



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ ۝



PATHOLOGY

MID | Lecture #2

Reversible and irreversible cell injury



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Color coding used in the modified:



Black: the original slides



Magenta: the doctor's explanation/words



Gray: additional information and explanation



Red: important information

Reversible and irreversible cell injury

cell injury and adaptations

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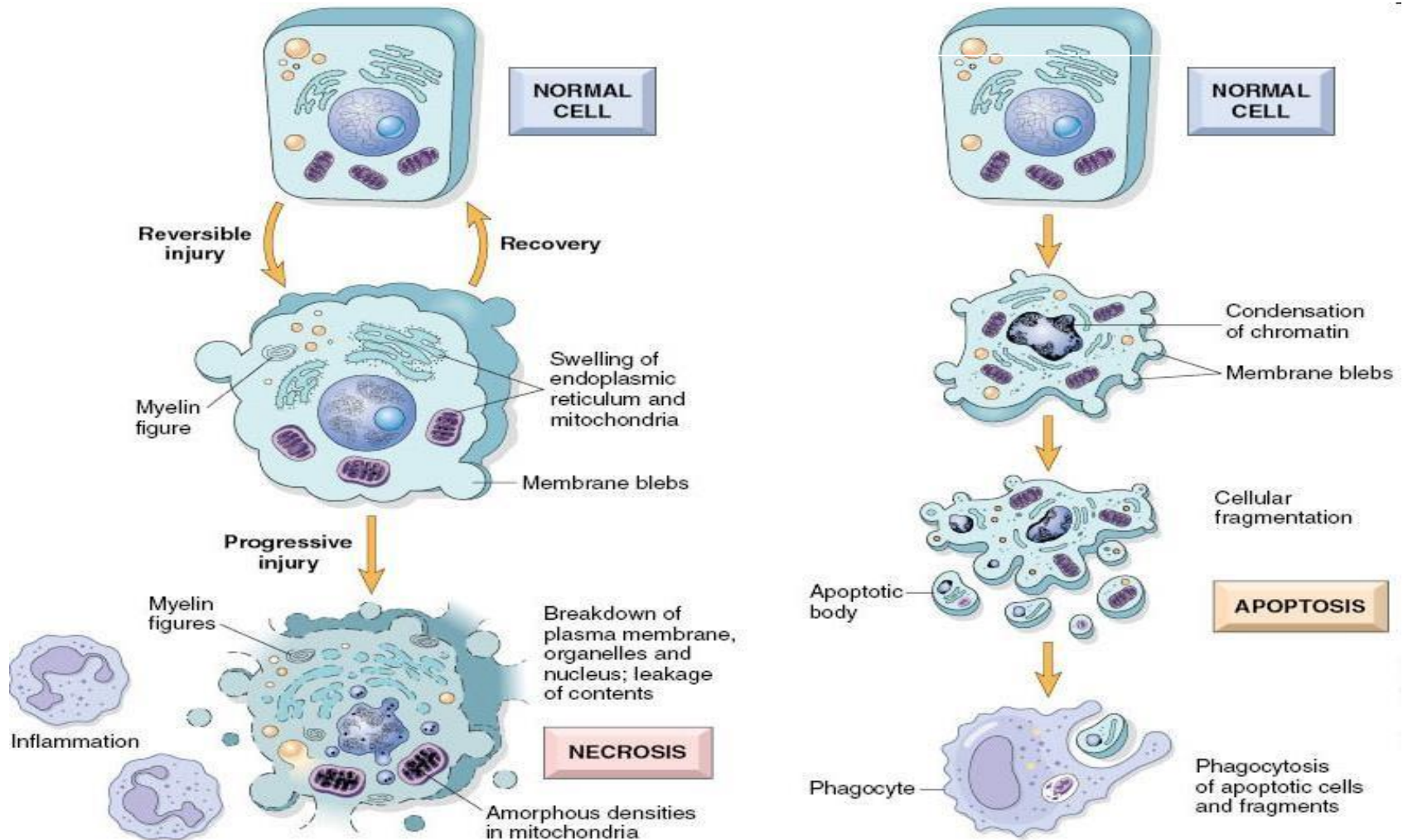
Outlines:

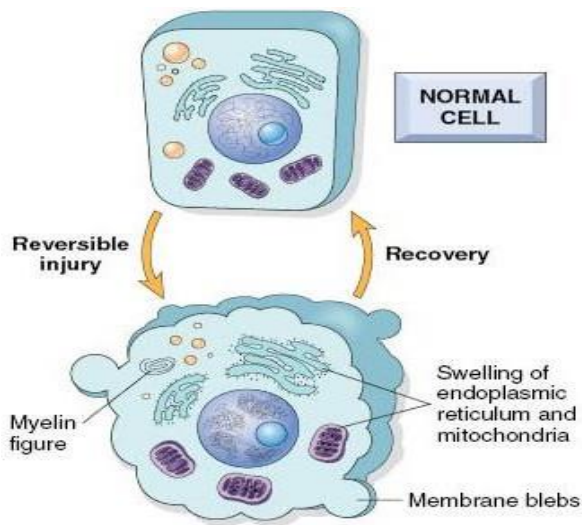
- Reversible injury.
- Irreversible injury (necrosis).
- Clinical implications. For irreversible injuries
- Patterns of necrosis.

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.

