جامعة الملك سعود
King Saud University

pathology
MED 439

MED439
KING SAUD UNIVERSITY

Inflammation and Repair L4

ربّي فهّمني، ألهمني..نور دربي.. بارِك في أوقاتي..
يسّر لي علمي .. احفظ لي ما تعلمت .. ذكرني ما نسيت ..
وانفعني بالعلم

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 Index:
Girl's Slides
Important
Male's Notes
Female's Notes
Extra information

Chronic Inflammation

Chronic inflammation

Is a response of prolonged duration in which inflammation, tissue Injury, and attempts at repair Coexist, in varying combinations

➔ It is a **slowly** evolving (weeks to months) type of inflammation that results in **fibrosis.**

➔ **Long** duration is a major factor leading to chronic inflammation.

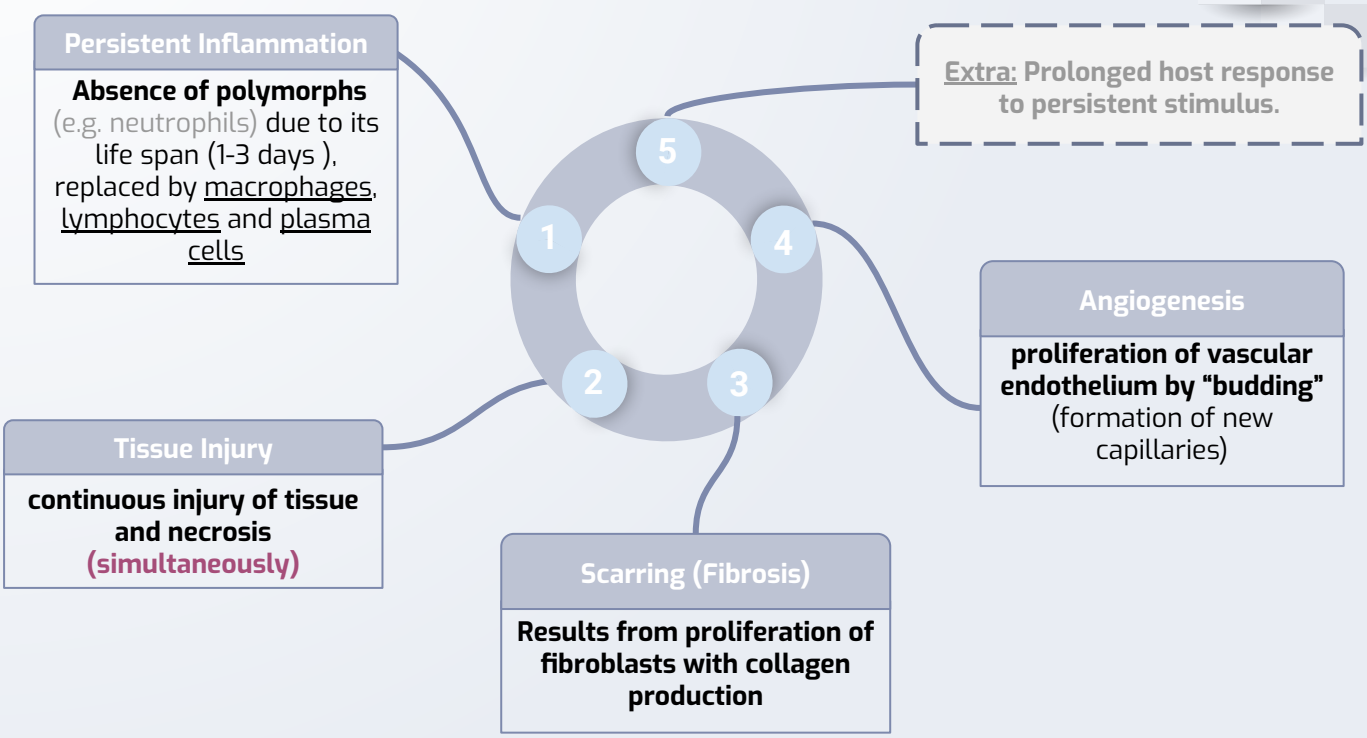
Extra information	Acute inflammation	Chronic inflammation
Cells	**Neutrophils** **Eosinophils** **Mast cells**	**Lymphocytes** **Plasma cells** **macrophages**
Nucleus	**Lobulated**	**Mononucleated- non lobular**
Duration	**Days to weeks**	**Months to years**

Note:

Macrophages are found in **both acute and chronic**, but are **increased at the end of acute inflammation**.

Chronic Inflammation

Features/ essential changes of chronic inflammation:



Causes of Chronic Inflammation

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. 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.

