What is pathology ?

is a science that study diseases by scientific methods at cellular and tissue levels .

In other words study the structural and functional changes that occur in diseases.

- **Disease** is the individual's reaction to **injury** and its effect on organs , tissues and body fluids.

- **Injury** is a stimulus that alters / disrupts normal anatomic or physiologic homeostasis. **(vs hemostasis)**

Homeostasis i.e. the balanced normal condition of the body

- The effect is recognized by structural and functional changes .
- The result of this effect is either compensated or decompensated .

Aspects of diseases

Etiology

- cause or causes.
- If unknown…idiopathic or primary.

Pathogenesis (mechanism of disease)

- A logical stages in evolution of the disease. The effect is recognized by structural and functional changes (pathophysiology).

Morphological (structural) changes

- Ultra structure (electronic microscope)
- Histological, Microscopical, Histopathological (light microscope)
- Gross, Macroscopical, Naked-eye

Functional consequences

- Signs & Symptoms

Pathology course:

General pathology :

deals with the basic cellular and tissue reaction to various injurious agents.

Systemic pathology :

studying diseases by systems, applying the general principles studied in general pathology.

practical aspects:

includes identification of gross, histological and sometimes ultra structural changes in diseases.

Aims of studying pathology

1. **Disease prevention.**

2. **Successful therapy.**

Study smart with Student Consult

KUMAR
ABBAS
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Robbins BASIC PATHOLOGY

NINTH EDITION

International Edition

ELSEVIER

Cellular injury, Cell death, & Adaptations

Adaptations

The cells are able to handle normal **(physiological)** and sometimes, abnormal **(pathological)** demands without get injured; to achieve this, a number of changes inside the cells occur that eventually lead to a new but altered steady state. These induced changes are referred to as **adaptations.**

The aim of adaptations is to preserve cell viability i.e. prevent cell injury.

If the limits of adaptive capability of the cells are exceeded (persistence of the injurious agent), or when no adaptive response is possible (sudden severe injurious agent that leaves no time for adaptive responses to take place), a sequence of events follows that are collectively known as **Cell injury.**

Cell injury

Cell injury is divided into :

1. **Reversible cell injury.**

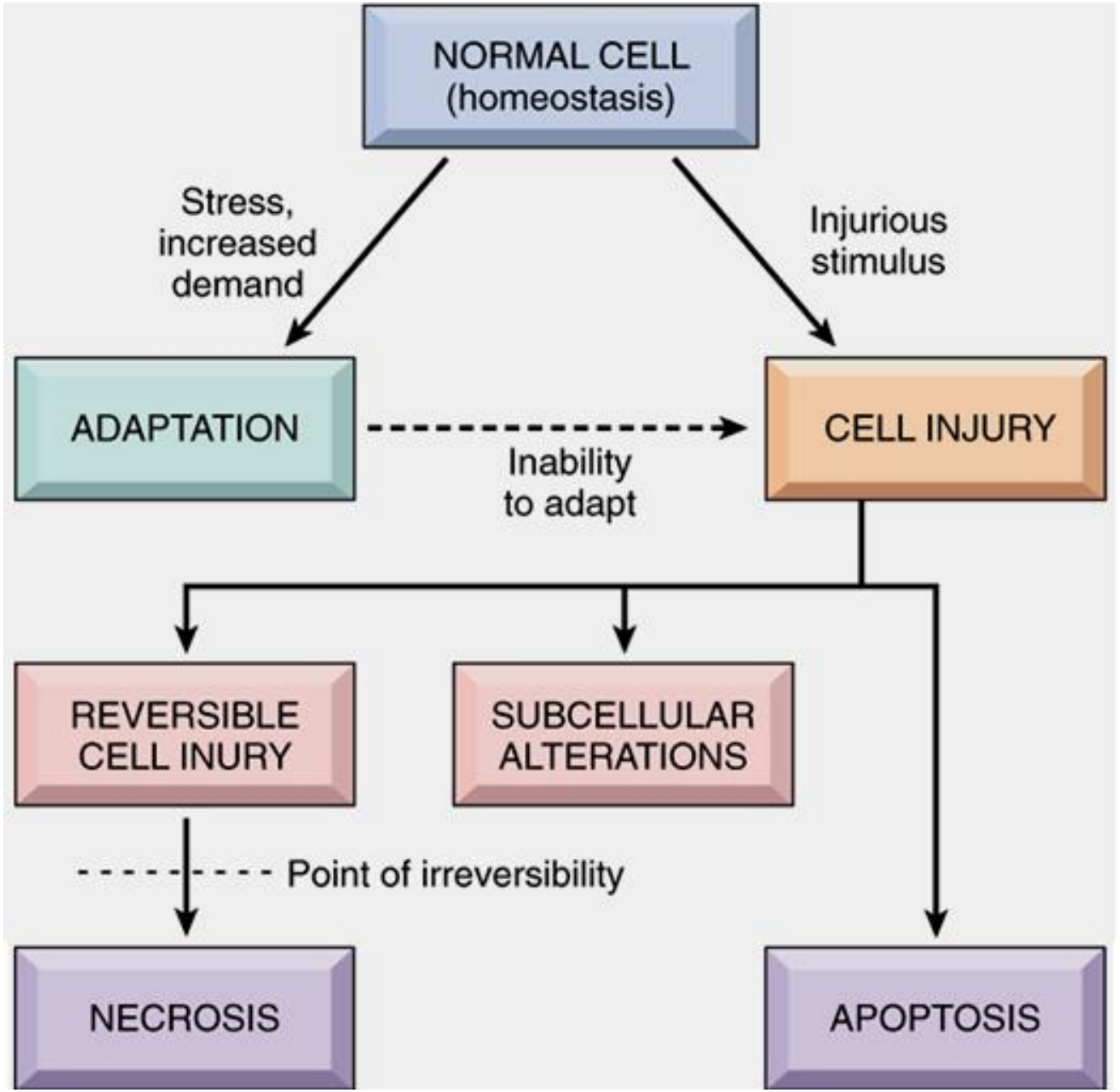
2. **Irreversible cell injury**.

1- Reversible cell injury: indicates that the changes will regress and disappear when the injurious agent is removed; the cells will return to normal, morphologically and functionally.

eg. angina pectoris (few minutes)

2- Irreversible cell injury: occurs when the injury persists or when it is so severe from the start. Cell alterations reach the point of no return and progression to cell death is inevitable.

eg. Myocardial infarction


NORMAL CELL
(homeostasis)
Stress,
increased
demand
Injurious
stimulus
ADAPTATION
Inability
to adapt
CELL INJURY
REVERSIBLE
CELL INURY
SUBCELLULAR
ALTERATIONS
Point of irreversibility
NECROSIS
APOPTOSIS

Classification of injurious agents (external & internal)

1. Hypoxia cardiac failure and / or respiratory failure , anemia

2. Physical agents. - Mechanical trauma. - Deep cold - Extreme heat - Radiation.

3. Chemical agents. - Poisons such as arsenic or cyanide - Air pollutants
- Insecticides - Drugs

4. Infectious agents. viruses, bacteria, fungi and parasites.

5. Immunological reactions. Hypersensitivity reactions, autoimmune diseases

6. Genetic derangement. hereditary diseases. Down's syndrome, sickle cell anemia.

7. Nutritional imbalances. Deficiency, Excess

Mechanisms of cell injury

Mechanisms of cell injury

Injurious agents induce cell injury through their effects on one or more of the following cellular targets :

1. Aerobic respiration.

2. Cell membranes.

3. Protein synthesis.

4. Cytoskeleton.

5. Genetic apparatus (chromosomes and their contents of genes).

The attack on one or more of the above targets is mediated by one or more of the following mechanisms :

A. ATP depletion

B. Loss of cell membranes permeability and cell membranes damage

C. Accumulation of oxygen-derived free radicals (oxidative stress)

D- Mitochondrial damage

A. ATP depletion

ATP is required for many anabolic as well as catabolic processes within the cell; these include:

1. Membrane transport

2. Protein synthesis

3. Lipid synthesis

4. Phospholipids turnover.

Normally there are two ways of ATP synthesis:

1. **Oxidative phosphorylation** of ADP to ATP within mitochondria; this occur normally, i.e. in the presence of adequate O_2 supply.

2. **Anaerobic glycolysis;** this occurs under conditions of oxygen lack (hypoxia). Glucose from the body fluids or through hydrolysis of glycogen is utilized for the production of ATP.

Depletion of ATP (frequently associated with both hypoxia and toxic chemicals) affects the following systems :

1. Reduction of the activity of plasma membrane energy- dependent sodium pump . Na^+ retention holds with it water .This eventuates in cellular edema.

2. A switch to anaerobic glycolysis:

This depletes glycogen and also results in the liberation of lactic acid and inorganic phosphates. These reduce the intracellular pH (increase cellular acidity) that interferes with the optimal activity of many cellular enzymes.

3. Increase in intracellular Ca^{++} :

Failure of the calcium pump leads to influx of Ca^{++} that has damaging effects on several cellular components.

4. Structural disruption of the protein synthetic apparatus:

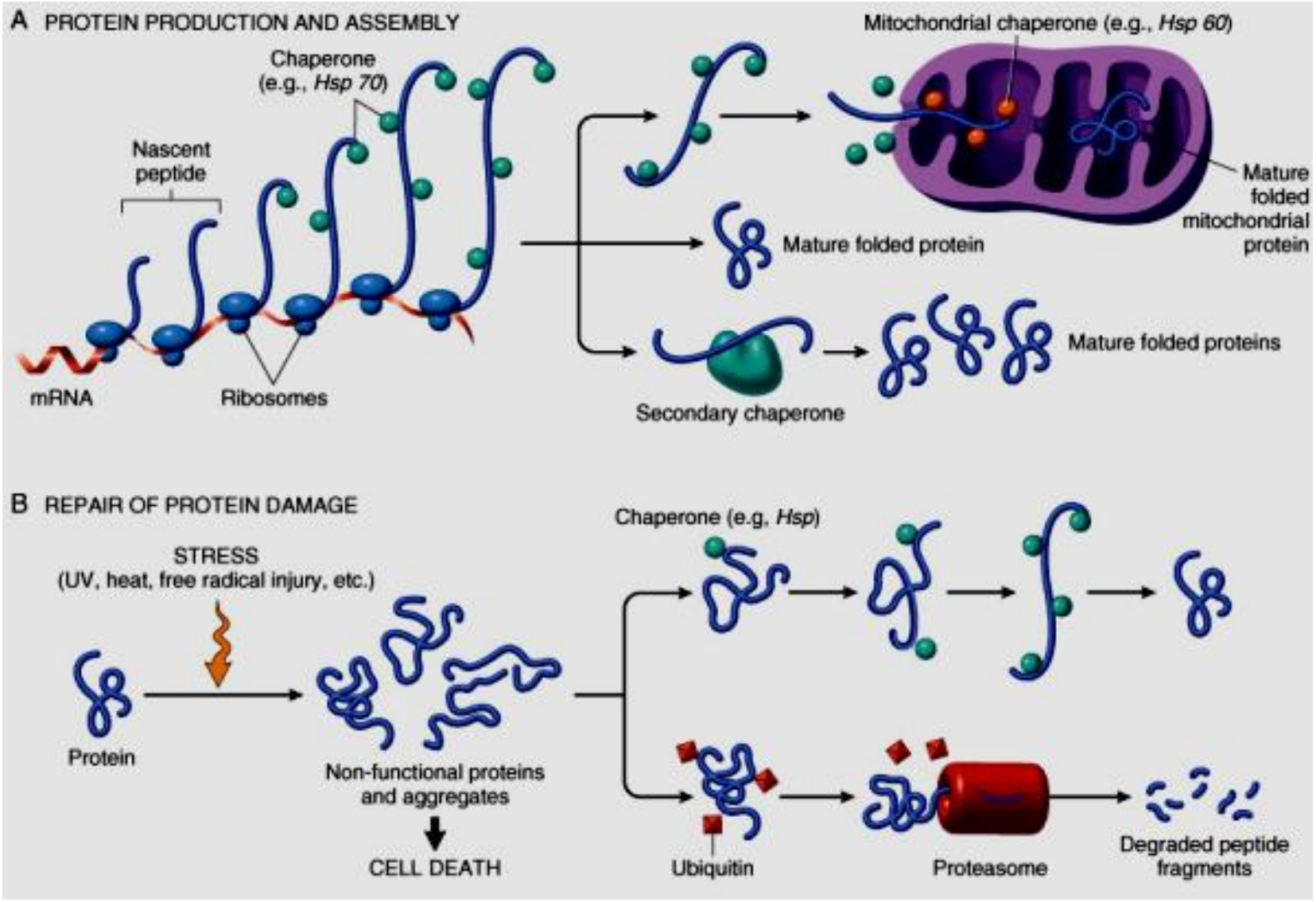
With prolonged or worsening ATP depletion, reduction in protein synthesis occurs due to :

a. Detachment of ribosomes from the rough endoplasmic reticulum.

b. Dissociation of polysomes into monosomes.

5. Unfolded protein response:

In cells deprived of O_2 or glucose, proteins may become misfolded and these trigger a cellular reaction called unfolded protein response that may lead to cell injury and even death. It also seen in cells exposed to heat and when proteins are damaged by enzymes (such as Ca^{++}-responsive enzymes) and free radicals.


A PROTEIN PRODUCTION AND ASSEMBLY
Chaperone
(e.g., Hsp 70)
Nascent
peptide
mRNA
Ribosomes
Mitochondrial chaperone (e.g., Hsp 60)
Mature
folded
mitochondrial
protein
Mature folded protein
Mature folded proteins
Secondary chaperone
B REPAIR OF PROTEIN DAMAGE
STRESS
(UV, heat, free radical injury, etc.)
Protein
Non-functional proteins
and aggregates
CELL DEATH
Chaperone (e.g, Hsp)
Ubiquitin
Proteasome
Degraded peptide
fragments

Mechanisms of protein folding and the role of chaperones

A- Chaperones, such as heat shock proteins (Hsp), protect unfolded or partially folded protein from degradation and guide proteins into organelles.

B- Chaperones repair misfolded proteins; when this process is ineffective, proteins are targeted for degradation in the proteasome, and if misfolded proteins accumulate they trigger apoptosis.

Elevation of intracellular Ca++

Sources and consequences of increased cytosolic calcium in cell injury.

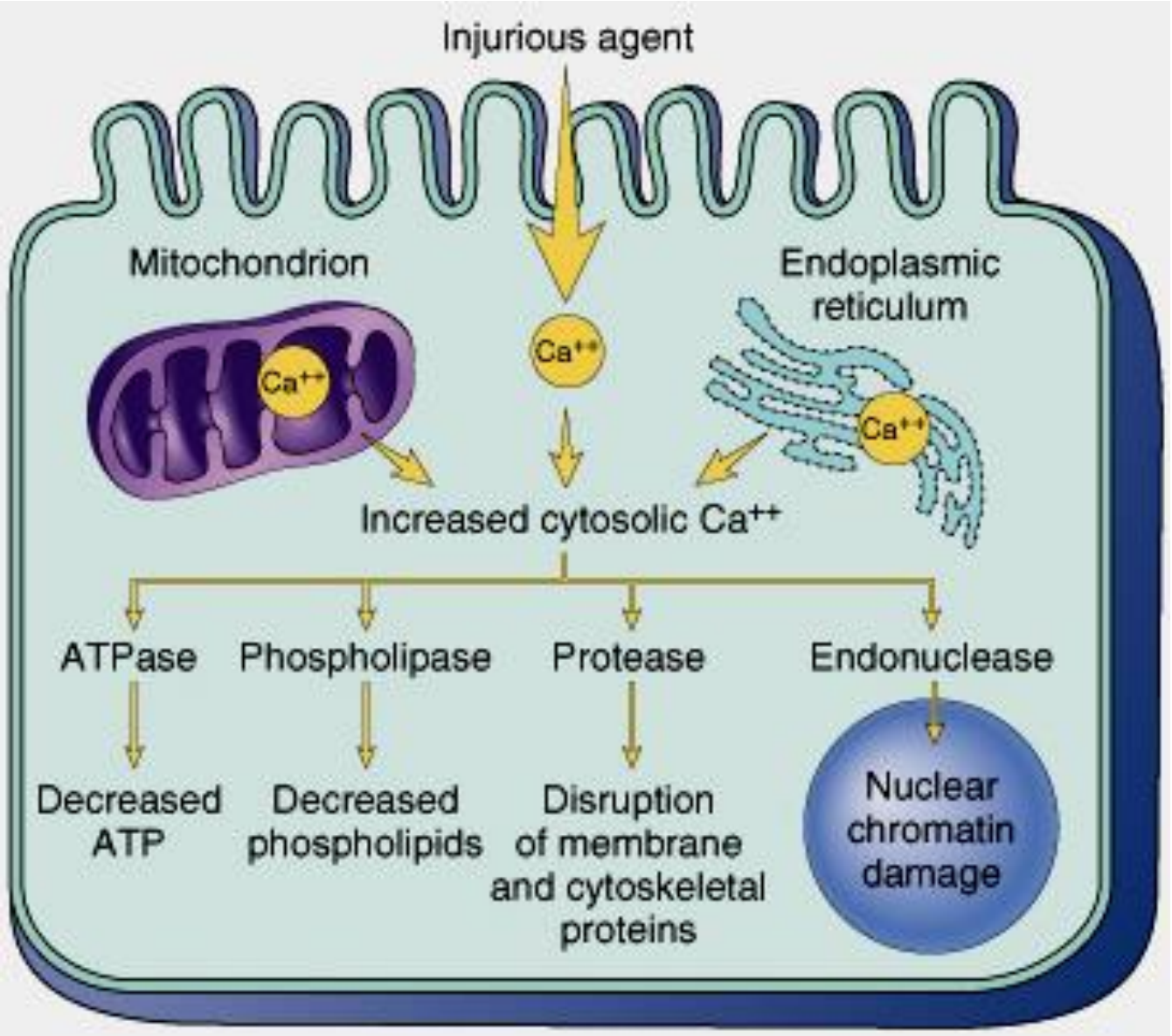
Elevation of intracellular Ca^{++} leads in turn to activation of a number of intracellular enzymes that include :

a. ATPase, which hastens ATP depletion .

b. Different degrading enzymes as phospholipases, proteinases and endonucleases .

These activated enzymes cause degradation of phospholipids (cell membranes damage), proteins (including structural cytoskeletal proteins), glycogen, RNA and DNA.

