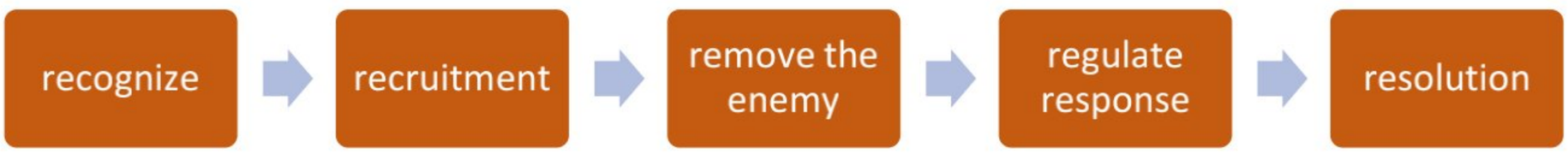
This file will have everything mentioned by the doctor in the review lecture and some nice tables which make the memorization easier.

ENJOY IT GUYS <3

We will start with some important concepts about inflammation:

1. Inflammation: is the response of vascularized tissue to injury by recruitment of cells and molecules from circulation to the site of need.
2. We have to know that in most of times the inflammation response is protective but, it can be fatal, injurious and leave scars and damage to the tissue.
3. Inflammatory process goes through steps (THE 5R's)



4. The cardinal signs of inflammation

Heat	Calor
Redness	Rubor
Pain	Dolor
Swelling	Tumor
Loss of function	Functio laesa

5. Causes of inflammation

Infections	Bacteria, fungi, viruses, parasites and their toxins
Necrosis	Ischemia, trauma, physical and chemical injuries, burns, frostbite, irradiation
Foreign bodies	Splinters, dirt, urate crystals (gout), Cholesterol crystals (atherosclerosis)
Immune reaction	Allergies and autoimmune diseases

nflammation	Characterized by *rubor* (redness), *dolor* (pain), *calor* (heat), *tumor* (swelling), and *functio laesa* (loss of function).
Vascular component	↑ vascular permeability, vasodilation, endothelial injury.
Cellular component	Neutrophils extravasate from circulation to injured tissue to participate in inflammation through phagocytosis, degranulation, and inflammatory mediator release.
Acute	Neutrophil, eosinophil, antibody (pre-existing), mast cell, and basophil mediated. Acute inflammation is rapid onset (seconds to minutes) and of short duration (minutes to days). Outcomes include complete resolution, abscess formation, or progression to chronic inflammation.
Chronic	Mononuclear cell (monocytes/macrophages, lymphocytes, plasma cells) and fibroblast mediated. Characterized by persistent destruction and repair. Associated with blood vessel proliferation, fibrosis. Granuloma: nodular collections of epithelioid macrophages and giant cells. Outcomes include scarring, amyloidosis, and neoplastic transformation.

6. Acute and chronic inflammation

Feature	Acute	Chronic
Onset	Fast	Slow
Cellular infiltrate	Neutrophils	Monocytes, macrophages, lymphocytes
Local and systemic signs	Prominent	Less prominent (that is why sometimes it's dangerous and those chronic diseases can be insidious)
Tissue injury	Mild and self-limited	May be sever and progressive

7. Disorders caused by inflammatory reaction (important)

Disorders	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Chronic	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes
Pulmonary fibrosis	Macrophages; fibroblasts

We will start talking about the 5R's of the inflammation response:

1. The initial phase of or the 1st R is recognizing the enemy and those are done via toll like receptors which tries to recognize PAMPs and sometimes there are other sensors which will sense that there was cell damage somewhere and they are called DAMPs in addition to circulating proteins.

The initial phases of inflammation are characterized by predominantly vascular phase that precedes the cellular phase caused by vascular dilatation and increased vascular permeability followed by emigration of inflammatory cells mainly white blood cells to the site of injury

Transudate	**Exudate**
Low protein content	High protein content
Low cell content	Cells and debris
Low specific gravity	Higher specific gravity
Caused by osmotic/hydrostatic pressure imbalance	Caused by increased vascular permeability and denotes inflammatory

Edema: is just simple excess fluids in the interstitium or serous cavities it can be transudate and it can be exudate

Pus: is always an exudate "purulent debris" which is what you see in the necrotic material when you have a small abscess formation.

The importance of the different between those two, because the pathogeneses and the reasons and etiology of each one is different, the exudate is more serious and indicates severe acute inflammation or cancer and other severe conditions

All of that could lead to recognizable signs redness erythema which you can see by your eye and if you take a section under the microscope you can see those changes in the subcutaneous tissue

The vascular phase is an active process:
The first thing which happens is the retraction of the endothelial cells induced by histamine that will start leaking fluids and sometimes the cells and proteins outside.

THEN this is followed by more active process by increased vascular permeability probably due to damage to the endothelial cells where more cells leak into outside the vascular structure.

