# Pathology of

# INFLAMMATION

## CH 2: Lecture III

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## Chronic Inflammation

- **Chronic** - weeks to months or years
  - **Fibrosis** – **Scarring**.
  - **Lymphocytes** and **macrophages**
- **Definition:** Inflammation of prolonged duration in which active inflammation, tissue injury and healing proceed simultaneously

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## Characteristics of chronic inflammation

- **Persistence or recurrence** of injurious agent
- **Prolonged inflammation**
- **Tissue destruction** by the inflammatory cells
- **Healing/repair:** involving new vessel formation (**angiogenesis**) and **fibrosis**.
- **Infiltration by mononuclear cells** (**macrophages**, lymphocytes, and plasma cells)

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## Chronic inflammation arises in the following settings:

1. **unresolved acute inflammation**

   **example: chronic abscess**

2. **repeated acute inflammation**

   **example: chronic pancreatitis**

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## Chronic inflammation arises in the following settings:

3. **delayed hypersensitivity reaction**

- **intracellular infectious agents**
  **example:** brucellosis, viral infections
- **Fungi, parasite**
- **repeated contact sensitivity**
  **example:** contact dermatitis

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## Chronic inflammation arises in the following settings:

4. **foreign body reaction**

- **endogenous material**
  example: fat, uric acid crystals in **gout**
- **exogenous material**
  example: suture material, asbestos, **silica**

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## Chronic inflammation arises in the following settings:

5. q **auto-immune disease**

   **example:** Hashimoto's disease

6. q **unknown**

   **example:** inflammatory bowel disease
   sarcoidosis

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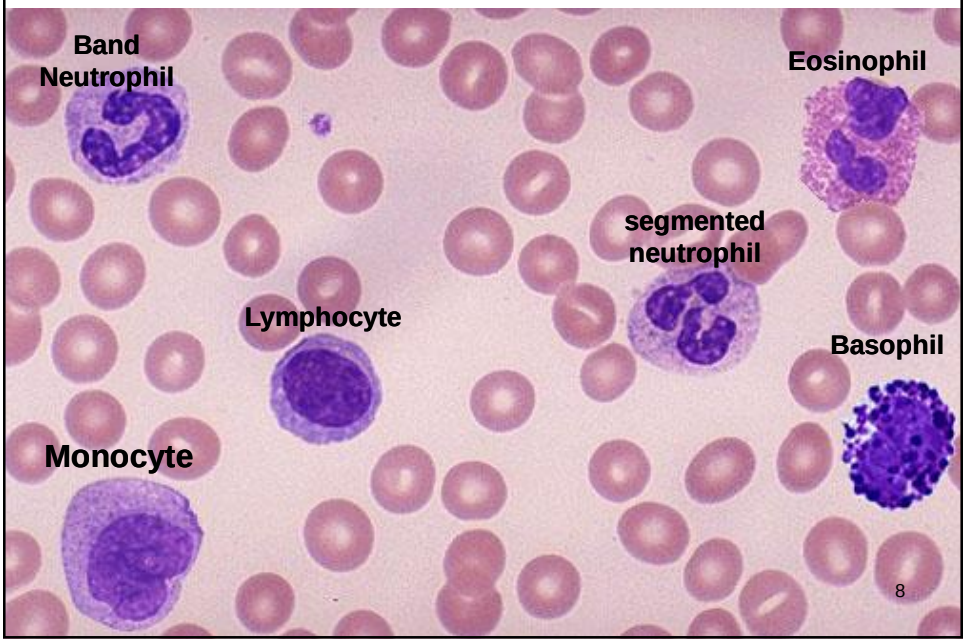
## White Blood Cells

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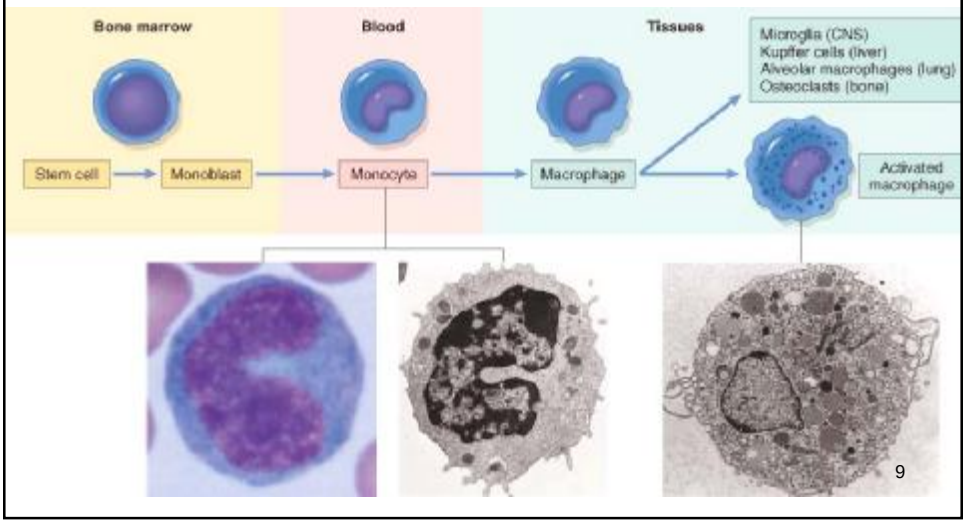
## Chronic inflammatory cells: Macrophages

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## Chronic inflammatory cells: Macrophages

- **The main cells in chronic inflammation.**
- **Called:**
  - **Kupffer cells** in the liver
  - **sinus histiocytes** in the lymph nodes & spleen
  - **alveolar macrophages** in the lungs
  - **microglial cells** in the CNS
  - **Osteoclasts** in the bone

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## Chronic inflammatory cells: Macrophages

- Derived from blood monocytes, where they begin to **emigrate** within the first 24-48 hrs after the onset on acute inflammation.
- They are **transformed** into big cells which are capable of phagocytosis (**macrophages**).
- Macrophages may also become **activated**, resulting in increased cell size and lysosomal enzymes, more active metabolism, & greater ability to kill ingested organisms.

