CELL DEATH

NECROSIS, APOPTOSIS, NECROPTOSIS AND AUTOPHAGY

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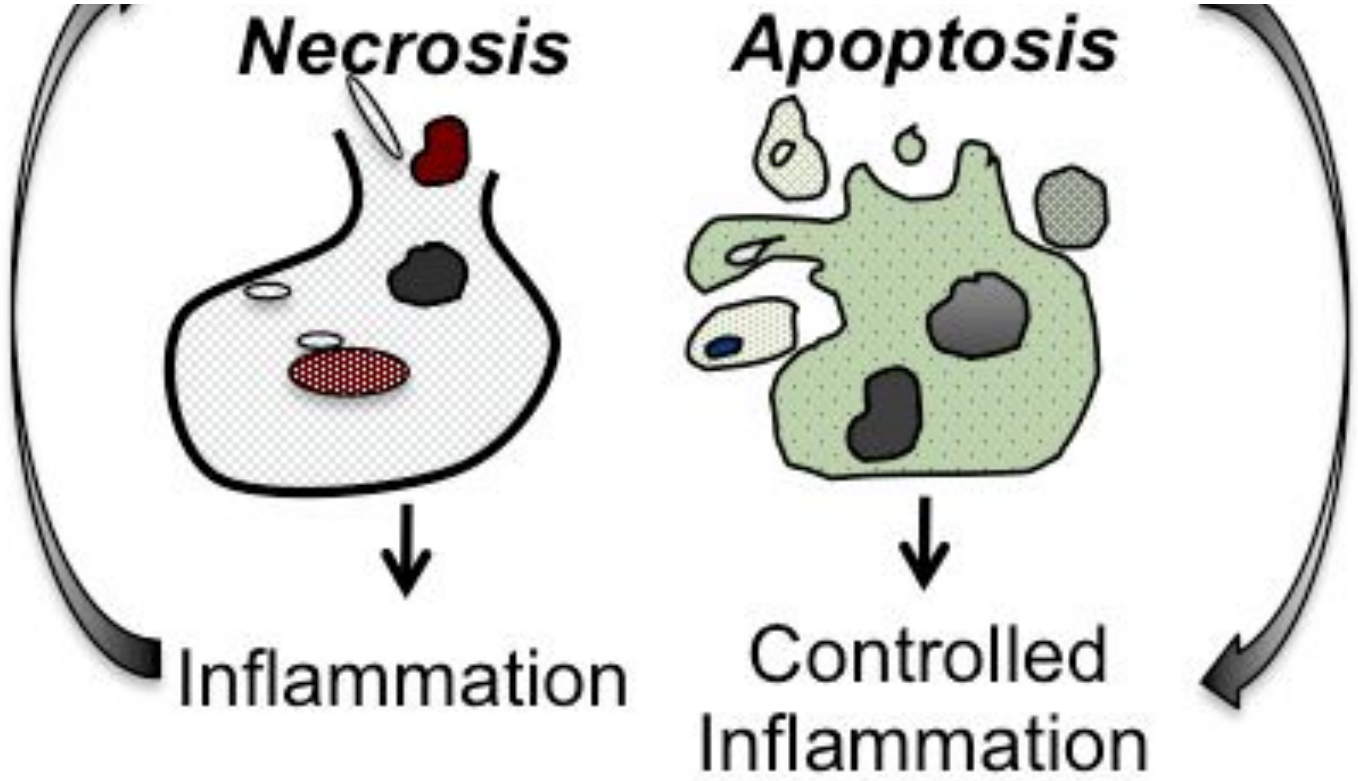
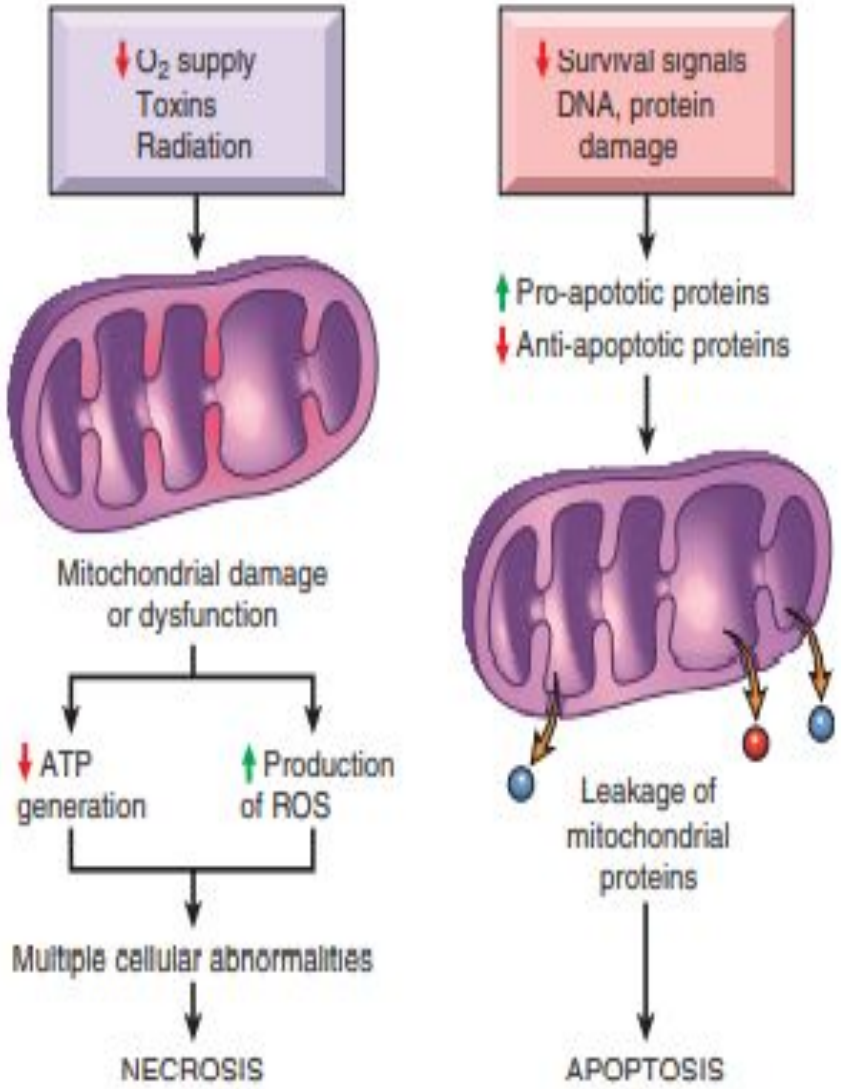


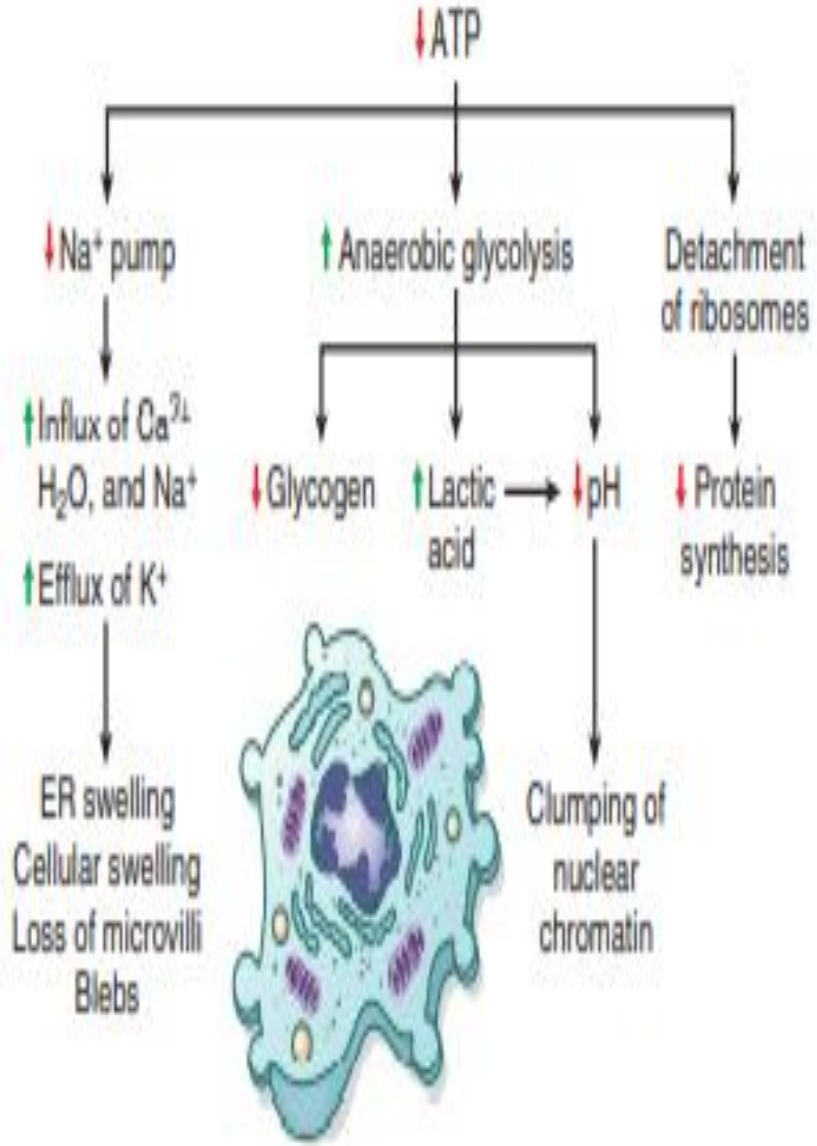
A Quick Recap

- Give causes of cell injury
- How damage to mitochondria causes cell injury
- How ATP depletion causes cell injury
- How loss of calcium homeostasis causes cell injury

