Cell injury

- It can occur as a result of an adverse stimulus which disrupts the normal homeostasis of affected cells.

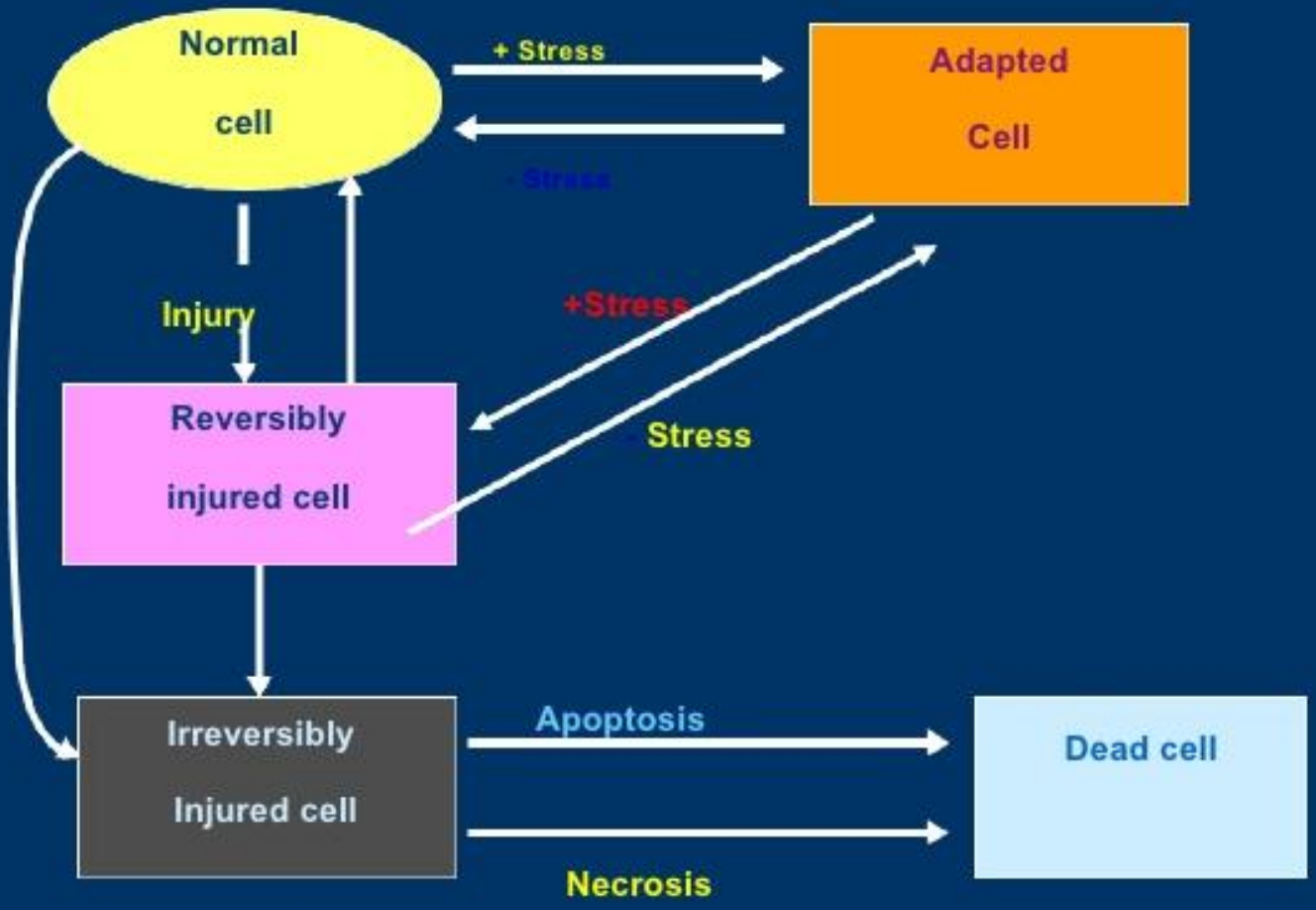
- Normal cell is in a steady state "**Homeostasis**"
- Change in Homeostasis due to stimuli - Injury
- Injury - Reversible / Irreversible
- Adaptation / cell death

- Cell injury can be reversible or irreversible.
- Depending on the extent of injury, the cellular response may be adaptive and where possible, homeostasis is restored.
- **Cell death** occurs when the severity of the injury exceeds the cell's ability to repair itself. Cell death is relative to both the length of exposure to a harmful stimulus and the severity of the damage caused. Cell death may occur by **necrosis** or **apoptosis**.

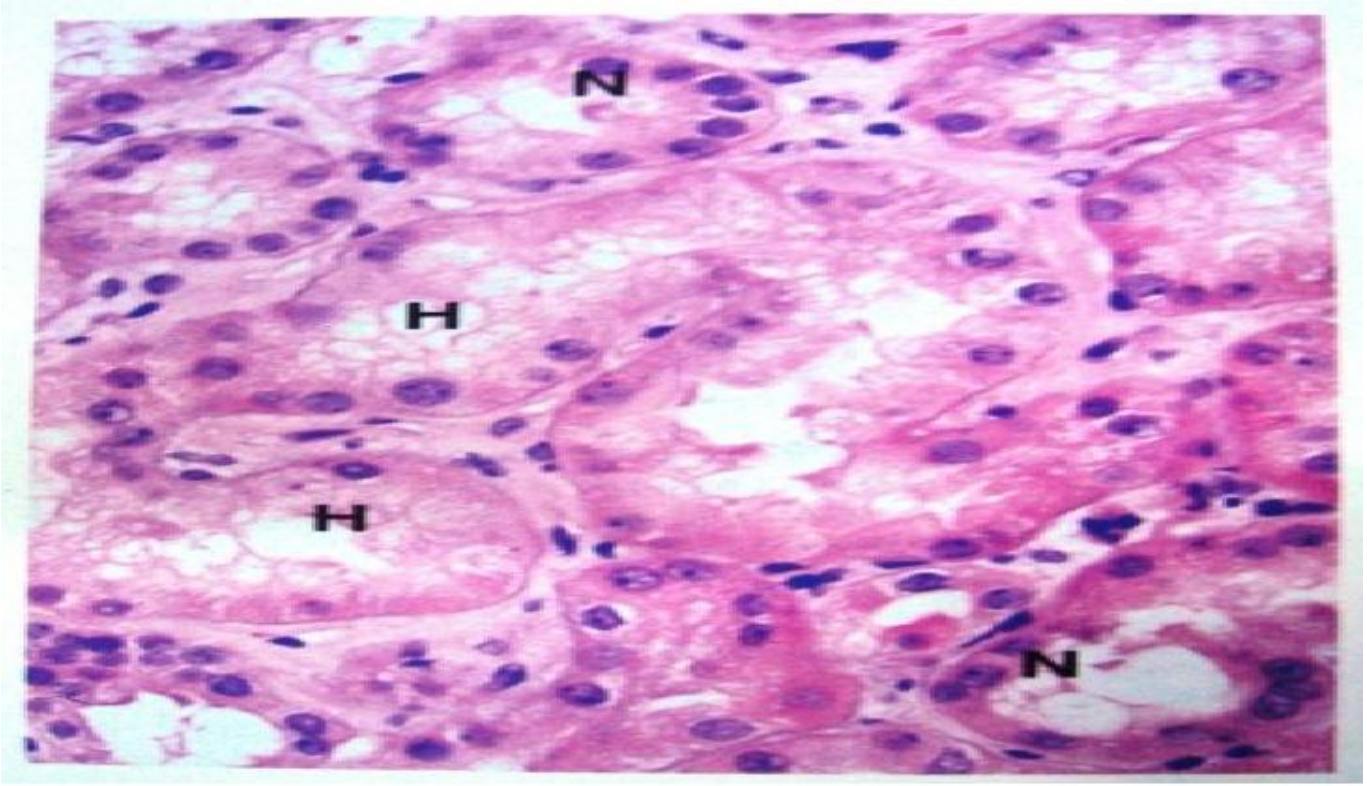
Types of damage

- **Sub-lethal (reversible)**
  - Cellular swelling
  - Fatty change
  - …….etc
- **Lethal (irreversible)**
  - Necrosis
  - Apoptosis

Overview


Normal
cell
+ Stress
Adapted
Cell
- Stress
Injury
+Stress
Reversibly
injured cell
Stress
Irreversibly
Injured cell
Apoptosis
Dead cell
Necrosis

Reversible cell injury



Hydropic degeneration: kidney

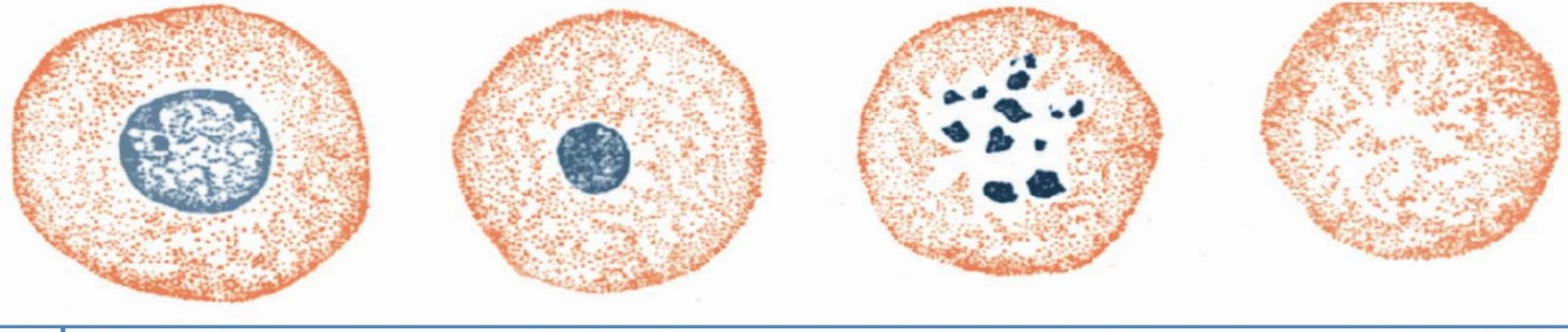
Cloudy swelling & hydropic change reflect failure of membrane ion pumps, due to lack of ATP, allowing cells to accumulate fluid

We shall study:

- Cell death
- Necrosis
  - Types
- Fate of necrosis
- Gangrene
  - types
- Apoptosis
  - types
- Difference between apoptosis and necrosis

Changes in the nucleus

- **Pyknosis**: **condensation** of chromatin of chromatin and shrinkage of the nucleus.
- **Karyorrhexis**: **fragmentation** of the nucleus.
- **Karyolysis**: **dissolution** of the nucleus.



Changes in cytoplasm staining

- **Opacification: denaturation of proteins lead to aggregation with resultant opacification of the cytoplasm.**

Forms of cell death

Two forms:

- **Necrosis** - killing - decay and destruction
- **Apoptosis** - suicide - programmed cell death

Necrosis

Definition: Localized death of cell or tissue occurring in the living body

Necrosis

- **Morphologic changes that follow cell death in living tissue**

- **Localized death of cell or tissue occurring in the living body**

Necrosis

1- Poisons: Chemical poisons (induce necrosis of the cell by coagulation of the cytoplasmic protein, vegetable poisons, bacterial toxins and parasitic toxins

2- Disturbances of circulation:

3- Traumatic injury:

4- Physical agents: Heat ,Cold, Electricity and Irradiation

5- Hypersensitivity: (antigen-antibody complexes).

6- Lack of nerve supply: improper nutrition of the tissue

7- Nutritional deficiency: functional disturbances within the cell

Necrosis

- Morphologic appearance of necrosis is the result of

enzyme digestion & denaturation of proteins

Histologically: increased eosinophilia, karyolysis (nuclear pallor), pyknosis (nuclear shrinkage), karyorrhexis (nuclear fragmentation).

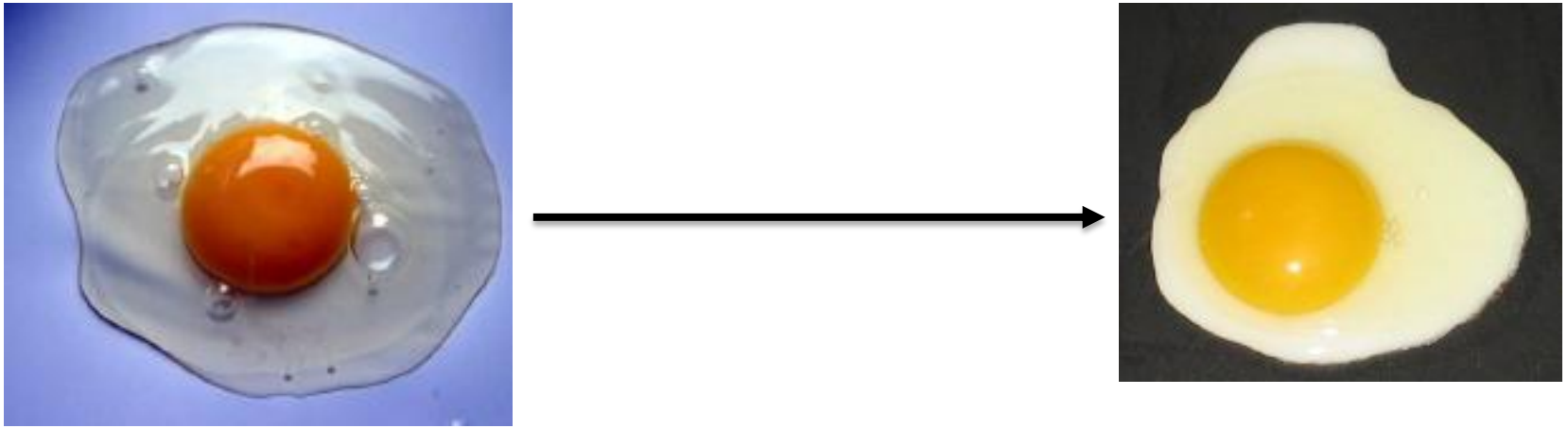
Types:

1. Coagulative: e.g. myocardial infarct
2. Liquefactive: e.g. bacterial or fungal infections, CNS hypoxia
3. Gangrenous: e.g. limb ischemia (usually a combination of coagulative and liquefactive necrosis), surgical term
4. Caseous: e.g. tuberculosis. characterized by granular debris w/obliteration of tissue architecture (gross: white & cheesy)
5. Fat necrosis

Morphological changes occur due to

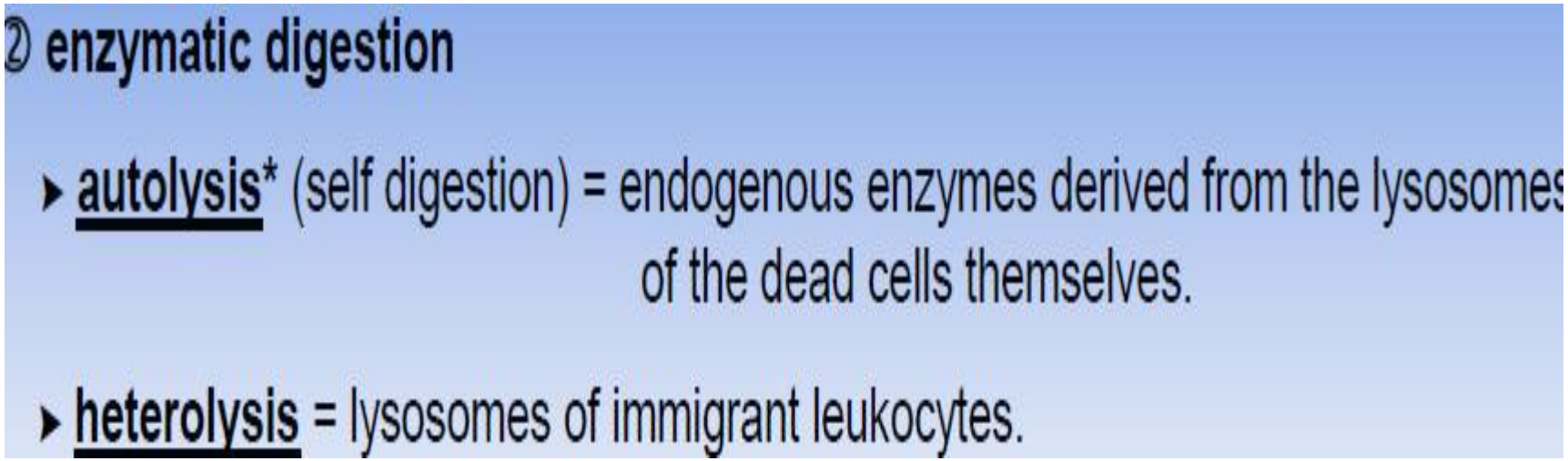
- 1) denaturation of protein
- 2)Enzymatic digestion

Denaturation of protein



Enzymatic digestion

- **Self digestion (autolysis)**
- **Heterolysis (by other cells)**



Indicators of Necrosis

- **Necrosis is recognized by:**

1) Changes in the nucleus

a) Swelling and clumping of chromatin

b) Pyknosis:condensation of chromatin and shrinkage of the nucleus

c) Kayorrhexis - fragmentation of the nucleus

d) Karyolysis - dissolution of the nucleus by the action of deoxyribonuclease

2) Changes in cytoplasmic staining

a) Positive staining with vital dyes reflecting abnormal membrane permeability

b) Opacification due to denaturation of proteins in the cytoplasm

c) Eosinophilia due to increased affinity to acidic dyes

Necrosis

Local death of tissue within the living body

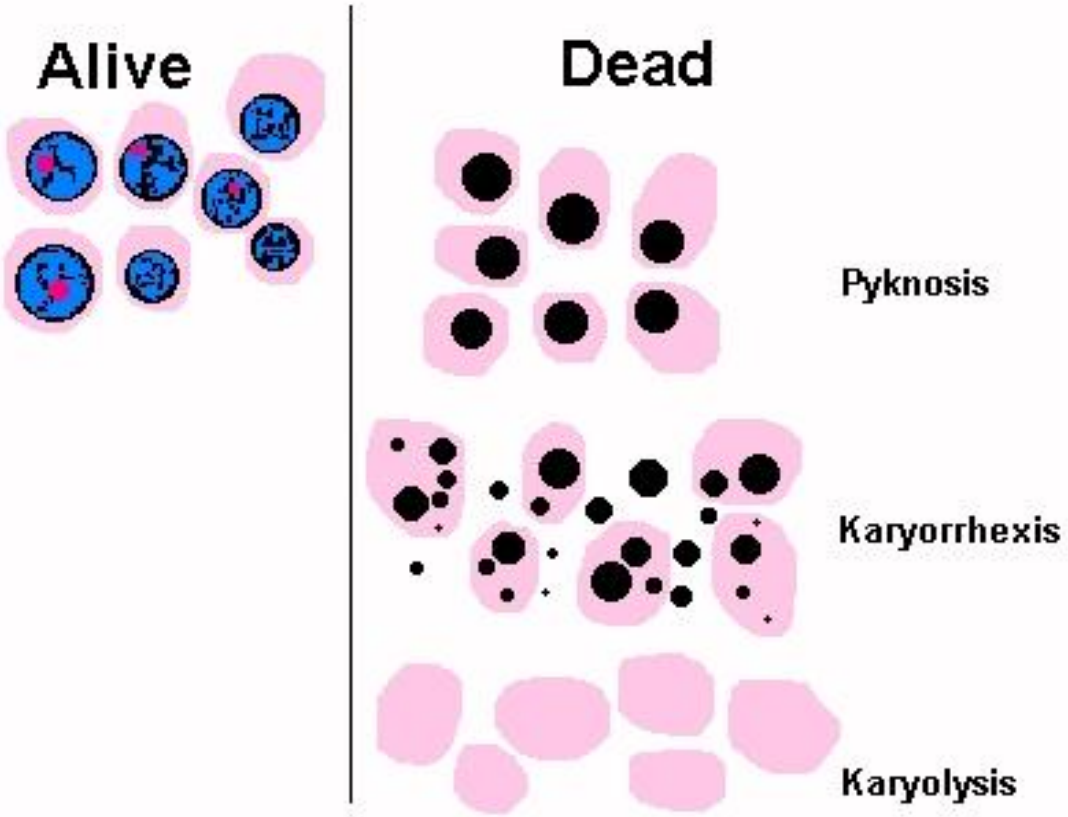
Necrotic changes of the cell

- Nuclear changes
  - Pyknosis
  - Karyorrhexis
  - Karyolysis
- Cytoplasmic changes
  - Degenerative changes ending with total disappearance of the cell

Types of tissue necrosis

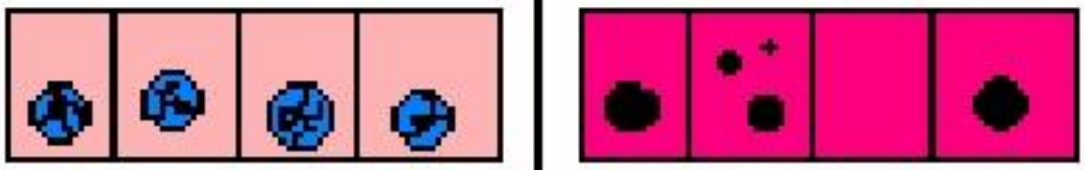
1- Coagulative
2- Caseous
3- Liquefactive
4- Fat necrosis

The nuclei tell you WHETHER cells have died.



Alive cells

Coagulative necrosis



Coagulative Necrosis

Local death of cells with the preservation of the general architecture of the tissue

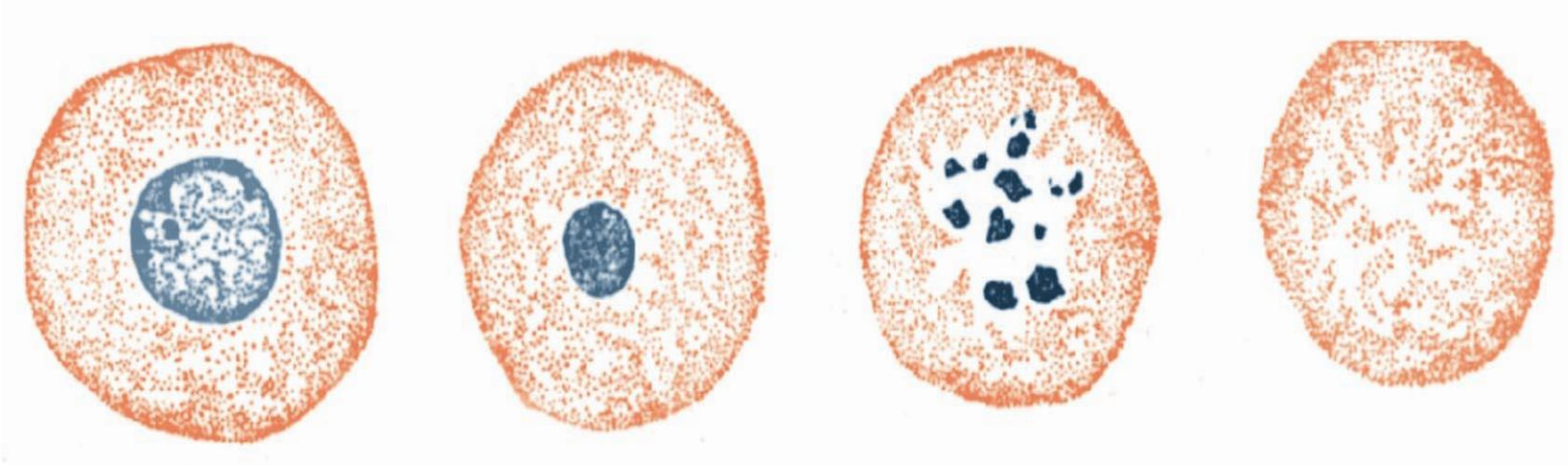
Cause:

- Local ischaemia (infarction)
- Bacterial toxins
- Locally acting poisons (mercuric chloride)
- Vit E+Selenium deficiency (white muscle disease)
- Mild burns

Occurrance:

- Diphtheretic inflammation of the intestine
- Infarction of the kidney and heart
- White muscle disease in lambs and calves

Zenker's necrosis
is coagulative necrosis of skeletal and cardiac muscles



Normal Pyknosis Karyorrhexis Karyolysis

Types:

① Coagulative necrosis:

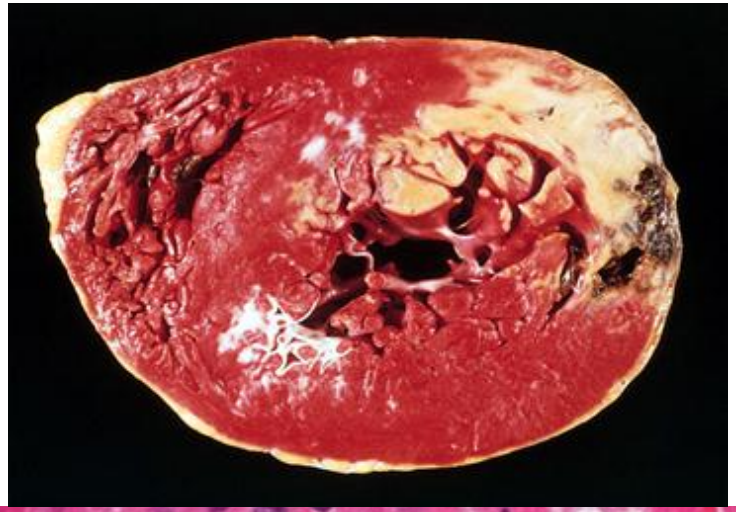
It's ch. by losing of cellular details and preservation of architecture

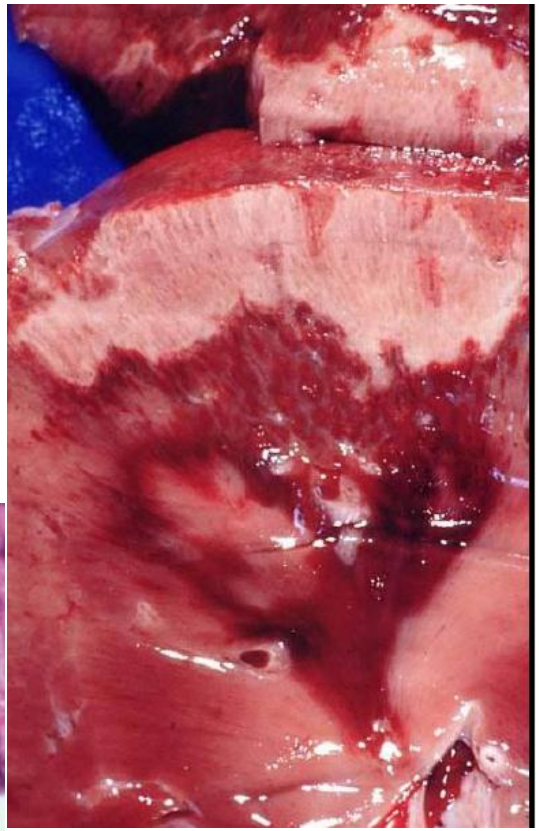
It's hypoxic or ischemic cell death in all tissues except brain (why?)

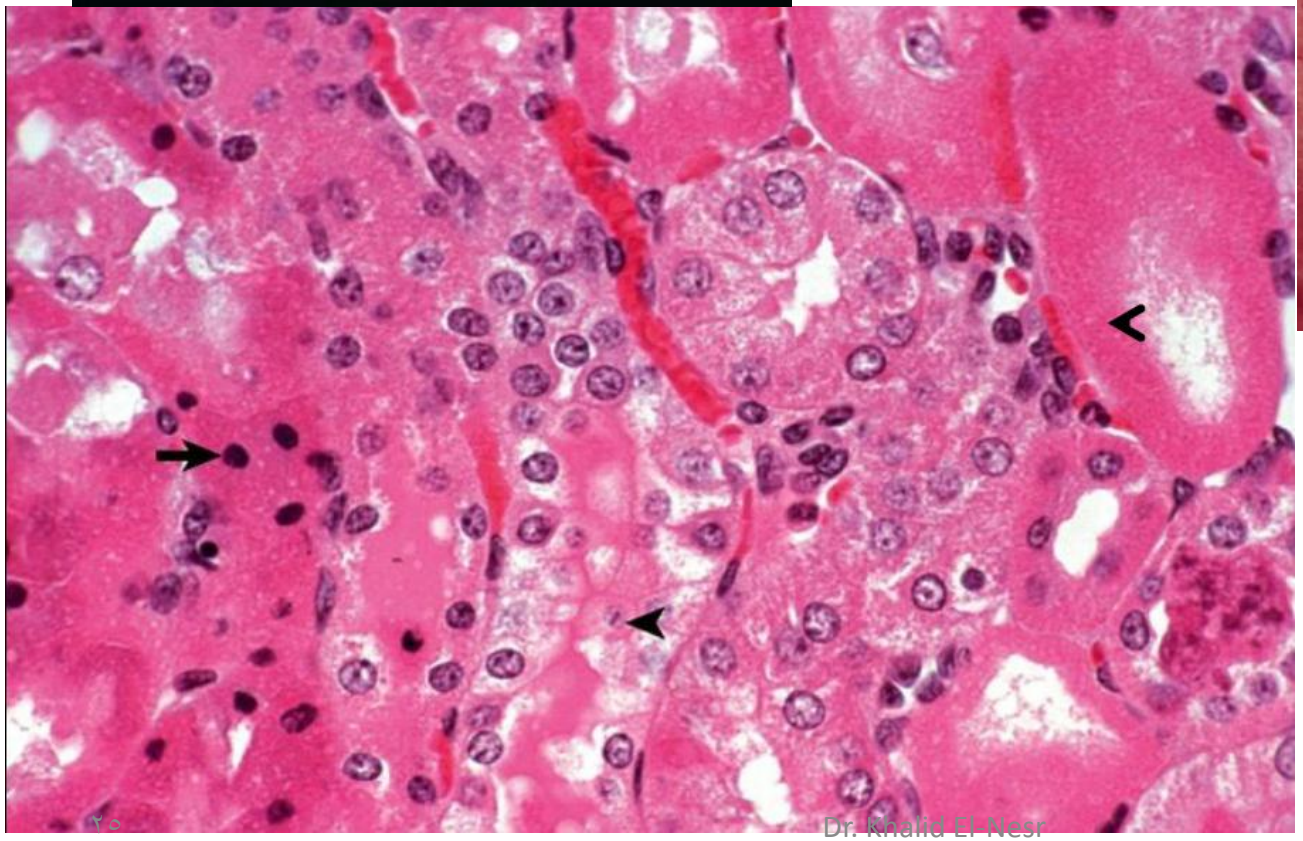
Gross features: The necrosis area is swollen, firm and pale.

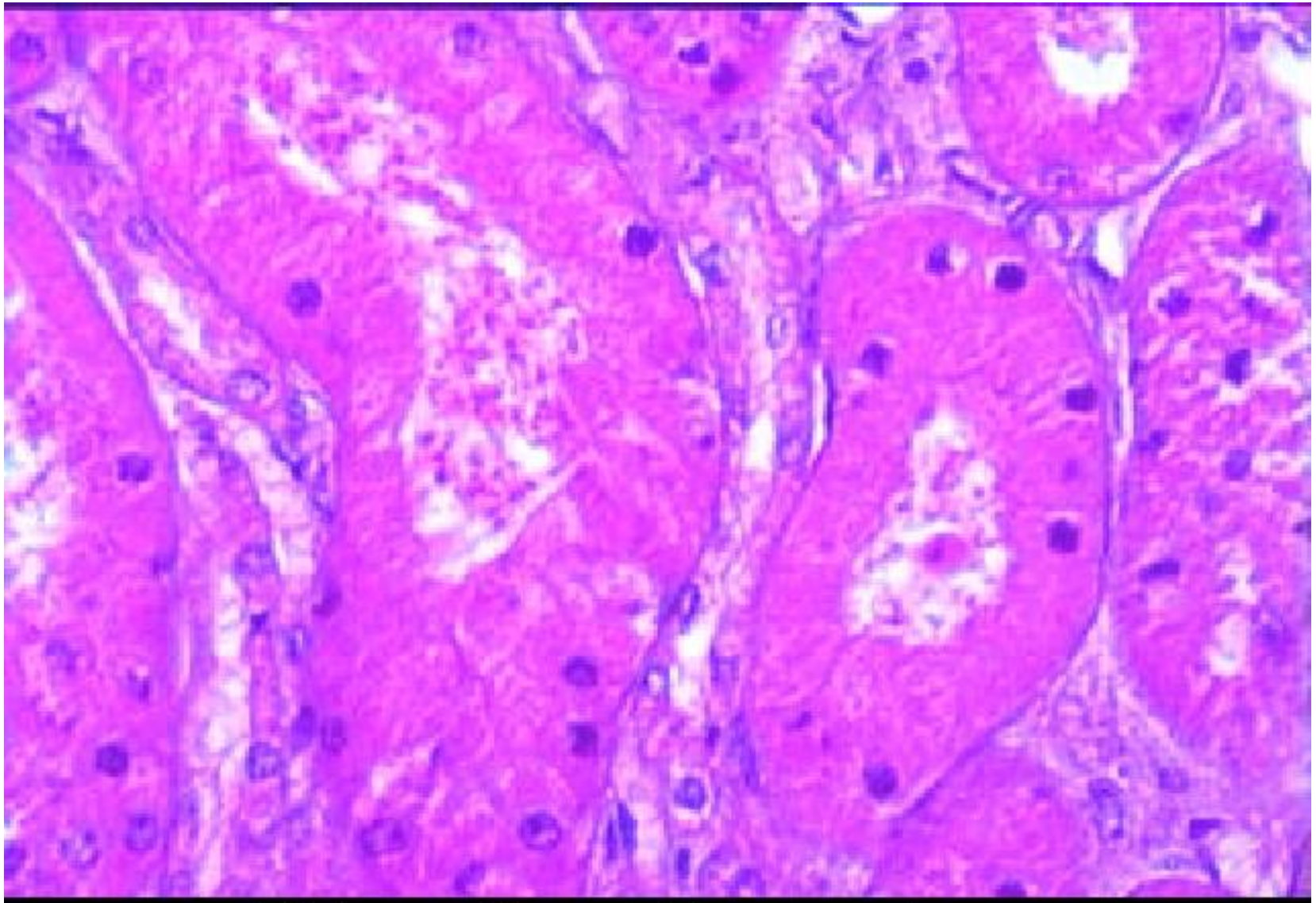
microscopic features: cell detail is lost, but architecture preserved. The dead cells retain their outline.

This type of necrosis is frequently caused by lack of blood supply as in case of infarction.





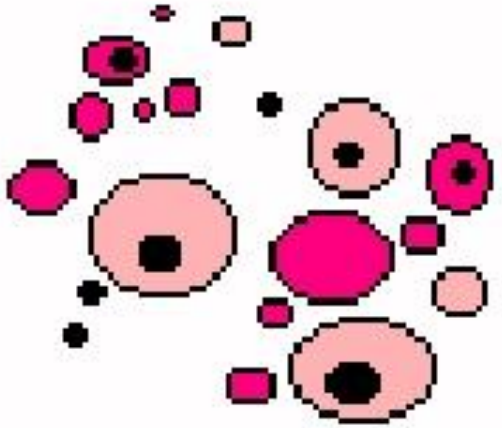




Kidney - Coagulative necrosis

Alive cells

Caseous necrosis



Caseous Necrosis

Local death of the cells and disintegeration and loss of architecture

Cause:

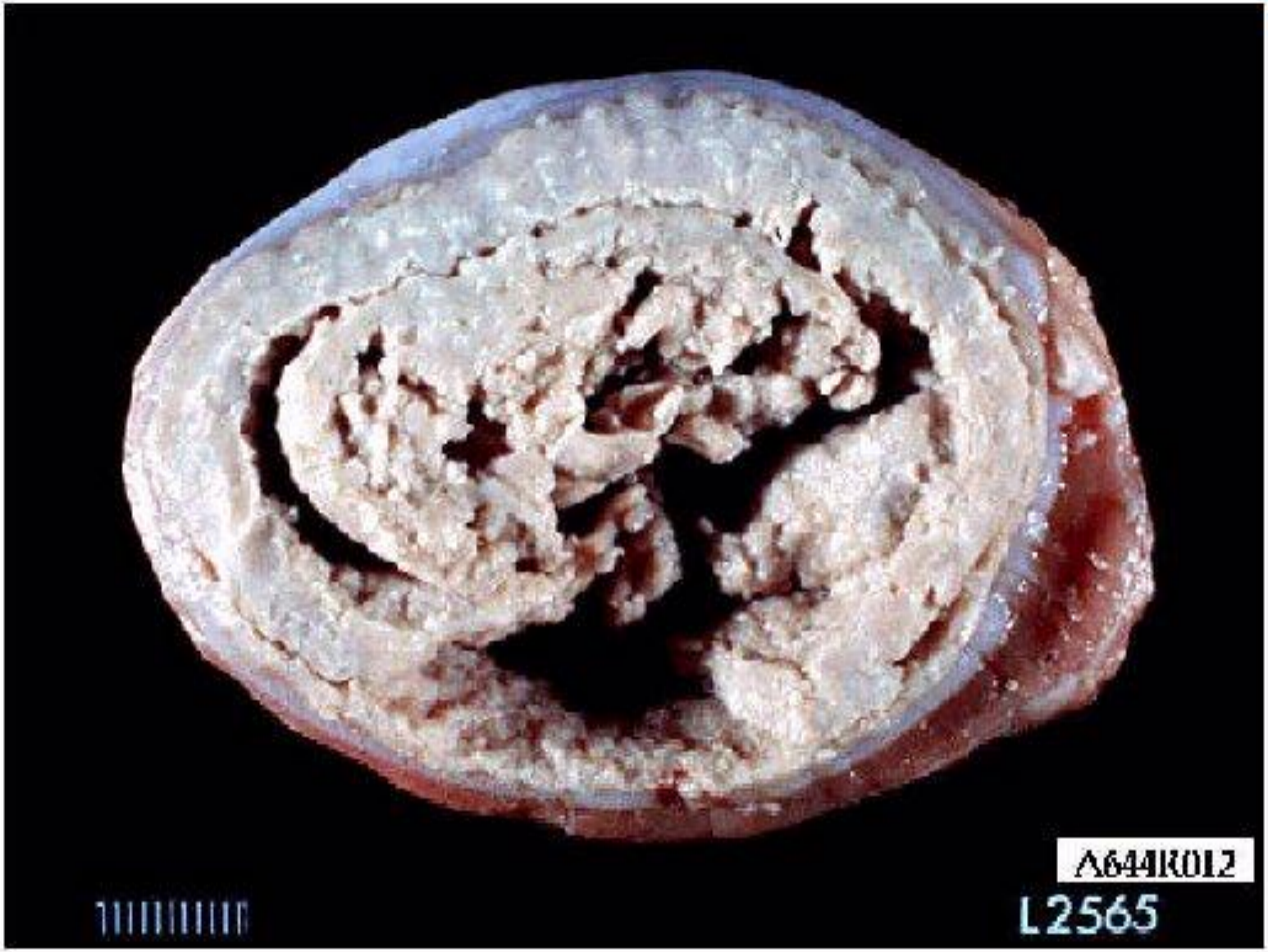
Long acting bacterial toxins (tuberculosis, corynebacterium ovis)

Occurrance:

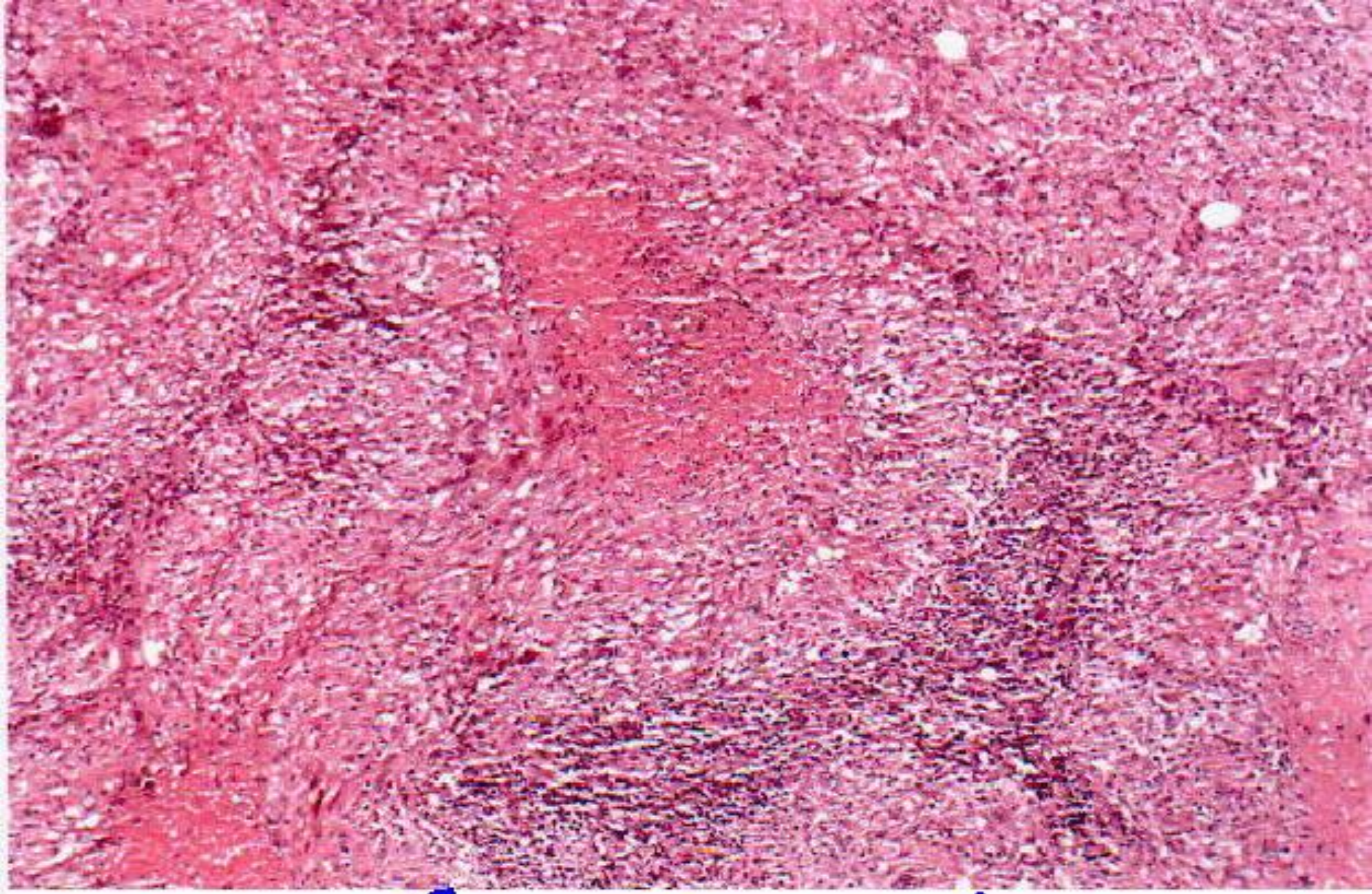
Tuberculous nodules
Lesions in caseous lymphadenitis

Characters:

- **Don’t retain cellular details (without dissolution) nor tissue architecture.**
- **Caseous = cheese like**



Lymph node
Caseous necrosis



Caseous necrosis

Fragmentation and disintegration of cells and loss of architecture

Liquefactive necrosis:

Soft and liquid grossly. Enzymes digest the cell and convert it to a formless proteinaceous mass. Ultimately, discharge of the contents forms a cystic space. i. e. central nervous system after ischemic injury; abscesses.

Liqefactive Necrosis

Local death and liquefaction of tissue

Cause

- Hypoxia
- Nutritional deficiency (vitamin E deficiency)
- Aflatoxins

Pyogenic infection (lysozymes from neutrophils)

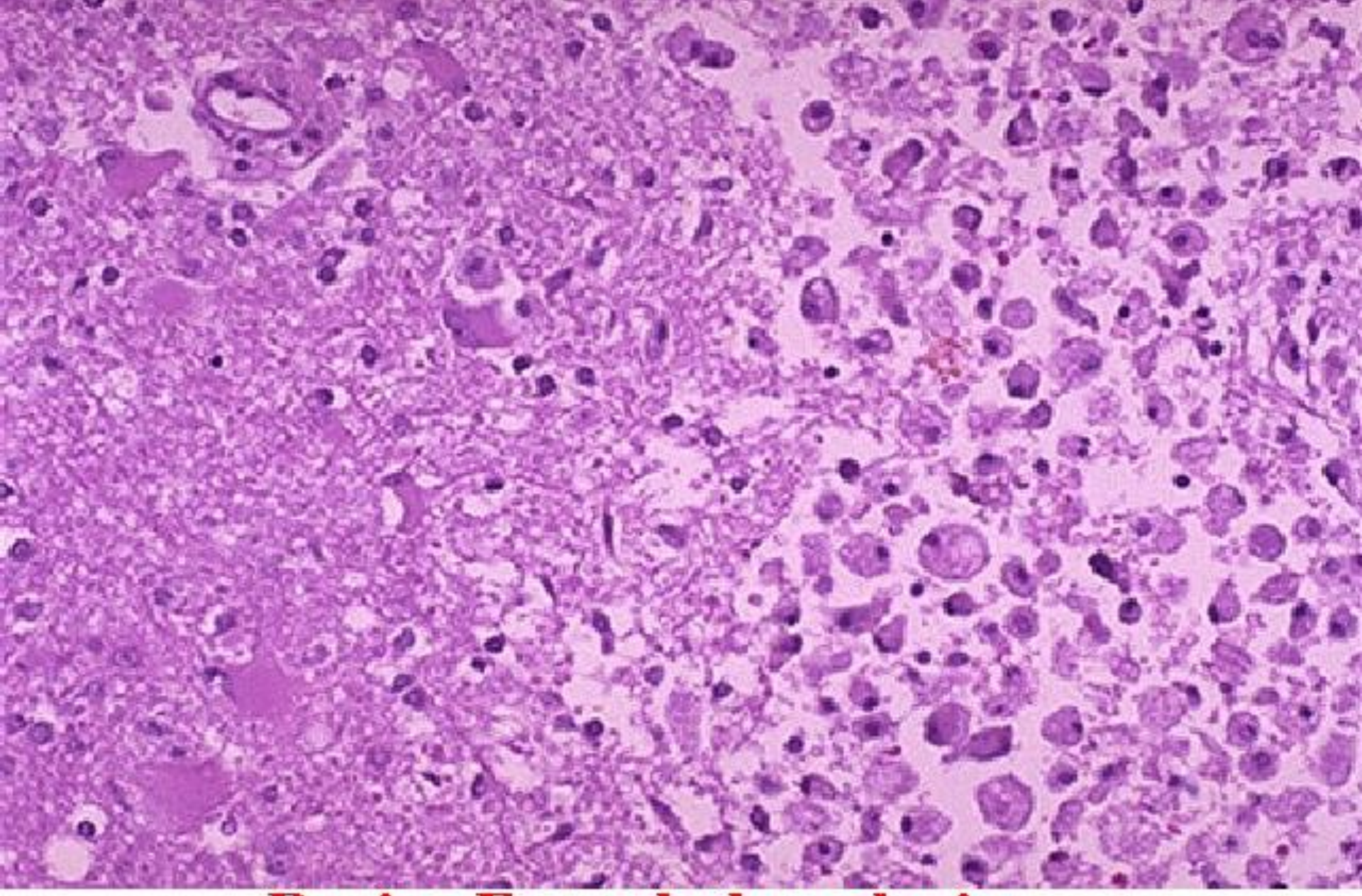
- Cyanides

Occurrance

Brain and spinal cord (low amount of coagulable protein)

Abscesses

Tuberculous nodules



Brain: Encephalomalacia

Many macrophages (foam cells) at the right

Fat necrosis:

Grossly:

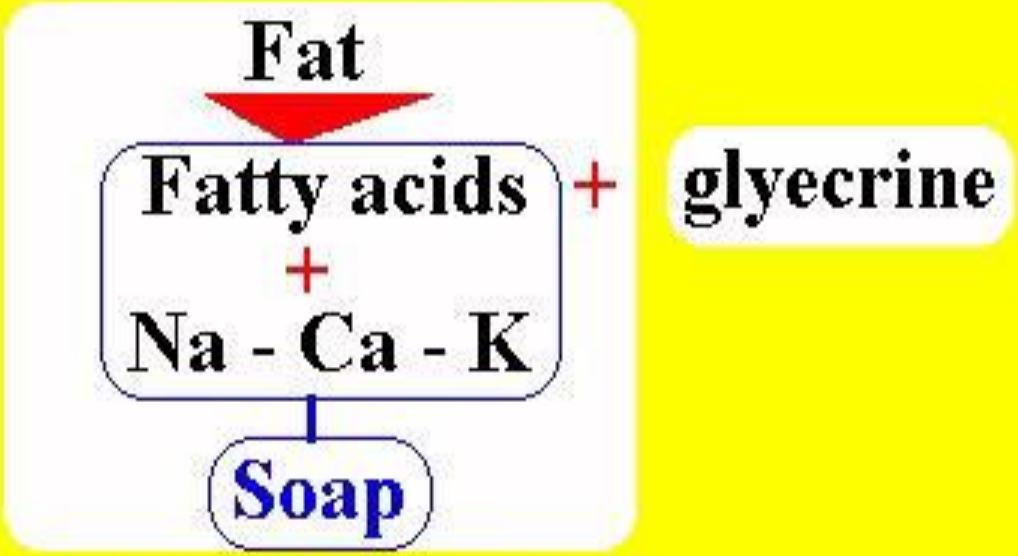
Opaque and chalky

histopathology:

outline of necrotic fat cells filled with amorphous basophilic material (calcium soaps). i. e. Digestion of peritoneal fat by pancreatic enzymes in pancreatic inflammation.

Fat Necrosis

Necrosis of adipose tissue and decomposition of fat



Cause and occurrance

Pancreatitis (abdominal fat due to effect of lipase)

Trauma (subcutaneous and perivaginal fat)

Starvation (incompletely utelized fat)

Fat necrosis:

Grossly:

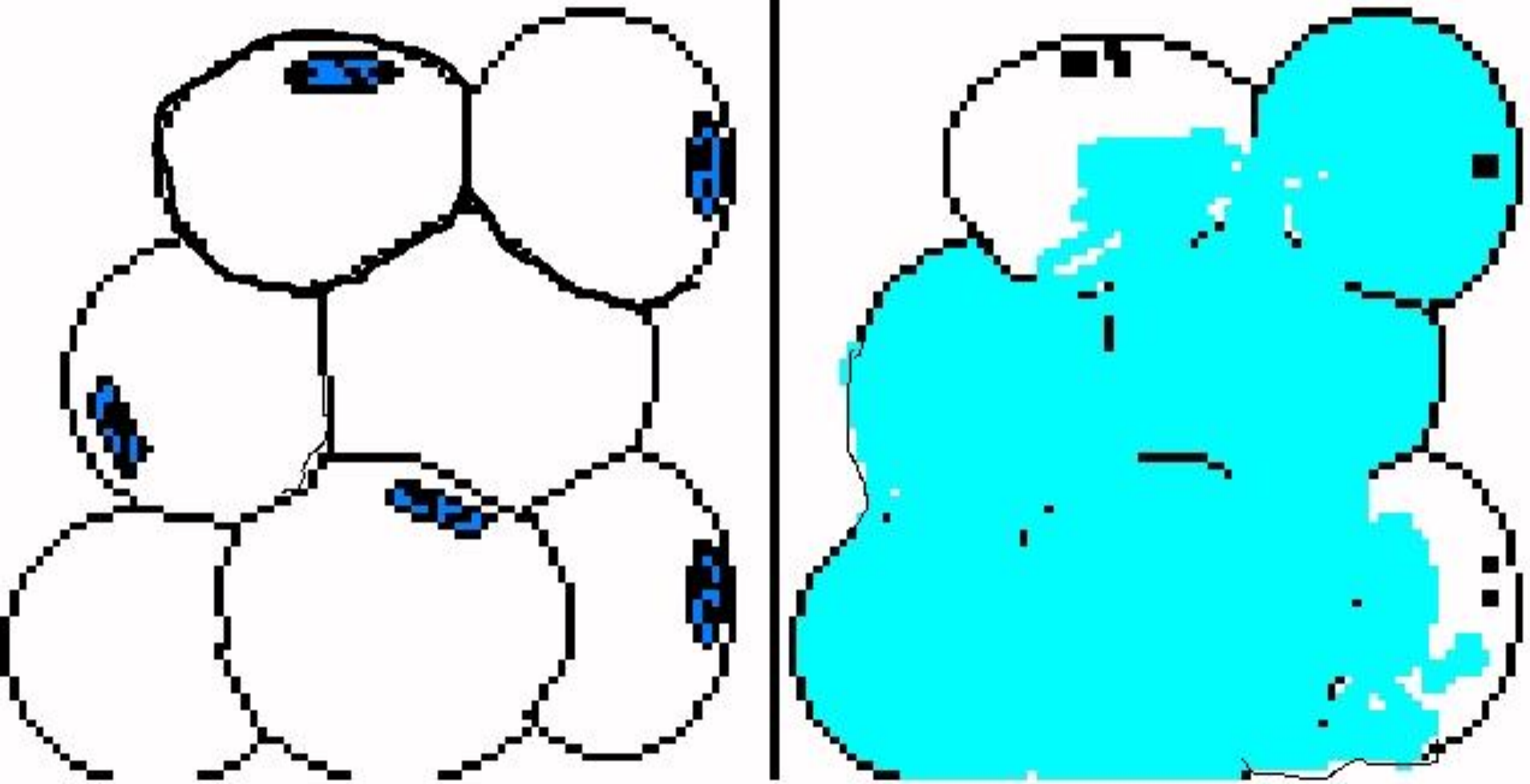
Opaque and chalky

histopathology:

outline of necrotic fat cells filled with amorphous basophilic material (calcium soaps). i. e. Digestion of peritoneal fat by pancreatic enzymes in pancreatic inflammation.

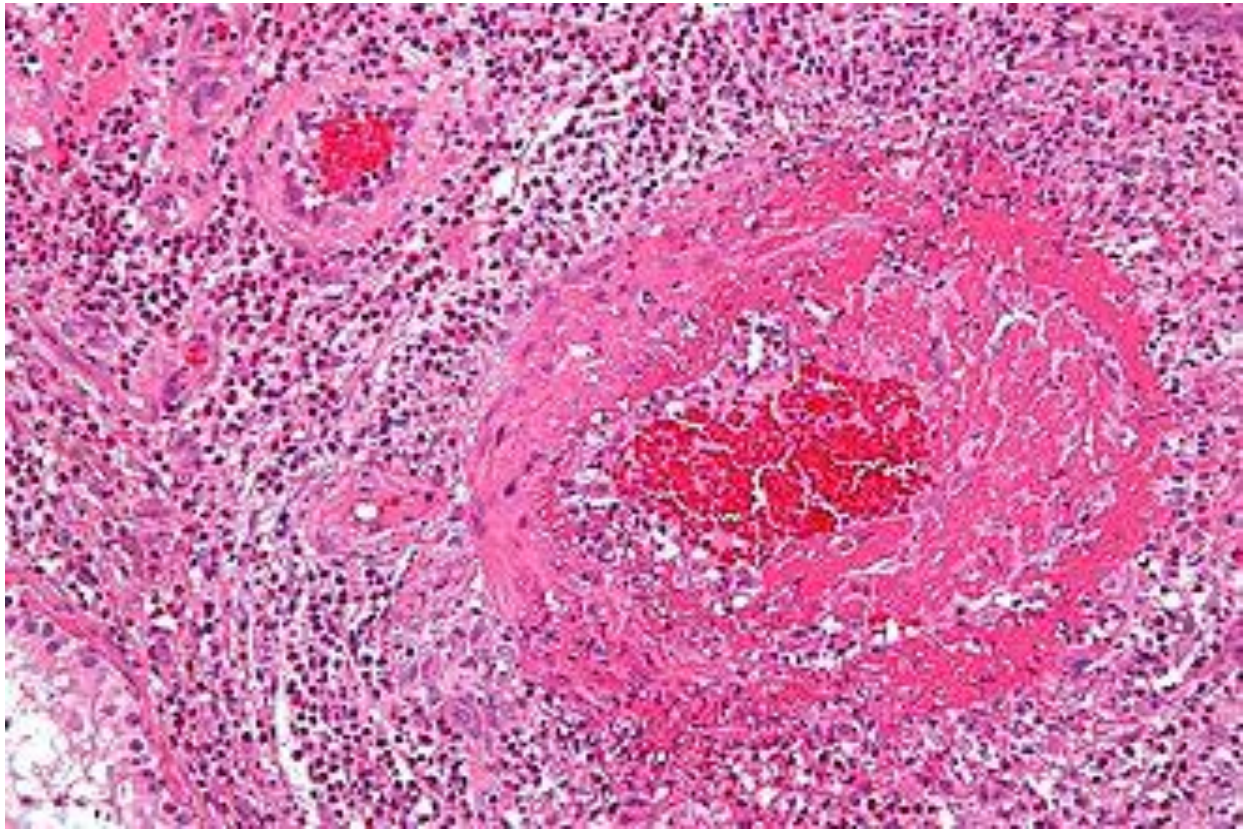
Healthy fat

Fat necrosis



Fibrinoid necrosis

- **Definition:** This is not a true degeneration but a strongly eosinophilic stain like fibrin.
- **Location:** interstitial collagen and blood vessels (small artery and arteriole)
- **Nature:** one kind of necrosis.
- **e. g. in allergic reactive diseases:** active rheumatism, polyarteritis nodose.
- **in non-allergic reactive diseases**: malignant hypertension.



Consequences of necrosis

①Acute or chronic inflammation

② shock or gangrene .

③ lysis and absorption

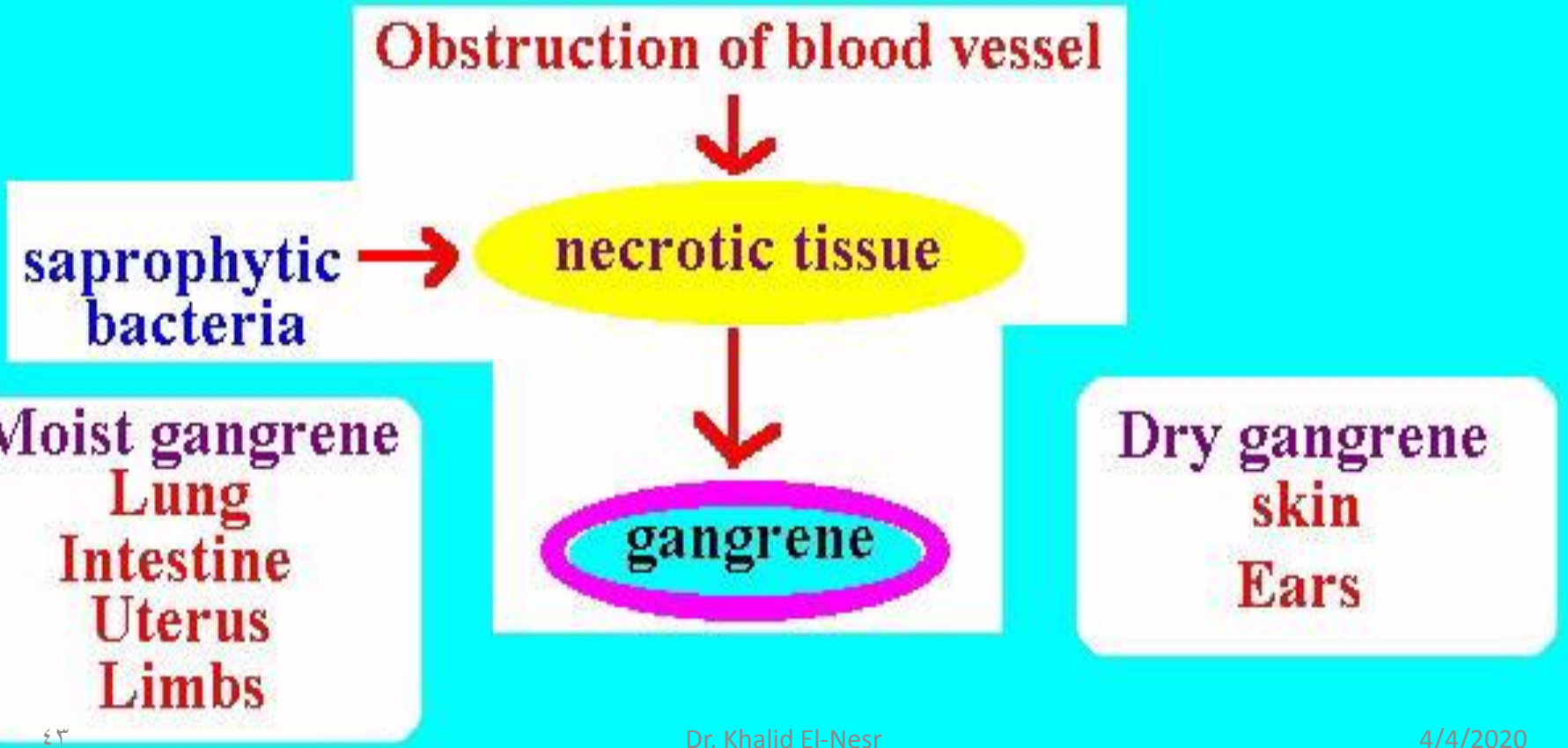
④ **dissolution and discharge: ulceration and cavity formation**

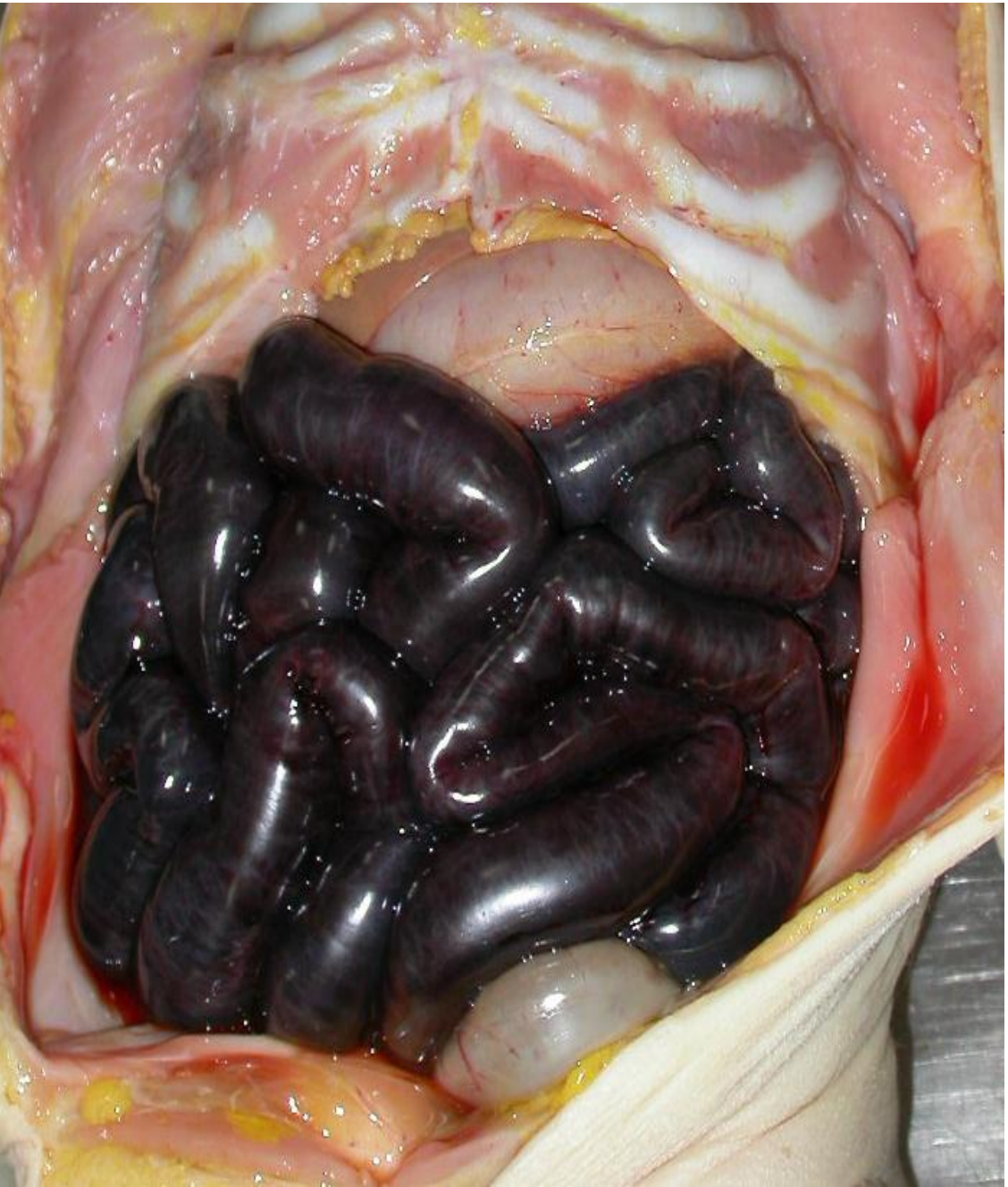
⑤ **Organization**

⑥ **Encapsulation, calcification.**

Gangrene

Putrefaction of necrotic tissue due to invasion with saprophytic bacteria
(clostridia - anaerobic streptococci) :





Moist gangrene

Apoptosis

Cell death controlled by genetic factors (physiologically programmed cell death)

Microscopical Picture

It is a physiological process characterized by

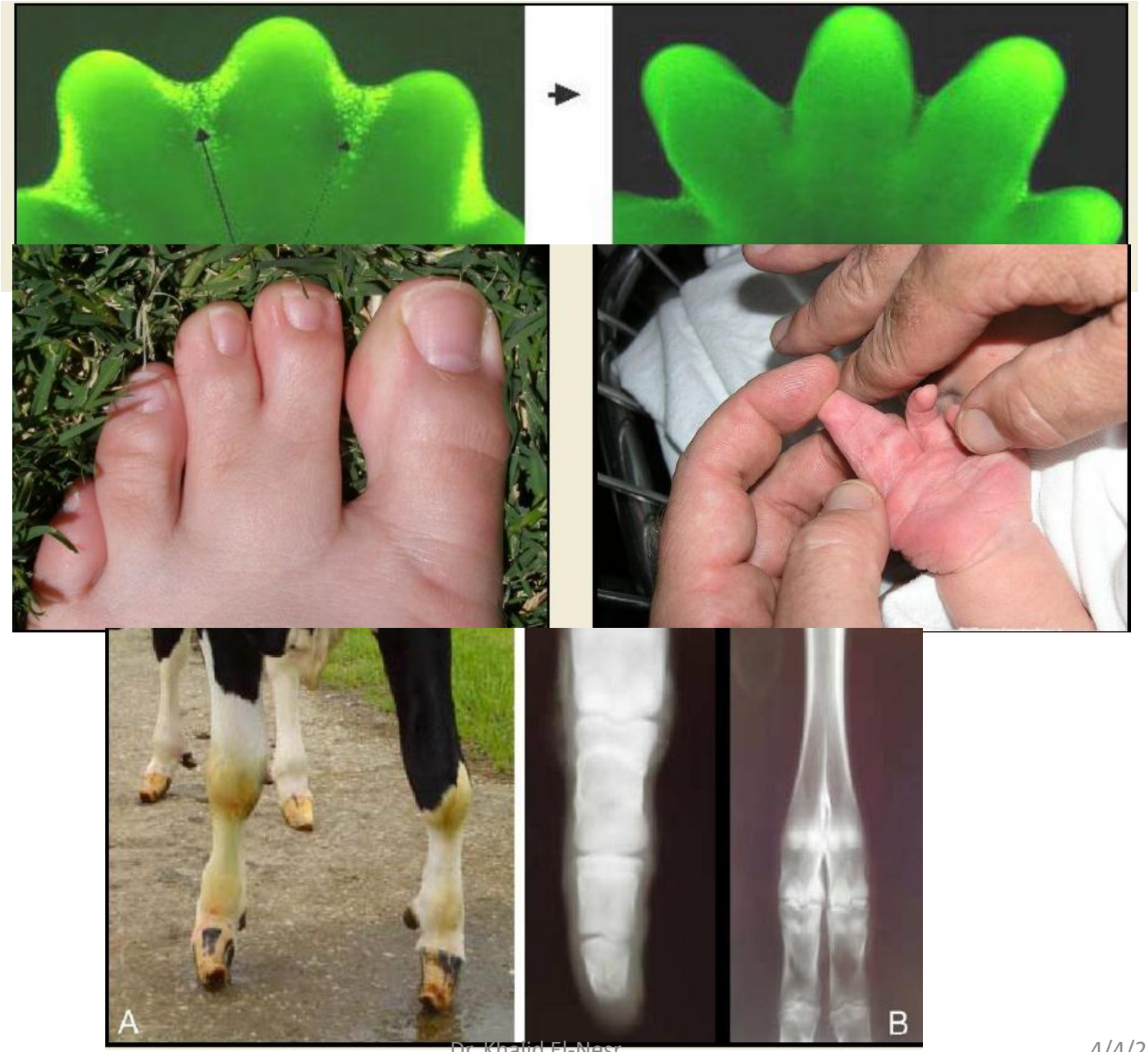
- Death of scattered single cells
- Absence of inflammatory reaction
- Chromatin condensation - rounding of nucleus and shrinkage of cell
- Dead cells are eventually phagoctosed by surrounded normal cells

genes involved in apoptosis

c-myc p53 bel-2

Definition:

- **The term apoptosis was first used by Kerr *et al. (1972) and it was used as shrinkage necrosis***
- **Apoptosis (from a Greek word meaning the dropping of leaves from a tree) is a term referring to the cytologically observable changes associated with a process of cellular self-destruction observed in all eukaryotes**

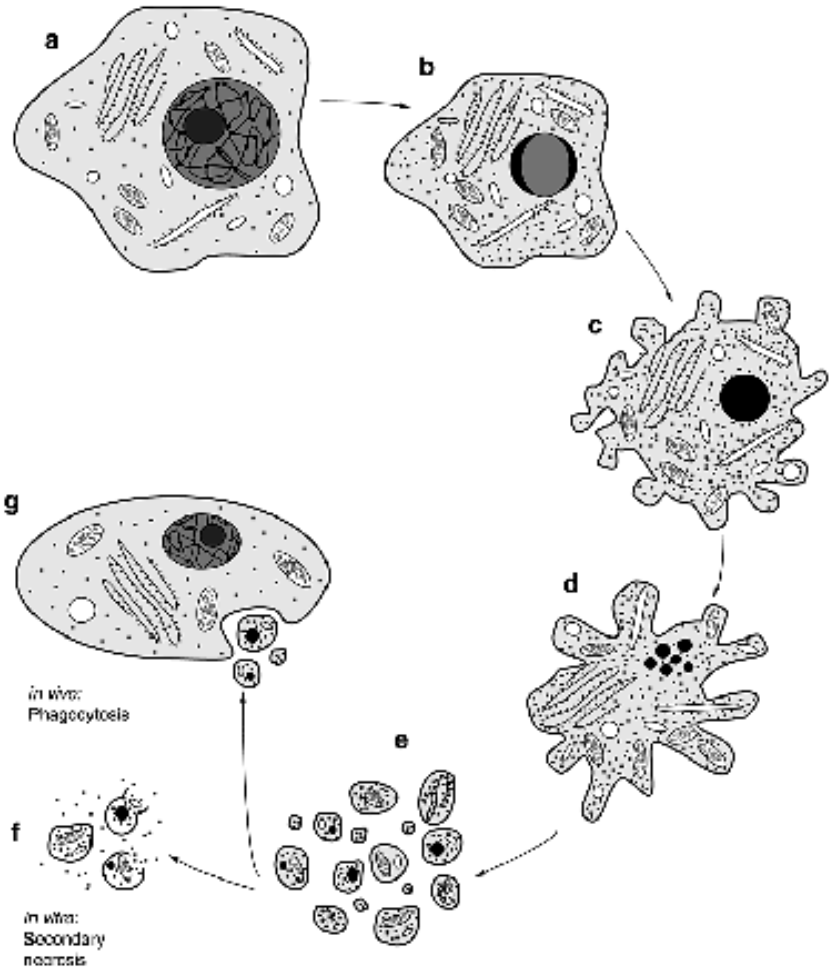

A
B

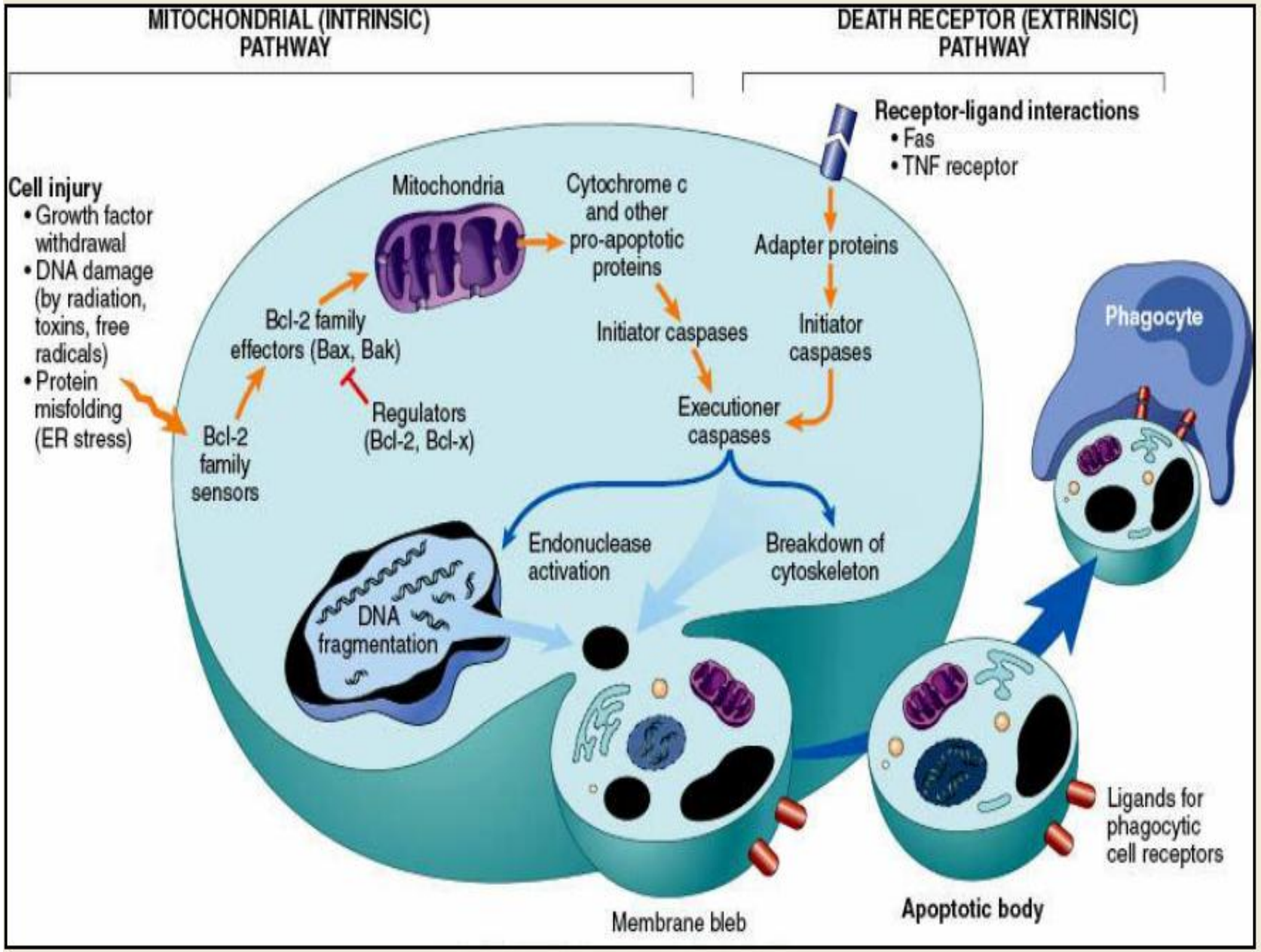
Causes

- During embryogenesis
- Cells undergoing normal turnover (uterine involution -skin)
- Immune system(cell death by cytotoxic cells)
- Neoplasms
- Pathologically (some viruses – radiation – drug damaging DNA)

Morphology of Apoptosis

Morphological changes that occur during apoptosis.
First, (a) the normal cell
(b) shrinks and the condensed chromatin collapses into crescents around the nuclear envelope
(c) the membrane begins to bulge and bleb
(d) the blebing increases and the cell finally breaks into a number of apoptotic bodies
(e) which lyse in vitro
(f) and are phagocytosed in vivo.




MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Cytochrome c and other pro-apoptotic proteins
Adapter proteins
Bcl-2 family effectors (Bax, Bak)
Initiator caspases
Initiator caspases
Phagocyte
Regulators (Bcl-2, Bcl-x)
Bcl-2 family sensors
Executioner caspases
Endonuclease activation
Breakdown of cytoskeleton
DNA fragmentation
Ligands for phagocytic cell receptors
Membrane bleb
Apoptotic body

APOPTOSIS .INFO

Morphology

- considerable apoptosis may occur in tissues before it is evident on histology

❶ **Cell shrinkage**
- cytoplasm has packed organelles

❷ **Chromatin condensation**
- dense aggregates of chromatin fragmentation

❸ **Formation of cytoplasmic blebs then apoptotic bodies**
± nuclear fragments

❹ **Phagocytosis of apoptotic cells / bodies**
- usually by macrophages with no inflammation

Microscopical appearance:

1- Death of scattered single cells

2- Dead cells form rounded, membrane bounded bodies which are eventually phagocytosed by adjacent normal cells

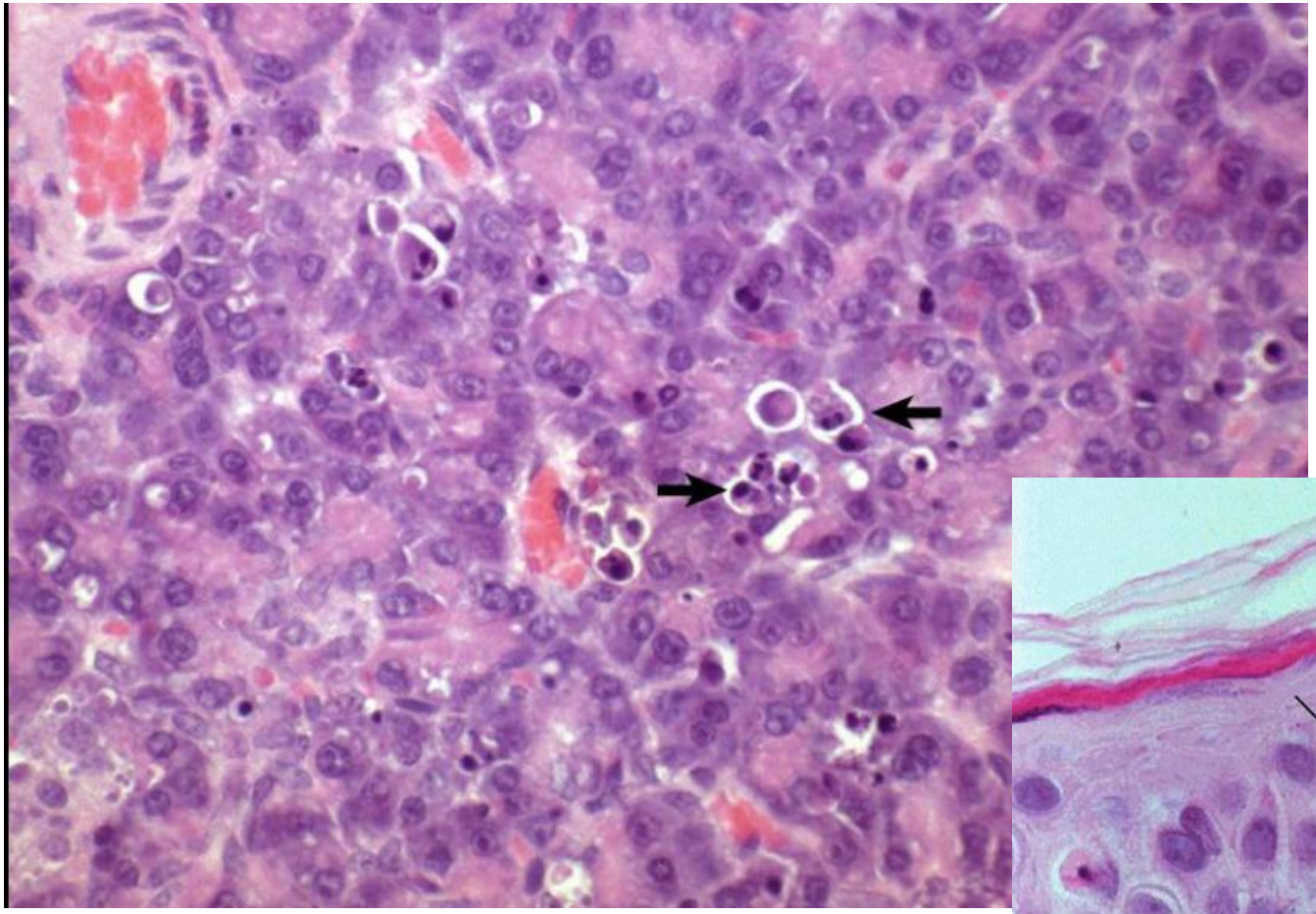
3- There is chromatin condensation and margination

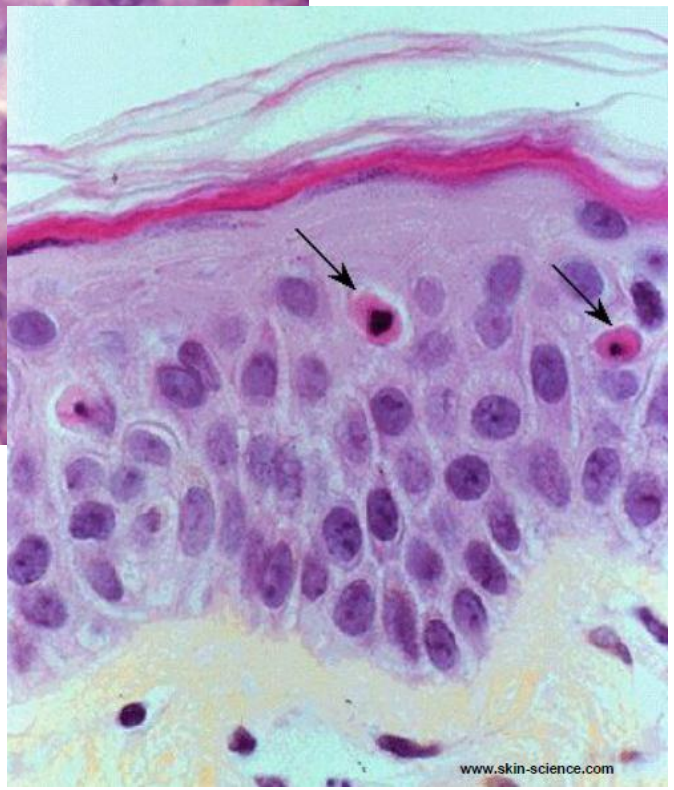
4- Rounding of the nucleus

5- Shrinkage and reduction of the cell volume

6- Abnormal mitosis

7- Absence of inflammatory response in the adjacent area.



