LECTURE: 04

Title: INNATE IMMUNITY AND IMMUNOLOGICAL BARRIERS

LEARNING OBJECTIVES:

The student should be able to:

- **Recognize that, natural (non-specific) immunity is an innate, and explain the reason of calling it non-specific immunity.**
- **Discus with giving examples, the protective barriers that contributes in innate immunity.**
- **Enumerate cellular and humoral elements involved in the natural immunity.**
- **Define the terms "endocytosis, exocytosis, painocytosis, phagocytosis, opsonization, and antigen-presentation".**
- **Enumerate some opsonins.**
- **Explain phagocytic oxygen dependent and oxygen independent mechanisms in killing engulfed pathogens.**
- **Enumerate some common macrophage secreted products.**
- **Explain the role of the macrophage in immunity, enumerates the different names of macrophages in different body organs, and discus the different mechanisms for killing engulfed pathogens by phagocytes.**
- **Identify the variable professional antigen presenting cells.**
- **Explain the role of the complement proteins in immunity.**
- **Enumerate common cells that contribute with the natural immunity.**

LECTURE REFRENCE:

1. TEXTBOOK: ROITT, BROSTOFF, MALE
IMMUNOLOGY. 6th edition. Chapter 1. pp 1-3. Chapter 2. pp. 15-31

2. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR IMMUNOLOGY. 5TH EDITION. Chapter 1. pg 3-12.

INNATE IMMUNITY

INTRODUCTION

The term of immunity refers to the total number of elements and mechanisms which are involved in the body protection processes, and the immunology deals with the understanding of how the host body can distinguishes the "**self** "elements from these of the "**non-self**" environmental agents. These non-self agents could be micro-organisms or their products, pollen, drugs, food, chemicals, and animal hair and dander. Such immunity recognizes and disposes these non-self agents in two ways **innate or acquired resistance.** Examples of these two types of immunity are illustrated in the **table 1-1**.

Type of Resistance	Examples
Nonspecific	**Mucous membranes** **Phagocytic cells** **Enzymes in secretions**
Adaptive	**Interferon**
Naturally acquired	**Placental transfer of antibody (passive)**
Artificially acquired	**Administration of antitoxin (passive)** **Vaccination (active)**

INNATE OR NATURAL "NONSPECIFIC" IMMUNITY

The physiological mechanisms of natural immunity exist from the time of birth, and their responding to various non-self agents is relatively non-specific, thus these mechanisms do not exhibit specificity, or in other words they do not depend on specific recognition of a foreign agents (a single defense barrier will afford protection against many various potential pathogens.). These defensive mechanisms are of two types **"humoral"** such as complement proteins, and **cellular** which involve the phagocytic cells.

COMPONENTS OF THE NONSPECIFIC IMMUNE SYSTEM

A. Mechanical barriers.

These barriers prevent the attachment and penetration of infectious pathogens to the host body these are; Intact skin, mucus , beating of cilia, coughing and sneezing, flushing actions, urine, saliva, tears, vomiting, and diarrhea.

B. Chemical and biochemical inhibitors of infection

Numerous substance found in body secretions provide a natural defense against microorganisms that invade the body **Table 1-2.**

1. **Chemicals** found in body secretions provide natural defense against pathogens, such as, hydrolytic enzymes in saliva, lysozyme in tears inhibit growth of gram positive bacteria, sialic acid in mucus, low pH in sebaceous gland secretions (organic acids), fatty acids interfere with the function of the cell membranes, A pH dependent polyamine found in sperm and seminal fluid, which inhibit growth of gram negative bacteria, and etc…..

2. **Acid pH** found in almost all physiologic secretions, e.g., urine and vaginal secretions, as well as HCl in the stomach.

