Immunology
3th Stage
Biology
Lec. 1

Immunology is the study of specific resistance to further infection by a particular microorganism or its products.

Immunology is the science which deals with the body's response to antigenic challenge.

Application of Immunology

1. It helps us to understand etiology and pathogenesis of diseases, e.g. rheumatic fever, asthma, acute glomerulonephritis, etc
2. Diagnosis of disease is possible using ELISA, etc
3. Development of vaccines
4. Treatment using antibodies
5. Transplantation and blood transfusion
6. Surveillance, i.e. immune surveillance
7. It helps to find out possible future susceptibility of a person to diseases with the help of HLA typing system.

Types of Immunity

The main function of the immune system is to prevent or limit infections by pathogenic microorganisms, such as bacteria, viruses, parasites, and fungi. The recognition of microorganisms and foreign substances is the first event in immune responses of a host. The body's defense mechanisms can be divided into:

(a) Innate (natural) immunity

(b) Acquired (adaptive) immunity.

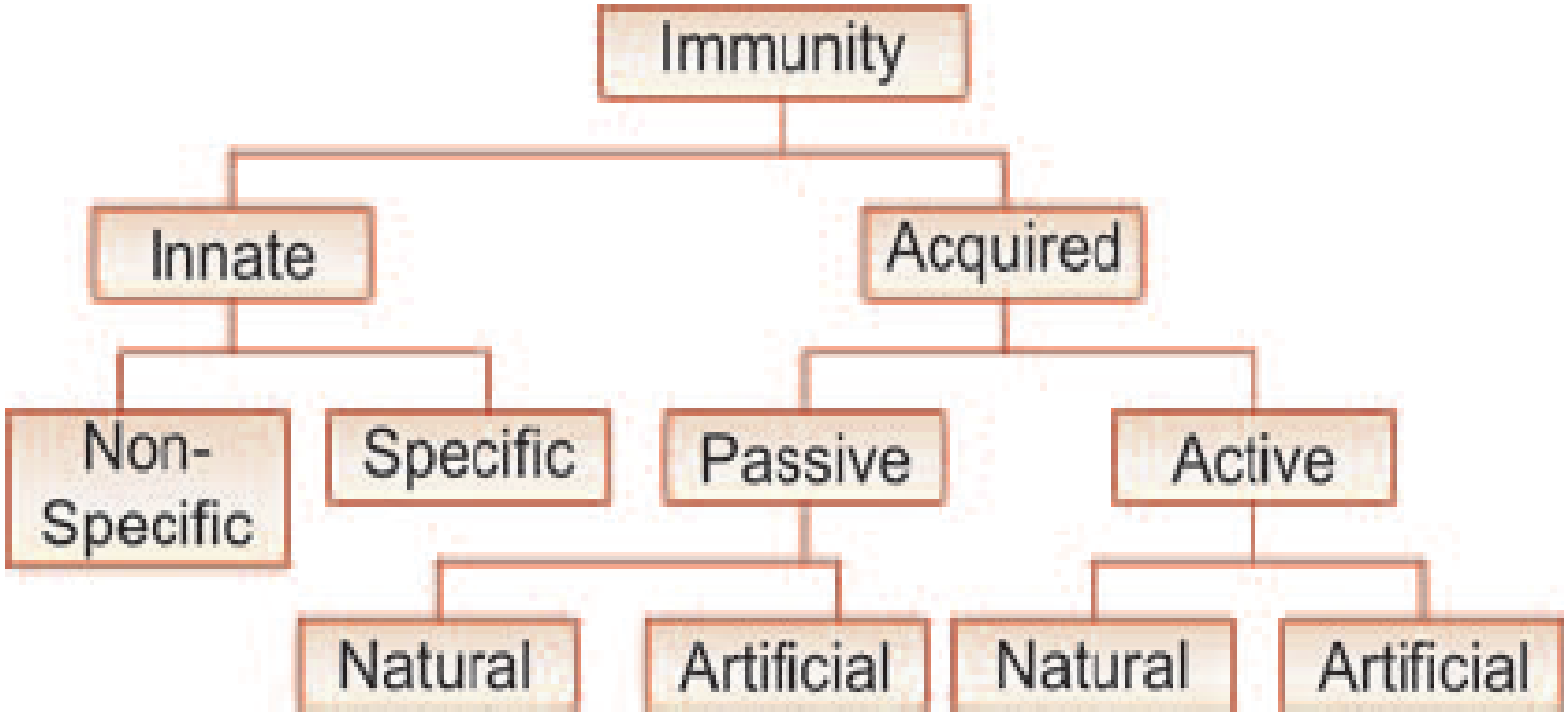


Fig. 12.1: Classification of immunity

Inflammatory responses:

Tissue damage caused by a wound or by an invading pathogenic microorganism induces a complex sequence of events, collectively known as the inflammatory responses. The end result of inflammation may be the activation of a specific immune response to the invasion or clearance of the invader by components of the innate immune system.

TABLE 11-1 Differences between innate and acquired immunity

Feature	Innate immunity	Acquired immunity
Definition	The resistance to infection that an individual possesses by virtue of genetic and constitutional makeup	The resistance that an individual acquires during life
Types	Nonspecific and specific	Active and passive
Time taken to develop	Hours	Days
Specificity	For structures shared by groups of related microbes	For antigens of microbes and for nonmicrobial antigens
Memory	None; repeated exposure brings response like primary response	Yes; secondary response much faster than primary response
Components		
Physical and chemical barriers	Skin, mucosal epithelia, and antimicrobial chemicals	Lymphocytes in epithelia and antibodies secreted at epithelial surfaces
Blood and tissue antimicrobial substances	Complement; leukins from leukocytes, plakins from platelets, lactic acid found in muscle tissue, lactoperoxidase in milk, and interferons (antiviral)	Antibodies
Cells	Phagocytes (macrophages and neutrophils) and natural killer cells	Lymphocytes

TABLE 11-2 Differences between cell-mediated and humoral immunity

Cell-mediated immunity	Humoral immunity
Immune response mediated by cells	Immune response mediated by antibodies
Protects against fungi, viruses, and facultative intracellular bacterial pathogens	Protects against extracellular bacterial pathogens and viruses infecting respiratory or intestinal tract; and prevents recurrence of viral infections
Mediates delayed (type IV) hypersensitivity	Mediates immediate (types I, II, and III) hypersensitivity
Only T-cell-dependent antigens lead to cell-mediated immunity	B cells directly bind soluble antigens resulting in production of antibodies
Both CD4+ and CD8+ T cells are involved	Only T_H cells are involved
Provides immunological surveillance and immunity against cancer	No major role in immunological surveillance
Participates in rejection of homografts and graft-versus-host reaction	May be involved in early graft rejection due to preformed antibodies

TABLE 12.1: Differences between active and passive immunity

	Active immunity	*Passive immunity*
1.	Produced actively by host's immune system	Received passively by the host. No participation by host's immune system
2.	Induced by infection or by contacts with immunogen	Conferred by introduction of vaccines, e.g. readymade antibody
3.	Afford durable and effective protein	Temporary and less effective protection
4.	Immunity effective after lag phase	Immunity effective immediately
5.	Immunological memory present, i.e. subsequent challenge more effective	No immunological memory
6.	Negative phase may occur	No negative phase
7.	Not applicable to immunodeficient hosts	Application to immunodeficient hosts
8.	Used as prophylaxis to increase resistance of body	Used for treatment of acute infection
9.	Both cell mediated and humoral immunity take part	Exclusively humoral immunity is involved
10.	No inheritance of immunity	May be acquired from mother

Thank you

Immunology
3th Stage
Biology
Lec. 2

Antigens

Molecules that can be recognized by the immunoglobulin receptor of B cells or by the T-cell receptor when complexed with major histocompatibility complex (MHC) are called antigens. The word antigen is a shortened form of the words “antibody generator.” Antigens are substances that react with antibodies, while immunogens are molecules that induce an immune response. In most cases, antigens are immunogens, and the terms are used interchangeably..

