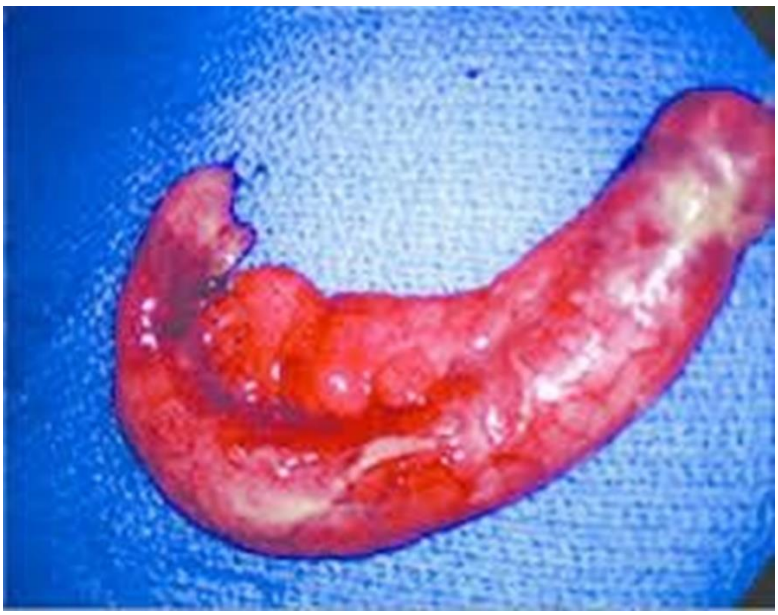
# Inflammation

the concept of inflammation is very important, you must know the details of the inflammatory process, how our tissues response to inflammatory conditions?



## What was mentioned in the lecture:

we'll kick in our inflammatory lecture by looking at this organ, this is an appendix, actually, the normal appendix is smaller and whiter, but this one is a red, enlarged and congested appendix, it is an inflamed appendix, this is a condition known as acute appendicitis,  those are the three major cardinal signs of inflammation of any organ.

# DEFINITION OF INFLAMMATION

## What was mentioned in the slide:

**“Response of vascularized tissue to injury (infections or tissue damage) recruitment of cells and molecules from circulation to the sites of need to eliminate the offending agent”**

## What was mentioned in the lecture:

if somebody asked you, what is the definition of inflammation? many people try to give a comprehensive and accurate definition of inflammation, this is the best definition of inflammation: it is a response of an alive tissue or vascularized tissue to injury, it is actually a response of a viable tissue (a live tissue or

vascularized tissue) to an injurious agent (offending agent) whether it's an infection or a tissue damage, this is probably the most comprehensive and accurate definition of inflammation, this response by a vascularized tissue to an injury, trauma, bacteria, virus, etc. will do this job by recruitment of cells and molecules from the circulation to the site of injury trying to get rid, destroy and eliminate that offending agent, for example if you have viral tonsillitis, you will have a response of your tonsils to this virus trying to get rid of the virus, during couple of days you will have swelling and congestion and a lot of cells infiltrating to the tonsils trying to get rid of that particular virus, after a couple of days you will be back to normal, so the best definition of inflammation is: it is a response of a viable or vascularized tissue to a certain type of injury, and there is a lot of different types of injurious agents, this process includes recruitment of cells and molecules from the circulation which will be needed at the site of injury so that your body can eliminate that offending agent.

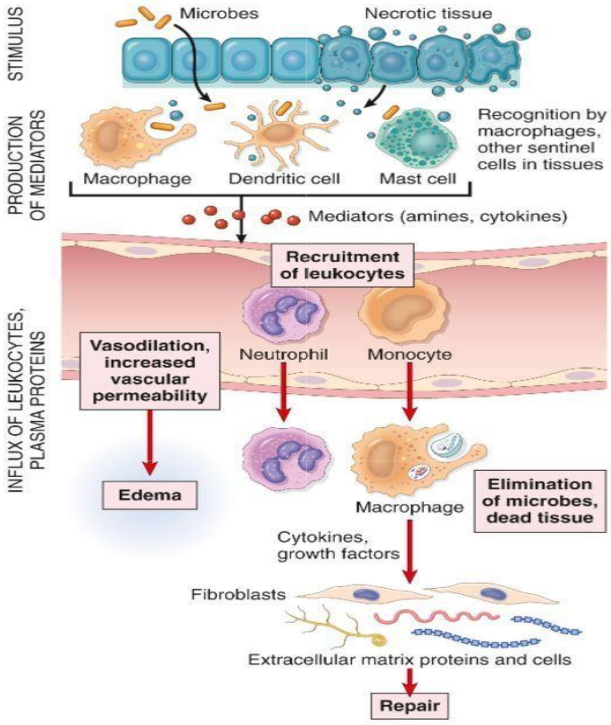
# Characteristics of Inflammation:

## What was mentioned in the slide:

- **Protective**
- **With no inflammation: infections can be fatal; wounds would never heal and injured tissue may sustain permanent damage**

## What was mentioned in the lectures:

the concept of this slide is really important, you have to understand that inflammation in general is protective, it bothers you and it is not a normal condition but it protects you from bad consequences from these offending agents, with no inflammation, infections can be fatal, in the 30s and 20s before we created antibiotics, simple tonsillitis and simple appendicitis used to be fatal, without inflammation your wounds will never heal and your injured tissue will sustain and experience permanent damage, because of the inflammation, we are fighting those fatal consequences, we are helping our body to heal the wounds, and we prevent or decrease or eliminate tissue damage, so in general it's protective and without inflammation your life will be exposed to many dangerous fatal events.




## What was mentioned in the lecture:

This figure summarizes all events of inflammation, we're going to talk about these, firstly, we'll have an offending microbe or (a bacilli bacteria for example) as a stimulus, which will cause tissue damage, and your cells will then recognize that this is an offending agent by either recognizing the microbes or recognizing the damaged tissue, this will stimulate many inflammatory cells like macrophages, dendritic cells and mast cells to secrete a lot of chemical mediators, in inflammation, initially we will have predominance of amines that will cause vasodilation and increased vascular permeability, and also we'll where also recruitment of inflammatory cells like neutrophils and monocytes, monocytes will be called macrophages as soon as they leaves the blood vessel into the tissue, they will be transformed to activated macrophage which we call tissue macrophages, and neutrophils or mickey mouse cells ( cells with trilobed nuclei), those cells will also stimulate the secretion of multiple mediators like cytokines and growth factors, trying to eliminate the microbe by different mechanisms like intracellular killing, then the reparative process will propagate and start with recruitment of fibroblasts and extracellular matrix proteins, then the reparative process ends, so those are the five steps of inflammation, we will talk about these in details.

# Typical inflamm. Rx. steps:

## What was mentioned in the slide:

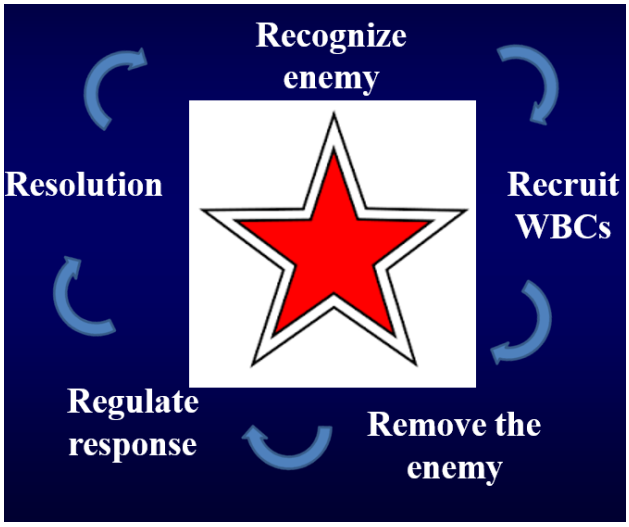
- **Offending agent recognized by cells and molecules**
- **WBCs & Pl. proteins recruited to injury site**
- **WBCs and Pl. proteins work together to destroy and eliminate the enemy**
- **Rx. Is then controlled and terminated**
- **Repair of damaged tissue (regeneration & fibrosis)**

## What was mentioned in the lecture:

the typical inflammatory reaction passes through five major steps: the first step -as we discussed- is recognizing the offending agent and the changes which this offending agent causes, likes changes in the structures of proteins or cells, the second step is recruitment of white blood cells or inflammatory cells in addition to recruitment and stimulation of different types of plasma proteins to go into and concentrate and focus at the site of injury, whether it's tonsils, appendix, liver, etc. in the third step all this cellular response and vascular response will try to eliminate and get rid of that particular injurious

agent whether it's bacteria, virus, etc. the fourth step is that by the time we eliminate the enemy- the bacteria or the virus- we don't need all these soldiers like white blood cells, proteins and chemical mediators to stay, because if they do, they might cause collateral damage, so the fourth step is when your body try to control, decrease and eliminate this inflammatory response so that there would be no more tissue damage, in the fifth step the repair process will start, the tissue which has been lost will be replaced by either regeneration, if there are regeneration abilities or by scar formation, so those are the five steps of inflammation, 1-recognizing of the offending agent 2-recruitment of inflammatory cells and plasma proteins 3-elimination of the injurious agent by phagocytosis ( intracellular killing) 4- then we have to control and eliminate and decrease the intensity of the response so that we will have no collateral damage 5-the final step is repair of damaged tissue.

# The 5 Rs:




## What was mentioned in the lecture:

so those are the five major steps or the five Rs, the five Rs are: **r**ecognizing the enemy, **r**ecruitment of white blood cells and plasma proteins, **r**emoving the enemy, **r**egulate and control and decrease the intensity of the inflammatory response and then **r**esolution and repair, each step of these comes before the next one, so recognizing the enemy comes before recruitment of white blood cells and plasma proteins, recruitment of WBCs and plasma proteins come before removing the enemy, removing the enemy comes before regulating response, and regulating response comes before the repair, there's some overlap between this and this between this and that, but those steps are consequential.

**TABLE 3.1** Features of Acute and Chronic Inflammation

| Feature | Acute | Chronic |
|---|---|---|
| Onset | Fast: minutes or hours | Slow: days |
| Cellular infiltrate | Mainly neutrophils | Monocytes/macrophages and lymphocytes |
| Tissue injury, fibrosis | Usually mild and self-limited | May be severe and progressive |
| Local and systemic signs | Prominent | Less |

## What was mentioned in the lecture:

Historically, in general -this has clinical implications- when you start seeing patients in the clinic, emergency room, operating room, the inflammation is divided into two main major categories: acute Inflammation الالتهاب الحادّ at one side and chronic inflammation الالتهاب المزمن on the other side, the difference between these two is based on the onset, cellular infiltration, type and extent of tissue injury and fibrosis, and local and systemic effects, you have to really understand the difference between acute and chronic inflammation, the onset of acute inflammation is really fast, so if somebody has acute bronchitis or acute tonsillitis, form minutes to hours, you will start having symptoms and signs and this will push the patient to go and seek medical advice, however, chronic inflammation is slower and takes days, weeks or sometimes months to appear and sometimes it doesn't show real symptoms until a severe damage has happened to the organ, this is why chronic inflammation is really insidious, you have to pay attention to these changes, regarding the cellular infiltrate, if I received an acutely inflamed appendix and have a tissue section and look at the cellular infiltrate, neutrophils will predominate, so the hallmark of acute inflammation is the predominance of neutrophils, there is always exceptions to the rules, however, at your level, acute inflammatory cells are neutrophils (the mickey mouse or the polymorphonuclear cells), however, in chronic inflammation, it is lymphocytes, macrophages and plasma cells, regarding tissue injury and fibrosis, most of the time (more than 90-95 percent of the time), acute inflammatory diseases are usually mild and they are self-limited, that's why when you have common cold, you'll have flu and fever for few days and then you'll be healed, so the treatment given is basically supportive treatment like antipyretics for fever and pain relievers, and antihistamines for the congestion, those are the major supportive treatments in acute inflammatory diseases, especially viral illnesses, however, chronic diseases, if they continue and they are not stopped they are severe, progressive and end up with a lot of damage, fibrosis and tissue injury, so this is the third component of the difference between acute and chronic inflammation, the fourth one is the presence of local and systemic signs, so if somebody has severe acute tonsillitis, immediately in one to two days, he will experience pain, sore throat, fever, etc. so the local and the systemic signs of acute inflammation are prominent, this is why acute inflammation will push you to go to the emergency room or to go to your doctor in your clinic, however in the chronic inflammation the local and systemic signs are much less, this is why things are being messed up and you do not pay attention, this is why in the chronic inflammation the local and systemic signs are less prominent. having said that does not mean that there is not a situation in which you have both, so sometimes there is a baseline of chronic inflammation and sometimes an acute attack comes on top, we call that acute in top of chronic, like chronic active gastritis, in which we have a chronic inflammation of the stomach and then and acute attack on top, in that case, neutrophils will appear on top of plasma cells, lymphocytes and macrophages, that happens due to an infection called helicobacter pylori, there's different terminology which are used to describe that in pathology.

# Cardinal signs of inflammation

## What was mentioned in the slide:

- **HEAT (*calor*)**
- **REDNESS (*rubor*)**
- **SWELLING (*tumor*)**
- **PAIN (*dolor*)**
- **LOSS OF FUNCTION (*functio laesa*)**

## What was mentioned in the lecture:

Regarding the cardinal signs of inflammation, those are the major signs of inflammation, any inflamed organ will express heat, if you put your hand on a patient's forehead who has inflammation you'll see fever, even if you touched the tonsils of a patient who has tonsillitis you'll feel that they are warm, this is called calor in the old Latin terminology, the organ will be congested having too much blood and will express redness, this is called rubor is Latin terminology, it will be swollen, inflamed tonsils will be large causing difficulty in swallowing, this is called tumor in Latin, the organ which is inflamed will also stimulate your pain receptors, causing pain, that is reflected by sore throat in tonsillitis, this is called dolor in Latin, ultimately this organ, which is inflamed, will have loss of function, for example if you have an inflamed big toe (like in gout), you'll not be able be able to move it, or if the ankle is swollen like in severe arthritis. You'll not be able to move, so those are the five cardinal signs of inflammation: heat (calor) redness (rubor), swelling (tumor), pain (dolor) of loss of function (functio laesa), each one of them is explained by certain mechanism of pathogenesis.

# Can inflammation be bad?

## What was mentioned in the slide:

- **Too much…damage**
- **Too little… damage**
- **Misdirected inflammation…autoimmune diseases and allergies**
- **Chronic inflammation…chronic diseases**

## What was mentioned in the lecture:

can inflammation be bad? of course, if there is too much inflammation sometimes, there will be too much damage to your tissues, on the other hand, if you don't have a proper inflammatory response, your immune system is not well equipped, you will have exposure to multiple opportunistic infections, so too much inflammation is not good and too little inflammation is also not good, because there will be damage by the offending agent, and if the inflammatory response is misdirected -this is the mechanism of autoimmune diseases and allergies- in which your tissue response will be misdirected, instead of attacking the virus or the bacteria in your sore throat, they will attack for example your kidney and causing glomerulonephritis, so this is the basis of autoimmune diseases where your immune response will damage your own tissue, chronic inflammation will cause chronic diseases, most of the chronic diseases which you see like chronic hepatitis, chronic glomerulonephritis, will end up sometimes damaging the kidney, heart, lungs, liver causing chronic liver disease, end stage renal disease, end stage pulmonary fibrosis, etc. so those are the four mechanisms of bad consequences of inflammation: too much damage, too little inflammation causing damage by the pathogenic agent, autoimmune diseases and chronic inflammation which cause chronic damage of organs.

**TABLE 3.2** Disorders Caused by Inflammatory Reactions

| 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 |

Listed are selected examples of diseases in which the inflammatory response plays a significant role in tissue injury. Some, such as asthma, can present with acute inflammation or a chronic illness with repeated bouts of acute exacerbation. These diseases and their pathogenesis are discussed in relevant chapters.

## What was mentioned in the lecture:

this table gives you examples of acute illnesses and chronic illnesses, you'll see many of those in your clerkships and rotations of internal medicine, pediatrics, OB/GYN (obstetrics, gynecologists), surgery, etc. firstly, acute respiratory distress syndrome or acute respiratory syndrome, this is a clinical syndrome which will see sometimes in those patients who are terminally ill with multiple organ failures in the ICUs, the main mechanism of injury in the lung is carried by neutrophils, in pathology whenever we do an autopsy on somebody who ended up dying from ARDS, what we see under the microscope when we take sections from the lung is diffuse alveolar damage (DAD) which will be explained in details in your

respiratory pathology section, so this is an acute illness, the pathologic term is diffuse alveolar damage, the main inflammatory cell is neutrophils who mediate the injury.
regarding acute bronchial asthma, patients with acute bronchial asthma might exhibit atopy, allergy, sneezing, bronchospasm, wheezing, difficulty of swallowing and other things, the mediators of these acute attacks is eosinophils and IgE antibodies.
acute glomerulonephritis is mediated by antibodies and complement system involving also sometimes monocytes, and monocytes tissue injury in the kidneys and nephrons.
regarding septic shock or septicemia (blood poisoning), it is caused by severe bacterial overgrowth in the blood in association with the impact on vital functions, and in many cases severe septicemia -specifically gram-negative bacterial septicemia- is lethal and can kill you and the major mediator responsible for tissue damage and vital organ damage in that case is the release of too many cytokines.
those are examples of acute clinical acute syndromes. some examples of chronic syndromes include chronic arthritis, rheumatoid arthritis, gouty arthritis, etc. those are mediated by injury by lymphocytes macrophages and sometimes antibodies -details will follow in your musculoskeletal system course-, when we talk about rheumatoid arthritis, osteoarthritis, septic arthritis, gouty arthritis, etc. so you will learn more about those are chronic diseases.
bronchial asthma can be also chronic, you do not need just only to treat acute attack of asthma, sometimes you have to have maintenance treatment to prevent the chronic condition of asthma, the mediators here again are the same, eosinophils and IgE antibodies.
regarding atherosclerosis, atherosclerosis is actually a chronic inflammatory response mediated by macrophages, lymphocytes and sometimes platelets, atherosclerosis can cause chronic ischemia with complications in the heart and the central nervous system in the form of acute myocardial infarction or strokes in your brain, regarding pulmonary fibrosis, many diseases of the lung will end up in pulmonary fibrosis or the end stage fibrosis where the major mediators are the macrophages and the fibroblasts, patients with pulmonary fibrosis need sometimes oxygen supply at home and this is a chronic condition which propagates over months and years, so those are examples of chronic diseases and those are examples of acute diseases and this is their mediators.

# 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 REACTIONS** | **Allergies and autoimmune diseases** |

## What was mentioned in the lecture:

what are the causes of inflammation? they are divided in major categorical boxes: infections, necrosis, foreign bodies and immune reactions, infections can be due to either bacteria, fungi, viruses, parasites and sometimes their toxins, each one of these is capable -especially bacteria- of secreting toxins like endotoxins and exotoxins (you will take details about these in your microbiology section) infections are a major cause of inflammation whether acute or chronic,
necrosis can happen by many reasons, like due to ischemia, ischemia can be due to blood vascular compromise or trauma which can also cut an artery and cause necrosis, causes of necrosis also include physical and chemical injuries like sunburn, frostbite قضمة البرد لما يتجمد الدم بعروقك, trauma or irradiation, all these can damage your blood vessels leading to necrosis which is also a major cause of inflammation.
the third group is foreign bodies, they include splinters, dirt, urate crystals which cause gouty arthritis by deposition in the joints especially the big toe, deposition of cholesterol clusters is the main underlying pathogenesis of the development of atherosclerosis which is responsible of many diseases some of which are actually fatal.
the fourth group of causes are the immune reactions including allergies, some people are allergic to certain medications or pollens when they are exposed to which their immune response is exaggerated, where sometimes severe reactions can cause damage or sometimes fatal reactions, and the big group of autoimmune diseases where your immune response will damage your own tissue, this is what we call misdirected inflammatory response, so those are the four major boxes of causes of inflammation: infections, necrosis, foreign bodies and immune reactions.

# Recognition of microbes and damaged cells:

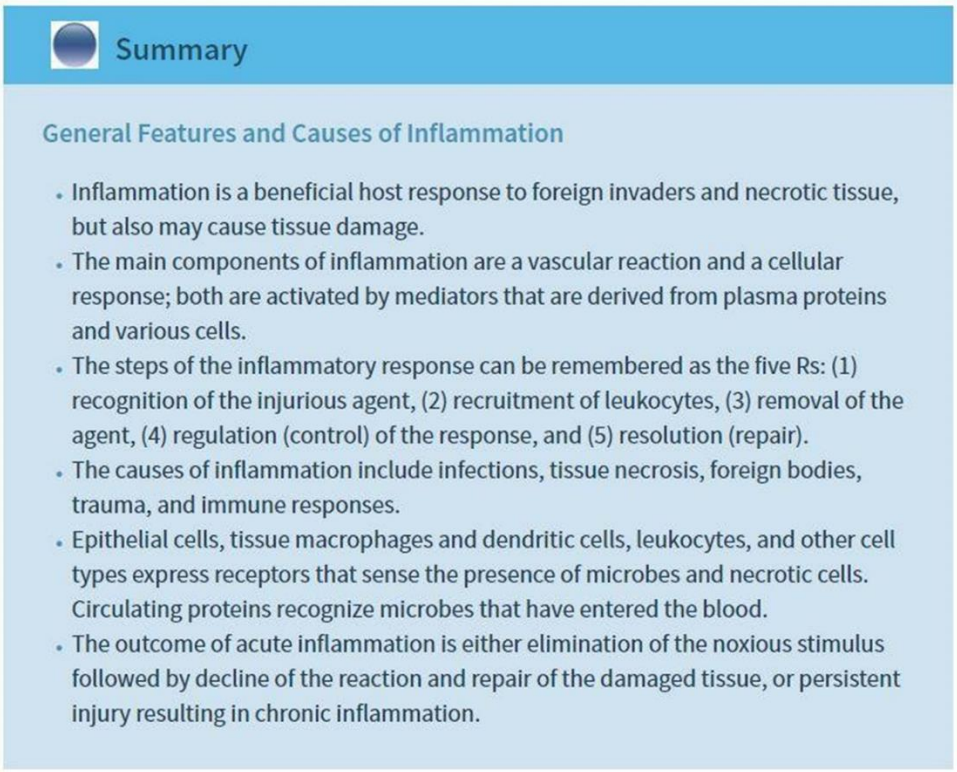
## What was mentioned in the slide:

- **First step in inflamm. response**
  - **Cellular receptors: Toll-like R (TLRs); on membranes and endosomes. Recognize Pathogen Associated Molecular Patterns (PAMPs)**
  - **Sensors of cell damage: recognize Damage- Associated Molecular Patterns (DAMPs) such as uric acid, ATP, K, & DNA. Consequently, multiple cytoplasmic proteins gets activated (called inflammasomes)**
  - **Circulating proteins: complement system, mannose-binding lectins and collectins.**

## What was mentioned in the lecture:

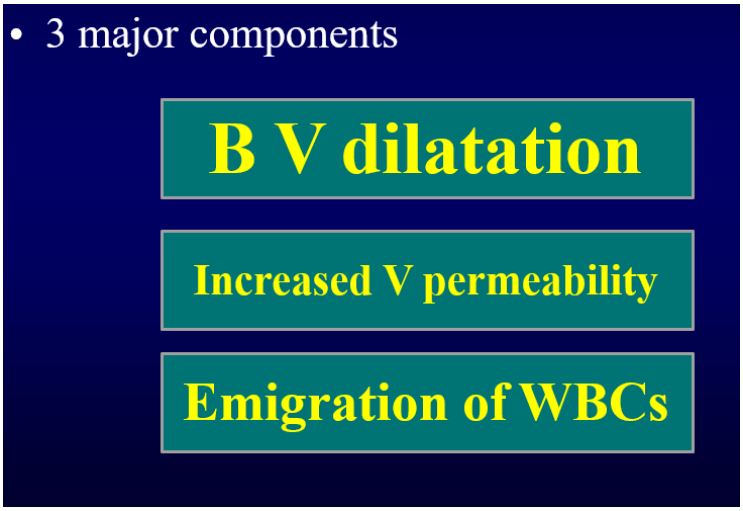
the first step of your inflammatory response is carried by toll-like receptors (TLRs) those are actually cellular receptors which are normally present in plasma membranes and endosomes, their function is that they recognize that there is something strange happening by a virus or a microbe because they'll cause some changes in the molecules of the cells, they recognize what we call pathogen-associated molecular patterns (PAMPs) immediately, there are sensors that recognize damaged tissue when there's necrosis

which can happen by radiation, ischemia, etc. also there are receptors that recognize DAMPs (damage associated molecular patterns) such as uric acid, ATP, potassium, DNA, because those sensors will be activated, consequently, multiple cytoplasm proteins gets activated which are called inflammasomes, , that will also cause recruiting of complement system proteins and some other proteins in the body some of which have also the ability to recognize those microbes or damaged cells, so this is the mechanism of the first step of the five Rs which is **r**ecognition of microbes and damaged cells.



