CELL INJURY for Medical (lecture 2)

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Lecture 2 outline

A. **Types of necrosis** : Coagulative, Liquefactive, Caseous, gangrenous, fibrinoid and fat necrosis.

B. **Apoptosis** : definition, morphologic features, regulation of apoptosis

C. **Comparison** between necrosis and apoptosis.

NECROSIS.

- Necrosis is changes that follow cell death in living tissue, due to enzymatic digestion and denaturation of intracellular protein in the injured cell.
- It occurs in irreversible injury. It is usually associated with inflammation in the surrounding tissue.
- It involves the death of a group of cells in one area.
- Necrosis can result in:
  - Cessation of function of the involved tissue or organ
  - Release of certain cellular enzymes that can be detected in blood. The level of these enzymes can be used as markers to diagnose the injury and also can help determine the time and the extent of injury eg. Cardiac enzymes in myocardial infarction (heart attack).
  - An inflammatory response

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 it's own enzymes.
- Autolysis is also seen in cells after death/ post mortem.
- Autolysis is also seen in some pathologic conditions in living organisms.

Types of necrosis

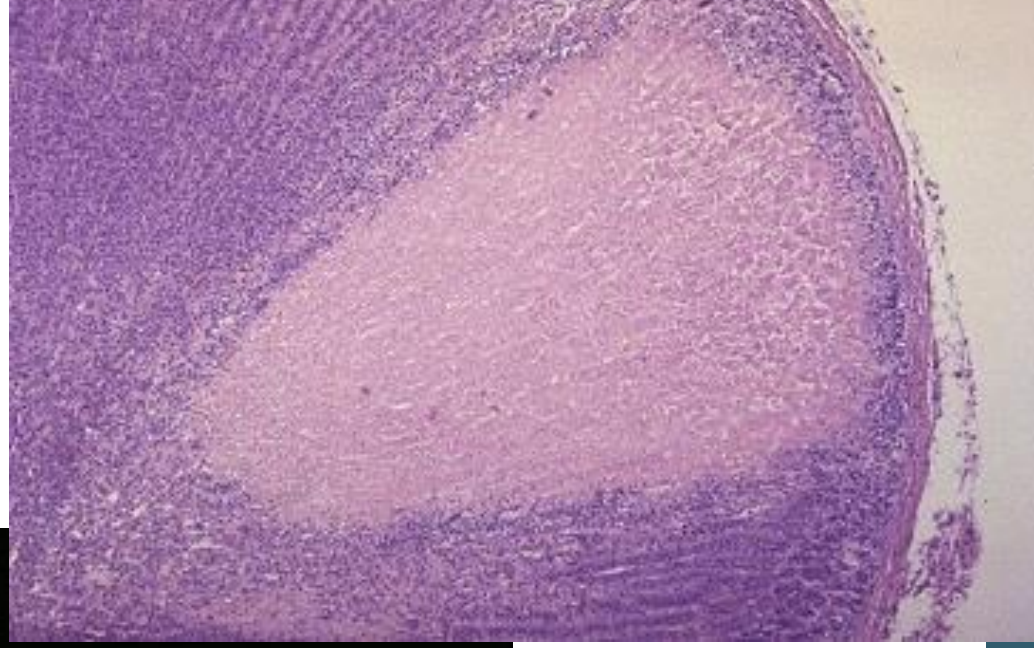
› There are 5 types of necrosis:

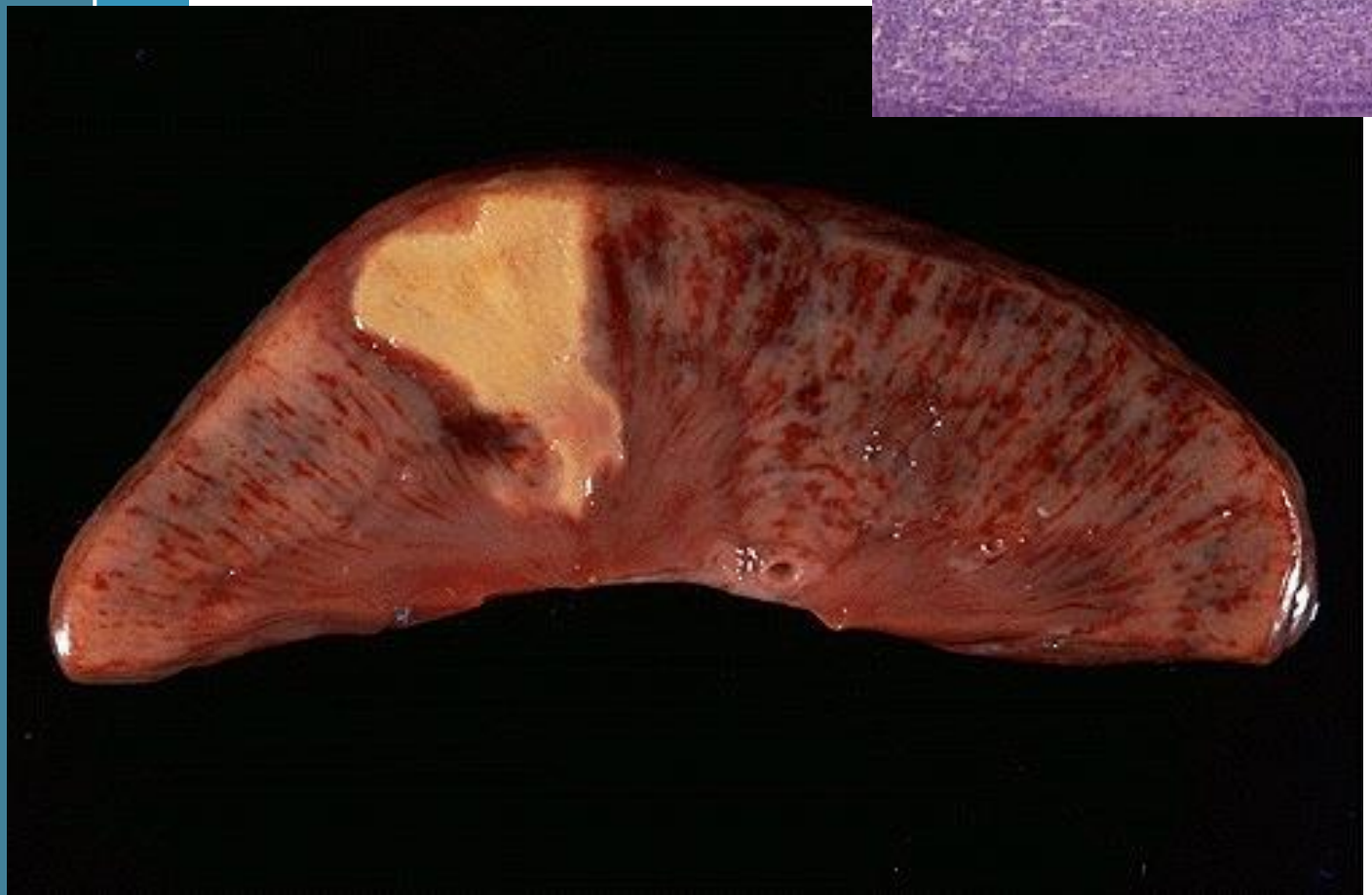
- **coagulative necrosis**
- **liquefactive necrosis**
- **caseous necrosis**
- **fat necrosis**
- **fibrinoid necrosis**

Coagulative necrosis:

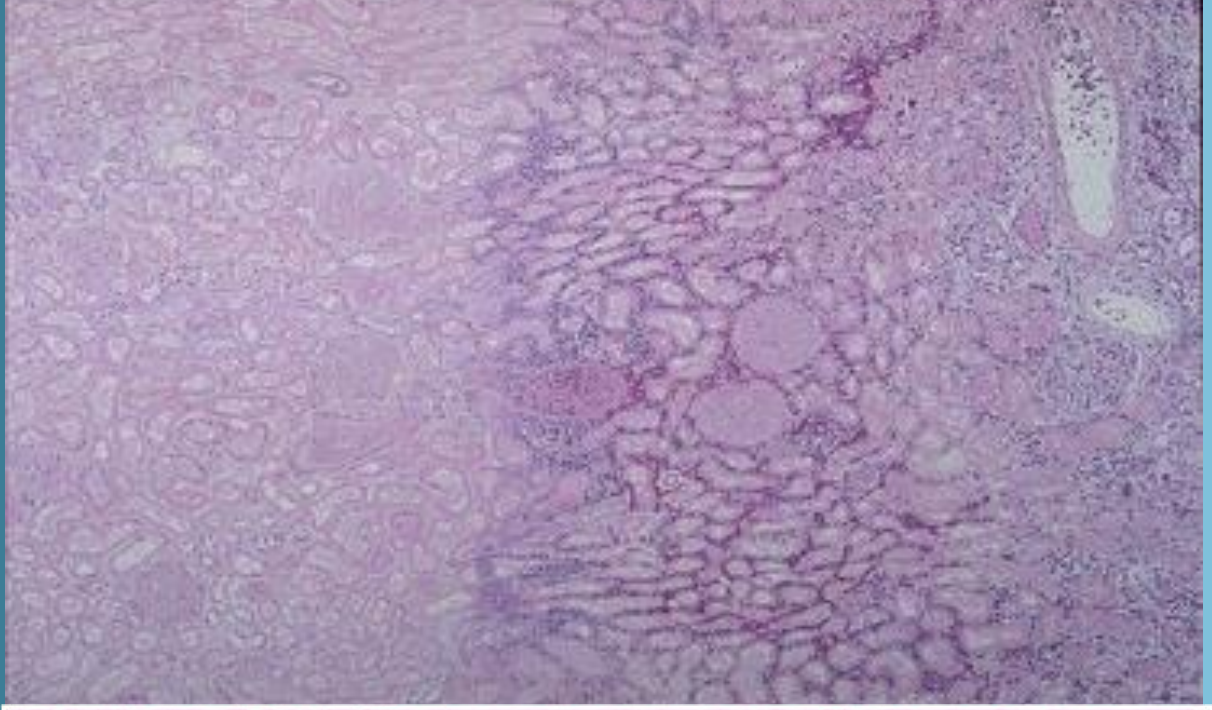
- Coagulative necrosis is characteristically seen when blood flow to an organ is affected leading to ischemic/hypoxic death of cells in that organ.
- It is seen in all organs except the brain. Coagulative necrosis is not seen in the brain.
- It causes infarct and is seen in heart (myocardial infraction), kidney (renal cortical necrosis/ infarct), spleen, liver (infarct) etc.
- Gross: The affected organ looks pale and firm/solid. It looks liked cooked meat or boiled egg.
- Microscopy: In tissue or organ showing coagulative necrosis, there is preservation of the general tissue architecture and initially the basic ghost outline of the 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.

