CELL INJURY for Medical (lecture 2)

Dr. Sufia Husain
Associate Prof & Consultant
College of Medicine
KSU, Riyadh
Sept. 2018

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.

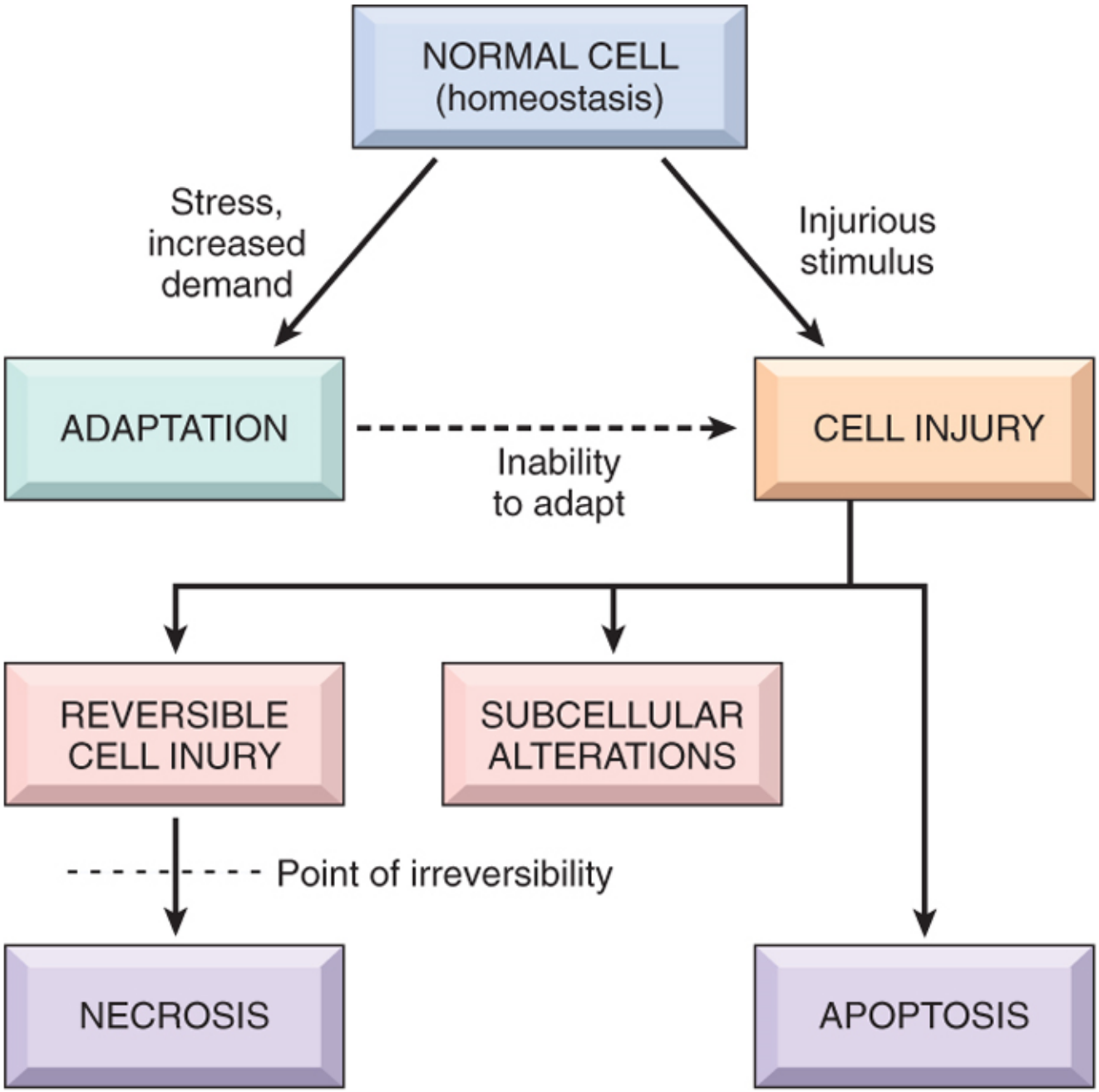


Figure 1-1 Stages in the cellular response to stress and injurious stimuli.

NECROSIS.

- Necrosis is a type of cell death, in which there is enzymatic digestion and denaturation of intracellular protein in the dying 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/ loss of function of the involved tissue/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 e.g. 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 seen in cells after death/ post mortem. Autolysis is also seen in some pathologic conditions in living organisms.

Types of necrosis

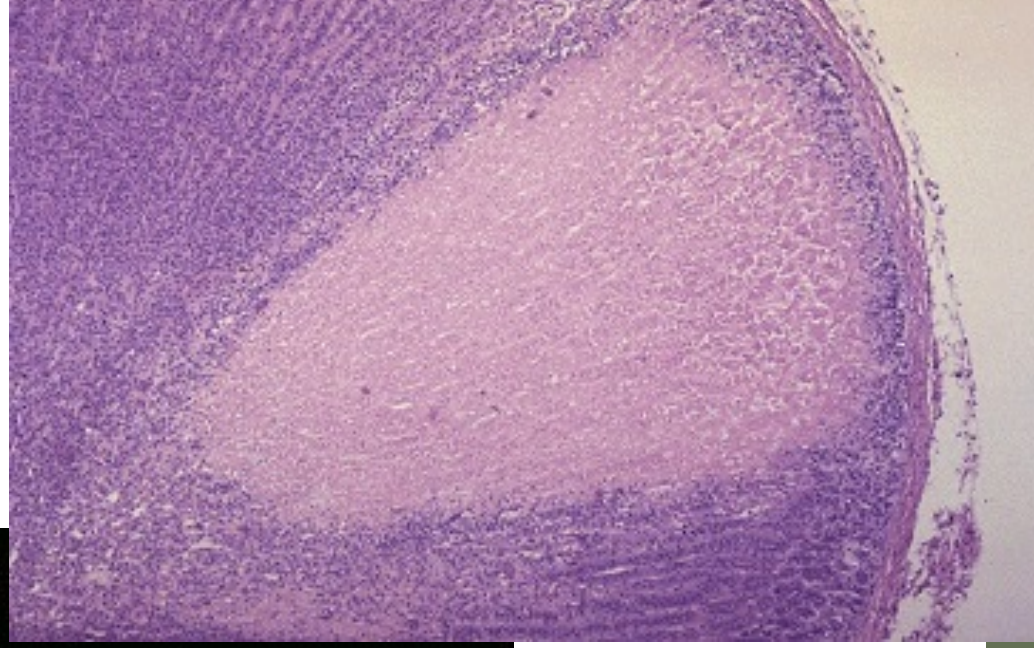
› There are 5 types of necrosis:

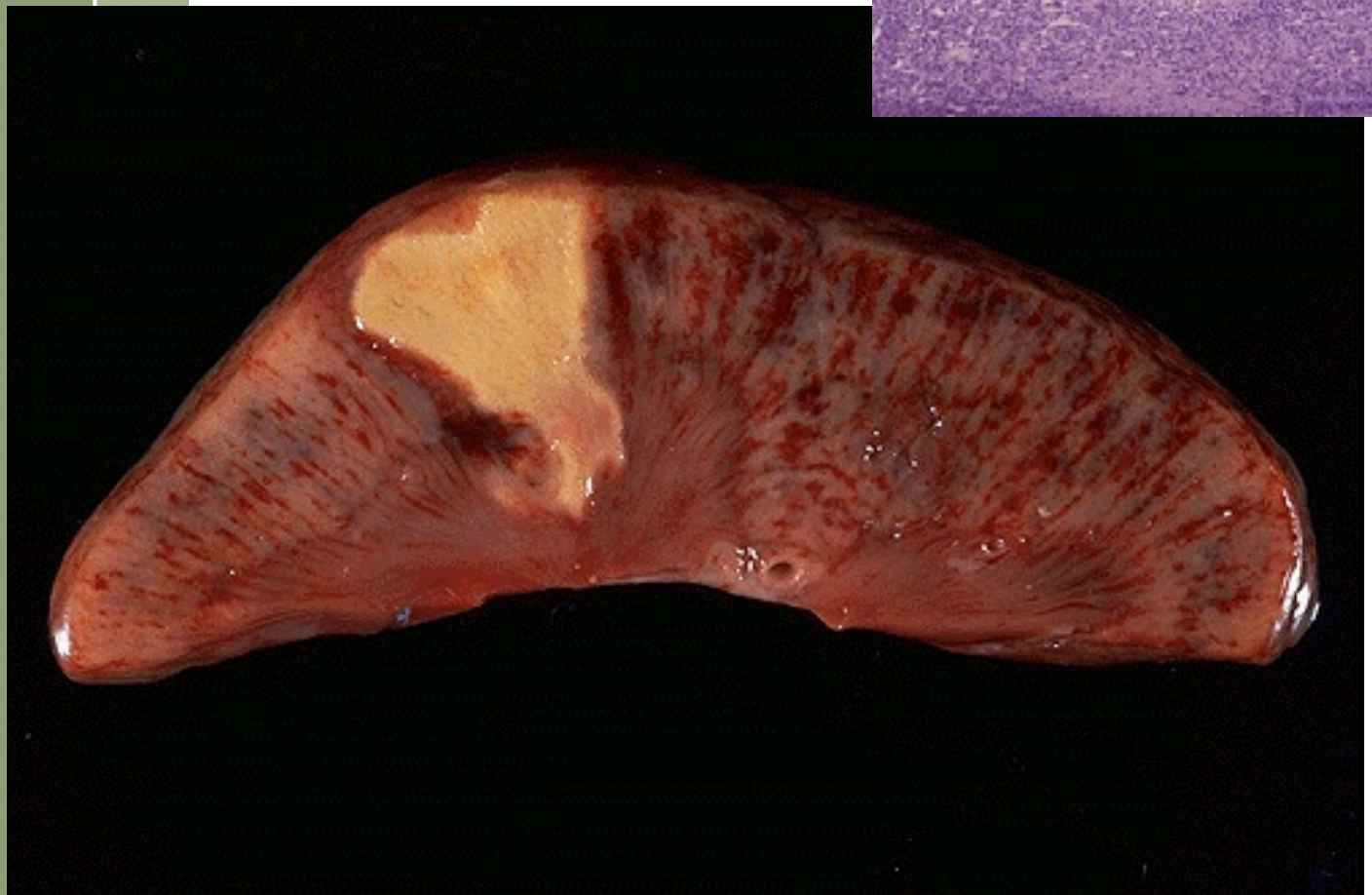
- **coagulative necrosis**
- **liquefactive necrosis**
- **caseous necrosis**
- **fat necrosis**
- **fibrinoid necrosis**

