# BIEN 500 Systems Physiology

## Blood cell and immunity

Dr. DeCoster

Part 1- Guyton (14th ed.) Chaps. 33 fwd

Lecture 06-Fall 2023

# Blood Cell-Erythrocyte- 1

- **<u>Erythrocytes (Red Blood Cells)</u>: transport hemoglobin, which in turn carries oxygen from the lungs to the tissues.**

- Other functions: contains **carbonic anhydrase**, an enzyme that catalyzes the reversible reaction between carbon dioxide ($CO_2$) and water to form carbonic acid ($H_2CO_3$)

$$H^+ + H_2CO_3 \Leftrightarrow CO_2 + H_2O$$

# Blood Cell-Erythrocyte- 2

- Water of the blood **transports** enormous quantities of **$\underline{CO_2}$** in the form of bicarbonate ion ($HCO_3^-$) from the **tissues to the lungs**, where it is reconverted to $CO_2$ and expelled into the atmosphere as a body waste product.

- Other functions: The hemoglobin is an excellent **acid-base buffer,** *so that the red blood cells are responsible for most* of the acid-base buffering power of whole blood.
- This keeps the blood pH quite stable, even during metabolic and other changes to the body ( for example, exercise).

# Blood Cell-Erythrocyte- 3

- **Shape: <u>Biconcave</u> discs** having a mean diameter of about 7.8 µm and a thickness of 2.5 µm at the thickest point and 1µm or less in the center. (What function may concave shape serve?)

- The average volume of the red blood cell is 90 to 95 $\mu m^3$

- **Deformable shape to squeeze through small blood vessels, which can be as small as 4 µm**

- Excess cell membrane exists, so extensive stretching is possible without rupturing the cell.

# Blood Cell-Erythrocyte- 4

- Hematocrit (the percentage of blood that is cells)
  - Gender difference (slightly lower hemoglobin in women)

- **Blood plasma (liquid component of the blood)**

- **Production of more erythrocytes when at <u>high</u> altitude**
- **(to compensate for what?)**

# Erythropoiesis-Genesis of Blood Cells

- Regulation: Tight control on erythrocyte total mass

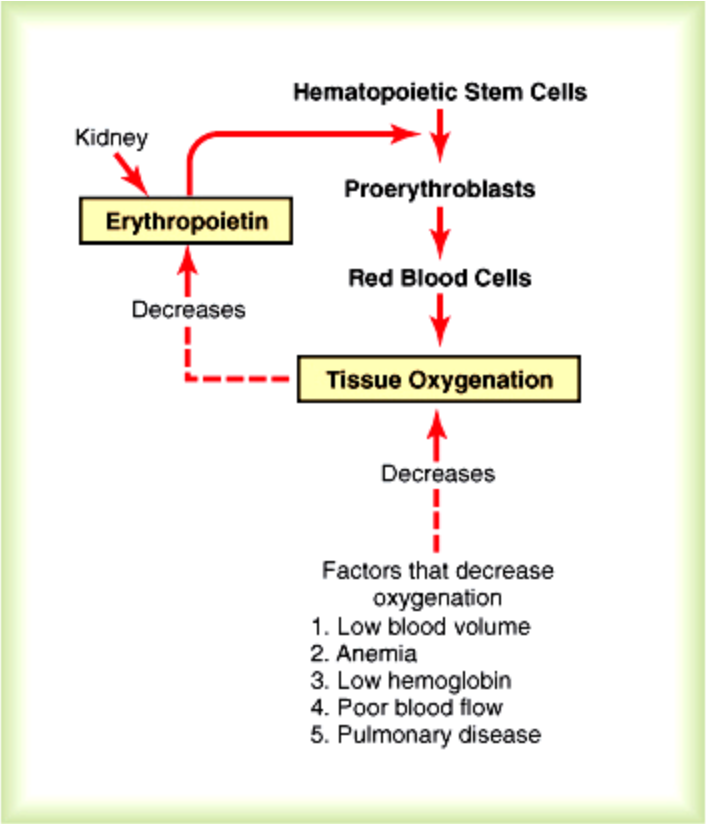
  Erythropoietin (EPO)

  – Glycoprotein found mostly in kidney

  – Increase erythrocyte production

  – Stimuli ➡⬆ erythropoietin production ➡ ⬆ erythrocyte by stimulating proerythroblast

- Stimuli: hypoxia, anemia, bone marrow dysfunction

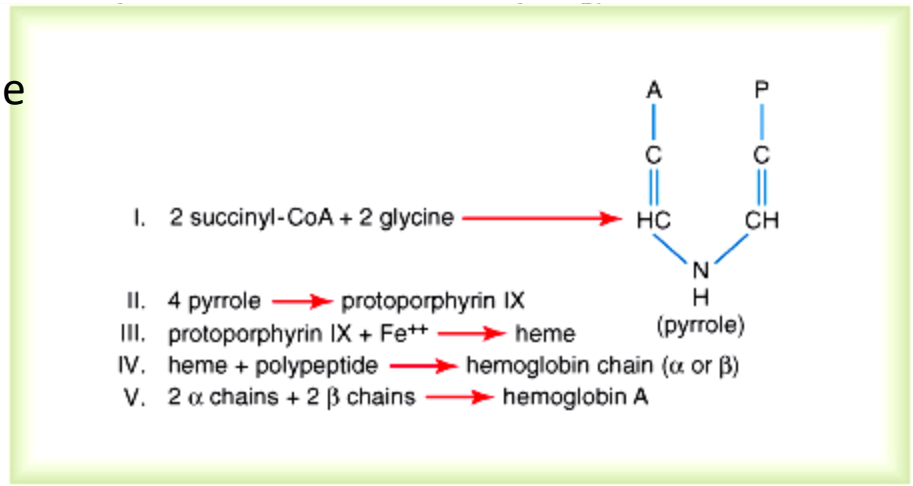


# Hemoglobin Formation- 1

## Hemoglobin (Hb): the oxygen carrier protein

• 1 Hb binds with 1 oxygen molecule (not ionic form) through coordination bond. Therefore, oxygen does not combine with the two positive bonds of the iron in the Hb molecule. Instead with have loose binding with one of the coordination bonds. Loose binding (why is loose important?)

