PATHOLOGY

بسم الله الرحمن الرحيم

MID (Last Lecture) – Lecture 11

Inflammation (Pt.6)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Done by:

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GENERAL NOTE:

STUDY THE PICTURES CAREFULLY AS THERE WILL BE PICTURES IN THE EXAM.

Dr. Mousa Abbadi

Before you go through the file, remember the five phases of inflammation (Rs).

MACROPHAGES

- **They are derived** from circulating **monocytes**, which have a short half-life of a couple of days, that get activated and recruited into tissues with a prolonged half-life of weeks and even months.

- **Secretion of mediators (TNF, IL-1, Chemokines..)**
- **Feedback loop with T cells**
- **Phagocytosis**

- Neutrophils could also do phagocytosis, which is the process of removal (the 3rd R of inflammation reactions).

- **Circulating monocytes (1 day half-life)**
- **Tissue Macs: Kupfer cells, sinus histiocytes, alveolar macrophages & microglia (mononuclear phagocytic system), half-life months.**

- After getting activated, they could stay for a long time and be a part of the tissues such as, **Kupfer cells** in the liver, **sinus histiocytes** in the lymphnodes, **microglia** in the brain.

- **Activation of Macs: M1 classic pathway, M alternative**

  - M1: pro-inflammatory pathway.
  - M2: anti-inflammatory pathway.

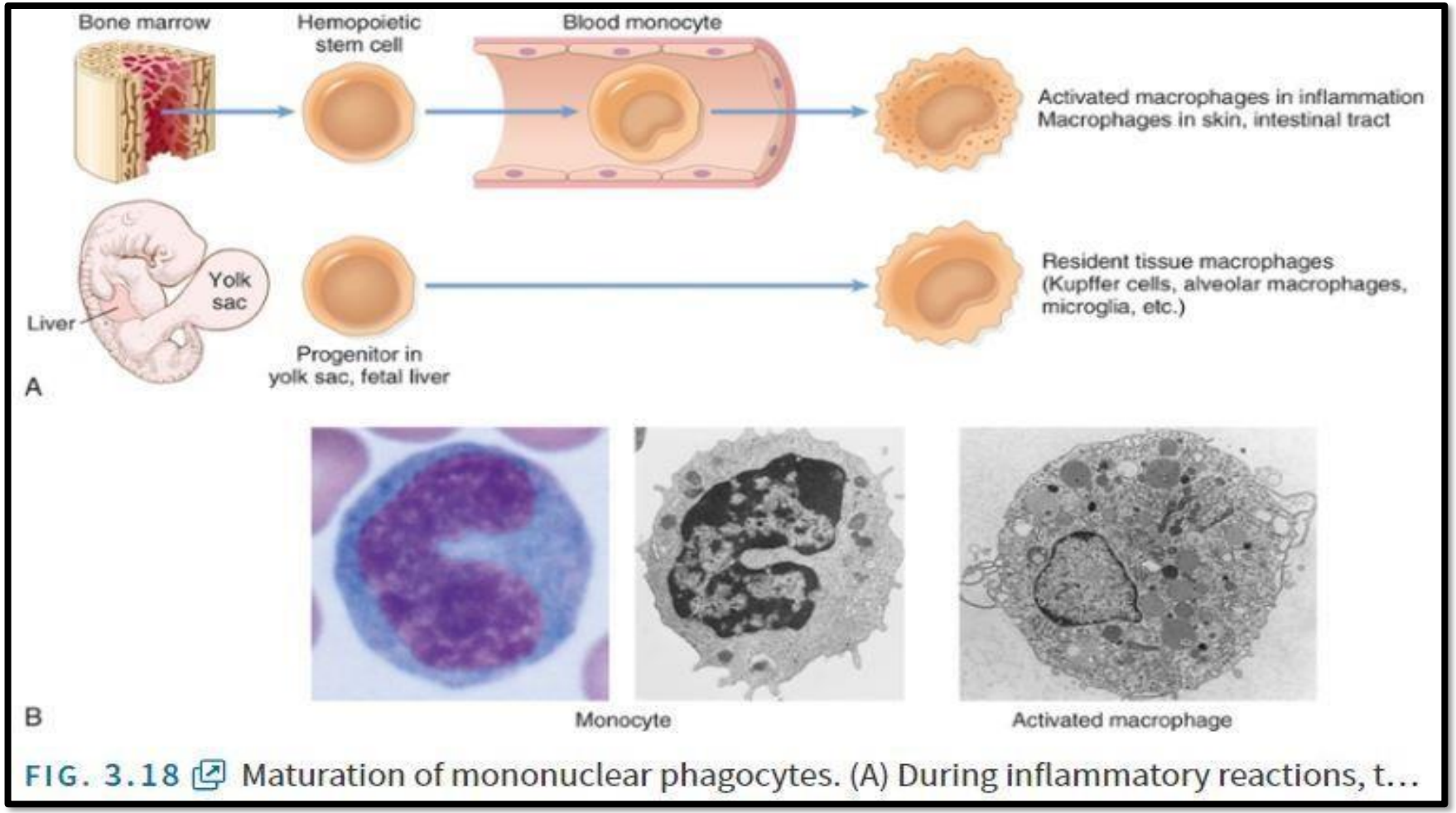
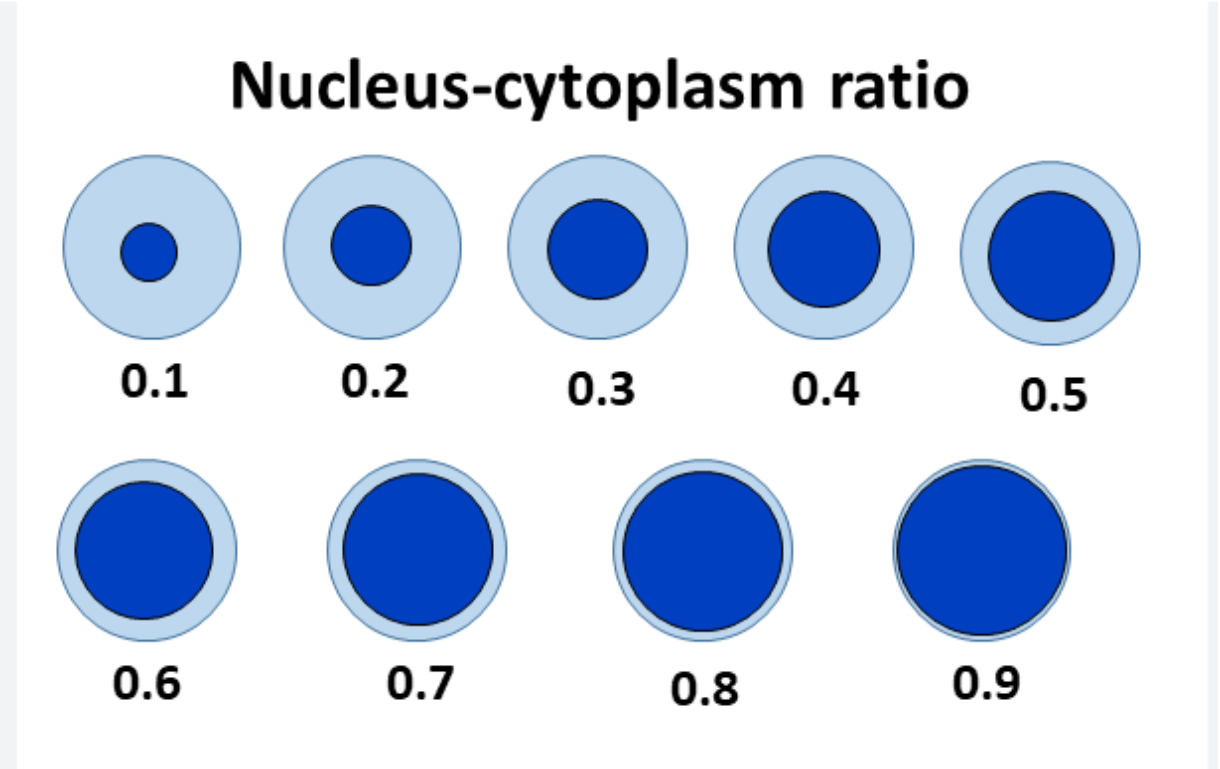


