Pathology

Modified slides no.1 V2

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Outlines:

- Reversible injury.
- Irreversible injury (necrosis).
- Clinical implications.
- Patterns of necrosis.

- The distinguishing factor between reversible and irreversible cell injury is the cell being able to return to its original state when the injurious agent is removed.

Reversible and irreversible cell injury

cell injury and adaptations

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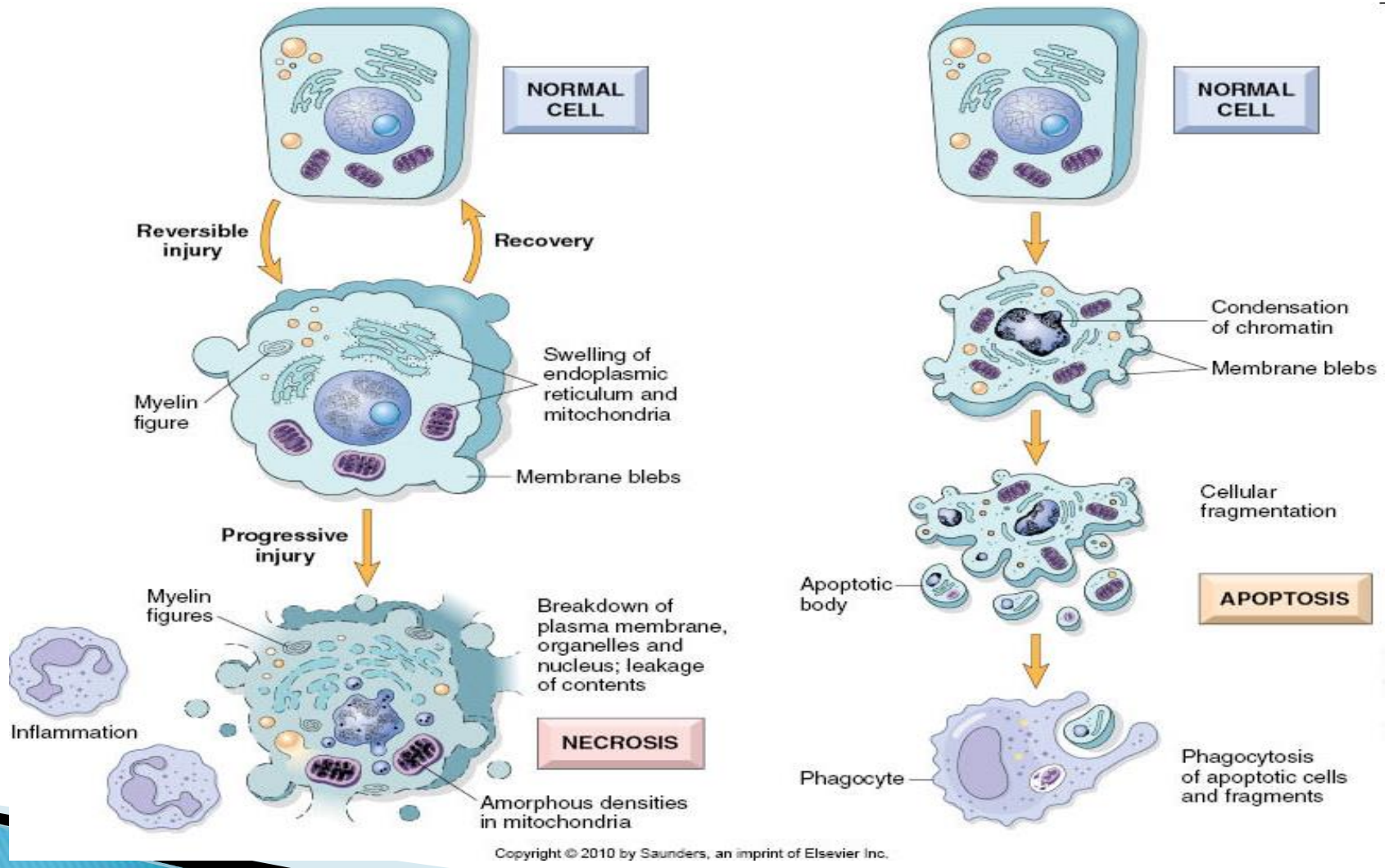
Cell injury:



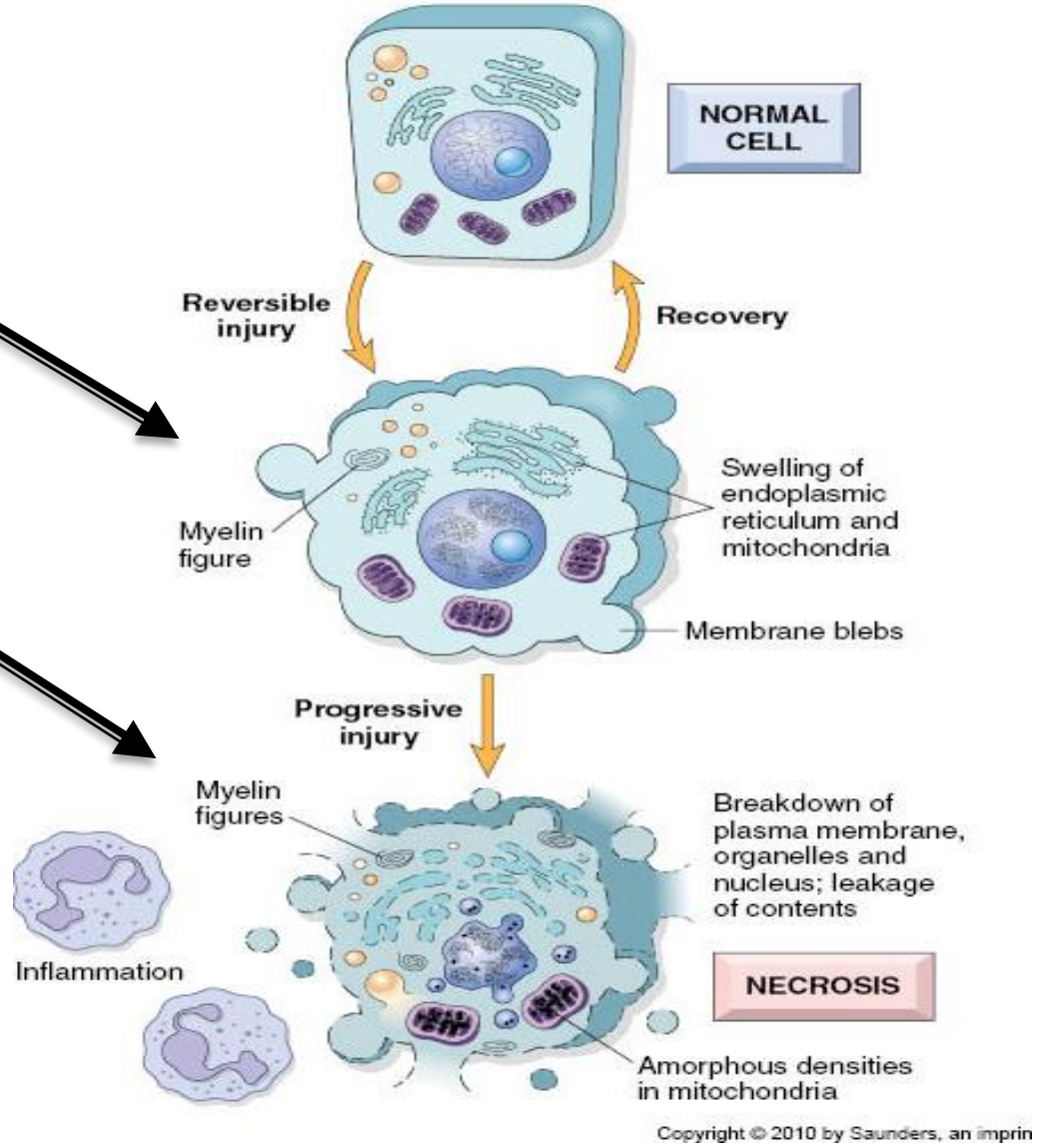
- When the cell is exposed to any injurious stimulus (more than what the cell can adapt to), it will first undergo reversible injury.

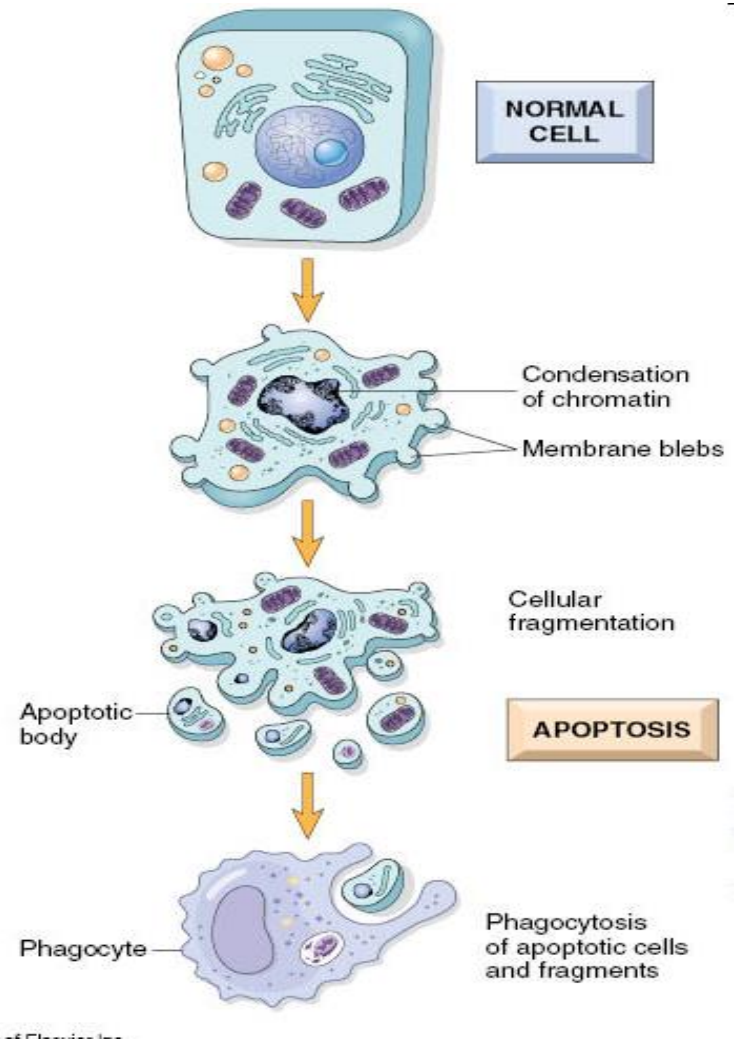
- As we can notice, the cellular membrane and the organelles (such as ER, and Mitochondria) have swollen due to the accumulation of water or fluids, though they remain intact. So if the injurious agent is removed, the cell will return to its normal functions.

