PSMU
Department of microbiology, virology and immunology

History of the development of immunology. Factors of innate immunity. The body`s immune system. Antigens

Connection

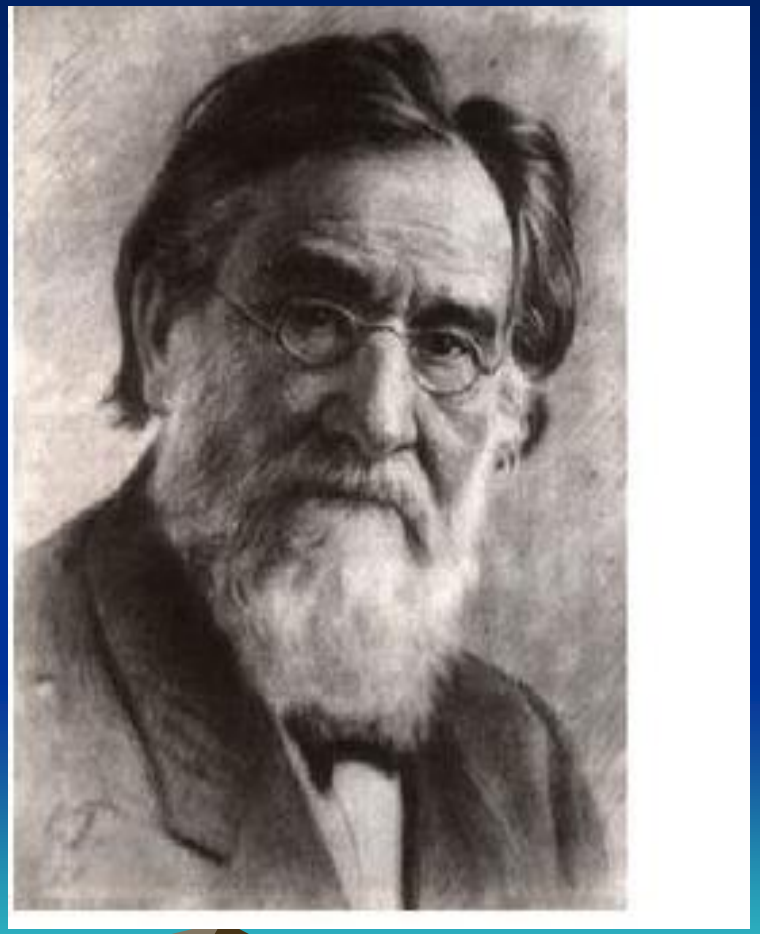
- **For two-way communication between the lecturer and students during the lecture, please contact o_hancho@pdmu.edu.ua**

The term **immunity** (lat. *immunitas* - freed *from* homage, save *norm* something) usually means resistance of the body to pathogenic microbes, their toxins or to other kinds of foreign substances, with genetic heterogeneity. Immunity is the complex of physiological defense reactions which determine the relative constancy of internal medium of the macroorganisms, hinder the development of the infectious process or intoxication and are capable of restoring the impaired functions of the organism. The resistance offered by the host to the harmful effect of pathogenic microbial infection is called **immunity.**

Phagocytosis

was discovered by Elie Mechnikoff

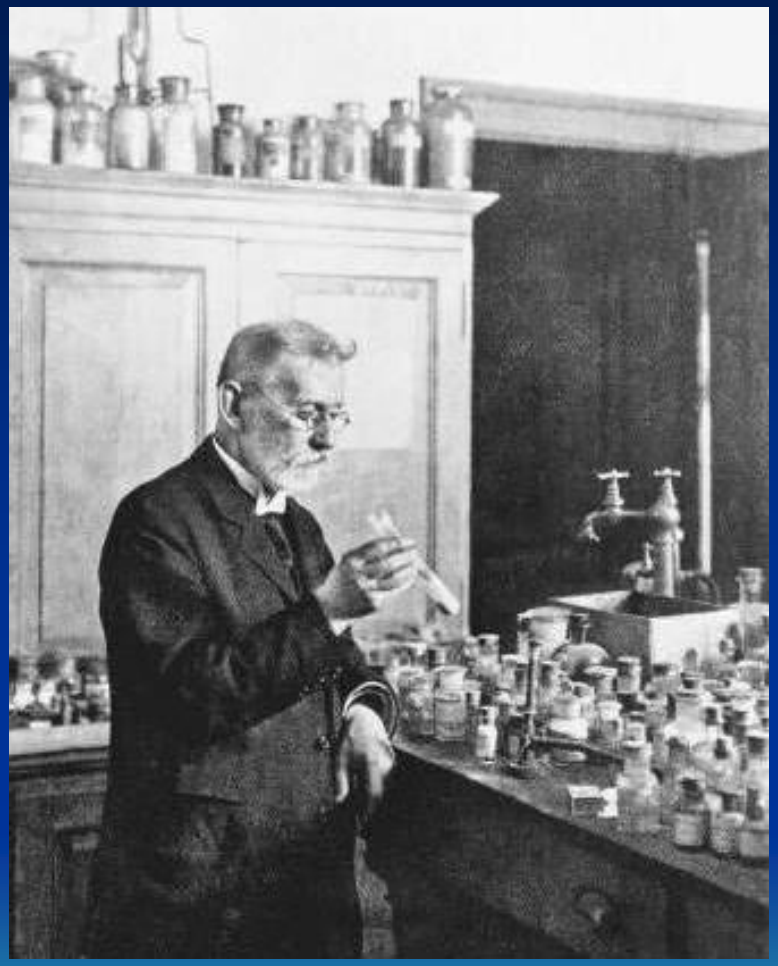
In 1883



1897

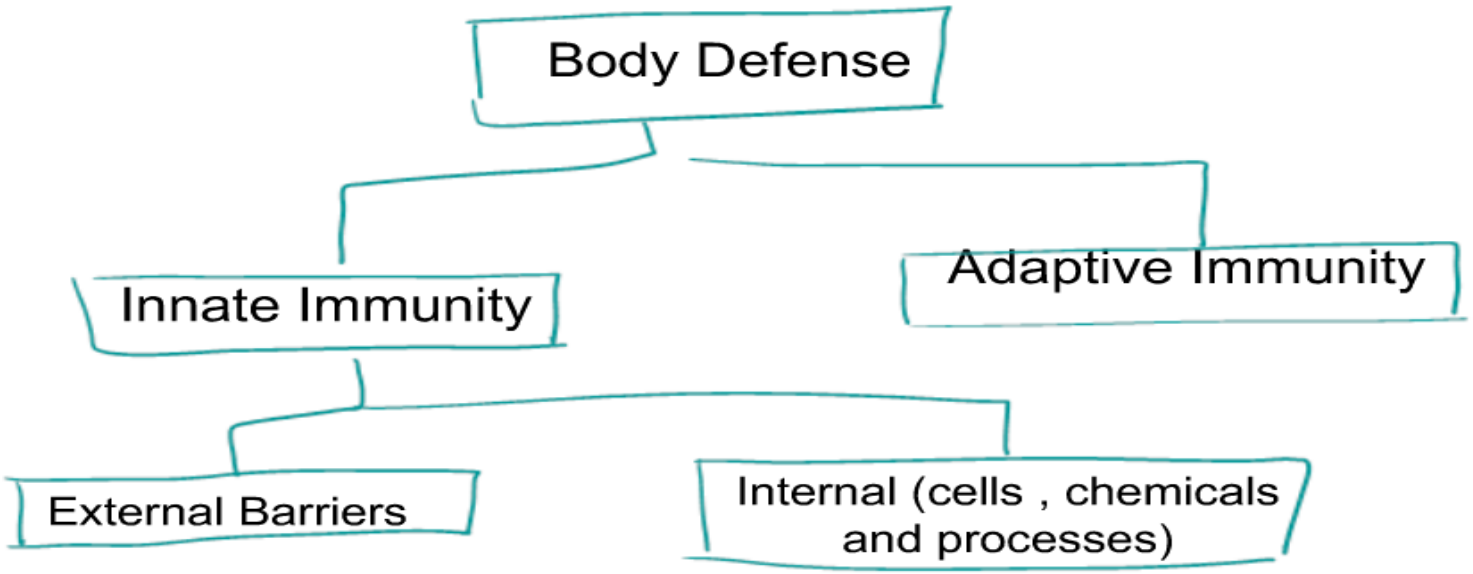
Paul Ehrlich proposed humoral theory of immunity

In 1908 they both received the Nobel Prize



Concept of Immunity

- Body's Defense: Overview



Types of immunity

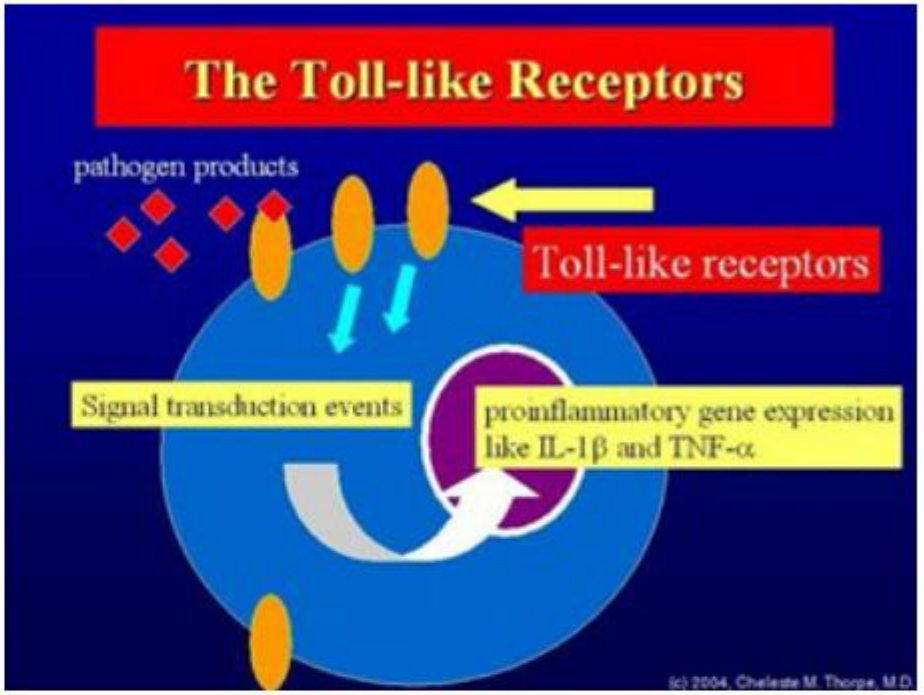
Immunity			
Innate		Acquired	
Non specific	Specific	Passive	Active
it indicates a degree of resistance to all infections	shows resistance to particular pathogen	Natural provides by transplacental Ig G Artificial - gamma-globulins in serum	Natural - post infection (after disease) Artificial – post vaccinal

An Overview of the Body's Defenses

Innate Immunity		Adaptive Immunity (Chapter 17)
First line of defense	**Second line of defense**	**Third line of defense**
• Intact skin • Mucous membranes and their secretions • Normal microbiota	• Phagocytes, such as neutrophils, eosinophils, dendritic cells, and macrophages • Inflammation • Fever • Antimicrobial substances	• Specialized lymphocytes: T cells and B cells • Antibodies

The Concept of Immunity

- Host **Toll-like receptors (TLRs)** attach to PAMPS
- **Pathogen-associated molecular patterns** (**PAMPs**)
- TLRs induce **cytokines** that regulate the intensity and duration of immune responses



Chemical Messengers of ImmuneSystem: Cytokines

- **Cytokines** are chemical messengers of immune system.
- Acts only on a cell that has receptor for it.
- They are soluble proteins or glycoproteins produced by cells of the immune system.
- There different types of cytokines and their common name reflect their function.

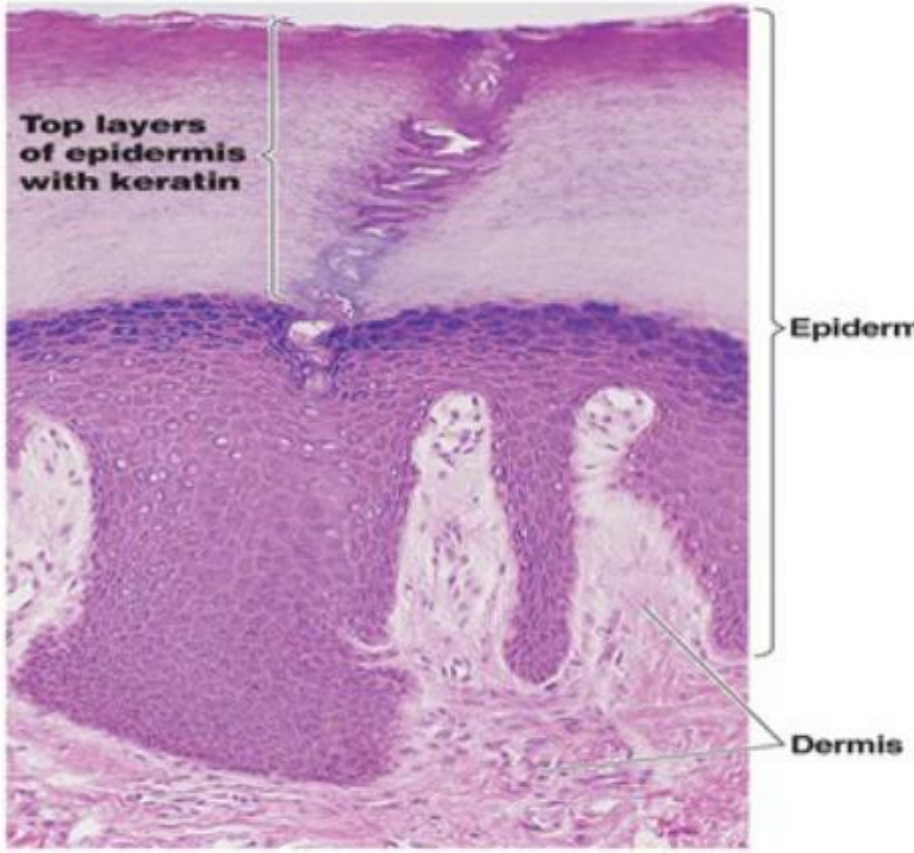
Killer (NK) Cells

  - **Interleukins** are cytokines that communicate between leukocytes
  - **Interferons** protect cells from viral infection.
  - **Chemokines** induces migration of leukocytes into area of infection.
  - Tumor Necrosis Factor(TNF-∞)