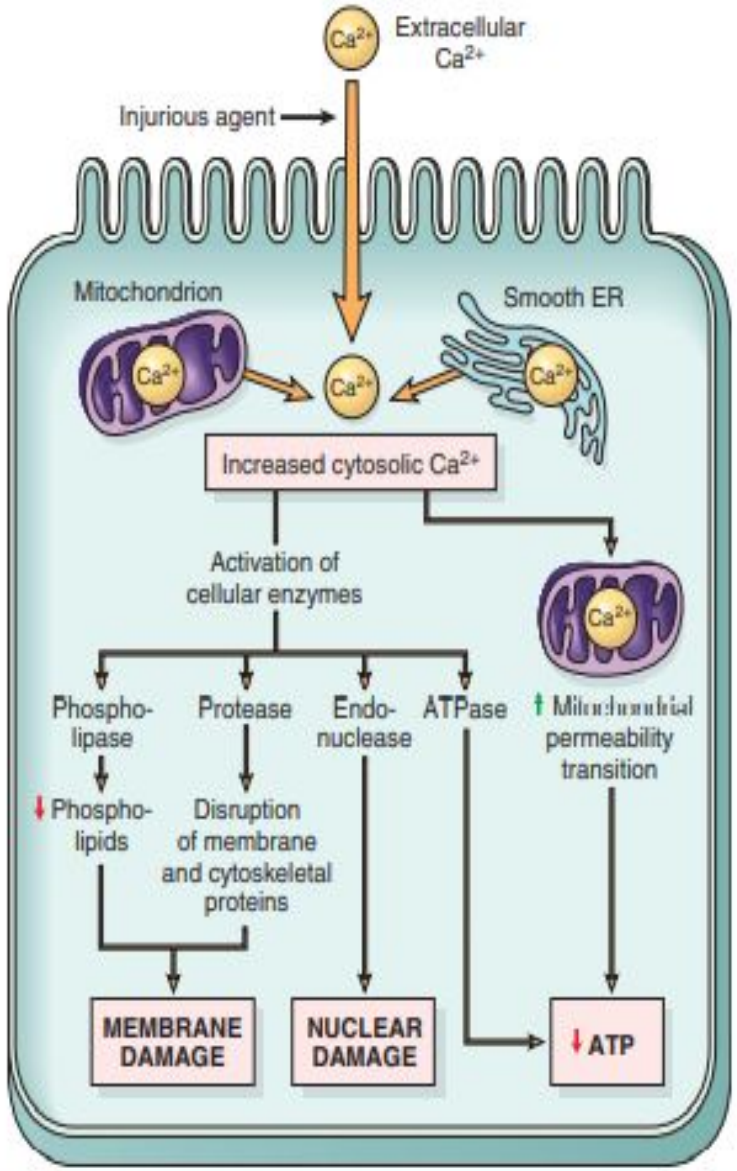
MITOCHONDRIAL DAMAGE



DEPLETION OF ATP



LOSS OF CALCIUM HOMEOSTASIS



Objectives

At the end of the session student's should be able to:

- Differentiate between apoptosis and necrosis
- Describe morphological features of necrosis and apoptosis
- Distinguish between different morphological subtypes of necrosis
- Understand different pathways of apoptosis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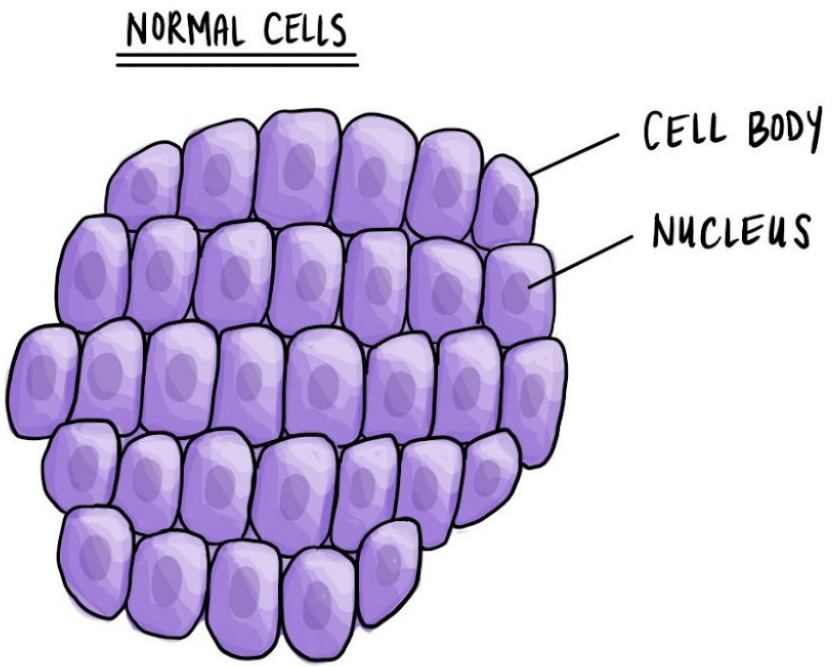
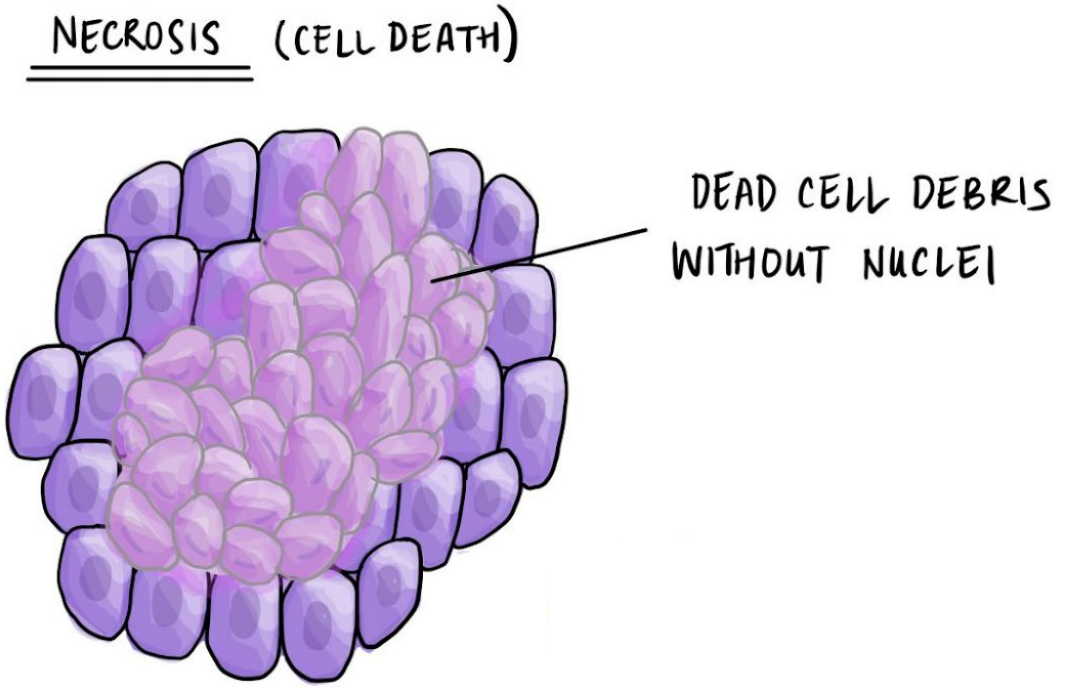
Necrosis

Necrosis is the pattern of cell death that occurs in response to injuries such as hypoxia, extremes of temperature, toxins, physical trauma, and infection with lytic viruses





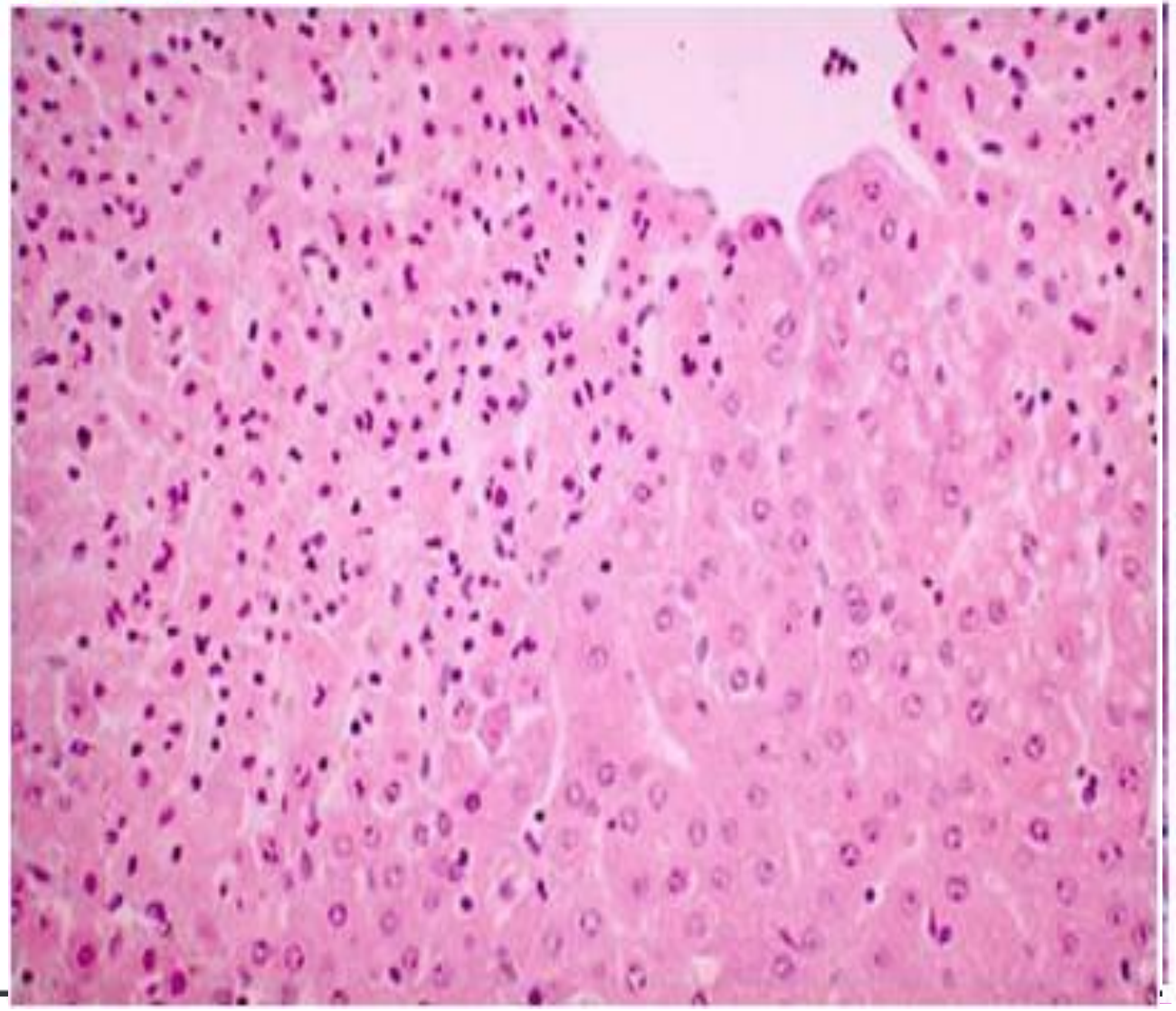
Necrosis

The morphologic appearance of necrosis is the result of **denaturation of intracellular proteins** and **enzymatic digestion** of the lethally injured cell

1. **Increased eosinophilia**
2. **Myelin figures**
3. **Calcium soaps**
4. **Glassy appearance**
5. **Nuclear changes**

- **Pyknosis**
- **Karyorrehxis**
- **Karyolysis**

Necrosis



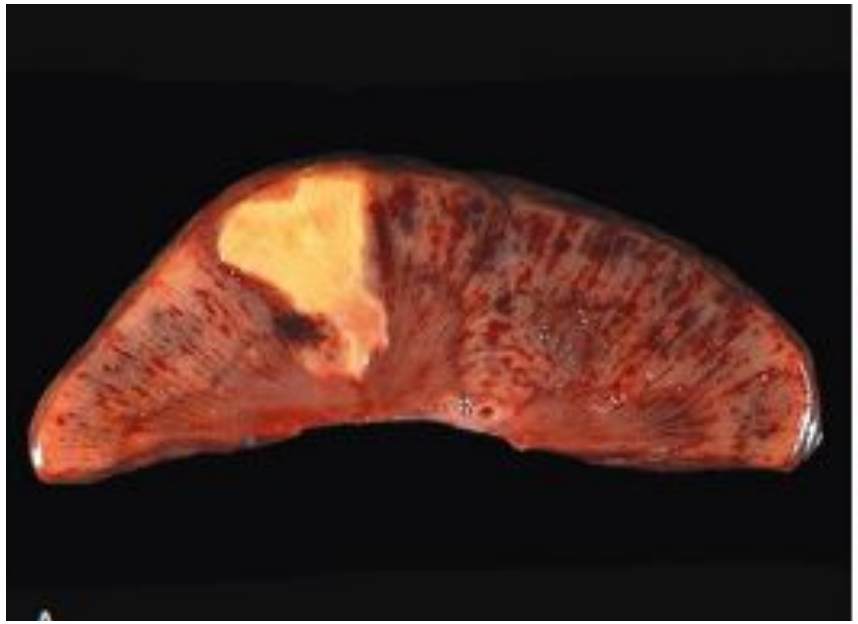
1. **Increased eosinophilia**
- loss of DNA, cytoplasmic RNA and denatured proteins
2. **Myelin figures**
- Large, whorled phospholipid masses from damaged cell membranes
3. **Calcium soaps**
- Calcification of myelin figures
4. **Glassy appearance**
- glycogen loss and increased vacuolization
5. **Nuclear changes**
   - **Pyknosis** :nuclear shrinkage and increased basophilia due to condensed chromatin
   - **Karyorrehxis** :Fragmentation of pyknotic nucleus
   - **Karyolysis** : basophilia of chromatin may fade

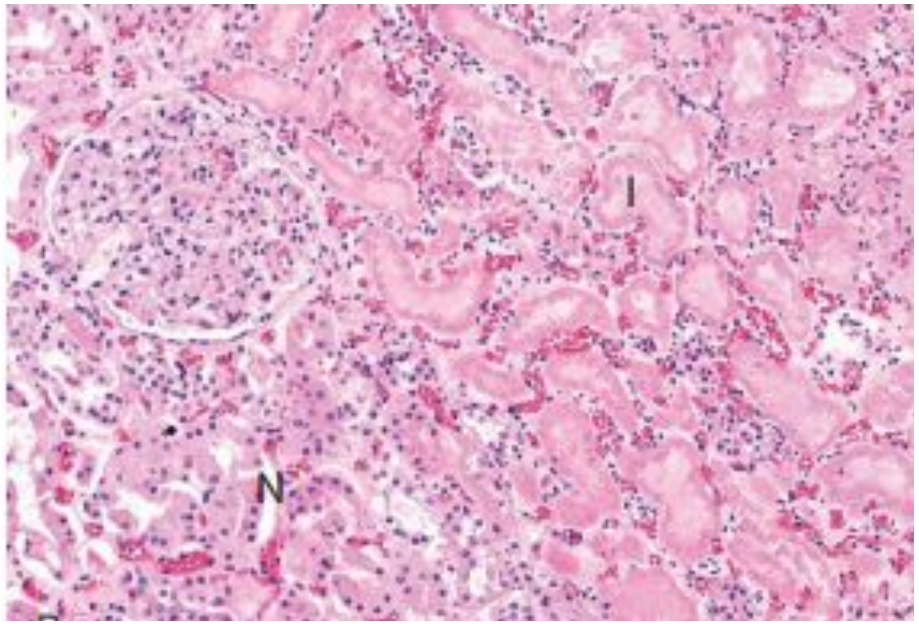
Morphological Types of Necrosis

1. **Coagulative**
2. **Liquefactive**
3. **Caseous**
4. **Gangrenous**
5. **Fat**
6. **Fibrinoid**

Coagulative Necrosis

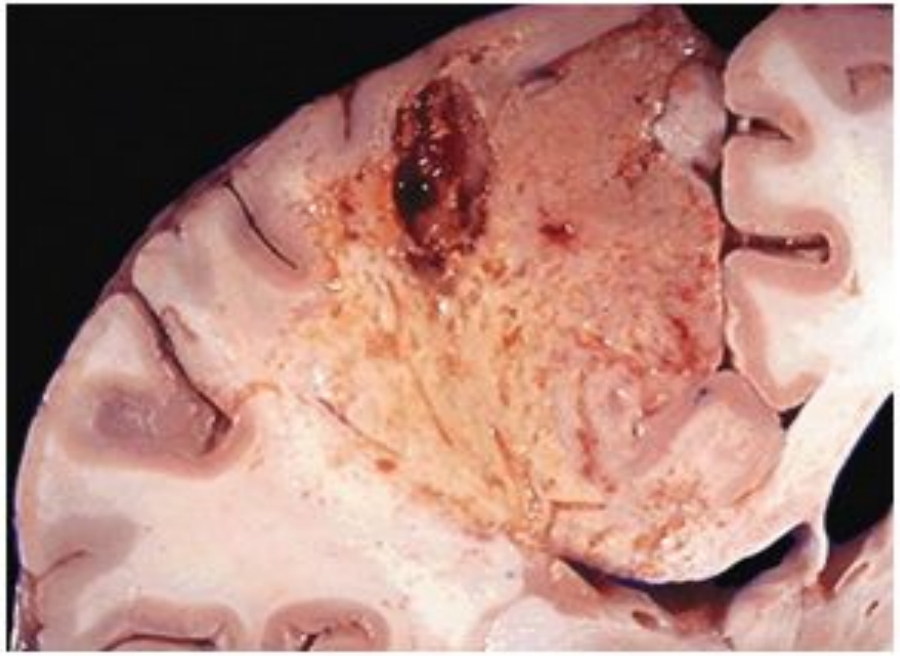
- Ischemia caused by obstruction in a vessel (infarct) may lead to coagulative necrosis of the supplied tissue in all organs except the brain
- Architecture of dead tissues is preserved for some days
- Firm texture (injury denatures structural proteins and enzymes and so blocks the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks)
- Phagocytosis and digestion of the cellular debris by infiltrating leukocytes

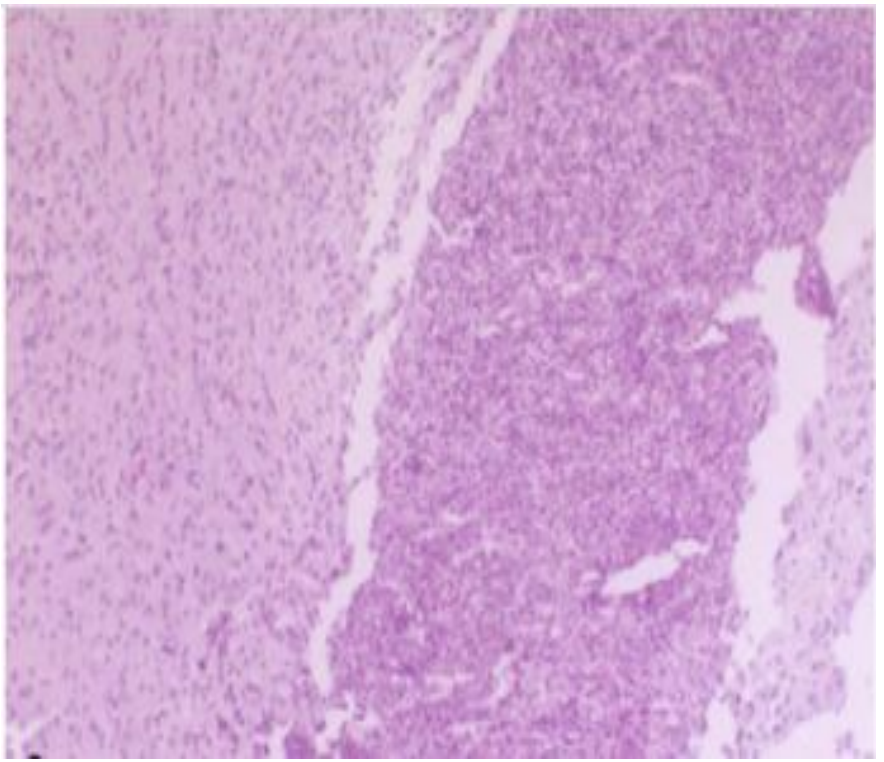




Liquefactive Necrosis

- Digestion of the dead cells, turning it into a liquid viscous mass
- It is seen in focal bacterial or, occasionally, fungal infections
- The necrotic material is frequently creamy yellow because of the presence of dead leukocytes and is called pus
- Hypoxic death of cells within the central nervous system often manifests as liquefactive necrosis



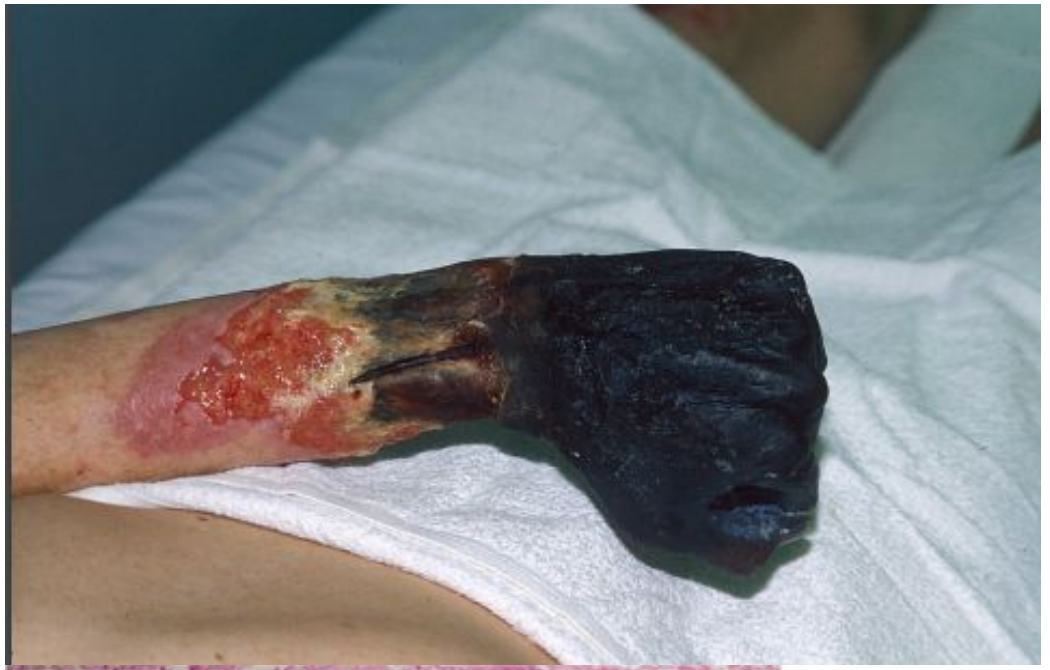


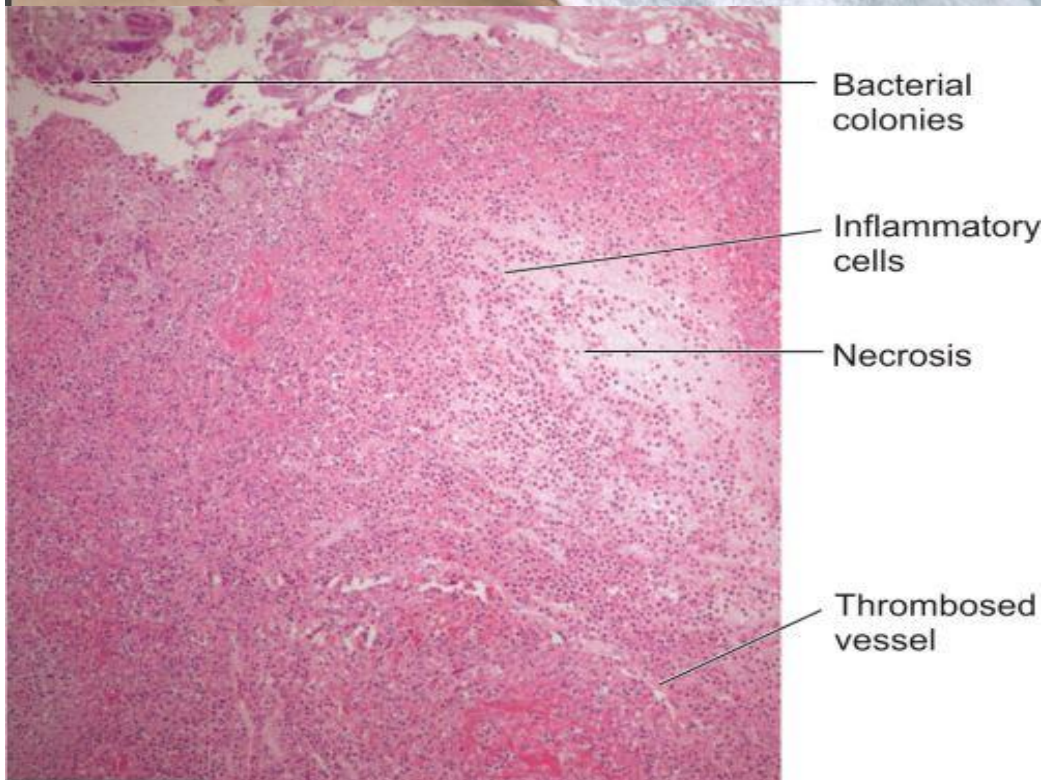
Gangrenous Necrosis

- Usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone necrosis

- Dry gangrene

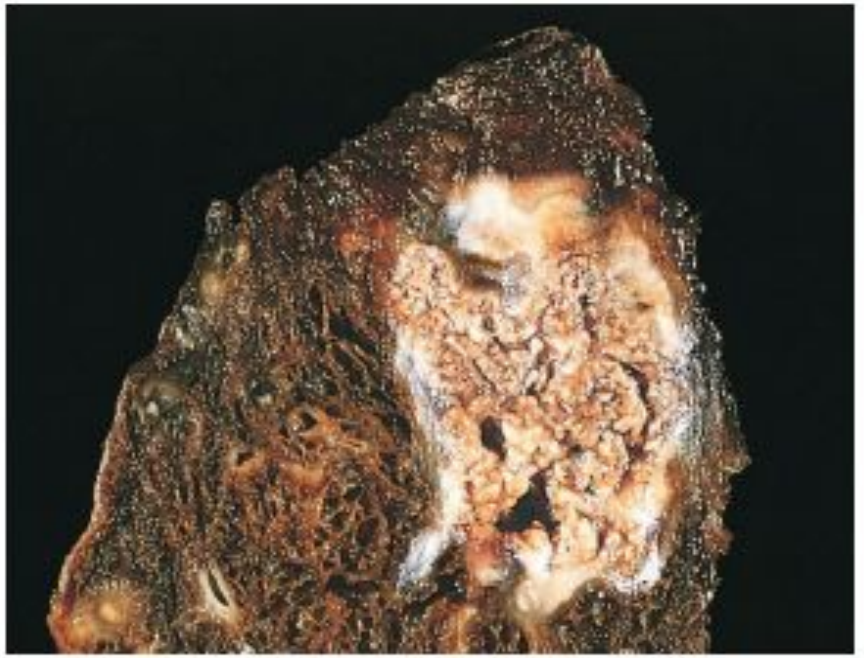
- When bacterial infection is superimposed there is more liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (giving rise to so-called wet gangrene)

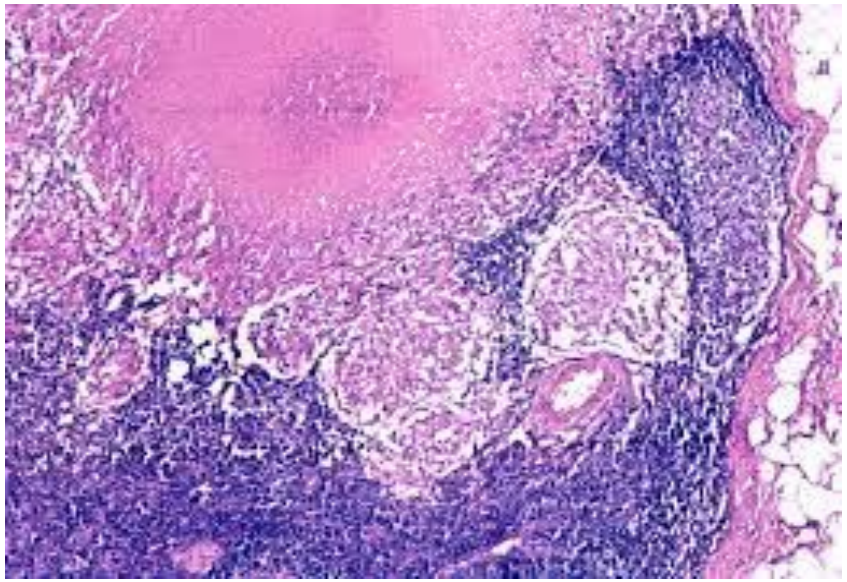


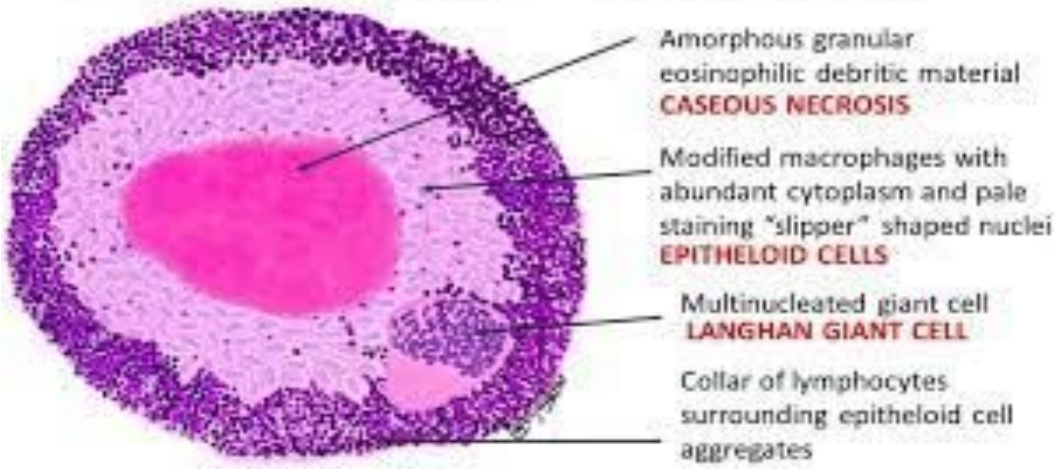


Caseous Necrosis

- Seen in foci of tuberculous infection, friable white (cheese like) appearance of the area of necrosis
- On microscopy, necrotic area appears as a structure less collection of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a granuloma