- However, if the injury is progressive, prolonged, or is very severe; the cell will enter into the irreversible cell injury phase, which is often called "Necrosis" or "Cell Death".

- What distinguishes irreversible injury from reversible injury is that in irreversible injury:

1- Cell membrane will be disrupted and there will be discontinuities in the membrane like a ruptured balloon.
2- The organelles' membranes are disrupted.
3- the cellular contents will leak outside, the nucleus will start to disappear.
4- inflammatory cells will detect the dying cell and Its contents, then it will engulf them through an inflammatory response to remove them.





- The other type of cell death which does not go through reversible/irreversible injury (and will be discussed in following lectures) is Apoptosis.

- As you can see, there are multiple differences in the pathway which the cell goes through, the main being:

-1) The cell doesn't swell up, but itrather shrinks and decreases in size.

-2) The shrinking isn't coupled with the disruption of cellular membrane as it remains intact.

-3) The cell will fall off like عنقود العنب into small apoptopic bodies, in which every apoptotic body is a part of the cellular membrane with enclosed cellular contents of organelles or nuclear material for example.

-4) At the end, the cell will disappear by the inflammatory cells which will come to engulf the cellular debris without causing or provoking a large or tense inflammatory response like the one in Necrosis.

- The professor emphasized that knowing the differences between all cell injuries is important

- NOTE:
- So we have two patterns of cell death: necrosis and apoptosis

Reversible injury

- If the damaging stimulus is removed >>>injured cells can return to normal

- **Morphology:**
- Cellular swelling/organ swelling
- Fatty change

NOTE: (morphological changes)

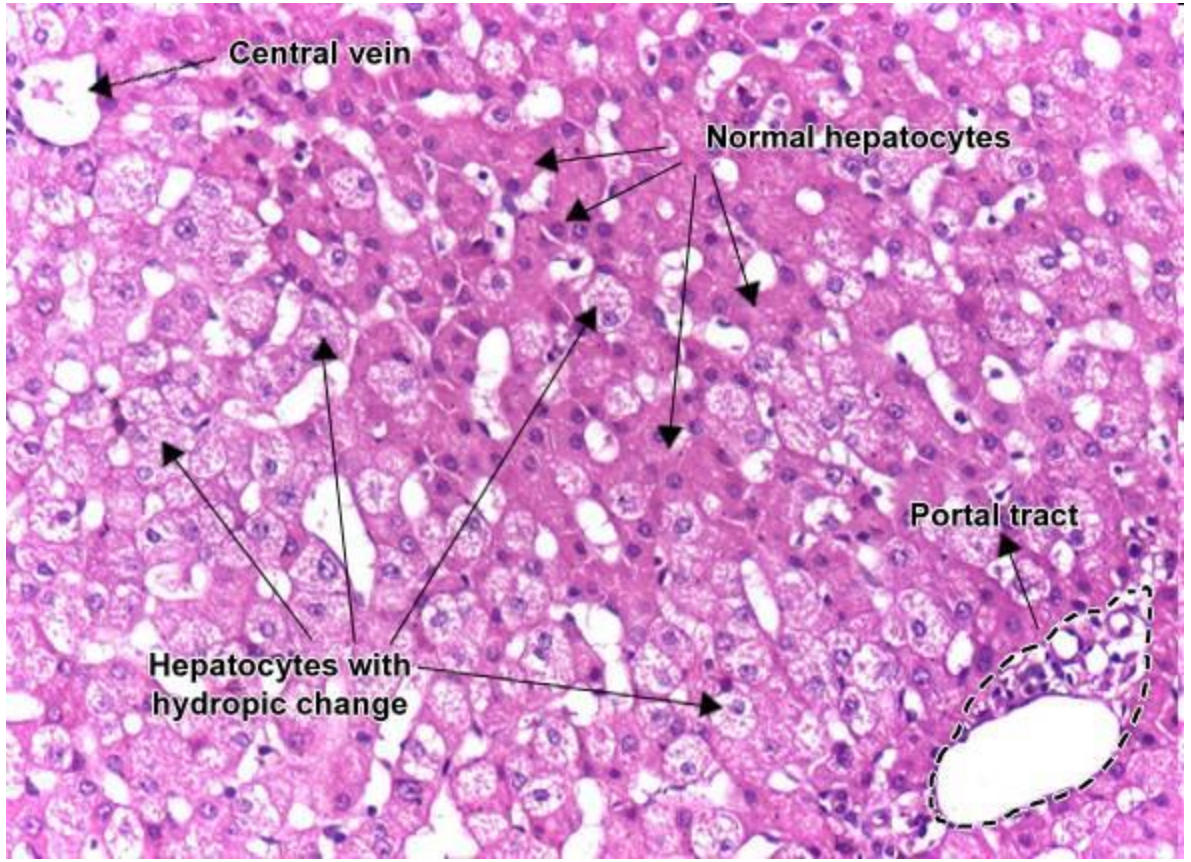
- Morphology changes could both be Macroscopic (seen by the naked eye) or Microscopic (seen only through microscopes), which could either be seen with a a Light Microscope (LM), or an Electron Microscope (EM).
- The ultra-structural changes can only be seen by the EM.

NOTE:

- Organ swelling reflects cellular swelling.

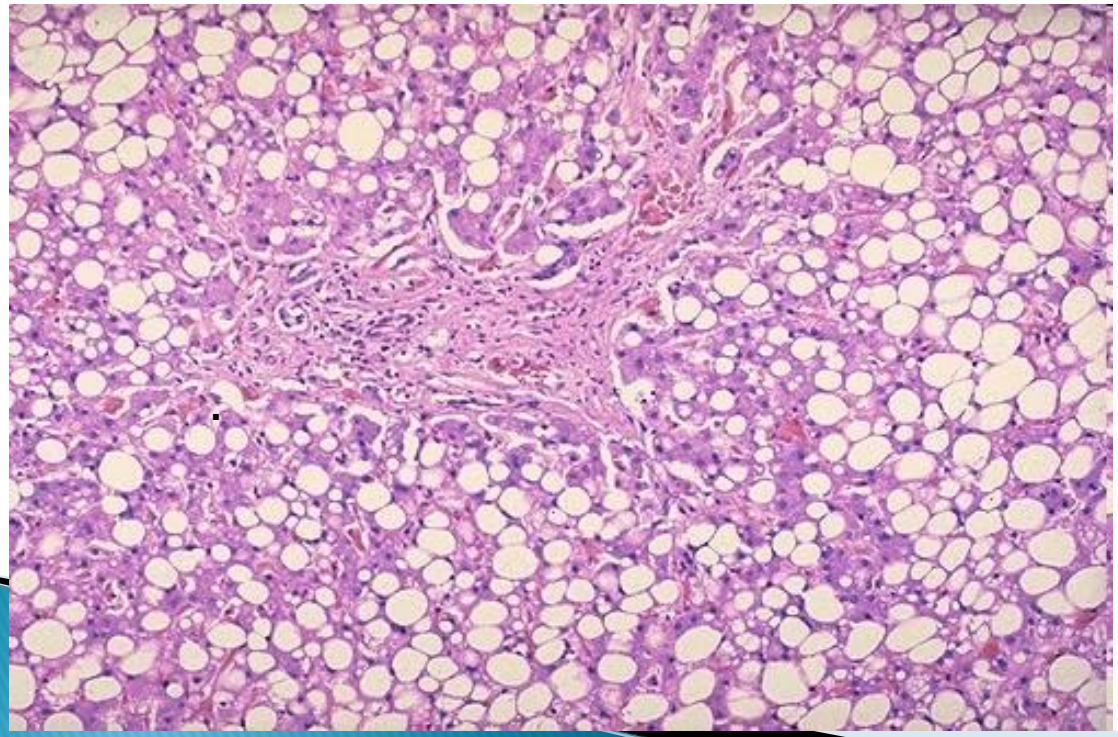
Reversible damage – cellular swelling

- The following image is an example on cellular swelling (which as we said is due to accumulation of water/fluids) in the liver.
- We can see that the Hepatocytes are undergoing 'Hydropic' change (swelling due to influx of water and accumulation of water content within the cell).
- Normal Hepatocytes (as indicated in the picture) have a pinkish stained cytoplasm, while the injured Hepatocytes with hydropic changes have a more whitish or bubbly cytoplasm.
- The question as to why there's water accumulation in the cell would be explained more in detail afterwards, but basically it is caused by the failure of the Na^{2+}/K^{+} ATP–dependent pump within the cell membranes (because the injured cell can't produce ATP) ➔ which causes intracellular sodium accumulation ➔ which increases intracellular osmotic pressure ➔ which drives and attracts water to the inside of the cell.