# ACUTE INFLAMMATION

## What was mentioned in the slide:




## What was mentioned in the lecture:

let's talk a little bit about acute inflammation, the first phase of acute inflammation is actually called the vascular phase or vascular-cellular phase, this phase is composed of three major components, firstly vascular dilatation, although some people say that if you have an injury the first response is actually transient vasoconstriction but this just continues for like few seconds and then the vascular dilatation will ensue, so the first phase of acute inflammation is blood vasodilation which have certain mechanisms which we'll talk about them in detail soon, the second phase is increased vascular permeability where the cells, proteins and fluids will escape from the intravascular compartment to the interstitium which will lead to edema, (swelling), this is why the appendix was swollen because there was a lot of cells and a lot of fluids leaked out from the blood vessels (intravascular compartment) to the interstitial compartment, this will be also followed by immigration or migration of white blood cells from the intravascular compartment into the interstitium, so those are the three major components of the first phases of acute inflammation, vasodilatation, then increased vascular permeability, there are many chemical mediators which will induce the increase in the permeability and then the migration or transmigration of white blood cells from the intravascular compartment to the tissue site of injury blood vessel dilatation can be passive or active, active blood dilation requires more energy and more work to happen.

To sum up: those are the features or the major components of acute inflammation, in the initial phases, there is blood vessel dilatation and increased vascular permeability which is an active process, blood vessel dilatation can be passive or active and what we mean by active and passive is that the active vasodilation requires more energy and more work to happen compared to the passive vasodilation, then what happens is the recruitment or the immigration of white blood cells from the intravascular compartment to the extravascular compartment .
Extra info: active vasodilation is caused by decreased tonus of smooth muscle in the vessel wall (muscle contraction requires energy) while passive vasodilation is related to increased pressure in lumen of a vessel.

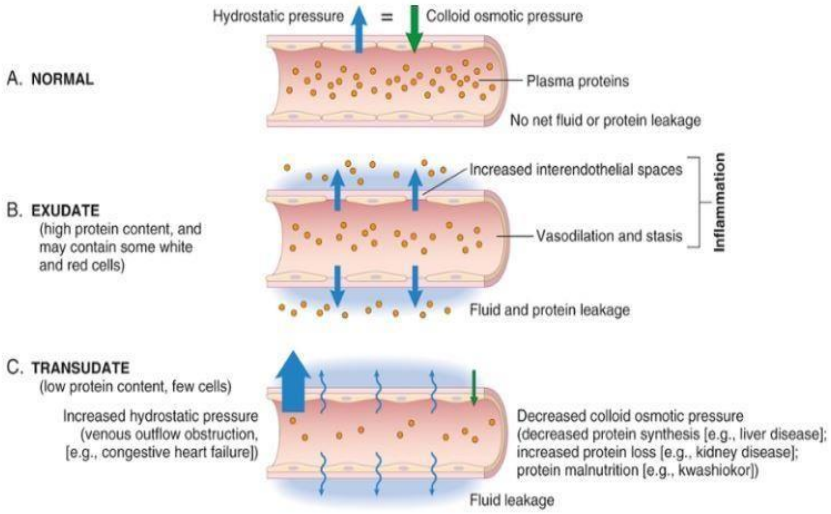



FIG. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue* …

## What was mentioned in the lecture:

Regarding the vascular phase or the initial vascular phase of inflammation: when the blood vessels in the normal equilibrium state, there are intracellular fluids and intracellular proteins while there is also extracellular fluids and proteins and there is a balance between them where hydrostatic pressure which is responsible mainly for pushing fluids from inside the blood vessel to outside and the colloid osmotic pressure which depends on the plasma proteins concentration sucks the fluid from the interstitium to the intravascular component, but during the phases of inflammation, there can be two different processes which you have to really understand: what we call an exudate and what we call s transudate, both of them are initial processes which occur in the initial phases of inflammation, the exudate is a process where high protein content and sometimes inflammatory cells sneaks outside the blood vessel, ,so the exudate - whether it's in the interstitial fluid or in other body fluids- it always causes high protein content and high cellular content, on the other hand the transudate is completely opposite, the protein content is low and the cellularity is low, this is why when you receive in the lab a sample of pleural fluid or peritoneal fluid for examination, we look at it, if it's clear and yellow then this is most likely a transudate, if it's thick and creamy and maybe bloody it is probably an exudate, exudates contain high protein content and cells, while transudates have low protein content and few cells, differentiating between those two is important, because the pathogenesis and the reasons and etiology of each one is different, the exudate is more serious and indicates severe acute inflammation, cancer and other severe conditions, transudates basically indicate a problem in the colloid pressure (hypoproteinemia) due to liver disease or kidney disease or malnutrition, this is what happens during those processes and this is the difference between normal, exudates and transudates.

| Transudate | Exudate |
|---|---|
| Low protein | High protein |
| Low cell content | Many cells & debris |
| Low specific gravity | Higher specific gravity |
| Caused by osmotic/hydrostatic pressure imbalance | Caused by increased vascular permeability and denotes inflammatory reaction |

### What was mentioned in the lecture:

this table gives you a comparison between transudates and exudates, transudates has a low protein while exudates have high protein level, sometimes we can measure them in the lab, transudate have a low cell content, however in the exudates there are many cells and cell debris, the specific gravity (remember form the medical physics course: specific gravity is the density compared to water) is low in the transudates and it's higher in exudates, if we ask ourselves: what are the causes of transudates, as we said, it's mainly due (the pathogenesis) to osmotic-hydrostatic pressure imbalance including oncotic pressure disorders, an exudate is mainly caused by increased vascular permeability and denotes a marked or a severe inflammatory reaction due to serious causes.

# EDEMA & PUS:

### What was mentioned in the slide:

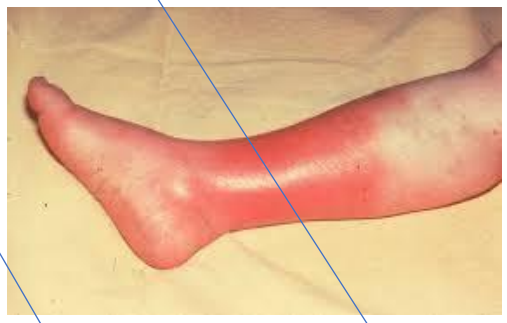
- **Edema: excess fluids in interstitium or serous cavities (either transudate or exudate)**
- **Pus: purulent exudate; inflammatory exudate rich in WBCs, debris, and microbes**

### What was mentioned in the lecture:

let's move a little bit to some definitions that you'll gonna hear about all your life as a physician, edema and pus: edema is basically excess fluids in the interstitium or serous cavities, like what is seen in patients with heart failure or liver failure who have severe lower limb edema where a lot of transudated fluids are moved from the intravascular compartment to the interstitium causing severe swelling in the leg, you're going to see a lot of patients with unilateral or bilateral pleural effusion or patients with ascites (ascites is accumulation of fluids in the peritoneal cavity), edema can be either due to transudates or exudates, this is why sometimes they remove some of these and send it to us to the lab to examine the protein content and the cellularity content and also to look for malignancy in in these fluids especially if we are dealing with a an older patient with bilateral pleural fusion or an older woman with severe ascites, so edema is just fluid and most of the time it is due to osmotic-hydrostatic pressure imbalance, on the other hand the word pus indicates an exudative process which is purulent, purulent means increased numbers of inflammatory cells which is rich in white blood cells, microbes, debris, and protein. so pus by definition is an exudate and it is an exudate with purulent material which means numerous white blood cells debris and microbes.  simply pus is the content of an abscess, if you had injury and inflammation in your fingertip and it becomes really yellow and it collects purely debris, sometimes you squeeze it or your mom will just rupture it to release it, which is the treatment for a small abscess like this and the content is pus, it is a purulent exudate.

Submucosal tissue

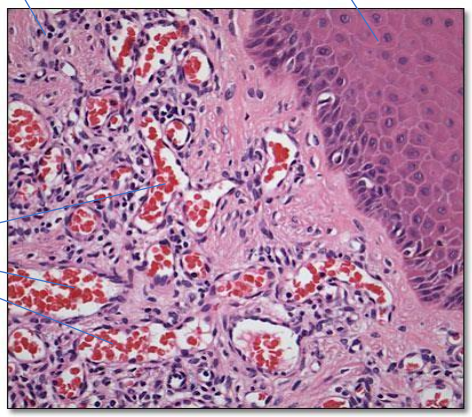
Keratinized stratified squamous epithelium



# Vascular changes (early events)

## What was mentioned in the slide:

- **Vasodilatation: histamine; increased blood flow causing redness (erythema) and heat**
- **Followed by increased permeability (exudate)**
- **Stasis; congestion and erythema**
- **PMNs accumulate and adhere to endothelium then migrate outside the vessel into the interstitium**



Blood vessels

## What was mentioned in the lecture:

let's go back to the vascular changes in the early events of acute inflammation, as you see in this picture this is not a normal leg, this is severe redness or erythema and this is mainly due a disease called cellulitis where the infection is involving the skin and subcutaneous tissue, and if you take a section from this and you look at the microscope, this is the squamous epithelium and this is the submucosal epithelium with numerous engorged and congested blood vessels with a lot of red blood cells which will give the redness when you examine the patient by your eye, the initial phase of inflammation or vasodilation is mediated by multiple chemical mediators of inflammation, the major mediator which is responsible for the vasodilation effect is the histamine, the major effect of histamine is increasing blood flow causing the submucosal dilatation and the redness you see by your eye, so initially there is a immediate vasodilation due to the release of histamine, sometimes in certain books they will tell you that there is actually a phase before that which is called a reflex transient vasoconstriction from the initial stimulus whether it's trauma or bacteria or heat or whatever, but for practical purposes the first vascular phase of inflammation is actually vasodilation due to histamine release, the initial phase is a little bit passive and we will explain what does that mean, and this will be followed by a more active process which will lead to leakage of more material from inside the blood vessel to the interstitium due to increased vascular permeability, both processes: the initial vasodilatation followed by more active process of increased vascular permeability will cause stasis which means that blood will stay over there, it does not move and this is what we call in pathology congestion and this will lead to the cutaneous changes termed erythema, the neutrophils or the polymorph nuclear cells (PMNs) accumulate and adhere to the endothelium of the vessels then try to migrate outside into the interstitium in the initial phases of acute inflammation in a process which we call diapedesis, so the diapedesis is the movement of the neutrophils and other white blood cells from intravascular compartment to the extravascular compartment in the initial phases of inflammation.

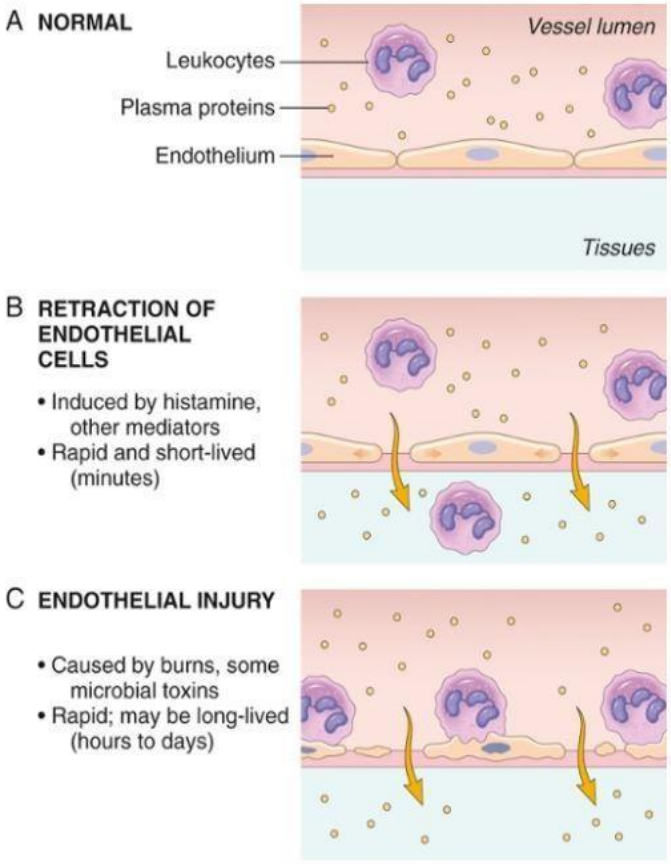
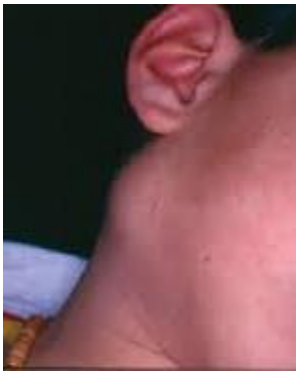



FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and …

## What was mentioned in the lecture:

Normally, the vascular wall is composed from a basement membrane lined by endothelial cells, in the normal state, the tips of endothelial cells touch each other, (endothelial cells are joined to each other), notice the lumen of the blood vessel, neutrophils and plasma proteins inside, this is in the normal equilibrium state where everything is moving smoothly, there is no movement or issues in the blood vessel diameter or the movement of cells or proteins from inside to outside, however, in the initial phases of inflammation, the initial change which happens due to a histamine -and also other chemical mediators of inflammation but the major one is histamine- is there is the retraction of the endothelial cells so there will be more gaps in between those endothelial cells, and this is basically the immediate rapid and short-lived process where cells and proteins and fluids can move from in the intravascular compartment to the extra extravascular compartment, this will be followed by a more active energy requiring step where there will be really damage to the endothelial cells and there will be more gaps between the endothelial cells and sometimes gaps in the basement membrane where more cells and proteins move out, this process is short-lived for example in burns or microbial toxin induced changes, but sometimes it is a little bit longer, so those are the initial phases of vascular changes in the initial phases of inflammation.

# Lymphatic vessels and lymph nodes:

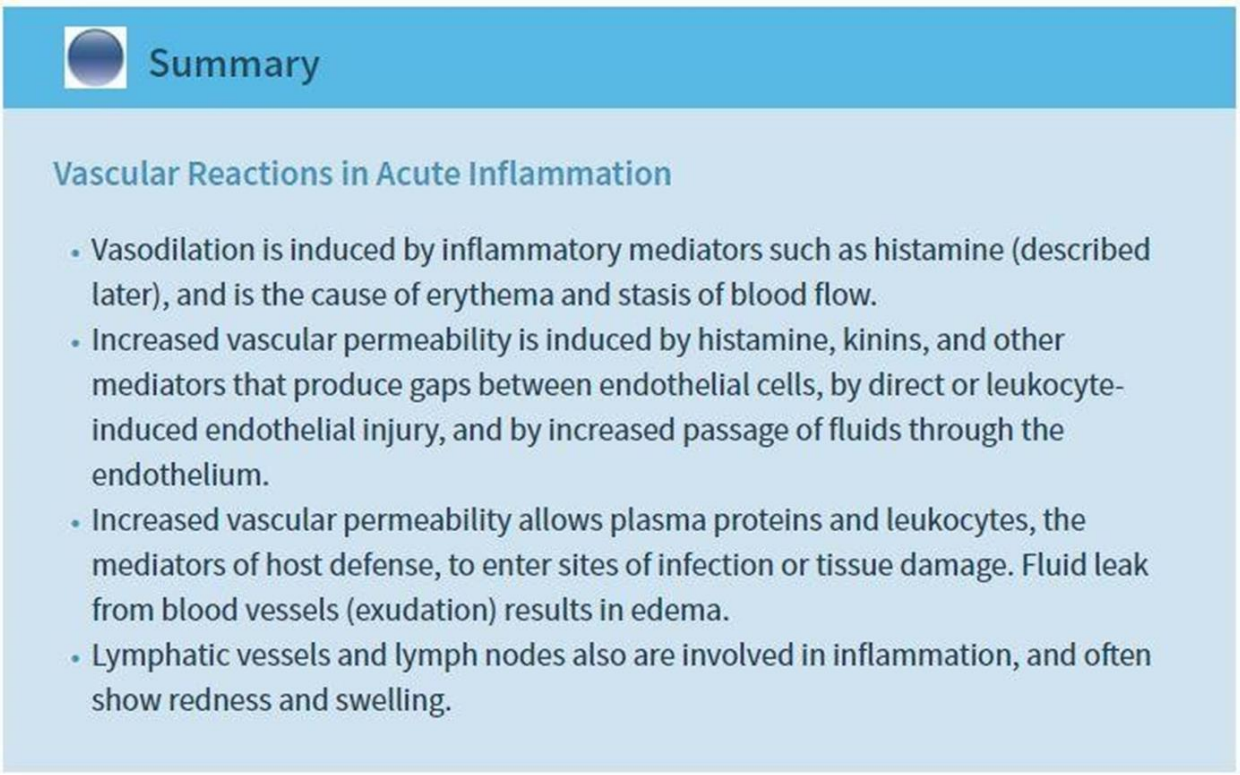


## What was mentioned in the slide:

- **Lymphangitis: inflammation and proliferation of lymphatic vessels to drain fluids and other elements**
- **Drainage to nearby lymph nodes; hence causing lymphadenitis (reactive lymphadenitis or inflammatory lymphadenitis)**

## What was mentioned in the lecture:

now what are the roles of lymphatic vessels and lymph nodes? there are many groups of lymph nodes like cervical lymph nodes, axillary lymph nodes, inguinal lymph nodes, paraaortic lymph nodes, etc. those are lymphatic tissues, they drain many of the active processes in your body, they drain a lot of metabolic changes in addition to draining and infiltration of cancer cells (therefore, lymph nodes are important in diagnosing so many abnormalities), this is why whenever we see somebody with an enlarged lymph nodes which we call lymphadenopathy (e.g. cervical lymphadenopathy, inguinal lymphadenopathy, auxiliary lymphadenopathy, etc.) especially if it's not responding to initial treatment such as antibiotics, this is serious and those patients come back to the hospital for further investigation where we try to figure out the major cause of lymph node enlargement, whether it's infectious or we are dealing with stage three cancer from somewhere draining into those lymph nodes, sometimes there will be an inflammation of those lymphatic vessels which drain to the lymph nodes, we call it lymphangitis and this will lead to lymphatic vessel proliferation and drainage of fluids into these lymph nodes causing an enlargement, so the presence of enlarged lymph nodes not responding to initial antibiotics or whatever treatment we give, we call it persistent lymphadenopathy, that always requires further investigation to make sure are we dealing with what we call reactive inflammatory lymphadenitis or a more serious process, you are going to see many patients with lymph nodes enlargements in the surgical floor and in the medical floor so those always come to you for further investigation.




# Leukocytes role:

## What was mentioned in the slide:

- **PMNs & Macrophages**
- **Recruitment and migration to tissue**
- **Eliminate the enemy (phagocytosis)**
- **Migration of leukocytes from BV to tissue is multistep process: adhesions; transmigration then movement toward the enemy area**

## What was mentioned in the lecture:

now what is the leukocytes role in inflammation -especially in an acute inflammatory process-? almost all the leukocytes play a role in inflammation, the main components of acute inflammatory response are the macrophages and neutrophils, they're responsible for the eliminating the microbes and the enemies by the process of phagocytosis, they also secrete mediators which will recruit more inflammatory cells at the site of injury and remember that the migration of leukocytes from the intravascular compartment to the outside is not a simple process, it's a multi-step process which require movement of those of those inflammatory cells toward the wall of blood vessel and then adhesion then transmigration then movement toward the site of injury, we will talk about these processes also in detail in future slides.

TABLE 3.3 Properties of Neutrophils and Macrophages

| | Neutrophils | Macrophages |
|---|---|---|
| Origin | HSCs in bone marrow | • HSCs in bone marrow (in inflammatory reactions)<br>• 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<br>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 extracellular traps.
This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

## What was mentioned in the lecture:

this table is extremely important and it gives you an overview of the differences between neutrophils and macrophages, their origin from where, the life span of each, remember that the lifespan of neutrophils is very short and this is why you see them more in the acute inflammatory process and if you see them in tissues under microscopic examination, this indicates an acute process rather than a chronic process, response to activating stimuli is more rapid in the neutrophils but more prolonged in macrophages and they differ in the production of reactive oxygen species, nitric oxide and degranulation.

# ADHESION (WBCs to endothelium)

## What was mentioned in the slide:

- **Steps:**
  - **1.Margination**
  - **2.Rolling**
  - **3.Adhering**
- **Selectins (initial weak adherence) and integrins (firm strong adherence)**

## What was mentioned in the lecture:

now let's talk a little bit about the adhesion of white blood cells to the endothelium, as we mentioned before, after the initial vascular phase of inflammation with retraction and damage to the endothelial cells where proteins and cells can migrate from the intravascular compartment to the extravascular compartment, the cells or white blood cells mainly when they move from inside to outside, there are multiple steps and this is an active process, we have to have something called margination followed by rolling followed by adhesion or adhering of those cells to the vascular wall and this process is also requires some receptors like selectins which carry initial weak adherence and then followed by stronger adhesions carried by receptors called integrins and then letting the cells going out from the intravascular compartment to the extravascular compartment.

