CHAPTER THREE
INFLAMMATION

General Features

Inflammation is defined as "the response of living vascularized tissues to harmful agents." It consists principally of vascular changes associated with leukocytes infiltration and systemic reactions." Inflammation is a fundamental and common pathologic process seen in many disease states. It is essentially a protective response, the aim of which is to get rid of the injurious agents (e.g., microbes, toxins) as well as its consequences (e.g., necrotic cells and tissues).

Or. Is the vascular and cellular response of living tissue to injury

Advantage of inflammation:

1. Destroy of any harmful agent.
2. Dilute **.**
3. Wall of the injury agent .

But also the inflammation is harmful when there is in control inflammatory process due to :

1- Distraction of the tissue and may be lead to death.

2- Also in case of laryngitis in the children causes swelling the larynx lead to suffocation.

3- The inflammation lead to rise in the blood pressure ,also lead to allergic reaction.

Cardinal sings of inflammation:

1- Redness (rubor): this is due to accumulation of the blood in the inflames area.

2- Swelling (tumer) : due to accumulation of inflammatory exudates in the inflames area.

3- Pain (dolor): due to pressure of inflammatory exudates on the nerve ending.

4- Heat (calor) : due to warm blood reach in the inflammatory area.

5- Loss of function .

Causes of inflammation:

1. Infections: bacterial, viral, parasitic and microbial toxins

2. Physical and chemical agents (trauma, thermal injuries, irradiation, toxins, strong acids, etc.)

3. Tissue necrosis (of any from or cause)

4. Foreign bodies (splinters, dirt, sutures)

5. Immune reactions (hypersensitivity and autoimmune reactions).

Type of inflammation according to :

1. Time

a- Acute inflammation (few min. to few days)

b- Sub acute inflammation (few weeks)

c- Chronic inflammation(weeks, months, years)

2. Type of exudate

a- Fibrin

b- Mucin

3. Organ (pericarditis , nephritis)

Example acute fibrinous pericarditis.

1-Acute inflammation is rapid in onset (seconds or minutes), of relatively short duration (minutes, hours, or at most a few days), characterized by the exudation of fluid and plasma proteins, & the emigration of leukocytes, predominantly neutrophils. and is associated histologically with the presence of polymophonuclear cell , the outcome of acute inflammation Characterize by resolution and abscess formation or change to chronic inflammation or death.

2-Chronic inflammation, in contradistinction, is of insidious onset, of longer duration, and is associated histologically with the presence of lymphocytes, macrophages, plasma cells, proliferation of blood vessels and fibroblasts. In both forms tissue necrosis of varying extent occurs. The vascular and cellular reactions of

both acute and chronic inflammation are mediated by chemical substances (chemical mediators) that are derived from plasma proteins or cells. Such substances, acting singly, in combinations, or in sequence, amplify the inflammatory response and influence its evolution.

ACUTE INFLAMMATION

Transudate is a fluid with low protein content (most of which is albumin) and a specific gravity of less than 1.012 .

Exudation is the escape of fluid, proteins, and blood cells from the vascular system into the interstitial tissue. An **exudate** is an extravascular fluid that has a high protein concentration and a specific gravity above 1.020. It involves significant alteration in the normal permeability of small blood vessels in the area of injury

Exudates = plasma +protein +leukocyte.

Edema refers to an excess of fluid in the interstitial tissues or body cavities; the accumulated fluid can be either an exudate or a transudate. Pus (purulent exudate) is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells and, in many cases, microbes (pyogenic bacteria). Acute inflammation a major components:

A. Vasodilation and increased blood flow(vascular response)

This is, sometimes, preceded by a transient constriction of arterioles, lasting a few seconds(3-5 sec). Vasodilation first involves the arterioles, which leads to an increase in blood flow; this in turn leads to opening of new capillary beds in the area with subsequent dilation of capillaries & venules. This process allows more blood to flow into the area,

a process known as **"active hyperemia"** (hyper- = increased; -emia = blood). These changes explain the clinically noted heat and redness. Vasodilation is induced by the action of several mediators (such as histamine) on vascular smooth muscles. It is possible that autonomic nerve impulses may also play a role in relaxation of arteriolar smooth muscle leading to their dilation.

