



College of Osteopathic
Medicine



Cellular Adaptation, Cellular Injury, and Cell Death

FOUNDATIONS OF OSTEOPATHIC MEDICINE

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Do.
Make.
Heal.
Innovate.
Reinvent the Future.

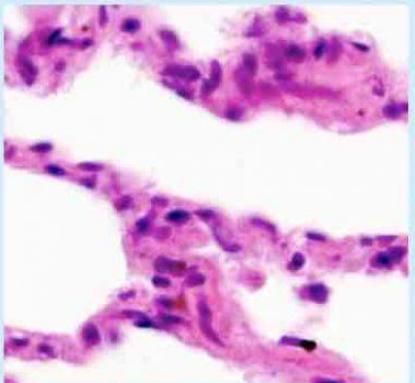
Session Objectives

- 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.

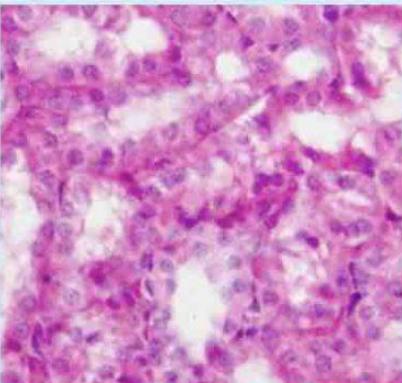
Topics

- Cellular adaptations
 - Hypertrophy
 - Hyperplasia
 - Atrophy
 - Metaplasia
- Cellular injury: causes, response, reversible v. irreversible. mechanisms
- Cellular death
 - Necrosis, apoptosis, other forms
- Cellular accumulations

8 TYPES OF EPITHELIAL TISSUES



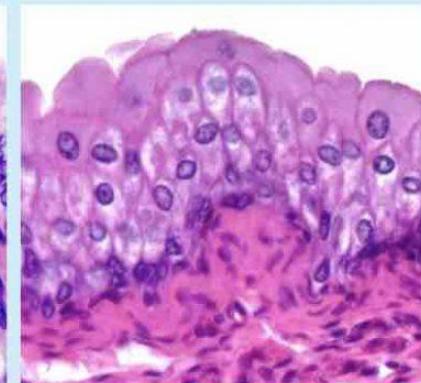
Simple Squamous
(Alveoli)



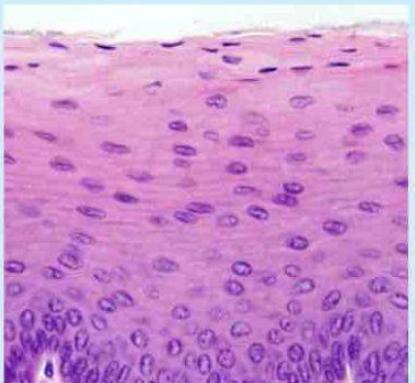
Simple Cuboidal
(Kidney)



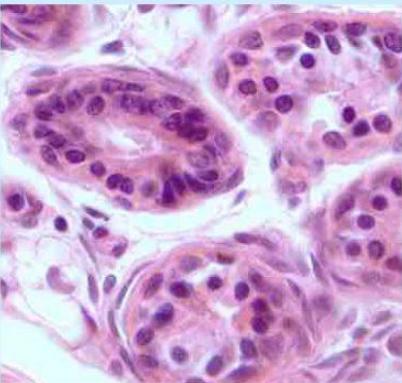
Simple Columnar
(Stomach)



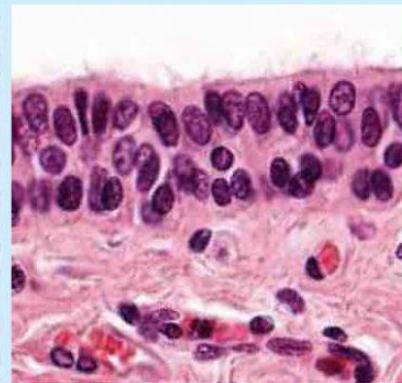
Transitional
(Bladder)



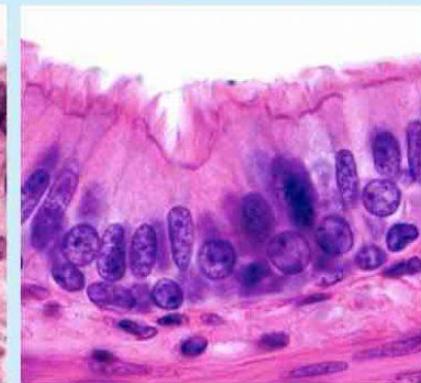
Stratified Squamous
(Esophagus)



Stratified Cuboidal
(Sweat gland)



Stratified Columnar
(Salivary duct)

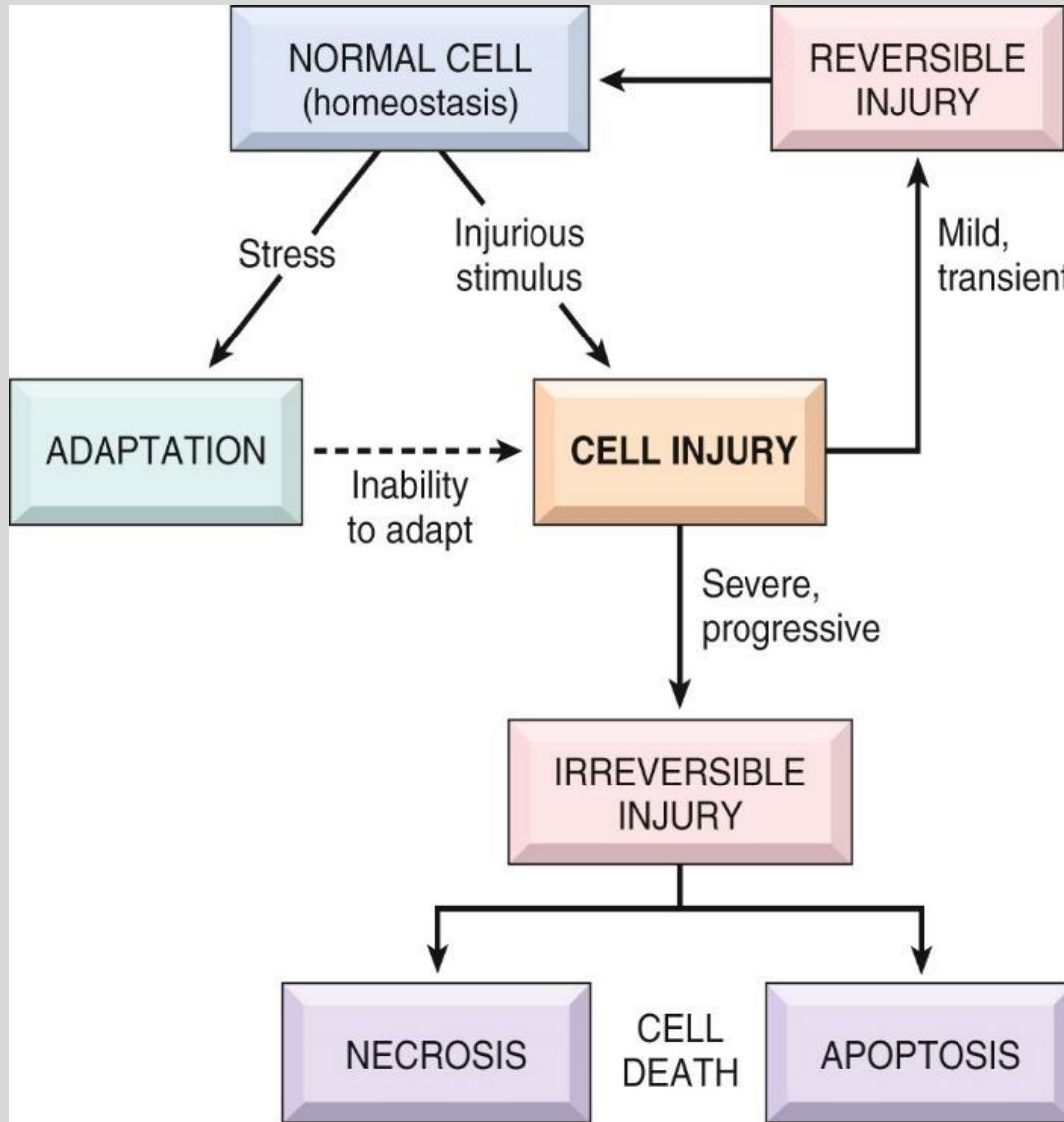


Pseudostratified
Columnar (Trachea)

rsscience.com

PATHOLOGY - Introduction

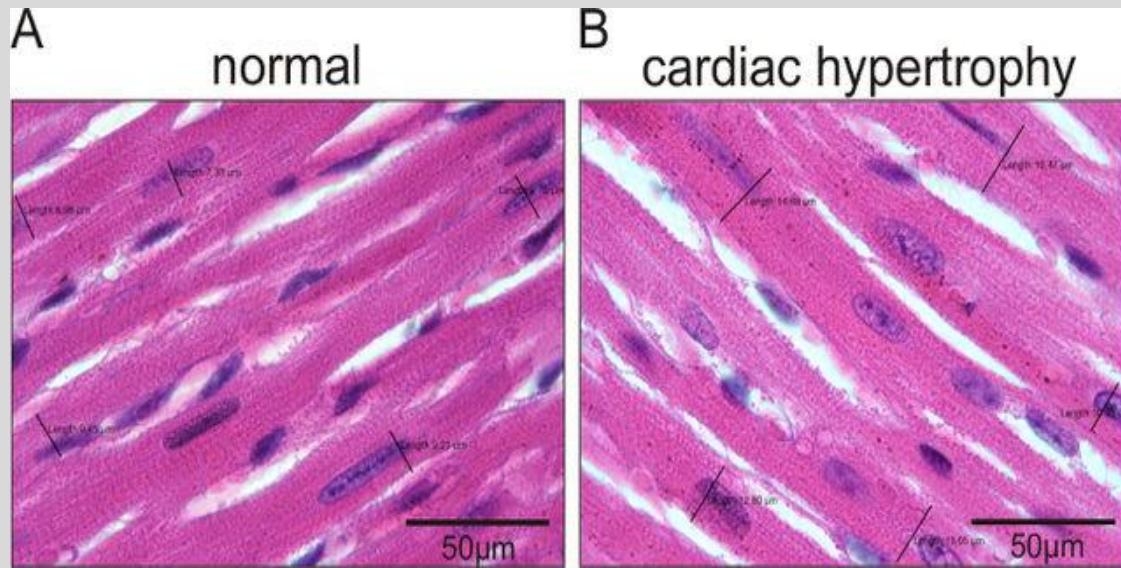
- **Study of the structural, biochemical, and functional changes in cells, tissues, and organs that underlie disease**
- **General Pathology v. Systemic Pathology**
 - causation (*etiology*)
 - biochemical and molecular mechanisms (*pathogenesis*)
 - associated structural (*morphologic changes*) and functional alterations in cells and organs
 - resulting clinical consequences (*clinical manifestations*)



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

Hypertrophy

- Increase in size of cells, results in increased size of organ; **no new cells**
- **Increased production of cellular protein**; results from activation of growth factors and direct effects of mechanical force on pathways which stimulate protein synthesis
 - **Physiologic** – increased functional demands, stimulation by growth factors, hormones
 - examples – uterine growth during pregnancy, skeletal muscle in response to increased demand – e.g body building
 - **Pathologic** – examples – heart in hypertension, aortic stenosis



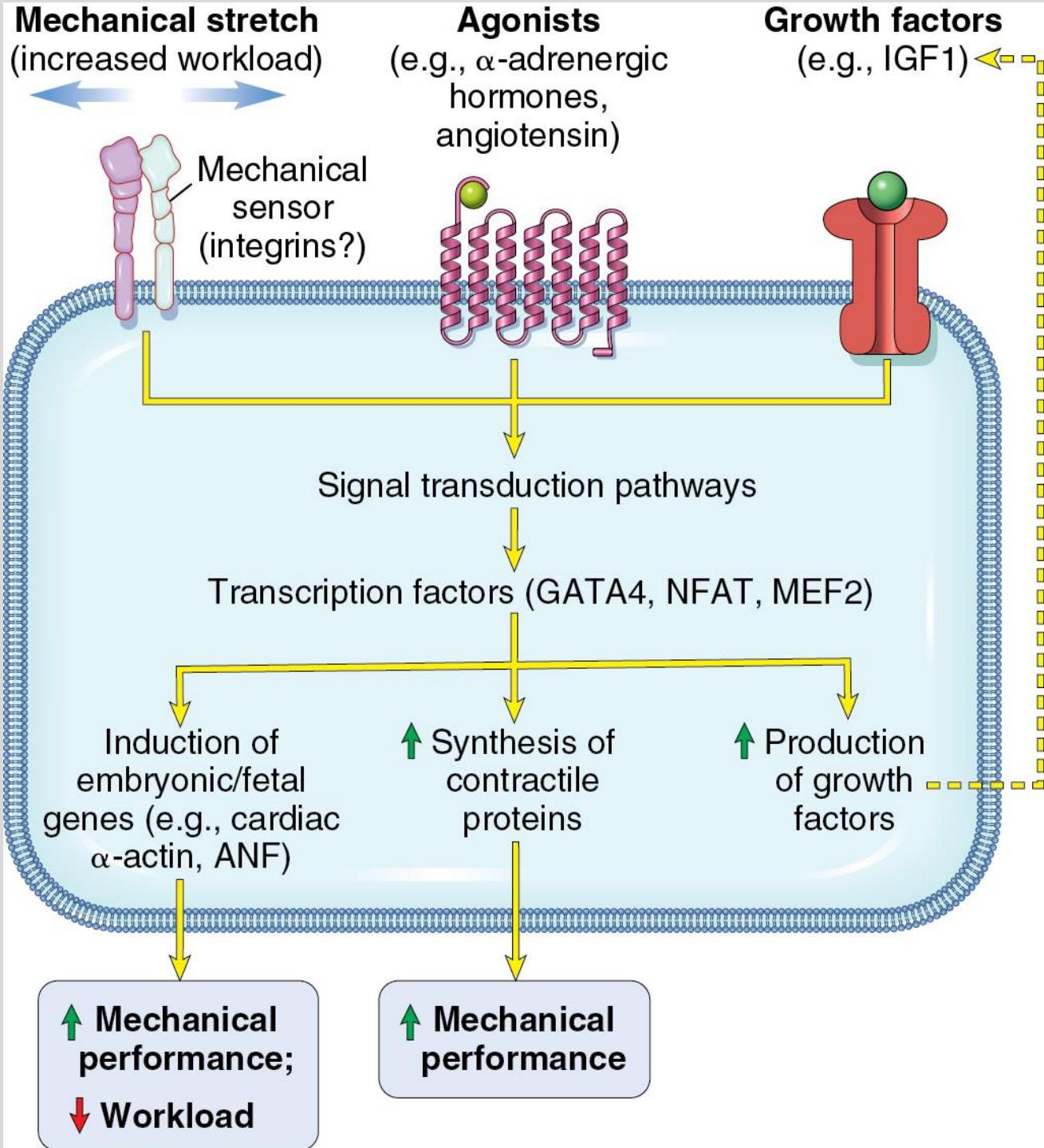
Mechanisms of Hypertrophy

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

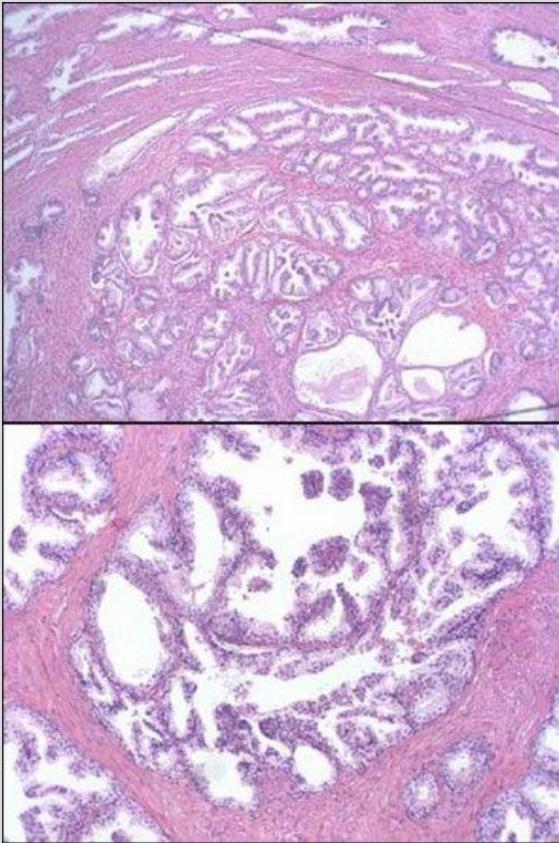
Fig. 2.26 Biochemical mechanisms of myocardial hypertrophy. Mechanical sensors appear to be the major triggers for physiologic hypertrophy, and agonists and growth factors may be more important in pathologic states.