First Line of Defense: Skin & Mucous Membranes

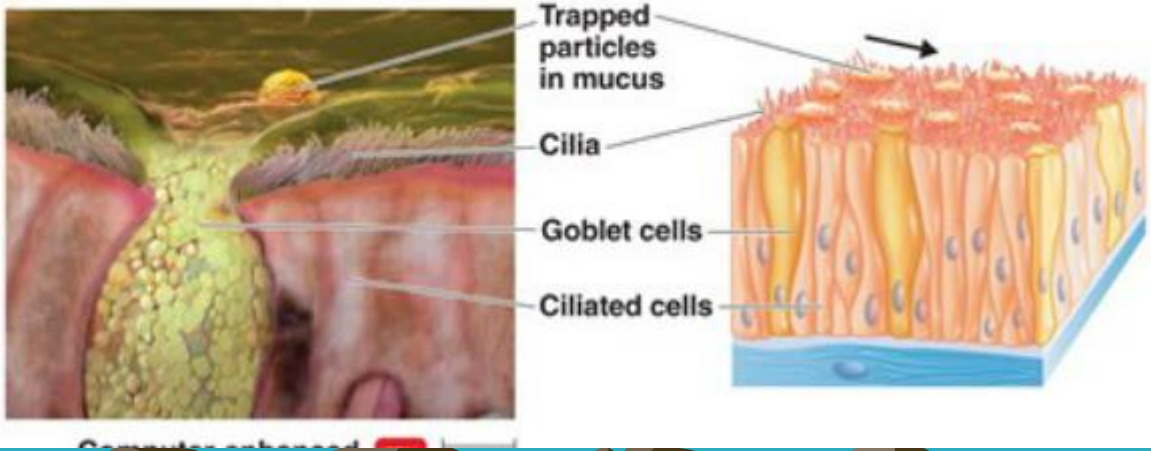
Physical Factors

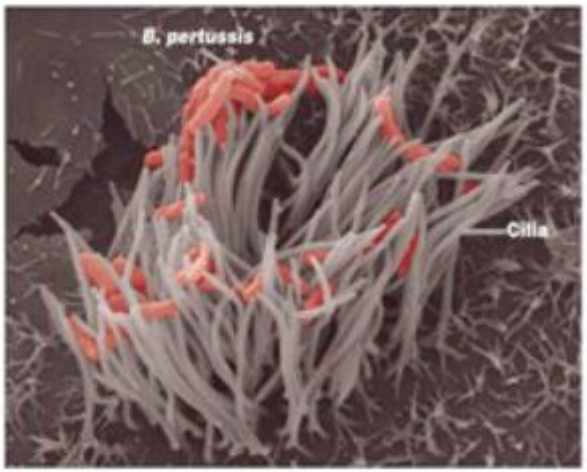
- **Skin**
- **Epidermis** consists of tightly packed cells with
  - **Keratin**, a protective protein
  - Periodic shedding
  - Dryness of skin



Physical Factors

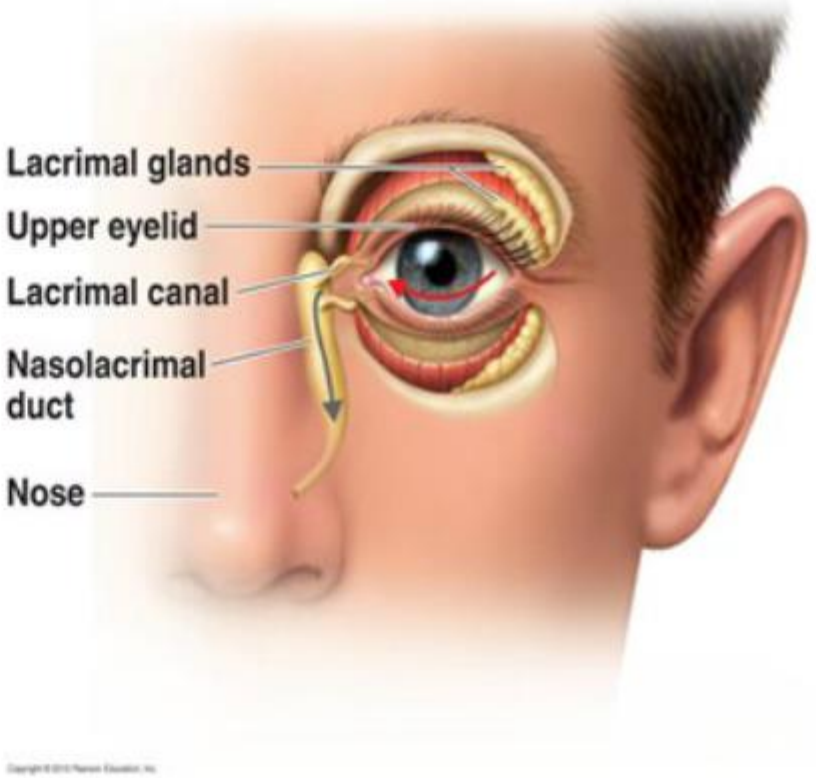
- **Mucous membranes**
- **Mucus**: Traps microbes
- **Ciliary escalator**: Microbes trapped in mucus are transported away from the lungs





Other Physical Factors

- **Lacrimal apparatus**: Washes eye and prevents microorganisms from settling on the surface.
- **Saliva**: Washes microbes off from surface of teeth and mucous membrane of mouth
- **Urine**: Flows out
- **Vaginal secretions**: Flow out
- **Peristalsis, defecation and Vomiting**



Chemical Factors

- Fungistatic fatty acid in **sebum**
- Low pH (3–5) of skin
- **Lysozyme** in **perspiration**, tears, saliva, and **urine**
- Low pH (1.2–3.0) of **gastric juice**
- Low pH (3–5) of **vaginal secretions**
- Metabolic by products **in Urine** inhibit microbes

lormal Microbiota and Innate mmunity

Normal microbiota provide **Microbial antagonism/competitive** exclusion:

Normal microbiota compete with pathogens or alter the environment

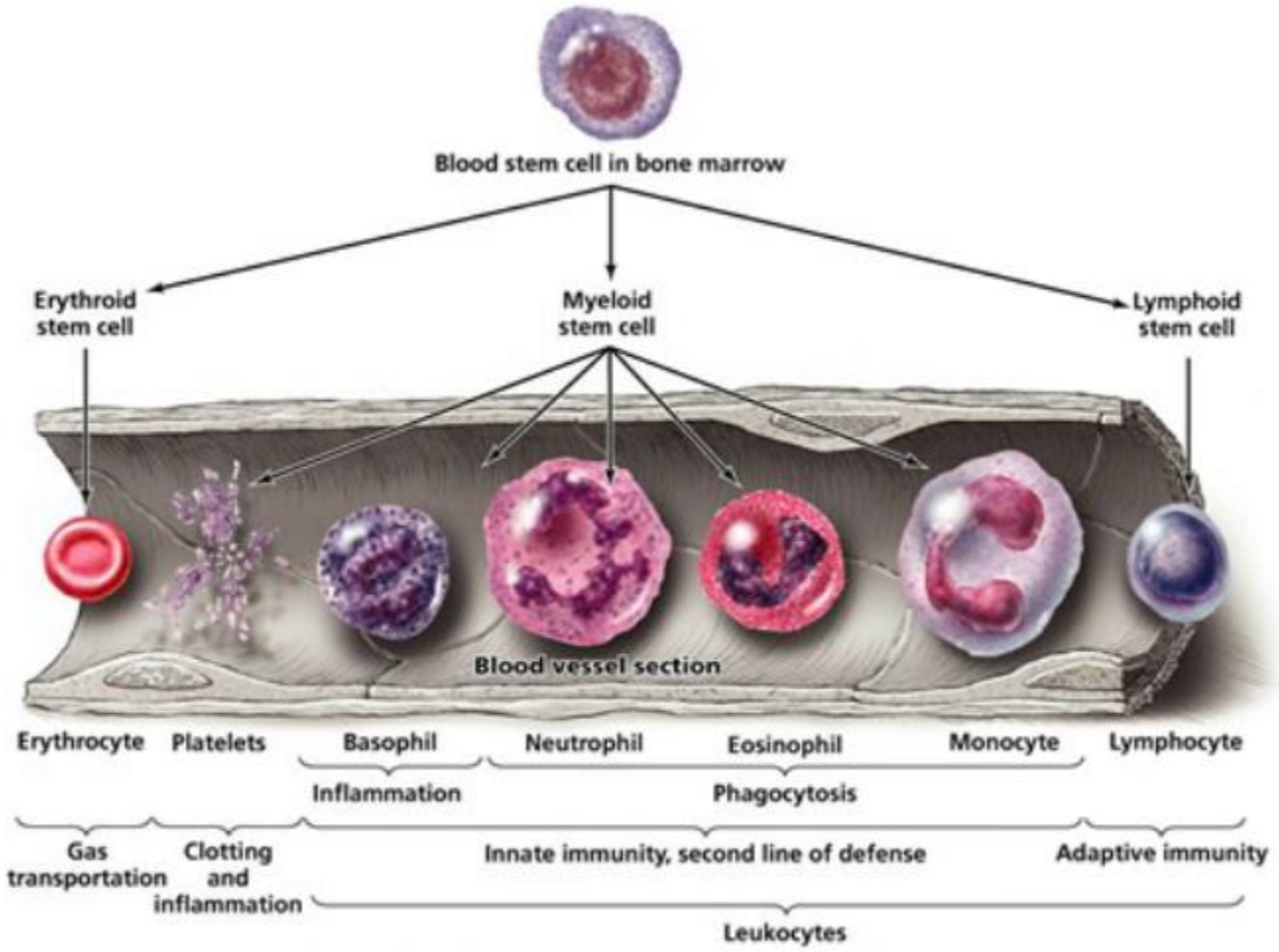
Various activities of the normal microbiota make it hard for pathogens to mpete

- Consumption of nutrients makes them unavailable to pathogens
- Create an environment unfavorable to other microorganisms by changing pH
- Helps stimulate the body's second line of defense
- Promote overall health by providing vitamins to host
- May be opportunistic pathogens

Second Line of Defense

- Does not include physical barriers
- Operates when pathogens succeed in penetrating the skin or mucous membranes
- Composed of cells (**phagocytes**), antimicrobial chemicals (**complements, interferons, defesins**), and processes (**phagocytosis, inflammation and fever)**
- Many of these components are contained or originate in the blood
- Nonspecific defense

Hematopoiesis of Formed Elements



Differential White Cell Count

- Percentage of each type of white cell in a sample of 100 white blood cells

Neutrophils	60–70%
Basophils	0.5–1%
Eosinophils	2–4%
Monocytes	3–8%
Lymphocytes	20–25%

The Concept of Immunity

- **Susceptibility**: Lack of resistance to a disease
- **Immunity**: Ability to ward off disease
- **Innate immunity**: Defenses against any pathogen
- **Adaptive immunity**: Immunity, resistance to a specific pathogen

Second Line of Defense

Phagocytosis

- *Phago*: From Greek, meaning eat
- *Cyte*: From Greek, meaning cell
- Ingestion of microbes or particles by a cell, performed by phagocytes

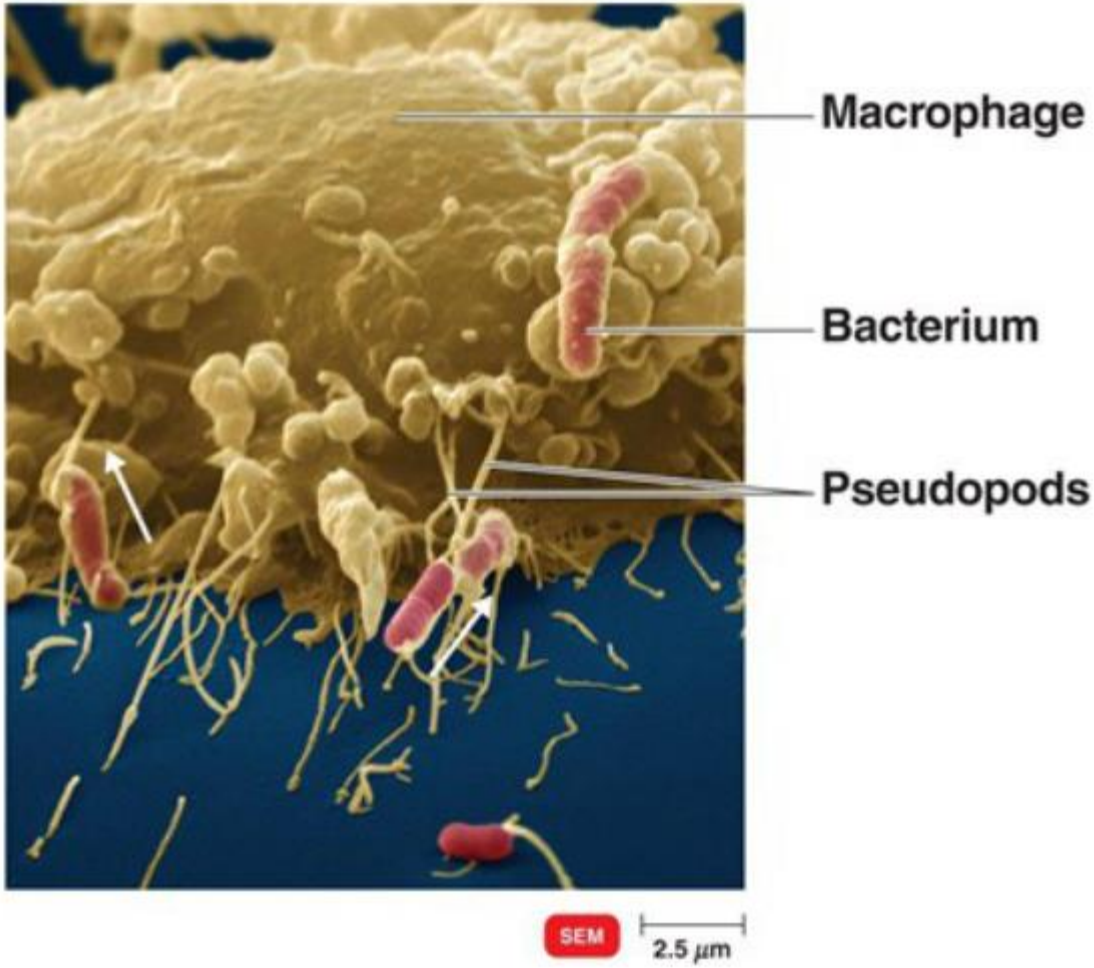


Figure 16.6

Phagocytes

- **Neutrophils**
- **Eosinophils and dendritic cells** to some extent.
- **Macrophages**
  - **Fixed macrophages (histiocytes):** resident in certain tissues