Notes: 1) Succinyl- CoA comes from Krebs Cycle
2) Glycine = what?
3) Each hemoglobin chain approx. 16 kDa
4) Whole hemoglobin molecule =4 chains,




Elsevier. Guyton & Hall: Textbook of Medical Physiology 11e - www.studentconsult.com

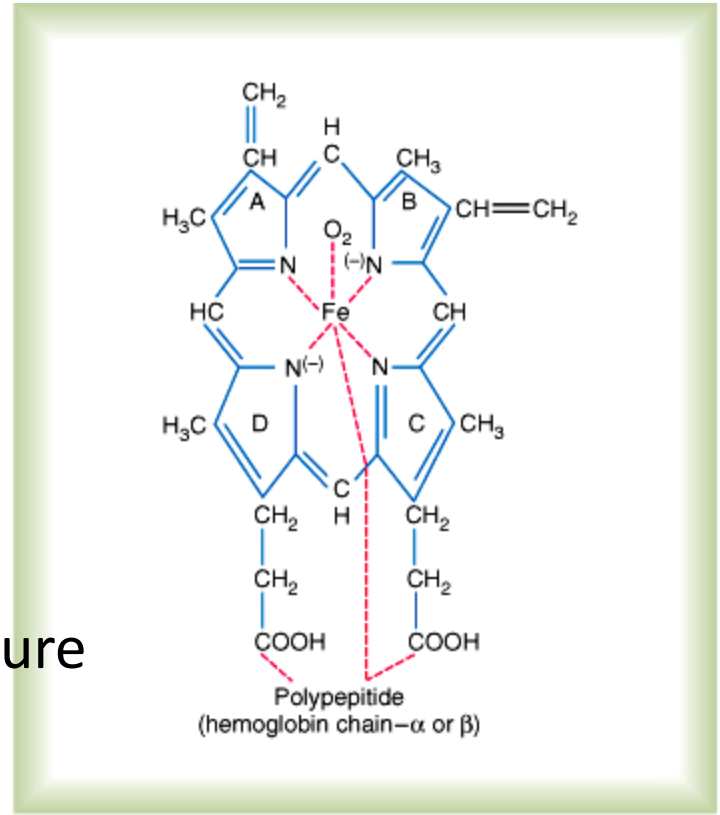
# Hemoglobin Formation- 2

- Higher binding strength to carbon monoxide than to oxygen

- Abnormal polypeptide chain

– Single amino acid mutation ➡ sickle cell anemia

– Formation of crystal at low oxygen level (long crystals which may rupture The cells)



# Destruction of Erythrocyte- 1

- No nucleus, no endoplasmic reticulum, no mitochondria
- Normally circulate about 120 days
- Relies on cytoplasmic enzymes to generate energy source
  - Metabolize glucose to generate adenosine triphosphate (ATP)
  - Maintain membrane pliability
  - Maintain iron transport
  - Maintain iron at ferrous (+2) and not ferric (+3) form
  - Prevent protein oxidation

***But wear-down of cytoplasmic enzymes may limit lifespan of each cell***

# Destruction of Hemoglobin

- Occurs When red blood cells burst and release their hemoglobin.
- Porphyrin to be degraded into bilirubin by macrophages in many parts of body (but especially by Kupffer cells of liver) .
- Anemia
  - Too few erythrocytes
  - Not enough Hb

# Anemias- 1

- **Two sources: Too few erythrocytes and not enough Hb**

- *Microcytic, hypochromic anemia*: Blood loss anemia
- *Aplastic anemia*: due to bone marrow aplasia (lack of functioning bone marrow)
- *Megablastic anemia*: insufficiency of vitamin B12, folic acid and/or intrinsic factor
- *Hemolytic anemia*: hereditary acquired
  - Short erythrocyte life-span
  - *Hereditary spherocytosis*: cell rupture due to spherical shape
  - *Sickle cell anemia*: cell rupture due to crystal formation
  - *Erythroblastosis fetalis*: fetal Rh+ erythrocytes attacked by antibodies from Rh- mother

# Anemias- 2

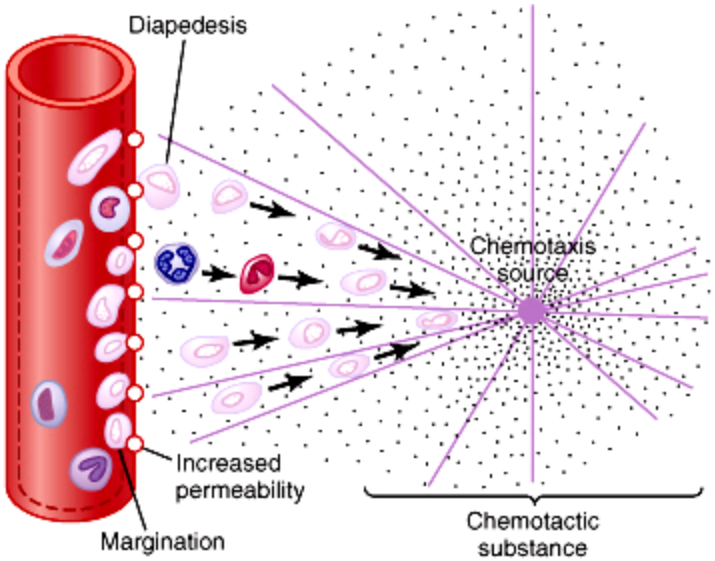
- Effects of anemia on function of the circulatory system

  ↓Blood Viscosity→ ↑Peripheral capillary dilates →↑blood return to heart → ↑cardiac output →↑blood flow →↑heart rate

(balancing or not balancing?)

