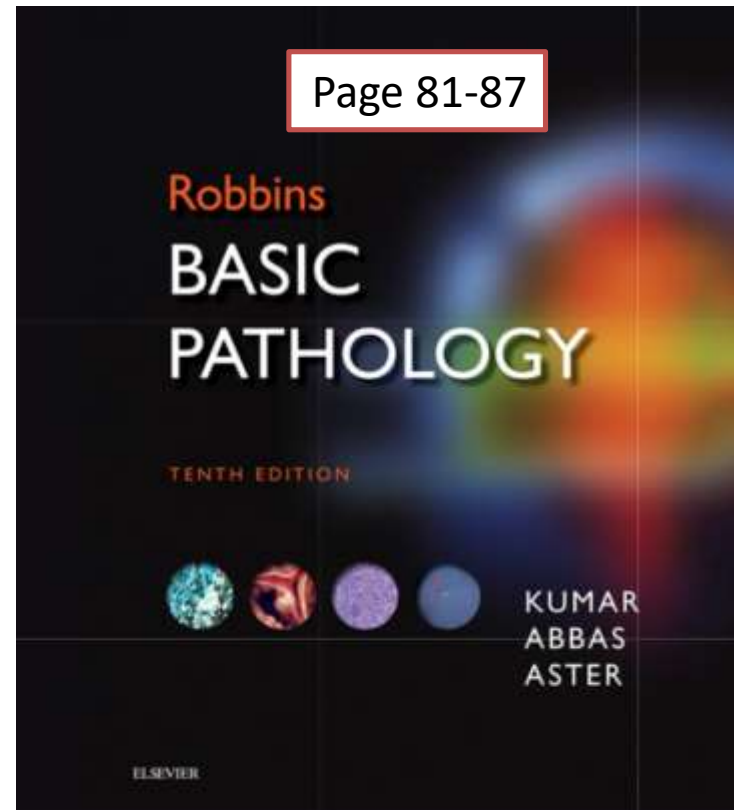


INFLAMMATION AND REPAIR
Chronic inflammation
Systemic effect of inflammation

Lecturer: Prof. Maha Arafah



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.

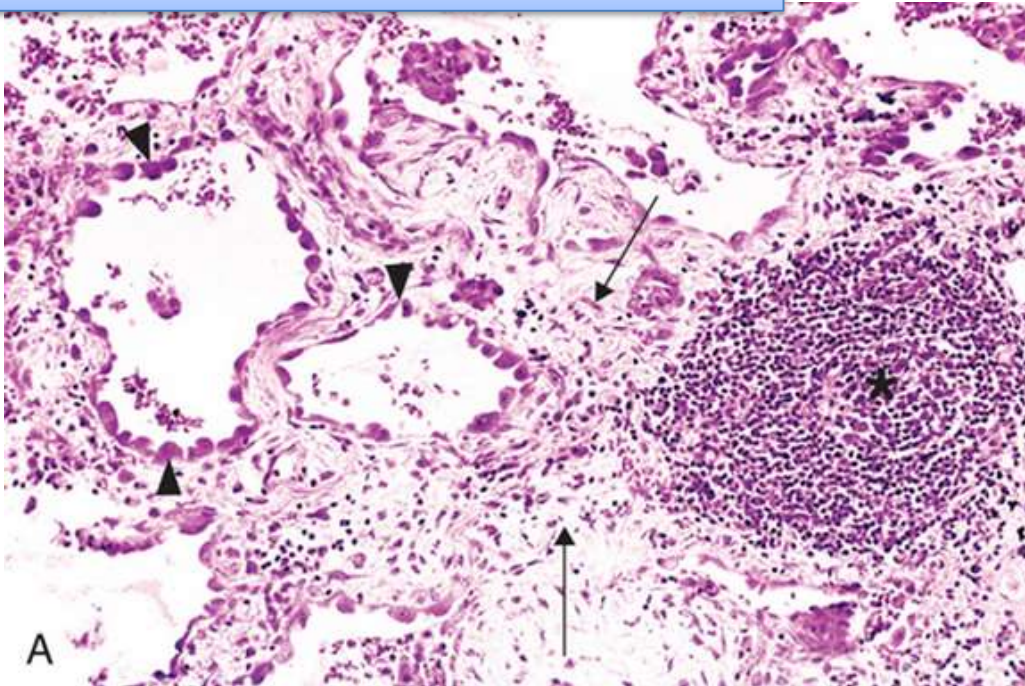
- Examples are nondegradable exogenous materials such as inhaled particulate silica, which can induce a chronic inflammatory response in the lungs (silicosis)
- Endogenous agents such as cholesterol crystals, which may contribute to atherosclerosis
- Other examples:
 - neurodegenerative disorders such 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

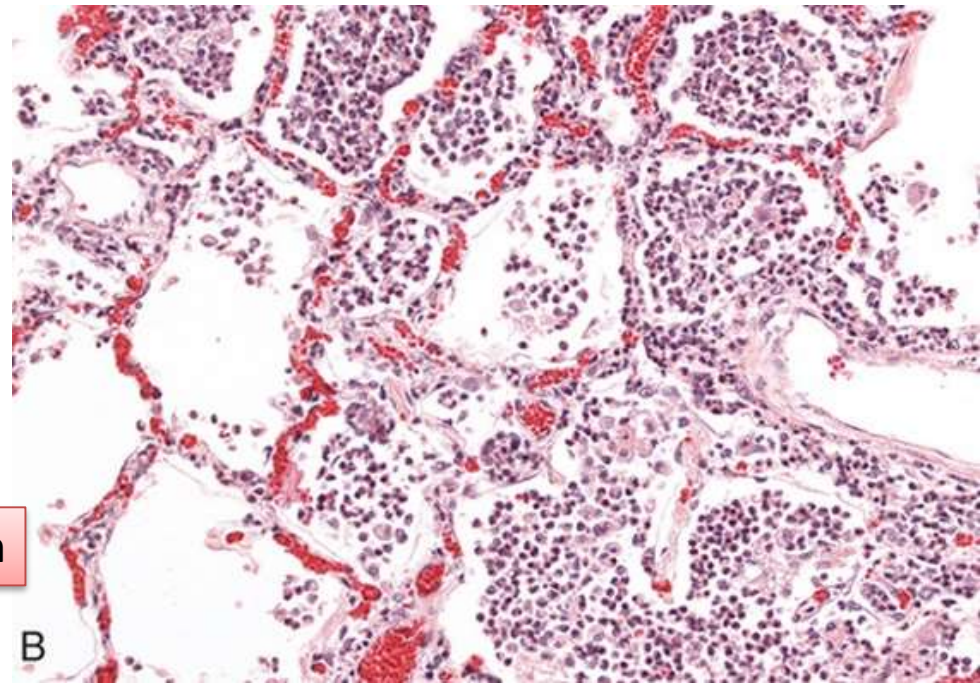
Acute inflammation is distinguished by vascular changes, edema, and a predominantly neutrophilic infiltrate