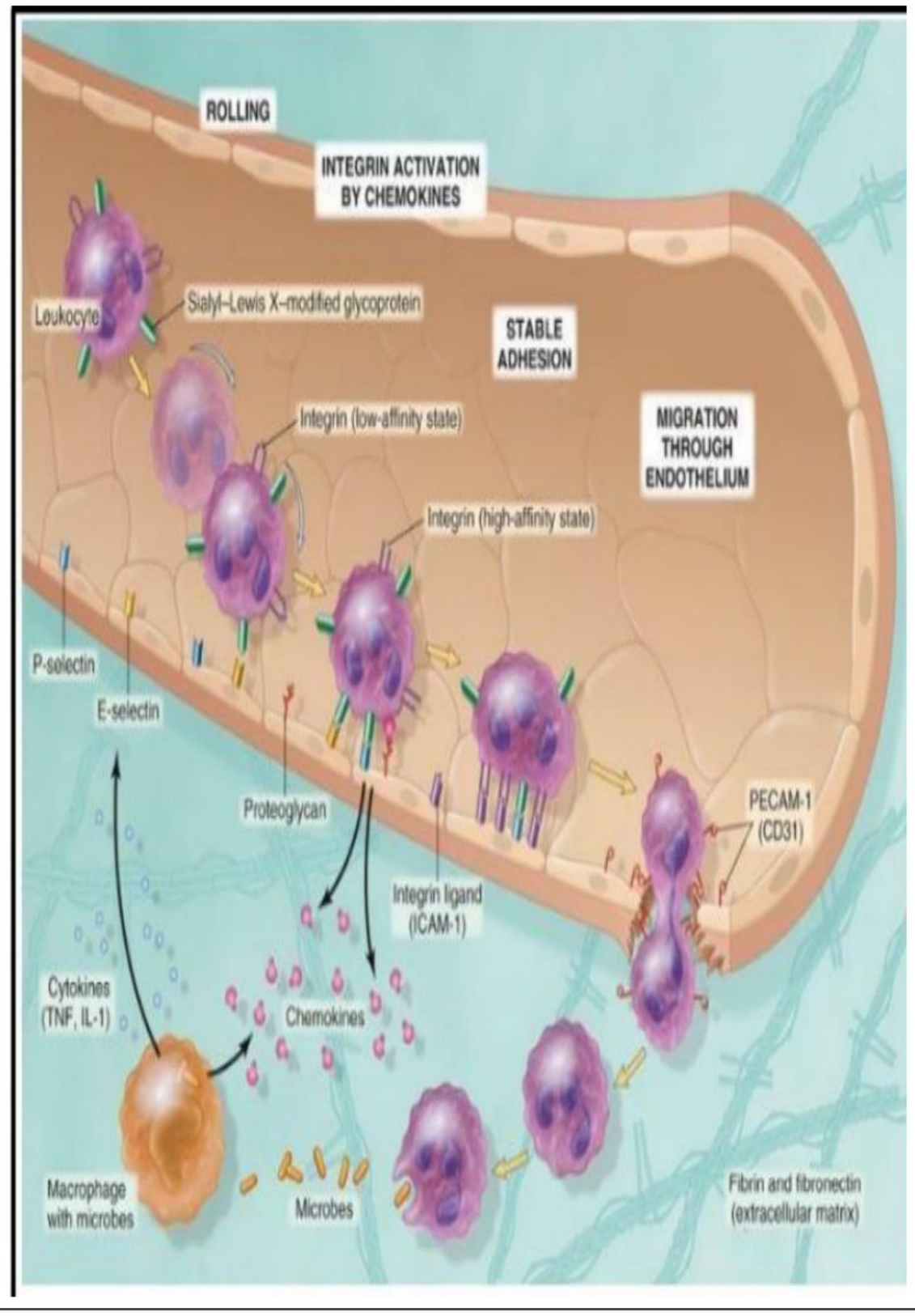
Lymphatic drainage
Its important because they are common presenting symptoms you will see on patients.
So, it must be investigated to rule out the presence of chronic specific diseases like tb or cancer

I will start talking about the role of leukocytes as part of the 2nd R
neutrophils and the macrophages are the ones which are recruited initially into the site of inflammation.
The next table is extremely important according to the doctor

TABLE 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil



Adhesions of white blood cells:

the adhesions of white blood cells to the endothelium is a very active process and there are steps which the tissue goes through:

1. the initial phase is margination where the white blood cells or the neutrophils go from the center of the lumen toward close to the wall of the endothelium.
2. Then cells start rolling on the wall of the endothelium followed by initial selectin with low affinity adherence to those surface cell receptors.
3. followed by more strong adhesions by integrins.
4. movement of the white blood cells from inside to outside the lumen through the function of PCAM or CD31 where the collagenase will damage the basement membrane and allow the cells to go back so that they can recognize the microbes and start the phagocytosis and killing the organism

REMEMBER there are two big families of endothelial adhesion molecules

1. SELECTINS
2. INTEGRINS

Transmigration:	**Chemotaxis:**
is CD31 or PECAM-1 platelet in the cell adhesion molecule expressed by the exquisites and the piercing through the basement membrane and induced by collagenases	is just the movement of white blood cells to the site of injury and the factors that activate this process are called chemoattractant

