

CELL INJURY

Lecture 2

{ وَقُلْ رَبِّ زِدْنِي عِلْمًا }

Objectives:

- Know the definition of apoptosis, tissue necrosis and its various types with clinical examples.
- Able to differentiate between necrosis and apoptosis.

Color Index:

Girl's Slides

Important

Male's Notes

Female's Notes

Extra information

NECROSIS

①	Necrosis is a type of cell death, in which there is enzymatic digestion and denaturation of intracellular protein in the dying cell. And is always pathological
②	It occurs in irreversible injury. It is usually associated with inflammation in the surrounding tissue.
③	It involves the death of a group of cells in one area. Not individual

In necrosis:

1

there is **loss of function** of the involved tissue/organ.

2

there is **release of certain cellular enzymes** into the blood and these enzymes can be detected in blood tests.

3

there is an **inflammatory response**

The level of these enzymes can be used as markers to diagnose the injury **I.e. High levels → Diagnosis of heart attack**, and also can help determine the time and the extent of injury e.g. Cardiac enzymes in myocardial infarction (heart attack). **E.g. troponin I**

Types Of Lysis

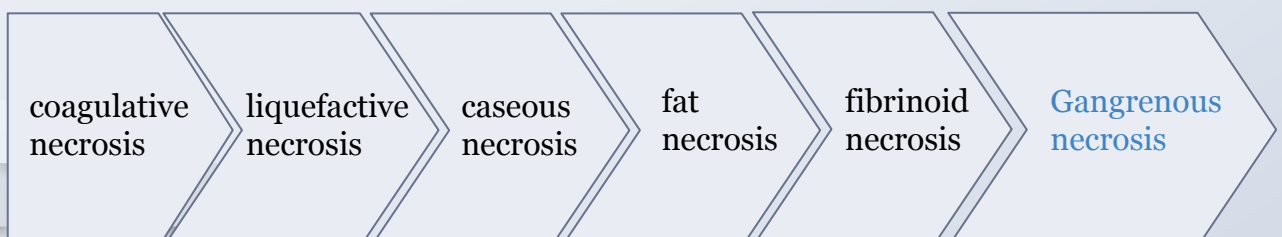
The enzymes used in this degradation of a cell come from:

- either the lysosomes of the dying cell itself referred to as **autolysis**.
- or from lysosomes of neighboring leukocytes referred to as **heterolysis**.

Autolysis: is the death/disintegration of cells or tissues by its own enzymes.

Autolysis is seen in cells after death/ post mortem. Autolysis is also seen in some pathologic conditions in living organisms. **Decomposition**

Types of necrosis



Coagulative necrosis

*Ischemia: Inadequate blood flow to an organ, which leads to decrease oxygen supply in an organ, which leads to **Hypoxia**

① Coagulative necrosis is characteristically seen when blood flow to an organ is affected leading to **ischemic***, **hypoxic death** of cells in that organ. (happens in highly vascular organs,)

② Coagulative necrosis **is seen in all organs except the brain**. It is not seen in the brain. It's almost always pathological and associated with inflammation

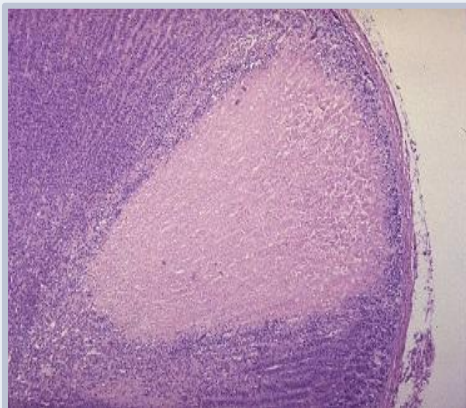
- ◀ in the heart → myocardial infarction.
- ◀ in the kidney → renal cortical necrosis or renal infarct
- ◀ in the spleen → splenic infarct
- ◀ in the liver → hepatic infarct etc.

Myocardial infarction, hyperlipidemia and atherosclerosis turn into coagulative necrosis after becoming complicated.

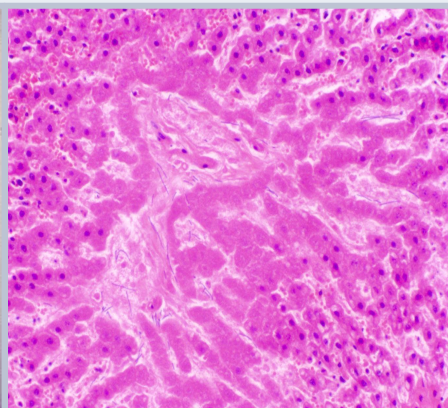
③ **Grossly:** the affected organ looks pale and firm/solid (coagulated). It looks like cooked meat or boiled egg. The tissue is firm and architecture is maintained for days after cell death, **Shape stays the same**.