Determinants of Antigenicity

1. Molecular size
2. Foreignness
3. Chemical-structural complexity
4. Stability
5. Other factors

- Biological system
- Dosage and route of the antigen

- Adjuvants

Adjuvants are the substances that when mixed with an antigen and injected with it boost the immunogenicity of the antigen. Adjuvants increase both the strength and the duration of immune response

Histocompatibility Antigens

Histocompatibility antigens are the cellular determinants specific for each individual of a species. These antigens are associated with the plasma membrane of tissue cells. Human leukocyte antigen (HLA) is the major histocompatibility antigen that determines the homograft rejection. Therefore, HLA typing is absolutely essential before carrying out transplantation of tissue or organ from one individual to another

Haptens

Haptens are small organic molecules that are antigenic but not immunogenic. They are not immunogenic because they cannot activate helper T cells. Failure of hapten to activate helper T cells is due to their inability to bind to MHC proteins; they cannot bind because they are not proteins and only proteins can be presented by MHC proteins. Moreover, haptens are univalent hence cannot activate B cells by themselves

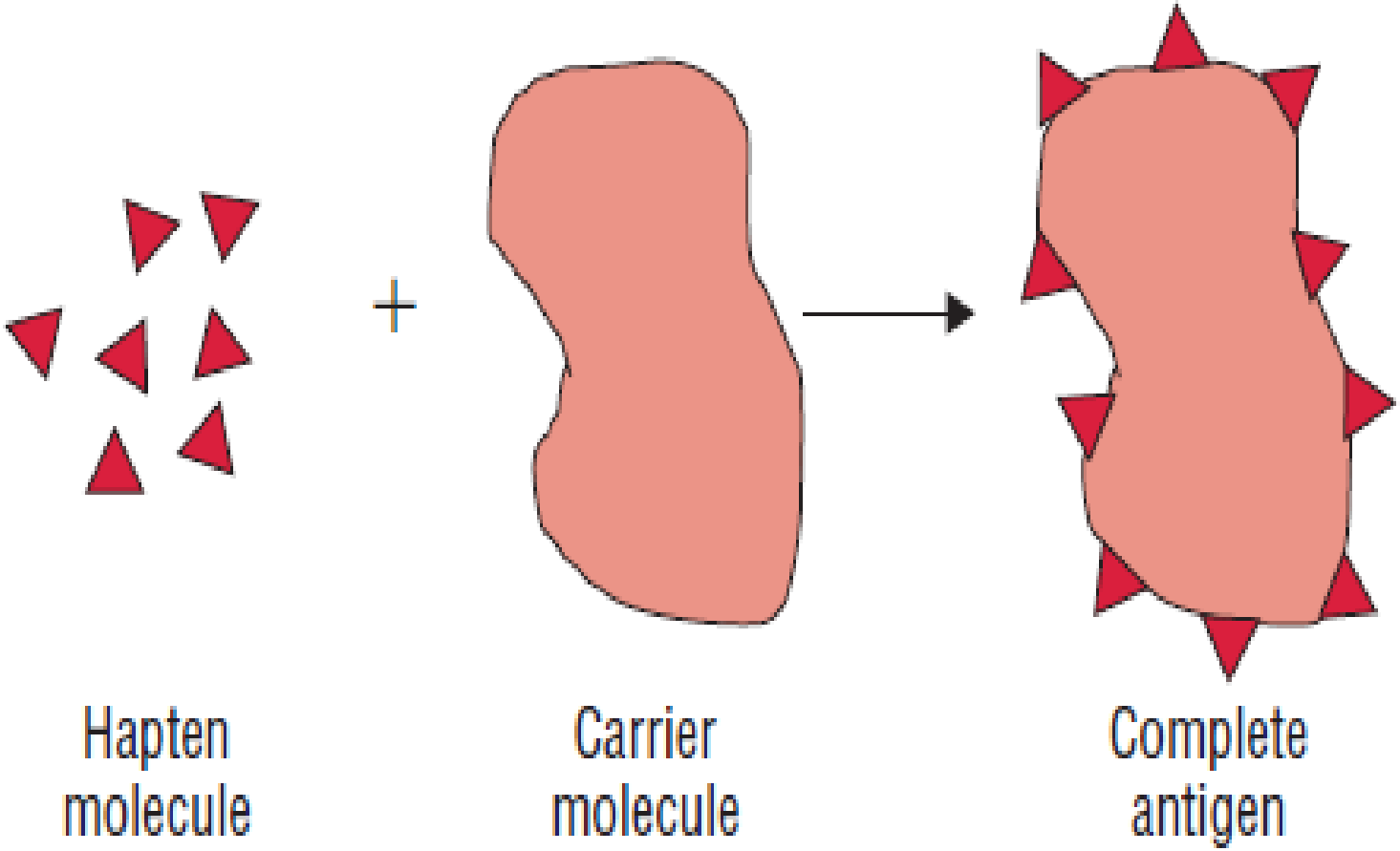
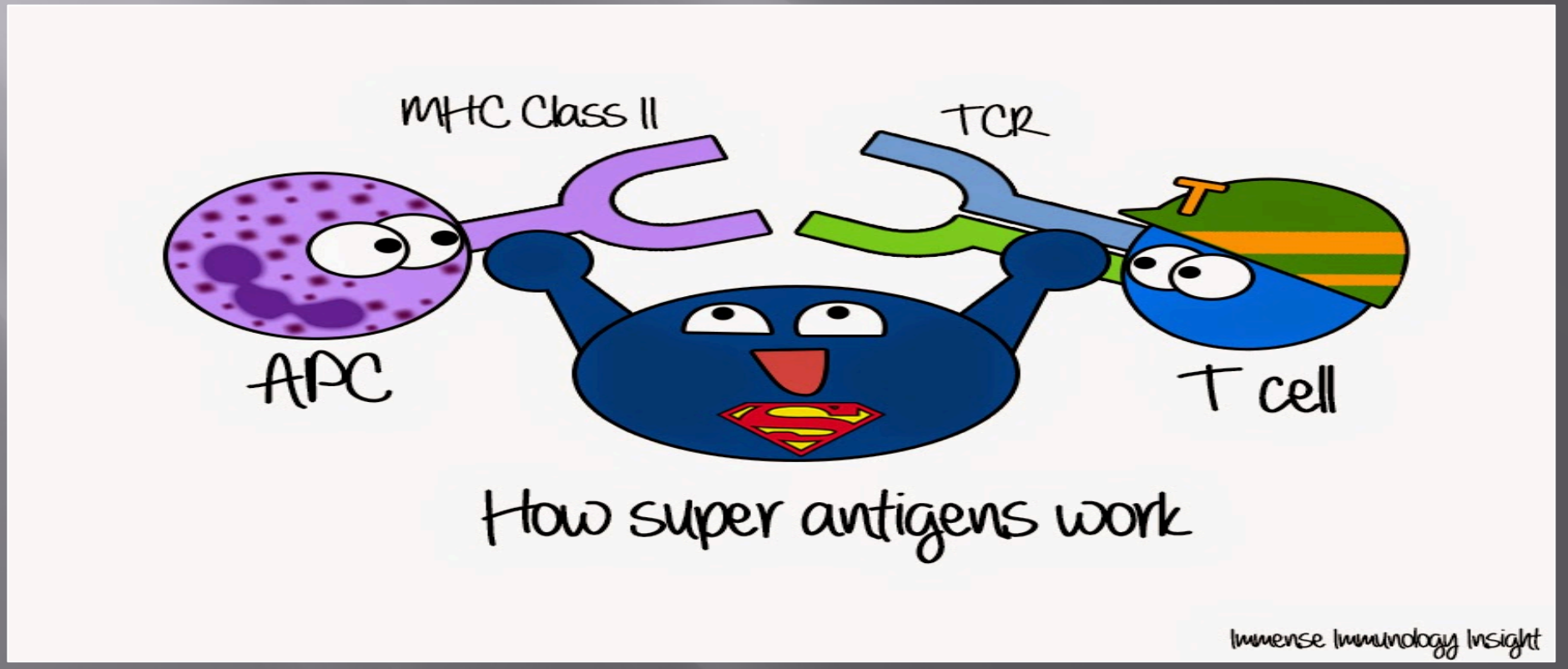


FIG. 12-1. Hapten–carrier conjugate.

Super-antigens

Superantigens are a class of molecules that can interact with APCs and T- lymphocytes in a nonspecific way.



Thank you

Immunology

3th Stage

Biology

Lec. 3

Antibodies

Antibodies are globulin proteins (immune-globulins) that are synthesized in serum and tissue fluids, which react specifically with the antigen that stimulated their production. Three types of globulins are present in the blood: alpha, beta, and gamma.

Antibodies confer protection in the following ways:

1. They prevent attachment of microbes to mucosal surfaces of the host.
2. They reduce virulence of microbes by neutralizing toxins and viruses.
3. They facilitate phagocytosis by opsonization of microbes.
4. They activate complement, leading to complement-mediated activities against microbes.