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## Chronic inflammatory cells: Macrophages

- under the influence of INF-γ, endotoxins, ECM like fibronectin and other products, they are activated; they increase in size, with eosinophilic cytoplasm, assume an epithelial-like appearance so they are called **"epithelioid macrophages"**.
- under the influence of IL-4 or INF-γ, several cells may fuse to give **"multinucleated giant cells"**.

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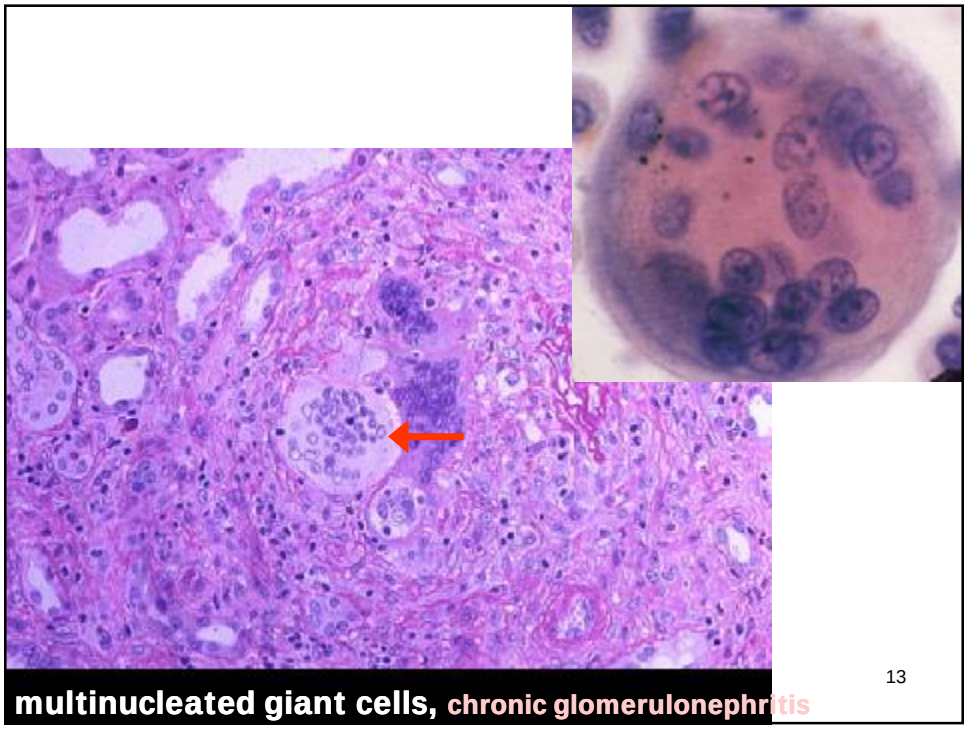
multinucleated giant cells, chronic glomerulonephritis
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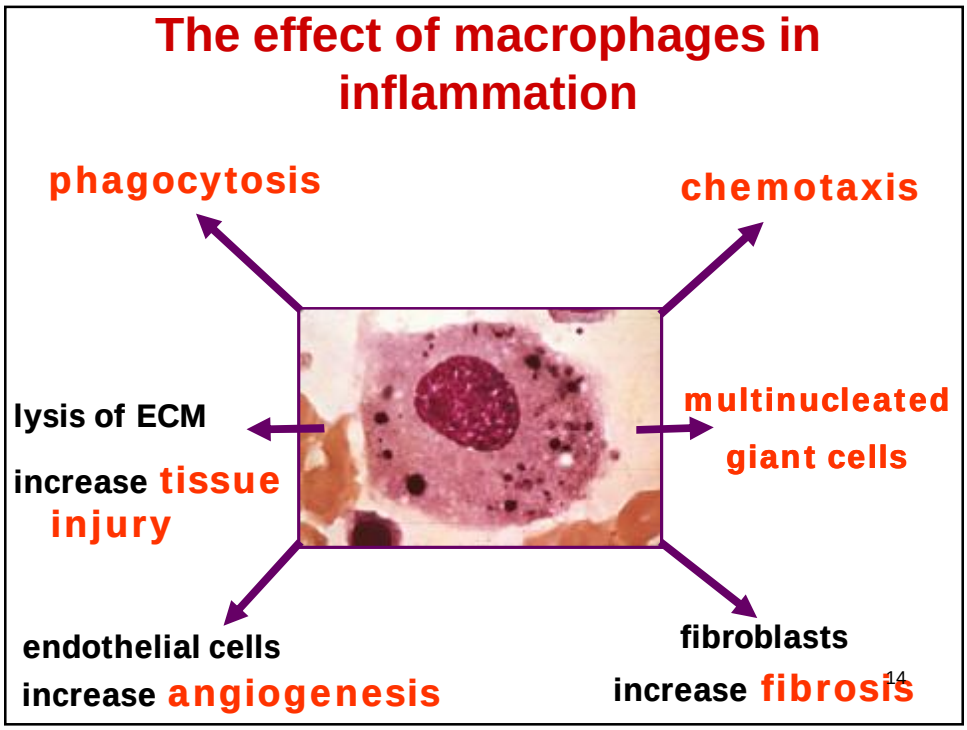
The effect of macrophages in inflammation
phagocytosis
chemotaxis
lysis of ECM
increase tissue injury
multinucleated giant cells
endothelial cells
increase angiogenesis
fibroblasts
increase fibrosis
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## The effect of macrophages in inflammation