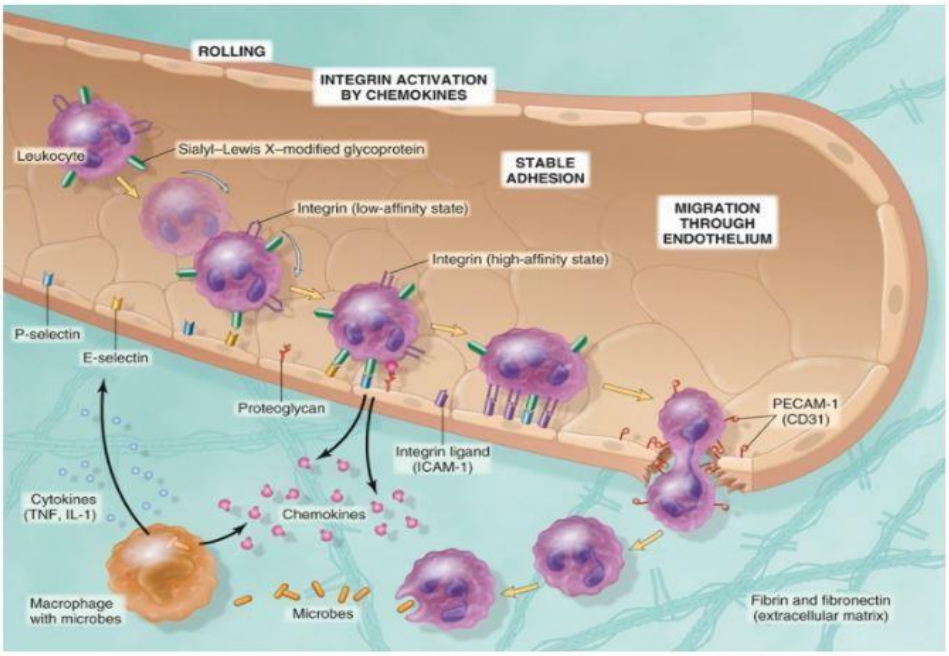



FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

## What was mentioned in the lecture:

This cartoon explains the steps by which a neutrophil or a macrophage moves from inside the lumen into the extravascular compartment, so that they can perform their functions, so the first step is margination in which the neutrophils move from the center of the lumen toward the wall of the blood vessel, so this process (the movement of those white blood cells -mainly neutrophils and macrophages- from the center of the lumen toward the wall) is called margination, what happens after that margination is that this white blood cell or neutrophil will start rolling on the wall, initially they will roll quickly because of the initial E-selectin binding process where the adhesion is weak followed by the stronger attachment by the other proteins which are called integrins (the ligand of integrins are called ICAM1) where the attachment is very strong to prepare the neutrophil to move from inside here to outside the blood vessel, so firstly margination (movement of the neutrophil from the center of the lumen towards the wall), then rolling of the cells into the wall, the attachment with the E-selectins will start and the rolling process will slow down followed by a stronger attachment with integrins, the second group of proteins which will really slow down the rolling process, and then the cell will move out from inside the blood vessel into the outside by a more active process utilizing the CD31 protein or PECAM-1, CD31 will damage the endothelial cells and the basement membrane so that there will be a big hole in the wall allowing the migrating cell to squeeze itself outside, some people say that this step is exactly what diapedesis means, not the whole process, in some books they will say the movement of neutrophils from here to here is called diapedesis, while in text other books they say this specific step is called diapedesis, so this those are the steps which you have to understand, and it's an active process where neutrophils and white blood cells move from inside the blood vessel to outside: margination followed by rolling followed by initial weak attachment with e-selectins followed by stronger attachment with integrins then transmigration, this process is called transmigration or diapedesis, movement of the cell itself to the inside through an active destruction of the endothelial cell and the basement membrane through the action of CD31, then they will go into the interstitium and they will start releasing chemical mediators of inflammation and continue their phagocytosis and intracellular killing which are steps which come later which we will explain more in details.

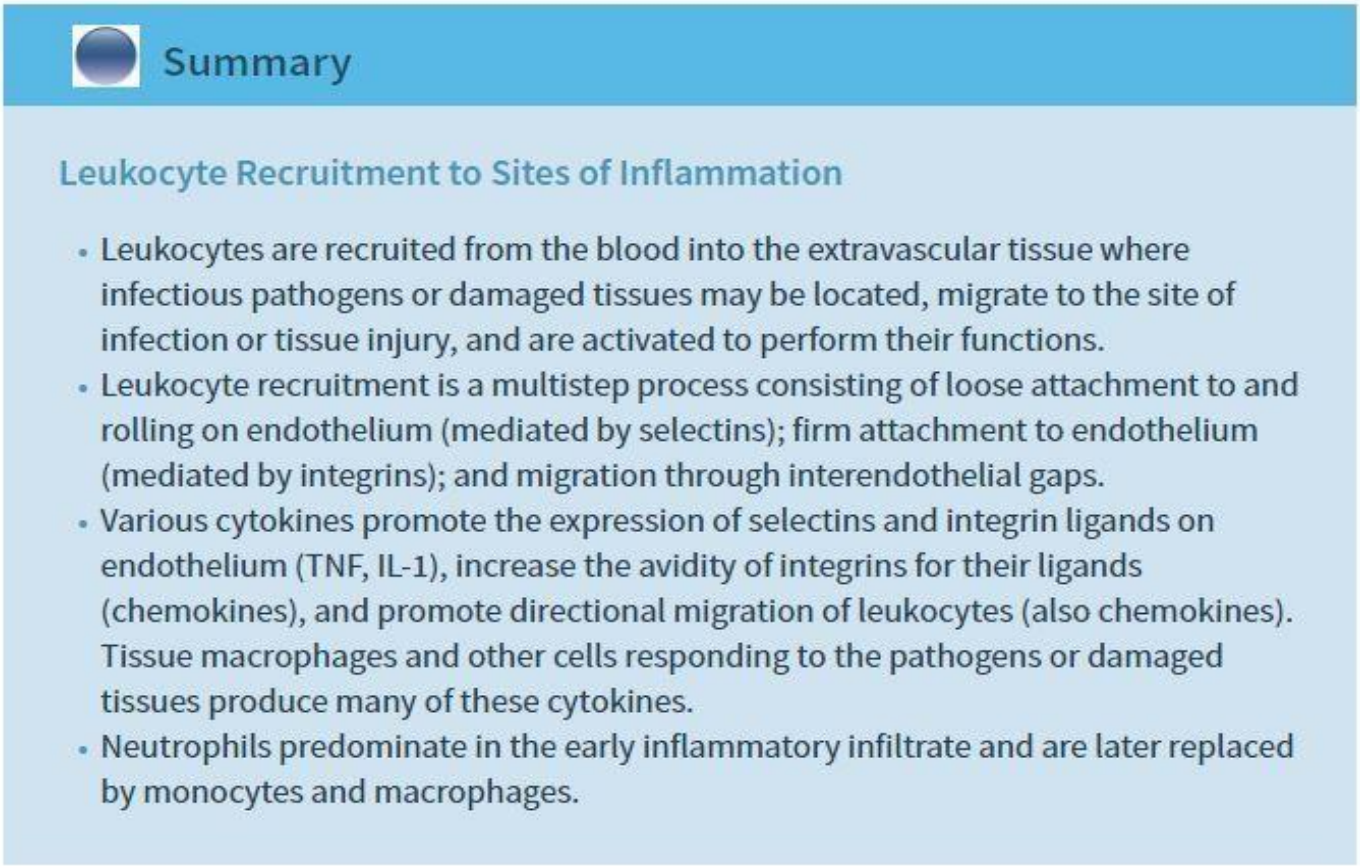
**TABLE 3.4** Endothelial and Leukocyte Adhesion Molecules

| Family | Molecule | Distribution | Ligand |
|---|---|---|---|
| Selectin | L-selectin (CD62L) | Neutrophils, monocytes T cells (naïve and central memory) B cells (naïve) | Sialyl-Lewis X/PNAd on GlyCAM-1, CD34, MAdCAM-1, others; expressed on endothelium (HEV) |
| | E-selectin (CD62E) | Endothelium activated by cytokines (TNF, IL-1) | Sialyl-Lewis X (e.g., CLA) on glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory) |
| | P-selectin (CD62P) | Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin; platelets | Sialyl-Lewis X on PSGL-1 and other glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory) |
| Integrin | LFA-1 (CD11aCD18) | Neutrophils, monocytes, T cells (naïve, effector, memory) | ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium) |
| | MAC-1 (CD11bCD18) | Monocytes, DCs | ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium) |
| | VLA-4 (CD49aCD29) | Monocytes T cells (naïve, effector, memory) | VCAM-1 (CD106); expressed on endothelium (upregulated on activated endothelium) |
| | α4β7 (CD49DCD29) | Monocytes T cells (gut homing naïve effector, memory) | VCAM-1 (CD106), MAdCAM-1; expressed on endothelium in gut and gut-associated lymphoid tissues |
| Ig | CD31 | Endothelial cells, leukocytes | CD31 (homotypic interaction) |

*CLA*, Cutaneous lymphocyte antigen-1; *GlyCAM-1*, glycan-bearing cell adhesion molecule-1; *HEV*, high endothelial venule; *ICAM*, intercellular adhesion molecule; *Ig*, immunoglobulin; *IL-1*, interleukin-1; *MAdCAM-1*, mucosal adhesion cell adhesion molecule-1; *PSGL-1*, P-selectin glycoprotein ligand-1; *TNF*, tumor necrosis factor; *VCAM*, vascular cell adhesion molecule.

## What was mentioned in the lecture:

this table explains the different types of selectins and the different types of integrins and the immunoglobulin CD31 which is responsible for endothelial cell injury, just remember that the selectins are group of proteins which are present in the endothelial cells and they are responsible for the initial weak attachment with these white blood cells preparing them for the next group of proteins 'integrins' where stronger attachments are present and they will hold the neutrophil or the white blood cell close to the endothelial cells preparing them for PECAM1 or CD31 where destruction of the basement membrane will happen and the cell will squeeze itself and sneak into the outside of the blood vessel, you don't have to memorize those, just remember the concept of selectins = the initial weak attachment followed by the stronger integrins attachment and then the CD31 function through helping the neutrophil to move to outside blood vessels.



# TRANSMIGRATION:

## What was mentioned in the slide:

- **CD 31 (PECAM-1), platelet endothelial cell adhesion molecule expressed both on leukocytes and endothelial cells**
- **WBC pierce through wall by collagenases**

## What was mentioned in the lecture:

this slide just explains a little bit more about CD31 (the other name is PECAM1: platelet endothelial cell adhesion molecule) which is expressed on both leukocytes and endothelial cells, so the white blood cell through the transmigration process will pierce through the wall by destroying the basement membrane and this process is actually by an enzyme called collagenase because the major component of the basement membrane is collagen type IV and laminin, so this enzyme will increase by amount through the function of CD31 making a hole in the basement membrane and helping the white blood cells to move and squeeze itself through the wall of the blood vessel into the outside interstitium.
So far we've finished the initial vascular phase, starting from the vascular dilatation due to histamine then the more active process of increasing vascular permeability then the movement of the inflammatory cells -mainly neutrophils and macrophages- from the intravascular compartment to the extravascular compartment, and we detailed this process, from margination, rolling, initial selectin weak attachment, the stronger integrin attachment to the wall of the endothelial cells then the active process of transmigration or diabetes due to the CD31 action utilizing the collagenase for destroying the basement membrane and movement of the cells to outside.

# CHEMOTAXIS:

## What was mentioned in the slide:

- **WBCs moving to injury tissue site**
- **Due to CHEMOATTRACTANTS (exogenous and endogenous):**

| Bacterial products | Peptides (N-…) |
|---|---|
| Cytokines | Chemokine family |
| Complement system | C5a |
| Lipoxygenase pathway AA | LTB4 |

## What was mentioned in the lecture:

we're going to talk about chemotaxis, this is going to be a term you will be hearing all your life when you're dealing with patients with inflammations like pneumonia, dermatitis, etc. remember that 'tis' is the suffix we end the organ with to indicate inflammation e.g. tonsil → tonsillitis, appendix→ appendicitis, etc. chemotaxis basically is the movement of white blood cells to the site of injury, if the site of injury is your tonsils, there's chemotaxis to the tonsils by the white blood cells, if the injury in your skin the movement of the white blood cells will be to your skin, so this process is also an active process and it is induced by a certain group of mediators which are called collectively chemoattractants, so those chemoattractants are the mediators which induce and help move the cells or chemotaxes the white blood cells to the site of injury , chemoattractants can be exogenous (from outside the body) they can be endogenous (produced inside your body), and there are many of those, some of them are certain bacterial products, especially the N-terminus group of bacterial peptides, the bacterial products are actually strong chemoattractants, they will induce and help move the white blood cells from the intravascular compartment into the site of injury, the other big group is called cytokines, this is a big group of mediators released by inflammatory cells (mainly lymphocytes and macrophages), the chemokine subgroup of the cytokines are the strong chemoattractant group, then there are specific plasma proteins which are the complement system proteins, a certain part of the complement system which is the C5a is the strongest chemoattractant among those complement system proteins, we will talk about the whole group of complement system proteins and their function as chemical mediators of inflammation, then we have additional groups from the arachidonic acid metabolites which is a cell membrane component in the lipo-oxygenase pathway, the leukotriene B4 is the strongest chemoattractant among the arachidonic acid metabolites, so those are the four major chemo attractants which will induce and help move the white blood cells from the intravascular compartment into the site of injury, the process is called chemotaxis, those mediators are called chemoattractants, and they include the peptides of the bacterial products, chemokines family of cytokines, C5a from the complement system and leukotriene B4 from the arachidonic acid metabolite or lipoxygenase pathway products.

# WBCs infiltrate in tissue:

## What was mentioned in the slide:

- **Depends on the age of inflammatory response and the type of stimulus**

| | |
|---|---|
| **Neutrophils (PMNs)** | **6-24 hours, acute phase** |
| **Macrophages and lymphocytes** | **24-48 hours and then may stay** |
| **Allergic reactions** | **Eosinophils** |

## What was mentioned in the lecture:

now after these inflammatory cells move into the tissues, sometimes as pathologists we receive things like skin sections, appendix removed, tonsils removed, etc. and we examine them by sectioning them and then we stain them and we look at the tissue infiltrate and decide what type of inflammation is there, if we see neutrophils this indicates acute inflammation and those are short-lived, they don't stay more than six to 24 hours (the maximum is 24 hours) in tissue, so if we received a tissue with neutrophils, this means recent acute inflammation, for example, when we receive appendix from the surgeons, we examine them and we look for the presence for neutrophils to confirm to the surgeon that this was a case of acute appendicitis and this gives him his justification for the surgical removal of the appendix, now the macrophages and lymphocytes are later on, they come after the first day (24 to 48 hours) and sometimes they may stay for a couple of days or a couple of weeks, so basically the neutrophils are the hallmark of acute inflammatory cells in tissues, macrophages, lymphocytes and plasma cells are the chronic inflammatory cells and they infiltrate the tissue in a later stage, in some specific conditions we see a lot of eosinophils, those are actually considered allergic reaction mediators, so whenever we have a nasal polyp from allergy for example, we see a lot of eosinophils there, in the last 10 to 15 years, there was specific type of inflammation in different types of tissue, it is called eosinophilic inflammation, e.g. eosinophilic gastritis, eosinophilic esophagitis, etc. and recently we are getting more inclined to have this specific type of inflammation.

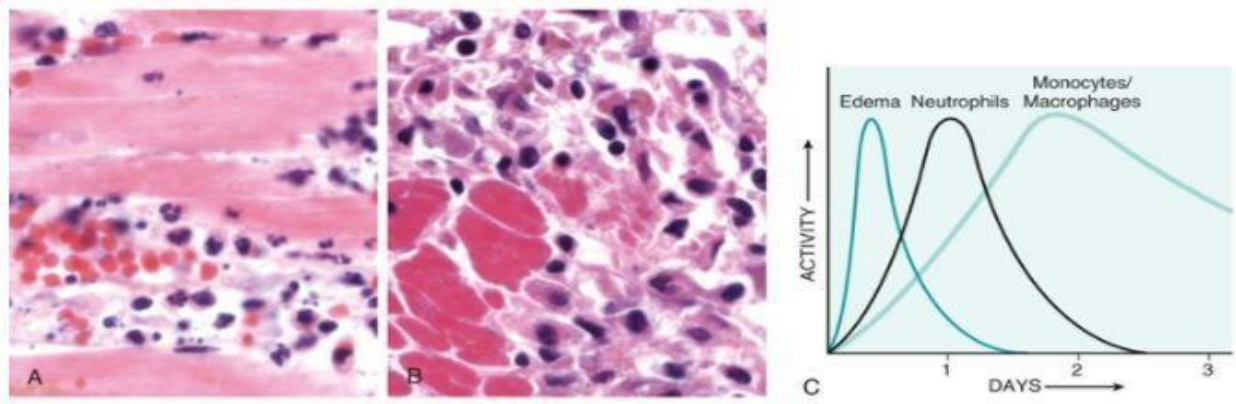



FIG. 3.5 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrograp…

## What was mentioned in the lecture:

This (figure A) is a micrograph of a section of skeletal muscle where there's a lot of neutrophils (notice these mickey mouse or polymorph nuclear cells), those are neutrophils so this is an acute inflammatory process, which indicates that those changes have been there just in the last 6 to 24 hours, followed by macrophages and lymphocytes which is more in the chronic phase (see figure B), the curve explains to you the sequence of phases in inflammation, first is the vascular phase where edema ensues followed by neutrophilic infiltration, so edema goes down in probably in one and a half day and the recruitment and the stimulation of the chemotaxis of neutrophils into the tissue of injury probably starts early and then phases down probably in the second day, then the chronic inflammatory cells starts to appear ( like macrophages, monocytes and plasma cells) and they take longer time to clear up so if you get the tissue here you see (after two days) macrophages and monocytes, if you get the tissue here neutrophils (after 6-24 hours) if you get the tissue very early which is really unusual for pathology, you just see an edema and congestion of the blood vessels, so those are the tissue images and this is the diagram which explains this process and sequence.

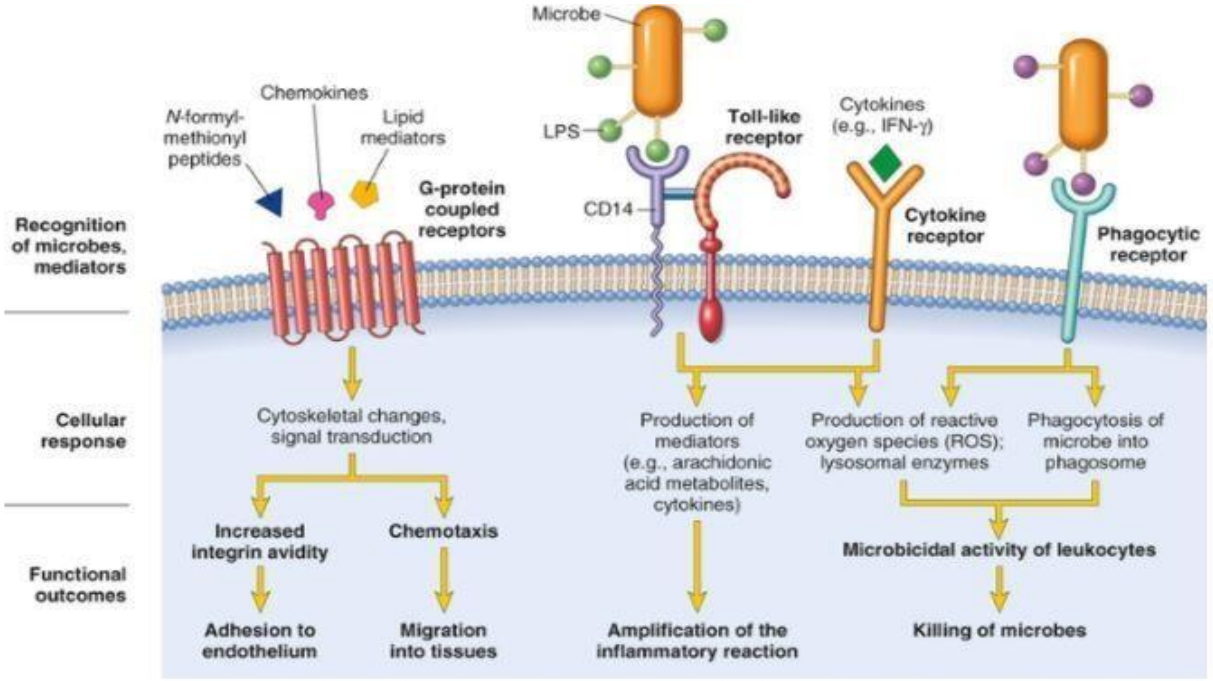



FIG. 3.6 Leukocyte activation. Various types of leukocyte cell surface receptors recogni…

## What was mentioned in the lecture:

the initial vascular phase is induced by recognition of a microbe or an injury by toll-like receptors, this will induce a lot of reactive changes and mediators including chemotaxis by chemokines which will enhance the movement of the cells into the site of injury, followed by killing the microorganism, at the initial phase of inflammation, there will be release of too many chemical mediators from multiple sources to amplify the inflammatory reaction so that the killing the of the microorganisms will be more efficient and induced by multiple active cellular processes like chemotaxis and adhesions of those cells.

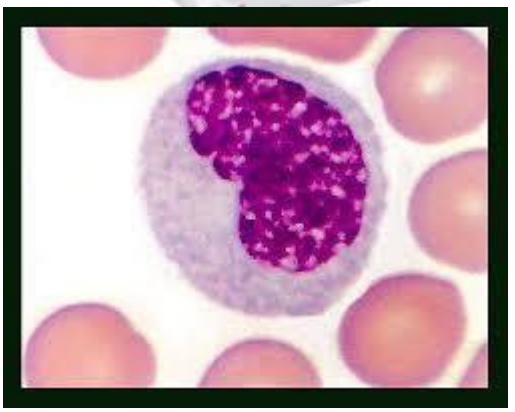
# LEUKOCYTE ACTIVATION:

## What was mentioned in the slide:

- **Phagocytosis and intracellular killing**
- **Neutrophils and monocytes**

## What was mentioned in the lecture:

the leukocyte activation is also an important function in the initial phase of inflammation, the two major cell types of the initial phase of inflammation are the neutrophils and the second one is the macrophage or the monocyte, the macrophage is the same like monocyte but we use the term monocyte to indicate the presence of circulating macrophages, so the circulating macrophages are called monocytes and when they reside in the tissue we call them tissue macrophages, those are the shapes of the white blood cells, neutrophils have multilobed nuclei and there is a lot of granules, while monocytes have a kidney-shaped nucleus, phagocytosis and intracellular killing is the main the function of those two cell types, the neutrophils and monocytes, so after recognizing the injury or recognizing the enemy, when the cell has phagocytosed the microorganism inside, the intracellular killing starts.



# PHAGOCYTOSIS:

## What was mentioned in the slide:

- **1. Recognition and attachment of the enemy: mannose receptors; opsonins (IgG, C3b)**
- **2. Engulfment forming phagocytic vacuole: phagosome**
- **3. Killing & degradation: reactive oxygen species (ROS); NO. H2O2-MPO-halide is the most potent bactericidal system of neutrophils**

## What was mentioned in the lecture:

the process of phagocytosis is a multi-step process, it's not just a quick action, it include multiple steps, the first step is recognizing the invading or foreign agent by specific receptors on the neutrophils or the macrophage, those include mannose receptors and opsonins, opsonins are surface receptors and they include immunoglobulins and C3b, so the initial phase of phagocytosis is recognizing that there is a foreign material like bacteria or virus outside, after the initial recognition of the foreign material, there is engulfment of this foreign material, it will be sacked in a certain vacuole inside the cytoplasm which is called a phagosome, after we form the phagosome which is basically a vacuole inside the cytoplasm of the inflammatory cell whether it's a neutrophil or a macrophage and there is a bacterium inside this phagosome, the killing and the degradation then starts by an active process through recruitment of reactive oxygen species, those are multiple chemicals including nitric oxide, $H_2O_2$, myeloperoxidase halide which is probably the strongest or the most important bactericidal system of the neutrophils, so those are the three major steps of phagocytosis and intracellular killing.

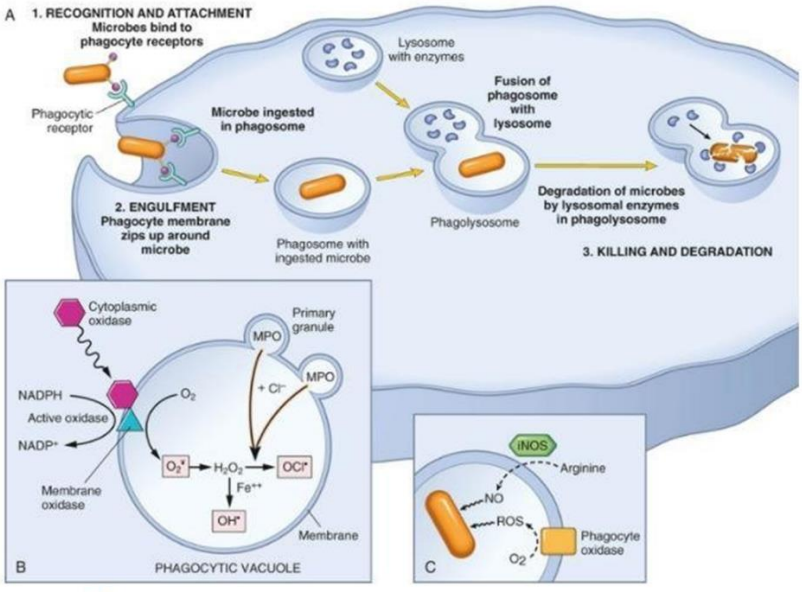



FIG. 3.7 Phagocytosis and intracellular destruction of microbes. (A) Phagocytosis of a p…

## What was mentioned in the lecture:

this is the cartoon which will summarize the process of phagocytosis, this is a bacterium, it will be recognized and caught by certain receptors like mannose receptors, then there will be an opening in the cytoplasmic membrane of the neutrophil or macrophage through those receptors and then there this will closing up forming a vacuole including the bacteria or the virus or the foreign body inside, this is called phagosome, so recognition, then attachment, then formation of the phagosome, then the lysozymes which are the granules inside the macrophages and the neutrophils will be recruited to fuse with the phagosome forming a phagolysosome, they fuse together, so that the chemicals (the reactive oxygen species like nitric oxide and myeloperoxidase) will come and attack, digest and kill the organism inside, the details of this process is more complicated, it involves utilizing multiple granules, like primary granules which include myeloperoxidase and additional cytoplasmic oxidases using oxygen radicals to help in the intracellular killing of those organisms, so this is a cartoon which explains the steps of the phagocytosis and intracellular killing, remember that those steps are also sequential, this step does not come before this, recognition, attachment, phagocytosis, formation of the phagosome, fusion of the lysozyme with the phagosome, then intracellular killing using reactive oxygen radicals.

# NITRIC OXIDE (NO)

## What was mentioned in the slide:

- **Soluble gas produced from Arginine by NO synthase (NOS)**
- **NOS 3 types: eNOS, nNOS, iNOS**
- **iNOS: intracellular killing stimulated by cytokines mainly IFN-ﻯ**
- **NO reacts with superoxide (O2-*) to form ONOO* radical peroxynitrite**

## What was mentioned in the lecture:

let's talk a little bit about the nitric oxide, in the last 10-15 years, this molecule attracted a lot of attention and research and there was a lot of good knowledge originated from the discovery of the nitric oxide in the body, nitric oxide is basically a soluble gas produced from arginine which is an amino acid by an enzyme called nitric oxide synthase (NOS), there are three types of nitric oxide synthase eNOS, iNOS and nNOS, the intracellular nitric oxide synthase (iNOS) is the one which is responsible for the intracellular killing which is stimulated by the cytokine family specifically the interferon γ , interferon γ is one of the cytokines, there's a lot of research on the interferons, now they are being utilized also as a target therapy for certain inflammatory autoimmune diseases and certain cancer treatment, the nitric oxide usually reacts with superoxide which is the $O_2^{-\cdot}$ to form what we call the radical peroxynitrate $ONOO^{\cdot}$ which is one of the strong reactive oxygen radicals, NO is involved in carcinogenesis, atherosclerosis and inflammation.

# GRANULE ENZYMES

## What was mentioned in the slide:

- **Present in PMNs and monocytes**
- **In PMNs: 2 types; large azurophil (primary) and smaller (secondary) granules.**

- **Primary G: MPO, other enzymes**
- **Secondary G: lysozyme, and others**
- **These are usually neutralized by anti- proteases (such as ǎ-1 antitrypsin: inhibits elastase) …deficiency…diseases**

## What was mentioned in the lecture:

Regarding the granules of neutrophils and macrophages, remember that the macrophages and neutrophils both have granules, however, the neutrophil is the one which is more heavily granulated, in neutrophils, there are two types of granules, the large big ones which we call the azurophil granules or the primary granules, the word azurophil was given because of the color of the dye reaction, but they are called primary granules because they are big, the smaller ones are the secondary granules, the primary granules are also are called primary G granules, they contain myeloperoxidase and some other enzymes which are needed in the intracellular killing, the secondary granules they have lysozymes and others and they are the ones which are utilized after the production of the phagolysosome in the later stages of phagocytosis, those can be injurious if they are not controlled so we always have checks and balances over them, they are usually neutralized by antiproteases such as α1- antitrypsin which inhibits the elastases, now remember that you have diseases that include α1-antitrypsin deficiency, there are bad consequences because there will be no inhibition of those lysozymes and enzymes released by the neutrophils and the macrophages and this will induce injury and chronic diseases.

# NEUTROPHIL EXTRACELLULAR TRAPS (NETs)

## What was mentioned in the slide:

- **Viscous meshwork of nuclear chromatin binds peptides and anti-microbial agents after PMN death (NETosis)**
- **Sepsis**
- **Maybe involved in SLE**

## What was mentioned in the lecture:

there's something called the neutrophil extracellular traps or NETs, those are basically a very thick viscous meshwork material which is composed of nuclear chromatin bound to peptides and anti-microbial agents, they are formed after the neutrophil dies, so even if the neutrophil died and ruptured, the chromatin material and intracytoplasmic material will go outside and they will cause a very thick viscous mesh work which will help trap those bacteria or invaders at the site of injury, so that they will be killed by other still-viable neutrophils, this is an additional function of neutrophil, even after it dies, the products of the chromatin material in particular will cause a viscous meshwork of nucleic acids and proteins helping to trap the organisms at the site of injury so that they can be localized and killed by other neutrophils which are still alive, recently, they discovered that neutrophil extracellular traps or NETs play a major role in the pathogenesis of sepsis, we are still waiting for more details on that, and also they found that they have a role in a disease which is an autoimmune disease called systemic lupus erythematosus, مرض الذئبة الاحمرارية it's an autoimmune that affects young females, the most common symptom of which is rash in their cheeks, but this is a multi-system autoimmune disease that affects the kidneys, the heart, the skin, the joints, etc. so probably in the next five to ten years we will have more clear idea about this process, NETosis or neutrophil extracellular traps, it is involved a process in the pathogenesis of sepsis and some autoimmune diseases.

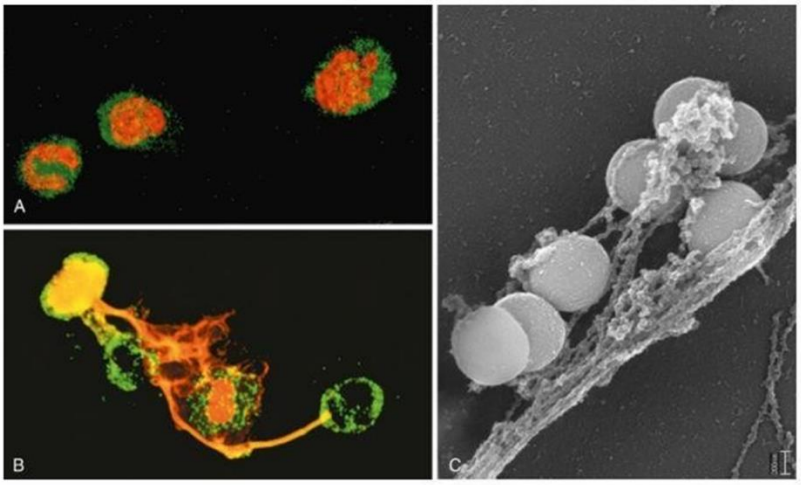



FIG. 3.8 Neutrophil extracellular traps (NETs). (A) Healthy neutrophils with nuclei stain…

## What was mentioned in the lecture:

This (figure C) is a high scanning picture explaining this thick viscous material, those are actually the bacterial cocci (the circles) and this is the net of the neutrophil (the threads) so they stick to those organisms so that they will stay in this area and will allow other inflammatory cells to come and killing them and this is another colored picture of the same process. (figure A and B)

# LEUKOCYTE-MEDIATED TISSUE INJURY

## What was mentioned in the slide:

- **A. Prolonged inflammation (TB and Hepatitis)**
- **B. Inappropriate inflammatory response (auto-immune diseases)**
- **C. Exaggerated response (asthma and allergic reactions)**

## What was mentioned in the lecture:

now although we have just mentioned that you need the white blood cells like neutrophils and macrophages for your defense mechanisms to help you get rid of pathogenic organisms, however, sometimes, there are an injury related to the infiltration of leukocytes in tissues, although we need them to protect us from invaders, if there is too much response there will be some injury, each inflammatory process can leave some side effects or tissue injury, but if there is a prolonged inflammation, specifically in the case when there is a very virulent and strong organism like mycobacterium tuberculosis which is a very virulent and strong bacteria that can induce prolonged inflammation causing tissue damage and tissue injury, the other example is certain types of hepatitis like hepatitis C which will cause chronic liver disease from this prolonged inflammation, so the first mechanism of how leukocytes can induce tissue injury is by the presence of prolonged inflammation either due to some virulent bacteria or a virulent virus like mycobacterium tuberculosis and chronic hepatitis C infection, which is the most common cause of chronic liver disease nowadays in the middle east, the second mechanism where leukocytes can induce tissue injury is if there is an inappropriate inflammatory response and this is the basic concept of autoimmune diseases, like systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, we are still in the process of understanding more and more of the basic mechanism of these diseases, why is your inflammatory response is inappropriate and exaggerated to the point that

they induce your own tissue damage? this is the second mechanism, the third mechanism is where the inflammatory response which you had is actually disproportionate or exaggerated to the antigenic stimuli and this is the basic mechanism of acute allergic reaction and bronchial asthma where simple flu or simple cold or simple stress will induce exaggerated allergic reaction causing signs and symptoms and diseases, so those the top three mechanisms where tissue injury and diseases can occur due to damage by those inflammatory cells. which indicates that sometimes although inflammation protects you, but it can be harmful and cause disease due to certain scenarios.

# OTHER FUNCTIONS OF ACTIVATED WBCs

## What was mentioned in the slide:

- **Amplify or limit reaction (cytokines)**
- **Growth factors secretion (repair)**
- **T-lymphocytes has also a role in acute inflammation (T-HELPER-17); produce cytokine IL-17 (deficiency cause disease)**

## What was mentioned in the lecture:

now what are the other functions of white blood cells? We always need those white blood cells to be recruited to the tissue of injury, there are certain additional functions which are committed by those white blood cells, the first one of them is amplification or on the other hand limitation of the inflammatory reaction (to regulate the inflammatory reaction) and those are the functions carried by the cytokines secreted from WBCs, either they can amplify the inflammatory reaction -if we need amplification like for example in the second or third phase of inflammation (where we **r**ecruit and **r**emove), we need amplification of the cytokines and we need amplification of the inflammatory process, I need more soldiers, more recruitment, more chemotaxis, etc. there are too many bacteria, the enemy numbers are high,- so in this scenario the white blood cells will produce cytokines to enhance and amplify the reaction however if we reach to the point in which most of the bacteria or the enemies are dead, now they're phagocytosed, they're killed by ROS inside the macrophages, I don't need any more army in the streets, they will produce cytokines to limit, contain and terminate the inflammatory reaction, the other major function which is helpful is growth factor secretions and this function is actually extremely important in the later phases of inflammation where repair starts and we will talk about this in detail, those white blood cells secrete growth factors that will help starting the repair process, the third function is related to T lymphocytes, recently, they've discovered that there are certain type of T cells, it's called T helper or CD4+ cells help in acute inflammation, T helper number 17 is a major player of in acute inflammation, so opposite to what we thought initially that lymphocytes do not play a role in acute inflammation, actually they discovered that T helper number 17 plays a major role in acute inflammation and they produce a cytokine called interleukin-17, when there is deficiency of interleukin-17 there's certain diseases where the immunity is decreased.

# TERMINATION OF ACUTE IR

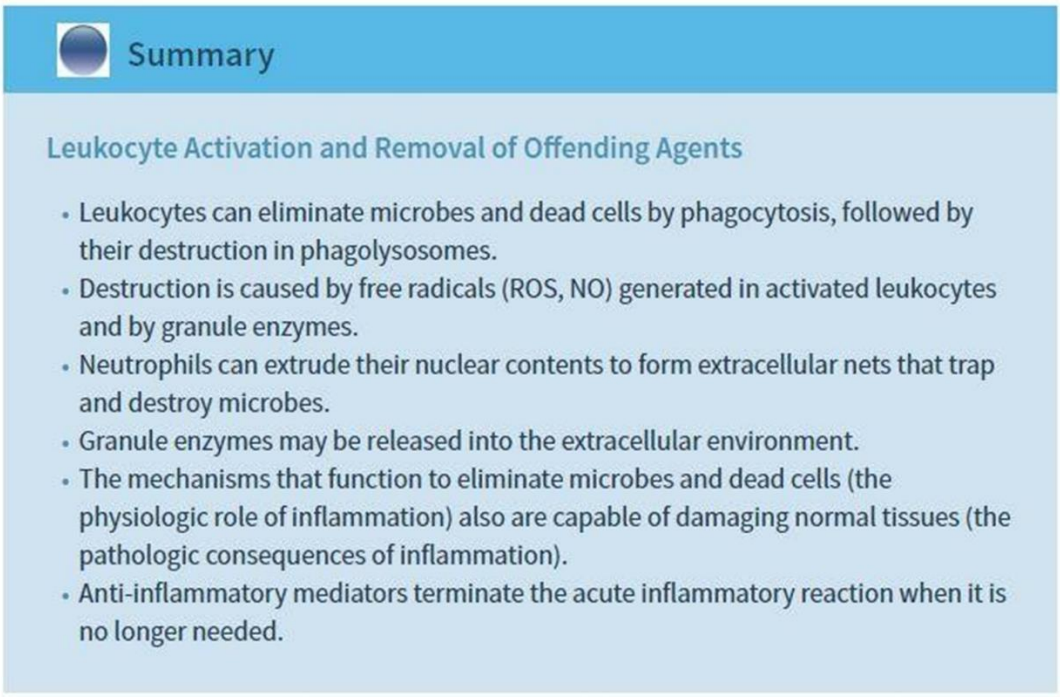
## What was mentioned in the slide:

| |
|---|
| Mediators are produced in rapid bursts |
| Release is stimulus dependent |
| Short half-lives |
| Degradation after release |
| PMNs short life (apoptosis) |
| Stop signals production (TGF-ß, IL-10) |
| Neural inhibitors (cholinergic): inhibits TNF |

## What was mentioned in the lecture:

after we killed almost all the organisms, bacteria, viruses, etc. in the first couple of days of inflammation, I need to terminate the acute inflammatory response, I don't want this inflammatory response to continue because there are side effects, those enzymes, mediators, etc. can injure the tissue as we have mentioned before, so the in the following phase we need to stop, terminate and control the acute inflammatory response, this table summarizes the seven major mechanisms of control.

- the first point in mediators is that they are produced in rapid bursts and this is important because we do not want those mediators which are released mainly by the inflammatory cells and cellular tissue components to be there continuously, they are released quickly as rapid bursts, they are not continuously being released into the circulation. (rapid burst means that they are released upon stimulation like an on/off switch, they are not continuously being released)
- the second point is that the release of these mediators are actually stimulus dependent, if the stimulus is there they are produced, if the stimulus is not there they are not produced, so as long as there is a pathogen and the pathogen is recognized and the cascade of inflammatory changes is still there, they will keep being released, however if this is gone, their release is terminated.
- the third mechanism is that most of these mediators have a short half-life, from seconds to minutes or maximum hours, so this helps that if they're not there due to the previous two mechanisms, they will not have prolonged half-lives.
- the fourth mechanism is that most of these mediators will be degraded after release, because most of the tissue at the site of injury is equipped by certain enzymes that are ready and capable of destroying those mediators, so most of these chemical mediators have enzymes to degrade them, and digest them.
- the fifth one is that the polymorph nuclear cells or neutrophils have a short life, so their half-life is actually short and they have certain mechanism in which they are dead by themselves, it's called apoptosis (programmed cell death), so the neutrophils which are the one of the major players of acute inflammation have a short life
- the sixth mechanism is that at the end of inflammation (at the start of the repair), there are certain mediators which are released like transforming growth factor β or interleukin-10, those two mediators are mediators of inflammation but they are released toward the last phases of inflammation, those are capable of stopping the signals for the initial mediators.
- The last mechanism is that there is certain neural inhibitors, like cholinergic inhibitors that inhibit the release of certain mediators such as tumor necrosis factor.




# MEDIATORS OF A. INFLAMMATION:
# Tissue macrophages, dendritic cells & mast cells

**What was mentioned in the slide:**

| | |
|---|---|
| **Vasoactive amines** | **Histamine, serotonin** |
| **Lipid products** | **PGs and LTs** |
| **Cytokines** | **IL, TNF and chemokines** |
| **Complement activation** | **C1-9** |

## What was mentioned in the lecture:

the mediators of acute inflammation are a big list, they are produced by inflammatory cells like tissue macrophages, dendritic cells and mast cells, all those cells can produce those mediators of inflammation which are responsible for all the functions of acute inflammatory response from the beginning to the end by repair, this table gives you the four major groups: the vasoactive amines, the most important of which is histamine and serotonin, serotonin was though in the past to be an animal vascular amine

component but recently it has been discovered that it is also present in human beings, histamine is the godfather or the major player of those vasoactive amines and its function is in the initial phase of inflammation which is inducing vasodilation, then we have the lipid products and those are the products of damage of the arachidonic acid of the cell membrane, they include predominantly two major groups: prostaglandins and leukotrienes, the third group is the cytokines as we have mentioned, they include interleukins, tumor necrosis factor and the big group of chemokine family which we said they are strong chemoattractants, cytokines are mainly produced by lymphocytes, and then the fourth group is a component of plasma proteins which we call complement system proteins, the major components of this system are C1-C9.

# GENERAL FEATURES OF MEDIATORS:

## What was mentioned in the slide:

- **Cell derived at the site: from granule release or synthesized upon stimulation**
- **Plasma proteins: needs activation**
- **Active mediators: needs stimulation**
- **Most mediators have short life span**
- **One can activate the other**

## What was mentioned in the lecture:

having mentioned the different groups of chemical mediators, what are the general features of those mediators? this is very important because it will make you understand the concepts which we have mentioned about the acute inflammatory response and then the termination and then the starting of the repair, so the first feature of these mediators is that they are cell-derived at the site of injury, so if there's no injury (e.g. there's no bacteria), cells don't have to release those chemical mediators of inflammation, we don't need this army if there is no injury, so they are cell-derived at the site of injury being secreted from certain granules or sometimes they are actually synthesized upon stimulation, when the cell machinery is ready, so this is the first important feature of those mediators, the second feature is that plasma proteins and specifically the complement system proteins which are present in small amounts in your plasma actually need stimulation to be active, they are present in the plasma in an inactive form, they do not exert any function unless they are activated, so they need to be activated to be functional, this is the second important feature, even the active mediators need stimulation so although the gun is and there the bullets are there but you need somebody to stimulate their activation, the other important feature as we have mentioned before is that most of these mediators have a short life span so they just go there in a rapid burst release, they excite the function and then they go, their lifespan is very short and this is very important because as we said we do not want the inflammatory process to be prolonged because of tissue injury, the last and an important feature of those mediators is that each one of these mediators can activate the release, stimulation and the activation of others in addition to that each one of these can inhibit the release and activation of others (those mediators are redundant and tropic).

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 |

## What was mentioned in the lecture:

this is table is very important and you have to memorize it, it contains the name of the mediator or the group of mediators, where are they produced, and what is or what are the major functions, histamine is from the vasoactive amines, it is produced by mast cells, basophils, and the platelets, the main functions of histamine are vascular, including vasodilatation, increased vascular permeability and endothelial activation.

prostaglandins which are arachidonic acid metabolite are also produced by mast cells and leukocytes, their function include vasodilation, but they are also included in the pathogenesis of pain and fever, this explains why do you have fever in acute inflammation and why do you have pain in your neck when you have tonsillitis, those symptoms are actually produced by certain mediators including prostaglandins.

Leukotrienes are also metabolites of arachidonic acid which is a cell membrane lipid, leukotrienes are secreted from the mast cells and leukocytes, they increase vascular permeability, some of them have a role in chemotaxis especially leukotriene B4, leukotrienes also have a role in leukocyte adhesion and activation.

Regarding the big family of cytokines, chemokines constitute a part of the cytokines family, but because they have a more specific function, they are separating them as two different groups, cytokines include tumor necrosis factor (TNF) and the interleukins with interleukin-1 and interleukin-6 being the most important, they are produced by macrophages, endothelial cells and mast cells, cytokines carry a wide range of functions, including endothelial activation by inducing them to express adherence molecules to prepare them to migration of leukocytes as a local effect, fever, metabolic changes and hypotension as systemic effects, notice that there is some overlap, prostaglandins induce fever and also cytokines can included in fever, prostaglandins can play a role in pain production, while kinins (especially bradykinins) also are players for the production of pain.

The chemokines' major function is chemotaxis, they are mainly produced by leukocytes

PAF (platelet activating factor) is a very important chemical mediator of inflammation and recently (in the last 15 years) they discovered that PAF can play a role in the development of ischemic heart disease

and atherosclerosis which are a major killers these days, it is produced by leukocytes and mast cells, it induces vasodilatation and increased vascular permeability in addition to other functions.
the complement system is a group of small plasma proteins, they are produced in the liver, but they are released and they stay in the plasma, upon stimulation, they have multiple functions including chemotaxis and direct target killing and we will talk about this in details later on

the kinins (especially the bradykinin prototype of the kinins) are also produced in the liver and they are plasma proteins, they are involved in initial phase of inflammation, they induce increased vascular permeability, smooth muscle contraction and vasodilation, also they an important player in pain (nociception)

they are important because most of these mediators are targets for therapy, for example bradykinin is involved in pain reception and you will take in pharmacology that some pain killers function by inhibiting bradykinin, some other painkillers inhibit synthesis of prostaglandins (antiprostaglandins), there are also antihistamines, all of us, when we get common cold ,we go to the pharmacy or to the emergency room and they give us antihistamine products to decrease the impact the of initial vascular phase of inflammation.

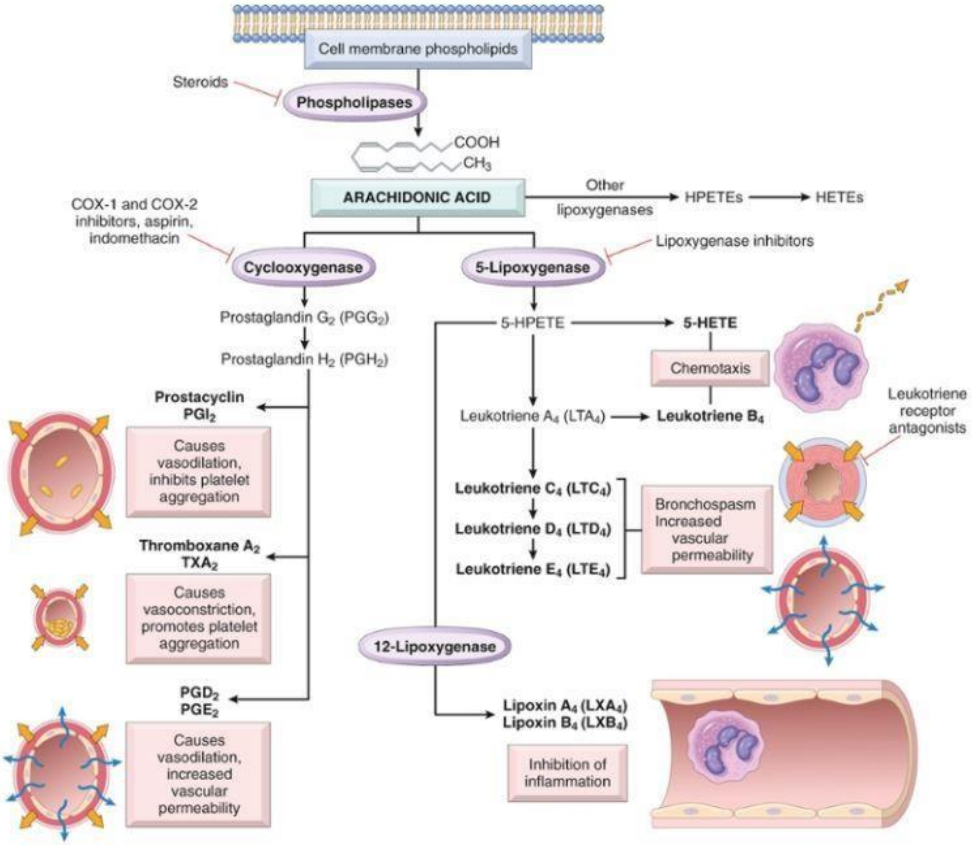



FIG. 3.9 Production of AA metabolites and their roles in inflammation. Clinically useful …

## What was mentioned in the lecture:

let's explain some of these chemical mediators of inflammation, a big group of those mediators of inflammation is what we call arachidonic acid metabolites, arachidonic acid is a cell membrane lipid which present everywhere and when those cell membrane phospholipids are degraded and digested they will produce multiple products which include important and critical chemical mediators of inflammation function, so the initial enzyme which digests the phospholipids in the cell membrane is phospholipase, it

is the major enzyme which will act on the phospholipids producing numerous particles of arachidonic acid, then the arachidonic acid goes into two different metabolic pathways: an arm in which another enzyme called cyclooxygenase (cox) (they are now dividing cyclooxygenase into cox-1 and cox-2), cyclooxygenase-1 and cyclooxygenase-2 will destroy arachidonic acid producing what we call the big group of prostaglandins, but if the arachidonic acid went into the other pathway (arm) which is called the 5-lipooxygenase pathway we will get products collectively called leukotrienes, steroids are very strong and potent anti-inflammatory drugs which functions mainly to inhibit phospholipase, so if you give a patient steroids, this drug will inhibit phospholipase and will inhibit the production of all those leukotrienes and the prostaglandins, this is how steroids function as a strong anti-inflammatory drugs, however the cyclooxygenase enzyme is inhibited by other anti-inflammatory drugs which are less potent and less critical, we call them cox-1 and cox-2 inhibitors, such as aspirin and indomethacin, and some other non-steroidal inflammatory drugs, so those inhibit the cyclooxygenase pathway and they will inhibit only the production of prostaglandins, that's why aspirin and indomethacin are considered anti-prostaglandins, this is how they are used in certain diseases to decrease the impact of inflammatory reaction , for the lipo-oxygenase pathway, it has additional certain lipoxygenase inhibitors, they are actually more recently introduced into the market, those will inhibit the production of leukotrienes.

let's go through some of these mediators and chemical compounds, cyclooxygenase enzyme will degrade arachidonic acid producing prostaglandins, the first one to be produced is a prostaglandin $G_2$, then prostaglandin $H_2$, then the cascade goes on producing prostacyclin (also called prostaglandin $I_2$), prostacyclin is an important chemical mediator of inflammation, it functions as a vasodilator -similar to histamine- and also it inhibits platelet aggregation, however, the product which is exactly after prostacyclin in the cascade is thromboxane $A_2$, thromboxane $A_2$ has the opposite function of prostacyclin, it causes actually vasoconstriction and stimulates and promotes platelet aggregation, why we are talking too much about this? because the imbalance between prostacyclin (prostaglandin $I_2$) and thromboxane $A_2$ ( where the thromboxane function overcomes the prostacyclin function) is thought to be involved in the development of atherosclerosis and ischemic heart disease, the last two prostaglandins are prostaglandin $D_2$ and prostaglandin $E_2$, those have less critical function, but at least to know that they can cause dilatation and increased permeability similar to prostaglandin $I_2$.

the lipoxygenase products they are mainly called leukotrienes including the products of 5-HPETE or 5-HETE, the products of 5-HETE are strong chemotactic agents, especially leukotriene $B_4$ which is one of the initial leukotrienes from the lipoxygenase pathway, its major function is chemotaxis or recruitment of white blood cells into the site of injury, the other three leukotrienes are $C_4$, $D_4$ and $E_4$, those are chemical mediators of inflammation which are thought to play a major role in the production of bronchial asthma , they induce constriction of the bronchial diameter (bronchospasm), they also will increase vascular permeability causing more edema, therefore antagonists of these products are now utilized as a targeted therapy to control acute attacks of bronchial (allergic) asthma, the last group of the lipoxygenase pathway are the lipoxyn$A_4$ and lipoxyn$B_4$ ,those are major inhibitors of inflammation and there's experiments now utilizing those as targeted therapy.

TABLE 3.6 Principal Actions of Arachidonic Acid Metabolites in Inflammation

| Action | Eicosanoid |
|---|---|
| Vasodilation | Prostaglandins $PGI_2$ (prostacyclin), $PGE_1$, $PGE_2$, $PGD_2$ |
| 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 |

Used to delay labor

## What was mentioned in the lecture:

this is another table which probably you will hate me because of, it summarizes the major functions of arachidonic acid metabolites, the other name of AA metabolites is eicosanoids, the major vasodilator of those AA metabolites is prostaglandin $I_2$ (prostacyclin), another vasodilators include prostaglandins $E_1$, $E_2$, $D_2$ , the major vasoconstrictor is thromboxane $A_2$, leukotrienes $C_4$, $D_4$, $E_4$ can also induce vasoconstriction (remember that the function depends on the receptor but not the ligand), and we said also that those leukotrienes are involved in the pathogenesis of acute bronchial asthma, the major vascular permeability inducers are the leukotrienes $C_4$, $D_4$, $E_4$, the major chemotactic agent is leukotriene $B_4$, smooth muscle contraction is induced by prostaglandins, mainly prostaglandin $C_4$, $D_4$, $E_4$, this is important because tomorrow, when you will rotate in the obstetric department you will see that the physicians utilize those prostaglandins to inhibit contractions and delay labor

# POINTS TO REMEMBER ABOUT AA METABOLISM:

## What was mentioned in the slide:

- Aspirin – cyclooxygenase
- Steroids – phospholipase and anti-inflammatory
- Prostacyclin (PGI2): vasodilator and – Pl aggregation
- Thromboxane A2: vasoconstrictor and + Pl aggregation
- TXA2-PGI2 imbalance: IHD & CVA
- PG (PGE2): pain & fever

## What was mentioned in the lecture:

what are the major points you need to remember from the arachidonic acid metabolism? aspirin inhibits cyclooxygenase and the COX-1 and COX-2 inhibitors also do the same thing, they inhibit the production of prostaglandins, steroids are major inhibitors of the phospholipase enzymes, they will inhibit the production of all prostaglandins and all leukotrienes, this is why steroids are very potent, strong and

sometimes dangerous anti-inflammatory drugs, prostacyclin or prostaglandin $I_2$ is a strong vasodilator and inhibits platelet aggregation, opposite to the function of the following prostaglandin which is thromboxane $A_2$ which is a major vasoconstrictor and stimulator of platelet aggregation, as we mentioned the imbalance between those two prostacyclin and thromboxane $A_2$ is thought to play a major role in the pathogenesis of ischemic heart disease and cerebrovascular accident strokes in the brain, prostaglandin $E_2$ is a major mediator for the production of pain and fever.

# CYTOKINES:

## What was mentioned in the slide:

- **Proteins secreted by many cells (activated lymphocytes, macrophages and dendritic cells)**
- **Mediate and regulate immune and inflammatory response**

## What was mentioned in the lecture:

let's move to the other big group of mediators which is the cytokines, (cyto: produced by cells, kines: have a kinetic function), they are proteins which are secreted by immune cells, predominantly activated lymphocytes, activated macrophages and dendritic cells, they are big group of chemicals that mediate and regulate your immune response and inflammatory response, they are targets of thousands of studies to help produce some effective medications, and understand their role in cancer angiogenesis and spread (metastasis) of certain cancers .

**TABLE 3.7** Cytokines in Inflammation

| Cytokine | Principal Sources | Principal Actions in Inflammation |
|---|---|---|
| **In Acute Inflammation** | | |
| TNF | Macrophages, mast cells, T lymphocytes | Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects |
| IL-1 | Macrophages, endothelial cells, some epithelial cells | Similar to TNF; greater role in fever |
| IL-6 | Macrophages, other cells | Systemic effects (acute phase response) |
| Chemokines | Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types | Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues |
| IL-17 | T lymphocytes | Recruitment of neutrophils and monocytes |
| **In Chronic Inflammation** | | |
| IL-12 | Dendritic cells, macrophages | Increased production of IFN-γ |
| IFN-γ | T lymphocytes, NK cells | Activation of macrophages (increased ability to kill microbes and tumor cells) |
| IL-17 | T lymphocytes | Recruitment of neutrophils and monocytes |

The most important cytokines involved in inflammatory reactions are listed. Many other cytokines may play lesser roles in inflammation. There is also considerable overlap between the cytokines involved in acute and chronic inflammation. Specifically, all the cytokines listed under acute inflammation may also contribute to chronic inflammatory reactions.
*IFN-γ*, Interferon-γ; *IL-1*, interleukin-1; *NK*, natural killer; *TNF*, tumor necrosis factor.

;

## What was mentioned in the lecture:

This table lists the major cytokines, their principal sources, and their principal actions in inflammation, in acute inflammation, we have tumor necrosis factor which is produced by macrophages, mast cells, and T lymphocytes, TNF stimulates the expression of the endothelial adhesion molecules and secretion of other cytokines, it also has systemic effects, TNF is one of the mediators which are subject to thousands of researches, especially in the pathogenesis of cancer and invasive malignancies.
Interleukin-1 is produced by macrophages, endothelial cells and some epithelial cells, IL- is similar to tumor necrosis factor, but it has a major role in fever in contrast to tumor necrosis factors, interleukin-1 among with the kinins are targets for the treatment of fever (they are targets for antipyretic drugs).
Interleukin-6 is produced by macrophages mainly, it is involved in acute phase response, patients with severe acute inflammation have systemic manifestations, this is why sometimes they come to the emergency room to get help, interleukin-6 is one the cytokines responsible for these manifestations.
the chemokines are important mediators for chemotaxes, recruitment of leukocytes at the site of injury and migration of cells in normal tissues
interleukin-17 is produced by T helper cells 17, it functions in recruitment of neutrophils in the acute phase of inflammation, this is why the old news about no role of lymphocytes in acute inflammation is wrong, we discovered that T helper 17 which produce interleukin-17 have an important role in induction of acute inflammation.
Regarding chronic inflammation, interleukin-12 is a mediator of chronic inflammation, it is produced by dendritic cells and macrophages, it induces increased production of interferon γ which is a major player in chronic inflammation.
interferon γ is produced by T lymphocytes and natural killer cells, it also activates macrophages and increases the ability of intracellular killing and phagocytosis,

interleukin 17 has a function in both acute inflammation and chronic inflammation, it stimulates recruitment of neutrophils and monocytes, this is a flip-flop phenomenon, T helper 17 lymphocytes produce interleukin-17 for recruitment of neutrophils in acute inflammation in addition to the same function by the t lymphocytes to recruit neutrophils in chronic inflammation, there is also a certain small role for neutrophils and chronic inflammation.

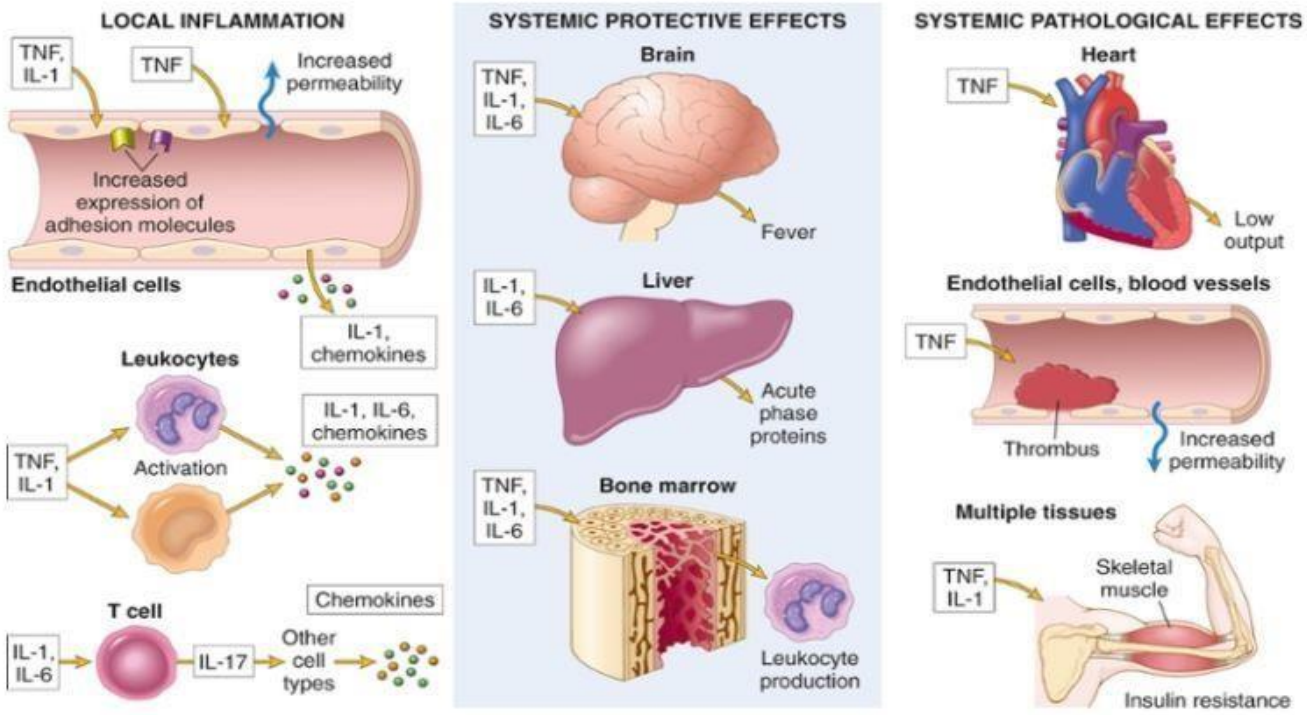



FIG. 3.10 Major roles of cytokines in acute inflammation. *PDGF,* Platelet-derived growt...

## What was mentioned in the lecture:

this is another important slide which will help you tie all ideas together, whenever we have an acute inflammatory response or let's any intense inflammatory response, we have local signs and symptoms (effects) of inflammation, but because many inflammation of mediators will be released into the bloodstream, they can have distant non-local functions, we call these functions and effects systemic, some of these systemic manifestations are protective, nice and helpful , while some of them can cause damage and even can be fatal.

Firstly, let's talk about the local inflammatory changes, they include increased vascular permeability, increased expression of adhesion proteins on endothelial cells, vascular dilatation, erythema, recruitment of inflammatory cells, activation of leukocytes, production of chemokines and production of other inflammatory cells, so locally there will be swelling because of edema, redness and erythema, all those are induced by the chemical mediators which we talked about previously.

Many cytokines (most importantly tumor necrosis factor, IL-1 and IL-6) induce systemic protective mechanisms, they go to the brain and produce fever, although fever sometimes can be dangerous, but it's beneficial, because it brings the patient to the clinician and we will start a treatment, those mediators can also stimulate the production of what we call acute phase proteins which have protective effects, sometimes we measure the level of acute phase proteins in the blood to determine if the patient is in acute distress or not, in addition to that, some of these mediators will go to the bone marrow and they will stimulate production of more hematopoietic cells to help in the fight against inflammation, those in general are considered protective systemic effects of inflammation, they are induced by production of those mediators which go to the blood vessels and have effects on the systemic body functions.

sometimes those systemic impacts can be pathological, for example, the mediators can go and cause depressing of the cardiogenic function, tumor necrosis factors is the major cardiogenic function inhibitor, so sometimes patients can get into heart failure from just severe acute inflammation!!! sometimes there will be endothelial cell injury, we said that the vascular compartment is an important part of the initial phase, so tumor necrosis factor can induce platelet aggregation and thrombus formation which will cause ischemia and shooting emboli , in, addition there is multiple other systemic bad effects like insulin resistance especially in skeletal muscle tissue, this resistance is induced by tumor necrosis factor and interleukin -1 .

# CHEMOKINES

## What was mentioned in the slide:

- **Small proteins, mainly**
- **chemoattractants**
- **40 different and 20 receptors**
- **4 groups: C-X-C; C-C; C; CX3-C**
- **They have G-protein coupled receptors**
- **2 main functions: A inflammation & maintain tissue architecture**

## What was mentioned in the lecture:

let's talk a little bit about chemokines, chemokines are small proteins whose major function is chemoattractanting, there are actually different chemokines and each one of them has different receptors, there are more than 40 different chemokine with more than 20 receptors, they are grouped in letters, they all have G-protein coupled receptors, they have two main functions: to induce acute inflammation and sometimes they are important to maintain tissue architecture, so although chemokines recruit white blood cells to the site of injury, they help maintain the tissue architecture, so that after repair, the architecture of the tissues must stay the same without further damage.

# COMPLEMENT SYSTEM:

## What was mentioned in the slide:

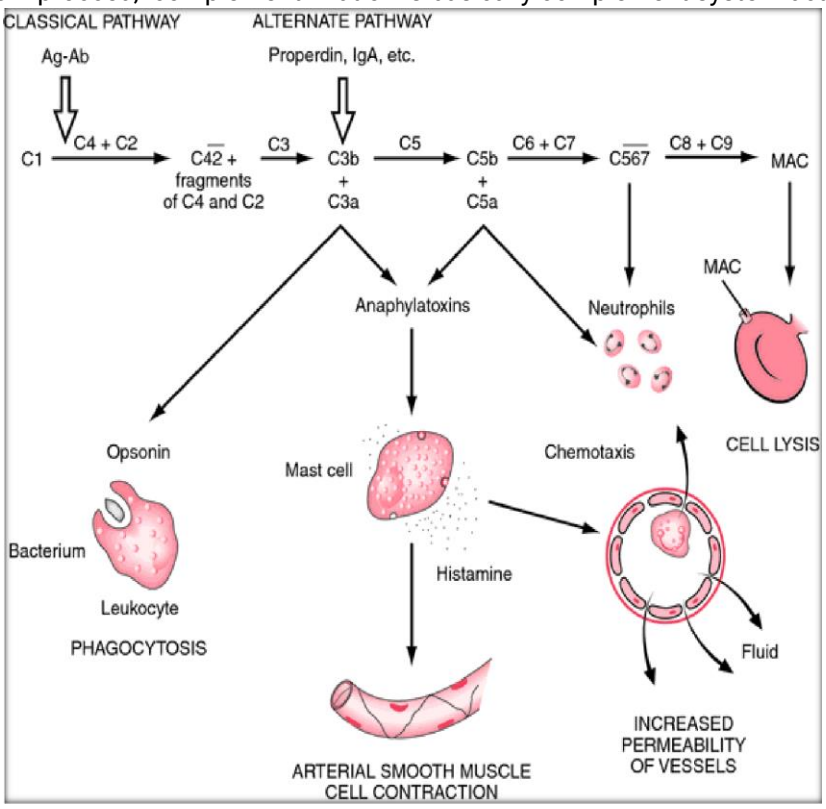
- **Soluble proteins (inactive) needs activation**
- **More than 20, C1-C9**

- **Innate & adaptive immunity**
- **Functions: vascular permeability, chemotaxis & opsonization**

- **C3 is most abundant; cleavage of which is the critical in all pathways**

## What was mentioned in the lecture:

the complement system is basically a small amount of soluble proteins which are produced by the liver, they are present in the plasma in an inactive form, they need stimulation and activation to do their functions, there's more than 20 protein component of this system, they are important in both innate and adaptive immunity, the major functions of the complement system is inducing vascular permeability, they are also important in chemotaxis, and also they are important in a process called opsonization, C1-C9 are the most important and the most abundant among the 20 different complement system component, C3 is the most abundant component of this system in the plasma, the other important point you need to remember about C3 in addition to being the most abundant in the serum is that cleavage of C3 will be the first gatekeeper, you cleave it and then the cascade of the pathways of metabolism and activation the complement system procced, complement fixation is basically complement system activation.




