Foundation Block, Pathology

INFLAMMATION AND REPAIR
Lecture 4

Chronic inflammation

Systemic effect of inflammation

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Objectives

1. **Define chronic inflammation with emphasis on causes, nature of the inflammatory response, and tissue changes.**

2. **Compare and contrast the clinical settings in which different types of inflammatory cells (eosinophils, macrophages, and lymphocytes) accumulate in tissues.**

3. **Describe the systemic manifestations of inflammation and their general physiology, including fever, leukocyte left shift, and acute phase reactants.**

CHRONIC INFLAMMATION

- *Inflammation of prolonged duration (weeks to years) in which continuing inflammation, tissue injury, and healing, often by fibrosis, proceed simultaneously*

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); the appearance of macrophages, lymphocytes and often plasma cells
2. Proliferation of vascular endothelium by 'budding' – formation of new capillaries (angiogenesis).
3. 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.
   - These include :
     - *Mycobacterium tuberculosis*
     - *Treponema pallidum* (the causative organism of syphilis)
     - certain viruses and fungi
   - All of which tend to establish persistent infections and elicit a T lymphocyte-mediated immune response called *delayed-type hypersensitivity*.

Chronic inflammation may arise in the following settings:

2. *Immune-mediated inflammatory diseases (hypersensitivity diseases):* Diseases that are caused by excessive and inappropriate activation of the immune system leading to *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.

Chronic inflammation may arise in the following settings:

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

Chronic inflammation may arise in the following settings:

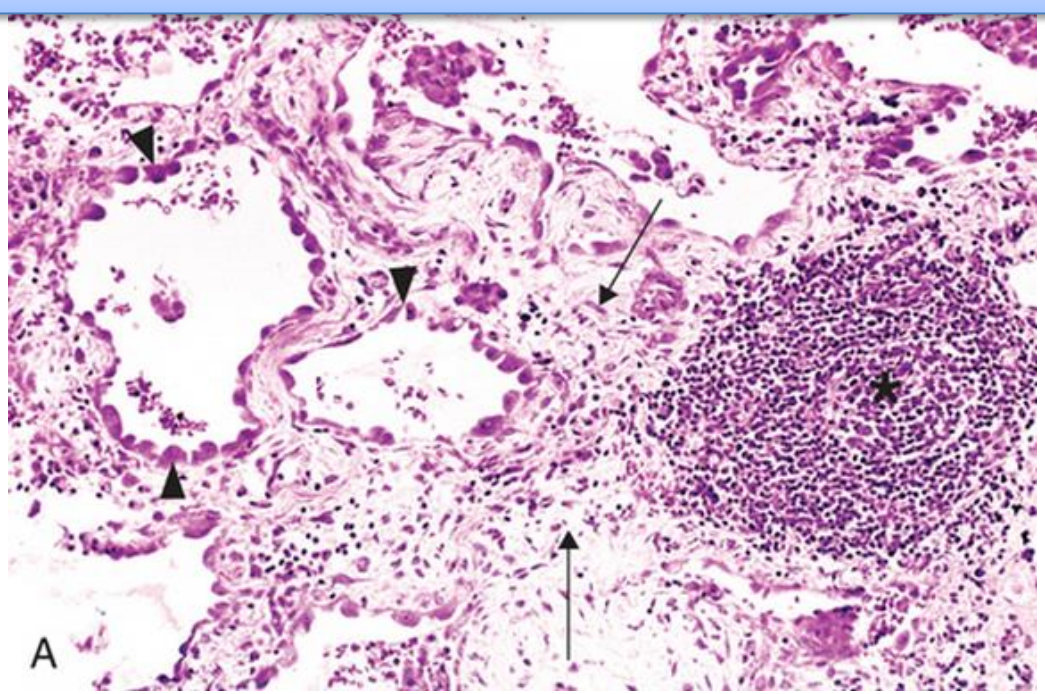
4. Mild forms of chronic inflammation may be important in the pathogenesis of many diseases
   - Such diseases include:
     - neurodegenerative disorders such as Alzheimer disease
     - atherosclerosis
     - metabolic syndrome and the associated type 2 diabetes,
     - and some forms of cancer in which inflammatory reactions promote tumor development

CHRONIC INFLAMMATION

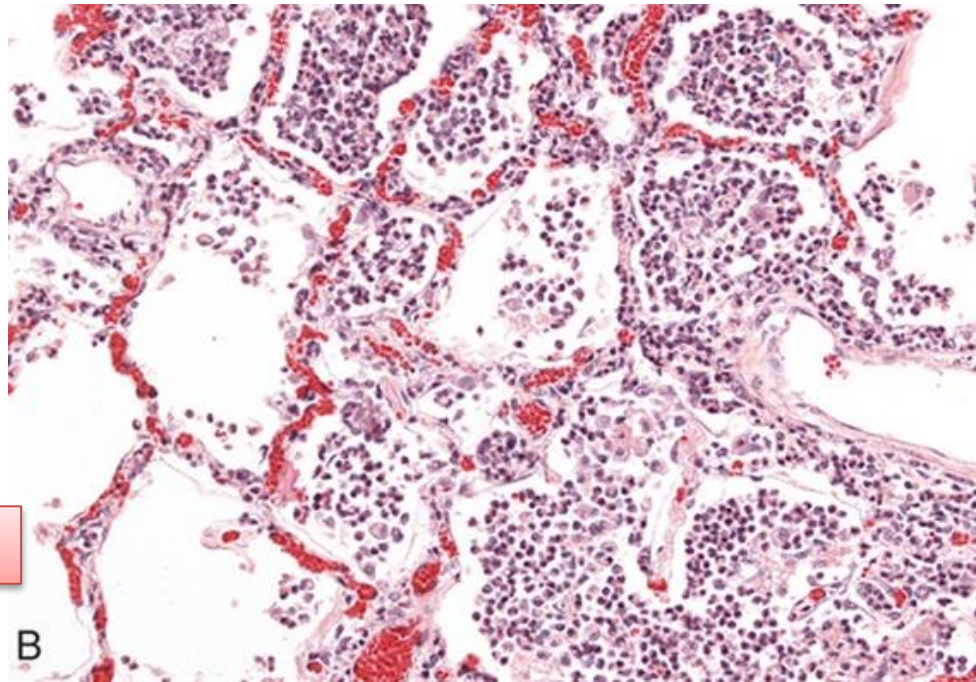
- Characterized by a 3 different set of reactions:
  1. *Infiltration with mononuclear cells,* including:
     i. Macrophages
     ii. Lymphocytes
     iii. Plasma cells
  2. *Tissue destruction,* largely induced by the products of the inflammatory cells
  3. *Repair,* involving new vessel proliferation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

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

1. Define chronic inflammation, its causes, effects and patterns



Lung chronic inflammation



Lung acute inflammation

Chronic inflammation patterns

Chronic non specific inflammation

- Features of chronic inflammation
- Examples:
  - 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

