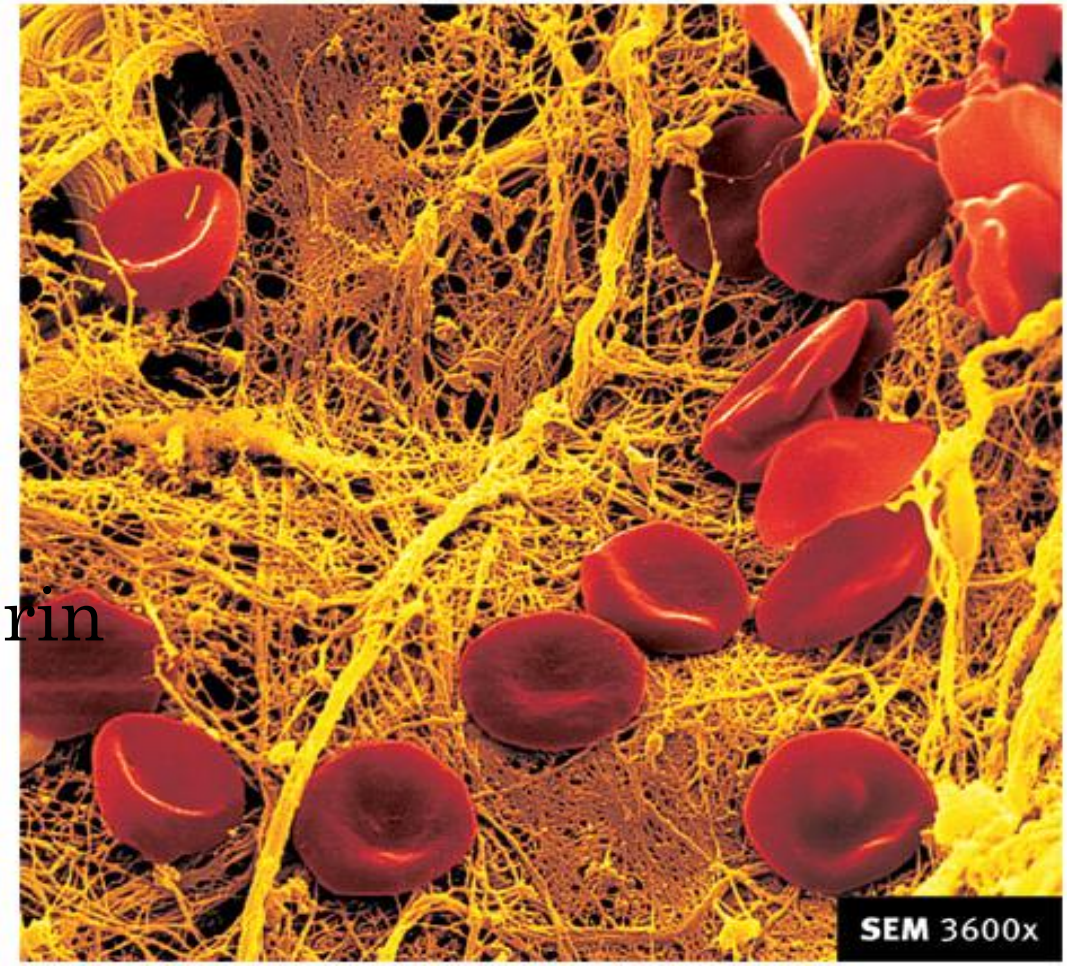




# Coagulation

- Stages
  - Activation of prothrombinase
  - Conversion of prothrombin to thrombin
  - Conversion of fibrinogen to fibrin
- Pathways
  - Extrinsic
  - Intrinsic





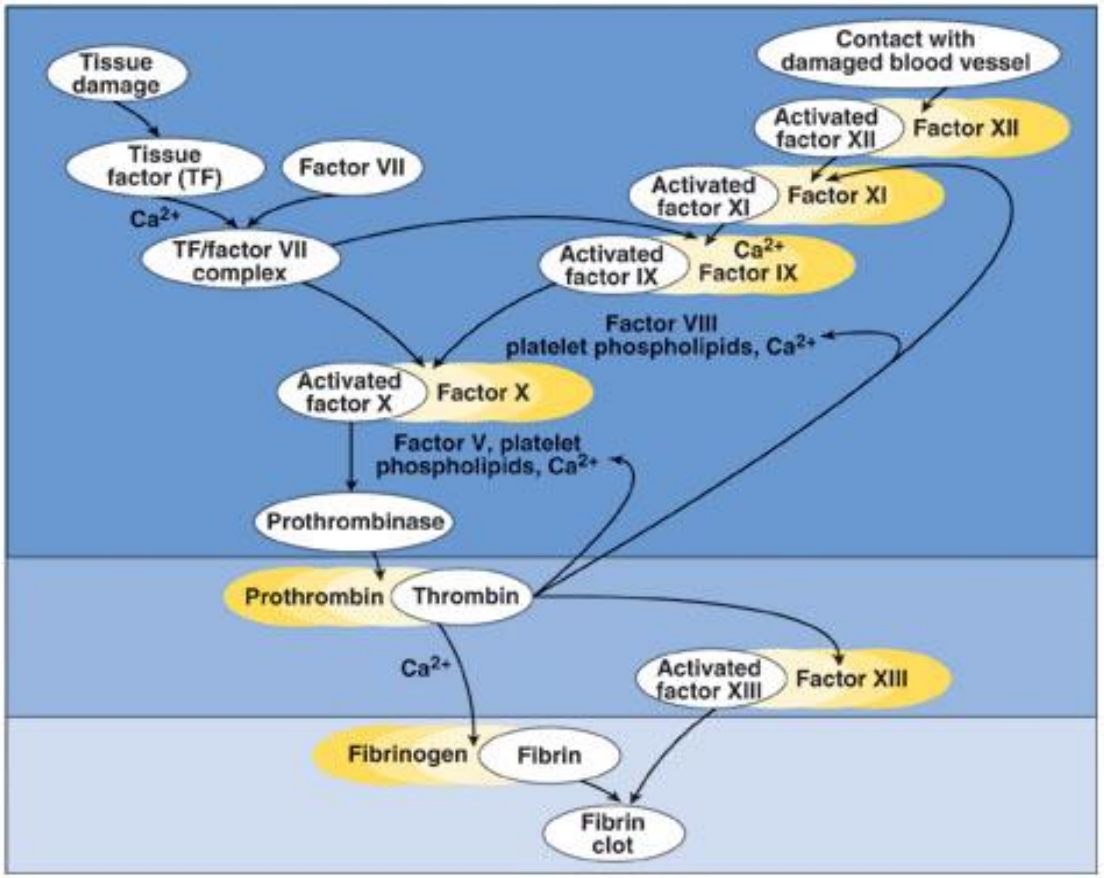
# Clot Formation



**Stage 1 can be activated in two ways:**

**Extrinsic clotting pathway** starts with tissue factor, which is released outside of the plasma in damaged tissue.

**Intrinsic clotting pathway** starts when inactive factor XII, which is in the plasma, is activated by coming into contact with a damaged blood vessel.