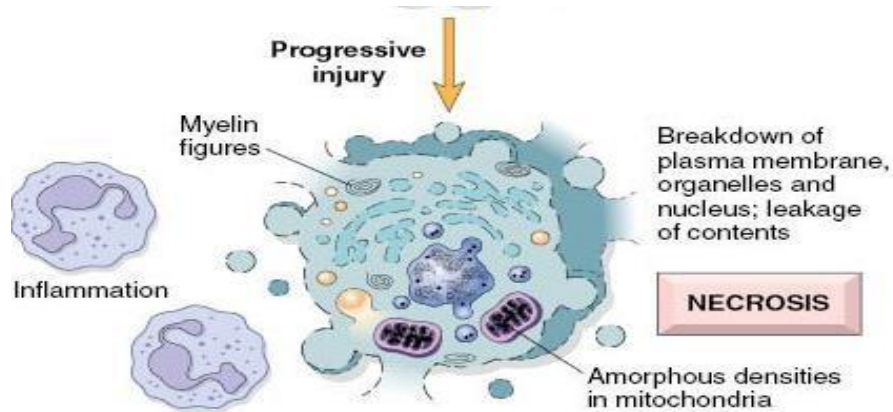
During reversible cell injury , the cell is alive but it is not functional

This is repeated in the next slides

In reversible injury, several changes can be noticed:

- 1) **Cell swelling** due to the accumulation of **water** inside the cell
(notice it is **not** the same as hypertrophy , because hypertrophy is an adaptive mechanism)
- 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 leads to cell death (necrosis)

In irreversible injury, several changes can be noticed:

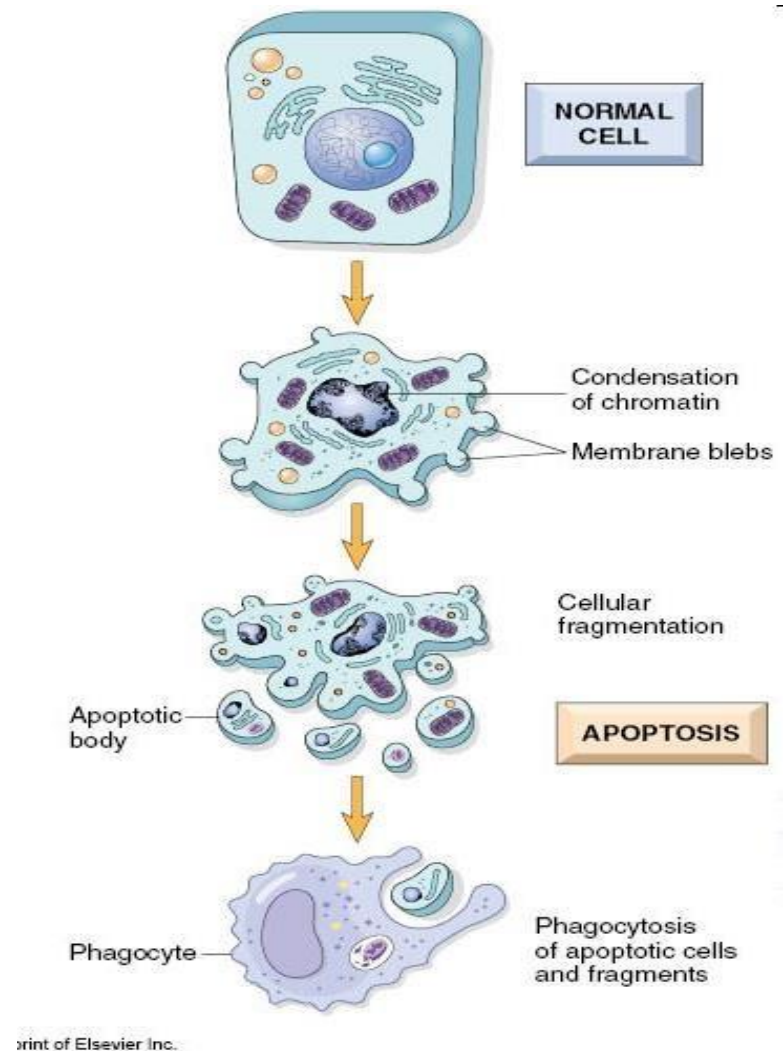
- 1) **Loss of cell membrane continuity** (similar to a rupture of a balloon after being overfilled with water)
- 2) **Disruption of organelles membranes**
- 3) **The nucleus starts to disappear**
- 4) **Leakage of cellular contents** including enzymes
- 5) **Inflammatory reaction** in which inflammatory 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: (morphology = the shape of the cell)

- 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**.

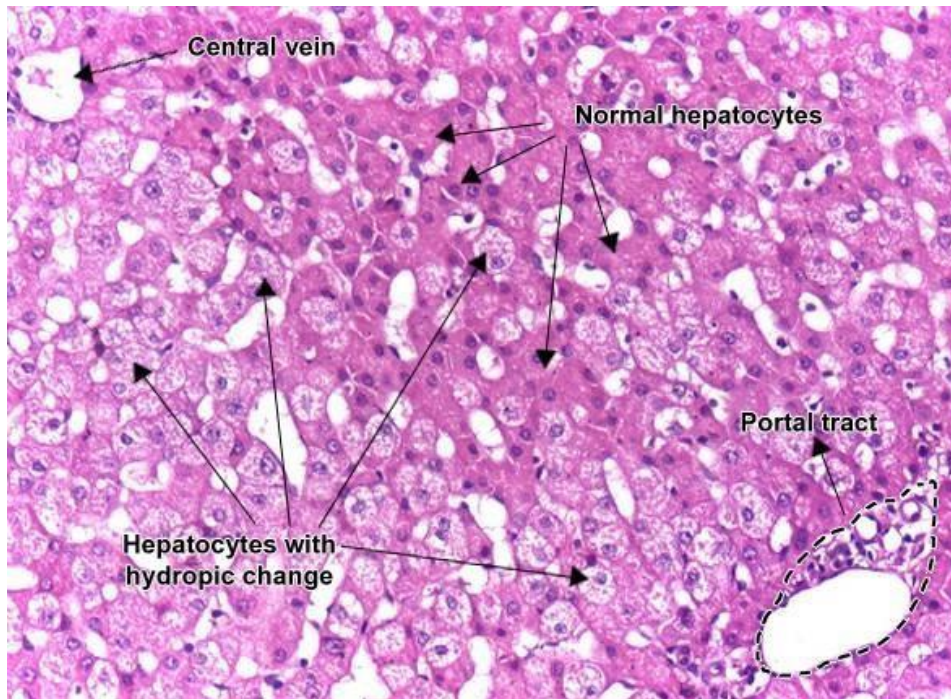
- **Morphology:**
- Cellular swelling/organ swelling
- Fatty change