    Ex: Knpffer's cell(liver), microglial cells(nervous system)
  - **Wandering macrophages**
    - Roam the tissues and gather at sites of infection
- Various phagocytes constitute the **Mononuclear phagocytic system**

Phagocytosis

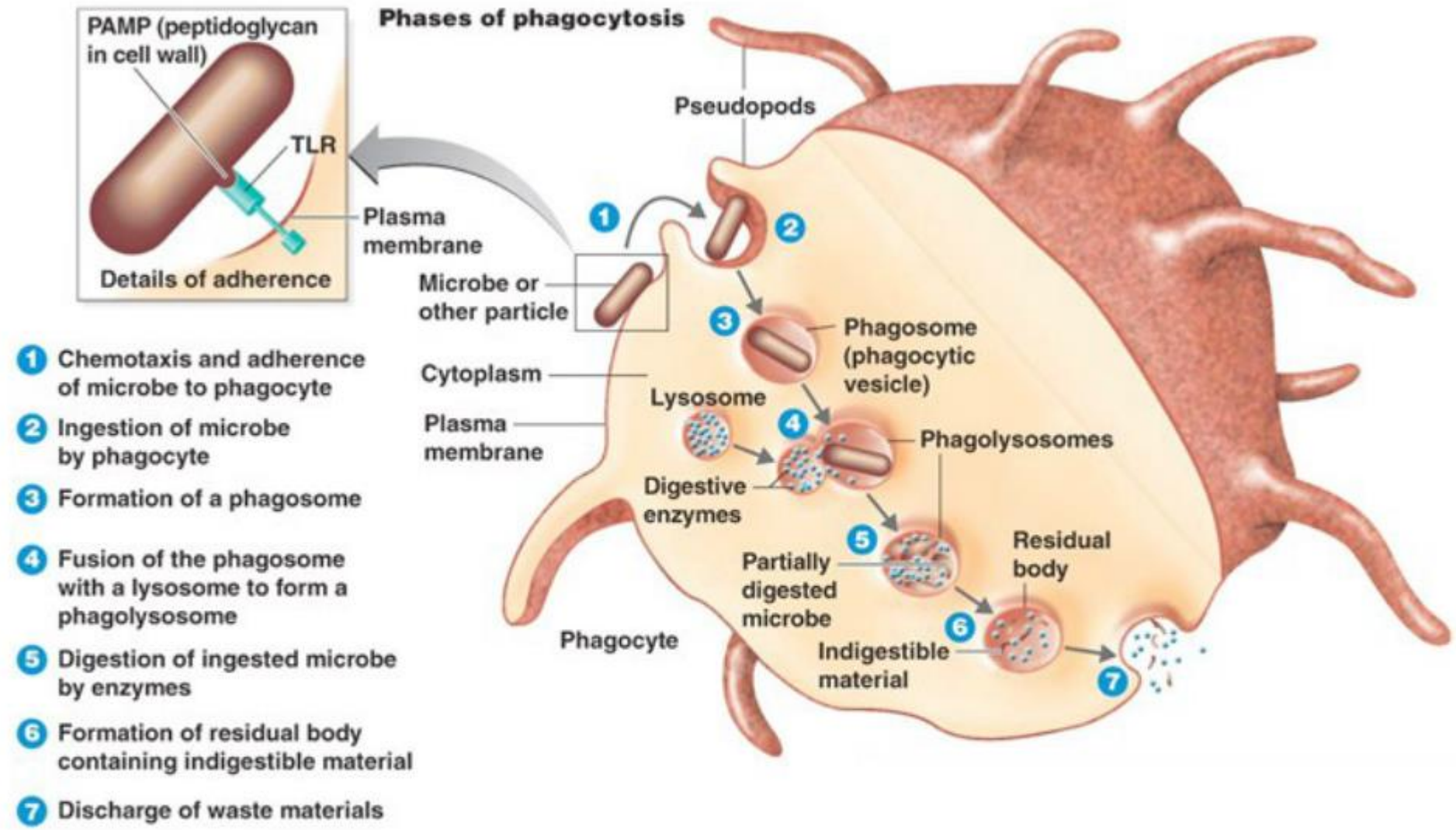


Figure 16.7

Antimicrobial Substances

The Complement System

- Set of serum proteins designated numerically according to the order of their discovery
- Serum proteins activated in a cascade
- Complement activation may occur in three pathways

- Activated by
  - Antigen-antibody reaction (Classical pathway)
  - Proteins C3, B, D, P and a pathogen (Alternate pathway)
  - Activated by lectins, produced by liver(Lectin pathway)

The Complement System

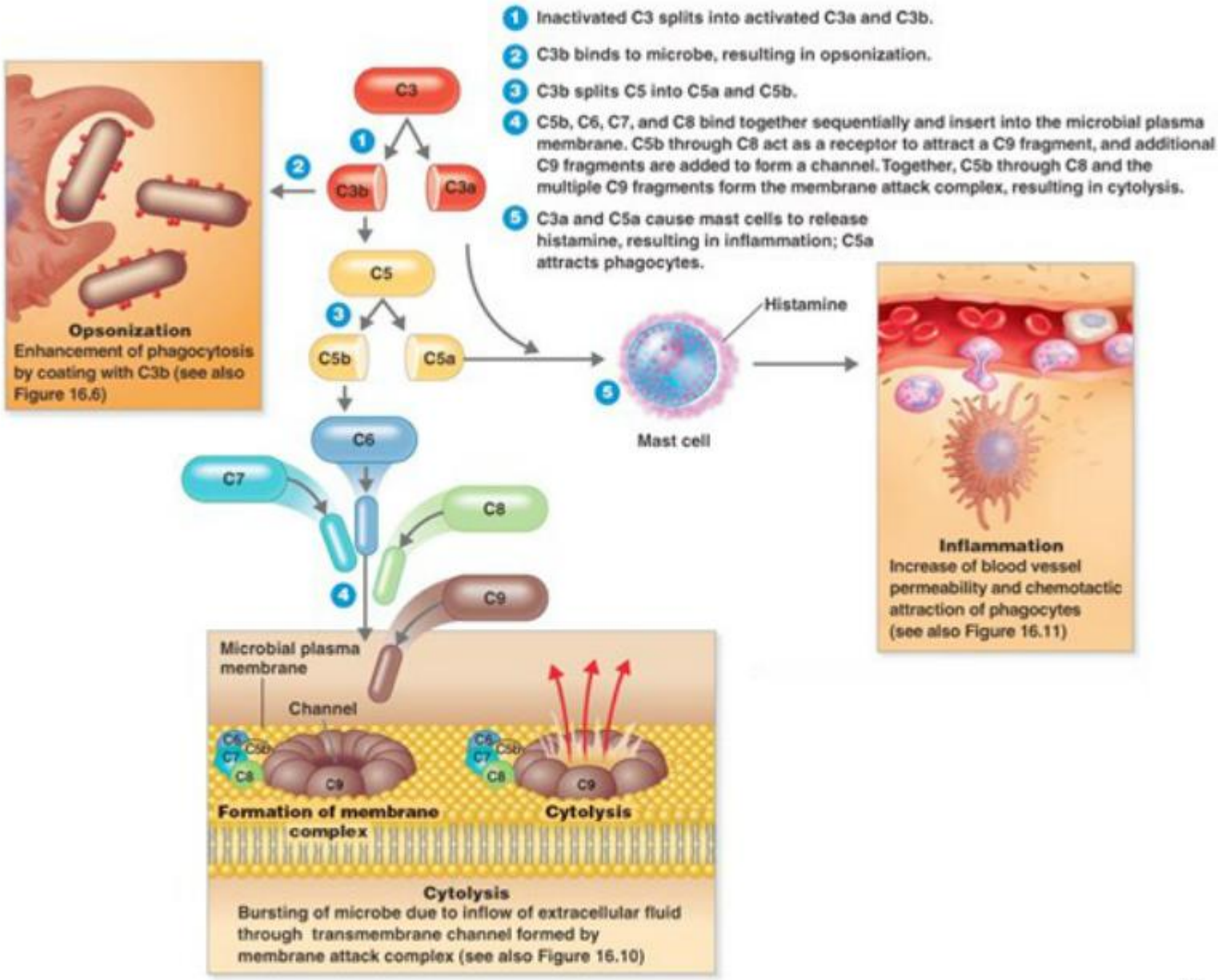


Figure 16.9

Effects of Complement Activation

- Opsonization or immune adherence: Enhanced phagocytosis
- Membrane attack complex: Cytolysis
- Attract phagocytes
- Inflammation

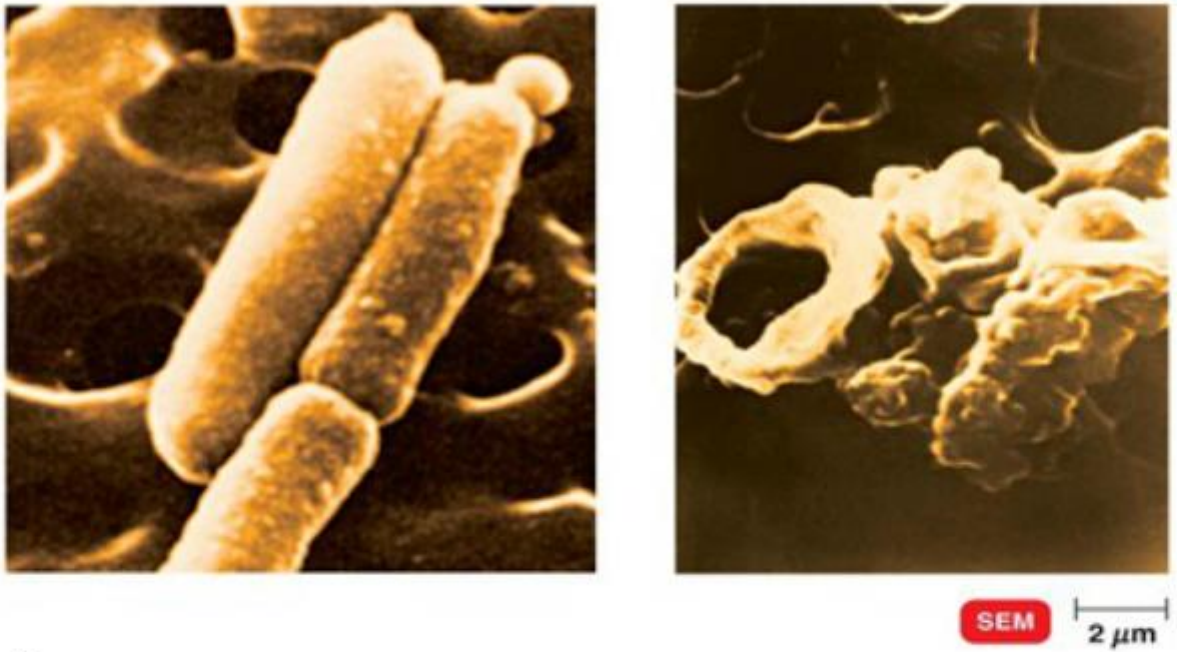
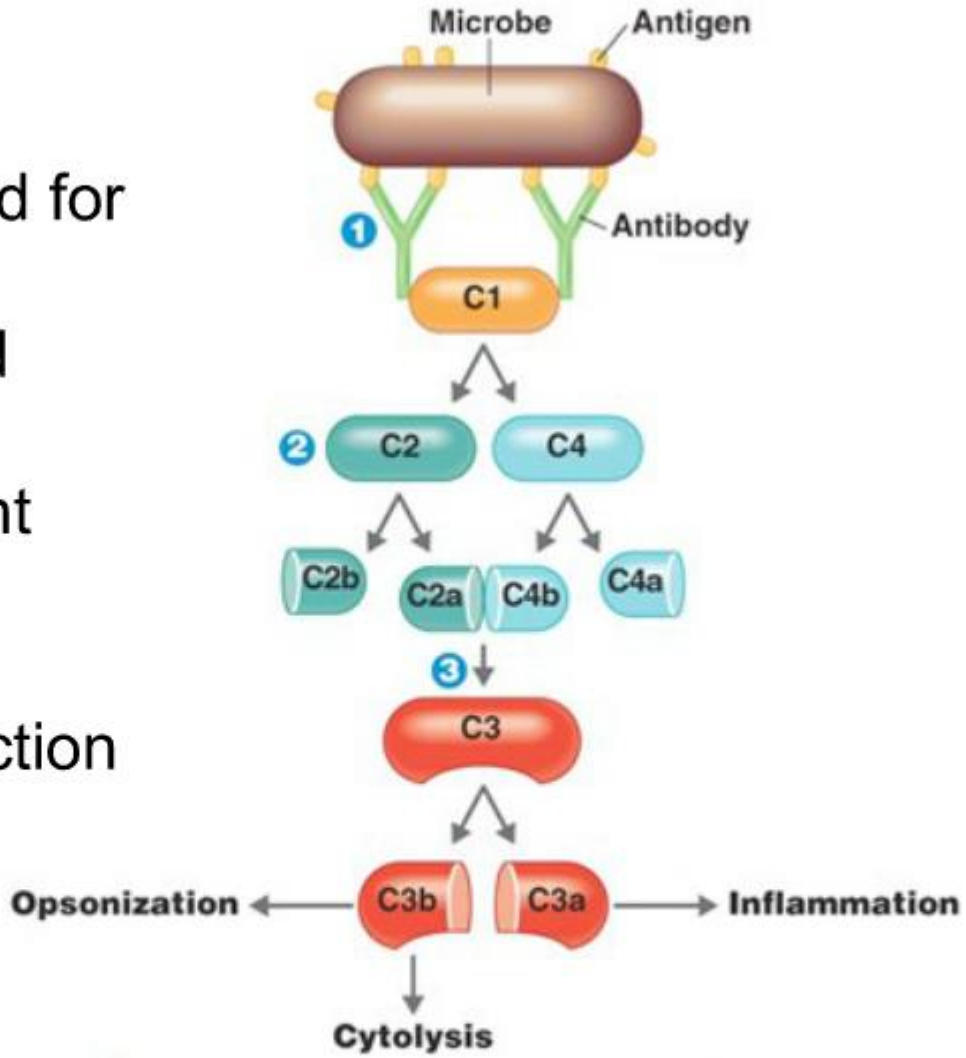


Figure 16.10

Classical Pathway of Complement Activation

- Complement named for the events of this originally discovered pathway
- Various complement proteins act nonspecifically to "complement" the action of antibodies



1. C1 is activated by binding to antigen–antibody complexes.
2. Activated C1 splits C2 into C2a and C2b, and C4 into C4a and C4b.
3. C2a and C4b combine and activate C3, splitting it into C3a and C3b (see also Figure 16.9).

