# INNATE IMMUNITY

Microbiology V

# TYPES OF IMMUNITY

Introduction:

- Pathogenic microorganisms have a unique ability of causing diseases in the human body.
- But in most cases, the defense mechanisms of our body, which are a complex network of interactive overlapping systems, protect us against the pathogenic microorganisms.

- **Immunity** is the capability of multicellular organisms to resist harmful microorganisms.
- It is the ability to ward off diseases through our defenses is called **resistance**
- Whereas lack of resistance, that is, vulnerability to disease is known as susceptibility.

- Immunity involves two types:

- 1. Innate immunity (nonspecific host defense)
- 2. Acquired immunity (specific host defense)

- **Innate immunity** (nonspecific host defense):

- The nonspecific host defences are integral components of human body present from birth and give resistance to infectious microorganisms or their products.
- These include:
  - first line of defence: skin and mucous membrane and
  - second line of defence: phagocytes, inflammation, fever and antimicrobial substances.

- **Adaptive immunity** (specific host defense):

- Is also called as acquired immunity.
- It is the specific defence immunity is a third line of defence, which comes about in response to a particular parasite and is directed at that parasite.
-
- It is based on specialised cells of the immune system called lymphocytes and the production of specific proteins called antibodies.

- The branch of science that deals with these immune responses and the phenomena responsible for this type of defence is called immunology.

**Innate immunity** (nonspecific host defense):

- All individuals possess the innate defences since birth.
- It depends upon the general well being of an individual and also on the nutrition, fatigue, age, sex and climate.

- They are also called **non-specific defences** because they act against each type of invading agent.

- They are normally inherited from the parents and are present naturally in all individuals of a species.
- Therefore, this may also be called as **species resistance** or **species immunity.**
- For example, all humans are naturally resistant to the infections of *Mycobacterium avium.*

- Similarly, many pathogens, which infect man, cannot attack other groups of vertebrates.

- Another type of innate resistance is observed in certain races of a particular species.
- This type of resistance is called **racial resistance** or racial immunity.

- Ex: black Africans affected by the genetic disease sickle-cell anaemia do not contract malaria
- Because the malarial parasite (*Plasmodium* spp.) cannot penetrate the distorted red blood cells.

| NON-SPECIFIC DEFENCES (INNATE IMMUNITY) | | SPECIFIC DEFENCES (ADAPTIVE IMMUNITY) |
|---|---|---|
| **First line of defense** | **Second line of defense** | **Third line of defense** |
| • Skin<br>• Mucous membranes<br>• Secretions of skin and mucous membranes | • Phagocytic leukocytes<br>• Antimicrobial proteins<br>• Inflammatory response<br>• Fever | • Lymphocytes<br>• Antibodies<br>• Memory cells |

Figure: overview of host defence or types of immunity

- **Innate defense mechanisms:**

- The human body has several non-specific lines of defence against potentially pathogenic microorganisms.

- The physical and certain chemical barriers operate to prevent pathogens from entering the body.

- The other non-specific defences:
  - act to destroy pathogens or
  - inactivate the toxic products that have gained entry
  - prevent the pathogens from damaging additional tissues.
  - Ex. cellular defences, inflammation, fever and molecular defences

**1. Physical Barriers**

- The skin and mucous membranes are the body's first line of defence against pathogens.
- They physically block the entry of pathogens into the body.

- **Skin:**
- Intact skin is one of the human body's largest organ that is impervious to most microorganisms.
- The skin has two distinct layers—an outer thin layer called **epidermis** and an inner layer called **dermis**.
- The epidermis is in direct contact with the external environment and consists of many layers of continuous sheets of tightly packed epithelial cells.

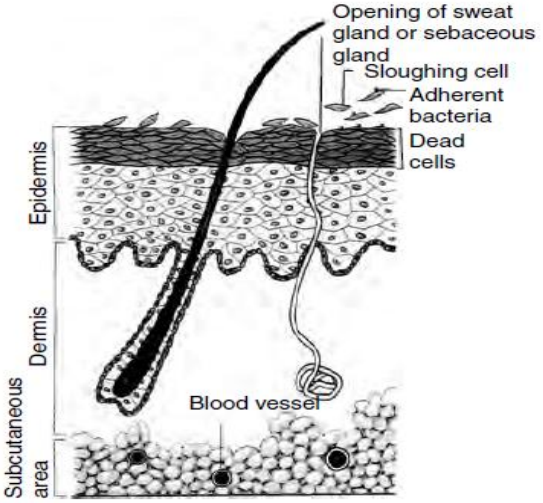



Figure 20.2 A diagrammatic sectional view of the intact human skin

- The epidermal cells are covered externally by dead cells, which are continuously sloughed off as the skin grows.

- These cells contain a protective protein called **keratin**, which is not readily degraded enzymatically by microorganisms.

- Continuous shedding of the outer epithelial cells removes those organisms that are adhered to them.

- Additionally, the outer layer of dead cells prevents infection by viruses that require live cells for their replication.

- Relative dryness and mild acidity (pH 5–6) of the skin also inhibits the growth of many microorganisms.

- Therefore, all these features make the skin an effective barrier to different kinds of microorganisms.

- The importance of skin as a protective physical barrier can be observed when breaks in the intact skin occur due to cut, bruise, burn, animal bite.

- This exposes the body to numerous microorganisms, which are able to establish infections through these sites and then ultimately enter the circulatory system and deep body tissues.

