

Pathogenesis and Host Defense Mechanisms

- Nonspecific Host Defense Mechanisms
- Specific Host Defense Mechanisms: An Introduction to Immunology

What is Pathogenesis?

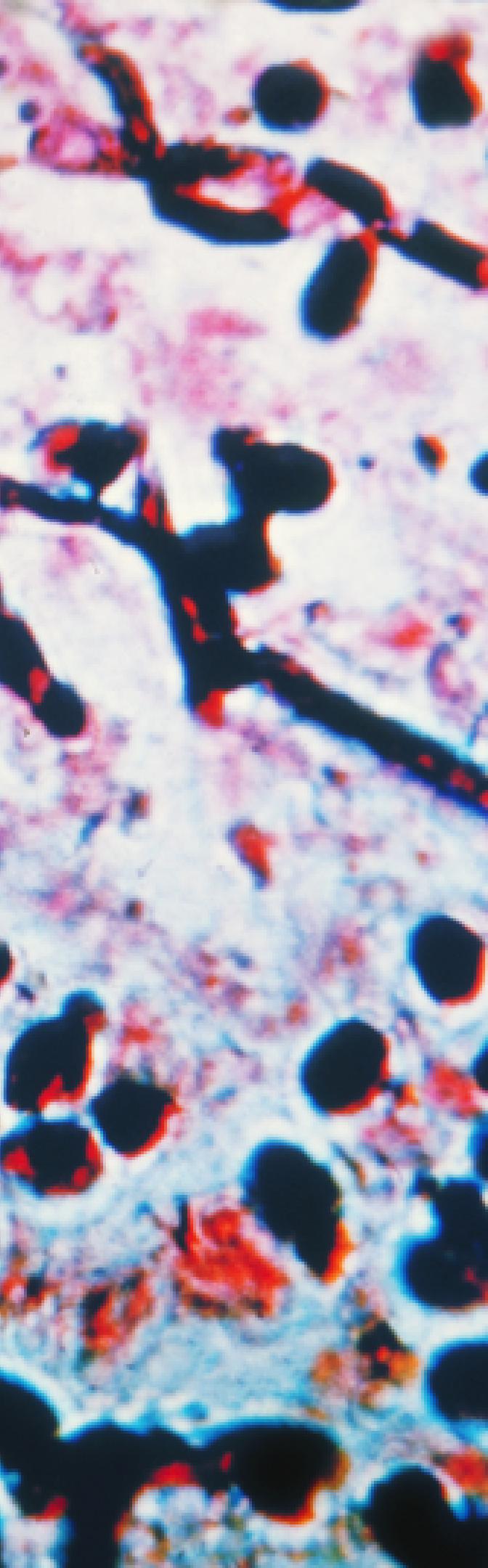
The prefix "path" comes from the greek word "pathos" meaning disease.

Pathogenesis- is the steps or mechanisms involved in the development of a disease. Disease can arise from pathogens that secrete toxins, from dysregulation of the immune system or simply from aging. Far more commonly, pathogenesis occurs as a consequence of complex interactions between an infecting pathogen and the immune system.

What is Host Defense Mechanisms?



Host defense mechanisms ways in which the body protects itself from pathogens can be thought of as an army consisting of three lines of defense. If the enemy (the pathogen) breaks through the first line of defense, it will encounter and, hopefully, be stopped by the second line of defense. If the enemy manages to break through and escape the first two lines of defense, there is a third line of defense ready to attack it

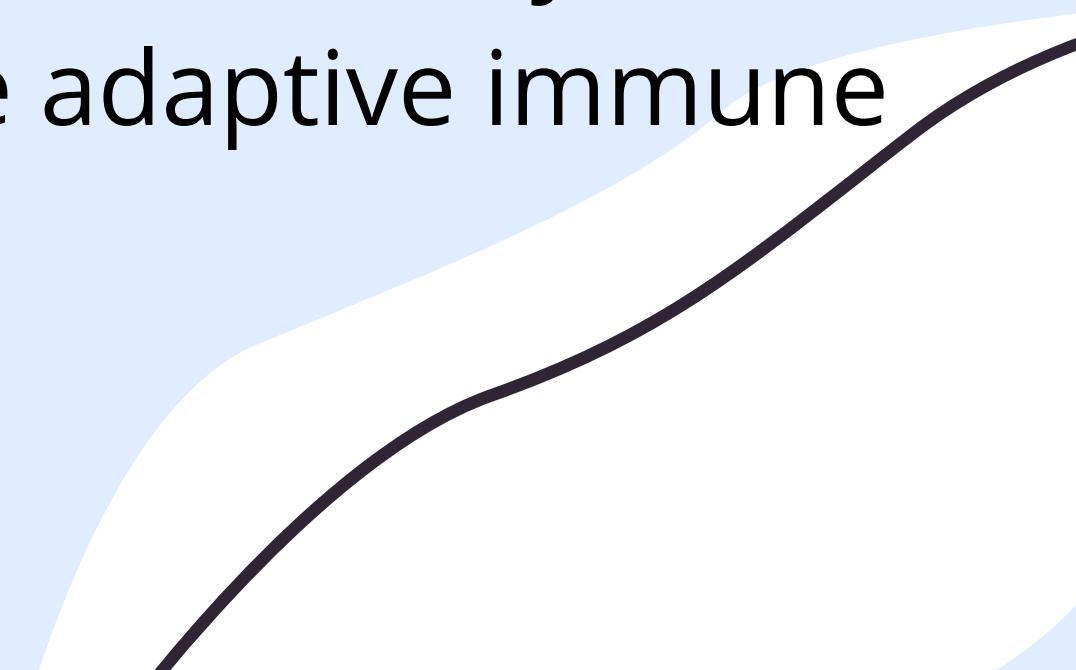
A vertical strip on the left side of the slide showing a microscopic view of various microorganisms, possibly bacteria or fungi, stained in red and blue. They appear as dark, irregular shapes against a lighter background.

Why infection does not always occur

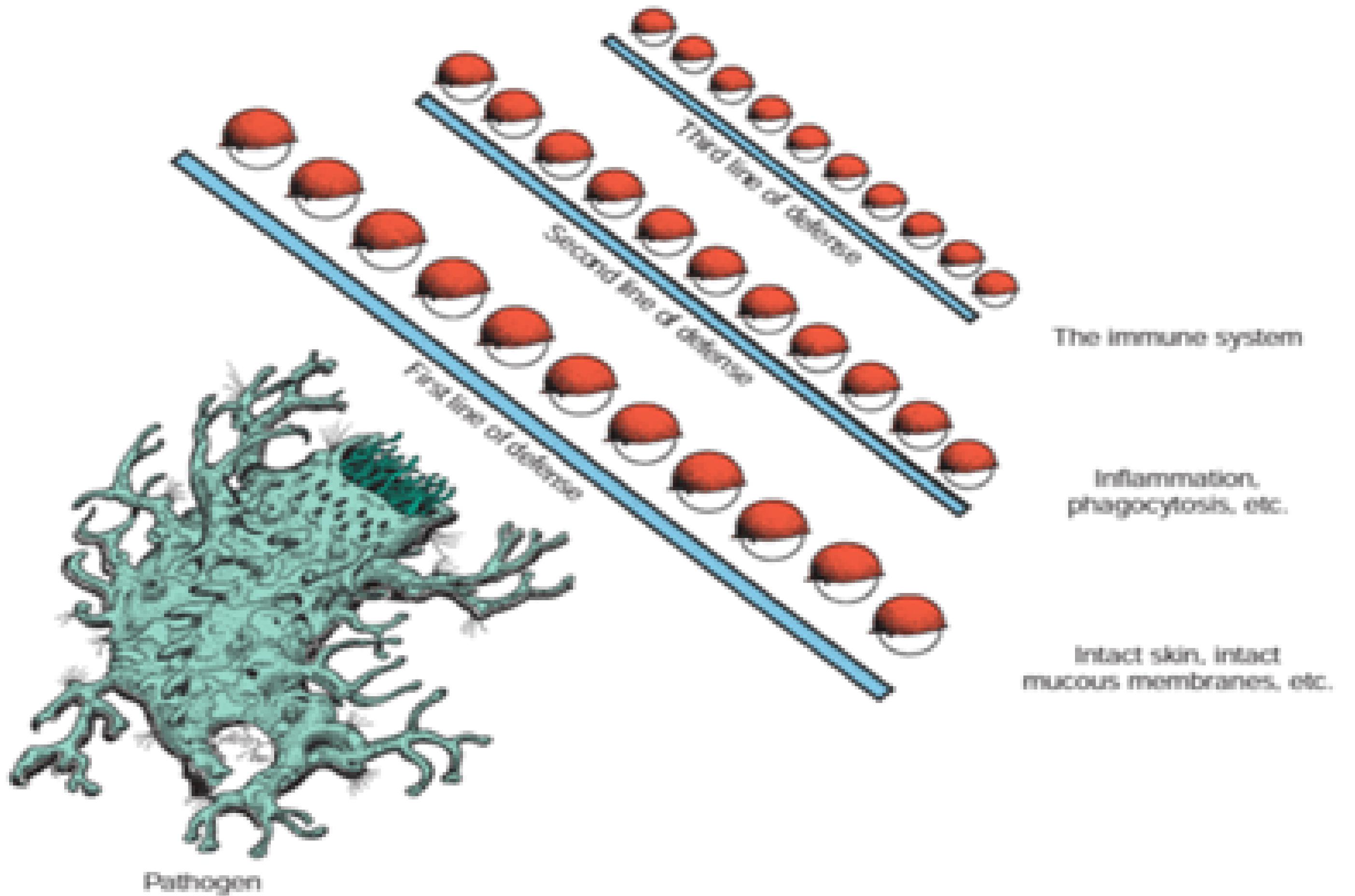
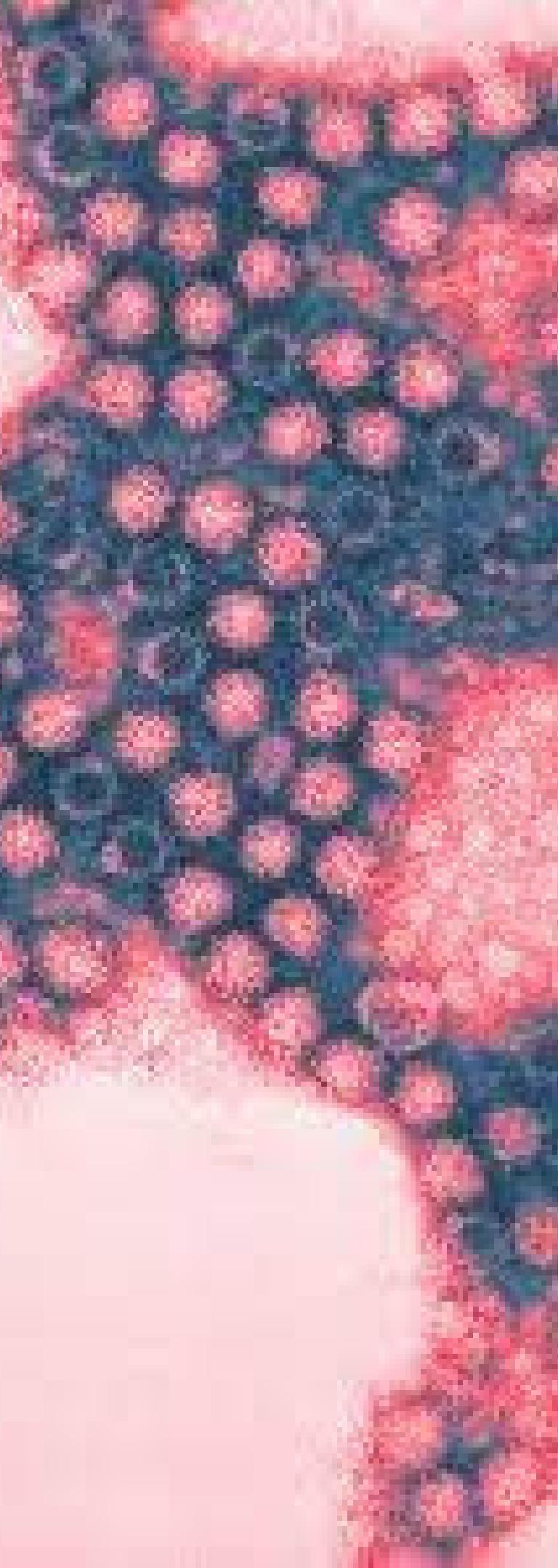
- The microbe may land at an anatomic site where it is unable to multiply.
- Many pathogens must attach to specific receptor sites before they are able to multiply and cause damage.
- The individual's nutritional and overall health status often influences the outcome of the pathogen-host encounter

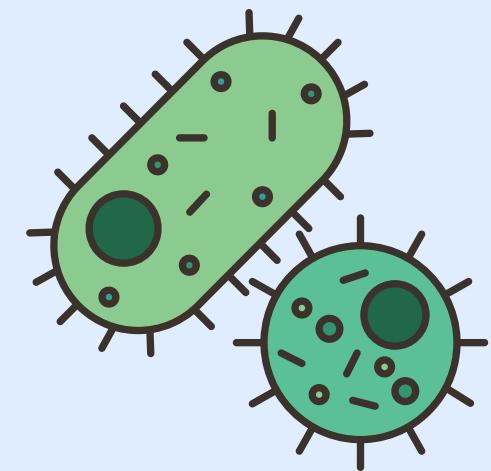
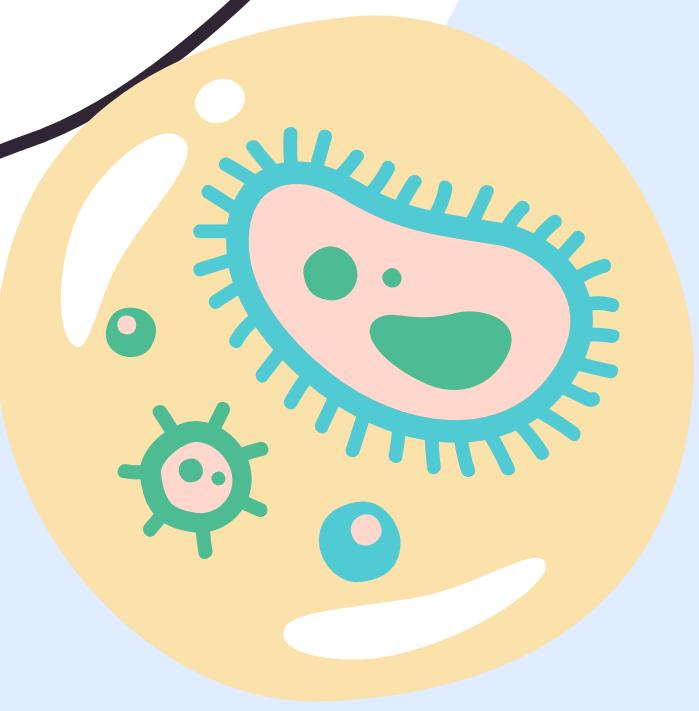


The first two lines of defense are nonspecific these are ways in which the body attempts to destroy all types of substances that are foreign to it, including pathogens. The third line of defense, the immune response, is very specific. In the third line of defense (or specific host defense mechanisms), special proteins called antibodies.



First- and second-line defenses are part of the innate immune system, whereas the third-line defenses are referred to as the adaptive immune system.





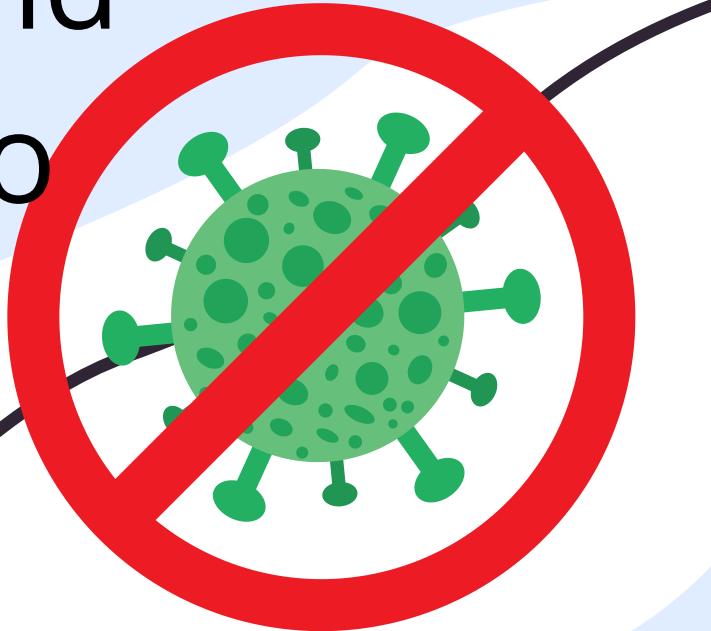
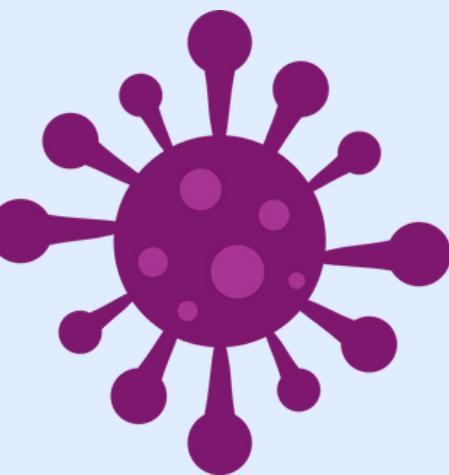
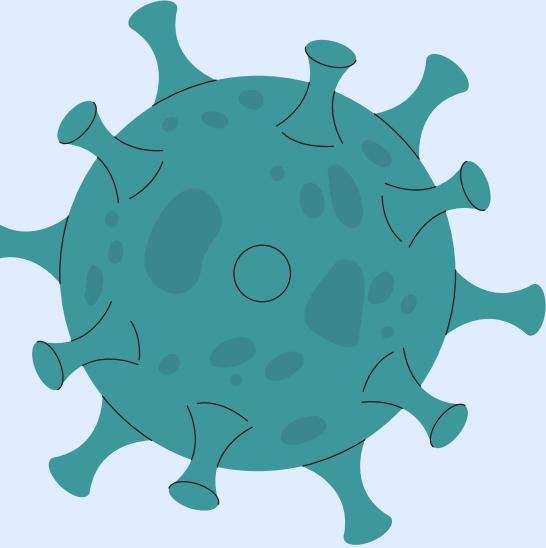
Humans and animals have survived on Earth for hundreds of thousands of years because they have many built-in or naturally occurring mechanisms of defense against pathogens and the infectious diseases that they cause. The ability of any animal to resist these invaders and recover from disease is attributable to many complex interacting functions within the body.



NONSPECIFIC HOST DEFENSE MECHANISMS



Nonspecific host defense mechanisms are general and serve to protect the body against many harmful substances. One of the nonspecific host defenses is the innate, or inborn, resistance observed among some species of animals and some persons who have a natural resistance to certain diseases. Innate or inherited characteristics make these people and animals more resistant to some diseases than to others.



First Line of Defense

Skin and Mucous Membranes as Physical Barriers

The skin and mucous membranes are the body's first line of defense against environmental pathogens. This function results from both physical and chemical factors. The intact, unbroken skin that covers our bodies represents a nonspecific host defense mechanism, in that it serves as a physical or mechanical barrier to pathogens.

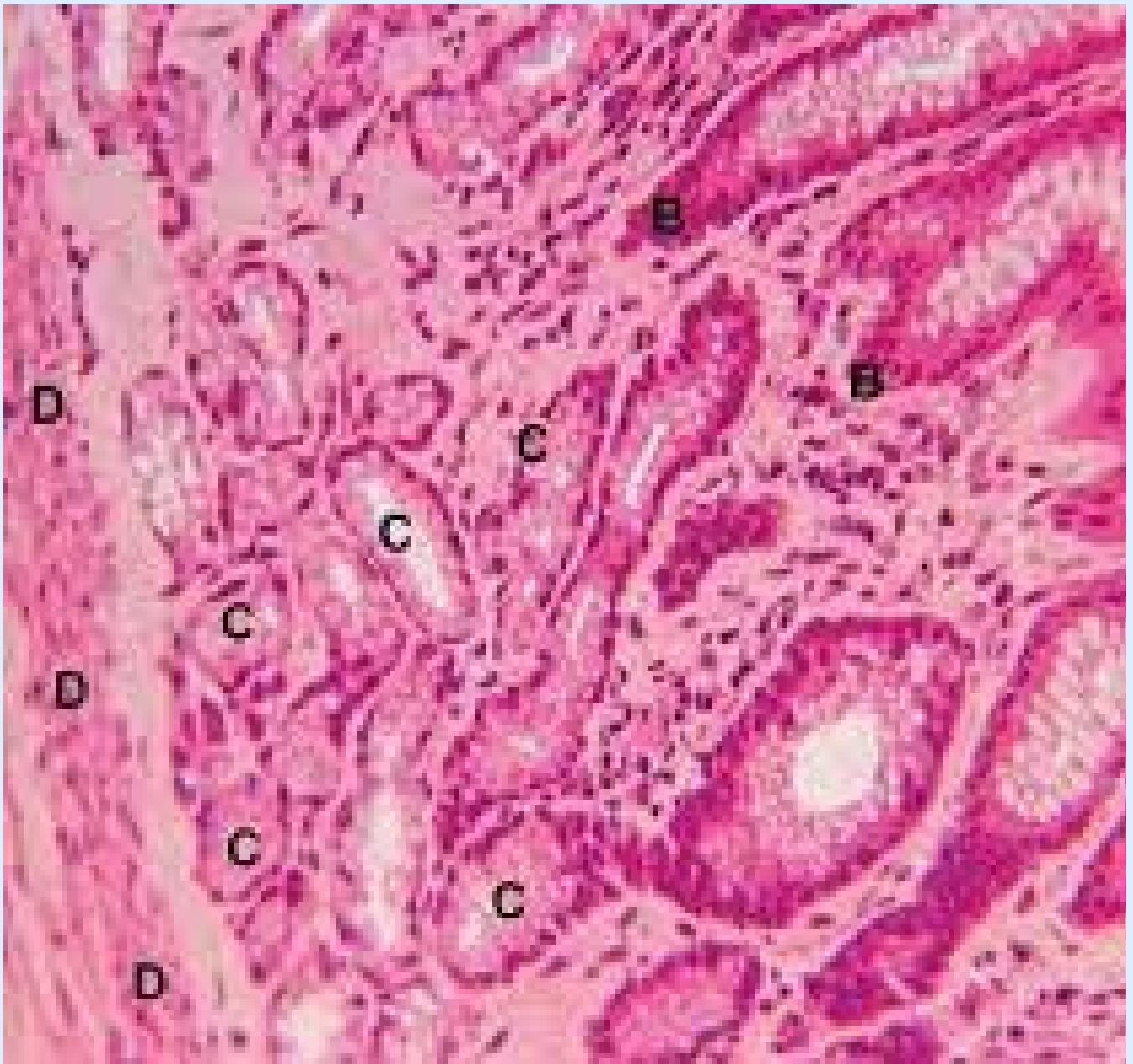
Mucous membranes

Saliva: Washes microbes from teeth and mouth mucous membranes.

Mucus: Thick secretion that traps many microbes.

Urination: Cleanses urethra.

Vaginal Secretions: Remove microbes from genital tract.



Although certain helminth infections are acquired by penetration of the skin by parasites, it is unlikely that many, if any, bacteria are capable of penetrating intact skin.

