

INFLAMMATION AND REPAIR

Lecture 4

Chronic inflammation & Systemic effect of inflammation

Editing File

Objectives:

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

Color Code:

Female's Notes

Male's Notes

Important

Extra



Define chronic inflammation:

Chronic inflammation :

It is **slow** evolving (weeks to months) resulting into fibrosis (تليف)

• essential changes of chronic inflammation:

01

Absence of polymorphs :

(e.g. neutrophils) due to its life span (1-3 days), replaced by macrophages, lymphocytes and plasma cells

02

Angiogenesis:

proliferation of vascular endothelium by "budding" (formation of new Tissue Injury capillaries)

03

Tissue Injury :

continuous injury of tissue and necrosis

04

Scarring (Fibrosis) :

Results from proliferation of fibroblasts with collagen production

Causes of chronic inflammation

1

1. Persistent infection by microbes that are difficult to eradicate

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

2

2. Prolonged exposure to potentially toxic agents

Nondegradable exogenous materials: inhaled particulate silica which can induce chronic inflammatory response in the lung (silicosis), e.g. **Asbestosis**
Endogenous agent: Cholesterol crystals, may contribute to **atherosclerosis.**

03

3. Hypersensitivity diseases (immune-mediated inflammatory diseases)

- **Autoimmune diseases:**
Rheumatoid arthritis
- **Inflammatory bowel disease**
- **Psoriasis** (الصدفية)
- **Allergic diseases:** results from excessive immune responses against common environmental substances such as bronchial asthma.

Other Examples:

- neurodegenerative disorders such as Alzheimer disease
- some forms of cancer in which inflammatory reactions promote tumor development, e.g. Chronic Bronchitis → Metaplasia (not precancerous) → Dysplasia (pre cancerous) → Cancer



Features of chronic inflammation

1

Infiltration with mononuclear (one nucleus) cells, including: Macrophages, Lymphocytes, Plasma cells

2

Tissue destruction, largely induced by the products of the inflammatory cells, such as ROS (reactive oxygen species)

3

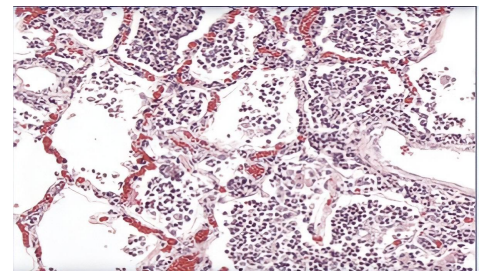
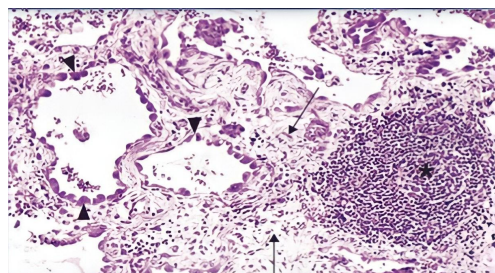
Repair, involving angiogenesis and fibrosis

it is characterized by a 3 different set of reactions:

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

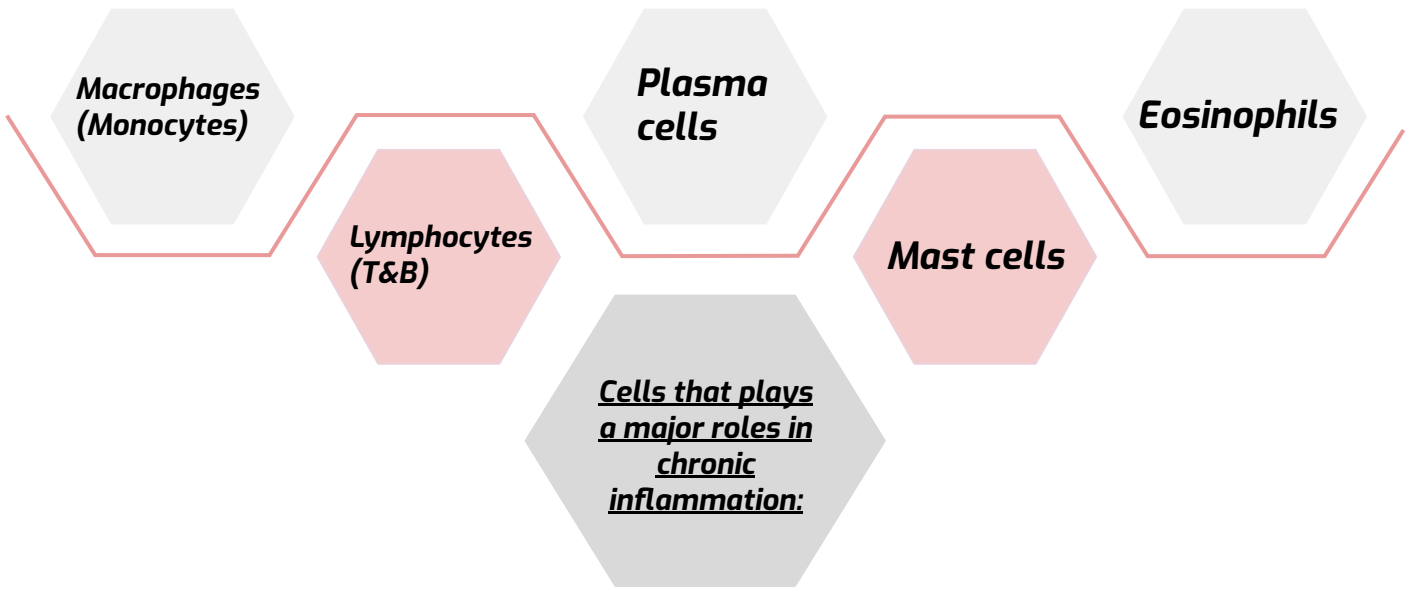
Lung **chronic** inflammation: i. Infiltration by lymphocytes ii. Angiogenesis iii. Fibrosis

Lung acute inflammation



Cells in Chronic Inflammation

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



macrophages

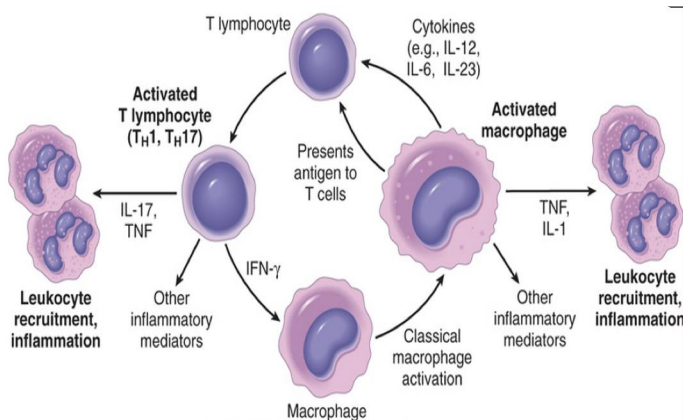
- Names of macrophages based upon their location

In blood = "Monocyte"	In tissue = "Macrophage"
Monocytes are likely to be seen in an inflammatory response to salmonella typhi infection.	Liver macrophages → kupffer cells
Under the influence of adhesion molecules and cytokines, monocytes migrates to the site of injury within 24-48 hours after the onset of acute inflammation.	Spleen and lymph node macrophages → sinus histiocytes
	Central nervous system macrophages → microglial cells
	Lung macrophages → alveolar macrophages



Features of Macrophages:

- It is the dominant cell in chronic inflammation.
- It is a developed monocyte.
- It secretes cytokines and growth factors that act on various cells.
- It destroys foreign invaders and tissues by activating other cells such as T lymphocytes.



Macrophages are **activated** by various stimuli including:

1. **Cytokines** (e.g. **IFN- γ**) secreted by sensitized T lymphocytes and natural killer (NK) cells
2. **Bacterial endotoxins**

Elimination of injurious agents such as microbes

Responsible for majority of **tissue injury**

Initiation the process of repair

Displaying antigens to T lymphocytes and responding signals from T cells, thus setting up a feedback loop

Secretion of inflammation mediators such as cytokines (TNF, IL-1, Chemokines, Eicosanoids)

The roles of activated macrophages in chronic inflammation:

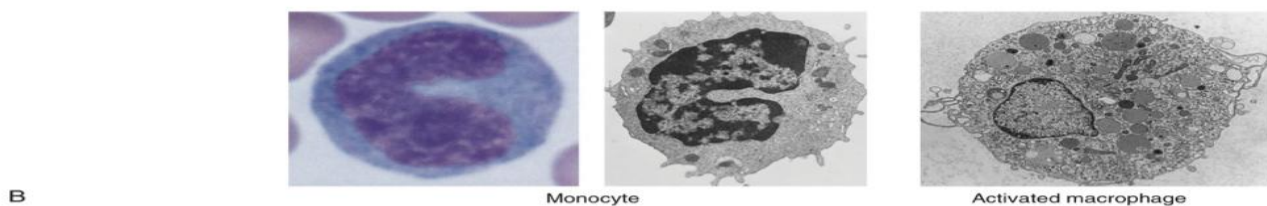
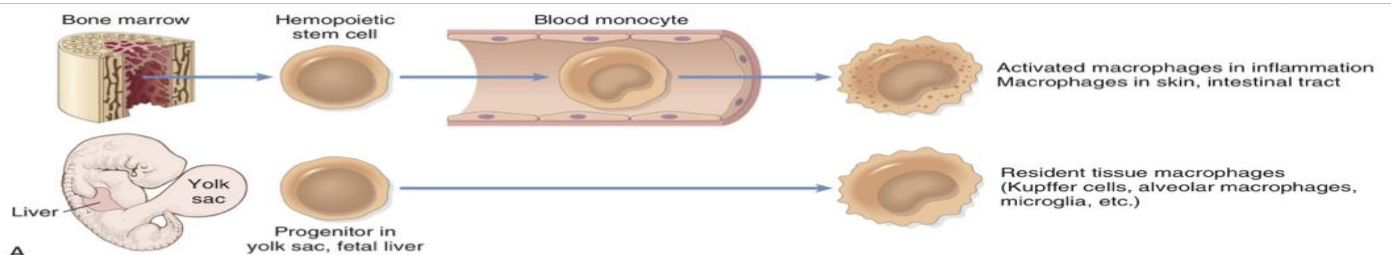
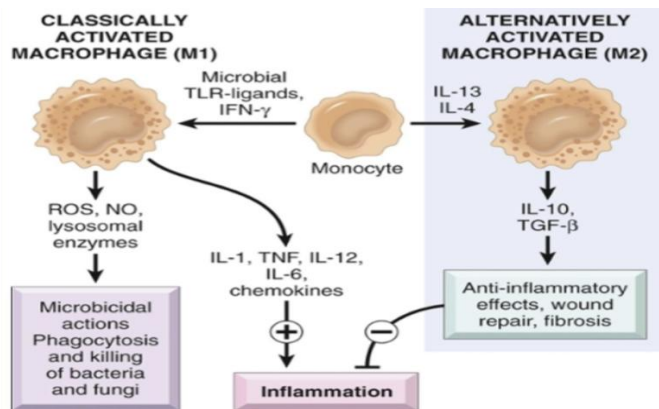


Fig. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, the majority of tissue macrophages are derived from hematopoietic precursors. Some long-lived resident tissue macrophages are derived from embryonic precursors that populate the tissues early in development. (B) The morphology of a monocyte and activated macrophage.

Role of Macrophages Cont.



