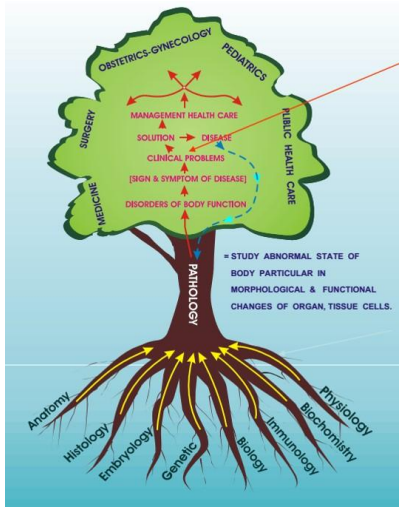

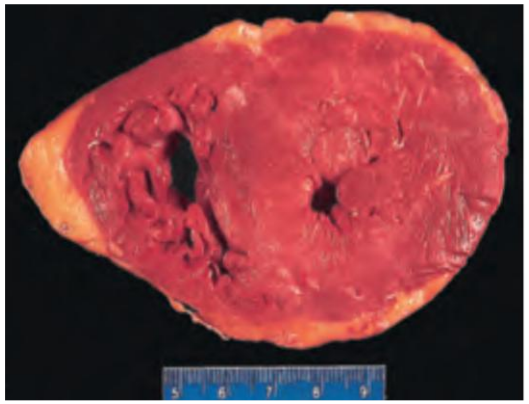

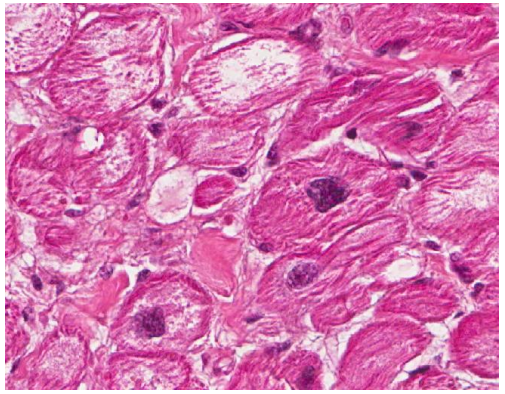

คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น
FACULTY OF MEDICINE KHON KAEN UNIVERSITY

Cellular adaptations, intracellular accumulations, cell injury and cell death

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Outlines

- Introduction to pathology
- Cell adaptations
- Intracellular accumulations
- Cell injury
- Cell death

Objectives of this study

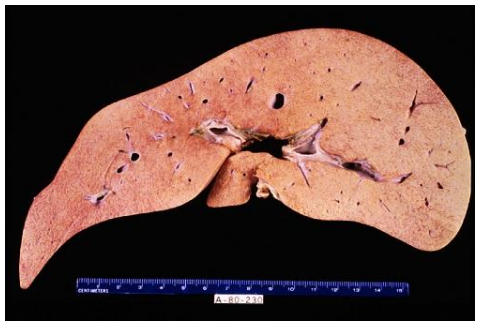
1. Describe overview of cellular responses to stress and noxious stimuli
2. Explain the overview of cell adaptations to stress
3. Describe the pathology of cell adaptations
4. Explain the overview of Intracellular accumulations
5. Explain mechanisms of reversible and irreversible injury
6. Distinguish between reversible and irreversible cell injury
7. Describe the overview and pathogenesis of cell death
8. Distinguish between necrosis and apoptosis
9. Explain the types of apoptosis
10. Explain the overview of autophagy
11. Describe types of necrosis

Pathology

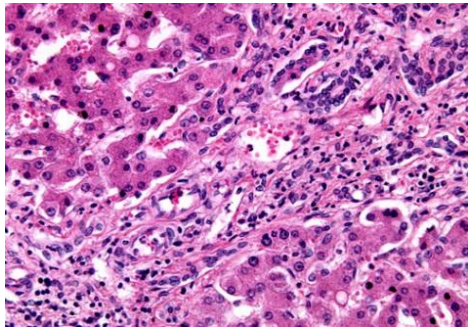
The study (logos) + Disease (pathos, suffering)

- There are two important terms that students will encounter throughout their study of pathology

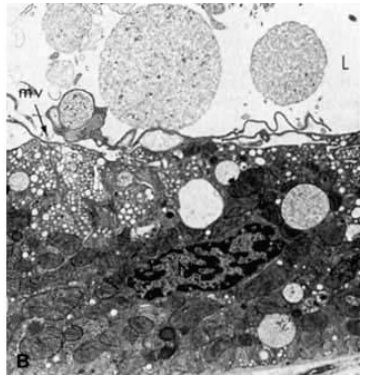
1. Etiology is the origin of a disease
2. Pathogenesis refers to the steps in the development of disease
3. Molecular and Morphologic changes
4. Functional Derangements and Clinical Manifestations



Macroscopic/Gross appearance

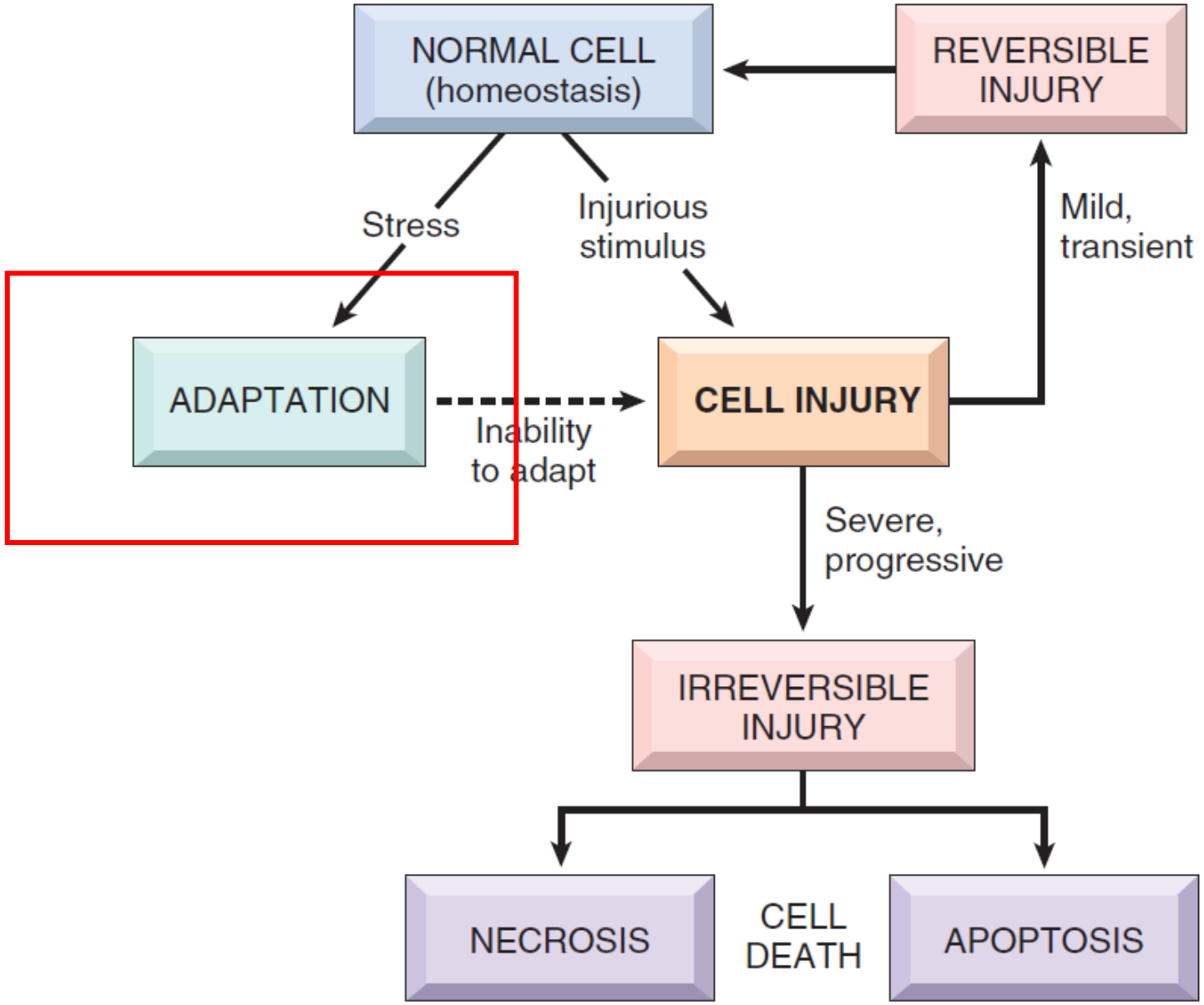


Microscopic

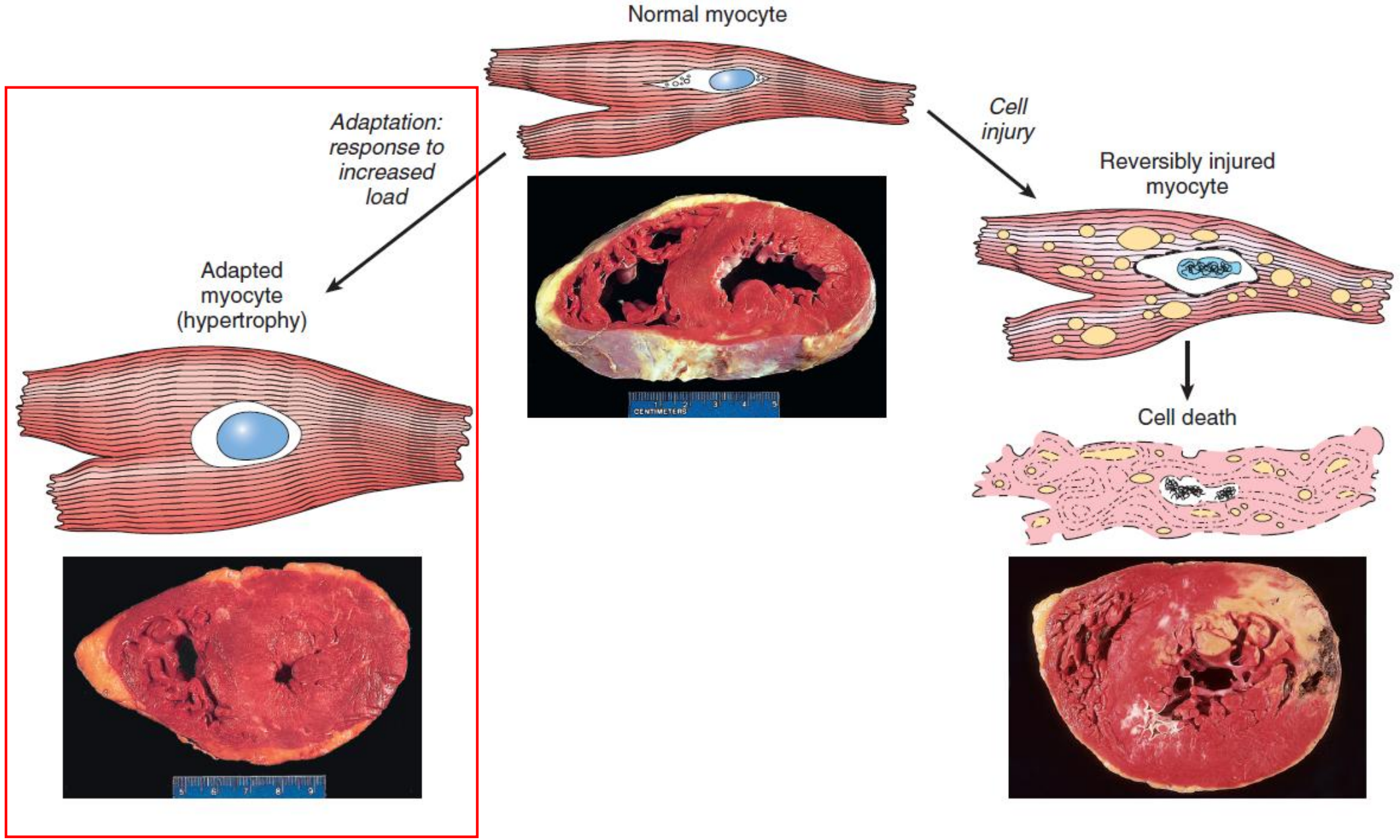


Ultrastructure

Rudolf Virchow: (1821-1902)



Robbins and Cotran pathologic basis of disease. 10th edition (2020)



Robbins and Cotran pathologic basis of disease. 10th edition (2020)

Cellular Responses to Injury

Nature of Injurious Stimulus	Cellular Response
Altered physiologic stimuli; some nonlethal injurious stimuli	Cellular adaptations
Increased demand, increased stimulation (e.g., by growth factors, hormones)	Hyperplasia, hypertrophy
Decreased nutrients, decreased stimulation	Atrophy
Chronic irritation (physical or chemical)	Metaplasia

Cell Adaptations

Reversible changes in their environment

- The number
- Size
- Phenotype
- Metabolic activity
- Functions of cells in response

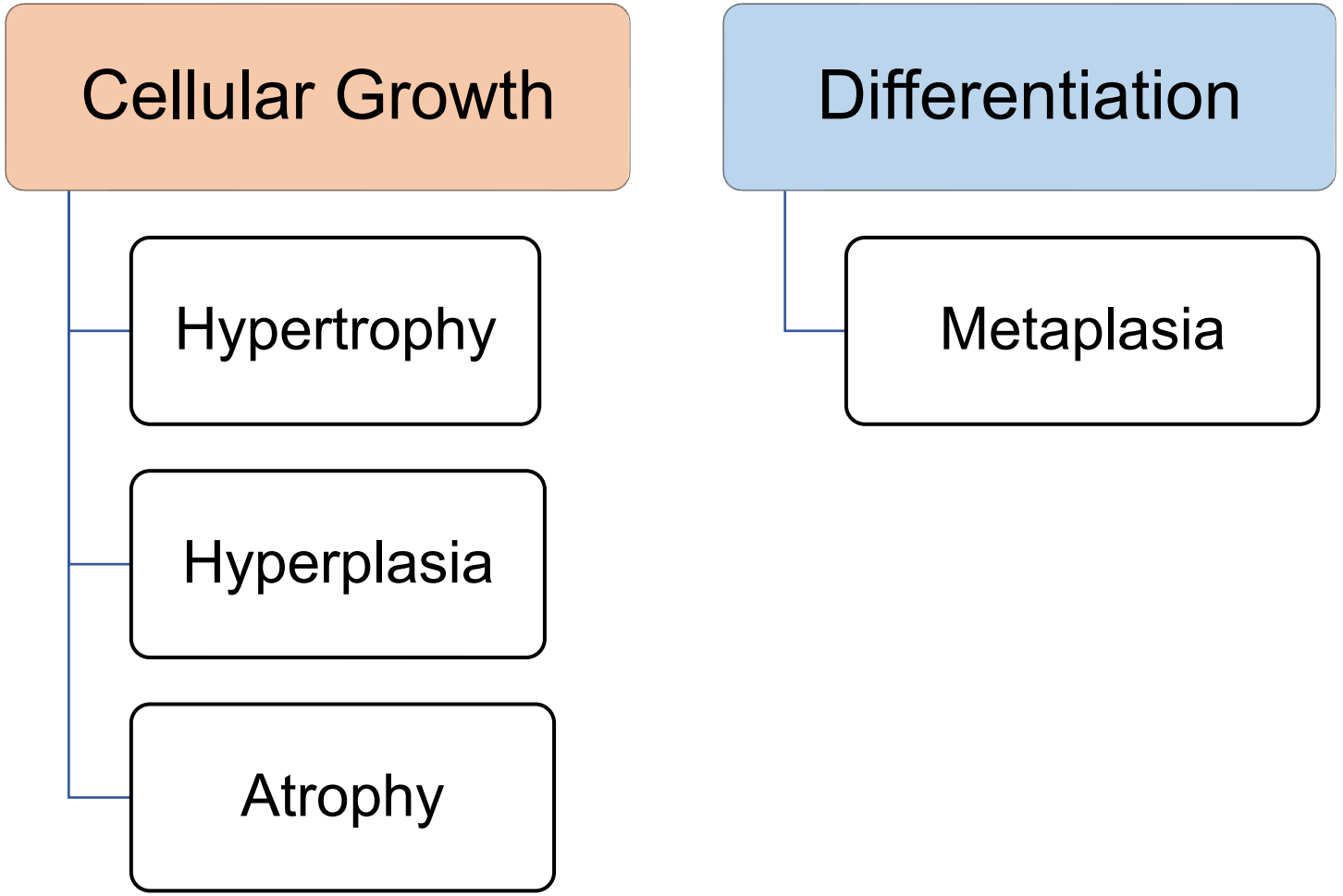
1. Physiologic adaptations

- Hormones (endogenous)
- Chemical mediators
- Exercise
- Aging
- Ex. the hormone induced enlargement of the breast and uterus during pregnancy)

2. Pathologic adaptations

- Stress according to disease or abnormality condition

Cell Adaptations



Proliferative Capacities of Tissues

1. Labile (continuously dividing) tissues

- Regenerate after injury as long as the pool of stem cells is preserved
- Skin, oral cavity, GI, vagina, and cervix mucosa
- Hematopoietic cell

Hyperplasia

2. Stable/Quiescent tissues

- Minimal replicative activity in their normal state
- These cells are capable of proliferating in response to injury or loss/ wound healing of tissue mass
- Liver, kidney, pancreas, endothelial cells, fibroblasts, osteoblast, salivary gland and smooth muscle cells

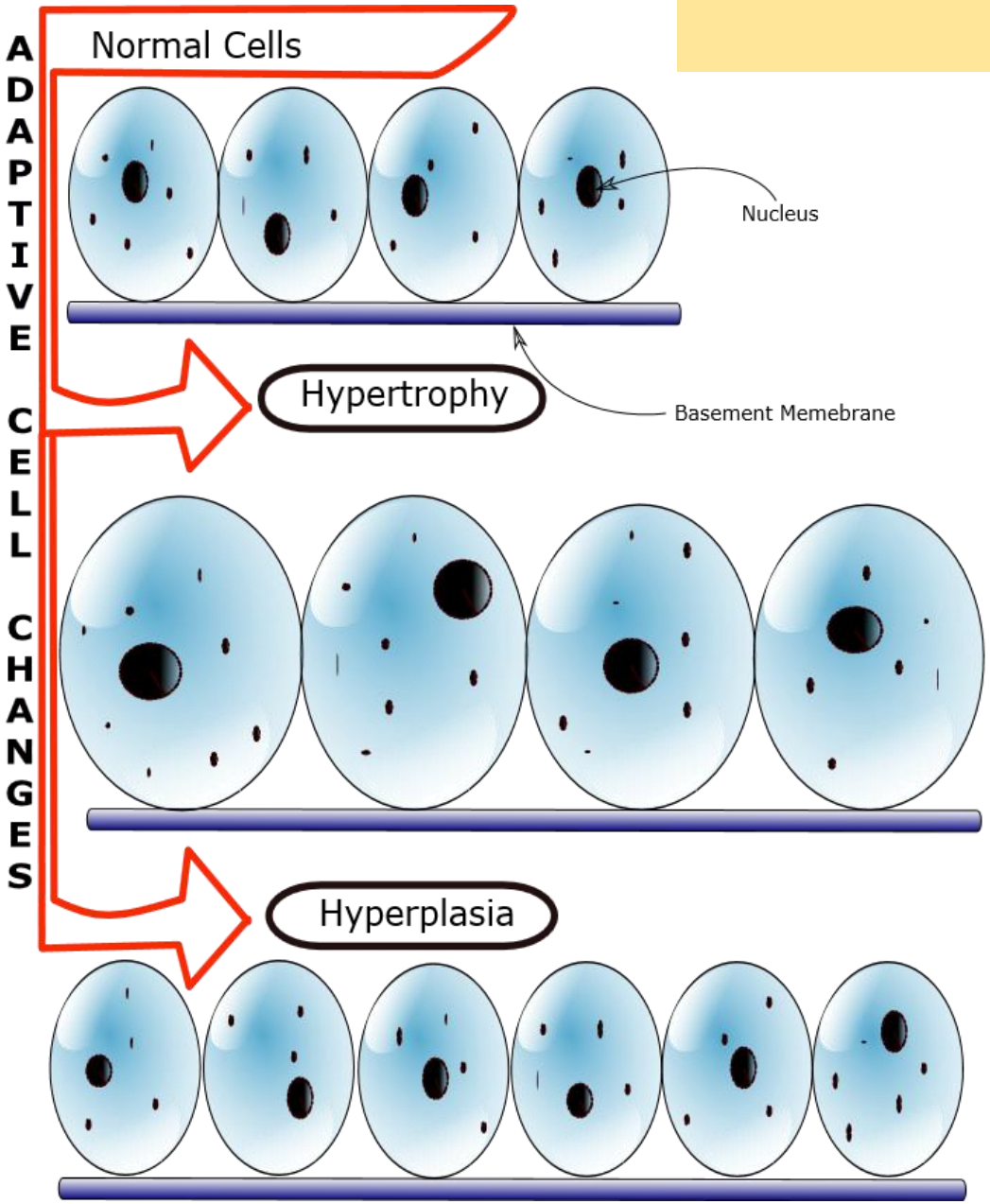
Hyperplasia /Hypertrophy

3. Permanent tissues

- Terminally differentiated and non-proliferative in postnatal life
- Repair is typically dominated by scar formation
- Neurons ,cardiac muscle cells, skeletal muscle

Hypertrophy

Hypertrophy

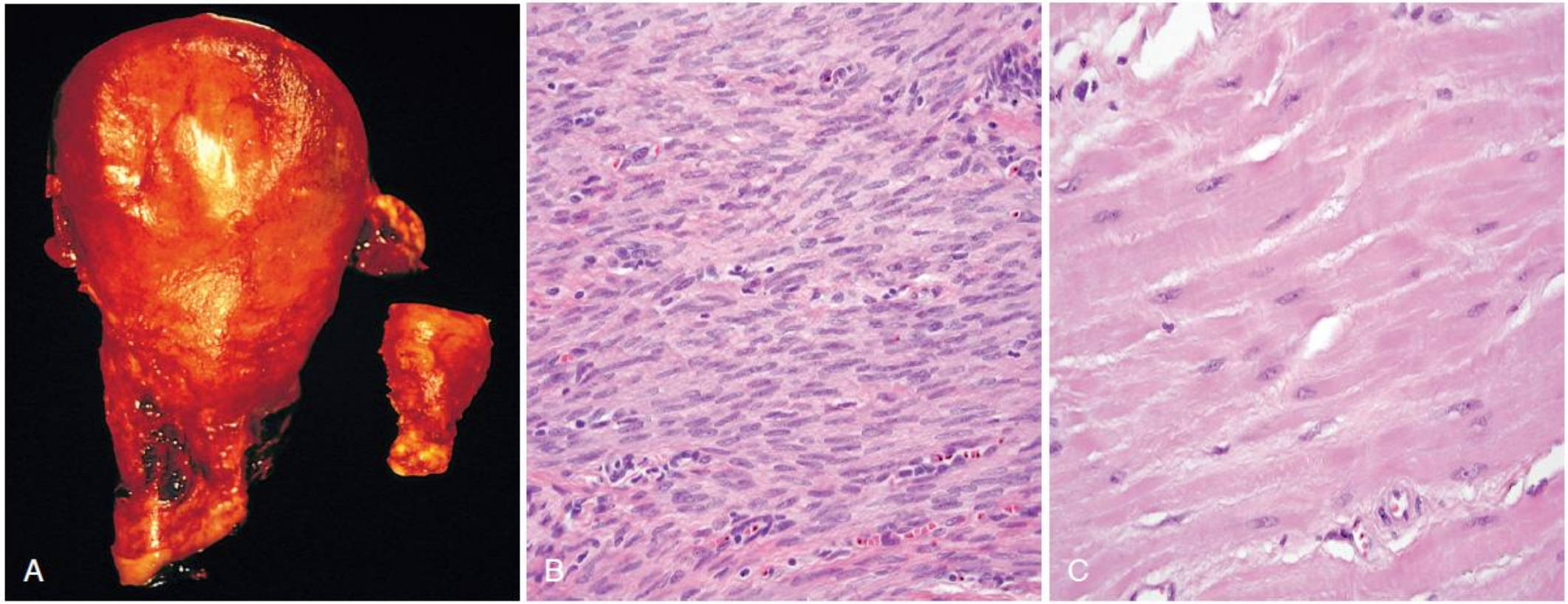


www.wikipedia.org

- Hypertrophy is an increase in the size of cells resulting in increase in the size of the organ
- Occurs in tissues incapable of cell division

Physiologic hypertrophy

- Hormone-induced enlargement an organ
  - Uterus (Estrogen)
  - Breast (Prolactin/Estrogen)
- Exercise/ weight training



Robbins and Cotran pathologic basis of disease. 10th edition (2020)

Pathologic hypertrophy

- **Predisposing factor**

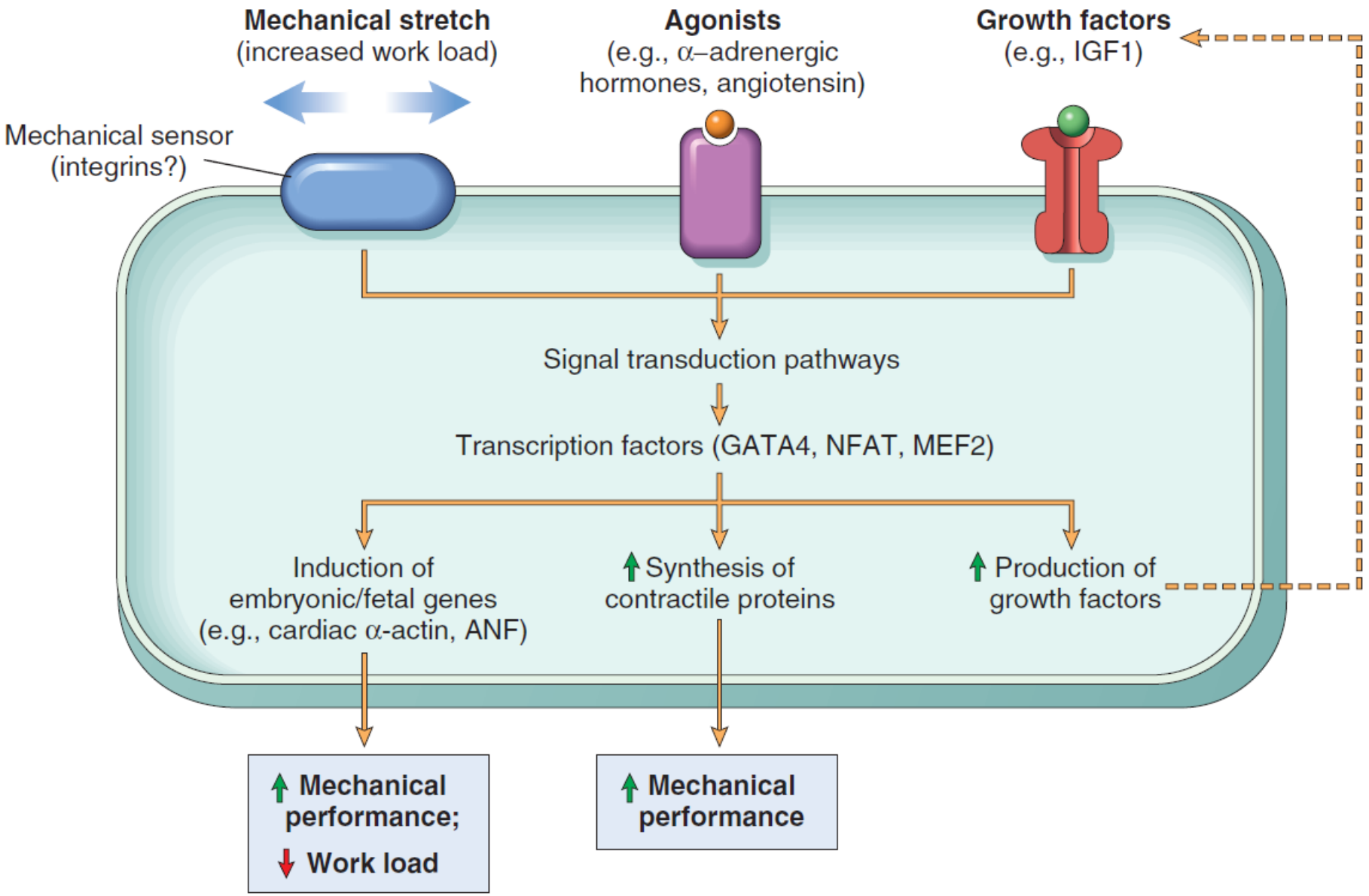
  - Hypertension

  - Congenital heart disease ex. aortic valve stenosis

- **Mechanisms of hypertrophy**

  1. Mechanism triggers

  2. Trophic triggers



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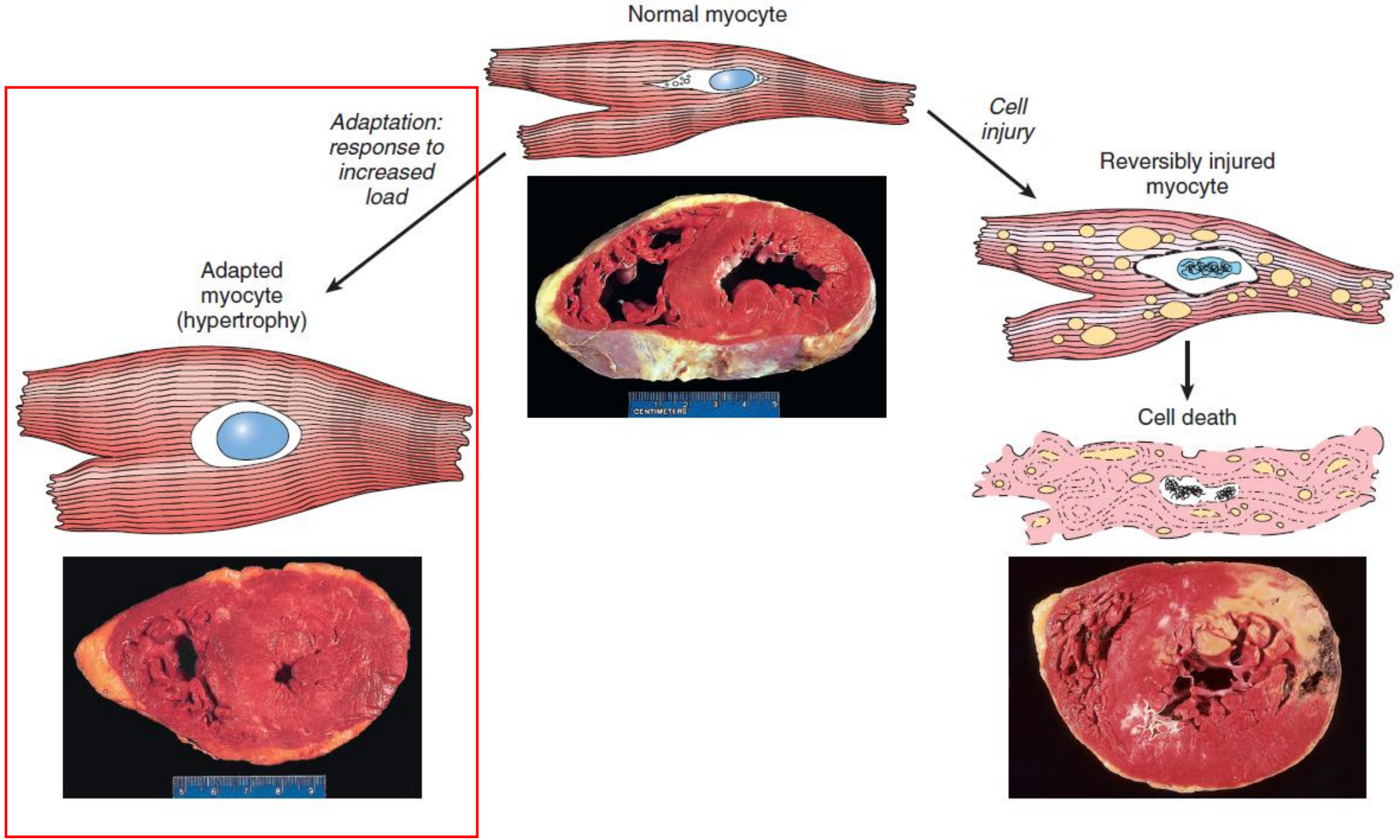

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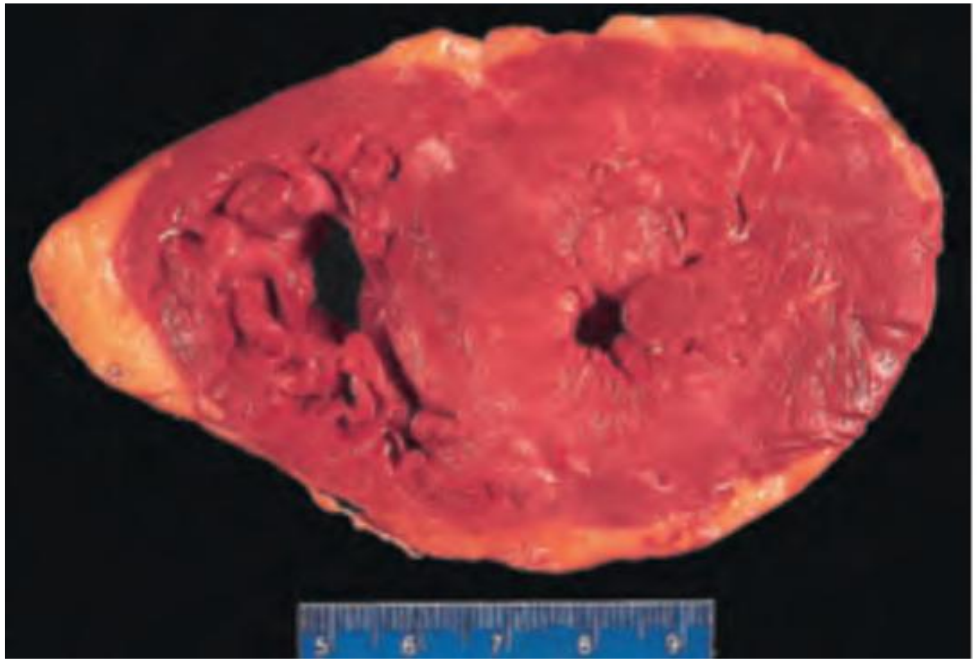
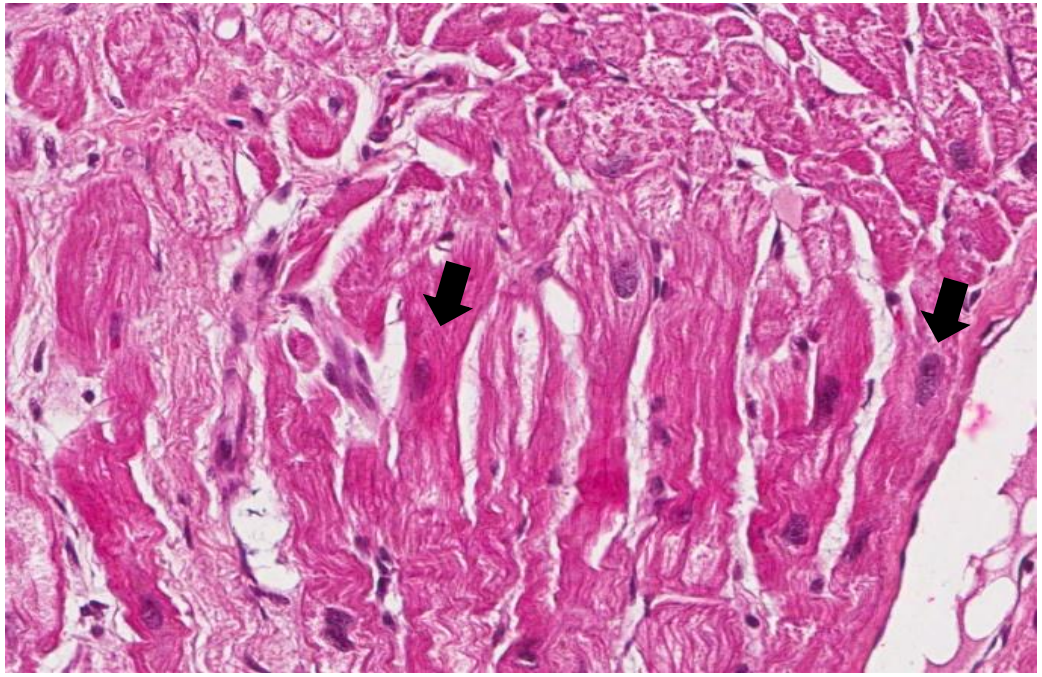
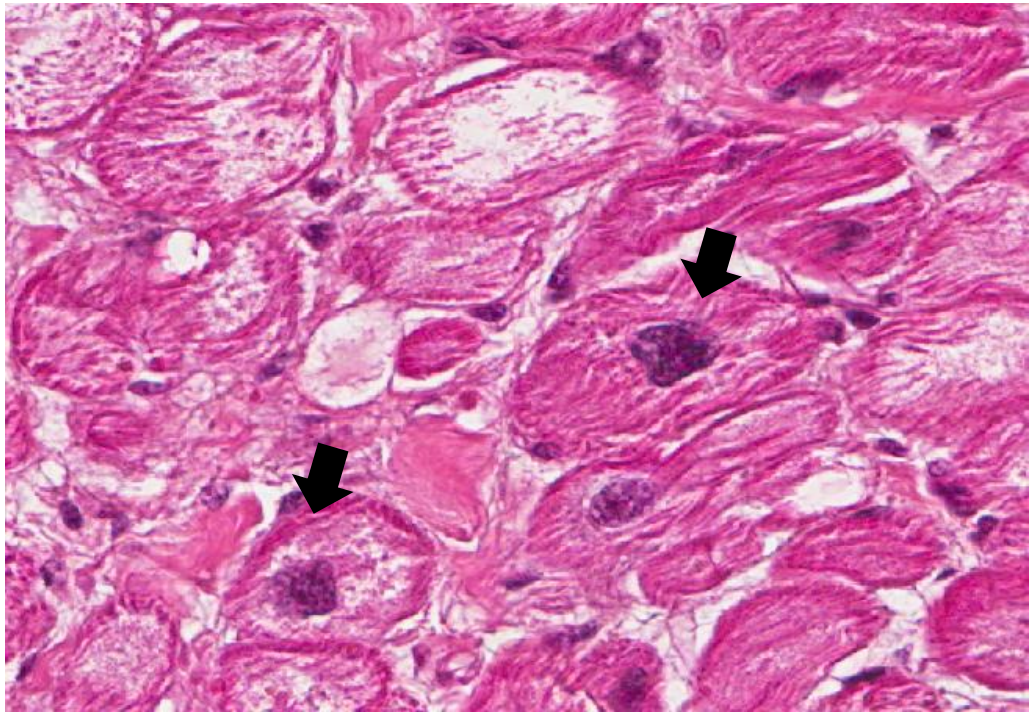
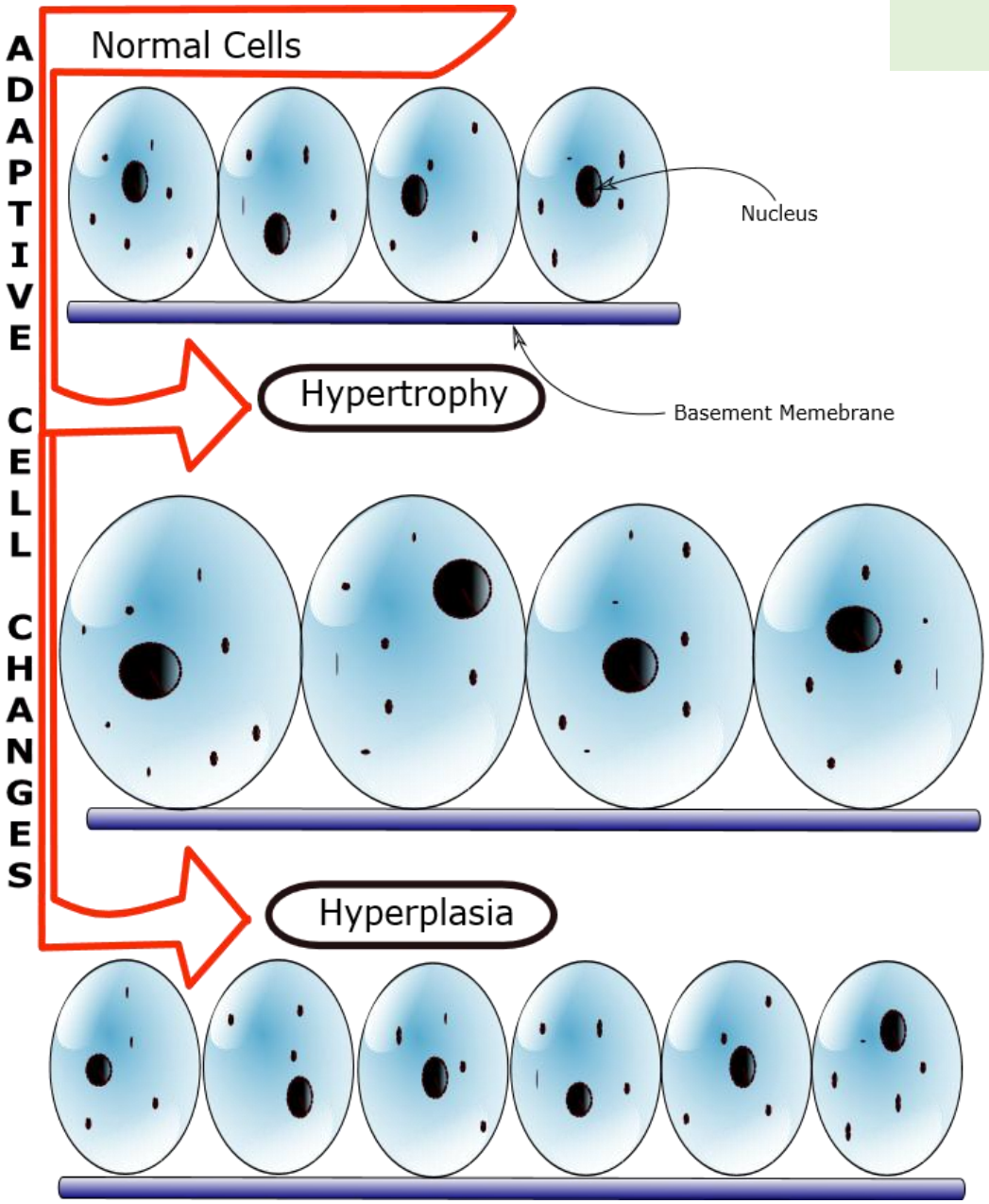