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

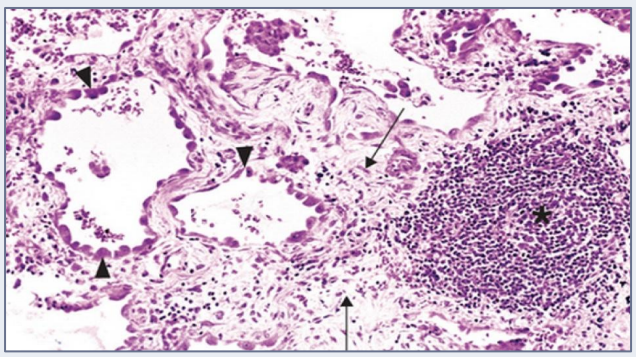
Chronic Inflammation

Chronic inflammation is characterized by a set of 3 different reactions:

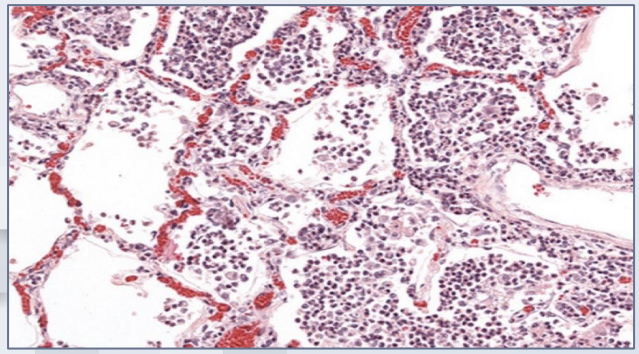
1. **Infiltration with mononuclear** (one nucleus) **cells**, including: Macrophages, Lymphocytes, Plasma cells
2. **Tissue destruction**, largely induced by the byproducts of the inflammatory cells, such as ROS (reactive oxygen species)
3. **Repair**, involving angiogenesis and fibrosis

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

Angiogenesis: A physiological process through which new blood vessels form from pre-existing vessels.



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



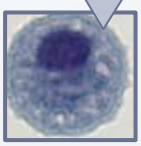
Lung **acute** inflammation

Cells in Chronic Inflammation

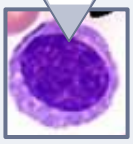
Complex interactions occur between several cell populations and their secreted mediators. It is mediated by the interaction of monocyte/macrophages with T and B lymphocyte, plasma cells and others

Cells that plays a major roles in chronic inflammation:

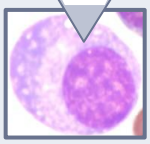
1. **Macrophages (Monocytes)**



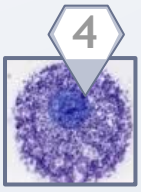
2. **Lymphocytes (T&B)**



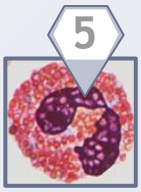
3. **Plasma cells**



4. **Mast cells**



5. **Eosinophils**



Role 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.

Names of macrophages based upon their location

In blood = "**Monocyte**"

- Monocytes are likely to be seen in an inflammatory response to **salmonella typhi infection.**
- Under the influence of adhesion molecules and cytokines, monocytes migrate to the site of injury within **24-48** hours after the onset of acute inflammation.

In tissue = "**Macrophage**"

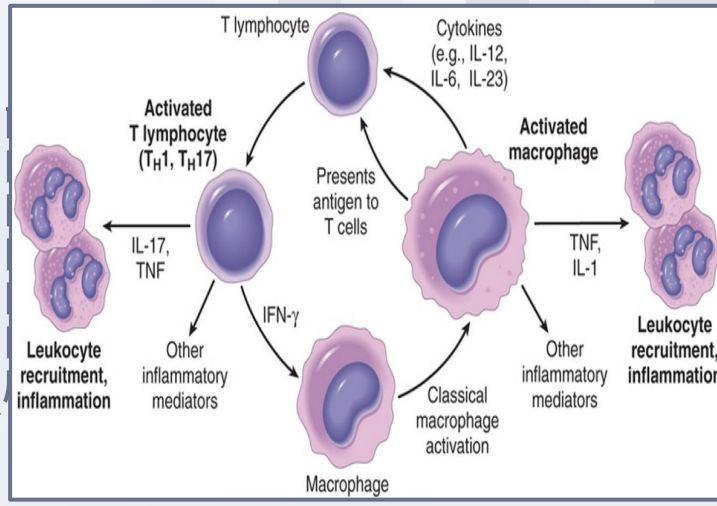
1. Liver macrophages → **kupffer cells**
2. Spleen and lymph node macrophages → **sinus histiocytes**
3. Central nervous system macrophages → **microglial cells**
4. Lung macrophages → **alveolar macrophages**

Cells in Chronic Inflammation

Role of Macrophages Cont.

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**



The roles of activated macrophages in chronic inflammation:

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)