Figure 16.12

Alternative Pathway of Complement Activation

- Activation occurs independent of antibodies
- Useful in early stages of infection before antibodies have been made

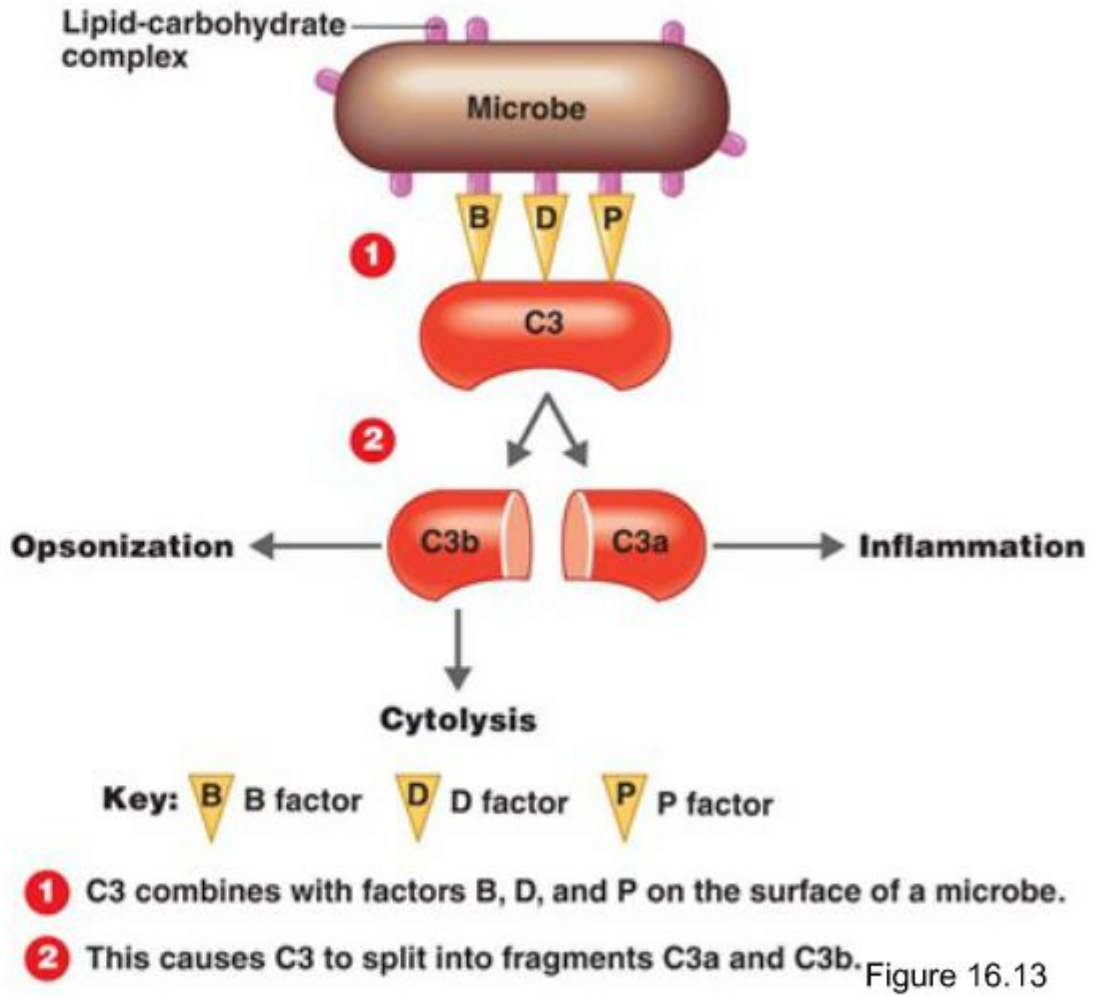


Figure 16.13

Lectin Pathway of Complement Activation

- Macrophages do phagocytosis , release cytokines.
- Cytokines stimulate the liver to produce lectin, which bind to carbohydrates on cell walls of bacteria and on some viruses.

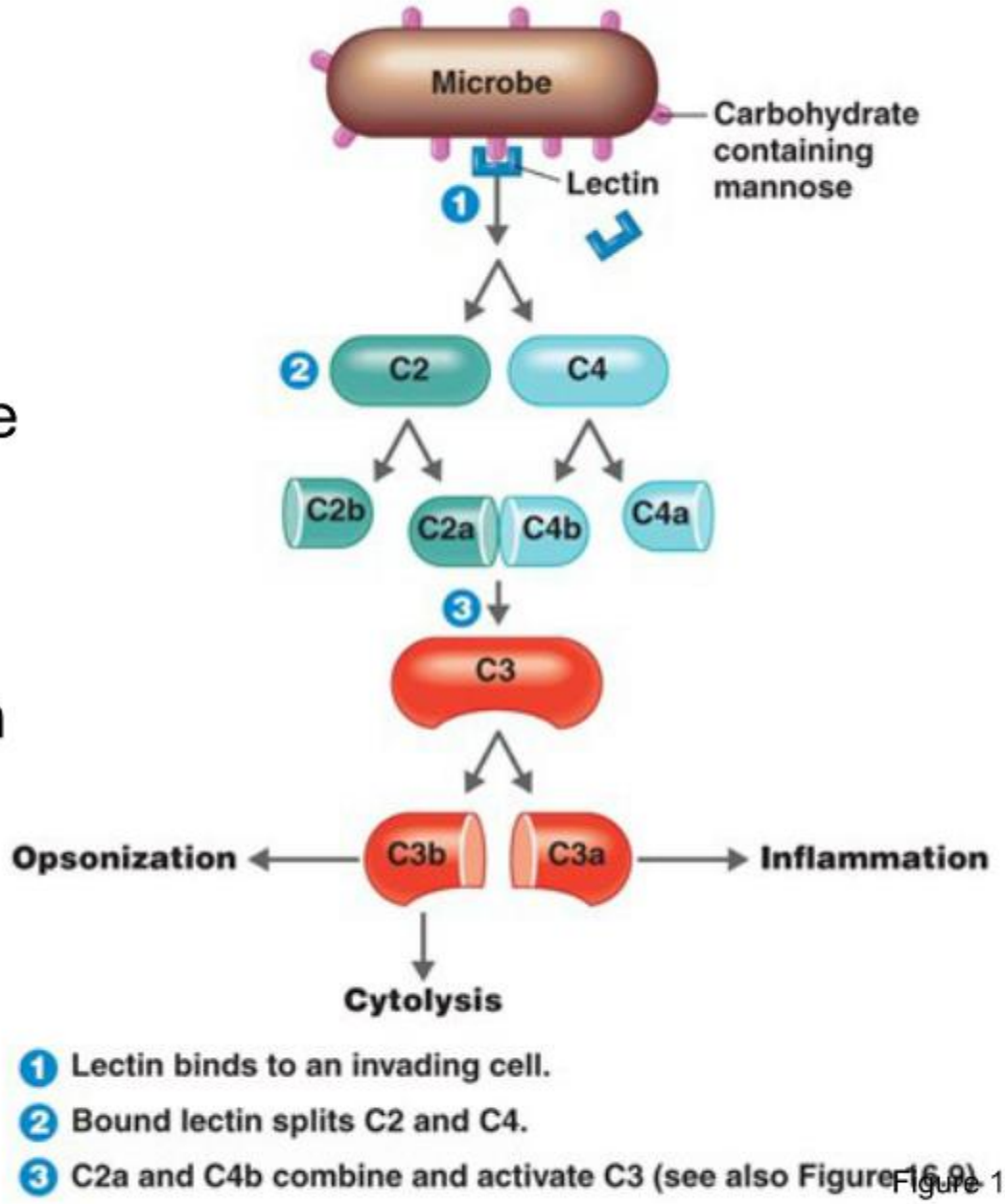


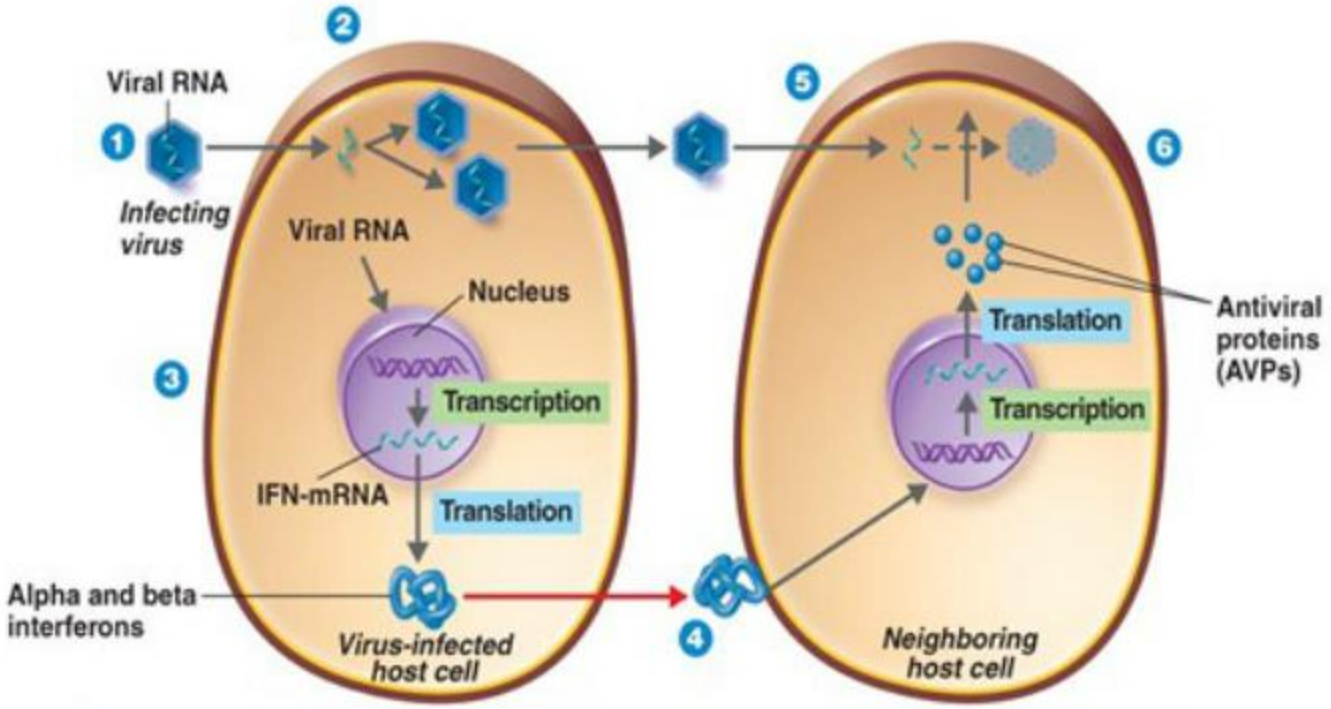
Figure 16.14

Antimicrobial Substances(Contd)

Interferons (IFNs)

- IFN-α and IFN-β: Cause cells to produce antiviral proteins that inhibit viral replication
- Gamma IFN: Causes neutrophils and macrophages to phagocytize bacteria

Antiviral Actions of Interferons (IFNs)



1. Viral RNA from an infecting virus enters the cell.
2. The infecting virus replicates into new viruses.
3. The infecting virus also induces the host cell to produce interferon mRNA (IFN-mRNA), which is translated into alpha and beta interferons.
4. Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase and protein kinase.
5. New viruses released by the virus-infected host cell infect neighboring host cells.
6. AVPs degrade viral mRNA and inhibit protein synthesis—and thus interfere with viral replication.

Figure 16.15

Antimicrobial Substances(Contd)

- **Iron –Binding Proteins**
  - **Ex: Transferrins**
  - Bind serum iron
- **Antimicrobial peptides**
  - Broad spectrum
  - Lyse bacterial cells

  Ex: Dermcidin

  Defensins
  - Shows synergy
  - Stable over wide range of pH
  - Sequester LPS
  - Attract dendritic cells, initiate adaptive immunity.

