Inflammation lecture 6

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INTRO

- My slides are detailed enough, you don't need a sheet. This applies to this lecture and to the neoplasia lectures that I will give you.

- I always do two sets of powerpoint presentations: 1.a detailed version which will be sent to you before the lectures (this summarises the book and adds to it) and 2. a smaller version that I will use in the lectures which will mainly contain pictures, but don't worry, everything in the detailed version will be discussed during the lecture.

- Please have a look at the book, it is a good habit to read from books.

- Please stop me at any time if you have a question or if you need an explanation of any point.

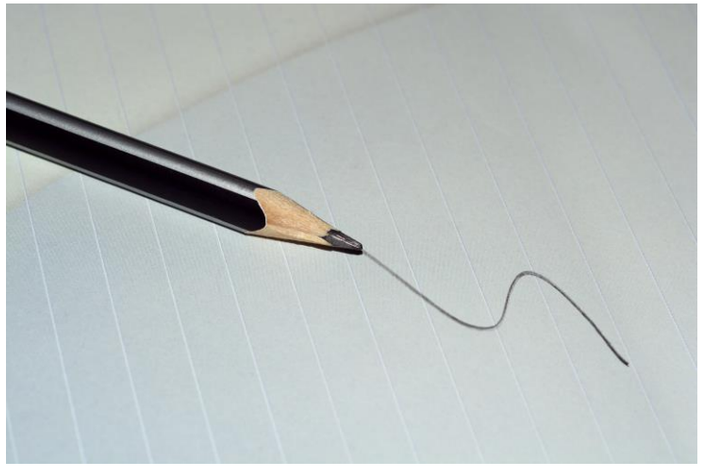
Topics to be covered

- 1. Outcomes of acute inflammation
- 2. Chronic inflammation: definition, causes, cells ad mediators
- 3. Granulomatous inflammation: a special type of chronic inflammation.
- 3. Systemic effects of inflammation

Think of inflammation as a battle
How do battles finish??

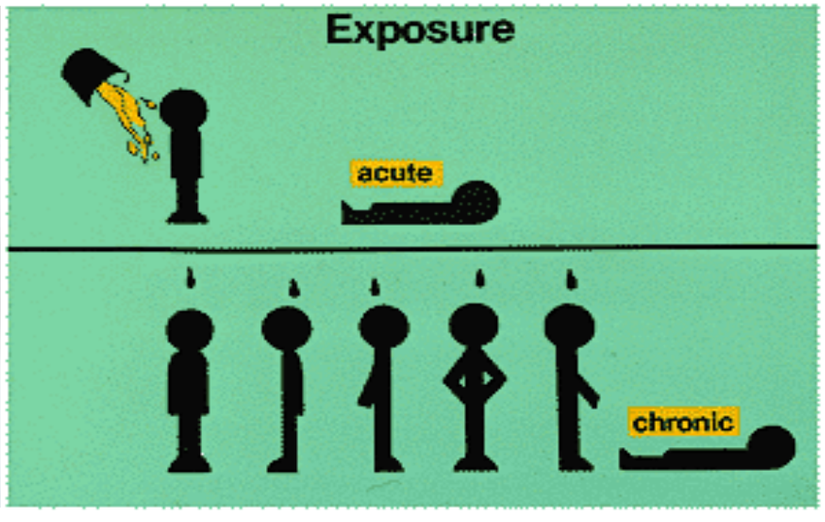
Outcome of acute inflammation; there are three possible outcomes:

Resolution



Fibrosis and scarring

Chronic

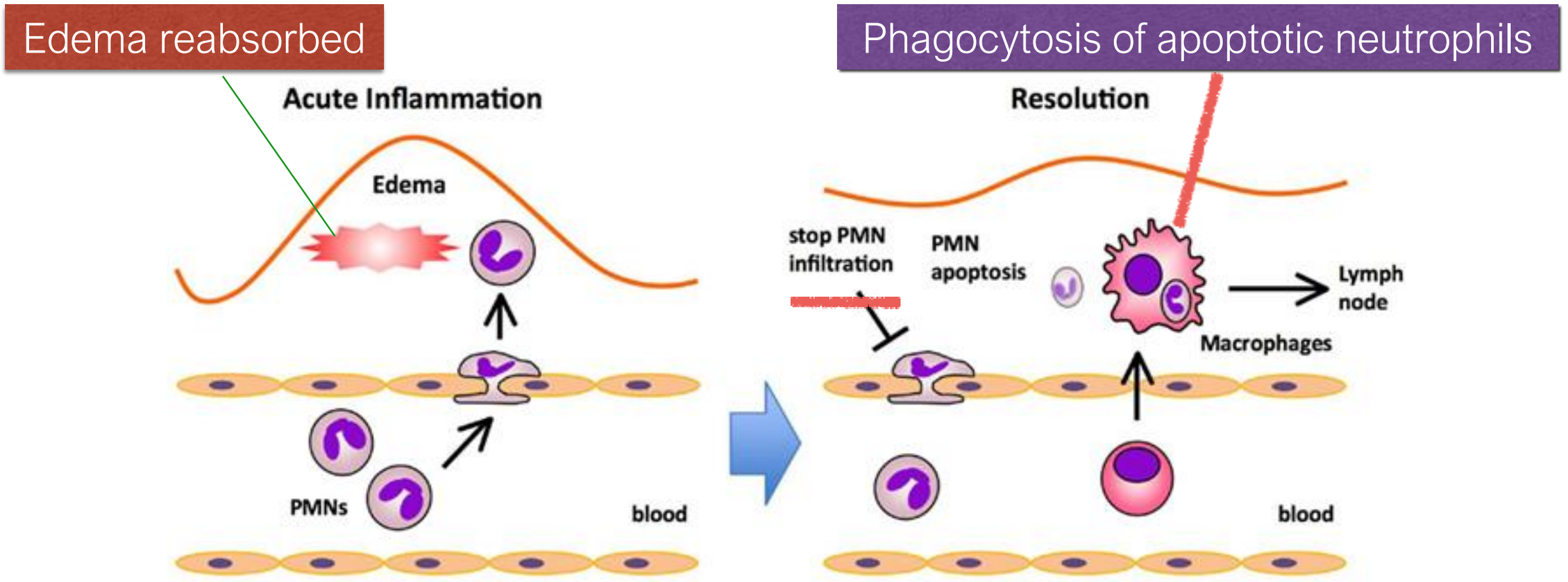


1.Resolution

-Resolution means: restoration of the site of acute inflammation to normal.

-Resolution involves **removal of cellular debris and microbes by macrophages**, and **resorption of edema fluid by lymphatics.**

Resolution


Edema reabsorbed
Phagocytosis of apoptotic neutrophils
Acute Inflammation
Edema
PMNs
blood
Resolution
stop PMN infiltration
PMN apoptosis
Lymph node
Macrophages
blood

Resolution

Happens when:

1. Injury is limited and short lived.
2. No or minimal tissue damage.
3. Injured tissue can regenerate.

2. Healing by connective tissue (fibrosis and scarring)

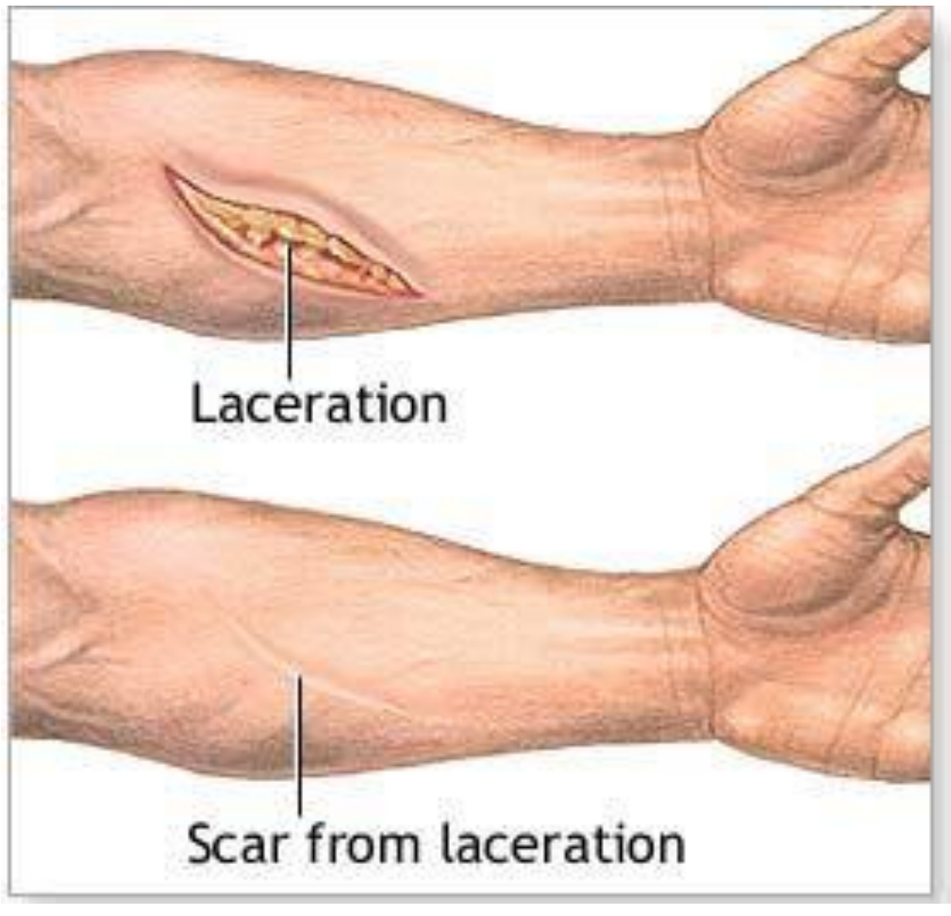
Happens when:

1.The inflammatory injury involves tissues that are incapable of regeneration, OR

2. When there is abundant fibrin exudation in tissue or in serous cavities (pleura, peritoneum) that cannot be adequately cleared.

-In these situations, connective tissue grows into the area of damage or exudate, converting it into a mass of fibrous tissue, a process also called *organization…you will study this with Dr Mousa.*