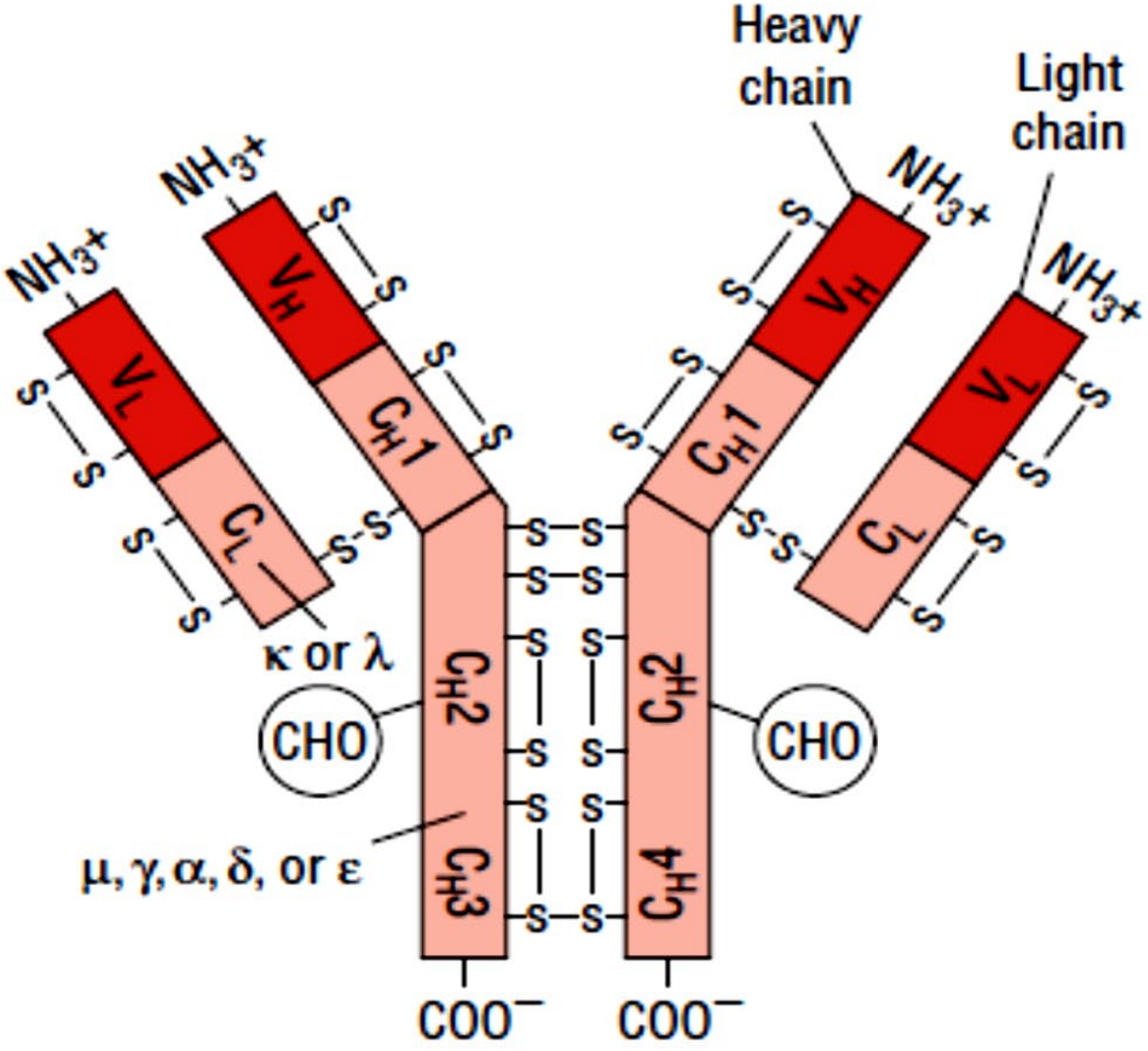


FIG. 13-1. Schematic diagram of monomer of the immunoglobulin.

TABLE 13-1 Classes of immunoglobulins and their heavy chains and subclasses

Class	Heavy chain	Subclasses
IgG	Gamma	γ_1, γ_2, γ_3, γ_4
IgM	Mu	None
IgA	Alpha	α_1, α_2
IgE	Epsilon	None
IgD	Delta	None

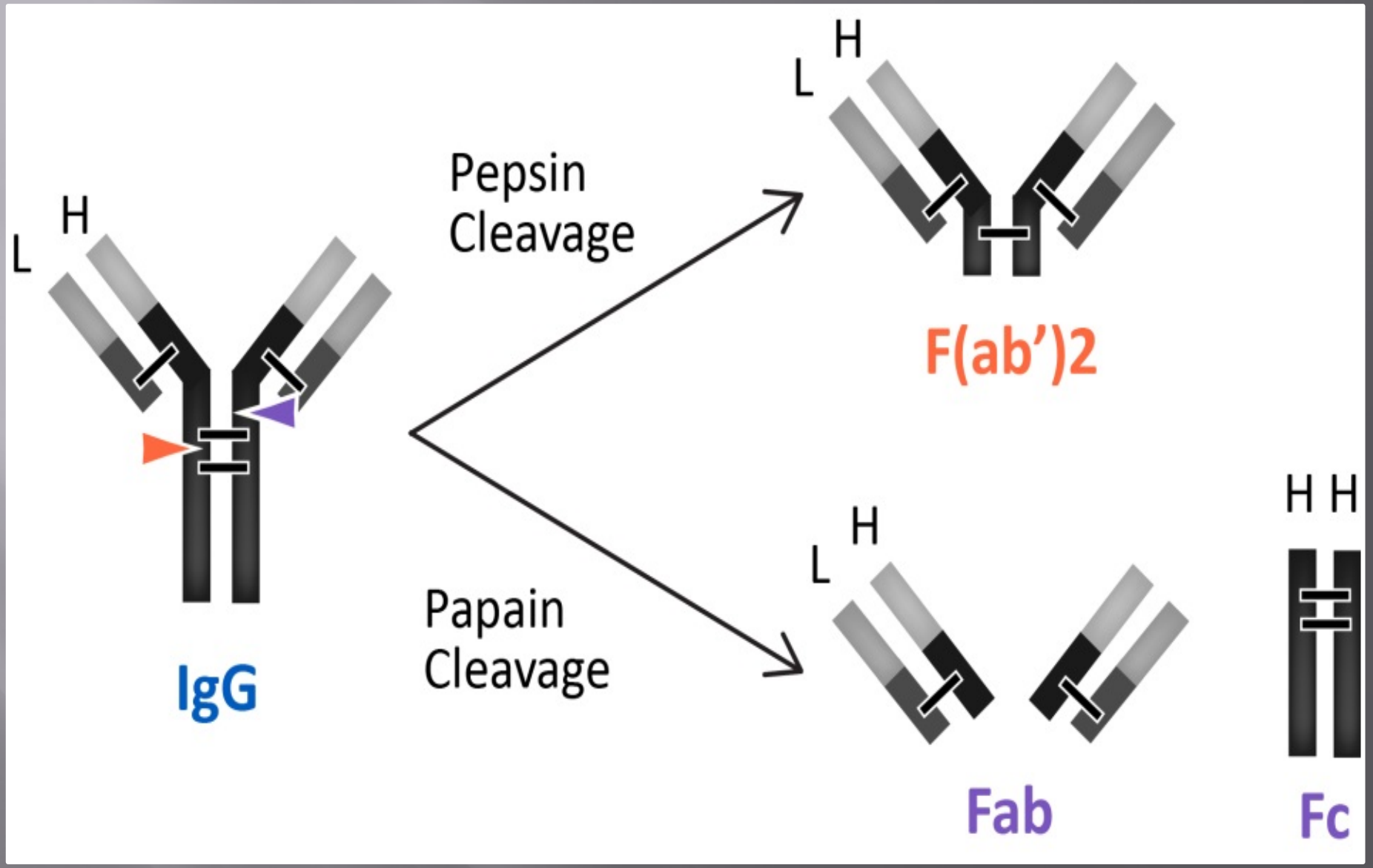

H
L
IgG
Pepsin
Cleavage
H
L
F(ab')2
Papain
Cleavage
H
L
Fab
H H
Fc

TABLE 13-2 Comparison of various properties of immunoglobulins

Characteristics	IgG	IgA	IgM	IgD	IgE
Structure	Monomer	Dimer	Pentamer	Monomer	Monomer
Percentage of total serum	80%	10–13%	5–8%	0.2%	0.002%
Location	Blood, lymph, and intestine	Blood, lymph, and B cell surface	Secretions	B cell surface, blood, and lymph	Bound to mast and basophil cell
Sedimentation coefficient	7	7	19	7	8
Molecular weight (kDa)	150	160	900	180	190
Carbohydrate (%)	3	8	12	13	12
Serum concentration (mg/mL)	12	2	1.2	0.03	0.00004
Half-life (days)	23	6–8	5	2–8	1–5
Heavy chain	$\gamma_1, \gamma_2, \gamma_3, \gamma_4$	α_1, α_2	μ	Δ	ε
Light chain	κ or δ	κ or δ	κ or δ	κ or δ	κ or δ
Complement binding	Classical pathway	Alternate pathway	Classical pathway	None	None
Placental transport	+	–	–	–	–
Present in milk	+	+	–	–	–
Seromucous secretion	–	+	–	–	–
Heat stability (56°C)	+	+	+	+	–
Binding to tissue	Heterologous	None	None	None	Homologous

Thank you

Immunology
3th Stage
Biology
Lec. 4

Complement System

Introduction

The term complement refers to the ability of a system of some nonspecific proteins in normal human serum to complement, i.e., augment the effects of other components of immune system, such as antibody. The complement system, which is an important component of the human innate host defense system, consists of approximately 20 proteins that are present in normal human serum.

Properties of Complement

Complement shows the following properties:

1. It is **present in sera of all mammals** including humans and in lower animals including birds, amphibians, and fishes.

2. **These are heat-labile substances** that are inactivated by heating serum at 56°C for 30 minutes.

3. These are glycoproteins and are synthesized primarily by liver cells and to a very less extent by macrophages and many other cell types

4. The **complement usually does not bind to the antigen or antibody but only to antigen–antibody complex**.

5. The importance of the complement lies in the fact that it **contributes to both the acquired and innate immunity of an individual.**

Effects of complement

There are four main effects of complement:

It causes lysis of cells (such as bacteria, viruses, allografts, and tumor cells).

It generates mediators that participate in triggering specific cell functions, inflammation, and secretion of immune-regulatory molecules.

It facilitates opsonization, the process by which bacteria are more readily and more efficiently engulfed by phagocytes.

It causes immune clearance, in which immune complexes from the circulation are removed and are transported to spleen and liver.

