

***MIRO451***

***Immunology***

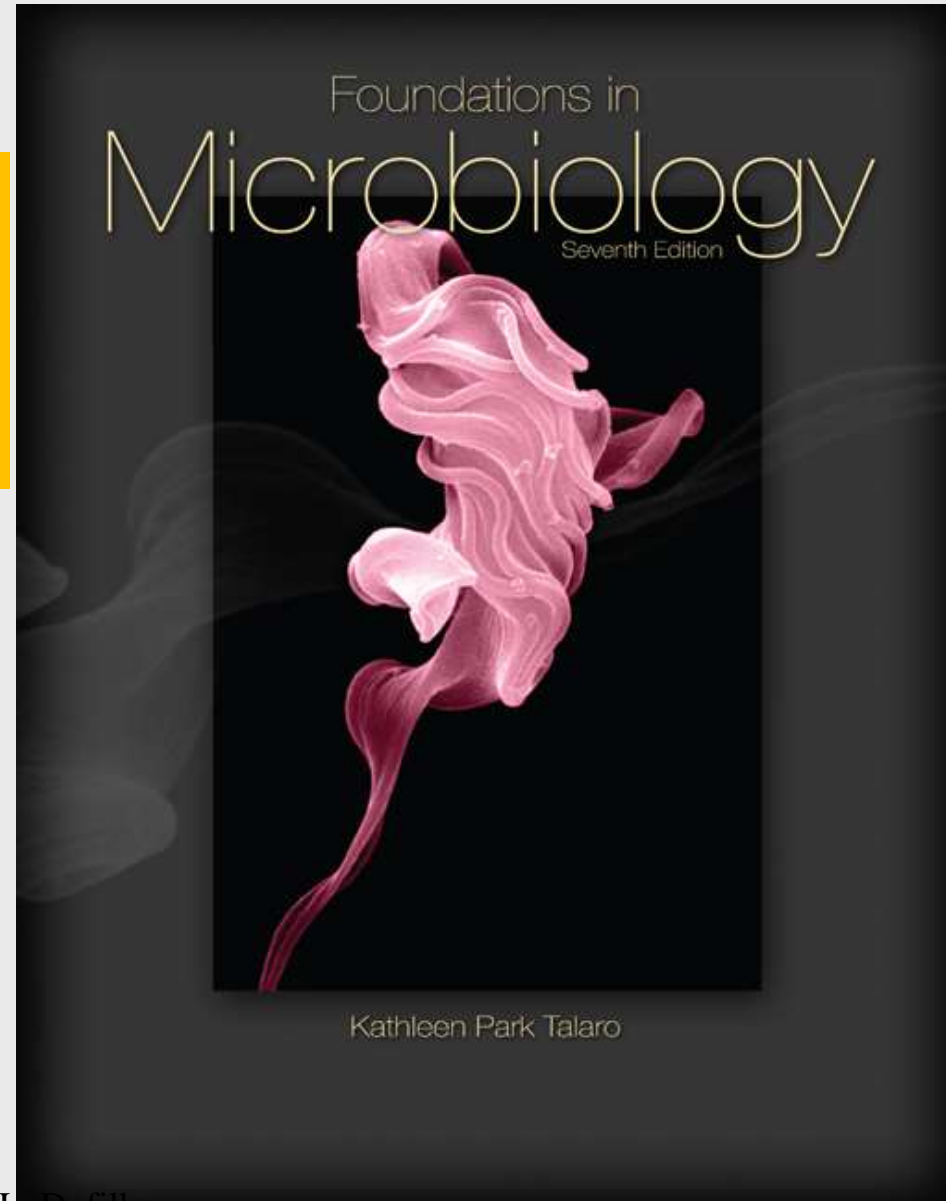
***Presented by***

***Prof. Nagwa Mohamed Aref***

***(Microbiology – Molecular Virologist)***

## Chapter 15

# Adaptive, Specific Immunity and Immunization



# 15.1 Specific Immunity – Adaptive Line of Defense

Third line of defense – acquired

- Dual System of B and T lymphocytes
  - Immunocompetence
- **Antigen** – Molecules that stimulate a response by T and B cells
- Two features that characterize specific immunity:
  - **Specificity**
  - **Memory**

# Classifying Immunities

- **Active immunity** –
- **Passive immunity** –
- **Natural immunity** –
- **Artificial immunity** –

- **Natural active immunity –**
- **Natural passive immunity –**
- **Artificial active immunity –**
- **Artificial passive immunity –**

Figure 15.1

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**Acquired Immunity**

**Natural Immunity**

is acquired through the normal life experiences not induced through medical means.

**Active Immunity**

is the consequence of a person developing his own immune response to a microbe.



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**Passive Immunity**

is the consequence of one person receiving preformed immunity made by another person.



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**Artificial Immunity**

is that produced purposefully through medical procedures (also called immunization).

**Active Immunity (same as vaccination)**

is the consequence of a person developing his own immune response to a microbe.



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**Passive Immunity**

occurs when one person receives preformed immunity made by another person.



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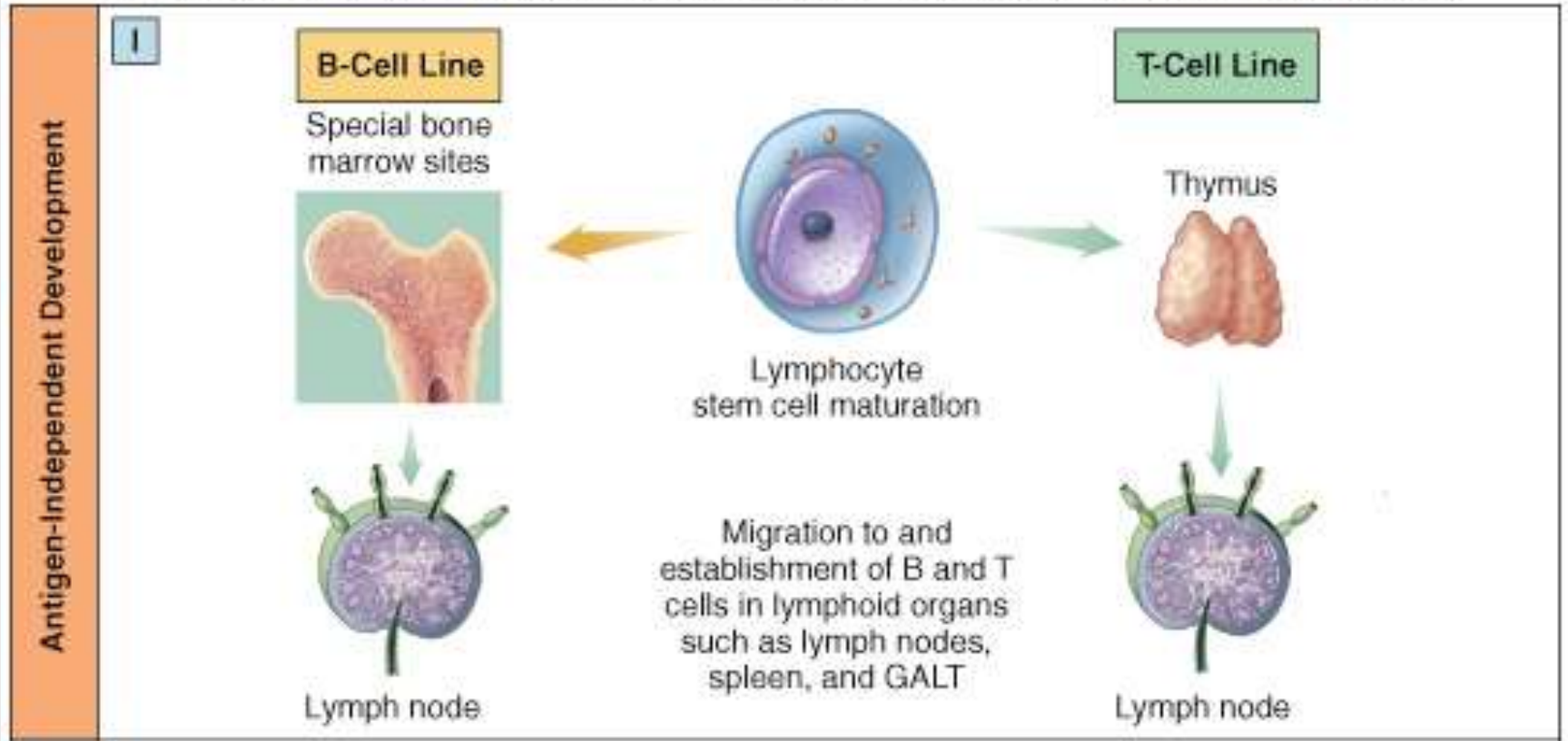
# Overview of Specific Immune Responses

Separate but related activities of the specific immune response:

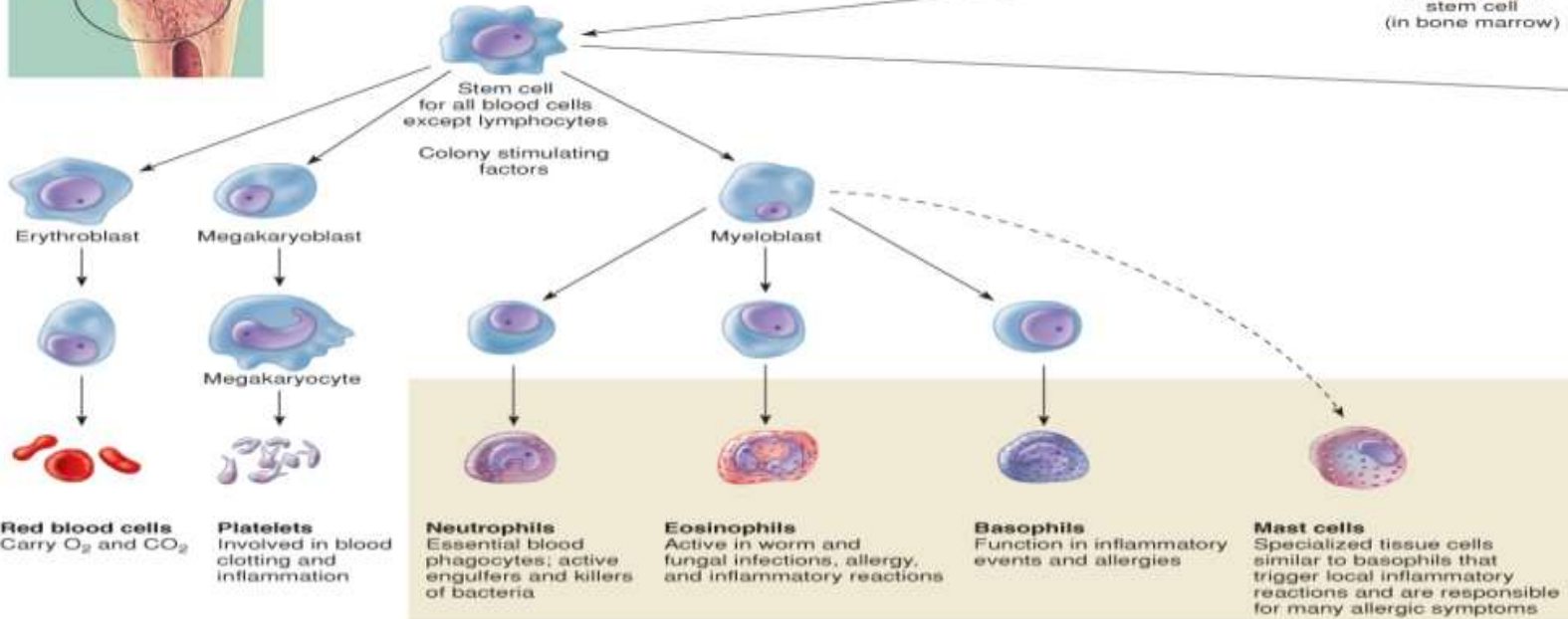
- Development and differentiation of the immune system
- Lymphocytes and antigen processing
- The cooperation between lymphocytes during antigen presentation
- B lymphocytes and the production and actions of antibodies
- T lymphocyte responses

Figure 15.2 (I)

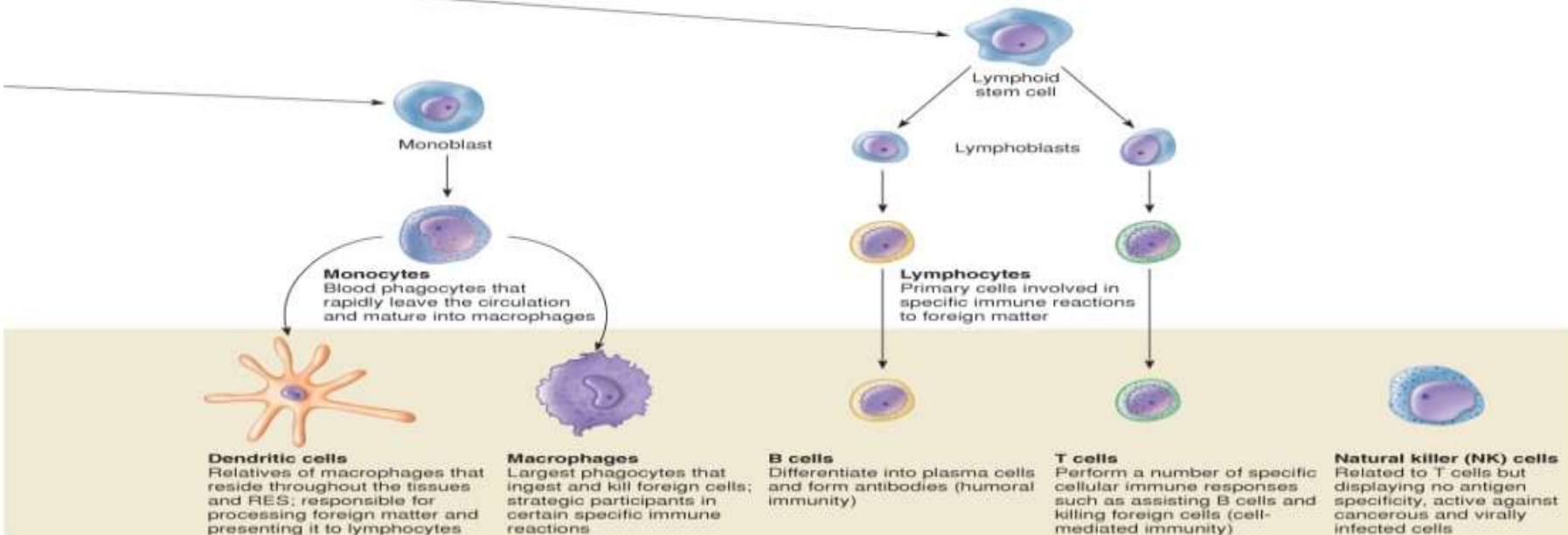
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# Receptors/Markers

Cell receptors or markers confer specificity and identity of a cell

- Major functions of receptors are:
  1. To perceive and attach to nonself or foreign molecules
  2. To promote the recognition of self molecules
  3. To receive and transmit chemical messages among other cells of the system
  4. To aid in cellular development