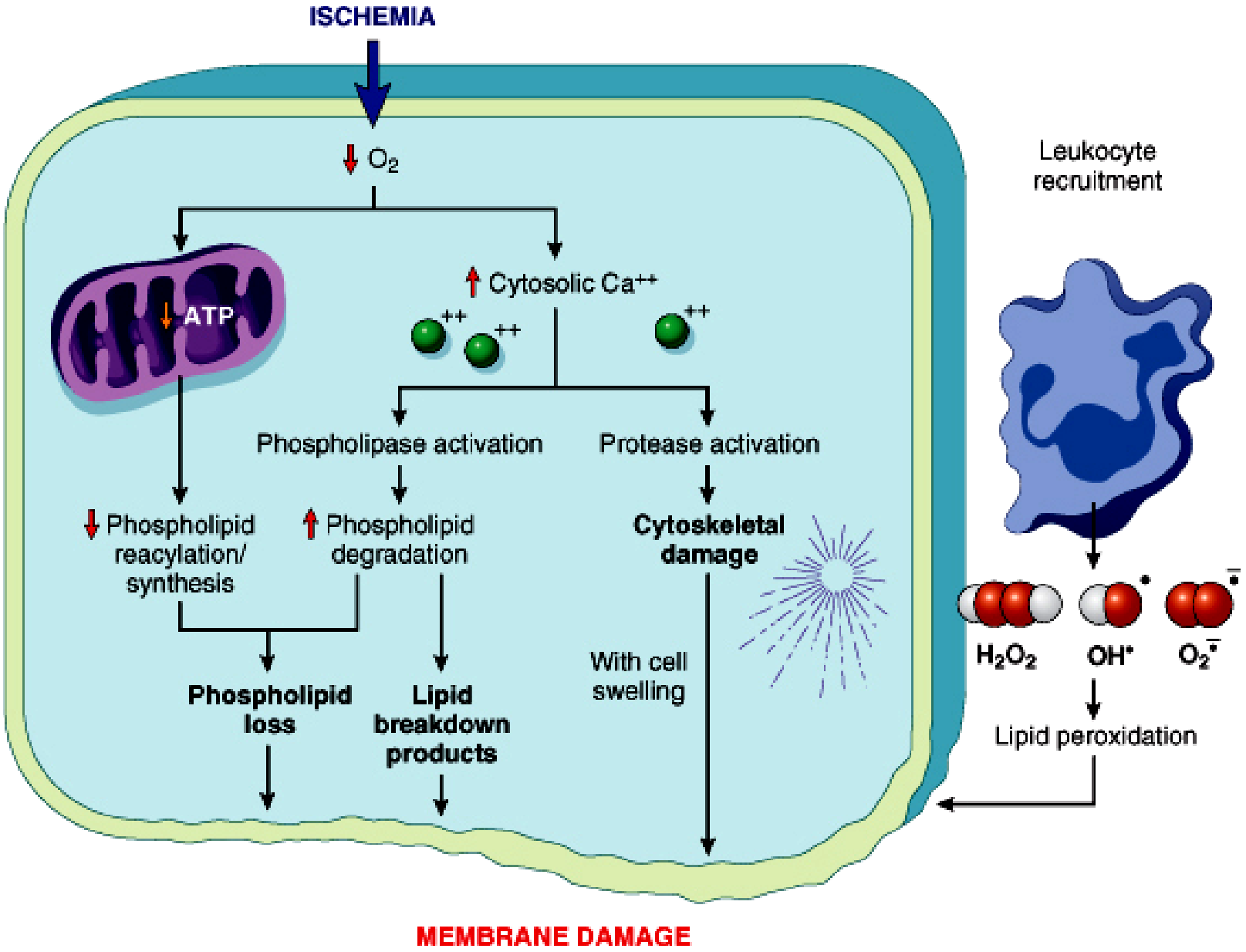
With such extensive damage there is no further possibility of survival and the cell starts to die.



Sources and consequences of increased cytosolic calcium in cell injury.

B. Loss of cell membranes permeability and cell membranes damage:

Mechanisms of membrane damage in cell injury



- Loss of selective membrane permeability (that leads eventually to overt membrane damage) is a regular feature of most forms of cellular injury.

- The effect is not limited to the cell membrane only but may also involve that of the mitochondria, ribosomes and lysosomes.

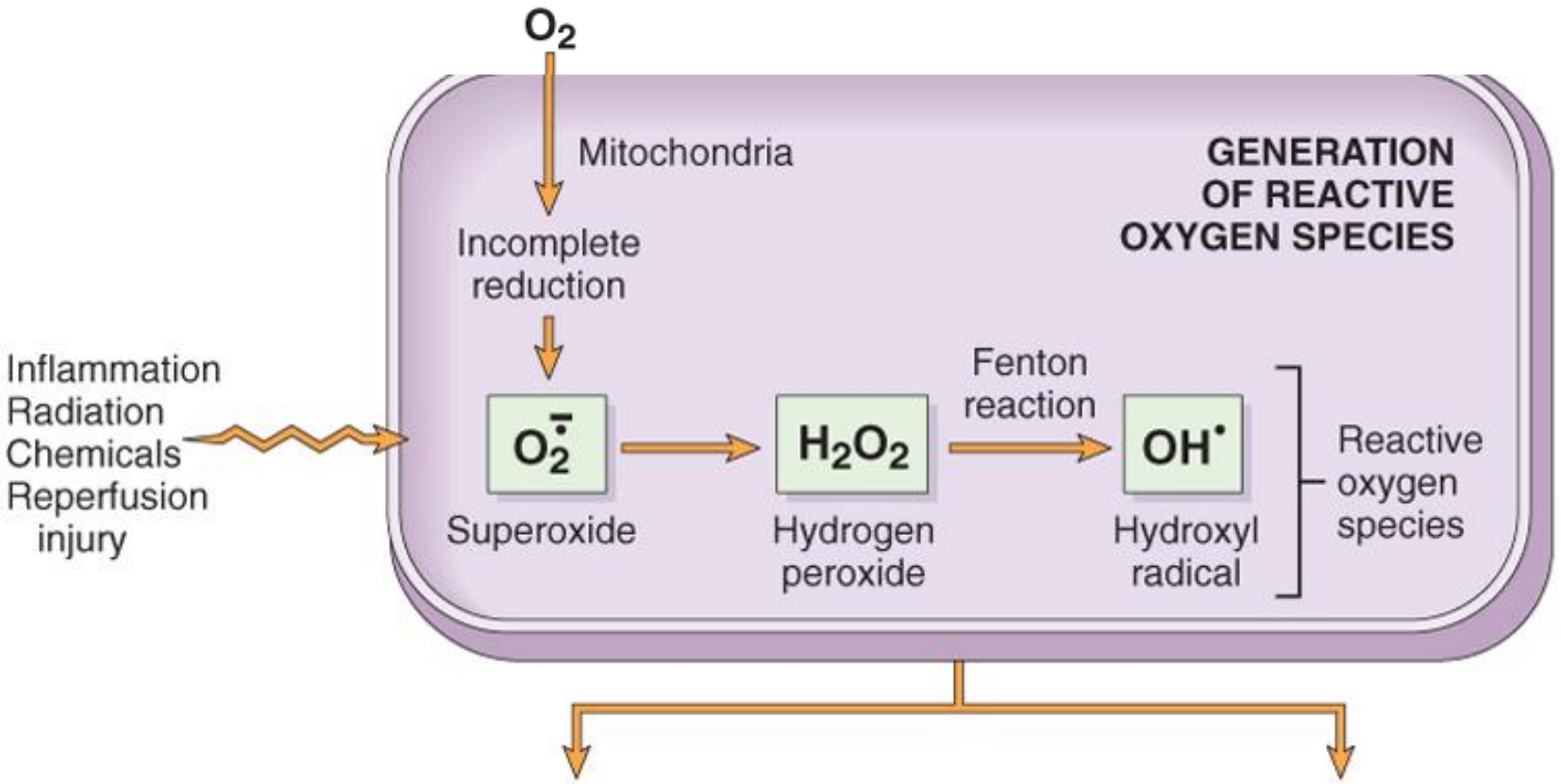
- The outcomes of this depletion are not only dysfunction of Na-K pump only but also failure the Ca^{++} pump that leads to influx of Ca^{++} with subsequent rise of intracellular Ca^{++} levels.

C.
Accumulation of oxygen-derived free radicals (oxidative stress) :

- Partially reduced reactive oxygen forms are produced as an avoidable byproduct of mitochondrial respiration.

- Some of these forms are free radicals, which are chemically reactive; having a single unpaired electron in the outer orbit, examples **include $O2^{-}$, H2O2 , & OH^{-} .**

- These can damage lipids, proteins and nucleic acids leading to various forms of cell injury.



PATHOLOGIC EFFECTS OF ROS: CELL INJURY AND DEATH

ROS react with:

- Fatty acids → oxidation → generation of lipid peroxidases → disruption of plasma membrane, organelles
- Proteins → oxidation → loss of enzymatic activity, abnormal folding
- DNA → oxidation → mutations, breaks

REMOVAL OF FREE RADICALS

Antioxidant mechanisms:

- SOD (in mitochondria) converts $O_2^{\bullet-} \rightarrow H_2O_2$
- Glutathione peroxidase (in mitochondria) converts $OH^{\bullet} \rightarrow H_2O_2$
- Catalase (in peroxisomes) converts $H_2O_2 \rightarrow H_2O + O_2$

- Cells normally have defense mechanisms to terminate these products and thus prevent injury caused by them.

- An imbalance between the generation and removal that result in excess of these products results in **oxidative stress,** which is associated with cell injury seen in many pathological conditions.

- Examples of the latter include inflammation, radiation, oxygen toxicity, various chemicals and reperfusion injury.

D- Mitochondrial damage

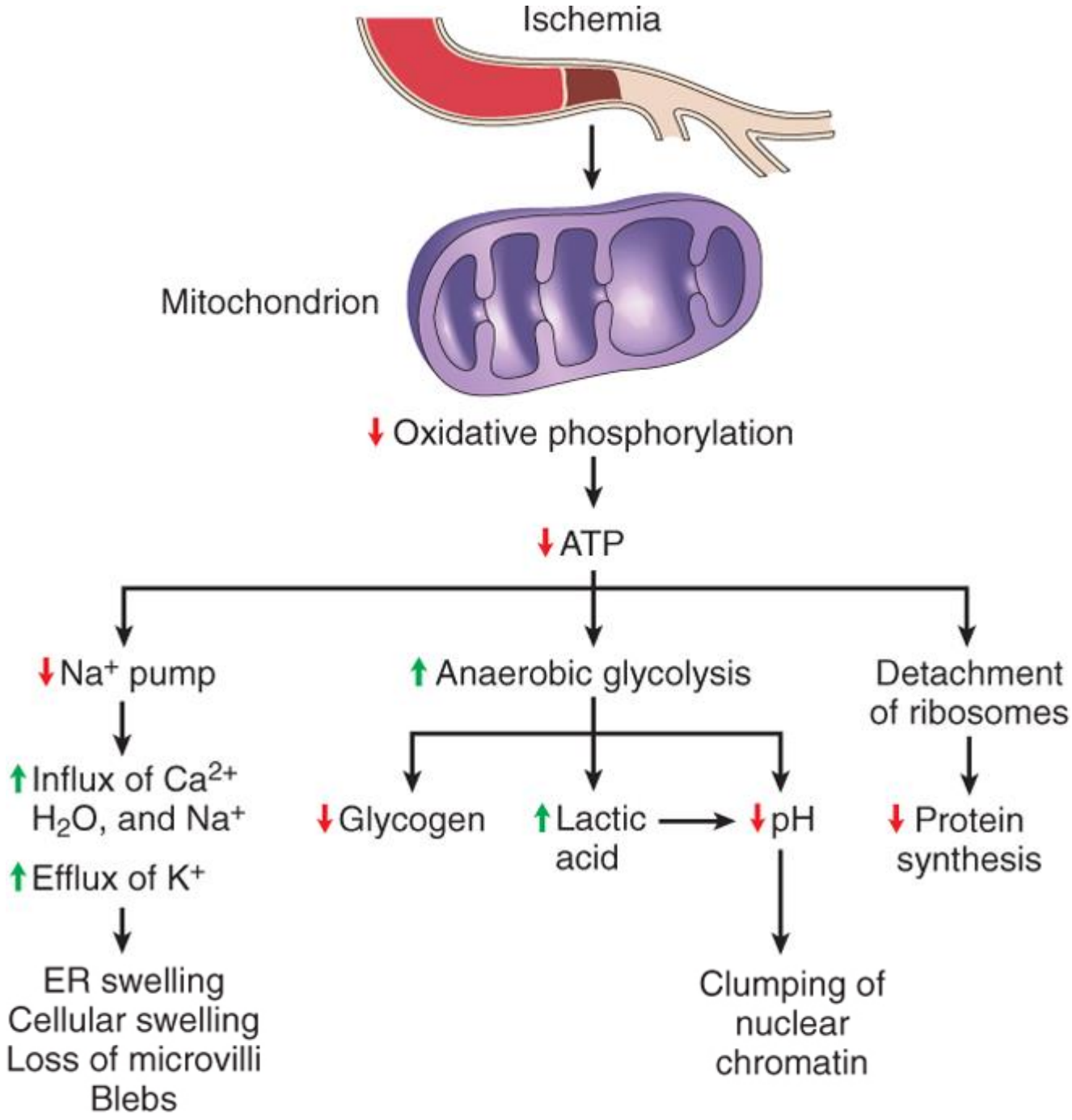
- **Mitochondria** are important targets for virtually all types of injurious agents, including hypoxia and toxins. It can be damaged by:

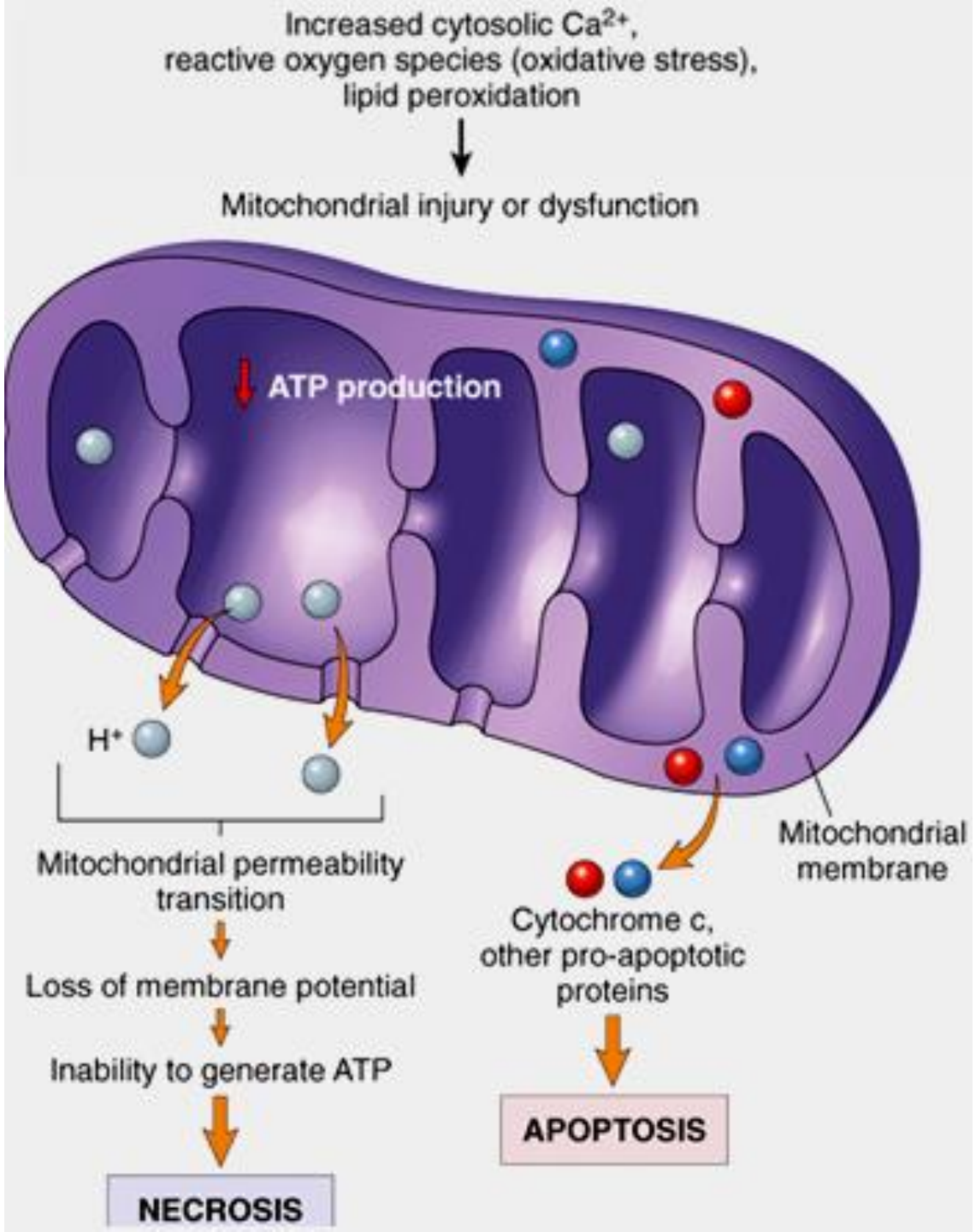
1. Oxidative stress. Hypoxia
2. Increase in cytoplasmic Ca^{++} .
3. Breakdown of phospholipids by activated phospholipases.

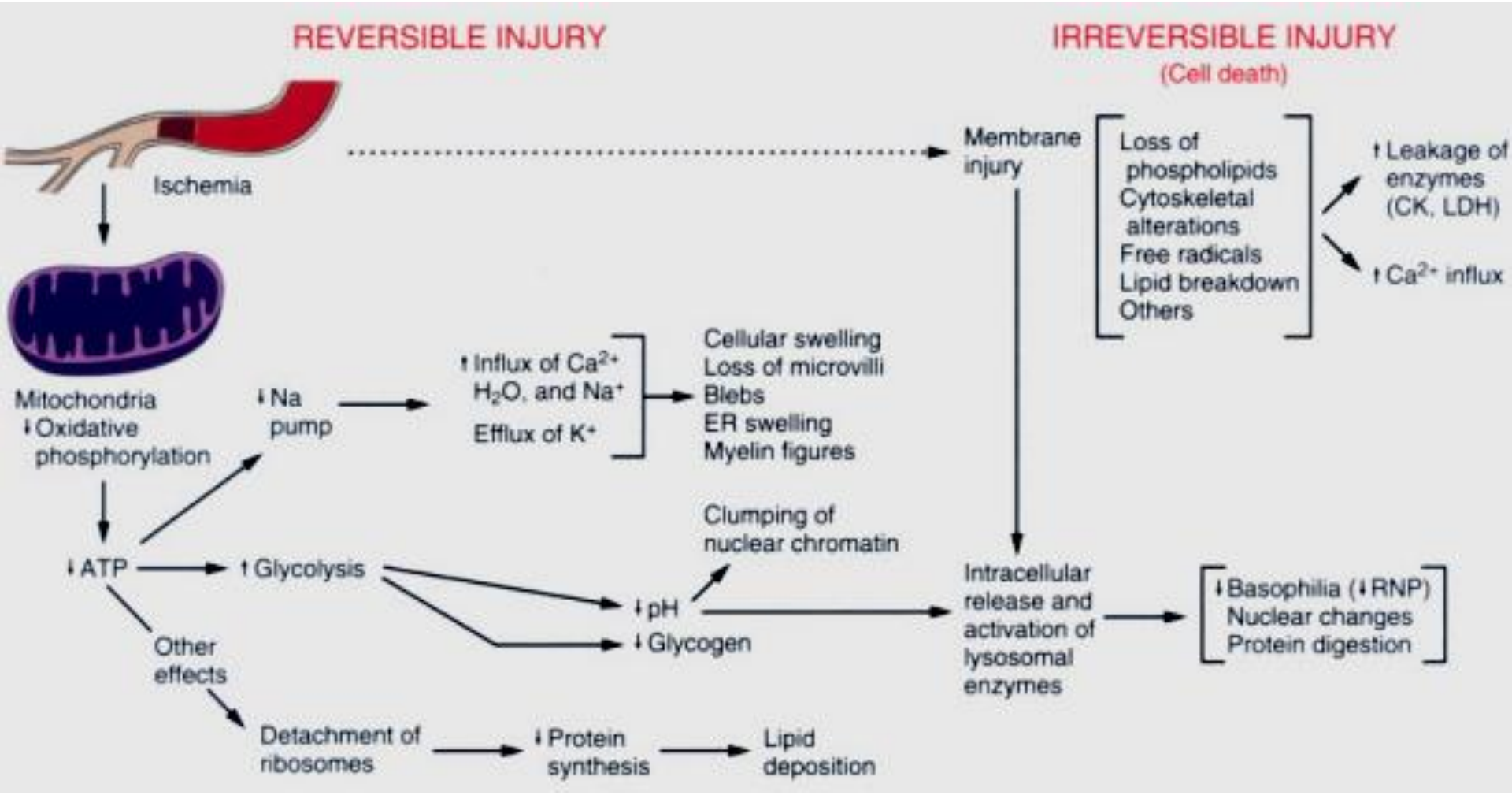
- Injury to mitochondria leads to increased permeability of its membrane that result in leakage from the mitochondria **of H^{+}** and **cytochrome C**.