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

Look at the figure, notice the process of maturation going from left to right, from **non-mature small** cells (stem cells) with a **big nucleus** and a **high nuclear-cytoplasmic ratio** to mature **big differentiated** cells, with **more organelles (machinery)** and **lower nuclear-cytoplasmic ratio**.

Nuclear-cytoplasmic ratio illustrated.



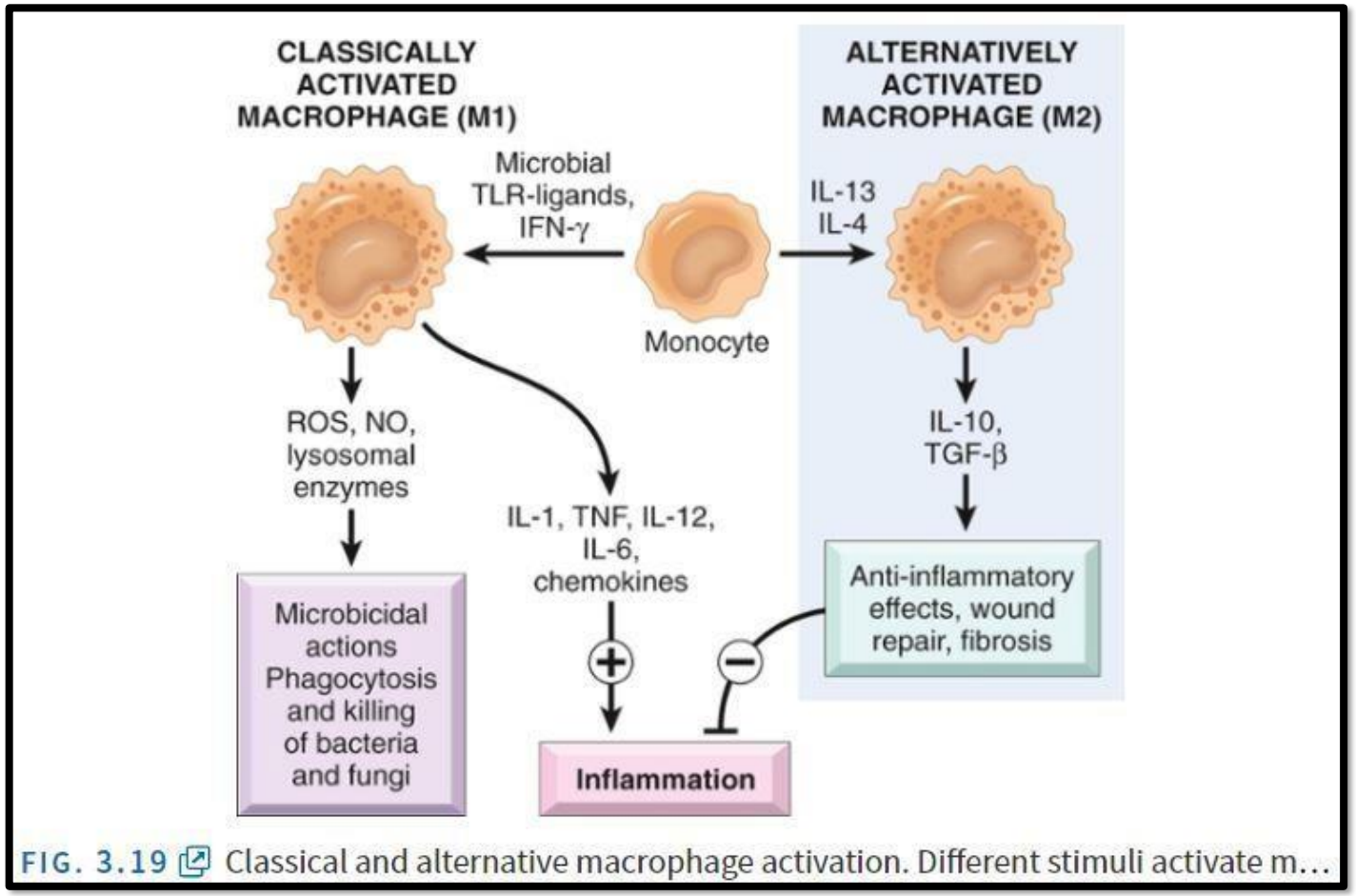


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

- **In the first three phases of inflammation,** macrophages will be activated through the classical pro-inflammatory M1 pathway by certain mediators, these macrophages will engulf pathogens by phagocytosis and will attract more leukocytes by releasing more inflammatory mediators.
- **In the last two phasis of inflammation**, in certain conditions and under the effect of certain mediators, macrophages will be activated by the alternative M2 pathway, these alternatively activated macrophages will act as anti-inflammatory cells releasing certain mediators that influence the regulation of reactions and the repairment of the inflamed tissue.

LYMPHOCYTES

- **T & B lymphocytes gets activated by microbes and environmental antigens**