Robbins and Cotran pathologic basis of disease. 10th edition, 2020





Hyperplasia



www.wikipedia.org

- Hyperplasia is characterized by an increase in cell number
- Occurs in tissues whose cells are able to divide or contain abundant tissue stem cells and stable cell

Mechanisms of hyperplasia

Hyperplasia is the result of growth factor-driven proliferation of mature cells

Intracellular signaling pathway

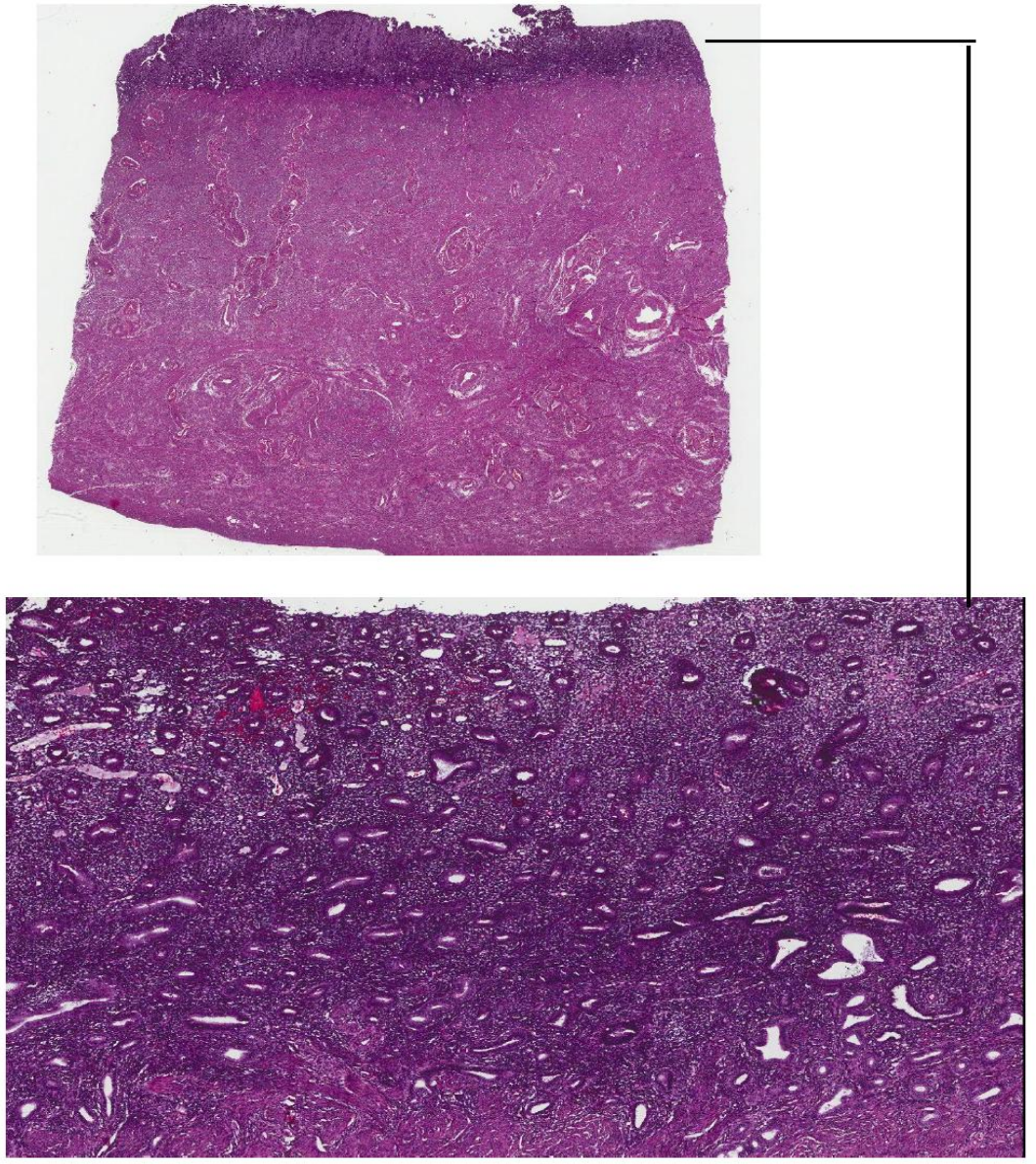
Transcription factor

Cell proliferation

Increased output of new cells from tissue stem cells

Physiologic hyperplasia

- **Hormonal hyperplasia**
- Glandular epithelium of the female breast at puberty and during pregnancy (Prolactin/Estrogen)
- Uterus (Estrogen)



Physiologic hyperplasia

- **Compensatory hyperplasia**

  - Partial hepatectomy

  - Transplantation

- **Adaptive hyperplasia**

  -Marrow is remarkable in its capacity to undergo rapid hyperplasia

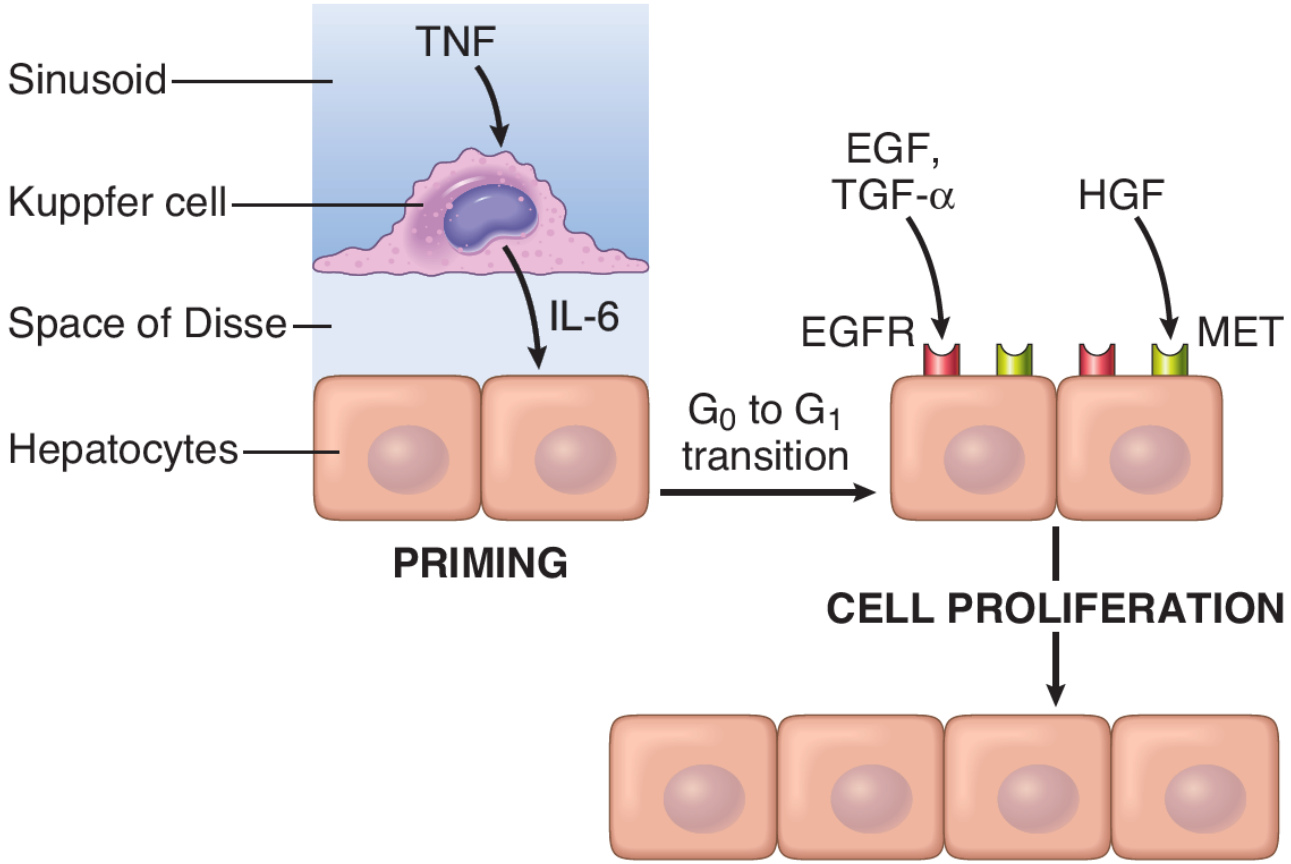
  - Secondary polycytemia

  -Lymphoid hyperplasia

Compensatory hyperplasia

Liver Regeneration

- Proliferation of remaining hepatocytes
- Repopulation from progenitor cells



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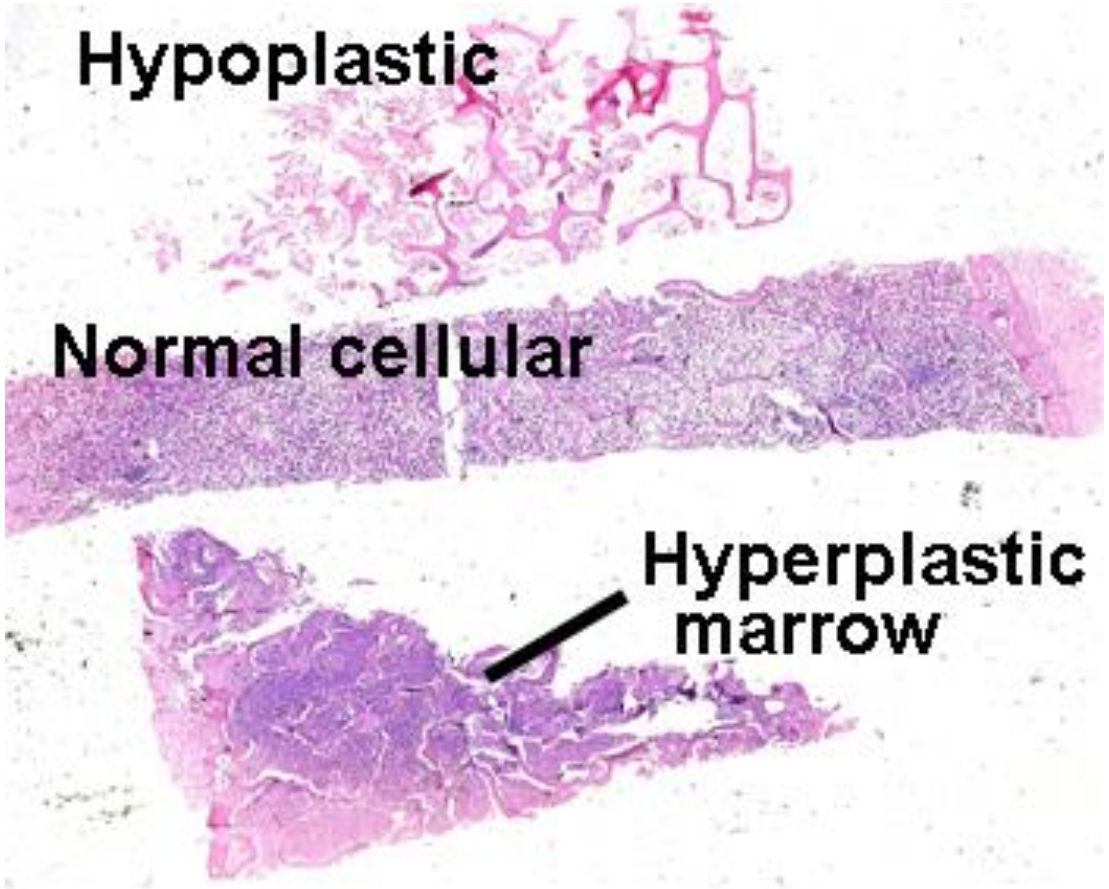
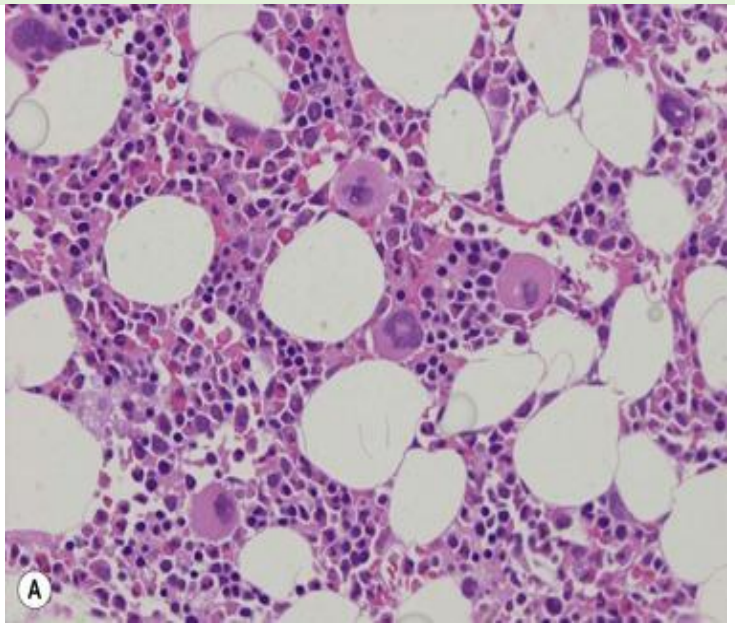
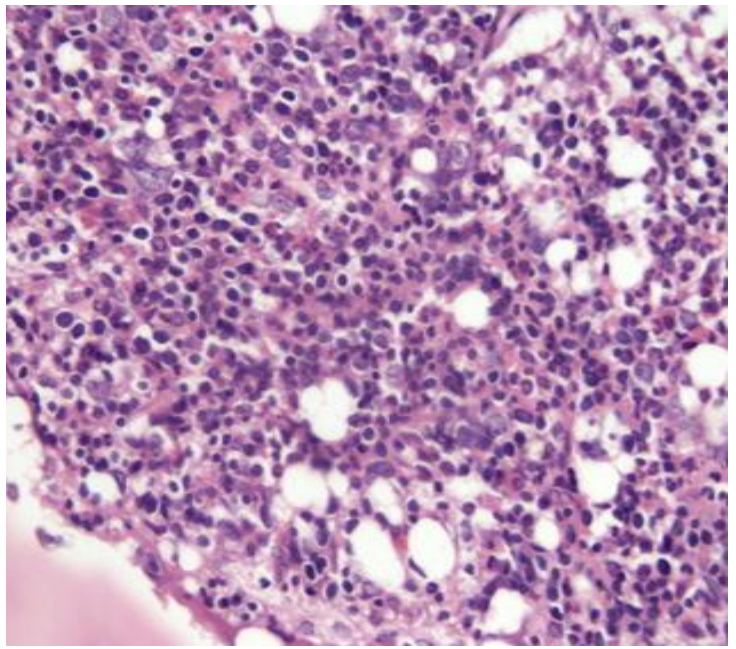
Adaptive hyperplasia





https://clinicalgate.com/normal-bone-marrow-histology/



El-Sherbiny S, et al.BAOJi Cancer Res Ther (2018)

Pathologic hyperplasia

- **Inappropriate actions of hormones or growth factors acting on target cells**

  >Endometrial hyperplasia

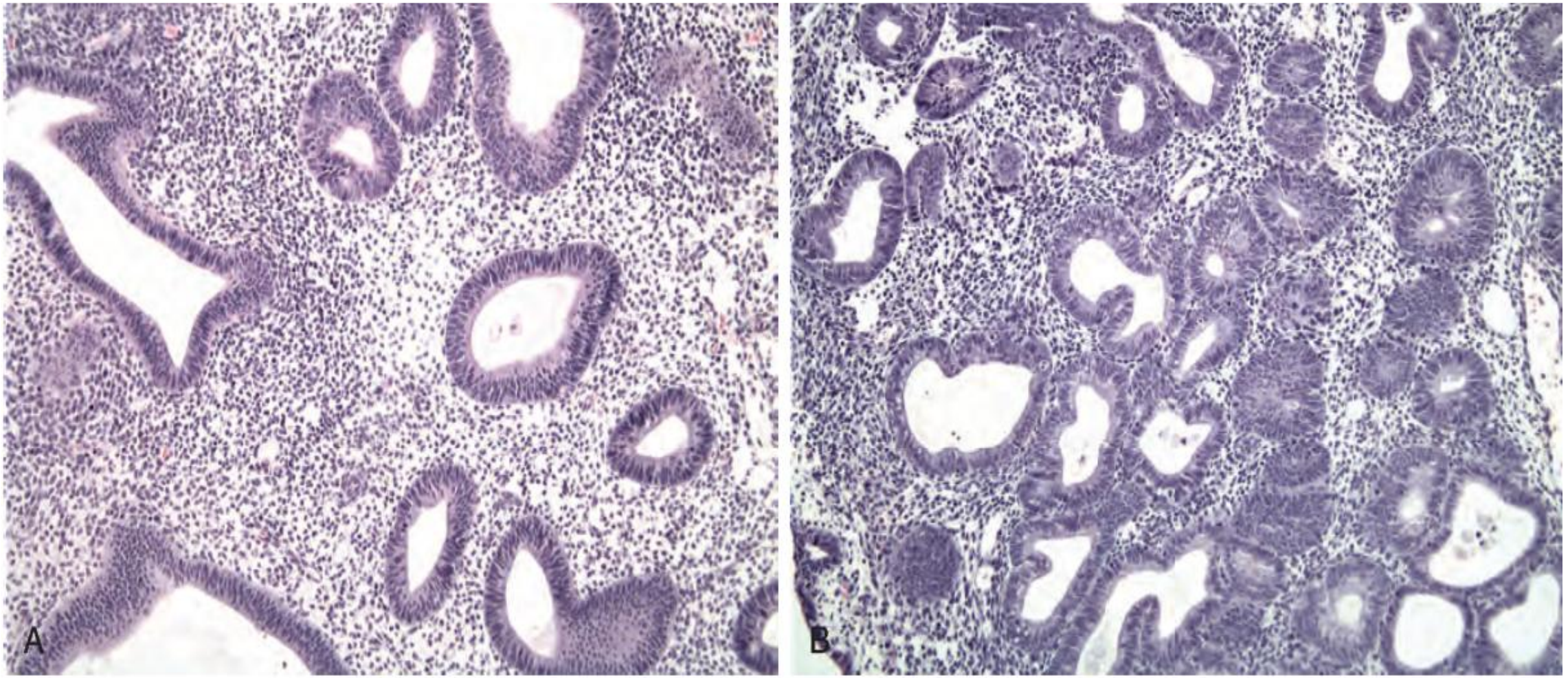
  - Imbalance of estrogen & progesterone

  - Pituitary gland or ovarian abnormalities

  >Benign prostatic hyperplasia

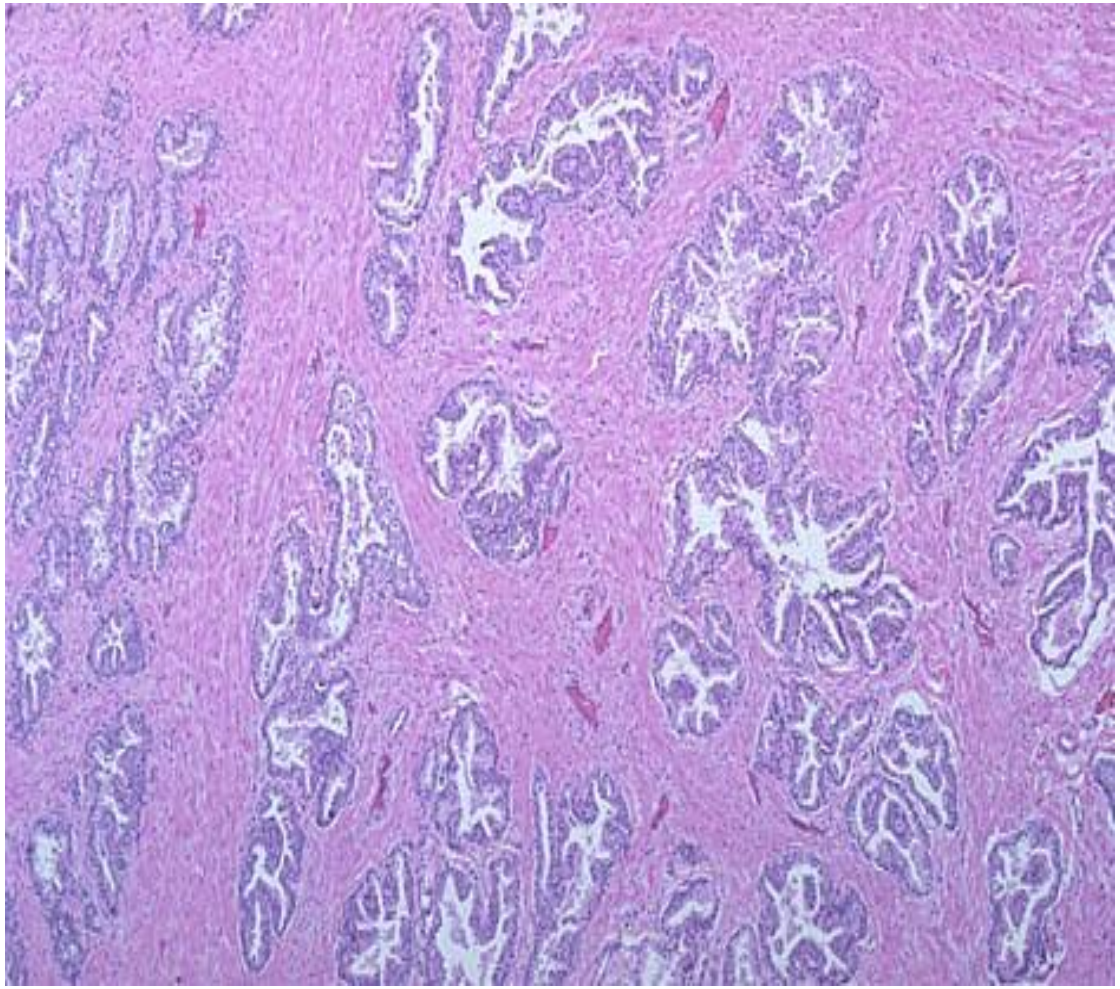
  - Excessive androgens hormone

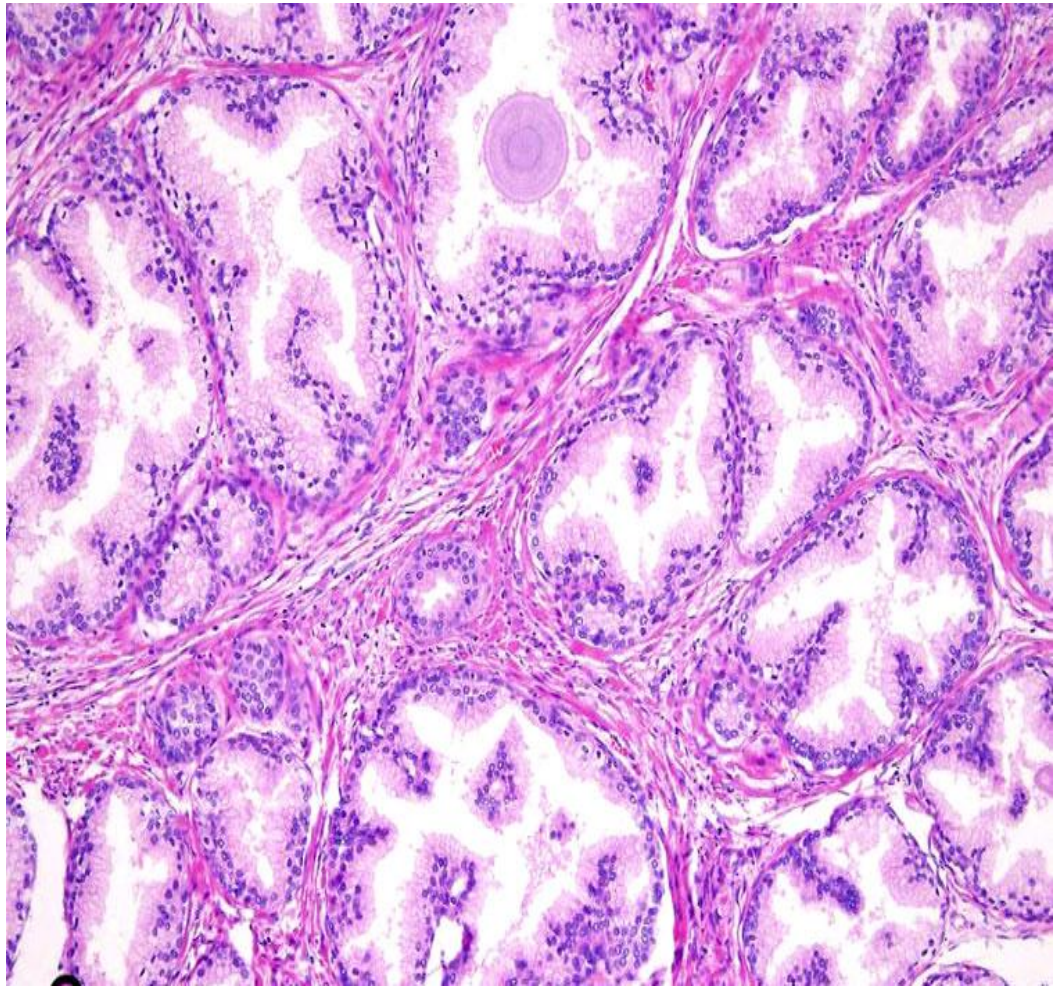
Endometrial hyperplasia



Robbin's pathology: clinicopathologic foundations of medicine. 7th edition, 2014

Benign prostatic hyperplasia



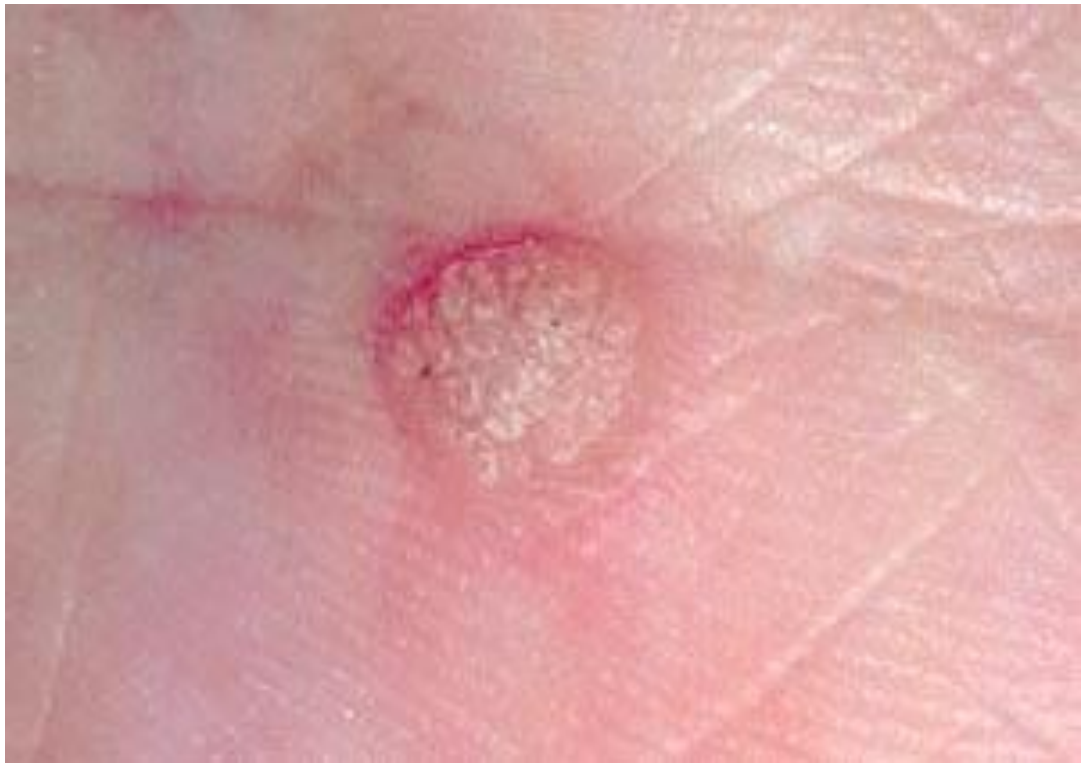


https://webpath.med.utah.edu/HISTHTML/NORMAL/NORM078.html

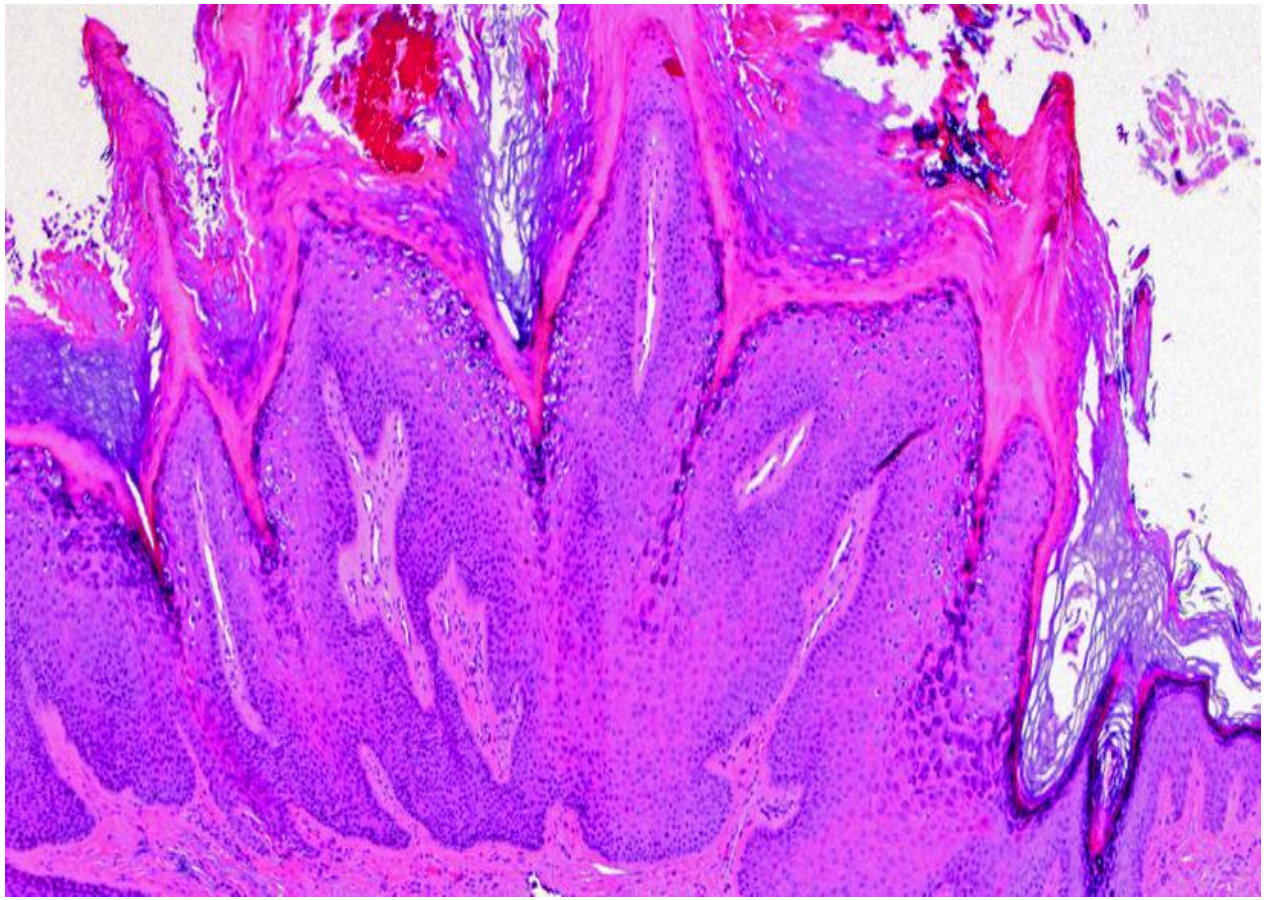
https://www.auanet.org/education/auauniversity

Pathologic hyperplasia

- **Viral infections**
  - Such as papillomaviruses
  - Viral wart" or "Verruca vulgaris"

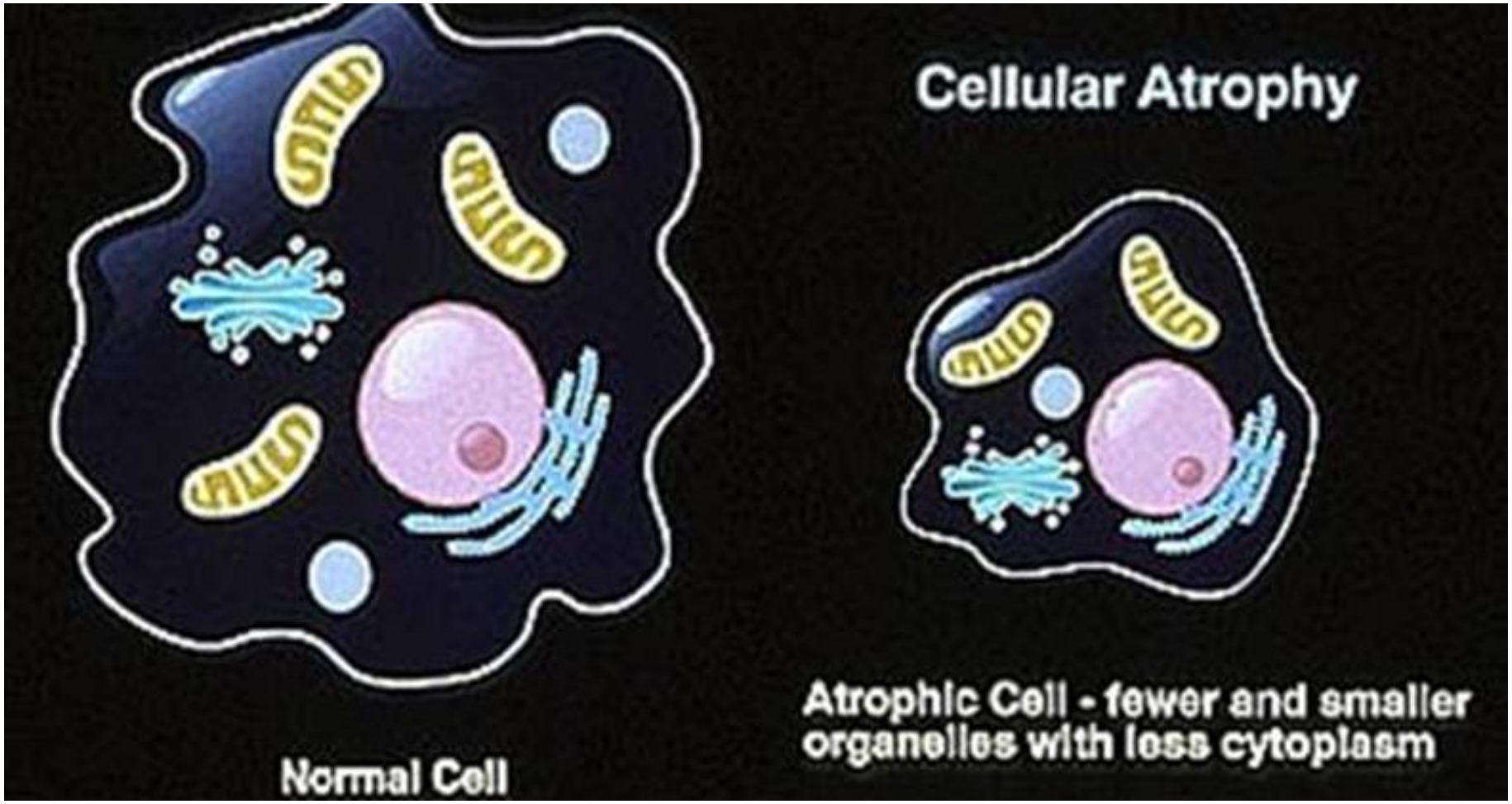


https://www.dentistry.uiowa.edu/oprm-verruca-vulgaris



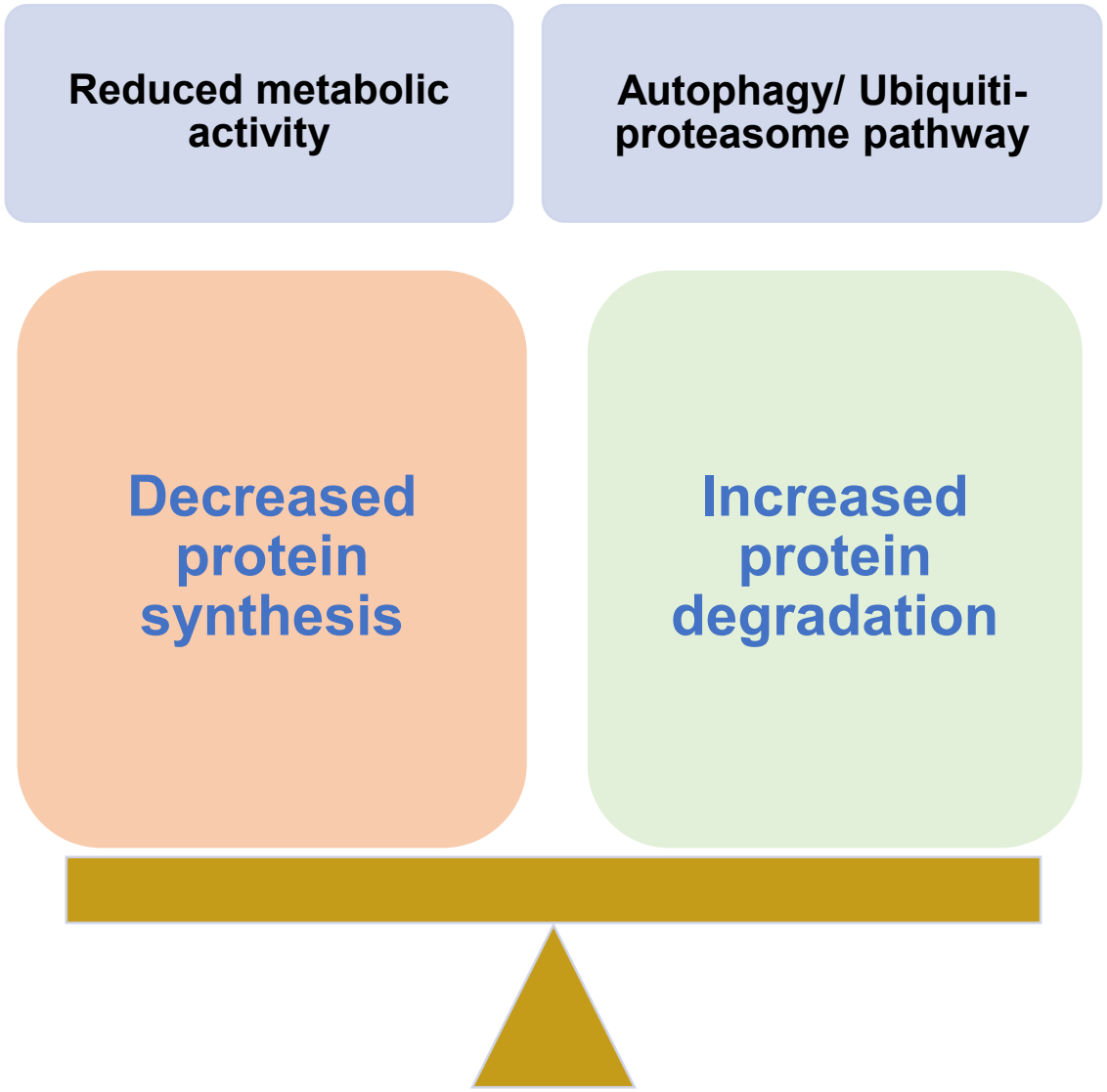
Atlas of Essential Dermatopathology (2012)