A Summary of Some Nonspecific Components of the First and Second Lines of Defense

Table 15.5 A Summary of Some Nonspecific Components of the First and Second Lines of Defense

First Line			Second Line				
Barriers and Associated Chemicals	Phagocytes	Extracellular Killing	Complement	Interferons	Defensins	Inflammation	Fever
Skin and mucous membranes prevent the entrance of pathogens; chemicals (*e.g.*, sweat, acid, lysozyme, mucus) enhance the protection	Macrophages, neutrophils, and eosinophils ingest and destroy pathogens	Eosinophils and NK lymphocytes kill pathogens without phagocytizing them	Components attract phagocytes, stimulate inflammation, and attack a pathogen's cytoplasmic membrane	Increase resistance of cells to viral infection, slow the spread of disease	Interfere with membranes, internal signaling, metabolism, and heat shock protein	Increases blood flow, capillary permeability, and migration of leukocytes into infected area; walls off infected region; increases local temperature	Mobilizes defenses, accelerates repairs, inhibits pathogens

The immune system

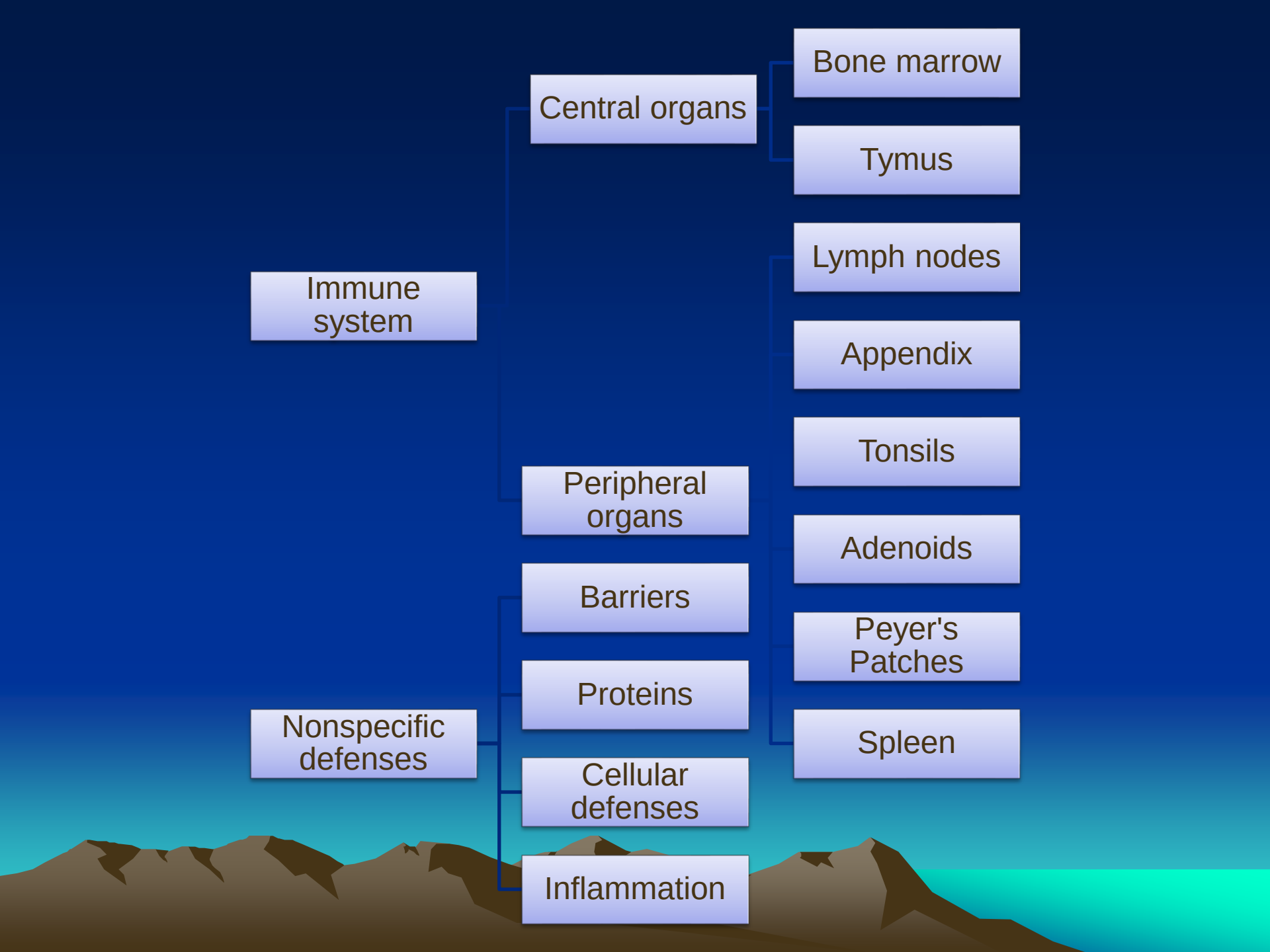
The immune system is:

Defense body mechanism

an interacting set of specialized cells and

proteins designed to identify and destroy

foreign invader


Immune system
Central organs
Bone marrow
Tymus
Peripheral organs
Lymph nodes
Appendix
Tonsils
Adenoids
Peyer's Patches
Spleen
Nonspecific defenses
Barriers
Proteins
Cellular defenses
Inflammation

The immune system

The immune system must be able to:
differentiate between material that is a normal component of the body (“self”) and material that is not native to the body “nonself”

A highly specialized receptors present for discriminating between ”self” and “nonself” body components

The immune system

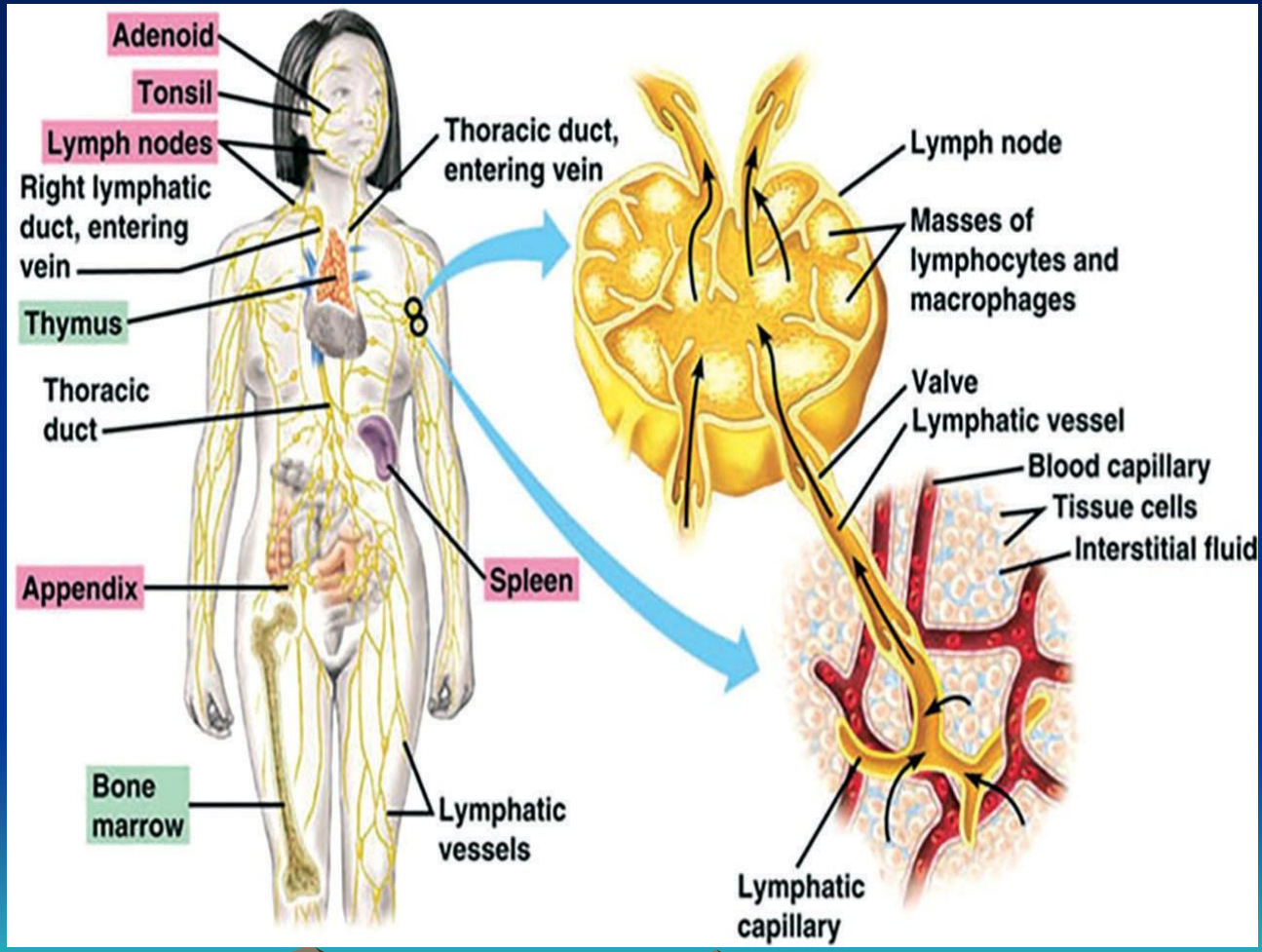
*The discrimination between “self” and “non-self” and the subsequent destruction and removal of foreign material is accomplished by the two arms of the immune system

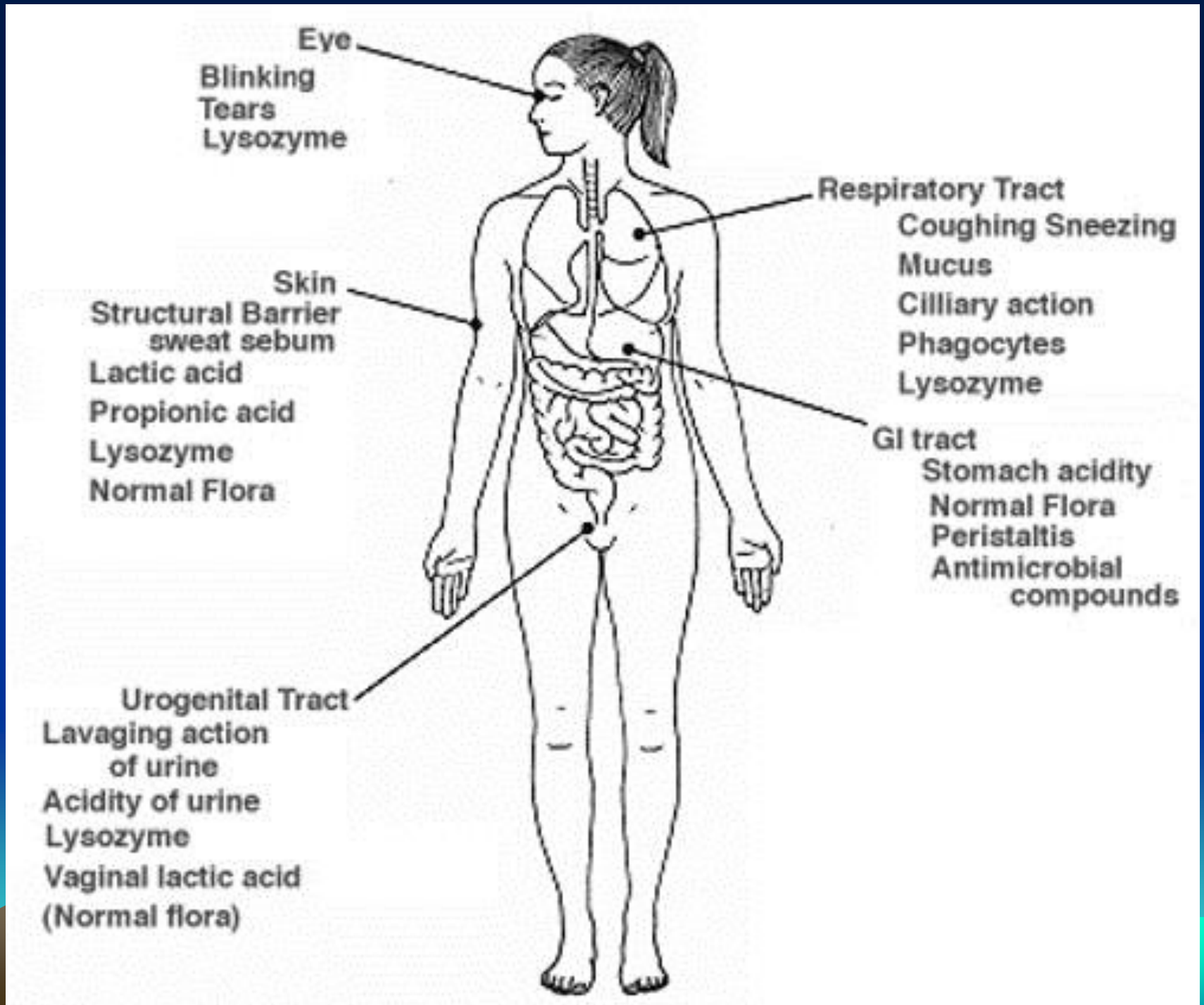
1) The innate (natural or nonspecific) immune system

2) The adaptive (acquired or specific) immune system

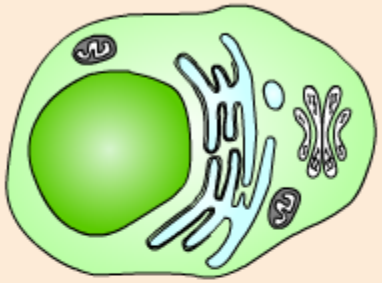
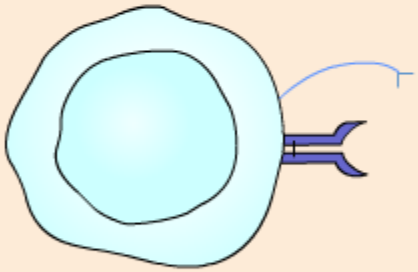
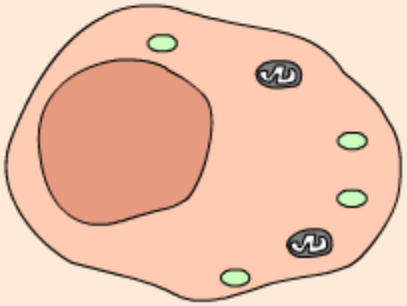
*These two systems perform many of their functions by cooperative interactions

