PATHOLOGY

Sheet no. 6

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CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

All cells collaborate to achieve the desired inflammatory response.

- **Macrophages**
- **Lymphocytes + plasma cells**
- **Eosinophils**
- **Mast cells + basophils** (sometimes)

Now let's talk about each one of them:

MACROPHAGES

- **Origin**: circulating monocytes (It's called Monocyte_Macrophages system), sometimes they add dendritic cells to them.
- **Secretion**: many mediators, most important are cytokines (TNF, IL-1 and chemokines).
- Feedback loop with T cells**, collaboration** between them.

Example: macrophages process and present antigen via MHC II to T-helper cells.

- **Phagocytosis**: two major cells: macrophages and neutrophile (PMNs)
- **Half-life**: for Circulating monocytes is 1-2 days at most, if they are NOT activated and recruited to tissue. Once they go to tissue (migration, rolling, adhesion, transmigration) and be activated they live for long time (for example: months).
- **Tissue Macs**: Kupfer cells (liver Macs), sinus histiocytes (lymph nodes and spleen), alveolar Macs, microglia (CNS- brain). (Mononuclear phagocytic system).
- **Activation of Macs**: two methods:

1. **M1** classic pathway, pro-inflammatory, most of them secrete mediators that enlarge and entice inflammation
2. **M2** alternative pathway, participate in initiation of R4 (regulation of inflammation).

1-Bone marrow gives

Hemopoietic stem cells that differentiate to macrophages.

2-progenitor in yolk sac and fetal liver, are the origin of Macs that circulate then go the tissue (kupffer, alveolar, microglia…)

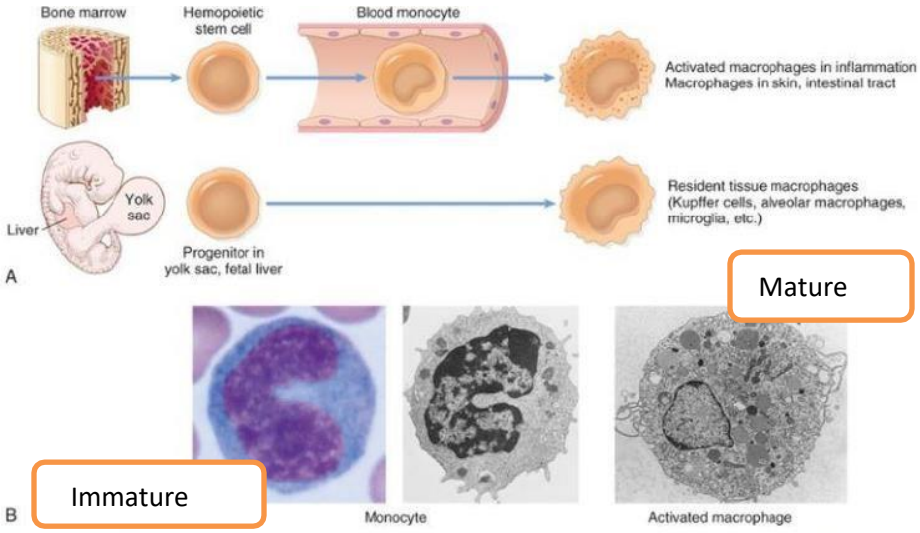


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

when we say that WBCs are right shifted = there are more mature cells than stem cells, and when we say that they are left shifted = there will be more stem cells than mature cells. And when a cell gets maturated = it will have a specific function different from its previous function.

IN GENERAL:

- The mother cell: small in size, big nucleus (nuclear/cytoplasmic ratio is high).

So when we take a peripheral smear looking for Leukemia for example, we look for blasts immature cells that have large bean shape nucleus.

- The mature cell: (when the cell gets into circulation) cell enlarges, nucleus get smaller, kidney shape, more abundant and functional cytoplasm, still can't see granules but they have more cytoplasmic organelles.

Note: granules same as lysosomes, but granules can be seen easier. Macs granules are less than PMNs'.