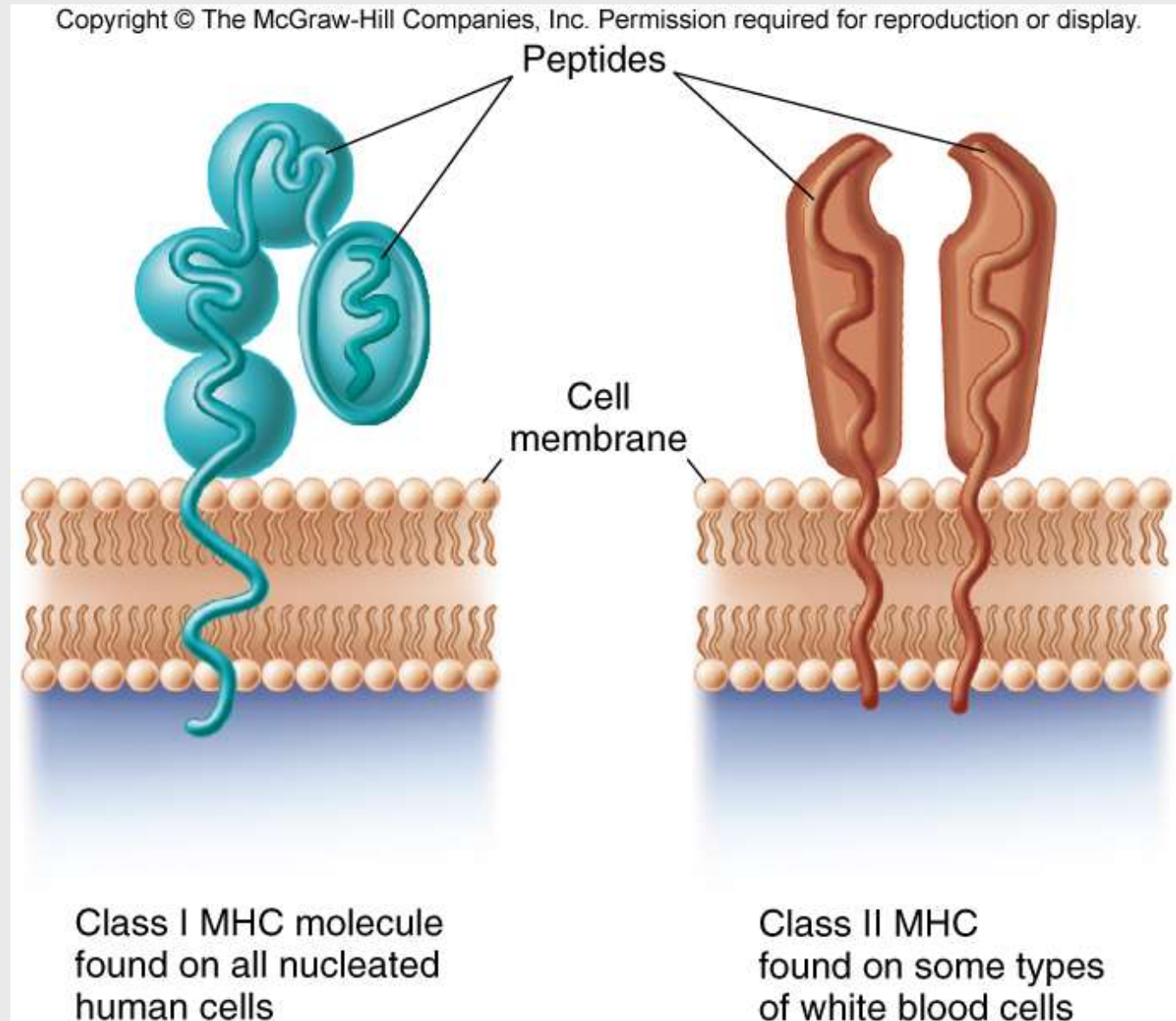
# Major Histocompatibility Complex (MHC)

- Receptors found on all cells except RBCs
- Also known as human leukocyte antigen (HLA)
- Plays a role in recognition of self by the immune system and in rejection of foreign tissue

# Functions of MHC

- Genes for MHC clustered in a multigene complex:
  - Class I – markers that display unique characteristics of self molecules and regulation of immune reactions
    - Required for T lymphocytes
  - Class II – regulatory receptors found on macrophages, dendritic cells, and B cells
    - Involved in presenting antigen to T-cells

Figure 15.3



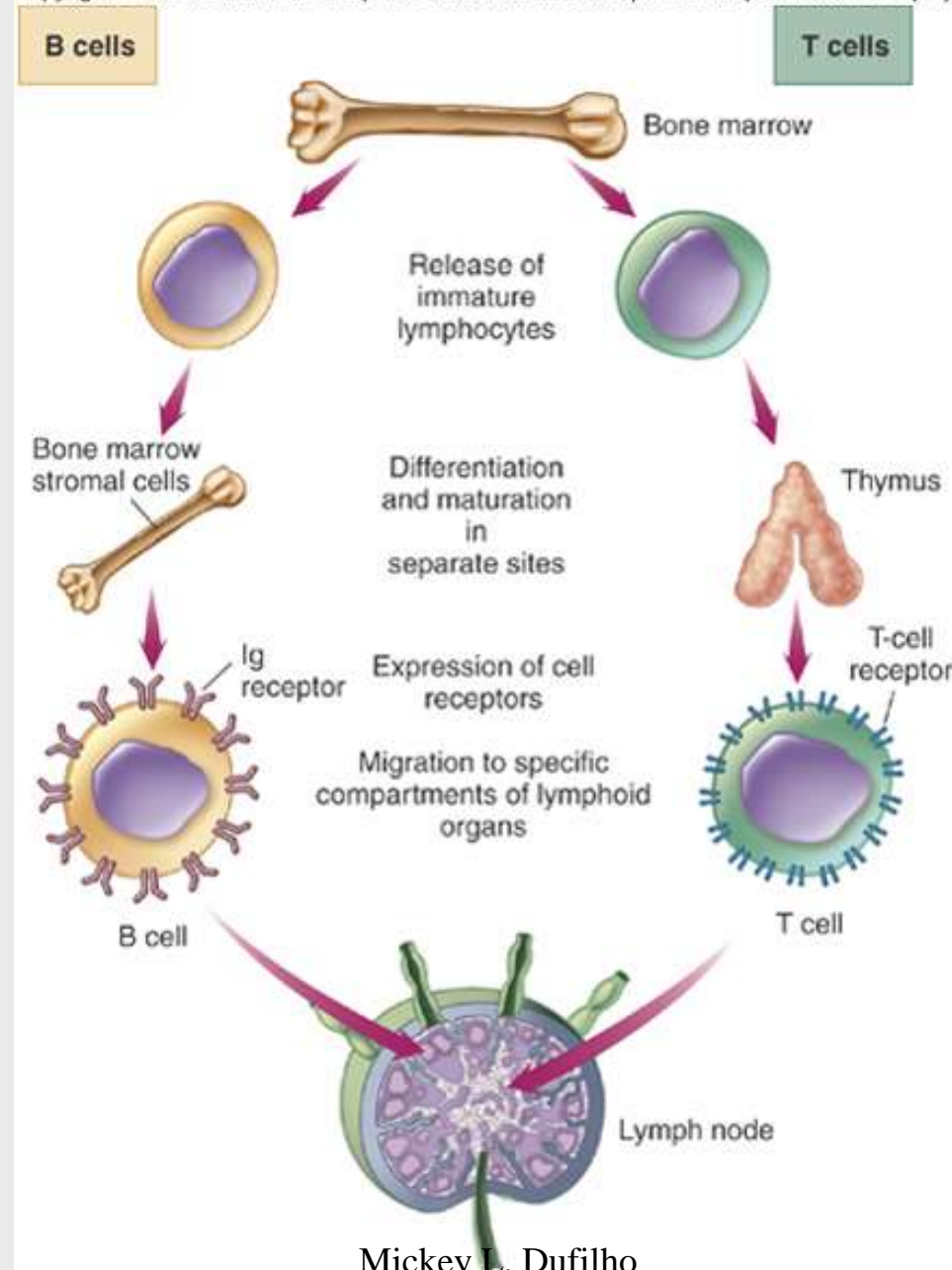
# Lymphocyte Receptors

- Lymphocyte's role in surveillance and recognition is a function of their receptors
- B-cell receptors – bind free antigens
- T-cell receptors – bind processed antigens together with the MHC molecules on the cells that present antigens to them

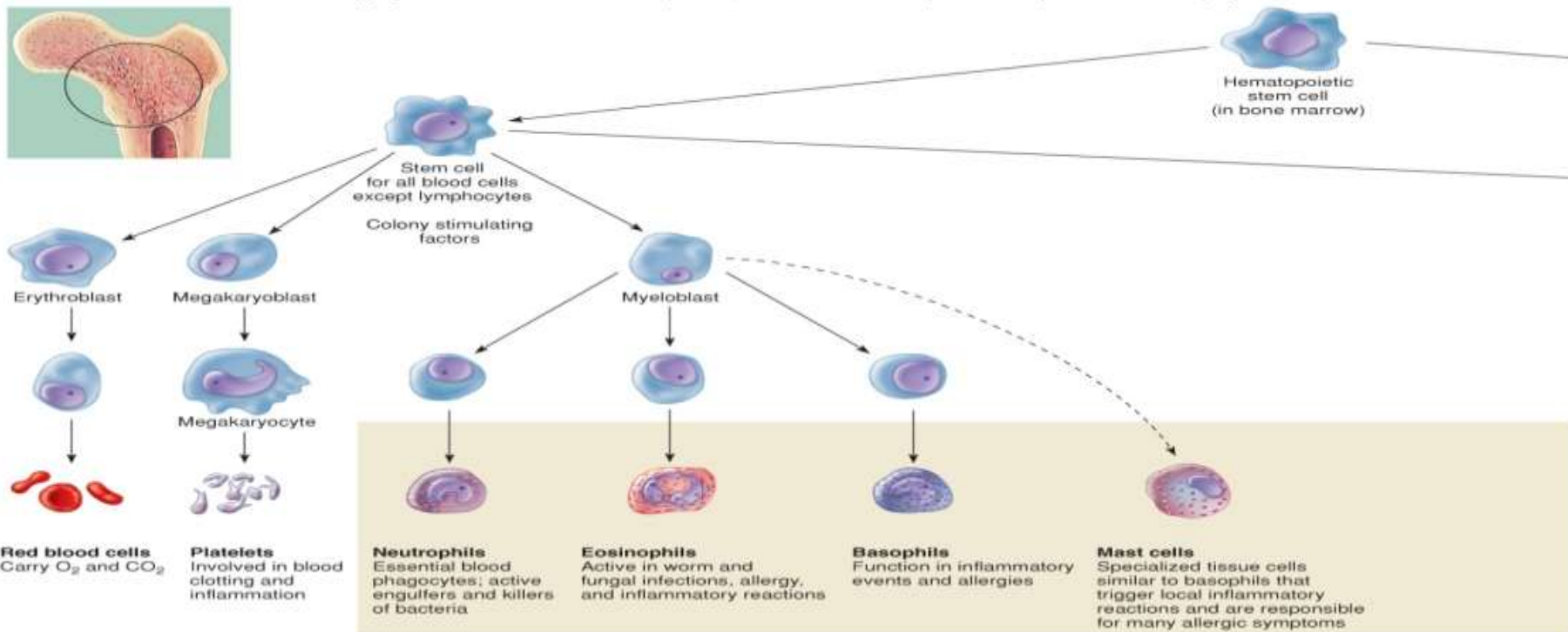
# Clonal Selection Theory

- Lymphocytes use 500 genes to produce a tremendous variety of specific receptors
- Undifferentiated lymphocytes undergo a continuous series of divisions and genetic changes that generate millions of different cell types
- Each cell has a particular/unique receptor specificity