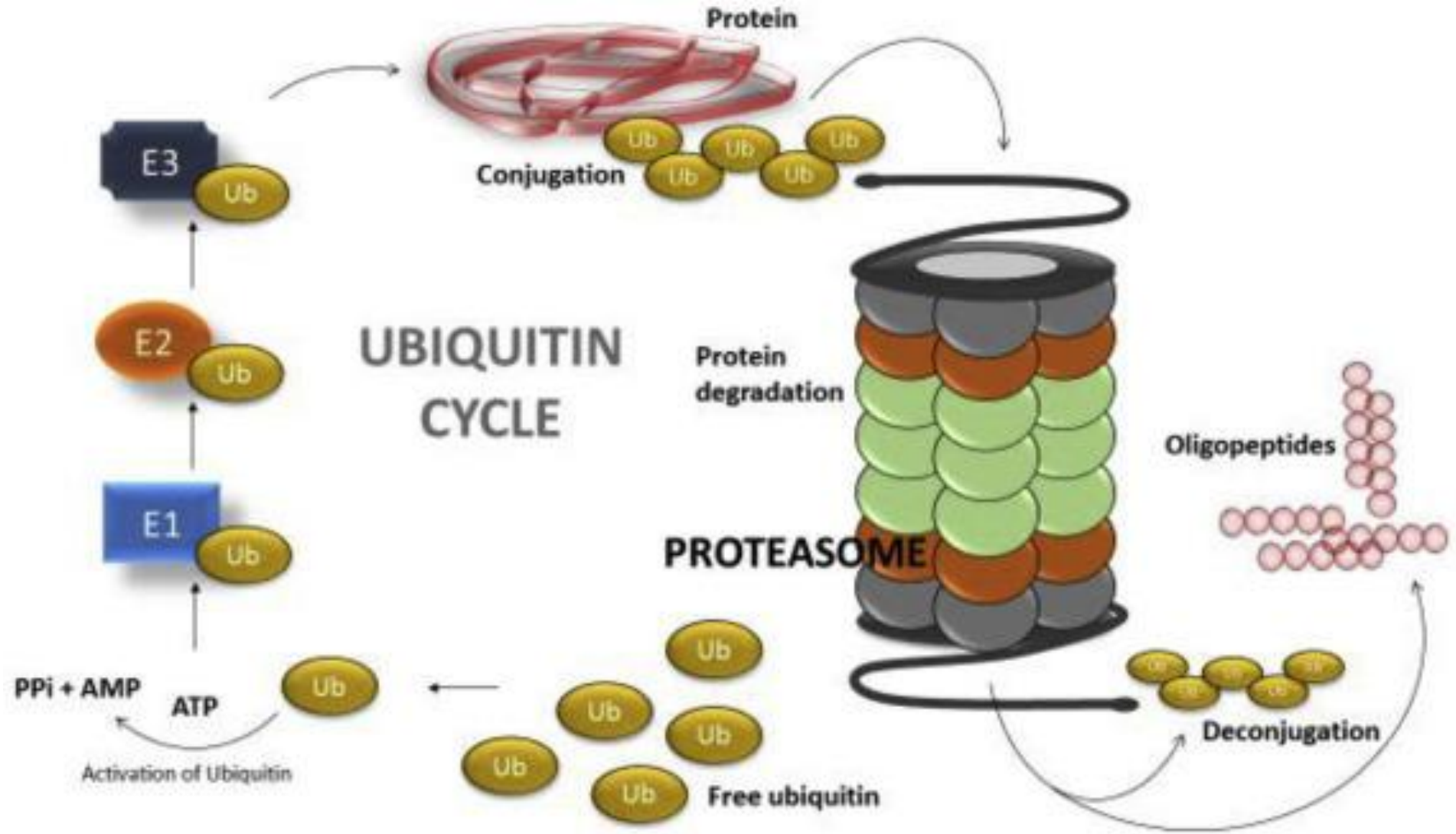
Atrophy



- Shrinkage in the size of the cell by the loss of cell substance
- The mechanisms consist of decreased protein synthesis and increased protein degradation in cells

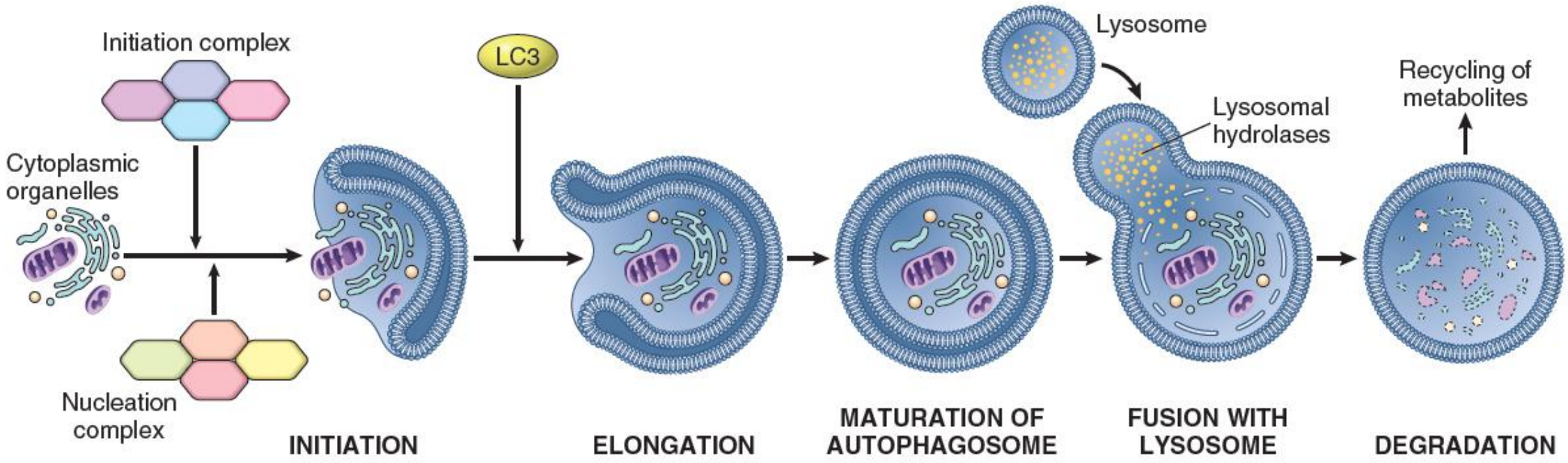
Mechanisms of atrophy





Nabavi et al (2018)

Autophagy



Robbins and Cotran pathologic basis of disease. 10th edition (2020)

Atrophy

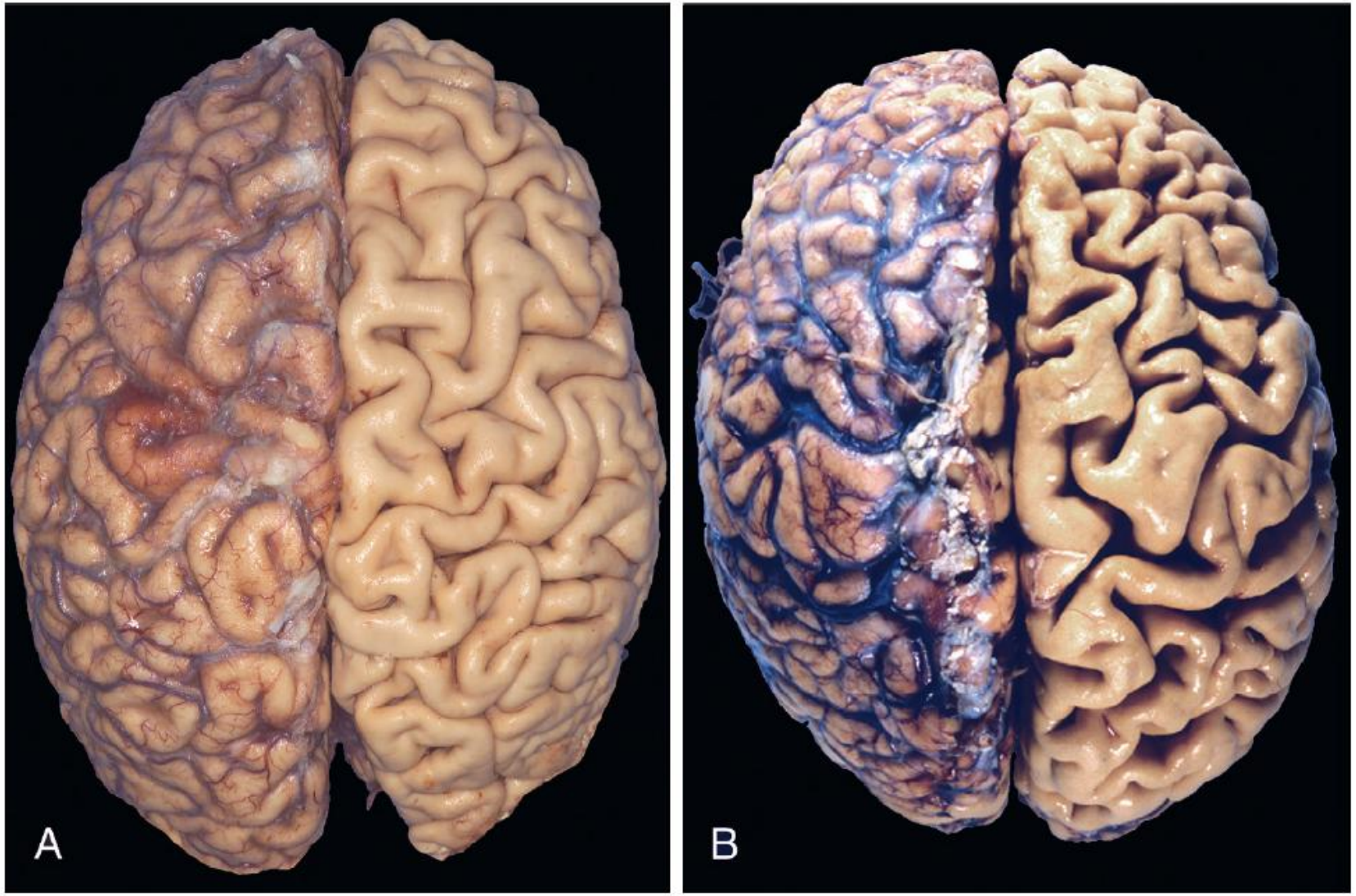
Physiologic atrophy

- Loss of hormone stimulation in menopause
- Aging atrophy
- Embryogenesis

Pathologic atrophy

- Atrophy of disuse
- Diminished blood supply
- Denervation atrophy
- Inadequate nutrition
- Pressure atrophy
- Loss of endocrine stimulation

Brain Atrophy



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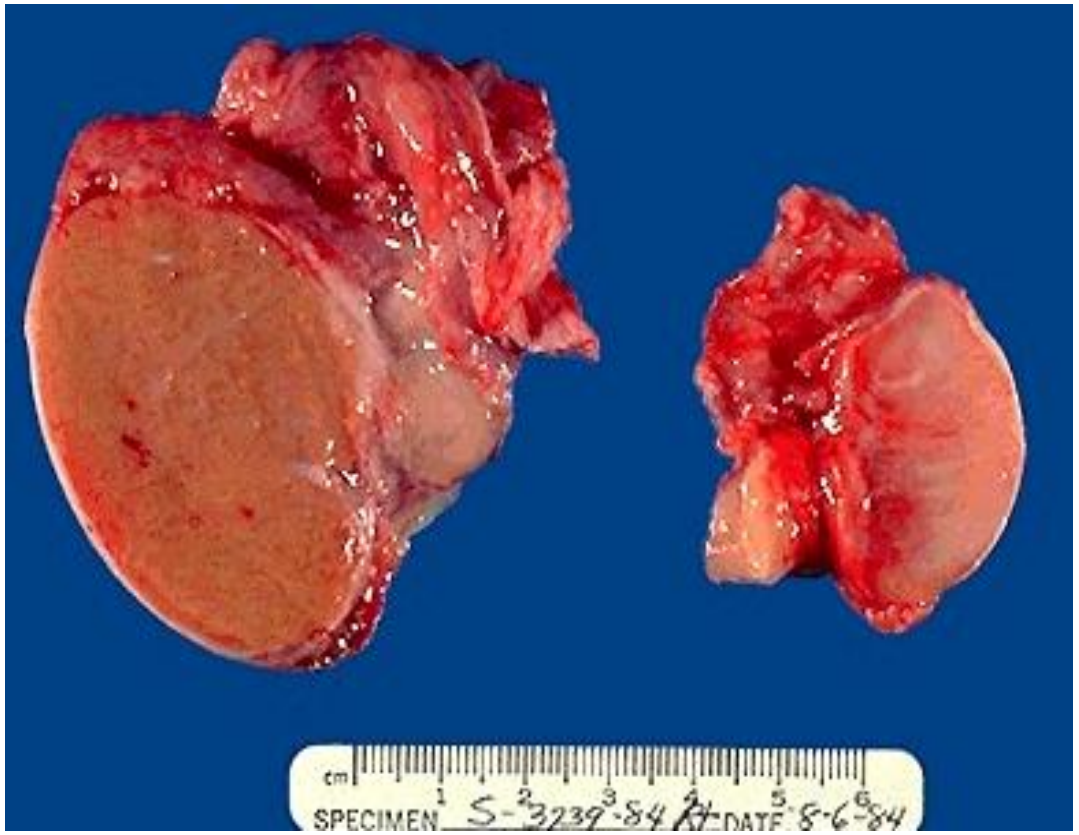
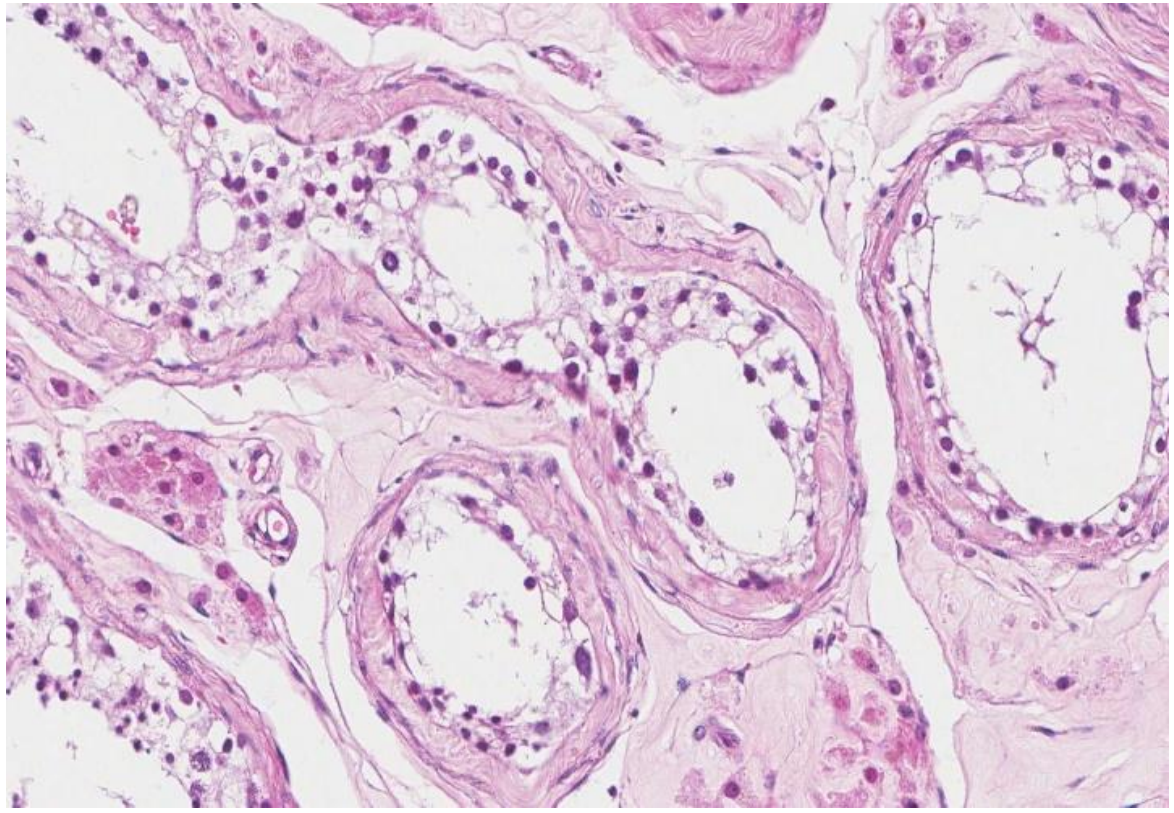


https://www.pathologyoutlines.com/topic/testisatrophy.html/



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Metaplasia

- Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type
- Able to withstand the adverse environment
- Altered differentiation pathway of tissue stem cells
- Reduced functions or increased propensity for malignant transformation
- 1) Epithelial metaplasia 2) Connective tissue metaplasia
- The most common epithelial metaplasia is *columnar to squamous*

Cause of metaplasia

- Chronic inflammation

  - HPV infection

- Chronic irritation

  - Habitual cigarette smoker

- Nutrition depletion

  - Vitamin A deficiency

- Trauma

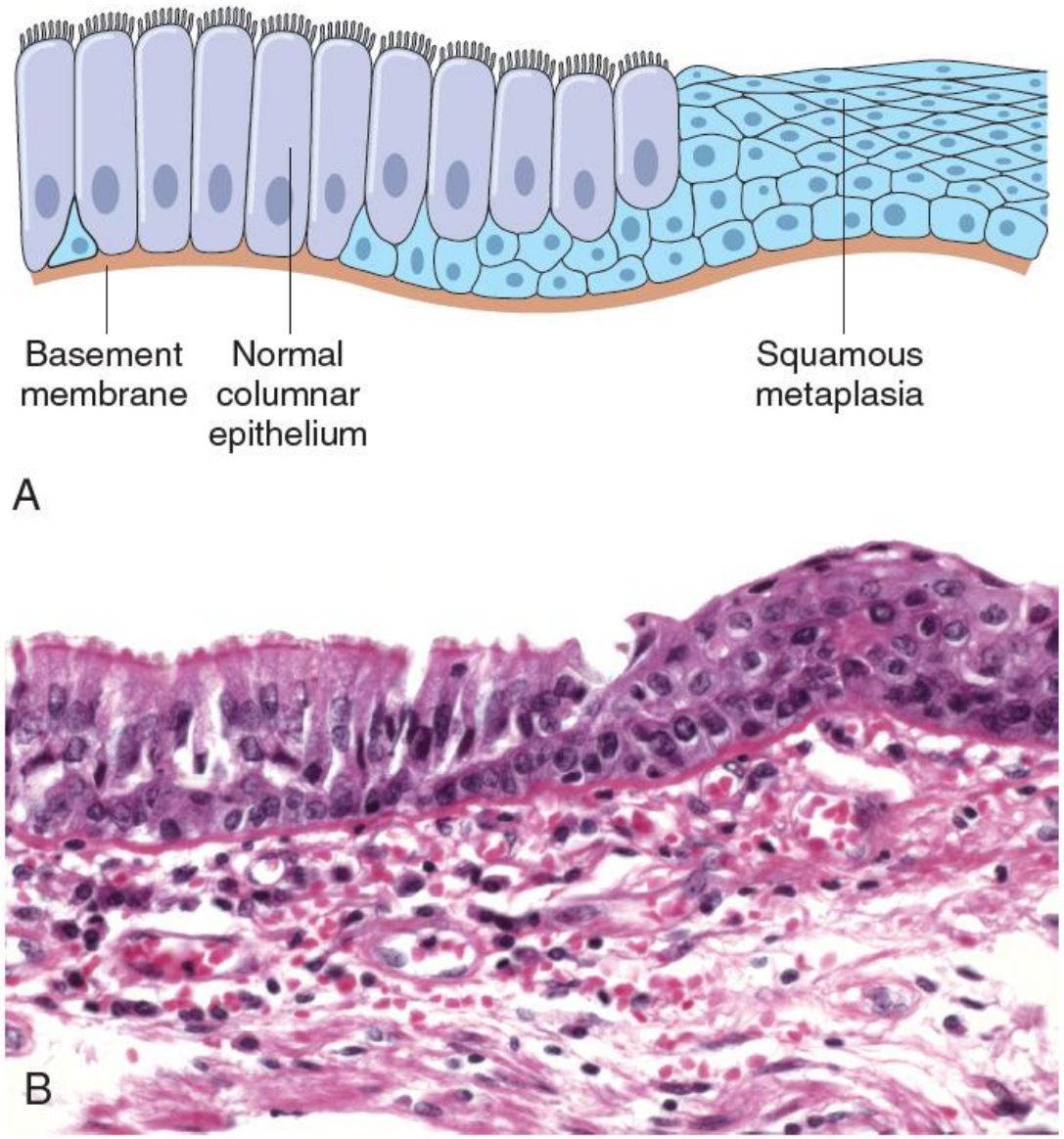
Mechanism of metaplasia

Growth factor, cytokines, extracellular matrix components

Stem cells /Undifferentiated mesenchymal cells

Phenotype alteration

Squamous metaplasia of bronchus



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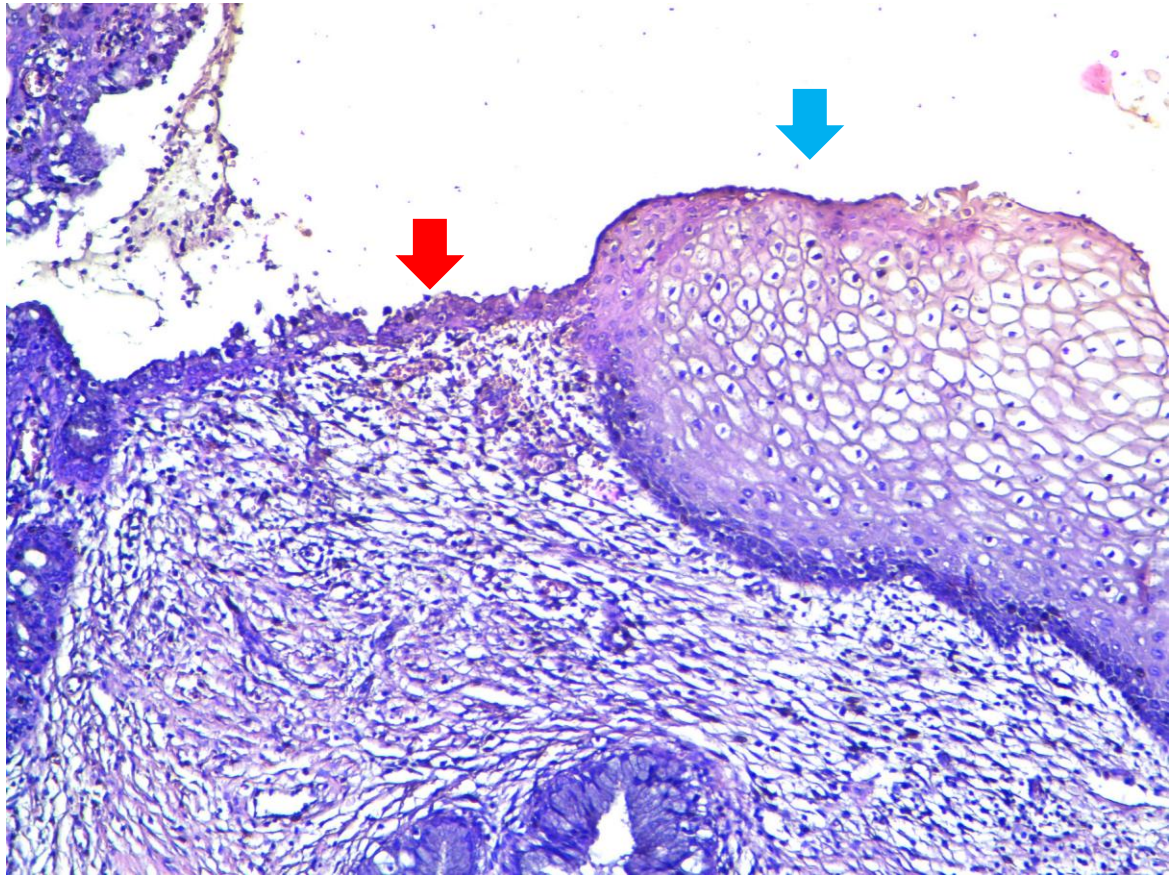
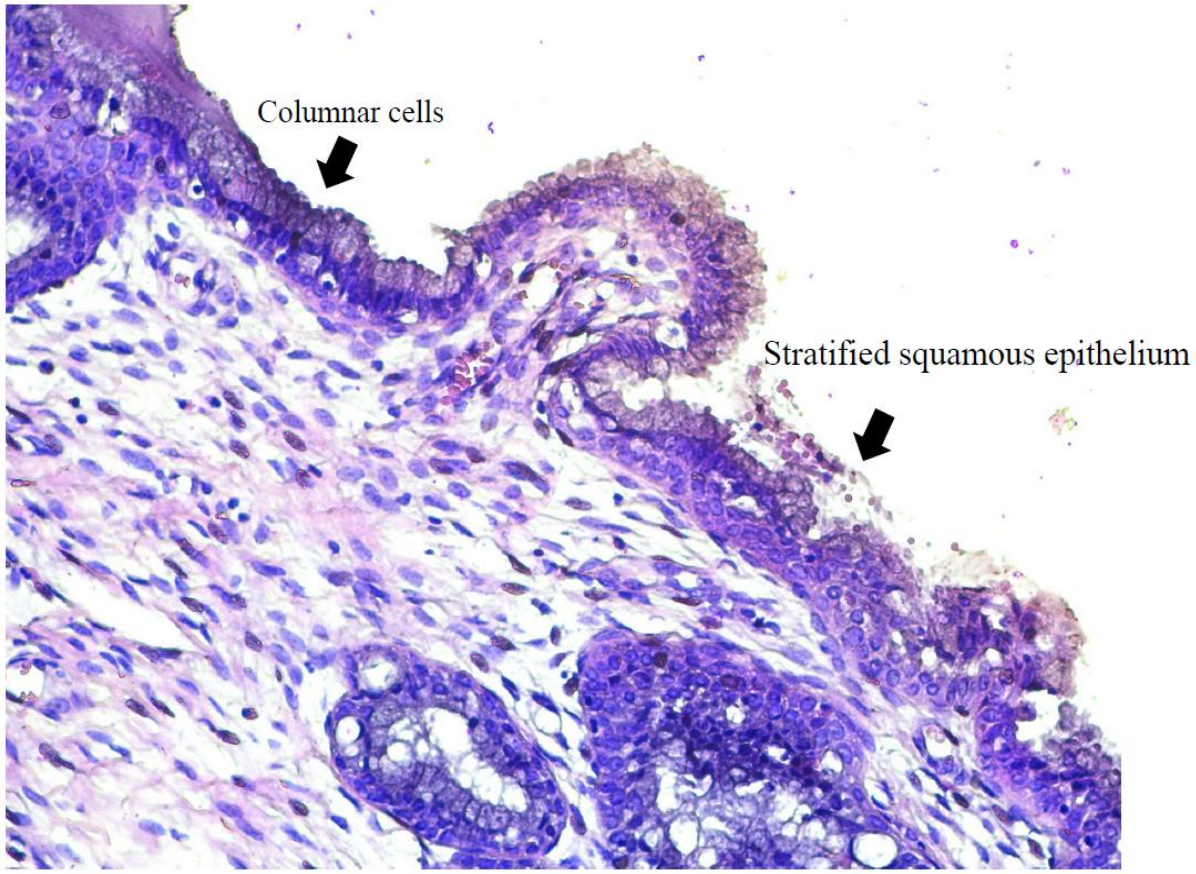
Squamous metaplasia of endocervix





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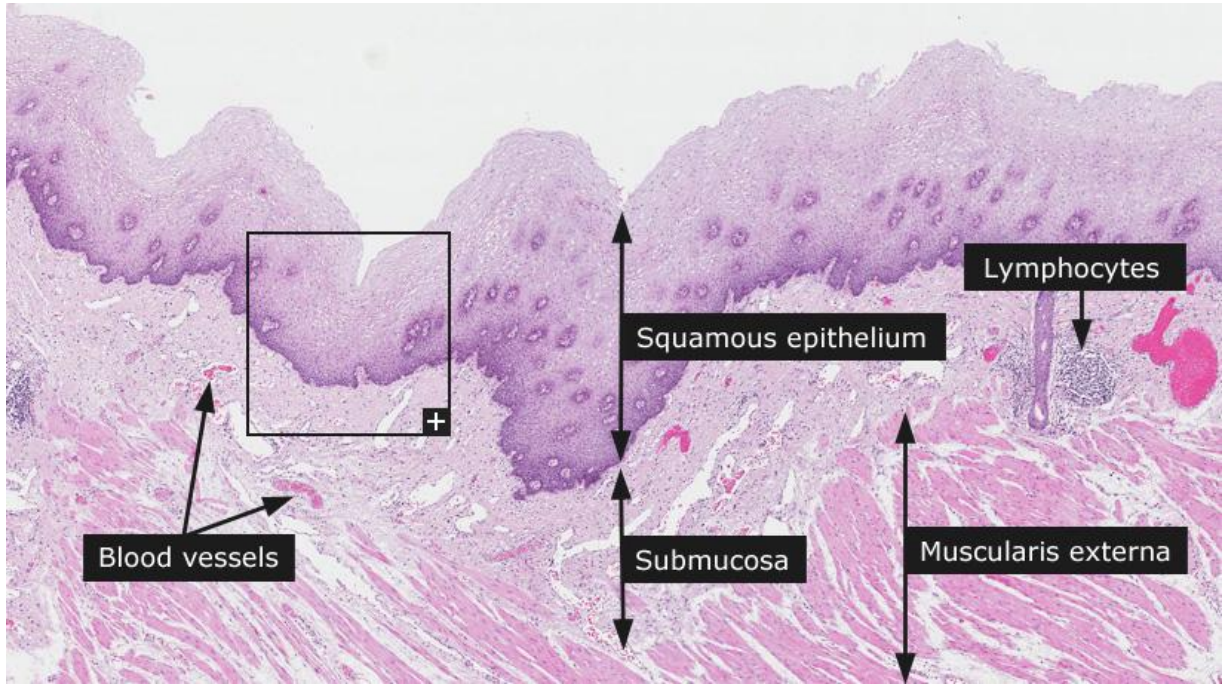
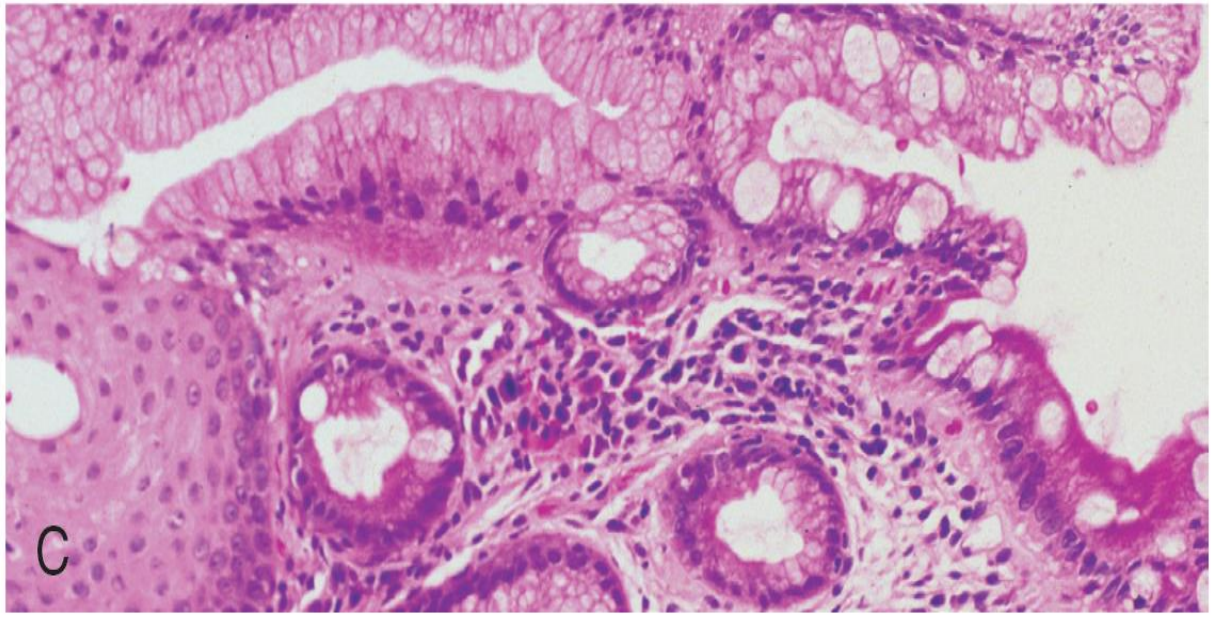
Columnar metaplasia of esophagus (Barrett esophagus)



https://www.proteinatlas.org/learn/dictionay/rnormal/esophagus



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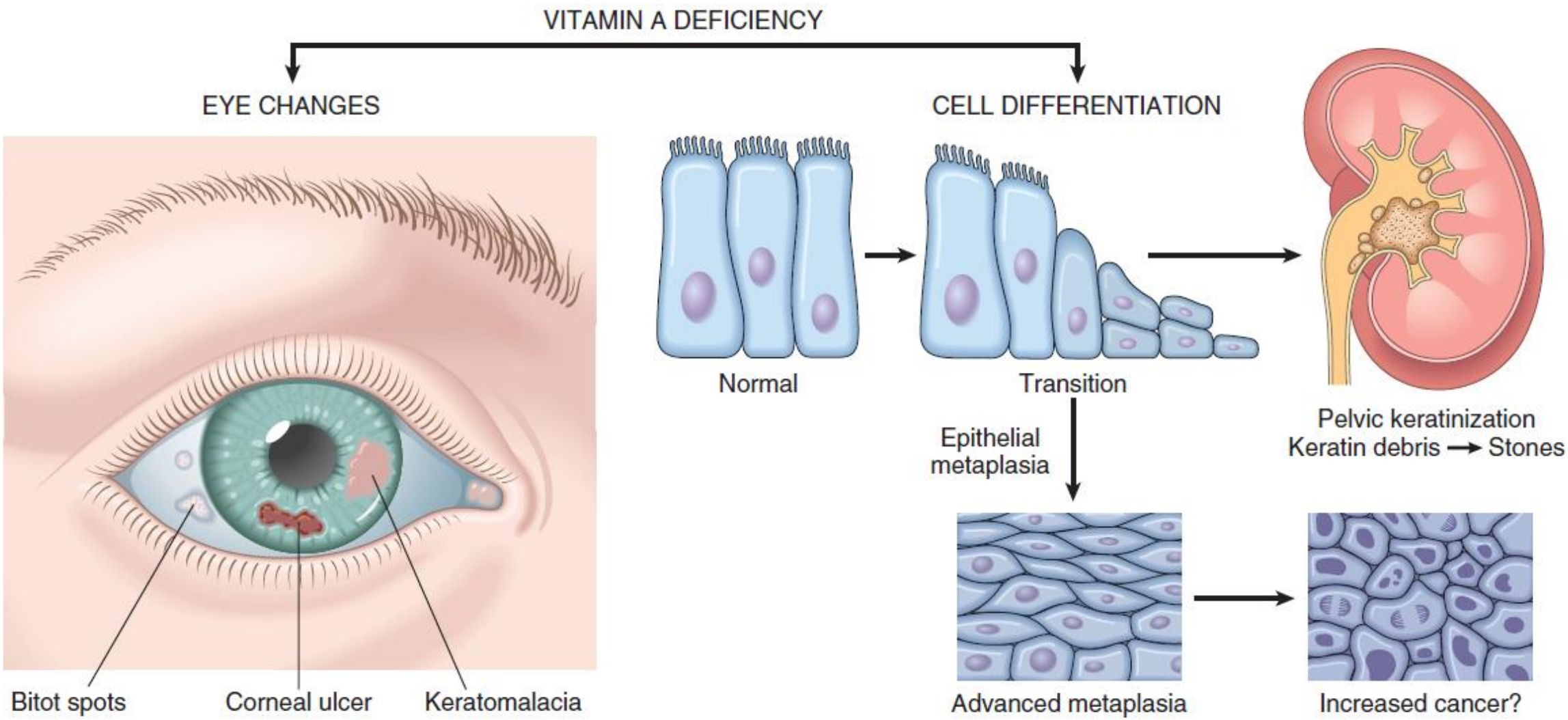
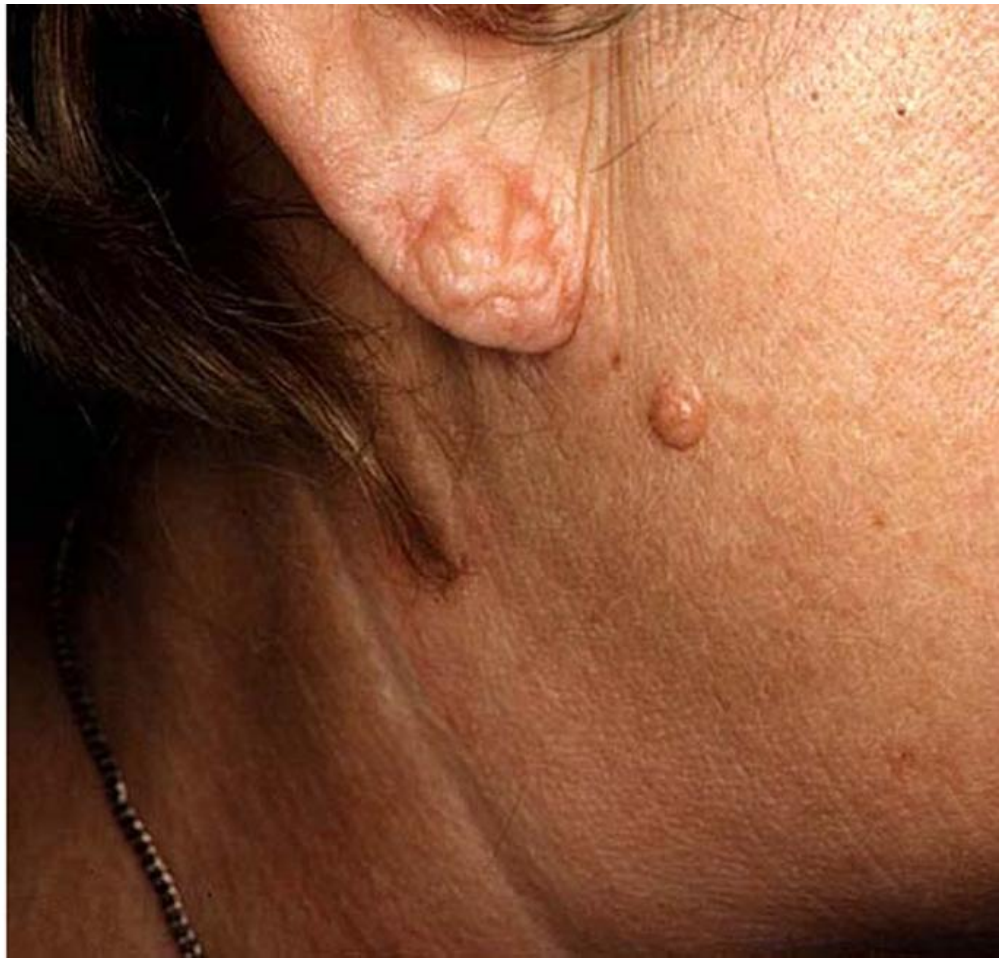
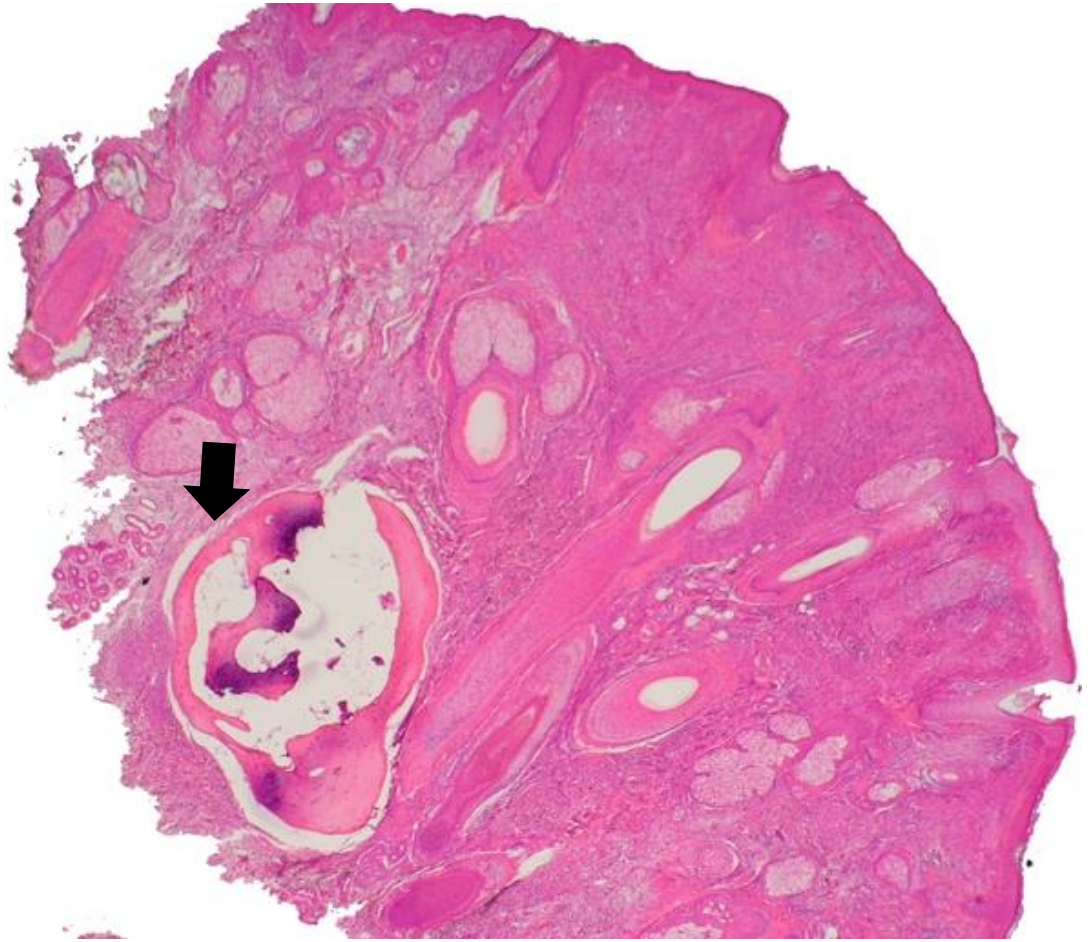


