

## VIII. CHRONIC INFLAMMATION

**Definition:** Chronic inflammation can be defined as a prolonged inflammatory process (weeks or months) where an active inflammation, tissue destruction and attempts at repair are proceeding simultaneously.

### Causes of chronic inflammation:

#### 1. Persistent infections

- □ Certain microorganisms associated with intracellular infection such as tuberculosis, leprosy, certain fungi etc characteristically cause chronic inflammation.
- □ These organisms are of low toxicity and evoke delayed hypersensitivity reactions.

**2. Prolonged exposure to nondegradable but partially toxic substances** either endogenous lipid components which result in atherosclerosis or exogenous substances such as silica, asbestos.

**3. Progression from acute inflammation:** Acute inflammation almost always progresses to chronic inflammation following:

Persistent suppuration as a result of uncollapsed abscess cavities, foreign body materials (dirt, cloth, wool, etc), sequestrum in osteomyelitis, or a sinus/fistula from chronic abscesses.

**4. Autoimmunity.** Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus are chronic inflammations from the outset.

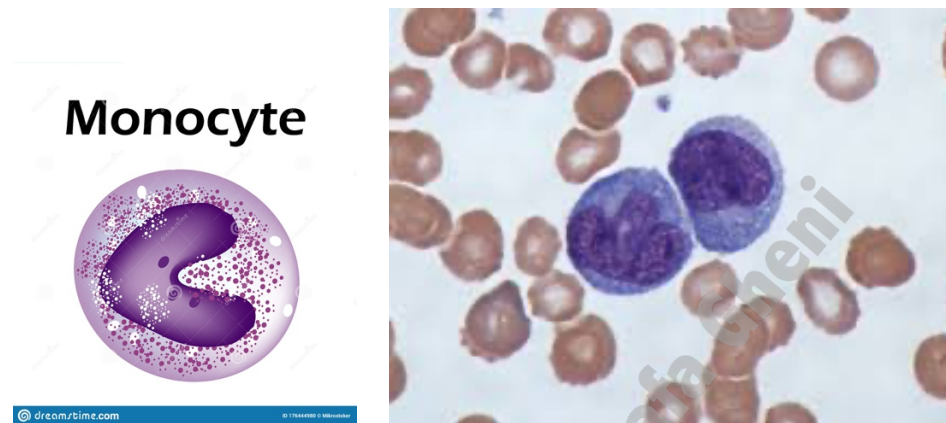
### Morphology:

#### Cells of chronic inflammation:

- □ **Monocytes and Macrophages** are the prima Dona (primary cells) in chronic inflammation. Macrophages arise from the common precursor cells in the bone marrow, which give rise to blood monocytes. These cells are then diffusely scattered in various parts of the body, in the liver (Kupffer cells), spleen, lymph

nodes (sinus histiocytes), lungs (alviolar macrophages), bone marrow, brain (microglia), skin (Langerhan's cells), etc.... These cells constitute the mononuclear- phagocytic system.

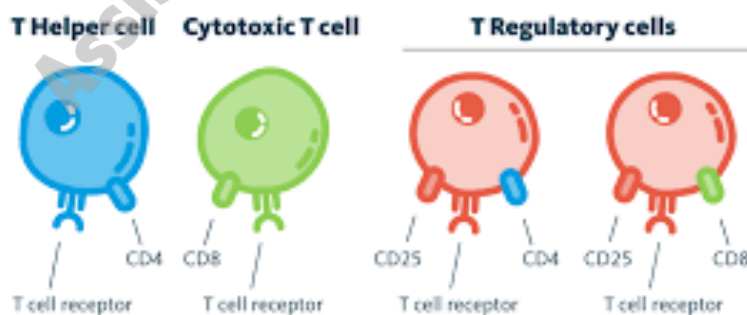
- Macrophages are scavenger cells of the body.



#### Other cells in chronic inflammation:

1. **T-Lymphocytes** are primarily involved in cellular immunity with lymphokine production, and they are the key regulator and effector cells of the immune system.

