2

Doctor 2021 - رَوْح - medicine - MU

pathology sheet

Doctor :

Dr. Bushra Tarawneh

DONE BY:

Ahmad Kamal

Hiba Makkawi

Manar Abdullah

Obaida Abusaif

corrected BY:

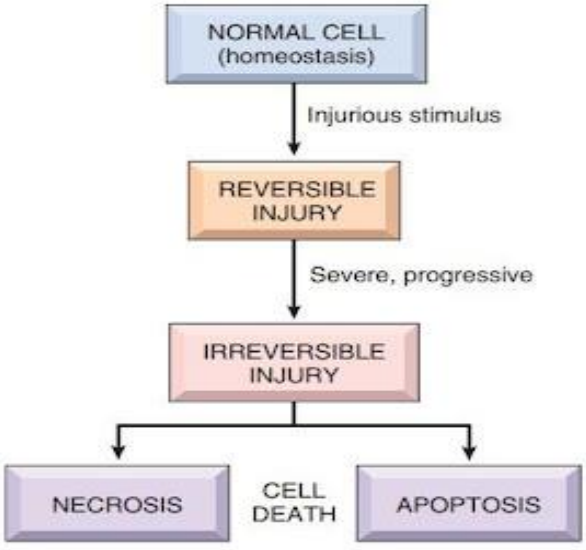
Shaimaa Ababneh

Long duration, rapid onse

Necrosis: Type of cell death caused by accidental process associated with inflammation

Always due to pathological conditions

Apoptosis: Programmed cell death regulated by specific enzyme or process, not associated with inflammation



-Cell Death:

- **Injured cells die by different mechanisms, depending on the nature & severity of the insult:**

- ***SEVERE DISTURBANCES*** **(loss of oxygen & nutrient supply or toxins) cause *a rapid* & uncontrollable form of death, *called "accidental"* cell death because injury is too *severe* to be repaired ☐ *Necrosis.***

"Accidental" ⟶ ***not regulated*** **by specific signals or *biochemical mechanisms or molecular pathway .***

- **In less severe injury, or cells need to be eliminated during normal processes ☐ activate a precise set of molecular pathways ☐ culminate in death ⟶**
  Apoptosis (programmed cell death)

-

☠ Distinguish between apoptosis VS necrosis according to functional ,mechanism ,causes & another main different

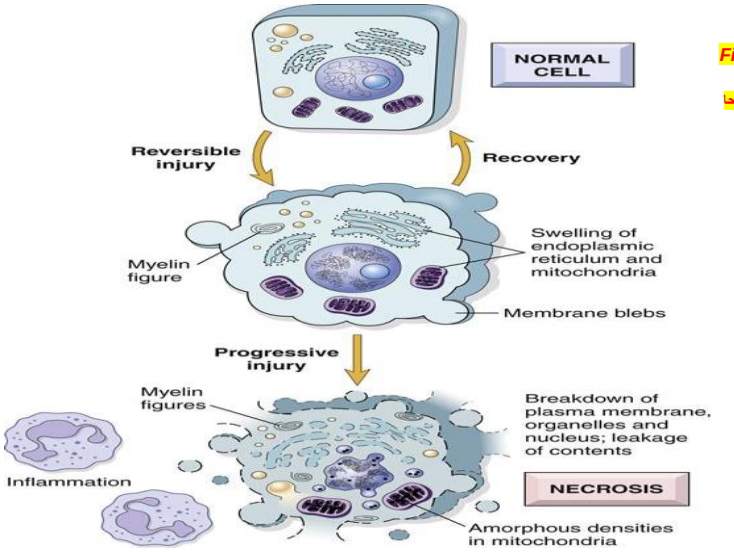
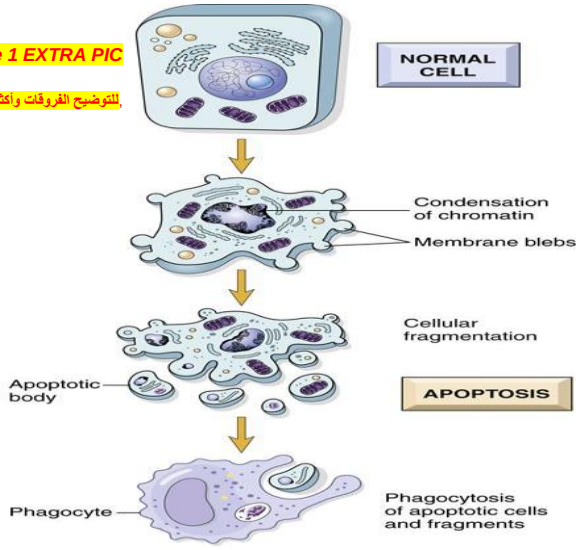
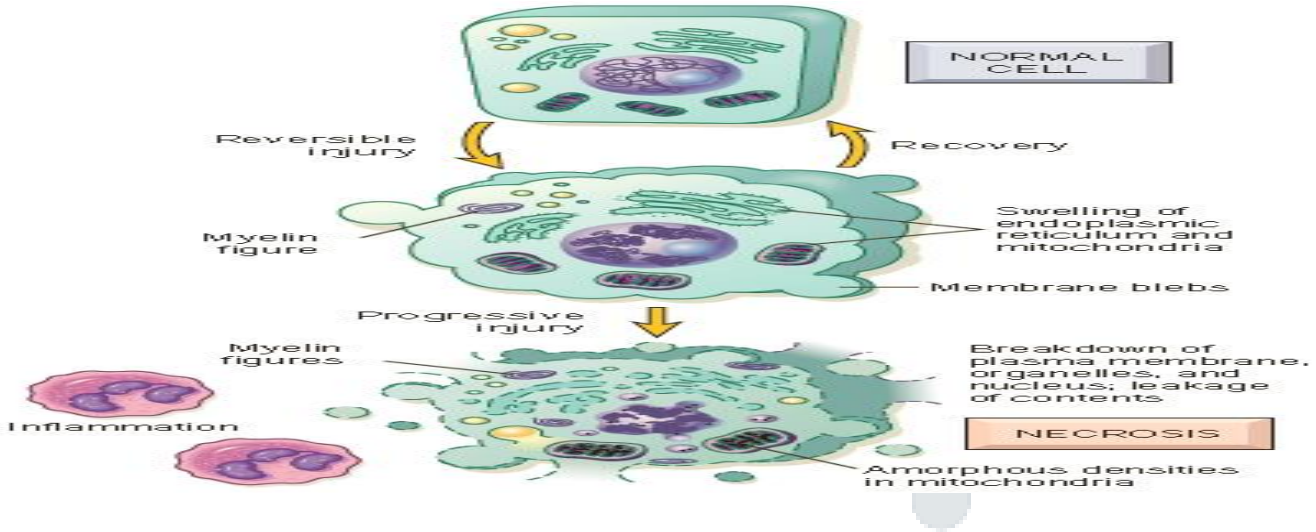


Figure 1 EXTRA PIC

للتوضيح الفروقات وأكثر وضوحا





-Necrosis:

- **A form of cell death in which *cellular membranes fall apart*, and cellular enzymes leak out and ultimately**
- **digest the cell.**
- **A sequence of morphologic changes that follow cell death in living tissue. First normal appearance, then ultrastructural changes and finally grossly changes.**
- **often is the culmination or accumulation of reversible cell injury that cannot be corrected.**
- **elicits a local host reaction, inflammation.**
- **We see neutrophils in acute inflammation**
- **We see macrophage in chronic one**
- **So always necrosis associated with local host macrophage ,neutrophils &lymphocyte**

These neutrophils approve this is necrosis

- ***Microscopic appearance of Necrotic dead cells:***
- ***Cytoplasmic***
- ***Nuclear***
- **- Eosinophilia: stained red by the dye eosin—the E in [H&E] stain)**

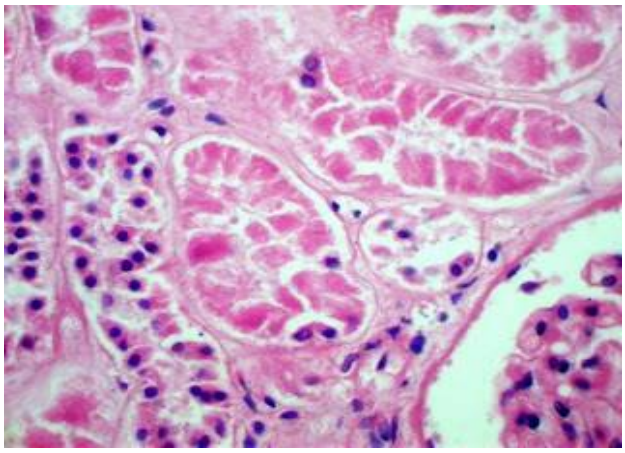
Cytoplasm stained with eosin

- **- Basophilia: stained blue by the dye hematoxylin—the H in [H&E] stain)**

Chromatin stained by hematoxylin so nucleus appears blue with this dye

The aim of stain H & E determine the type of cell component to know a normal histological so you can diagnosis the disease

-Microscopic appearance of Necrotic cell: Cytoplasmic



<Changes of cytoplasm>

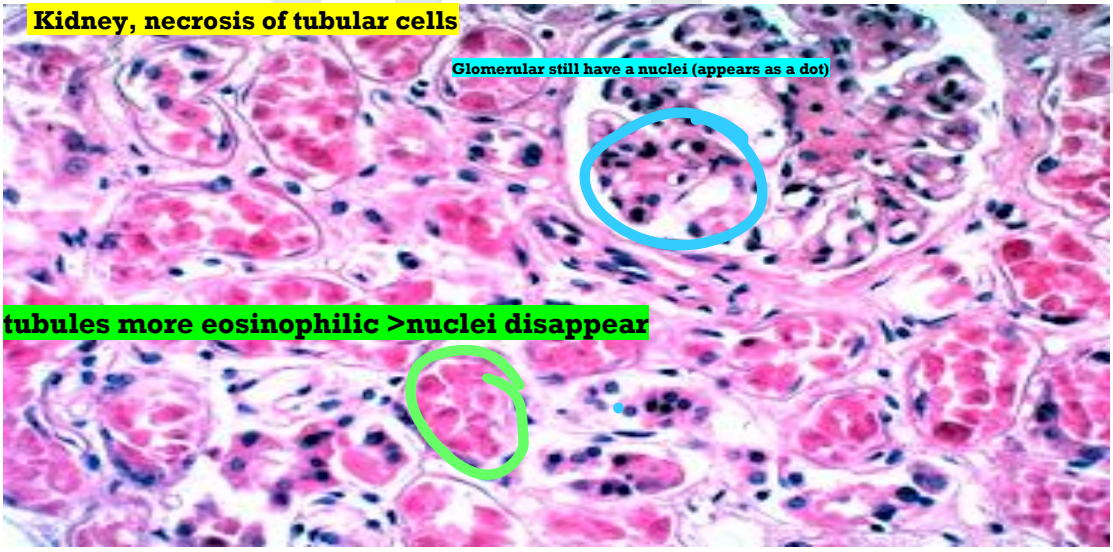
☠ **Increased eosinophilia why? attributable to:**
+increased binding of eosin to denatured cytoplasmic proteins:
Be more red

☠ **loss of basophilic ribonucleic acid (RNA) in the cytoplasm.**

- **A glassy, homogeneous appearance, mostly because of the loss of lighter staining glycogen particles.**
- **Cytoplasm vacuolated & appears "moth-eaten "; due to enzymes.**

☠ **Q type: All of the following are correct from the cytoplasmic changes in necrosis cell death except:**

A. increased binding of eosin to natured cytoplasmic proteins احد)
الخيارات)

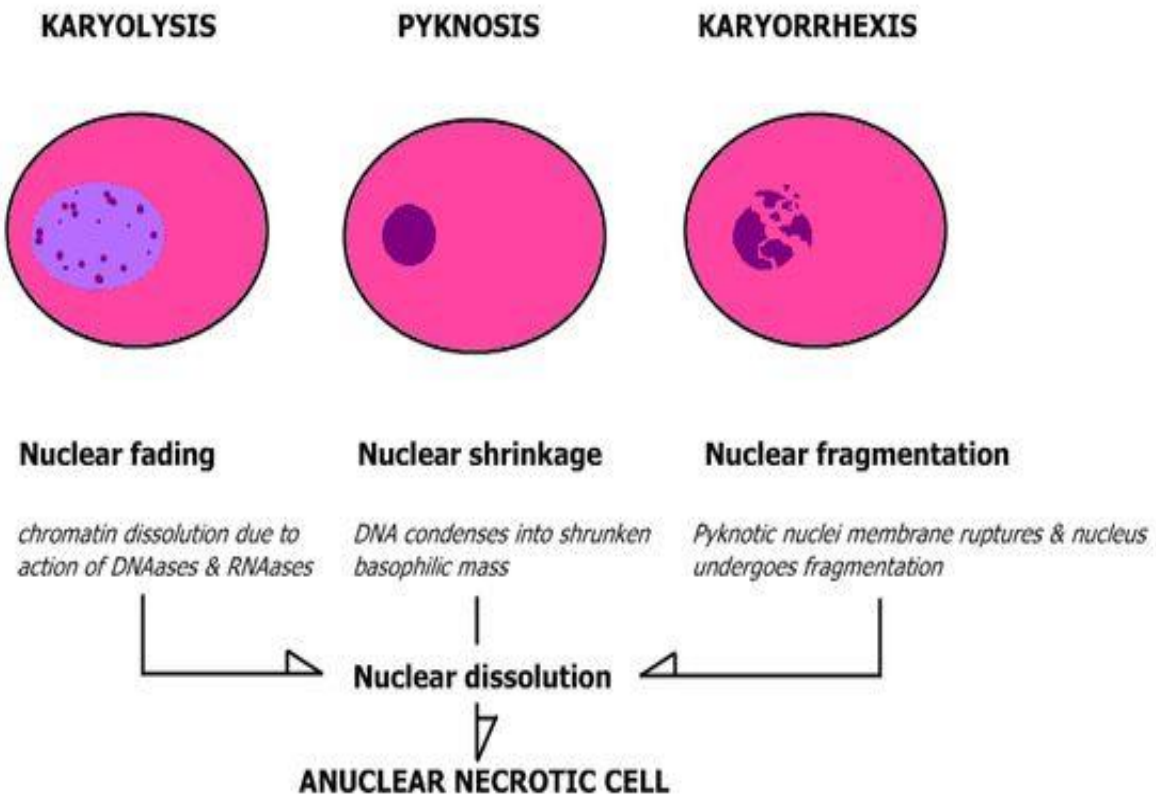


-Microscopic appearance of Necrotic cell: Nuclear

Nuclear changes □ **due to break down of DNA; three patterns**

- ***Pyknosis*: shrinkage and increased basophilia.**
- ***Karyorrhexis:* fragmentation of pyknotic nucleus.**
- ***Karyolysis*: decrease basophilia of chromatin,**
  DNase: (deoxyribonuclease, DNA digestion)

In 1-2 days the nucleus in a dead cell may completely disappear.