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



Case

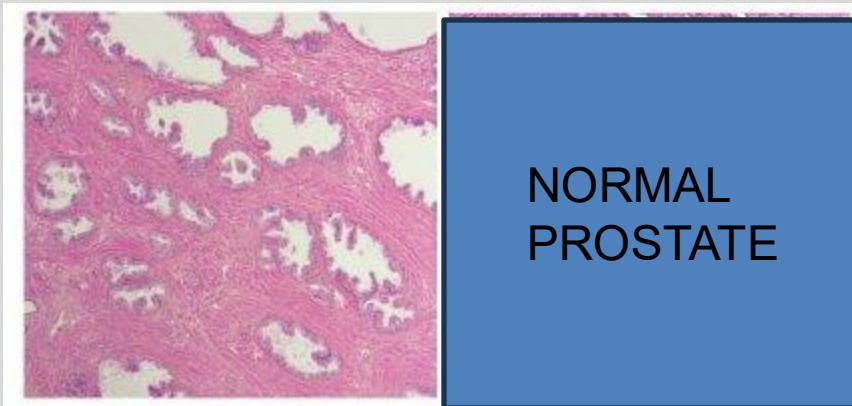
A 70 year old man complains of difficulty urinating, weak urinary stream, and having to get up several times at night to urinate (nocturia). His PSA is mildly elevated. He undergoes a transurethral resection of his prostate.



Prostate gland – what type of epithelium is present?

Is there an increase in number of cells?

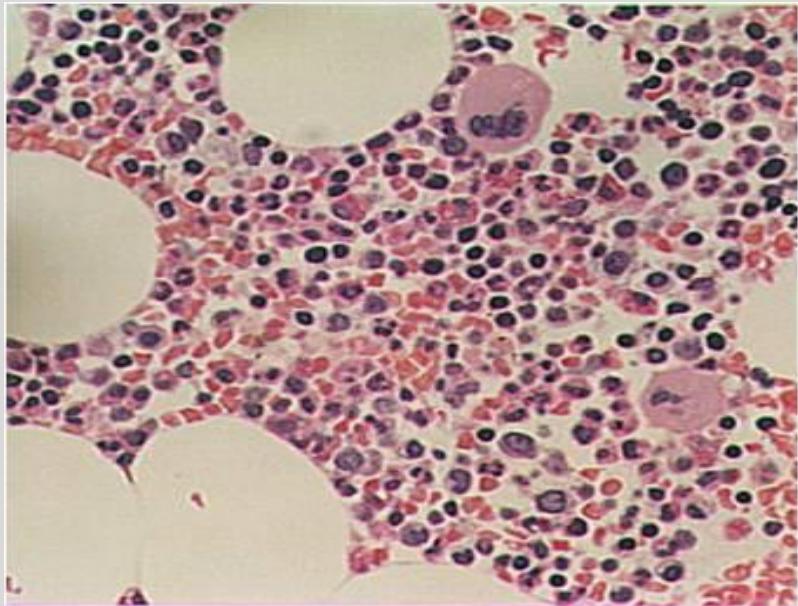
What is this cellular adaptation called?



https://www.researchgate.net/publication/24696427_A_New_Feature_For_Detection_of_Prostate_Cancer_Based_On_RF_Ultrasound_Echo_Signals/figures?lo=1

Case

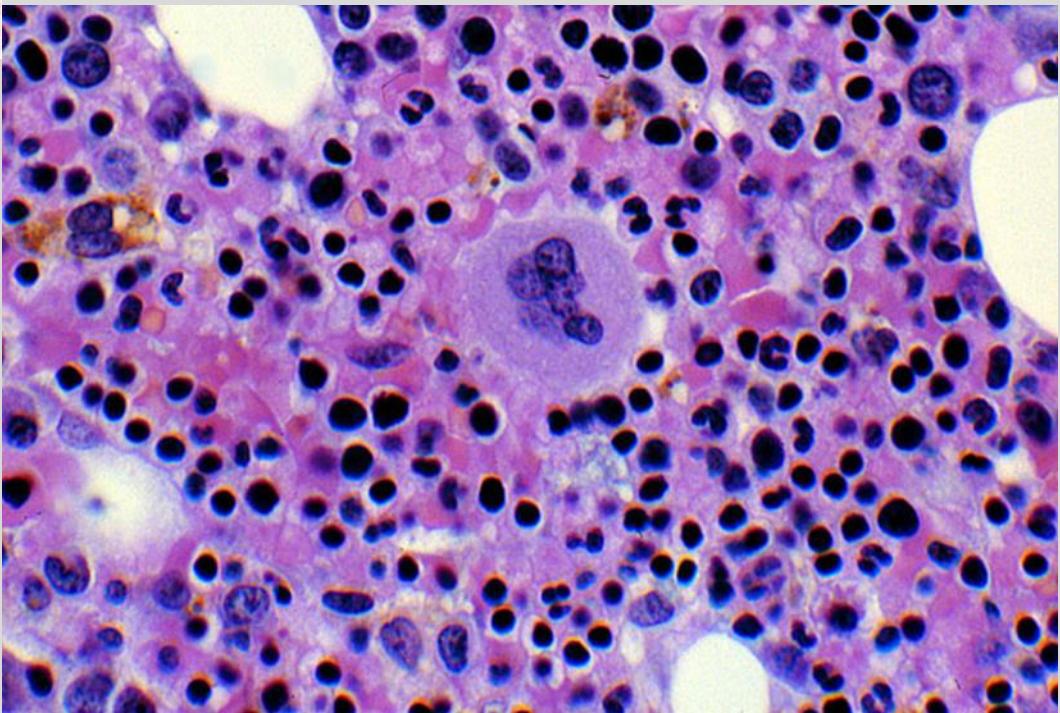
A 45 year old woman is pale and weak and blood studies indicate a decrease in her red blood cell count. She is diagnosed with anemia. However, her bone marrow biopsy shows an increase in red blood cell precursor cells indicating an attempt to compensate for the decrease in the peripheral blood.



Normal bone marrow



Increased erythroid
precursors



What process is going on in the bone marrow?

- A.Hyperplasia
- B.Hypertrophy
- C.Metaplasia
- D.Atrophy
- E.Dysplasia

Answer A

- Bone marrow may undergo rapid hyperplasia in response to a deficiency of mature blood cells. In the setting of acute bleeding or premature breakdown of red cells (hemolysis), feedback loops involving the growth factor erythropoietin are activated that stimulate the growth of red cell progenitors, allowing red cell production to increase

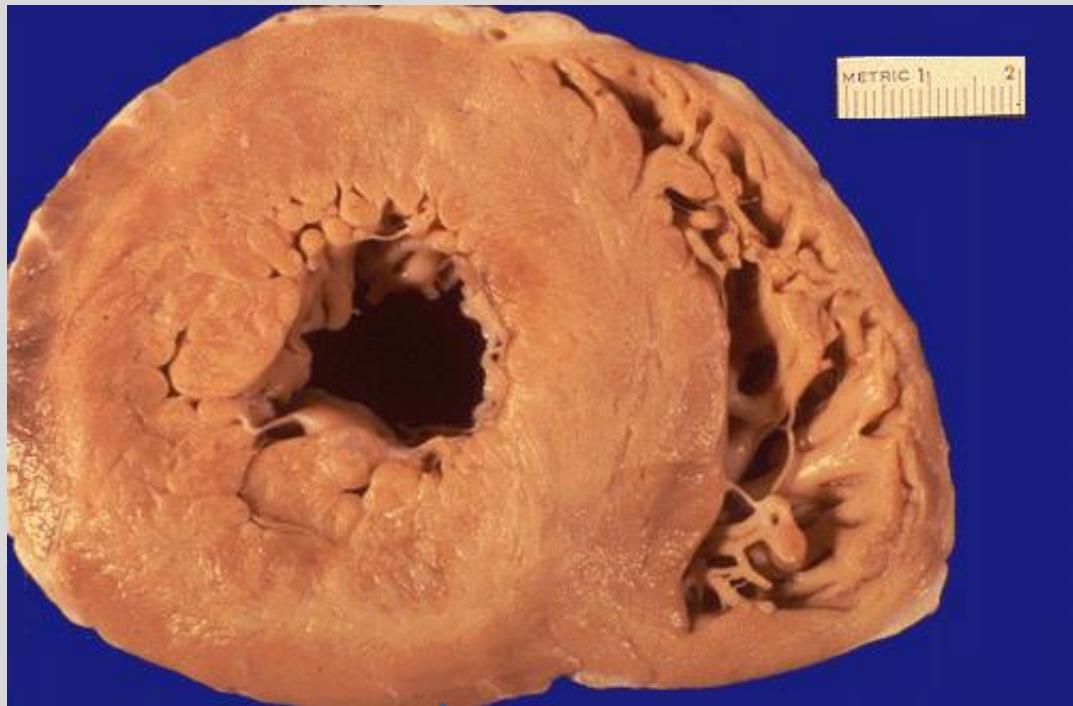
Hyperplasia

- **Increased number** of cells in organ or tissue in response to stimulus
- Can only occur in tissue if cells are **capable of dividing**
- **Hyperplasia and hypertrophy may occur together in some tissue types (not permanent)**
- **Result of growth factor–driven proliferation of mature cells and, in some cases, by increased output of new cells from tissue stem cells**
- **Physiologic –due to hormones or growth factors when needed to increase functional capacity of hormone-sensitive organs, or when there is need for compensatory increase after damage or resection**
(breast at puberty/pregnancy, compensatory hyperplasia of liver)
- **Pathological – e.g, inappropriate or excessive hormonal (endometrial hyperplasia, BPH) or growth factors acting on target cells**

Increased cell division associated with hyperplasia increases risk of acquiring genetic aberrations that can drive unrestrained proliferation and give rise to cancer

CELLULAR ADAPTATION - HYPERTROPHY

NORMAL HEART



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

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

PERMANENT TISSUE

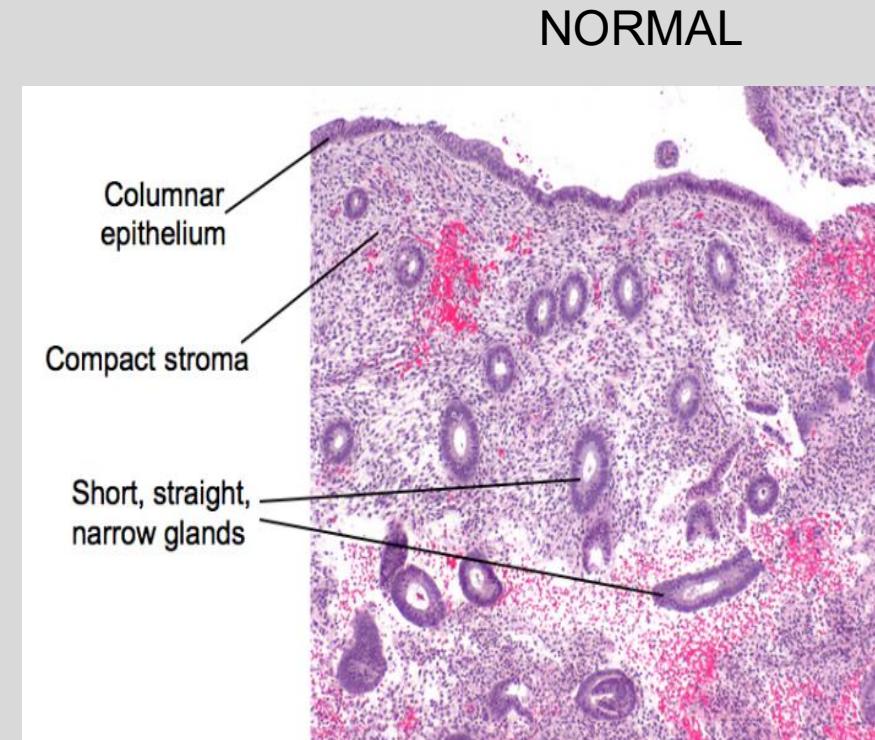
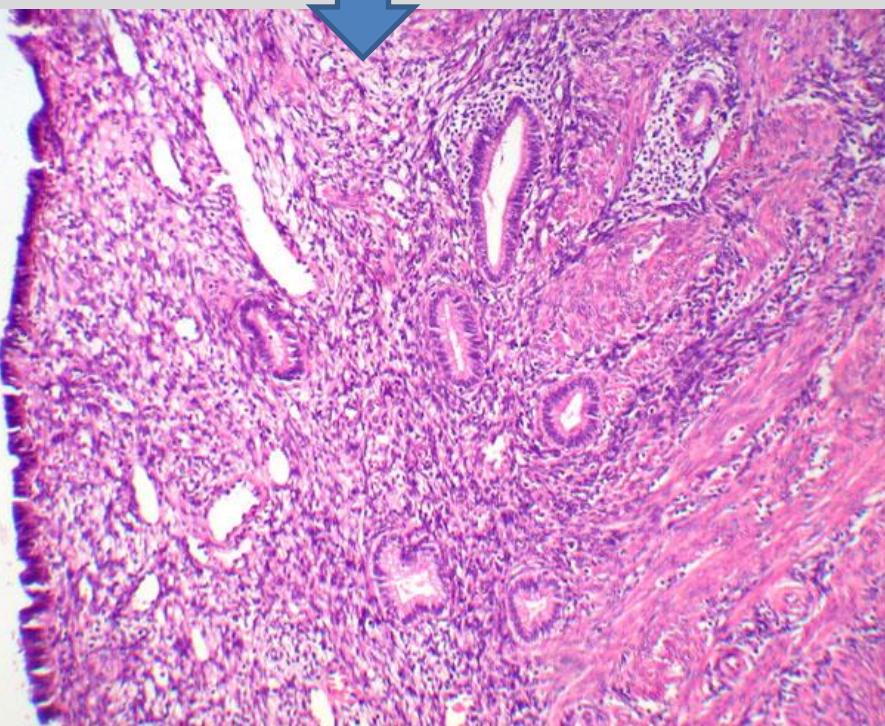
- Cardiac muscle, skeletal muscle, nervous tissue
- Generally does not regenerate
- More info to follow in Healing and Repair
- *Most common stimulus for hypertrophy of skeletal and cardiac muscle - increased workload*
- Muscle cells respond by synthesizing more protein

Case

A 70 year old woman has a hysterectomy because of multiple benign smooth muscle tumors of her uterus (“fibroids”).

The uterus is small and has no other significant visible pathology. In processing the uterus a sample of the endometrium is taken and seen under the microscope.

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



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

Atrophy

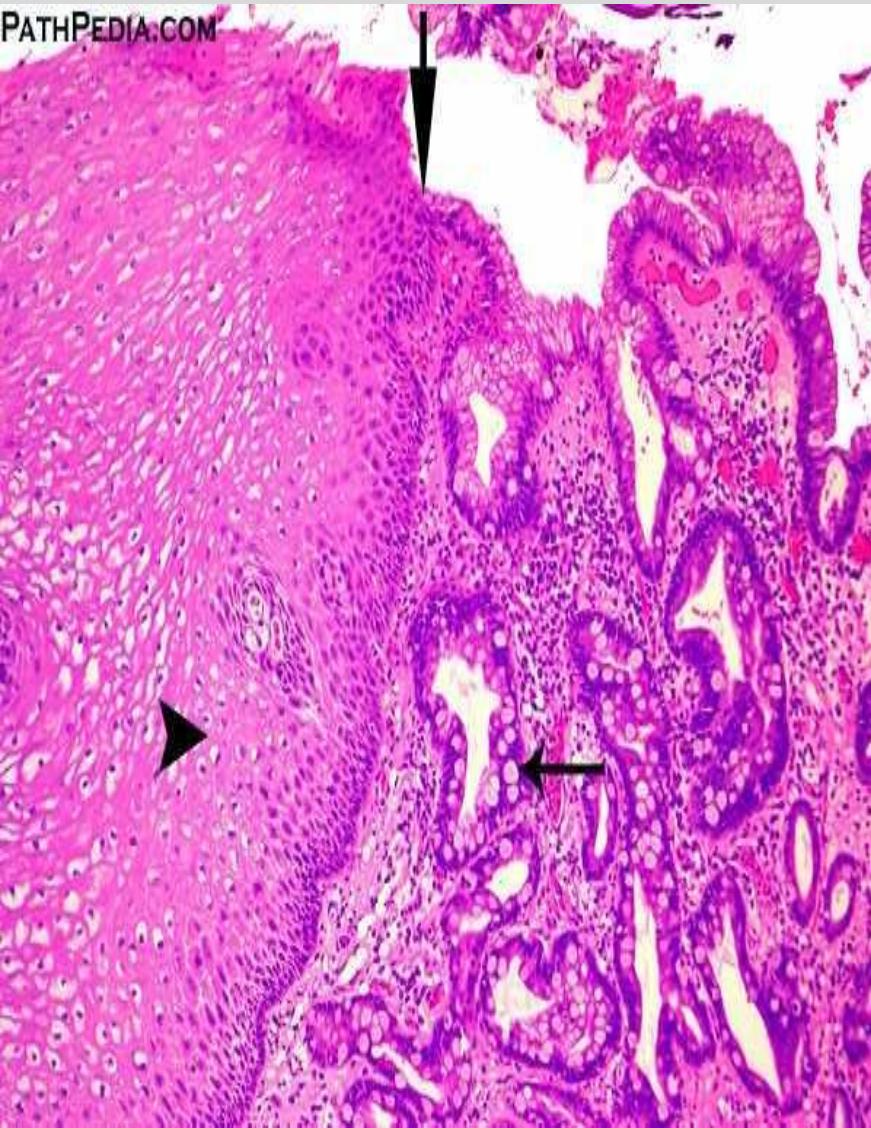
- **Reduction in size due to decrease in cell size and number**
- **Decreased protein synthesis and increased protein degradation in cells**
- **Physiologic** - normal development, uterus post partum
- **Pathologic** – disuse (decreased workload), denervation, decreased blood supply, decreased nutrition, decreased hormone stimulation, pressure
- Common causes of atrophy include:
 - *Decreased workload (disuse atrophy)*
 - *Loss of innervation (denervation atrophy)*
 - *Diminished blood supply (chronic ischemia, eg. atherosclerosis)*

