

# INFLAMMATION AND REPAIR

## Lecture 4

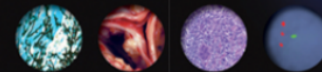
Chronic inflammation  
Systemic effect of inflammation

Page 81-87

Robbins

# BASIC PATHOLOGY

TENTH EDITION



KUMAR  
ABBAS  
ASTER

ELSEVIER

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# Objectives

- 1. Define chronic inflammation with emphasis on causes, nature of the inflammatory response, cells involved and tissue changes.**
- 2. Describe the systemic manifestations of inflammation and their general physiology, including fever, leukocyte left shift, and acute phase reactants.**

# CHRONIC INFLAMMATION

- **It is slow evolving (weeks to months) resulting into fibrosis**
- The essential changes are:
  1. Absence of polymorphs (natural life span of 1–3 days); replaced by macrophages, lymphocytes and often plasma cells
  2. Continuous tissue injury and necrosis
  3. Angiogenesis: Proliferation of vascular endothelium by 'budding' (formation of new capillaries)
  4. Proliferation of fibroblasts with collagen production leading to Fibrosis.

Chronic inflammation may arise in the following settings:

1. *Persistent infections* by microbes that are difficult to eradicate.

e.g.

- *Mycobacterium tuberculosis*
  - *Treponema pallidum* (the causative organism of syphilis)
  - certain viruses and fungi
- Persistent infections elicit a T lymphocyte-mediated immune response called *delayed-type hypersensitivity*.



## 2. *Immune-mediated inflammatory diseases* (*hypersensitivity diseases- Autoimmune diseases*)

e.g.

- Rheumatoid arthritis
- Inflammatory bowel disease
- Psoriasis

or

- Immune responses against common environmental substances that cause *allergic diseases*, such as bronchial asthma.

### *3. Prolonged exposure to potentially toxic agents.*

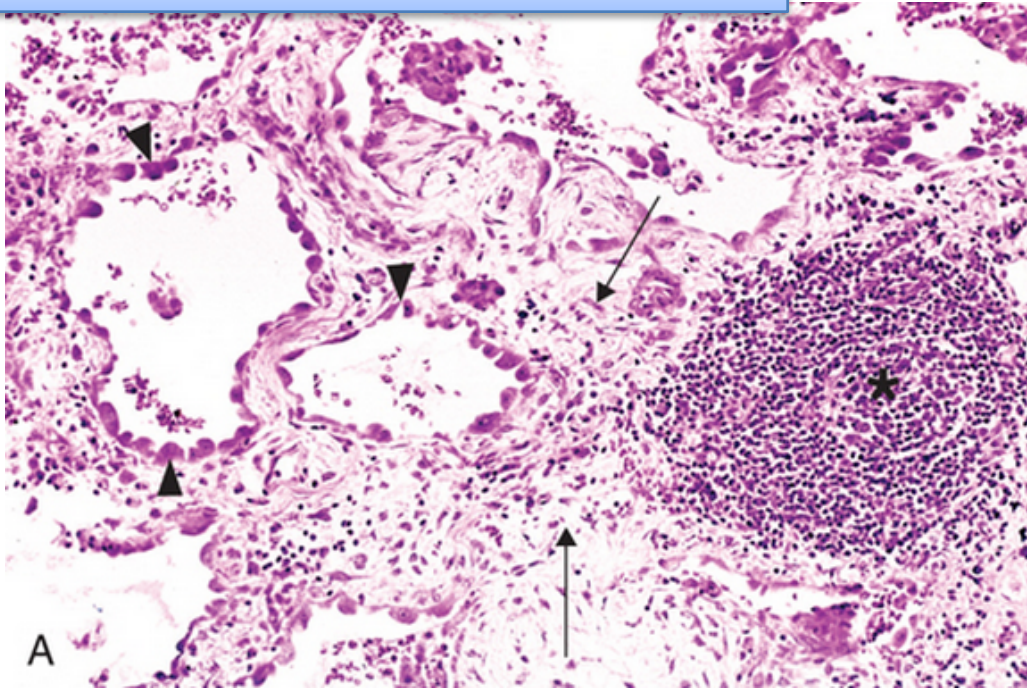
- Examples are nondegradable exogenous materials such as inhaled particulate silica, which can induce a chronic inflammatory response in the lungs (silicosis)
- Endogenous agents such as cholesterol crystals, which may contribute to atherosclerosis
- Other examples:
  - neurodegenerative disorders such as Alzheimer disease
  - some forms of cancer in which inflammatory reactions promote tumor development

## Features of chronic inflammation

- Chronic inflammation is characterized by a 3 different set of reactions:
  1. *Infiltration with mononuclear cells*, including:
    - i. Macrophages
    - ii. Lymphocytes
    - iii. Plasma cells
  2. *Tissue destruction*, largely induced by the products of the inflammatory cells
  3. *Repair*, involving new vessel proliferation (angiogenesis) and fibrosis

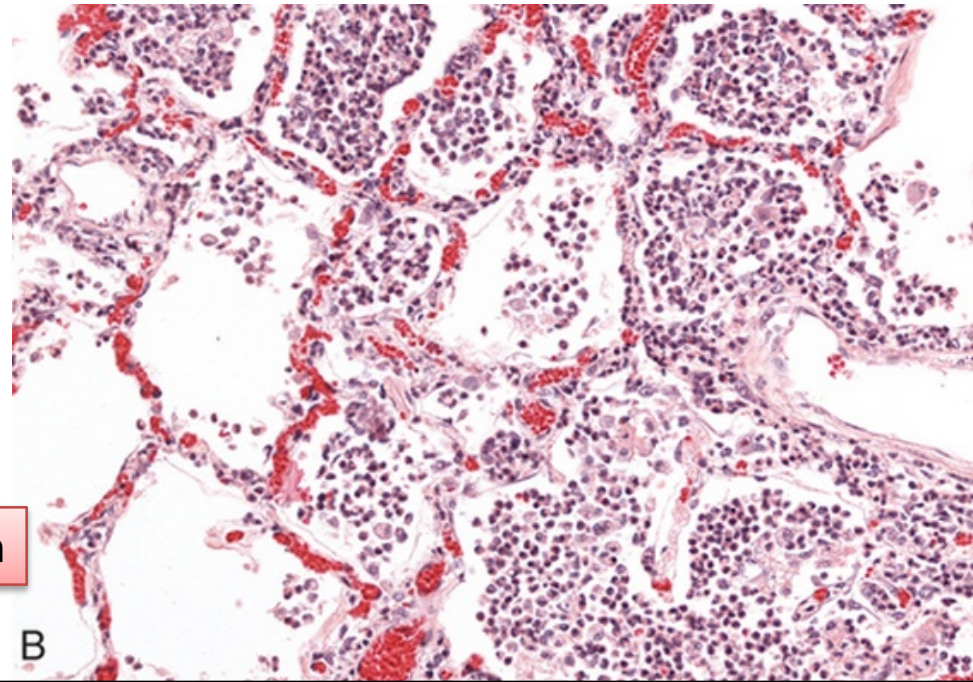
Acute inflammation is distinguished by vascular changes, edema, and a predominantly neutrophilic infiltrate

## Features of chronic inflammation



- Lung chronic inflammation:
- i. Infiltration by lymphocytes
  - ii. Angiogenesis
  - iii. fibrosis

Lung acute inflammation



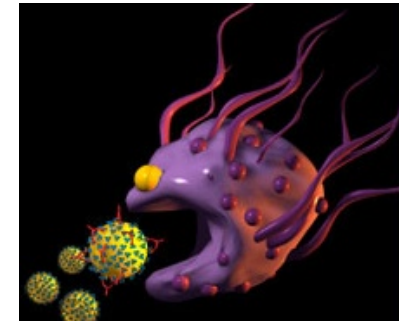
## Cells in Chronic inflammation

- Complex interactions between several cell populations and their secreted mediators.
- Mediated by the interaction of monocyte/macrophages with T and B lymphocyte, plasma cells and others