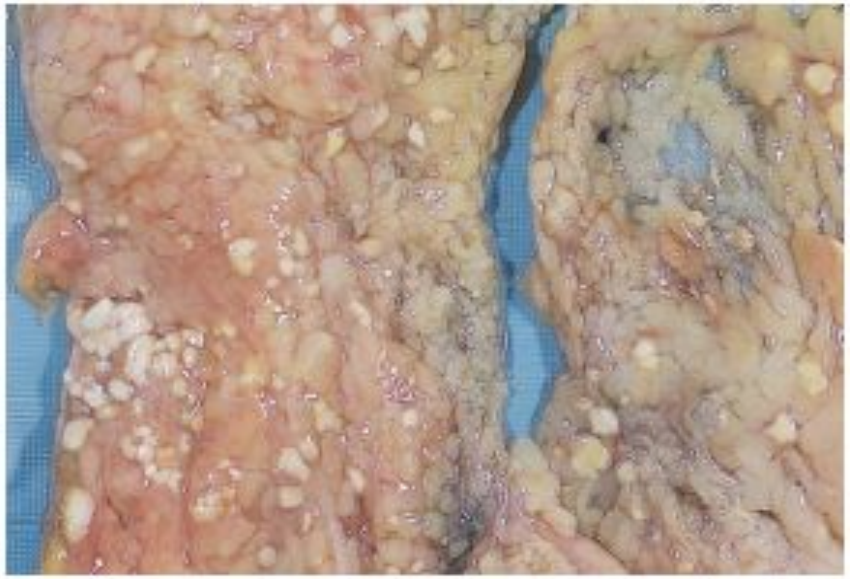


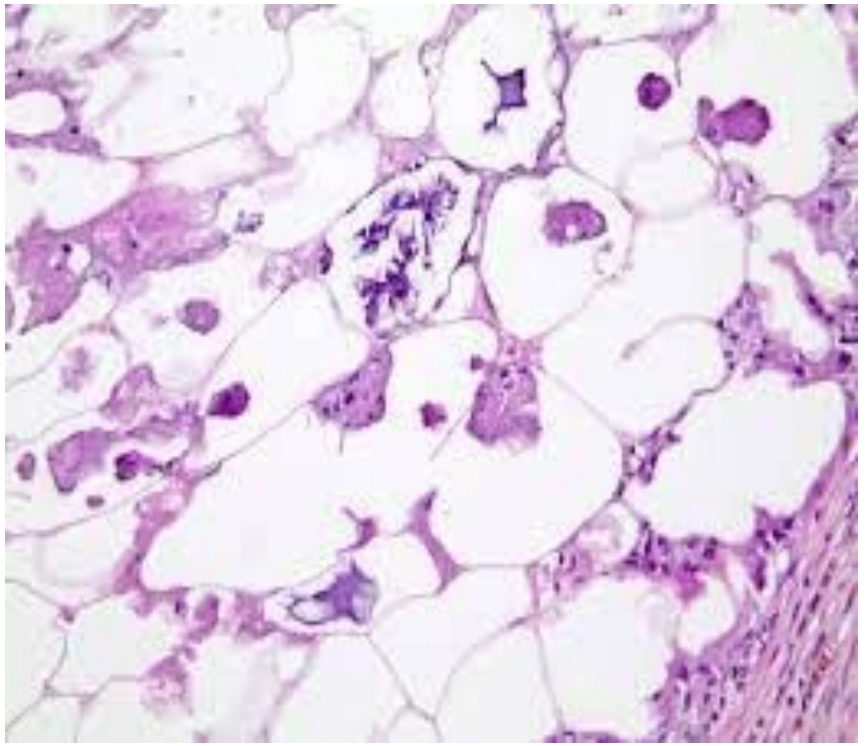
Fat Necrosis

- Focal areas of fat destruction, typically resulting from release of activated pancreatic lipases

- The fatty acids, derived, combine with calcium to produce grossly visible chalky-white areas (fat saponification), which enable the surgeon and the pathologist to identify the lesions

- On histologic examination the necrosis takes the form of foci of shadowy outlines of necrotic fat cells, with basophilic calcium deposits, surrounded by an inflammatory reaction



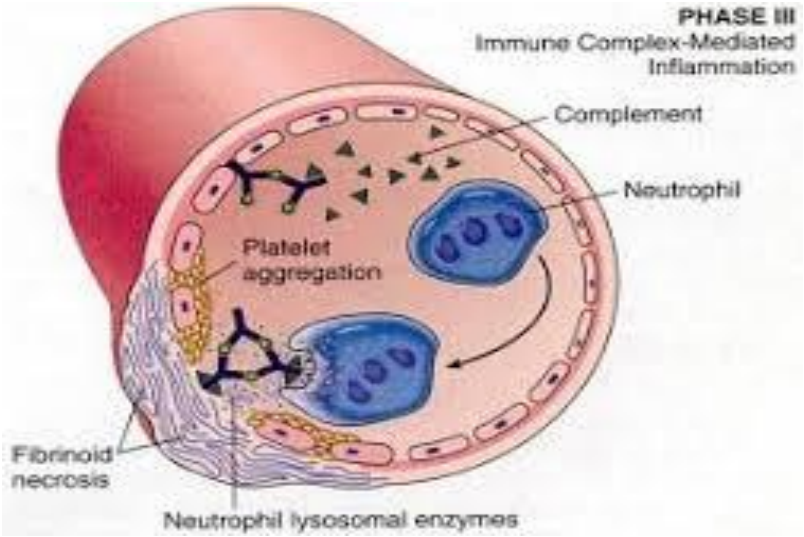


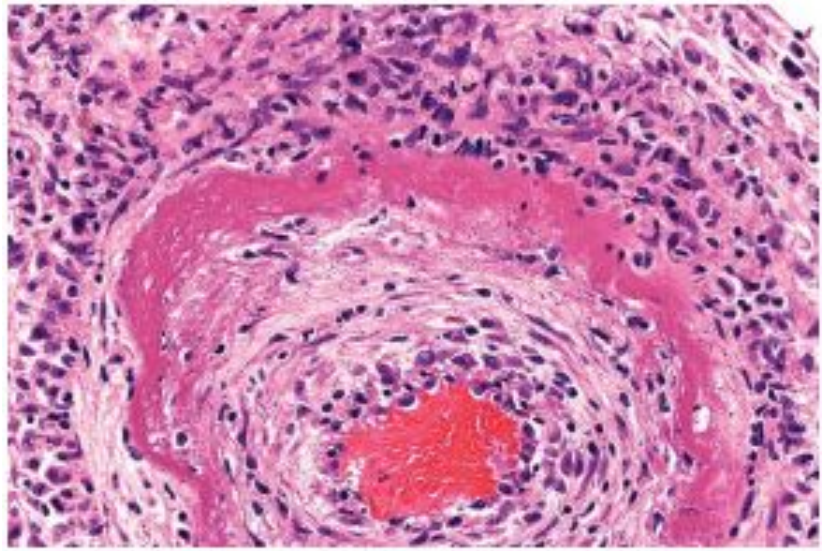
Fibrinoid Necrosis

- It 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





Morphological Types of Necrosis

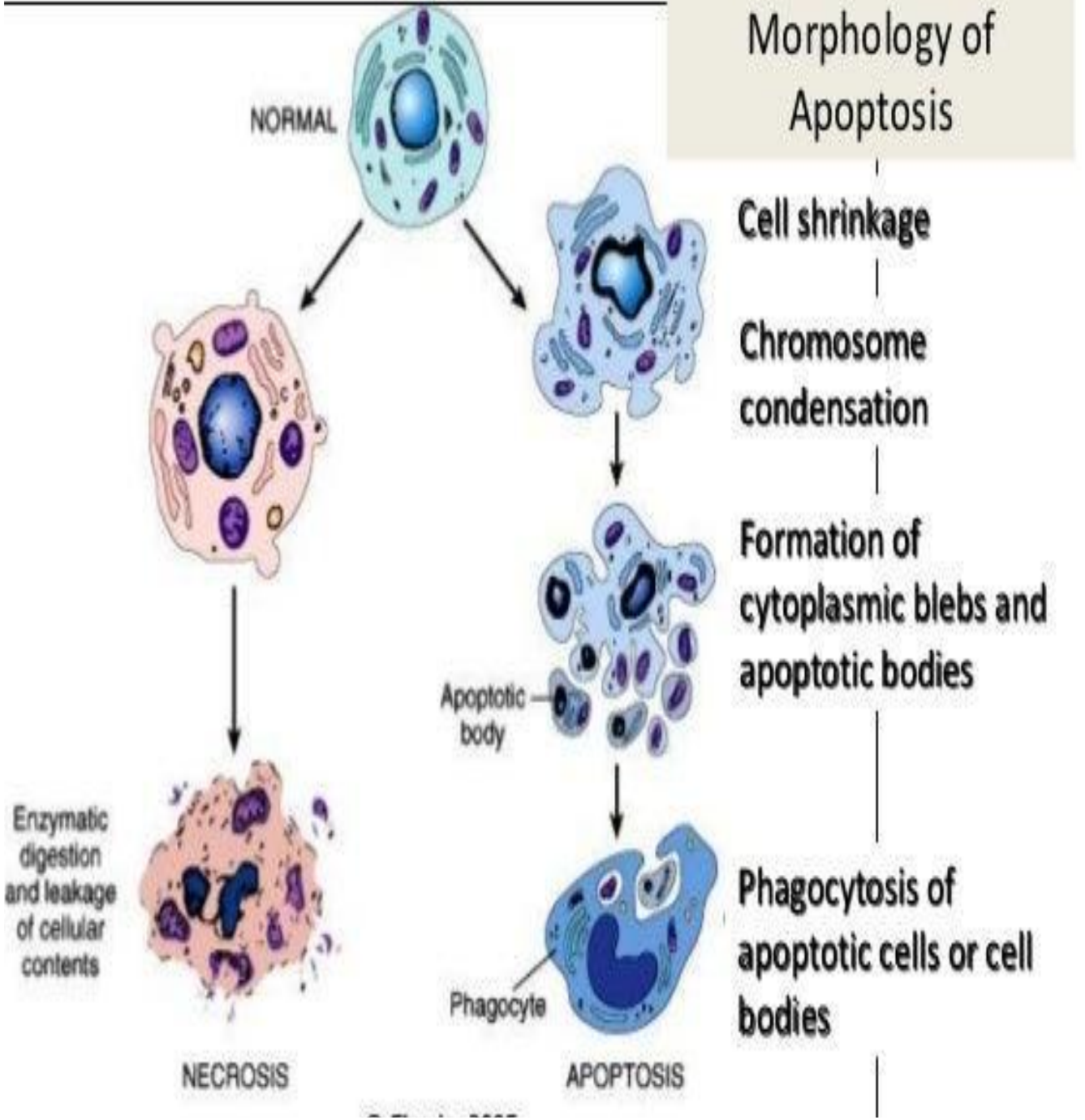
Type	Mechanism	Pathologic Changes
Coagulative necrosis	Most often results from interruption of blood supply, resulting in denaturation of proteins; best seen in organs supplied by end arteries with limited collateral circulation, such as the heart and kidney	General architecture well preserved, exce for nuclear changes; increased cytoplasm binding of acidophilic dyes
Liquefactive necrosis	Enzymatic liquefaction of necrotic tissue, most often in the CNS, where it is caused by interruption of blood supply; also occurs in areas of bacterial infection	Necrotic tissue soft and liquefied
Caseous necrosis	Shares features of both coagulation and liquefaction necrosis; most commonly seen in tuberculous granulomas	Architecture not preserved but tissue not liquefied; gross appearance is soft and cheese-like; histologic appearance is amorphous, with increased affinity for acidophilic dyes
Gangrenous necrosis	Most often results from interruption of blood supply to a lower extremity or the bowel	Changes depend on tissue involved and whether gangrene is dry or wet
Fibrinoid necrosis	Characterized by deposition of fibrin-like proteinaceous material in walls of arteries; often observed as part of immune-mediated vasculitis	Smudgy pink appearance in vascular wall actual necrosis may or may not be presen
Fat necrosis	Liberation of pancreatic enzymes with autodigestion of pancreatic parenchyma; trauma to fat cells	Necrotic fat cells, acute inflammation, hemorrhage, calcium soap formation, clustering of lipid-laden macrophages (in the pancreas)

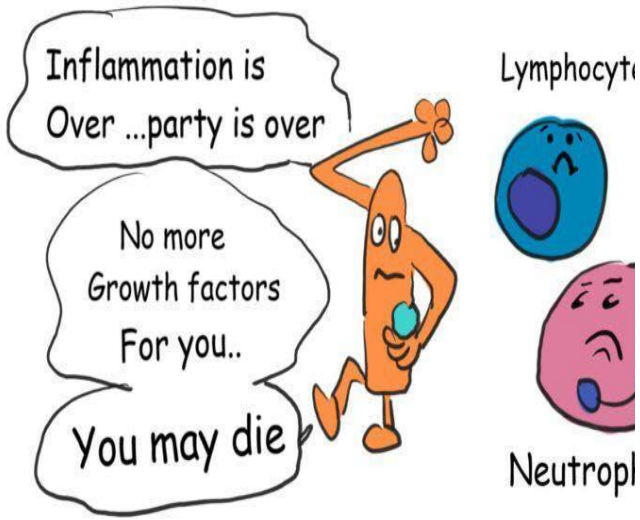
Apoptosis

- Apoptosis induced by a tightly regulated suicide program in which cells destined to die activate intrinsic enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins

- The plasma membrane of the apoptotic cell and bodies remains intact, but its structure is altered in such a way that these become "tasty" targets for phagocytes

- Falling off or Programmed cell death





Lymphocyte

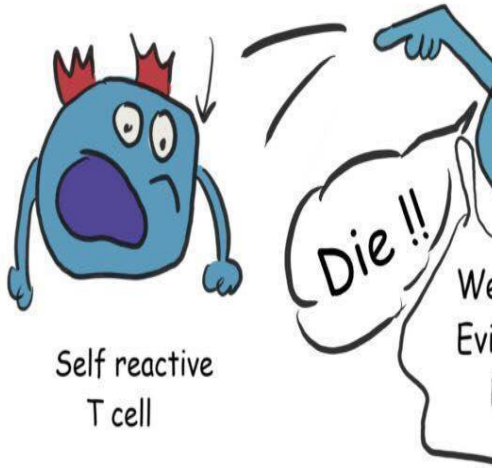
Neutrophil

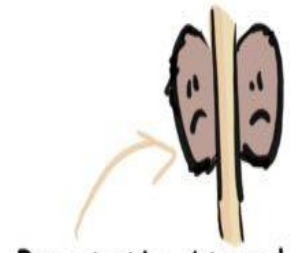
1. After Serving the purpose

2. Self destructive cells

Phy
Cause

Creative-Med-





Prostatic Atrophy

Low estrogen
Low progesterone

Endometrial shedding → Menses

Ovarian atresia

Low estrogen

6. Hormonal

Castration

Menopause

Creative-Med-Doses
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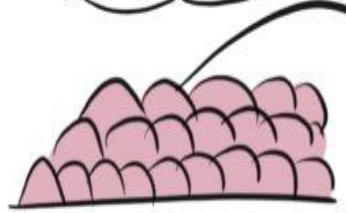
Physiological
Causes of Apoptosis

5. Old cells in highly Proliferating organs

Breasts after weaning

Old cells must die to give space to new cells

No respect for elders
Huh, new generation...