For example , in hepatitis, the liver will enlarge and tender

Because of the damage in the bilayer of lipids in membranes

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 (non-functional mitochondria)

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

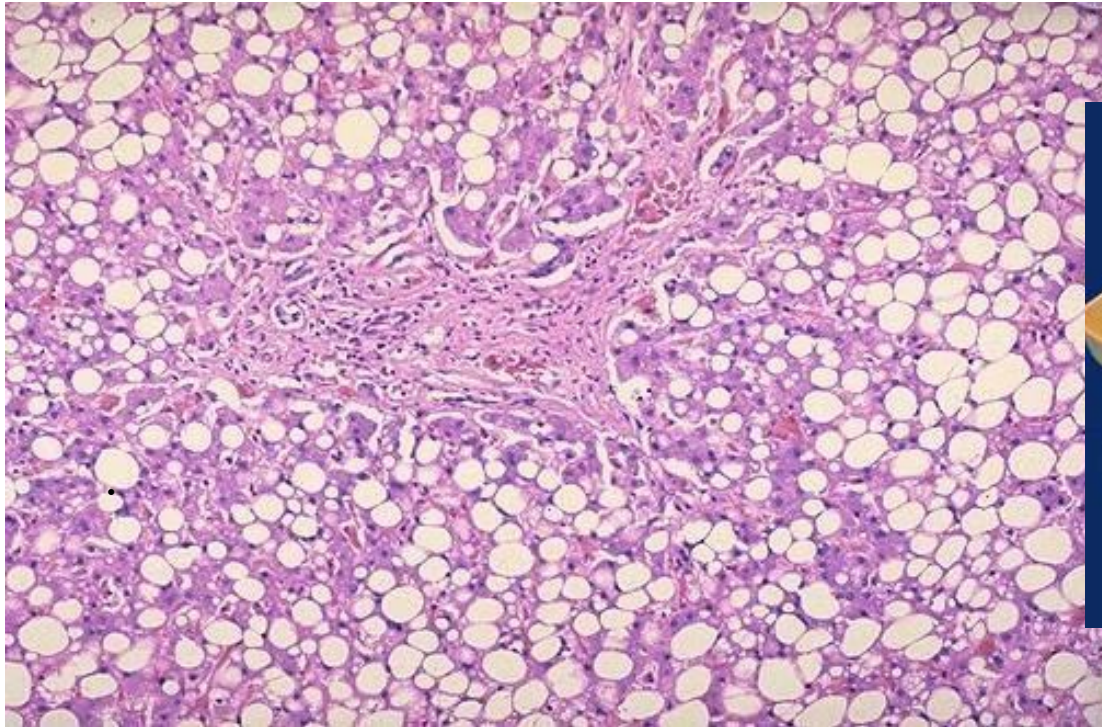
Accumulation of Na^+ causes water to move into the cell resulting in cell swelling

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 (fat 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);

The mitochondria will be non-functional and the energy production will stop that's why the cell becomes nonfunctional

- (3) dilation of ER **With time, ribosomes detach from ER , decreasing protein synthesis**

- (4) nuclear clumping of chromatin. **Nucleus still intact, it will appear very dark blue under the microscope**

- (5) Cytoplasmic myelin figures **derived from phospholipids (fat damage) 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:

The loss of membrane integrity results in losing the outline of the cell

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.

This helps the body to identify the place of inflammation (cellular damage) so immune cells can deal with it and clean the area.

Necrosis is always accompanied with local inflammatory reaction

Morphology irreversible injury (Necrosis)

- Increased cytoplasmic eosinophilia.  In reversible injury the cytoplasm will be more whitish due to swelling
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 to eosin.

2-Reduced proteins transcription and translation resulting in decreased RNA content (normally basophilic (blue)) leading to more eosinophilia

Under electron microscope:

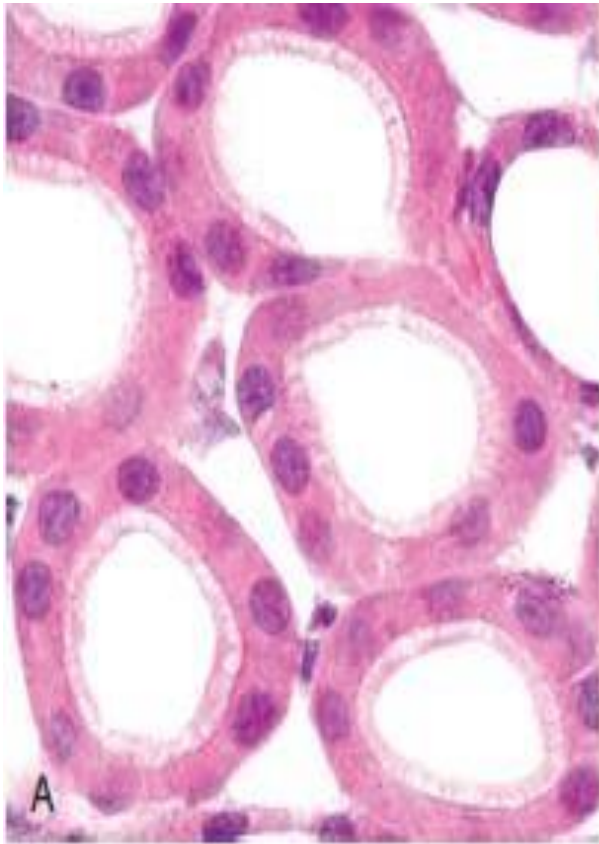
- Marked dilatation of ER , mitochondria.
- Mitochondrial densities.
- More myelin figures due to increased membranes damage
- **Nuclear changes (3 stages):** Seen under LM using H&E
- **Pyknosis:** shrinkage and increased basophilia; More blue staining using H&E
- **Karyorrhexis** :fragmentation; of the nuclear material
- **Karyolysis:** basophilia fades Degradation of the nuclear material