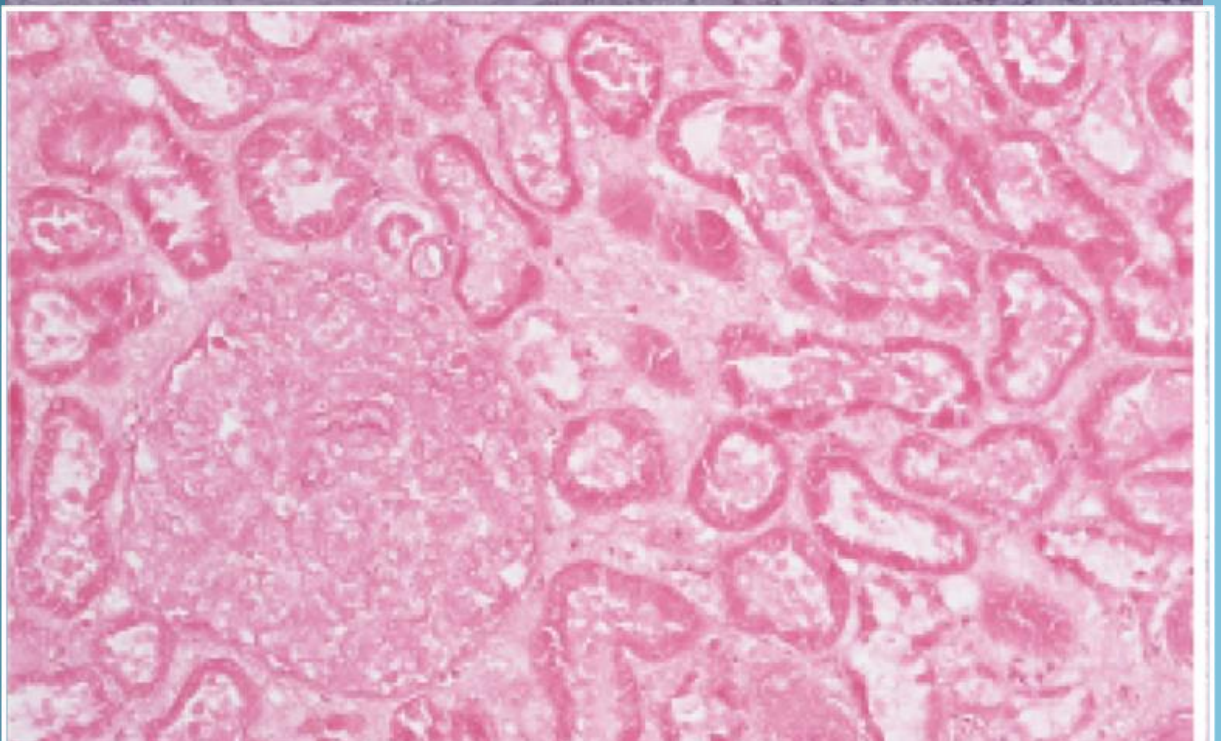
Kidney: coagulative necrosis





Gross: tissue is firm

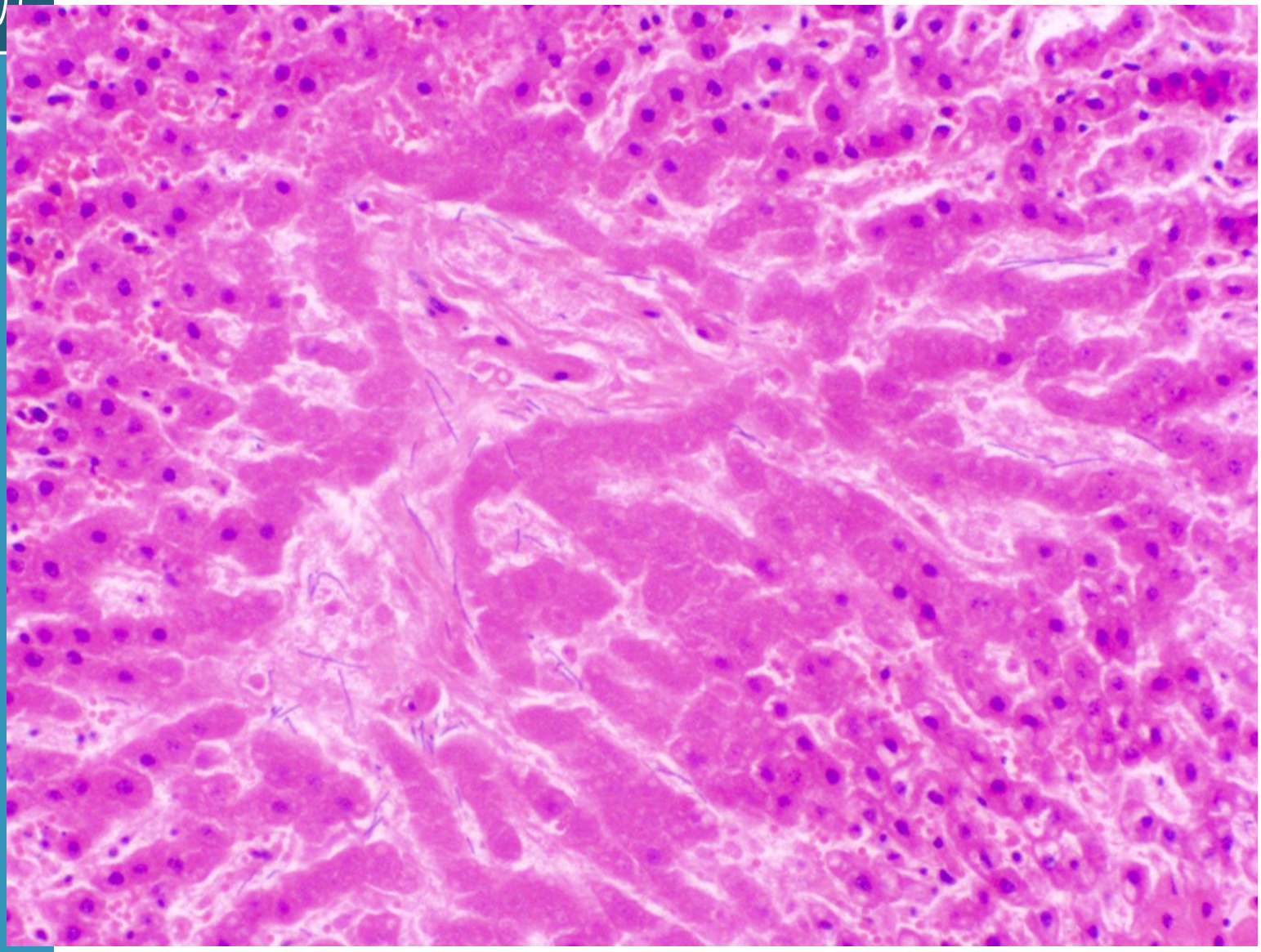




Kidney: coagulative necrosis

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

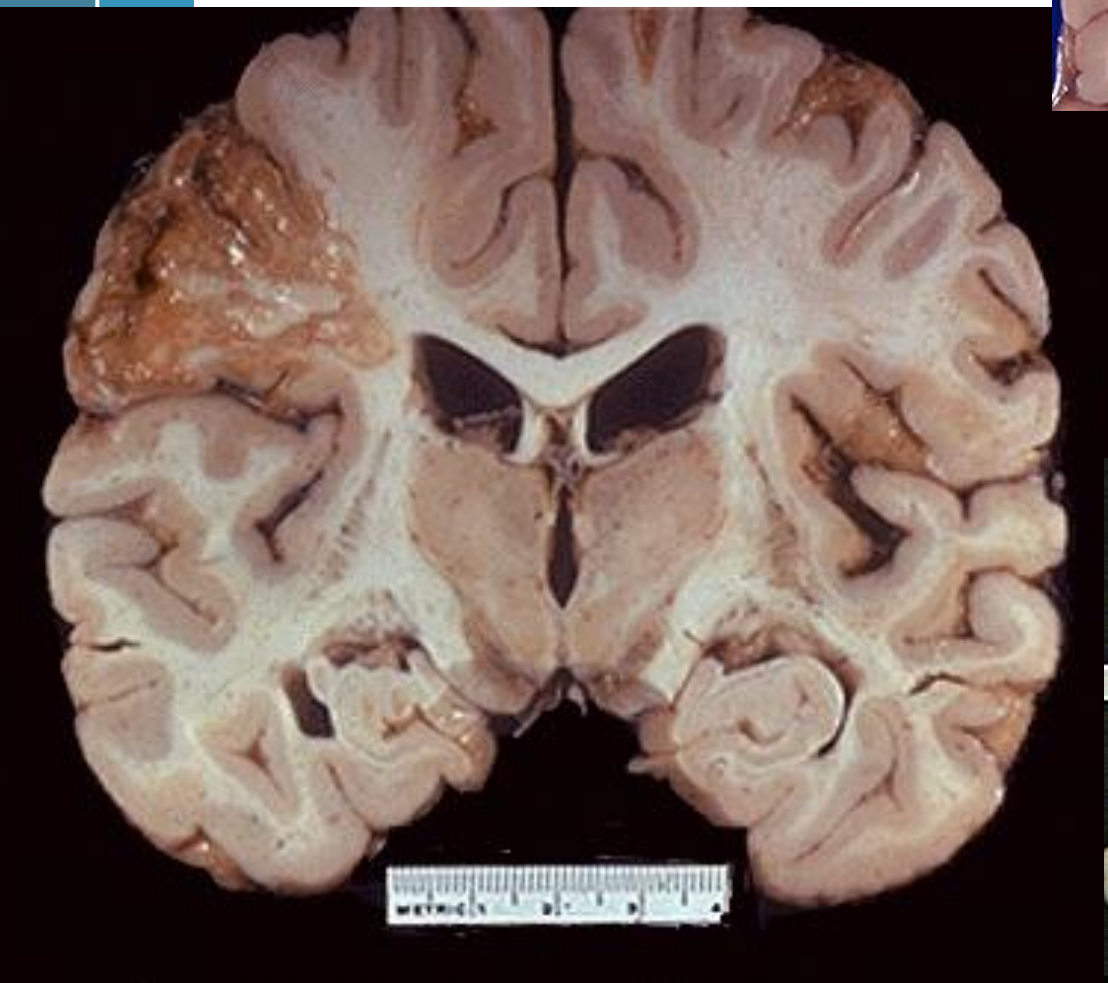
Liver coagulative necrosis

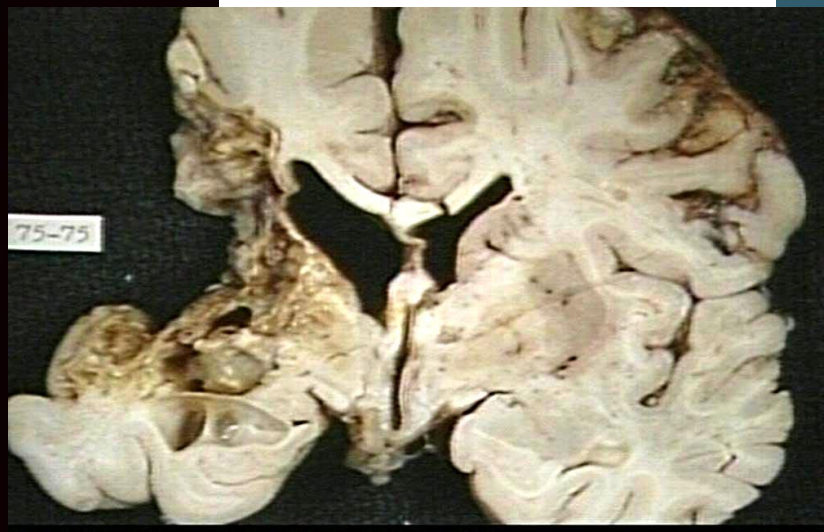


Liquefactive necrosis

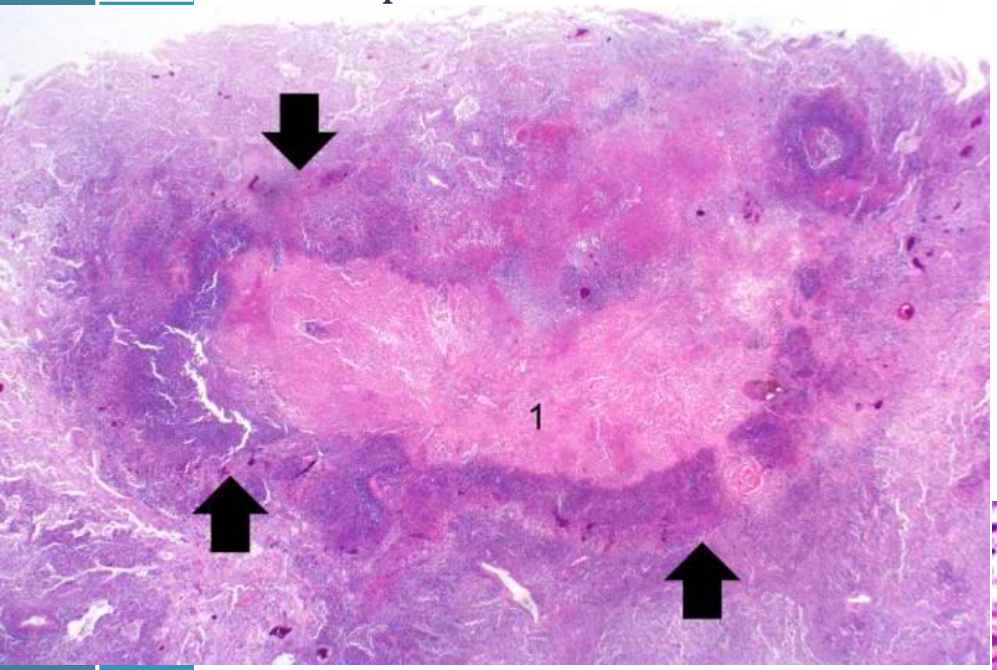
- is a type of necrosis which results in transformation of the tissue into a liquid viscous mass.
- Is characteristically seen in hypoxic cell death in the central nervous system/brain and in suppurative infections (pus or abscesses) especially bacterial.