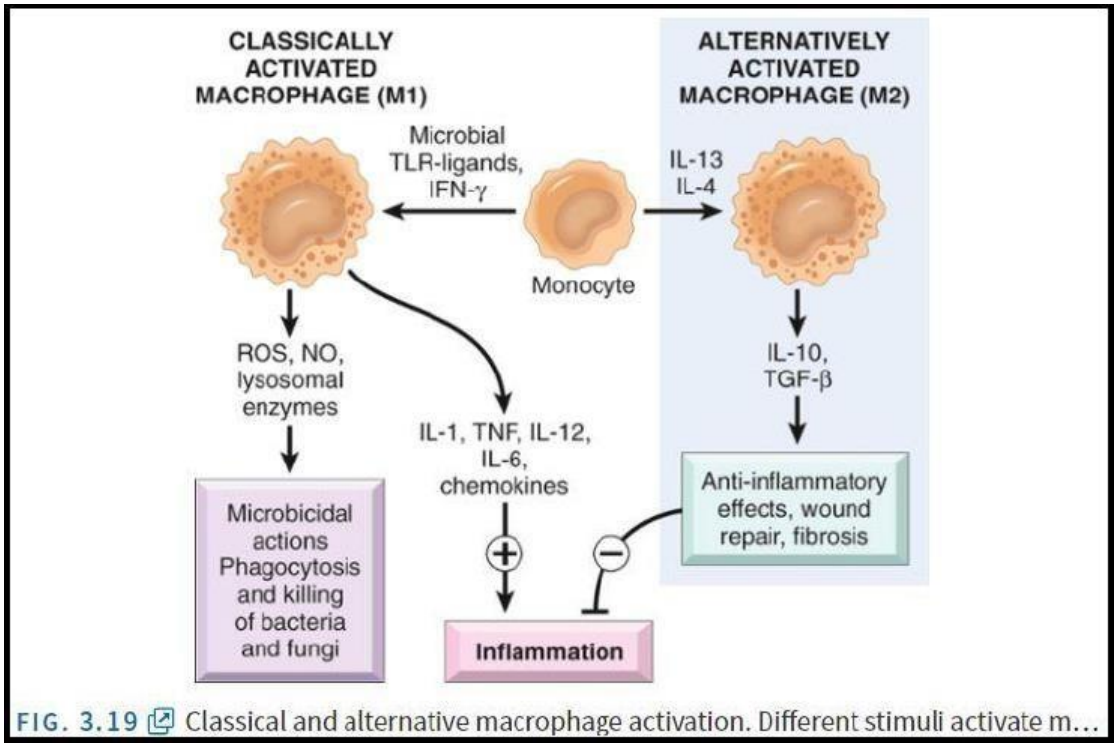


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

Activation of macrophages:

Classic M1 pathway:

- Microbial (bacterial, virus) TLR ligands (TLR= toll like receptor), IFN-ɣ, stimulate the activation of monocytes to M1 classic pathway.

Remember: IFN-ɣ is secreted by T cells and NK cells.

- Pro-inflammatory (promote inflammation)
- Phagocytosis, killing bacteria and fungi
- Secrete cytokines, ROS, NO, lysosomal enzymes
- R3 (removing) stage

Alternative M2 pathway:

- IL-13, IL-4 (interleukins) activate Macs in M2 pathway
- Secretion: IL-10, TGF-β (transfer growth factor, the major player in repair)
- Anti-inflammatory effects (R4), and stimulation for repair wounds and fibrosis (R5).

LYMPHOCYTES

- T & B lymphocytes get activated by many factors, include microbes and environmental antigens.
- Viruses stimulate T lymphocytes mostly (viral illness shows less fever, leukocytes are less, in tissue you find more lymphocytes than neutrophils). Bacterial infections usually appear by increasing in B cellsand neutrophils.
- In chronic inflammation lymphocytes are more abundant than plasma cells or Macs. Chronic inflammation in LUNG, TONSIL, INTESTINE haveT lymphocytes more.
- CD4+ are T-helper lymphocytes, CD8+ are suppressor cytotoxic Tlymphocytes.
- B cells mature to plasma cells secreting immunoglobulins (usually inbacterial infection).
- Lymphocytes secrete lymphokines

T-helper cells types are up to 20 and more. Most important:

T_H1	INF-&, 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

1. **T-H1**: secrete (interferon gamma), that activates Macs in M1 pathway.
2. **T-H2**: secrete IL-4 & IL-13 that activate Macs in M2 pathway. Secrete IL-5 that activates eosinophils
   (for example: in Hodgkin's lymphoma cancer we can find eosinophiles because of their activation by IL-5).
3. **TH17**: secrete IL-17 (acute mediator for recruitment of PMN and monocyte) and induce chemokines. It can recruit PMN into chronic inflammations.

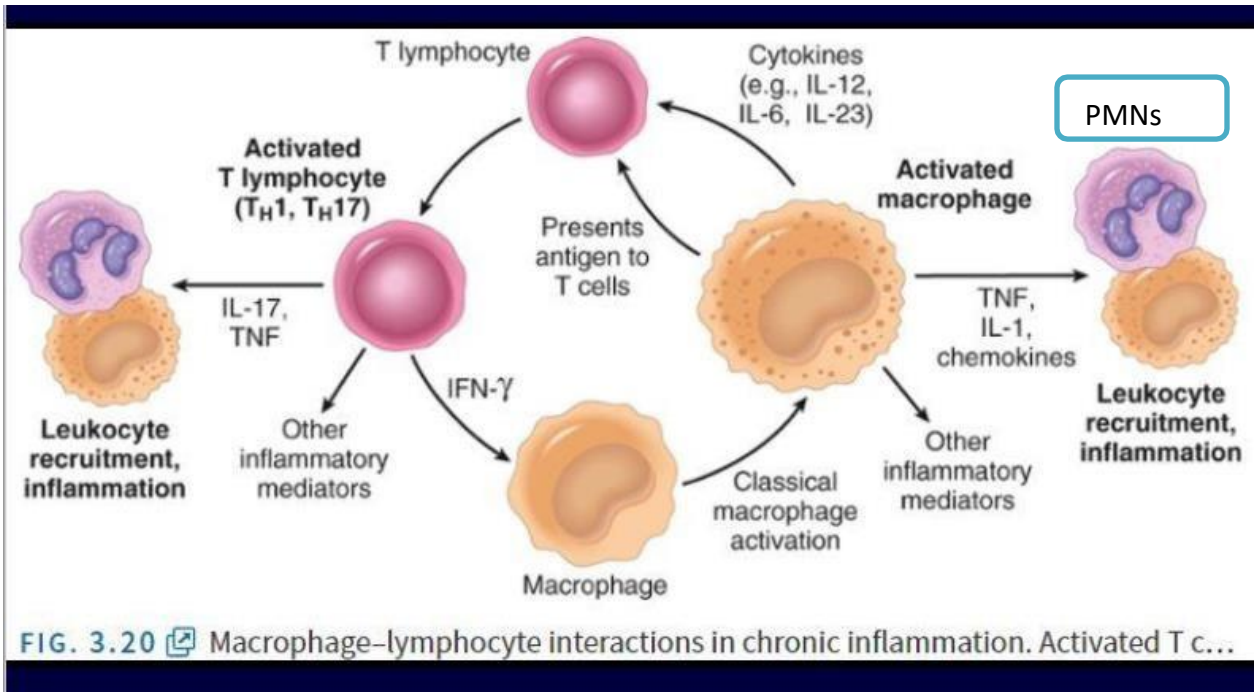
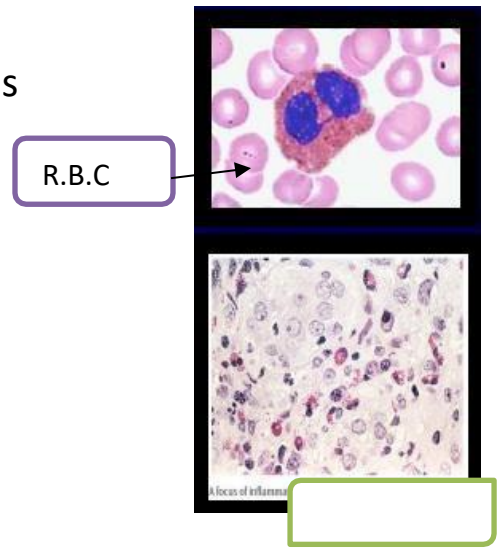


FIG. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T c…

Again, all cells collaborate between hematopoietic cells and PMNs and Macs, which is very close, you can't separate them.

- Macs secrete TNF & IL-1 & chemokines to recruit leukocytes
- Macs secrete IL-6 / IL-12/ IL-23 for activating T lymphocytes
- T cells secrete IFN-ɣ for activation of Macs in M1 pathway, IL-17 & TNF for recruitment of leukocytes.