Some features of cellular damage are **common between both reversible and irreversible injury** like (myelin figures and mitochondrial swelling) but what **distinguishes irreversible damage is nuclear damage, mitochondrial dysfunction and loss of plasma membrane**

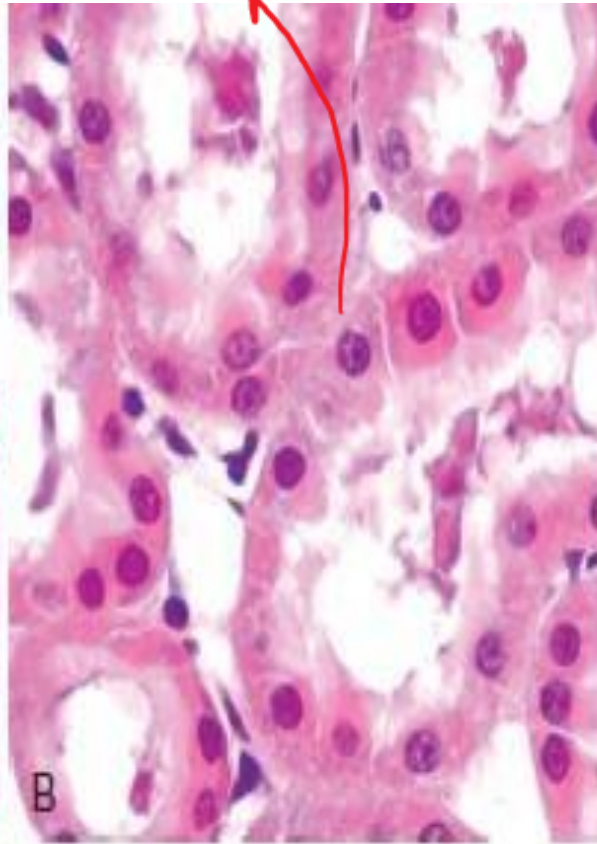
Normal, reversible and irreversible cell injury

Swollen but still

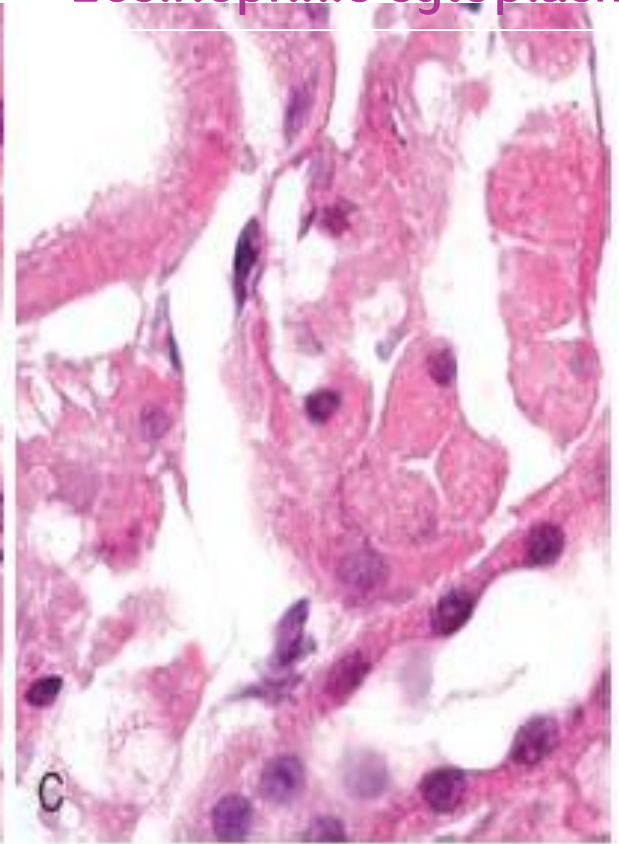
Disrupted nuclei
Eosinophilic cytoplasm



Normal



Reversible



Irreversible

Cell death

- Different mechanisms, depending on nature and severity of injury

Some cells are so delicate they can't withstand injury like neurons They can withstand ischemia for only few minutes while limbs can survive from ischemia lasting 2 or 3 hours

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

Cut of blood supply

Induced damage

Severe, like:
Viral
Bacterial ...