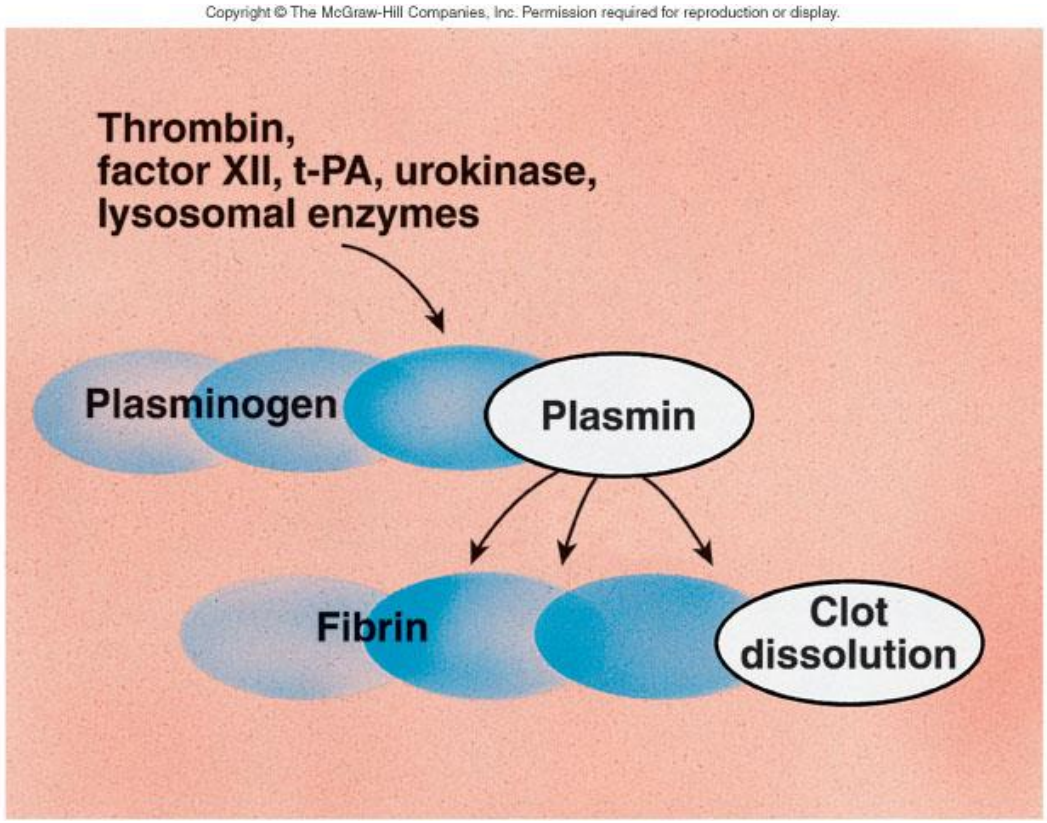



**Stage 1:** Damage to tissue or blood vessels activates clotting factors that activate other clotting factors, which leads to the production of prothrombinase. The activated factors are within *white ovals*, whereas the inactive precursors are shown as *yellow ovals*.

**Stage 2:** Prothrombin is activated by prothrombinase to form thrombin.

**Stage 3:** Fibrinogen is activated by thrombin to form fibrin, which forms the clot.

# Fibrinolysis



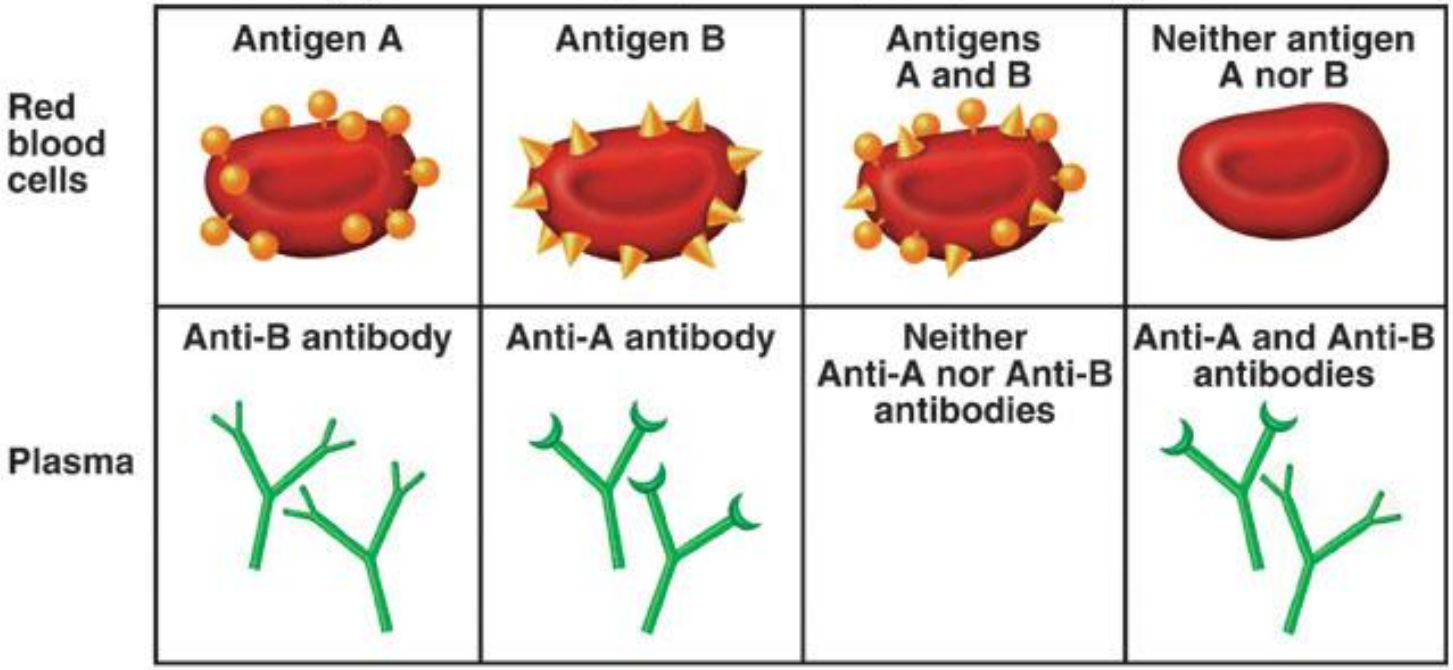

- Clot dissolved by activity of plasmin, an enzyme which hydrolyzes fibrin

# Blood Grouping

- Determined by antigens (agglutinogens) on surface of RBCs
- Antibodies (agglutinins) can bind to RBC antigens, resulting in agglutination (clumping) or hemolysis (rupture) of RBCs
- Groups
  - ABO and Rh

# ABO Blood Groups






**Type A**
Red blood cells with type A surface antigens and plasma with anti-B antibodies

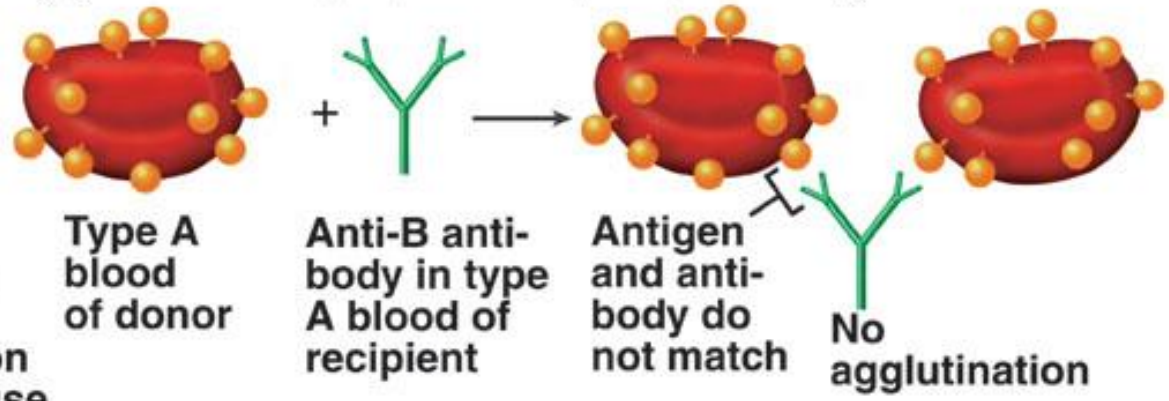
**Type B**
Red blood cells with type B surface antigens and plasma with anti-A antibodies

**Type AB**
Red blood cells with both anti-A and anti-B surface antigens, and neither anti-A nor anti-B plasma antibodies