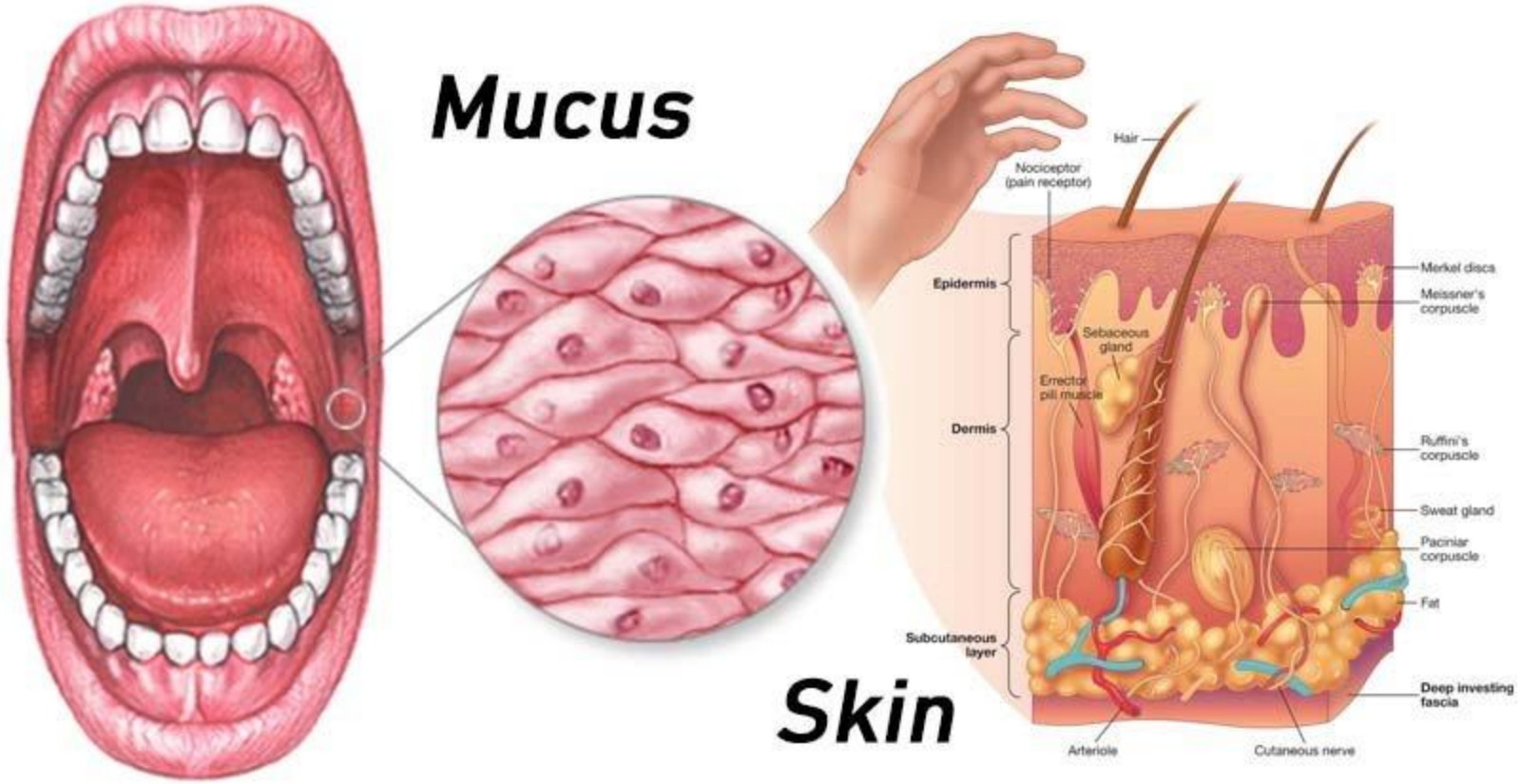
**Mucous membranes:**

- The mucous membranes line the entire gastrointestinal, respiratory and genitourinary tracts.
- It consist of an epithelial layer and an underlying connective tissue layer.

- The epithelial layer of a mucous membrane secretes a fluid called **mucus** or **mucin**
- Its a slightly viscous glycoprotein produced by goblet cells of mucous membrane.

- The mucus accumulates on the surface of the cells, where it traps microorganisms and prevents them from penetrating into the epithelial cells.

# Physical barriers of innate immunity



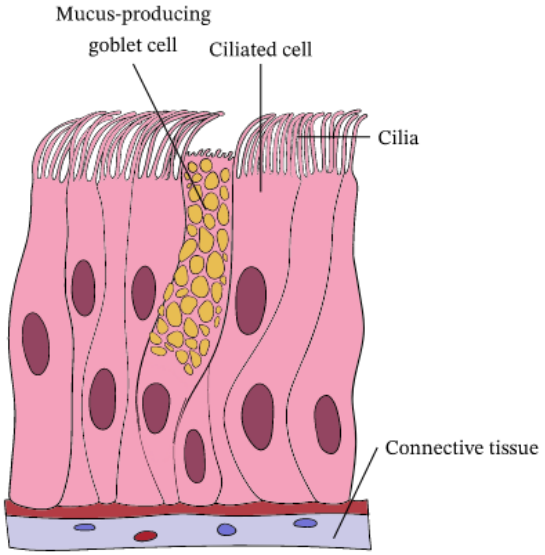
- Mucus also contains antimicrobial substances, such as:
- **Lactoferrin:** an iron-binding protein that deprives microbes of iron
- **Lysozyme:** an enzyme that digests the cell wall of bacteria) and
- **Defencins:** small proteins that make holes in microbial membranes.