- **Apoptosis:**
- Less severe injury

UV light induced sun damage

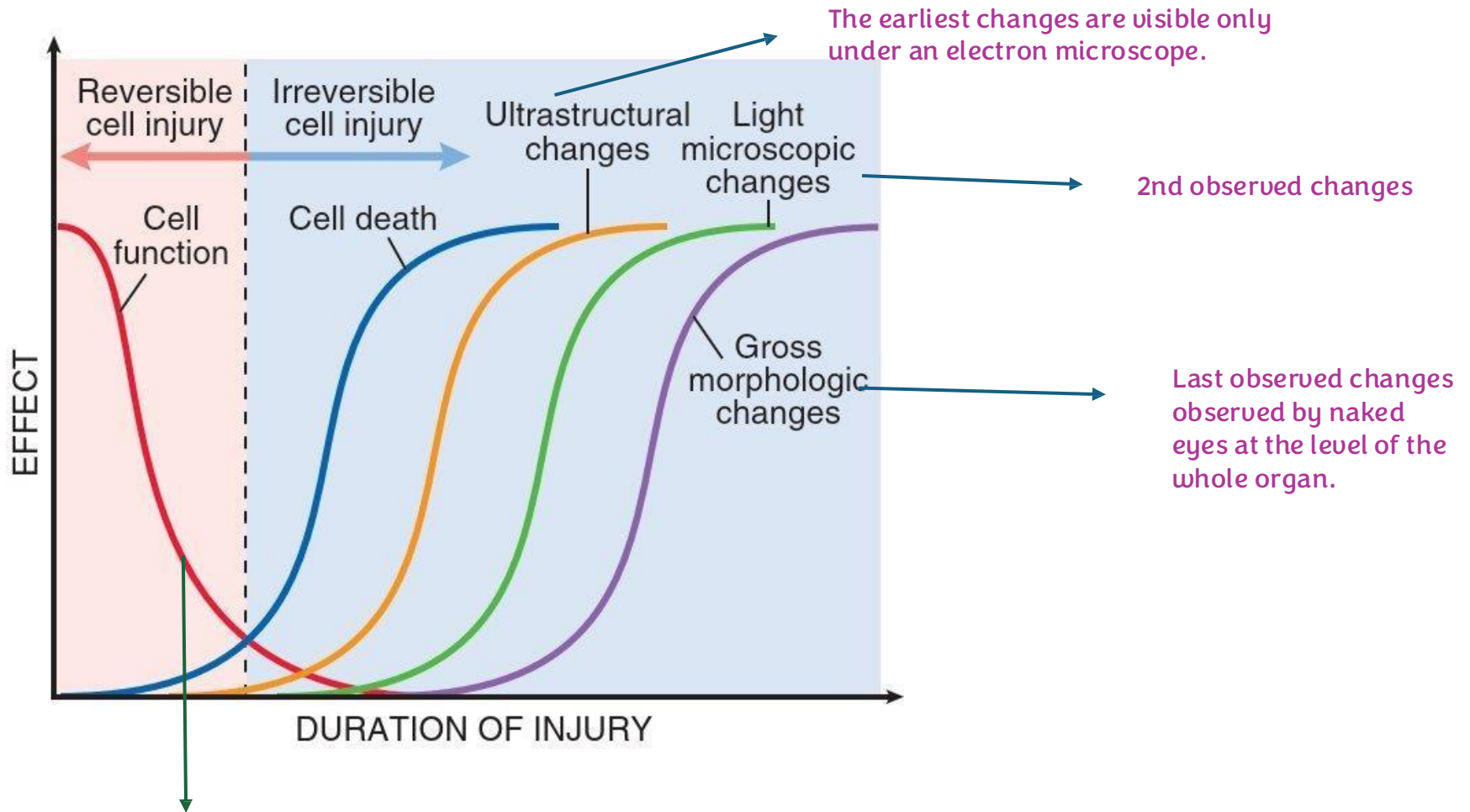
Aging of cells

Loss of growth factors, all these injuries are trivial

- 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.



Cell function begins declining immediately once reversible injury starts.

Apoptosis will be covered in details in a single lecture

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.

Very important in comparison

Due to increased water content

Cellular and enzymatic content leaks out

That's why it's called clean suicide

Nucleus will disappear in both mechanisms eventually

No physiologic necrosis

Clinical implications

In necrosis

- 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 MI, 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 viral hepatitis, the doctor measures liver enzymes, AST and ALT, in the blood to detect liver damage.

Morphologic Patterns of tissue necrosis

(Etiologic clues)

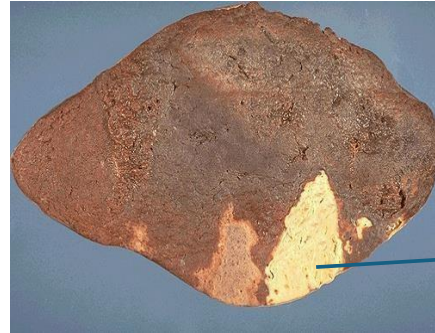
Coagulative necrosis

- Conserved tissue architecture **initially**
- Enzyme dysfunction.
- Anuclear eosinophilic on LM
- Wedge shaped, why?

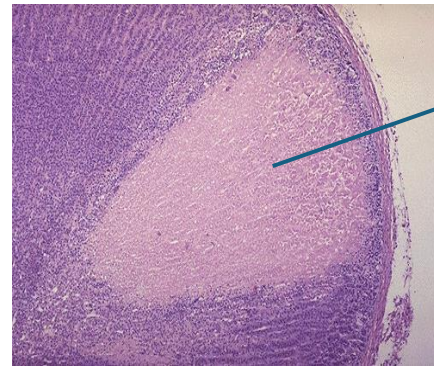
(following blood supply)

- Leukocyte lysosomal enzymes and phagocytosis required for clearance.
- **Cause:** Ischemia to a solid organ (**infarcts**) except the **brain**

- Ischemia is blood deprivation.
- Infarction is cell death (necrosis).
- Prolonged ischemia leads to infarction.



Pale wedge-shaped area
(macroscopic image)



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

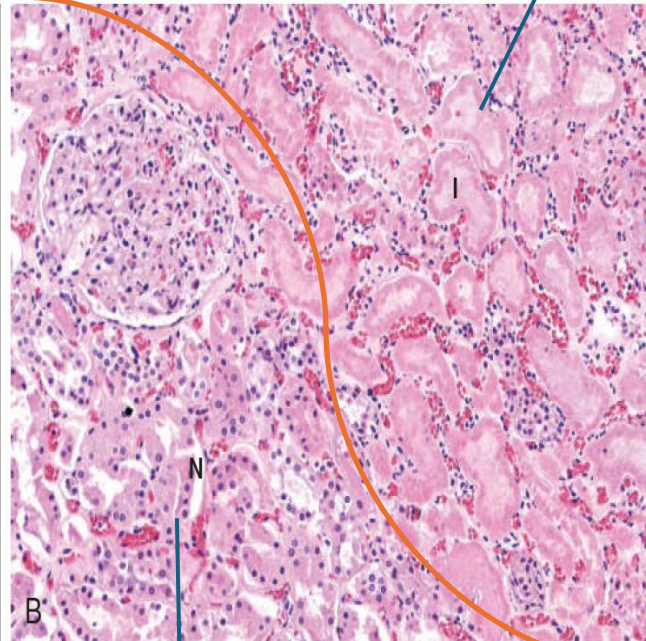
Coagulative necrosis

It's named "coagulative" because the architecture in coagulative necrosis is preserved because ischemia causes enzymatic dysfunction, preventing degradation, so cells maintain their shape for a few days until inflammatory cells begin the clearance of dead cells.