Atrophy

- Reduced trophic signals (e.g., produced by growth receptors) causes decrease in protein synthesis
- *Degradation of cellular proteins occurs mainly by the ubiquitin-proteasome pathway*
 - Ubiquitin ligases activated by disuse, nutrition deficits
 - Ligases attach ubiquitin to proteins targeting them for degradation in proteasomes
- Atrophy often accompanied by autophagy – starved cell eats its own parts to decrease nutrient demands

Case

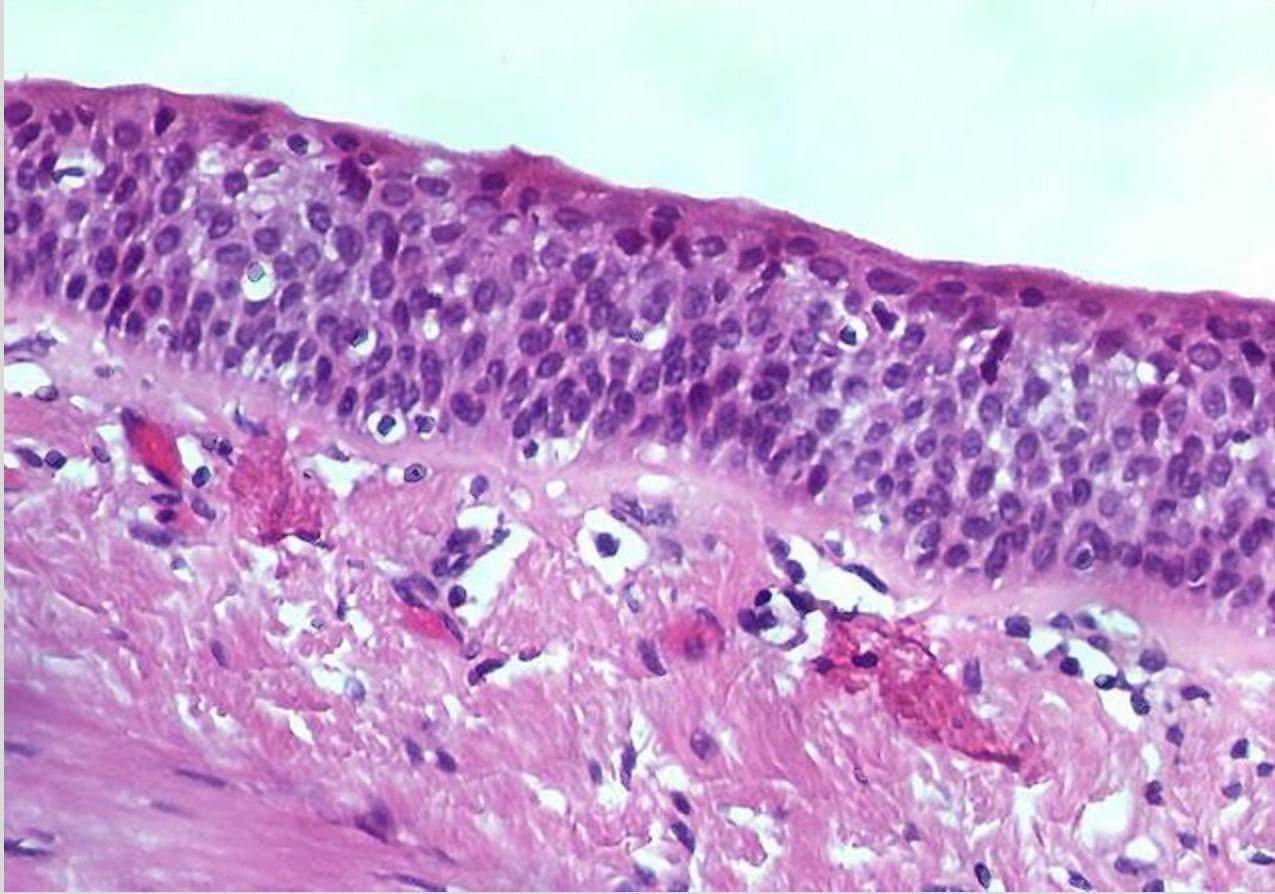
- A 52 year old man presents with a 6 month history of heartburn. Last year he was diagnosed with reflux esophagitis. A recent endoscopy confirmed an irregular gastroesophageal junction with no masses.



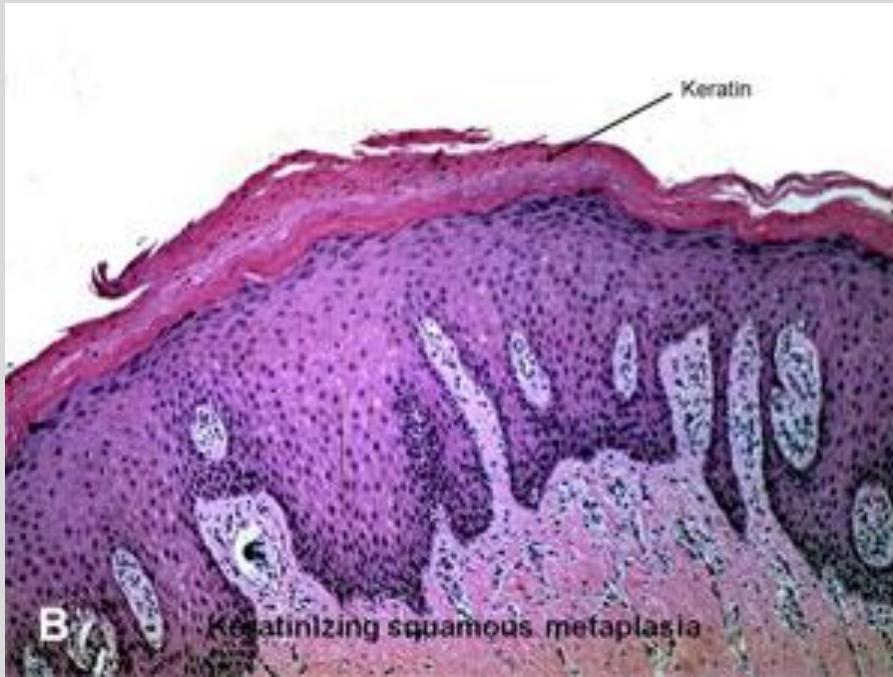
- What is the normal epithelium of the esophagus?
- Why?
- What types of epithelium are seen in the photo?
- Why are there two types of epithelium?
- What is this process called?

Metaplasia

- **Reversible change: one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type**
- Adaptive response: one cell type sensitive to a particular stress is replaced by another cell type better able to withstand the stress
- Reversible, but if persists can lead to dysplasia and malignant transformation
- Most common is columnar to squamous
- Results from either reprogramming of local tissue stem cells, or, colonization by differentiated cell populations from adjacent sites
- Stimulated by signals generated by cytokines, growth factors, and ECM components in cells' environment

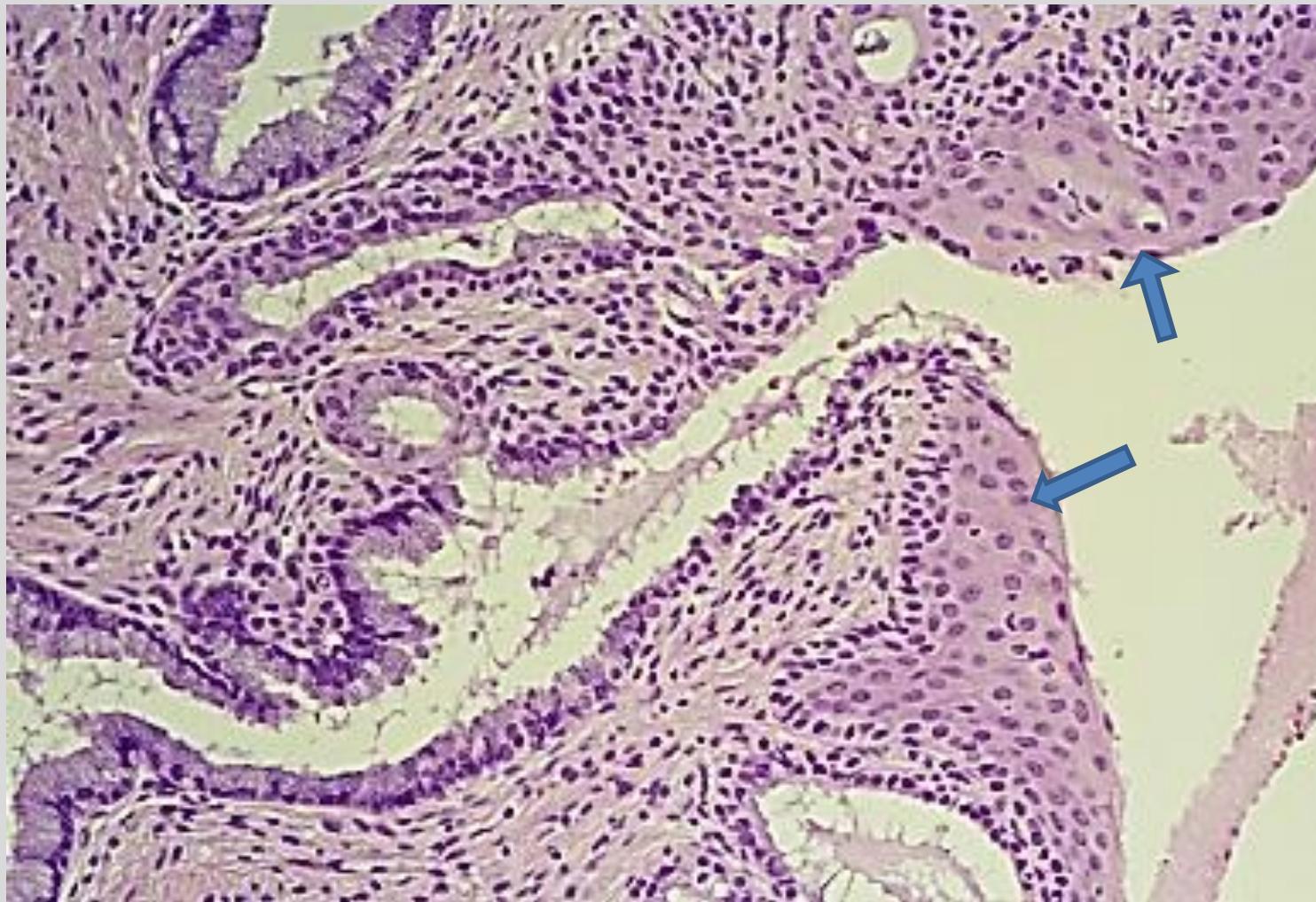


Metaplastic bronchial epithelium – what is normal?



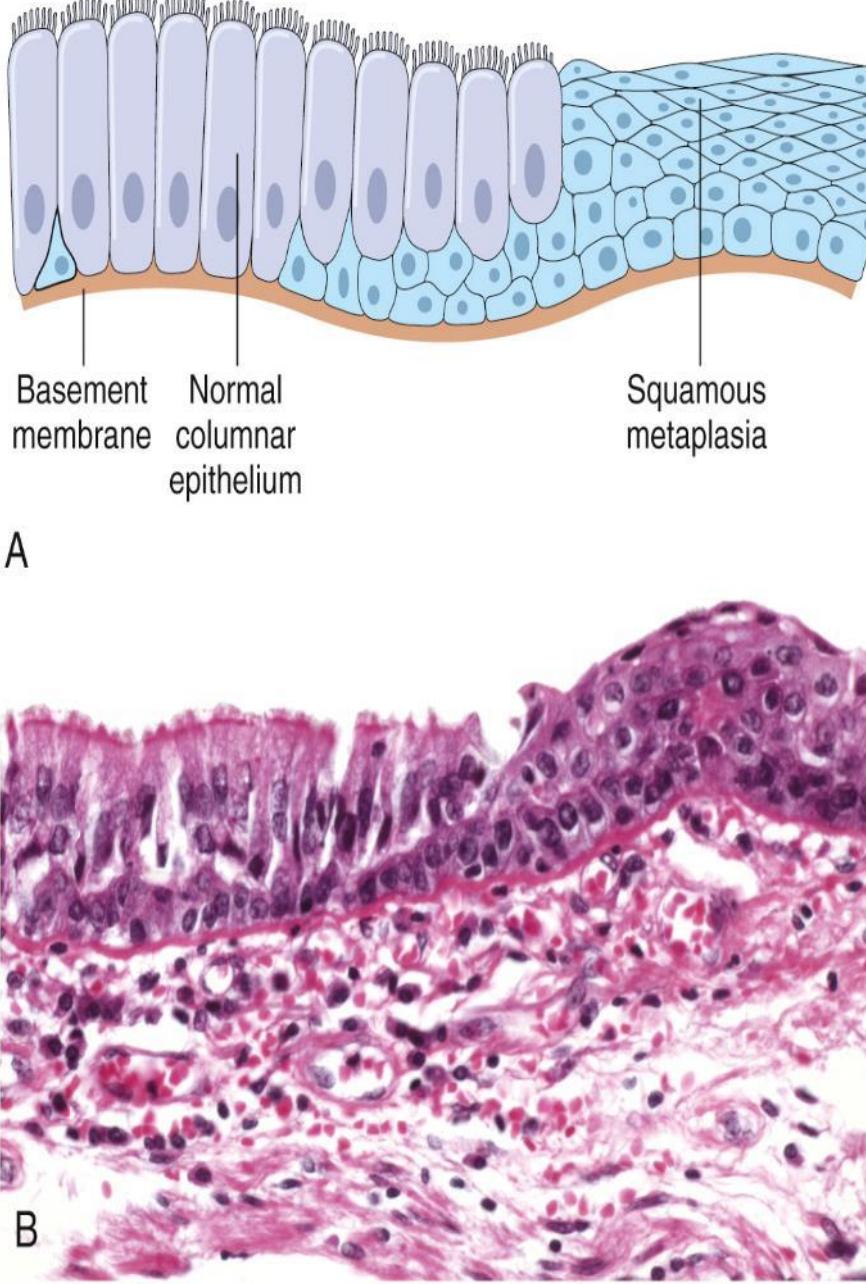
Keratinizing squamous metaplasia of urinary bladder- why might this occur?
What epithelium normally lines the bladder?

Cervix with squamous metaplasia



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

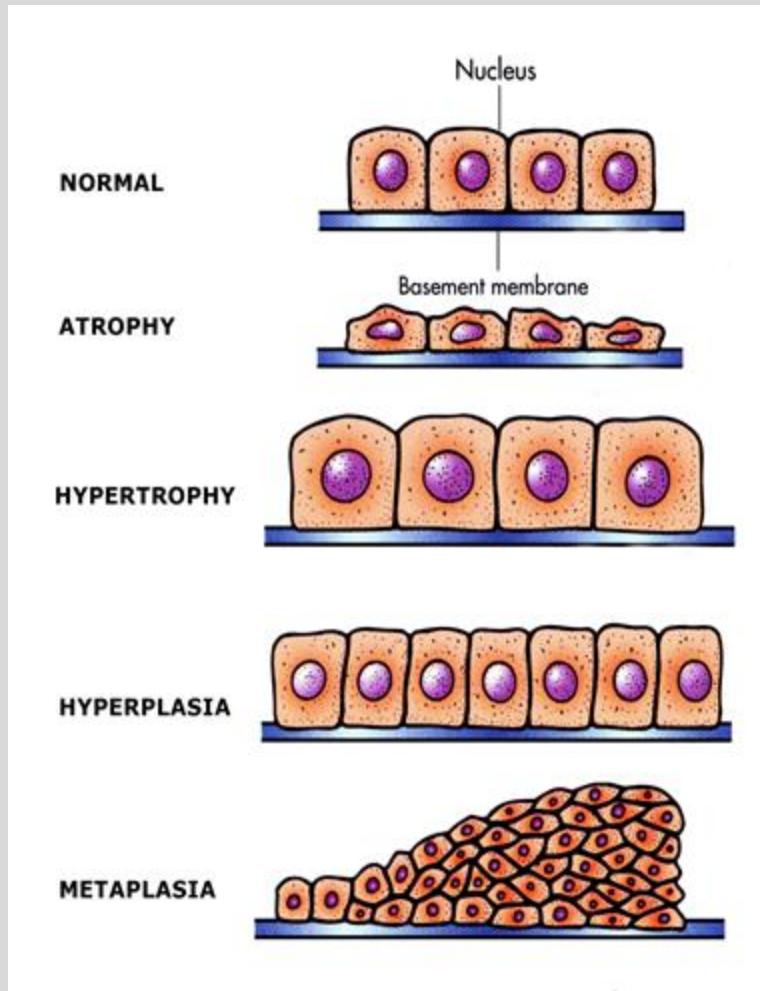
Metaplasia of columnar to squamous epithelium



Tissue	Normal	Metaplasia	Stimulus
Upper respiratory tract	Pseudostratified columnar epithelium	Squamous epithelium	Cigarette smoke
Urinary bladder	Transitional epithelium	Squamous epithelium	Bladder stone
Esophagus	Squamous epithelium	Columnar epithelium	Gastro-esophageal reflux (Barrett's Esophagus)
Cervix	Glandular epithelium	Squamous epithelium	Low pH of vagina

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, ch. 2

REVIEW



Cell injury – multiple causes

- Decreased oxygen – hypoxia (via decreased blood flow, anemia, etc.)
- Physical agents – trauma, temperature, radiation, electricity
- Chemicals, drugs
- Infectious agents
- Immunological reactions
- Genetic abnormalities
- Nutrition abnormalities (starvation, obesity, etc.)