- The mucous membrane of the nose has also mucus-coated hairs that filter the inhaled air and trap the microorganisms, dust particles and other pollutants.

- Similarly, elimination of microorganisms and other particulate bodies from the lower respiratory tract is facilitated by the cilia covering the cells of the mucous membrane.

- Synchronous movement of these ciliary cells
  - propels the mucus along with embedded microorganisms and particles upwards towards the throat
  - they are ejected out by cough or sneeze.

- Microorganisms are also prevented from entering the lower respiratory tract by the small epiglottis
- Covers the larynx (voicebox) during swallowing.

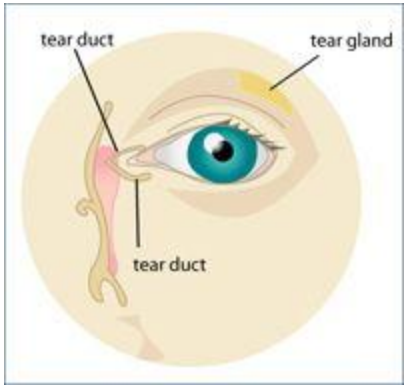


**Other physical barriers:**

- Besides the skin and mucous membranes, several other factors also help to protect certain epithelial cells.

**Tears:**

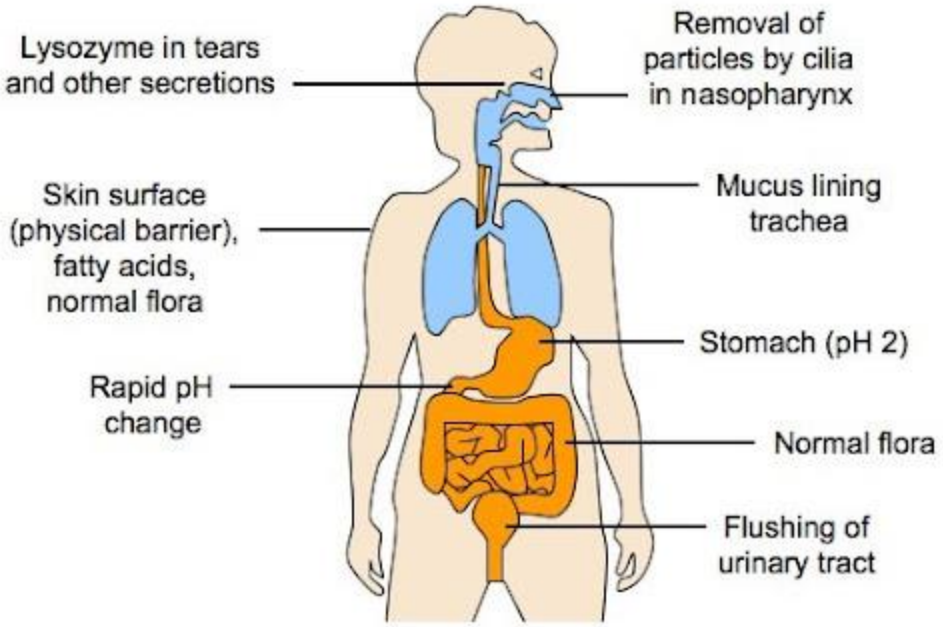
- Lacrimal fluid produced by the lacrimal glands
- Spread over the surface of the eyeball
- Evaporate or pass into the nose as fast as they are produced.
- This process of continuous washing helps to keep the microorganisms away from settling on the surface of the eye.
- Tears contain large amounts of **lysozyme** and other antimicrobial substances.



- **Saliva:**
- secreted in the mouth from the **salivary glands**
- helps to dilute the number of microorganisms
- wash them  from the surface of teeth and the mucous membrane of the mouth into the stomach,
- the acidic environment kills most of them.

- **Urine:**
- The flow and slightly acidic pH
- keeps the urinary tract clean by preventing microbial colonisation.

- **Vaginal secretions:** also move the microorganisms out of the female genital tract.




Physical barriers of the innate immune system

**2. Chemical Barriers:**

- **Lysozyme:**
- It is an enzyme that degrades the cell walls of Gram-positive bacteria and to a lesser extent, Gram-negative bacteria.
- Lysozyme specifically breaks the chemical bonds on peptidoglycan, thus destroying the bacterial cell walls.

- Lysozyme is found in some body fluids, including tears, sweat, saliva, mucus and colostrum and thus confers antimicrobial activity to them.

- The process of swallowing, sneezing and coughing also exposes the bacteria to body fluids containing lysozyme and thus reduces the number of potential pathogens.

**Acidity:**

- Body tissues are protected by the low pH caused by acid production.

**Sebum:**

- Sebaceous (oil) glands of the skin produce an oily substance called **sebum**
- Lipid deposits are broken down by the resident microorganisms of the skin into free fatty acids.
- This contributes to the acidity of the skin and inhibits the growth of certain pathogenic bacteria and fungi.

**Gastric juice:**

- produced by the glands of the stomach.
- Its a mixture of hydrochloric acid, enzymes and mucus.
- Very low pH (1.2–3.0).

- Most of the microorganisms entering the digestive tract are unable to tolerate the low pH of the stomach and thus get destroyed in this environment.

**Lactic acid and acetic acid:**

- In the lower intestinal tract, the resident microorganisms protect the host against invasion of pathogens by producing acidic metabolic fermentation products such as lactic acid and acetic acid.