④ **Microscopy:** in the beginning there is preservation of the general tissue architecture. The basic ghost outline of the affected/coagulated cell remains preserved for a few days but the nucleus is lost. The cell cytoplasm is eosinophilic. Ultimately, the necrotic cells are removed by phagocytosis by the macrophages (they act like vacuum cleaners) and the affect area is replaced by fibrosis (Healing take place by it, similar to scar) (has no function)

Looks like a wedge shaped outline with no nuclei (because of karyolysis)



Kidney: coagulative necrosis



Liver coagulative necrosis



Gross: tissue is firm

Ischemia

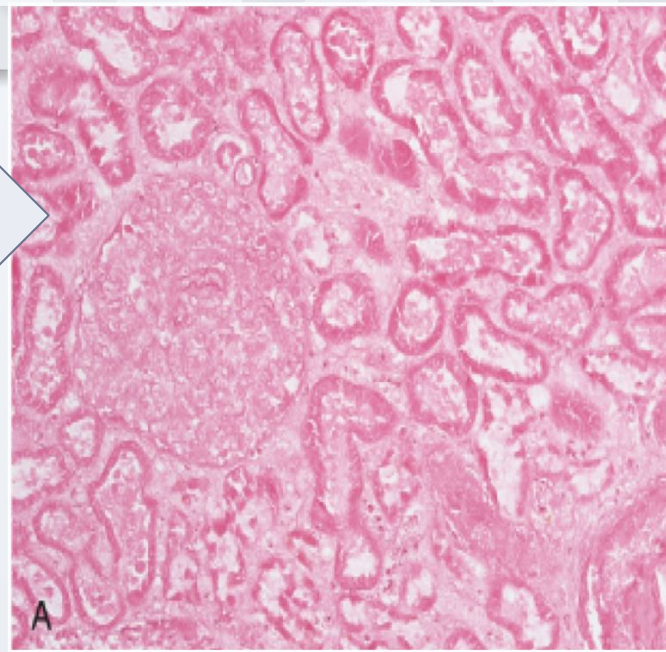
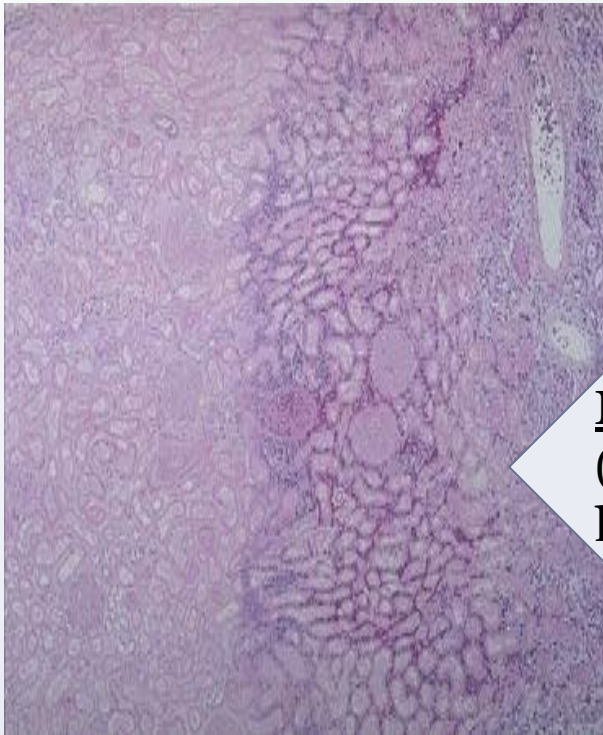
Hypoxia

Cell Injury

Cell death
(necrosis)

Kidney: coagulative necrosis

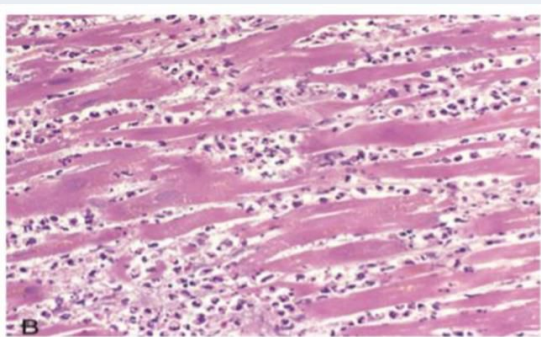
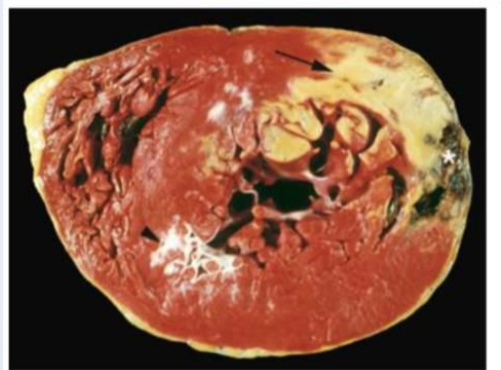
No nucleus



Micro: Cell outlines are preserved (cells look ghostly), and everything looks red.

Case example:

A patient dies from myocardial infarction, which is a very common disease. It affects the left ventricle and appears as the image shows. Yellowish and hemorrhagic in the ventricle area of the heart. symptoms include severe chest pain and a high number of blood cells (because necrosis is accompanied by inflammation). Structure is preserved as we can see.



We can know a patient has a rupture in the cytoplasmic membrane (I.e. necrosis) if Troponin I is high.