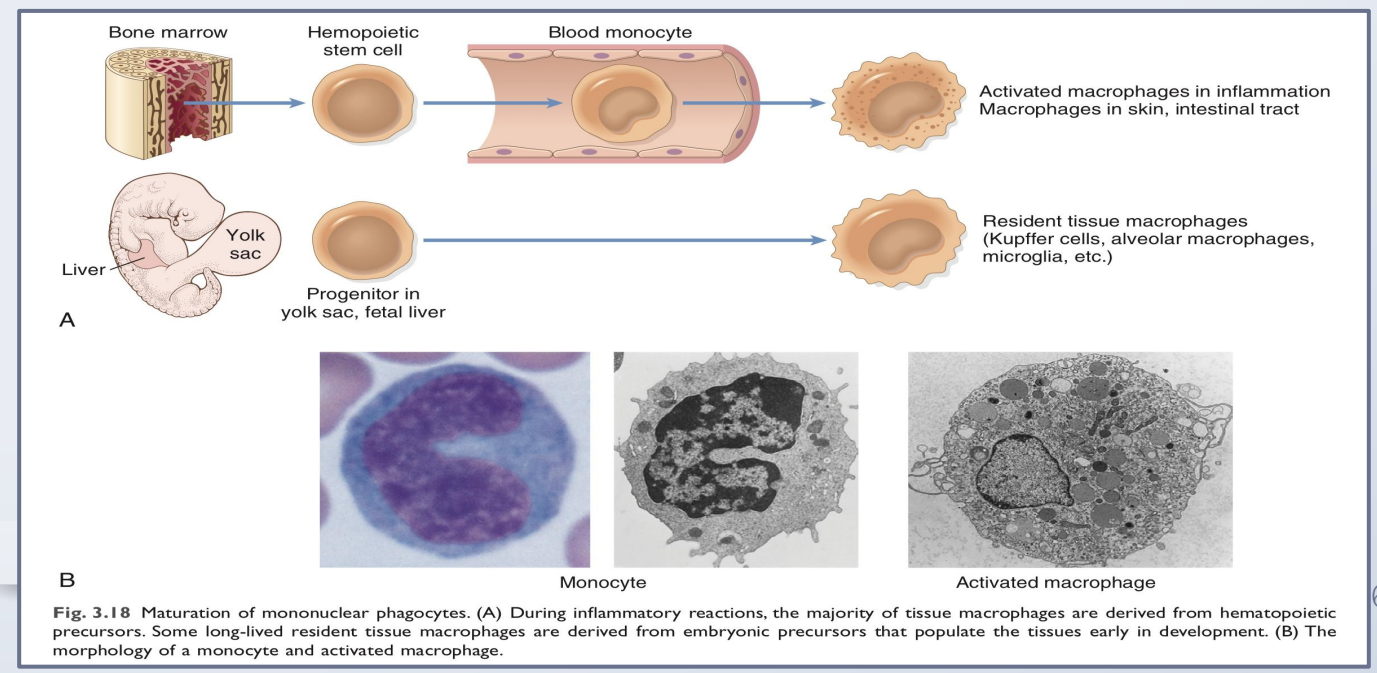
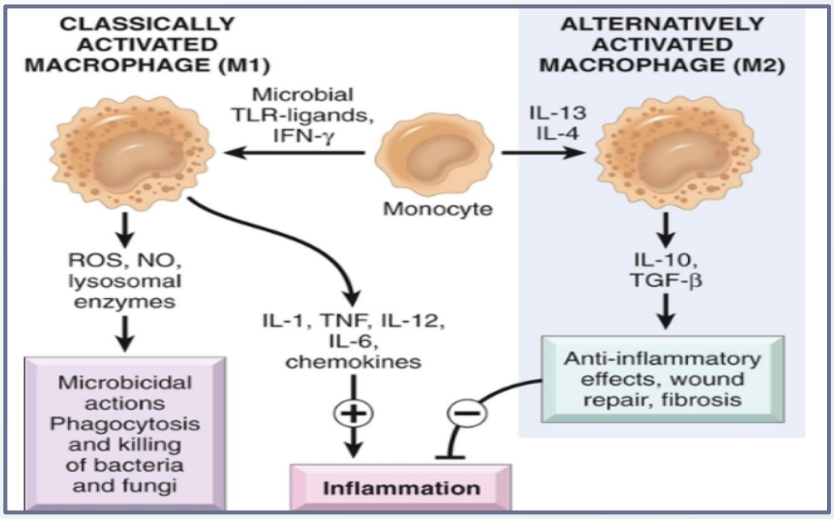


Fig. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, the majority of tissue macrophages are derived from hematopoietic precursors. Some long-lived resident tissue macrophages are derived from embryonic precursors that populate the tissues early in development. (B) The morphology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

Cells in Chronic Inflammation

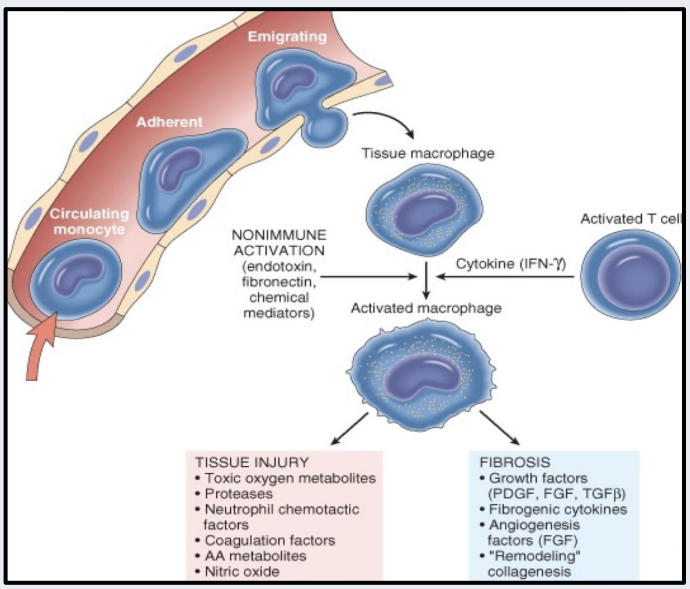
Role of Macrophages Cont.

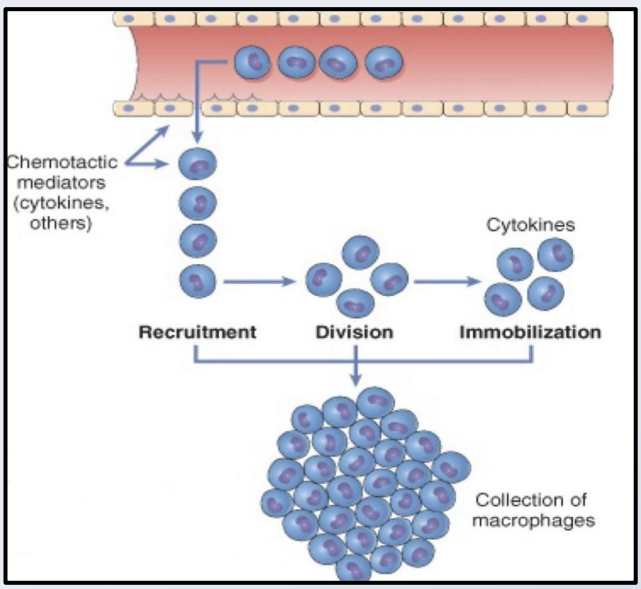


In some instances, if the irritant is **eliminated**, macrophages eventually **disappear** (either dying off or making their way via lymphatics into the lymph nodes).

In <u>chronic inflammation</u>, 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**





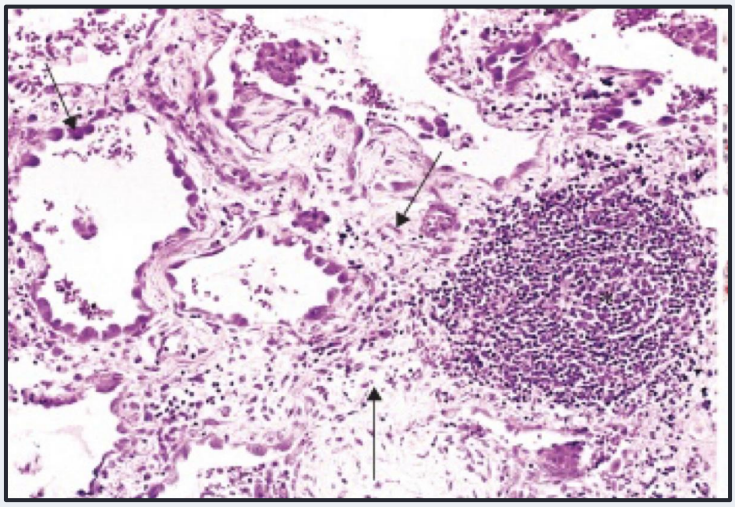
A collection of activated macrophages is known as a ***granuloma***

Granuloma inflammation : is the Presence of epithelioid cells surrounded by collar of mononuclear leukocyte (lymphocytes and plasma cells).
Will be discussed later in lec5

Cells in Chronic Inflammation

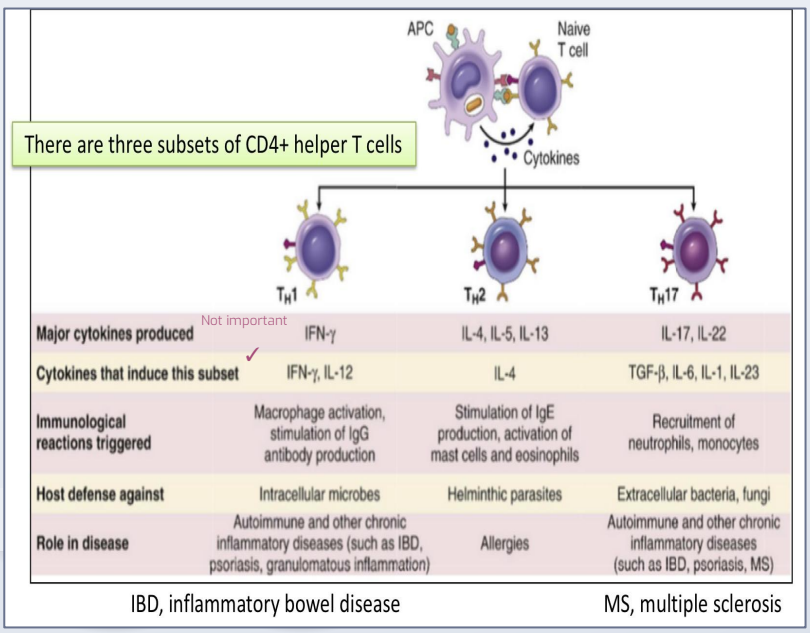
Role of Lymphocytes:

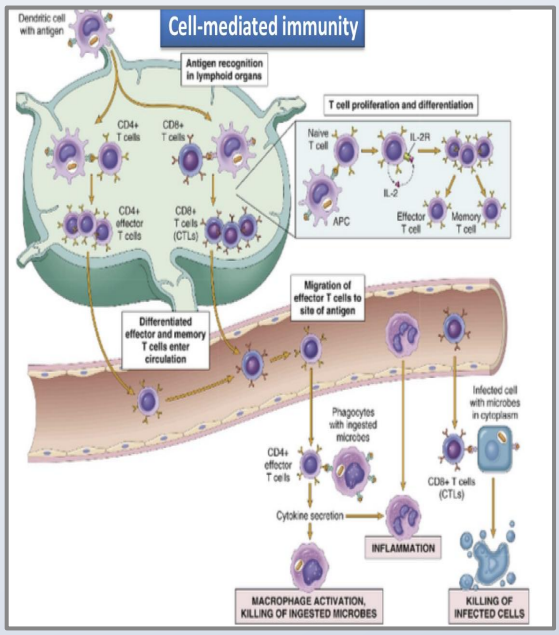
- Both T and B lymphocytes migrate into inflammation sites, It is most commonly seen in chronic inflammation (because when they're activated inflammation tends to be severe and persistent).
- **Role:** mediators of adaptive immunity which provide defense against infectious pathogens.



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.



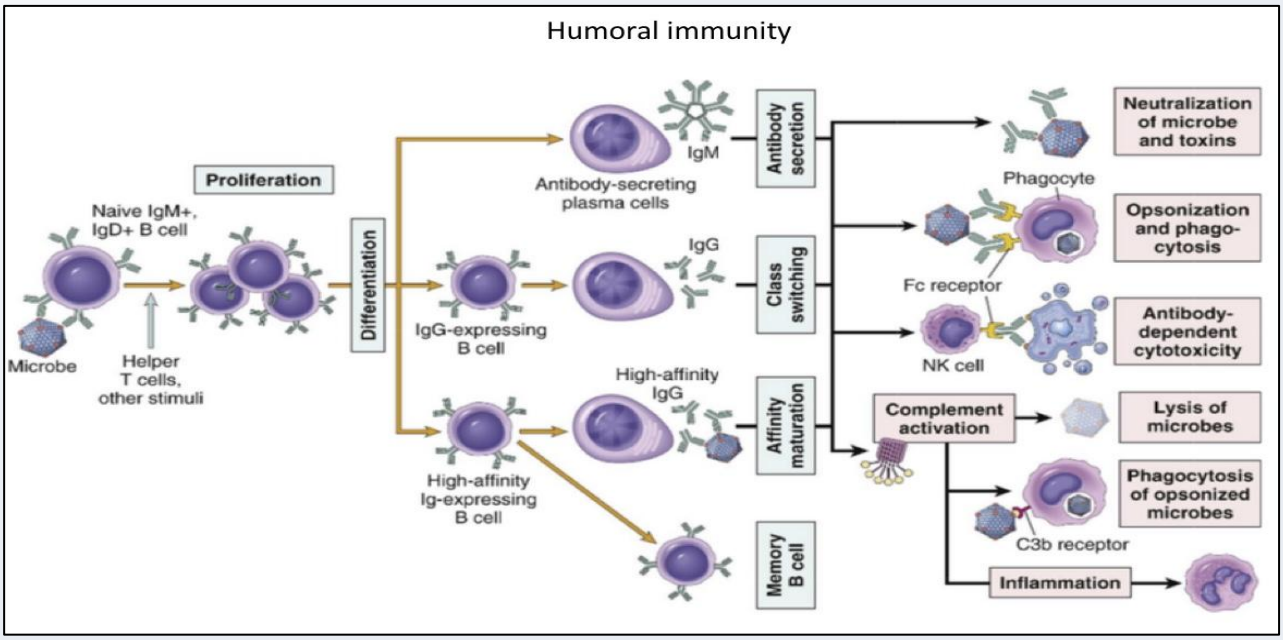


Cells in Chronic Inflammation

Role of Lymphocytes:

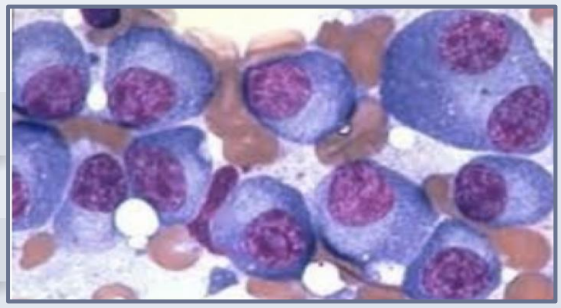
B lymphocytes

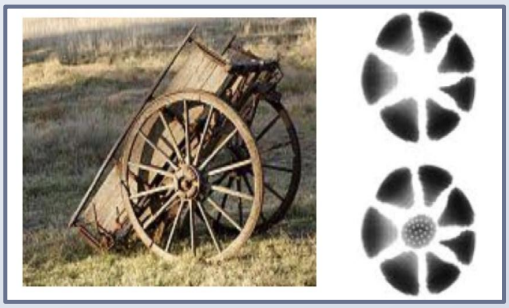
- Function: Humoral immunity
- Naive/immature B lymphocytes recognize antigens.
- Under the influence of **TH cells** and other stimuli, the **B Cells** are activated to proliferate and to differentiate into antibody-secreting **plasma cells**.



Role of Plasma cells:

- **Lymphoid cells** (Mature B lymphocytes)
- 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.

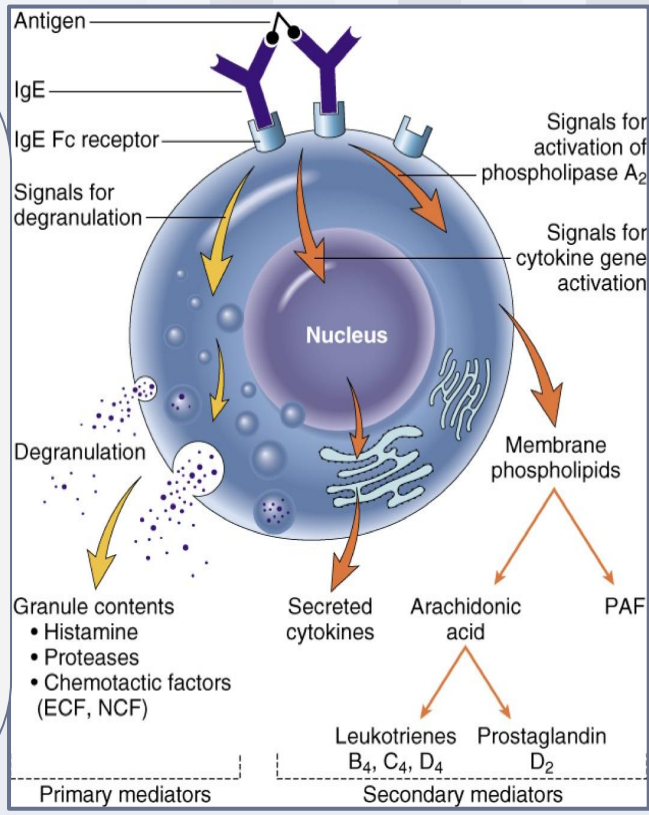




Cells in Chronic Inflammation

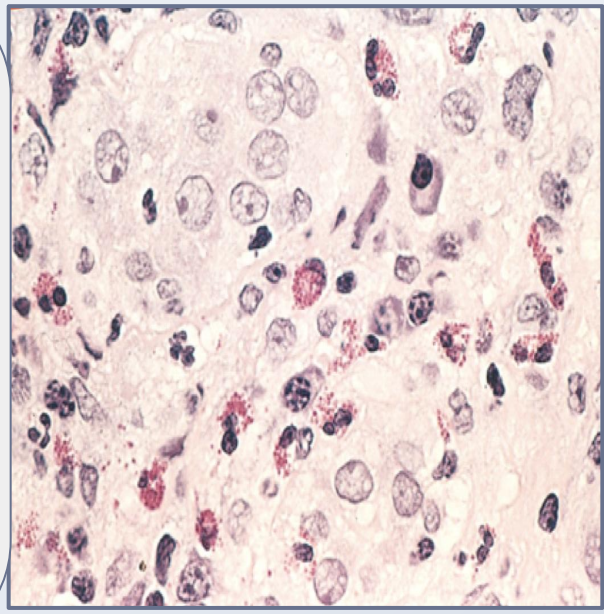
Role of Mast cells

- 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 (mostly by mast cells but can also be secreted by basophils), 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

Patterns of Chronic Inflammation

Chronic **nonspecific** inflammation

Non specific = Granulation tissue.

Features of chronic inflammation:

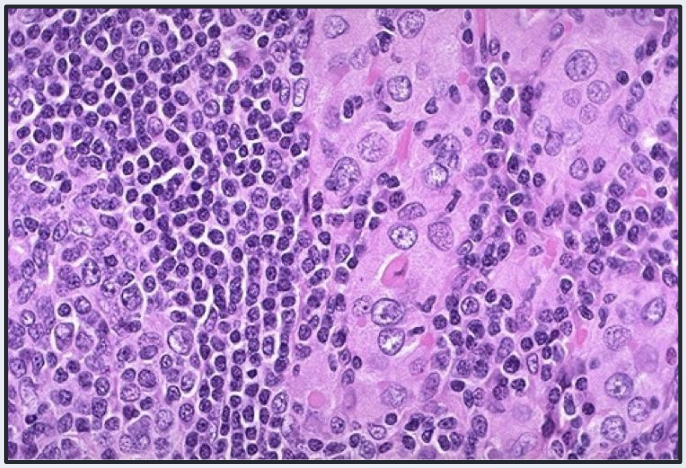
- ➔ **Foreign material**, e.g. silicates, including asbestos
- ➔ **Autoimmune diseases**, e.g. autoimmune thyroiditis

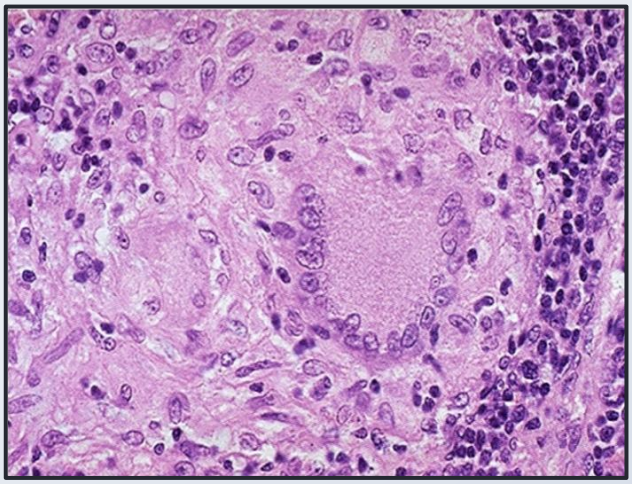
Chronic **Granulomatous** inflammation

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 response:

- It is inflammation, even if it is localized, it's associated with cytokine-induced systemic reactions.
- It is a generalized nonspecific inflammatory response triggered by locally generated inflammatory mediators and cytokines going into the blood and having a *systemic effect.*

Clinical and pathological changes

Leukocytosis
occurs in bone marrow
(IL-1 and TNF)

Fever, **malaise***, **anorexia**
(IL-1 and TNF)

Acute-phase proteins
increased secretion by liver
(IL-1, IL-6, and TNF)

*General discomfort

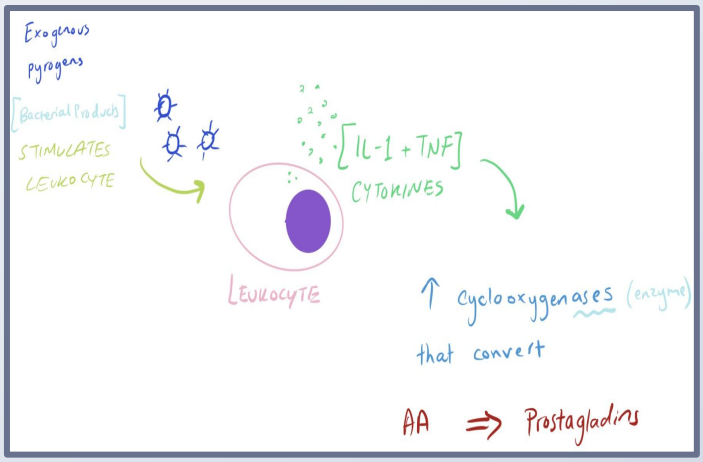
1- Fever

- ➔ Characterized as an elevation in body temperature
- ➔ Produced in response to presence of **pyrogens** in the blood
- ➔ Pyrogen:
  - ◆ **Exogenous:** bacterial products
  - ◆ **Endogenous:** substances produced during Inflammation interleukin 1 (IL-1) and tumor 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.**

prostaglandins:
-come from the metabolism of arachidonic acid by cyclooxygenase
-analgesics work as anti-prostaglandins

What are the chemical mediators that induce fever?

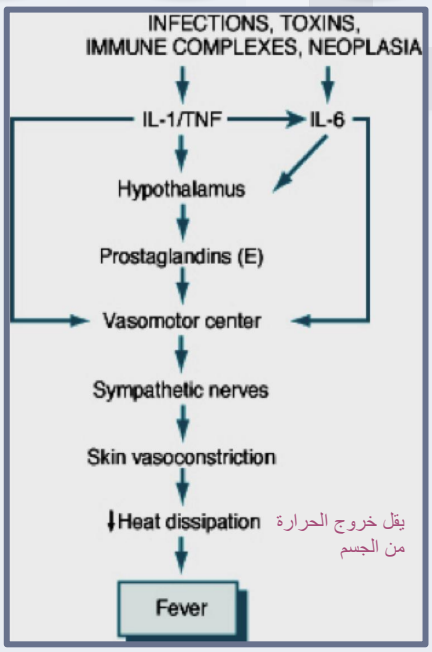
1. IL1
2. TNF
3. Prostaglandins (E)



Systemic Effects of Inflammation

Fever cont.

- ➔ In the hypothalamus, the prostaglandins, especially PGE2, stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level.
  Why hypothalamus? Because it's responsible for body temperature
- ➔ NSAIDs (nonsteroidal anti-inflammatory drugs), including aspirin, reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.



*NSAIDs are used to treat a variety of symptoms such as pain, inflammation, and stiffness caused by rheumatoid arthritis and tendonitis. NSAIDs are also used to treat several other conditions, such as:

- Osteoarthritis
- Muscle aches
- Dental pain
- Pain caused by gout

They may also be used to reduce fever or relieve minor aches caused by the common cold, They work basically by inhibiting the pathway that causes inflammation.

2- leukocytosis

*Normal range 4,000-11,000

- It is when WBCs count climbs* to 15,000-20,000 cells/µl
  Accelerated release of WBC from bone marrow before they are fully mature.
- "Left shift" means there is a high number of immature WBCs present that most commonly indicates inflammation or infection.
- Normally, only mature WBCs leave bone marrow

Shift to left is a sign to Acute Inflammation

Systemic Effects of Inflammation

2- leukocytosis

Types of Leukocytosis:

01 **Neutrophilia**
When **bacterial infections** induce an increase in the blood neutrophil count

02 **Lymphocytosis**
When **viral infections**, such as infectious mononucleosis, mumps, and German measles cause an absolute increase in the number of lymphocytes

03 **Eosinophilia**
Where some allergies and **parasitic infestations** increase the number of blood eosinophils (**bronchial asthma and hay fever**)

04 **Leukopenia**
When certain infections (**typhoid fever and infections caused by some viruses such as rickettsiae or protozoa**) are associated with a *decreased* number of circulating white cells

3- Acute phase protein (Plasma proteins synthesized by liver)

1. C-reactive protein (CRP)
2. Liposaccharide binding protein
3. Serum Amyloid A (SAA)
4. A-2 Macroglobulin
5. Haptoglobin
6. Fibrinogen
7. Ceruplamin

➔ 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**

Acute phase protein (Plasma proteins synthesized by liver) cont.

- ➔ 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*

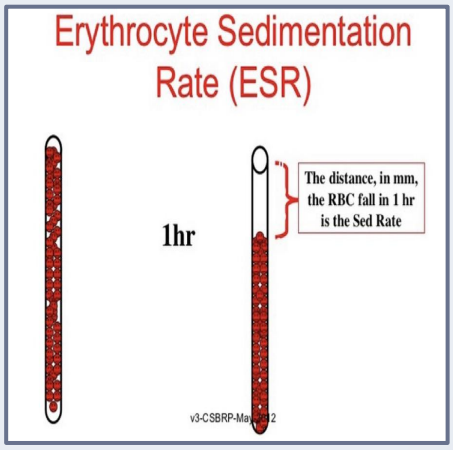
Increased erythrocyte sedimentation rate (ESR)

سرعة نزول الدم للأسفل داخل أنبوب إختبار

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

Done outside the body (test tube), is a sign to Acute inflammation

Erythrocyte sedimentation rate (ESR) is a type of blood test (laboratory exam) that measures how quickly erythrocytes settle at the bottom of a test tube that contains a blood sample. Normally, red blood cells settle relatively slow. A faster-than-normal rate may indicate inflammation in the body.



(ESR)

TNF

IL-1

IL-6

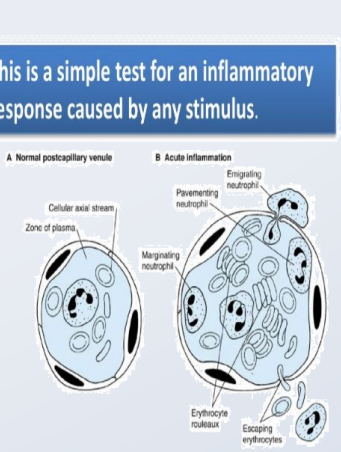
Synthesis of these proteins makes erythrocytes sticky

Hepatic synthesis of some plasma proteins most notably fibrinogen

Rapid agglutination of erythrocytes

Erythrocyte sedimentation rate (ESR)

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

Summary of Systemic signs of inflammation

Clinical systemic signs

1- **fever or pyrexia**: caused by chemical mediators
2-**malaise**:increased in fatigue, muscle pain discomfort
3-**chills** رجفة
4-**vomiting** (in children)

Laboratory systemic signs

1-**Increased erythrocytes sedimentation rate (ESR)** which causes the blood to be more viscous, because of increased WBC, (rich in cells and poor in plasma or serum because of exudate)
2-**increased CRP(C reactive proteins)**
A type of acute phase proteins that are secreted by the (liver) in reaction to inflammation(it is not specific)

CRP serve as a marker for increased risk of myocardial infarction in patients with coronary artery disease

MCQs

1-The duration of chronic inflammation is?			
a- day to week	b- month to year	c- 1 day	d- 2 weeks
2- physiological process which a new blood vessels is formed from pre-existing vessels.			
a- Chronic inflammation	b- Granuloma inflammation	c- Angiogenesis	d- Acute inflammation
3-which one of these **is not** an essential change in chronic inflammation?			
a- tissue injury	b- scarring(fibrosis)	c- angiogenesis	d- acute inflammation
4-if the irritant is eliminated the….			
a-neutrophils disappear	b- macrophage disappear	C-eosinophils disappear	d- nothing happens
5-Exogenous is substances released by			
a-Bacteria	b-Virus	C-parasite	d-fungi
6-Function of B lymphocytes is humoral immunity			
a-True	b- False	c-أنت شخص تبدأ بحرف الـ ح.....أنت حاذق	D-بالله قدم تقاعد مبكر

SAQs

1-a collection of activated macrophage is known as ?

2-macrophage are activated by ?

3-What is the patterns of chronic inflammation?

4- Eosinophils are abundant in?

5- What does CRP stand for?

Answers:
1-granuloma
2-cytokines (IFN-γ) and bacterial endotoxins
3-Specific and non-specific
4-Immune reactions
5-C-reactive protein (CRP)

1-b. 2-c. 3-d.
4-b. 5-a. 6-a

- غادة العثمان
- ماجد العسكر

- البندري العنزي
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- رغد العسيري
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- علي الماطري
- محمد السنيدي
- محمد السياري
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Editing File

Any Qs, Thoughts, Feedback .. pleases let us know <3

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