Response to Injury – cellular level- activation of response pathways

- **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

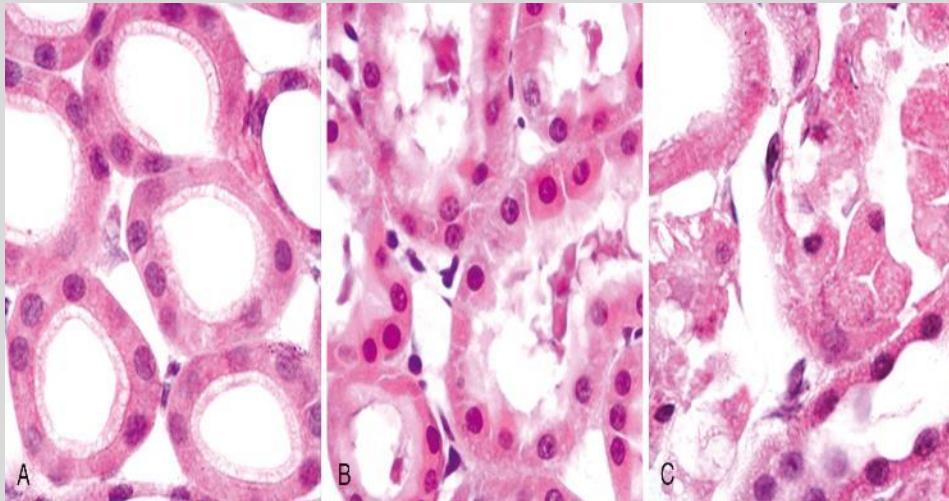
Case

A 58 year old man with a history of unstable angina presents with shortness of breath, chest pain, and diaphoresis. Within 30 minutes of these signs and symptoms, what **reversible** changes may take place in the myocardial area supplied by the coronary artery which is being occluded by a thrombus?

- A. Nuclear pyknosis
- B. Infiltration by neutrophils
- C. Cellular swelling
- D. Fibrosis
- E. Granulation tissue formation

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

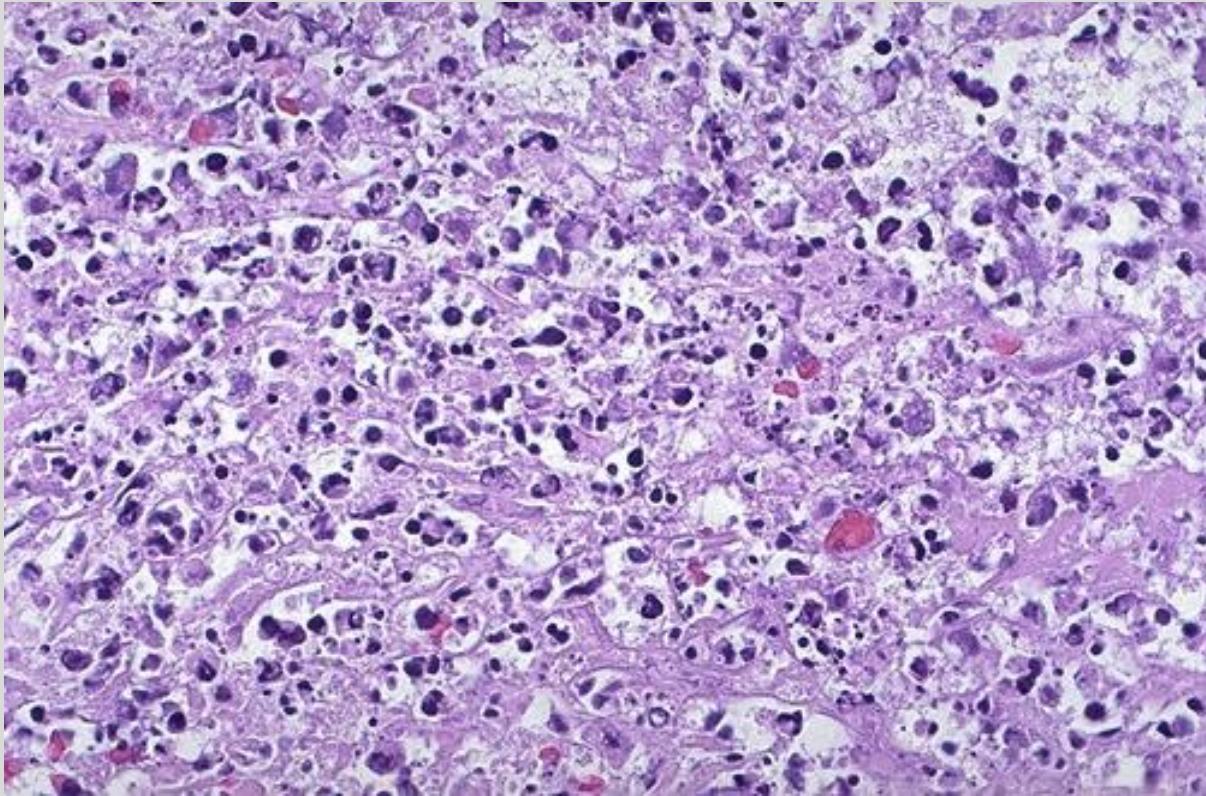


Swelling – acute and **reversible**: 0 to approximately 30 minutes

Ischemia causes decreased oxidative phosphorylation and decreased ATP which then leads to decreased function of Na^+ pump and subsequent influx of Ca , H_2O and Na^+ : resulting in cell swelling

Case continued

The patient arrives at the hospital one hour after onset of signs and symptoms. EKG changes are consistent with a transmural acute myocardial infarct. Myocardial enzymes are also consistent with the diagnosis.



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.

- **Damage to mitochondria causes decreased oxidative phosphorylation and therefore decreased ATP**
- **Reduced Na/K pump leads to cell swelling (hydropic change, vacuolar degeneration) – reversible**
- **Increase in anaerobic glycolysis – decreases glycogen, increases lactic acid, decreases pH (chromatin clumping)**
- **Decrease in protein synthesis**
- **Failure of CA pump----Ca enters cell causing membrane and nuclear damage via activation of phospholipases, proteases, endonuclease, and ATPases**
- **Denaturation of intracellular proteins, enzymatic digestion of cell, contents leak out and elicit inflammation**

Mechanisms of cell death

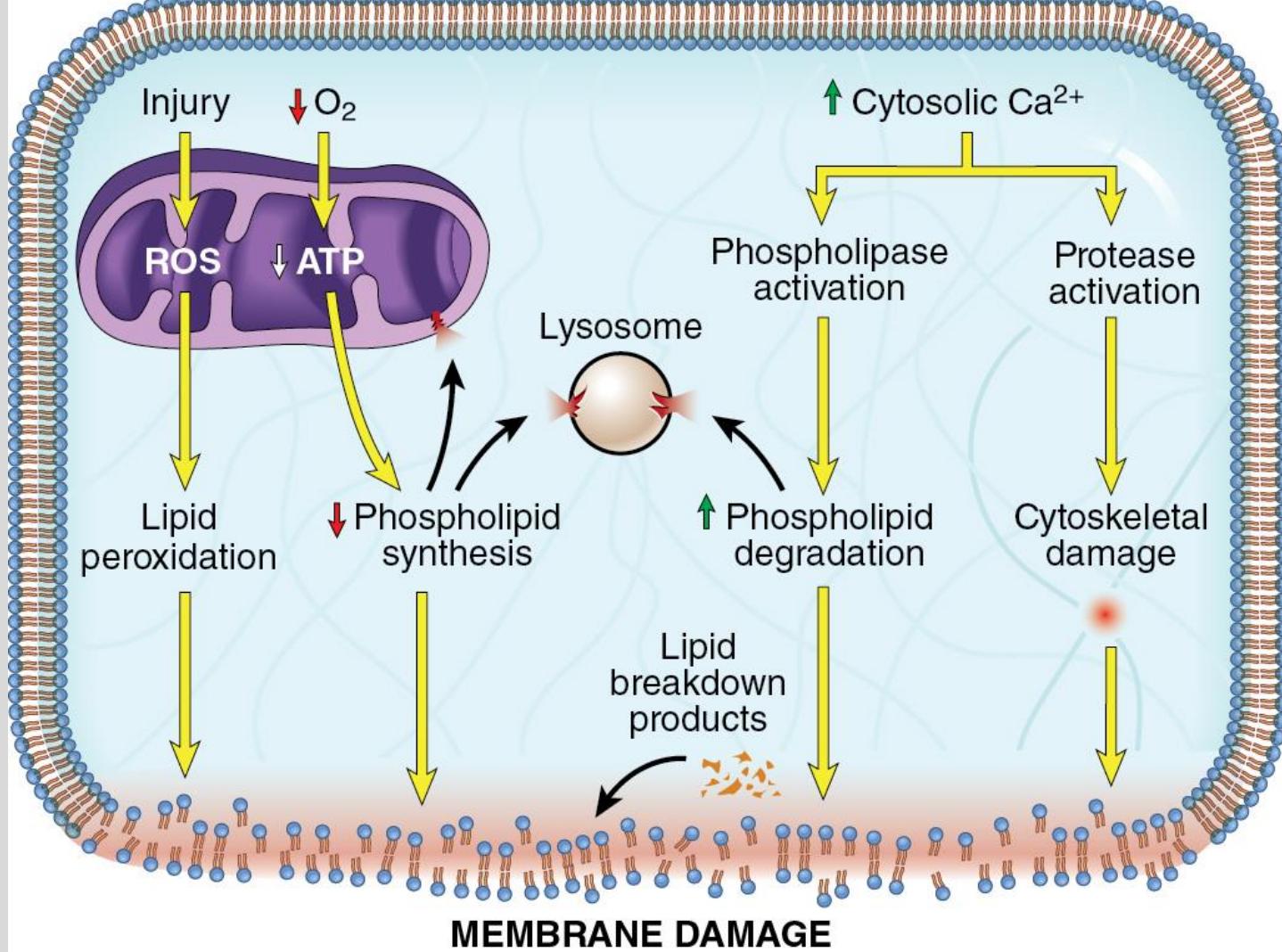
- Mitochondrial damage
- Membrane damage
- Damage to DNA
- Oxidative stress: Accumulation of oxygen-derived free radicals
 - Generation of free radicals
 - Removal of free radicals
 - Pathologic effects of free radicals
- Disturbance in calcium homeostasis

Mitochondrial damage- Consequences

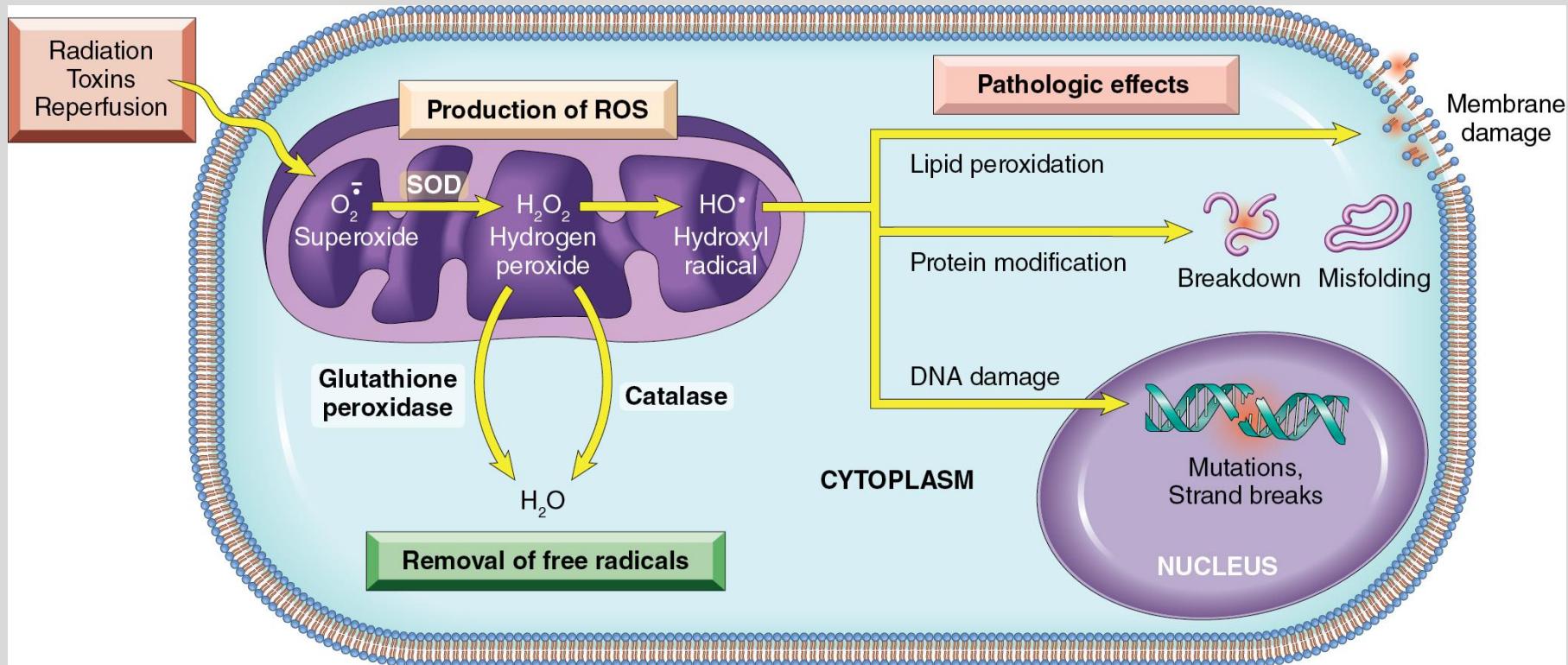
- **ATP depletion**
- Formation of a high-conductance channel in mitochondrial membrane: ***mitochondrial permeability transition pore***
- Opening of pore leads to loss of mitochondrial membrane potential, resulting in failure of oxidative phosphorylation and progressive ATP depletion
- Activity of the *plasma membrane energy-dependent sodium pump* (Na^+, K^+ -ATPase) is **reduced causing sodium to enter and accumulate inside cells and potassium concentrations to fall**
- Water follows sodium into cell (osmotic drive) - leads to **cell swelling and ER dilation**
- Oxidative phosphorylation ceases, resulting in decrease in cellular ATP leading to increased rates of glycogenolysis and glycolysis
- *Glycogen stores rapidly depleted*. Glycolysis under anaerobic conditions results in accumulation of *lactic acid* - **decreases intracellular pH**, resulting in decreased activity of many cytosolic enzymes.
 - Ultimately, there is irreversible damage to mitochondrial and lysosomal membranes, and the cell undergoes *necrosis*
- Also **Calcium pump fails**, see later
- Incomplete oxidative phosphorylation also leads to the formation of ROS, many deleterious effects, see later

Membrane damage

- Membrane damage affects integrity and functions of all cellular membranes
 - In ischemic cells, membrane defects may be the result of ATP depletion and calcium-mediated activation of phospholipases
 - Plasma membrane can also be damaged directly by bacterial toxins, viral proteins, lytic complement components, and other physical and chemical agents.
-
- **Reactive Oxygen Species:** Oxygen free radicals cause injury to cell membranes by lipid peroxidation
 - **Decreased phospholipid synthesis**
 - **Increased phospholipid breakdown:** Severe cell injury associated with increased degradation of membrane phospholipids, probably due to activation of calcium-dependent phospholipases by increased cytosolic and mitochondrial Ca^{2+} .
 - Phospholipid breakdown leads to accumulation of *lipid breakdown products*: detergent effect on membranes.
 - **Cytoskeletal abnormalities**. Cytoskeletal filaments anchor/connect plasma membrane to cell interior; proteases activated by cytosolic Ca^{2+} may damage them leading to detachment of cell membrane from cytoskeleton  stretching and rupture