Under the microscope, there no nuclei in the cells. And a lot of WBCs

clot happens after death (post-mortem), while thrombus is before death (pre-mortem)

Liquefactive necrosis

is a type of necrosis which results in transformation of the tissue into a liquid viscous material. **Happens in in highly liquid filled/surrounded organs.**

necrosis is characteristically seen in:

1- Ischemic (hypoxic) cell death in the brain/central nervous system.

2- And it is also seen in the necrosis that **results from infections** especially suppurative bacterial infection (suppurative = pus or abscess producing).

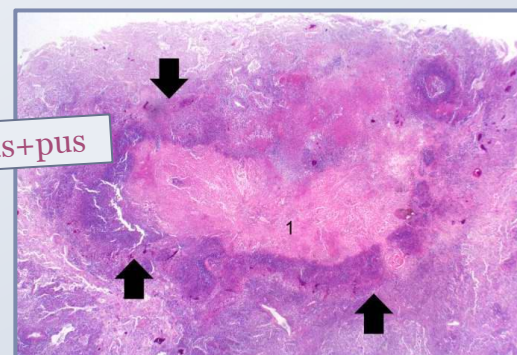
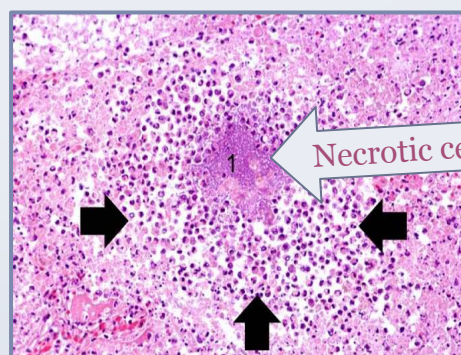
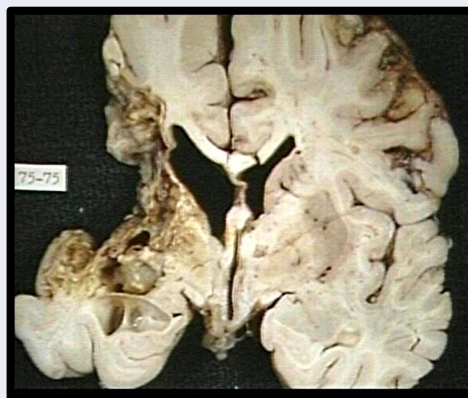
In infections the affected tissue is softened/liquefied by the action of hydrolytic (digestive) enzymes released from the lysosomes in the neutrophils.

The affected area becomes soft and liquefied with a creamy yellow center containing necrotic cells and neutrophils and is called pus/abscess. (Pus leaks out of the body and then is gone, whereas Abscess is collection of pus in the body)

Remember: what type of necrosis results from infection?

Note: the reason for liquefactive necrosis following ischemic injury in the brain is poorly understood.

Ultimately, the necrotic cells are phagocytosed.



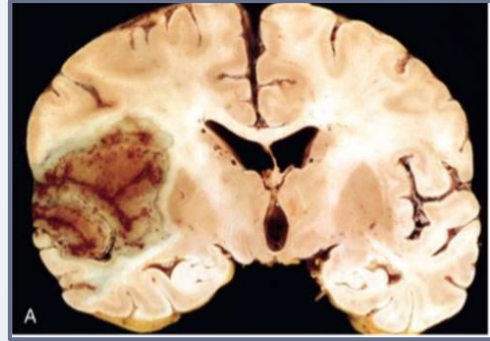
Liquefactive necrosis (center labeled one) is necrosis and surrounded by neutrophils.

Necrotic cells+pus

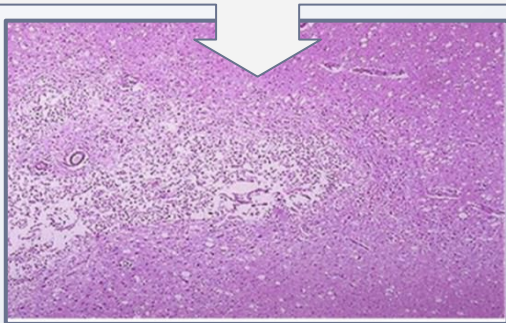
Case example:

Patient came to hospital and he cannot move his right leg, right arm and hand, he also cannot talk or breath well (if at all) after he died we checked cross section of his brain:

We see an area in the brain tissue showing a yellowish discoloration with hemorrhage



After taking a biopsy and look at it using a microscope we see that there is a complete loss of the Architecture, and all we can see is a big cavity surrounded by inflammatory cells (macrophages)



Etiology (cause):
atherosclerosis in carotid artery (in neck)

Ischemic necrosis in brain becomes..
Liquefactive necrosis

Caseous necrosis

is a type of coagulative necrosis classically seen in **tuberculosis** (infection by mycobacterium tuberculi).