Macroscopic pallor	Microscopic pallor (eosinophilia)
Because of blood deprivation (ischemia)	Because the cells are anucleated (dead) (devoid of nuclei)

This is another example of coagulative necrosis (in the kidney.)

Coagulative necrosis



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

Nuclei in the right side are for inflammatory cells

on the left, cells have intact nuclei

Liquefactive necrosis

Causes:

- I. **Focal (localized) infections by Bacterial and fungal organisms.**

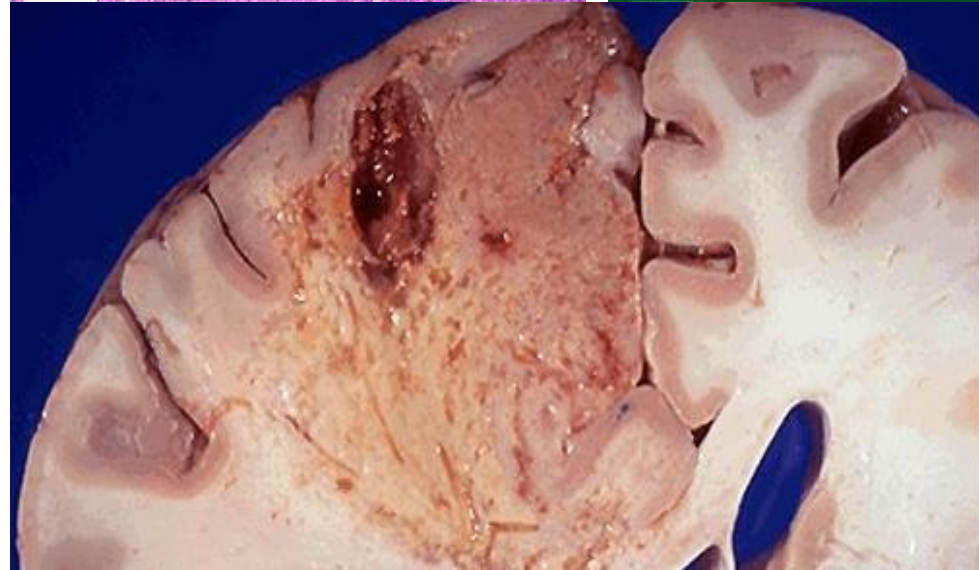
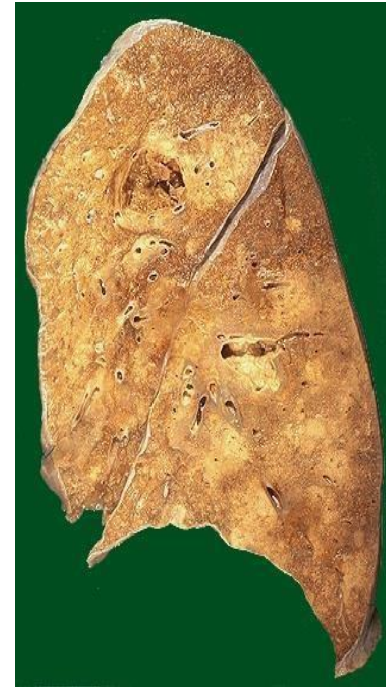
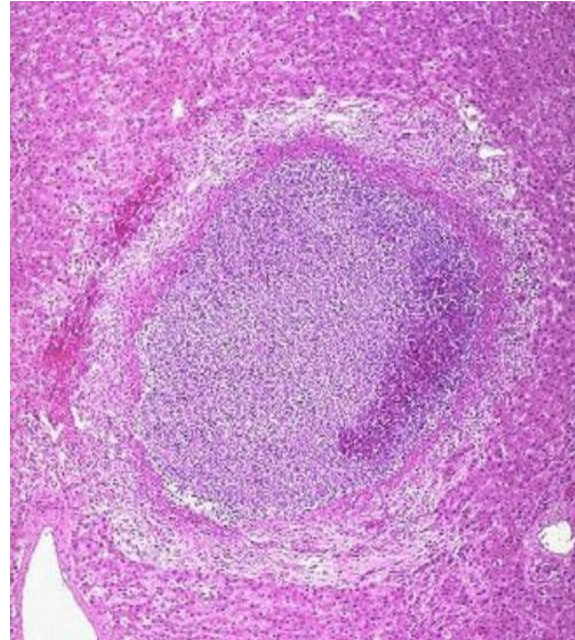
Pus (or abscess)

Microscopically, it's filled with inflammatory cells, mainly neutrophils

- II. **CNS infarcts**

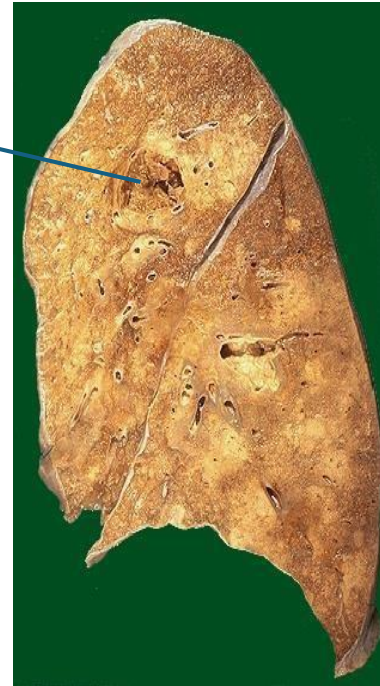
Ischemia to CNS organs, such as the brain and spinal cord, results in a liquefactive pattern of necrosis rather than the coagulative necrosis seen in other solid organs.