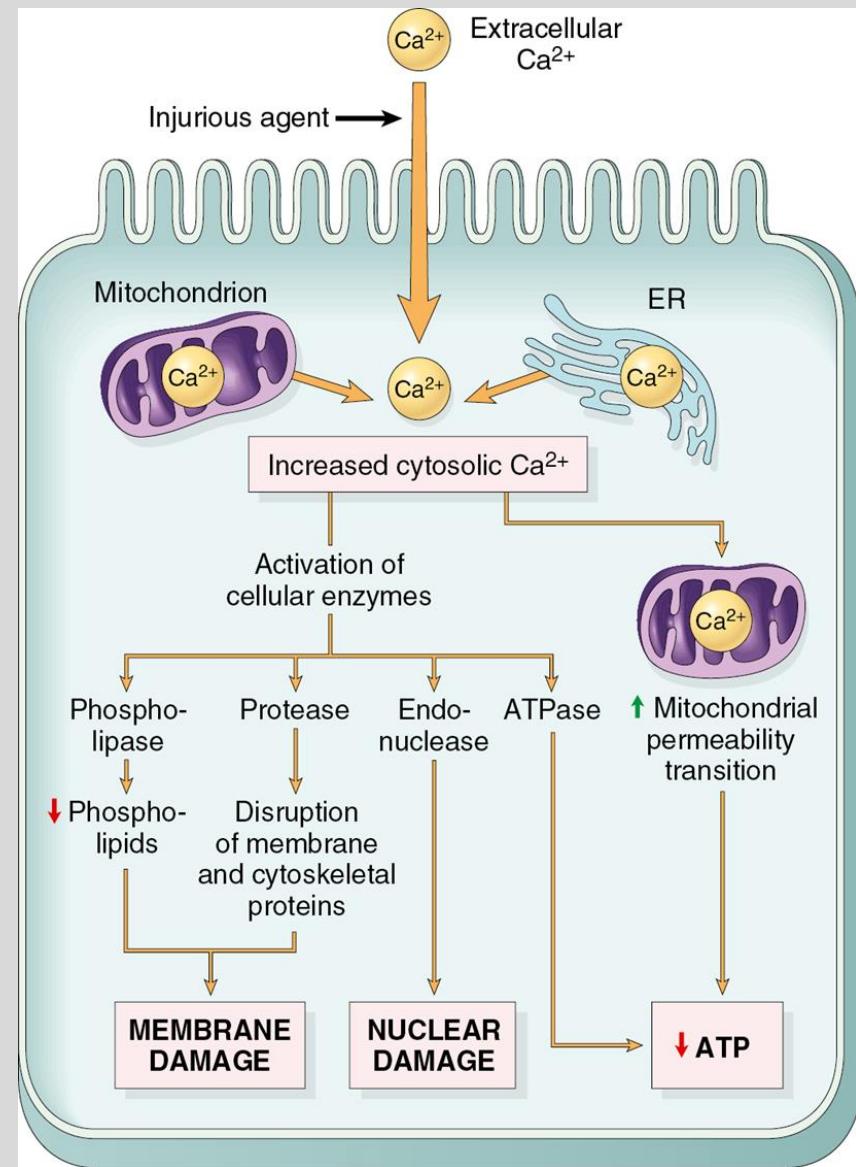
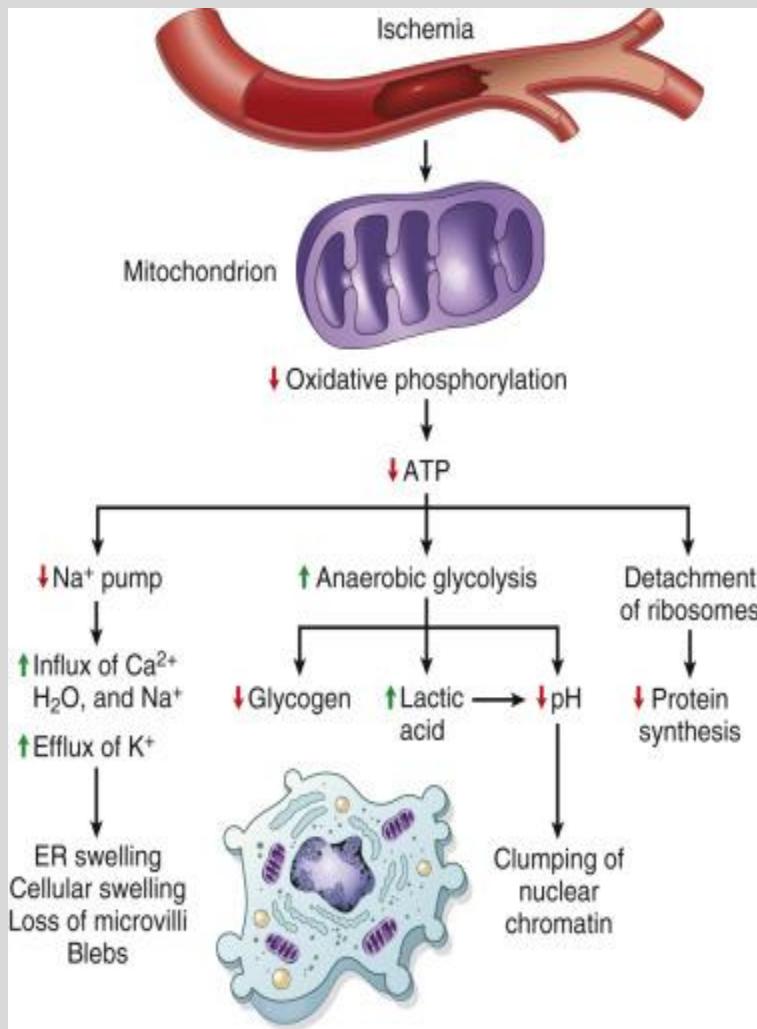


- Free radicals: unstable - decay spontaneously
- Cells have multiple nonenzymatic and enzymatic mechanisms to remove free radicals and minimize injury:
 - *Antioxidants* either block free radical formation or inactivate (e.g., scavenge) free radicals, e.g., lipid-soluble vitamins E and A, ascorbic acid 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 $\text{O}_2\bullet^-$:
 - 1. *Catalase*, present in peroxisomes, decomposes H_2O_2 ($2\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + 2\text{H}_2\text{O}$).
 - 2. *Superoxidase dismutases* (SODs) are found in many cell types and convert $\text{O}_2\bullet^-$ to H_2O_2 ($2\text{O}_2\bullet^- + 2\text{H} \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$).
 - 3. *Glutathione peroxidase* also protects against injury by catalyzing free radical breakdown ($\text{H}_2\text{O}_2 + 2\text{GSH} \rightarrow \text{GSSG}$ [oxidized glutathione] + $2\text{H}_2\text{O}$).



Calcium Homeostasis Disturbances

- **Calcium ions normally act as second messengers in several signalling pathways, but if released into the cytoplasm of cells in excessive amounts, can cause cell injury**
- Most intracellular Ca^{2+} is sequestered in mitochondria and the ER
- Ischemia and certain toxins cause an excessive increase in cytosolic Ca^{2+} , initially because of release from intracellular stores, and later due to increased influx across the plasma membrane
- **Failure of CA pump**
- Accumulation of Ca^{2+} in mitochondria results in opening of mitochondrial permeability transition pore and failure of ATP generation
- Increased cytosolic Ca^{2+} activates several enzymes with potentially deleterious effects on cells
 - *phospholipases* (which cause membrane damage)
 - *proteases* (which break down both membrane and cytoskeletal proteins)
 - *endonucleases* (which are responsible for DNA and chromatin fragmentation),
 - *ATPases* (thereby hastening ATP depletion).



Reversible v irreversible cell injury

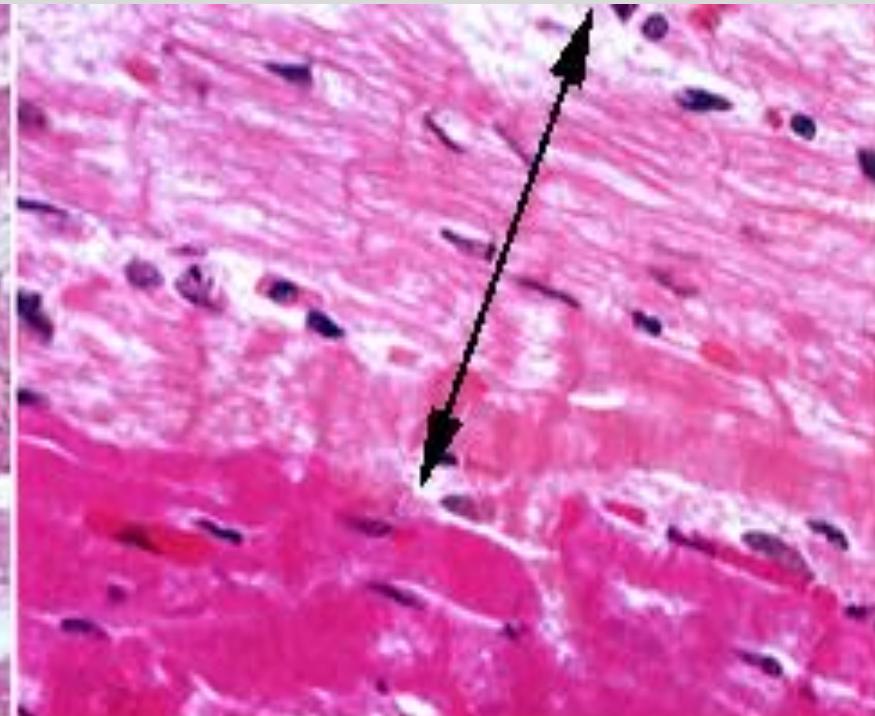
- Two *phenomena consistently characterize irreversibility*
- *inability to reverse mitochondrial dysfunction* (lack of oxidative phosphorylation and ATP generation) even after resolution of original injury
- *profound disturbances in membrane function* - injury to lysosomal membranes results in the enzymatic dissolution of the injured cell characteristic of necrosis.

What is Necrosis?

- Pathologic process, consequence of severe injury
- Main causes include
 - loss of oxygen supply (ischemia)
 - exposure to microbial toxins
 - burns and other forms of chemical and physical injury
 - situations in which active proteases leak out of cells and damage surrounding tissues (e.g., pancreatitis)
- Characterized by **denaturation of cellular proteins, leakage of cellular contents through damaged membranes, local inflammation, and enzymatic digestion of the lethally injured cell**
- When damage to membranes is severe, lysosomal enzymes enter cytoplasm and digest cell
- Cellular contents also leak through the damaged plasma membrane into extracellular space, where they elicit a host reaction (inflammation)
- Note: Some specific substances released from injured cells have been called *damage-associated molecular patterns (DAMPs)*.



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

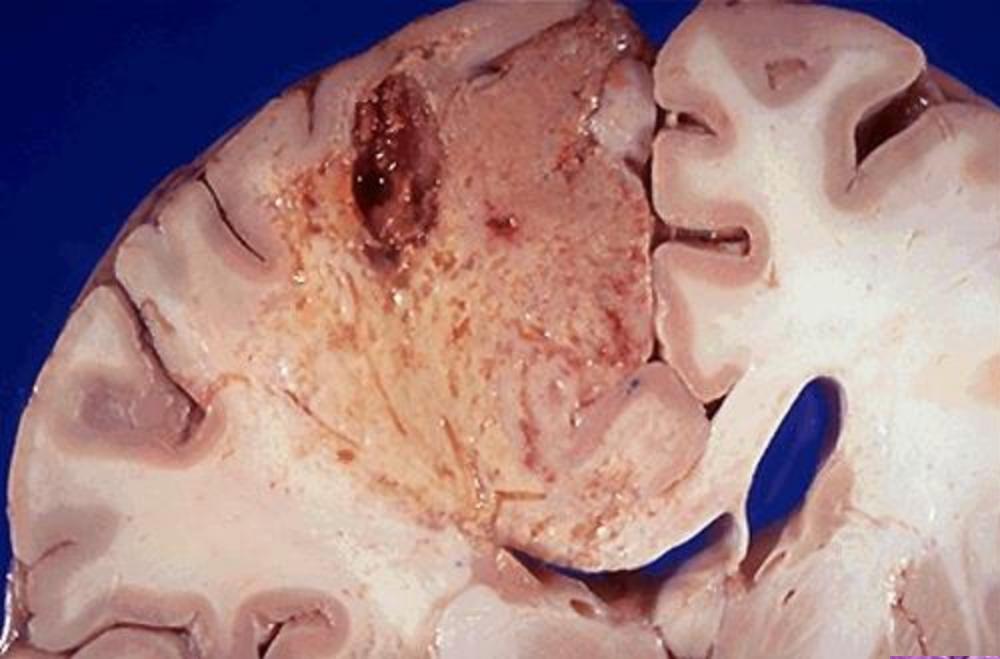


Ischemic areas show loss of nuclei to pyknosis & karyolysis; increased eosinophilia of cytoplasm but retention of tissue architecture

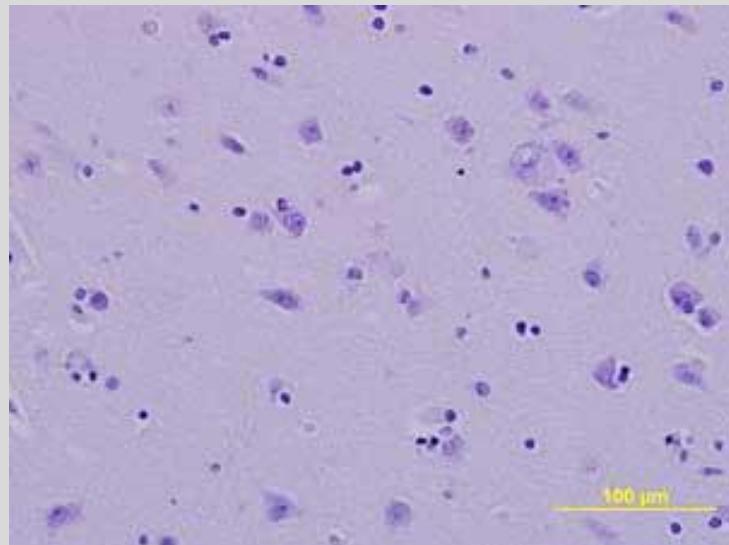
What type of necrosis does myocardium undergo?
Morphologic pattern

Coagulative necrosis

- Architecture (cell outlines) preserved,
nucleus disappears
- Increased eosinophilia seen at first because
of denatured cytoplasmic proteins
- **Local area of coagulative necrosis – infarct**
- Heart, kidney, solid organs

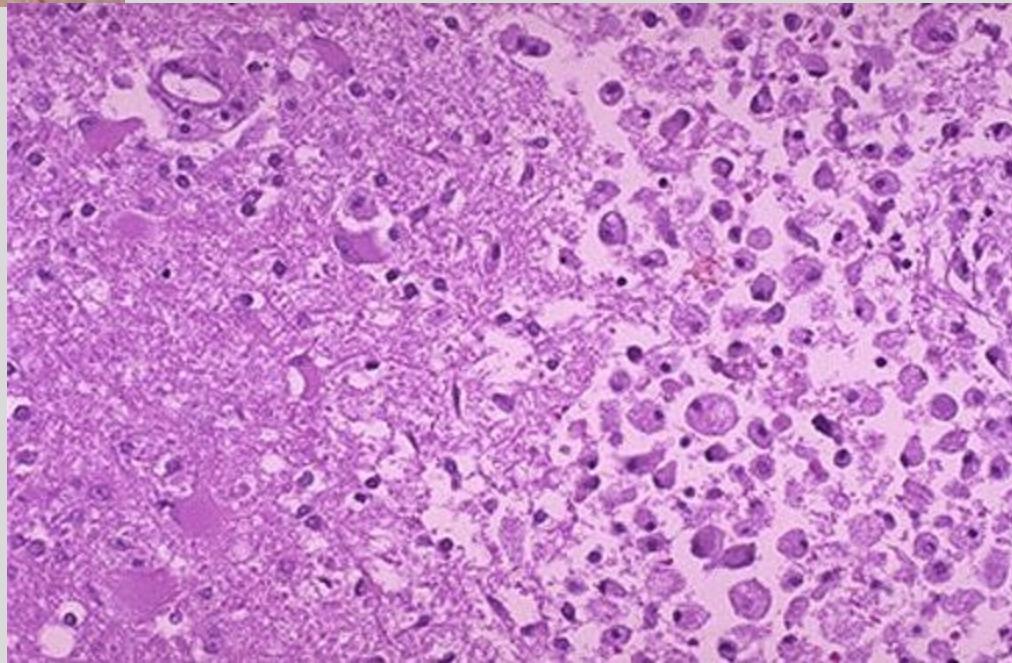


Normal



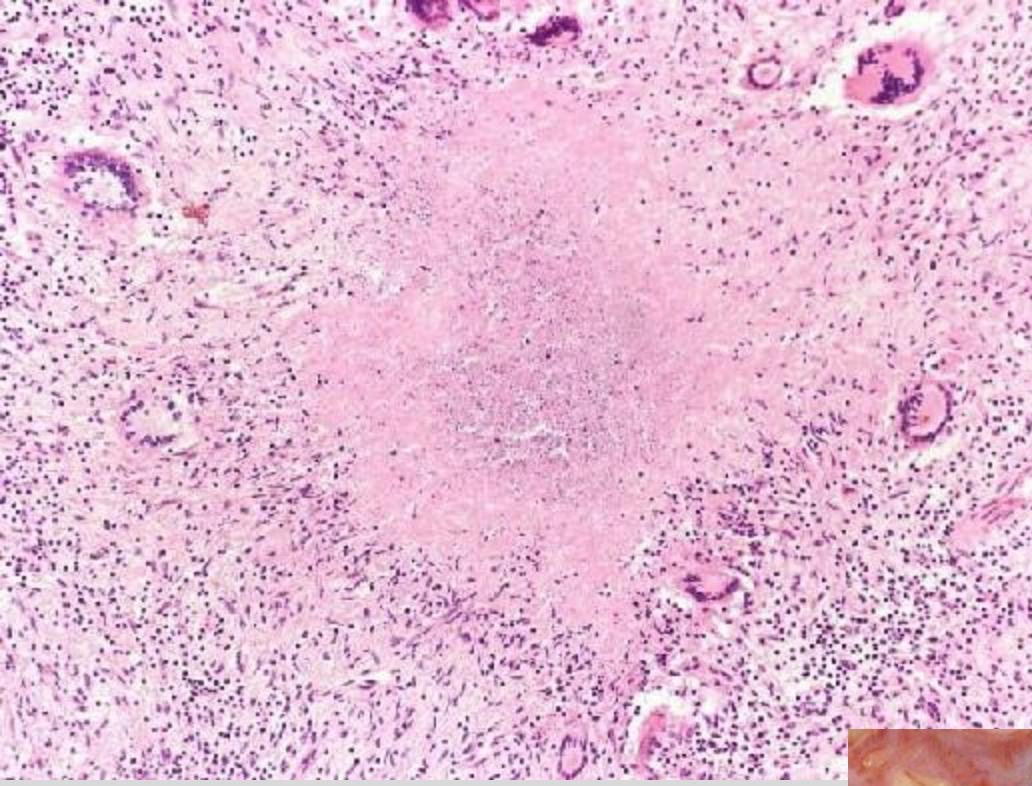
What Organ?