* The **H+** leads to loss of mitochondrial membrane potential, which is critical for mitochondrial oxidative phosphorylation thus leading to **ATP depletion.**

* The **cytochrome C** result in leakage of cytochrome C, **can trigger apoptotic cell death.**


Ischemia
Mitochondrion
↓ Oxidative phosphorylation
↓ ATP
↓ Na+ pump
↑ Influx of Ca2+ H2O, and Na+
↑ Efflux of K+
ER swelling
Cellular swelling
Loss of microvilli
Blebs
↑ Anaerobic glycolysis
↓ Glycogen
↑ Lactic acid
↓ pH
Clumping of nuclear chromatin
Detachment of ribosomes
↓ Protein synthesis


Increased cytosolic Ca^{2+},
reactive oxygen species (oxidative stress),
lipid peroxidation
Mitochondrial injury or dysfunction
ATP production
H^+
Mitochondrial permeability transition
Loss of membrane potential
Inability to generate ATP
NECROSIS
Cytochrome c, other pro-apoptotic proteins
APOPTOSIS
Mitochondrial membrane



Postulated sequence of events in reversible and irreversible ischemic cell injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia can cause direct membrane damage. ER, endoplasmic reticulum; CK, creatine kinase; LDH, lactate dehydrogenase; RNP, ribonucleoprotein

Examples of reversible cell injury

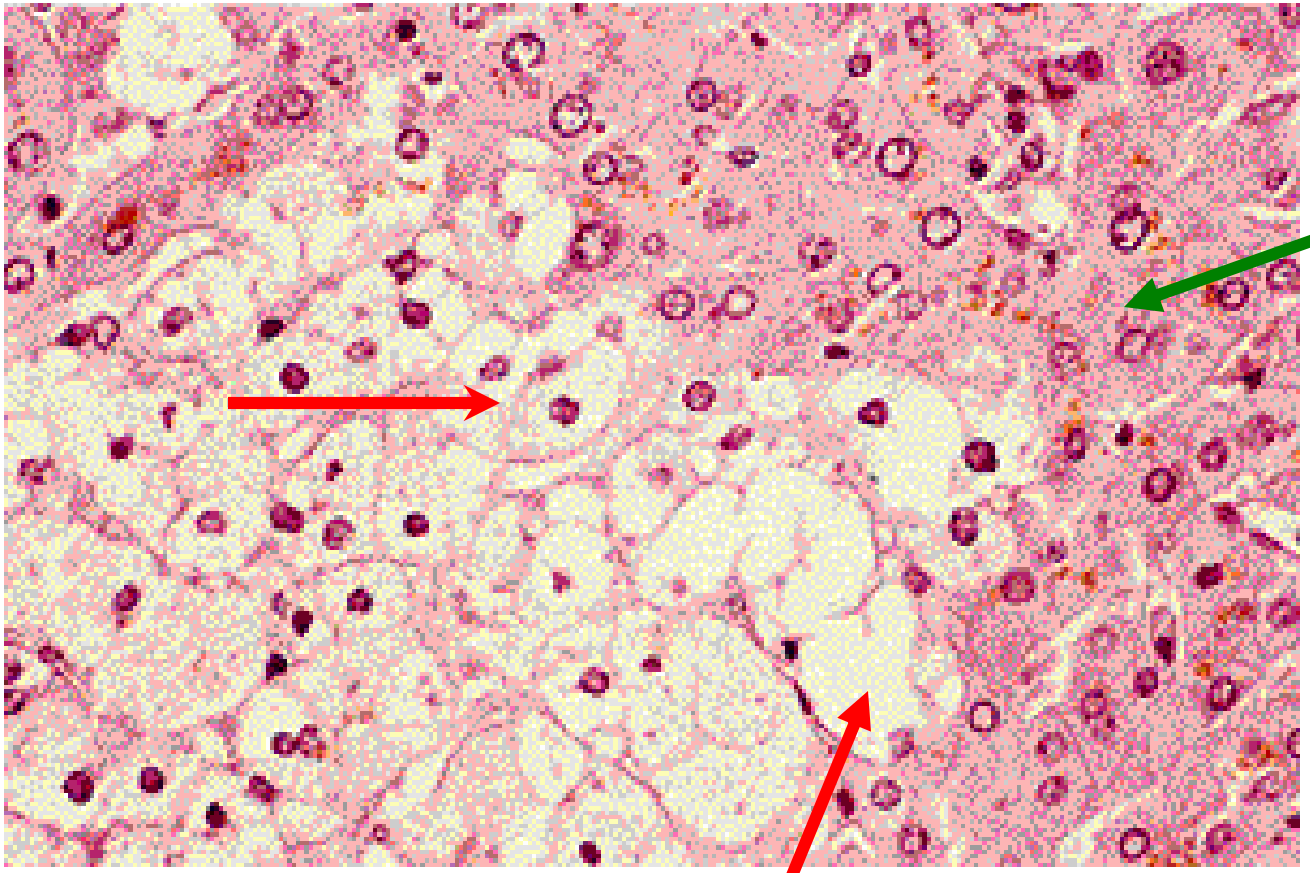
Examples of reversible cell injury

1. Acute cellular swelling (hydropic change, hydropic degeneration)

This is an early change in many examples of reversible cell injury. The extra-fluid may be seen by light microscopy as an increase in the size of the cell with pallor of the cytoplasm **(cloudy swelling).** With further water accumulation clear vacuoles are created within the cytoplasm **(vacuolar degeneration).**

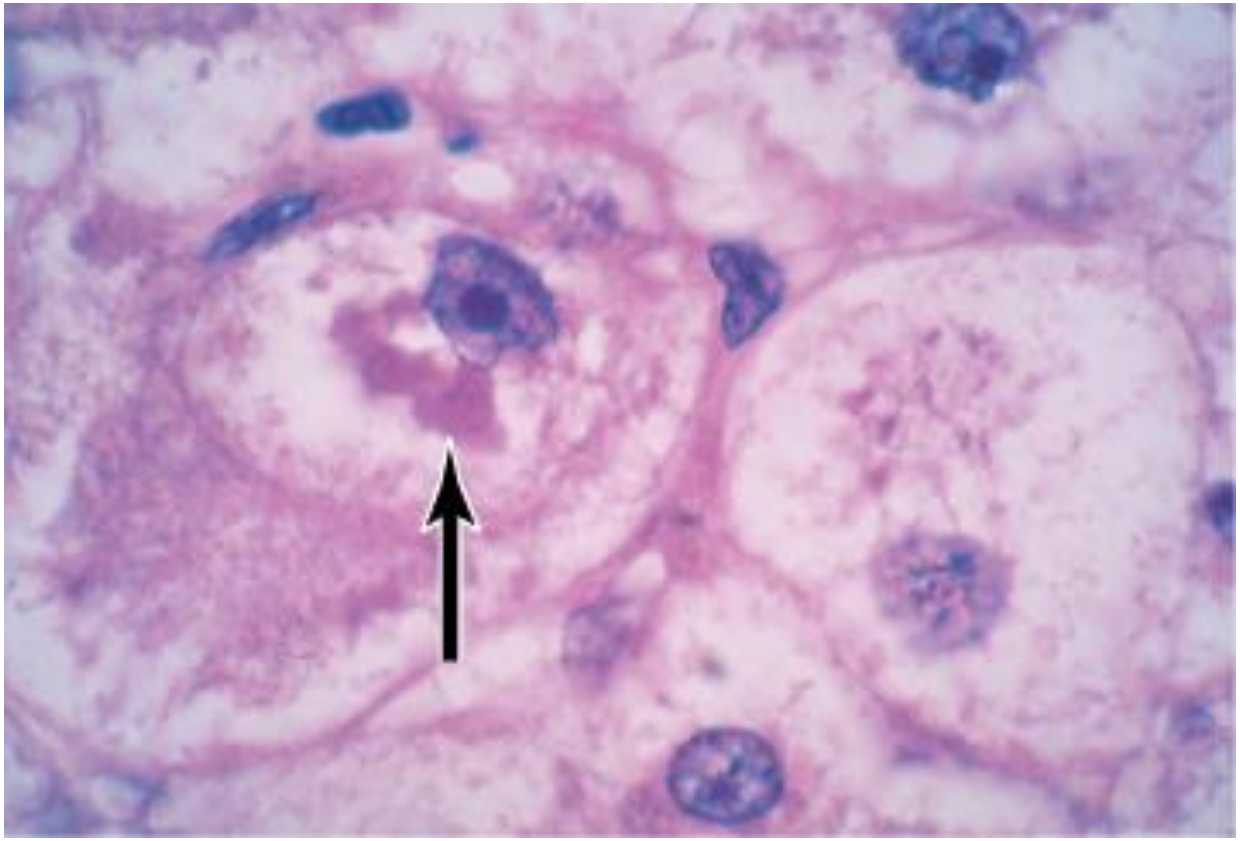
2. Fatty change

Hydropic change - Liver-



Section of the liver subjected to a poison. Normal liver cells (right) contrast with injured cells (left). Injured cells are swollen, pale and vacuolated.

Cellular swelling in hepatocytes in alcoholic liver disease



The nuclei and plasma membranes are largely intact, suggesting viability. The swollen hepatocyte on the left also shows **alcoholic hyalin (liver Mallory bodies)** ***(arrow)*** **.**

Reversible injury : The ultrastructural changes of reversible cell injury include :

(1) plasma membrane alterations

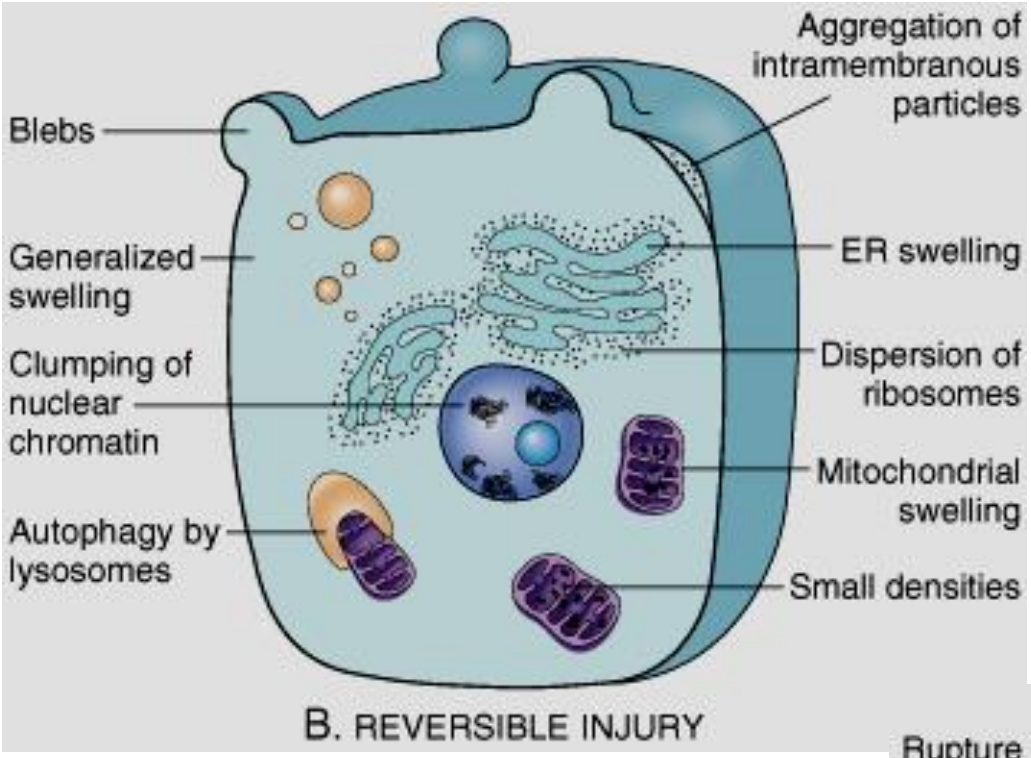
- blebbing
- blunting or distortion of microvilli
- loosening of intercellular attachments

(2) mitochondrial changes

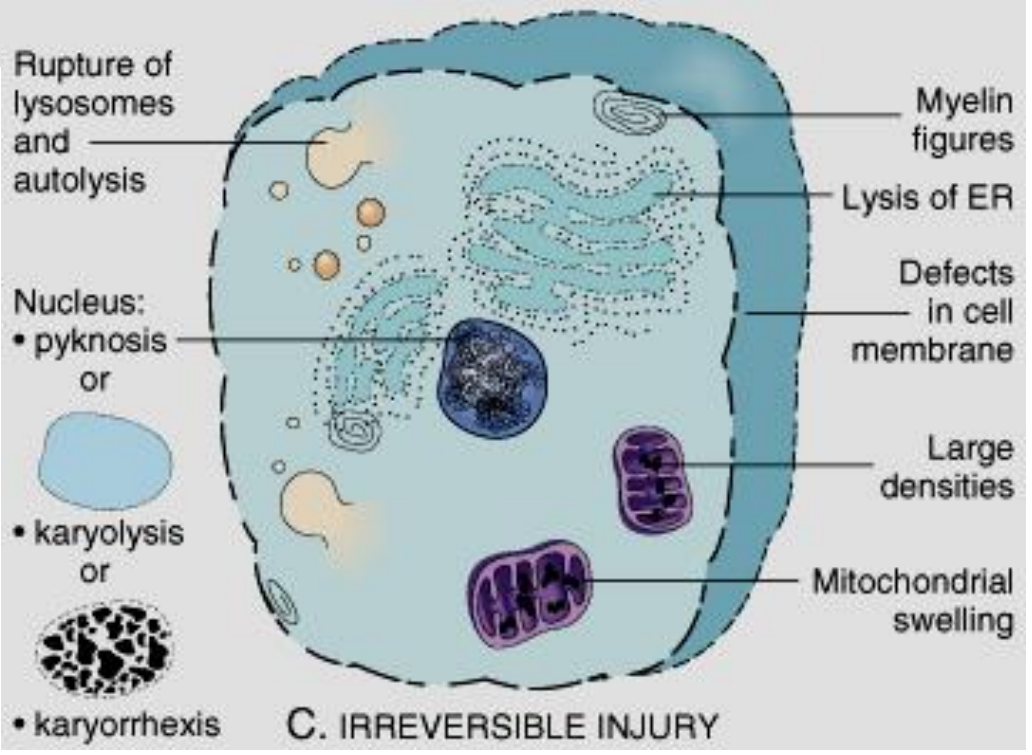
- swelling
- the appearance of phospholipid -rich amorphous densities;

(3) dilatation of the endoplasmic reticulum with detachment of ribosomes and dissociation of polysomes and

(4) nuclear alterations, with disaggregation of granular and fibrillar elements.

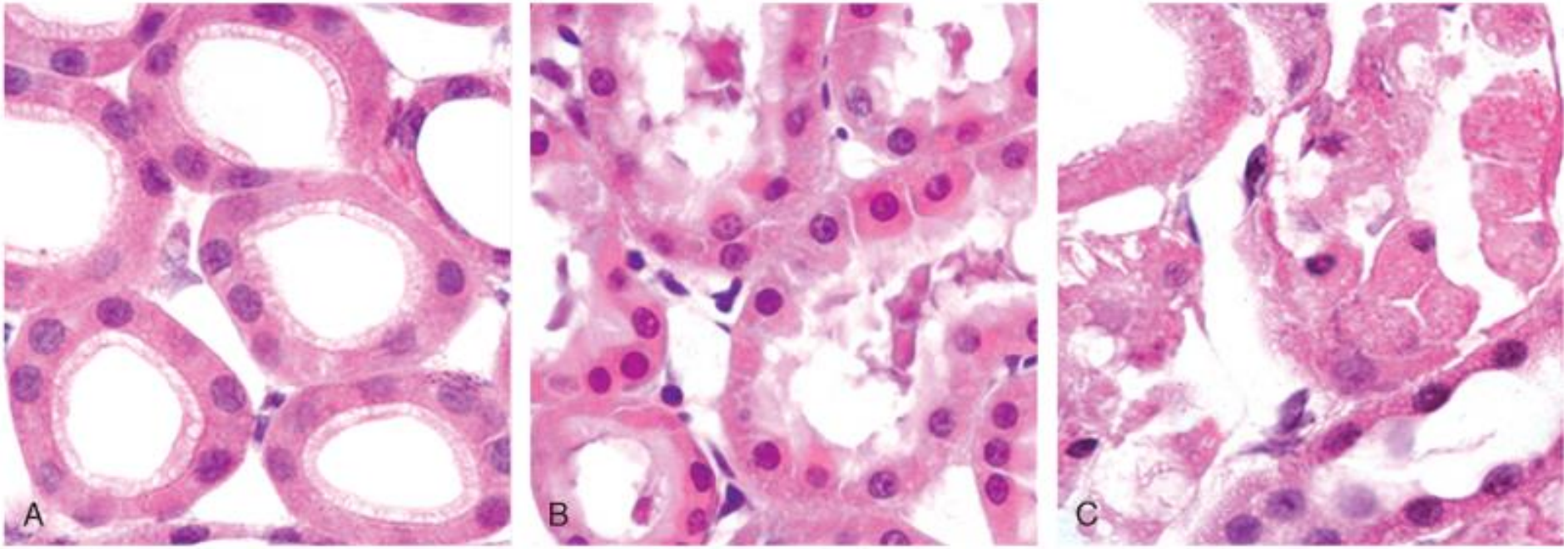


B. REVERSIBLE INJURY



C. IRREVERSIBLE INJURY

Morphologic changes in reversible and irreversible cell injury (necrosis)



A- Normal kidney tubules with viable epithelial cells.

B- Early (reversible) ischemic injury showing surface blebs ,increased eosinophilia of cytoplasm, and swelling of occasional cells.

C- Necrotic (irreversible) injury of epithelial cells, with loss of nuclei and fragmentation of cells and leakage of contents.

Irreversible cell injury

- Mitochondrial damage is one of the most reliable early features of this type of injury.
- Damage to cell membranes is more severe than in reversible injury, resulting in **leakage of the cellular constituents** outside their normal confines.
- liberation and activation of lysosomal enzymes (proteinases, nucleases etc.), which are also normally bounded by membranes.

These liberated and activated enzymes digest both cytoplasmic and nuclear components **(autolysis).**

The end result is total cell necrosis, which is the morphological expression of cell death.

Cell death is represented by :

A- Necrosis **B- Apoptosis**

A- Necrosis:

− death of group of cells during life.

- morphological changes that follow results from the degrading action of enzymes on irreversibly damaged cells with denaturation of cellular proteins.

- There are cytoplasmic as well as nuclear changes.

Cytoplasmic changes:

Normally with hematoxylin-eosin stain (H&E), the hematoxylin stains acidic materials (including the nucleus) blue whereas eosin stains alkaline materials (including the cytoplasm) pink.

The necrotic cell is more eosinophilic than viable cells (i.e. more intensely (pinkish) this is due to:

1. loss of cytoplasmic RNA (RNA is acidic so stains with hematoxylin bluish).
2. increased binding of eosin to the denatured proteins.

The cell may have more glassy homogeneous appearance than normal cells; this is due to loss of glycogen particles (which normally gives a granular appearance to the cytoplasm). When enzymes have degraded the organelles, the cytoplasm becomes vacuolated and appears moth-eaten.