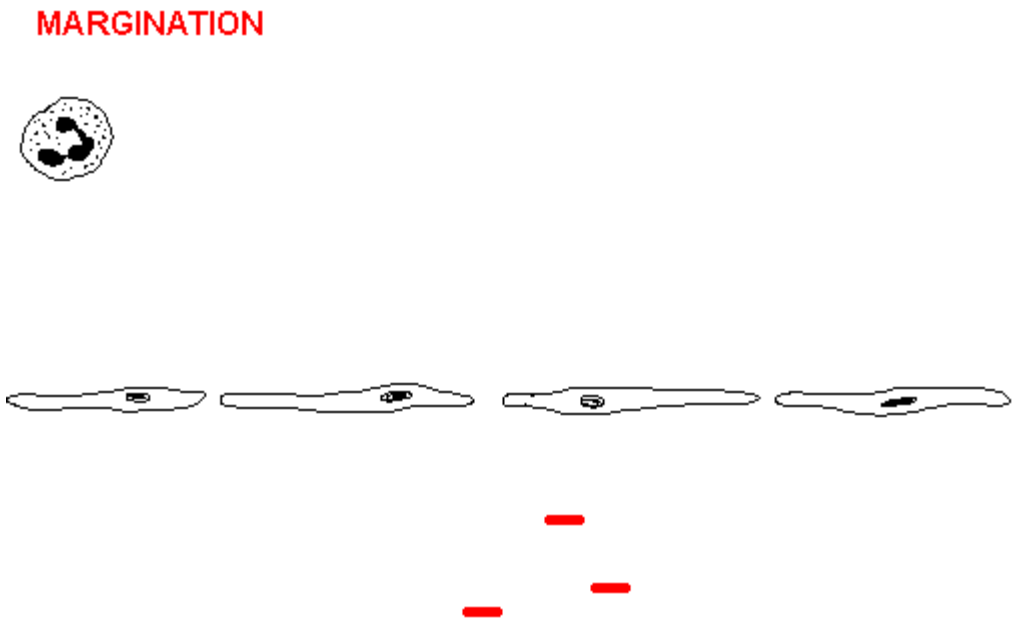
# Diapedesis

- Neutrophils and Monocytes
  - Circulate in the blood stream before squeezing through pores of blood vessels to the tissues; a process known as diapedesis.
  - Migrated monocytes that reside in tissues mature into tissue macrophages.




- Chemotactic agents (chemotaxis) such as remnants of necrotic / inflammed tissues, toxins from bacteria, complement complex and reaction products due to blood clotting. Serve as a gradient for attraction.
- Effective up to 100 µm

# Diapedesis



# Phagocytosis- 1

- Three selective procedures

  – Smooth surfaces resist phagocytosis; the reverse is likely for rough surfaces

  – Protein coating (glycocalyx) repels whereas non-protein coating (as in dead tissues) facilitates

  – Recognition of foreign materials: opsonization (coating of foreign materials surface with proteins (antibodies, complement molecules), which are then recognized by phagocytic cells)

- Phagocytosis by neutrophils: direct engulfment, formation of pseudopodia, the foreign materials are broken down by digestive enzymes stored in phagosome

- Phagocytosis by macrophages: mechanism similar to neutrophils, can be more powerful, engulf much larger particles

# Phagocytosis- 2

- Phagocytosed foreign materials are broken down by digestive enzymes and oxidative agents

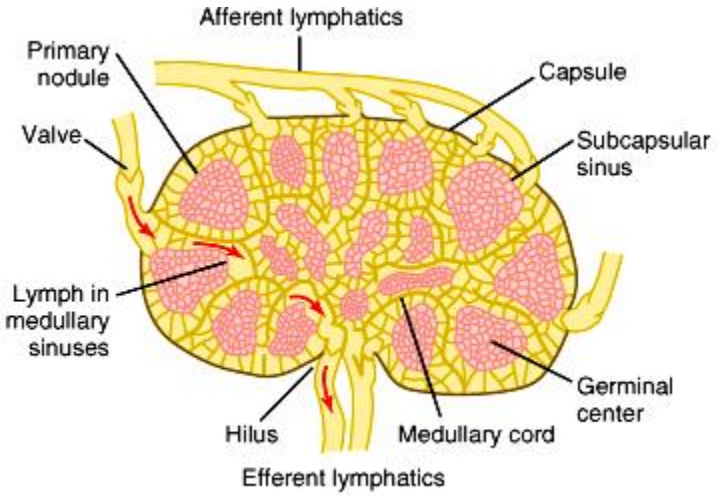
  – Superoxide $O_2^-$
  – Hydrogen peroxide $H_2O_2$
  – Hydroxyl ion $OH^-$
  – Myeloperoxidase catalyzes the formation of hypochlorite from hydrogen peroxide and chloride ions. Hypochlorite is very bactericidal.

$$H_2O_2 + Cl^- + H^+ \rightarrow HOCl + H_2O$$

# Monocyte-Phagocyte System (MPS)- 1

- Reticuloendothelial system (RES) in old literature
- Also called monocyte-macrophage system
- Lymph nodes
- General pathway: Afferent lymphatics (collecting from lymph) → medullary sinuses

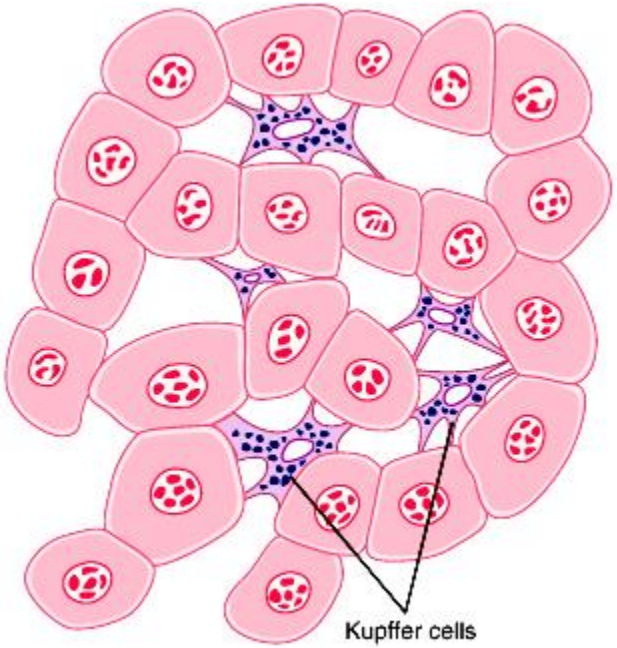
  → hilus → efferent → efferent lymphatics empty into venous blood



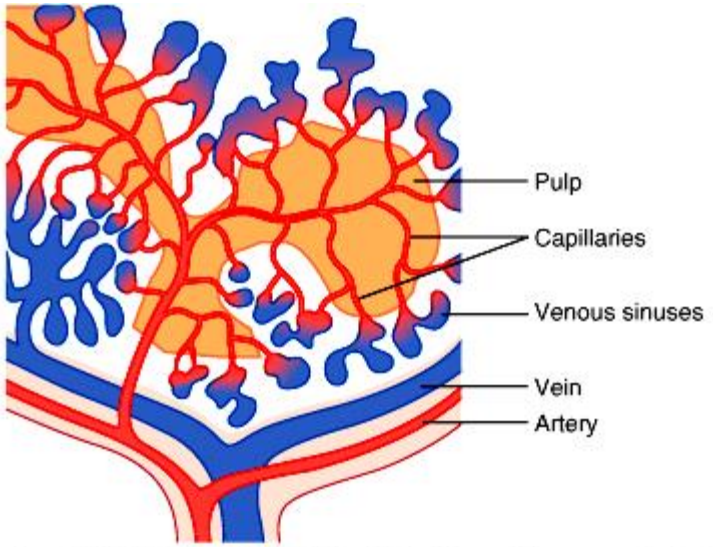
# Monocyte-Phagocyte System (MPS)- 2

**Lung: alveolar macrophages** at alveolar walls; formation of foreign body giant cells around non-digestible foreign objects; appearance of multi-nucleation