C. Physiologic factors that contribute to innate immunity.

1. **Body temperature.**
2. **Oxygen tension**
3. **Hormonal balance.**
4. **Age**

Product	Mechanism of Action
Organic acids	Found at low pH in sebaceous gland secretions; many microbes susceptible to low concentrations
Fatty acids	Interfere with functions of the cell membrane
Saliva	Contains enzymes which damage the microbial cell wall and membrane and cause leakage of cytoplasm; also contains anybodies which opsonize microbes and , with the participation of complement, may lyse cells
Tears	Contain lysozyme, which lyses bacteria, particularly gram-positive bacteria, by destroying the bacterial cell wall
Lactoferrin	Binds iron, interfering with microbial acquisition of this essential metabolite
HCl	Denatures proteins
Bile acids	Interfere with vital functions of the cell membrane
Trypsin	Hydrolyzes proteins of cell membrane and wall
Mucus	Entraps foreign particles; sialic acid content blocks attachment of influenza virus to epithelial cells
Spermine	A pH dependent polyamine found in sperm and seminal fluid; inhibits growth of gram positive bacteria

Table 1-2 Biological Activities of Secretory Products Important in Innate Immunity

D. Phagocytosis. It is a process by which particulate e.g., such as bacteria are ingested and digested by the phagocytic cells (figure 1-1).

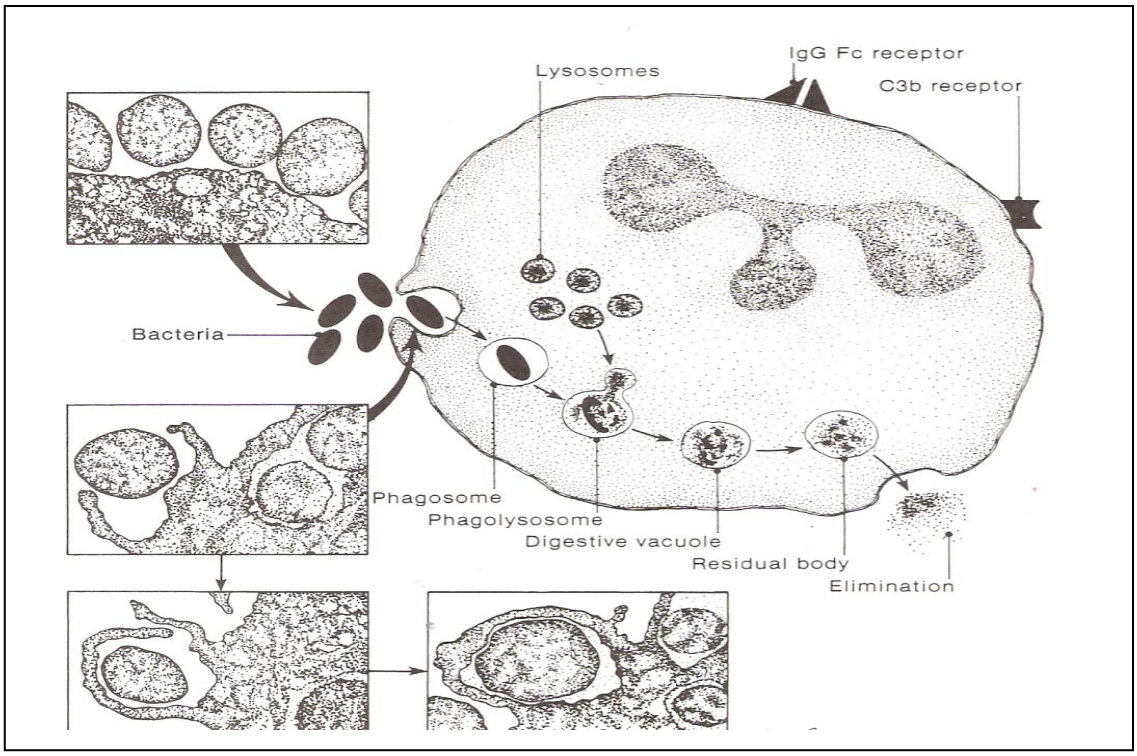

Figure 1-1. The process of phagocytosis, the electron microscopic views (insets) demonstrate the phagocytosis of a mycoplasma cell by a neutrophil. IgG Fc receptor = receptor for the Fc segment of immunoglobulin G; C3b receptor = receptor for complement component C3b.

1. General considerations

a. Phagocytosis requires energy, which is generated through glucose metabolism.
b. It is one form of the endocytosis; the other form is **painocytosis**, which is the internalization of the fluid and solutes.
c. Synthesis of new cell membrane
d. An active cytoplasmic contractile protein system.