Robbins and Cotran pathologic basis of disease. 10th edition, 2020

Connective tissue metaplasia

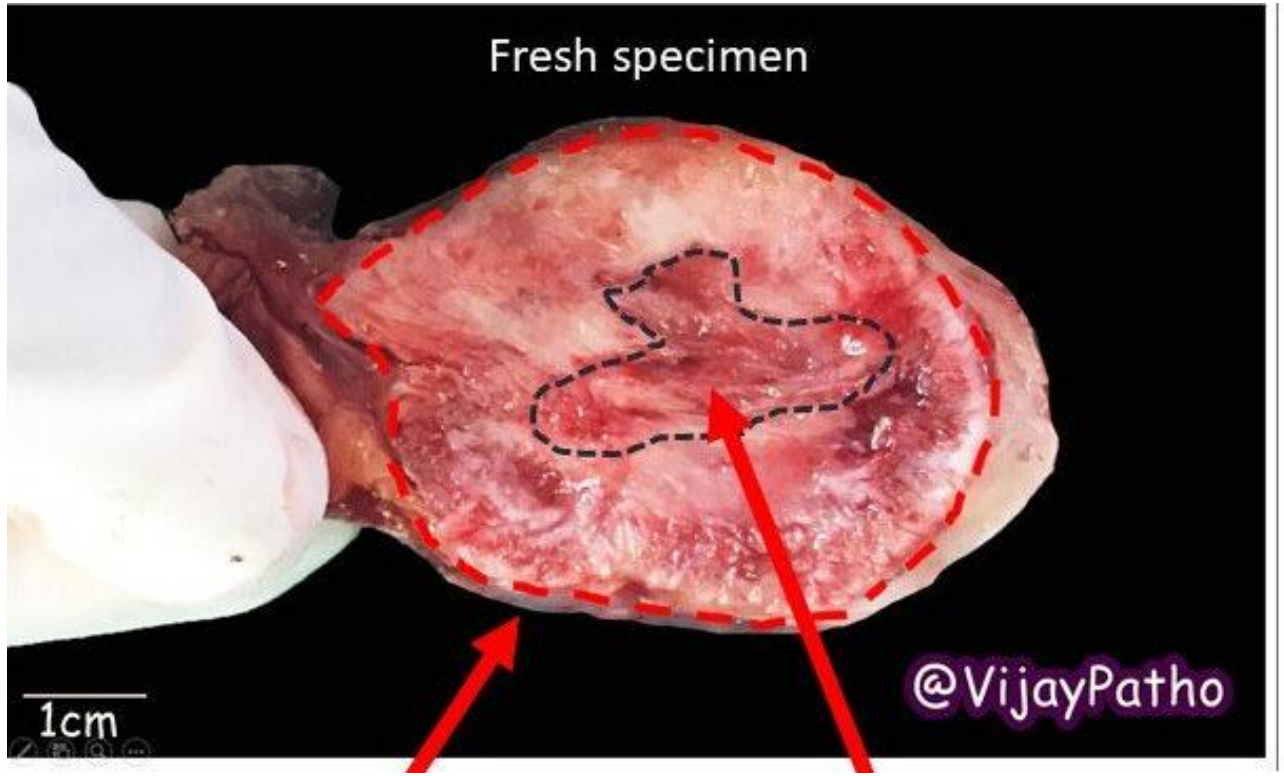


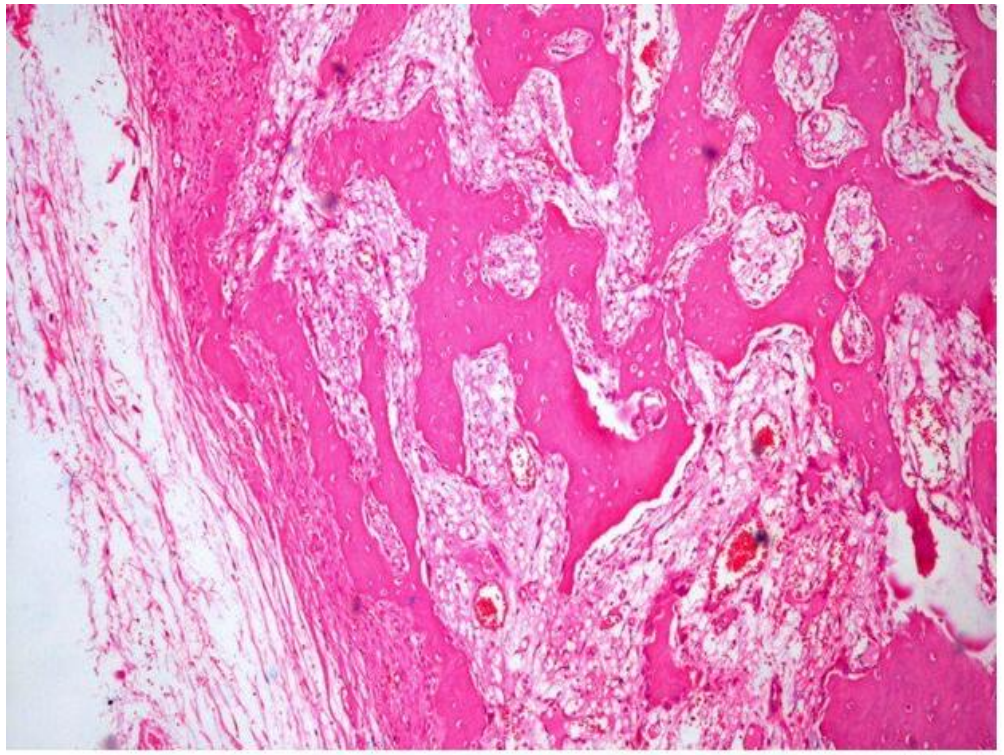
Bony (Osseous) metaplasia at skin



Department of Histopathology, Darent Valley Hospital, Dartford, UK

Myositis ossificans





Bone formation in muscle

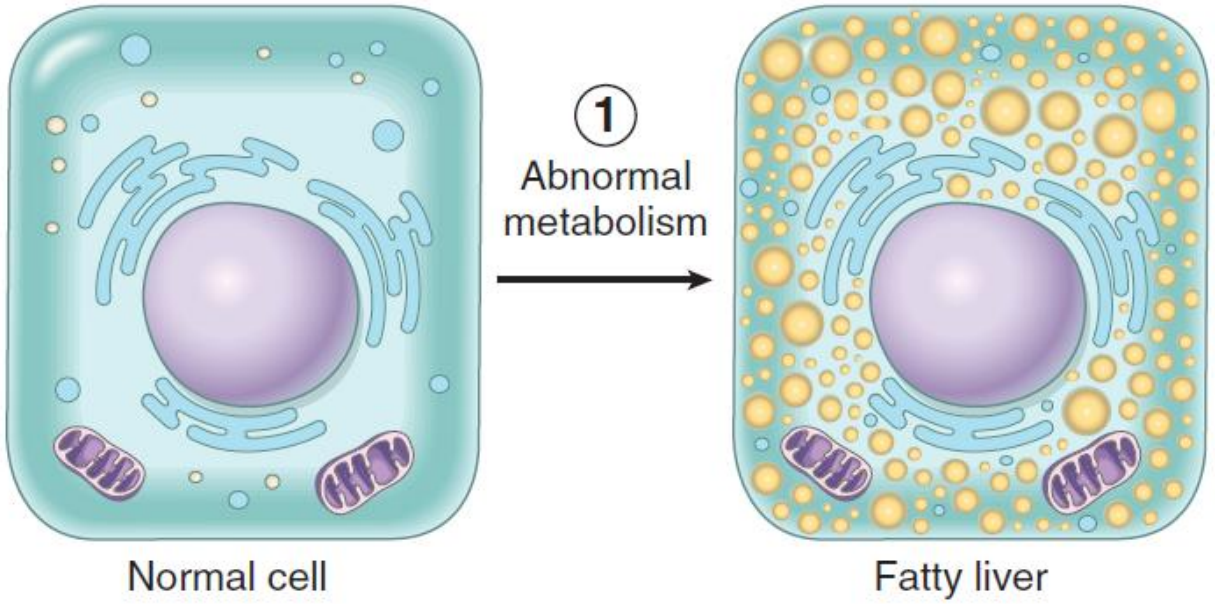
Intracellular accumulations

Intracellular Accumulations

➢ Some circumstances cells may accumulate abnormal amounts of various substances → harmless or associated with varying degrees of injury

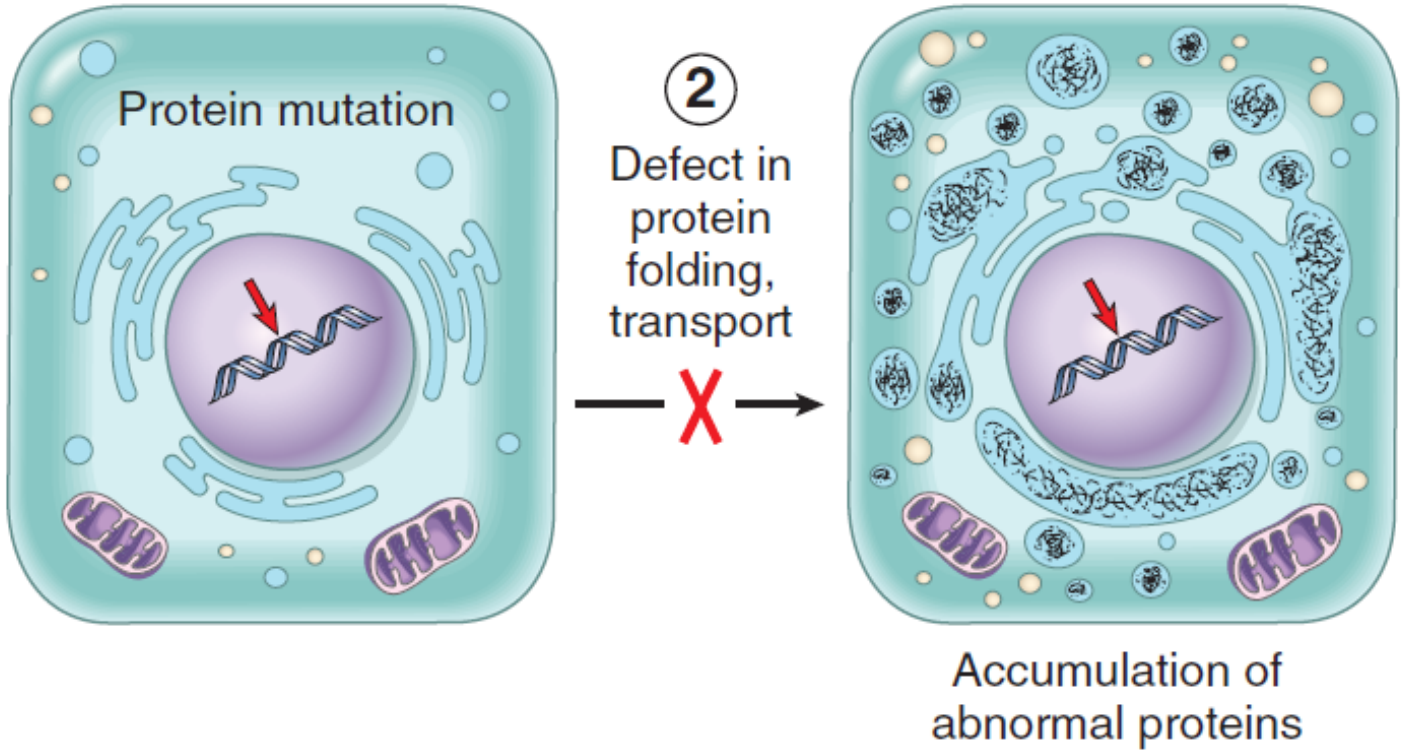
Mechanisms of intracellular accumulation:

1. Abnormal metabolism, as in fatty change in the liver



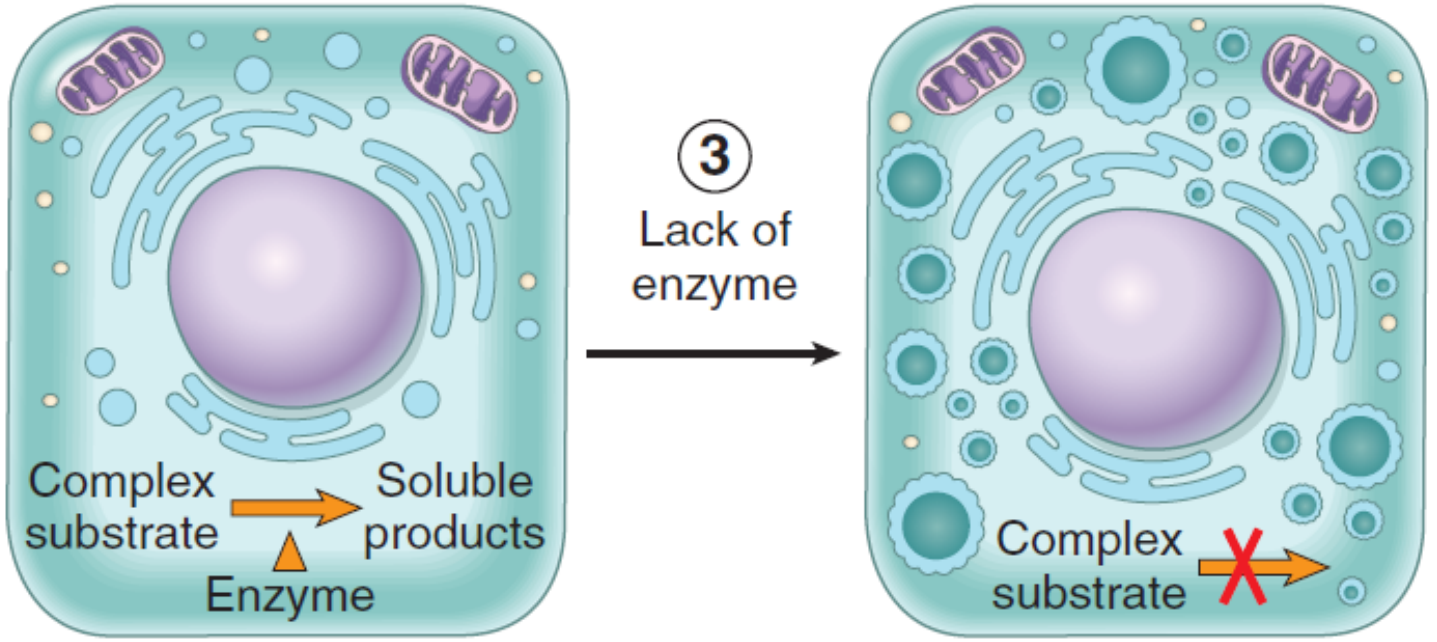
Intracellular Accumulations

2. Mutations causing alterations in protein folding and transport, so that defective molecules accumulate intracellularly



Intracellular Accumulations

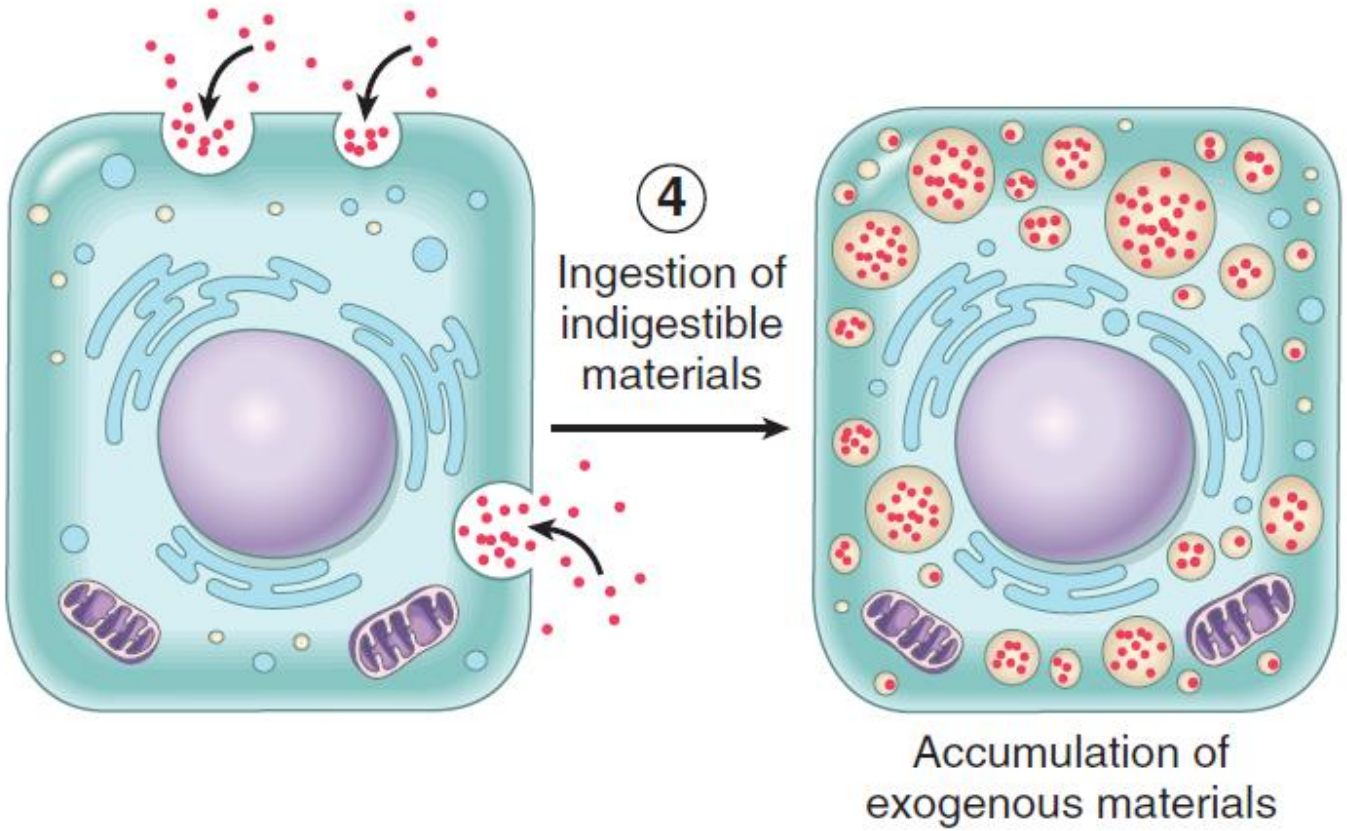
3. Deficiency of critical enzymes responsible for breaking down certain compounds, causing substrates to accumulate in lysosomes, as in lysosomal storage diseases



Lysosomal storage disease: accumulation of endogenous materials

Intracellular Accumulations

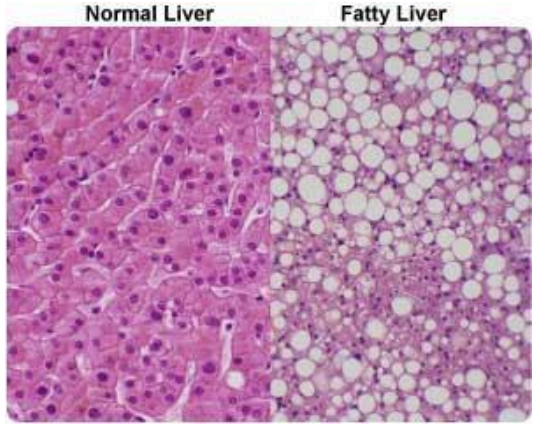
4. Inability to degrade phagocytosed particles, as in carbon pigment accumulation

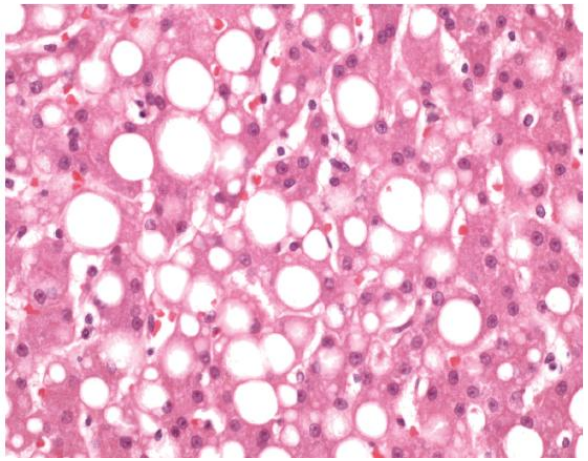


Types of Accumulations

1. Lipids

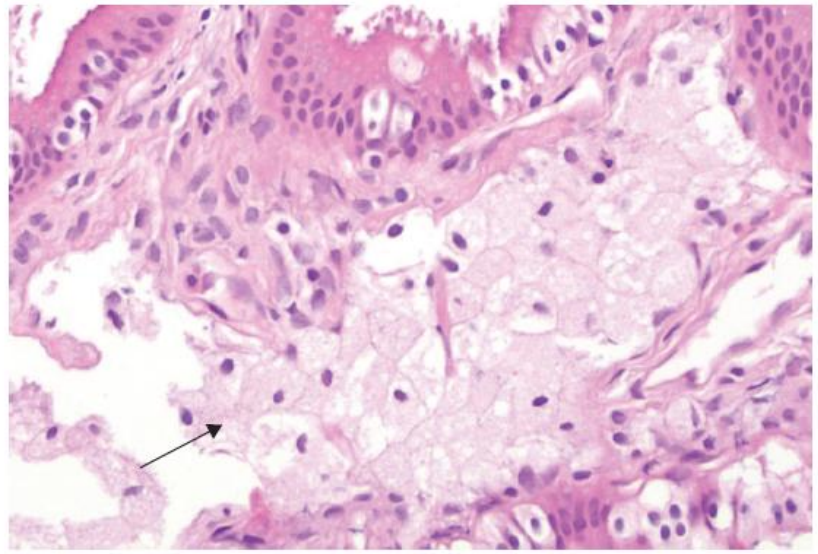
- Steatosis and fatty change (liver, heart, muscle, kidney)





The large, clear lipid droplets that fill the cytoplasm of many hepatocytes

- Cholesterol and cholesterol esters (atherosclerosis, xanthomas, inflammation and necrosis, cholesterolosis

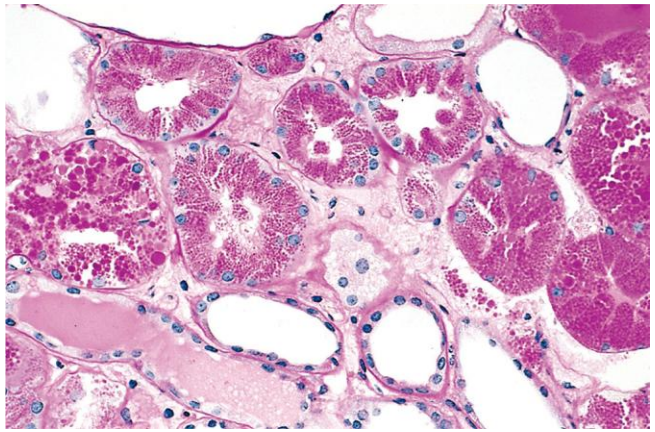


Cholesterol-laden macrophages (foam cells)

Types of Accumulations

2. Proteins

- Reabsorption droplets in kidneys
- Synthesis of excessive amounts
- Defects in protein folding → may lead to "unfolded protein response"



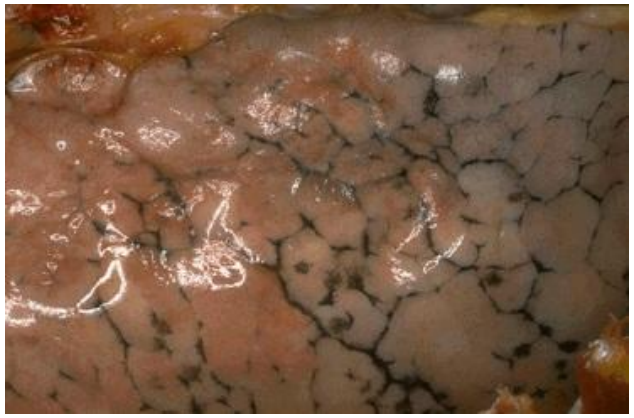
Protein reabsorption droplets

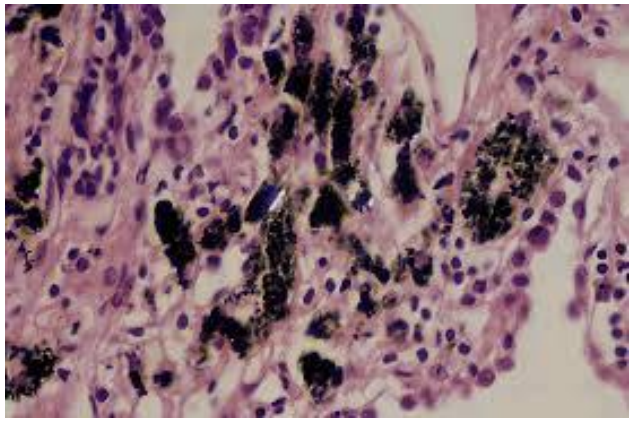
3. Glycogen

- Abnormalities in the metabolism of either glucose or glycogen
- Glycogen storage diseases
- Diabetes mellitus

4. Pigments

4.1 Exogenous pigments (carbon, coal dust) → anthracosis





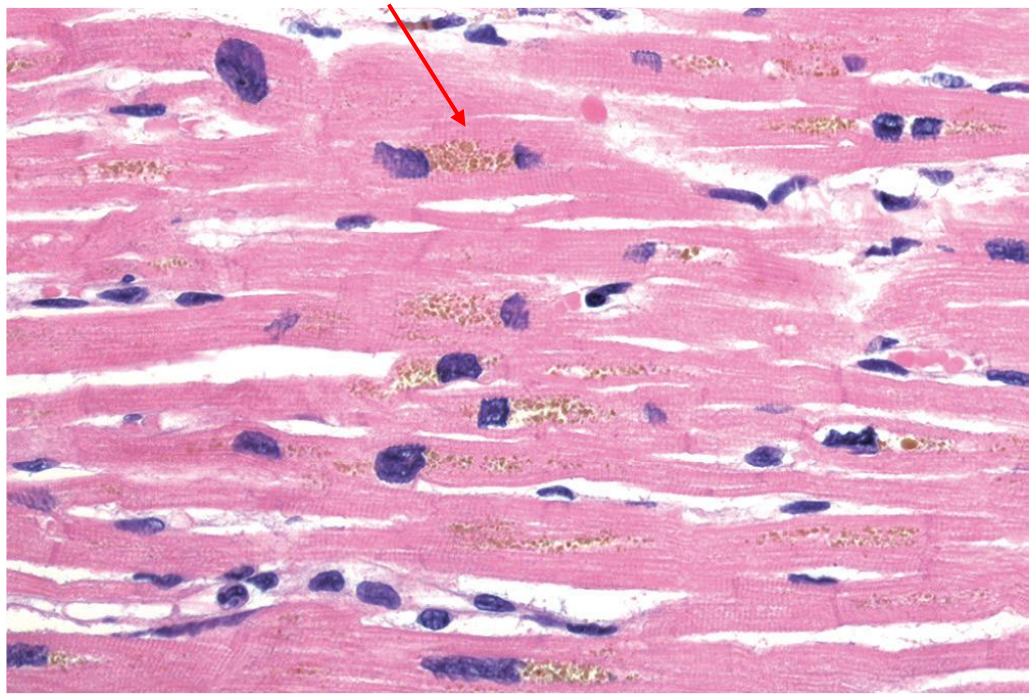
Types of Accumulations

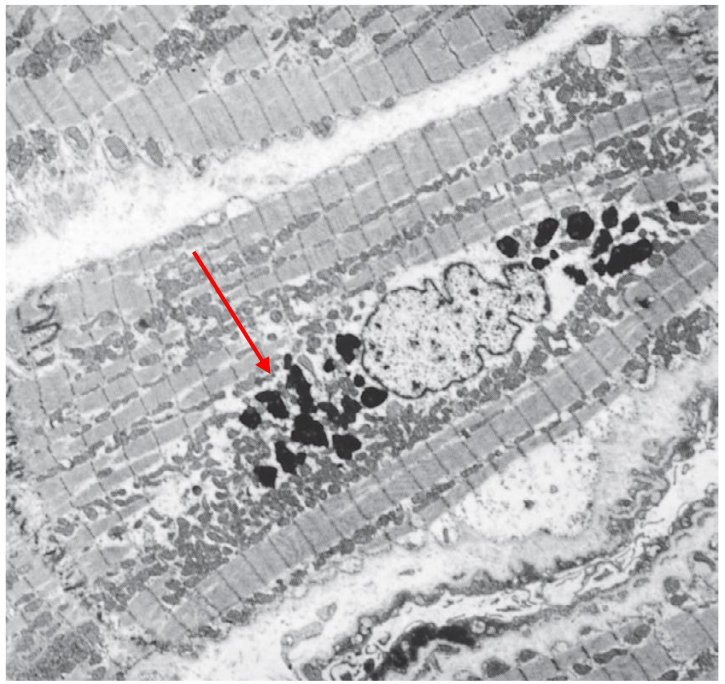
4.2 Endogenous pigments

- ***Lipofuscin***

- "wear-and-tear pigment" , complexes of lipid and protein, marker of past free radical injury, intralysosomal location

- insoluble brownish-yellow granular (heart, liver, brain) as a function of age or atrophy

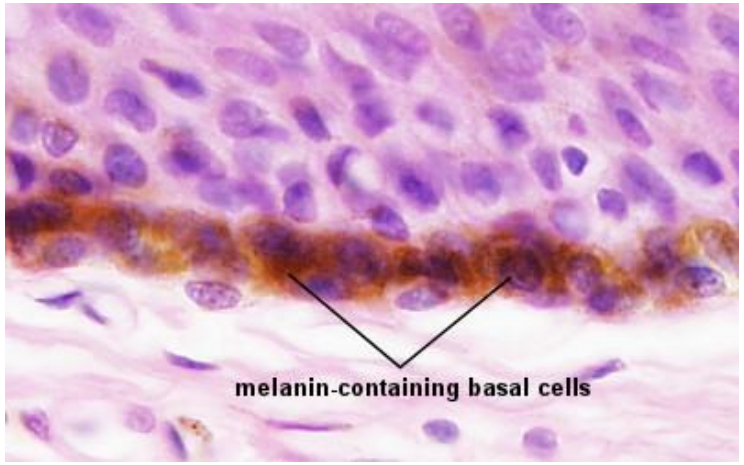




Types of Accumulations

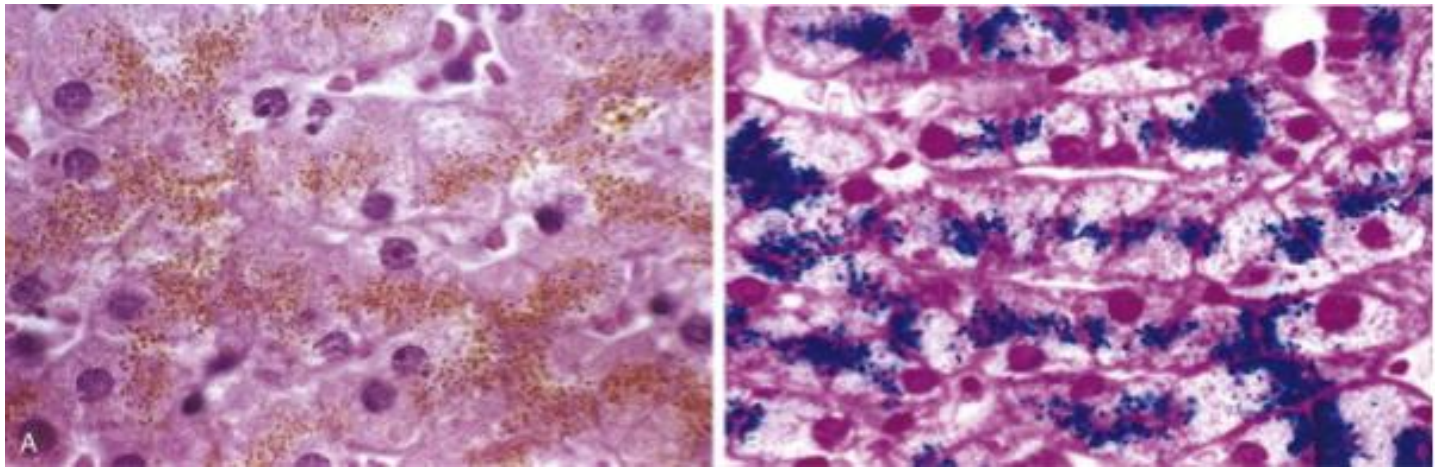
- ***Melanin***

- An endogenous, brown-black pigment
- synthesized by melanocytes located in the epidermis
- Melanosis



- ***Hemosiderin***

- Hemoglobin-derived granular pigment that is golden yellow to brown
- Local or systemic excess of iron ex. *hereditary hemochromatosis*
- Hemosiderosis

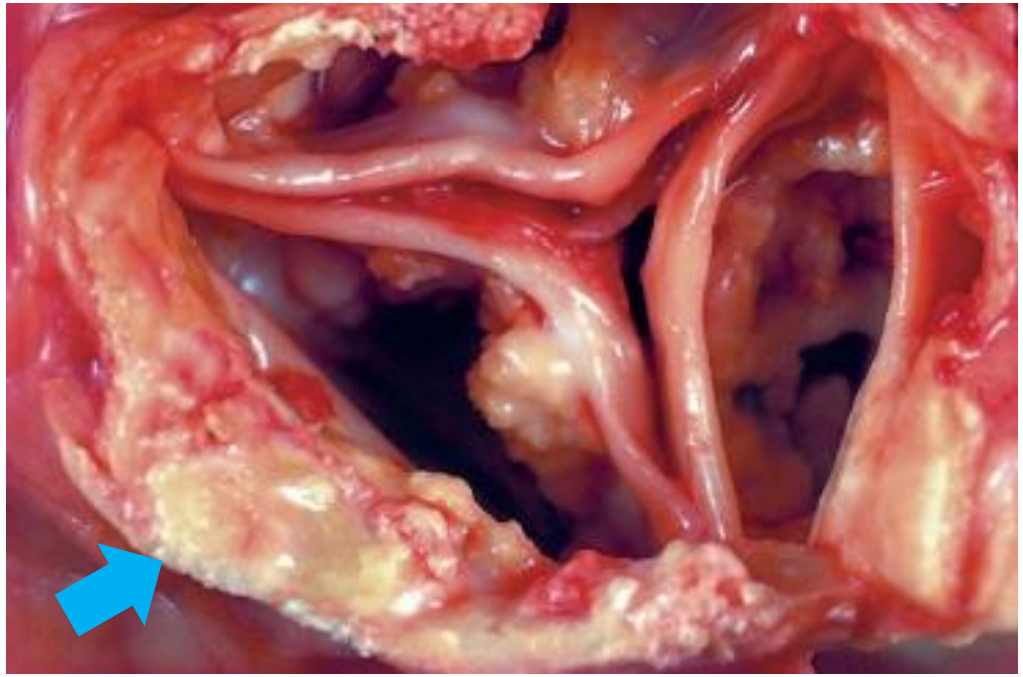


Pathologic Calcification

- A common process in a wide variety of disease states
- Abnormal deposition of calcium salts, smaller amounts of iron, magnesium, and other minerals

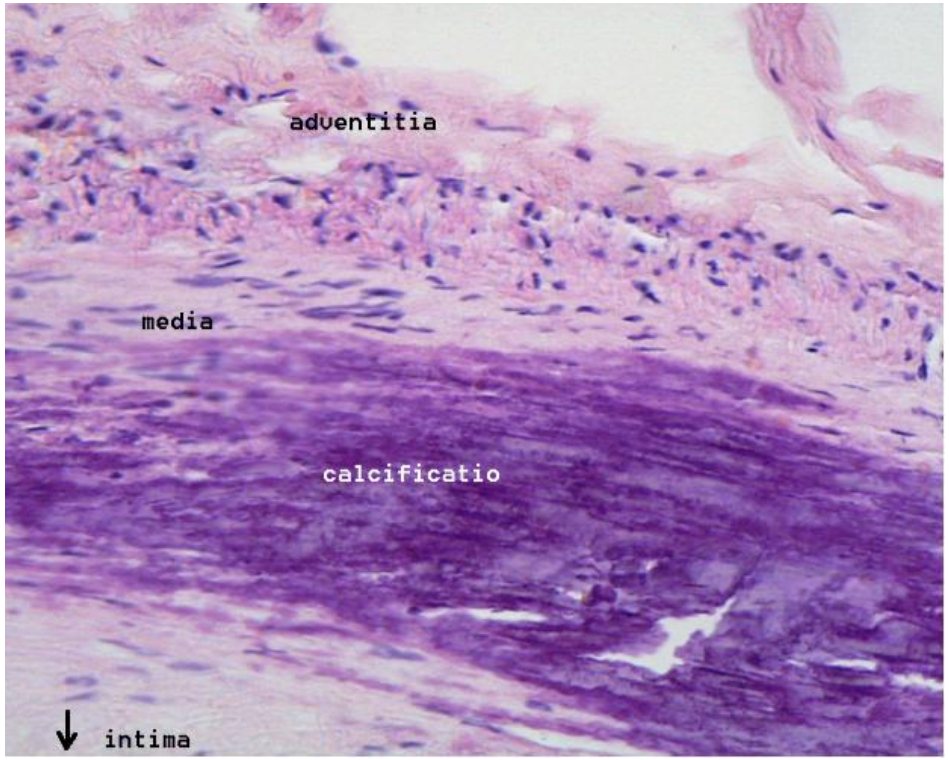
1. Dystrophic Calcification

- Deposition of calcium and other minerals in dead tissue
- Normal serum Ca++ levels
- Initiation phase: precipitate of calcium phosphate begin to accumulation intracellularly in mitochondria
- extracellular in membrane- bound vesicle
- Propagation phase: mineral deposited form the mineral cristals



Bacterial Endocarditis

Dystrophic Calcification



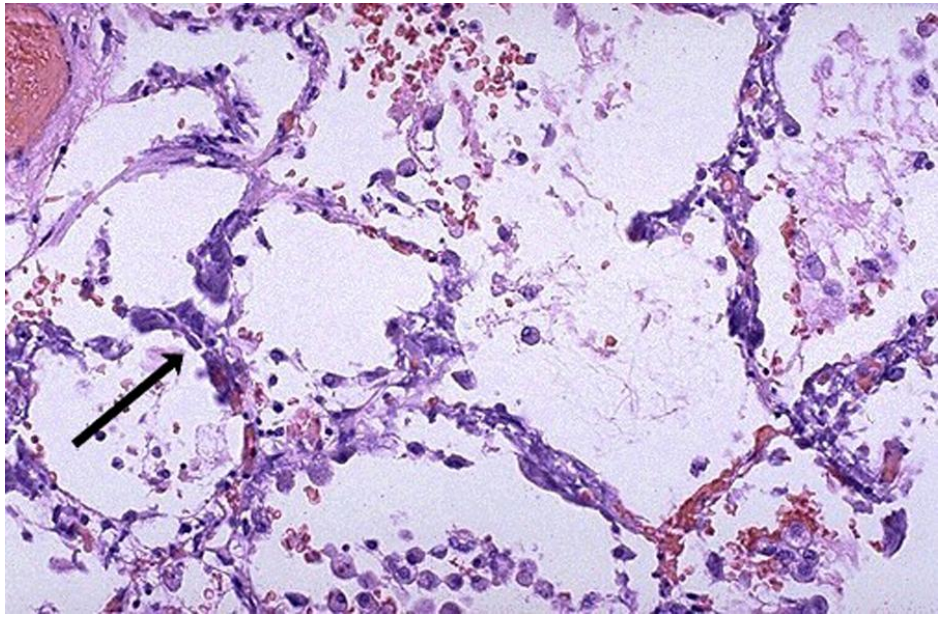
Mönckeberg's sclerosis

2. Metastatic Calcification

- Calcium deposits in normal tissue in hypercalcemic states
- Common organs: kidney, lung, stomach, blood vessel, cornea