- **Hepatocytic macrophages: Kupffer cells;** filtration of blood for bacteria from re-entering into the blood stream
- **Spleen and bone marrow:** combat invading microorganisms that succeed in entering blood stream; spleen pulp; artery enters → blood passes out of capillaries → cords of red pulp → blood squeezes through a trabecular network → returns through venous sinuses. - similar to lymph nodes but filters blood rather than lymph. Macrophages serve as a filter in the spleen.





# Neutrophils and Macrophages in Inflammation- 1

- Vasodilation → permeability of blood vessel, leakage of fluid into interstitial space → clotting → migration of granulocytes and monocytes into the tissue → swelling → edema

- Some tissue products that produce these reactions include: Histamine, bradykinin, serotonin, prostaglandins, complement fragments, blood clotting factors and lymphokines

- Wall-off the area of injury from the remaining tissues

# Neutrophils and Macrophages in Inflammation- 2

- Tissue macrophage as a **first line of defense against infection**
- Neutrophil as a **second line of defense against infection**

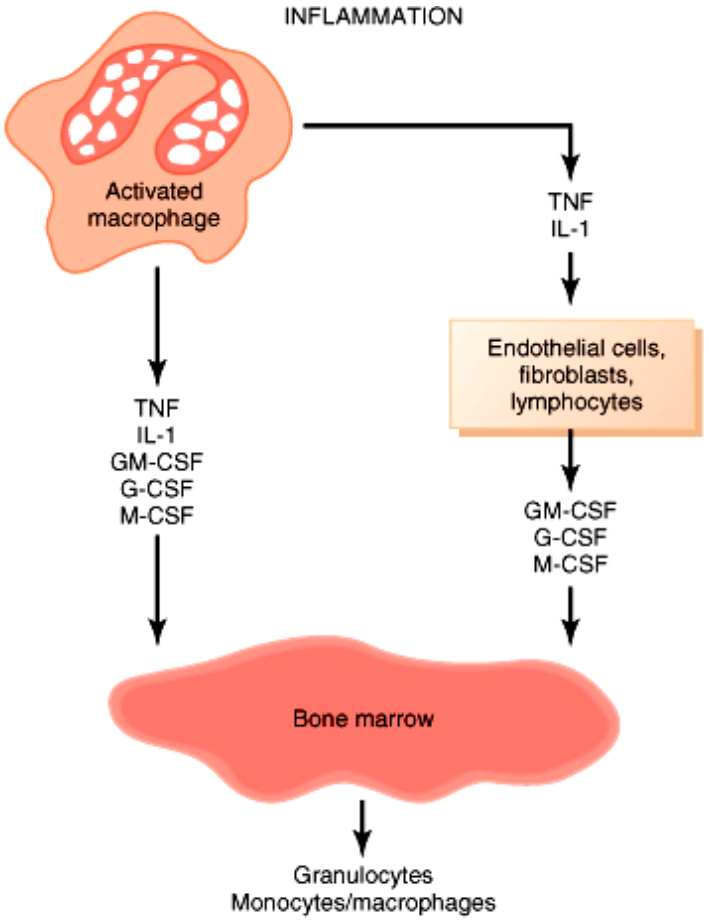
  – Capture of flowing neutrophil by adhesion molecules on the surface of both neutrophil and endothelial cells, aka margination
  – Open-up of blood vessels, aka diapedesis
  – Chemotactic effects
  – Positive feedback system: neutrophilia= increased # of neutrophils in the blood.

- Secondary macrophage invasion as a **third line of defense**
- Production of granulocytes and monocytes as a **fourth line of defense**

# Feedback control of macrophage and neutrophil response mediated by cytokines- 1

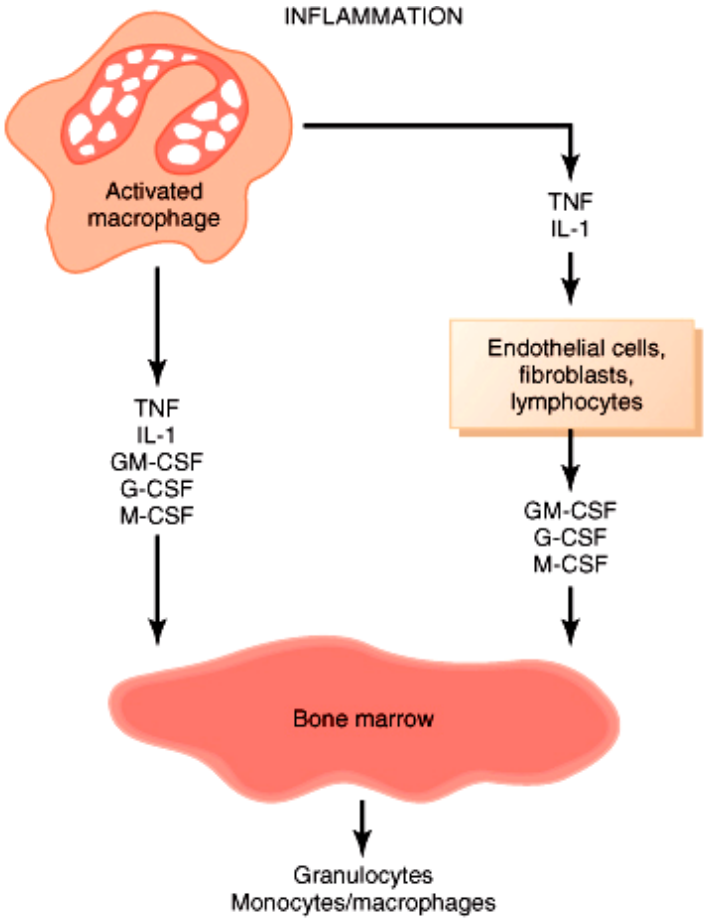
- Large number of **cytokines**

- Small chemical/biological molecules that affect other and/or own cells
  - Tumor necrosis factor (TNF)
  - Interleukin-1 (IL-1)
  - Granulocyte-monocyte colony stimulating factor (GM-CSF)
  - Granulocyte colony-stimulating factor (G-CSF)
  - Monocyte colony-stimulating factor (M-CSF)



# Feedback control of macrophage and neutrophil response mediated by cytokines- 2

- Activated macrophage secretes <u>cytokines</u> to simulate
  - bone marrow
  - Endothelial cells, fibroblasts and lymphocytes
- Which in turn stimulates bone marrow
- Activated macrophage secretes cytokines; dead areas and fluids over time form pus.