EOSINOPHILS



In tissue

- The name due to their color, pinkish granules
- Often 2 nuclei
- They have granules that secrete IgE for example: Bronchial asthma is caused mainly due to IgE release.
- We find them also in allergies

- Parasite diseases = more eosinophils
- Granules contain major basic proteins toxic to parasites.
- May cause tissue damage

- Recently pathologists have determined specific type of chronic inflammation, (non-specific =Macs & lymphocytes & plasma cells). Two types of specific chronic inflammation in this lecture: eosinophilic inflammation & Granulomatous

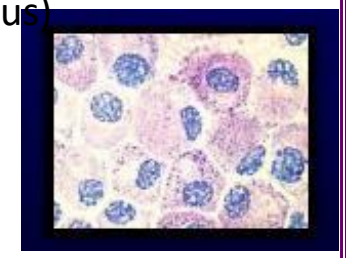
Example:

(Identifying under microscopes) for children who come with vomiting and loss of weight, they find change in lower part of esophagus, they find red rings, if we look under microscopes it will appear hundreds of eosinophils

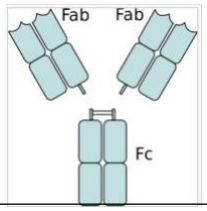
= eosinophilic esophagitis (a chronic inflammation)

- Some scientists say that the chronic disease may contain an elements of allergy

MAST CELLS



- Scientists don't know many details about their function.
- **Abundant in** soft tumor tissues (such as fibroid in uterus)
- **Active in** both acute and chronic inflammation
- Have a lot of **granules** (little pink\ purple)
- MC (mast cells) and basophils **express** FceRI (Receptor forFC) binds with FC portion of IgE leading to degranulation releasing of Histamine and PG of their granules (food allergy, venom, drug allergy).
- In chronic inflammation, cytokines.
  Focus on macrophages, PMN and lymphocytes more than Mast cells



FC portion of antibody

NEUTROPHILS IN CHRONIC INFLAMMATION:

1. Can stay for longer after acute inflammation (due to <u>persistent microbes</u> or continuous activation by cytokines (remember IL-17)).
2. <u>Chronic osteomyelitis</u> (inflammation of bone marrow) is very bad disease, so acute osteomyelitis is a medical emergency we should treat it early (next semester we will study it.
3. <u>Lung damage</u> by smoking, one of the main reasons for inflammation in the lung is the activation of neutrophils by smoking
4. If there is a background of chronic disease and then infected by an acute (<u>acute on top of chronic</u>) ex. <u>Chronic Active Gastritis</u> means that the disease is chronic and acute one has come. Chronic active pancreatitis = chronic disease and an acute visited the body ☺

<u>Four chronic diseases special infiltration for PMNs</u>

GRANULOMATOUS INFLAMMATION

"Please all of you, you must understand everything about this topic – extremely important "- Dr.Mousa

- It is a specific type of chronic inflammation.
- The tissue in this situation is infiltrated by Granuloma, this is the definitive sign of granulomatous inflammation.
- Granulomas are collection of activated macrophages (bigger than monocytes, more active, more granules, can kill more, smaller nucleus…) & few lymphocytes and sometimes plasma cells.
- In histology, activated macrophages = (epithelioid histocytes)
  Why epithelial?
  epithelial = small nucleus & abundant cytoplasm, ioid = looks like
- Caseating means in old days, when they had a patient with tuberculosis, his lung fill with white nodules squeezing them appears a casein material.

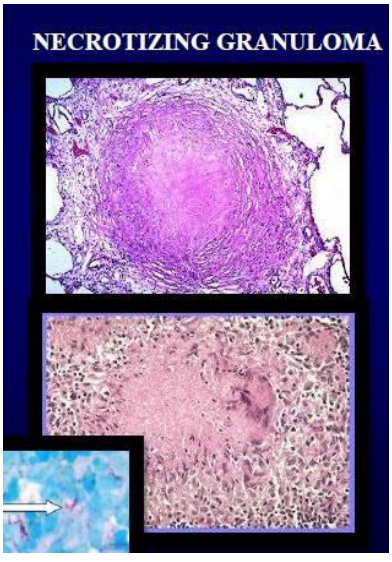
- **Immune granulomas** (can see them in certain type of auto immune diseaselike rheumatoid arthritis) **vs foreign body type** (granuloma formed around a foreign body).
- Granulomas are not exclusive for granulomatous inflammation, they could appear in other immune reactions.
- We should know the difference between this inflammation types:

1 -Necrotizing (caseating) (central necrosis)

Vs

2- non-necrotizing (no necrosis)

Necrotizing granuloma



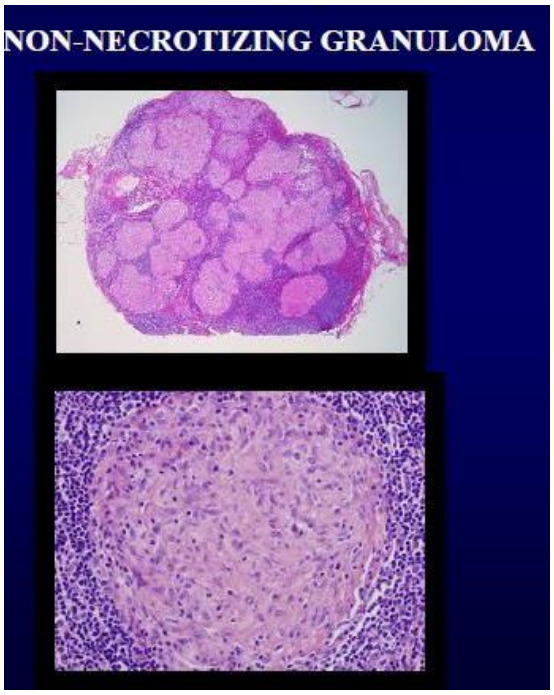
- In the middle of granule its pink= no nucleus (central necrosis) which indicates that it is necrotizing.
- The common type of infections that cause it is Tuberculosis
- Mostly Bacterial disease and infections
- Can occur in any place
- The 1st picture is lung tissue, the 2nd is for lymph node

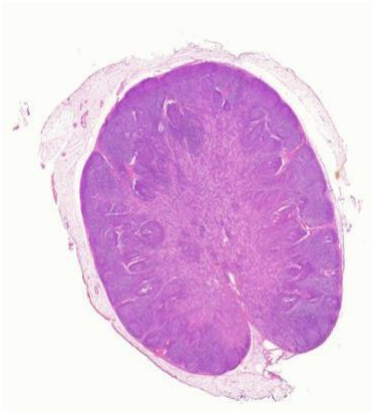
For extra detection we use special type of stain (fungal, TB tuberculosis) = Ziehl Neelsen stain (acid fast stain), the background of stain is blue, if there is bacilli it will be pinkish color

Extra : Ziehl-Neelsen staining is a bacteriological stain used to identify acid-fast organisms , mainly mycobacteria

Non-necrotizing granuloma

- This a lymph node
- Normally its blue with lymph nodes follicles, but here it's been replaced by granuloma.
- No necrotizing center (there are nuclei in the center)





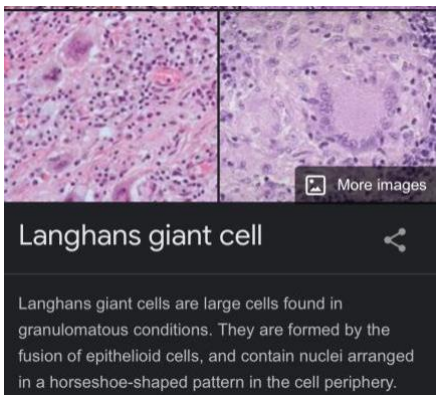
Normal

As usual another table to memorize

H.W, read about cat-scratch disease, find the cause agent?

Ans.

Bartonella henselae bacteria, kittens younger than 1 year are more likely tohave it. Most cats show NO infection signs. ☹



Mentioned in the table below ..

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

Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. Prolonged inflammation results in damage to the GI tract.