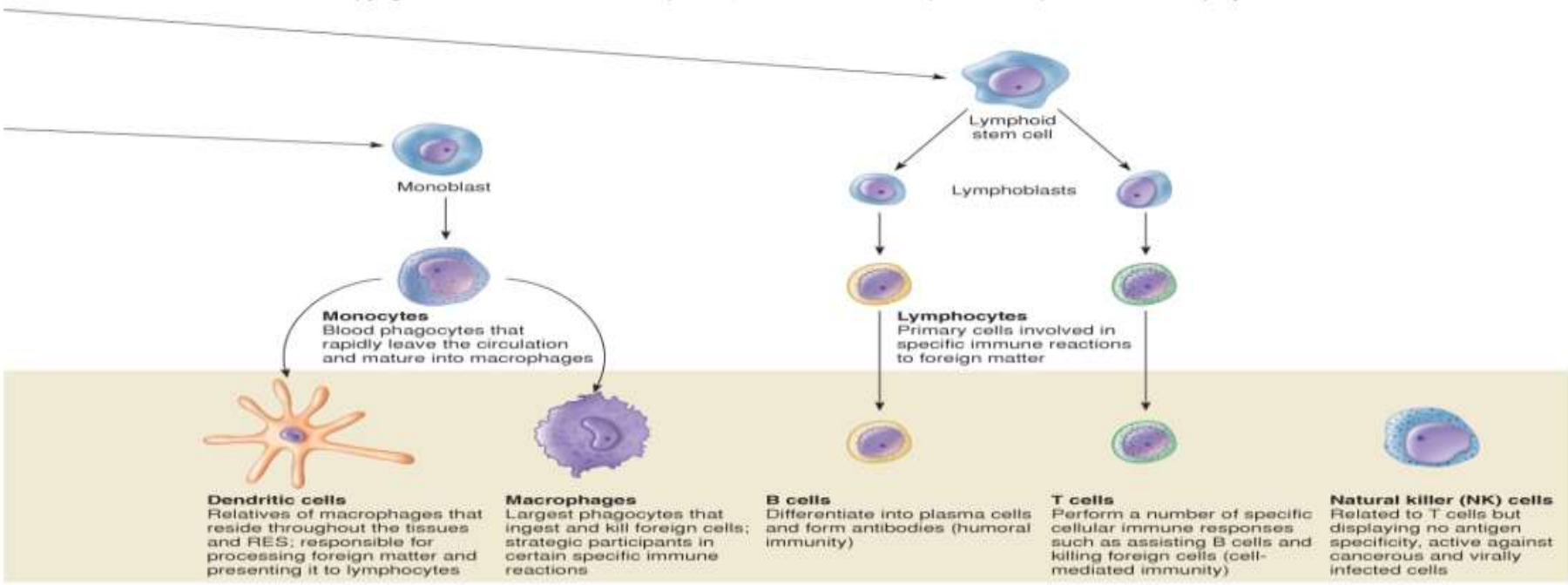
Figure 15.4





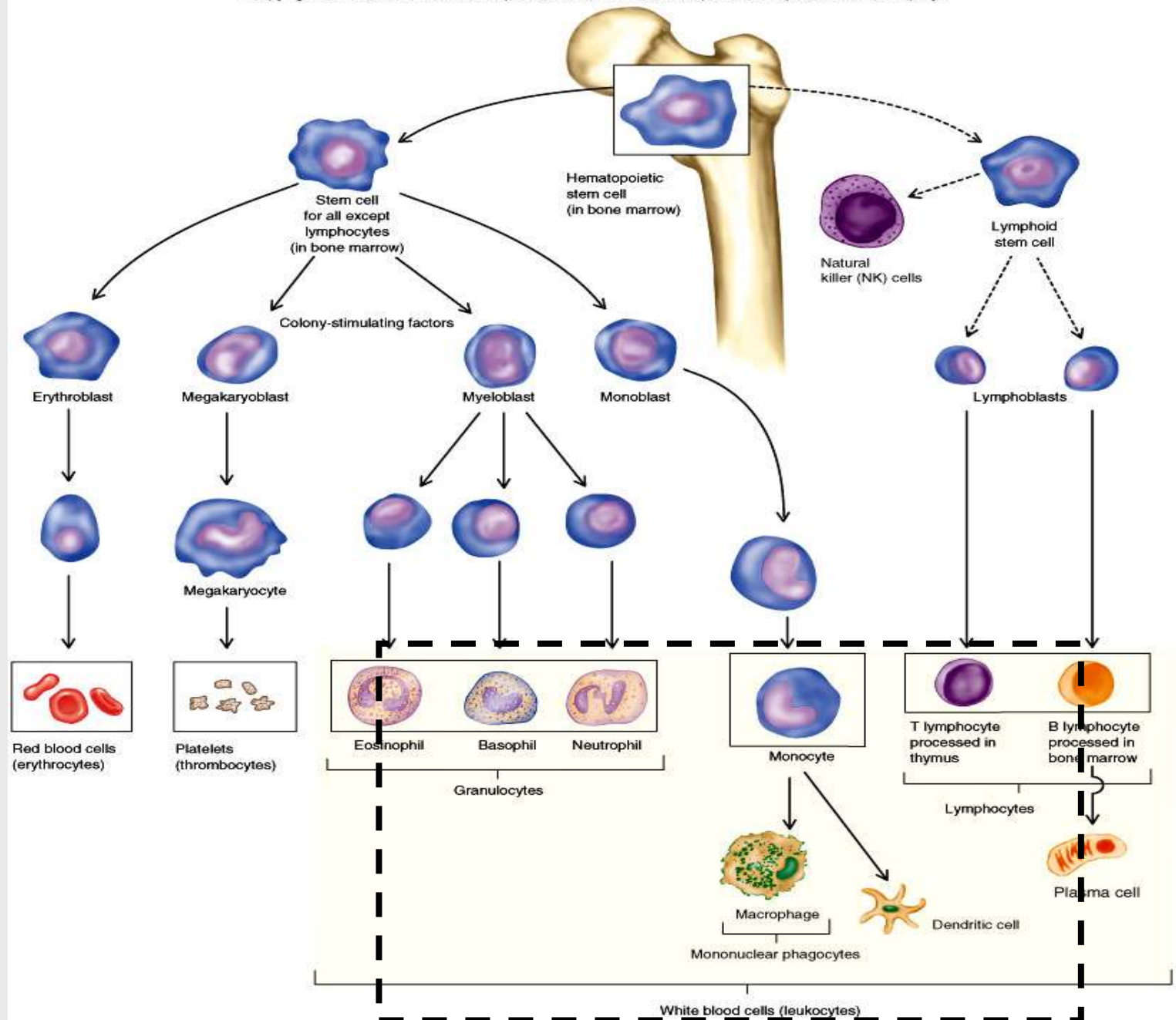


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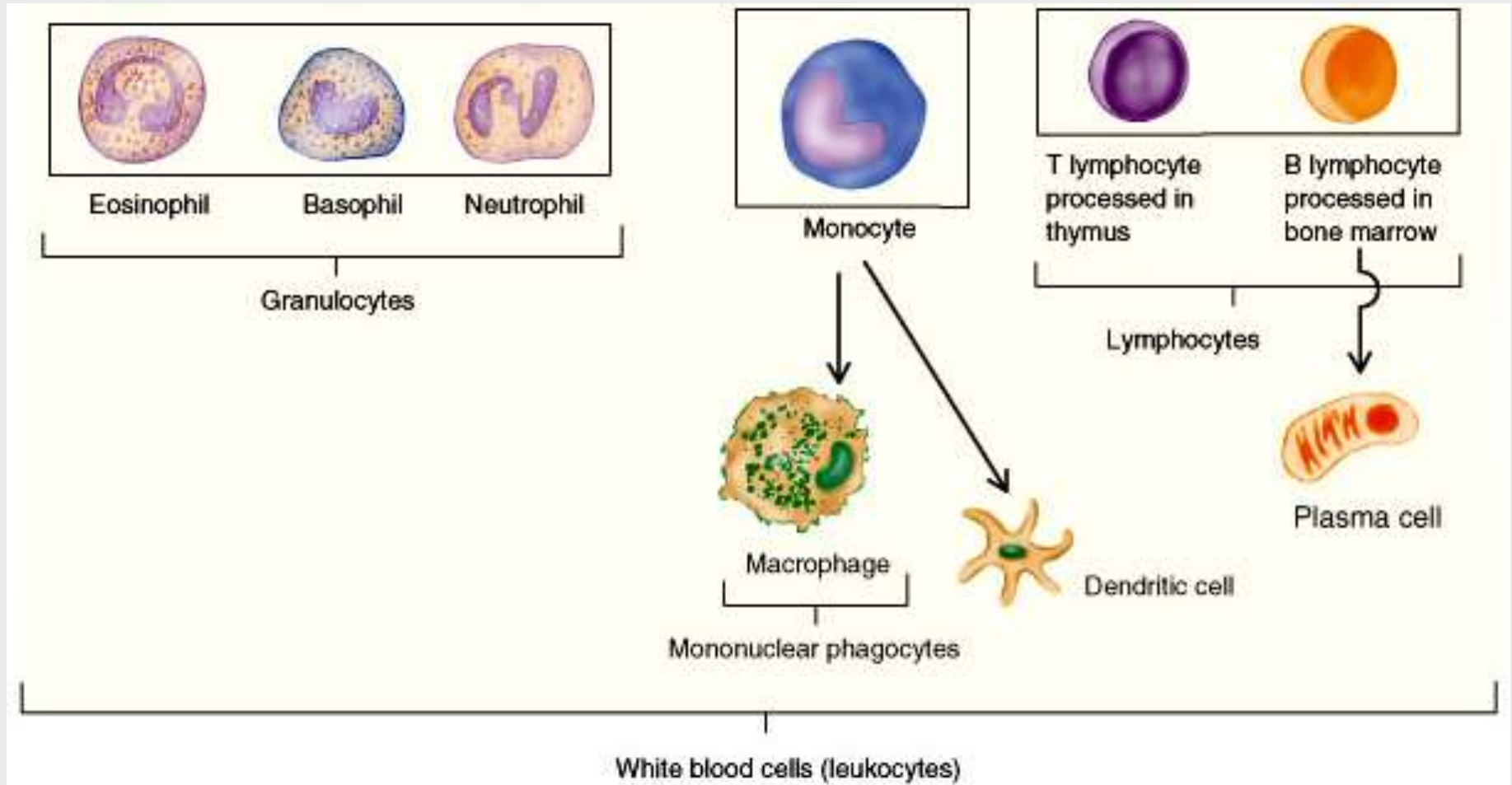


# Cells of the Immune System

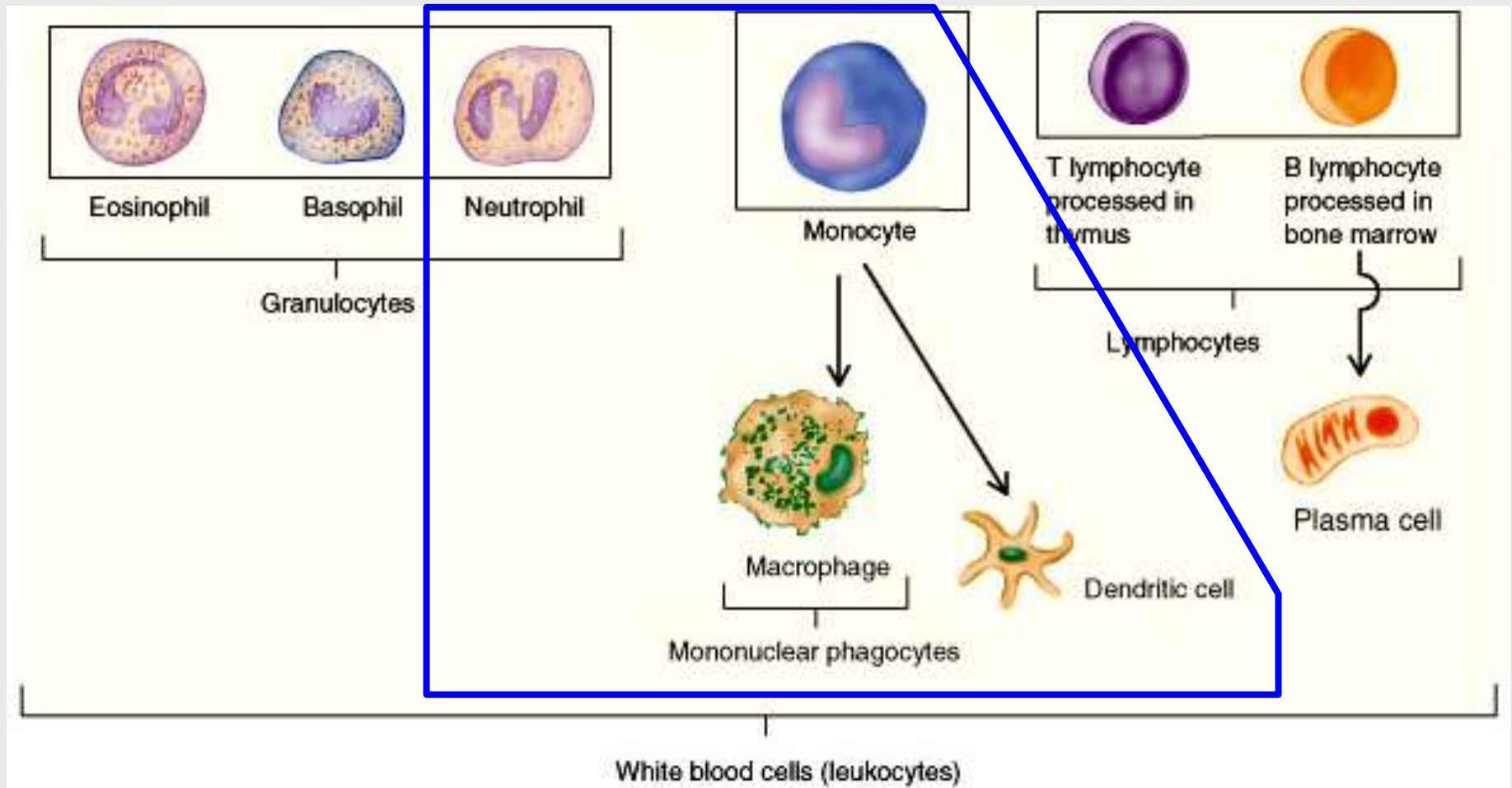
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# Leukocytes = White Blood Cells