# Immunity and Allergy

**Immunity-**results from general processes rather than from processes directed at specific diseases or organism

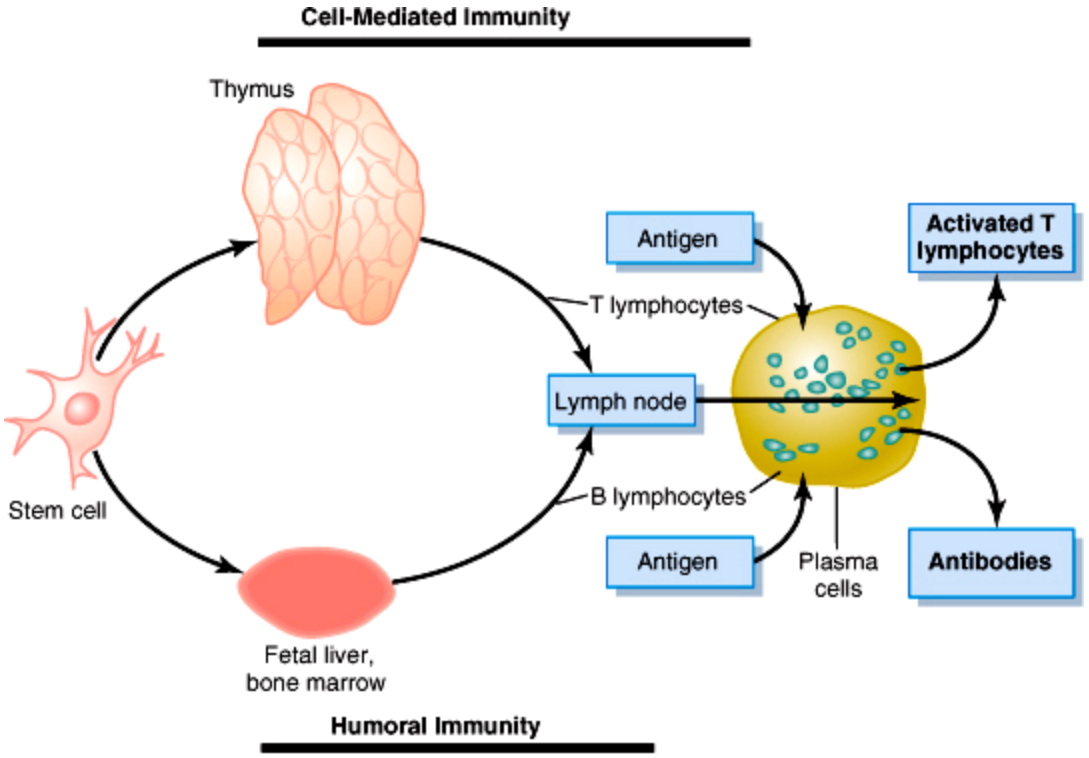
- **Phagocytosis of bacteria and other invaders**
- Stomach acid and digestive enzymes to destroy swallowed organisms
- Skin to resist invasion by organisms
- **Attachment of toxin, foreign organisms by blood components for targeted destruction** (eg, complement complex, natural killer lymphocyte)

- **Acquired immunity-** does not develop until after the body is first attacked by pathogens (virus, bacteria, and toxins, for example)
  - Specific target
  - 2 basic types: **antibodies (Ab) produced by B lymphocyte-humoral immunity and activated T lymphocyte-cell-mediated immunity**