➔ **Pyknosis: chromatin clustered more, dark &dense appears so cause increased in basophile**
➔ **Karyorrhexis: slicing chromatin so fragmentation of nucleus**
➔ **Karyolysis: raptured the chromatin**

☠ **Pay attention, very important**

-Specific Morphologic Patterns (Types) of Necrosis:

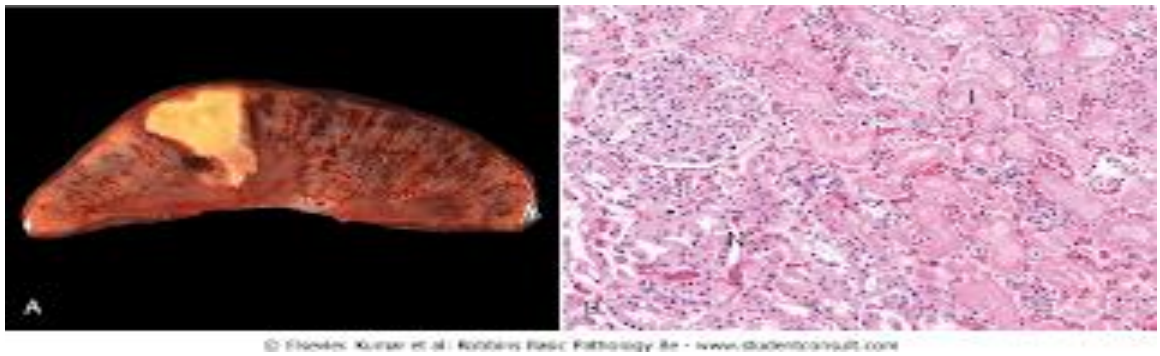
- **Coagulative necrosis**
- **Liquefactive necrosis**
- **Gangrenous necrosis**
- **Caseous necrosis**
- **Fat necrosis**
- **Fibrinoid necrosis**

Coagulative necrosis:

- **Preservation of the structural outline of the dead (*coagulated*) cell for days**
- **The *most common* form of necrosis (particularly in myocardium, liver, kidney)**
- **Characteristic of infarcts (areas of necrosis caused by ischemia) in all solid organs *except the brain.***
- **Mechanism*: denaturation* of proteins & enzymes blocking cellular proteolysis preserve cell outline.**

☠ **Caused by ischemia**

Proteins and enzymes are the reason behind destroy cell membrane, but in this case both parties and enzymes are denatured so this lead to preserve cell membrane



A: Well demarked area, blockage of blood supply to this area

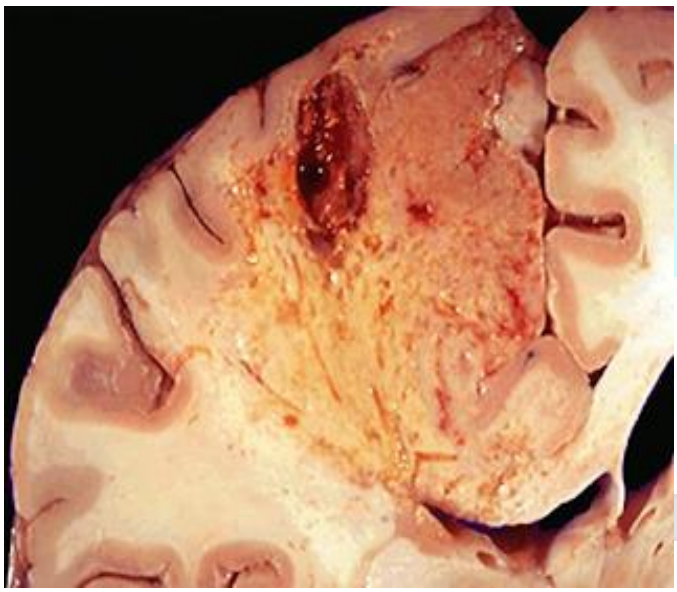
leads to necrosis

B: Observed glomeruli , ghost cells "Nuclear with high eosinophilic cytoplasm

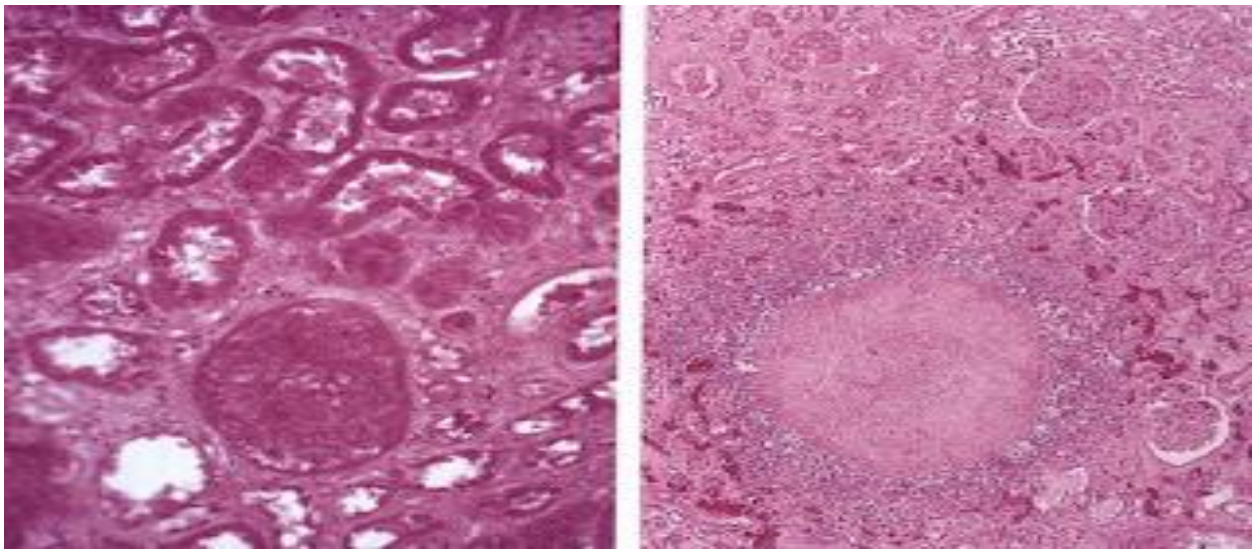
- **Cytoplasmic & nuclear changes. However cell membrane is still intact (موضع سؤال)**
- **Cab be occurred in any type of cell body except brain (موضع سؤال)**

Liquefactive necrosis:

- **Typically, in brain**



- **Focal bacterial and fungal infections.**
- **Hypoxic & death of cells within the central nervous system.**
- **Microbes -rapid accumulation of inflammatory cells-enzymes of leukocytes digest ("liquefy") the tissue.**
- **If acute infection - creamy**



yellow & is called pus

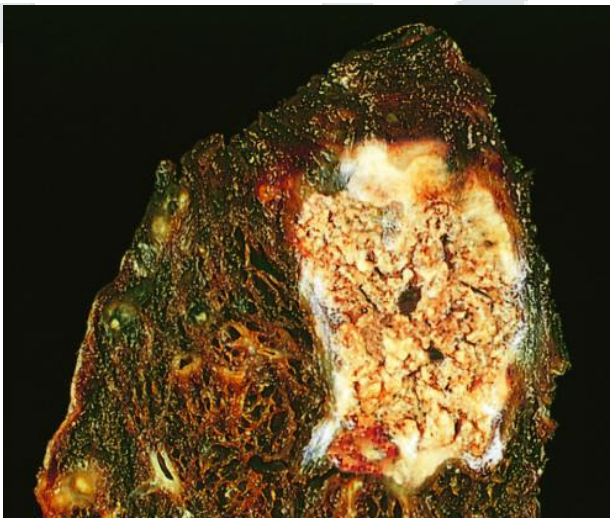
Inflammatory cells

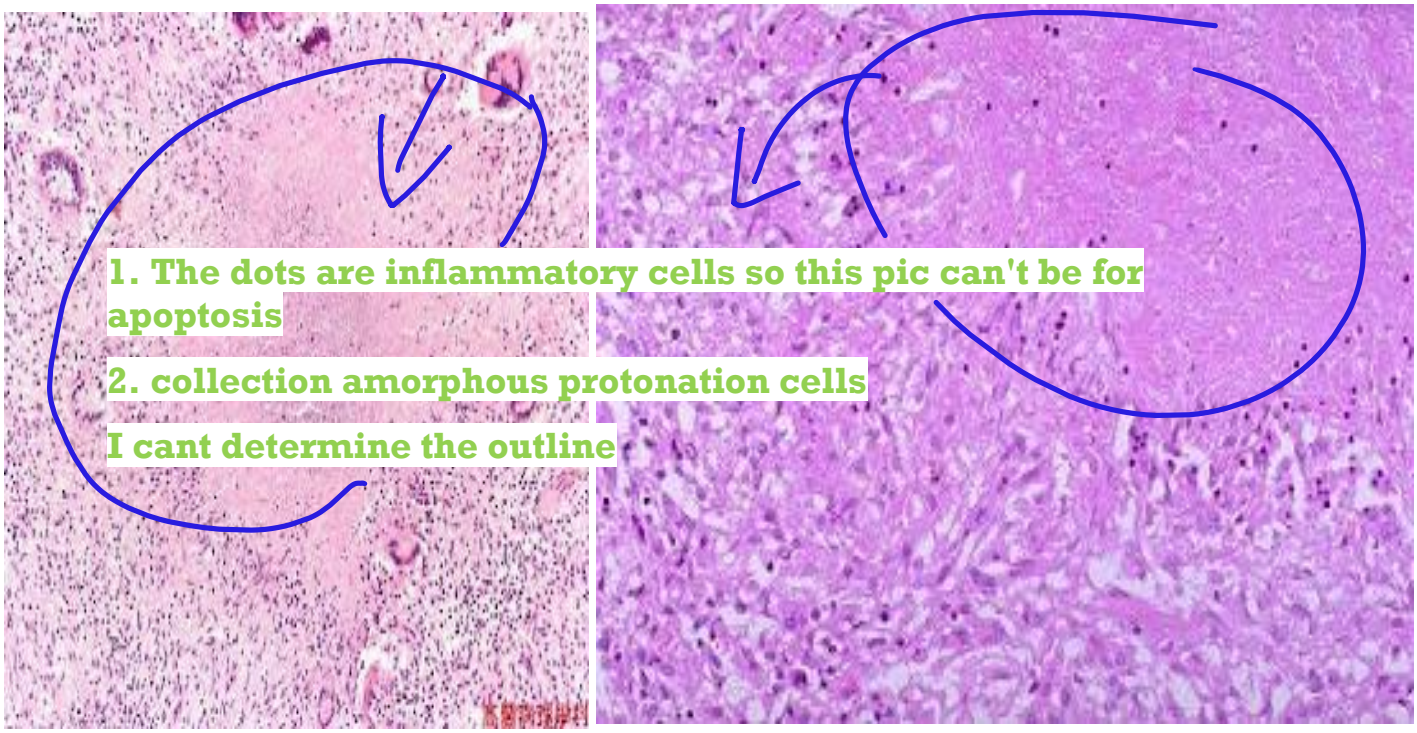
-Caseous Necrosis:

- Most often encountered in foci of tuberculous infection. TB starts in lung (multiple nodules in lung)
- Caseous means "cheese like" : friable yellow-white appearance of the area of necrosis on gross examination.

Microscopic examination:

- A collection of fragmented or lysed cells with an amorphous granular pink appearance.
- Architecture -completely obliterated, cellular outlines- cannot be discerned We can't see cell membrane of each cell
- Surrounded by a collection of macrophages and other inflammatory cells; this is called a granuloma
- Caused this one associated with chronic inflammation





-Fat necrosis:

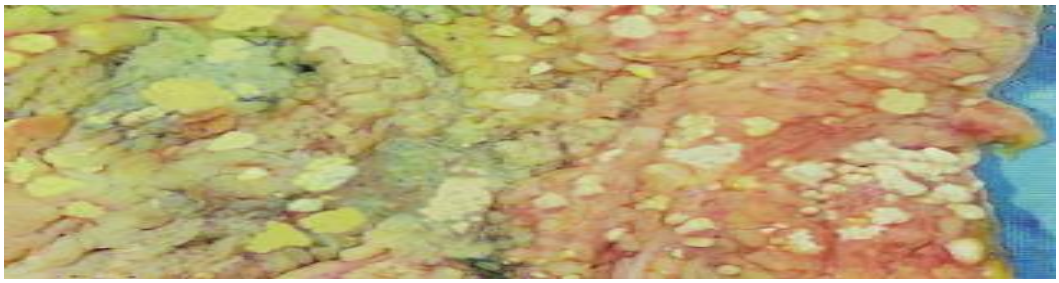
- **Fat destruction.**
- **the release of activated pancreatic lipases (Digestive enzymes lead to district of adipocytes) into the substance of the pancreas and the peritoneal cavity((Made from CA and adipose tissue) Acute pancreatitis) : Diagnosed by salt appearance on peritoneal cavity**
- **lipases +adipose tissue = cleaves triglycerides = fatty acids**
- **fatty acids bind and precipitate calcium ions, forming in soluble salts.**

***Adipocytes in microscope appears with extrinsic nucleus**

These salts look:

+chalky white on gross examination.