Increased Vascular Permeability and decreased blood flow

Increased vascular permeability leads to the escape of exudates into the extravascular tissue. This is driven by the increased hydrostatic pressure owing to increased blood flow through the dilated vessels and is perpetuated through the loss of proteins from the plasma that reduces the intravascular osmotic pressure and increases the osmotic pressure of the interstitial fluid. Several mechanisms have been proposed for the increased vascular permeability, that include

1. Formation of endothelial gaps in venules due to endothelial cells contraction. This is the most common mechanism & is elicited by several mediators e.g. histamine, bradykinin, and leukotrienes. Binding of these mediators to receptors on endothelial cells leads to stimulation of contractile proteins (such as myosin). The result is contraction of the endothelial cells and separation of intercellular junctions that eventuate in intercellular gaps formation.

2. Junctional retraction caused by chemical mediators such as TNF and IL-1; these induce structural reorganization of the cytoskeleton of the cells.

3. Direct endothelial cell injury as by burns or infections. Because of endothelial damage and exposure of the subendothelial thrombogenic collagen, this type is frequently associated with platelets adhesion with subsequent thrombosis.

4. Leukocyte-dependant injury due to accumulation of leukocytes and their activation products (such as toxic oxygen radicals and proteolytic enzymes) during the inflammatory response. These lead to endothelial cell damage.

According to the above mechanism ,there are three basic patterns of increase permeability

1- **An immediate transient :** response lasting for 3-10 min or less, mediated mainly by the action of histamine and leukotrienes on endothelium.

2- **A prolong response** that is most noticeable after direct endothelial injury, or necrosis of endothelial cell reach peak after one or several days for example, after burns

3- **A delayed response** starting at about 6-12 hrs. and lasting for about 8 hrs. mediated principally by kinins, complement product. due to Distraction of endothelial cell.

B. Cellular response (emigration and activation of leukocyte and phagocytosis):

A critical function of inflammation is to deliver leukocyte to the site of injury and to activate the leukocytes(neutrophile and macrophage) in the site of inflammation to engulf, destroy or weaken of their pathogen.

Leukocyte left the lumen of the blood vessel migration to word and aggregation and act at the site of inflame area that called extravasation. Which include:

1. Rolling , margination , pavementing
2. Migration (chemotaxis)
3. Phagocytosis

1. Rolling

Histamine stimulated endothelial cell to produce p-selectin adhesion molecule and leukocyte which have CHO attach with p-selectin but the attachment is weak lead to rolling of the leukocyte. After that the pro inflammatory cytokine such as TNFα which release from residue macrophage after engulfing the pathogen. The cytokine activate the antigrine which present on the surface of leukocyte, and these antigrine family attachment with the endothelial cell this called **pavementing**.

Than the leukocyte move along the endothelial cell and extend large pseudopods to the gab present between the endothelial , than the crawal and cross the endothelial cell this condition called **emigration** or transmigration. After that the leukocyte migration to the pathogen ,this process called chemotaxis. The force which attract the leukocyte to the pathogen called chemoattractants factor either exogenous or endogenous Chemokines (chemoattractants) act on the adherent leukocytes and stimulate the cells to migrate toward the site of injury or infection.

Chemoattractants of neutrophil

1. Bacterial products
2. Complement fragment

Chemoattractants of macrophage

1. C3a , C5a of complement
2. Distraction of neutrophil
3. Ab-Ag complex

Thus, the leukocytes are retained at the site where they are needed. The type of emigrating leukocyte varies with the age of the inflammatory response and with the type of stimulus. In most forms of acute inflammation, neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours, and then are replaced by monocytes in 24 to 48 hours. After entering tissues, neutrophils are short-lived; they undergo apoptosis (self destruction) and disappear after 24 to 48 hours, whereas monocytes (by now called macrophages: macro- = large and phage = eater) survive longer and thus outlive neutrophils and become more apparent. There are, however, exceptions to this pattern of cellular exudation. In certain infections—for example, those produced by Pseudomonas organisms—neutrophils predominate over 2 to 4 days; in viral infections, lymphocytes may be the first cells to arrive; in some hypersensitivity reactions and parasitic infestations, eosinophils may be the main cell type.