The immune system



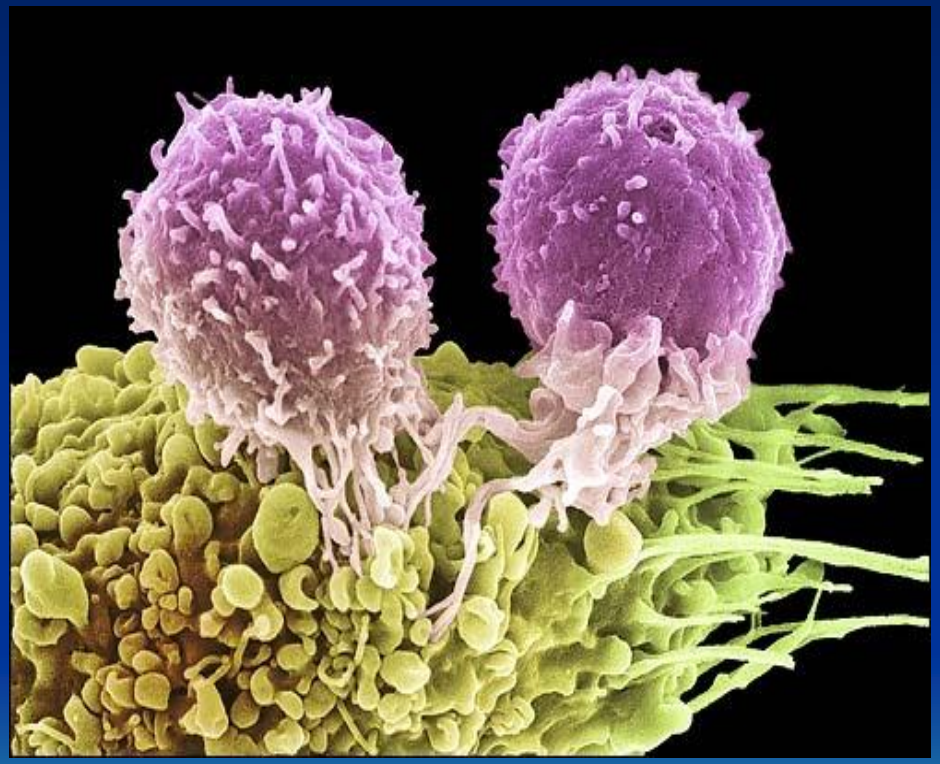

Eye
Blinking
Tears
Lysozyme
Respiratory Tract
Coughing Sneezing
Mucus
Cilliary action
Phagocytes
Lysozyme
Skin
Structural Barrier
sweat sebum
Lactic acid
Propionic acid
Lysozyme
Normal Flora
GI tract
Stomach acidity
Normal Flora
Peristaltis
Antimicrobial
compounds
Urogenital Tract
Lavaging action
of urine
Acidity of urine
Lysozyme
Vaginal lactic acid
(Normal flora)

CELLS AND ORGANS OF IMMUNE SYSTEM

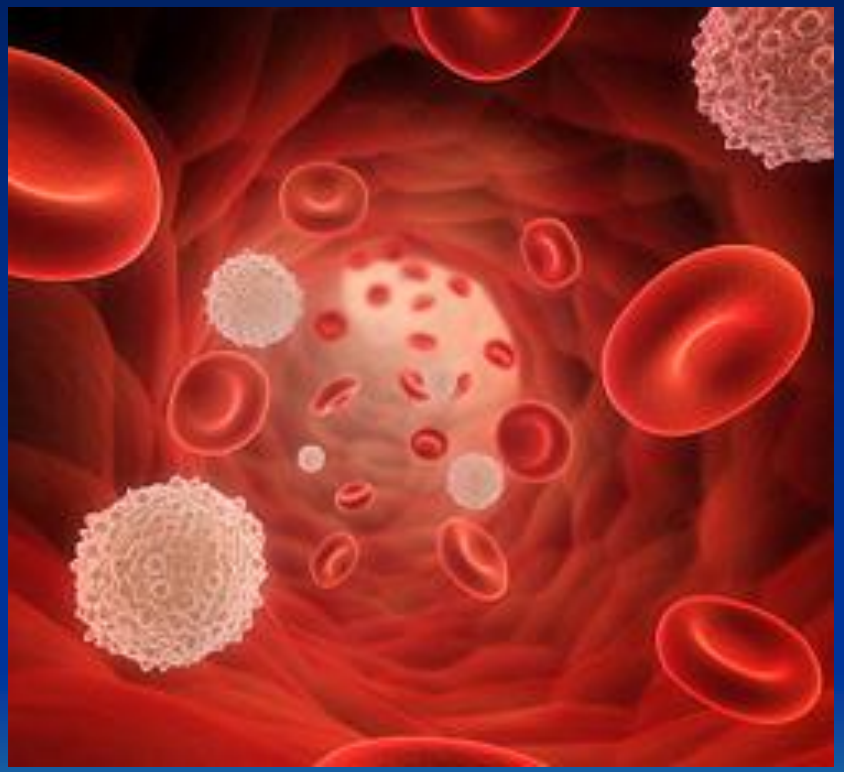
Cell Type	Precursor (factors)	Activity (cells/μL)
B cell 	Lymphoid stem cell (IL-7, IL-3); B progenitor (IL-4,IL-2, IL-5, IL-6).	Plasma cell: secretes antibodies. Memory cell: immunity. (Total lymphocytes: 2750 cells/μL or 20-40% of WBC.)
T cell 	Lymphoid stem cell; B progenitor (IL-4); Thymocyte (IL-7, IL-2, IL-4).	T helper cell (CD4+): secrete cytokines. Cytotoxic T lymphocyte (CD8+):Eliminate altered self-cells. Memory cell: long-term immunity.
Null cell 	Lymphoid stem?	Natural Killer (NK) cell: anti-tumor and anti-viral cytotoxic activity. (5-10% of lymphocytes in blood.)

Lymphocytes
Monocytes
Granulocytes
Organs

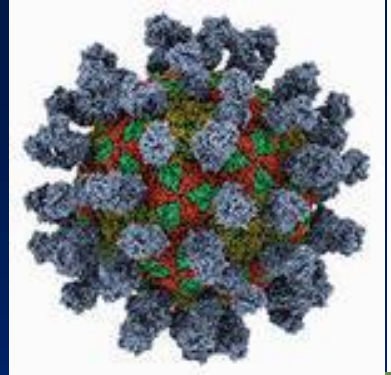
T -cells

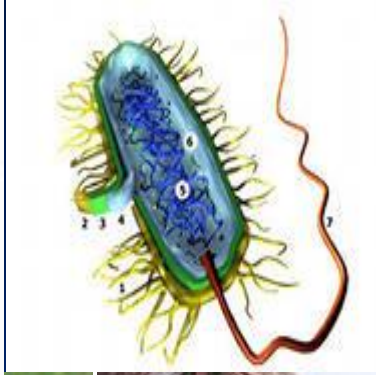


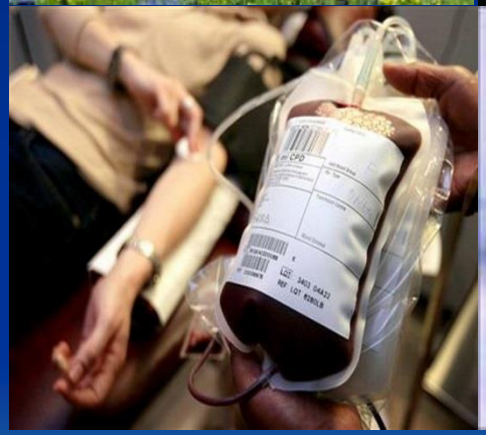
B -cells



Antigens







What happens upon antigen exposure?

Exposure to Antigen (Naturally-acquired or artificial)

Virgin lymphocyte pool

B lymphocytes
T lymphocytes

PRIMARY RESPONSE

effector cells

memory cell pool

SECONDARY RESPONSE

effector cells

memory cell pool

Activated T lymphocytes
Plasma cells

Regulatory
Cytotoxic

Antibodies

Antigens

* A foreign substance, when introduced into human body, stimulate formation of specific antibodies or sensitized lymphocytes

* Antigens have the ability to combine specifically with antibodies produced or sensitized T-lymphocytes induced

Antigens

Haptens:

- Low molecular weight substances

- These substances not immunogenic by itself

- If couple to a larger carrier molecule (albumin, globulins), they become immunogenic

- Examples :

simple chemicals and drugs:

penicillin, sulphonamid, aspirin, cosmetic, tranquillizers, neomycin skin ointment

Types of Antigens

Exogenous Antigens

1- Bacterial antigens:

a- Antigens related to bacterial cells
- Somatic antigen (O): part of cell wall gm –ve bacter.
- Capsular antigen: usually polysaccharide
- Flagellar Ag (H) : a protein made of flagellin
- Fimbrial Ag: surface antigens in fimbriated bacilli

b- Antigen secreted by bacteria:
- Exotoxins
- Enzymes

2- Viral antigens:
a- protein coat viral antigens
b- Soluble antigens (soluble nucleoproteins as in influenza)

Types Of Antigens

Endogenous antigens

Human tissue antigens:

a- Blood group antigens:
A, B and Rh antigens

b- Histocompatibility antigens:
Glycoprotein molecules on all nucleotide cells:
- Major histocompatibility complex antigens (MHC)
- Human leucocyte antigen (HLA)

Major Histocompatibility Complex Antigens (MHC)

* MHC has an important function in presentation of antigens to T-cells

* Helper T-cells recognize foreign antigens on surface of APCs, only when these antigens are presented in the groove of MHC II molecule

* Cytotoxic T-cells will only recognize antigens, on the surfaces of virus infected cells or tumor cells only when these antigens are presented in the groove of Class I molecule (MHC restriction)

Superantigens (SAgs)

* They activate multiple clones of T-lymphocytes

* Bacterial toxins:

  Staph. aureus toxic shock syndrome toxin (TSST) and enterotoxins

  Strpt. pyogenes pyrogenic toxin A

* They have the ability to bind both class II MHC molecules and TCR β chain

* They act as a clamp between the two, providing a signal for T-cell activation

Superantigens (SAgs)

* They are active at very low concentration causing release of large amounts of cytokines

* The massive T-cell activation and release of large amounts of cytokines cause systemic toxicity

* This method of stimulation is not specific for the pathogen

* It does not lead to acquired immunity i.e no memory

Antigen Binding And Recognition Molecules

Antigens are recognized by and bind to:

1) B-cell receptors (BCR) :

- These are membrane-bound immunoglobulins (IgM and IgD) on B-cells
- BCRs can be secreted in plasma as antibodies

2) T-cell receptors (TCR)

- α and β chains anchored to T-cells
- There is a groove which binds small peptides presented by MHC on surface of APCs

3) MHC molecules

They are essential for presentation of peptides so that they can be recognized and bind to TCRs

Factors influencing Immunogenicty

1-Foreigness :

Foreign substances are immunogenic

2- Molecular size:

High molecular weight increase immunogenicty

3- Chemical structure complexity:

High complexity increase immunogenicty

4- Route of administration:

Parenteral routes are more immunogenic to oral route

Factors influencing Immunogenicty

5- Method of administration:

a- Antigen dose:

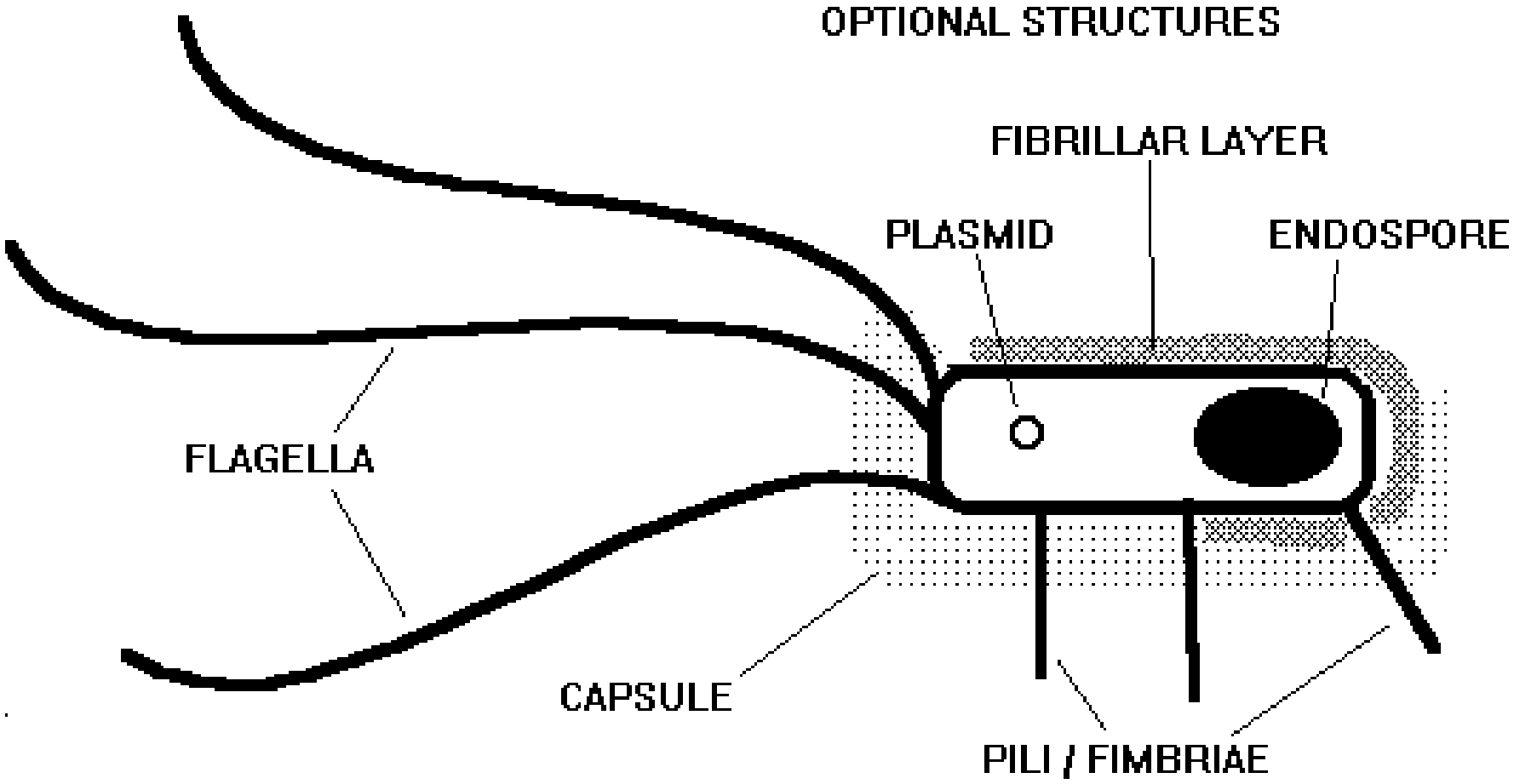
Appropriate dose → optimum antigenicty

Low dose → low- zone tolerance

High dose → high-zone tolerance

b- Adjuvant:

Substance when injected with an antigen enhance immunogenicty


OPTIONAL STRUCTURES
FIBRILLAR LAYER
PLASMID
ENDOSPORE
FLAGELLA
CAPSULE
PILI / FIMBRIAE

Bacterial antigens

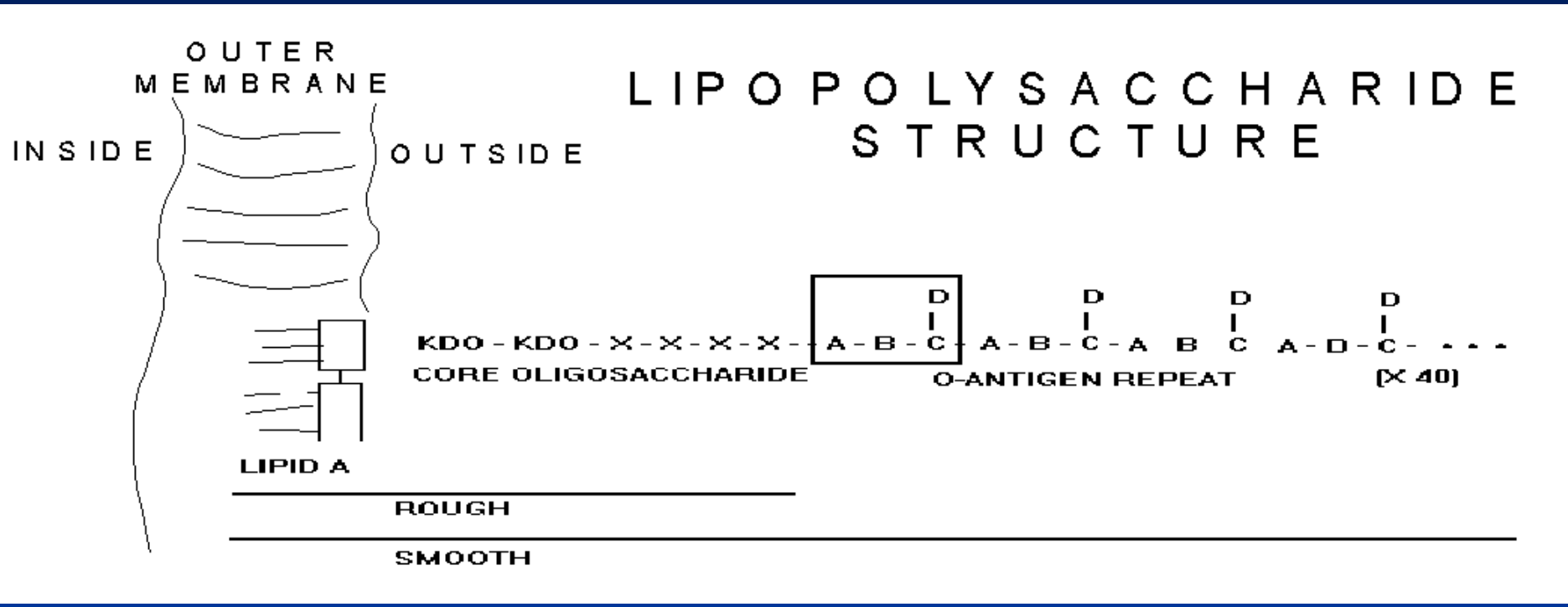
- **O antigen**

  may be present or not, depending on species

  r**epeating units** of 3 to 5 sugars

  smooth with O antigen
  rough without (ending at core)
  LPS of bacteria without O antigen
  sometimes called lipooligosaccharide (LOS)

  antigenic and highly **variable** among species and strains


OUTER MEMBRANE
INSIDE
OUTSIDE
LIPOPOLYSACCHARIDE STRUCTURE
D
D
D
D
KDO - KDO - X - X - X - X - A - B - C - A - B - C - A B C A - D - C - - - -
CORE OLIGOSACCHARIDE
O-ANTIGEN REPEAT
(X 40)
LIPID A
ROUGH
SMOOTH

Bacterial antigens

Capsule (slime layer), K antigen

not impermeable

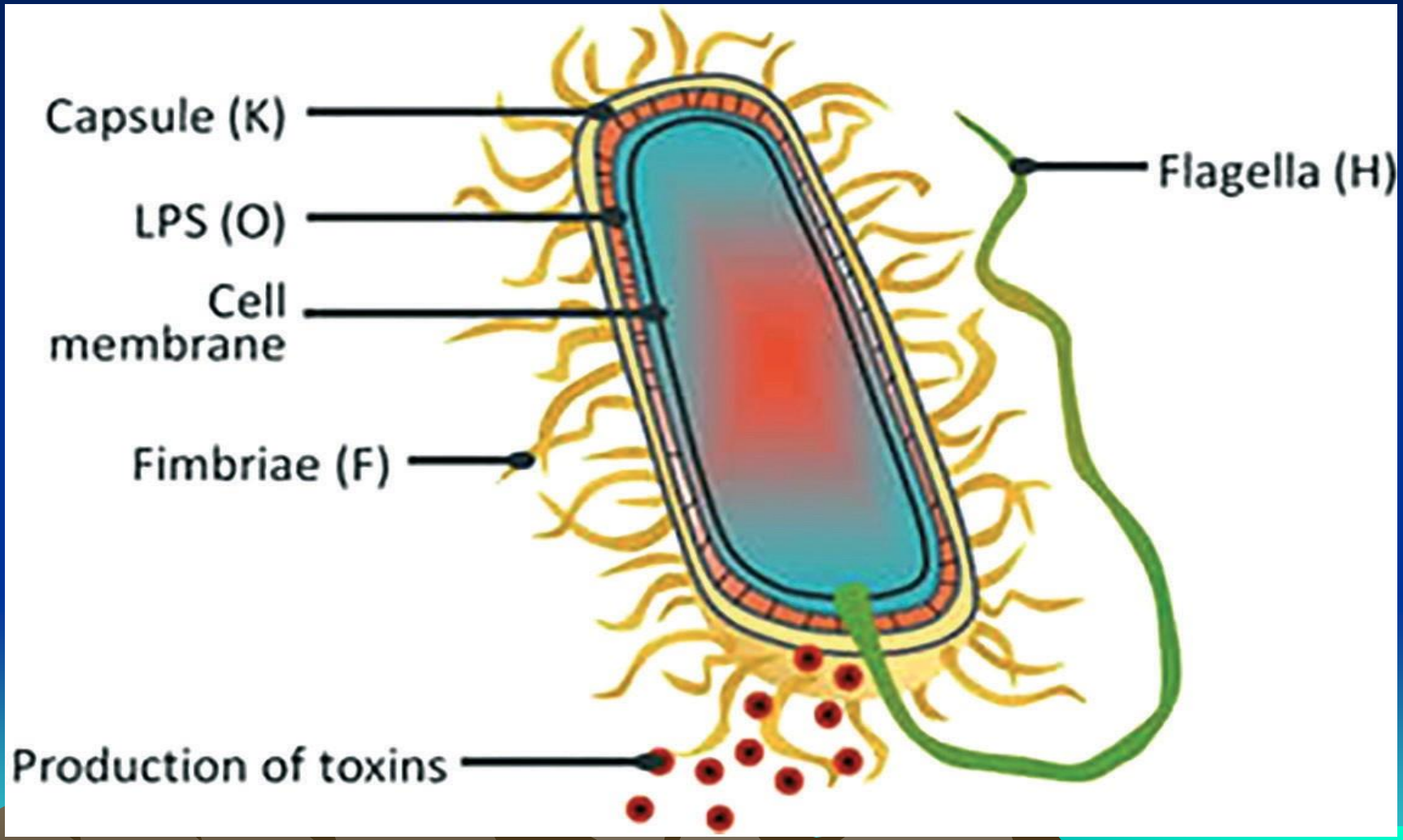
Both gram-positive and gram-negative bacteria can make capsules

polysaccharide

(exception: *Bacillus anthracis* (anthrax) poly-glutamate)

virulence - inhibit complement - phagocytosis

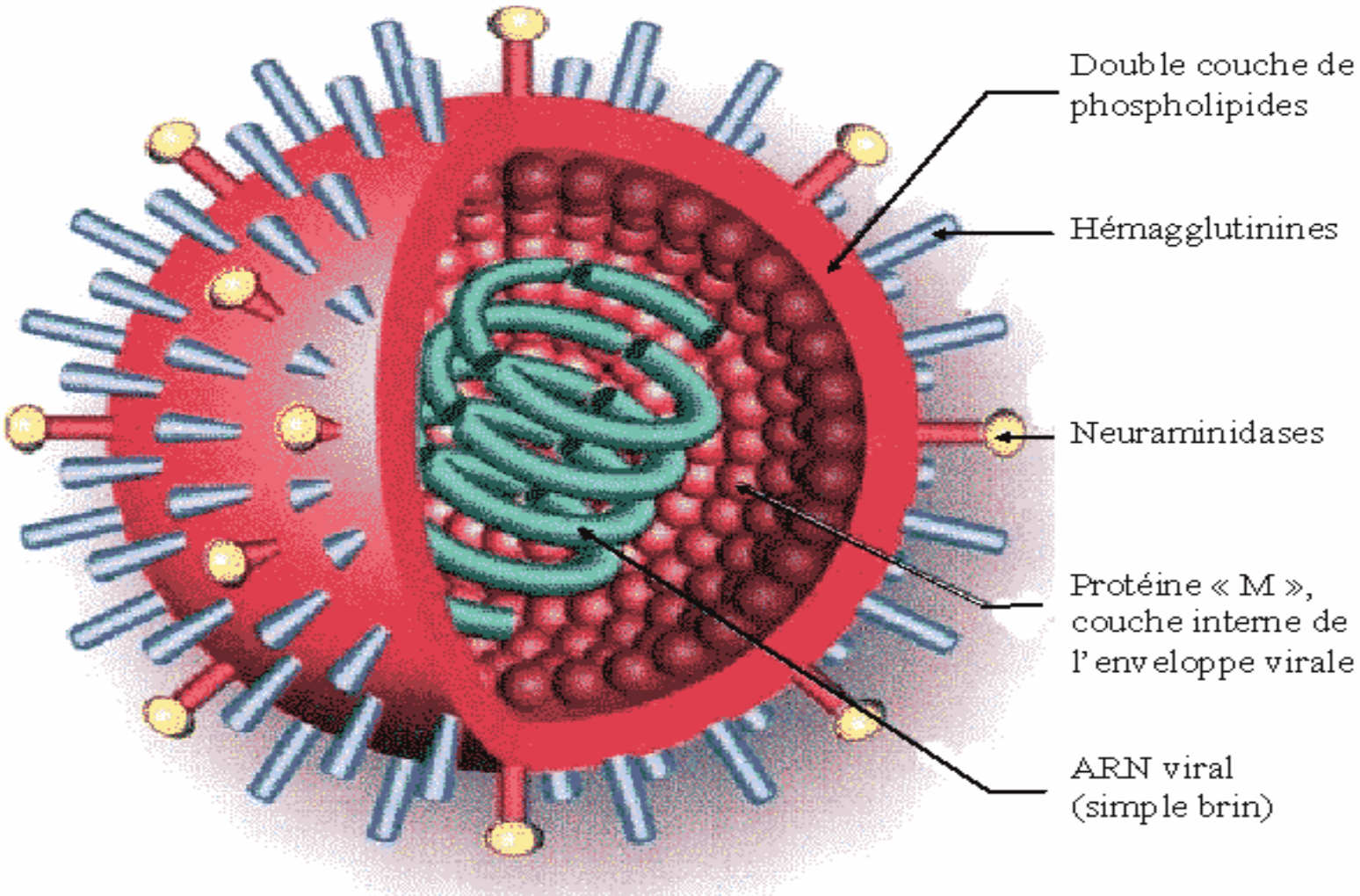
Bacterial antigens



Bacterial antigens

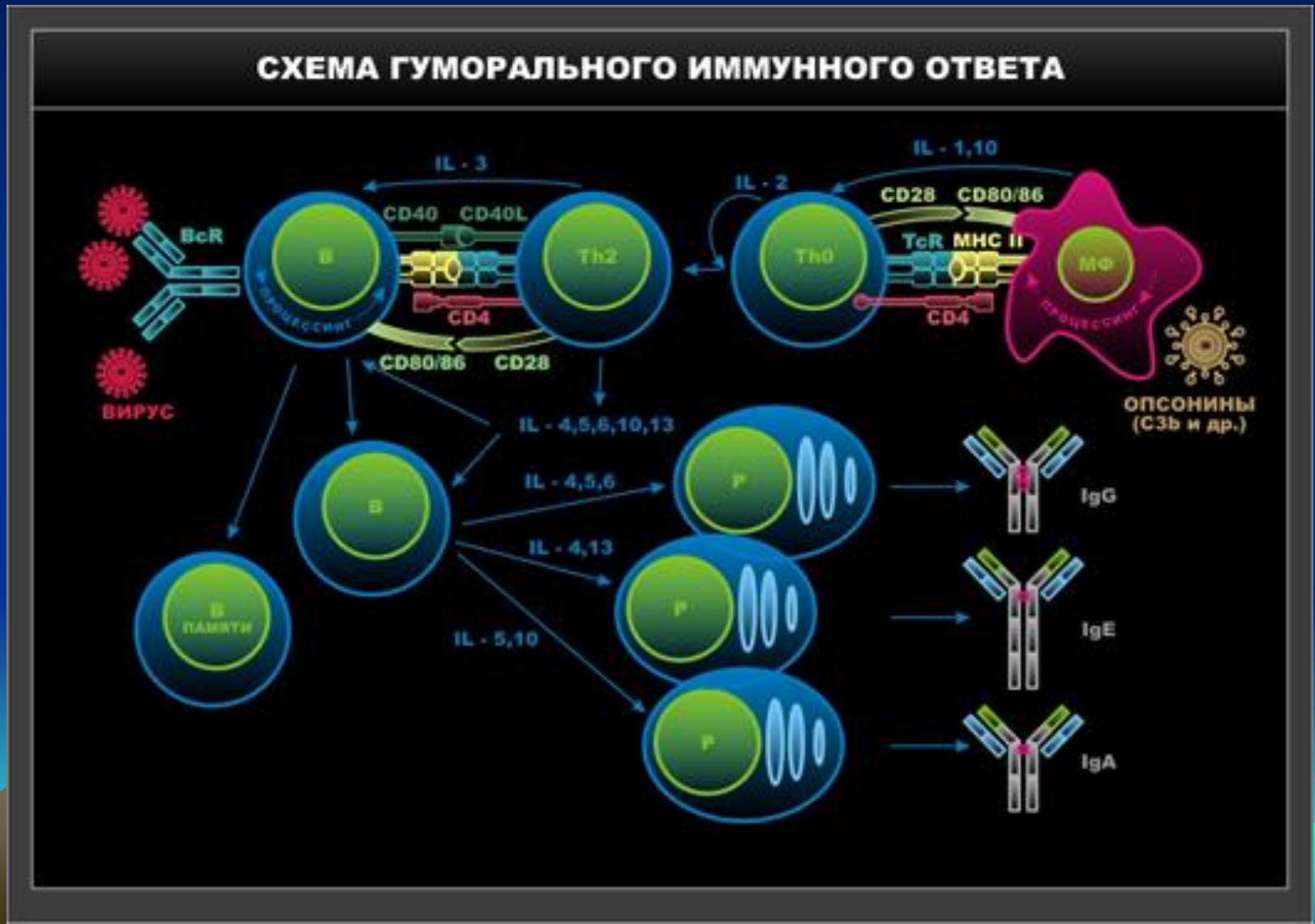
- **Flagella** - H antigen
  - propeller
  - motility and chemotaxis
  - recognized by TLR5