Activation of Complement

- Complement activation takes place through any of the following three pathways:

1. The classical pathway
2. The alternative pathway
3. The lectin pathway

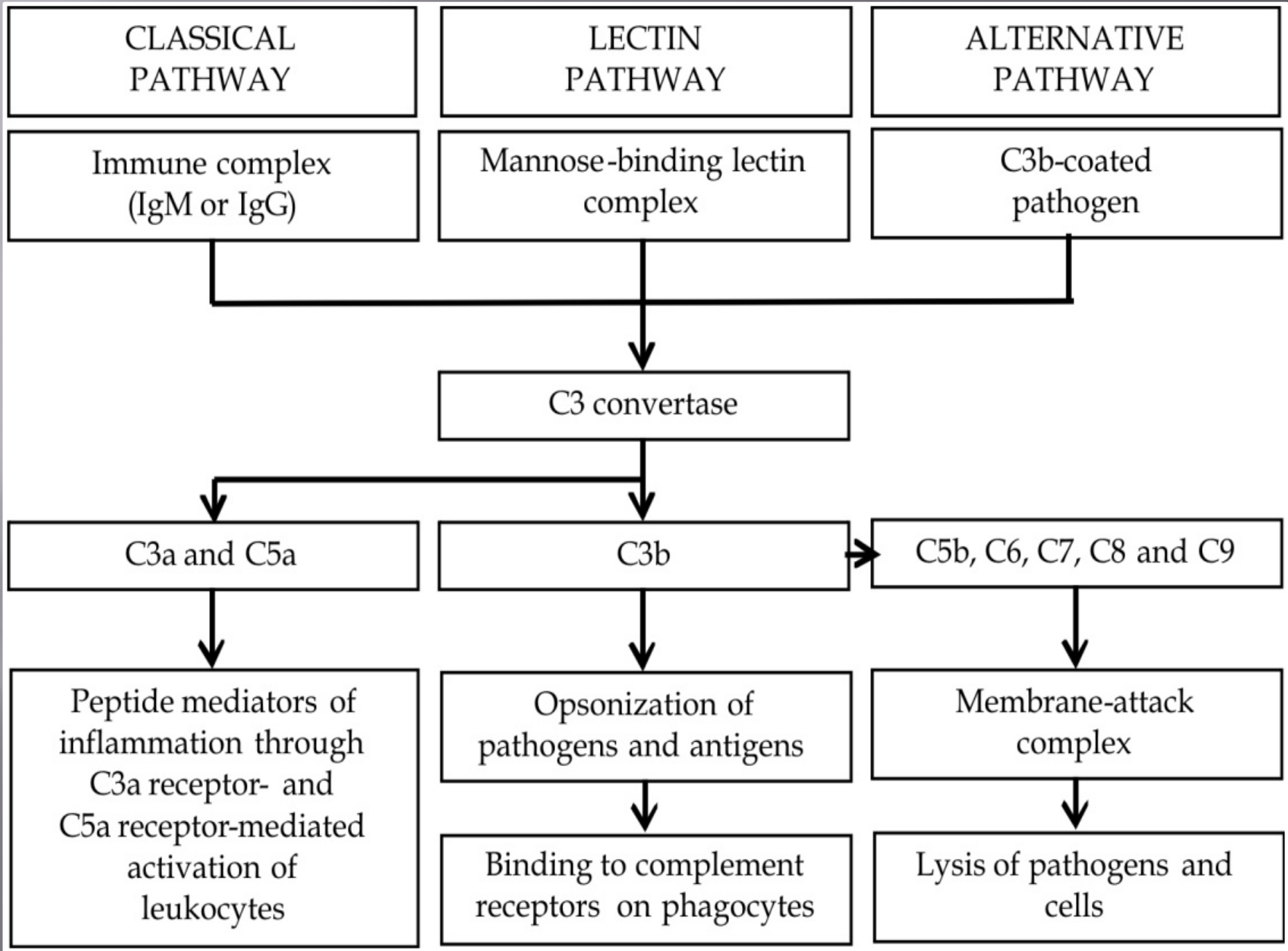

CLASSICAL PATHWAY
LECTIN PATHWAY
ALTERNATIVE PATHWAY
Immune complex (IgM or IgG)
Mannose-binding lectin complex
C3b-coated pathogen
C3 convertase
C3a and C5a
C3b
C5b, C6, C7, C8 and C9
Peptide mediators of inflammation through C3a receptor- and C5a receptor-mediated activation of leukocytes
Opsonization of pathogens and antigens
Membrane-attack complex
Binding to complement receptors on phagocytes
Lysis of pathogens and cells

TABLE 15-2 Diseases associated with complement deficiencies

Deficiency	Disorder	Salient features
C1 esterase inhibitor	Hereditary angioedema	Transient but recurrent localized edema in the skin, gastrointestinal tract, and respiratory tract
C1q	Associated with hypogammaglobulinemia and severe combined immunodeficiency disease	Repeated infections
C2 and C4	Similar to SLE	Due to failure in clearance immune-mediated complexes
C3	Severe recurrent pyogenic infections	*Streptococcus pneumoniae* infections
C5	Impaired chemotaxis	Increased susceptibility to bacterial infection
C5-C8	Bacteremia	Gram-negative diplococci and toxoplasmosis

Thank you

Immunology

3th Stage

Biology

Lec. 5

Structure and Function of Immune System

Lymphoid Tissues and Organs

The specific immune response to antigen is of two types:

(a) **humoral or antibody-mediated immunity**, mediated by antibodies produced by plasma cells;

(b) **cell-mediated immunity**, mediated by sensitized lymphocytes.

The immune system is organized into several special tissues, which are collectively termed lymphoid or immune tissues. The tissues that have evolved to a high degree of specificity of function are termed lymphoid organs.

Central (Primary) Lymphoid Organs

Central or primary lymphoid organs are the major sites for lymphopoiesis. These organs have the ability to produce progenitor cells of the lymphocytic lineage. These are the organs in which precursor lymphocytes proliferate, develop, and differentiate from lymphoid stem cells to become immunologically competent cells. The primary lymphoid organs include **thymus and bone marrow**. **In mammals, T cells mature in thymus and B cells in fetal liver and bone marrow**. After acquiring immunological competency, the lymphocytes migrate to secondary lymphoid organs to induce appropriate immune response on exposure to antigens.

Peripheral (Secondary) Lymphoid Organs

Peripheral or secondary lymphoid organs consist of (**a**) lymph nodes, (**b**) spleen, and (**c**) non-encapsulated structures, such as mucosa-associated lymphoid tissues (MALT). These organs serve as the sites for interaction of mature lymphocytes with antigens.

Lymph nodes

They play a very important and dynamic role in the initial or inductive states of the immune response. The lymph node has two main parts: **cortex** and **medulla**.

Functions of the lymph nodes: Lymph nodes serve the following functions:

- They act as filter for the lymph, the fluid, and cellular content of the lymphocytic circulatory system.
- They also provide sites for mingling of lymphocytes, monocytes,
- and dendritic cells for initiation of immune responses.
- They phagocytes microbial pathogens and other foreign substances.

Spleen

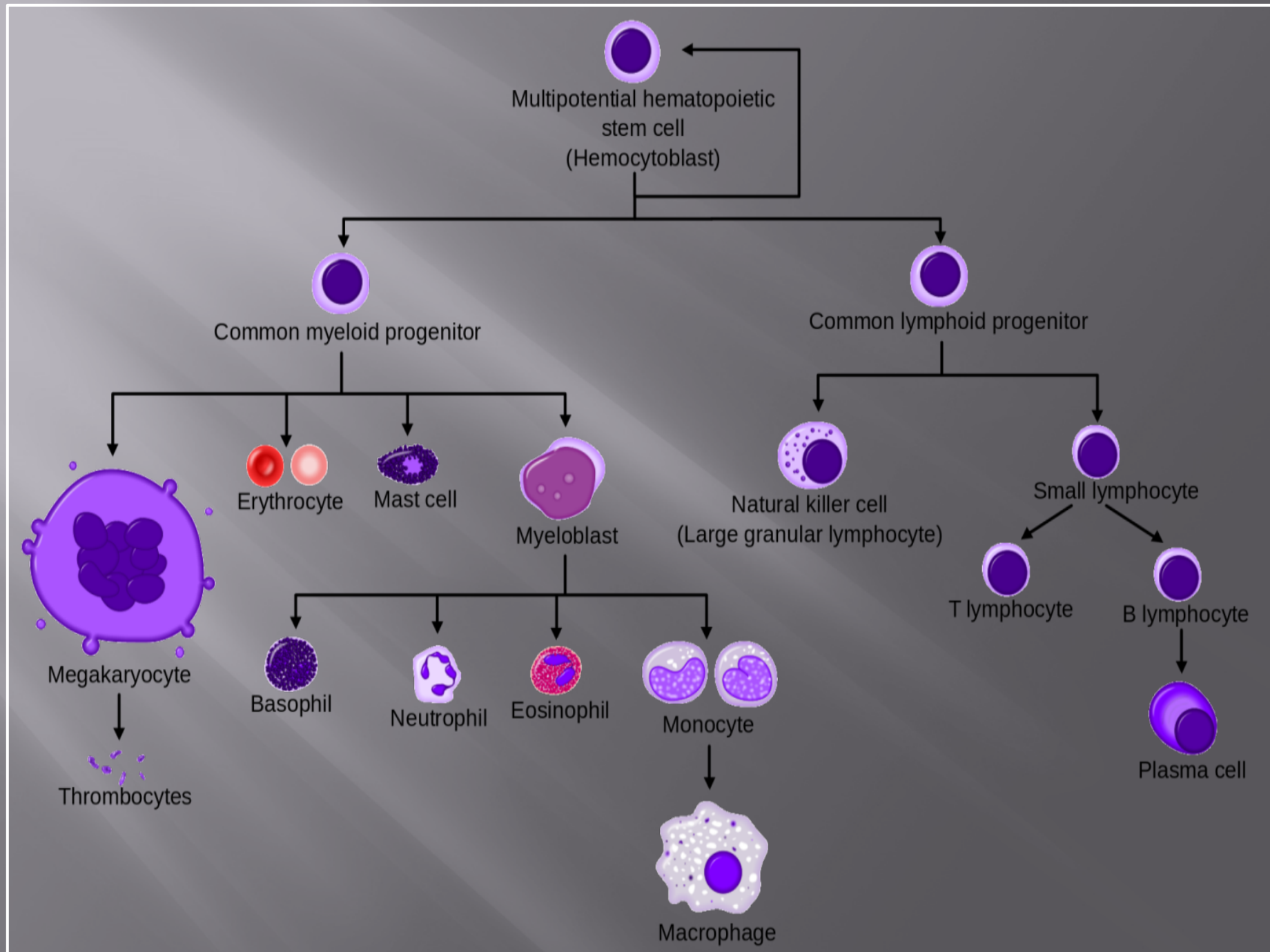
The spleen is the largest lymphoid organ. It is a large, ovoid secondary lymphoid organ situated high in the left abdominal cavity.

