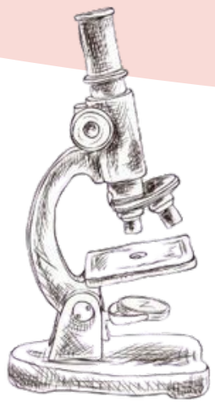
MED444
KING SAUD UNIVERSITY



PATHOLOGY TEAMWORK

MED444

Chronic inflammation systemic effect of inflammation

OBJECTIVES

- List and describe the outcome of acute inflammation.
- 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

Editing file

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

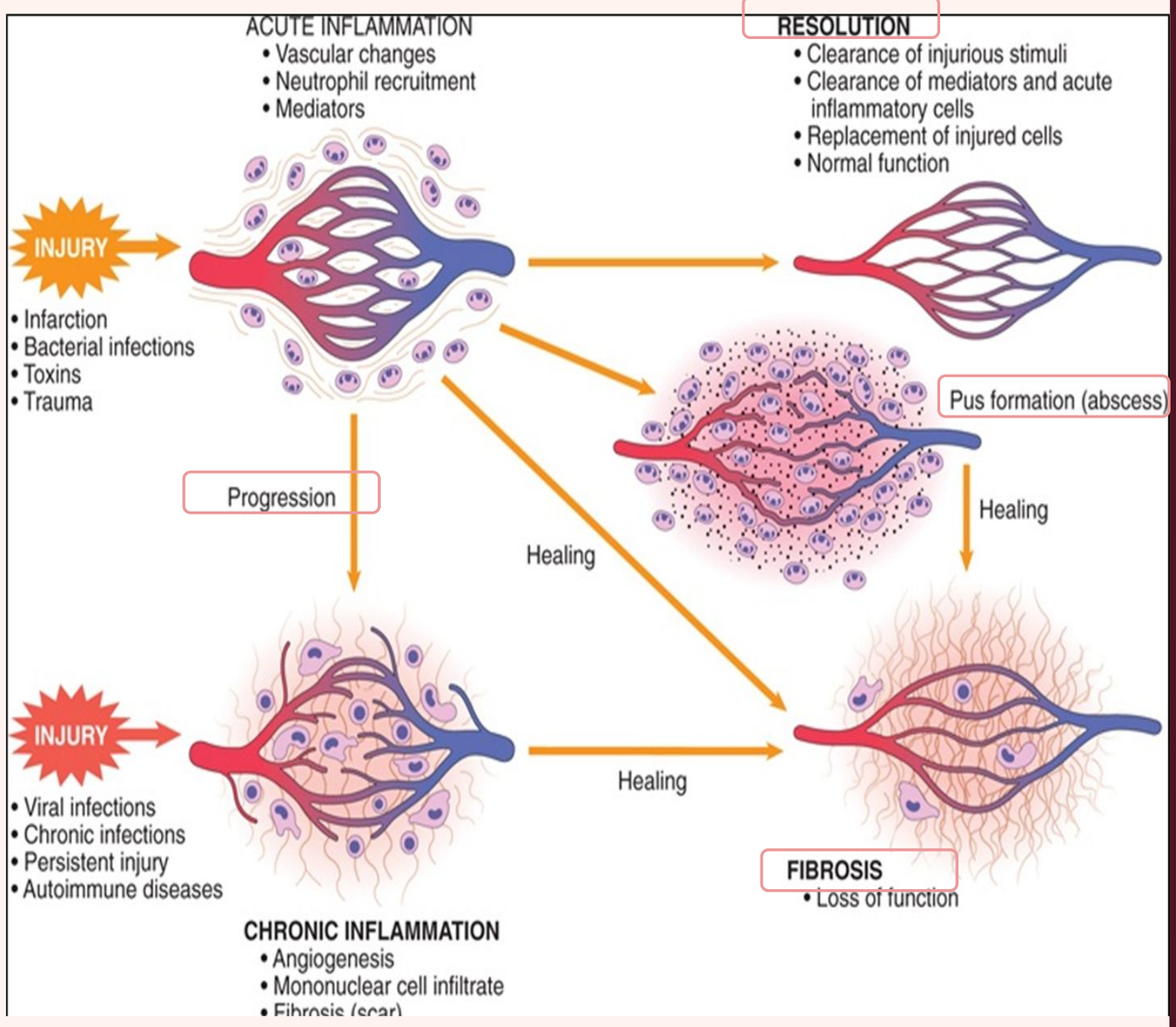
EXTRA INFO (GREY)

GIRL'S SLIDES

Outcomes of Acute Inflammation

Acute inflammation may have one of the four outcomes:

1. Complete Resolution
2. Healing by connective tissue replacement (fibrosis)
3. Progression of the tissue response to chronic ammation
4. Abscess formation



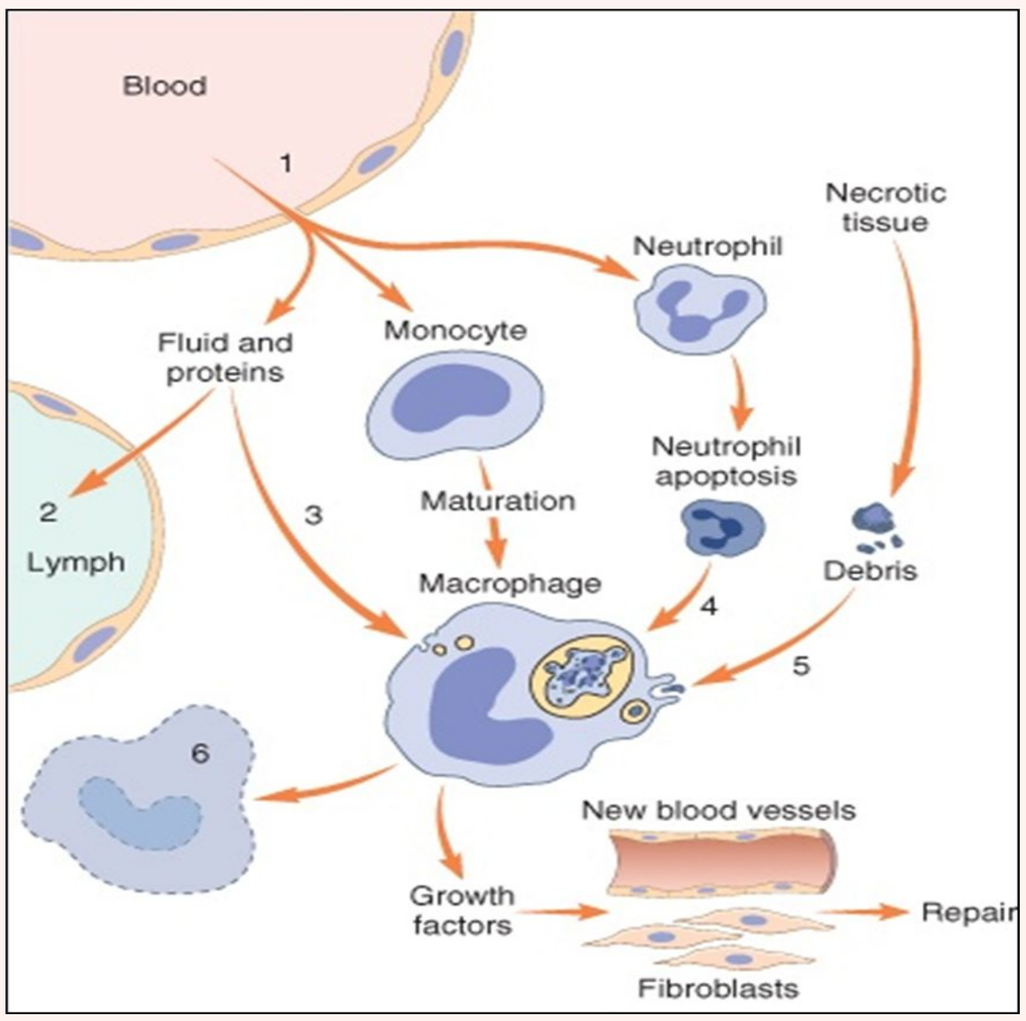
Events in the resolution of inflammation:

*process of ending or being brought to an end

1. Neutralization, decay, or enzymatic degradation of the various chemical mediators: normalization of vascular Permeability, and cessation* of leukocyte emigration and apoptosis.

1. The necrotic debris, edema fluid, and inflammatory cells are cleared by phagocytes and lymphatic drainage.

1. Lymph node become enlarged and inflamed



CHRONIC INFLAMMATION

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

The essential changes of CHRONIC INFLAMMATION:

1- Absence of polymorphs :

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

2- Angiogenesis:

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

3- Tissue Injury :

continuous injury of tissue and necrosis.

4- Scarring (Fibrosis) :

Results from proliferation of fibroblasts with collagen production.