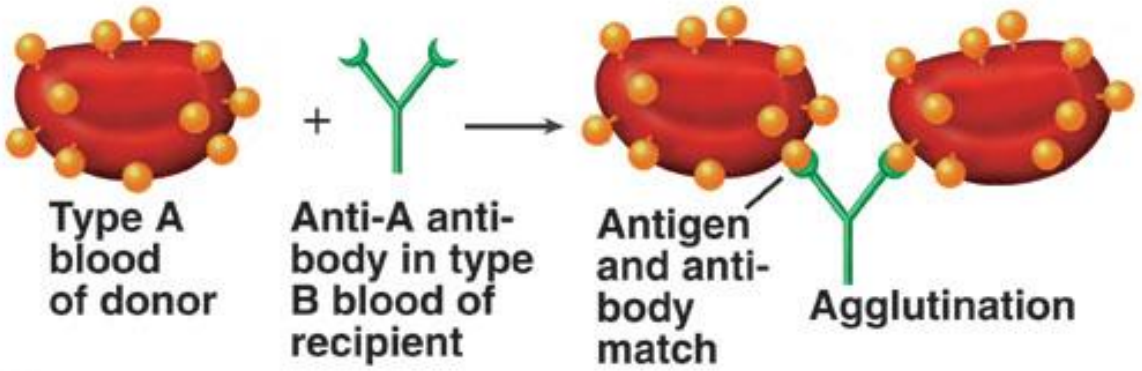
**Type O**
Red blood cells with neither type A nor type B surface antigens, but both anti-A and anti-B plasma antibodies

# Agglutination Reaction






(a) No agglutination reaction. Type A blood donated to a type A recipient does not cause an agglutination reaction because the anti-B antibodies in the recipient do not combine with the type A antigens on the red blood cells in the donated blood.

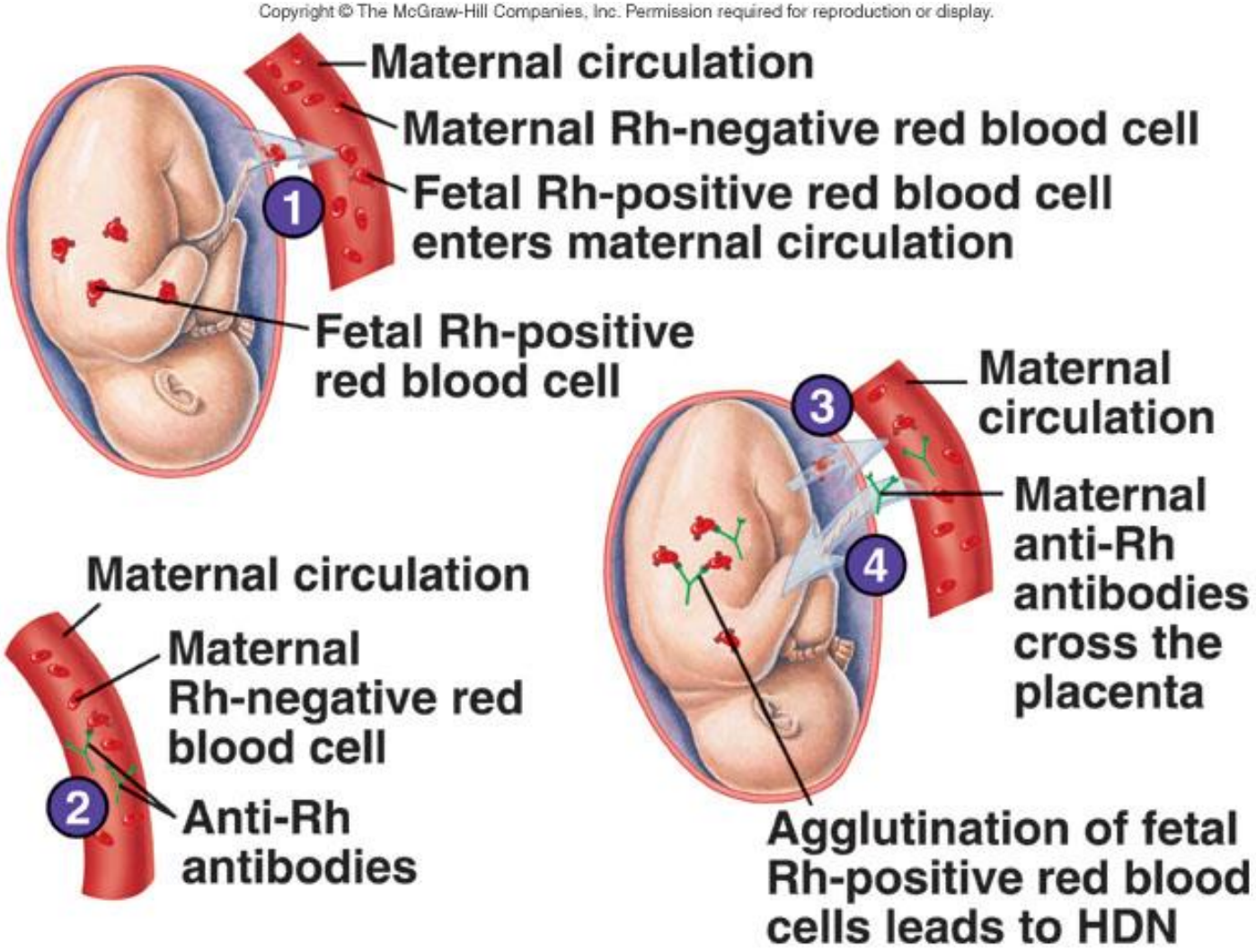



(b) Agglutination reaction. Type A blood donated to a type B recipient causes an agglutination reaction because the anti-A antibodies in the recipient combine with the type A antigens on the red blood cells in the donated blood.

# Rh Blood Group

- First studied in rhesus monkeys
- Types
  - Rh positive: Have these antigens present on surface of RBCs
  - Rh negative: Do not have these antigens present
- Hemolytic disease of the newborn (HDN)
  - Mother produces anti-Rh antibodies that cross placenta and cause agglutination and hemolysis of fetal RBCs

# Erythroblastosis Fetalis



# Blood Disorders

- Erythrocytosis: RBC overabundance
- Anemia: Deficiency of hemoglobin
  - Iron-deficiency
  - Pernicious
  - Hemorrhagic
  - Hemolytic
  - Sickle-cell
- Hemophilia
- Thrombocytopenia
- Leukemia
- Septicemia
- Malaria
- Infectious mononucleosis
- Hepatitis

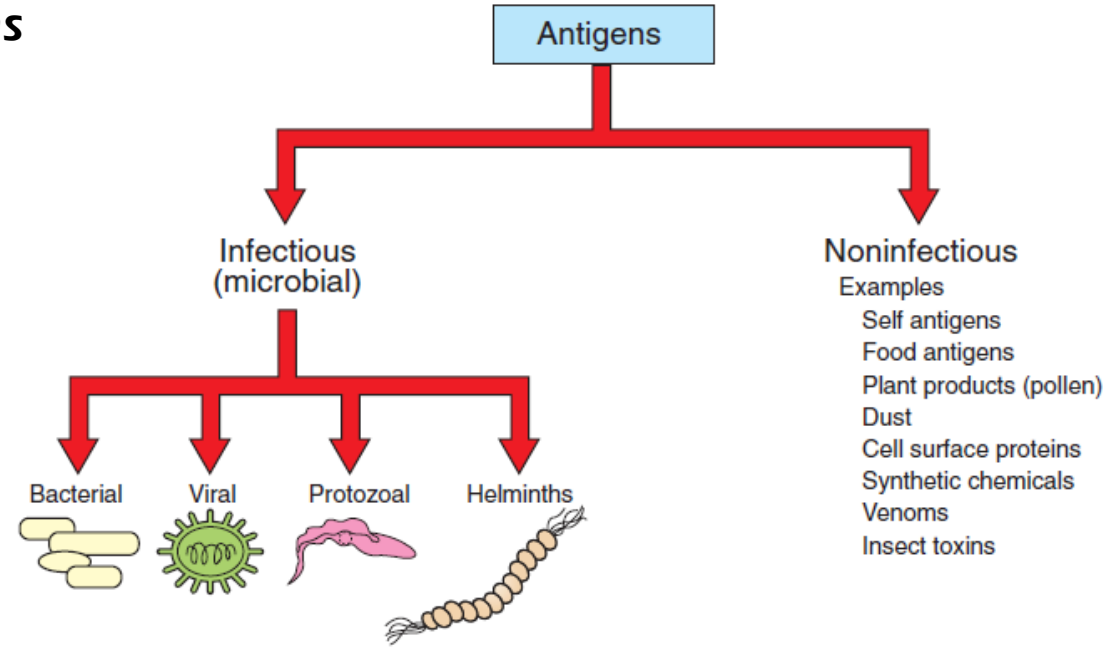
# Antigens and Innate Immunity

- Body's Defense Against Invading Antigens:
  - 1. Both nonimmune and immune mechanisms defend against invading antigens.
  - 2. A first line of defense includes physical and chemical barriers such as the skin and internal body fluids.
  - 3. A second line of defense consists of phagocytic cells of the myeloid and macrophage-monocyte lineages.
  - 4. Macrophage-derived cytokines can induce a variety of physiological processes to help combat infectious antigens.