In some instances, if the irritant is *eliminated*, macrophages eventually *disappear* (either dying of or making their way via lymphatics into the lymph nodes).

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

1. **Continuous recruitment** of monocytes from the circulation
2. **Local proliferation** of macrophages at the site of inflammation
3. **Immobilization of macrophages**

A collection of activated macrophages is known as a **granuloma**

Lymphocytes:

Role of Lymphocytes:

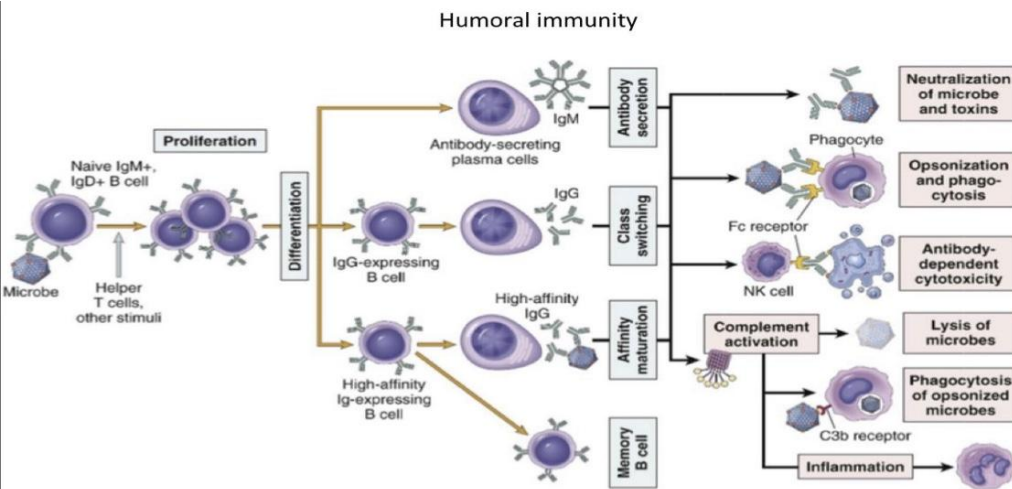
- Both T and B lymphocytes migrate into inflammation sites, **It is most commonly seen in chronic inflammation** (because when they're activated inflammation tends to be severe and persistent).
- **Role:** mediators of adaptive immunity which provide defense against infectious pathogens.

T lymphocytes

- Are activated to secrete cytokines.
- CD4+ Helper T lymphocytes promote inflammation and influence the nature of the inflammatory reaction.
- 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.

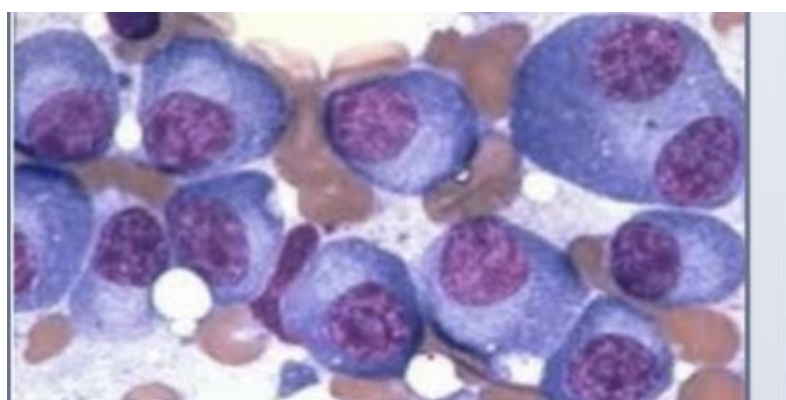
B lymphocytes

- **Function:** Humoral immunity
- Naive/immature B lymphocytes recognize antigens.
- Under the influence of **TH cells** and other stimuli, the **B Cells** are activated to proliferate and to differentiate into antibody-secreting **plasma cells**.



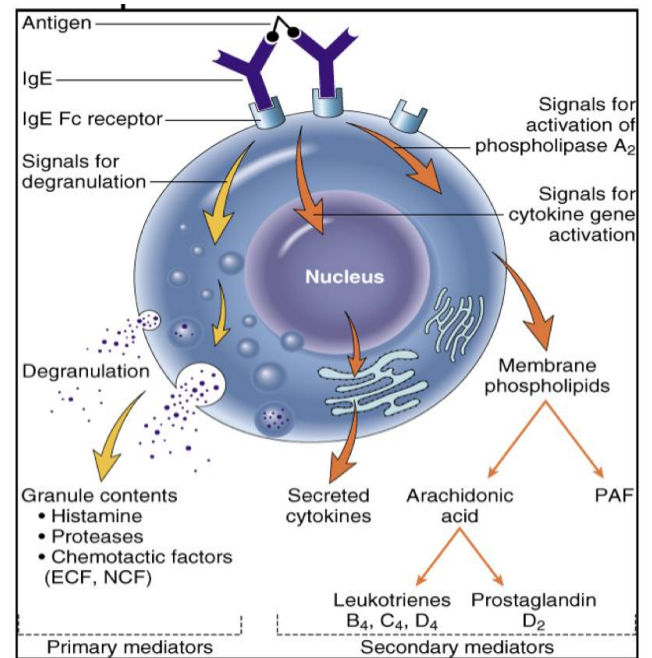
Role of plasma cells

- **Lymphoid cells** (Mature B cells)
- Common cell in chronic inflammation
- **Primary source of antibodies** (immunoglobulins)
- Antibodies are important in inflammation e.g. Neutralize antigen and clearance of foreign antigen.
- **Morphology of Plasma cells:**
 - Eccentric nucleus (not circular or placed centrally)
 - Shows a cartwheel/clock face pattern of nuclear chromatin with a perinuclear halo.



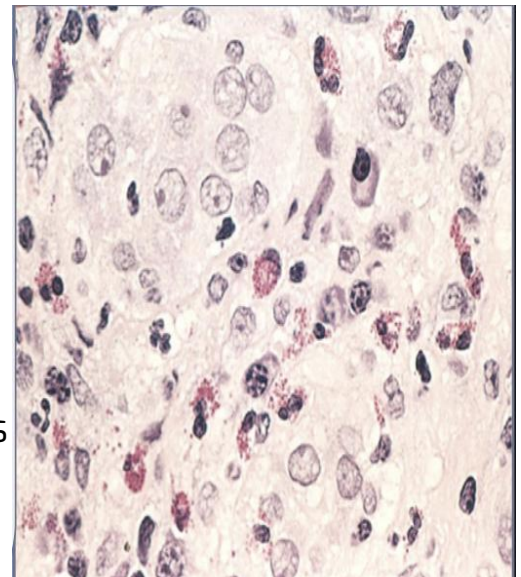
Role of mast cells

- First cell to release its content and induce inflammation
- Widely distributed in connective tissues
- participates in both acute and chronic inflammatory reactions.
- Express on their surface the receptor that binds to the **FC** portion of **IgE** antibody
- Degranulate and release mediators, such as histamine and products of AA oxidation.



Role of Eosinophils

- Abundant in immune reactions involving allergies and parasitic infections mediated by IgE.
- Respond to chemotactic agents derived largely by mast cells
- A granular cell (reddish, acidophilic, has 2 lobes) that contains **major basic protein** that is toxic to parasites and leads to the **lysis** of mammalian epithelial cells



IgE (immunoglobulin E)- is a type of antibody secreted by plasma cells

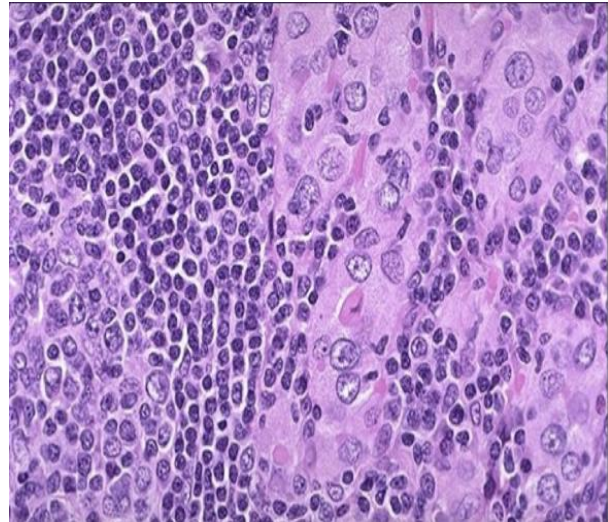
Patterns of Chronic Inflammation

01 Chronic **nonspecific** inflammation
Non specific = Granulation tissue.

Features of chronic inflammation:

→ **Foreign material**, e.g. silicates, including asbestos

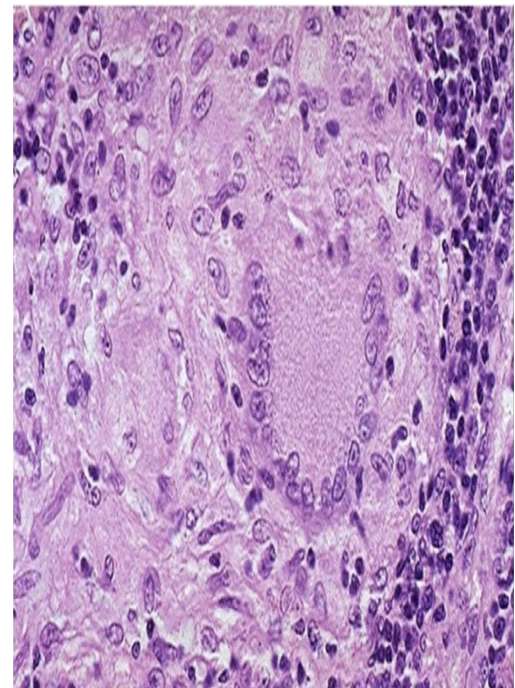
→ **Autoimmune diseases**, e.g. autoimmune thyroiditis



02 Chronic **Granulomatous** inflammation
Specific =: Granulomatous inflammation (granulomas are present)

A type of chronic inflammation in which there is an accumulation of modified macrophages (epithelioid cells) in small clusters surrounding lymphocytes.

Reminder: a collection of macrophages is known as **granuloma** Example: tuberculosis **Note:** Granuloma in the lung is a specific diagnosis of TB



Systemic effects of Inflammation

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

Fever Produced in response to Pyrogens

Types of Pyrogens:

1

Exogenous pyrogens: Bacterial products

2

Endogenous pyrogens: Interleukin 1 (IL1) and Tumour necrosis factor(TNF)

1st

Bacterial products stimulate leukocytes to release cytokines such as IL-1 and TNF

2nd

that increase the enzymes (cyclooxygenases)

3rd

that convert AA into prostaglandins

Chemical mediators which are the inducing cause of fever are:

1. IL-1
2. TNF
3. Prostaglandins

Fever

1

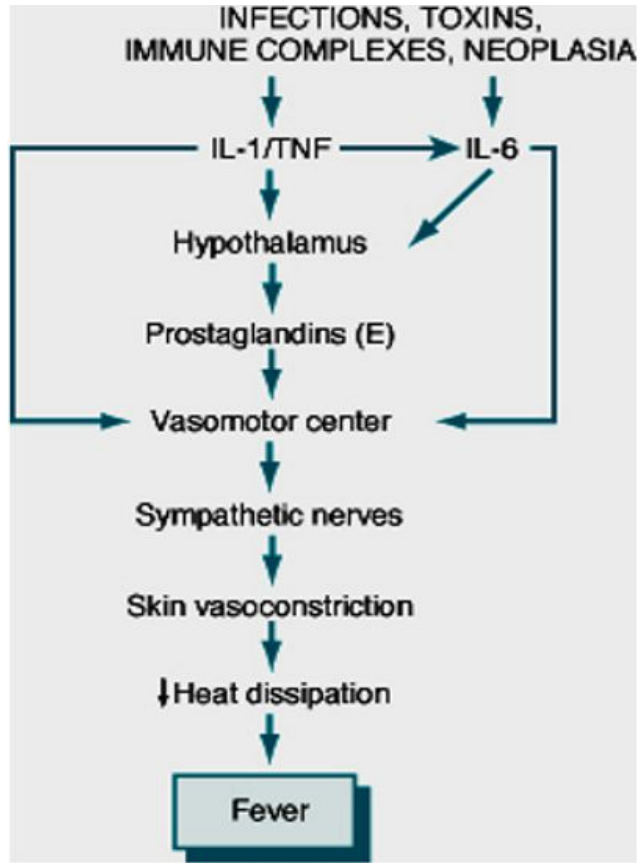
In the hypothalamus, the prostaglandins, especially PGE2

2

stimulate the production of neurotransmitters such as cyclic AMP

3

Which function to reset the temperature set-point at a higher level



4

NSAIDs, including aspirin reduce fever

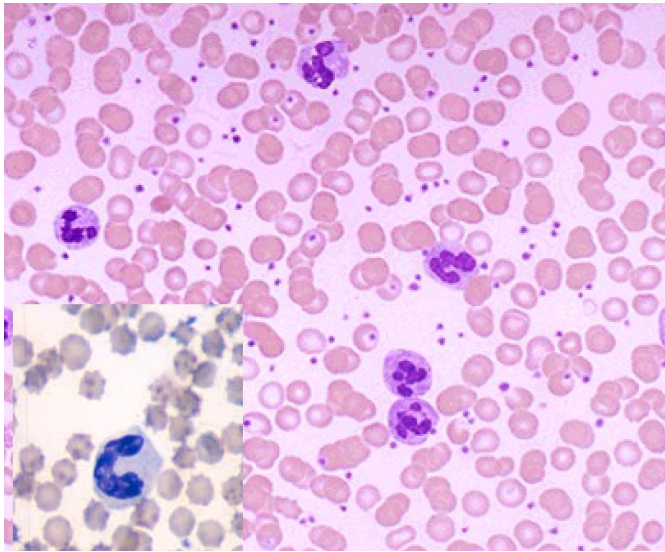
5

By inhibiting cyclooxygenase

6

And thus blocking prostaglandin synthesis

Leukocytosis



"Band" Neutrophils

Segmented Neutrophils



Shift to left



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)
 α -2 macroglobulin
Haptoglobin
Ceruloplasmin
fibrinogen

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

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

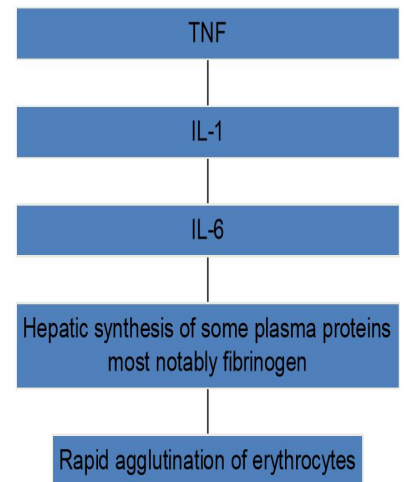
Prolonged production of these proteins (especially SAA) in states of chronic inflammation can cause: secondary amyloidosis

Erythrocyte sedimentation rate (ESR)

Increased erythrocyte sedimentation rate (ESR)

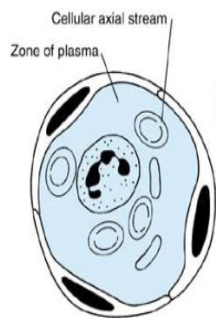
The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes.

(ESR)

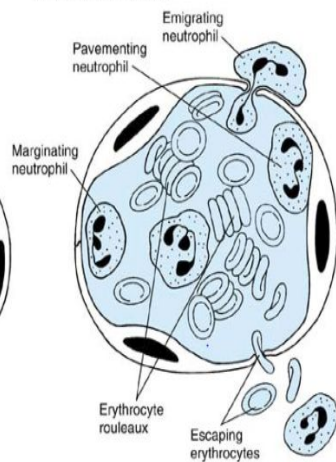


Erythrocyte sedimentation rate (ESR)

A Normal postcapillary venule



B Acute inflammation



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

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



Erythrocyte Sedimentation Rate (ESR)



1hr



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

A 40-year-old woman had bilateral silicone breast implants placed two years ago. Since that time, she has noted increased firmness with slight deformity of the breast on the left. The implants are removed, and there is evidence for leakage of the implant contents on the left. Which of the following cell types is most likely to be most characteristic of the inflammatory response in this situation?

Mast cell	Eosinophil	Giant cell	Neutrophil
-----------	------------	------------	------------

A 40-year-old woman has had a chronic cough with fever and weight loss for the past month. A chest radiograph reveals multiple nodules from 1 to 4 cm in size, some of which demonstrate cavitation in the upper lobes. A sputum sample reveals the presence of acid fast bacilli. Which of the following cells is the most important in the development her lung lesions?

Neutrophil	Macrophage	Mast cell	Platelet
------------	------------	-----------	----------

An experiment, *Enterobacter cloacae* organisms are added to a solution containing leukocytes. Engulfment and phagocytosis of the microbes is observed to occur. Next a substance is added which enhances engulfment. Which of the following substances is most likely to produce this effect?

Complement C3b	immunoglobulin M	NADPH oxidase	P-selectin
----------------	------------------	---------------	------------

1-Chemical mediator which is the inducing cause of fever are:

A) Prostaglandin	B) TNF	C) IL-1	D) All of them
------------------	--------	---------	----------------

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

A) C-reactive protein (CRP)	B) Haptoglobin	C) Fibrinogen	D) None
-----------------------------	----------------	---------------	---------

3- AS a exogenous pyrogens

A) Bacterial products	B) TNF	C) IL-1	D) All
-----------------------	--------	---------	--------

Q4) *kupffer cells are located in the*

A) liver	B) Spleen	C) CNS	D) Lungs
----------	-----------	--------	----------

Q5) *B&T lymphocytes are most commonly seen in acute inflammation ?*

A) true	B) false		
---------	----------	--	--

Q6) *a collection of macrophages is known as*

A) lymphocytes	B) granuloma	C) epithelioid cells	D) immunoglobulins
----------------	--------------	----------------------	--------------------

"I never dreamt of success. I worked for it." -Este Lauder



Leaders:

Lama Al-Jamili

Salem Abokhanjar

Sub-Leader:

Manar Al-Abdullah

Members:

Lama Bin Salamh
Rahmah Alzahrani
Noyer Awad
Rahaf alamri
Layan Alhelal
Taif alshehri
Renad Aldawayan
laila almeshariy
Alanoud Albawardi
Reema Alrashedi

Shouq Alhathal
Tarfa albaz
Jumana AL-qahtani
Lama Alrumaih
Ayah Sayed
Shahad Helmi
Norah Alsewailem
Leen Alhadlaq
Arwa Alenzi
Reem Al Kulaibi

Mohammed Alwahibi
Sultan Alosaimi
Rakan alobaid
Abdullah Abdulrazaq
Ibrahim Al Hazza
Nawaf Alzaben
Abdelaziz Alabdulraman

Organizer:

Aya Alhossain
Abdulmajeed Namshah

➤ Made by