scar formation



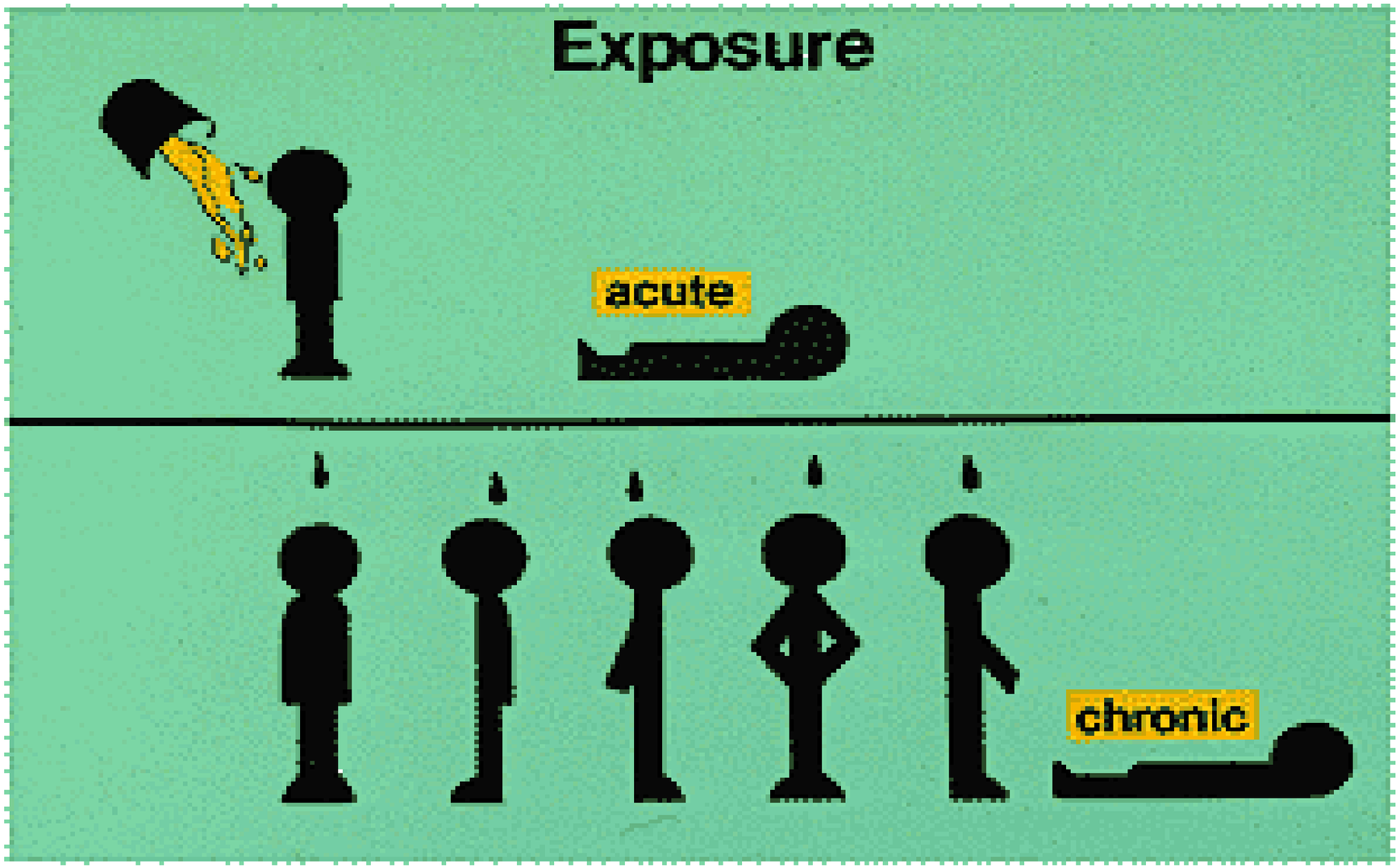
3. Chronic inflammation

Happens when:

-There is substantial tissue destruction,

-Or if the inflammatory response cannot be resolved, as a result of either the persistence of the injurious agent or some interference with the normal process of healing.

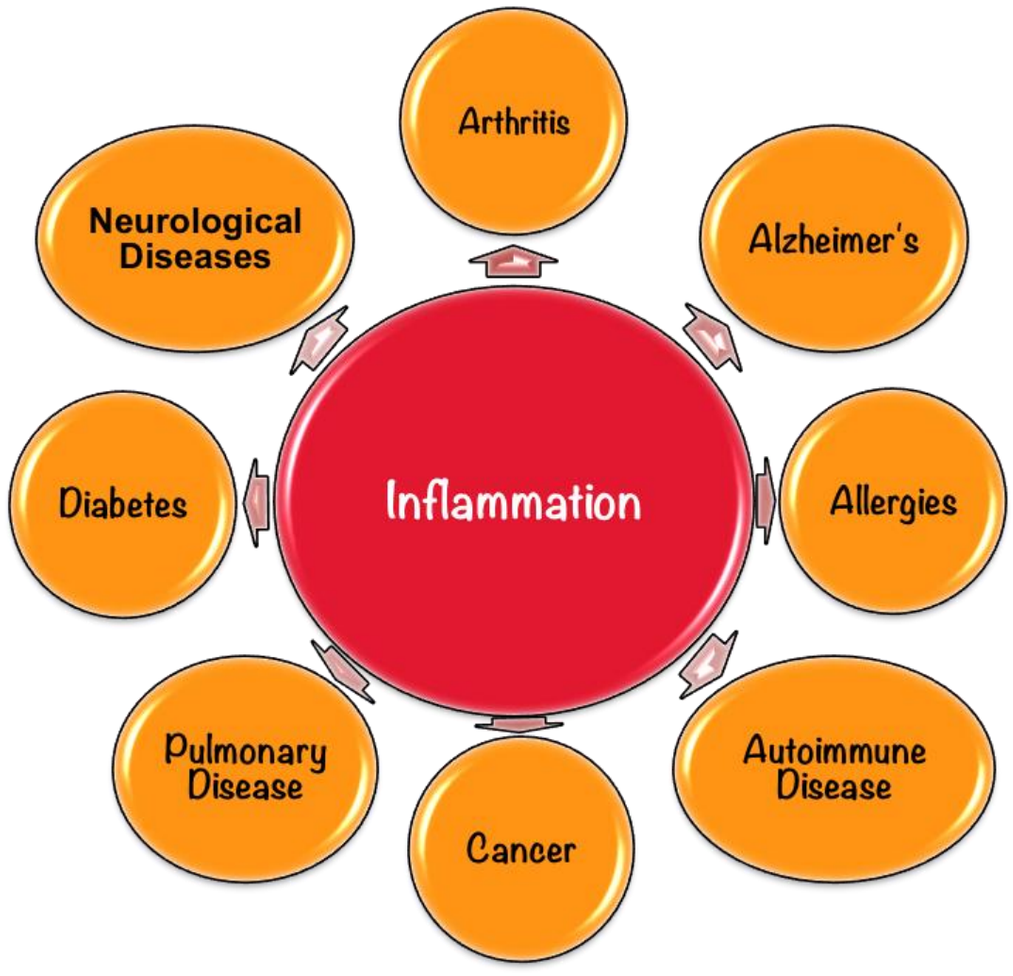
Acute versus chronic



Chronic inflammation: definition

Chronic inflammation is a response of prolonged duration (weeks or months) in which (1)inflammation, (2)tissue injury and (3)attempts at repair *coexist*, in varying combinations.

Chronic inflammation plays a role in many diseases.



NOTE

Chronic inflammation may follow acute inflammation

OR: may begin *insidiously,* as a low grade response *without* any manifestations of a preceding acute reaction.

Insidious means: gradual, subtle, happening slowly.

Causes of chronic inflammation:

- 1- un-resolving acute inflammation
- 2-Persistent infections: (TB, Syphilis, Fungi, viruses)
- 3-Prolonged exposure to toxic agents. (Silica, plasma lipids like in atherosclerosis)
- 4-Autoimmune disease (Rheumatoid arthritis, Inflammatory bowel disease)

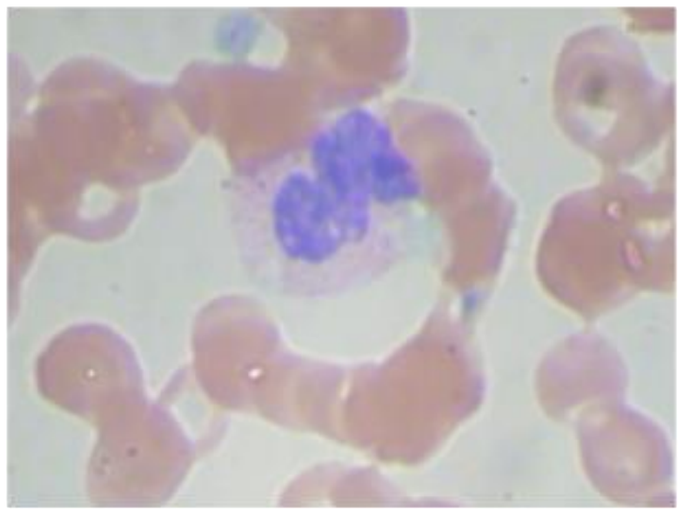
Characteristics of Chronic inflammation

- 1. Infiltration with mononuclear cells.
- 2.Tissue destruction
- 3.Repair (new angiogenesis & Fibrosis)

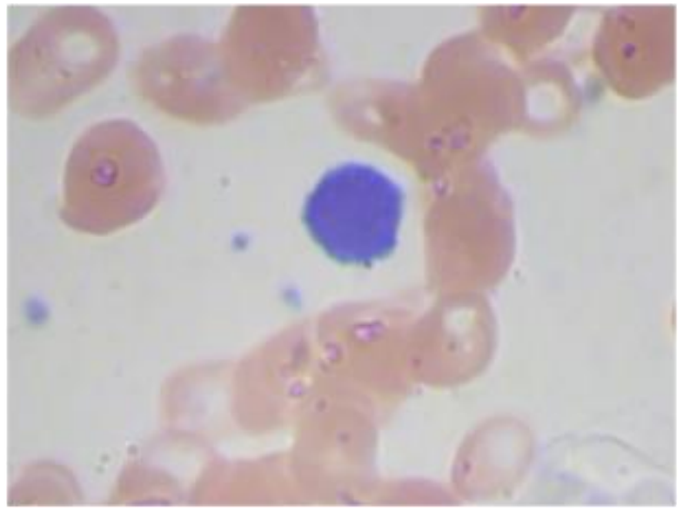
What are the mononuclear cells?

- Mononuclear white blood cells (WBC) contain one single nucleus.. like monocytes and lymphocytes. these cells predominate in chronic inflammation

- Polymorphonuclear are WBCs with multi-lobed nuclei, like the neutrophils, which are predominant in acute inflammation.



Polynuclear

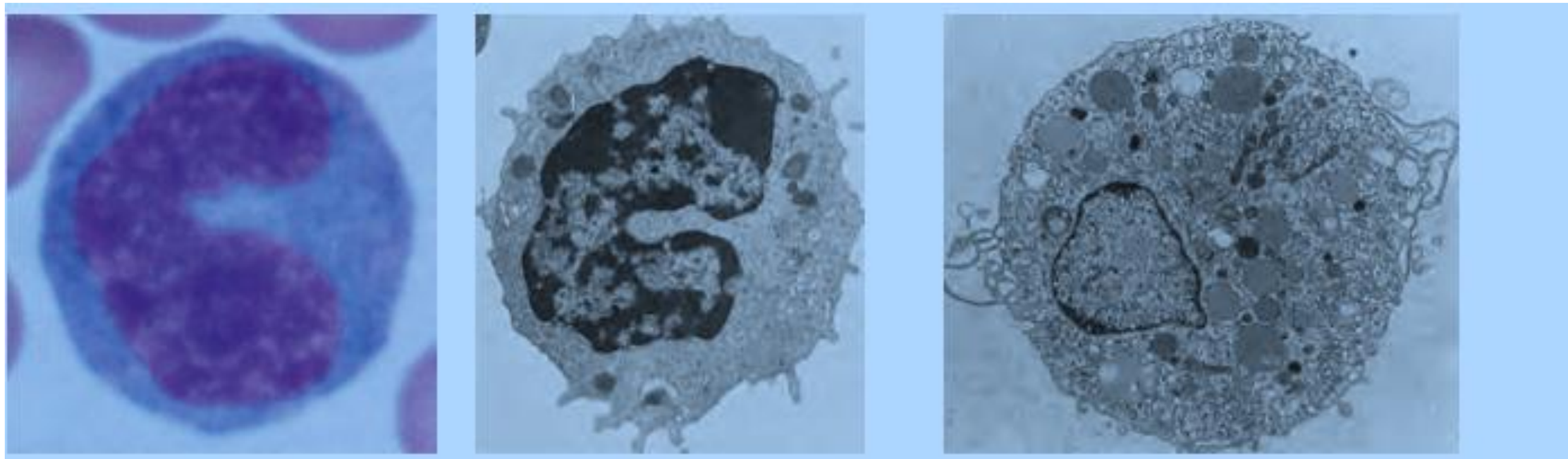


Mononuclear

- Cells of chronic inflammation

- Macrophages (monocytes)
- Lymphocytes
- Plasma cells
- Eosinophils
- Mast cells
- *AND.. NEUTROPHILS.. you can still see these in chronic inflammation.*

Macrophages



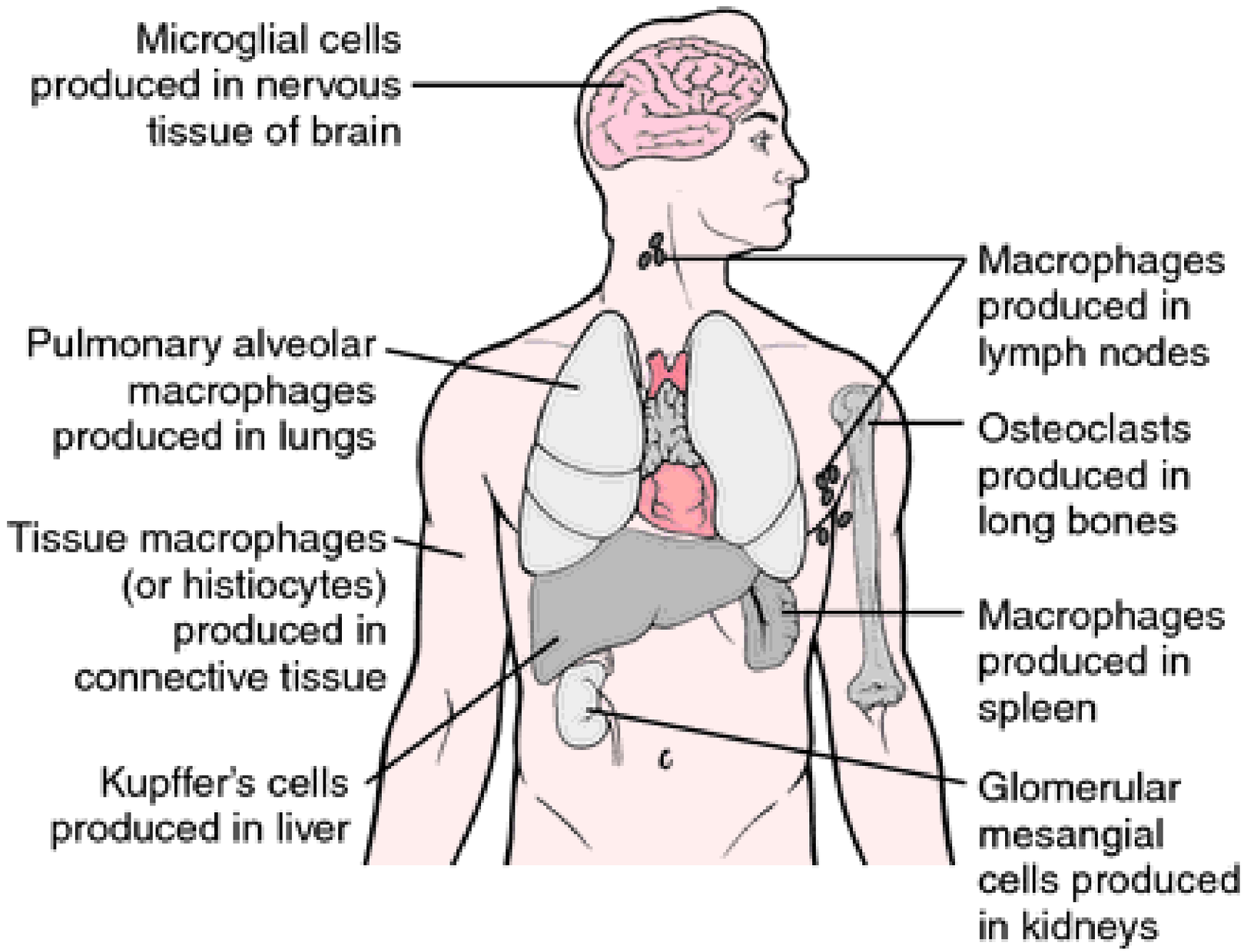
Monocyte

Activated macrophage

Macrophages

- Are the <u>dominant</u> cells of chronic inflammation
- derived from blood monocytes
- normally diffusely scattered in most connective tissues, and also in organs such as the liver (Kupffer cells), spleen and lymph nodes (called sinus histiocytes), central nervous system (microglial cells), and lungs (alveolar macrophages)… ALL these form the **mononuclear phagocyte system.**

Mononuclear phagocyte system



Note:

The half life of blood monocytes is about 1 day, whereas the life span of tissue macrophages is several months or year

Role of macrophages

1. Phagocytosis.

2. Macrophages **initiate tissue repair** and are involved in scar formation and fibrosis.

3. Macrophages **secrete mediators of inflammation,** such as cytokines (TNF, IL1, chemokines, and others) and eicosanoids.

4. Macrophages **display antigens to T lymphocytes and respond to signals from T cells**

Macrophage activation

- There are two paths of macrophage activation
- 1. Classical pathway resting in activated macrophages called M1 macrophages that play a major role in inflammation
- 2. Alternative pathway resulting in M2 macrophages that play a role in anti-inflammation and tissue repair and necrosis.

Classical pathway

- induced by 1. *microbial products* such as endotoxin, which engage TLRs and other sensors; 2. *T cell–derived signals*, importantly the cytokine IFNγ, in immune responses; or by 3. *foreign substances* including crystals and particulate matter.

-Classically activated (also called M1) macrophages produce NO and ROS and up-regulate lysosomal enzymes, all of which enhance their ability to **kill ingested organisms, and secrete cytokines that stimulate inflammation.**

-These macrophages are important in host defence against microbes and in many inflammatory reactions.

Alternative pathway

- induced by cytokines *other than IFNγ*, such as **IL4 and IL13, produced by T lymphocytes and other cells**.

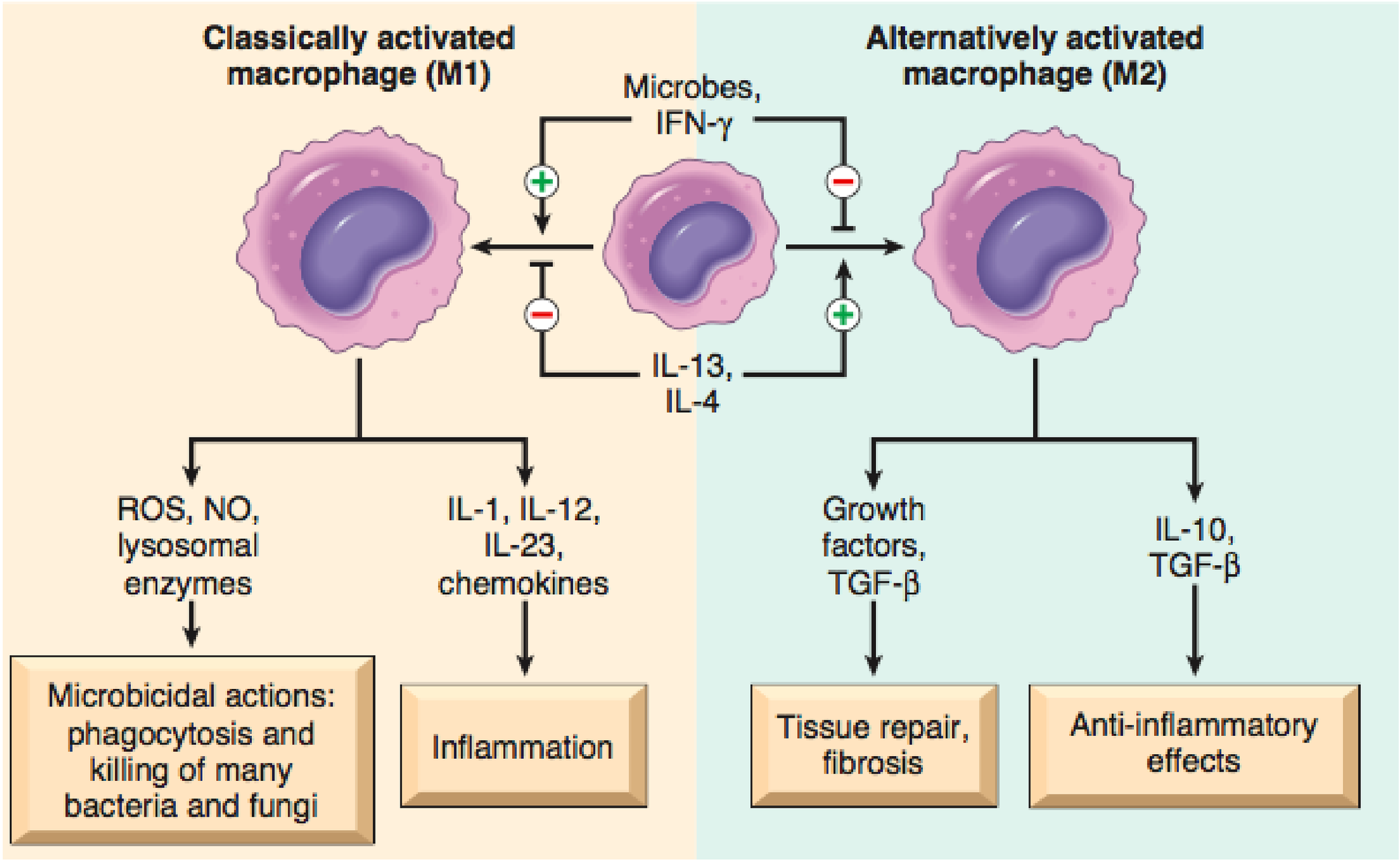
-These macrophages are <u>not actively microbicidal</u> and their cytokines may actually <u>*inhibit the classical activation pathway*</u>; instead, the principal function of alternatively activated (M2) macrophages is in **tissue repair.** -They secrete <u>growth factors that promote angiogenesis, activate fibroblasts, and stimulate collagen synthesis.</u>

Note

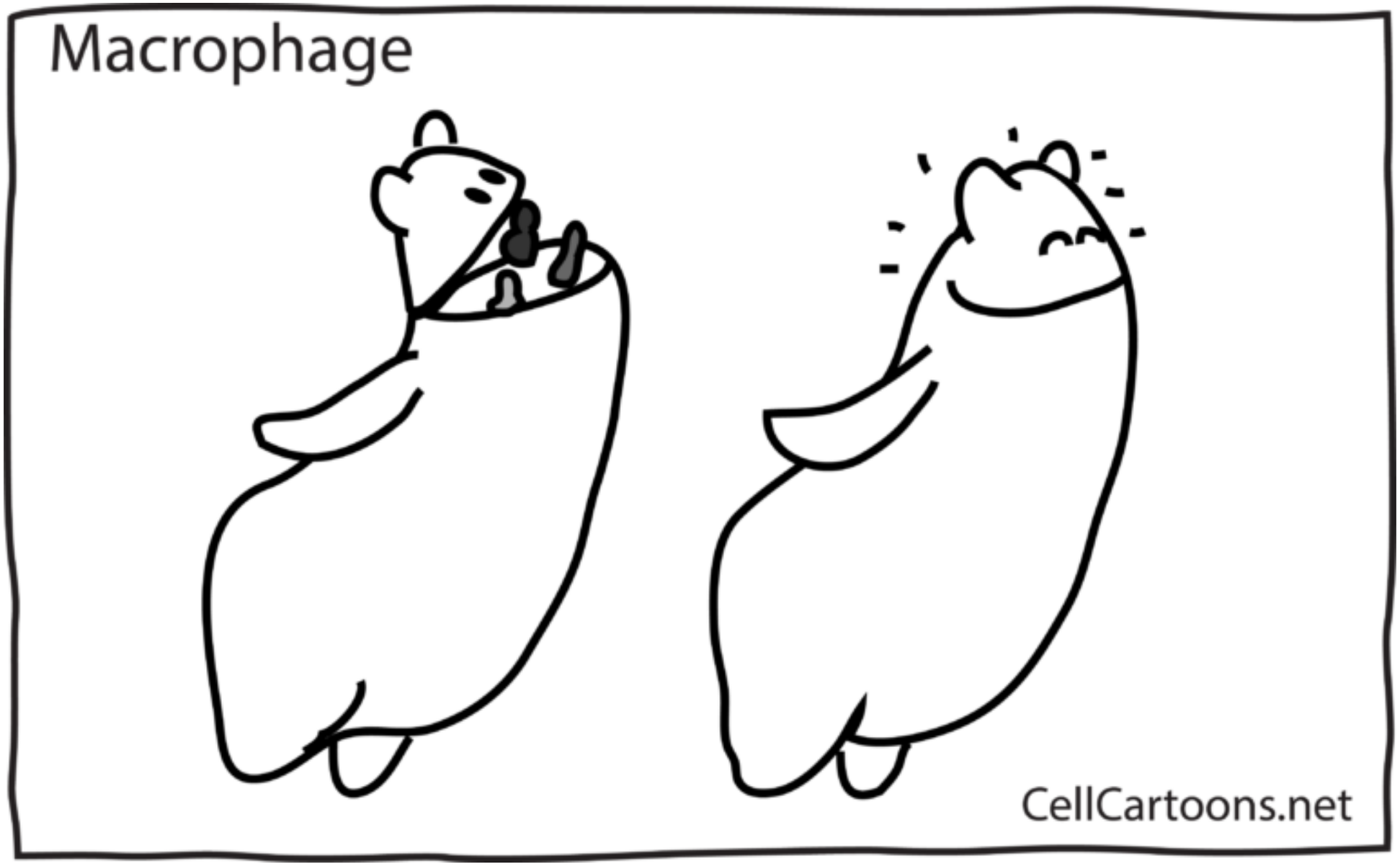
It is probable that in response to most injurious stimuli, the first activation pathway is the classical one, designed to destroy the offending agents, and this is **followed by** alternative activation, which initiates tissue repair.

However, such a precise sequence is *not well - documented in most inflammatory reactions*.

MI and M2 macrophages



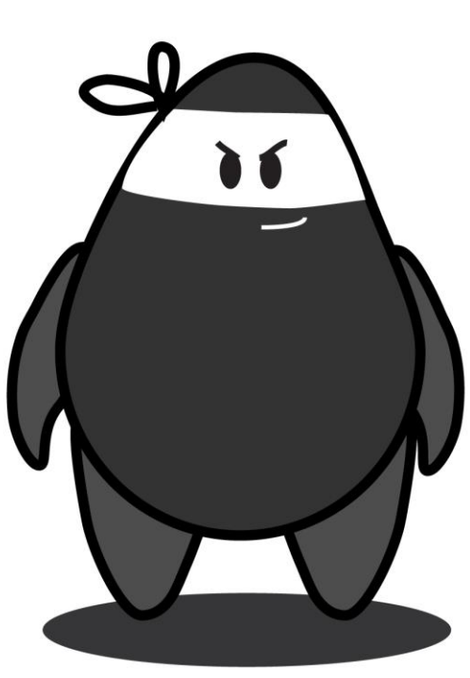
What's the shared trait between macrophages and med students?



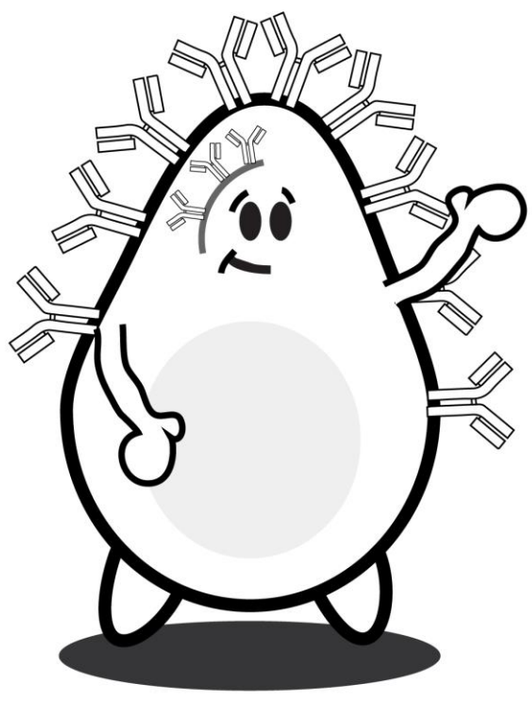
Lymphocytes

Lymphocytes

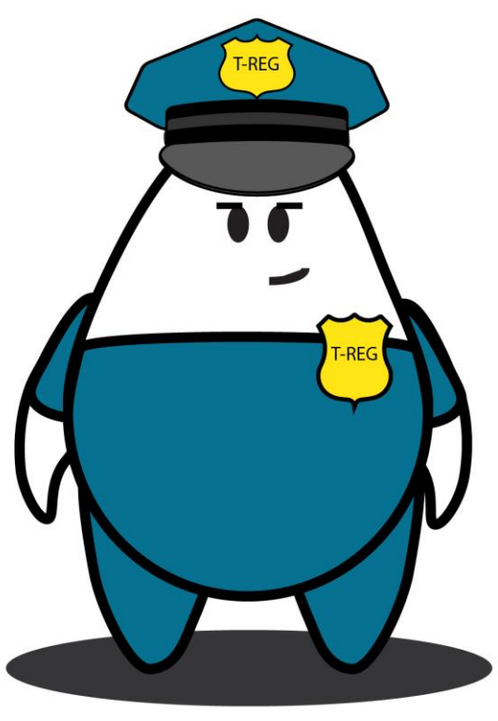
CD8 T Cell



B Cell



Regulatory T Cell



CD4 T Cell

CellCartoons.net

Lymphocytes

- Lymphocytes play a major role in immune reactions but are also important in inflammation.
- There are mainly 3 types of lymphocytes: B and T lymphocytes and natural killer cells (NK)
- Inflammatory reactions where lymphocytes are activated tend to be **persistent and severe**.
- Lymphocytes may be the **dominant** population in the chronic inflammation seen in **autoimmune and other hypersensitivity diseases**.
- *Lymphocytes are recruited to the site of inflammation via cytokines secreted by activated macrophages, mainly TNF, IL1, and chemokines*

T Lymphocytes

-There are two main types of T lymphocytes: T helper lymphocytes (CD4) and Cytotoxic T lymphocytes (CD8).

- Helper T “helps” several other cells during immune responses, they orchestrate the immune response.

-Cytotoxic T cells are killer T that kill other cells.

-There are several subtypes of T helper cells that play a major role in chronic inflammation:

. T_H1 cells produce the cytokine IFNγ, which activates macrophages by the classical pathway.

. TH2 cells secrete IL4, IL5, and IL13, which recruit and activate eosinophils and are responsible for the

alternative pathway of macrophage activation.

. T 17 cells secrete IL17 and other cytokines, which induce the secretion of chemokines responsible for recruiting neutrophils (and monocytes) into the reaction.

-Both T_H1 and T_H17 cells are involved in defence against many types of bacteria and viruses and in autoimmune diseases.

-T_H2 cells are important in defence against helminthic parasites and in allergic inflammation.

Don’t worry too much about these details.. you will study them again in immunology.

Interaction between T lymphocytes and macrophages

-Lymphocytes and macrophages interact in a bidirectional way, and these interactions play an important role in propagating chronic inflammation.

-Macrophages display antigens to T cells, express membrane molecules (called costimulators), and produce cytokines (IL12 and others) that stimulate T cell responses.

-Activated T lymphocytes, in turn, produce cytokines, which recruit and activate macrophages, promoting more antigen presentation and cytokine secretion.

-The result is a cycle of cellular reactions that fuel and sustain chronic inflammation

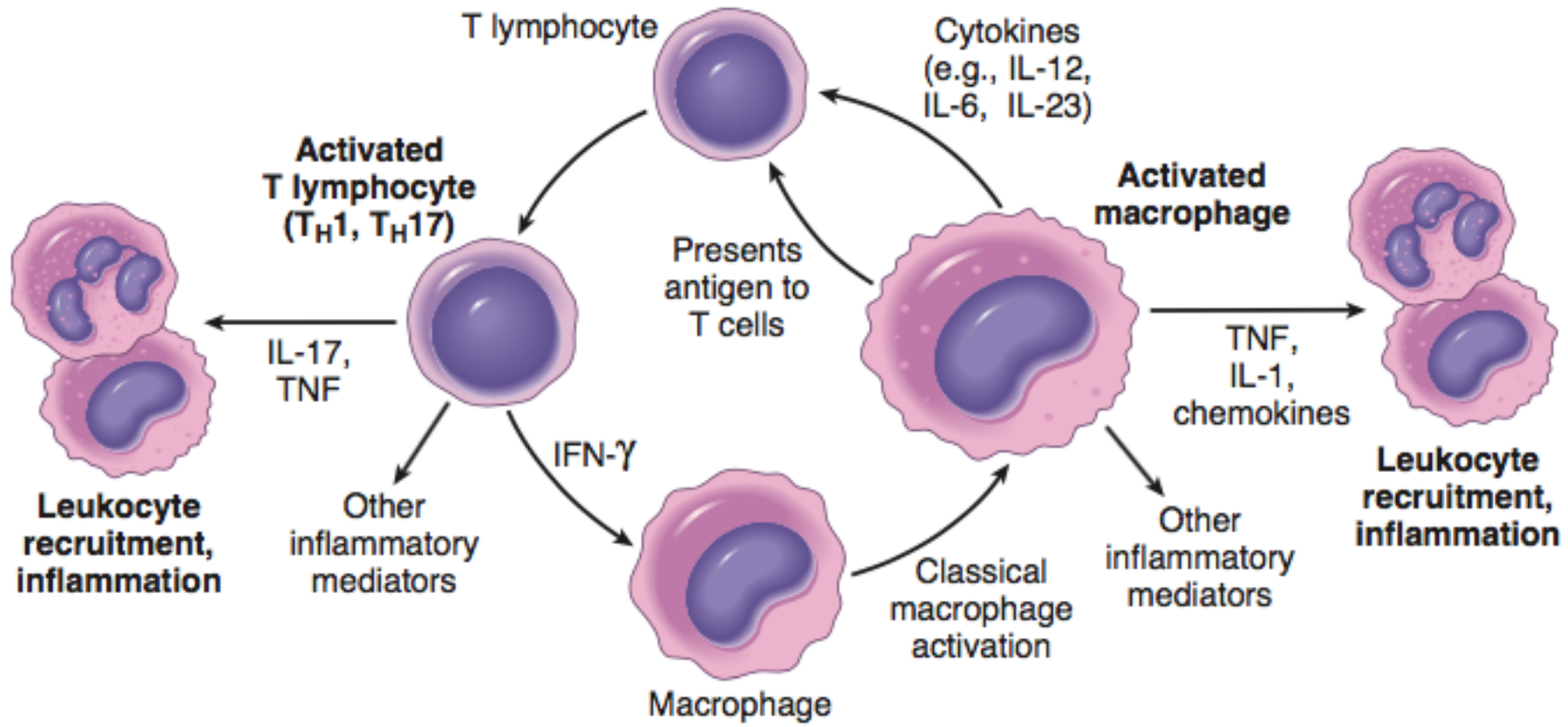
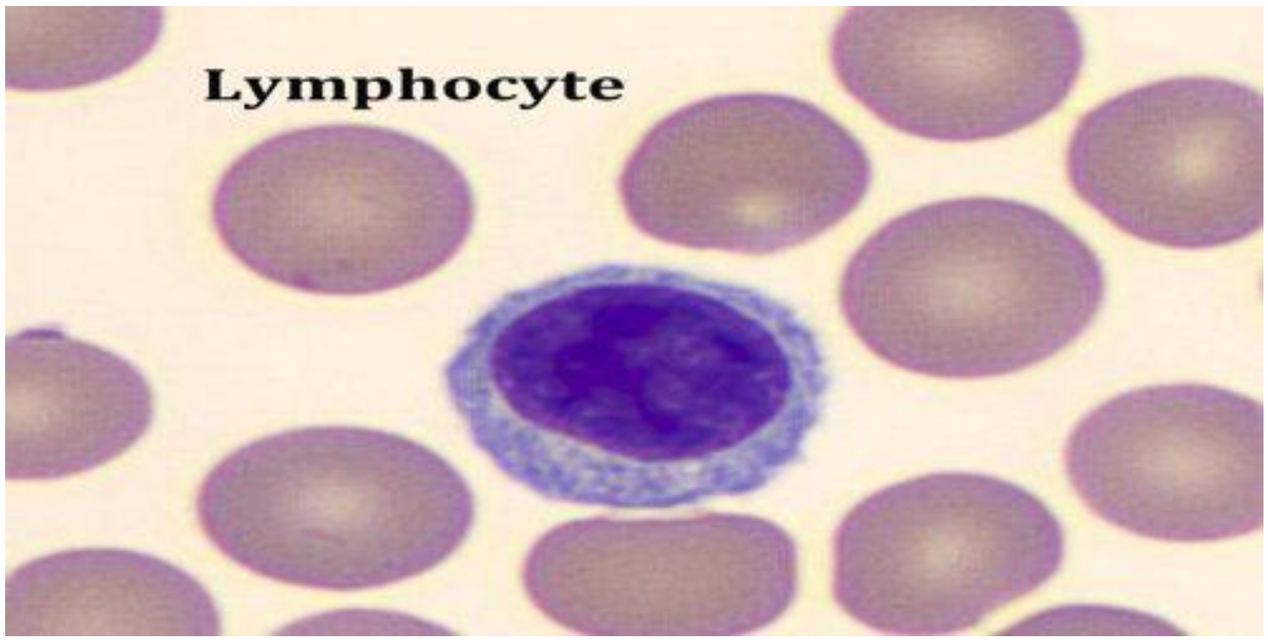


Figure 3-21 Macrophage-lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN-γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12.

B lymphocytes

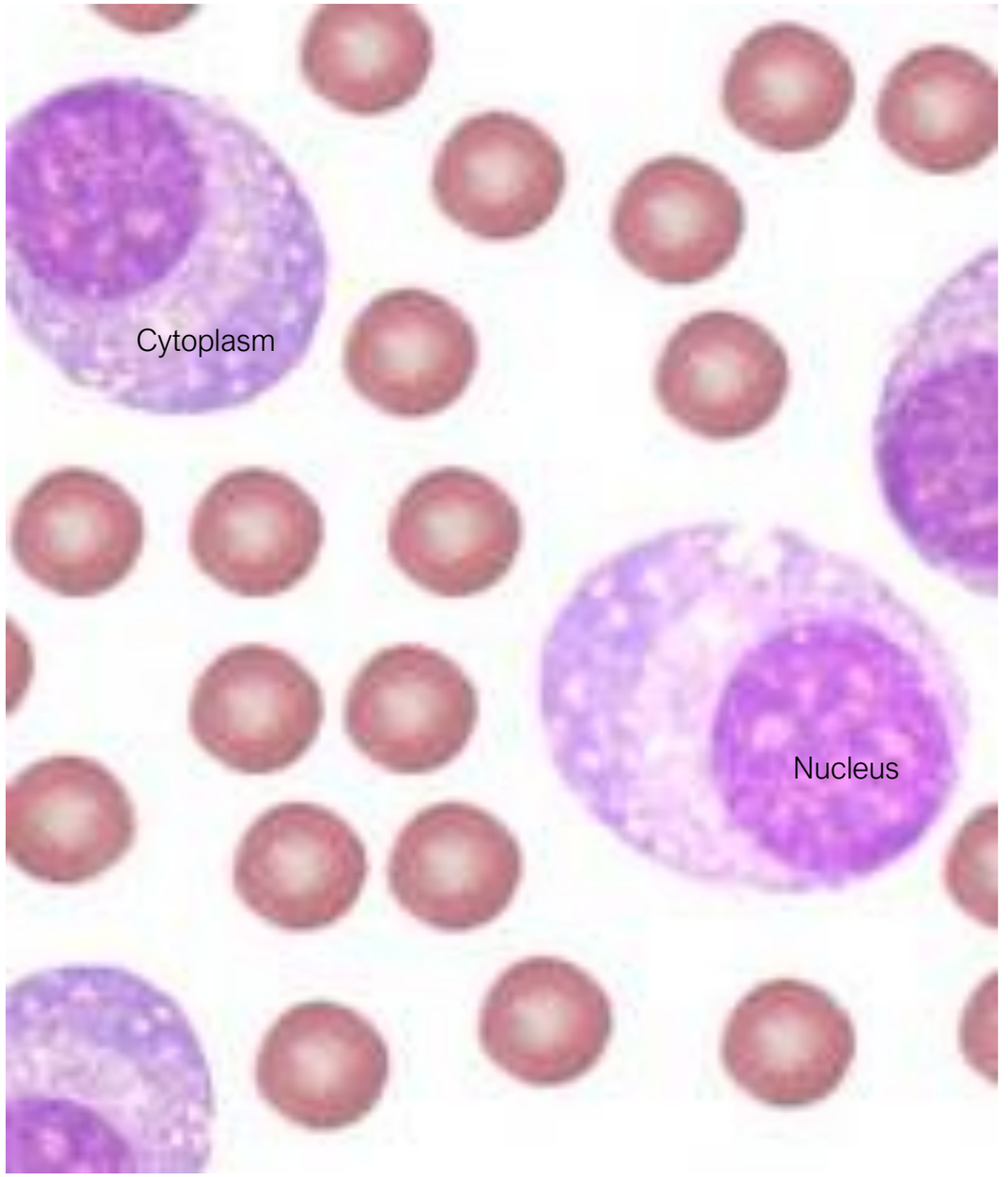
-Activated B lymphocytes can accumulate in sites of chronic inflammation

-They differentiate to plasma cells that secrete antibodies.



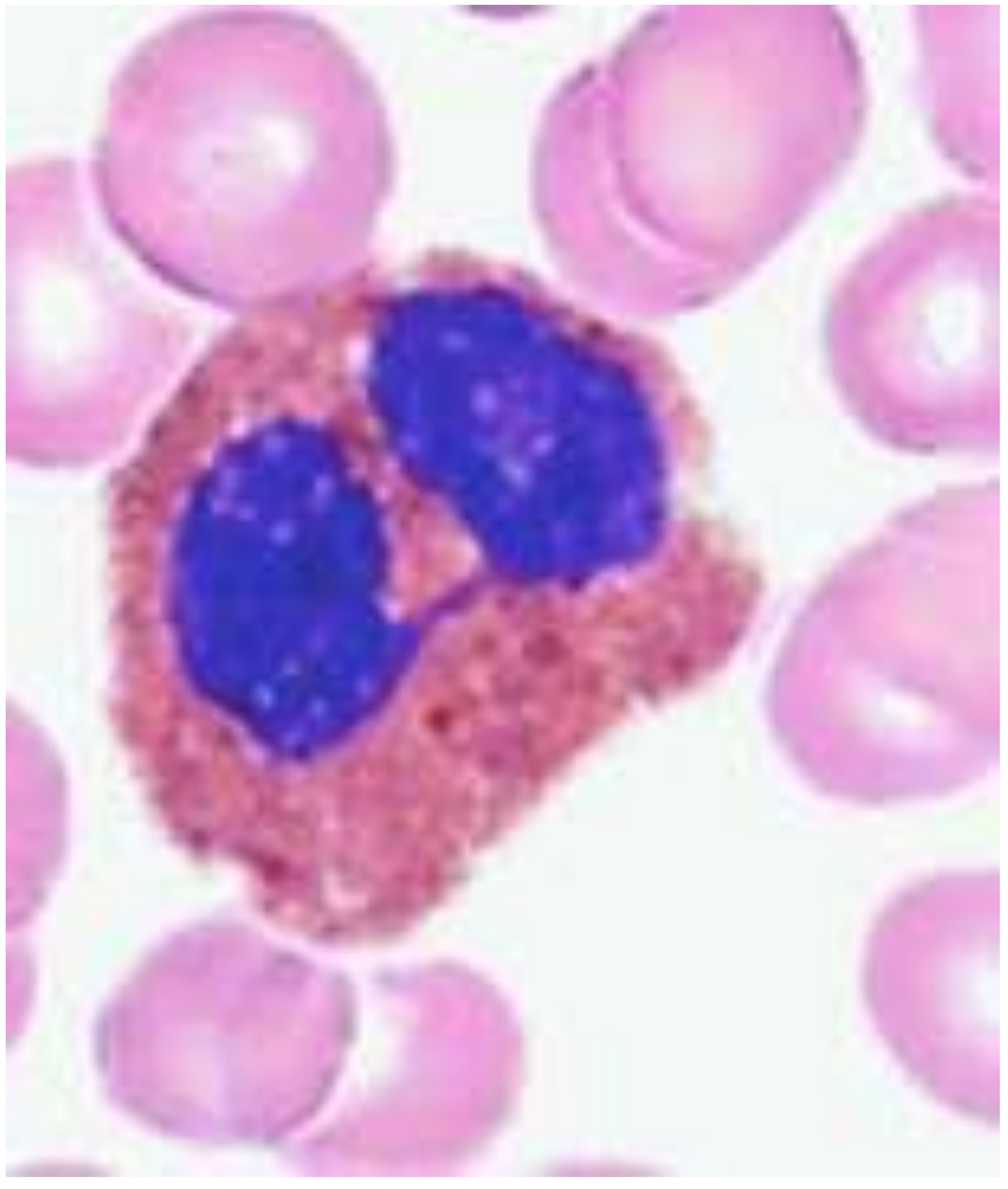
Plasma cells

- Plasma cells are derived from activated B lymphocytes
- They secrete antibodies.
- Note that they have large amount of cytoplasm that pushes the nucleus to the periphery of the cell.
- This cytoplasm is needed as it contains the organelles needed for protein (antibodies) synthesis.



Eosinophils

- Note that eosinophils are polymorphonuclear cells.
- They contain beautiful red (eosinophilic) granules
- They are my favourite cells !!!!



Eosinophils

-**Eosinophils** are abundant in immune reactions mediated by IgE and in parasitic infections

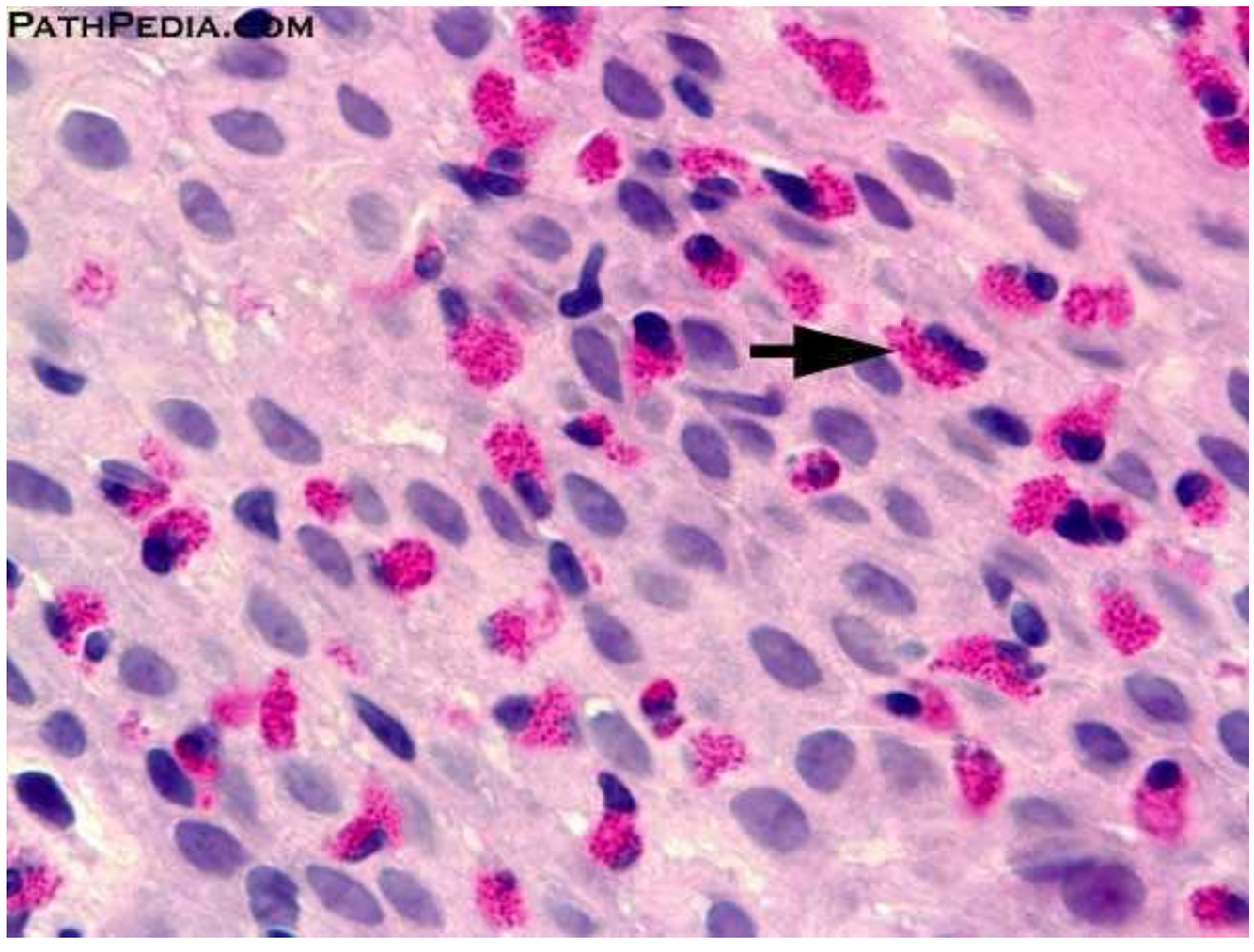
-Their recruitment is driven by adhesion molecules and special chemokines (e.g., eotaxin) derived from leukocytes and epithelial cells.

-Eosinophils have granules that contain *major basic protein,* a highly cationic protein that is toxic to parasites

Eosinophils are seen mainly in two types of inflammatory responses:

- 1.parasitic infections
- 2.as part of immune reactions mediated by IgE, typically associated with allergies.

Inflammatory infiltrate rich in eosinophils.

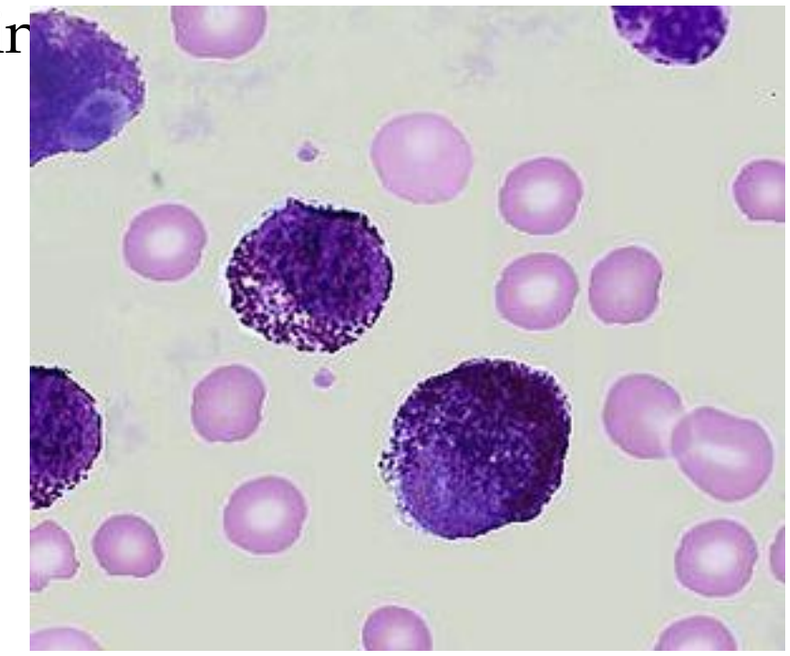


Mast cells

Mast cells are widely distributed in connective tissues and participate in both acute and chronic inflammatory reactions.

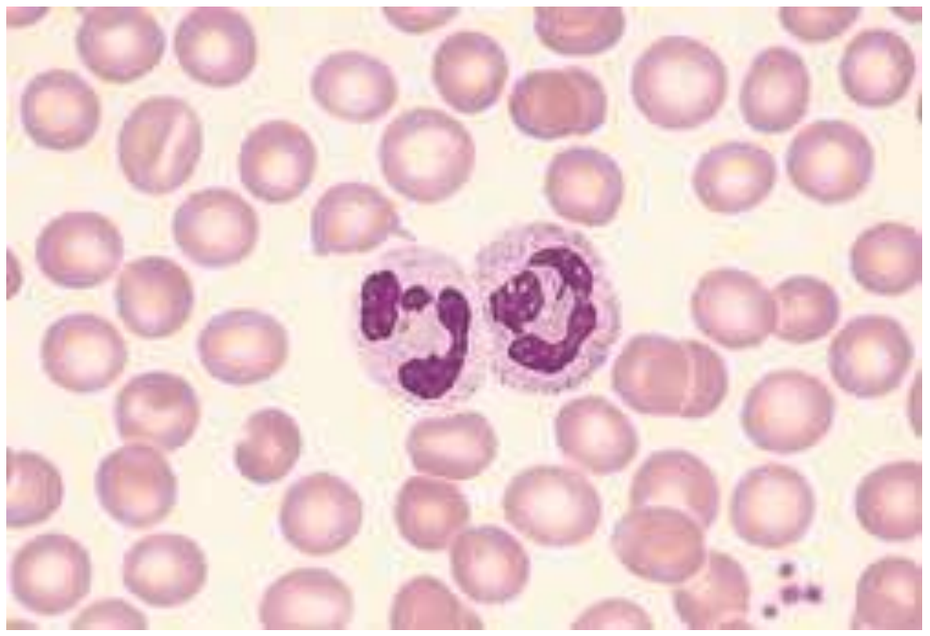
Mast cells play a role in allergic reactions to foods, insect venom, or drugs, sometimes with catastrophic results (e.g., anaphylactic shock).

Mast cells are also present in chronic in



NEUTROPHILS

Although **neutrophils** are characteristic of acute inflammation, many forms of chronic inflammation, lasting for months, continue to show large numbers of neutrophils, induced either by persistent microbes or by mediators produced by activated macrophages and T lymphocytes.



Granulomatous inflammation

- This is a special type of chronic inflammation characterised by the presence of aggregates of macrophages called granulomas.

- SO; a granuloma is an aggregate of many activated macrophages (= epitheloid histiocytes, called as such because when the macrophages are activated they might look morphologically like epithelial cells.)

Granulomatous inflammation:Definition

Granulomatous inflammation is a form of chronic inflammation characterised by collections of activated macrophages, often with T lymphocytes, and sometimes associated with central necrosis.

Granulomas

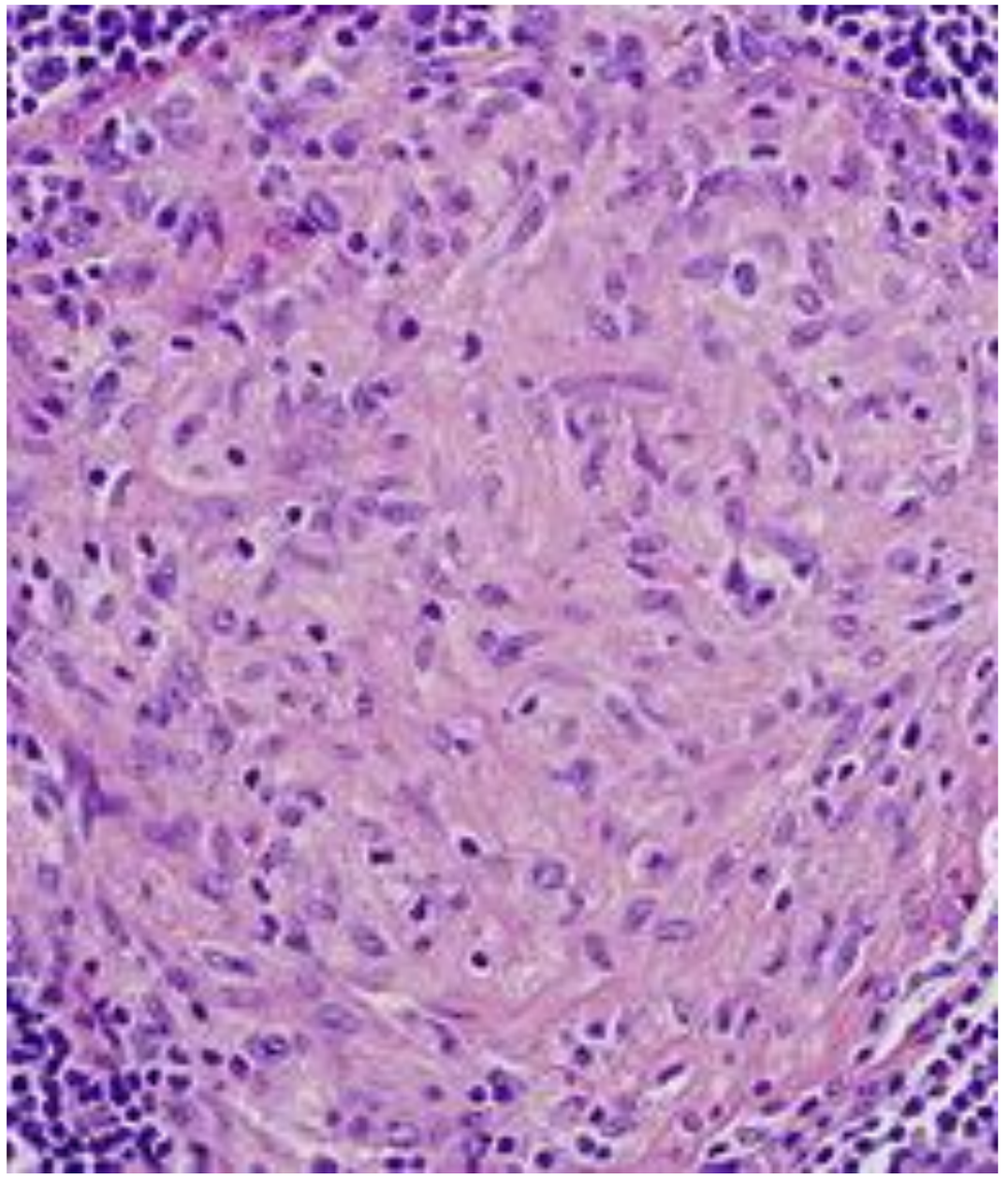
-Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate. In this attempt there is often strong activation of T lymphocytes leading to macrophage activation

-The activated macrophages may develop abundant cytoplasm and begin to resemble epithelial cells, and are called *epithelioid cells*.

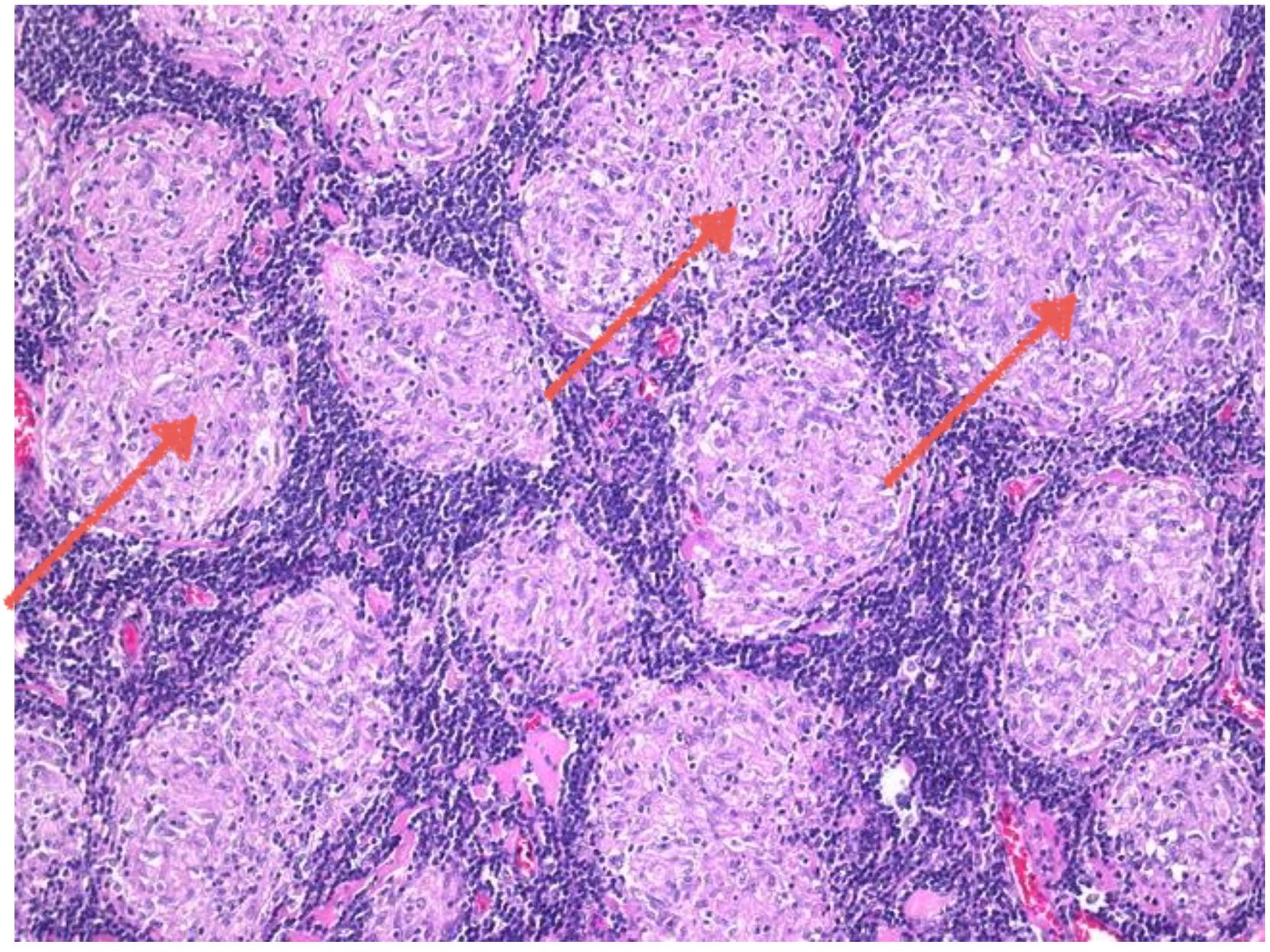
-Some activated macrophages may fuse, forming multinucleate *giant cells*.

- Granuloma: this rounded structure in the picture is composed of many macrophages.

- note that the periphery there are lymphocytes… remember the bidirectional activation of these 2 cells.. it plays a major role in granuloma formation.

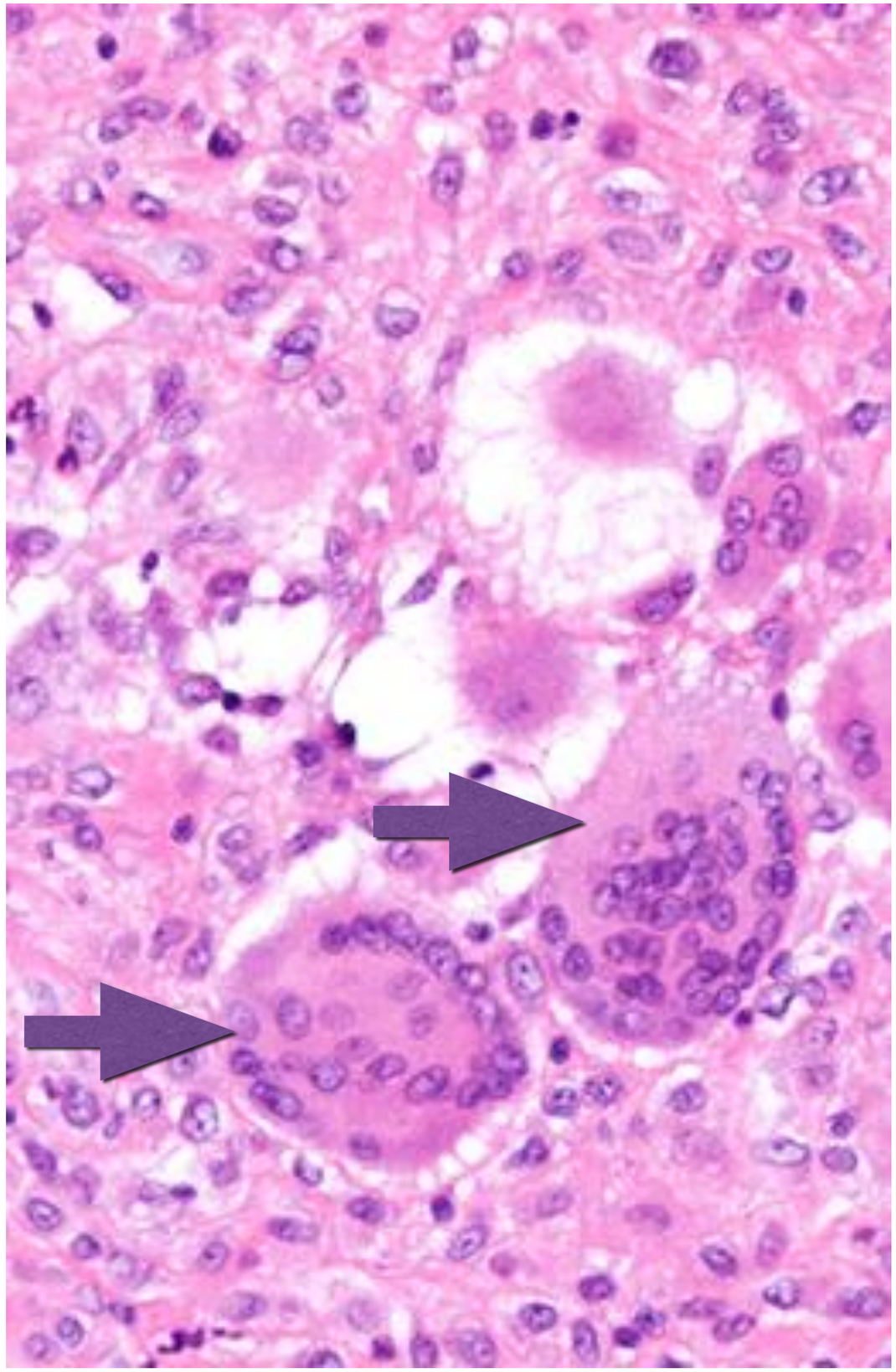


Multiple granulomas, arrows



Giant cells within granulomas

these are fused macrophages, the share the same cytoplasm and contain multiple nuclei



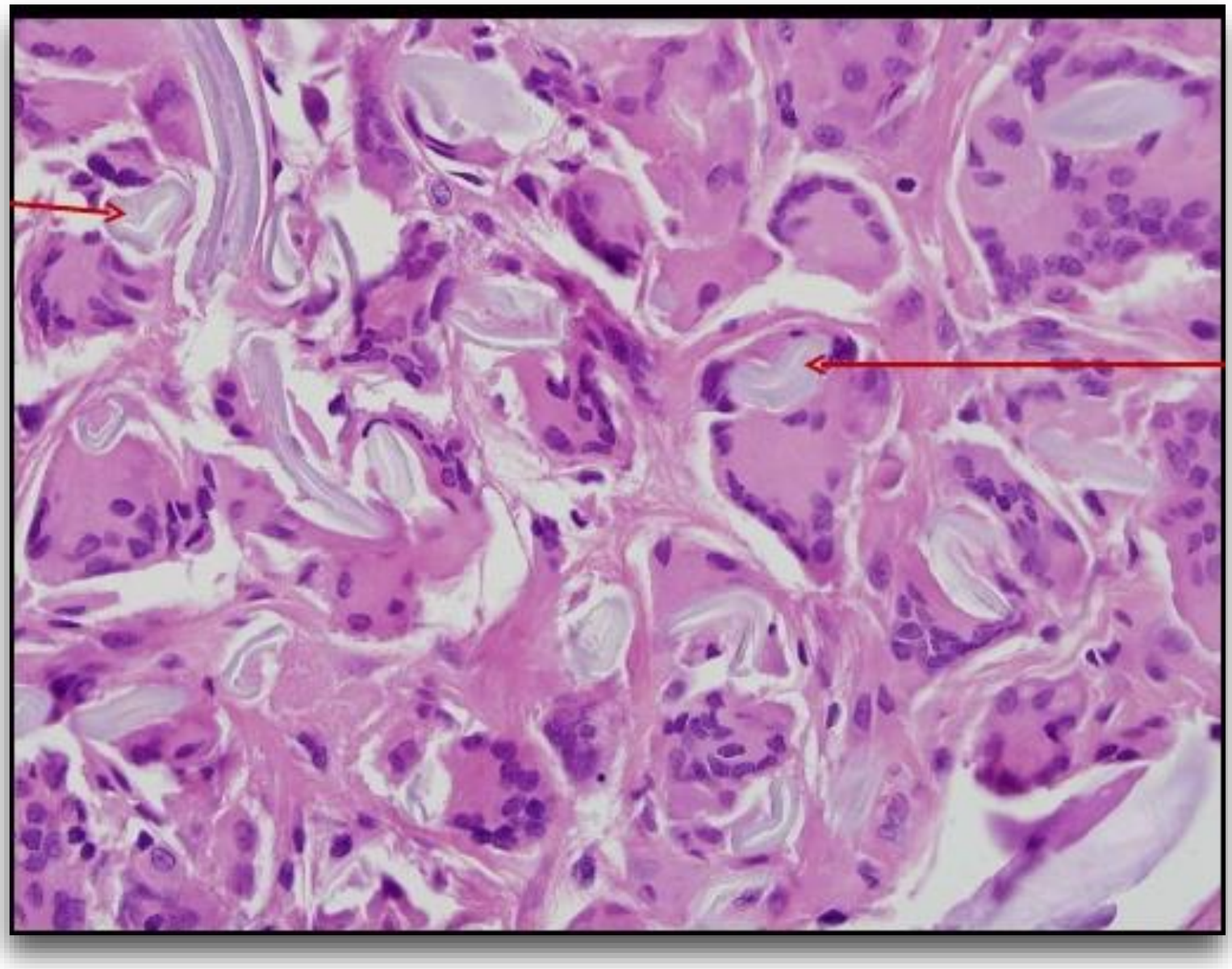
Types of granulomas

There are two types of granulomas, which differ in their pathogenesis:

• **Foreign body granulomas** are incited by relatively inert foreign bodies, in the absence of T cell–mediated immune responses. Typically, foreign body granulomas form around materials such as talc (associated with intravenous drug abuse) , sutures, or other inert material that are large enough to preclude phagocytosis by a macrophage and do not incite any specific inflammatory or immune response.

• **Immune granulomas** are caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response. This type of immune response produces granulomas usually when the inciting agent is difficult to eradicate, such as a persistent microbe or a self antigen. In such responses, macrophages activateT cells to produce cytokines, such as IL2, which activates other T cells, perpetuating the response, and IFN γ, which activates the

Suture granuloma, a type of foreign body granuloma.



Caseating granulomas

-In granulomas associated with certain infectious organisms (most classically *Mycobacterium tuberculosis*), a combination of **hypoxia** and **free radical–mediated injury** leads to a central zone of necrosis.

-Grossly, this has a granular, cheesy appearance and is therefore called **caseous necrosis.**

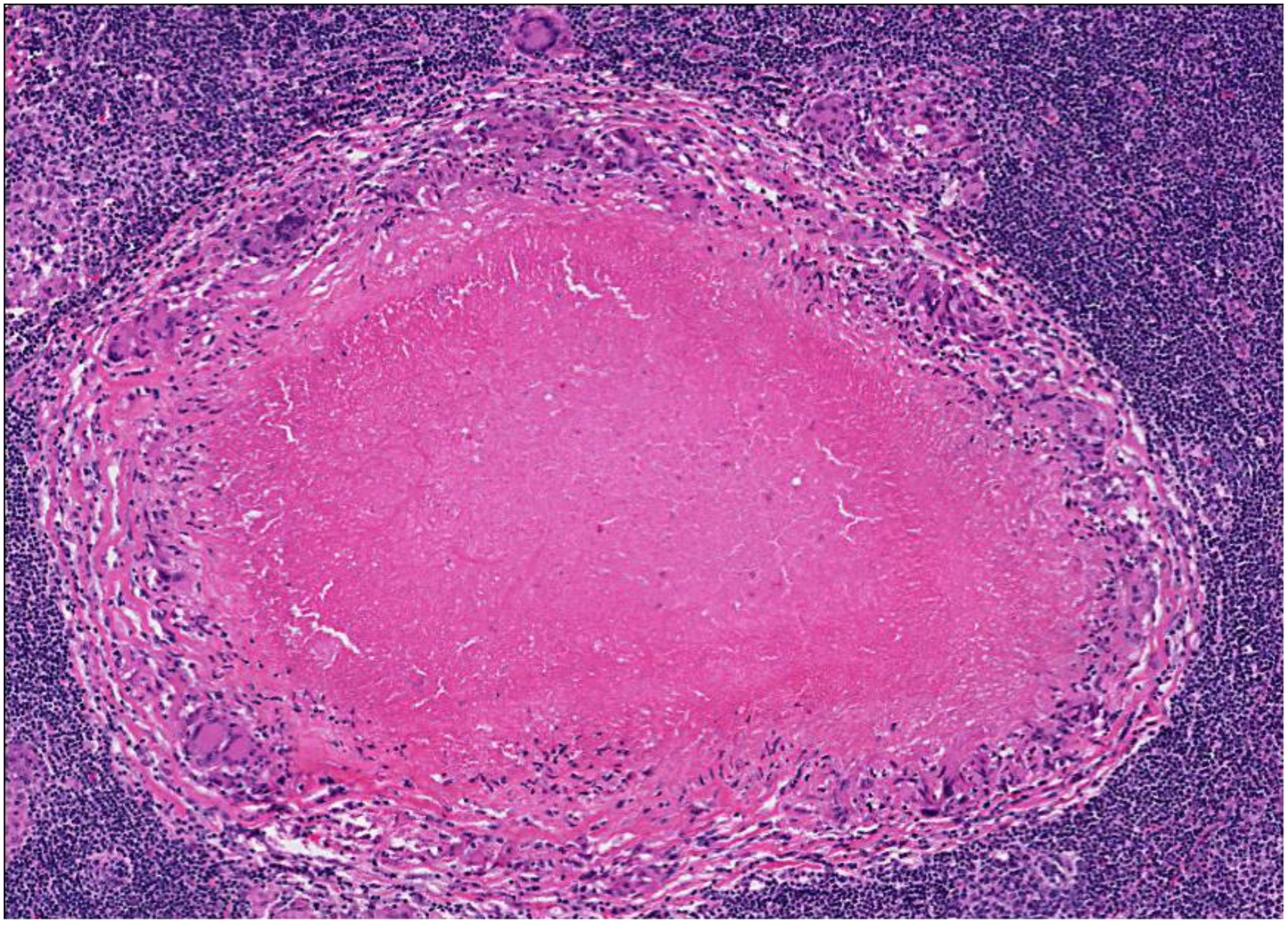
-Microscopically, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with complete loss of cellular details.

Caseating granuloma

- Grossly caseation appears like white cheesy-like material.

- Caseation is mainly seen in tuberculosis (TB)

Caseating granuloma: note the pink structureless material in the centre (the caseous necrosis)



Important note

- there are several diseases that cause granulomas.
- Most granulomas look similar under the microscope.
- Rarely, there might be features that are specific to the underlying cause of the granuloma, like in gout (because we see the granuloma around create crystals) but in the majority of situations there are no specific features.

some causes of granulomas..this is not to be memorised, just have a look!

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, possibly self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

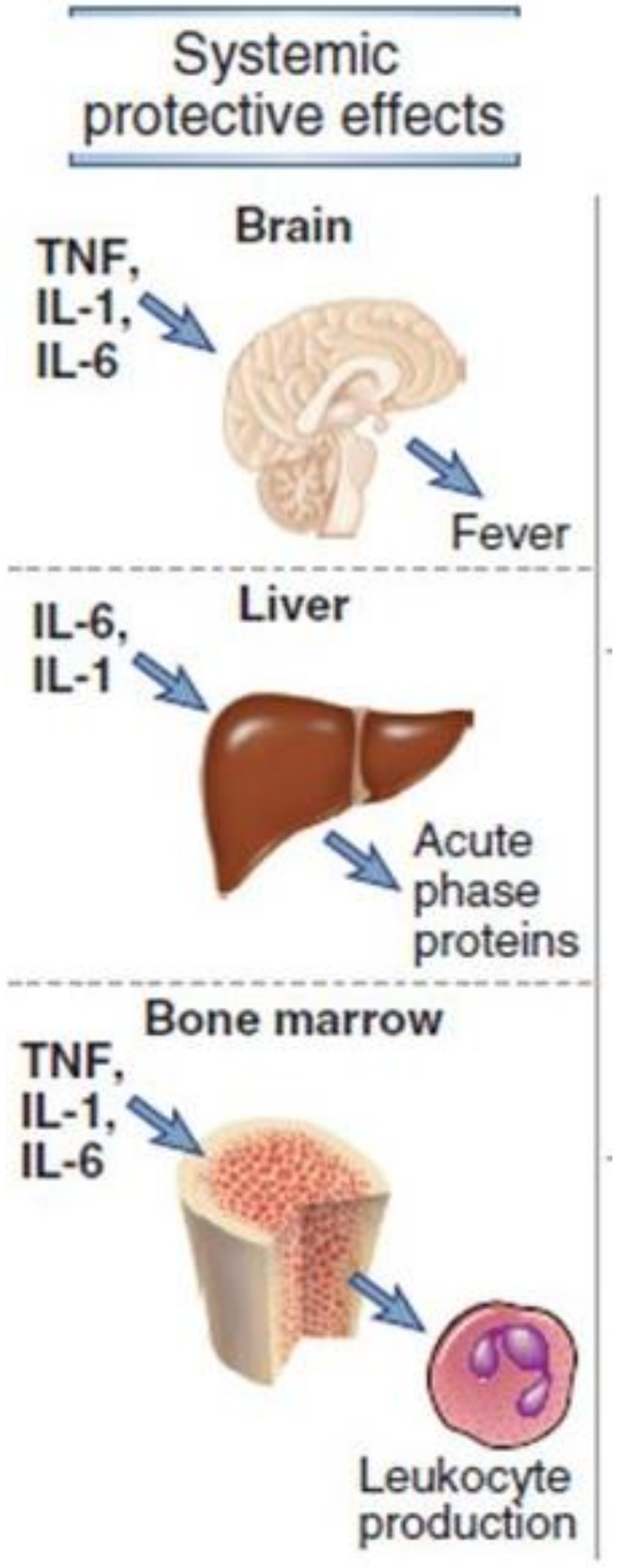
Important causes of granulomatous inflammation

- Diseases associated with granulomatous inflammation include:
- 1.Tuberculosis
- 2.Leprosy
- 3.Sarcoidosis
- 4.Crohn disease

- Note that TB causes caseating and non caseating granulomas
- Sarcoidosis causes non caseating granulomas and is a diagnosis by exclusion.

Systemic effects of inflammation

the inflammatory mediators secreted during inflammation have widespread effect on the body



Systemic effects of inflammation

- = acute phase reaction:
- Most importan mediators: TNF, IL 1 , IL 6.

- Fever,
- elevated acute phase proteins,
- leukocytosis.
- Increased heart rate and blood pressure.

Fever

-Caused by pyrogens

-Pyrogens are substances that stimulate prostaglandin synthesis in the hypothalamus.

-PG in hypothalamus.. Stimulate production of neurotransmitters which increase temperature.

-there are Internal (IL 1 and TNF) and external pyrogens(bacterial lipopolysaccharides).

Acute phase proteins

- Acute phase proteins: plasma proteins synthesised in the liver due to influence of cytokines, mainly IL 6.
- Most important: C reactive protein (CRP), fibrinogen and serum amyloid A (SAA)
-

-CRP and SAA act as opsonins.

-Fibrinogen binds to RBCs so they form aggregates that sediment more rapidly at unit gravity than individual erythrocytes. This is measured clinically by ESR.

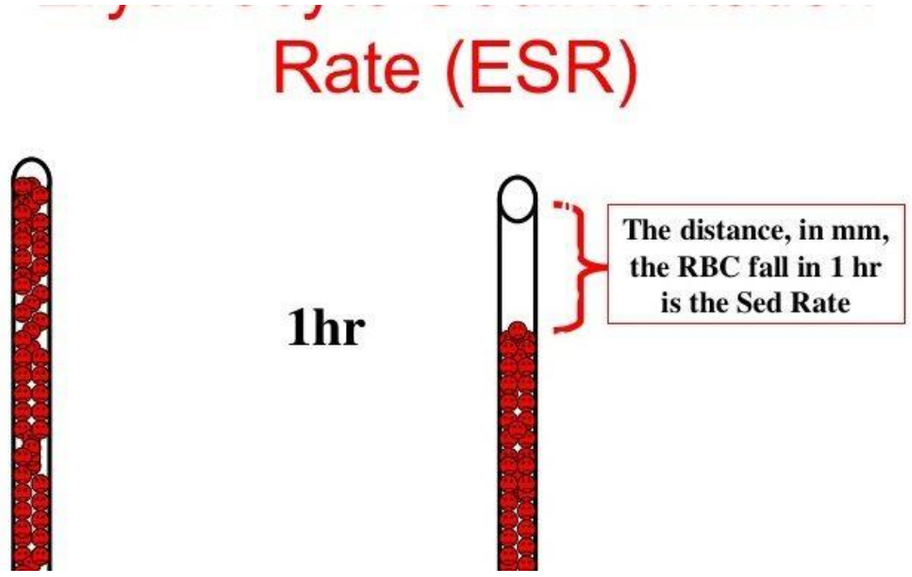
•Erythrocyte sedimentation rate.

ESR

•Measures the sedimentation of RBCs .

•Good measure of inflammation. Elevated

due to increased fibrinogen.



Leukocytosis

- WBCs 15-20 000 cells/ml in inflammation.
- Rarely reaches 40-100000 =leukemoid reaction.

Systemic effects of inflammation

Fever (1-4 C) elevation	**Exogenous pyrogens (LPS) & endogenous pyrogens (IL-1 & TNF). All induce PGE2 secretion**
Acute phase proteins	**CRP, SAA, ESR, Hepcidin**
Leukocytosis (increase WBC)	**15-20 K if more than 40 (leukemoid reaction), left shift**
Others	**Tachycardia, Increase BP, Chills, Rigors, decreased sweating, anorexia, somnolence, and malaise**

Question

- A 45 year old woman presented with chronic cough.The chest X ray showed enlarged hilarious lymph nodes. Histological examination of these nodes showed multiple granulomas. Which of the following statements is correct about her condition?

- A. Non- caseating granulomas are diagnostic of sarcoidosis.
- B. Non caseating granulomas rule out the possibility of tuberculosis
- C. Giant cells within the granulomas result from fused activated macrophages.
- D. Granulomas have a long differential diagnosis that includes infections, some of which are acute.

Question explained

- A 45 year old woman presented with chronic cough.The chest X ray showed enlarged hilarious lymph nodes. Histological examination of these nodes showed multiple **granulomas**. Which of the following statements is correct about **her condition**? **When you are faced with a clinical scenario question, don't panic, it's usually easy, just make sure you know the point of the question, here we are simply asking about granulomatous inflammation**

- A. Non- caseating granulomas are diagnostic of sarcoidosis. **Wrong. Granulomas look similar and rarely have diagnostic features. sarcoidosis is a systematic disease that affects mainly the lungs and hilarious lymph nodes, it is a diagnosis of exclusion**

- B. Non caseating granulomas rule out the possibility of tuberculosis. **Wrong, although caseation is almost always diagnostic of TB, TB cases caseating and non-caseating ones**.

- C. Giant cells within the granulomas result from fused activated macrophages.**Correct**

- D. Granulomas have a long differential diagnosis that includes infections, some of which are acute.**wrong. granulomas can be caused by infections, but they are a form of chronic inflammation not acute, so they occur with chronic infections.**

thank you!