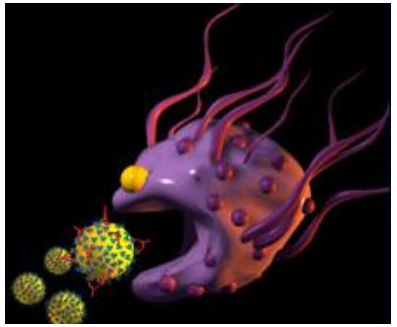
Cells in Chronic inflammation

- 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

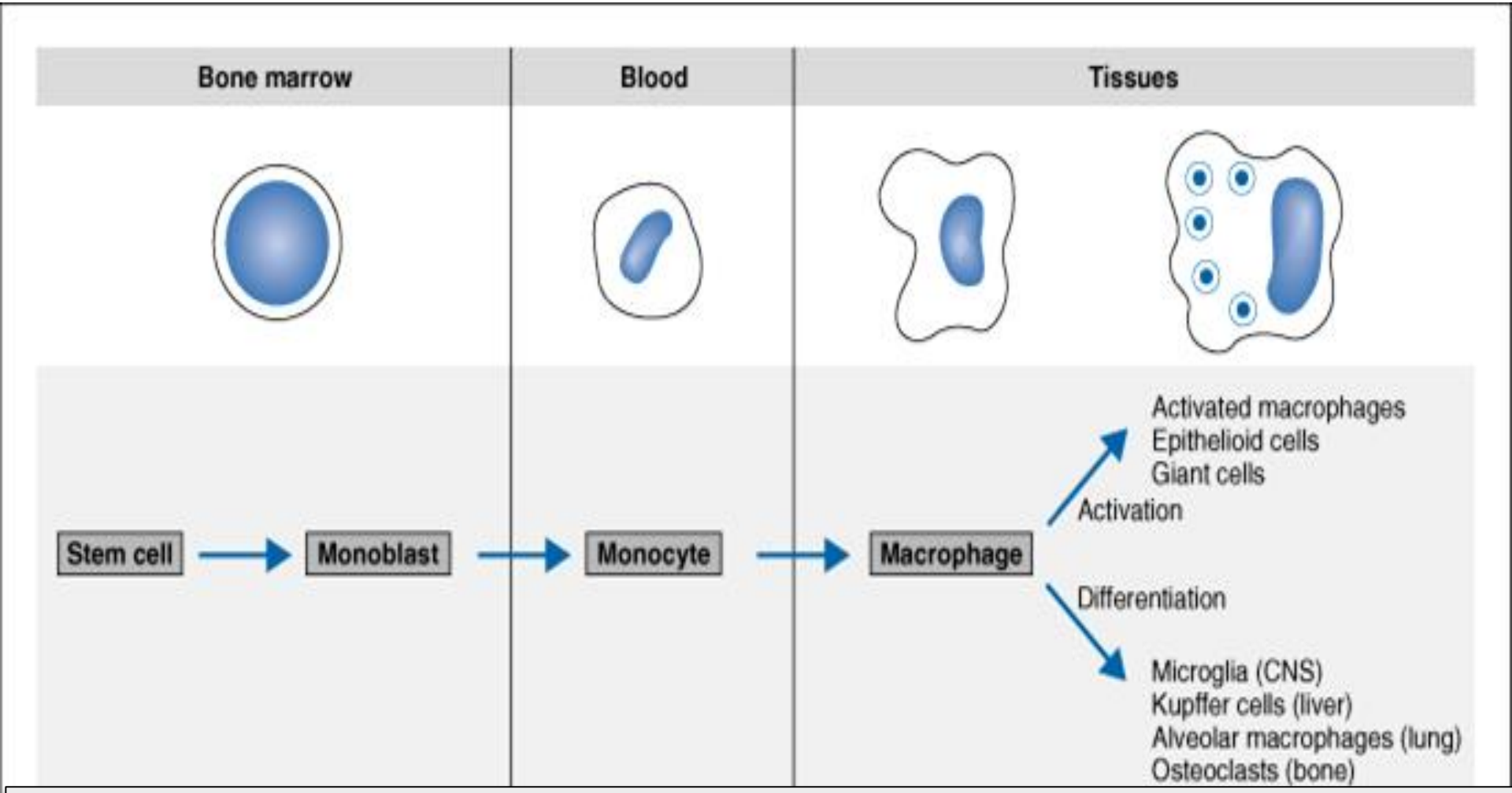
- In tissue:
  - the liver (Kupffer cells)
  - spleen and lymph nodes (sinus histiocytes)
  - central nervous system (microglial cells)
  - and lungs (alveolar macrophages)

- 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)

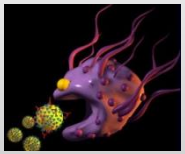


2. Different types of inflammatory cells accumulate in tissues

mononuclear phagocyte system



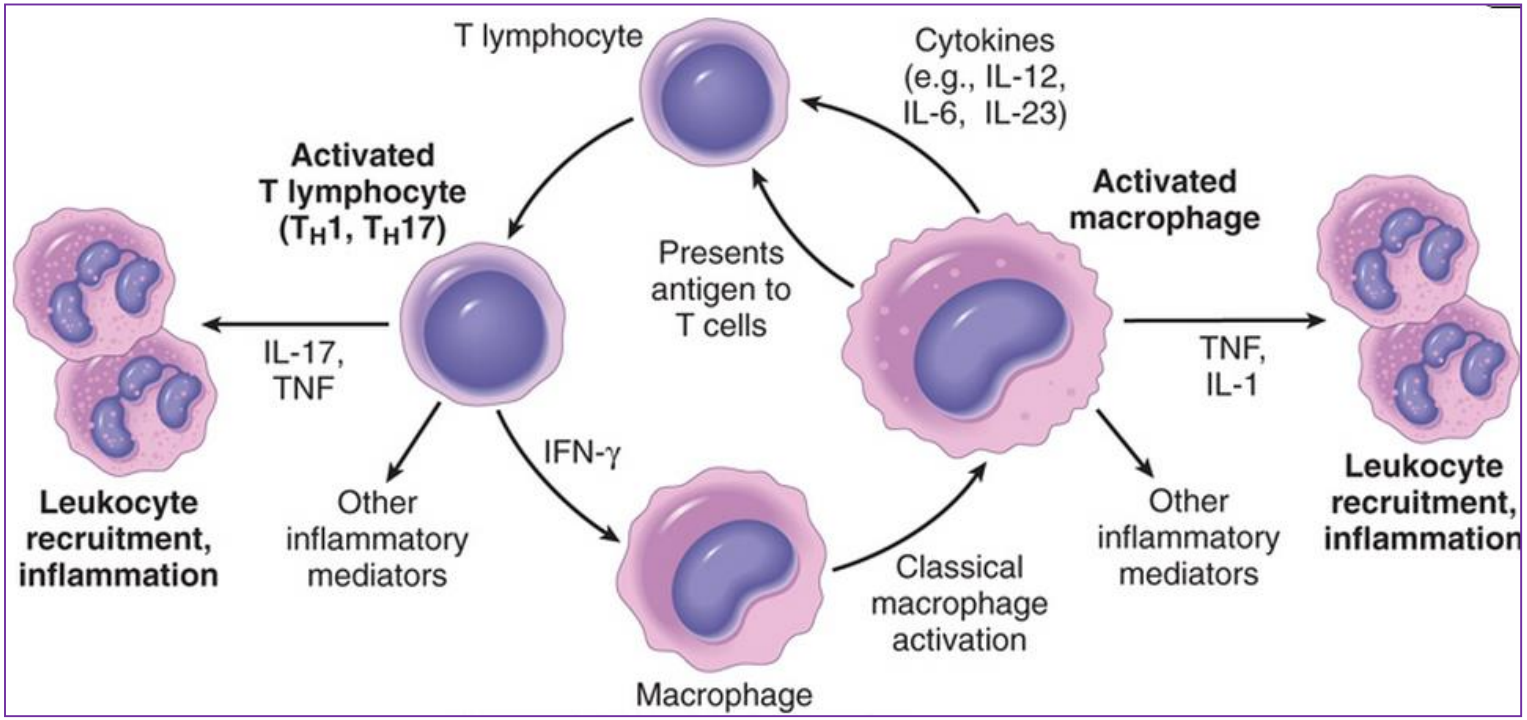
monocytes begin to emigrate into extravascular tissues quite – early in acute inflammation and within 48 hours they may constitute the predominant cell type

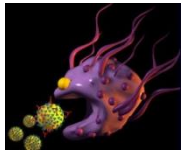


MONONUCLEAR CELL INFILTRATION

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

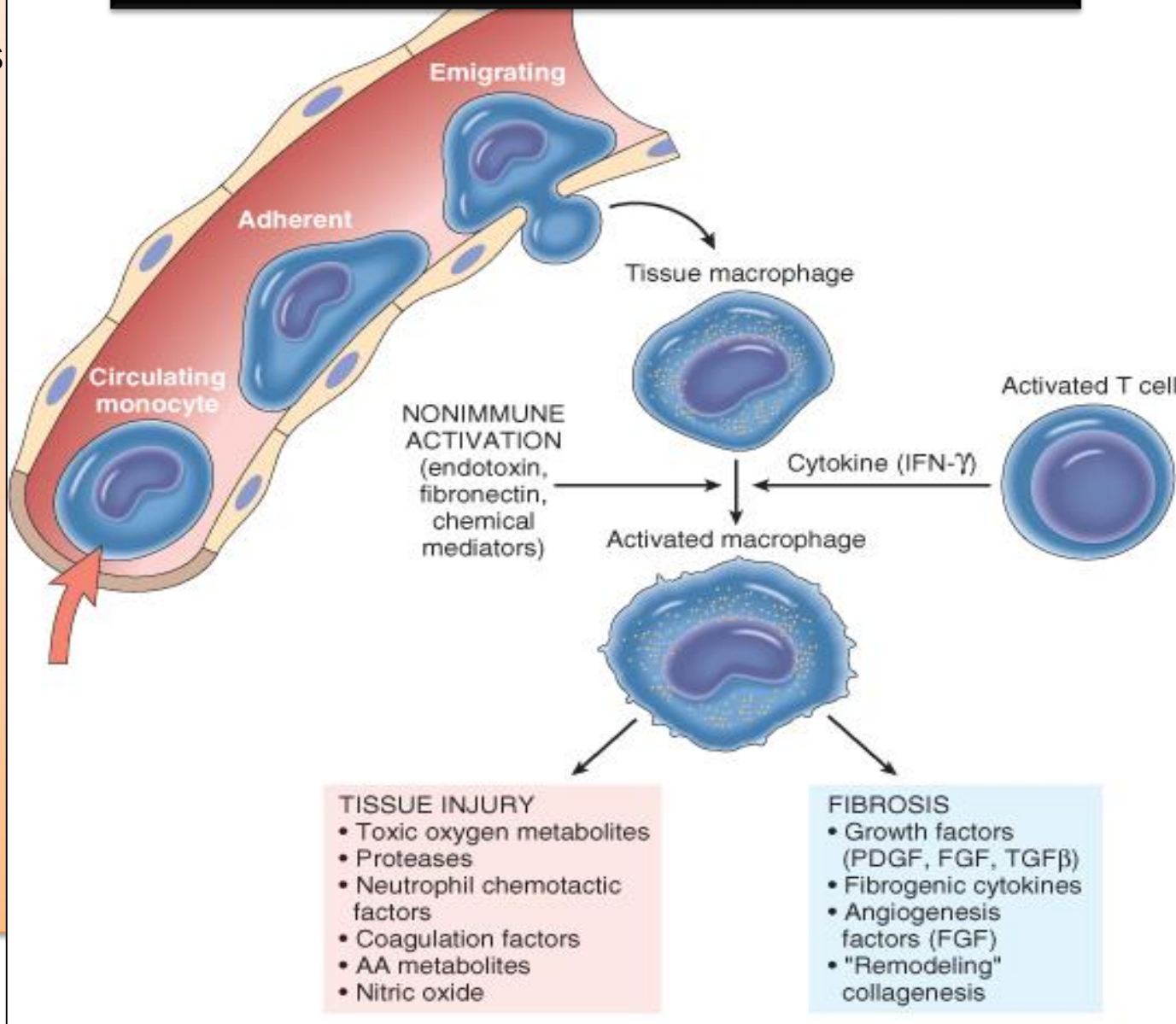




2. Different types of inflammatory cells accumulate in tissues

- 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

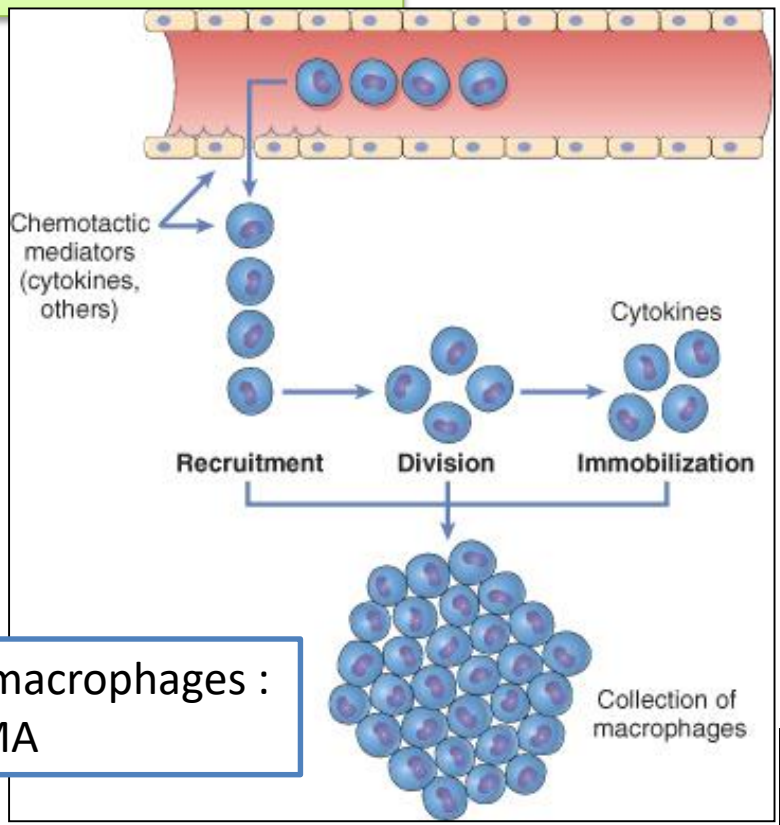
The roles of activated macrophages in chronic inflammation



Macrophages

- 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*

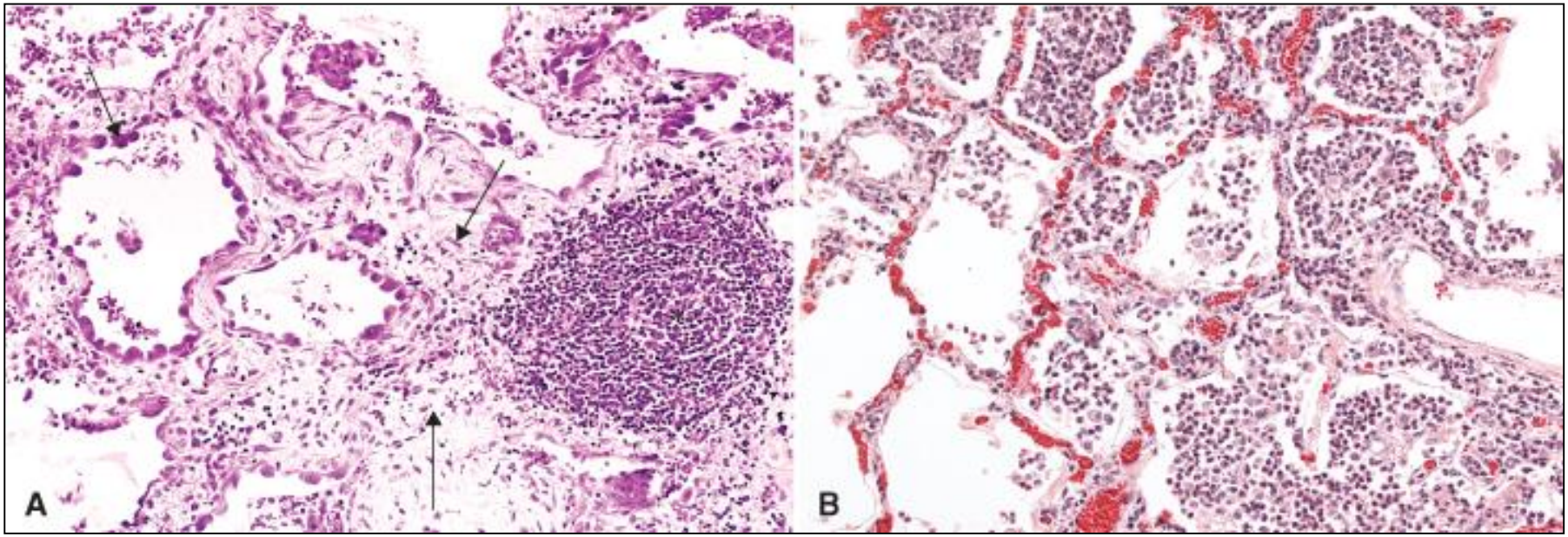


Collection of activated macrophages : GRANULOMA

CELLS IN CHRONIC INFLAMMATION

Lymphocytes

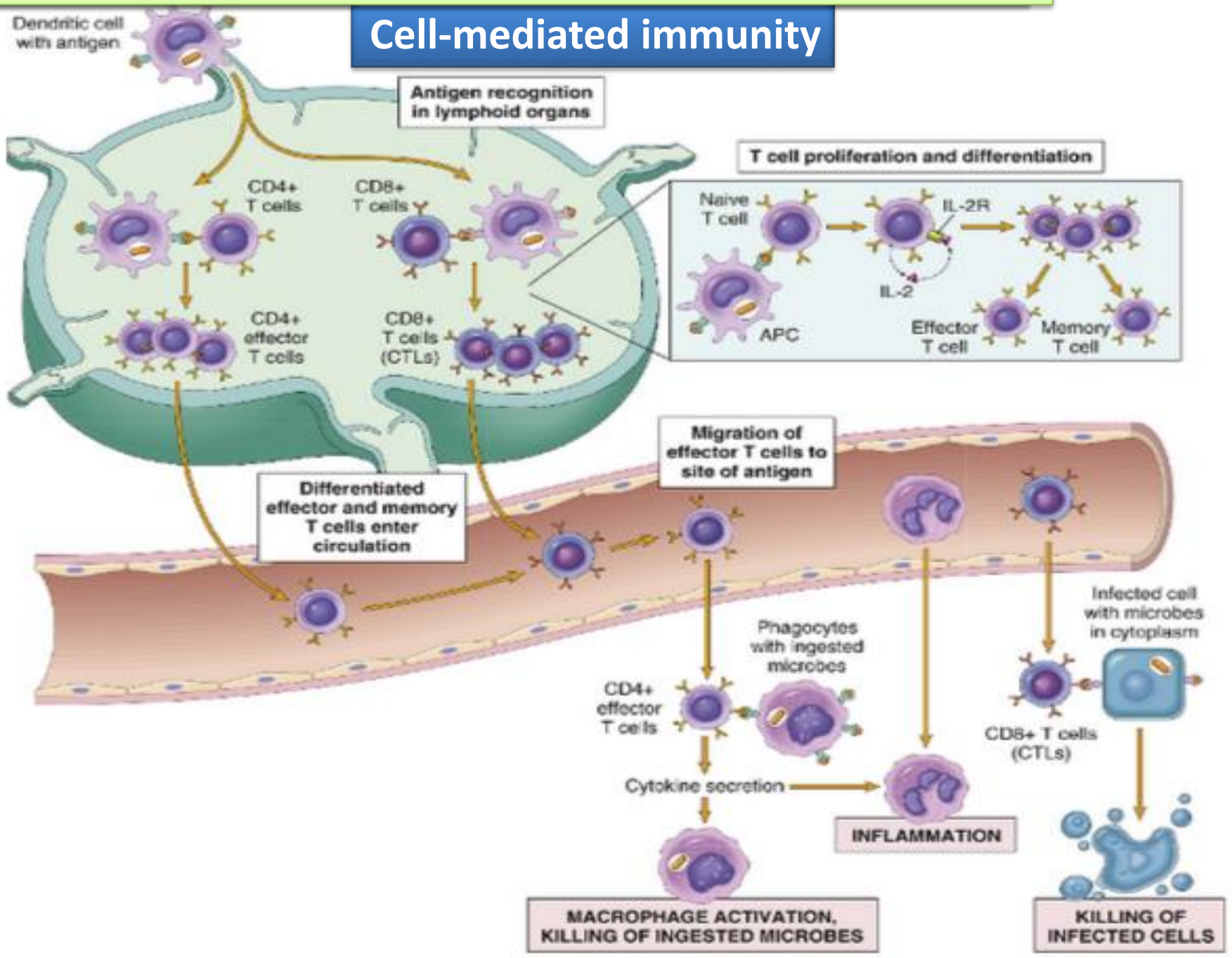
– ***Both T & B Lymphocytes migrates into inflammation site***



Lymphocytes

- B lymphocytes may develop into *plasma cells,* which secrete antibodies
- T lymphocytes are activated to secrete cytokines:
  - *CD4+ T lymphocytes promote inflammation and influence the nature of the inflammatory reaction*

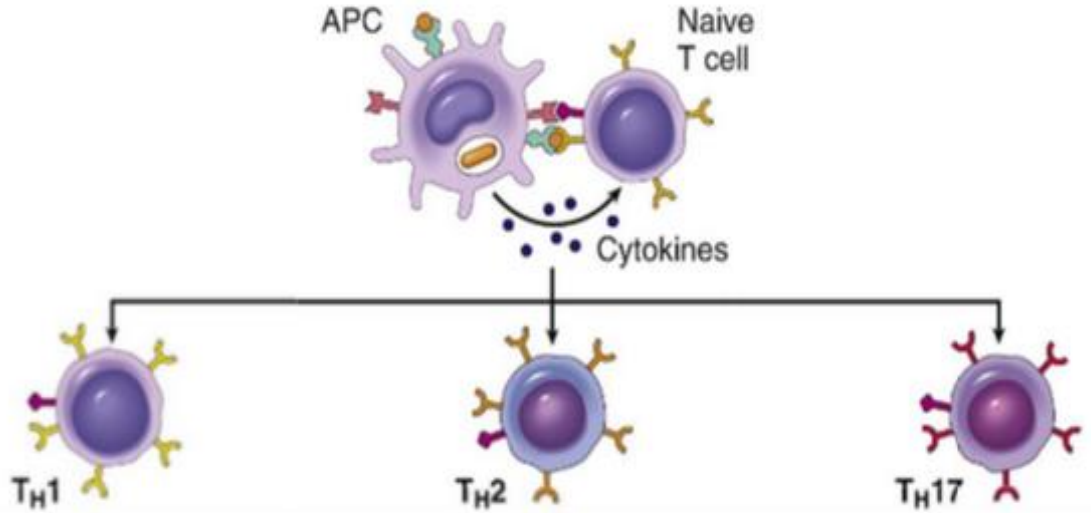
2. Different types of inflammatory cells accumulate in tissues



2. Different types of inflammatory cells accumulate in tissues

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.



	T_H1	T_H2	T_H17
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

CD4+ helper T cells

There are three subsets of CD4+ helper T cells :

- T_H1 cells produce the cytokine IFN-γ,

Function: activates macrophages in the classical pathway.

- T_H2 cells secrete IL-4, IL-5, and IL-13

Function: recruit and activate eosinophils and are responsible for macrophage activation.

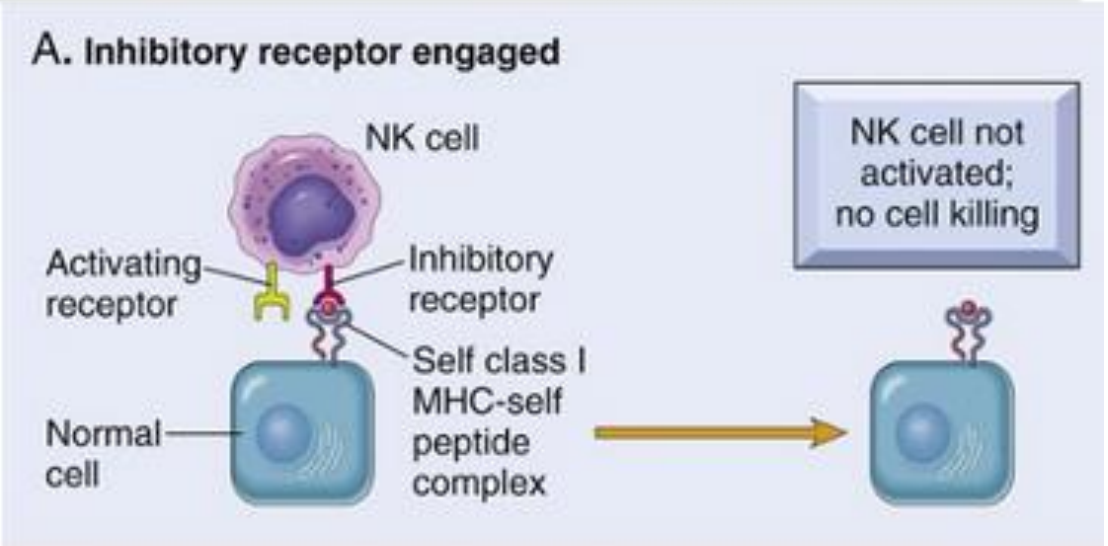
- T_H17 cells secrete IL-17 and other cytokines

Function: induce the secretion of chemokines responsible for recruiting neutrophils and monocytes into the reaction.

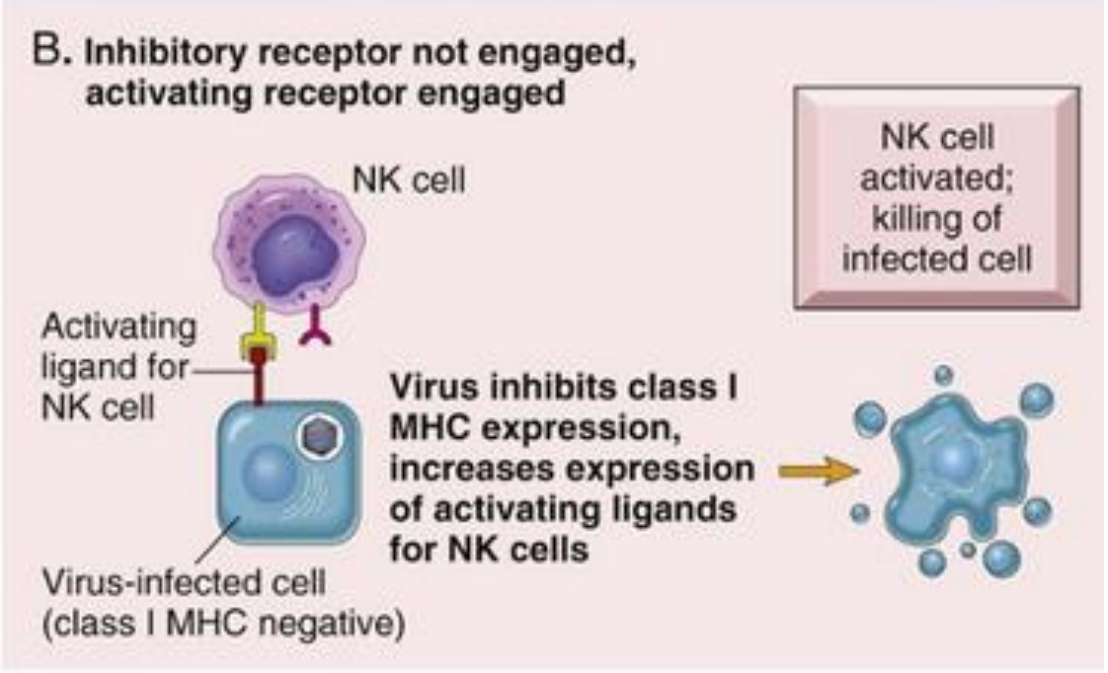
2. Different types of inflammatory cells accumulate in tissues

Activating and inhibitory receptors of natural killer (NK) cells

Healthy cells express self class I MHC molecules, which are recognized by inhibitory receptors, thus ensuring that NK cells do not attack normal cells.



In infected and stressed cells, class I MHC expression is reduced so that the inhibitory receptors are not engaged, and ligands for activating receptors are expressed.
The result is that NK cells are activated and the infected cells are killed.



2. Different types of inflammatory cells accumulate in tissues

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.

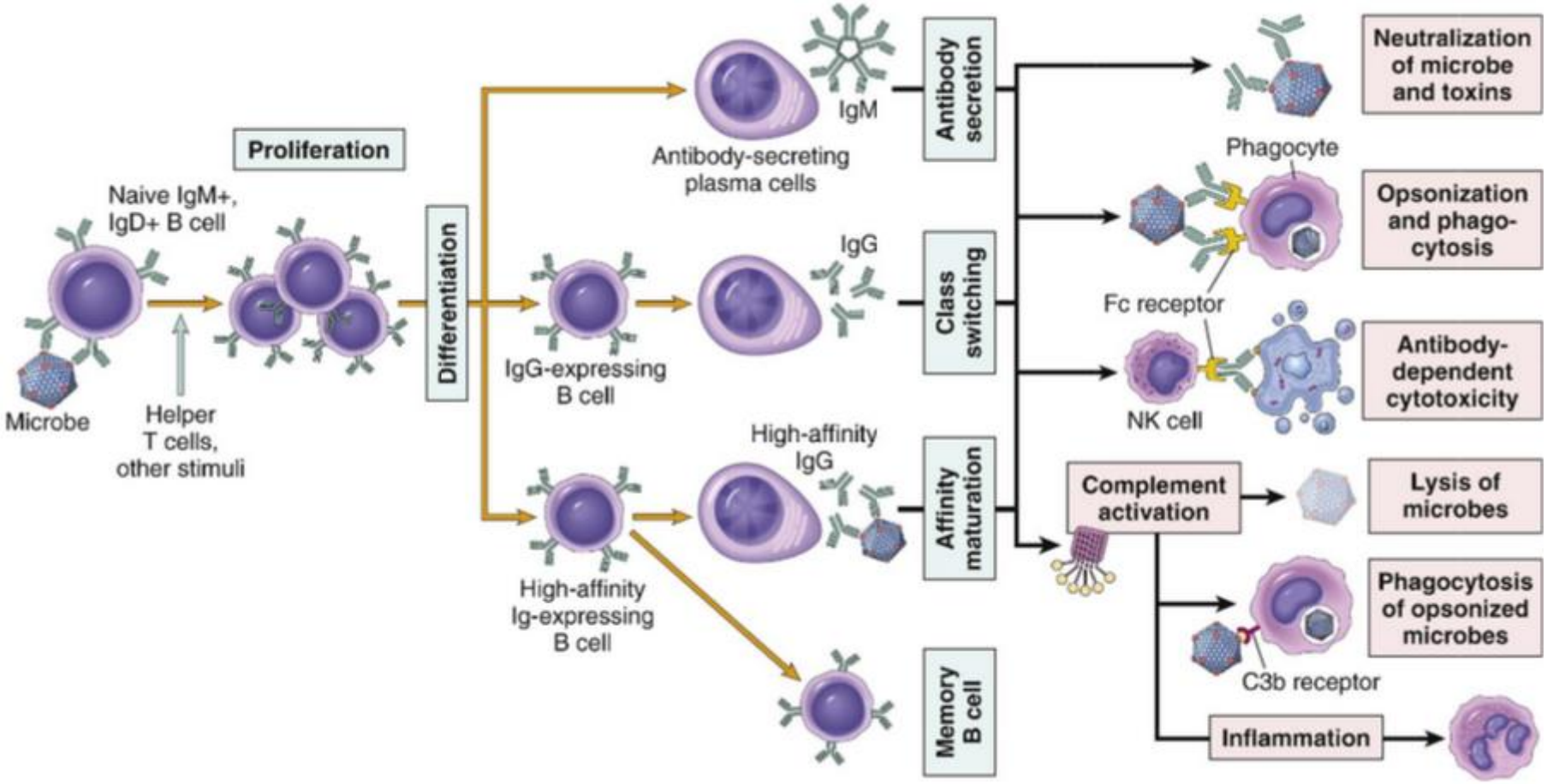
Some of the activated B cells undergo heavy-chain class switching and affinity maturation, and some become long-lived memory cells.

Antibodies of different heavy-chain classes (isotypes) perform different effector functions.

Note that the antibodies shown are IgG; these and IgM activate complement; and the specialized functions of IgA (mucosal immunity) and IgE (mast cell and eosinophil activation) are not shown.

2. Different types of inflammatory cells accumulate in tissues

Humoral immunity



OTHER CELLS IN CHRONIC INFLAMMATION

Plasma cells

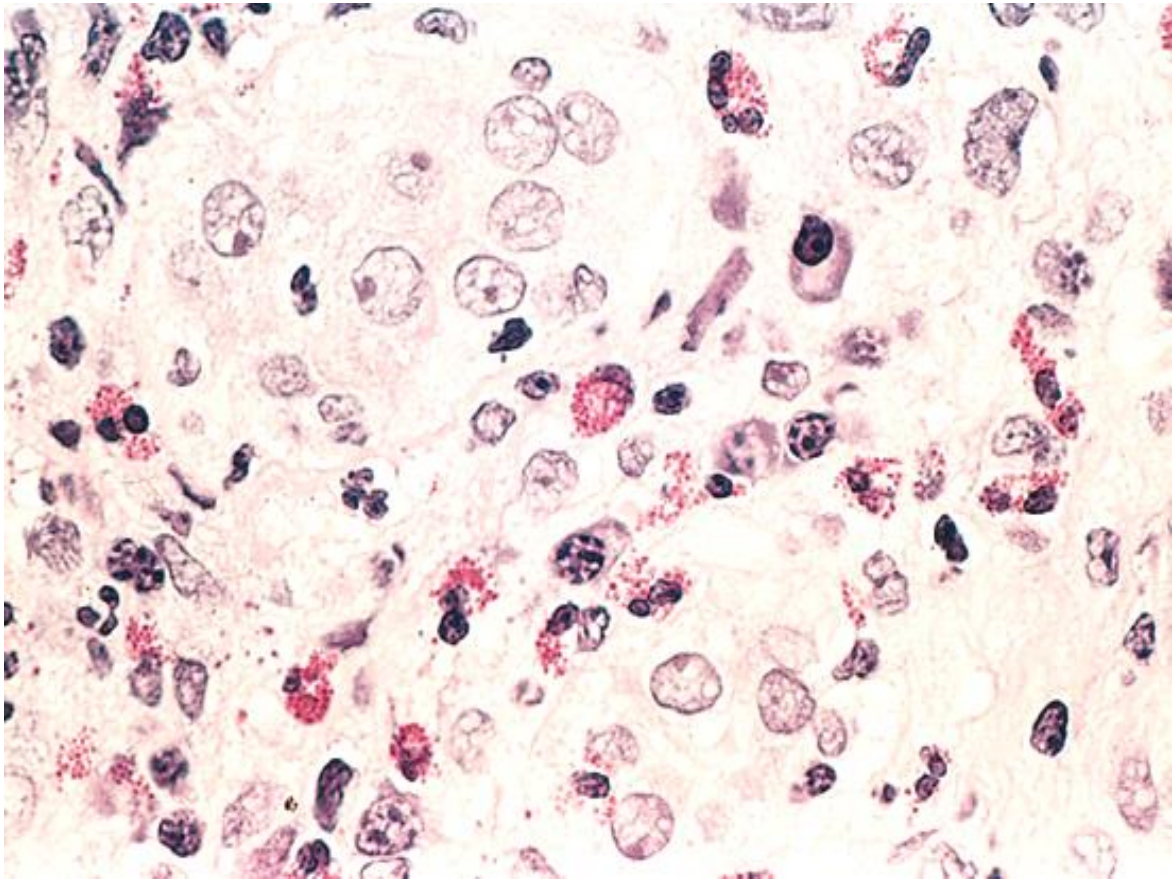
- **Lymphoid cell (Mature B cells)**
- **Common cell in chronic inflammation**
- **Primary source of antibodies**
- **Antibodies are important in inflammation e.g. neutralize antigen and clearance of foreign Ag**

2. Different types of inflammatory cells accumulate in tissues

Eosinophils

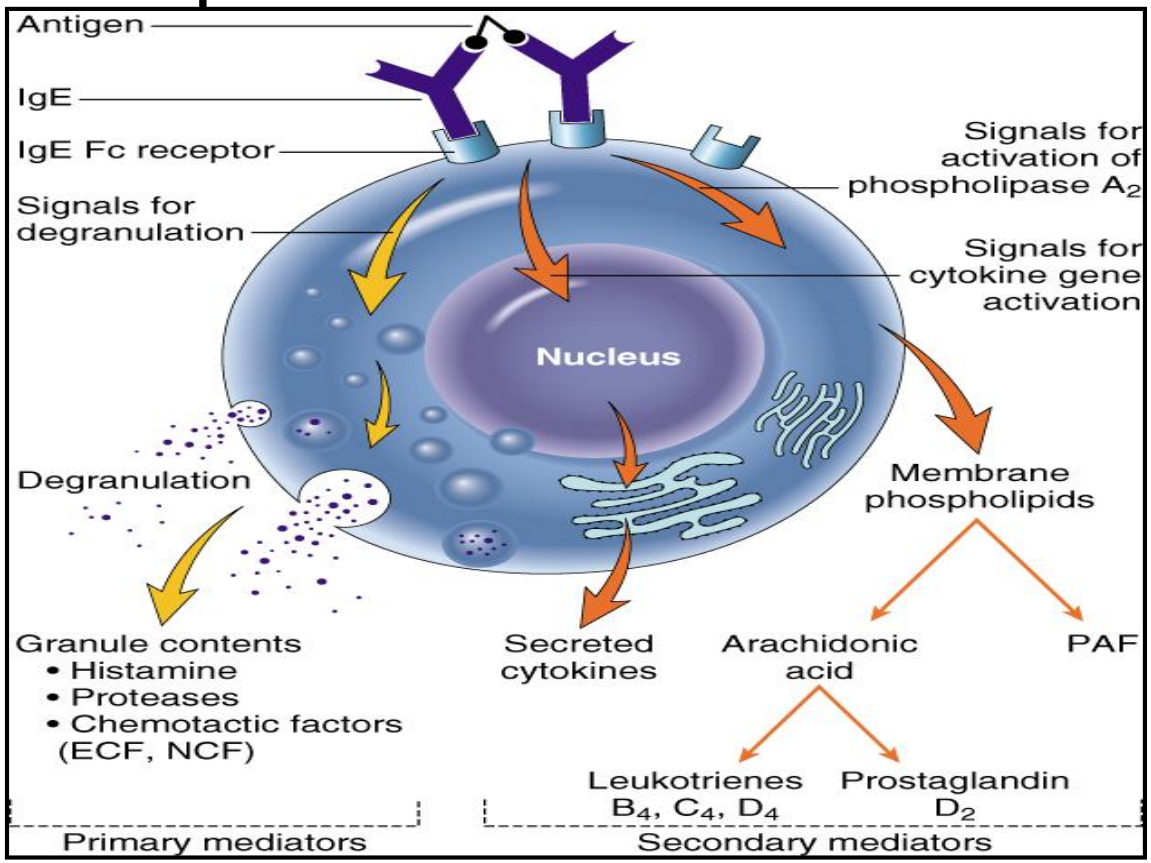
are abundant in immune reactions mediated by IgE and in parasitic infections

- 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



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

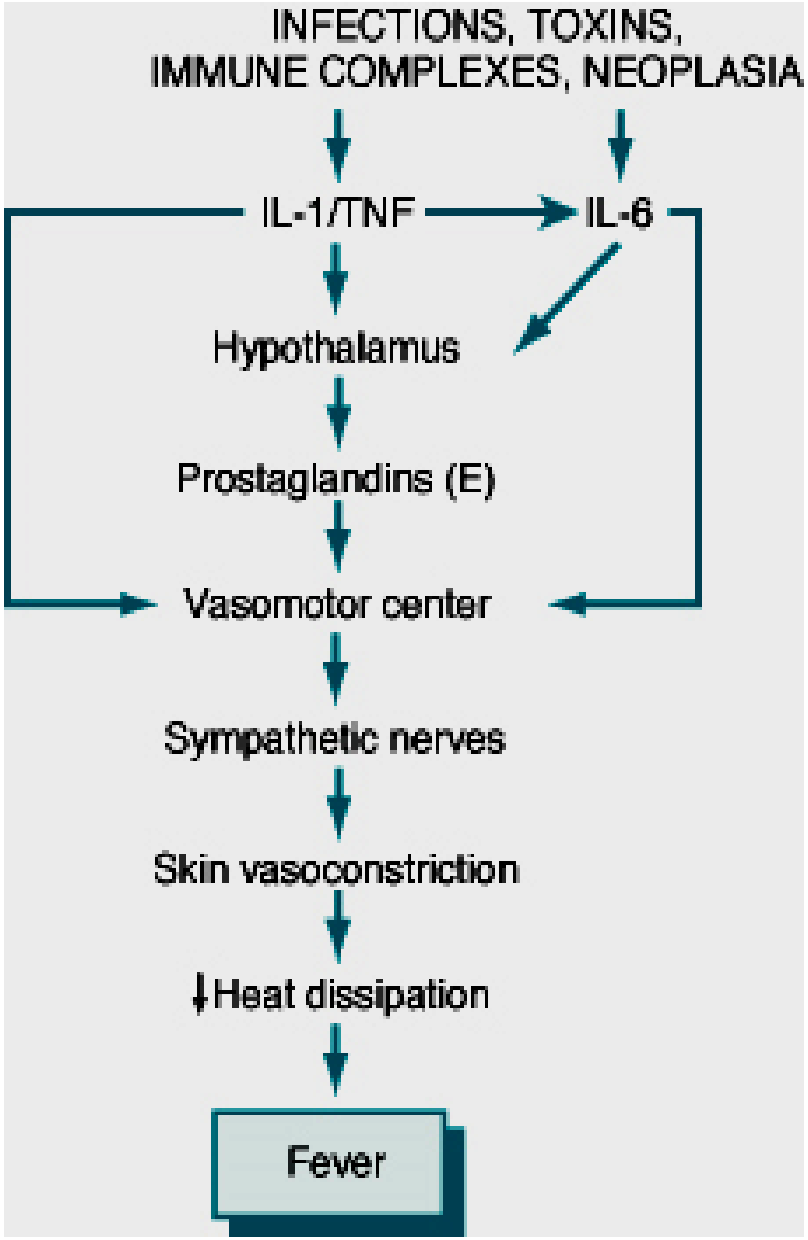
Fever
Produced in response to Pyrogens

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

Fever

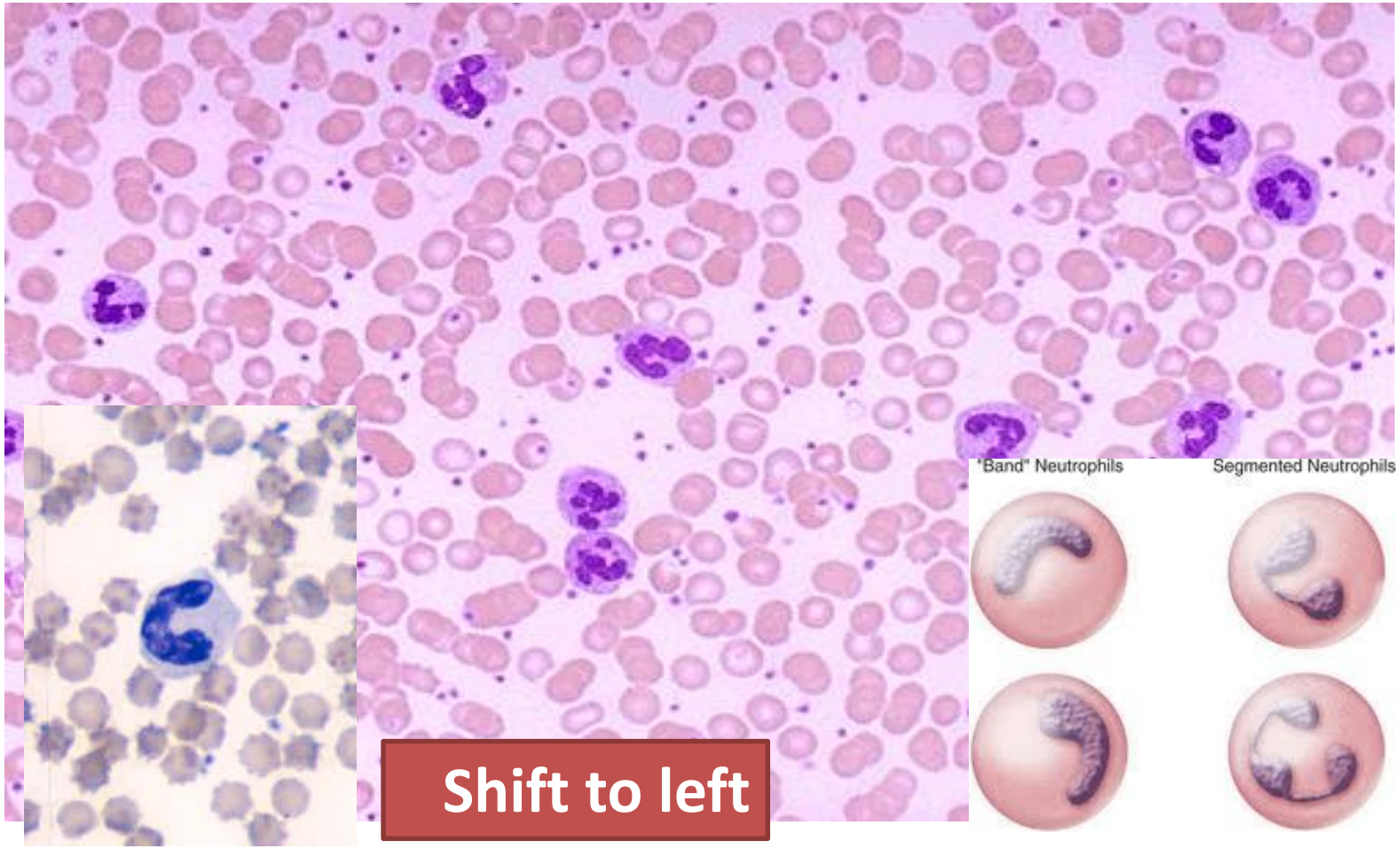
- In the hypothalamus, the prostaglandins, especially PGE_2, stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level.

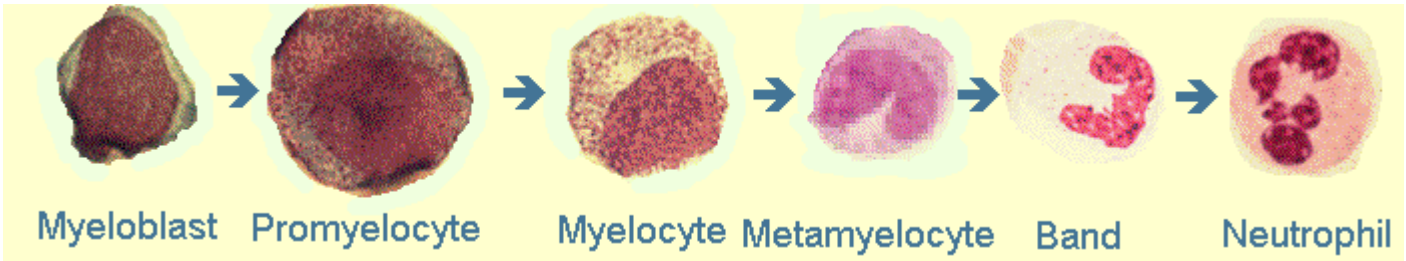
- NSAIDs, including aspirin , reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.



3. systemic manifestations of inflammation

Leukocytosis





Inflammation
Systemic Manifestations

Leukocytosis:

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

most bacterial infection (Neutrophil)

Lymphocytosis:

Infectious mononucleosis, mumps, German measles

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

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

Elevation of C reactive protein

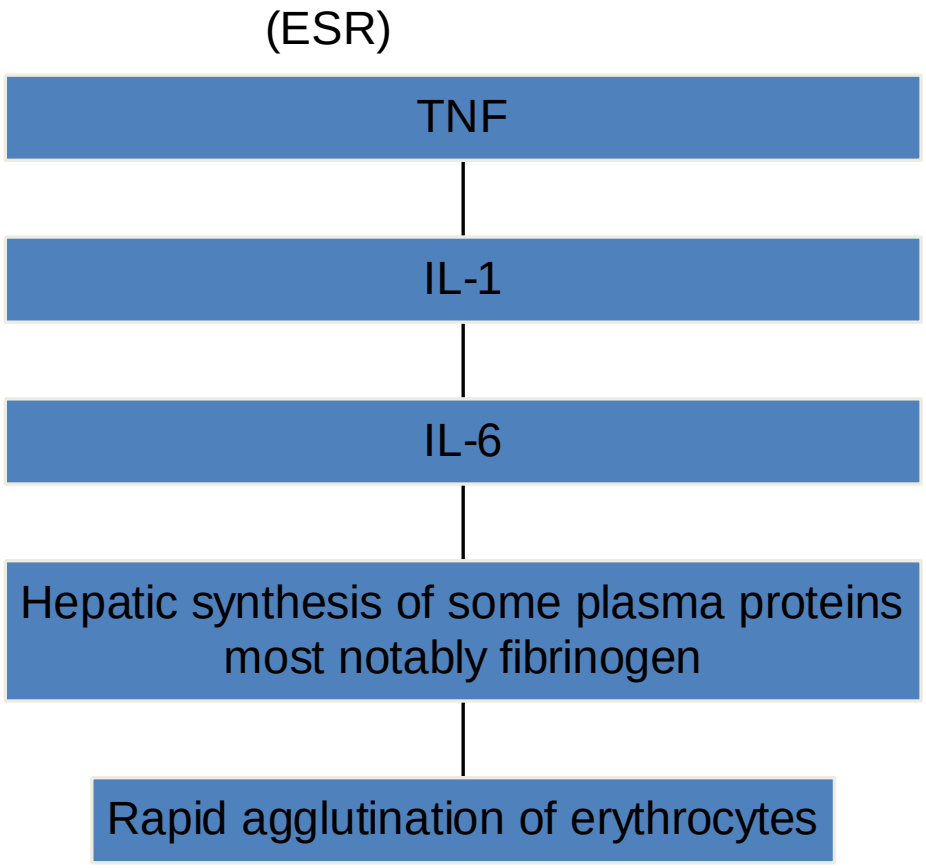
Acute Phase Proteins

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

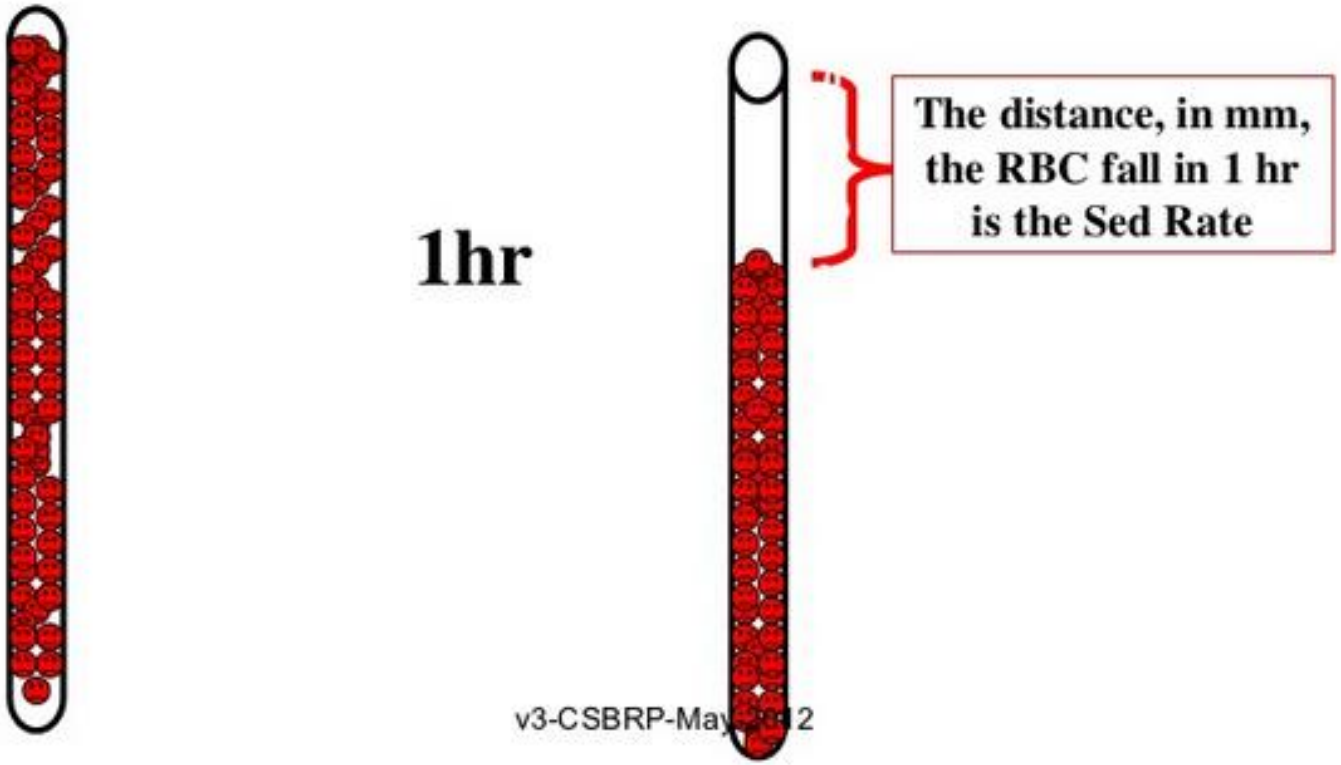
Detection of elevated levels of acute phase proteins is an indication of an inflammatory response

Increased erythrocyte sedimentation rate (ESR)

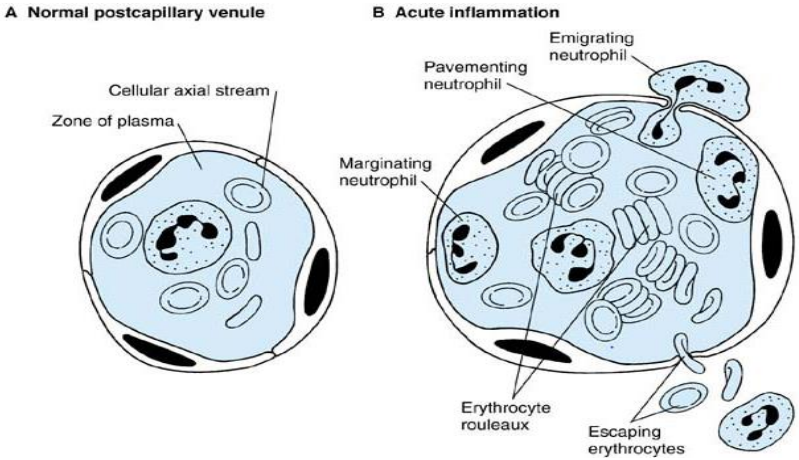
- The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes.



Erythrocyte Sedimentation Rate (ESR)



Erythrocyte sedimentation rate (ESR)



Summary

1. **Chronic inflammation is different from acute inflammation with respect to causes, nature of the inflammatory response, and tissue changes.**
2. **Different clinical settings associated with different types of inflammatory cells (eg, eosinophils, monocyte-macrophages, and lymphocytes) accumulate in the tissues.**
3. **The systemic manifestations of inflammation include fever, leukocyte left shift, and acute phase reactants.**

Cell-mediated immunity

Dendritic cells (DCs) capture microbial antigens from epithelia and tissues and transport the antigens to lymph nodes. During this process, the DCs mature, and express high levels of MHC molecules and costimulators. Naive T cells recognize MHC-associated peptide antigens displayed on DCs.
The T cells are activated to proliferate and to differentiate into effector and memory cells, which migrate to sites of infection and serve various functions in cell-mediated immunity.

CD4+ effector T cells of the TH1 subset recognize the antigens of microbes ingested by phagocytes, and activate the phagocytes to kill the microbes; other subsets of effector cells enhance leukocyte recruitment and stimulate different types of immune responses.

CD8+ cytotoxic T lymphocytes (CTLs) kill infected cells harboring microbes in the cytoplasm.

Some activated T cells remain in the lymphoid organs and help B cells to produce antibodies, and some T cells differentiate into long-lived memory cells.