- The affected tissue is softened/liquefied by the action of hydrolytic enzymes released from the lysosomes in the brain cells or in case of an abscess due to the enzymes released from the neutrophils.
- Ultimately, most necrotic cells are phagacytosed.
- The affected area is soft with liquefied creamy yellow centre containing necrotic cells, and neutrophils and is called *pus/abscess.*

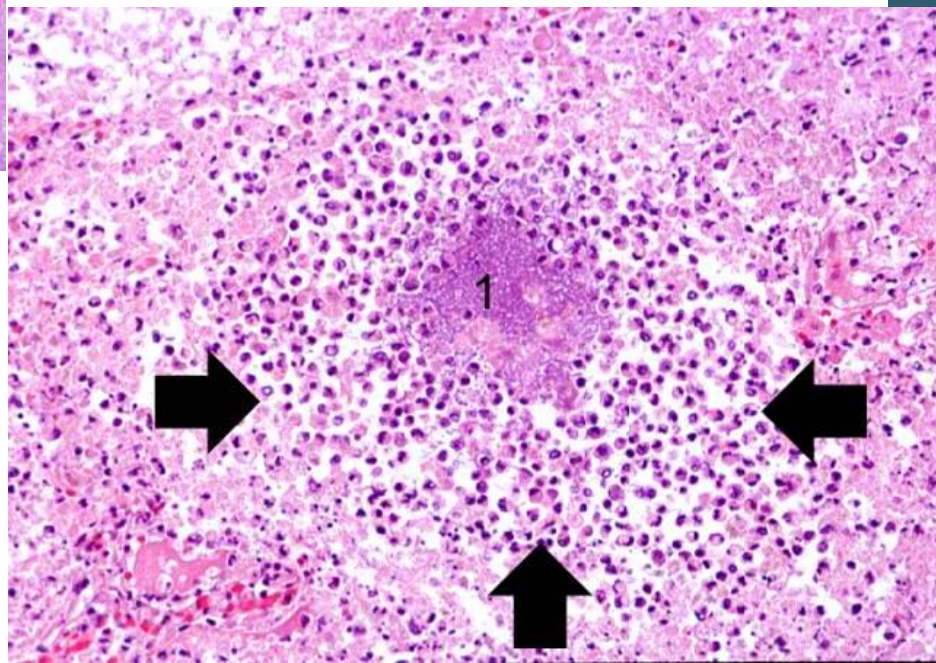
Liquefactive necrosis





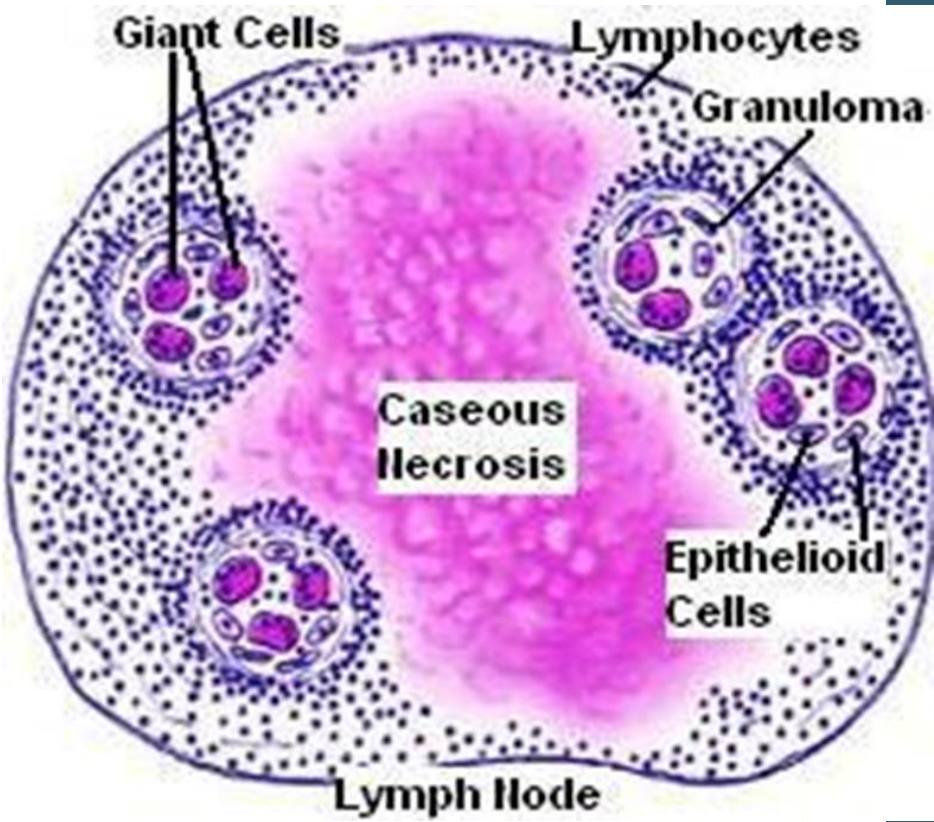
Liquefactive necrosis (center labeled one is necrosis and surrounding is neutrophils.