- Antibodies: recognition of antigens
  - immunization

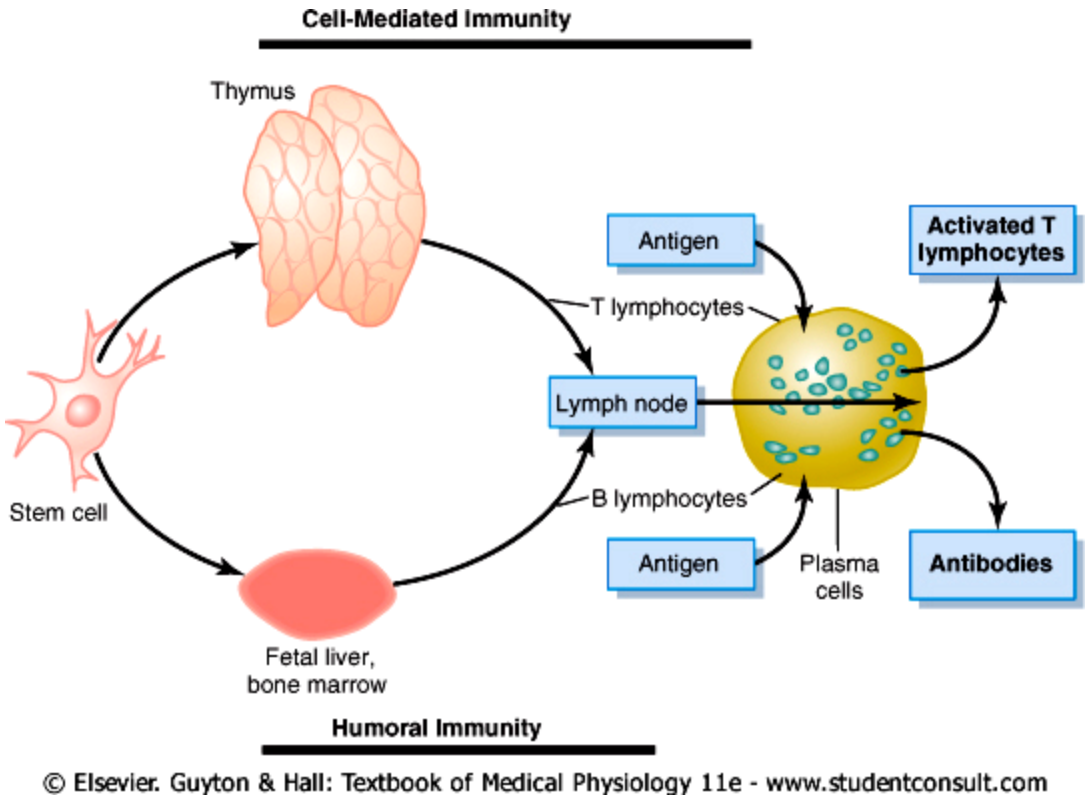
# Lymphocyte- 1

- Location: lymph node, spleen, submucosa of the GI tract and bone marrow
- Organism interception at lymph node before they can be spread
- Lineage: pluripotent hematopoietic stem cell
- **T lymphocytes** are preprocessed at thymus (hence “T”) to generate tolerance against own antigens: own-self ´ foreign; diversification against different specific antigens
- **B lymphocytes** are preprocessed at liver and bone marrow; a special organ called the bursa of Fabricius (hence “B”); diversification of antibodies against different specific antigens



# Lymphocyte- 2

- Diversification due to the combination of different gene segments
- Sensitization: activation of specific T lymphocyte and/or B lymphocyte for antibody secretion



# Mechanism for Activation

**interactions:** direct binding due to molecular recognition; non-covalent, intermolecular force and interactions (eg, electrostatic, hydrophobic, van der Waals and hydrogen bonding)

- **B lymphocyte:** antigen on surface receptor → activation
- **T lymphocyte:** surface receptor protein (aka T cell receptor (TCR))

- **After phagocytosis, macrophage processes the foreign organisms and becomes antigen-presenting cell (APC);** also direct cell contact for activation; also secretes cytokines (or lymphokines; eg interleukin 1) to target cells such as lymphocytes

- **Helper T cell (TH cell):** secretes lymphokines; activates B lymphocytes

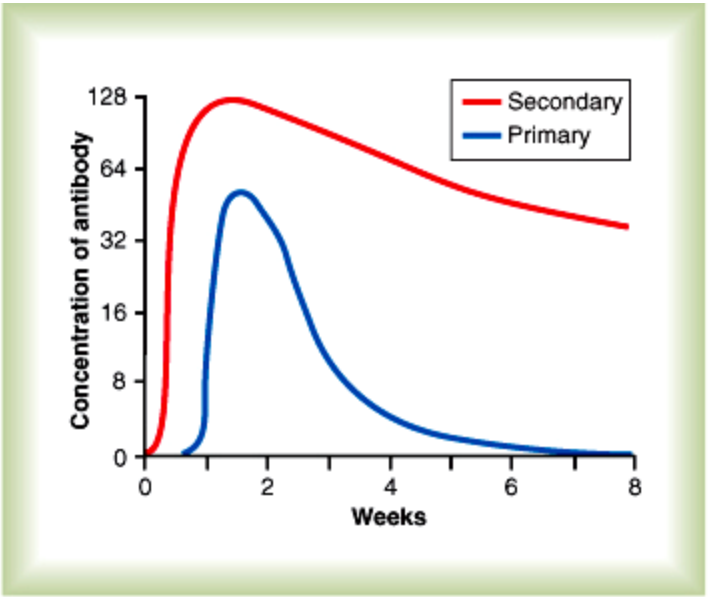
- APC → T cell → activated TH cell which secretes lymphokines that activates B lymphocytes for antibody production; high quantity of antibody

- APC also interact with B lymphocyte directly; low quantity of antibody

- Activated B → lymphocyte plasma cell → antibody production

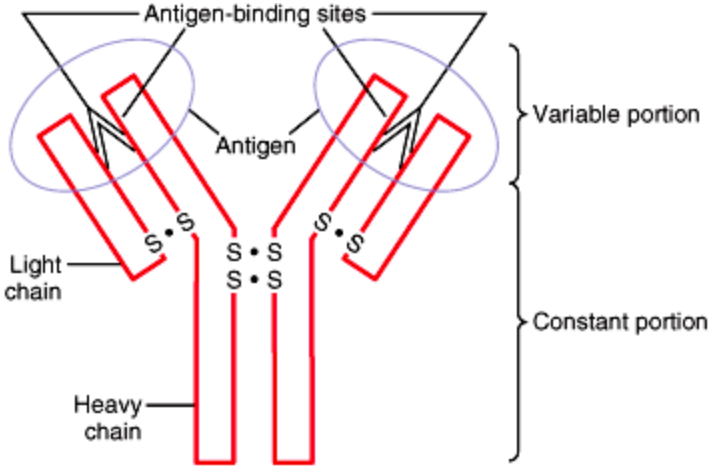
# B Lymphocyte System

- Some activated B lymphocyte → memory cell
- Memory cell
  - Circulate throughout the body
  - Activated during the 2º attack from the same pathogenic stimulus
  - More potent and more rapid response during the second time of exposure to the same pathogenic stimulus



# Antibody- 1

- Protein: immunoglobulins (Ig)
- **Polypeptide chain: light chain (LC) and heavy chain (HC)**
- **Constant region (CR)-**recognized by complement complex, variable region (VR)-antigen recognition





- Disulfide bond linkage
- Size: order of 10 nm
- Specificity-different shape in VR for antigen recognition
- Affinity constant (Ka): measure of binding strength of Ab-Ag interactions;
- Y shape

# Antibody- 2

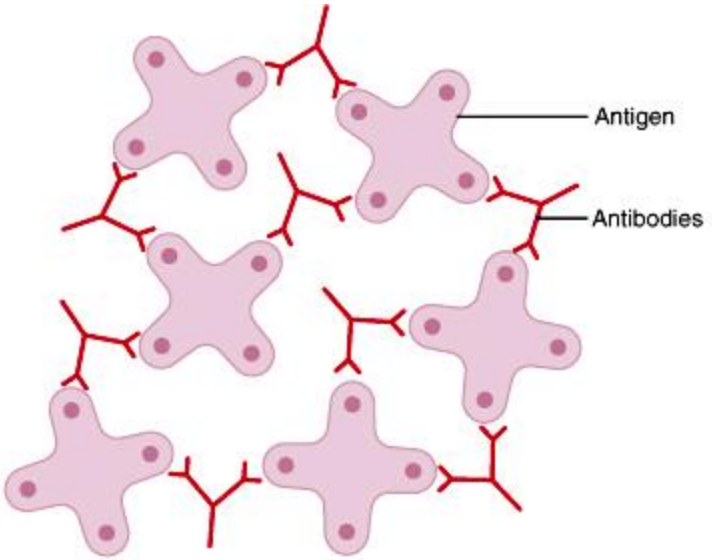
- Class of antibody
  – IgG, IgM, IgA, IgE, IgD