- **They are the main cells seen in tissue with chronic inflammation**
- **CD4 +ve T-cells secrete cytokines inducing inflammation**

  - **The two types of lymphocytes are:** T lymphocytes and B lymphocytes, B lymphocytes are responsible for humoral immunity, when B cells mature, they give plasma cells.

  - We have two types of T lymphocytes:
    - Cd8+ T suppressor cell.
    - Cd4+ T helper cells, has three types with multiple functions.

Cd: cluster designation proteins that are used as cell markers.

CD4+ T CELLS

T_H1	**INF-ℵ, activates Macs in classic pathway**
T_H2	**IL-4, IL-5 & IL-13; activates eosinophils and Macs alternative pathway**
T_H17	**IL-17 , induce chemokines secretion and recruits PMNs**

Notice the difference between the three types of T helper cells. In the last decade, researchers focused on T helper 17 cells because they are involved in both acute and chronic inflammations, they are also the cells that make IL-17.

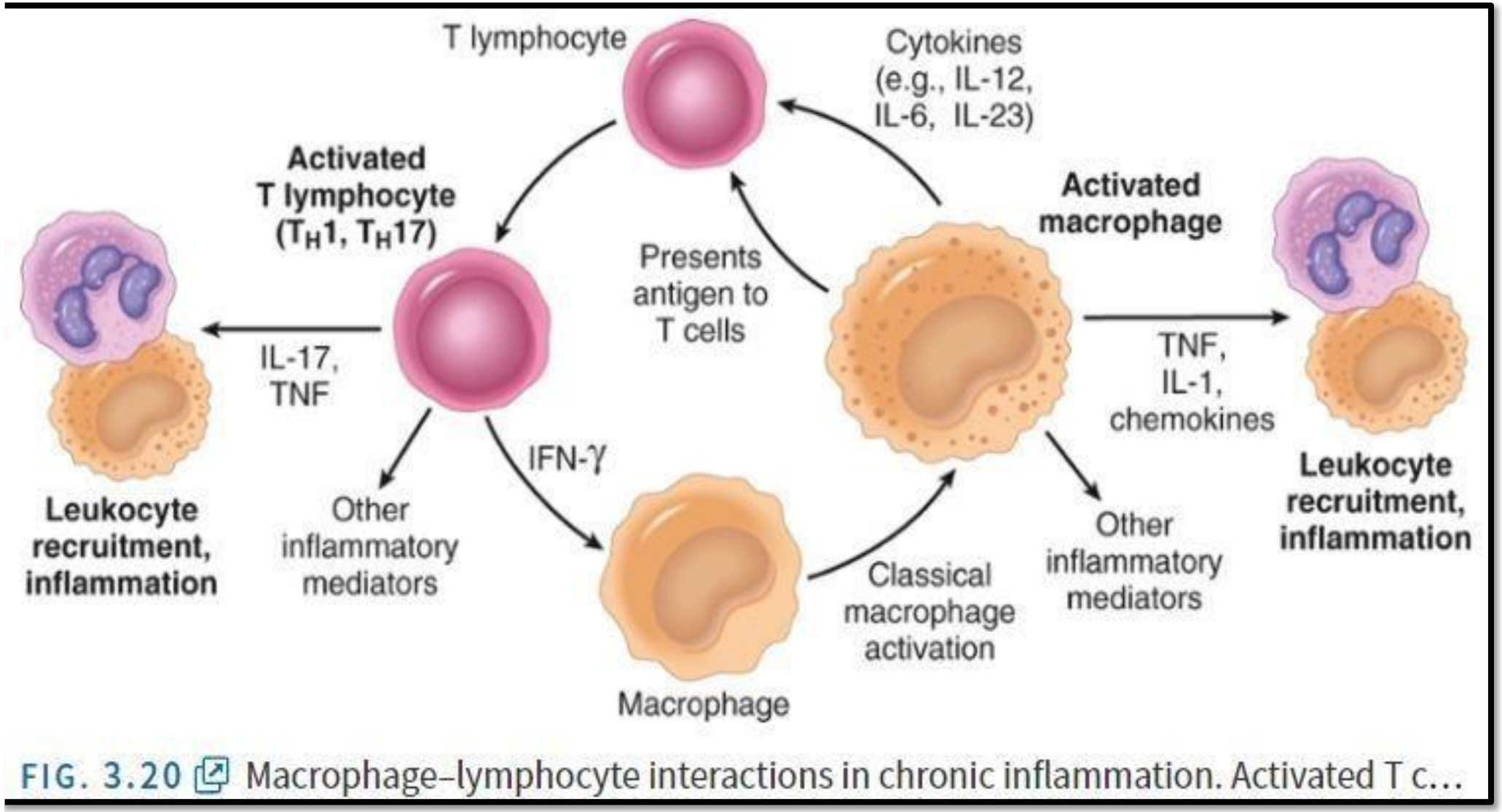


FIG. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T c…

This figure gives you an idea about the complexity of coordination between lymphocytes, macrophages, and neutrophils, give it a look.