What type of necrosis?



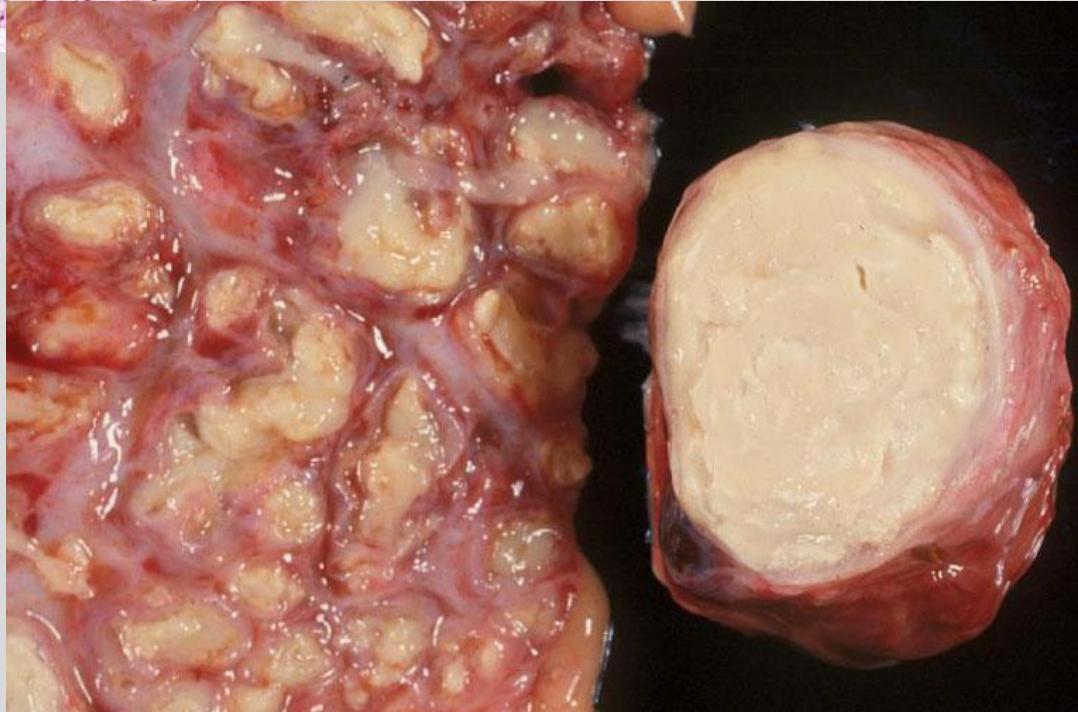
Liquefactive necrosis

- Digestion of dead cells resulting in liquid, viscous mass
- Brain, abscess (bacteria)
- Neutrophils release lysosomal enzymes that digest tissue, then protein degradation



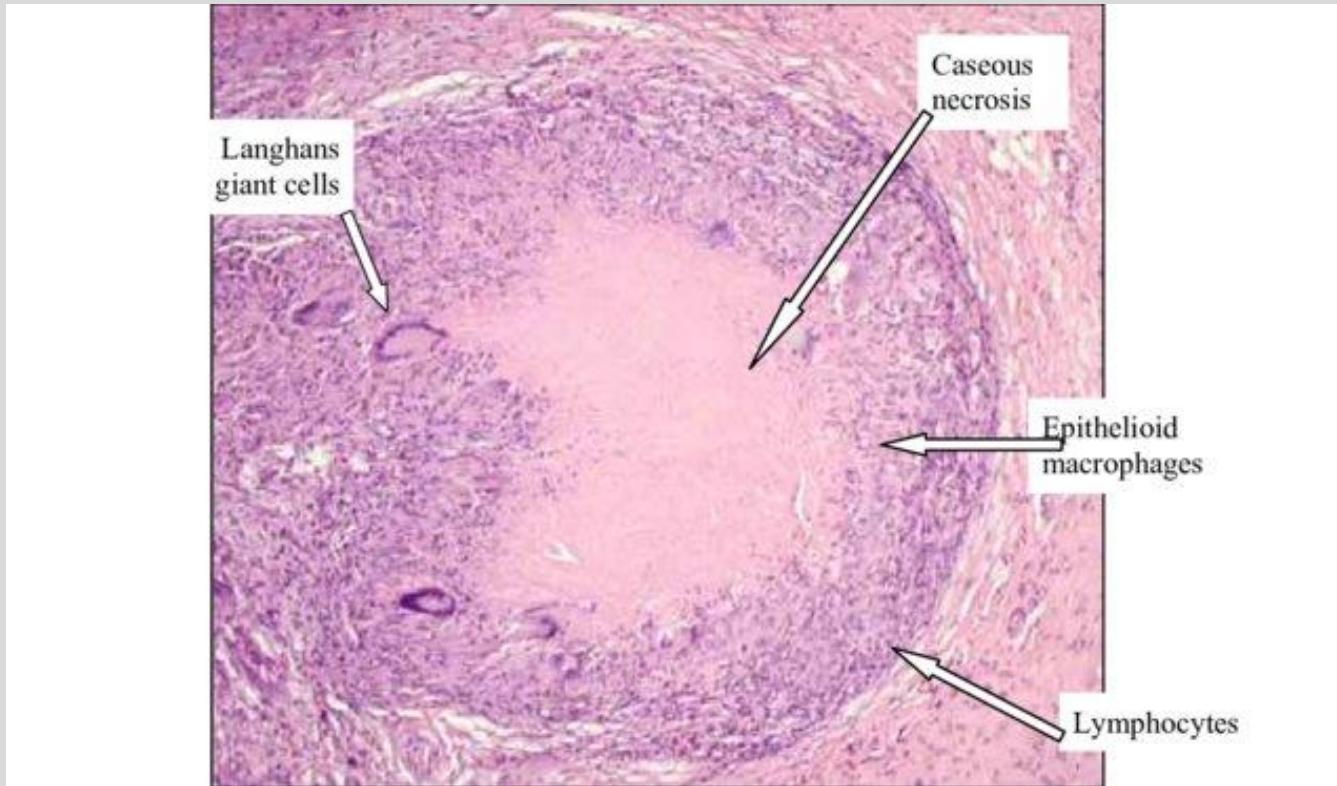
Examples?

What type of necrosis?



Caseous Necrosis

- Caseous (cheeselike) - friable white appearance of the area of necrosis
- Specific, microscopic: necrotic area: structureless collection of fragmented or lysed cells and amorphous granular debris enclosed within collection of macrophages (epithelioid) = **granuloma**
- **Granulomatous/granuloma** - small nodular delimited aggregation of mononuclear inflammatory cells, usually a collection of modified (epithelioid) macrophages, generally surrounded by a rim of lymphocytes.
- Tuberculosis, fungal infections

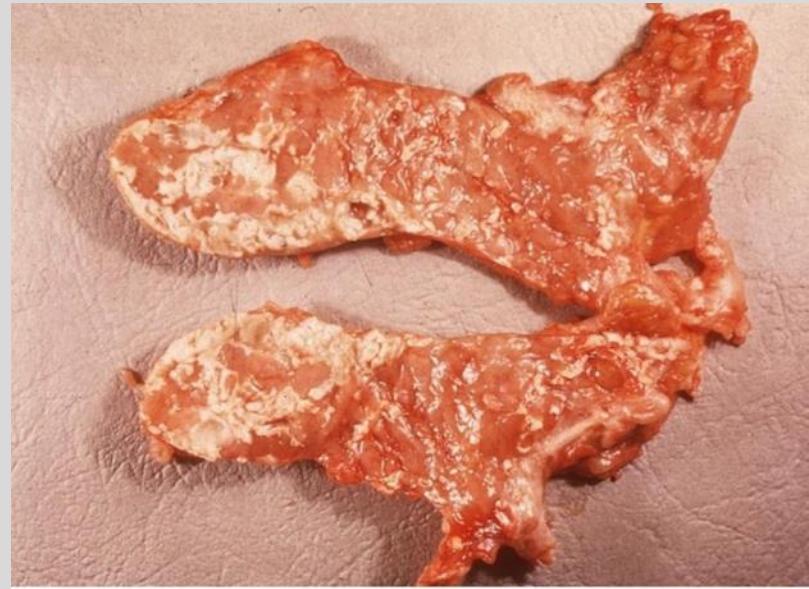
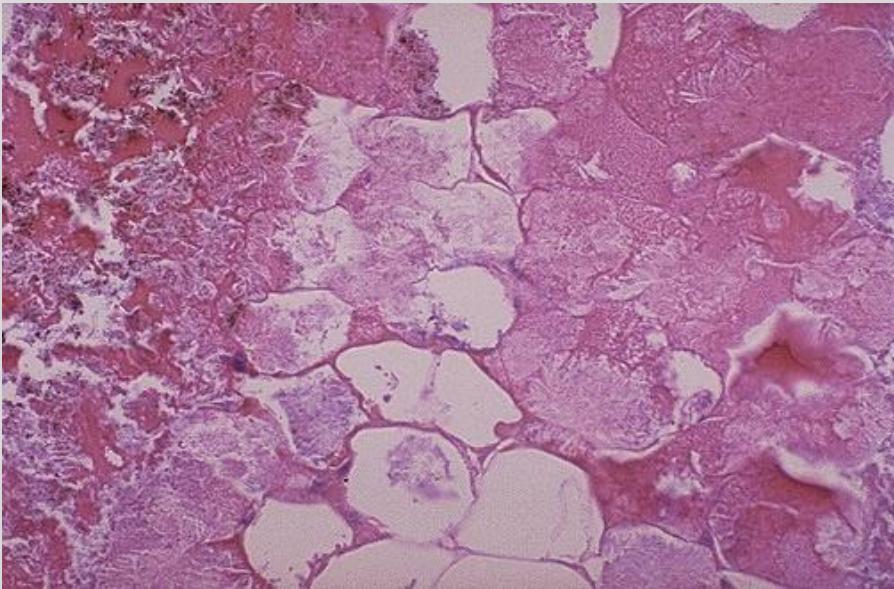


Centrally, caseous necrosis is apparent as amorphous pink material

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

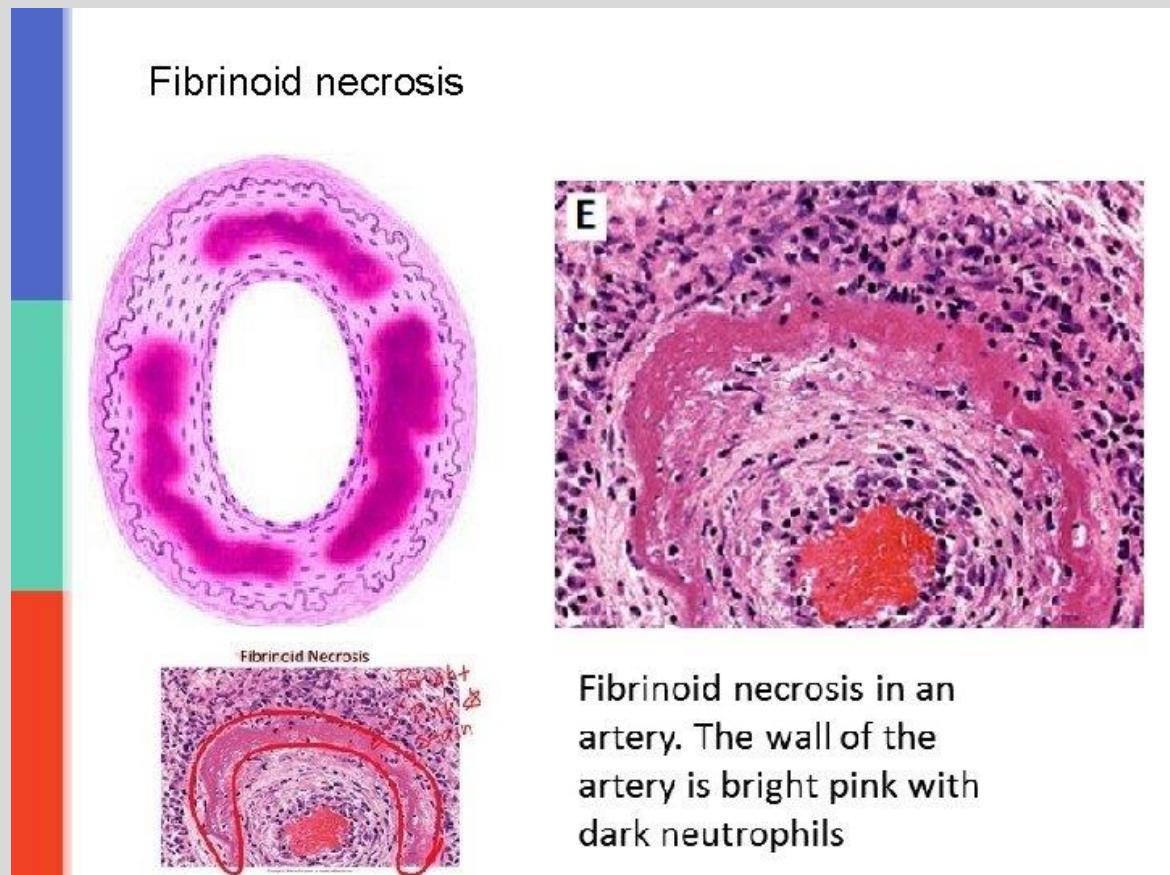


<http://picasaweb.google.com/lh/photo/2bVfmGoECVga4crlnneb67w>

Fatty necrosis – Areas of fat destruction, release of lipase enzyme which breaks down fatty acids in cell membranes
e.g., acute pancreatitis (peripancreatic fat)

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)



Gangrenous necrosis

- Not specific pattern of cell death
- Term commonly used in clinical practice
- Usually refers to limb that has lost blood supply and undergone necrosis (typically coagulative necrosis) involving multiple tissue planes
- When bacterial infection is superimposed, there is increased liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (**wet gangrene**).

Apoptosis

- Type of cell death induced by tightly regulated suicide program: **cells destined to die activate intrinsic enzymes (caspases) that degrade cellular DNA and nuclear and cytoplasmic proteins**
- **Regulated mechanism of cell death:** eliminates unwanted and irreparably damaged cells, with least possible host reaction
- Characterized by enzymatic degradation of proteins and DNA, initiated by **caspases**, and recognition and removal of dead cells by phagocytes
- Apoptotic cells break up into plasma membrane–bound fragments (apoptotic bodies), contain parts of cytoplasm and nucleus

Apoptosis

- Necrosis is always pathologic
- Apoptosis may be part of normal function:
 - destruction of cells during embryogenesis
 - hormone withdrawal involution (menstruation)
 - end of acute inflammatory response/immune response
- Pathological apoptosis:
 - DNA damage – e.g., radiation, chemotherapy
 - accumulation of misfolded proteins – CNS deg dxs
 - infections (especially viral) – HIV, hepatitis

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* .