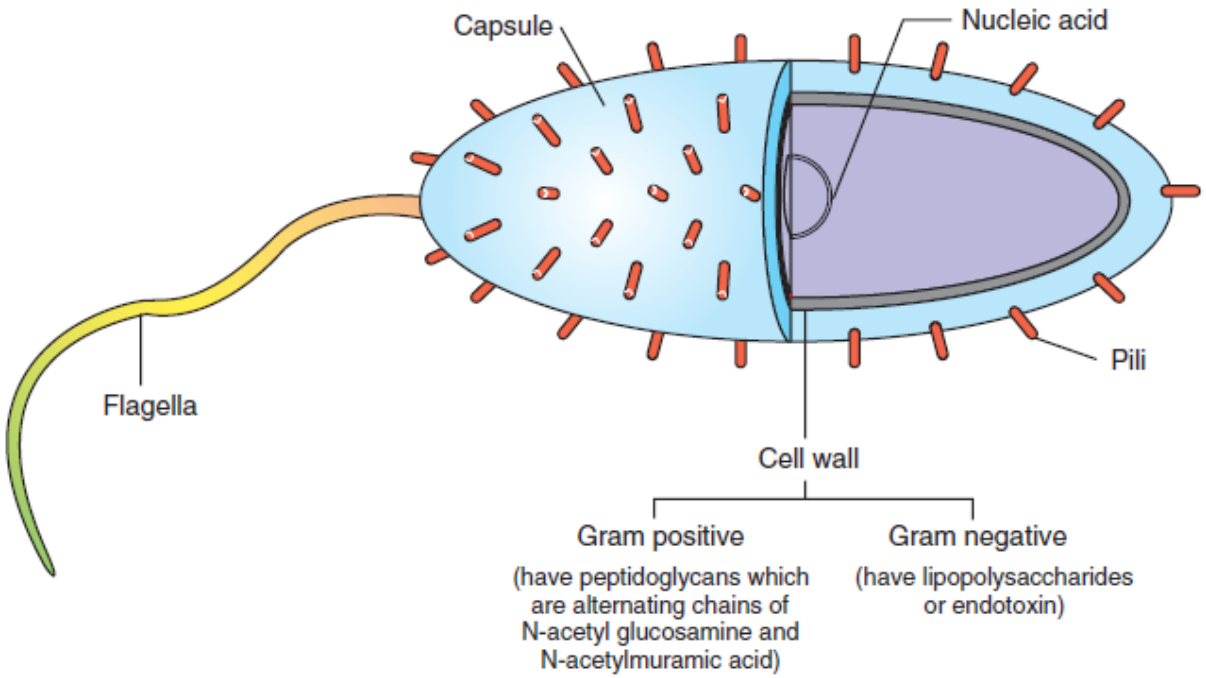
# ANTIGENS

- An antigen, or immunogen, is defined as any substance that is capable of stimulating immune cells (T and B cells) to induce an immune response.

- Antigens can be broadly divided into two large categories:
  - (1) infectious (microbial)
  - (2) noninfectious



# ANTIGENIC STRUCTURES OF BACTERIA

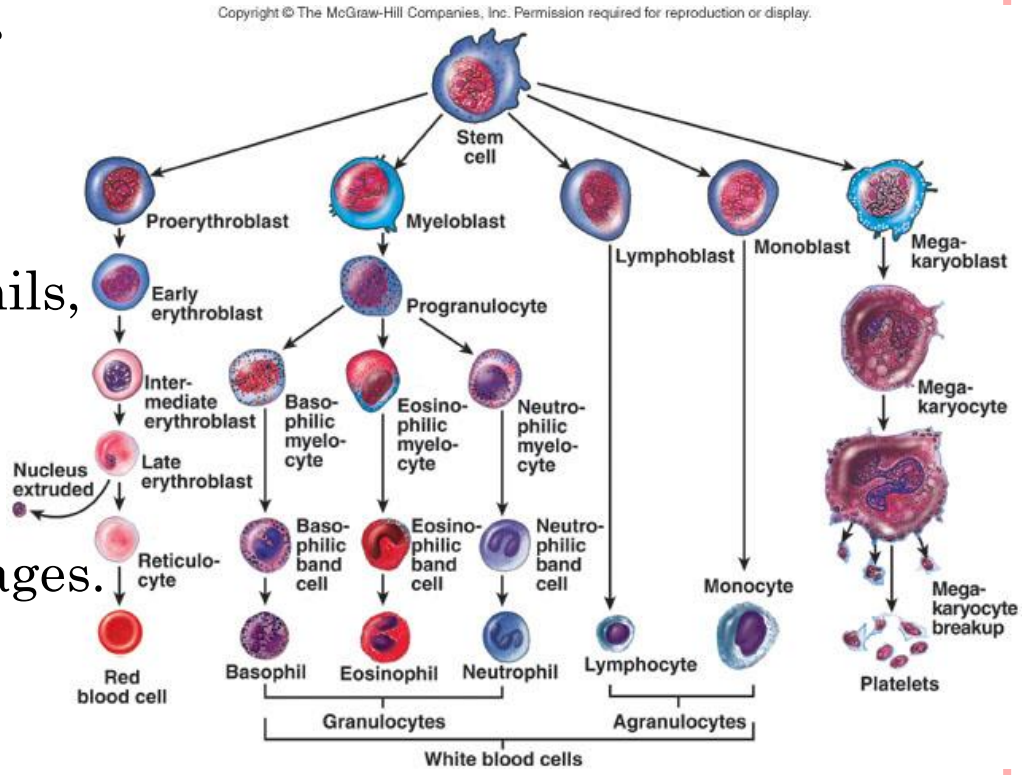


# Body's Defense Against Invading Antigens

- First line of defense
  - Physical nonimmune defense barriers
    - skin
      - secretion of sebum, low pH, secretion of enzymes
      - dendritic cells (Langerhans cells) and γ-δ T cells that contribute to warding off invading pathogens
    - internal body surfaces such as the gastrointestinal (GI), reproductive, respiratory, and the urogenital tracts.
  - Body fluids
    - mucus in the mucosal tissues (respiratory, urogenital, and GI tracts),
    - saliva, tears, gastric juices, and urine
      - are rich in enzymes (e.g., lysozymes) and are low in pH.