# Macrophages

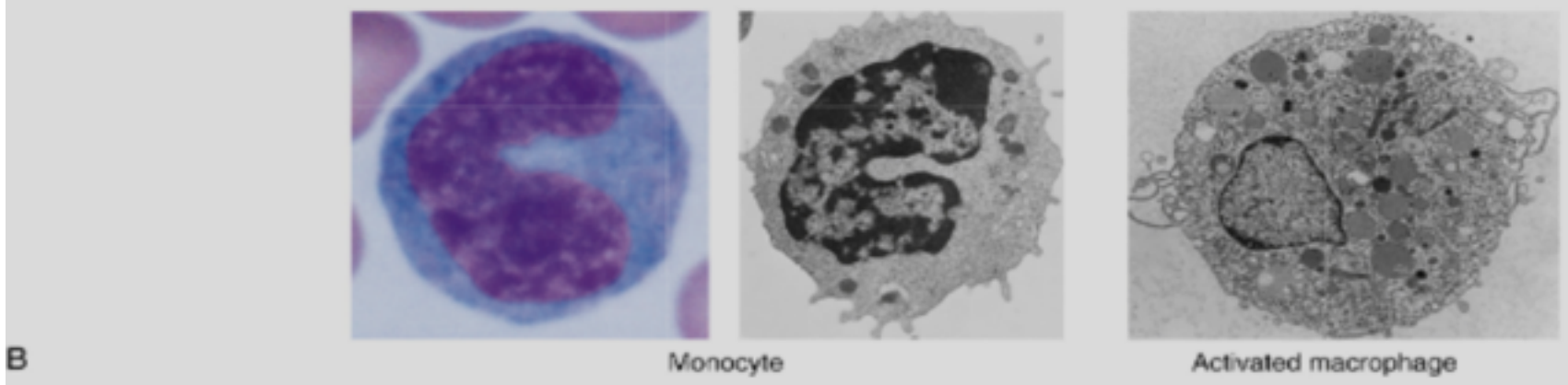
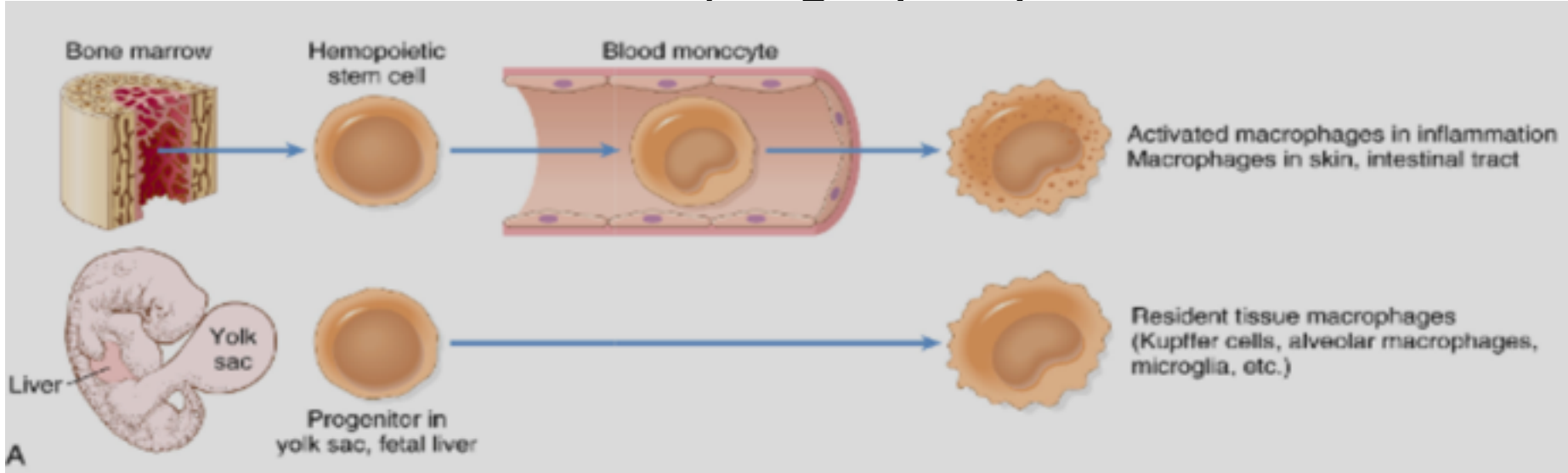
- In tissue:
  - the liver (Kupffer cells)
  - spleen and lymph nodes (sinus histiocytes)
  - central nervous system (microglial cells)
  - and lungs (alveolar macrophages)
- In blood: monocytes
  - Under the influence of adhesion molecules and chemokines, they migrate to a site of injury within 24 to 48 hours after the onset of acute inflammation (macrophages)

*Monocytes are likely to be seen in an inflammatory response to salmonella typhi infection*

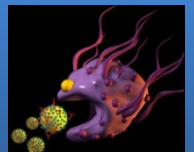




# mononuclear phagocyte system



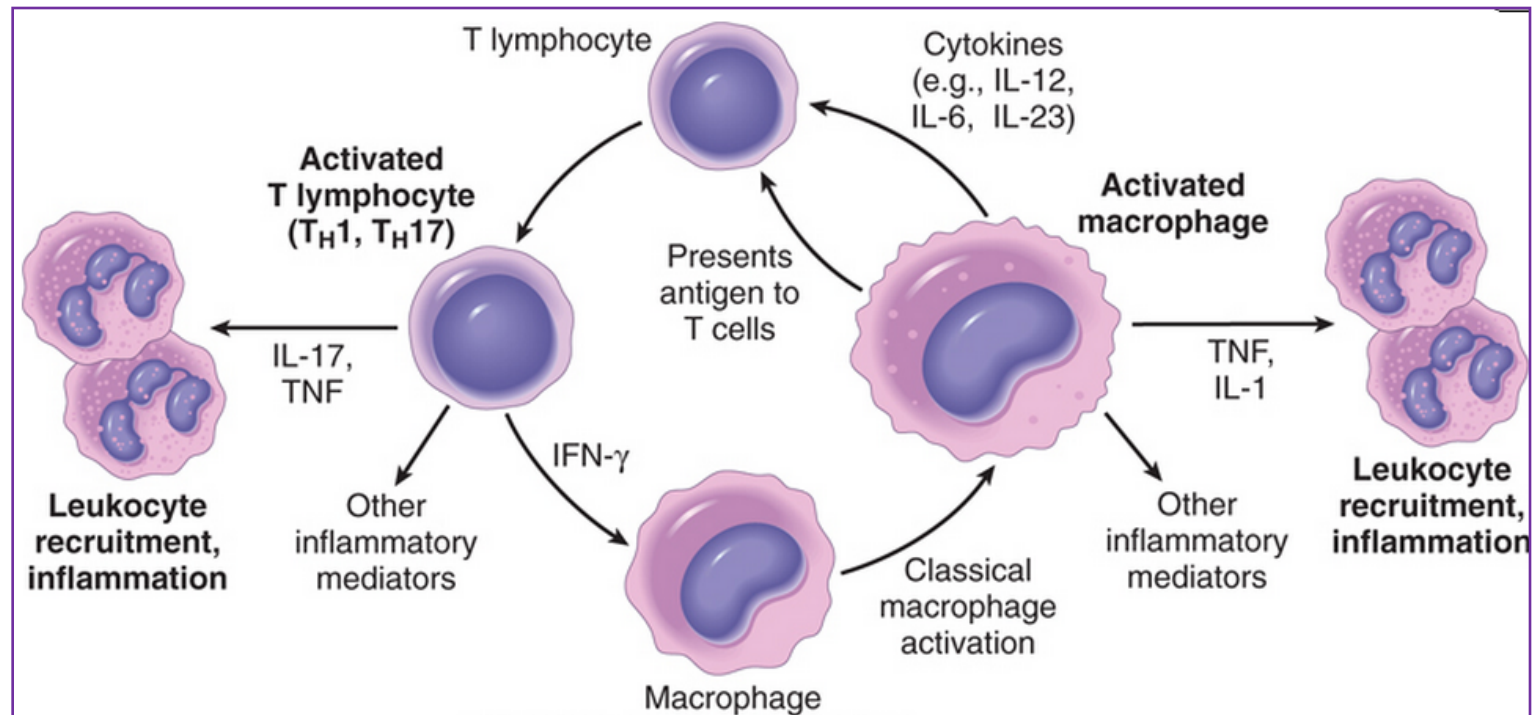
monocytes begin to emigrate into extravascular tissues quite – early in acute inflammation and within 48 hours they may constitute the predominant cell type



## MONONUCLEAR CELL INFILTRATION

### Macrophages

- Macrophages may be *activated* by a variety of stimuli, including:
  - cytokines (e.g., IFN- $\gamma$ ) secreted by sensitized T lymphocytes and by NK cells
  - bacterial endotoxins