EOSINOPHILS (pt.1)

- **Granules contain major basic proteins toxic to parasites.**

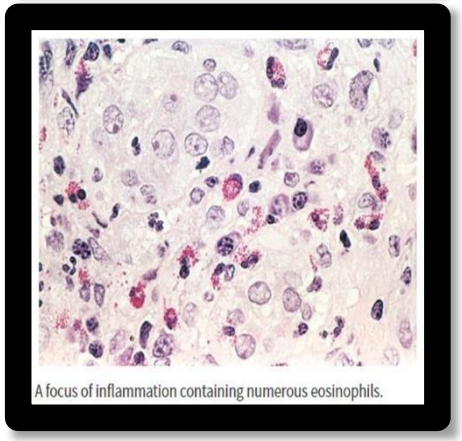
➢ **Eosinophils have a bi-lobed nucleus**, with heavy granulated cytoplasm that appear pink, that is why they are called eosinophils.

- **IgE and parasitic infections.**

➢ **Eosinophils** are mediated by the release of IgE, parasitic infections, especially in the GI tract will induce an inflammation with the stimulation of eosinophils.

- **May cause tissue damage.**

➢ **They can cause tissue damage**, they are also considered chronic inflammatory cells, but they could be involved in acute inflammatory reactions by making degranulation without persisting in the tissue such in acute asthmatic attack, if the patient is dead from this acute asthmatic attack, and you take a biopsy from the bronchus, you won't see eosinophils, but they could have done a degranulation process that caused the death and then disappeared.



The common stain used in studying tissue is the hematoxylin and eosin stain, eosin-stained tissue appears pink while hematoxylin-stained tissue appears blue.

EOSINOPHILS (pt.2)

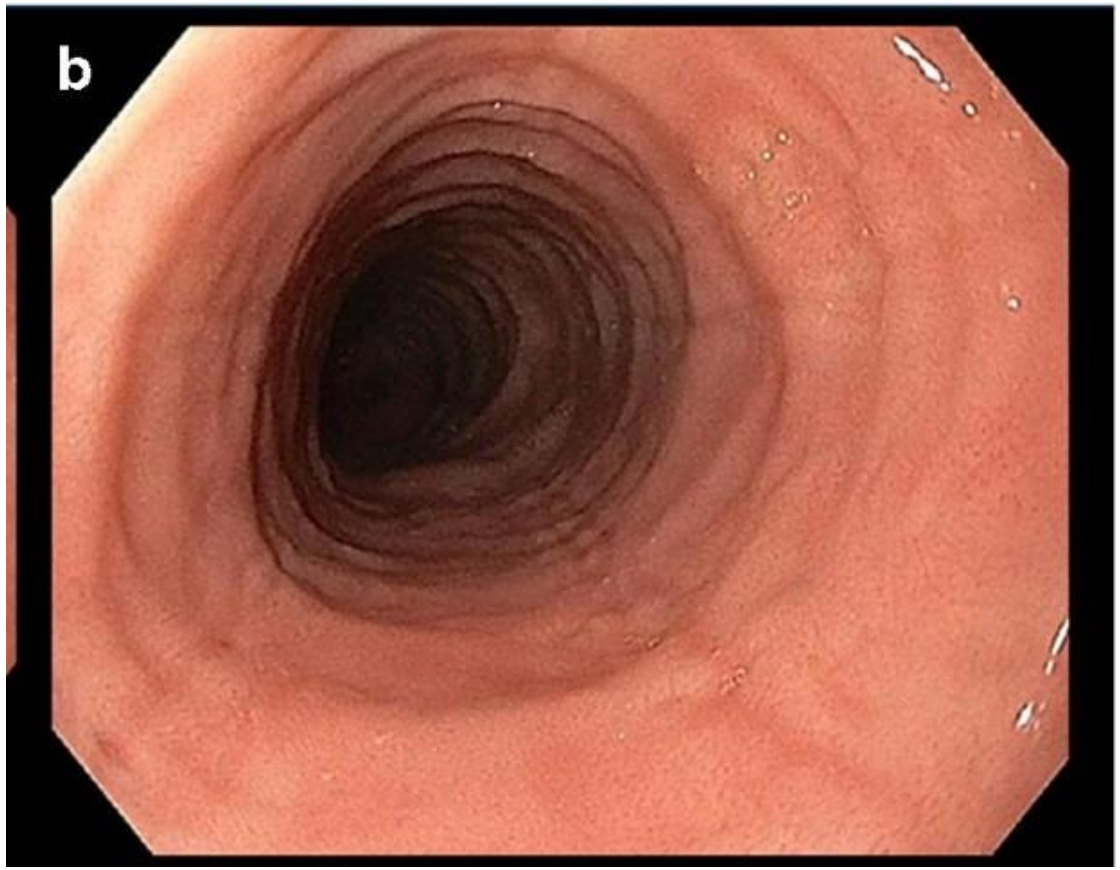
- **Eosinophilic inflammation.**

➢ **A discovery made in the last decade is the eosinophilic inflammation**, a specific type of chronic inflammation caused by tissue infiltration with eosinophils, the first organ that this type was first seen is the esophagus, with eosinophilic esophagitis, we can see it in both adults and children. To make the right diagnosis, doctors go through the esophagus with an endoscope, if they see red esophageal rings, which is a characteristic of eosinophil esophagitis, they take a biopsy and introduce it to a pathologist to investigate it under the microscope, if he sees a certain number of eosinophils per a high-power field, he diagnose the patient with eosinophilic esophagitis.