Chemotaxis

After extravasation, leukocytes emigrate in tissues toward the site of injury; this is achieved by a process called chemotaxis. Chemotaxis is defined as locomotion oriented along a chemical gradient of chemoattractants. All granulocytes, monocytes and, to a lesser extent, lymphocytes respond to chemoattractants (chemotactic stimuli)

with varying rates of speed. Both exogenous and endogenous substances can act as chemoattractants. The former is exemplified by bacterial products.

Endogenous

chemoattractants, however, include several chemical mediators:

1. Components of the complement system, particularly C5a
2. Products of the lipoxygenase pathway, mainly leukotriene B4 (LTB4)
3. Cytokines (secreted from cells) e.g., IL-8 Leukocyte Activation This refers to induction of a number of responses within leukocytes, which are mediated by microbes, products of necrotic cells, antigen-antibody complexes, and cytokines. These mediators trigger several signaling pathways in leukocytes that result in an increase in cytoplasmic Ca++ and activation of enzymes.

The activation of leukocytes is reflected functionally as follows:

1. Production of arachidonic acid (AA) metabolites
2. Secretion of lysosomal enzymes and other microbicidal substances
3. Modulation of leukocyte adhesion molecules allowing firm adhesion to endothelium
4. Activation of macrophages: through the release of IFN-γ (major macrophage-activating cytokine), which is secreted by natural killer (NK) cells.
4. Activation of phagocytosis through stimulation of opsonins-receptors. The process of coating a particle, such as a microbe, to make it vulnerable for phagocytosis is called opsonization; substances that do this are opsonins.

Phagocytosis

Phagocytosis is one of the major functions of the accumulated neutrophils and macrophages at the inflammatory focus, being responsible for eliminating the injurious agents. Phagocytosis involves three distinct but interrelated steps:

1. Recognition and attachment of the particle to be ingested by the leukocyte
2. Its engulfment, with subsequent formation of a phagocytic vacuole
3. Killing and degradation of the ingested material.

Recognition and Attachment

Although neutrophils and macrophages can engulf bacteria without attachment to specific receptors, typically the phagocytosis of microbes and dead cells is initiated by recognition of these particles by receptors expressed on the leukocyte surface. The

efficiency of phagocytosis is greatly enhanced when microbes are opsonized by specific proteins (opsonins) for which the phagocytes express high-affinity receptors. The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins.

Engulfment

Binding of a particle to phagocytic leukocyte receptors initiates the process of active phagocytosis. During engulfment, extensions of the cytoplasm (pseudopods) flow around the particle to be engulfed, eventually resulting in complete enclosure of the particle within a phagosome created by the plasma membrane of the cell. The limiting membrane of this phagocytic vacuole then fuses with the limiting membrane of a lysosomal granule forming phagolysosome. This fusion results in discharge of lysosomal contents into the phagolysosome. **Killing and Degradation**

The ultimate step in the elimination of infectious agents and necrotic cells is their killing and degradation within neutrophils and macrophages, which occur most efficiently after activation of these phagocytes. Microbial killing is accomplished largely by oxygen-dependent mechanisms, which depends on the production of reactive oxygen species, particularly H2O2.. Oxygen-independent degradation depends on the release of granules, containing proteolytic enzymes such as defensins (antibacterial peptide attacking bacterial cell membrane), proteolytic enzymes such as elastases, lysozymes, and cationic proteins. The major basic protein of eosinophils has limited bactericidal activity but is cytotoxic to many parasites. After killing, acid hydrolases, which are normally stored in lysosomes, degrade the microbes within phagolysosomes. Macrophages are excellent phagocytes and are particularly good at engulfing and processing antigenic substances and presenting altered antigens to other cells (lymphocytes) for ultimate destruction.

CHEMICAL MEDIATORS OF INFLAMMATION:

Chemical mediator are soluble diffuse molecule act locally at the site of inflammation or more distant site and chemical mediator con be classified into

1- Exogenous Chemical mediator: bacterial product and toxin which activated complement lead to induce inflammatory process.