- IgG
  – bivalent binding sites
  – About 3/4 of Ab population

- IgE: allergic reaction

- IgM: 10 binding sites, so can
- Bind a lot of antigen

- Ab-Ag interactions
  – 1-1 correspondence
  – 1-many correspondence (IgM, For example)





- Action
  – Direct attack
    – Agglutination, precipitation, neutralization, lysis
      - Activation of complement system

# Compliment System- 1

- Collective term of about 20 proteins
- Bactericidal; Constant Region of Ab binds to C1, which activates a cascade of sequential reactions
- Enzyme precursors in the reactions are normally inactive but can be activated by the classical pathway
- Amplification
- **Components** are found in plasma

Proteins of the blood

Includes chemotactic agents

- **Also includes components**

That leak out into tissue spaces

--Opsonization- activates phagocytosis

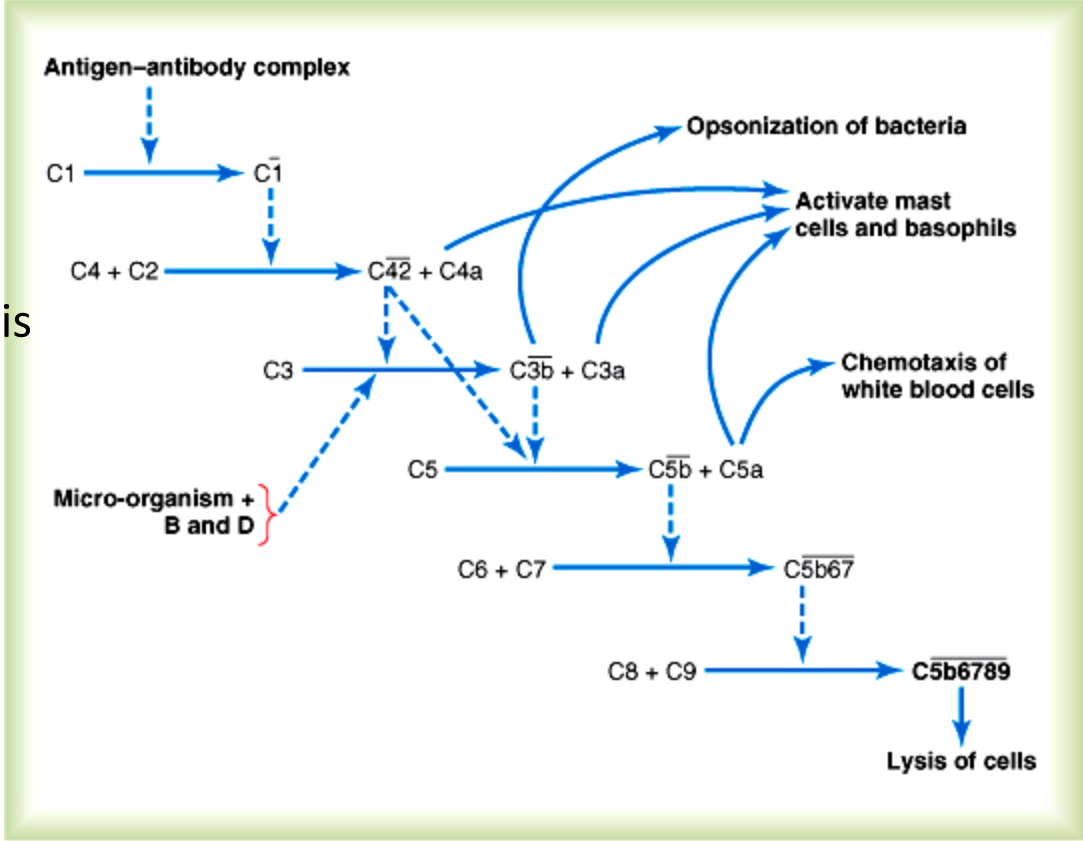
By neutrophils and macrophages,

Causing the cells to engulf bacteria-

- Another End result:

-cell lysis-inactivation

Of the infecting agent.



# Compliment System- 2

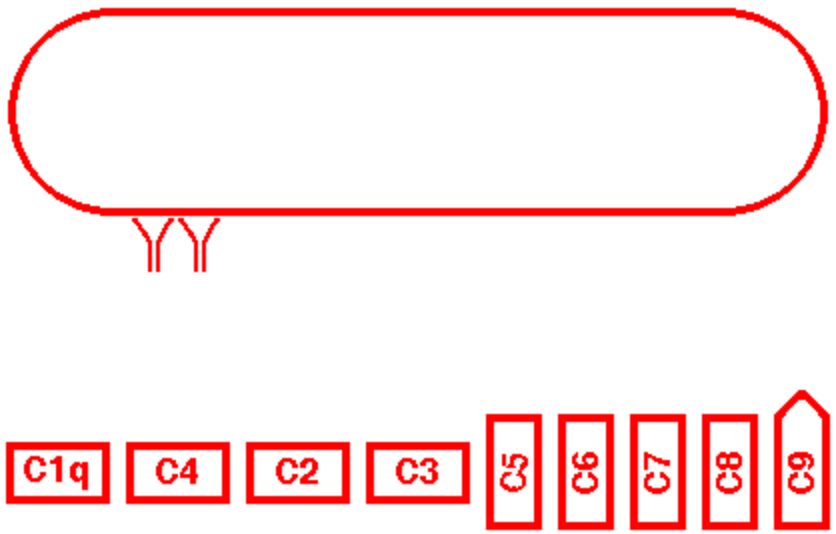
- Effects
  – Opsonization by C3b, then recognized by neutrophils and macrophages
  – Lytic complex (C5b6789) is large enough to allow ions and small molecules to be leaked out of the cell
  – Agglutination: cause adhesion of invading organisms
  – Neutralization: render viruses non-virulent
  – Chemotaxis: induce phagocytes to migrate to infected/injured areas
  – Activation of mast cells and basophils these cells release histamine, heparin and several other substances into the local fluids.