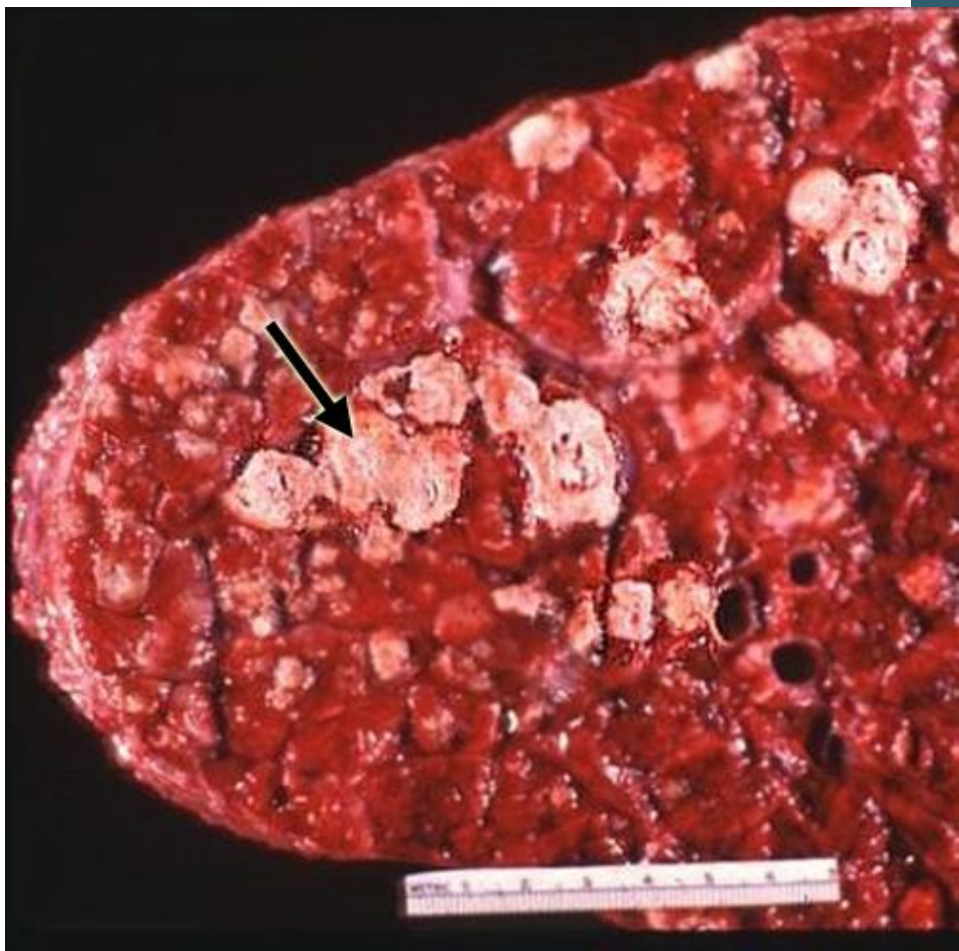


Caseous necrosis

- is a type of coagulative necrosis classically seen in tuberculosis (infection by mycobacterium tuberculi).
- Gross: White, soft, curd like, cheesy-looking "caseous" material.
- On microscopic examination, the necrotic area appears as amorphous pink granular debris surrounded by a collar of epitheloid cells (modified macrophages), lymphocytes and giant cells. This is known as granuloma.
- Here the tissue architecture is completely obliterated.



