PATHOLOGY

Medical Committee
The University of Jordan

■ SHEET

□ SIIDE

Lecture Number: 10

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Morphology of Inflammation

We talked about the mechanisms of inflammation, and we have to know that the morphology depends on the mechanisms of inflammation and changes that happen during inflammation.

Morphology means what we see under the microscope or what we see on the patient himself; so it is the study of form and structure.

You will simply see:

- Dilated blood vessels
- Edema
- Inflammatory cells

These are the main changes that happen during inflammation and are reflected by the morphological changes.

Patterns of morphology of inflammation could be classified to four types, depending on the *severity of the insult* and the *response of the tissue* (did it heal or not?)

- Serous
- Fibrinous
- Suppurative
- Ulceration

Morphology of acute inflammation

1) Serous inflammation

- Inflammation is not that severe and doesn't cause much destruction.
- Mostly fluid accumulation (edema) that will be **absorbed by lymphatics**.
- Doesn't contain many cells because it's not a severe insult and doesn't cause much destruction to the tissue.

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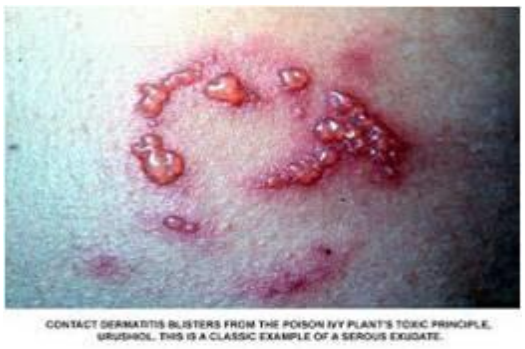
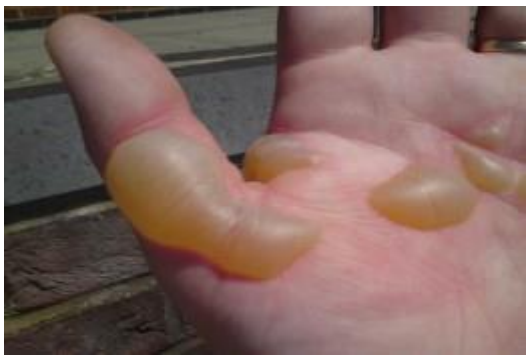
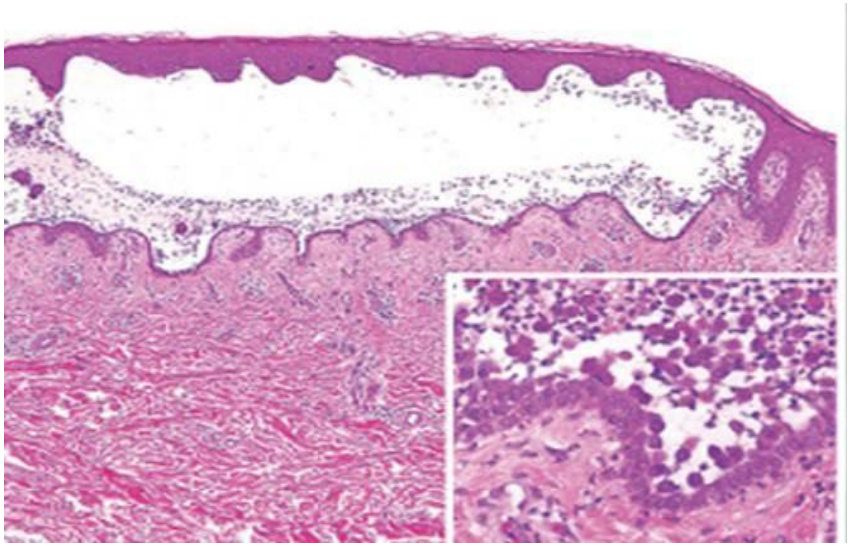
- Example:
  - *Blisters* you get from burns (while cooking, for example)



CONTACT DERMATITIS BLISTERS FROM THE POISON IVY PLANT'S TOXIC PRINCIPLE, URUSHIOL. THIS IS A CLASSIC EXAMPLE OF A SEROUS EXUDATE.