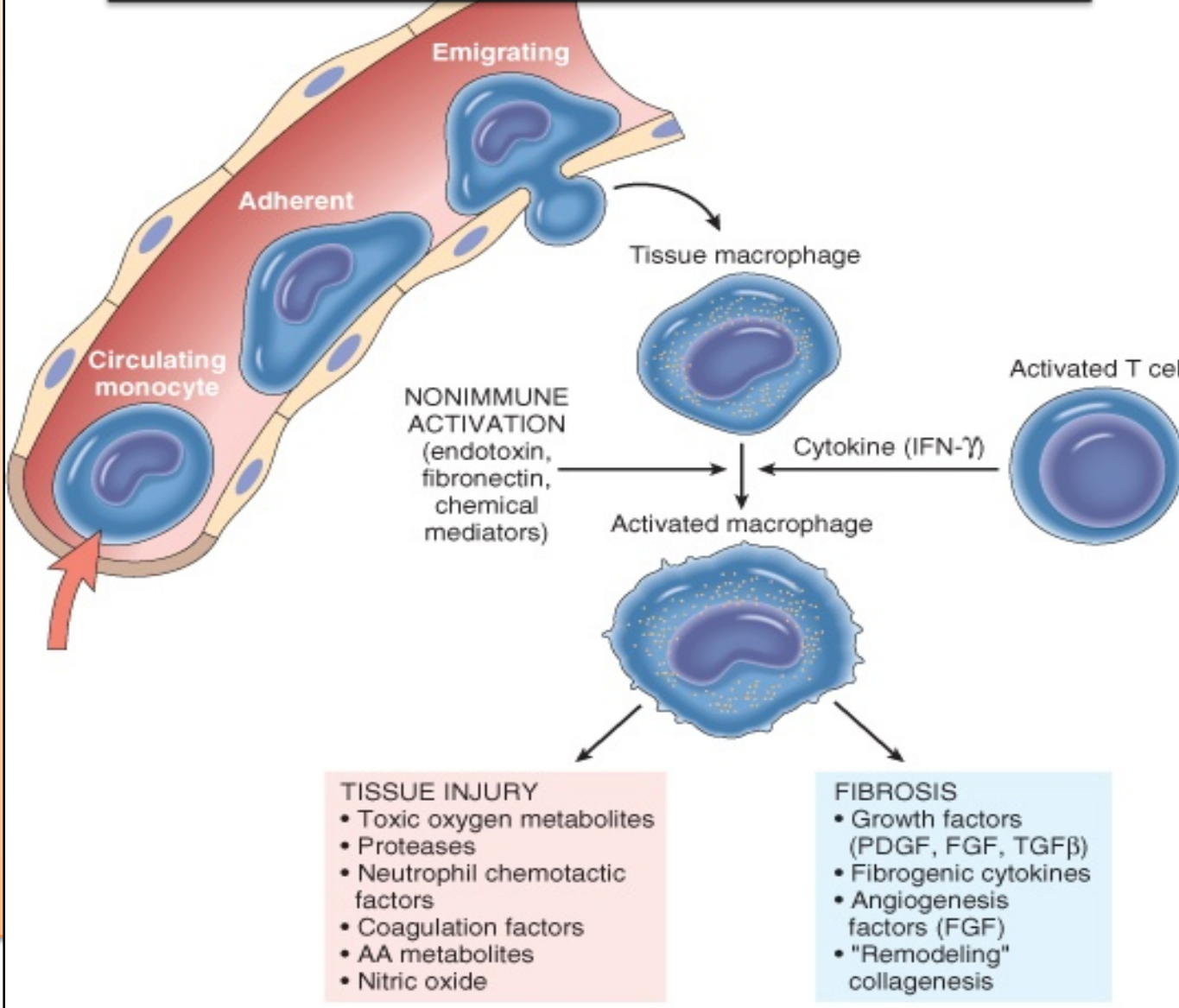




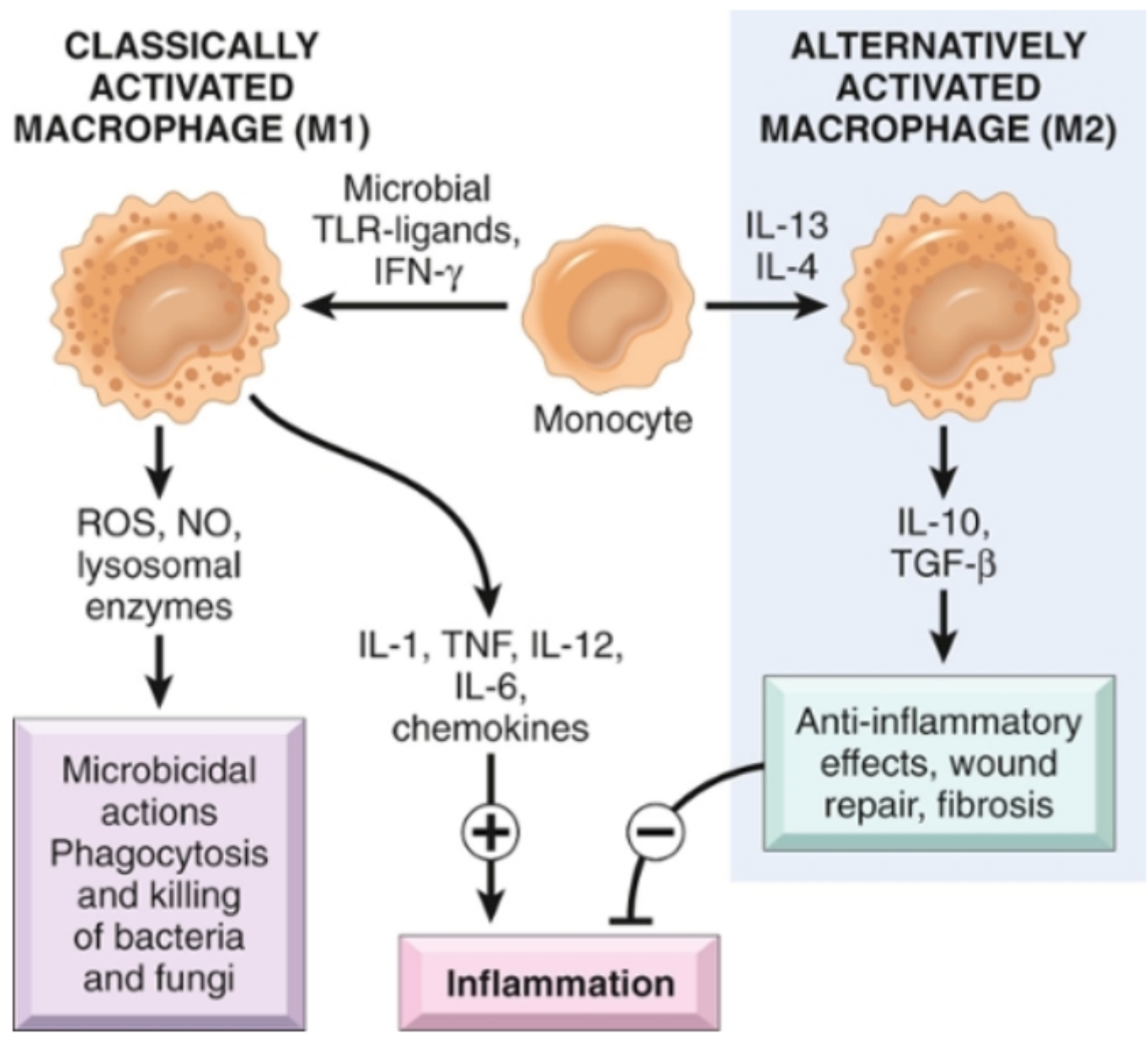
# Different types of inflammatory cells accumulate in chronic inflammation

## The roles of activated macrophages in chronic inflammation

- to eliminate injurious agents such as microbes
- to initiate the process of repair
- secrete mediators of inflammation, such as cytokines (TNF, IL-1, chemokines, and eicosanoids).
- display antigens to T lymphocytes and respond to signals from T cells, thus setting up a feedback loop
- It is responsible for much of the tissue injury in chronic inflammation



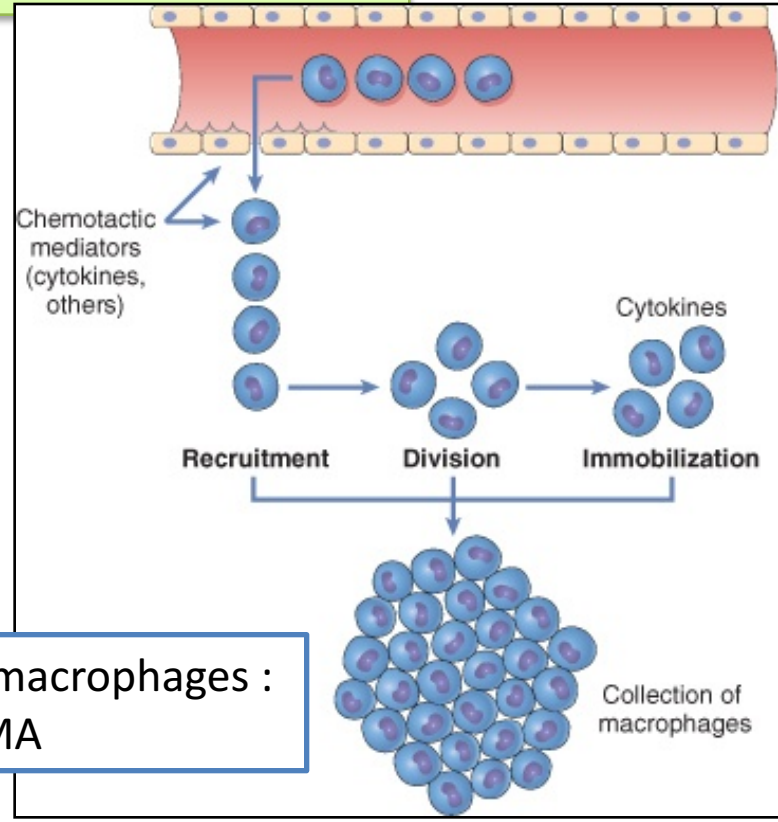
# Different types of inflammatory cells accumulate in chronic inflammation