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

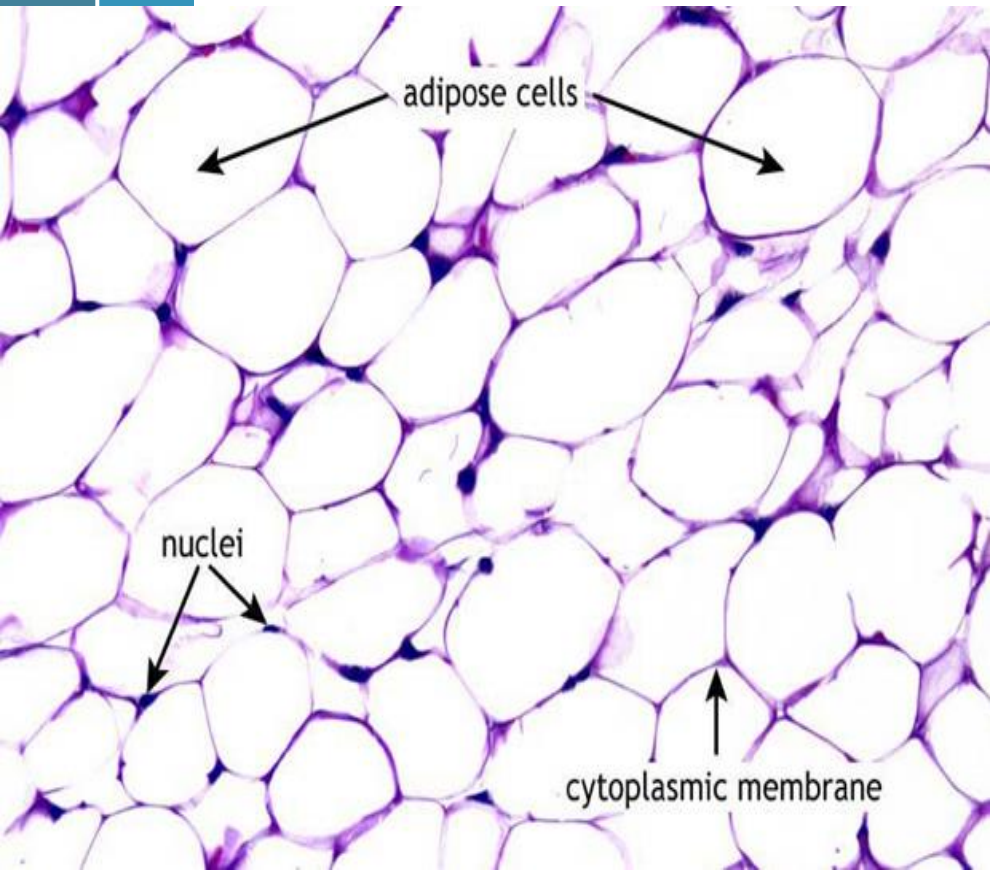


Fat necrosis

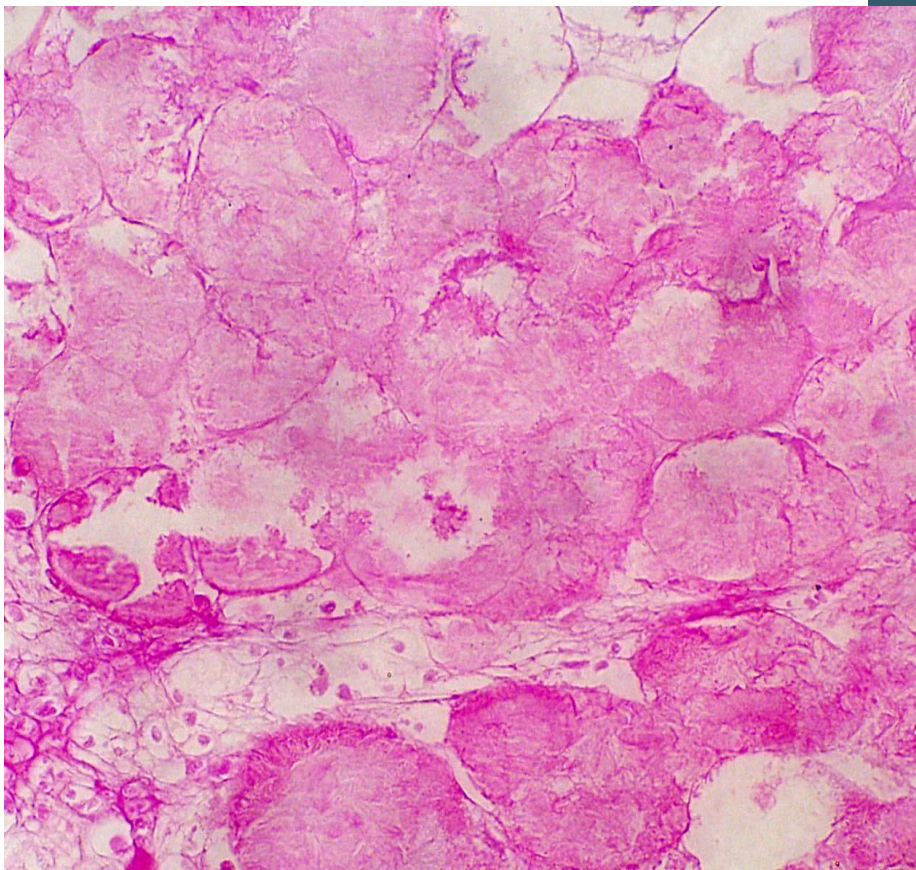
- Is focal areas of fat destruction/ necrosis due to enzymatic action of lipase (which is released from injured pancreatic tissue) into the surrounding fat in the abdominal cavity.
- It is typically seen in acute pancreatitis.
- Damaged cells release lipases, which breakdown the fat cells into glycerol and free fatty acids. The produced fatty acids combine with calcium in the blood to produce calcium soaps (called as fat saponification) which looks like chalky white spots in the necrotic fat.
- The outlines of necrotic/dead fat cells can be seen. Inflammation is minimal.
- Fat necrosis can also be seen in breast fat and other fatty areas due to traumatic injury.

Figure 1-21 Foci of fat necrosis with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown.

› Normal adipose tissue



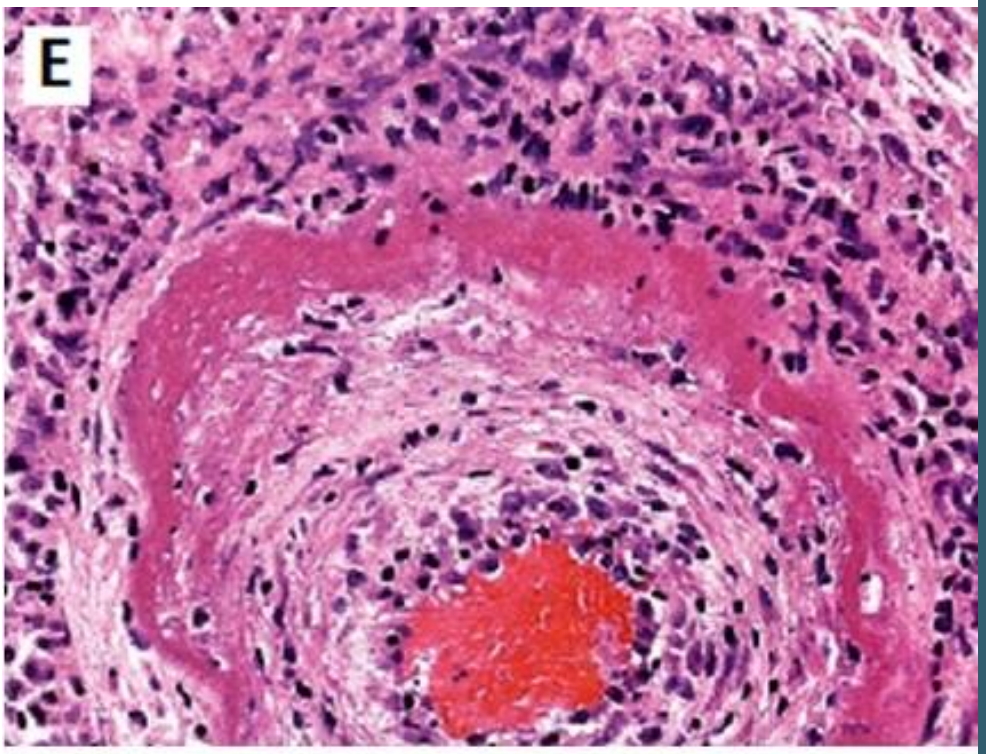
› Fat necrosis



Fibrinoid necrosis

- Is necrosis in the blood vessels (arteries, arterioles and capillaries)
- 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.

Fibrinoid necrosis



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

Gangrenous necrosis

- G**angrenous necrosis** is term commonly used in clinical practice by surgeons. It can be dry or wet.
- **Dry gangrene/ mummification:** it is a form of coagulative necrosis that develops in ischemic tissue, where the blood supply is inadequate. It is without infection. Dry gangrene is often due to peripheral artery disease is usually seen in limbs, especially the leg, that has lost its blood supply and has undergone coagulative necrosis. Dry gangrene is dry non-infected ischemic necrosis of tissue. It is seen as a complication in atherosclerosis and diabetes mellitus. The affected part is dry, shrunken and dark reddish-black.
- **Wet/ infected gangrene**: When there is superadded bacterial (putrefactive) infection the coagulative necrosis is modified by the action of the bacteria into liquefactive necrosis, and it is called **wet gangrene**. So, initially there is coagulative necrosis and then there is superaddedinfection leading to 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. (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), so the limb has to be amputated. The limb becomes foul smelling and black and starts decomposing.

NOTE: Diabetes mellitus is a risk-factor for peripheral vascular disease and thus for dry gangrene, but also a risk factor for wet gangrene, particularly in patients with poorly controlled blood-sugars, as elevated serum glucose creates a favorable environment for bacterial infection


CM

APOPTOSIS

- *Apoptosis* is programmed cell death. Apoptosis means “falling off”. It is a type of cell suicide.
- Is results from activation of ‘death pathway genes’.
- 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.

It can be

- Physiological or adpative.
- Pathologic.

- NOTE: Apoptosis and necrosis sometimes coexist.

