➢ Second line of defense (Non-specific)

When antigens cross the first line of defense i.e. mucus membrane, skin, mucous, lysozyme & HCl barriers and enter into tissues, then Second line of defense is stimulated which involves many cells & proteins to block way of antigens to body tissues.

Second line defense Components

Cells

i. Macrophage
ii. Neutrophils
iii. Natural Killer Cells
iv. Mast Cells & Basophils

Cytokines or Chemicals

i. Bradykinin (Secreted by tissue cells)
ii. Histamine (Released by mast Cells)
iii. Serotonin (Secreted by tissues Cells)
iv. Chemotactin (Secreted by mast Cells)

➢ Role of Macrophages & Neutrophils

Monocytes/ Macrophages: *(3-8%, agranulocyte, large kidney shaped nucleus, phagocytic nature)*

Monocytes have a large, kidney-shaped nucleus surrounded by ample blue-gray-staining cytoplasm. When monocytes leave the bloodstream and move into tissues, they enlarge and become macrophages, which engulf microbes and cellular debris.

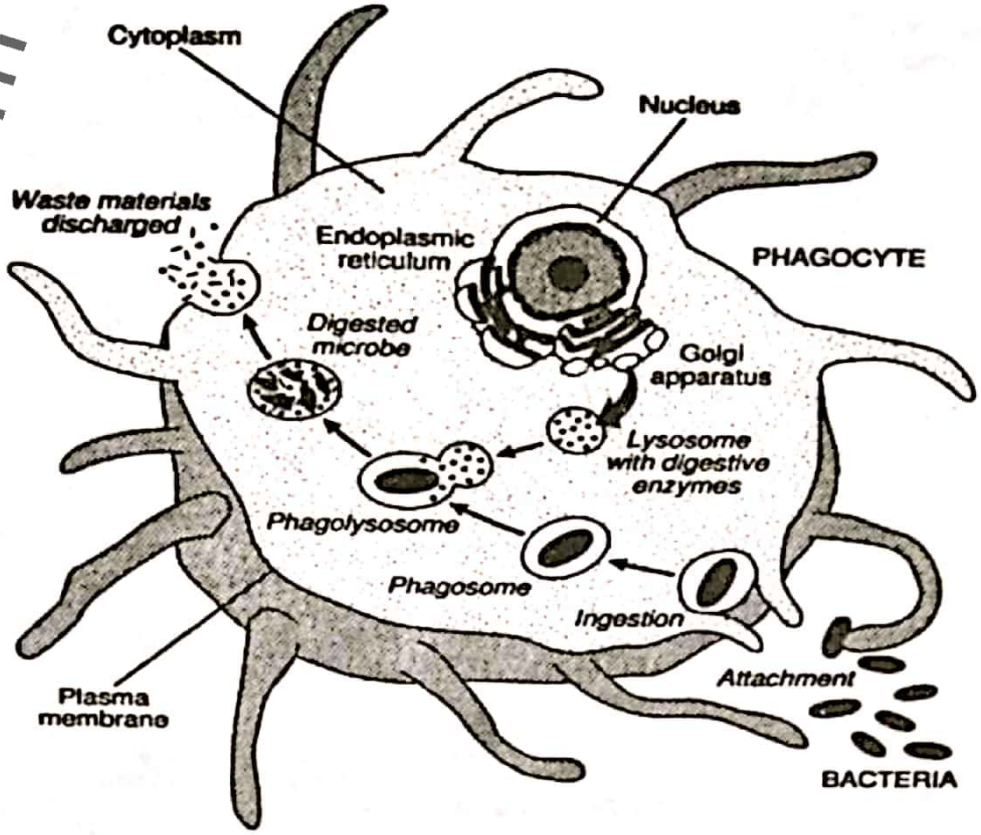
Neutrophils: *(60-70%, Granulocyte, polymorphonuclear, phagocytic, wound healing)*

Neutrophils are most numerous cells of granulocytes, referred to as polymorphonuclear leukocytes (PMNs). Neutrophils are the first leukocytes to arrive at a site of infection, responding by **chemotaxis, secreted by damaged tissue**. The neutrophils, by **phagocytosis,** actively engulf bacteria, which are then destroyed by the various antibiotic proteins (such as defensins and lysozymes) contained within the granules. The neutrophils, usually destroyed in the process, contribute, together with other dead tissue, to the formation of pus.