2. Phagocytic cells include:

a. **Neutrophils** (polymorphonuclear leukocytes, PMNs) are granulocytes that circulate in the blood and migrate quickly in resp0nse to local invasion by microorganisms.
b. **Monocytes**, it differentiated into **macrophages**, when they migrate into tissues, which reside in all body tissues. For example:

(1) **Kupffer cells** of the liver are macrophages.
(2) **Histiocytes** in connective tissues are macrophages.
(3) **Microgial cells** are the nervous system macrophages.

3. Movements of phagocytic cells

a. Amoeboid movement. The movement of the phagocytic cells in and out of the blood vesseles and through out the tissues is called diapedesis.

b. Chemotaxis. The movement of phagocytic cells towards other cells or organisms by cytoplasmic streaming in response to chemical agents called Chemotaxis **(Table 1-3)**.

Chemotaxin	Source	Comment
N-Formylmethionine	Bacteria	Activates arachidonic acid metabolism
Endotoxins	Bacteria	Activates the alternative complement pathway
Leukotrienes	Arachidonic acid	Products of the lipoxygenase pathway
C5a	Complement	Also causes degranulation of PMNs
Fibrinopeptides	Fibrinogen	Generated via Fibrinolytic pathway
Histamine	Mast cells	Also increases capillary permeability
Platelet-activating Factor (PAF)	Mast cells, PMNs	Also aggregates platelets and causes release of serotonin and histamine
Eosinophil Chemotactic factor	Mast cells	Peptide released on degranulation
Lymphokines	Lymphocytes	Some may also interfere with cell movement (e.g., migration inhibition factor; MIF)

Table 1-3 Factors Chemotactic for Polymorphonuclear Leukocytes (PMNs)

4. Ingestion and vacuole formation

a. When contact with a particle is made, the phagocytic cell engulfs it, surrounding the particle with a part of its cell membrane
b. Once the phagocyte engulfs the particle, the membrane enclosing the particle pinches off and moves into the cytoplasm of the cell, forming a phagocytic vacuole, or **phagosomes**.
c. Lysosome, which are membrane-bound bags of enzymes, fuse with phagosomes to form a **phagolysosome**.

5. Intracellular destruction inside the phagolysosome, the engulfed materials is destroyed by the hydrolytic enzymes in the lysosomes.

a. Lysosomes contain granules of two types:

(1). **Primary granules** also called (azurophilic granules, because they stained dark blue with Wright stain). They contain many hydrolytic enzymes; such as myeloperoxidase, lysozyme, and arginine-rich basic (cationic) proteins. These primary granules represent about 33% of all lysosomal granules.

(2). **Secondary granules** represents about 67% of all lysosomal granules, and they include; alkaline phosphatase, lactoferrin, and lysozyme.

b. Secondary granules release their contents into phagosomes first, usually before the vacuole has completely pinched off.

c. The contents of the secondary granules are partially expelled into the interstitial space; this is called **exocytosis or regurgitation.**

(1). When the process of exocytosis is accelerated the primary granules are released out into the extracellular space, which cause **inflammation** and **tissues destruction.**

(2). Other mechanisms of phagocyte degranulation which can led to tissue damage include:

(a). Reverse endocytosis caused by immune complexes deposited on basement membranes.

(b). Neutrophil cell death.

(c). Perforation of the cell membrane by ingested crystalline substances, such as monosodium urate in patients with gout.

d. The contents of the lysosomal granules are important in breaking down ingested material and in killing microorganisms. The granule contents destroy foreign particles by two mechanisms:

(1). certain portions kill microorganisms by **Oxygen independent mechanisms**:

(a). Hydrolytic enzymes include cathapsin, glycosidase, phosphatase, phospholipase, and arylsulfatase. These chemical substances degrades the slow-reacting substance of anaphylaxis (SRS-A).

(b). Cationic proteins (not enzymes but basic peptides containing large amounts of arginine in polypeptide form e.g., nuclear histone) kill microbes by interacting with essential microbial enzymes and transport proteins.

(c). Lysozyme, a mucopeptidase, attacks bacterial cell wall.

(d). Lactoferrin acts by binding iron.