Causes of chronic inflammation:

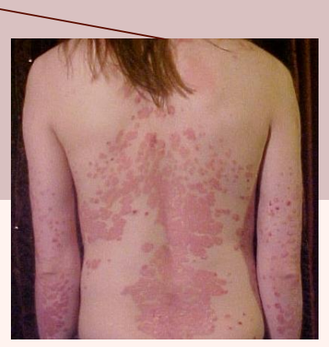
1- Persistent infections by microbes that are difficult to eradicate

[E.g. Mycobacterium tuberculosis, Treponema pallidum (the causative organism of syphilis), certain viruses and fungi.]

Persistent infections elicit (stimulate) 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.]



Bowel=gastrointestinal tract(GIT)

Causes of chronic inflammation:

Cont.

3- Prolonged exposure to potentially toxic agents.

[e.g. - nondegradable exogenous materials: inhaled particulate silica, which can induce a chronic inflammatory response in the lungs (silicosis)

-Endogenous agents: 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.

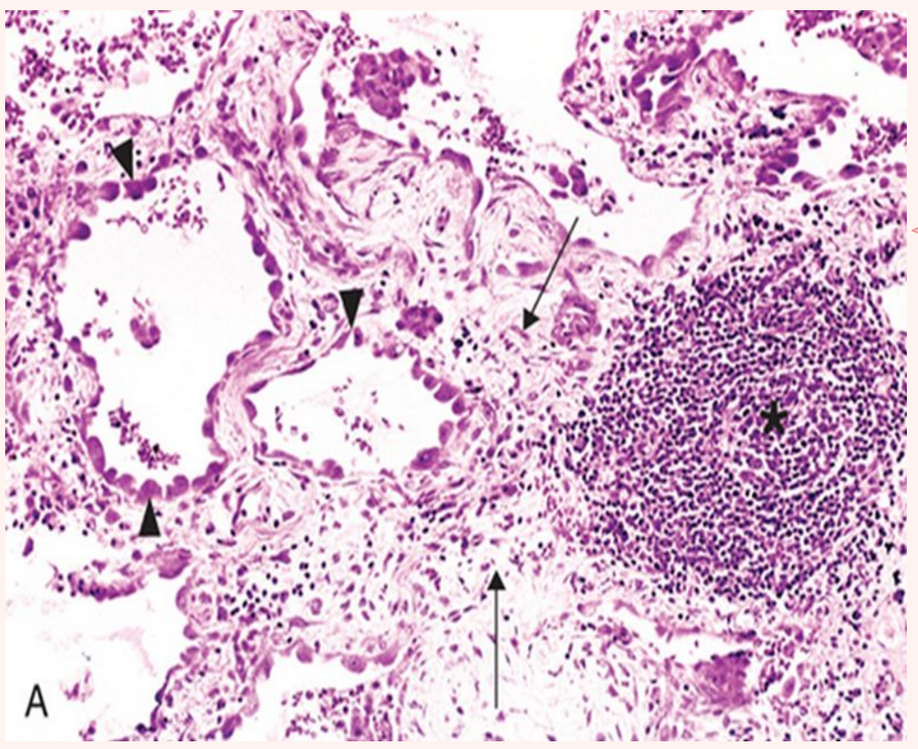
Chronic inflammation is characterized by a 3 different set of reactions:

1- Infiltration with mononuclear cells, including:
Macrophages.
Lymphocytes.
Plasma cells.

2- Tissue destruction, largely induced by the products of the inflammatory cells.
Such as ROS (reactive oxygen species)

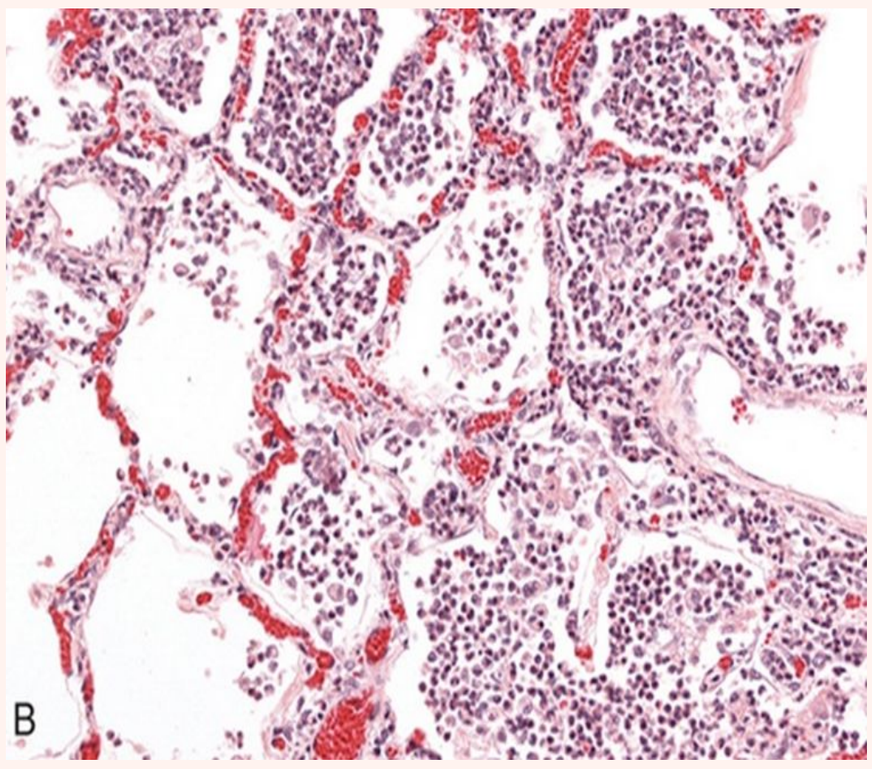
3- Repair, involving new vessel proliferation (angiogenesis) and fibrosis

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



Lung chronic inflammation:
Infiltration by lymphocytes,
Angiogenesis, fibrosis

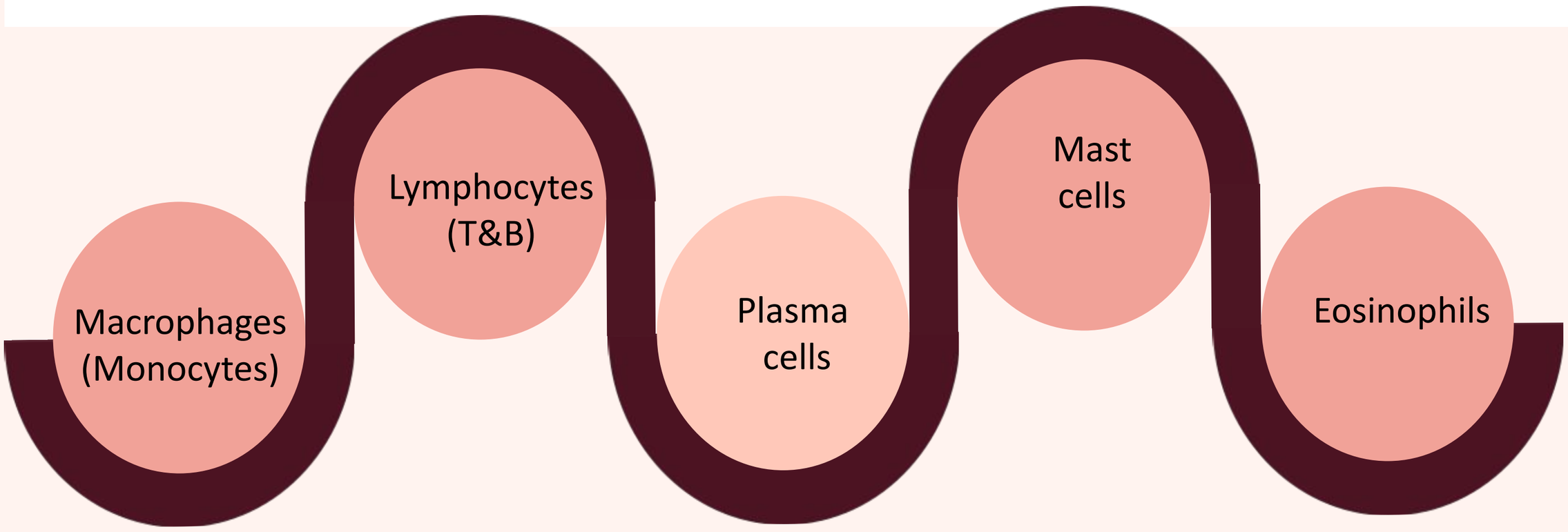
Lung acute inflammation



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
- Main cells of chronic inflammation are macrophages and lymphocytes

Cells that plays a major roles in chronic inflammation:



Macrophages/ monocytes

In blood: “monocytes”

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

-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)

In tissue:”macrophage”

