CHRONIC INFLAMMATION

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DEFINITION AND CAUSES. Chronic inflammation is defined as prolonged process in which tissue destruction and inflammation occur at the same time. Chronic inflammation can be caused by one of the following 3 ways:

1. Chronic inflammation following acute inflammation.
When the tissue destruction is extensive, or the bacteria survive and persist in small numbers at the site of acute inflammation e.g. in osteomyelitis, pneumonia terminating in lung abscess.

2. Recurrent attacks of acute inflammation. When repeated bouts of acute inflammation culminate in chronicity of the process e.g. in recurrent urinary tract infection leading to chronic pyelonephritis, repeated acute infection of gallbladder leading to chronic cholecystitis.

3. Chronic inflammation starting *de novo*. When the infection with organisms of low pathogenicity is chronic from the beginning e.g. infection with *Mycobacterium tuberculosis*.

GENERAL FEATURES OF CHRONIC INFLAMMATION

Though there may be differences in chronic inflammatory response depending upon the tissue involved and causative organisms, there are some basic similarities amongst various types of chronic inflammation. Following general features characterize any chronic inflammation:

1. MONONUCLEAR CELL INFILTRATION. Chronic inflammatory lesions are infiltrated by mononuclear inflammatory cells like phagocytes and lymphoid cells. Phagocytes are represented by circulating monocytes, tissue macrophages, epithelioid cells and sometimes, multinucleated giant cells. The macrophages comprise the most important cells in chronic inflammation. These may appear at the site of chronic inflammation from:

i) chemotactic factors and adhesion molecules for continued infiltration of macrophages;
ii) local proliferation of macrophages; and
iii) longer survival of macrophages at the site of inflammation.

The blood monocytes on reaching the extravascular space transform into tissue macrophages.

Besides the role of macrophages in phagocytosis, they may get activated in response to stimuli such as cytokines (lymphokines) and bacterial endotoxins. On activation, macrophages release several biologically active substances e.g. acid and neutral

proteases, oxygen-derived reactive metabolites and cytokines. These products bring about tissue destruction, neovascularisation and fibrosis.

Other chronic inflammatory cells include lymphocytes, plasma cells, eosinophils and mast cells.
In chronic inflammation, lymphocytes and macrophages influence each other and release mediators of inflammation.

2. TISSUE DESTRUCTION OR NECROSIS. Tissue destruction and necrosis are central features of most forms of chronic inflammatory lesions. This is brought about by activated macrophages which release a variety of biologically active substances e.g. protease, elastase, collagenase, lipase, reactive oxygen radicals, cytokines (IL-1, IL-8, TNF-□), nitric oxide, angiogenesis growth factor etc.
3. PROLIFERATIVE CHANGES. As a result of necrosis, proliferation of small blood vessels and fibroblasts is stimulated resulting in formation of inflammatory granulation tissue. Eventually, healing by fibrosis and collagen laying takes place.

TYPES OF CHRONIC INFLAMMATION

histological features are used for classifying chronic inflammation into 2 corresponding types:

1. **Chronic non-specific inflammation.** It is characterized by non-specific inflammatory cell infiltration e.g. chronic osteomyelitis, lung abscess.
   A variant of this type of chronic inflammatory response is chronic suppurative inflammation in which infiltration by polymorphs and abscess formation are additional features e.g. actinomycosis.

2. Chronic granulomatous inflammation. It is characterised by formation of granulomas e.g. tuberculosis, leprosy, syphilis, actinomycosis, sarcoidosis etc.

GRANULOMATOUS INFLAMMATION

Granuloma is defined as a circumscribed, tiny lesion, about 1 mm in diameter, composed predominantly of collection of modified macrophages called epithelioid cells, and rimmed at the periphery by lymphoid cells. The word *'granuloma'* is derived from *granule* meaning circumscribed granule-like lesion, and *-oma* which is a suffix commonly used for true tumours but here it indicates a localized inflammatory mass or collection of macrophages.