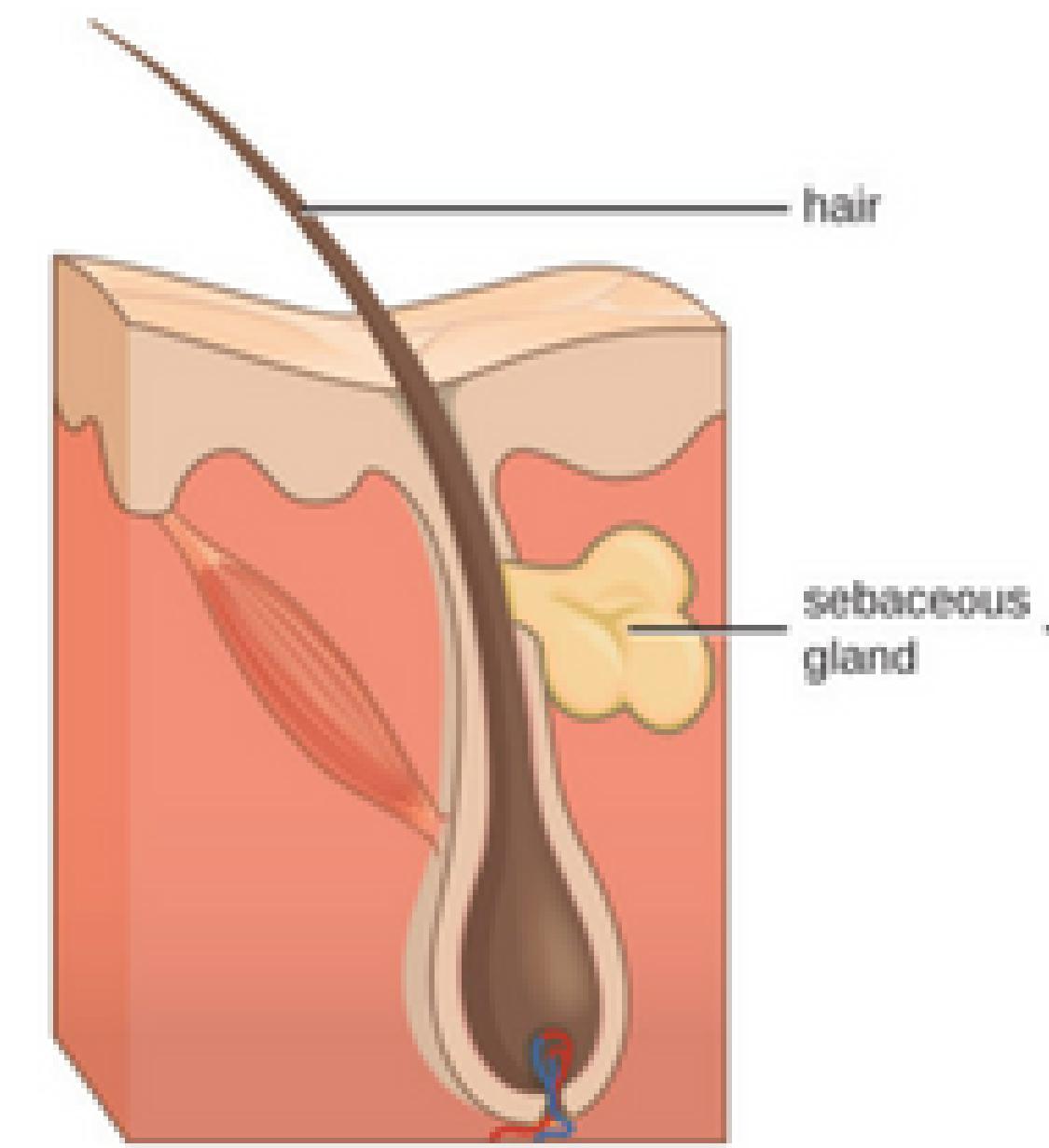


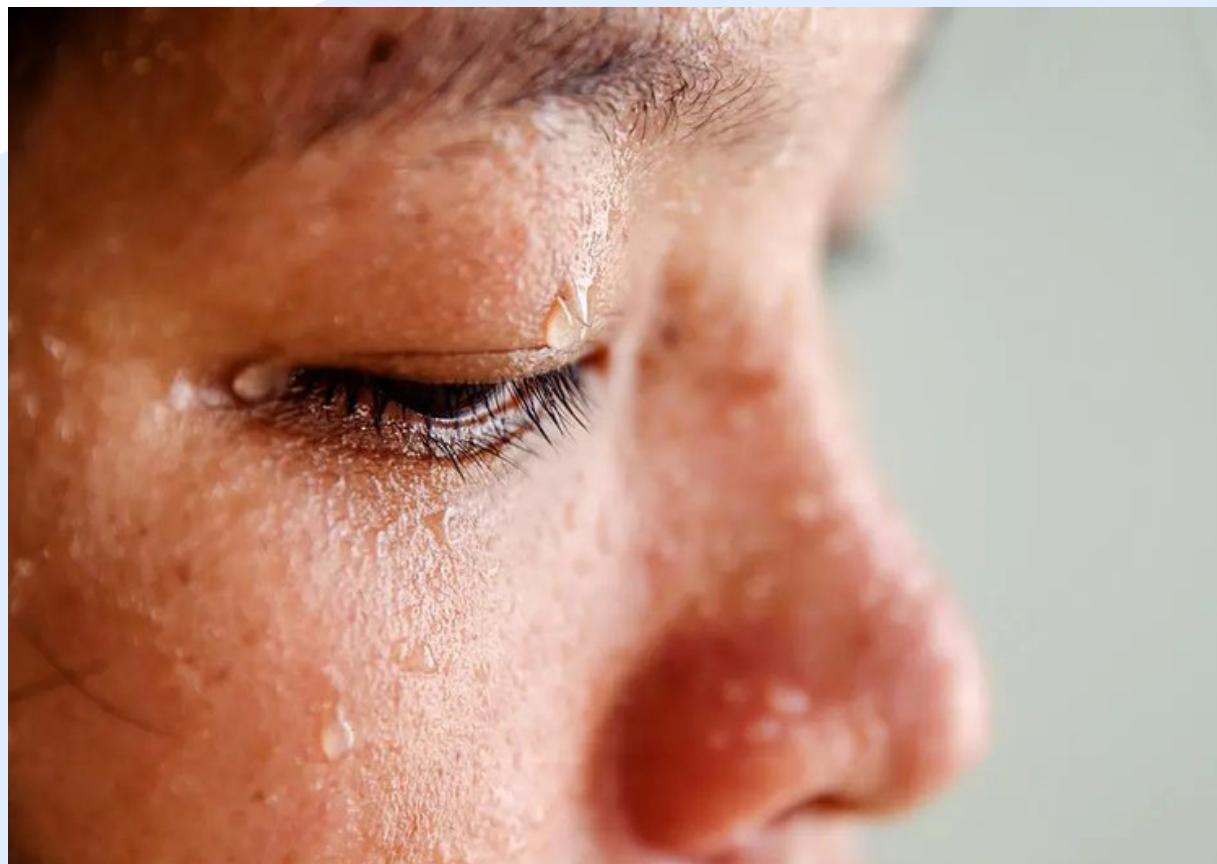
In most cases, it is only when the skin is cut, abraded (scratched), or burned that pathogens gain entrance or when they are injected



Chemical Factors

Not only does skin provide a physical barrier, but there are several additional factors that account for the skin's ability to resist pathogens. The dryness of most areas of skin inhibits colonization by many pathogens. Also, the acidity and temperature of the skin inhibit the growth of pathogens.





Perspiration



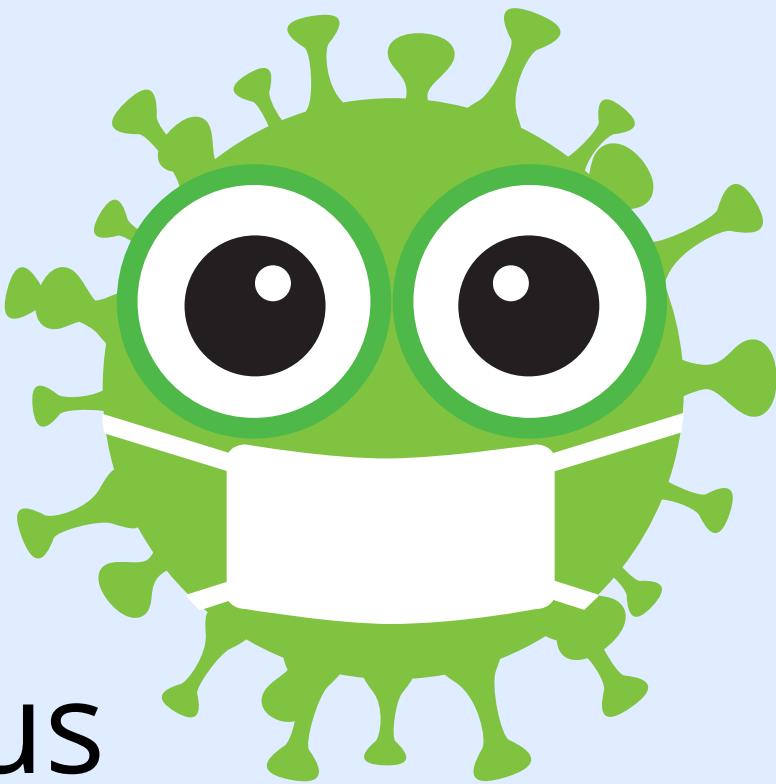
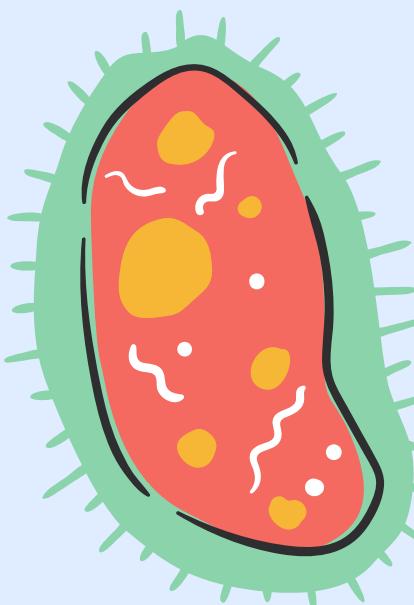
Sloughing off of
dead skin cells



Swallowing

Microbial Antagonism

When resident microbes of the indigenous microflora prevent colonization by new arrivals to a particular anatomical site, it is known as microbial antagonism. This is another example of a nonspecific host defense mechanism.



Second Line Defense

Pathogens able to penetrate the first line of defense are usually destroyed by nonspecific cellular and chemical responses, collectively referred to as the second line of defense. A complex sequence of events develops involving production of fever, production of interferons, activation of the complement system, inflammation, chemotaxis, and phagocytosis.



Transferrin

Transferrin, a glycoprotein synthesized in the liver, has a high affinity for iron. Its normal function is to store and deliver iron to host cells. Transferrin serves as a nonspecific host defense mechanism by sequestering iron

Fever

Normal body temperature fluctuates between 36.2°C and 37.5°C , with an average of about 37°C . A body temperature greater than 37.8°C is generally considered to be a fever. Substances that stimulate the production of fever are called pyrogens or pyrogenic substances.



Second line of defense

Fever

Pyrogens are substances that stimulate fever

External, e.g. bacterial endotoxin

Internal (endogenous), e.g. interleukins (IL-1)

Body temperature increases in response to pyrogens to:

Stimulate WBC to deploy & destroy microbes

increase in immunological response

(e.g. proliferation and activation of lymphocytes)

Slow down growth of or kill pathogens



Interferons

Interferons are small, antiviral proteins produced by virus infected cells. They are called interferons because they “interfere” with viral replication. The three known types of interferon, referred to as alpha, beta, and gamma interferons, are induced by different stimuli, including viruses, tumors, bacteria, and other foreign cells. These are a class of proteins produced by certain animal cells, such as lymphocytes and macrophages.

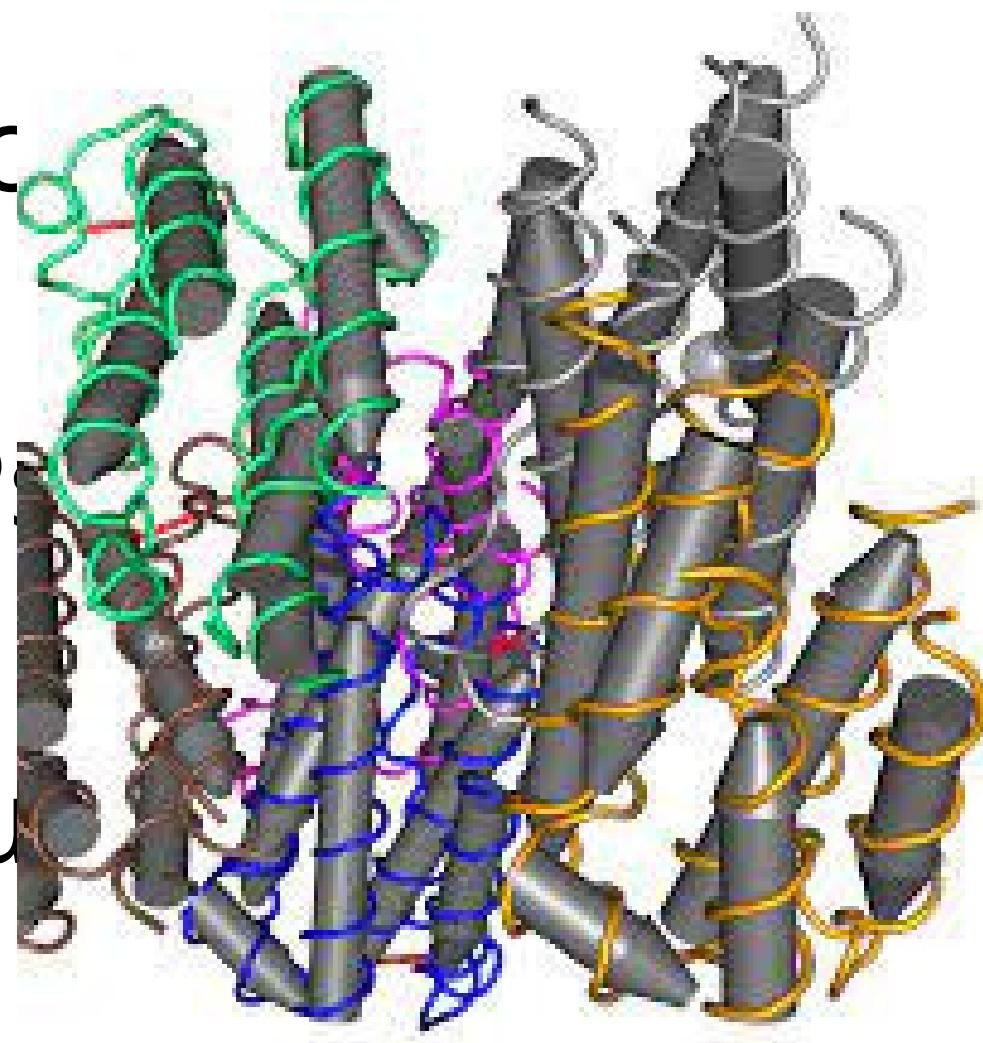
Interferons: Antiviral proteins that interfere with viral multiplication.

Have no effect on infected cells.

Host specific, but not virus specific.

Interferon alpha and beta: Produced by virus infected cells and diffuse to neighboring cells. Cause uninfected cells to produce antiviral proteins (AVPs).

Interferon gamma: Produced by lymphocytes. Causes neutrophils to kill bacteria.



The Complement System

Complement is not a single entity, but rather a group of approximately 30 different proteins that are found in normal blood plasma. These proteins make up what is called “the complement system” because it is complementary to the action of the immune system. The proteins of the complement system, sometimes collectively referred to as complement components, interact with each other in a stepwise manner, known as the complement cascade

Inflammation

Damage to the body's tissues triggers a local defensive response called inflammation, another component of the second line of defense. The body normally responds to any local injury, irritation, microbial invasion, or bacterial toxin by a complex series of events collectively referred to as inflammation or the inflammatory response.





Inflammatory Response

Promote changes in blood vessels that allow more fluid, more phagocytes, and antimicrobial proteins to enter the tissues

Functions of Inflammation

1. Destroy and remove pathogens
2. If destruction is not possible, to limit effects by confining the pathogen and its products.
3. Repair and replace tissue damaged by pathogen and its products.

Inflammation Four cardinal signs

Primary functions Major events
Redness Heat Swelling Pain



Primary functions
Localize infection
Neutralize toxins at injury site
Repair damage tissue
Major events
Vasodilation
Increase permeability of capillaries
Mobilization of leukocytes to site of injury (chemotaxis & emigration)
Phagocytosis



Second line of defense

Acute phase proteins

set of plasma proteins whose level increases during infection
to enhance host defense mechanisms

e.g. complement proteins, coagulating factors, transferrins

Cytokines

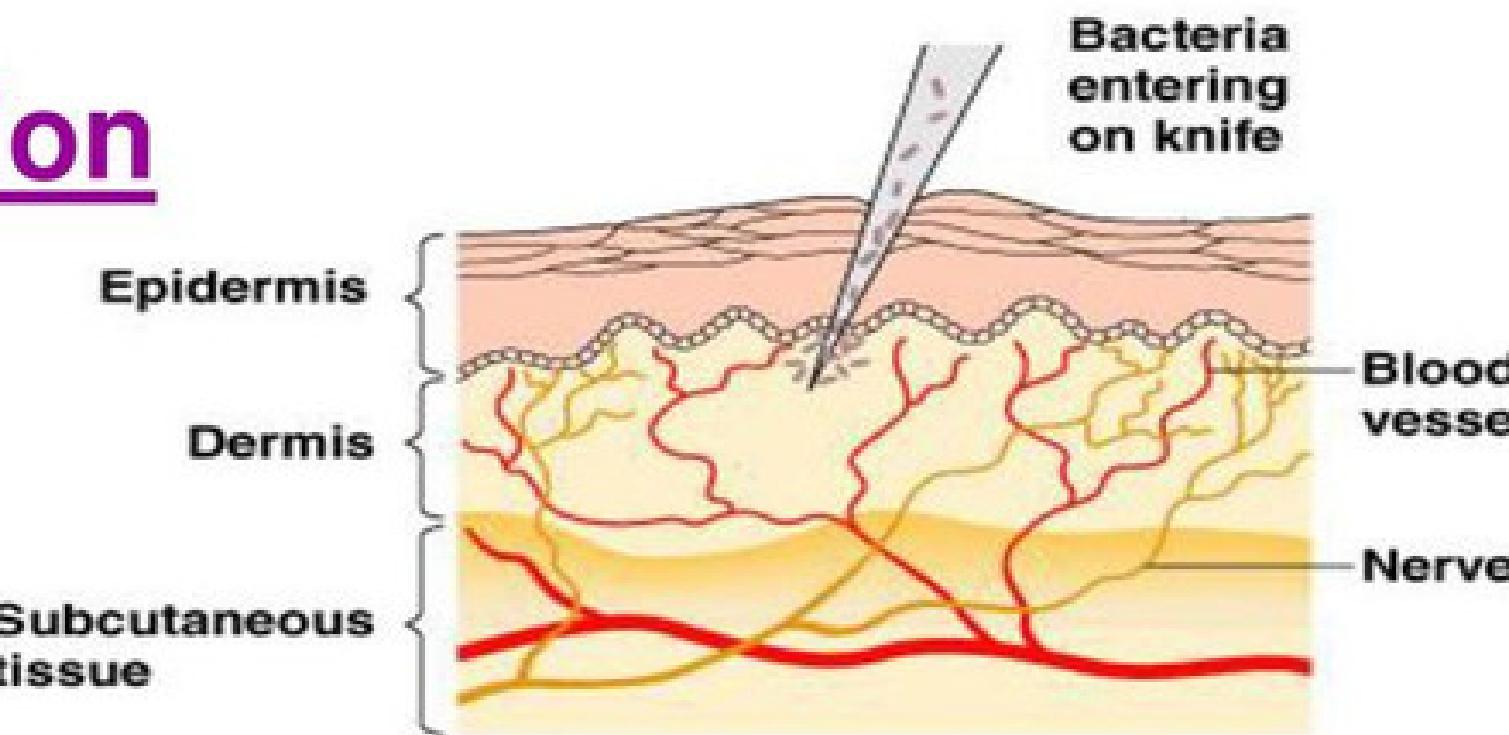
small secreted proteins produced by cells

Communication between different defense systems

Examples: interleukins, interferons

Second Line of Defense

Inflammation

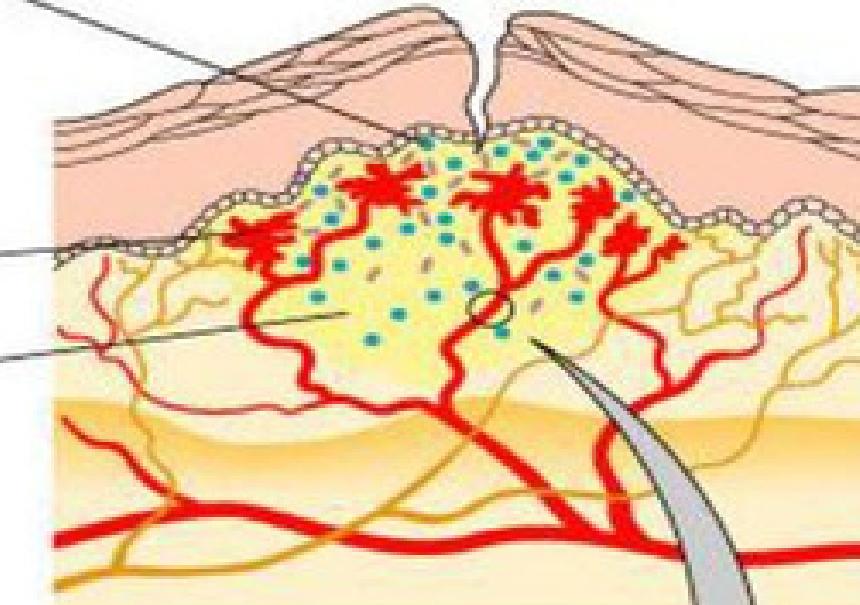


(a) Tissue damage

- 1 Chemicals such as histamine, kinins, prostaglandins, and leukotrienes (represented as blue dots) are released by damaged cells

