Structured Notes According to

PATHOLOGY

Revision friendly **Fully Colored Book/Structured Notes**

For Best results, watch the video lectures along with reading notes

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In case of any discrepancy between book and videos, Dr. Preeti Sharma's videos on PrepLadder should be considered.

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1 CELL INJURY

Insight of Cell Injury

- The most common cause of cell injury is Hypoxia.
- The most common cause of Hypoxia is Ischemia.
  - The blood supply is hampered, causing a decrease in the oxygen level.
- The most sensitive cell to Hypoxia is the Brain/Neurons. (3-5 mins)
- The most resistant cell to Hypoxia is a Fibroblast

Cell injury

Injury

↓

Adaptation

↓ fails

Reversible cell injury

↓ injury continues

Irreversible cell injury

↓

Cell Death

Types of Cell Injury

00:03:28

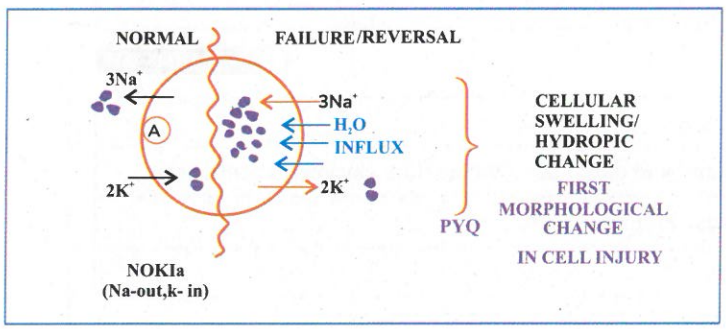
Reversible Cell Injury

00:05:22

- First change of cell injury: Mitochondrial Dysfunction→decrease in ATP production.

The process of ATP failure includes:

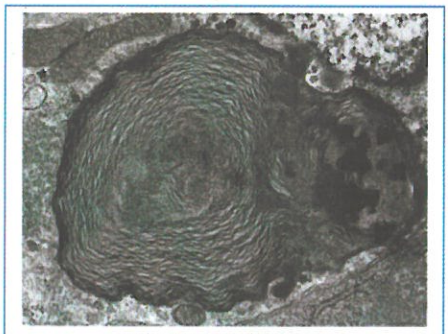
1. **Failure of Na+ K+ ATPase Pump**



- There is H_2O influx.
  - It is referred to as Cellular swelling/Hydropic Change (First Morphological change in cell injury).
  - This is responsible for the following:
    - Cellular swelling
    - Endoplasmic reticulum swelling
    - Flattening of the microvilli
    - Formation of cytoplasmic blebs
    - Formation of Myelin Figures, also called Concentric Lamellation.
      - → Composition: Phospholipids (primarily) and Ca^{2+}
      - → Myelin figures(phospholipids) are derived from Membrane of the cell.

PYQ: AIIMS 2019

PYQ: FMGE 2023



Electron Microscope

Important Information

Myelin figures/concentric lamellation:

- Seen in reversible & irreversible cell injuries (more in irreversible injury)

2. **Anaerobic Glycolysis**
   - The pH will become acidic, causing the nuclear chromatin to clump.
3. **Decrease in Protein Synthesis**
   - The ribosome detachment is seen→ decrease in protein synthesis→development of fats (fatty change).

Irreversible Cell Injury

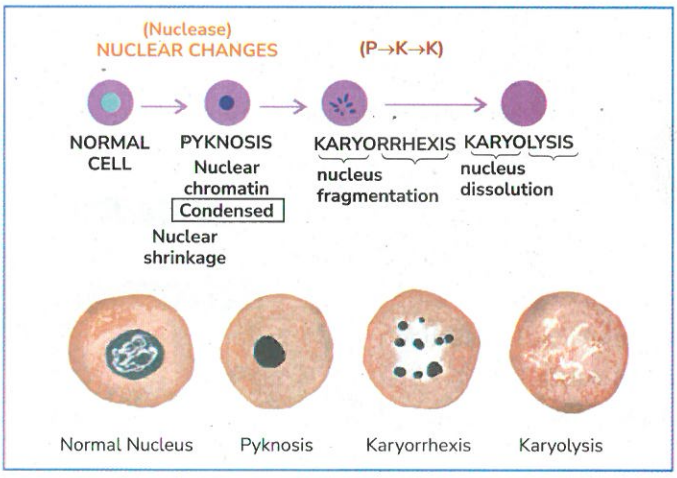
00:22:28

Two defining moments of irreversible cell injury are:	
1. **Severe Membrane Damage:** The inflow of calcium occurs. It causes the activation of three enzymes: PYQ: FMGE 2019 a. Phospholipase b. Protease c. Nuclease	2. **Severe Mitochondrial Damage:** The calcium sits on the mitochondria causing Amorphous Flocculent Densities.

Nuclear Changes in the Cell Injury:

PYQ: AIIMS 2019

Three stages of nuclear changes in cell injury are:
1. **Pyknosis**: The nucleus becomes small and dark due to the nuclear chromatin condensing.
2. **Karyorrhexis**: There will be Nuclear Fragmentation.
3. **Karyolysis**: The nucleus gets dissolved.



Previous Year Questions

Q. What is the first change in the cell injury?
Ans. Mitochondrial Dysfunction

Q. Which is the first morphological change in the cell injury?
Ans. The cellular swelling or Hydropic Change.

Q. What is the composition of Myelin Figures?
Ans. Primarily made up of phospholipids and a minor presence of calcium.

Q. What is the composition of Amorphous Flocculent Densities?
Ans. Calcium

Q. The injury with which the Amorphous Flocculent Densities are associated?
Ans. Irreversible Cell Injury

Q. The three stages of nuclear change in the cell injury?
Ans. Pyknosis, Karyorrhexis and Karyolysis

Cell Death - Necrosis

00:33:25

Definition

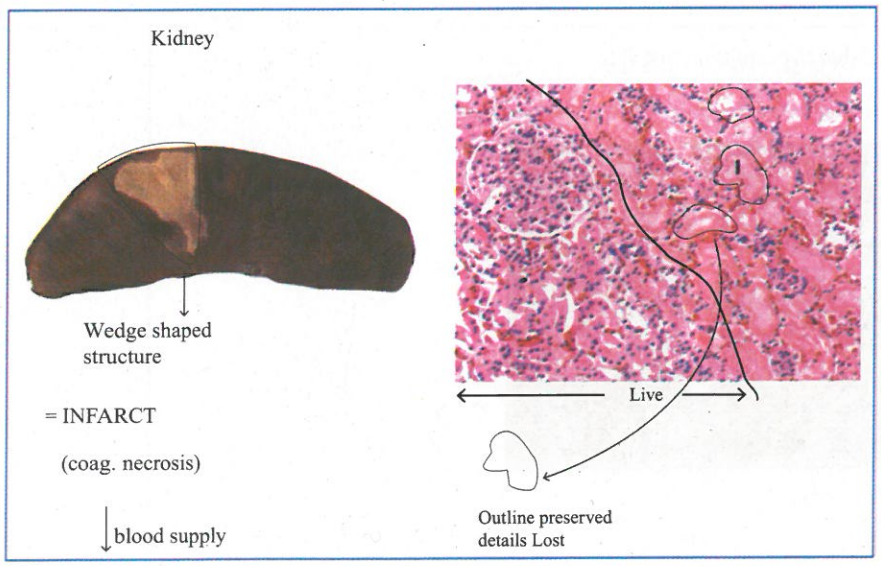
- It is a Pathological Cell Death,associated with inflammation.

Microscopic Examination

- It appears pink (Eosinophilic)
- Amorphous
- Inflammation +

Types of Necrosis

1. **Coagulative Necrosis:**
   - It is the most commonly occurring Necrosis.
   - M.O.A - Denaturation of the proteins.
   - It occurs in the solid organs kidney, liver, heart (M/C)
   - Occurrence of infarct (Wedge shaped structures) in the organs.
   - Leading to the formation of multiple ghost cells, causing a Tombstone Appearance.
   - The tissue architecture is preserved even after the death of the cells.



Important Information

Ghost Cells:

- Ghost cells are associated with coagulative Necrosis.
- Occurs in a skin-generated tumor, Pilomatrixoma.
- Tombstone appearance is seen in coagulative necrosis (also seen in P.vulgaris).

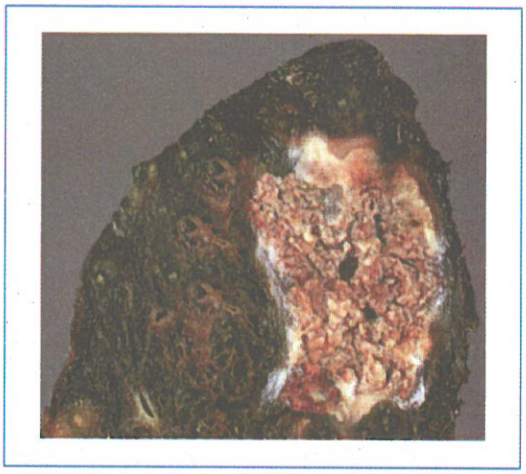
2. Liquefactive Necrosis:

PYQ: FMGE 2019

- It mostly occurs in CNS and Pancreas.
- This occurs because they are rich in Hydrolytic Enzymes.
- It is also called Colliquative Necrosis.
- The tissue architecture is not preserved.

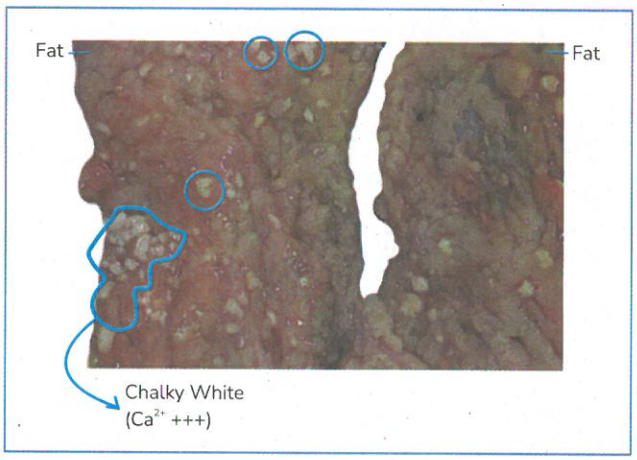
3. Caseous Necrosis:

- Associated with the high lipid content in the cell walls.
- There is cheese-like appearance of the organs.
- It is the combination of Coagulative Necrosis (m/c) and Liquefactive Necrosis.
- Most common examples include tuberculosis, fungal infection (histoplasmosis; coccidioidomycosisis), syphilis, etc.

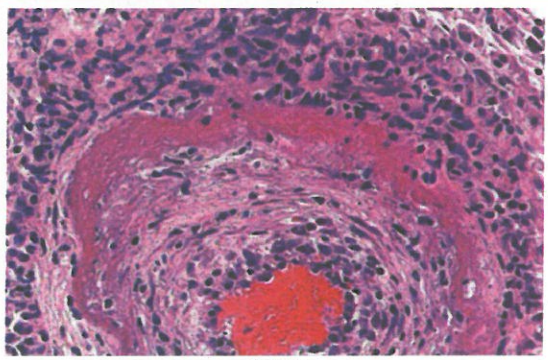


4. Fat Necrosis:

- It occurs in the fat-rich organs, e.g. breasts , omentum, etc.
- It causes the breakdown of fats into fatty acids.
- A Chalky White appearance is seen.
- It also occurs around the pancreas due to peripancreatic fat.



5. **Fibrinoid Necrosis:**
   - Associated with the antigen-antibody reactions (immune complex deposition).
   - Some examples are:
     - Polyarteritis Nodosa (PAN)
     - Rheumatic Heart Disease (RHD) shows Aschoff Bodies.
     - SLE
     - Malignant Hypertension (HTN)



PAN

6. **Gangrene:**
   - Blackish discoloration of the organs.
   - Foul smelling.
   - Dry gangrene:Coagulative Necrosis with a line of demarcation.
   - Wet gangrene: Liquefactive Necrosis + Infection without any line of demarcation.

7. **Zenker's Degeneration:**
   - It is a type of Coagulative Necrosis.
   - It occurs in typhoid or Enteric fever.
   - Complication seen in: Recuts abdominis and diaphragm

Previous Year's Questions

Q. What is the most common type of Necrosis?
Ans. Coagulative Necrosis

Q. Which are the most common organs affected by Coagulative Necrosis?
Ans. Heart

Q. Which necrosis happens inside the pancreas?
Ans. Liquefactive Necrosis

Q. Which necrosis happens around the pancreas?
Ans. Fat Necrosis

Q. Zenker's Degeneration can be seen in which skeletal muscles?
Ans. Rectus Abdominis andDiaphragmatic Muscle

MCQ:

Q. Myelin figures are derived from?

A. Cytoplasm
B. Nucleus
C. Cell Membrane
D. Ribosomes

Q. A 61-YEAR-OLD female patient presents with left-sided chest pain radiating to the left arm and jaw. The patient explains that the pain has increased severely over the past 40 minutes. She is immediately rushed to the hospital. Cardiac enzymes are elevated. The patient was admitted and started on thrombolytic therapy. However, on the fifth day of observation, she suddenly collapses and dies. Which of the following Necrosis are you most likely to find in this patient's heart?

A. Liquefactive Necrosis
B. Coagulative Necrosis
C. Fat Necrosis
D. Fibrinoid Necrosis

Q. A 45-year-old female patient complained of being hit in the chest by a football while passing by a garden 4 weeks back. Initially, her left breast was tender and swollen. But over the weeks, the tenderness has subsided. However, she now notices a lump in the peri-areolar region which is firm to hard in consistency. Radiological investigations reveal calcific deposits. Which of the following best describes the phenomenon above?

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

01:04:15

Cell Death - Apoptosis

PYQ: AIIMS 2018, 2019

Definition:

- Apoptosis is a Greek word that means "falling off."
- It is both physiological as well as pathological cell death.
- Mitochondria play a pivotal role in apoptosis.
- It is a programmed cell death, now known as Caspase Dependent Programmed Cell Death.

ATP Usage:

- ATP use occurs (active process)

Inflammation:

- No inflammation will occur.

Examples of Apoptosis

• **Physiological Apoptosis** ○ Organogenesis (Embryogenesis), For example, Fingers and hand formation , any defect leads to Syndactyly. ○ Neutrophils Clearance ○ Endometrial Shedding	• **Pathological Apoptosis** ○ Councilman Bodies, seen in viral Hepatitis (Hepatitis C-Virus) ○ Civatte/ Colloid/ Cytoid Bodies, seen in Lichen Planus.

Important Information

Chemotherapy:

- It causes cancer cell death.
- It's a combination of Apoptosis (80%) and Necrosis (20%).

Caspase

01:12:24

- It consists of Cysteine Residue.
- It breaks after aspartic acid residues.
- It is an Enzyme.

Mechanism of Apoptosis

PYQ: AIIMS 2019

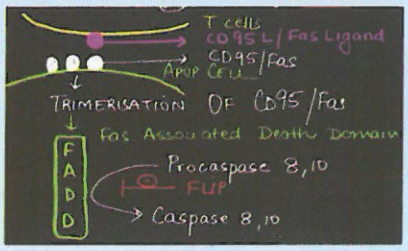
The mechanism is classified into two processes.

1. Initiation

- It is dependent on Caspase 8, 9, and 10. There are two pathways to apoptosis initiation.

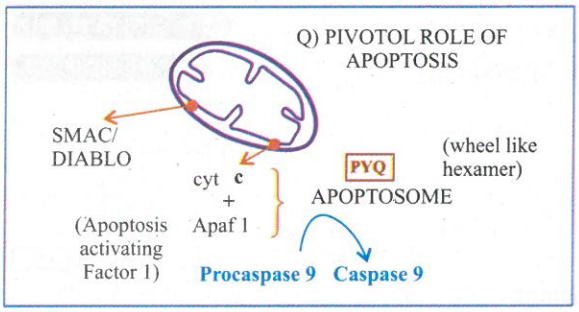
A. Extrinsic Pathway: PYQ: AIIMS 2019

- It happens on the surface of the cell.
- The cell wanting to die will have CD95 / Fas, and the supporting cell will have CD95 Ligand / Fas Ligand.
- It leads to the occurrence of Trimerisation of CD95/ Fas
- The Fas Associated Death Domain (FADD) will activate Procaspase 8, 10 into Caspase 8, 10.
- The process is inhibited by FLIP (anti-apoptotic molecule)
- It is also called Death receptor pathway.



B. Intrinsic Pathway:

- It is also called Mitochondrial Pathway
- It happens within the cell.
- It occurs when the cells undergo stress.
- The stress is detected by the stress sensors: BIM, BID, BAD, NOXA and PUMA.
- The sensor increases the pro-apoptotic factor and decreases the anti-apoptotic factors.
- The Apoptosome activates Procaspase 9 into Caspase 9. PYQ: AIIMS 2020



Pro-Apoptotic	Anti-Apoptotic
• p53 • BAK • BAX • BCL XS	• BCL 2 • MCL 1 • BCL XL

2. Execution:

- It occurs after the Initiation process.
- It is dependent on Caspase 3, 6, and 7.
- It activates three enzymes: Phospholipase, Protease, Endonuclease

Important Information

Endonuclease:

- It is called Internucleosomal Cleavage
- It breaks the DNA after 180-200 bp

Once the execution takes place, the cell falls off into small bodies called Apoptotic bodies(cell membrane bund organelle with or without nucleus). These apoptotic bodies give an "Eat me" signal to Macrophages, causing Phagocytosis.

Efferocytosis

01:38:10

- The apoptotic bodies express eat-me signals through C1q, Thrombospondin and PS (Phosphatidyl Serine).
- In a normal cell, Phosphatidyl Serine is found in the inner leaflet. However, in apoptotic cells, it comes out.
- There is Phosphatidyl Serine Flipping.
- The flipping of PS is a signal for the Macrophage. A defect in this process results in Scott Syndrome.
- The Macrophage engulfs the apoptotic bodies, which is called Efferocytosis.

Defects in Efferosome

- SLE
- COPD
- Bronchiectasis
- Cystic fibrosis

Important Information

Survival of Cancer cells:

- Cancer cells express CD47 ("Do not Eat me" Signal) to Macrophages.

Update Robbins 10e-

01:43:55

- Pro apoptotic molecules [BAK, BAX, BCL XS]: BH 1 - 3
- Anti-apoptotic molecules [BCL2, MCLI, BCL XL]: BH 1 - 4
- Stress sensors [BIM, BID, BAD, NOXA, PUMA]: BH 3 only
- SMAC / DIABLO: Proapoptotic
- Glucocorticoids: Proapoptotic
- Sex Steroids: Antiapoptotic

PYQ: NEET PG 2019

PYQ: AIIMS 2023

Identification of Apoptosis

01:47:57

- Marker: Annexin V (marker for testing PS flipping)
- Molecular Marker: CD95/ Fas
- Microscopic Examination: Nuclear Chromatic Condensation. (The cytoplasm will be pink and Nucleus will be blue, along with cellular shrinkage)
- Stain: Tunel Stain (TdT dUTP Nick End Labelling)
  - Positive: Apoptosis
  - Negative: Necrosis
- Gel Electrophoresis: Step Ladder Apoptosis

Important Information

Smearing:

- Referred to the DNA gel Electrophoresis, where the ink smudges till the end continuously.
- Smearing is seen only in Necrosis whereas Step Ladder is seen both in Apoptosis and Necrosis.

- As Neuronal cells don't have caspases, the hallmark of neuronal apoptosis is AIF(apoptosis-inducing factor).

2 NEWER CELL DEATHS

Newer Cell Deaths

- Necroptosis
- Pyroptosis
- Ferroptosis
- Anoikis

CELL DEATH	
Necrosis	• Morphology • Inflammation
Apoptosis	• Programmed cell death
Necroptosis	Necrosis + Apoptosis Definition: Caspase independent programmed cell death Inflammation + • Physiological: Growth Plate Formation in Human Body • Pathological: Steatohepatitis (fatty liver),Pancreatitis, Reperfusion Injury (MI)

Updates: **Robbins 10th Edition**

- Programmed Necrosis (New terminology for necroptosis)
- Apoptosis can`t kill Cytomegalovirus as it has caspase inhibitors, then Necroptosis will be carried.

Mechanism of Necroptosis

STEP 1 - TNF comes & bind to TNF receptor

↓

STEP 2 - Due to binding trio occurs

→ RIPK -1

→ RIPK - 3 [Receptor interacting Protein kinase]

→ PROCASPSE 8 (will never get activated)

↓

STEP 3 - MLKL phorphorylation

↓

Cell death

↓

CMV dies

Pyroptosis

00:08:48

Pyro means Fever + tosis means cell death.

- Associated with microorganisms.

Examples:

- Initially studied for Shigella and salmonella

Bacteria
↓ enters the body
Binds to NOD Receptors (gets activated)
↓
Inflammasomes
↓
activates CASPASE 1→activates IL-1→ fever
4, 5, 11 } cell death

Anoikis

00:12:27

Type of apoptosis

- Lack of natural environment
- Example: Cells kept in an unnatural environment - Cell dies.

Q1. Choose the incorrect statement about Necroptosis

a. Is it caspase-independent cell death
b. RIP 1&3 is formed
c. Caspase 8 is required
d. Growth plate formation follows necroptosis

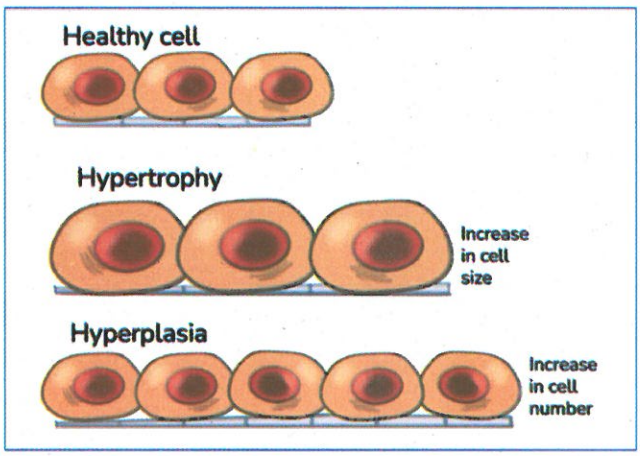
Q2. Choose the incorrect statement about pyroptosis

a. Seen in response to shigella
b. TLR is used
c. Caspase 1 is required
d. IL1 activated

Cell Injury - Cellular Adaptations

00:16:23

- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia
- Dysplasia - Pre-cancer



Differentiation between Hypertrophy and Hyperplasia 00:18:17

Features	Hypertrophy	Hyperplasia
Basic Difference	Increase in Size of cells	Increase the number of cells
Mechanism	Increase in transcription factors: GATA4, NFAT, MEF2 Are being elevated: More RNA & more protein Hence the size increases. • DNA $\xrightarrow{\text{Transcription}}$ RNA → Protein	One cell — two — four — eight cells and so on • Happens by division/mitosis
Examples	1. Bodybuilders - Skeletal Muscle Hypertrophy 2. Obstruction - Proximal to Obstruction	**For Females** • Endometrial Hyperplasia due toIncreased Estrogen **For Males** • Benign prostatic hyperplasia/Nodular Hyperplasia of the Prostate ○ Testosterone $\xrightarrow{\text{5 alpha reductase type 2}}$ Dihydrotestosterone (metabolite) → hyperplasia

Common Examples are:

Both Hypertrophy & Hyperplasia

1. Gravid Uterus - Pregnant Uterus shows the Hypertrophy (most common) and Hyperplasia
   - In question, if both options are given then opt for both
   - In any situation, select one then Gravid uterus is Hypertrophy.
2. Hyperplasia - changes in breast
   - In puberty and pregnancy - Hyperplasia

Atrophy 00:29:46

- Cell size decreases
- Cell number decreases

Mechanism of action

UPP: Ubiquitin Proteasome Pathway

Examples
• Disuse Atrophy – Fracture → cast for six weeks → muscle atrophy • Denervation Atrophy:Polio • Ischemic Atrophy: Senile → Alzheimer's Disease • Malnutrition • Endometrial atrophy: Less estrogen → type 2 CA-endometrium (worst prognosis)
More estrogen → endometrial hyperplasia • Endometrial Cancer Type 1

- All cellular adaptations are Reversible.
- The toughest to revert is Atrophy.

Metaplasia

- 100% reversible
- One tissue ⇌ another tissue

Mechanism of action	Examples:
• Reprogramming of the Stem Cells.	• Epithelial to epithelial

1) **Squamous metaplasia - most common condition**

Pseudostratified ciliated columnar epithelium

↓ Chronic Smoker
↓ Vitamin A (deficiency/excess)

squamous (end result) epithelium

2) **Barrett's Esophagus** - Precancerous adenocarcinoma of the esophagus (cancer)

Squamous epithelium —GERD→ intestinal columnar epithelium

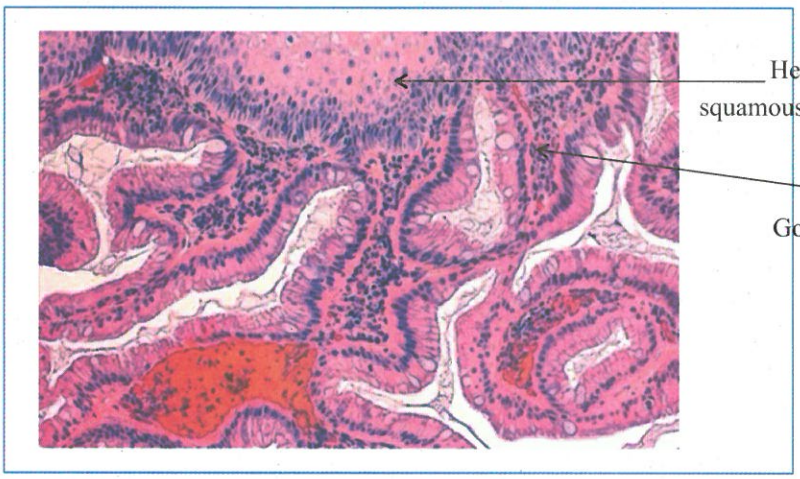
↓

Contains goblet cells

↓

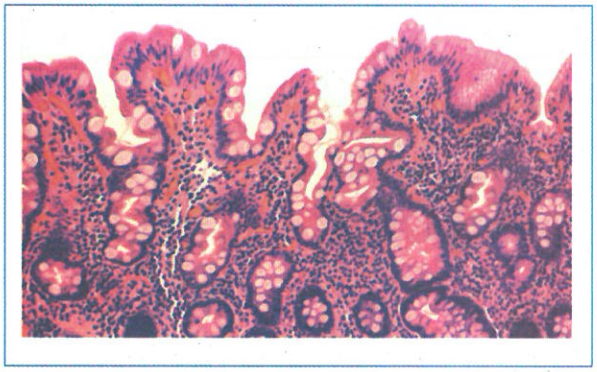
Acidic mucin

Alcian blue positive (special stain)



Q. Hallmark of Barrett Esophagus

- Goblet cells



Q. Where do you see Mesenchymal metaplasia

- Myositis(muscle) + ossificans(calcium/bone)
- Muscle changes to bone→occurs due to trauma

Breast is one such organ where all the adaptation happens.

- In Puberty & Pregnancy Hypertrophy and Hyperplasia both occurs, M/C is hyperplasia.
- Atrophy occurs in postmenopausal occurs → old age ladies
- Metaplasia -Squamous Metaplasia of the lactiferous Ducts (SMOLD), M/c seen in chronic smokers female

MCQs

Q. All are true for metaplasia except?

a. Slow growth
b. Reversible with treatment
c. Irreversible
d. Can be precancerous

Q. What is the histopathological difference between Barrett's epithelium and gastric mucosa?

a. Barrett's mucosa is acidic and stains alcian blue positive
b. Barrett's is alkaline and stains Prussian blue positive
c. Barrett's alcian blue negative because it's neutral
d. Gastric mucosa is alkaline and stains alcian blue positive

Q. A 47-year-old man visits an outpatient clinic with complaints of heartburn and chest pain for the past 6 months. His pain is retrosternal and was initially only associated with intake of solid foods, but it now occurs with liquid as well. Antacids don't relieve his pain anymore. He is worried about the pain as it is getting worse. Physical examination, including abdominal examination, is normal. He has lost 2.7 kg(6 lbs).

Laboratory investigation reveals: Hgb - 10 gm, Platelet count - 168 * 10.9/ L.
Esophagogastroduodenoscopy reveals an exophytic mass in the lower third of the esophagus.
Which of the following is the most likely diagnosis in the patient?

a. Squamous Cell Carcinoma
b. Leiomyoma
c. Gastric Ulcers
d. Adenocarcinoma

3 INTRACELLULAR ACCUMULATIONS

Pigment

00:00:35

- Exogenous
- Endogenous - Melanin

Melanin

- Present in skin, hair & eyes.
- In the brain, melanin is present in the substantia nigra.

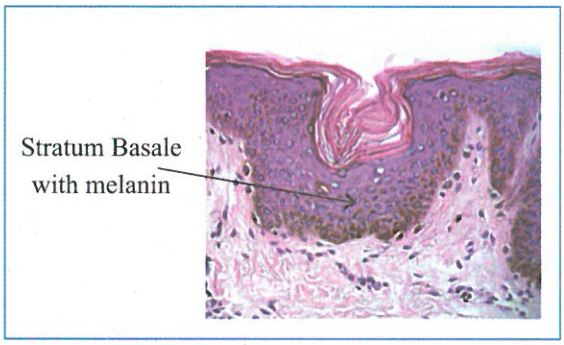
Important Information

- Parkinson's disease → decrease in dopaminergic neurons → decrease in dopamine → pale substantia nigra

Melanin Stain

00:02:40

- In the skin, there is a brownish stain around the basal layer (stratum basale) which shows the presence of melanin brown-black pigment.



- The blackish color representation of the melanin stain is known as the Masson Fontana Silver stain.

- The bluish color stain is known as the Schmorl stain.