Functions of the spleen: The spleen plays a major role in:

- Mounting immune responses to antigens in the blood stream.
- Filtering or clearing of (a) infectious organisms; (b) aged or defectively formed elements (e.g., spherocytes, ovalocytes); and (c) particulate matter from the peripheral blood.

Mucosa-associated lymphoid tissues

Mucosa-associated lymphoid tissues (MALT) consist of the lymphoid tissues of the intestinal tract, genitourinary tract, tracheobronchial tree, and mammary glands. All of the MALT are non-capsulated and contain both T and B lymphocytes.


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Thrombocytes
Plasma cell
Macrophage

Thank you

Immunology

3th Stage

Biology

Lec. 6

Lymphocytes

The lymphocytes consist of two main functional classes: B cells and T cells.

The lymphocytes are classified depending upon where they undergo their development and proliferation: (*a*) T lymphocytes or T cells undergoing development in the thymus or (*b*) B lymphocytes, or B cells undergoing development in the bone marrow.

	T cells	B cells
Ag receptor	TCR related to Ig	BCR is membrane-bound Ig
Ag recognition	in context of MHC on APC or accessory cells	can recognize Ag alone
Functional subsets	Th (helper) and Tc	subsets of B cells not different in function
Secrete	Cytokines	Ig (as Ab) and cytokines
Surface markers	CD4 and CD8	Ig (among many others)
When Ag-activated	Become (proliferating) lymphoblasts	Become lymphoblasts, then become plasma cells
Costimulation required?	Yes	No

The T lymphocytes perform two important groups of functions as follows:.

Regulation of immune responses: Regulatory function is mediated primarily by helper ($CD4^+$) T cells, which produce interleukins.

Various effector functions: Effector functions are mediated primarily by cytotoxic ($CD8^+$) T cells, which kill allografts, tumor cells, and virus-infected cells.

TABLE 16-2 Comparison of Th-1 cells and Th-2 cells

Features	Th-1 cells	Th-2 cells
Enhances cell-mediated immunity and delayed hypersensitivity	Yes	No
Enhances antibody production	No	Yes
Activation of cytotoxic T lymphocytes	Yes	No
Stimulated by IL-12	Yes	No
Stimulated by IL-4	No	Yes
Produces IL-2 and gamma interferon	Yes	No
Produces IL-4, IL-5, IL-6, and IL-10	No	Yes

TABLE 16-3 Differences between helper T cells (CD4) and cytotoxic T (CD8) cells

Helper T cells	Cytotoxic T cells
Carries CD4 marker	Carries CD8 cells
Helps or induces immune responses	Predominantly cytotoxic
Recognize antigen in association with class II MHC	Recognize antigen in association with class I MHC
Macrophages are activated to kill intracellular microorganisms by secreting cytokines	Destroy virus-infected and tumor cells directly

Plasma cells

Plasma cells originate from terminally differentiated B cells. Plasma cells are oval or egg-shaped structures characterized by a stellate (star-like pattern) nucleus, nonstaining Golgi, and basophilic cytoplasm.

The main function of the plasma cells is to produce and secrete all the classes of immunoglobulins into the fluids around the cells.

Natural killer cells

Natural killer (NK) cells are morphologically described as

1. Large granular lymphocytes.
2. Lack T-cell receptor, CD3 proteins, and surface IgM and IgD.
3. Prior exposure does not increase the activity.
4. Thymus is not required for development.
5. Number remains normal in severe combined immunodeficiency disease.

Major Histocompatibility Complex

Histocompatible antigen denotes the cell surface antigens that induce immune responses to an incompatible host, resulting in allograft rejection. The MHC in humans is known as human leukocyte antigens (HLA) complex.

1. **Class I**: HLA-A, HLA-B, and HLA-C.
2. **Class II**: HLA-DR, HLA-DQ, and HLA-DP. All of these are present within HLA-D region of HLA complex.
3. **Class III**: Complement loci that encode for C2, C4, and factor B of complement system and TNFs alpha and beta.

Thank you

Immunology
3th Stage
Biology
Lec. 7

Cytokines

Cytokines are biologically active substances secreted by monocytes, lymphocytes, and other cells and are actively involved in innate immunity, adoptive immunity, and inflammation. Cytokines were initially identified as products of immune cells that act as mediators and regulators of immune processes.

TABLE 17-1 Important functions of the main cytokines

Cytokine	Source	Functions
IL-1	Macrophages	Activates helper T cells, causes fever
IL-2	Th-1 cells	Activates helper, cytotoxic T cells and B cells
IL-3	Th cells, NK, and mast cells	Supports growth and differentiation, stimulates histamine release
IL-4	Th-2 cells	Stimulates B-cell growth, increases isotype switching and IgE, up-regulates class II MHC expression
IL-5	Th-2 cells	Stimulates B-cell differentiation, increases eosinophils and IgA
Interferon-α	Leukocytes	Inhibits viral replication
Interferon-β	Fibroblasts	Inhibits viral replication
Interferon-γ	Th-1, Tc, and NK cells	Inhibits viral replication, increases expression of class I and II MHC, stimulates phagocytosis and killing by macrophages and NK cells
Tumor necrosis factor	Macrophages	Activates neutrophils and increases their adhesion to endothelial cells, mediates septic shock, causes necrosis of tumors, lipolysis, wasting, antiviral and antiparasitic effects
Transforming growth factor-β	Platelets, mast cells, and lymphocytes	Induces increased IL-1 production, induces class switch to IgA, limits inflammatory response, and promotes wound healing

Immunological Tolerance

Immunological tolerance is a state of specific immunologic unresponsiveness to a particular antigen to which a person has been exposed earlier. The immune tolerance prevents the body to mount immune response against the self-antigen.

Mechanisms of Tolerance

Suggested mechanism of tolerance includes:

1. Clonal deletion: Clones of B and T lymphocytes that recognize self-antigens are selectively deleted in embryonic life, hence are not available to respond on subsequent exposure to antigen. This is known as clonal deletion.

2. Clonal anergy: Clonal anergy means a condition in which clones of B and T lymphocytes that recognize self-antigens might be present but cannot be activated.

3. Suppression: In this mechanism, clones of B and T lymphocytes expressing receptors that recognize self-antigens are preserved. However, expression of immune responses following antigen recognition might be inhibited by active suppression.

Types of Immune Tolerance

The immune tolerance may be of two types: **natural or acquired.**

- **Natural tolerance:** Natural tolerance is nonresponsiveness to self-antigens. It develops during the embryonic life, and any antigen that comes in contact with the immune system during its embryonic life is recognized as self-antigen.
- **Acquired tolerance**: Acquired tolerance develops when a potential immunogen induces a state of unresponsiveness to itself. The antigen needs to be repeatedly or persistently administered to maintain the acquired tolerance.

Immunodeficiency

When a system errs by failing to protect the host from disease causing agents or from malignant cells, the result is immunodeficiency. Immunodeficiency diseases and syndromes are the causes of significant mortality and morbidity, as well as a source of extremely valuable information about the physiology of the human immune system.

Immunodeficiency can occur in T cells, B cells, complement, and phagocytes—the major components of the immune system. A functional defect of the immune system is suspected when a patient:

Hypersensitivity

Introduction

Hypersensitivity reaction denotes an immune response resulting in exaggerated or inappropriate reactions harmful to host. It is a harmful immune response in which tissue damage is induced by exaggerated or inappropriate immune responses in a sensitized individual on re-exposure to the same antigen

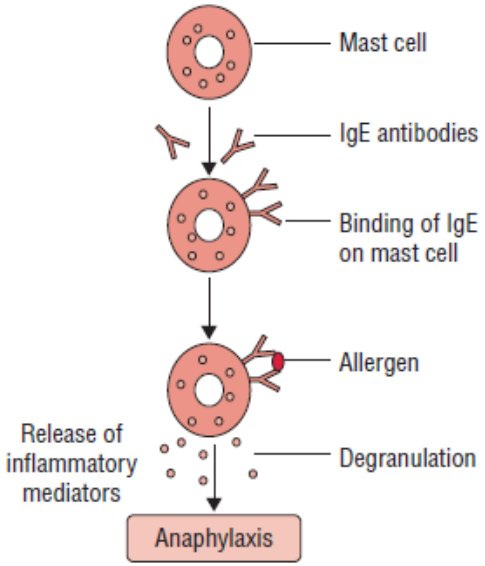


FIG. 19-1. A schematic diagram showing type I hypersensitivity reaction.