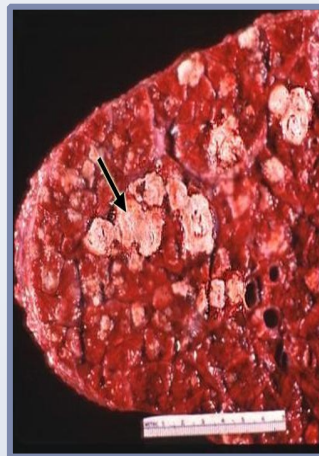
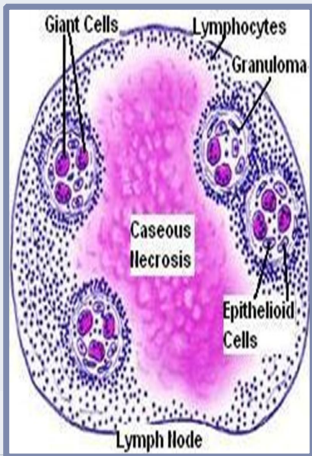
Here the tissue architecture is completely obliterated.

Grossly:

it is white, soft, curdy, cheesy-looking "caseous" material.

microscopic examination:

The necrotic area appears as amorphous pink granular debris surrounded by a collar of epithelioid cells (they are modified macrophages), lymphocytes and giant cells. This is known as granuloma.



Caseous necrosis causes chronic inflammation.

Can occur with tuberculosis (a common disease that can affect the lung, spleen or lymphoid)

Tuberculosis lung with a large area of caseous necrosis. The caseous debris is yellow-white and cheesy

Fat Necrosis

1

It is necrosis of fat cells. Also called enzymatic necrosis

2

Typically, it is seen in **acute pancreatitis**, in which the injured pancreatic cells release the **lipase enzymes** into the surrounding fat in the abdominal cavity and cause enzymatic digestion of fat cells.

Acute pancreatitis: most common cause of fat necrosis, caused by: **Alcoholism**

3

The released lipase breaks down the fat cells into glycerol and free fatty acids. The produced fatty acids combine with calcium circulating in the blood to produce calcium soaps which looks like chalky white spots in the necrotic fat. This process is called as **fat saponification**.

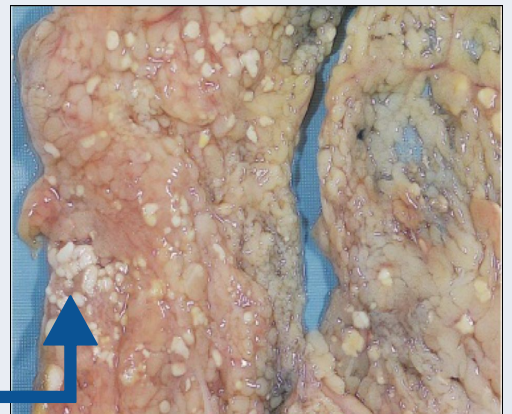
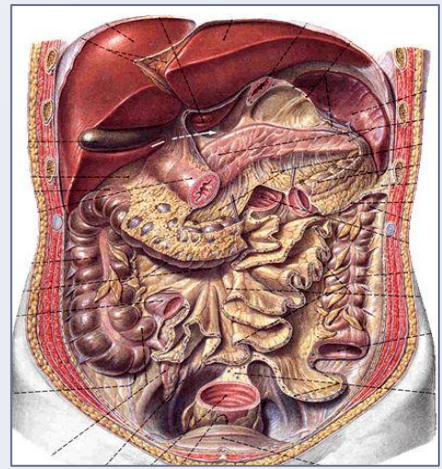
Foci of fat necrosis with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown.

4

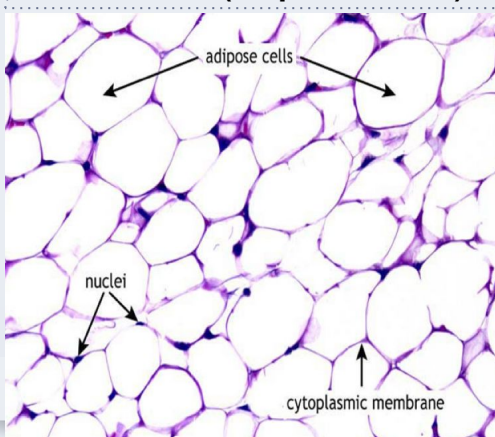
Microscopy: the outlines of necrotic/dead fat cells can be seen. Inflammation is minimal.

5

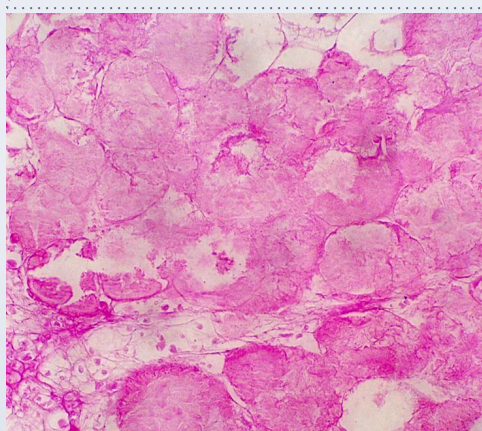
Fat necrosis can also be seen in breast fat and other fatty areas due to traumatic injury.



- Normal fat (adipose tissue)



- Fat necrosis



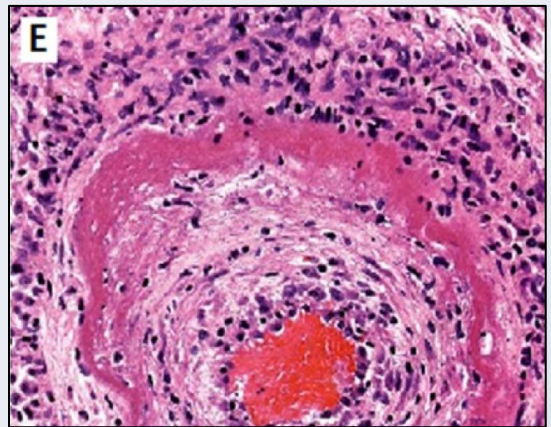
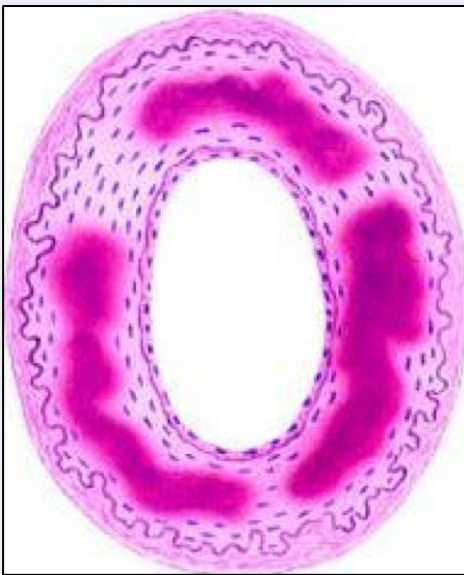
No nucleus is seen (macrophages can be confused as nuclei)

*what is the condition in which blood vessels are seen as necrotic?

Fibrinoid necrosis

- It is necrosis in the blood vessels (arteries, arterioles and capillaries). Like the renal blood vessels
- There is deposition of fibrin material in the arterial walls, which appears smudgy and acidophilic/eosinophilic.
- It is seen in immune mediated diseases (autoimmune diseases) and also seen in malignant hypertension.

Antigen-antibody complex: is a large, abnormal molecule set in the blood vessel walls that may cause inflammatory reactions → fibrinoid necrosis → diseases like ulcer, renal failure.



Fibrinoid necrosis in an artery. The wall of the artery is bright pink with dark neutrophils

Gangrenous Necrosis

- Non pathological term / clinical.

- It is a term commonly used in clinical practice by surgeons. It can be dry or wet.

Dry gangrene / mummification

***Only Coagulative necrosis**

Non-infected ischemic coagulative necrosis of tissue. It is without superadded infection. It can be seen as a complication of peripheral artery disease e.g. atherosclerosis and diabetes mellitus. The affected part is dry, shrunken and dark reddish-black, seen in a limb with inadequate blood supply resulting in ischemia of that limb.

Wet/ infected gangrene

***Coagulative + Liquefactive Necrosis**

Dry gangrene in addition to superadded bacterial (putrefactive) infection. In wet gangrene the coagulative necrosis is modified by the action of the bacteria into liquefactive necrosis. Wet gangrene usually develops rapidly due to blockage of venous (mainly) and/or arterial blood flow. The bacteria is usually saprogenic (i.e. it lives in the gut or the soil and it can thrive in low oxygen states) **Therefore they can develop with ischemia.** e.g. gram-positive Clostridia or Bacillus fusiformis. It has a poor prognosis compared to dry gangrene because the infection can spread to the rest of the body (septicemia) and be life threatening (death). **The limb becomes foul smelling and black and starts decomposing.**

High chance of occurring in a time of war or in a place with frequent natural disasters.

Treatment of gangrene: amputation.

NOTE

Diabetes mellitus is a risk-factor for dry gangrene and for wet gangrene (patients with poorly controlled blood-sugars, as elevated serum glucose creates a favorable environment for bacterial infection).



APOPTOSIS

It is a pathway of cell death in which cells destined to die activate their own enzymes to degrade their own nuclear DNA and proteins

Apoptosis is programmed cell death. Apoptosis means “falling off”. It is a type of cell suicide.

Remember: never a group of cells, small clusters or single cells only

Is results from activation of ‘death pathway genes’

It can be:

1. Physiological Situations

Sometimes the body produces harmful lymphocytes and they are also destroyed by apoptosis.

The programmed destruction of cells during **embryogenesis**

Apoptosis in proliferating cells e.g. intestinal epithelial lining is always being replaced.

Hormone-dependent: e.g. **endometrial cell breakdown during the menstrual cycle**, the regression of the lactating breast after weaning, and prostatic atrophy after castration (adaptive atrophy).

Cells that after performing their function undergo apoptosis e.g. neutrophils and lymphocytes in inflammation.

Another example is the apoptosis of the extra skin between the fingers on the fetus inside the womb

2. Pathologic Conditions (cell is infected)

Cell death produced by injury e.g. radiation.

Pathologic atrophy in organs e.g. pancreas, parotid gland and kidney

Corticosteroid induced atrophy of the neonatal thymus

In certain diseases e.g. in viral hepatitis the infected hepatocytes undergo apoptosis (acidophilic bodies) or injury of skin epidermal cells (keratinocytes) leads to apoptosis of keratinocytes (Civatte bodies).

Cell death in tumors (usually accompanied by necrosis).

Another example is in chemotherapy we try to induce cell death (Apoptosis)

Mechanism of Apoptosis*

*The Order is important

1 The death pathway genes are activated which trigger apoptosis.

2 Cell shrinkage.

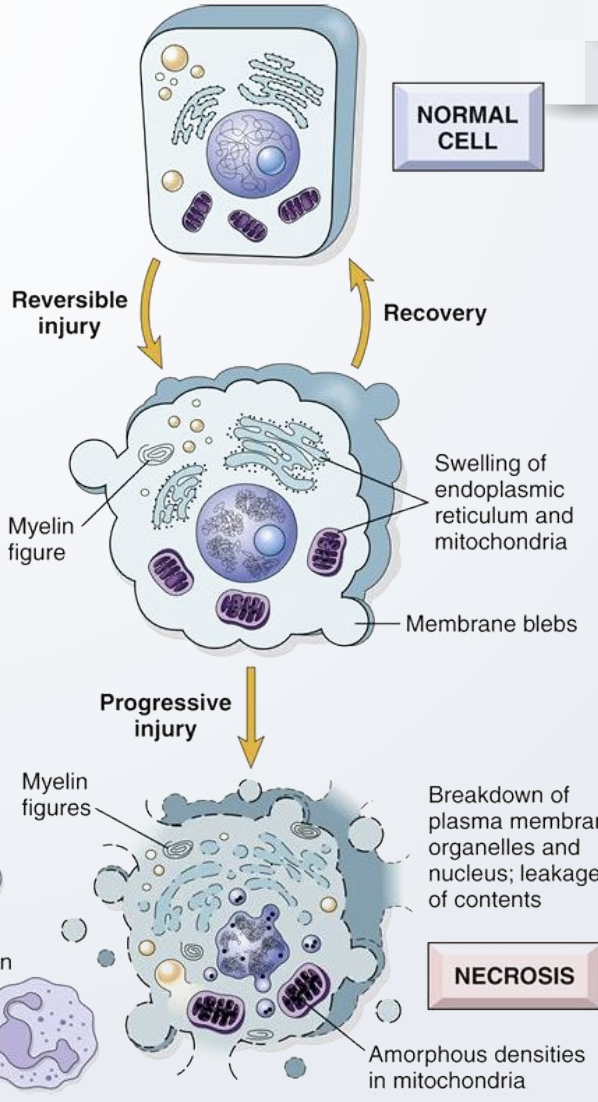
3 **Chromatin condensation in the nucleus:** This is the most characteristic feature of apoptosis. The nucleus may break up into fragments.

4 **Formation of cytoplasmic blebs (later turn into apoptotic body) and apoptotic bodies:** The apoptotic cell first shows surface blebbing, then fragments into membrane-bound apoptotic bodies. The apoptotic bodies contain cytoplasmic content with or without nuclear material

5 The cell's **plasma membrane remains intact.**

The plasma membrane of the apoptotic cell sends signal to macrophages, inviting the macrophages to phagocytose it.

6 **Phagocytosis of apoptotic bodies by the macrophages.** Because, during the entire process, the apoptotic body is bound by plasma membrane there is no release of the cytoplasmic content into the surrounding tissue and therefore **there is no inflammation.**



Apoptosis does not accompany inflammation and has no protein/enzyme burst.

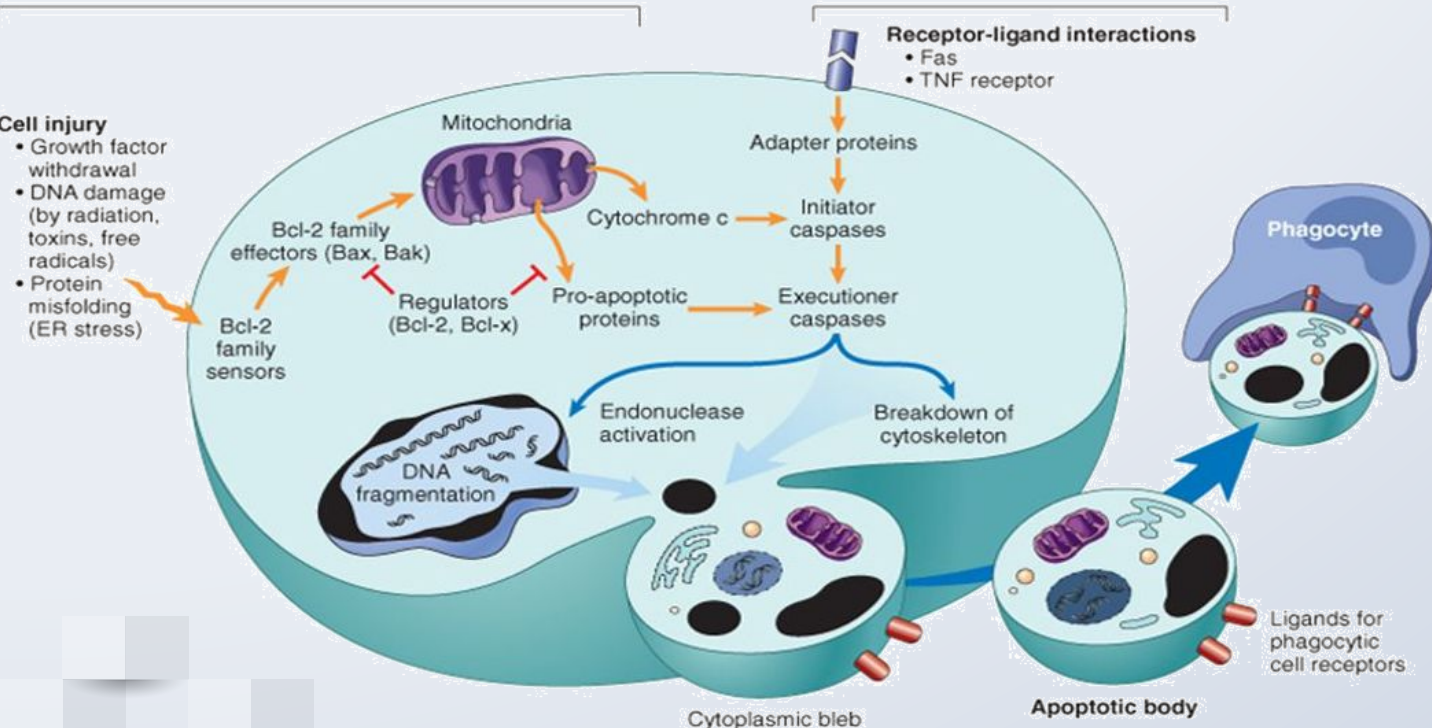
Necrosis & apoptosis

***There are two pathways for the mechanism of apoptosis:**

Extrinsic: Out
Intrinsic: in

MITOCHONDRIAL (INTRINSIC) PATHWAY

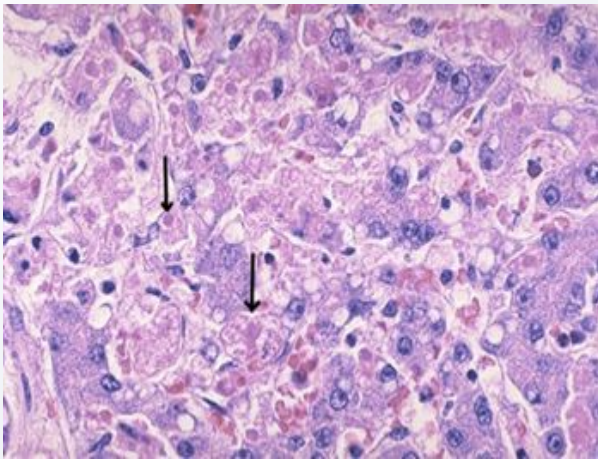
DEATH RECEPTOR (EXTRINSIC) PATHWAY



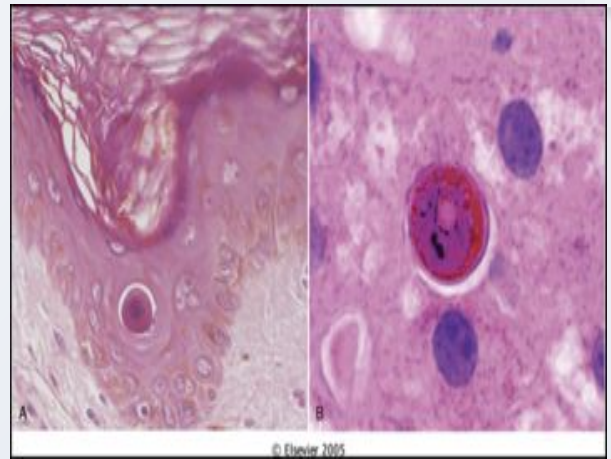
Morphology of Apoptosis

- On histology apoptosis involves single cells or small clusters of cells. The apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with dense nucleus. **There is no inflammation.**

apoptosis in liver cell



apoptosis in epidermis.



Important enzymes of apoptosis

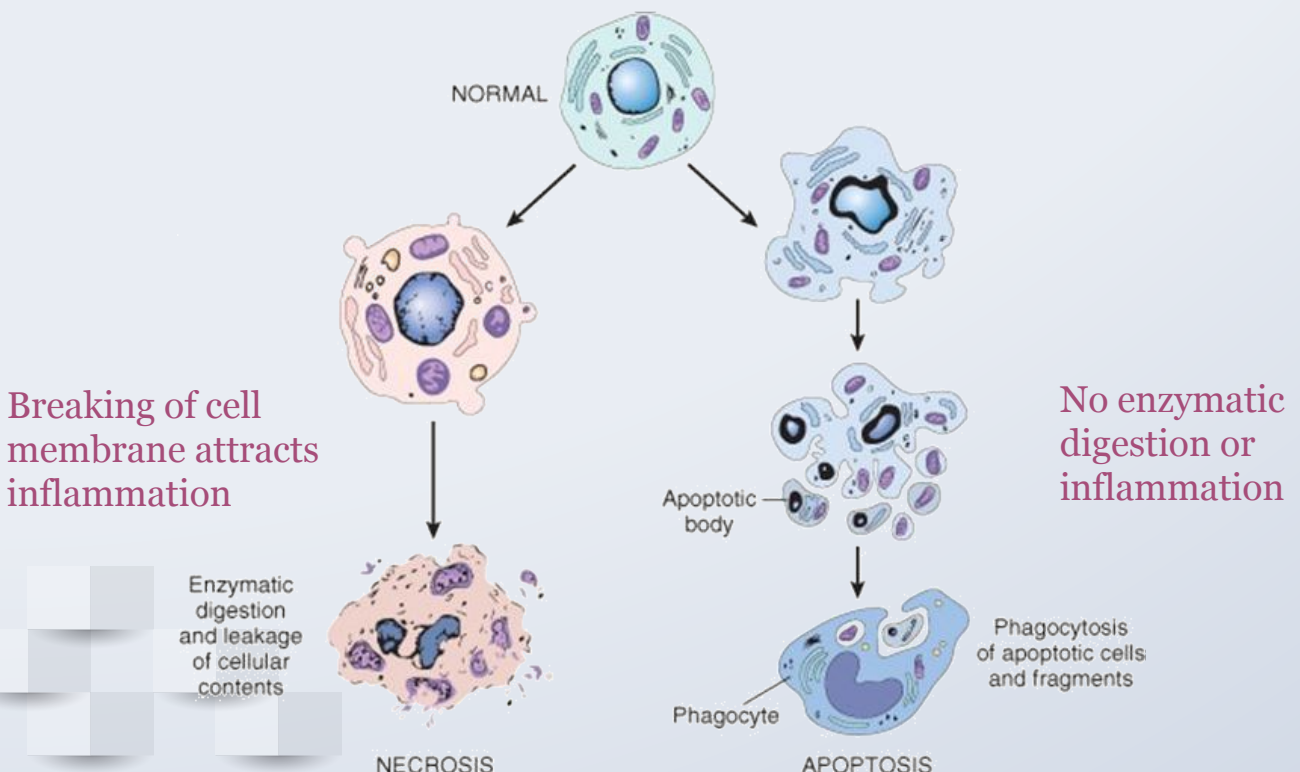
- Cysteine proteases called caspases
- Ca²⁺ dependent endonucleases
- Mg²⁺ dependent endonucleases

Regulation of apoptosis

It is mediated by a number of genes and their products e.g:

- bcl-2 gene inhibits apoptosis
- bax genes facilitates apoptosis
- p53 facilitates apoptosis by inhibiting bcl2 and promoting bax genes.

The changes seen in necrosis (left) and apoptosis (right). Apoptosis is different from necrosis. In necrosis there is loss of membrane integrity, enzymatic digestion of cells, and frequently an inflammatory reaction. Apoptosis and necrosis sometimes coexist.



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). Almost always pathological because of ischemia(which can never be normal)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage. Can be both

*may also be seen in apoptosis

MCQs

3-B-A
2-A-B
1-D-C

Q1: 1- blood vessel necrosis is:

- | | | | |
|----------------------|-------------------------|--------------------------|-----------------------|
| A) Gangrene necrosis | B) Coagulative necrosis | C) Liquefactive necrosis | D) Fibrinoid necrosis |
|----------------------|-------------------------|--------------------------|-----------------------|

Q2: apoptosis is classified as:

- | | | | |
|-------------------------|------------------------------|--------------------------|-----------------------|
| A) Programed cell death | B) Non-programmed cell-death | C) Accidental cell death | D) Mitotic cell death |
|-------------------------|------------------------------|--------------------------|-----------------------|

Q3: coagulative necrosis may happen in all organs except:

- | | | | |
|--------------|--------------|---------------|--------------|
| A) The heart | B) The brain | C) The kidney | D) The liver |
|--------------|--------------|---------------|--------------|

Q4: which of the following statements accurately compares apoptosis with necrosis:

- | | | | |
|---|--|--|--|
| A) Apoptosis results in cell rupture, unlike necrosis | B) Both are triggered as a result of physical injury | C) Necrosis can cause inflammation, while apoptosis does not | D) Both are important in embryological development |
|---|--|--|--|

Q5: dry gangrene is NOT:

- | | | | |
|-------------------------|--------------------------|---------------------------------|-----------------|
| A) Coagulative necrosis | B) Liquefactive necrosis | C) Without superadded infection | D) Both B and C |
|-------------------------|--------------------------|---------------------------------|-----------------|

Q6: The most characteristic feature of apoptosis is:

- | | | | |
|--|----------------------|-------------------|-----------------------|
| A) Chromatin condensation in the nucleus | B) Happens in groups | C) Cell shrinkage | D) Leakage of enzymes |
|--|----------------------|-------------------|-----------------------|

SAQs

Q1: How does Autolysis accelerate cell death?

Q2: What type of necrosis is seen in tuberculosis granuloma?

Q3: What type of necrosis might cause a hard breast mass after a car accident?

Q4: Mention the important enzymes in apoptosis and the genes that regulate it.

1- It doesn't. Autolysis takes a place when a dead cell's own enzymes digest it (digest the cell itself).
2- Caseous necrosis
3- Fat necrosis saponification
4- Slide 14

Helpful videos:

what is necrosis and apoptosis:

<https://www.youtube.com/watch?v=1vaEVcMfa1E>

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