Viral antigens



Structure simplifiée du virus Influenza

Humoral immune responce



T Cells and Cellular Immunity

- Lymphocytes produced in the red bone marrow and mature under the influence of the thymus to become **T cells**
- Circulate in the lymph and blood and migrate to the lymph nodes, spleen, and Peyer's patches
- Part of the cell-mediated immune response because they act directly against various antigens
  - Endogenous invaders
  - Many of the body's cells that harbor intracellular pathogens
  - Abnormal body cells such as cancer cells that produce abnormal cell surface proteins

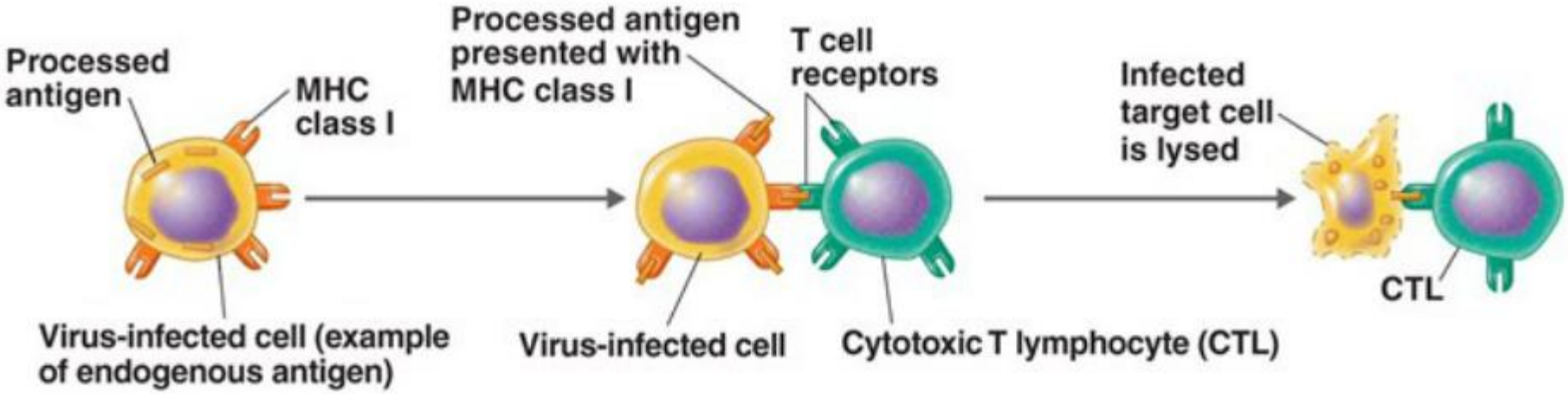
Classes of T cells: Helper T cells

- T cells have receptors specific for an antige
- T cells are also classified by the glycoprotei surcface called cluster of differentiation(CD)
- T helper cells (T_H)($CD4^+$ T cells)
  - When activated TH cells produce cytokines and differentia
  - TH1: $\mathbf{T_H1}$ produces IFN-γ, which activates cells related to mediated immunity, macrophages, and Abs
  - TH2: TH2 activate eosinophils and B cells to produce IgE
  - Memory cells

T Cytotoxic Cells

- **$CD8^+$** or **T_c** cells
- **CD8 cells** gets differentiated to CTL aft
  activation by antigens and interaction wi
- Target cells are self carrying **endogeno**
  antigens
- Activated into **cytotoxic T lymphocytes**
  - Induce **apoptosis** in target cell
- CTL releases **perforin** and **granzymes**

Classes of T cells: T Cytotoxic Cells



1. A normal cell will not trigger a response by a cytotoxic T lymphocyte (CTL), but a virus-infected cell (shown here) or a cancer cell produces abnormal endogenous antigens.
2. The abnormal antigen is presented on the cell surface in association with MHC class I molecules. $CD8^+$ T cells with receptors for the antigen are transformed into CTLs.
3. The CTL induces destruction of the virus-infected cell by apoptosis.

Figure 17.11

Classes of T cells: T Regulatory Cells

- Formerly called T suppressor cells.
- Make up 5-10% of T cells.
- Subset of CD4+ (T helper cells)
- Combat autoimmunity

Chemical Messengers of ImmuneSystem: Cytokines

- **Cytokines** are chemical messengers of immune system.
- Acts only on a cell that has receptor for it.
- They are soluble proteins or glycoproteins produced by cells of the immune system.
- There different types of cytokines and their common name reflect their function.

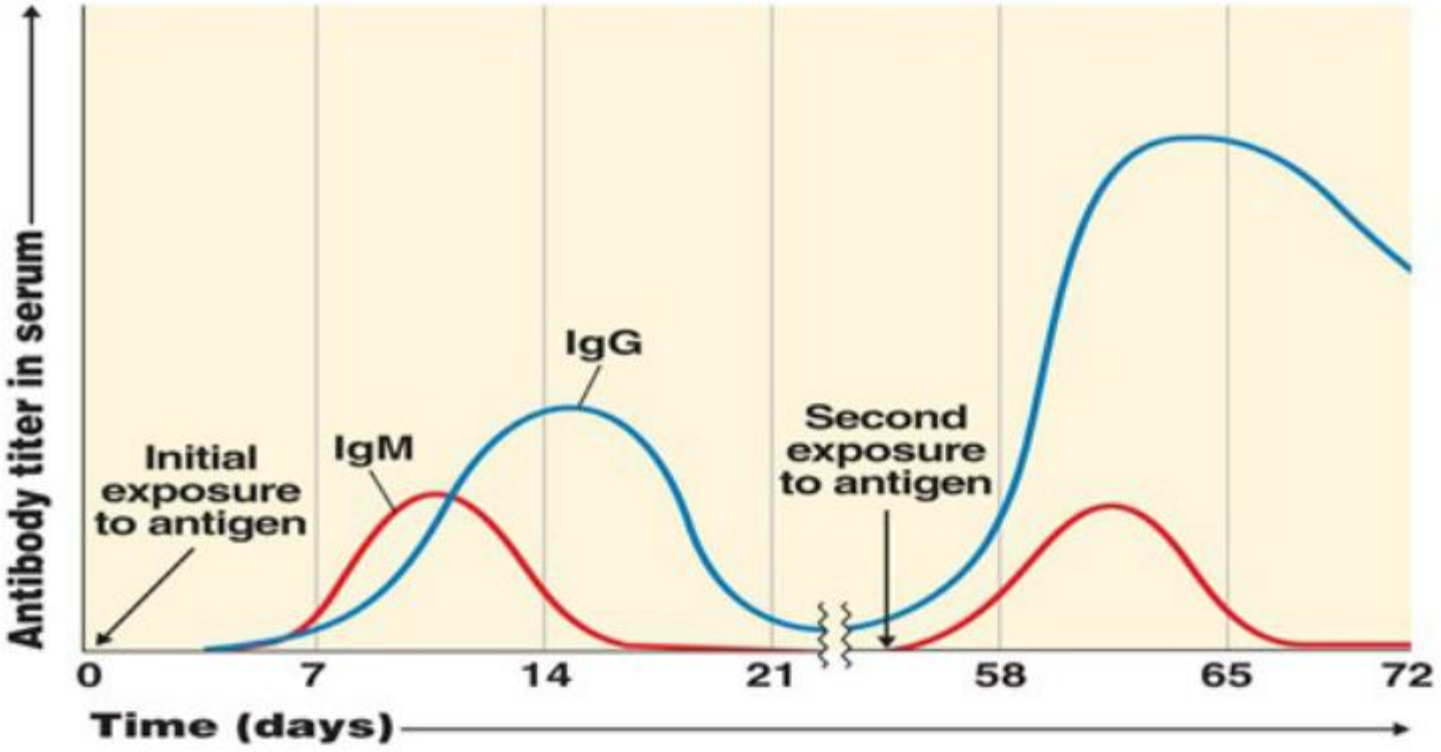
Killer (NK) Cells

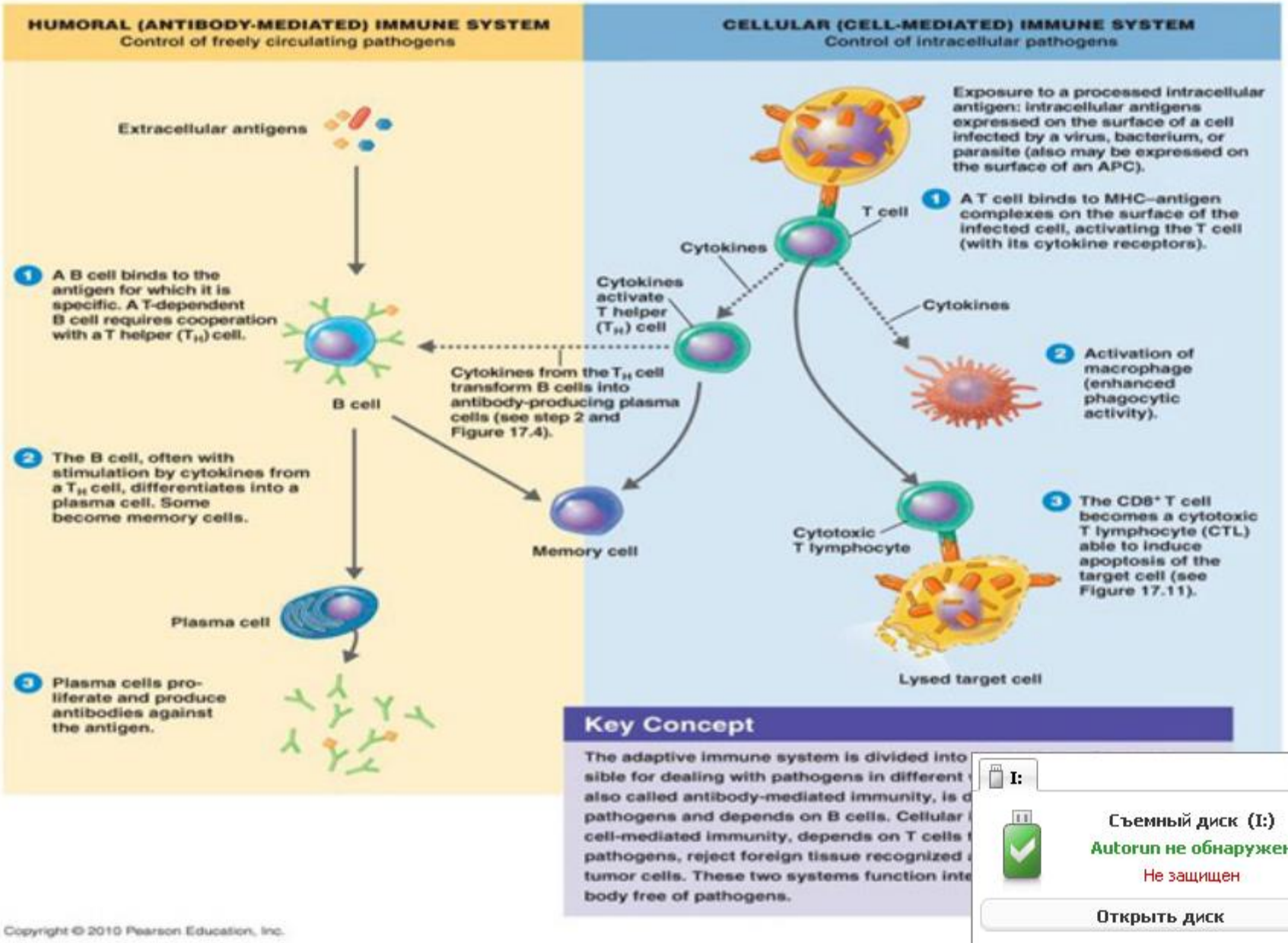
  - **Interleukins** are cytokines that communicate between leukocytes
  - **Interferons** protect cells from viral infection.
  - **Chemokines** induces migration of leukocytes into area of infection.
  - Tumor Necrosis Factor(TNF-∞)

Immunological Memory

The primary and secondary response to an antigen

- Adaptive immunity keeps the memory
- The second exposure to the same antigen stimulates the memory cells , thus the response is rapid and more intense than the first exposure
- A similar response occurs with T cells also.





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Thanks