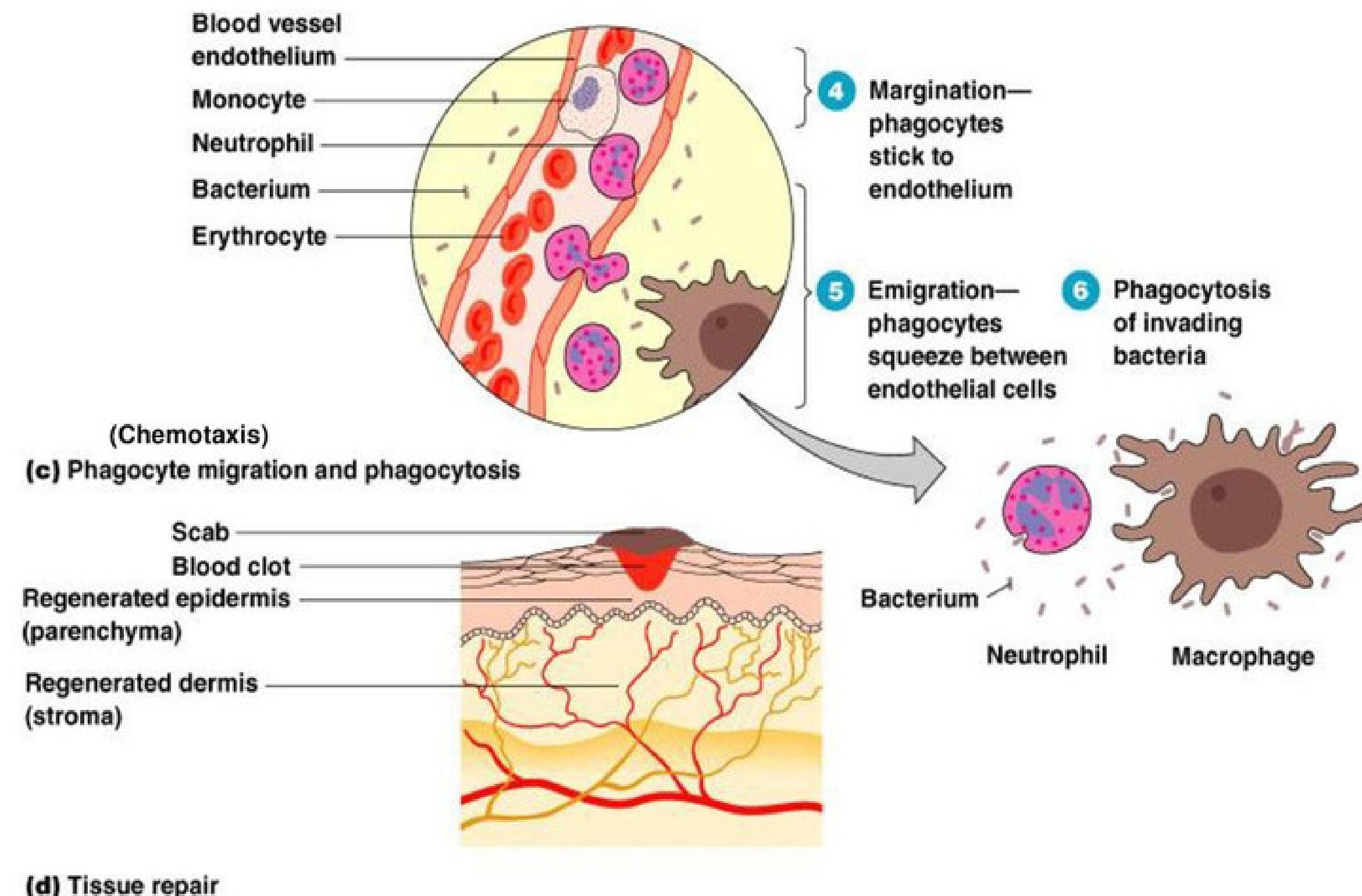
- 2 Blood clot forms

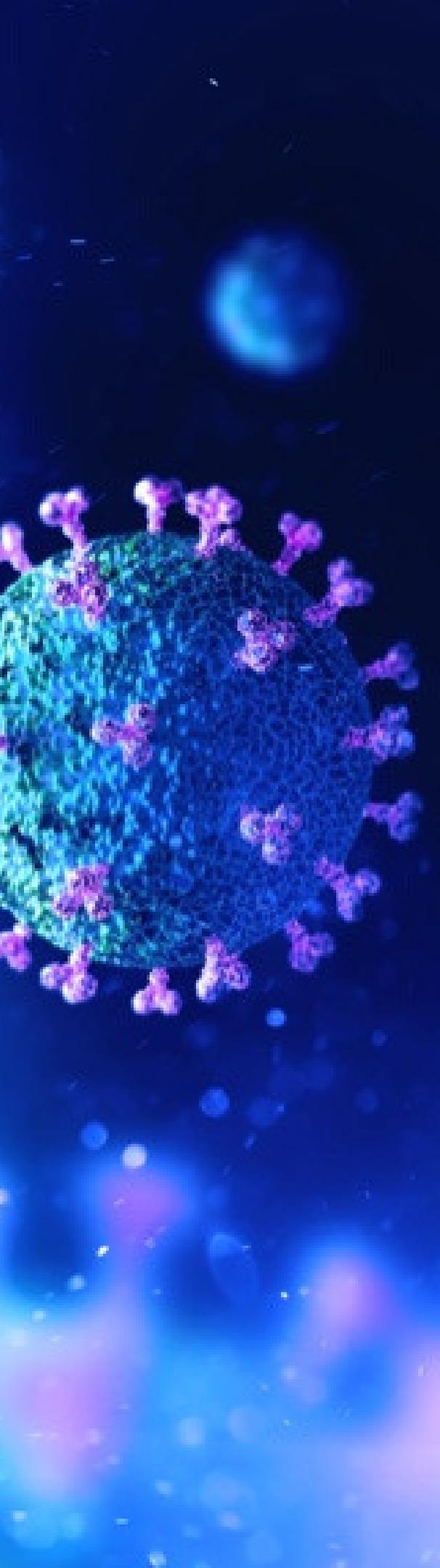
- 3 Abscess starts to form (yellow area)



(b) Vasodilation and increased permeability of blood vessels

Inflammation – cont.





Second Line of Defense

Phagocytosis

Phagocytosis is carried out by white blood cells: macrophages, neutrophils, and occasionally eosinophils.

Wandering macrophages: Originate from monocytes that leave blood and enter infected tissue, and develop into phagocytic cells.

Fixed Macrophages (Histiocytes): Located in liver, nervous system, lungs, lymph nodes, bone marrow, and several other tissues.



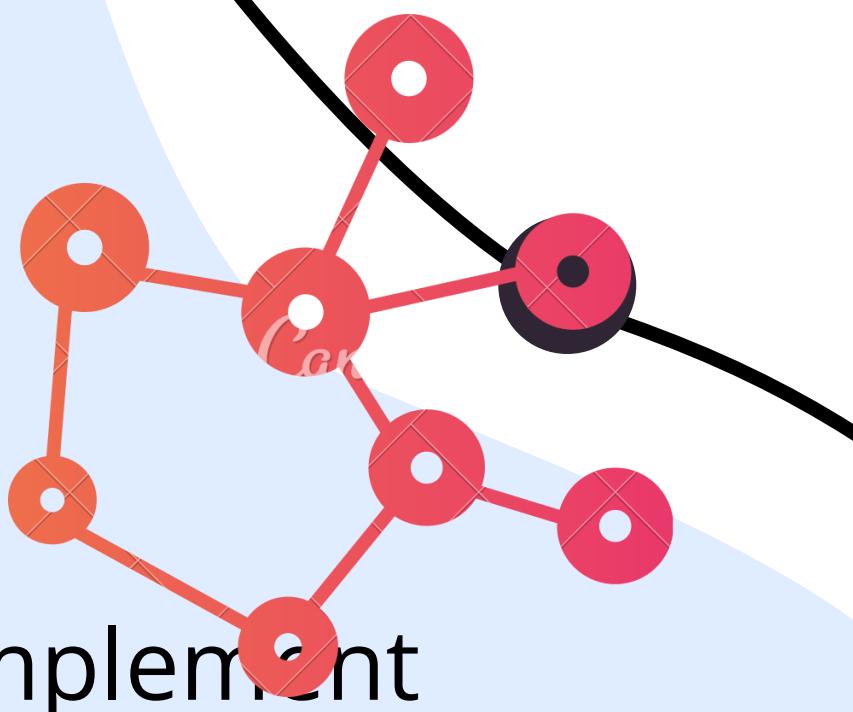
Process of Phagocytosis

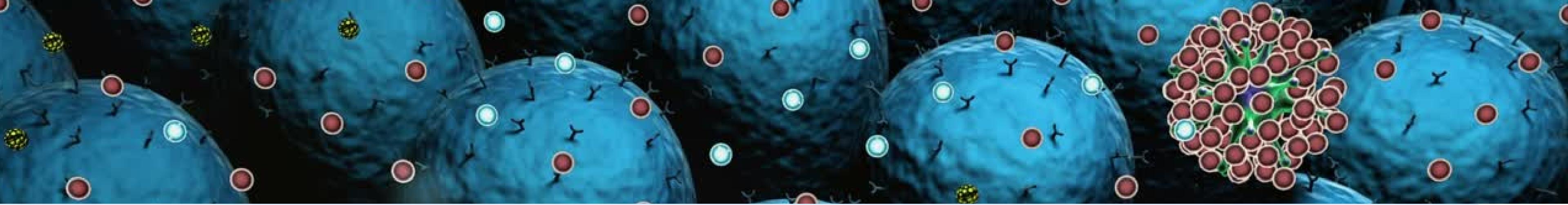
Antimicrobial Proteins

1. The complement system

About 30 serum proteins activated in a cascade
Effects of Complement Activation

1. Opsonisation - enhancing phagocytosis of antigens
2. Chemotaxis - attracting macrophages and neutrophils
3. Cell Lysis - rupturing membranes of foreign cells
4. Clumping of antigen-bearing agents



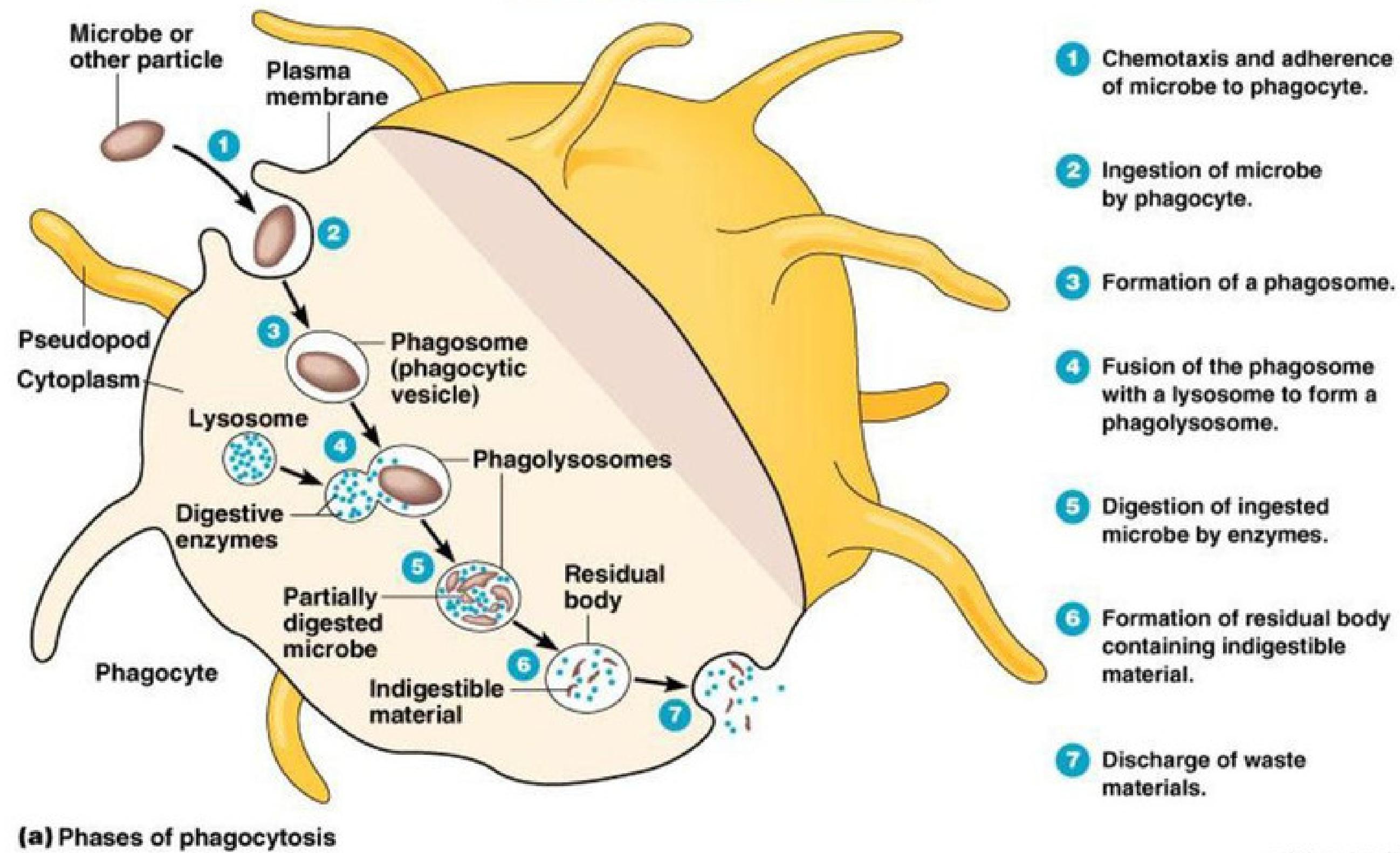


Phagocytosis is the ingestion of microorganisms or other matter by a cell. Many white blood cells engulf invasive microorganisms by the process of phagocytosis. The steps in phagocytosis are:

1. Chemotaxis is the process by which phagocytes are attracted to microorganisms.
2. Attachment: The phagocyte then adheres to the microbial cell. This adherence may be facilitated by opsonization – coating the microbe with plasma proteins.
3. Ingestion: Pseudopods of phagocytes engulf the microorganism and enclose it in a phagosome to complete ingestion.
4. Digestion: Lysosomes fuse with the phagosome to form a digestive vacuole. The microbe is killed and digested.

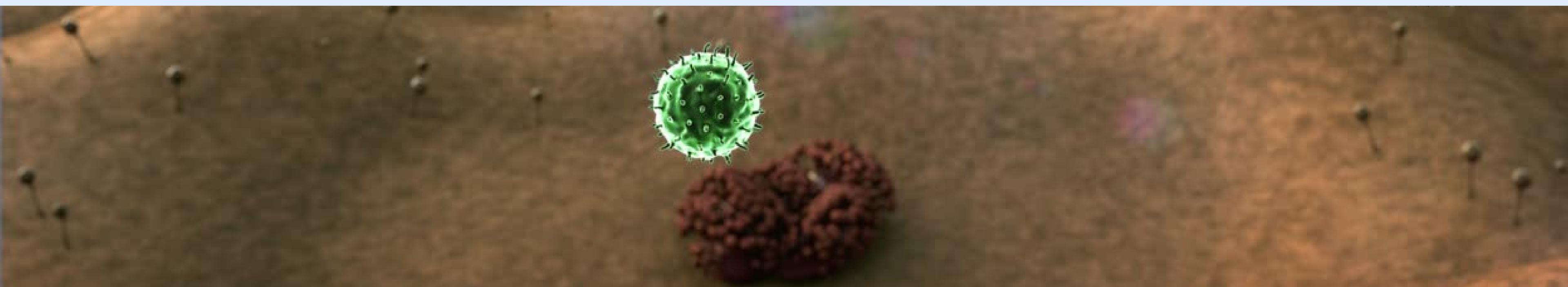
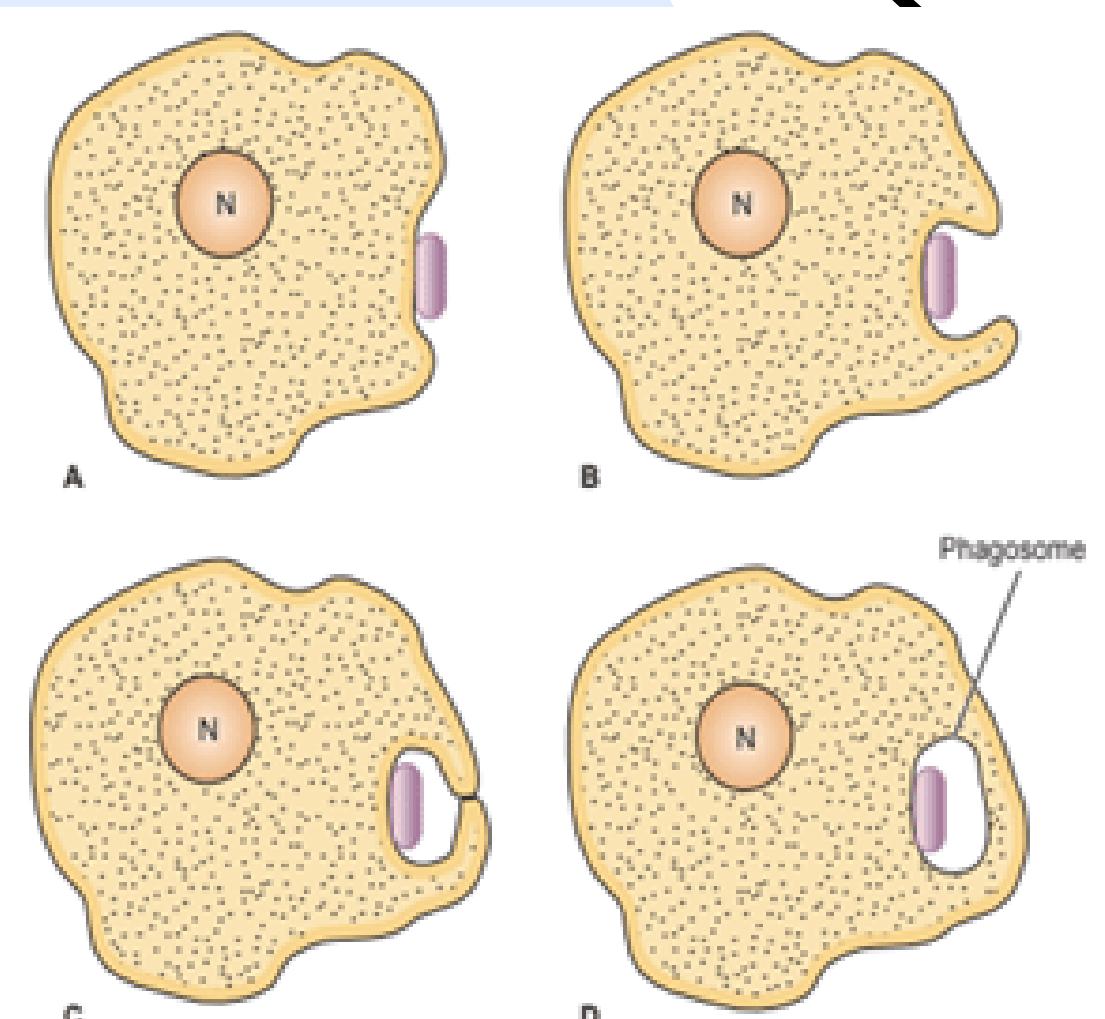
Second Line of Defense

Phagocytosis



The ingestion phase of phagocytosis.

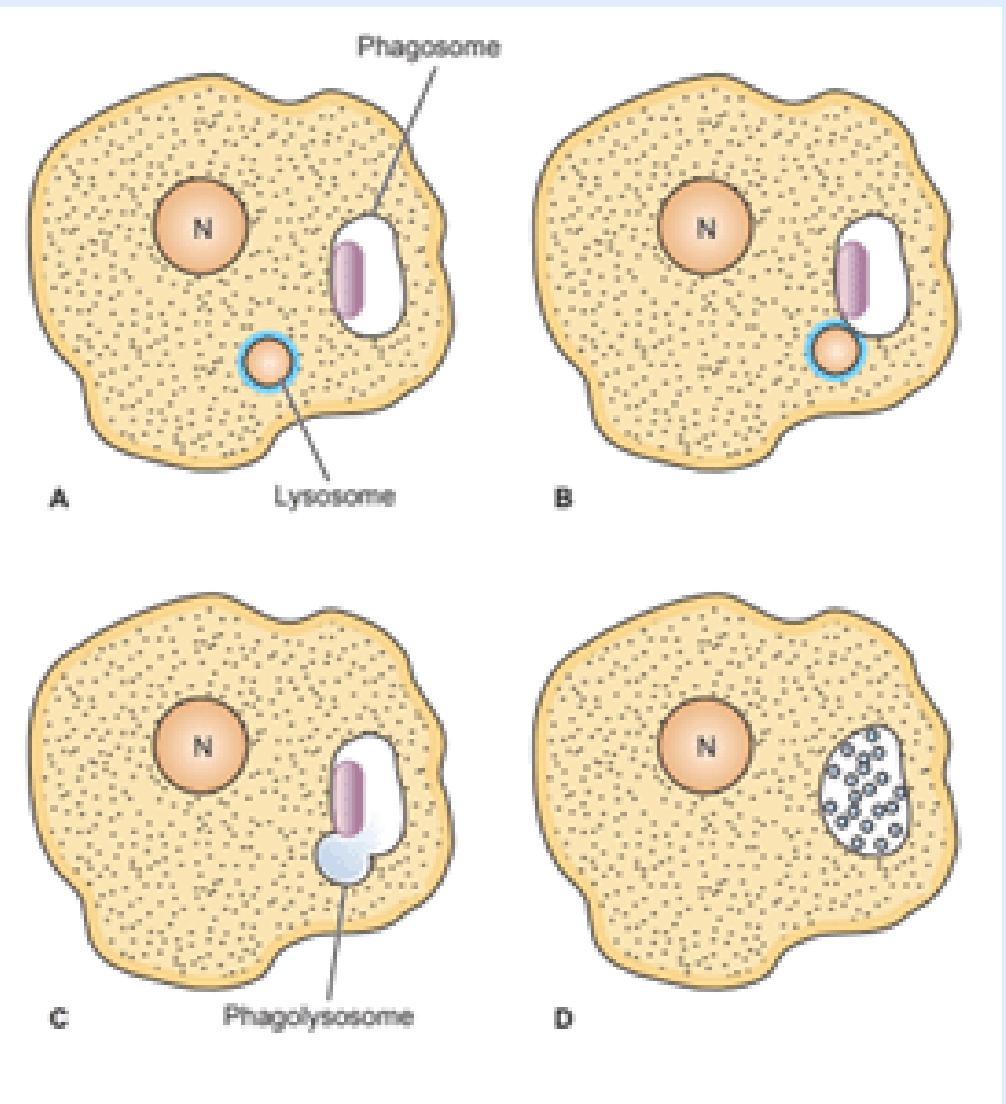
- (A) A phagocyte has attached to a bacterial cell.
- (B) Pseudopodia extend around the bacterial cell.
- (C) The pseudopodia meet and fuse together.
- (D) The bacterial cell, surrounded by a membrane, is now inside the phagocyte. The membrane-bound structure, containing the ingested bacterial cell, is called a phagosome. N, nucleus.





The digestion phase of phagocytosis.

- (A) A lysosome, containing digestive enzymes, approaches a phagosome.
 - (B) The lysosome membrane fuses with the phagosome membrane.
 - (C) The lysosome and phagosome become a single membrane-bound vesicle, known as a phagolysosome. The phagolysosome contains the ingested bacterial cell plus digestive enzymes.
 - (D) The bacterial cell is digested within the phagolysosome.
- N, nucleus.





Disorders and Conditions that Adversely Affect Phagocytic and Inflammatory Processes

Leukopenia an abnormally low number of circulating leukocytes.

When a patient has an abnormally low number of circulating leukocytes.

Neutropenia an abnormally low number of circulating neutrophils.

When a patient has an abnormally high number of circulating leukocytes, the condition is known as **leukocytosis (which is usually the result of an infection)**.

Leukemia is a type of cancer in which there is a proliferation of abnormal leukocytes in the blood. Actually, there are several different types of leukemia, classified by the dominant type of leukocyte.



Disorders and Conditions Affecting Leukocyte Motility and Chemotaxis

The inability of leukocytes to migrate in response to chemotactic agents may be related to a defect in the production of actin, a structural protein associated with motility. Some drugs (e.g., corticosteroids) can also inhibit the chemotactic activity of leukocytes. Decreased neutrophil chemotaxis also occurs in the inherited childhood disease known as Chediak-Higashi syndrome

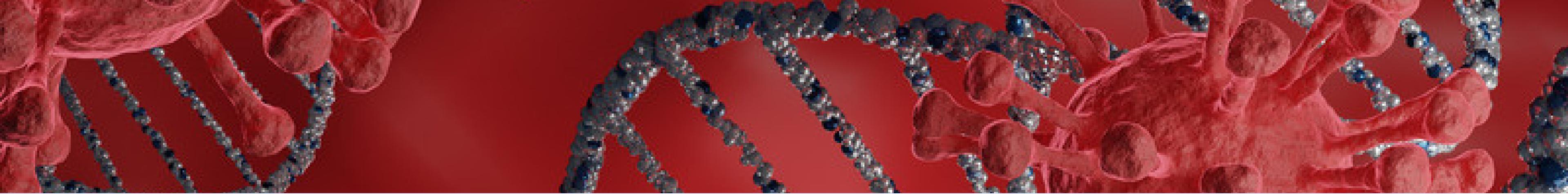
(CHS). In addition, the PMNs of individuals with CHS contain abnormal lysosomes that do not readily fuse with phagosomes, resulting in decreased bactericidal activity.

CHS is characterized by symptoms such as albinism, central nervous system abnormalities, and recurrent bacterial infections.

TABLE 15-2

Additional Factors that Can Impair Host Defense Mechanisms

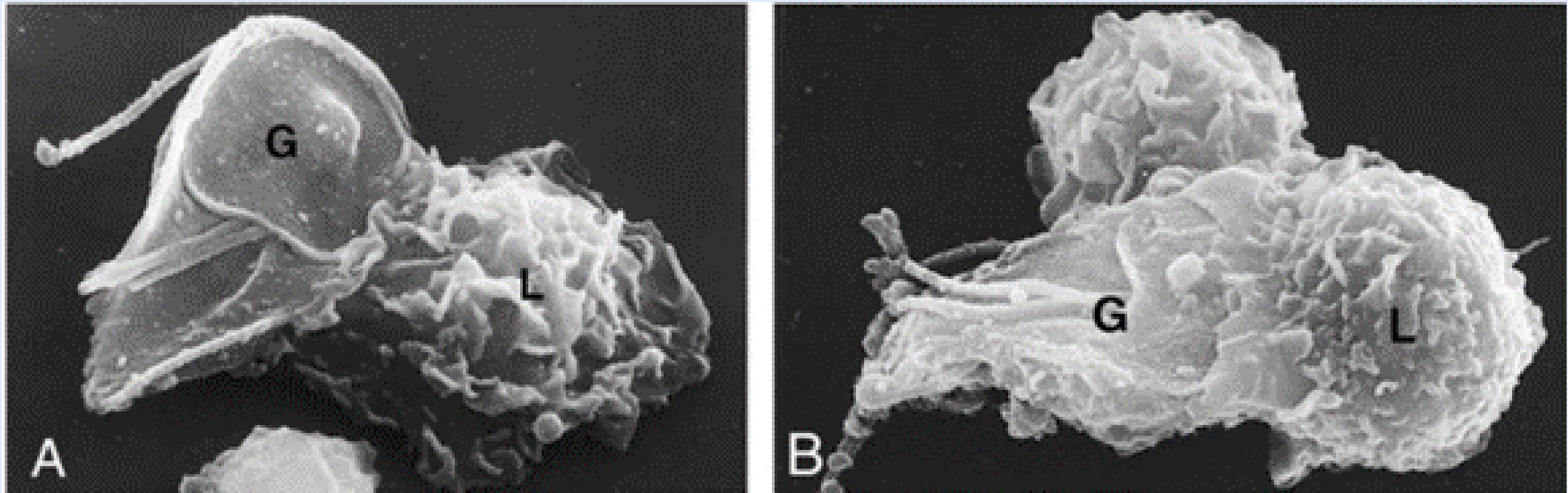
FACTOR	COMMENTS
Nutritional status	Malnutrition is accompanied by decreased resistance to infections
Increased iron levels	High concentrations of iron make it easier for bacteria to satisfy their iron requirements; high concentrations of iron reduce the chemotactic and phagocytic activities of phagocytes; increased iron levels may result from a variety of conditions or habits
Stress	People living under stressful conditions are more susceptible to infections than people living under less stressful conditions
Age	Newborn infants lack a fully developed immune system; the efficiency of the immune system and other host defenses declines after age 50
Cancer and cancer chemotherapy	Cancer chemotherapeutic agents kill healthy cells and malignant ones
AIDS	Destruction of the AIDS patient's helper T cells (T_H cells) decreases the patient's ability to produce antibodies to certain pathogens (discussed in Chapter 16)
Drugs	Steroids and alcohol, for example
Various genetic defects	B-cell and T-cell deficiencies, for example



Disorders and Conditions Affecting Intracellular Killing by Phagocytes

The phagocytes of some individuals are capable of ingesting bacteria, but are incapable of killing certain species. This is usually the result of deficiencies in myeloperoxidase or an inability to generate superoxide anion, hydrogen peroxide, or hypochlorite. Chronic granulomatous disease (CGD) is an often fatal genetic disorder that is characterized by repeated bacterial infections.

The PMNs of individuals with CGD can ingest bacteria but cannot kill certain species. In one form of CGD, the person's PMNs are unable to produce hydrogen peroxide. In another hereditary disorder, the individual's PMNs completely lack myeloperoxidase. Their PMNs do possess other microbicidal mechanisms, however, so these individuals usually do not experience recurrent infections.



Scanning electron micrographs (A,B) illustrating the phagocytosis of
Giardia
trophozoites (G) by rat leukocytes (L).

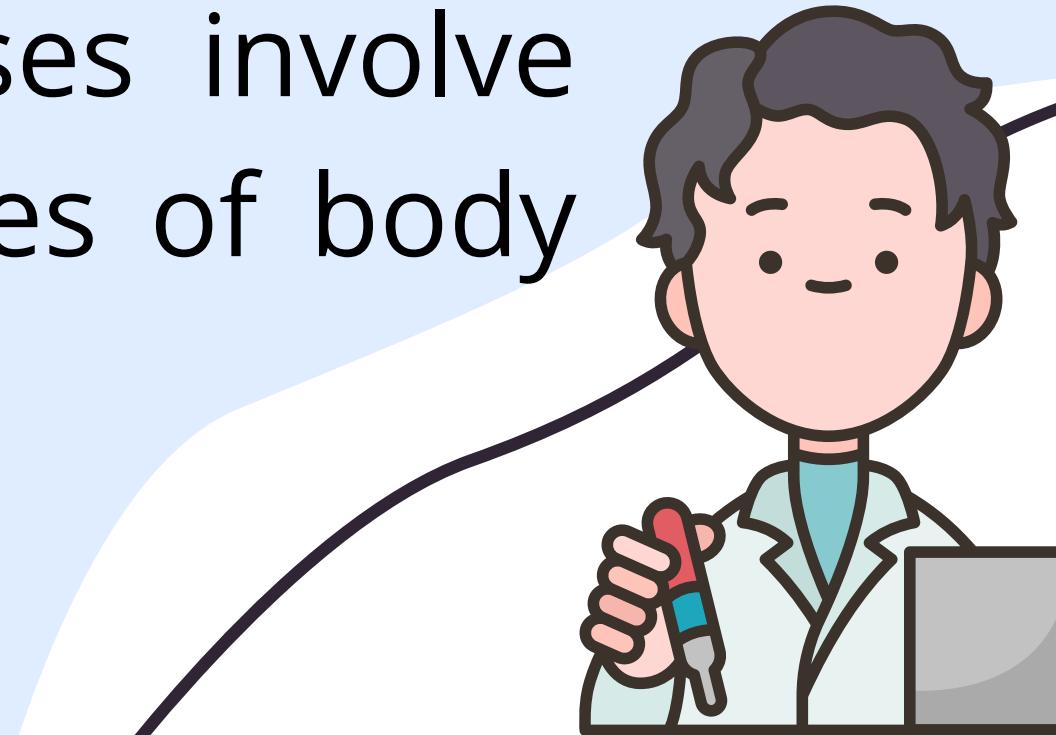




SPECIFIC HOST DEFENSE MECHANISMS

Immunology

Immunology is the scientific study of the immune system and immune responses. The immune system is considered to be the third line of defense. It is considered a specific host defense mechanism because it springs into action to defend against a specific pathogen (or other foreign object) that has gained entrance to the body. Immune responses involve complex interactions among many different types of body cells and cellular secretions.



Origins of Immunology

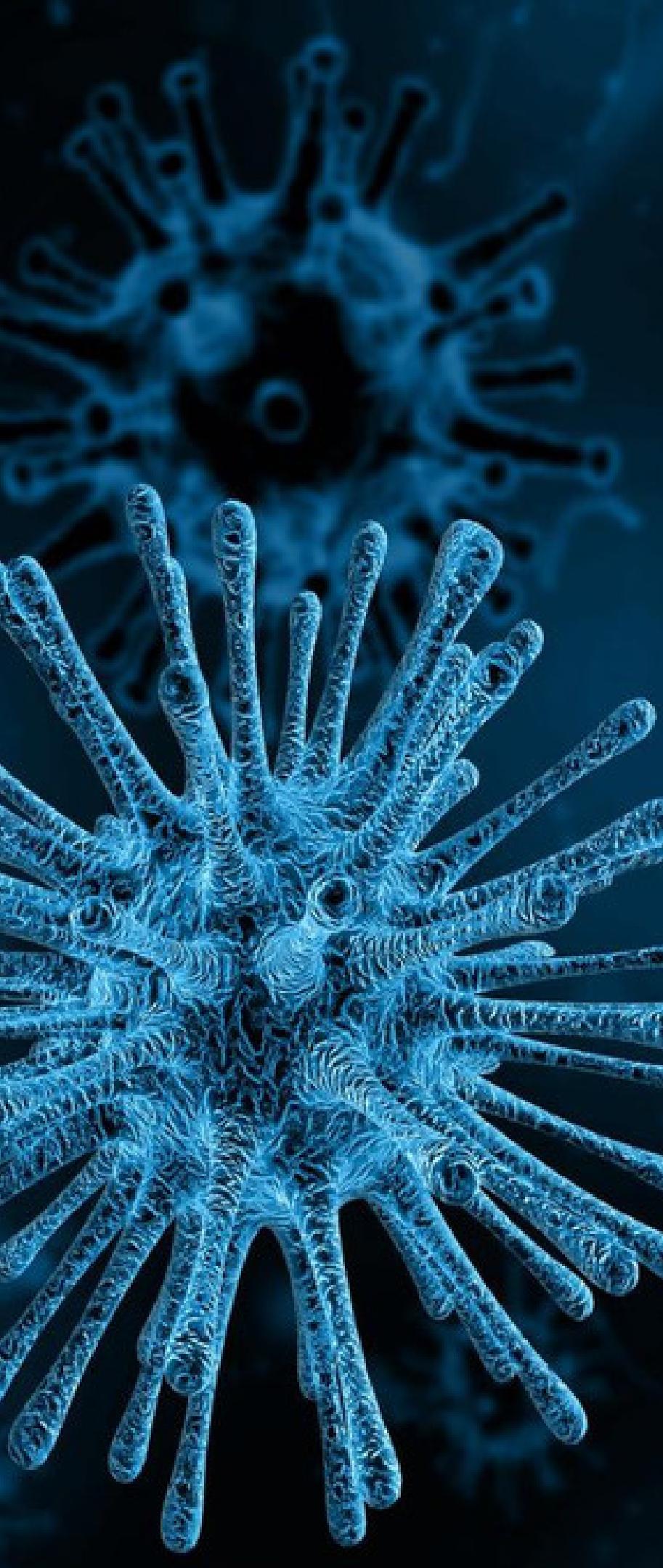


- Edward Jenner's small pox vaccine which is first administered in 1796.
- Louis Pasteur's vaccines against anthrax, cholera, and rabies (developed in the late 1800s)
- Emil Behring and Kitasato Shibasaburo discovered antibodies while developing a diphtheria antitoxin (1890). At the same time Elie Metchnikoff discovered phagocytes and introduced the cellular theory of immunity
- By late 1910, the main elements of clinical immunology had been described, and immunochemistry had become a quantitative science.
- Major advances in immunology began to take shape in the late 1950s, when the focus shifted from serology to cells.

The Key to Understanding Immunology

An understanding of immunology boils down to an understanding of two terms and that is antigens and antibodies.

- > Antigens are molecules that stimulate the immune system to produce antibodies.
- > Antibodies are proteins produced by the immune system in response to antigens.



Primary Functions of the immune system

The primary functions of the immune system are to differentiate between “self” and “non-self”, and destroy that which is non-self.

Major Arms of the Immune System

There are two major arms of the immune system: **humoral immunity and CMI**

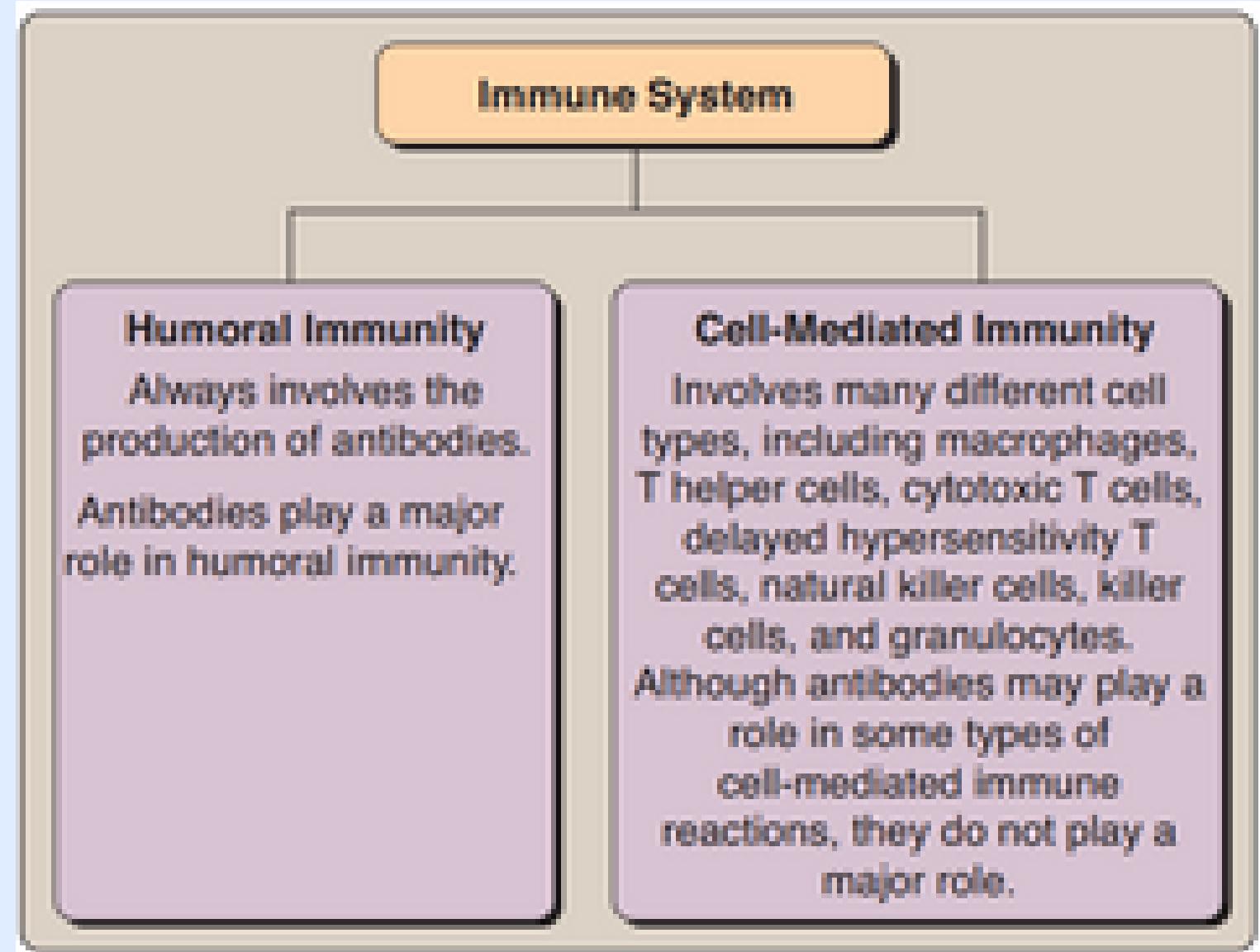
Humoral Immunity

Humoral immunity always involves the production of antibodies in response to antigens. It is named humoral immunity because it involves substance found in the humors, or body fluids.

Humoral immunity involves B lymphocytes, more commonly known as B cell.

Cell- Mediated Immunity (CMI)

The second major arm of the immune system—CMI— involves various cell types, with antibodies only playing a minor role. These immune responses are referred to as cell-mediated immune response





IMMUNITY

A significant result of immune responses is to make a person resistant to certain infectious diseases.

When one is resistant to a certain disease one is said to be immune.

Humans are immune to certain infectious diseases simply because they are humans.

ACQUIRED IMMUNITY



Immunity that results from the active production or receipt of protective antibodies during one's lifetime. If the antibodies are actually produced within the person's body, the immunity is called active acquired immunity; such protection is usually long lasting.

There are two type of acquired immunity:

1. Active acquired immunity
2. Passive acquired immunity



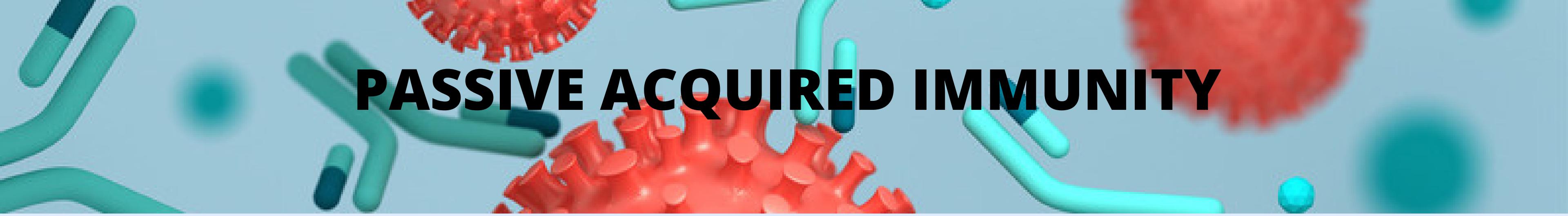
ACTIVE ACQUIRED IMMUNITY

Results when exposure to a disease organism triggers the immune system to produce antibodies to that disease.

There are two type of active acquired immunity:

Natural active acquired immunity - Immunity that is acquired in response to the entry of a live pathogen into the body.

Artificial active acquired immunity - Immunity that is acquired in response to vaccines.



PASSIVE ACQUIRED IMMUNITY

In passive acquired immunity, the person receives antibodies that were produced by another person or by more than one person. This is when a person receives antibodies, rather than producing them.

Types of Passive acquired immunity

Natural passive acquired immunity – Immunity that is acquired by a fetus when it receives maternal antibodies in utero or by an infant when it receives maternal antibodies contained in colostrum.

Artificial passive acquired immunity – Immunity that is acquired when a person receives antibodies contained in antisera or gamma globulin.

VACCINES

A vaccine is defined as material that can artificially induce immunity to an infectious disease, usually after injection or, in some cases, ingestion of the material. A person is deliberately exposed to a harmless version of a pathogen (or toxin), which will stimulate that person's immune system to produce protective antibodies and memory cells, but will not cause disease in that person.

It is used to stimulate the body's immune response against diseases



TYPES OF VACCINES

Attenuated vaccines

- An attenuated vaccine is a vaccine developed by reducing the virulence of the pathogen, but still keeping it viable.

Examples:

Chicken pox (varicella), measles (rubeola), mumps, German measles (rubella), polio (oral Sabin vaccine), rotavirus, smallpox, yellow fever



TYPES OF VACCINES

Inactivated vaccines

- Vaccines made from pathogens that have been Inactivated viruses or viral antigens: killed by heat or chemicals and can be produced faster and more easily, but they are less effective than live other vaccines.

Examples:

Hepatitis A, Influenza, Polio, Rabies



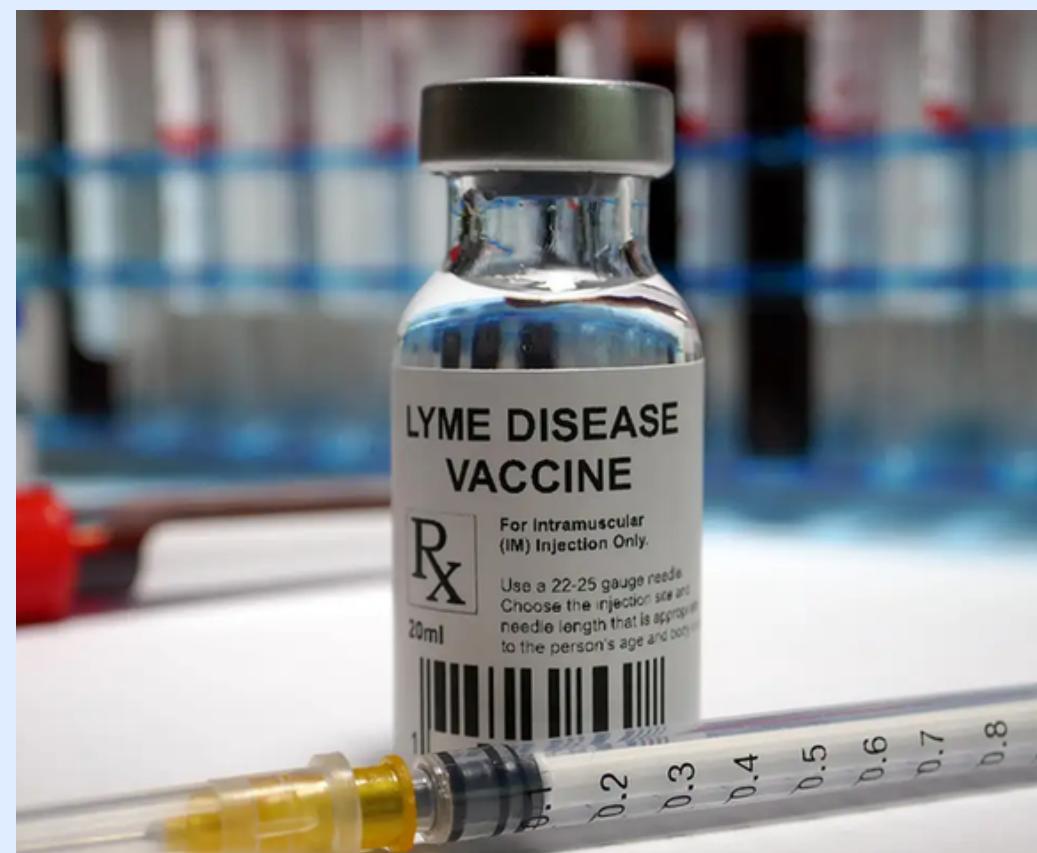
TYPES OF VACCINES

Subunit vaccines

- A subunit vaccine (or acellular vaccine) is one that uses antigenic (antibody-stimulating) portions of a pathogen, rather than using the whole pathogen.

Examples:

Hepatitis B, Lyme disease, whooping cough



TYPES OF VACCINES

Conjugated vaccines

- This type of vaccine are made by conjugating bacterial capsular antigens (which by themselves are not very antigenic) to molecules that stimulate the immune system to produce antibodies against the less antigenic capsular antigens.

Examples:

Hib (for protection against *Haemophilus influenzae* type b), meningococcal meningitis (*Neisseria meningitidis* serogroup C), pneumococcal pneumonia



TYPES OF VACCINES

Toxoid vaccines

- A toxoid is an exotoxin that has been inactivated (made nontoxic) by heat or chemicals. Toxoids can be injected safely to stimulate the production of antibodies that are capable of neutralizing the exotoxins of pathogens, such as those that cause tetanus, botulism, and diphtheria.

Examples:

Diphtheria, Tetanus



TYPES OF VACCINES

DNA vaccines

- are often referred to as the third-generation vaccines, use engineered DNA to induce an immunologic response in the host against bacteria, parasites, viruses, and potentially cancer.
- DNA vaccines or gene vaccines are only experimental. A particular gene from a pathogen is inserted into plasmids, and the plasmids are then injected into skin or muscle tissue.

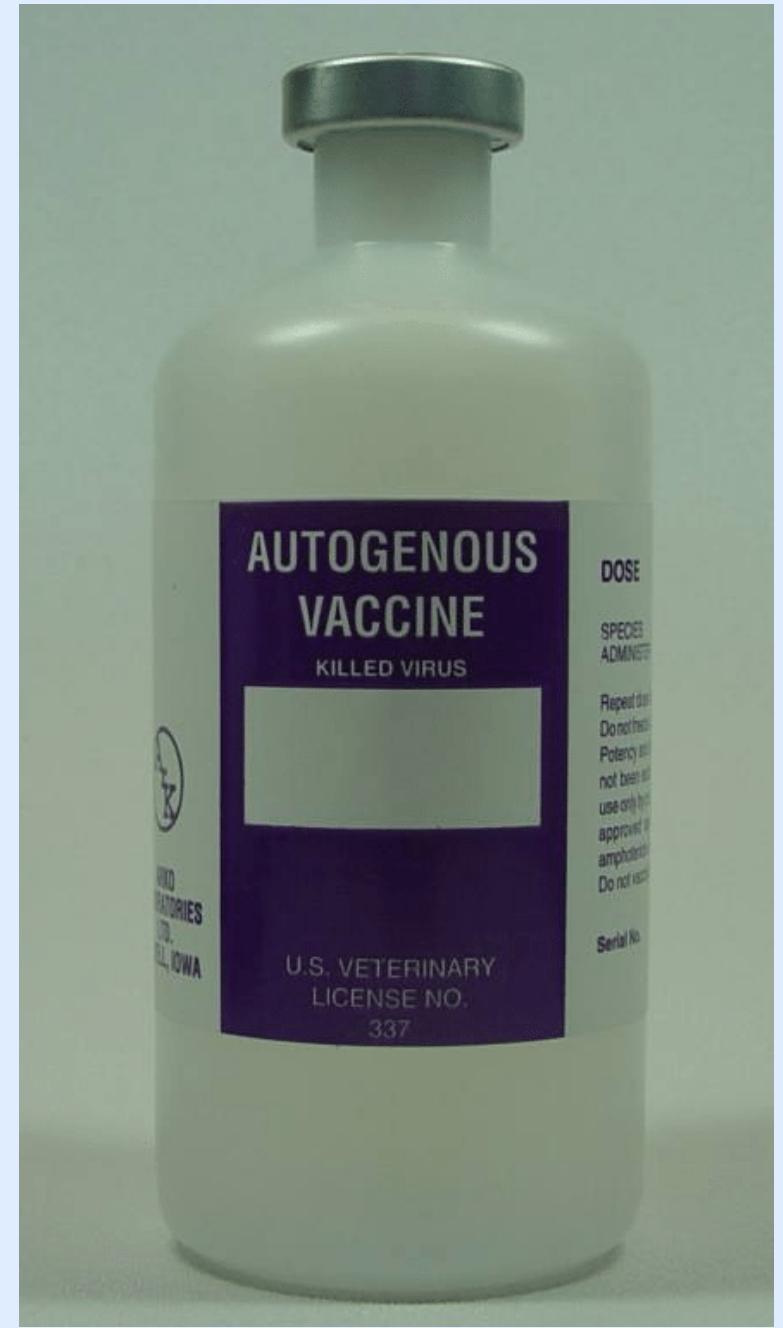
Example:

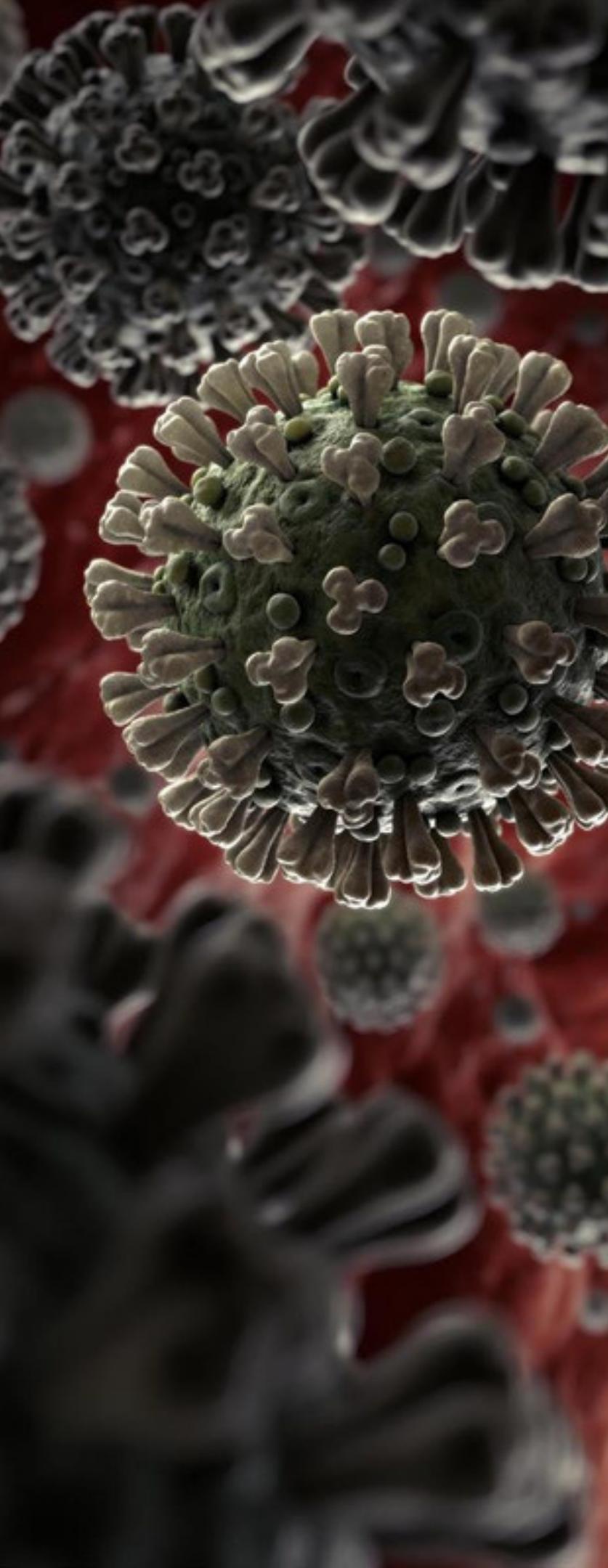
- Laboratory animals have been successfully protected using this technique, and reports of the induction of cellular immune responses in humans to a malarial parasite antigen, using DNA vaccines.

TYPES OF VACCINES

Autogenous vaccines

- An autogenous vaccine is one that has been prepared from bacteria isolated from a localized infection, such as a staphylococcal boil. The pathogens are killed and then injected into the same person to induce production of more antibodies.





CELLS OF THE IMMUNE SYSTEM

The Immune system involves very complex interactions among many different types of cells and cellular secretions.

The major cell types that participate in immune responses are:

- T lymphocytes (T cells)
- B lymphocytes (B cells)
- NK cells
- Macrophages

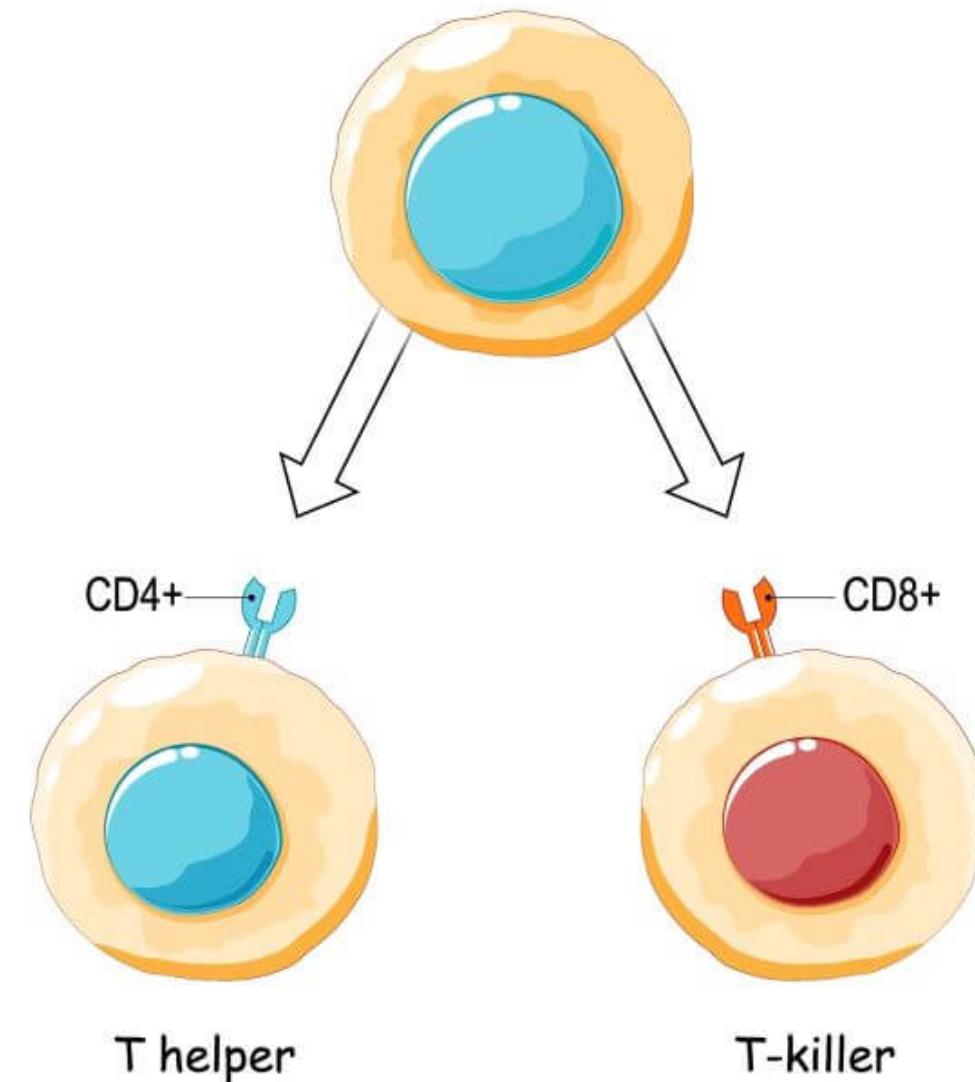
T Lymphocytes (T cells)

- T lymphocytes are part of the immune system and develop from stem cells in the bone marrow but do not mature there.
- are regulators of adaptive function, serving as primary effectors for cell-mediated immunity.

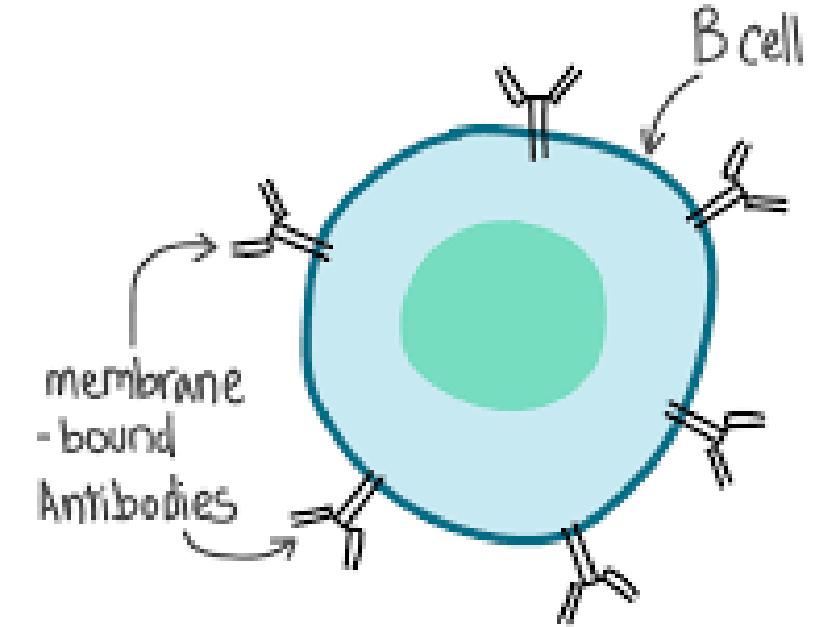
There two types of T cells

- **Helper T cell** - refer to a type of T cell that provides help to other cells in the immune response.
- **Cytotoxic T cell** - refer to a type of immune cell that can kill certain cells, including foreign cells, cancer cells, tumors and cells infected with a virus.

T cell
(adaptive immune response)



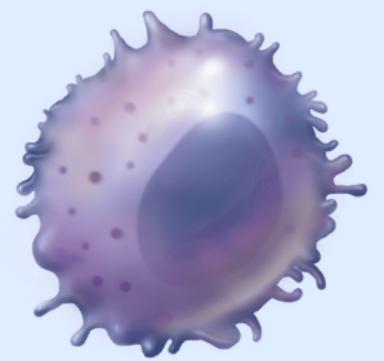
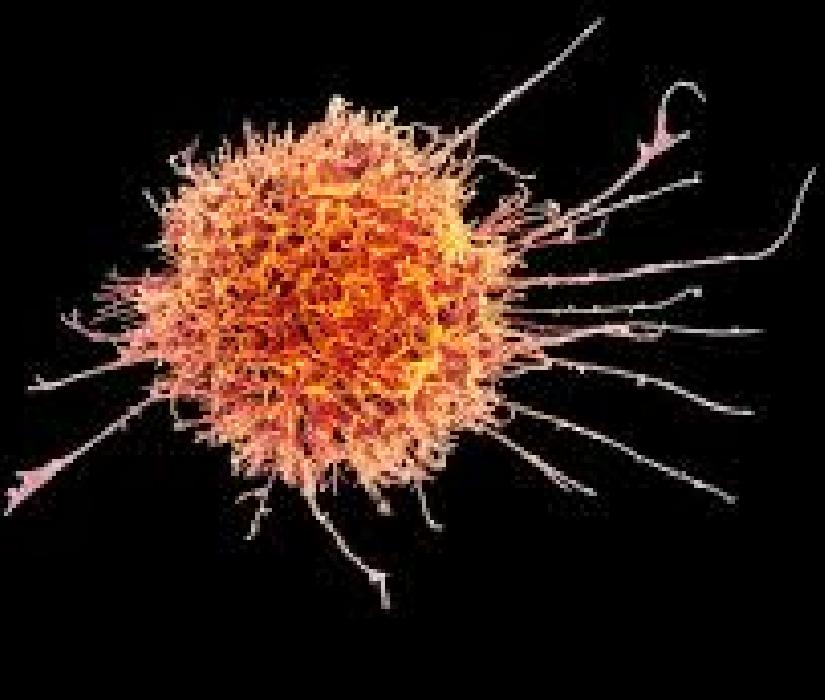
B lymphocytes (B cells)



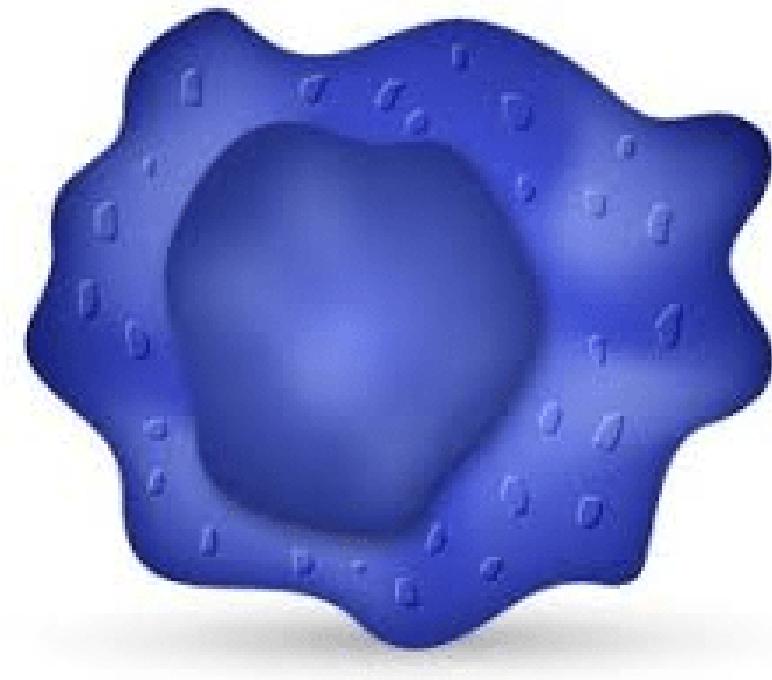
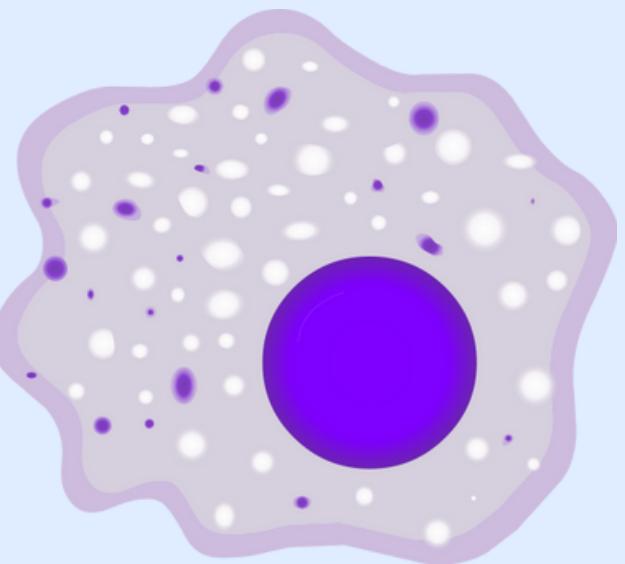
- A type of white blood cell that makes antibodies. B lymphocytes are part of the immune system and develop from stem cells in the bone marrow.
- are at the center of the adaptive humoral immune system
- are responsible for mediating the production of antigen-specific immunoglobulin (Ig) directed against invasive pathogens (typically known as antibodies).

Natural Killer Cells (NK cells)

- As the name implies, NK cells kill target cells, including foreign cells, host cells infected with viruses or bacteria, and tumor cells.
- NK cells are in a subpopulation of lymphocytes called large granular lymphocytes.
- Although NK cell activity is not dependent on antibodies, NK cells have receptors on their surface for the FC region of IgG antibodies. These receptors enable the cells to attach to and kill antibody-coated target cells; this is known as **antibody-dependent cellular cytotoxicity**.



Macrophages



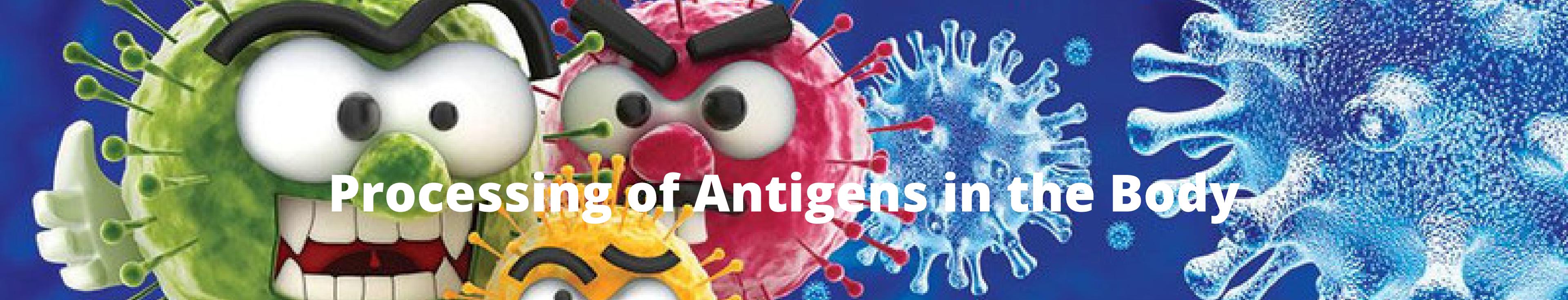
- are effector cells of the innate immune system that phagocytose bacteria and secrete both pro-inflammatory and antimicrobial mediators. In addition, macrophages play an important role in eliminating diseased and damaged cells through their programmed cell death.
- they are also secreting signals that help activate other cell types to fight against infections.



Most antigens are foreign organic substances that are large enough to stimulate the production of antibodies; in other words, an antigen generates antibody production.

Substances capable of stimulating the production of antibodies are said to be antigenic.

Some small molecules called haptens may act as antigens only if they are coupled with a large carrier molecule such as a protein.

A vibrant, cartoon-style illustration of several viruses. In the foreground, there's a large green virus with a white face, black eyes, and a wide, toothy grin showing red and white teeth. Next to it is a pink virus with a similar face. Behind them are smaller, blue and yellow viruses. The background is a dark blue textured surface.

Processing of Antigens in the Body

For antibodies to be produced within the body, a complex series of events must occur, some of which are not completely understood.

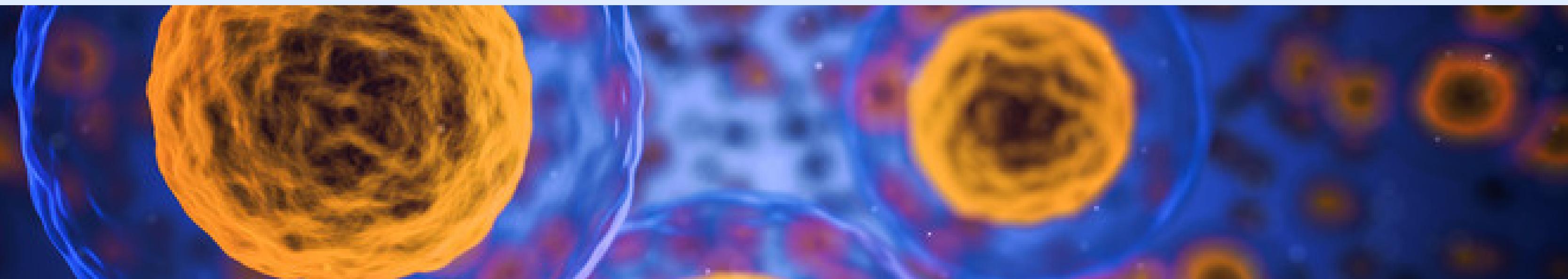
It is known that macrophages, T cells, and B cells often are involved in a cooperative effort.

T-dependent antigens

- The majority of antigens are referred to as T-dependent antigens, because T cells (specifically, TH cells) are involved in their processing. In other words, processing of these antigens is dependent on T cells. The processing of T-dependent antigens also involves macrophages and B cells.

T-independent antigens

- Other antigens are known as T-independent antigens, the processing of which requires only B cells.
- T-independent antigens are large polymeric molecules (usually polysaccharides) containing repeating antigenic determinants; examples include the lipopolysaccharide (LPS) found in the cell walls of Gram-negative bacteria, bacterial flagella, and bacterial capsules.

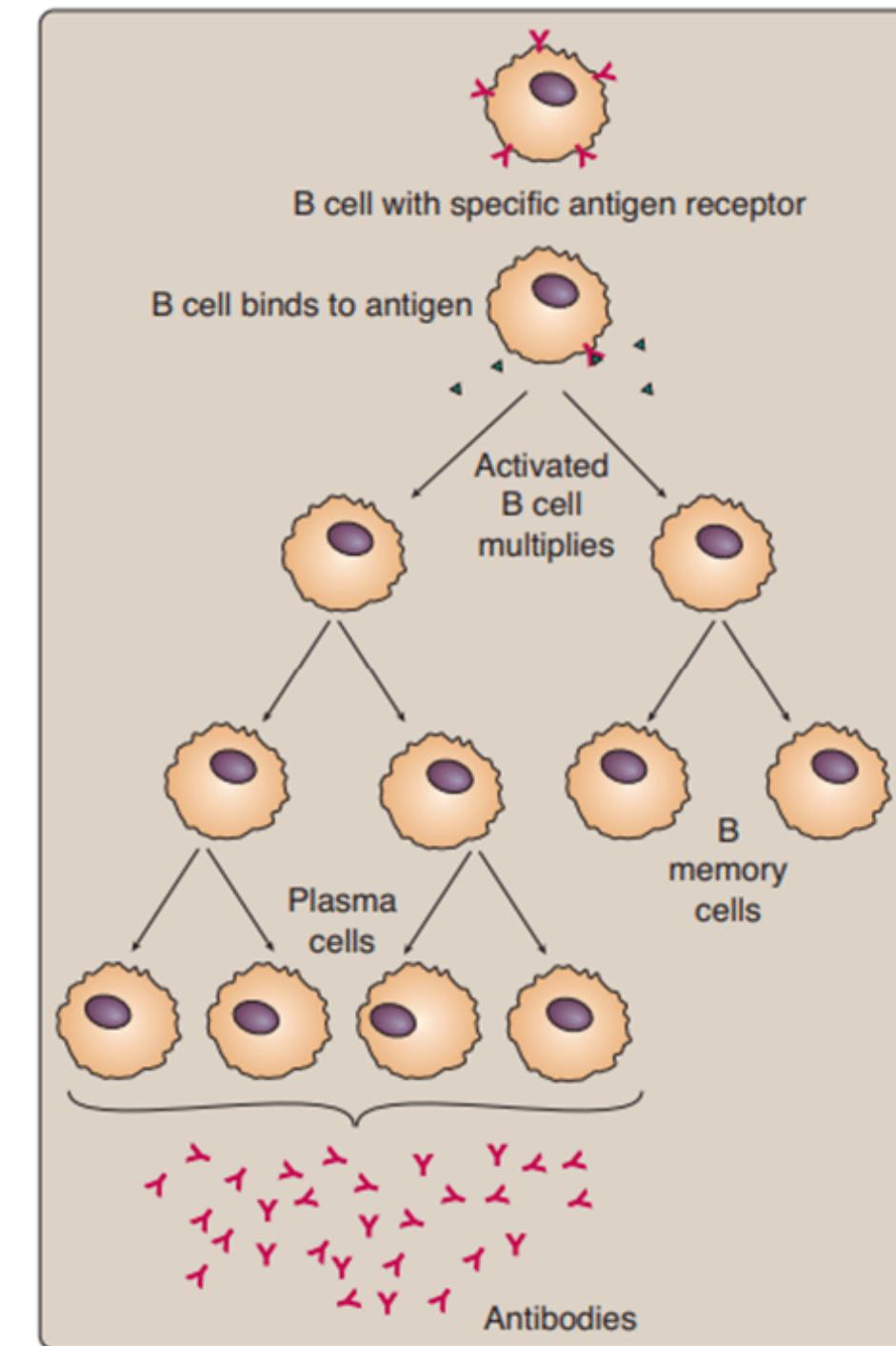


Primary response

- It is the initial response to a particular antigen.
- In the primary response to an antigen, it takes about 10 to 14 days for antibodies to be produced. When the antigen is used up, the number of antibodies in the blood declines as the plasma cells die.

Secondary response

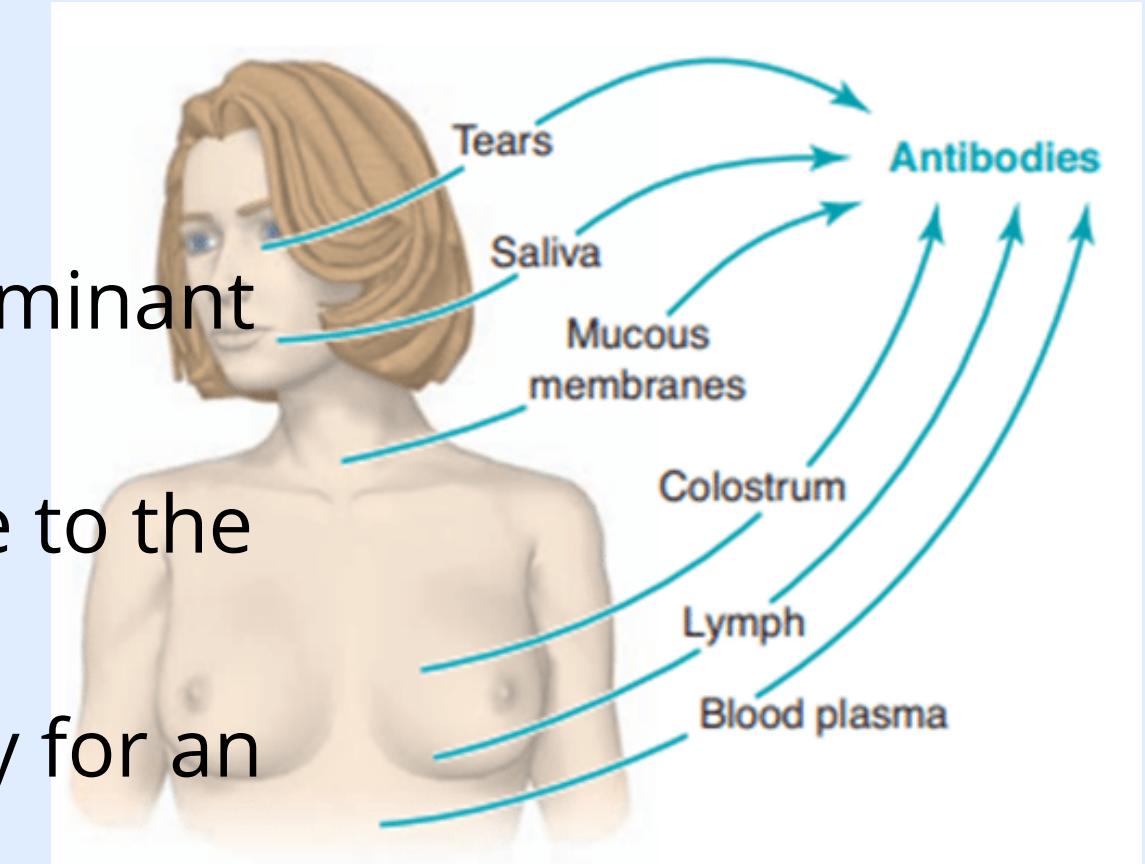
- also known as anamnestic response, or memory response.
- It is the reaction of the immune system when it contacts an antigen for the second and subsequent times.





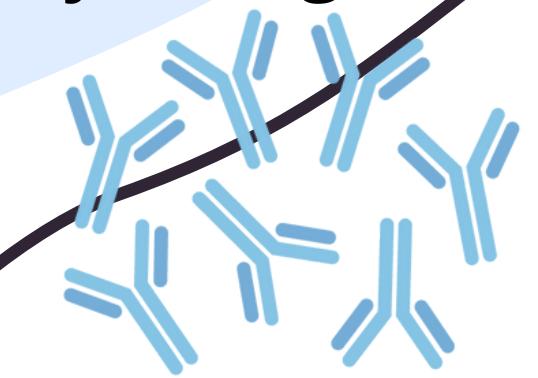
Antibodies

- are usually very specific, binding only with the antigenic determinant that stimulated their production.
- antibodies are proteins produced by lymphocytes in response to the presence of an antigen
- An antibody is an immunoglobulin having particular specificity for an antigen.



Antibody Structure

- As previously mentioned, antibodies belong to a category of glycoproteins called immunoglobulins. All antibodies are immunoglobulins, but not all immunoglobulins are antibodies.
- Antibodies are produced by plasma cells in response to stimulation of B cells by foreign antigens.

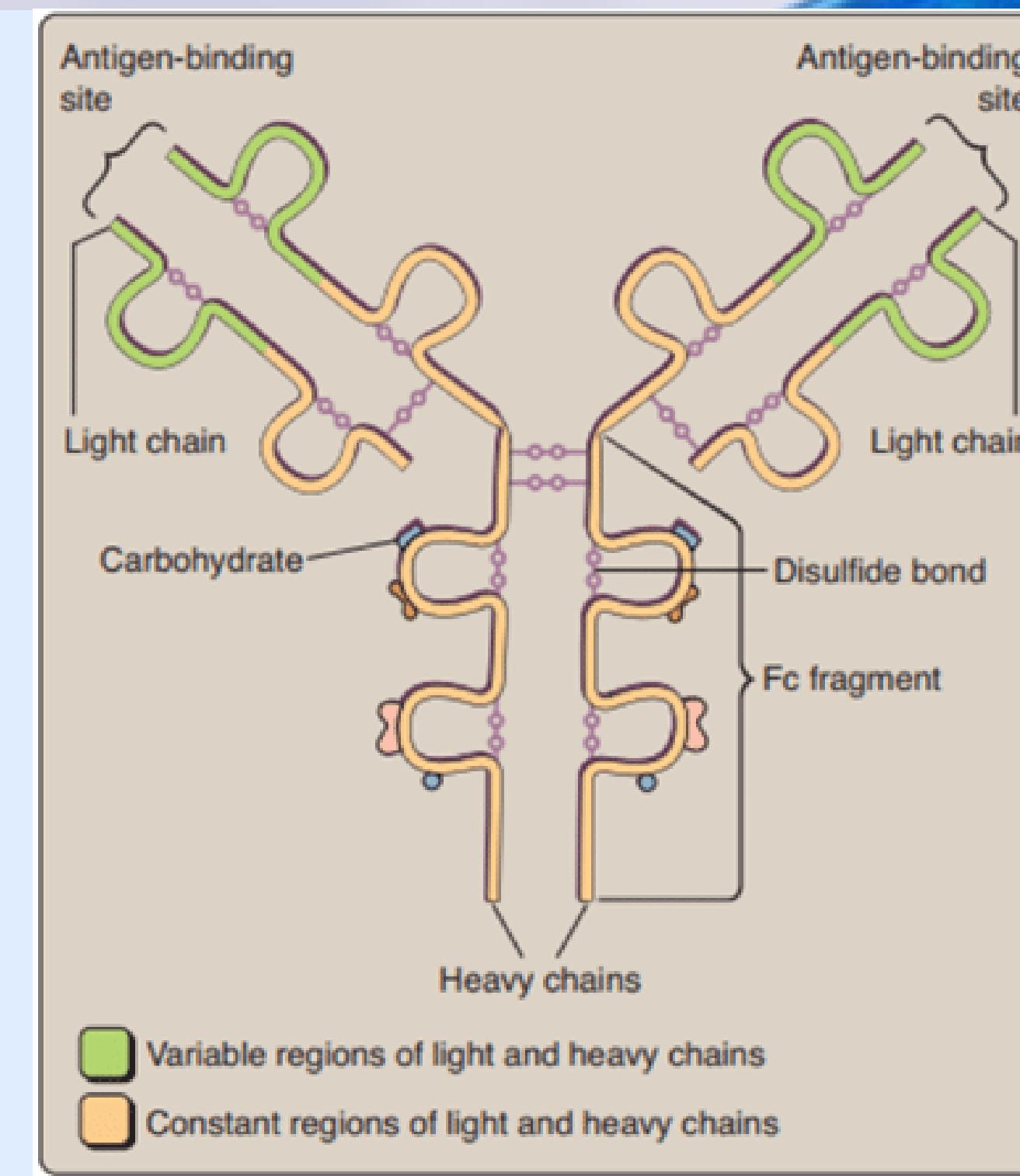




Immunoglobulin

- The primary function of immunoglobulins is to elicit humoral immunity by binding to the foreign antigen.
- The basic structure of an immunoglobulin molecule resembles the letter Y.
- In this basic form, the molecule is referred to as a monomer.
- The five immunoglobulin classes are IgA, IgD, IgE, IgG, and IgM.

Basic structure of a monomeric immunoglobulin molecule



Immunoglobulin Classes

1. IgA

- It is the most abundant type of antibody in the body, comprising most of the immunoglobulin in secretions and a significant amount of circulating immunoglobulin.
- In secretions, it serves to protect the mucosal tissues from microbial invasion and maintain immune homeostasis with the microbiota.
- It is found in mucous membranes, especially in the respiratory and digestive tracts. It is also found in saliva, tears, and breastmilk.

2. IgD

- It is found in large quantities on the surface of B cells.
- Its function is unknown, but it is possible that the IgD molecules on the B cell's surface serve as antigen receptors and determine which specific antigen that particular B cell is able to respond to.

Immunoglobulin Classes

3. IgE

- Plays a major role in allergic responses.
- In atopic individuals, IgE is produced in response to allergens.
- It is found on the surfaces of basophils and mast cells.

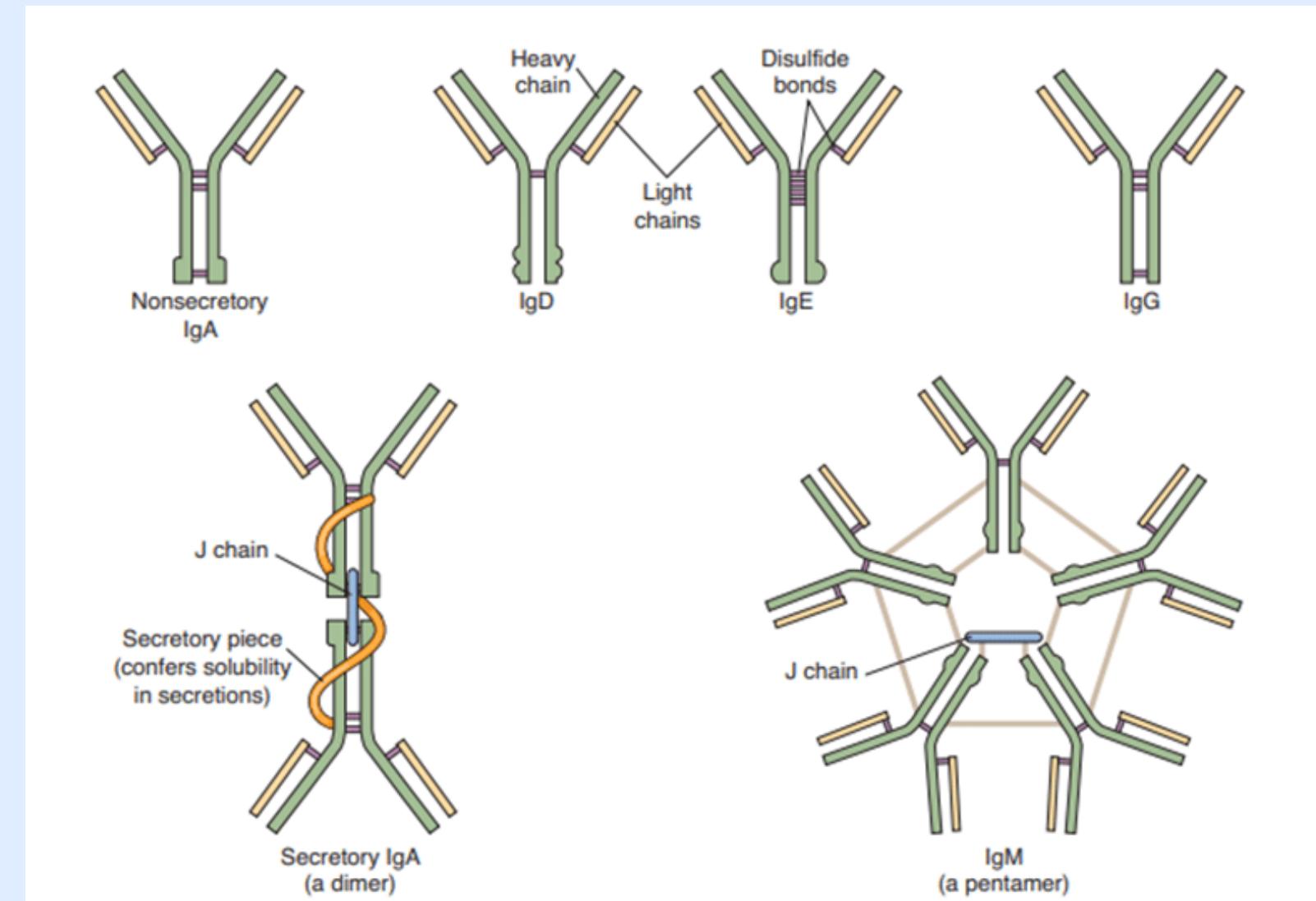
4. IgG

- It is the lightest of the immunoglobulins.
- Maternal IgG antibodies that cross the placenta help protect the newborn during its first months of life.
- Antigen-bound IgG can bind to and activate complement, a process known as **“complement fixation.”**
- IgG molecules can bind to a wide range of cellular receptors to promote phagocytosis and antibody-dependent cytotoxicity.
- IgG antibodies are longlived, sometimes persisting for the lifetime of the individual.

Immunoglobulin Classes

5. IgM

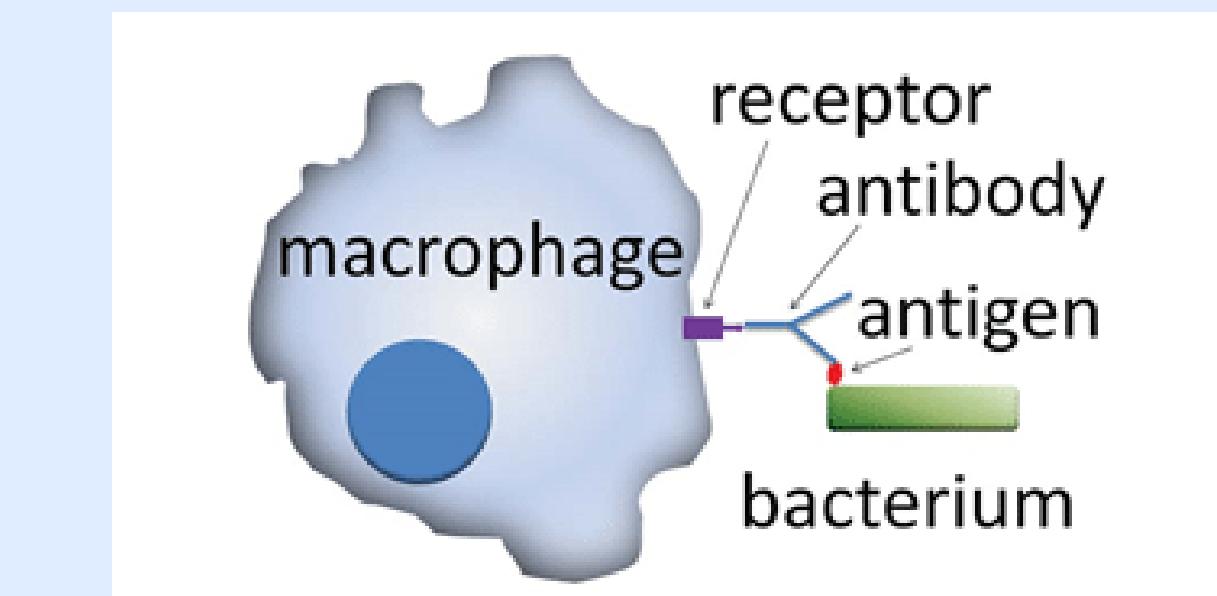
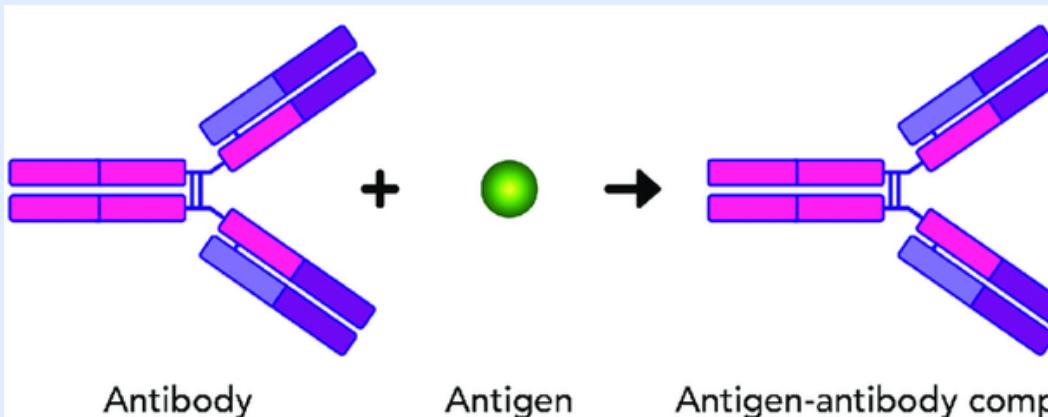
- It serves as the first line of host defense against infections and it also plays an important role in immune regulation and immunological tolerance
- IgM antibodies are relatively short-lived, remaining in the bloodstream for only a few months.
- Provides protection in the earliest stages of infection.
- Because of its large size, IgM does not cross the placenta.



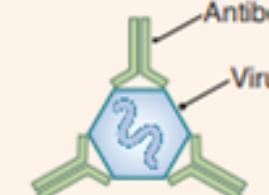
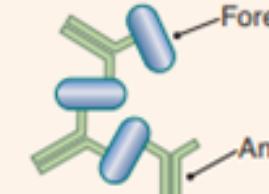
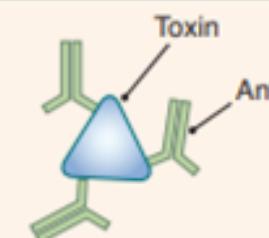
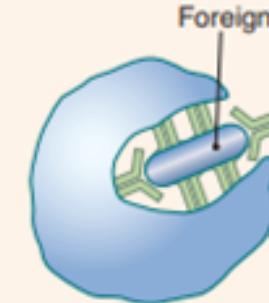
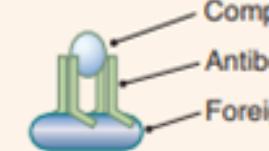
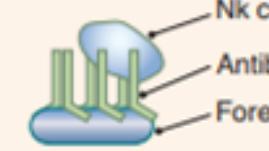
Antigen-Antibody Complexes

The combination of an antibody and an antigen is called an **antigen-antibody complex, Ag-Ab complex, or immune complex.**

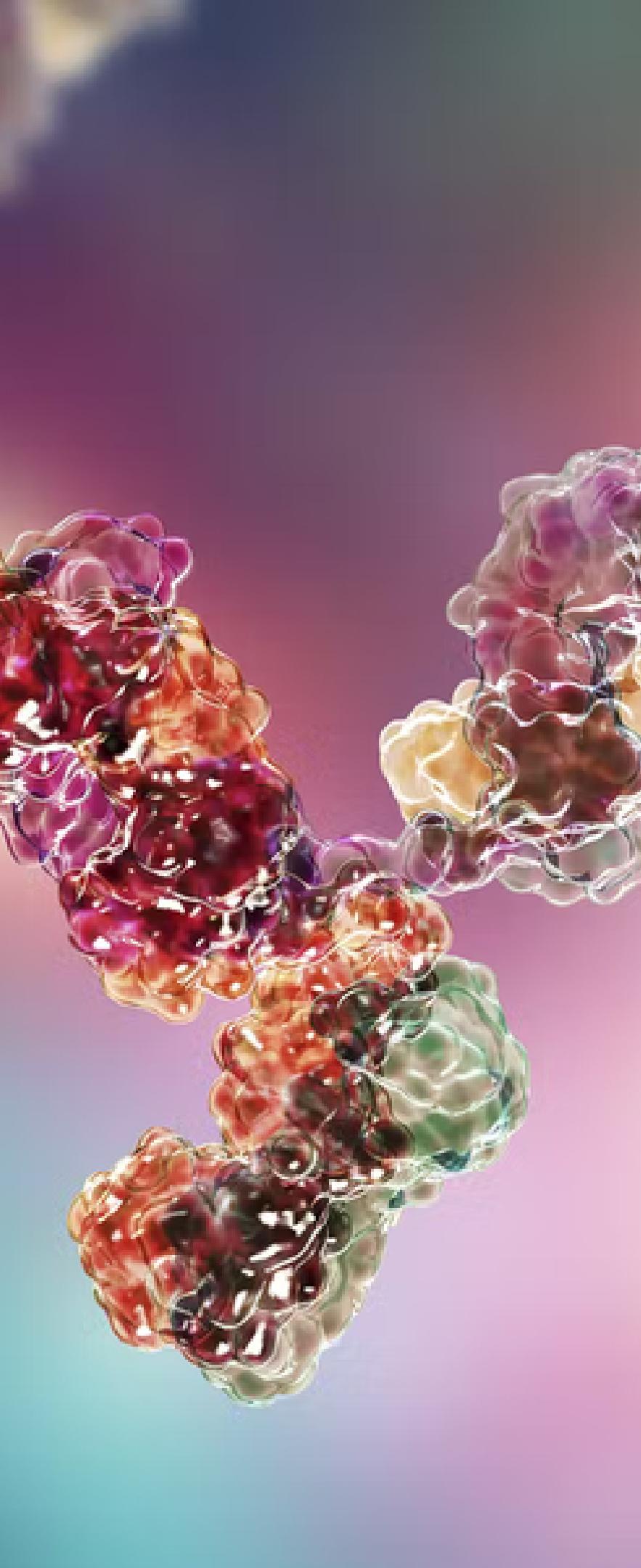
Antigen-antibody complexes are capable of activating the complement cascade (by the classical pathway), resulting in, the activation of leukocytes, lysis of bacterial cells, and increased phagocytosis as a result of opsonization.



Antigen-Antibody Interactions and Their Effects

INTERACTION	EFFECTS
Prevention of attachment	A pathogen coated with antibody is prevented from attaching to a cell. 
Clumping of antigen	Antibodies link antigens together, forming a cluster that phagocytes can ingest. 
Neutralization of toxins	Antibodies bind to toxin molecules to prevent them from damaging cells. 
Help with phagocytosis	Phagocytes can attach more easily to antigens that are coated with antibody. 
Activation of complement	When complement attaches to antibody on a cell surface, a series of reactions begins that activates complement to destroy cells. 
Activation of NK cells	NK cells respond to antibody adhering to a cell surface and attack the cell. 

(Courtesy of Cohen BJ. Memmler's The Human Body in Health and Disease, 11th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.)



Monoclonal Antibodies

- Purified antibodies that are directed against specific antigens have been produced in laboratories by an innovative technique in which a single plasma cell that produces only one specific type of antibody is fused with a rapidly dividing tumor cell.
- Monoclonal antibodies are also being evaluated for possible use in fighting diseases, killing tumor cells, boosting the immune system, and preventing organ rejection.

Hypersensitivity reactions

The term hypersensitivity refers to an overly sensitive or overly reactive immune system.

In such situations, the immune system, in an attempt to protect the person, causes irritation or damage to certain cells and tissues in the body.

Hypersensitivity reactions are divided into two general categories:

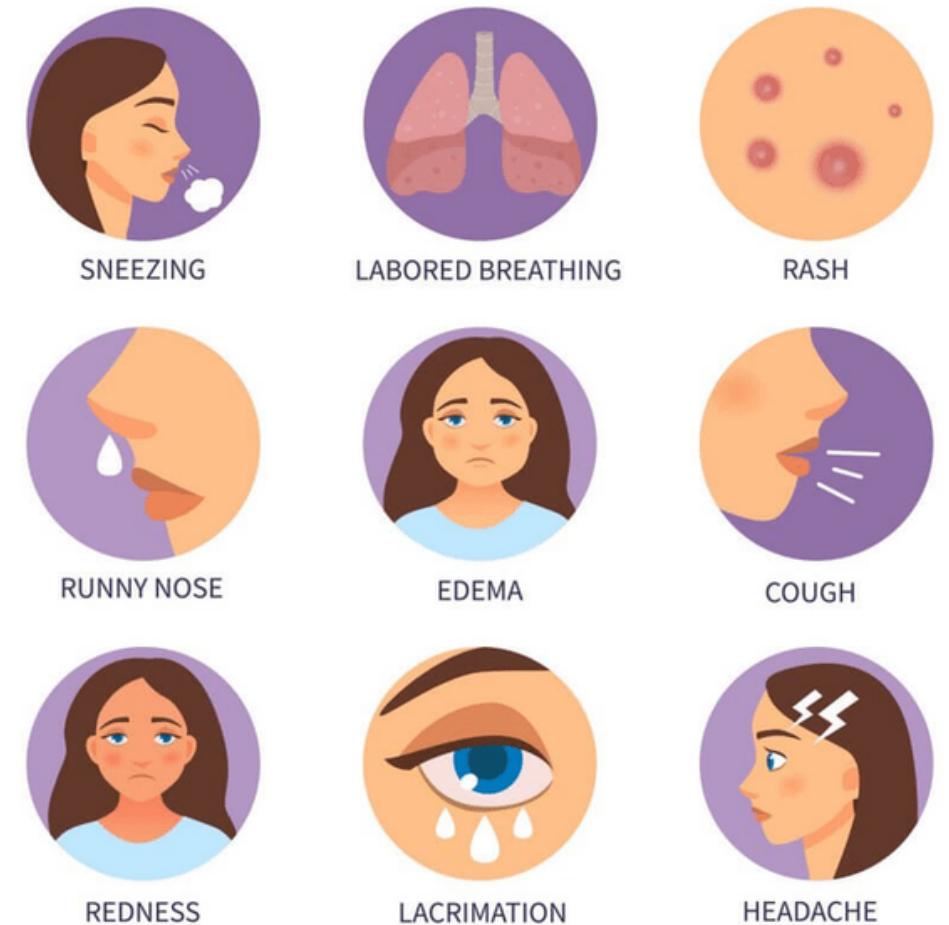
Immediate-type hypersensitivity reactions

- occur from within a few minutes to 24 hours after contact with a particular antigen.
- There are three categories of immediate-type hypersensitivity reactions, referred to as type I, type II, and type III hypersensitivity reactions.

Delayed-type hypersensitivity reactions

- usually takes more than 24 hours to manifest itself.
- Delayed-type hypersensitivity reactions are also known as type IV hypersensitivity reactions and cell-mediated reactions.

ALLERGY SYMPTOMS

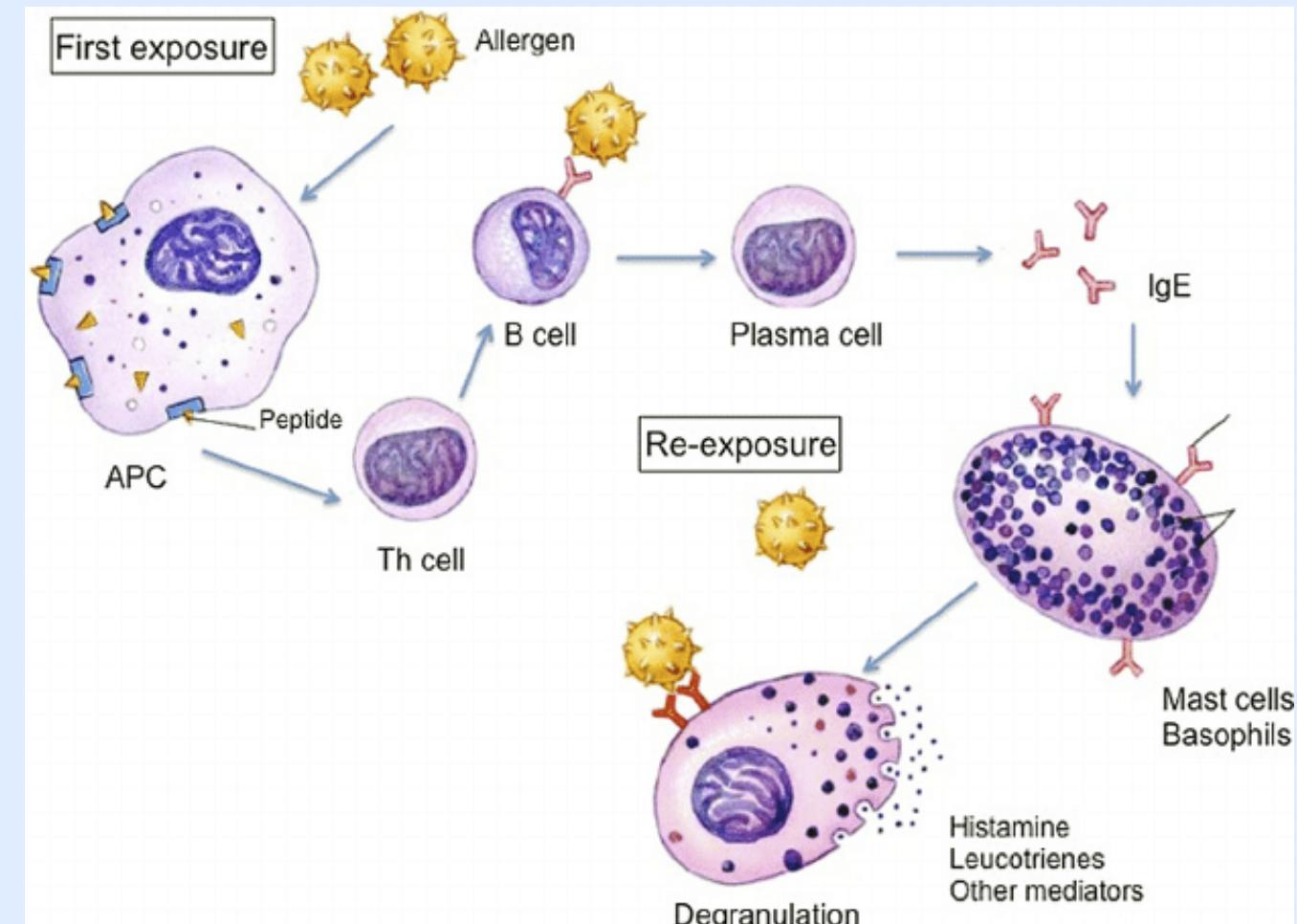


Type I Hypersensitivity Reactions

- also known as anaphylactic reactions.
- This include classic allergic responses such as hay fever symptoms, asthma, hives, and gastrointestinal symptoms that result from food allergies; allergic responses to insect stings and drugs; and anaphylactic shock.
- **Localized reactions** usually involve mast cell degranulation, whereas **systemic reactions** usually involve basophil degranulation.

The Allergic Response

- People who are prone to allergies are described as being atopic.
- They produce IgE antibodies when they are exposed to allergens (antigens that cause allergic reactions). Following their production, IgE antibodies bind to the surface of basophils and mast cells.
- Degranulation of the basophils and mast cells occurs when allergen binds to these IgE antibodies.



Localized Anaphylaxis

- The reaction is limited to a specific target tissue or organ.
- Tendency to manifest localized anaphylactic reactions is inherited and is called **atopy**.
- Atopic allergies, which afflict at least 20% of the population in developed countries.
- include a wide range of IgE-mediated disorders (e.g. allergic rhinitis, asthma, atopic dermatitis, food allergies)

Systemic Anaphylaxis

- this occurs throughout the body and thus tends to be a more serious condition than localized anaphylaxis. It may lead to a severe, potentially fatal condition known as anaphylactic shock.
- The shock reaction usually occurs immediately (within 20 minutes) after re-exposure to the allergen.
- The first symptoms are flushing of the skin with itching, headache, facial swelling, and difficulty breathing; this is followed by falling blood pressure, nausea, vomiting, abdominal cramps, and urination (caused by smooth muscle contractions). In many cases, acute respiratory distress, unconsciousness, and death may follow shortly.



Mild, localized symptoms

Generalized allergic reaction

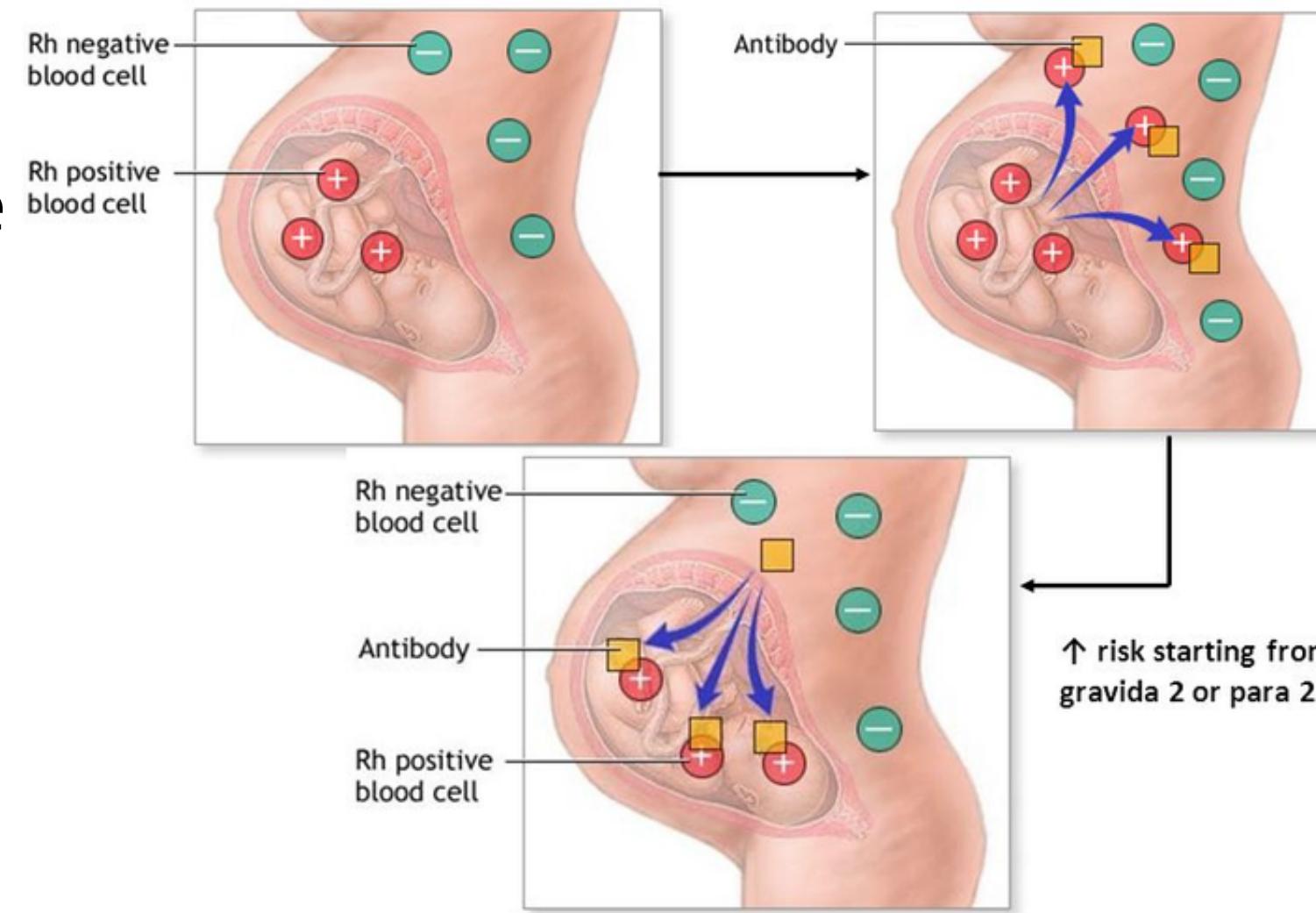
Anaphylaxis

Severe anaphylaxis

Type II Hypersensitivity Reactions

- are cytotoxic reactions, meaning that body cells are destroyed during these reactions.
- include the cytotoxic reactions that occur in incompatible blood transfusions, Rh incompatibility reactions, and myasthenia gravis; all of these reactions involve IgG or IgM antibodies and complement.

ERYTHROBLASTOSIS FETALIS

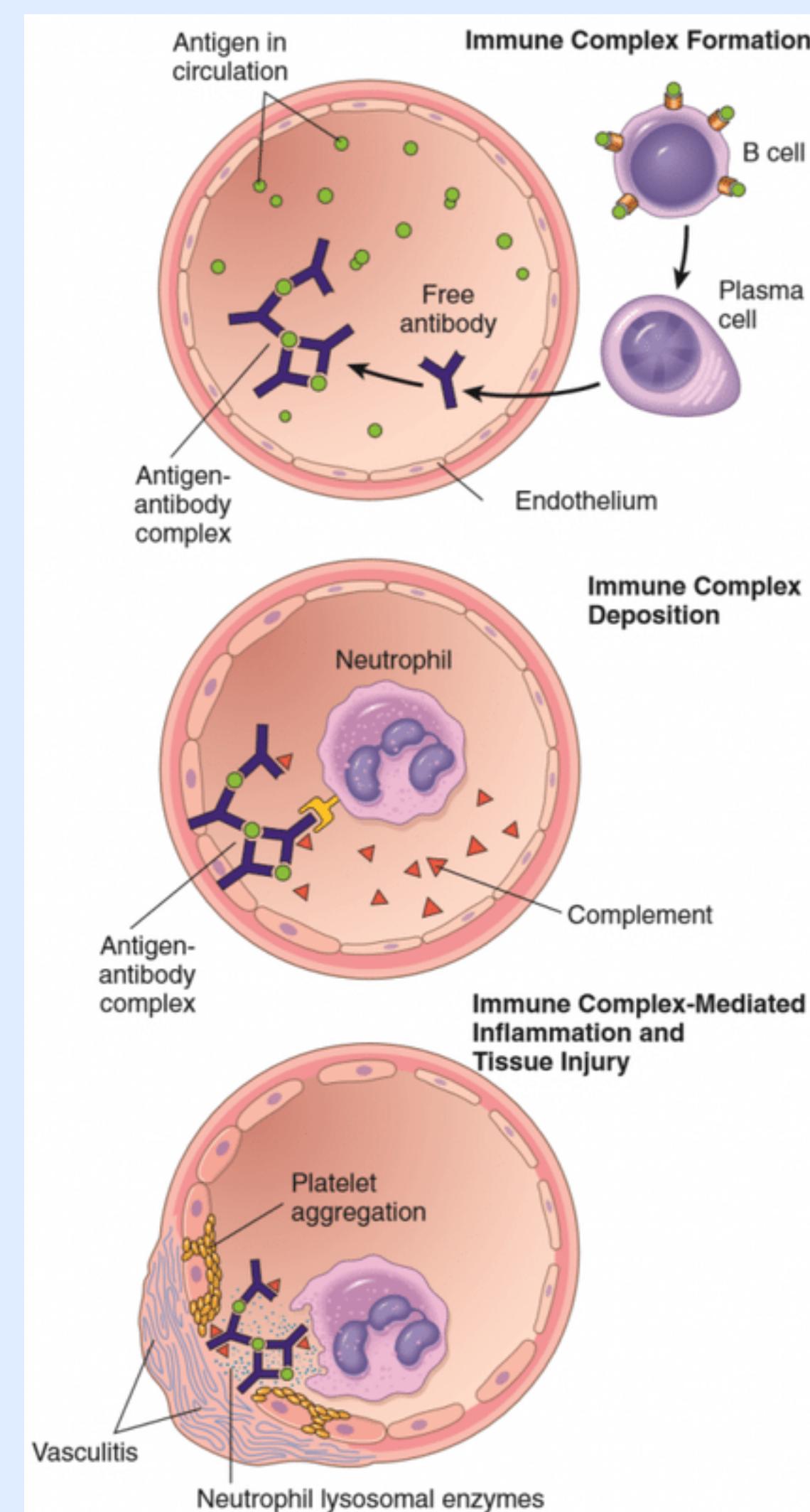


A typical type II hypersensitivity reaction might follow this sequence:

- Step 1.** A particular drug binds to the surface of a body cell.
- Step 2.** Antidrug antibodies then bind to the drug.
- Step 3.** This initiates complement activation on the cell surface.
- Step 4.** The complement cascade leads to lysis of the body cell.

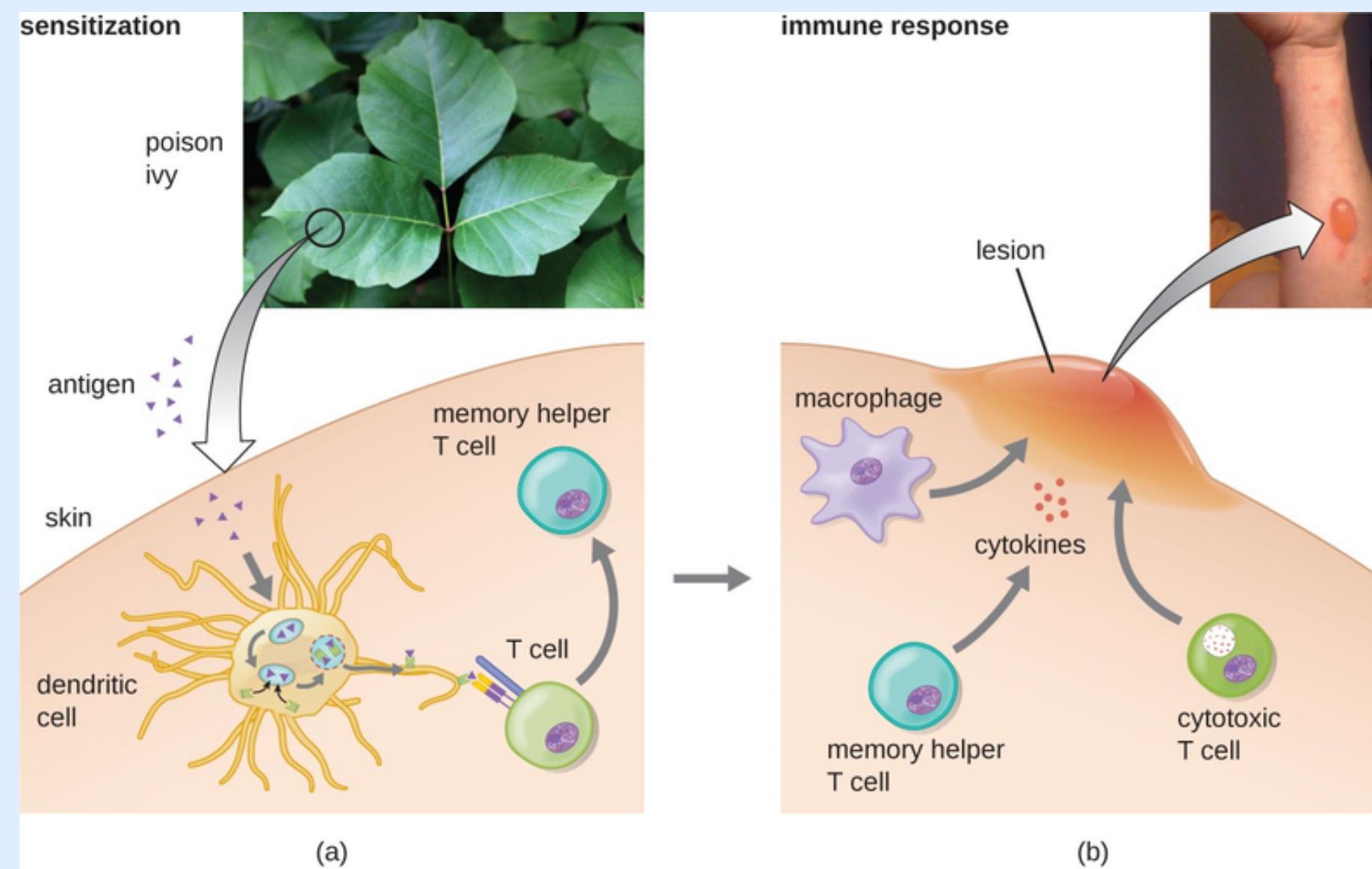
Type III Hypersensitivity Reactions

- occurs when there is an excess of antigen, leading to small immune complexes being formed that fix complement and are not cleared from the circulation.
- It involves soluble antigens that are not bound to cell surfaces (as opposed to those in type II hypersensitivity).
- Examples: Serum sickness, Arthus reaction



Type IV Hypersensitivity Reactions

- Type IV hypersensitivity reactions are also known as delayed-type hypersensitivity reactions or cell-mediated immune reactions. They typically take 24 to 48 hours to manifest themselves.
- It can occur in response to contact with certain allergens resulting in what is called contact dermatitis or in response to some diagnostic procedures as in the tuberculin skin test



Autoimmune Diseases

- An autoimmune disease results when a person's immune system attacks that person's body tissues as if they were nonself or foreign.
- This may occur with certain tissues that are not exposed to the immune system during fetal development, so that they are not recognized as self. Such tissues may include the lens of the eye, the brain and spinal cord, and sperm.