Reversible damage – fatty change

- This damage happens more to organs/cells that deal with Fat metabolism.
- As we can see on the macroscopic level (the image on the right); the image shows a section of the liver with fatty yellowish greasy cut surface. Also, the liver will indeed be enlarged.
- On the Microscopic level (the image on the left), the damage is reflected by the appearance of white lipid-rich droplets inside the cytoplasm of cells. The intracellular fat accumulation will also be discussed in more detail later.



Other changes

- (1) plasma membrane alterations (blebbing, blunting)
- (2) mitochondrial change (swelling and black densities);
- (3) dilation of ER
- (4) nuclear clumping of chromatin.
- (5) Cytoplasmic myelin figures

- These changes are seen with an EM.

1) Plasma membrane will remain intact as this is Reversible damage
2) --
3) Soon after dilatation of ER, its Ribosomes would begin to detach
4) Again, the Nucleus will remain intact
5) The Myelin figures are produced from the disruptions of the membrane of the cell and the membrane of the organelles.

These changes are also seen in irreversible cell injury in a much more advanced and severe form

Irreversible injury (necrosis)

- NOTE: Important defining features of the cell irreversible injury:

1. **Irreversible Mitochondrial dysfunction**
2. Loss of **plasma membrane and intracellular membranes** >>> cellular enzymes leak out
3. Loss of **DNA and chromatin structural integrity**.

- Local inflammation.
  - Which Always accompanies Necrosis

- NOTE:
- Because the mitochondria is the ATP factory in the cell; there would be no ATP generation at all.

- Even organelle enzymes and proteins will leak out the cell (they will leak to the cytoplasm, then to the outside of the cell.
- Intracellular enzymes can gain access to the bloodstream and we can detect them by certain laboratory investigations, as will be discussed later on.

Morphology irreversible injury (Necrosis)

- NOTE: the mentioned morphological changes are mainly electron microscopic morphological changes.

- Increased cytoplasmic eosinophilia.
- Marked dilatation of ER , mitochondria
- Mitochondrial densities.
- More myelin figures.

- **Nuclear changes:**
- **Pyknosis**: shrinkage and increased basophilia;
- **Karyorrhexis**: fragmentation of nuclear material.
- **Karyolysis**: basophilia fades (degradation of nuclear material)

- Increased cytoplasmic eosinophilia (pinkishness when using H&E stain, the routinely used stain in the laboratory) can be observed by the LM.
- Increased eosinophilia means more binding to eosin and less binding to haematoxylin; and it occurs in the necrotic cell due to:
- 1) A lot of degraded or denatured proteins in the cytoplasm which will bind the eosin.
- 2) Decrease of the transcription and the translation of proteins in the cell; because it is a nonfunctional cell ➔ so, the RNA will be decreased in the cytoplasm (RNA binds to haematoxylin which gives the cell a bluish color under the LM (we call the bluishness basophilia)) ➔ loss of bluish color (basophilia) ➔ more eosinophilia.

- NOTE: because of more damage of the membranes and membrane phospholipids ➔ which will lead to the accumulation of the meylin fatty materials inside the necrotic cell.

Nuclear changes:

Pyknosis: shrinkage and increased basophilia;

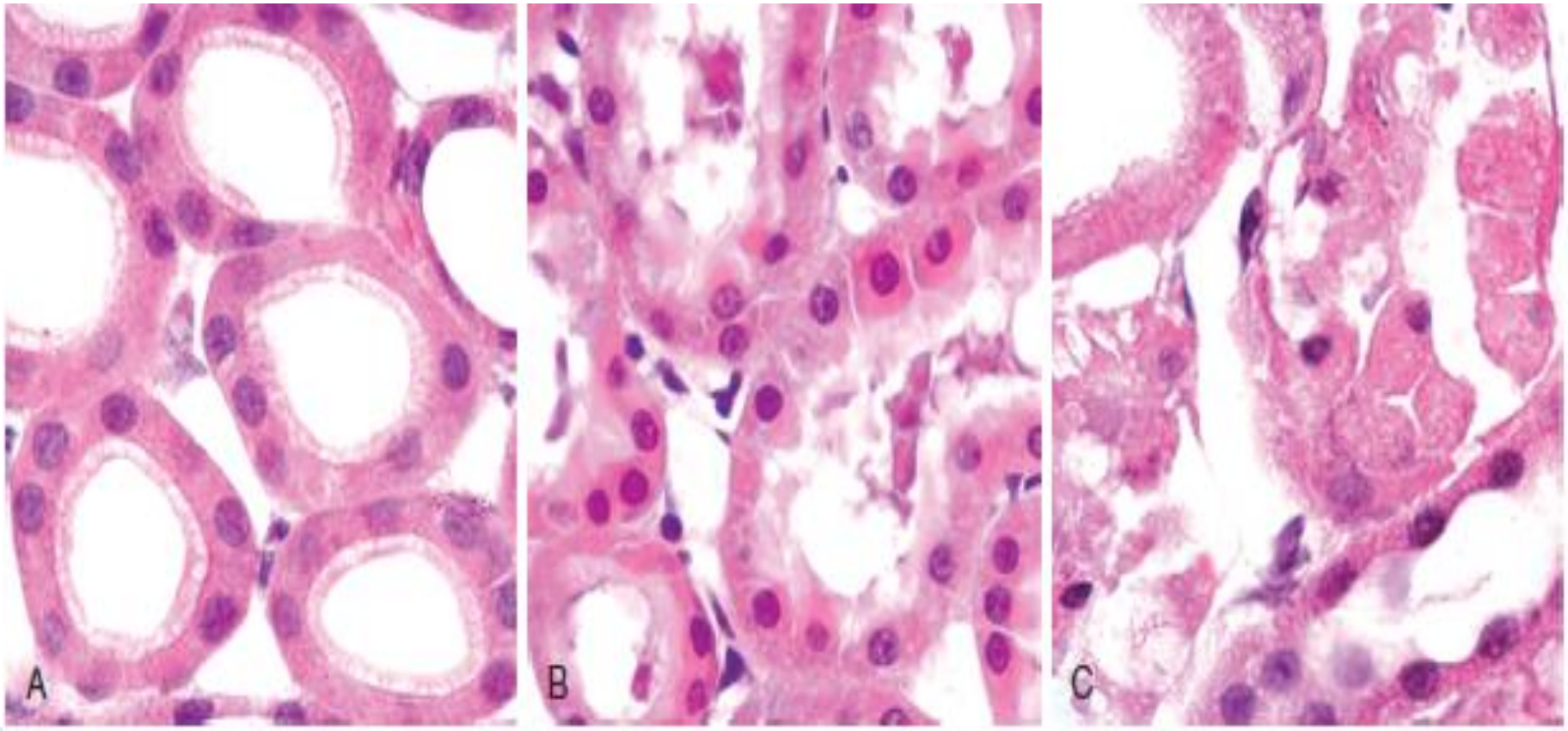
Karyorrhexis: fragmentation of nuclear material.

Karyolysis: basophilia fades (degradation of nuclear material)

- The complementing this slide:
- Necrotic nuclear changes can be observed under the LM by H&E stain.
- Basophilia: dark blue colorization under the LM.
- Karyolysis: degradation of the nuclear material and the fading of the nuclear basophilia.

Normal, reversible and irreversible cell injury

- Normal
- Reversible
- Irreversible



- Lost nuclei, DNA & the nuclear material.
- Cells are disrupted Nucleus disappears /fades.

- Cells look swollen
- Nucleus intact

Cell death

- Different mechanisms, depending on nature and severity of injury.

- Also depends on the status of the cell.

- **Necrosis:**
- Rapid and uncontrollable.
- Severe disturbances
- Ischemia, toxins, infections, and trauma

- What are the causes of necrosis?

- When cells are programmed to die because of aging.
- We also call apoptosis "Clean cell suicide" because there will be no inflammatory reaction at its site.

- Apoptosis is associated with less severe forms of injury, for example:
- 1) UV light-induced sun damage to the cells.
- 2) Aging of the cells.
- 3) Loss of the growth factor (GF) signal that reaches the cell.

- **Apoptosis: (Cell Suicide)**
- Less severe injury.
- Regulated by genes and signaling pathways
- Precisely Controlled.
- Can be manipulated.
- In healthy tissues.
- Clean cell suicide.

- Just like the uses of chemotherapeutic agents in the management of cancers.

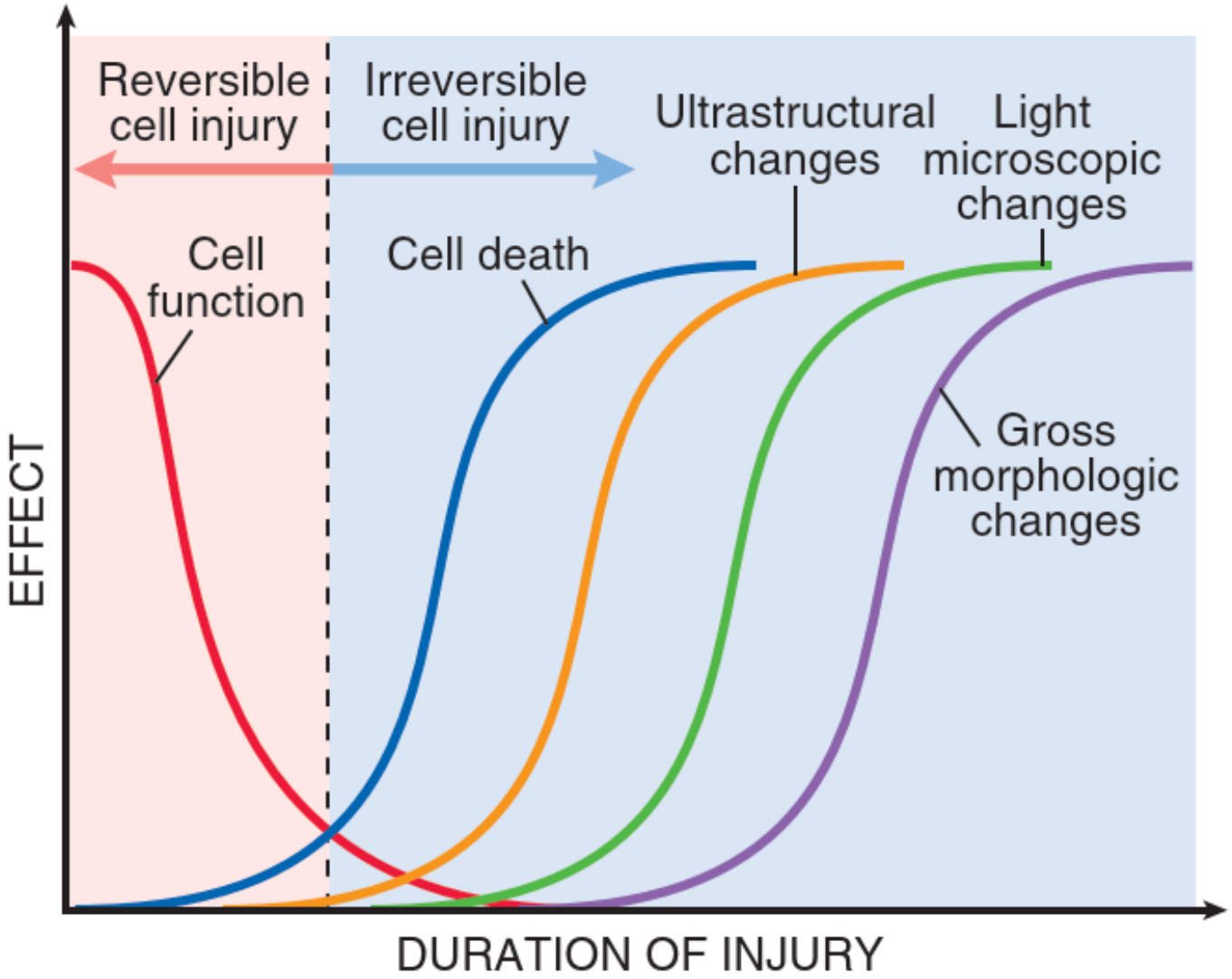
- **Necroptosis.**

- A mixture of necrosis and apoptosis at the same time.

- The injured cell is always malfunctional.
- Loss/Decrease in function is a shared feature of both, reversible and irreversible injury.
- After the onset of injury, as you can see in the graph, the cell function will begin to decline.

- Regarding the chronological order of the cell injury:
- The Ultrastructural changes are the first to appear (under EM), followed by Light microscopic changes, and then, in the end, the gross morphologic changes on the organ level.

- So, it takes time to see gross morphological changes on the organ with the naked eye, while the ultrastructural changes are the first to appear.



- This table is important as it summarizes the differences between Necrosis and Apoptosis in a simplified manner:

Table 1–1 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic; means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

DNA, deoxyribonucleic acid.

Clinical implications

- NOTE:
- It is important to detect the site of injury

- Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a means of detecting tissue-specific necrosis using blood or serum samples.

- Cardiac enzymes, liver enzymes.

- NOTE:
- When the cell is dead or the plasma membrane is injured ➔ the cellular content and the cellular enzymes will leak out the cell and they will gain access to the bloodstream.
- We can detect these tissue-specific enzymes and infer (or know) what bodily tissue is injured.

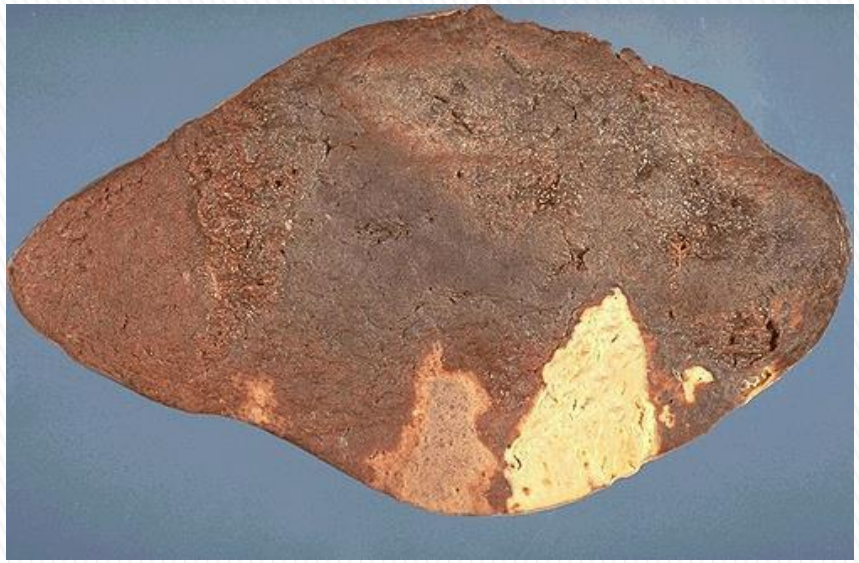
Morphologic Patterns of tissue necrosis
(Etiologic clues)

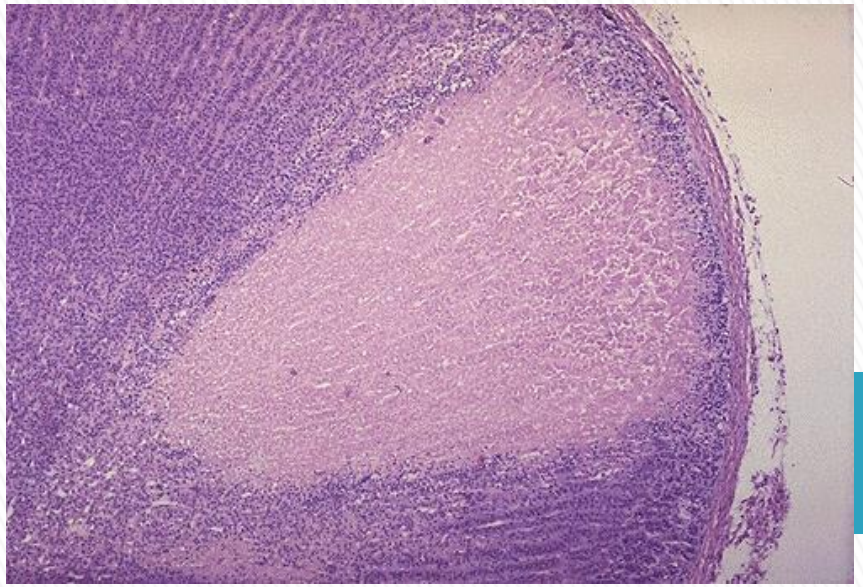
- NOTE:
- Morphological patterns can be used to know the cause of the injury or have an idea about it at least.

- The complementing this slide:
- Examples of conditions where we detect cellular contents or enzymes of an injured cell in the bloodstream:
- 1) Myocardial injury (after a cases of myocardial ischemia or myocarditis): we can make sure that a patient has myocardial injury by detecting the cardiac enzymes in the blood and see if they are elevated.
- 2)Hepatic injury (hepatic toxicity because of certain drugs or because of viral infections(viral hepatitis)): we can make sure that a patient has hepatic injury by detecting the hepatic enzymes AST & ALT in the blood.

Coagulative necrosis

- Conserved tissue architecture initially.
- Enzyme dysfunction.
- Anuclear eosinophilic on LM
- Wedge shaped (following blood supply)
- Leukocyte lysosomal enzymes and phagocytosis required for clearance.
- Ischemia to all solid organ (**infarcts)** except the brain