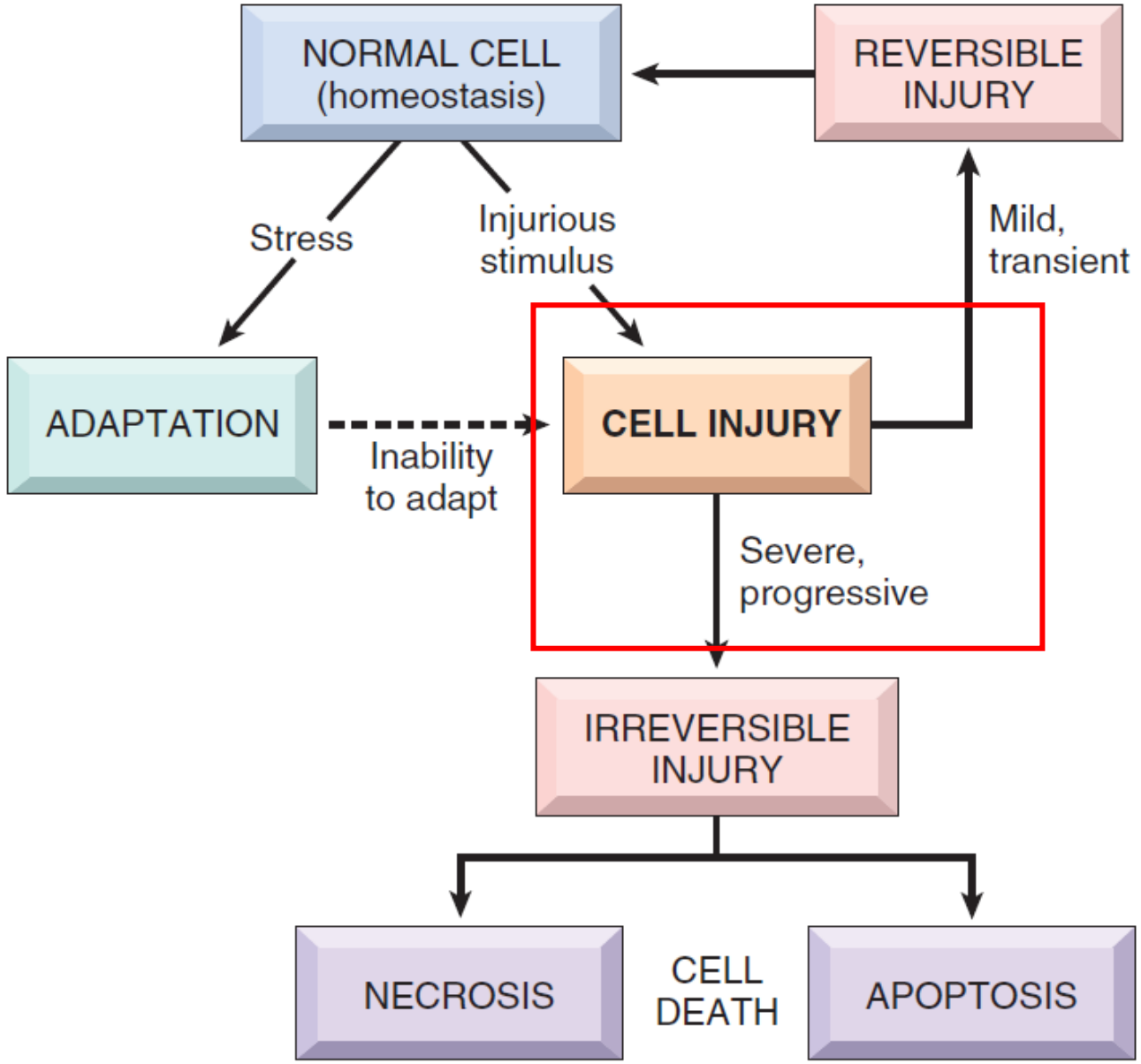
Hypercalcemia -increased secretion of PTH

- destruction of bone tissue
- vitamin D-related disorders
- renal failure
- cancer

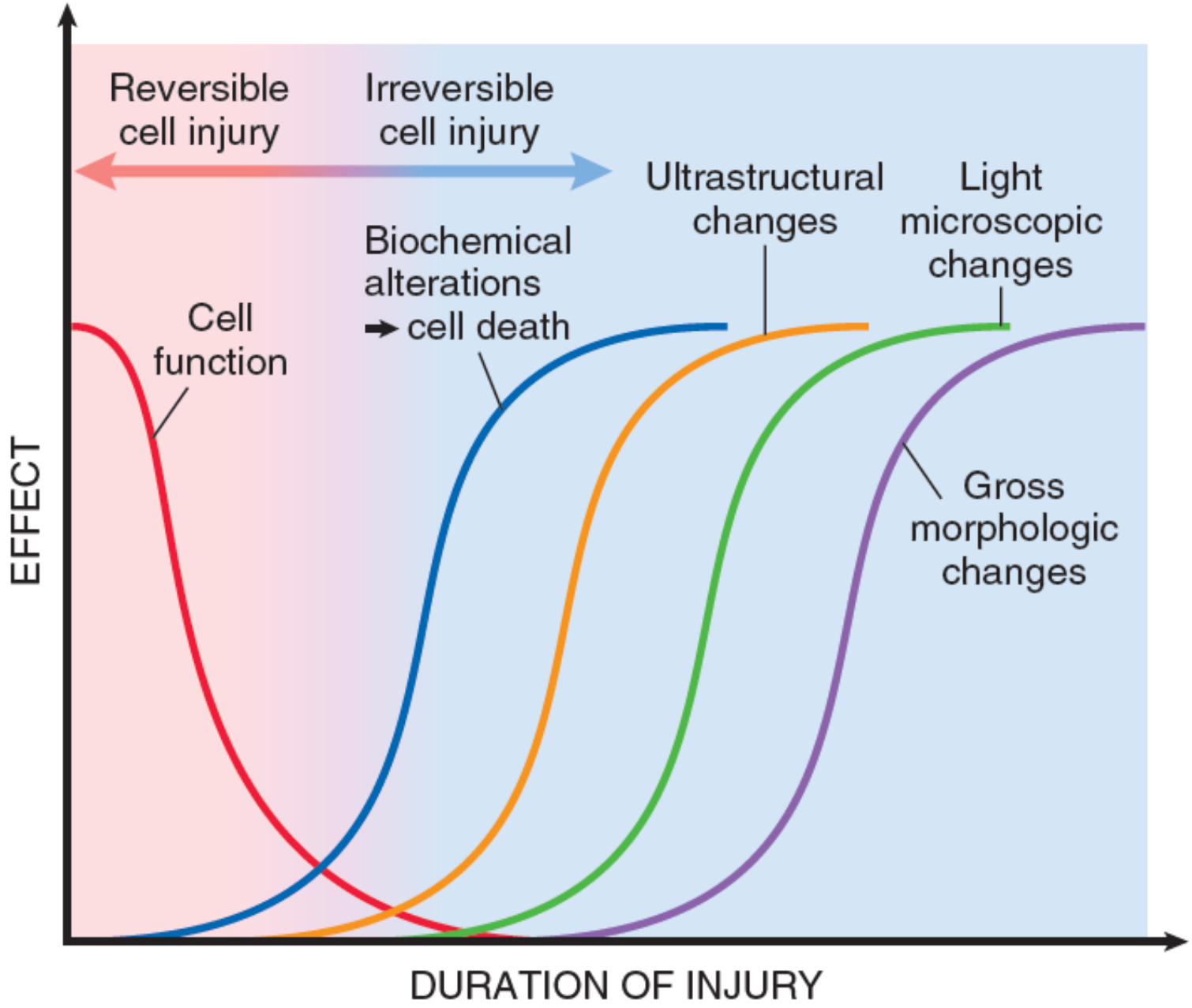


Alveolar walls from a hypercalcemia patient with breast cancer

Cell injury



Robbins and Cotran pathologic basis of disease. 10th edition (2020)


Reversible cell injury
Irreversible cell injury
Ultrastructural changes
Light microscopic changes
Biochemical alterations → cell death
Cell function
Gross morphologic changes
EFFECT
DURATION OF INJURY

Cell Injury

- Reversible cell injury>> early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed
- Irreversible cell injury>> pathologic changes that are permanent and cause cell death, they cannot be reversed to normal state
- Reversible/ Irreversible injury depend on the type, severity and duration of injury
- Cell death >> the result of irreversible injury

Cell Injury

Causes of Cell Injury:

1. **Hypoxia (loss of aerobic oxidative respiration)**
2. Ischemia (loss of blood supply)
3. Physical agents (temperature, trauma, radiation)
4. Chemical agents and drugs
5. Infectious agents (virus, bacteria, fungi, and protozoans)
6. Immunologic reactions (autoimmune reactions)
7. Genetic derangements
8. Nutritional imbalances
9. Intracellular accumulation ex. protein, calcification
10. Aging

Important aspects of cell injury

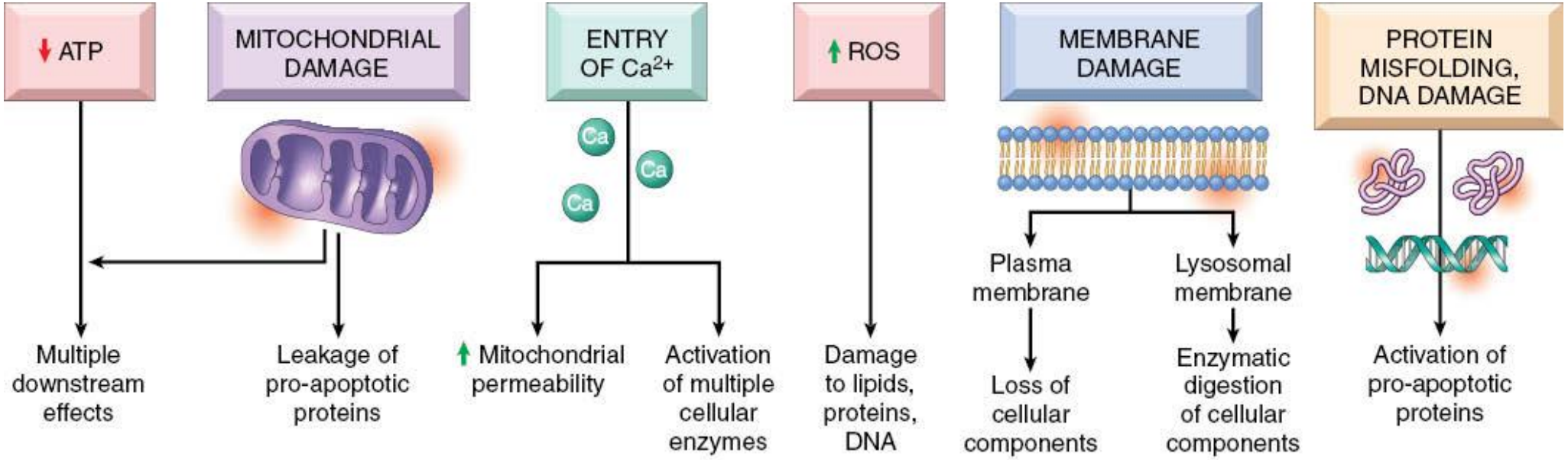
1. Wide-spread effect of changes
2. Time factor
3. Cell susceptibility to injury
4. Types of injury, duration and its severity

Susceptibility of Cells to Ischemic Necrosis

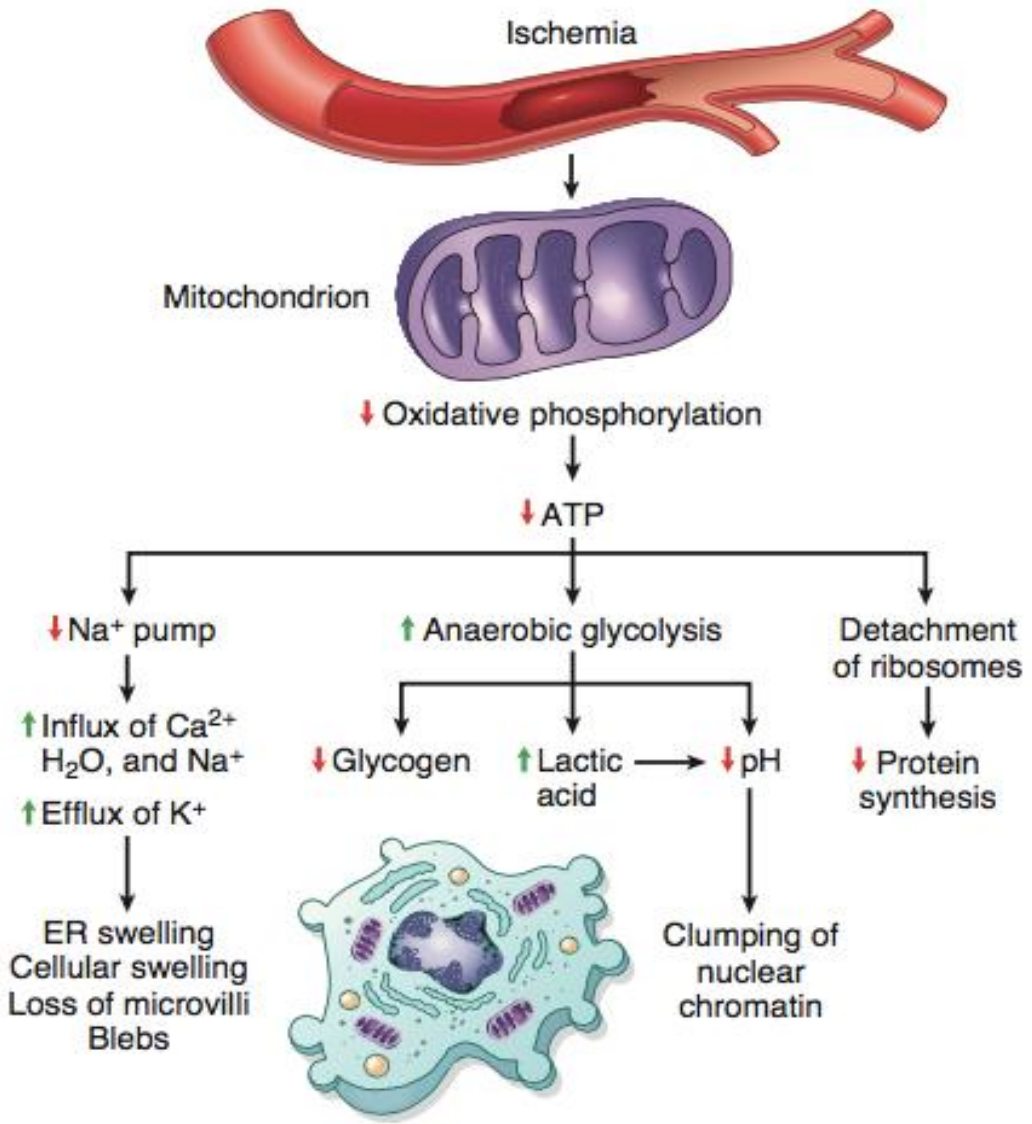
High	Neurons (3-4 min)
Intermediate	Myocardium, hepatocytes, renal epithelium (30 min-2hr)
Low	Fibroblasts, epidermis, skeletal muscle (many hours)

General Biochemical Mechanisms of cell injury

1. ATP depletion
2. Loss of intracellular calcium homeostasis
3. Oxygen and oxygen-derived free radicals/reactive oxygen species
4. Defects in membrane permeability
5. Irreversible mitochondrial damage
6. The unfolded protein response (ER stress)



1. ATP depletion



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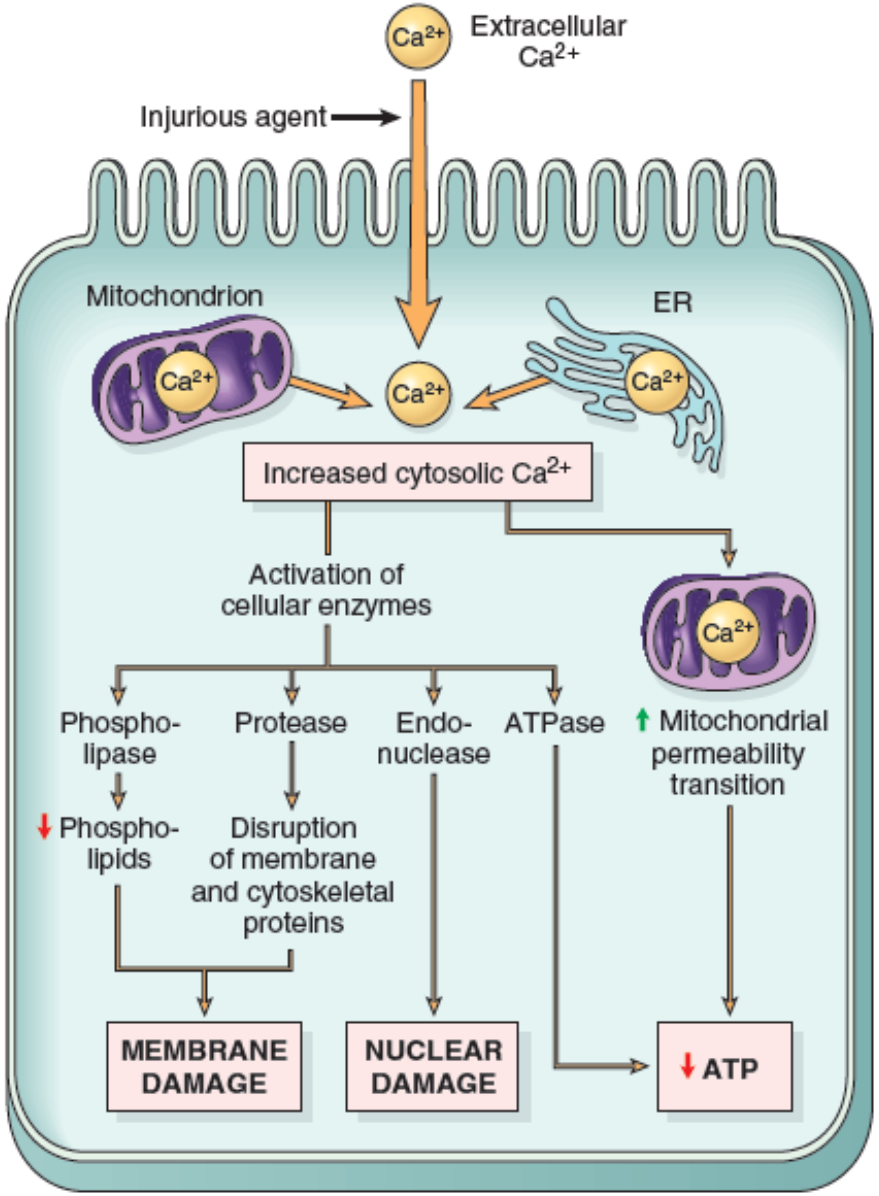
2. Loss of intracellular calcium homeostasis



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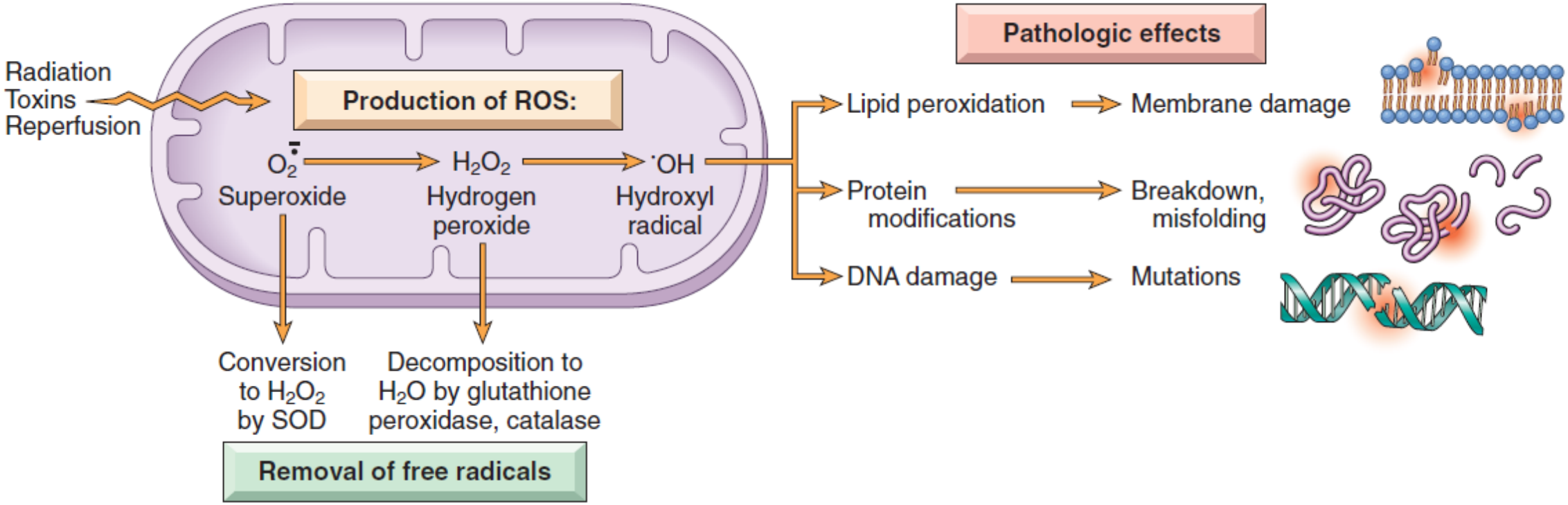
3. Oxygen and oxygen-derived free radicals



- Lipid peroxidation leading to membrane damage
- Protein damage
- DNA damage

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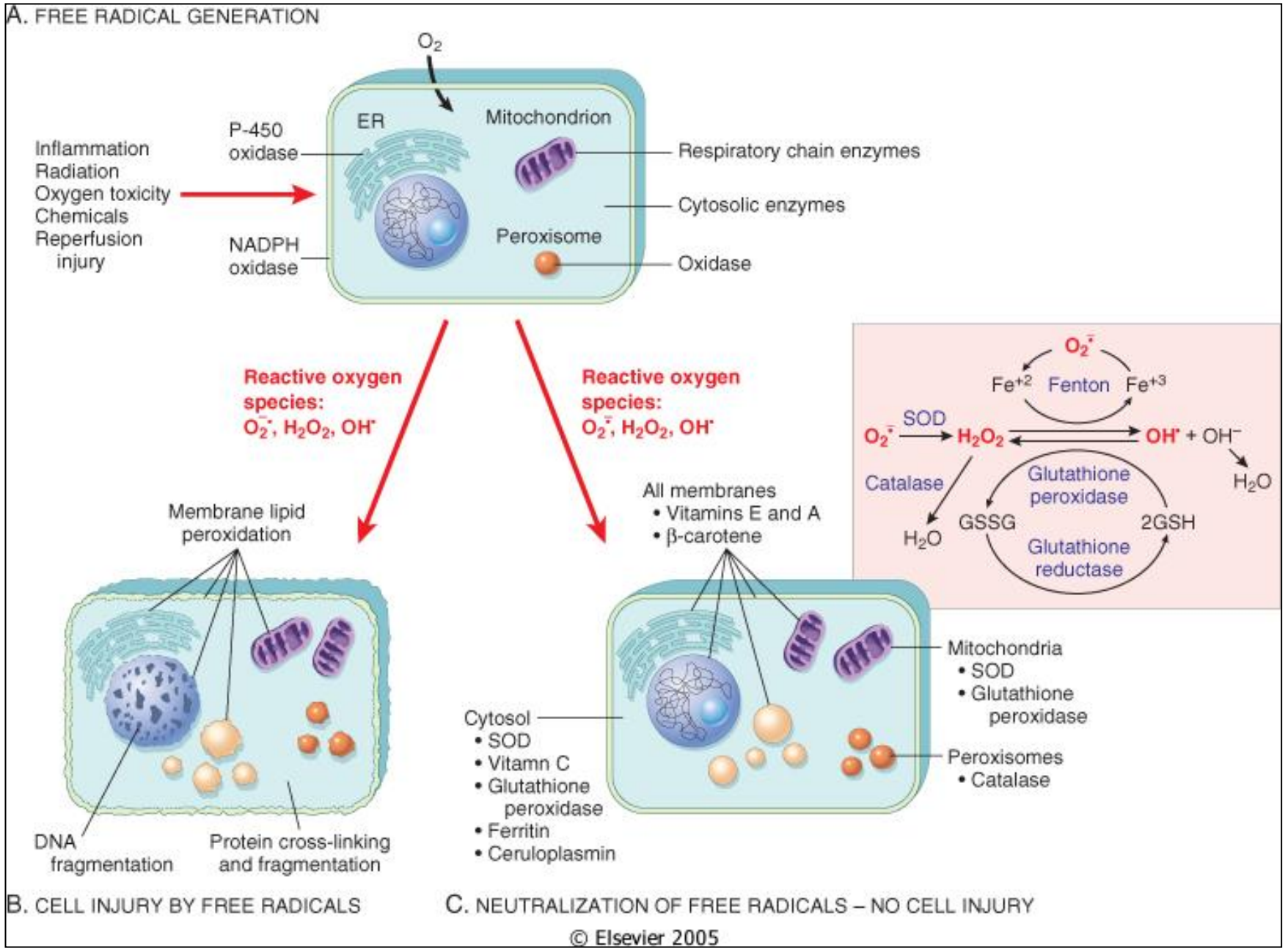
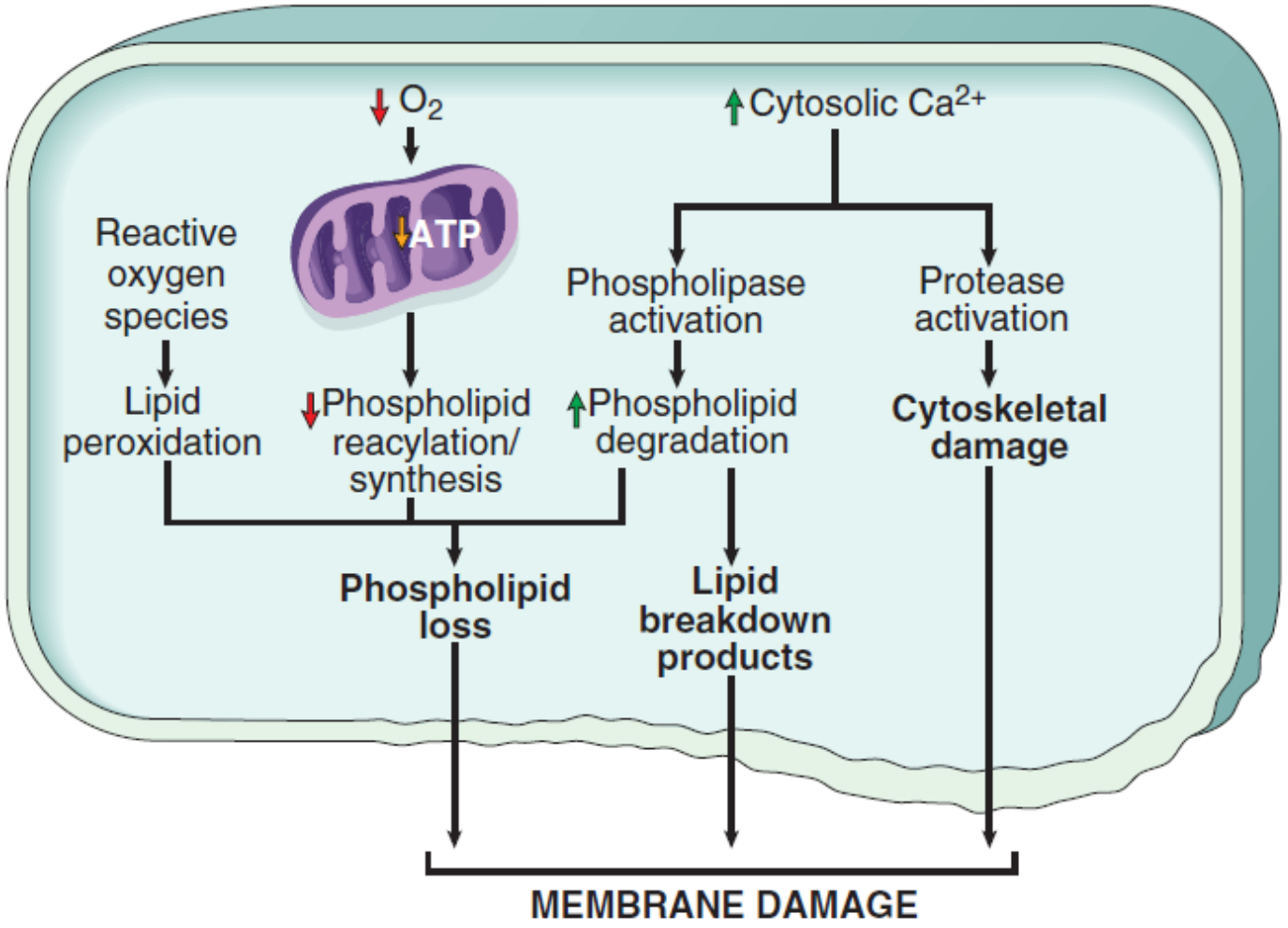


Robins and Cotrans Pathologic Basis of Disease, 2005

Free radicals and diseases

- Some examples are:-
  - oxygen toxicity, ischamia/reperfusion injury, radiation injury (hydrolyses H_2O to OH & H)
  - metabolism of drugs, toxins, pollutants (eg. Paracetamol to reactive metabolite;CCl_4 to CCl_3, cigarette smoke)
  - leukocyte killing of bacteria or in non-bacterial inflammations, release of iron in haemorrhages enhances oxidative stress (important in CNS)
  - lipid peroxidation of low-density lipoproteins in atherosclerosis, cancer production (damage to DNA), aging
  - Therapies for combating oxidative stress are available for prevention or treatment with antioxidants and/or free-radical scavengers.

4. Defects in membrane permeability



- Plasma membrane
- Mitochondrial membrane
- Lysosomal membrane

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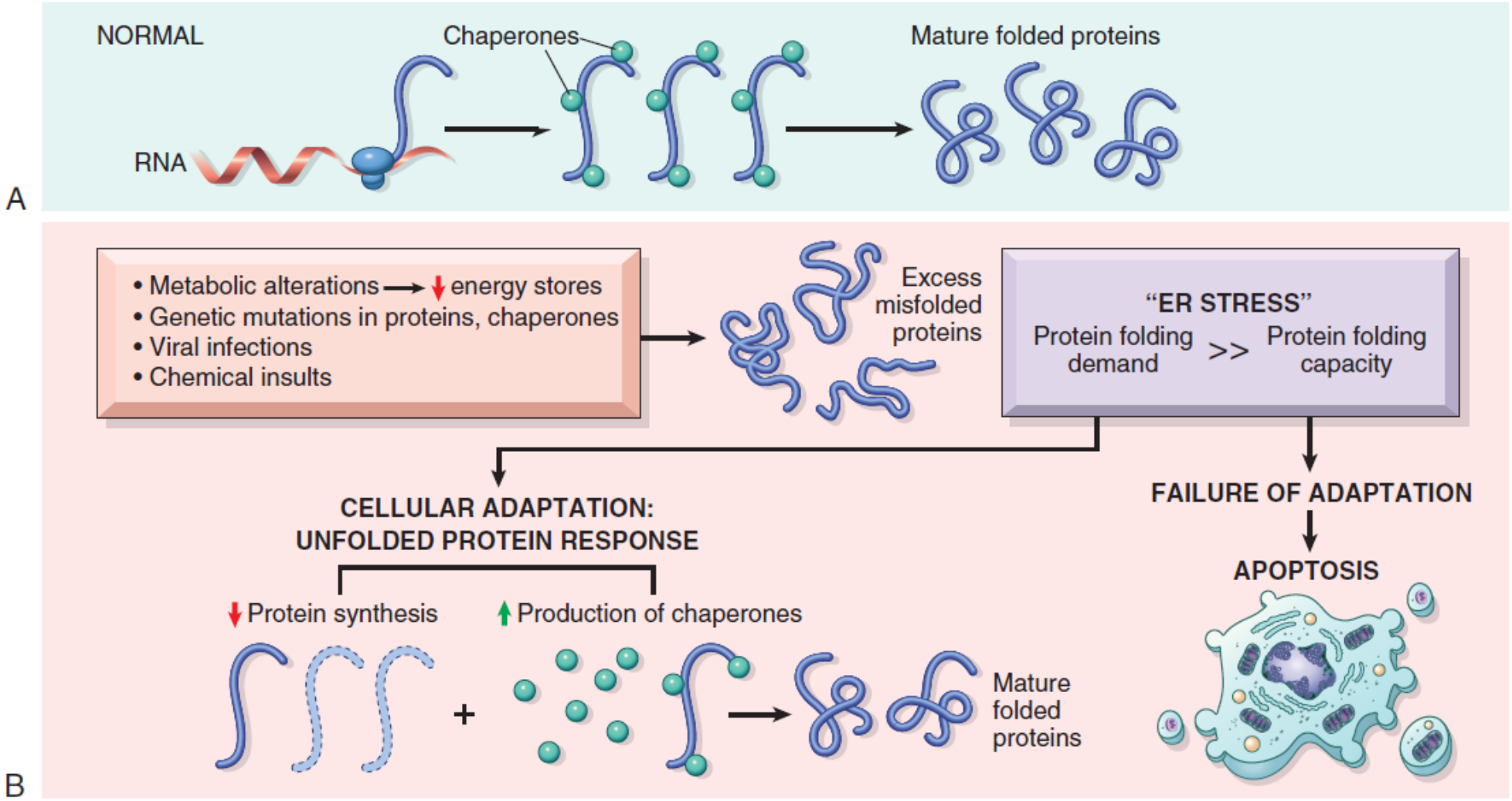
5. Mitochondrial Damage

- **3 major consequences:**
  - Mitochondrial permeability transition (**MPT**) pore opens → loss of mitochondrial membrane potential → decreased oxidative phosphorylation / decreased ATP
  - Production of reactive oxygen species
  - Leakage of pro-apoptotic proteins

6. The unfolded protein response and *(ER)* stress



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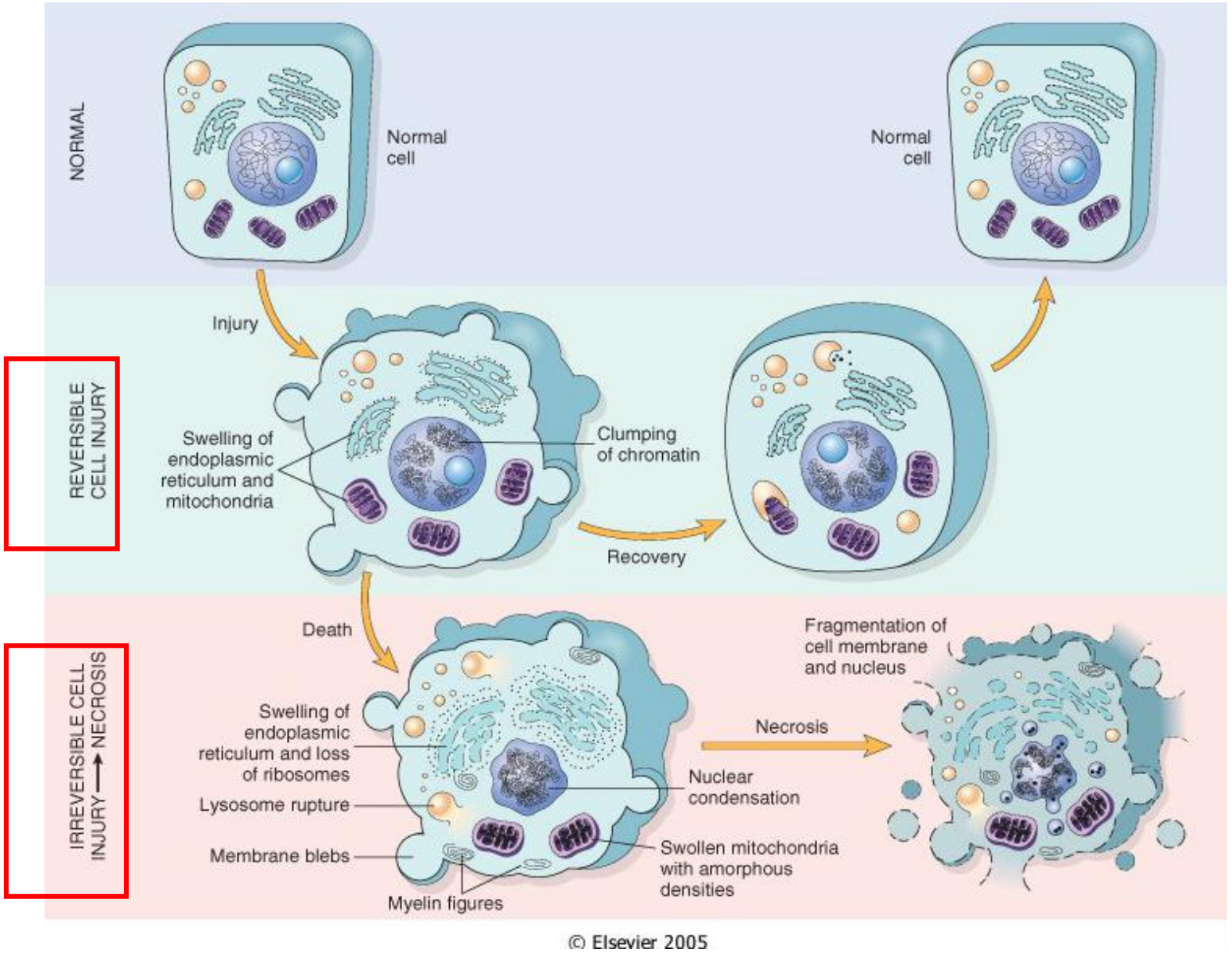
Characteristics of Reversible Vs. Irreversible Injury



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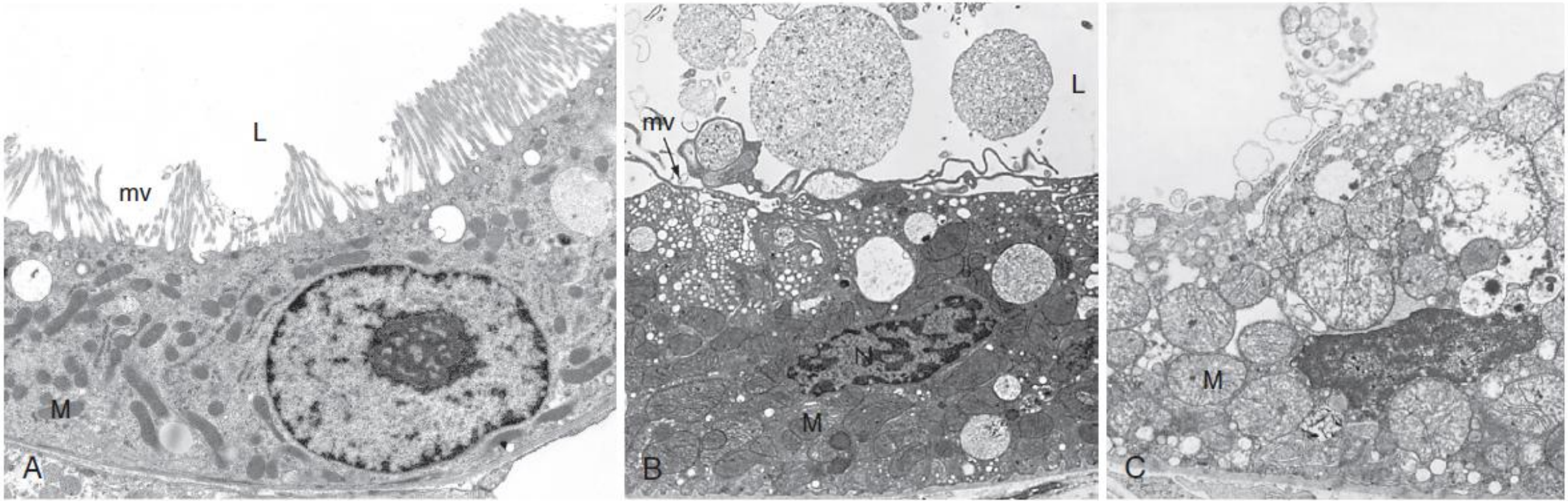
Organelles	Reversible injury	Irreversible injury
Plasma membrane:	loss of microvilli, blebbing	disruption
Mitochondria:	modest swelling	massive swelling, leakage
Endoplasmic reticulum	dilation with detachment of polysomes	extensive disruption and fragmentation, myelin figures
Nuclease	Clumping Chromatin	Nuclear condensation , fragmentation, lysis
Lysosome	Lysosome swelling Vacuolar degeneration Fatty change	Lysosome rupture



