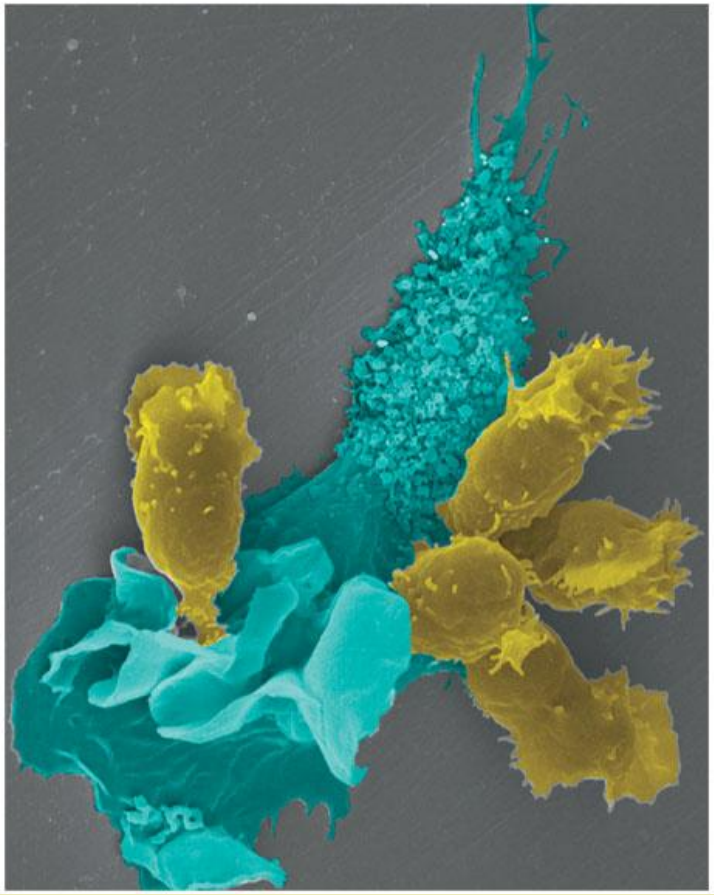
Foundations in Microbiology

Fifth Edition

Talaro

Chapter

15



The Acquisition of Specific Immunity and Its Applications

Chapter 15

Chapter Overview

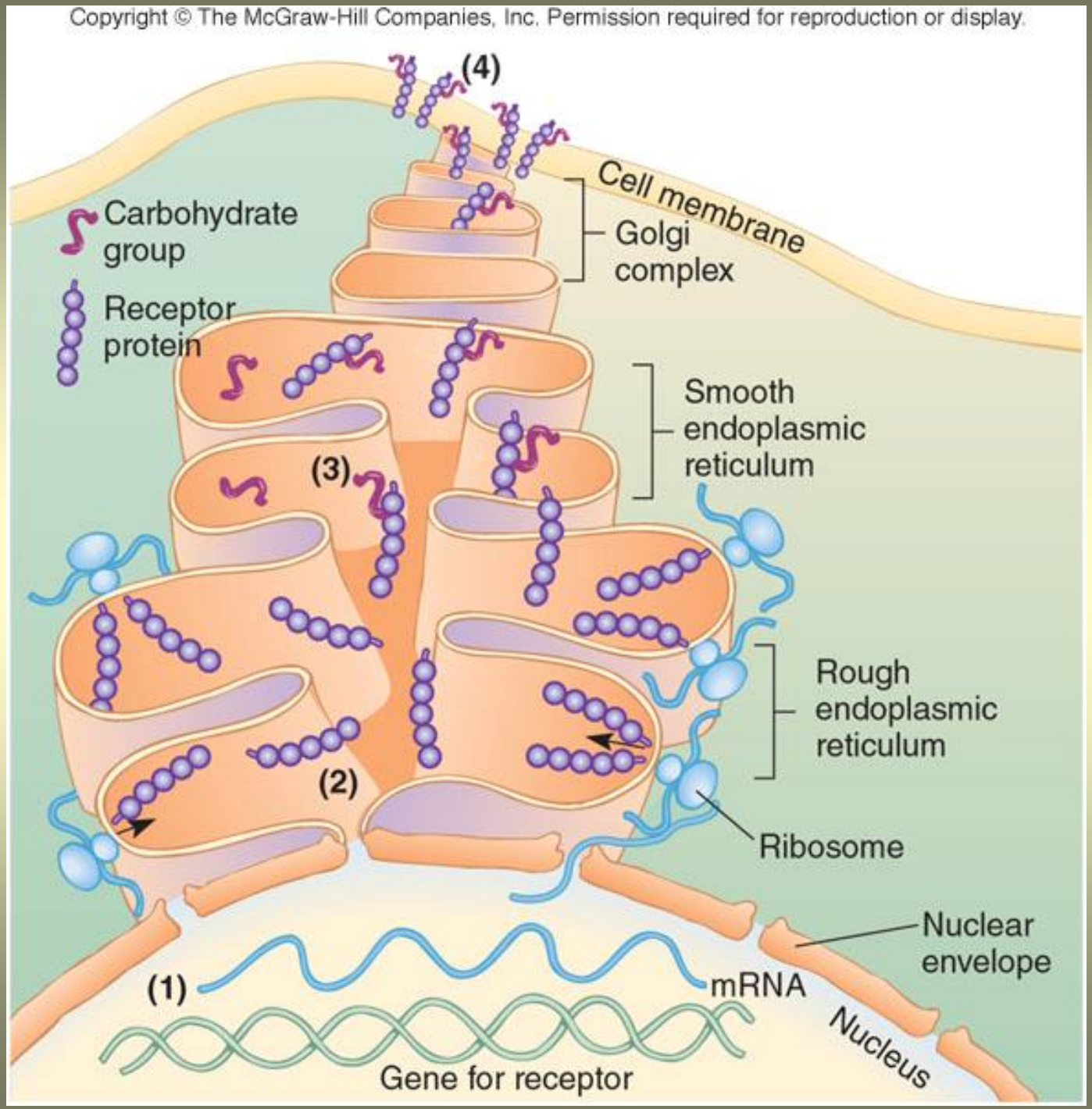
1. Development of the Dual Lymphocyte System
2. Entrance and Processing of Antigens and Clonal Selection
3. Activation of Lymphocytes and Clonal Expansion
4. Products of B Lymphocytes: Antibody Structure and Functions: Humoral Immunity
5. How T cells Respond to Antigen: Cell-Mediated Immunity

Preliminary concepts

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

How are receptors formed?

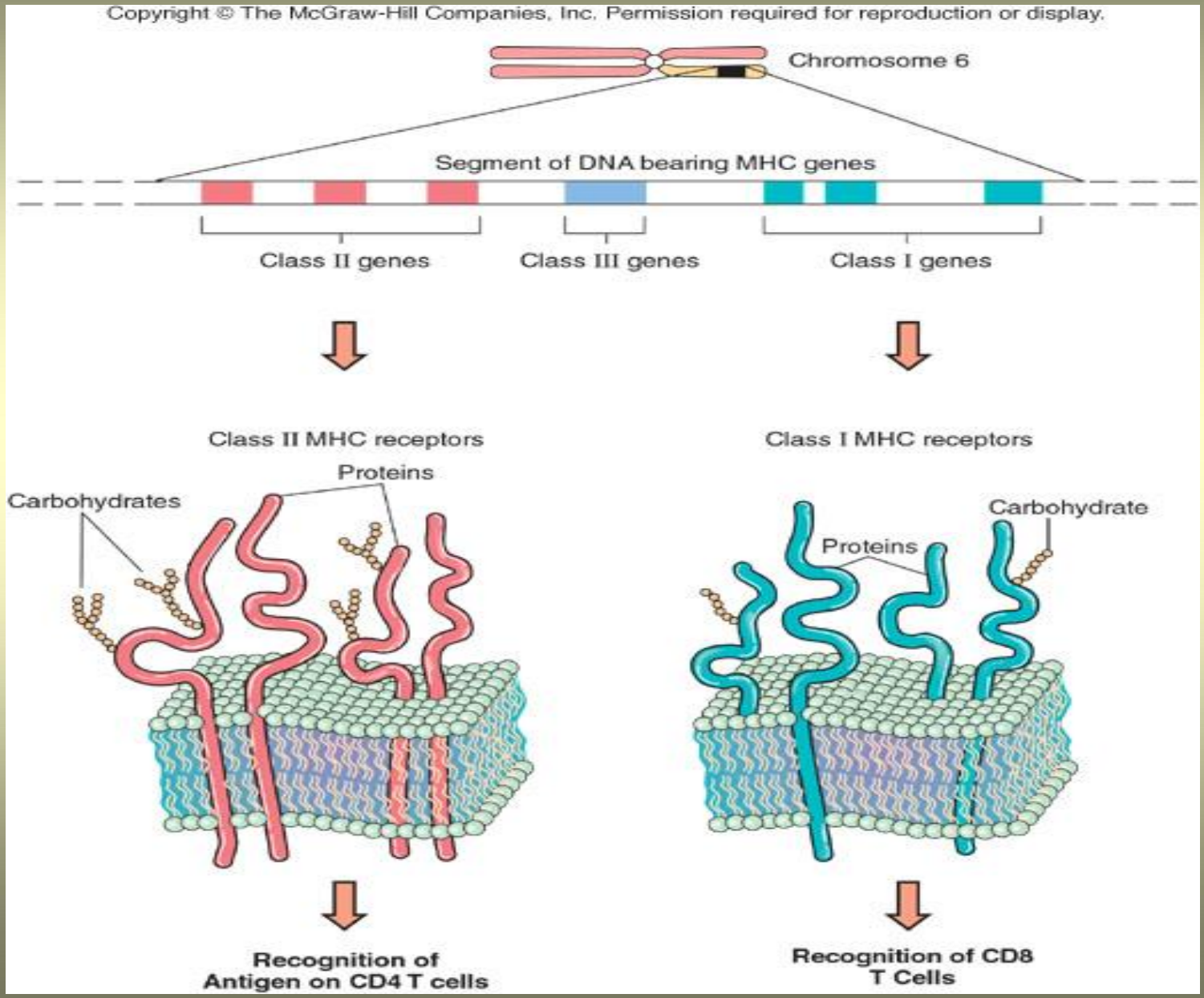
- As a cell matures, certain genes that encode cell receptors are transcribed & translated into protein products with a distinctive shape, specificity and function.
- Receptor is modified & packaged by the endoplasmic reticulum & Golgi complex.
- It is ultimately inserted into the cell membrane, accessible to antigens, other cells, and chemical mediators. (See next slide)



Major Histocompatibility Complex (MHC)

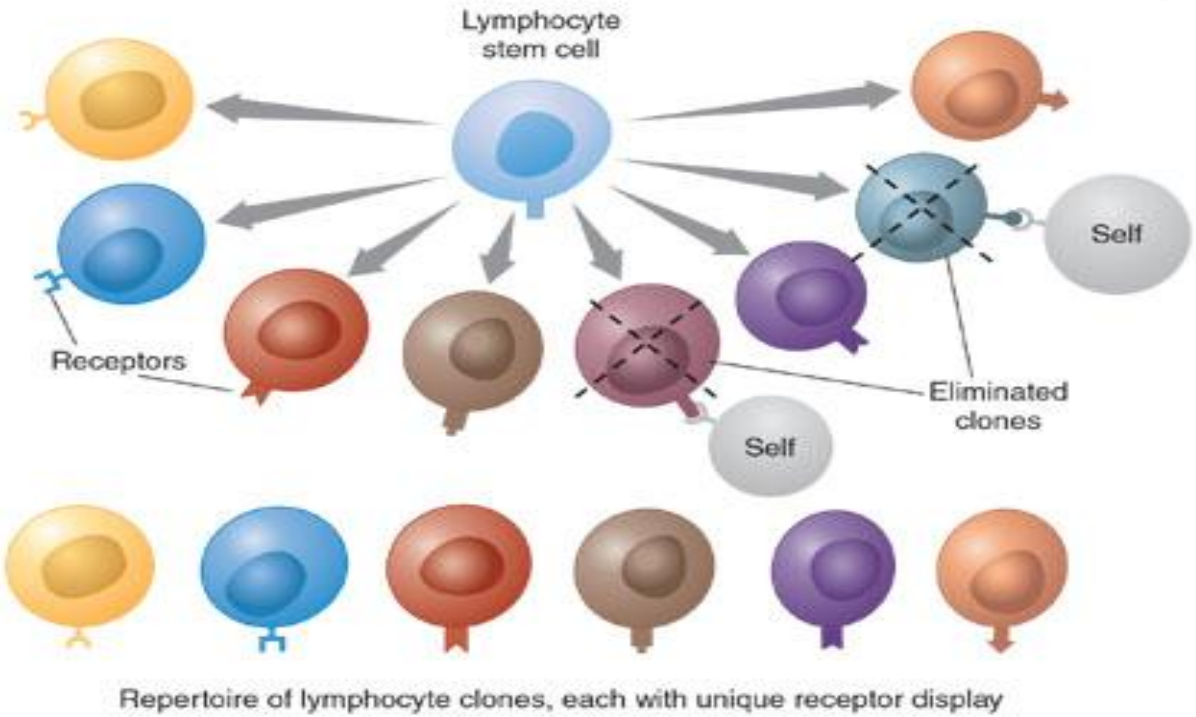
- Receptors found on all cells except RBCs
- Also known as human leukocyte antigen (HLA)
- Plays a role in recognition of self by the immune system and in rejection of foreign tissue
- Genes for MHC are located on chromosome 6, clustered in a multigene complex of classes I, II, III

