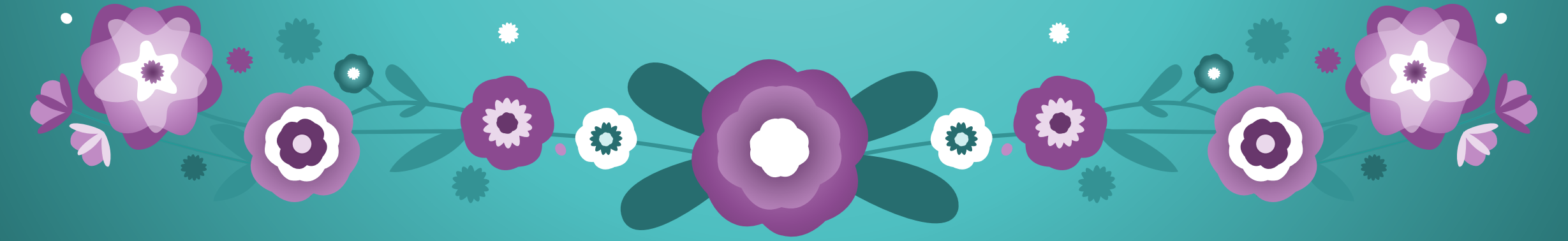
Cell Adaptation, Cell Injury and Cell Death

pathology

LEC 3

Dr. Methaq Mueen



4- Gangrenous Necrosis:

- This is a type of coagulative necrosis that occurs due to ischemia (e.g. in bowel, limb etc.).
- There is necrosis of tissue with superadded putrefaction.
- **Gangrene= Necrosis + infection + putrefaction**

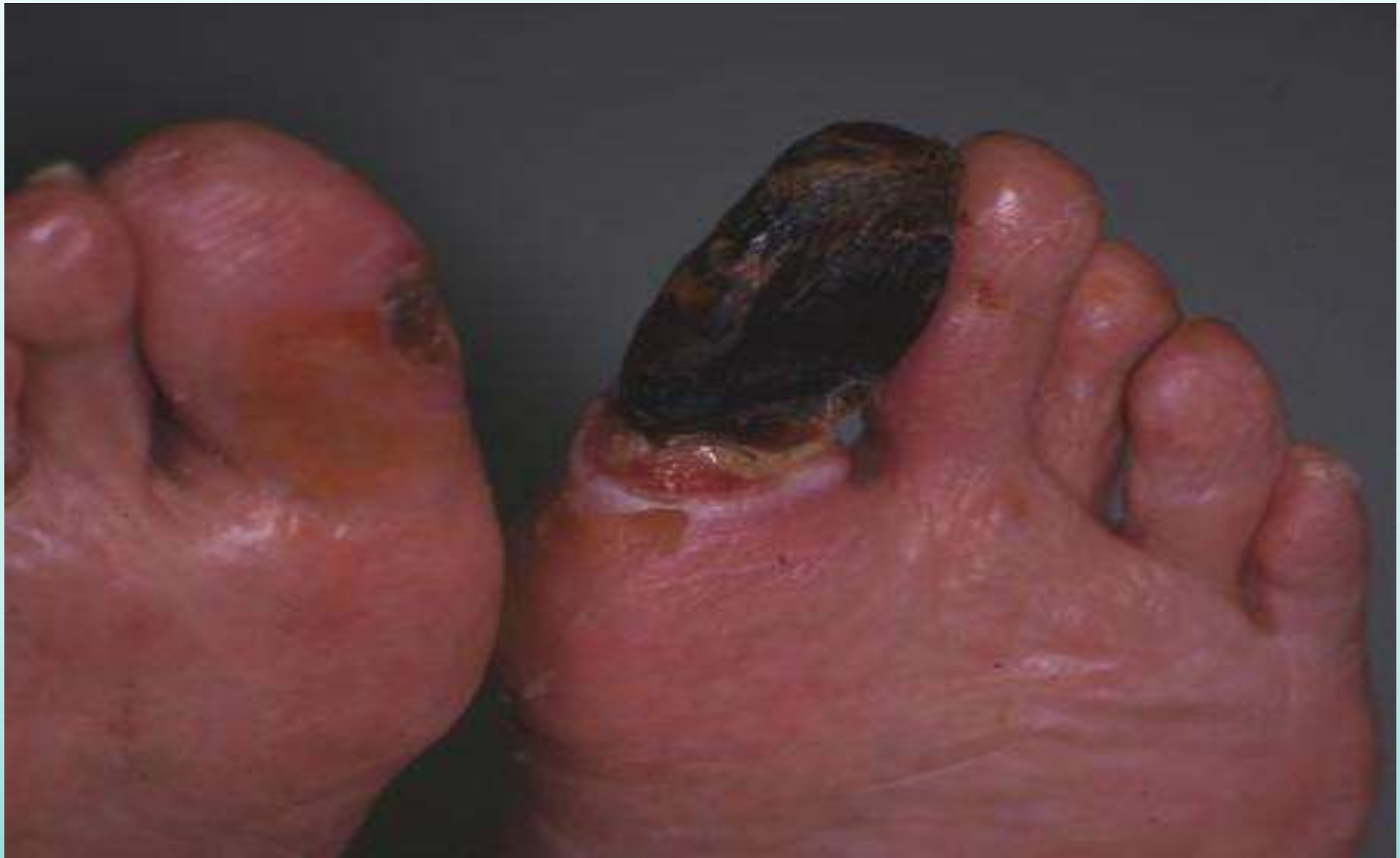
(Due to enzymatic decomposition).

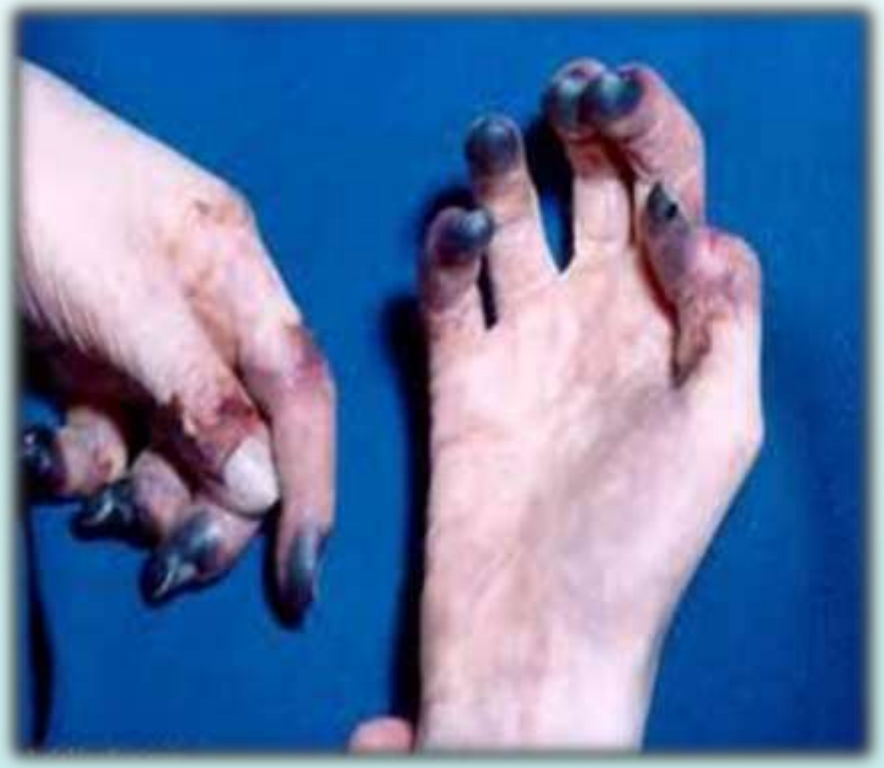
- Gangrene is classified into 3 types -
  1. Dry gangrene
  2. Wet gangrene
  3. Gas gangrene

A. Dry Gangrene

- occurs in the **distal part** of the limb due to **ischemia**,
- Typical examples of a dry gangrene are on the toes and feet of an old patient due to atherosclerosis.
- Usually initiated at the toe region which is farthest from the blood region, This gangrene **slowly grows upwards** and reaches a point where the blood supply is adequate enough to keep the whole tissue viable.
- The affected part is **dry**, shrunken and dark black, resembling mummified flesh.
- The dark coloration is due to liberation of hemoglobin from hemolyzed red blood cells which is converted by hydrogen sulfide (H_2S) produced by the bacteria, resulting in formation of **black iron sulfide** that remains in the tissues.
- A "Line of separation" is well formed between the gangrenous part and the viable part.