A. Normal kidney

B. Reversible changes

C. Dying Cell

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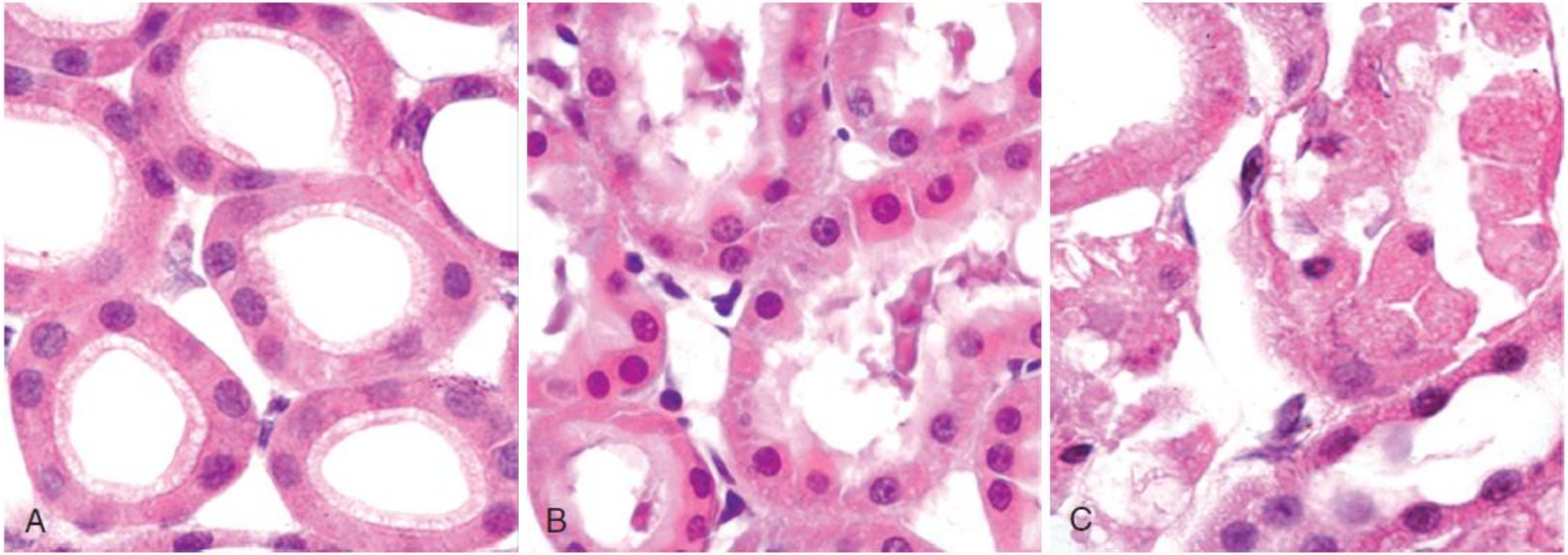

A. Normal kidney

B. Reversible changes

C. Dying Cell

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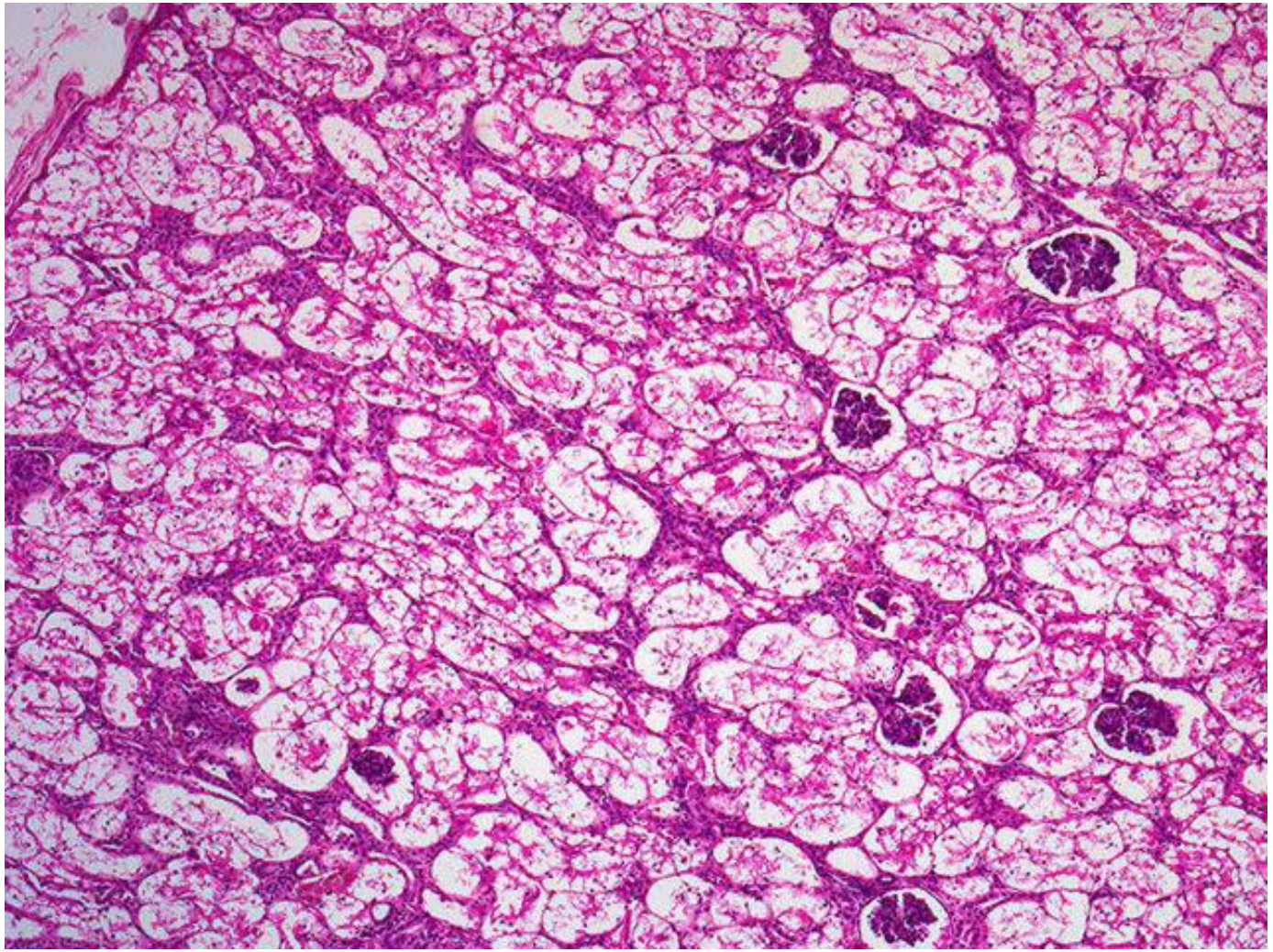
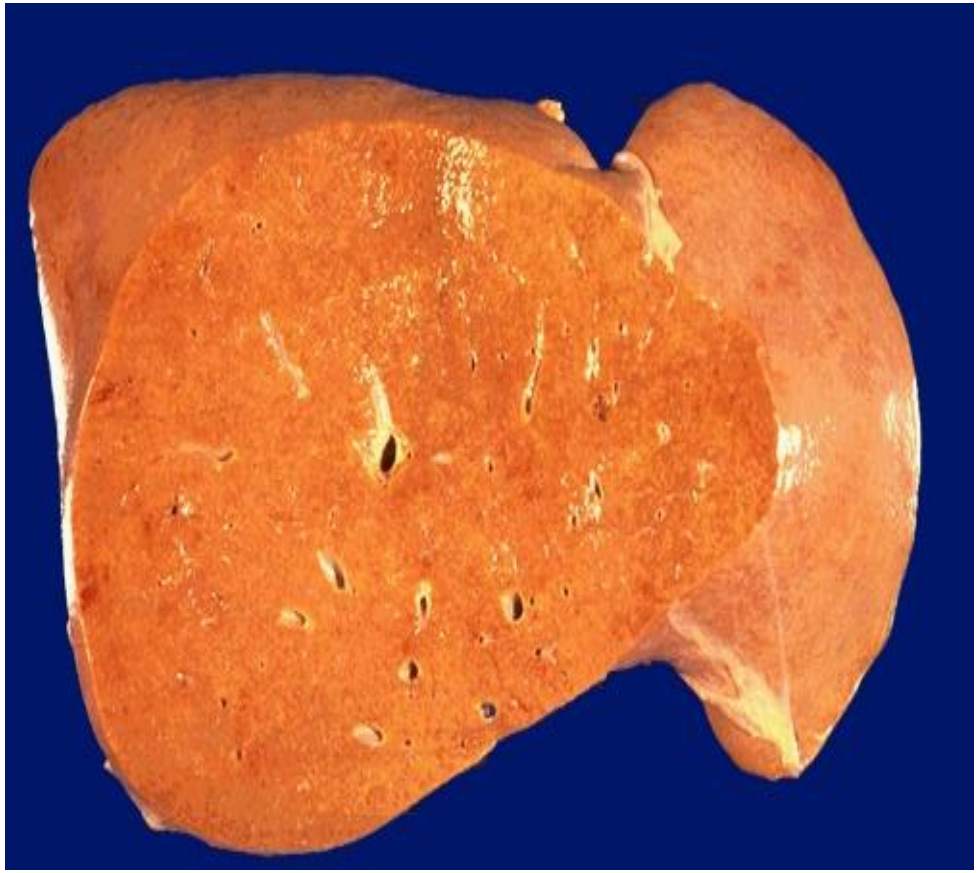
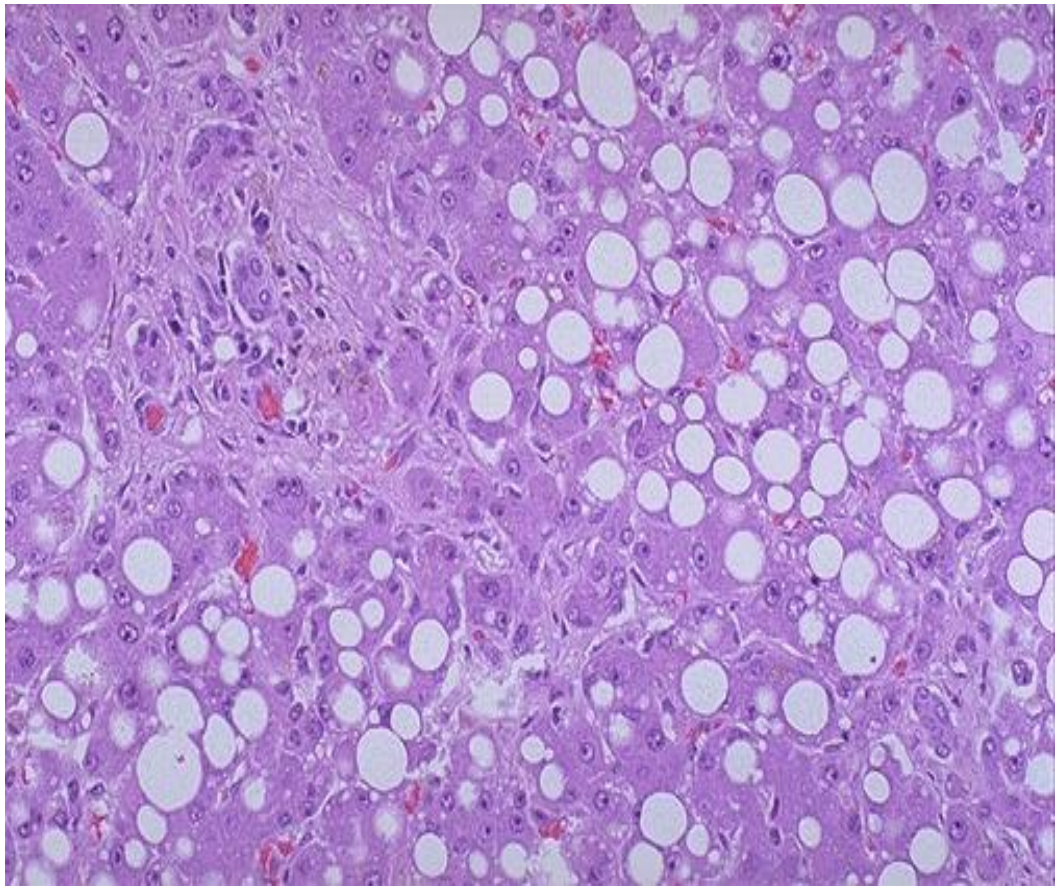
Hydropic Change/Ballon Degeneration



- Early signs of cellular degeneration in response to injury
- The accumulation of water in the tubular cells
- Due to hypoxia of the tissue with a resultant decrease in aerobic respiration in the mitochondria and a decreased production ATP

Fatty Liver Change

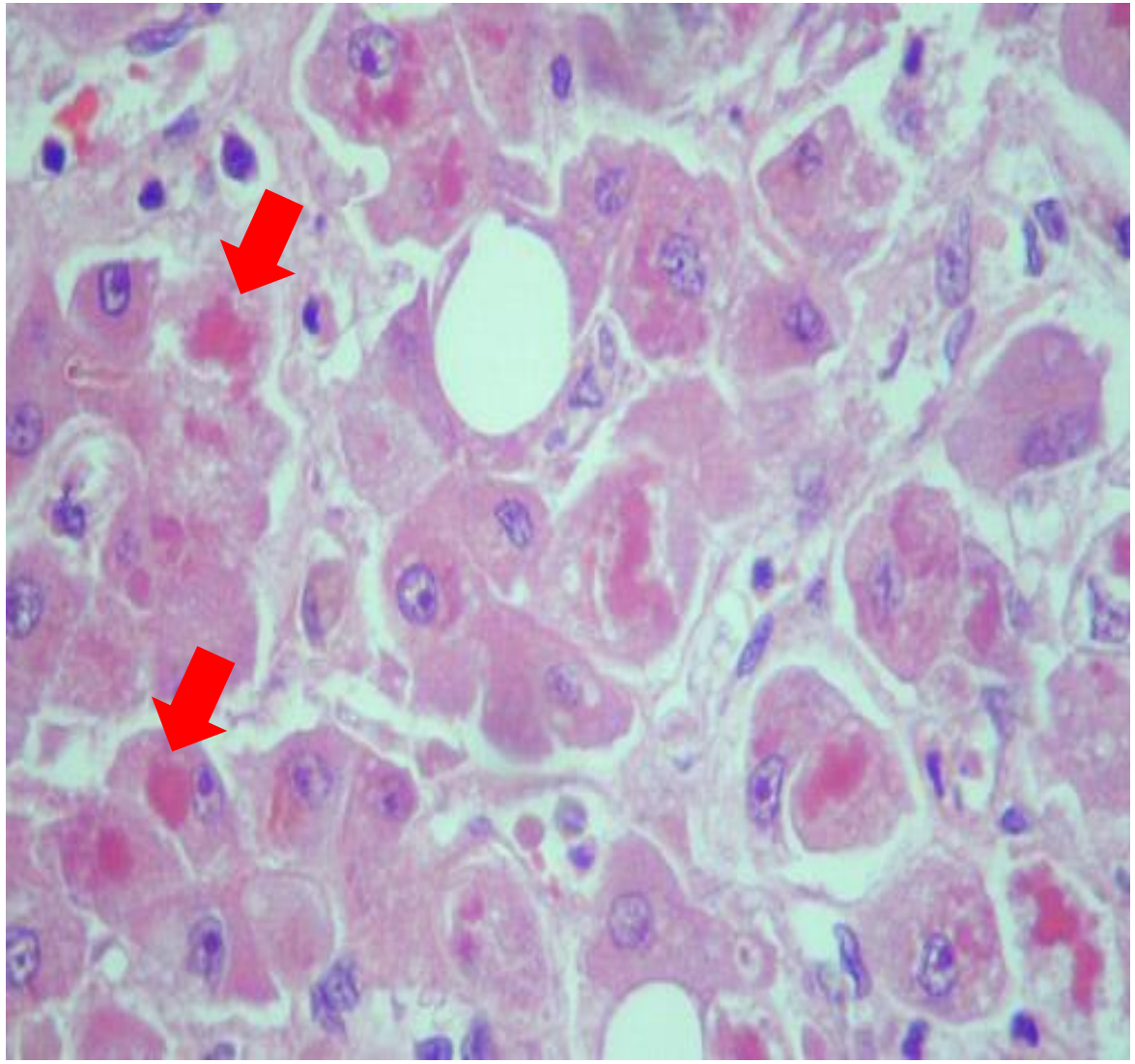




- The lipid accumulates when lipoprotein transport is disrupted and/or when fatty acids accumulate.
- Alcohol, the most common cause, is a hepatotoxin that interferes with mitochondrial and microsomal function in hepatocytes, leading to an accumulation of lipid.

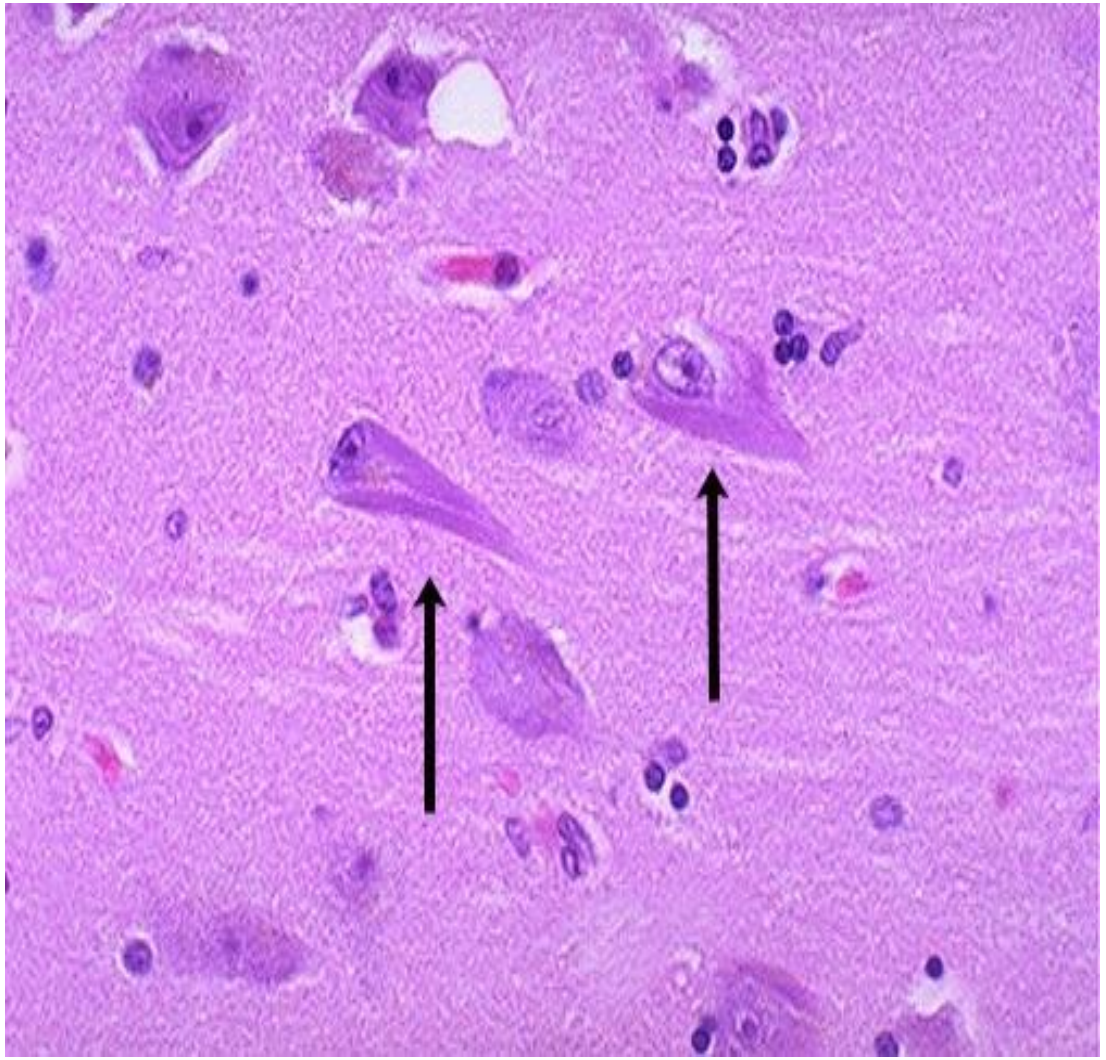
Mallory Bodies

- Cytoplasmic organelle damage leads to a variety of injury patterns
- **Mallory bodies** (the red globular material) composed of cytoskeletal filaments in liver cells chronically damaged from alcoholism.



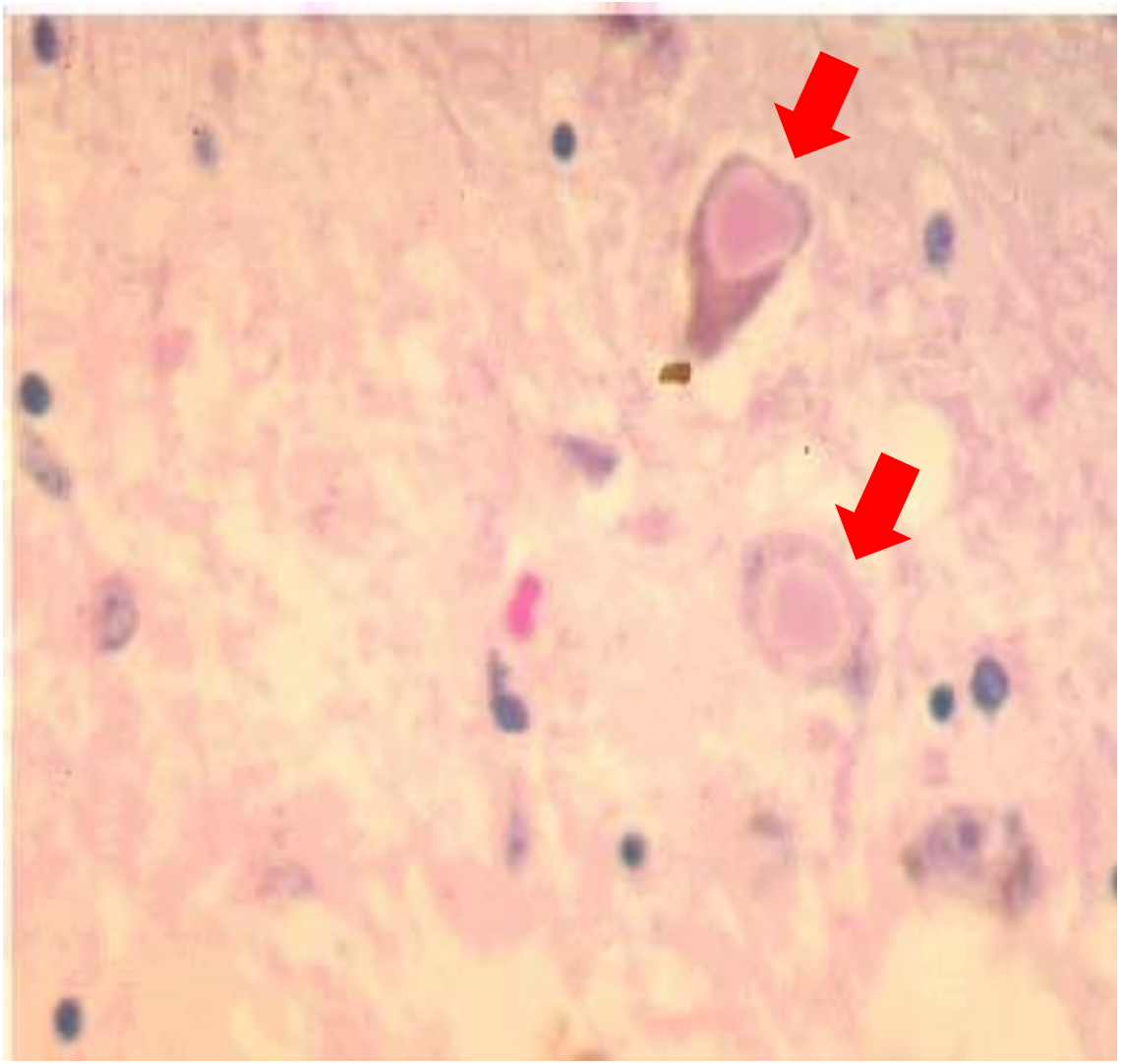
Neurofibrillary Tangles

- Neurofibrillary tangles in neurons of a patient with Alzheimer's disease.
- The cytoskeletal filaments are grouped together in the elongated pink tangles.

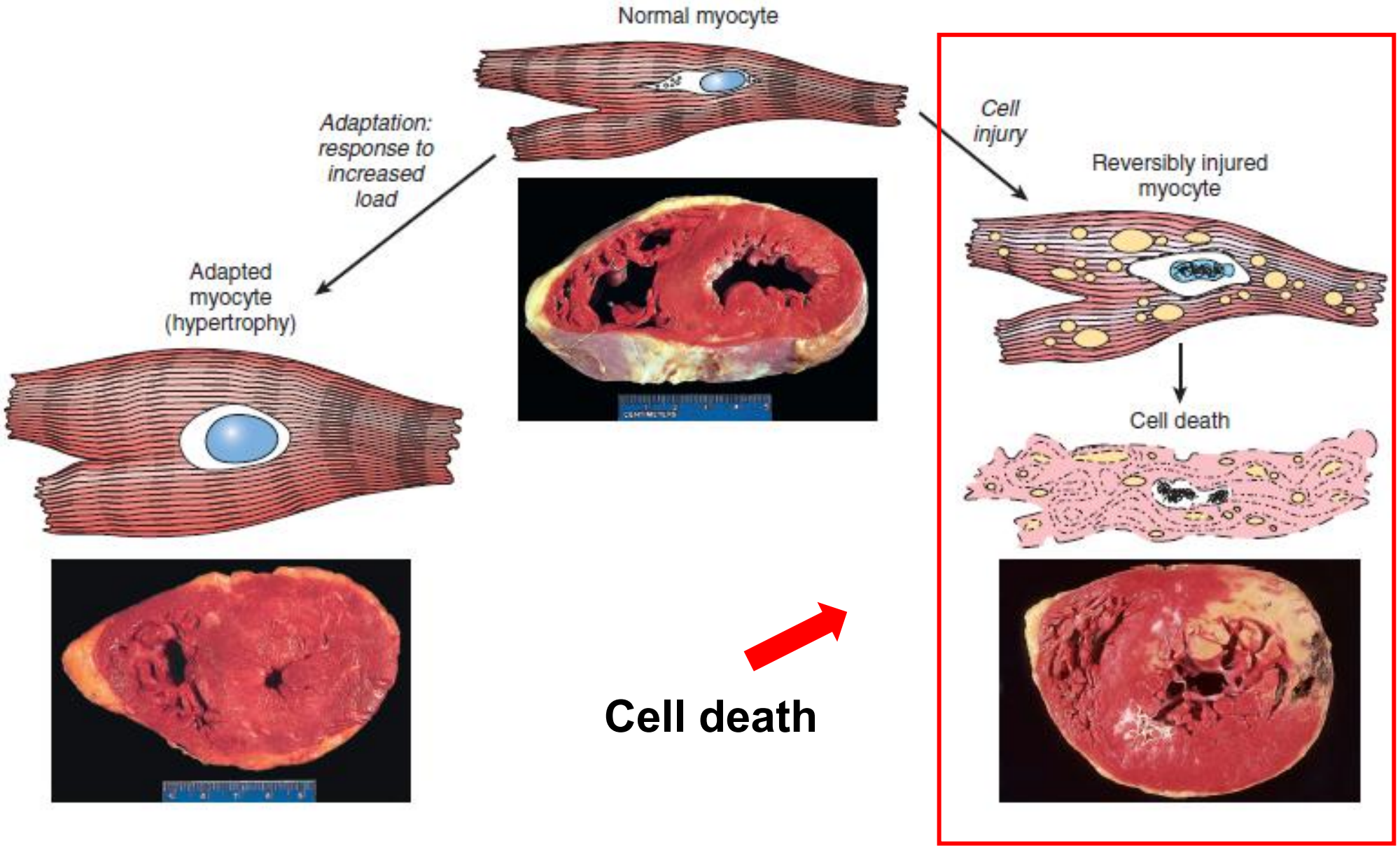


Lewy bodies

- The intracytoplasmic eosinophilic inclusions with a clear halo around.
- **Lewy bodies** are abnormal aggregates of protein that develop inside nerve cells.



Cell death



Cell death

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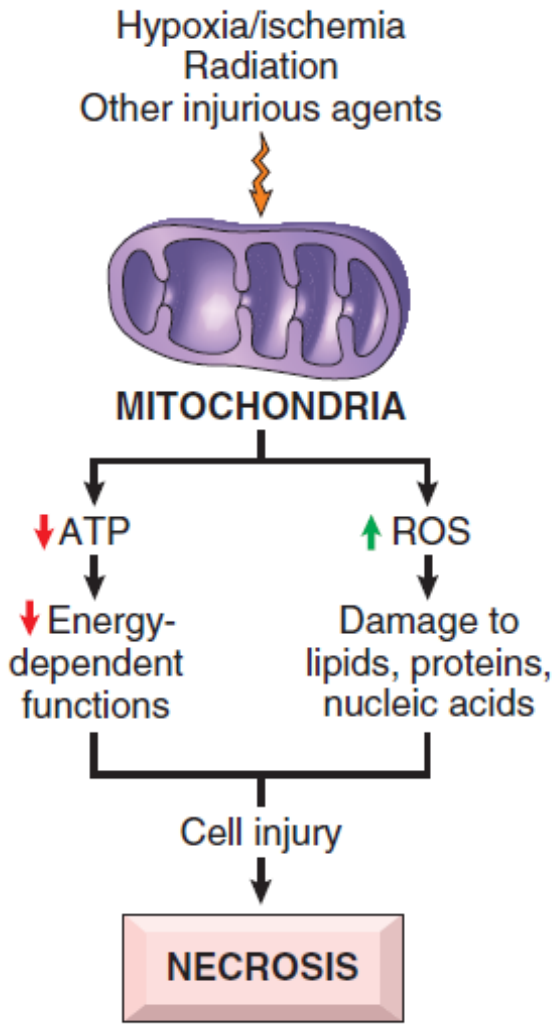
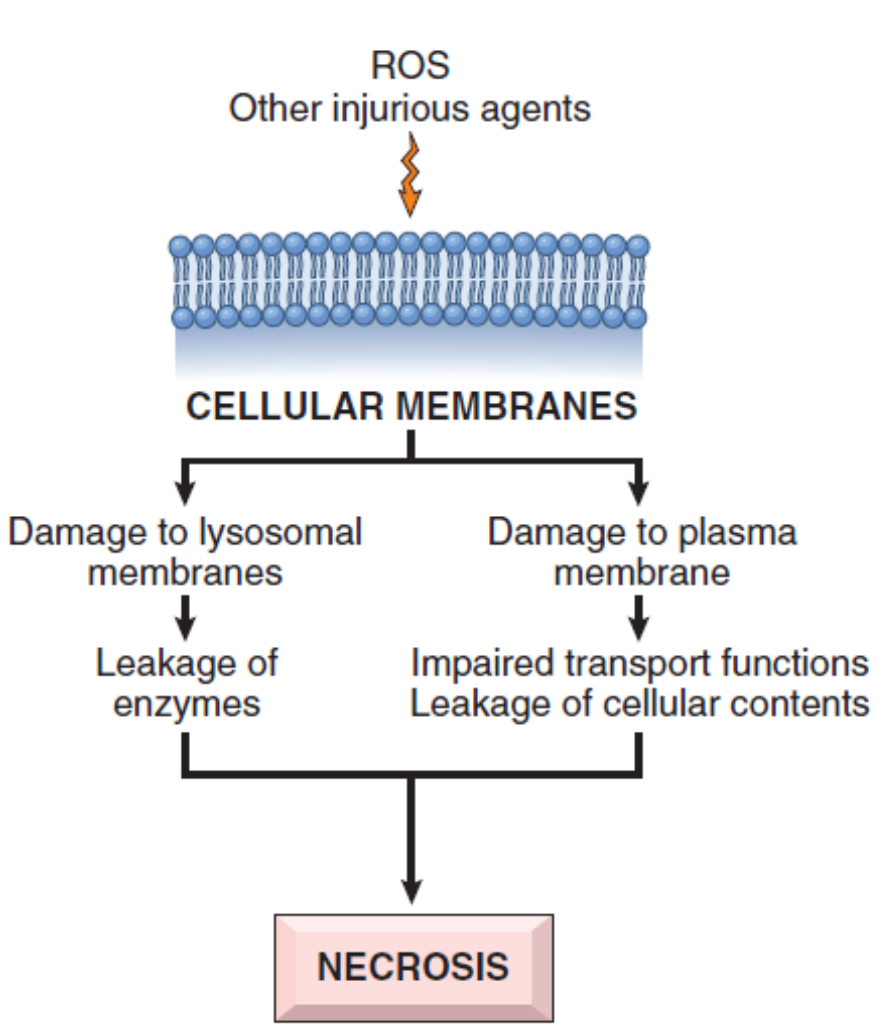
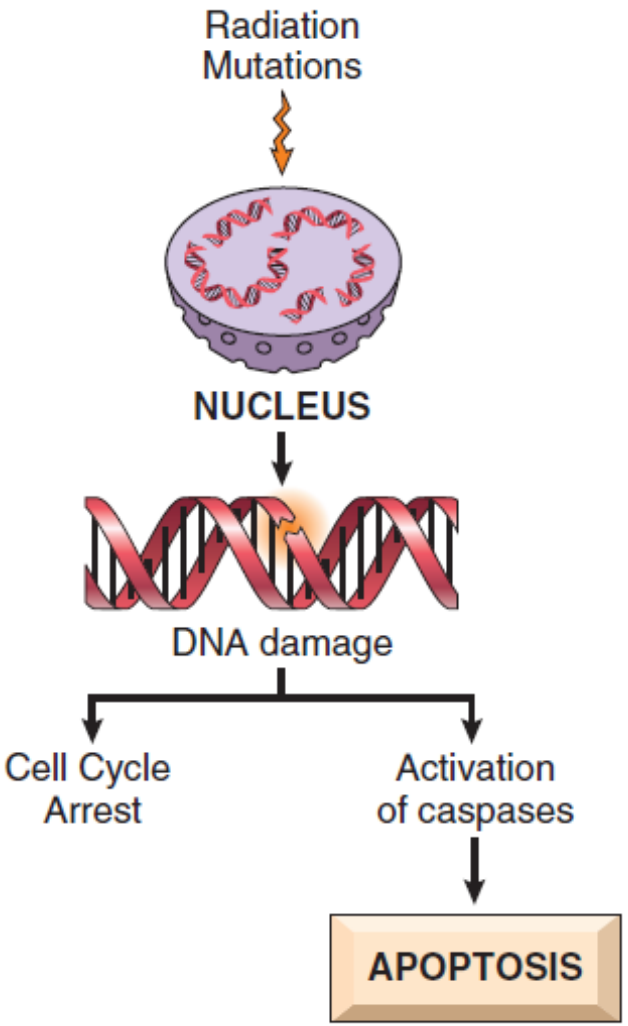
Cell Death

- Death of cells occurs in two ways:
  - **Necrosis**--(irreversible injury) changes produced by **enzymatic digestion** of dead cellular elements
  - **Apoptosis**--vital process that helps eliminate unwanted cells--an internally **programmed** series of events effected by dedicated gene products







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Types of Cell Death

1. Apoptosis

- Greek language, which originally refers to falling of leaves from trees in the autumn
- **"Programmed cell death"**
- **Physiologic:**
  1. The programmed destruction of cells during embryogenesis
  2. Hormone-dependent involution in the adult
  3. Elimination of potentially harmful self-reactive lymphocytes
- **Pathologic:**
  1. Injurious stimuli – radiation, cytotoxic chemotherapy
  2. Viral diseases
  3. Pathologic atrophy in parenchymal organs after duct obstruction

Morphological Forms of Programmed Cell Death

Type I = Apoptosis

Type II = Autophagic Cell Death

Type III = Non-lysosomal

Kerr, Wyllie, and Currie, 1972; Schweicheland Merker, 1973; Clarke 1990Kerr, Wyllie, and Currie, 1972; Schweicheland Merker, 1973

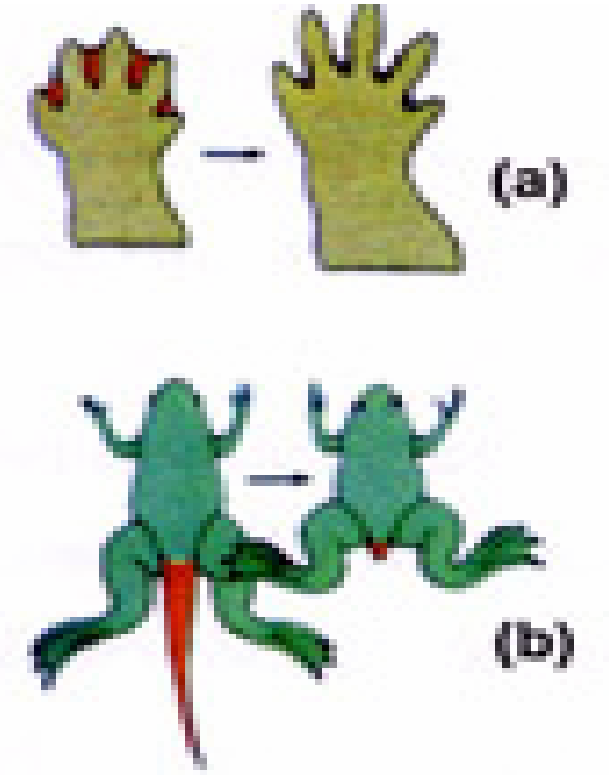
Apoptosis (Physiology)

- In the human body ~ 100,000 cells are produced every second by mitosis and a similar number die by apoptosis.