**Vaginal secretions:**

- Acidic pH 4 maintained due to the presence of *Lactobacillus* and *Streptococcus* species
- Non-pathogenic and acid-tolerant
- Form lactic acid by the fermentation of glycogen produced by vaginal epithelium.
- This low pH discourages the growth of most of the pathogenic microorganisms.

**Iron-binding proteins:**

- There are some proteins present in the mucus and blood, which bind iron by chelation.
- These compounds limit the growth of pathogens by depriving iron
- Ex: lactoferrin and transferrin.

- **Lactoferrin** is presentin tears, semen, bile, breast milk and secretions of nasopharyngeal, bronchial, cervical and intestinal mucosa.
- **Transferrin** is present in serum and the intercellular spaces of tissues and organs.

**Interferons:**

- They are a family of related, low-molecular weight, regulatory glycoproteins
- Produced by eukaryotic cells in response to viral infections and other microbial pathogens that reproduce within host cells.

- Human interferons are classified as IFN-α, IFN-β and IFN-γ.
- Produced in very low quantities
- Only few neighbouring cells are protected from the pathogens.

- Interferons do not block the entry of the pathogen
- But they prevent their replication within the protected cells.

**Fibronectin:**

- It is a high-molecular weight glycoprotein that can interact with certain bacteria.

- It binds to the surface components of *Staphylococcus aureus*
- Helps in its non-specific clearance from the body.

- It also covers the receptors of certain epithelial cells
- To block the attachment of microbial pathogens.

**Complement:**

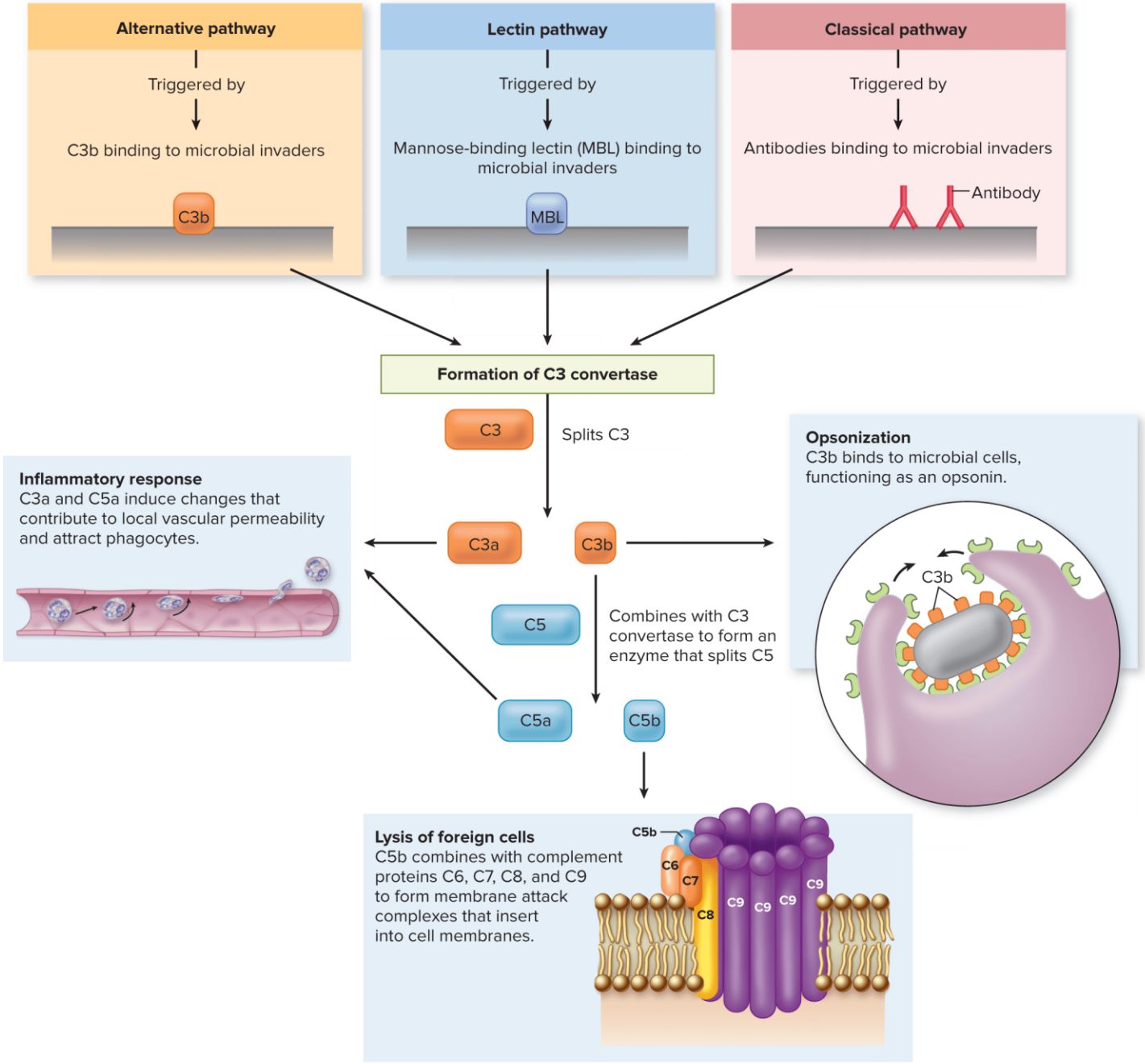
- Blood contains a family of more than eleven glycoprotein molecules, collectively called **complement.**
- Plays an important role in the removal of invading bacterial pathogens.

- The complement glycoproteins are designated as C1, C2, C3 and so forth.
- Numbers indicating their order of discovery.

- Complement system work together in an autocatalytic fashion.
- When one complement becomes activated, it activates another complement component and so on.
- It leads to various non-specific defense responses in the host that protect the body against microbial infections.

- The non-specific initiation of the complement system is called as the **alternate pathway**.

- The central activator of this pathway is the complement component C3.
- C3 gets activated by substances of the microorganism
- It activates other complement components C6 to C9
- Forms a **membrane attack complex (MAC)**
- Penetrates the cytoplasmic membrane forming a pore
- Results in osmotic lysis of the bacterial cell.


Alternative pathway
Triggered by
C3b binding to microbial invaders
C3b
Lectin pathway
Triggered by
Mannose-binding lectin (MBL) binding to microbial invaders
MBL
Classical pathway
Triggered by
Antibodies binding to microbial invaders
Antibody
Formation of C3 convertase
C3
Splits C3
C3a
C3b
C5
Combines with C3 convertase to form an enzyme that splits C5
C5a
C5b
Inflammatory response
C3a and C5a induce changes that contribute to local vascular permeability and attract phagocytes.
Opsonization
C3b binds to microbial cells, functioning as an opsonin.
C3b
Lysis of foreign cells
C5b combines with complement proteins C6, C7, C8, and C9 to form membrane attack complexes that insert into cell membranes.
C5b
C6
C7
C8
C9
C9
C9
C9

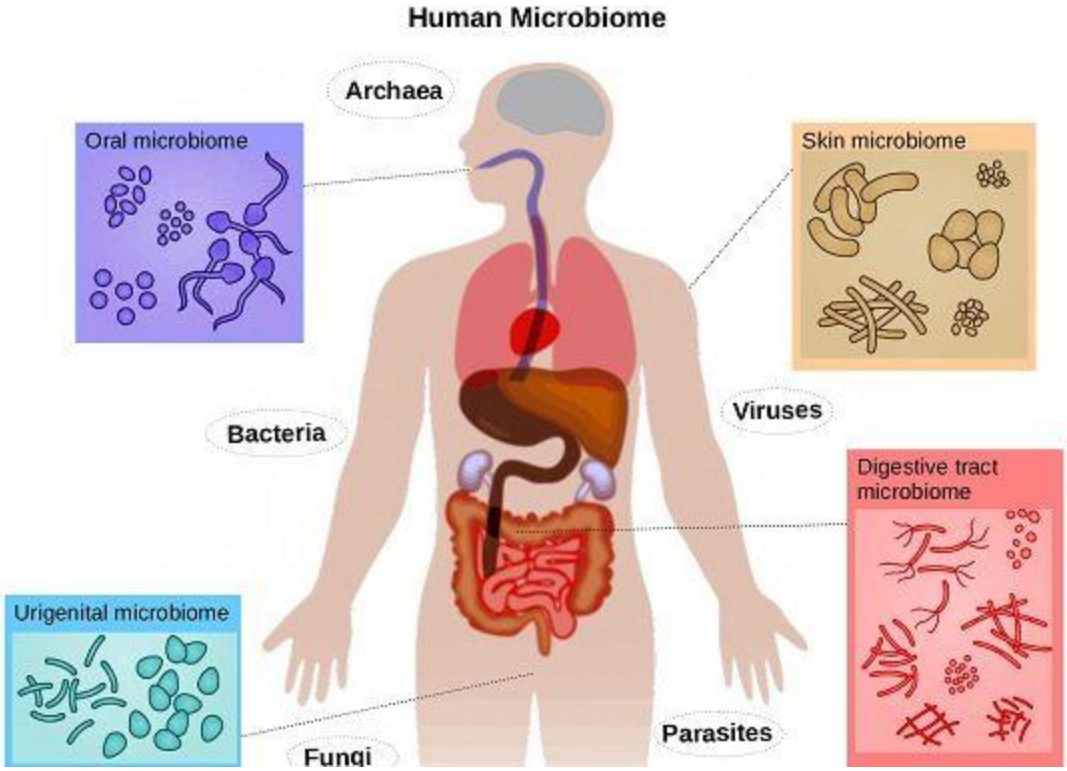
**3. Normal Indigenous Microbiota:**

- The body surfaces of humans are associated with microbial populations called as indigenous microbial populations, **normal microflora** or **normal microbiota**.

- Distinct microbial populations inhabit the surface tissues of skin, oral cavity, gastrointestinal tract, respiratory tract and genitourinary tract.

- Most of these are bacteria and non-pathogenic.

- They grow on the body surfaces and thus suppress colonisation by pathogens.


Human Microbiome
Archaea
Oral microbiome
Skin microbiome
Viruses
Bacteria
Digestive tract microbiome
Urigenital microbiome
Parasites
Fungi

Normal microbiota contribute to the non-specific defence by following ways:

1. Producing anti-microbial substances known as **allelopathic substances**
   - prevents the establishment of infection by pathogenic microorganisms.
   - Ex: resident microorganisms of the skin produce low-molecular weight unsaturated fatty acids that possess antimicrobial activity.