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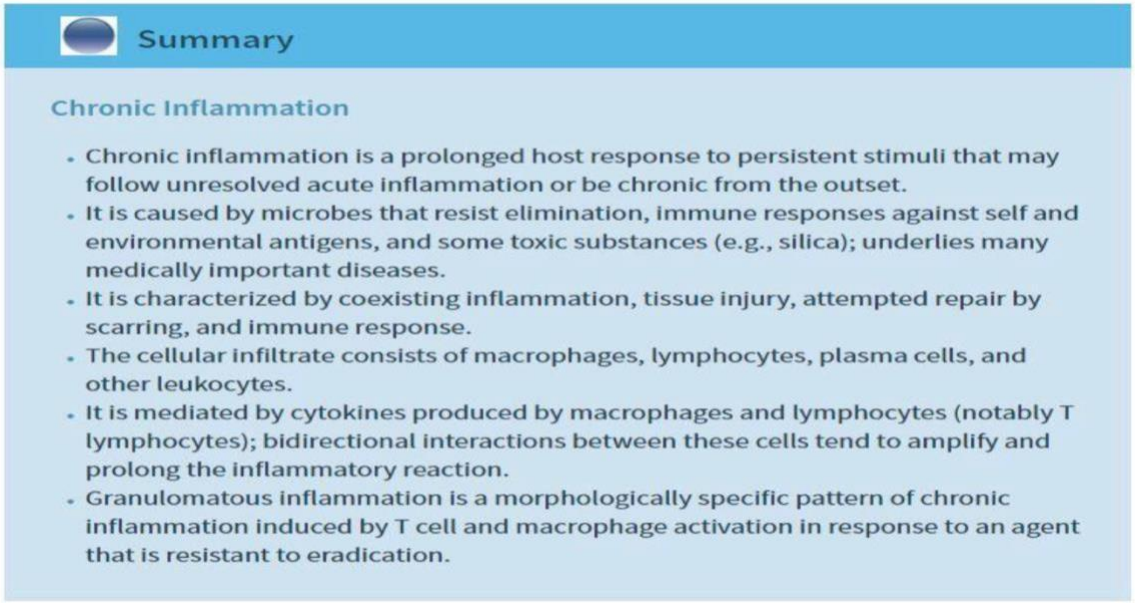
Sarcodosis is diagnosed by elimination, meaning it is diagnosed by excluding any other disease because its cause is unknown



Systemic effects of inflammation

- It is any inflammation that is associated with systemic effects due to cytokines release (acute phase response).
- Cytokines like TNF, IL-1, IL-6, and 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**

- Leukocytosis is the increase in white blood cells (15 – 20 k), which is normally 5 – 8 k.
- Leukemoid reaction is the severe increase in WBC
- If the WBCs are monoclonal this may indicate leukemia, if the WBCs are polyclonal this indicates leukemoid reaction.

Sepsis and septic shock

- It is simply defined as severe bacterial infection
- They happen due to large amount of mediators in blood, specifically (TNF, IL-1)
- It could lead to DIC (Disseminated intravascular coagulation), hypotensive shock (low blood pressure), and hypoglycemia (low blood sugar) caused by the bacteria consuming the sugar.
- Patient may reach multi organ failure and even death.
- It could be caused by no infectious etiology like: pancreatitis, severe burns, severe trauma (damage).
- These symptoms are called “Systemic Inflammatory Response Syndrome” (SIRS)

Some Que. From (2020 mid)Testbank:

1) TNF is a:
A-Cytokine
B-Chemokine
C-Lipid
D-Complement protein

2) -Which of the following cells and molecules are involved in asthma?
A-IgE and eosinophils
B-Cytokines
C-Macrophages and neutrophils
D-Complement proteins

3) A liver biopsy showed that a patient has a noncaseating granuloma. Which of the following disease can cause this condition?

A-Tuberculosis

B-Sarcoidosis

C-Syphilis

D-Asthma

4) -Which of the following is true regarding M2 pathway?

A-It is also called the classical pathway

B-It is activated by the presence of microbes

C-It stops inflammation and promotes repair

D-Macrophages start producing IL-1 and chemokines

5) A tissue biopsy from the colon for one of your patients who suffered from diarrhea was taken. The pathologist calls you and is worried about a parasitic infestation. The most likely inflammatory cellular infiltrate that he observed would be:

a. Lymphocytes

b. Plasma cells

c. Eosinophils

d. Macrophages

e. Eosinophils, fibroblasts and tissue macrophages.

ANSWERS :

1) A

2) A

3) B

4) C

5) C

V2

*The modification is highlighted in yellow.