Intestinal Crypt cell

New cell

Old cell

Heat

reased Mitochondrial Permeability

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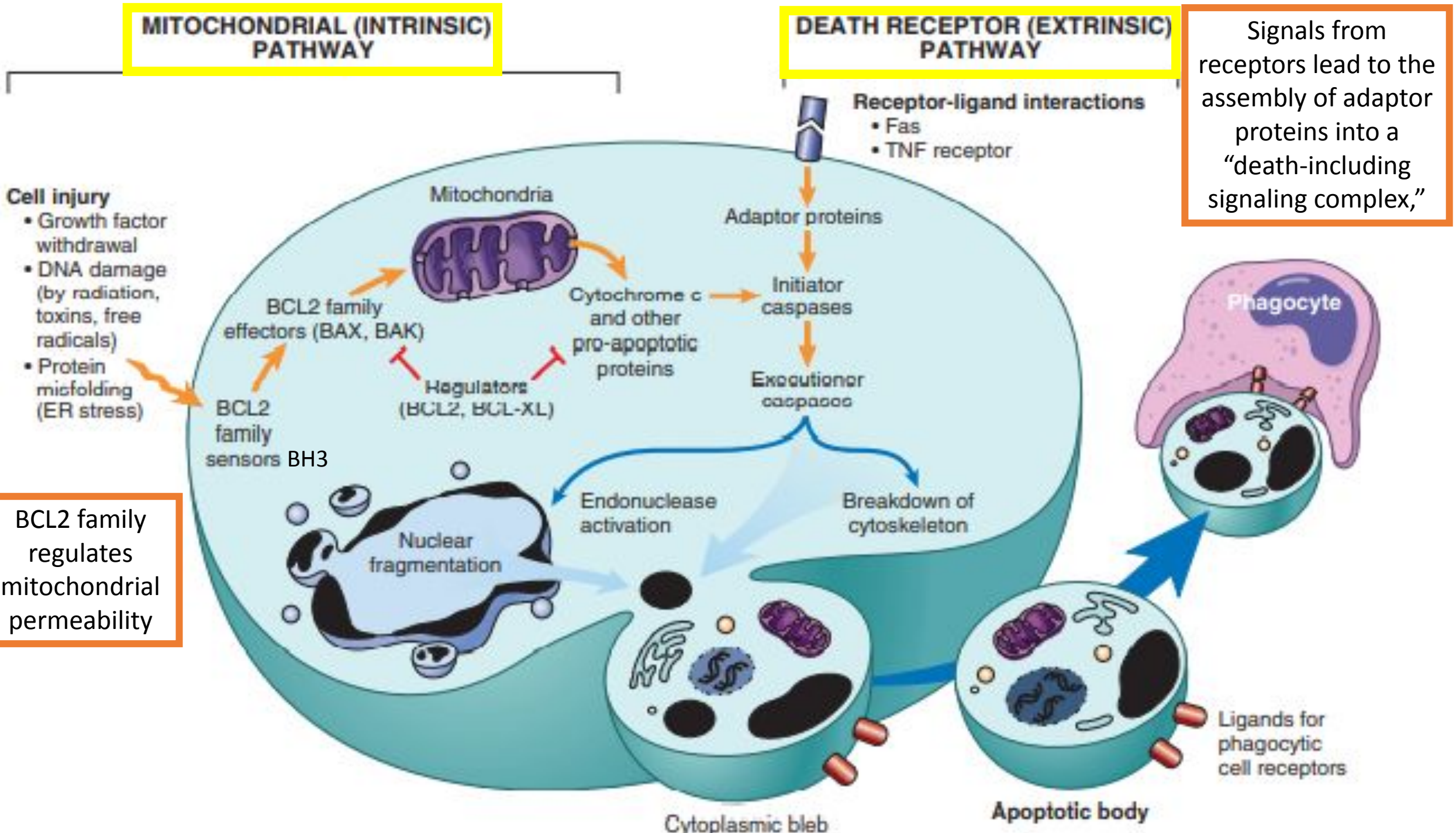
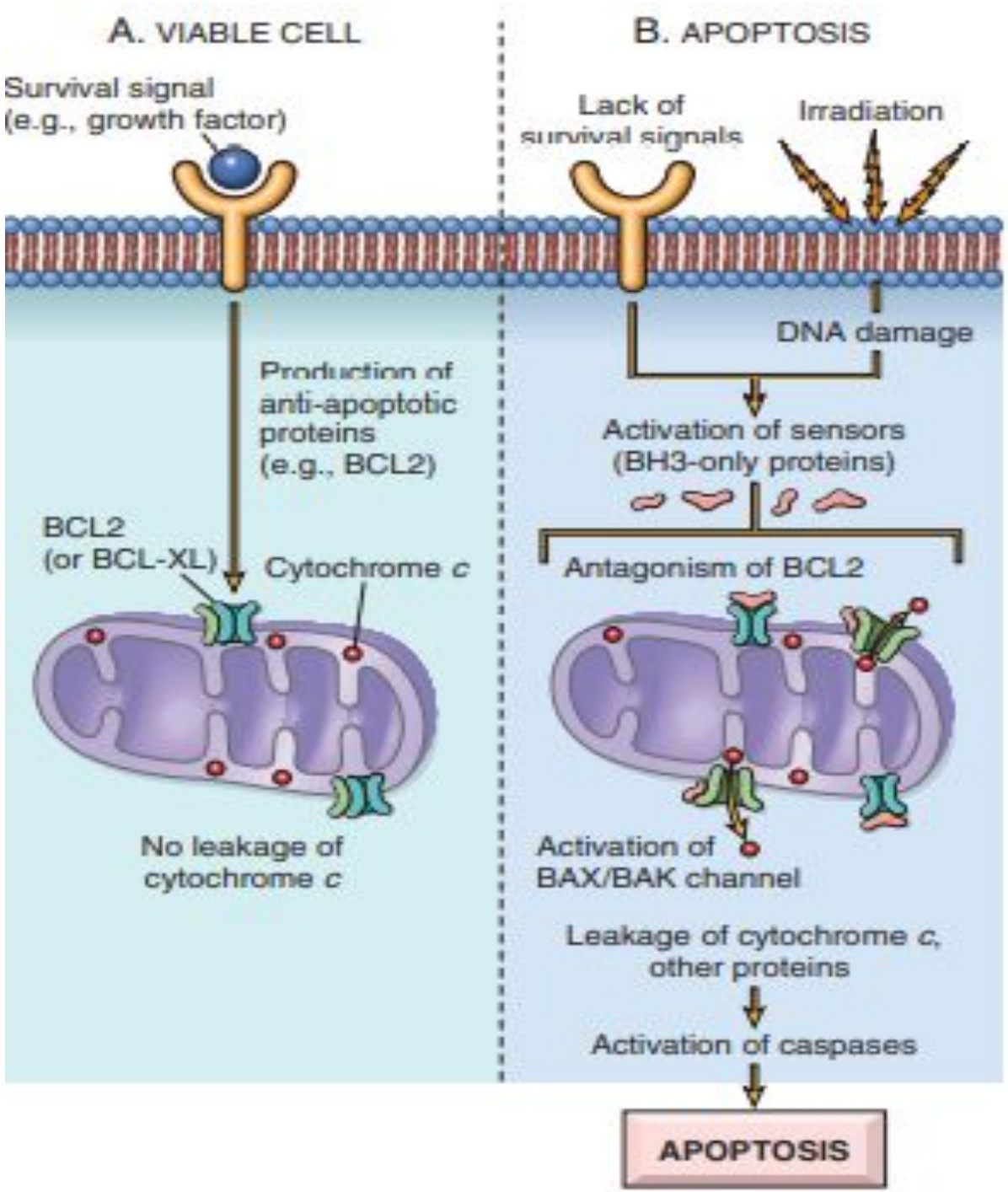


Signals from receptors lead to the assembly of adaptor proteins into a "death-including signaling complex,"

BCL2 family regulates mitochondrial permeability


A. VIABLE CELL
B. APOPTOSIS
Survival signal
(e.g., growth factor)
Lack of
survival signals
Irradiation
DNA damage
Production of
anti-apoptotic
proteins
(e.g., BCL2)
Activation of sensors
(BH3-only proteins)
BCL2
(or BCL-XL)
Cytochrome c
Antagonism of BCL2
No leakage of
cytochrome c
Activation of
BAX/BAK channel
Leakage of cytochrome c,
other proteins
Activation of caspases
APOPTOSIS