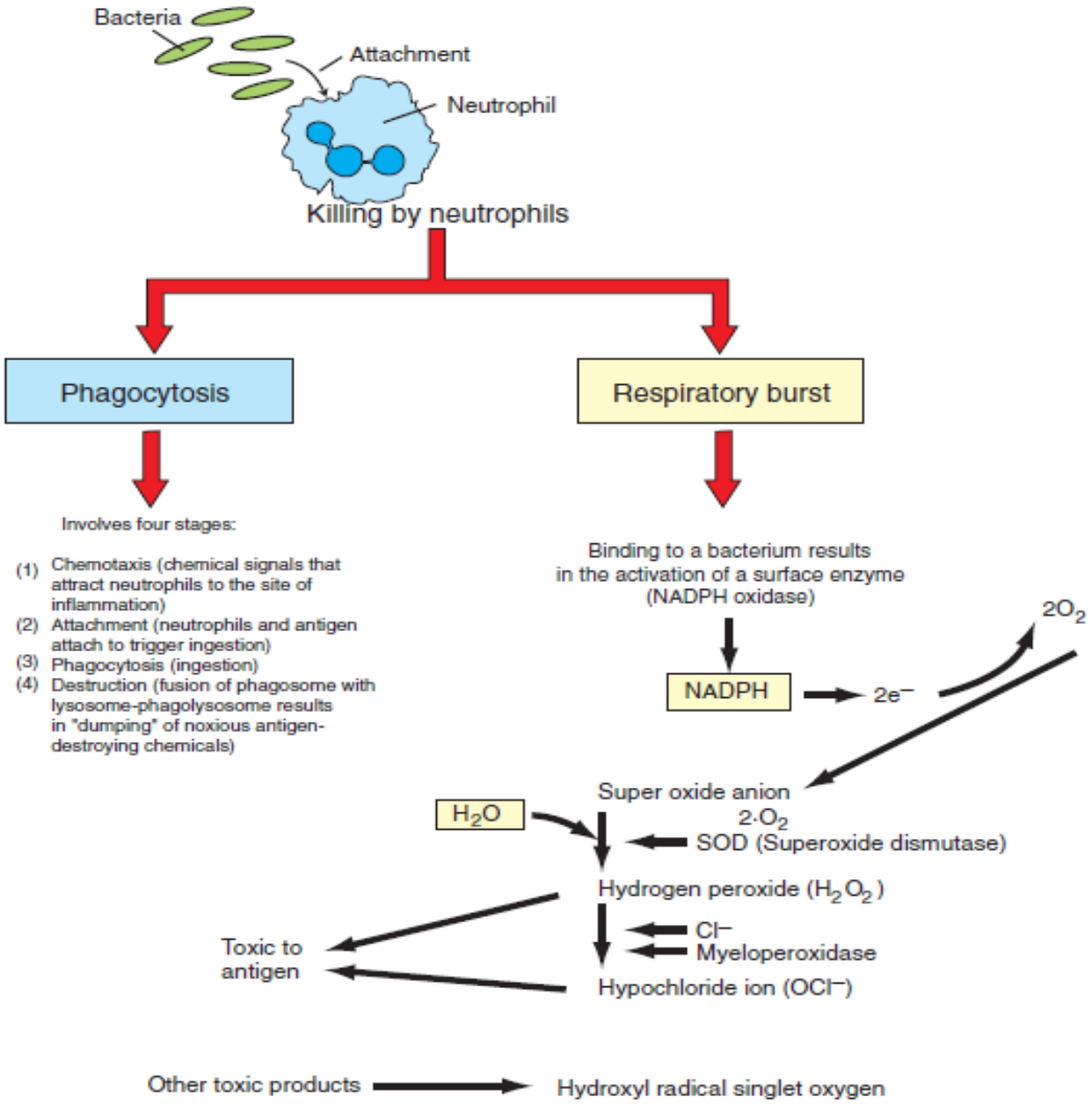
# Body's Defense Against Invading Antigens

- Second line of defense
- phagocytic cells, which are an integral part of innate immunity.
  - Myeloid lineages
    - neutrophils, eosinophils, basophils
  - Macrophage-monocyte lineages
    - Monocytes, macrophages.



# NEUTROPHILS

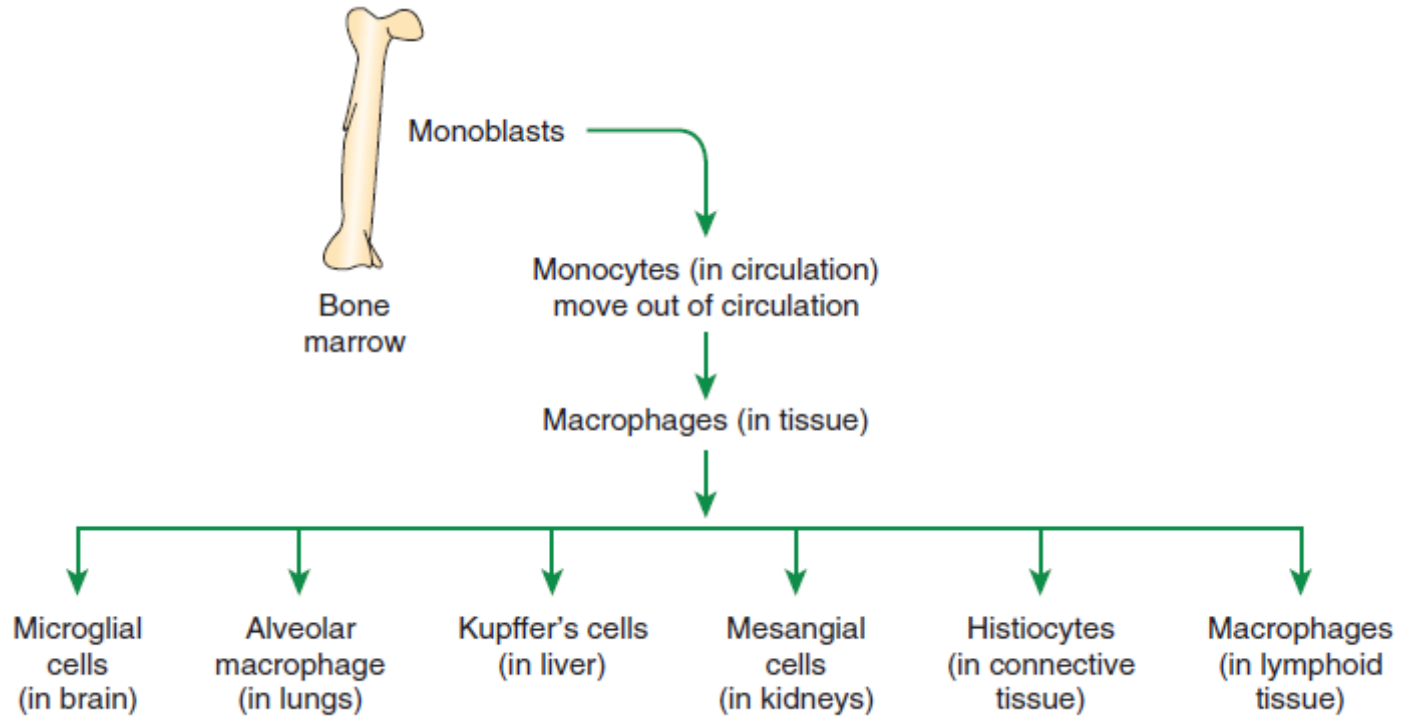
- Largest percentage of WBCs in most species (60% to 65%)
- short life span in the blood (~12 hours), but in tissues to several days
- multilobulated nuclei and a cytoplasm rich in granules
  - primary granules contain important bactericidal enzymes (myeloperoxidase, lysozymes, acid hydrolases, . . . )
  - secondary granules include lysozymes, lactoferrin, and collagenases
- first responder cells to combat invading antigens
- destroy antigens by two different but complementary mechanisms:
  - (1) phagocytosis
  - (2) respiratory burst


Bacteria
Attachment
Neutrophil
Killing by neutrophils
Phagocytosis
Respiratory burst
Involves four stages:
(1) Chemotaxis (chemical signals that attract neutrophils to the site of inflammation)
(2) Attachment (neutrophils and antigen attach to trigger ingestion)
(3) Phagocytosis (ingestion)
(4) Destruction (fusion of phagosome with lysosome-phagolysosome results in "dumping" of noxious antigen-destroying chemicals)
Binding to a bacterium results in the activation of a surface enzyme (NADPH oxidase)
NADPH
2e⁻
2O2
Super oxide anion
H2O
2·O2
SOD (Superoxide dismutase)
Hydrogen peroxide (H2O2)
Cl⁻
Myeloperoxidase
Toxic to antigen
Hypochloride ion (OCl⁻)
Other toxic products
Hydroxyl radical singlet oxygen

# Macrophages

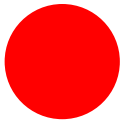
- Elastases and collagenases released from dying neutrophils are chemoattractant for macrophages
- Macrophages are attracted by
  - bacterial products
  - chemotactic factors released from damaged tissues.
- Secrete large quantities of cytokines and chemokines
- Some of these cells present antigens to the immune system.
- Differ in their morphology based on tissues and thus have different names