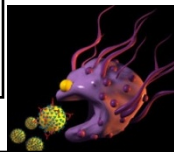
## Macrophages/Monocytes

- In chronic inflammation, macrophage accumulation persists, this is mediated by different mechanisms:

- Recruitment of monocytes from the circulation*
- Local proliferation of macrophages*
- Immobilization of macrophages*



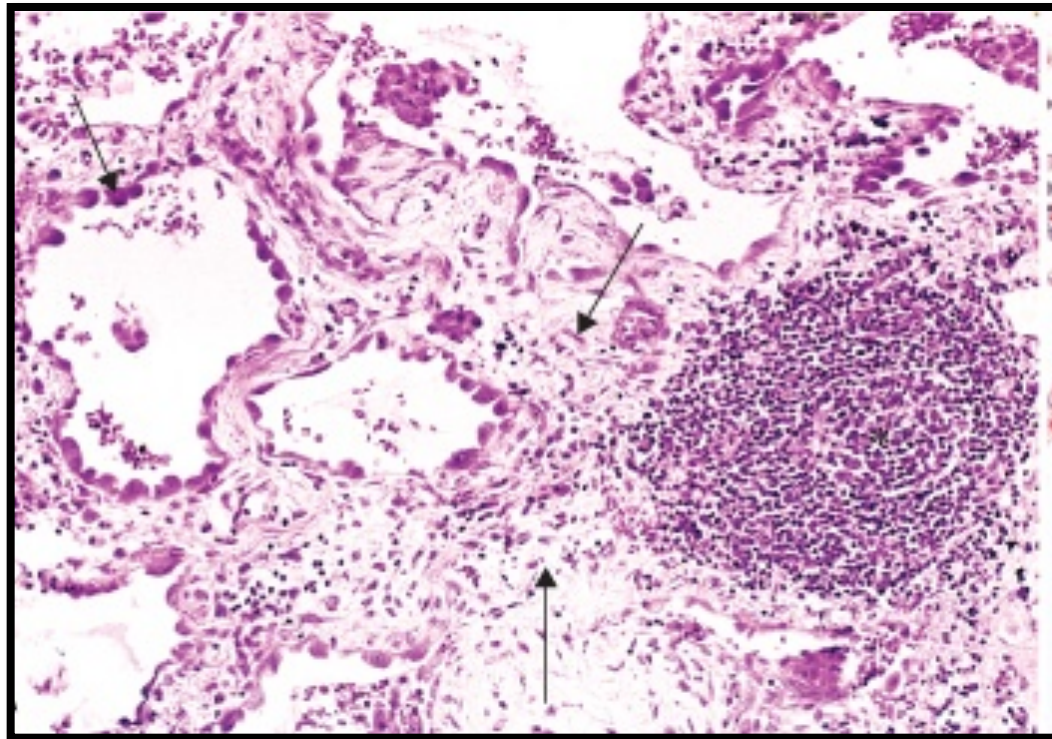
Collection of activated macrophages :  
GRANULOMA



## ***CELLS IN CHRONIC INFLAMMATION***

### **Lymphocytes**

- Both T & B Lymphocytes migrates into inflammation site, most commonly seen in tissue affected by chronic inflammation
- Role: mediators of adaptive immunity, which provides defense against infectious pathogens



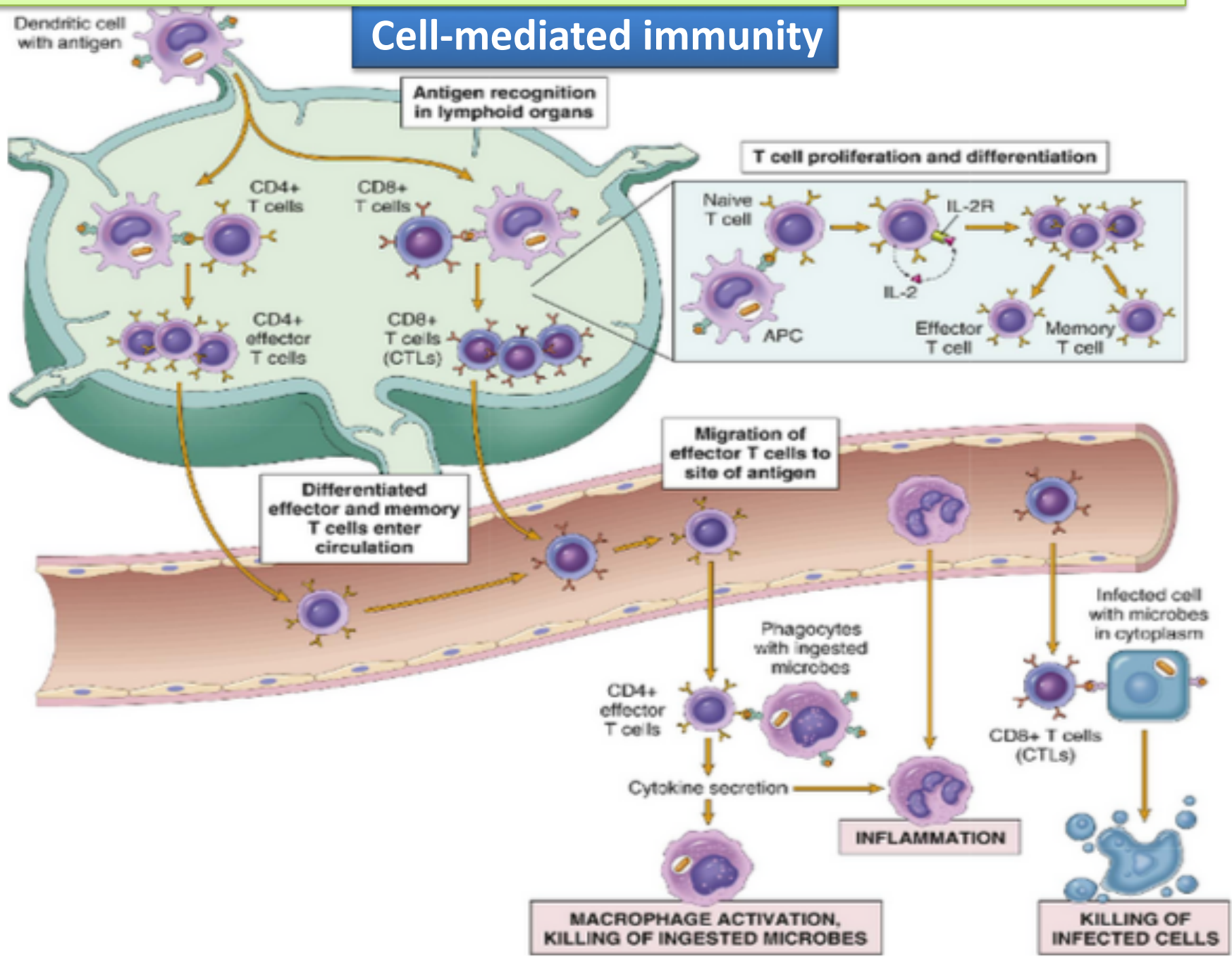
# Lymphocytes

- T lymphocytes are activated to secrete cytokines:
  - *CD4+ T lymphocytes promote inflammation and influence the nature of the inflammatory reaction*



# Different types of inflammatory cells accumulate in chronic inflammation

## Cell-mediated immunity

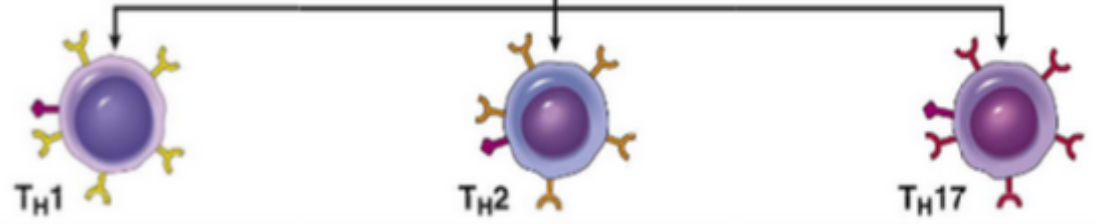
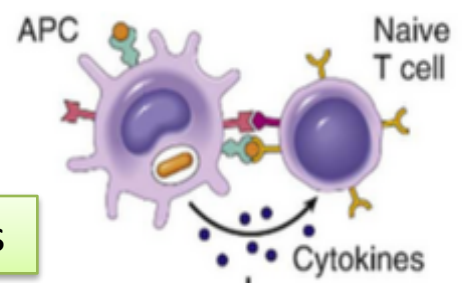


# Different types of inflammatory cells accumulate in chronic inflammation

## Subsets of helper T (TH) cells

In response to stimuli (mainly cytokines) present at the time of antigen recognition, naive CD4+ T cells may differentiate into populations of effector cells that produce distinct sets of cytokines and perform different functions.