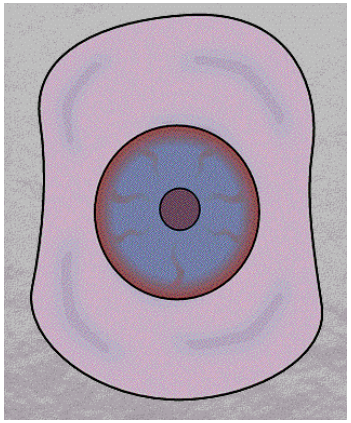
Nuclear changes:

The earliest change is **chromatin clumping,** which is followed by one of two changes:

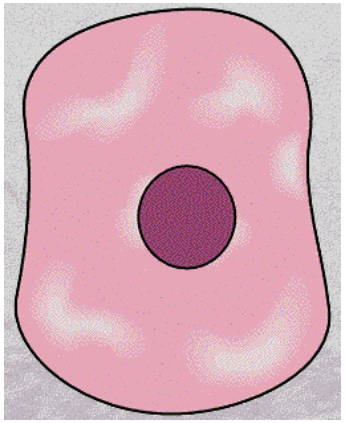
1. The nucleus may shrinks and transformed into small wrinkled mass **(pyknosis),** with time there is progressive disintegration of the chromatin with subsequent disappearance of the nucleus altogether **(karyolysis)** **or**

2. The nucleus may break into many clumps **(karyorrhexis).**

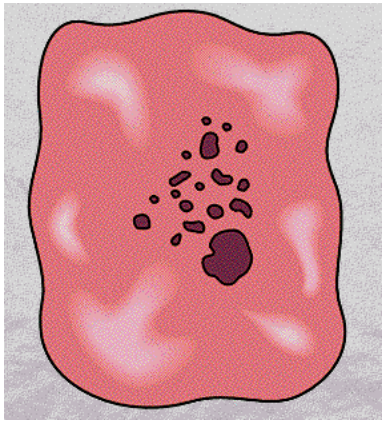
Cell necrosis & Nuclear changes



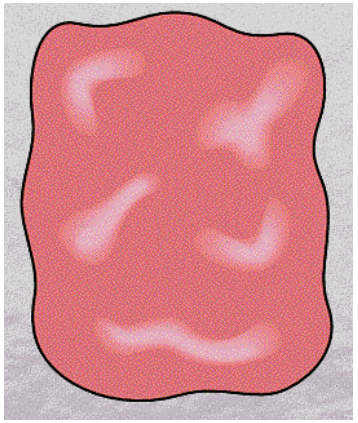
normal



pyknosis



karyorrhexis

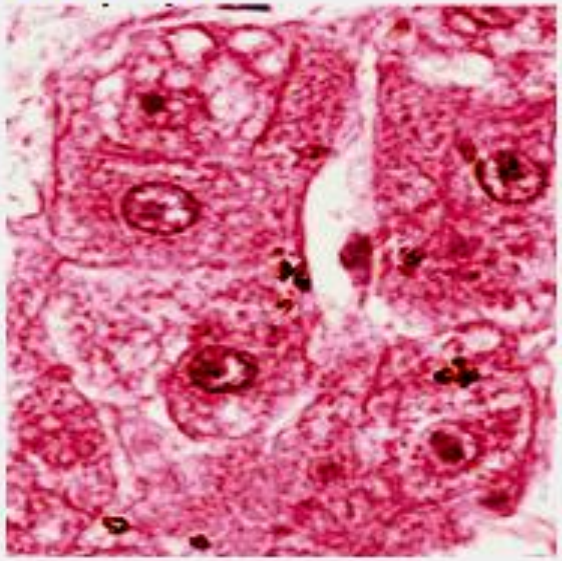


karyolysis

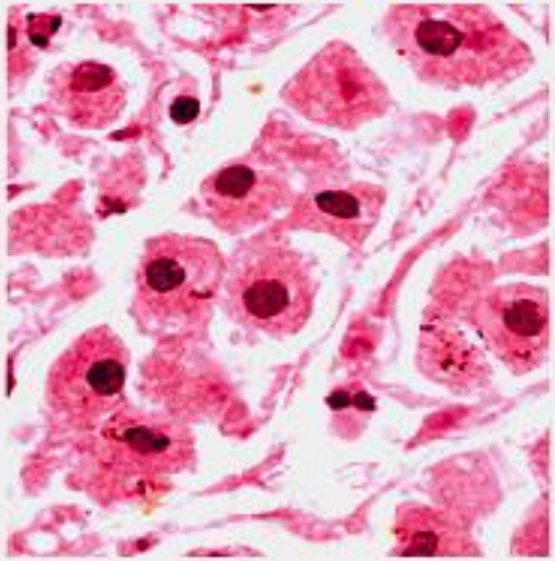
Next

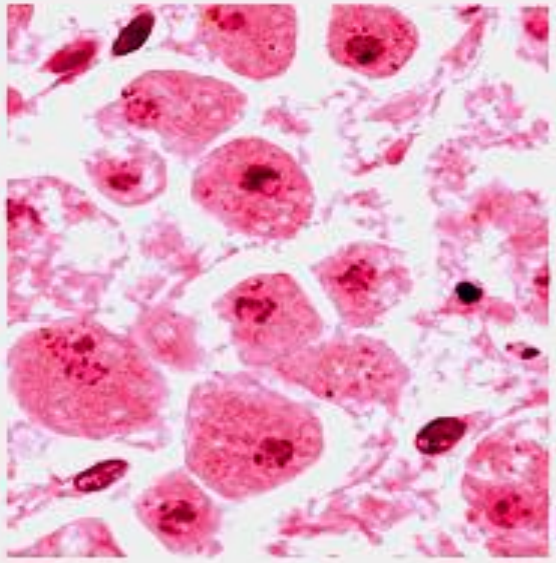
Liver cell necrosis & Nuclear changes

normal



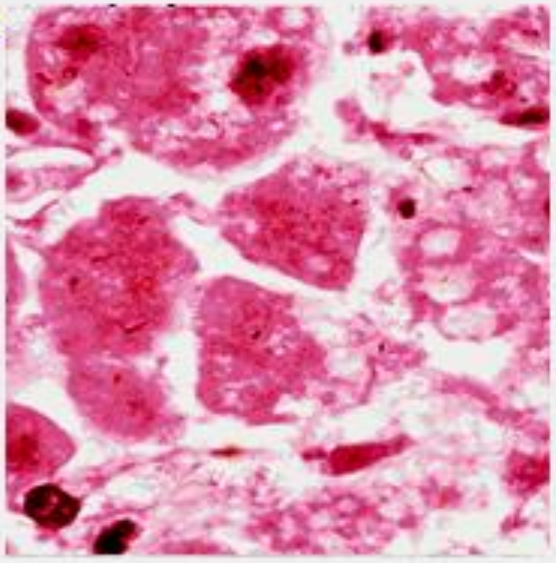
pyknosis





karyorrhexis

karyolysis



Types of cell necrosis

1. Coagulation (coagulative) necrosis.

2. Liquefaction (liquefactive) necrosis.

3. Fat necrosis.

4. Caseation (caseous) necrosis.

5. Gangrenous necrosis.

6. Fibrinoid necrosis.

7. Gummatous necrosis.

1− Coagulation necrosis:

- Results from sudden severe ischemia in solid organs.

heart, kidney . The etiology of coagulative necrosis is usually vascular with loss of blood supply.

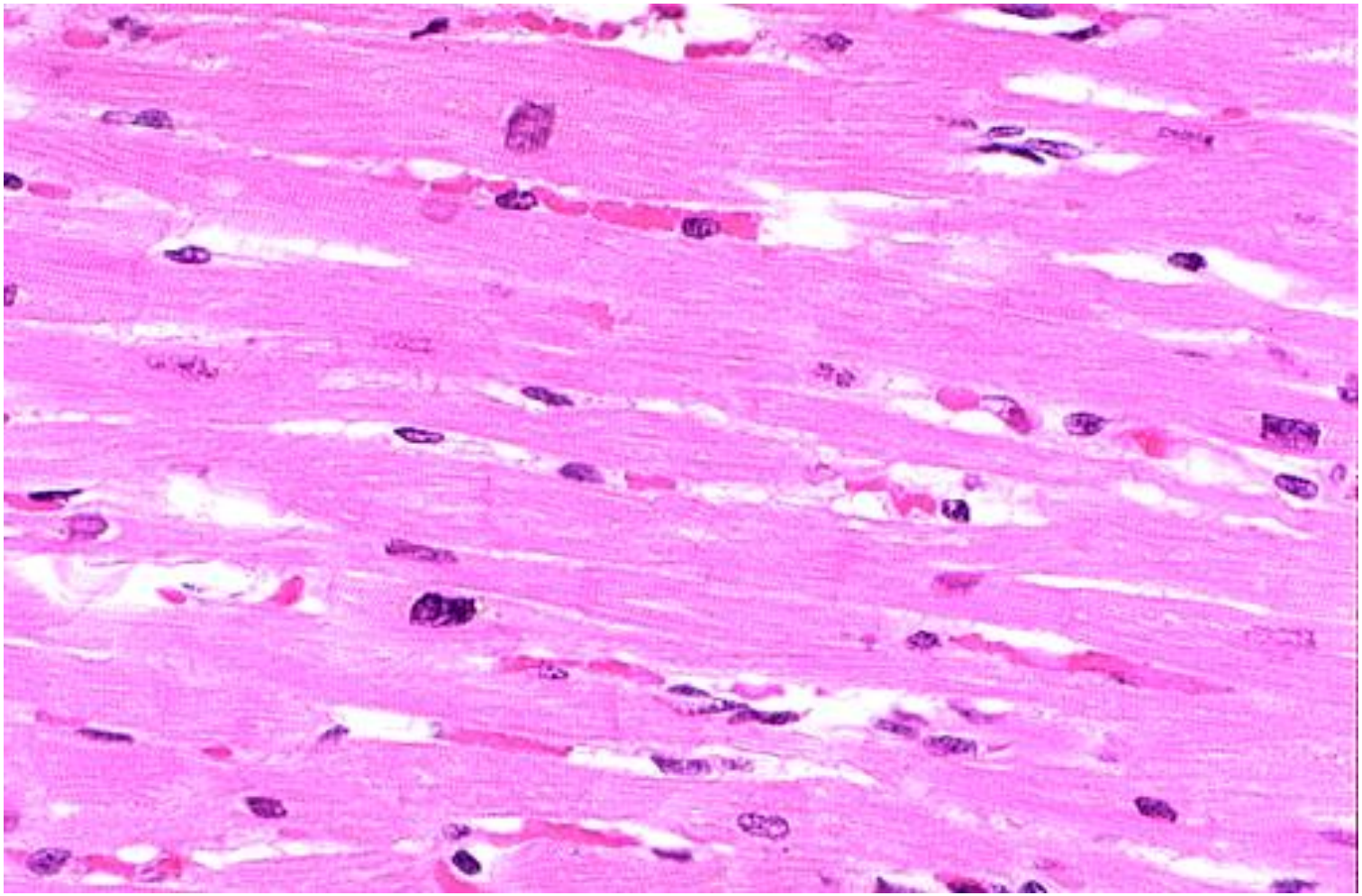
- Microscopically the fine structural details of the affected tissue (and cells) are lost but their outlines are maintained.

- The nucleus is lost.

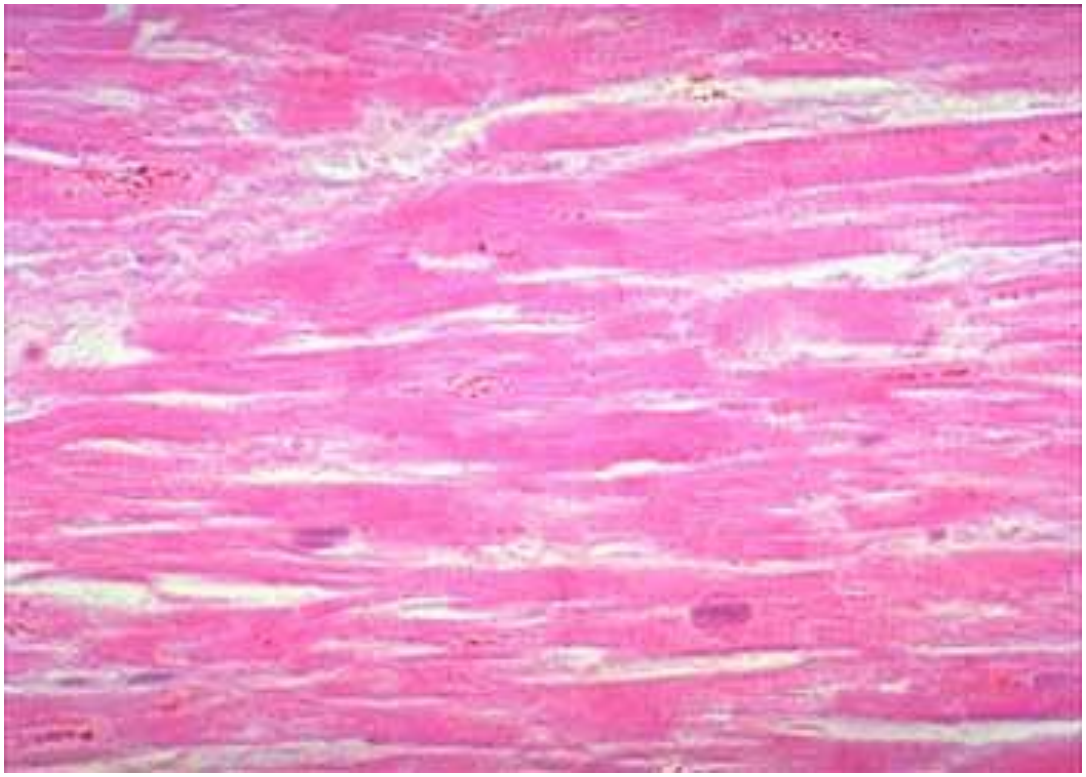
- The cytoplasm is converted into homogeneous deeply eosinophilic and structureless material.

Normal cardiac muscle in longitudinal section

- shows a syncytium of myocardial fibers with central nuclei.
- Faint pink intercalated discs cross some of the fibers.

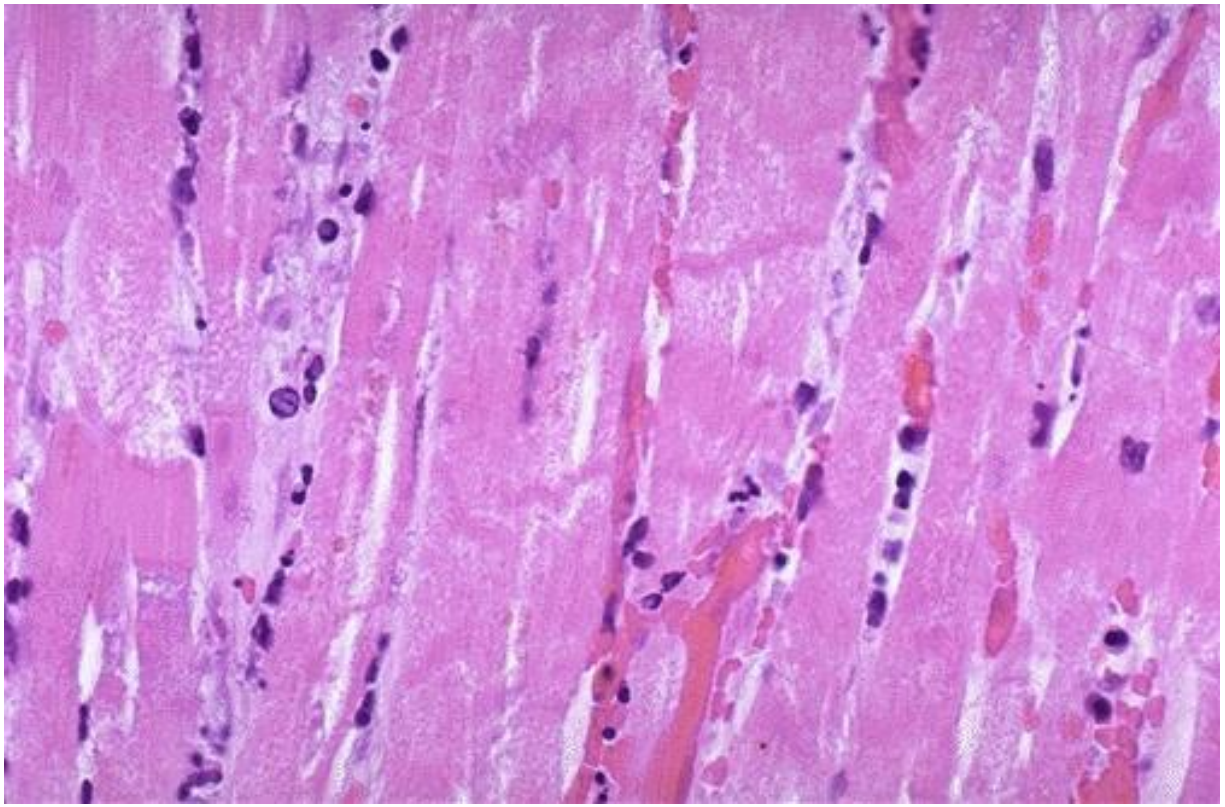


Coagulative necrosis – myocardium – myocardial infarction



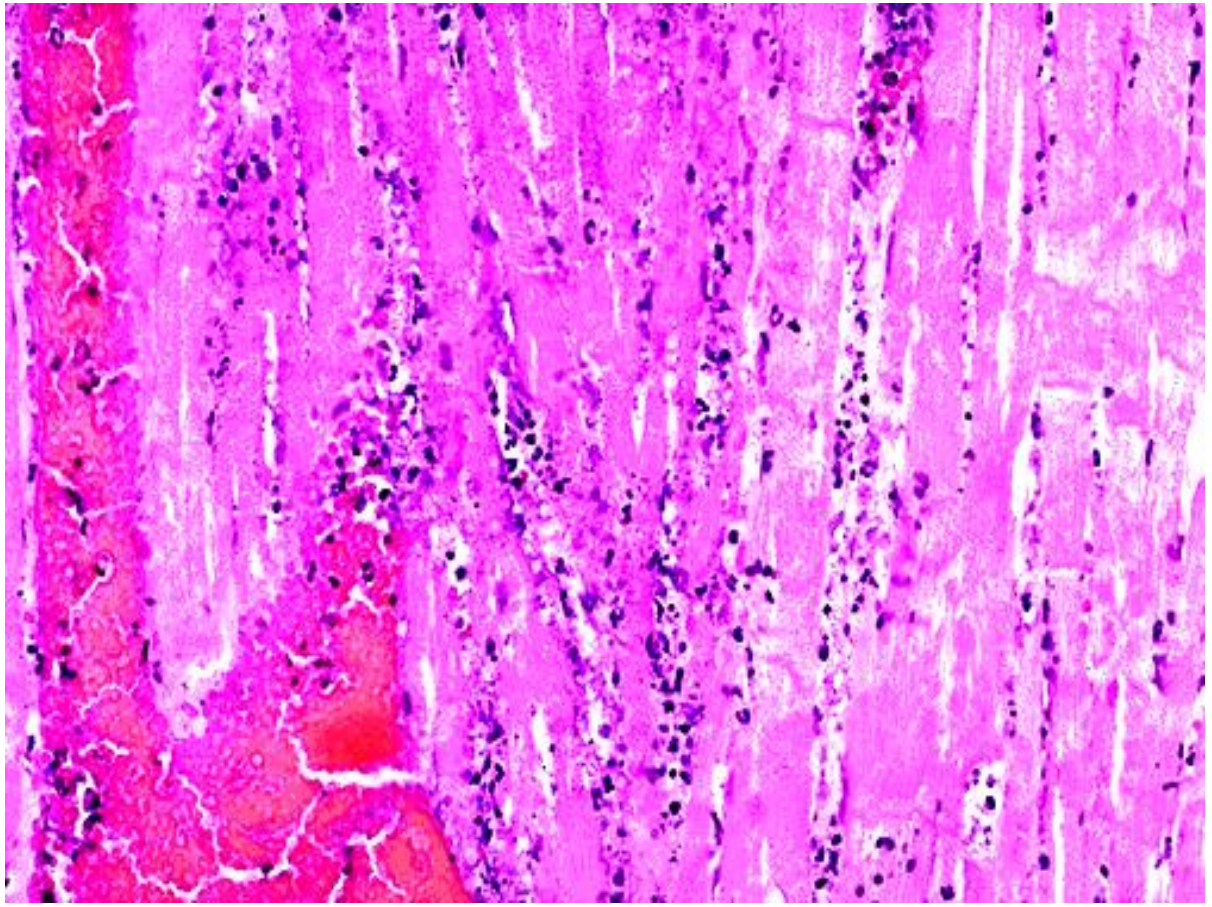
- The outlines of myocardial fibers are maintained.
- The cytoplasm is rather homogeneous, deeply eosinophilic, devoid of cross striation and there are no nuclei.