# MACROPHAGES

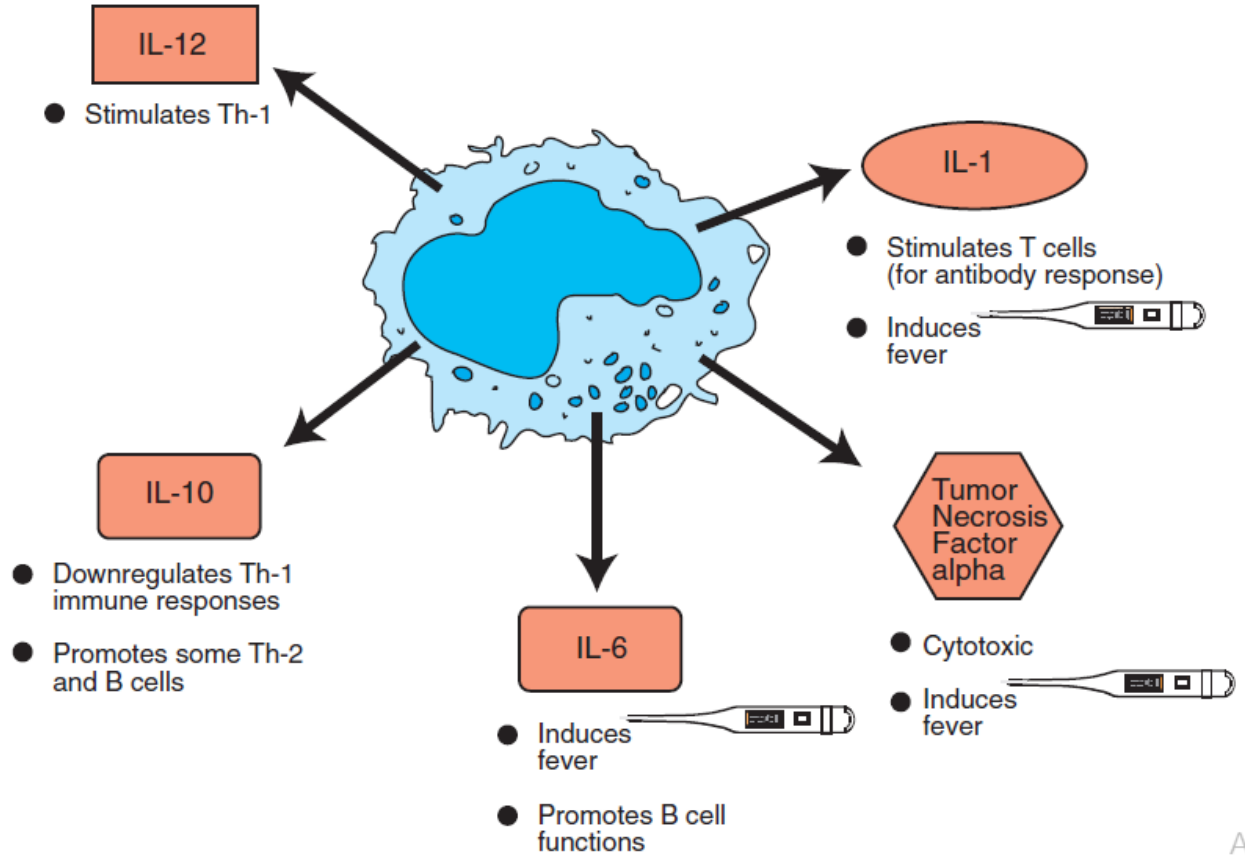


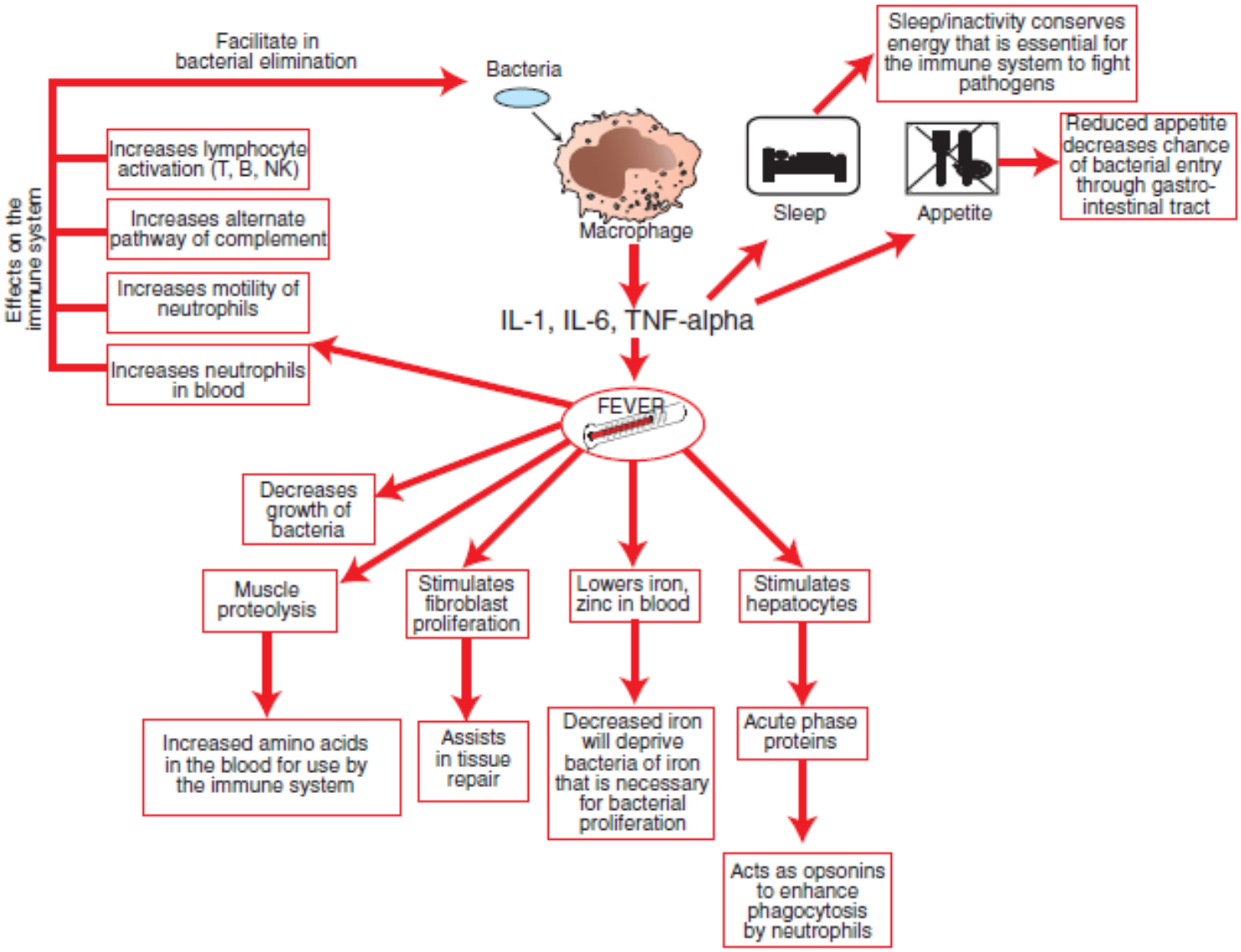
# MACROPHAGE-DERIVED CYTOKINES

- Induction of fever, which is mediated by the release of pyrogenic cytokines such as IL-1, IL-6, and TNF-α by macrophages
- Fever:
  - accelerates the mobility of neutrophils,
  - Enhances their phagocytic ability,
  - activates lymphocytes and complement proteins
  - impeding the growth of bacteria
- act on the liver to stimulate acute phase proteins that function as opsonins to promote phagocytosis
- act on the sleep-associated regions in the hypothalamus to promote sleep
- present antigens to stimulate T cells in order to start the specific adaptive immune response