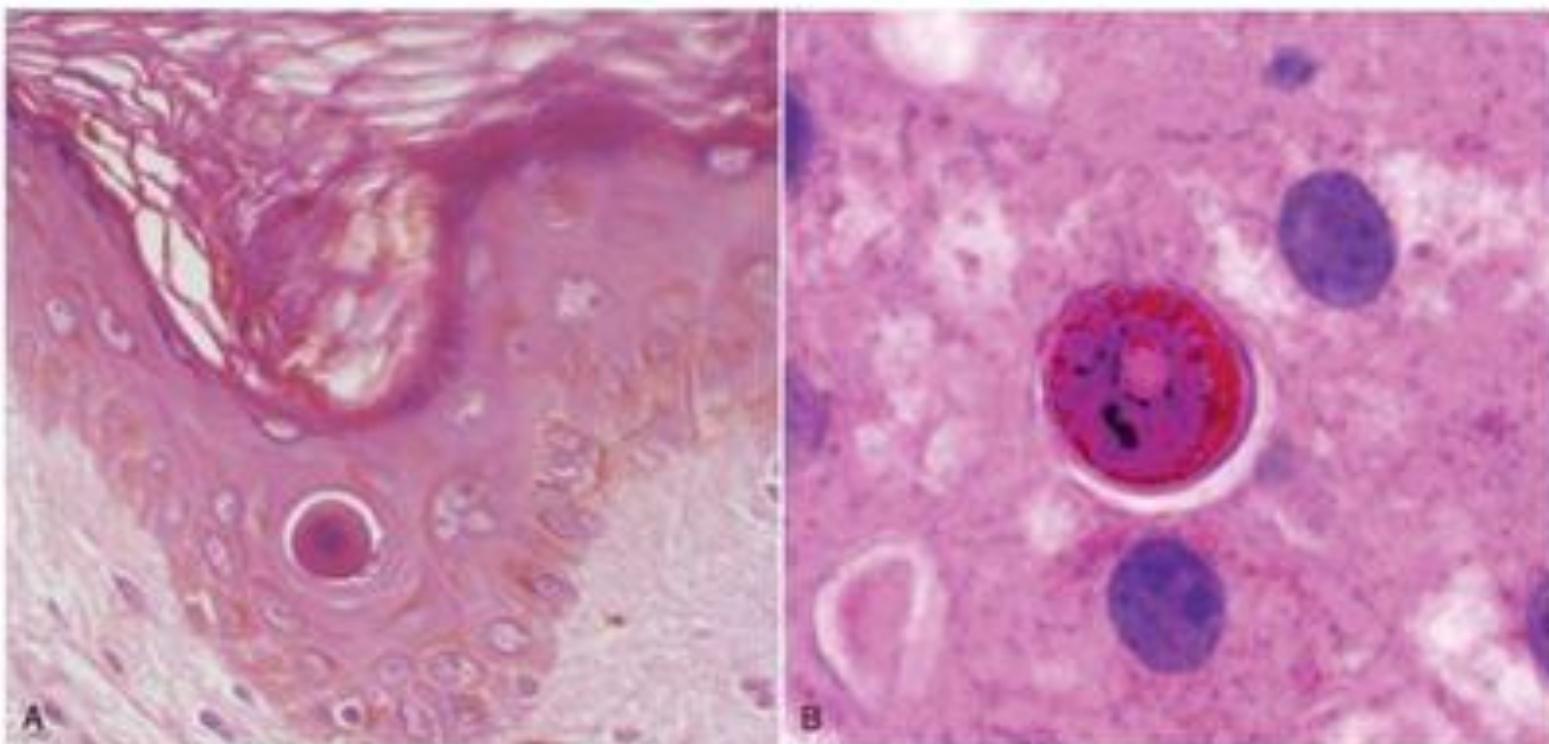
Apoptosis: pathological

- **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

Apoptosis - Features

- Very eosinophilic cytoplasm
- Cell shrinkage
- Nuclear shrinkage (pyknosis)
- Membrane blebbing
- Nuclear fragmentation (karyorrhexis)
- Apoptotic bodies (phagocytosed)

Apoptosis - skin



Apoptosis - Mechanisms

- Results from activation of enzymes called **caspases**
 - **Initiation** phase - some caspases become catalytically active and cause cascade of other caspases
 - **Execution** phase - terminal caspases trigger cellular fragmentation and demise
 - Regulation of caspases depends on finely tuned balance between amount and activity of **pro-apoptotic and anti-apoptotic proteins**
 - **Two distinct pathways converge on caspase activation: the mitochondrial pathway and the death receptor pathway**
 - Pathways intersect, but generally induced under different conditions, involve different initiating molecules, and serve distinct roles in physiology and disease
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- Robbins and Cotran, Pathologic Basis of Disease, 11th ed. 2025

Apoptosis – Intrinsic (Mitochondrial) pathway

- **Results** from increased permeability of mitochondrial outer membrane with consequent release of death-inducing (**pro-apoptotic**) molecules from mitochondrial intermembrane space into cytoplasm – releases **cytochrome c**
- **Leads** to leakage of pro-apoptotic proteins from mitochondrial membrane into cytoplasm and subsequent caspase activation
- Inhibited by anti-apoptotic members of the BCL2 family, which are induced by survival signals, including growth factors
- Changes in proportions of anti (e.g., Bcl-2) and pro- apoptotic (e.g., BAX, BAK) factors lead to increased mitochondrial permeability and cytochrome c release
 - An ‘apoptosome’ formed by interaction of cytochrome c, Apaf-1, d-ATP/ ATP and procaspase-9 with subsequent initiation of caspase cascade which induces apoptosis (binds to **caspase-9, critical initiator caspase of the mitochondrial pathway**)
 - Active caspase-9 then triggers a cascade of caspase activation) by cleaving and activating other pro-caspases, which mediate execution phase of apoptosis

Apoptosis – Extrinsic (Death Receptor Initiated) Pathway

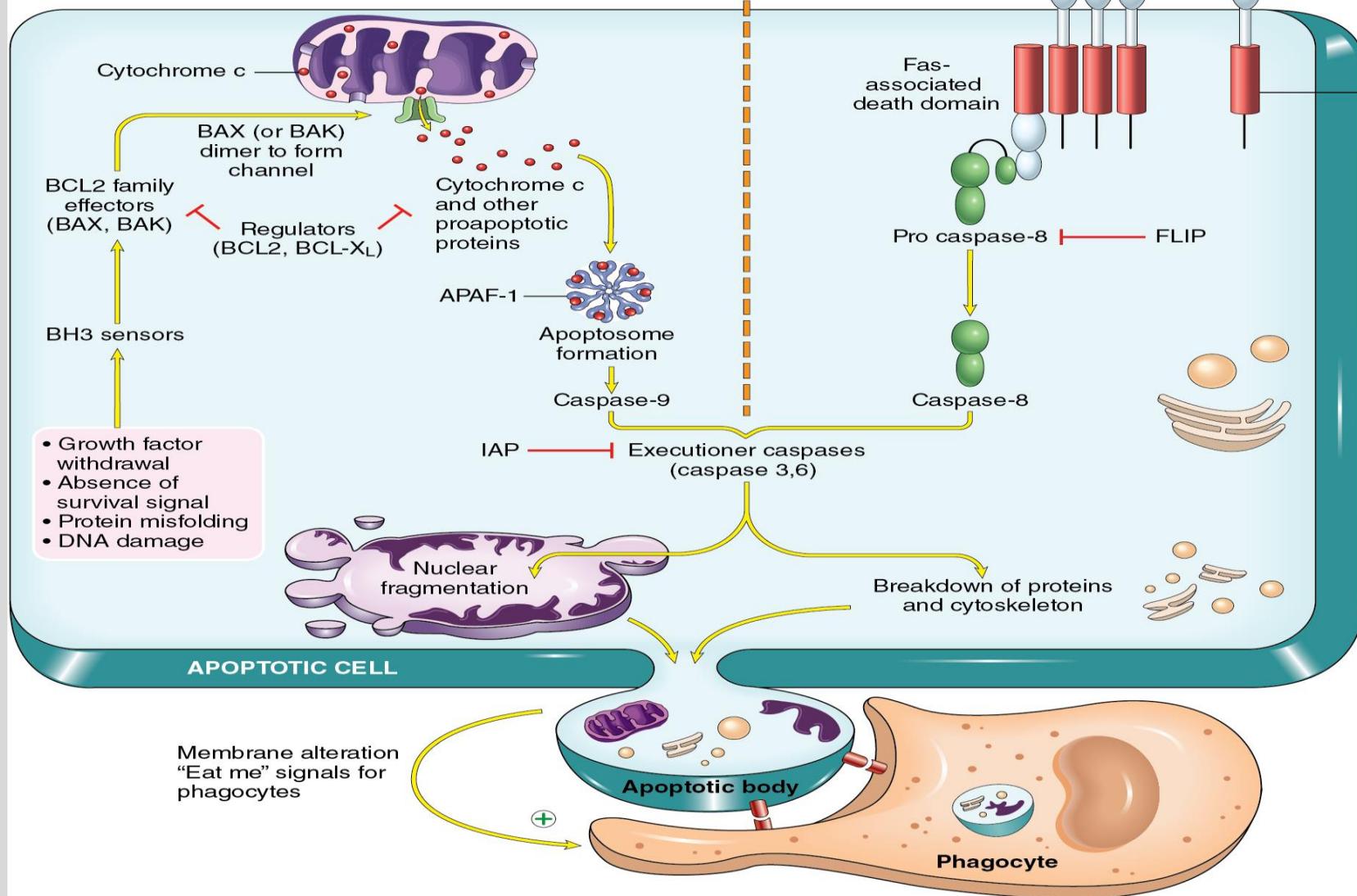
- Initiated by engagement of **plasma membrane death receptors**
- Death receptors = members of TNF receptor family that contain a cytoplasmic domain involved in protein-protein interactions: death domain needed for delivering apoptotic signals
- Best-known death receptors are the type 1 TNF receptor (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.

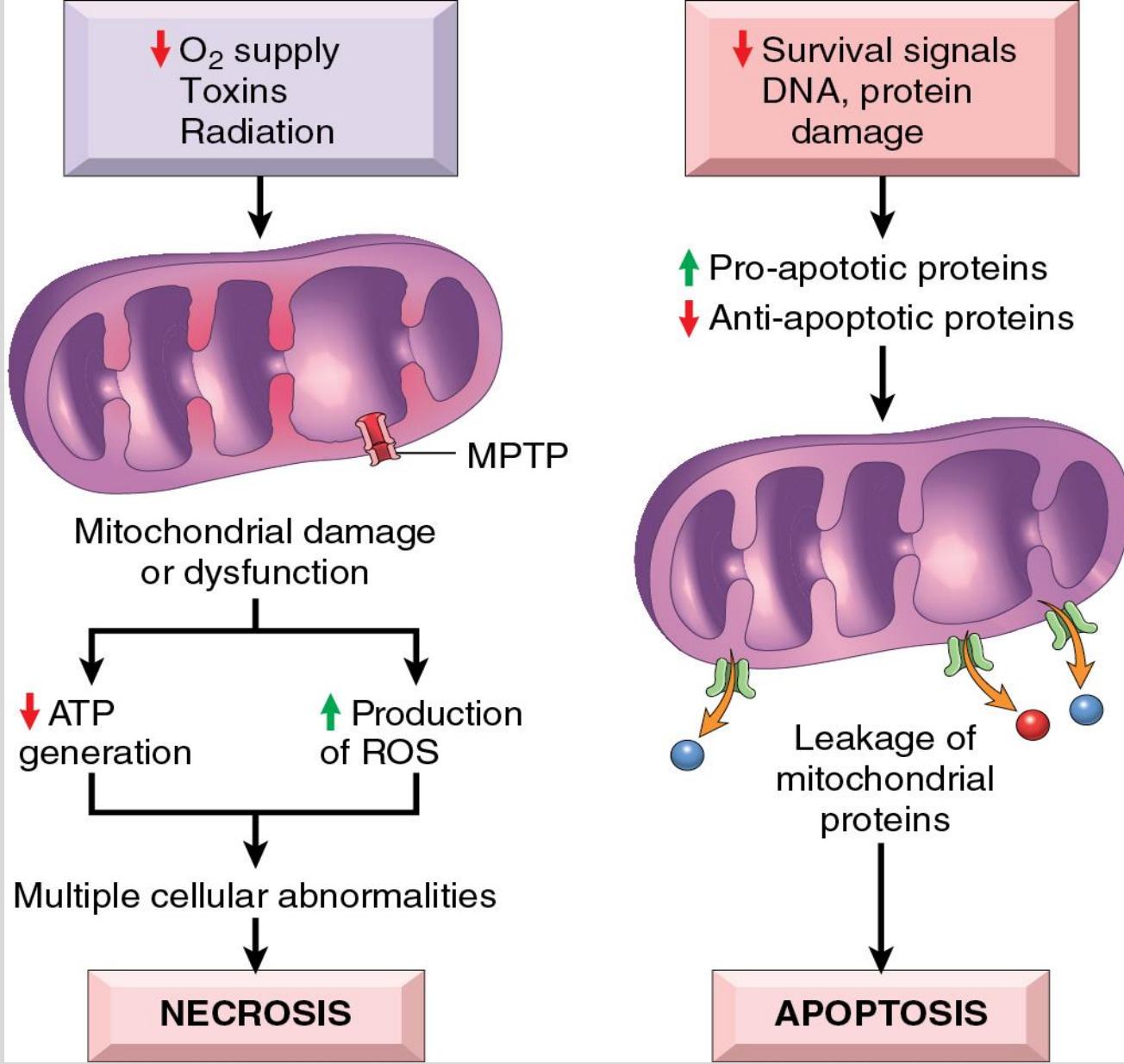
Death receptor (extrinsic) pathway eliminates self-reactive lymphocytes and is a mechanism of cell killing by cytotoxic T lymphocytes

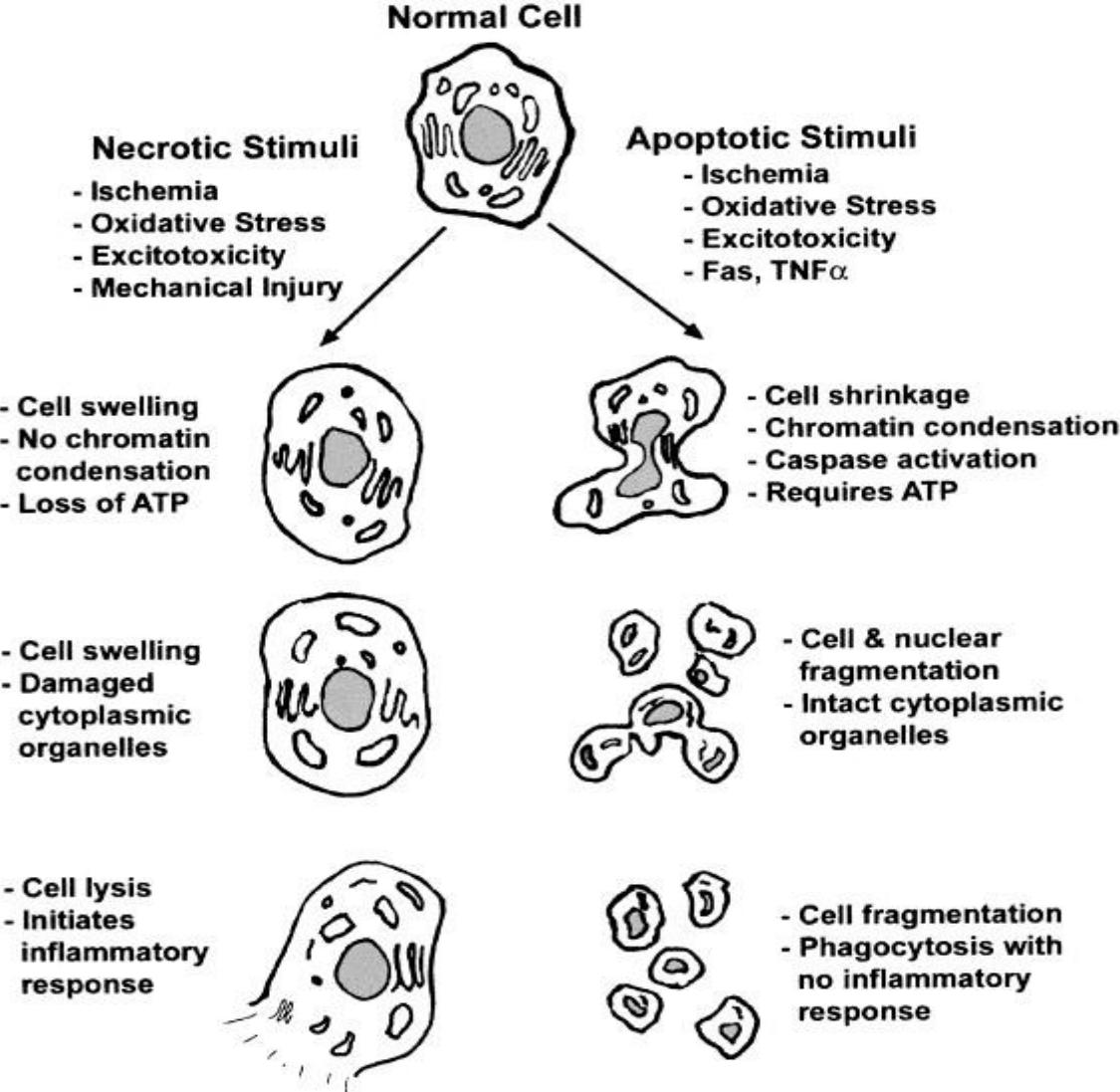
Apoptosis

- Intrinsic and extrinsic pathways converge to activate caspase cascade that mediates the final phase of apoptosis
- Intrinsic mitochondrial pathway activates the initiator caspase-9
- Extrinsic death receptor pathway activates caspase-8 and caspase-10 - active forms of these caspases trigger rapid and sequential activation of **executioner caspases, e.g., caspase-3 and caspase-6, which then act on many cellular components**
- Removal of dead cells- formation of apoptotic bodies breaks cells up into “bite-sized” fragments that are edible for phagocytes
- Apoptotic bodies may also become coated with natural antibodies and proteins of the complement system, notably C1q, recognized by phagocytes.
- Many ligands induced on apoptotic cells act as “eat me” signals and are recognized by receptors on phagocytes that bind and engulf these cells

