IMMUNOLOGICAL DISORDERS

IMMUNITY

- Is the state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion.
- It is the capability of the body to resist harmful microbes from entering it.
- Immunity involves both specific and non-specific components

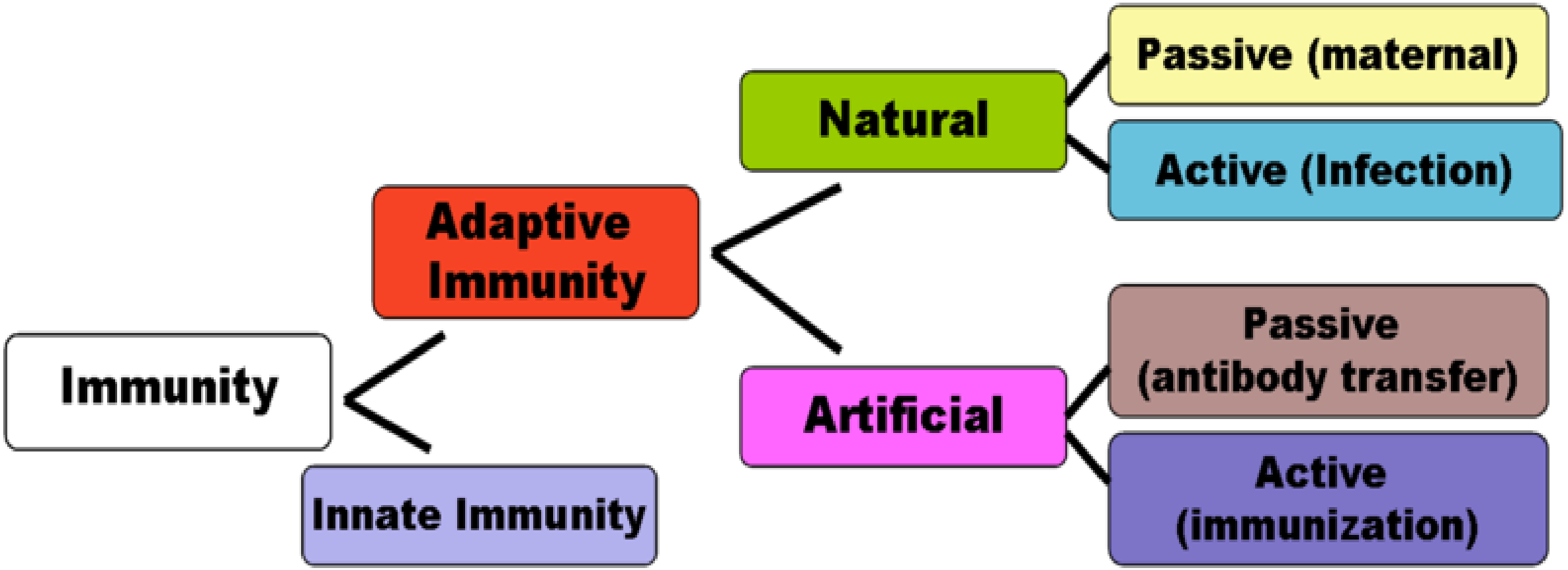
IMMUNE SYSTEM

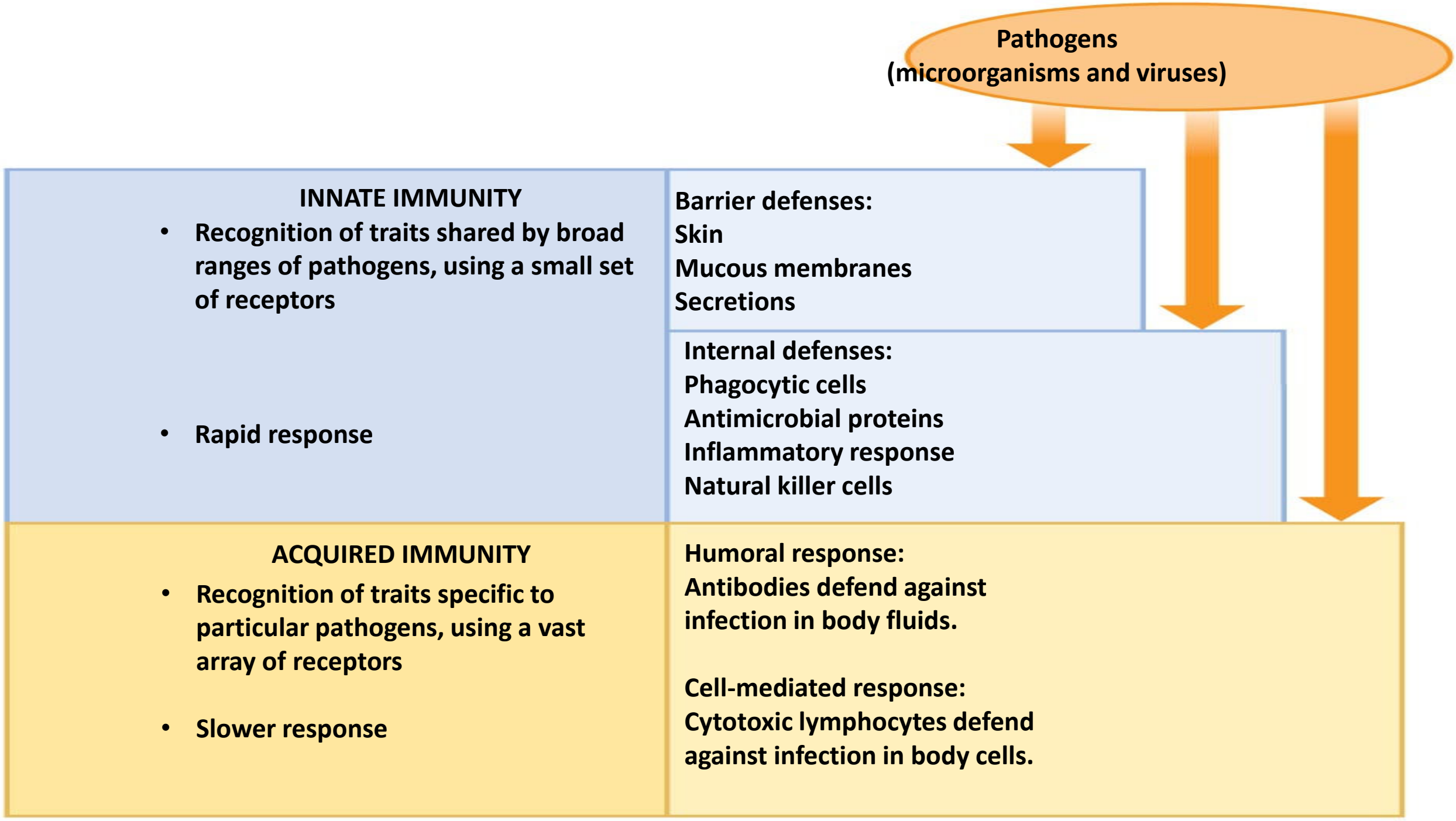
- is a system of biological structures and processes within an organism that protects against disease.
- To function properly, an immune system must detect a wide variety of agents, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue.
- The immune system recognizes foreign bodies and responds with the production of immune cells and proteins
- Barriers help an organism to defend itself from the many dangerous pathogens it may encounter

BARRIER DEFENSES

- Barrier defenses include the skin and mucous membranes of the respiratory, urinary, and reproductive tracts
- Mucus traps and allows for the removal of microbes
- Many body fluids including saliva, mucus, and tears are hostile to microbes
- The low pH of skin and the digestive system prevents growth of microbes

CLASSIFICATION





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INNATE IMMUNITY

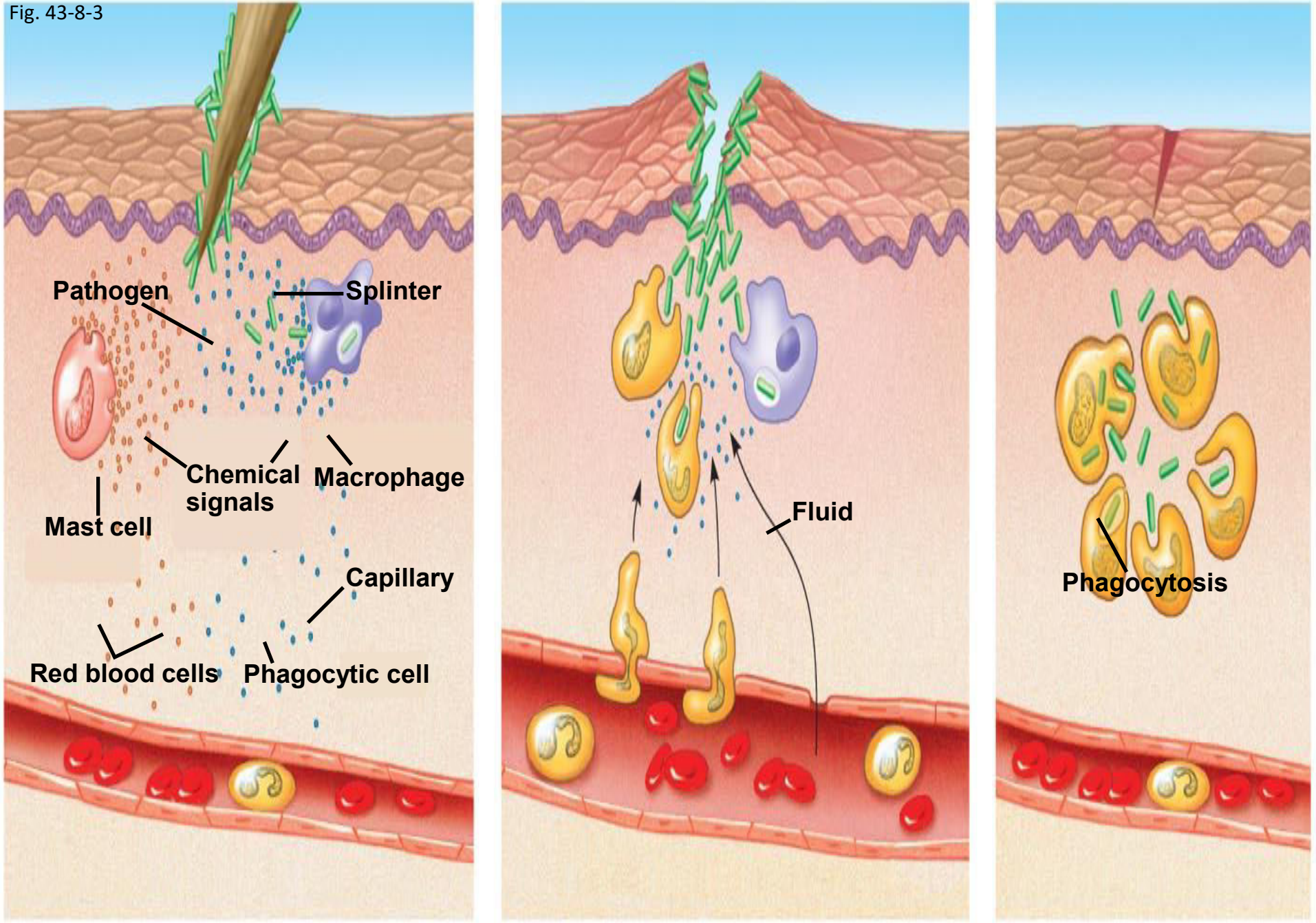
- nonspecific immunity
- is the natural resistances with which a person is born.
- It provides resistances through several physical, chemical and cellular approaches.
- Microbes first encounter the epithelial layers, physical barriers that line skin and mucous membranes.
- Subsequent general defenses include secreted chemical signals (cytokines), antimicrobial substances, fever, and phagocytic activity associated with the inflammatory responses.
- The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes.
- Through these approaches, innate immunity can prevent the colonization, entry and spread of microbes.