MHC receptors



Functions of MHC

- Class I – markers that display unique characteristics of self molecules & regulation of immune reactions
  - Required for T lymphocytes
- Class II – receptors that recognize & react with foreign antigens. Located primarily on macrophages & B cells
  - Involved in presenting antigen to T cells
- Class III – secreted complement components, C2 and C4



Repertoire of lymphocyte clones, each with unique receptor display

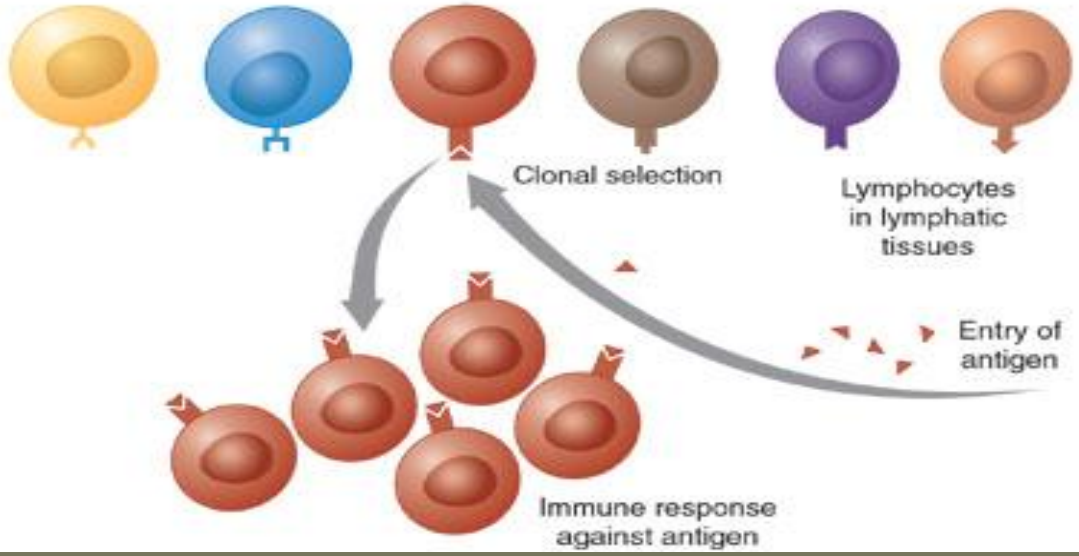
(a) **Antigen-Independent Period**

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 or deleted 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 immature or naive lymphocytes that are ready to further differentiate under the influence of certain organs and immune stimuli.

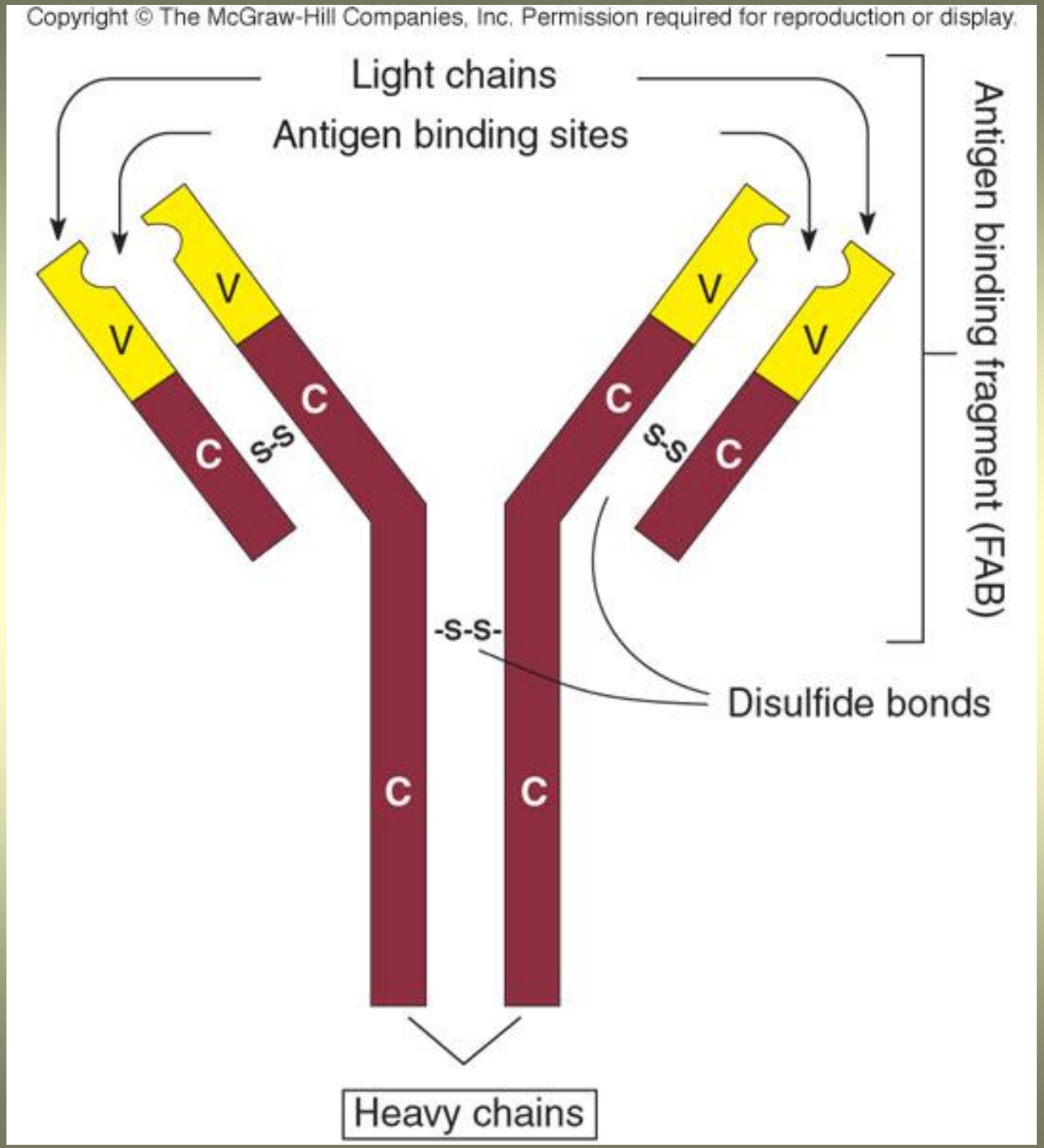


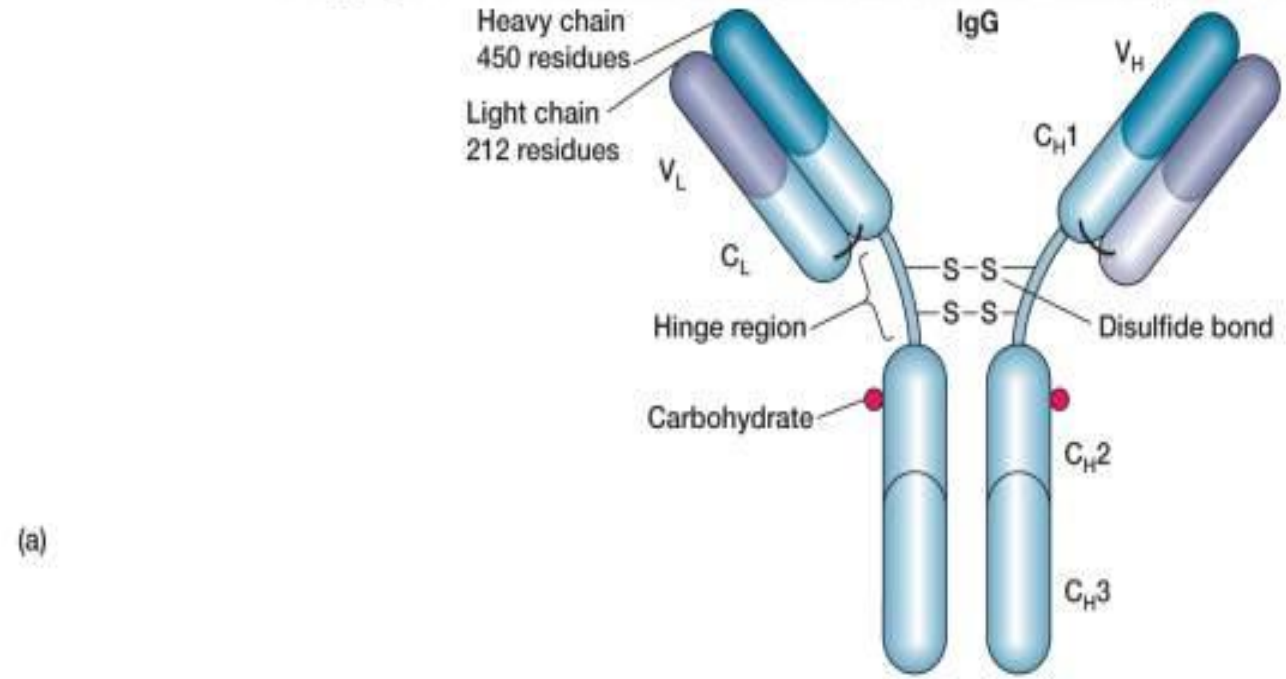
(b) **Antigen-Dependent Period**

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.

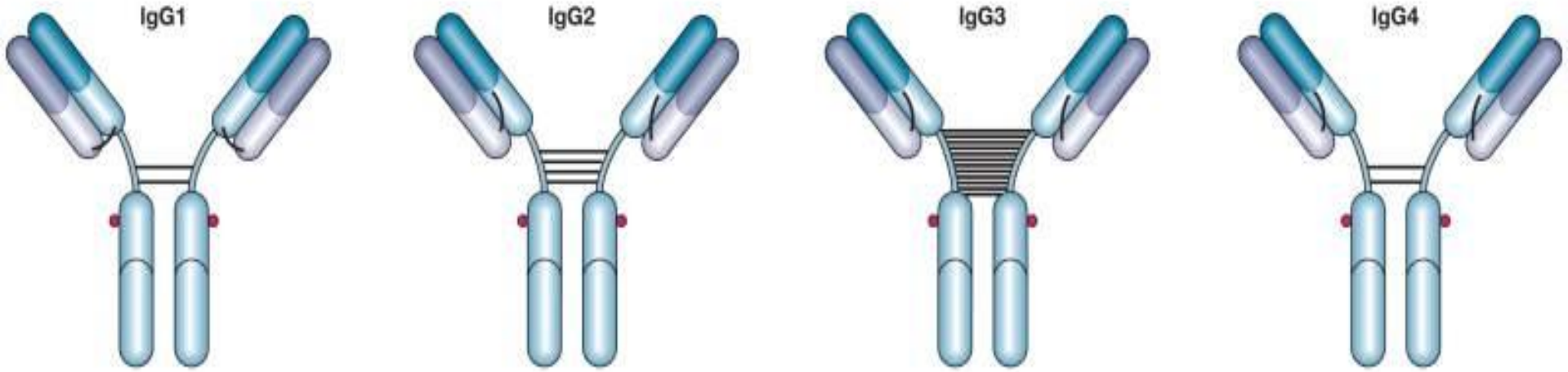
Specific B cell receptor: Immunoglobulin

- Large glycoproteins that serve as specific receptors of B cells
- Composed of 4 polypeptide chains
  - 2 identical heavy chains
  - 2 identical light chains
- Y shaped
- Variable regions
- Constant regions