“DRY” GANGRENE

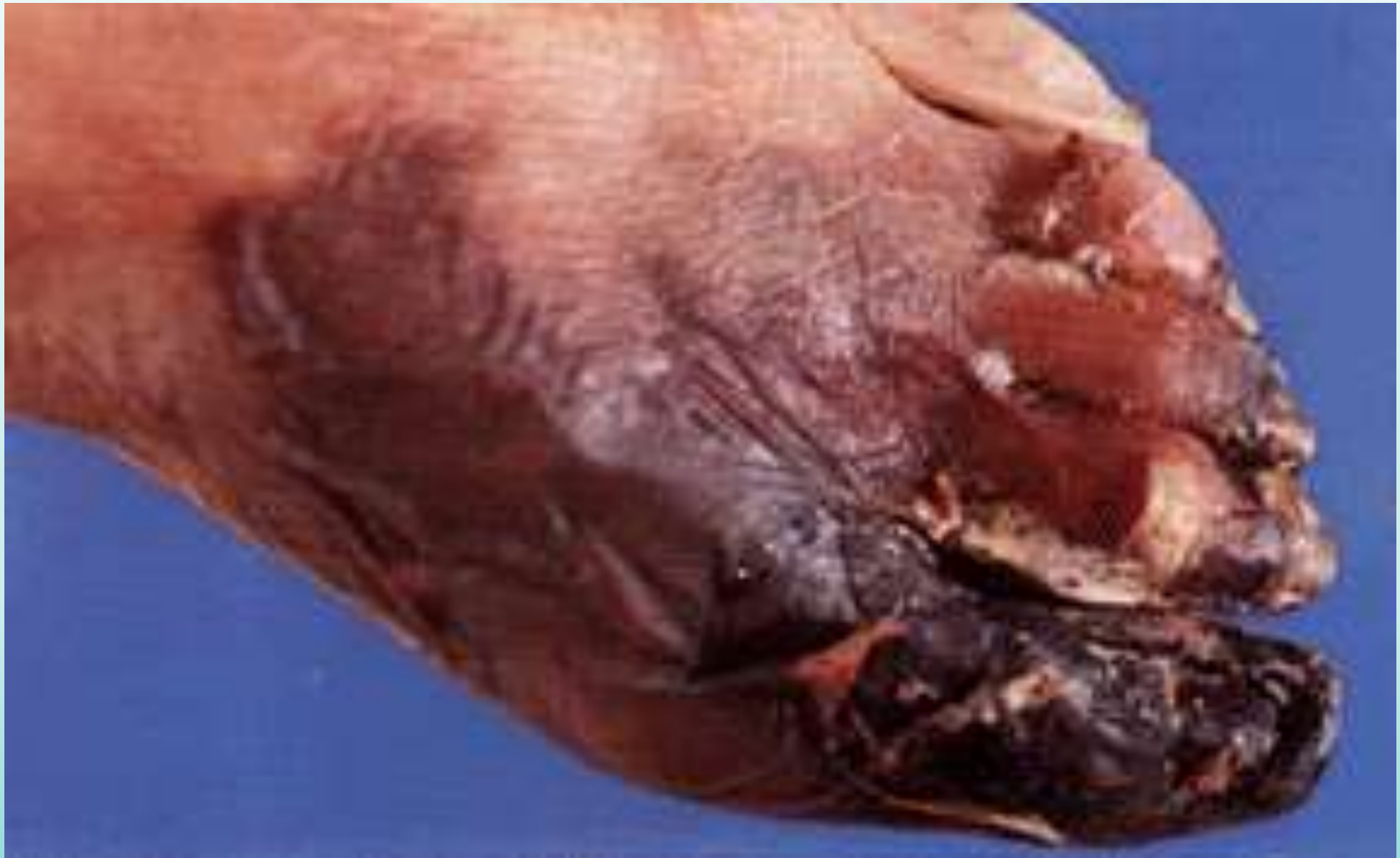




B. Wet gangrene

- Usually occurs in the moist tissues and organs such as the mouth, bowel, lung, cervix.
- **Diabetic leg & Bedsores** are other examples with **high sugar contents** in the necrotic tissue which is **favorable for the bacteria to grow.**
- Wet gangrene usually develops rapidly due to blockage of venous and less commonly arterial blood flow from thrombosis or embolism.
- At the affected part, **stuffed blood** encourages the formation and growth of the invading bacteria and the toxic products formed by the bacteria are absorbed causing the **systemic manifestations of septicaemia,** and then finally to **death.**
- There is **NO clear demarcation of any line of separation.**

“WET” GANGRENE



Ganagrene of lower limb

Dry gangrene

Wet gangrene

Comparison between dry and wet gangrene

Dry gangrene

- Limb, toes fingers
- Arterial obstruction
- Dry shrunken black
- Presence of line of demarcation
- Better prognosis

Wet gangrene

- mouth, bowel, lung, cervix
- Venous obstruction
- Dark moist swollen
- No clear line of demarcation
- Poor prognosis

C. Gas gangrene

- is a special form of wet gangrene that is caused by a gas-forming **Clostridia (Clostridium perfringens which** is a gram positive anaerobic bacteria) which enters into the tissues through open contaminated wounds.
- Or this invasion can also occur as a complication of operation on colon which usually contains the bacteria Clostridia.
- The bacteria produces many **toxins** which can produce **necrosis** and **edema** locally and are absorbed producing systemic manifestations.

5- Fat Necrosis.

- There are two types of fat necrosis

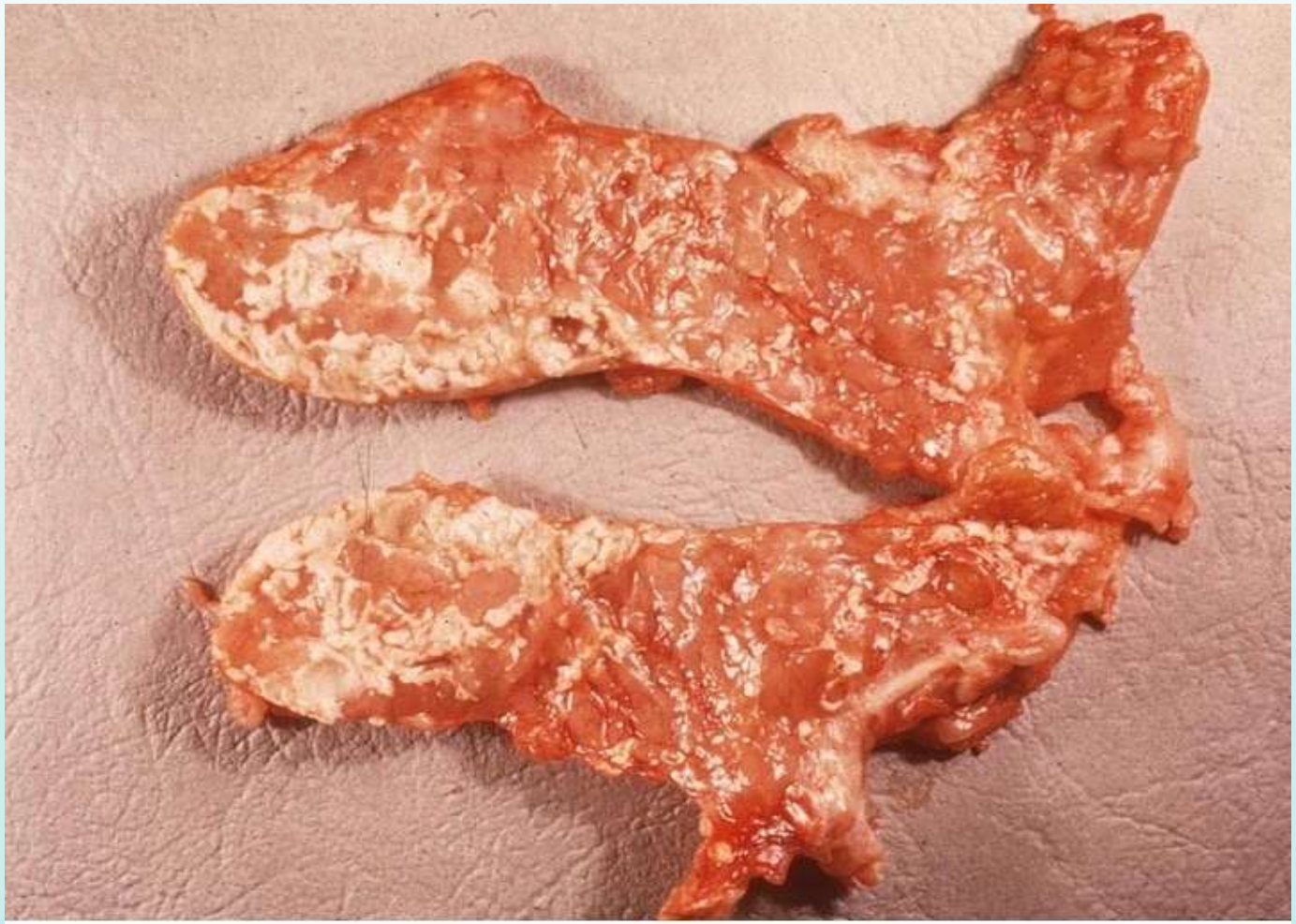
1. Traumatic Fat Necrosis. 2. Enzymatic Fat Necrosis.

- **Traumatic Fat Necrosis**
- Fat necrosis often occurs in women with very large breasts or in response to a bruise or blow to the breast.
- Is a condition in which painless, round, firm lumps caused by damaged and disintegrating fatty tissues form in the breast tissue.
- Fat necrosis can also seen after surgery on the breast, post radiotherapy on breast cancer.
- These lumps are not malignant and there is no reason to believe that they increase a woman's risk of cancer.
- **Microscopically** characterized by foamy macrophages (even giant cells formation) infiltrating necrotic breast tissue.

2- Enzymatic Fat Necrosis

- It describes focal areas of fat destruction, typically occurring after pancreatic injury (mainly acute pancreatitis).
- There is release of pancreatic enzymes (mainly lipase) as a result of injury, into adjacent fatty tissue of greater omentum.
- These enzymes will liquefy fat cells membranes & hydrolyze triglycerides esters within these fat cells & result in the formation of fatty acids combine with calcium.
- These combined fatty acids will produce grossly chalky white areas (Fat Saponification).
- **Microscopically**, there are shadowy outlines of necrotic fat cells with basophilic calcium deposits & a surrounding inflammatory reaction.