2- Endogenous Chemical mediator :produce from immune system which distroid cell membrane lead to release Chemical mediator

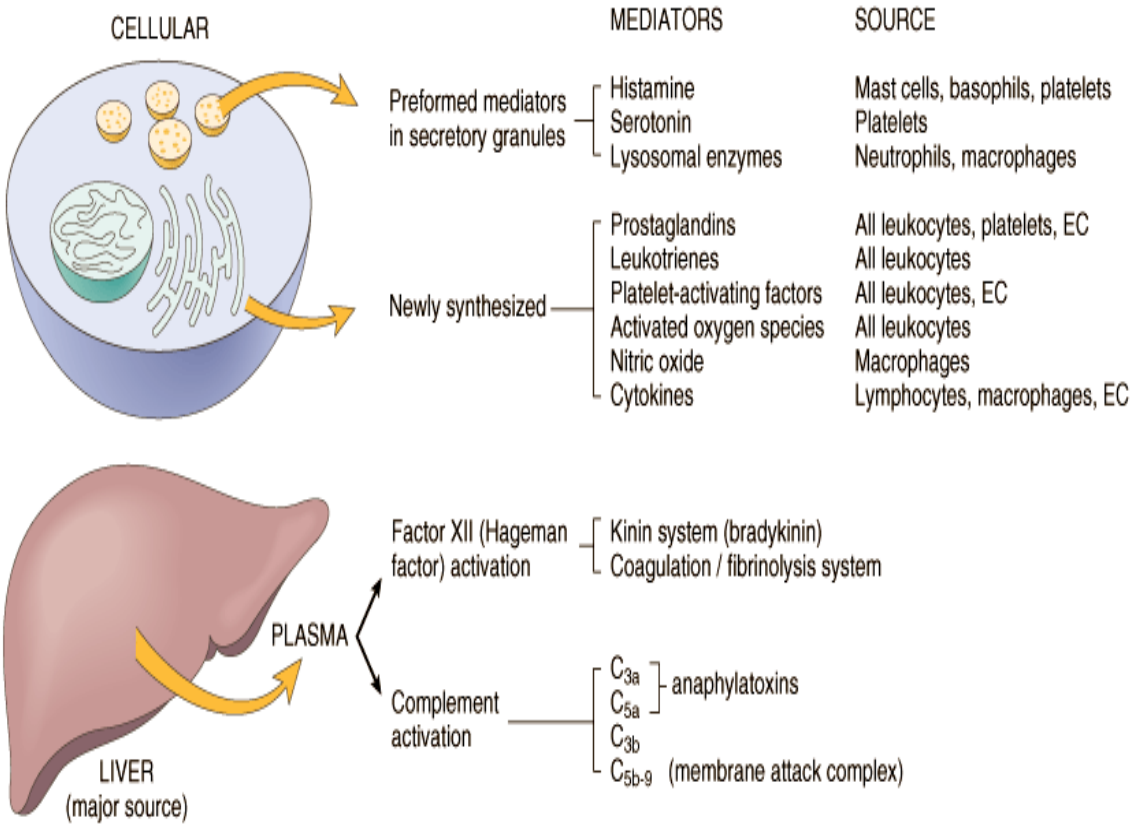
Source of Chemical mediator:

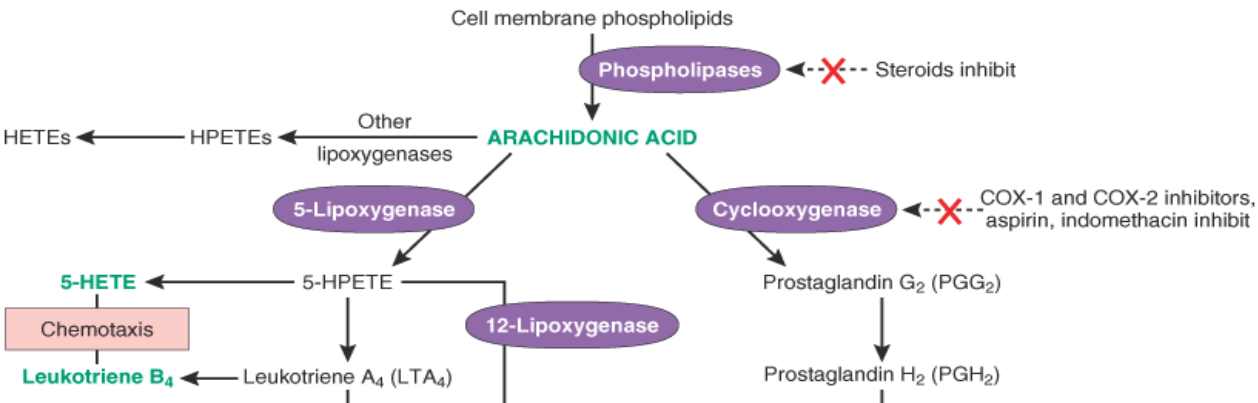
1- Cell derived Chemical mediator

a- Preformed molecule which storage granules eg. Histamine in mast cell.