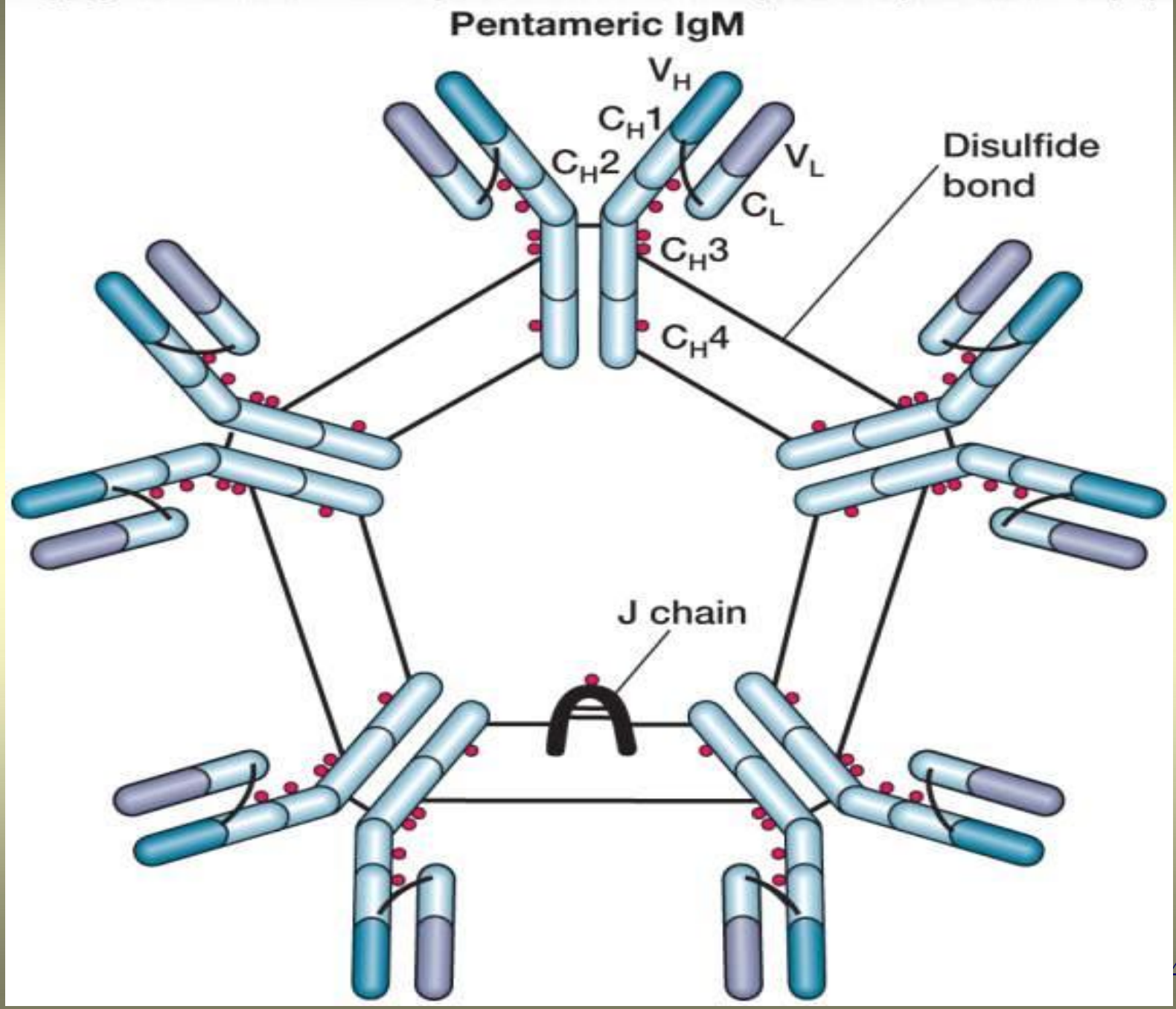


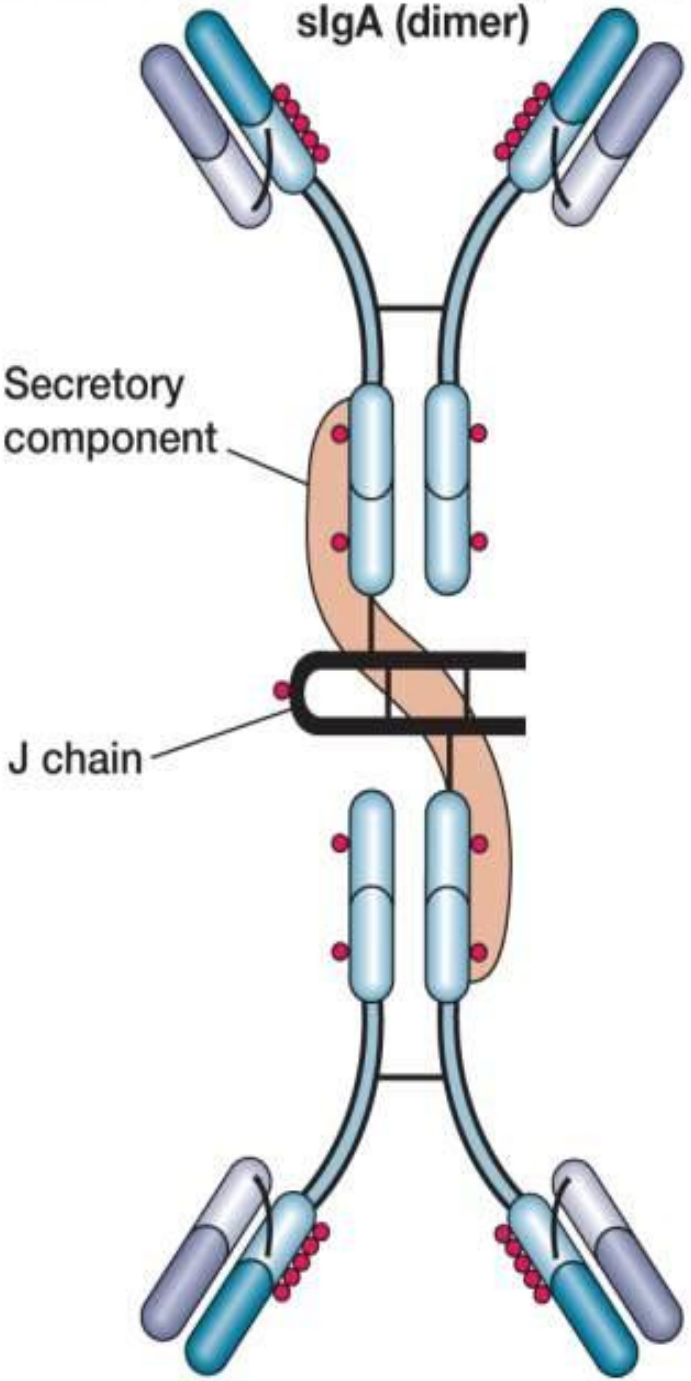


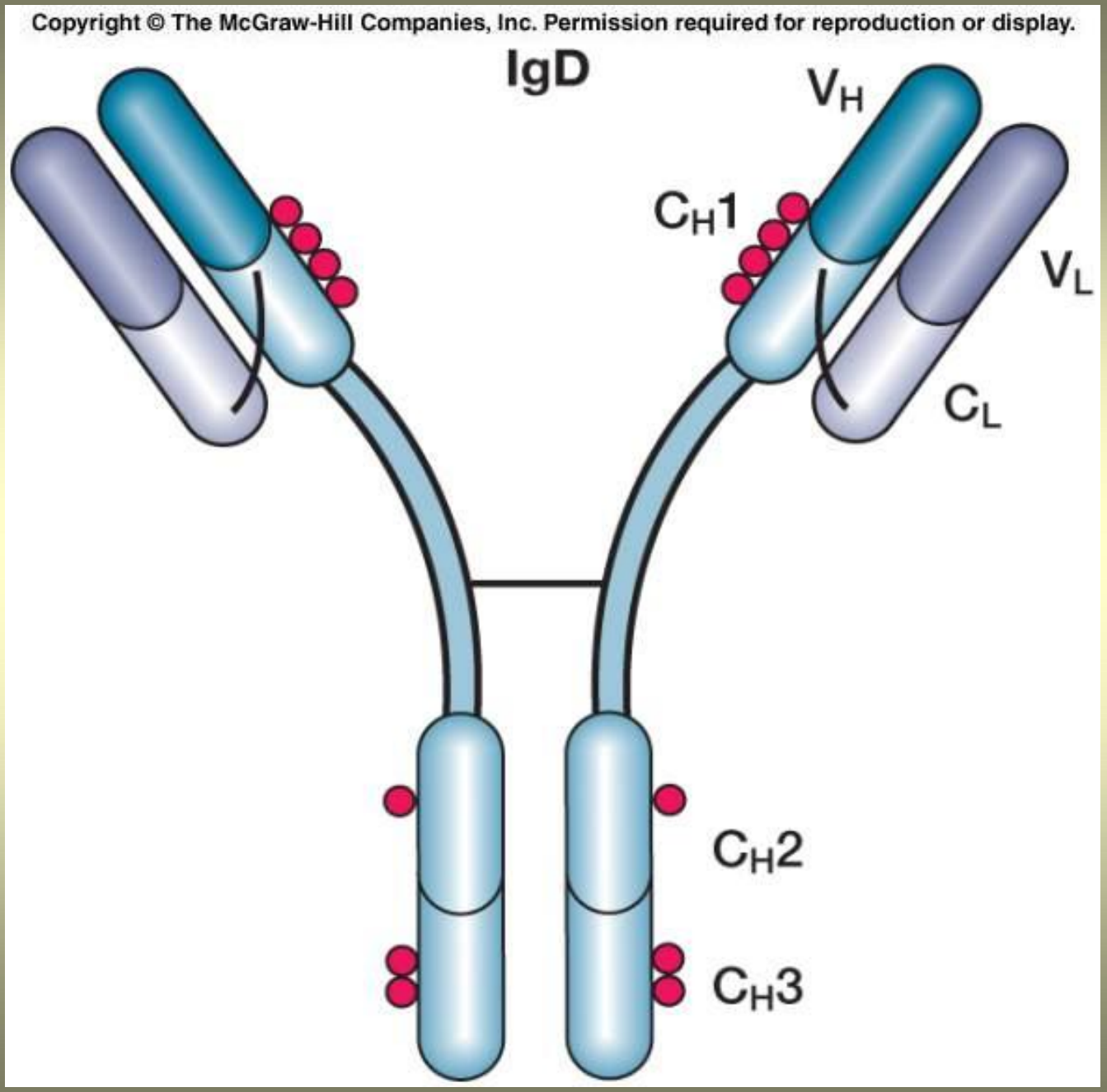
(a)

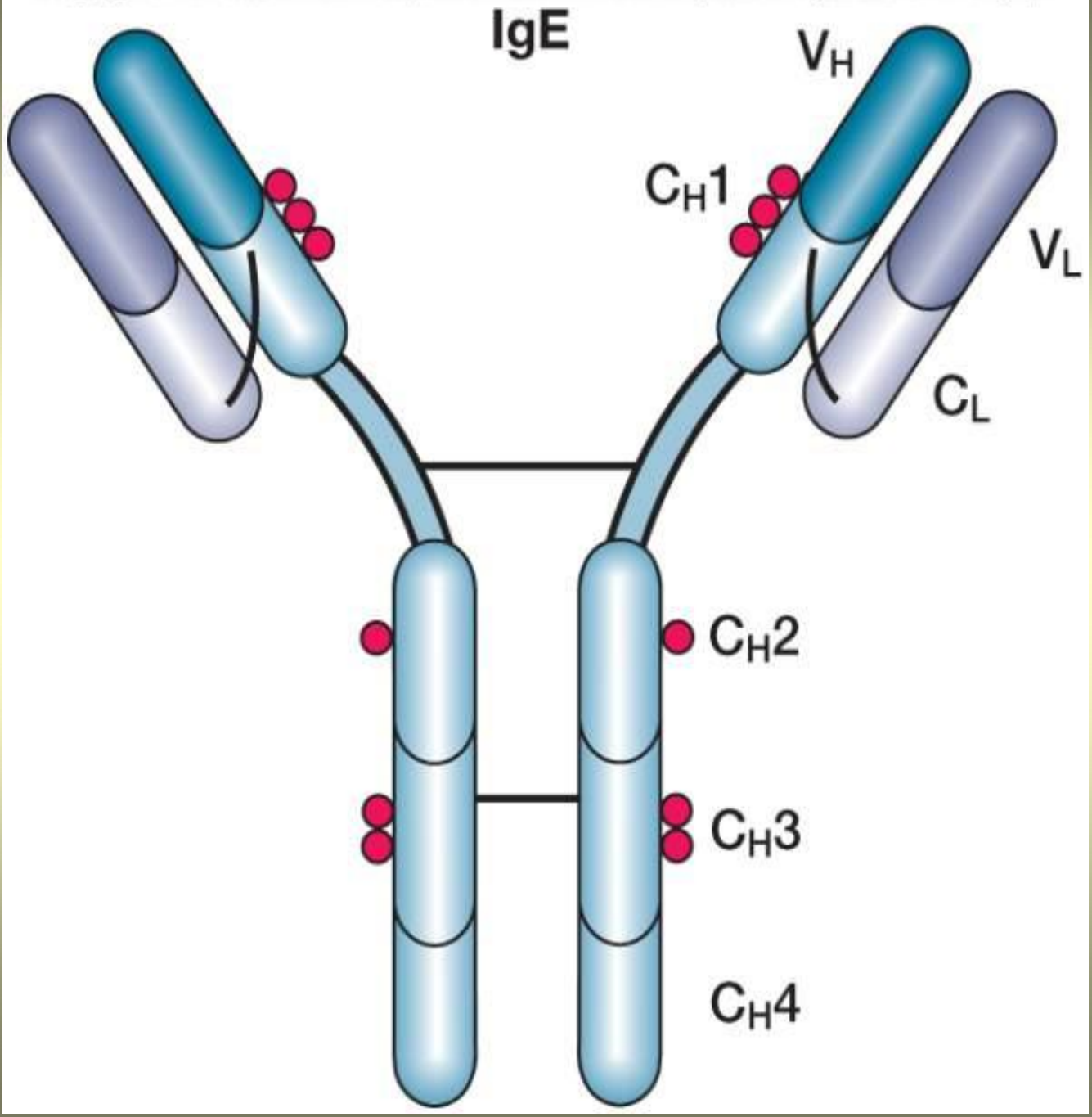


(b)