(2). Other microbicidal compound are generated by **oxygen dependent mechanisms** which include the microbicidal compounds that produced as a result of the respiratory burst that accompanies phagocytosis.

6. Respiratory burst during phagocytosis

a. The metabolic events which during phagocytosis, are resulted in the production of different number of toxic oxygen metabolites such as **superoxide anion**, **hydrogen peroxide**, **singlet oxygen**, **hydroxyl radicals**, **halide** (**e.g., chloride ion**), **myeloperoxidase**, and **hypochlorite (Table 1-4).**

b. In the respiratory burst the following events take place:

(1). Oxygen consumption increase.
(2). Hexose **monophosphate shunt (HMPL) is stimulated**
(3). Production of hydrogen peroxide (H_2O_2) increases. H_2O_2 is a reactive oxidizing agent that kills microbes.
(4). Superoxide **anion**, singlet oxygen, and hydroxyl radicals are produced.

(a). Superoxide anion is molecular oxygen that has picked up an extra electron.

(I) Superoxide anion is extremely toxic to bacteria and tissue, but is very unstable; it is likely converted to H_2O_2 by the enzyme **superoxide dismutase.**

(II). H_2O_2 still toxic to bacteria but is not as potent. The H_2O_2 is broken down by the enzyme **catalase.**

(III). A reduced in the production of superoxide anion and eventually of H_2O_2 is found in the neutrophils of persons suffering from chronic granulomatous disease (CGD).

(b). In **singlet oxygen,** one of the electrons has moved to an orbit of higher energy.
(c). Hydroxyl radicals are highly unstable oxidizing agents that react with most organic molecules they encounter.

(5). Myeloperoxidase, in the presence of toxic oxygen metabolites such as H_2O_2, catalyzes toxic peroxidation of a variety of micro-organisms. Myeloperoxidase comprises 7% of the weight of the neutrophils.

c. The oxygen-dependent agents can combine and act synergistically.

(1). Hypochlorite, the product of the reaction, is more antimicrobial than each of its three components {myeloperoxidase, H_2O_2, and halide (a chloride ion)} alone.

(2). There are several **mechanisms** whereby such an activated halide could damage micro-organisms; for example:

(a). Halogenations of the bacterial cell wall
(b). Decarboxylation of amino acids with the resultant production of toxic aldehydes.

1. Enzymatic generation of superoxide anion Glucose + NADP (via the HMPS) → NADPH + pentose phosphate
2. Spontaneous generation of singlet oxygen, hydrogen peroxide, and hydroxyl radicals Superoxide anion + hydrogen ions → hydrogen peroxide + singlet oxygen Superoxide anion + hydrogen peroxide → hydroxyl radicals + singlet oxygen
3. Enzymatic generation of halogenating compounds Hydrogen peroxide + halide (e.g., a chloride ion) + myeloperoxidase → hypochlorite

Table 1-4 Production of Toxic Oxygen metabolites during the Respiratory Burst that Accompanies Phagocytosis. (HMPS = Hexose monophosphate shunt pathway of glycolysis: NADP, NADPH = nicotinamide adenine dinucleotide phosphate and its reduced form).

7. Secreted products. In the addition to the intracellular destruction, phagocytic cells secrete various compounds that have a protective effect in the body. Among these are:

a. Factors that influence **cell differentiation** (e.g., colony-stimulating factor)
b. Cytotoxic factors (e.g., tumor necrosis factor)
c. Hydrolytic enzymes (proteinase such as collagenase, lipase, and phosphatase).
d. Endogenous pyrogen (interleukin-1; IL-1)
e. Complement components C1 to C5, and properdin and factor B, D, I, and H of the alternative pathway.
f. Alpha interferon
g. Various **plasma proteins** and **coagulation factors**
h. Oxygen metabolites such as H_2O_2 and superoxide anion.
i. Arachidonic acid metabolites such as prostaglandins, thromboxanes, and leukotrienes.