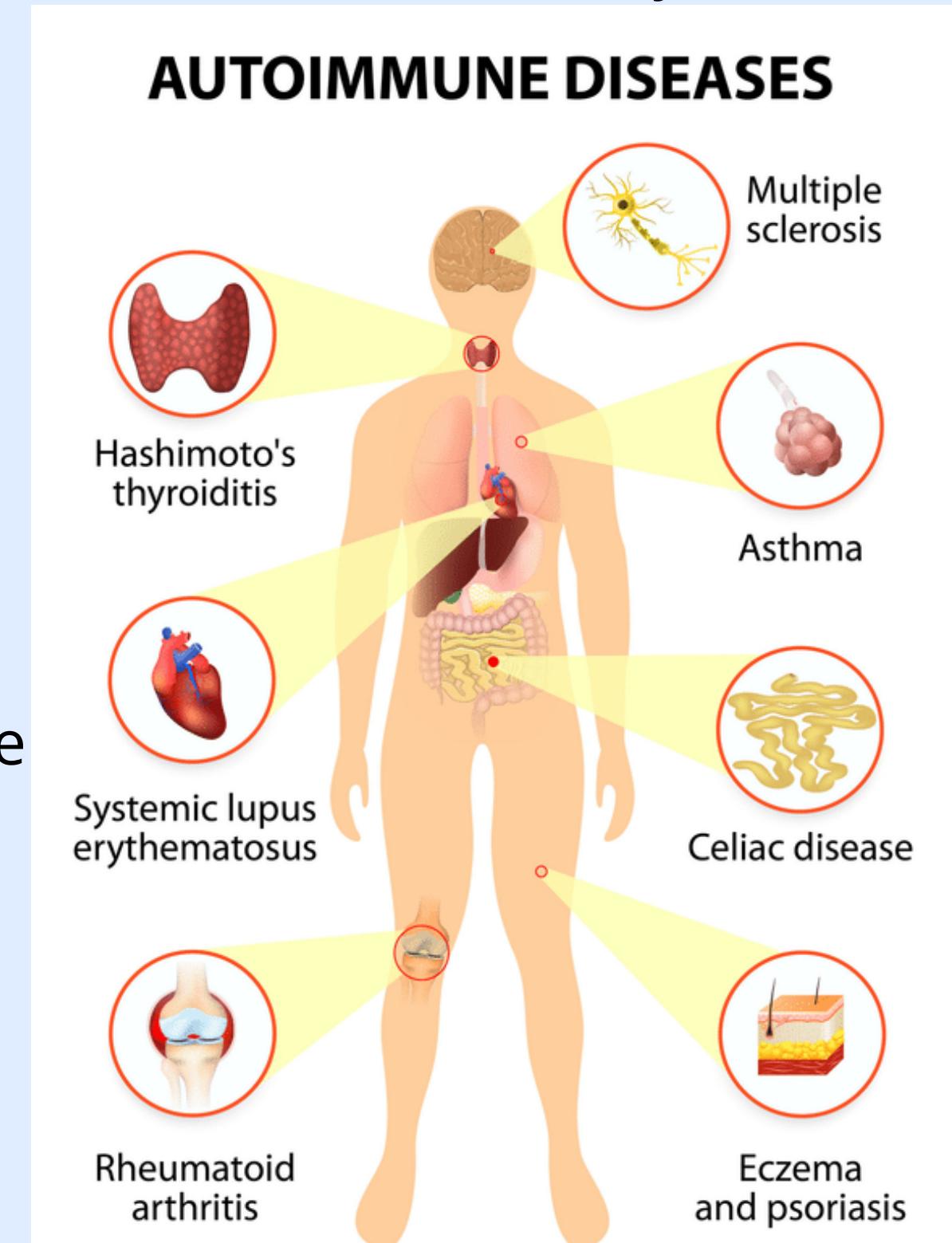
Autoimmune diseases can be classified as organ-specific and non-organ-specific:

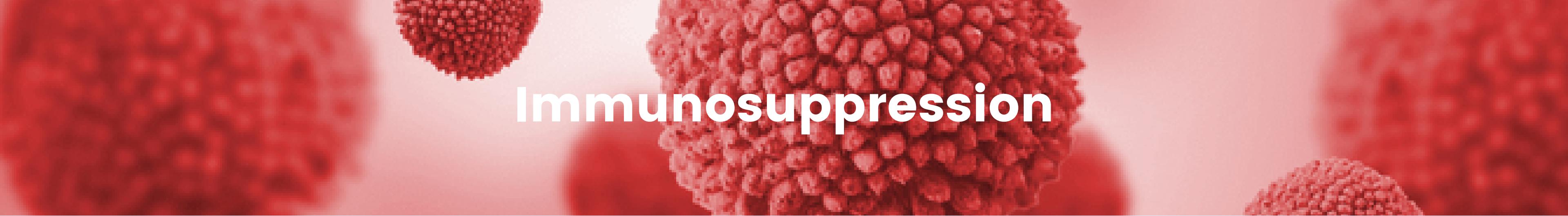
Organ specific autoimmune diseases - are those where a particular organ or tissue is preferentially targeted by the patient's immune system.

Examples: Type 1 diabetes, Addison disease, Myasthenia gravis.

Non-organ specific autoimmune diseases - the autoantibodies are not organ restricted and present in many different tissues

Examples: Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Dermatomyositis.



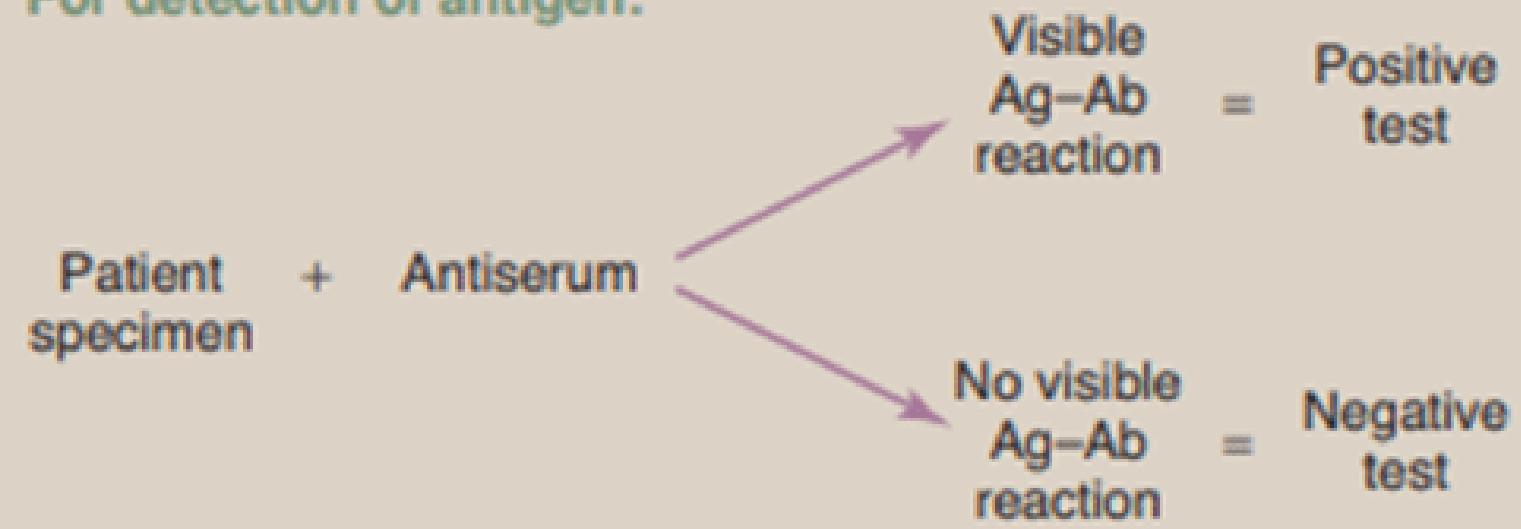


Immunosuppression

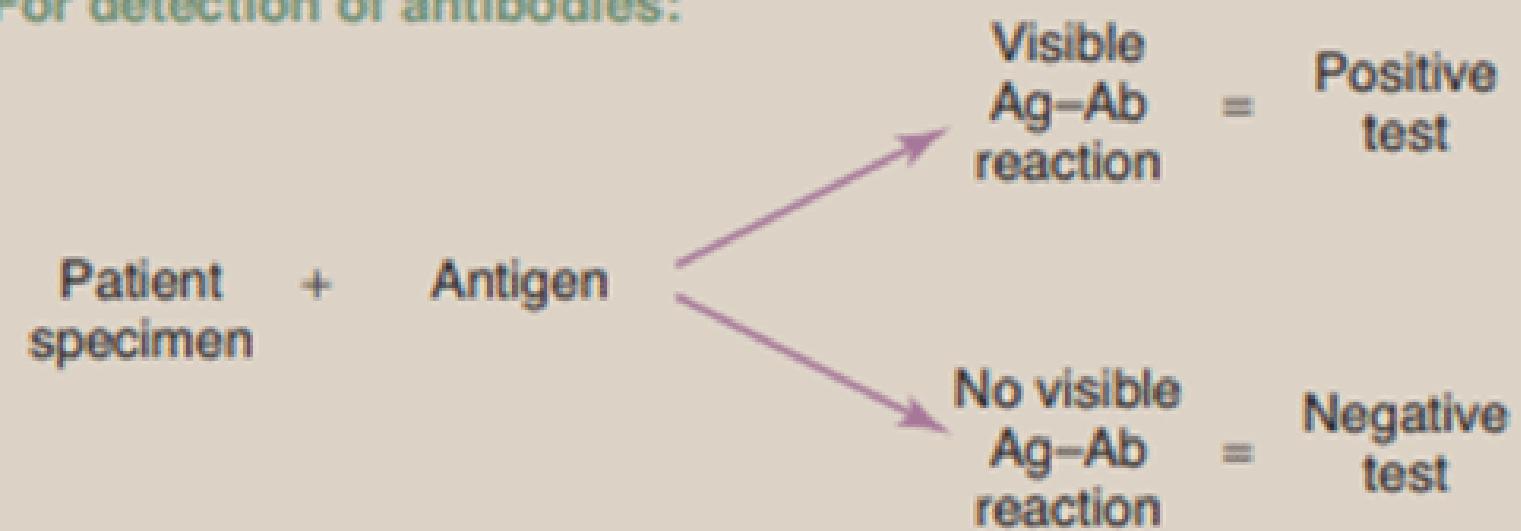
- If a person's immune system is not functioning properly, that person is said to be immunosuppressed, immunodepressed, or immunocompromised.
- Persons who produce an insufficient amount of antibodies are said to have **hypogammaglobulinemia**. Their resistance to infection is lower than normal, so they usually do not recover from infectious diseases as readily as most other persons. One type, called Bruton's hypogammaglobulinemia, is a hereditary disease in which the numbers of circulating B cells are profoundly low or totally absent.
- The most common cause of immune deficiency worldwide is malnutrition. In addition, there are acquired and inherited immunodeficiencies.
 - **Acquired immunodeficiencies** - may be caused by drugs (e.g., cancer chemotherapeutic agents and drugs given to transplant patients), irradiation, or certain infectious diseases (e.g., HIV infection)
 - **Inherited immunodeficiencies**- can be the result of deficiencies in antibody production, complement activity, phagocytic function, or NK cell function.

Immunodiagnostic Procedures

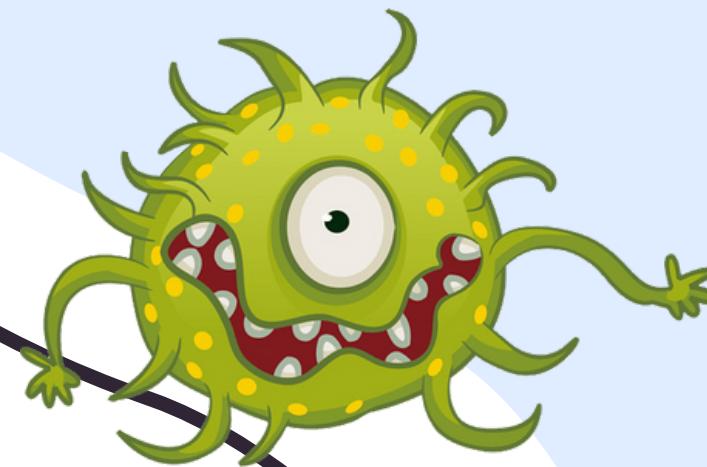
For detection of antigen:



For detection of antibodies:



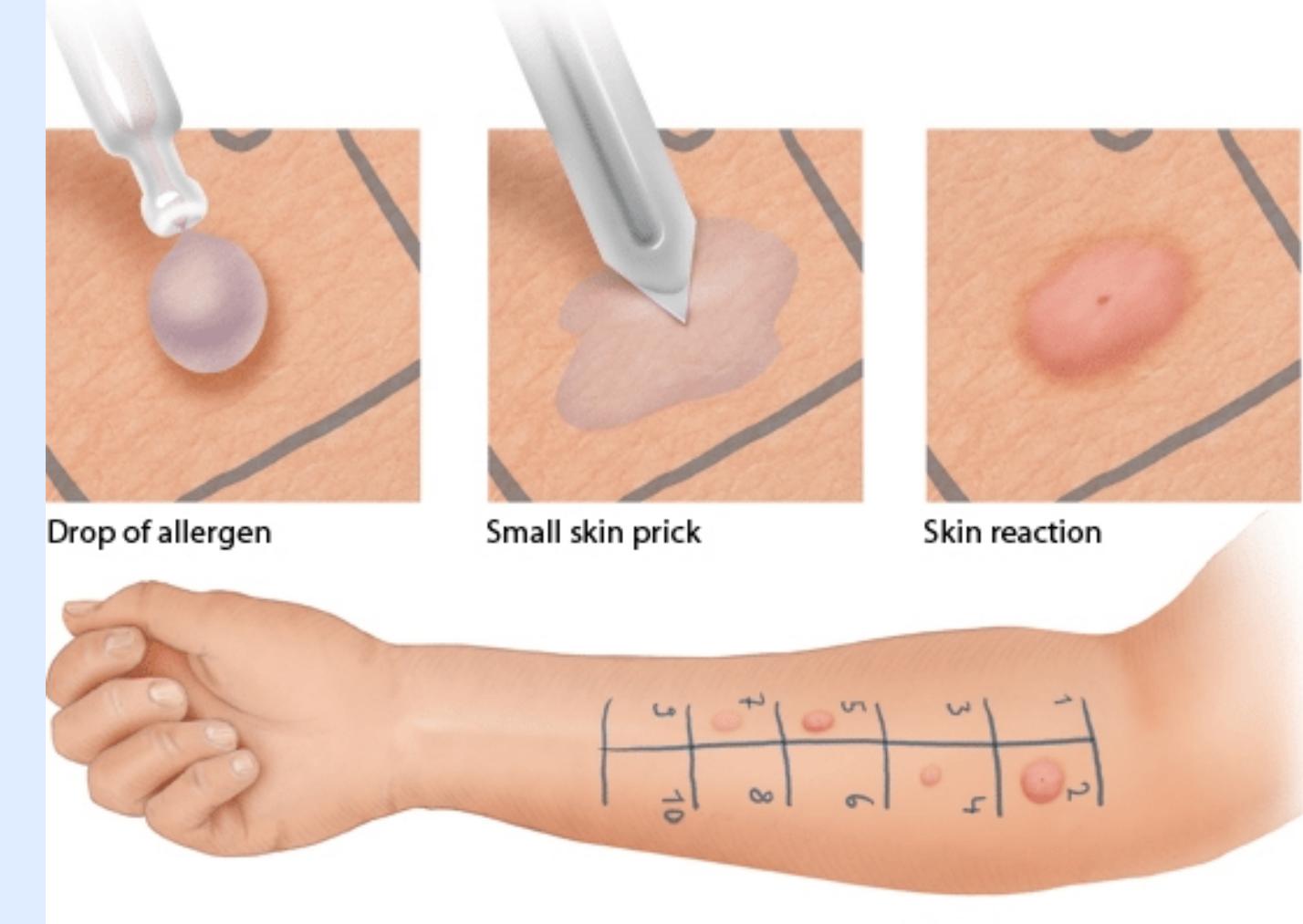
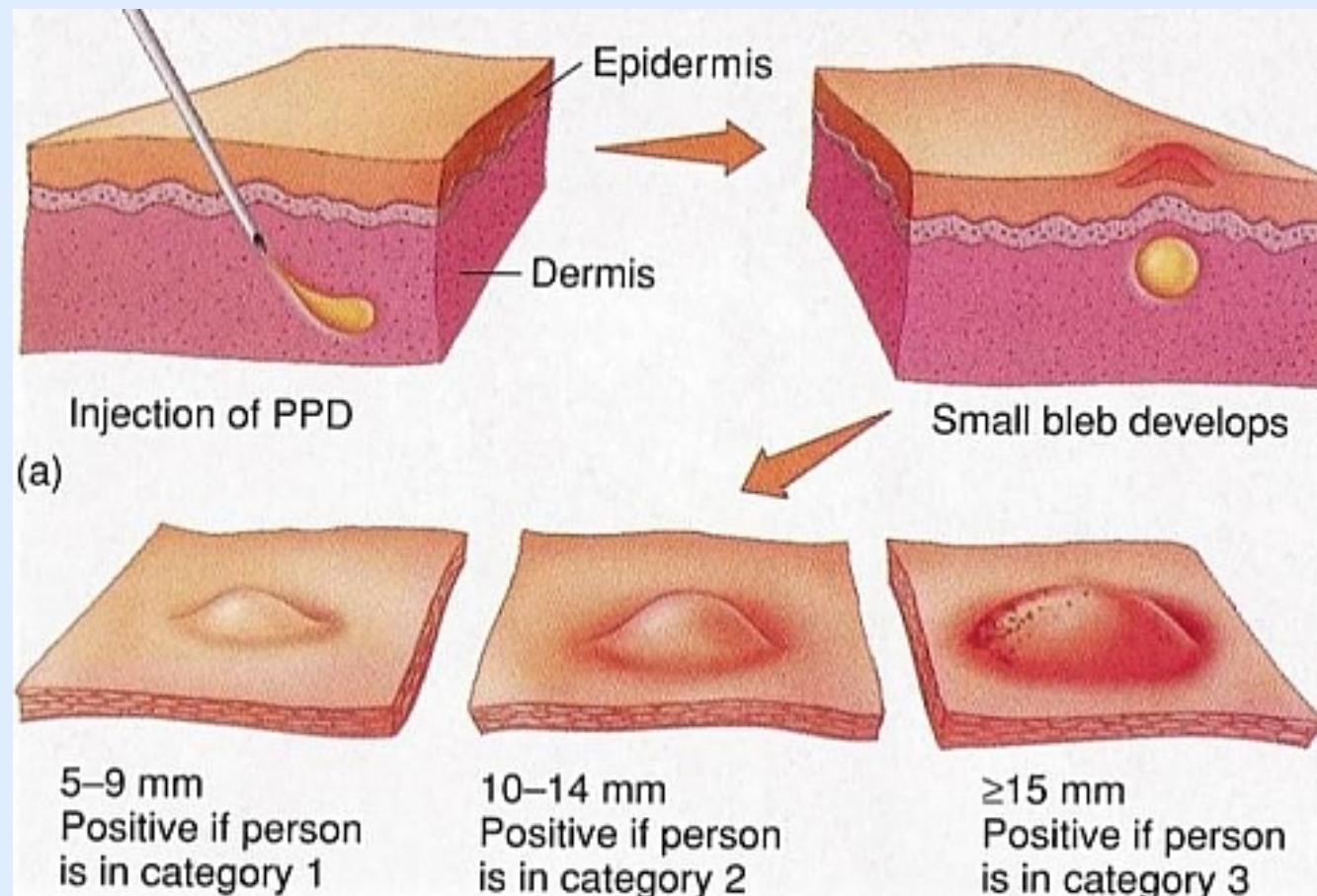
Immunodiagnostic Procedures for Detection of Antibodies in a Patient's Serum



REACTION IN VITRO	REAGENTS			RESULTS	
	Antigen	Antibody	Other	Positive	Negative
Agglutination	Red blood cells or bacteria	Patient's serum		Clumping	No clumping
Precipitin	Toxins, hormones, proteins	Patient's serum	Agar or solution	Precipitate	No precipitate
Lysis by Complement	Cells, bacteria	Patient's serum	Complement	Lysis	No lysis
Fluorescent Antibody Technique	Pathogen	Patient's serum	Fluorescein-tagged rabbit antihuman antiserum	Fluorescent pathogen	No fluorescence
Capsular Swelling (Quellung Reaction)	Encapsulated bacteria	Patient's serum		Capsule appears to swell	No appearance of swelling
Enzyme-linked assay	Test microbe	Patient's serum	Enzyme-linked antibody + Substrate	Color change	No color change

Skin Testing as a Diagnostic Tool

- Skin testing is another type of IDP, but one that is performed *in vivo* (in the patient) rather than *in vitro* (in the laboratory).
- In skin testing, antigens are injected within or beneath the skin (intradermally or subcutaneously, respectively).
- An example of a commonly used skin test is the TB skin test
- Skin testing is also used to determine the allergens to which an atopic individual is allergic.



Procedures Used in the Diagnosis of Immunodeficiency Disorders



- In addition to IDPs, tests are performed in the Immunology Laboratory that enable the assessment of a patient's immune status and evaluation of immunodeficiency disorders.
- These include tests to diagnose B-cell deficiency states (humoral immunodeficiencies), cell-mediated immunodeficiencies, combined humoral and cell mediated immunodeficiencies, phagocytic deficiency states, and complement deficiencies.

Thank you!

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Joanna Marie Bernal
Jarmil Edward Santos