They could be bacterial, peptides, chemokine family from the complement system

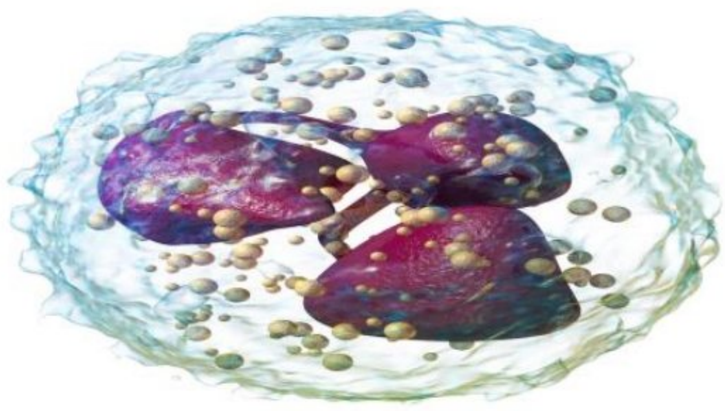
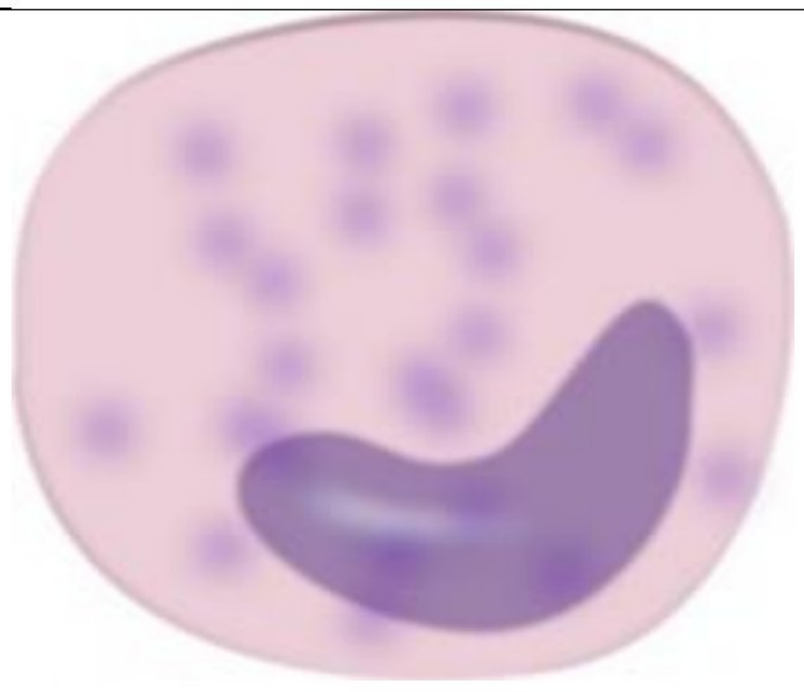
The strongest chemotactic agent C5A from the arachidonic acid metabolite pathway and LTB4

WBCs infiltrate in tissue:

acute inflammation	neutrophils
chronic inflammation	macrophage lymphocytes and plasma cells
allergic reactions and parasitic infections	too many eosinophils

Leukocytes activation

the activation needs receptors from outside to inside so that the inflammatory process will start cascading into the system most of those leukocytes whether they are neutrophils or macrophages have to be activated to exert their function

Neutrophils	(polymorphonuclear leukocyte) “mickymouse” with 3 nuclei. They have granules containing enzymes	
Monocytes	we call the monocytes when they are circulating and when they go to the tissue, we call them tissue macrophages they have coffee bean nucleus abundant place less granules here but more prominent	

Activation of leukocytes leads to phagocytosis
The phagocytosis process also goes through steps:

1. first the recognition through certain receptors of those foreign material
2. then they engulf and phagocytose the organism or the injurious agent forming what we call the phagosome
3. and then the intracellular killing is done by reactive oxygen species such as nitric oxide H2O2 and the most important bactericidal system in the neutrophil is the **myeloperoxidase halide**

The nitric oxide is extremely important it is a soluble gas produced by arginine by an enzyme which called **synthase** there are three types of those synthesis:

the most important one is iNOS nitrogen oxide

nitric oxide synthase which is responsible for the intracellular killing stimulated by **cytokine family interferon gamma** and then the nitric oxide reaction with **superoxide o2** forming on which is a very strong **radical peroxynitrite**
all those are materials which are responsible, and they function in the intracellular killing process

The granules primary granules large, smaller granules read this about yourself

The traps or knit neutrophil extra traps it's important to understand this happens **after the death** of the neutrophil
it's a viscous meshwork or thick viscous of nucleochromatin which tries to keep the injurious agent at the site of injury so that it would be easier for other macrophages to come and deal with these bad guys

in the last five years there was a lot of research on sepsis and the role of traps and sepsis and in addition to another autoimmune disease which is called **systemic lupus erythematosus**

sometimes the leukocytes will induce injury and specifically if there's
1. prolonged inflammation like tb and **hepatitis c**
2. the inflammatory reaction is inappropriate, and which underlines the basics of autoimmune diseases
3. and sometimes the **response is exaggerated** such as you can see sometimes in bronchial asthma and allergic reactions.

So, all those leukocytes mediated tissue injury which can present the patient to the emergency room or to the clinics complaining of some sort of disease.

There are other functions of activated blood cells

1. amplification or decrease the intensity of reactions through mediators through cytokines some of them enters and increase and activate the response.
2. some of them decrease growth factors which are important in repair like transforming growth factor beta
3. 3.and the new addition of the T lymphocyte subdivisions from T helper CD4 t suppressor CD8 and then the T helper 17 subtype which induces interleukin-17 which plays a role both in acute and chronic inflammation.

Now we don't want the inflammatory response to continue because otherwise there will be some injury so there are multiple mechanisms in which the body will terminate the acute inflammatory response

1. all mediators are produced in rapid bursts
2. most of these are stimulus dependent
3. they have short half-lives
4. degraded upon release
5. the PMN, the neutrophils which are one of the major sources of those mediators they have short half-life
6. there are also mediators which will stop signal production of certain mediators
7. sometimes there's neural inhibitors

Those are seven mechanisms how our body terminates or decreases the intensity of the response to prevent further injury

The mediators of inflammation:

1. Vasoactive amines: histamine and serotonin
2. Lipid products
3. Cytokines
4. Complement system

General features of mediators:

1. They are cell derived at the site of injury they are released by piercing granules into the system and sometimes they are stimulated and synthesized upon activation at the site of injury.
2. Plasma proteins are present in small amounts synthesized by the liver, but they need stimulation the big example **is the complement system.**
3. Active mediators need stimulation even if they are active, they need to have a stimulatory stimulus.
4. They have a short lifespan.
5. one can activate the other.

There will be 2 questions on the next table :)

TABLE 3.5 Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

It's time to have a small break, refill your coffee and take some fresh air
And remember, you are here because you deserve to be here
You are clever, successful and amazing, have a faith in that please.