Features of chronic inflammation



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

Lung acute inflammation



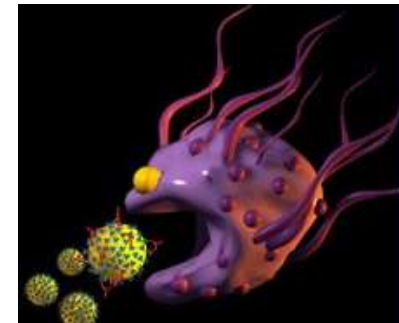
Cells in Chronic inflammation

- 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

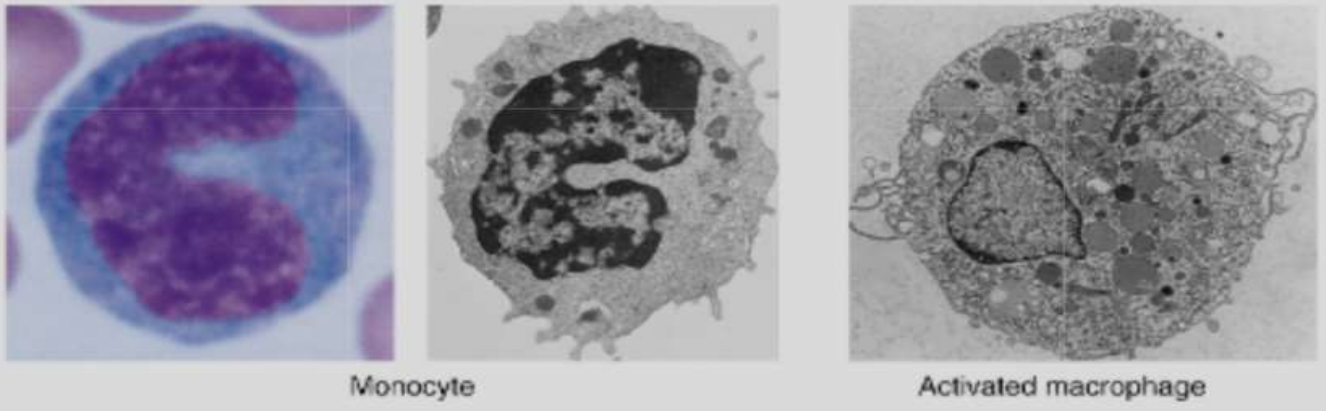
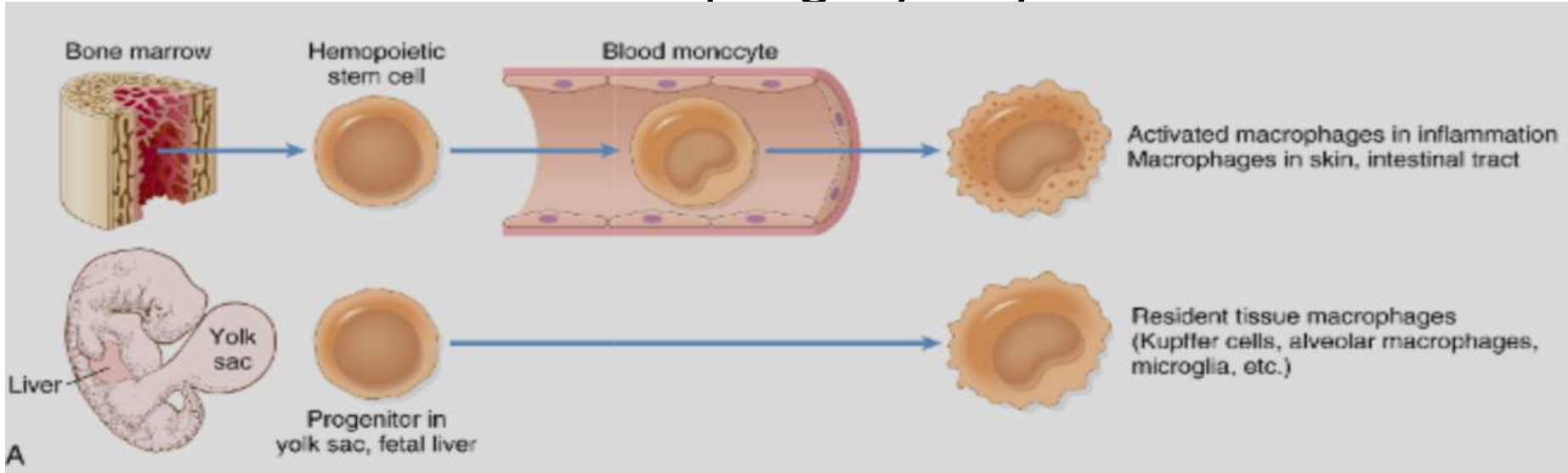
- In tissue:
 - the liver (Kupffer cells)
 - spleen and lymph nodes (sinus histiocytes)
 - central nervous system (microglial cells)
 - and lungs (alveolar macrophages)
- In blood: monocytes
 - Under the influence of adhesion molecules and chemokines, they migrate to a site of injury within 24 to 48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

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



Different types of inflammatory cells accumulate in chronic inflammation

mononuclear phagocyte system



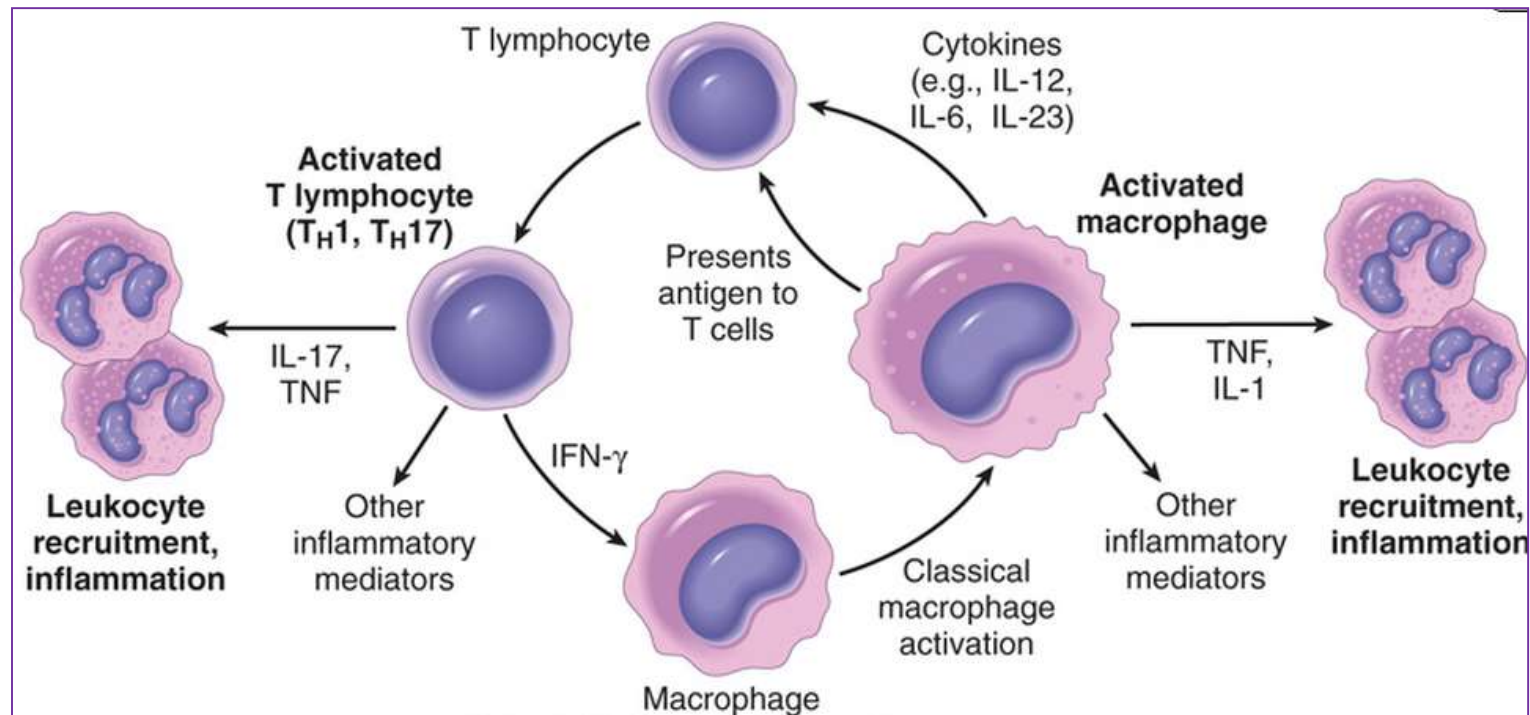
monocytes begin to emigrate into extravascular tissues quite – early in acute inflammation and within 48 hours they may constitute the predominant cell type