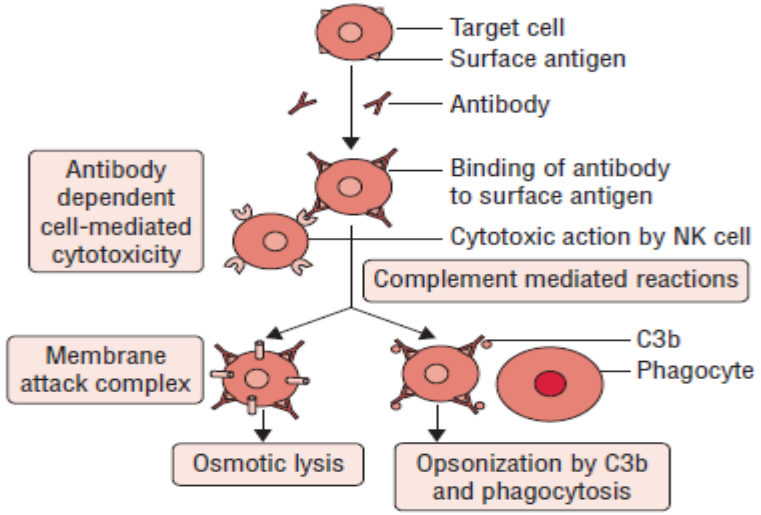


FIG. 19-2. A schematic diagram showing type II hypersensitivity reaction.

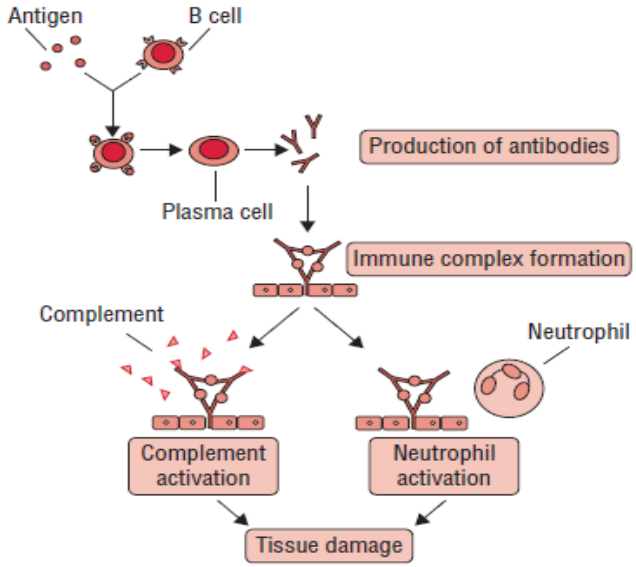


FIG. 19-3. A schematic diagram showing type III hypersensitivity reaction.

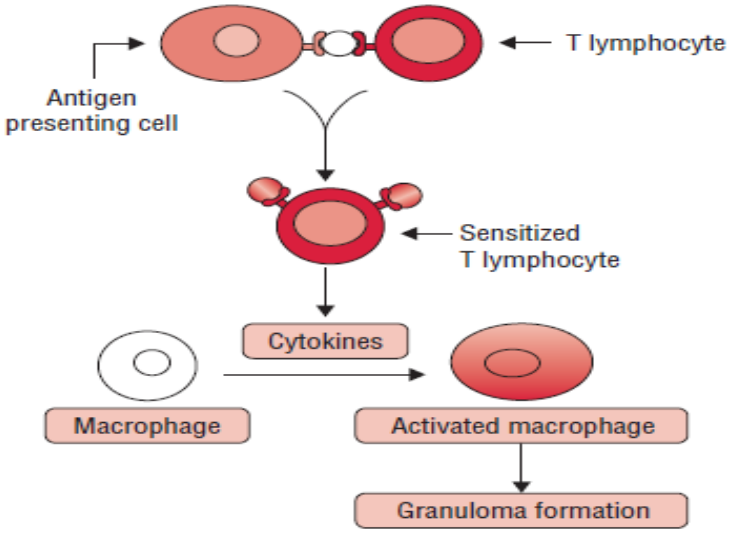


FIG. 19-4. A schematic diagram showing type IV hypersensitivity reaction.

Thank you

Immunology

3th Stage

Biology

Lec. 8

Antigen–Antibody Reactions

Introduction

The interactions between antigens and antibodies are known as antigen–antibody reactions. The reactions are highly specific; **they have been used in many diagnostic tests for the detection of either the antigen or the antibody *in vitro*.** The antigen and antibody reactions also form the **basis of immunity against microbial diseases *in vivo***. In the host, it may cause tissue injury in **hypersensitivity reactions** and in **autoimmune diseases**.

TABLE 14-1 Commonly used tests in clinical microbiology

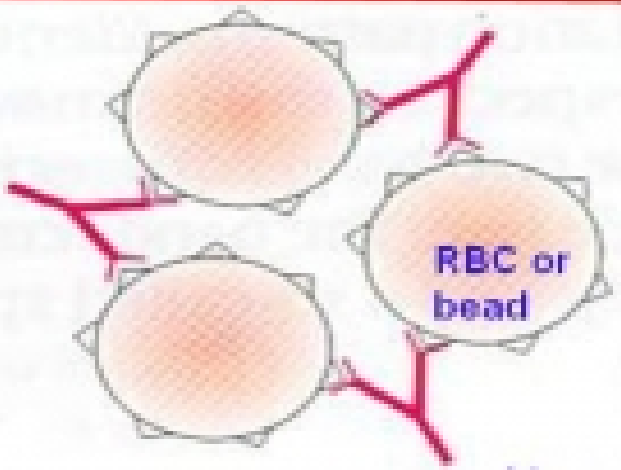
Test	Uses
Flocculation test	Detection of reaginic antibodies in syphilis by VDRL test
Radial immunodiffusion	Detection of fungal antigen and antibodies
Counter-current immunoelectrophoresis	Detection of both antigen and antibodies in bacterial, viral, fungal, and parasitic diseases
Slide agglutination test	Identification of bacterial isolates, such as *Salmonella*, *Shigella*, *Vibrio*, etc.
Tube agglutination test	Detection of antibodies in bacterial infections, e.g., Widal test for enteric fever
Latex agglutination test	Quantitation and detection of antigen and antibodies
Hemagglutination test	Detection of both antigens and antibodies in viral and parasitic infections
Coagglutination test	Detection of microbial antigens
Complement fixation test	Quantitation and detection of antibodies
Direct immunofluorescence test	Detection and localization of antigen in a cell or tissue
Indirect immunofluorescence test	Detection of specific antibodies in the serum
Sandwich ELISA	Detection of antigens and antibodies
Indirect ELISA	Quantitation and detection of antibodies
Radioimmunoassay	Quantitation of hormones, drugs, etc.
Western blot	Detection of antigen-specific antibody

Precipitation vs. Agglutination (know difference)

Immune complex formation with molecular antigens

Soluble Ag and soluble Ab

Precipitation



Immune complex formation with antigenic particles (e g. erythrocytes, latex particles , bacteria)

Beads or RBCs are coated with antigen

Agglutination

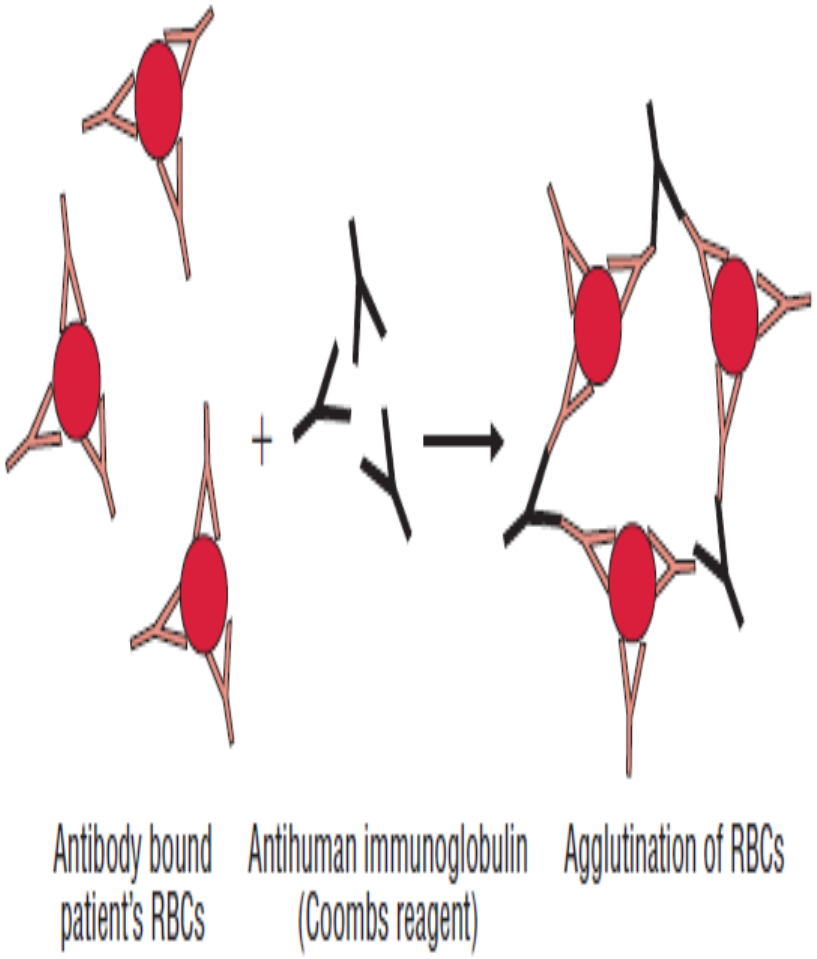


FIG. 14-9. Principle of the direct Coombs' test.

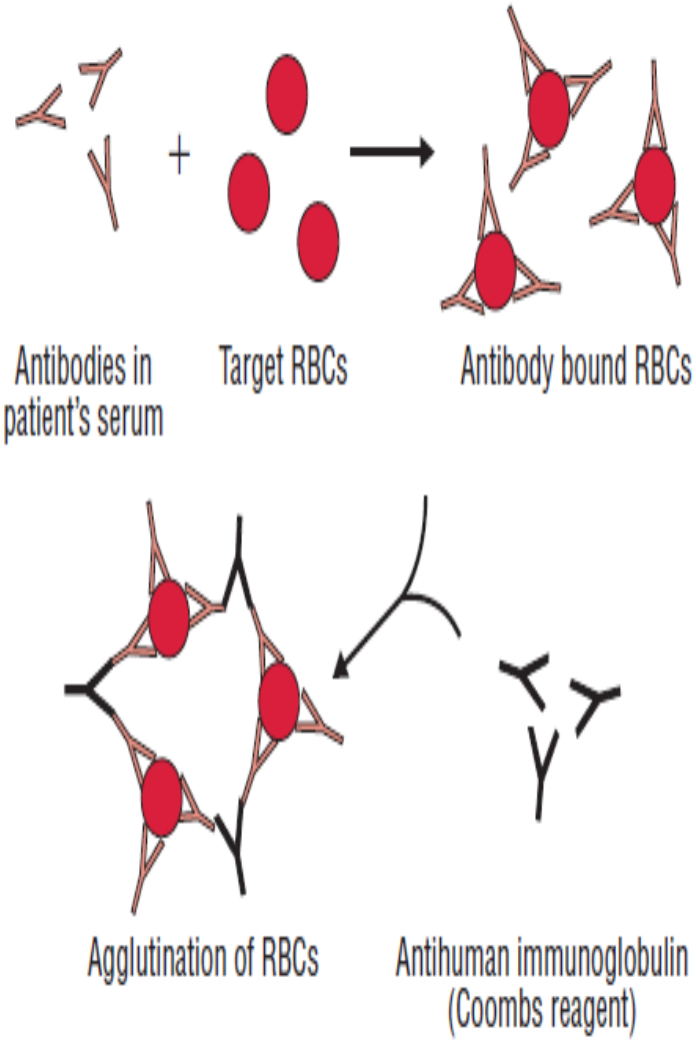


FIG. 14-10. Principle of the indirect Coombs' test.

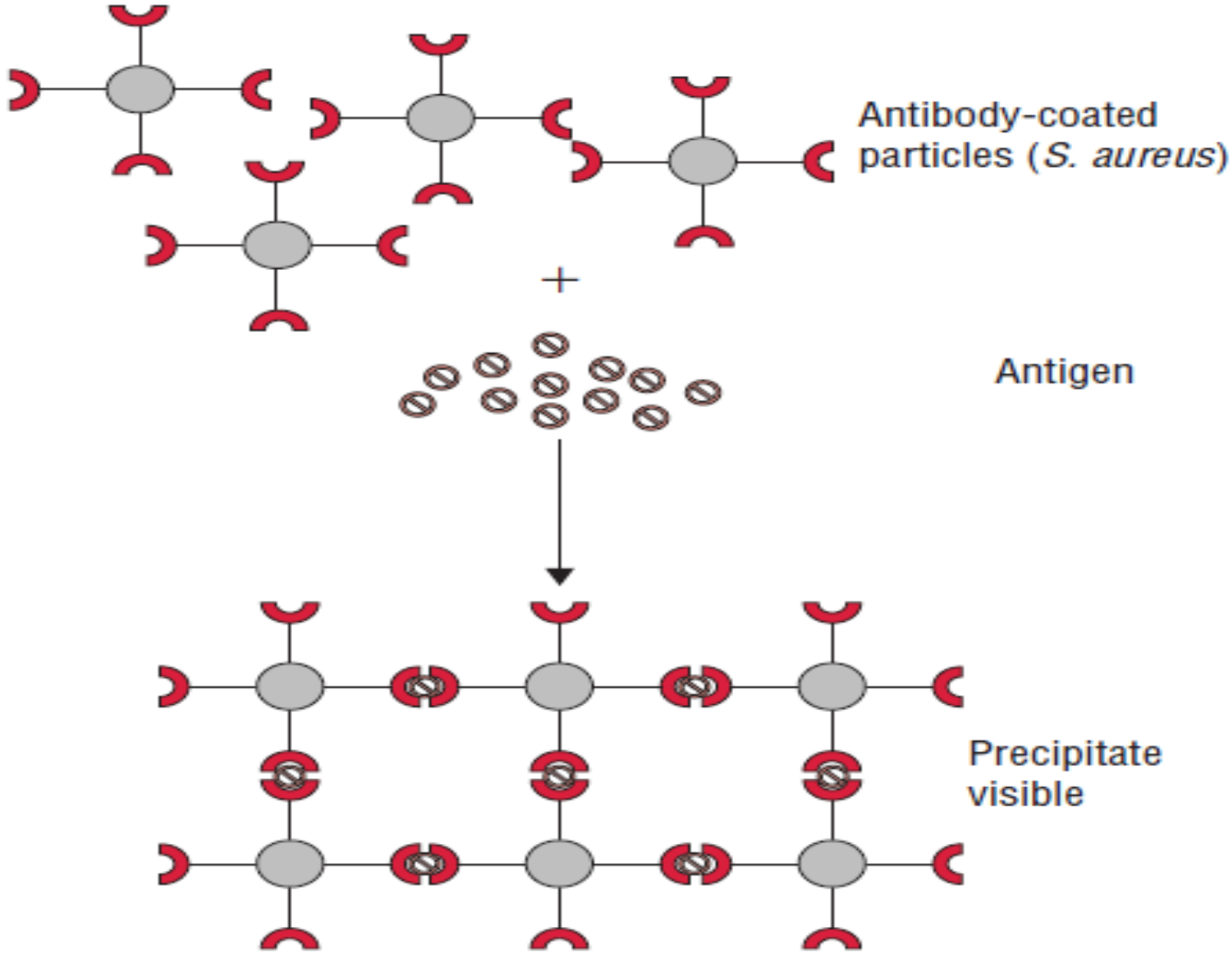


FIG. 14-11. Principle of the coagglutination.