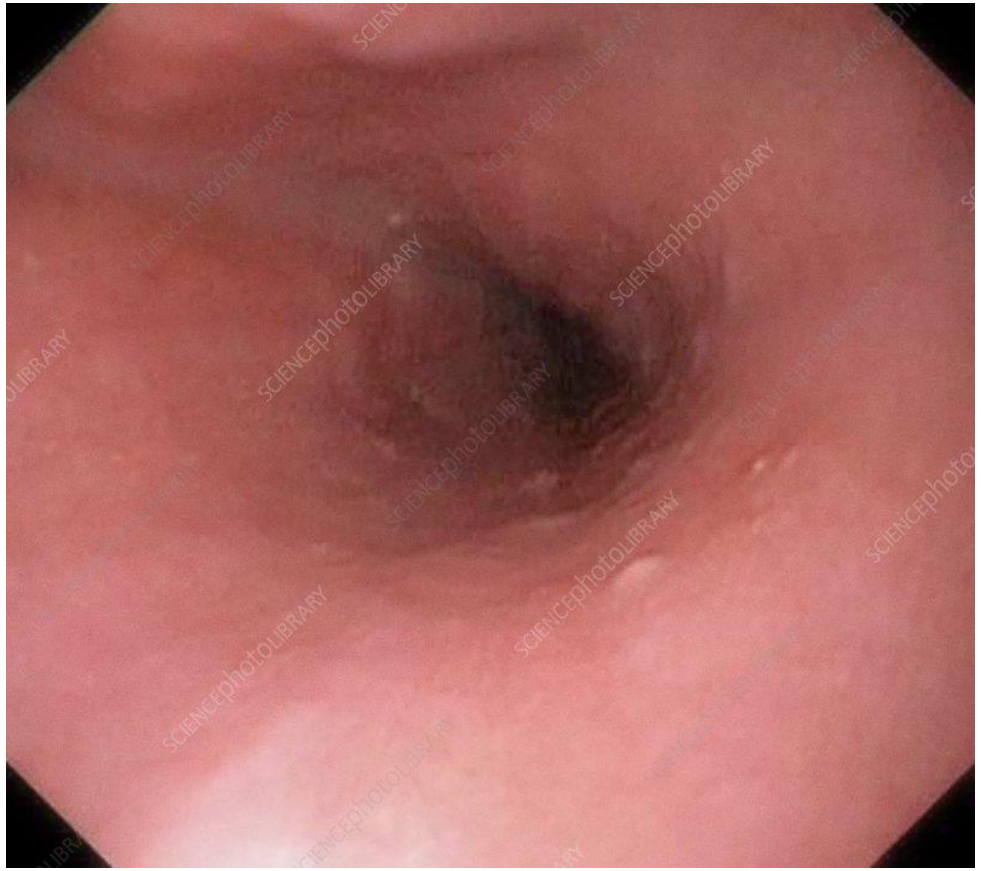
➢ **Eosinophils are the main cells that get stimulated in acute allergic reactions**, they release their mediators of allergy by a degranulation process.

➢ **If a patient who is allergic to penicillin was injected with penicillin**, the body will start to generate eosinophils that get degranulated releasing their mediators leading to sever systemic manifestation and high levels of cytokines, these cytokines will affect the cardiac output, threatening the patient's life.

THESE PICTURES ARE EXTRA AS THEY ARE FOR ILLUSTRATION ONLY



Red esophagus rings due to eosinophilic esophagitis



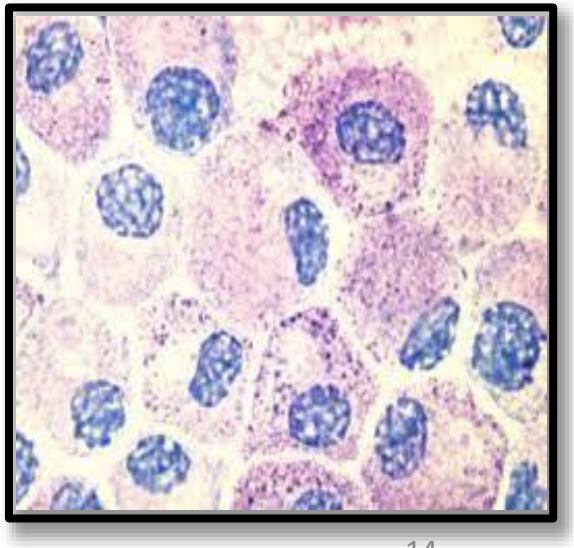
Normal healthy esophagus

MAST CELLS

- **Mast cells** has a single prominent nucleus and basophilic granules, you could see it in both chronic and acute inflammation, you could also see it in tumors such in fibroid or leiomyomas of the uterus.

- **Abundant in soft tissues**
- **Active in both acute and chronic inflammation**
- **MC and basophils express FcεRI binds with FC portion of IgE leading to degranulation releasing Histamine and PG (food allergy, venom, drug allergy)**

- **The third note will be illustrated more in the immunology course**, just know that these cells are involved in allergic reactions.



- **In chronic inflammation**

  cytokines

- **They are involved in chronic inflammation releasing cytokines.**

NEUTROPHILS IN CHRONIC INFLAMMATION

- **Neutrophils are involved in chronic inflammation** in certain cases of infection or a disease, such as inflammation caused by tuberculosis in necrotizing granuloma.

- **Can stay longer after acute inflammation (persistent microbes or continuous activation by cytokines)**
- **Chronic osteomyelitis**

- **We don't want any clinician to miss the diagnosis of osteomyelitis,** even if it is acute, it should be treated quickly with injections of antibiotics, if osteomyelitis becomes chronic it could lead to bone destruction mediated by the involvement of neutrophils.

- **Lung damage by smoking**

- **Smoking damages the lung leading to COPD** (chronic obstructive pulmonary disease), characterized by emphysema and chronic bronchitis mediated by neutrophils.

- **Acute on chronic (or acute on top of chronic inflammation)**

- **In certain diseases you could have acute inflammation**, then after you heal from it another chronic inflammation happens, then acute on top of chronic inflammation which is also called **active chronic,** microscopically you will see a background of chronic inflammation (macrophages, lymphocytes, plasma cells) and some neutrophils on top of that. In pancreas, it is called chronic relapsing pancreatitis such case happens with alcoholic patients, they face an injury every time a destruction happens in the pancreatic tissue.

GRANULOMATOUS INFLAMMATION:

Very Important

- **A form of specific chronic inflammation**

It is characterized by tissue **destruction** and **infiltration** by granuloma.