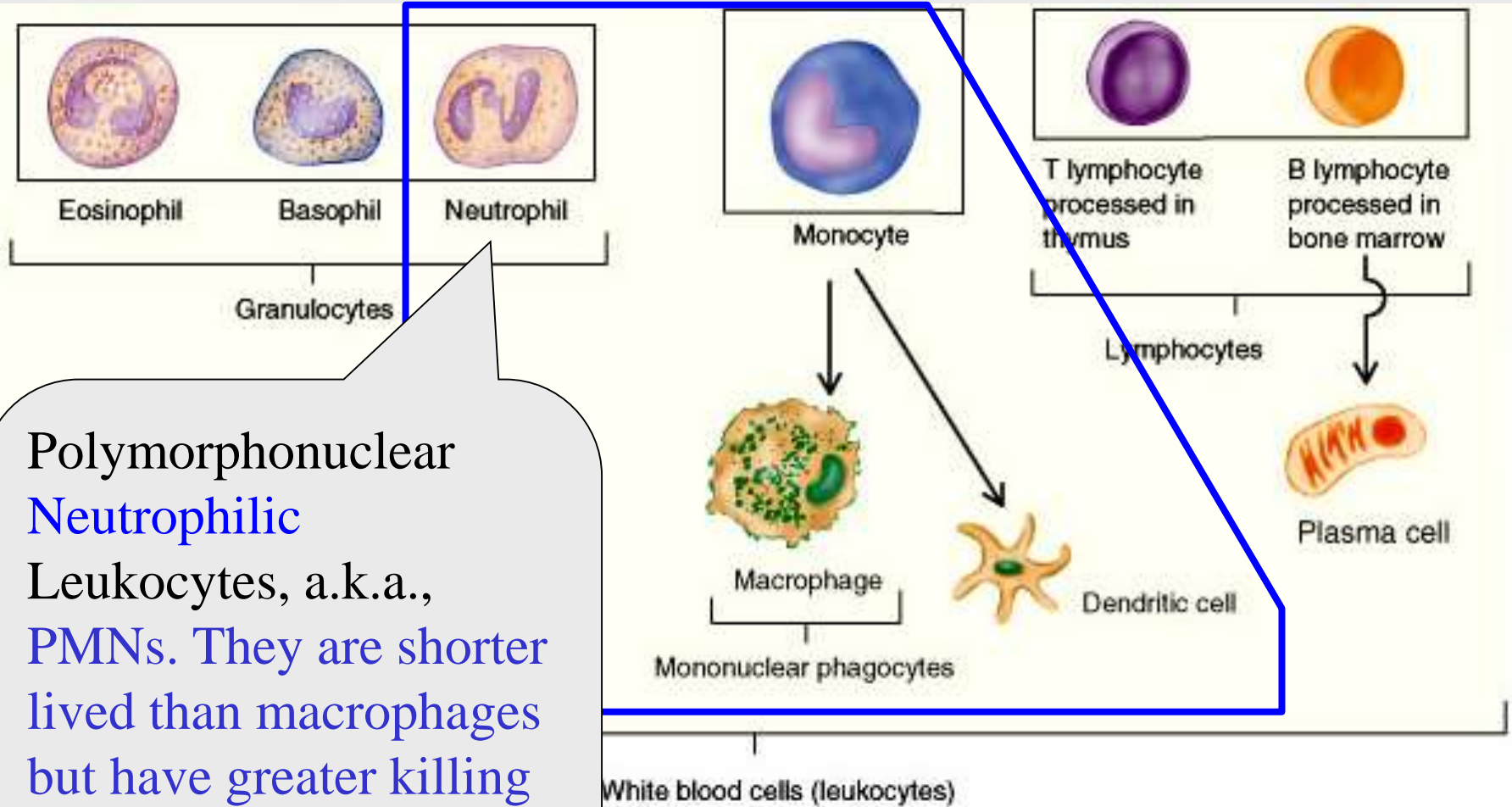


# Phagocytic Leukocytes



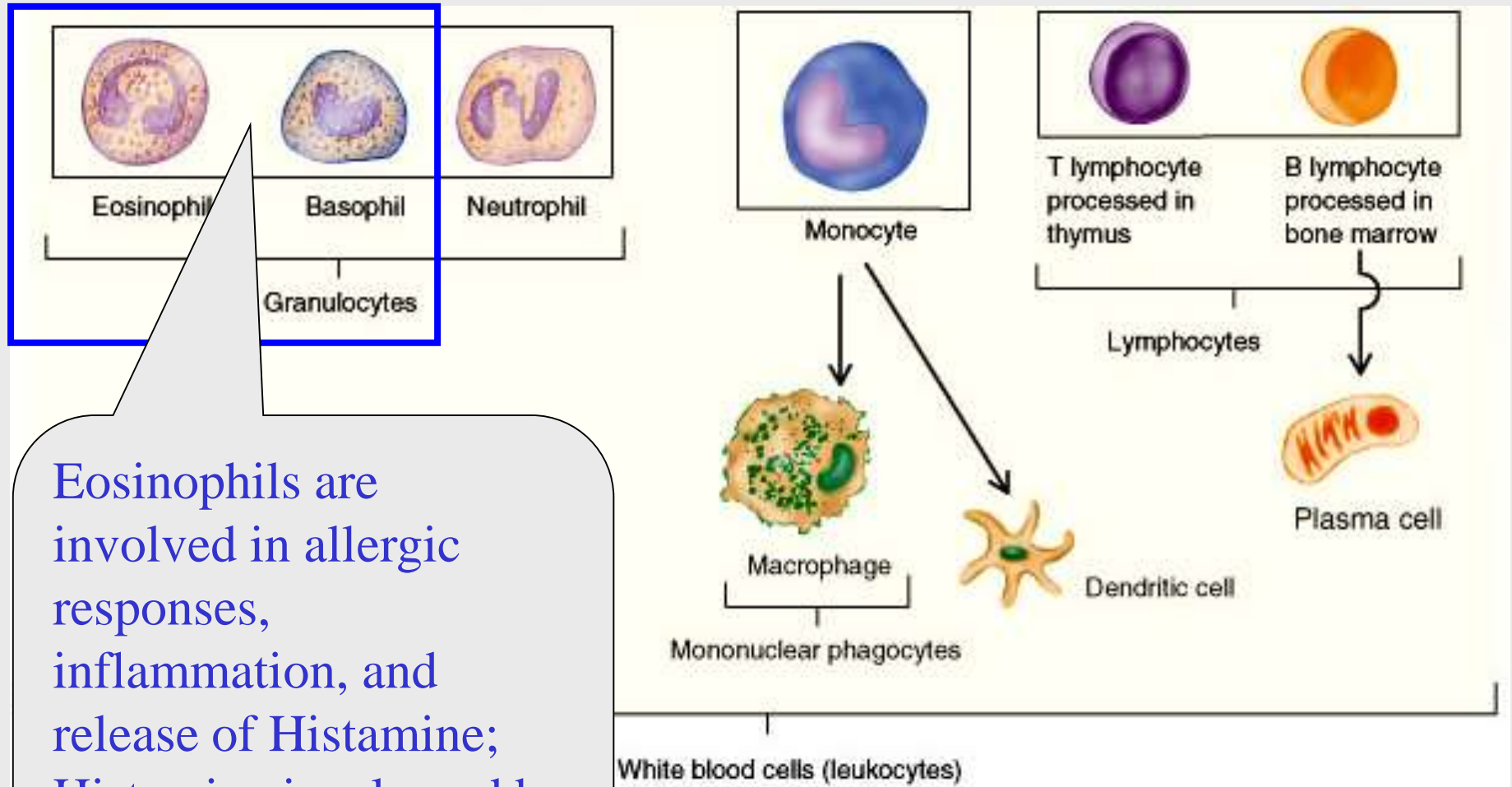


# PMNs

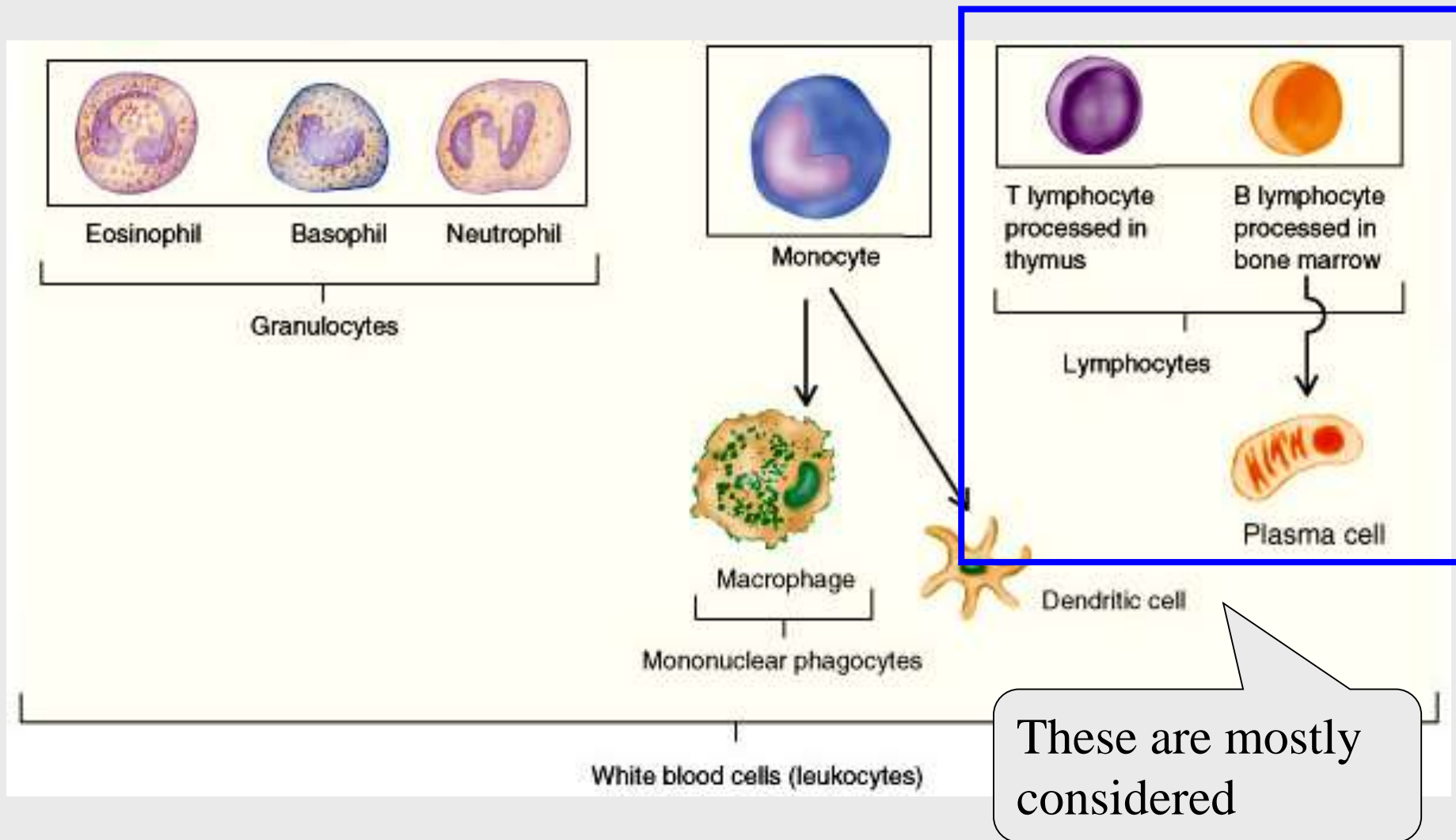


Polymorphonuclear  
Neutrophilic  
Leukocytes, a.k.a.,  
PMNs. They are shorter  
lived than macrophages  
but have greater killing  
power.

# Non-Phagocytic Granulocytes



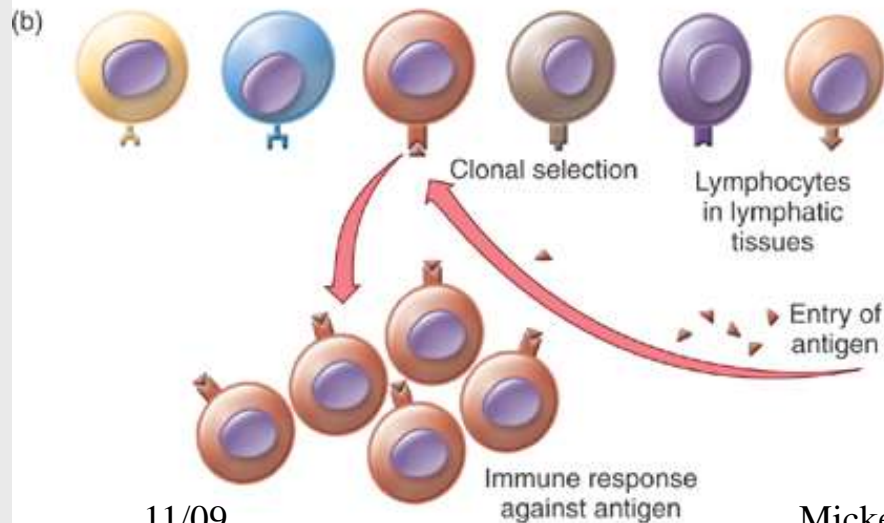
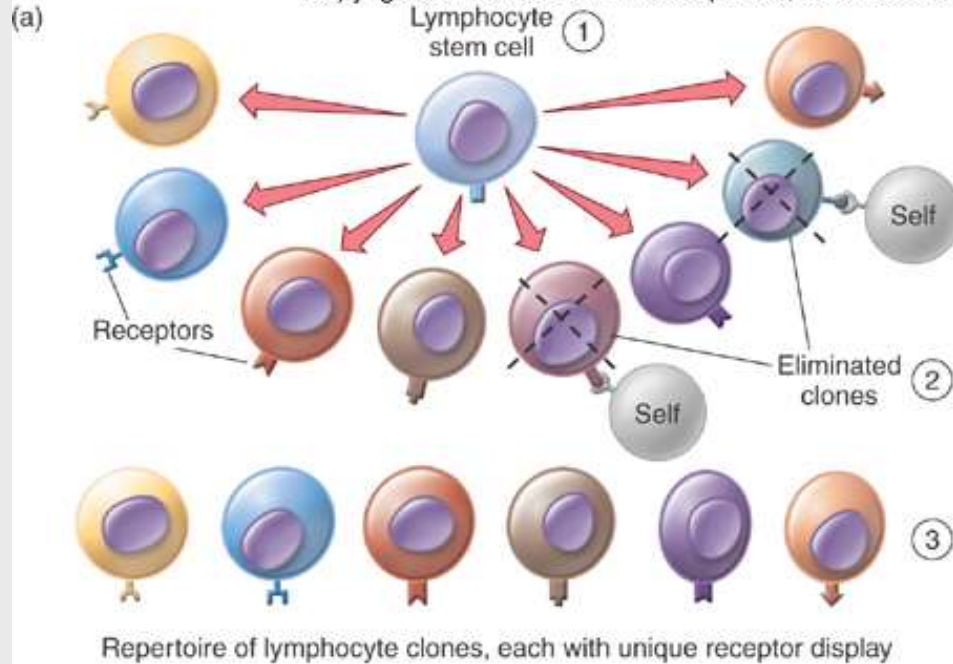
# Mediators of Adaptive Immunity





# Figure 15.5

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## (a) Antigen-Independent Period

1. During development of early lymphocytes from stem cells, a given stem cell undergoes rapid cell division to form numerous progeny.

During this period of cell differentiation, random rearrangements of the genes that code for cell surface protein receptors occur. The result is a large array of genetically distinct cells, called clones, each clone bearing a different receptor that is specific to react with only a single type of foreign molecule or antigen.

2. At this same time, any lymphocyte clones that develop a specificity for self molecules and could be harmful are eliminated from the pool of diversity. This is called immune tolerance.

3. The specificity for a single antigen molecule is programmed into the lymphocyte and is set for the life of a given clone. The end result is an enormous pool of mature but naive lymphocytes that are ready to further differentiate under the influence of certain organs and immune stimuli.

## (b) Antigen-Dependent Period

4. Lymphocytes come to populate the lymphatic organs, where they will finally encounter antigens. These antigens will become the stimulus for the lymphocytes' final activation and immune function. Entry of a specific antigen selects only the lymphocyte clone or clones that carries matching surface receptors. This will trigger an immune response, which varies according to the type of lymphocyte involved.

# Specific B-Cell Receptor: Immunoglobulin

Receptor genes of B cells govern immunoglobulin (Ig) synthesis

- Large glycoproteins that serve as specific receptors of B cells
- Composed of 4 polypeptide chains:
  - 2 identical heavy chains (H)
  - 2 identical light chains (L)
- Y shaped arrangement – ends of the forks formed by light and heavy chains contain a wide range of variable **antigen binding sites**
- Variable regions
- Constant regions

Figure 15.6 (a)

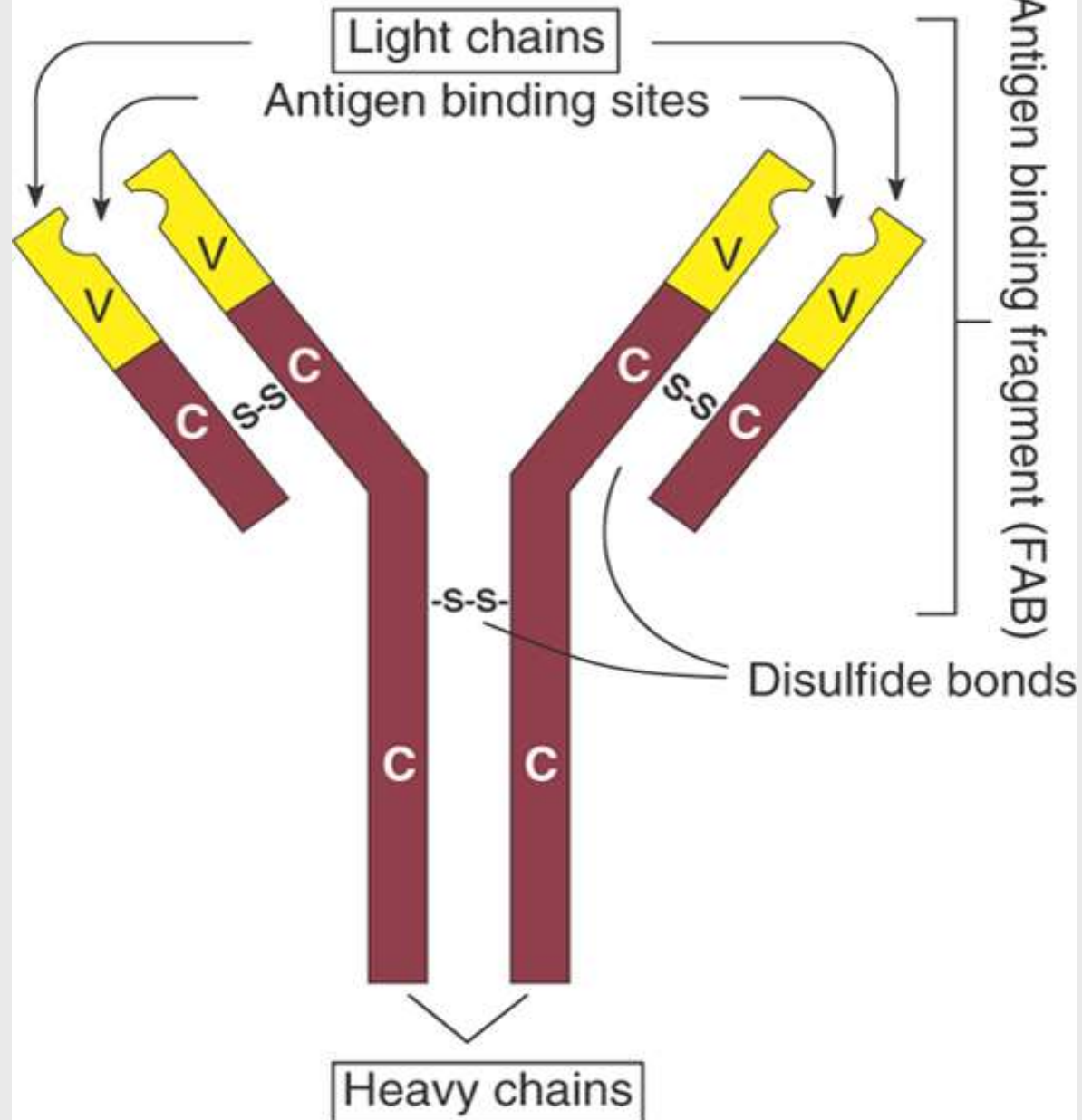
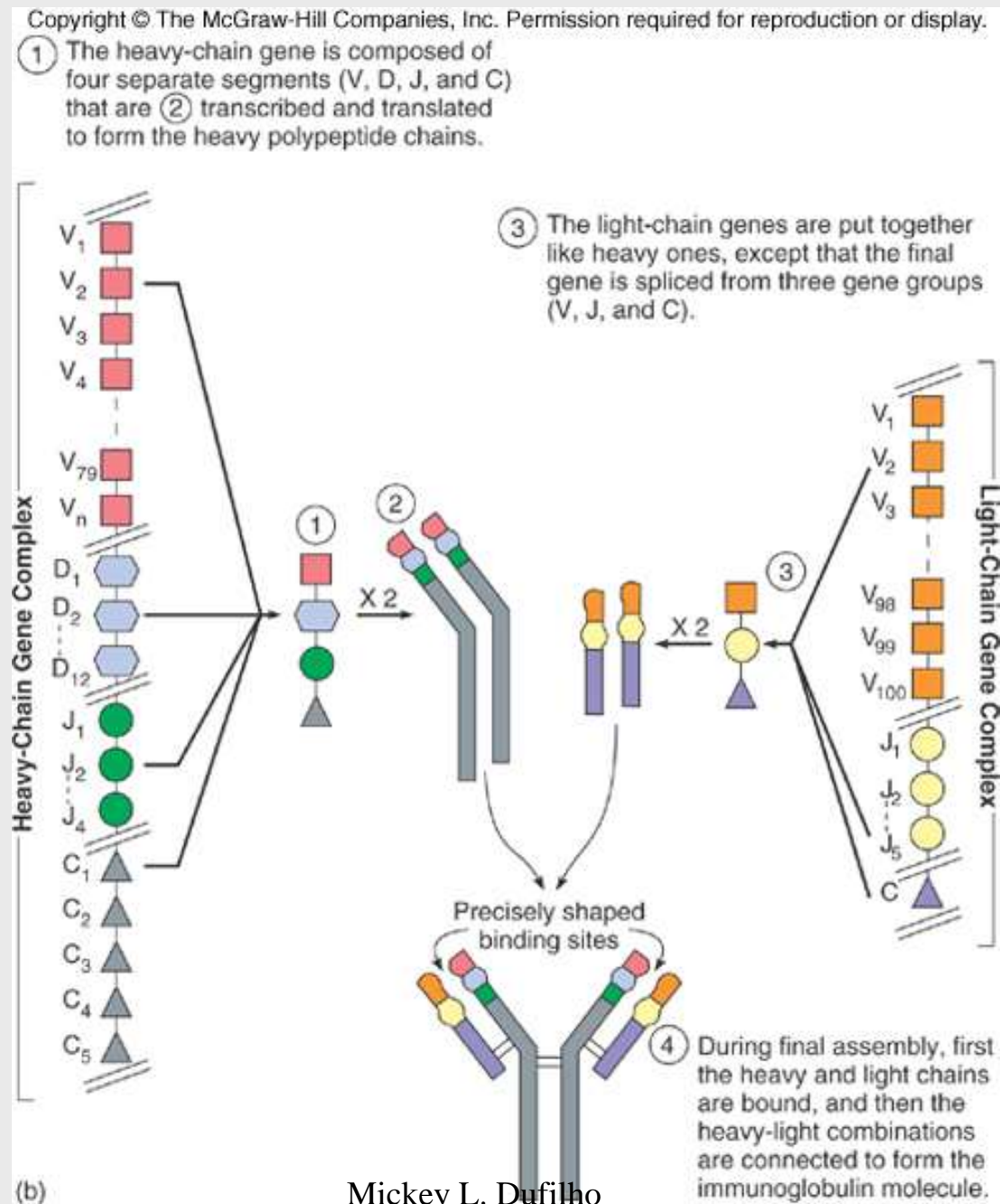


Figure 15.6 (b)



# T-Cell Receptors for Antigen

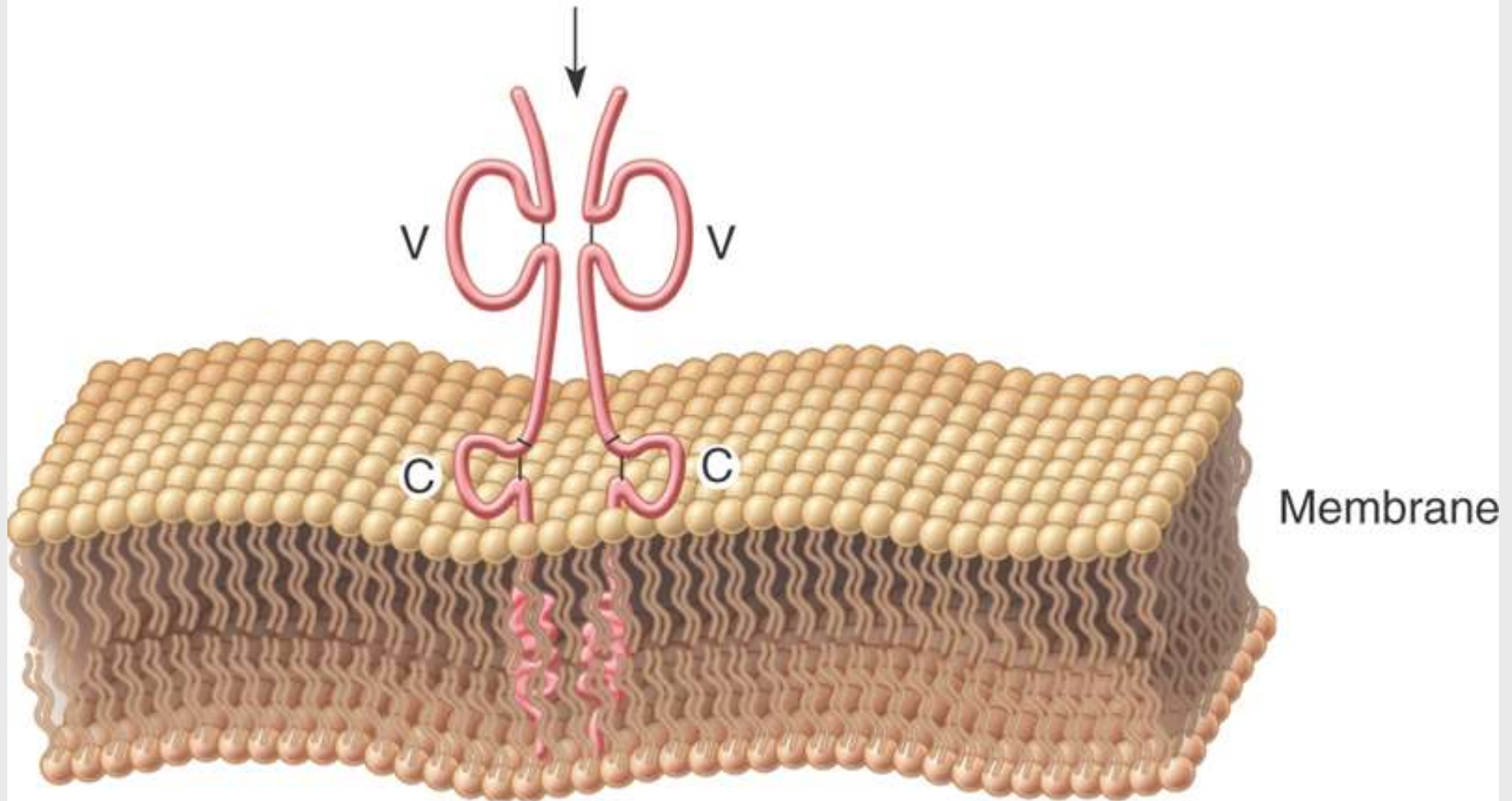
- Formed by genetic recombination, with variable and constant regions
- 2 parallel polypeptide chains
- Small, not secreted



## Figure 15.7 Proposed structure of the T-cell receptor

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Antigen binding site



# 15.3 Lymphocyte Responses and Antigens

- B-cell maturation
  - Directed by bone marrow sites that harbor stromal cells, which nurture the lymphocyte stem cells and provide hormonal signals
  - Millions of distinct B cells develop and “home” to specific sites in the lymph nodes, spleen, and GALT  
(The digestive tract's immune system is often referred to as **gut-associated lymphoid tissue (GALT)** and works to protect the body from invasion. GALT is an example of MALT mucosa-associated lymphoid tissue. In [gastrointestinal tract](#), [thyroid](#), [breast](#), [lung](#), [salivary glands](#), [eye](#), and [skin](#))
  - Come into contact with antigens throughout life
  - Have immunoglobulin as surface receptors for antigens



**MALT** is populated by lymphocytes such as T cells & B cells, as well as plasma cells and macrophages, each of which is well situated to encounter antigens passing through the mucosal epithelium. In the case of intestinal MALT, M cells are also present, which sample antigen from the lumen and deliver it to the lymphoid tissue.

The components of MALT are sometimes subdivided into the following:

**GALT** ([gut-associated lymphoid tissue](#). [Peyer's patches](#) are a component of GALT found in the lining of the [small intestines](#).)

**BALT** (bronchus-associated lymphoid tissue)

**NALT** (nose-associated lymphoid tissue)

**LALT** (larynx-associated lymphoid tissue)

**SALT** (skin-associated lymphoid tissue)

**VALT** (vascular-associated lymphoid tissue. A newly recognized entity that exists inside arteries; its role in the immune response is unknown.)

**CALT** (conjunctiva-associated lymphoid tissue in the human eye)

# Lymphocyte Responses and Antigens

- T-cell maturation
  - Maturation is directed by the thymus gland and its hormones
  - Different classes of T-cell receptors termed CD
    - **Cluster of differentiation**
      - CD4 and CD8
  - Mature T cells migrate to lymphoid organs

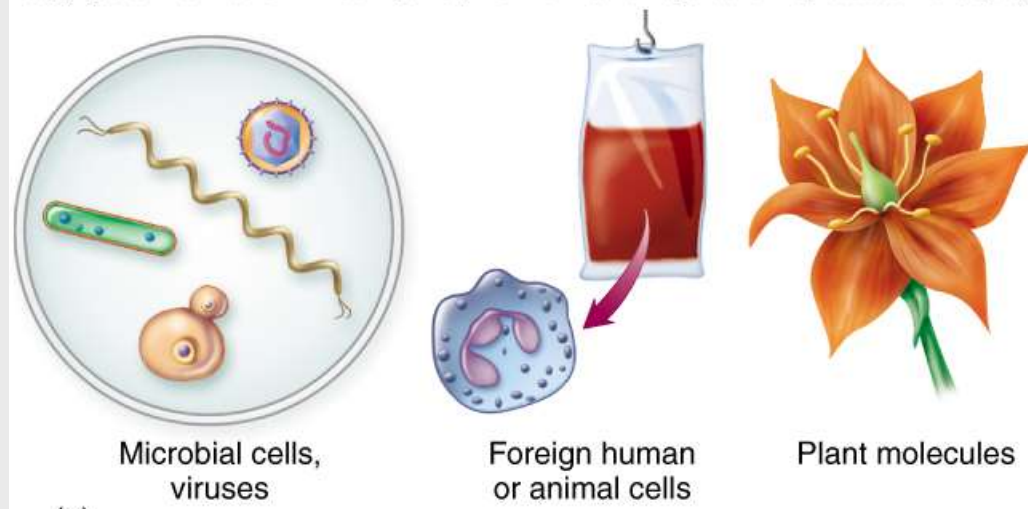
# Entrance and Processing of Antigens and Clonal Selection

- **Antigen** (Ag) is a substance that provokes an immune response in specific lymphocytes
- Property of behaving as an antigen is **antigenicity**
  - Foreignness, size, shape, and accessibility

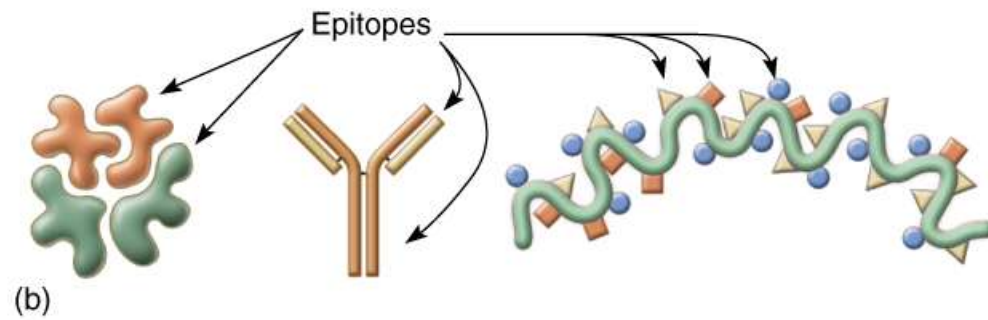
# Characteristics of Antigens

- Perceived as foreign, not a normal constituent of the body
- Foreign cells and large complex molecules over 10,000 MW are most antigenic
- Antigenic determinant, **epitope** – small molecular group that is recognized by lymphocytes
- Antigen has many antigenic determinants

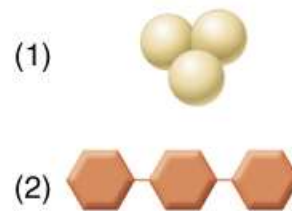
Figure 15.8



(a)



(b)



(1)

(2)



(c)

Mickey L. Dufilho

# Antigenic Determinants (Epitopes)



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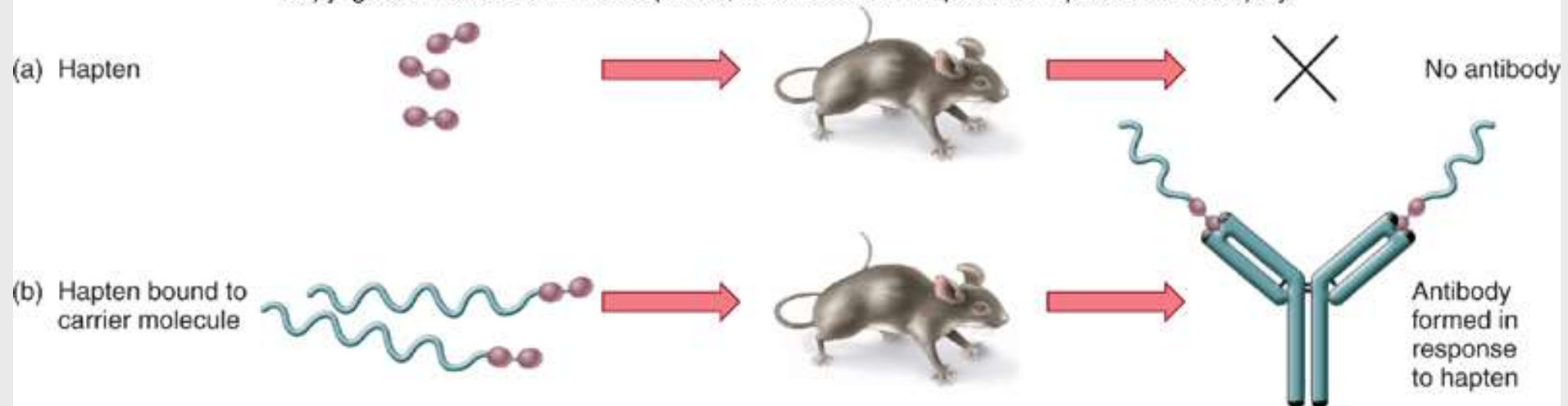
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Antigens are macromolecules, usually of molecular weight greater than 10,000, such as proteins and polysaccharides. They are recognized by the immune system as foreign.

## Figure 15.9 The hapten-carrier phenomenon

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# Special Categories of Antigens

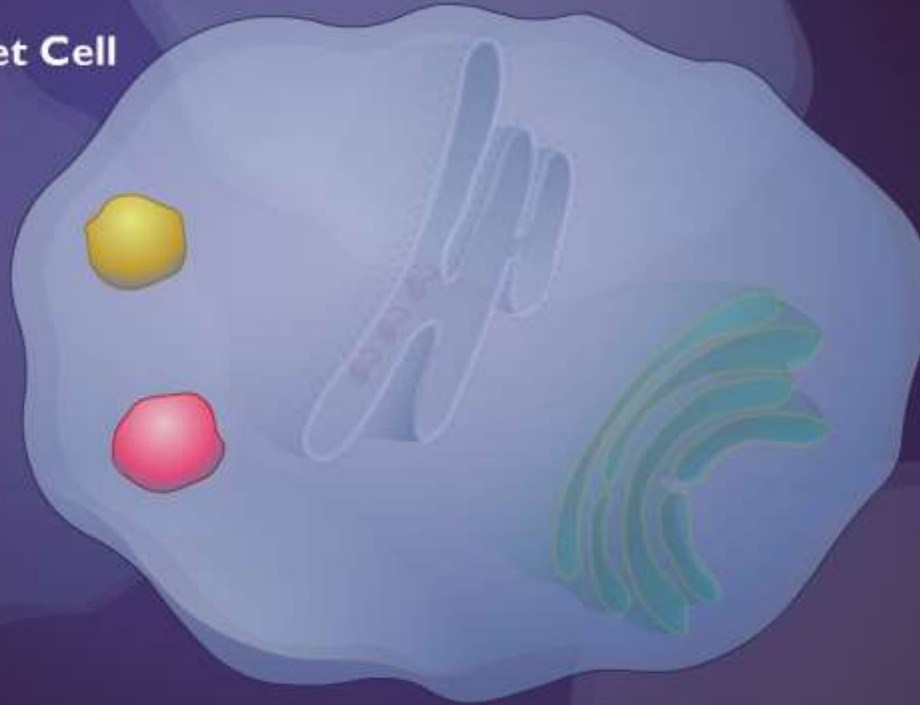
- **Autoantigens** – molecules on self tissues for which tolerance is inadequate
- **Alloantigens** – cell surface markers of one individual that are antigens to another of that same species
- **Heterophilic antigens** – molecules from unrelated species that bear similar antigenic determinants
- **Superantigens** – potent T cell stimulators; provoke an overwhelming response
- **Allergen** – antigen that provokes allergy

# Antigen Processing and Presentation to Lymphocytes

- T-cell dependent antigens must be processed by phagocytes called antigen presenting cells (APC)
- APCs modify the antigen; then the Ag is moved to the APC surface and bound to MHC receptor
- Antigen presentation involves a direct collaboration among an APC, and a T helper cell
  - Interleukin-1 is secreted by APC to activate  $T_H$  cells
  - Interleukin-2 is produced by  $T_H$  to activate B and other T cells

# Antigen Processing

Target Cell



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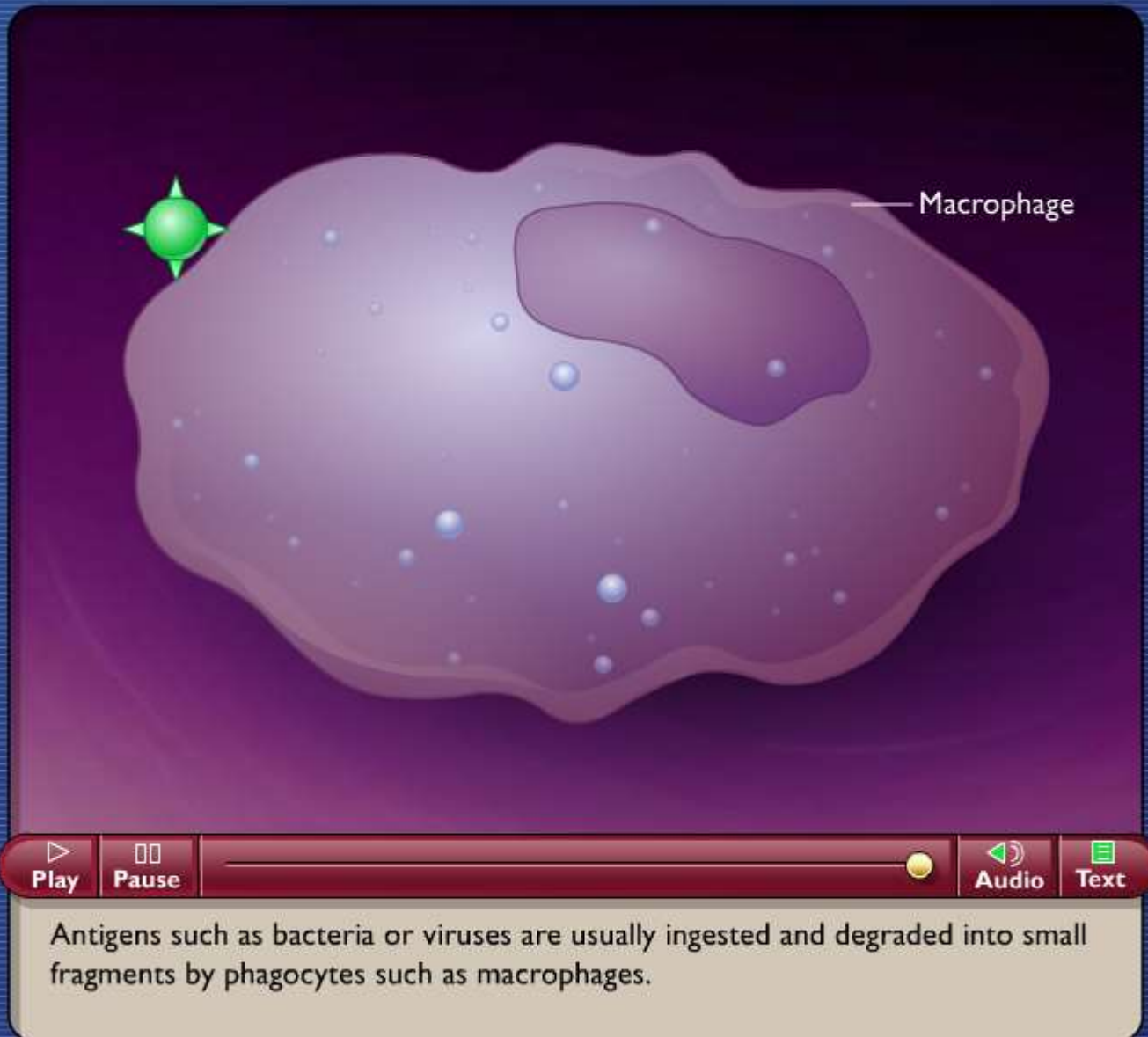
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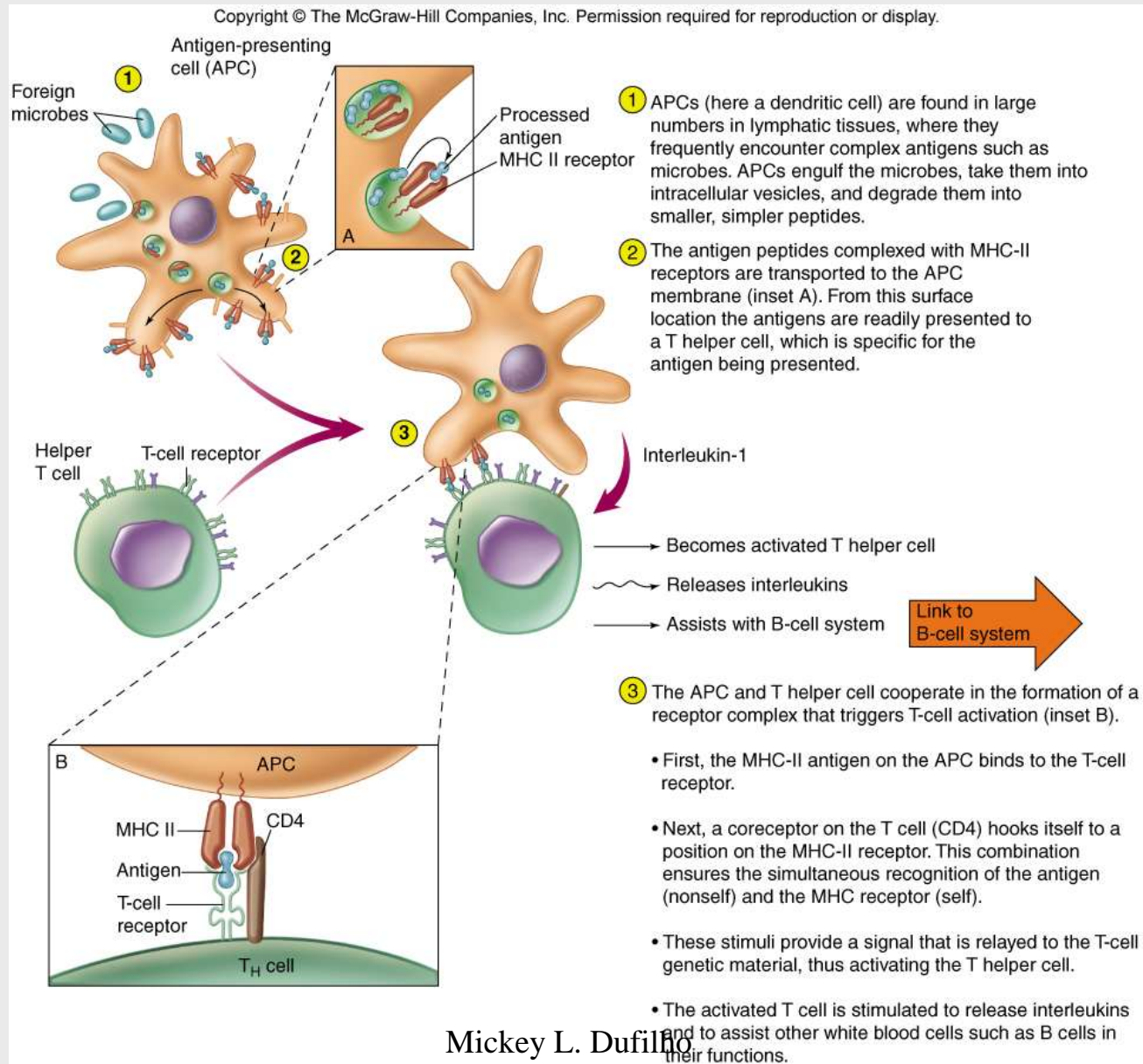
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Antigens are processed differently, depending on whether they originate within or outside the cell. Proteins produced within the cell such as viruses or self-proteins are broken down into fragments. Fragments of foreign proteins are antigens.

# T-cell Dependent Antigens



# Figure 15.10

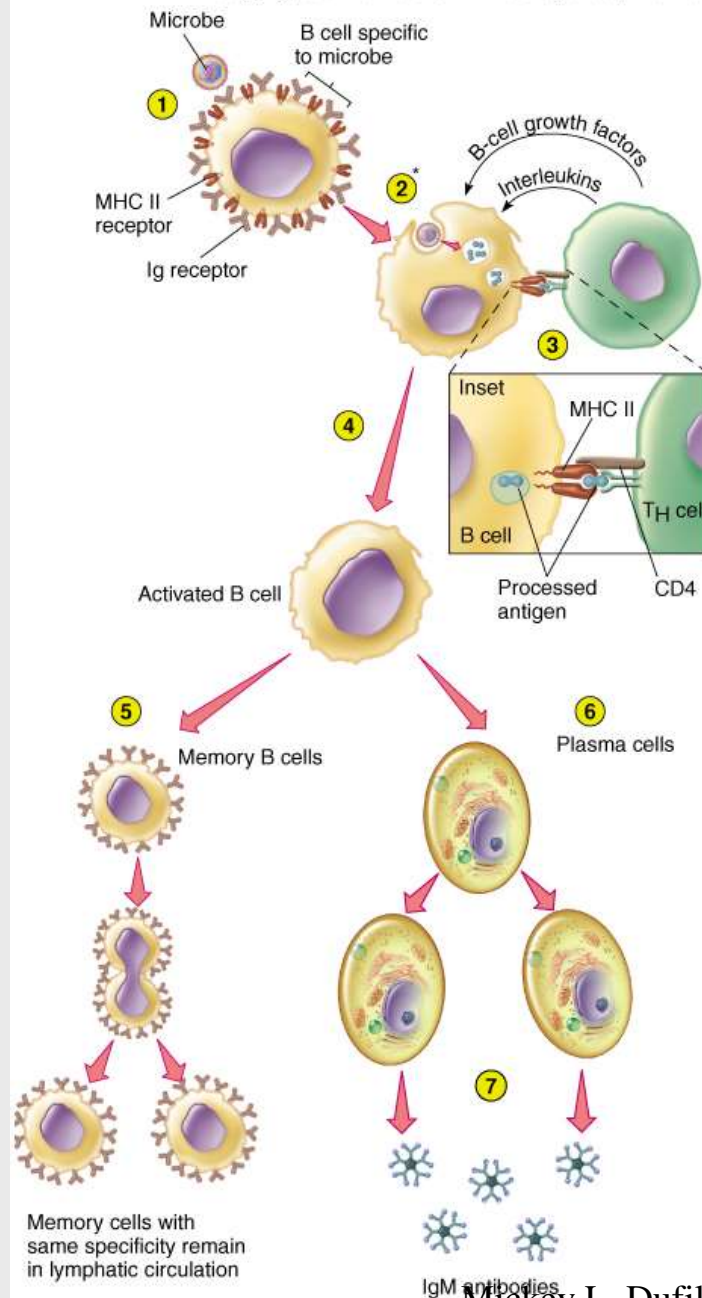


# 15.5 B Cell Responses

- B-cell activation and antibody production
  - Once B cells process the Ag, interact with  $T_H$  cells, and are stimulated by growth and differentiation factors, they enter the cell cycle in preparation for mitosis and clonal expansion
  - Divisions give rise to plasma cells that secrete antibodies and memory cells that can react to the same antigen later



Figure 15.11



### 1. Clonal Selection and Antigen Binding

B cells can independently recognize microbes (example here is a virus) and their foreign antigens, and can bind them with their Ig receptors. This is how the initial selection of the antigen-specific B-cell clone occurs.

### 2. Antigen Processing and Presentation

Once the microbe is attached, the B cell endocytoses it, processes it into smaller protein units, and displays these on the MHC II complex (similar to other APCs). This event readies the antigen for presentation to a specific T<sub>H</sub> cell.

### 3. B Cell/T<sub>H</sub> Cell Cooperation and Recognition

For most B cells to become functional, they must interact with a T helper cell that bears receptors for antigen from the same microbe. This T cell has previously been activated by an APC (see figure 15.10). The two cells engage in linked recognition, in which the MHC II receptor bearing antigen on the B cell binds to both the T-cell antigen receptor and the CD4 molecule on the T cell (inset).

### 4. B-Cell Activation

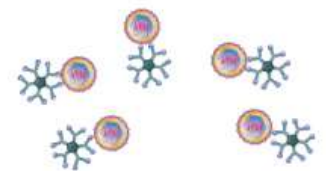
The T cell gives off additional signals in the form of interleukins and B-cell growth factors. The linked receptors and the chemical stimuli serve to activate the B cell. Such activation signals an increase in cell metabolism, leading to cell enlargement, proliferation, and differentiation.

### 5-6. Clonal Expansion/Memory Cells

The activated B cell undergoes numerous mitotic divisions, which expand the clone of cells bearing this specificity and produce memory cells and plasma cells. The memory cells are persistent, long-term cells that can react with the same antigen on future exposures.

### 7. Plasma Cells/Antibody Synthesis

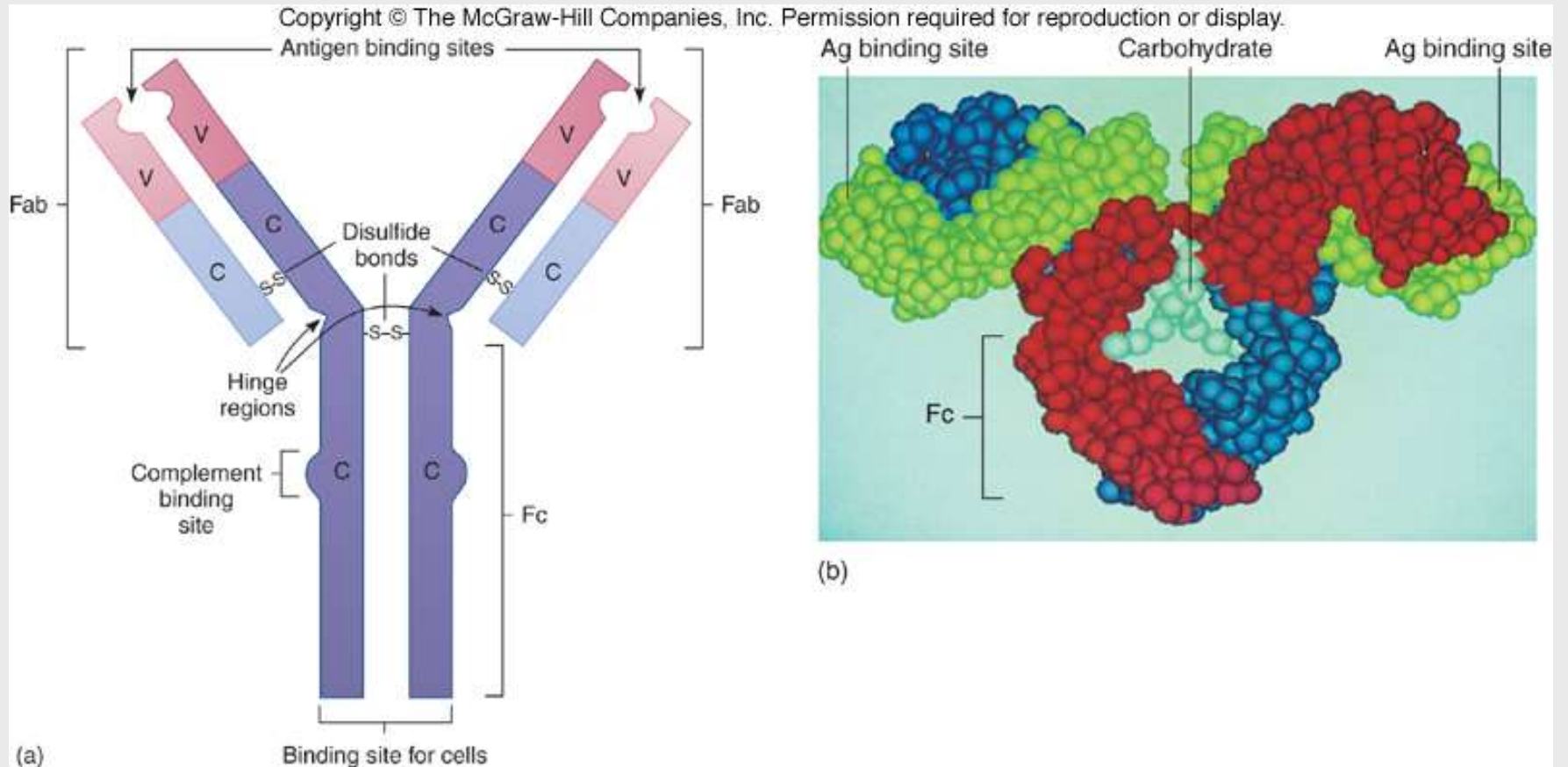
The plasma cells are short-lived, active secretory cells that synthesize and release antibodies. These antibodies (here IgM) have the same specificity as the Ig receptor and circulate in the fluid compartments of the body, where they react with the same antigens and microbes shown in step 1.