    What is the effect on blood flow?

- ↑Local blood flow

- ↑ Leakage of fluid and protein to the tissue
  – Inflammatory effects

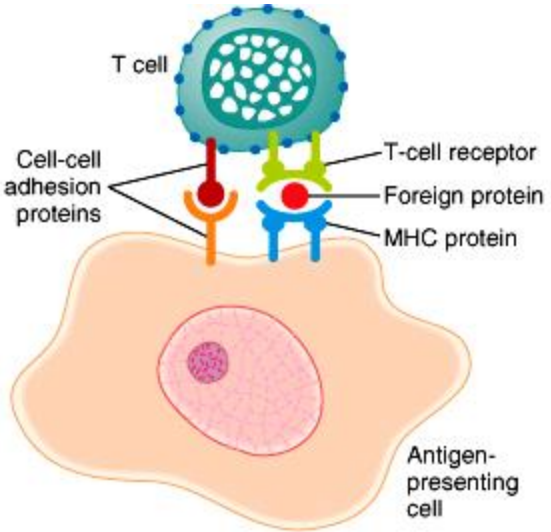
# Complement Proteins




- Complement proteins are present in circulation and can be activated by a variety of mechanisms. Attached immunoglobulins can set off the "classic pathway" as shown above schematically. The complement cascade can generate active compounds such as C3b that functions as an opsonin, or C5a that attracts neutrophils. If the C5-9 complex (the "membrane attack complex") is generated, the cell to which the complex is attached can be lysed by perforation of its cell membrane.

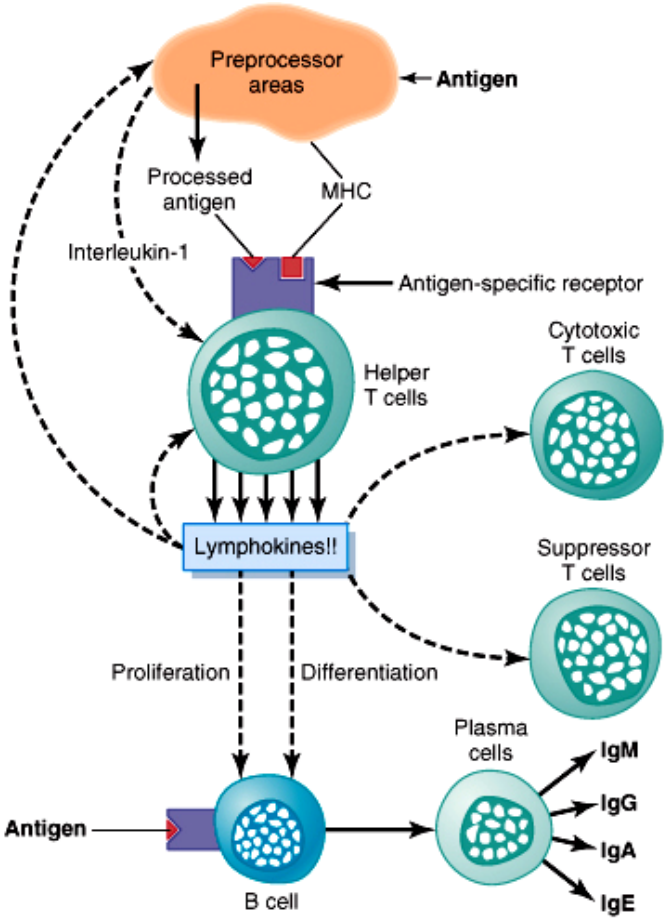
# Cell-Mediated Immunity

- **Antigen-presenting cell (APC)**
- Helper T (TH) cell
- Major histocompatibility complex (MHC)
  - MHC type 1: presents Ag to cytotoxic T (Tc) cell
  - MHC type 2: presents Ag to TH cell
- T cell receptor (TCR)
- Suppressor T cell



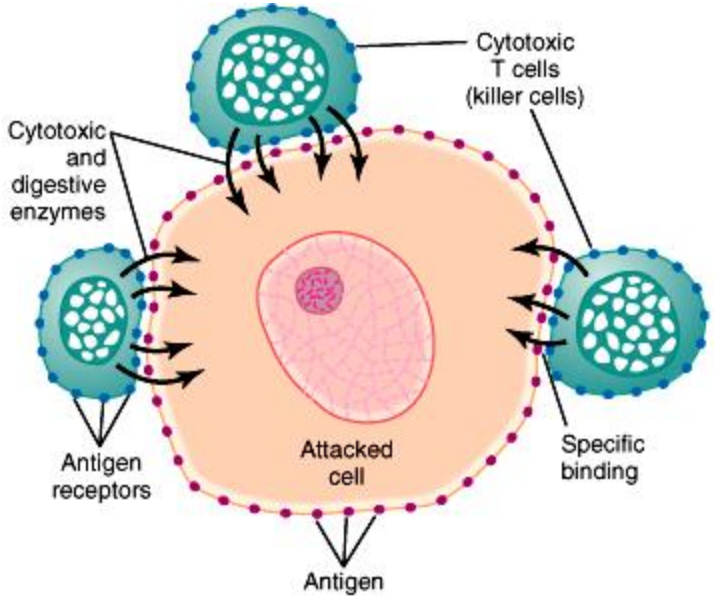
# T- Lymphocyte- 1

- **Helper T (TH) cell:** most numerous
- Major regulator for virtually all immune functions
- Secretes lymphokines: IL-2, 3,4,5,6, GM-CSF, interferon g
- Target cell of AIDS (*bad news*)



# T- Lymphocyte- 2

- **Cytotoxic T (Tc) cell:** direct attack on microorganisms
- Binds tightly to microorganisms or APC
- Perforin: hole-forming protein that punches holes on the attacked cell
- Releases cytotoxic and digestive enzymes
- Target: virus, cancer cells and other foreign cells (why cancer cells?)



# T-Lymphocyte- 2

- **Suppressor T cell:** regulates the activity of other cells such as $T_H$ and $T_C$
- Prevents excessive immune reactions
- Mediates immune tolerance

# Immunization

- To produce acquired immunity against specific diseases by injecting dead/inactive form of microorganisms that cause the diseases

- Need the full or part of the antigenic region
  – Destroy the toxic nature of the toxins
  – Mutate the form of microorganisms at the DNA level

- To produce acquired immunity against specific diseases by injecting antibody without Ag or activated T cells or both made from donor blood (I am legend!?)

# The End!