- **Granuloma: activated macrophages (epithelioid histiocytes); lymphocytes and sometimes plasma cells.**

Chronic

When macrophages are activated, the nucleus to cytoplasm **ratio** is **decreased**, and the cell has more organelles, making it have an epithelioid **(epithelium-like) appearance**.

Epithelioid histiocytes can coalesce forming giant **muti-nucleated** cells (10-20 cells).

a) **Necrotizing (central necrosis)**

b) **non-necrotizing (no necrosis)**

2 Morphologies

See Next Slide

- **Immune granulomas vs foreign body type**

Not Important for now (know the names only for surprise Qs)

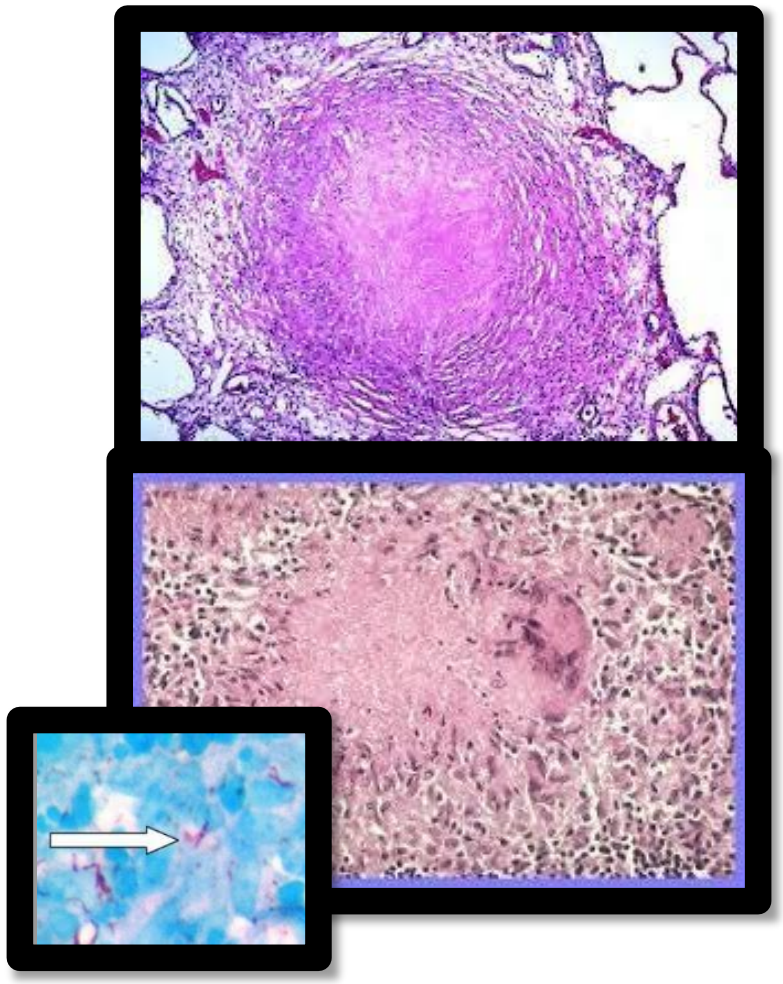
It is diagnosed by histopathologists after taking a biopsy and examining it microscopically.

Radiology cannot specifically determine the presence of granulomatous inflammation.

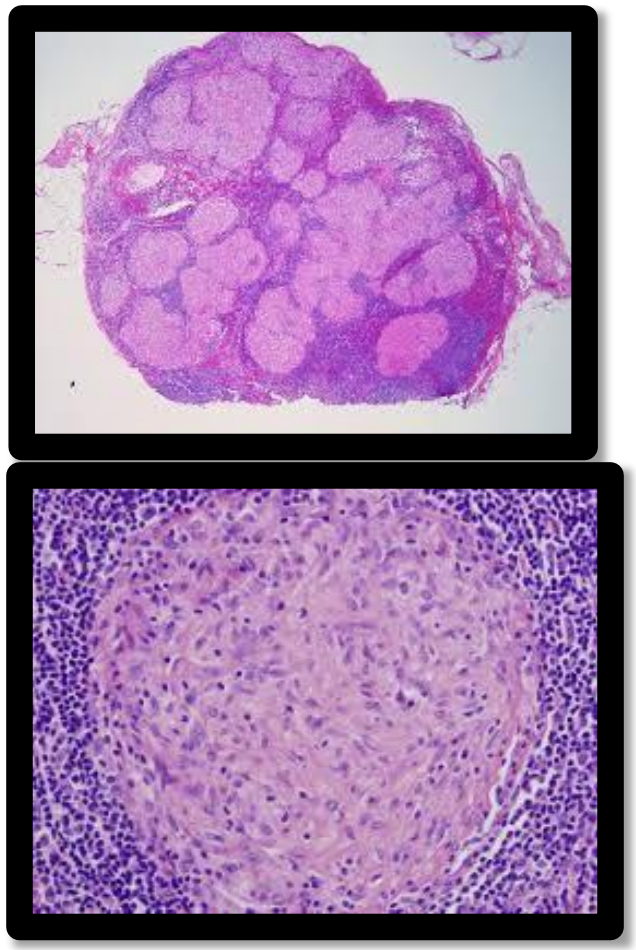
MORPHOLOGY OF GRANULOMATOUS INFLAMMATION