8. Tests for measuring phagocytic functions are:

1. **Assays for metabolism and the generation of toxic molecules**

    a. **General considerations.** These assays are used in the diagnosis of **chronic granulomatous disease (CGD).** They determine whether phagocytic cells are using the Hexose monophosphate shunt and are going through the oxidative burst, thereby generating toxic materials to kill microorganisms.
    b. **Chemiluminescence.** Singlet oxygen produces a small amount of light when its electron returns to its original orbit. If normal levels of singlet oxygen are being generated, the light produced can be measured as chemiluminescence.
    c. **Nitoblue tetrazolium (NBT) reduction.** The NBT test is usually used to assay the phagocytic function of neutrophils.

(1) NBT, a yellow, water-soluble dye, converts to **formazan,** a purple, water-insoluble in superoxide anion during the phagocytic process. Thus, counting the formazan positive (f +) cells gives an indication of neutrophil function.
(2) The assay has two **parts:**

(a) Resting. Dye is placed on the cells, but nothing is administered to trigger oxidation. Normally, 1 % to 2 % of resting neutrophils are f +.
(b) Stimulated. Neutrophils are stimulated to phagocytize.
(i) In normal individuals, 100% of the neutrophils can be stimulated to be f +.
(ii) Patients with CGD lack certain enzymes associated with the HMP shunt [e.g., nicotinamide-adenine dinucleotide phosphate

(NADPH) oxidase] and therefore their neutrophils do not kill intracellular; no cells are f + in either the resting or stimulated state.

(3) The NBT test is particularly useful in **genetic counseling** (CGD is usually an X-linked disease). If the mother is a carrier, she may have 1% to 2 % f + in resting neutrophils and an intermediate value (e.g., 50 %) when stimulated.

2. Assays for ingestion and killing of microorganisms.

In some phagocytic disorders, the cells show a defect in uptake or in killing, with normal NBT values. In the se cases, the cells are evaluated for their phagocytic and microbicidal activities.

a. **Phagocytosis**. Cells can be incubated with bacteria or other engulfable materials (e.g., latex or polystyrene particles) for 1 to 3 hours, then stained and examined for uptake or the foreign bodies.

b. **Microbial activity**. Intracellular killing by phagocytic cells can be measured by direct plate counting of mixtures of microorganisms and cells.

(1) In this test, the **microbicidal or intracellular killing assay,** viable bacteria are added to a tube of neutrophils and incubated for 30 to 60 minutes.

(2) Counting the surviving bacteria by culture of he mixture, and comparing the counts to a control tube with bacteria but no neutrophils, gives the percentage of kill. A normal population of cells will kill 85 % to 90 % of the bacteria within 30 minutes.

(3) The viability of the engulfed microbes can be determined more easily of a cridine orange, a fluorescent dye , is added to the culture medium. When observed with a fluorescence microscope, live bacteria will stain green while dead organisms will appear red.

3. Assays for Chemotaxis

a. Two procedures are available for testing the ability of neutrophils to move in a directed migratory pattern toward a chemotactic stimulus such as endotoxins or the complement split product C5a.

(1) The neutrophils and the stimulus can be separated by a nitrocellulose membrane with a pore size of 3 to 5 μ, he cells that migrate through the small pores can be counted by staining and observation of the opposite side of the membrane.

(2) The migration may occur through an agar menstruum, with the cells migrating from a well punched in the agar toward a chemoattractant placed in a second well.

b. The assay must be done in parallel with a normal blood specimen o provide a frame of reference.

E. Opsonization

1. Opsonins are substances that bind to particles and make them more susceptible to phagocytosis.

a. Phagocytosis can occur in a very simple system. For example, if neutrophils, saline, and bacteria are combined, phagocytosis will occur.

b. Phagocytosis can be remarkably enhanced in the presence of serum or plasma, however, because the blood constituent contains opsonins.

2. Opsonins found in serum include the following:

a. Split products of the complement cascade.

(1) Complement component C3b is the most important opsonin; also, iC3b and C5b are active in this process.

(2) Phagocytic cells possess membrane receptors for these molecules **(Table 1-5)**.

(3) Thus, bacteria and other foreign particles with one of these molecules on their surface will have an enhanced interaction with the phagocyte.