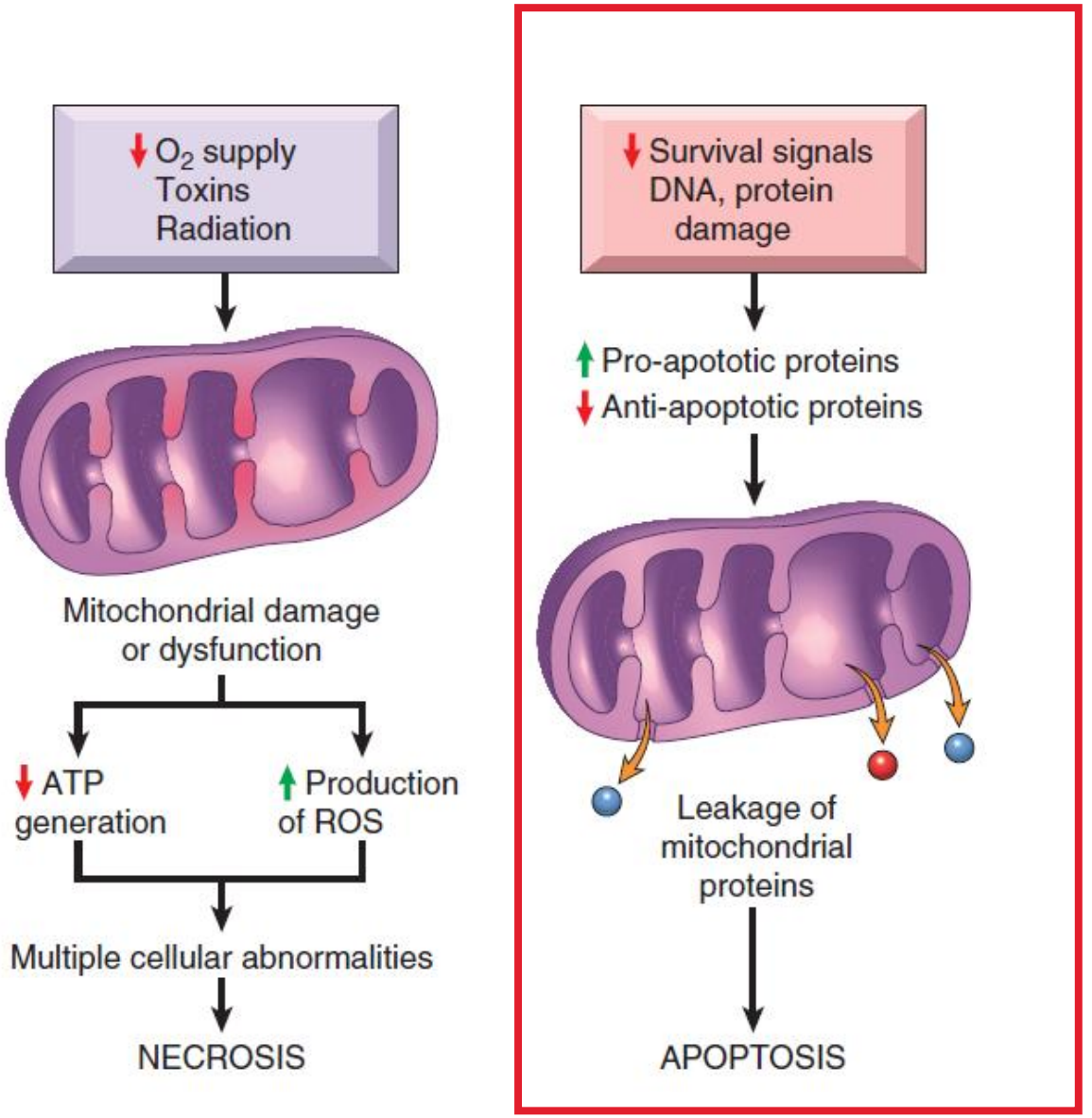
- Development and morphogenesis
  - During limb formation separate digits evolve
  - Ablation of cells no longer needed (tadpole)

- Homeostasis
  - Immune system
  - >95% T and B cells die during maturation (negative selection)

- Deletion of damaged/ dangerous cells



Mechanisms of Cell Death



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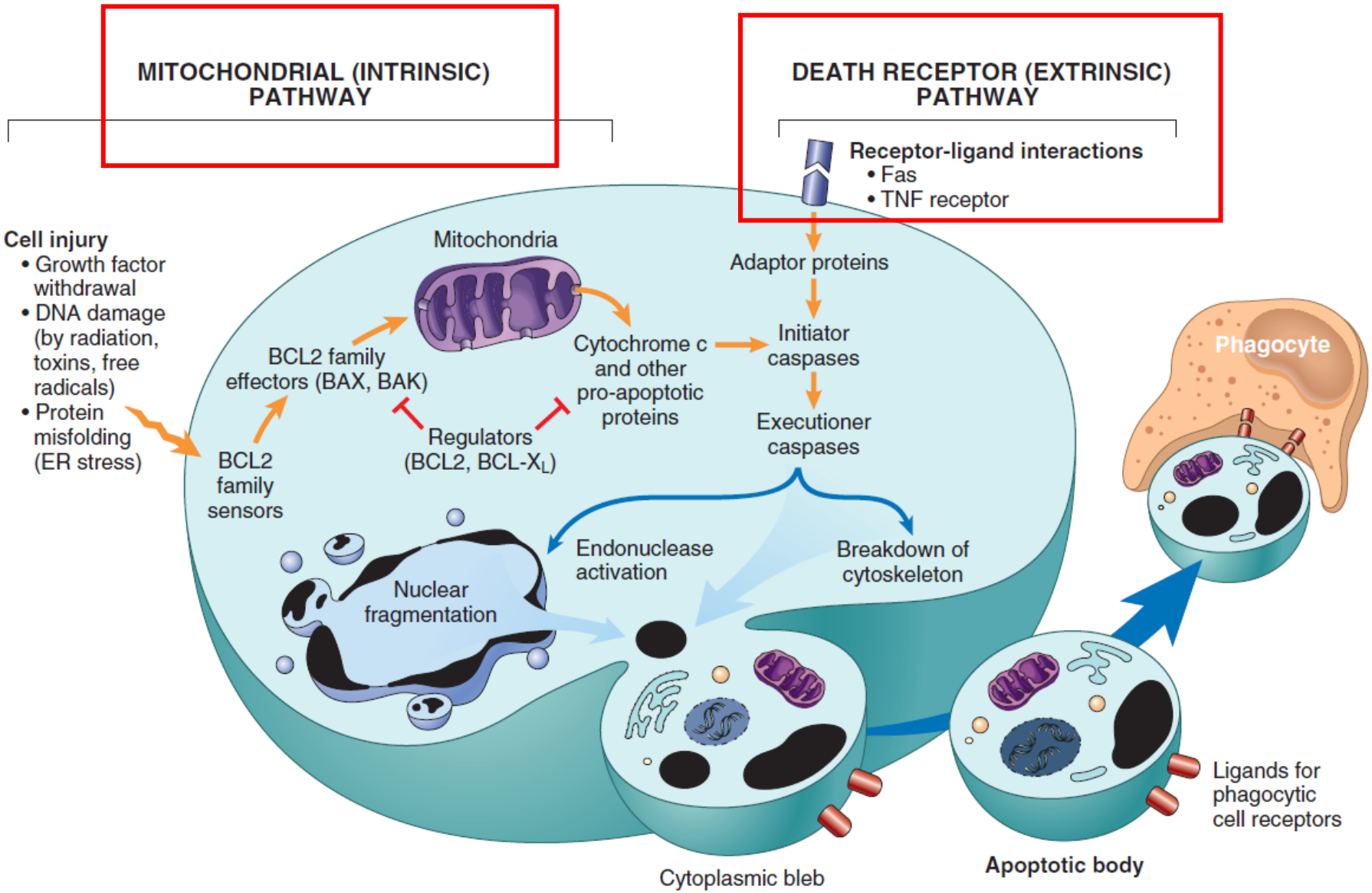

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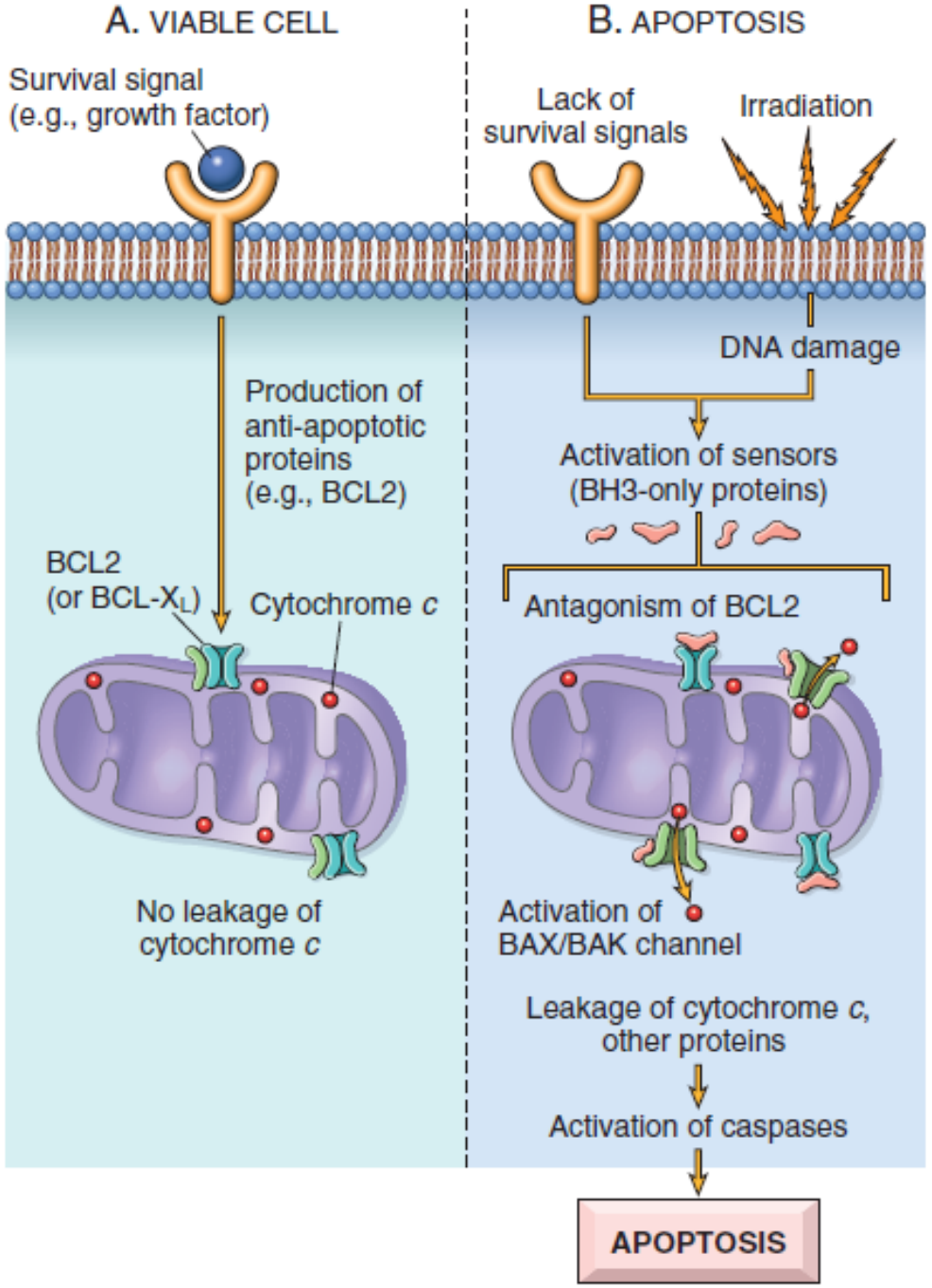

Intrinsic pathway

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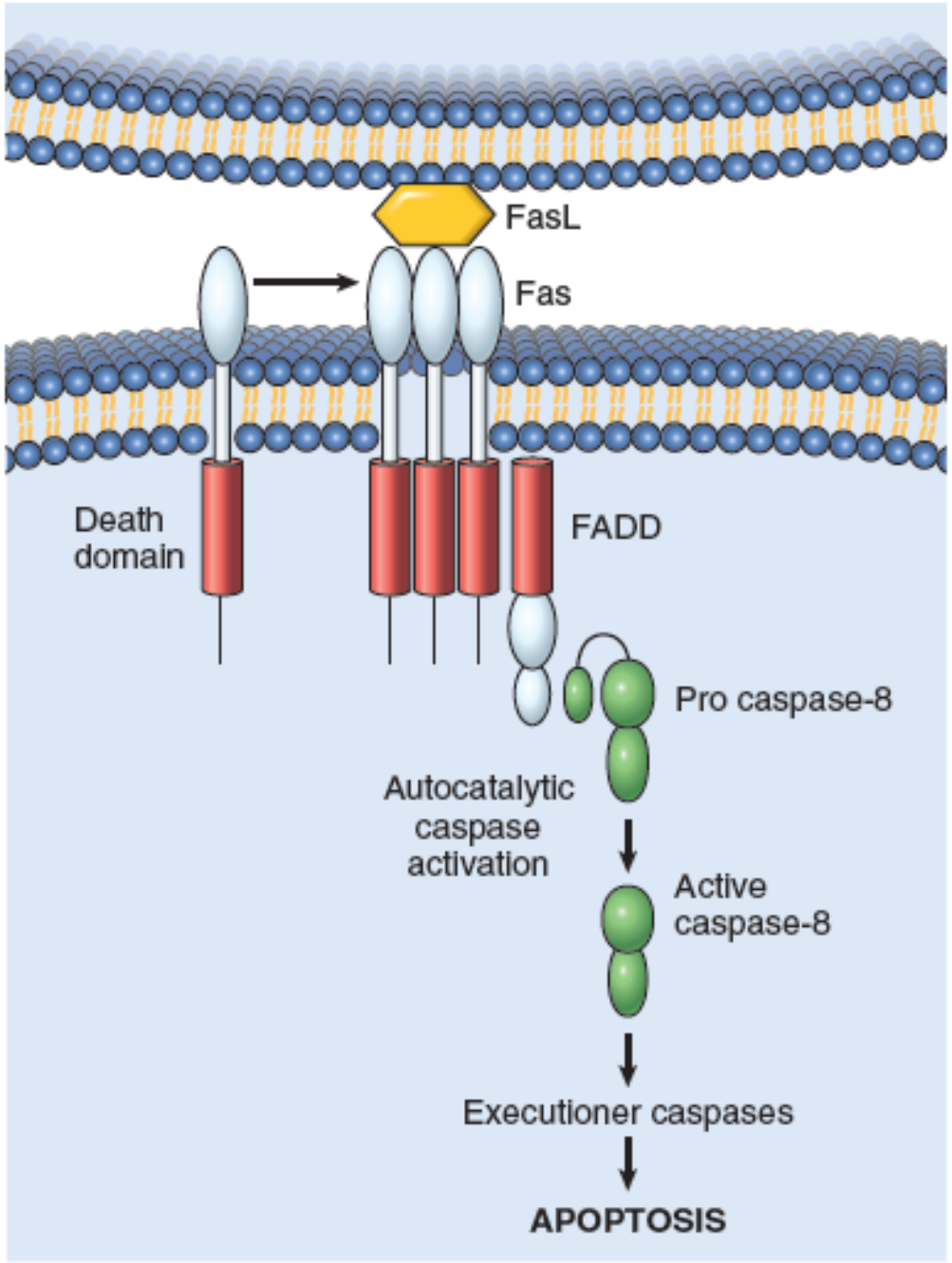

Extrinsic pathway

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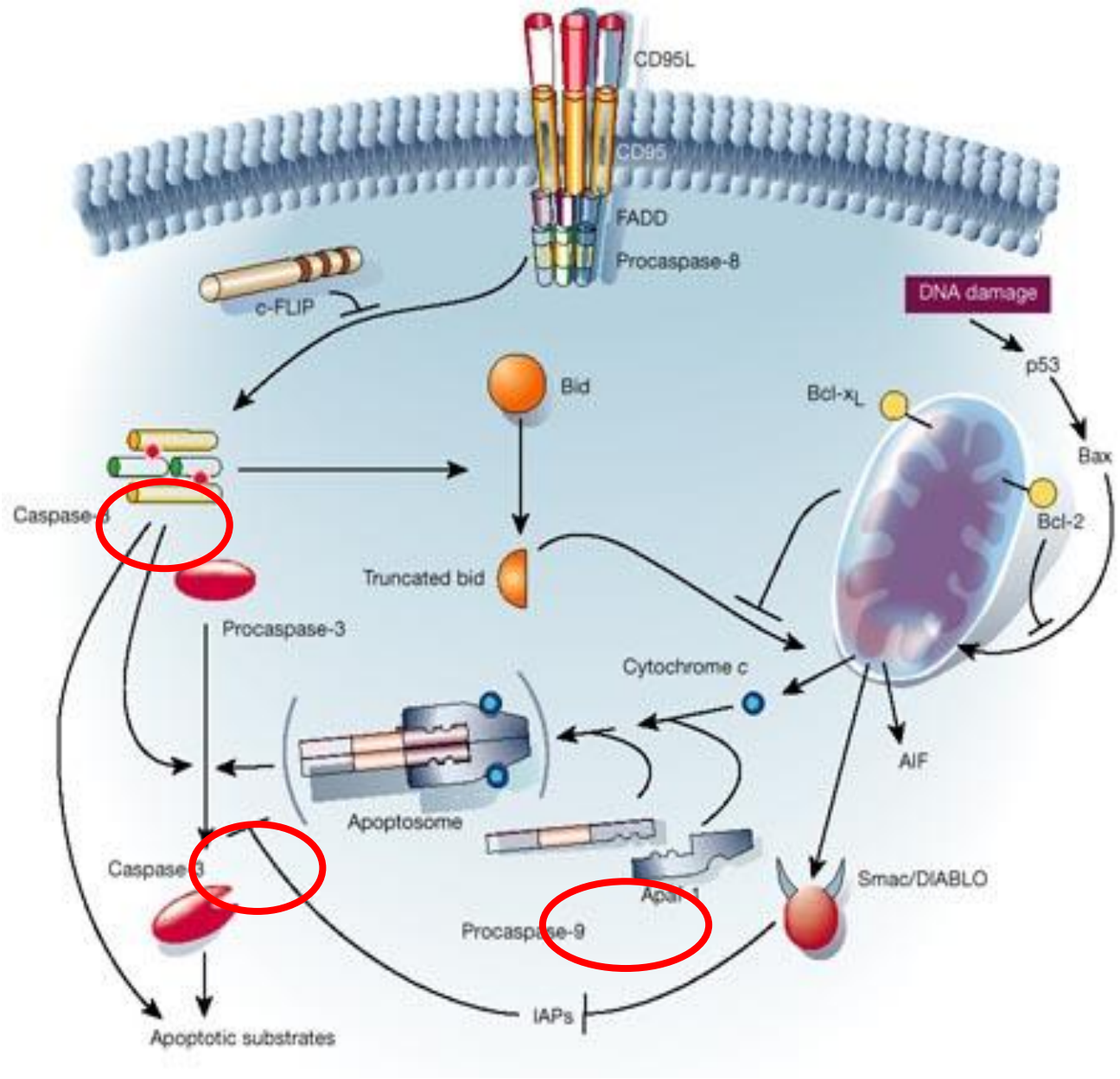
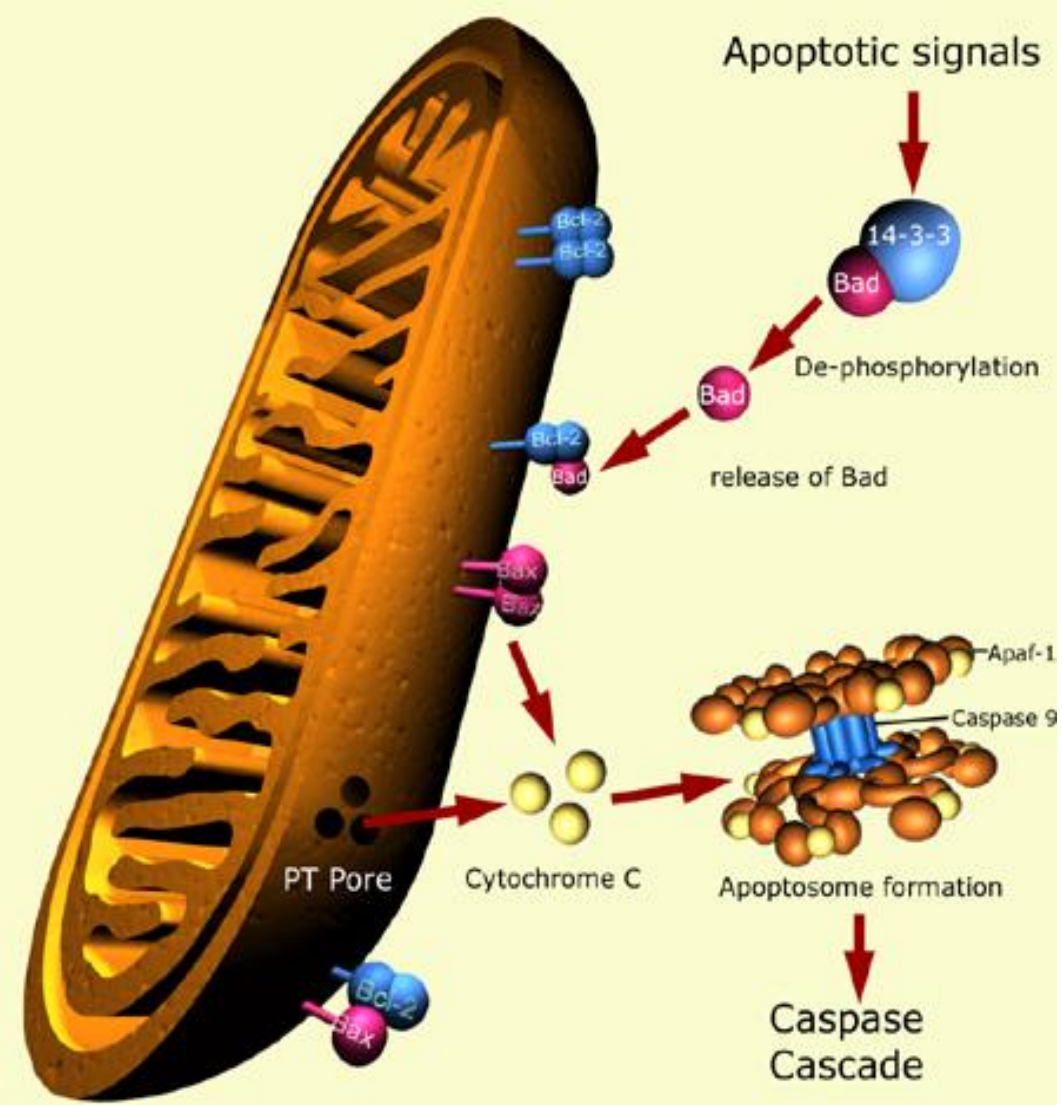
Two pathways



- Death receptor (left)
- Mitochondrial (right)
- Intrinsic pathway- Caspase 9
- Extrinsic pathway- Caspase 8
- **Both Converge**
  - **Caspase 3 activation**
- Then branch causing eventual cell death

Role of mitochondria in apoptosis



Disrupts the normal function of the **anti-apoptotic bcl-2 proteins**/Activation of **pro-apoptotic proteins BAX**

↓

the formation of pores in the mitochondria

↓

the release of cytochrome C and other pro-apoptotic molecules

+ Apaf-1

↓

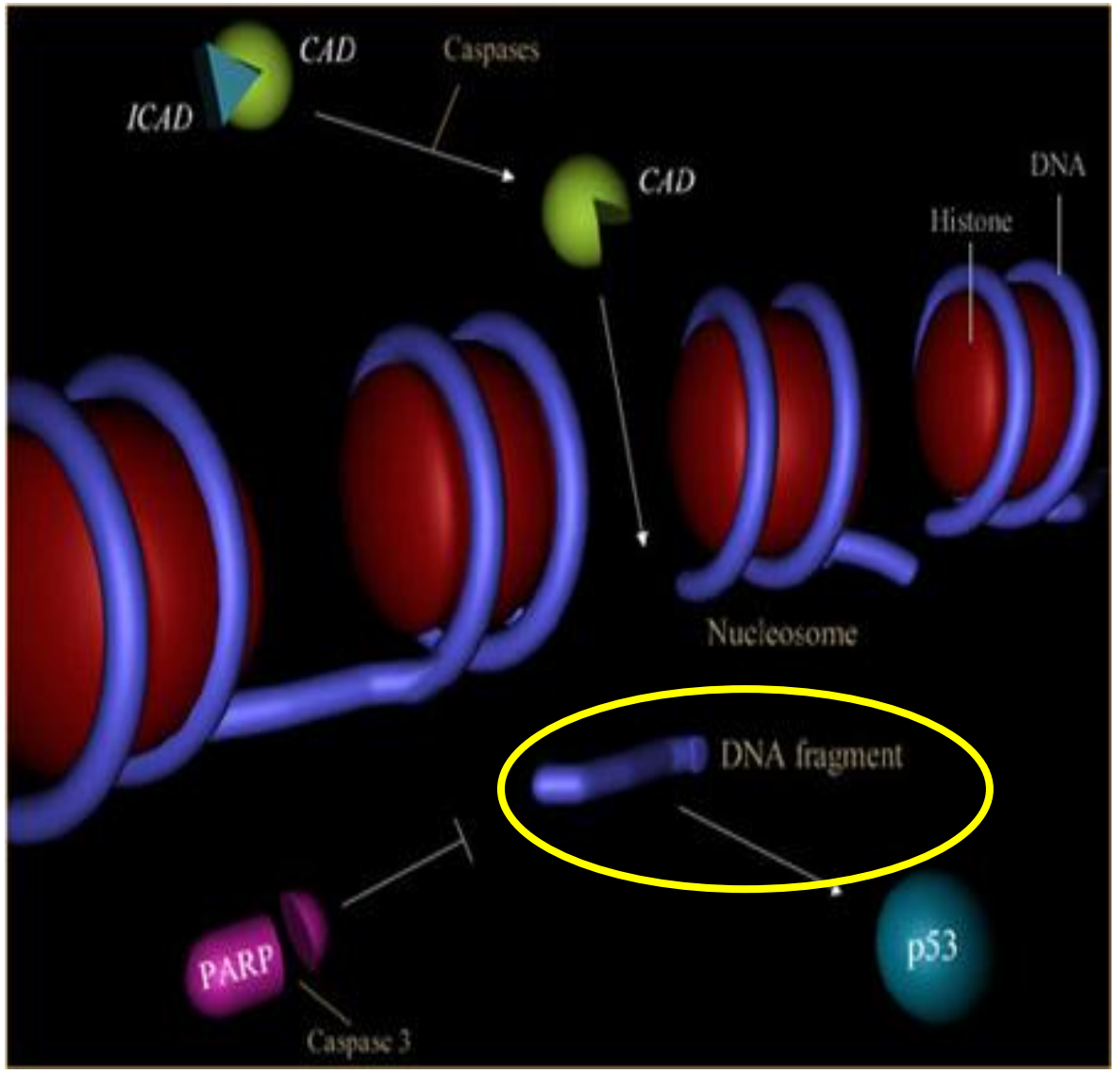
Apoptosome

↓

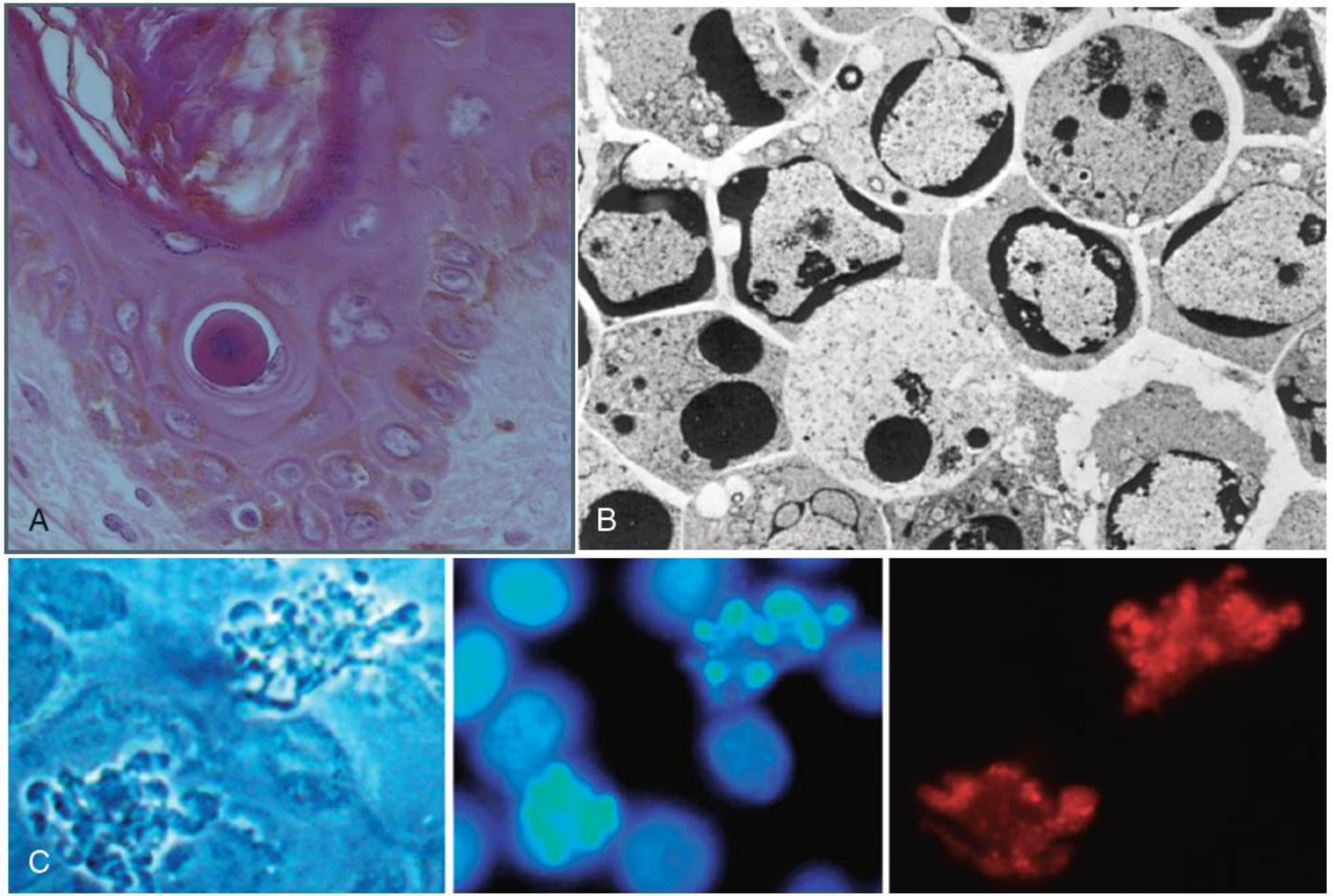
Activation of the caspase cascade

Caspases and Apoptosis

- The hallmarks of apoptosis is the cleavage of chromosomal DNA into nucleosomal units
- The caspases play an important role in this process by activating DNases, inhibiting DNA repair enzymes, breaking down structural proteins in the nucleus



Apoptotic cell



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Autophagy

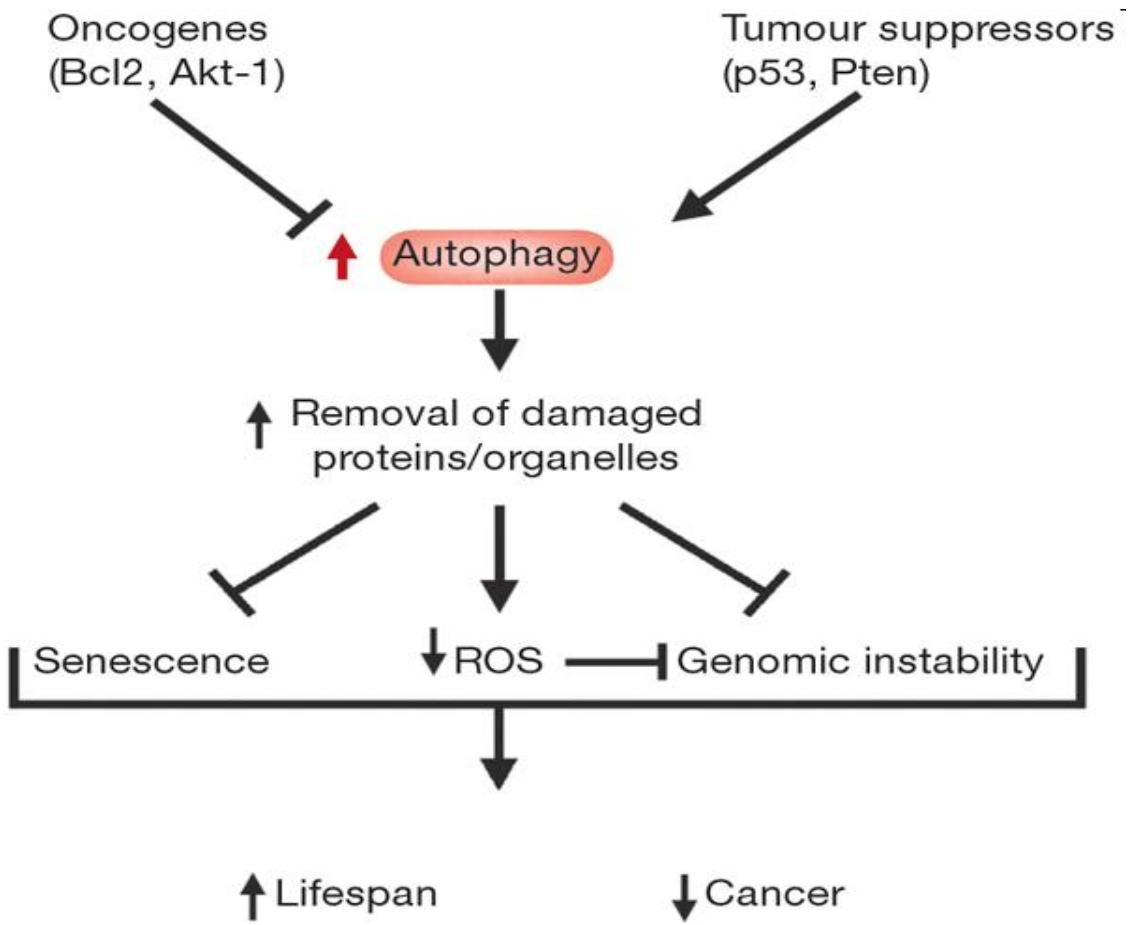
- A regulated process for the removal of damaged proteins and organelles.
- Stimulated by environmental factors such as starvation
- The removal of damaged cellular components, especially damaged mitochondria, might decrease the level of reactive oxygen species (ROS)

↓

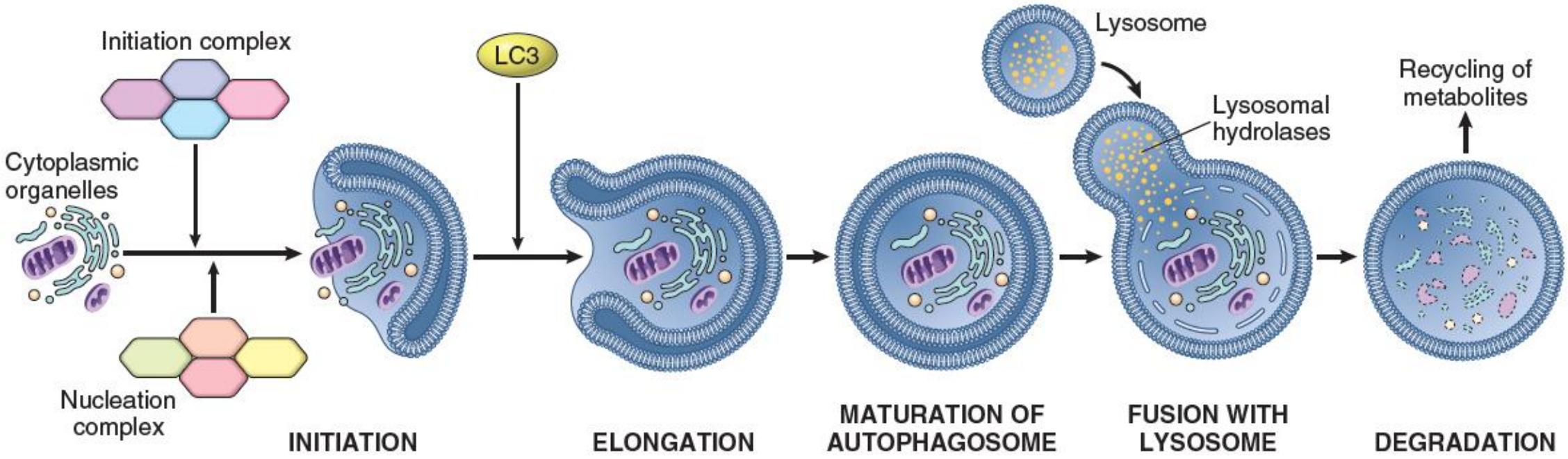
reduce genomic instability or forestall cellular senescence

↓

reduce the incidence of cancer and prolong lifespan



Autophagy



- Formation of a double membrane within the cell which envelops the materials to be degraded into a vesicle called an **autophagosome**.
- The autophagosome then fuses with a lysosome forming an **autolysosome** whose hydrolytic enzymes degrade the materials.

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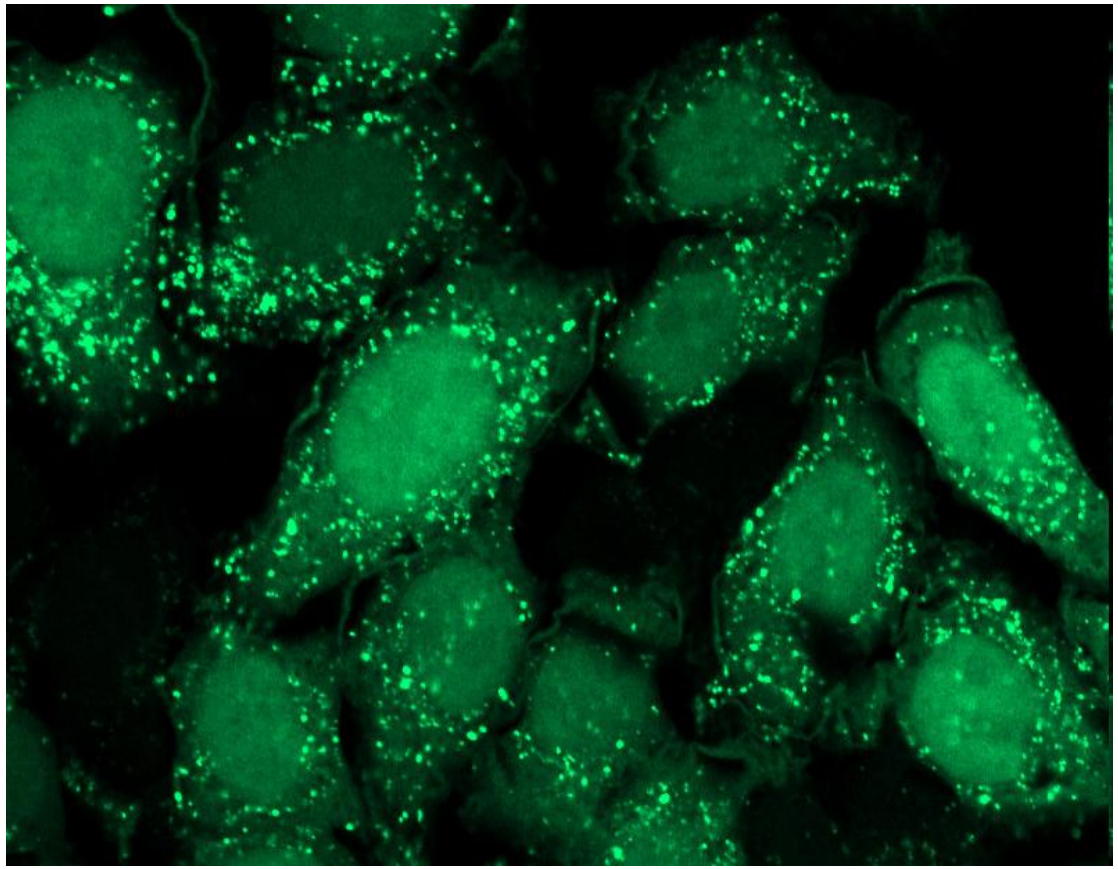


- The confocal microscopy image shows stable HeLa cells expressing **EGFP-LC3.**
- An autophagy-inducing small molecule increases the formation of **autophagosomes (green punctate structures)** in these cells.

Sarkar *et al.* Nature Chemical Biology 3(6):331-338 (2007).