Myocardial infarction is **about 1 to 2 days old**



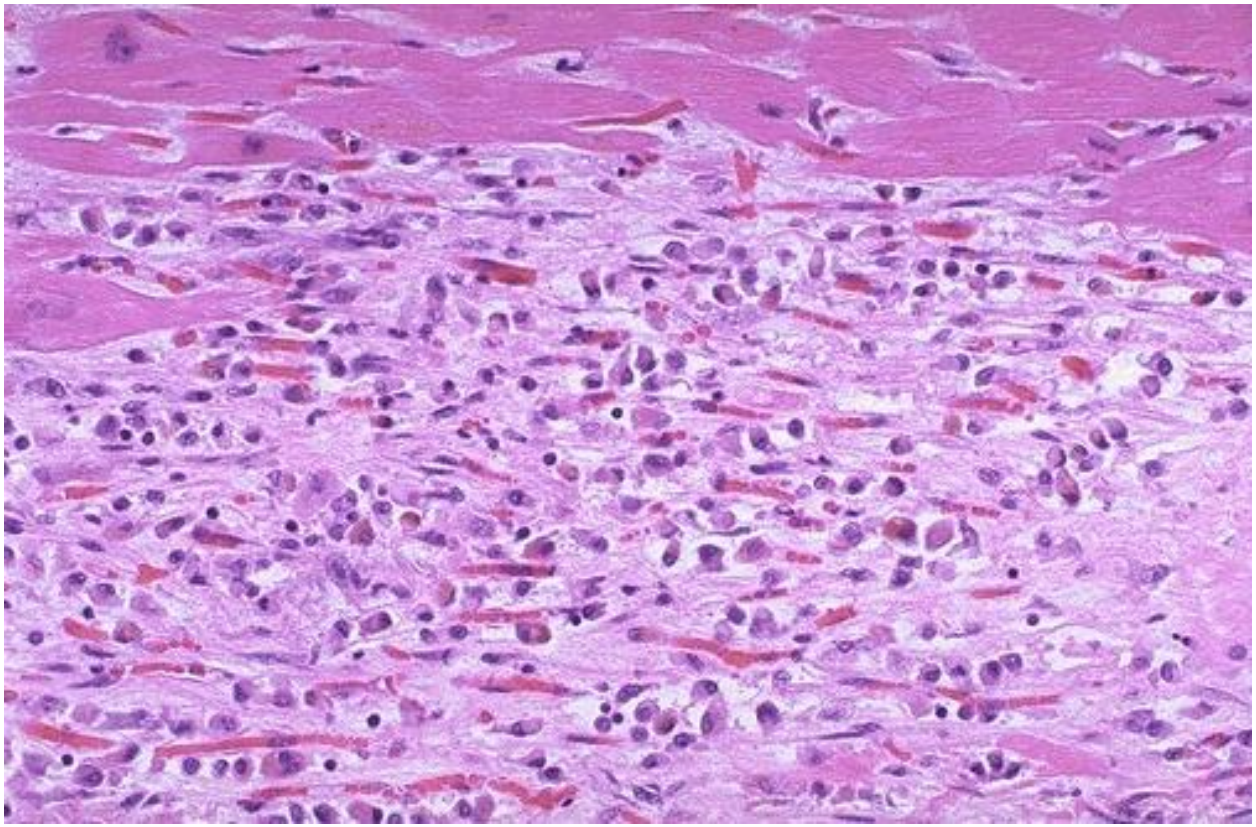
- The nuclei of the myocardial fibers are being lost.
- The cytoplasm is losing its structure, because no well-defined cross- striations are seen.
- Acute inflammatory cell started to infiltrate in between the fibers.

Myocardial infarction is **about 3 to 4 days old**



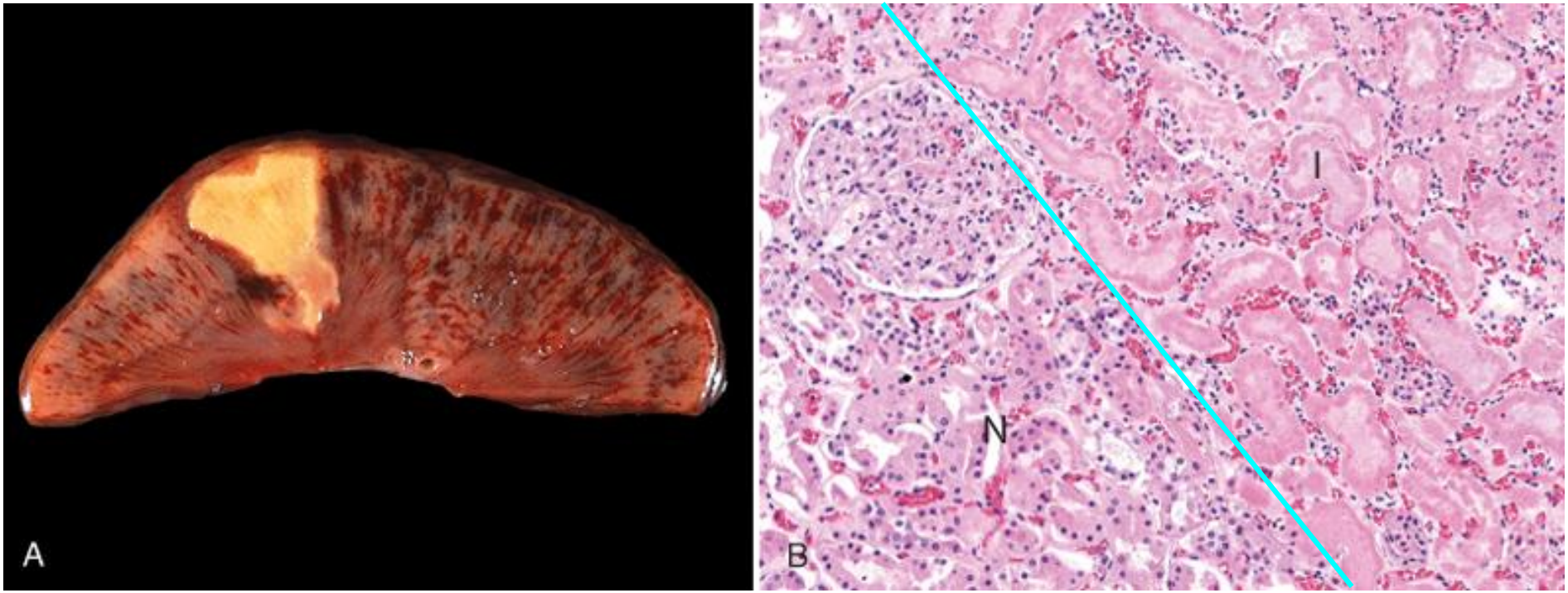
- There is an extensive acute inflammatory cell infiltrate.
- The outlines of myocardial fibers are still discernible.
- The cytoplasm is rather homogeneous, deeply eosinophilic, devoid of cross striation and there are no nuclei.

Myocardial infarction of **1 to 2 weeks** in age



- Note that there are remaining normal myocardial fibers at the top.
- Below these fibers are many macrophages along with numerous capillaries and little collagenization (granulation tissue).

Coagulative necrosis kidney

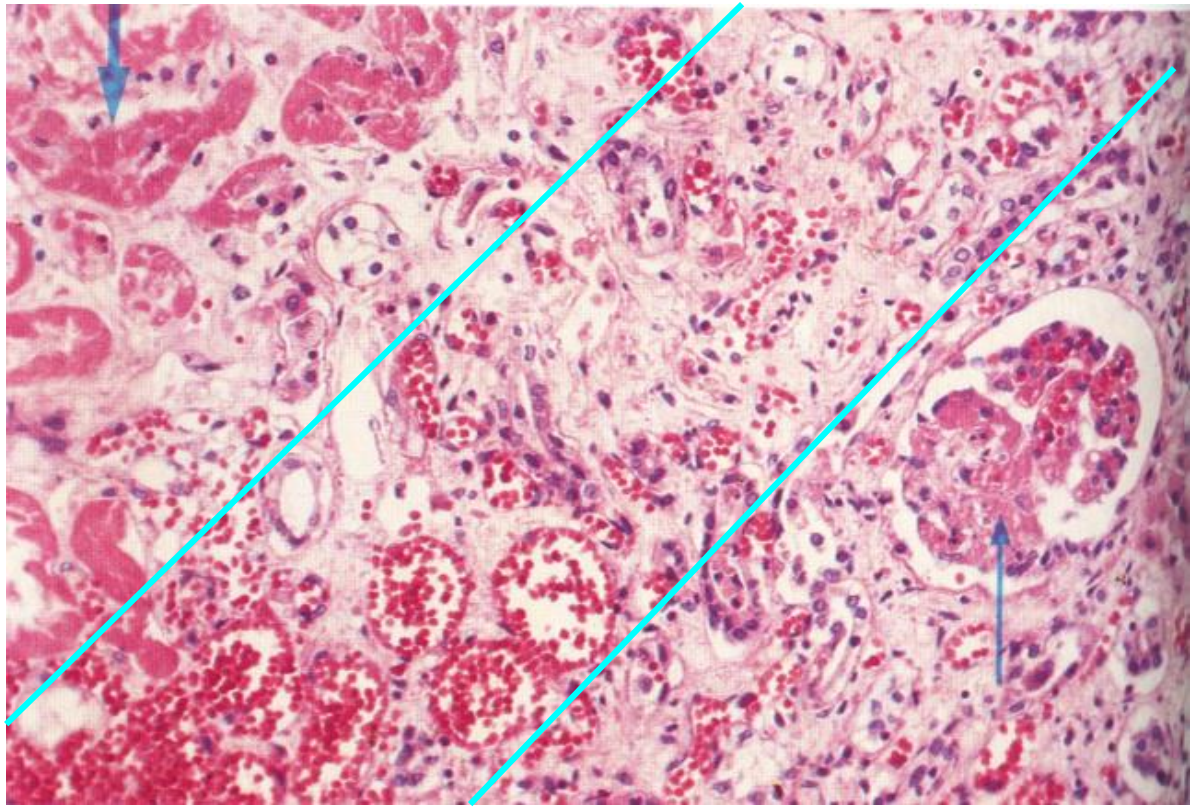


A- A wedge-shaped kidney infarct (yellow) with preservation of the outlines.

B- Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I). The necrotic cells show preserved outlines with loss of nuclei, and an inflammatory infiltrate is present (difficult to discern at this magnification).

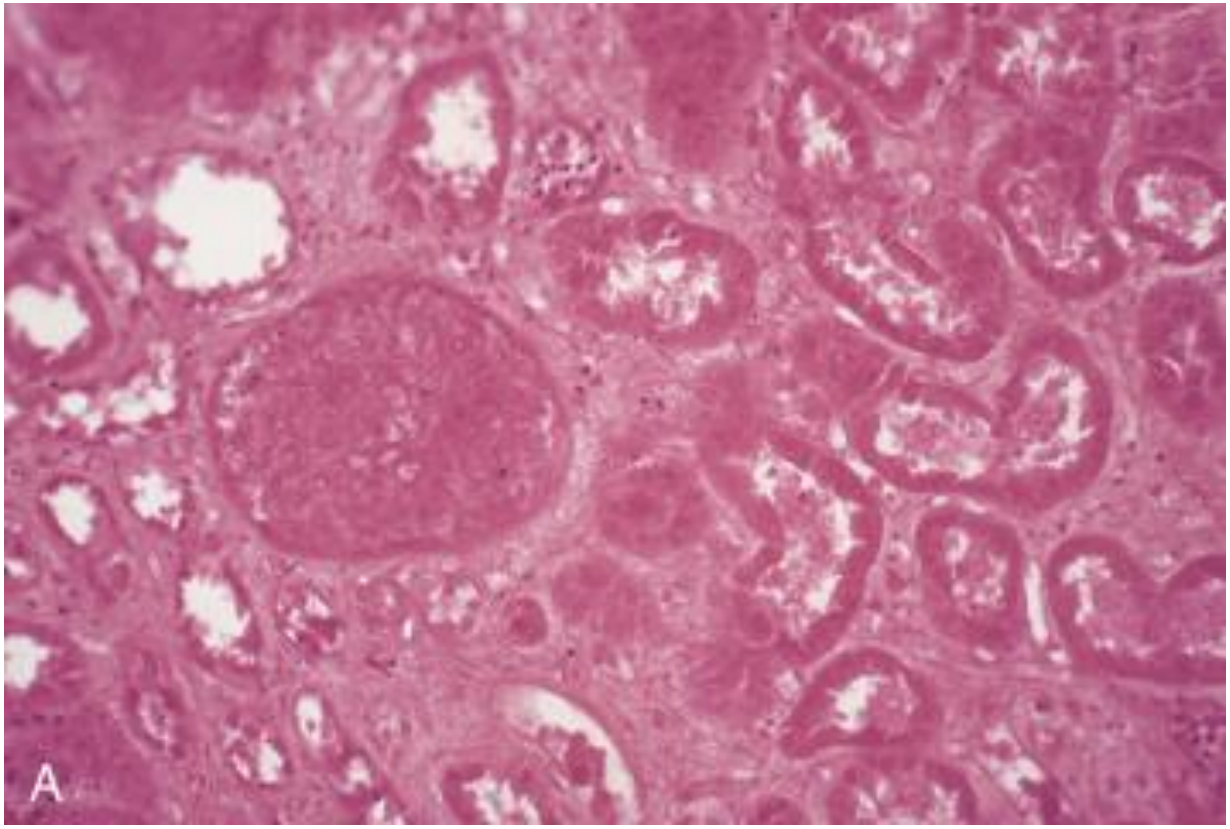
Infarcted zone

Line of demarcation



Unaffected zone

Coagulative necrosis kidney



- with loss of nuclei and more eosinophilia of cytoplasm
- preservation of basic outlines of glomerular and tubular architecture.

Spleen infarction

Two large infarctions. **Since the etiology of coagulative necrosis is usually vascular with loss of blood supply**, the infarct occurs in a vascular distribution. Thus, infarcts are often **wedge-shaped** with a base on the organ capsule.

2- Liquefaction necrosis:

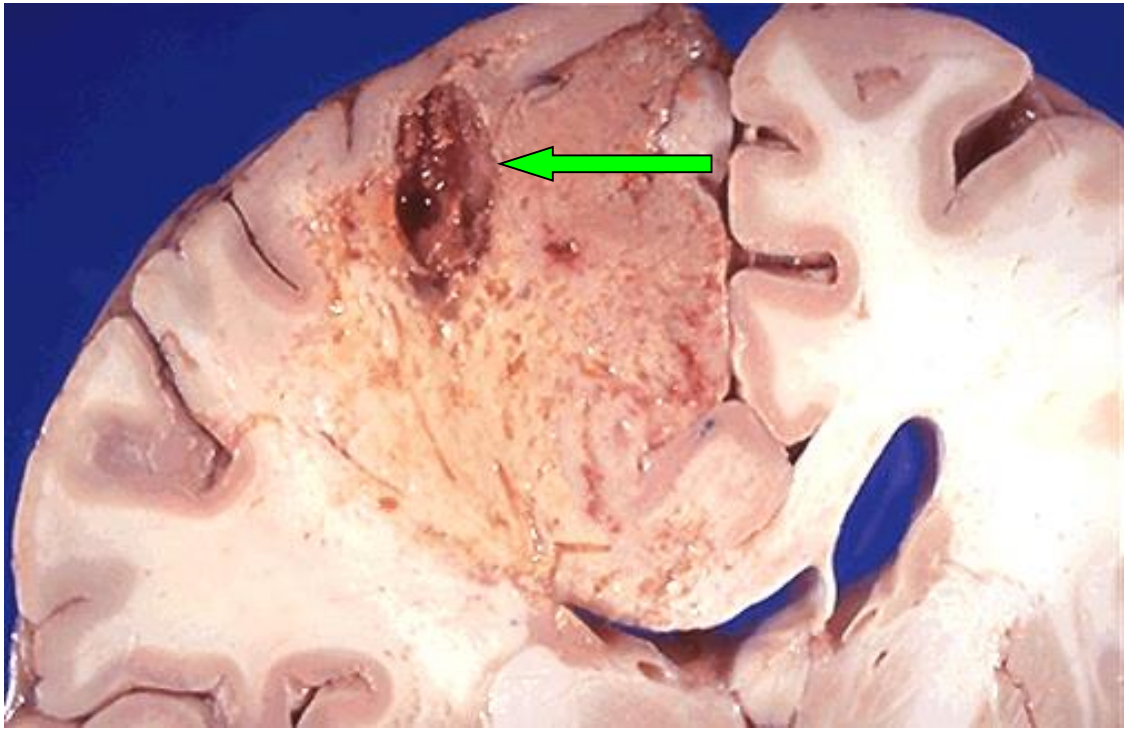
Seen in two situations:

1. Brain infarcts. i.e. ischemic destruction of brain tissue.
2. Abscesses. i.e. suppurative bacterial infections.

- characterized by complete digestion of dead cells by enzymes and thus the necrotic area is eventually liquefied, i.e. converted into a cyst filled with debris and fluid.

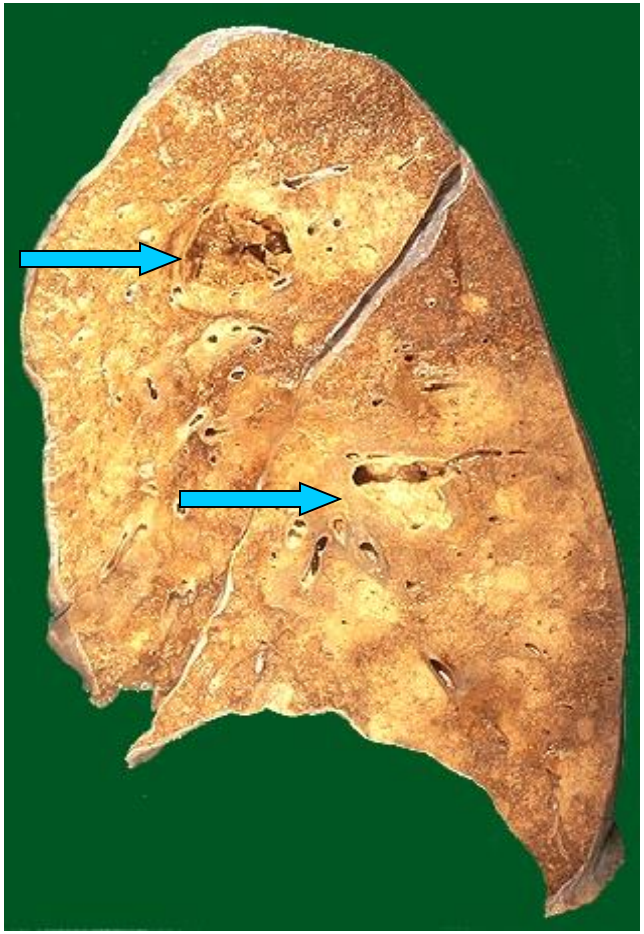
- typically occur in organs in which the tissues have a lot of lipid (such as brain) or when there is an abscess with lots of acute inflammatory cells whose release of proteolytic enzymes destroys the surrounding tissues.