b- Newly synthesis

2- Plasma derived Chemical mediator:





Function of Chemical mediator:

1- Vascular dilatation like histamine

2- Increase vascular permeability like kinin system

3- Leukocyte attract like C5a

4- Paine +fever LIKE prostaglandin

5- Smooth muscle contraction histamine

MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

Many variables may modify the basic inflammatory response; these include

1. The nature and intensity of the injury
2. The site and tissues affected
3. The responsiveness of the host

Several types of inflammation are recognized, which vary in their morphology and clinical correlates.

Serous inflammation is characterized by the outpouring of a thin fluid that is derived from either the plasma or the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. In these serous cavities the accumulated fluid is called effusion. (**Fig. 3-5**) The skin blister resulting from a burn or viral infection represents a large accumulation of serous fluid, either within or immediately beneath

the epidermis of the skin. Fibrinous inflammation With more severe injuries and the resulting greater vascular permeability, larger molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and

deposited in the extracellular space. A fibrinous exudate develops in such cases. The latter also occurs when there is a stimulus for coagulation in the interstitium (e.g., cancer cells). A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium, and pleura. (**Fig. 3-6**)

Microscopically, fibrin appears as an eosinophilic meshwork of threads or amorphous coagulated mass. Fibrinous exudates may be removed by fibrinolysis and clearing of other debris by macrophages. However, when the fibrin is not removed, it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue is called organization. When this occurs within the pericardial sac it leads either to opaque fibrous thickening of the pericardium or, more often, to the development ofibrous strands that reduce and may even obliterate the pericardial space. Suppurative (purulent) inflammation This is characterized by the production of large amounts of pus or purulent exudates consisting of neutrophils, necrotic cells, and edema fluid. Certain bacteria (e.g., staph. aureus, St. pyogenes, Pneumococci, gonococci, meningococci and E. coli) produce this localized suppuration and are therefore called pyogenic (pus-producing) bacteria. A common example of an acute suppurative inflammation is **acute (suppurative) appendicitis**. (**Fig. 3-7**) An **abscess** is a localized collection of purulent inflammatory fluid (pus) caused by suppuration buried in a tissue, an organ, or a confined space. Pus is a thick creamy yellow or blood-stained fluid. Abscesses are produced by deep seeding of pyogenic bacteria into a tissue. They have a central region that appears as a mass of necrotic leukocytes and tissue cells. There is usually a zone of preserved neutrophils around this necrotic focus, and outside this region vascular dilation and fibroblastic proliferation occur, indicating the beginning of repair. In time, the abscess may become walled off and ultimately replaced by connective tissue. A common example of an abscess is the skin furuncle. (**Fig. 3-8**)

Ulcers An ulcer is a local defect, or excavation of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue. Ulceration occurs only when tissue necrosis and resultant inflammation exist on or near a surface.

It is most commonly encountered in:

1. Inflammatory necrosis of mucosa-lined cavities e.g. mouth, larynx, stomach, intestines, or genitourinary tract. (**Fig. 3-9**) 2. Subcutaneous inflammation of the lower extremities in older persons who have circulatory disturbances that predispose to extensive necrosis. Ulcerations are best exemplified by peptic ulcer of the stomach or duodenum, in which acute and chronic inflammation coexist. Pseudomembranous inflammation of mucous membranes Severe injury may be associated with extensive epithelial necrosis with sloughing. This creates large shallow ulcers. Fibrin, dead epithelium, neutrophils, red cells and bacteria mix together to produce a white or cream-colored false (pseudo-) membrane covering the affected mucosa. Diphtheria and psudomembranous colitis are typical examples.