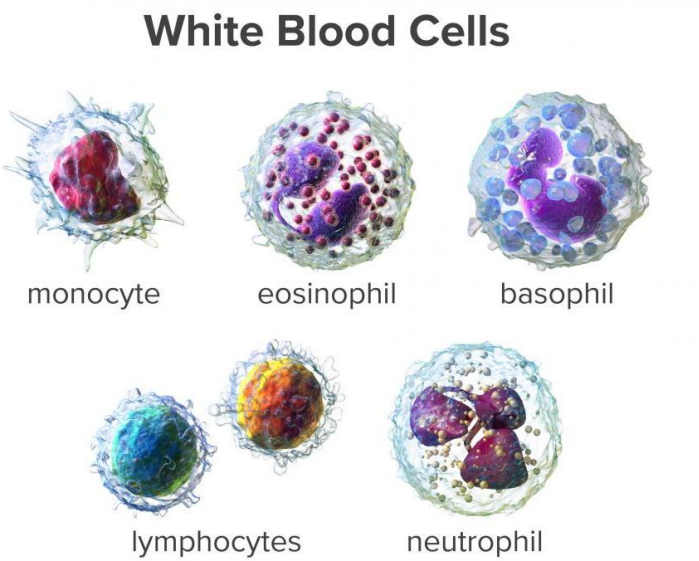
2. Inhibiting infection by not allowing the pathogens to **attach** the host surface.

3. **Competition** with potential pathogens for space and nutrients.

4. Influencing specific **clearing** mechanisms to rid the body or a particular area of pathogens.

## 4. Phagocytosis

- Phagocytosis is a major form of non-specific defence in the body.
- It is engulfment and ingestion of a microorganism or a foreign particle by a cell.
- The cells that perform this function are collectively called **phagocytes.**
- Ex: White blood cells (WBC) or leukocytes such as:
- monocytes, neutrophils, macrophages etc.



**The mechanism of phagocytosis:**

- Phagocytosis occurs in four main phases.

**1. Chemotaxis**

**2. Adherence**

**3. Ingestion**

**4. Digestion**

**1. Chemotaxis**:

- It is the **chemical attraction** of phagocytes to microorganisms or other foreign material.
- The attracting chemicals may be the substances released by the parasite, components of damaged tissue cells and peptides derived from complement.

**2. Adherence**:

- It is the **attachment** of the phagocyte's plasma membrane to the surface of the microorganism.

- Surface receptors of the phagocyte bind to the surface molecules of the microbial cell.

- The interaction between the phagocyte and the microbial cell is greatly facilitated by a process known as opsonisation**.**

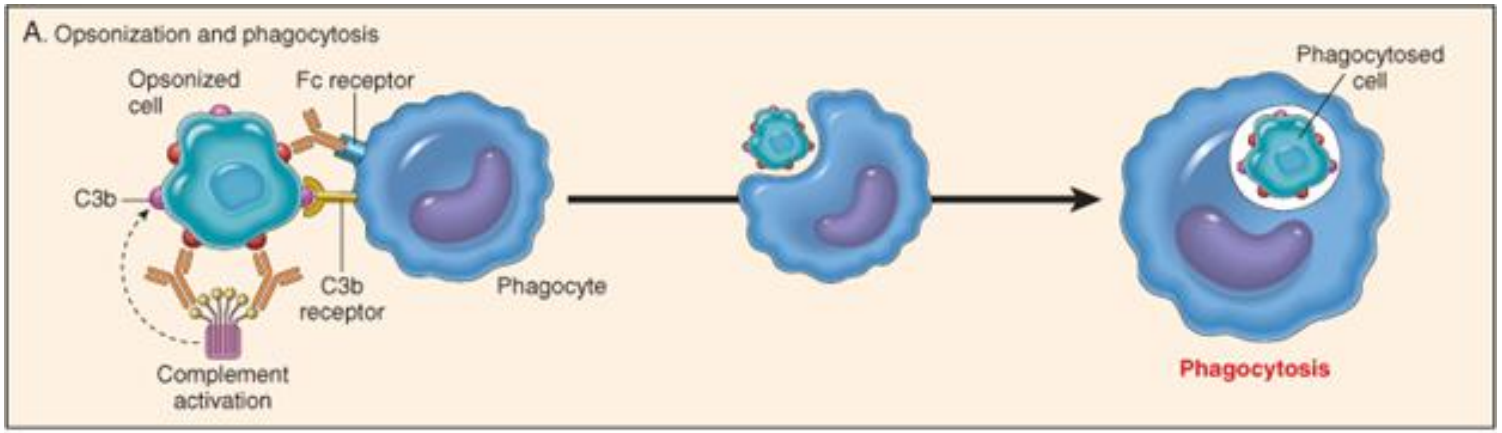
- **Opsonisation** is a process in which the microbial cell is coated by complement proteins and by antibodies and promote phagocytosis.

- The agents that enhance phagocytosis are called **opsonins**.
- Ex. Complement proteins and antibodies.

- **Complement** proteins are constitutive elements of the **blood**

- **Antibodies** are synthesized only in response to antigens and are constituents of the **adaptive defence system**.

- Opsonisation forms a **link** between the non-specific **innate** defence system and the specific **adaptive** defence system.



**3. Ingestion**:

- Microorganism is engulfed by the pseudopods of the phagocytic cell
- Transported by **endocytosis** across the cell membrane
- It is contained within a vacuole called a **phagosome** or **phagocytic vesicle**.