Liquefactive necrosis - brain -



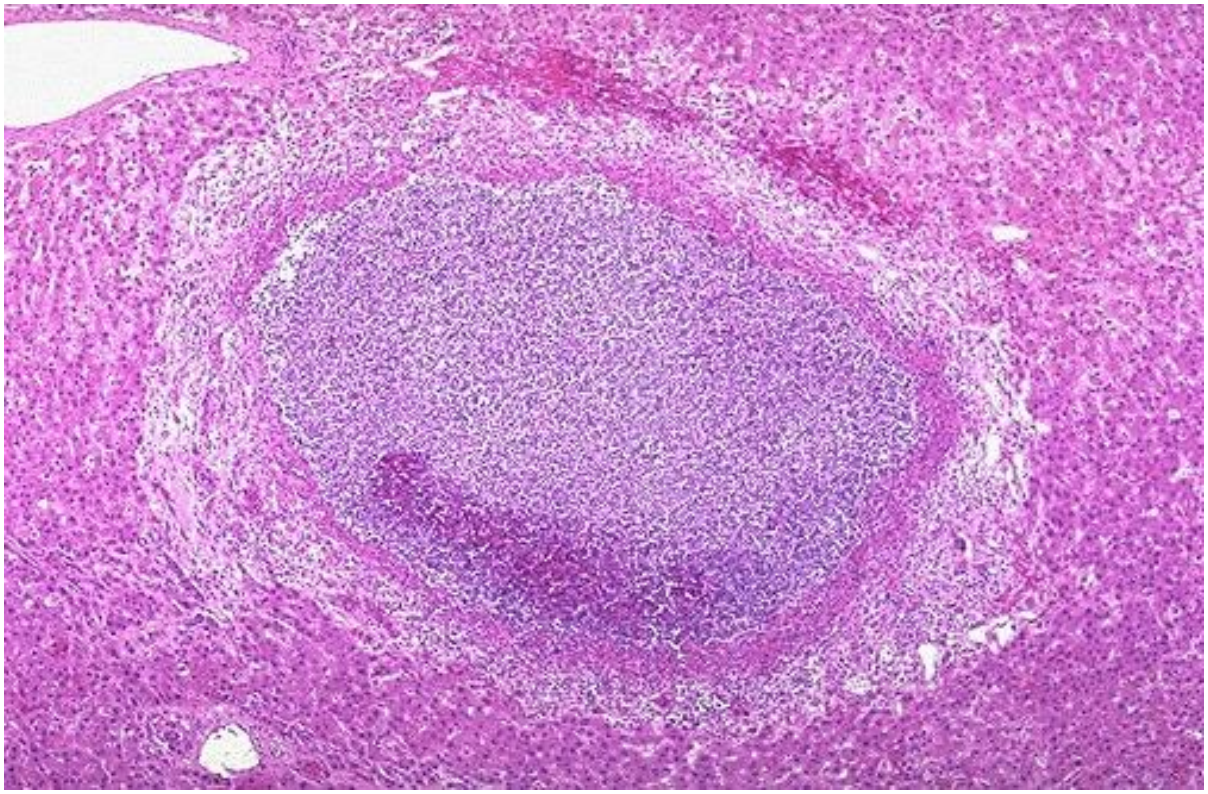
The infarcted area is converted into a cavity (cyst) through liquefaction of the necrotic cells.

Liquefactive necrosis - Lung abscess - Bronchopneumonia



One abscess appears in the upper lobe and one in the lower lobe.

liver abscess - liquefactive necrosis -



The liver shows a small abscess here filled with many neutrophils.

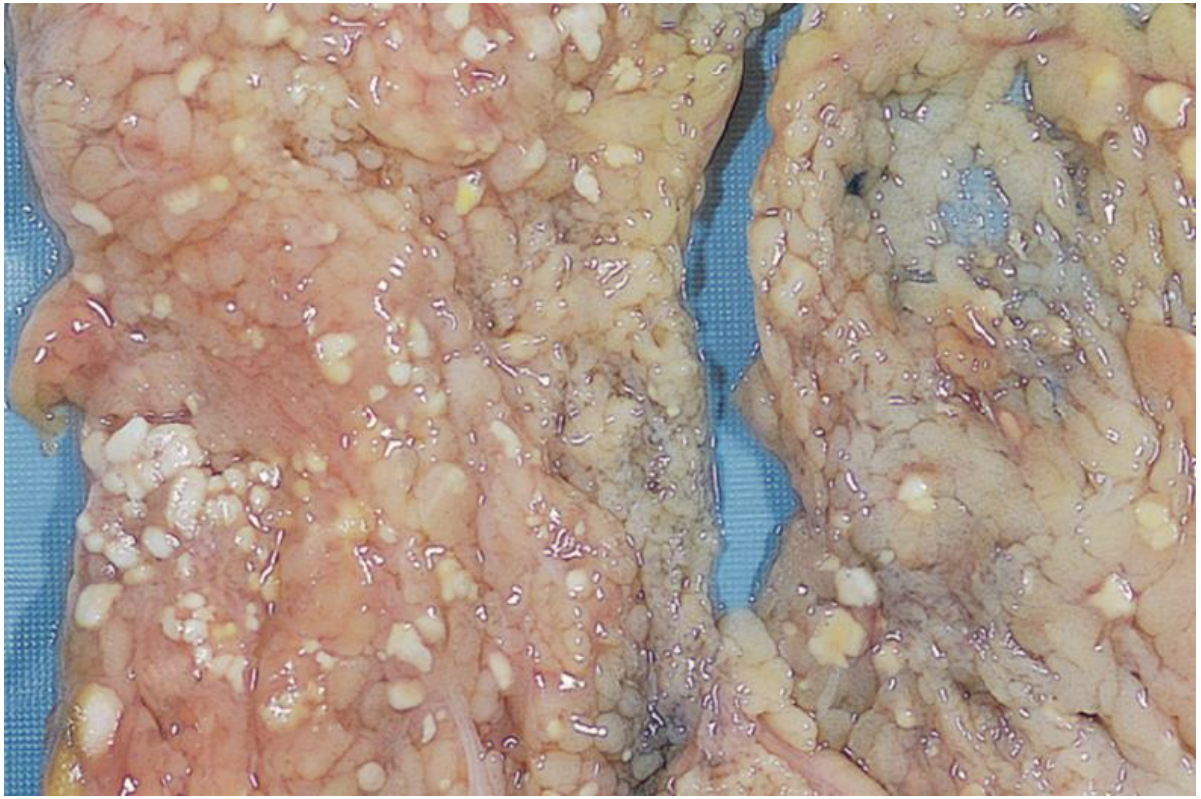
3- Fat necrosis:

- a specific pattern of cell death seen in adipose tissue due to action of lipases (chemical trauma). It is most commonly seen in **acute pancreatitis.** The released fatty acids from necrotic cells, complex with calcium to create calcium soaps.

These are seen grossly as chalky white deposits.

- Fat necrosis can also be induced by mechanical trauma as in female breast **(traumatic fat necrosis)**.

Fat necrosis - mesentery - in acute pancreatitis



The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.

4- Caseous necrosis (caseation):

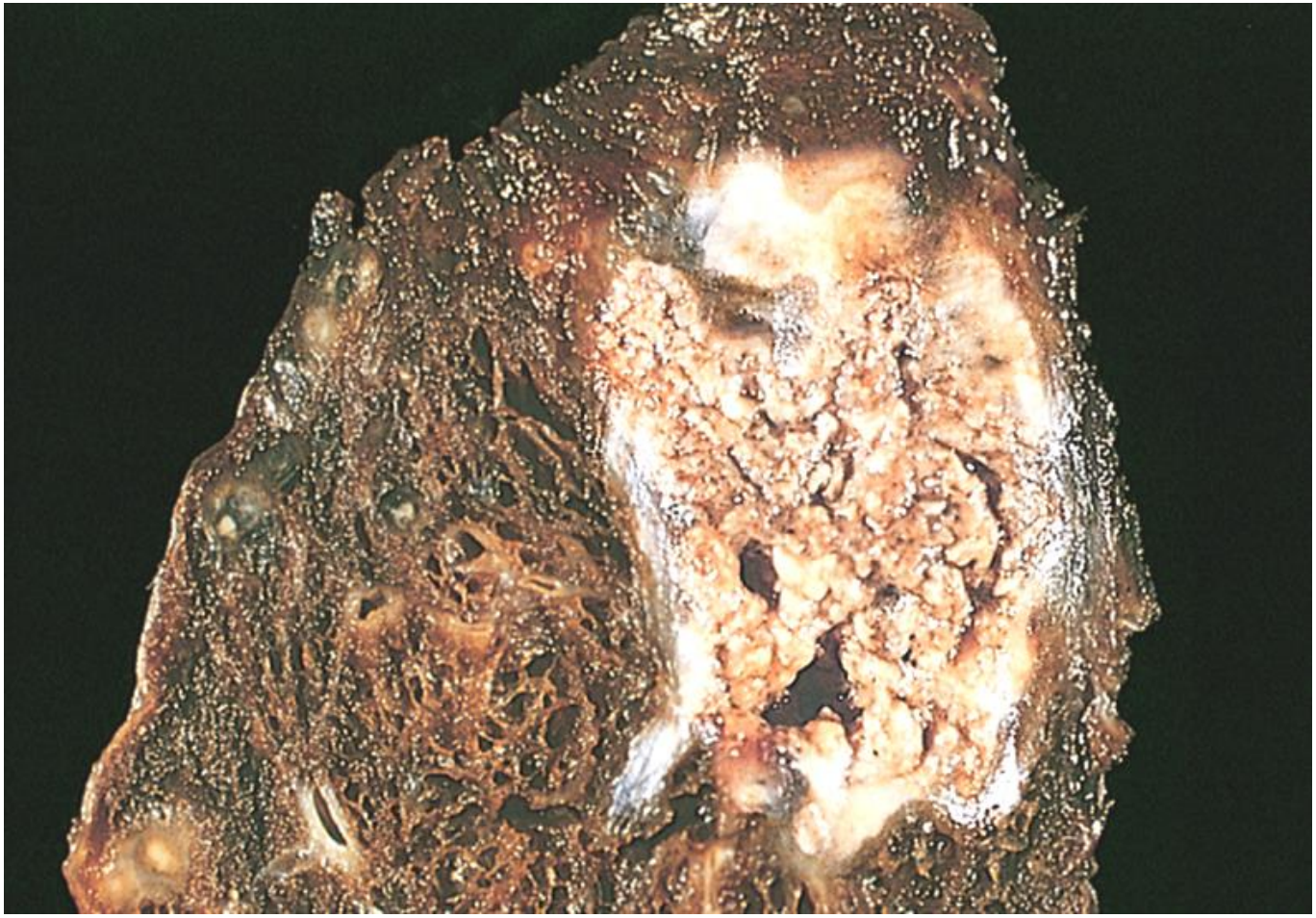
- This combines the features of coagulative and liquefactive necroses.
- It is encountered principally in the center of tuberculous granulomas.

The body response to tuberculous infection is a specific form of chronic inflammation referred to as granulomatous inflammation.

The morphologic unit of this is called granuloma.

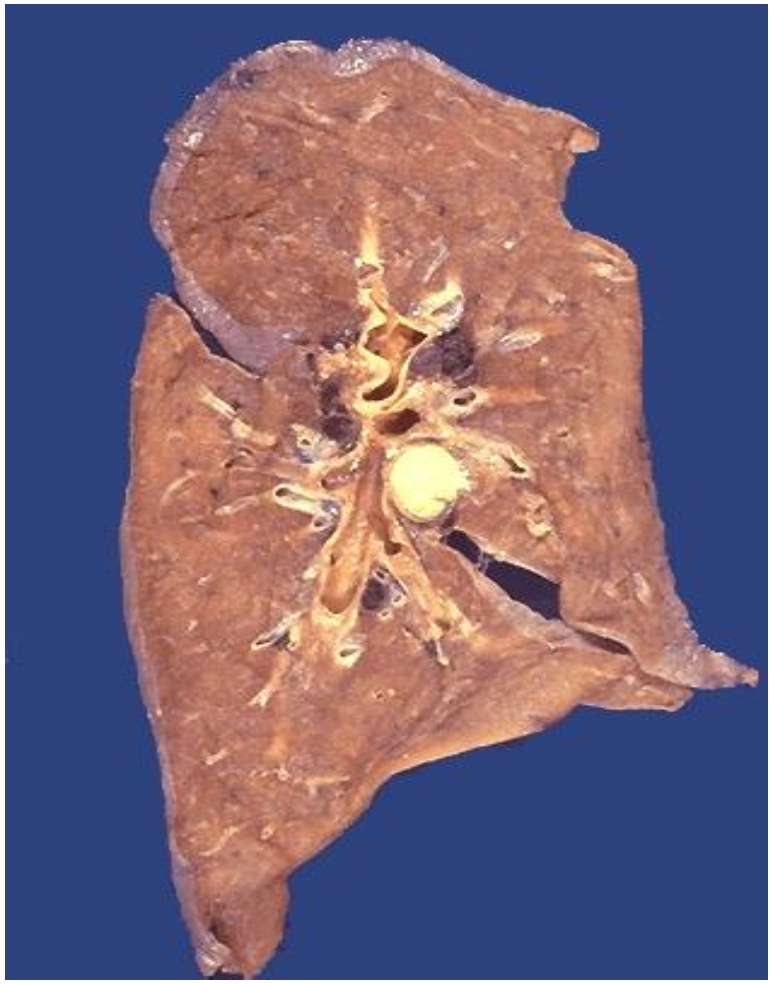
- Grossly the caseous material is soft, friable, whitish- gray cheesy material.
- Microscopically the area is surrounded by granulomatous inflammation. It has distinctive amorphous granular pinkish debris.

Caseous necrosis

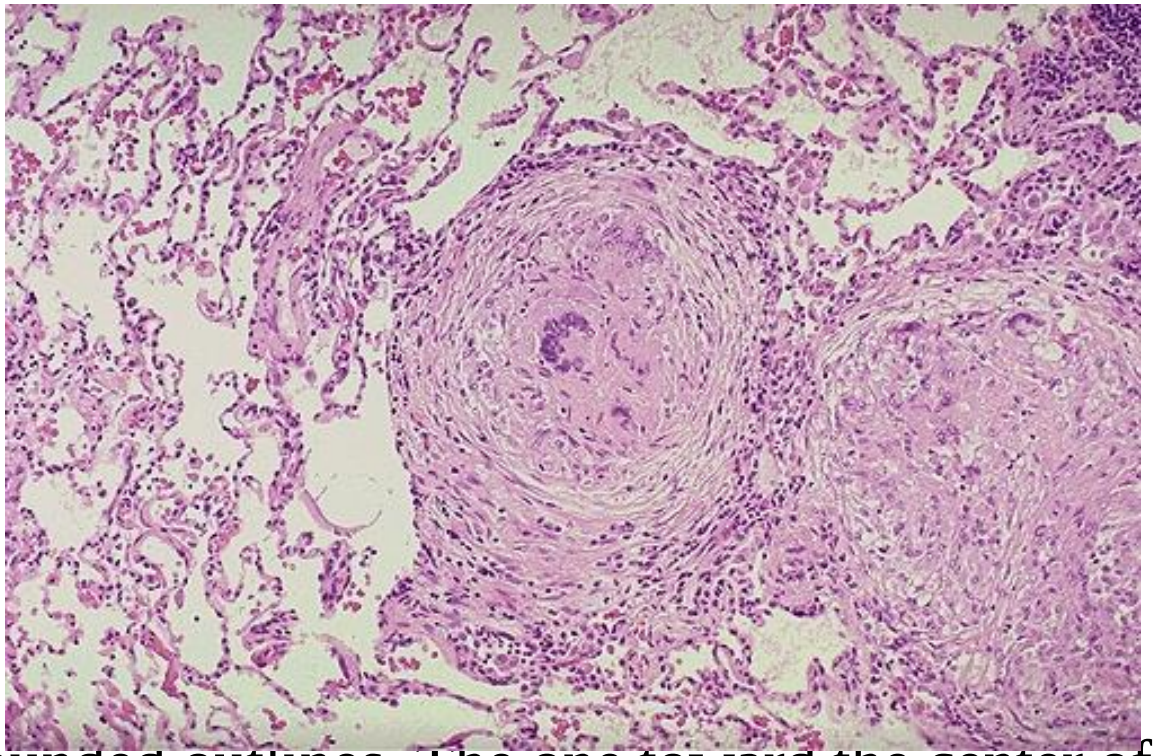


A tuberculous lung with a large area of caseous necrosis containing yellow-white and cheesy debris.

Gross appearance of caseous necrosis in a hilar lymph node infected with tuberculosis

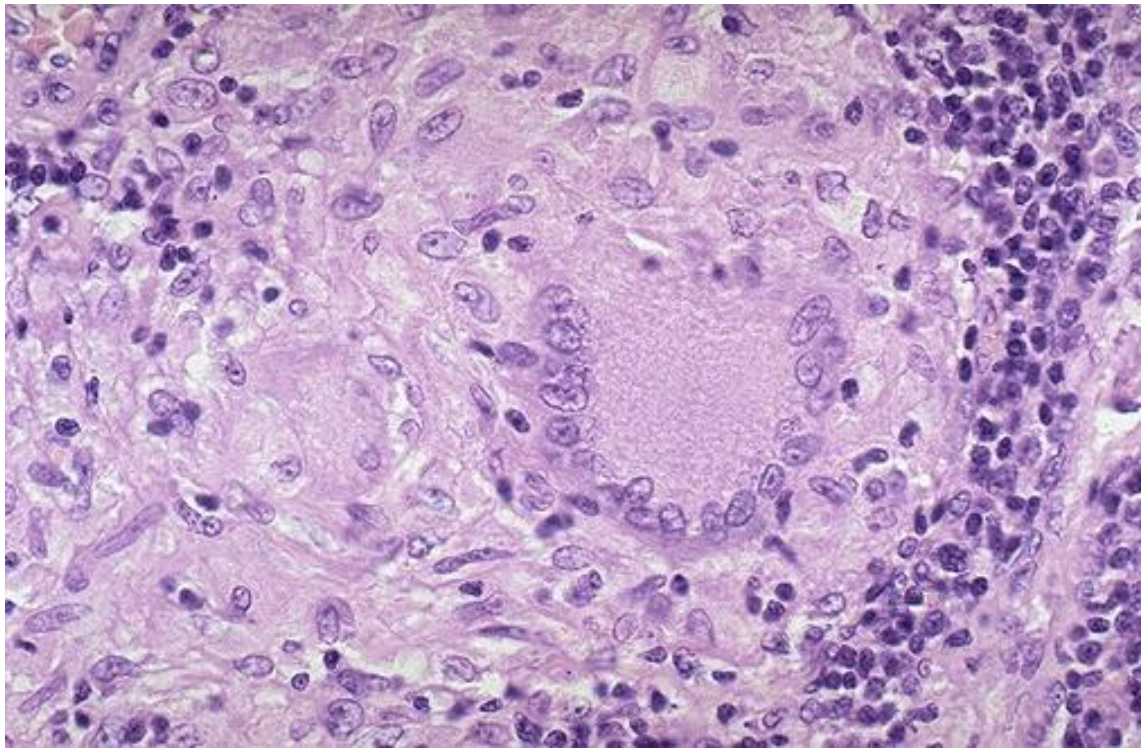


Tuberculosis. TB granuloma



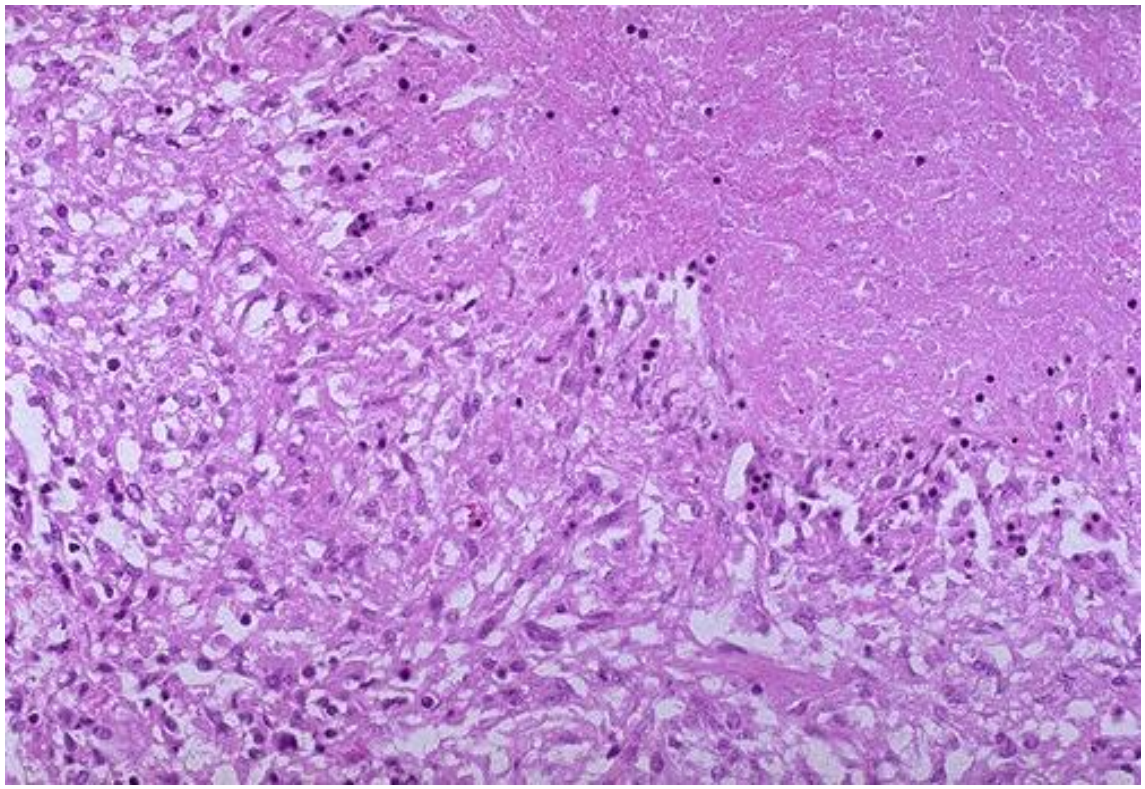
They have rounded outlines. The one toward the center of the photograph contains several Langhans giant cells.
Granulomas are composed of transformed macrophages called epithelioid cells along with lymphocytes, occasional polymorphonuclear cells , plasma cells, and fibroblasts. The localized, small appearance of these granulomas suggests that the immune response is fairly good.

