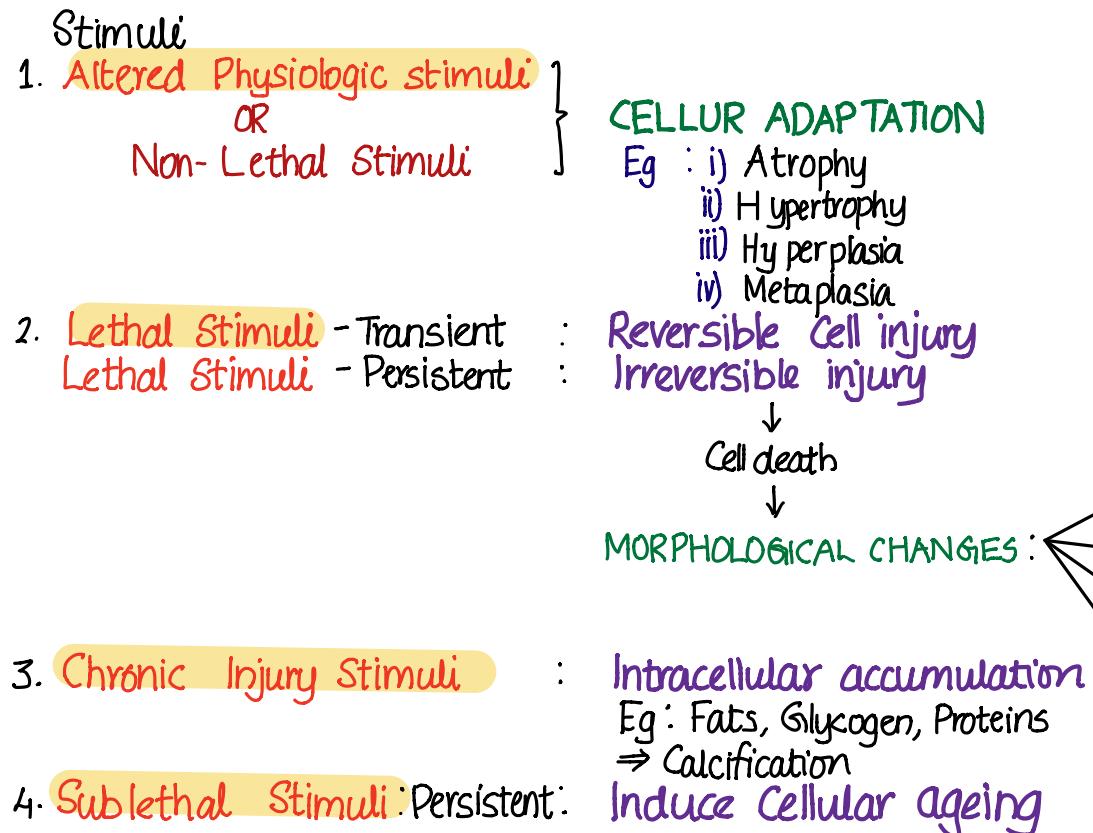


# CELL PATHOLOGY AND AGEING

## CELLULAR RESPONSE



## CELLULAR ADAPTATIONS

- Stimuli → Cell → Change in their Number, Size, Phenotype, functions
- ↓
- Removal → Comeback to N State
- ∴ CELLULAR ADAPTATIONS ARE REVERSIBLE
- These are both Physiologic & Pathologic
- ↓
- Pregnant Uterus
- ↓
- Barrett's Esophagus

## HYPERTROPHY

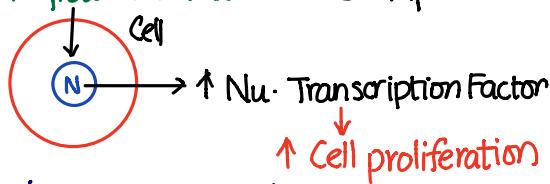
- definition : Size of cell ↑ but Number of cell same
- Mechanism : ↑ in synthesis of cellular protein
- Is also both Physiological & Pathological
- ↓
- Eg: Pregnant uterus  
(both hypertrophy & hyperplasia)
- ↓
- Eg : Cardiac Enlargement  
d/t Valvular defect.



## HYPERTROPHY

- def : No. of cell Increased . But size of cell remains same

- Mechanism : i) **Growth Factor** : Most important mechanism



ii) ↑ tissue stem cells

↑ no. of cells

- Both **Physiologic** & **Pathological**

- Pregnant uterus

- Pregnant Breast

- **Compensatory Hyperplasia**

Liver regeneration  
after Liver Resection

• ↑ Estrogen on the endometrium

Endometrial Hyperplasia

## ATROPHY

- def : Size & no. of cell are decreased .

- Mechanisms : i) ↓ protein synthesis

ii) **Ubiquitin Proteasome  
Degradation pathway**

iii) **Autophagy**

Self Eating

### **INTRACELLULAR PROTEIN DEGRADATION PATH WAY**

Ubiquitin -Ligase activation

↓  
Ubiquitin

+  
Target protein

These are taken into

↓  
⊕  
Activate **proteasome**  
(organelle)