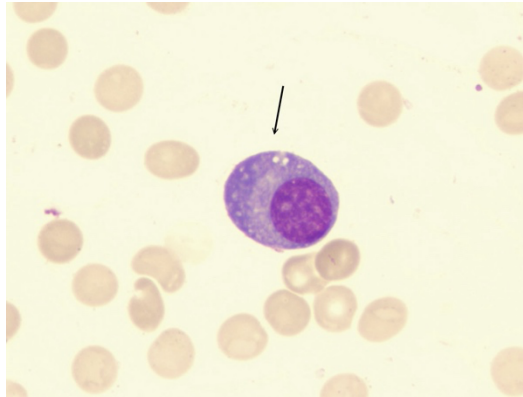
#### Different types of T cells



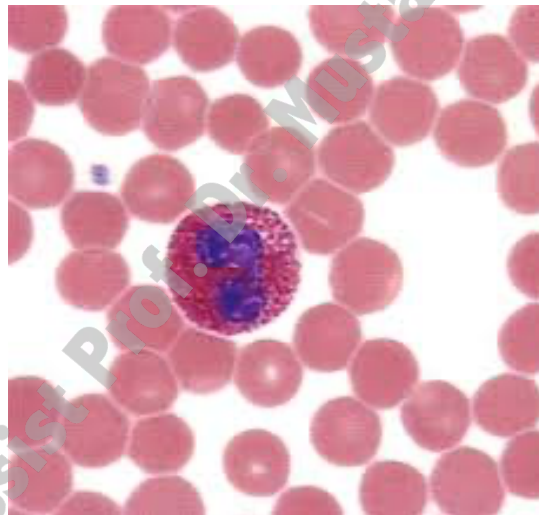
2. **B-lymphocytes and Plasma cells** produce antibody directed either against persistent antigen in the inflammatory site or against altered tissue components.

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3.



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4. Mast cells and eosinophils appear predominantly in response to parasitic infestations & allergic reactions.
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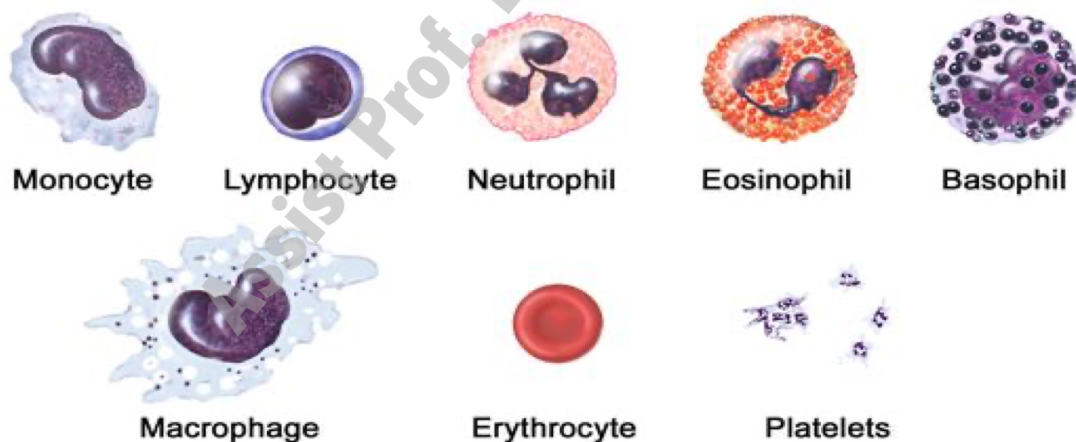
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Though neutrophils are hallmarks of acute inflammatory reactions, large numbers of neutrophils may be seen in some forms of chronic inflammation, notably chronic osteomyelitis, actinomycosis, & chronic lung diseases induced by smoking and other stimuli.

Thus, the overall differentiation points between acute and chronic inflammations include

<u>Characteristics</u>	<u>Acute inflammation</u>	<u>Chronic inflammation</u>
Duration	Short	Relatively long
Pattern	Stereotyped	Varied
Predominant cell	Neutrophils	Macrophages, plasma cells
Tissue destruction	Mild to moderate	Marked
Fibrosis	Absent	Present
Inflammatory reaction	Exudative	Productive

### Blood Cells



### Classification of chronic inflammation:

Chronic inflammation can be classified into the following two types based on histologic features:

**1) Nonspecific chronic inflammation:** This involves a diffuse accumulation of macrophages and lymphocytes at site of injury that is usually productive with new fibrous tissue formations. E.g. Chronic

cholecystitis.

## 2) Specific inflammation (granulomatous inflammation):

**Definition:** Granulomatous inflammation is characterized by the presence of granuloma. A granuloma is a microscopic aggregate of epithelioid cells. Epithelioid cell is an activated macrophage, with a modified epithelial cell-like appearance (hence the name epithelioid). The epithelioid cells can fuse with each other & form multinucleated giant cells. So, even though, a granuloma is basically a collection of epithelioid cells, it also usually contains multinucleated giant cell & is usually surrounded by a cuff of lymphocytes and occasional plasma cells. There are two types of giant cells:

a. **Foreign body-type giant cells** which have irregularly scattered nuclei in presence of indigestible materials.

b. **Langhans giant cells** in which the nuclei are arranged peripherally in a horse -shoe pattern which is seen typically in tuberculosis, sarcoidosis etc...

Giant cells are formed by fusion of macrophages perhaps by a concerted attempt of two or more cells to engulf a single particle.

### **Pathogenesis:**

There are two types of granulomas, which differ in their pathogenesis.

#### **A. Foreign body granuloma**

These granulomas are initiated by inert foreign bodies such as talc, sutures (non- absorbable), fibers, etc... that are large enough to preclude phagocytosis by a single macrophage and do not incite an immune response.

#### **B. Immune granulomas**

Antigen presenting cells (macrophages) engulf a poorly soluble inciting agent. Then, the macrophage processes and presents part of the antigen (in association with MHC type2 molecules) to CD4+T helper 1 cells which become activated. The activated CD4+ T-cells produce cytokines (IL-2 and interferon gamma).The IL-2 activates other CD4+T helper cells and perpetuates the response while IFN- $\gamma$  is important in transforming macrophages into epithelioid cells and multinucleated giant cells. The cytokines have been implicated not only in the formation

but also in the maintenance of granuloma.

Macrophage inhibitory factor helps to localize activated macrophages and epitheloid cells.

### **Causes:**

Major causes of granulomatous inflammation include:

- a) **Bacterial:** Tuberculosis, Leprosy, Syphilis, Cat scratch disease, Yersiniosis
- b) **Fungal:** Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Blastomycosis
- c) **Helminthic:** Schistosomiasis
- d) **Protozoal:** Leishmaniasis, Toxoplasmosis
- e) **Chlamydia:** Lymphogranuloma venerum
- f) **Inorganic material:** Berylliosis
- g) **Idiopathic:** Acidosis, Cohn's disease, Primary biliary cirrhosis

## **I. SYSTEMIC EFFECTS OF INFLAMMATIONS**

The systemic effects of inflammation include:

1. Fever
2. Endocrine & metabolic responses
3. Autonomic responses
4. Behavioral responses
5. Leukocytosis
6. Leukopenia
7. Weight loss

a. **Fever**

**Fever** is the most important systemic manifestation of inflammation. It is coordinated by the hypothalamus & by cytokines (IL -1, IL-6, TNF- $\alpha$ ) released from macrophages and other cells.

b. **Endocrine and metabolic responses** include:

- The liver secretes acute phase proteins such as:

C-reactive proteins

Serum Amyloid A

Complement and coagulation proteins

- Glucocorticoids (increased)

- Vasopressin (decreased)

c. **Autonomic** responses include:

- Redirection of blood flow from the cutaneous to the deep vascular bed.

- Pulse rate and blood pressure (increased)

- Sweating (decreased)

d. **Behavioral** responses include:

- Rigor, chills, anorexia, somnolence, and malaise.

e. **Leucocytosis** is also a common feature of inflammation, especially in bacterial infections. Its usual count is 15,000 to 20,000 cells/mm<sup>3</sup>. Most bacterial infections induce neutrophilia. Some viral infections such as infectious mononucleosis, & mumps cause **lymphocytosis**. Parasitic infestations & allergic reactions such as bronchial asthma & hay fever induce **eosinophilia**.

**f. Leukopenia** is also a feature of typhoid fever and some parasitic infections.

**g. Weight loss** is thought to be due to the action of IL-1 and TNF- $\alpha$  which increase catabolism in skeletal muscle, adipose tissue and the liver with resultant negative nitrogen balance.