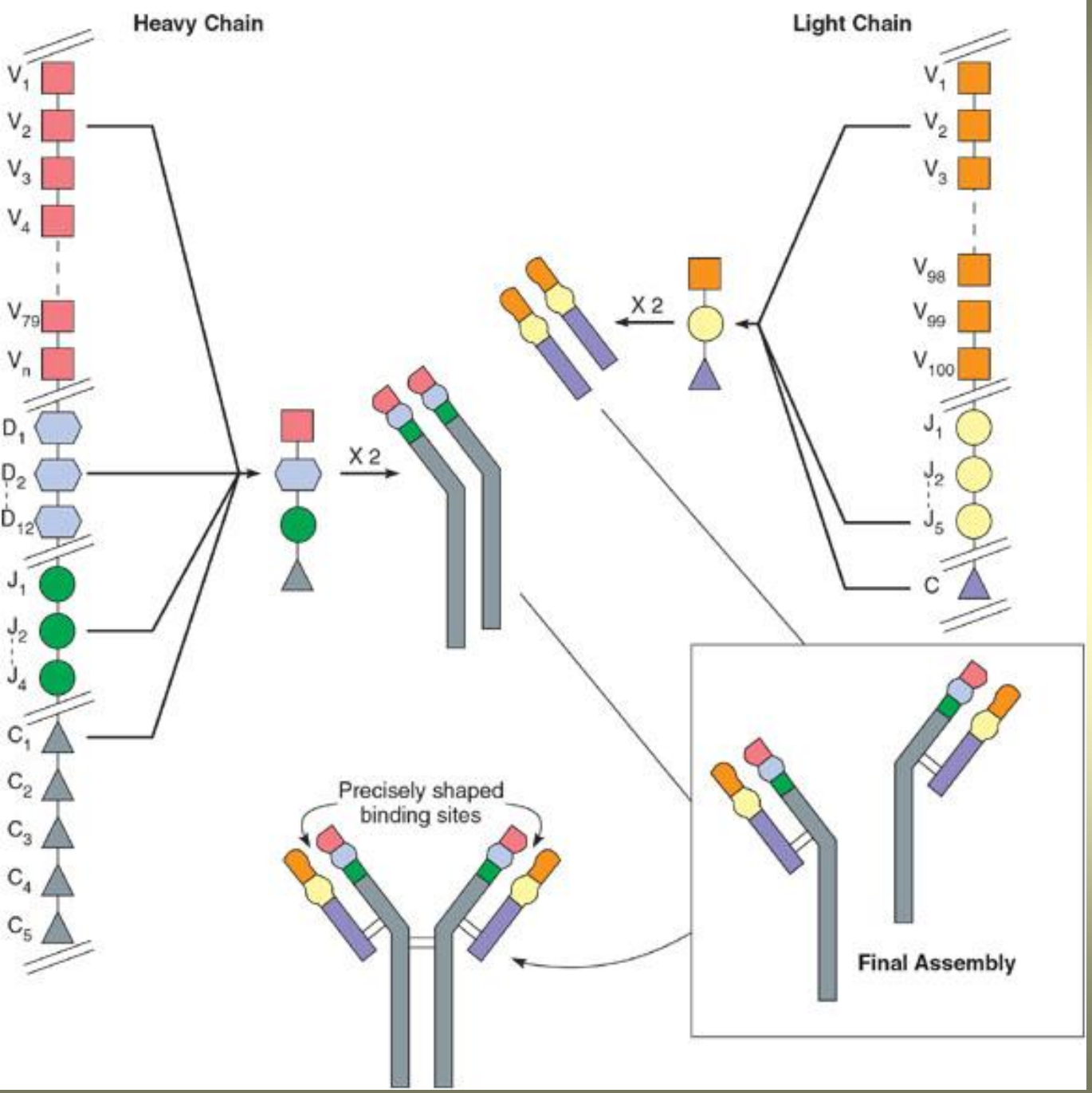






Immunoglobulins

- Immunoglobulin genes lie on 3 different chromosomes
- Undifferentiated lymphocyte has 150 different genes for the variable region of light chains & 250 for the variable region and diversity region of the heavy chain
- During development, recombination causes only the selected V and D genes to be active in the mature cell.



Video

2050: Finally pissed enough to act, the Earth produces antibodies to the human race.

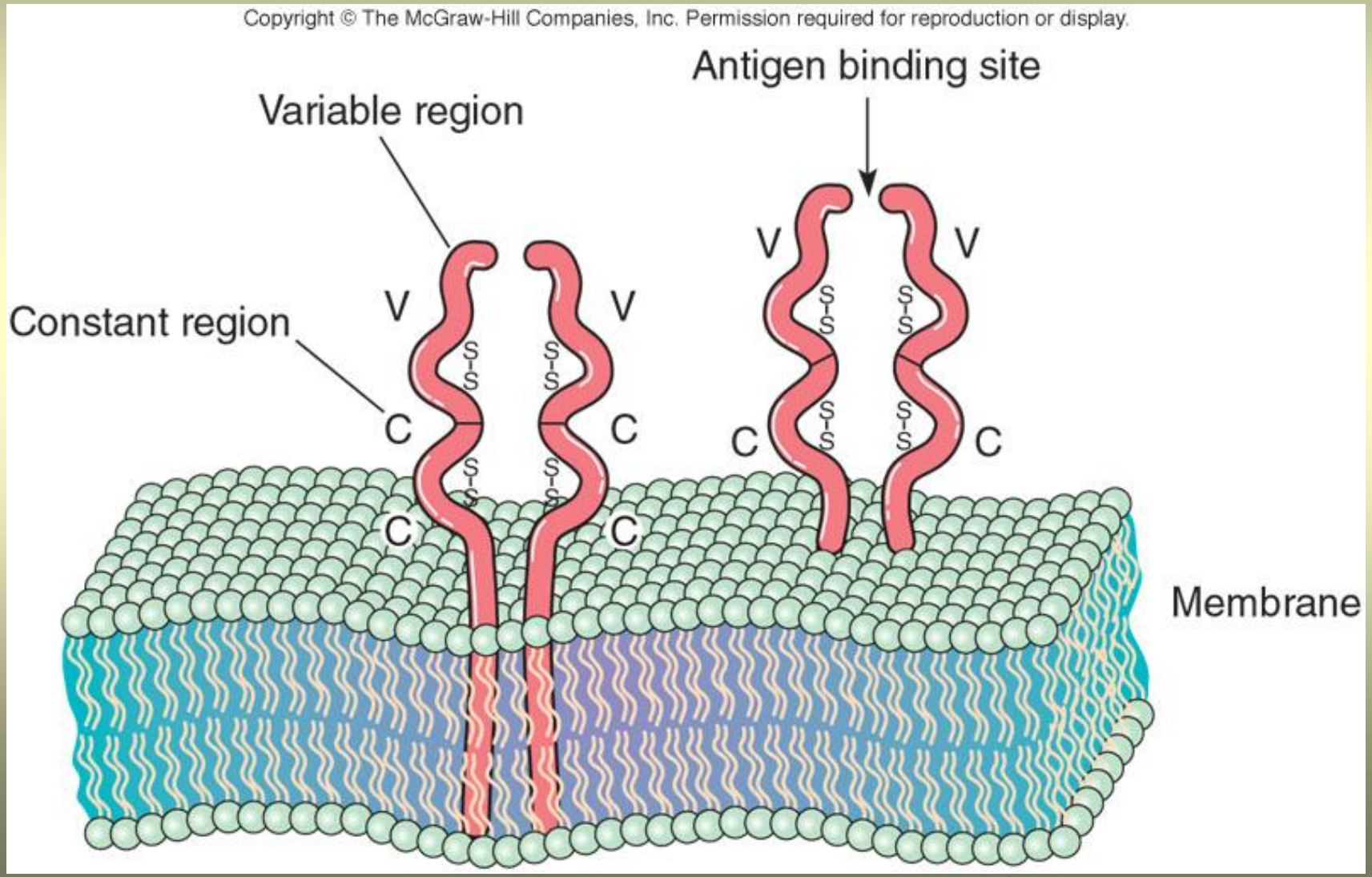
B cell receptors

- Once synthesized, immunoglobulin is transported to cell membrane & inserted there to act as a receptor
- First receptor on most B cells is a small form of IgM & mature B cells carry IgD receptors

T cell receptors

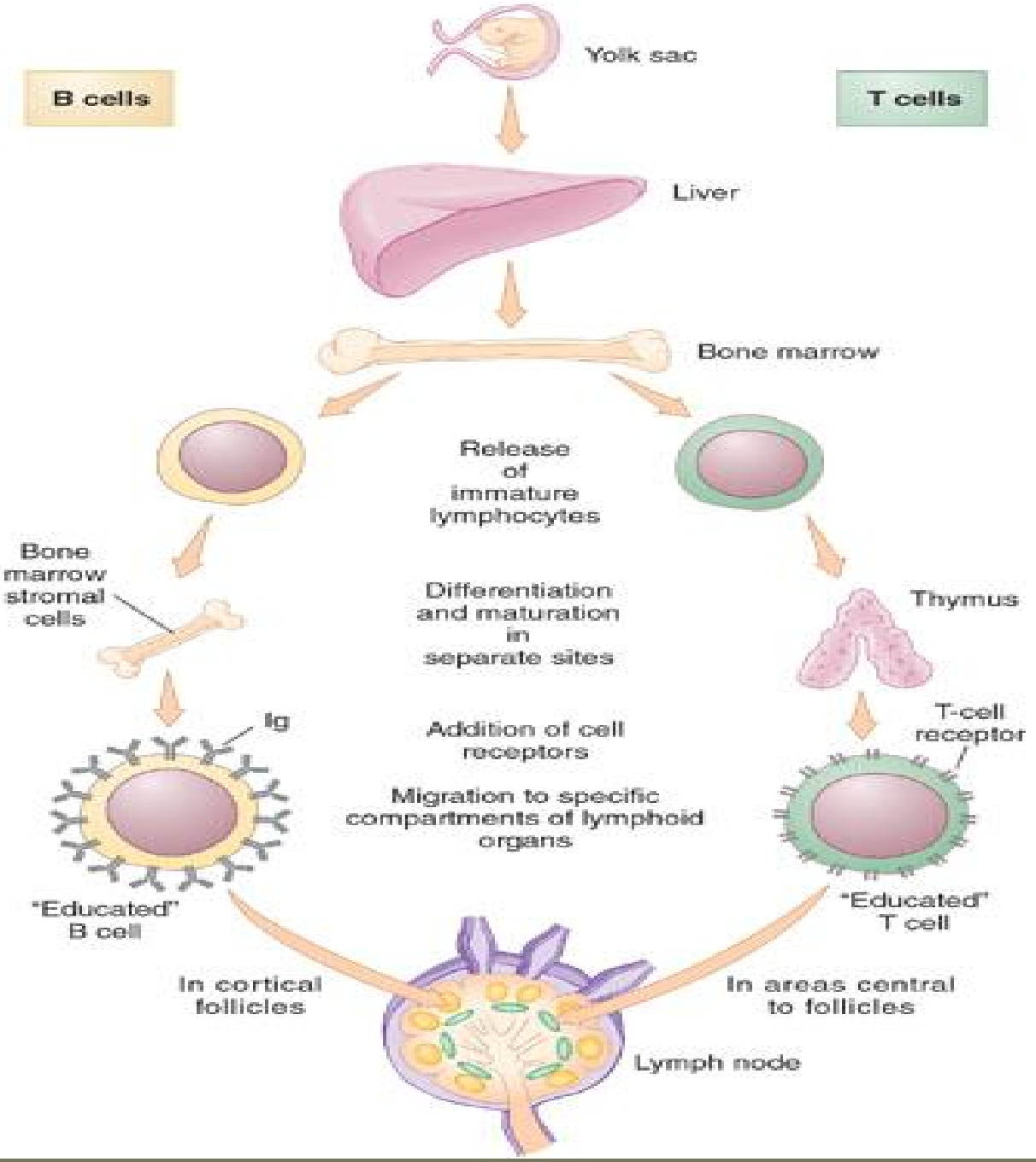
- Formed by genetic recombination, having variable and constant regions
- 2 parallel polypeptide chains
- Small, without humoral functions

T cell receptors



Development of the Dual Lymphocyte System

- Starting in the embryonic & fetal stages, stem cells in the yolk sac, liver, and bone marrow release immature lymphocytes into the circulation
- These undifferentiated cells must mature to be able to react to antigen
- Maturation occurs differently for B and T cells



B cell maturation

- Directed by bone marrow sites that harbor stromal cells, which nurture the lymphocyte stem cells & provide hormonal signals
- Millions of distinct B cells develop & home to specific sites in the lymph nodes, spleen, and GALT where they come into contact with antigens throughout life

T cell maturation

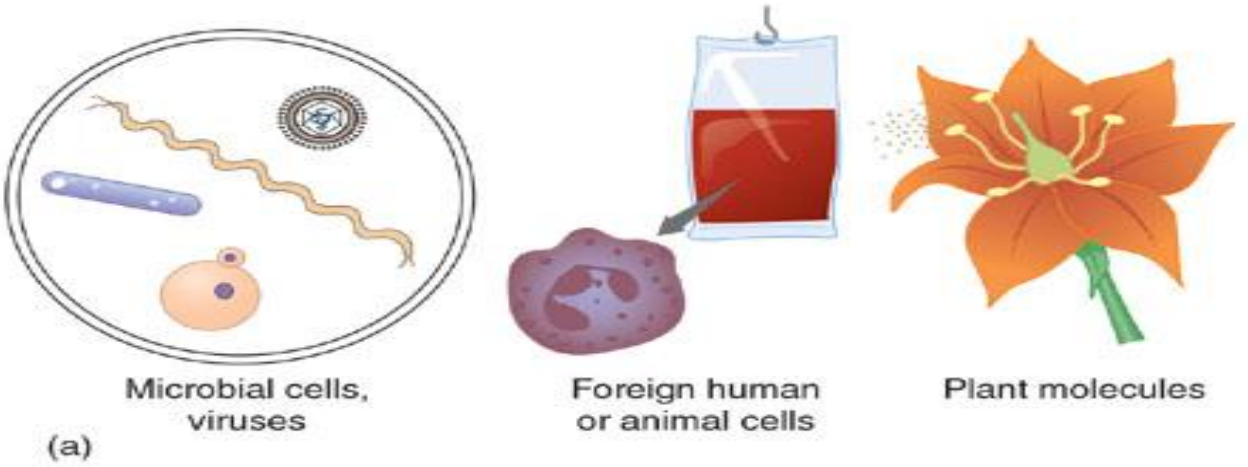
- Maturation is directed by the thymus gland and its hormones
- 7 classes of T-cell receptors termed CD cluster
- Mature T cells migrate to lymphoid organs and occupy specific sites