- **After activation**, macrophages secrete a wide variety of biologically active products, that can result in the tissue injury and fibrosis. These products include:

**1) Tissue injury:**

- **Proteases** & **plasminogen activator**.
- **Complement** component and **coagulation factors**.
- **Reactive oxygen species** and **NO**
- **Arachidonic acid metabolites**
- **Cytokines**

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## The effect of macrophages in inflammation

**2) Fibrosis:**

- **growth factors:** influence the proliferation of smooth muscle cells and fibroblasts and the production of extracellular matrix
- **cytokines**
- **angiogenesis factors**
- **collagenase**

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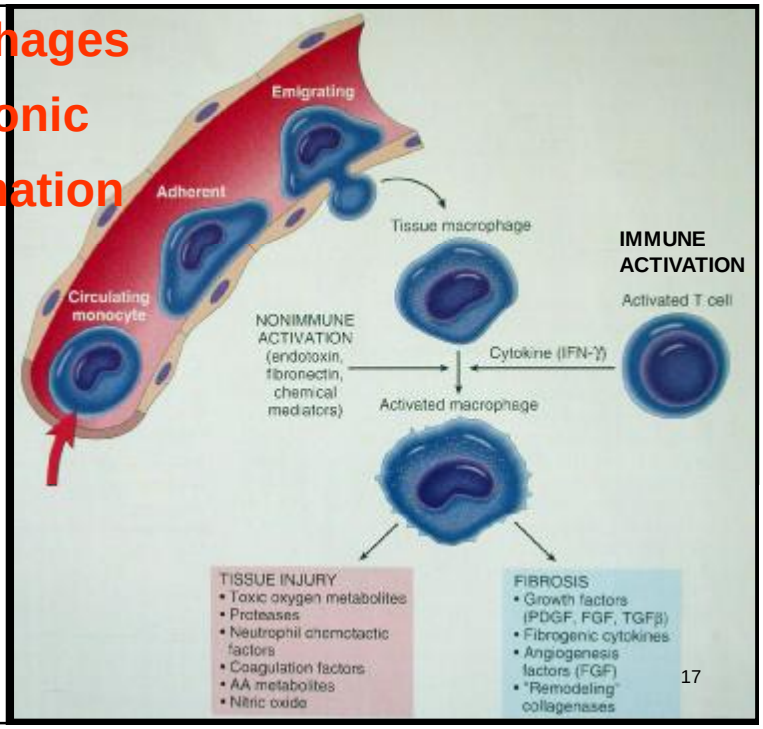
## Macrophages in chronic inflammation

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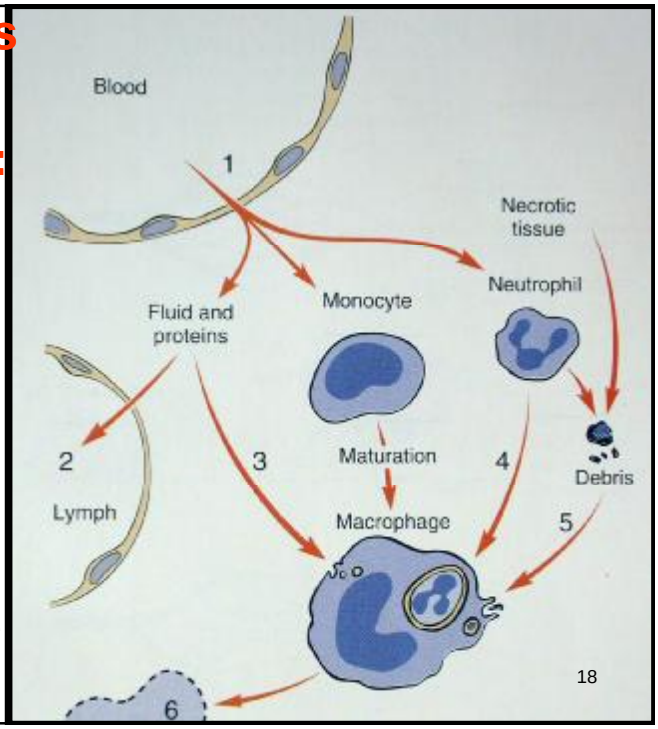
## Macrophages in acute inflammtion:

Macrophages can **engulf** excess **fluid**, **apoptotic neutrophils** and **debris** resulting from acute inflammation, thus participating in **resolution** of acute inflammation

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## Chronic inflammatory cells: Lymphocytes

- They are mobilized in any specific stimulus (infection), or in non-immune stimulus like in infarction or tissue trauma.
- **T-lymphocytes:** have a reciprocal relation with the number of macrophages involved in the chronic inflammation.
- **B-lymphocytes:** responsible for the **production of antibodies** through the **differentiation into plasma cells.**

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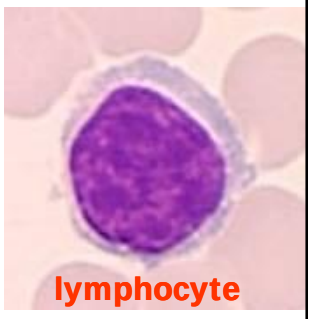
## Chronic inflammatory cells: Lymphocytes

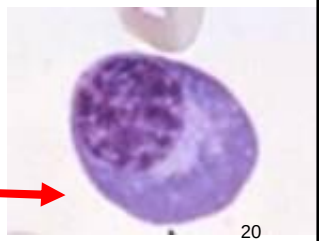
**T-lymphocytes:**

- **cellular immunity**
- **macrophage interaction**


lymphocyte

**B-lymphocytes:**

- **antibody-mediated immunity**
- **transform to plasma cells**


plasma cells

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## T-Lymphocytes–macrophages interaction

- Lymphocytes are initially activated by interaction with macrophages presenting antigen fragments on their cell surface
- The activated lymphocytes then produce a variety of mediators, including IFN-γ to activate macrophages.
- Activated macrophages in turn release cytokines, including IL-1 & TNF, that further activate lymphocytes and other cell types
- The end result is an inflammatory focus where **macrophages and T cells can persistently stimulate one another until the triggering antigen is removed**, or some modulating process occurs.