## What was mentioned in the lecture:

This figure depicts two ways to activate the complement system, the classic pathway and the alternate pathway: the classic pathway of activation is by antigen-antibody complex, when an invader comes it stimulate production of antibodies, the antibodies bind the antigens, then the antigen-antibody complexes will start activating the complement system and this is called classical pathway, the other pathway is initiated through either IgA or other certain products, it's called the alternate pathway, the activation starts at the cleavage of C3 component and then the cascade will continue inducing multiple functions.

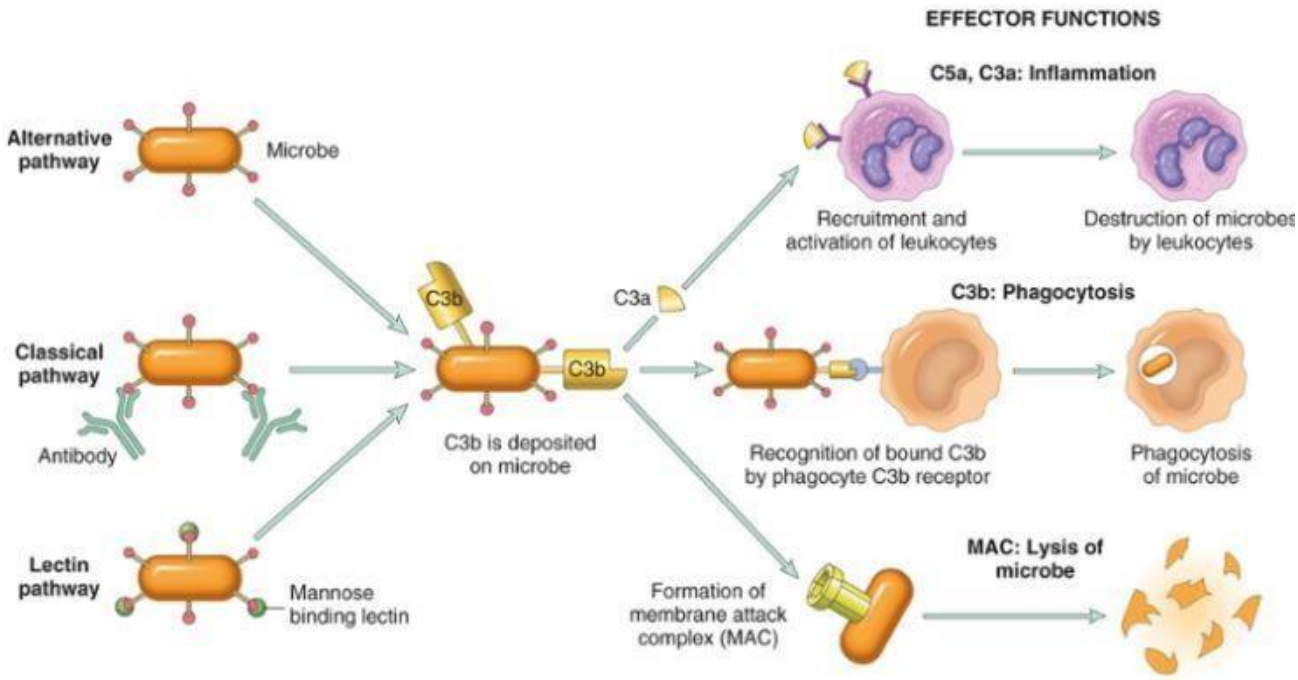



FIG. 3.11 The activation and functions of the complement system. Activation of compl...

## What was mentioned in the lecture:

There are actually three pathways which can activate the complement system cascade: 1- the alternative pathway by certain receptors in the microbial products directly activating C3, 2- the classical pathway again by antigen-antibody complex on the surface of bacteria or viruses, antigen-antibody complexes will come and they will activate the complement system starting by the cleavage of C3 which is the most abundant, 3- the third pathway is through lectins, it's called the lectin pathway in which there is mannose receptor binding to lectin inducing activation of C3, the cleavage of C3 produces the active part C3a will work as a chemotactic agent which stimulates recruitment and activation of leukocytes, also activation of the complement system will result in formation of C5a which is also a chemotactic agent, in addition to that, the C3b which is another product after the activation is a very important stimulator of phagocytosis, it helps the macrophage and the neutrophil in the phagocytosis process, the continuous stimulation of the cascade leads to the activation of C5, C6, C7, C8, C9, they will produce something called MAC or membrane attack complex, this MAC is important to lyse and attack the cell membrane of the microbial agents.

# REGULATORY PROTEINS FOR CS:

## What was mentioned in the slide:

- **C1 inhibitor: if deficient hereditary angioedema**
- **Decay accelerating factor (DAF), which inhibit C3 convertases and CD59 inhibits MAC Abnormalities cause PNH**
- **Factor H: proteolysis of C3 convertase; mutations cause hemolytic uremic syndrome**
- **CS protein deficiencies can occur leading to infection susceptibility**

## What was mentioned in the lecture:

as we mentioned previously, there are seven mechanisms to control the inflammatory response, there are also specific four major mechanisms by which we can regulate the functions, release and the activation of complement system, there are inhibitors of the complement system, for example there is a C1 inhibitor, this C1 inhibitor normally present to control and to inactivate C1, so that the cascade activation will be decreased, if C1 inhibitor is deficient, that will cause a condition known as exaggerated angioedema. hereditary angioedema is caused by deficiency of C1 inhibitor, we'll have an exaggerated inflammatory response when we have the increased quantity of C1.

there is another regulator which is called decay accelerating factor DAF, this factor inhibits C3 convertase which is an enzyme responsible for activation of C3 , there is also CD59 which inhibits the MAC (membrane attack complex) , abnormalities in those two factors is the major cause of a disease called paroxysmal nocturnal hemoglobinuria (hemoglobin in the urine), those patients will suffer from hemoglobinuria (PNH) especially at night, due to deficiency of those factors.

factor H inhibits proteolysis of C3 convertases, mutation of this factor is a major cause of a disease called hemolytic uremic syndrome which is a very serious and critical end result of certain major diseases.

# OTHER MEDIATORS:

## What was mentioned in the slide:

- **Platelet activating factor (PAF): platelet aggregation and other functions**
- **Protease activating receptors (PARs): platelet aggregation**
- **Kinins: vasoactive peptide, Bradykinin the active; VD, increase permeability, smooth muscle contraction and pain.**
- **Neuropeptides: Substance P and neurokinin A**

## What was mentioned in the lecture:

We have another mediators of the inflammatory response, like platelet activating factor which embarks on platelet aggregation and other functions of platelets, another one is protease activating receptor, which also play a role in platelet aggregation, since those two are important in platelet aggregation, they are incriminated in the pathogenesis of atherosclerosis and thromboembolic diseases in addition to the prostaglandin $I_2$ and thromboxane $A_2$.

kinins are a specific group of vasoactive peptides, the most important is of which is bradykinin, they cause vascular changes, including vascular dilatation, increased permeability, and smooth muscle contraction which makes them play a role in active labor after at the end of the pregnancy , they have also therapeutic implications which we will talk about in pharmacology, they are also involved in the production of pain, there are some neuropeptides like substance P and neurokinin which also function as mediators, so those are additional mediators.

**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 was mentioned in the lecture:

This table summarizes the functions and the mediator responsible, vasodilation is predominantly mediated by histamine and prostaglandins, increased vascular permeability have a bunch of mediators including the complement system proteins: C3a and C3b, histamine, and leukotrienes $C_4$, $D_4$, $E_4$. Chemotaxis, lymphocytes recruitment and activation are mediated by tumor necrosis factor, interleukin-1, chemokines, C3a and C5a from the complement system and leukotriene $B_4$ which is a very potent and strong chemotactic agent, production of fever as a manifestation of acute inflammation is mediated by interleukin-1, tumor necrosis factor and prostaglandins and this is why some of those are targeted by certain medications to decrease the impact of fever on human tissue (antipyretic medications).

some of the pathophysiology of the production of pain is known to us and much is not known, but we know the prostaglandins and bradykinin are the two major mediators playing a major role in the pathogenesis and the production of pain, also they are targets for treatment.

Regarding tissue damage, any of those can have tissue damage, but predominantly, the tissue damage as a bystander from inflammatory response is due to leukocytes lysosomal enzymes from the granules and reactive oxygen species.

## Summary

### Actions of the Principal Mediators of Inflammation

- Vasoactive amines, mainly histamine: vasodilation and increased vascular permeability
- Arachidonic acid metabolites (prostaglandins and leukotrienes): several forms exist and are involved in vascular reactions, leukocyte chemotaxis, and other reactions of inflammation; antagonized by lipoxins
- Cytokines: proteins produced by many cell types; usually act at short range; mediate multiple effects, mainly in leukocyte recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and chemokines
- Complement proteins: Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization and phagocytosis of microbes and other particles, and cell killing
- Kinins: produced by proteolytic cleavage of precursors; mediate vascular reaction, pain

# MORPHOLOGY OF ACUTE INFLAMMATION

## What was mentioned in the slide:

- **The critical issue is blood vessel dilatation and accumulation of WBCs and fluids in the extravascular tissue.**

| Edema | Fluid and proteins in interstitium |
|---|---|
| Redness | *rubor* |
| Warmth | *calor* |
| Swelling | *tumor* |
| Loss of function | *Functio laesa* |
| Pain | *dolor* |

## What was mentioned in the lecture:

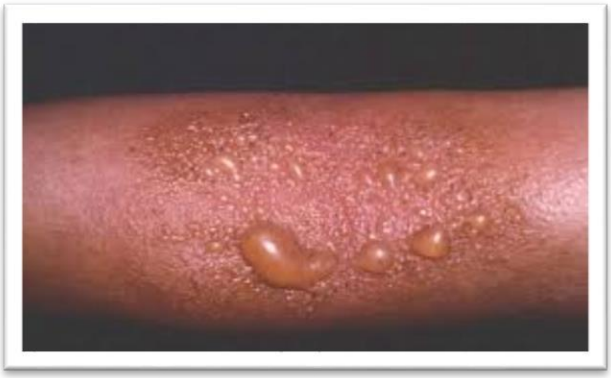
let's move to another topic which is the morphological features of acute inflammation, what we mean by that is how the tissue will look like in the presence of acute inflammation, as we mentioned, there are a lot of phases in the inflammatory response, but morphologically, in things you can see in your eye, things you need a light microscope to look at, and things you need an electron microscope to look like the neutrophil traps, the critical issue is here the initial vascular phase and the accumulation of white blood cells and fluids in the extravascular tissue.

we explained previously what edema means, edema means that there are too much fluids and proteins in the interstitium after the initial vascular phase which include vascular dilatation and increased vascular permeability, fluids and proteins leaks out to the interstitium and there will be edema, so the organ which is involved in inflammation will be edematous and enlarged whether it was a finger, a thigh or a tonsil, etc. the redness is explained by the presence of too many blood vessels in that area, and warmth is because of the presence of active angiogenesis and vascular changes there, the organ which is involved will be hot and red, and because of the presence of pain and edema, there will be loss of function, both of them will play a role in making a person less functional in that specific organ, regarding pain, there are certain mediators which mediate the production of pain, pain is a good thing and a bad thing, the bad thing is that it not good to have pain, and the good thing is that pain will take you go the hospital and treatment will start early.

# SEROUS INFLAMMATION:

## What was mentioned in the slide:

- **Cell poor fluid (transudate)**
- **Serous effusions**
- **Skin blisters**
- **Seromas**

## What was mentioned in the lecture:

what are the gross and microscopic features of those common morphological changes? In acute inflammation mainly, there is something which we call serous inflammation, serous inflammation is basically an acute inflammatory response which is transudative in nature, so there are transudates, there's too much fluid but very little cells and debris, common examples include the serous effusions like a patient who has bilateral pleural effusion due to heart failure, or hypoproteinemia due to liver failure disease, when the oncotic pressure is decreased, more fluids leak out into the interstitium and there will be fluids in body cavities, so whenever we tap those fluids to examine for malignancy, culture it or measure the proteins, they will look yellow and clear , when we examine them under the microscope, we see that the cellularity is very low, skin blisters is another example.

many of you have gone to the dead sea or to Aqaba and they will have those first degree burns in which there are skin blisters, what is present in those areas is actually serous transudates resulted from the acute injury which is the burns.

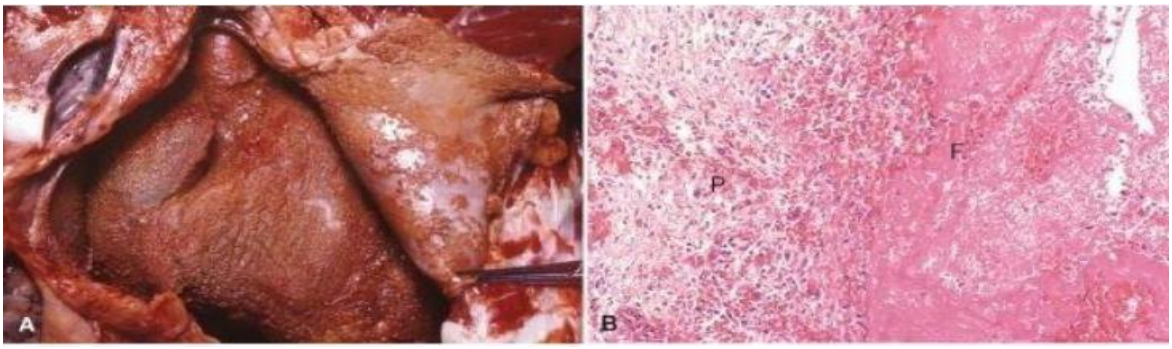
the other common example is seromas, seroma means a sac or a collection of serum which is composed of transudates, those are common after surgery, certain surgeries will induce the production of seromas like hernia repair and breast surgery, sometimes, 1-3 weeks after the surgery, patients come back with a swollen and when you do an ultrasound examination, you find collection of serous fluids, and when you aspirate, they look clear and yellow, you tap these seroma twice or three times to disappear.

Remember: the pleura is a membrane covering the lungs, it is composed of two layers, accumulation of fluid between these two layers is called pleural effusion

# FIBRINOUS INFLAMMATION:

**What was mentioned in the slide:**

- **Large vascular leakage + coagulation**
- **Body cavities: pericardium**



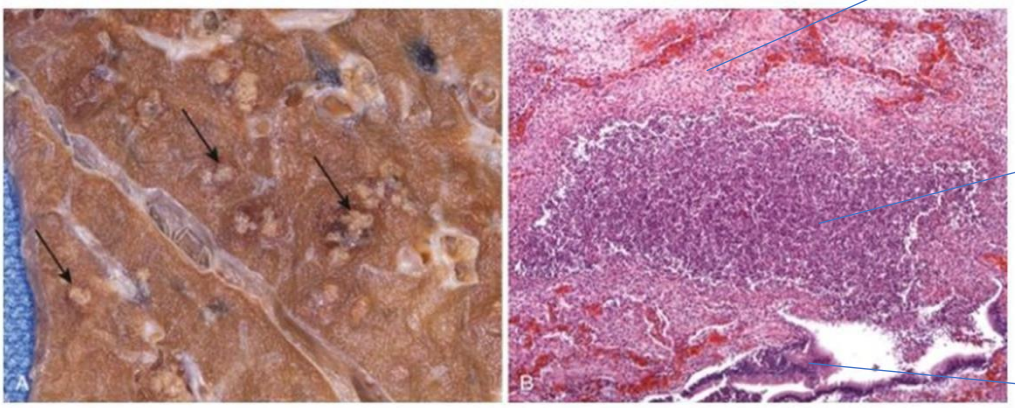

**What was mentioned in the lecture:**

the other type of acute inflammation is what we call fibrinous inflammation, fibrinous inflammation is a little bit similar to the serous inflammation, however, this time the vascular leakage is big, in addition to that there are a lot of coagulation which occurs in the fluid pouring out into the area, fibrinous inflammation is characteristically seen in certain body cavities especially the pericardium, in the pathology department sometimes, if a patient comes with fibrinous pericarditis he has to be treated quickly because otherwise the pericardium will thicken, so the thickened pericardium is formed because of the fibrinous inflammation with the large vascular leakage and a lot of coagulum, proteins, and platelets, this will sometimes cause fatal consequences in the heart unless it is treated quickly,
so what they do is that they open the chest and they do what we call pericardial window and they drain this fluid, sometimes they give us the fluid for examination and sometimes they give us a small piece of the pericardium to examine, histologically, It looks like an inflammatory response with coagulation, platelets and a lot of fibers producing this pinkish material, we have fibrinous pleuritis in the pleura and fibrinous pericarditis, fibrinous inflammation is common in those two areas .

# PURULENT (SUPPURATIVE) INFLAMMATION, ABSCESS:

**What was mentioned in the slide:**

- **Pus: exudate rich in PMNs + debris + edema**
- **Bacteria (staph.)**
- **Abscess: localized collection of pus**



The area around the abscess is the inflamed lung tissue

This purple thing is the abscess

The bronchial epithelium

FIG. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung i…

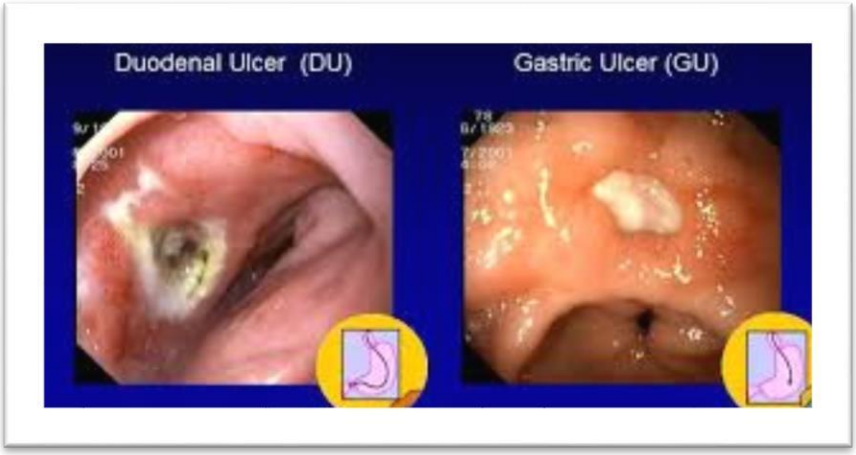
**What was mentioned in the lecture:**

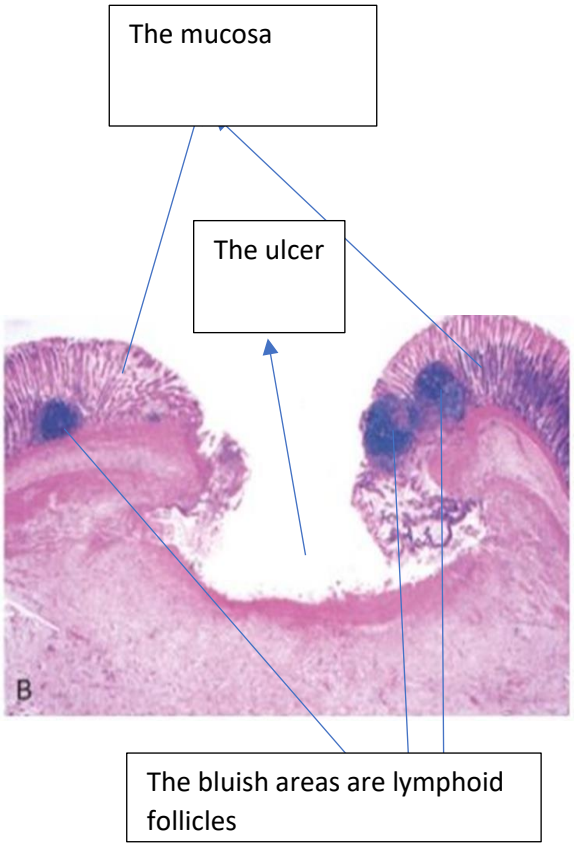
the third one is the purulent or suppurative inflammation, basically, this inflammation means an abscess collection, this type of inflammation includes exudates which are rich with cells (especially neutrophils), edema, bacteria and cell debris, purulent inflammation indicates severe acute inflammation to the point the body cannot cope with this inflammatory response and it will form small pockets of suppurative inflammation , this (the left figure) is a lung section form a patient who died from severe pneumonia, this is how the gross appearance when we cut the lung, those (the arrows of the left figure) are micro abscesses, and under the microscope, these lesions looks like a collection of neutrophils, notice the left figure, abscesses are rich in acute inflammatory cells (mainly neutrophils), bacteria, etc. because the process starts started in the bronchial region, it's called bronchopneumonia , staphylococcus aureus bacteria causes necrotizing supportive inflammation wherever it goes, if somebody asks you, what is an abscess? it is a localized collection of pus or exudate rich in cells and debris.

# ULCERS:

**What was mentioned in the slide:**

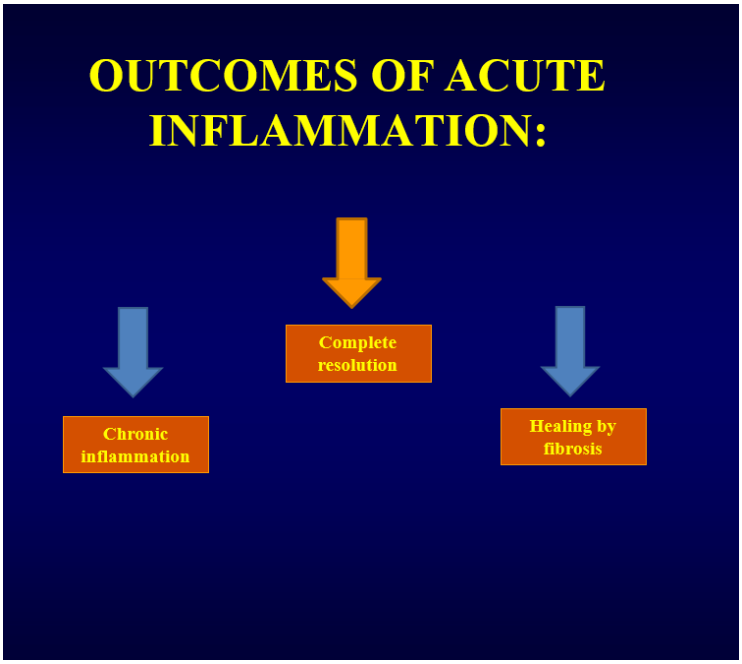
- **Defect on a surface**
- **Common in mucosal surfaces and skin**
- **Mostly acute and chronic inflammation**




**What was mentioned in the lecture:**

the fourth one is ulcerative inflammation or ulcers, by definition, an ulcer is a defect on a mucosal surface, figure B is a microscopic image of a stomach, notice the defect of mucosa, so whenever there's a discontinuity of a mucosal surface this is what we call an ulcer, this (the left figure) is how it looks like in the bronchoscopic appearance when the gastroenterologist introduces the bronchoscope to look at those ulcers, those a gastric ulcer and a duodenal ulcer, if you take a section from these, you will see a definite defect and a big deep ulcer in the mucous , those lymphoid follicles are always associated with chronic inflammation, these ulcers are common in the mucosal surfaces of the skin and other mucous membrane, they can be acute and chronic and sometimes they can be acute on top of chronic, sometimes the patient will have chronic gastritis due to helicobacter pylori bacteria and then he will have an acute attack on top of the chronic attack causing severe bleeding.