Diapedesis: The squeezing of neutrophils from blood capillaries to site of infection is called diapedesis.

Phagocytosis: Phagocytosis is a nonspecific defense mechanism in which various phagocytes engulf and destroy the microorganisms of disease. Among the important phagocytes are the circulating white blood cells called **neutrophils** and **monocytes.** In the tissues, the monocytes are transformed into phagocytic cells called **macrophages.** The macrophages move through the tissues of the body performing phagocytosis and destroying antigens. Phagocytes also initiate the processes of the immune system.

The process of phagocytosis begins with **attachment** and **ingestion** of microbial particles (Figure) into a bubble like organelle called a **phagosome.** Once inside the phagocyte, the phagosome containing the microorganism joins with a **lysosome,** which contributes enzymes. The fusion of phagosome and lysosome results in a **phagolysosome.** Microorganisms are destroyed within minutes, and the microbial debris is eliminated from the cell in the process of **egestion.** In the immune process, chemical portions of the microorganism called **antigenic determinants** are displayed on the surface of the phagocyte to stimulate the immune process.



The process of phagocytosis, a type of nonspecific defense to disease

Phagocytosis is enhanced by products of the immune system called antibodies. These protein molecules bind to microorganisms and encourage engulfing by phagocytosis.

Role of Natural killer Cells (1-5 %, bean shaped kidney, Granulocyte, Cytotoxic)

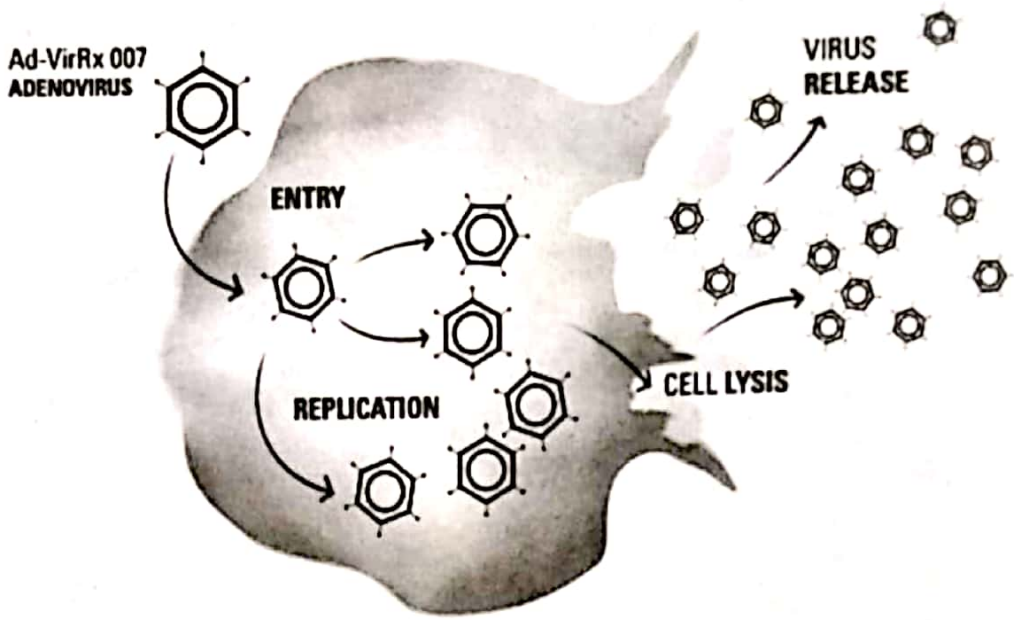
NK cells belong to the innate immune system and form a first line of defense against a wide variety of pathological challenges. Particularly, they provide protection against viral and bacterial infections and they help to detect and limit the development of cancer. Natural Killer Cells were first described as cells that have the ability to kill tumor cells without any priming or prior activation (remember that e.g. cytotoxic T cells need priming by antigen presenting cells) and their name is ultimately connected to this 'natural' ability to kill.