+ basophilic in histological sections stained with H&E

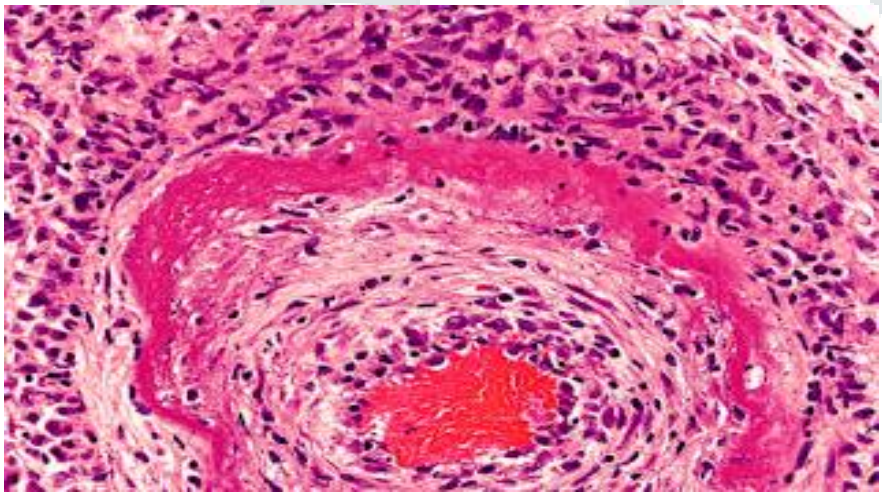


-Fibrinoid necrosis:

- **In immune reactions: complexes of antigens and antibodies are deposited in the walls of blood vessels.**
- **Severe hypertension.**
- **Deposited immune complexes and plasma proteins that leak into the wall of damaged vessels produce a bright pink, amorphous appearance**

Cause vasculitis

A bright pink, amorphous appearance on H&E preparations called fibrinoid (fibrin-like) by pathologists.



-Gangrenous necrosis:

- **Not a distinctive pattern**

- **Commonly used in clinical practice.**
  - **Usually refers to the condition of a limb (generally the lower leg) lost blood supply *coagulative necrosis* involving multiple tissue layers.(ischemia)**
-
- **Bacterial infection is superimposed *liquefactive necrosis* because of the destructive contents of the bacteria & the attracted leukocytes (resulting in so-called "wet gangrene").**
  - ✓ **Wet gangrene: coagulative necrosis with bacterial infection**

*Fate of Necrosis:

- **Most of necrotic tissue is removed by leukocyte (Phagocytosis) combined with extracellular enzyme digestion**
- **If necrotic tissue is not eliminated it attracts Ca^{++} salts dystrophic calcification (Unwanted)**

Chorionic inflammation most of them go to the dystrophic calcification

Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a means of detecting tissue-specific necrosis using blood or serum samples:

- **Cardiac muscle, isoform of creatine kinase & troponin.**
- **Hepatic bile duct epithelium, enzyme alkaline phosphatase,**
- **Hepatocytes contain transaminases**

-After destroying cells some enzymes will leak out to blood stream and consider a sign of information

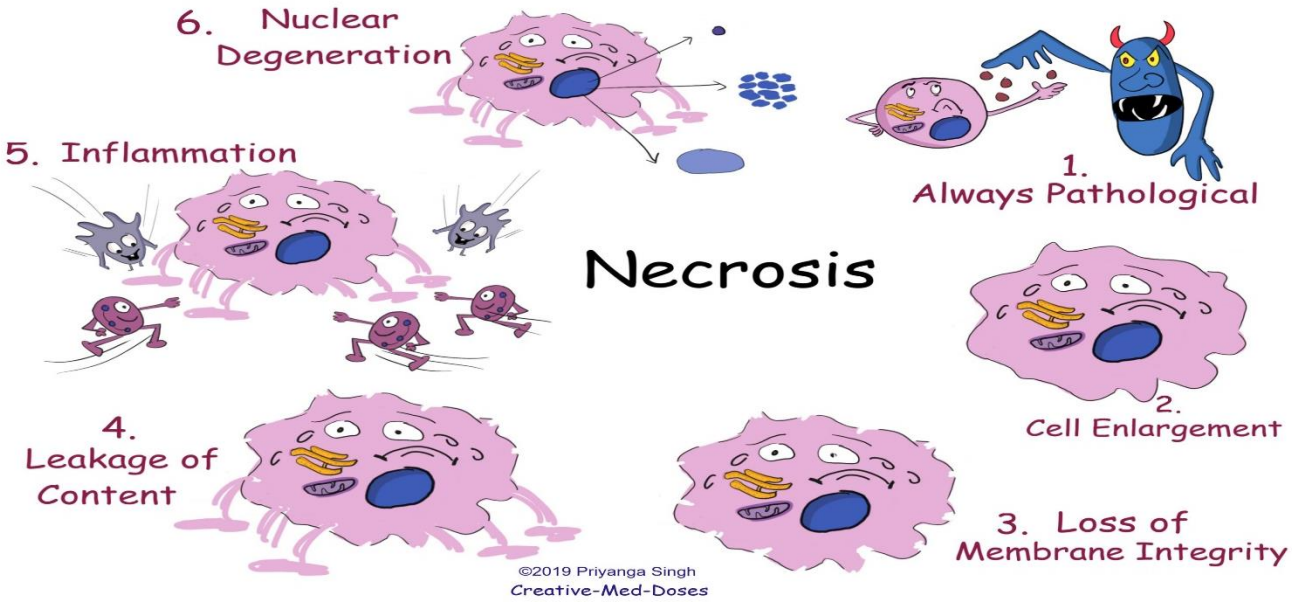
-We use liver function test to measure enzyme amount so any

damage of cells could be associated with leakage of specific enzyme or protein

Q asked from the doc:

1) **Which type of necrosis associated with salt deposit? Fat necrosis**
2) **Which of the following associated with immune complex deposit? Fibrinoid**

3) **Which of the following associated with TB? caseous**
4) **Which type of necrosis majorly associated with brain? Liquefactive**
5) **which consider bacterial infection? Pus**



Necrosis

EXTRA PIC

TO REVISION

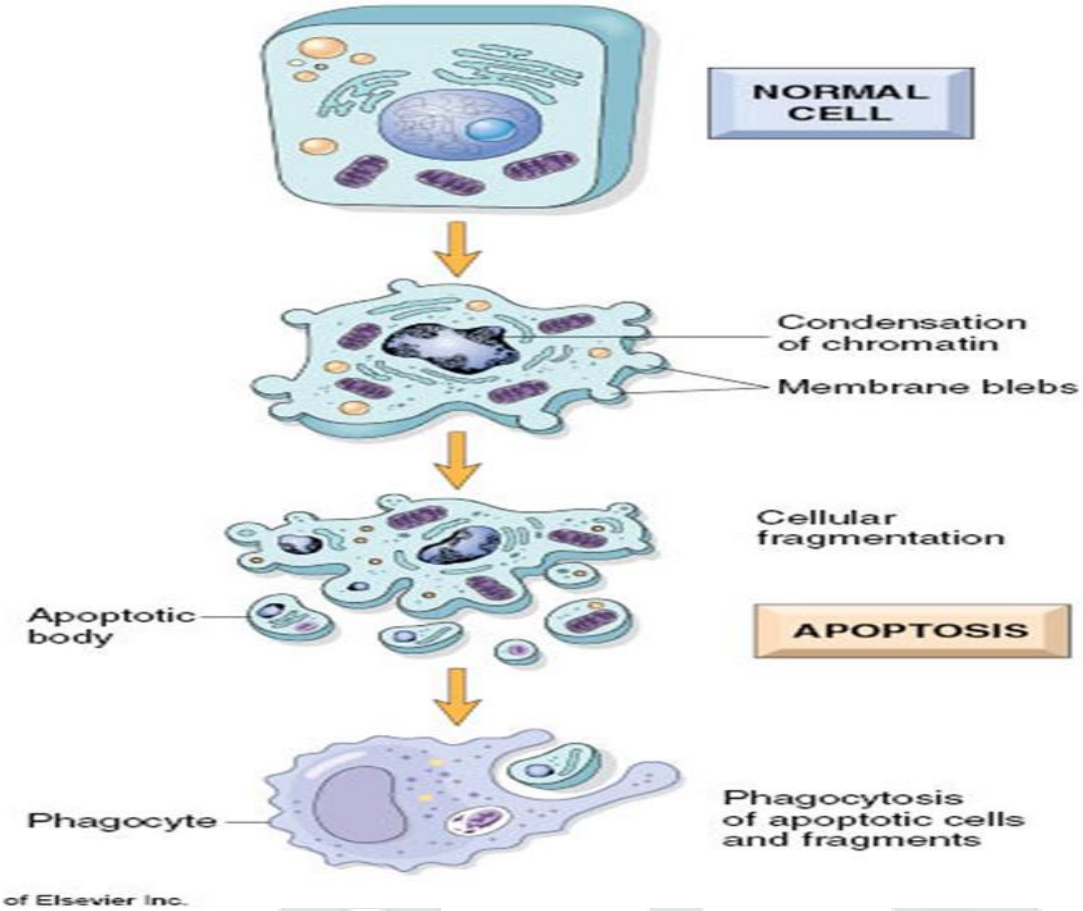
	Example	Histology	
Coagulative	Ischemia	Eosinophilia	Coagulation
Liquefactive	Abscesses	Neutrophil & debris	Liquid-factive
Caseous	TB & Fungi	Lymphocytes & macrophages	Cheese-eous
Fat	Pancreatitis	Saponification/Ca++	Fat
Fibrinoid	Vasculitis	Fibrin thickening	N/A
Gangrenous	Foot ulcers	Coag + Lique	Gangrene