Apoptosis in Physiologic Situations

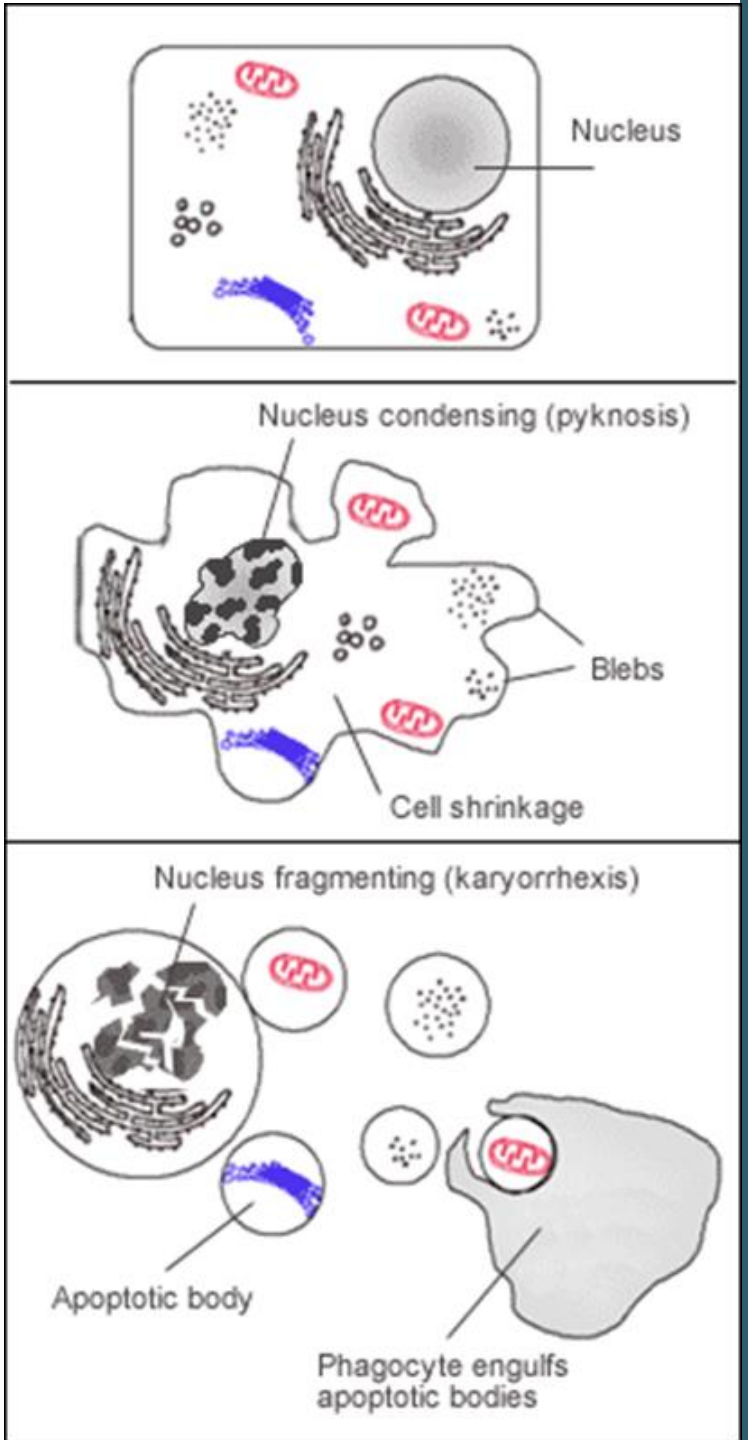
- The programmed destruction of cells during embryogenesis.
- Hormone-dependent: e.g. endometrial cell breakdown during the menstrual cycle, the regression of the lactating breast after weaning, and prostatic atrophy after castration (adaptive atrophy).
- Apoptosis in proliferating cells e.g. intestinal epithelial lining is always being replaced.
- Cells that after performing their function undergo apaotosis e.g neutrophils and lymphocytes in inflammation.
- Sometimes body produced harmful lymphocytes and they are also destroyed by apoptosis.

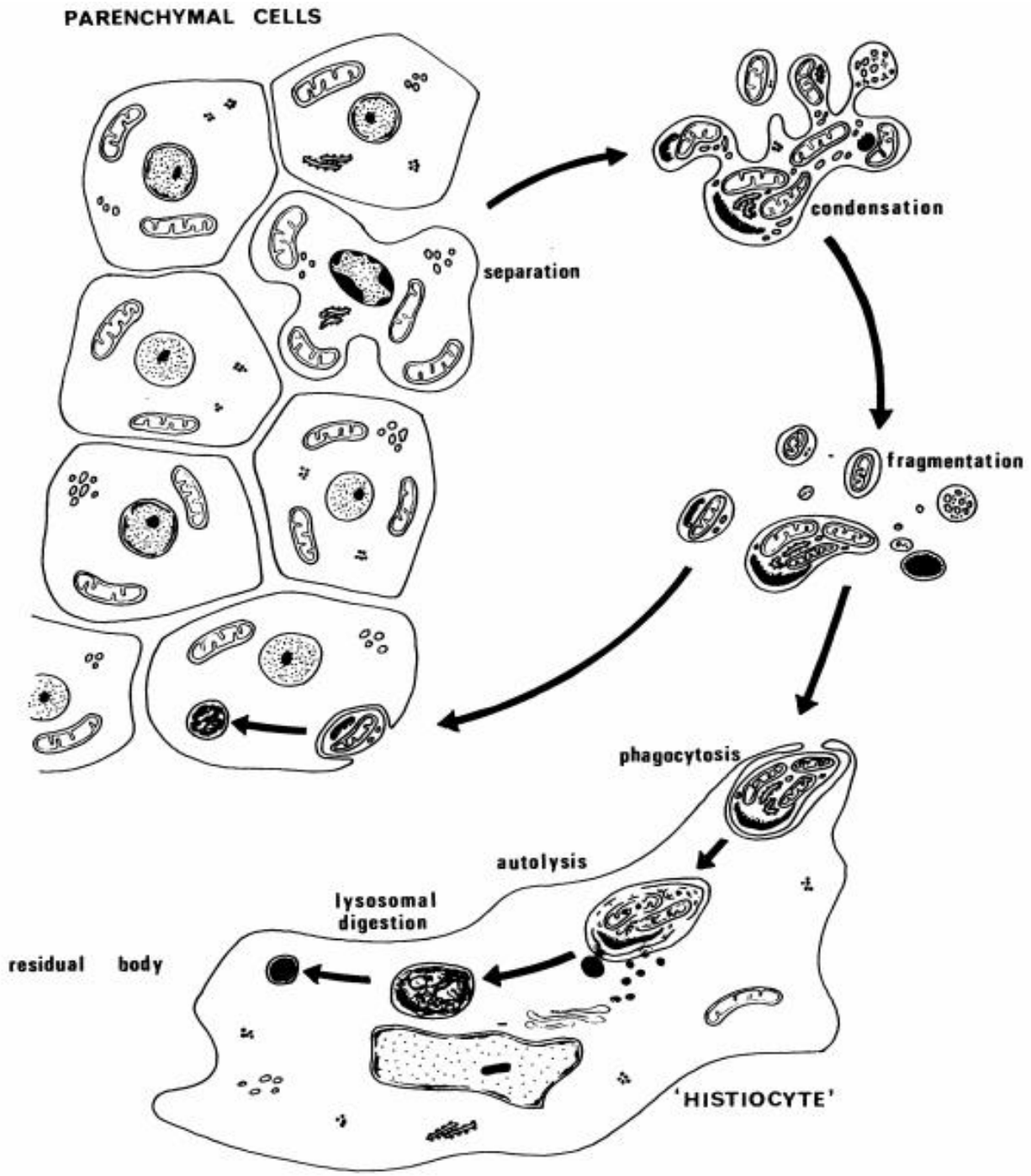
Apoptosis in Pathologic Conditions

- Cell death produced by injury e.g. radiation.
- In certain diseases e.g. viral hepatitis the infected hepatocytes undergo apoptosis (acidophilic bodies) or injury of skin cells (keratinocytes) leads to apoptosis of keratinocytes (Civatte bodies).
- Pathologic atrophy in organs e.g. pancreas, parotid gland, and kidney
- Corticosteroid induced atrophy of the neonatal thymus
- Cell death in tumors (usually accompanied by necrosis).