# MACROPHAGE-DERIVED CYTOKINES




Facilitate in bacterial elimination
Bacteria
Sleep/inactivity conserves energy that is essential for the immune system to fight pathogens
Reduced appetite decreases chance of bacterial entry through gastro-intestinal tract
Sleep
Appetite
Macrophage
Effects on the immune system
Increases lymphocyte activation (T, B, NK)
Increases alternate pathway of complement
Increases motility of neutrophils
Increases neutrophils in blood
IL-1, IL-6, TNF-alpha
FEVER
Decreases growth of bacteria
Muscle proteolysis
Stimulates fibroblast proliferation
Lowers iron, zinc in blood
Stimulates hepatocytes
Increased amino acids in the blood for use by the immune system
Assists in tissue repair
Decreased iron will deprive bacteria of iron that is necessary for bacterial proliferation
Acute phase proteins
Acts as opsonins to enhance phagocytosis by neutrophils

# Acquired Immunity

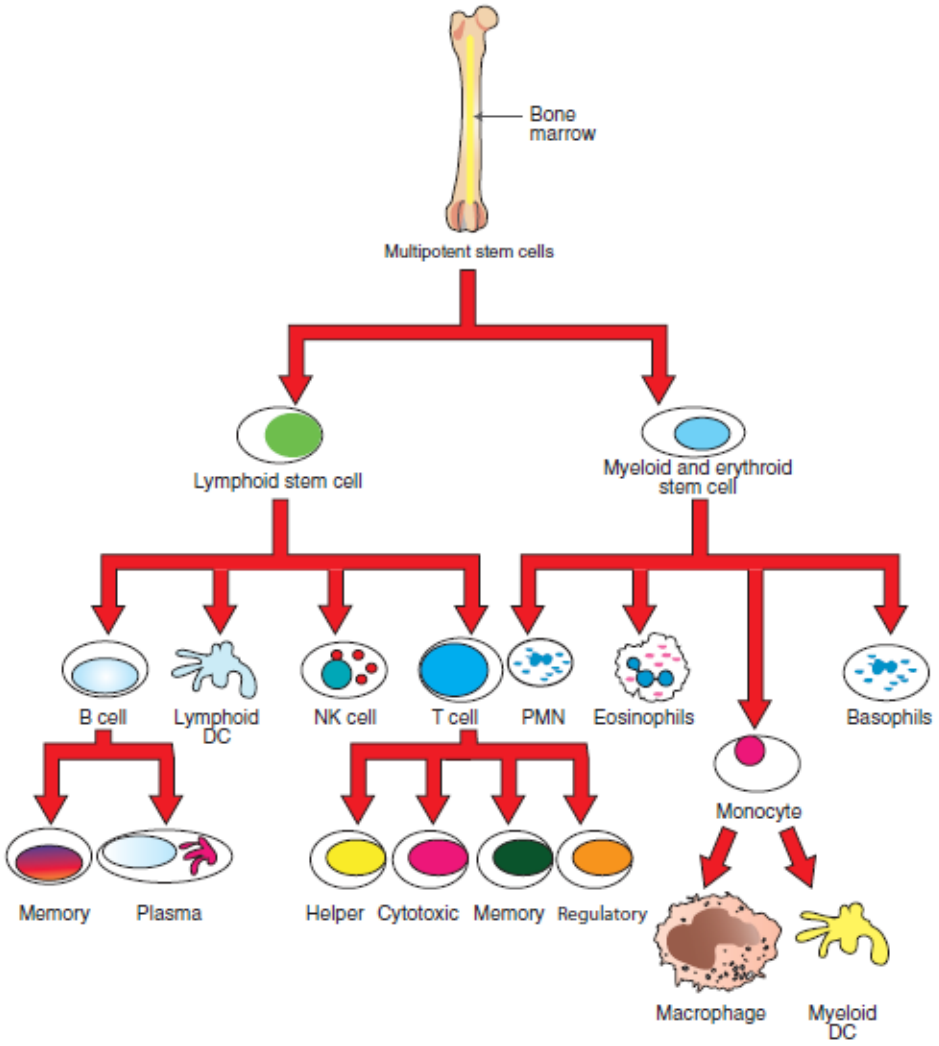
Introduction

- Key features of innate immunity include
  - (1) rapid response against invading pathogens;
  - (2) nonspecificity;
  - (3) physical, chemical, and cellular (phagocytic cells, NK cells) barriers.
- The response of the innate immune system, however, is not long-lasting and does not induce immunological memory
- Acquired immunity, which involves activation of T and B lymphocytes provides long-lasting immunity
- Antigen-presenting cells (APCs), a part of the innate immune system, play a central role in activating lymphocytes.
- Activated T lymphocytes (T cells) secrete cytokines that are essential for defense against intracellular pathogens, activation of other cells, and coordination of immune responses.
- B lymphocytes (B cells) have two main functions:
  - (1) secreting antibodies that bind specifically to the antigen that induced the antibody response
  - (2) acting as APCs

# Different types of immune cells

- All cells of the immune system are derived from multipotent stem cells that are located primarily in the marrow of long bones.
  - lymphoid stem cells
    - T, B, natural killer (NK), and lymphoid dendritic cells
  - myeloid stem cells
    - monocytes, which mature in tissues to become
      - macrophages or dendritic cells
- Mature cells are found circulating throughout the body but concentrate in the peripheral lymphoid organs (e.g., lymph nodes, spleen) and gut-associated lymphoid tissues, where most of the complex interactions with antigens take place.

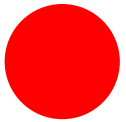
# LYMPHOPOIESIS



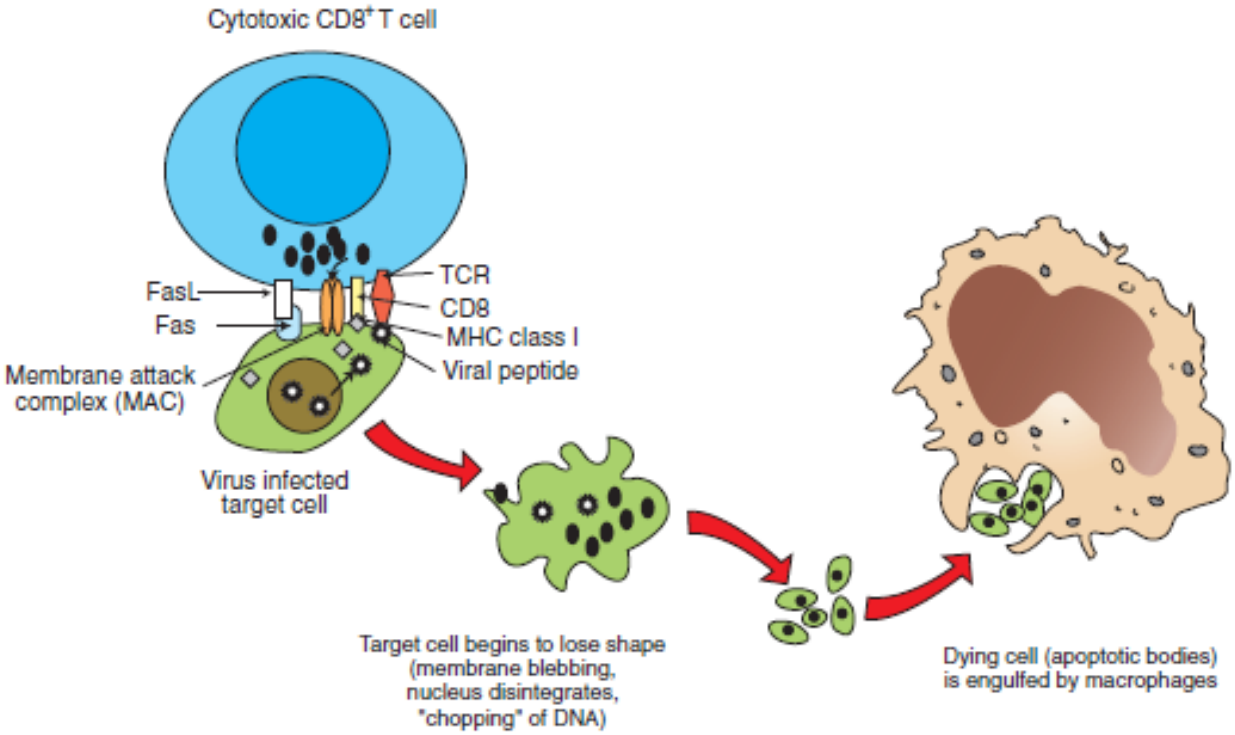
# T-Cells

- All T cells express a T-cell antigen receptor (TCR), CD28 and related molecules, and either CD4 (helper cells) or CD8 (cytotoxic cells)