Langhans giant cell



The typical giant cell for infectious granulomas (TB) is called **a Langhans giant cell** and has the nuclei lined up along one edge of the cell (Horseshoe). The process of granulomatous inflammation takes place over months to years.

Caseating granuloma



Microscopically, caseous necrosis is characterized by a cellular pink areas of necrosis, as seen here at the upper right, surrounded by a granulomatous inflammatory process.

5- Gangrenous necrosis:

- not represent a distinctive pattern of cell death, but is still in use as a term in **surgical practice**.

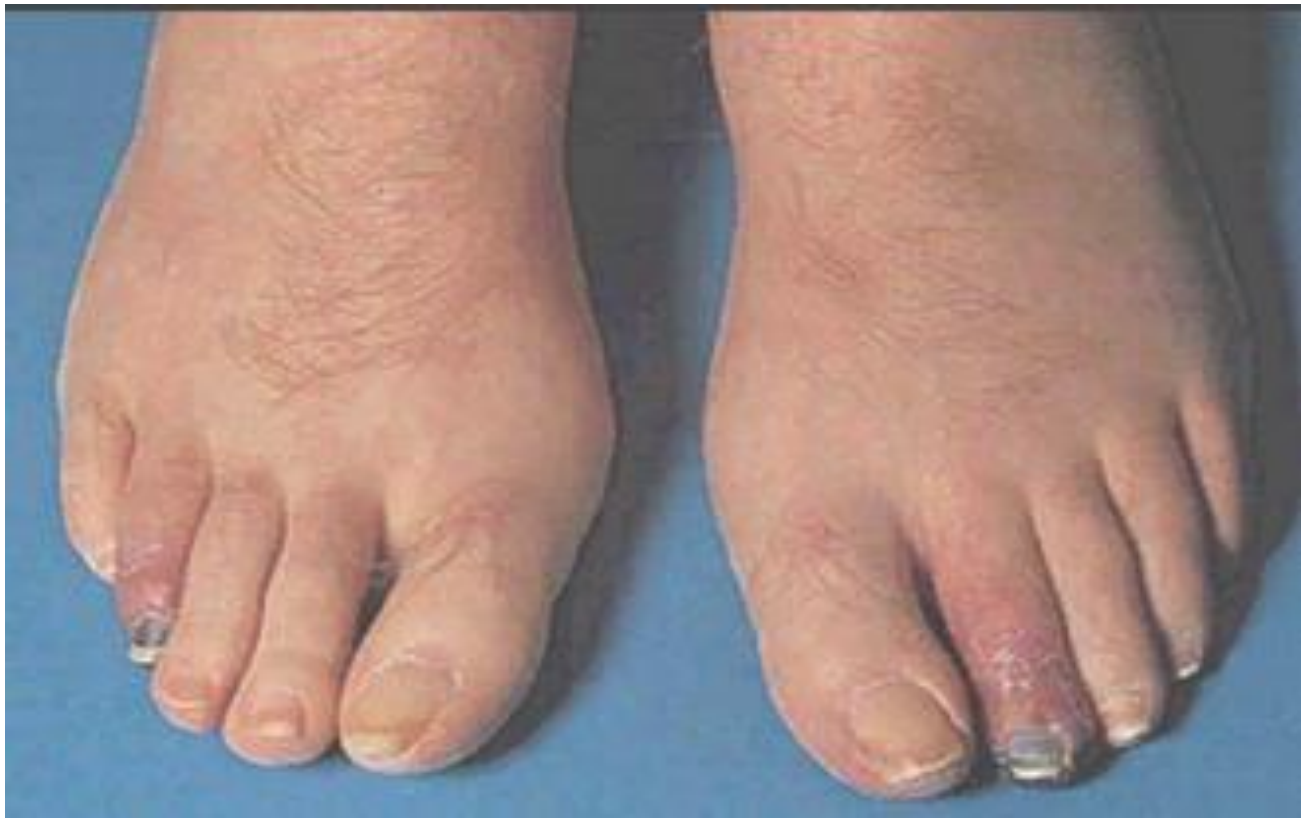
- It describes a limb (usually the lower) that has lost its blood supply and has subsequently attacked by bacteria.

- a combination of coagulative necrosis modified by liquefactive action of enzymes derived from bacteria and inflammatory cells.

- When the coagulative pattern is dominant the affected parts shrink and appear contracted (dry); the process is termed **dry gangrene.**

- Conversely, when the liquefactive action is more prominent, the affected parts are swollen (edematous); the term **wet gangrene** is used.

Dry gangrene



Mainly coagulative necrosis from the anoxic injury. This is gangrene, or necrosis of the toes that were involved in a frostbite injury.

a frostbite injury

wet gangrene

liquefactive component from superimposed infection in addition to the coagulative necrosis from loss of blood supply. This patient had diabetes mellitus.

6. Fibrinoid necrosis

intense eosinophilic staining of involved (necrotic) tissue. like fibrin.

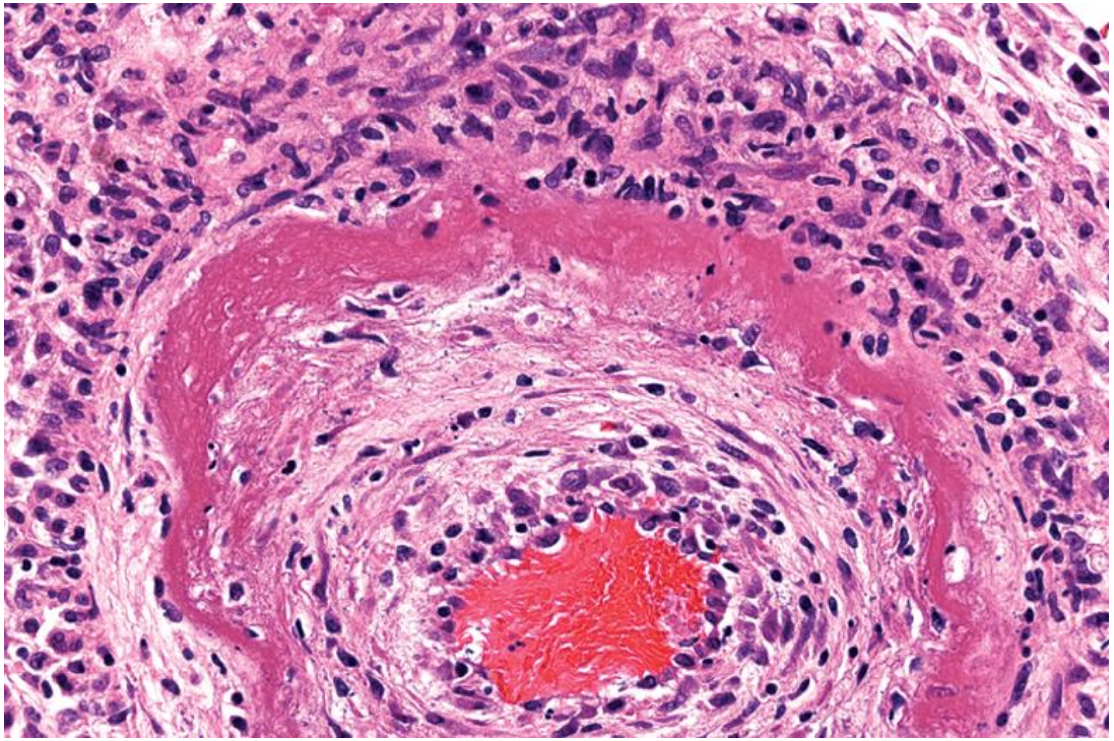
Examples:

- Fibrinoid necrosis of blood vessels in malignant hypertension.

- Fibrinoid necrosis of collagen in connective tissue diseases.

- Fibrinoid necrosis of blood vessels in vasculitis.

Fibrinoid necrosis in an artery in a patient with polyarteritis nodosa



The wall of the artery shows a circumferential bright pinkish area of necrosis with protein deposition and inflammation (dark nuclei of neutrophils).

7- Gummatous necrosis

- Derived its name from Gumma, a necrotic lesion seen in the tertiary stage of syphilis.
- It is a modified coagulative necrosis.

Fate of necrotic tissue

- Body treats necrotic tissue as foreign.
- It stimulates an inflammatory reaction that eventually remove the necrotic tissue and prepare for the process of **repair.**

Repair process by:

- Regeneration
- Organization

Both of these require controlled proliferation, migration, differentiation of cells and of extracellular matrix and its interaction with cells.

B- Apoptosis:

B- Apoptosis: a distinctive pattern of cell death.

Necrosis may be regarded as a morphological expression of cellular **"homicide" ,** whereas apoptosis is **"suicide".**

It is an, energy-dependent process for deletion of unwanted individual cells.

Examples include:

1. During embryogenesis i.e. it is responsible for shaping various organs and structures (morphogenesis).

2. Hormone-dependant involution.

a. Physiological e.g. involution of the endometrium during the menstrual cycle **or** lactating breast after weaning.

b. Pathological e.g. atrophy of the prostate after castration.

3. Deletion in proliferating cells e.g.

a. Physiological e.g. intestinal crypt epithelium.

b. Pathological e.g. in tumors.

4. Cell death induced by cytotoxic lymphocytes.

5. Through injurious agents that cause irreparable DNA damage that triggers apoptotic pathway of cell death e.g. heat, radiation and drugs.

Thus, failure of cells to undergo apoptosis may result in:

a. Anomalous development of various organs and tissues.

b. Progressive acceleration of tumor growth.

c. Autoimmune diseases.

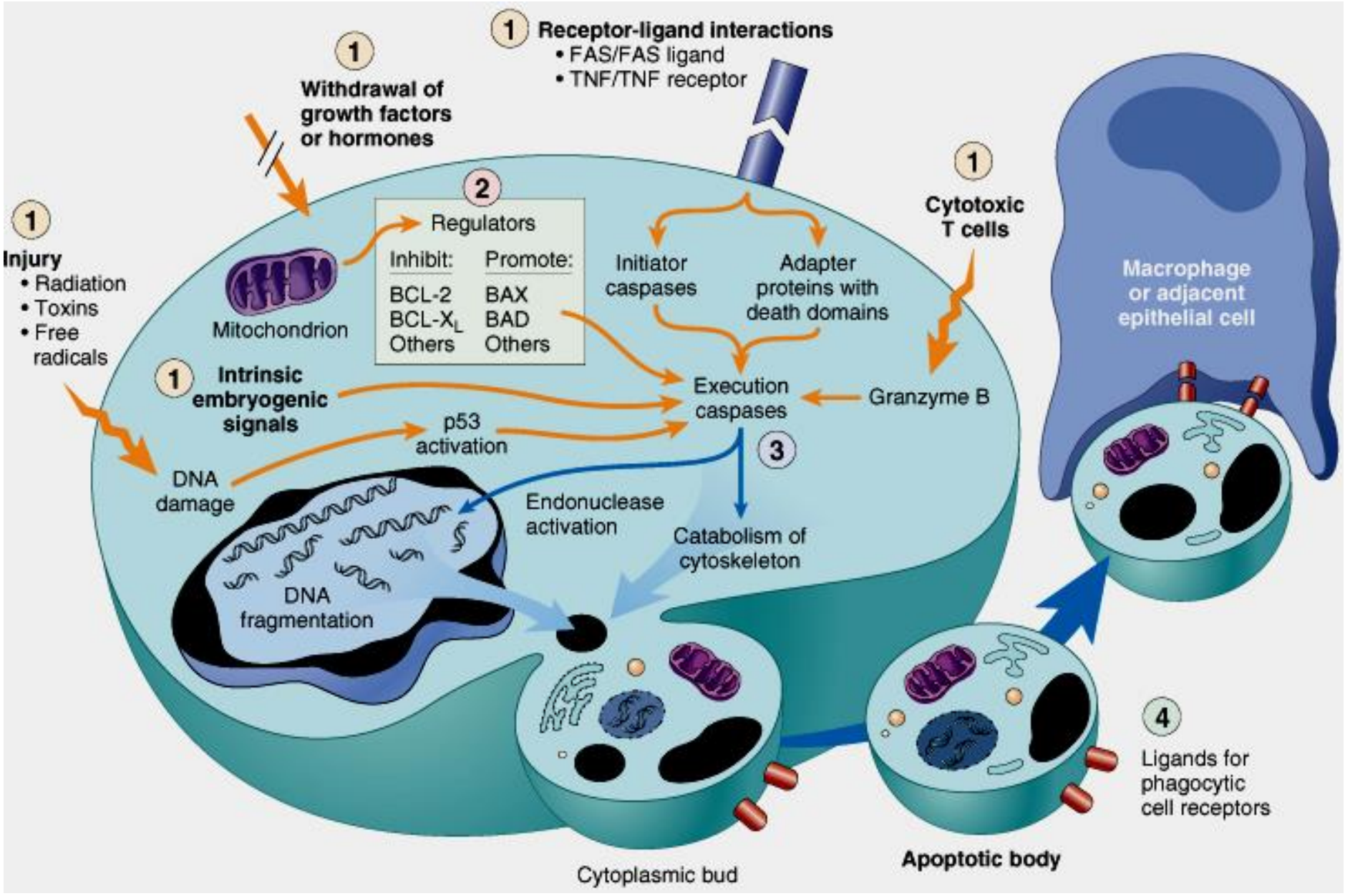
Mechanisms of apoptosis

Intrinsic - Mitochondrial pathway : is triggered by

- loss of survival signals, DNA damage and accumulation of misfolded proteins .
- leakage of pro-apoptotic proteins from mitochondrial membrane into the cytoplasm, where they trigger caspase activation; inhibited by anti-apoptotic members of the Bcl family, which are induced by survival signals including growth factors.

Extrinsic - Death receptor pathway:

is responsible for elimination of self-reactive lymphocytes and damage by cytotoxic T lymphocytes; is initiated by engagement of death receptors (members of the TNF receptor family) by ligands on adjacent cells.


1
Receptor-ligand interactions
• FAS/FAS ligand
• TNF/TNF receptor
1
Withdrawal of growth factors or hormones
1
Injury
• Radiation
• Toxins
• Free radicals
2
Regulators
Inhibit: Promote:
BCL-2 BAX
BCL-XL BAD
Others Others
Mitochondrion
Initiator caspases
Adapter proteins with death domains
1
Cytotoxic T cells
Macrophage or adjacent epithelial cell
1
Intrinsic embryogenic signals
p53 activation
Execution caspases
Granzyme B
DNA damage
3
Endonuclease activation
Catabolism of cytoskeleton
DNA fragmentation
4
Ligands for phagocytic cell receptors
Cytoplasmic bud
Apoptotic body

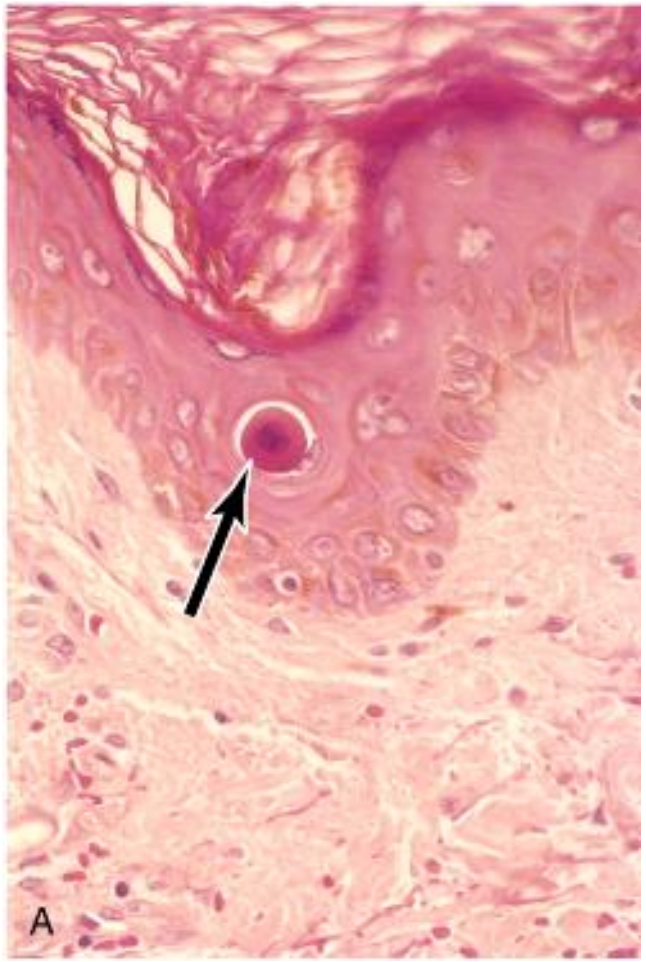
Morphology of apoptosis:

- Apoptosis usually involves single cells or clusters of cells.

- apoptotic cell appears as rounded or oval with intensely eosinophilic (red) cytoplasm. The nuclear chromatin is aggregated under the nuclear membrane with nuclear shrinkage (pyknosis). This is followed by nuclear fragmentation (karyorrhexis).
- Then cytoplasmic budding occur and each nuclear fragment will be contained within one bud. The resulting structure is called **apoptotic body.** These fragments are quickly extruded and phagocytosed or degraded.

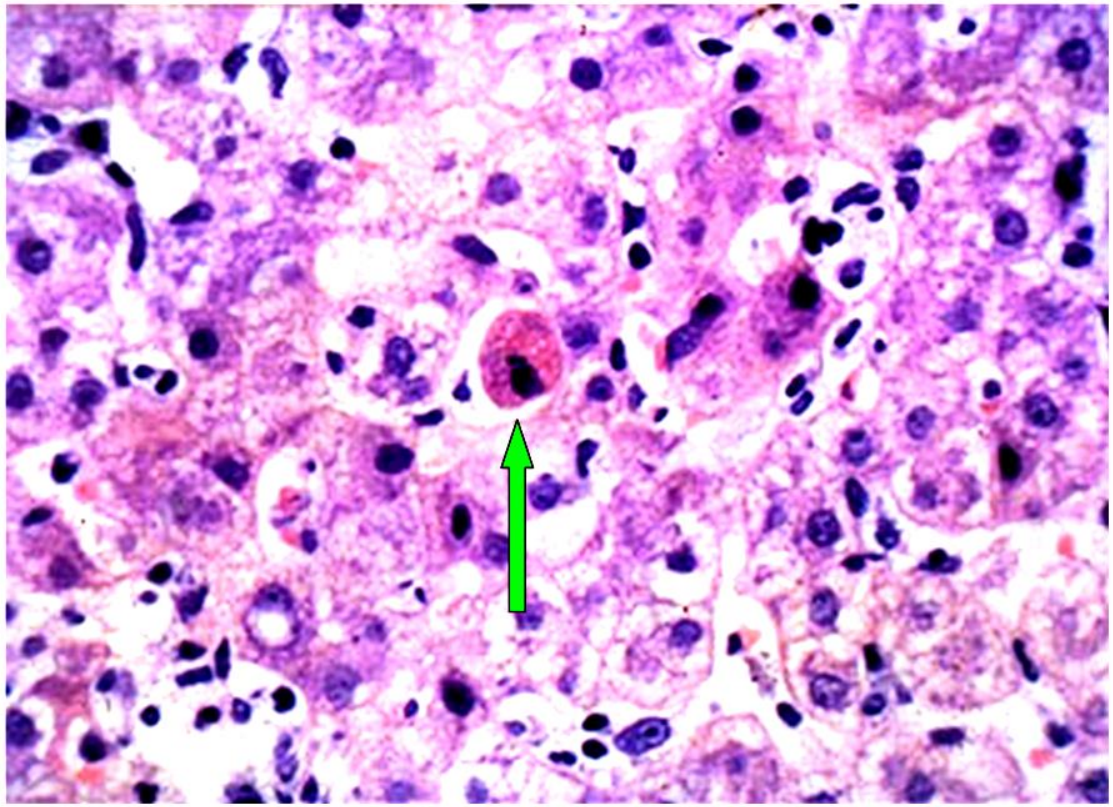
- Apoptosis does not trigger an inflammatory response.