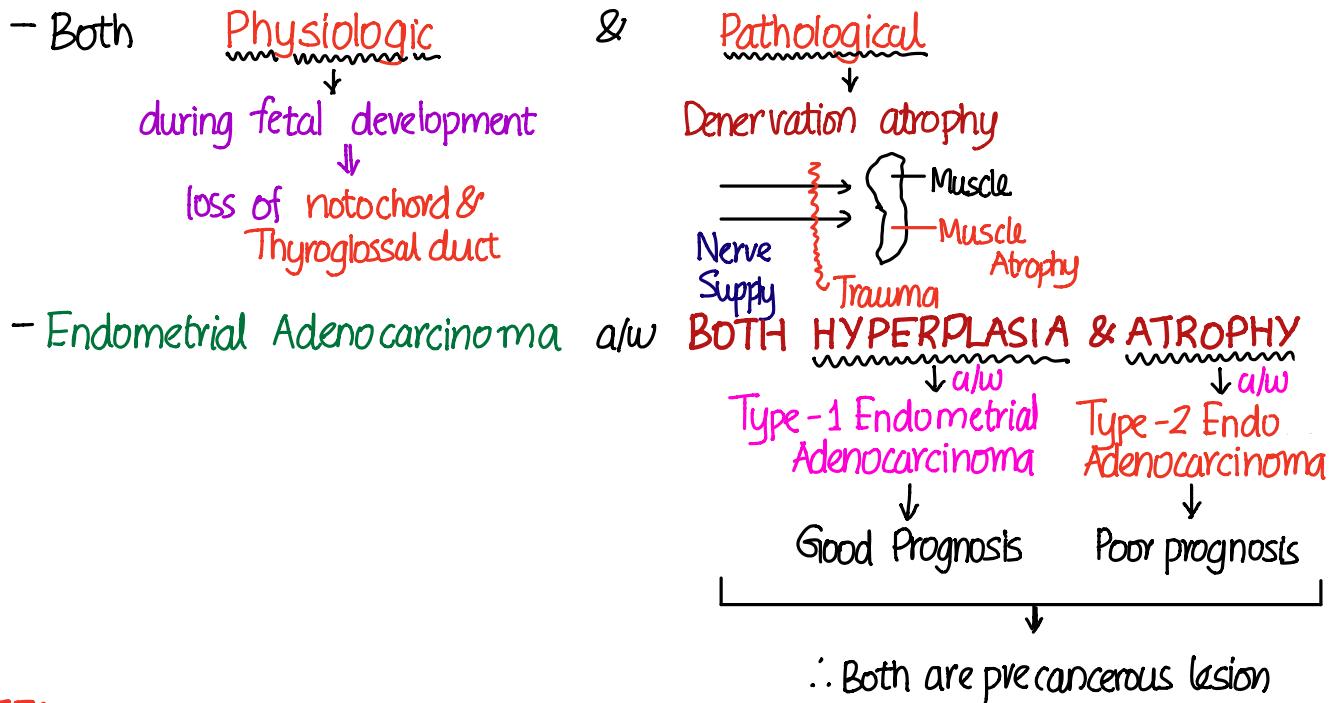
↓  
degradation of  
Ubiquitin + Tar. protein

↓  
ATROPHY

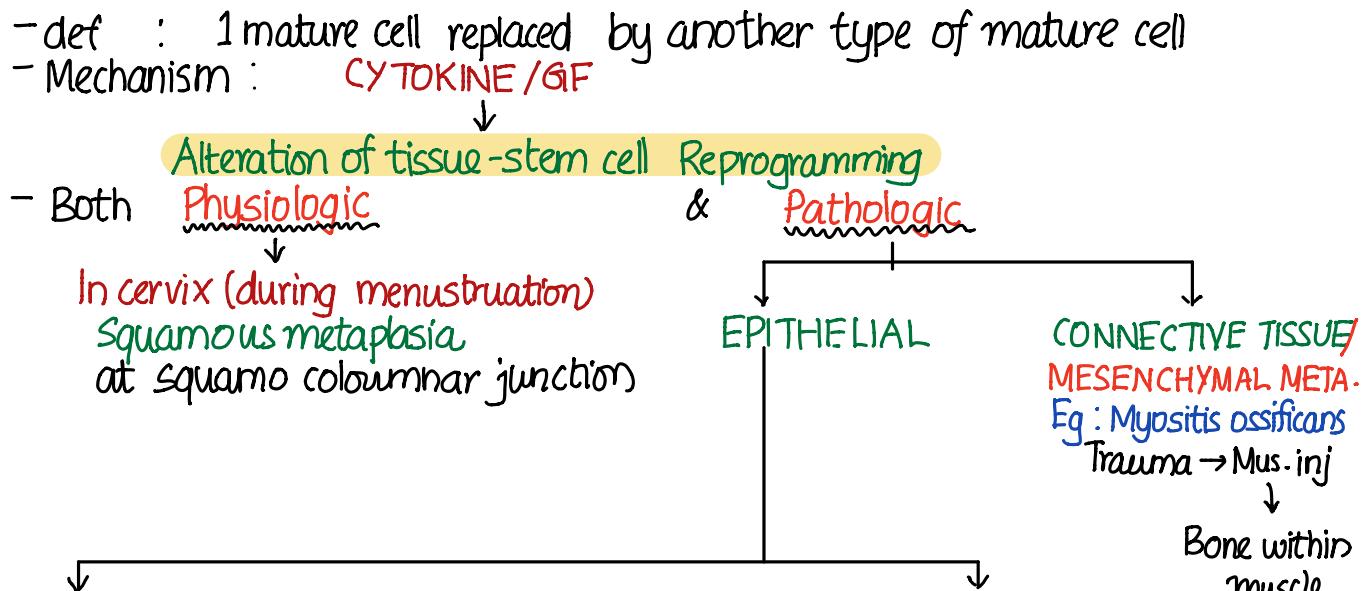
↓  
**Double membrane bound  
Autophagosome**  
(Contain Ubi + Tar. pro)

↓  
Combine with **Lysosome**  
↓  
Degradation of  
Protein

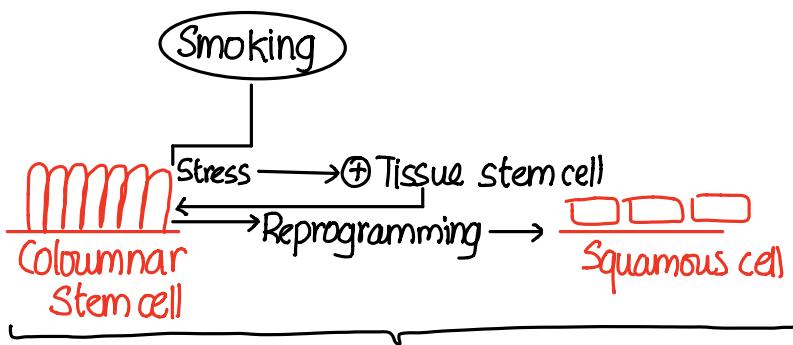




## METAPLASIA



### MC Type :



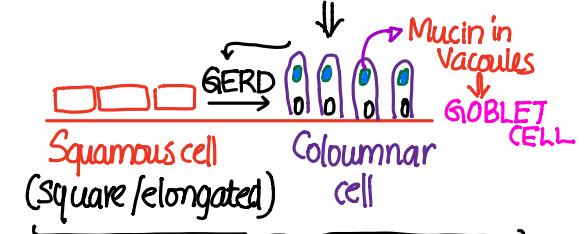
### Squamous Metaplasia of Resp. Tract

(MC Type of metaplasia)

# d/t Vitamin A deficiency  
Vitamin A excess

### BARRETT'S EOSOPHAGUS

- MCC : Gastro eosophageal Reflux Disease (GERD)



### Columnar Metaplasia

• d/t to the presence of GLOBELET CELLS aka INTESTINAL METAPLASIA

(Hallmark of Barret's E)

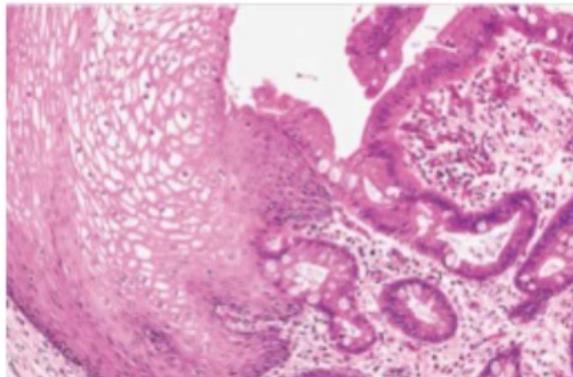
• Stain for GLOBELET CELLS:

Alcian Blue Stain : pH = 2.5 (acidic)  
for intestinal Goblet : pH = alkaline

# Risk of Barret's Esophagus : Adenocarcinoma of Esophagus

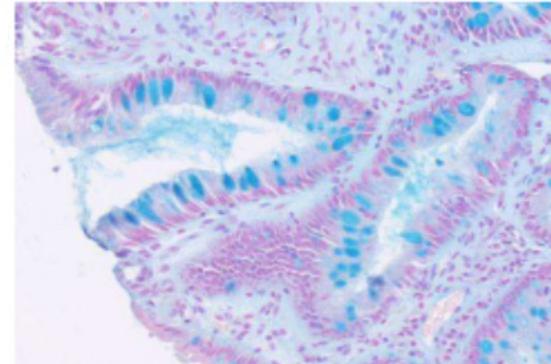
# Metaplasia → Dysplasia → Carcinoma

Exception : Apocrine metaplasia of breast tissue  
have no risk of malignancy



### BARRETT'S ESOPHAGUS

Showing squamous to columnar metaplasia (Columnar metaplasia).



### ALCIAN BLUE STAIN OF BARRETT'S MU-

#### COSA:

shows the blue-staining goblet cells, a few specialized columnar cells, and the clear-staining gastric-type surface columnar cells

### CELL - INJURY

- MCC of cell injury : ISCHAEMIA

↓  
HYPOXIA → OXIDATIVE STRESS  
on mitochondria

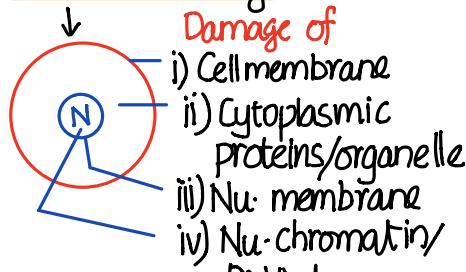
↓  
# Free radicals production

### FREE RADICALS

aka = Oxidants

= Reactive oxygen species (ROS)

- FR are normally produced d/t incomplete oxidation within mitochondria
- Def : Any chemical species with unpaired e<sup>-</sup> (outer orbit)
- Mechanism of action : by oxidative damage



### FREE - RADICAL (Oxidant)

- i) OH<sup>•</sup> : MOST REACTIVE
- ii) H<sub>2</sub>O<sub>2</sub>
- iii) O<sub>2</sub><sup>•</sup>
- iv) ONOO<sup>-</sup>

- i) Vitamins : A / C / E
- ii) Proteins : Transferrin, Ceruloplasmin
- iii) Enzymes : Catalase, Glutathione SOD (Superoxide dismutase)



### \*\*\* HYPOXIA

↳ Most - susceptible

NEURONS : Survival time 3-4 min

CARDIAC : 20-40 min (n 30 min)

FIBROBLAST : hrs to days

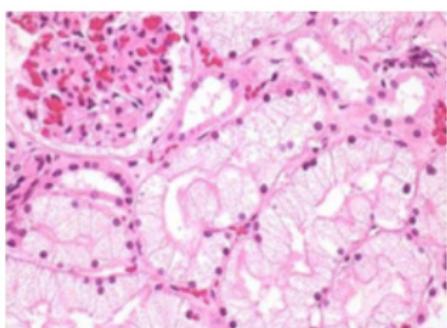
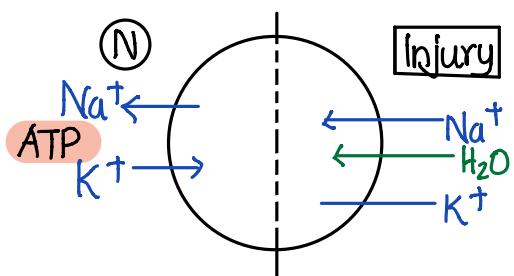
### Types of Cell injury

Transient stimuli  
Reversible injury

Persistent stimuli  
Irreversible Injury

### REVERSIBLE INJURY

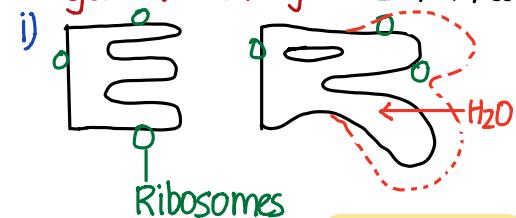
Ischaemia ( $\downarrow O_2$ )  
 $\downarrow$  oxidative phosphorylation in mitochondria  
 $\downarrow$  ATP production ( $\downarrow$  5-10 % of Normal)



#### HYDROSTATIC CHANGE OR CLOUDY SWELLING

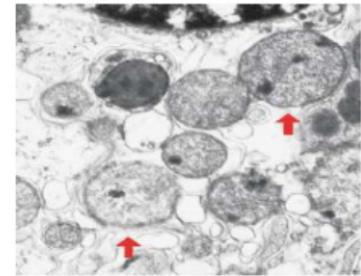
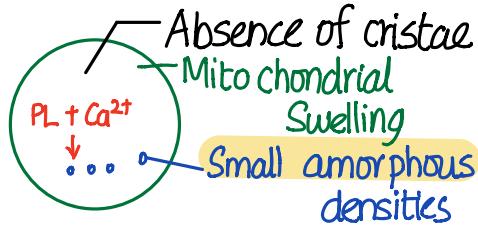
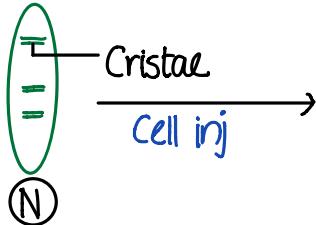
**Sign of reversible injury** due to cytoplasmic distension by excessive water entry.

- ① First Sign : Cell Swelling  
 $\Rightarrow$  except for Apoptosis  
 First Sign: Cell Shrinkage
- ② Vacuolar Degeneration/  
Hydropic Degeneration  
 • d/t intracellular water accumulation  
 • aka CLOUDY SWELLING  
 Eg: Acute Tubular necrosis of Kidney
- ③ Organelle changes : EM Examination



- ii) Ribosomal detachment

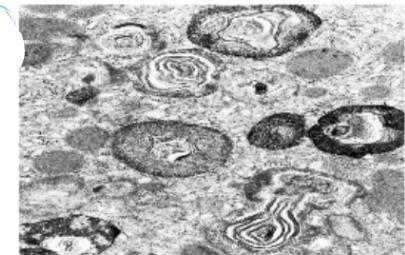
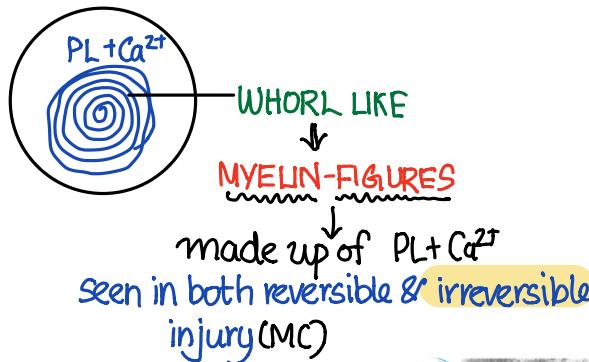
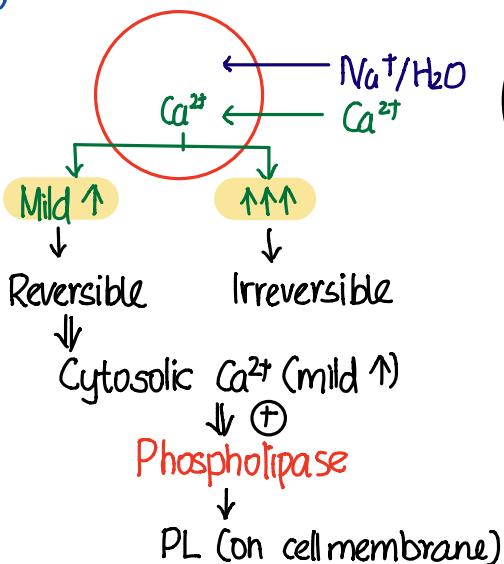
### iii) Mitochondria



#### REVERSIBLE INJURY :

Electron microscopy (Ultrastructurally) showing markedly swollen mitochondria containing small amorphous densities made up of electron-dense deposits consisting of calcium and proteins.

iv)



#### MYELIN FIGURES

Electron microscopy (Ultrastructurally) showing myelin figures derived from damage of the cell membrane (whorls of lamellated phospholipid and calcium).

### # Nucleus - damage



In Reversible injury

- i. Disaggregation of granular/fibrillary Nu. chromatin

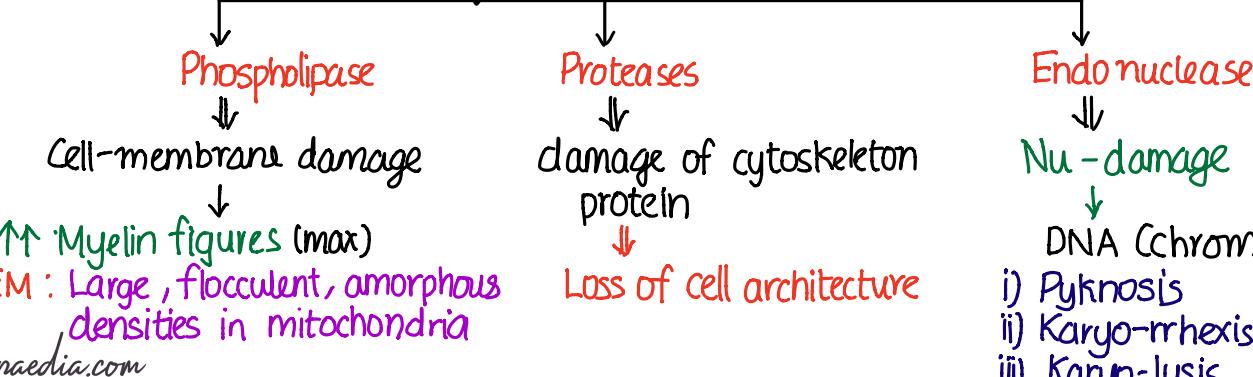
## IRREVERSIBLE INJURY

- because of Persistent lethal stimuli



↑ Cytosolic  $\text{Ca}^{2+}$

↓ ⊕/Activates



## i) PYKNOSIS

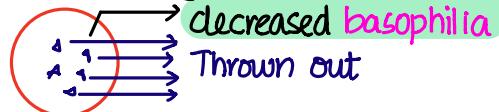


: Clumping / Condensation of chromatin + Shrinkage of Nucleus

## ii) Karyo-nrhexis : Nuclear fragmentation



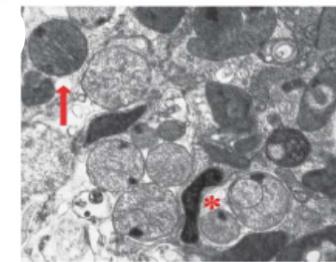
## iii) Karyolysis : Chromatin Lysis & dissolution



Irreversible injury → Cell death

↓  
Morphological changes

↓ Necrosis      ↓ Apoptosis      ↓ Necroptosis      ↓ Pyroptosis



### IRREVERSIBLE INJURY

Electron microscopy (Ultrastructurally) showing markedly swollen mitochondria containing large flocculent amorphous densities made up of electron-dense deposits consisting of calcium and proteins.

## NECROSIS

- 2 patterns of Necrosis

### i. COAGULATIVE NECROSIS

\* MC pattern of necrosis  
⇒ Denaturation of Protein



Tissue architecture: Preserved

Eg: Ischaemic infarction of solid organs Eg: Heart (MC)

Kidney

Liver

# EXCEPT IN BRAIN :  
Ischaemic infarction

### ii. LIQUEFACTIVE NECROSIS

⇒ d/t ↑ Lysosomal permeability



Enzymes leak out



Enzymatic damage of cell.  
(HYDROLYTIC DAMAGE)

⇒ Tissue architecture: Lost

Eg i) Ischaemic infarction of Brain

∴ there is no stromal support  
∴ absence of collagen

also brain is rich in Liquefactive enzymes

ii) Infections

## SPECIAL TYPES

### 1. GANGRENE

- MC site : LOWER LIMB

#### ① Dry gangrene

\* tissue architecture is preserved  
∴ Eg of Coagulative necrosis

#### ② Wet gangrene

\* Bacterial contamination ⇒ Toxin / Enzyme release  
\* Type of Liquefactive necrosis



## 2. CASEOUS NECROSIS

- It's called like this ∵ of cheesy appearance : Gross
  - Yellowish-White debris
- Seen in TB : Cheesy d/t presence of MYCOLIC ACID
- On microscopic examination : Coagulative & Liquefactive Necrosis
  - Amorphous, Granular, Pink structure
- considered as Variant of Coagulative Necrosis

## 3. FAT NECROSIS

It may be due to

a) Enzymes

Acute pancreatitis



Lipase released



act on Lipids

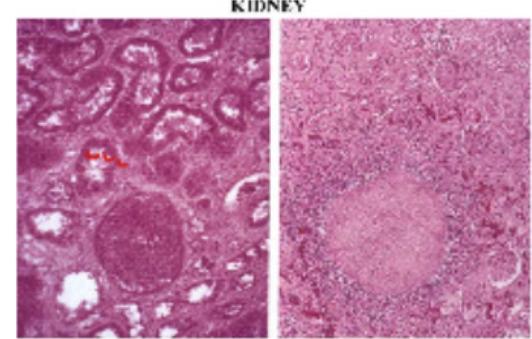
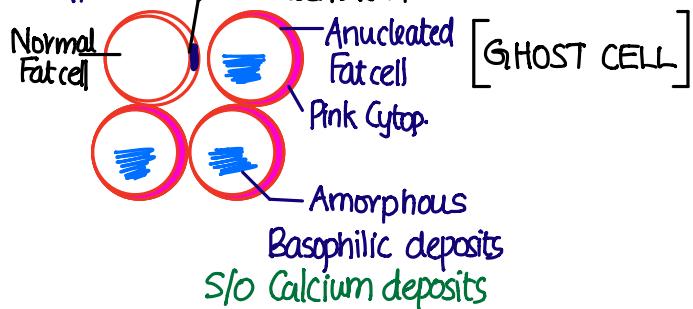


Release FA &  
Combine with Ca<sup>2+</sup>

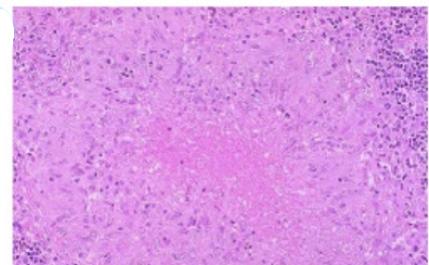
called Saponification

∴ GROSS : Chalky white  
appearance

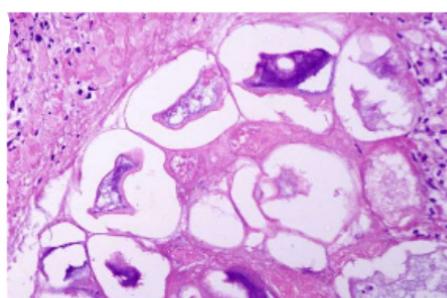
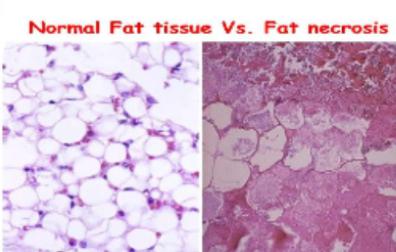
M/E :



CASEOUS NECROSIS (GROSS).  
Lung Tuberculosis with caseous necrosis consisting of yellow-white and cheesy debris.

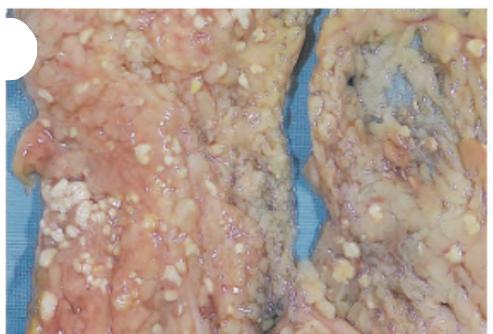


CASEOUS NECROSIS ( MICROSCOPY )  
Lung Tuberculosis with eosinophilic caseous necrosis and epithelioid cells.



## FAT NECROSIS

Normal fat cells with eccentric nuclei is seen in image (a).  
Image (b) shows fat necrosis where anucleated ghost cells are seen



FAT NECROSIS  
showing Chalky white necrosis.

## 5. FIBRINOID NECROSIS

- Presence of Fibrin + Immune Complex [Ag + Ab]

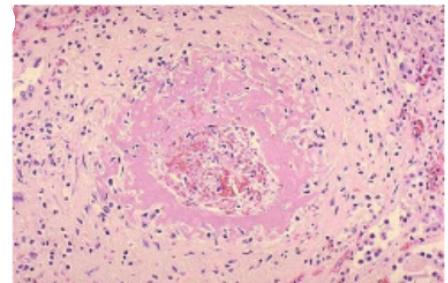
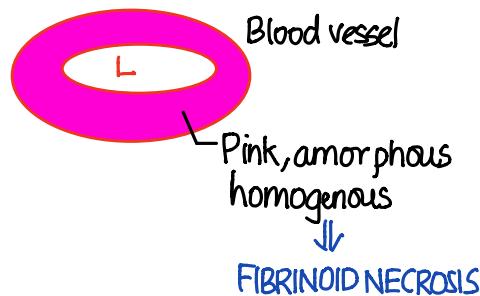
- Pathology : Vessel wall damage



Coagulation pathway → Fibrin formation

- Seen in i. Vasculitis : **Polyarteritis Nodosa**
- ii. Malignant HTN

- M/E



#### FIBRINOID NECROSIS

Showing deposition of fibrin (pink material) on the wall of arteriole as a consequence of malignant hypertension.

## NECROSIS

- \* ↑ Lysosomal permeability
  - ↓ Enzymes
  - ↓ Cell membrane damage
  - ↓ IC content leak outside & acts as chemoattractant
  - ↓ INFLAMMATION
- \* Always pathological

## APOPTOSIS

- \* d/t ↑ mitochondrial permeability
  - ↓ Intact Cell membrane intact
  - ∴ No leaking
  - ∴ NO INFLAMMATION
- \* Apoptosis both physiological & pathological.

## APOPTOSIS

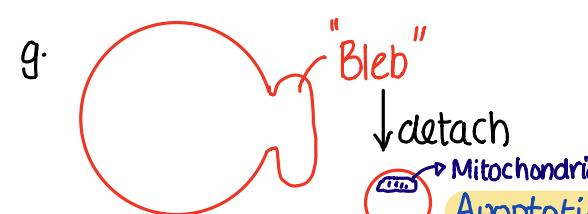
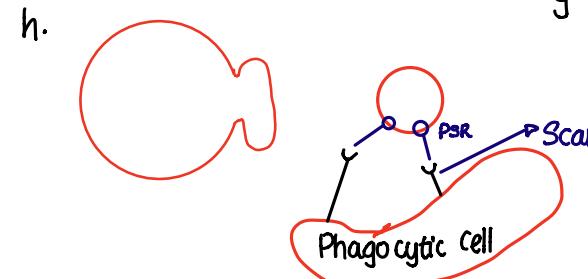
- falling-off the cells from the tissue (literal meaning)
- Programmed Cell death is seen in
  - i. Apoptosis
  - ii. Necroptosis
  - iii. Pyroptosis
  - iv. Neutrophilic Extracellular Trap (NET)
- Energy depend. process ≫ Programmed Cell Death (active process)
- Apoptosis is PHYSIOLOGICAL (MC)

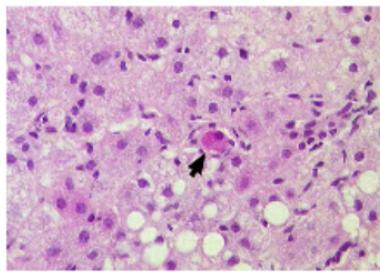
- Eg :
1. Organogenesis / Embryogenesis
  2. Neo vascularisation
  3. Killing of inflammatory cells after completing their function
  4. Elimination of auto-reactive cell (to prevent Auto immunity)

## PATHOLOGICAL

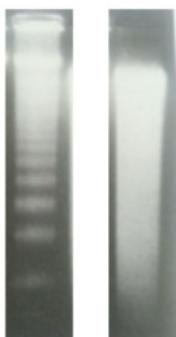
- Eg
1. Chemotherapy or Radio therapy (Apoptosis + Necrosis)
  2. Glucocorticoid induce apoptosis (to prevent autoimmunity)
  3. Graft v/s Host disease
  4. Councilman bodies in Vira Hepatitis. These are apoptotic bodies
  5. Misfolding of protein

## - MORPHOLOGY

- a. Cell-Shrinkage
  - b. MOST CHARACTERISTIC FEATURE: Chromatin condensation
  - c. 2nd MOST " " : Cell-Membrane intact.
  - d. NO INFLAMMATION
  - e. 
  - f.  Phosphatidyl-Serine Receptor (Lipid Receptor)  
EAT-ME SIGNAL
  - g.   
"Bleb"  
detach  
Mitochondria
  - h.   
Phagocytic cell  
PSR (Phagocytic Surface Receptor)  
Scanger R (Scanning Receptor)
- APOPTOTIC BODIES:**  
Cell membrane bound structures with tightly arranged organelles with or without nuclear fragments. Examples are Councilman bodies in viral hepatitis
- ANNEXIN - V : MARKER OF APOPTOSIS**



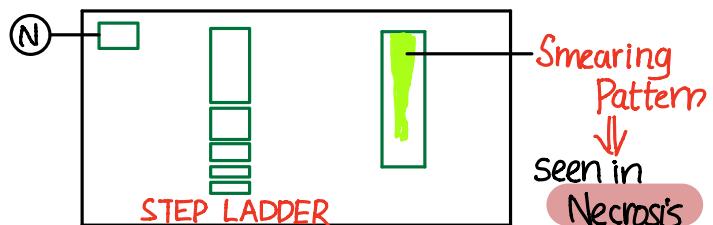
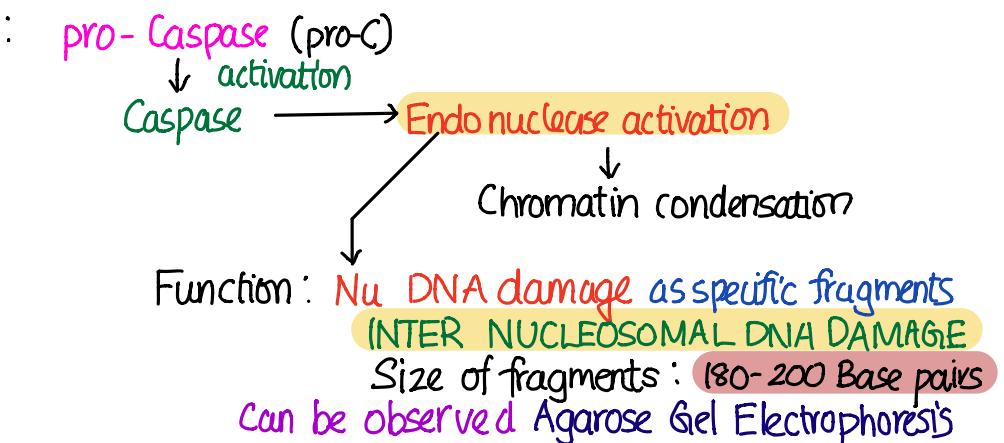
## - BIOCHEMISTRY



### AGAROSE GEL ELECTROPHORESIS

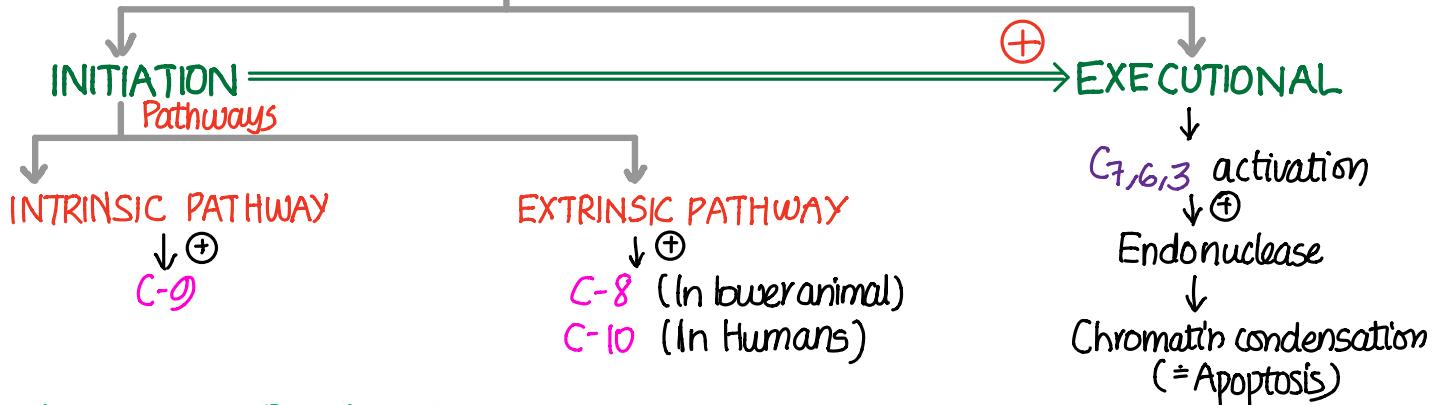
A) Step ladder pattern of apoptosis. It is due to endonuclease induced internucleosomal damage  
B) Diffuse smearing pattern seen in necrosis.

Step ladder seen in  
i) Apoptosis : Characteristic  
Notes: Apoptosis



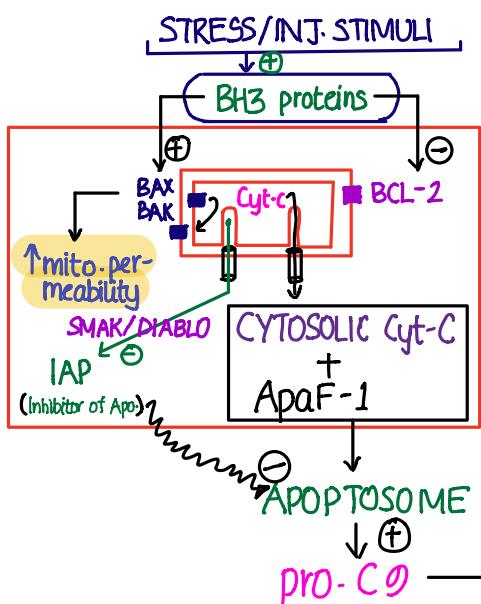
# MECHANISM OF APOPTOSIS

2 events



## INTRINSIC PATHWAY

- aka Mitochondrial pathway as mitochondria is the M. important organelle
- It's a major pathway



## # PROTO-ONCOGENE

### a. PRO-APOPTOTIC

- BAX
- BAK
- BCL-X<sub>S</sub>
- BH<sub>3</sub> only proteins family (on cell surface)

### \* STRESS-SENSORS

- Bim
- Bad
- Bid
- PUMA
- NOXA

### b. ANTI-APOPTIC

- BCL-2
- BCL-X<sub>L</sub>
- MCL-1

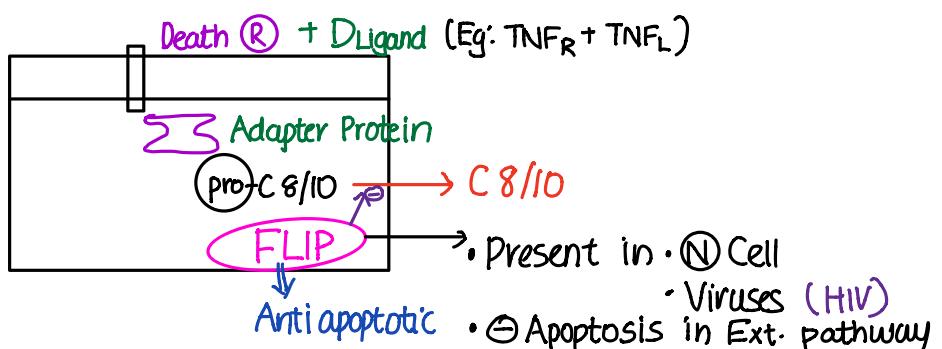
# SMAK / DIABLO : Inhibits IAP

: They are pro-apoptotic

## EXTRINSIC PATHWAY

- aka Death Receptor mediated pathway

- i) TNF - Receptor : MOST WELL-DEFINED
- ii) FAS / CD95



- # FLIP : • Anti-apoptotic protein present in • Normal cell  
• Viruses (HIV)
- θ apoptosis at extrinsic pathway by inhibiting the formation of C8/10

# Hallmark of Apoptosis activation : Caspase activation

Hallmark of neuronal apoptosis activation: AIF (Apoptosis Inducing Factor)  
→ No caspases

### Clinicopathological Co-relation

→ Misfolding of proteins → ↑↑ Misfolded protein : Feature of neurological disorders  
~~↓ ↗~~  
 Caspase  
 ↓  
 Apoptosis

- i. Alzheimer ds
- ii. Parkinson's ds
- iii. Huntington ds

## NECROPTOSIS

- Programmed cell death without caspase activation
  - Necrosis + Apoptosis
    - ↓ Morphology      ↓ Programmed cell death
  - Mechanism :
    - TNFR + TNF
      - ↓ Recruits
      - RIP-1 + RIP-3 (Receptor Interacting Protein)
    - ↓ without caspase
    - Mitochondrial Stress
      - ↓ FR production
      - i. Cell swelling  
ii. CM damage  
iii. Inflammation
    - ↓ C-8
      - ↓ Apoptosis (Extrinsic)
- } MORPHOLOGY OF NECROSIS = NECROPTOSIS  
 ∵ considered as variants of Necrosis
- NECROPTOSIS is both Physiologic & Pathologic
- Eg : Mammalian Bone growth plate formation
- i. Neurological disorder  
ii. Pancreatitis

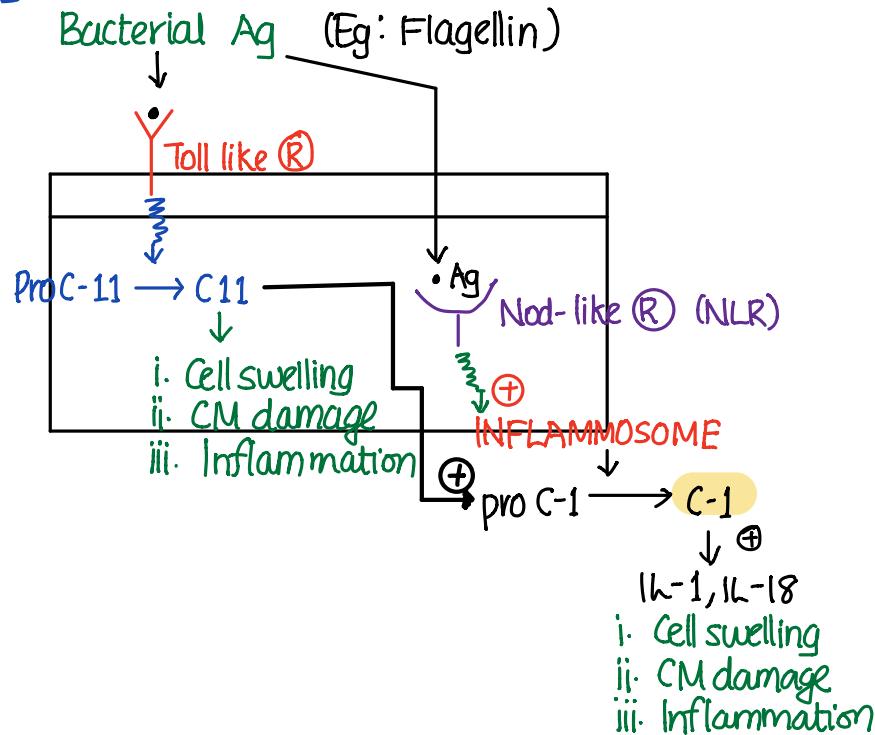
## PYROPTOSIS

- Pyrogen induced Apoptosis

→ IL-1



- Variant of necrosis
- Mechanism :



## Chronic Injurious Stimuli

leads to

Intracellular accumulations

i. ① Substances

Lipid (MC)  
Glycogen  
Proteins

Pigments

i. Lipofuscin  
ii. Hemosiderin  
iii. Melanin

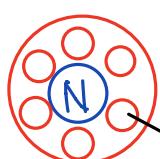
ii. Abnormal Substances

Coal / Silica

iii. Calcification

## LIPID

- MC intracellular accumulation
- aka STEATOSIS ( $\uparrow$  Lipid deposit  $\in$  in cell)
- it can be Triglycerides (TG) : MC Lipid accumulation

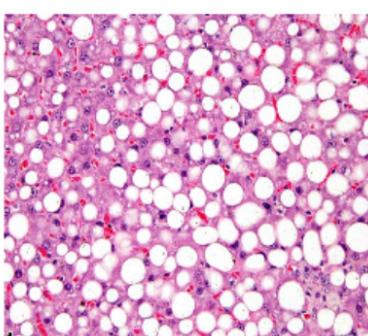


Clear Vacoules

Cholesterol  
C. Esterases  
Phospholipid

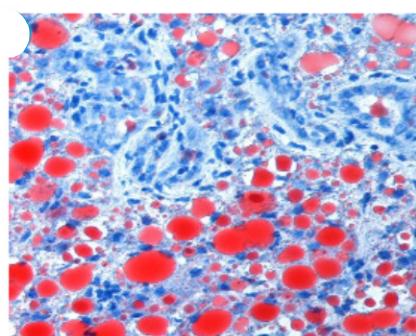
Akoholic / NAFLD / Hepatitis / Viral

- SPECIAL STAIN
- i. Oil-Red-O-stain : Lipid will be Red
  - ii. Sudan Black-B : Lipid will be black

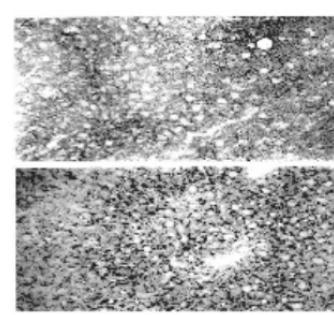


INTRACELLULAR FAT.

It will appear as clear space with eccentric nuclei displaced by fat within cells.



OIL RED O STAIN  
Fat Globules will appear Orange Red. Best for lipid detection on frozen section.



SUDAN BLACK STAIN  
showing Fat Globules as black deposit