Our trip will end sooner or later, be clever how YOU want to be when it ends <3

ARACHIDONIC ACID METABOLITES (EICOSANOID)

The arachidonic acid metabolites are big group of mediators

damage of the cell membrane happens by the phospholipase which will release arachidonic acid which have two pathways:

1. lipoxygenase pathway
2. cyclooxygenase pathway

	Inhibitors	Inhibitor function
lipoxygenase pathway	Lipoxygenase inhibitor	decrease the inflammatory response from the leukotrienes from the lipoxygenase pathway
cyclooxygenase pathway	Steroids, aspirin, indomethacin, cox 1, cox 2	will decrease the whole amount of inflammation of prostaglandin arm from the cyclooxygenase pathway

prostaglandin I2, thromboxane A2 one of them **causes vasodilation and inhibits platelet aggregation** the other one is the opposite and the imbalance between these two **is incriminated in the pathogenesis of ischemic heart disease**

Leukotriene D4 is a strong chemotactic factor and those leukotrienes C4, D4, E4 they cause **bronchospasm,** and they are incriminated **in the pathogenesis of bronchial asthma where bronchospasm is the main feature**

بدي اصدمكم واحكيلكم انه برضه هاد الجدول حفظ :)

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, P(PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

POINTS TO REMEMBER:

- Aspirin – inhibit cyclooxygenase
- Steroids – is the main stem phospholipase inhibitor
- Prostacyclin (PGI2): vasodilator and inhibit platelet aggregation
- Thromboxane A2: vasoconstrictor and stimulate platelet aggregation
- imbalance between those two is incriminated in ischemic heart disease and cardiovascular accidents.
- PG (PGE2): major mediators to produce pain and fever and anti-prostaglandins are used to be painkillers and antibiotics

cytokines are a big group of proteins are secreted by many cells **activated by lymphocytes macrophages and dendritic cells** they actually big group of mediators and regulators of immune and inflammatory response.

Major groups of cytokines that is important in acute inflammatory response:
TNF, IL-1, IL-6, IL-17, chemokines.
Major groups of cytokines that is important in chronic inflammatory response:
interleukin-17 which is secreted by T helper number 17 play a role both in acute and chronic inflammation

local inflammatory features they are characterized by vascular and cellular phase due to the release of multiple mediators	1. **systemic effects** some of it which are protective some of it which are pathologic and sometimes it hurts the presence of fever protects the central nervous system and it brings the patient to the clinician 2. **acute phase** proteins which are non-specific amounts in the serum which we sometimes can measure like c reactive protein it gives me an indication that there is an acute inflammatory process, so this is also another side effect 3. some of these mediators will stimulate the hematopoiesis in the in the bone marrow	**bad and the harmful impact**s of systemic pathological features decrease in the cardiac output increase the incidence of vascular thrombosis and insulin resistance

chemokines are small group proteins they have two functions they are involved in as a chemical mediator of acute inflammation and, they maintain tissue architecture.

complement system: are multiple proteins and more than 20

1. important ones are c1 to c9
2. involved in innate adaptive immunity.
3. they have multiple functions vascular chemical taxes and opsonization
4. c3 is the most abundant cleavage of which is the major player in all critical pathways.

The three main pathways stimulating the cleavage of c3 to get activate to activate the cascade of complement fixation:

1. alternative pathway classic by alternative pathway induced by microbes and their receptors.

2. classic pathways antigen antibody complexion trying to fix or activate the complement.
3. lectin pathway where certain amino receptors binding into the microbial agent and then stimulating the cleavage of c3.

Then, activated c3 will go on and cause chemotaxis c5a c3a are strong chemotactic agents c3b helps opsonization or phagocytosis

** **opsonization means helping neutrophils and macrophages to phagocytose those foreign materials**

and then we have the mac or the membrane attack complex which is a multiple of c9s they make holes of the organisms and kill it and those are **the three end results of activation the cascade of complement system.**

they have regulatory proteins those complement system from C1 to C3 DF CD59 and sometimes the other factors