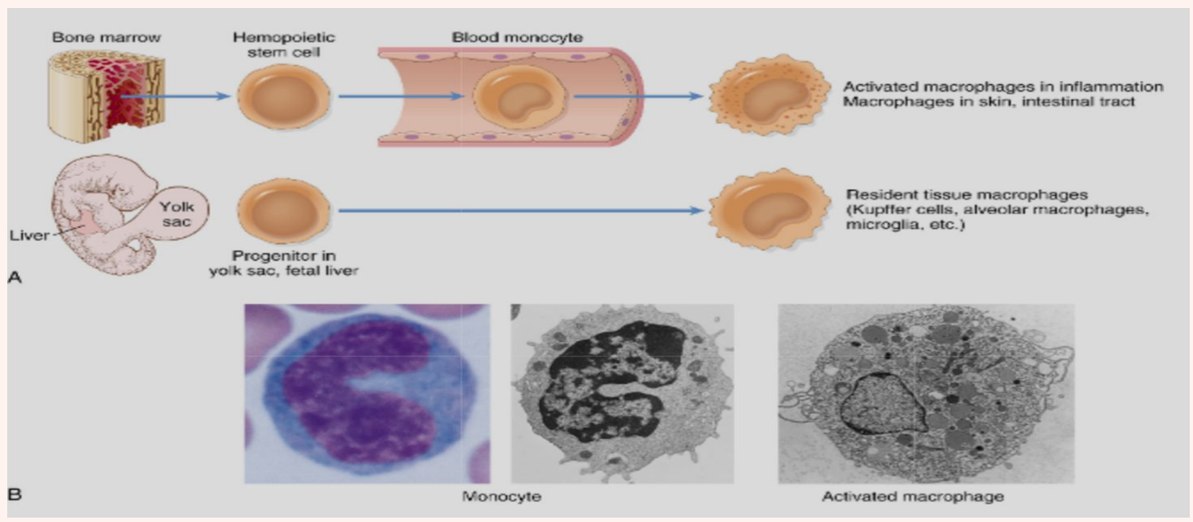
-liver macrophage ->> Kupffer cells

-spleen and lymph nodes macrophage ->> sinus histiocytes

-central nervous system macrophage ->> microglial cells

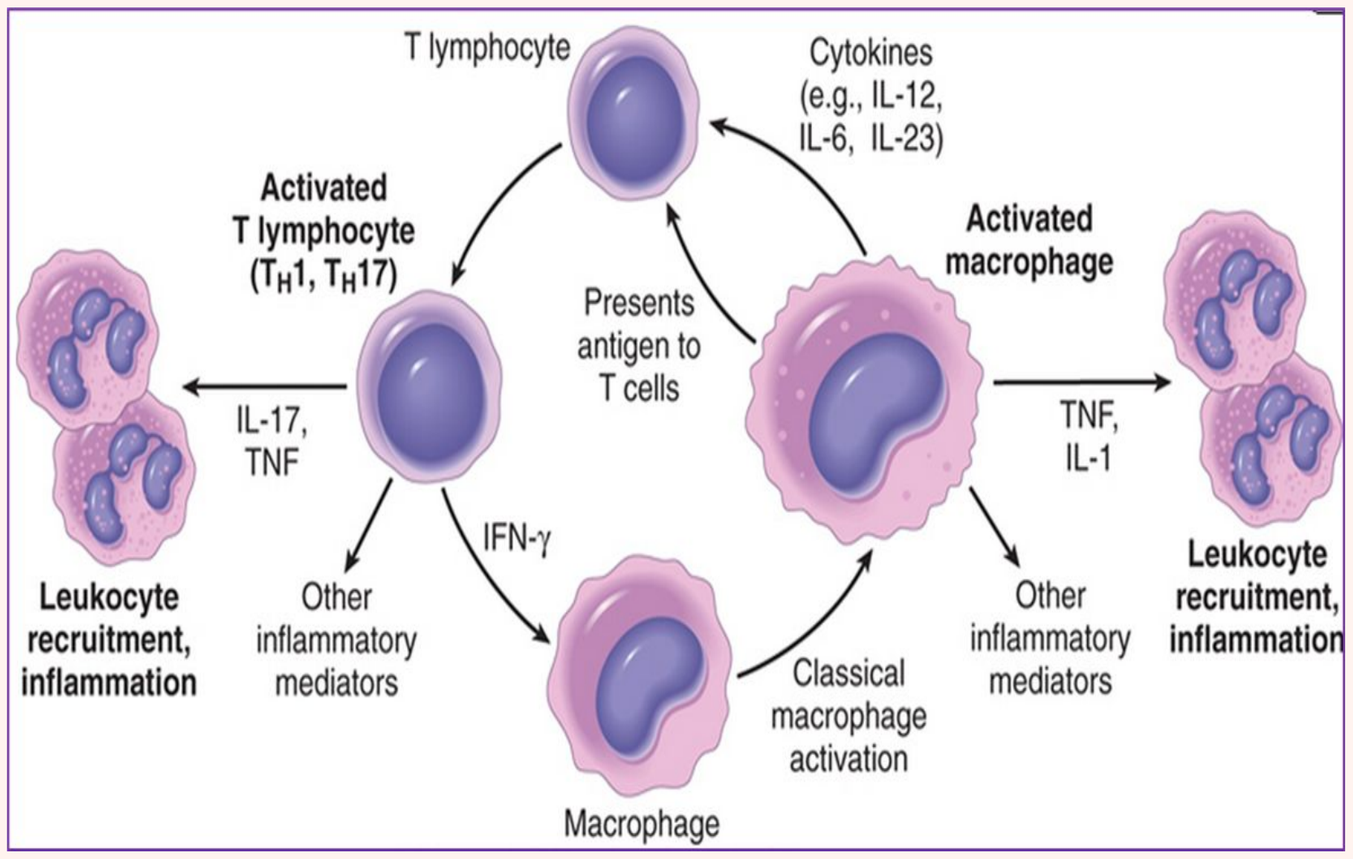
-lung macrophage ->> alveolar macrophages

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



Role of Macrophages

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

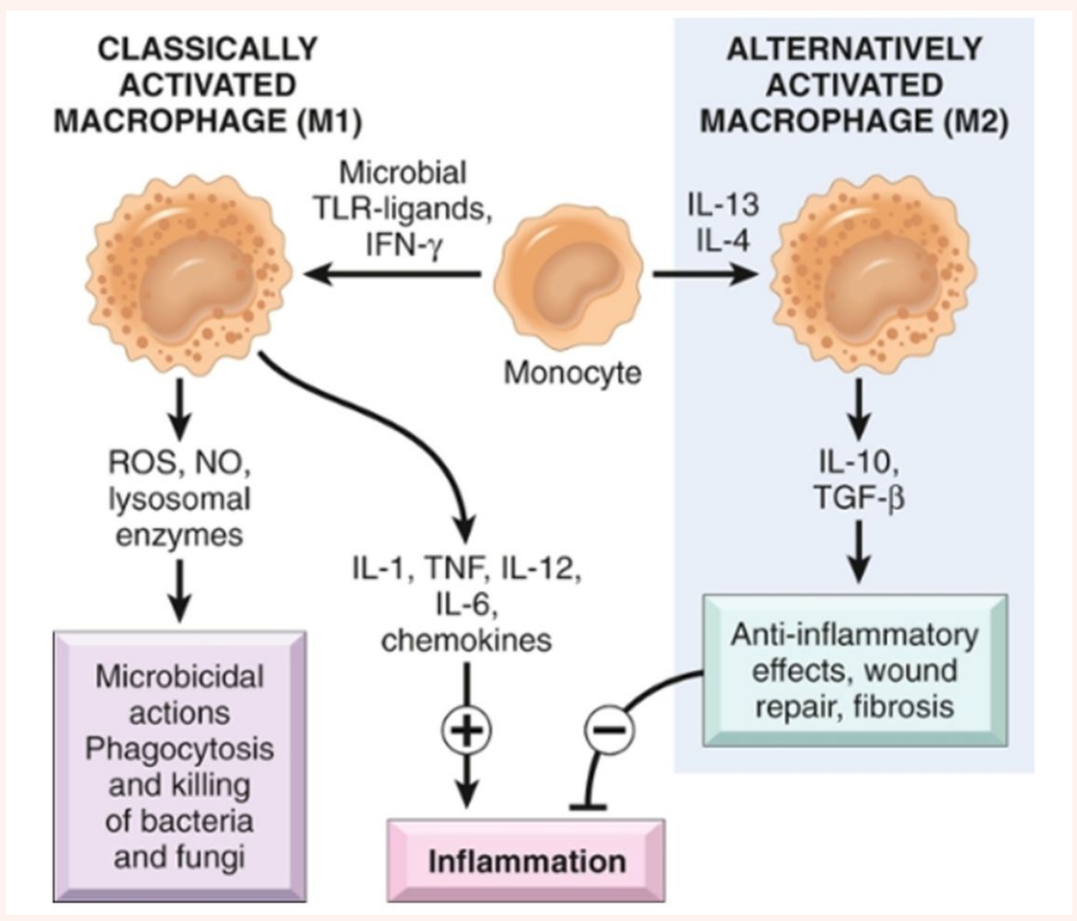
Elimination of injurious agents such as microbes