-Apoptosis:

- **Apoptosis - suicide - programmed cell death- regulated cell death.**
- **is a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.**
- **Apoptosis = "falling off" Greek**
- ***Can be pathologic and physiologic***
- **Doesn't elicit inflammation.**
- **Apoptotic body: each contains nuclear fragment or cytoplasmic**

component and show a ligand for phagocytosis

- Finally, this apoptotic body eliminate



of Elsevier Inc.

- The adaptation of uterus is hypertrophy & hyperplasia they back to normal structure *by APOPTOSIS*
- During to a INDIDVIDUAL CELL by its own enzyme

Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways

Turn over; stomach every 2-5 day turn over to all mucosal lining of the stomach to prevent ruptured of stomach wall by → acid

{must have criteria to proliferative, rate of return, a capacity of cell to live for specific period)

RBC everyday synthesis but every 120 days is destroyed

During embryogenesis (implantation, organogenesis, developmental involution, separation of digits in limb development) **regulated by** apoptosis

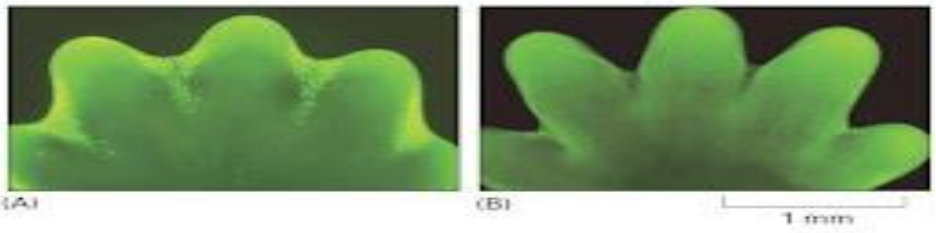


Figure 16-19 Essential Cell Biology, 2/e. (© 2004 Garland Science)

adult multicellular organisms cell death is a regular occurrence. In humans EACH HOUR!

Can be pathologic:

Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

- **Bacterial infections cause Necrosis**
- **Viral infections cause Apoptosis**

- The plasma membrane ***remains intact.***
- Apoptotic bodies (contain portions of the cytoplasm and nucleus) become **targets for phagocytosis** before their contents leak out.
- Normally, there is **a biochemical pathways that control** the balance of death- and survival-inducing signals..

Apoptosis is regulated by these pathways

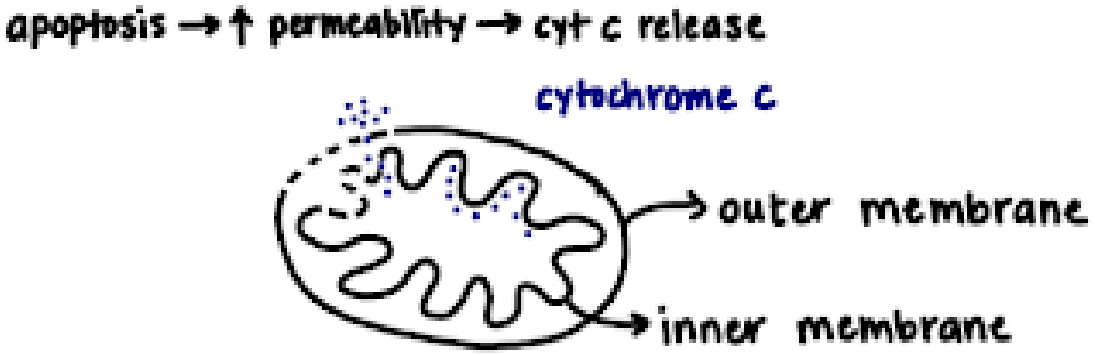
- ☐ *Activation of enzymes* ***called caspases*** **through two main pathways:**
  1- Mitochondrial pathway (intrinsic)
  2- Death receptor pathway (extrinsic)
- *(Dr quest)* ***The name of enzyme that cause Activation of enzymes? called caspases***

-Intrinsic pathway; mitochondrial pathway:

+ In most physiologic & pathologic situations.

Mitochondria contain several proteins capable of inducing apoptosis ⟵ **Cytochrome c. specific enzyme in mitochondria**

↑ **mitochondrial permeability** ⟵ permeable membrane ⟵ cytochrome c ⟵ leaks **triggering caspase 9** ⟵ activate apoptosis



Once the this membrane inner & outer is intact (pores) appear the ,cytochrome to stimulation the caspase 9

-Intrinsic pathway; mitochondrial pathway:

- **BH3 protein:** a group of sensors (called BH3 proteins because they contain the third domain seen in Bcl-family)
- Activated when:

1. Cells are deprived of growth factors & survival signals.
2. Cells are exposed to agents that damage DNA.
3. Cells accumulate unacceptable amounts of misfolded proteins.

☠ They shift the life-sustaining balance in favor of pro-apoptotic Bak and Bax.

☠ **The first step in apoptosis in intrinsic pathway is activated BH3(sensor) then the BAK, BAX will be activated (initiation of the apoptosis) , then antiapoptotic will stop inactivated** { موضع سؤال}

Intrinsic pathway; mitochondrial pathway

A family of more than 20 proteins (prototype is Bcl-2) controls the permeability of mitochondria.

+ proapoptotic members of the family are Bax & Bak.	**+ Antiapoptotic members are BCL-2 & BCL-xL**
+ Activated by BH3 proteins (sensor)	**+ produced in response to growth factors & survival signals.**
+ when stimulated→dimerize →insert into mitochondrial membrane → form channels →cytochrome c escapes into cytosol	**+ maintain the integrity of mitochondrial membranes → holding proapoptotic in check.**

- **Growth factors produce so antiapoptotic is activated**
- **In cancer cell the antiapoptotic activation and inhibition the proapoptotic, to escape from apoptosis**
-

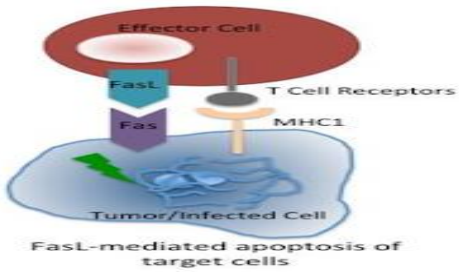
-Extrinsic pathway; death receptor pathway:

- **Tumor necrosis factor (TNF)** receptor family.
- The prototypic death receptors are the **type I TNF** receptor & **Fas (CD95).**

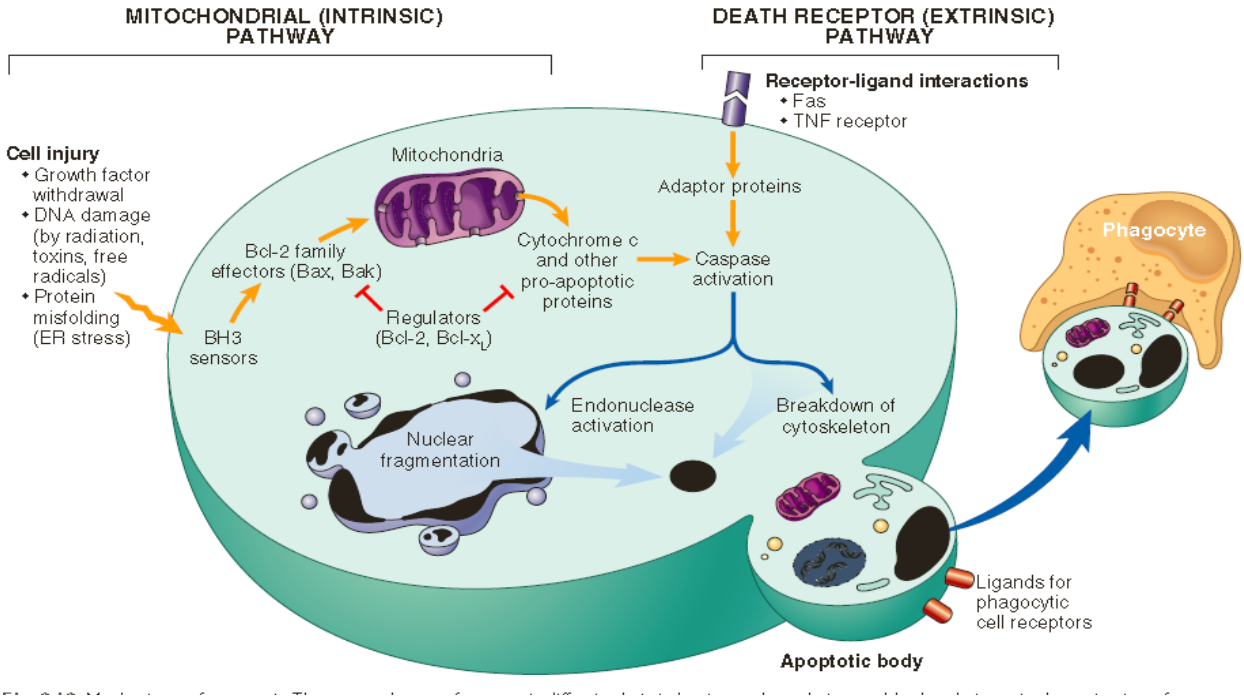
- contain a cytoplasmic regions “**death domain**”
- **Fas ligand (FasL)** : membrane protein expressed on **activated T lymphocytes**.

- **T cells (their function is activation the caspase not to engulf)**recognize fas expressing target , fas molecules are **cross linked** by **fasL** ***to activate caspase 8***

Figure 1



مهم جددا



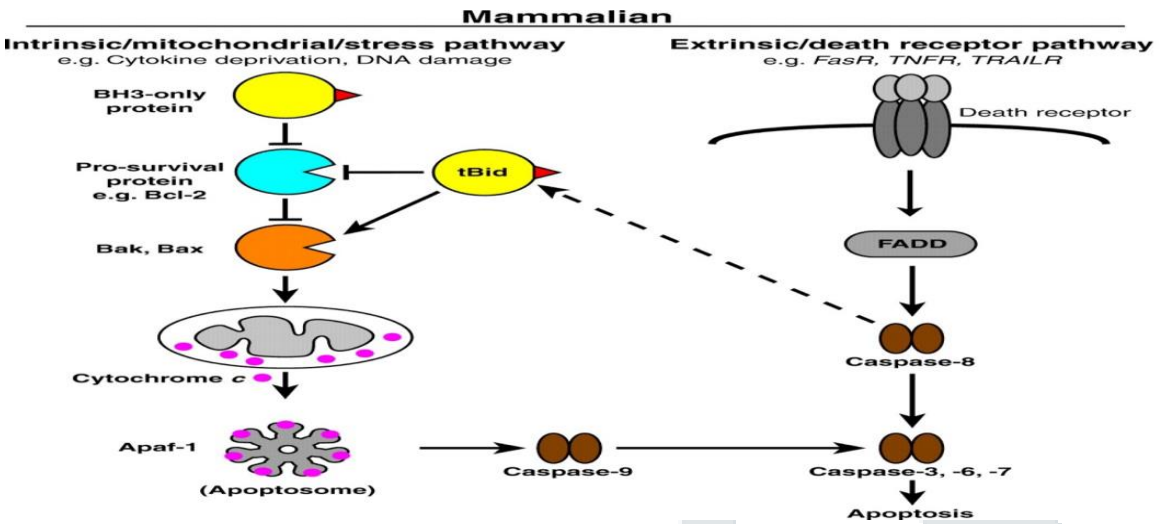
In Either pathway:

- After caspase-9 or caspase-8 is activated it cleaves & thereby activates additional caspases that cleave numerous targets activate enzymes **that degrade the cells’ proteins & nucleus.**

- The result is the characteristic cellular fragmentation of apoptosis.
-

☠ **Which of the following is characteristic features to apoptosis process ?**

A. Cellular creeps
B. DNA damage
C. Mitochondrial leakage
D. Cellular fragmentation ☑



Clearance of apoptotic cells:

- **entice phagocytes by producing a number of**

"eat-me" <u>signals:</u>

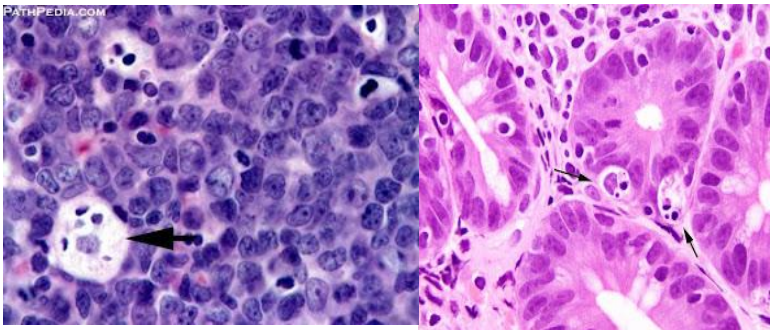
"flips" phospholipid to the outer leaflet, expose phosphatidylserine.

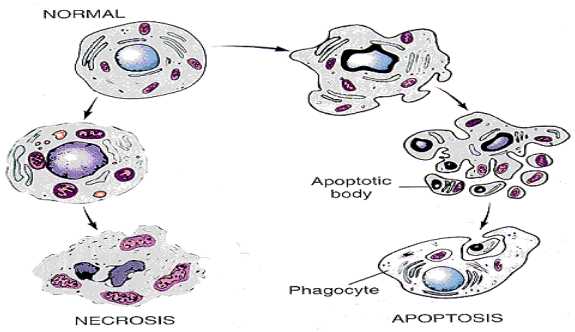
+ secrete soluble factors that recruit phagocytes.

Happens before the cells undergo membrane damage and release their contents… So no inflammation!

Morphology:

- Involves single cells or small clusters
- ☠ Cells shrink rapidly, retain **intact plasma membrane**
- Formation of cytoplasmic buds
- Fragmentation into **apoptotic bodies**
- Apoptotic bodies phagocytized rapidly before inflammatory response.





*-*Necrosis Vs Apoptosis مهم

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized 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 and protein damage

Number of cell that affected:
Necrosis : more than one cell many

-Other Pathways of Cell Death:

Necroptosis

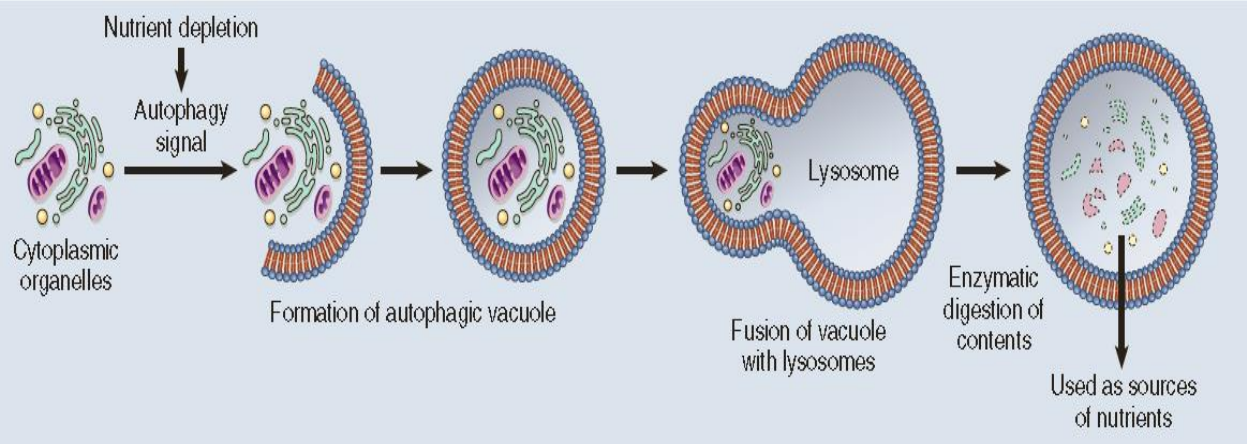
- Features **both** of necrosis and apoptosis.
- initiated by engagement of TNF receptors → receptor interacting protein (RIP) kinases are activated→ initiating dissolution of the cell like necrosis

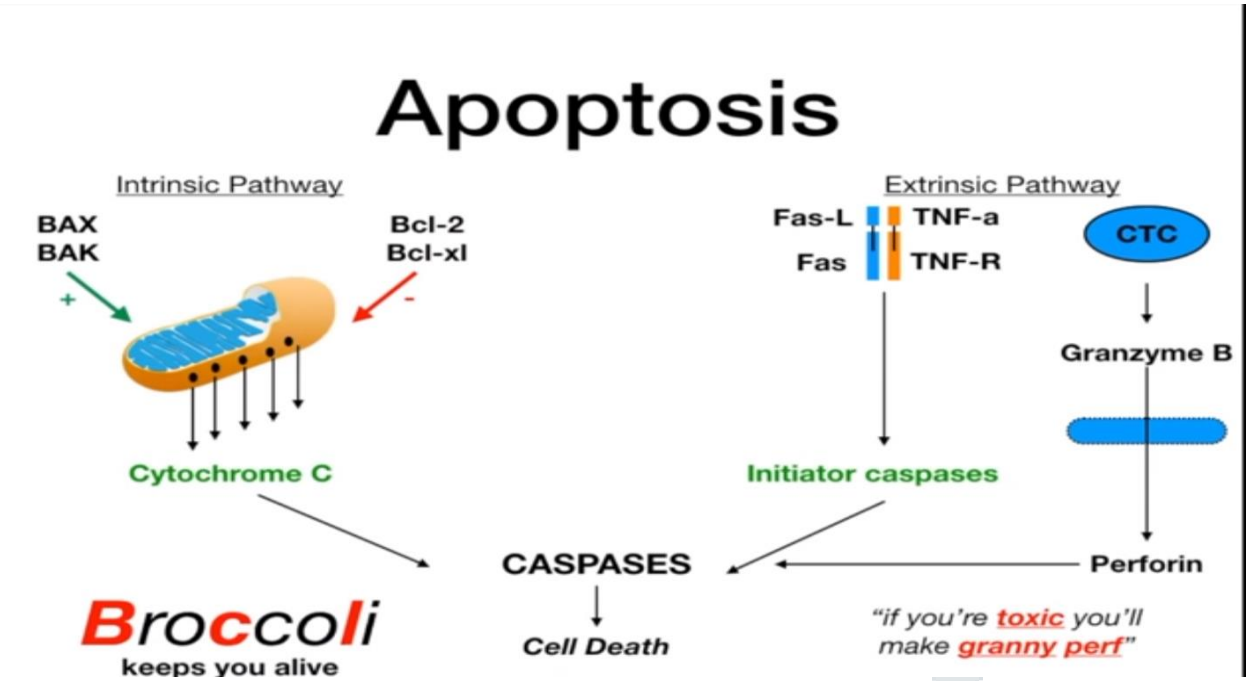
Pyroptosis

- activation of a cytosolic danger-sensing protein complex called the **inflammasome.**
- Greek, *pyro* = fire
- Used by infectious microbes
- Fever + inflammation + apoptosis

Autophagy

- **("self-eating")**
- **refers to lysosomal digestion of the cell's own components.**
- Nutrient deprivation
- Survival pathway





إشارَةٌ بها أفهم، لستُ اللَّبيب لكنَّني الظَّامئ، خريرُ عينٍ واحدَةٍ يكفِي. أرنِي الحقَّ أنظُر إليه، أختارُه بفضلِك، لاَ تُغادِرني، لا تقُل هذا فراقُ بينِي وبينَك، منْ للأبتَرِ الأخوبِ المُلقَى العَمِه، اصطَنِعنِي للخَيرِ ولك، اصنَعْني واصنَع لي، كلّ الَّذِي أردتُ احتَرق في لظَى التِّيه، تخلَّيتُ عن مُرادِي، قدَّمتُكَ يا ربّ، مُرادُكَ يُغنِي..

• ثناءُ بلعابد.

لا تنسونا من صالح دعائكم

#لجنة_الطب_والجراحة