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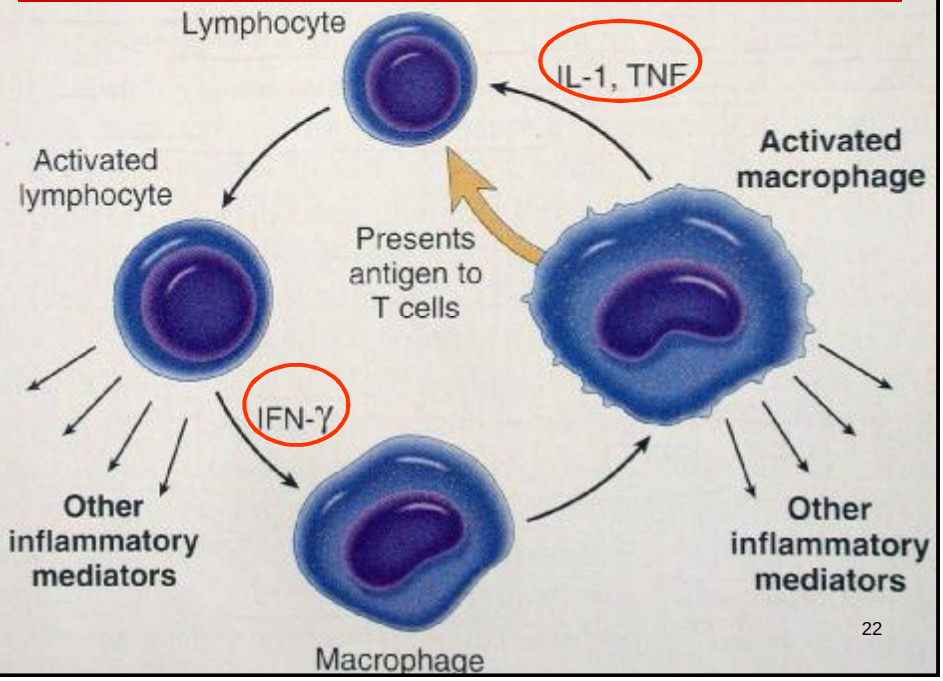
## T-Lymphocytes – macrophages interaction:

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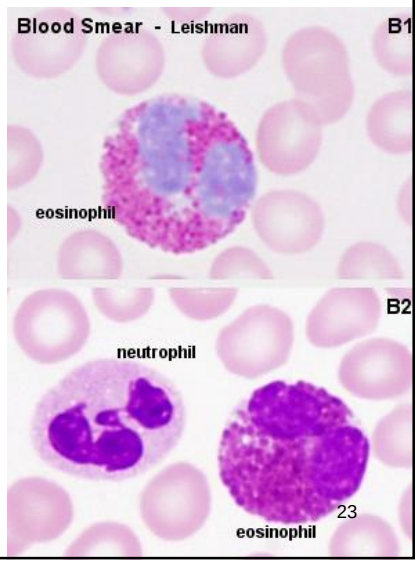
## Chronic inflammatory cells: Eosinophils

- found in inflammation induced by **parasitic infections** or in **allergic reactions** involving IgE, **Type I hypersensitivity reactions**.
- Eotaxin is a specific chemokine for eaosinophils.
- major basic protein (MBP) is a protein found in the granules of eosinophils.
- It is **toxic to parasites** and causes tissue damage.

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## Chronic inflammatory cells: Mast cells

- widely distributed in tissues, especially around blood vessels.
- Has **IgE receptors**, and so it is **important in allergic reactions and in anaphylactic shock**.
- They are the primary **source of histamine**, mediating acute inflammation, and cytokines like TNF, so participating in chronic inflammation.

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## Chronic inflammation: morphological types

1. **non specific:**
   - general features of inflammation
     example: chronic cholecystitis, chronic pyelonephritis
2. **Granulomatous:**
   - histological pattern (granulomas)
     example: leprosy, sarcoidosis, syphilis

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## Chronic inflammation

1. **non specific:**
   - Characterized by granulation tissue
     - formation of new blood vessels
     - inflammatory cells
     - fibroblasts
     - collagen
   - aim: repair by replacement of injured tissue by fibrous tissue

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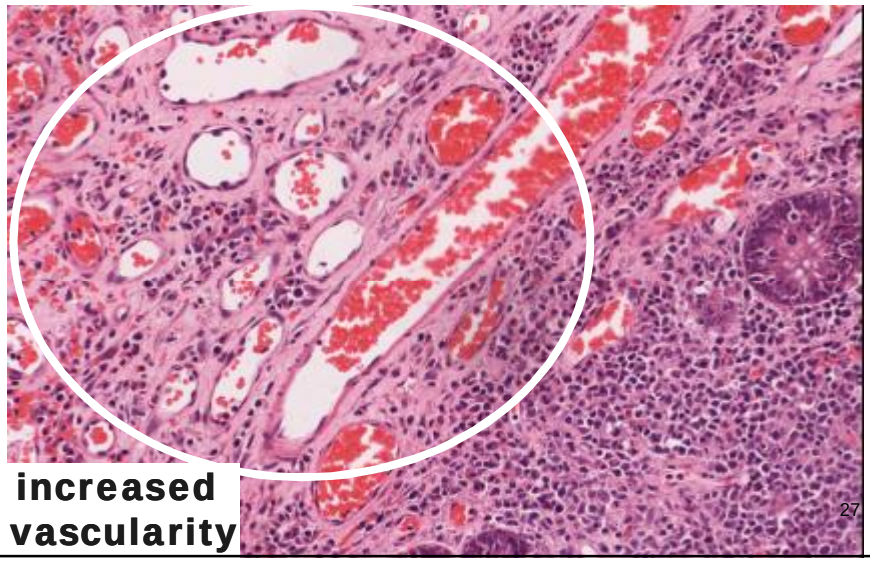
## Chronic inflammation
### 1. non specific type - morphology



increased vascularity

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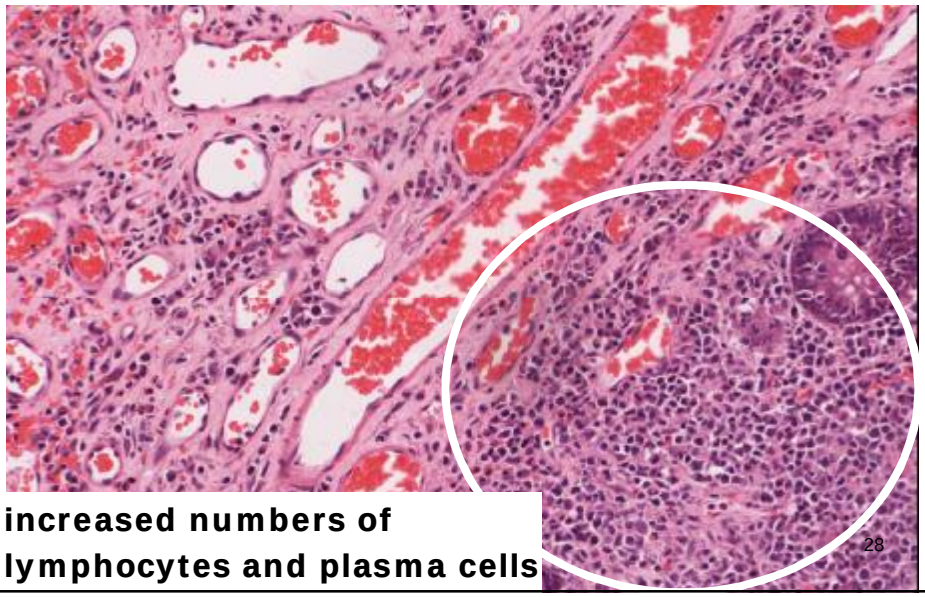
## Chronic inflammation
### 1. non specific type - morphology



increased numbers of lymphocytes and plasma cells

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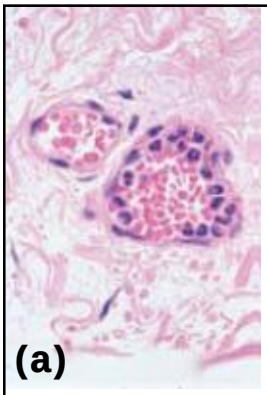
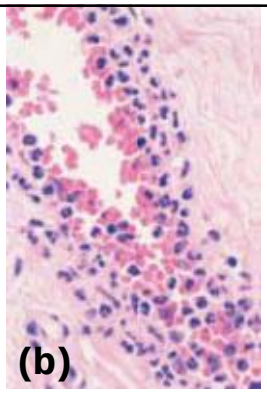


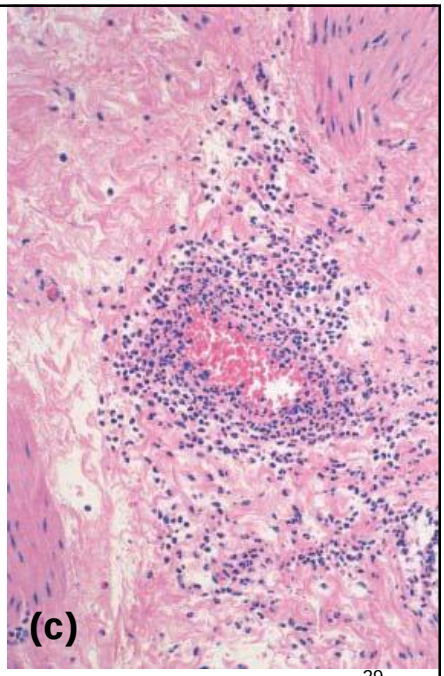




- **Formation of the acute inflammatory exudate:**

**(a) Early vascular changes**

**(b) Migration of neutrophils**

**(c) Early formation of exudate**




**Acute inflammation**

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# Chronic inflammation

## 2. Granulomatous type

- **Defined as aggregates of activated macrophages that assume an epithelial or squamoid-like appearance (epithelioid macrophages).**
- Seen in few pathological conditions, so once identified, the differential diagnosis is limited.
- Important **defense mechanism** aiming at either eradication of the causative microorganism, or "walling off" of the particles that are resistant to killing and degradation, thus preventing their spread.

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**Infectious**

**Non-infectious**

**Table 2-5. EXAMPLES OF GRANULOMATOUS INFLAMMATION**

**Bacterial**

Tuberculosis (*Mycobacterium tuberculosis*)
Leprosy (*Mycobacterium leprae*)
Syphilitic gumma (*Treponema pallidum*)
Cat-scratch disease (*Bartonella henselae*)

**Parasitic**

Schistosomiasis (*Schistosoma mansoni, S. haemotobium, S. japonicum*)

**Fungal**

*Histoplasma capsulatum*
Blastomycosis
*Cryptococcus neoformans*
*Coccidioides immitis*

**Inorganic Metals or Dusts**

Silicosis
Berylliosis

**Foreign Body**

Suture, breast prosthesis, vascular graft

**Unknown**

Sarcoidosis

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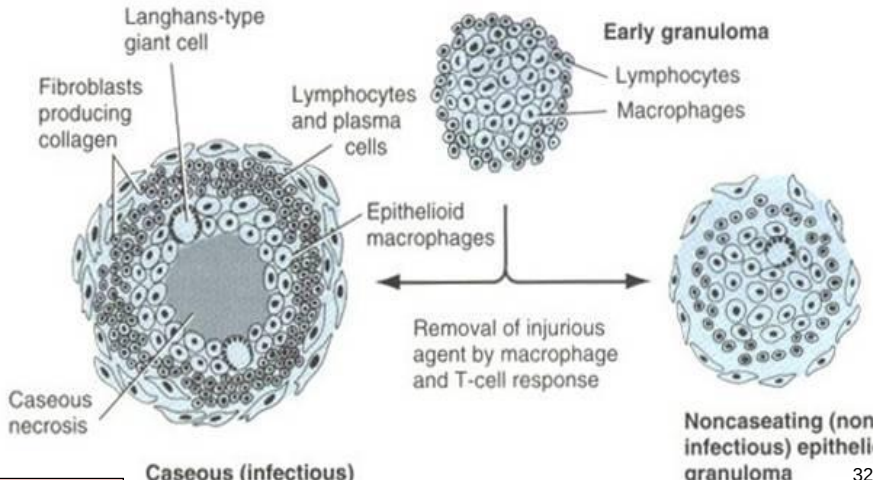
# Chronic inflammation

## 2. Granulomatous type

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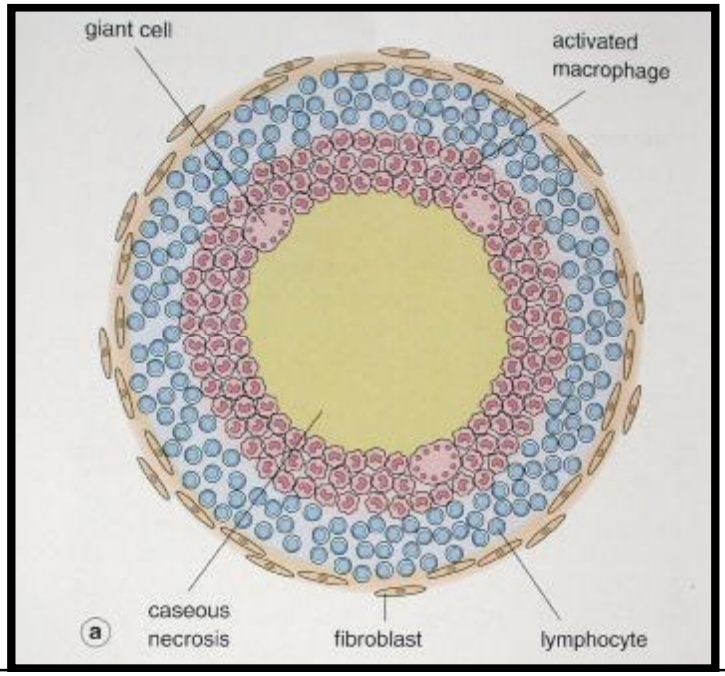
**Infectious** **Non-infectious**

## Granulomatous inflammation

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**Granulomatous disease:**

Here are numerous **granulomas** in upper lung fields in a case of active pulmonary tuberculosis

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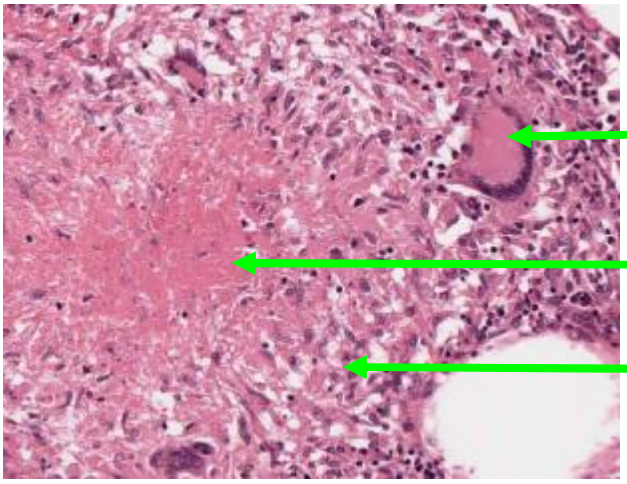
## Chronic inflammation
### granulomatous type - morphology



- Langhans giant cell
- caseous necrosis
- epitheloid macrophages

**miliary tuberculosis**

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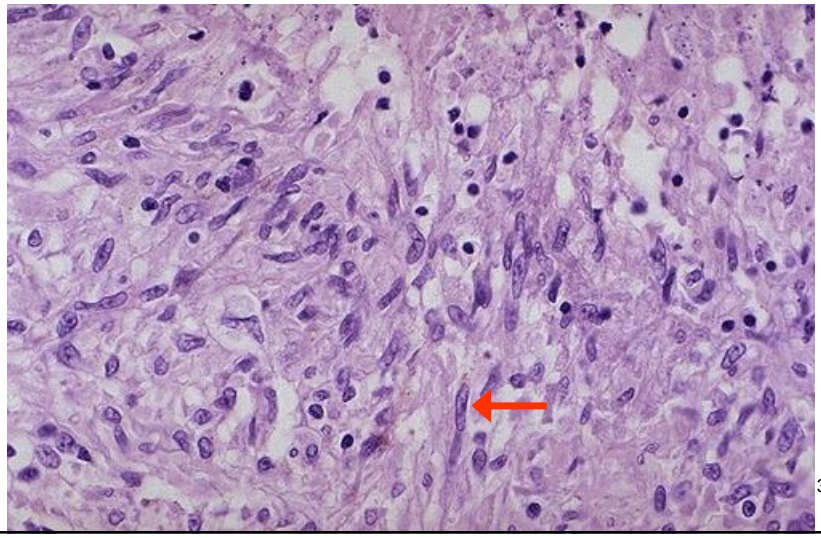
These are **epithelioid cells** around the center of a granuloma. They get their name from the fact that they have lots of pink cytoplasm **similar to squamous epithelial cells**. Their **nuclei tend to be long**



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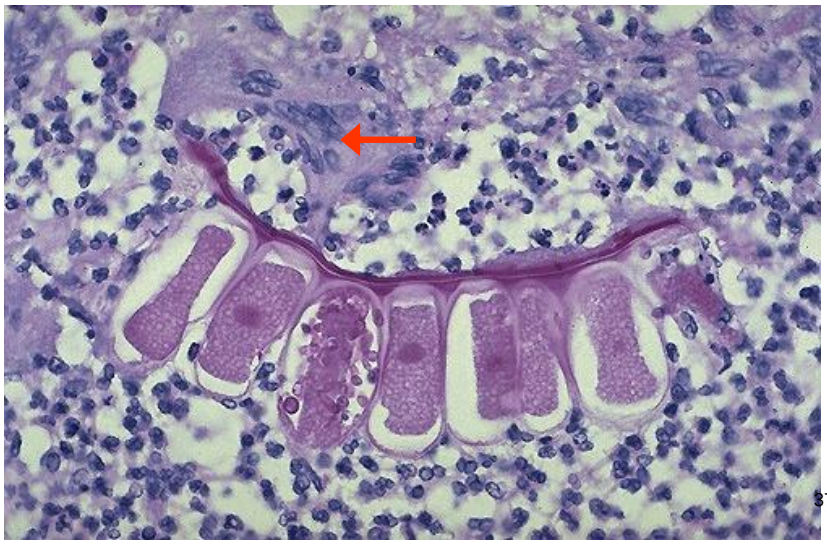
Here is a **foreign body giant type cell** at the upper left of center adjacent to a segment of vegetable material aspirated into the lung.



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## Inflammation: The other defense lines

- The **lymphatics, lymph nodes & mononuclear phagocyte system** form the secondary defense lines.
- During inflammation, lymphatics help in **draining edema fluid together with leukocytes, debris and micro-organisms into the lymph nodes**, resulting in **lymphangitis** and **lymphadenitis**.

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## Inflammation: The other defense lines

- **Bacteremia** develops if the micro-organisms failed to be contained within the lymph nodes and gain access into the blood stream.
- Failure of containment of the micro-organism leads to seeding of distant sites. Heart valves "**endocarditis**", meninges "**meningitis**", kidney "**renal abscesses**", and joints "**septic arthritis**" are the favored sites. **The phagocytic cells in the liver, spleen and bone marrow constitute the next defense line**.

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## Systemic Effects of Inflammation

- Called the **acute phase response** that is **characterized by**:
  - **Fever**
  - **Malaise**: a feeling of general discomfort
  - **Anorexia**: loss of appetite
  - **Somnolence**: tendency to sleep
  - **Wasting**: accelerated degeneration of skeletal muscles
  - **Hypotension**
  - **Alteration in the circulating leukocytes**
  - **hepatic synthesis of plasma proteins**

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## Systemic Effects of Inflammation

- **Cytokines IL-1, IL-6, and TNF** are the most important mediators of the acute phase reaction
- These cytokines are produced by leukocytes and other cells in response to infection, immune and toxic injury
- TNF induces the production of IL-1, which in turn stimulates the production of IL-6
- **TNF and IL-1** act on the thermoregulatory center to **cause fever by the production of prostaglandins**

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## Systemic Effects of Inflammation

- **IL-6** stimulates **hepatic synthesis of plasma proteins**, mainly fibrinogen
- **IL-1 and TNF** cause **increase production of leukocytes** by the bone marrow
- Some infections cause selective increase in the leukocyte count:
  - **Bacteria: PMNs**
  - **Parasites with allergy: eosinophils**
  - **Viruses: lymphocytes**

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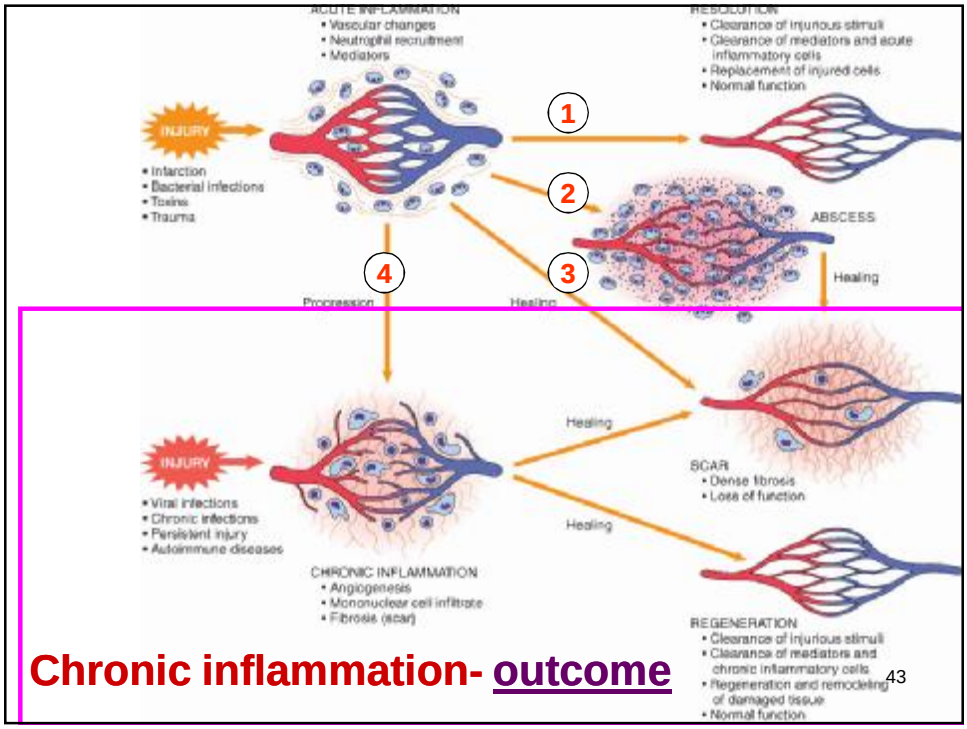


**Chronic inflammation- outcome**

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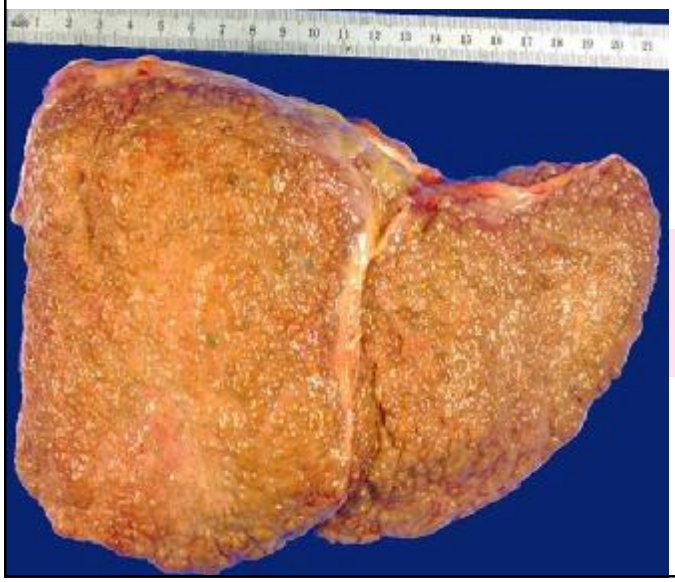
## Chronic Inflammation

**outcome - prolonged exposure to toxic agents**



**Liver cirrhosis**

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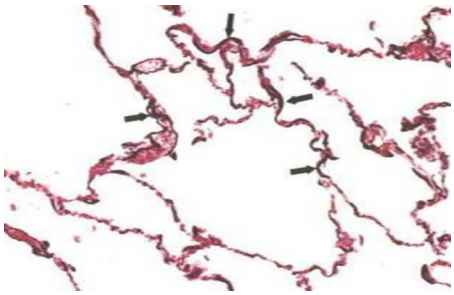
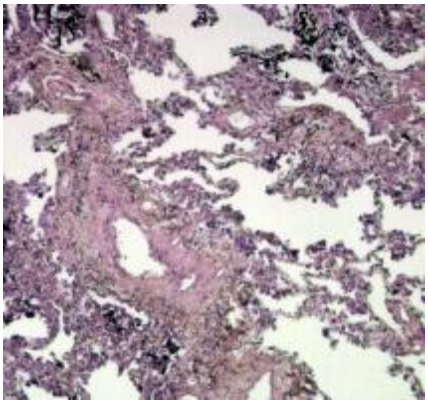
# Chronic Inflammation

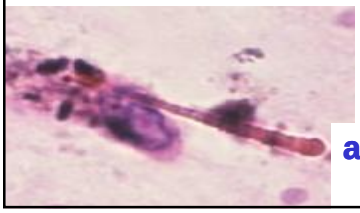
**outcome - prolonged exposure to toxic agents**



normal lung



interstitial fibrosis



asbestos body

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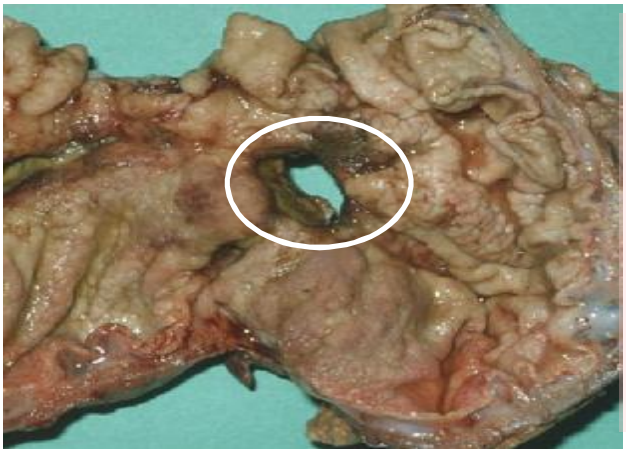
# Chronic Inflammation

**outcome - persistent infection**



q chronic ulcer of the stomach with perforation

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| Acute versus Chronic Inflammation: | | |
|---|---|---|
| | Acute | Chronic |
| Duration | Short (days) | Long (weeks to months) |
| Onset | Acute | Insidious |
| Inflammatory cells | Neutrophils, macrophages | Lymphocytes, plasma cells, macrophages, fibroblasts |
| Vascular changes | Active vasodilatation, increased permeability | New vessel formation (granulation tissue) |
| Fluid exudation & edema | + | – |
| Cardinal signs | + | – |

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| Acute versus Chronic Inflammation: | | |
|---|---|---|
| | Acute | Chronic |
| Tissue necrosis | – (Usually) | + (ongoing) |
| Fibrosis | – (Usually) | + |
| Systemic manifestations | Fever, often high | Low–grade fever, weight loss, anemia |
| Changes in peripheral blood | Neutrophil leukocytosis; lymphocytosis (in viral infections) | Frequently none; variable leukocyte changes, increased plasma IG |

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