MONONUCLEAR CELL INFILTRATION

Macrophages

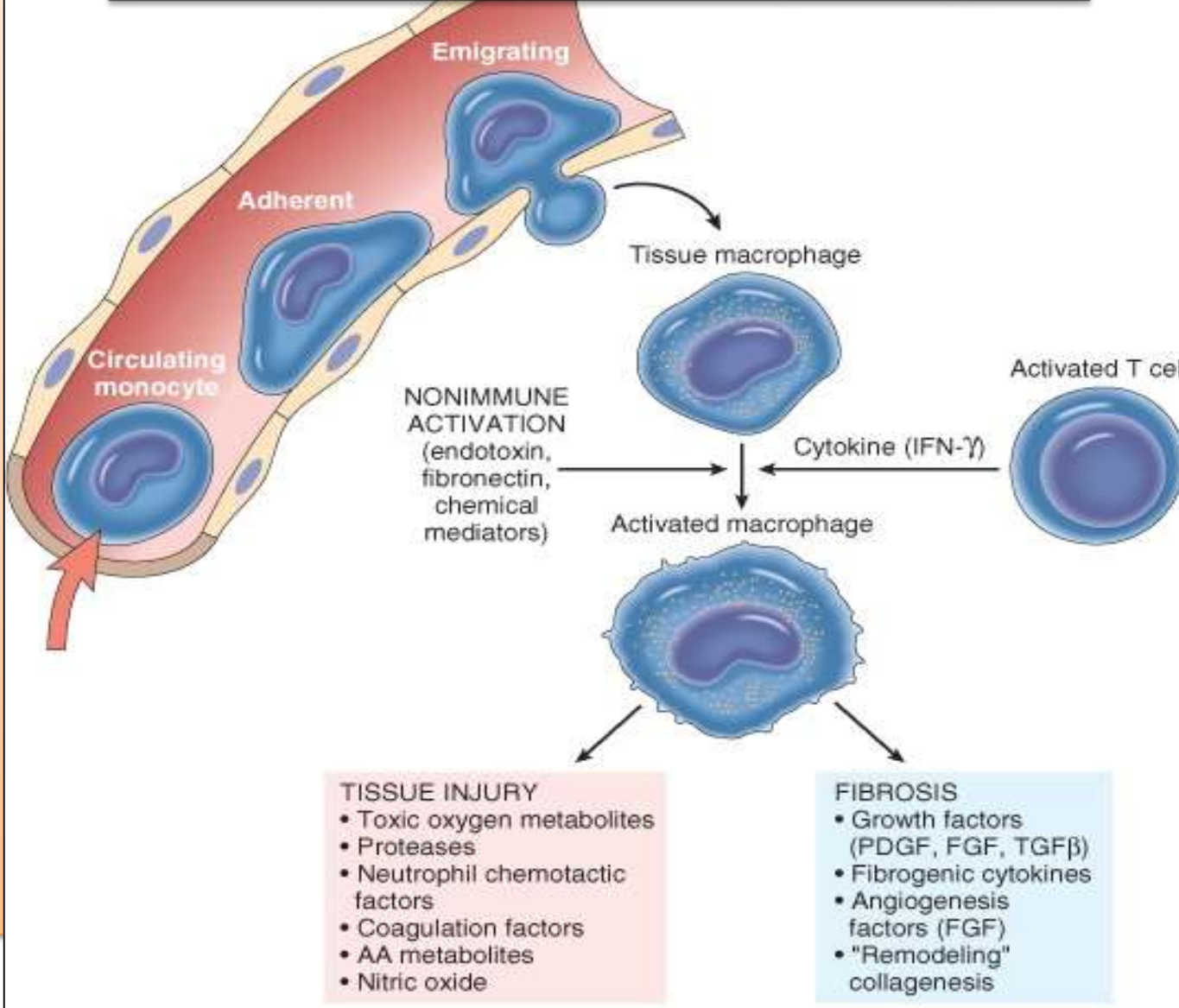
- Macrophages may be *activated* by a variety of stimuli, including:
 - cytokines (e.g., IFN- γ) secreted by sensitized T lymphocytes and by NK cells
 - bacterial endotoxins



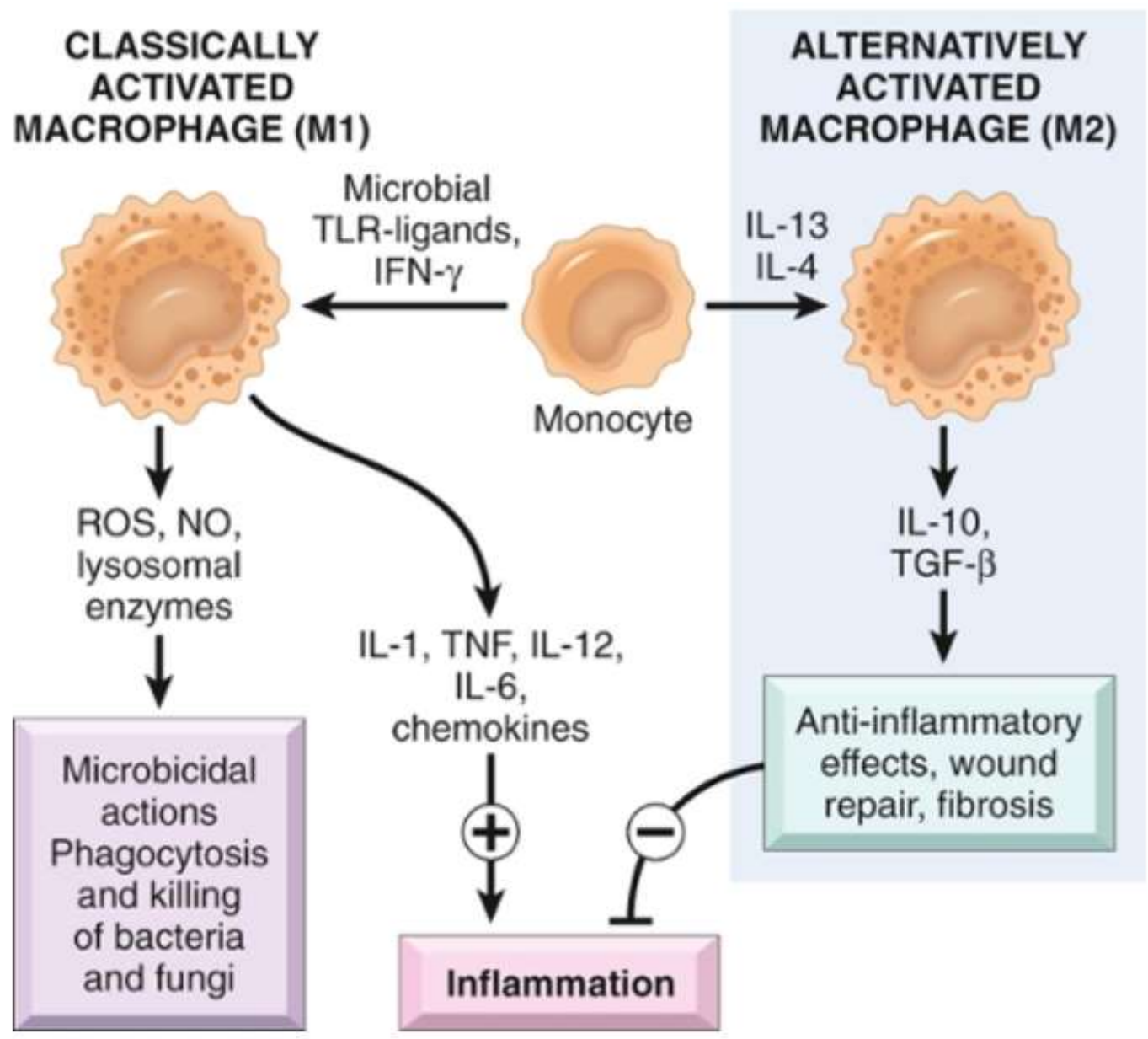
Different types of inflammatory cells accumulate in chronic inflammation

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



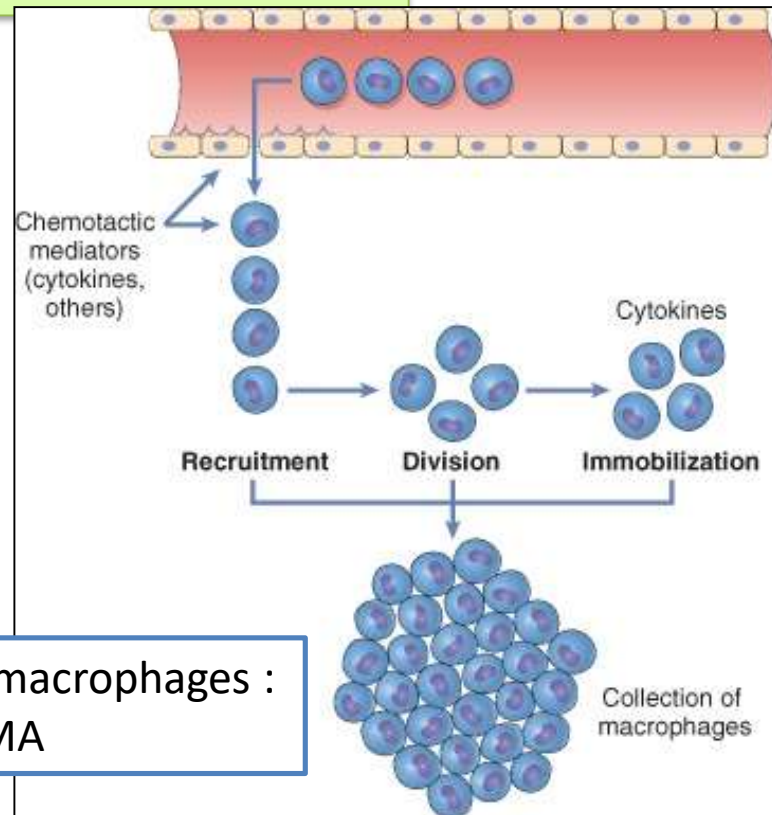
Different types of inflammatory cells accumulate in chronic inflammation



Macrophages/Monocytes

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

1. *Recruitment of monocytes from the circulation*
2. *Local proliferation of macrophages*
3. *Immobilization of macrophages*