MITOCHONDRIAL (INTRINSIC) PATHWAY







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

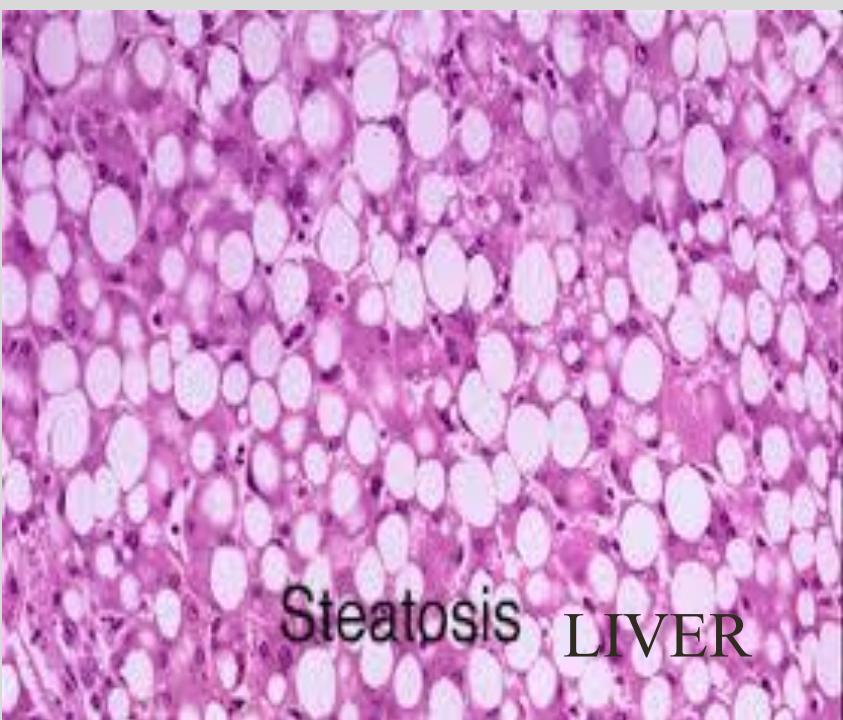
Other mechanisms of cell death

- **Necroptosis** resembles necrosis morphologically, but like apoptosis is genetically controlled form of cell death
 - Necroptosis is triggered by ligation of TNFR1 and by proteins found in RNA and DNA viruses.
 - **Caspase independent** and depends on RIPK1–RIPK3 complex
 - RIPK1–RIPK3 signaling leads to phosphorylation of MLKL, which then forms pores in the plasma membrane
 - Release of cellular contents evokes an inflammatory reaction like necrosis
-
- **Pyroptosis** occurs in cells infected by **microbes**.
 - Involves activation of caspases, which cleave and activate pore-forming function of GSDMD, resulting in lytic death of infected cell and release of inflammatory mediators
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- **Ferroptosis** is an iron-dependent pathway of cell death induced by lipid peroxidation

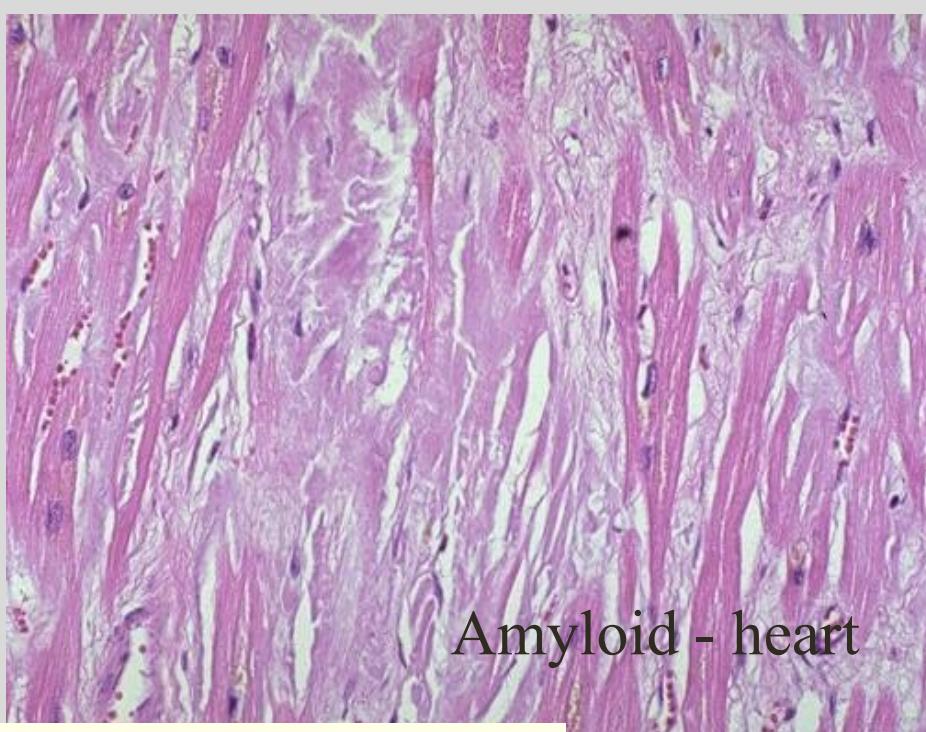
Cellular accumulations

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

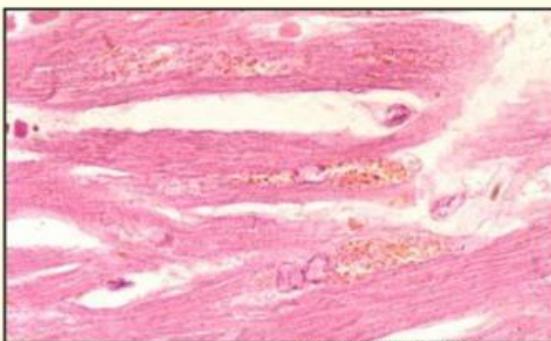


Steatosis LIVER

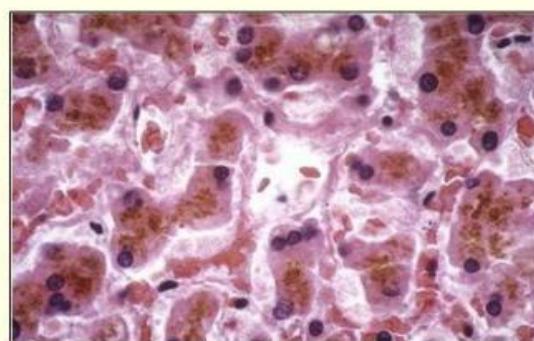


Amyloid - heart

Lipofuscin – Striated Muscle and Liver



Source: TUSDM



Source: TUSDM

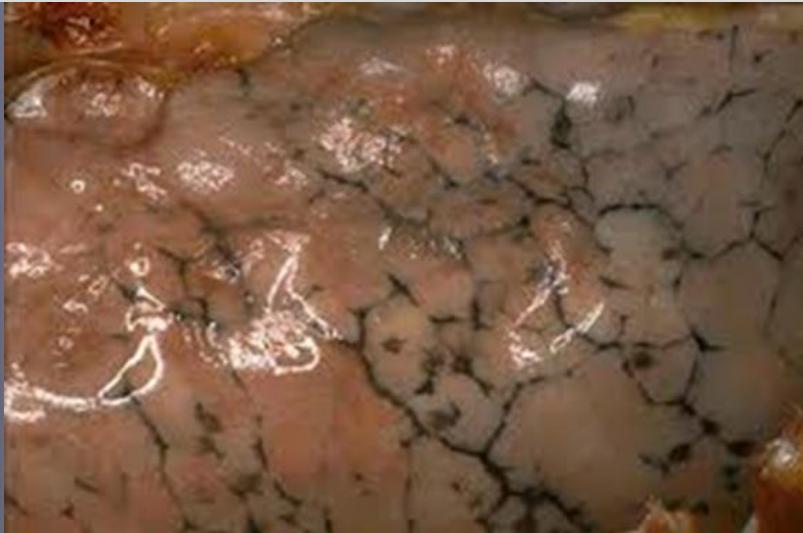
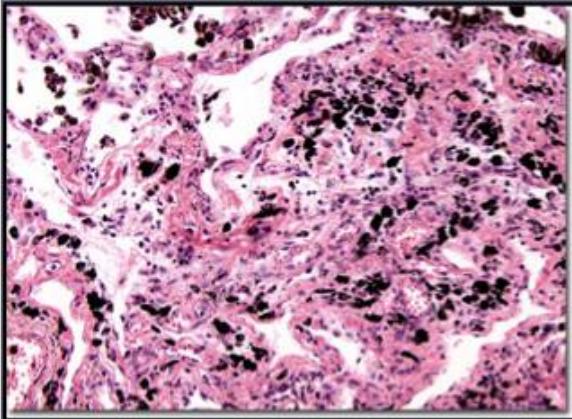
Microscopic

Cardiac muscle

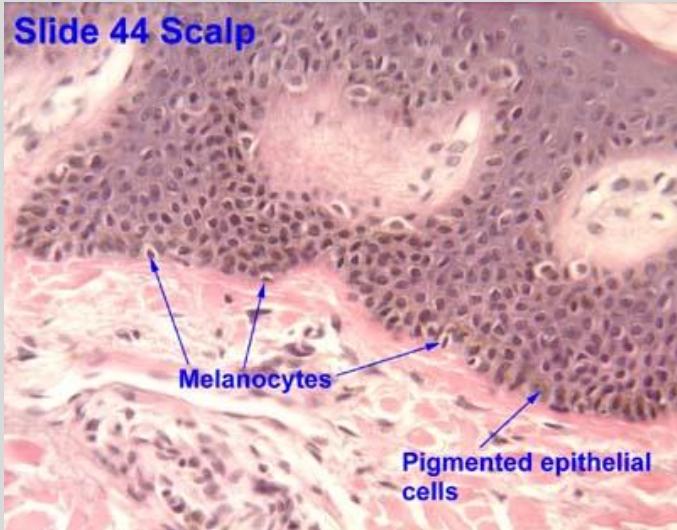
Liver

79

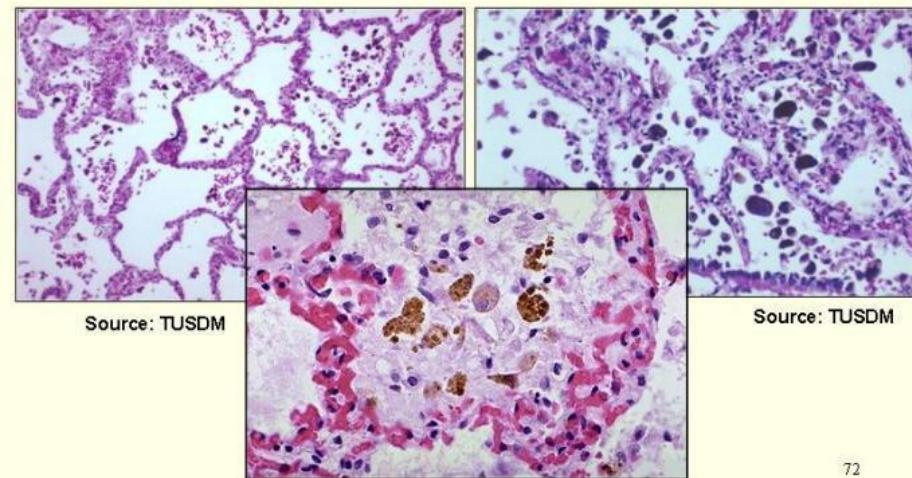
Anthracosis



Slide 44 Scalp

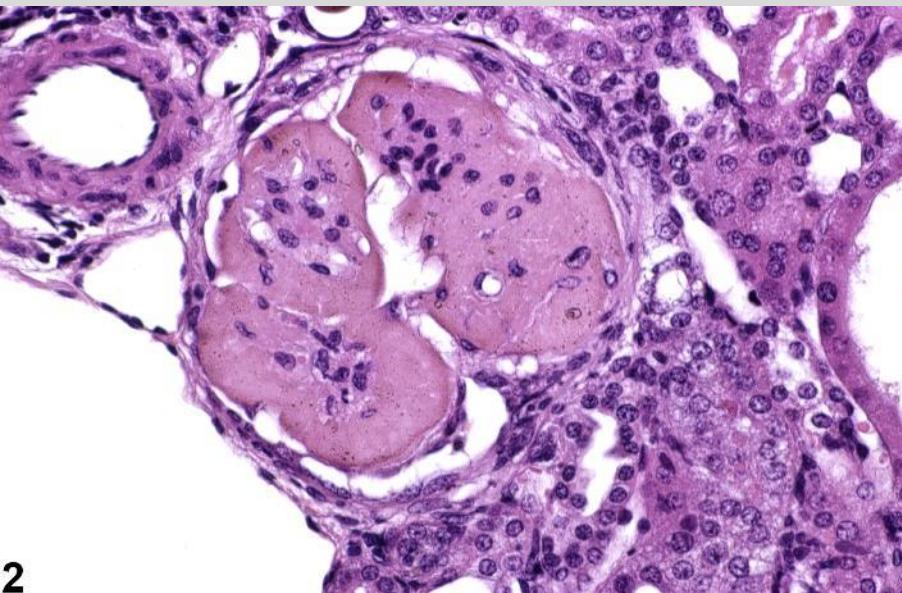


Hemosiderin – Lung Alveoli



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

Hyaline change

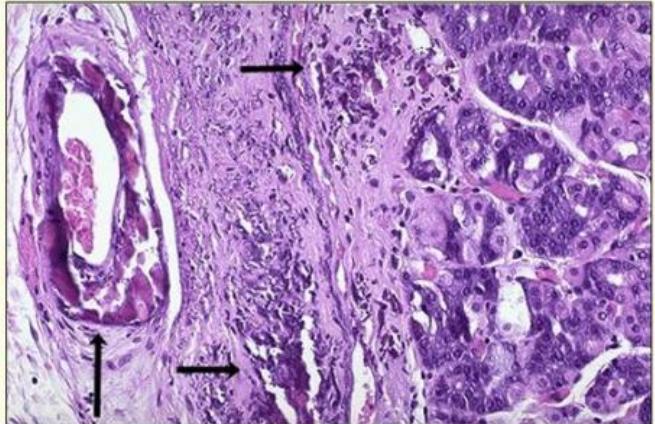
Hyaline usually refers to an alteration within cells or in extracellular space that gives a homogeneous, glassy, pink appearance in routine histologic sections stained with H&E -used as descriptive histologic term rather than a specific marker for cell injury

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

Pathologic Calcification

- Dystrophic Calcification
 - **Normal serum calcium**, areas of necrosis, damage
 - Calcium can be intracellular, extracellular or both
 - Calcium deposition on abnormal tissue
- Metastatic Calcification
 - **Normal tissue, hypercalcemia is usually present**
 - No specific relationship to malignancy
 - Four major causes (1) hyperparathyroidism (2) bone destruction (e.g. tumors) (3) Vitamin D disorders (4) renal failure
 - Seen especially in kidney, lung, gastric mucosa

Dystrophic Calcification – Stomach Injury

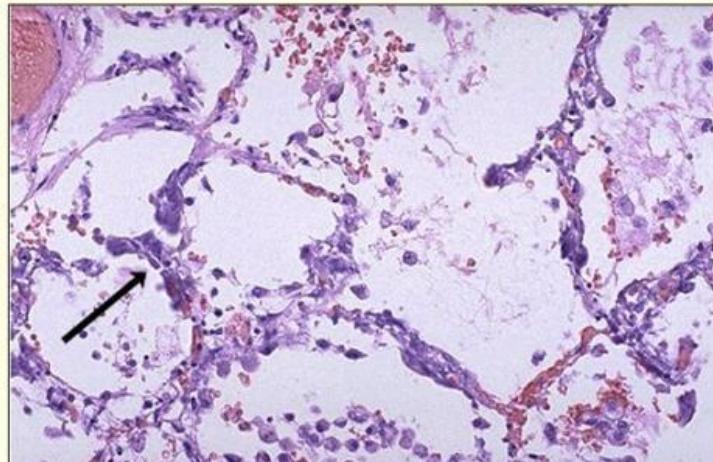


Source: TUSDM

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Metastatic Calcification Hypercalcemia - Lung



Source: TUSDM

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Summary Slide

- Cellular adaptations – metaplasia, hypertrophy, hyperplasia, atrophy
- Cell injury – reversible v. irreversible
 - Pyknosis, karyorrhexis, karyolysis
 - Mitochondrial damage, loss of ATP
 - Failure of Na/K pump – cellular edema
 - Failure of Ca pump – activation of enzymes
- Necrosis – coagulative, liquefactive, caseous, fat, fibrinoid
- Apoptosis – two pathways
- Cellular accumulations – steatosis, amyloid, lipofuscin, anthracosis, hemosiderin
- Pathological calcification – dystrophic (normal calcium, abnormal tissue), metastatic (hypercalcemia, normal tissue)

Lecture Feedback Form:

<https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R>