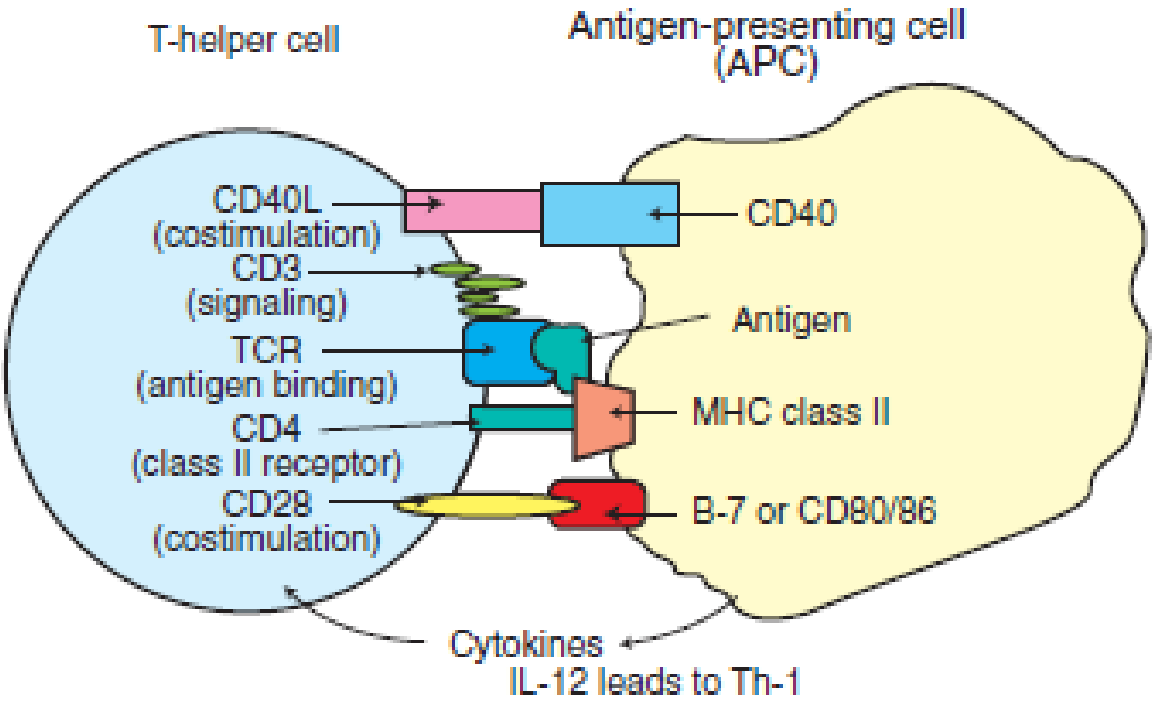
- TCR specifically binds to antigenic peptides that are presented by APCs
  - T-helper (Th) cells secrete proteins called cytokines that act on other immune cells to provide help and coordinate immune responses. The cells express the CD4 receptor
  - Cytotoxic T cells express the CD8 molecule (but not CD4) and have granules that are rich in serine esterase granzymes. Also have perforins and lymphotoxins that are important in initiating cytotoxicity and killing infected and abnormal cells



# Cytotoxic T-cell

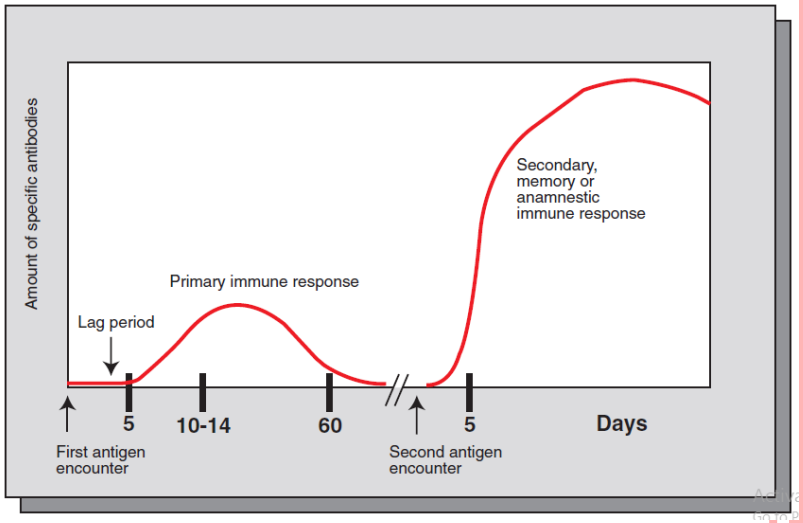


# T-HELPER CELL



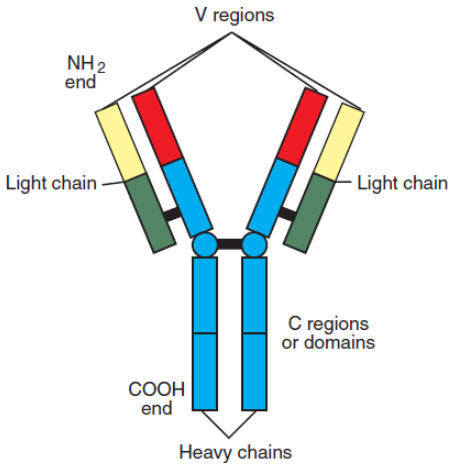
# ANTIBODIES

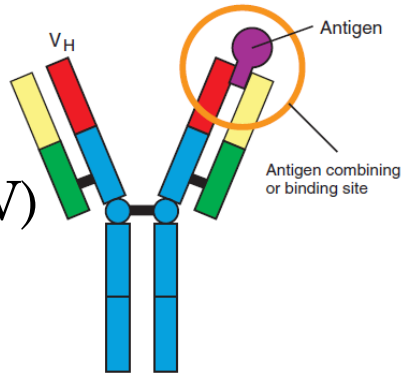
- exposure of an animal to a foreign antigen usually elicits a specific immune response. This response may involve the production of:
  - (1) specifically reactive T cells or
  - (2) antibodies able to bind specifically with the foreign antigen
- First exposure to an antigen:
  - Lag period
  - First immune response
- Second exposure to an antigen:
  - Secondary or anamnestic immune response



# ANTIBODIES (IMMUNOGLOBULINS)

- products of B lymphocytes
  - on the surface of B cells, as antigen receptors (BCRs),
  - or free in blood and secretions after being secreted by B cells
    - can neutralize antigens and assist in their removal
- made of four glycoprotein molecules
  - 2 heavy (H) chains, 2 light (L) chains
  - Constant parts (C) , Variable parts (V)
  - Antigen-binding or combining site



# IMMUNOGLOBULINS

- Five isotypes: IgM, IgG, IgA, IgE, IgD
- IgM:
  - Soluble
  - 10 identical antigen-combining site
  - The predominant immunoglobulin in primary immune responses
  - Present in blood, not other body fluids
- IgG:
  - two antigen-combining sites
  - The predominant immunoglobulin in secondary immune responses
  - able to move out of the circulatory system and appears in body fluids and also in secretions

# IMMUNOGLOBULINS

- IgA:
  - Predominant immunoglobulin in secretions
  - Produced by plasma cells (mature B cells) located under body surfaces such as skin, mammary glands, and the intestinal, respiratory, genital, and urinary tracts
  - Its main role is to prevent antigen from attaching to mucosal surfaces.
  - Blocks penetration of antigen into the body
- IgE:
  - Mostly bound to basophils and mast cells (inflammatory and allergic reaction mediators) through its Fc portion
  - Is able to bind antigen while attached to these cells, thereby eliciting allergic reactions
- IgD:
  - Is primarily bound to the B cells, and secreted in negligible amounts