Microscopic Features

NECROTIZING GRANULOMA



NON-NECROTIZING GRANULOMA

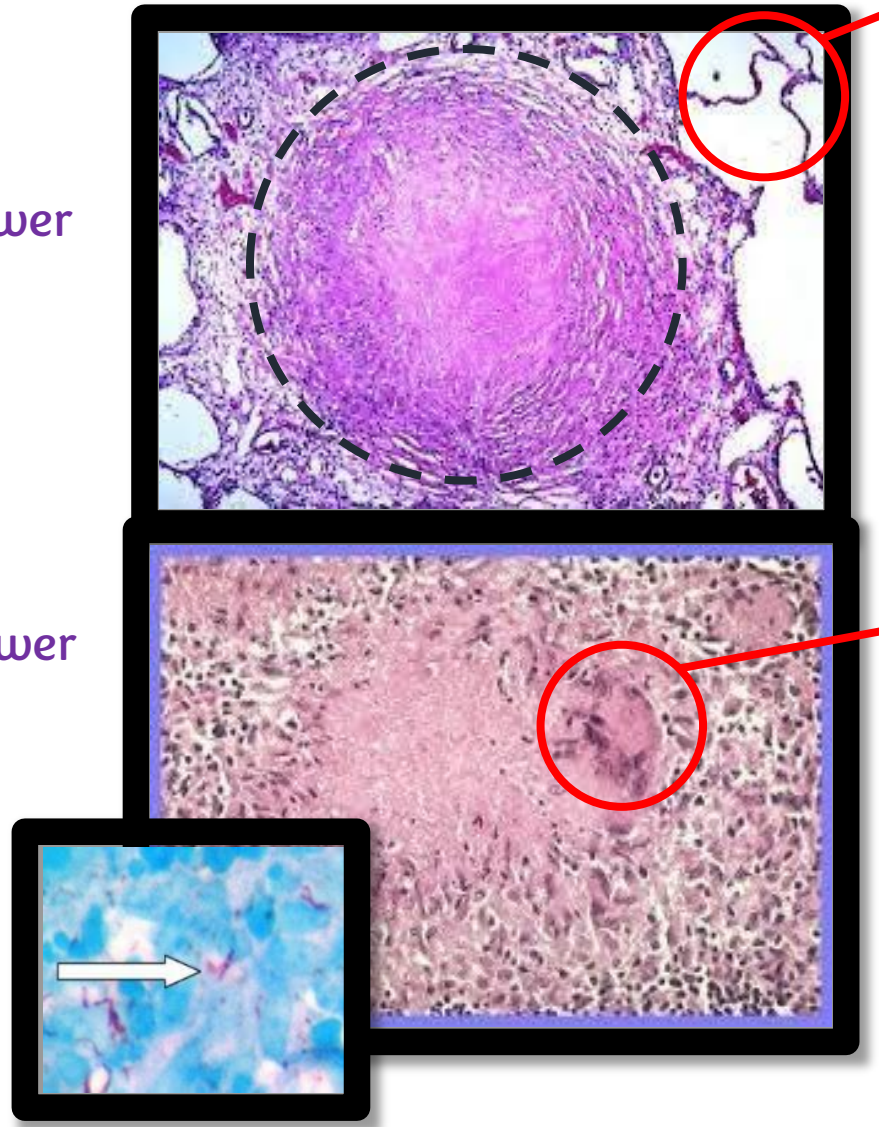


See Next Slides for explanation

NECROTIZING GRANULOMA (Extra Slide)

Low Power

High Power



Normal Lung tissue (alveolae; parenchyma)

In the center of the image above, the parenchymal structure is lost.

Notice the spherical structure (black-dotted):

- At the circumference, we can see pinkish nucleated cells (blue basophilic dots).
- The nucleated cells are granuloma.
- In the center, the nuclei of the cells are gone → ***NECROSIS*** (notice the lost basophilia).

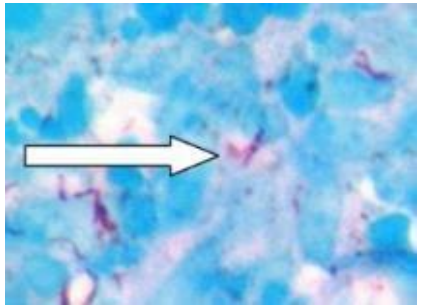
Multi-nucleated giant cell

The rest of the cells around are epithelioid histiocytes (we identify them by high power microscopy)

The **old** name for necrotizing granuloma is **caseating granuloma** (recall caseous necrosis)

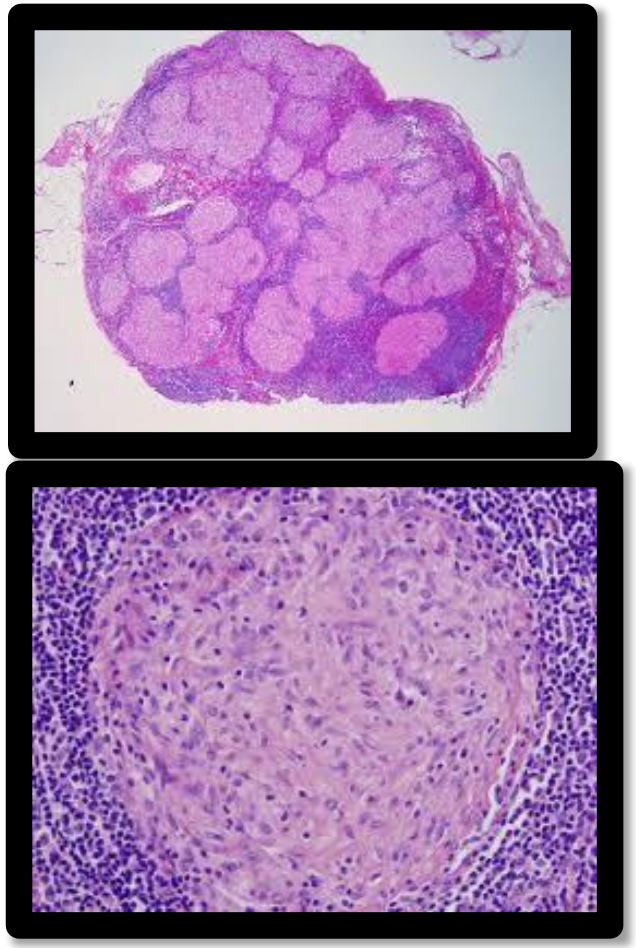
NECROTIZING GRANULOMA (Extra Slide)

- Necrotizing (caseating) granuloma is caused by **microorganisms**.
- The main causative agent is ***Mycobacterium tuberculosis* (TB)**.
- We need to apply special stains for microorganisms.
- This helps identify the etiological basis relatively quickly as culturing might take a long time; maybe weeks. (Recall the long 24-hour binary fission time of *Mycobacterium tuberculosis*).
- We use the **"ZN" Ziehl-Neelsen stain** (acid-fast bacilli stain).
- *Mycobacterium tuberculosis* are acid-fast bacilli.
- We also apply fungal stains as fungi can also cause necrotizing granuloma.
- If the causative organism is detected, the patient is subjected to the appropriate treatment.