EFFECTS OF ACUTE INFLAMMATION

Beneficial Effects

1. Dilution of Toxins by the edema fluid
2. Production of protective Antibodies & promotion of immunity
3. Fibrin meshwork formation that forms a scaffold for inflammatory cell migration & also limits the spread of infections
4. Cell Nutrition Harmful Effects

1. Swelling & edema that can be detrimental for e.g. acute epiglottitis that may be life threatening
2. Rise in tissue pressure that contributes to tissue necrosis
3. Digestion of adjacent viable tissue
4. Sever damaging allergic reaction
5. Generalized increase in vascular permeability can cause shock as seen in anaphylactic reactions.

OUTCOMES OF ACUTE INFLAMMATION

In general, acute inflammation may have one of three outcomes

1. Complete resolution The battle between the injurious agent and the host may end with restoration of the site of acute inflammation to normal. This is called resolution and is the usual outcome when

a. the injury is limited or short-lived

b. there has been little tissue destruction

c. the damaged parenchymal cells can regenerate

2. Healing by fibrosisThis occurs

a. after extensive tissue destruction

b. when the inflammatory injury involves tissues that are incapable of regeneration

c. when there is abundant fibrin exudation.

When the fibrinous exudate in tissue or serous cavities (pleural, peritoneal, synovial) cannot be adequately cleared, connective tissue grows into the area of exudate, converting it into a mass of fibrous tissue—a process also called **organization.**

3. Progression to chronic inflammation Acute to chronic transition occurs when the acute inflammatory response persists, owing either to the perseverance of the injurious agent or to some interference with the normal process of healing. For example, failure of acute bacterial pneumonia to resolve may lead to extensive tissue destruction and formation of a cavity in which the inflammation continues to smolder, leading eventually to a chronic lung abscess.

CHRONIC INFLAMMATION

Although it may follow acute inflammation, it frequently begins from the outset as a chronic ,insidious, and low-grade, smoldering response. Chronic inflammation is the cause of tissue damage in some of the most common and disabling human diseases, such as rheumatoid arthritis, atherosclerosis, tuberculosis, and chronic lung diseases. Chronic Inflammation may complicate acute inflammation. The latter is almost always a suppurative type of inflammation that presents as a purulent discharge (pus) as seen in abscess. The cause is either a delay in the evacuation of an abscess, or

presence of foreign-body within inflamed area (dirt, wood, metal or a sequestrated bone) Causes of chronic inflammation include

1. Persistent infections by certain microorganisms such as tubercle bacilli, Treponema pallidum, certain viruses, fungi, and parasites. These organisms are of low toxicity and evoke delayed type hypersensitivity reaction.

2. Prolonged exposure to toxic agents either exogenous as inhaled silica particles, or endogenous such as toxic plasma lipids that are thought to be responsible for atherosclerosis. The latter is thought to be a chronic inflammatory process of the arterial wall.

3. Autoimmunity Under certain conditions, immune reactions develop against the individual's own tissues, leading to autoimmune diseases. In these diseases, autoantigens activate a self-perpetuating immune reaction that results in chronic inflammation with associated tissue damage. Examples of this type include several common chronic inflammatory diseases, such as rheumatoid arthritis and lupus erythematosus. Morphologic features of chronic inflammation In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration,

chronic inflammation is characterized by:

1. Infiltration with mononuclear cells including macrophages, lymphocytes, and plasma cells.

2. Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.

3. Attempts at healing by fibrosis of the damaged tissue, achieved by proliferation of small blood vessels (angiogenesis) & fibroblasts. Mononuclear cell infiltration The macrophage is the dominant cells in chronic inflammation. The mononuclear phagocyte system (reticuloendothelial system) consists of closely related cells of bone

marrow origin, including blood monocytes and tissue macrophages. The latter are diffusely scattered in connective tissues or located in organs such as the liver (Kupffer cells), spleen and lymph nodes (sinus histiocytes), and lungs (alveolar macrophages). From the blood, monocytes migrate into various tissues and differentiate into macrophages. The half-life of blood monocytes is about 1 day, whereas the life span of tissue macrophages is several months or years. When the monocyte reaches the extravascular tissue, it undergoes transformation into a larger phagocytic cell, the macrophage. Macrophages may be activated by a variety of stimuli, including cytokines (e.g., IFN-γ) secreted by sensitized T lymphocytes, NK cells, bacterial endotoxins, and other chemical mediators. Activation results in increased cell size, and greater ability to phagocytose and kill ingested microbes. Activated macrophages secrete a wide variety of biologically active products that result in the tissue injury and fibrosis. In short-lived acute inflammation, if the irritant is eliminated, macrophages eventually disappear (dying off or travel through lymphatics to lymph nodes). The products of activated macrophages serve to eliminate injurious agents such as microbes and to initiate the process of repair, but are also responsible for much of the tissue injury in chronic inflammation; these products include