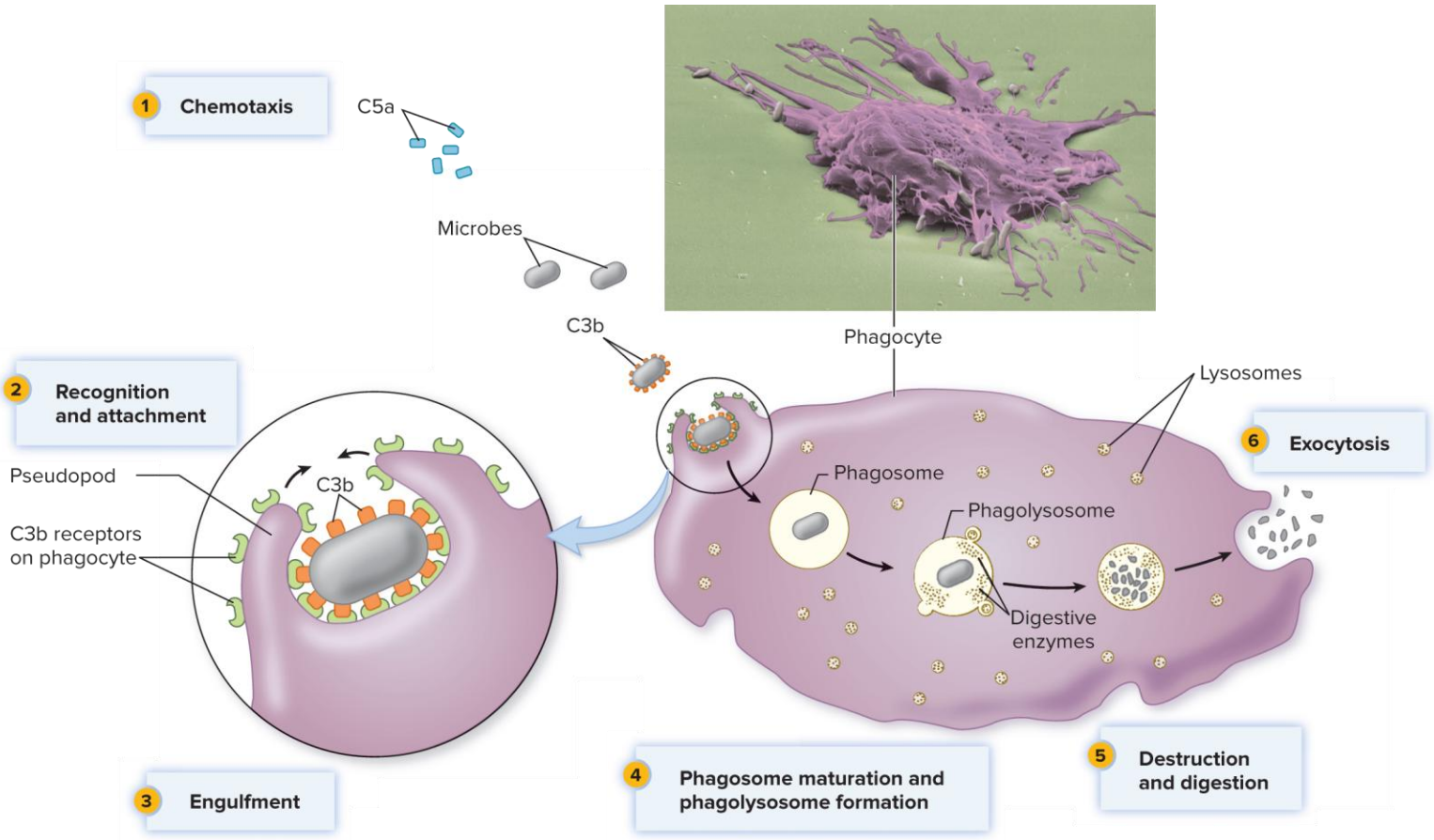
**4. Digestion**:

- Phagosome migrates to and fuses with a lysosome producing a **phagolysosome**.
- Lysosomes secretes the hydrolytic enzyme that digests & kills the microbes.

- Some indigestible material is left in the phagolysosome called as **residual body**.

- This residual body then moves towards the cell boundary and discharges its wastes outside the cell.

# Phagocytosis process:



**Inflammation:**

- It is an important defense mechanism of host to prevent infection.
- It is induced in response to **tissue damage** caused by microorganism, toxins or by mechanical means.

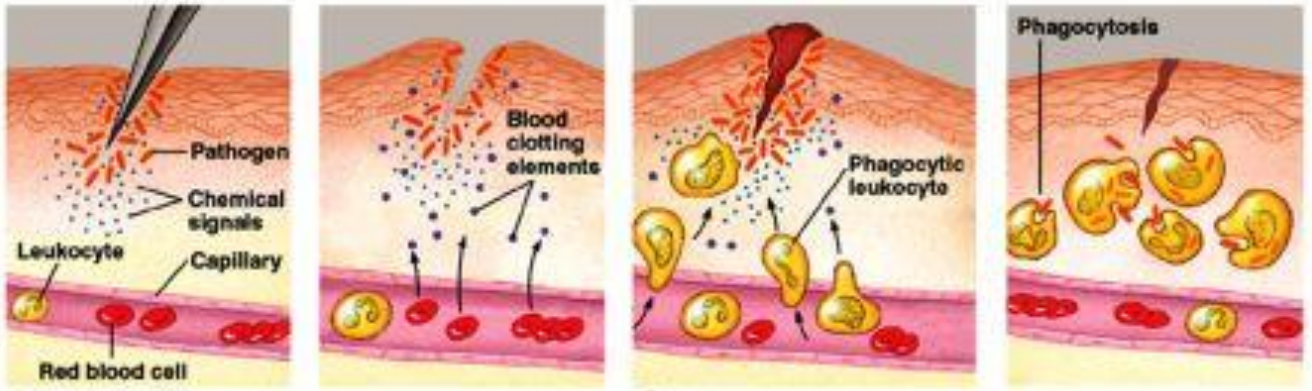
- The inflammation may be:
  - **Acute:** Ex: in response to tissue damage or
  - **Chronic** – Ex: Arthritis, cancer etc.