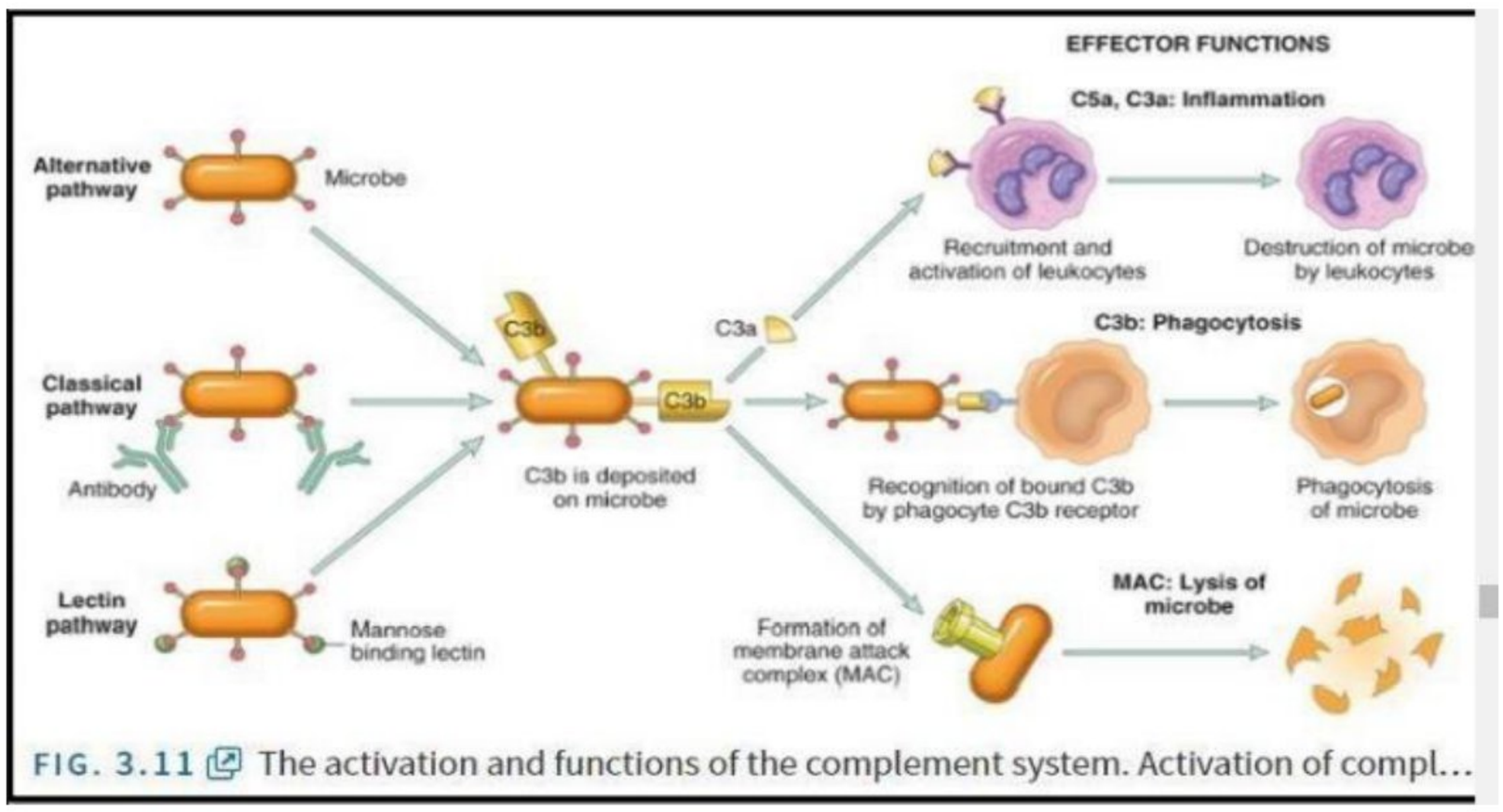


FIG. 3.11 The activation and functions of the complement system. Activation of compl…

remember just to focus on the KININS because they are involved in the production of pain and smooth muscle contractions during pregnancy

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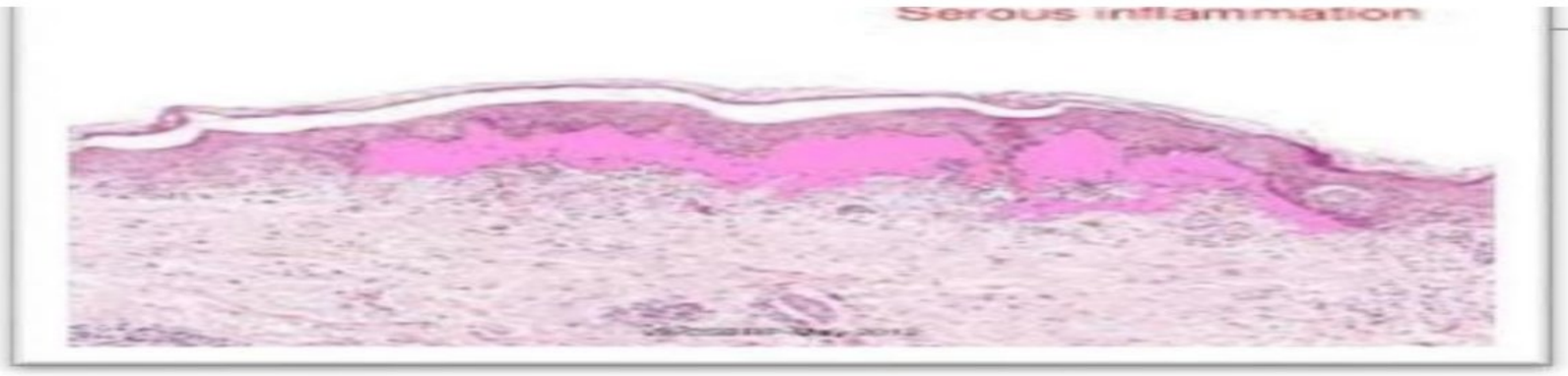
TABLE 3.8 Role of Mediators in Different Reactions of Inflammation

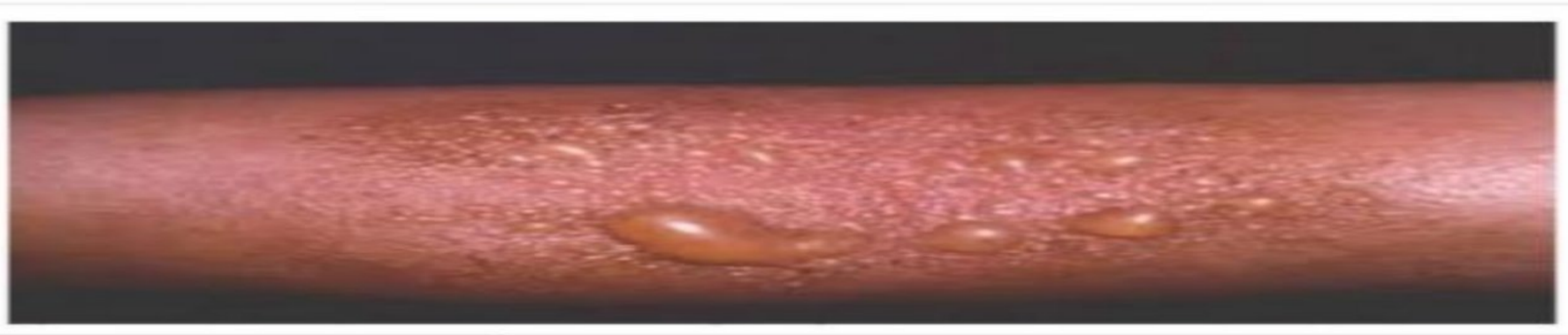
Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine
	Prostaglandins
Increased vascular permeability	Histamine
	C3a and C5a (by liberating vasoactive amines from mast cells, other cells)
	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1
	Chemokines
	C3a, C5a
	Leukotriene B_4
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes
	Reactive oxygen species

What are the different morphologic appearances of acute inflammation?