1. Toxic substances to microbes and host cells (e.g., toxic O2 species, NO, and proteases)
2. Chemoattractants to other inflammatory cells
3. Growth factors the cause of fibroblast proliferation, collagen deposition, and angiogenesis. Other cells in chronic inflammation

Other cell types present in chronic inflammation include lymphocytes, plasma cells, eosinophils, and mast cells:

Lymphocytes are mobilized in immune and nonimmune inflammation.

Antigen-stimulated T and B-cells use various adhesion molecules (predominantly the integrins) and chemokines to migrate into inflammatory sites. Lymphocytes and macrophages interact in a bidirectional way and these reactions play an important

role in chronic inflammation. Macrophages display antigens to T cells that stimulate them. Activated T lymphocytes produce cytokines, and one of these, IFN-γ, which is a major activator of macrophages.

Plasma cells develop from activated B lymphocytes and produce antibody directed against persistent antigen in the inflammatory site.

Eosinophils are abundant in immune reactions mediated by IgE and in parasitic infections. The recruitment of eosinophils involves extravasation from the blood and their migration into tissue by processes similar to those for other leukocytes. One of the chemokines that is especially important for eosinophil recruitment is eotaxin. Eosinophils have granules that contain major basic protein that is toxic to parasites.

Mast cells are widely distributed in connective tissues and participate in both acute and persistent inflammatory reactions. Mast cells express on their surface the receptor that binds the Fc portion of IgE antibody. In acute reactions, IgE antibodies bound to the cells' Fc receptors specifically recognize antigen, and the cells degranulate and release mediators, such as histamine and products of AA oxidation. Mast cells are also present in chronic inflammatory reactions, and may produce cytokines that contribute to fibrosis.

Neutrophils although characteristic of acute inflammation, many forms of chronic inflammation continue to show large numbers of neutrophils, induced either by persistent microbes or by mediators produced by macrophages and T lymphocytes. In chronic bacterial infection of bone (osteomyelitis), a neutrophilic exudate can persist for many months. Neutrophils are also important in the chronic damage induced in lungs by smoking and other irritant stimuli. Mediators of chronic inflammation.

GRANULOMATOUS INFLAMMATION

This is a distinctive pattern of chronic inflammatory reaction characterized by focal accumulations of activated macrophages, which often develop an epithelioid (epithelial-like) appearance. Causes

Granulomatous inflammation is encountered in a number of immunologically mediated infectious and some noninfectious conditions, these include

1. Tuberculosis
2. Sarcoidosis
3. Cat-scratch disease
4. Lymphogranuloma inguinale
5. Leprosy
6. Brucellosis
7. Syphilis,
8. Some fungal infections
9. Berylliosis
10. Reactions of irritant lipids

Recognition of granulomas in a biopsy specimen is important because it shortens the list of the differential diagnosis. A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelioid cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells. The epithelioid cells have a pale pink granular cytoplasm with indistinct cell borders and a vesicular nucleus that is oval or elongate. Older granulomas develop an enclosing rim of fibroblasts and connective tissue. Frequently, epithelioid cells fuse to form giant cells in the periphery or sometimes in the center of granulomas. These **giant cells** may attain diameters of 40 to 50 μm. They have a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (foreign body-type giant cell). There are two types of granulomas, which differ in their pathogenesis.

1. Foreign body granulomas, which are provoked by foreign bodies. Typically, foreign body granulomas form when material such as talc (associated with intravenous drug abuse), sutures, or other fibers are large enough to preclude phagocytosis by a single macrophage and do not incite any specific inflammatory or immune response. Epithelioid cells and giant cells form and are opposed to the surface of the foreign body and/or actually include it. The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it appears refractile