- A white blood cell engulfs a microbe, then fuses with a lysosome to destroy the microbe
- There are different types of phagocytic cells:
- Neutrophils engulf and destroy microbes
- Macrophages are part of the lymphatic system and are found throughout the body
- Eosinophils discharge destructive enzymes
- Dendritic cells stimulate development of acquired immunity

Inflammatory Responses

- Following an injury, mast cells release histamine, which promotes changes in blood vessels; this is part of the inflammatory response
- These changes increase local blood supply and allow more phagocytes and antimicrobial proteins to enter tissues
- Pus, a fluid rich in white blood cells, dead microbes, and cell debris, accumulates at the site of inflammation

Fig. 43-8-3



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ACQUIRED IMMUNITY

- Adaptive immunity /Specific
- sub-divided into two major types depending on how the immunity was introduced:
- **Naturally acquired immunity** occurs through contact with a disease causing agent, when the contact was not deliberate
- **Artificially acquired immunity** develops only through deliberate actions such as vaccination.

N/B:

Memory cells are only produced in active immunity.

Protection for active immunity is permanent whereas in passive immunity it is only temporary.

Antigens are only encountered in active immunity.

Active immunity takes several weeks to become active but passive is immediate**.**

NATURAL ACQUIRED IMMUNITY

- Subdivided into:
- **Naturally acquired active immunity:** occurs when a person is exposed to a live pathogen, and develops a primary immune response, which leads to immunological memory. This type of immunity is “natural” because it is not induced by deliberate exposure. Many disorders of immune system function can affect the formation of active immunity such as immunodeficiency (both acquired and congenital forms) and immunosuppression.
- **Naturally acquired passive immunity:** Maternal passive immunity is a type of naturally acquired passive immunity, and refers to antibody-mediated immunity conveyed to a fetus by its mother during pregnancy through placenta. IgG is the only antibody isotype that can pass through the placenta. Passive immunity is also provided through the transfer of IgA antibodies found in breast milk that are transferred to the gut of the infant, protecting against bacterial infections, until the newborn can synthesize its own antibodies.

ARTIFICIAL ACQUIRED IMMUNITY

- **Artificially acquired active immunity:** can be induced by a vaccine, a substance that contains antigen. A vaccine stimulates a primary response against the antigen without causing symptoms of the disease.
- **Artificially acquired passive immunity:** is a short-term immunization induced by the transfer of antibodies, which can be administered in several forms; as human or animal blood plasma, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, and in the form of monoclonal antibodies (MAb). Passive transfer is used prophylactically in the case of immunodeficiency diseases, such as hypogammaglobulinemia. It is also used in the treatment of several types of acute infection, and to treat poisoning. Immunity derived from passive immunization lasts for only a short period of time, and there is also a potential risk for hypersensitivity reactions, and serum sickness, especially from gamma globulin of non-human origin.

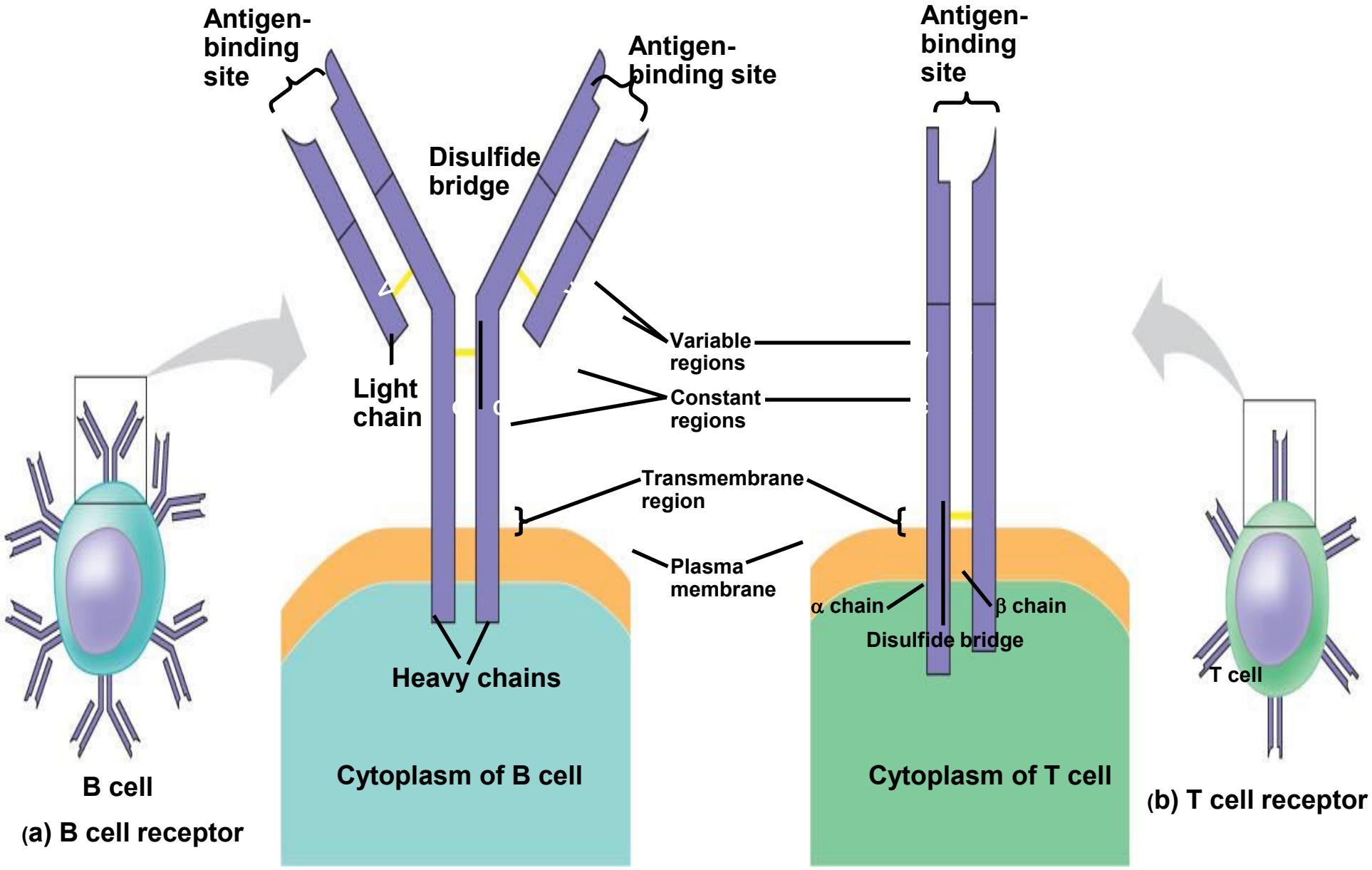
IN ACQUIRED IMMUNITY, LYMPHOCYTE RECEPTORS PROVIDE PATHOGEN-SPECIFIC RECOGNITION

- White blood cells called **lymphocytes** recognize and respond to antigens, foreign molecules
- Lymphocytes that mature in the **thymus** above the heart are called **T cells**, and those that mature in bone marrow are called **B cells**
- Lymphocytes contribute to immunological memory, an enhanced response to a foreign molecule encountered previously
- **Cytokines** are secreted by macrophages and dendritic cells to recruit and activate lymphocytes
- The acquired immune system has three important properties:
- Receptor diversity
- A lack of reactivity against host cells
- Immunological memory

ACQUIRED IMMUNITY: AN OVERVIEW

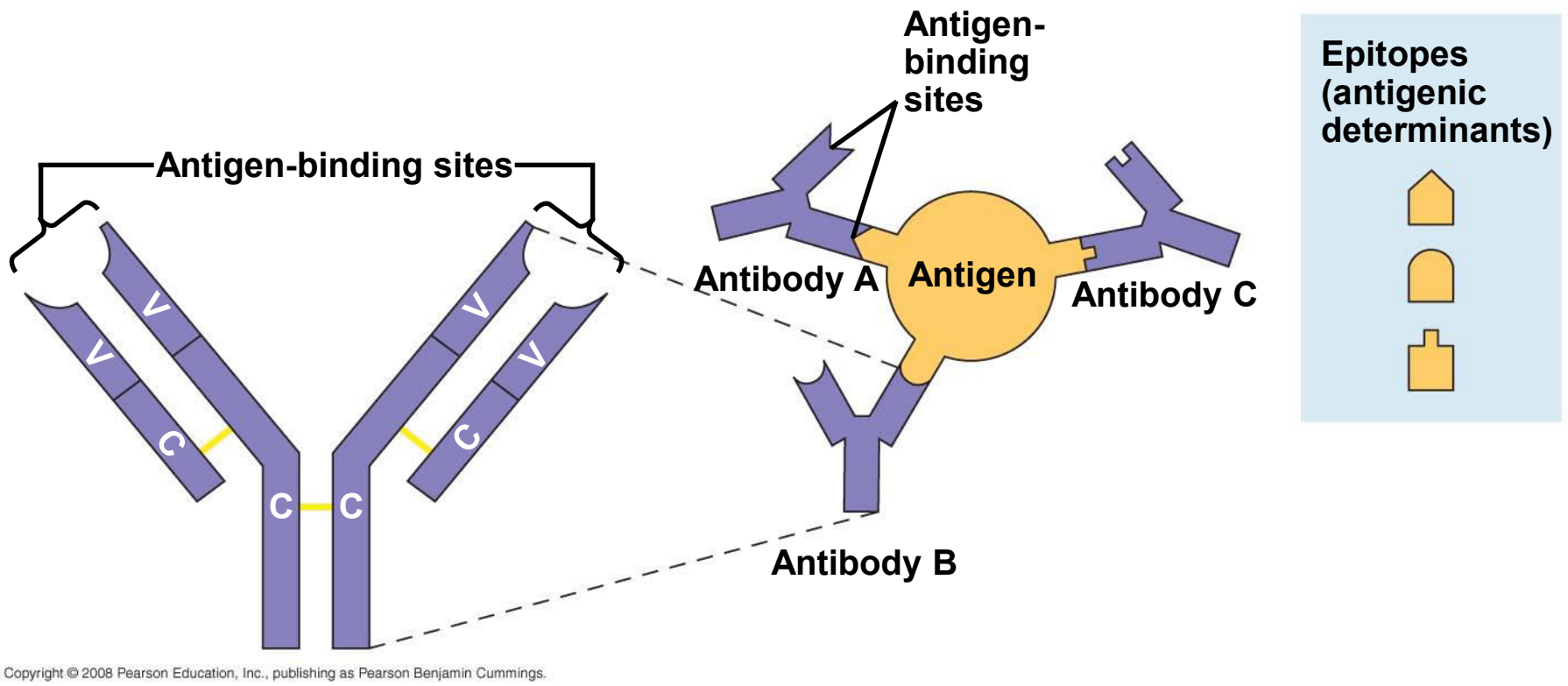
- B cells and T cells have receptor proteins that can bind to foreign molecules
- Each individual lymphocyte is specialized to recognize a specific type of molecule
- All antigen receptors on a single lymphocyte recognize the same epitope, or antigenic determinant, on an antigen
- B cells give rise to plasma cells, which secrete proteins called **antibodies or immunoglobulins**

Fig. 43-9



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Fig. 43-10

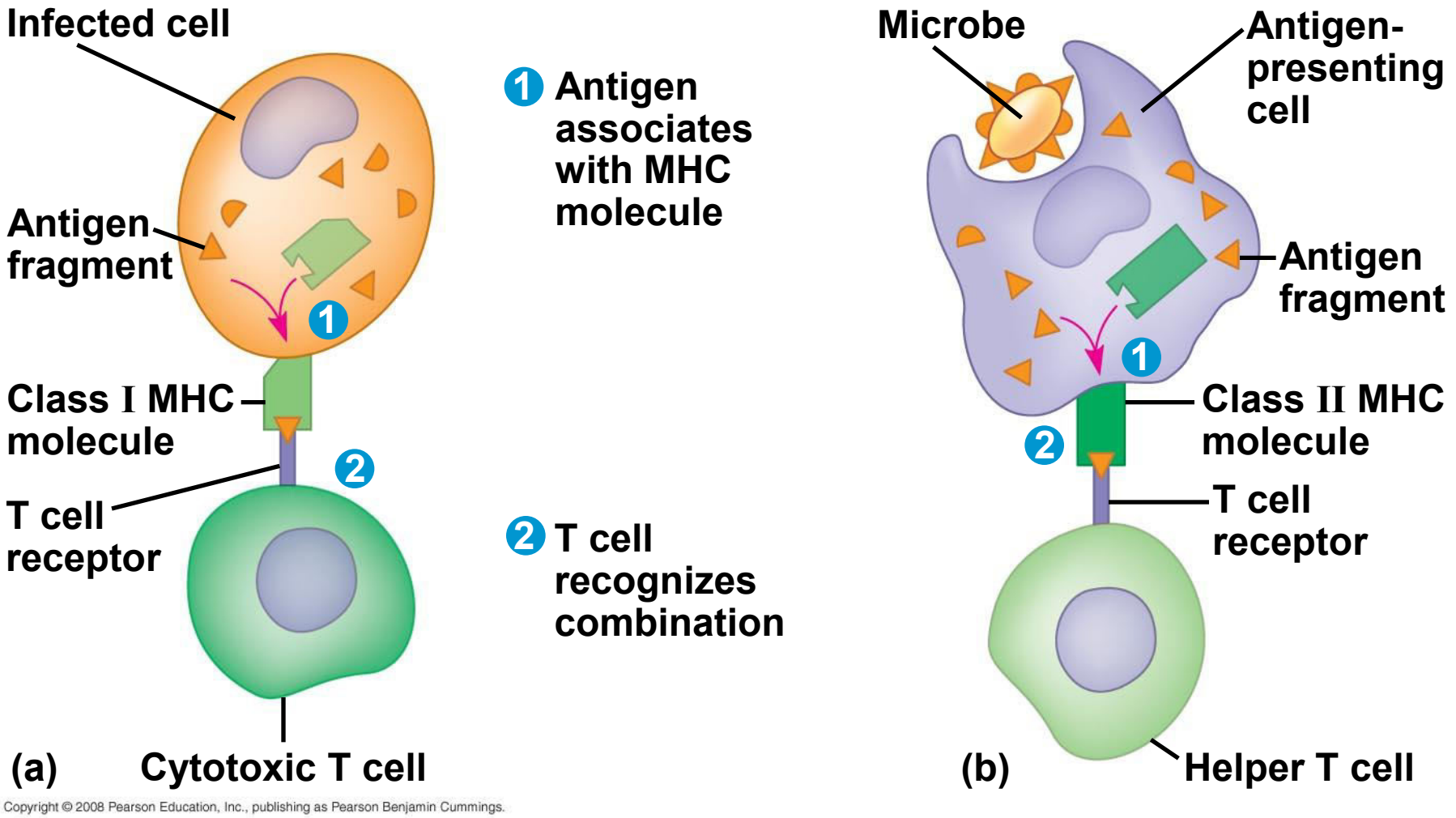


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THE ROLE OF THE MHC

- In infected cells, MHC molecules bind and transport antigen fragments to the cell surface, a process called **antigen presentation**
- A nearby T cell can then detect the antigen fragment displayed on the cell's surface
- Depending on their source, peptide antigens are handled by different classes of MHC molecules:
- Class I MHC molecules are found on almost all nucleated cells of the body
- They display peptide antigens to cytotoxic T cells
- Class II MHC molecules are located mainly on dendritic cells, macrophages, and B cells
- Dendritic cells, macrophages, and B cells are antigen-presenting cells that display antigens to cytotoxic T cells and helper T cells

Fig. 43-12



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Hypersensitivity Reactions

A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign agent.

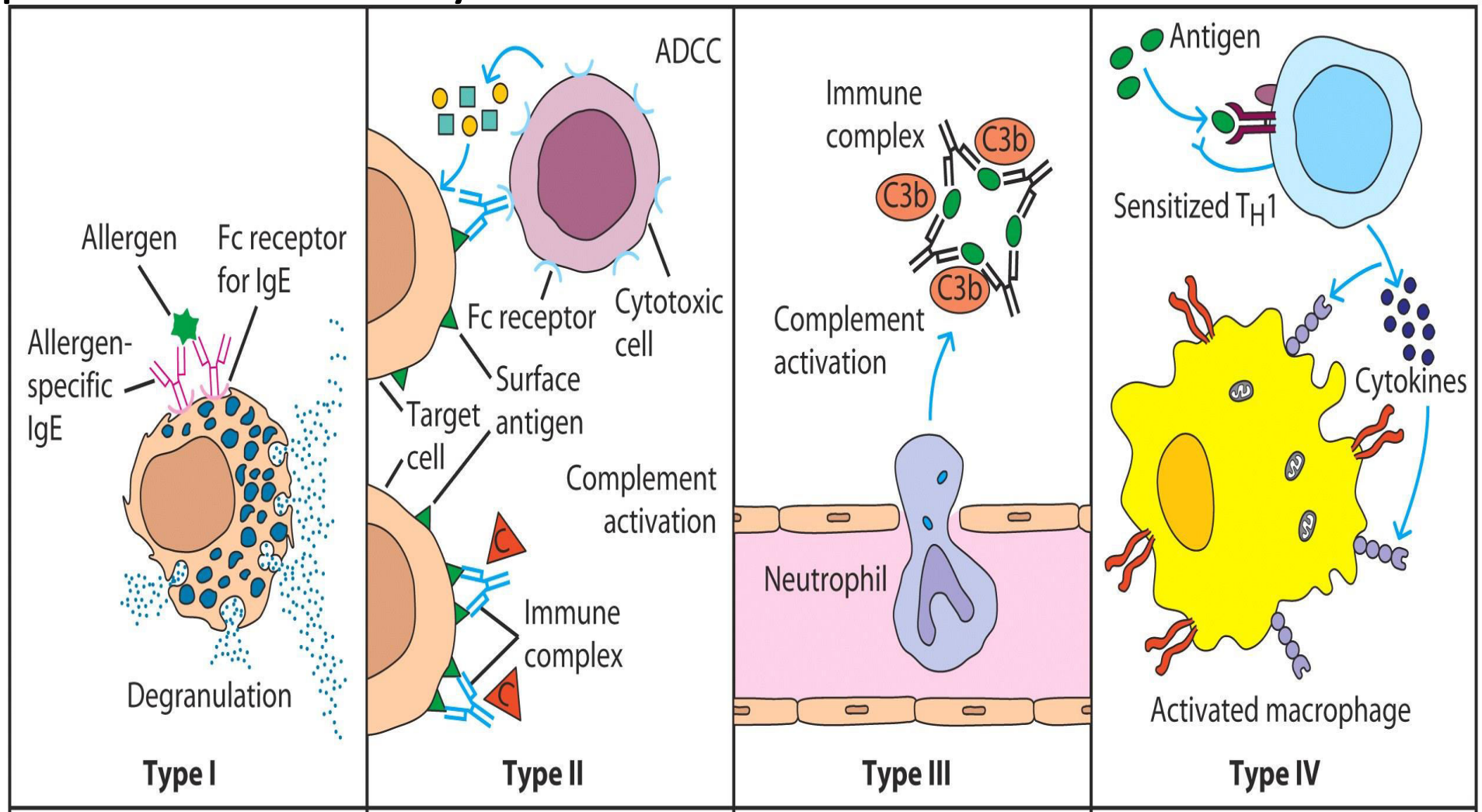
Four Types of Hypersensitivity Reactions:

- **Type I (Anaphylactic) Reactions**
- **Type II (Cytotoxic) Reactions**
- **Type III (Immune Complex) Reactions**
- **Type IV (Cell-Mediated) Reactions**

Hypersensitivity

- 4 types of HS
  - Type I: IgE-mediated degranulation of mast cells → acute anaphylactic response
  - Type II: IgG / IgM on cells → c' lysis
  - Type III: Immune complexes → c' activation, inflammation
  - Type IV: T_{DTH} activate macs → chronic inflammation
- Types I – III involve Abs, Type IV is CMIR

Hypersensitivity Reactions



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity

Type I (Anaphylactic) Reactions

- Occur within minutes of exposure to antigen
- Antigens combine with IgE antibodies
- IgE binds to mast cells and basophils, causing them to undergo *degranulation* and release several mediators:
  - Histamine: Dilates and increases permeability of blood vessels (swelling and redness), increases mucus secretion (runny nose), smooth muscle contraction (bronchi).
  - Prostaglandins: Contraction of smooth muscle of respiratory system and increased mucus secretion.
  - Leukotrienes: Bronchial spasms.
- Anaphylactic shock: Massive drop in blood pressure. Can be fatal in minutes.

Fig

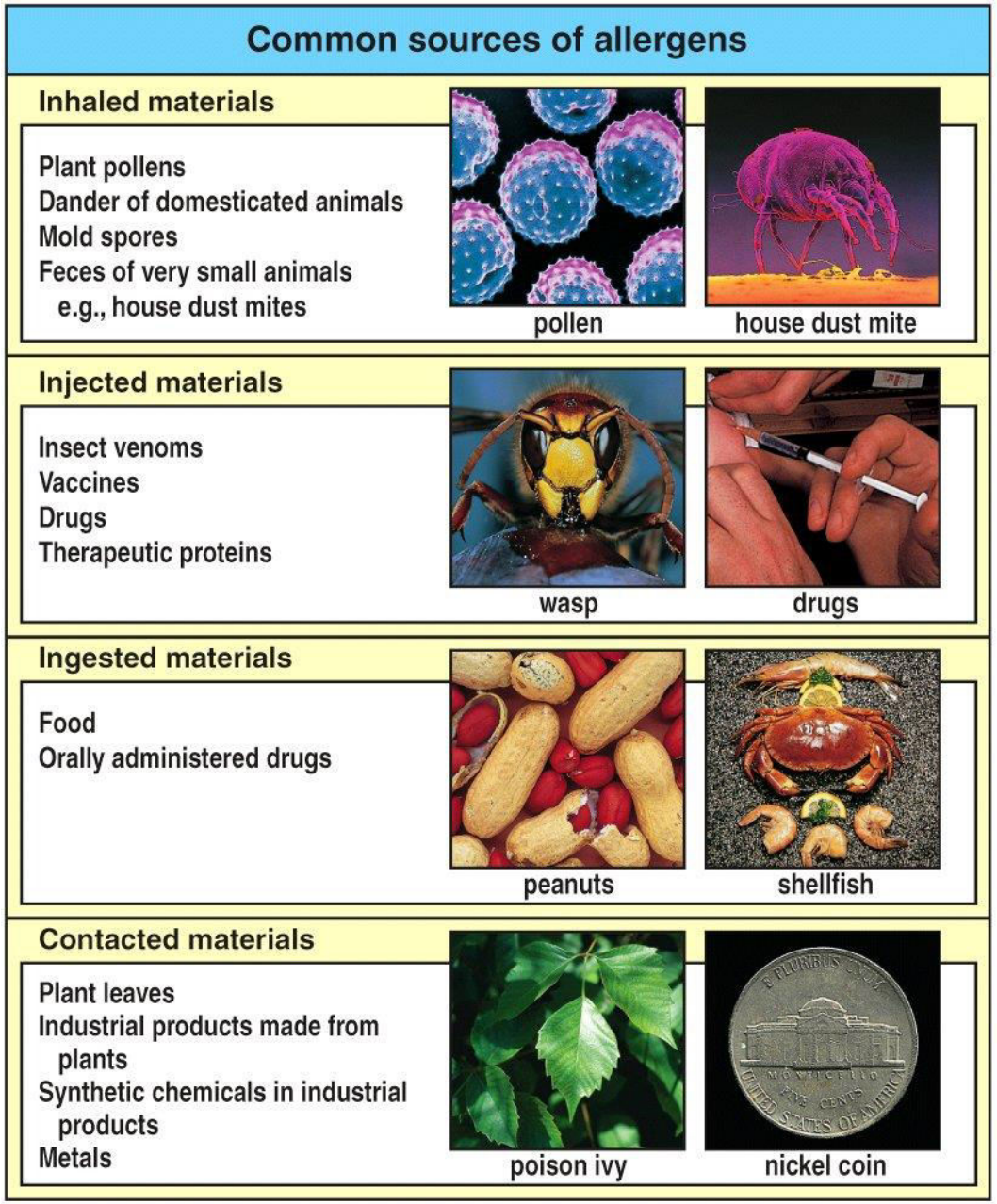


Figure 10-1 The Immune System, 2/e (© Garland Science 2005)

Type I HS Reactions

- Localized anaphylaxis (atopy)
  - cutaneous anaphylaxis – wheal & flare
    - (P-K Rx)
  - urticaria
  - allergic rhinitis (hay fever)
  - food allergies
  - atopic dermatitis (allergic eczema)
  - asthma (lower resp. tract)



Identifying HS-I: Allergy Testing

- skin test: small doses of allergen
  - look for wheal & flare
- measure IgE levels



Type II (Cytotoxic) Reactions

- Involve activation of complement by IgG or IgM binding to an antigenic cell.
- Antigenic cell is lysed.
- Transfusion reactions:
  - ABO Blood group system: Type O is universal donor. Incompatible donor cells are lysed as they enter bloodstream.
  - Rh Blood Group System: 85% of population is Rh positive. Those who are Rh negative can be sensitized to destroy Rh positive blood cells.
    - Hemolytic disease of newborn: Fetal cells are destroyed by maternal anti-Rh antibodies that cross the placenta.

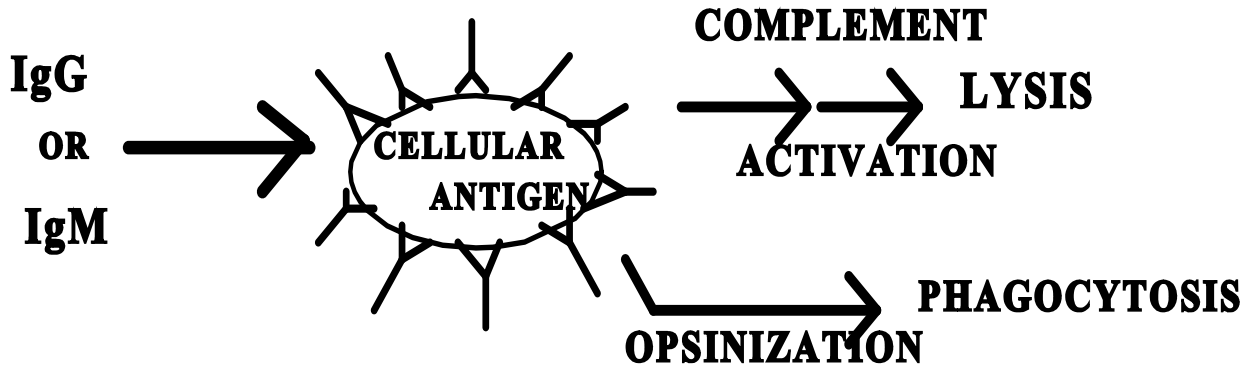
Type II Hypersensitivity

- Ab-mediated cytotoxicity
- Abs vs. cell surface Ags → C’ lysis or ADCC
- most common HS-II Rx involve rbc
  - transfusion Rx
  - hemolytic disease of the newborn (HDN)
  - autoimmune hemolytic anemic (AIHA)

TYPE II HYPERSENSITIVITY

B. TYPE II CYTOTOXIC REACTIONS - IgG OR IgM MEDIATED, COMPLEMENT INVOLVED, REACTIONS MOST OFTEN EFFECT CELLULAR ELEMENTS IN INTIMATE CONTACT WITH CIRCULATING PLASMA

EXAMPLES: HEMOLYTIC ANEMIA, TRANSFUSION REACTIONS



Type II Hypersensitivity Rx

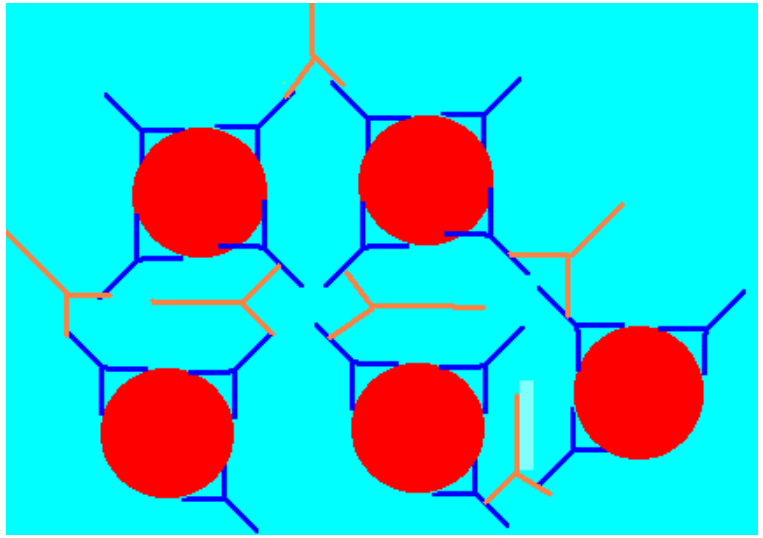
- Hemolytic Transfusion Rx
  - ABO incompatible transfusion can → immediate disaster
    - IgM isohemagglutinins bind rbc → activate C'
    - rapid intravascular lysis, agglut.
    - renal failure, death
  - Dx: clinical SS, hemoglobinuria, hemolysis
  - Trt: stop TF; diuretics
  - Prevent by crossmatch:
    - patient serum (Abs) + donor rbc (Ags)

Hemolytic Disease of Newborn (HDN)

- involves Rh blood group system
  - 3 genes C, D, E: D most immunogenic
  - get Rh Abs only by exposure to Ags
  - Abs mostly IgG
- HDN (erythroblastosis fetalis)
  - Rh(D) negative mom with Rh+ fetus makes Abs vs baby rbc that enter mom circ. at birth
  - next pregnancy: IgG Abs cross placenta, destroy fetal rbc → jaundice, brain damage

HDN

- Prevent HDN by giving mom RhoGAM after birth
  - anti-Rh Abs that lyse baby rbc in mom circ.
  - Abs also prevent sensitization (activ. of B cells)
- Dx HDN in baby with Coombs test
  - detects Abs already on baby rbc
  - add Coombs rgt (anti-IgG) to baby / cord blood
    - look for clumping



Type II Hypersensitivity

- Other HS-II Rx = autoimmune hemolytic anemia (AIHA)
  - autoAbs can result from drugs (e.g., penicillin) that stick to rbc → Abs → C' activation

Type III (Immune Complex) Reactions

- Involve reactions against ***soluble*** antigens circulating in serum.
- Usually involve IgA antibodies.
- Antibody-Antigen immune complexes are deposited in organs, activate complement, and cause inflammatory damage.
  - Glomerulonephritis: Inflammatory kidney damage.
- Occurs with slightly high antigen-antibody ratio is present.

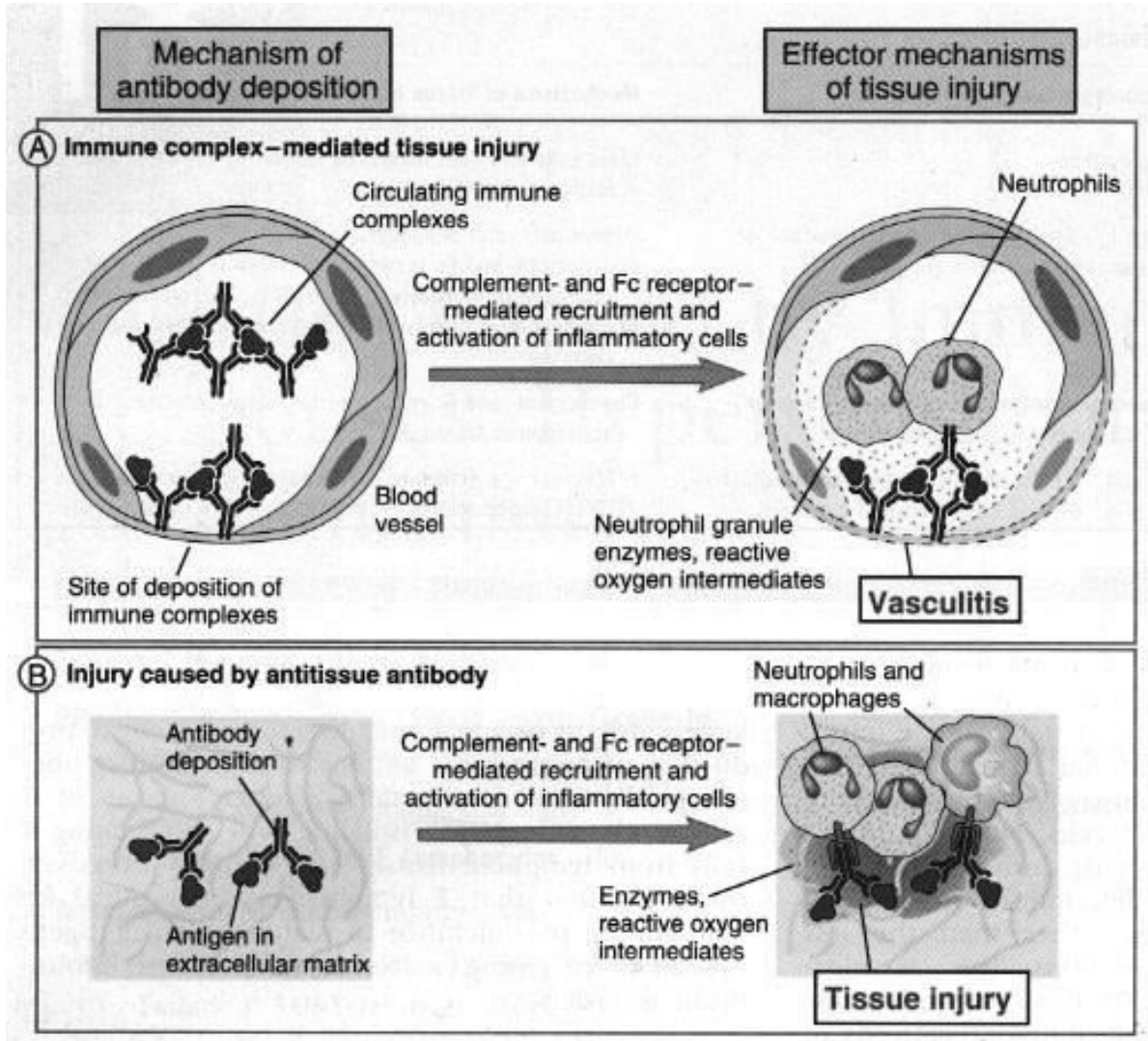
TYPE III HYPERSENSITIVITY

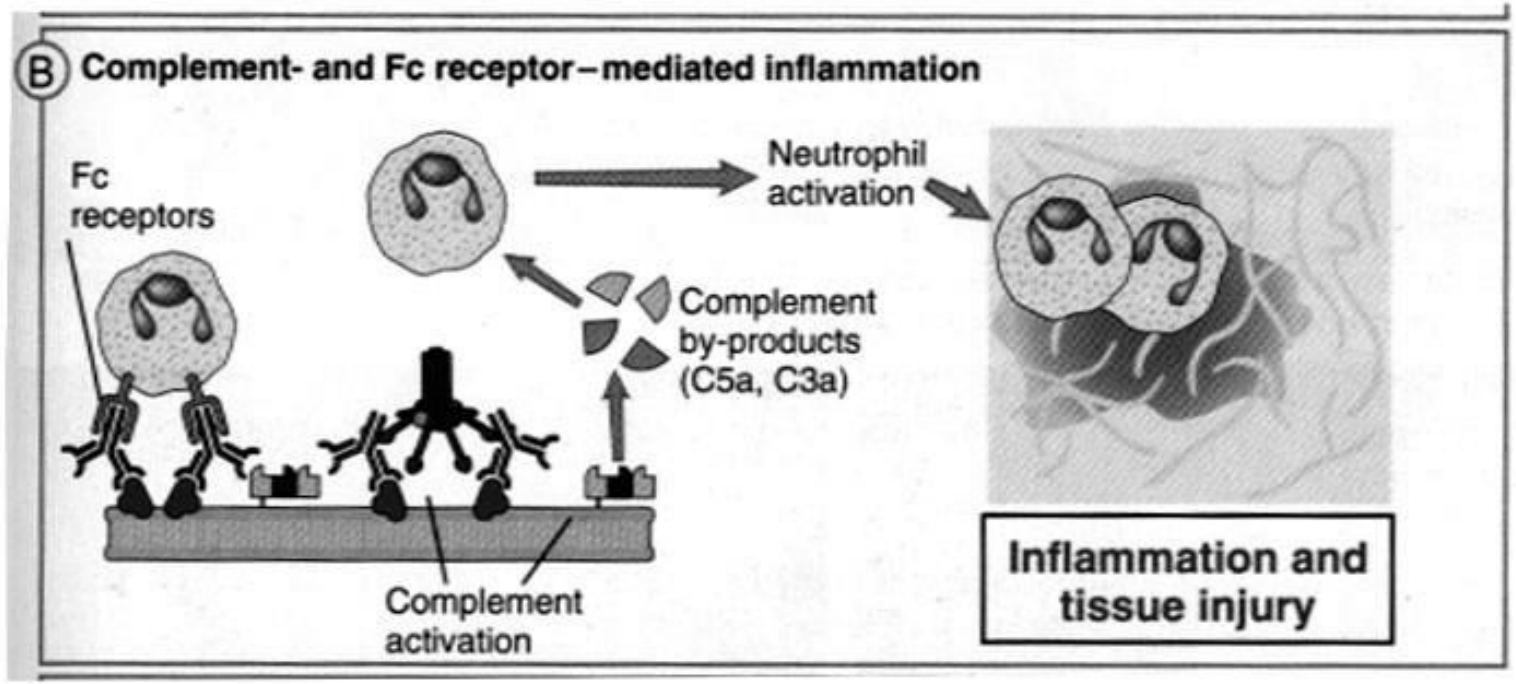
C. TYPE III IMMUNE COMPLEX REACTIONS –
IgG OR IgM MEDIATED, COMPLEMENT INVOLVED, CHARACTERIZED BY FORMATION OF IMMUNE COMPLEXES, TISSUE DAMAGE

EXAMPLES:

1) **SERUM SICKNESS - DISEASE CAUSED BY ANTIBODY PRODUCED TO HORSE OR BOVINE SERUM USED IN ANTITOXINS. AGGREGATES OF IgG ACTIVATE COMPLEMENT**

2) **ARTHUS REACTION - DERMAL INFLAMMATORY RESPONSE, CAUSED BY REACTION OF ANTIBODY TO ANTIGEN IN SKIN.**


Mechanism of antibody deposition
Effector mechanisms of tissue injury
A Immune complex–mediated tissue injury
Circulating immune complexes
Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells
Neutrophils
Blood vessel
Neutrophil granule enzymes, reactive oxygen intermediates
Site of deposition of immune complexes
Vasculitis
B Injury caused by antitissue antibody
Antibody deposition
Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells
Neutrophils and macrophages
Enzymes, reactive oxygen intermediates
Antigen in extracellular matrix
Tissue injury


B Complement- and Fc receptor–mediated inflammation
Fc receptors
Neutrophil activation
Complement by-products (C5a, C3a)
Complement activation
Inflammation and tissue injury

Type III Hypersensitivity

- immune complex reactions
- 2 types of harmful Rx
  - Arthus Rx from localized immune complexes
  - serum sickness from circulating complexes

Arthus Rx

- intradermal injection of Ag
- complexes deposit on blood vessel walls, kidney, etc
- damage mech: C' activ. → inflammation
  - C3a / C5a chemotactic for neutrophils, cause degranulation of mast cells
  - "frustrated phagocytes" – neuts. bind C3b on complexes - can't phago → dump granules in tissues → damage
- examples of Arthus-type Rx
  - insect bite
  - pneumonitis / farmer's lung

Serum Sickness

- generalized HS-III – circulating immune complexes
- induced by injection of foreign proteins (antitoxin)
- complex deposit in capillary beds
- SS: vasculitis – rash, fever, joint pain, etc.
- damage mech. same as Arthus: C' and neutrophils
- diseases characterized by circulating complexes
  - glomerulonephritis
  - lupus (SLE), rheumatoid arthritis, chronic infections

Type IV (Cell-Mediated) Reactions

- Involve reactions by T_D memory cells.
  - First contact sensitizes person.
  - Subsequent contacts elicit a reaction.
- Reactions are *delayed* by one or more days (delayed type hypersensitivity).
  - Delay is due to migration of macrophages and T cells to site of foreign antigens.
- Reactions are frequently displayed on the skin: itching, redness, swelling, pain.
    - Tuberculosis skin test
    - Metals
    - Latex in gloves and condoms (3% of health care workers)
- Anaphylactic shock may occur.

TYPE IV HYPERSENSITIVITY

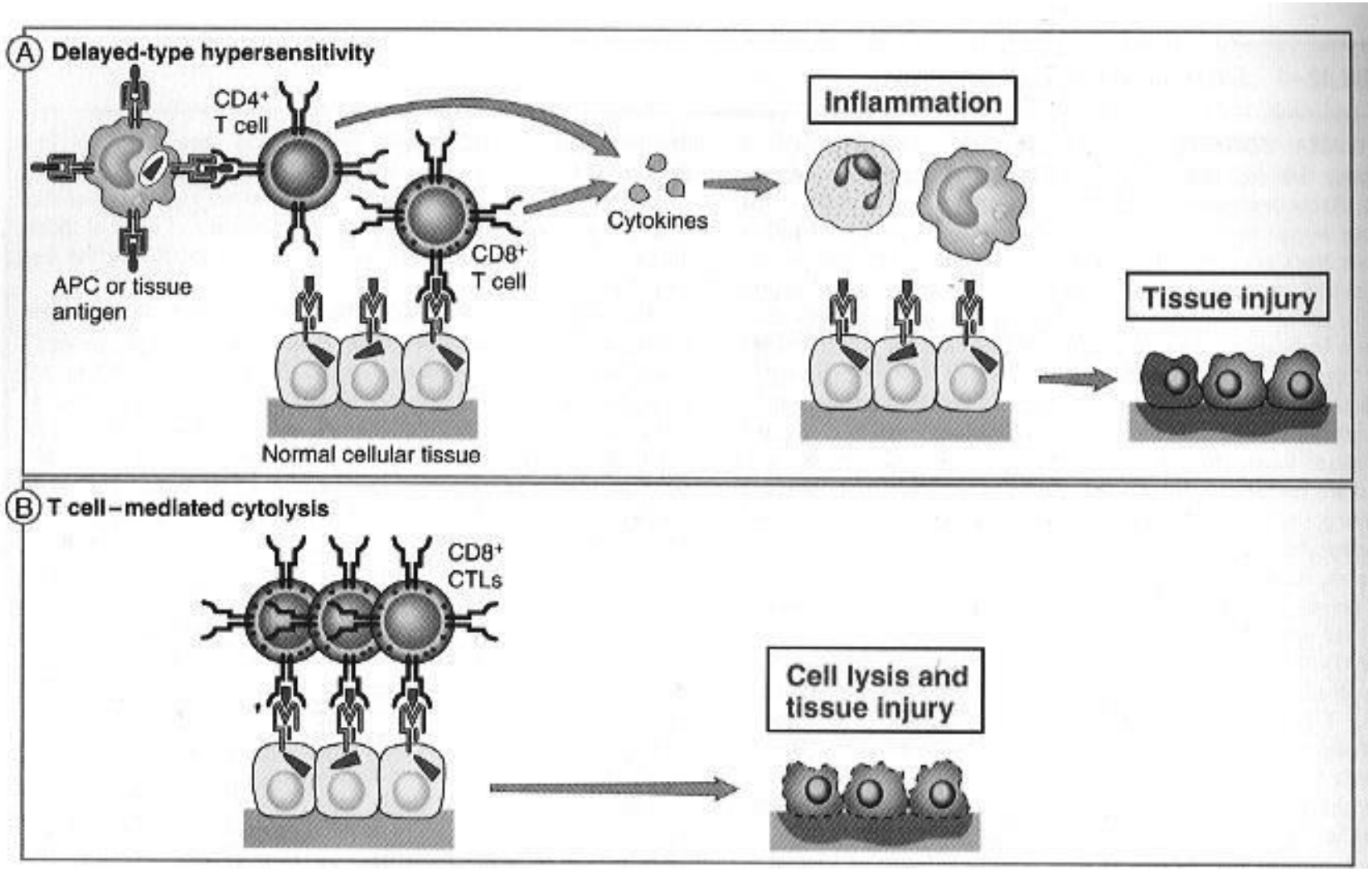
D. TYPE IV - CELL MEDIATED OR DELAYED HYPERSENSITIVITY

T-CELL MEDIATED, SENSITIZED TO LOCALLY DEPOSITED ANTIGEN. REACTION MEDIATED BY RELEASE OF LYMPHOKINE AND/OR DIRECT CYTOTOXICITY

EXAMPLES: CONTACT SENSITIVITY (POISON IVY)

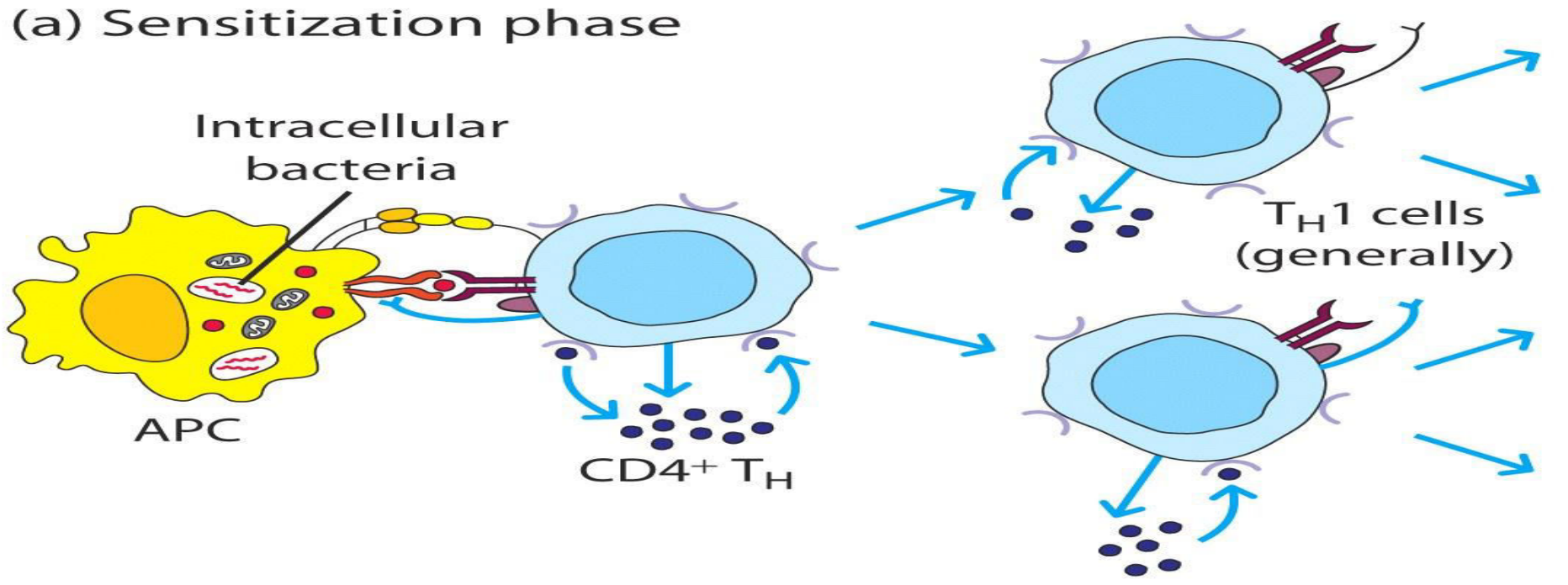
Type IV Hypersensitivity (DTH)

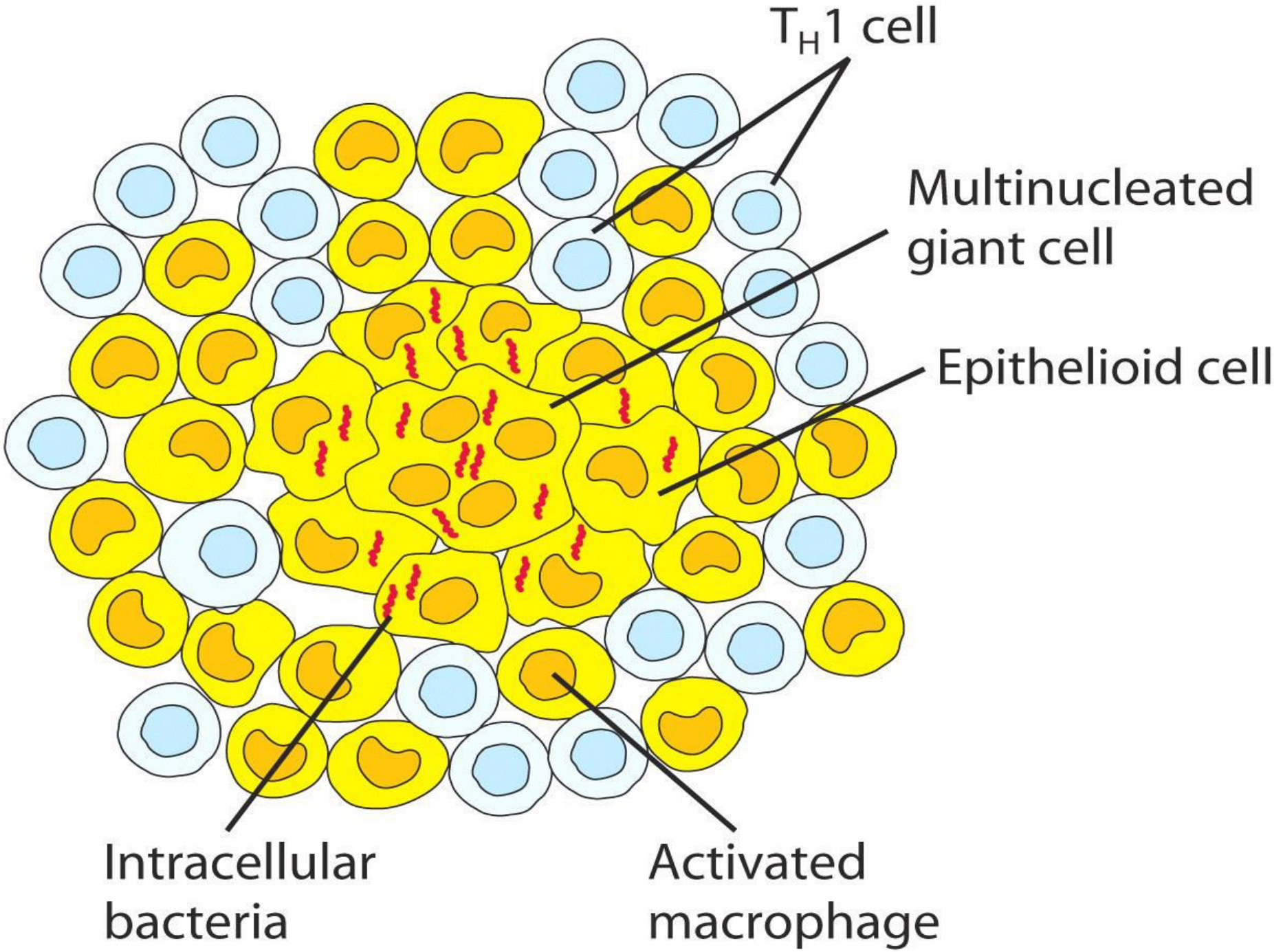
- delayed vs. immediate Rx
- cell-mediated IR; NO Abs involved
- localized Rx at site of Ag encounter


A Delayed-type hypersensitivity
CD4+ T cell
APC or tissue antigen
CD8+ T cell
Normal cellular tissue
Cytokines
Inflammation
Tissue injury
B T cell–mediated cytolysis
CD8+ CTLs
Cell lysis and tissue injury

DTH

- sensitization phase = activation of T_H cells
  - activated T_H → T_{DTH} (subset of T_H1 that activates macs) → memory & effector cells




T_H1 cell
Multinucleated giant cell
Epithelioid cell
Intracellular bacteria
Activated macrophage

DTH

- detect DTH with skin test
  - TB skin test: inject PPD → 48 hr → lump
  - patch test for poison ivy / oak sensitivity
  - lepromin Ag for leprosy

- DTH is an important CMIR defense pathogens



WHAT IS HIV??

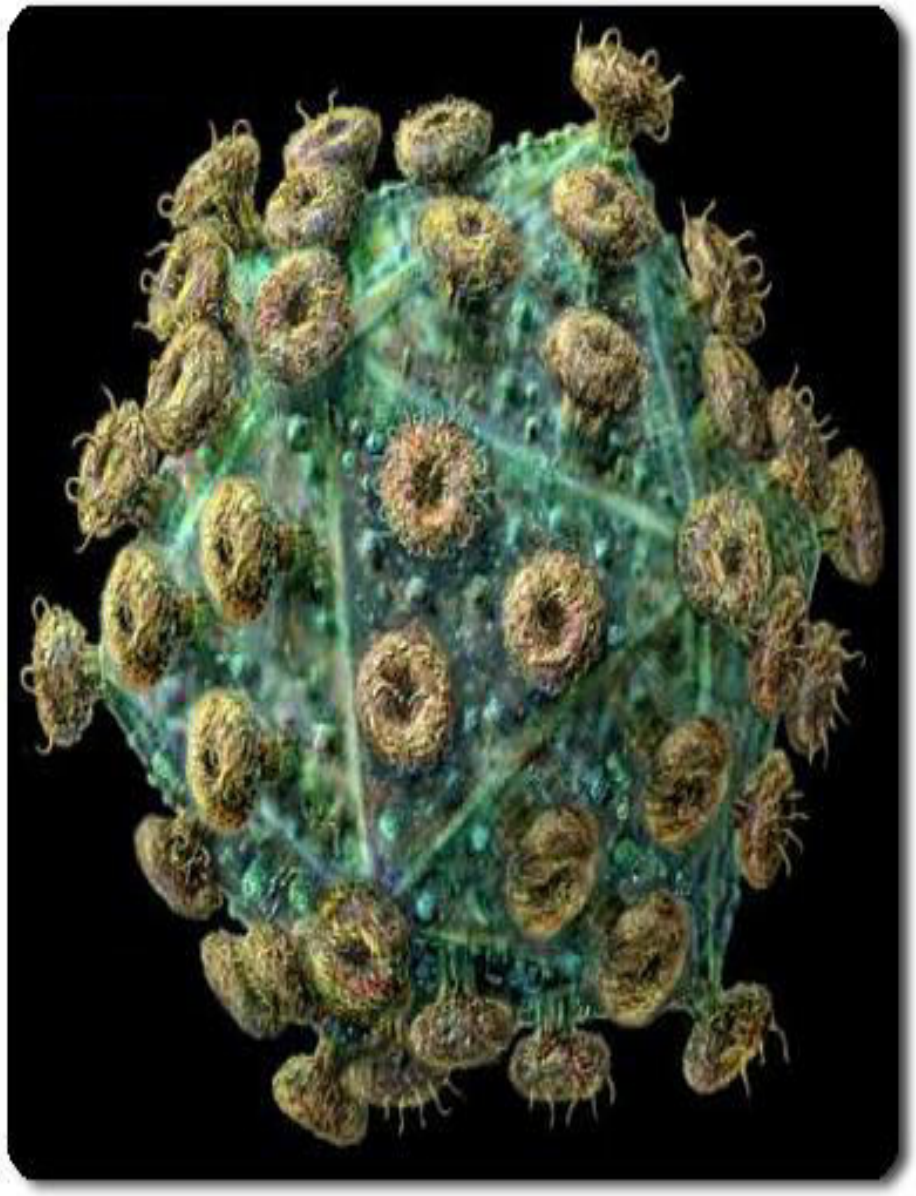
- “Acquired Immunodeficiency Syndrome”
- HIV is the virus that causes AIDS
- Disease limits the body’s ability to fight infection due to markedly reduced helper T cells.
- Patients have a very weak immune system (defense mechanism)
- Patients predisposed to multiple opportunistic infections leading to death.

- “Acquired Immunodeficiency Syndrome”
- HIV is the virus that causes AIDS
- Disease limits the body’s ability to fight infection due to markedly reduced helper T cells.
- Patients have a very weak immune system (defense mechanism)
- Patients predisposed to multiple opportunistic infections leading to death.

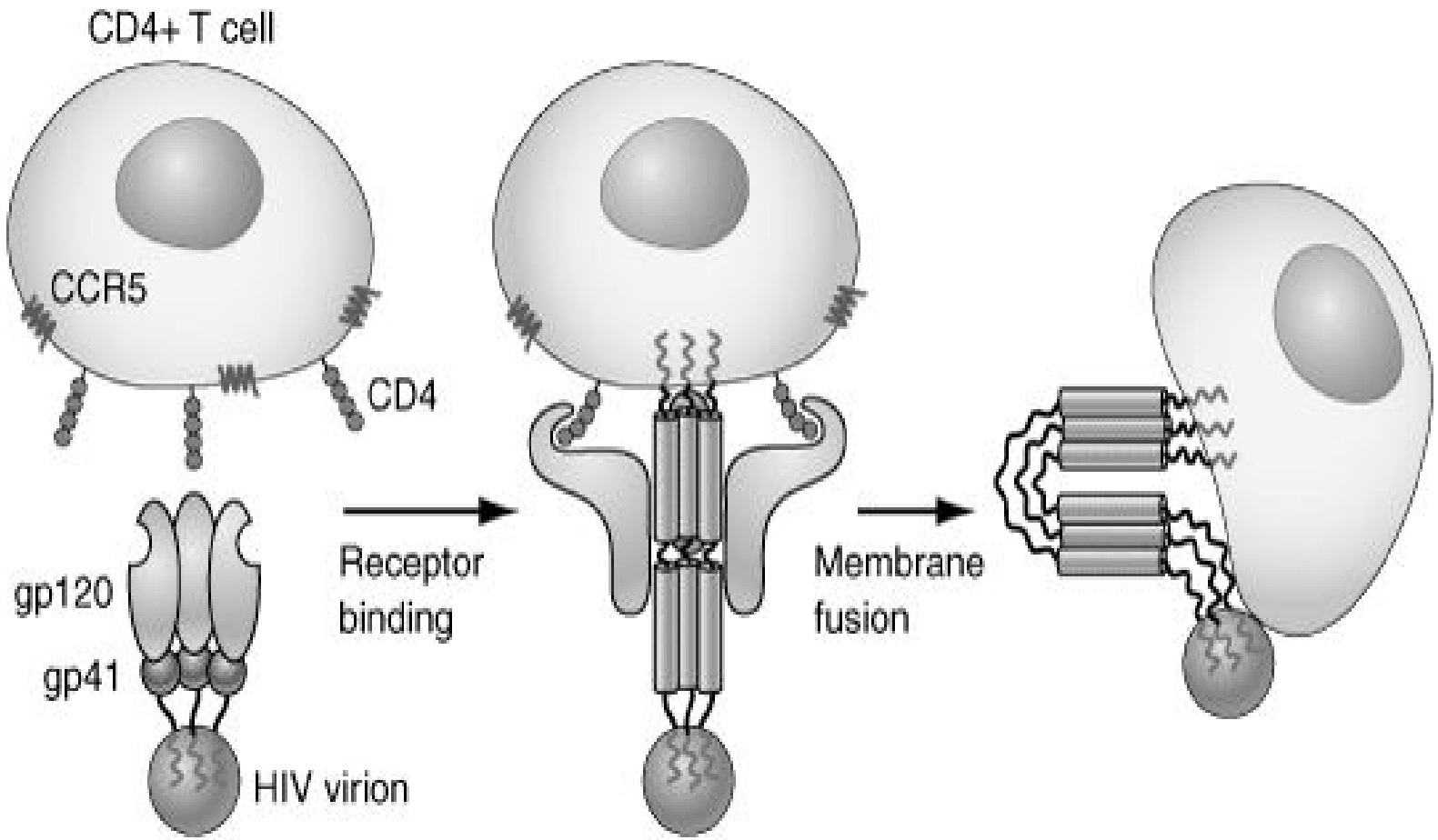
AIDS (definition)

- Opportunistic infections and malignancies that rarely occur in the absence of severe immunodeficiency (eg, *Pneumocystis* pneumonia, central nervous system lymphoma).
- Persons with positive HIV serology who have ever had a CD4 lymphocyte count below 200 cells/mcL or a CD4 lymphocyte percentage below 14% are considered to have AIDS.

HIV

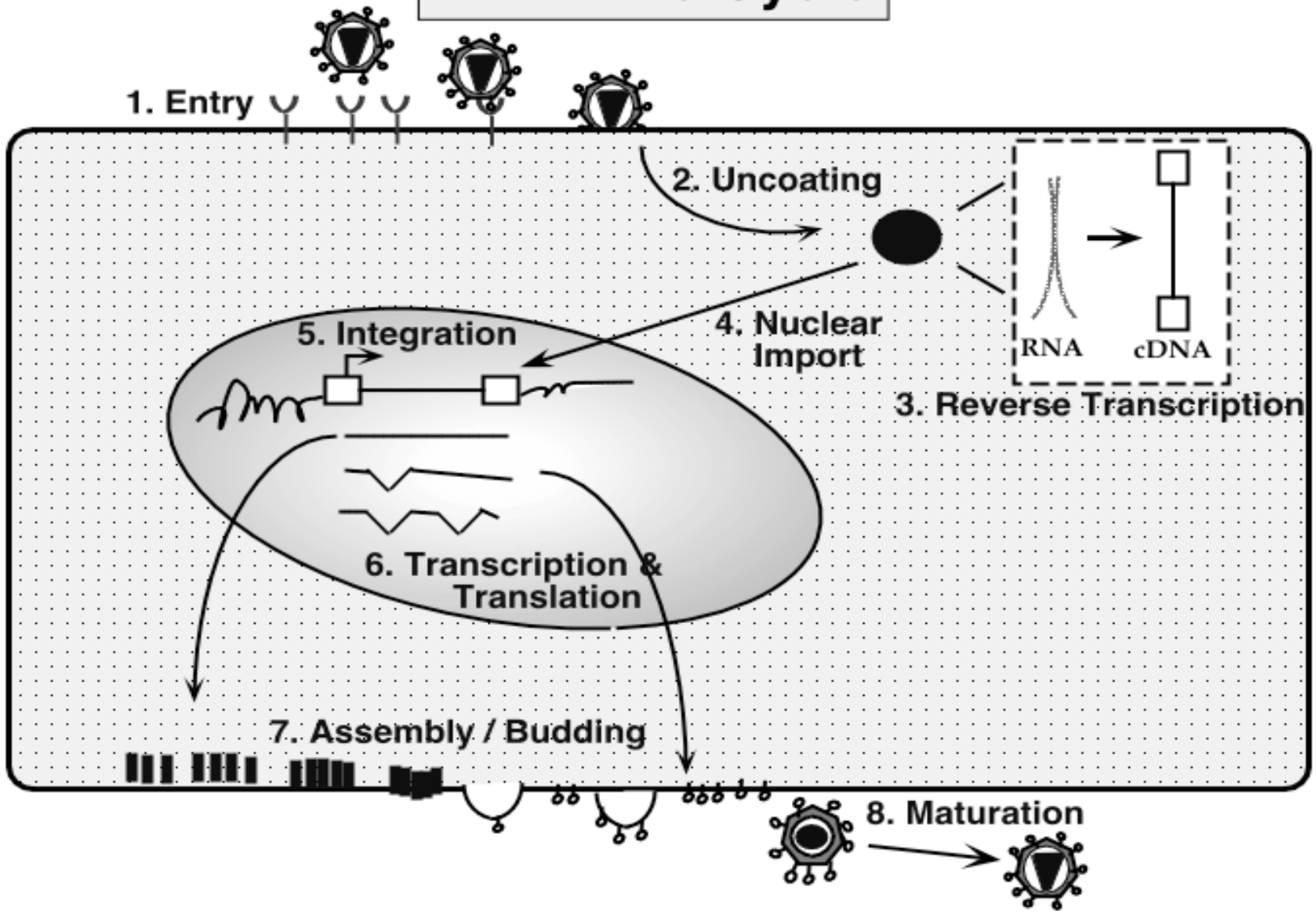


- Retroviruses transcribe RNA to DNA.
- These knob-like structures responsible for binding to target cell.



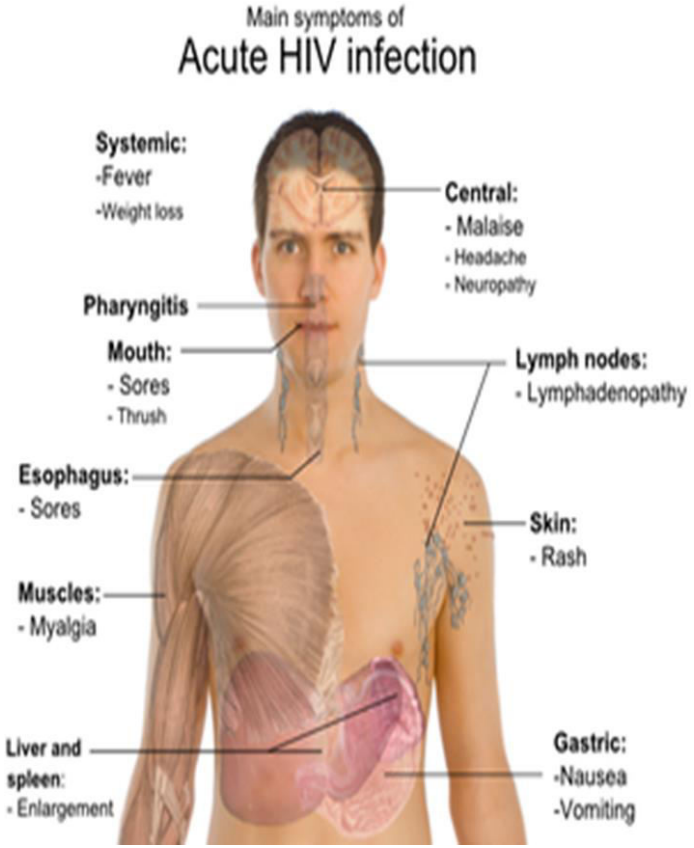
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

HIV-1 Life Cycle



Stage 1 – Primary Stage

- Short, flu-like illness - occurs one to six weeks after infection
- Mild symptoms
- Infected person can infect other people



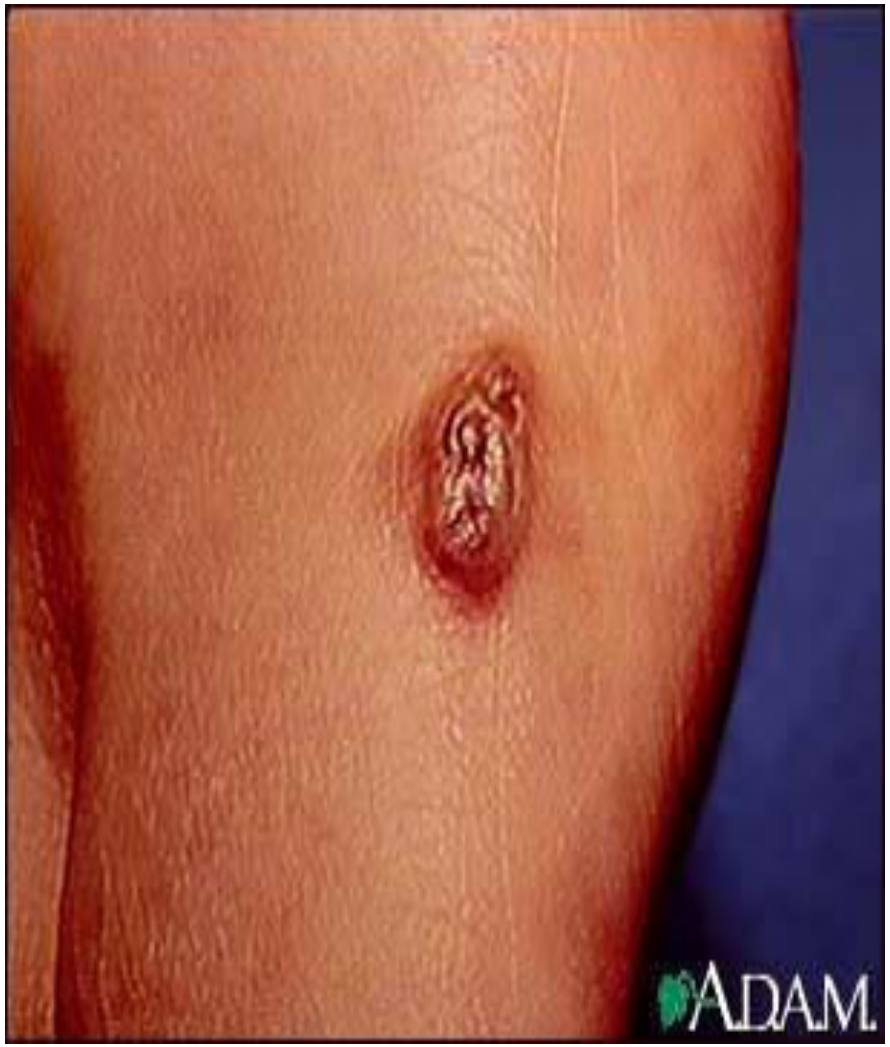
REHMAN MEDICAL INSTITUTE

- Lasts for an average of ten years
- This stage is free from symptoms
- There may be swollen glands
- The level of HIV in the blood drops to low levels
- HIV antibodies are detectable in the blood

- The immune system deteriorates
- Opportunistic infections and cancers start to appear.



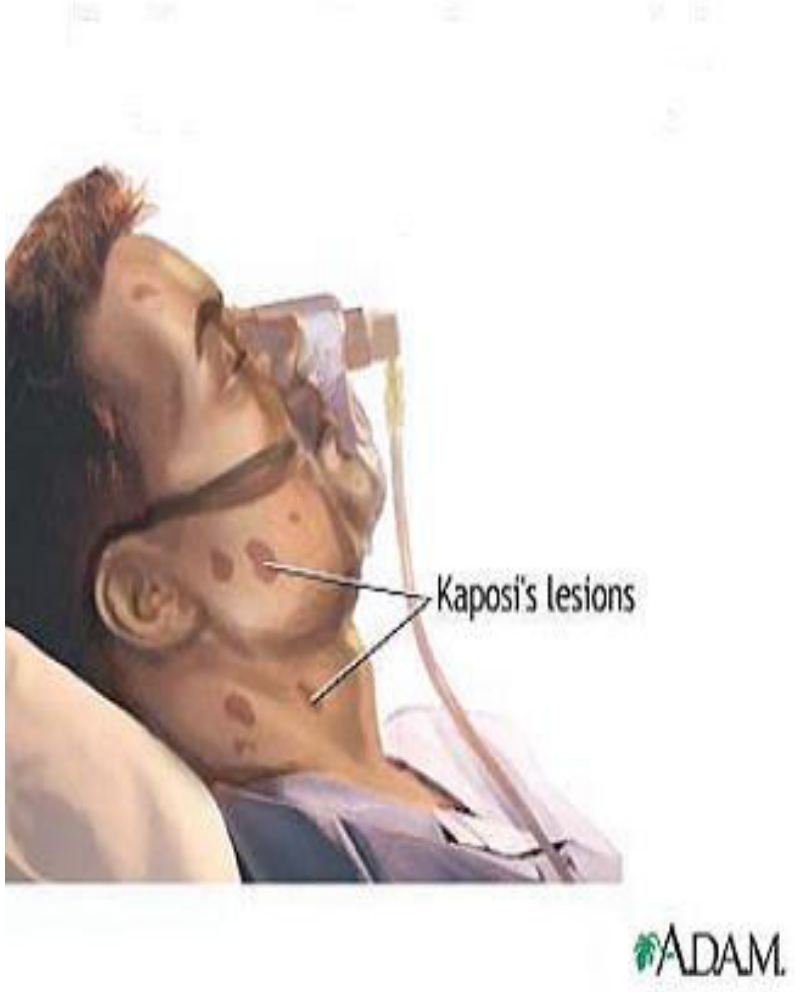
- The immune system weakens too much as CD4 cells decrease in number.



Opportunistic Infections associated with AIDS

CD4<500

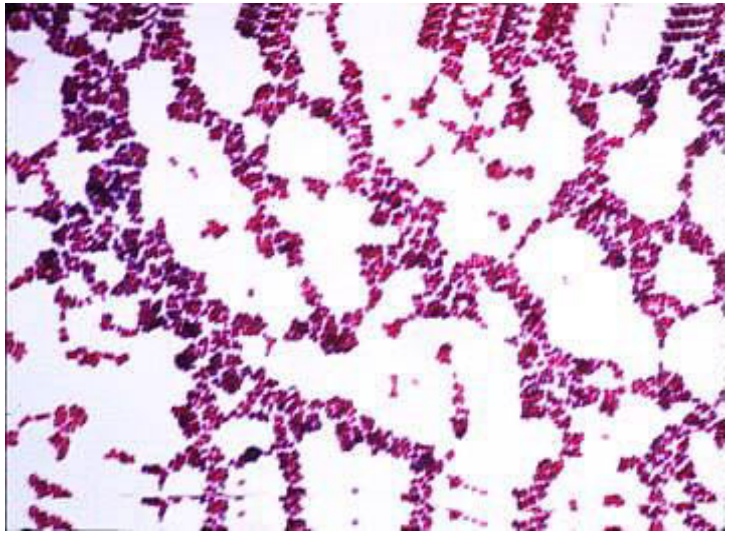
- Bacterial infections
- Tuberculosis (TB)
- Herpes Simplex
- Herpes Zoster
- Vaginal candidiasis
- Hairy leukoplakia
- Kaposi’s sarcoma



Opportunistic Infections associated with AIDS

CD4<200

- Pneumocystic carinii
- Toxoplasmosis
- Cryptococcosis
- Coccidiodomycosis
- Cryptosporiosis
- Non hodgkin’s lymphoma



CD4 <50

- Disseminated mycobacterium avium complex (MAC) infection
- Histoplasmosis
- CMV retinitis
- CNS lymphoma
- Progressive multifocal leukoencephalopathy
- HIV dementia