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

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

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

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

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

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

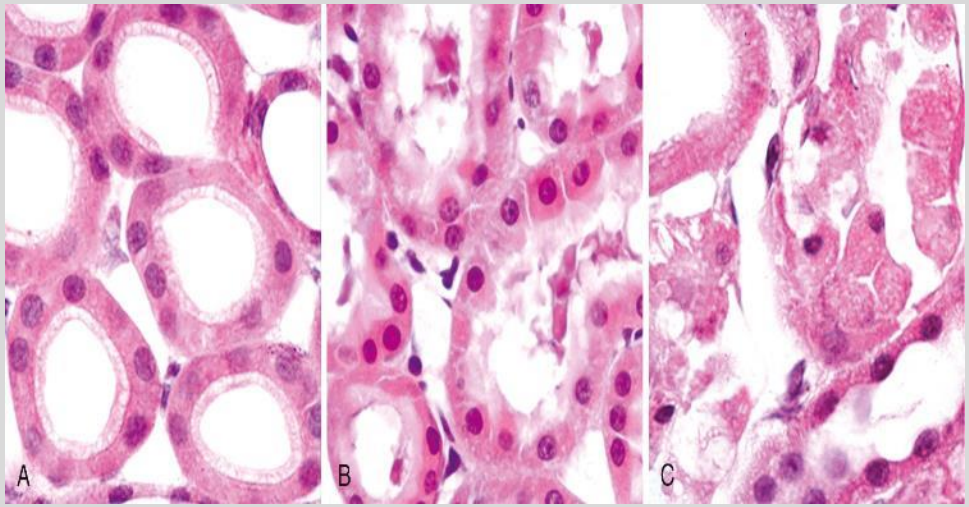
C. Cellular swelling

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, H2O and Na: resulting in cell swelling

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

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

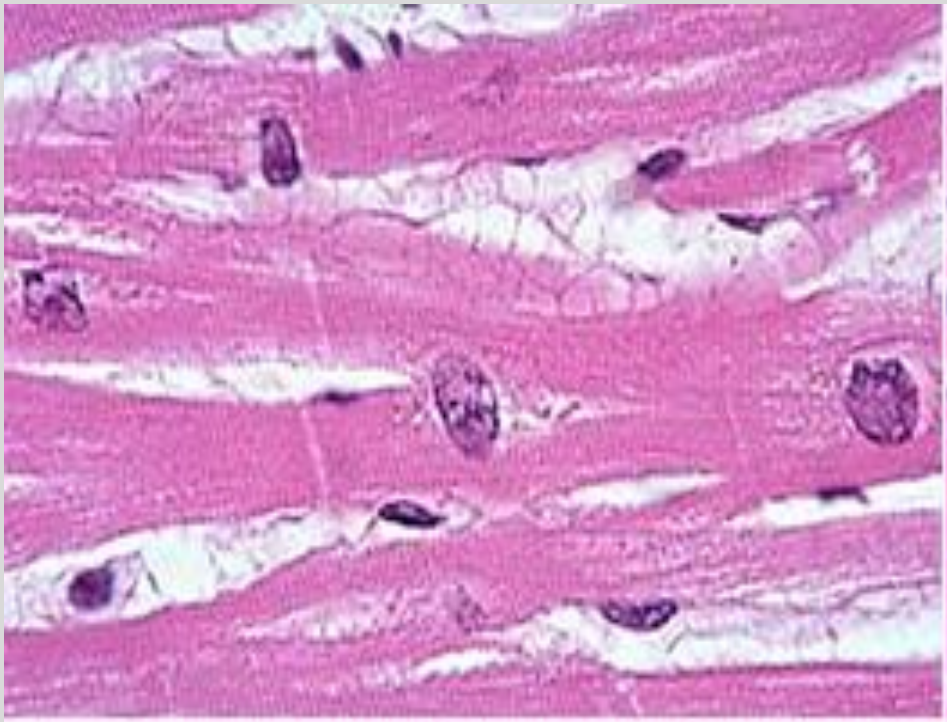
- Activity of the *plasma membrane energy-dependent sodium pump* (Na^+,K^+-ATPase) is **reduced causing sodium to enter and accumulate inside cells and potassium concentrations to fall**
- Water follows sodium into cell (osmotic drive) - leads to ***cell swelling*** **and ER dilation**