➢ Apoptosis & Normal Cell Identification by NK cells

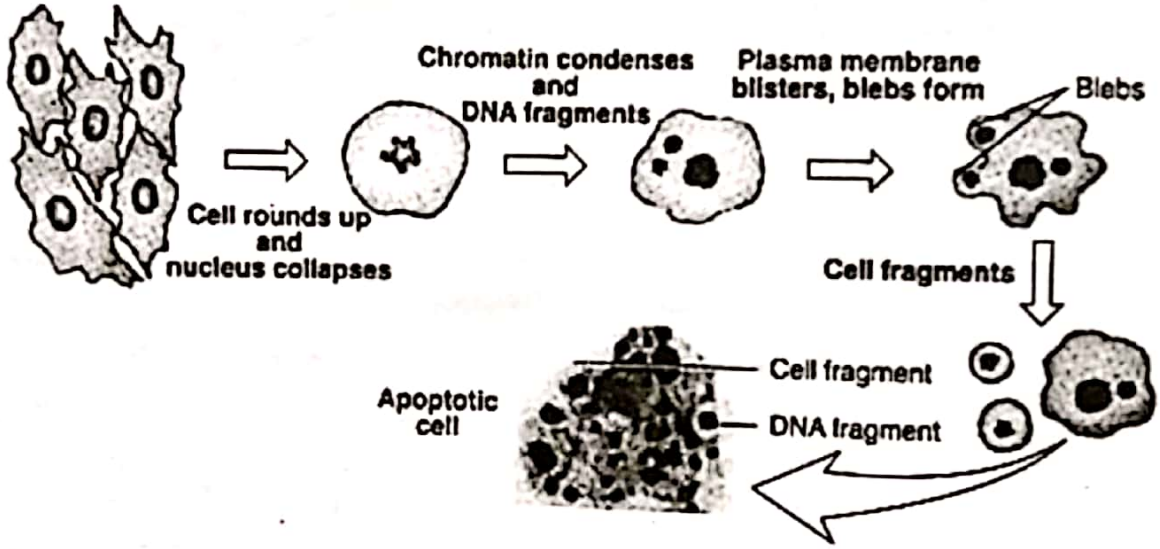
NK cells can secrete perforin which perforate the infected cell & then granzymes (proteases) which initiate apoptosis by mitochondrial enzymes & constitute a second line of defense mechanism during an immune reaction. One could imagine that cells which display a natural ability to kill need to be controlled very strictly to protect healthy cells from attack. Therefore, in addition to a variety of different activating receptors, NK cells express inhibitory receptors that recognize innate MHC class I (this is also referred to as recognition of 'self'').This is a very efficient mechanism of control as almost all 'normal' cells express MHC class I.

Lysis: It is the bursting / destruction of infected cell with production on multiple of antigens in this case body cell is destroyed along with production of antigens.

Apoptosis: It is the destruction of cell along with destruction of antigens.