Center liquefies and digested tissue is removed by phagocytosis



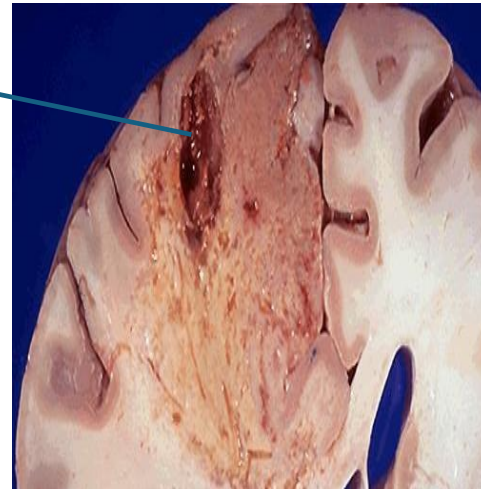
Cavitary lesion of the lungs

Microscopically, it's filled with inflammatory cells, mainly neutrophils



Cavitary lesion corresponding to an area of infarction (the lesion forms after clearance)

In this form of necrosis, the dead cells are completely digested, transforming the tissue into a viscous liquid that is eventually removed by phagocytes (microglia) to give **cavitary lesion** (fluid-filled cavity).



Gangrenous necrosis

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



(Diabetic foot)

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



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

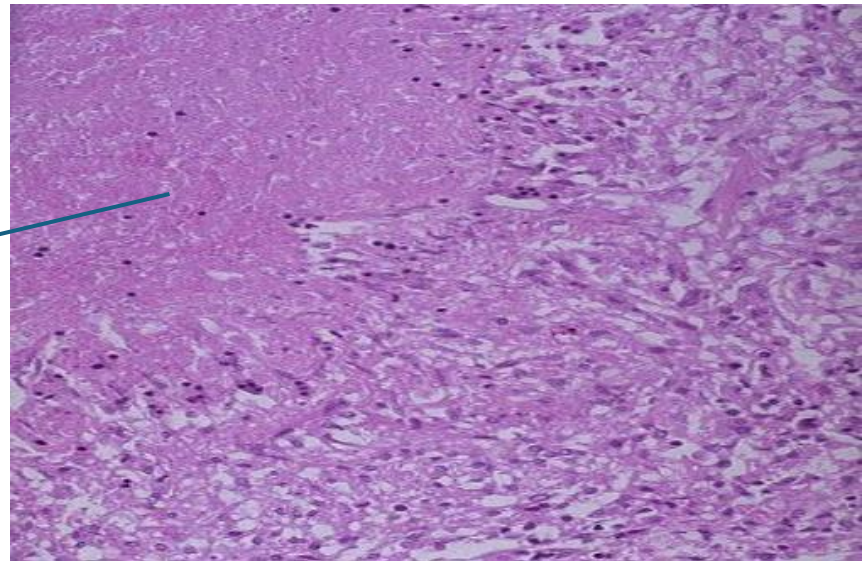
Caseous necrosis, classically seen in tuberculosis (TB), is named for the accumulation of a cheese-like material.

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

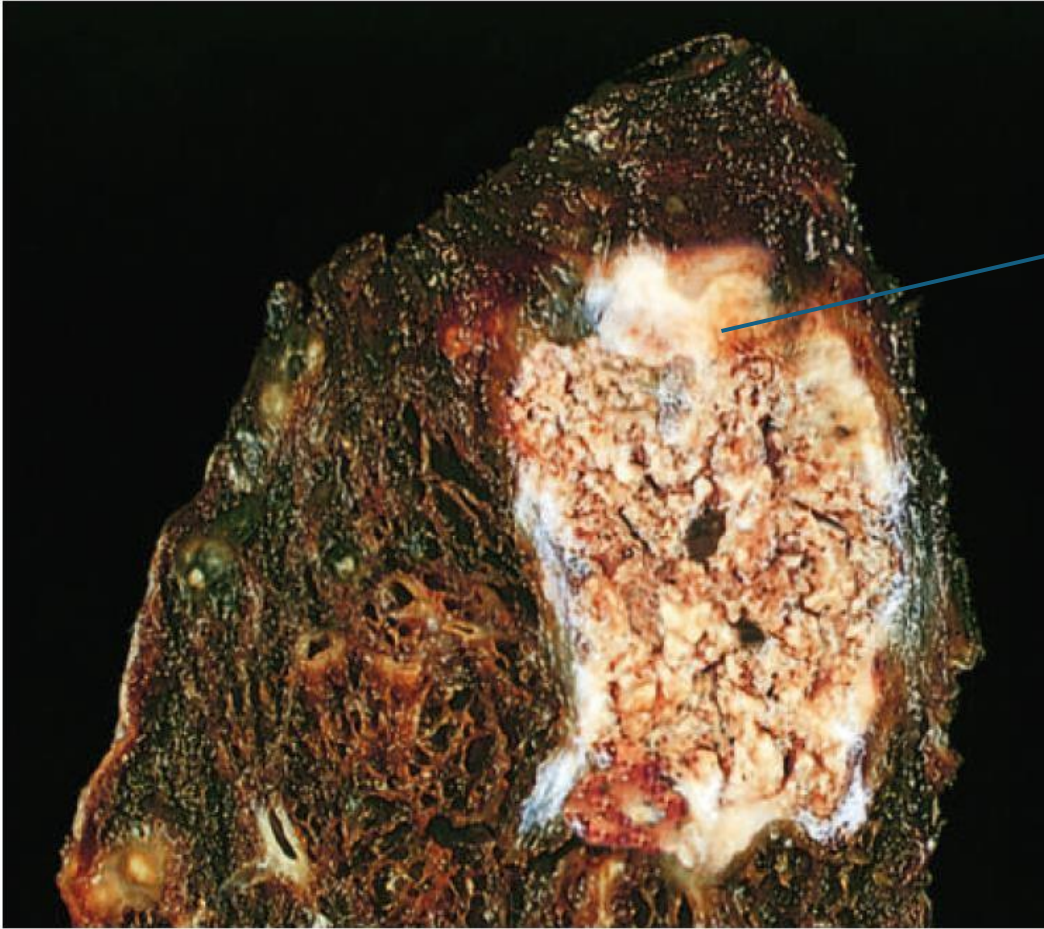
Microscopically, it is characterized by an acellular central area of debris, surrounded by a collection of macrophages forming a structure called caseating granuloma.