Receptors	Recognized Complement Component	Function
CR1	C4b, C3b, iC3b	Aids target cell ingestion; allows factor I to cleave C3b to C3dg; important in clearing immune complexes from the body
CR3	iC3b	Aids target cell ingestion; important in cell adherence to surfaces
CR4	iC3b, C3dg	Not well studied but presumed to aid in attachment of phagocyte to target

Table 1-5 Phagocytic Cell Receptors for Complement-Derived Opsonins

b. Antibodies

(1) Phagocytic cells have a receptor (Figure 1-1) for the Fc portion of the IgG molecule (Figure 1-2), thus enhancing the strength of interaction between the cell and the antibody-coated (i.e., antibody-opsonized) particle that is being engulfed.

(2) IgG1 and IgG3 are most active in this process; IgG2, IgG4, and IgA may also be opsonins for phagocytosis.

c. Other opsonin in serum

(1) **Fibronectin** is a glycoprotein that opsonizes and acts like glue to cause neutrophil and their targets to stick together.

(2) **Leukotrienes** are derivatives of arachidonic acid; some of the leukotrienes are opsonins. Leukotrienes **LTB_4** is chemotactic as well.

(3) **Tuftsin** a tetrapeptide split product of an IgG-like molecule called **leukokinin**, is found in the spleen. Tuftsin stimulates chemotactic and phagocytic activities.

F. Humoral factors contributing to nonspecific immunity

1. Antibody-mediated complement activation in bacteriolysis

a. Normal serum can kill and lyse gram-negative bacteria.

(1) This property is probably due to the combined action of antibody and complement, both of which are present in normal serum.

(2) The activity is destroyed by heating at 56° C for 30 minutes, due to the inactivation of complement.

b. Bacteriolysis begins with the lytic action of antibody-activated complement on the outer lipopolysaccharide layer of the cell wall.

(1) A bacterial cell wall contains two layers: an outer membrane layer of lipoproteins and lipopolysaccharide and inner layer of mucopeptide (peptidoglycan).

(2) The antibody and complement disrupt the lipopolysaccharide layer of the cell wall. Complement becomes an esterase which provides for the majority of this enzymatic activity.

c. Once the lipopolysaccharide layer is weakened, lysozyme, a mucopeptidase present in serum, can enter and destroy the mucopeptide layer. The end result is the destruction of the bacterial cell.

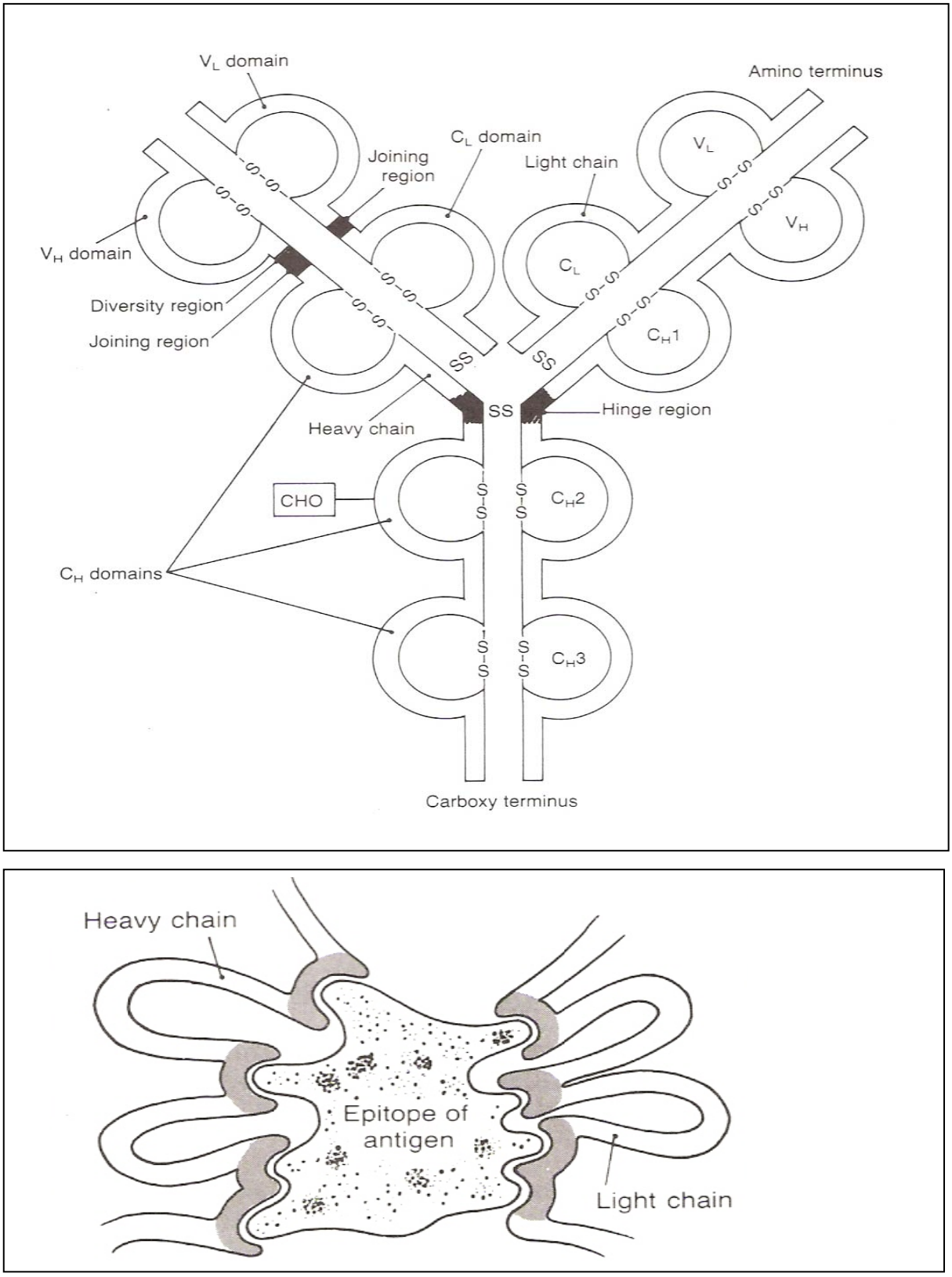

Figure 1-2. Basic unit (monomer) of the IgG molecule, consisting of four polypeptide chains linked covalently by disulphide bonds (S-S) with intra chain disulfide linkages as well. The loops correspond to domains within each chain. V = variable domain; C = constant domain; L = light chain; H = heavy chain; CHO = carbohydrate side chain. The inset shows the complementarity-determining (hypervariable) regions (CDRS) [shaded] and framework regions (FRS) [open] of each variable domain in the paratopic region. Similar hypervariable regions are found in α and β chains of the T cell receptor for antigen.

2. Nonantibody humoral factors contributing to nonspecific immunity

a. **Chemotactic factors** attract phagocytes; the chemotaxin C5a is an extremely important split product of C5 generated during complement activation.

b. **Properdin** is involved in complement activation by the alternative pathway. As a bactericide, properdin is believed to work in conjunction with antibody and complement (plus magnesium ions).

c. **Interferons** are proteins produced, usually, by virally infected cells, and they protect other cells in the area. (Although there are other triggers for interferon release, virus infection is the most common and natural one).

(1) Types of interferons

(a) **Alpha interferon** secreted by macrophages and other leukocytes. It is induced by viruses or synthetic polynucleotides.

(b) **Beta interferon** is secreted by fibroblasts, also by viruses or synthetic polynucleotides.

(c)

(d) **Gamma interferon** is also called **immune interferon**. It is secreted by T lymphocytes following stimulation with the specific antigen to which the lymphocyte has been sensitized.

(2) Protective effects of interferons

(a) Interferons activate cellular genes, inducing neighboring cells to produce antiviral proteins that interfere with the translation of viral messenger RNA (mRNA).

(b) Interferons block viral translation by two enzyme mediated processes.

(i) **Protein kinase** transfers a phosphate group from adenosine triphosphate (ATP) to an initiation factor required for protein synthesis. This phosphorylation inactivates the initiation factor, and viral protein synthesis is inhibited.

(ii) **Oligonucleotide polymerase** synthesizes adenine trinucleotide. This activates an endonuclease which cleaves mRNA, preventing viral replication.

(c) Other protective actions of interferons are to:

(i) Enhance T cell activity..
(ii) Activate macrophages
(iii) Enhance the expression of major histocompatibility complex (MHC) molecules on cell membranes
(iv) Increase the cytotoxic action of natural killer (NK) cells

d. Beta lysin is an antibacterial protein released from blood platelets when they rupture, as in clot formation. It is active primarily against gram-positive bacteria.

e. Lactoferrin and **transferrin** are iron binding proteins that compete with bacteria for that essential metabolite.

f. Lactoperoxidase is found in saliva and milk. Its mechanisms of action are similar to that of myeloperoxidase.

g. Lysozyme hydrolyzes the mucopeptide layer of the cell wall of many different bacteria, making the cell susceptible to osmotic lysis. This enzyme is present in serum, tears, saliva, nasal secretions, and other body fluids, as well as in lysosomal granules.

G. Lymphocytic cells contributing to nonspecific immunity.

2. Natural killer cells. These are large granular lymphocytes appear to function in immune surveillance.

a. Source and location

(1) NK cells are innate, or naturally occurring cytotoxic lymphocytes: they are present in the body from the time of birth, and are not induced by immunologic insult.
(2) They arise from bone marrow precursors but are of a lineage distinct from that of either T or B cells.
(3) NK cells make up 10% to 15 % of the lymphocytes in the peripheral blood and 1 % to 2 % of the lymphocytes in the spleen. They are absent from the lymph nodes.

b. Functions

(1) NK cells are cytotoxic for tumor cells and virally infected autologus cells.
(2) They also have been reported to play a role in resistance to some bacterial, fungal, and parasitic infections, and to participate in regulation of the immune response through the secretion of lymphokines such as IL-2.
(3) Recent evidence suggests that NK cells, not killer (K) cells, may be responsible for antibody-dependent cell-mediated cytotoxicity (ADCD).

c. Mode of actions

(1) NK cells kill their targets by perforating the cell membrane, causing holes to form.

(a) The molecules that are responsible for the pore formation are called **perforins.**

(i) Following intimate cellular contact, perforins are released from granules within the NK cell cytoplasm.
(ii) The perforins insert into the target cell membrane and polymerize, in the presence of calcium ions, forming channels within the cytoplasmic membrane of the target cell.

(b) The end result is depolarization, abnormal ion flux, and essential metabolite leakage from the cytoplasm.

(2) NK cells have membrane receptor for the Fc portion of antibodies IgG1 and IgG3, but will kill targets in the absence of antibody.
(3) Their target range is broad, and they are not subject to MHC restriction. That is, cytotoxicity by NK cells does not require that the NK cell recognize MHC molecules on the target cells.
(4) NK cells release numerous cytokines during their interaction with the target cells, including alpha and gamma interferons, IL-1 and IL-2, B cell growth factor, lymphotoxin (TNF-β).
(5) The cytotoxic activity of NK cells can be significantly enhanced by exposure to IL-2 and the interferons.
(6) NK cells do not possess antigenic specificity and do not require immunologic memory following exposure to virus-infected cells or tumor cells.

3. **Antibody dependent cytotoxic cells (ADCC)** these cells can kill target cells without the participation of complement if the target cells are coated with specific antibody.

a. Functions. ADCC is thought to play a role in antitumor and antigraft immunity and may be involved in antiviral protection as well.

b. Types of cells

(1) ADCC has been attributed to a unique subset of lymphocytes called **killer (K) cells**.

(2) CD16 is a membrane receptor for the Fc portion of IgG1 and IgG3, which would explain the mechanism of target recognition and interaction.

(3) In addition to NK cells, macrophages and neutrophils also participate in ADCC.

4. **Lymphokines activated killer cells (LAK)**

   a. The LAK cell is another naturally occurring cytotoxic cell. It is a quiescent lymphocyte that is induced into an active cytotoxic state by IL-2, a lymphokine.

   b. The LAK cell is similar in many ways to the NK cell but has an even broader target cell range.

5. **Tumor-infiltrating lymphocytes (TILs)** are a type of LAK cell that has been cultured in vitro with IL-2 in the presence of a specific tumor cell. TILs demonstrate enhanced tumoricidal activity when infused back into the donor of the lymphocytes and tumor cells.

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