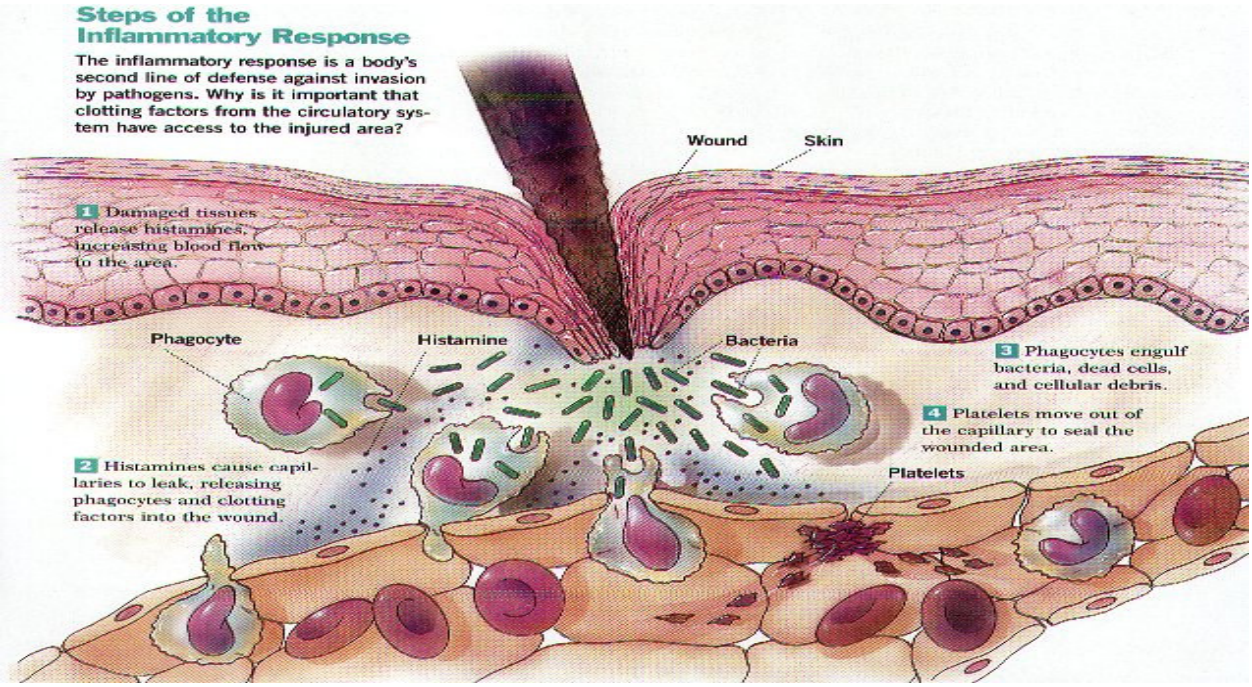
Natural (innate) Immunity
Elements of Innate Immunity
Chapter-1 and Glossary

Various stimuli cause cell injury, they induce :
A complex vascular and cellular response called **: INFLAMMATION.**

CELL INJURY CAN RESULT FROM :

- Hypoxia.
- Physical & chemical agents .
- Microbial agents. (defective immunity)
- Immune reactions. (abnormal responses)
- Genetic factors .
- Nutritional imbalances.

The main function of the immune
system is to prevent ,control & eliminate microbial infections .
(But may also react against non- infectious agents .)



In spite of the constant exposure to microbes *clinical infections* are **QUITE RARE**.

Sub clinical infections are **COMMON.** (No symptoms or signs of infection.)