Coagulative necrosis:

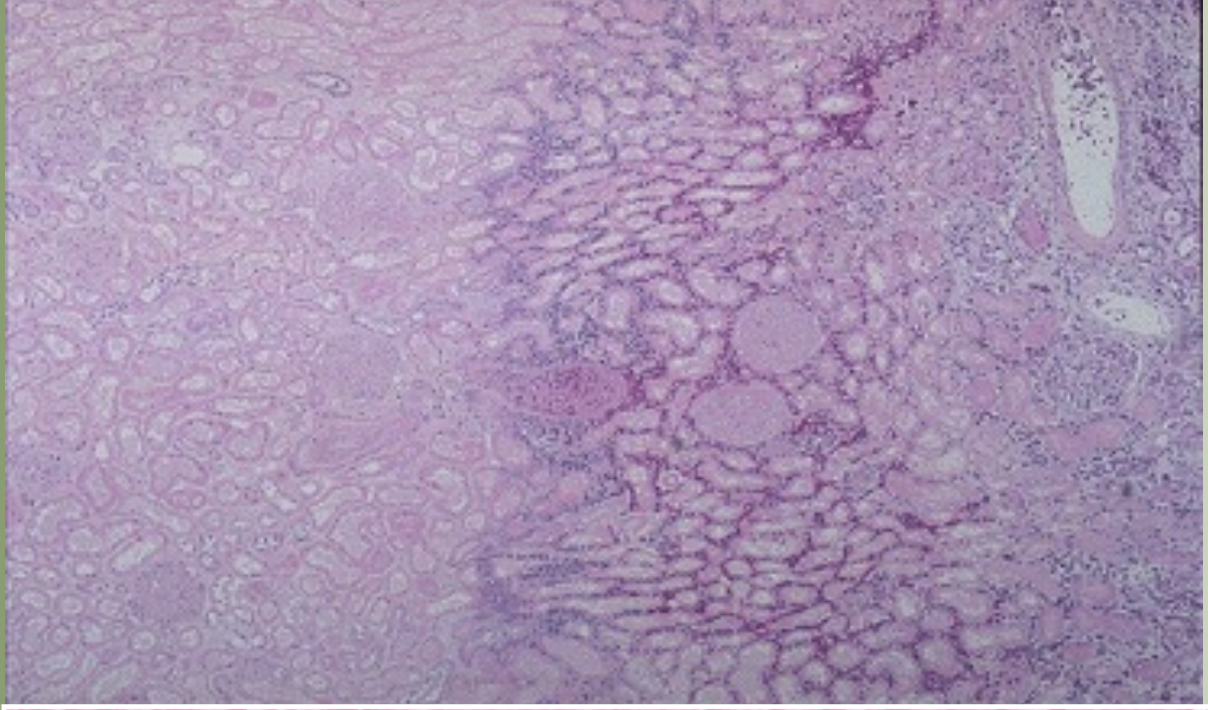
- Coagulative necrosis is characteristically seen when blood flow to an organ is affected leading to ischemic/hypoxic death of cells in that organ.
- It is seen in all organs except the brain. Coagulative necrosis is not seen in the brain.
- It is infarction of the affected organ. It can be seen in heart (called as myocardial infraction), kidney (called as renal cortical necrosis/ infarct), spleen, liver (splenic or hepatic infarct) etc.
- Gross: The affected organ looks pale and firm/solid. It looks like 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 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 vacum cleaners).