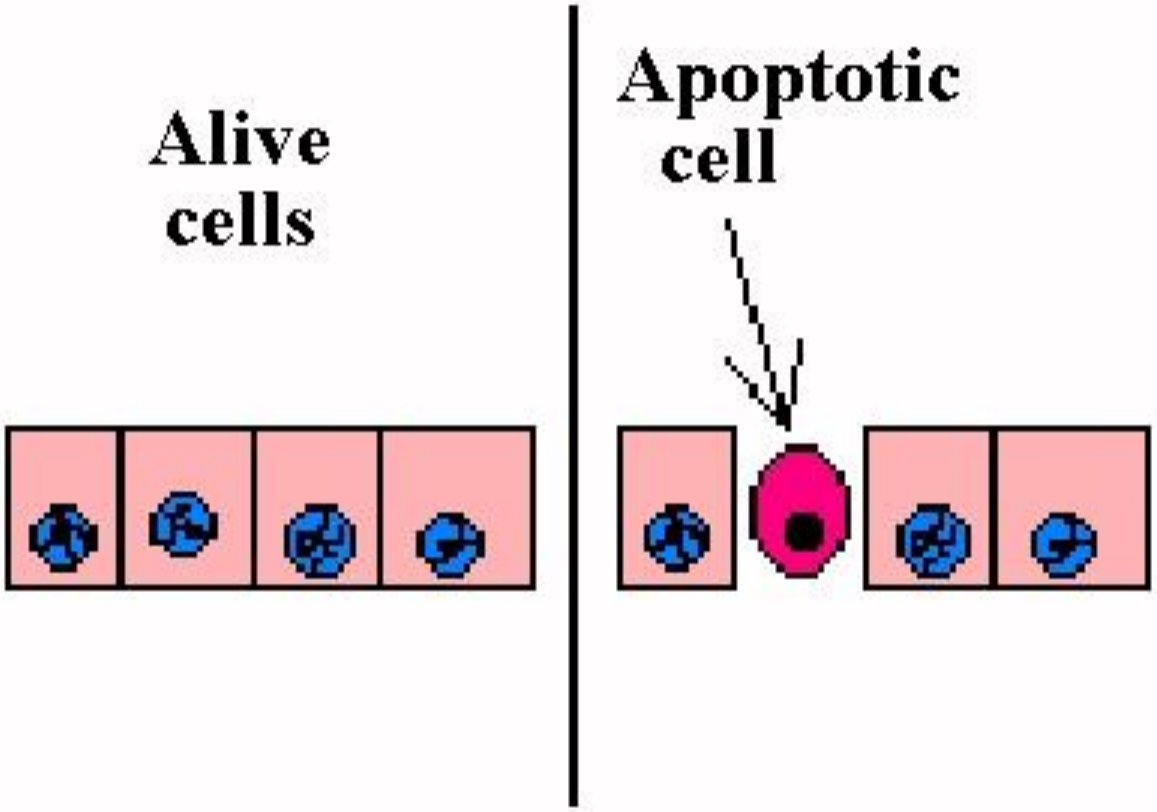

www.skin-science.com

Apoptosis in embryological development:

There are 3 type of apoptosis occurring in embryos;

a- Morphogenetic apoptosis: which is involved in alteration of tissue form, e.g., death of interdigital cells for separation of the fingers , *During embryonic development, apoptosis is involved in elimination of transitory organs and tissues, and tissue remodeling*

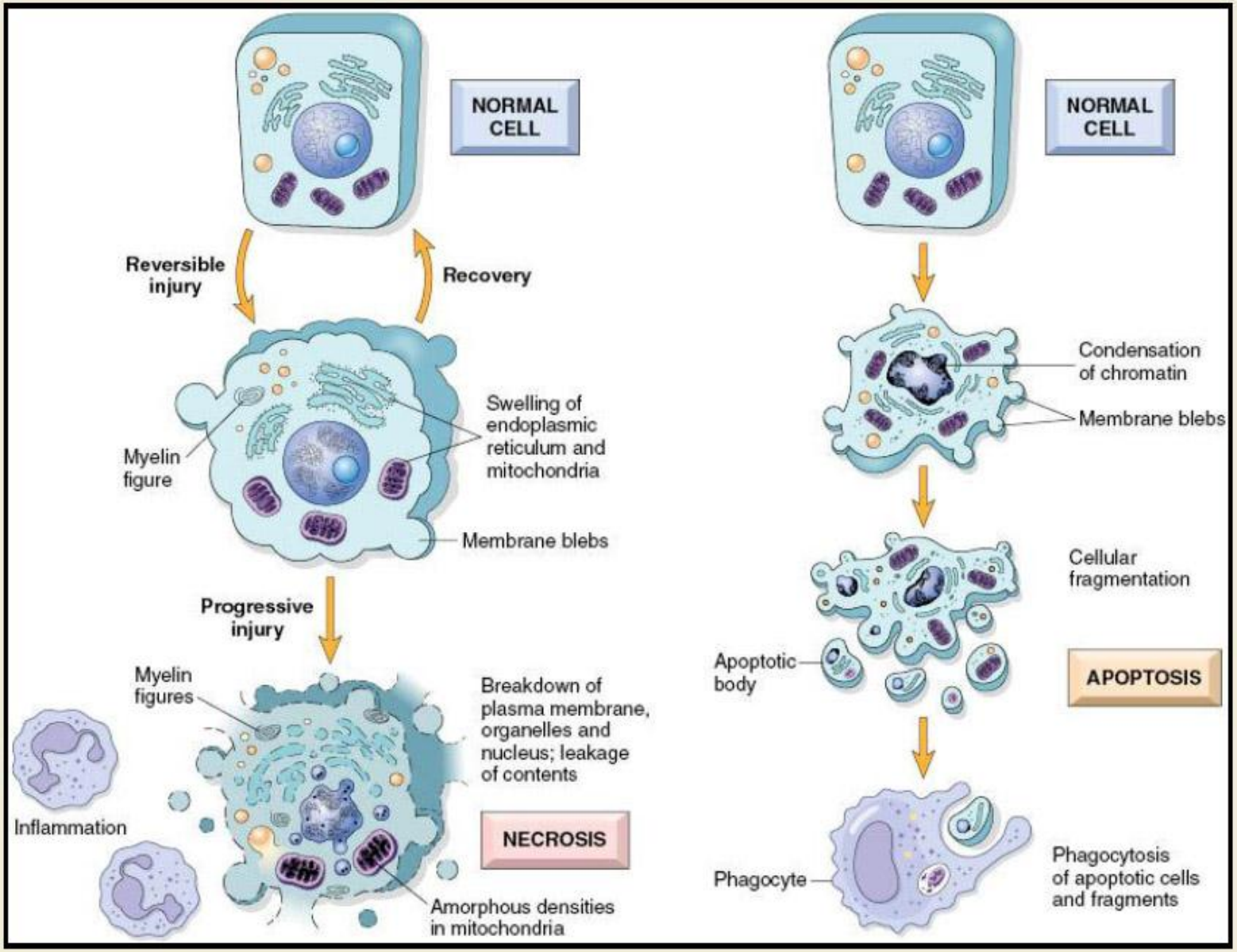
b- Histogenic apoptosis: occurs in differentiation of tissue and organs as seen in hormonally-controlled differentiation of the accessory sex organs from Mullerian and Wollfian ducts.

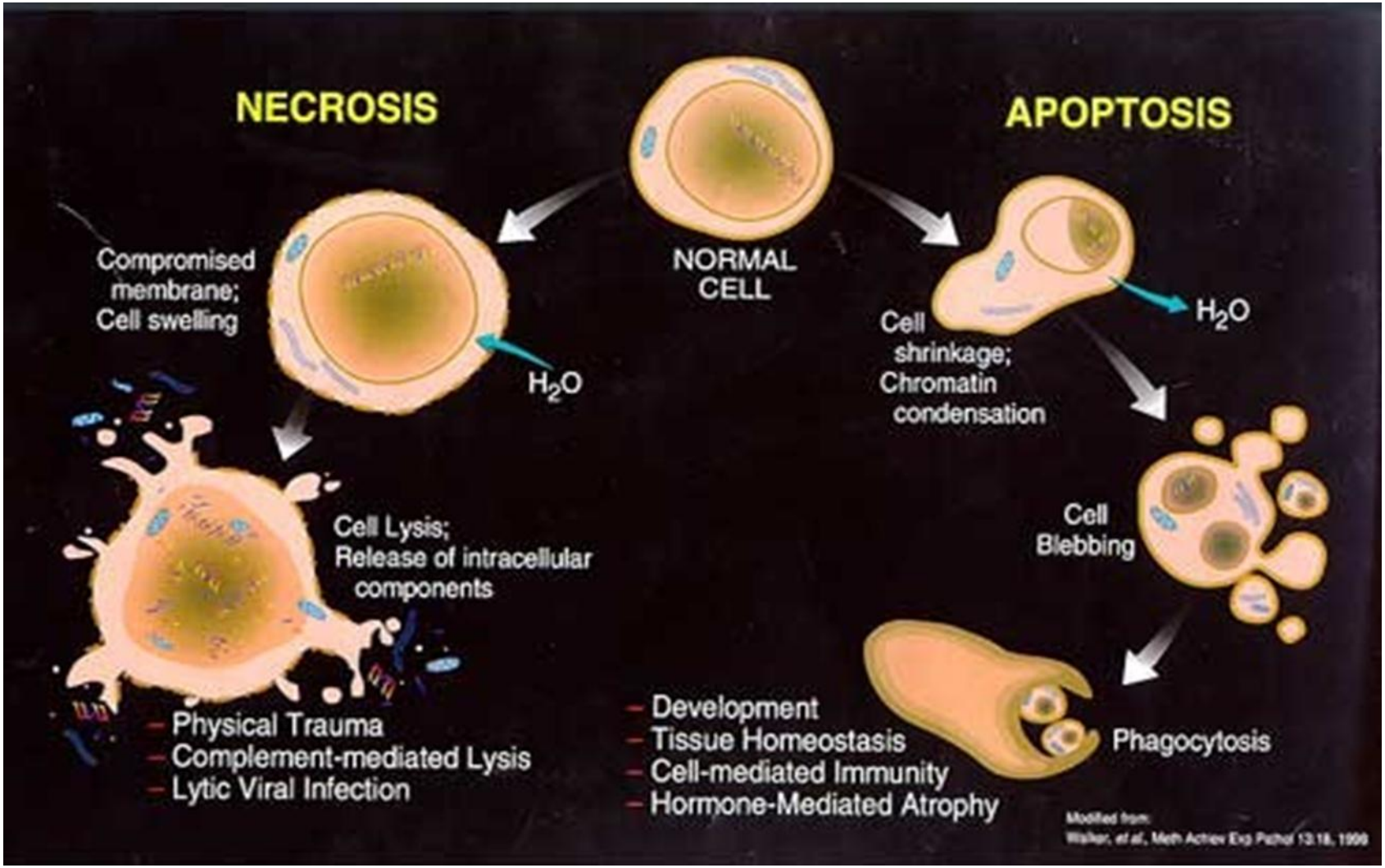

Alive cells
Apoptotic cell

Compare ?

Necrosis	apoptosis

items	Necrosis	apoptosis
Cell size	Swelling	shrinkage
Nucleus	Pyknosis - karyorrhexis - karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact - (blebbing)
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
inflammation	Frequently occured	No
Physiologic or pathologic role	pathologic	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage


NORMAL CELL
Reversible injury
Recovery
Swelling of endoplasmic reticulum and mitochondria
Myelin figure
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments


NECROSIS
APOPTOSIS
NORMAL CELL
Compromised membrane; Cell swelling
H_2O
Cell shrinkage; Chromatin condensation
H_2O
Cell Lysis; Release of intracellular components
Cell Blebbing
– Physical Trauma
– Complement-mediated Lysis
– Lytic Viral Infection
– Development
– Tissue Homeostasis
– Cell-mediated Immunity
– Hormone-Mediated Atrophy
Phagocytosis
Modified from:

شكرا لكم