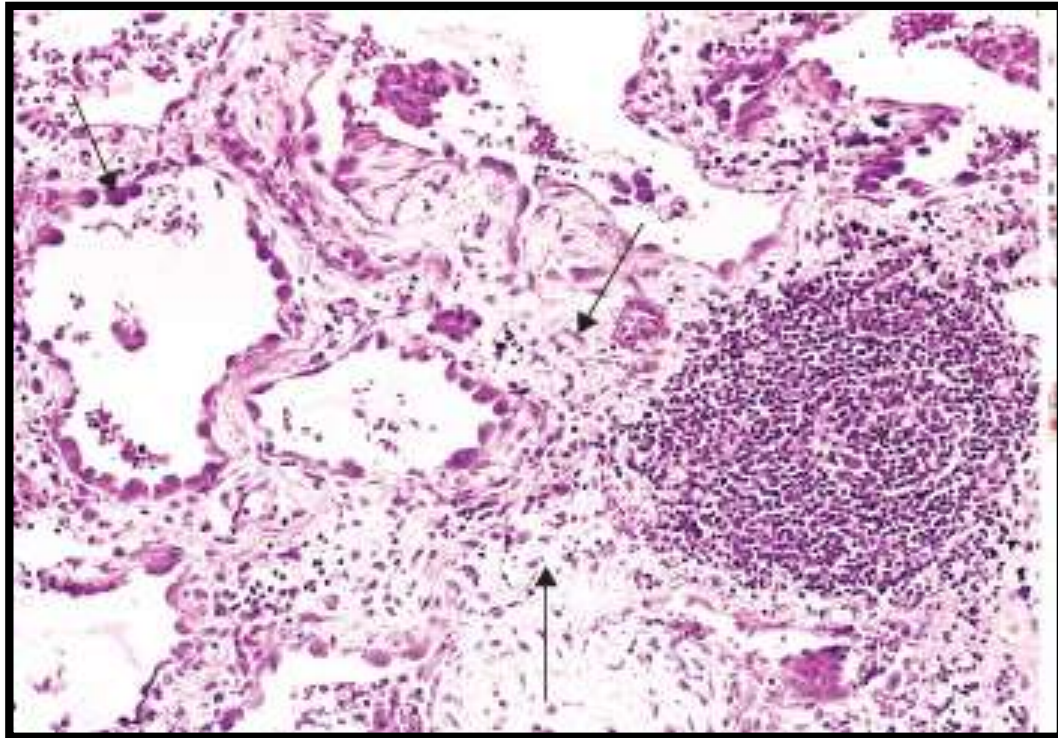
Collection of activated macrophages :
GRANULOMA



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

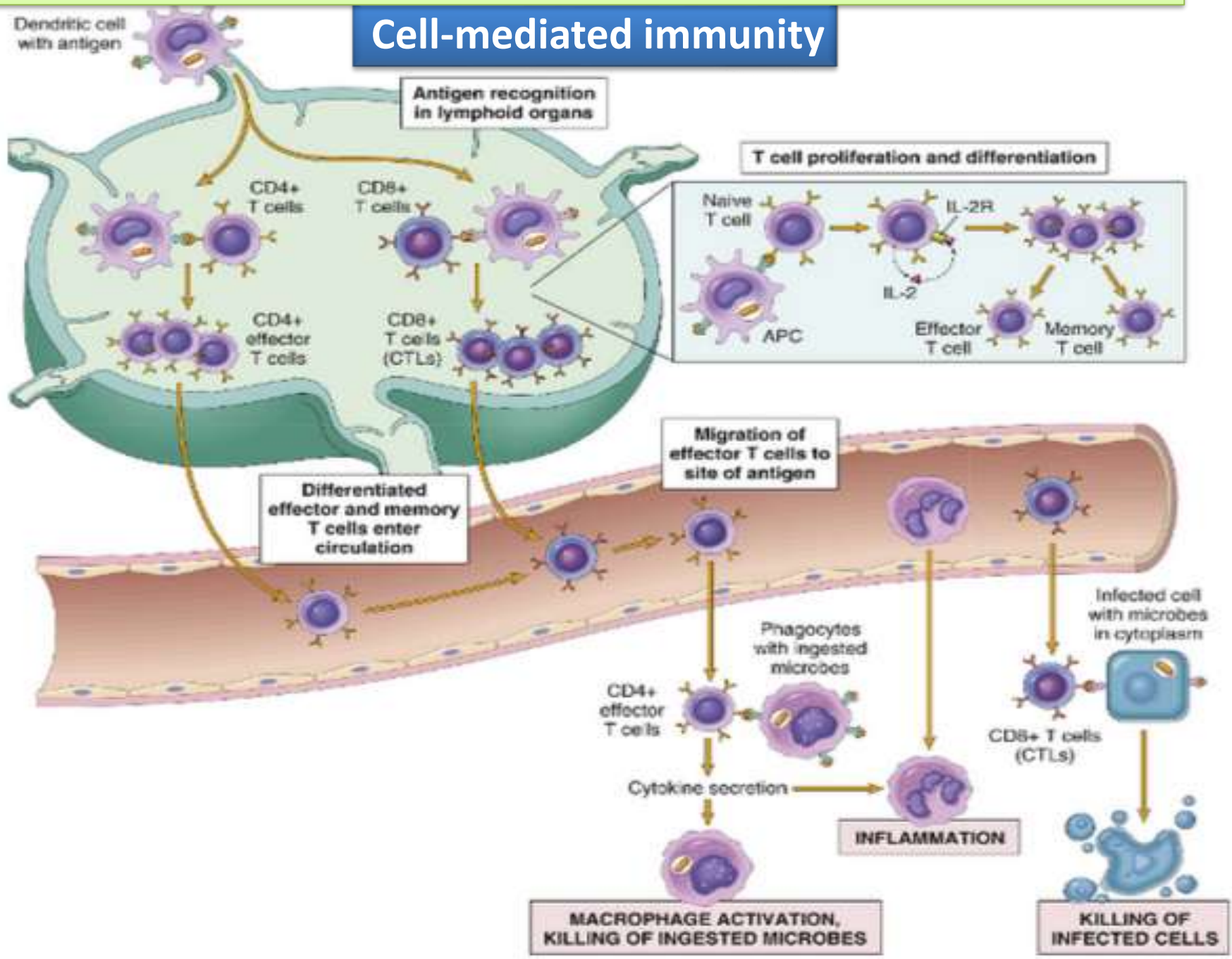


Lymphocytes

- 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

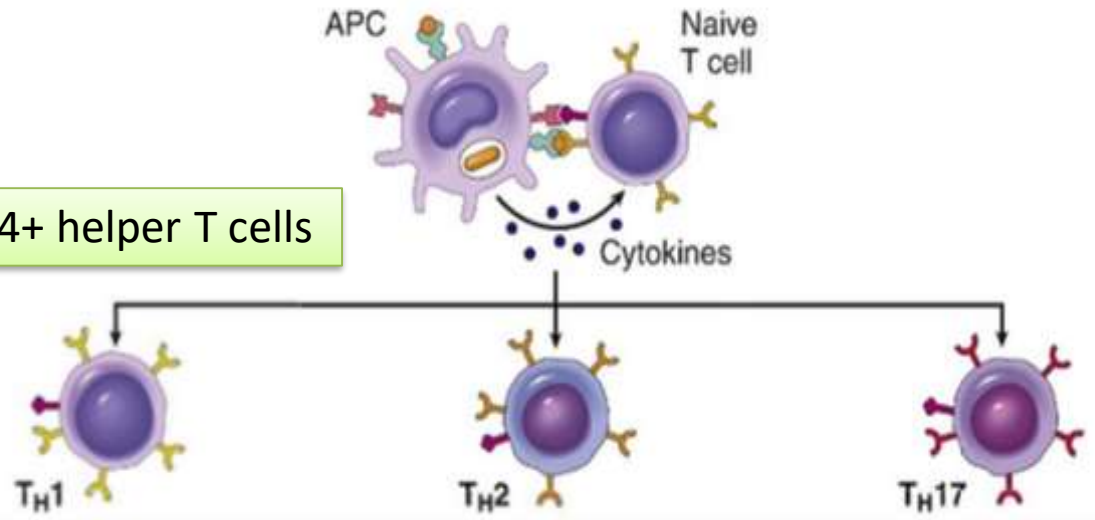


Different types of inflammatory cells accumulate in chronic inflammation

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



Major cytokines produced	IFN- γ	IL-4, IL-5, IL-13	IL-17, IL-22
Cytokines that induce this subset	IFN- γ , IL-12	IL-4	TGF- β , IL-6, IL-1, IL-23
Immunological reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	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