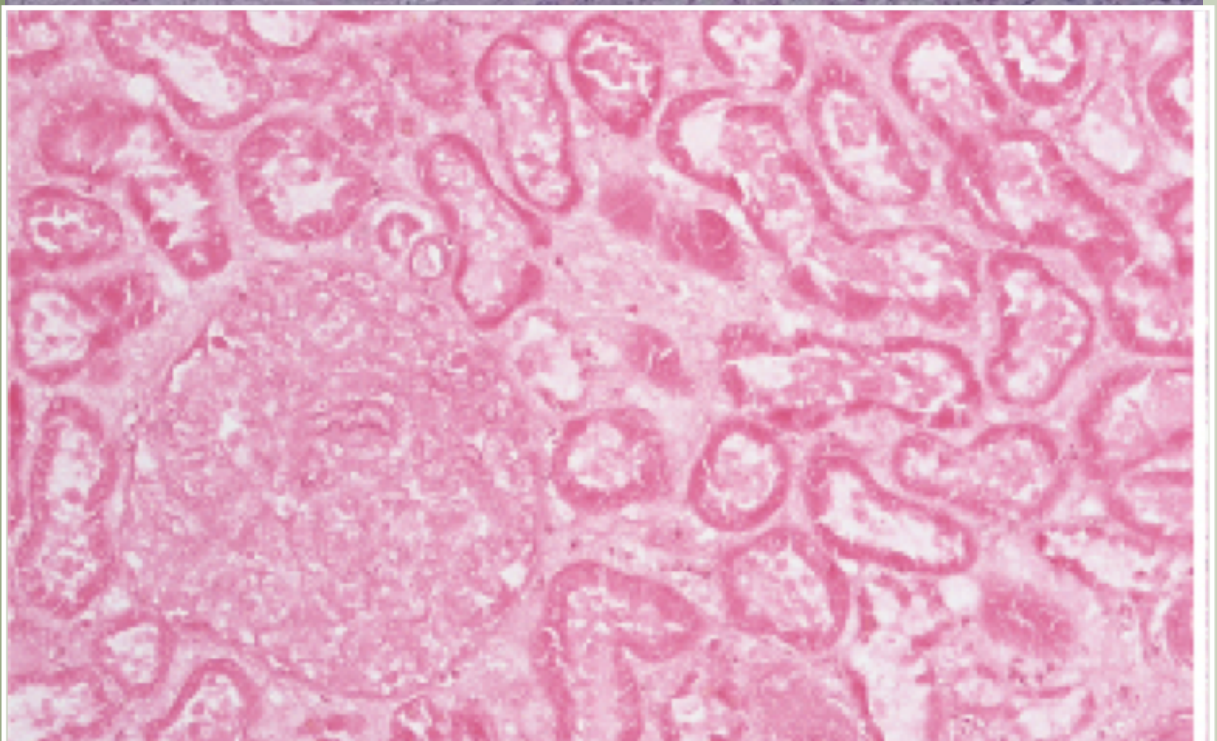
Kidney: coagulative necrosis





Gross: tissue is firm

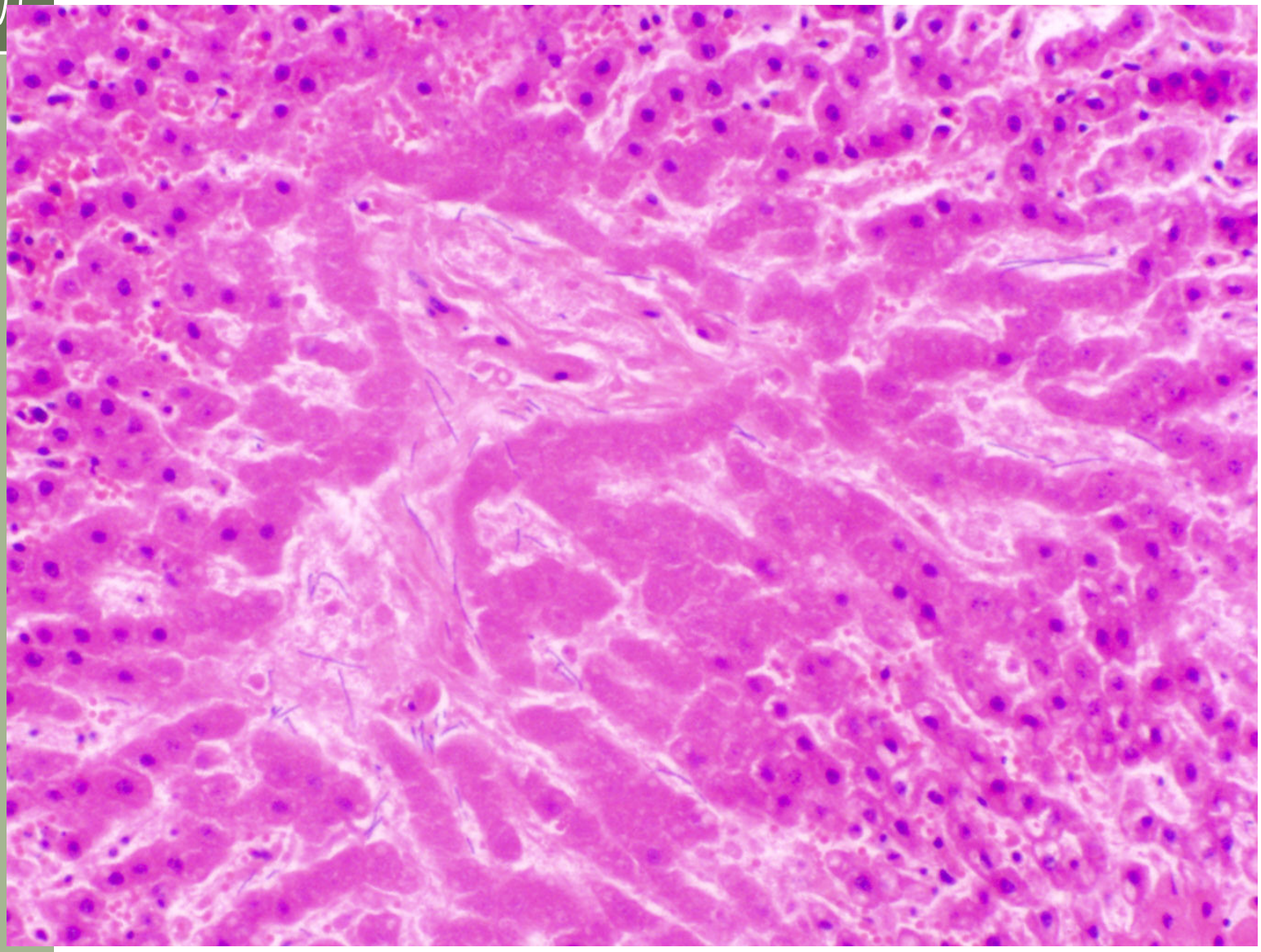




Kidney: coagulative necrosis

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

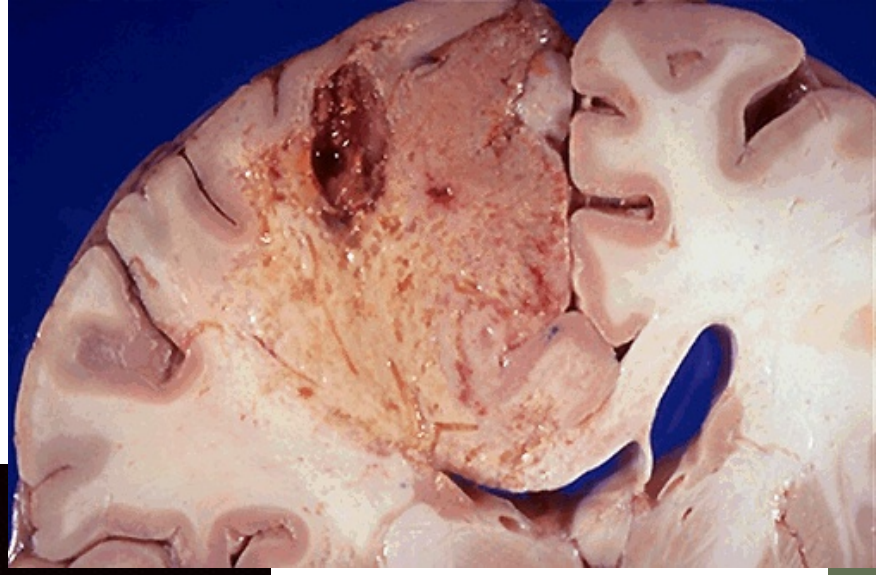
Liver coagulative necrosis

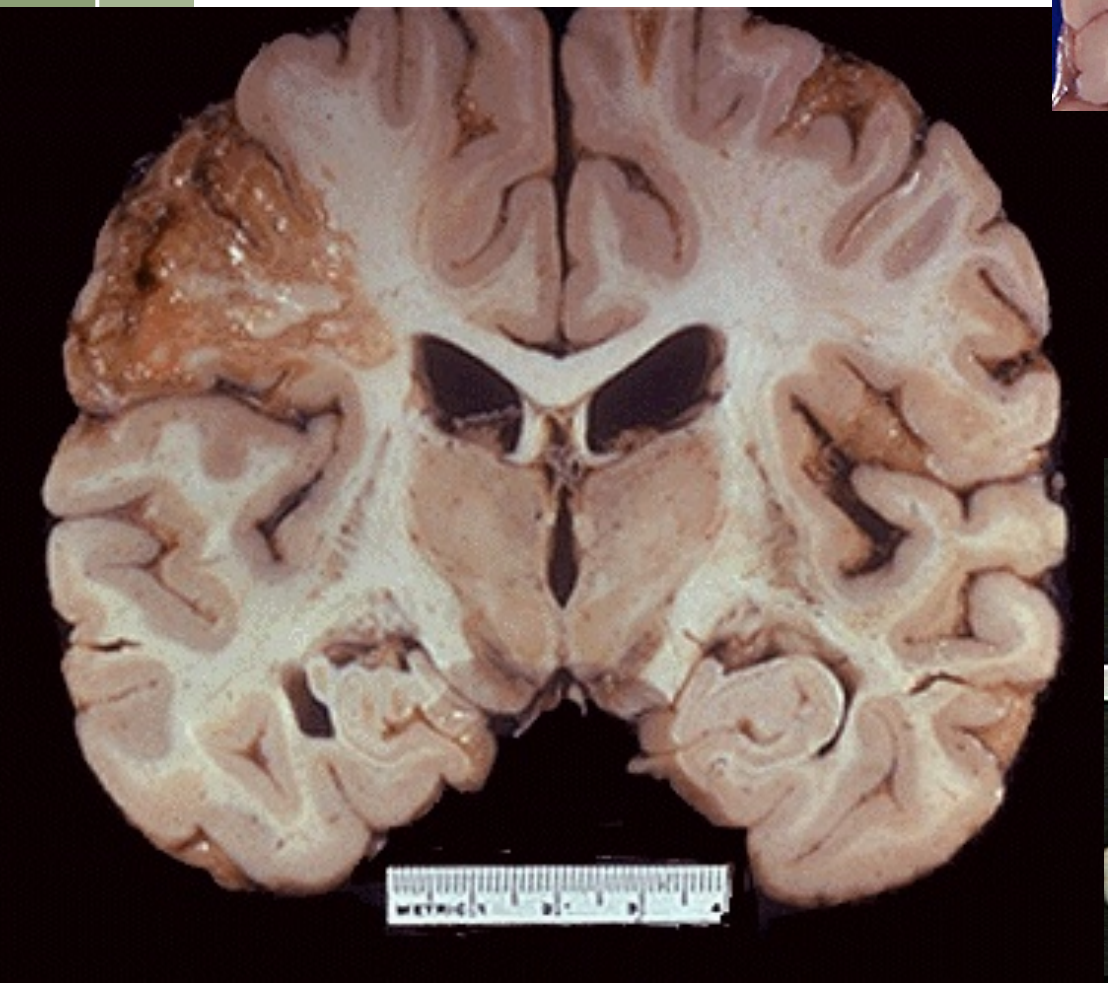


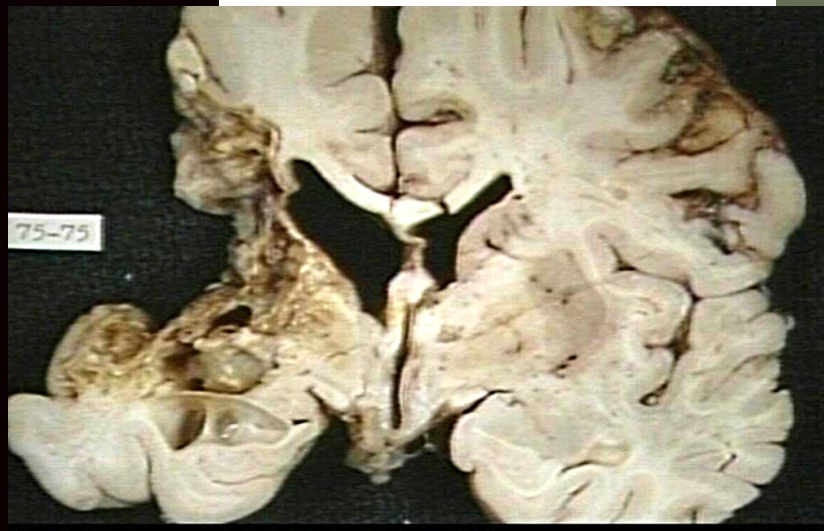
Liquefactive necrosis

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

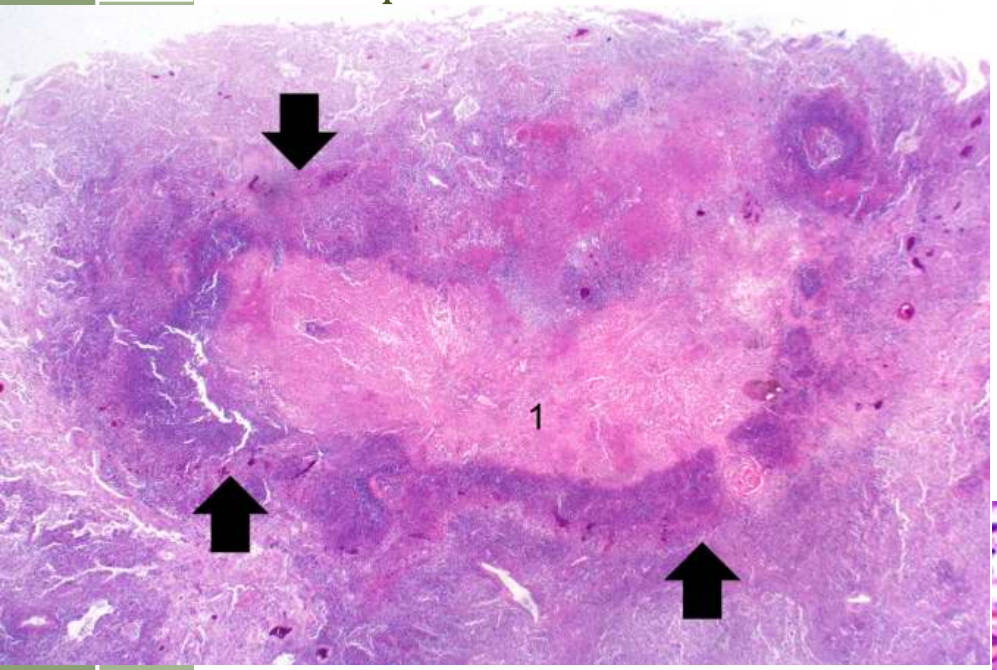
Liquefactive necrosis

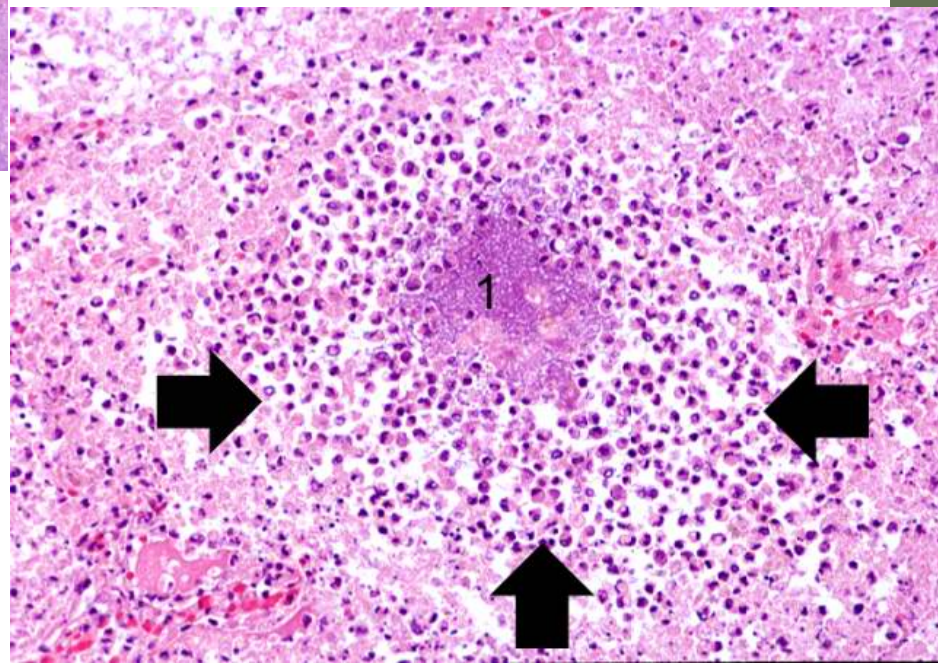






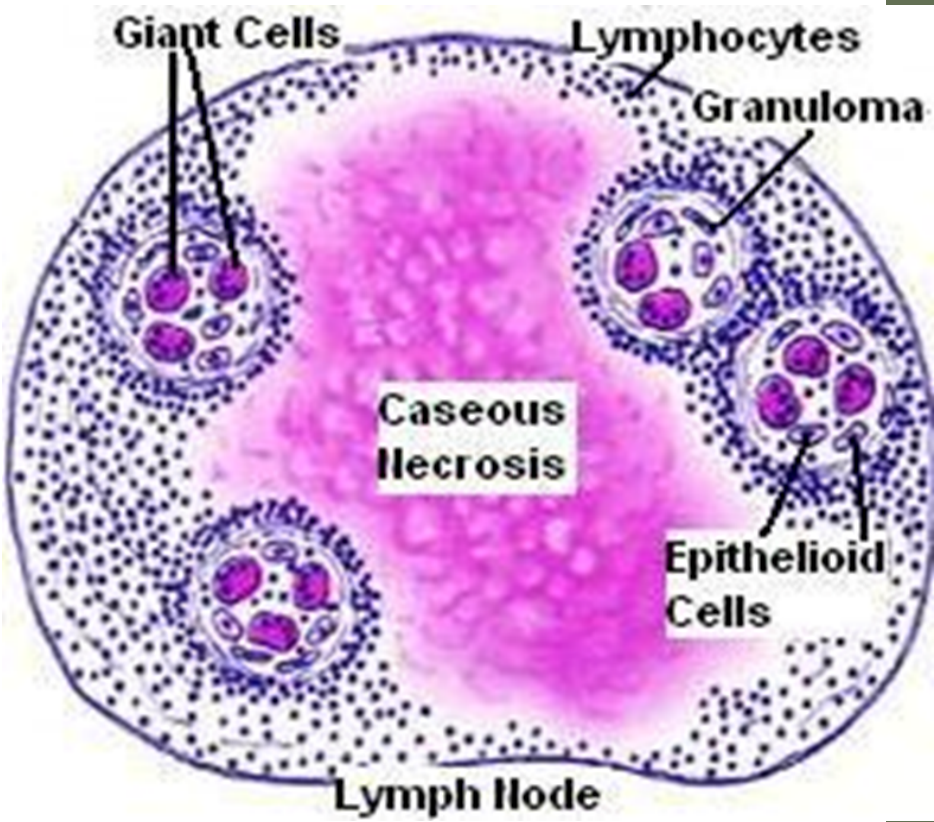
Liquefactive necrosis (center labeled one is necrosis and surrounding is neutrophils.



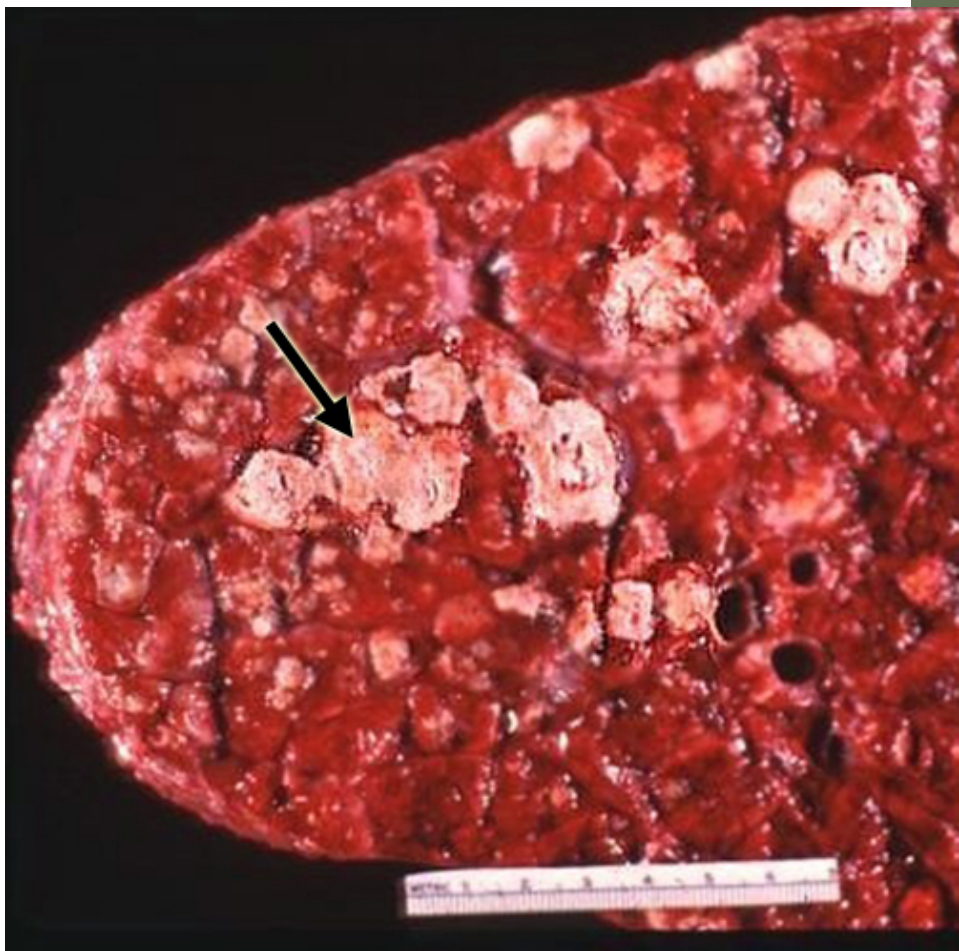


Caseous necrosis

- is a type of coagulative necrosis classically seen in tuberculosis (infection by mycobacterium tuberculi).
- Grossly: it is white, soft, curdy, cheesy-looking “caseous” material.
- On microscopic examination, the necrotic area appears as amorphous pink granular debris surrounded by a collar of epitheloid cells (they are 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

- It is necrosis of fat cells.
- Typically, it is seen in acute pancreatitis in which the injured pancreatic cells release the lipase enzyme into the fat in the abdominal cavity and cause enzymatic digestion of fat cells.
- 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.
- 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.

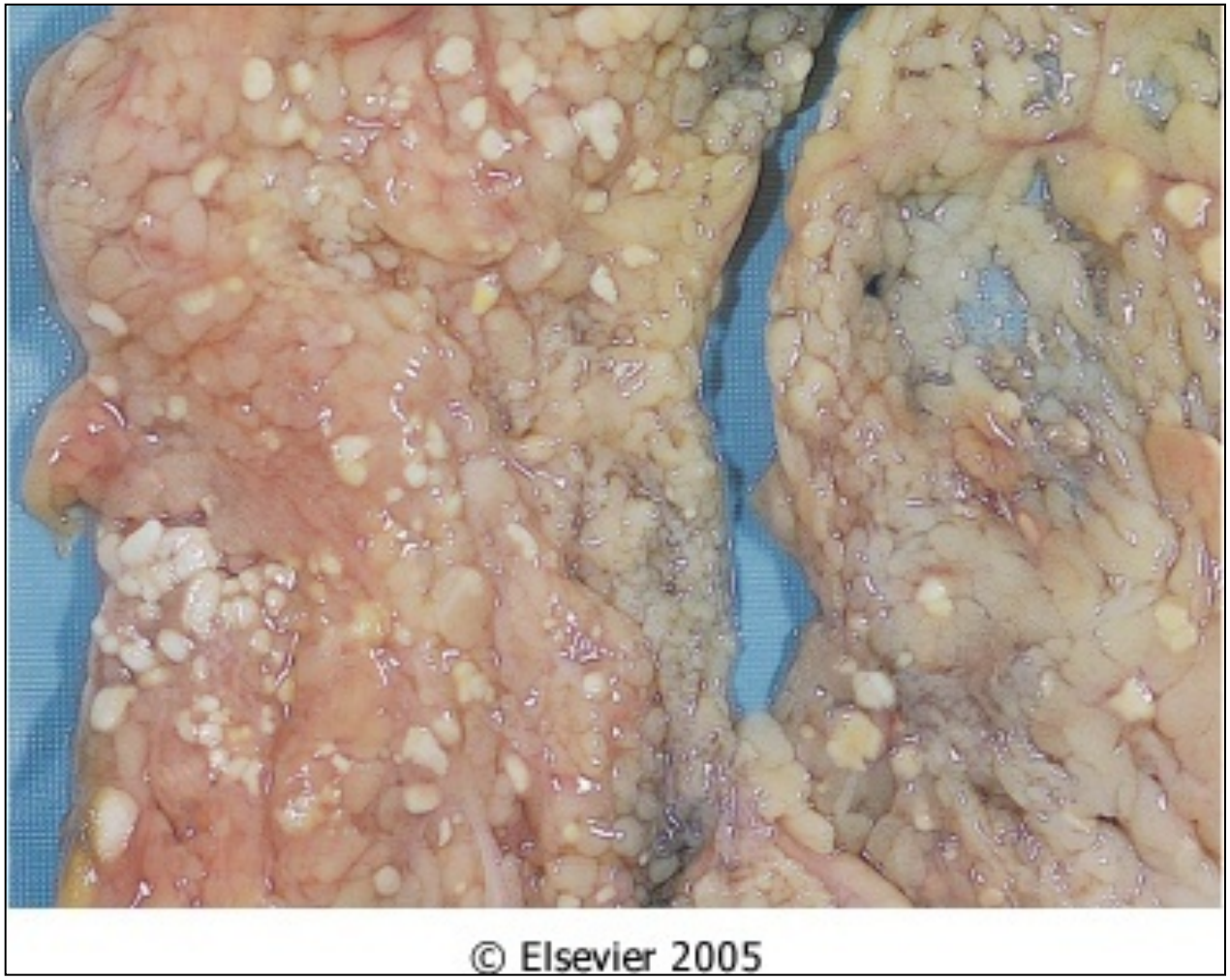
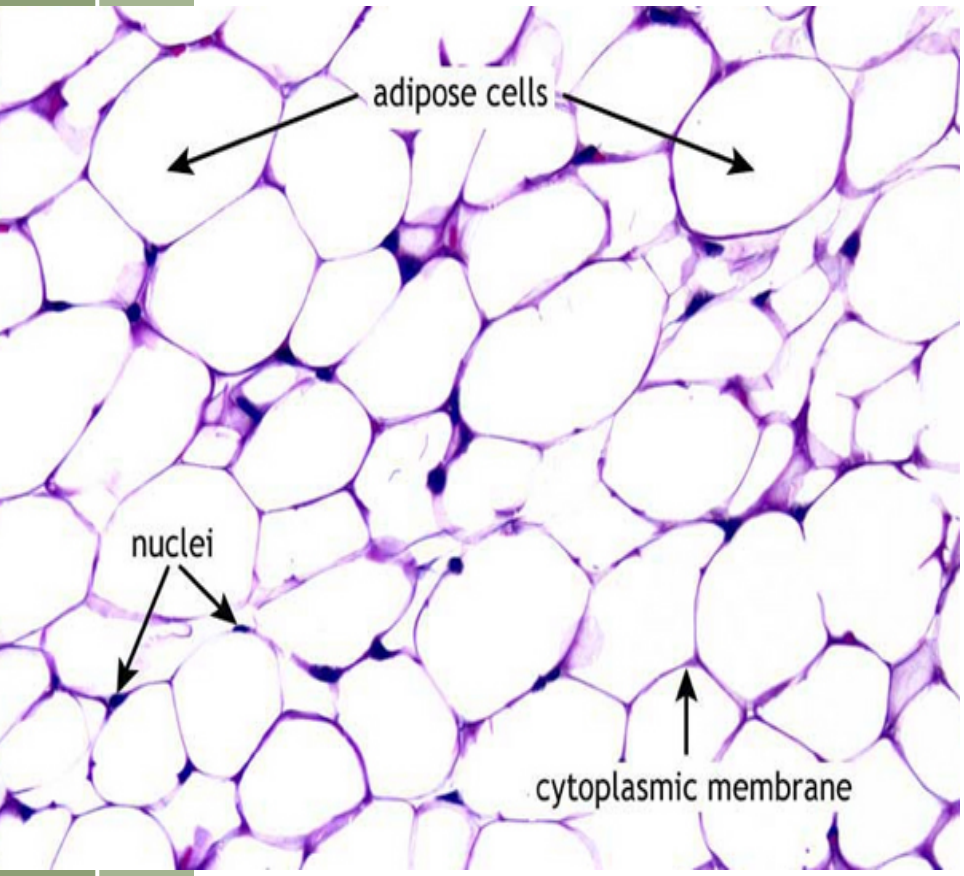
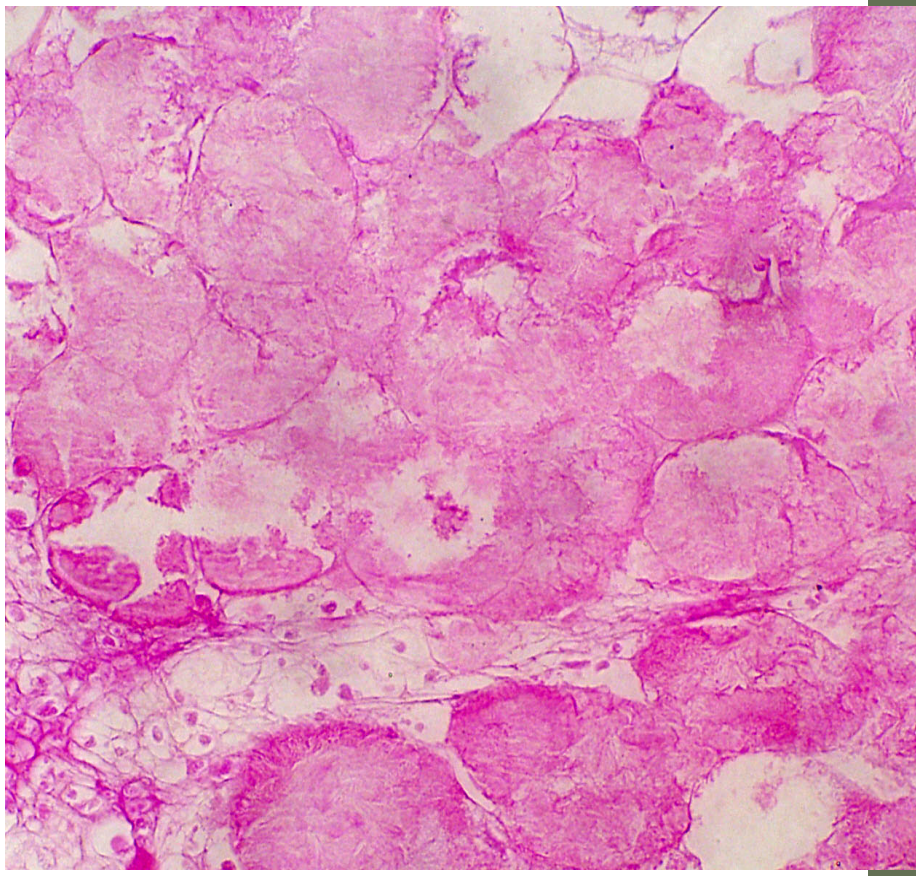


Figure 1-21 Foci of fat necrosis with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown.

› Normal adipose tissue



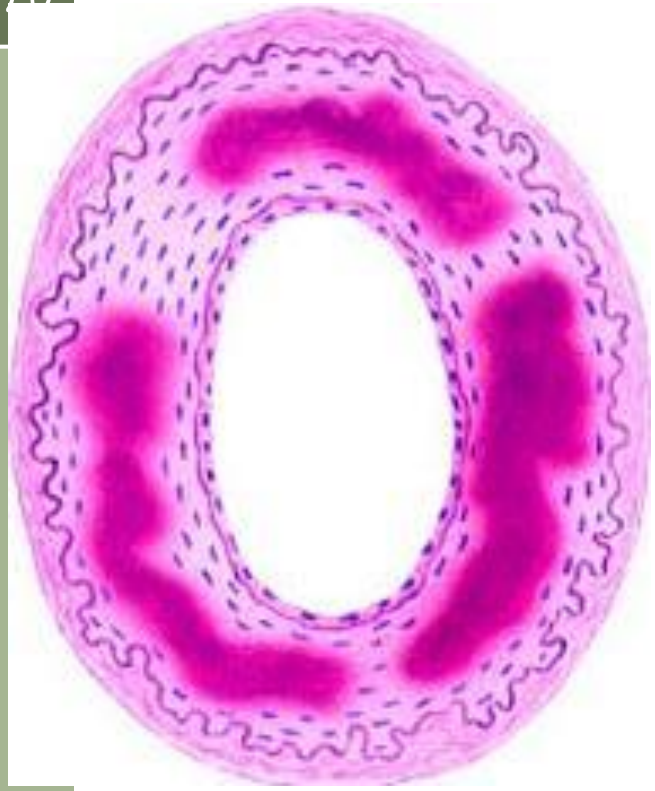
› Fat necrosis

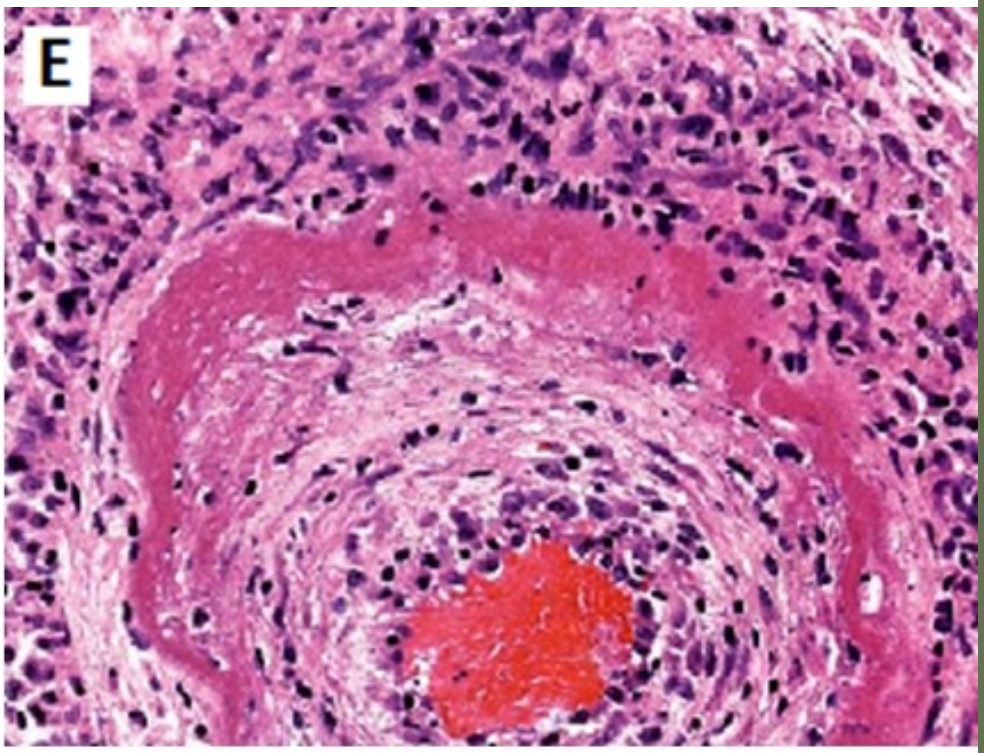


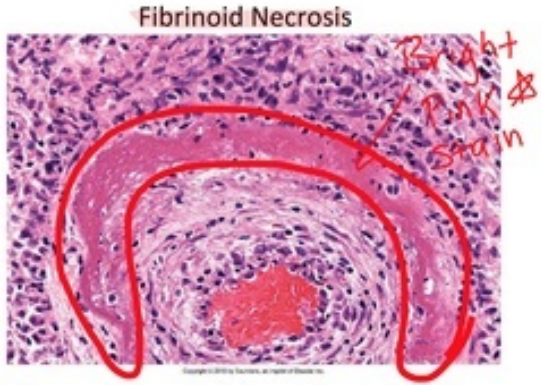
Fibrinoid necrosis

- 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

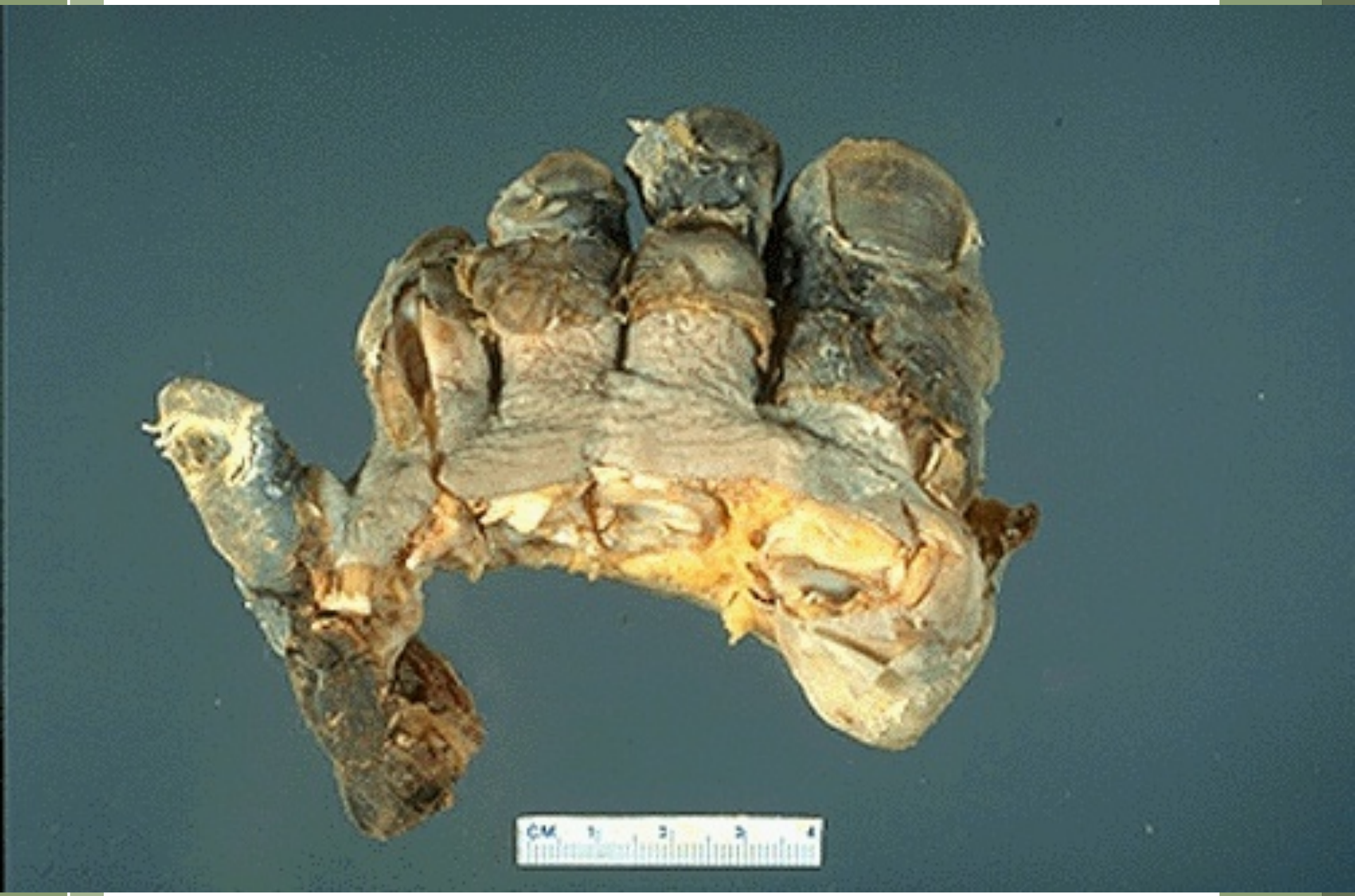
It is a term commonly used in clinical practice by surgeons. It can be dry or wet.

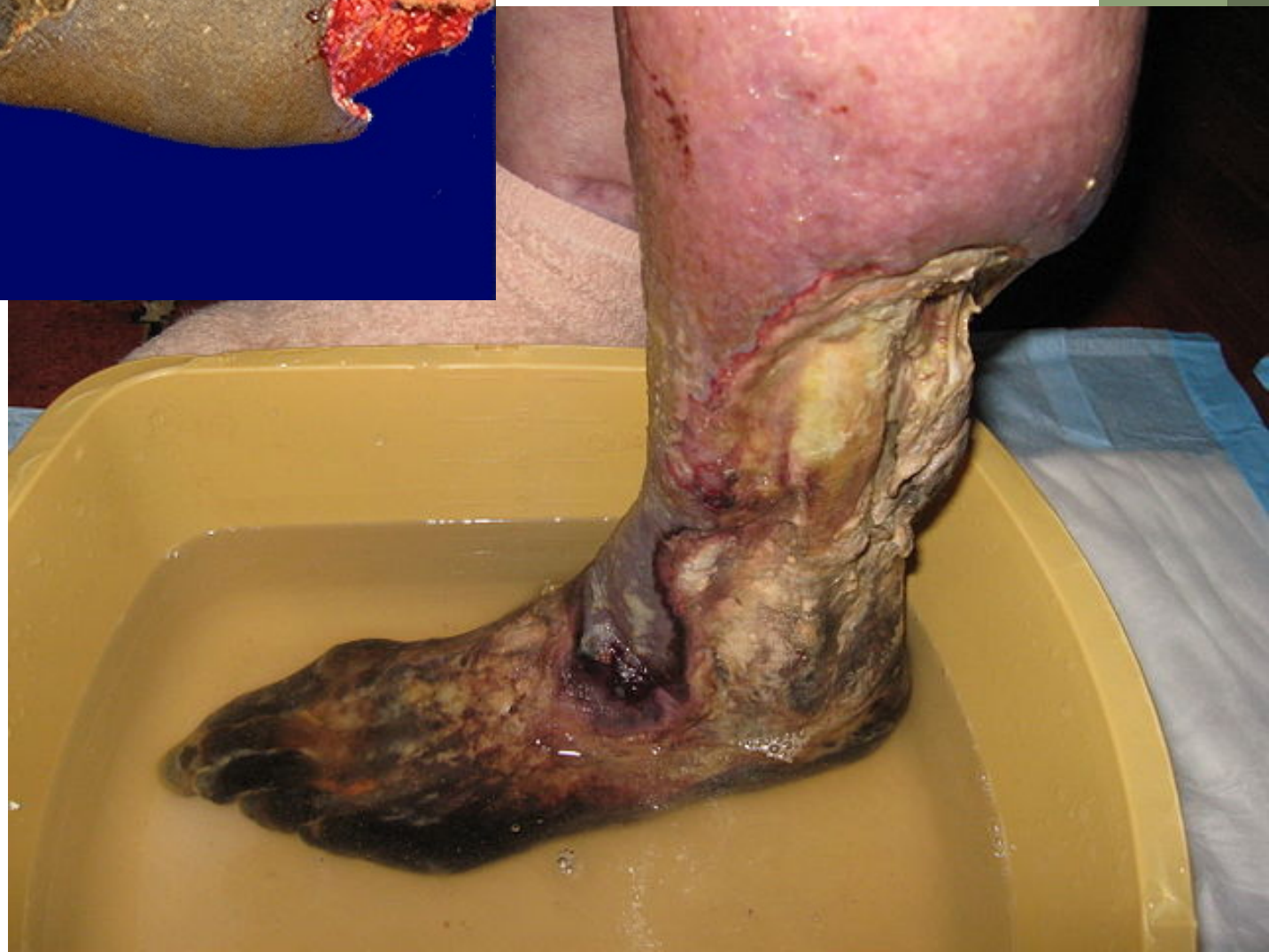
- **Dry gangrene/ mummification:** it is a form of coagulative necrosis that develops in ischemic tissue (where the blood supply is inadequate). Dry gangrene is usually seen in a limb that has lost its blood supply and undergone coagulative necrosis. Dry gangrene is non-infected ischemic coagulative necrosis of tissue. It is without superadded infection. It is seen as a complication of peripheral artery disease e.g. atherosclerosis and diabetes mellitus. The affected part is dry, shrunken and dark reddish-black.

- **Wet/ infected gangrene**: it is dry gangrene with 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 superadded infection 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) 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.

Treatment of gangrene: amputation.

NOTE: Diabetes mellitus is a risk-factor for dry gangrene, and also a risk factor for wet gangrene (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/ adapative.
- Pathologic.

- NOTE: Apoptosis and necrosis can sometimes coexist.

Apoptosis in Physiologic Situations

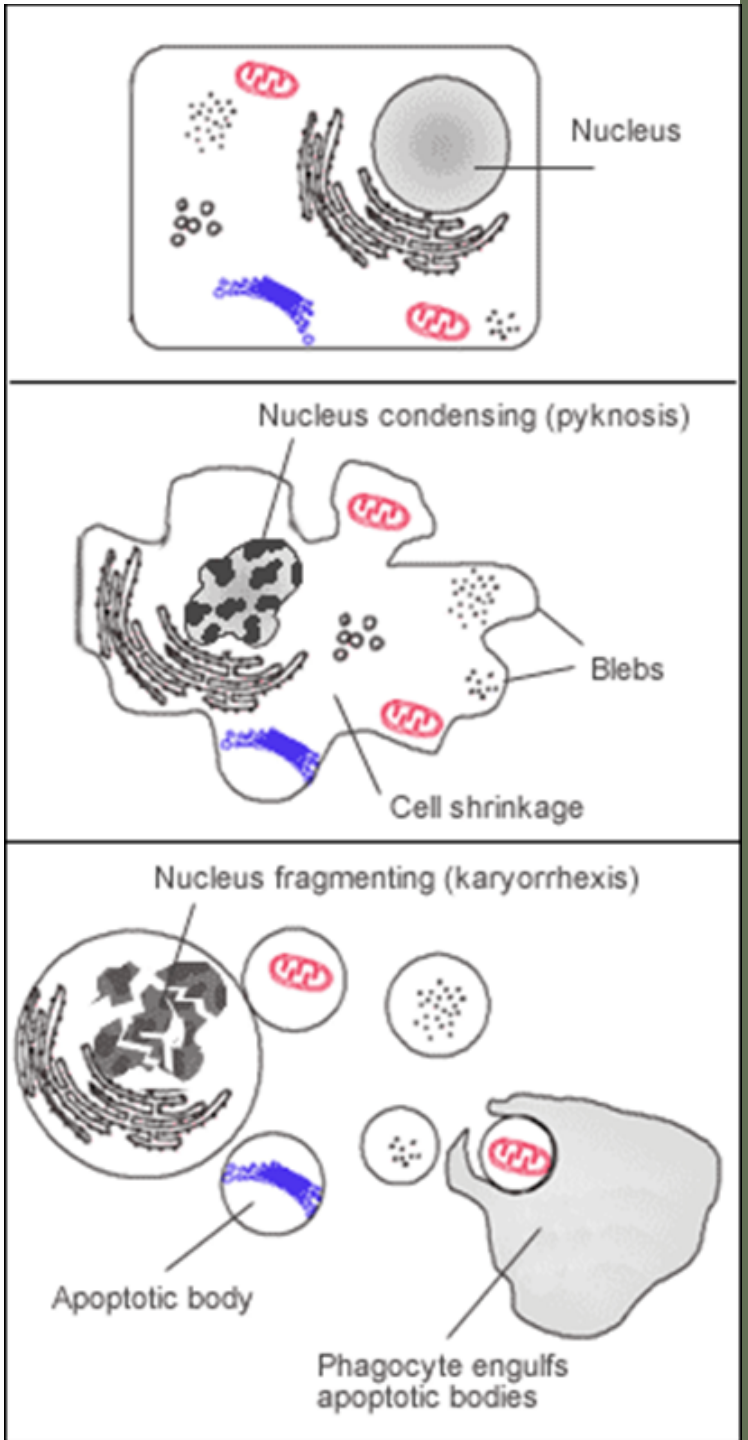
- The programmed destruction of cells during embryogenesis.
- Hormone-dependent: e.g. endometrial cell breakdown during the menstrual cycle, the regression of the lactating breast after weaning, and prostatic atrophy after castration (adaptive atrophy).
- Apoptosis in proliferating cells e.g. intestinal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

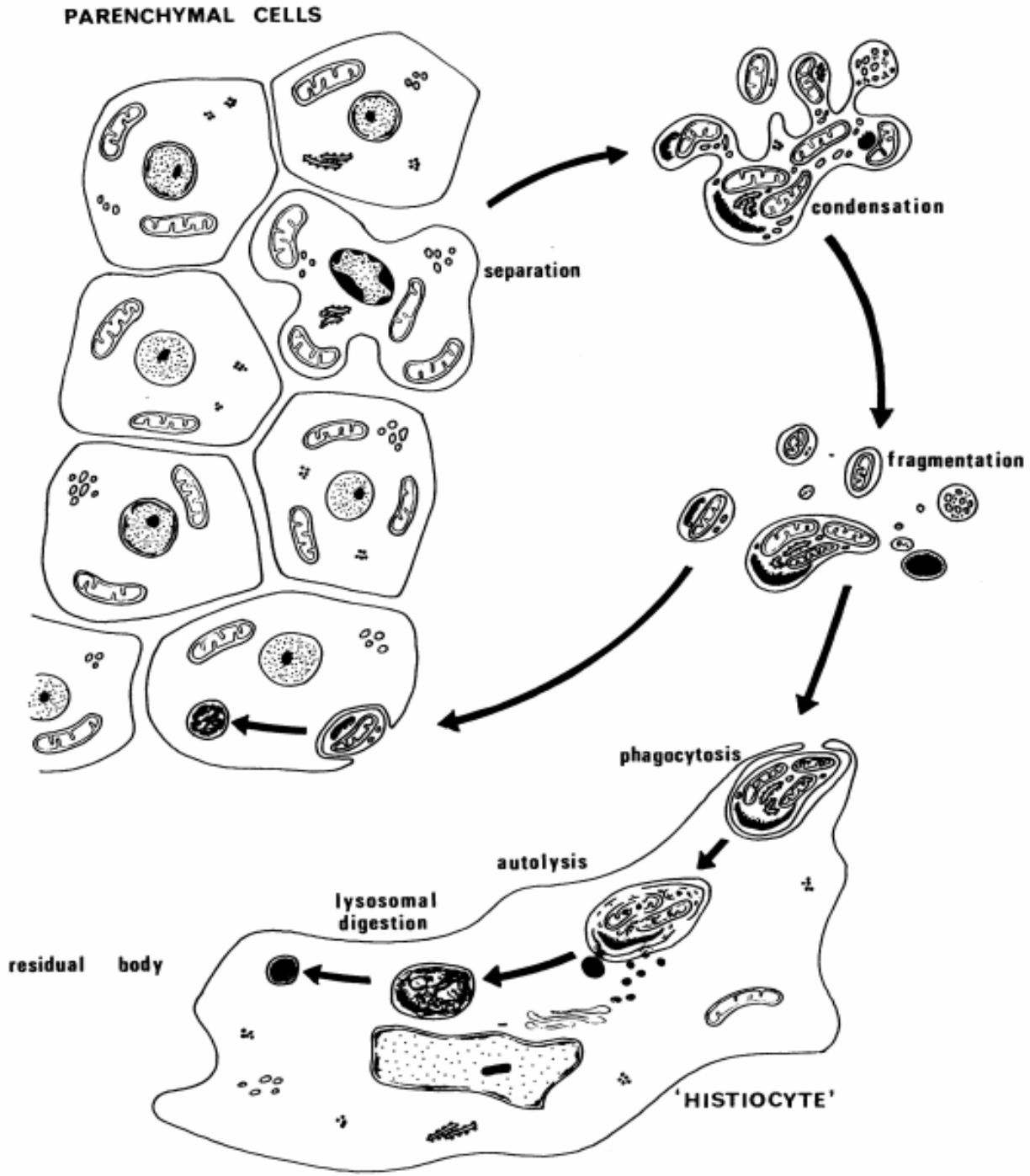
Apoptosis in Pathologic Conditions

- 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

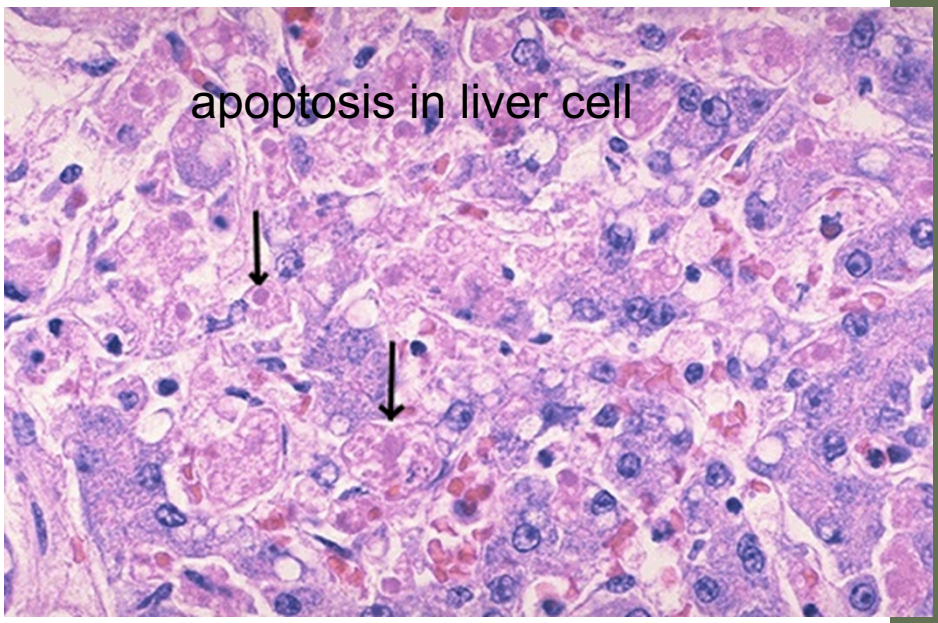
- **The death pathway genes are activated which trigger apoptosis.**
- **Cell shrinkage.**
- **Chromatin condensation in the nucleus:** This is the most characteristic feature of apoptosis. The nucleus may break up into fragments.
- **Formation of cytoplasmic blebs and apoptotic bodies:** The apoptotic cell first shows surface blebbing, then fragments into membrane-bound apoptotic bodies. The apoptotic bodies contain cytoplasmic content with or without nuclear material.
- **The cell's plasma membrane remains intact**. The plasma membrane of the apoptotic cell sends signal to macrophages, inviting the macrophages to phagocytose it.
- **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.




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

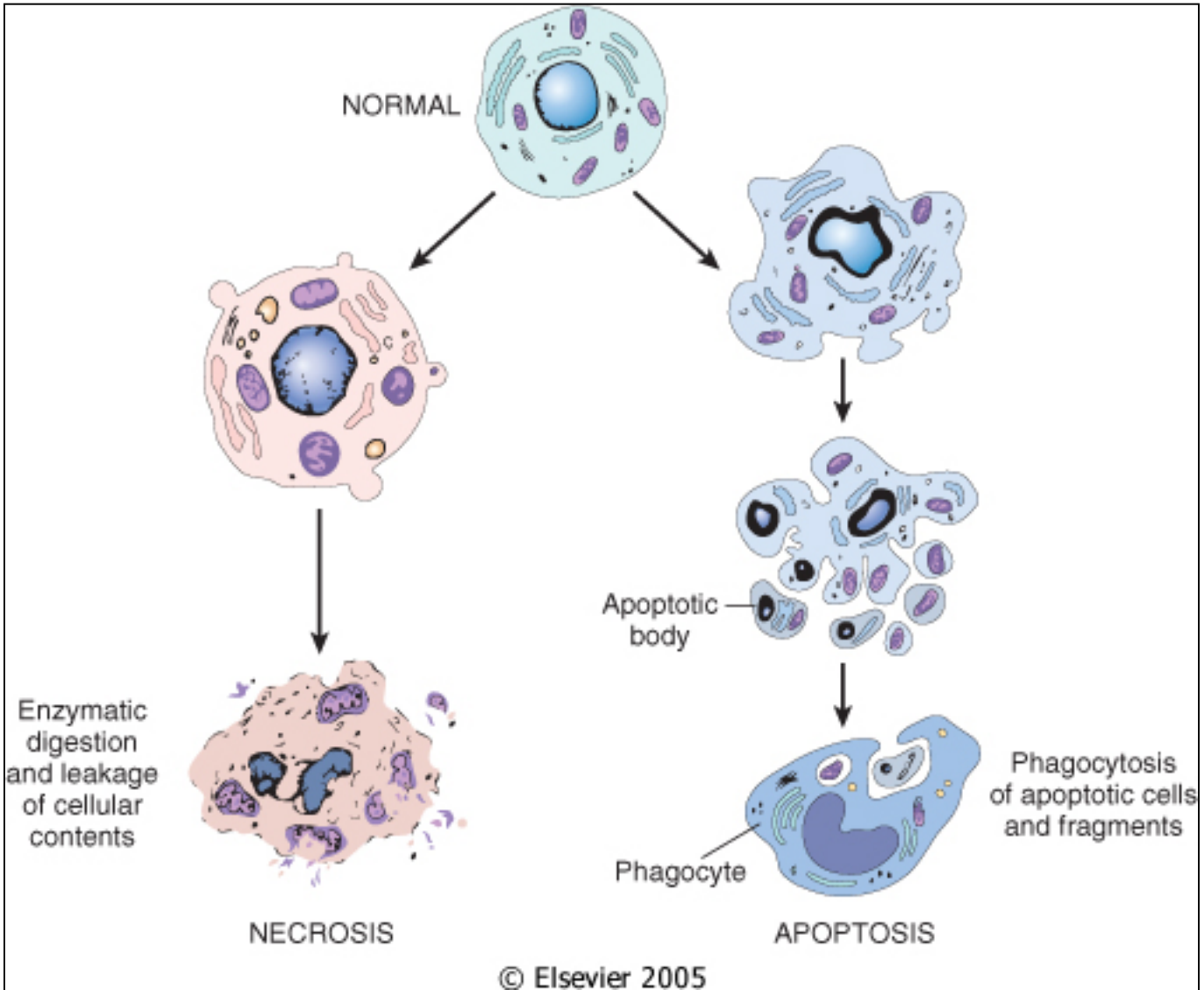
1. Cysteine proteases named *caspases*
2. Ca2+- and mg2+-dependent endonucleases

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