1. serous inflammation where it is cell poor fluid which is a transudate which occurs sometimes in minor cell injuries or minor superficial trauma.
2. serous effusions for example patients with heart failure or chronic liver disease they will have this decrease oncotic pressure leading to serious effusion bilateral in the lung or ascites skin blisters.
3. seromas are common collection of just cell poor or just serum at the site of surgery like breast surgery.
4. fibrinous inflammation is a collection of large air large amounts of vascular leakage that causes coagulum, and this is characteristically found on body cavities like pericardium and pleural fluids.
5. purulent means pus means exudate a lot of neutrophils cells and this is the basic mechanism of the formation of abscess anywhere in the body in the lung or anywhere in the body the treatment is always drainage followed by proper coverage by antibiotic
6. ulcers: loss of continuity in a tissue

1+2





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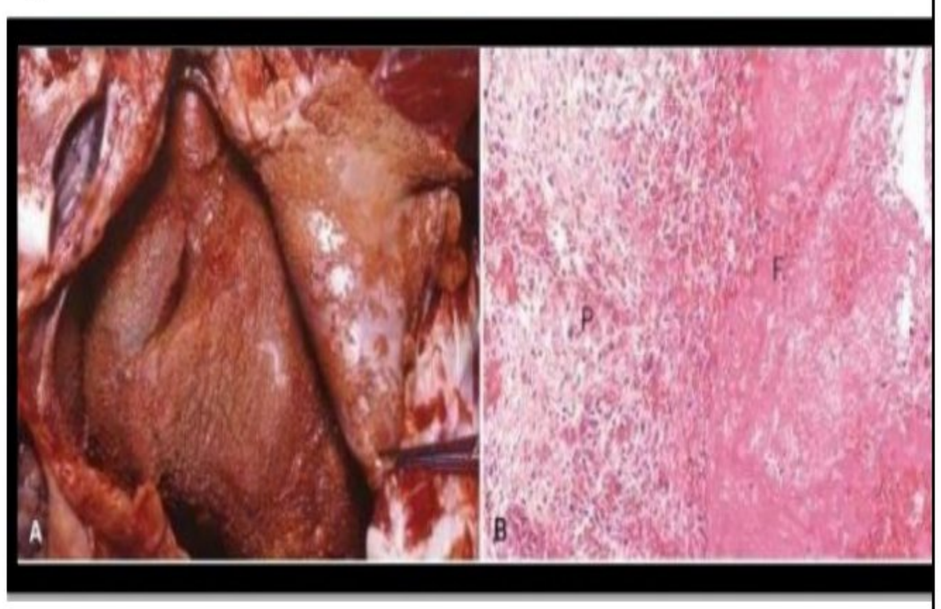

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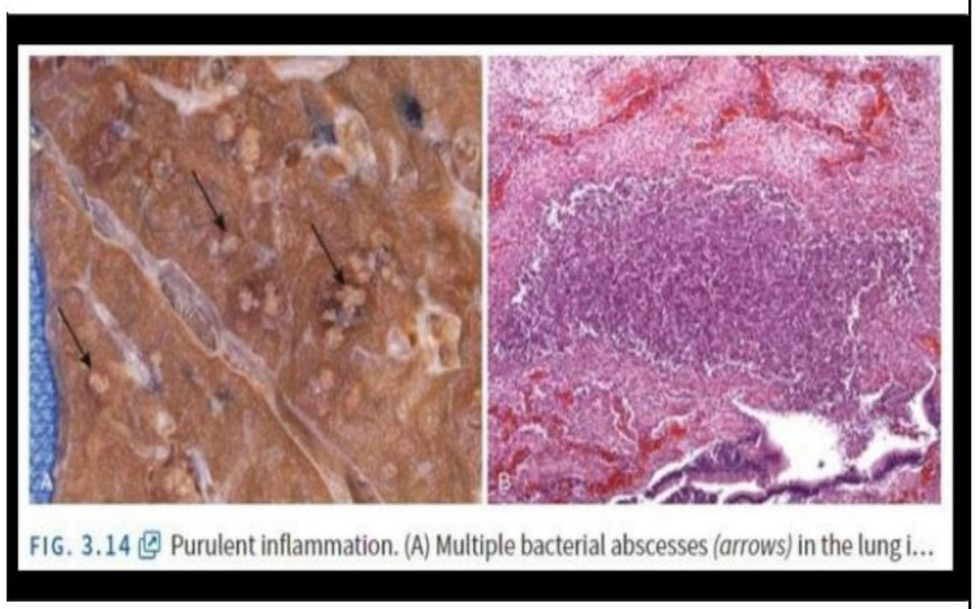

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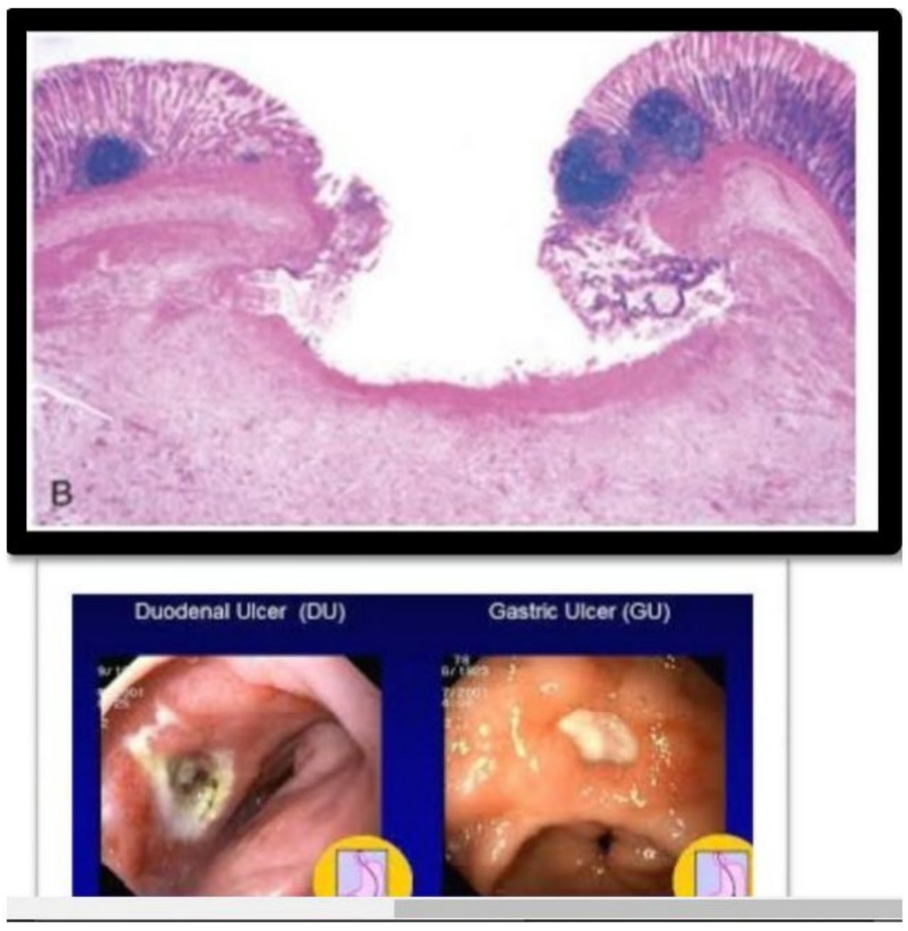


chronic inflammation:

occurs because of prolonged inflammation and the tissue tries to repair it and with time the fibrosis occurs and then another attack and this depends on multiple factors and this may follow acute inflammation and sometimes they are low grade chronic inflammation which goes for years and years until they damage the organ

Causes of chronic inflammation:

1. parasitic infection due to virulent organisms like TB, fungi, viruses.
2. hypersensitivity reaction rheumatoid arthritis asthma multiple sclerosis which will end up sometimes fibrosis in organs.
3. prolonged exposure to toxic agents exogenous or indigenous like silica silicosis or atherosclerosis which is induced by the position of cholesterol

How do you recognize chronic inflammation in the tissue?

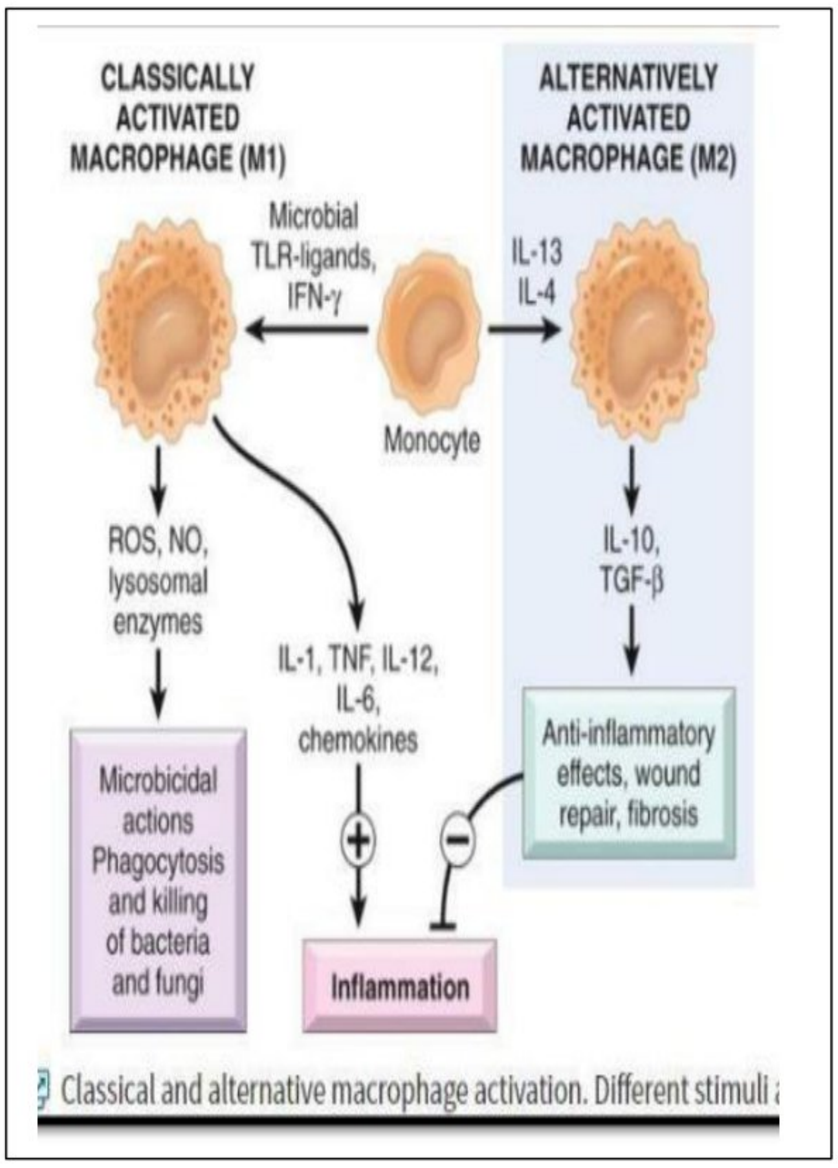
1. inflammatory cells are different they are macrophages lymphocytes and plasma cells
2. there is more tissue destruction
3. there are always attempts to heal by angiogenesis

Macrophages

1. they have multiple functions they have longer duration of life
2. they have to get activated and by activation the nucleus becomes smaller cytoplasm becomes bigger and more granulated.

they have two pathways

1. the classic m and m1 pathway where the function of those activated m1 macrophages is pro activator of inflammation
2. the m2 pathway will be anti-inflammatory and they are needed in the phase of repair



Classical and alternative macrophage activation. Different stimuli a

LYMPHOCYTES

we have T lymphocytes B lymphocyte and then multiple subdivisions

B cells are basically the precursors of mature plasma cells

the CD4 or CD helper T cells are important because they are important secretors of cytokines

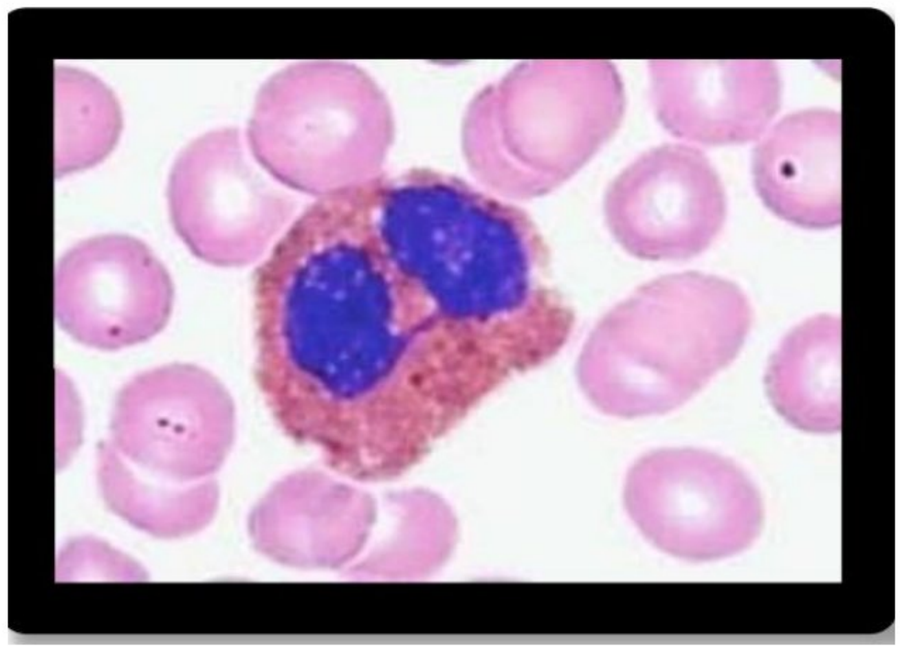
there is T helper one T helper 2 and then recently discovered that the helper 17 secreting **interleukin 17** with multiple inflammatory functions.

Eosinophils

Eosinophils are important because they produce IgE and they are common and parasitic infections the granules have basic major proteins, and they may cause tissue damage

The recognition of these cells is referenced because they have an eosinophilic pink cytoplasm granulated and two nuclear

Remember: they present in allergy, parasitic infection and eosinophilic inflammation



MAST CELLS

they have some granules, and they are common in soft tissue neoplasms

Granulomatous inflammation

- specific type of chronic inflammation
- granuloma: activated epithelioid macrophages or tissue histocytes surrounded by collection of lymphocytes and plasma cells.
- if they are necrotizing, they are called discretizing granulomatous inflammation (caseating)

- if they are non-necrotizing, they don't have necrosis in the center of them they are called non-necrotizing granules inflammation (non-caseating)
  remember: there are multiple granulomas in the lymph node there is no necrosis the prototype of this characteristic but not pathogenic of a disease called sarcoidosis **remember that sarcoidosis is disease or explosion**
- they are immune granulomas and there's also foreign body types

just read this table and make sure that you memorize what mycobacterium do, and sarcoidosis is caused by unknown

it diagnosed by exclusion when you have necrotizing granulomas you always have to rule out organisms on top of the list is mycobacterium

The any inflammatory response whether it's acute and chronic will have systemic effects fever is one of them and those are the mediators acute phase proteins
those are the ones which we can measure in the serum leukocytosis because of the induction of hematopoiesis in the bone marrow and you have to **differentiate between leukocytosis and leukemoid reaction**
leukemoid reaction: is when there is actually very high leukocytosis which is not explained at this point

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocyt occasional Langhans giant cells; central necro with amorphous granular debris; acid-fast bac
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseatin granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages; plasma cell infiltrate; central cells are necrotic without los of cellular outline; organisms difficult to ident 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 w of the intestine, with dense chronic inflammatory infiltrate

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

you have to make sure this is not leukemia by doing certain markers utilizing flow cytometry phenotypic analysis of peripheral blood
there are other features like tachycardia increased blood pressure chills rigors all those are could be features of acute inflammation