- Viewing blisters under the microscope, we can see that there's a layer of epidermis on the top, and a layer of dermis in the bottom. These two layers are separated by what looks like an empty space, but is actually fluid. This fluid contains a VERY little amount of cells, and that's mainly why it appears empty.



Histology flashback

- Exudative inflammation.
  But why not Transudative?
  1) **Inflammation** usually causes exudation.
  2) Because the serous fluid **contains proteins**, it should be exudate by definition although it contains no cells.

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Remember:

Types of edema:

Exudate: Extravascular fluid rich in proteins and cells, and is usually caused by *inflammation.*

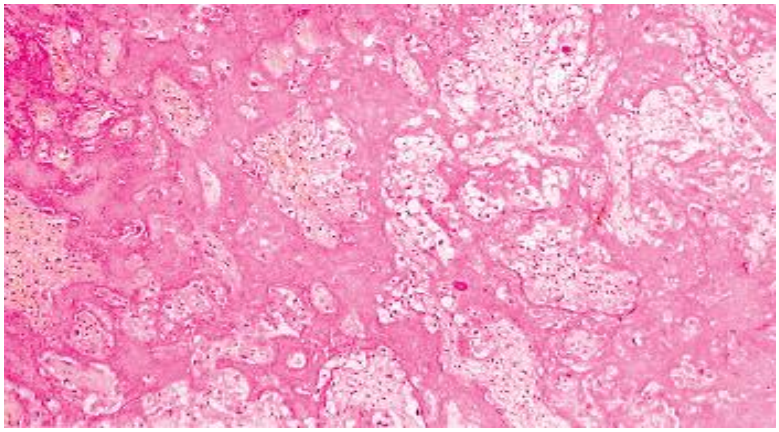
Transudate: Extravascular fluid with very little protein, and is usually due to *pressure imbalances*.

Remember that the first changes that happen in inflammation are vascular changes; so you have *increased vascular permeability* and an *increase in diameter* so you will **always** have edema regardless of the type of inflammation. Edema is one of the four cardinal signs of inflammation, and if you have edema only (fluid only) it's a serous inflammation (like blisters).

However, not all types of edema are related to inflammation; for example, transudate edema is related to pressure imbalances.

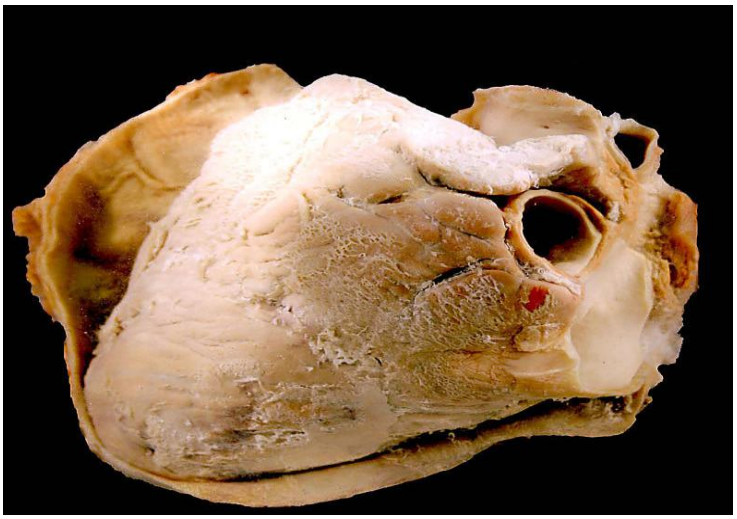
2) Fibrinous inflammation

- This inflammation is more severe than Serous inflammation.
- Fluids are present but more proteins will go out especially *Fibrin* (*you can see fibrin* microscopically and macroscopically). There are other proteins (we cannot see them because they are soluble), but Fibrin is the most visible and apparent under the microscope.
- The main cause of this type of inflammation is an increase in permeability (gaps between endothelial cells widen enough to allow a lot of proteins to get out).
- Under the microscope Fibrin (fibrinogen) has a pink, meshwork appearance(fibers). And you can also see some fluids.