All defense mechanisms are collectively called :

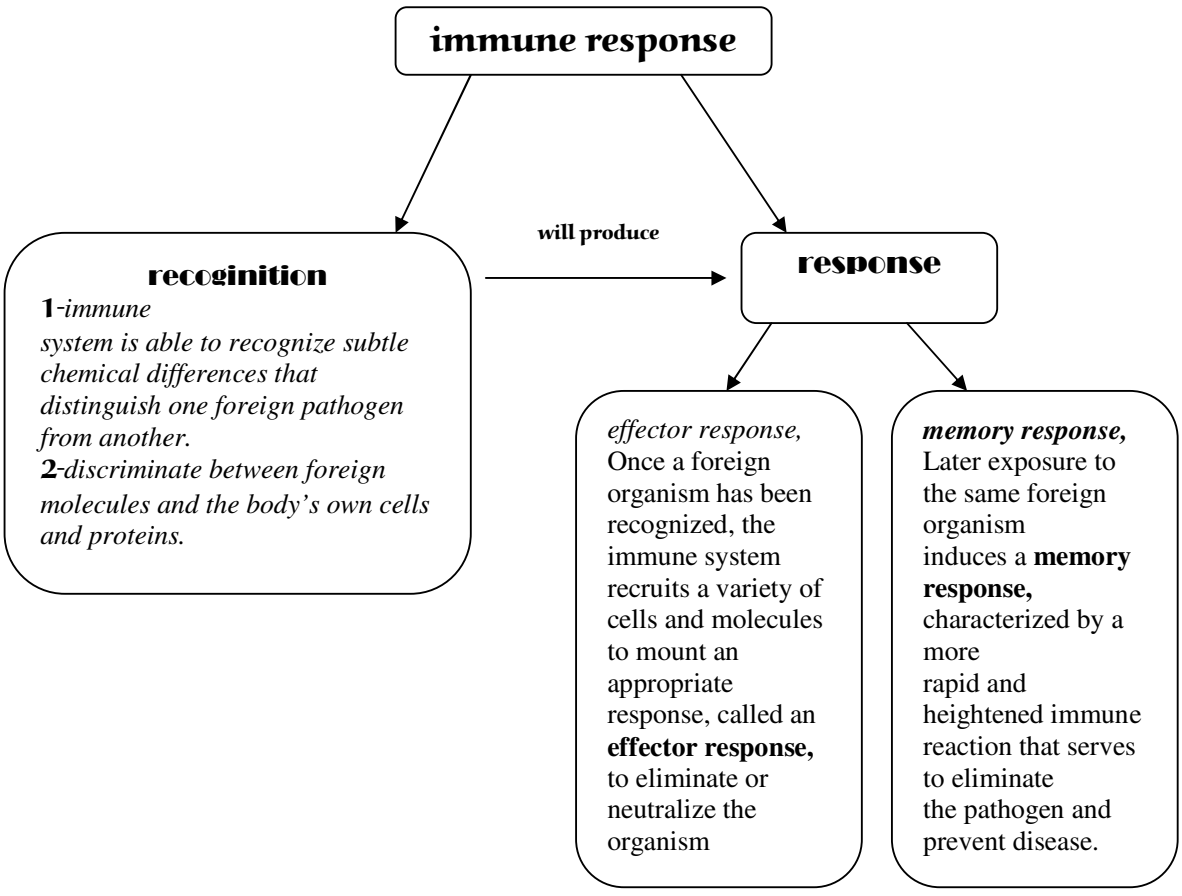
(IMMUNITY)

Immunity is divided into :

- natural (innate) immunity .
- acquired immunity .

Innate and adaptive immunity operate in cooperative and interdependent ways. The activation of innate immune responses produces signals that stimulate and direct subsequent adaptive immune responses.

Functionally, an immune response can be divided into two related activities—*recognition and response.*



differences between the natural and acquired immunity

	Natural immunity	Acquired immunity
Mechanism of recognition of microbes	Cell surface receptors	receptors on phagocyte & lymphocytes
Effector mechanisms .	non-specific	specific
Immunologic memory.	no retention of memory	There is Immunologic memory.

However, the 2 systems are :

1. Well - integrated, and

2. Connected by a cytokine network.

INNATE IMMUNITY SERVE AS:

- A critical early defense ,(mobilized within minutes after invasion by microbes)
- A warning signal that a microbe is invading the tissues .(phagocyte receptors)
- It stimulate & later influence adaptive Immunity.(secrete cytokines & activate cells).

e.g. A progressing **extracellular infection** ,that *by –pass natural defense mechanisms* may be followed by : an adaptive antibody-mediated response (humoral immunity),

and an **intracellular infection** by : an adaptive cell-mediated response .

TABLE 1-2 Summary of nonspecific host defenses

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

Summary of nonspecific host defenses :

1.Anatomic barriers

- **Skin :** Mechanical barrier retards entry of microbes.
- **Acidic environment** (pH 3–5) retards growth of microbes.
- **Mucous membranes :** Normal flora compete with microbes for attachment sites and nutrients.
- **Mucus** entraps foreign microorganisms.
- **Cilia** propel microorganisms out of body.

Disruption of the anatomic barriers:

- Burns , cut wounds , skin diseases: Predispose to infections.
- Aseptic techniques. (taking a blood sample, I/V catheters etc.)
- Disruption of the mucus membrane, (oral cavity).

2.Physiologic barriers

- **Temperature:** Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of pathogens.

- **Low pH Acidity:** of stomach contents kills most ingested microorganisms.

- **Chemical mediators:** Lysozyme cleaves bacterial cell wall.
  Collectins : disrupt cell wall of pathogens.

- **Natural antibiotics :** defensins , cryptidins.

Physiological functions:

- Coughing , sneezing , voiding urine, tears , saliva in oral cavity etc.
- Inability to cough (chest trauma, muscle disease)
- Urine retention .

3. Circulating effecter cells :

A. Neutrophils.

B. Macrophages.

C. Natural killer (NK) cells.

D. Eosinophils, (parasitc immunity).

E. Mast cells ,(mediators).

E. Platelets (coagulation).

Phagocytic cells recognize microbes by surface receptors:

e.g. Toll-like receptors (TLRs), ***recognize :*** lipopolysaccaride (LPS) on gram –ve bacteria .

Pattern-recognition receptors on cells ***recognize :*** Pathogen-associated molecular patterns. (PAMPs.)

Neutrophiles:

- Mediate the early phase of inflammation.
- They are recruited to the sites of infection by a process termed **chemotaxis** which is stimulated by **cytokines**.

PMN LEUKOCYTES :

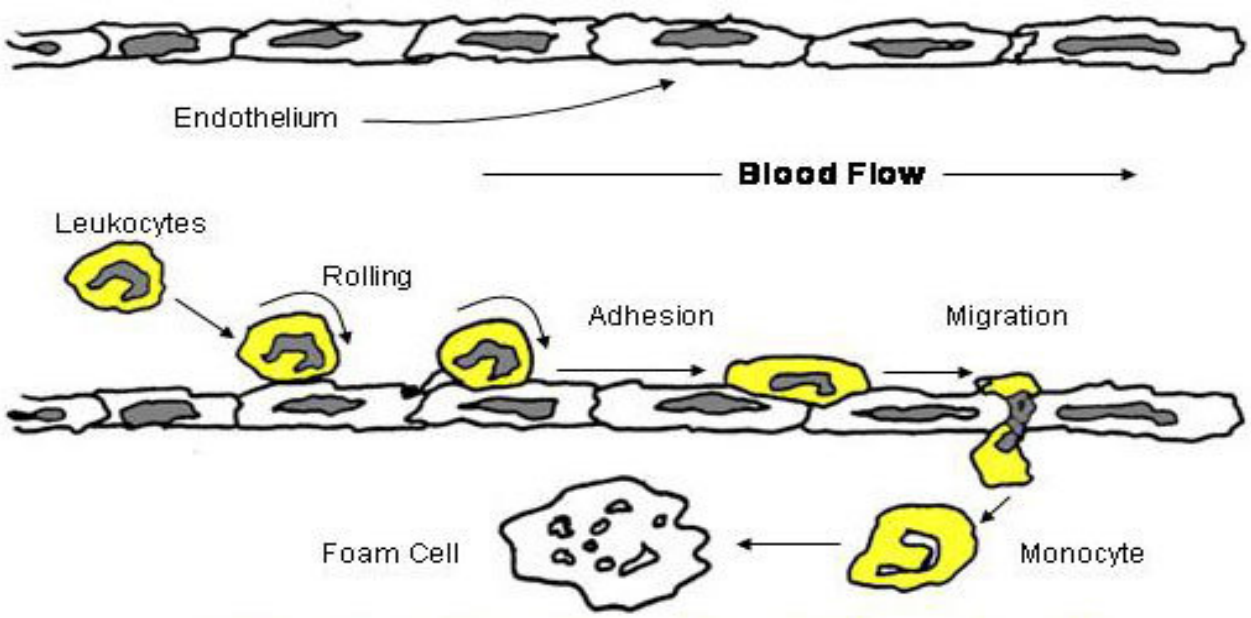
- Neutrophils (60-70 percent. WBC.)
  - Short-lived cells.
  - *Extra-cellular infections.*
  - Contain enzymes.
  - Perform killing by:
    - Oxygen- dependent mechanisms.
    - Oxygen- independent mechanisms.

Chemotaxis involve adhesion Molecules :

1. Selectins .
2. Integrins.

Steps in *chemotaxis* involve :

1. Rolling (loose adherence)
2. Activation .
3. Stable adherence.
4. Transmigration .



Longitudinal cross section of blood vessel

Adhesion molecules produced by endothelial cells cause leukocytes (white blood cells), such as monocytes, to roll and adhere. Once monocytes traverse the endothelium, they become engorged with oxidized lipids and form foam cells, leading to atherosclerosis. Rolling and adhesion occur in eddies associated with arterial branching and sheer stress.

MONONUCLEAR CELLS :

- Monocytes → Macrophages .
- Long-lived cells.
- Contain enzymes & *secrete* many cytokines .
  - Control *intra-cellular infections*.
- Professional **phagocytic cells.**
- **Antigen – presenting cells**
- important in **both natural & adaptive immunity.**

Monocytes enter tissues differentiate into Macrophages & become resident in :

1. Sub epithelial connective tissue.
2. Interstitia of organs .
3. Vascular sinusoids of the liver & spleen.
4. Lymph nodes . (They constitute the mononuclear phagocyte system)

THEREFORE:

- Macrophages are strategically located at sites ***where microbes enter***.

- They recognize microbes first , become activated and secrete cytokines that attract neutrophils .

MACROPHAGES ARE STIMULATED:

- lipopolysaccaride LPS.
- Bacterial DNA.

They secrete cytokines, attract Neutrophils & induce a local inflammatory response .

The cytokines produced by macrophages include :