- Main aim of inflammation is to **prevent spread** of injected microorganism or toxin from site of injection and kill them on spot by **phagocytosis**.

**Characteristics of Inflammation:**

- Rubor: redness
- Tumor: swelling
- Calor: heat
- Dolor: pain
- Functio laesa: loss of function

# Inflammatory response:




1. Histamine & prostaglandins released
2. Capillaries dilate Clotting begins
3. Chemotactic factors attract phagocytic cells
4. Phagocytes consume pathogens & cell debris

## Steps of inflammatory response

**Step I: Tissue damage and Release of histamine:**

- Tissue damage caused by toxin, microorganism or mechanical injury release histamine.

**Step II: Vasodilation:**

- Histamine acts on surrounding blood capillaries and causes vasodilation.
- When vasodilation occurs, speed of blood flow decreases so that Neutrophils get chance to settle at the site of infection.

- **Step III: Increased permeability:**
- At the same time histamine increases the permeability of blood capillaries leading to leakage of fluid from blood capillaries.
- This results in accumulation of fluid causing edema.

**Step IV: Extravasation:**

- Within few hours, Neutrophil migrates to the site of tissue damage by the process of chemotaxis and passes through capillaries wall and enter into tissue space by the process called extravasation.

- Extravasation completes in 4 steps:
- **Rolling:** neutrophils attach loosely to endothelium by low affinity interaction between glycoprotein-mucin of Neutrophil.

- **Activation of chemotactic stimus:** chemokines are secreted and Neutrophil are attracted.

- **Arrest and adhesion:** ICAMS and integrin stabilize adhesion of neutophil and endothelium.

- **Transendothelial migration:** Neutrophil enter through endothelium layer.

**Step V: Phagocytosis:**

- Neutrophil kills the injected microorganism or toxins by phagocytosis and release molecular mediators that contributes to inflammatory response.
- At the same time activates effectors cells.

**Step VI: Inflammatory response:**

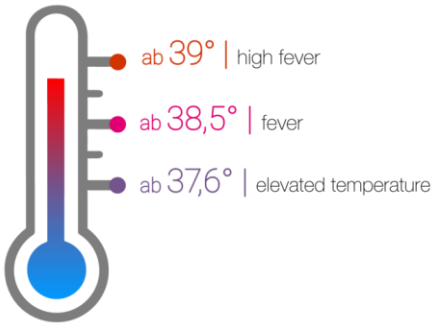
- As inflammatory response develops, various cytokines and other inflammatory mediators act on endothelium of local blood vessels, including increased expression of cell adhesion molecules (CAMs).
- The epithelium is then said to be inflamed.

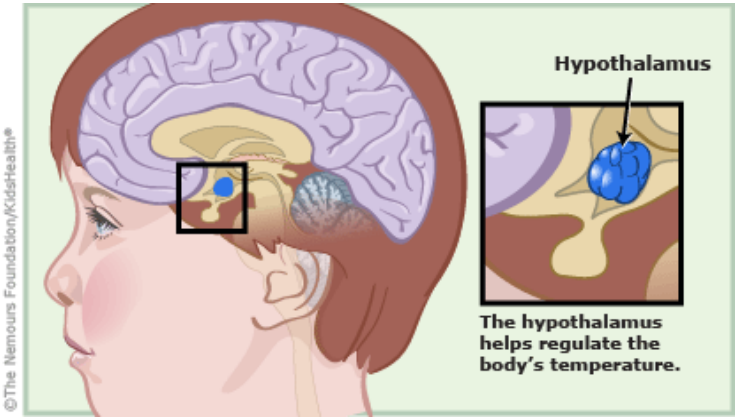
- Neutrophils are the first cell types to bind to inflamed endothelium and extravasate into tissue.

**Fever**

- Fever is defined clinically as an oral temperature **above 37.8 °C** (100.5 °F)
- Fever is an **abnormal** increase in **body temperature** that may provide a non-specific mechanism of defence against disease.

- Many microorganisms produce certain substances that enter the blood stream
- It results in fever by directly or indirectly stimulating the base of the brain called the **hypothalamus**
- Hypothalamus is body's thermostat & normally set at 37°C (98.6°F)
- Certain microbial substances affect it and stimulate it to raise the body temperature.



- The rise in temperature is also mediated by the release of the **interleukin-1** and **alpha tumour necrosis factor (α-TNF)** produced by phagocytes like macrophages

- This increases cell metabolism and blood vessels constrict, thus denying blood to the skin and keeping its heat within the body.
- The patient thus experiences cold skin and shivering along with the fever.

- When the infection subsides, the body heat-losing functions, such as vasodilation and sweating, become operative.

- Fever **inhibits** the **growth** of certain microorganisms and the increased metabolism of the body may help **tissue repair** more rapidly and raises the level of **phagocytosis**.

- If the temperature rises above 40.6 °C (105°F), dehydration, convulsions and death may result.