Mechanism of Apoptosis

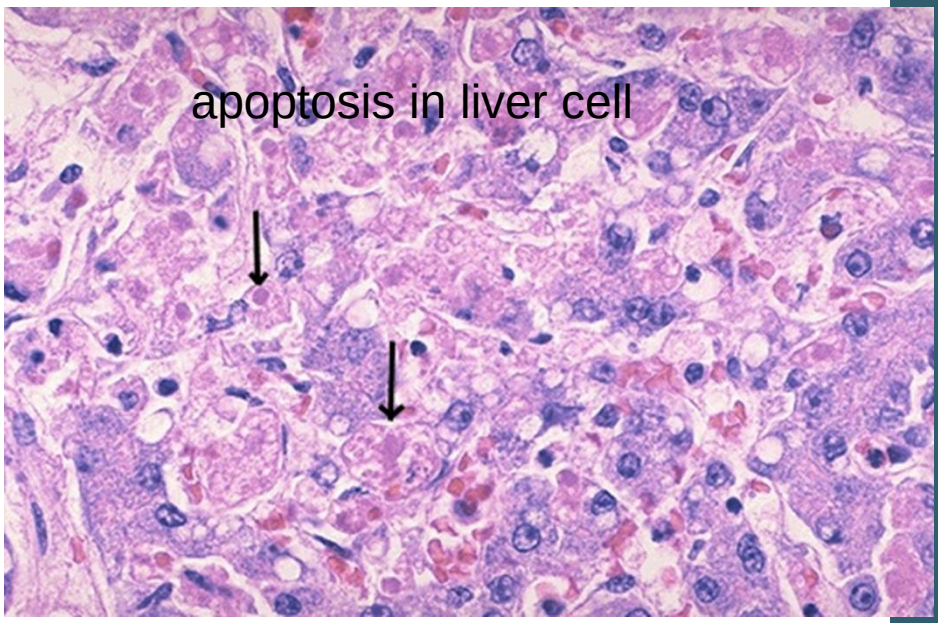
- **Activation by death pathway genes**
- **Cell shrinkage.**
- **Chromatin condensation in the nucleus:** This is the most characteristic feature of apoptosis. The nucleus may break up into fragments.
- **Formation of cytoplasmic blebs and apoptotic bodies:** The apoptotic cell first shows surface blebbing, then fragments into membrane-bound apoptotic bodies. The apoptotic bodies contain cytoplasm and organelles, with or without nuclear material.
- **The cell's plasma membrane remains intact**. The plasma membrane of the apoptotic cell sends signal to macrophages to phagocytose it.
- **Phagocytosis of apoptotic bodies, mainly by macrophages.** There is no release of the cytoplasmic content and therefore there is no inflammation in the surrounding tissue.




PARENCHYMAL CELLS
separation
condensation
fragmentation
phagocytosis
autolysis
lysosomal digestion
residual body
'HISTIOCYTE'

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.



Important enzymes of apoptosis

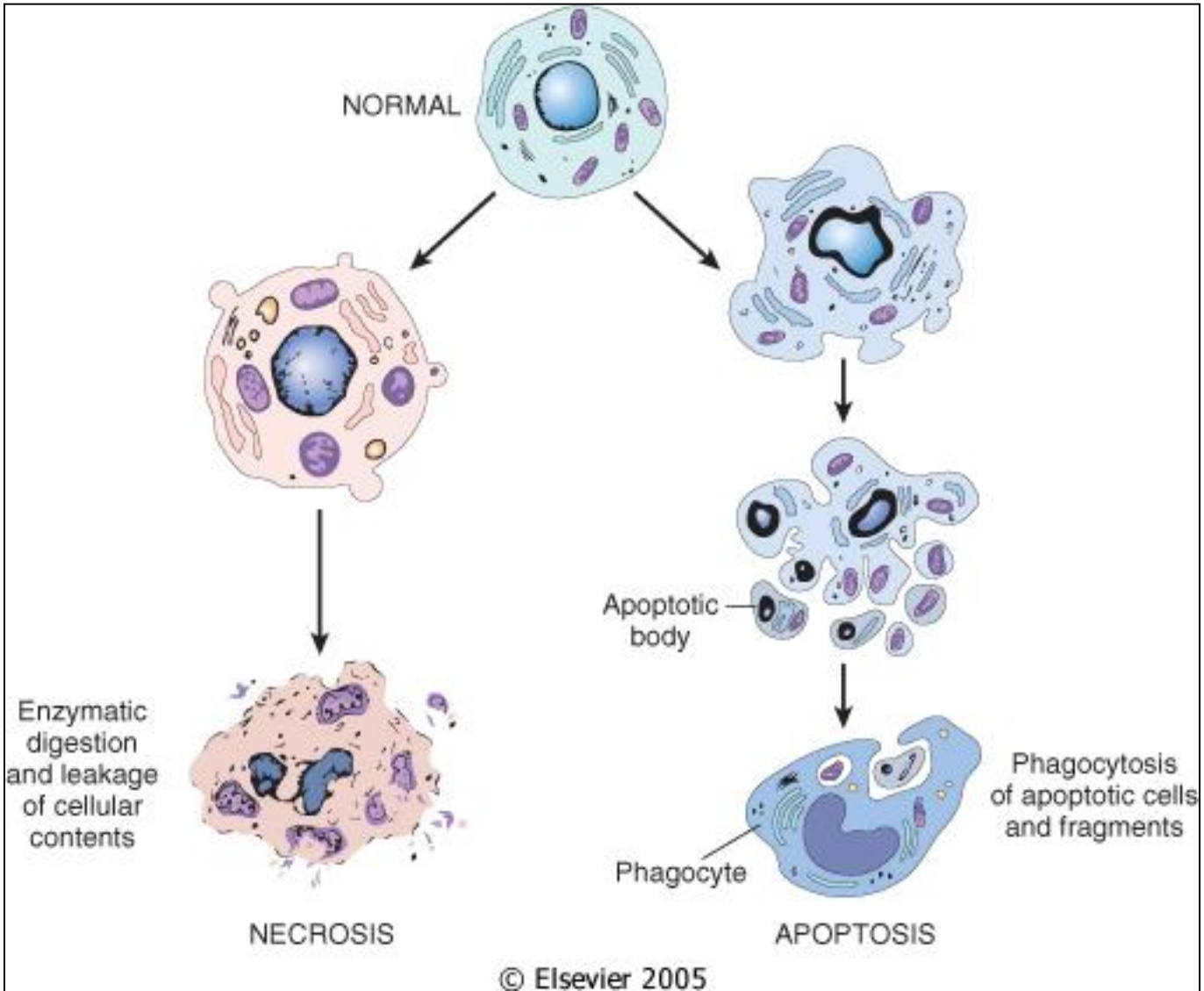
1. Cysteine proteases named *caspases*
2. Ca2+- and mg2+-dependent endonucleases

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)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage