بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pathology | Lecture #2

# Reversible and Irreversible Cell Injury


Written by : Rayyan Theeb
Hashem Alhalalmeh

Reviewed by : NST

# Reversible and irreversible cell injury

**cell injury and adaptations**

**Manar Hajeer, MD, FRCPath**

**University of Jordan , school of medicine**

# Outlines:

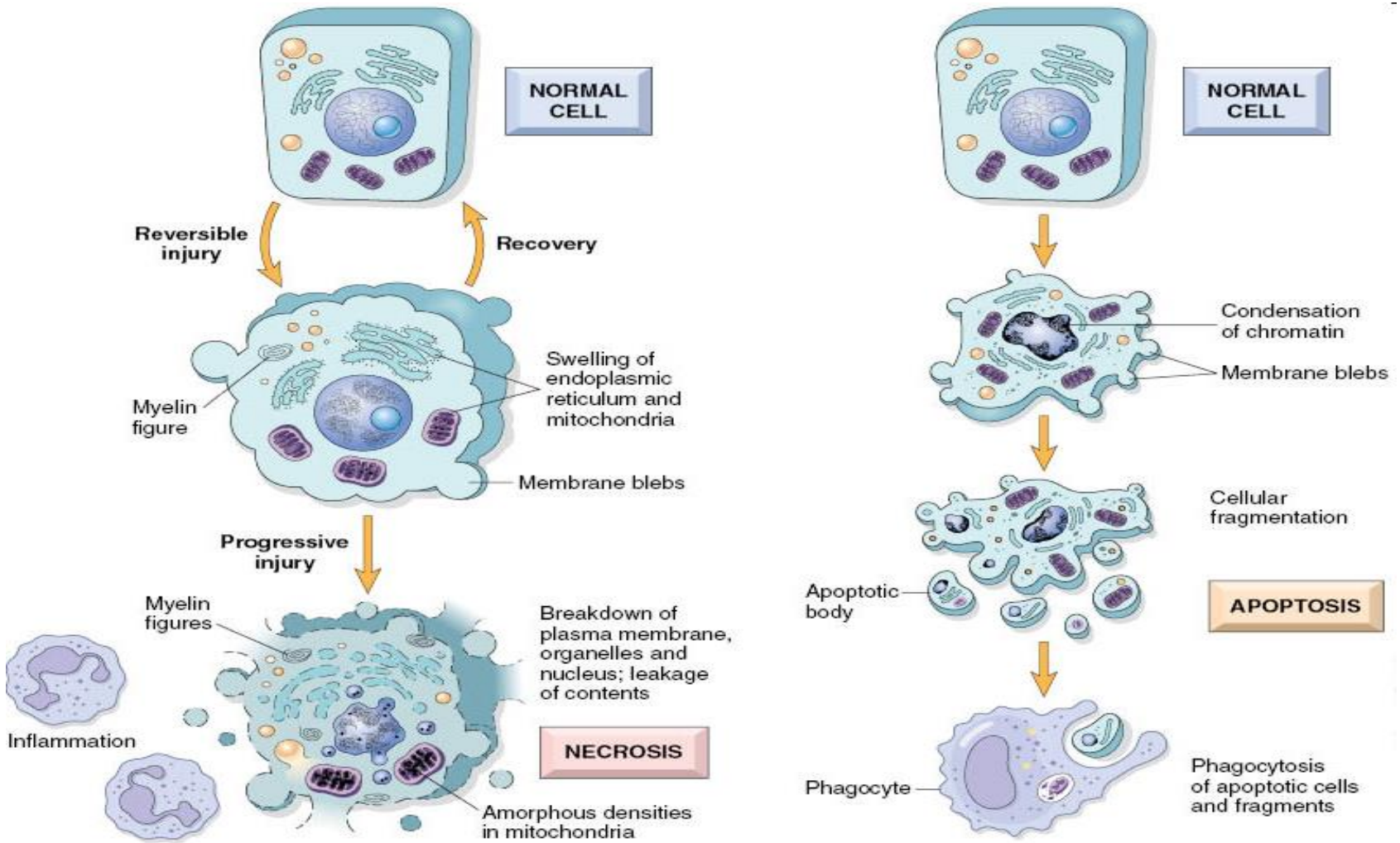
- Reversible injury.
- Irreversible injury (necrosis).
- Clinical implications. For irreversible injuries
- Patterns of necrosis.

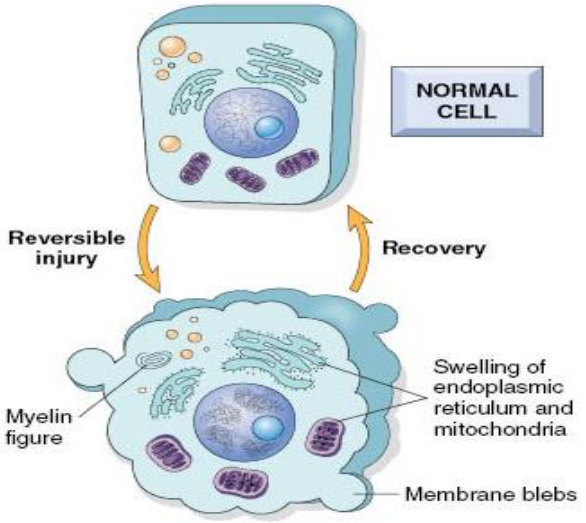
# Cell injury:

Cell injury is classified based on the ability of the cell to return to its normal state after the removal of the injurious stimulus into two types:

1- Reversible injury

2- Irreversible injury






When a normal cell is exposed to an injurious stimulus, it first undergoes reversible injury.

In reversible injury, several changes can be noticed:

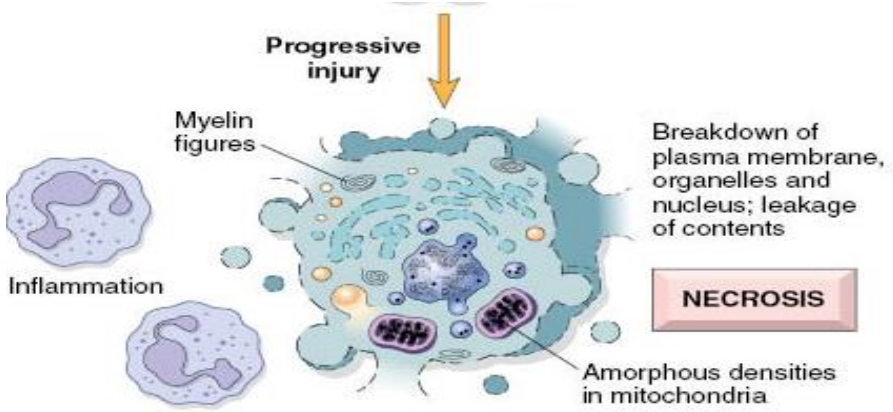
1- **Cell swelling** due to the accumulation of water inside the cell

2- Formation of **membrane blebs and bulges**

3- **Swelling of different cellular organelles** such as ER and mitochondria

4- Appearance of **black densities** in the mitochondria

However, the cell membrane, organelles and nucleus are still intact



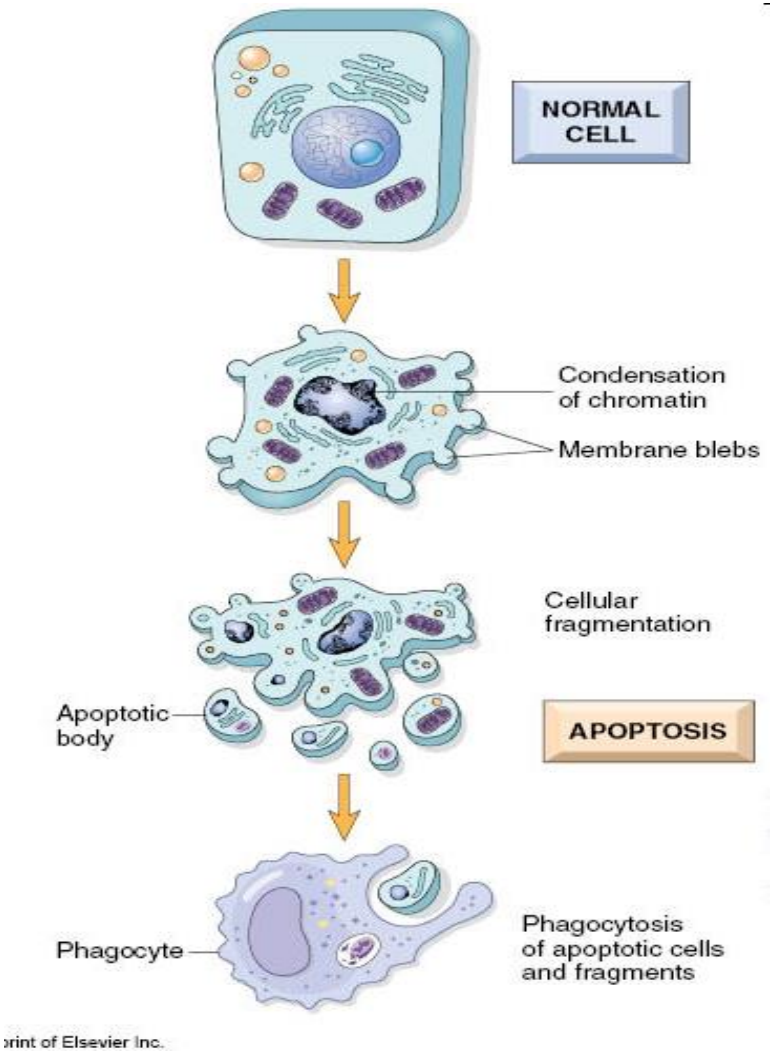

If the injury is prolonged or progressive, the cell will enter into the irreversible cell injury **"the point of no return"**
This lead to cell death (necrosis)

In irreversible injury, several changes can be noticed:
1- **Loss of cell membrane continuity** (similar to a rupture of a balloon after being overfilled with water)
2- **Disruption of organelles membranes**
3- **The nucleus starts to disappear**
4- **Leakage of cellular contents** including enzymes
5- **Inflammatory reaction** in which inflammatory cells -mainly neutrophils- engulf the dead cell

Apoptosis, another type of cell death, doesn't go through reversible or irreversible cell injury

It has several characteristics:
1- **Shrinkage of the cell.**
2- Cell and organelles membranes remain **intact**.
3- Fragmentation of the cell into small **apoptotic bodies** – each consisting of a portion of the plasma membrane enclosing cytoplasmic components, organelles, or nuclear fragments.

At the end, the cell will disappear by a few inflammatory cells without provoking an intense inflammatory reaction as in necrosis.




Apoptosis will be discussed in a separate lecture

# Reversible injury

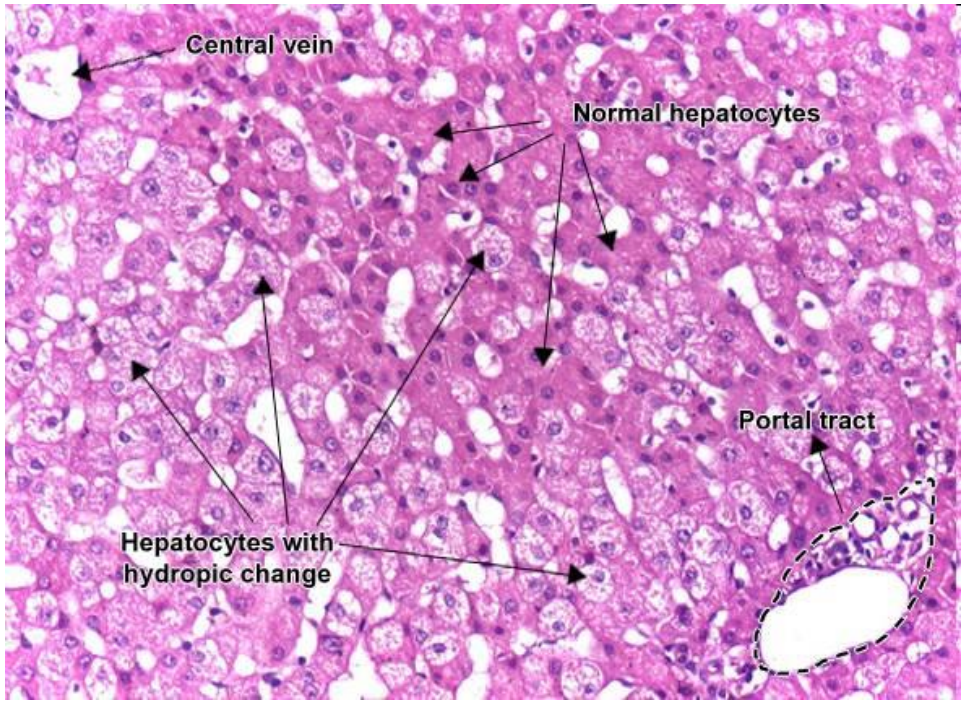
- If the damaging stimulus is removed >>>
  injured cells can return to normal

In pathology, Morphology is divided into two types:
1- **Macroscopic** morphology: refers to changes that can be observed using **naked eye** at the level of the whole organ.
2- **Microscopic** morphology: refers to changes observed under **microscope** (mainly light microscope).
**Ultrastructural changes** can only be seen by **electron microscope**.

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

# Reversible damage – cellular swelling

A section from the liver shows hepatocytes undergoing **hydropic** change ( called hydropic because of the accumulation of water) Normal hepatocytes have a pinkish cytoplasm while injured hepatocytes appear whitish or bubbly.




Accumulation of water occurs due to the failure of Na+/K+ ATP dependent pump in the cell membrane

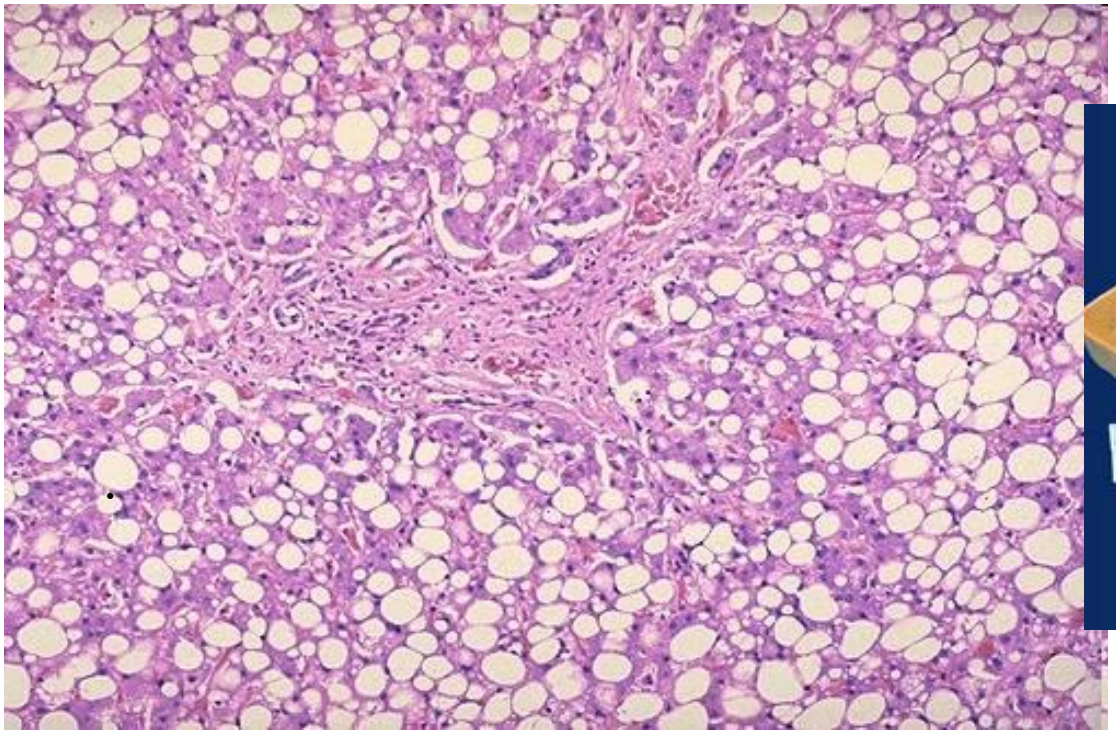
In injured cells, there is no ATP production

Failure of this pump leads to accumulation of Na+ inside the cell and K+ outside the cell

Accumulation of Na+ causes water to move into the cell resulting in cell swelling

# Reversible damage – fatty change

This morphological change occurs mainly in organs involved in fat metabolism.
Macroscopically, liver appears enlarged, yellow and greasy.
Microscopically, lipid-rich droplets accumulate inside hepatocytes cytoplasm



A fatty, yellow and greasy liver section

## Other changes

Seen under electron microscope

- (1) plasma membrane alterations (blebbing, blunting)

  Membrane still intact
- (2) mitochondrial change (swelling and **black** densities);
- (3) dilation of ER — With time, ribosomes detach from ER
- (4) nuclear clumping of chromatin. — Nucleus still intact
- (5) Cytoplasmic myelin figures derived from phospholipids of the altered plasma and organelle membranes

These changes are also sometimes seen in irreversible injury ,but they are much more severe

# Irreversible injury (necrosis)

Defining features of necrosis:

1. **Irreversible Mitochondrial dysfunction** No ATP production
2. Loss of **plasma membrane and intracellular membranes** integrity >>> cellular enzymes leak out

Contents of organelles leak into the cytoplasm, and cytoplasmic contents leak out of the cell.
They can enter the bloodstream where they can be detected by certain laboratory investigations

3. Loss of **DNA and chromatin structural integrity**.

- Local inflammation.

Necrosis is always accompanied with local inflammatory reaction

# Morphology irreversible injury (Necrosis)

Under electron microscope

- Increased cytoplasmic eosinophilia. Seen under LM using H&E

Eosinophilia means more pink staining using H&E

Increased eosinophilia is due to two reasons:
1- Accumulation of degraded proteins in the cytoplasm which attracts and binds eosin
2- Reduced proteins transcription and translation resulting in decreased RNA content (normally basophilic (blue)) leading to more eosinophilia

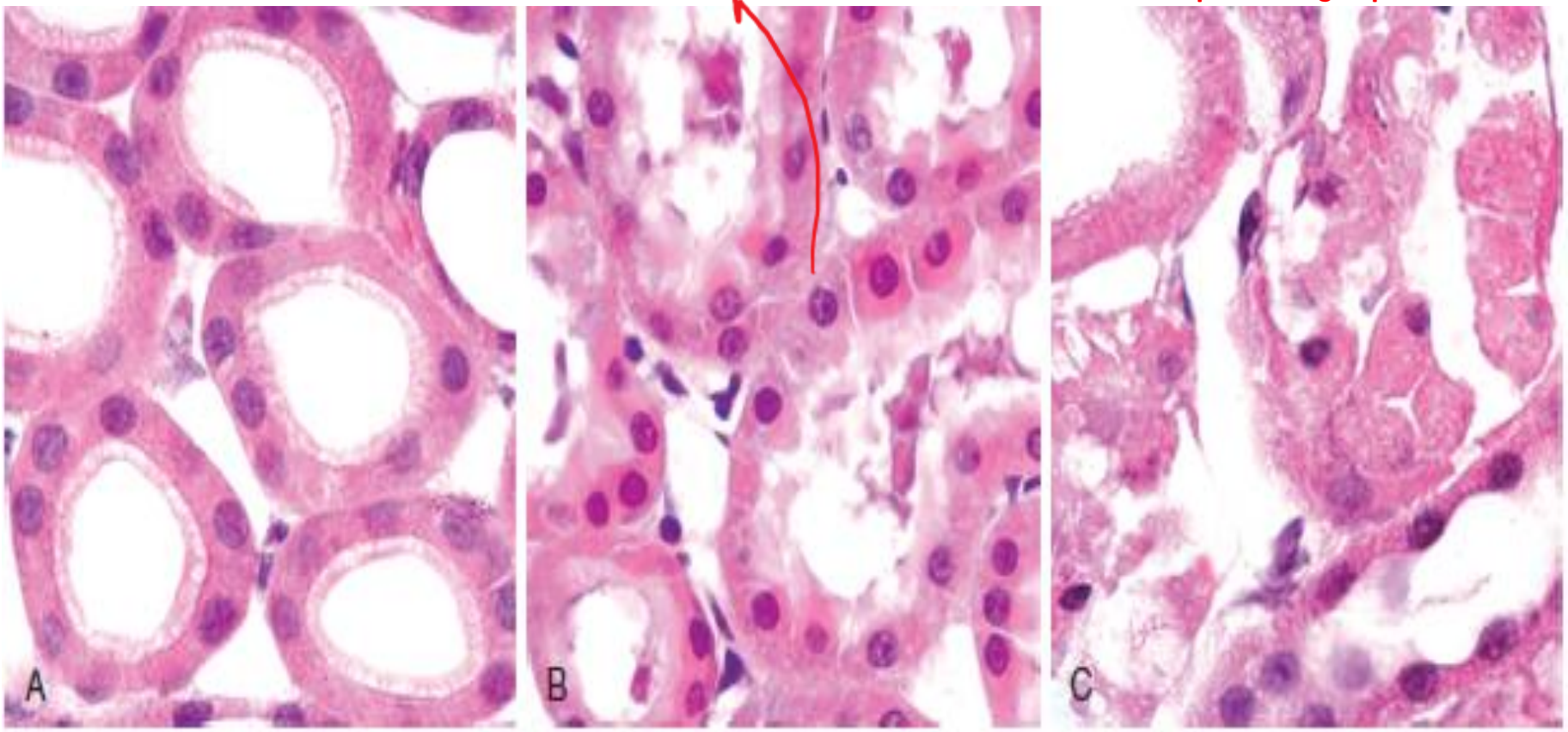
- Marked dilatation of ER , mitochondria.
- Mitochondrial densities.
- More myelin figures due to increased membranes damage

- **Nuclear changes (3 stages):** Seen under LM using H&E
- **Pyknosis**: shrinkage and increased basophilia; More blue staining using H&E
- **Karyorrhexis** :fragmentation; of the nuclear material
- **Karyolysis**: basophilia fades Degradation of the nuclear material

# Normal, reversible and irreversible cell injury

Swollen but still intact

Disrupted nuclei
Eosinophilic cytoplasm




Normal

Reversible

Irreversible

# Cell death

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

- **Necrosis:**
- Happens when the injurious stimulus is Rapid and uncontrollable.
- Severe disturbances
- Ischemia, toxins, infections, and severe trauma

Cut of blood supply

Induce damage

Severe, like:
Viral
Bacterial …

In all these events, the damage is rapid and the injury is severe, so we end up with necrosis.

- **Apoptosis:**
- Less severe injury, like:

UV light induced sun damage

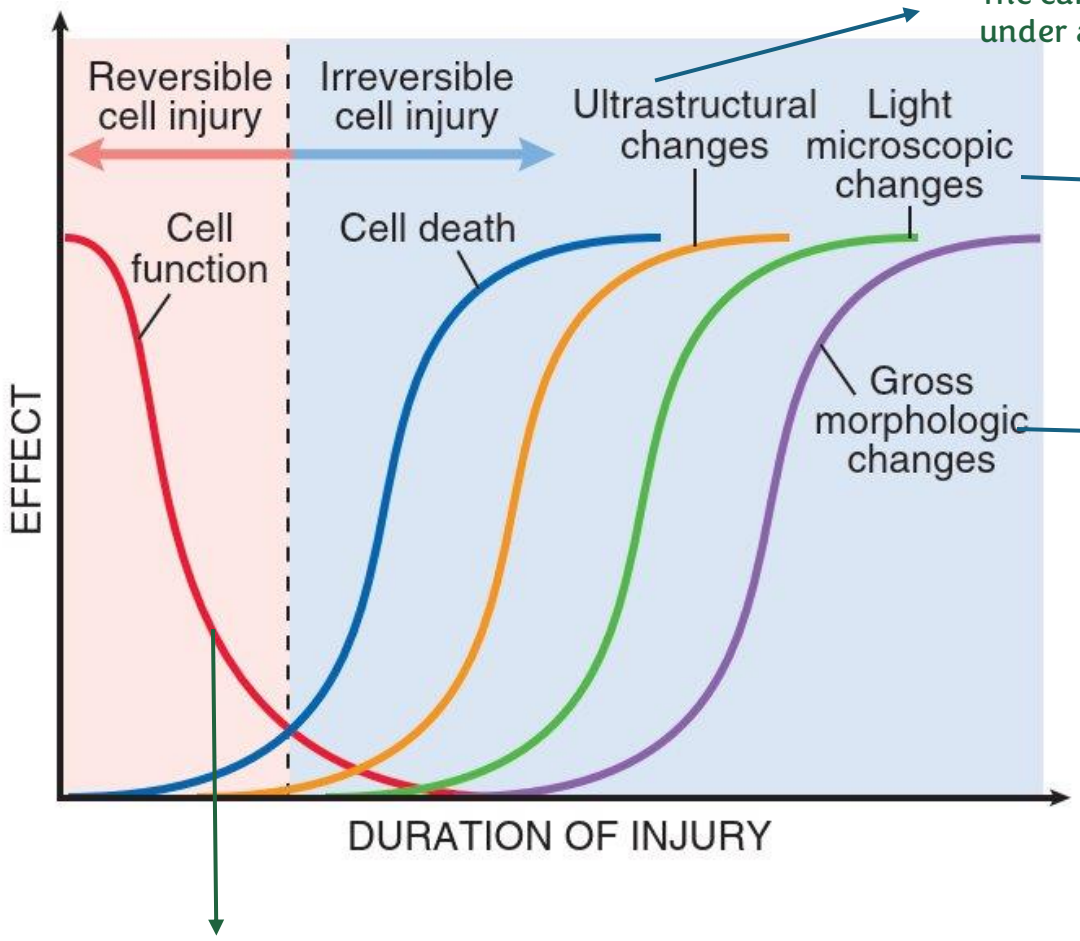
Aging of cells

Loss of growth factors, all these injuries are trivial

- Highly Regulated by genes and signaling pathways
- Precisely Controlled.
- Can be manipulated.
- In healthy tissues.
- Clean cell suicide.

- **Necroptosis.** the mixture of necrosis and apoptosis at the same time

# An injured cell loses its function, whether the damage is reversible or irreversible.




The earliest changes are visible only under an electron microscope.

2nd observed changes

Last observed changes observed by naked eyes at the level of the whole organ.

Cell function begins declining immediately once reversible injury starts.

# Very important table

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.

Due to increased water content

Cellular and enzymatic content leaks out

And every part goes into apoptotic body in order for macrophages to easily engulf them

That's why it's called clean suicide

No physiologic necrosis

# 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.

- Cardiac enzymes, liver enzymes.

Myocardial injuries, such as ischemia or myocarditis, can be detected by measuring cardiac enzymes in the blood.

When a patient complains of cardiac chest pain and myocardial infarction is suspected, the doctor checks cardiac enzymes. If the enzymes are elevated, it confirms an injury in the heart.

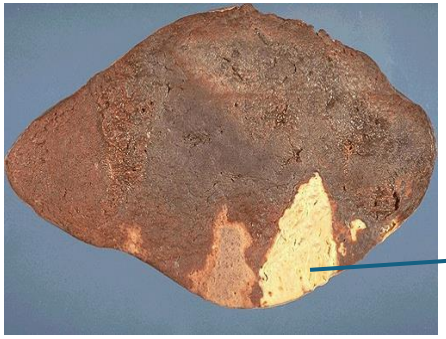
In cases of hepatic injury, such as drug-induced toxicity or viral hepatitis, the doctor measures liver enzymes, AST and ALT, in the blood to detect liver damage.

# Morphologic Patterns of tissue necrosis

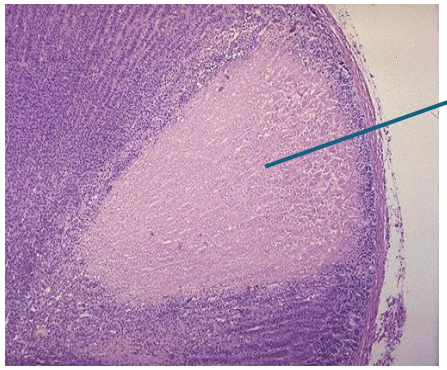
## (Etiologic clues)

# Coagulative necrosis

- Conserved tissue architecture initially, for a few days, before the onset of inflammation that'll cause the damage in the tissue architecture
- 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



Pale wedge-shaped area (macroscopic image)



Anuclear wedge-shaped area of dead cells (microscopic image)

Macroscopically, the area of coagulative necrosis appears pale at the organ level due to loss of blood supply from ischemia.

The architecture in coagulative necrosis is preserved because ischemia causes enzymatic dysfunction, preventing degradation, so cells maintain their shape for a few days until blood supply returns and neutrophils and inflammatory cells begin phagocytosis and clearance of dead cells.

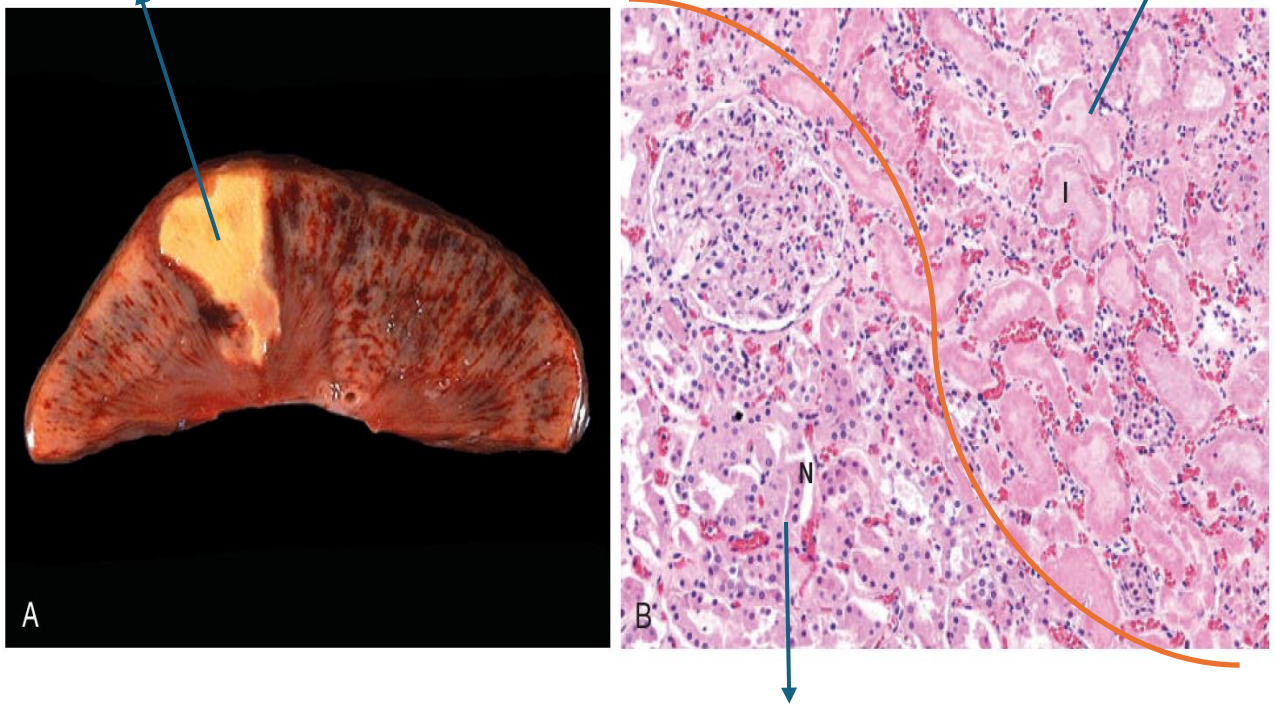
Macroscopically, coagulative necrosis appears as a wedge-shaped pale area due to loss of blood supply.

Microscopically, it appears as a wedge-shaped area of eosinophilic cells that are devoid of nuclei because they are dead.

This is another example of coagulative necrosis in the kidney.

# Coagulative necrosis

Macroscopically, there is a wedge-shaped area of tissue damage.

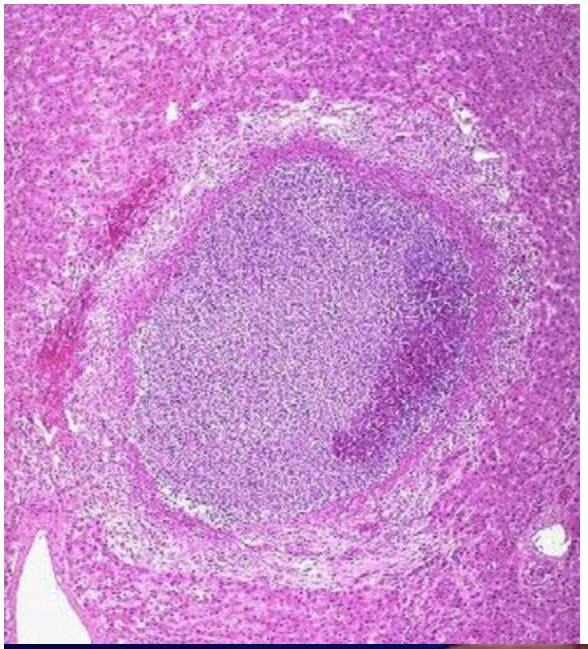


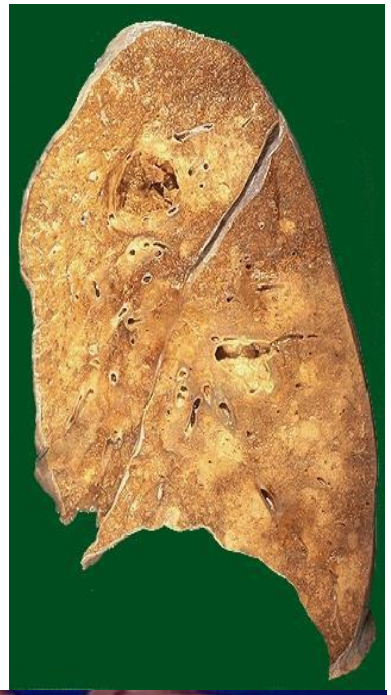

while on the right, the tubules have lost their nuclei but their structure remains preserved for a few days.

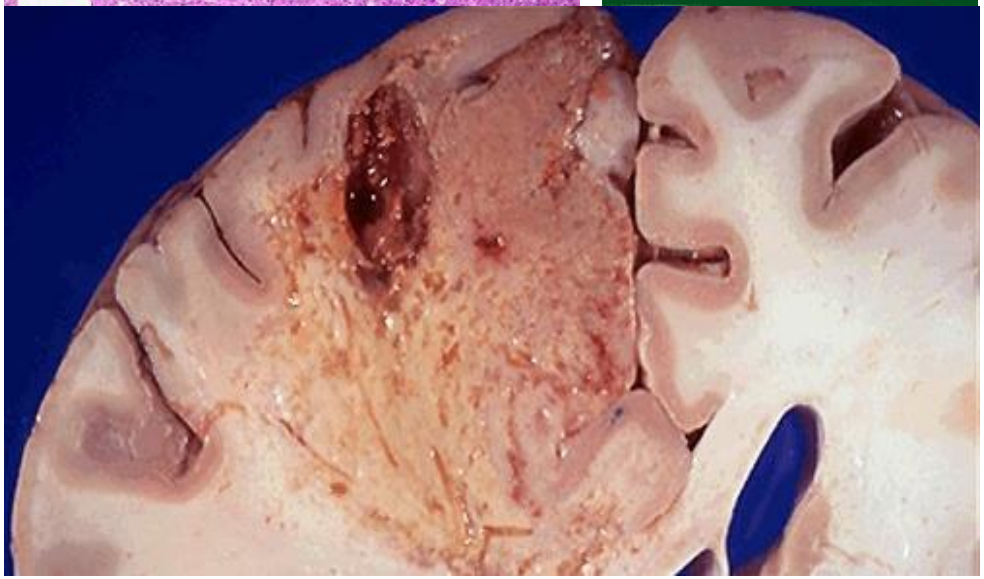
on the left, cells have intact nuclei

# Liquefactive necrosis

- Focal infections by Bacterial and fungal organisms.
- Pus.
- CNS infarcts Ischemia to CNS organs, such as the brain and spinal cord, results in a liquefactive pattern of necrosis rather than the coagulative necrosis seen in other solid organs.
- Center liquefies and digested tissue is removed by phagocytosis



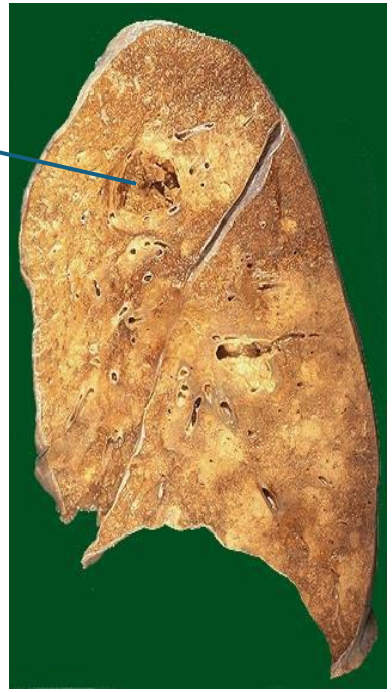




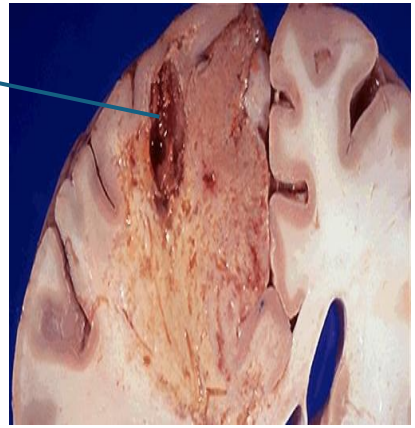
In liquefactive necrosis, a liquid material accumulates, often associated with focal bacterial or fungal infections that produce pus. Macroscopically, it appears as a cavitary lesion, and microscopically, it is characterized by a collection of inflammatory cells, mainly neutrophils.

The tissue liquefies because it is digested and removed by phagocytes.

Cavitary lesion of the lungs



Cavitary lesion corresponding to an area of infarction



# Gangrenous necrosis

Amputation of the distal foot shows blackish discoloration of the skin due to ischemic necrosis affecting the skin, underlying subcutaneous tissue, muscle, and bone.

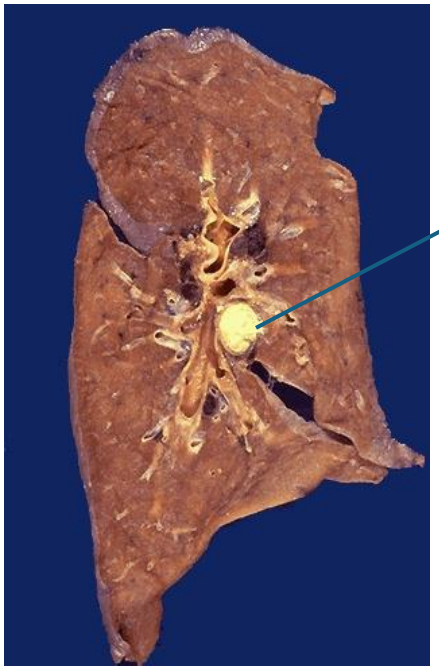
- Clinical term
- It is coagulative necrosis, but it occurs at multiple tissue levels.
- Dry vs wet

Gangrenous necrosis, or gangrene, can be complicated by a superimposed infection, which is called wet gangrene as in the picture to the left, whereas dry gangrene occurs without infection.

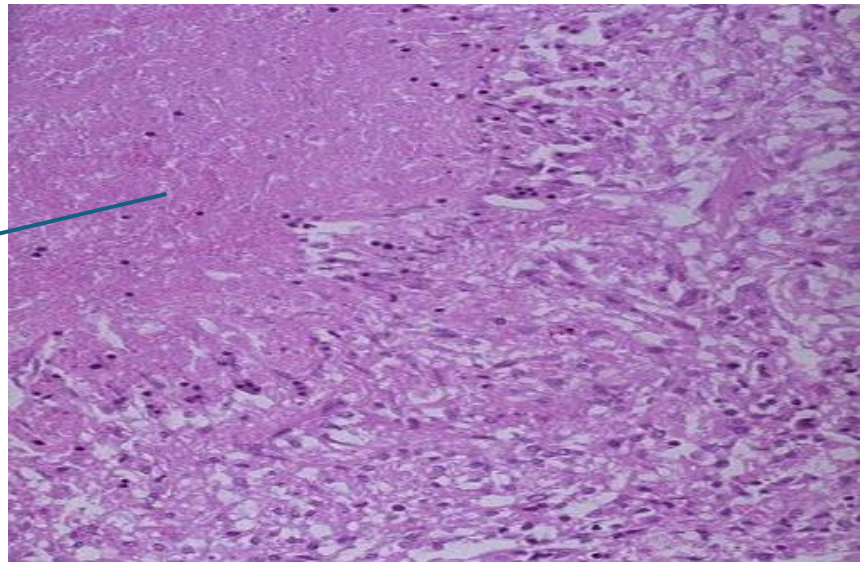
# Caseous necrosis

Caseous necrosis, classically seen in tuberculosis, is named for the accumulation of a cheese-like material.

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

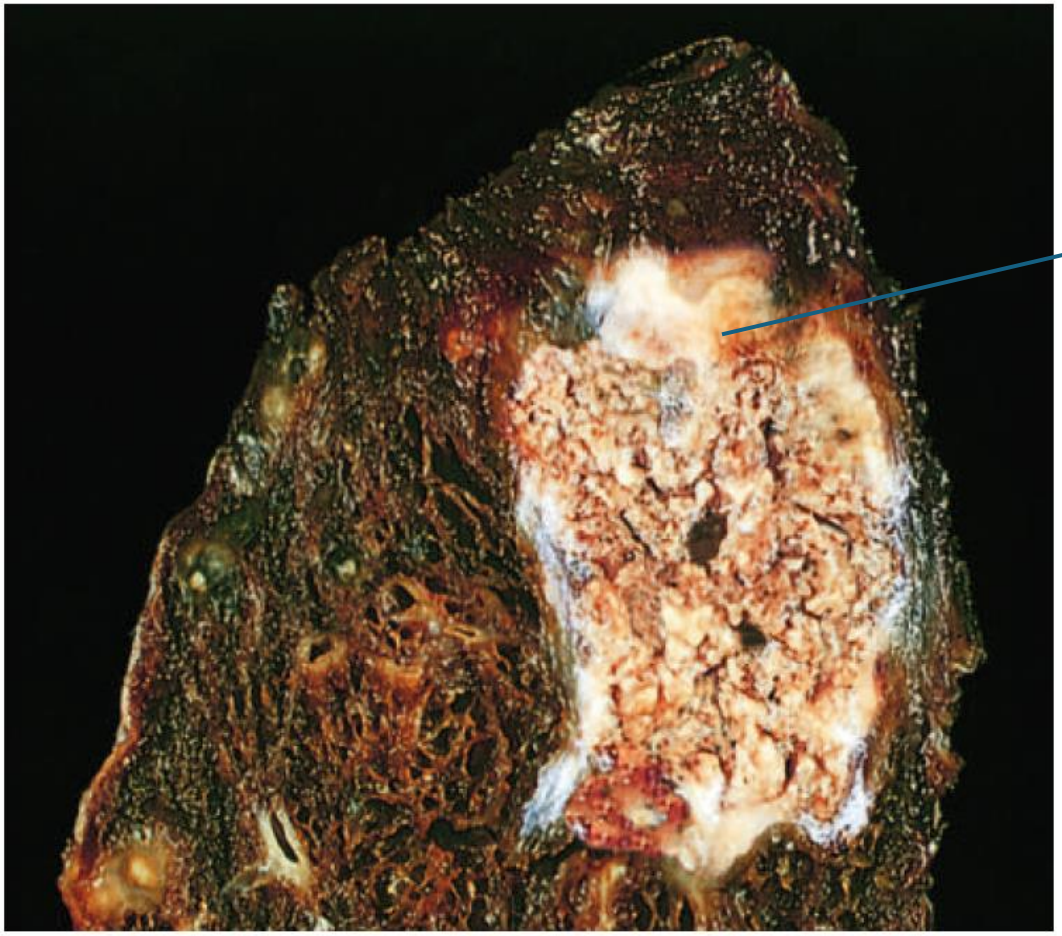


Yellowish to whitish is a cheesy-like material, the tissue architecture isn't preserved anymore, like in coagulative necrosis.



Microscopically, it is characterized by an acellular central area of necrotic material, usually surrounded by a collection of macrophages forming a structure called a granuloma.

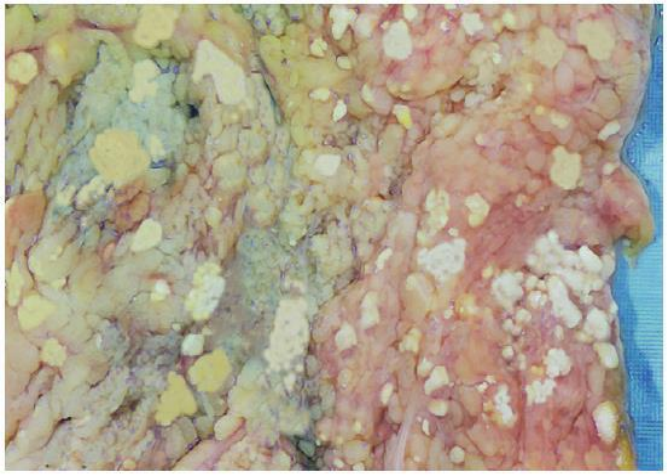
# Caseous necrosis



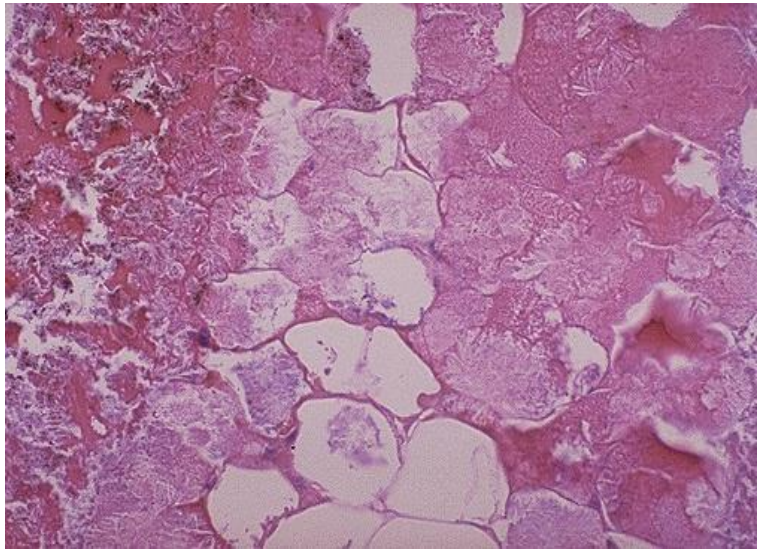
Yellowish to whitish cheesy-like material in the section of the lung

# Fat necrosis

- **Usually** Occurs in acute pancreatitis
- Due to release of pancreatic lipases
- **This will lead to** Focal fat destruction
- **Upon fat digestion it'll cause** Released FA's combine with Ca2+ (saponification) to produce the whitish chalky appearance
- **Microscopically we can see** Shadows of necrotic fat cells **with lost nuclei**



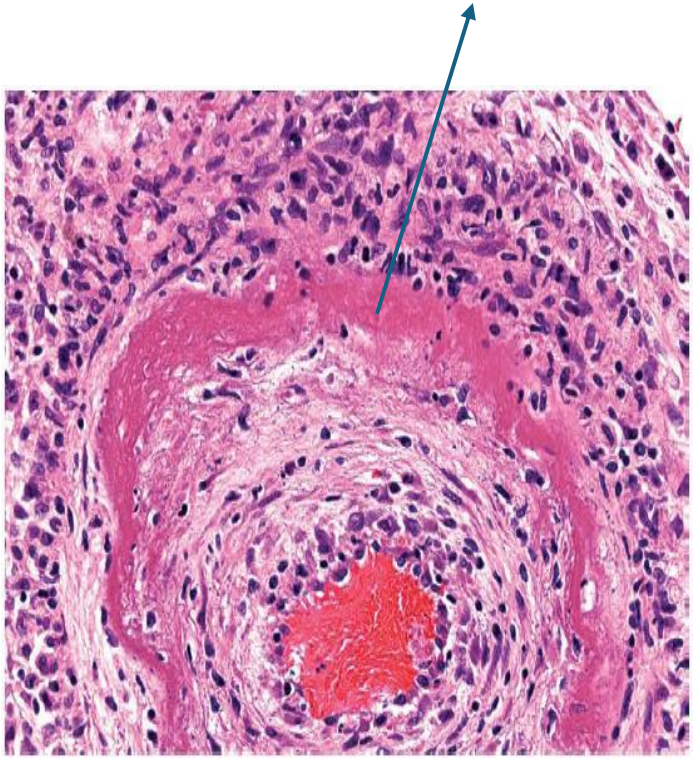
The pancreas is surrounded by fat in the abdomen, and the lipases will digest this fat. And here we can see a chalky white material on the fatty tissue.



# Fibrinoid necrosis

The fibrin material is the pink ring-like material deposited in the wall of the blood vessel

- Visible only microscopically.
- **Caused by** Deposits of antigen –antibody and fibrin complexes in arterial walls
- Seen in vasculitis (PAN)
- **Also can be seen in** Severe hypertension.



It's seen in vasculitis, which is an autoimmune disease like PAN, which is polyarthritis nodosa.

# رسالة من الفريق العلمي:

الحمد لله رب العالمين أولاً وآخراً،
ومبارك عليكم يا أهل غزة يا من عانيتم وتعبتم وصبرتم وكنتم النور والحياة لهذه الأمة خلال عامين كاملين،
ونسأله سبحانه تمام النعمة برؤية آلاف الأسرى محررين بين أهاليهم قريباً إن شاء الله في غزة وفلسطين.

أما بعد:

فهنيئا لمن صبر،
وهنيئا لمن ثبت،
وهنيئاً لمن اصطفاه الله شهيداً ثابتاً في وجه العدو مقبلاً غير مدبر،
هنيئا لمن أحسن الظن بالله سبحانه،
وهنيئا لمن دعم إخوانه وآزرهم،

وسحقاً لمن طعن في أهل غزة وأبطالهم وهمز ولمز، وردد مقولات بعض وكالات الإعلام ورموز الضلالة في تشويههم ومحاربتهم،
سحقاً لمن ضيق على إخواننا في قُوْتهم ومعيشتهم وغذائهم ودوائهم ودخولهم وخروجهم،

نحمد الله تعالى ونشكره ونستغفره،
الحمد لله
الحمد لله
الحمد لله

الشيخ أحمد السيد

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