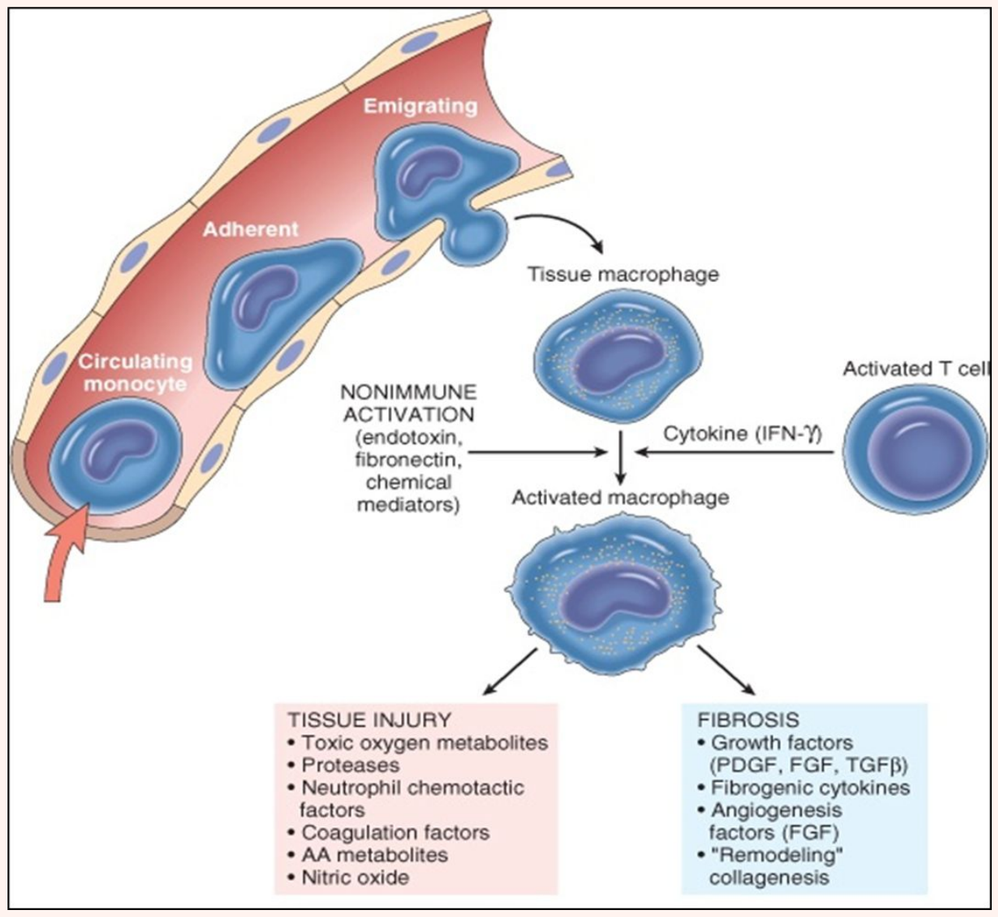
initiate the process of repair

Secretion of inflammation mediators, such as cytokines (TNF, IL-1, chemokines, eicosanoids)

Responsible for majority of tissue injury in chronic inflammation

Display antigens to T lymphocytes and respond signals from T cells, thus setting up a feedback loop





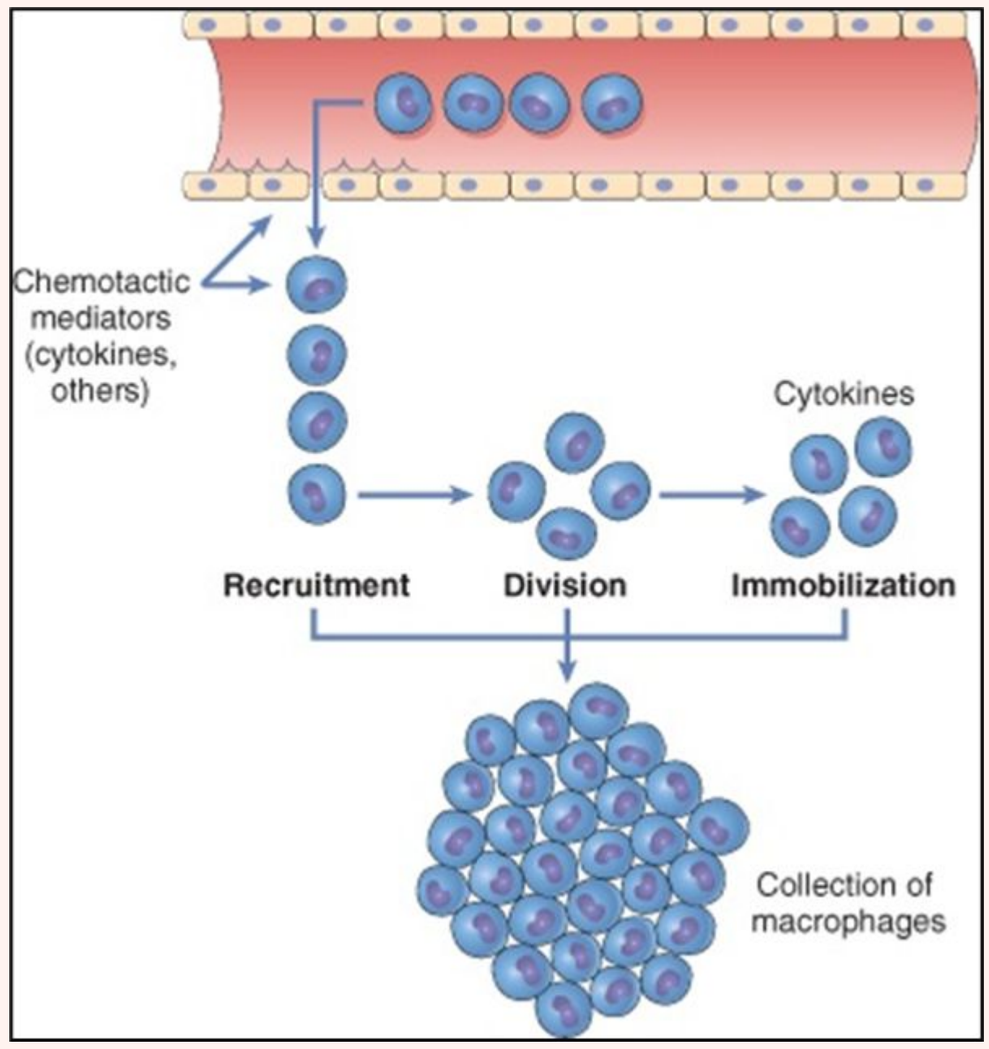
Macrophages Cont.

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**

A Collection of <u>activated</u> macrophages :

GRANULOMA

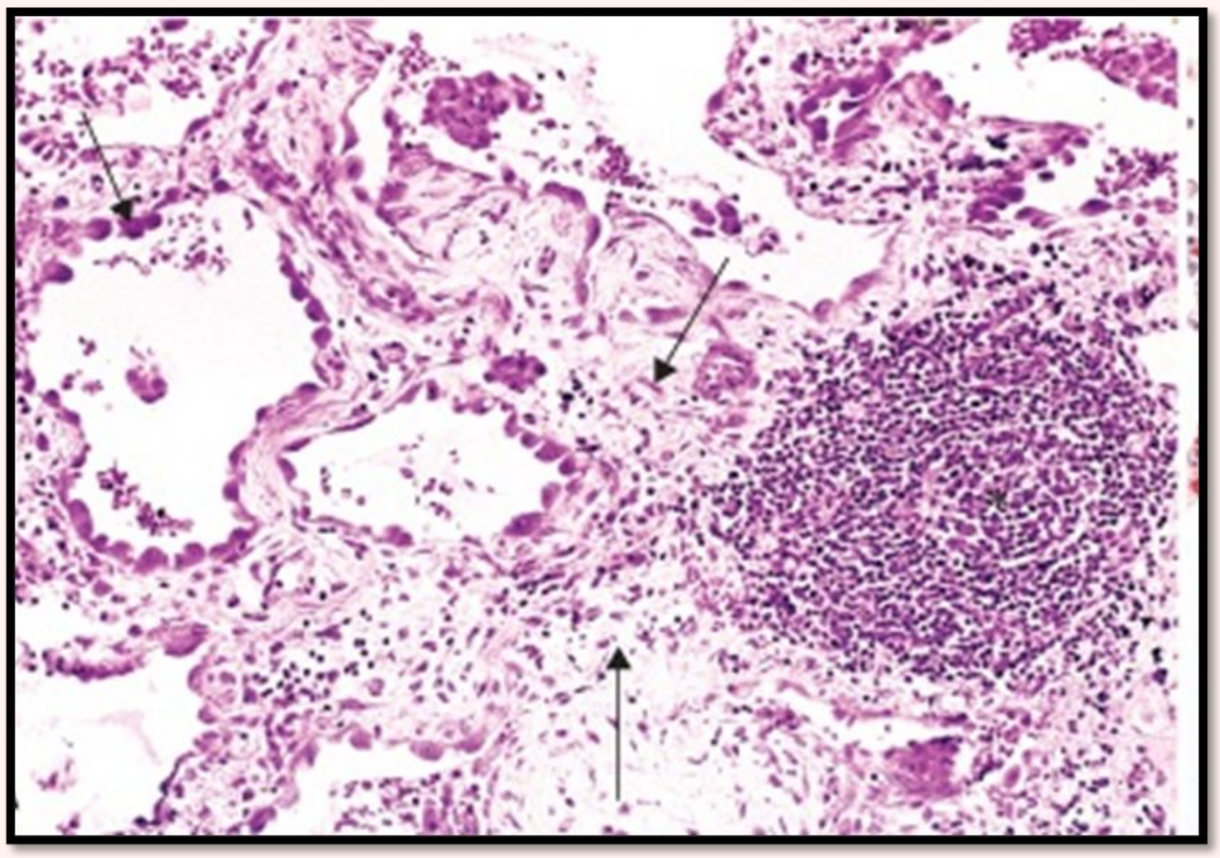


Lymphocytes

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,the inflammation tends to be severe and persistent).

