بسم الله الرحمن الرحيم

PATHOLOGY

MID – Lecture #2

Reversible & irreversible cell injury

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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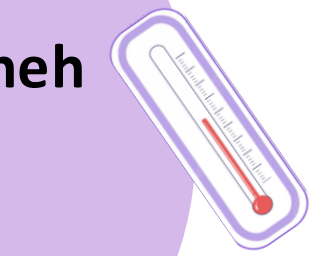

Reversible and Irreversible cell injury

Cell injury and adaptation

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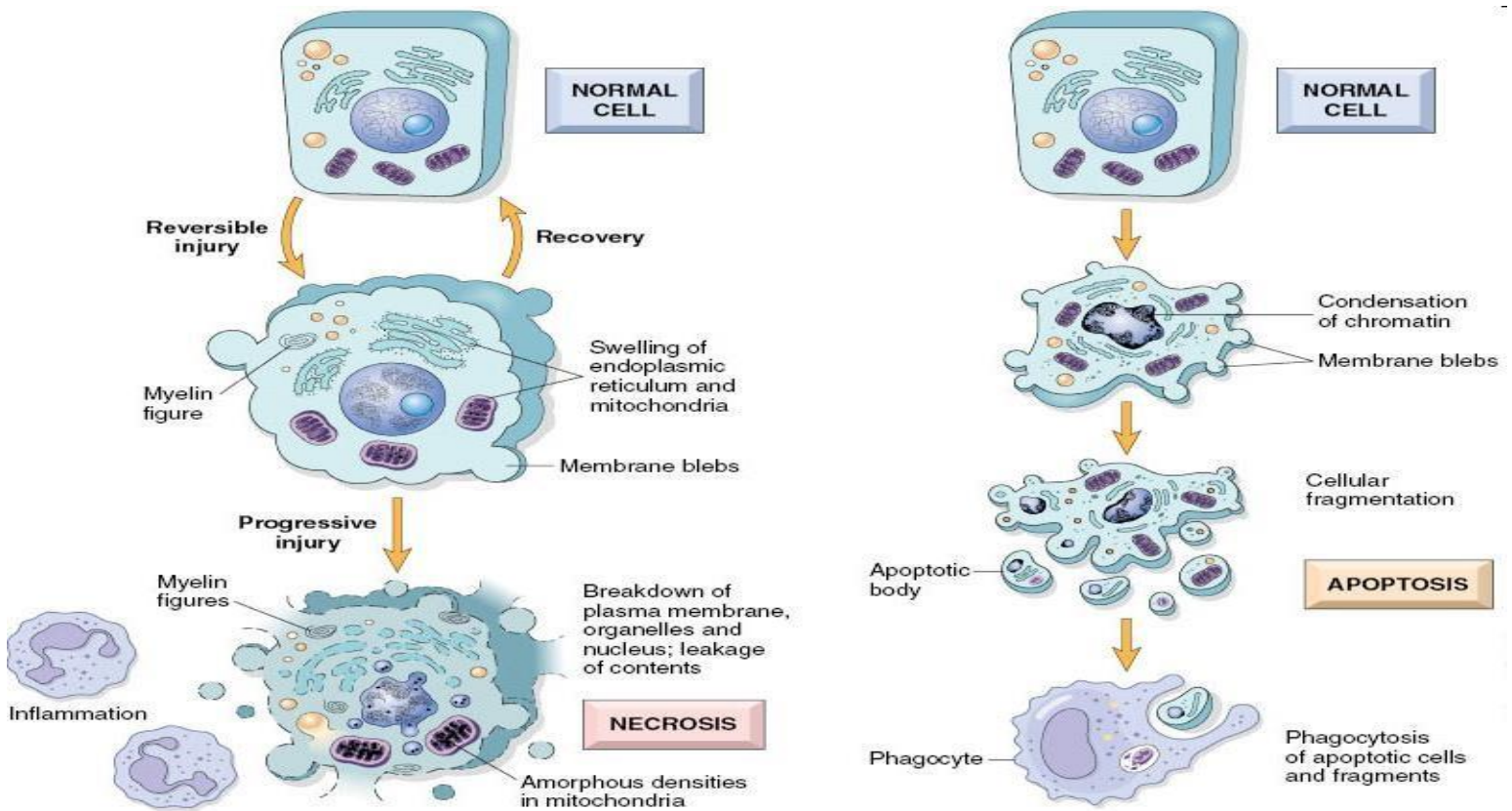
Outlines:

- ✓ Reversible injury.
- ✓ Irreversible injury (necrosis).
- ✓ Clinical implications. (For irreversible injuries)
- ✓ Patterns of necrosis.

Cell injury:

- **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**
- **In reversible injury the cell can go back to normal while in irreversible injury the cell is at the point of no return**

✓ **WE HAVE TWO PATTERNS OF CELL DEATH :** Necrosis & Apoptosis



- The normal cell which contains nucleus and many organelles

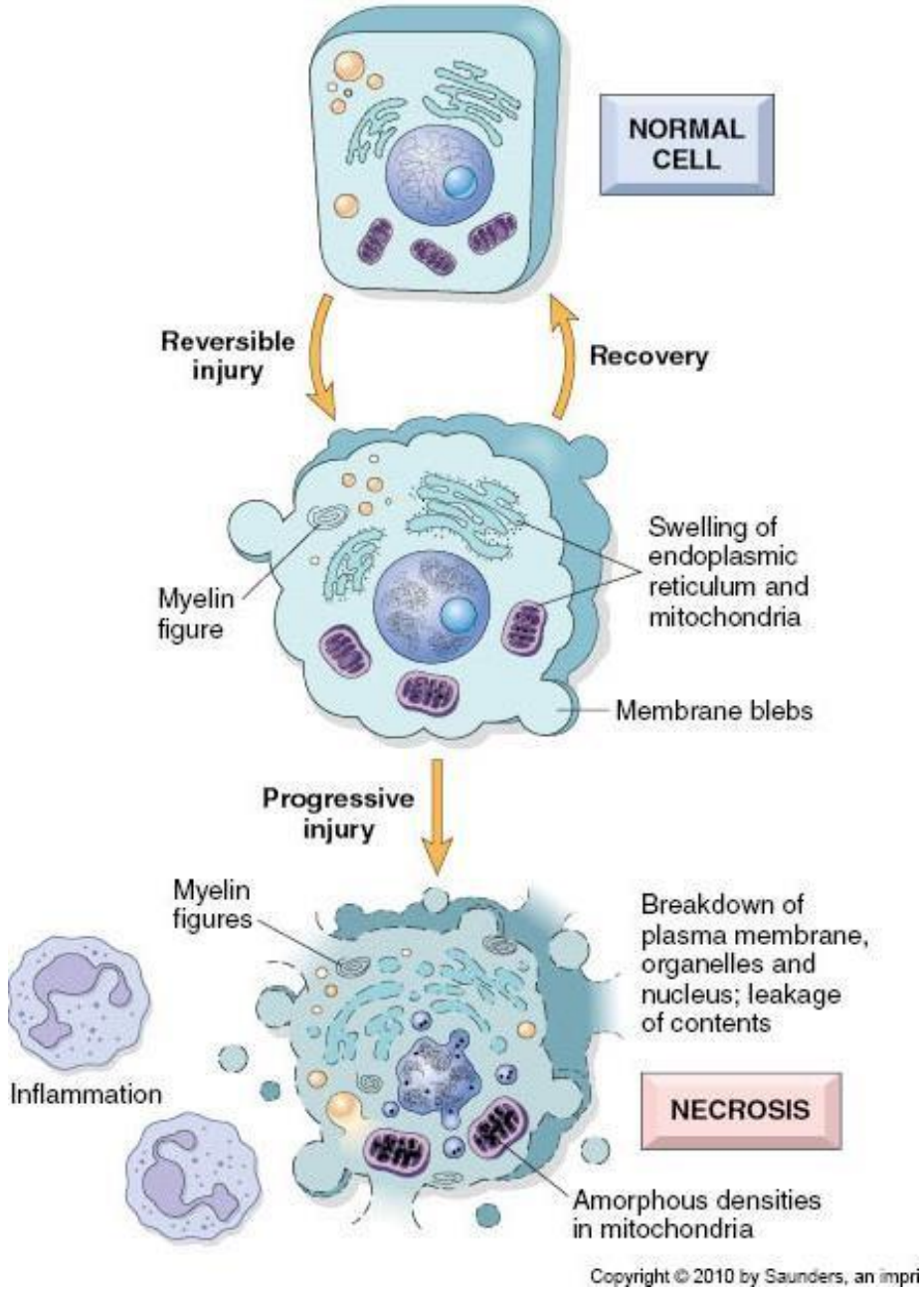
- When the cell is exposed to any injurious stimulus (more than what the cell can adapt to) , it will first undergo reversible injury

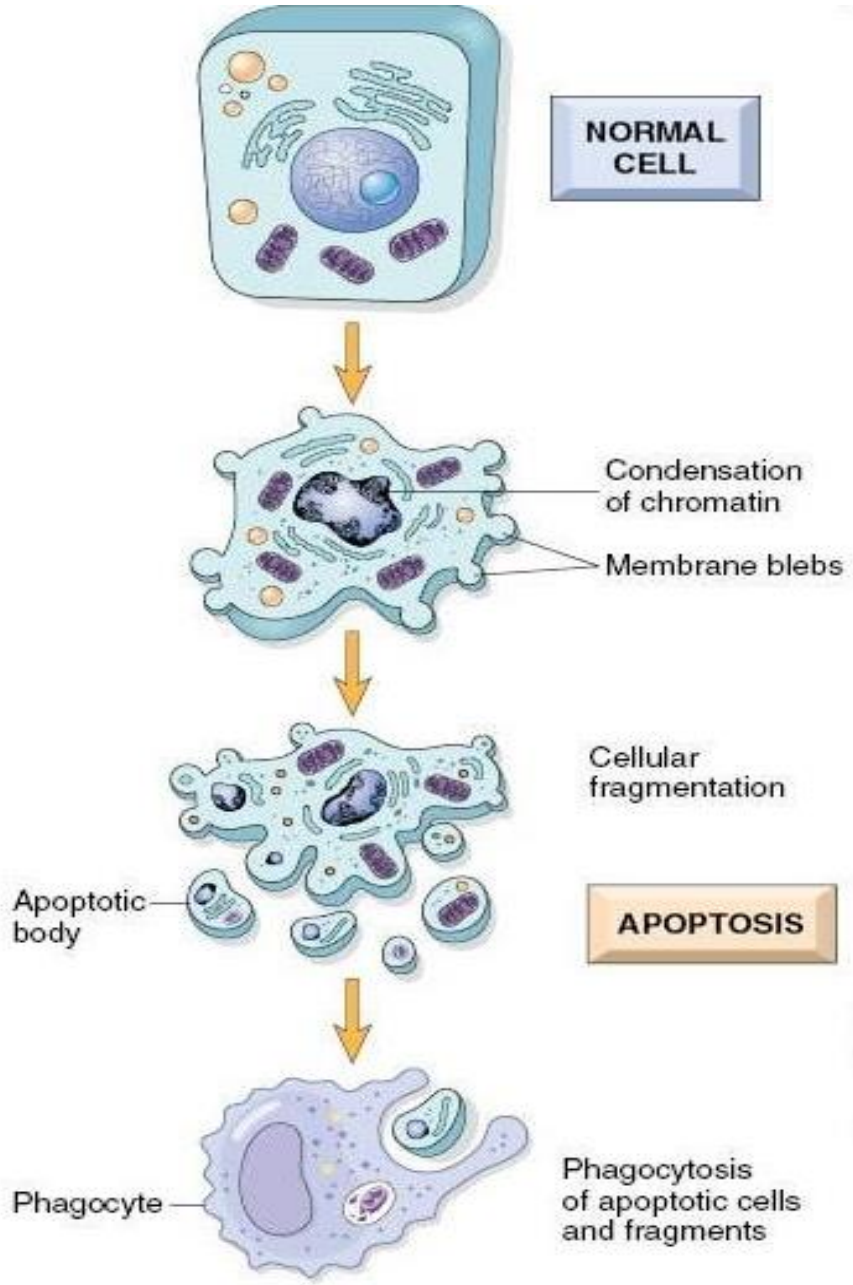
- As we can notice , the cellular membrane and the organelles (such as ER and mitochondria) have swollen (and we have membrane blebs and membrane bulgings) due to the accumulation of water or fluids through **they remain intact** . So if the injurious agent is removed , the cell will return to its normal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

- However , if the injury is progressive , prolonged or 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 :

✓ Cell membrane will be disrupted and there will be discontinuities in the membrane like a ruptured balloon
✓ The organelles' membranes are ruptured
✓ The cellular contents will leak outside and the nucleus will start to disappear
✓ Inflammatory cells (mainly the neutrophils) will detect the dying cell and its contents , then they will engulf them through an inflammatory response to remove them





- **The normal cell which contains nucleus and many organelles**
- **The other type of cell death which does not go through reversible/irreversible injury (and will be discussed in the following lectures) is Apoptosis**

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

✓ The cell doesn't swell up , it shrinks and decreases in size

✓ The shrinking isn't coupled with the disruption of cellular membrane as **it remains intact**

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

✓ At the end , the cell will disappear by few inflammatory cells which will come to engulf the cellular debris without causing or provoking a large or dense inflammatory response like the one in Necrosis

✓ **THE DOCTOR EMPHASISED THAT KNOWING THE DIFFERENCES BETWEEN CELL INJURIES IS IMPORTANT**

Reversible injury

- If the damaging stimulus is removed >>> injured cells can return to normal **This is the rule of reversible injury**

- **Morphology**: **Morphological changes in (Form , Structure or shape)**
- Cellular swelling/organ swelling **Organ swelling reflects cellular swelling**
- Fatty change

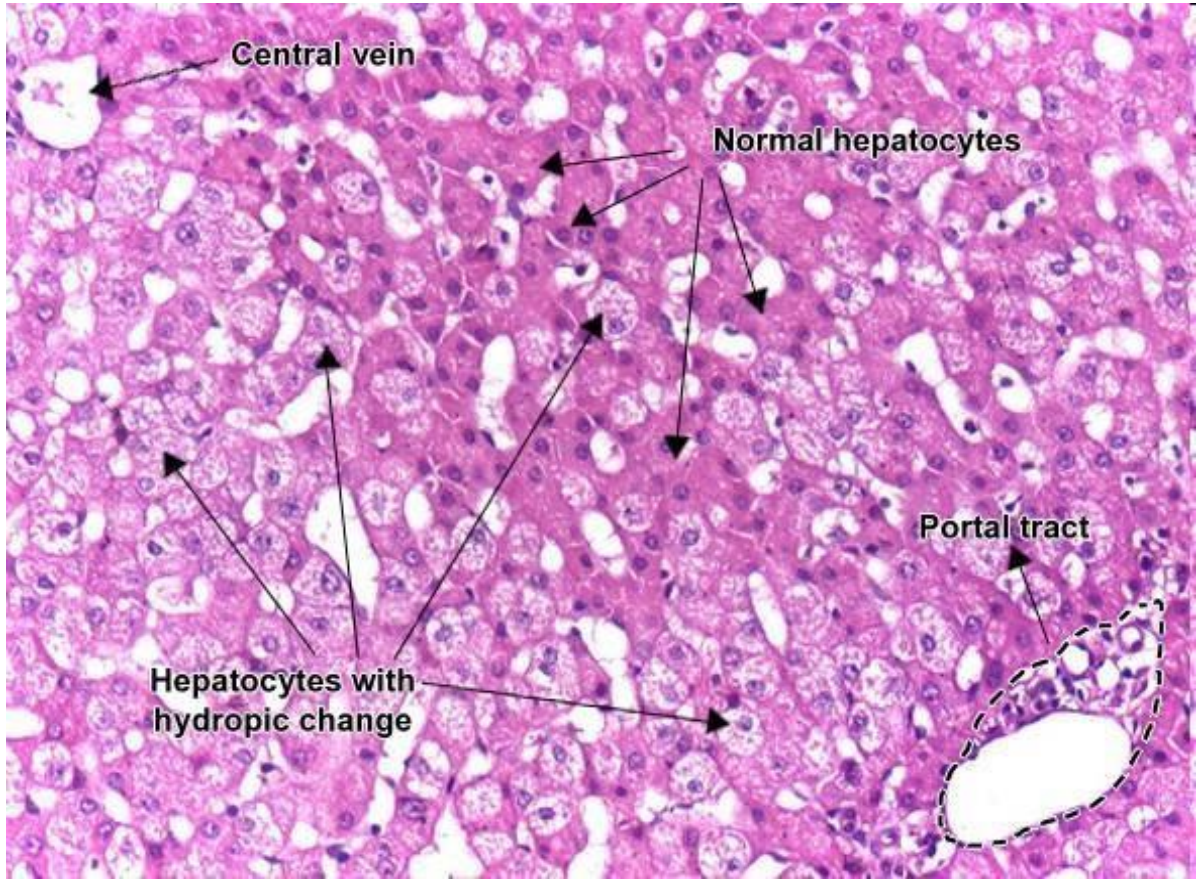
✓ **Morphology Changes could be Both Macroscopic (seen by the naked eye at the level of the whole organ) OR Microscopic (seen only through microscopes , which could be either seen with Light Microscopes LM or Electron Microscopes EM).**

✓ **The ultra-structural changes can only be seen by Electron Microscope**

Reversible damage – cellular swelling

FIRST MORPHOLOGIC CHANGE

- The following image is an example on cellular swelling (which is due to accumulation of water/fluids) in the liver
- We can see that the Hepatocytes are undergoing into **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/K ATP-dependent pump within the cell membrane (because the injured cell can't produce ATP) –> which causes intracellular osmotic pressure –> which drives and attracts water to the inside of the cell.



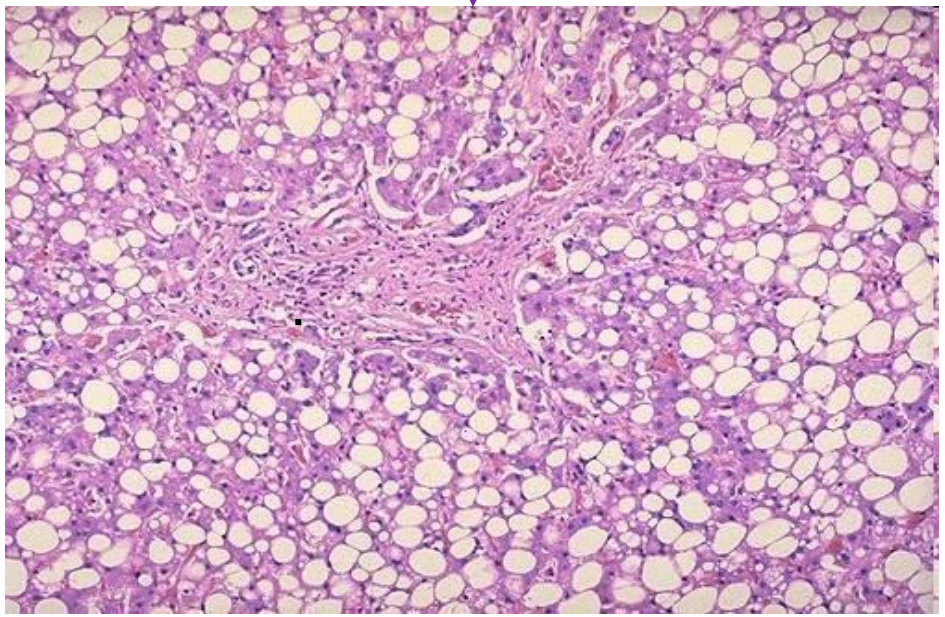
-Hepatocytes are the main functional cells of the liver, making up about 70-80% of the liver's mass.

Reversible damage – fatty change

SECOND MORPHOLOGIC CHANGE

This damage happens more to organ/cells that deal with Fat metabolism

As we can see on the microscopic level , this damage is reflected by the appearance of white lipid-rich droplets inside the cytoplasm of cells. The intracellular fat accumulation will be discussed later



As we can see on the macroscopic level , this image shows a section of the liver with fatty yollowish greasy cut surface.
Also , the liver will indeed be enlarged

Other changes

- Plasma membrane alterations (blebbing , blunting)

Plasma membrane will remain intact as this is Reversible damage

- Mitochondrial change (swelling and densities)
- Dilation of ER

Soon after dilation of ER , its ribosomes would begin to detach

- Nuclear clumping of chromatin.

However , the nucleus will remain intact

- Cytoplasmic myelin figures

The myelin figures are produced from the disruption of the membrane of the cell and the membrane of the organelles

These changes are seen with an EM , they can also be seen in irreversible cell injury in a much advanced and severe form

Irreversible injury (necrosis)

Important defining (typical) features of the cell in irreversible injury :

- ✓ **Irrversible Mitochondrial dysfunction**

Because the mitochondria is the ATP factory , there would be no ATP generation at all and the mitochondria won't go back to the normal state

- ✓ Loss of **plasma membrane and intracellular membranes** >>>cellular enzymes leak out

Even organelle enzymes and proteins will leak out the cell (they will first leak to the cytoplasm and then to the outside of the cell) . Intracellular enzymes can gain access to the bloodstream and can be detected by certain laboratory investigations.

- ✓ Loss of **DNA and chromatin structural integrity**.

ENDING UP WITH A DEAD CELL

- ✓ **Local Inflammation**

Which always accompanies Necrosis

Morphology irreversible injury (Necrosis)

✓ Increased cytoplasmic eosinophilia.

Increase cytoplasmic eosinophilia (pinkishness when H&E , the routinely used stain in the laboratory)

Increased eosinophilia means more binding to eosin and less binding to hematoxylin , and it occurs in the necrotic cell due to :

- A lot of degraded or denatured proteins in the cytoplasm which will bind the eosin
- 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 hematoxylin which gives the cell a bluish colour under the LM (We call it the bluish basophilia) –> loss of bluish colour (basophilia) more eosinophilia

✓ Marked dilatation of ER , mitochondria.

✓ Mitochondrial densities.

✓ More myelin figures.

Because of more damage of the membrane and membrane phospholipids –> which will lead to the accumulation of the myelin fatty materials inside the necrotic cell

✓ THE MENTIONED MORPHOLOGICAL CHANGES CAN MAINLY SEEN UNDER ELECTION MICROSCOPE

Morphology irreversible injury (Necrosis)

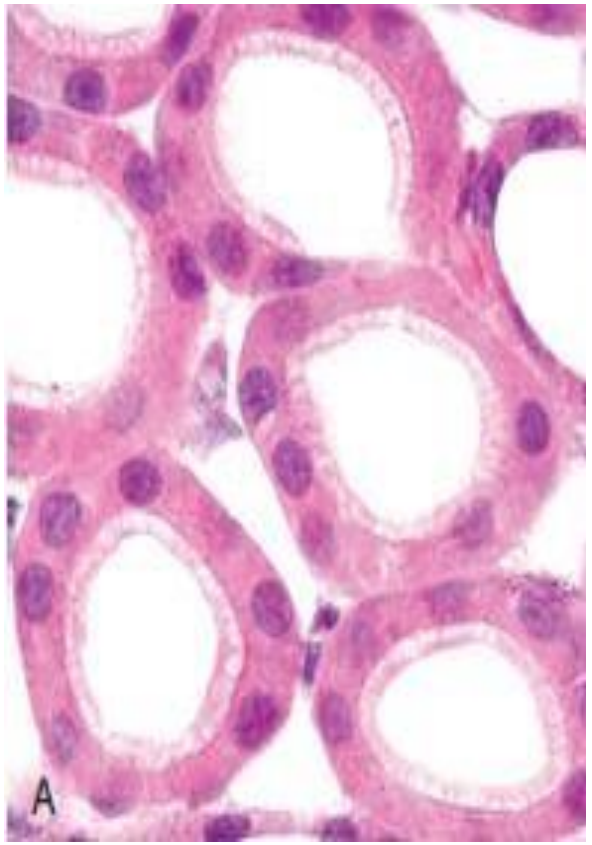
Nuclear changes : Necrotic nuclear changes can be observed under LM by H&E stain

- ✓ **Pyknosis**: shrinkage and increased basophilia
- ✓ **Karyorrhexis** :fragmentation;
- ✓ **Karyolysis**: basophilia fades

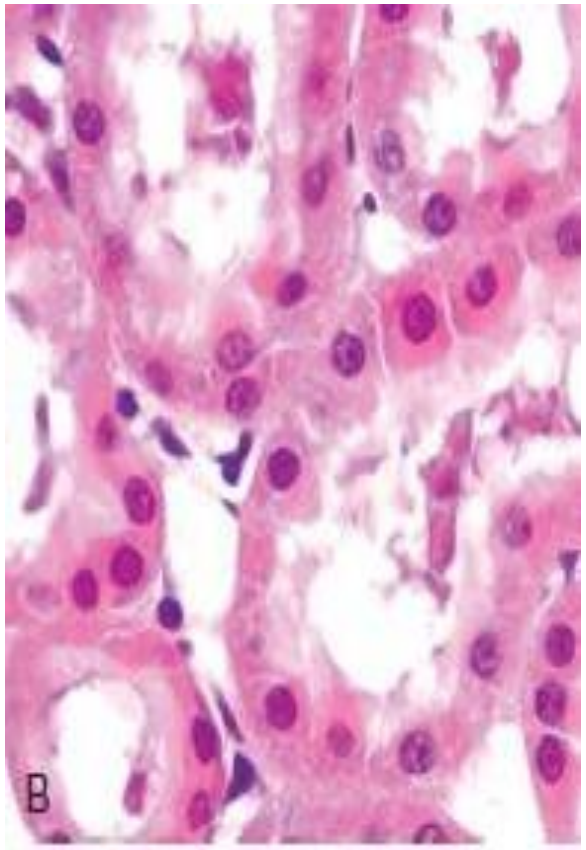
Degradation of the nuclear material and the fading of the nuclear basophilia

✓ Basophilia : The dark blue colorisation under the Light Microscope

Normal, reversible and irreversible cell injury

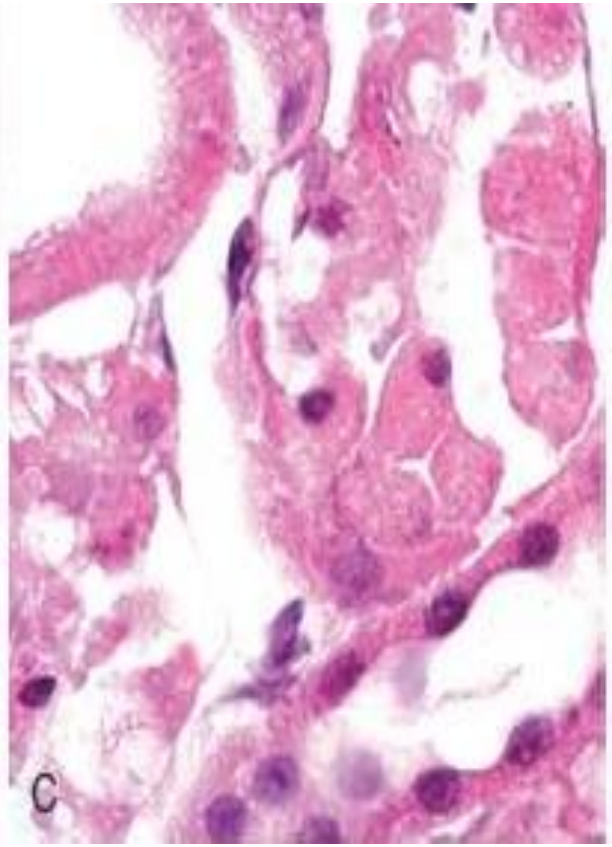


NORMAL



Reversible

- ✓ Cells look swollen
- ✓ Nucleus intact



Irreversible

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

Cell death

✓ **WE HAVE TWO MECHANISMS OF CELL DEATH :** Necrosis & Apoptosis

✓ Different mechanisms, depending on nature and severity of injury/ **Also depends on the status of the cell.**

Necrosis:

What are the causes of necrosis?

- Rapid and uncontrollable.
- Severe disturbances
- Ischemia , cut of blood supply , toxins, severe infections like viral or bacterial infections , and trauma

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**:

- Less severe injury.
- Regulated by genes and signaling pathways
- Precisely Controlled.

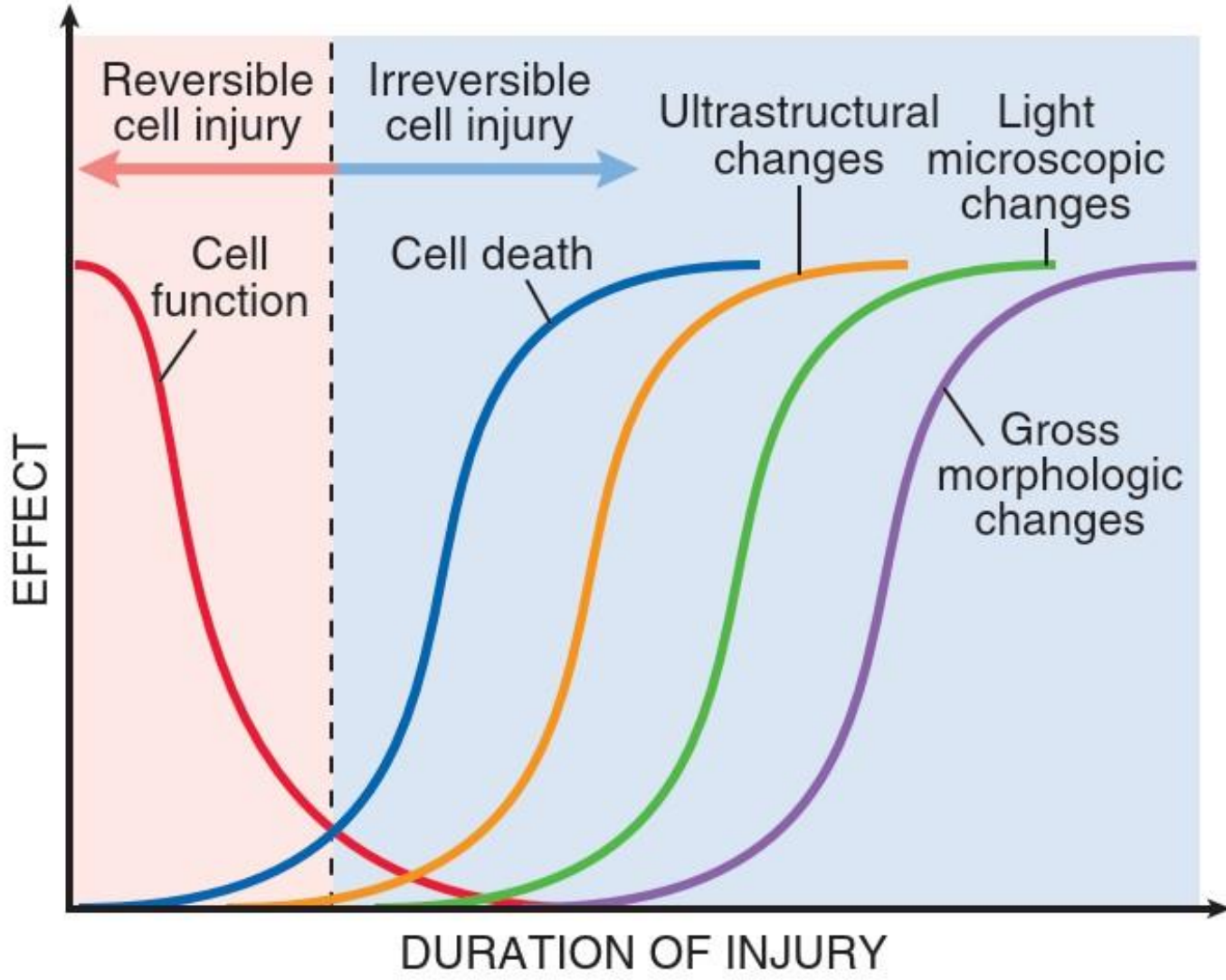
- Can be manipulated(**just like the uses of chemotherapeutic agents in the-management of cancer)**

- In healthy tissues.
- Clean cell suicide.

✓ **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.**

Necroptosis : A mixture of necrosis and apoptosis at the same time.

- ✓ **The injured cell (reversible or irreversible) is always malfunctional (nonfunctional) .**
- ✓ **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 morphology 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 summarize the differences between Necrosis and Apoptosis in a simplified manner:

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

And every part will go into an apoptotic body in order for the macrophages to engulf them and remove them

Thats why they call it the clean cell suicide

Clinical implications

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

- Cardiac enzymes, liver enzymes.

- ✓ **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.**

- ✓ **For example , if we have myocardial injury in heart after cases of cardiac ischemia or myocarditis , we can distinguish the injury by detecting the cardiac enzymes in the blood**
- ✓ **The same applies to the liver , liver enzymes also will leak out to the blood in cases of hepatic injury like hepatic toxicity by certain medications , viral infections or hepatitis , so we detect the hepatic enzymes the AST & ALT in the blood**

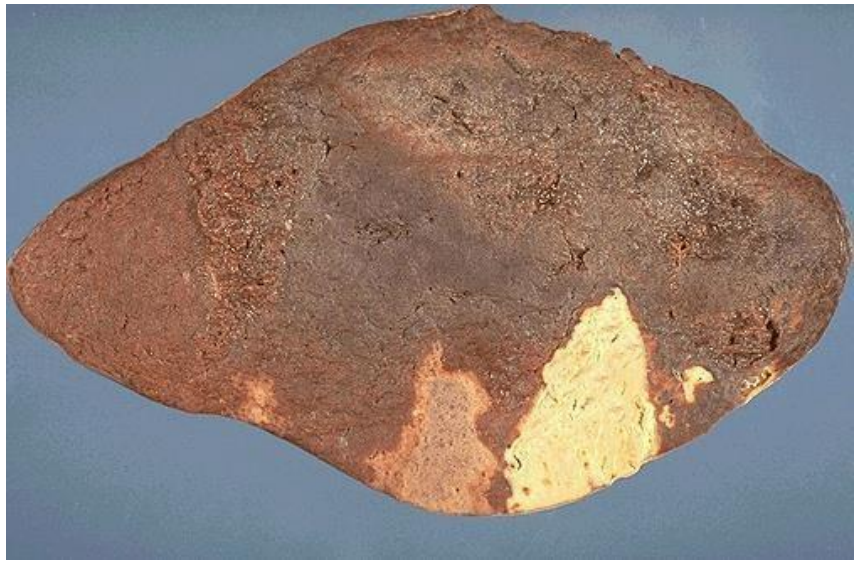
Morphologic Patterns of tissue necrosis

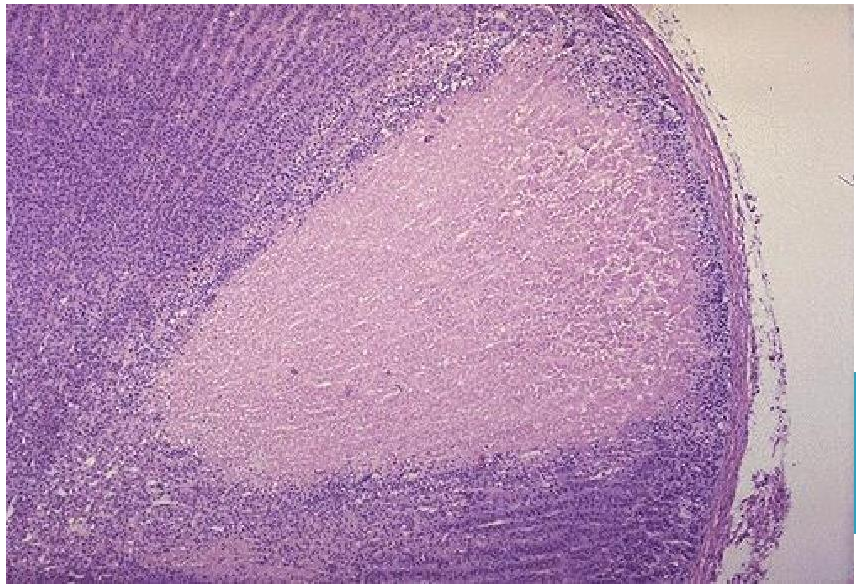
(Etiologic clues)

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

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





✓ **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 complement 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?

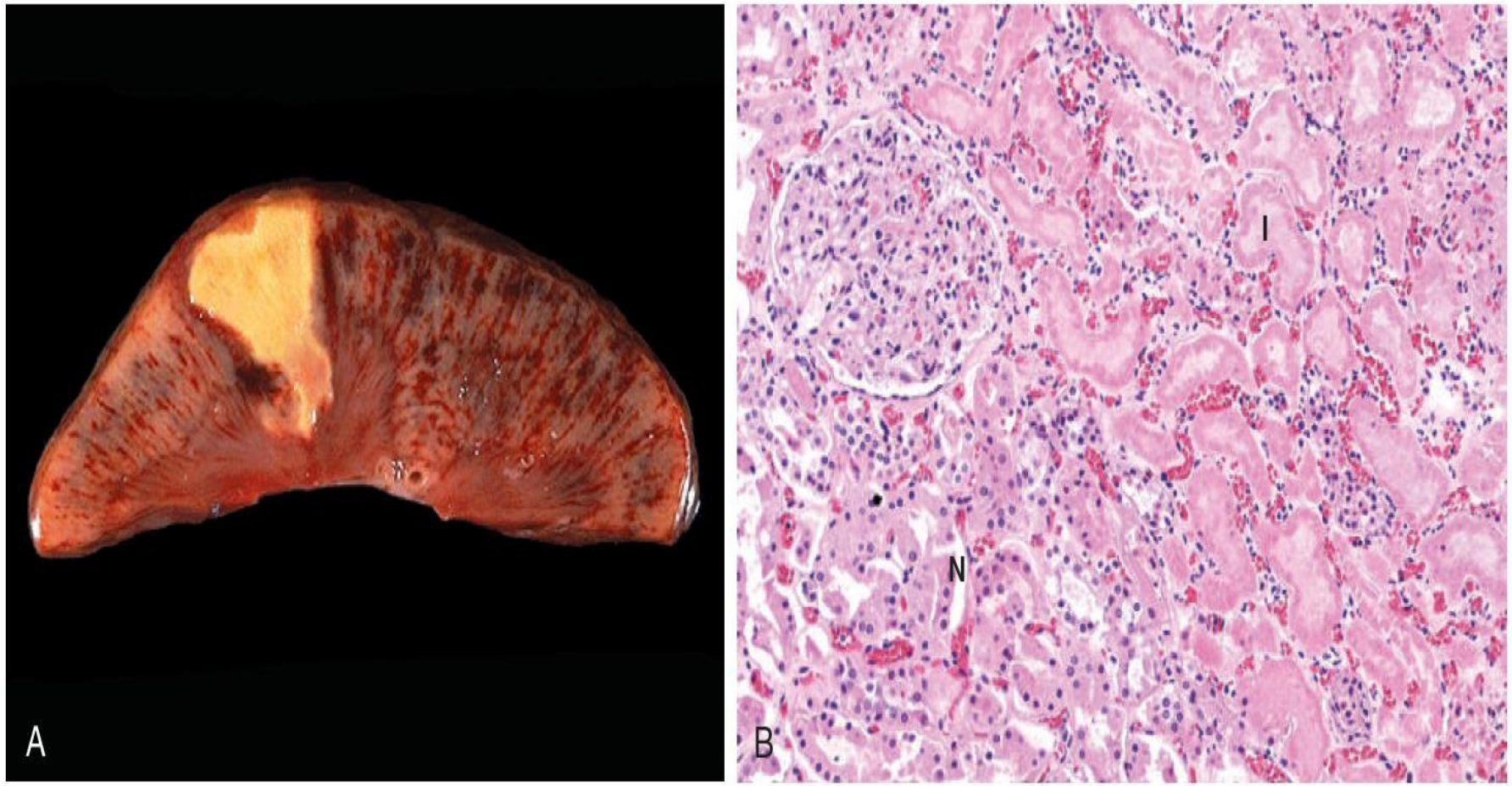
That is because ischemia causes enzymatic dysfunction ➔ degradative enzymes will be nonfunctional ➔ dead cells won't be degraded & they will preserve their shape for at least few days (1-3 days) before the onset of inflammation.

- 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.

- Ischemic to all solid organs result in coagulative necrosis, except in the brain which will result in another type of necrosis.

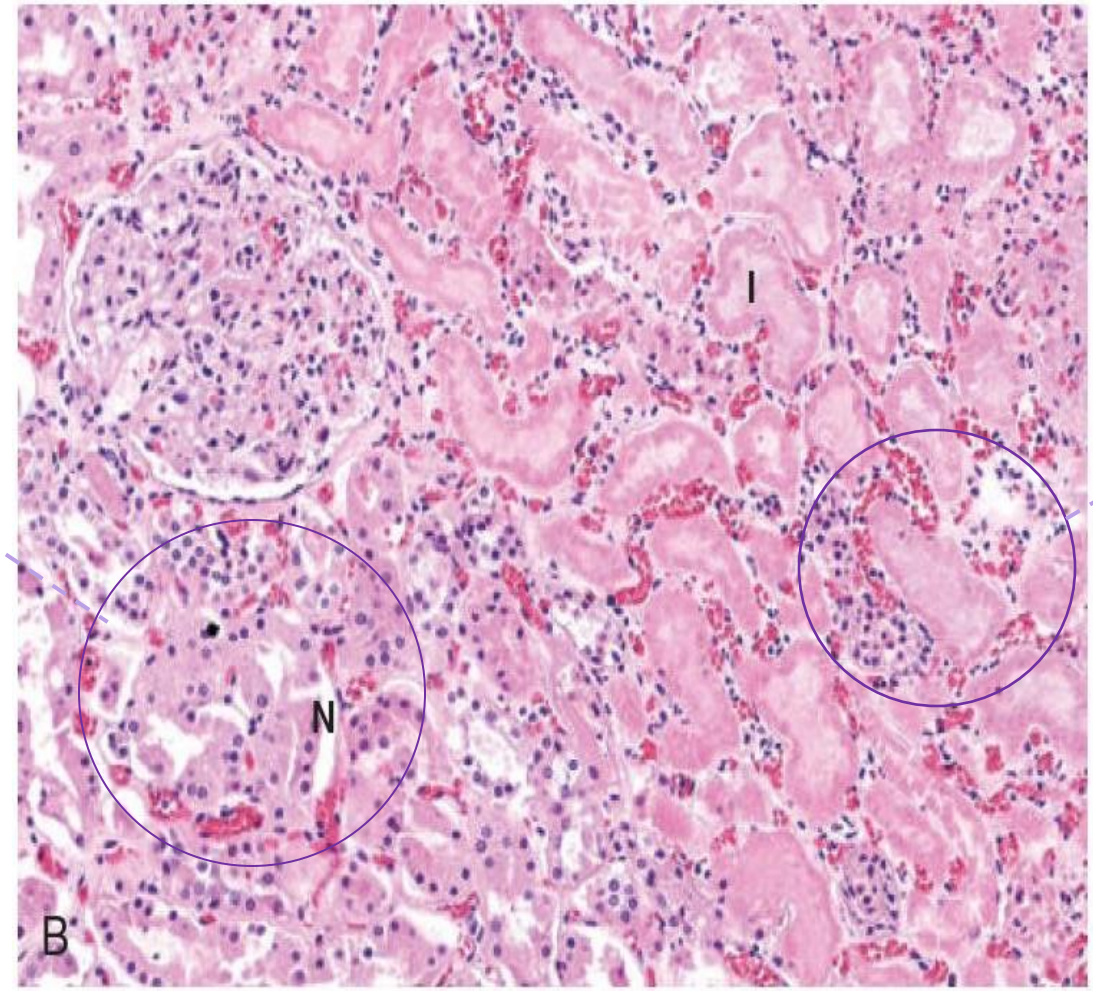
Coagulative necrosis

An example of coagulative necrosis in the kidneys:



NOTE : Notice the wedge-shaped pallor macroscopically!

Under the microscope, we can see here intact nuclei.

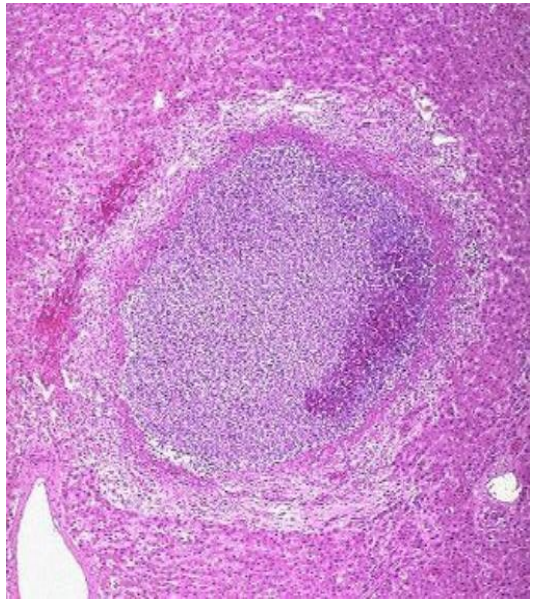


there is tubules (damaged dead cells) with lost nuclei.

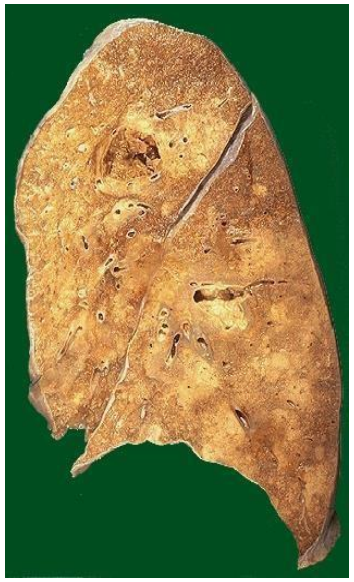
- ✓ The dead cells still preserved their shape and they will preserve it in the first few days after damage ;because it is a coagulative necrosis.

Liquefactive necrosis

- Focal infections by Bacterial and fungal organisms. Which are usually accompanied by production of Pus. Material
- CNS infarcts
- Center liquefies and digested tissue is removed by phagocytosis



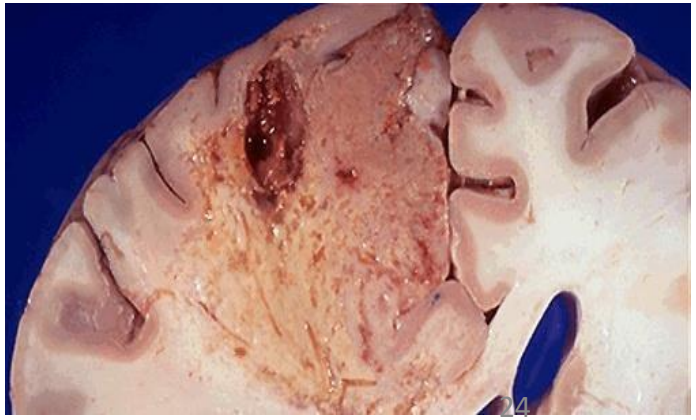
Under the microscope, liquefactive necrosis is characterized by a collection of inflammatory cells, mainly acute inflammatory cells (neutrophils).



Macroscopically, liquefactive necrosis appears as a cavity lesion in the lung.

- ✓ 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.

This is an image of a brain with a cavitary lesion corresponding to an area of infarction.



Gangrenous necrosis **We also call it gangrene.**

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

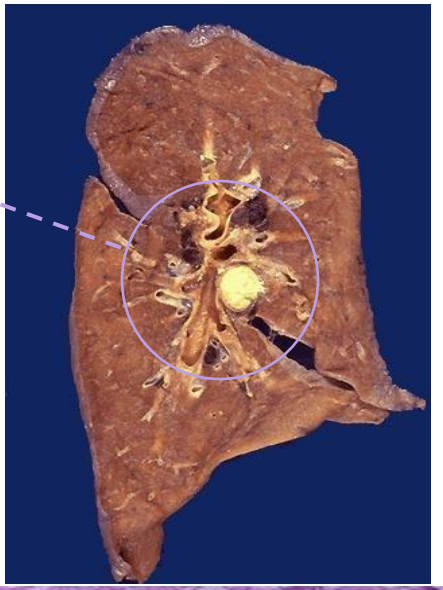
- **Gangrenous necrosis is coagulative type of necrosis but it occurs on multiple tissue levels.**

- **The amputated distal part of the leg and the blackish discoloration of the skin due to ischemic necrosis of the skin , underlying subcutaneous tissue ,underlaying 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.**

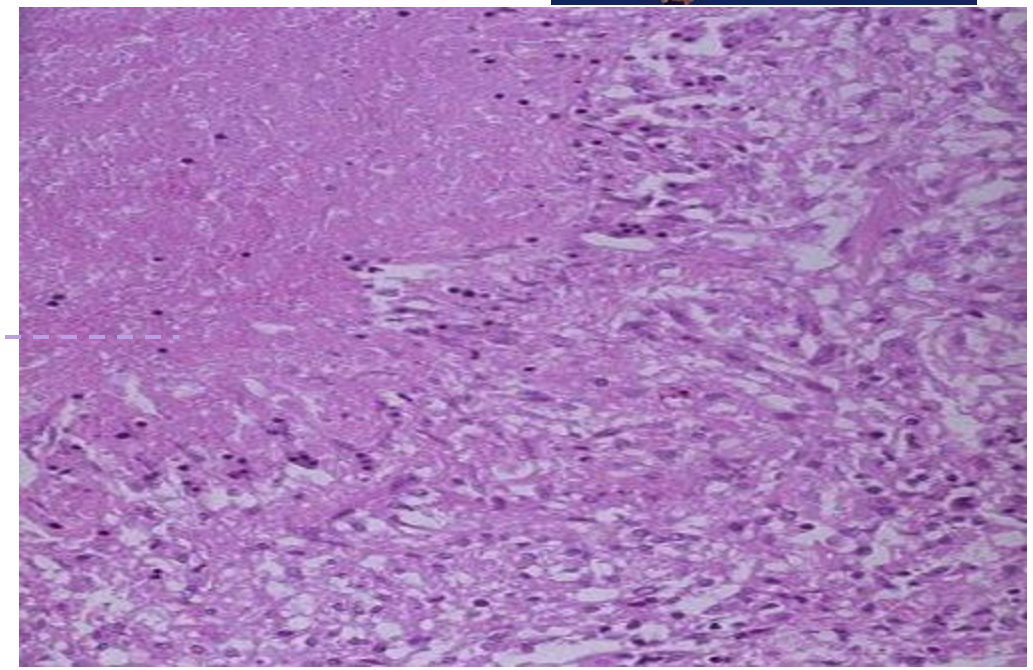
Caseous necrosis

- “Cheese like”
- Tissue architecture is not Preserved **(Not like coagulative necrosis)**
- Acellular center
- Usually enclosed by collection of macrophages. (granuloma)
- Most often seen in TB

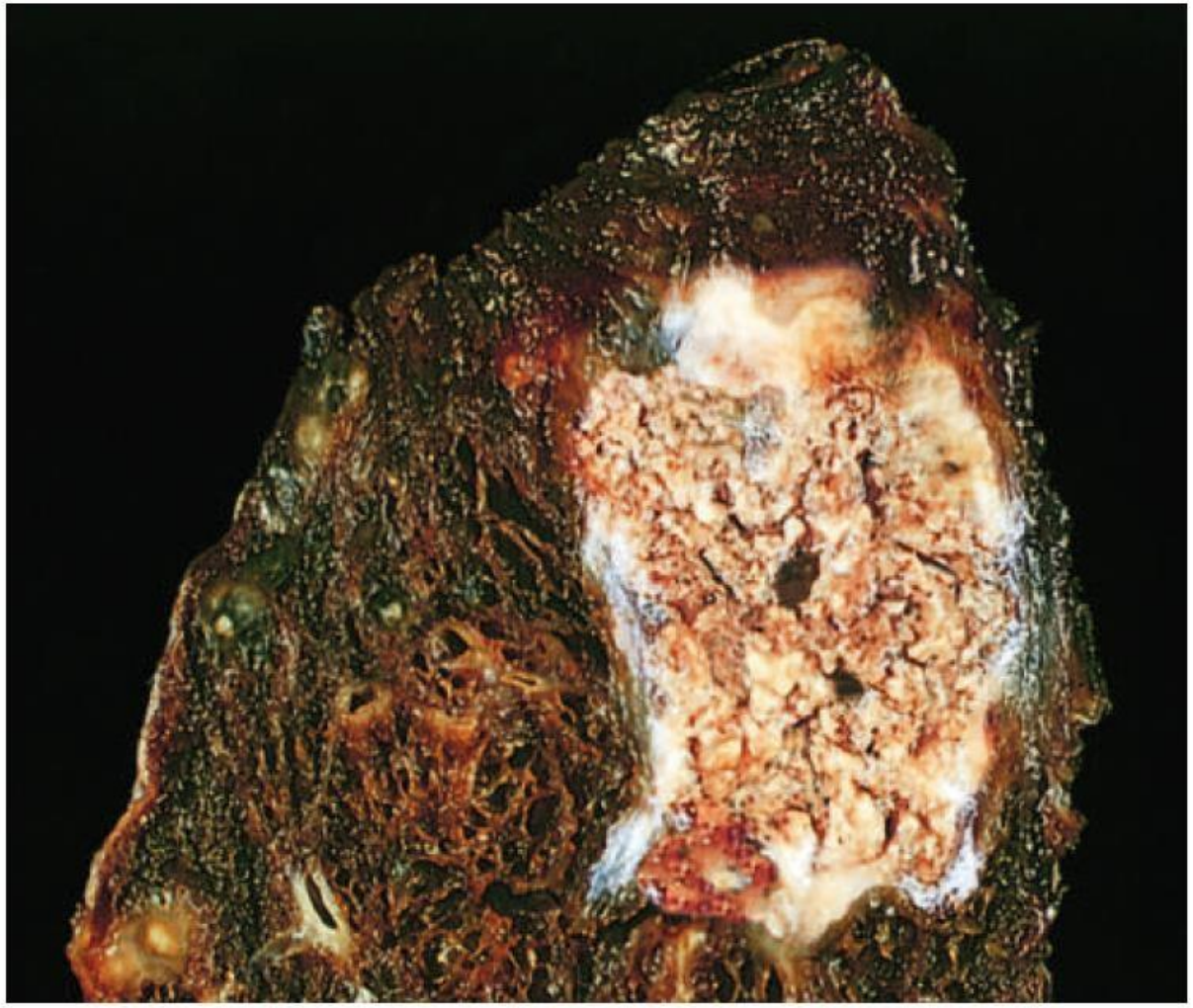
Classically seen in cases of tuberculosis. It is called “caseous” because of the accumulation of a yellowish or whitish cheesy like material.



Characterized under the microscope by the appearance of an a cellular 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



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

Fat necrosis

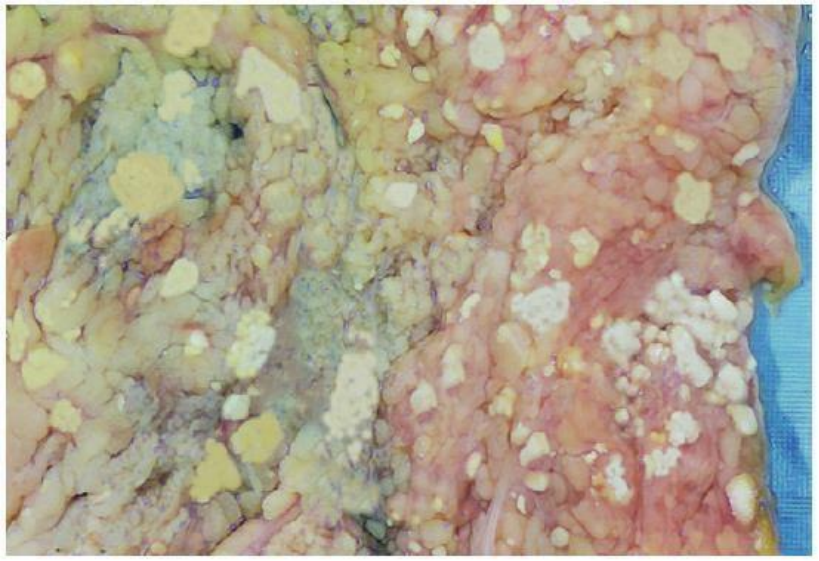
From its name ➔ necrosis of adipocytes.

- 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

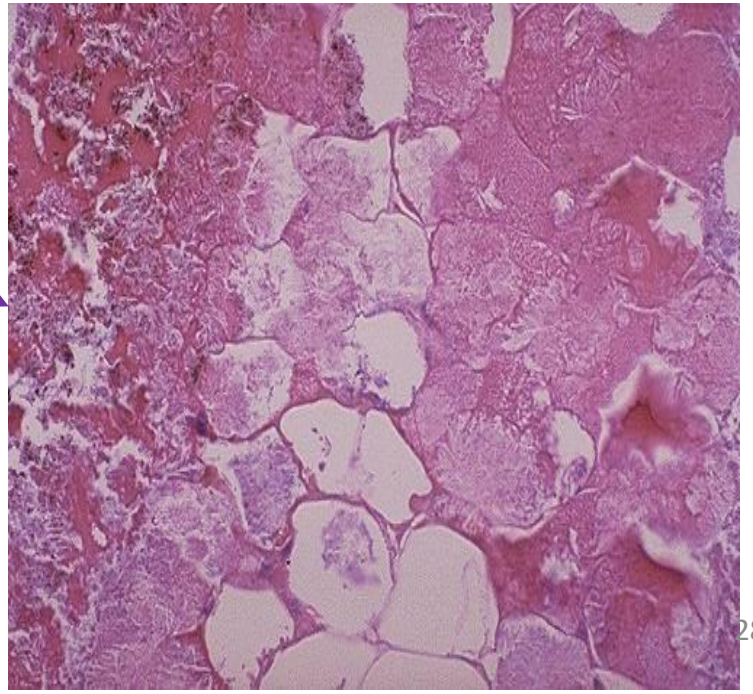
The pancreas is surrounded by fat in the abdomen and the released pancreatic lipases are going to digest it.Upon the digestion of the fat, fatty acids (FA) are going to be released.

Fatty acids (FA's) have high binding capacity to calcium

Under the microscope, there is a shadow of the dead cells with lost nuclei.



Notice the chalky white material in the fat tissue.



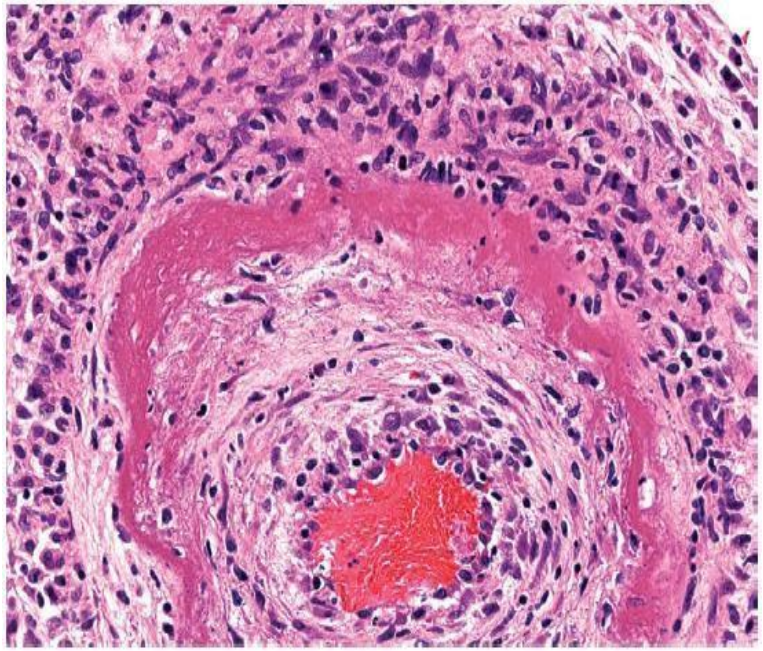
Fibrinoid necrosis

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

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

- Seen in vasculitis (PAN), (Vasculitis is an autoimmune disease.One example is the poly arthritis Nodesa (PAN))
- Severe hypertension.



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

And we are done , How it was?

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	9	The captions above images	Switch the captions
	9	Intercellular	Intracellular
	9	Microscopic	Macroscopic
	10	Reversible	Irreversible
	11	Intercellular	Intracellular
V1 → V2	24	The captain below images	Switch the caption

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. ROBBINS and CORTAN Pathological Basis of Disease

اللهم أحينا في الدنيا مؤمنين طائعين وتوفنا مسلمين تائبين اللهم ارحم تضرعنا بين يديك وقوّمنا إذا اعوججنا وادعتّا اذا استقمنا وكن لنا ولا تكن علينا، اللهم نسألك يا غفور يا رحيم أن تفتح لأدعيتنا أبواب الاجابه يا من إذا سأله المضطر اجاب يامن يقول للشيء كن فيكون، اللهم لا تردنا خائبين وآتنا أفضل ما يؤتى عبادك الصالحين، اللهم ولا تصرفنا عن بحر جودك خاسرين ولا ضالين ولا مضلين واغفر لنا الى يوم الدين برحمتك يا أرحم الرحمين.