There are three subsets of CD4+ helper T cells



<b>Major cytokines produced</b>	IFN- $\gamma$	IL-4, IL-5, IL-13	IL-17, IL-22
<b>Cytokines that induce this subset</b>	IFN- $\gamma$ , IL-12	IL-4	TGF- $\beta$ , IL-6, IL-1, IL-23
<b>Immunological reactions triggered</b>	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
<b>Host defense against</b>	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
<b>Role in disease</b>	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, granulomatous inflammation)	Allergies	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, MS)

IBD, inflammatory bowel disease

MS, multiple sclerosis

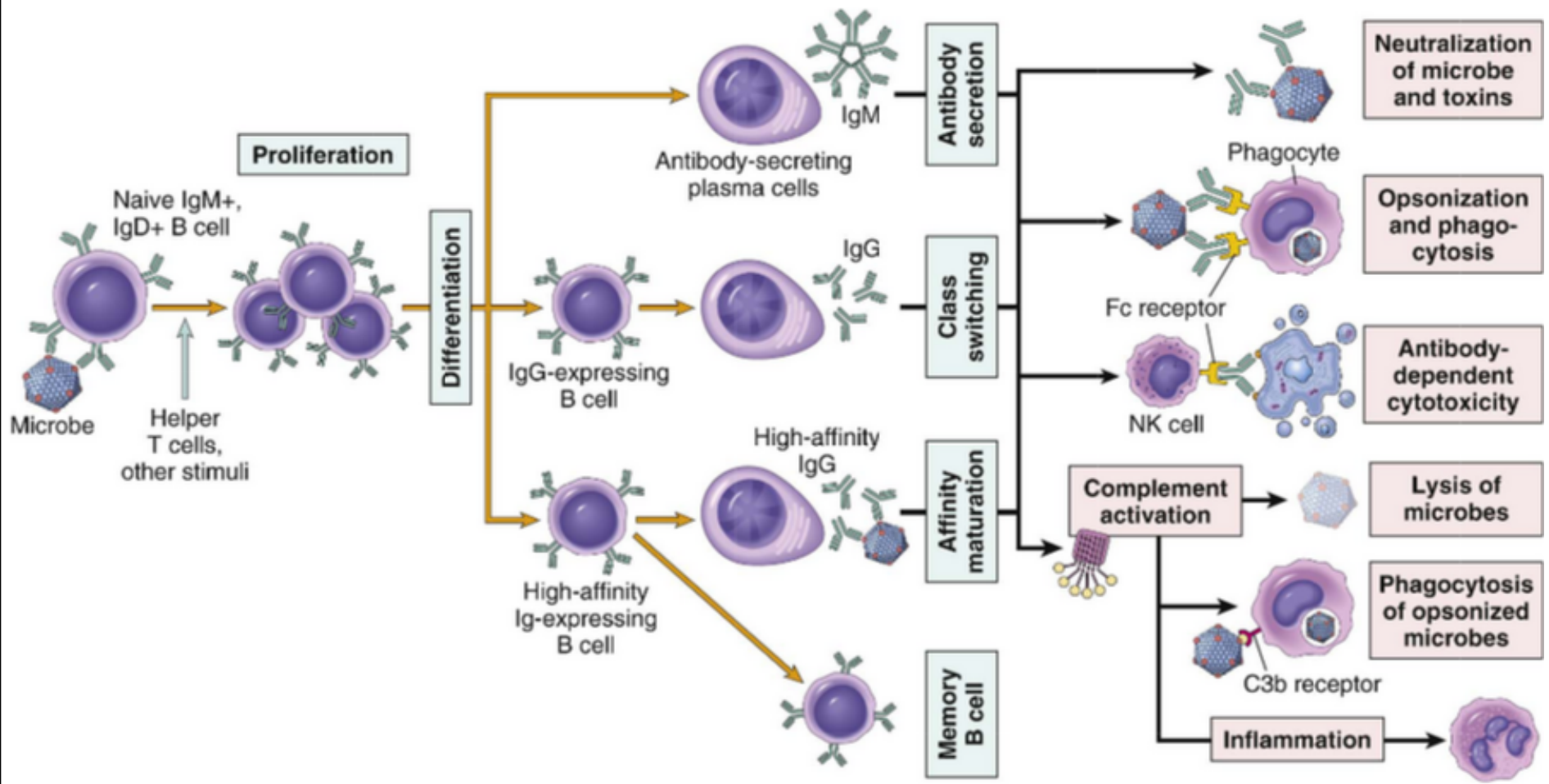
## B lymphocytes

- B lymphocytes may develop into *plasma cells*, which secrete antibodies (Humoral immunity)
- Naive B lymphocytes recognize antigens, and under the influence of TH cells and other stimuli, the B cells are activated to proliferate and to differentiate into antibody-secreting plasma cells.



# Different types of inflammatory cells accumulate in chronic inflammation

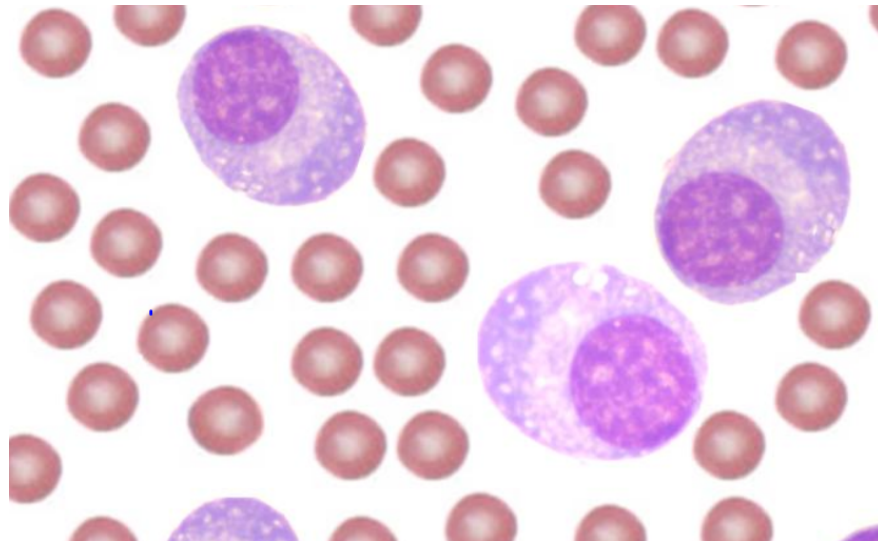
## Humoral immunity



## ***OTHER CELLS IN CHRONIC INFLAMMATION***

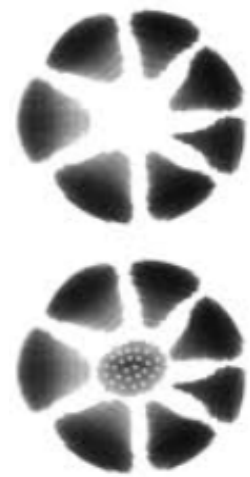
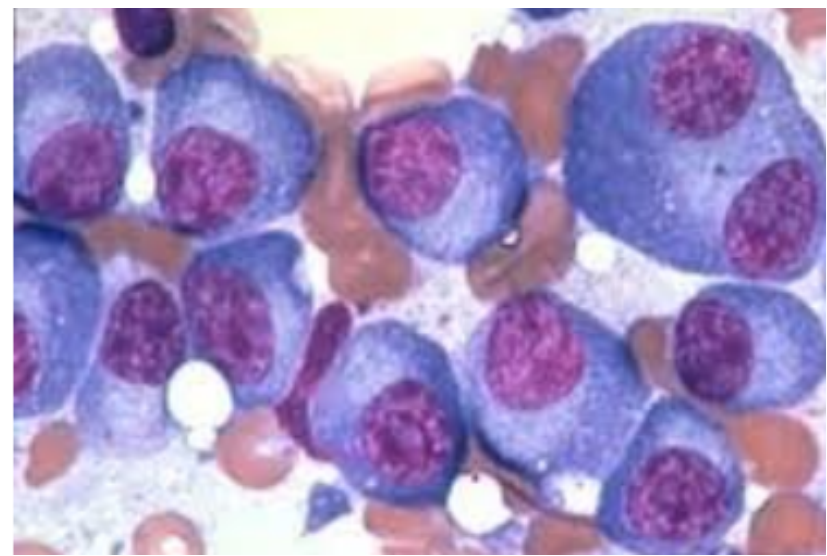
### **Plasma cells**

- **Lymphoid cell (Mature B cells)**
- **Common cell in chronic inflammation**
- **Primary source of antibodies**
- **Antibodies are important in inflammation e.g. neutralize antigen and clearance of foreign antigen**



# Plasma cells

**Morphology of plasma cells:**  
Cells has an eccentric nucleus shows a cartwheel or clock face pattern of nuclear chromatin with a perinuclear halo

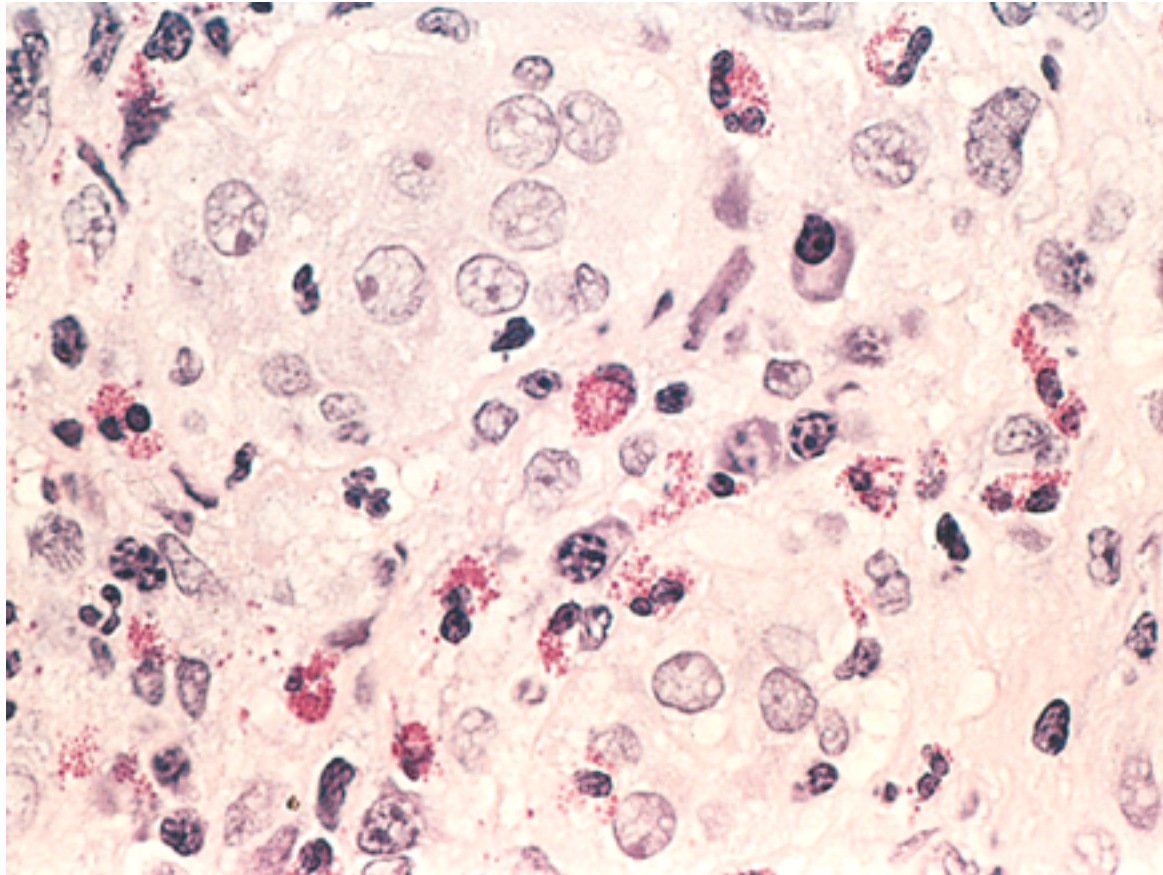




## Eosinophils

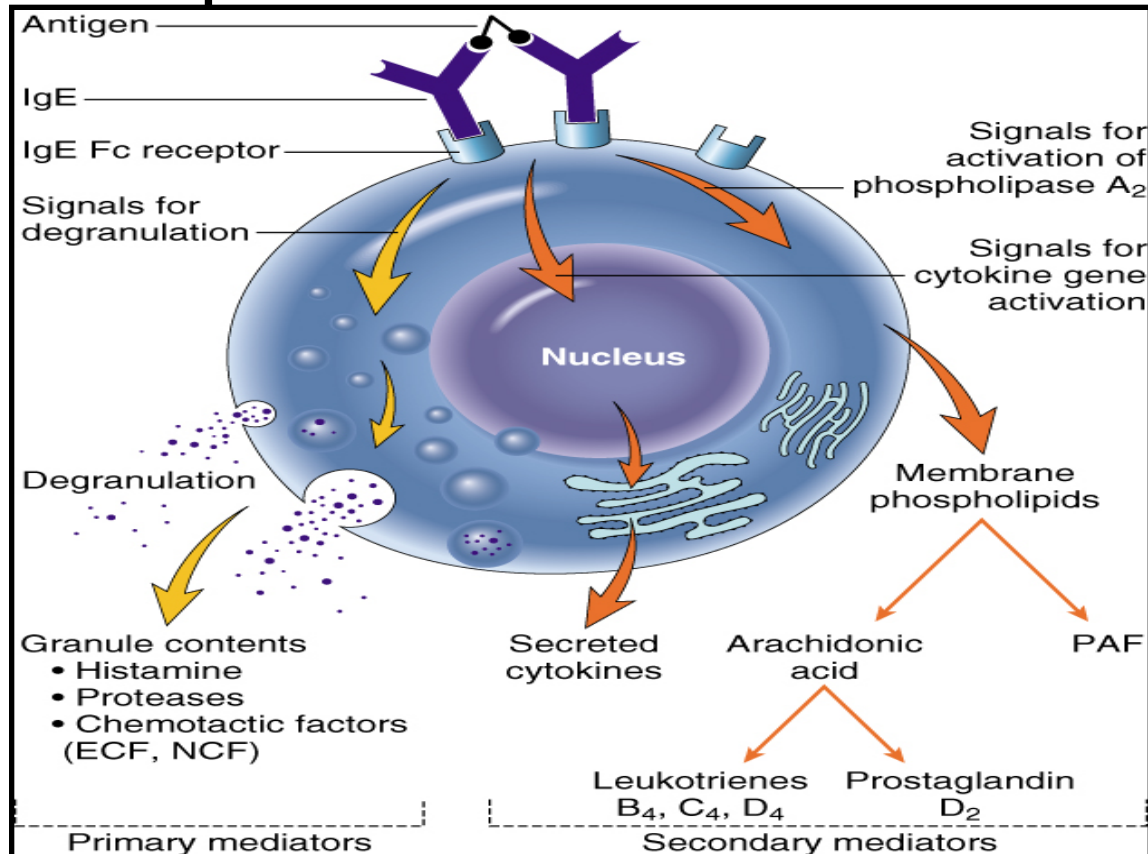
are abundant in immune reactions mediated by IgE in allergic reaction and in parasitic infections

- respond to chemotactic agents derived largely from mast cells
- Granules contain major basic protein: toxic to parasites and lead to lysis of mammalian epithelial cells



## Mast cells

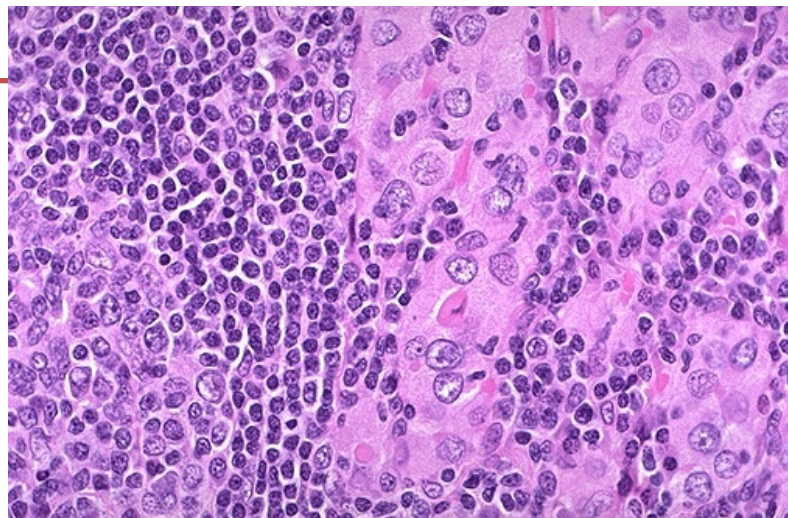
- are widely distributed in connective tissues
- express on their surface the receptor that binds the Fc portion of IgE antibody
  - the cells degranulate and release mediators, such as histamine and products of AA oxidation



# Chronic inflammation patterns

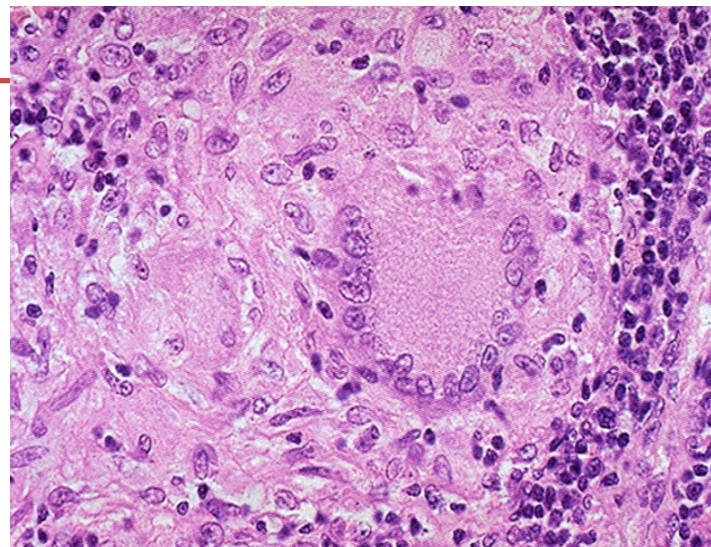
## Chronic non specific inflammation

- Features of chronic inflammation e.g.:
  - Foreign material, e.g. silicates, including asbestos.
  - Auto-immune diseases, e.g. auto-immune thyroiditis



## Chronic granulomatous inflammation

- Chronic inflammation in which modified macrophages (epithelioid cells) accumulate in small clusters surrounded by lymphocytes. The small clusters are called: **(GRANULOMAS)**
- Example: TUBERCULOSIS





# Objectives

- 1. Define chronic inflammation with emphasis on causes, nature of the inflammatory response, cells involved and tissue changes.**
- 2. Describe the systemic manifestations of inflammation and their general physiology, including fever, leukocyte left shift, and acute phase reactants.**

# Systemic effects of Inflammation

- **Acute phase reaction/response**
  - IL-1 and TNF
    - Fever
    - Malaise
    - Anorexia
- **Bone marrow**
  - IL-1 + TNF
    - Leukocytosis
- **Lymphoid organs**
- **Liver**
  - IL-6, IL-1, TNF
    - Acute phase proteins
      - C-reactive protein
      - Lipopolysaccharide binding protein
      - Serum amyloid A
      - a-2 macroglobulin
      - Haptoglobin
      - Ceruloplasmin
      - fibrinogen



# Fever

## Produced in response to Pyrogens

- Types of Pyrogens:
  - **Exogenous pyrogens:** Bacterial products
  - **Endogenous pyrogens:**  
Interleukin 1 (IL1) and Tumour necrosis factor (TNF)
- Bacterial products stimulate leukocytes to release cytokines such as IL-1 and TNF that increase the enzymes (cyclooxygenases) that convert AA into prostaglandins.

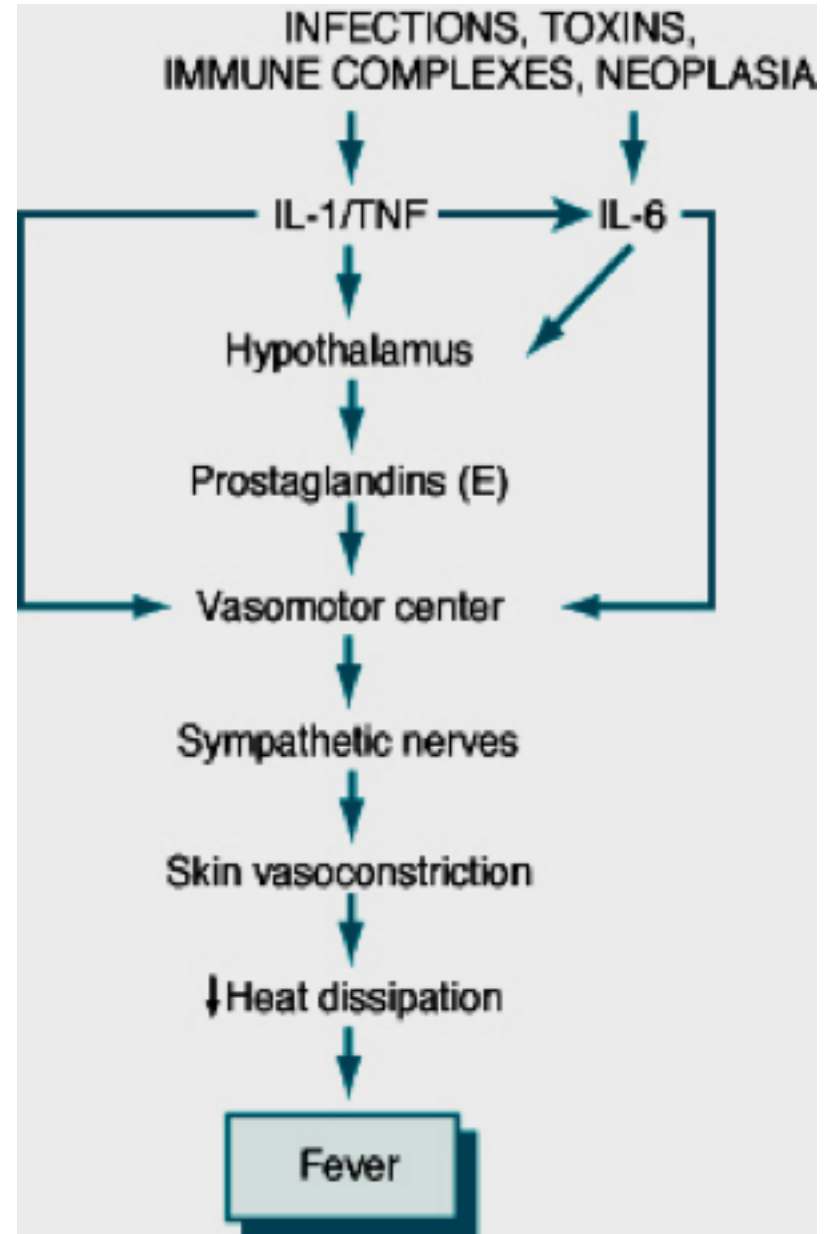
**Chemical mediators which are the inducing cause of fever are:**

1. IL-1
2. TNF
3. Prostaglandins

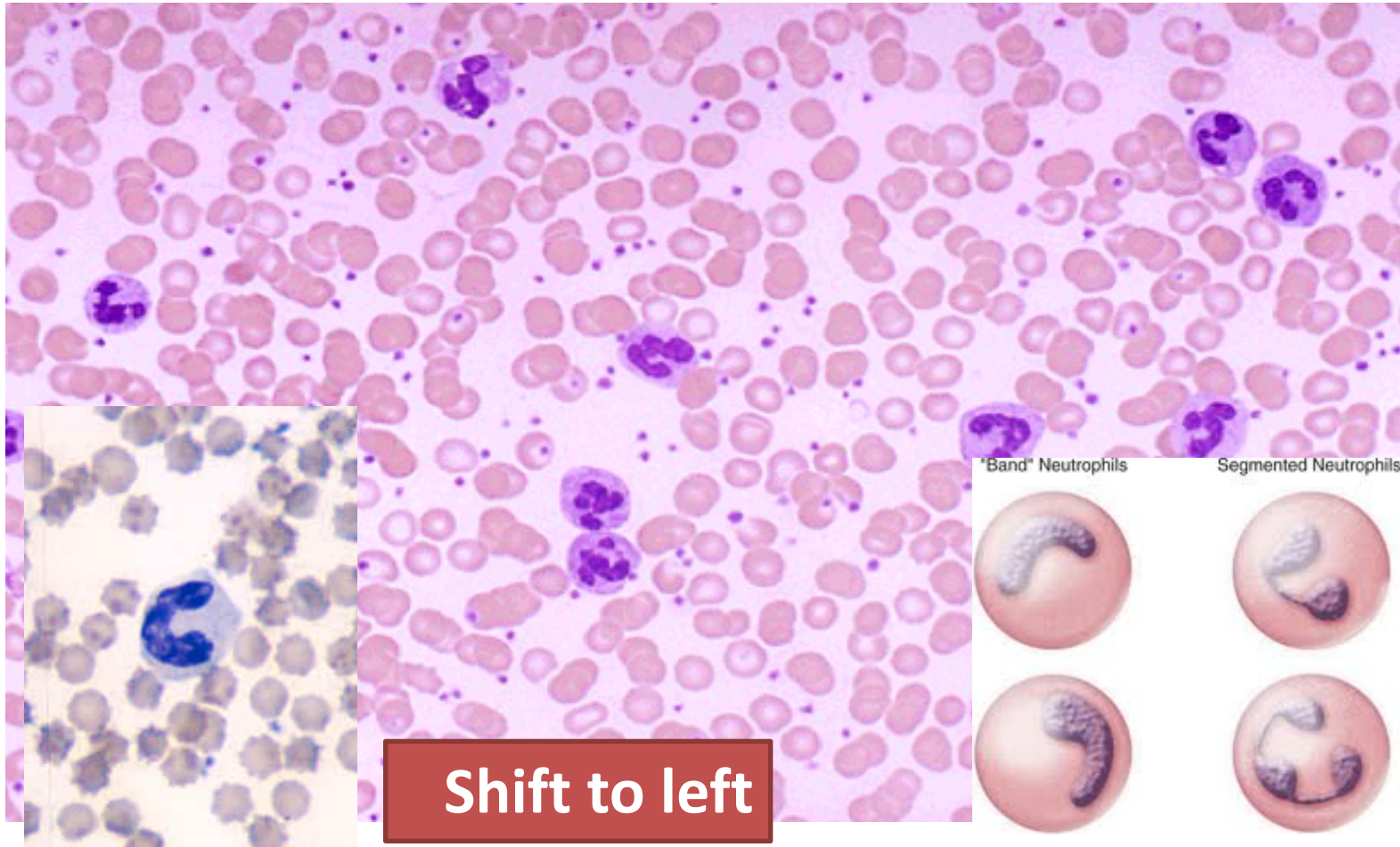
## Systemic manifestations of inflammation

- In the hypothalamus, the prostaglandins, especially  $\text{PGE}_2$ , stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level.
- NSAIDs, including aspirin, reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.