Types of Cell Death

2. Necrosis

➢ The most common pattern of cell death

➢ Two principal processes influence the changes of necrosis:

1-Enzymatic digestion of the cell

2-Denaturation of proteins

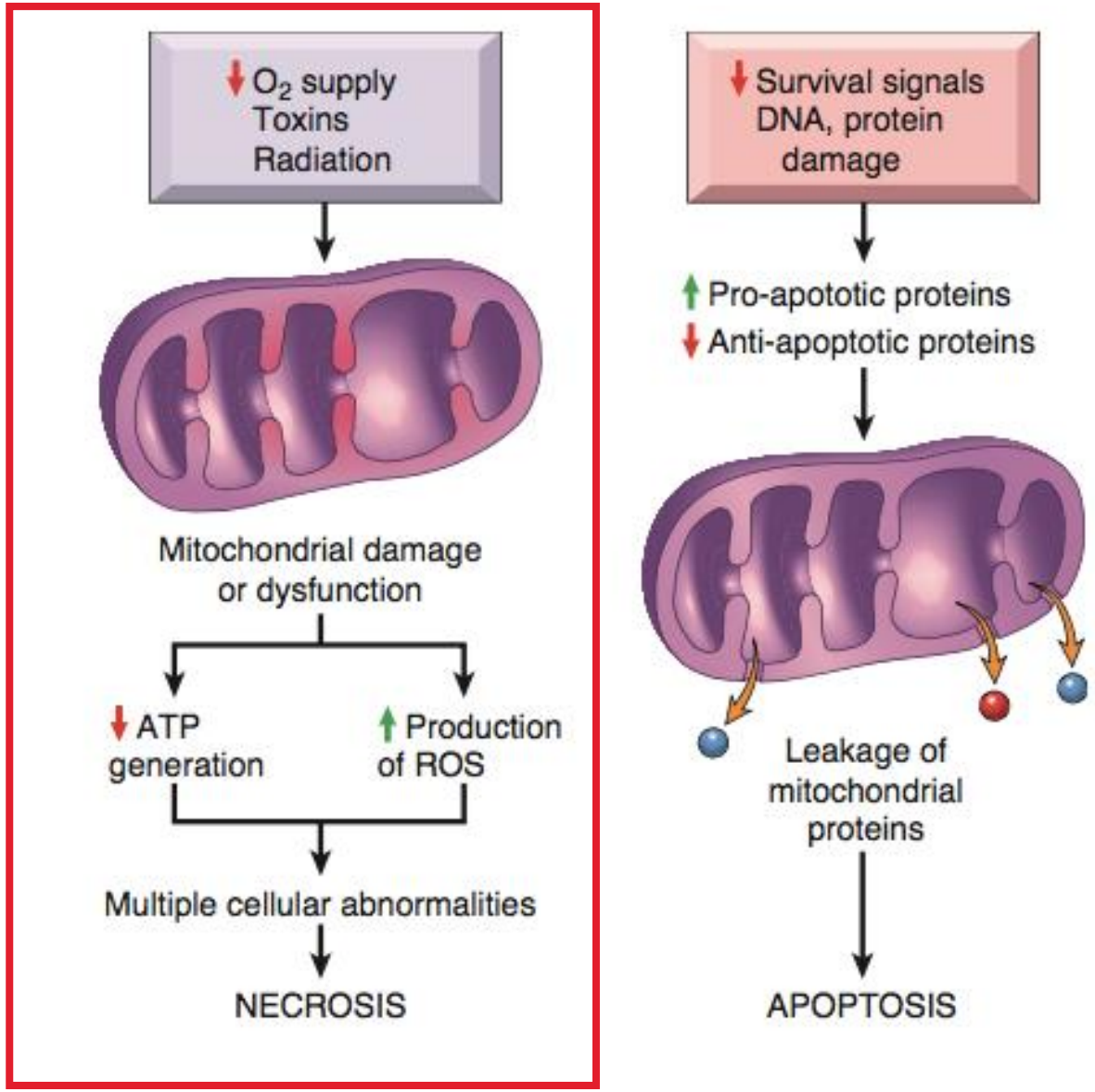
➢ These enzymes are derived either from dying cells themselves= ***autolysis***

➢ Lysosomal enzymes of leukocytes, referred to as= ***heterolysis***

➢ Causes of necrosis:

Mechanical
Chemical
Physical
Infectious agents
Hypoxia/anoxia
Ischemia

Mechanisms of Cell Death



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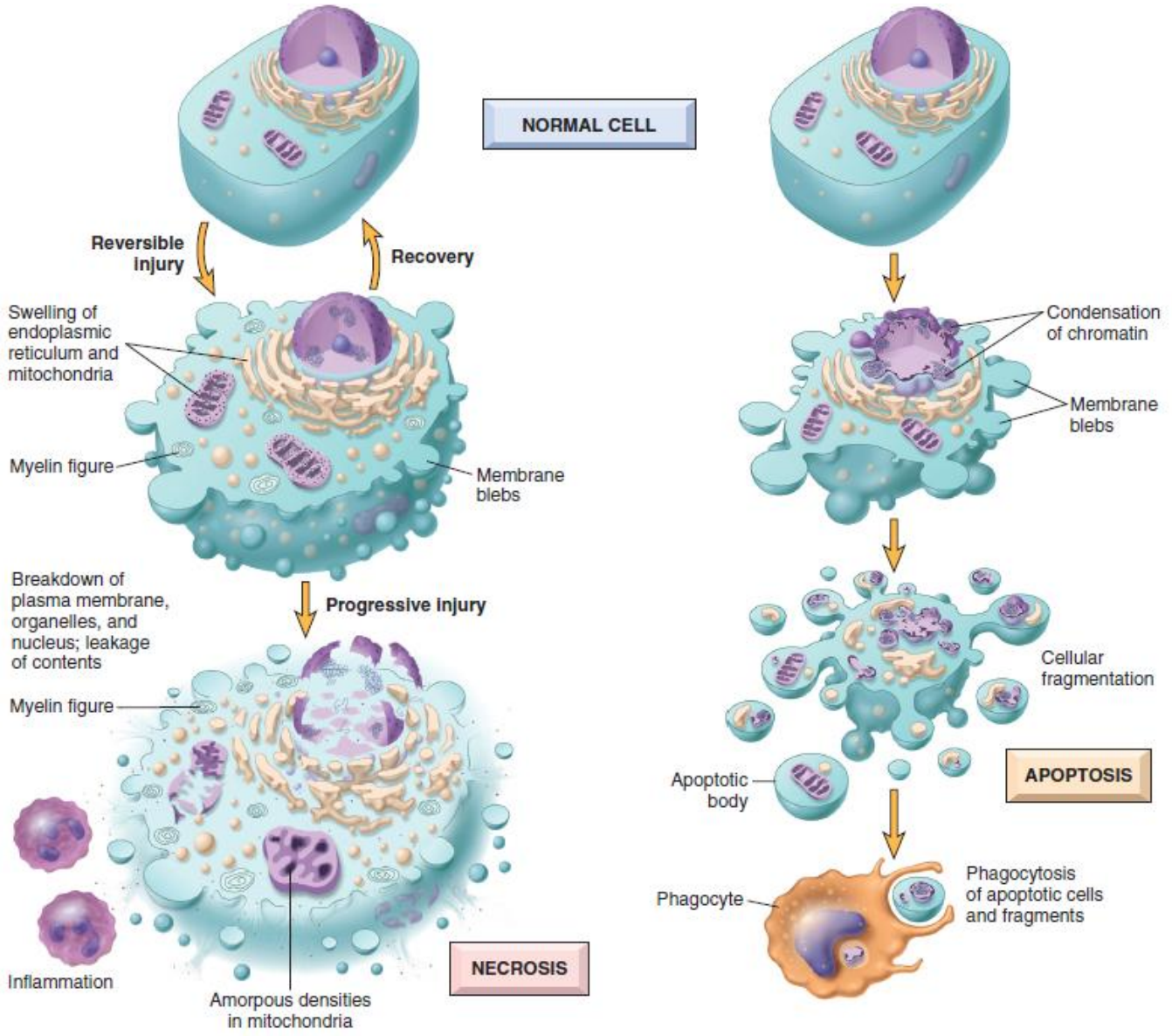
Features of Cell Death



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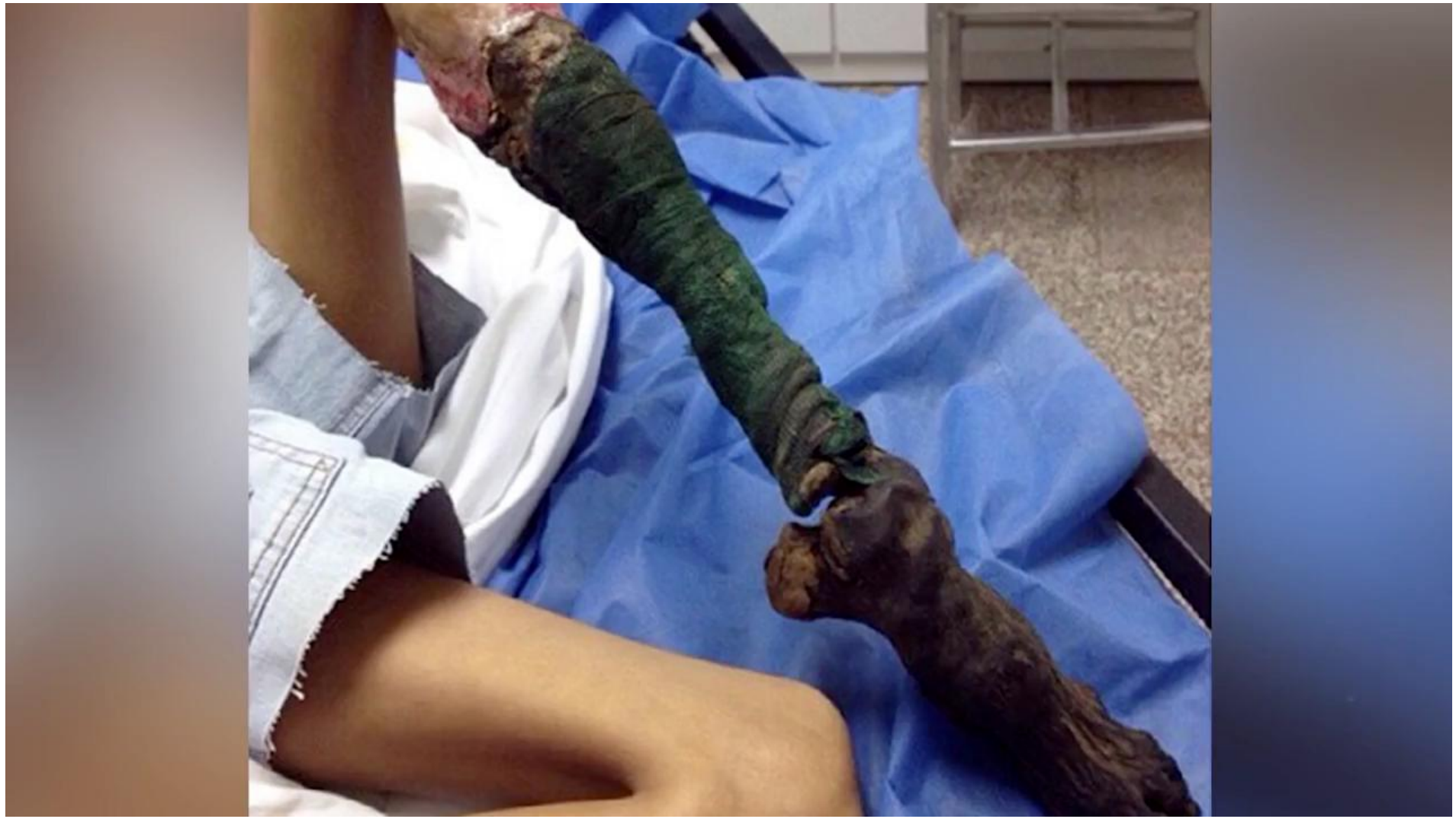
Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation (round nucleosome)
Plasma membrane	Disrupted	Intact
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Pathologic	Physiologic and Pathologic

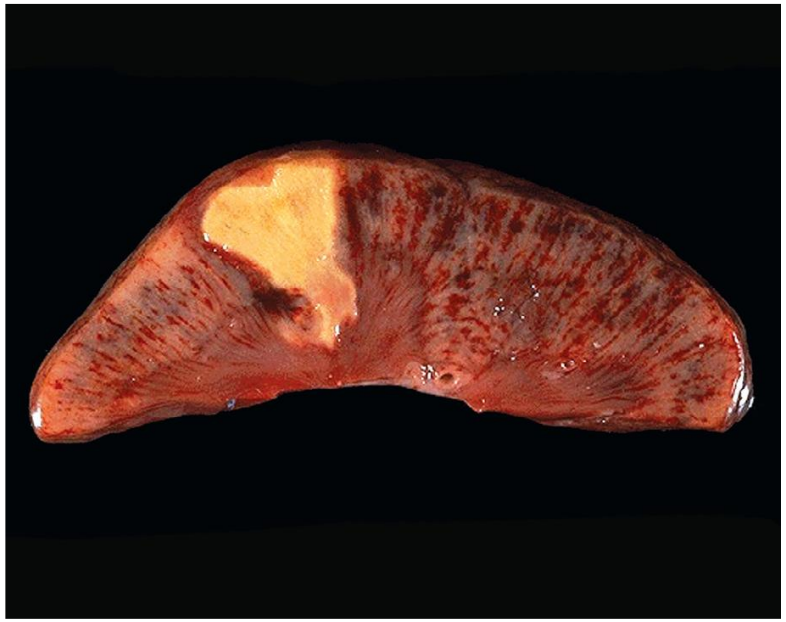


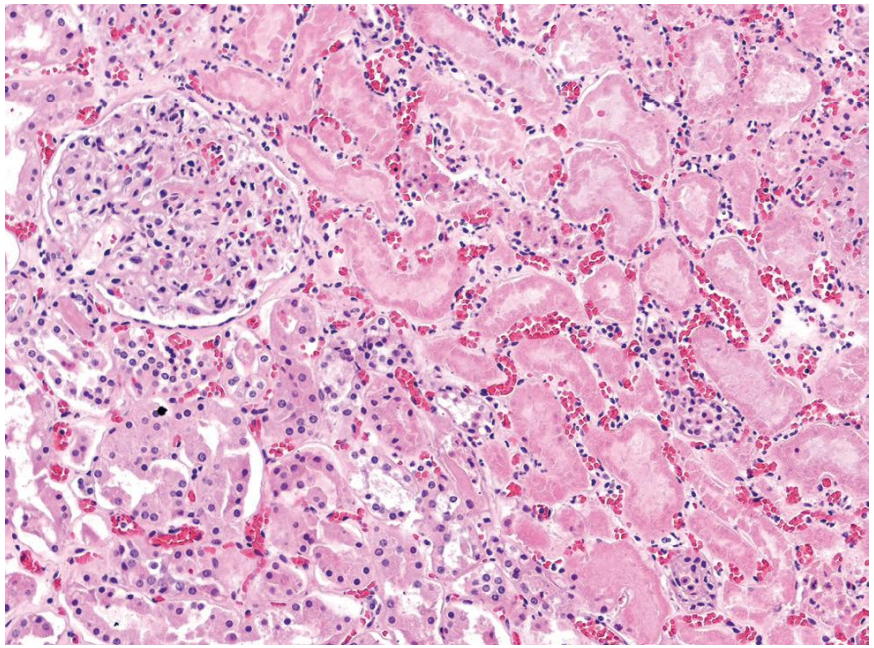
Patterns of Necrosis

- Coagulative necrosis ex. Myocardial infarction
- Liquefactive necrosis: ex. Cerebrum in fraction
- Caseous necrosis : ex. Tuberculosis lesion
- Fat necrosis : ex. Pancreatitis
- Gangrenous necrosis : ex.Necrosis of distal limbs
- Fibrinoid necrosis : ex. Polyarteritis nodosa

Coagulative necrosis

- **Most common pattern** of necrosis
- Results from sudden severe ischemia (is encountered mostly in solid organs: ex. kidney, heart, spleen, adrenal gland
- Intracellular acidosis which denatured structural proteins and enzymes
- Macroscopic appearance: consistency, yellowish colour, dry appearance
- Microscopic appearance : **Preservation of cell outlines**, Loss of nuclei





Types of infarct

- **Red (heamorrhagic) infarct**

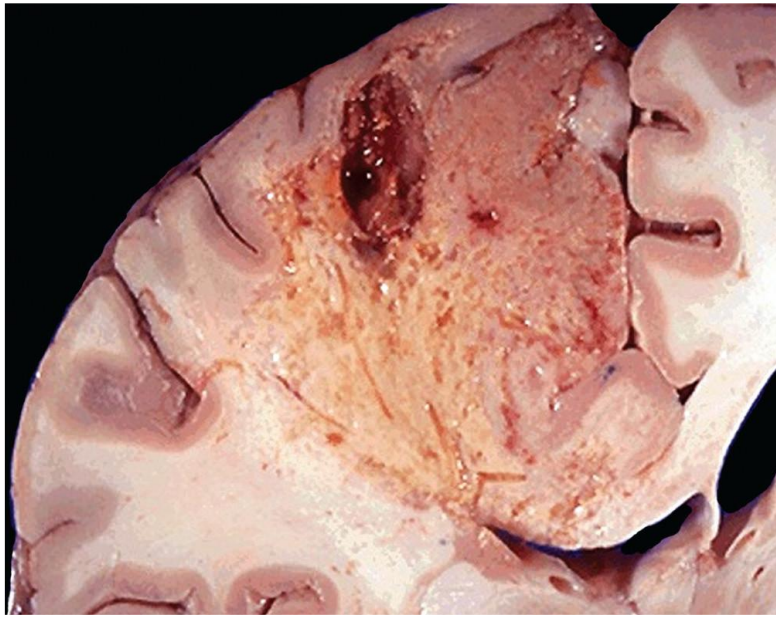
- Venous occlusion/ congestion ex. torsion
- Loose tissue where hemorrhage can occur and blood can collect ex. Lung
- Tissues with dual blood supply ex. Lung, small intestine
- When flow is re-established ex. Angioplasty

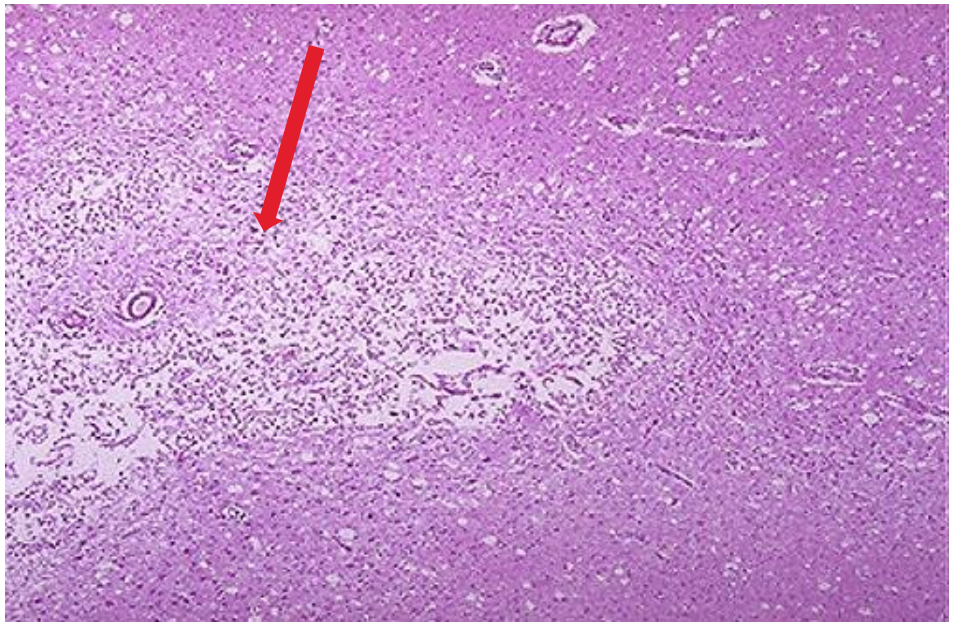
- **White infarct**

- Arterial occlusion
- Solid tissue where hemorrhage limited
- Tissues with single blood supply ex. Kidney, spleen, heart, retina, brain, liver

Liquefactive necrosis

- The dead cells undergo disintegration and affected tissue is liquefied
- Rapid action of hydrolytic enzymes
- Characteristic of **ischemic necrosis of brain, pancreas** also common in bacterial lesions
- **Gross morphology-** necrotic area becomes very soft and fluidly
- **Microscopic** –Loss of architecture ,cystic space

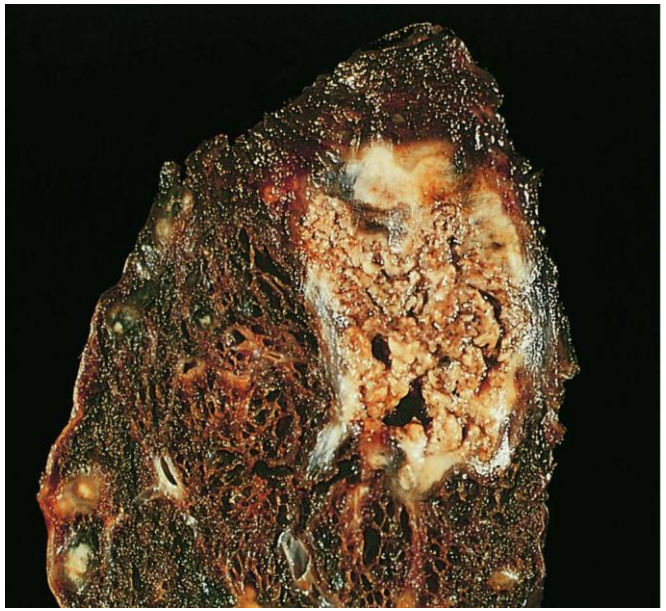


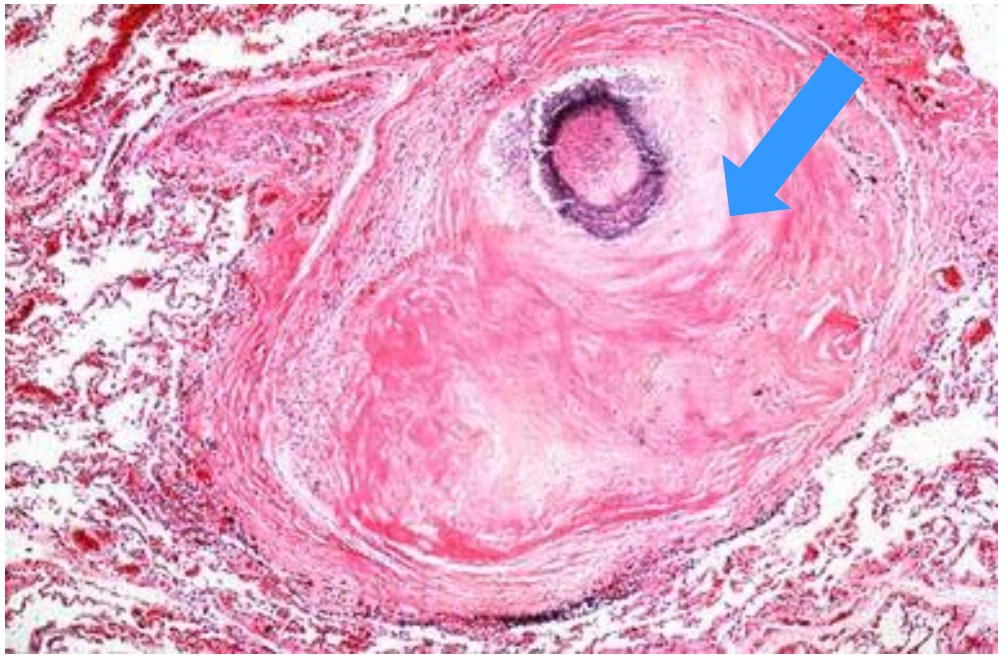


http://library.med.utah.edu

Caseous necrosis

- Combination of coagulative and liquefactive necrosis
- Cheese-like lesion
- Common in tuberculousis
- **Gross morphology:** caseous necrosis appears grossly as soft, friable, whitish-gray debris
- **Microscopic:** caseous necrosis appears as amorphous eosinophilic material,cell debris





Fat necrosis

➢ **Two type :**

-**Traumatic fat necrosis** : Following severe injury tissue with high fat content ex. Breast

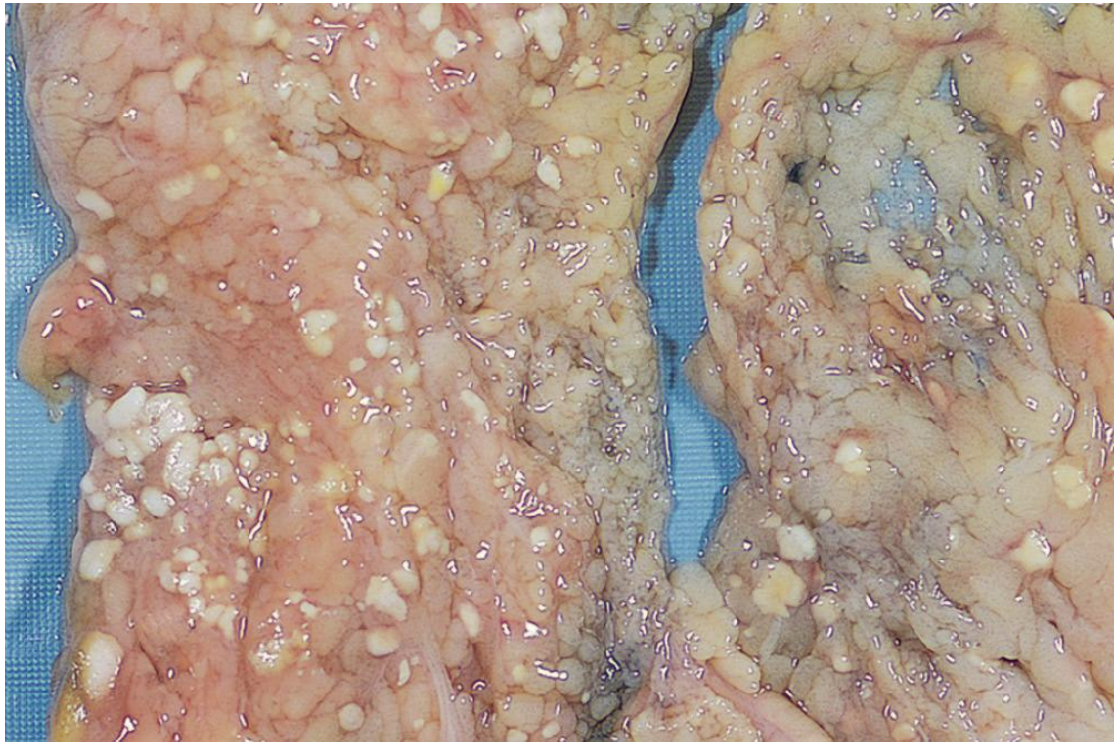
- **Enzymatic fat necrosis :**

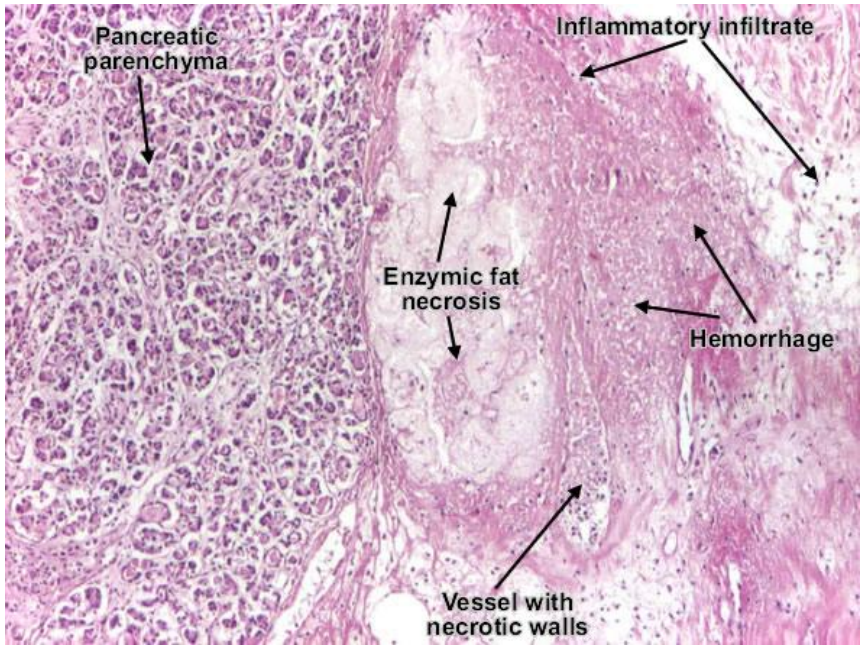
Necrosis in adipose tissue due to *action of activated lipases* ex. *acute pancreatic necrosis* by pancreatic enzymes (proteolytic and lipolytic)

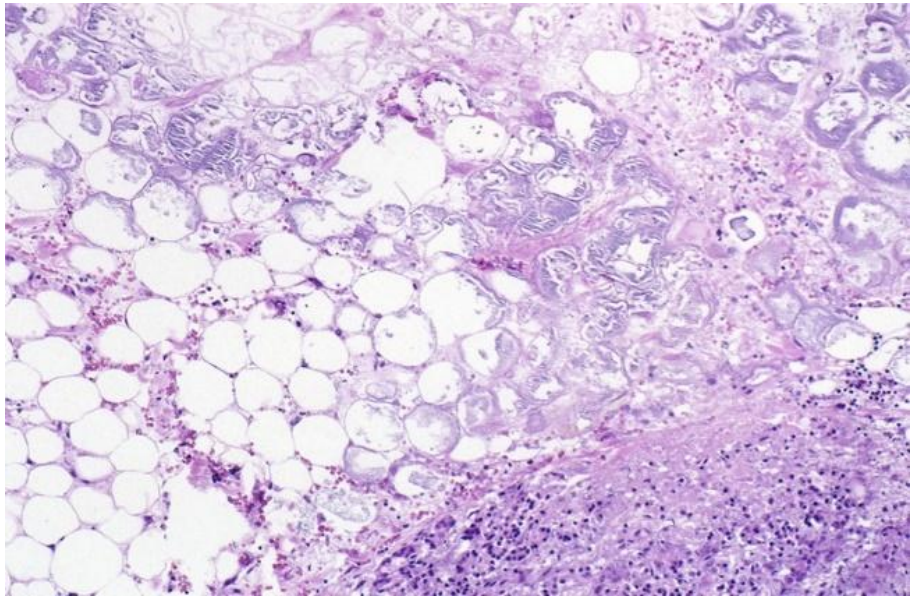
Fatty acids then complex with calcium to create calcium soaps (saponification)

- Gross morphology :opaque and chalky white or yellowish
- Microscopic: ghost cells anucleate cells composed of amorphous granular debris, calcification

Fat necrosis







Gangrenous necrosis

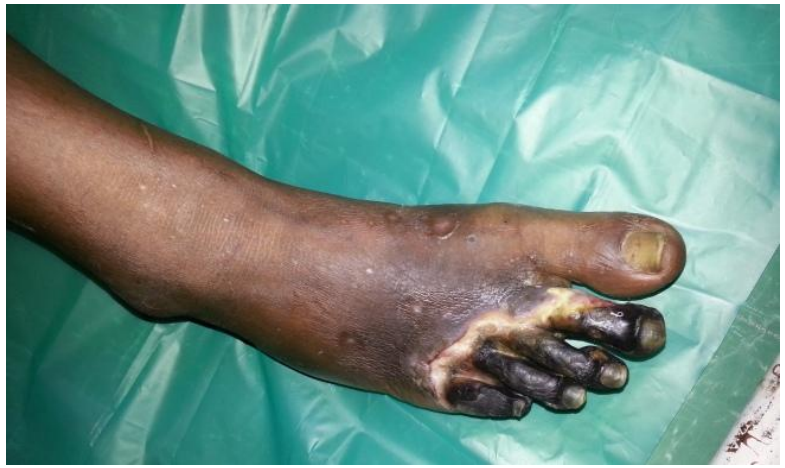
- Necrosis (secondary to ischemia) usually with superimposed infection
- There are three major types of gangrene:

Dry gangrene>> necrotic tissue appears black and dry , occurs in extremities

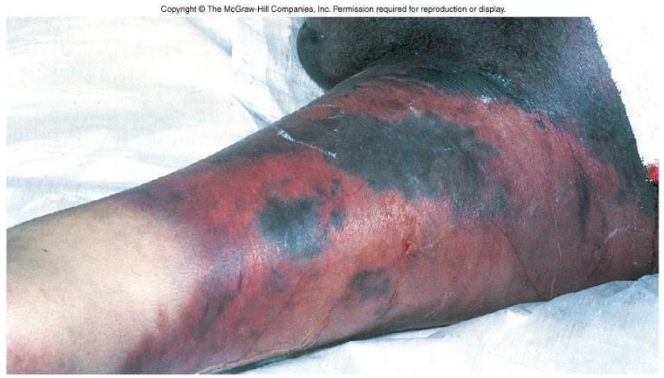
Wet gangrene>> severe bacterial inection, extremities and internal organs, tissue swollen, reddish-black

Gas gangrene>> wound infection caused by *Clostridium perfringens*, tissue destruction , gas production by fermentative action of bacteria

****crepitus-** a sound that can be detected by palpation of necrotic tissues**



Pic from V.G.R diabetes



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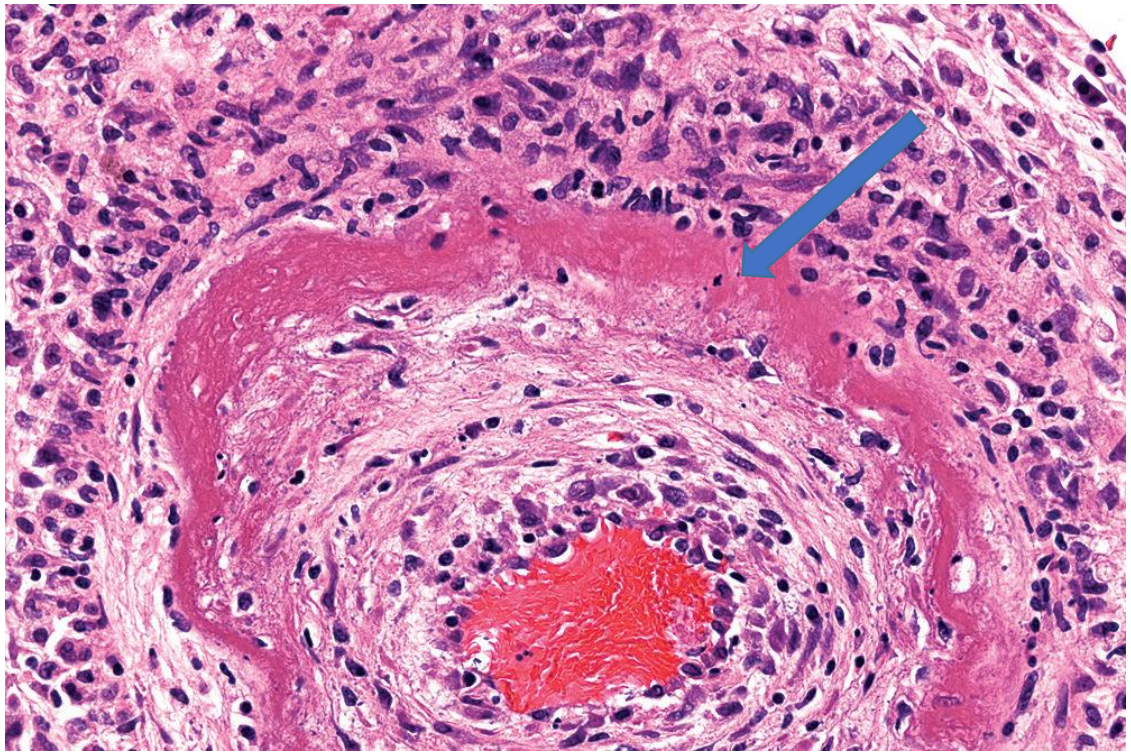
Fibrinoid necrosis

- Usually in immune reactions complexes are deposited in the wall of arteries
- Connective tissue necrosis
- Ag-Ab complex deposit in arterial wall
- Loss of normal structure of collagen fiber
- Circumferential bright pink area of necrosis with protein deposit and inflammation



Polyarteritis nodosa

Other Mechanisms of Cell Death

- **Necroptosis**

  - resembles necrosis morphologically

  - like apoptosis is a genetically controlled form of cell death

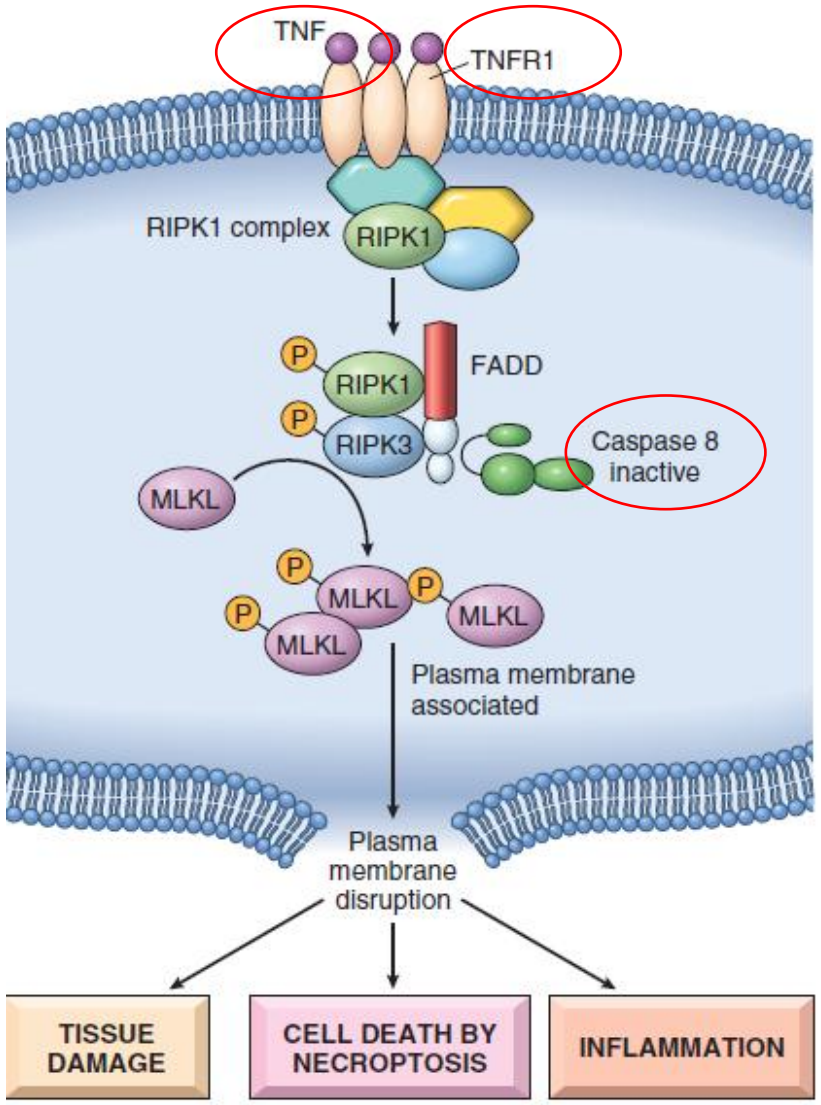
- **Pyroptosis**

  - occurs in cells infected by microbes

  - Activated caspase-1, which cleaves the precursor form of IL-1

- **Ferroptosis**

  - iron-dependent pathway of cell death induced by lipid peroxidation

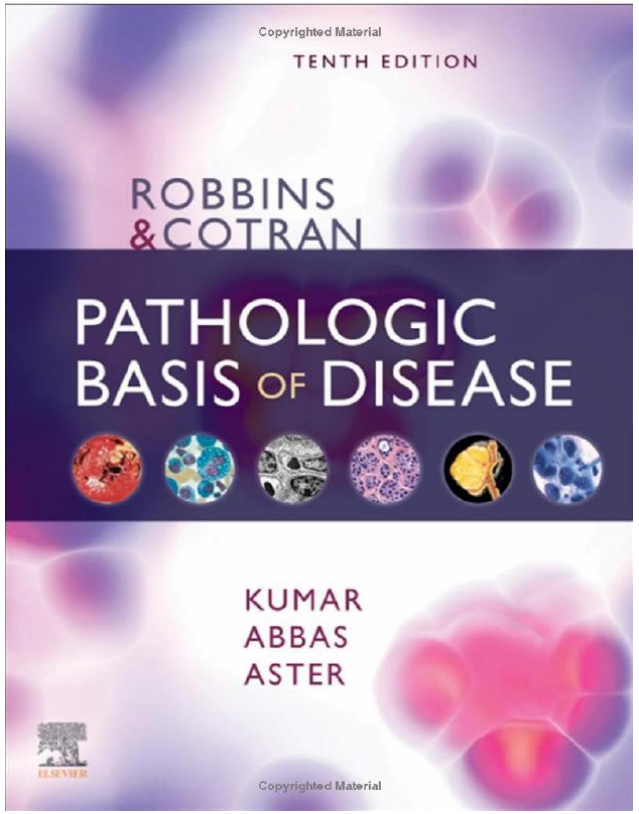


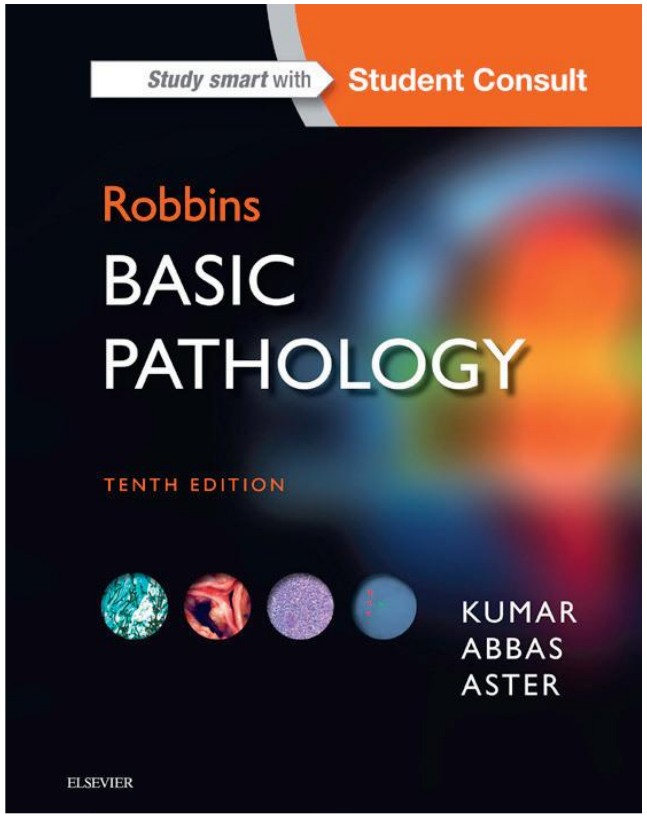
Necroptosis (programmed necrosis)

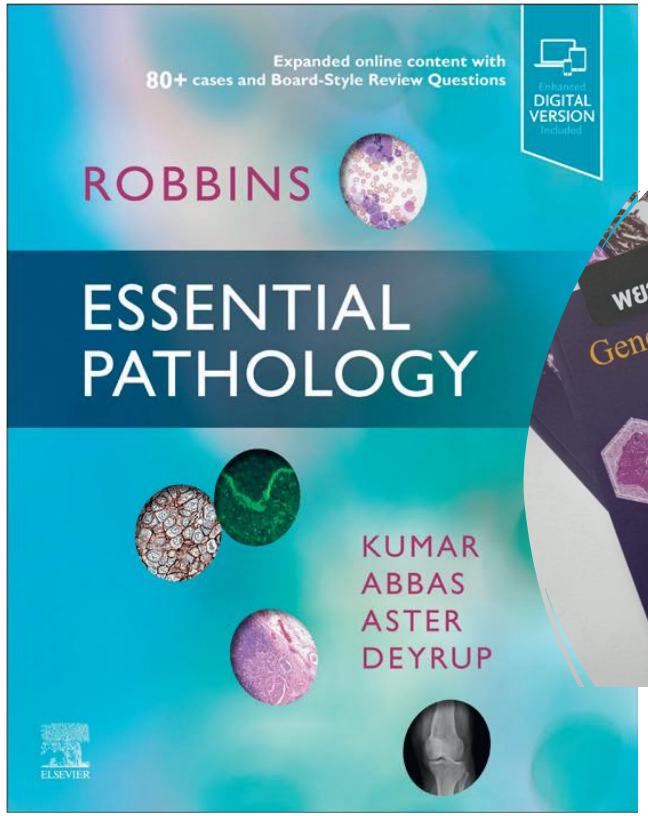
Any Questions?

References

1. Robbins and Cotran Pathologic Basis of Disease, 10th edition
2. Robbins Basic Pathology , 10th edition
3. Robbins Essential Pathology, 10th edition







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