Fat necrosis of acute pancreatitis



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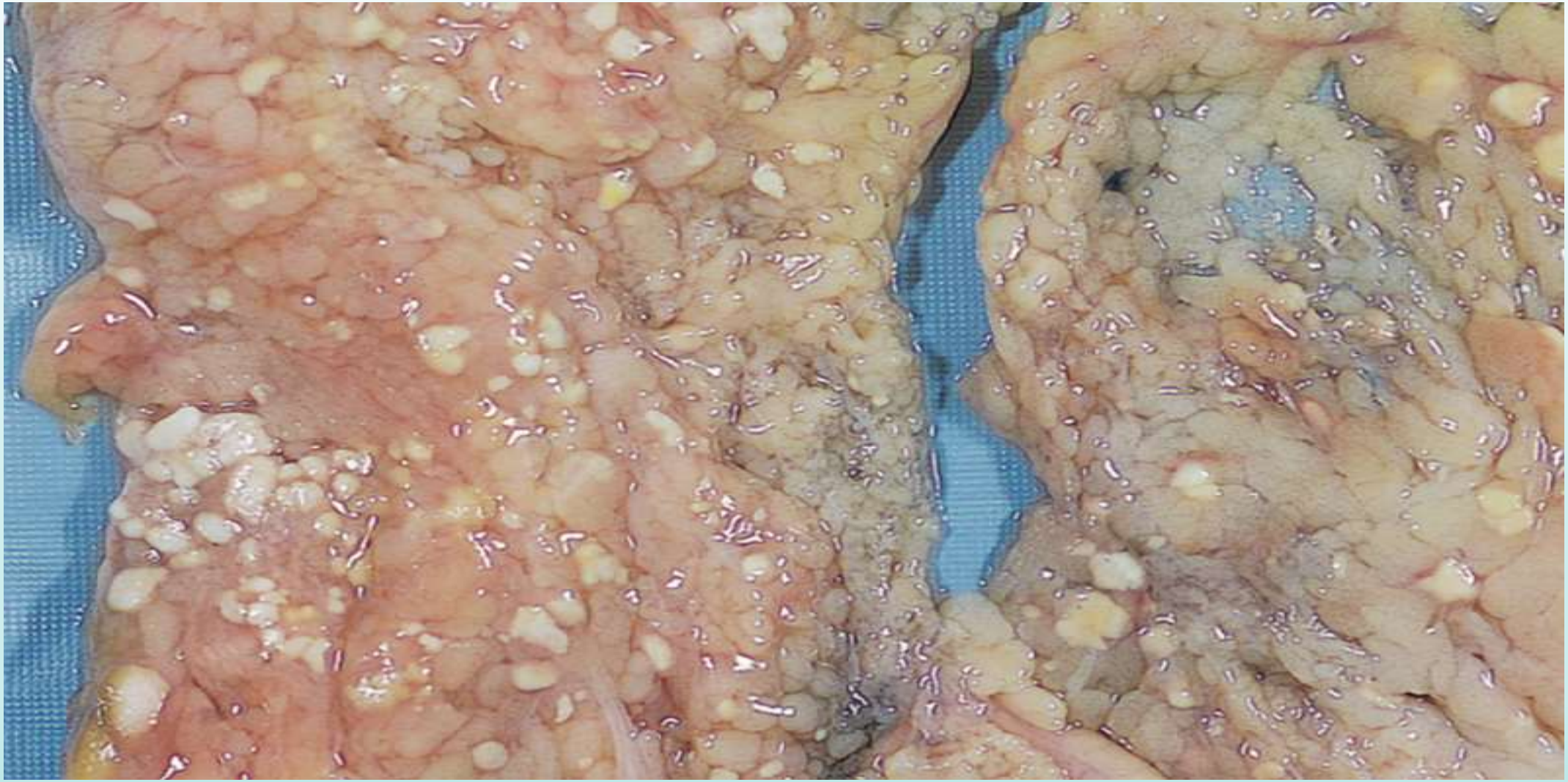
Injury to the pancreatic acini leads to release of powerful enzymes which damage fat through lipases; these liberate fatty acids which complex with calcium leading to the production of soaps, and these appear grossly as the soft, chalky white areas seen here on the cut surfaces.

Fat necrosis in acute pancreatitis.

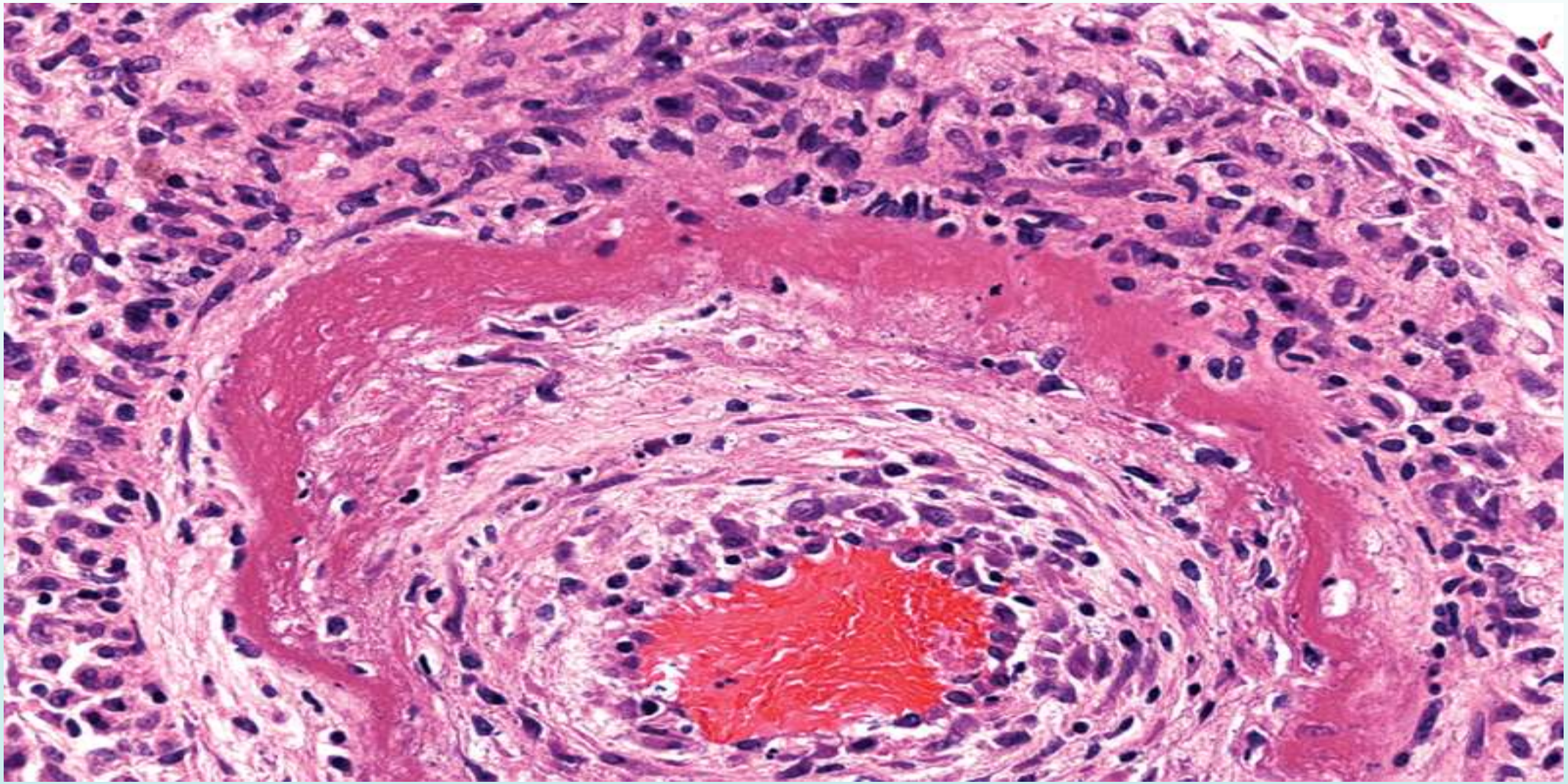


The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.

Fibrinoid necrosis is a special form of necrosis usually seen in immune reactions involving blood vessels.

This pattern of necrosis typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries.

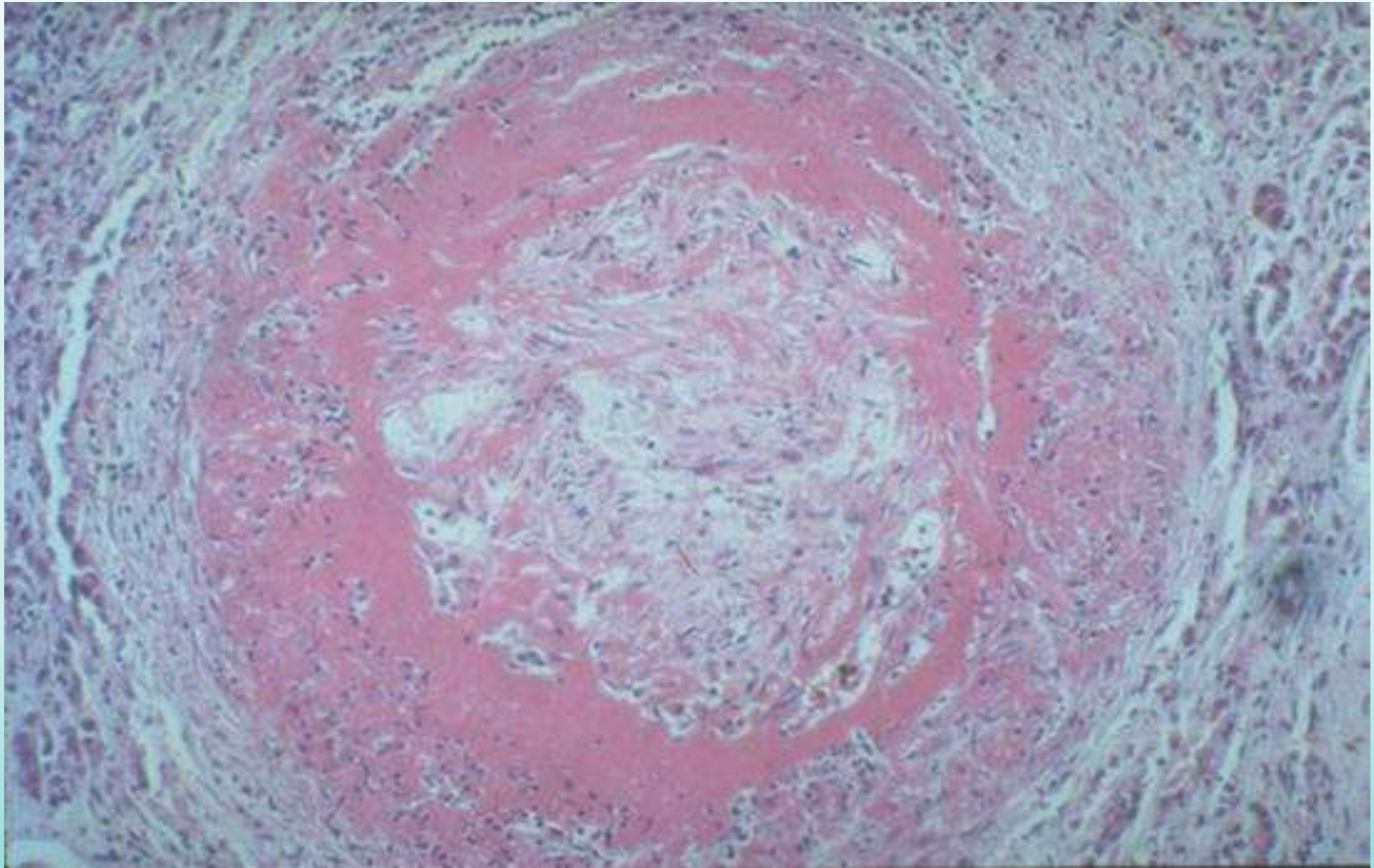
Deposits of these "immune complexes," together with fibrin that has leaked out of vessels, result in a **bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like**) by pathologists . Usually seen in vasculitis.



Fibrinoid necrosis of an artery in polyarteritis nodosa.

The wall of the artery shows a circumferential bright pink area of necrosis with protein deposition and inflammation (dark nuclei of neutrophils).

FIBRINOID NECROSIS



•APOPTOSIS

"The word "apoptosis" is used in Greek to describe the "dropping off" or "falling off" of petals from flowers, or leaves from trees.
, the second half of the word being pronounced like "ptosis" (with the "p" silent), which comes from the same root "to fall", and is already used to describe the drooping of the upper eyelid

Apoptosis(Programmed Cell Death):

- Apoptosis is a pathway of cell death
- induced by a tightly regulated intracellular suicide program,
- cells destined to die activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.

Examples of apoptosis

Apoptosis in physiologic situations

Apoptosis in pathologic situations

Examples of Physiological conditions:

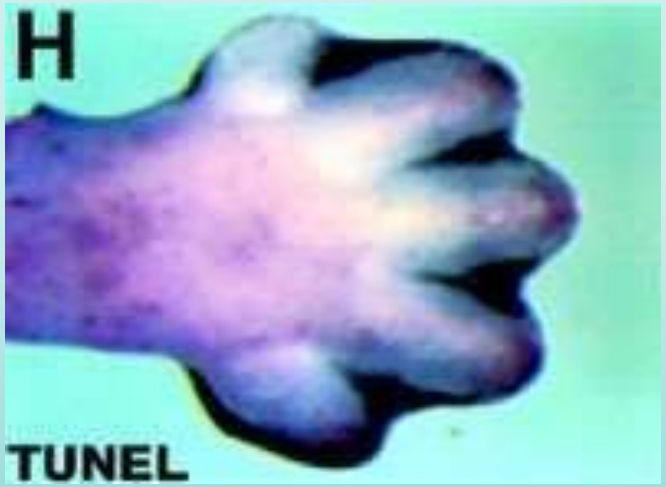
1. **The programmed destruction of cells during embryogenesis**, including implantation, organogenesis.

2. **Hormone-dependent involution in the adult,** such as endometrial cell breakdown during the menstrual cycle

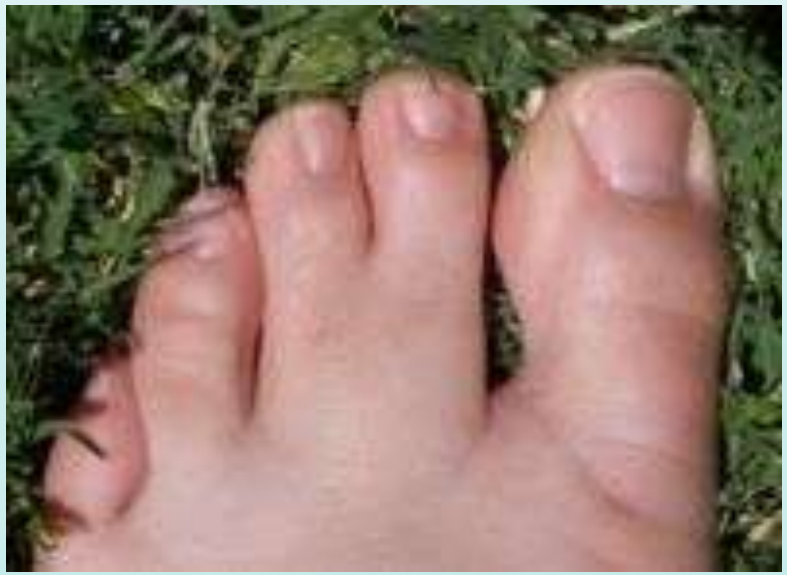
3. **Death of host cells (inflammatory cells),** like neutrophils in an acute inflammatory response, and Lymphocytes at the end of an immune response.

4. **Elimination of potentially harmful self-reactive lymphocytes**, either before or after they have completed their maturation.

Apoptosis in bud formation during which many interdigital cells die. They are stained black by a TUNEL method



Incomplete differentiation in two toes due to lack of apoptosis



Examples of Pathological conditions:

- **1-Cell death produced by a variety of injurious stimuli,** such as DNA damage due to radiation & anticancer drugs, this damage DNA may result in malignant transformation of the cells.
- **2- Cell injury in certain viral diseases,** such as viral hepatitis.
- 3. **Cell death in tumors,** most frequently during regression but also in actively growing tumors.

Morphologic Features of Apoptosis:

1- Cell shrinkage.

2- **Chromatin condensation**. This is the most characteristic feature of apoptosis. The chromatin aggregate peripherally, under the nuclear membrane, into dense masses of various shapes and sizes (**Karyorrhexis**).

3**. Formation of cytoplasmic blebs and apoptotic bodies.** The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without nuclear fragments.

4.Phagocytosis of apoptotic cells or cell bodies, usually by macrophages.

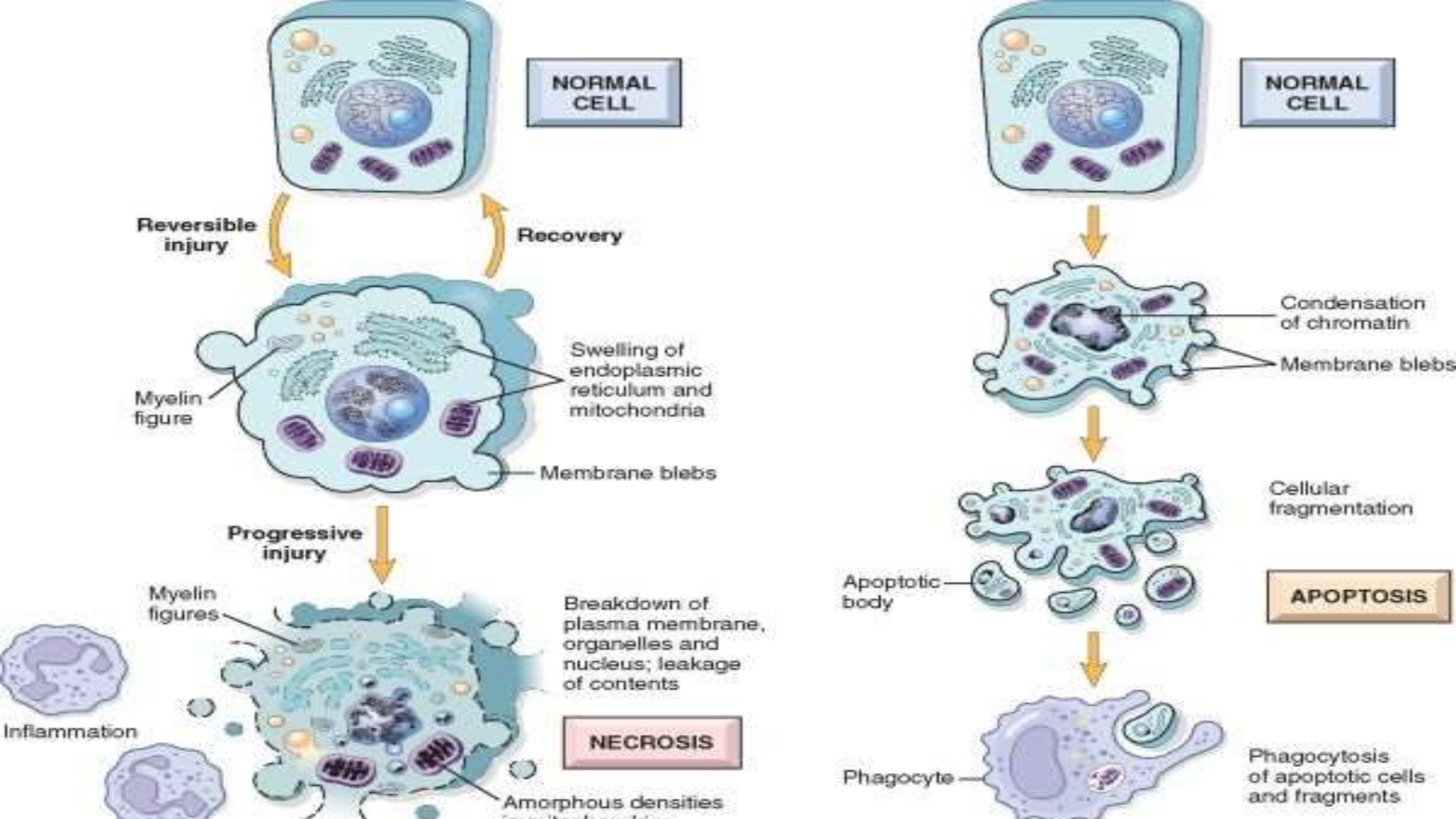
5.Apoptosis does NOT induce inflammation.

Plasma membranes remain intact during apoptosis.

MIC: examination of apoptotic areas in tissues stained with hematoxylin and eosin, apoptosis involves single cells or small clusters of cells. The apoptotic cell shrunk and appears as a round or oval mass of intensely eosinophilic cytoplasm with dense nuclear chromatin fragments

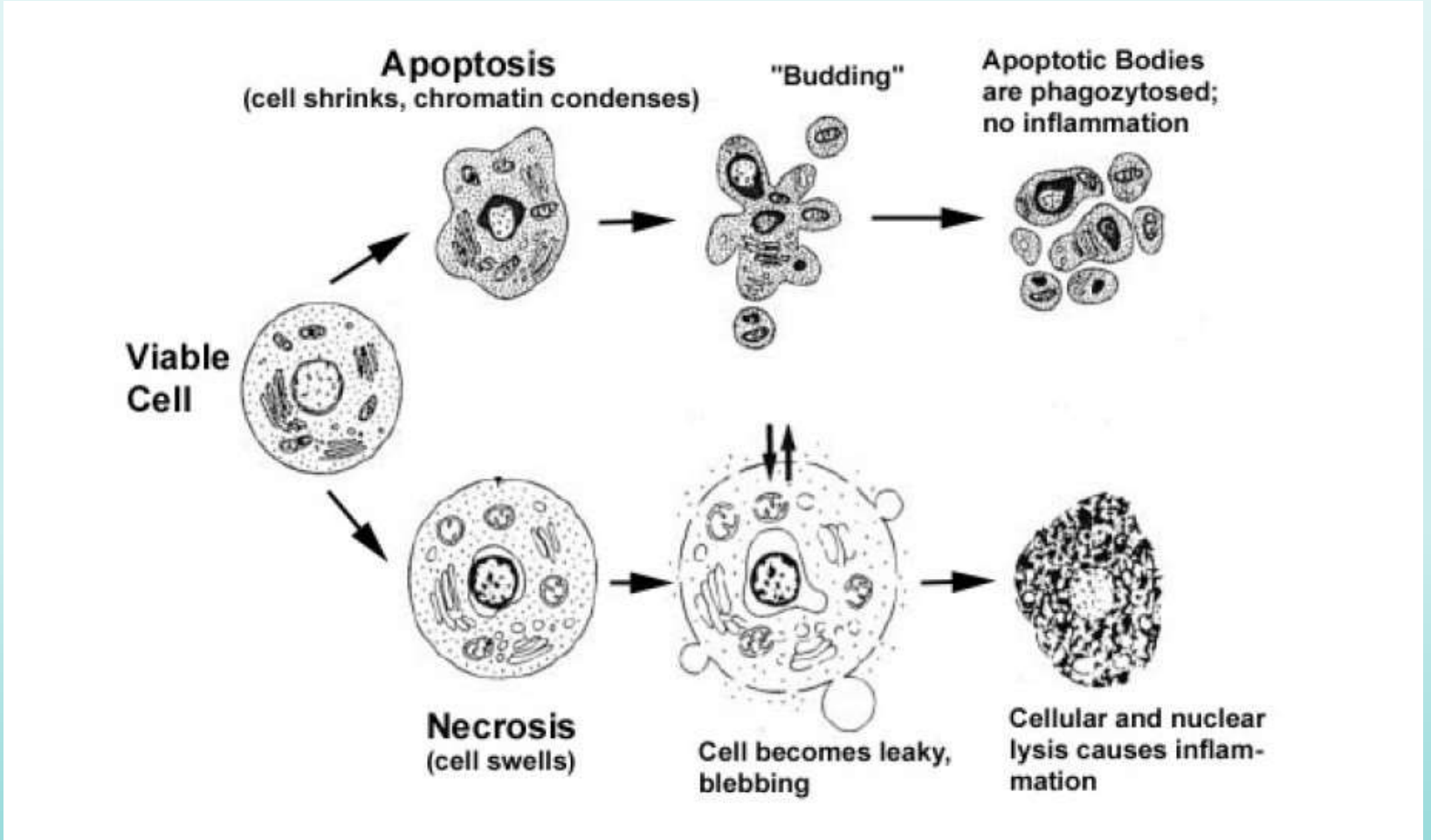
Morphologic features of Apoptosis

- 1. **Cell shrinkage.**
- **2. Nuclear chromatin condensation and fragmentation**
- **3. Apoptotic bodies formation**
- **4. Phagocytosis of apoptotic bodies by adjacent cells or macrophages.**
- **5. Intact membrane.**


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
NECROSIS
Inflammation
Amorphous densities
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments

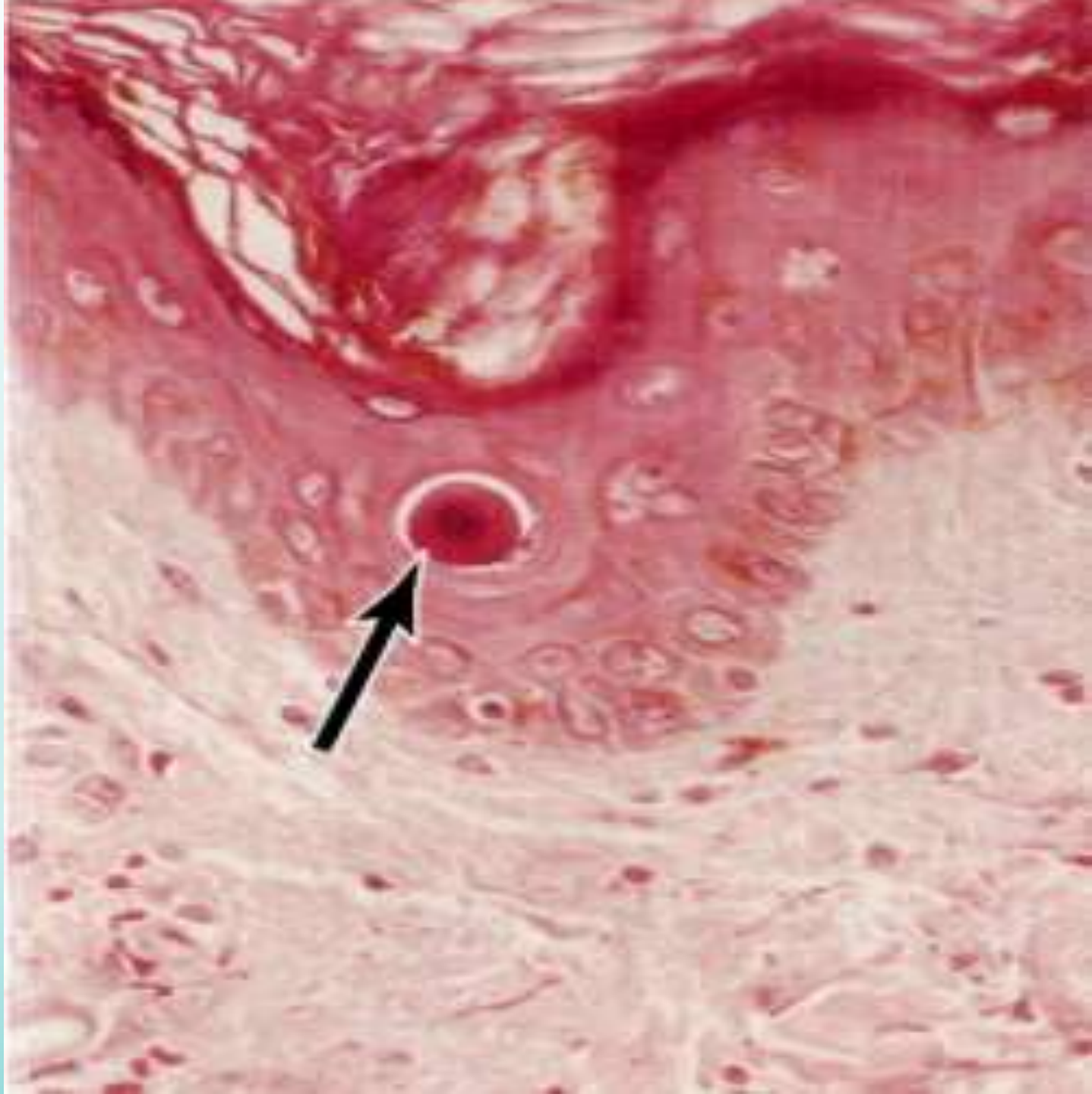
Cell death mechanisms

- Death by suicide
- Death by injury



The cytoplasm is intensely esoniphilic (pinkish) and the nucleus condensed (pyknotic)

Apoptosis of epidermal keratinocyte



Two distinct pathways converge on caspase acticvation

Mitochondrial pathway

- Intrinsic pathway

The death receptor pathway

- Extrinsic pathway

Mechanisms of apoptosis:

Apoptosis is induced by a cascade of molecular events that result in activation of caspases, which are responsible for the features of apoptosis.

The process of apoptosis may be **divided into**

initiation phase, (**CASPASES activation)**

execution phase, **(cell death by activated CASPASES)**

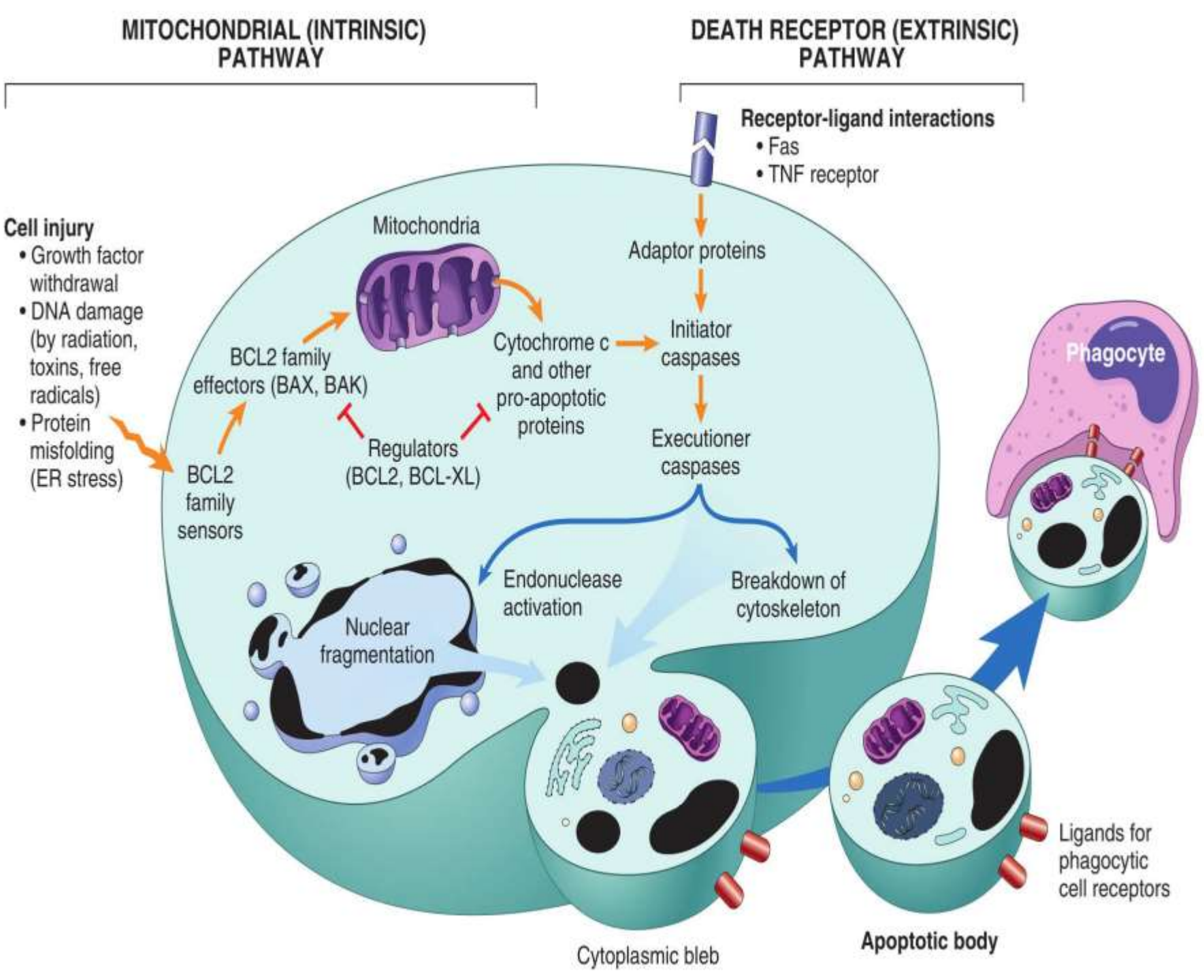
Initiation of apoptosis occurs principally **by signals from two pathways** :

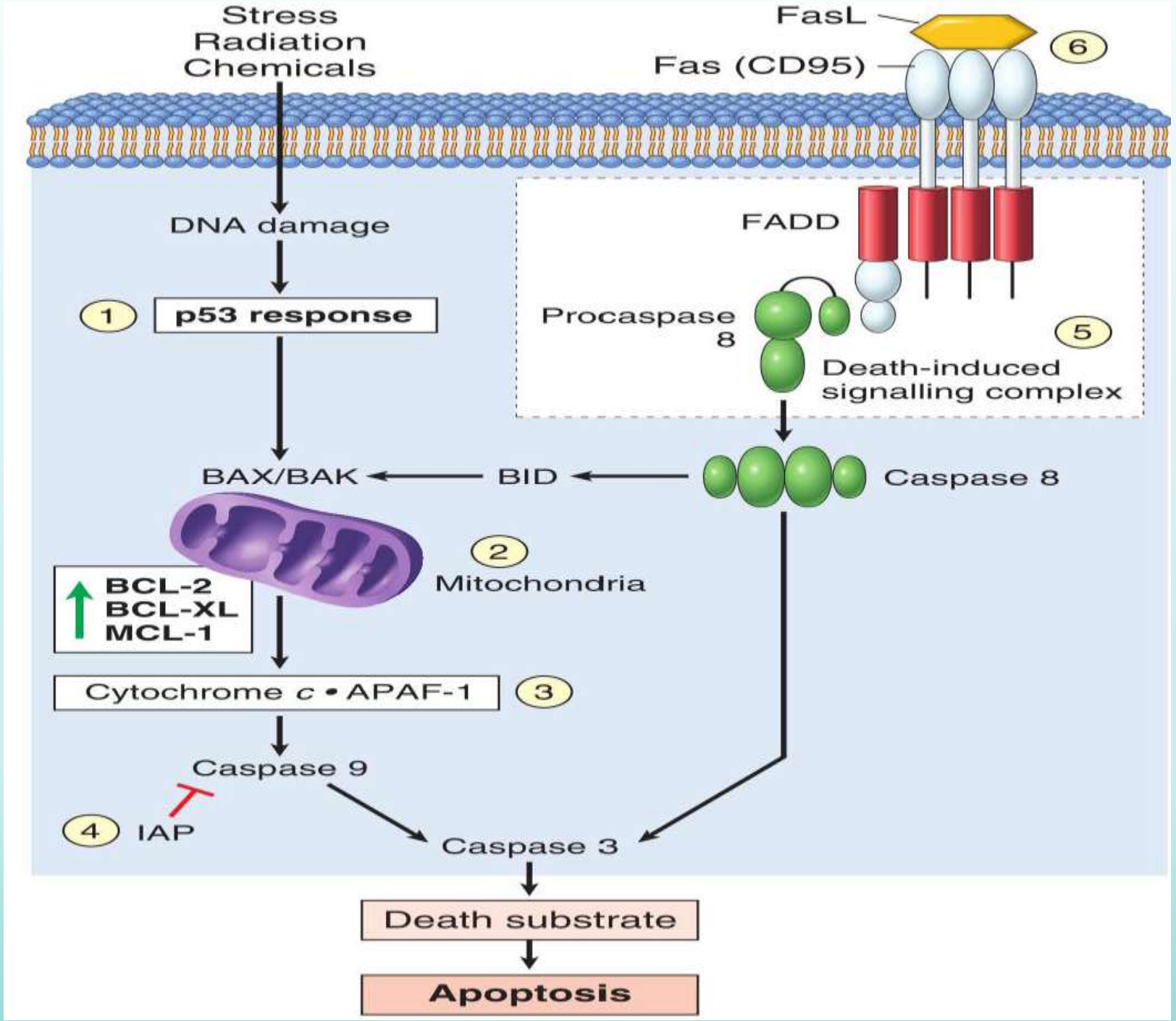
1- Extrinsic, or receptor-initiated, pathway

2- Intrinsic or mitochondrial pathway.

Extrinsic, receptor initiated, pathway:

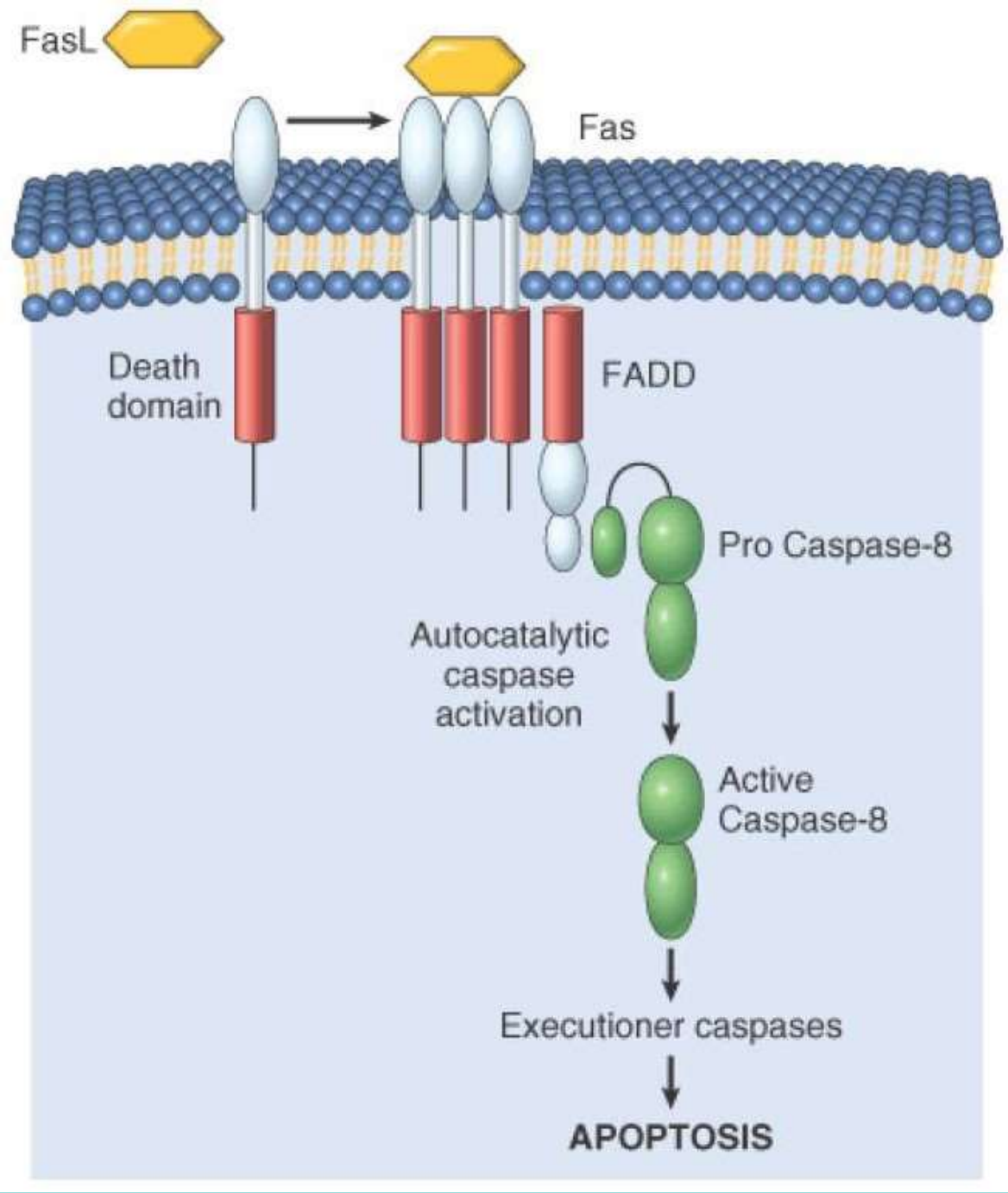
- This pathway is initiated by group of receptors (death receptors), that are present on a variety of cells.
- These death receptors are members of family {called tumor necrosis factor(TNF)} which contain death domain, which is essential for delivering of apoptotic signals,
- The best-known death receptors are the type 1 TNF receptor (TNFR1) and a related protein called Fas (this Fas protein is responsible for initiation phase of apoptosis by **activation of caspases)**
- This pathway of apoptosis can be inhibited by a **protein called FLIP** (prevent the activation of caspases by Fas proteins),

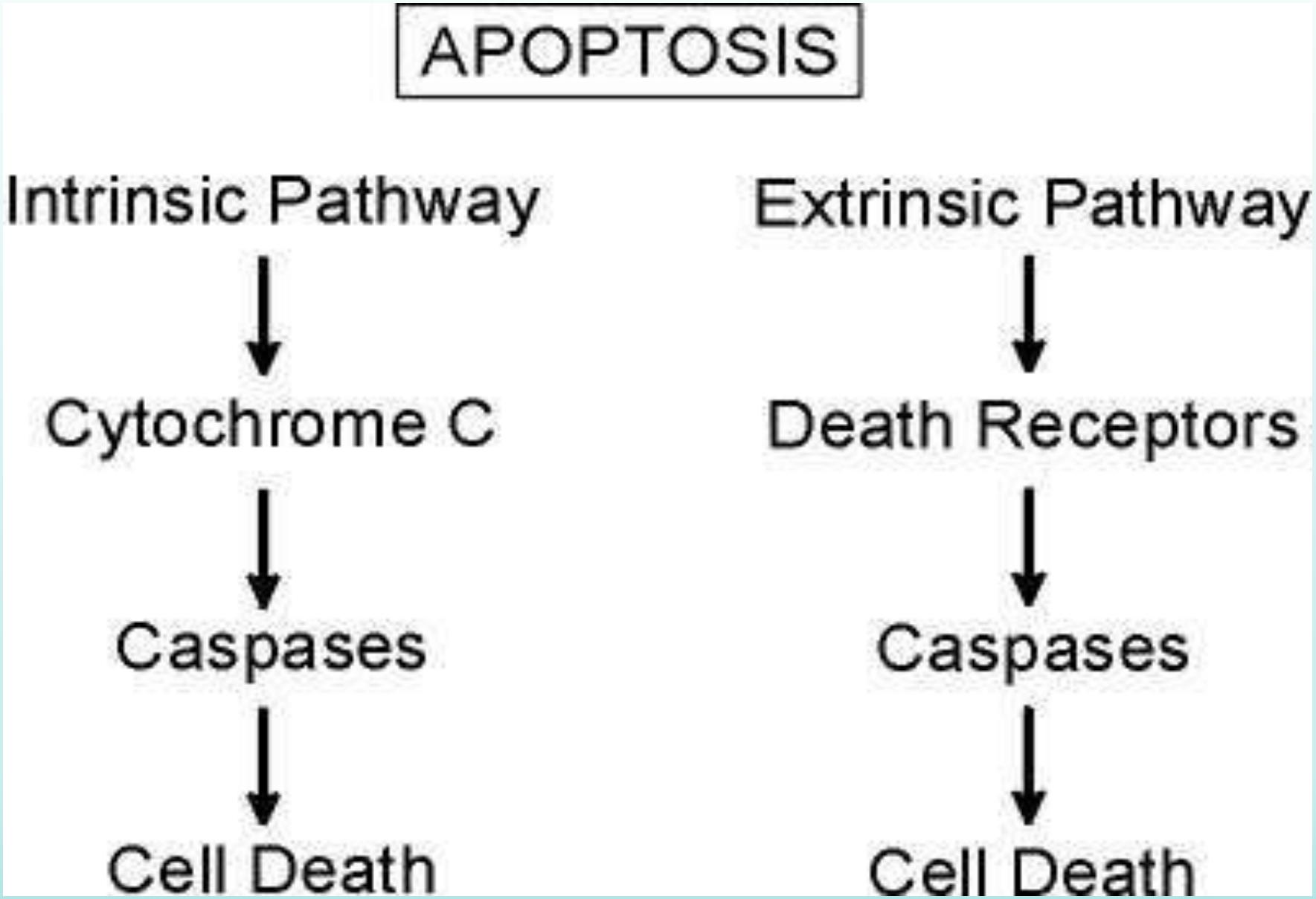

MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
BCL2 family effectors (BAX, BAK)
Cytochrome c and other pro-apoptotic proteins
Initiator caspases
Regulators (BCL2, BCL-XL)
Executioner caspases
BCL2 family sensors
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Ligands for phagocytic cell receptors
Cytoplasmic bleb
Apoptotic body


Stress
Radiation
Chemicals
FasL
6
Fas (CD95)
DNA damage
FADD
1
p53 response
Procaspase
8
5
Death-induced
signalling complex
BAX/BAK
BID
Caspase 8
2
Mitochondria
BCL-2
BCL-XL
MCL-1
Cytochrome c • APAF-1
3
Caspase 9
4
IAP
Caspase 3
Death substrate
Apoptosis

- Extrinsic pathway

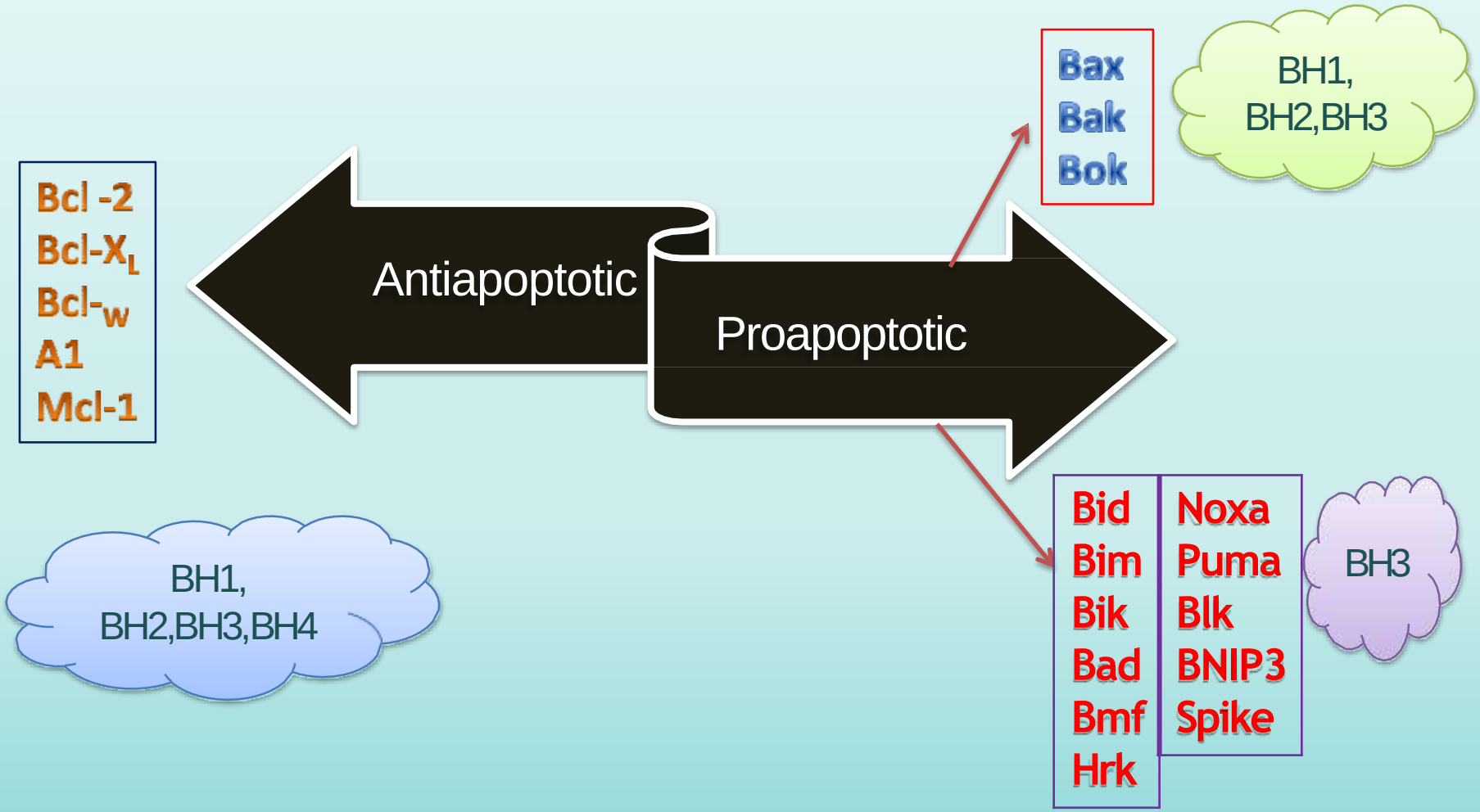
The death receptor pathway




APOPTOSIS
Intrinsic Pathway
Cytochrome C
Caspases
Cell Death
Extrinsic Pathway
Death Receptors
Caspases
Cell Death

Bcl-2 family members

A very large family with 30 members identified and belongs to both:



Mechanisms of Apoptosis

The fundamental events in apoptosis is the activation of enzymes called CASPASES

Caspases are central initiators and executioners of apoptosis

Caspases

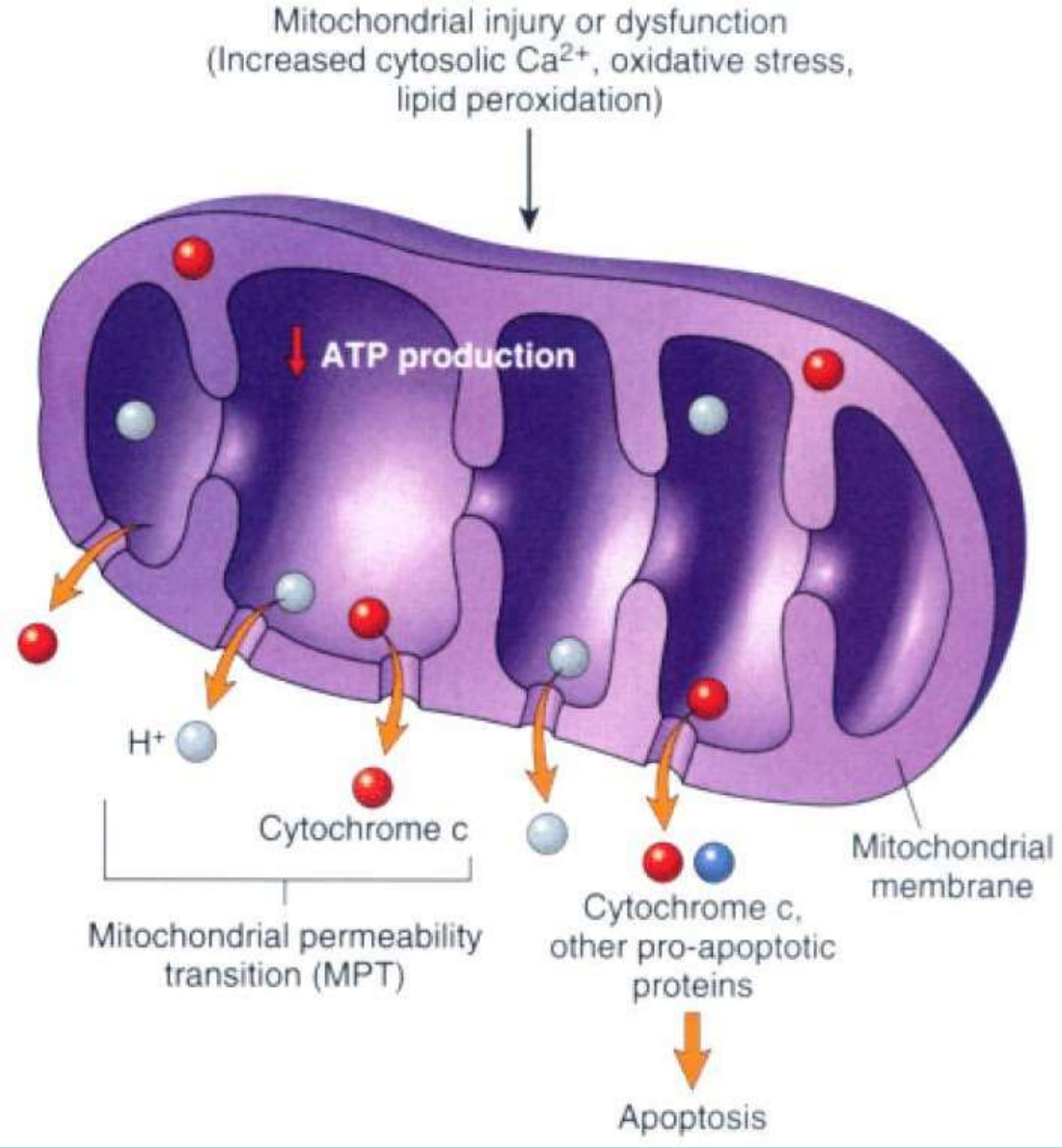
- Cysteine proteases
- Cysteine-dependent ASPartate-specific proteASES

The Intrinsic (Mitochondrial) Pathway.

- Apoptosis is occurred in this pathway as a result of increased permeability mitochondrial membrane releasing a protein called **cytochrome C** to the cytoplasm initiate the suicide program of apoptosis.
- This change in permeability of mitochondrial membrane is due to replace of normally present **anti- apoptotic proteins (Bcl-2)** by **pro- apoptotic proteins like BAX and BAK .**
- These pro- apoptotic proteins will induce apoptosis by activation of **caspases.**

Excution phase of Apoptosis

- **This final pathway of apoptosis**,
- characterized by group of distinctive biochemical events that result from synthesis & activation of **Caspases enzymes**.
- These Caspases will result in morphological changes of apoptosis **by induce the followings processes**:
- 1-protein cleavage,
- 2-protein Cross linkage,
- 3-DNA breakage, &
- 4-removal of dead cells by phagocytosis.



Mitochondria contain several proteins that are capable of inducing apoptosis

The choice between cell survival and death is determined by the permeability of mitochondria

Difference Between Apoptosis and Necrosis

- Necrosis (pathological cell death): dying cells swell and lyse; toxic contents leak out and result in inflammatory response.

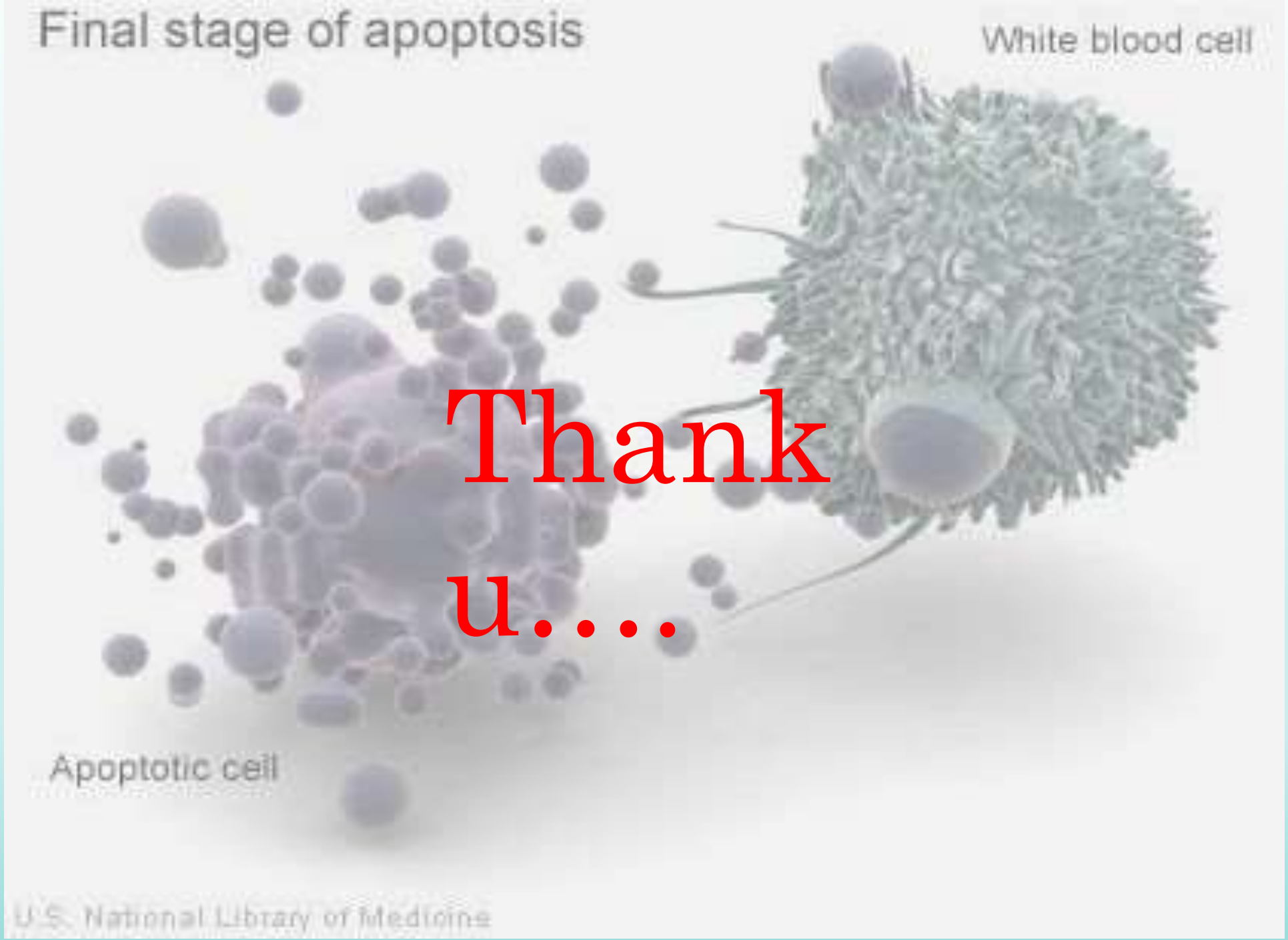
- Apoptosis (physiological or programmed cell death): dying cells shrink, are engulfed by other cells, leave no trace, and don't result in harmful outcomes

Differential features of apoptosis and necrosis

Apoptosis	Necrosis
Affects single cells	Affects groups of neighboring cells
No inflammatory response	Significant inflammatory response
Cell shrinkage	Cell swelling
Membrane blebbing but integrity maintained	Loss of membrane integrity
Increased mitochondria membrane permeability, release of proapoptotic proteins and formation of apoptotic bodies	Organelle swelling and lysosomal leakage
Chromatin condensation and non-random DNA fragmentation	Random degradation of DNA
Apoptotic bodies ingested by neighboring cells	Lysed cells ingested by macrophages

Necroptosis

- As the name indicates, this form of cell death is a hybrid
- that shares aspects of both necrosis and apoptosis. The following features characterize necroptosis
- is a form of programmed cell death that is controlled by death signals and displays a death pattern like that of necrosis
- Found in **inflammation** and **ischemia-reperfusion injury**


Final stage of apoptosis
White blood cell
Apoptotic cell
U.S. National Library of Medicine

Thank u….