- Role: mediators of adaptive immunity which provide defense against infectious pathogens.

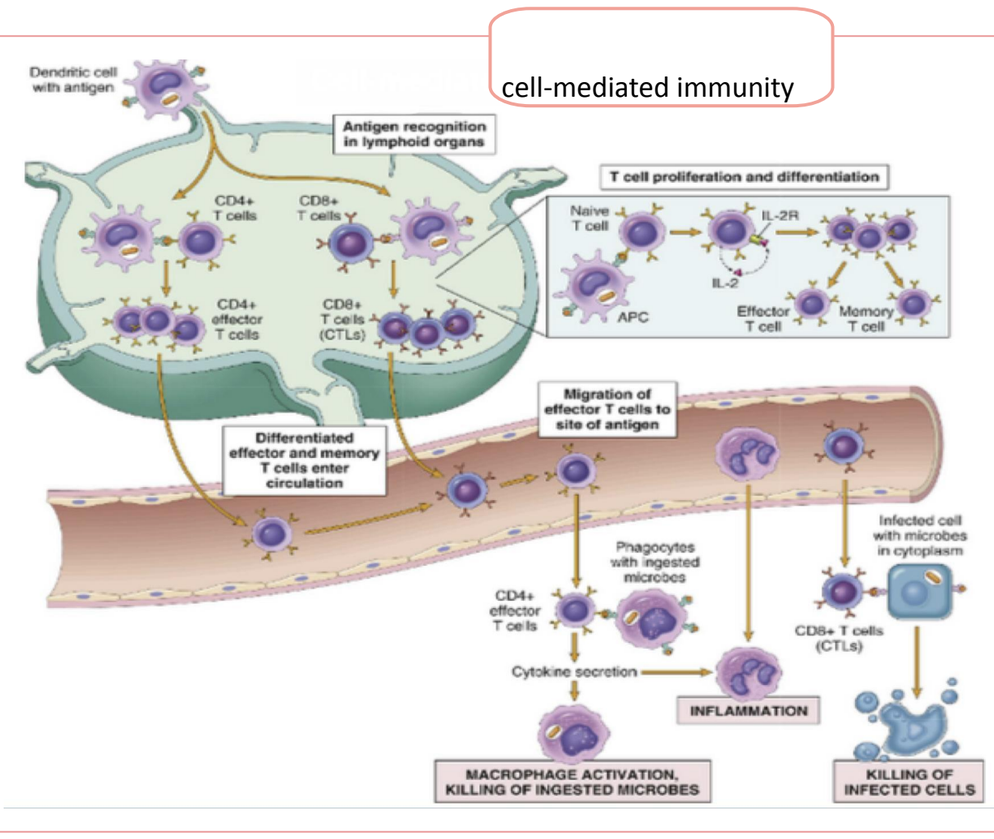


T lymphocytes

●Are activated to secrete cytokines.

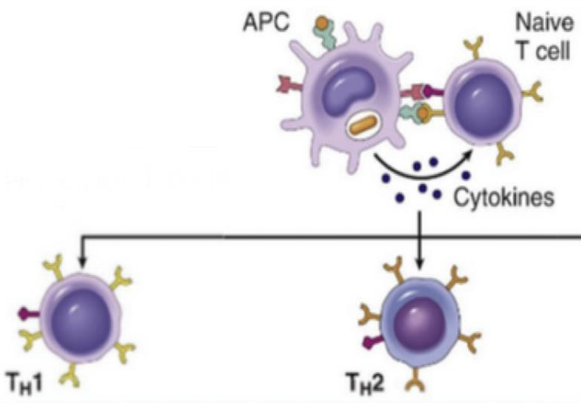
- <u>CD4+ Helper T lymphocytes</u> promote inflammation and influence the nature of the inflammatory reaction.

● 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.



cell-mediated immunity

There are three subsets of CD4+ helper T cells



	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)

B lymphocytes

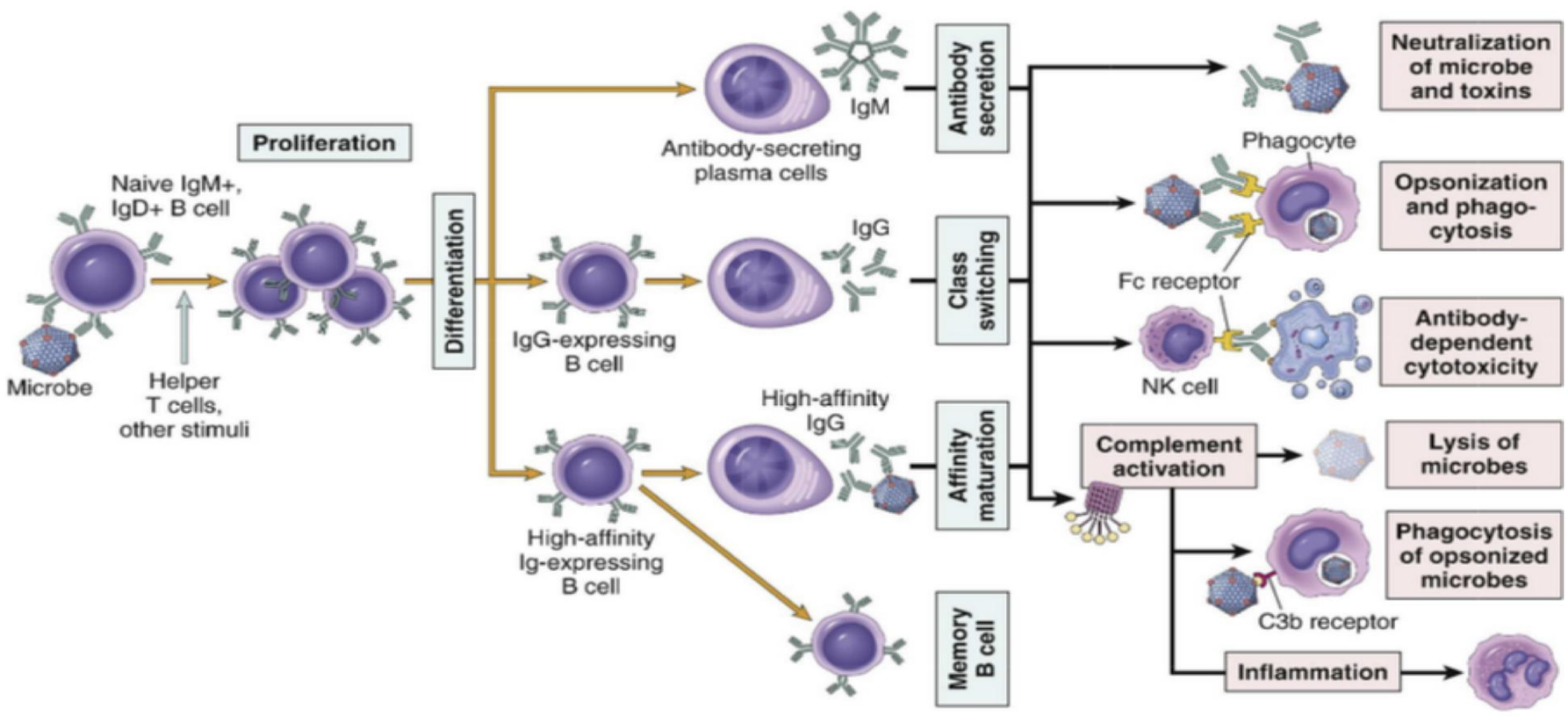
B lymphocytes may develop into plasma cells

Function: secrete antibodies (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**

Humoral immunity



Plasma cells

Lymphoid cells (Mature B lymphocytes)

Common cell in chronic inflammation

Primary source of antibodies (immunoglobulins)

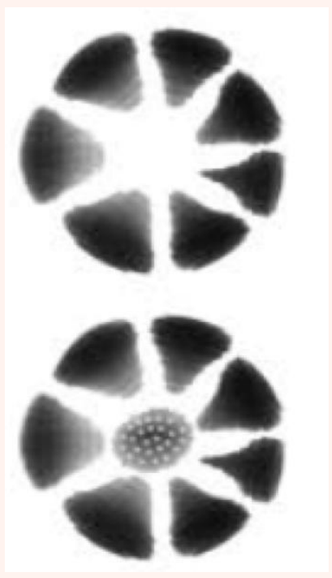
Antibodies are important in inflammation e.g. Neutralize antigen and clearance of foreign antigen

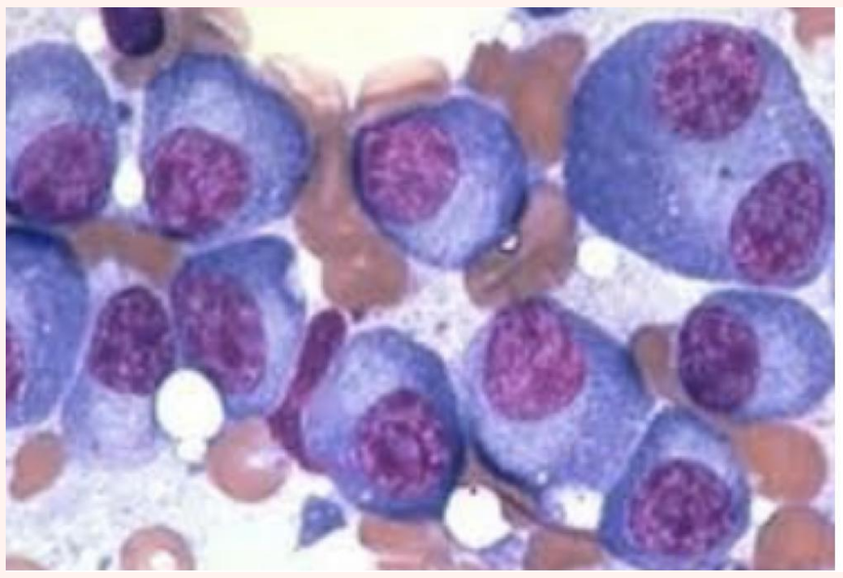
- Morphology of Plasma cells:

- Eccentric nucleus (not circular or placed centrally)
- Shows a cartwheel/clock face pattern of nuclear chromatin with a perinuclear halo. corresponding to the Golgi apparatus

Doctor said its important to remember the histological shape of the plasma cells

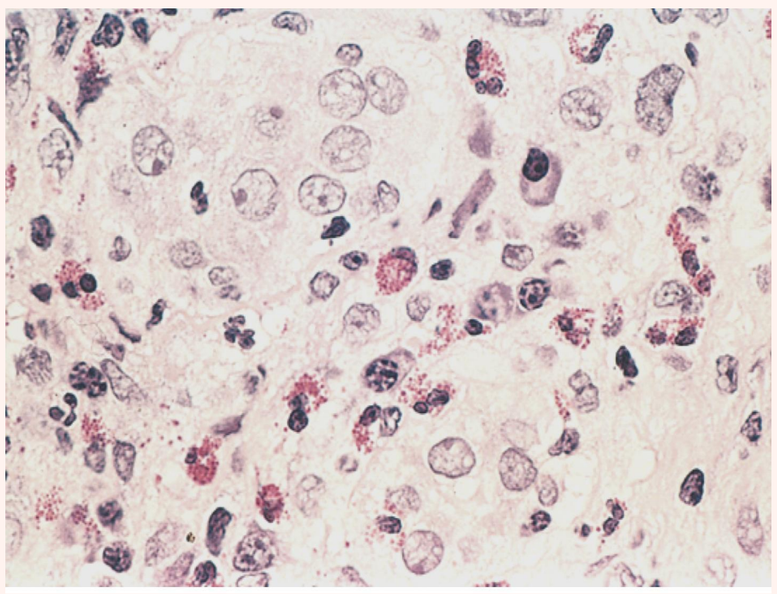
Both d.maha and d.fadi said it is important





Eosinophils

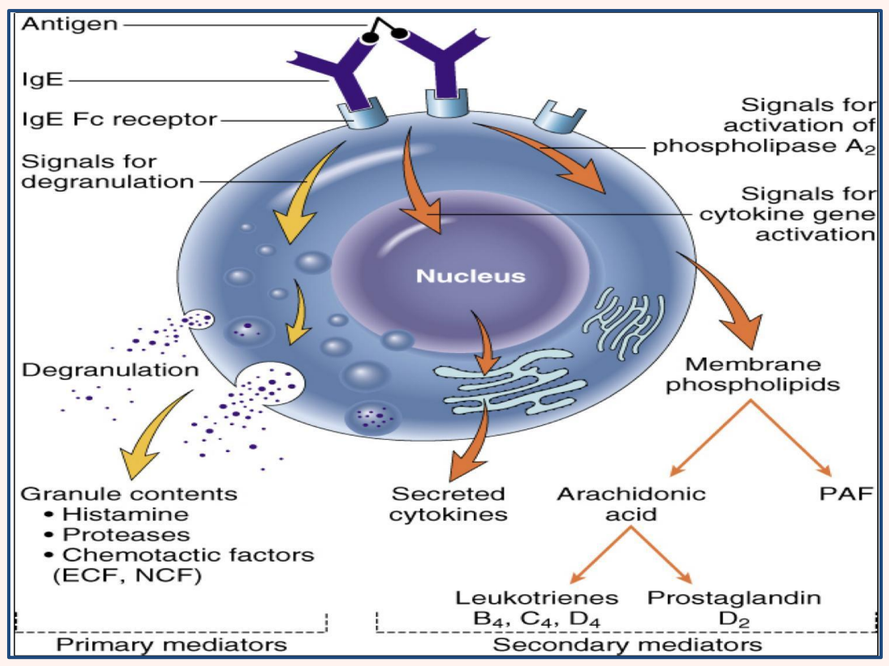
- Abundant in immune reactions involving allergies and parasitic
infections mediated by IgE.
- Respond to chemotactic agents derived largely by mast cells
- A granular cell (reddish, acidophilic, has 2 lobes) that contains major basic protein that is toxic to parasites and leads to the lysis of mammalian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



Mast cells

- Widely distributed in <u>connective tissues</u>
- Express on their surface the receptor that binds to the **FC** portion of **IgE** antibody

-the cells degranulate and release mediators, such as histamine and products of AA oxidation



Patterns of Chronic Inflammation

chronic **non specific** inflammation;

Non specific = Granulation tissue

Features of chronic inflammation e.g.:

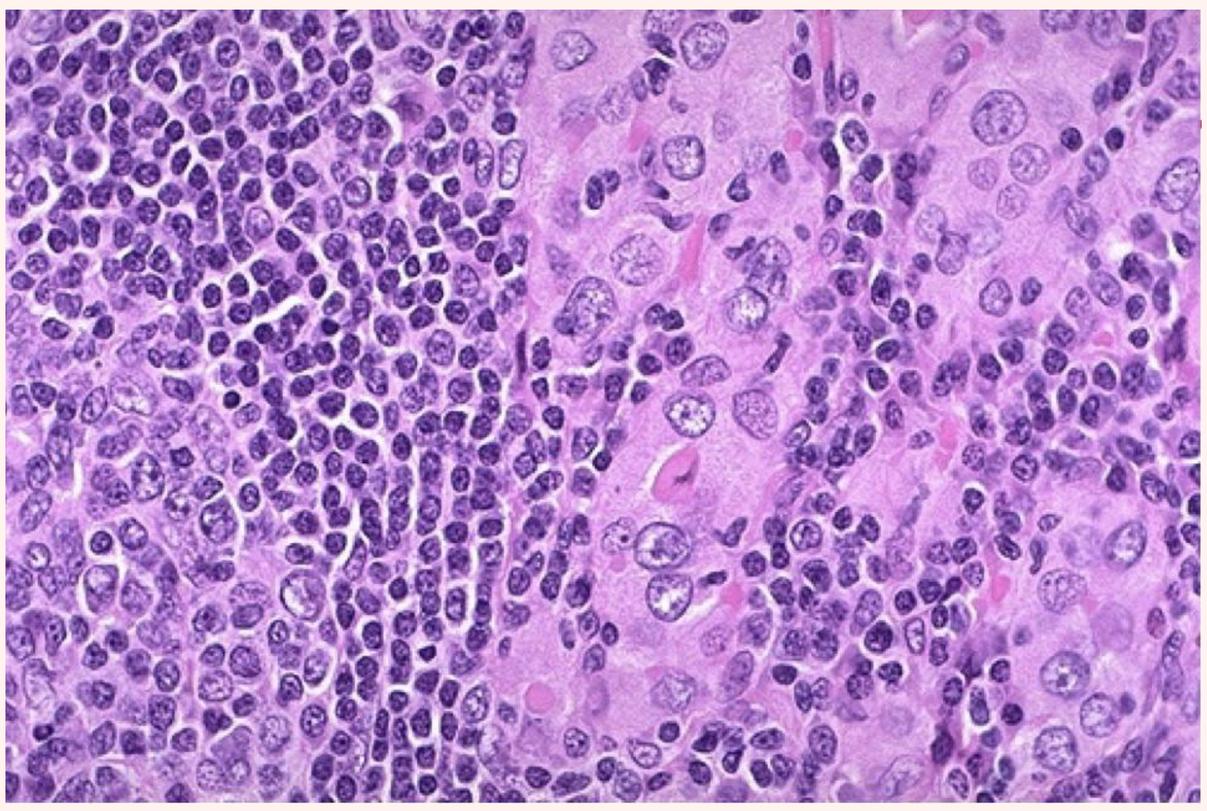
– **Foreign material**, e.g. silicates, including asbestos.

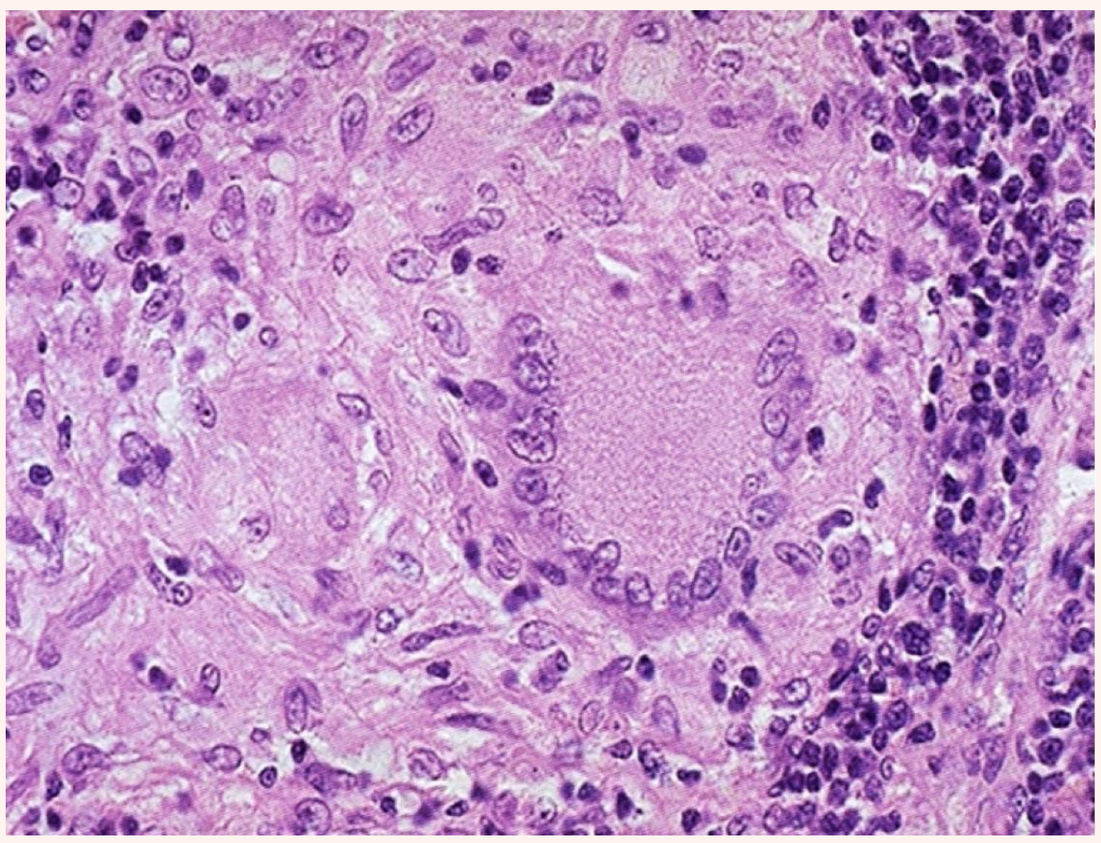
– **Auto-immune diseases**, e.g. auto-immune thyroiditis

Chronic **granulomatous** inflammation:

Specific =: Granulomatous inflammation (granulomas are present)

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

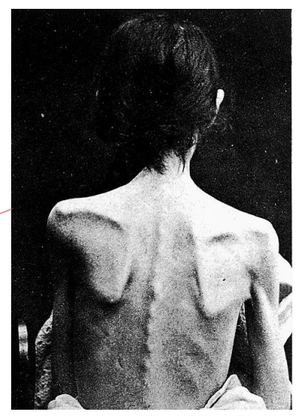




Systemic effects of Inflammation

- **Acute phase reaction/response**
  - effect of IL-1 and TNF Lead to:

fever — malaise — anorexia



- **Bone marrow**
  - effect of IL-1 + TNF (Tumor necrosis factor)
    - Lead to Leukocytosis
- **Lymphoid organs:** enlarged draining lymph node
  - effect of antigen stimulation

  Lead to reactive lymphoid hyperplasia
- **Liver**
  - effect of IL-6, IL-1, TNF Lead to increased serum acute phase proteins such as:

- C-reactive protein
- Lipopolysaccharide binding protein
- Serum amyloid A
- fibrinogen
- a-2 macroglobulin
- Haptoglobin
- Ceruloplasmin

Fever
Produced in response to Pyrogens

مسببات الحرارة

Characterized as an elevation in body temperature

- Types of Pyrogens:

1- **Exogenous pyrogens:** Bacterial products

2- **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 (Arachidonic acid) into prostaglandins.

prostaglandins:

-come from the metabolism of arachidonic acid by cyclooxygenase

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

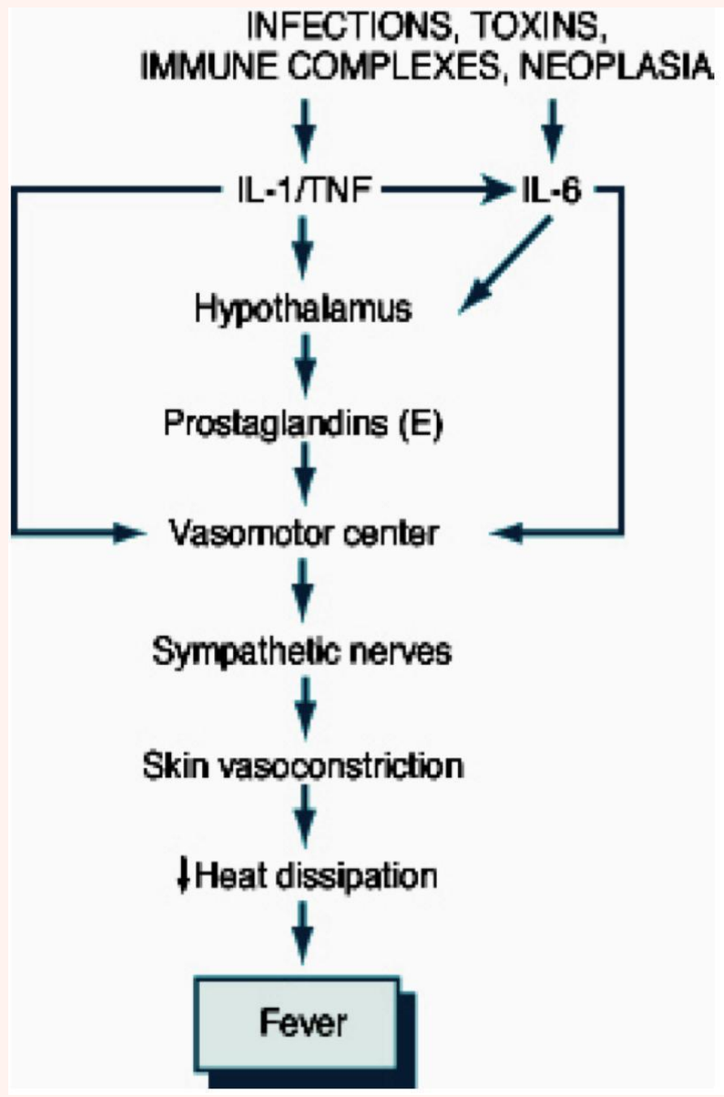
Important

IL-1 — TNF — Prostaglandins

Fever

- 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.

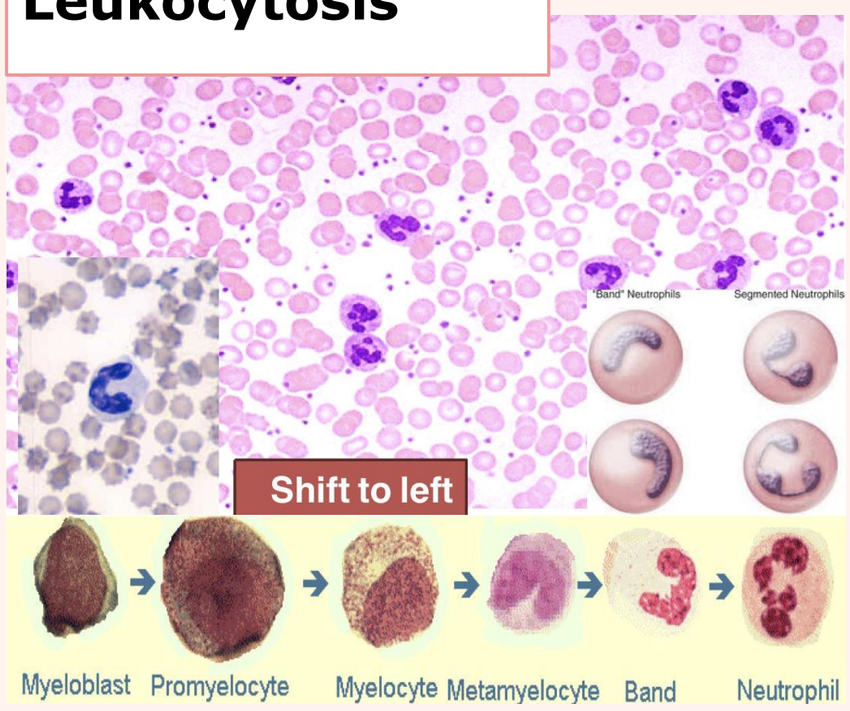
- NSAIDs, including aspirin , reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.



Inflammation Systemic

Manifestations

Leukocytosis



"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

Leukocytosis:

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

most bacterial infection (Neutrophil)

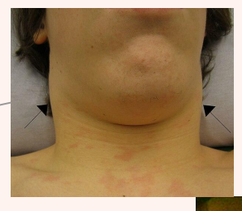
Lymphocytosis:

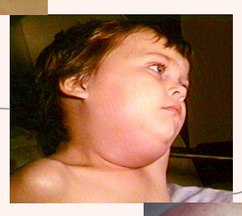
Viral infections:

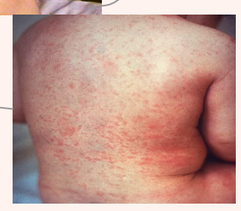
Infectious mononucleosis,

mumps,

German measles (Lymphocytes)







يتشابهون لكن مسبب المرض الفيروس مختلف

Eosinophilia:

bronchial asthma,

hay fever, parasitic infestations

Leukopenia:

typhoid fever,

infection with rickettsiae/protozoa

associated with a decreased number of circulating white cells

Acute phase proteins

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

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

secondary amyloidosis

- 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

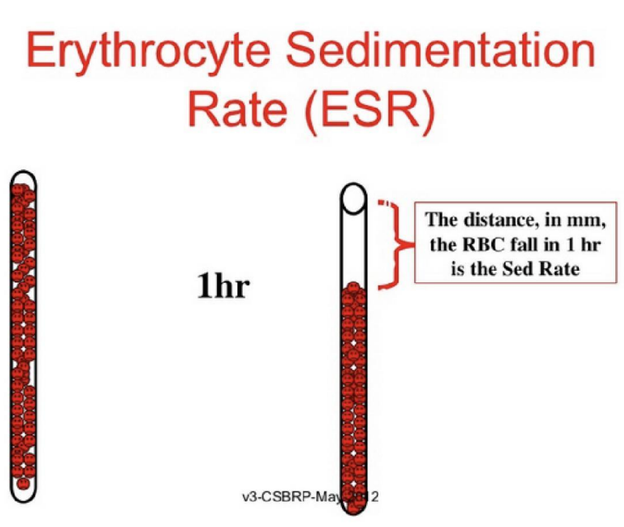
- Elevated serum levels of CRP serve as a marker for acute inflammation and increased risk of myocardial infarction in patients with coronary artery disease.

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.

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



(ESR)

TNF

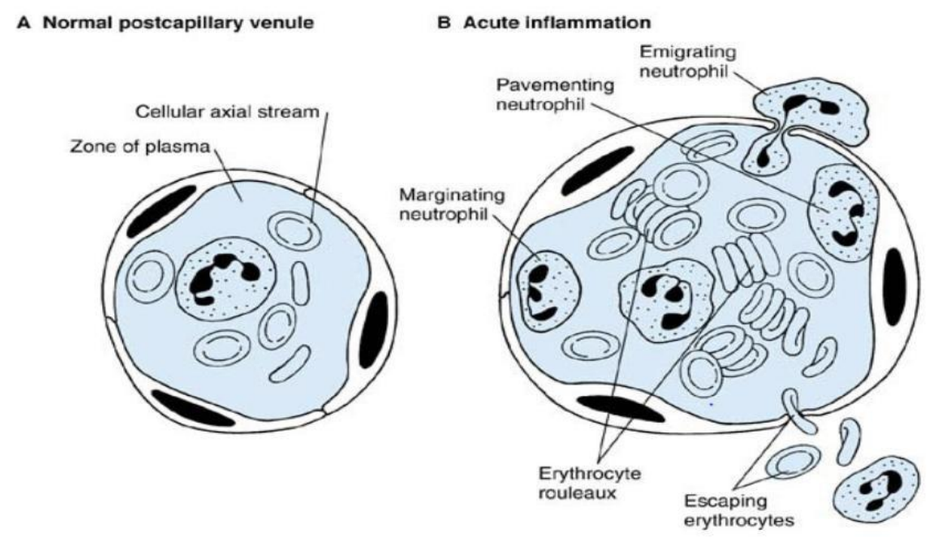
IL-1

IL-6

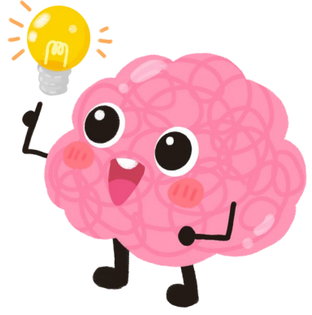
Hepatic synthesis of some plasma proteins most notably fibrinogen

Rapid agglutination of erythrocytes

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



Fibrinogen changes the charge of RBC membranes and that makes them attracted to each other and form (rouleaux)



KEYWORDS

Prolonged exposure to potentially toxic agents	exogenous materials: silica —> (silicosis) endogenous agents: cholesterol crystals —> atherosclerosis
mononuclear cells	Macrophages. Lymphocytes.Plasma cells.
ROS	Tissue destruction
Repair	vessel proliferation (angiogenesis) and fibrosis
salmonella typhi infection,	Monocytes are likely to be seen in blood
Acute phase reaction/response	Systemic effects of Inflammation: Fever,Malaise ,Anorexia
Bone marrow	Systemic effects of Inflammation :Leukocytosis
Shift to left	Leukocytosis
1. IL-1 2. TNF 3. Prostaglandins	Chemical mediators of fever

Take home message

- The outcome of acute inflammation include complete resolution, necrosis and ulceration with healing by fibrosis or progress to chronic inflammation

- Chronic inflammation is a prolonged process (weeks or months) of active inflammation, tissue destruction, and healing all coexist in varying combinations. It can follow acute inflammation, or present as a low-grade, smoldering response without prior acute reaction.

- In chronic inflammation, there are:
  - Infiltration with mononuclear inflammatory cells, including macrophages, lymphocytes, and plasma cells
  - Tissue destruction, induced by persistent injury and/or inflammation
  - Attempts at healing by connective tissue replacement, accomplished by vascular proliferation (angiogenesis) and fibrosis

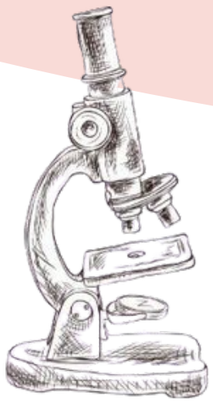
- The systemic manifestations of inflammation include fever, leukocyte left shift, increased serum acute phase reactants and ESR

MCQ

1- One of these cells can not be found in chronic inflammation which one?			
A) Lymphocytes	B) Neutrophils	C) Plasma cells	D) Macrophages
2- Macrophages in the liver are called?			
A) microglial cells	B) alveolar macrophages	C) sinus histiocytes	D) Kupffer cells
3- Which of these cells are most seen in chronic inflammation?			
A) Lymphocytes	B) Neutrophils	C) Plasma cells	D) Basophils
4- One of these chemical mediators can cause fever ?			
A) IL-1	B) IL-6	C) Histamine	D) Nitric acid
5- What is Exogenous pyrogens ?			
A) IL-1	B) TNF	C) fibrinogen	D) Bacteria products

Question 1	B
Question 2	D
Question 3	A
Question 4	A
Question 5	D

PATHOLOGY TAEM 444



PATHOLOGY TEAMWORK

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Ritaj Alsubaie — LEADER

Manar Alqahtani — LEADER

Abdulaziz Essam — LEADER

Shaden Alotaibi

Rahaf Al turki

Layal Alkhalifah

Norah Alnoshan

Noor Altalag

Aram Alzahrani

Nisreen Alotaibi

Lana Alfouzan

Seeta bin aqeel

Lujain Darraj

Hessa Alamer

Sahar Alfallaj

Nora Albahily

Abdulmalik Aldafs

Abdulmohsen Alrahaimi

Ibrahim Abdallah

Ibrahim Al Bin Ali

Lubna Alamri

Fahad Albalawi

Jana Alrumaihi

Hmood Alsehali

Osama Alotaibi

Ziyad BuKhari

Abdullah Alzoom

Khalid Alkanhal

Mazen Alzahrani

Rakan Alarifi

Mohammed Alshaiban

Abdullah khalid

Sulaiman abdulkarim

pathology.444ksu@gmail.com