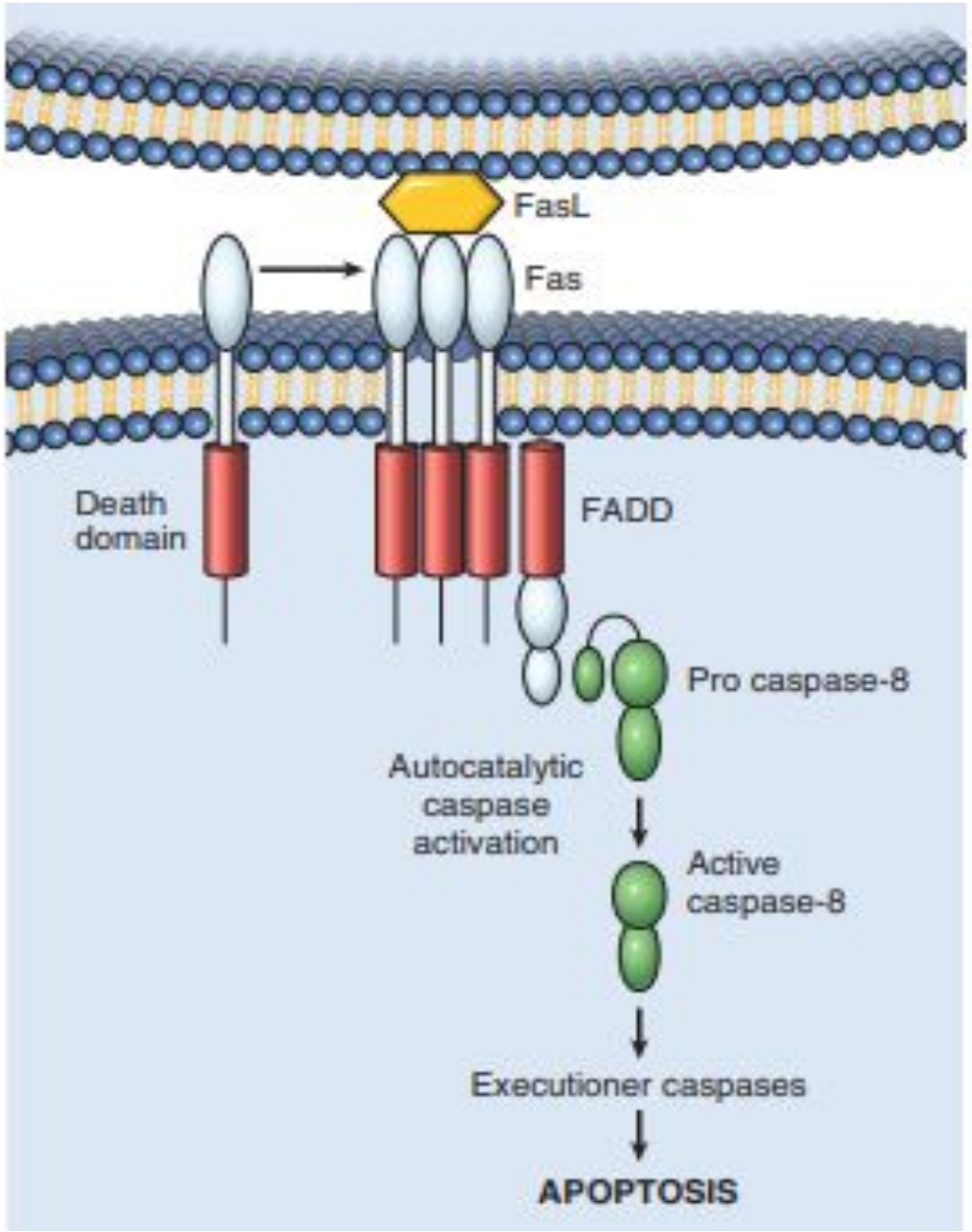
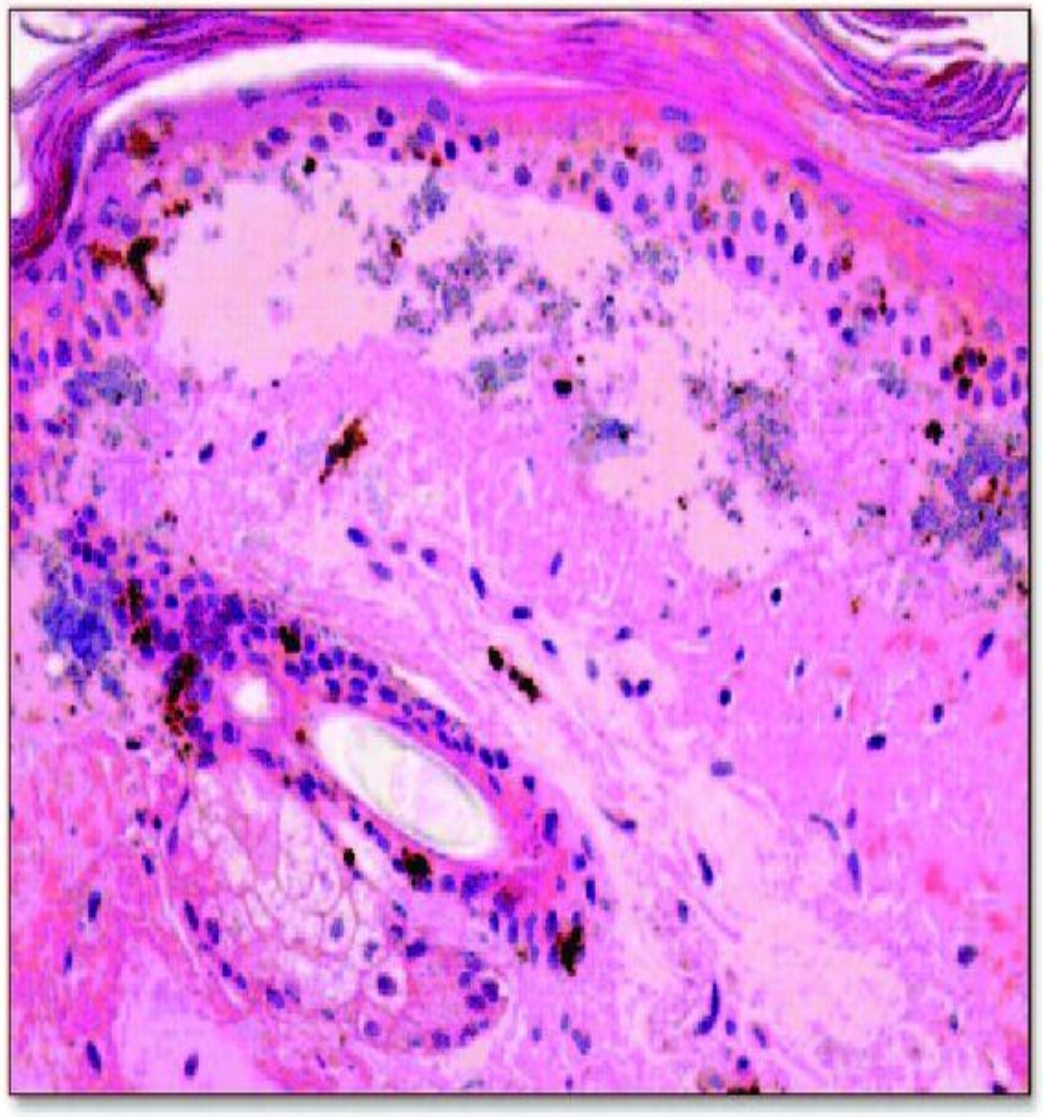
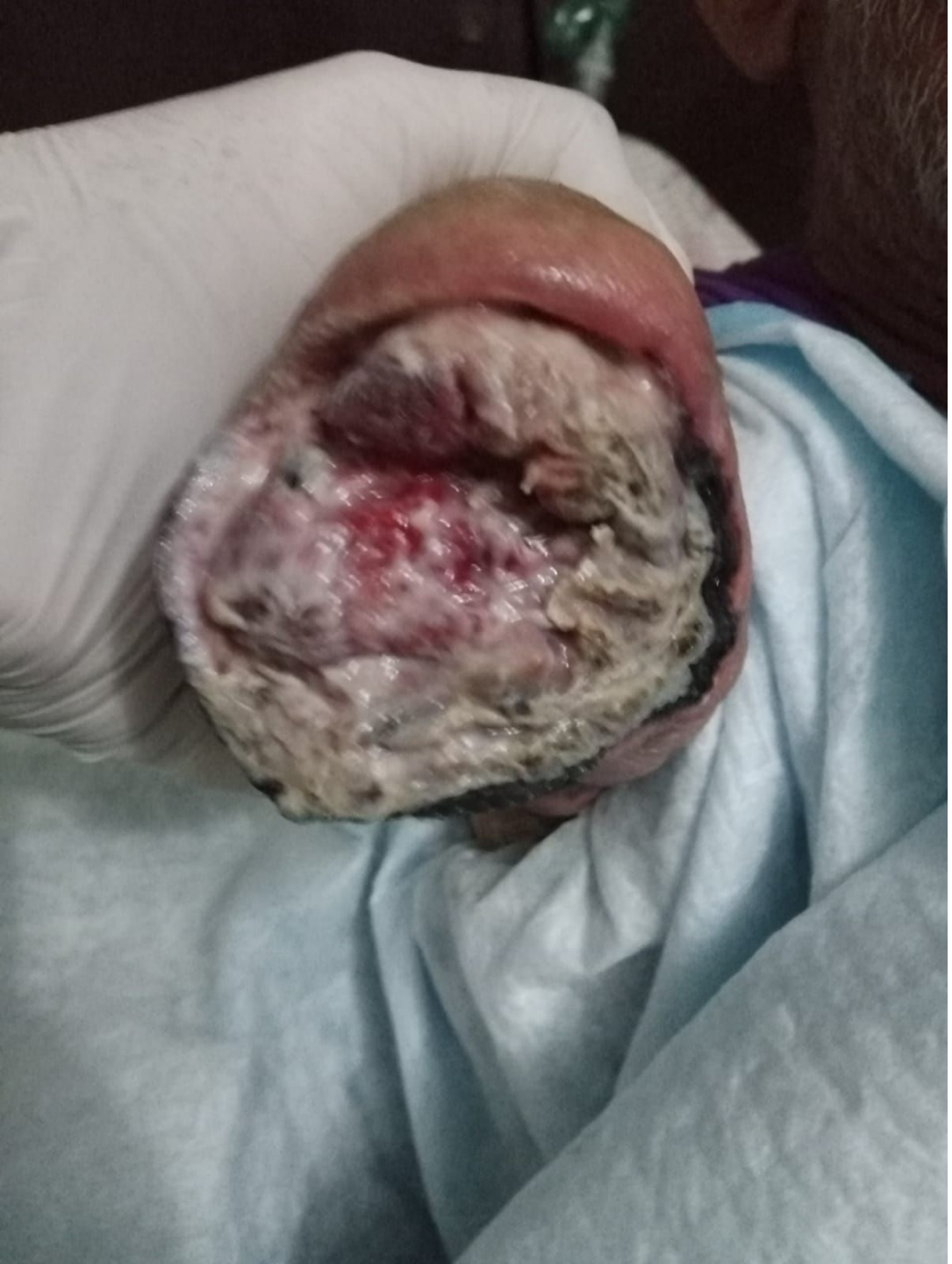

FasL
Fas
Death
domain
FADD
Pro caspase-8
Autocatalytic
caspase
activation
Active
caspase-8
Executioner caspases
APOPTOSIS

Table 2-2 Features of Necrosis and Apoptosis

Feature	
Cell size	
Nucleus	
Plasma membrane	
Cellular contents	
Adjacent inflammation	
Physiologic or pathologic role	

85 years old known diabetic, suddenly developed blackening of right arm





MICROBIOLOGY

Source : PUS CULTURE

Organism Isolated :

Growth of Klebsiella pneumoniae isolated.

Sensivity Medicine	1	2
AMOXIL/AMPICILLIN	R	
AUGMENTIN/AMOX-CLAV	R	
PIPERACILLIN + TAZOBACTAM (TANZO)	R	
CEFOTAXIME/CLAFORAN	R	
CEFTRIOXONE/ROCEPHIN	R	
CEFEXIME/CEFSPAN	R	
CEFEPIME/MAXIPIME	R	
CEFOPERAZONE + SULBACTUM(SULZONE/CEBEC)	R	
MEROPENEM	R	
GENTAMICIN	R	
AMIKACIN	R	
POLYMYXIN B	S	
TIGECYCLINE	S	
COLISTEN	S	

Remarks :

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Which of the following is a characteristic feature of apoptosis?

A. Cell swelling
B. Plasma membrane rupture
C. Inflammation in surrounding tissue
D. Formation of apoptotic bodies
E. Random DNA degradation

The most common type of necrosis seen in ischemic infarction of solid organs (except brain) is:

A. Liquefactive necrosis
B. Fat necrosis
C. Coagulative necrosis
D. Caseous necrosis
E. Fibrinoid necrosis

Which enzyme group plays the central role in apoptosis?

A. Lysozymes
B. Caspases
C. Catalases
D. Phospholipases
E. Kinases

Liquefactive necrosis is most commonly associated with:

A. Myocardial infarction
B. Tuberculosis
C. Brain infarction
D. Fat trauma
E. Autoimmune vasculitis

Which of the following is TRUE regarding necrosis?

A. It is always a programmed process
B. Cell membrane integrity is preserved
C. It does not induce inflammation
D. It is associated with ATP depletion
E. DNA fragmentation is orderly

Intrinsic pathway of apoptosis is primarily triggered by:

A. Death receptors (Fas–FasL interaction)
B. Complement activation
C. Mitochondrial cytochrome c release
D. Neutrophil enzymes
E. Bacterial toxins

Fibrinoid necrosis is typically seen in:

A. Viral infections
B. Immune-mediated vascular damage
C. Brain infarction
D. Pancreatitis
E. Hypoxic liver injury

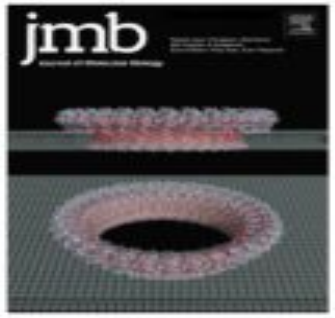
Q- What happens if there is defective apoptosis and increased cell survival?

Cancer/Autoimmune disorders

Q- Name conditions with increased apoptosis and excessive cell death ?

Neurodegenrative disorders/Ischemic cell injury/death of virus infected cells

Additional Read



Apoptosis, Pyroptosis, and Necroptosis—Oh My! The Many Ways a Cell Can Die

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https://doi.org/10.1016/j.jmb.2021.167378
Edited by Shao Feng

Abstract

Cell death is an essential process in all living organisms and occurs through different mechanisms. The three main types of programmed cell death are apoptosis, pyroptosis, and necroptosis, and each of these pathways employs complex molecular and cellular mechanisms. Although there are mechanisms and outcomes specific to each pathway, they share common components and features. In this review, we discuss recent discoveries in these three best understood modes of cell death, highlighting their singularities, and examining the intriguing notion that common players shape different individual pathways in this highly


"We all die. The goal isn't to live forever, the goal is to create something that will"
- Chuck Palahniuk

Thank