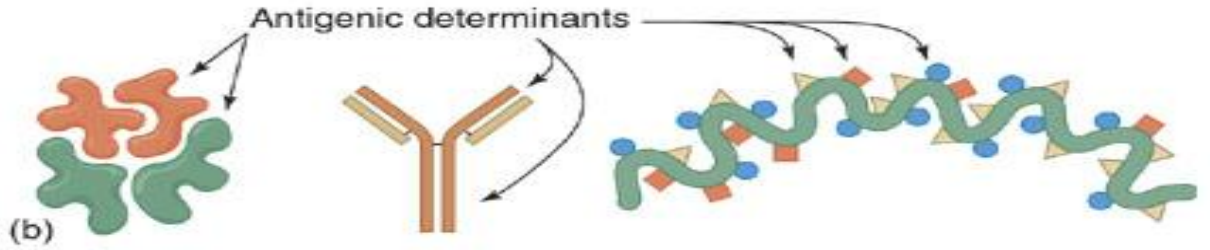
Entrance and Processing of Antigens and Clonal Selection

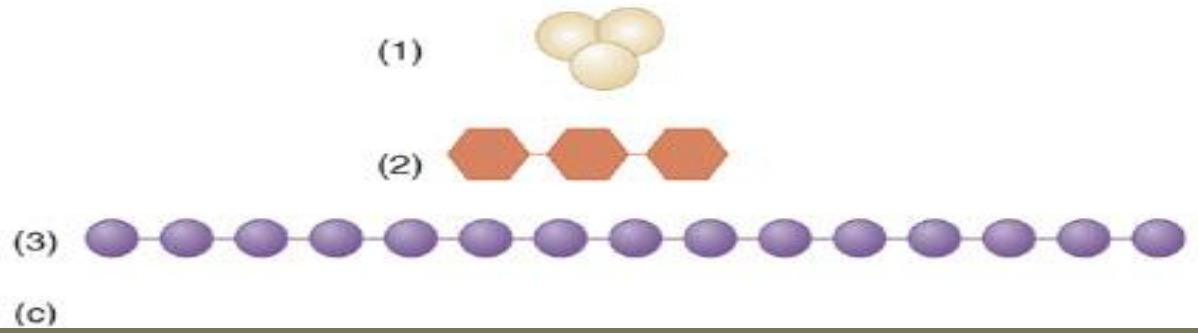
Antigen (Ag)

- substance that provokes an immune response in specific lymphocytes
- perceived as foreign, not a normal constituent of the body
- Foreign cells & large complex molecules over 10,000 MW are most antigenic
- Foreign molecules less than 1,000 MW (haptens) are not antigenic unless attached to a larger carrier
- Antigenic determinant, epitope – small molecular group that is recognized by lymphocytes. An antigen has many antigenic determinants.

Antigens





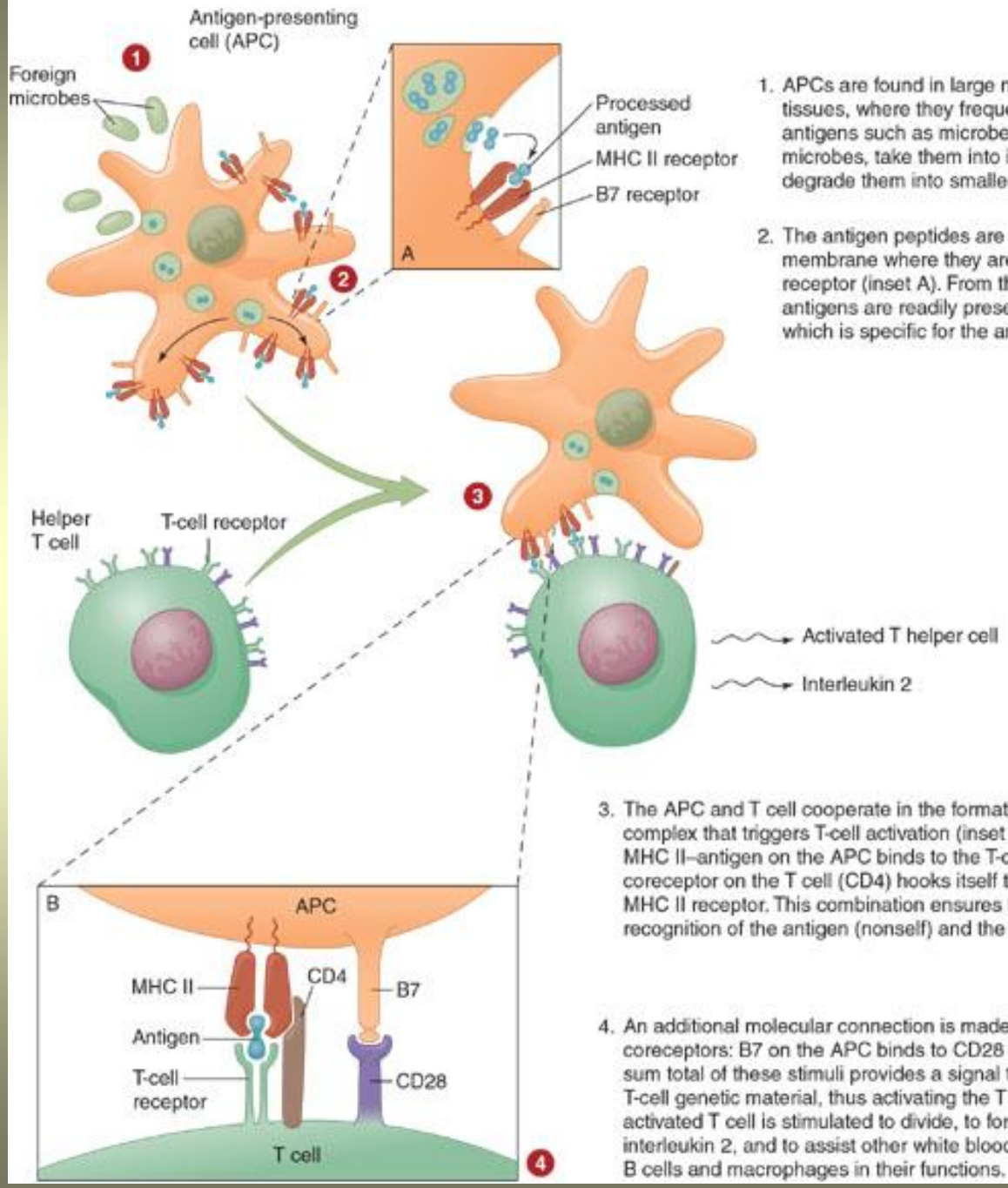


Antigen Binding by Antibodies

Video

Activation of Cooperation

- T-cell dependent antigens must be processed by phagocytes called antigen presenting cells (APC).
- An APC alters the antigen and attaches it to its MHC receptor.
- Antigen presentation involves a direct collaboration among an APC, a T helper cell and an antigen-specific B or T cell.
- Interleukin -1 is secreted by APC to activate T_{H1} cells
- Interleukin-2 is produced by T_{H2} to activate B & other T cells



1. APCs are found in large numbers in lymphatic tissues, where they frequently encounter complex antigens such as microbes. APCs engulf the microbes, take them into intracellular vesicles, and degrade them into smaller, simpler peptides.

2. The antigen peptides are transported to the APC membrane where they are bound to the MHC II receptor (inset A). From this favorable location the antigens are readily presented to a helper T cell, which is specific for the antigen being presented.

3. The APC and T cell cooperate in the formation of a receptor complex that triggers T-cell activation (inset B). First the MHC II–antigen on the APC binds to the T-cell receptor. Next, a coreceptor on the T cell (CD4) hooks itself to a position on the MHC II receptor. This combination ensures the simultaneous recognition of the antigen (nonself) and the MHC receptor (self).

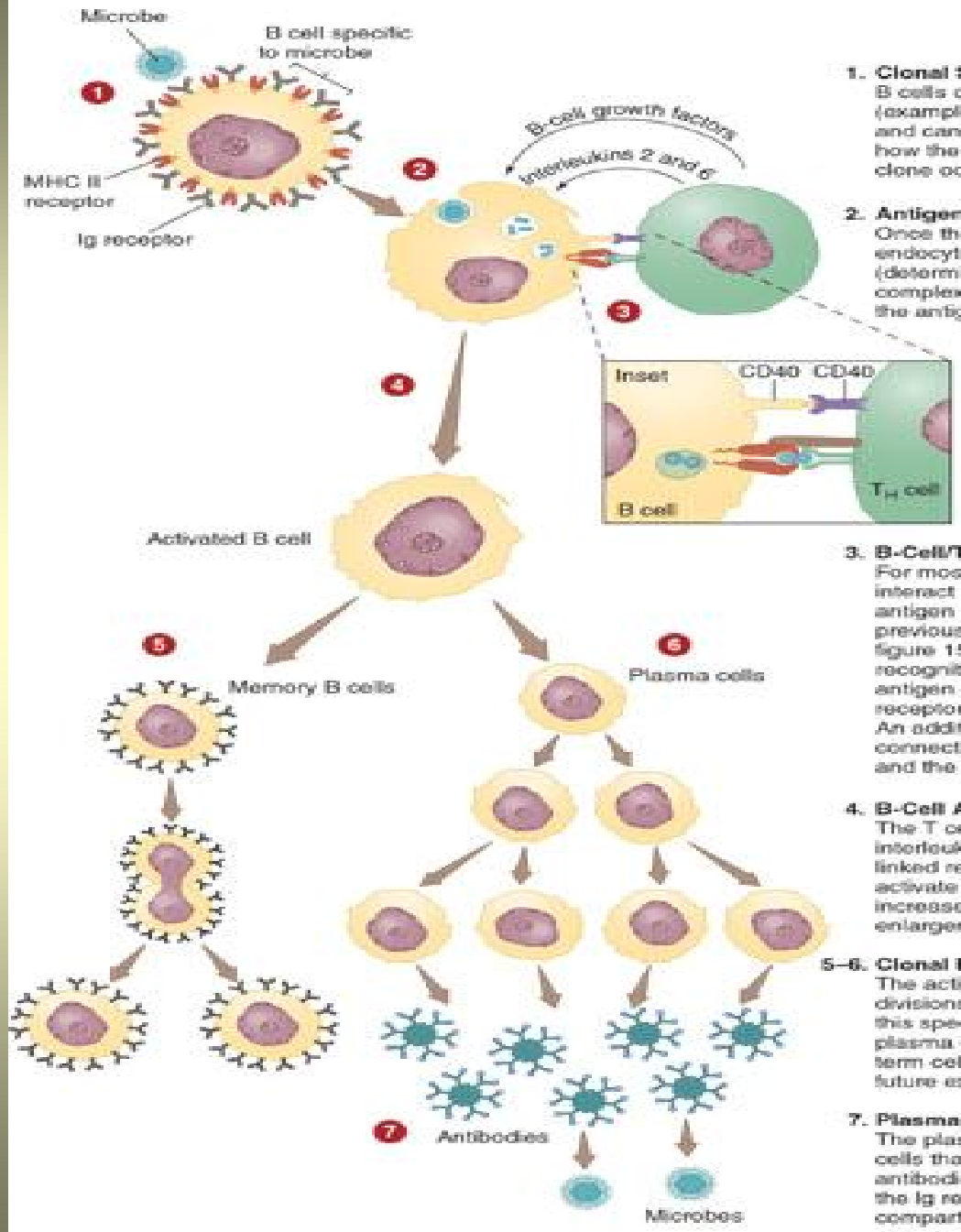
4. An additional molecular connection is made between two other coreceptors: B7 on the APC binds to CD28 on the T cell. The sum total of these stimuli provides a signal that is relayed to the T-cell genetic material, thus activating the T helper cell. The activated T cell is stimulated to divide, to form a cytokine, interleukin 2, and to assist other white blood cells such as B cells and macrophages in their functions.

Activation of Lymphocytes and Clonal Expansion

Video

B cell activation & 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. Video
- Divisions give rise to plasma cells that secrete antibodies and memory cells that can react to the same antigen later. Video



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 (determinants), and displays these on the MHC II complex (similar to other APCs). This event readies the antigen for presentation to a specific T_H cell.

3. **B-Cell/T_H 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 a different APC (see figure 15.12). 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 receptor on the T cell (inset). An additional stimulus comes in the form of a connection between the CD40 ligand on the B cell and the CD40 receptor on the T cell.

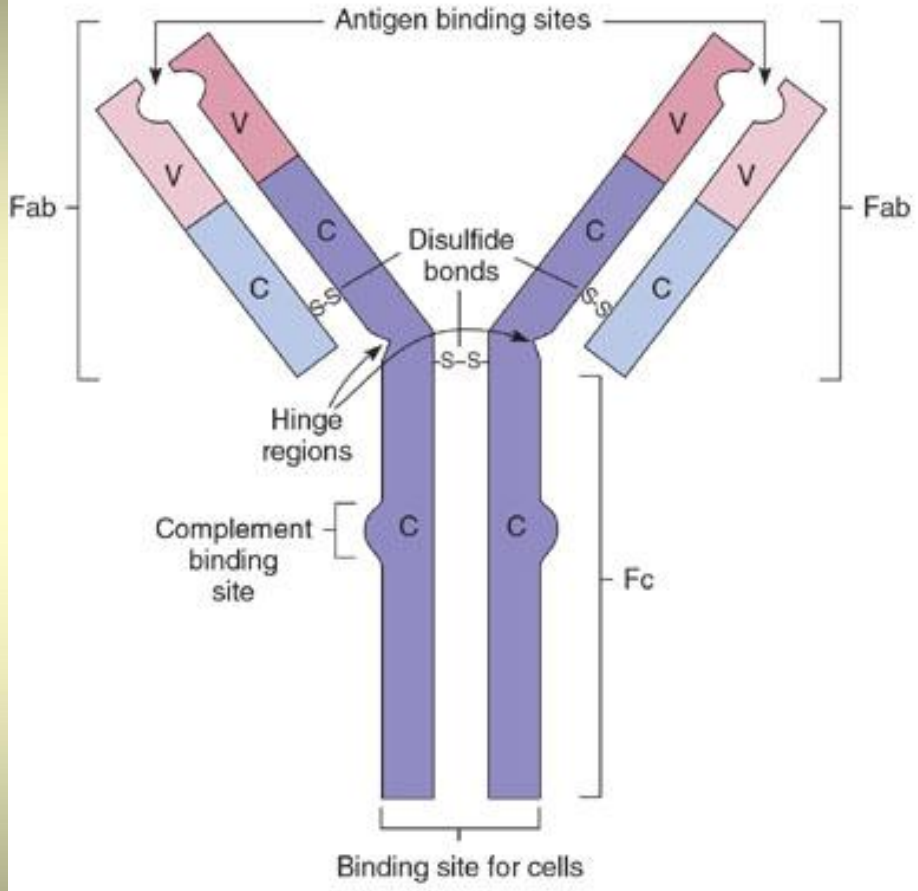
4. **B-Cell Activation**
The T cell gives off additional signals in the form of interleukins 4 and 6 and B-cell growth factors. The linked receptors and the chemical stimuli serve to activate the B cell. Such activation signals an increase in cell metabolism, leading to cell enlargement, proliferation, 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.

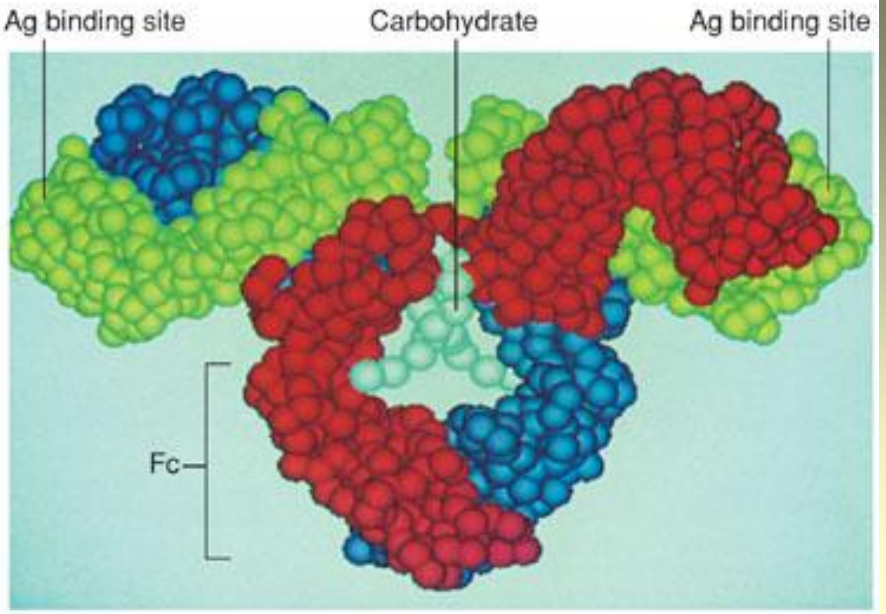
7. **Plasma cells/Antibody Synthesis**
The plasma cells are short-lived, active secretory cells that synthesize and release antibodies. These antibodies (here IgM) have the same specificity as the Ig receptor and circulate in the fluid compartments of the body, where they react with the same antigens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

Nature of antibodies

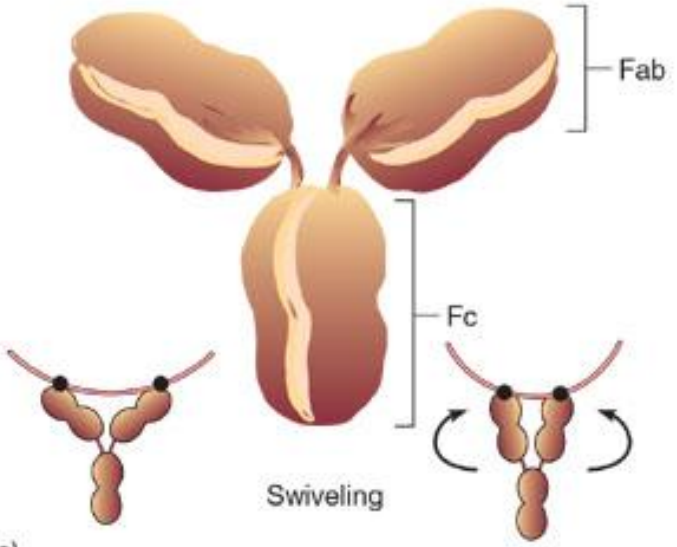
- Immunoglobulins
- A large Y-shaped protein
- Consists of 4 polypeptide chains
- Contains 2 identical fragments (Fab) with ends that bind to specific antigen
- Fc binds to self



(a)



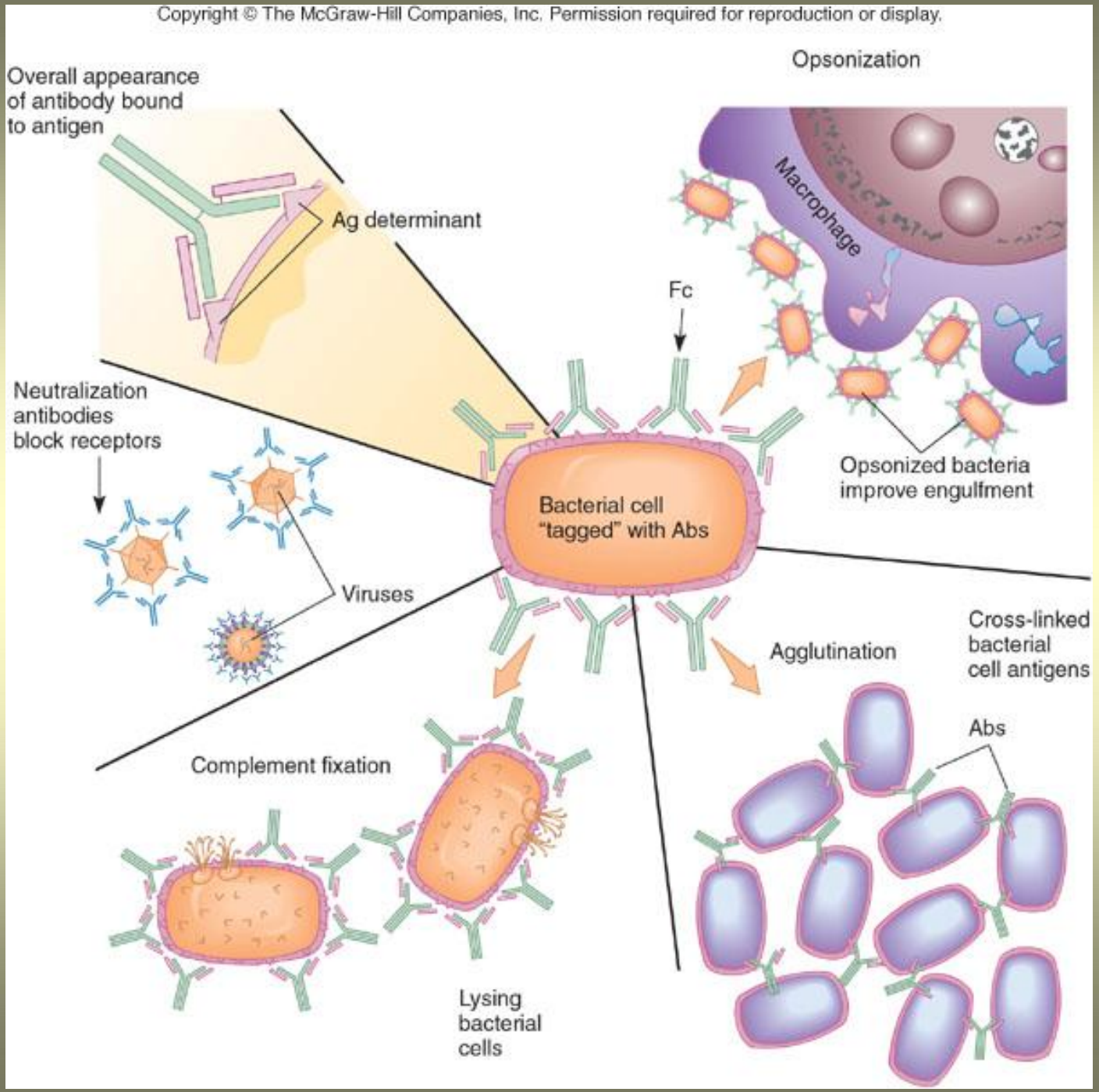
(b)



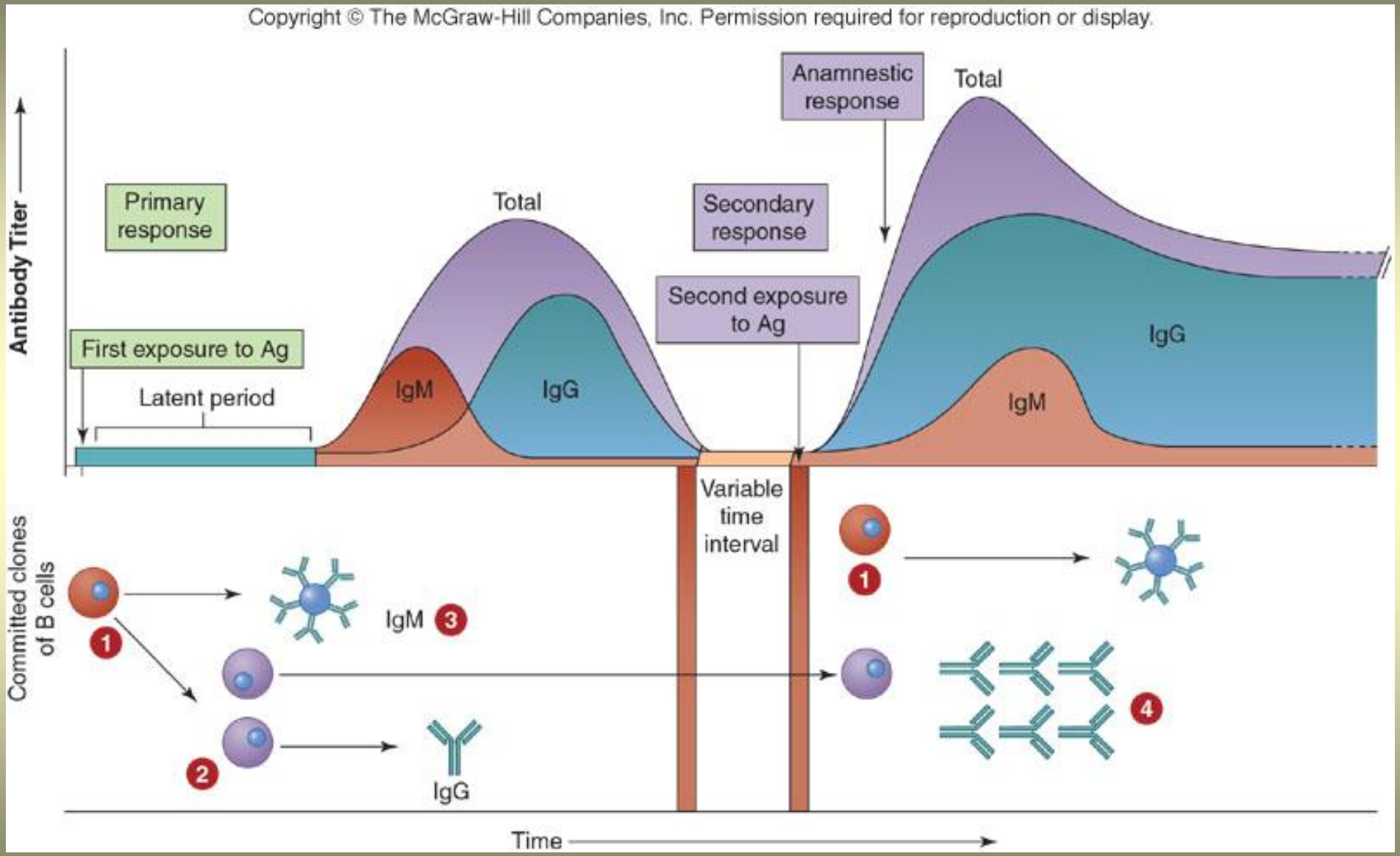
(c)

Ag-Ab reactions

- Opsonization
- Neutralization
- Agglutination
- Complement fixation



- Primary response – after first exposure to an Ag immune system produces IgM and a gradual increase in Ab titer
- Secondary response –after second contact with the same Ag, immune system produces a more rapid, stronger response due to memory cells



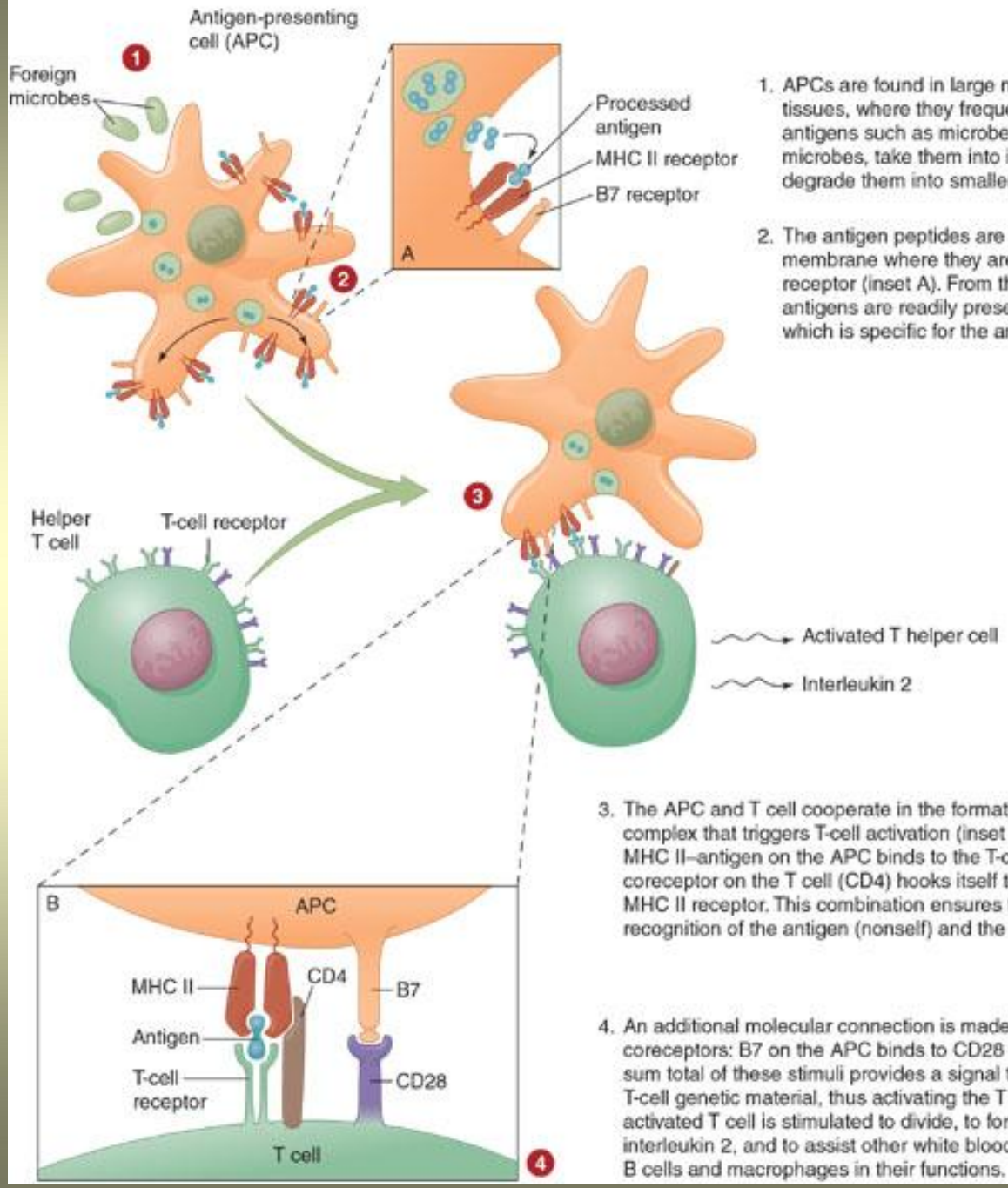
"Your problem is in the gene that makes antibodies, but since the Biophase Corp. now has a patent on that gene, I can't do anything for you."

Macrophages

- Phagocytic actions of macrophages, monocytes, and neutrophils Video
- Macrophage process antigens and present them to T cells
- Macrophage recognition by the T cell and the release interleukins activate and begin the immune reaction

Cooperation of Activation begins with the processing of the antigen by an Antigen Presenting Cell (APC) in this case, a Macrophage

Video



1. APCs are found in large numbers in lymphatic tissues, where they frequently encounter complex antigens such as microbes. APCs engulf the microbes, take them into intracellular vesicles, and degrade them into smaller, simpler peptides.

2. The antigen peptides are transported to the APC membrane where they are bound to the MHC II receptor (inset A). From this favorable location the antigens are readily presented to a helper T cell, which is specific for the antigen being presented.

3. The APC and T cell cooperate in the formation of a receptor complex that triggers T-cell activation (inset B). First the MHC II–antigen on the APC binds to the T-cell receptor. Next, a coreceptor on the T cell (CD4) hooks itself to a position on the MHC II receptor. This combination ensures the simultaneous recognition of the antigen (nonself) and the MHC receptor (self).

4. An additional molecular connection is made between two other coreceptors: B7 on the APC binds to CD28 on the T cell. The sum total of these stimuli provides a signal that is relayed to the T-cell genetic material, thus activating the T helper cell. The activated T cell is stimulated to divide, to form a cytokine, interleukin 2, and to assist other white blood cells such as B cells and macrophages in their functions.

T cells & Cell Mediated Immunity

- T cells act directly against Ag and foreign cells.
- T cells secrete cytokines that act on other cells.
- Sensitized T cells proliferate into long-lasting memory T cells.

Video

T-dependent antigen triggering

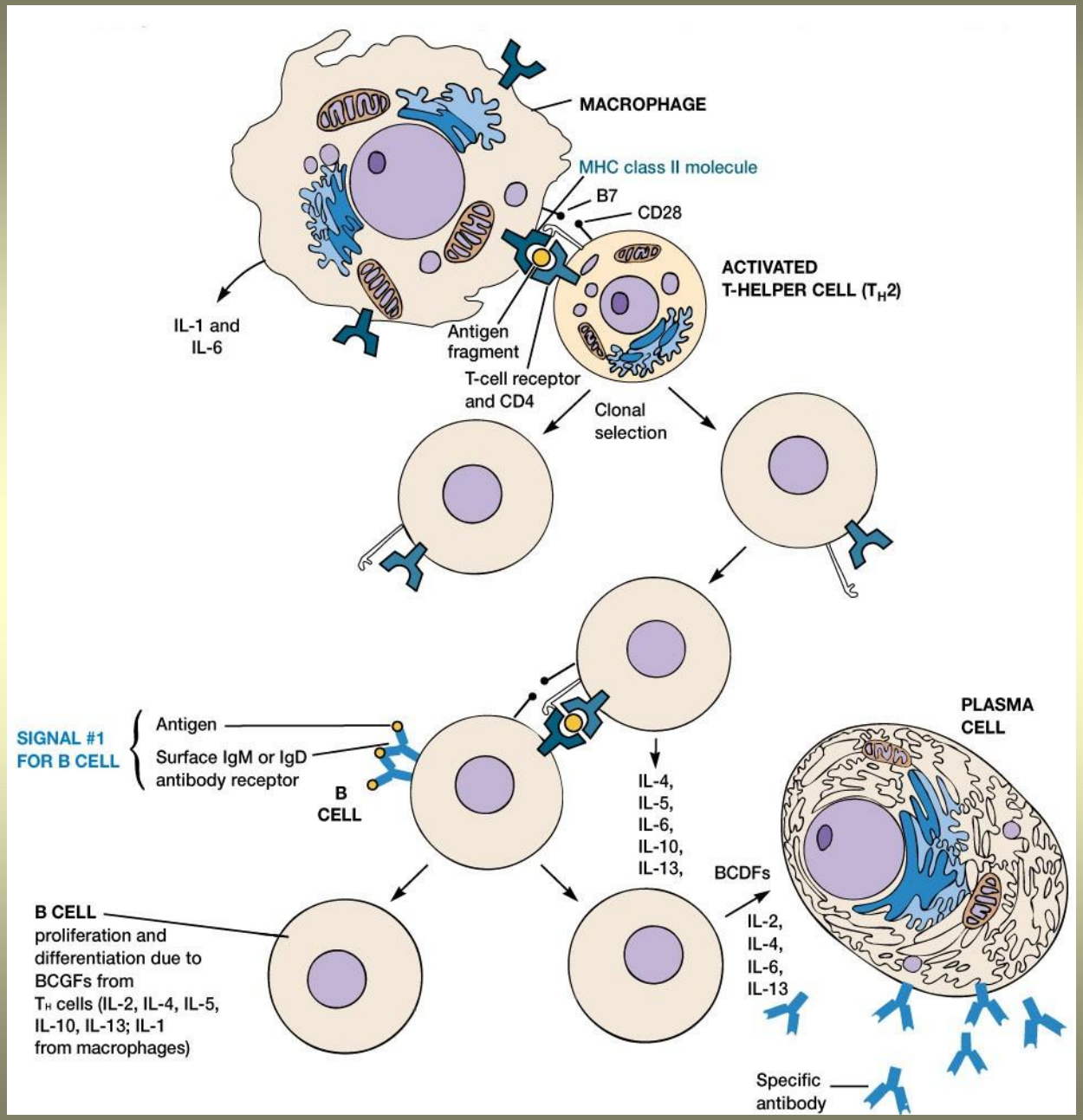
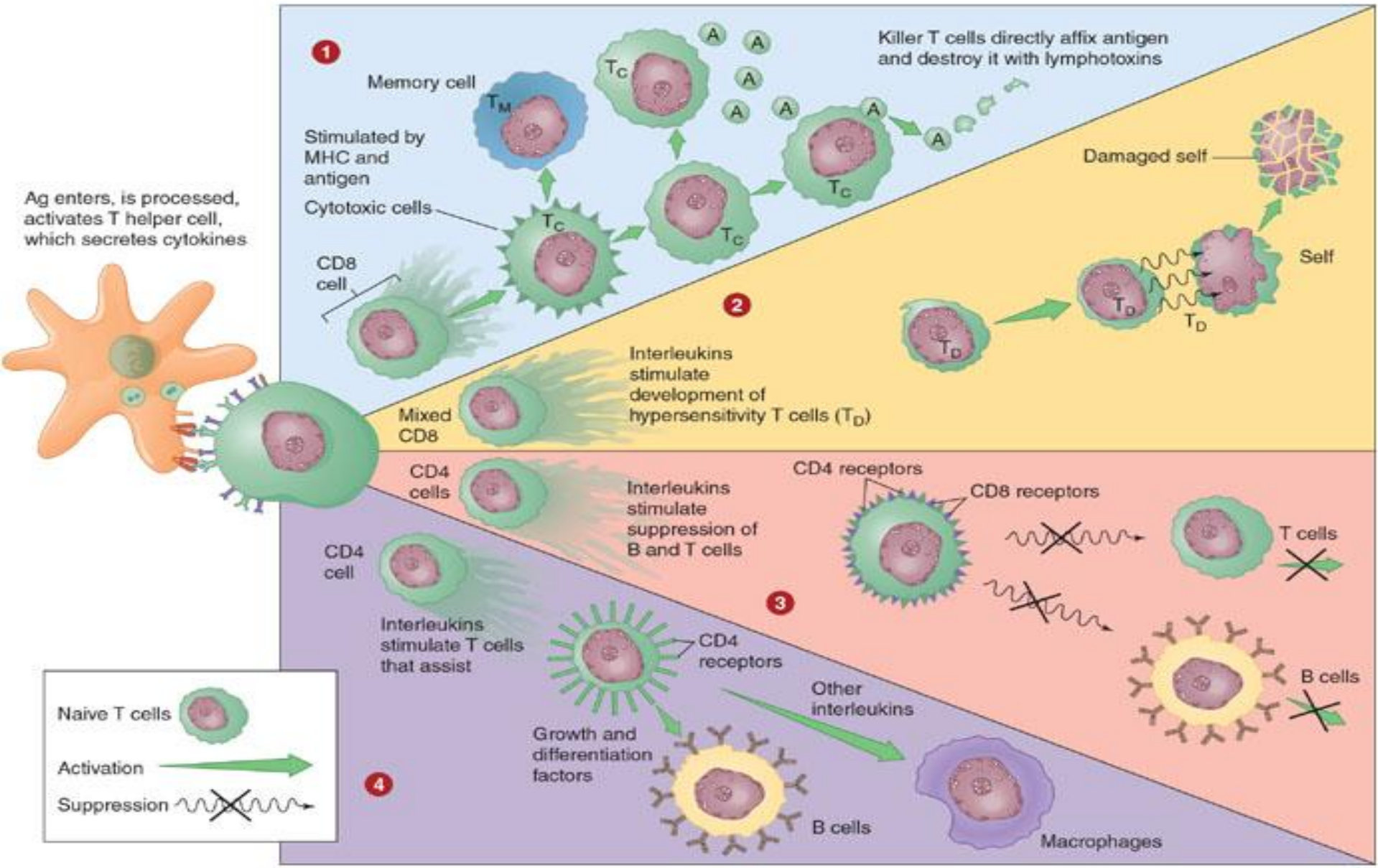


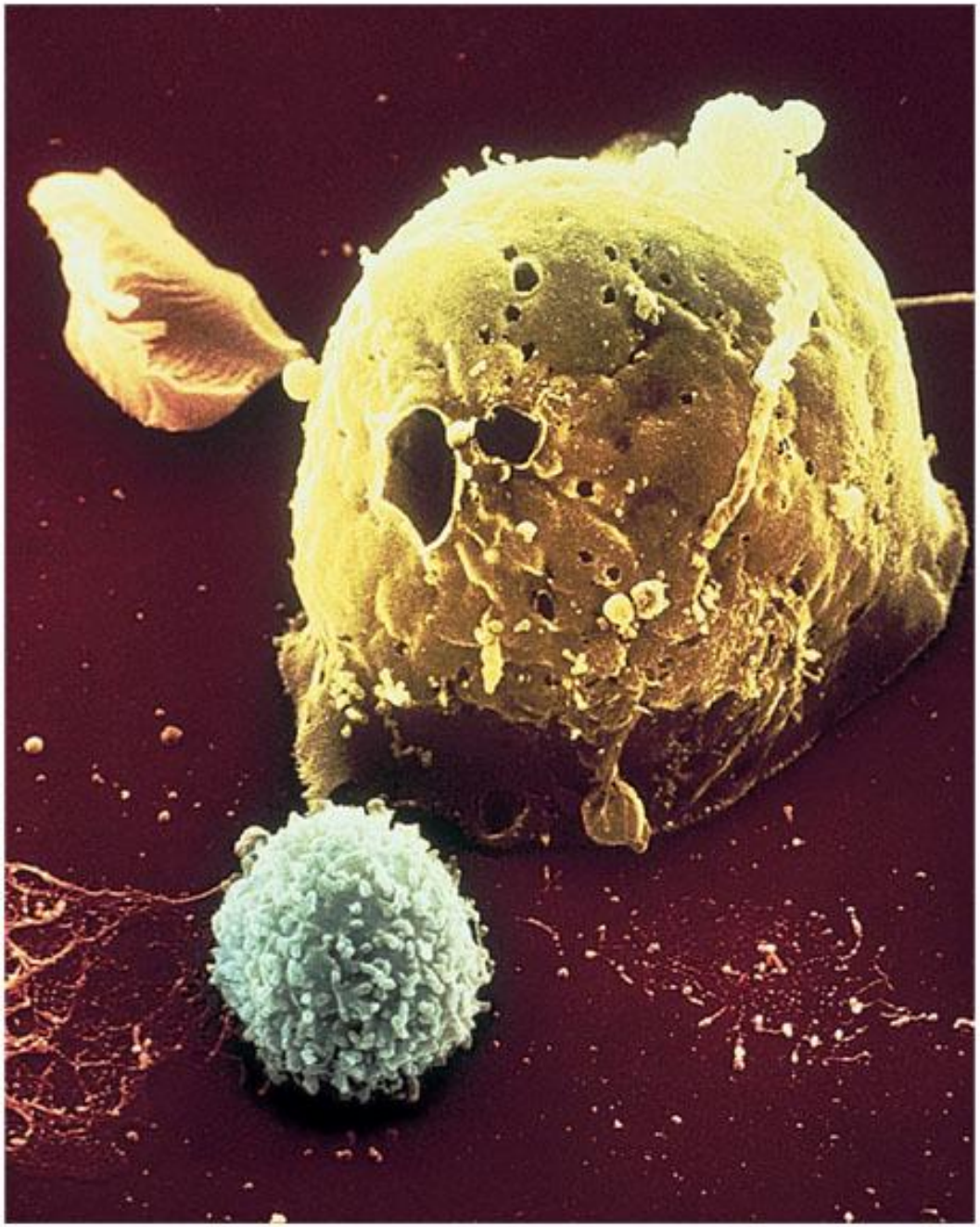
Figure 32.28

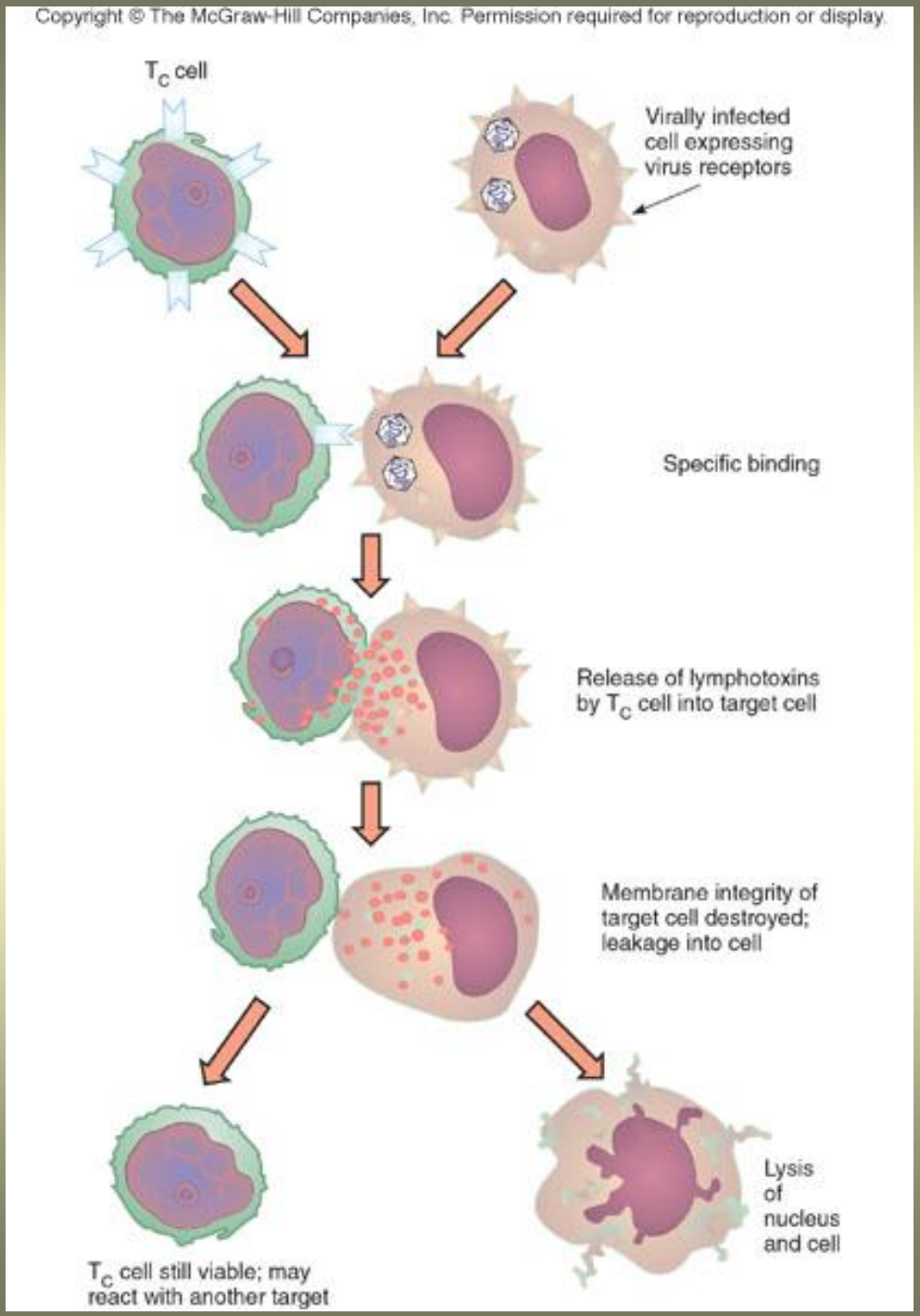
4 types of T cells

1. **T helper cells** (CD4 or T_H) assist other T and B cells; conductor of immune response
2. **Cytotoxic T cells** (CD8 or T_C) destroy foreign or abnormal cells by secreting perforins that lyse cells Video
3. **Delayed hypersensitivity cells** (T_D) responsible for allergies occurring several hours or days after contact
4. **T suppressor cells** (T_S) limit the actions of other T cells and B cells



1. T_C cells destroy certain microbes and foreign cells.
2. T_D cells react with allergens and cause a type of hypersensitivity that damages self.
3. T_S cells limit the actions of B and T cells.
4. T_H cells assist in the actions of B and T cells.





Video

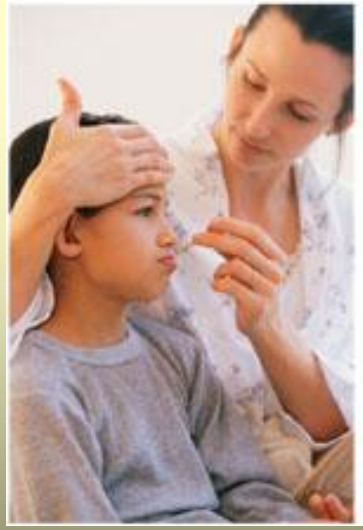
Acquired immunity

- Natural immunity – acquired as part of normal life experiences
- Artificial immunity - acquired through a medical procedure such as a vaccine
- Active immunity – results when a person is challenged with Ag that stimulates production of Ab. It creates memory, takes time and is lasting
- Passive immunity – preformed Ab are donated to an individual. It does not create memory, acts immediately, and is short term.

Acquired Immunity

Natural Immunity
is acquired through the normal life experiences of a human and is not induced through medical means.

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



Passive Immunity
is the consequence of one person receiving a performed immunity made by another person.

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

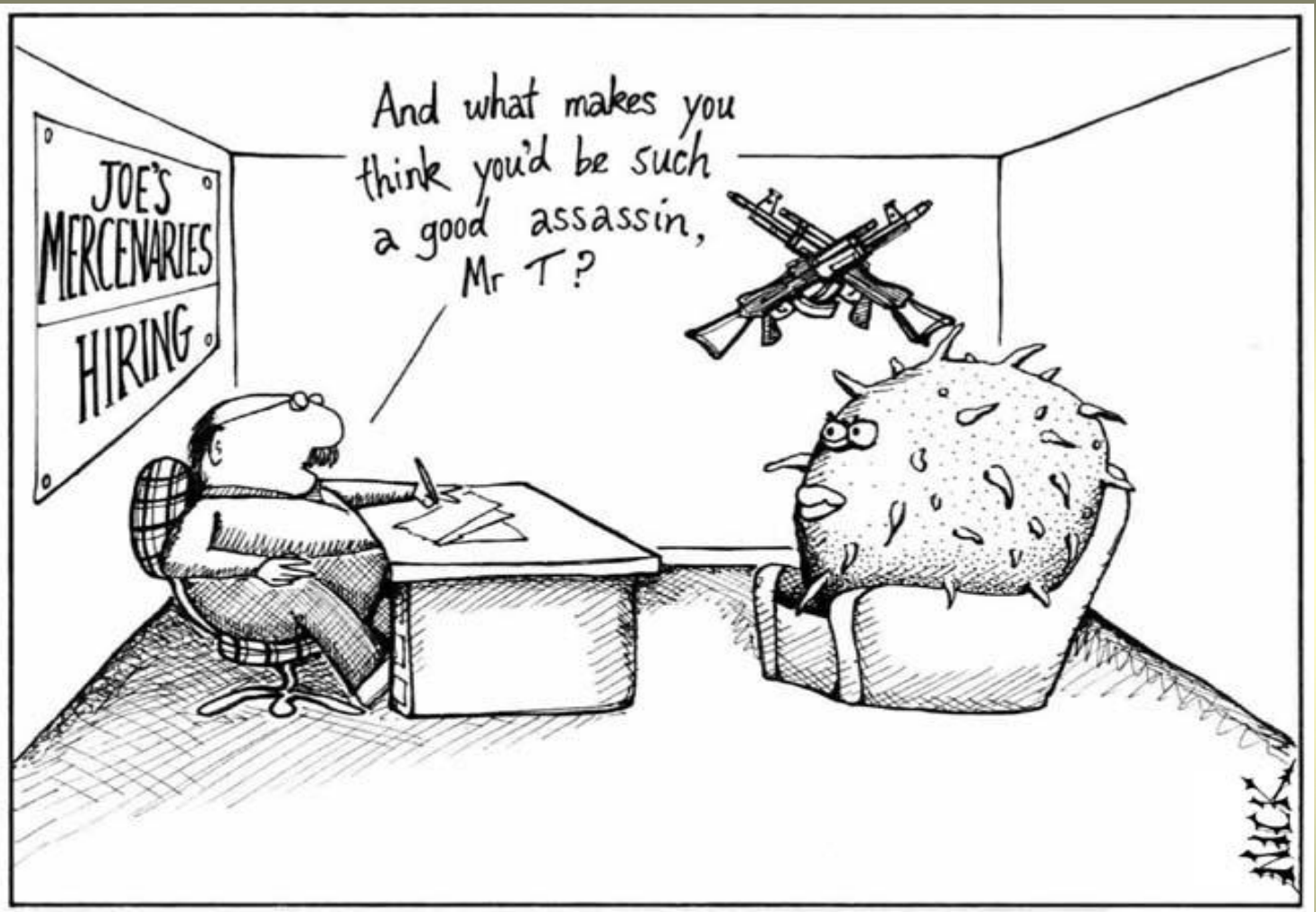
Active Immunity
is the consequence of a person developing his own immune response to a microbe.

Passive Immunity
is the consequence of one person receiving a performed immunity made by another person.

Types of acquired immunity

- **Natural active** immunity – acquired upon infection and recovery
- **Natural passive** immunity – acquired by a child through placenta and breast milk
- **Artificial active** immunity – acquired through inoculation with a selected Ag
- **Artificial passive** immunity – administration of immune serum or globulin


off the mark
by Mark Parisi
www.offthemark.com
REALIZING MANKIND MUST COPE WITH A DEPLETING OZONE, DR. REZNICK BEGINS EXTENSIVE RESEARCH REGARDING ACQUIRED IMMUNITY TO THE SUN'S HARMFUL RAYS.



As each disease is finally eradicated, redundant lymphocytes increasingly find themselves looking for other work.