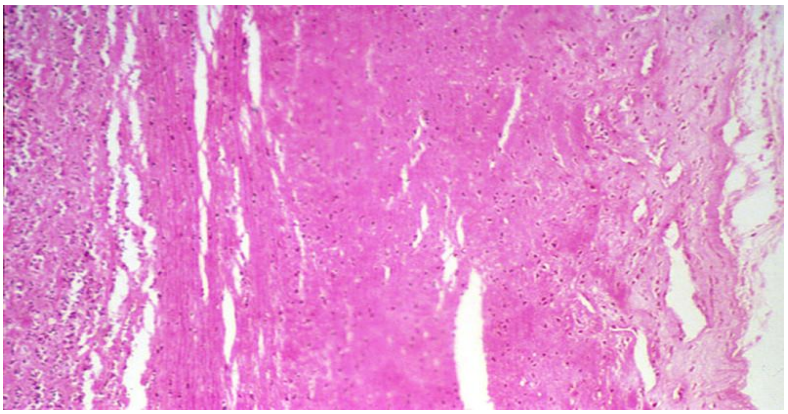


- Example:
  - *Fibrinous pericarditis*

    Fibrin is the whitish material on the surface



and this is what it looks like under the microscope:



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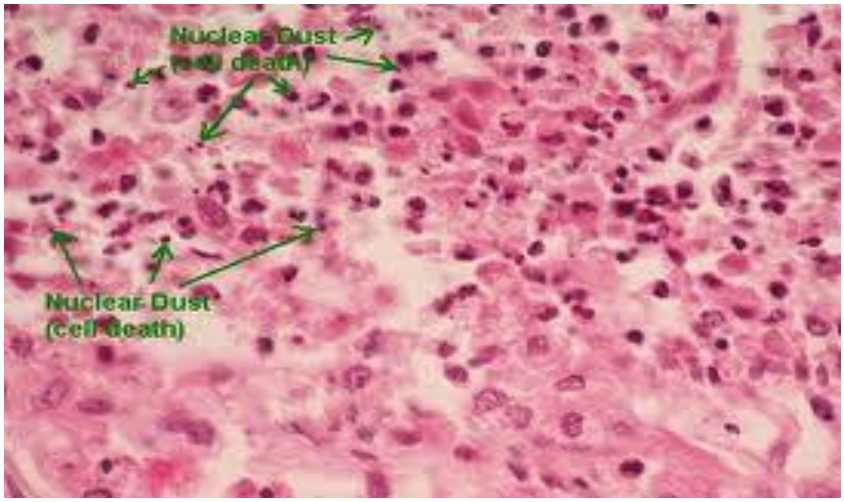
3) Suppurative inflammation

- There's ***pus***, and it is the main characteristic of suppurative inflammation.
  Pus = neutrophils + nuclear debris + fluid
- Severe inflammation caused mainly by pathogens and mainly bacteria.
- Will cause an efflux of many cells, because this type of inflammation **causes tissue destruction** so you need loads of *neutrophils* in the area of infection. This leads to more cells in the exudate and extracellular spaces which will form the pus.

- So basically:
  Tissue destruction → efflux of many cells → more cells in the exudate → Pus
- Exudative inflammation
  So we could say that pus is an exudate, formed at the site of inflammation, and contains neutrophils, nucleur debris and a protein-rich fluid.
- You'll have macrophages at a later stage because we mentioned that in this type of inflammation there's tissue destruction and cells need to be cleared by phagocytosis and so you'll need macrophages for this process.