The red things on the background are the organisms.

NON-NECROTIZING GRANULOMA (Extra Slide)



The top image shows a lymph node with the sinuses inside and surrounded by the capsule (recall 0502111 histology).

The red structures (abundant cytoplasm) are granulomas.

Features:

- Epithelioid histiocytes (red granuloma)
- Plasma cell (black dots [I can't see any black, but just know it])
- Lymphocytes
- **NO** Necrosis (non-necrotizing ⇔ non-caseating)

- So, we also apply acid-fast stains + fungal stains.
- Usually, the stains have negative results here.
- Most of the time, non-necrotizing granuloma are not caused by organisms, unlike necrotizing granuloma (mostly TB).

NON-NECROTIZING GRANULOMA (Extra Slide)

- Sarcoidosis is an autoimmune disease of unknown etiology (Nobel prize potential ☺) where non-necrotizing granuloma destroys the tissues.
- It can occur in various places in the body.
- Sarcoidosis diagnosis is done by exclusion (after making sure other possibilities are not present).
- We don't diagnose with sarcoidosis in the report of the patient's case.
- We write in the report that the patient has (this is the proper way):
  1. Non-necrotizing granulomatous inflammation
  2. Negative acid-fast bacilli test
  3. Negative fungal test
  4. We add a comment that:

     "The features raise the possibility of sarcoidosis **after exclusion**."
- The reason we use exclusion is that if we treat the patient with sarcoidosis treatment (which is steroids to stop the autoimmune inflammation) without making sure that the cause is not a microorganism, we will reduce the immunity of the patient and help the microorganism further destroy the tissue without adequate immune response. This may kill the patient.

Remember the definition of granulomatous inflammation

1. Chronic
2. Specific

The Dr. said that these 6 are the only causes.

TABLE 3.9 Examples of Diseases With Granulomatous Inflammation

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 macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
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 undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

Caused by *Bartonella henselae*
Gram (-) bacillus

Summary

Chronic Inflammation

- Chronic inflammation is a prolonged host response to persistent stimuli that may follow unresolved acute inflammation or be chronic from the outset.
- It is caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many medically important diseases.
- It is characterized by coexisting inflammation, tissue injury, attempted repair by scarring, and immune response.
- The cellular infiltrate consists of macrophages, lymphocytes, plasma cells, and other leukocytes.
- It is mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes); bidirectional interactions between these cells tend to amplify and prolong the inflammatory reaction.
- Granulomatous inflammation is a morphologically specific pattern of chronic inflammation induced by T cell and macrophage activation in response to an agent that is resistant to eradication.

SYSTEMIC EFFECTS OF INFLAMMATION:

- **Any inflammation can be associated with systemic effects due to cytokines release**

  “ ACUTE PHASE RESPONSE”

- **TNF, IL-1, IL-6, & type 1 interferons**

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**

Explanation of the previous slide (EXTRA):

- Acute phase proteins:
  - CRP (C-Reactive Protein): Non-specific; produced in the liver.
  - Other types exist (see last slide).

- Leukocytosis (increased WBCs):
  - Cytokines cause the recruitment of leukocytes from the bone marrow.
  - If there is hypersensitivity to cytokines → too many leukocytes (40K >> 15-20K).
    - In certain inflammatory clinical cases, high WBCs may indicate leukemia (leukocyte cancer); we check if the cells are cancerous or not by flow cytometry.
    - Cancer cells are monoclonal; reactive (non-cancerous) are polyclonal.
    - If no leukemia present (الحمد لله), this is called a leukemoid reaction.

SEPSIS & SEPTIC SHOCK:

Fatal and usually associated with gram-negative bacilli

- **Severe bacterial infections**
- **Large amounts of mediators (TNF & IL- 1)**
- **Leading to: DIC, hypotensive shock, insulin resistance & hypoglycemia (Septic shock)**
- **May be caused by noninfectious etiology: pancreatitis, severe burns, severe trauma.**
- **All called "systemic inflammatory response syndrome" SIRS**

Hypoglycemia can happen if the bacteria "ate" our sugar!

DIC: Disseminated Intravascular Coagulation
Symptoms:

- **Thrombosis in BV**
- **Shutting down vital organs**

Summary

Systemic Effects of Inflammation

- Fever: Cytokines (TNF, IL-1) stimulate production of PGs in hypothalamus
- Production of acute-phase proteins: C-reactive protein, others; synthesis stimulated by cytokines (IL-6, others) acting on liver cells
- Leukocytosis: Cytokines (CSFs) stimulate production of leukocytes from precursors in the bone marrow
- In some severe infections, septic shock: Fall in blood pressure, disseminated intravascular coagulation, metabolic abnormalities; induced by high levels of TNF and other cytokines

For any feedback, scan the code or click on it.

Corrections from previous versions:

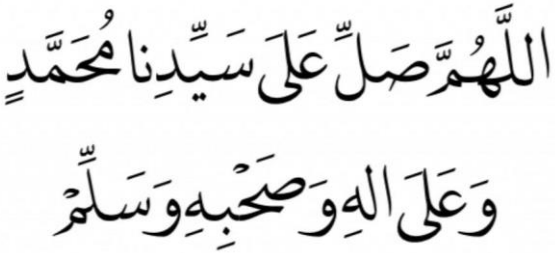
Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	26	Hypotensive shock can happen if the bacteria "ate" our sugar!	Hypoglycemia can happen if the bacteria "ate" our sugar!
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

- Robbin’s Basic Pathology 11th edition



Hello BATMAN! Thank you for your words
Hope you enjoy this file too.
P.S.: Batman is sb who regularly rates the files!