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.

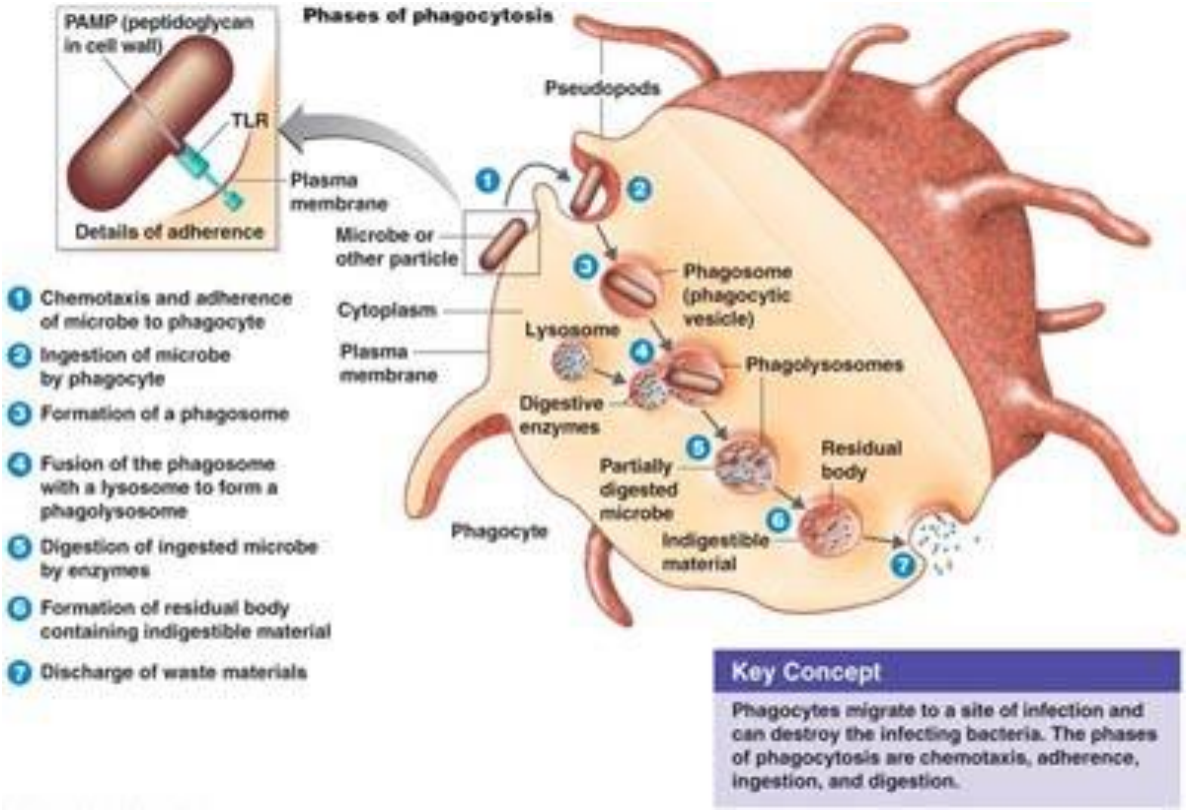
C. Physiologic factors that contribute to innate immunity.

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

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

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

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).



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 pinocytosis, 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 vessels and throughout 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).

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

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)

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 are 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 represent 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 (H2O2) increases. H2O2 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 H2O2 by the enzyme superoxide dismutase.

(II). H2O2 still toxic to bacteria but is not as potent. The H2O2 is broken down by the enzyme catalase.

(III). A reduced in the production of superoxide anion and eventually of H2O2 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 H2O2, 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, H2O2, 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.

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).

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

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 H2O2 and superoxide anion.

i. Arachidonic acid metabolites such as prostaglandins, thromboxanes, and leukotrienes.

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.

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

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