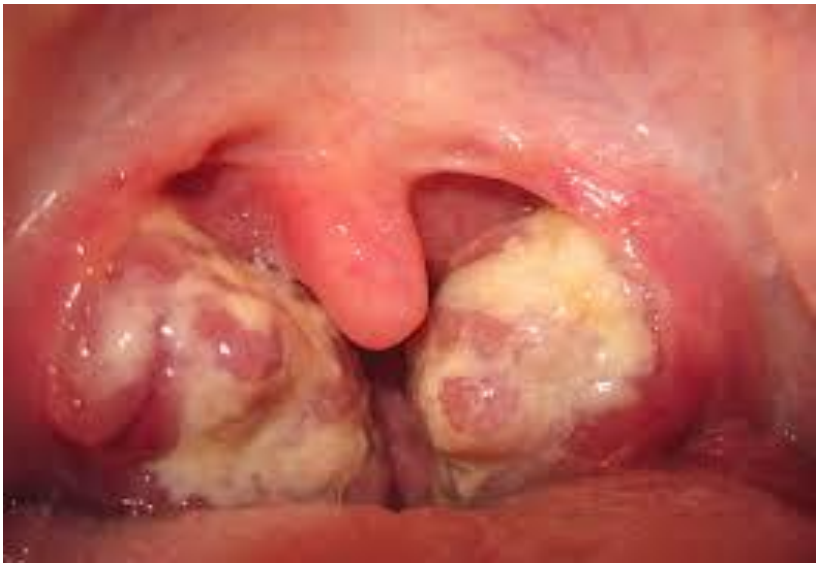
> ❖ Fluids are cleared by → lymphatics.
> ❖ Tissue destruction and cells are cleared by → phagocytosis.

- Under the microscope, you can see a lot of neutrophils and nuclear debris. Nuclear debris is basically composed of bits of chromatin and parts of ruined cells, which is why they're also called "*nuclear dust*"



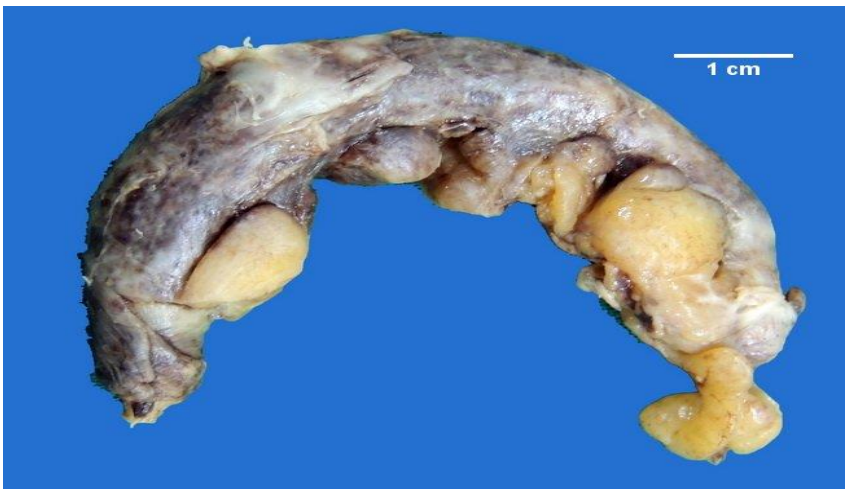
- Main cells: Neutrophils and Macrophages
- Examples:
  - *Suppurative tonsillitis*: which is caused by a bacterial infection and is treated by antibiotics.

    Looking at a picture of suppurative tonsillitis, you can see a whitish shiny material called pus.



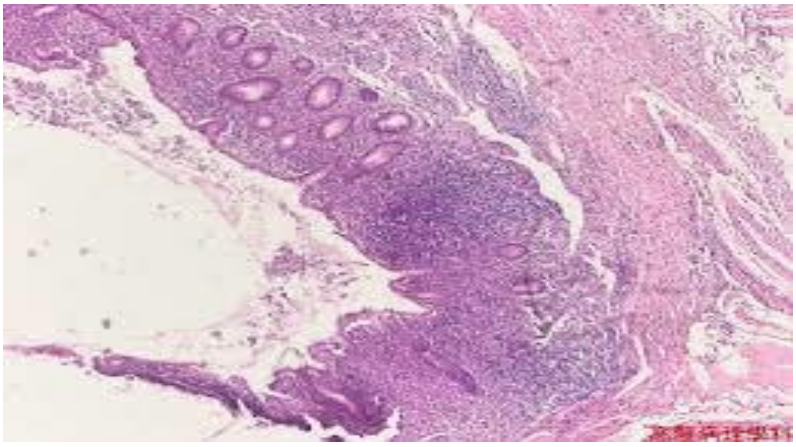
  - *Acne*: (a type of skin disease) where you have a whitish material coming out. This is called pus, and is basically fluid with nuclear dust (debris) and neutrophils.

- *Suppurative Appendicitis*: The appendix is normally formed of crypts, lined by columnar epithelium which means it secretes materials. Anything that is columnar is secretory. It also contains mucin-secreting cells.



In cases of inflammation of the appendix, you have *loads of neutrophils*.

- This is what it looks like under the microscope:



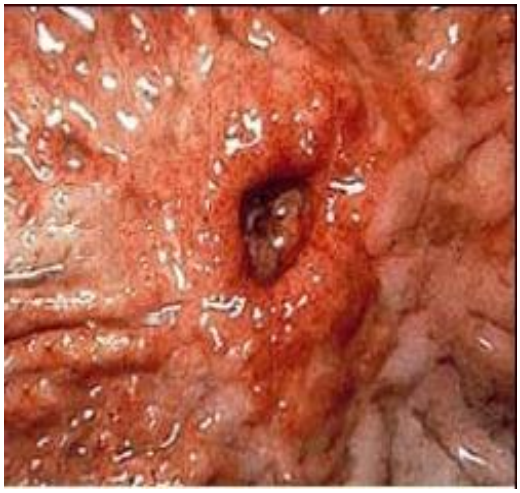
4) Ulceration

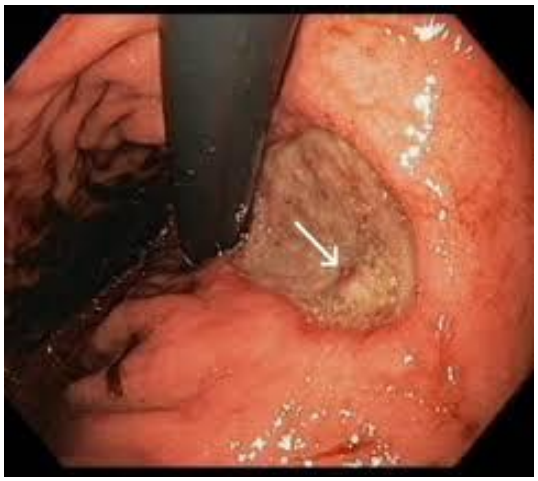
- Really severe inflammation
- An ulcer is a **local defect** caused by necrosis of cells and sloughing (getting rid of; shedding) of necrotic and inflammatory tissue, and this defect can't

be replaced by the normal tissue; so there's no complete regeneration. The defect in the mucosa can be replaced later by other processes.

- Example:

Gastric ulceration

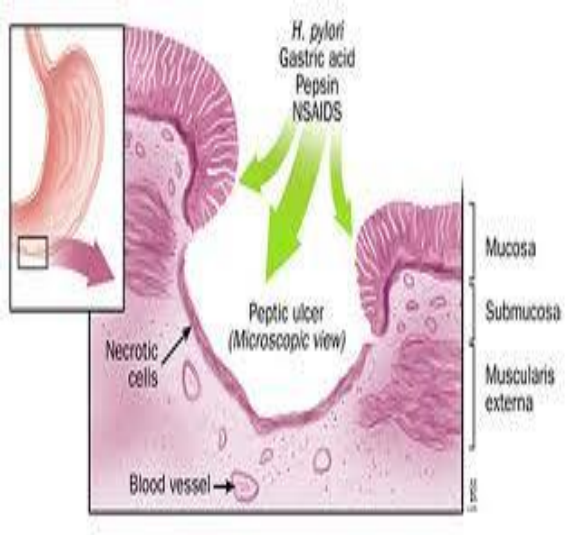




Normal mucosa is nice and shiny, but the mucosa is defected in ulcers and appears different than the mucosa around it.

Read only:
(I only added this to help you understand)

Mucosa is moist tissue that lines certain parts of the inside of your body. It is in your nose, mouth, lungs, and the urinary and digestive tracts. Glands in this tissue release a thick fluid called ***mucus***.



This person had a severe inflammation

↓

Neutrophils were recruited to the site of inflammation

↓

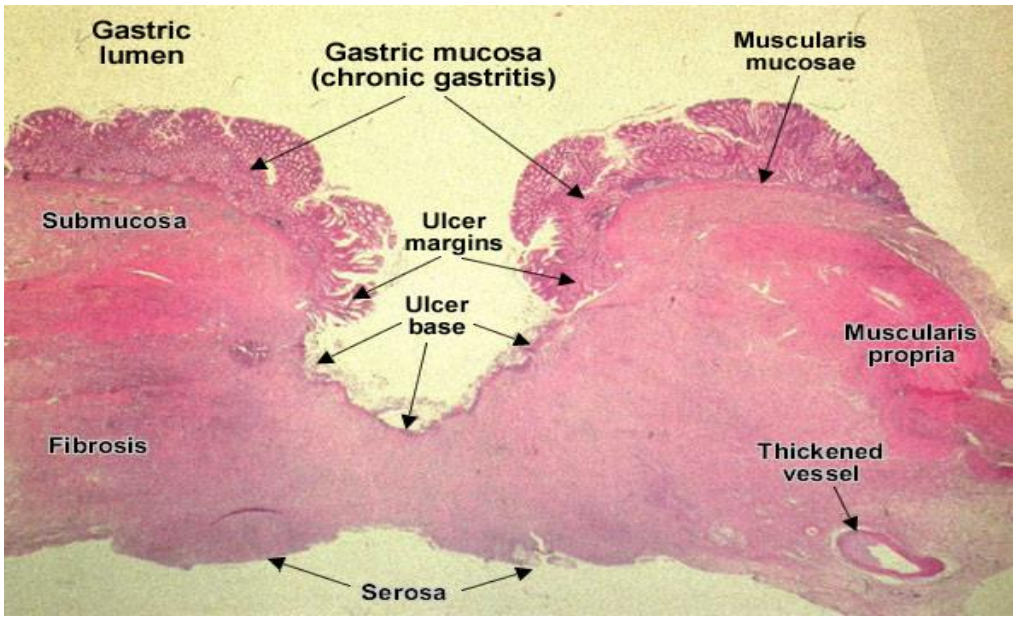
This results in necrotic tissue which was sloughed leaving a defect.

↓

Morphology involves: A red colour around the ulcer, which is the inflammation around it; appearance of defected mucosa and of course swelling.

(Redness and swelling (edema) will occur in all types of inflammation even inflammation occurring in internal tissues.)

- So again, morphologically, ulcers appear as defects differing in appearance from the surrounding area.
  Ulcers are defects.
- If there is fibrosis (replacement by connective tissue; scarring), acute ulcer will become chronic ulcer (we'll take about this later)
- CLINICAL IMPORTANCE:



An ulcer has a margin (edge) and a base, and it's very important when you start your clinical years to recognize how ulcer margins are, because **ulcers aren't always related to inflammation**. An ulcer is a defect so it could be due to any cells dying and you can have malignant ulcers, so it's very important to differentiate a benign ulcer which is an inflammatory ulcer from a malignant ulcer. And the main way to differentiate a benign ulcer from a malignant ulcer microscopically is *by looking at the margins of the ulcer.*

- So if you choose to do GI in the future and you do endoscopy and you see an ulcer, you can have an idea of the nature of the ulcer even without histology.

Regular margins → benign (most likely).
Irregular margins → malignant (most likely).

We say most likely because you can't say this is benign or malignant for sure just by looking at the ulcer, which is why you still need histology.

The doctor talks about the exam a little bit; she said that her questions will be from the material and from what she explained, but she'll try to stimulate our thinking. Her questions will mostly be clinical scenarios and they won't be difficult; if you understand the concept you will know how to answer.

Question : "There's an inflammation caused by bacteria in the tonsils, and the inflammation is severe, what do you expect the morphology to be?"

Answer : *suppurative*.

So these are the morphological patterns of inflammation and they're very easy:

1) Serous
2) Fibrinous
3) Suppurative
4) Ulceration

And they go from the least severe to the most severe, we started with fluid only (serous), and then fluid and proteins (Fibrinous), then fluid and cells (Suppurative), and the necrosis with sloughing (Ulceration), which is not replaced.

Outcomes of acute inflammation:

- **Complete resolution**
- **Healing by connective tissue (scarring)**
- **Progression to chronic inflammation**

1) Complete resolution.

We talked about acute inflammation in the previous lectures; we said that acute inflammation is simply a process that protects our bodies. So if we have an injury, we fight the injury and we get rid of the microbe. And this is the most common and most desired outcome.

If we have an injury for example, inflammation happens, and *everything goes back to normal*; fluid is absorbed, the dying cells are killed by macrophages, and healing happens.

So if you lost a mucosal cell, after healing you'll have a mucosal cell, if you lost a squamous cell it'll be replaced by a squamous cell and if you lose a columnar cell it'll be replaced by a columnar cell.

2) Healing by connective tissue (scarring)

Sometimes healing doesn't cause resolution; for example epithelial cells are not replaced by epithelial cells, they are **replaced by fibroblasts.**

Under the microscope, you can see elongated fibroblasts and fibers. While epithilal cells could be squamous, cuboidal, transitional or columnar, **fibroblasts are elongated cells**. Fibroblasts have more fibrillary material in fibrous tissue than cells do. With time, we have a *decreased number of cells and more fibers.*

When does this happen? Why do injuries go back to normal in some cases and leave scars in other cases?

Healing depends on many factors:

A) Capability of tissue cells to multiply (Location)

For example, if you have a cardiac attack you'll have necrosis in certain parts of the muscle of the heart, but myocardial cells cannot regenerate, so they can't be replaced by myocardial cells and they'll be replaced by *fibrosis* (formation of fibrous cells and fibrous tissue in a reparative process).

CLINICAL SIGNIFICANCE:

You can know if someone had a heart attack in the past just by dissecting the heart because you'll find fibrosis.

So fibrosis tells you that there was an ischemic event in the past.

B) Severity of the injury and damage happening

If the injury is *very* severe, and the tissue damage is too much, it cannot be replaced, and will be healed by scarring.

If you have a clean, surgical wound, and the margins are nicely tied to each other, then you'll have resolution.

But if the defect is more than that, some of it will be replaced by normal tissue and some of it will be replaced by fibrous tissue causing fibrosis.

C) Type of injury

D) Ability of lymphatics to get rid of fluids

Let's take *pleural effusion* (is excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs) as an example. In pleural effusion (which is a very severe type of effusion) you have abundant fluid that can't be cleared; loads of excess fluids build around the lungs. In this case you have a very little amount of cells.

The excess fluid results from the *lymphatics not being able to clear the large amount of fluid that can cause fibrosis.*

Causes of fibrosis in the lung:

1) Previous pleural effusion
2) *Asbestosis*; caused by a material known as asbestos.
   If you have a patient with fibrosis you need to ask about the history of asbestos exposure. Inhalation of asbestos particles causes asbestosis

   A student asked what Asbestos is, and the doctor said that it's a chemical material that was mainly used in buildings that have roofing..
   Asbestosis can end in Mesothelioma (a type of lung cancer) years and years later.

3) Progression to chronic inflammation

In this case, inflammation is not resolved and will become chronic inflammation.

And this happens when the body can't get rid of the injury simply because the *body can't phagocytose the agent*.

Examples:

* ***Tattoo pigments***

In this case there is an inflammatory response; the macrophages *try* to get rid of the pigments but they cannot. So the pigment will stay there and will become a chronic response, and there will be a continuous influx of macrophages.

* ***Uric acid crystals***

Again, the macrophages cannot destroy these crystals because they haven't any enzymes to destroy the crystals and this will cause a continuous process; it'll change to chronic inflammation.

* ***Autoimmune diseases***

Where we cannot get rid of the causative agent because our immune system is attacking and recognizing its own tissues, leading to a continuous process and chronic inflammation.