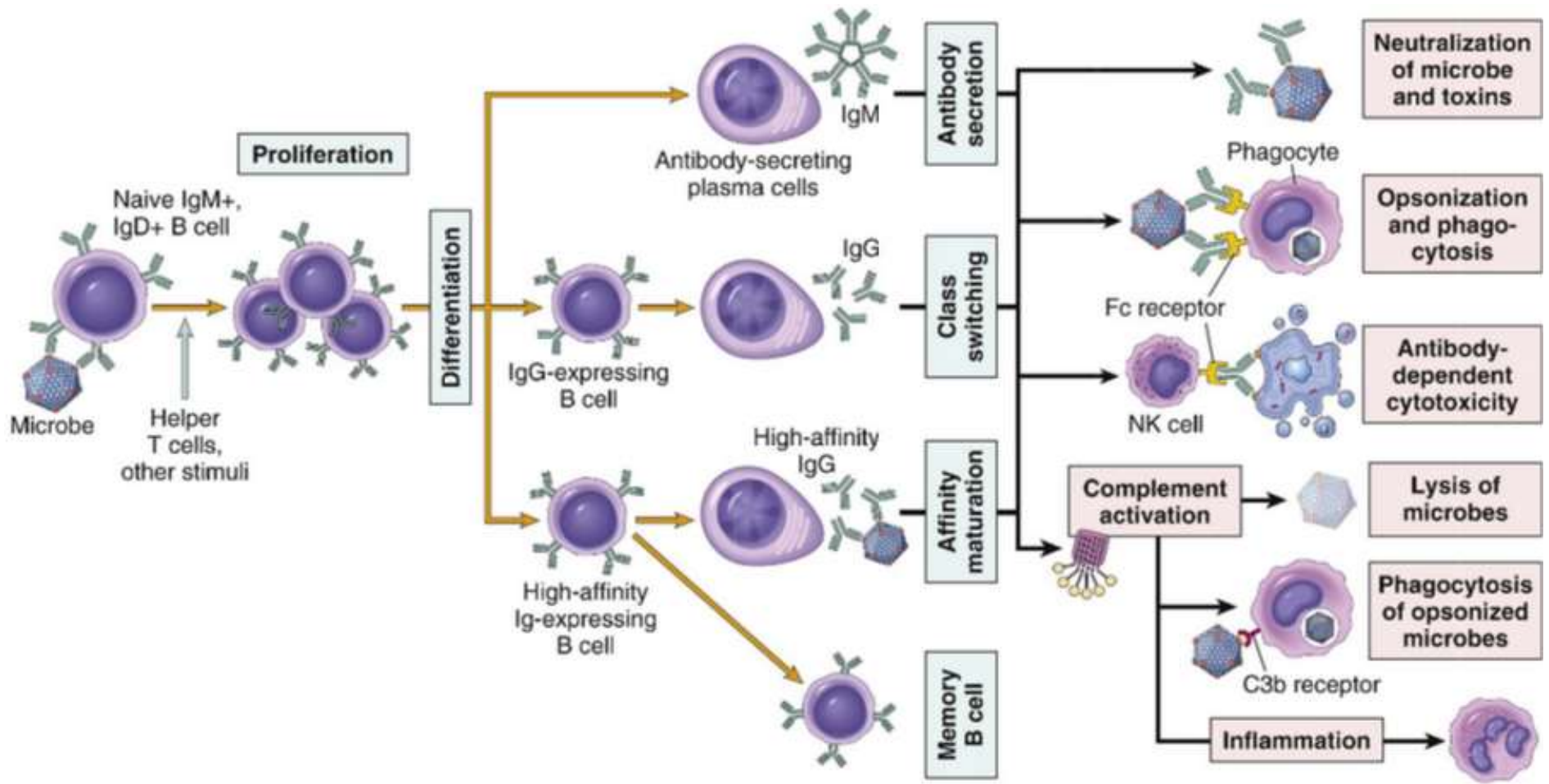
MS, multiple sclerosis

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

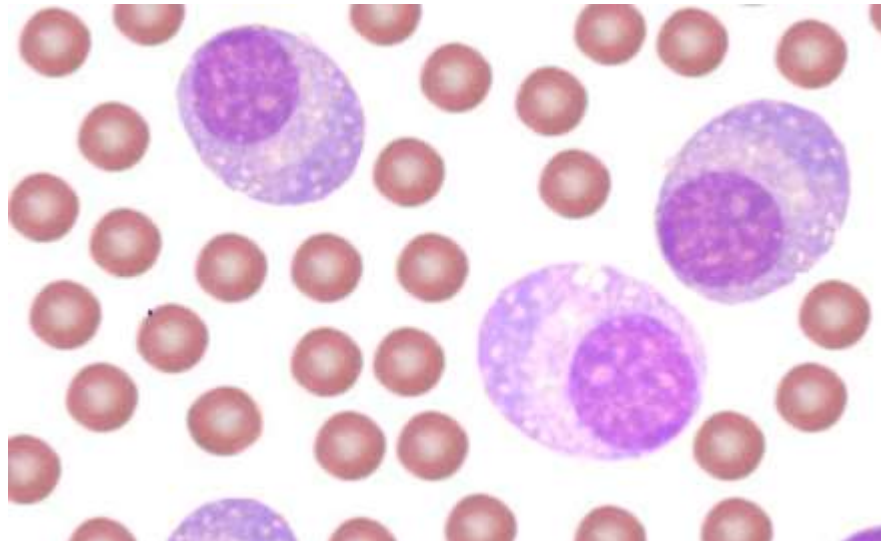
Humoral immunity



OTHER CELLS IN CHRONIC INFLAMMATION

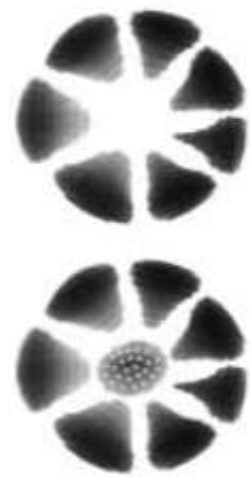
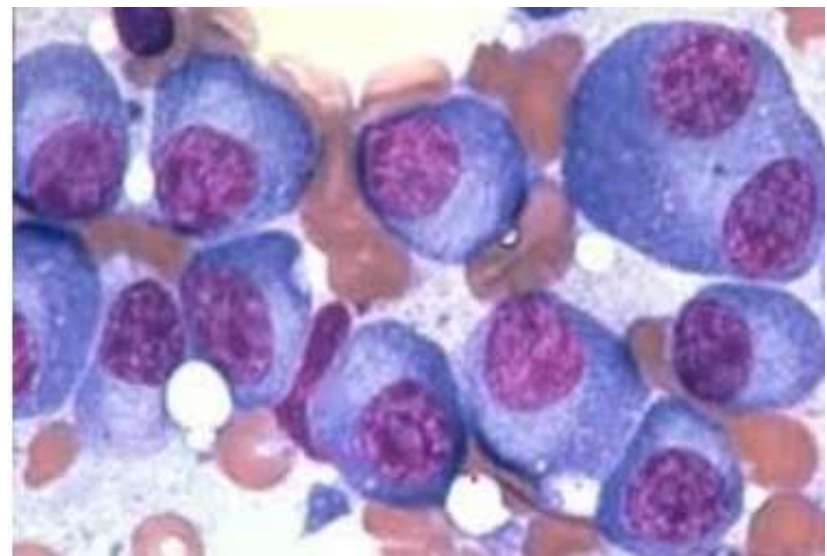
Plasma cells

- **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

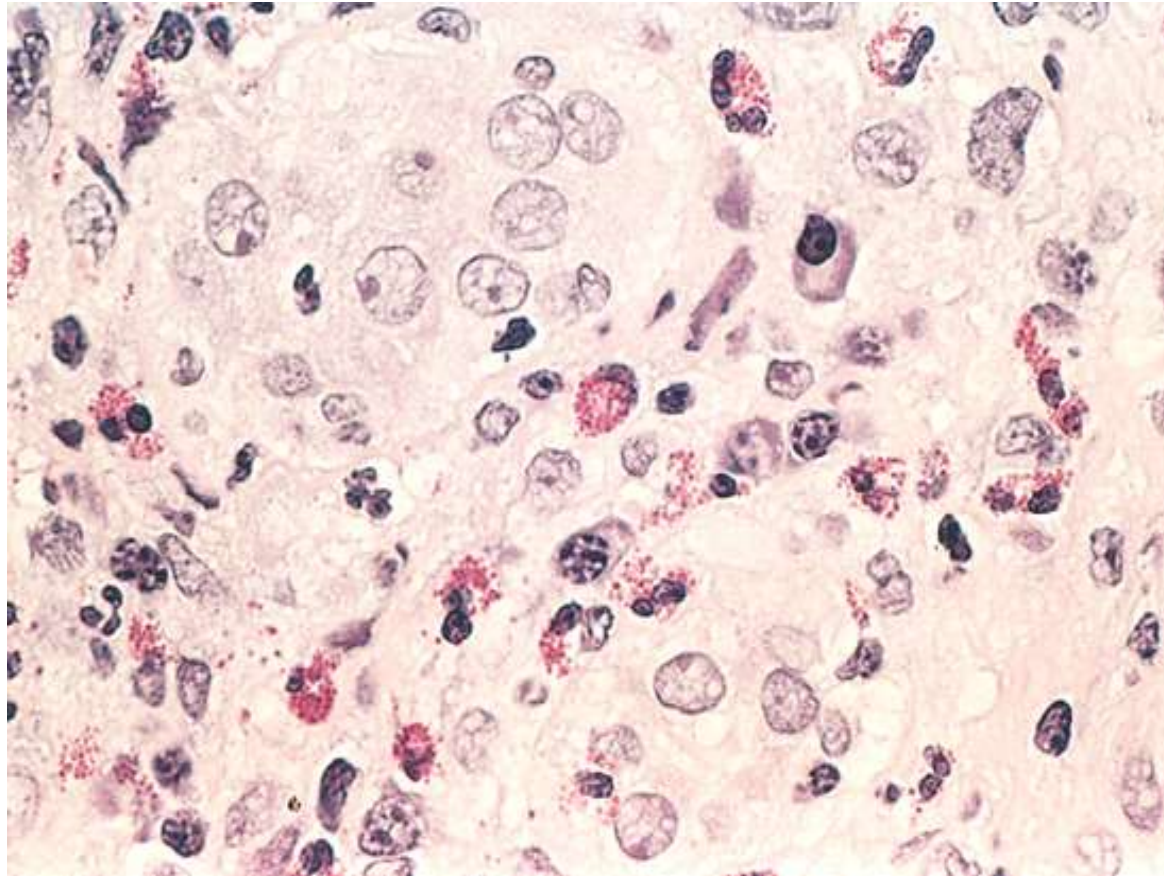
Morphology of plasma cells:
Cells has an eccentric nucleus shows a cartwheel or clock face pattern of nuclear chromatin with a perinuclear halo



Eosinophils

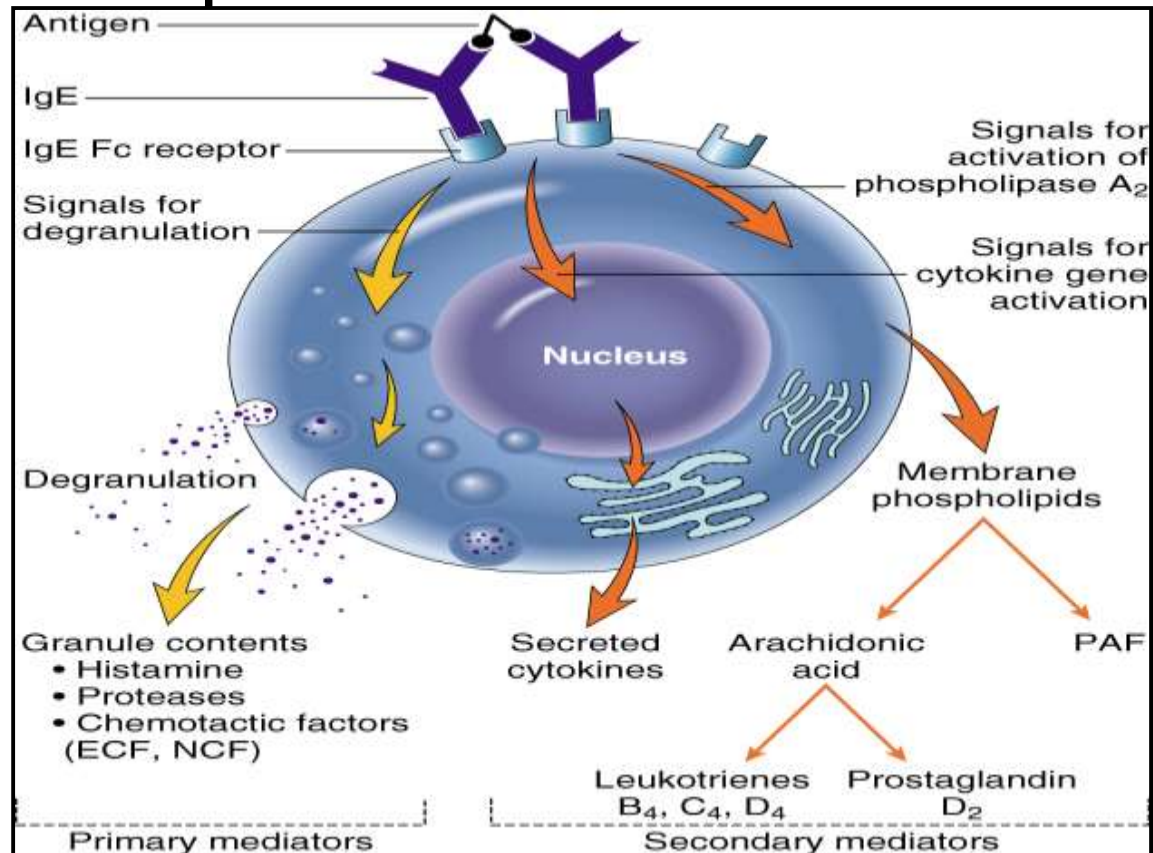
are abundant in immune reactions mediated by IgE in allergic reaction and in parasitic infections

- 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

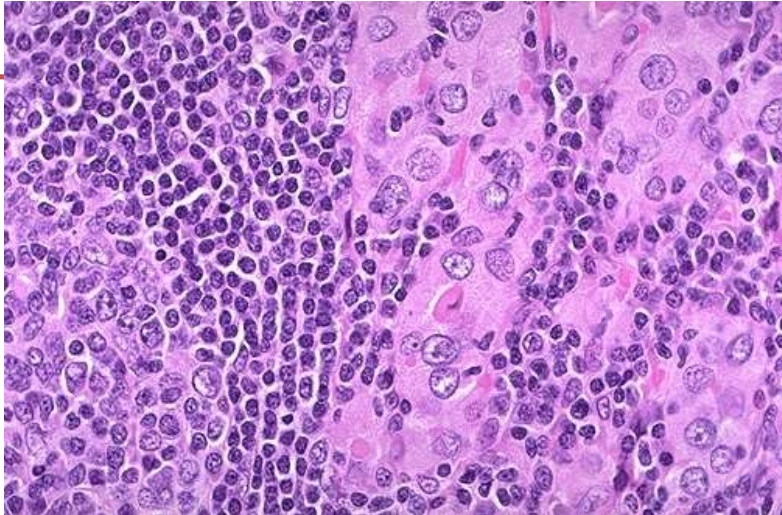
- are widely distributed in connective tissues
- express on their surface the receptor that binds the Fc portion of IgE antibody
 - the cells degranulate and release mediators, such as histamine and products of AA oxidation



Chronic inflammation patterns

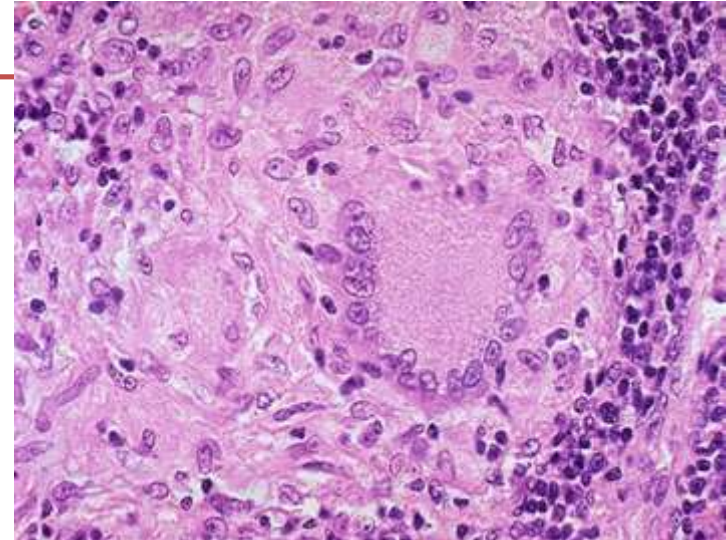
Chronic non specific inflammation

- 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.