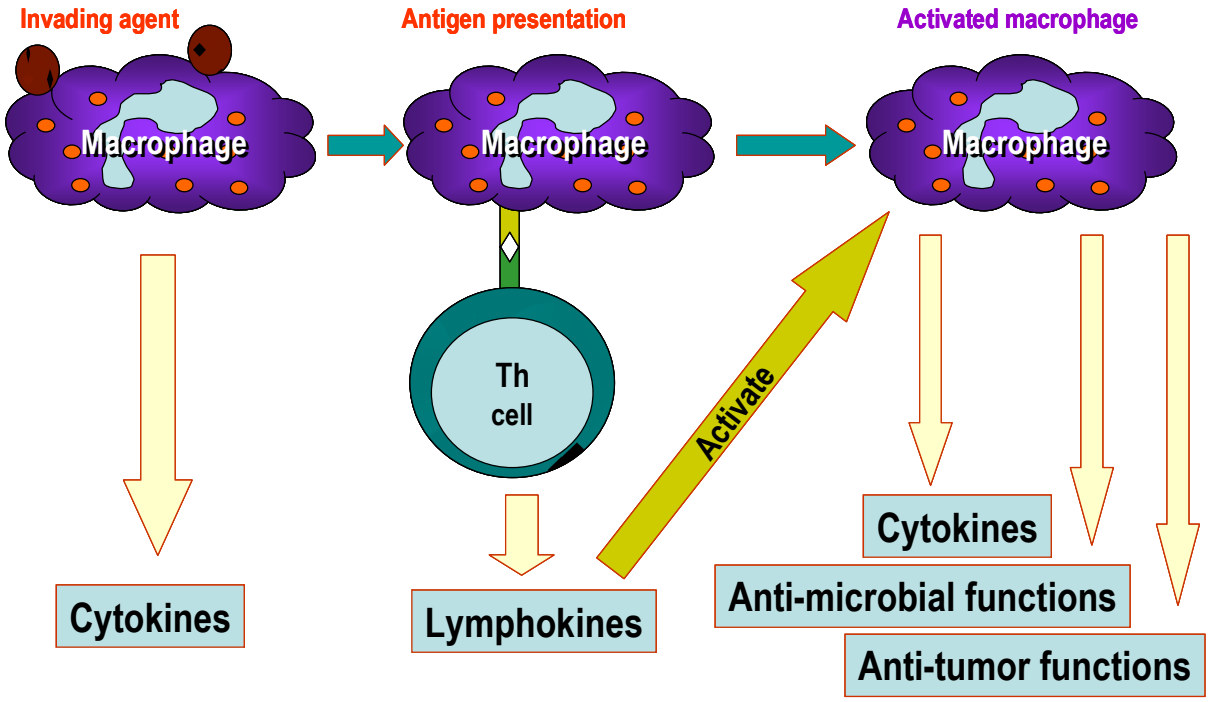
- IL-1 (interleukin 1).
- TNF (tumor necrosis factor).
- IL-6.
- IL-8.
- IL-12.

TABLE 2-7 Some factors secreted by activated macrophages

Factor	Function
Interleukin 1 (IL-1)	Promotes inflammatory responses and fever
Interleukin 6 (IL-6), TNF-α	Promote innate immunity and elimination of pathogens
Complement proteins	Promote inflammatory response and elimination of pathogens
Hydrolytic enzymes	Promote inflammatory response
Interferon alpha (IFN-α)	Activates cellular genes, resulting in the production of proteins that confer an antiviral state on the cell
Tumor necrosis factor (TNF-α)	Kills tumor cells
GM-CSF, G-CSF, M-CSF	Promote inducible hematopoiesis

Functions of macrophages :

1. Induce local inflammation.
2. Perform phagocytosis.
3. Activate coagulation .
4. Enhance antigen presentation.
5. Initiate tissue repair .



<u>Mechanism of intracellular killing by Phagocytic cells :</u>

1. Lysosomal enzymes .
2. Production of reactive oxygen intermediates .
3. Production of nitric oxide (intercellular signals).
4. Circulating effecter proteins

Natural killer : a class of large granular cytotoxic lymphocytes that do not have T- or B-cell receptors. they are antibody-independent killers of tumor cells and also participate in antibody-dependent cell-mediated cytotoxicity

NK-CELLS are activated by:

1. IL-12.
2. IL-15.

Produced by macrophages.

Functions:

1. anti-viral activity.
2. anti- tumor activity

Circulating effecter proteins:

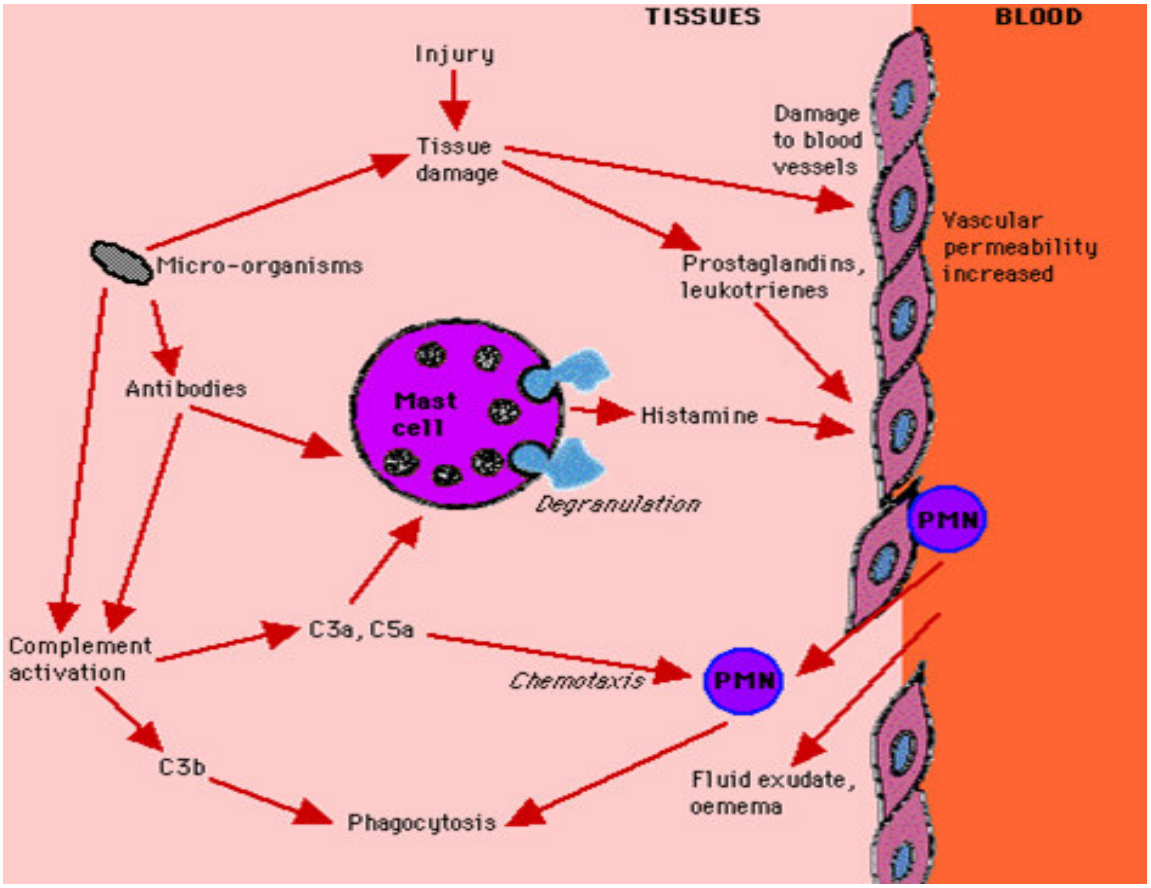
The complement proteins :

Activation of the complement system lead to initiation of important effects which include :

1. Release of chemotactic factors .
2. Opsonisation of microbes .
3. Lysis of target cells .

Other circulating effecter proteins :

1. Mannose- binding lectin .
2. C – reactive protein .
3. Coagulation factors.
4. Cytokines .



Cytokines of innate immunity :

1. Interferon's. (Anti-viral).
2. IL-1, TNF & Chemokines, (mediate inflammation.)
3. IL-12 & IL-15: (NK-CELLS.)
4. Interferon-gamma:(act on macrophages.)
5. IL-6: (act on bone marrow)
6. IL-10 & TGF-B : (Limit local inflammation.)

0ther functions of cytokines :

❖ The cytokines IL-1 , IL-6 & TNF-alpha.

Coordinate body responses to infections they act on the :

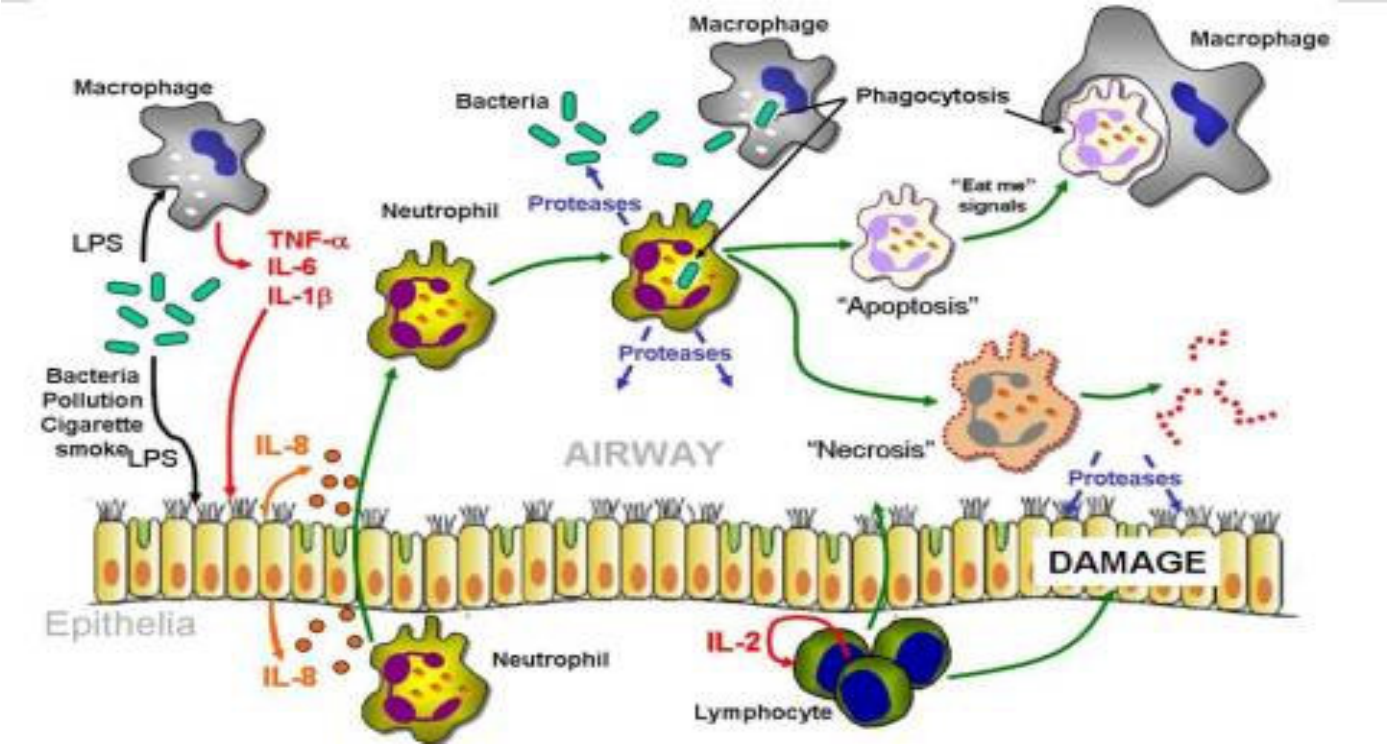
1. Liver to induce the synthesis of acute phase proteins.

2. Bone marrow to stimulate mobilization of neutrophils .

3. Hypothalamus to increase body temperature.(fever).

4. Fat & muscle to supply proteins & energy.

5. T- & B- Lymphocytes to become activated & produce adaptive immune responses.



SUMMARY :

1. Natural Immunity is the first line of defense.
2. It influence & stimulate subsequent adaptive immune responses .
3. The immune response is a :
   - Protective.
   - Sub clinical .
   - Localized reaction.