Antibodies react with microbes



Figure 15.12



# Antibody Diversity

V<sub>1</sub> · V<sub>2</sub> · V<sub>3</sub> · V<sub>4</sub> · V<sub>5</sub> · V<sub>100-300</sub> · J<sub>1</sub> · J<sub>2</sub> · J<sub>5</sub> · C

V<sub>1</sub> · V<sub>2</sub> · V<sub>3</sub> · V<sub>4</sub> · V<sub>5</sub> · V<sub>100</sub> · D<sub>1</sub> · D<sub>2</sub> · D<sub>4</sub> · J<sub>1</sub> · J<sub>2</sub> · J<sub>6</sub> · μ · γ · δ · ε · α



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Human cells do not have enough DNA to have separate genes for each antibody molecule. Instead, different segments of DNA can be mixed and matched to form different antibodies.

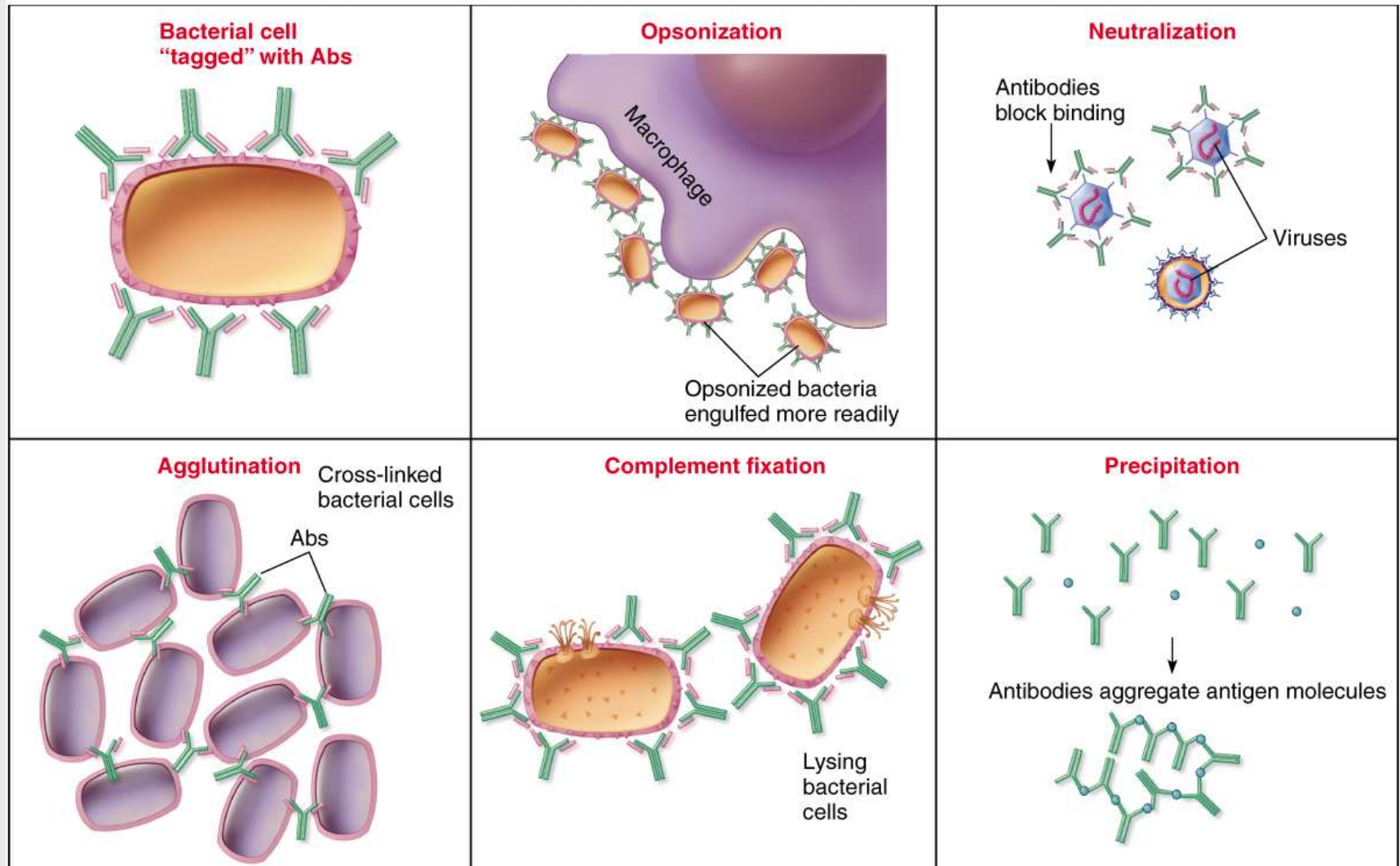
# Antibody-Antigen Interactions

Principle antibody activity is to unite with the Ag, to call attention to, or neutralize the Ag for which it was formed

- **Opsonization** —
- **Agglutination** —
- **Neutralization** —
- **Precipitation** —
- **Complement Fixation** —

# Figure 15.14


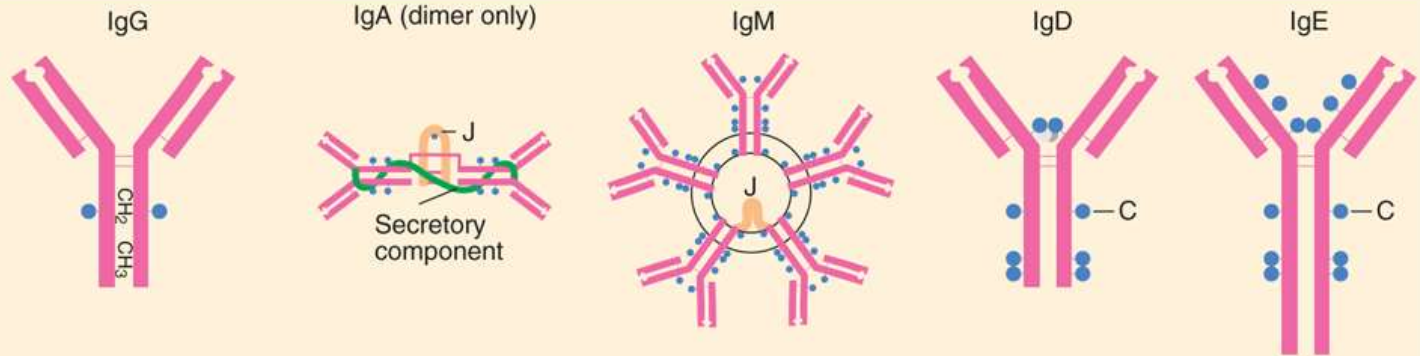
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# Functions of the Fc Fragment

- Fc fragment binds to cells – macrophages, neutrophils, eosinophils, mast cells, basophils, and lymphocytes
- Certain antibodies have regions on the Fc portion for fixing complement
  - Binding of Fc may cause release of cytokines



**TABLE 15.2**  **Characteristics of the Immunoglobulin (Ig) Classes**

	Monomer	Dimer, Monomer	Pentamer	Monomer	Monomer
<b>Number of Antigen Binding Sites</b>	2	2 or 4	10	2	2
<b>Molecular Weight</b>	150,000	170,000–385,000	900,000	180,000	200,000
<b>Percentage of Total Antibody in Serum</b>	80%	13%	6%	0.001%	0.002%
<b>Average Life in Serum (Days)</b>	23	6	5	3	2.5
<b>Crosses Placenta?</b>	Yes	No	No	No	No
<b>Fixes Complement?</b>	Yes	No	Yes	No	No
<b>Binds To</b>	Phagocytes	Epithelial cells	NA	NA	Mast cells and basophils
<b>Biological Function</b>	Long-term immunity; memory antibodies; neutralizes toxins, viruses	Secretory antibody; on mucous membranes	Produced at first response to antigen; can serve as B-cell receptor	Receptor on B cells for antigen recognition	Antibody of allergy; worm infections

C = carbohydrate.

J = J chain.

# Antibodies in Serum

- If separated by electrophoresis, globulin separates into 4 bands:
  - Alpha-1 ( $\alpha_1$ ), alpha-2 ( $\alpha_2$ ), beta ( $\beta$ ), and gamma ( $\gamma$ )
- Most are antibodies
- $\gamma$  is composed primarily of IgG;  $\beta$  and  $\alpha_2$  are a mixture of IgG, IgA, and IgM



Figure 15.15 Pattern of human serum after electrophoresis

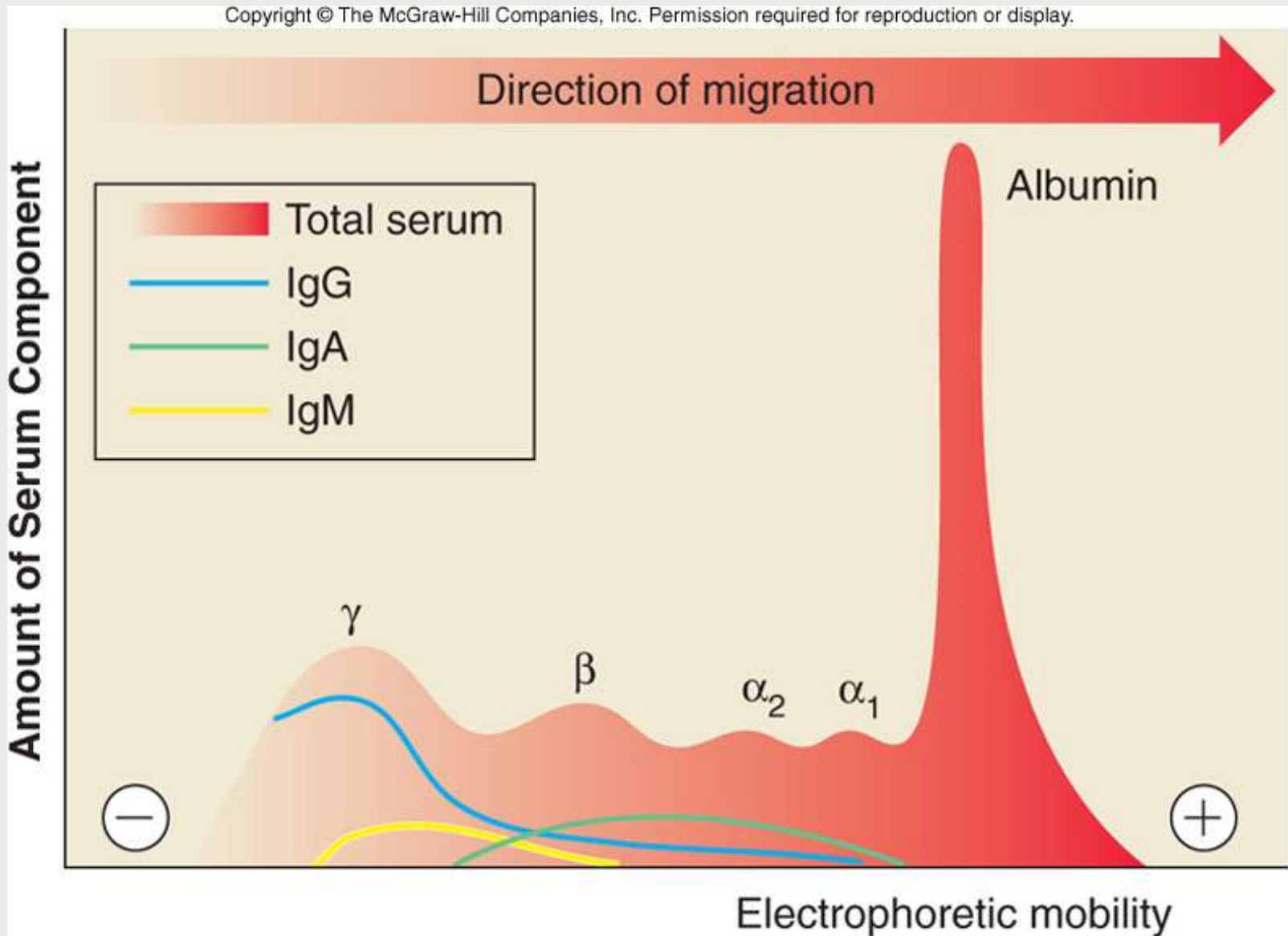
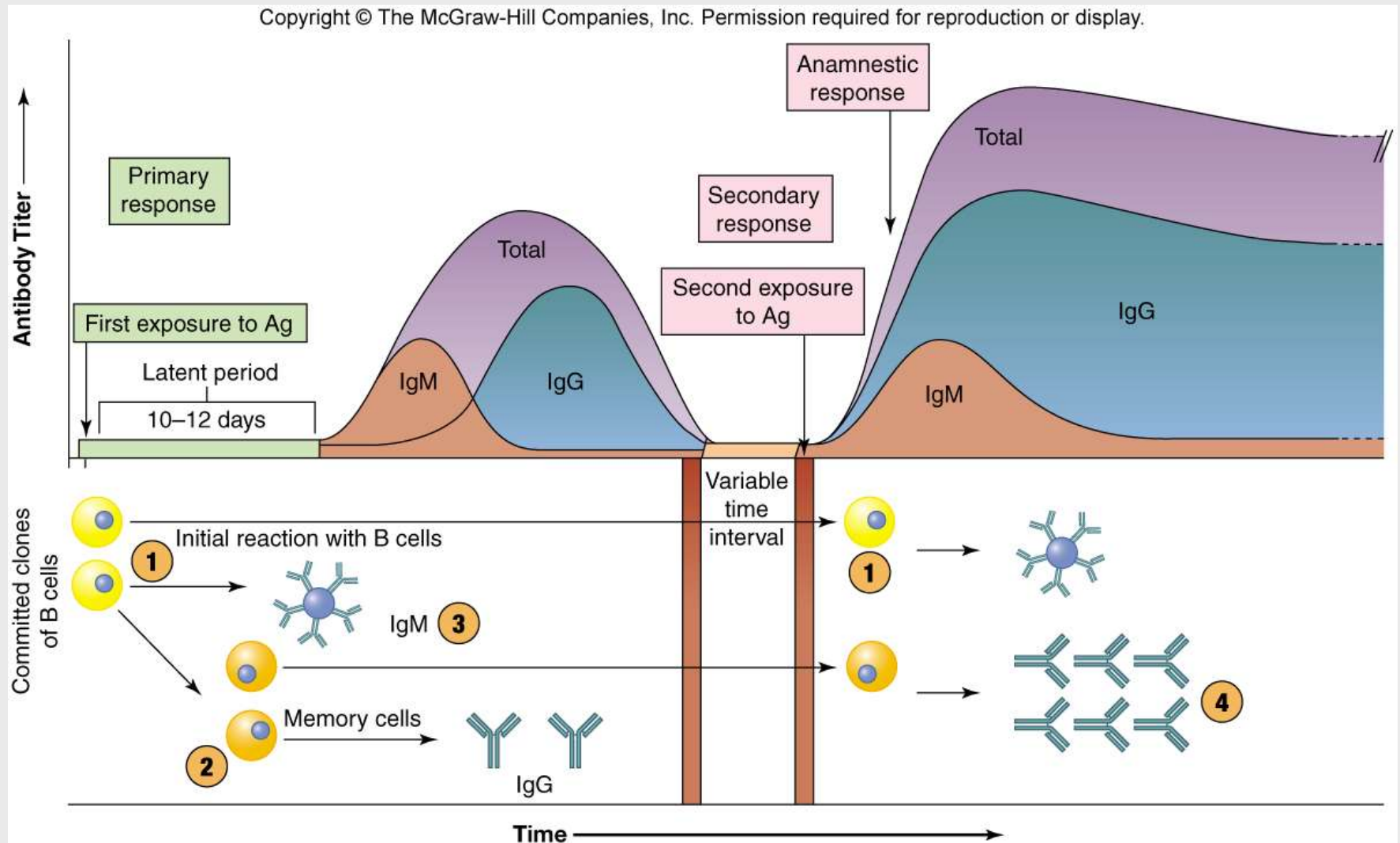