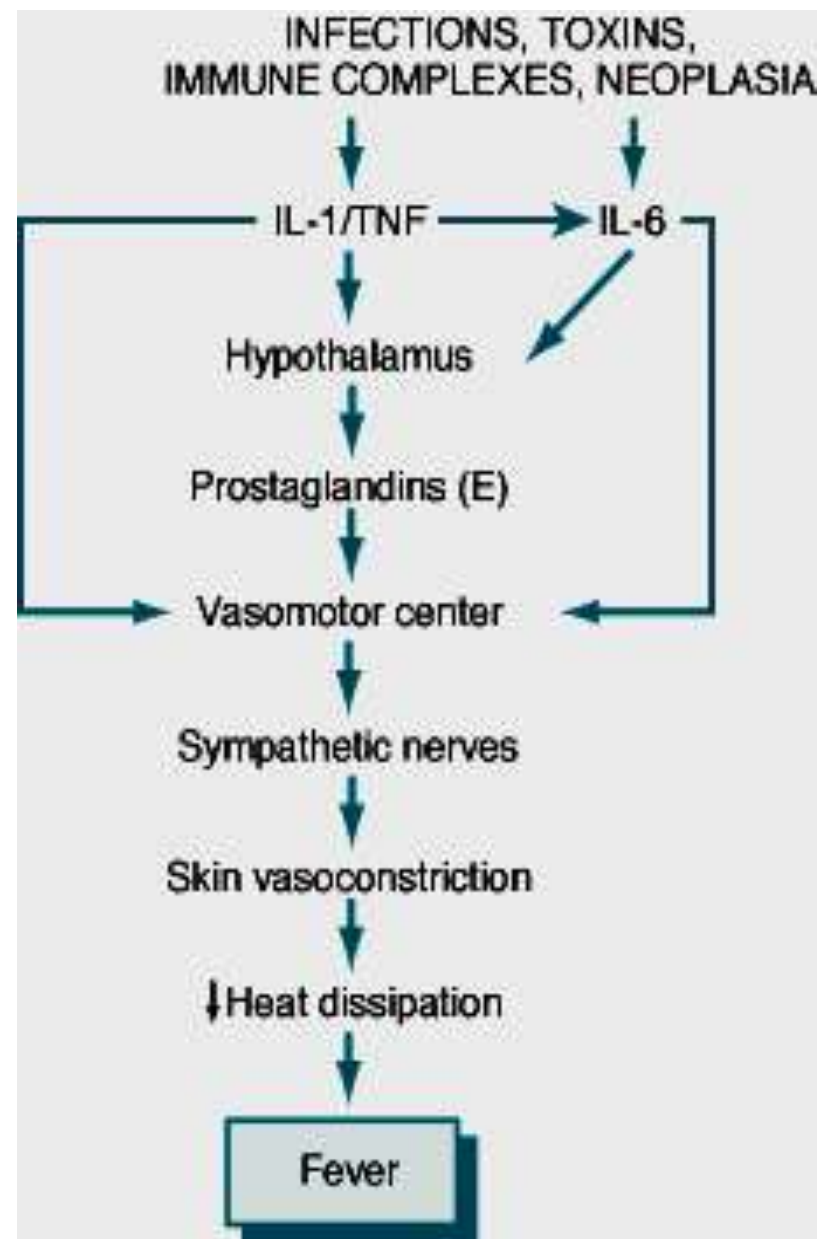
Chemical mediators which are the inducing cause of fever are:

1. IL-1
2. TNF
3. Prostaglandins

Systemic manifestations of inflammation

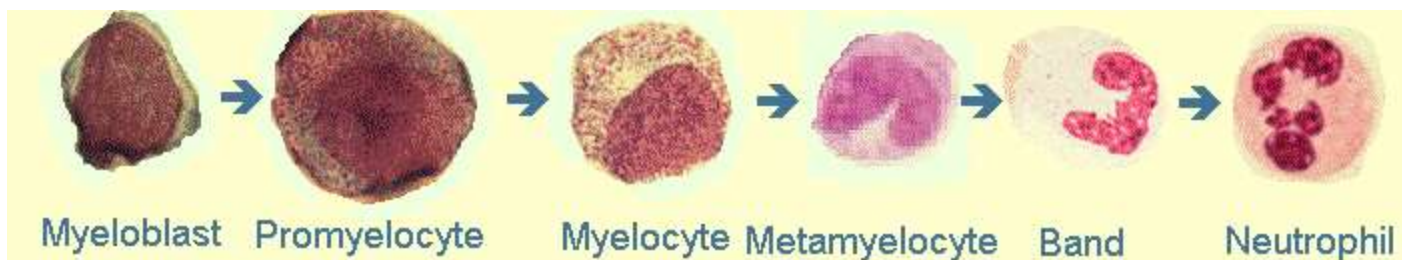
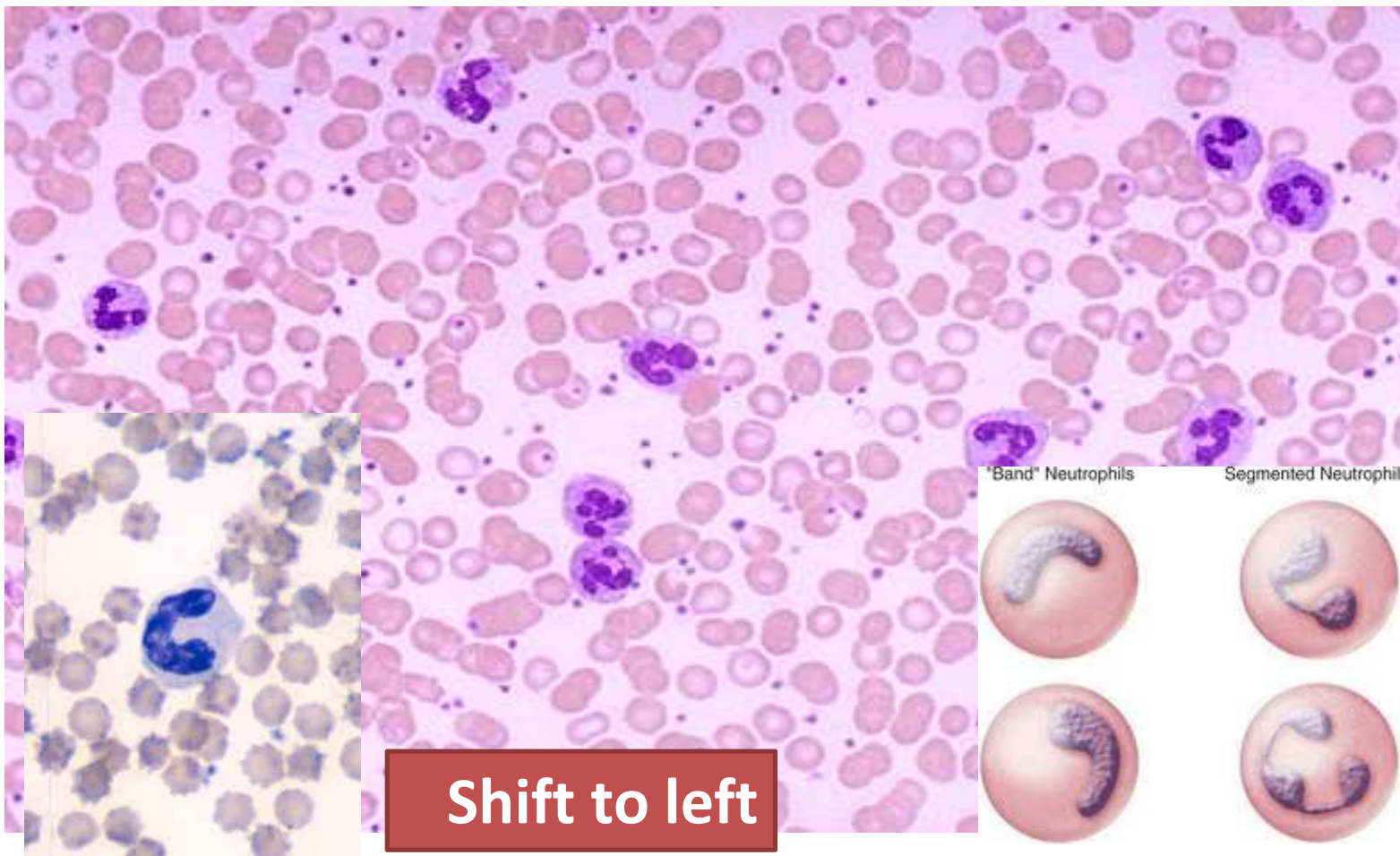
- In the hypothalamus, the prostaglandins, especially PGE_2 , stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level.
- NSAIDs, including aspirin, reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.