So to sum up:

The outcomes of acute inflammation are:

1) Complete healing
   - ❖ If the injury is limited or short-lived
   - ❖ Little tissue destruction

     These two points are really important because even if you have short-lived injury but too much tissue destruction the outcome will be fibrosis.
   - ❖ The body gets rid of the fluid → by lymphatics

     And it gets rid of necrotic tissue and the cells like neutrophils and leukocytes → by phagocytosis

2) Healing by fibrosis (connective tissue)
   - ❖ You'll end up with a scar
   - ❖ Happens if there's *significant tissue destruction*, or *if the tissue can't regenerate* (like the myocardium), or *if you have abundant fluid that can't be cleared* (like pleural effusion).

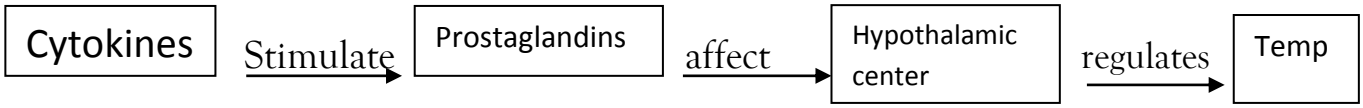
3) Progression to chronic inflammation

Systemic effects of inflammation:

Inflammation is a localized process but the mediators in inflammation can cause systemic effects and collateral damage so that all the body will be involved. These effects are:

- Fever
- Increase in serum proteins
- Leucocytosis
- Pain

1) **Fever:**



Cytokines stimulate Prostaglandins, and Prostaglandins affect the hypothalamic center, which regulates temperature.

Scientists assumed that in simple organisms fever results in fighting off the microorganisms, because microorganisms live at a certain temperature and if you change this temperature the microorganism will die. So it is thought that we evolved from these simple organisms and that's why we get fevers (So it is thought that fever can fight microorganisms).

2) **Increase in serum proteins:**

There are several serum proteins that increase during inflammation, and this is a very important clinical point.

These proteins include:

- CRP (C-reactive protein)
- Fibrinogen
- Serum amyloid

CLINICAL SIGNIFICANCE:

If you have a patient with a disease and you don't know if this disease is inflammatory or not, you take a serum sample from that patient and you measure these serum proteins.

High level of proteins → this patient most likely has inflammation.

CRP is the most important serum protein clinically, because it gives you a clue if there's inflammation or not.

If you have someone with a problem in his knee, and you want to know if this problem inflammatory or not, you measure the level of CRP in the serum…

High level of serum CRP → you know that the problem in his knee is most likely of inflammatory nature.

These proteins are **secreted for opsonization**, but we use them clinically to recognize inflammatory reactions.

3) Leucocytosis

Leuco = Leukocyte (White blood cell)
So we have an increase in white blood cells

Increased Neutrophils → acute inflammation Increased lymphocytes → chronic inflammation Increased Eosinophils → most likely an allergic reaction

CLINICAL SIGNIFICANCE:

The **CBC test** (Complete Blood Count) concentrates on the number of Neutrophils, Lymphocytes, Basophils and Eosinophils. The number of macrophages isn't shown in the test.

Cytokines	Increase →	The production of White blood cells from their bone marrow precursors.

Cytokines increase the production of WBC from their bone marrow precursors.

A question that might come in the exam:

Cytokines do all the following **EXCEPT**:

You should know that Cytokines stimulate <u>all chemical processes of inflammation</u> (including chemotaxis and stimulation of complement proteins) except one process (which is physical), this process is called: ***Margination***

Leucocytosis is important in diagnosis of Leukemia and differentiation between Leukemia and inflammation.

How?

Leukemia → VERY high WBC count and <u>immature</u> Leukocytes which indicates that there are problems in the precursors in bone marrow.

Inflammation → Loads of white blood cells but they are all <u>mature</u> because cytokines are stimulating the precursors to produce mature white blood cells.

4) <u>Pain</u>

Produced by Prostaglandins, Cytokines (IL1) and Kinin.

"YOU ARE WHAT YOU BELIEVE YOURSELF TO BE."
— PAULO COELHO