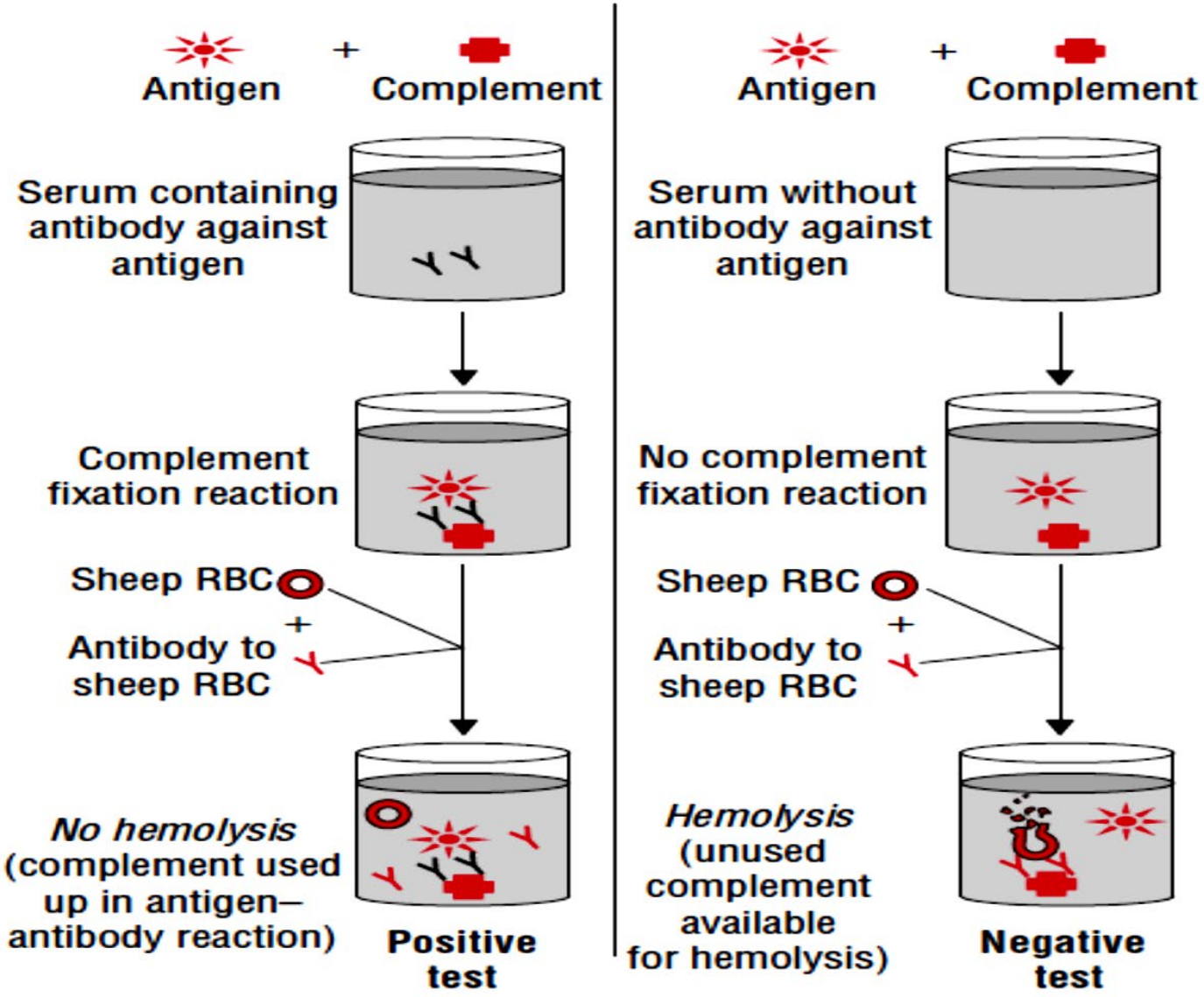


FIG. 14-12. Complement fixation test.

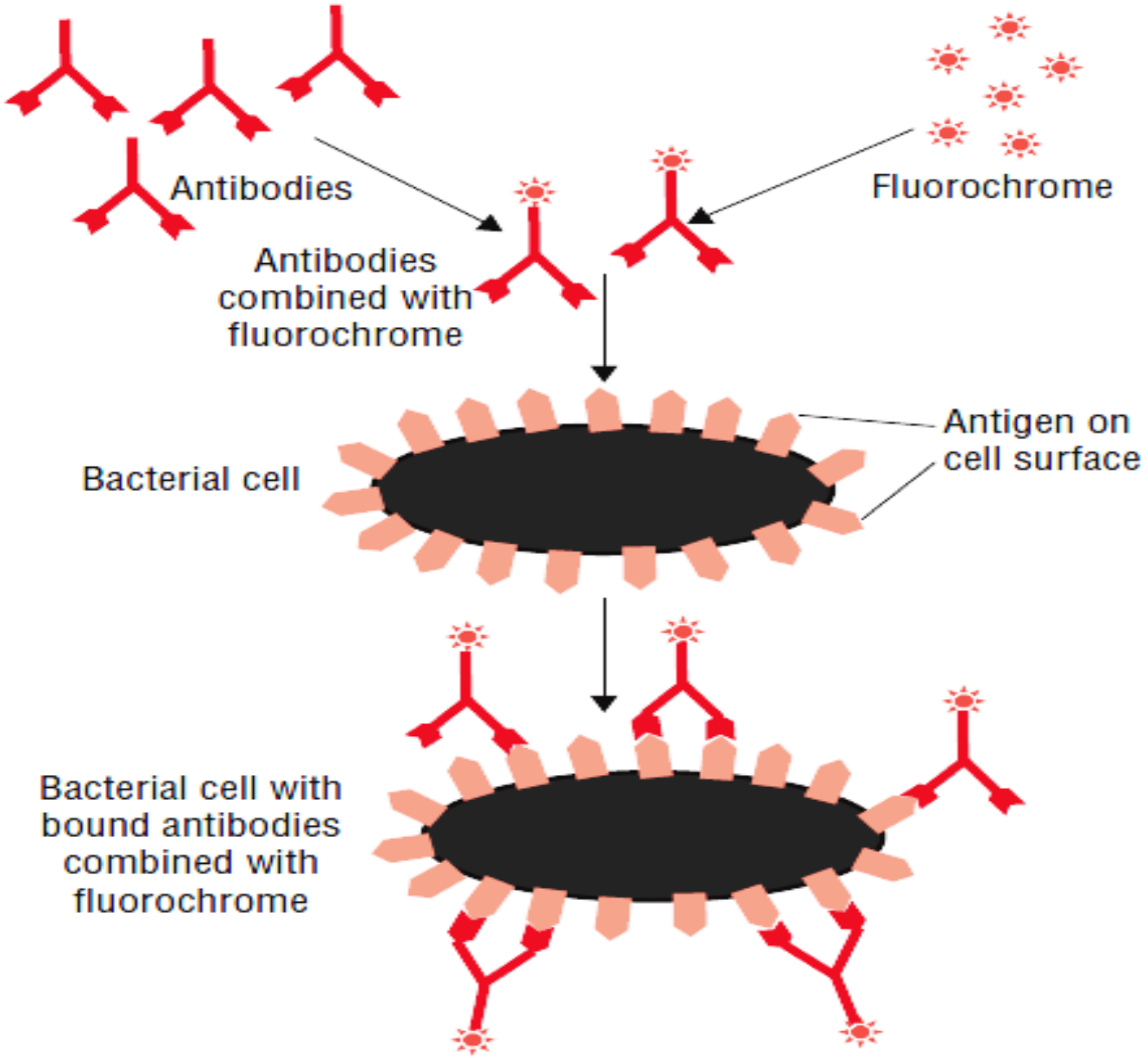


FIG. 14-13. Direct fluorescent antibody test.

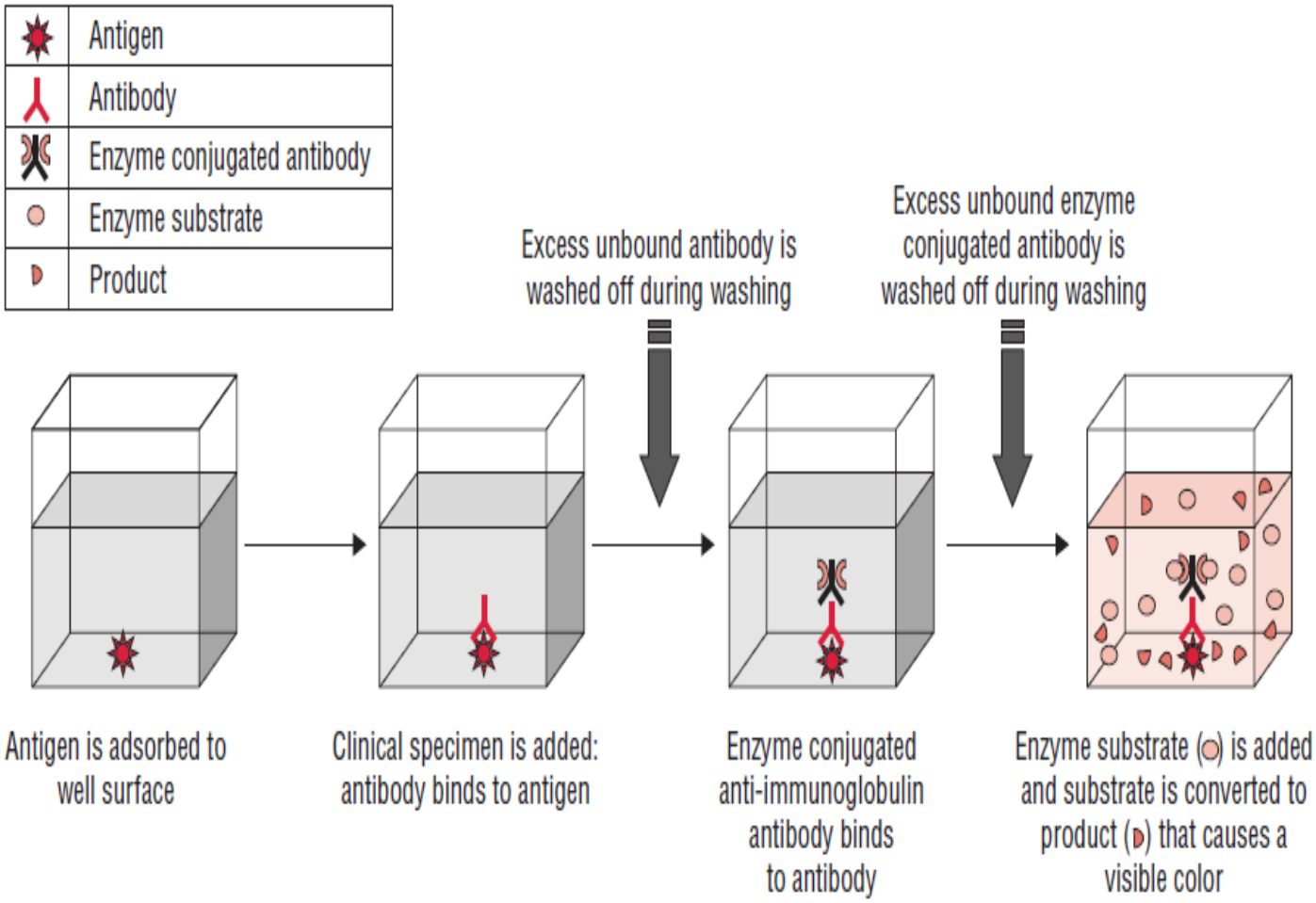


FIG. 14-14. Indirect ELISA test.

Thank you