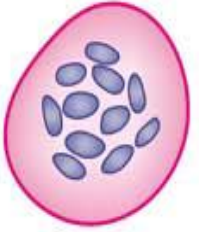



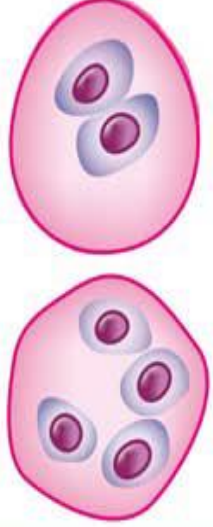
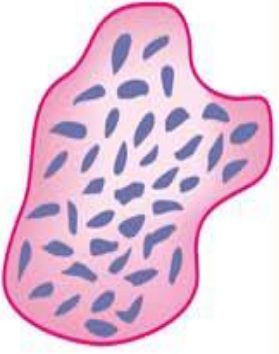




Giant cells of various types. A, Foreign body giant cell with uniform nuclei dispersed throughout the cytoplasm. B, Langhans' giant cells with uniform nuclei arranged peripherally or clustered at the two poles. C, Touton giant cell with circular pattern of nuclei and vacuolated cytoplasm. D, Anaplastic tumour giant cell with nuclei of variable size and shape. E, Reed-Sternberg cell. F, Osteoclastic tumour giant cell.

INFLAMMATORY GIANT CELLS		
		
A, Foreign body type	B, Langhans' type	C, Touton type

TUMOUR GIANT CELLS		
		
D, Anaplastic tumour giant cell	E, Reed-Sternberg cells	F, Osteoclastic tumour giant cell

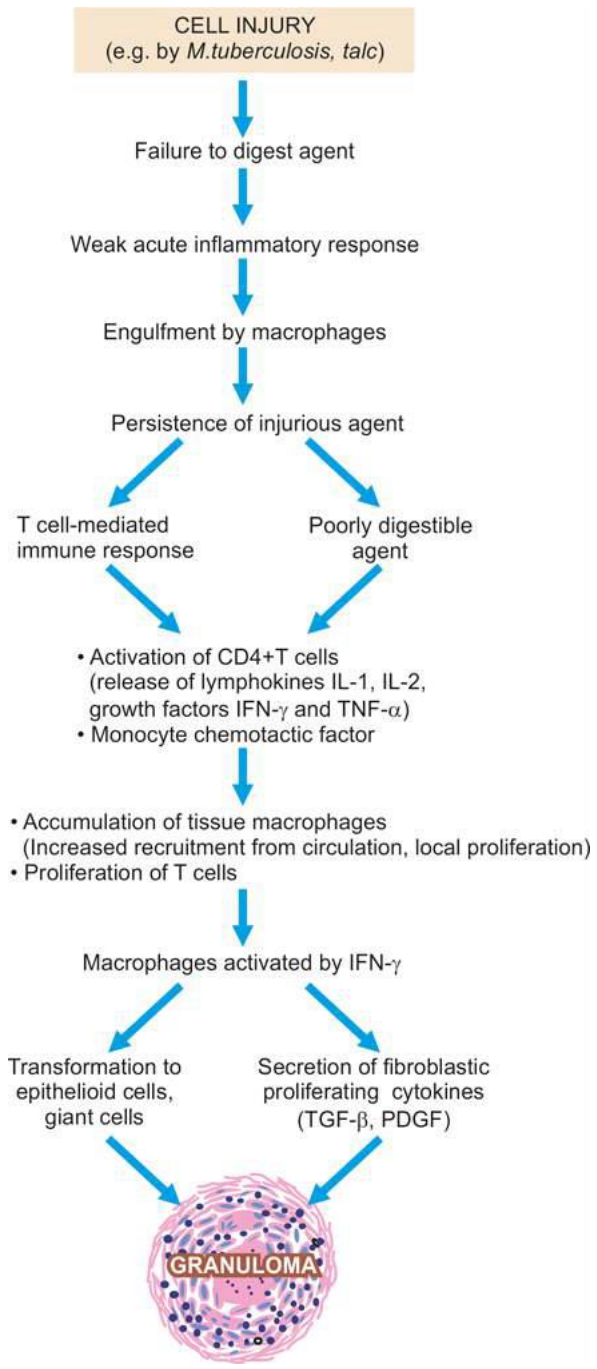
# GRANULOMATOUS INFLAMMATION

## *Granuloma*

- Circumscribed, tiny lesion, about **1 mm** in diameter,
- Collection of modified macrophages called epithelioid cells, and rimmed at the periphery by lymphoid cells.
- *Granule* meaning circumscribed granule-like
- Lesion, and *-oma* which is a suffix commonly used for true tumours but here it indicates a localised 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.



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- $\gamma$  and TNF- $\alpha$ )
- Monocyte chemotactic factor

- Accumulation of tissue macrophages  
(Increased recruitment from circulation, local proliferation)
- Proliferation of T cells

Macrophages activated by IFN- $\gamma$

Transformation to  
epithelioid cells,  
giant cells

Secretion of fibroblastic  
proliferating cytokines  
(TGF- $\beta$ , PDGF)

GRANULOMA

**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 transform into epithelioid cells.

**2. CD4+ T cells** Macrophages, being antigen-presenting cells, having failed to deal with the antigen, present it to CD4+ T cells.

- These lymphocytes get activated and elaborate lymphokines (**IL-1, IL-2, interferon-g, TNF-a**).

**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-g* activates macrophages.

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

iv) *Growth factors* (transforming growth factor-b, platelet derived growth factor) elaborated by activated macrophages stimulate fibroblast growth.

Thus, a granuloma is formed having 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



# COMPOSITION OF GRANULOMA

**1. Epithelioid cells** epithelial cell-like appearance. They are modified macrophages/histiocytes which are somewhat elongated cells having slipper-shaped nucleus.

The nuclear chromatin of these cells is vesicular and lightly-staining, while the cytoplasm is abundant, pale-staining with hazy outlines so that the cell membrane of adjacent epithelioid cells is closely apposed.

**Epithelioid cells are weakly phagocytic.**

**2. Multinucleate giant cells** 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 the **horseshoe** or as a **ring**, or may be clustered at the **two poles** (**Langhans' giant cells**), or they may be present 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.**

**3. Lymphoid cells** As a cell-mediated immune reaction to antigen, the host response by lymphocytes is integral to composition of a granuloma.

Plasma cells indicative of accelerated humoral immune response are present in some types of granulomas.

**4. Necrosis** Necrosis may be a feature of some granulomatous conditions e.g. **central caseation necrosis** in tuberculosis, so called because of its dry cheese-like appearance.

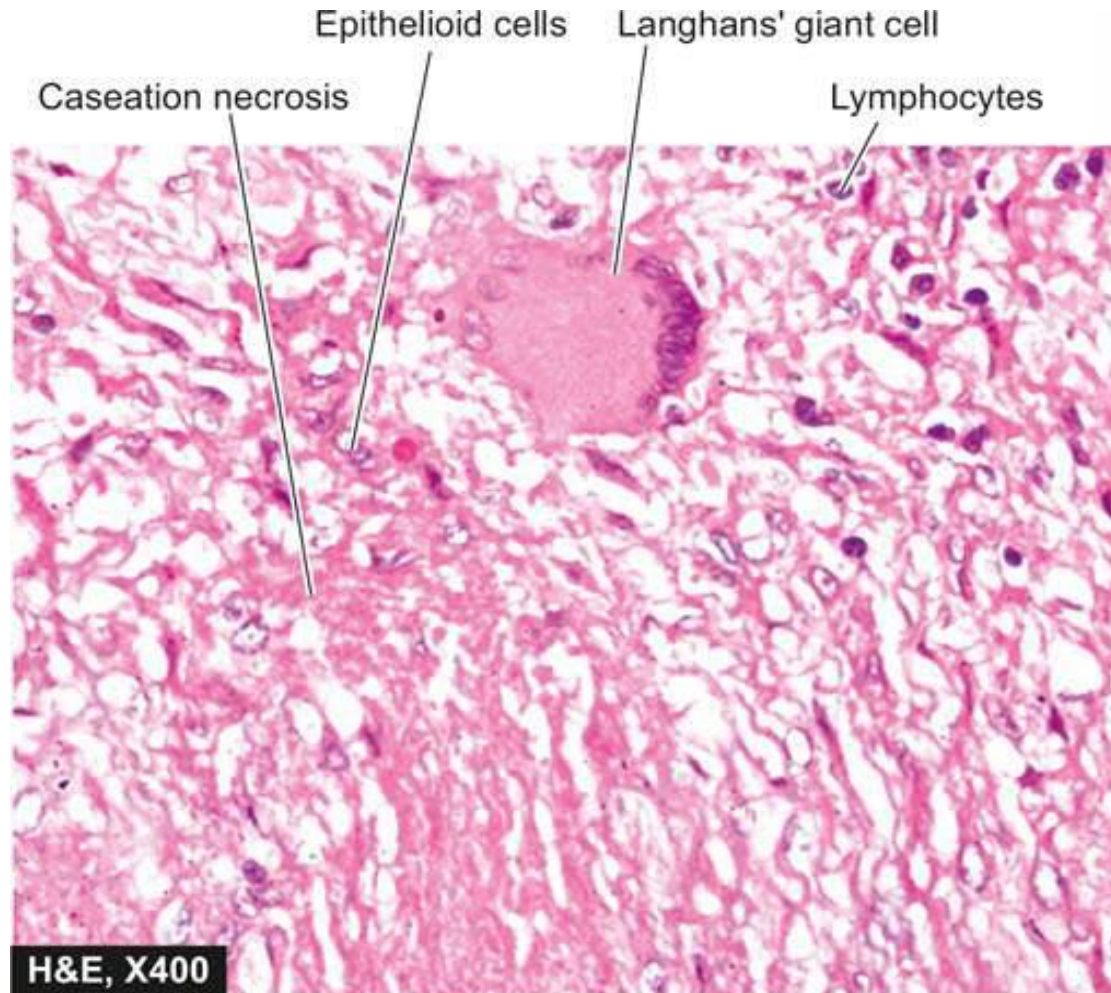
**5. Fibrosis** Fibrosis is a feature of **healing** by proliferating fibroblasts at the periphery of granuloma.

# The classical example

tissue response to **tubercle bacilli** which is called *tubercle* seen in tuberculosis

- A fully-developed tubercle is about 1 mm in diameter with central area of caseation necrosis,
- surrounded by epithelioid cells and one to several multinucleated giant cells (commonly Langhans' type),
- Surrounded at the periphery by lymphocytes and bounded by fibroblasts and fibrous tissue

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.



▣ A granuloma is a circumscribed collection of epithelioid cells surrounded at the periphery by lymphocytes and may contain a few multinucleate giant cells.

▣ A granuloma is formed as a host inflammatory response to a poorly degradable agent by eliciting delayed type hypersensitivity (type IV reaction).

▣ Formation of a granuloma involves engulfment of the invading agent by the macrophages, failure to degrade the antigen, morphologic change of macrophages to epithelioid cells, and incoming CD4+ T cells which elaborate various cytokines which contribute to proliferation and activation of cells.

▣ A granuloma may have necrosis in the centre and eventually heals by fibrosis.

▣ Granulomatous diseases include infections (bacterial, fungal, parasitic) autoimmune inflammatory, and foreign bodies.

Schematic evolution of tubercle. In fully formed granuloma, the centre is composed of granular caseation necrosis, surrounded by epithelioid cells and Langhans' giant cells and peripheral rim of lymphocytes bounded by fibroblasts.