## What was mentioned in the lecture:

now let's talk about outcomes of acute inflammation, each one of us will have an acute inflammatory response at a certain time in his life, 95 percent will go back to normal, however there are different types of outcomes of acute inflammation, the preferred outcome and the most common outcome is complete resolution, the acute inflammation comes, it goes through the five stages which we have mentioned and then tissue repair will start and most of the tissue will go back the pre acute episode phase, but however this is not what happens always in real life, so either there's a complete resolution, or some of those will go and heal but, the healing process sometimes might include fibrosis and scar formation, which will have sometimes a negative impact on the cosmetic appearance of that organ or the function of that organ, if you have one attack of acute inflammation with a small scar or fibrotic healing process, it doesn't look good, but mostly it does not impact the function, however if this process was severe enough to the point that the fibrous scar is so big and huge, this may impact on the function, especially in certain anatomical areas.

so the first outcome is complete resolution, second outcome is healing by fibrosis, the third one is that we cannot get rid of the acute inflammation due to certain reasons and this acute inflammation will transform to chronic inflammation which comes and goes repeatedly, and whenever there is an attack, there is tissue damage, at the end, sometimes the chronic inflammation will be so severe, prolonged and progressive up to the point with damaging that particular organ, so those are the three possible outcomes of acute inflammation the most desirable one is to have a complete resolution.

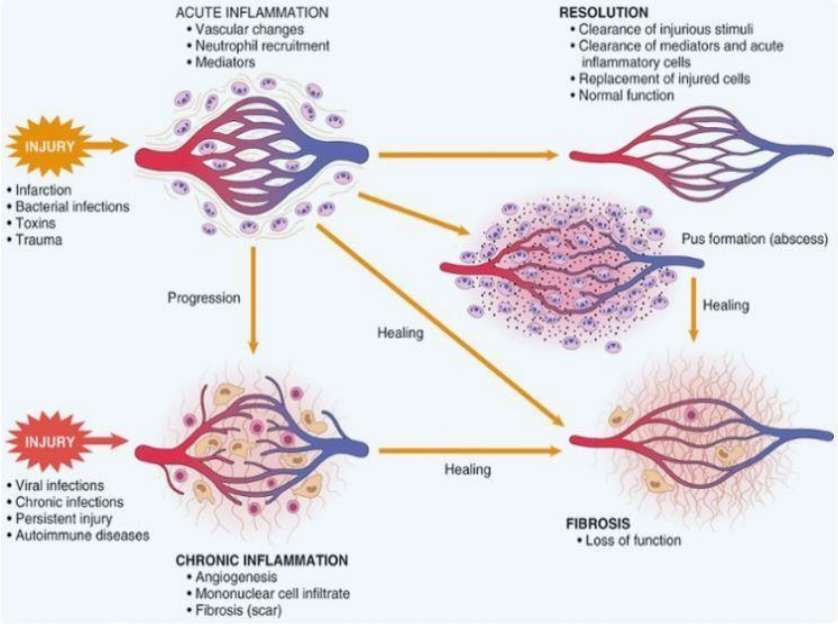



FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

## What was mentioned in the lecture:

to summarize the outcomes of acute inflammation, this is a diagram which explains, the initial injury, the vascular phases and the presence of acute inflammation, at the end of this acute inflammation, there might be complete resolution and the tissue will go back to the pre-inflammatory stage, this is the first outcome which we would like to have most of the time, the second outcome is the presence of too much tissue destruction or severe acute inflammation up to the point that the healing process needs tissue repair by forming a fibrous car in that area, the tissue characters here will not be exactly the same as the pre-inflammatory stage, because there is a scar tissue and depending on the amount of this scar tissue (fibrotic tissue) the impact on the function will ensue, if the acute inflammation was progressive due to a virulent injurious agent or bad immunity, there will be chronic inflammation with new vascularization and too much changes in the tissue, sometimes including severe fibrosis and scar formation leading to a loss of function.

# CHRONIC INFLAMMATION:

## What was mentioned in the slide:

- **Prolonged inflammation (weeks-months- years): inflammation, tissue injury and attempts at repair coexist at the same time with varying degree.**
- **May follow acute inflammation but may be insidious or smoldering**

## What was mentioned in the lecture:

let's talk now about chronic inflammation, chronic inflammation is defined as a prolonged inflammation where the exact date and time when it had started is not really clear, but it lasts for maybe weeks, months, and sometimes years, with this prolonged chronic inflammatory response, there will be an associated tissue injury, with each tissue injury, your body is trying to repair, after various cycles of injury then repair, and if the chronic inflammation did not stop, there will be severe fibrosis embarking on the function of that organ, e.g. if you have chronic active hepatitis for 10-15 years at the end cirrhosis or fibrosis of the liver leading to liver failure will end up in that organ.
most of the time chronic inflammation follows acute inflammation, however, in certain circumstances

that's not the case, sometimes the chronic inflammatory phase is so subclinical that it doesn't bother you anymore, so the chronic inflammation is insidious, it will not present itself clinically and those are slightly dangerous because sometimes when the clinical picture is presented it will be too late.

# CAUSES OF CHRONIC INFLAMMATION

**What was mentioned in the slide:**

| | |
|---|---|
| **Persistent infections** | **Mycobacteria (TB), viruses, fungi, parasites. Delayed hypersensitivity reaction. Granulomatous inflammation.** |
| **Hypersensitivity diseases** | **RA, asthma, MS. May end in fibrosis of end organs** |
| **Prolonged exposure to toxic agents (exogenous or endogenous)** | **Silica (silicosis) Atherosclerosis (cholesterol)** |
| **Other associated diseases** | **Alzheimer's, Metabolic syndrome of DM** |

**What was mentioned in the lecture:**

what are the causes of chronic inflammation? there are multiple reasons for it, for example, if you have persistent infections especially with certain tough virulent bad organisms like mycobacterium tuberculosis and certain viruses like hepatitis C virus in the liver, fungi and some parasites, sometimes there is delayed hypersensitivity reaction to these organisms, the persistent infection sometimes causes specific type of inflammation -which we will talk about- called granulomatous inflammation, which is a specific type of chronic inflammation.

the second reason for the etiology of chronic inflammation is hypersensitivity diseases and those are a big group of autoimmune diseases which you will take in detail in the future, those include rheumatoid arthritis, bronchial asthma (it comes in acute and chronic forms), multiple sclerosis, etc.

all those can end up in fibrosis and organ failure, the third reason which causes chronic inflammation is when you have a prolonged exposure to toxic agents whether exogenous or endogenous, an example for that: there's a disease called silicosis, it happens due to accumulation of silica in the lung, the patient's occupation will expose them daily to parts of silica which can be inhaled into the lung tissue and then this will induce fibrosis and a disease called silicosis in the lung, the other common disease is atherosclerosis due to cholesterol clusters which are actually produced endogenously, so atherosclerosis is considered a

chronic inflammatory response,  there's other diseases associated diseases like Alzheimer's disease or metabolic syndrome of diabetes mellitus
we understand the pathophysiology of some of those diseases, bit with other diseases, we understand just part of it, so it will take some time to understand the changes and why in those diseases we will have chronic inflammatory response and tissue damage.

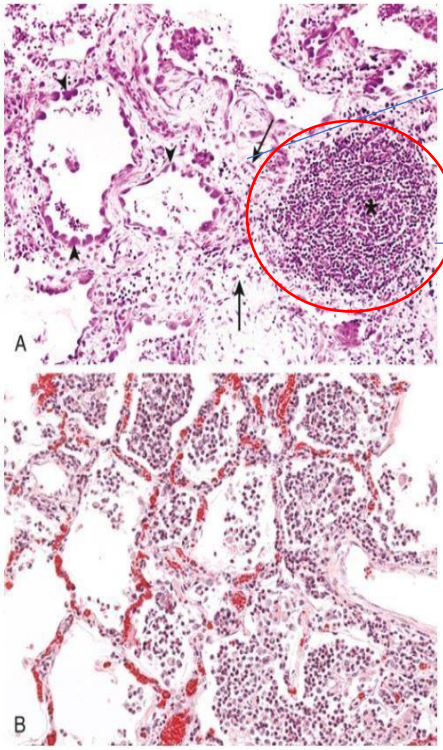
# MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION:

**What was mentioned in the slide:**

- **Infiltration by chronic inflammatory cells (macrophages, lymphocytes and plasma cells)**
- **Tissue destruction**
- **Attempts at healing by angiogenesis and fibrosis**

**What was mentioned in the lecture:**

if you have a tissue with chronic inflammation, what are the microscopic or morphologic features of the chronic inflammatory response? as we have mentioned, in the acute inflammatory response, the tissue cell infiltrate is composed of predominantly neutrophils, but in chronic inflammation, the inflammatory cells which are present and can be seen under the microscope are macrophages, lymphocytes and plasma cells, so whenever I see those cells in large numbers, then this must be a chronic inflammation, this is the first critical feature of chronic inflammation, in addition to this, you'll see that there is tissue damage (tissue destruction), the chronic inflammatory response is associated with tissue destruction in varying degrees, and if there is severe tissue destruction, you must see severe changes, (e.g. replacement of the normal liver parenchyma by thick bands of fibrosis in cirrhotic patients, etc.), in addition to that your body is not standing, he is always attempting to induce repair and healing by producing new blood vessels a process which we called angiogenesis, and then replacement of the lost tissue by scar tissue which is rich in collagen.



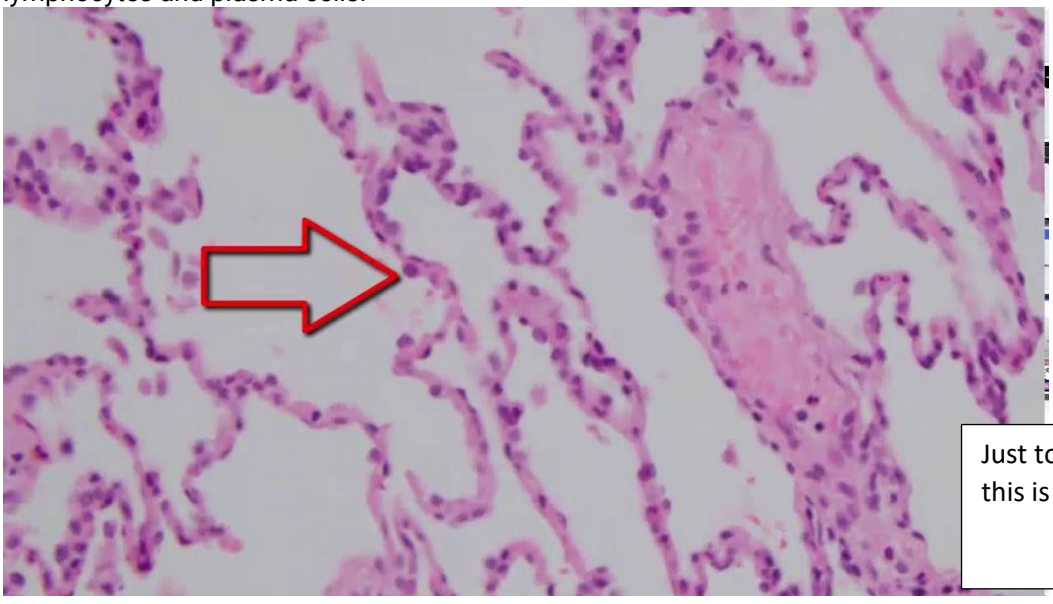

Notice the young fibrous tissue

The inflammatory follicle

FIG. 3.17 (A) Chronic inflammation in the lung, showing all three characteristic histolo…

## What was mentioned in the lecture:

both of these micrographs are from sections from the lung using hematoxylin & eosin stain, let's go to the bottom micrograph first, those are the alveoli, they are still parenchymal and the architecture is still will preserved, the alveoli are full of those neutrophils, this is severe acute lobar pneumonia where the alveoli is filled with acute inflammatory cells (mostly neutrophils).
The micrograph above depicts a chronic inflammation of the lung, this is another lung where the alveoli has been damaged and replaced by fibrous tissue, this is young fibrous tissue and there is a chronic inflammatory follicle, if you look at those cells at high power, you'll see that those are macrophages, lymphocytes and plasma cells.



Just to ensure understanding : this is a normal lung tissue.

# CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

**What was mentioned in the slide:**

- **Macrophages**
- **Lymphocytes**
- **Eosinophils**
- **Mast cells**

**What was mentioned in the lecture:**

the mediators which we have talked about previously are not only involved in acute inflammation, chronic inflammation also requires mediators of chronic inflammation and all of these cells: macrophages lymphocytes, eosinophils, and mast cells, all of these play a role in producing many of these chemical mediators similar to the cells of the acute inflammatory response.

# MACROPHAGES

**What was mentioned in the slide:**

- **Secretion of mediators (TNF, IL-1, Chemokines.)**
- **Feedback loop with T cells**
- **Phagocytosis**
- **Circulating monocytes (1-day half-life)**
- **Tissue Macs: Kupfer cells, sinus histiocytes, alveolar macrophages & microglia (mononuclear phagocytic system), half-life months**
- **Activation of Macs: M1 classic pathway, M alternative pathway**

**What was mentioned in the lecture:**

macrophages (when they in the circulation, they are called monocytes) secrete cytokines, like tumor necrosis factor, interleukin-1 and chemokines, in addition to that, they have a strong connection with T cells, there's always communication between the macrophages and the T cells, T cells give the macrophages a feedback about increasing or decreasing the inflammatory response, the third function of the macrophages is the phagocytosis, phagocytosis is a peculiar function of macrophage and neutrophils, when macrophages are circulating in the blood, before they get recruited and before they get activated into the tissue to transform to tissue macrophages (tissue monocytes or tissue histiocytes), the half-life of them is short, it is approximately one day, but when they get into the tissues, the half-life is extended sometimes to months or weeks, examples of those tissue macrophages are the Kupfer cells of the liver, the sinus histiocytes of lymph nodes, alveolar macrophages in the lung, and microglia of the brain, all of these are successors of circulating monocytes, they constitute what we call the mononuclear phagocytic system, and they all have a prolonged half-life, regarding the activation of the macrophages, -

as we said the chronic inflammatory response requires activation and mediators similar to acute inflammation- there are two different pathways for activation of macrophages: there is the classic pathway which we call it M1 pathway, and then the alternative pathway or the m2.

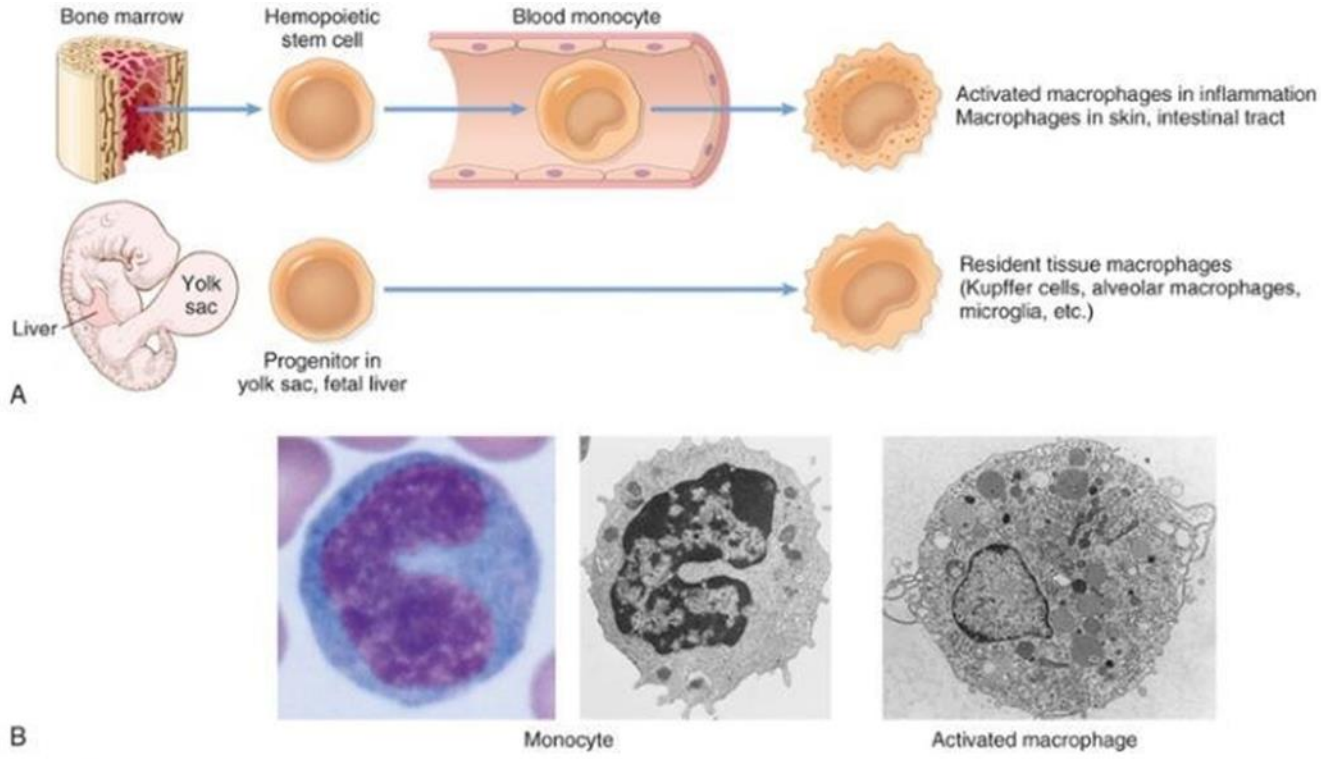



FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

## What was mentioned in the lecture:

the macrophages are produced by the bone marrow in adults from hematopoietic stem cells after they mature, this is the classic appearance of those circulating monocytes, they have a clear cytoplasm, less granules and a kidney shaped nucleus, when they get activated and become activated macrophages in the tissue, they become bigger, more granulated and the nuclear-cytoplasmic ratio become less (the cytoplasm become bigger compared to the nucleus), in fetal life, they are produced from the yolk sac as a progenitor cells which then mature into tissue macrophages, morphologically, this is the way the monocyte looks like when it is circulating, it has less granules and kidney shaped nucleus, but when they mature into tissue macrophages, the cytoplasm become more busy with more lysosomes and organelles, the cytoplasmic processes also increase, and the nuclear cytoplasmic ratio becomes smaller.

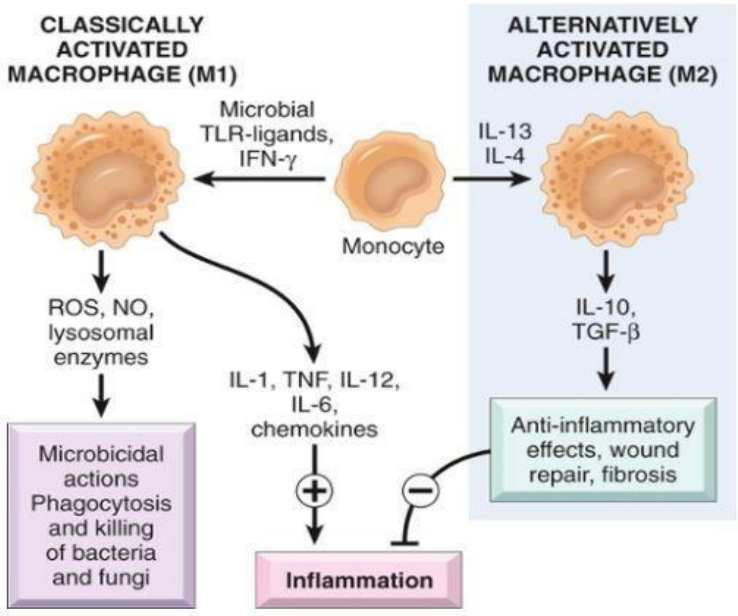



FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

## What was mentioned in the lecture:

the classically activated macrophages (those who are activated by M1 pathway) ensues in controlling and producing many of the chemical mediators of inflammation and they are and involved in the process of killing the organism and ultimately resolution of an acute inflammation and resolution of a chronic inflammation later on, so the classic M1 pathway of macrophages is actually pro-inflammatory, macrophages activated this way induce excess inflammatory mediators and they're active in trying to fight the invading organisms, the major driver of recruitment of those monocytes in the M1 pathway are different stimuli, those include microbial Toll-like receptors ligand, which we talked about and the interferon γ, those are the two major drivers which will push the monocyte to go through this M1 pathway, which is the pro-inflammatory pathway, leading the macrophages to secretion of interleukin-1, tumor necrosis factor and different chemokines, ending up in augmenting the inflammatory response. however there is another pathway of activation which is the alternative pathway or M2, there are certain cytokines -specifically interleukin-13 and interleukin-4, that will push the monocytes to go into this pathway, leading to activation of those M2 macrophages which secrete interleukin-10 and transforming growth factor β, those will have anti-inflammatory effects, it is like M2 macrophages are trying to control or inhibit the inflammatory response, so that the repair or reparative process will start, so this is how the monocytes get into and enter the m2 alternative active pathway for repair.

# LYMPHOCYTES:

**What was mentioned in the slide:**

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

**What was mentioned in the lecture:**

as we mentioned, the inflammatory response also needs additional inflammatory cells, of those are the lymphocytes, T and B lymphocytes can get activated by multiple agents like microbes and environmental antigens, they are also part of the components of cellular infiltrate in chronic inflammation, the T cells are divided into multiple subvariants, one of them is what we call CD4+ positive cells or T helper cells, CD is the cluster designation which are basically membranous antigens which define each cell type from the others, we have more than probably 200 CDs now for lymphocytes, the major two types of lymphocytes are the T cells and the B cells, there are certain markers for T cells and certain markers for B cells, major mature cell markers for T cells are CD2, CD2, CD5, CD7 and then either CD4 or CD8, CD4+ are the T helpers while CD8 are for the T cytotoxic cells, T helper cells are active in secreting multiple cytokines which will induce inflammation, not only the T cells play a role in the inflammatory response, but the B cells and plasma cells also play a role in production of antibodies and the plasma cells are a major cell infiltrate in chronic inflammation.

# CD4+ T CELLS:

**What was mentioned in the slide:**

| | |
|---|---|
| **TH1** | **INF-ɣ, activates Macs in classic pathway** |
| **TH2** | **IL-4, IL-5 & IL-13; activates eosinophils and Mac's alternative pathway** |
| **TH17** | **IL-17, induce chemokines secretion and recruits PMNs** |

## What was mentioned in the lecture:

let's talk a little bit about in details about different types of CD4+ T cells or T helpers, t helper cells are not one single clone, they're either T helper 1 , t helper 2 and there is t helper 17, the T helper 1 are the ones which secrete interferon γ and they have an important role in activation on the macrophages in classic pathway, so the T helper 1 are the ones which are pro-inflammatory, they augment the inflammatory response and they push the macrophages to go in the classic pathway to induce more mediators.

T helper 2 produce different types of cytokines, like interleukin-5 and interleukin-13, they also activate eosinophils, however they push the macrophages into alternative pathway which means suppressing or controlling or trying to decrease the intensity of the inflammatory response, this is how complex this becomes, then we discovered the T helper 17 which secretes interleukin-17 inducing more cytokines production and playing a role in both acute and chronic inflammation, in the acute inflammation by recruiting more neutrophils, so those are the different types of C4+ T cells.

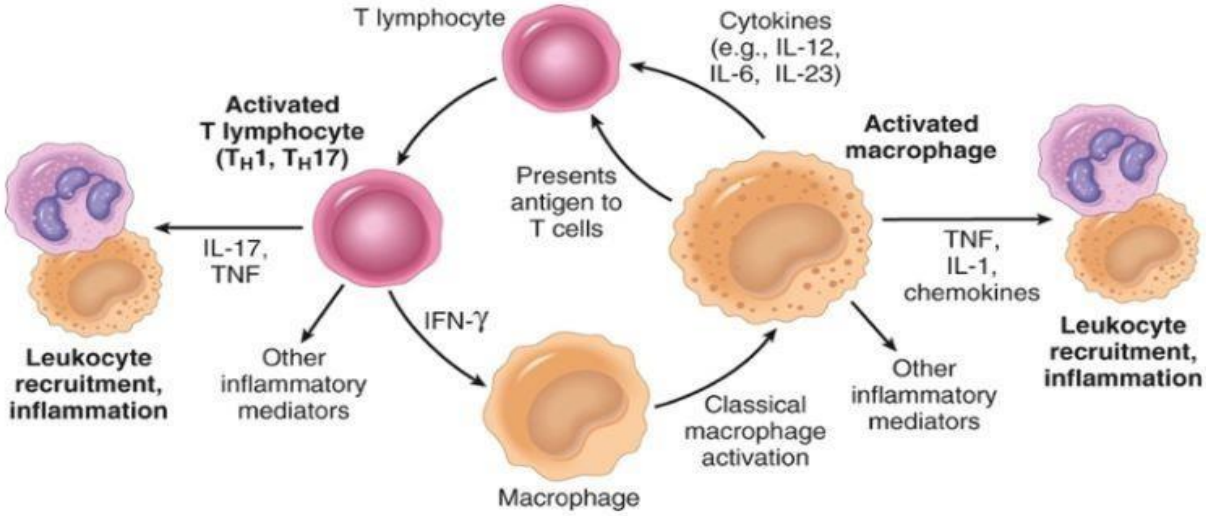
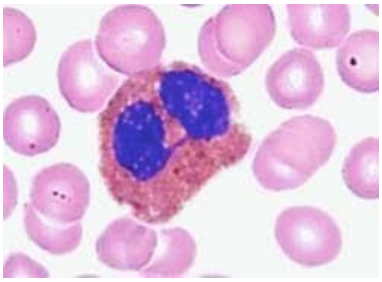


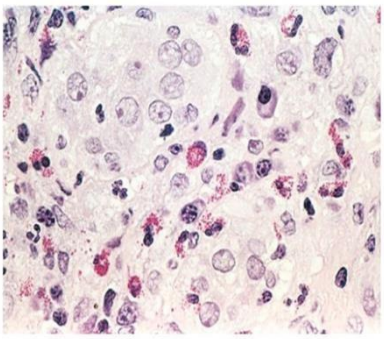

FIG. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T c...

## What was mentioned in the lecture:

This is a small cartoon to help you understand the close relationship between the neutrophils and the monocytes and how they interact very closely in the production of cytokines and recruitment in different phases of inflammation, whether in activating the monocytes in the classic pathway or at the alternative pathway, at all stages of inflammation, there's a close relationship between the neutrophils and monocytes. just try to look at this diagram a couple of times to realize the complexity and the relationship between neutrophils and macrophages, they both have similar functions, for example phagocytosis is one of the things which both macrophages and neutrophils can do.

# EOSINOPHILS:





A focus of inflammation containing numerous eosinophils.

**What was mentioned in the slide:**

- **IgE and parasitic infections**
- **Granules contain major basic proteins toxic to parasites**
- **May cause tissue damage**
- **Eosinophilic inflammation**

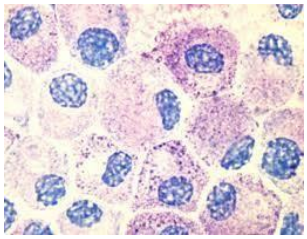
**What was mentioned in the lecture:**

let's move now to another important inflammatory cell type, they are called the eosinophils, the name came because of the eosinophilic color of the cytoplasm, their cytoplasm is pink and granulated and their nuclei are bilobed, those the hallmark features of eosinophils. This is how we recognize eosinophils whether if we examine a sample of blood (like the above figure) or a tissue (like the down figure)
This (the down figure) is a tissue image with too many eosinophils whose the cytoplasm is pink, the eosinophils are important Inflammatory cells that are closely related to IgE (immunoglobulin E) production which is an important antibody in allergic anaphylactic reactions, they are probably the main cell infiltrate whenever we get exposed to parasitic infection, so whenever we see a lot of eosinophils in the tissue we suspect either an allergic reaction or a parasitic infestations ,of course those cytoplasmic granules have major basic proteins which can be used in functions of eosinophils, however too much infiltration of the eosinophils into tissue can cause damage actually, in the last 10 to 15 years we are getting exposed to a new type of chronic inflammation which is called eosinophilic inflammation, we have sometimes something called eosinophilic gastritis where the stomach is filled with eosinophils, and we have eosinophilic esophagitis which is common mostly in children and young females, we still do not know details about this type of inflammation, but eosinophilic inflammation is a chronic specific type of inflammation, this type of inflammation that can occur in any organ.

# MAST CELLS:

**What was mentioned in the slide:**

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



**What was mentioned in the lecture:**

mast cells are part of the inflammatory cell response, they are actually abundant in soft tissues, especially in the case soft tissue tumors, whenever we receive a lipoma (a cancer in adipose tissues) or whatever soft tissue neoplasm or tumor, they are full of those mast cells, they are involved both in acute and chronic inflammation. mast cells and basophils -which are granulated types of inflammatory cells- express the FCER1 receptors which bind the Fc portion of the IgE, this binding stimulates degranulation and release of histamine from these cells, this happens specifically whenever we get exposed to food allergy, venom (like snake bites), drug allergy, etc. so they are closely related to the eosinophils function, mast cells are abundant in different types of tissues and they have actually more role in chronic inflammation than in acute inflammation by producing many cytokines, they are heavily granulated, the NC ratio is low and the color of the granule on H&E is slightly basophilic.

# NEUTROPHILS IN CHRONIC INFLAMMATION:

**What was mentioned in the slide:**

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

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

**What was mentioned in the lecture:**

as we mentioned before neutrophils or polymorph nuclear cells or mickey mouse cells' main role is acute inflammation, however, this does not mean that there is no role for neutrophils in chronic inflammation, actually, they can stay longer after the persistent continuous injury by microbes or continuous activation by cytokines, there so sometimes you can see both lymphocytes, macrophages, plasma cells, etc. as cells of chronic inflammation and there is also neutrophils in the neighborhood, you can see them frequently in cases of chronic osteomyelitis which is the inflammation of the bone and the bone marrow, osteomyelitis is mainly a chronic process, but in chronic osteomyelitis, you can see -in addition to plasma cells macrophages and lymphocytes- neutrophils, the other important point to remember is that lung damage from smoking is also mediated by neutrophils in lung tissue. Neutrophils are also seen in the cases of acute exacerbation (acute on top of chronic)

# GRANULOMATOUS INFLAMMATION:

**What was mentioned in the slide:**

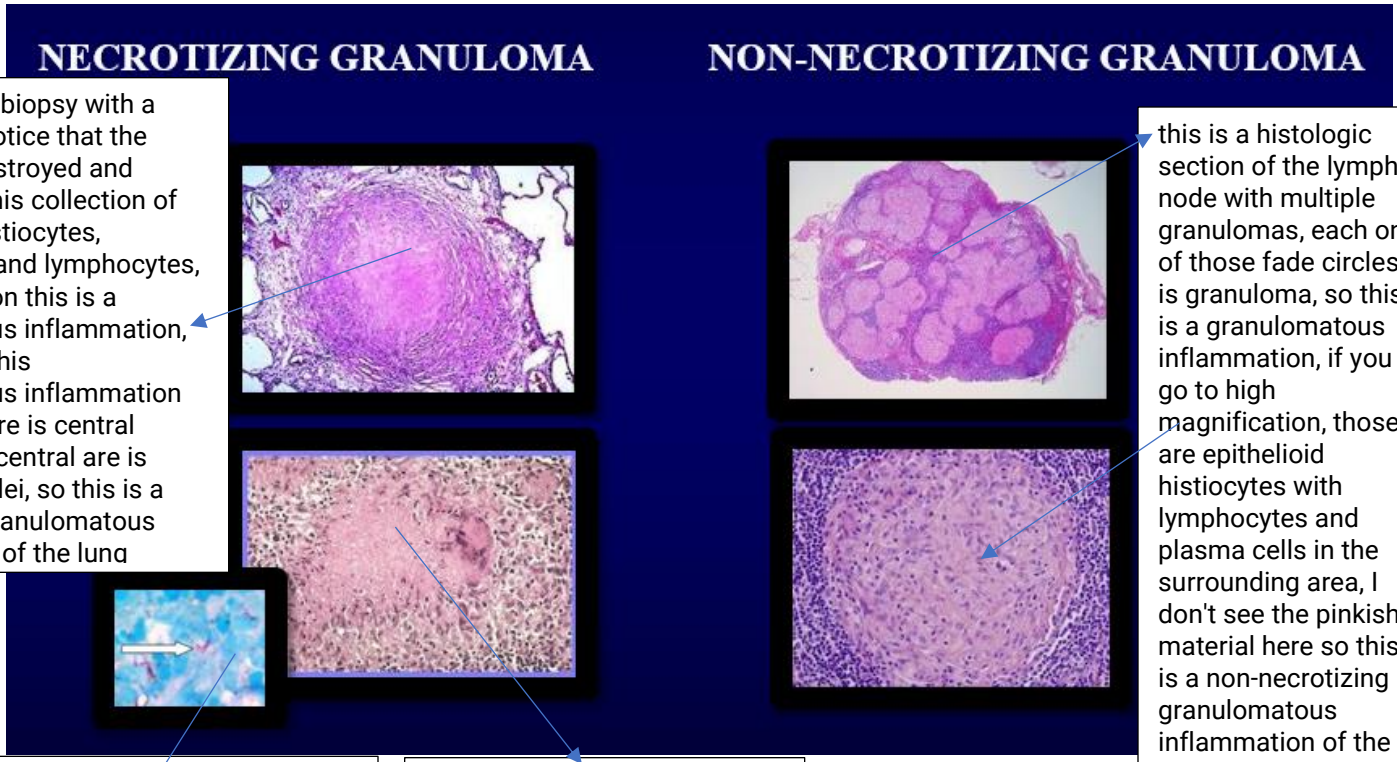
- **A form of specific chronic inflammation**
- **Granuloma: activated macrophages (epithelioid histiocytes); lymphocytes and sometimes plasma cells.**
- **Necrotizing (central necrosis) or non-necrotizing (no necrosis)**
- **Immune granulomas vs foreign body type**

**What was mentioned in the lecture:**

we move now to an important subtype of chronic inflammation; this is a topic which you all need to understand from now, granulomatous inflammation is basically a specific type of chronic inflammation, it is chronic inflammation of a specific type, and the specificity of this chronic inflammation is characterized by the presence of granulomas in the tissue, a granuloma is basically composed of activated macrophages which are called epithelioid histiocytes in addition of lymphocytes and sometimes plasma cells, so the collection of epithelioid histocytes which are activated macrophages in addition to lymphocytes and plasma cells forming a collection of those cells is called a granuloma, there

are two types of granulomas: granulomas which has central necrosis, they're called necrotizing granulomas and the other type is the granulomas which has no central necrosis, they're called non-necrotizing granulomas, in the old days they used to call them caseating granulomas and non-caseating granulomas, because the necrosis -grossly, by naked eye- looks like a cheesy material (casein means white or cheesy or milky), but the proper pathologic name is necrotizing granulomas or necrotizing granulomatous inflammation where central necrosis is present in those granulomas or non-necrotizing granulomatous inflammation, this division is critical because the differential diagnosis of these is different from the differential diagnosis of these, so whenever I have a kidney biopsy, liver biopsy, skin biopsy, lung biopsy, etc. and I see granulomas, I have to decide if these granulomas are necrotizing and there is differential for that or if they are non-necrotizing which have a different type of differential.
granulomas are not only those two types, there is something called immune granulomas, and there are foreign body type granulomas, whenever you have a foreign body entering your tissue (like a splinter), there's an inflammatory reaction, in this case, you'' see under the microscope what we called foreign body type cell granulomatous response, the immune granulomas are different, those are the ones which we see sometimes in rheumatoid arthritis, which is induced by autoimmune diseases.

# MORPHOLOGY OF GRANULOMATOUS INFLAMMATION




this is a lung biopsy with a granuloma, notice that the alveoli are destroyed and replaced by this collection of epithelioid histiocytes, plasma cells and lymphocytes, so by definition this is a granulomatous inflammation, if we look at this granulomatous inflammation and see if there is central necrosis, the central are is devoid of nuclei, so this is a necrotizing granulomatous inflammation of the lung

this is a histologic section of the lymph node with multiple granulomas, each one of those fade circles a is granuloma, so this is a granulomatous inflammation, if you go to high magnification, those are epithelioid histiocytes with lymphocytes and plasma cells in the surrounding area, I don't see the pinkish material here so this is a non-necrotizing granulomatous inflammation of the lymph node

the prototype and the top differential of a necrotizing granuloma regardless of the tissue involved is caused by mycobacterium tuberculosis, this is why whenever we have necrotizing granulomatous inflammation, we go beyond that and apply a special stain for TB and special stains for fungus
the special stain of TB is called acid fast stain or Ziehl–Neelsen staining, where the background is blue green and you can see the acid fast bacilli or the mycobacterium organisms appear as red snappers or red pink bacilli, you have to do at least acid fast stain to make sure this is not TB whenever you have necrotizing granulomas

This is another granuloma, it is composed of epithelioid histocytes, plasma cell and multinucleated giant cells, and there is a central necrosis, the way we recognize central necrosis in histology is the presence of pinkish material without blue nuclear material, so this is necrotizing granulomatous inflammation.

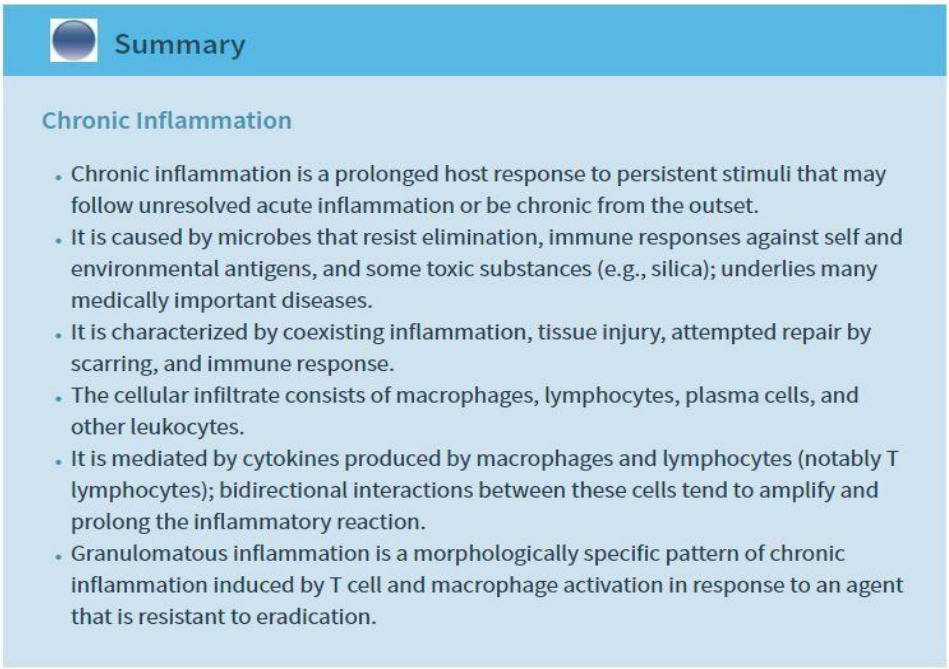
**TABLE 3.9** Examples of Diseases With Granulomatous Inflammation

| 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 |

## What was mentioned in the lecture:

this is a very important table, it has to be stuck in your mind throw your training years, this table will give you examples on diseases which causes granulomatous inflammation,
tuberculosis is on top of the list, specifically, it causes granulomas that are necrotizing or caseating.
and the second one is leprosy الجذام, which is a disease caused by another species of the mycobacterium organisms called mycobacterium leprae it causes non-necrotic granulomatous inflammation.
Syphilis مرض الزهري, ينتقل جنسيًا is also another cause of granulomatous inflammation, it is caused by a bacterium called Treponema pallidum, it causes forming of gummas, which are a certain type of granulomas.
there's also a disease called cat scratch disease, people who have cats at home can get scratched when the organism is transferred from cats to humans causing granulomatous inflammation of the lymph nodes (like we seen in the previous slide) especially the axillary and cervical lymph nodes due to the cat scratch organisms.
the other major disease which you have really to understand from now is a disease of unknown etiology, it is called sarcoidosis, sarcoidosis a disease of an unknown etiology, the major hallmark of tissue damage by this disease is the presence of non-caseating or non-necrotizing granulomas (could be in the lymph nodes) this is a disease of unknown etiology, it is characterized by the presence of non-necrotizing or non-caseating granulomas the third point which you have to remember about sarcoidosis is that it is a disease which is mainly diagnosed after exclusion, diagnosis after exclusion is a term that you will learn in your surgery and medical rotations, you do not make the diagnosis of sarcoidosis until you rule out (exclude) all other diseases, this is what we call diagnosis by exclusion.
the last disease which is characterized by the presence of granuloma is a subtype of inflammatory bowel disease, there's a certain group of inflammatory bowel diseases that affects mainly the colon and the terminal ilium, they are called inflammatory bowel diseases, there're two types: Crohn's disease and ulcerative colitis, one of the major characteristic features of Crohn's disease is the presence

of non-necrotizing granulomas in the terminal ilium, so this is why you have to do further investigation when you see a tissue with granulomatous inflammation, you have to investigate if is it necrotizing or non-necrotizing, then you have to do the organism stain to delineate the specific etiology of that disease, remember that sarcoidosis is a disease of unknown etiology, we don't know the cause characterized by the necrotizing granulomas, and the diagnosis is usually made after excluding all other causes of granulomas.




# SYSTEMIC EFFECTS OF INFLAMMATION:

## what was mentioned in the slide:

- **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** |

## What was mentioned in the lecture:

let's talk a little bit about the systemic effects of inflammation, we have eluded into that in some of the previous slides, any type of inflammation can be associated with systemic effects, mainly due to the circulating cytokines or mediators, predominantly what we call acute phase response, this is a good thing because this will make the patient sick and will push him to go to the emergency room or to the clinic to seek medical help, the acute phase response is predominantly due to multiple cytokines including tumor necrosis factor, interleukin-1, interleukin-6 and type 1 interferons, the major effects of inflammation include fever, patients with inflammation are febrile, usually 1-4 degrees higher than normal, either 38 to 41 depending on the severity of the infection or inflammation, the fever can be produced either by exogenous pyrogens, that includes the lipopolysaccharides of the bacterial membranes, or endogenous pyrogens like interleukin-1 and tumor necrosis factor, those are the two which are important in producing increased temperature or fever, them all of these exogenous and endogenous pyrogens will induce the release of prostaglandin $E_2$ which is also responsible for fever.
Also there are multiple proteins whose serum concentration increases upon inflammation, some of them we can measure their concentration in the serum, those are called acute phase proteins, on top of the list is the C-reactive protein and erythrocyte sedimentation rate, those are acute phase reactions which we can measure in the lab, they are non-specific meaning that they do not indicate a specific disease, however, they can give you an idea that the patient has severe acute inflammation.
Leukocytosis means increasing in the number of white blood cells, many of inflammatory mediators will go to the bone marrow and induce hematopoiesis, so sometimes the white blood cells count is pushed up to 15-20 Kilo, whenever you have too much or severe leukocytosis, you have to differentiate the leukemoid reaction versus leukemia, so whenever you have a young child with acute appendicitis or acute tonsillitis and you do the white blood count and the white blood count was 45 , and you look at the differential count and it was many neutrophils, then mostly this is a leukemoid reaction, the word leukemoid means leukemia-like, so it's not really malignancy, however you have to investigate these by specific delineation by immunophenotyping of the white blood cells to make sure that those are non-neoplastic white blood cells, we do usually flow cytometry in those and we reassure the patient if it is just a leukemoid reaction.
there are multiple other systemic effects, including tachycardia, increased blood pressure, chills, rigors, decreased sweating, anorexia, somnolence and malaise, all of those can be seen in different types of inflammation, some of them might present some of them might be absent, and they all indicate that the patient is sick, and the patient has an acute response, all of them are induced by the effects or the impacts of those circulating mediators.

# SEPSIS & SEPTIC SHOCK:

## what was mentioned in the slide:

- **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**

## What was mentioned in the lecture:

let's talk a little bit about septicemia and septic shock, this is a very important topic and a common disease, you will see many patients in the ICU, especially surgical, medical, pediatric, neonatal ICU, etc. sepsis (septic shock) is by definition a severe bacterial infection (bacterial sepsis), this sepsis is due to very large amounts of mediators -specifically tumor necrosis factor and interleukin-1), those are the two

major cytokines that play a major role in the production of sepsis or septic shock, this severe acute bacterial infection will lead to disseminated intravascular coagulation which is sometimes fatal, also sepsis causes a hypotensive shock in which blood pressure will drop down and the heart rate will go up, sepsis will also induce insulin resistance and hypoglycemia, all those are features of septic shock and, sepsis is an acute emergency, the patient has to be treated quickly, otherwise -if he reaches to a point of irreversible septic shock- most of the time the patient will end up with multi-organ failure and death.
it is not always caused by infectious agents, sometimes a septic shock can be induced by or caused by non-infectious etiology, for example severe cases of pancreatitis, severe cases of burns when there is like 85-90% percent of your tissues has a severe second of third degree of burn and sometimes severe cases of trauma, in all of these cases, the patient will have too much inflammatory mediator impacting all vital function causing a shock state, all these symptoms are collectively called systemic inflammatory response syndrome (SIRS).