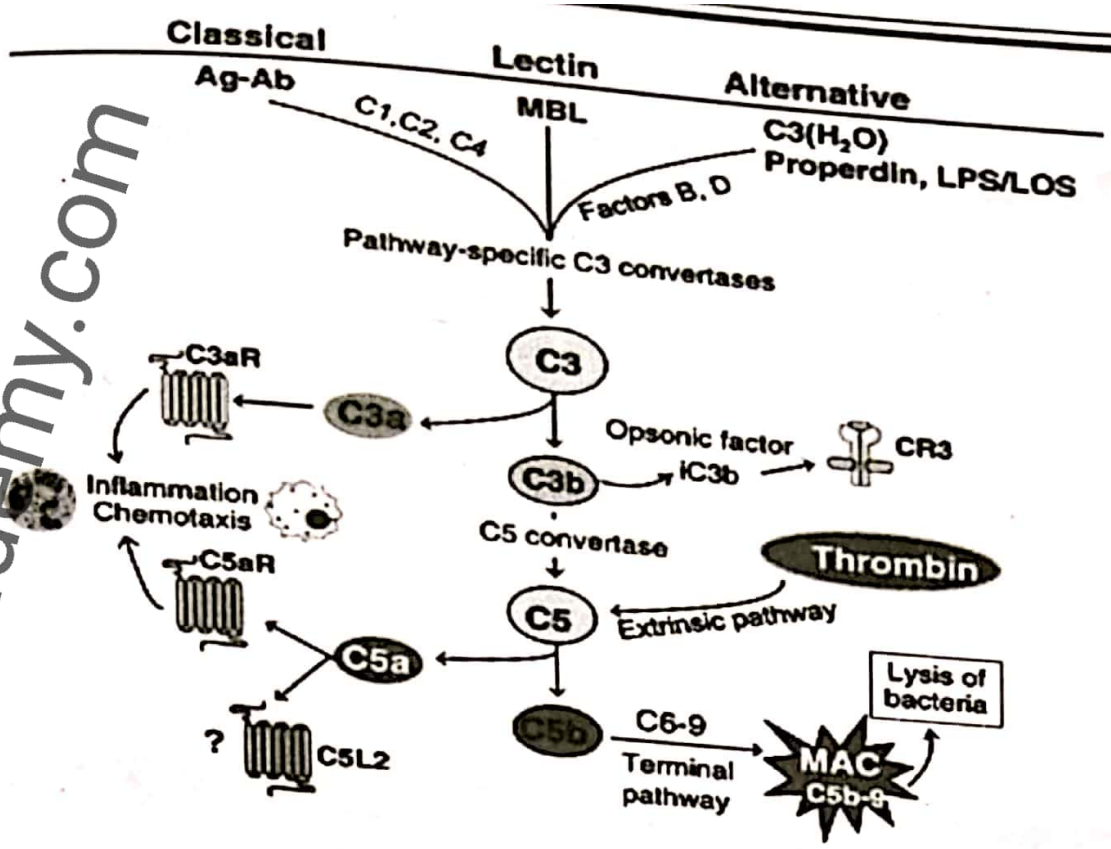
Cell lysis mechanism



Apoptosis mechanism

➢ The complement system (arsenal system)

The complement system is a series of thirty plasma proteins which are grouped into nine classes C1 to C9 that circulate in the blood as arsenal system which is stimulated classically or by alternate pathways. The **classical pathway** operates with the highly specific immune system and is initiated when certain antibodies unite with antigens and stimulate the complement system in a **cascade of reactions.** In the pathway, certain complement components react with one another and produce new substances that induce other components to react e.g. Antigen-Antibody complex (Agn+IgG or Ag-Ab) stimulates C1 which stimulates C2 and then C2 is divided into C2a & C2b then C3 is stimulated which is divided into C3a & C3b then C2aC3b is combined which stimulates C4 which is divided into C4a & C4b then C2aC3bC4b combined & stimulating C5 which is divided into C5a & C5b, C5b then stimulating & bonding C5bC6C7C8C9 which is attached to antigen plasma membrane & perforate it to initiate apoptosis. The results of these numerous reactions are substances that induce other complement components into action. The substances encourage destruction of microbial membranes or otherwise "complete" the defensive process. Many immune reactions stimulate the complement system.



Complement system activation

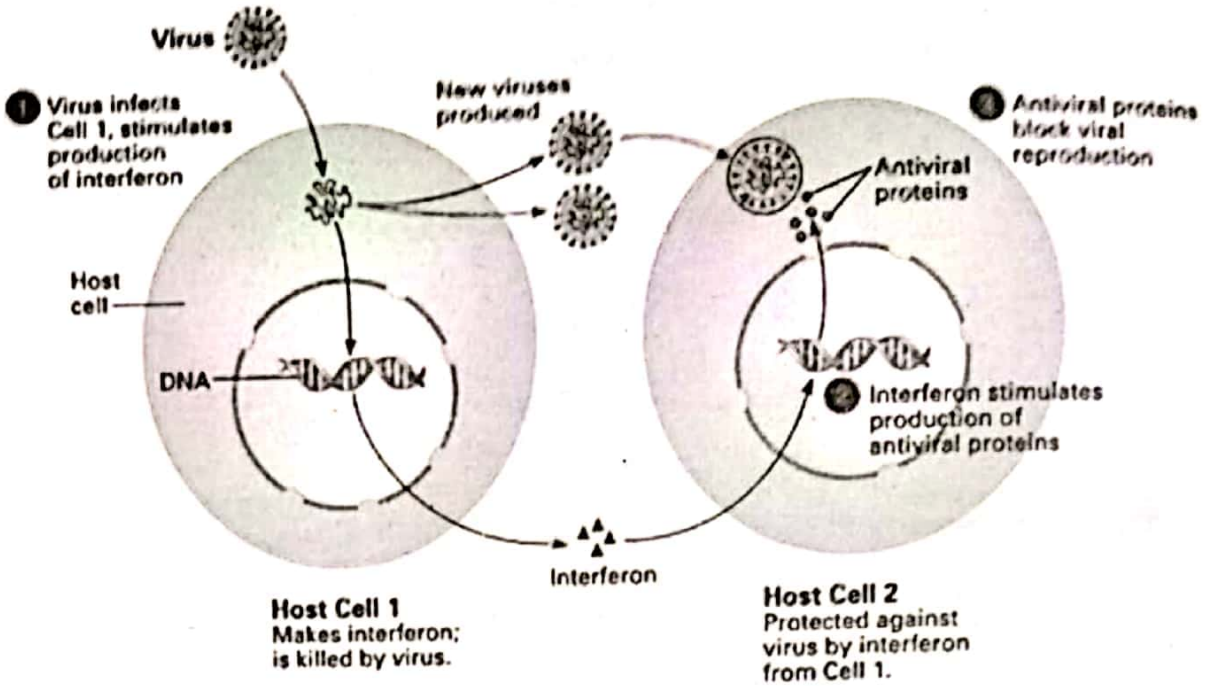
Interferon

Definition: Interferon belong to the large family of cytokines. Interferon is not a toxin designed to poison a key molecule in the cell. Instead, it is a message that is read by human cells. Interferon is one of a growing class of cytokines, proteins that deliver instructions from cell to cell. Interferons are named after their ability to "interfere" with viral replication within host cells. Today, more than 10 mammalian IFN species and numerous subspecies have been discovered, each with individual properties, but all having antiviral activity.

Interferon (IFN) Types

Interferons are currently classified into two groups: type I & type II and type I. The type I IFNs include all IFNα & IFNβ, Humans have 12 different IFNαs and a single IFNβ. The IFNα and IFNβ differ substantially in their specific antiviral activities. Type I interferon is secreted by virus infected cells including lymphocytes, endothelial cells and epithelial cells. Type II IFN is only one IFN, IFNγ. Interferon gamma is produced by T lymphocytes, NK cells, & macrophages when stimulated with antigens.

Interferon function: Alpha-interferons can modify immune function and gamma-interferon plays a role in defense. Apart from these duties in controlling abnormal growth, they also play supporting roles in the day-to-day maintenance of normal cellular growth levels. Interferon can send just the right instructions, directing the immune system to destroy hairy cell leukemia cells (Hairy cell leukemia is a rare, slow-growing cancer of the blood in which your bone marrow makes too many B cells (lymphocytes), a type of white blood cell that fights infection. These excess B cells are abnormal and look "hairy" under a microscope) or inhibiting the growth of blood vessels nourishing a Kaposi's sarcoma (a type of cancer in which blood vessels are grown in form of patches).



Interferon mechanism of action

➢ Inflammation as a Nonspecific Immunity (2nd line of defense)

Inflammation is a nonspecific response to any trauma occurring to tissues. Inflammation mobilizes components of the immune system, sets into motion repair mechanisms, and encourages phagocytes to come to the area and destroy any microorganisms present. Inflammation can be controlled by nervous stimulation (hypothalamus) and chemical substances called **cytokines i-e** Bradykinin (Secreted by tissue cells), Histamine (Released by mast Cells), Serotonin (Secreted by tissues Cells), Chemotactin (Secreted by mast Cells). These chemical products of tissue cells and blood cells are responsible for many of the actions of inflammation. In some types of inflammation, phagocytes accumulate in the whitish mass of cells, bacteria, and debris called pus. These chemical causes vascular permeability to cause leaking of fluid into tissues which causes swelling and it is called inflammation or edema.

Symptoms of inflammation: It is accompanied by signs and symptoms that include heat, swelling, redness, and pain.

i. Swelling due to increased blood supply & accumulation of tissue fluid.
ii. Redness due to increased blood supply
iii. Warmth due to increased blood supply
iv. Pressure over receptors due to expansion of tissue causes pain.

Inflammation lasts until infection has eradicated completely.

➢ Inflammatory response in arthritis

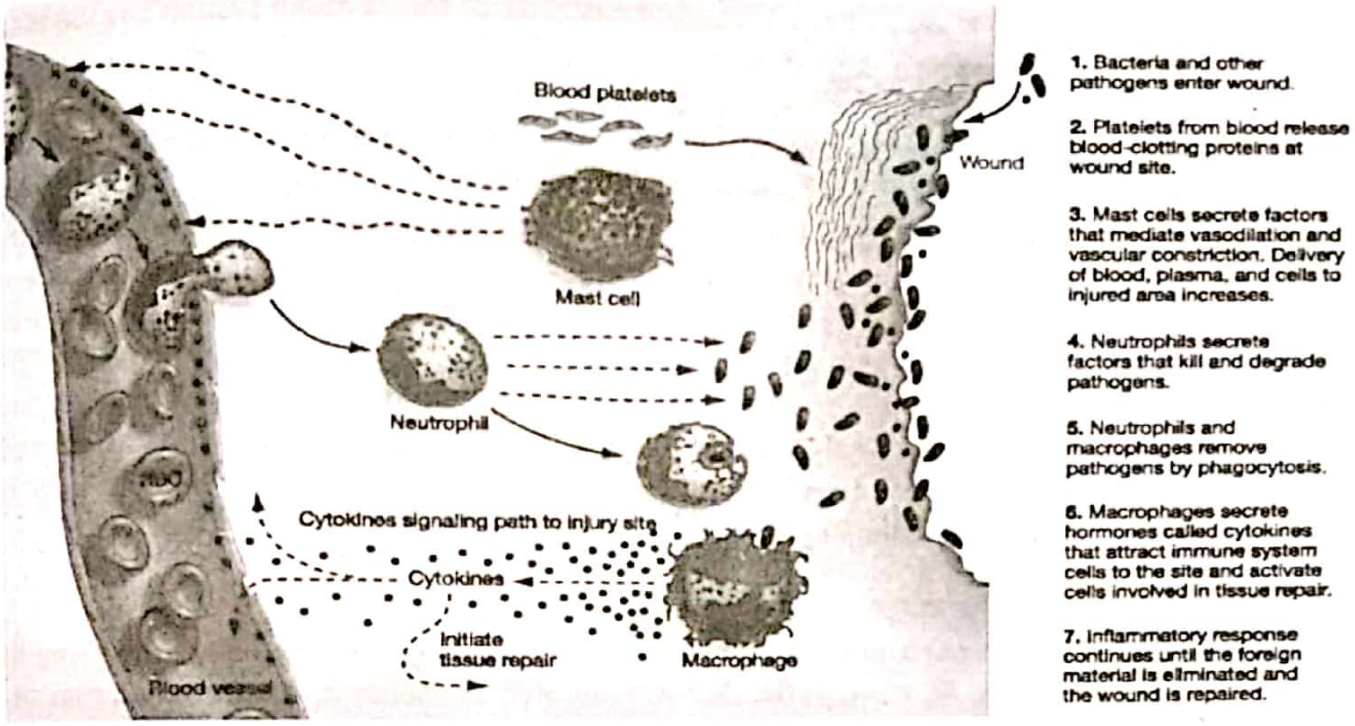
The main function of immune system to protect us from foreign particles and diseases. The immune response may be normal or abnormal. Inflammation is the first immune response which increases the mobility of immune cells and cytotoxic chemical to infected tissues. Rheumatoid arthritis is the inflammation of synovial joints as an auto immune response. It causes chronic arthritis at several joints.

Symptoms:

i. Early morning stiffness of joints
ii. Loss of appetite

iii. Low grade fever

iv. Swelling of hands & feet



Inflammatory response

➢ Pyrexia (A Natural Immune Response)

We were designed with a complex mechanism of our own immune system called pyrexia. It is a rise in the body's core temperature, above 37 Centigrade (98-100 Fahrenheit) which is a common medical sign known as a fever or hyperthermia. It is a mechanism developed by the immune system to reduce the severity of illness by preventing bacteria and viruses from multiplying. This activation of the immune system has worked for centuries before medicine was invented. Most individuals view a fever as something that is bad or harmful, but it is a sign that our body is working in our favor to fight disease. As the individual's body temperature goes up, there may be a sensation of cold until the temperature levels off and stops rising. People's normal body temperatures may vary and are affected by factors such as eating, exercise, sleeping, and day time. Our body temperature is usually at its highest at around 6 pm and at its lowest at about 3 am.

Pyrogens:

Any substance or agent which induces pyrexia or fever is called pyrogen.

Examples: endogenous pyrogen a low-molecular-weight protein that is produced by phagocytic leukocytes in response to stimulation by exogenous pyrogens and released into the circulation; it induces fever by acting on hypothalamus to raise the set-point (37 Centigrade) of the hypothalamic thermostat. The pyrogen produced by monocytes and macrophages is not identical to that produced by neutrophils and eosinophils; the mononuclear phagocytes also produce a greater amount of pyrogen for a longer period of time than do the polymorphonuclear cells. exogenous pyrogens a fever-producing agents of external origin, e.g., bacterial endotoxins (lipopolysaccharide (LPS), present in the cell wall of gram-negative bacteria) and other microbial products, antigen-antibody complexes, viruses and synthetic polynucleotides, incompatible blood and blood products, the action is mediated by endogenous pyrogen.

Mechanism of Pyrexia

The mechanism of fever appears to be a defensive reaction by the body against infectious disease. When bacteria or viruses invade the body and cause tissue injury, one of the immune system's responses is to produce pyrogenic substances which then stimulate the hypothalamus to produce central prostaglandin, where they modified the functioning of the hypothalamus, the part of the brain that regulates body temperature. The pyrogens inhibit heat-sensing neurons and excite cold-sensing ones, and the altering of these temperature sensors deceives the hypothalamus into thinking the body is cooler than it actually is, it also enabling hypothalamus to shunt blood away from the extremities to the internal core of the body. This induces shivering that also raises temperature. Lipopolysaccharides (LPS) from gram-negative bacteria may stimulate peripheral production of prostaglandin from hepatic Kupffer cells. LPS-stimulated fever may also be neurally mediated. The hypothalamus raises the body's temperature above the normal range, thereby causing a fever. The above-normal temperatures are thought to help defend against microbial invasion because they stimulate the motion, activity, and multiplication of white blood cells and increase the production of antibodies. At the same time, elevated heat levels may directly kill or inhibit the growth of some bacteria and viruses that can tolerate only a narrow temperature range.

Treatment of Pyrexia

In most cases, fever does not need to be treated, because it is a sign that the body is working hard to defeat an infection or disease. An **antipyretic**, such as ibuprofen or aspirin or paracetamol, may be given for pain or excessive crying related to a fever. Non-medical treatment for fevers include removing layers of clothing, lowering room temperature, applying a cold sponging etc.

Benefits of Pyrexia

During fever, temperature is raised due to which blood flow is also increased to the body parts.

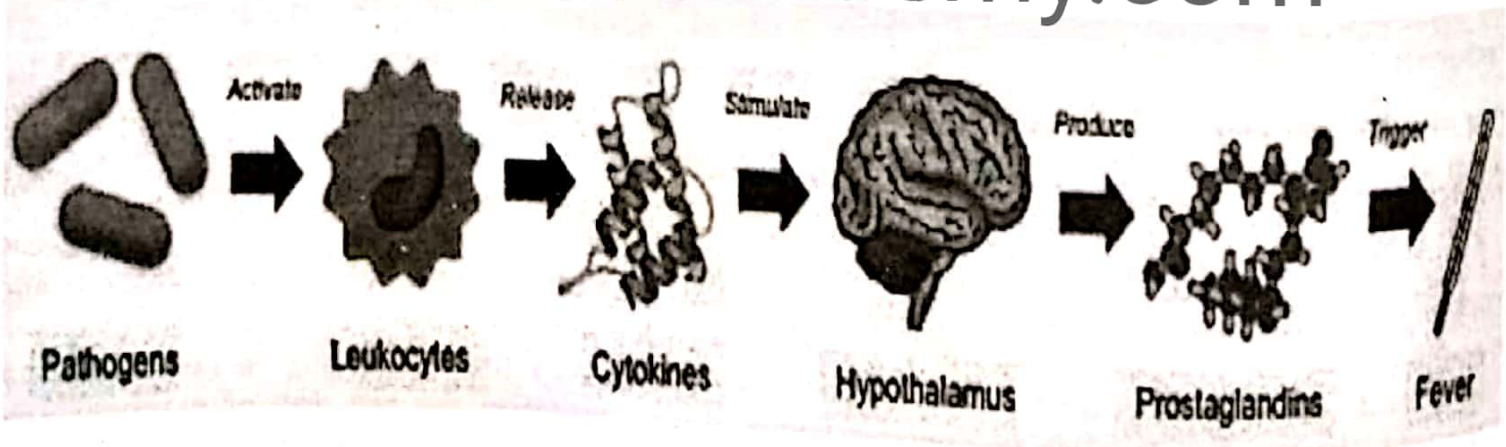
i. Increased blood flow provide more macrophages, neutrophils, NK cells to infected site.

ii. High temperature creates non favorable environment for antigen.