- 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*

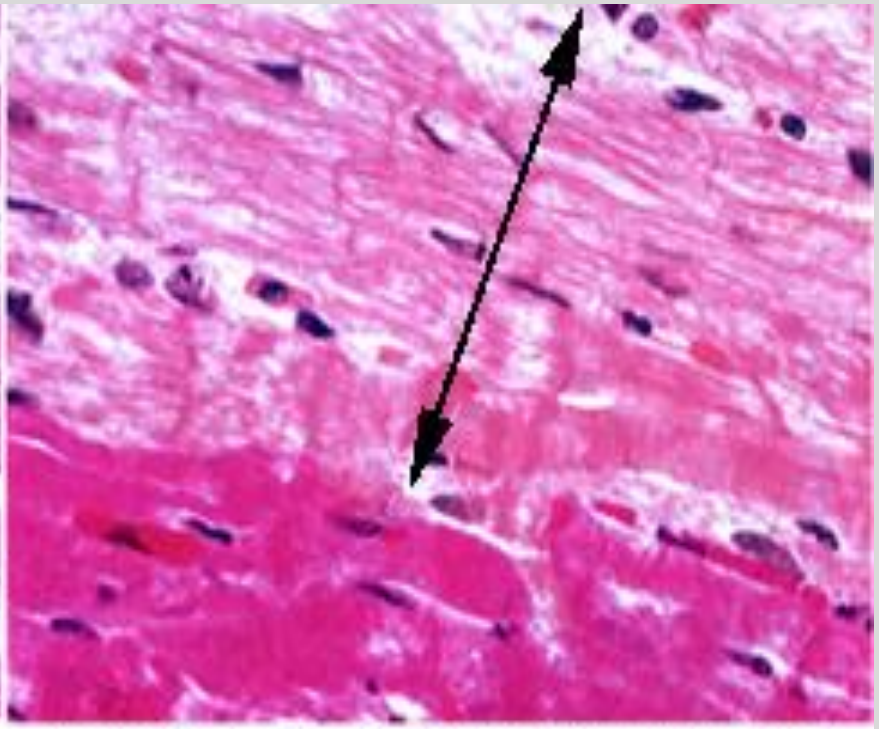
- *Also* ***Calcium pump fails****, see later*
- Incomplete oxidative phosphorylation also leads to the formation of ROS, many deleterious effects, see later

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.



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

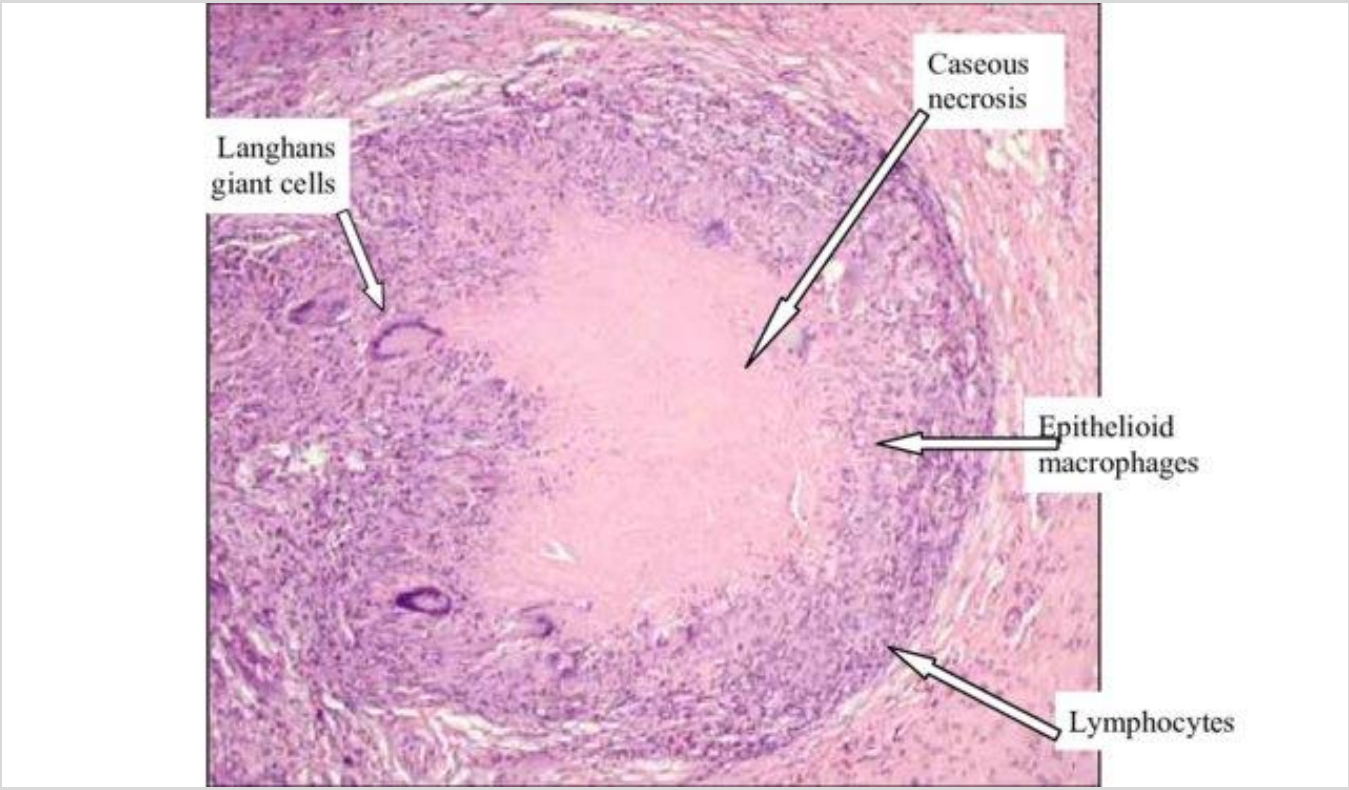
http://studydroid.com/printerFriendlyViewPack.php?packId=506801

Liquefactive necrois

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

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 (epitheloid) = **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

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

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

Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025, Ch. 2

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