Figure 15.16



# 15.6 T Cells & Cell-Mediated Immunity

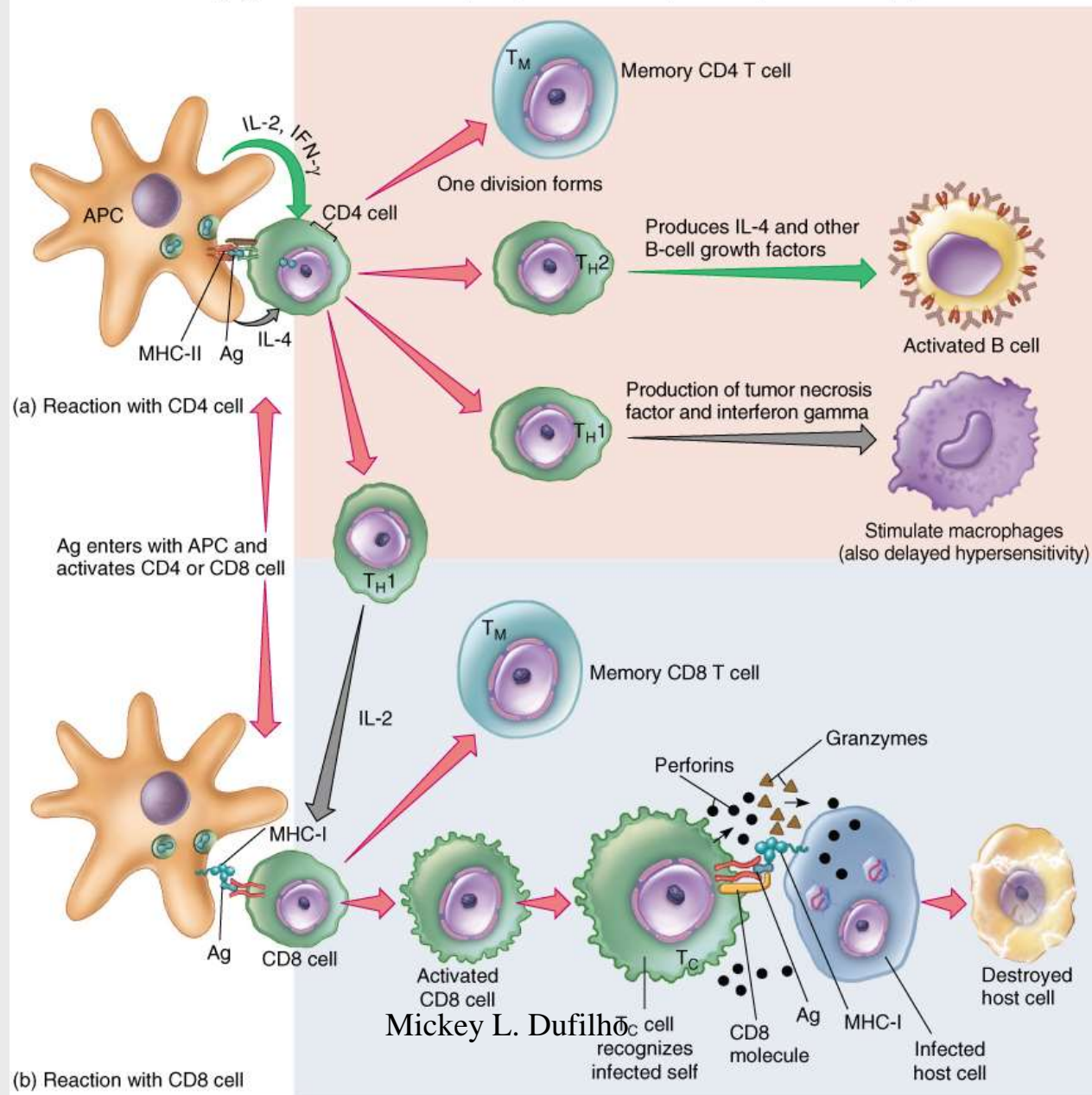
- Cell-mediated immunity requires the direct involvement of T lymphocytes
- T cells act directly against Ag and foreign cells when presented in association with an MHC carrier
- T cells secrete cytokines that act on other cells
- Sensitized T cells proliferate into long-lasting memory T cells

**TABLE 15.3** Characteristics of Subsets of T Cells

Types	Primary Receptors on T Cell	Functions/Important Features
T helper cell 1 (T <sub>H</sub> 1)	CD4	Activates other CD4 and CD8 cells; secretes IL-2, tumor necrosis factor, and interferon gamma; responsible for delayed hypersensitivity; interacts with MHC II receptors
T helper cell 2 (T <sub>H</sub> 2)	CD4	Drives B-cell proliferation, secretes IL-4, IL-5, IL-6, IL-10; can dampen T <sub>H</sub> 1 activity
T cytotoxic cell (T <sub>C</sub> )	CD8	Destroys a target foreign cell by lysis; important in destruction of complex microbes, cancer cells, virus-infected cells; graft rejection; requires MHC I for function

# Figure 15.17

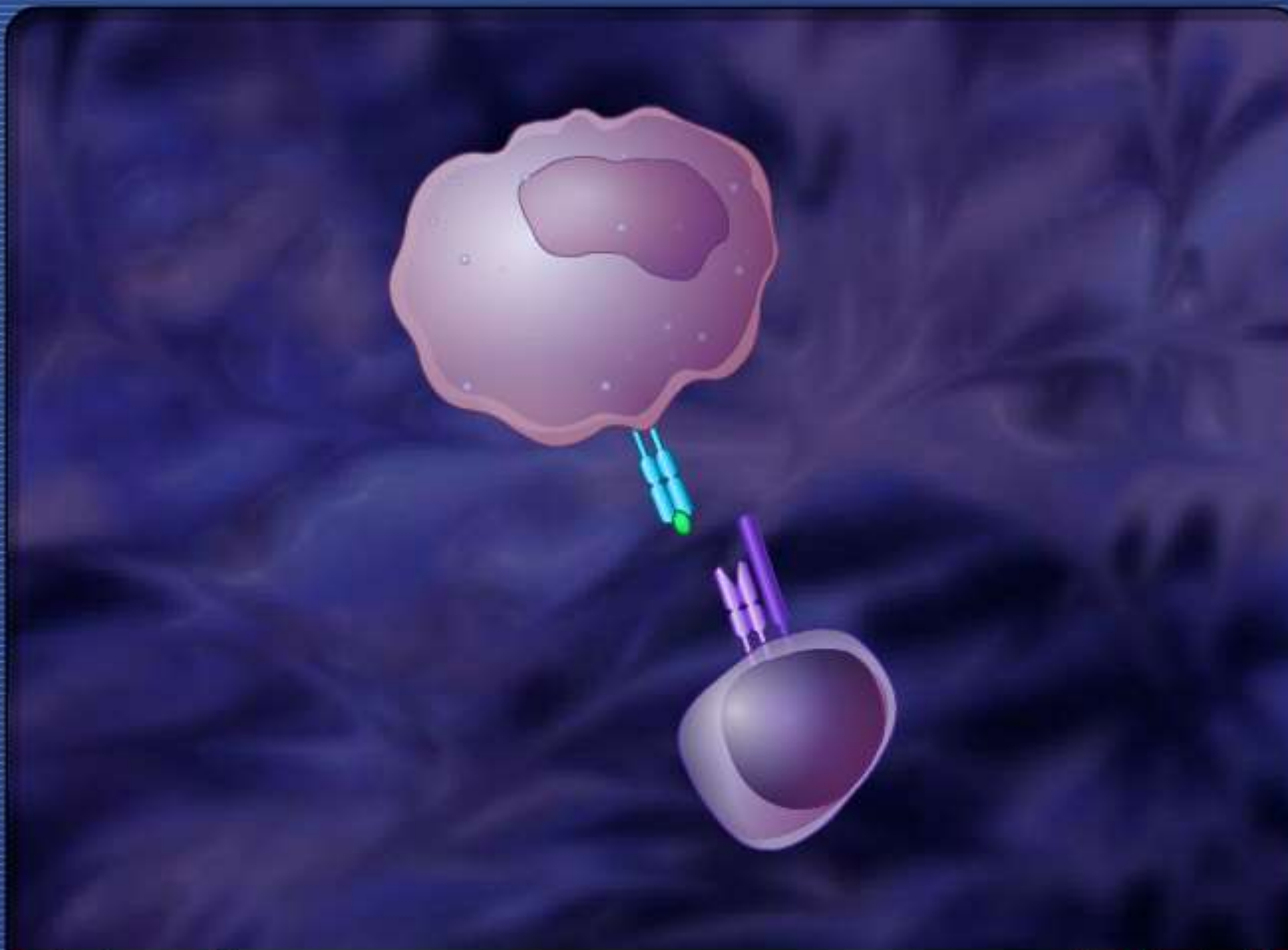
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# T Cells and Superantigens

- Reaction has drastic consequences
- Superantigens are a form of a virulence factor
- Provoke overwhelming immune responses by large numbers of T cells
  - Release of cytokines
  - Blood vessel damage
  - Toxic shock
  - Multiorgan damage



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Audio☰  
Text

Antigens are normally processed by antigen-presenting cells and presented to T-helper cells on Class II MHCs. Only the T-helper cells with T-cell receptors capable of interacting with the antigen are stimulated to produce cytokines.



# 15.7 Immunization: Manipulating Immunity

- **Passive immunity** – immune serum globulin (ISG), gamma globulin, contains immunoglobulin extracted from pooled blood; **immunotherapy**
- **Artificial active immunity** – deliberately exposing a person to material that is antigenic but not pathogenic

# Vaccine Preparation

Most vaccines are prepared from:

1. Killed whole cells or inactivated viruses
2. Live, attenuated cells or viruses
3. Antigenic molecules derived from bacterial cells or viruses
4. Genetically engineered microbes or microbial agents



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Text

There are a variety of ways to produce vaccines. Traditionally, vaccines have consisted of killed or inactivated pathogens.

## TABLE 15.4

### Checklist of Requirements for an Effective Vaccine

- It should have a low level of adverse side effects or toxicity and not cause serious harm.
- It should protect against exposure to natural, wild forms of pathogen.
- It should stimulate both antibody (B-cell) response and cell-mediated (T-cell) response.
- It should have long-term, lasting effects (produce memory).
- It should not require numerous doses or boosters.
- It should be inexpensive, have a relatively long shelf life, and be easy to administer.

# Genetically Engineered Vaccines

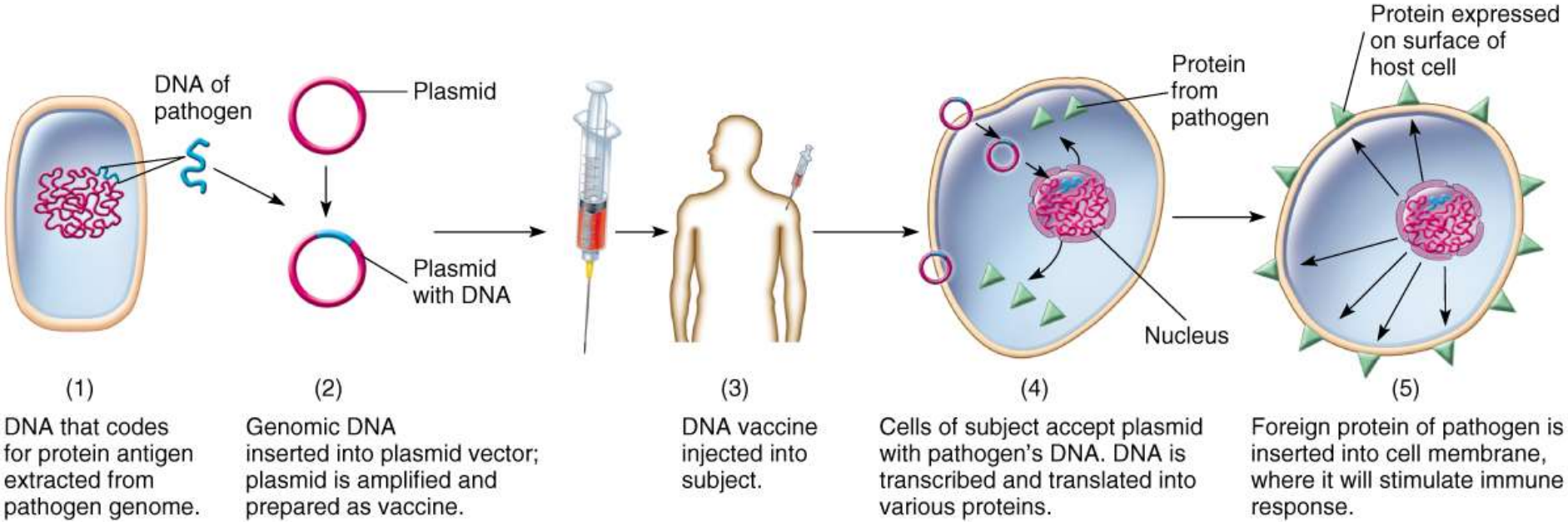
- Insert genes for pathogen's antigen into plasmid vector, and clone them in an appropriate host
  - Stimulated the clone host to synthesize and secrete a protein product (antigen), harvest and purify the protein – hepatitis
- “Trojan horse” vaccine – genetic material from a pathogen is inserted into a live carrier nonpathogen; the recombinant expresses the foreign genes
  - Experimental vaccines for AIDS, herpes simplex 2, leprosy, tuberculosis

# Genetically Engineered Vaccines

- DNA vaccines – create recombination by inserting microbial DNA into plasmid vector
- Human cells will pick up the plasmid and express the microbial DNA as proteins causing B and T cells to respond, be sensitized, and form memory cells
  - Experimental vaccines for Lyme disease, hepatitis C, herpes simplex, influenza, tuberculosis, malaria

Figure 15.20

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# Route of Administration and Side Effects

- Most administered by injection; few oral, nasal
- Some vaccines require **adjuvant** to enhance immunogenicity and prolong retention of antigen
- Stringent requirements for development of vaccines
- More benefit than risk
- Possible side effects include local reaction at injection site, fever, allergies; rarely back-mutation to a virulent strain, neurological effects

# Herd Immunity

- Immune individuals will not harbor it, reducing the occurrence of pathogens – **herd immunity**
- Less likely that a nonimmunized person will encounter the pathogen

Figure 15.2 (II-V)