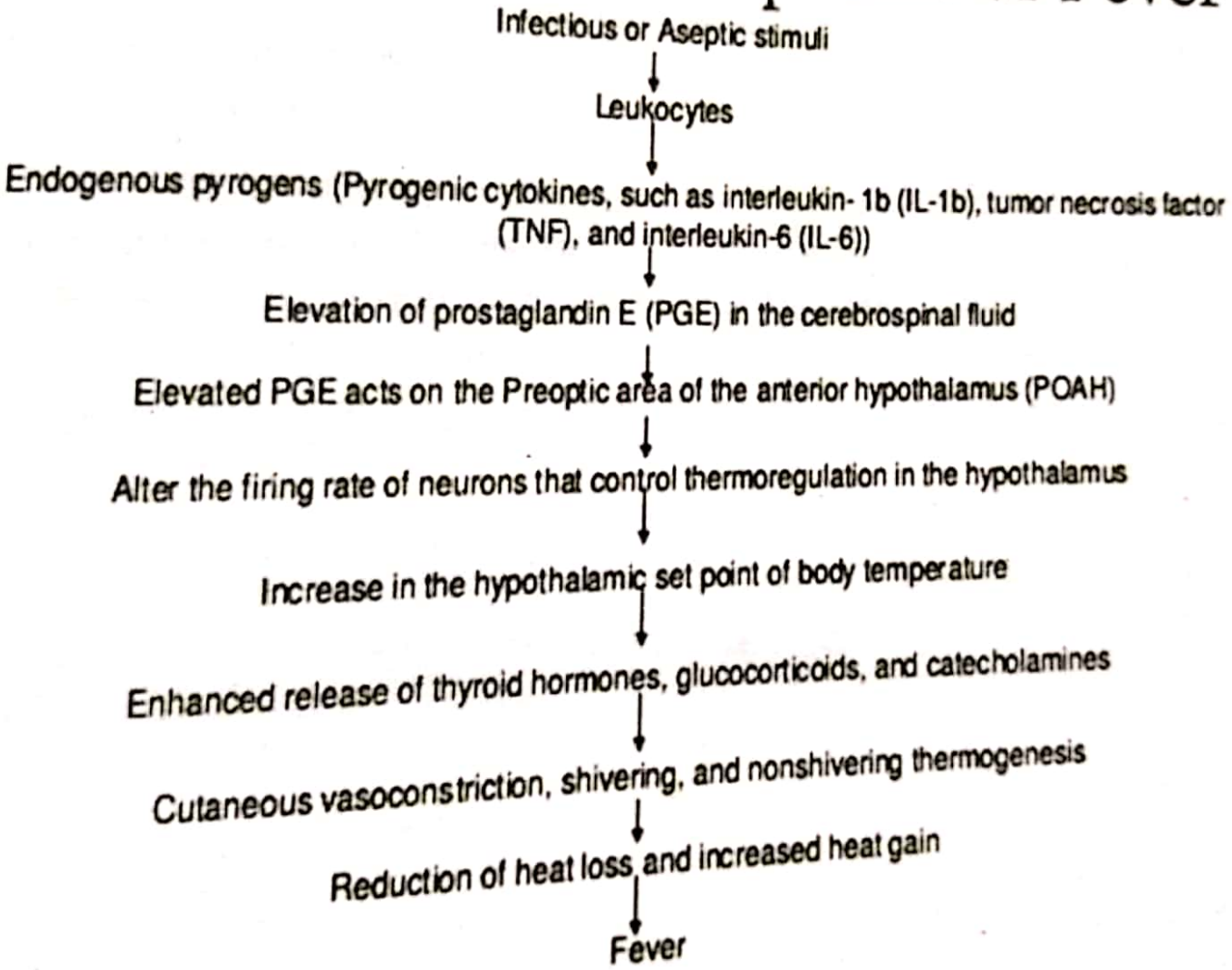
iii. More interferon is produced which safeguard the healthy cells from viral attack.

iv. It causes walling off iron which bacteria feed on.

v. High temperature, directly Kill microbes.



Mechanism of development of Fever



Mechanism of Pyrexia