Fever



Systemic manifestations of inflammation

Leukocytosis



Inflammation

Systemic Manifestations

Leukocytosis:

WBC count climbs to 15,000 or 20,000 cells/ μ 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

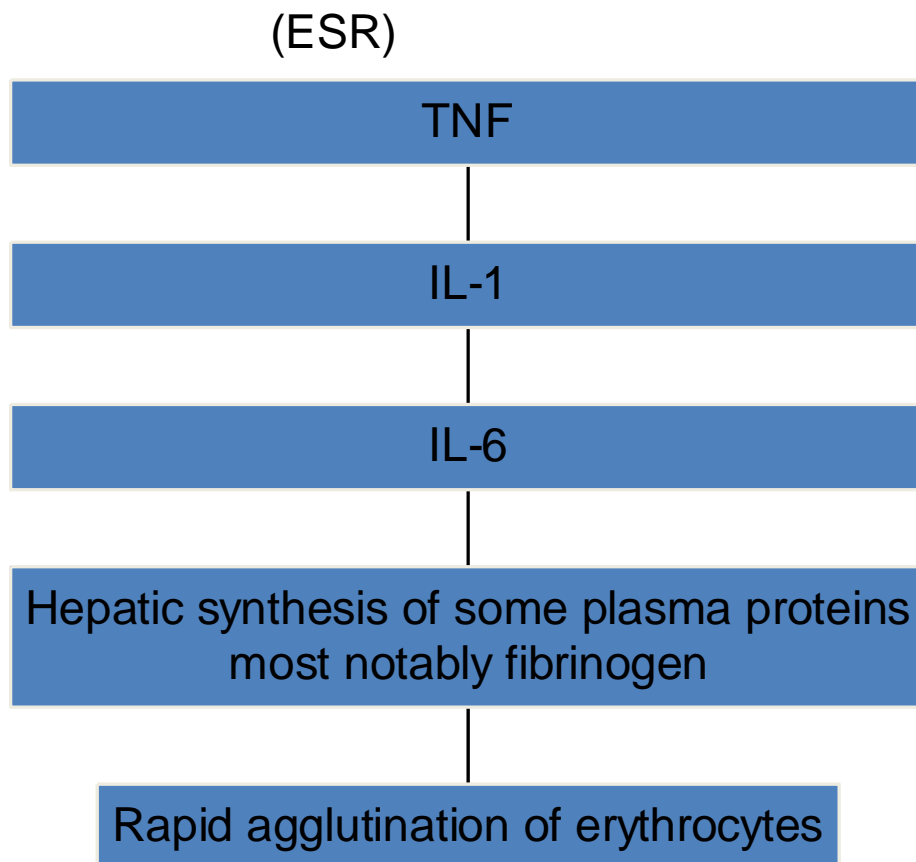
- Elevated serum levels of CRP serve as a marker for acute inflammation and increased risk of myocardial infarction in patients with coronary artery disease.

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

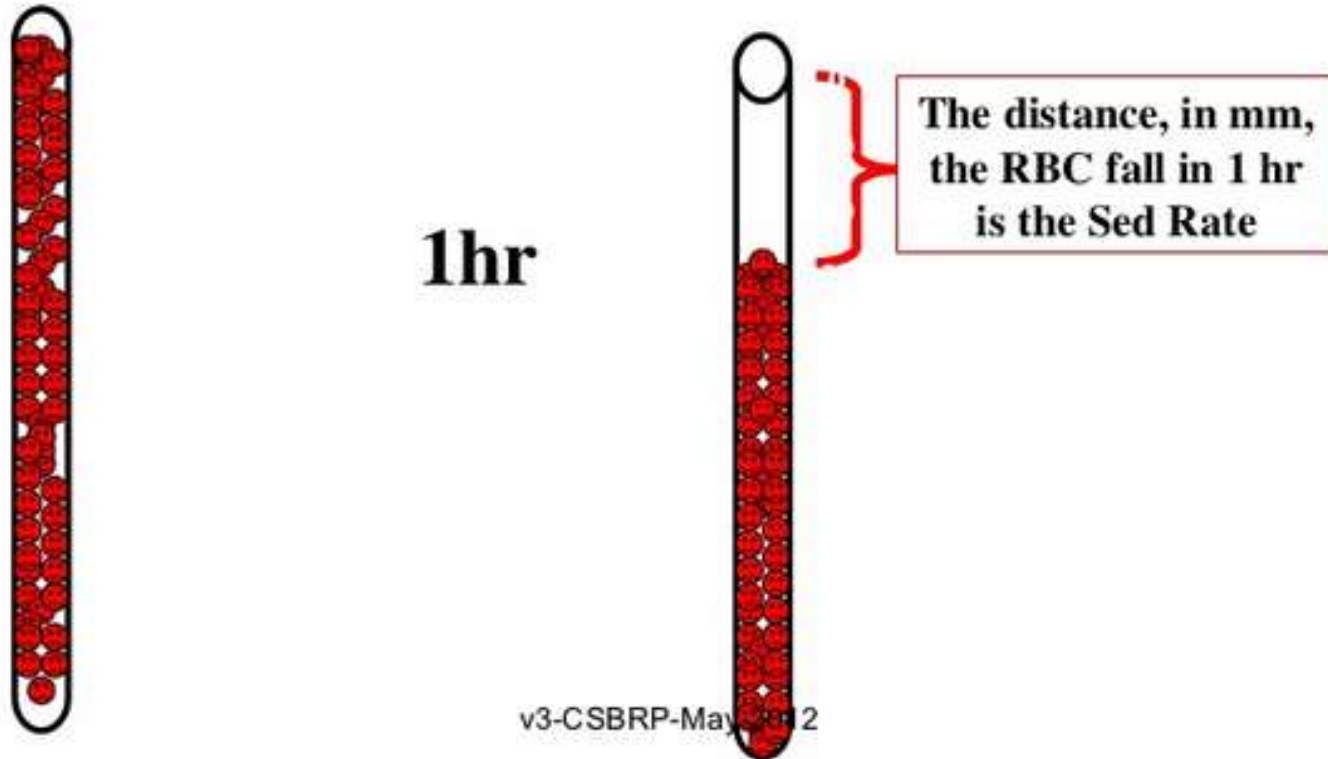
Systemic manifestations of inflammation

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.



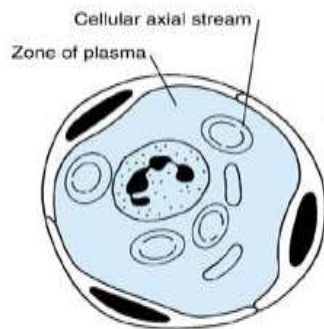
Erythrocyte Sedimentation Rate (ESR)



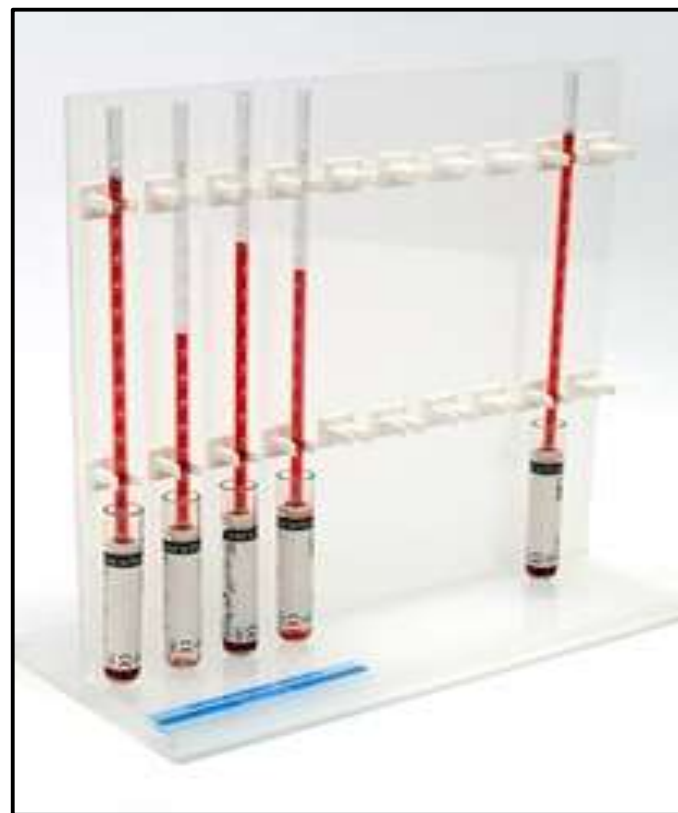
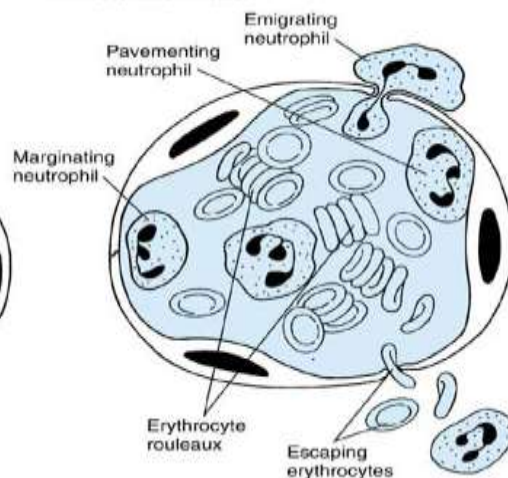
Erythrocyte sedimentation rate (ESR)

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