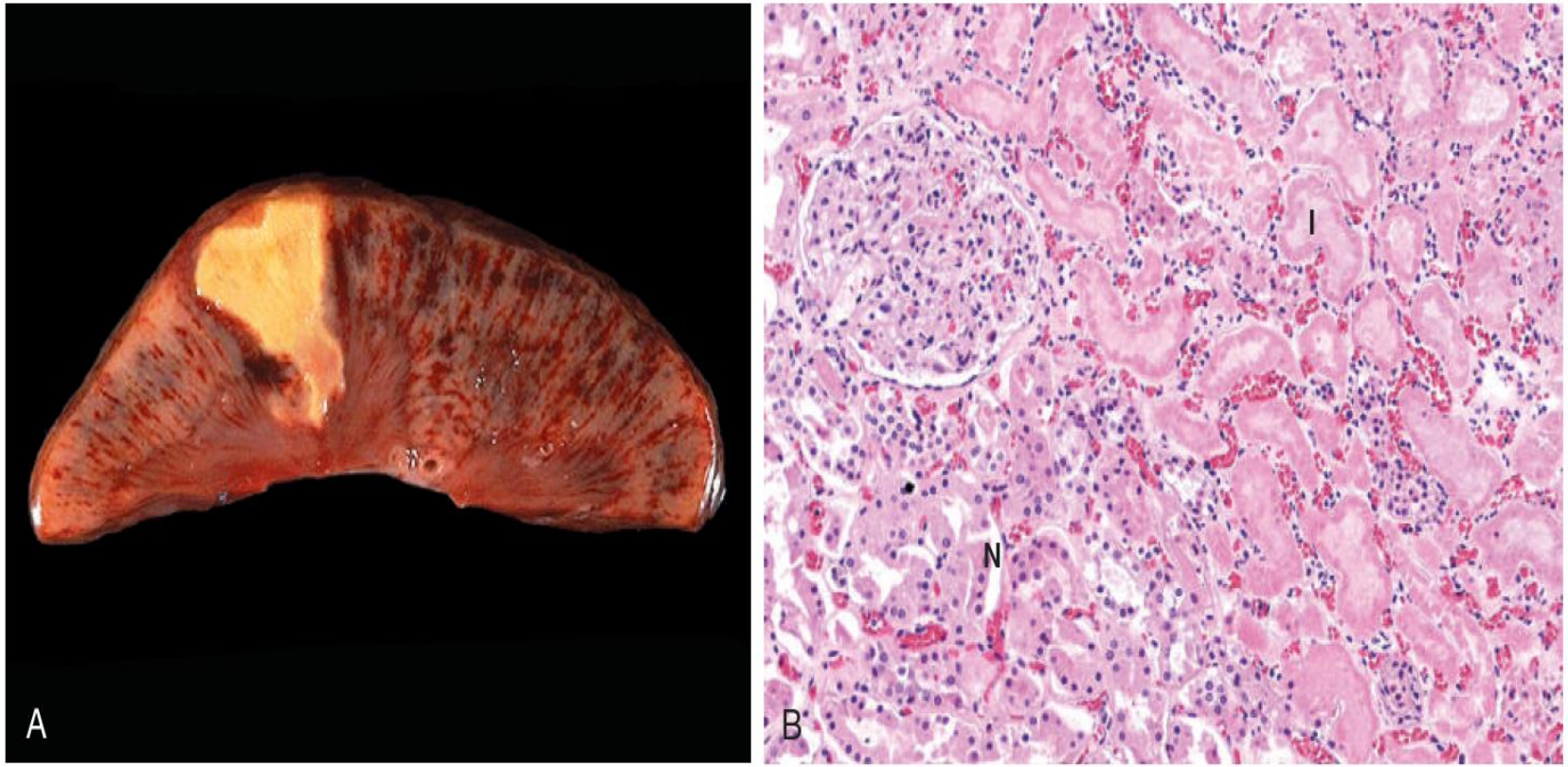


- NOTE:
- It is called coagulative necrosis because the tissue architecture is conserved initially for a few days before the onset of inflammation which will damage it.

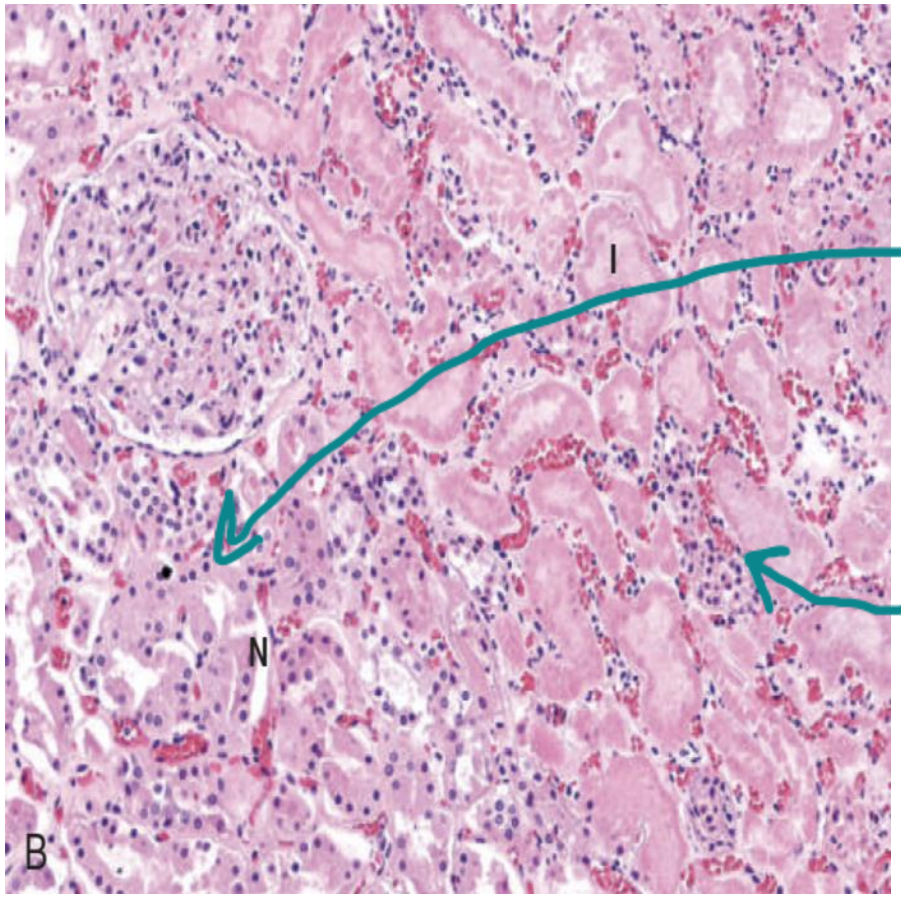
- The complementing this slide:
- Macroscopically, at the level of the organ; the coagulative necrosis area will appear pale ➔ because the underlying mechanism of coagulative necrosis is ischemia (loss of blood supply).
- So, the wedge-shaped area of pallor is due to the cut of blood supply.
- In the wedge-shaped area the cells are devoid of nuclei because they are dead cells.
- Now, why the architecture of the damaged tissue is conserved? That is because ischemia causes enzymatic dysfunction ➔ degradative enzymes will be nonfunctional ➔ dead cells won't be degraded & they will preserve their shape for at least few days (1-3 days) before the onset of inflammation.
- Later on when the blood supply comes back; the neutrophils and inflammatory cells will start the process of phagocytosis and clearance of the dead cells.
- Ischemia to all solid organs result in coagulative necrosis, except in the brain which will result in another type of necrosis.

Coagulative necrosis

- NOTE:
- An example of coagulative necrosis in the kidneys:



- NOTE:
- Notice the wedge-shaped pallor macroscopically!

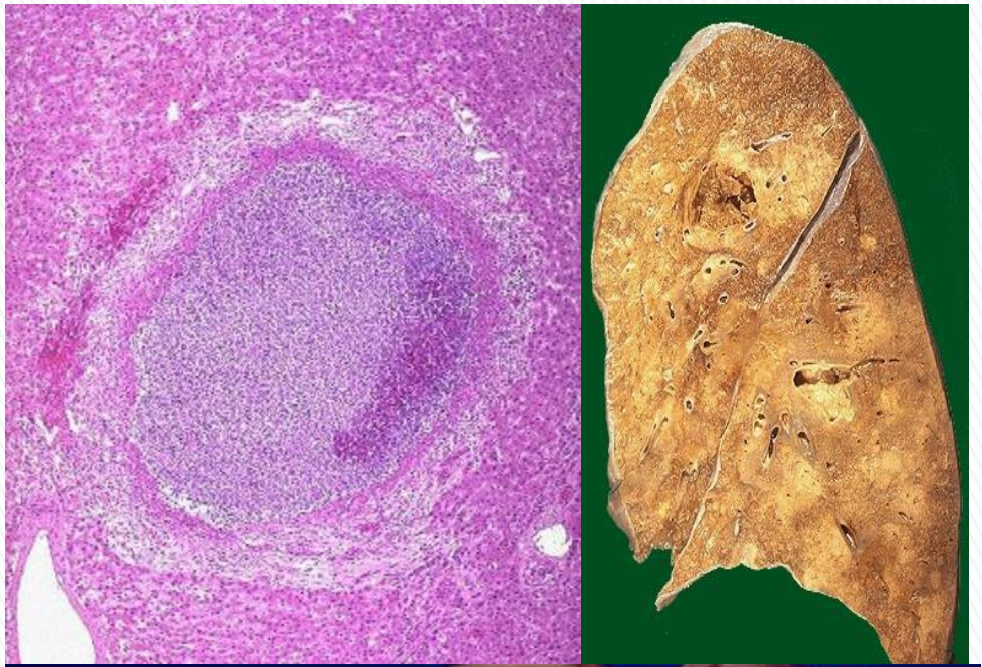


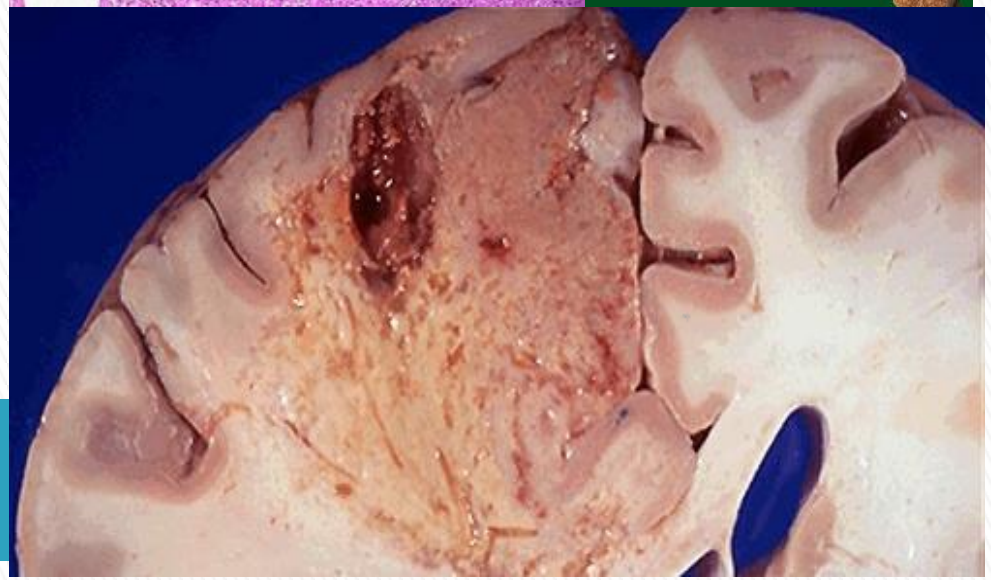
- The complementing this slide:
- Under the microscope, we can see here on the right side cells with intact nuclei.
- On the left side, there is tubules (damaged dead cells) with lost nuclei.
- The dead cells still preserved their shape and they will preserve it in the first few days after damage; because it is a coagulative necrosis.

Liquefactive necrosis

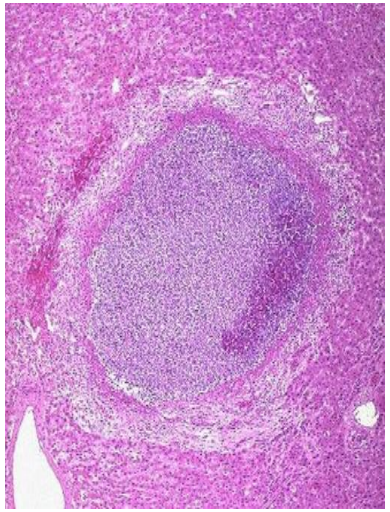
- Focal infections by Bacterial and fungal organisms.
- Pus.
- CNS infarcts
- Center liquefies and digested tissue is removed by phagocytosis

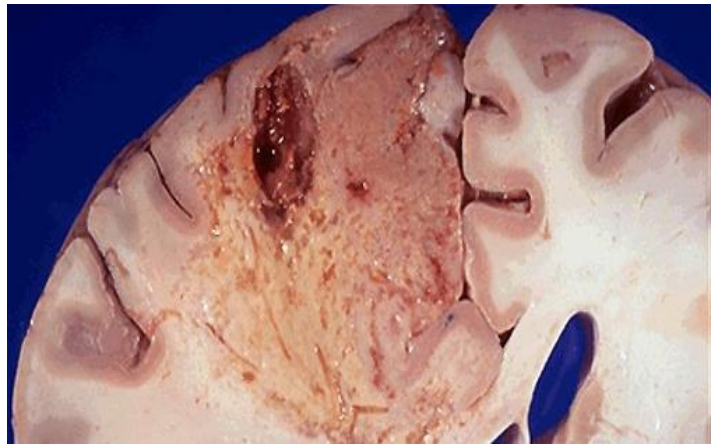
- NOTE:
- From its name, it is a liquid form of material that accumulates.
- It is associated with ischemia to the CNS ➔ which will result in a liquefactive pattern of necrosis instead of the coagulative necrosis which occurs in the other solid organs.





- The complementing this slide:
- Macroscopically, liquefactive necrosis appears as a cavitary lesion in the lung.
- Under the microscope, liquefactive necrosis is characterized by a collection of inflammatory cells, mainly acute inflammatory cells (neutrophils).
- The lower image is an image of a brain with a cavitary lesion corresponding to an area of infarction.





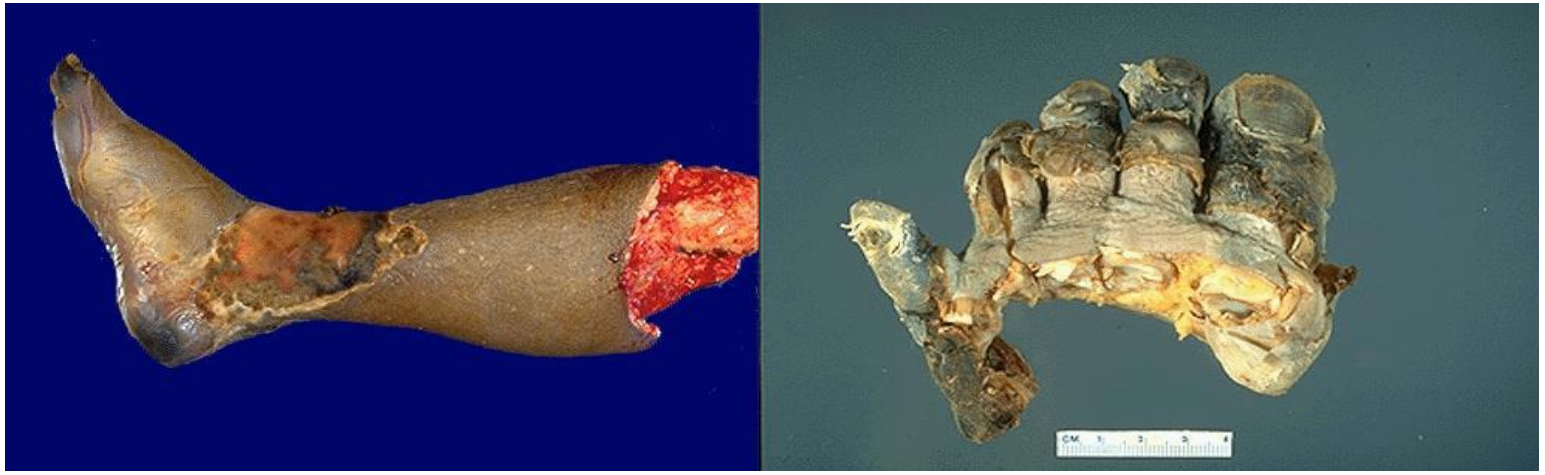
Gangrenous necrosis

- Clinical term
- It is coagulative necrosis
- Dry vs wet

NOTE:
Gangrenous necrosis is a coagulative type of necrosis but it occurs on multiple tissue levels.

NOTE:
We also call it gangrene.

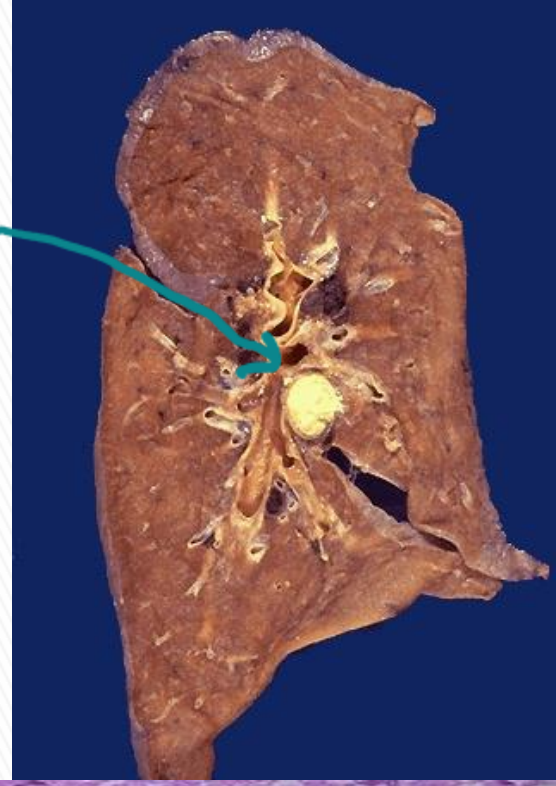
- The complementing this slide:
- Notice the amputated distal part of the leg and the blackish discoloration of the skin due to ischemic necrosis of the skin, underlying subcutaneous tissue, underlying muscles and underlying bone ➔ basically a coagulative type of necrosis but at multiple tissue levels.
- It can be accompanied by a superimposed infection, in which we call it a wet gangrene, just like in the amputated leg image.
- It can be also not accompanied by an infection, in which we call it a dry gangrene.



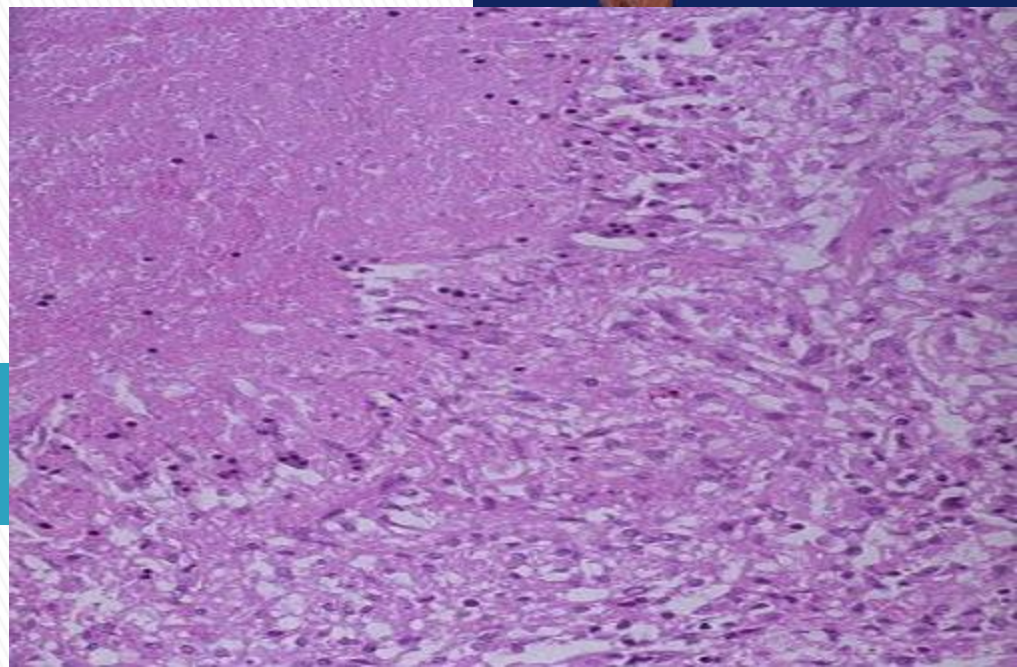
Caseous necrosis

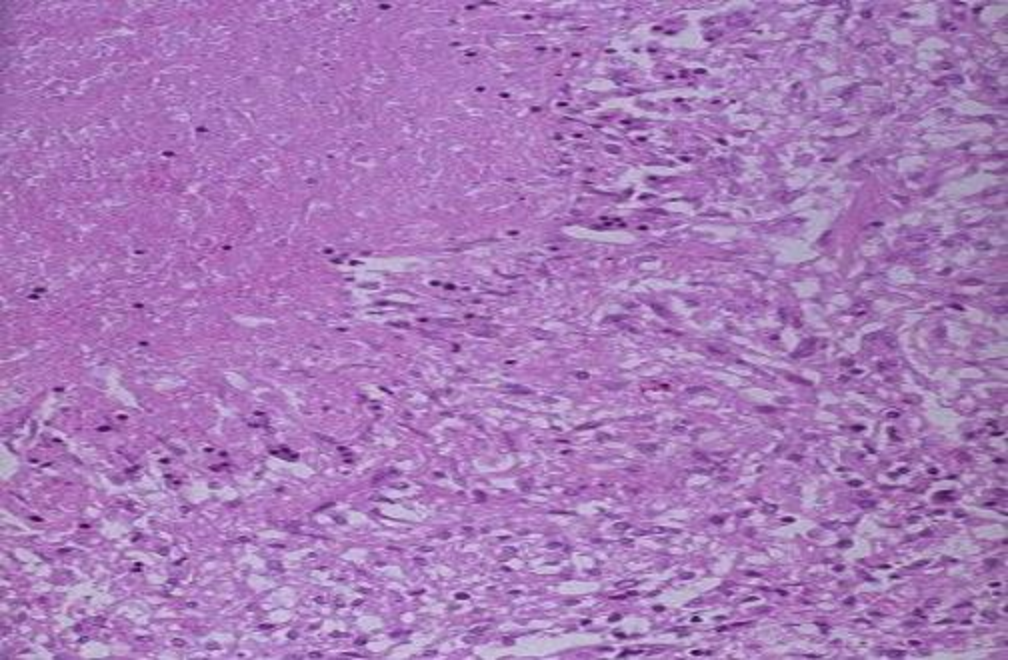
- "Cheese like"
- Tissue architecture is not preserved
- Acellular center
- Usually enclosed by collection of macrophages. (granuloma)
- Most often seen in TB

- NOTE:
- Classically seen in cases of tuberculosis.
- It is called "caseous" because of the accumulation of a yellowish or whitish cheesy-like material.



- NOTE:
- Not like coagulative necrosis!

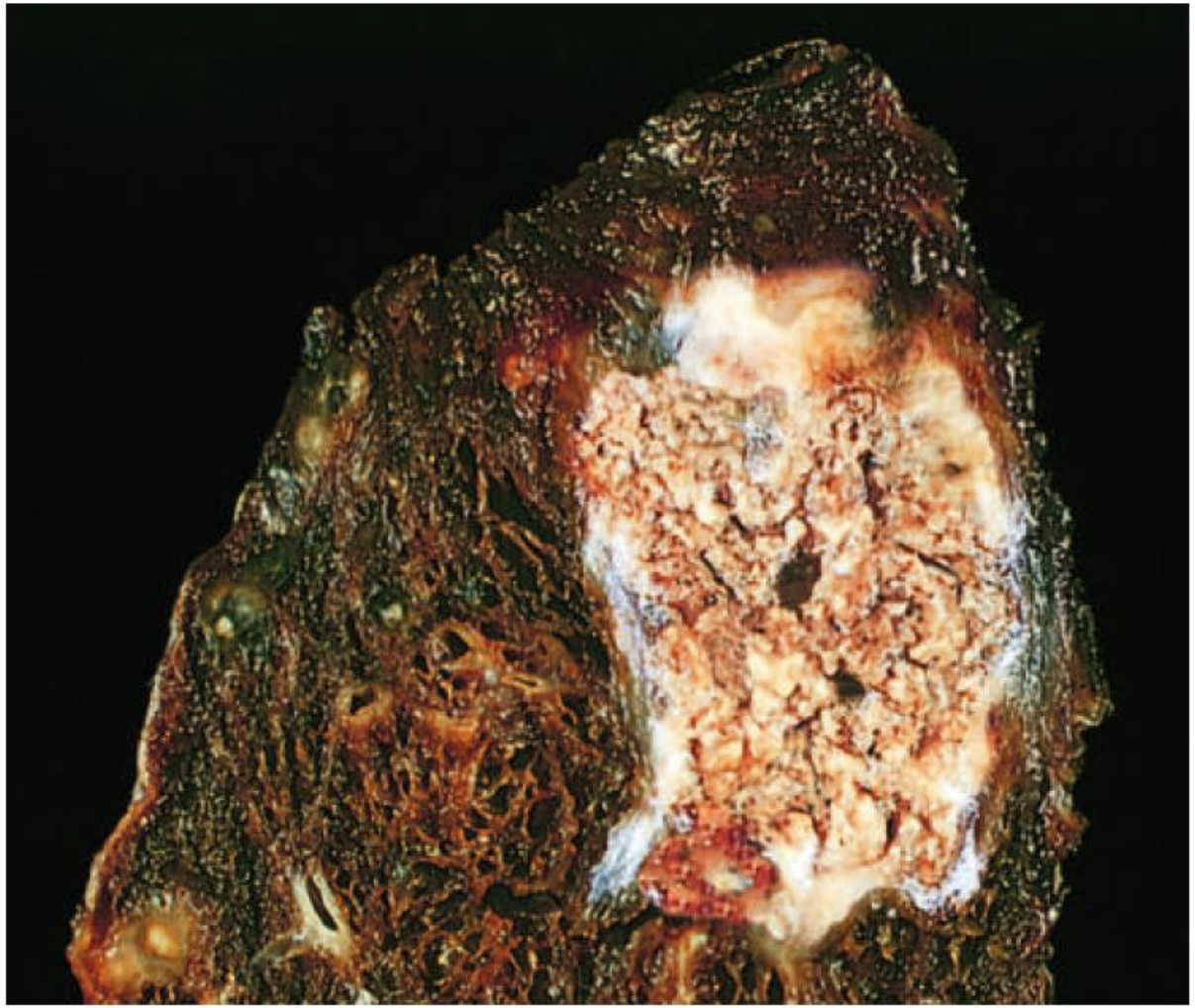




- The complementing this slide:
- Characterized under the microscope by the appearance of an acellular center of necrotic material which is usually enclosed or surrounded by a collection of macrophages to form a structure under the microscope which we call it a granuloma.

Caseous necrosis

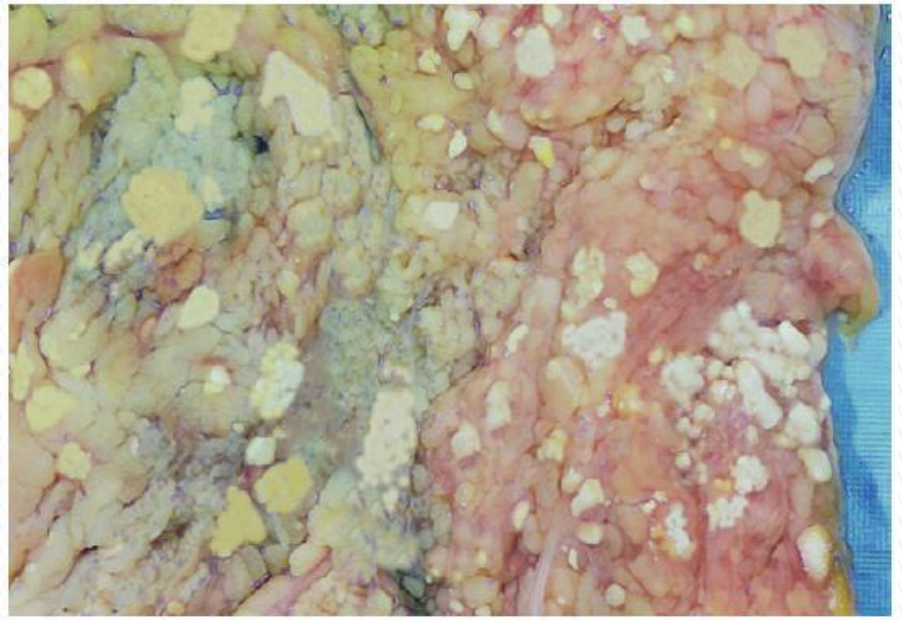
- NOTE:
- Notice the whitish cheesy-like material in the section from the lung.

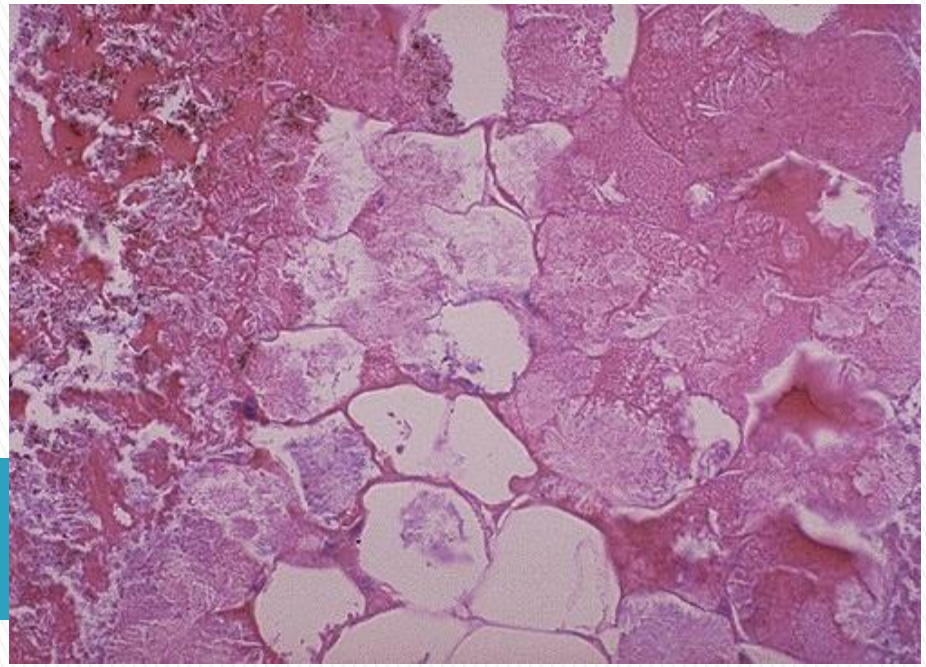


Fat necrosis

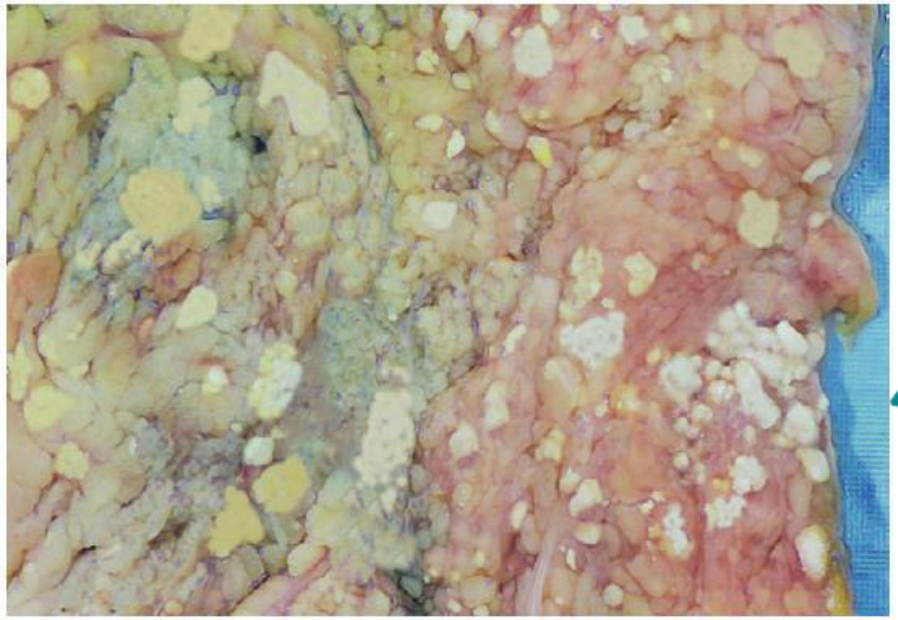
- NOTE:
- From its name ➔ necrosis of adipocytes.

- Occurs in acute pancreatitis
- Due to release of pancreatic lipases
- Focal fat destruction
- Released FA's combine with Ca2+ (saponification) to produce the whitish chalky appearance
- Shadows of necrotic fat cells

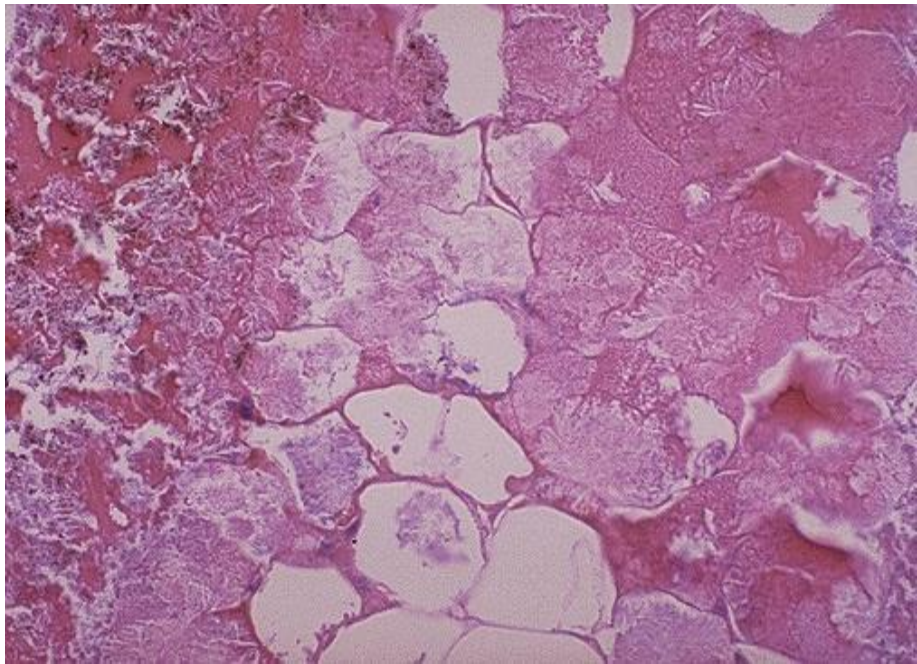




- NOTE:
- The pancreas is surrounded by fat in the abdomen and the released pancreatic lipases are going to digest it.
- Upon the digestion of the fat, fatty acids (FA) are going to be released.



- The complementing this slide:
- Fatty acids (FA's) have high binding capacity to calcium.
- Notice the chalky white material in the fat tissue.
- Under the microscope, there is a shadow of the dead cells with lost nuclei.

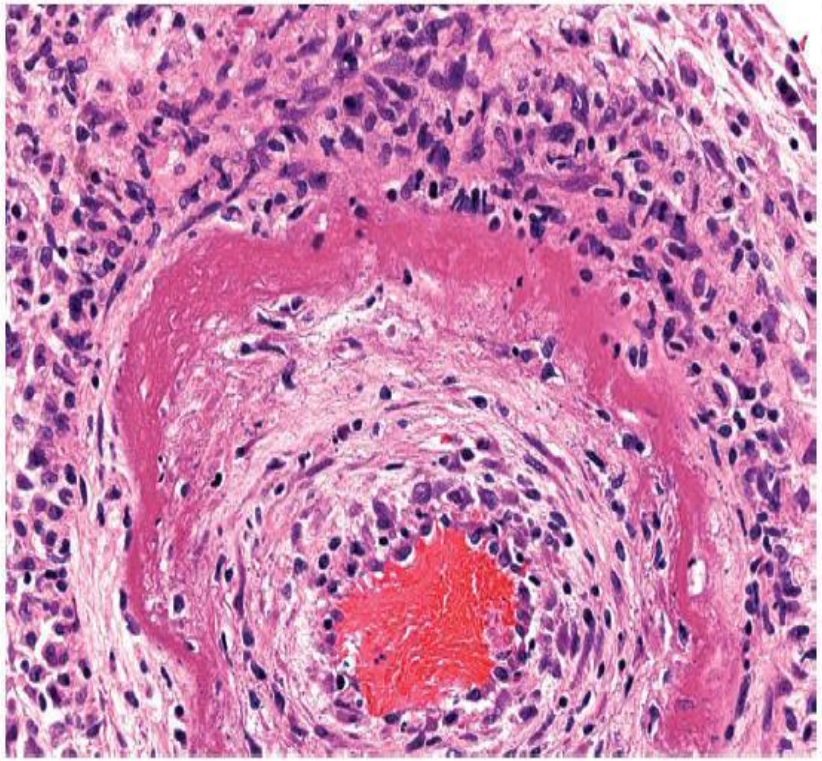


Fibrinoid necrosis

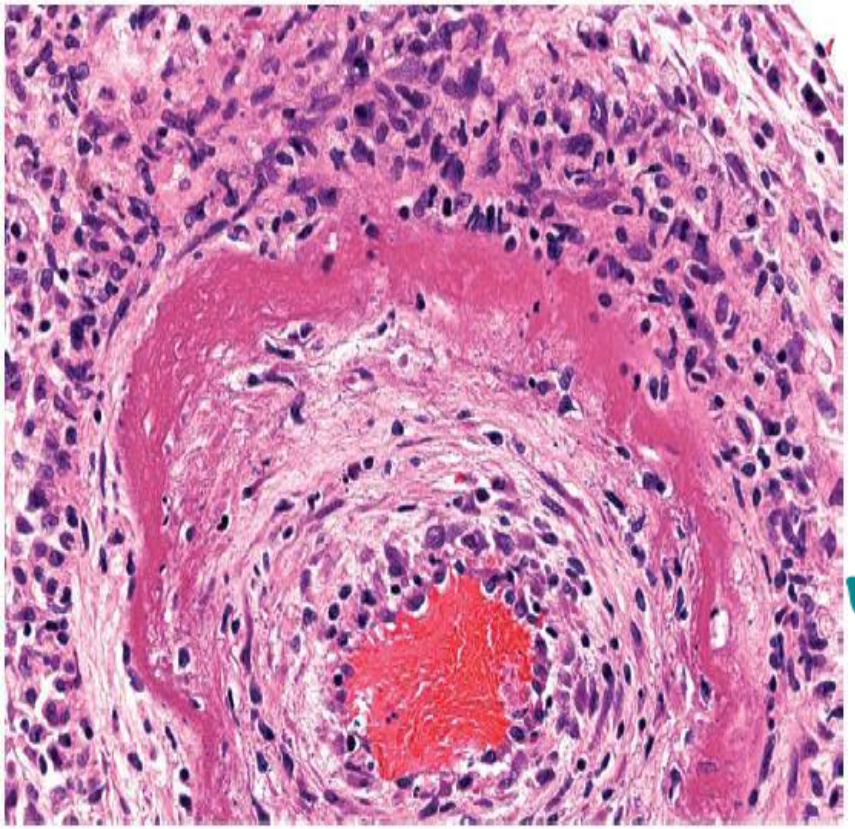
- NOTE:
- It is a peculiar type of necrosis because we can't see it grossly or by the naked eye.

- Visible only microscopically.
- Deposits of antigen –antibody and fibrin complexes in arterial walls
- Seen in vasculitis (PAN)
- Severe hypertension.

- NOTE:
- Vasculitis is an autoimmune disease.
- One example is the polyarteritis nodosa (PAN)



- NOTE:
- Fibrinoid necrosis is caused by deposits of antigen–antibody complexes accompanied by fibrin in the walls of the blood vessels.



- The complementing this slide:
- As you can see here, the fibrin material is the pink ring-like material deposited in the wall of this blood vessel.

V2

- Slide 22: Macroscopically instead of **Microscopically**