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



Caseous necrosis

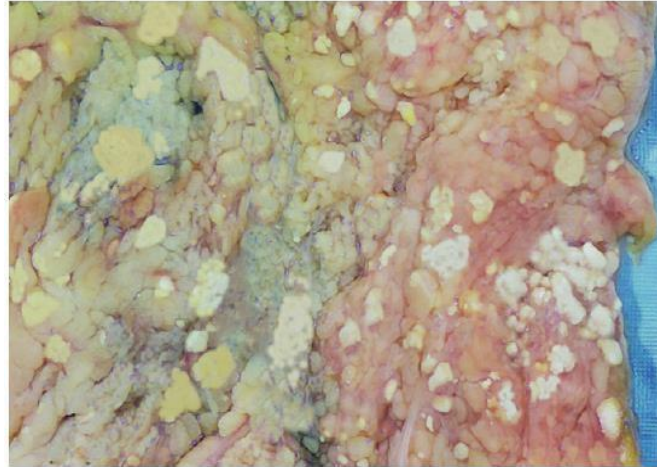


Yellowish to whitish
cheesy-like material
in the section of the
lung

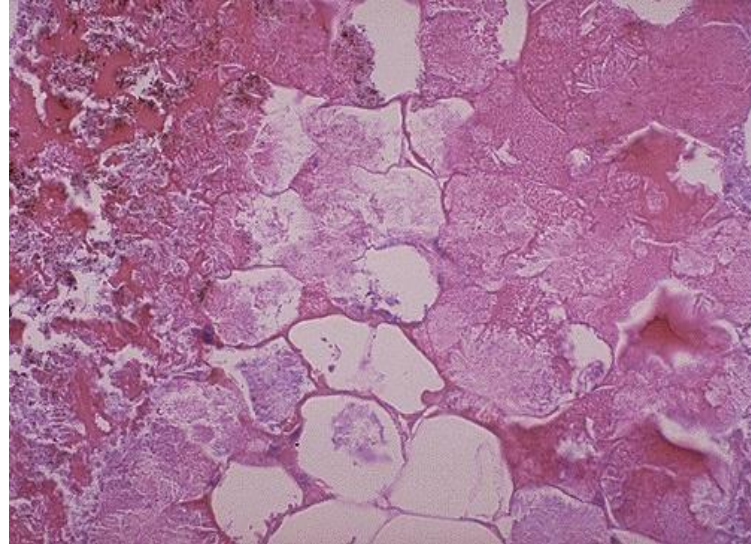
Fat necrosis

- 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 Ca^{2+} (saponification) to produce the whitish chalky appearance
- Microscopically we can see Shadows of necrotic fat cells with lost nuclei

Always in necrosis, we see shadows of cells microscopically, because the membrane and nucleus are lost in necrotic cells



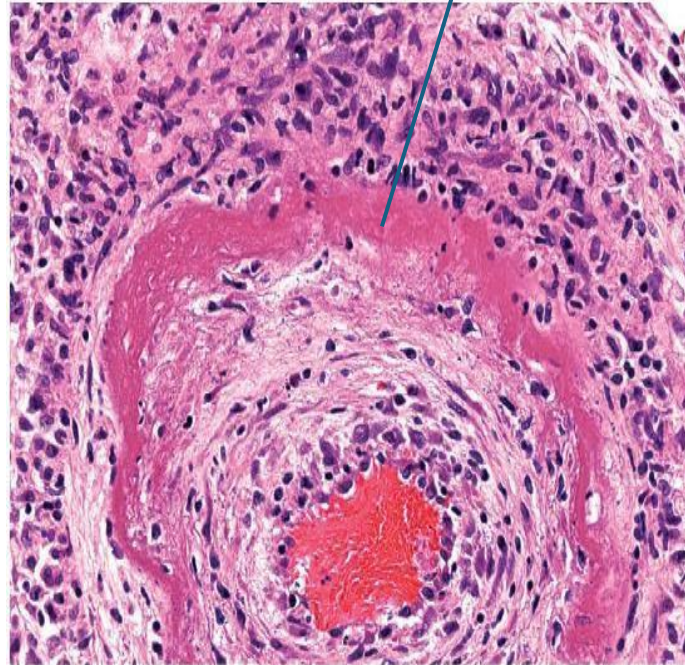
The pancreas is surrounded by fat in the abdomen, and the lipases will digest this fat. And here we can see a chalky white material on the fatty tissue.



Fibrinoid necrosis

- 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.

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



It's seen in vasculitis, which is an autoimmune disease (so antibodies attacks antigens in our bodies) like PAN, which is polyarteritis nodosa.

Quiz



Good luck

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



Versions	Slide # and Place of Error	Before Correction	After Correction
v0 → v1	Slide 30	Polyarthritis Nodosa	Polyarteritis Nodosa
v1 → v2			

Additional resources:

References Used:

1. Dr. Manar lecture

2. Robbins, Cotran & Kumar Pathologic Basis of Disease 11th Edition.

دَيْبٌ لِلْمَجْدِ وَالسَّاعُونَ قَدْ بَلَّغُوا جَهْدَ النُّفُوسِ وَأَلْقُوا دُونَهُ الْأَزْرَارَ
وَكَابَدُوا الْمَجْدَ حَتَّى مَلَأَ أَكْثَرُهُمْ وَعَانَقَ الْمَجْدَ مَنْ أَوْفَى وَمَنْ صَبَرَ
لَا تَحْسِبِ الْمَجْدَ تَمَرًا أَنْتَ أَكَلَهُ لَنْ يَبْلُغَ الْمَجْدَ حَتَّى تَلْعَقَ الصَّبْرَ
وَقَوْلُ اللَّهِ أَبْلَغُ وَأَحْكَمُ... (يَا أَيُّهَا الَّذِينَ آمَنُوا اصْبِرُوا وَصَابِرُوا)

رسالة من الفريق العلمي: