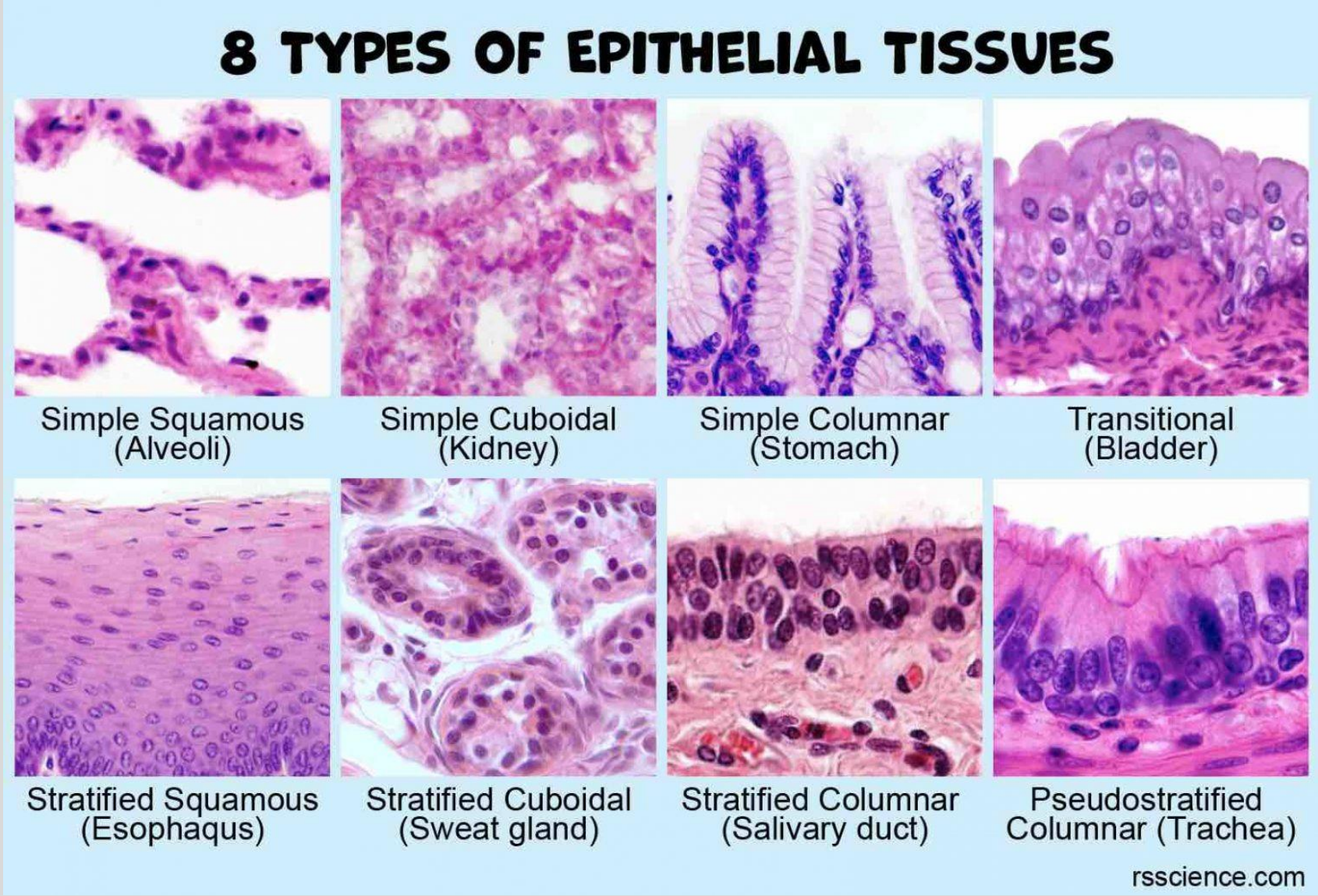
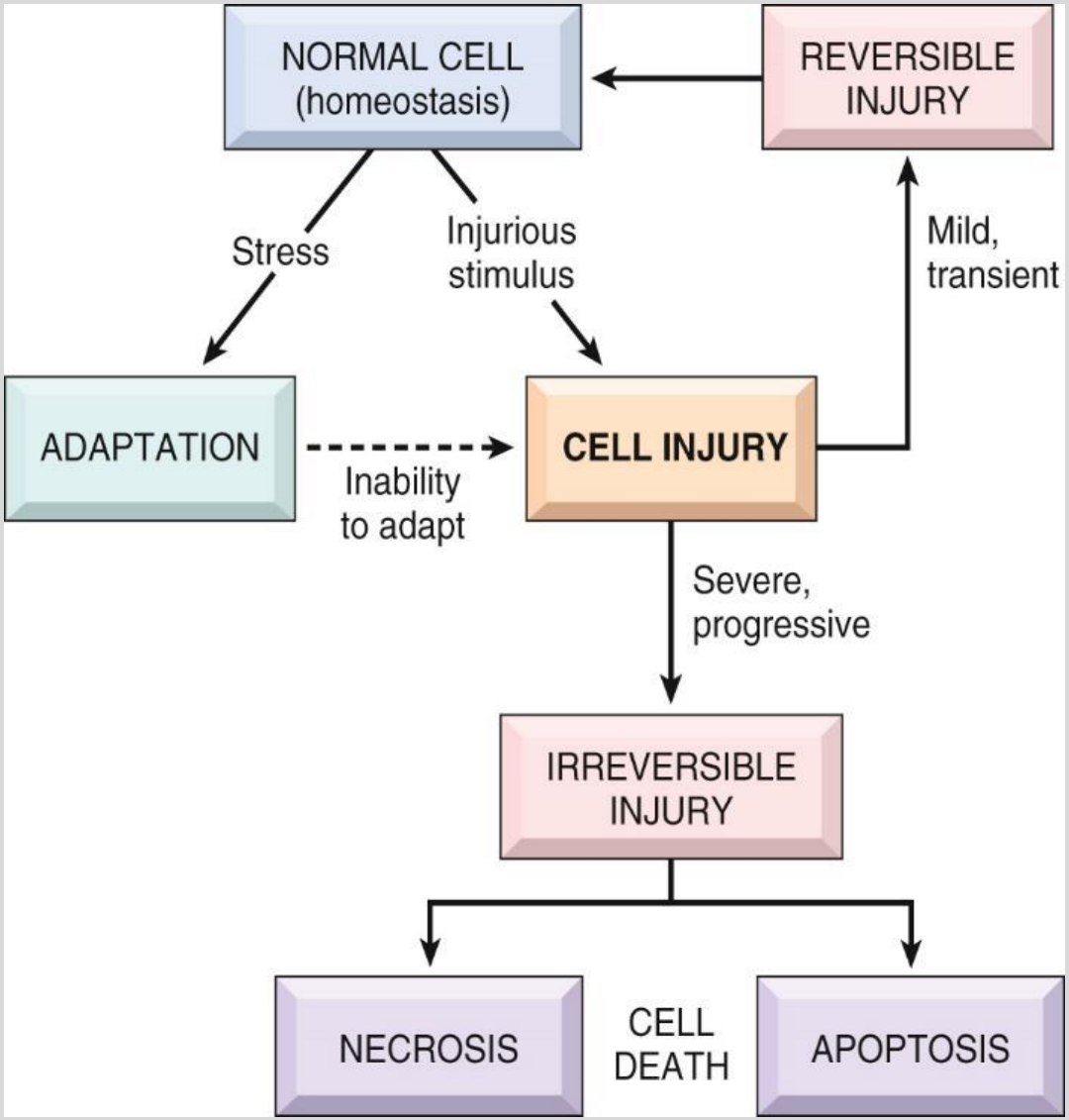
Session Objectives

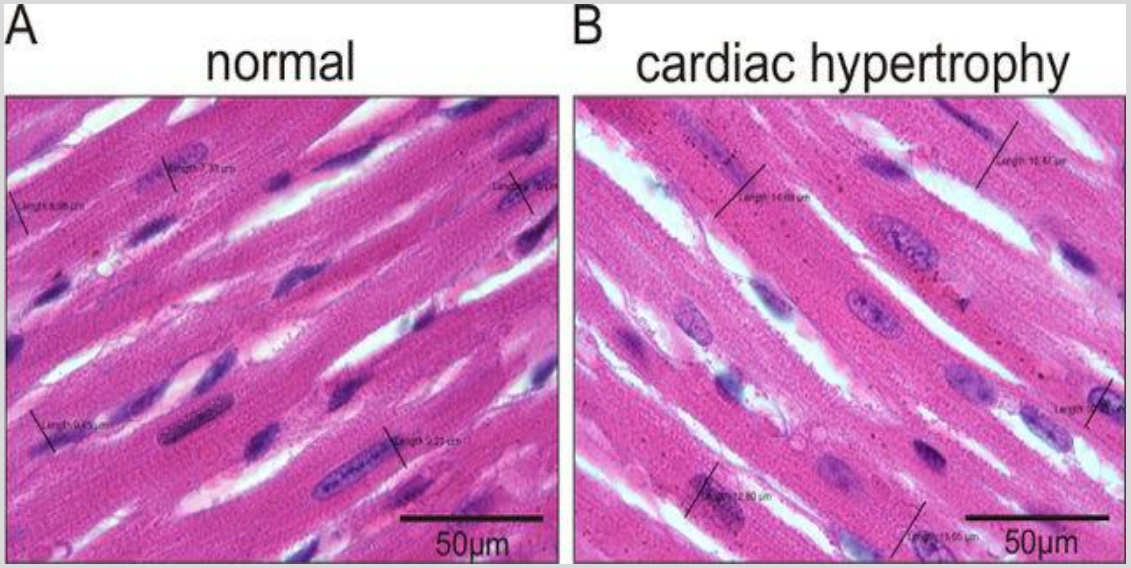
- Discuss and compare the cellular adaptations of **metaplasia, hyperplasia, hypertrophy, and atrophy**. Give examples of each.
- Discuss and distinguish various causes of **cell injury**.
- Discuss and distinguish the **reversible and irreversible events of cell injury from a cellular, functional, and morphological perspective**.
- Describe and compare the **different types of necrosis** and discuss the **mechanism of apoptosis and its differences from necrosis.**
- Discuss and describe **some cellular accumulations** and their significance.



https://rsscience.com/epithelium-classification-and-types/



Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025



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https://www.researchgate.net/publication/320639540_Echocardiographic_and_Histological_Examination_of_Cardiac_Morphology_in_the_Mouse/figures?lo=1

Mechanisms of Hypertrophy

Result of increased cellular protein production:

- Mechanical sensors in cell detect increased load
- Sensors activate complex downstream signaling pathways, e.g., (PI3K)/AKT pathway and G-protein–coupled receptor–initiated pathways
- Some signaling pathways stimulate increased production of growth factors (e.g., TGF-β) and vasoactive agents
- Lead to activation of transcription factors which increase expression of genes that encode contractile proteins

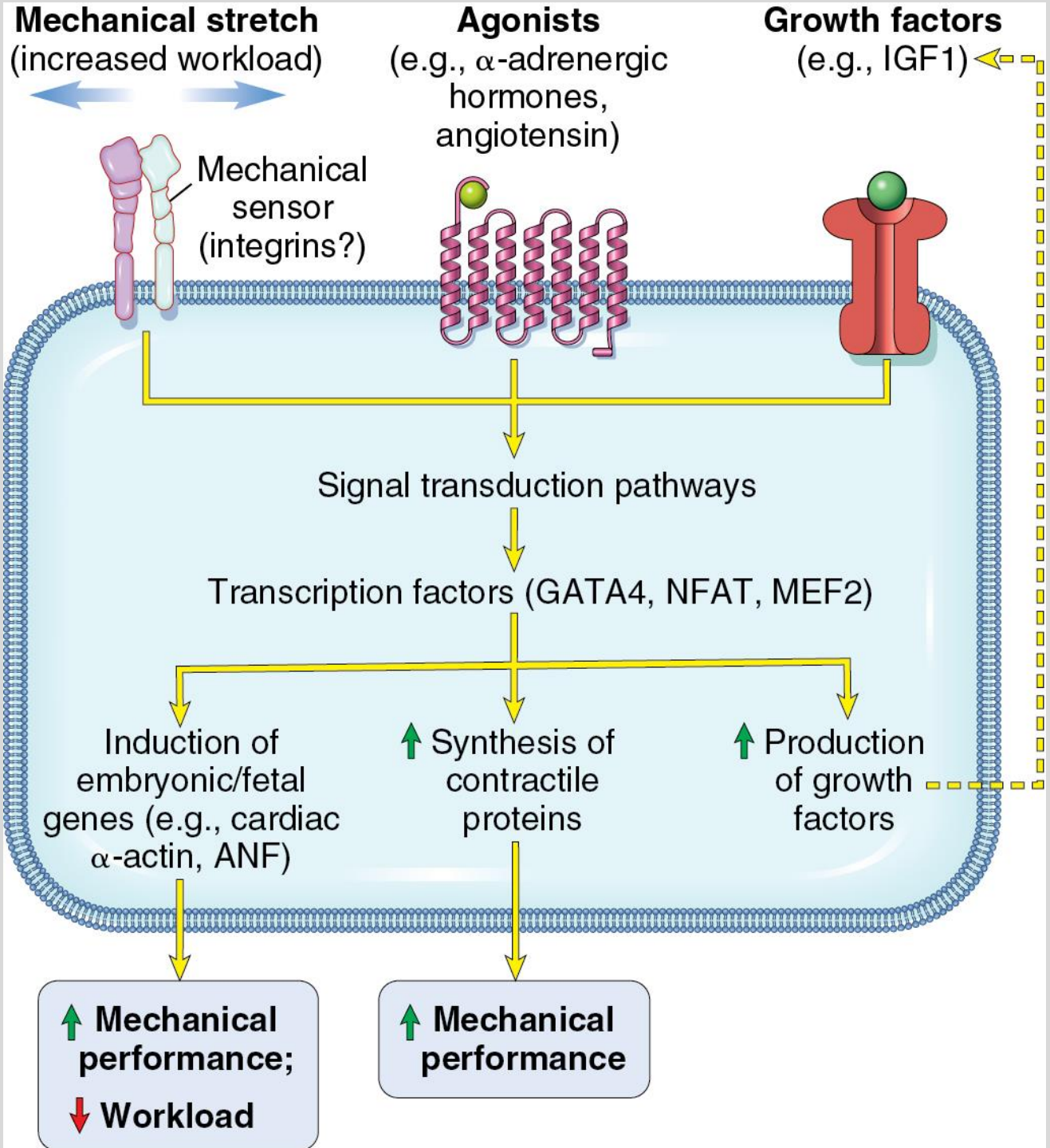
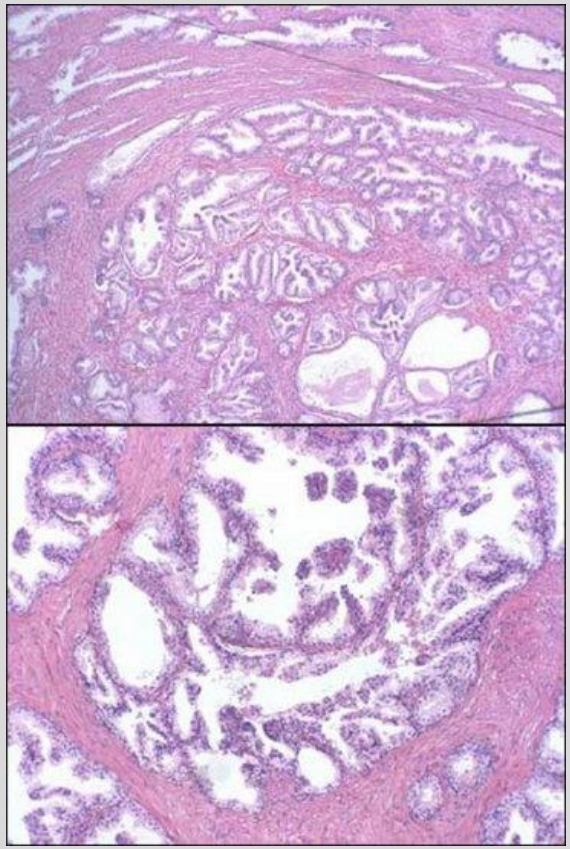


Fig. 2.26 Biochemical mechanisms of myocardial hypertrophy. Mechanical sensors appear to be the major triggers for physiologic hypertrophy, and agonists and growth factors may be more important in pathologic states.

Robbins and Cotran, Pathologic Basis of Disease, 11th ed. 2025

Case

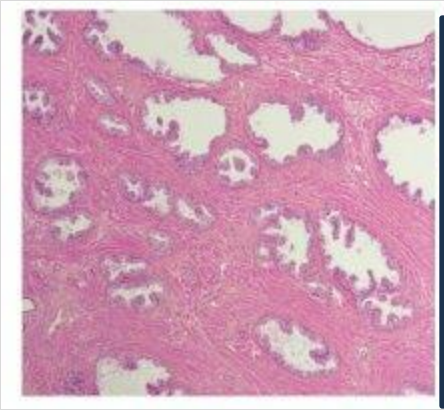
A 70 year old man complains of difficulty urinating, weak urinary stream, and having to get up several times at night to urinate (nocturia). His PSA is mildly elevated. He undergoes a transurethral resection of his prostate.



Prostate gland – what type of epithelium is present?

Is there an increase in number of cells?

What is this cellular adaptation called?



NORMAL PROSTATE

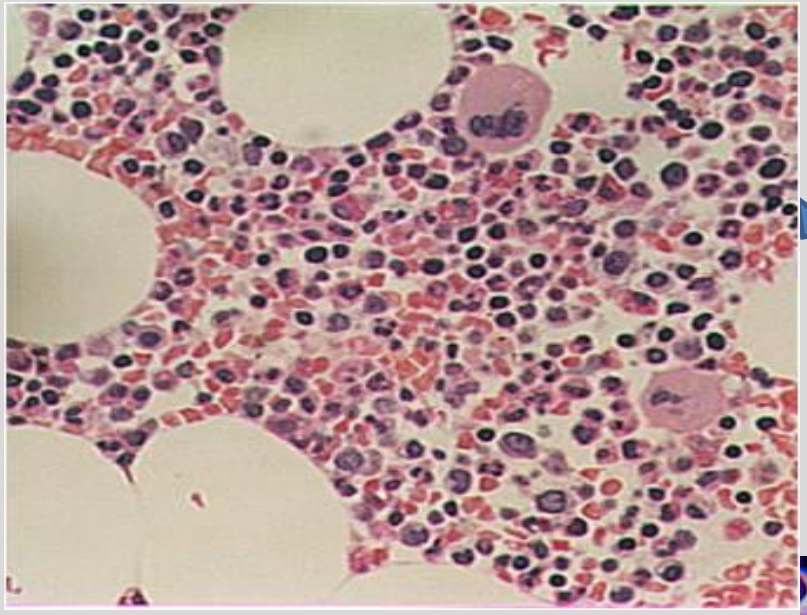
https://www.researchgate.net/publication/224696427_A_New_Feature_For_Detection_Of_Prostate_Cancer_Based_On_RF_Ultrasound_Echo_Signals/figures?lo=1

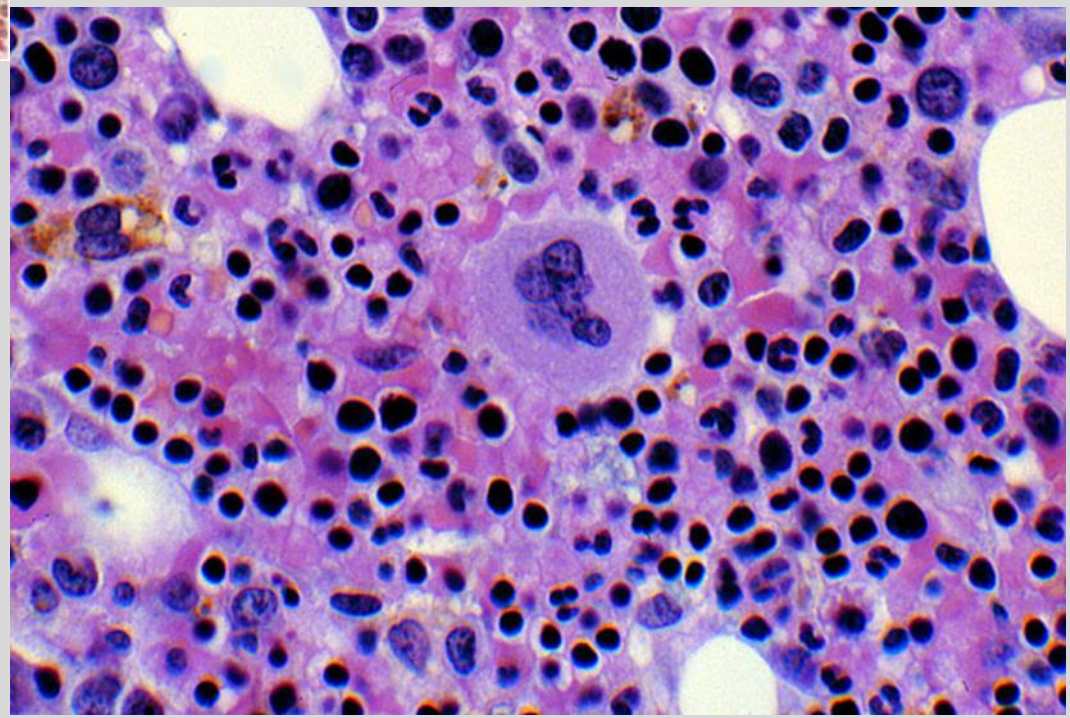
https://www.researchgate.net/publication/306259924_Benign_Prostate_Disorders/figures?lo=1

Case

A 45 year old woman is pale and weak and blood studies indicate a decrease in her red blood cell count. She is diagnosed with anemia. However, her bone marrow biopsy shows an increase in red blood cell precursor cells indicating an attempt to compensate for the decrease in the peripheral blood.

Normal bone marrow





Increased erythroid precursors

http://www.uaz.edu.mx/histo/pathology/ed/ch_20a/c20a_s47.htm

CELLULAR ADAPTATION - HYPERTROPHY

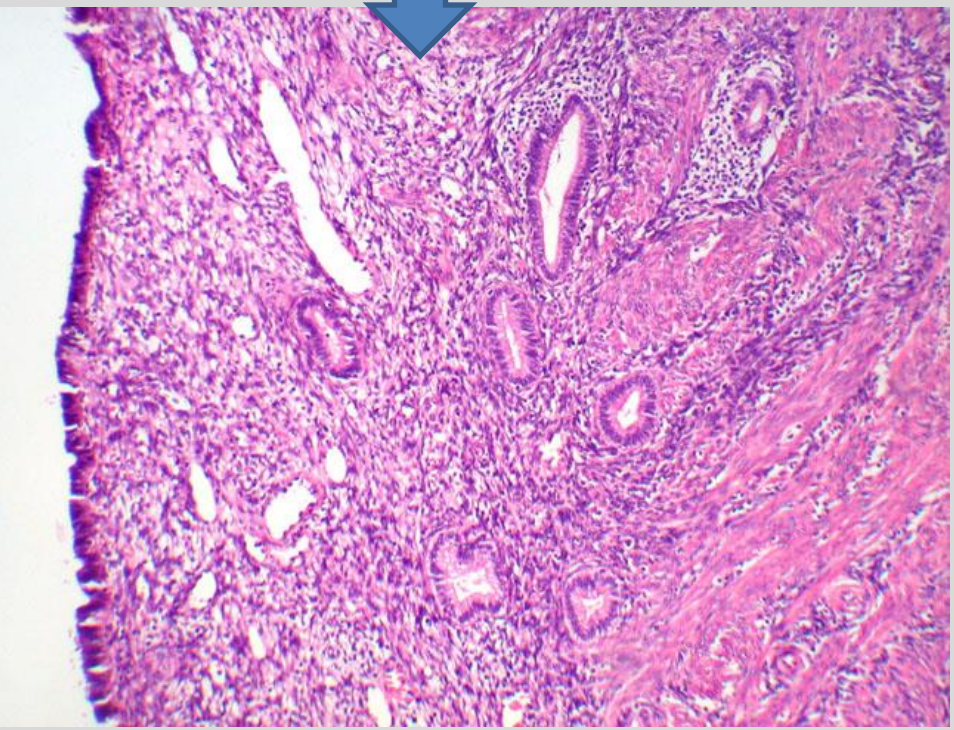
NORMAL HEART

http://www.med.uottawa.ca/patho/eng/Public/cardio/lab2.html

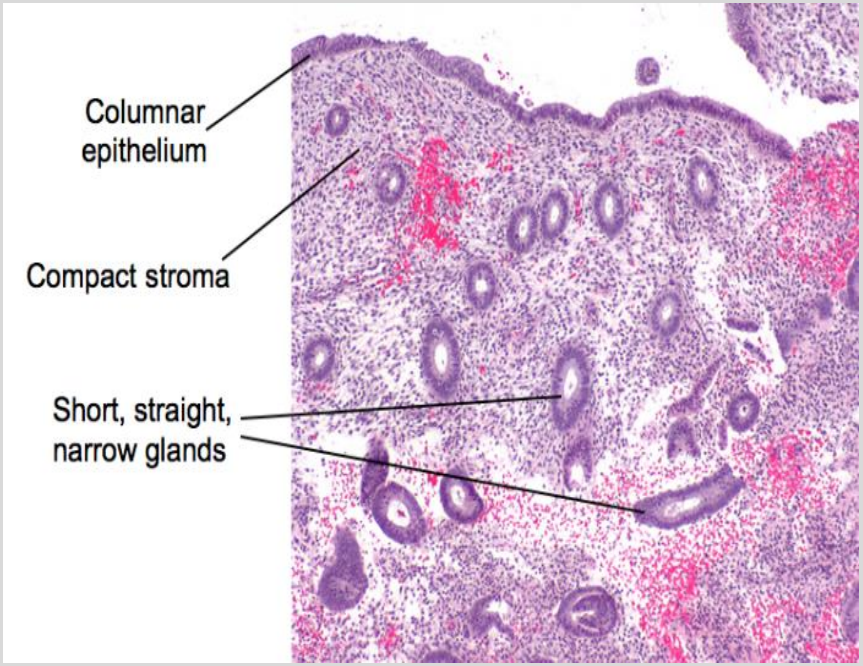
Patient with hypertension has a hypertrophic heart. Why is the heart NOT Hyperplastic?

http://library.med.utah.edu/WebPath/NEOHTML/NEOPL001.html

Endometrium of 70 year old woman. What type of epithelium? What type of cellular adaptation? Physiologic or pathologic?

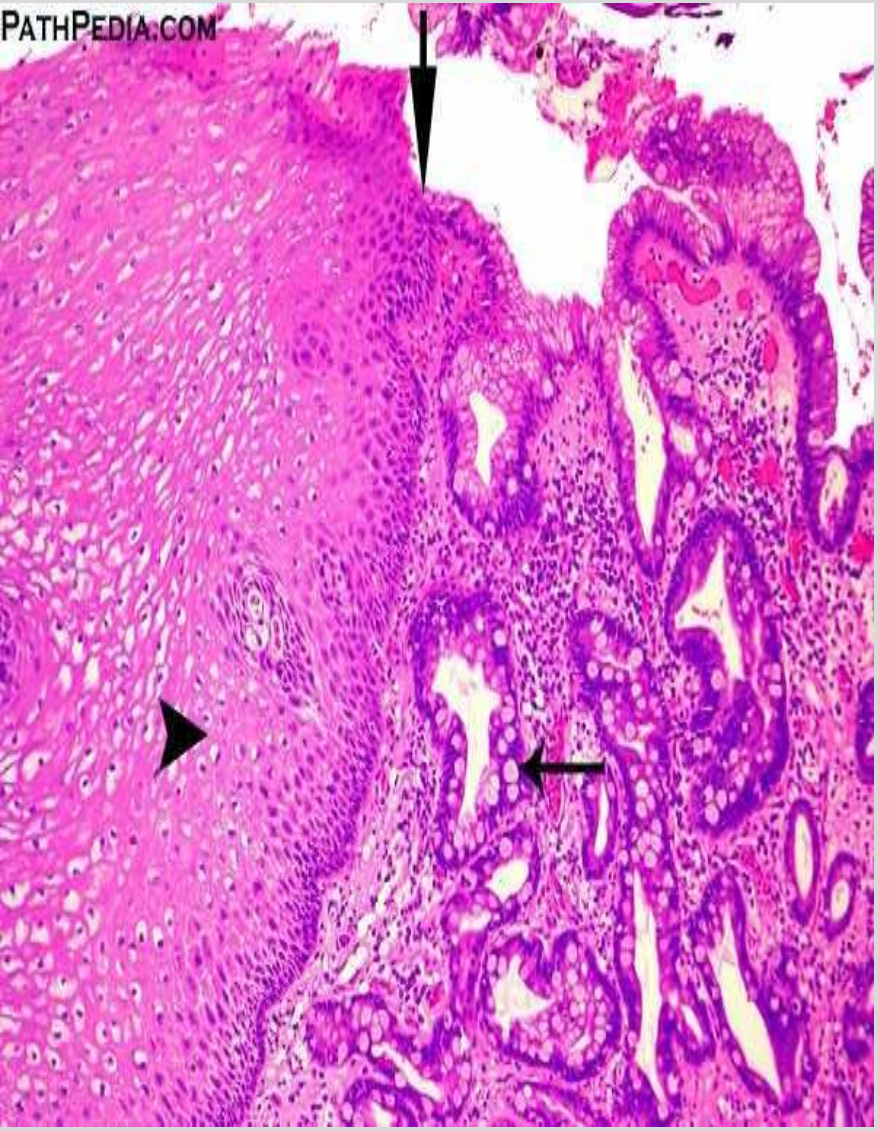


NORMAL



https://histologyblog.com/2015/04/30/histoquarterly-endometrium/

http://catherinebuhariwallabiol3500.blogspot.com/2009/10/endometrium.html

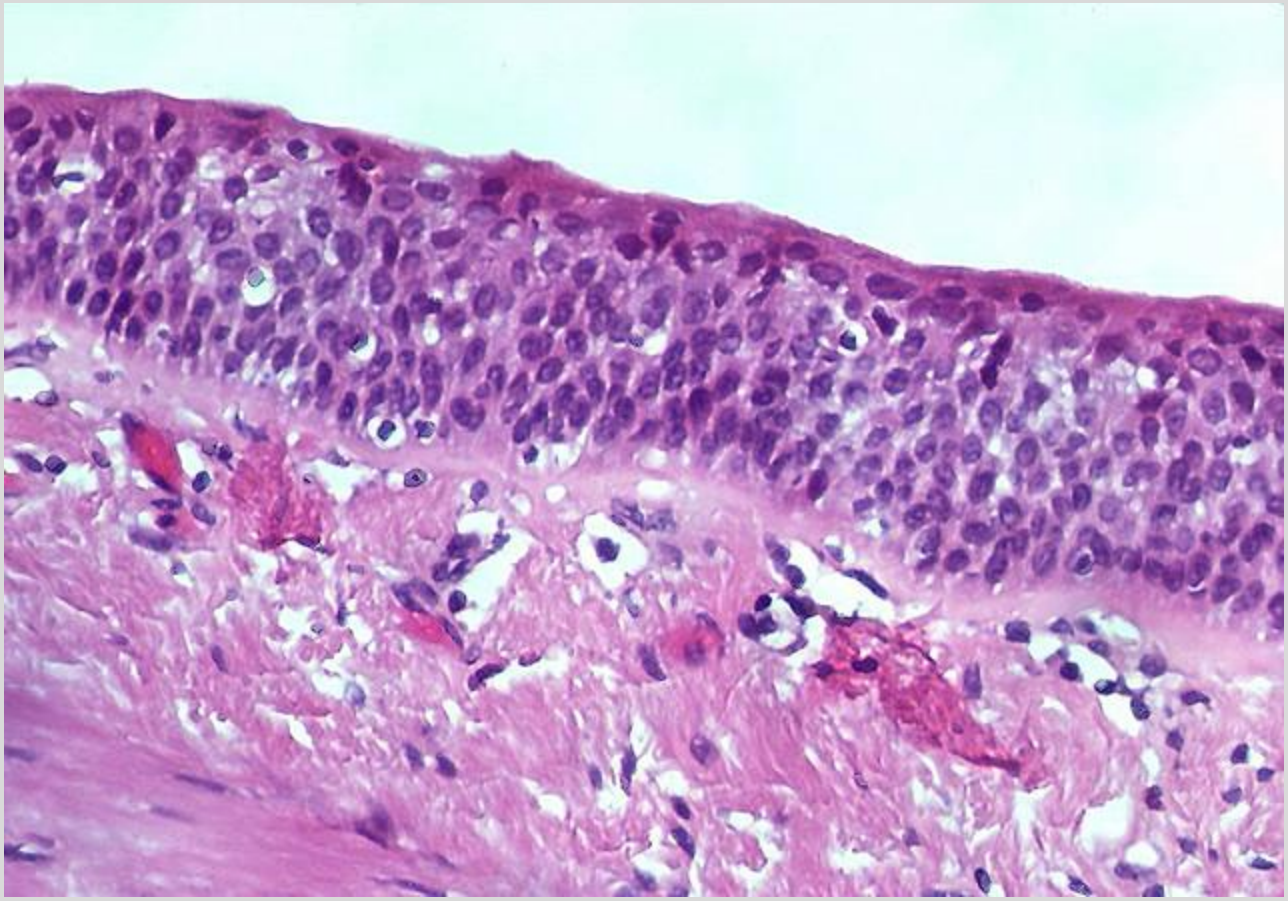


- What is the normal epithelium of the esophagus?
- Why?

- What types of epithelium are seen in the photo?
- Why are there two types of epithelium?

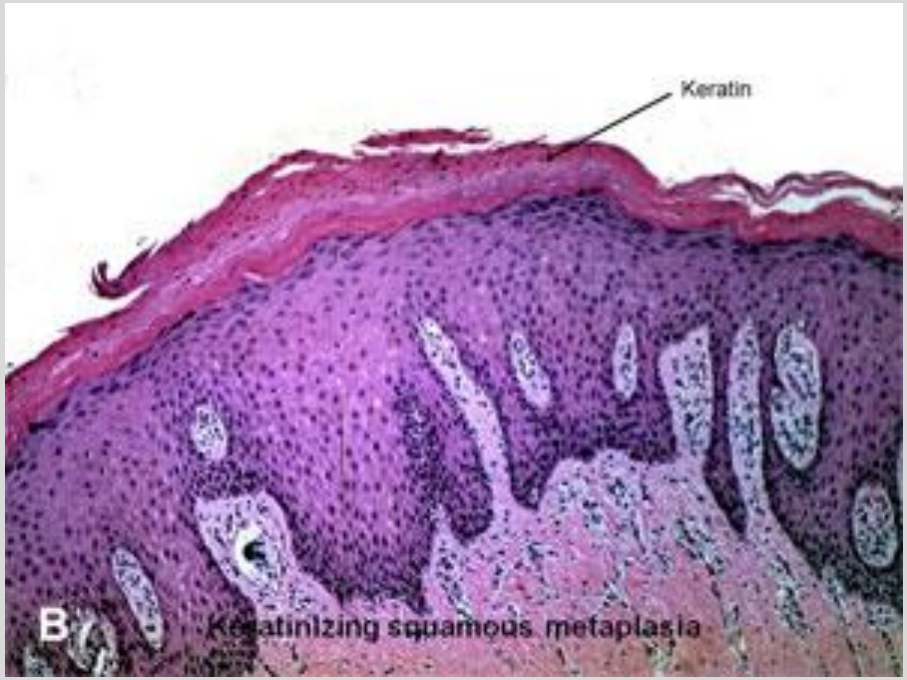
- What is this process called?

http://www.pathpedia.com/education/eatlas/histopathology/esophagus/barretts_metaplasia.aspx



Metaplastic bronchial epithelium – what is normal?

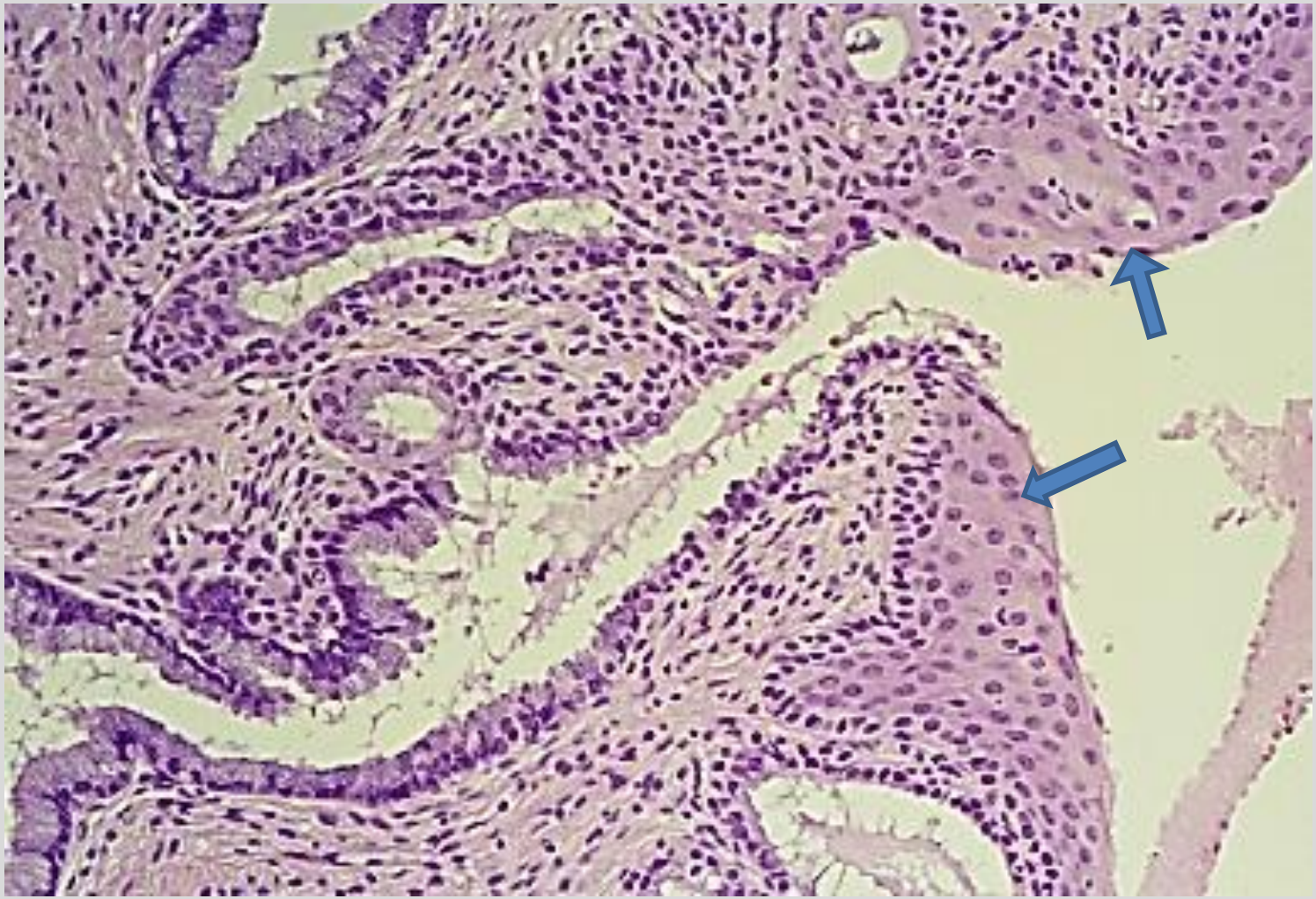
http://librepathology.org/wiki/index.php/Squamous_metaplasia



Keratinizing squamous metaplasia of urinary bladder- why might this occur?
What epithelium normally lines the bladder?

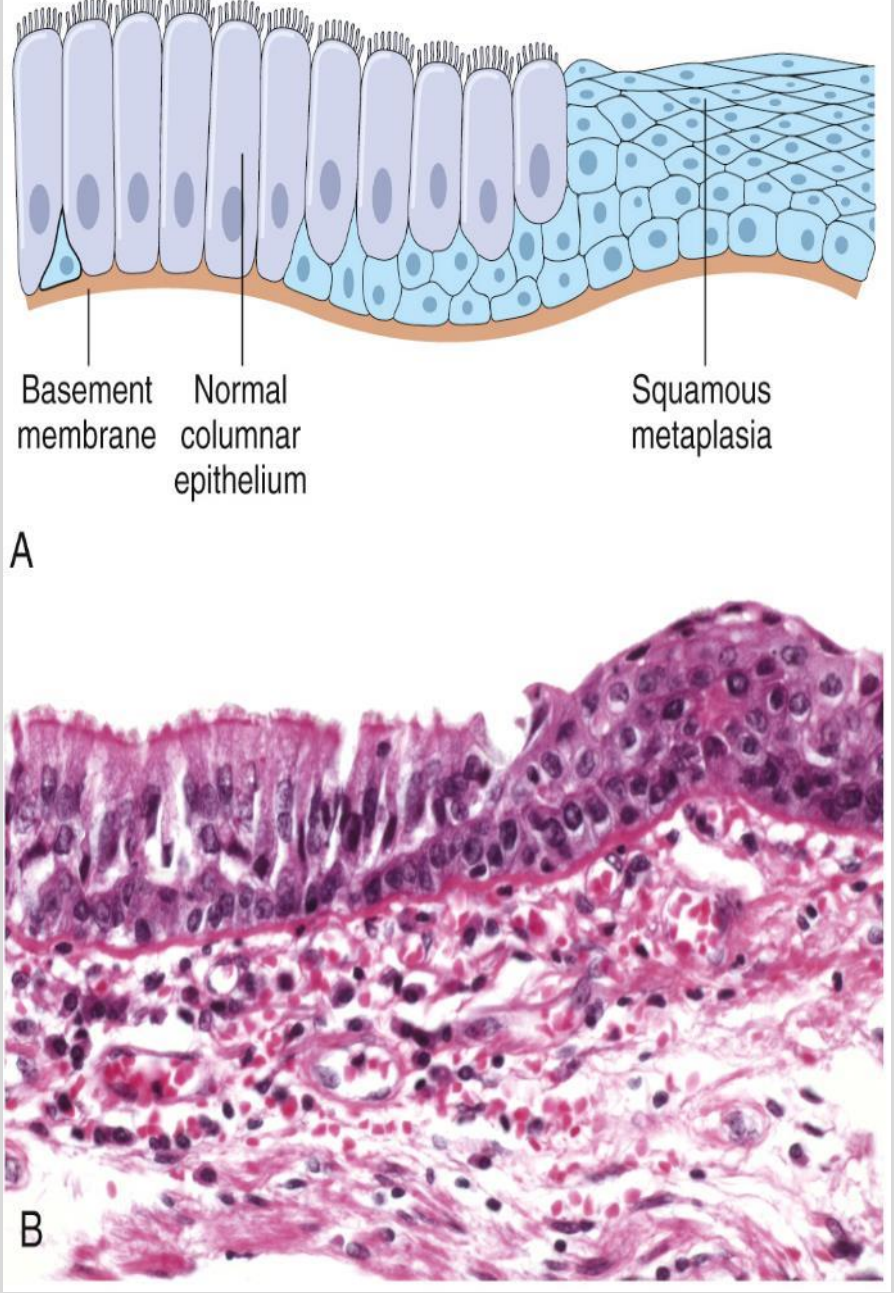
https://www.auanet.org/education/modules/pathology/bladder-lesions/squamous-metaplasia.cfm

Cervix with squamous metaplasia



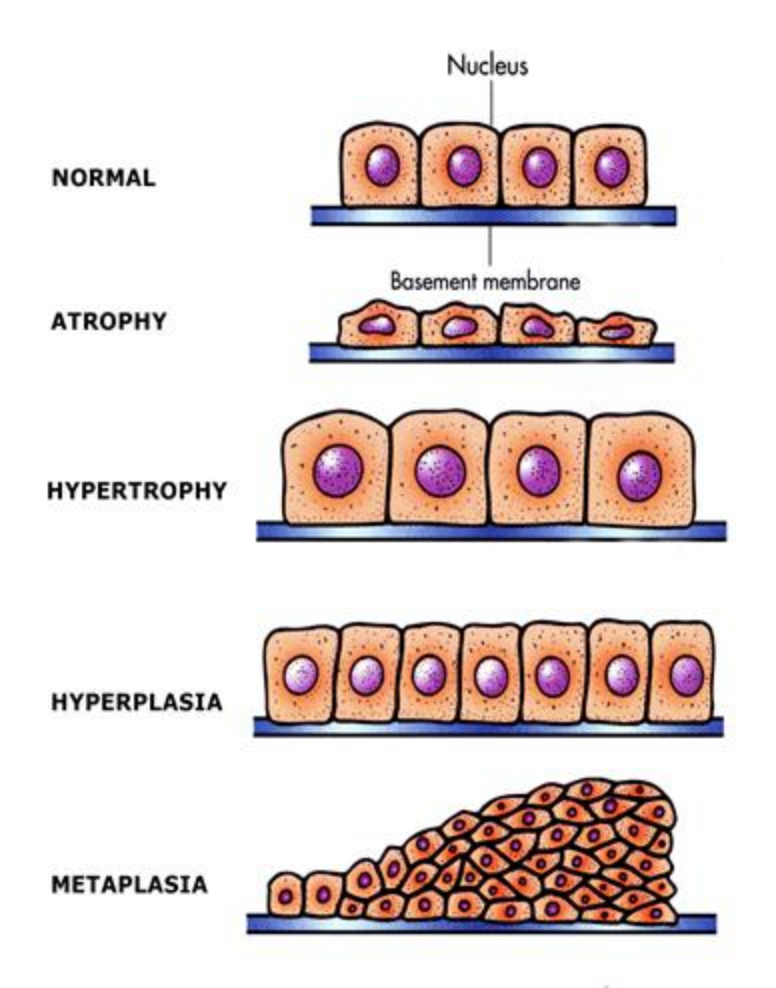
https://tulane.edu/som/departments/pathology/training/neoplasia_image_08.cfm

Metaplasia of columnar to squamous epithelium



Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 2. Figure 2.28

REVIEW



https://quizlet.com/518606252/06-cellular-adaptation-flash-cards/

- **Integrated stress response:** Network of intracellular signaling pathways: modulate gene expression and protein synthesis for cells to adapt to cell injury, respond to stressors

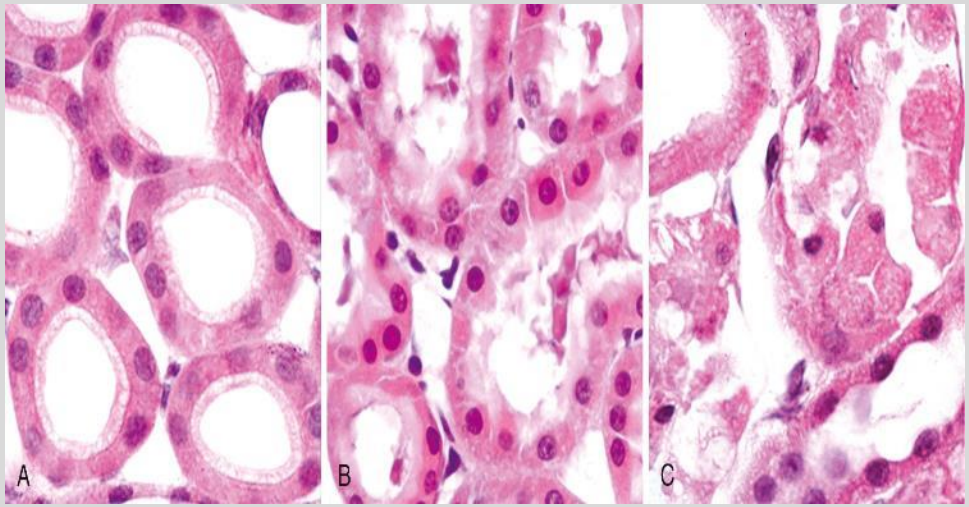
- **Unfolded protein response (ER stress):** Accumulation of misfolded proteins in the ER activates stress adaptive mechanisms; if unchecked, can trigger cell death via apoptosis

- **Autophagy:** Process in which a cell eats its own contents (response to stress in **physiologic** states (e.g., aging and exercise) and in **pathologic** processes (e.g., hypoxia, oxidative stress, organelle, and membrane damage).
    - Nucleation and formation of an isolation membrane, phagophore
    - Formation of a vesicle, the **autophagosome** (regulated by many proteins), from the isolation membrane: intracellular organelles and cytosolic structures sequestered
    - Maturation of autophagosome by fusion with lysosomes, to deliver digestive enzymes that degrade contents of the autophagosome

Robbins and Cotran, Pathologic Basis of Disease, 11th ed. 2025

Cellular swelling - earliest manifestation of cell injury; micro: small clear vacuoles within the cytoplasm; (represent distended and pinched-off segments of ER)

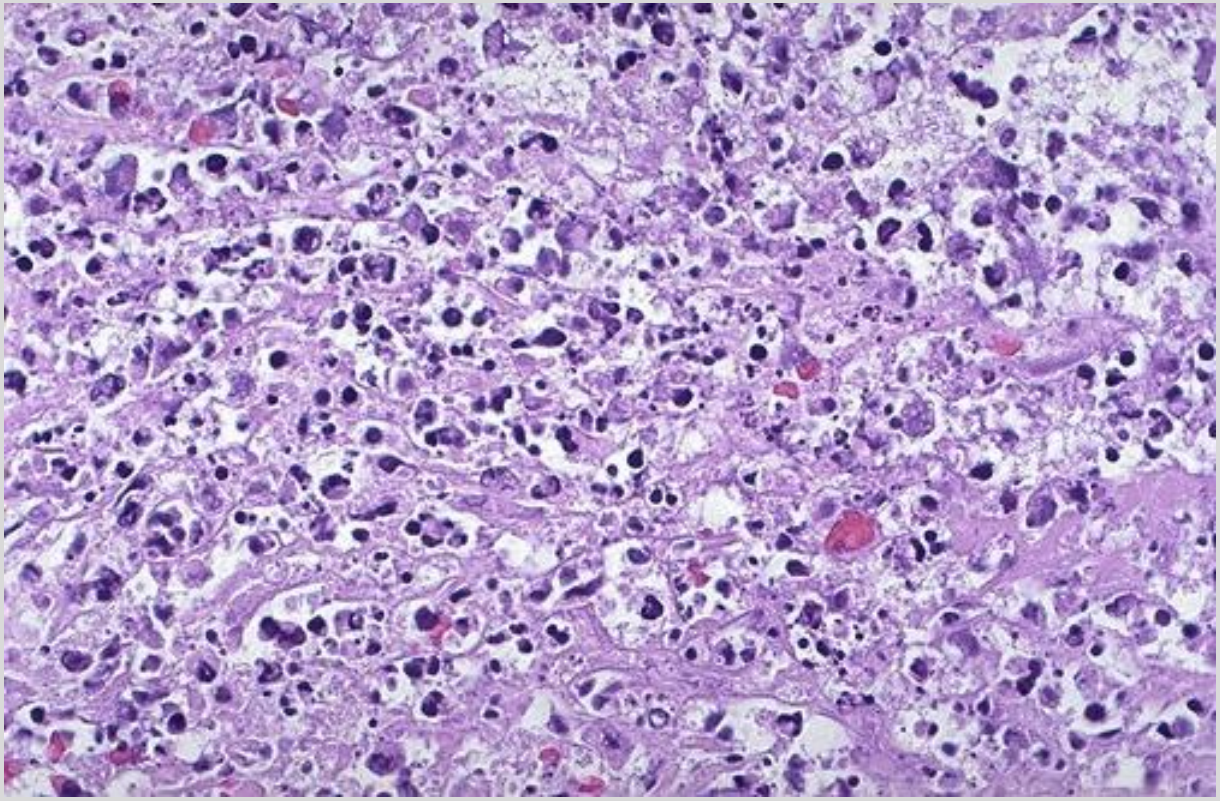
- AKA **hydropic change or vacuolar degeneration**
- Cytoplasm of injured cells appears **red** (eosinophilic) due to loss of RNA
- Eosinophilia becomes worse with progression toward necrosis



Swelling – acute and **reversible**: 0 to approximately 30 minutes

Ischemia causes decreased oxidative phosphorylation and decreased ATP which then leads to decreased function of Na+ pump and subsequent influx of Ca, H2O and Na: resulting in cell swelling

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 2, Fig. 2.5



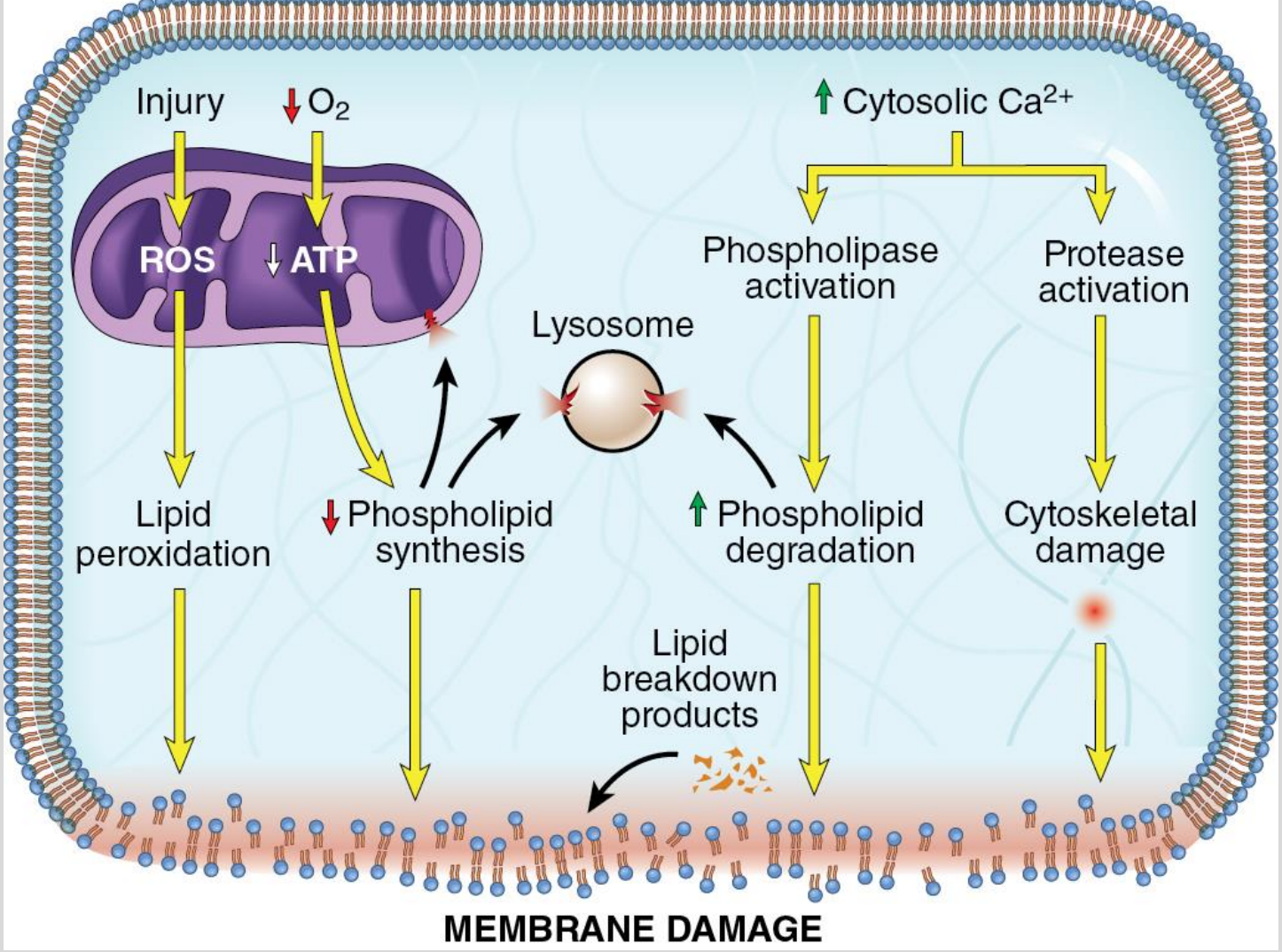
Many nuclei have become **pyknotic (shrunken and dark)** and have undergone **karyorrhexis (fragmentation)** and **karyolysis (dissolution).**

When cellular injury is severe, cell death (necrosis) occurs

Nuclear changes:

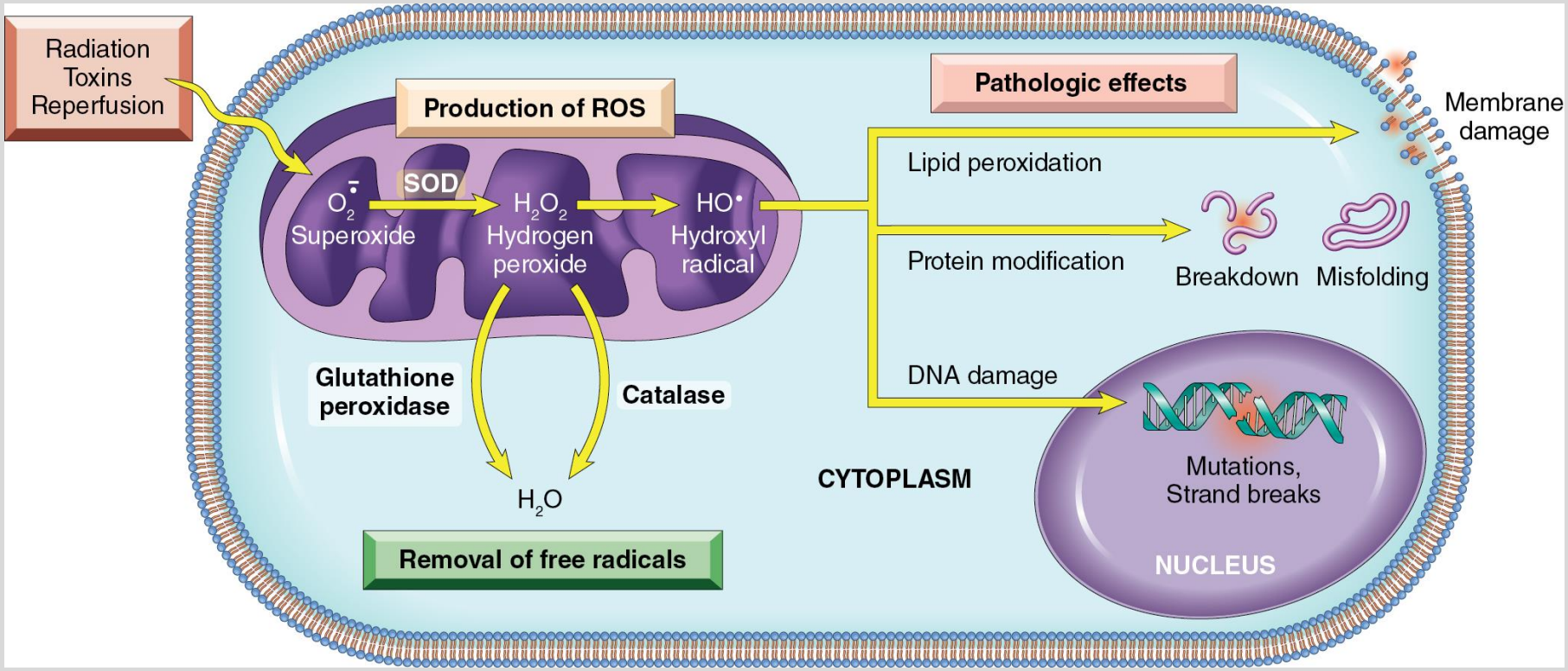
- basophilia of the chromatin fades **(karyolysis),** reflects loss of DNA because of enzymatic degradation by endonucleases
- **pyknosis,** characterized by nuclear shrinkage and increased basophilia.
- **Karyorrhexis** pyknotic nucleus undergoes fragmentation
- With time (1 or 2 days), the nucleus in the necrotic cell totally disappears.

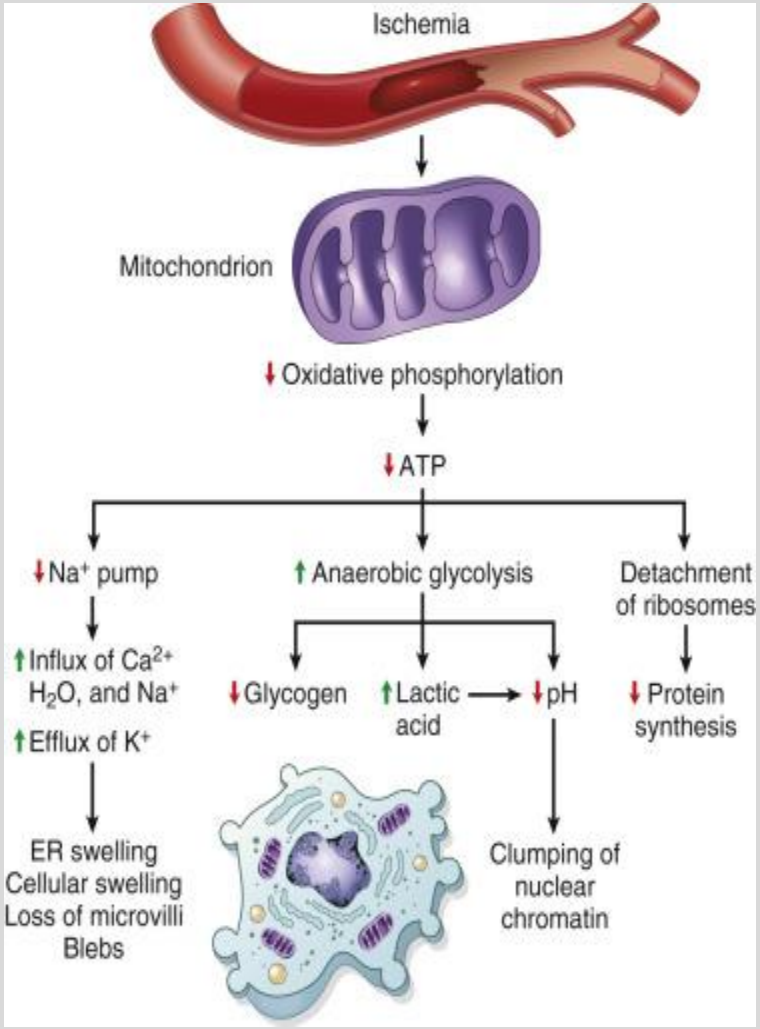
http://drpersian.blogfa.com/9004.aspx

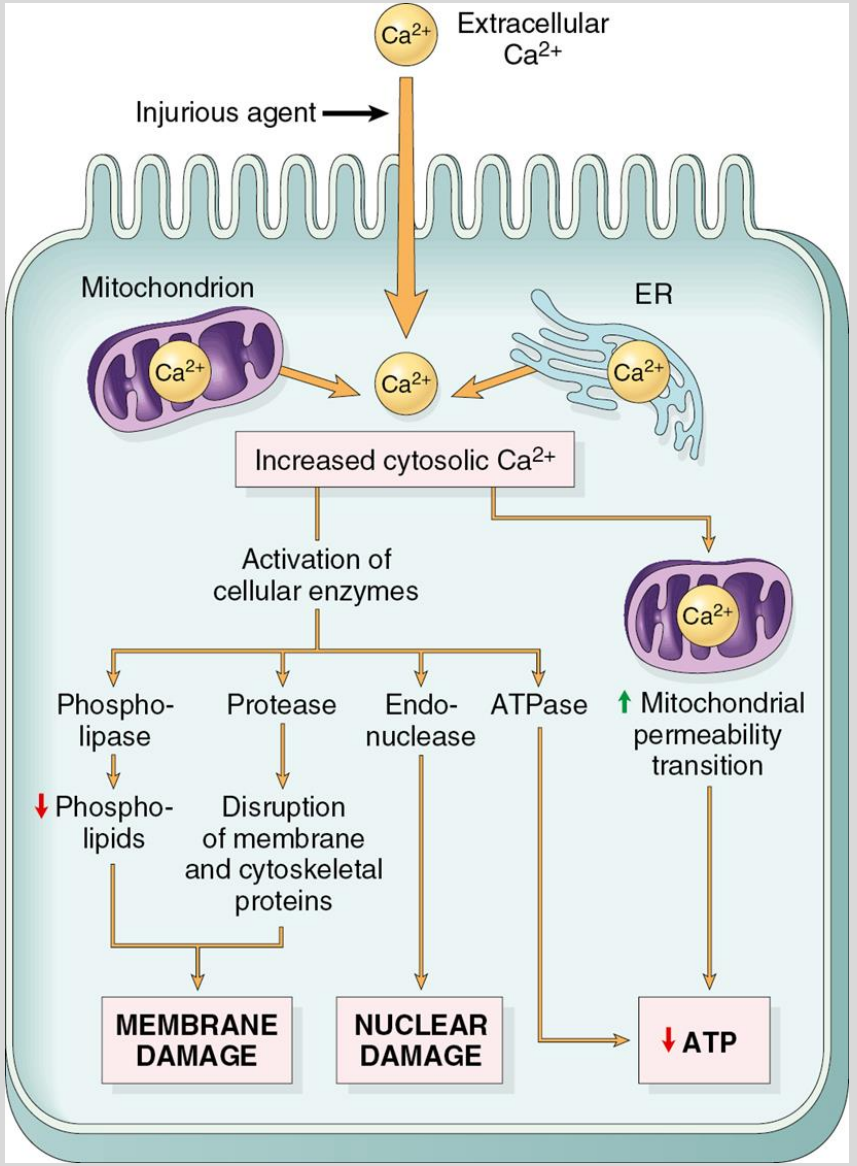


Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025

- Free radicals: unstable - decay spontaneously
- Cells have multiple nonenzymatic and enzymatic mechanisms to remove free radicals and minimize injury:
  - *Antioxidants* either block free radical formation or inactivate (e.g., scavenge) free radicals, e.g, lipid-soluble vitamins E and A, ascorbic acid and glutathione
  - Free *iron* and *copper* can catalyze formation of ROS. Normally, reactivity of these metals is minimized by binding to storage and transport proteins (e.g., transferrin, ferritin, lactoferrin, and ceruloplasmin)
  - Several *enzymes* act as free radical–scavenging systems and break down H_2O_2 and $O2\bullet^-$:
  - 1. *Catalase,* present in peroxisomes, decomposes H_2O_2 ($2H_2O_2 \rightarrow O_2 + 2H_2O$).
  - 2. *Superoxidase dismutases* (SODs) are found in many cell types and convert $O2\bullet^-$ to H_2O_2 ($2\ O2\bullet^- + 2H \rightarrow H_2O_2 + O_2$).
  - 3. *Glutathione peroxidase* also protects against injury by catalyzing free radical breakdown ($H_2O_2 + 2GSH \rightarrow$ GSSG [oxidized glutathione] + $2H_2O$).







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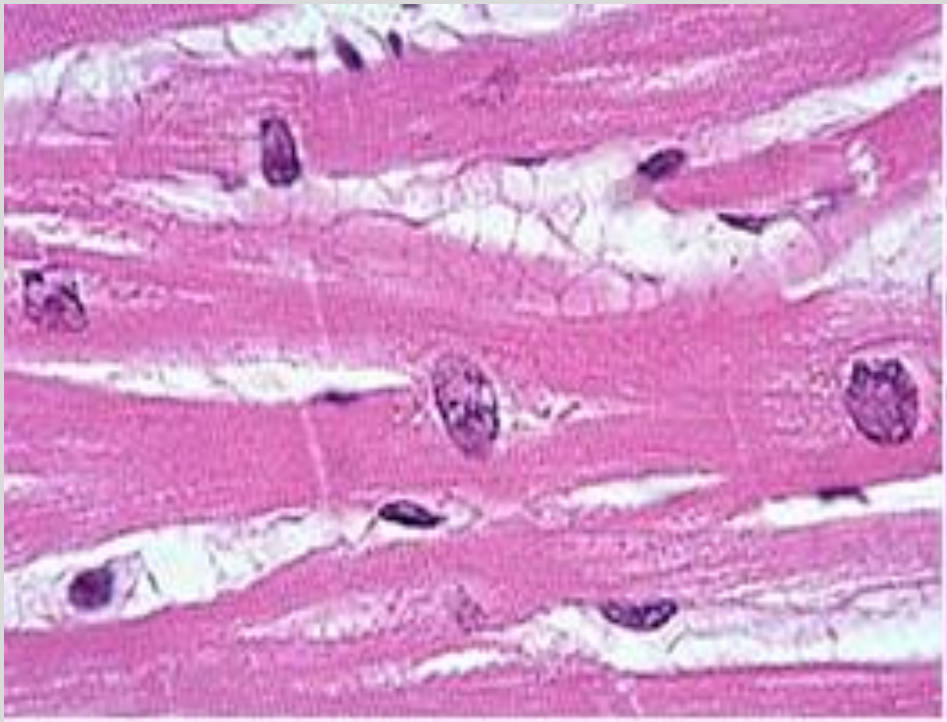
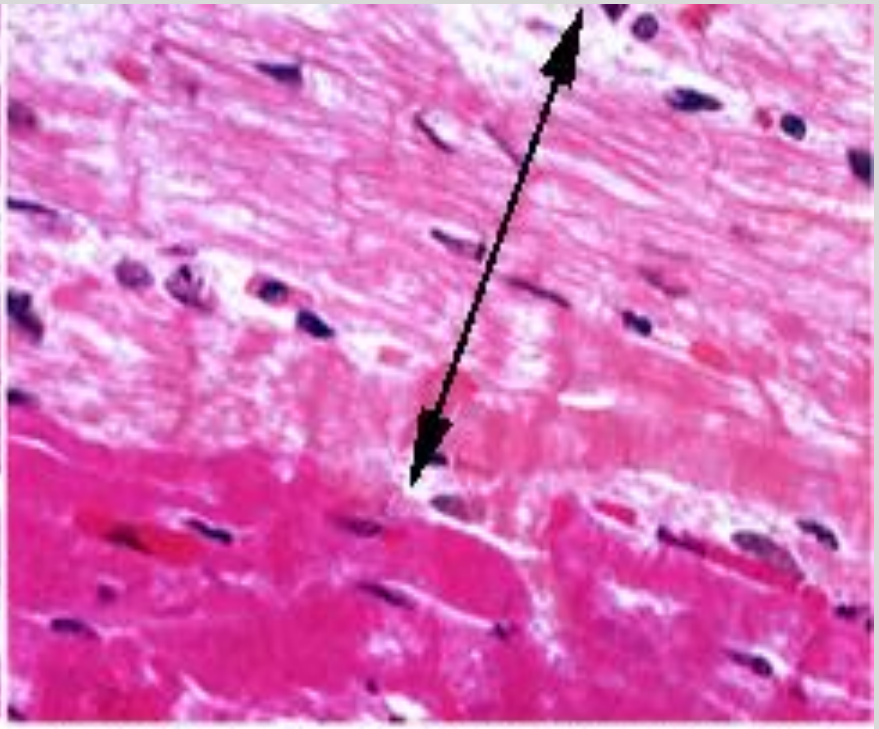
Robbins and Cotran Pathologic Basis of Disease, 11th ed,. 2025



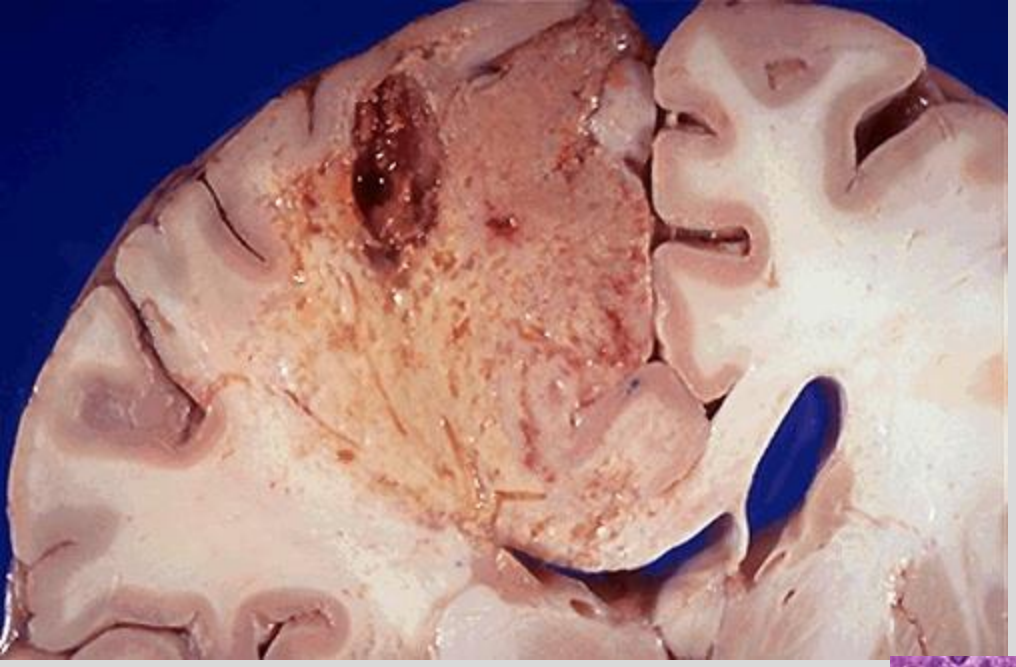
Normal Myocardium: nuclei are basophilic, open, delicate; striations are visible in eosinophil cytoplasm



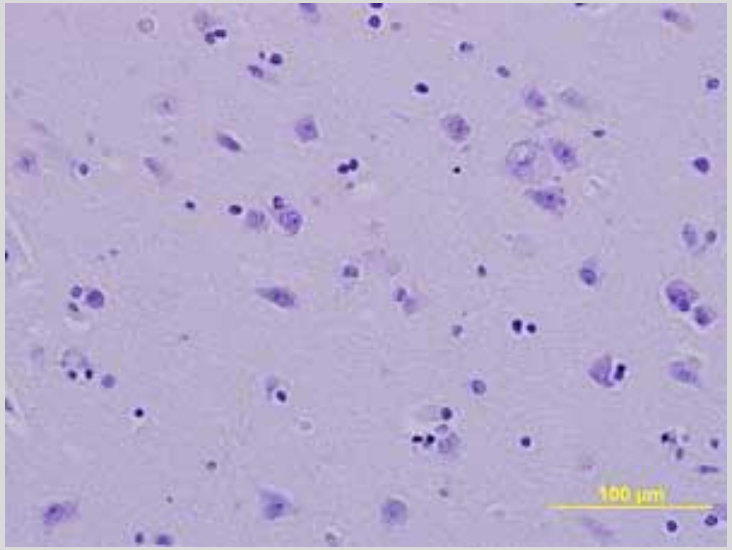
Ischemic areas show loss of nuclei to pyknosis & karyolysis; increased eosinophilia of cytoplasm but retention of tissue architecture

What type of necrosis does myocardium undergo? Morphologic pattern

http://studydroid.com/printerFriendlyViewPack.php?packId=506801

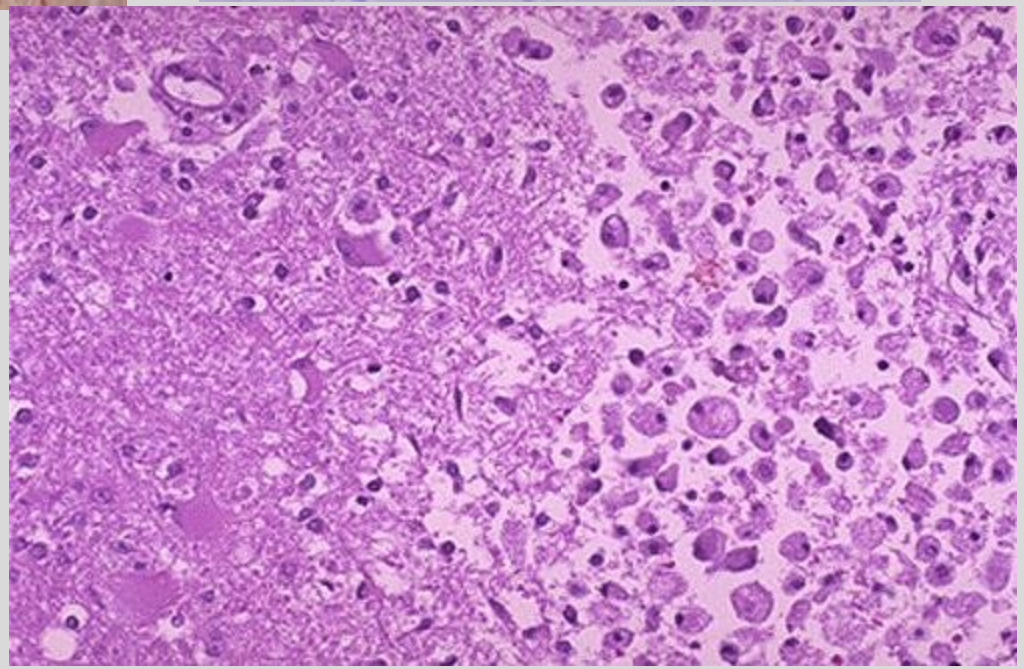


Normal



What Organ?

What type of necrosis?



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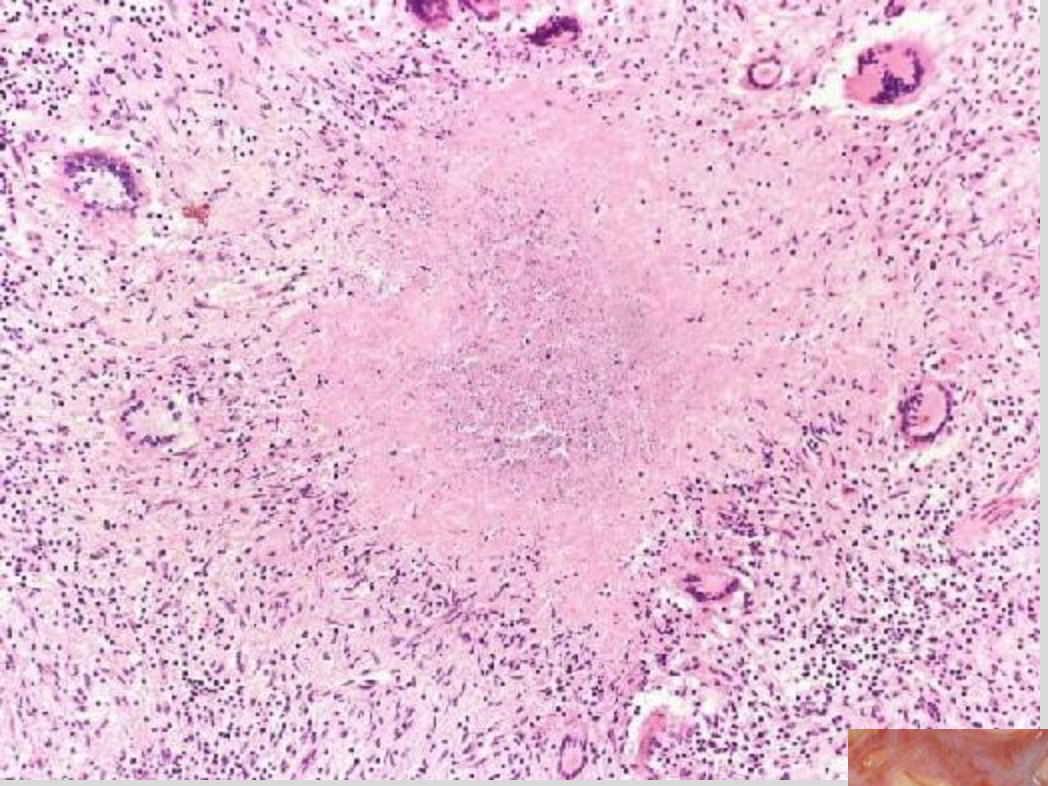
http://library.med.utah.edu/WebPath/CINJHTML/CINJ025.html



What type of necrosis?

Examples?

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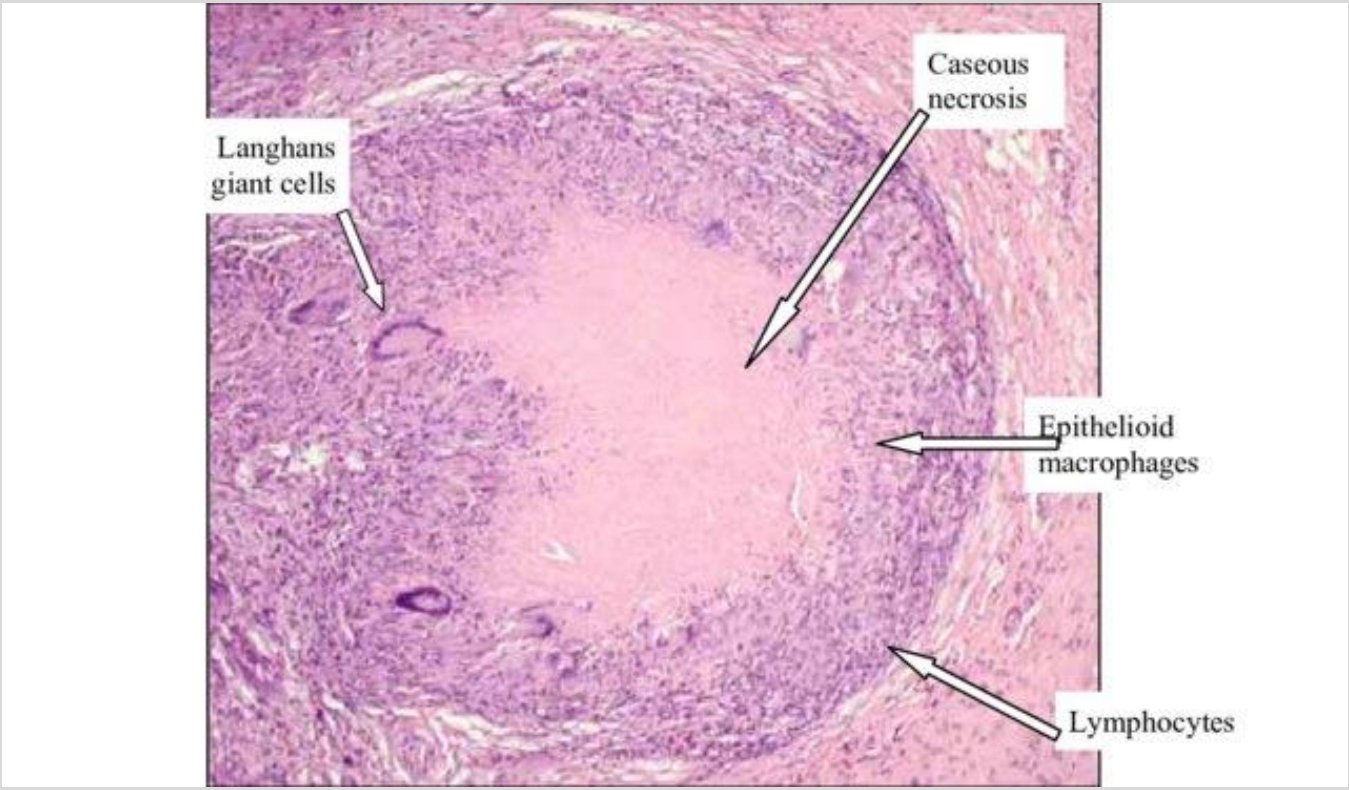
http://pathology.class.kmu.edu.tw/ch16/Slide161.htm

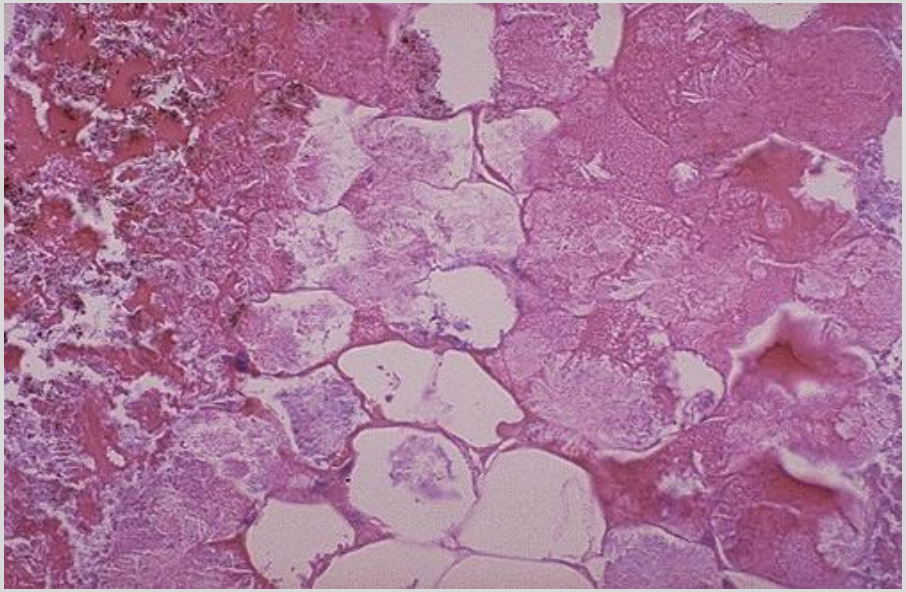


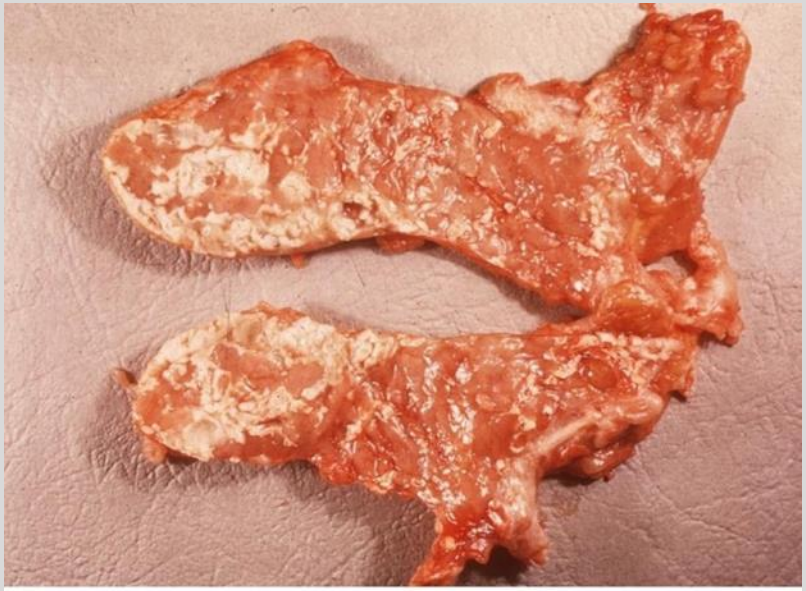
Centrally, caseous necrosis is apparent as amorphous pink material

https://www.researchgate.net/publication/44138406_Cytokines_and_tuberculosis_an_investigation_of_tuberculous_lung_tissue_and_a_comparison_with_sarcoidosis/figures?lo=1 Juanita Bezuidenhout

Case

A 68 year old male alcoholic presents with mid-epigastric abdominal pain and nausea. His serum amylase and lipase levels are markedly elevated





http://picasaweb.google.com/lh/photo/2bVfmGoECVga4crlneb67w

Fatty necrosis – Areas of fat destruction, release of lipase enzyme which breaks down fatty acids in cell membranes

e.g., acute pancreatitis (peripancreatic fat)

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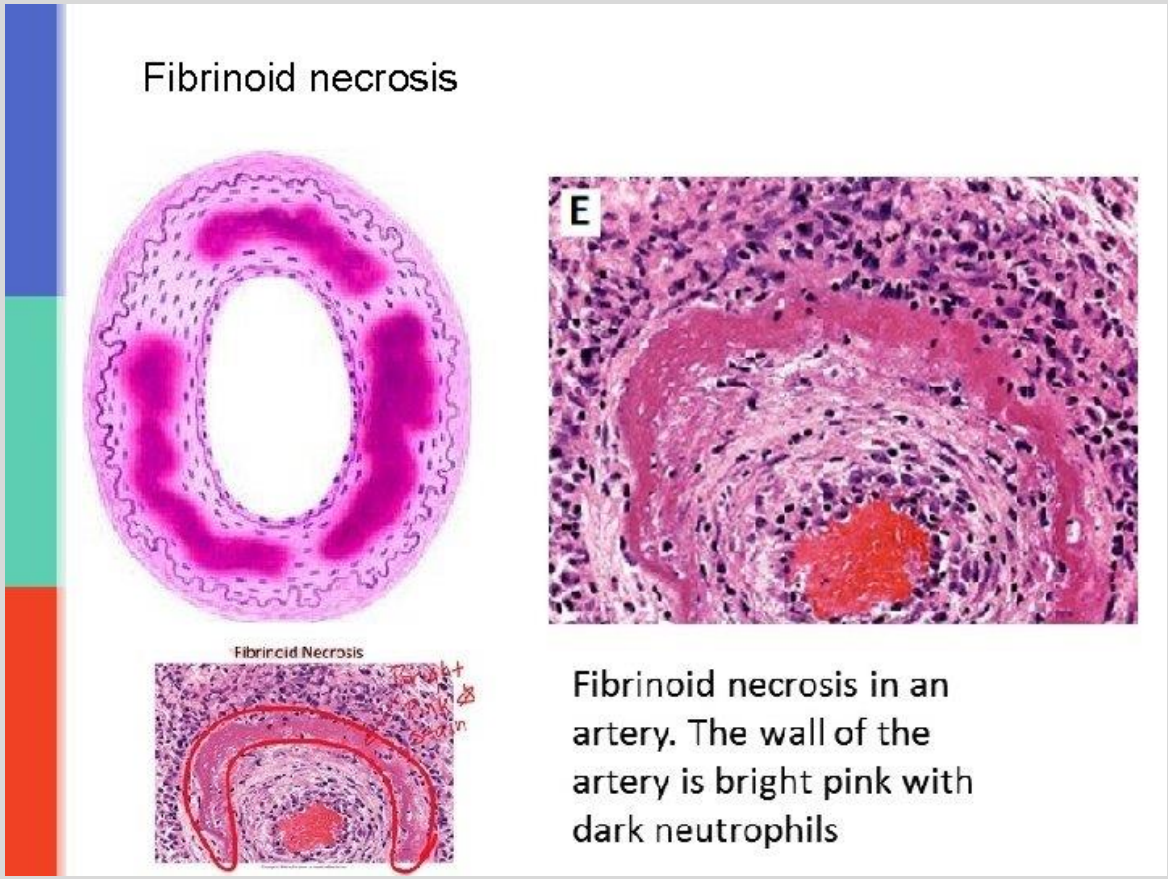
http://library.med.utah.edu/WebPath/CINJHTML/CINJ027.html

https://bdshelp.wordpress.com/2011/01/17/necrosis

Fibrinoid necrosis – usually seen in vascular damage caused by immune reactions; Ag-Ab deposits in blood wall; immune complexes combine with fibrin: vessels wall damage

Deposits of immune complexes, along with plasma proteins that have leaked out of vessels, result in **a bright pink, amorphous appearance** in H&E stains called "fibrinoid" (fibrin-like)



https://slidetodoc.com/pathology-chapter-cell-injury-for-first-year-medical/
Dr. Sufia Husain

Apoptosis: Physiological

- **Normal phenomenon to eliminate cells no longer needed, or mechanism to maintain a constant number of various cell populations in tissues.**

- *Removal of supernumerary cells (excess of required number) during development*
- *Involution of hormone-dependent tissues on hormone withdrawal, (e.g,* endometrial cell breakdown during the menstrual cycle)
- *Cell turnover in proliferating cells populations, e.g.,* epithelial cells in intestinal crypts to maintain constant cell numbers (*homeostasis*).
- *Elimination of lymphocytes that do not produce functional antigens receptors (e.g* immature lymphocytes in the bone marrow and thymus and germinal center B cells)
- *Elimination of potentially harmful self-reactive lymphocytes* to prevent autoimmunity
- Death of host cells that have served their useful purpose, e.g., neutrophils in an *acute inflammatory response,* and lymphocytes at the end of an *immune response* .

Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025

Apoptosis: **pathological**

- **Apoptosis eliminates cells that are injured beyond repair** without eliciting a host reaction, limiting collateral tissue damage

- *DNA damage* - protective by preventing survival of cells with DNA mutations that can lead to malignant transformation
- *Accumulation of misfolded proteins* - cell death triggered by improperly folded intracellular proteins and the subsequent ER stress response
- Certain *infections, esp.* viral infections, because of the virus itself (e.g., adenovirus and HIV infections) or host immune response (as in viral hepatitis)
  - Important host response to viruses: cytotoxic T lymphocytes (CTLs) specific for viral proteins induce apoptosis of infected cells in an attempt to eliminate reservoirs of infection
  - The same CTL-mediated mechanism is responsible for killing tumor cells, cellular rejection of transplants, and tissue damage in graft-versus-host disease.
- May also contribute to *pathologic atrophy in parenchymal organs after duct obstruction, e.g.,* in the pancreas, parotid gland, and kidney

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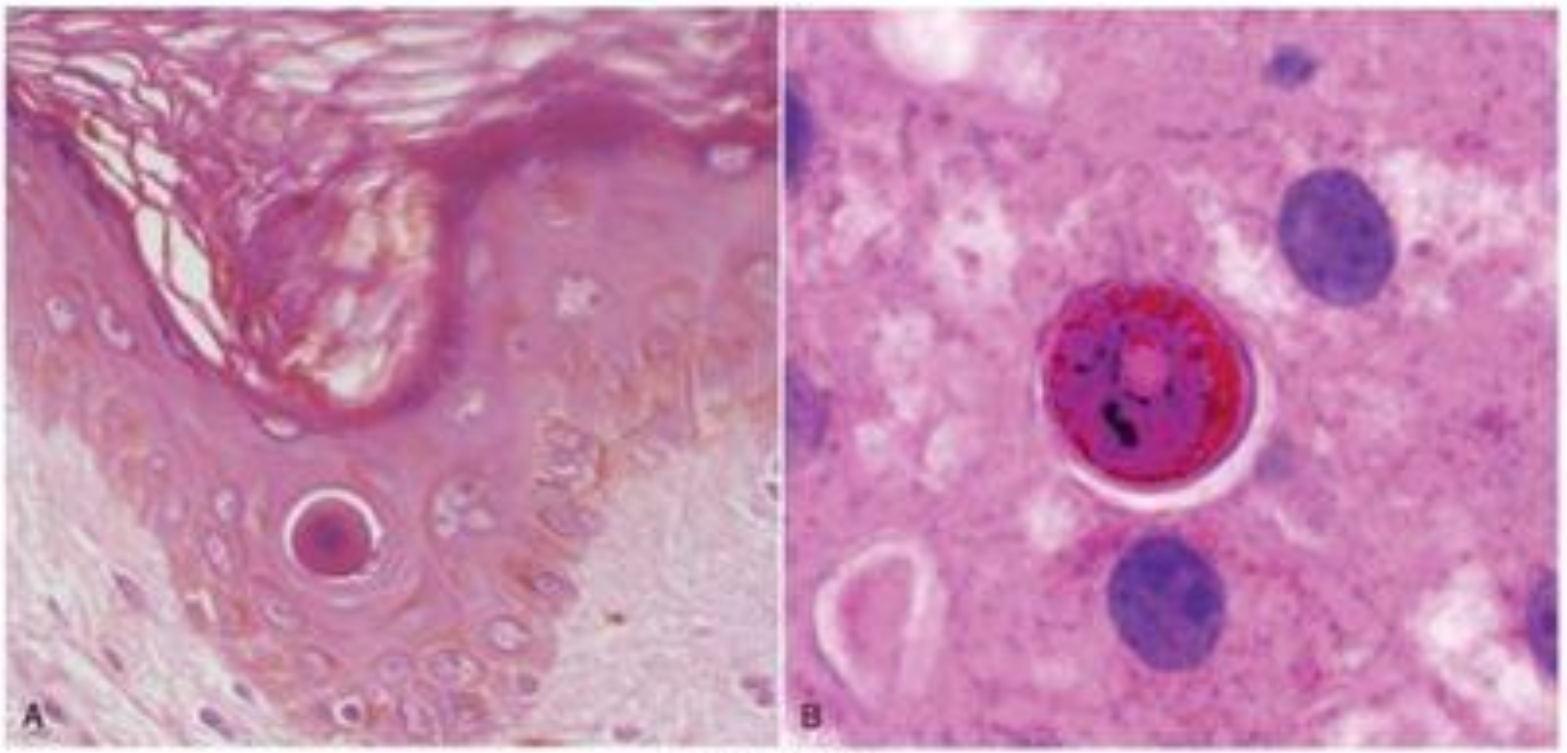
Apoptosis - skin



https://www.studyblue.com/notes/note/n/final-path/deck/9508072

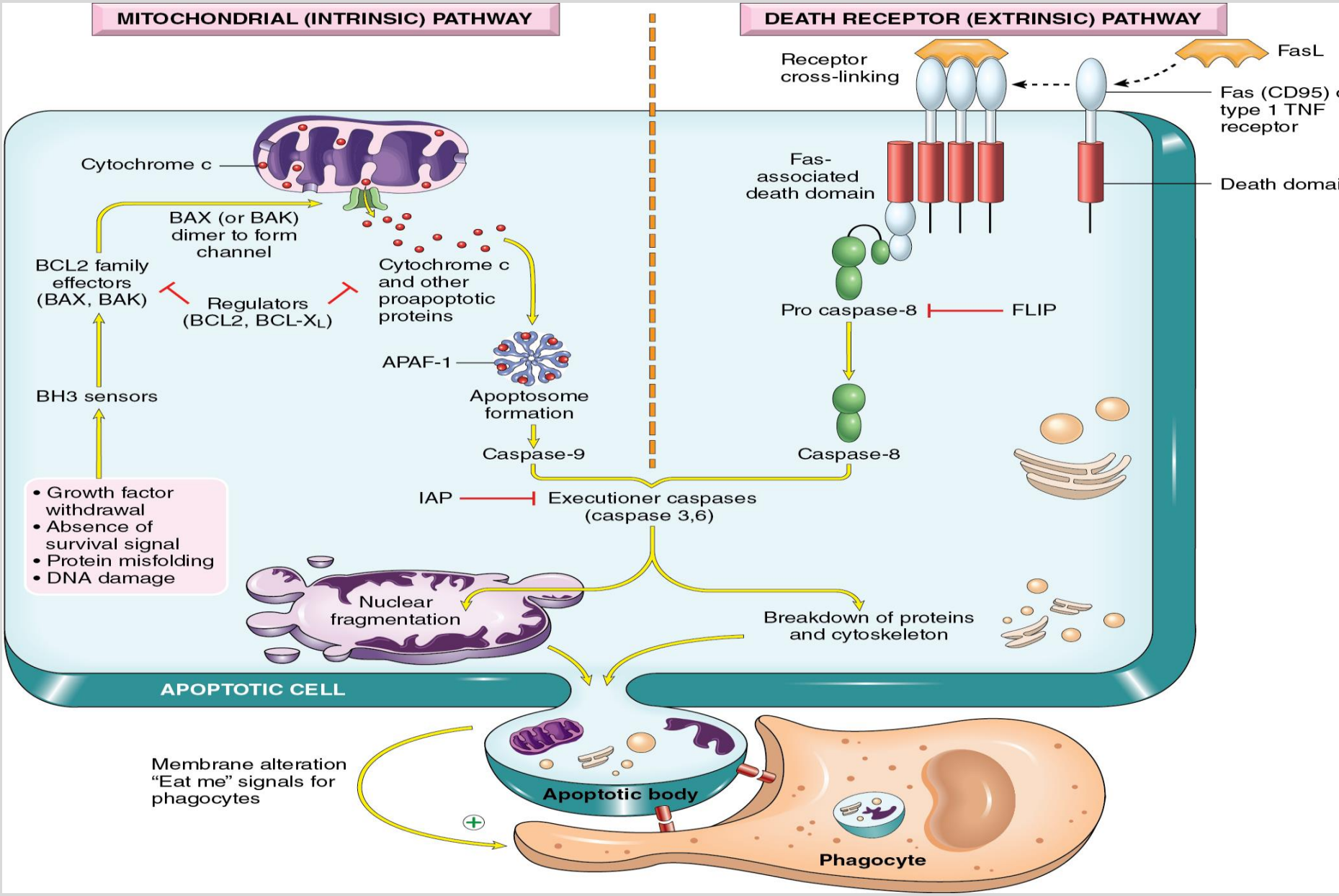
Apoptosis – Extrinsic (Death Receptor Initiated) Pathway

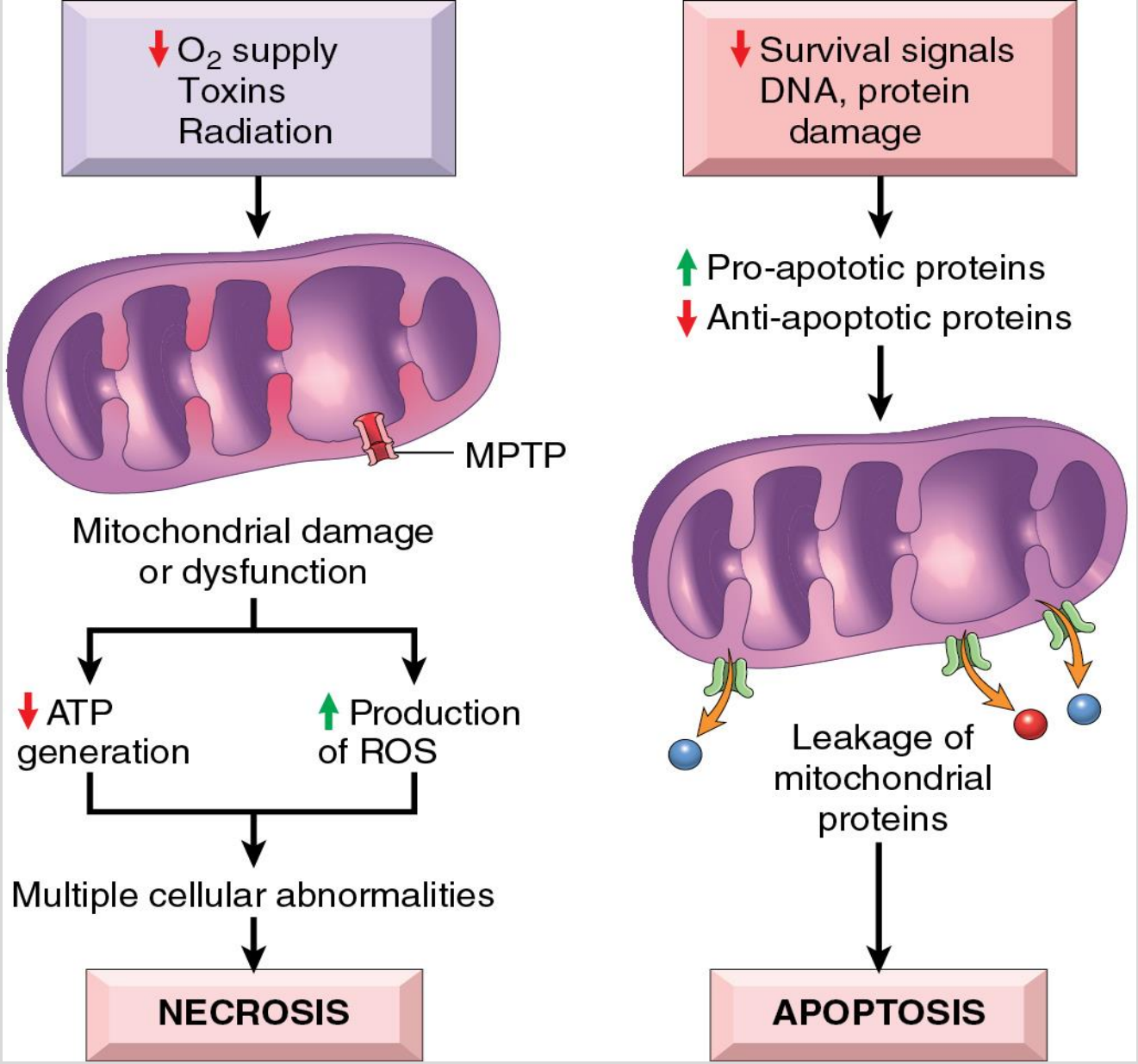
- Initiated by engagement of **plasma membrane death receptors**
- Death receptors = members of TNF receptor family that contain a cytoplasmic domain involved in protein-protein interactions: death domain needed for delivering apoptotic signals

- Best-known death receptors are the type 1 TNF receptor (TNFR1) and related protein called Fas (CD95),

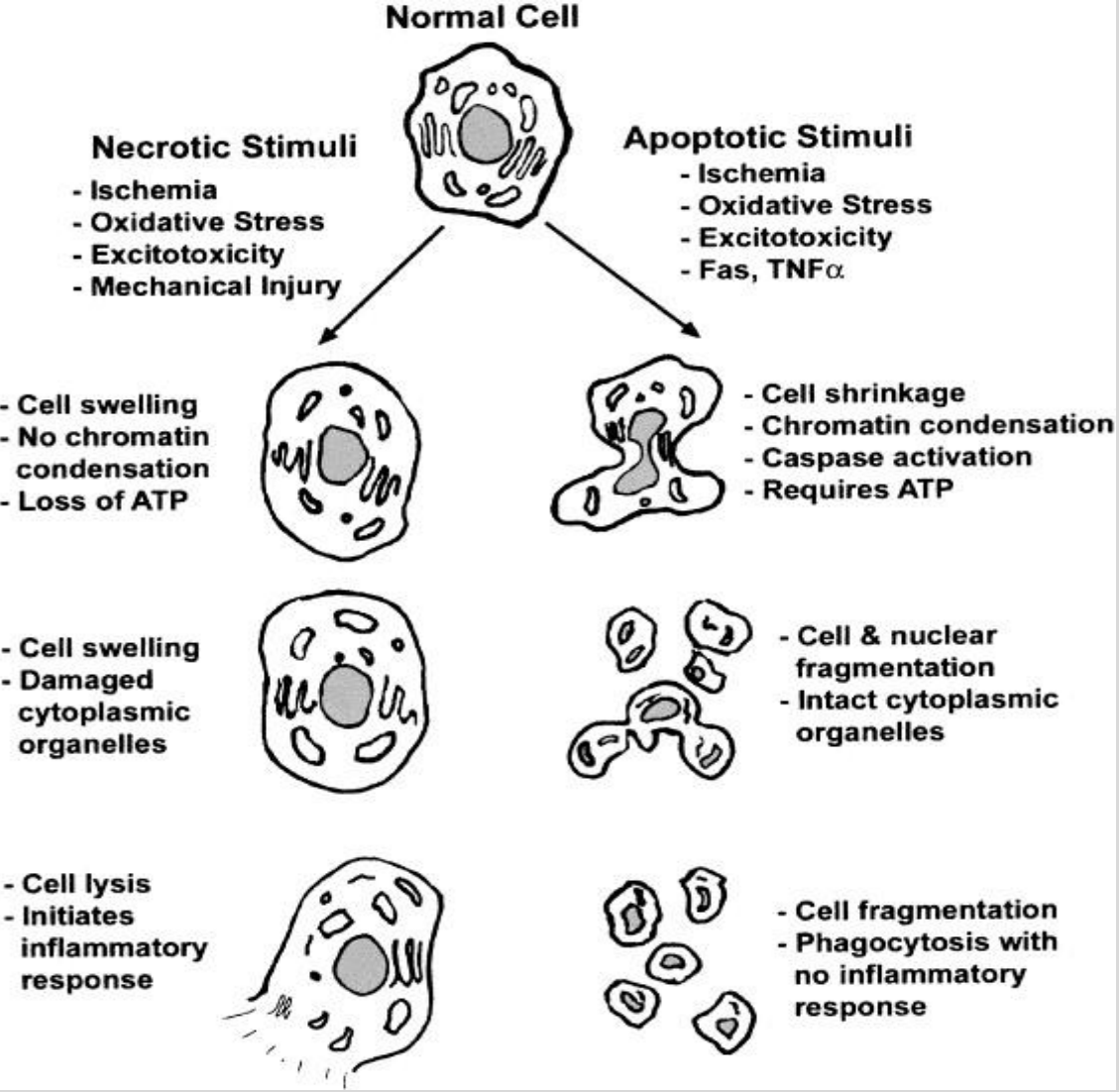
- Extrinsic apoptosis pathway can be inhibited by a protein, FLIP - binds to pro-caspase-8, blocking FADD binding.

Death receptor (extrinsic) pathway eliminates self-reactive lymphocytes and is a mechanism of cell killing by cytotoxic T lymphocytes


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor cross-linking
FasL
Fas (CD95) type 1 TNF receptor
Death domai
Fas-associated death domain
Cytochrome c
BAX (or BAK) dimer to form channel
BCL2 family effectors (BAX, BAK)
Regulators (BCL2, BCL-XL)
Cytochrome c and other proapoptotic proteins
APAF-1
Apoptosome formation
Caspase-9
Pro caspase-8
FLIP
Caspase-8
BH3 sensors
• Growth factor withdrawal
• Absence of survival signal
• Protein misfolding
• DNA damage
IAP
Executioner caspases (caspase 3,6)
Nuclear fragmentation
Breakdown of proteins and cytoskeleton
APOPTOTIC CELL
Membrane alteration "Eat me" signals for phagocytes
Apoptotic body
Phagocyte



Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025



Cell shrinkage. Cell size reduced, cytoplasm dense and eosinophilic: contrasts with necrosis, in which early feature is cell swelling, not shrinkage

Chromatin condensation. Most characteristic feature of apoptosis. Chromatin aggregates peripherally, under nuclear membrane, into dense masses

Formation of cytoplasmic blebs and apoptotic bodies.Apoptotic cell first shows extensive surface membrane blebbing, followed by fragmentation of dead cells into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles

Phagocytosis of apoptotic cells or cell bodies, usually by macrophages

Robbins, 11th ed., 2025

http://imgarcade.com/1/necrosis-vs-apoptosis/

Cellular accumulations

Main mechanisms leading to abnormal intracellular accumulations:

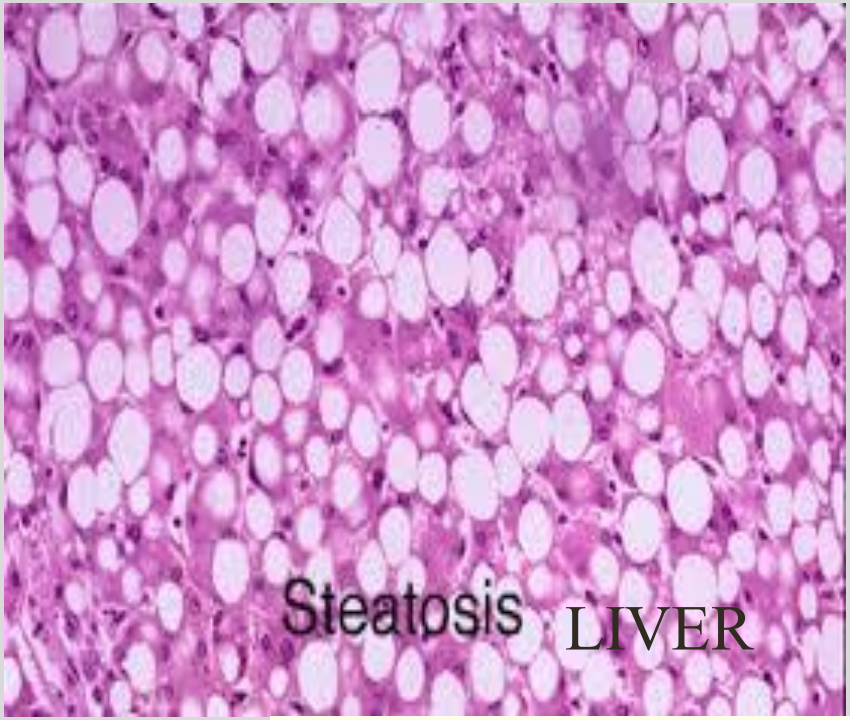
•*Inadequate removal* of a normal substance due to defects in production and transport, e.g., fatty change (steatosis) in the liver

•Accumulation of an endogenous substance because of genetic or acquired *defects in its folding, transport, or secretion*

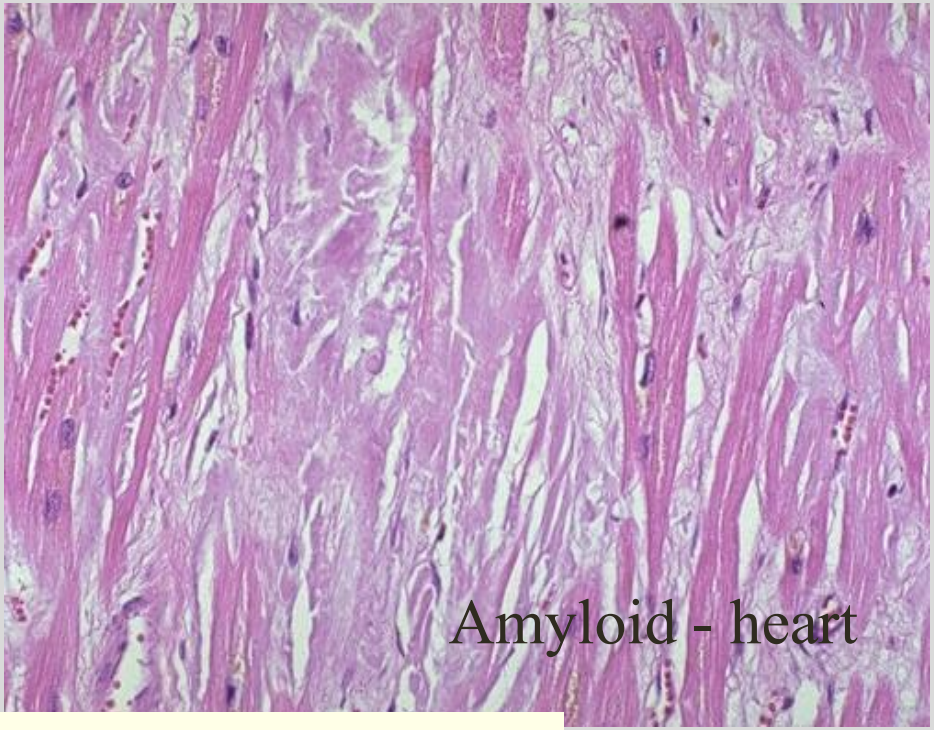
•*Failure to degrade* a metabolite due to inherited enzyme deficiencies, typically lysosomal enzymes.

•Deposition and accumulation of an *abnormal exogenous substance* when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites

- **Lipid** – steatosis – reversible cell injury, especially seen in liver
- **Protein** – normal or abnormal – example of abnormal: amyloid
- **Pigments** - anthracosis, melanin, hemosiderin, lipofuscin
- **Lipofuscin** – "wear and tear" pigment: polymer of lipids and phospholipids in complex with protein may derive from lipid peroxidations, free radical injury



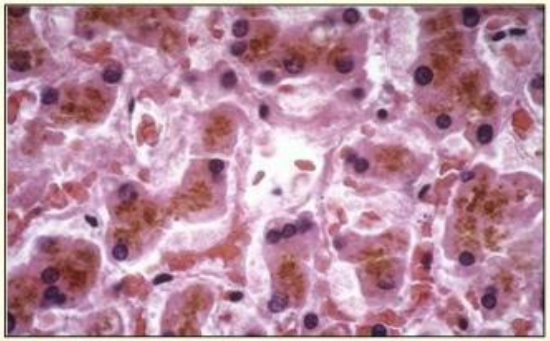
LIVER



Amyloid - heart

Lipofuscin – Striated Muscle and Liver

Source: TUSDM



Source: TUSDM

Microscopic

Cardiac muscle

Liver

79

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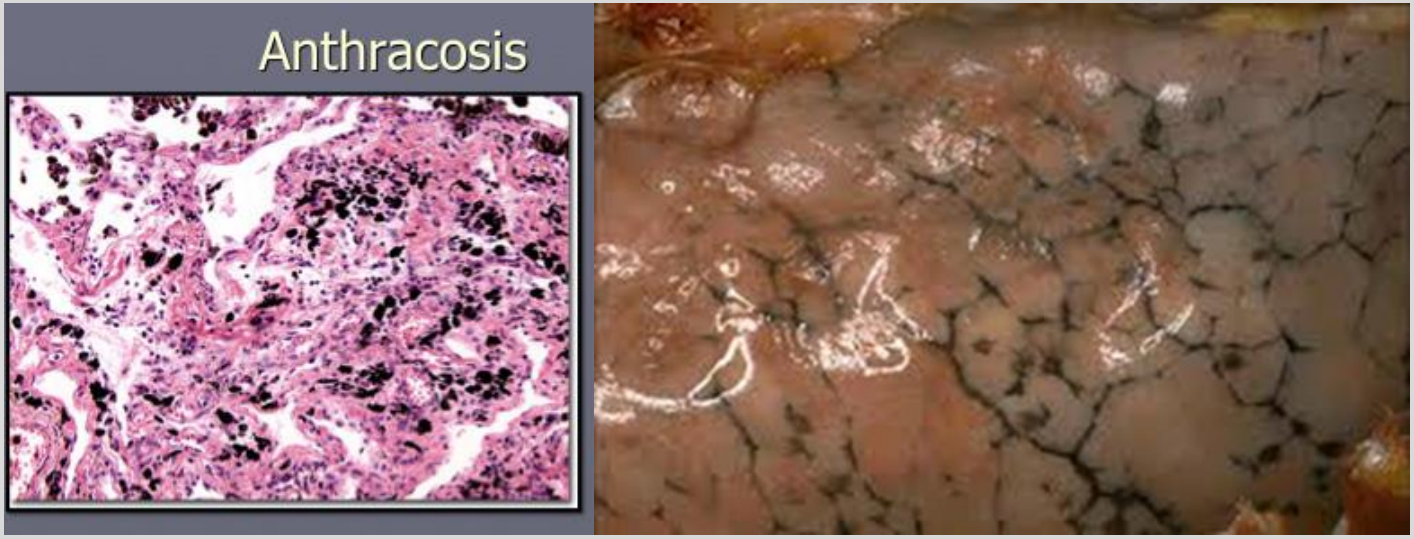
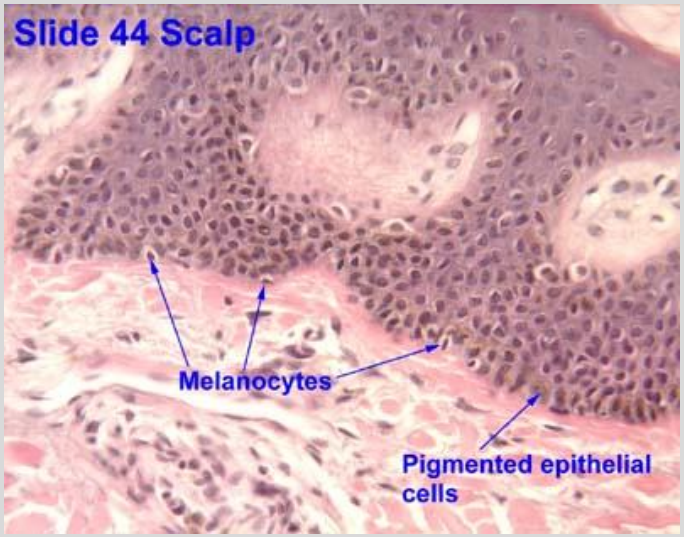
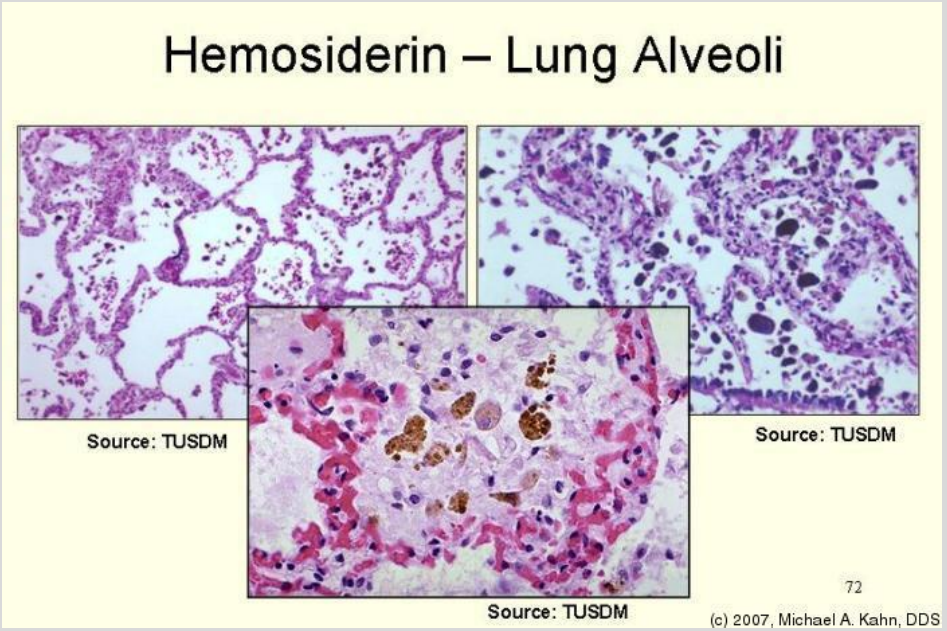
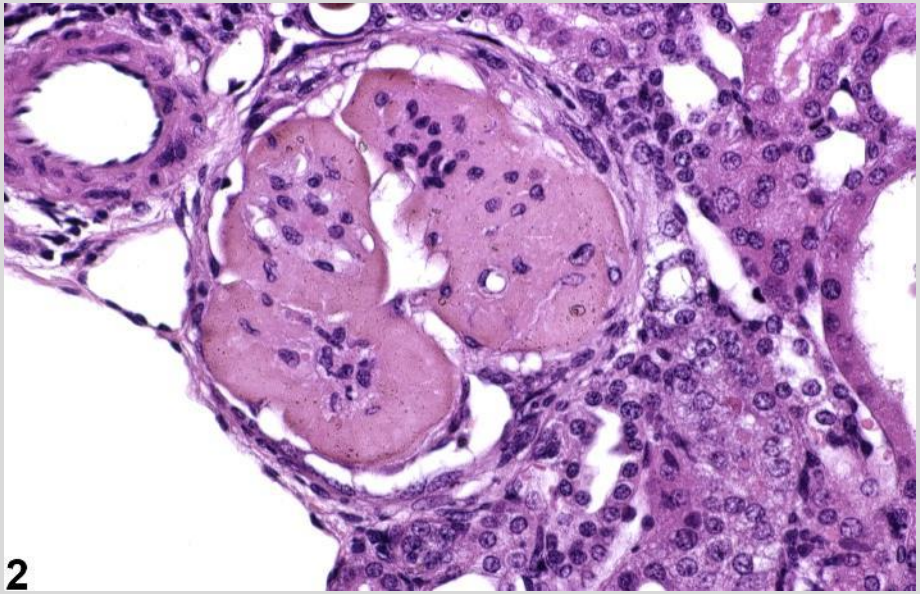
https://www.pathology.med.umich.edu/greensonlab/M2liverlecture.htmhttp://library.med.utah.edu/WebPath/IMMHTML/IMM042.htmll







http://library.med.utah.edu/WebPath/CINJHTML/CINJ050.htmhttp://ocw.tufts.edu/Content/51/lecturenotes/551831/552092l



https://ntp.niehs.nih.gov/atlas/nnl/urinary-system/kidney/HyalineGlomerulopathy

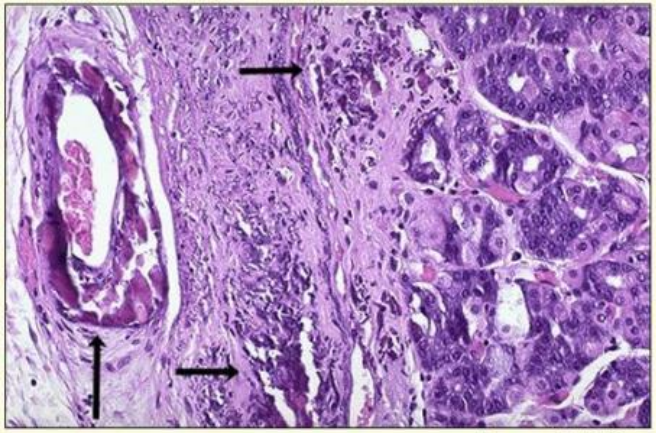
Hyaline change

H*yaline* usually refers to an alteration within cells or in extracellular space that gives a homogeneous, glassy, pink appearance in routine histologic sections stained with H&E -used as **descriptive** histologic term rather than a specific marker for cell injury

This morphologic change is produced by a variety of alterations - does not represent specific pattern of accumulation

Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025

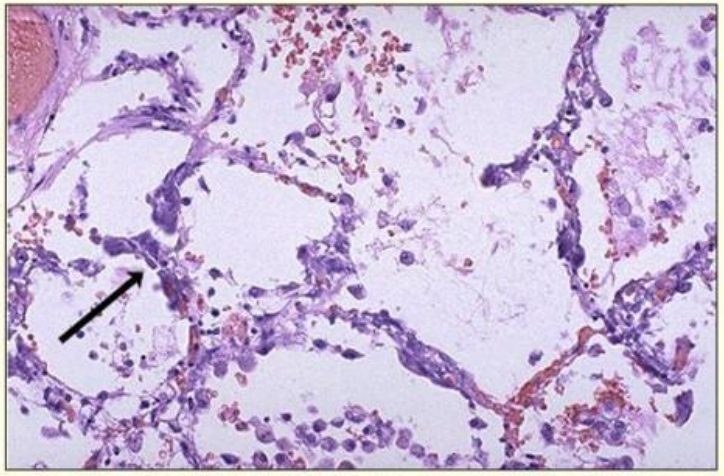
Dystrophic Calcification – Stomach Injury



Source: TUSDM

87

Metastatic Calcification Hypercalcemia - Lung



Source: TUSDM

82