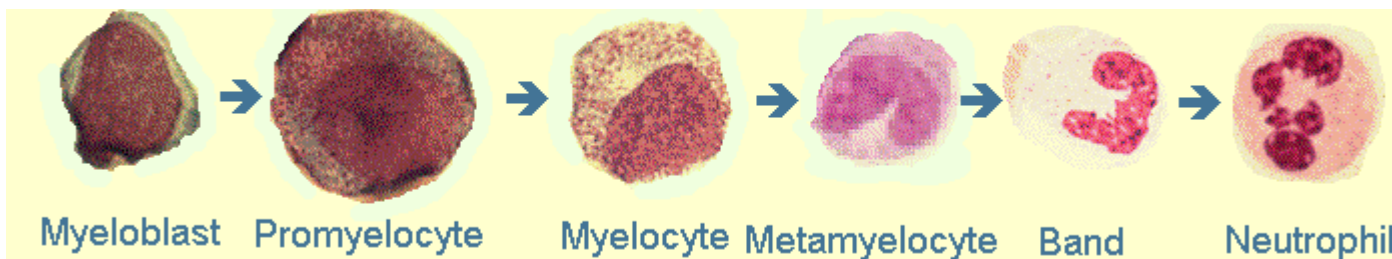
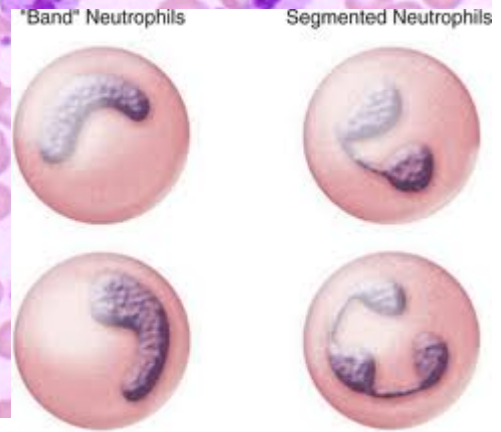
## Fever



# Leukocytosis



Shift to left



# Inflammation

## Systemic Manifestations

### Leukocytosis:

WBC count climbs to 15,000 or 20,000 cells/ $\mu$ l

**most bacterial infection (Neutrophil)**

### Lymphocytosis:

**Viral infections: Infectious mononucleosis, mumps,**

**German measles ( Lymphocytes)**

**Eosinophilia: bronchial asthma, hay fever, parasitic infestations**

**Leukopenia: typhoid fever, infection with rickettsiae/protozoa**

## Acute Phase Proteins

Acute Phase Proteins are normally found in the blood at low concentrations, but following hepatic stimulation by IL-6 their concentration increases

Detection of elevated levels of acute phase proteins is an indication of an inflammatory response

C-reactive protein (CRP)  
Lipopolysaccharide binding protein  
Serum amyloid A (SAA)  
a-2 macroglobulin  
Haptoglobin  
Ceruloplasmin  
fibrinogen

CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement

## Acute phase proteins

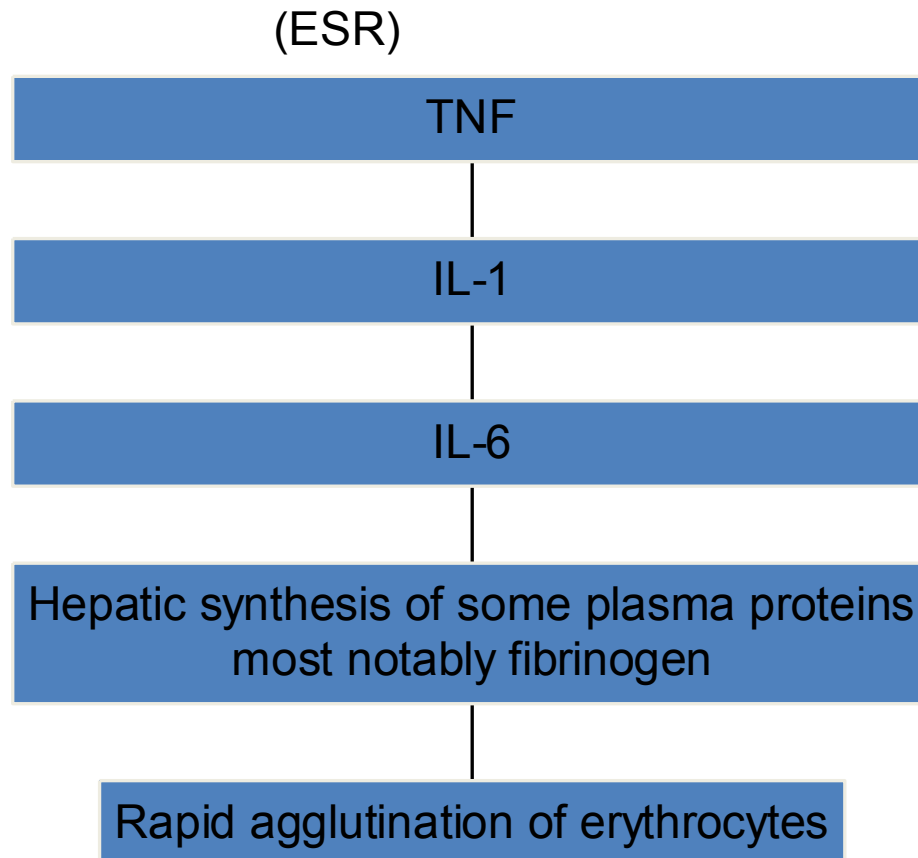
- Elevated serum levels of CRP serve as a marker for acute inflammation and increased risk of myocardial infarction in patients with coronary artery disease.

**Prolonged production of these proteins (especially SAA) in states of chronic inflammation can cause:**  
*secondary amyloidosis*

## Systemic manifestations of inflammation

### Increased erythrocyte sedimentation rate (ESR)

- The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes.





# Erythrocyte Sedimentation Rate (ESR)



**1hr**



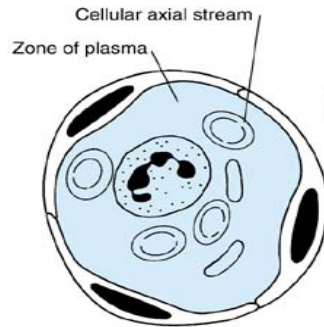
The distance, in mm,  
the RBC fall in 1 hr  
is the Sed Rate



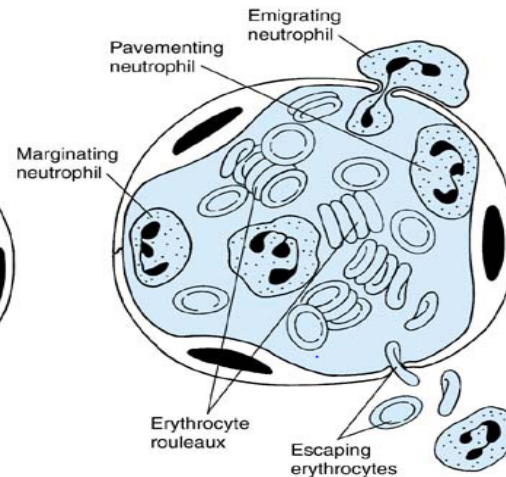
# Erythrocyte sedimentation rate (ESR)

This is a simple test for an inflammatory response caused by any stimulus.

A Normal postcapillary venule



B Acute inflammation



Fibrinogen binds to red cells and causes them to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual red cell

- 1. Define chronic inflammation with emphasis on causes, nature of the inflammatory response, cells involved and tissue changes.**
- 2. Describe the systemic manifestations of inflammation and their general physiology, including fever, leukocyte left shift, and acute phase reactants.**