PATHOGENESIS OF GRANULOMA. Formation of granuloma is a type IV granulomatous hypersensitivity reaction . It is a protective defense reaction by the host but eventually causes tissue destruction because of persistence of the poorly digestible antigen e.g. *Mycobacterium tuberculosis, M. leprae*, suture material, particles of talc etc.

The sequence in evolution of granuloma is briefly outlined below:

1. Engulfment by macrophages. Macrophages and monocytes engulf the antigen and try to destroy it. But since the antigen is poorly degradable, these cells fail to digest and degrade the antigen, and instead undergo morphologic changes to epithelioid cells.

2. CD4+ T cells. Macrophages, being antigen-presenting cells, having failed to deal with the antigen, present it to CD4+ T lymphocytes. These lymphocytes get activated and elaborate lymphokines (IL-1, IL-2, interferon-□, TNF-□).

3. Cytokines. Various cytokines formed by activated CD4+ T cells and also by activated macrophages perform the following roles:

i) IL-1 and IL-2 stimulate proliferation of more T cells.

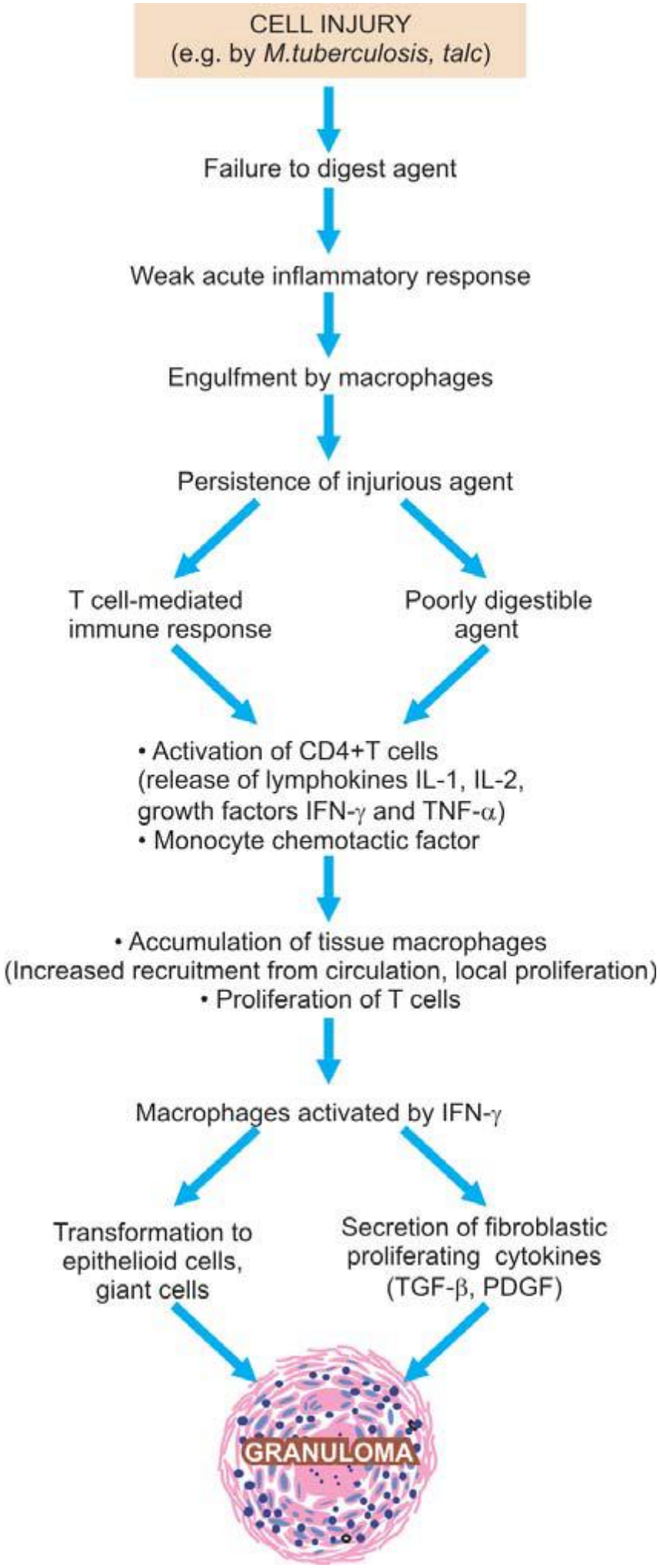
ii) Interferon-□ activates macrophages.

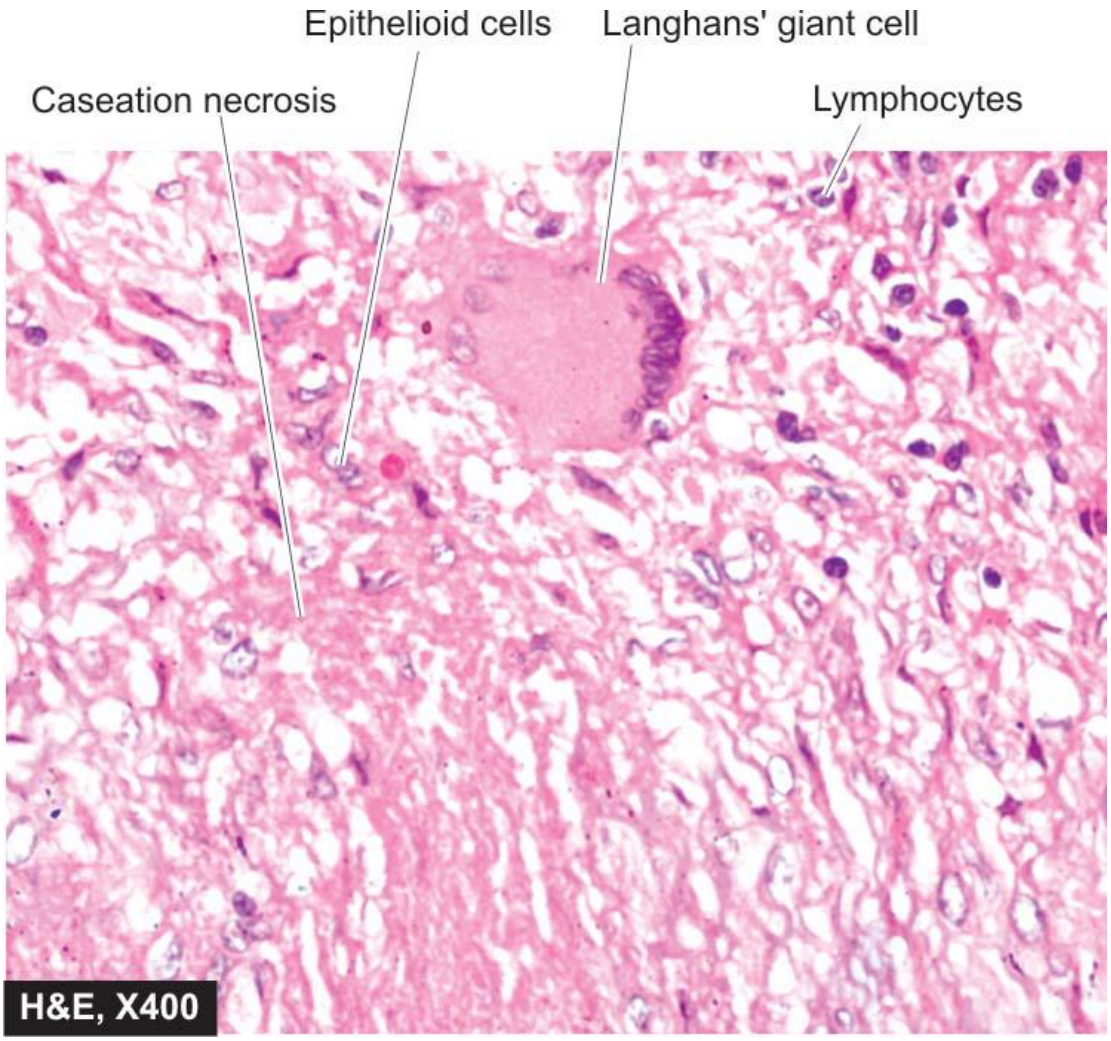
iii) TNF-□ promotes fibroblast proliferation and activates endothelium to secrete prostaglandins which have role in vascular response in inflammation.

iv) Growth factors (transforming growth factor-□, plateletderived growth factor) elaborated by activated macrophages stimulate fibroblast growth.

Thus, a granuloma is formed of macrophages modified as epithelioid cells in the centre, with some interspersed multinucleate giant cells, surrounded peripherally by lymphocytes (mainly T cells), and healing by fibroblasts or collagen depending upon the age of granuloma.

COMPOSITION OF GRANULOMA. In general, a granuloma has the following structural composition:


CELL INJURY
(e.g. by M.tuberculosis, talc)
Failure to digest agent
Weak acute inflammatory response
Engulfment by macrophages
Persistence of injurious agent
T cell-mediated immune response
Poorly digestible agent
• Activation of CD4+T cells (release of lymphokines IL-1, IL-2, growth factors IFN-γ and TNF-α)
• Monocyte chemotactic factor
• Accumulation of tissue macrophages (Increased recruitment from circulation, local proliferation)
• Proliferation of T cells
Macrophages activated by IFN-γ
Transformation to epithelioid cells, giant cells
Secretion of fibroblastic proliferating cytokines (TGF-β, PDGF)
GRANULOMA



Morphology of a tubercle. There is central caseation necrosis, surrounded by elongated epithelioid cells having characteristic slipper-shaped nuclei, with interspersed Langhans' giant cells. Periphery shows lymphocytes.

Features	Acute inflammation	Chronic Inflammation
Onset	**Fast (minutes or hours)**	**Slow (days)**
Cellular infiltrate	**Mainly neutrophiles**	**Macrophages & lymphocytes**
Tissue injury , fibrosis	**Usually mild (Self limited)**	**Often severe & progressive**
Systemic signs	**Prominent**	**Less prominent**

Systemic Effects of Inflammation

It consists of several clinical and pathologic changes

1. Fever, characterized by an elevation of body temperature, usually by l'to 4'C, is one of the most prominent manifestations especially when inflammation is associated with infection.

2. <u>Elevated of plasma level of Acute-phase proteins</u>, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold.

Three of the best-known of these proteins

are **C-reactive protein** (CRP), **fibrinogen,** and **serum amyloid A** (SAA) proteins.

3. <u>Leukocytosis</u>: a common feature of inflammatory reactions, especially those induced by bacterial infections. The leukocyte count usually climbs to 15,000 or 20,000cells/pl, especially neutrophil (called **neutrophilia**).

* Viral infections, such as mumps, and German measles, cause an absolute increase in the number of lymphocytes (**lymphocytosis**).

*Certain infections such as typhoid fever and rickettsiae are associated with a decreased number of white blood cells (**leucopenia)**

4. **Other manifestations** include

Increased pulse and blood pressure, decreased sweating, rigors (shivering), chills, anorexia, and malaise.

Giant Cells

A few examples of multinucleate giant cells exist in normal tissues (e.g. osteoclasts in the bones, trophoblasts in placenta, megakaryocytes in the bone marrow). However, in chronic inflammation when the macrophages fail to deal with particles to be removed, they fuse together and form multinucleated giant cells. Besides, morphologically distinct giant cells appear in some tumours also.

Multinucleate giant cells. In granuloma Multinucleate giant cells are formed by fusion of adjacent epithelioid cells and may have 20 or more nuclei. These nuclei may be arranged at the periphery like horseshoe or ring, or are clustered at the two poles (Langhans' giant cells), or they may be presen centrally (foreign body giant cells). The former are commonly seen in tuberculosis while the latter are common in foreign body tissue reactions. Like epithelioid cells, these giant cells are weakly phagocytic but produce secretory products which help in removing the invading agents.