Apoptosis



- Apoptosis of epidermal keratinocyte.
- The cytoplasm is intensely esoniphilic (pinkish) and the nucleus condensed (pyknotic).

Apoptotic liver cell in a case of acute viral hepatitis (HBV) (Councilman body or acidophilic body) (arrow)



Apoptosis of a liver cell in viral hepatitis. The cell is reduced in size and contains brightly eosinophilic cytoplasm and a condensed nucleus.

Compare & contrast necrosis with apoptosis

- **Apoptosis**
  - Active process
  - Occur in single cells
  - physiological&pathological
  - No inflammatory reaction
  - Step - ladder appearance on gel electrophoresis for DNA material.
- **Necrosis**
  - Passive process
  - Affects mass of cells
  - Always pathological
  - stimulates Inflammation
  - Smudge pattern.

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome - size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids

Feature	Necrosis	Apoptosis
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

Intracellular accumulations

Intracellular accumulations

The accumulated substance falls into one of three categories:

1. A normal cellular constituent accumulated in excess :
   e.g. lipid, protein, and carbohydrates.
2. An abnormal substance that is a product of abnormal metabolic pathway.
3. A pigment i.e. a colored substance.

accumulation is either:

- harmless **or** severely toxic to the cell.

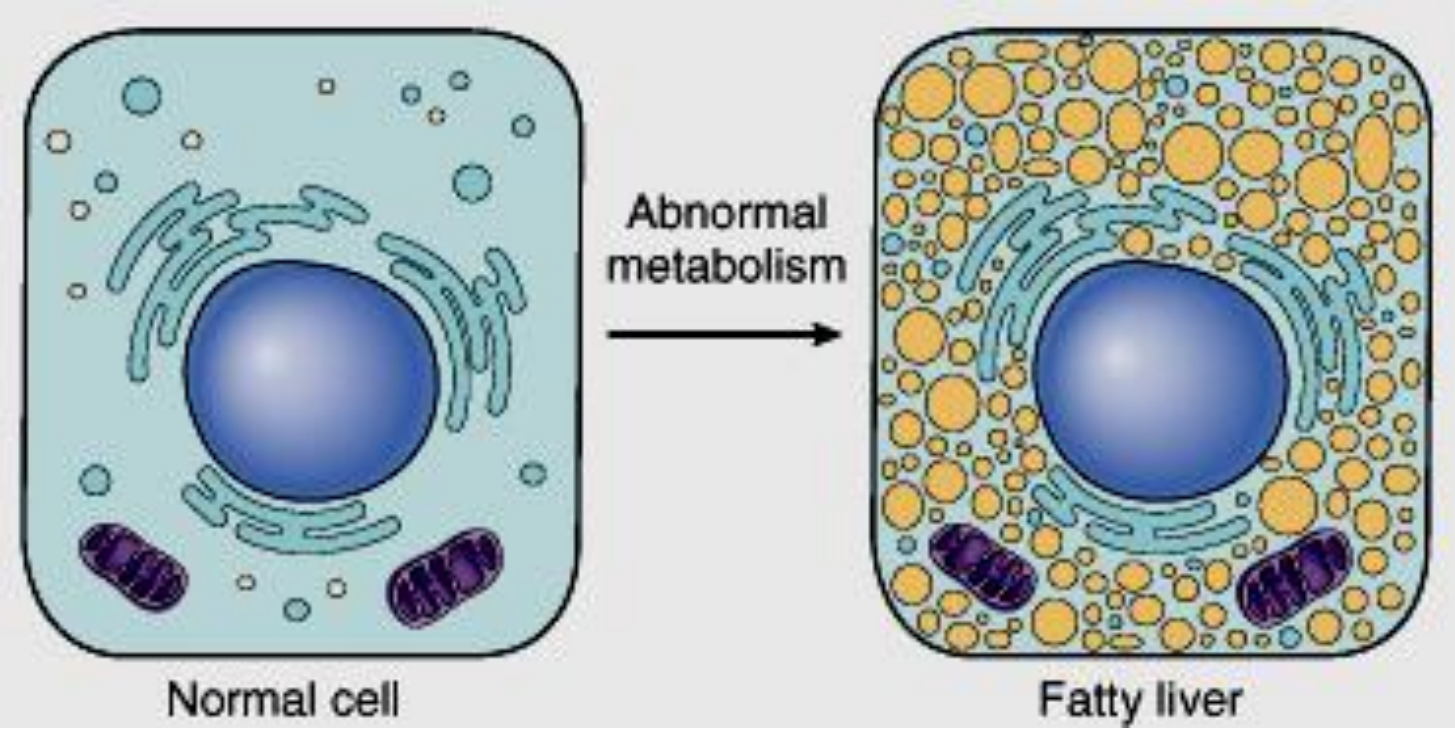
- **nuclear or cytoplasmic.**
  Within the cytoplasm, the accumulated substance is most frequently within the lysosomes.

Mechanisms of abnormal intracellular accumulations

1. Abnormal metabolism:

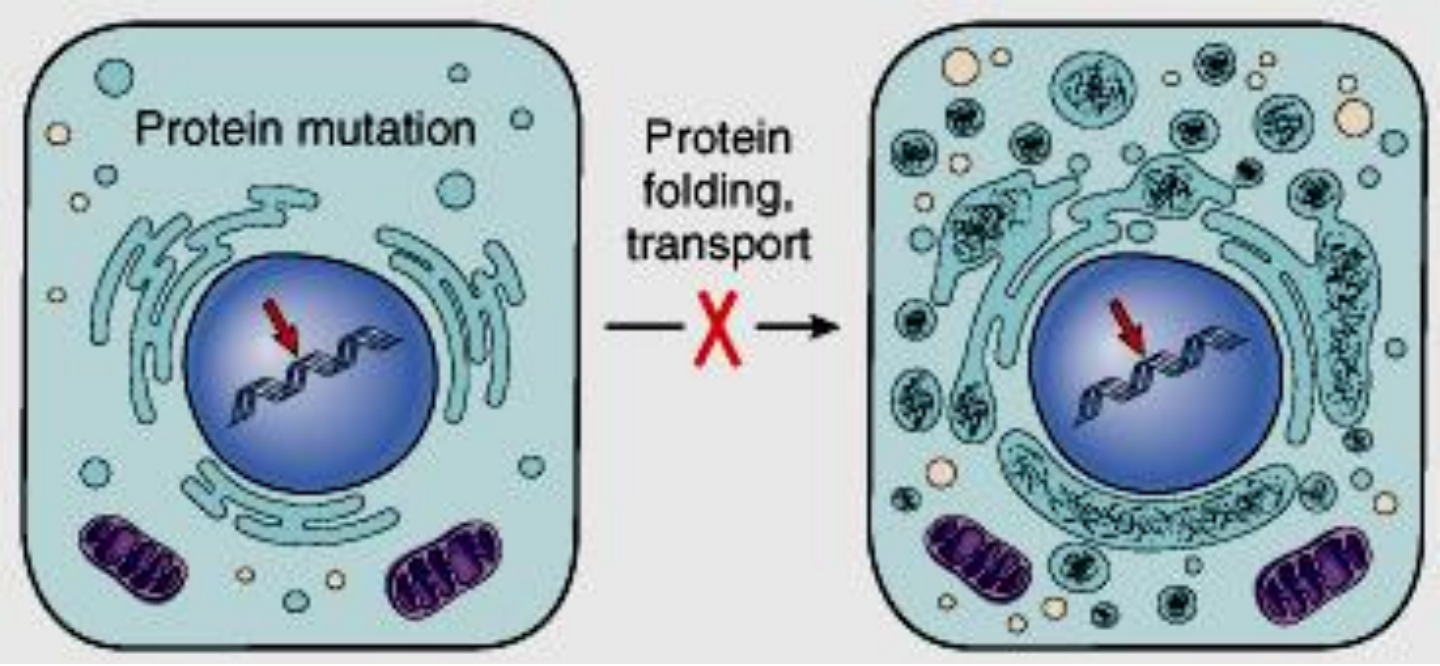
A normal substance is produced at a normal rate, but the rate of its removal is inadequate. e.g.

- fatty change of the liver and
- occurrence of protein droplets in the epithelial cells of proximal convoluted tubules in cases of proteinuria due to leaky glomeruli.



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

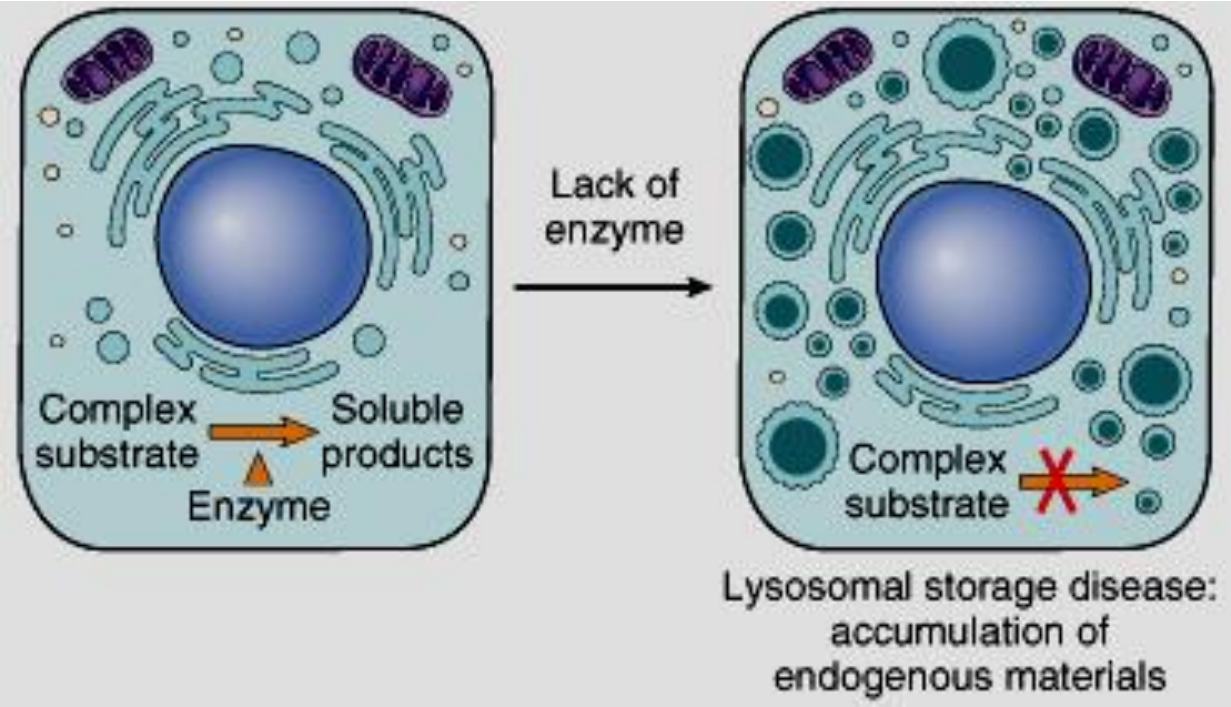
A protein is composed of amino acids linked in specific sequences by peptide bonds and coiled and folded into complex globular or fibrous structures. A change in this configuration may result in interference with its transport so that it gets accumulated at the site of production.



3. A normal or abnormal substance is produced but cannot be metabolized.

This is most commonly due to lack of an enzyme, which is genetically determined **(inborn error of metabolism).** Such a deficiency of enzymes blocks a specific metabolic pathway resulting in the accumulations of unused metabolite(s) proximal to the block.

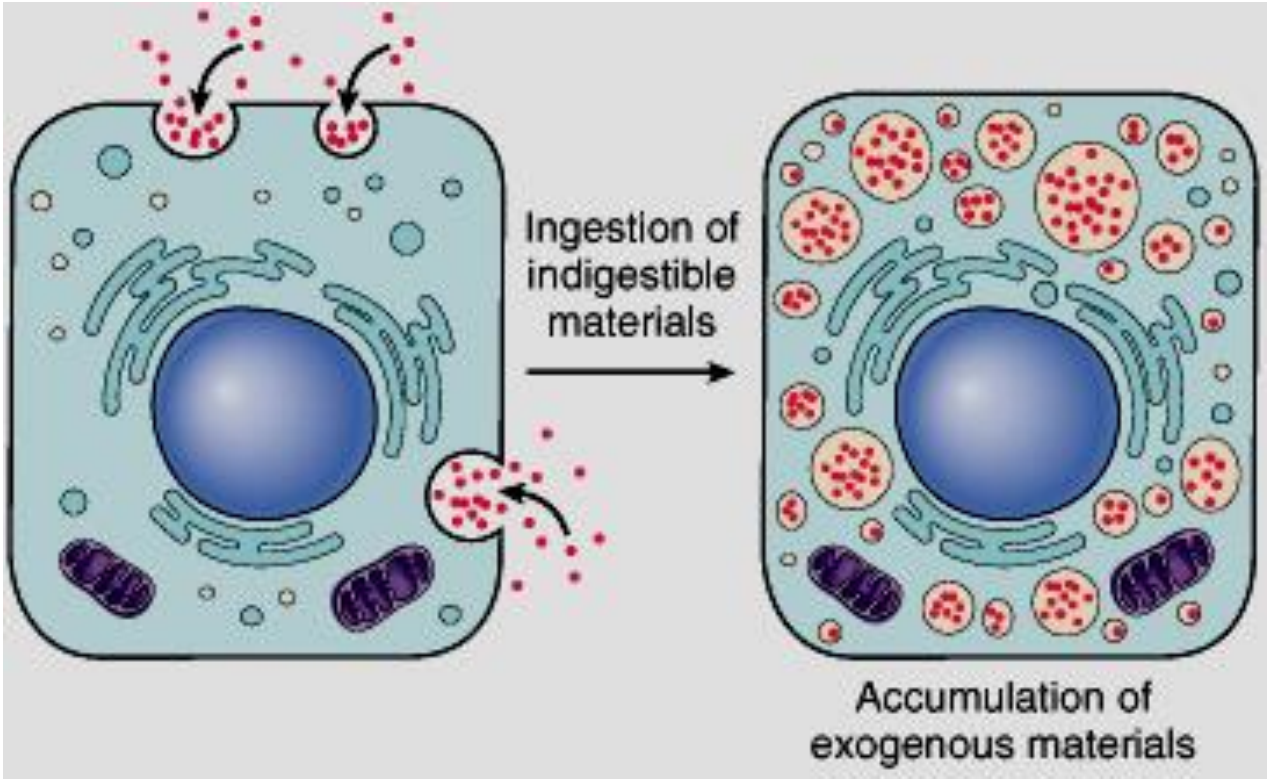
The resulting diseases are referred to as **storage diseases.**



4. An abnormally exogenous substance:

is deposited and accumulates because the cell is incapable to get rid of it (through enzymatic degradation or transport it to the outside).

e.g carbon particles in anthracosis & silica particles in silicosis.



Accumulation of lipids

Fatty change:

This refers to abnormal accumulation of fat of triglyceride type within parenchymal cells.

It is an example of reversible (non-lethal) cell injury and is often seen in the **liver,** because of the central role of this organ in fat metabolism.

Free fatty acids are transported to the liver from two sources:

1. adipose tissue.
2. ingested food.

Etiology:

In the liver these fatty acids are esterified to triglycerides.

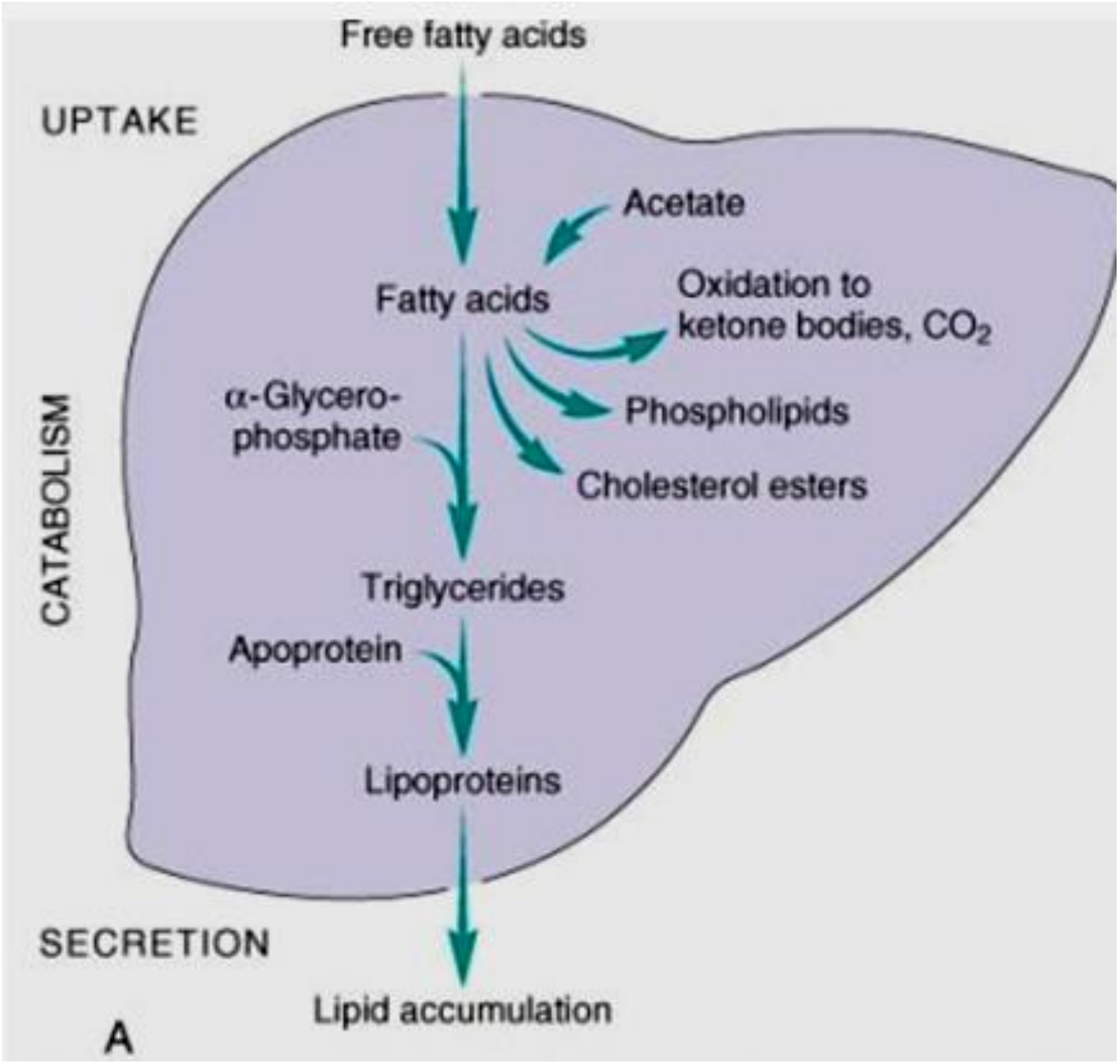
In the liver mild fatty change shows no gross changes, but with progressive accumulation, the organ enlarges and become increasingly yellow, soft and greasy to touch.

Microscopic features:

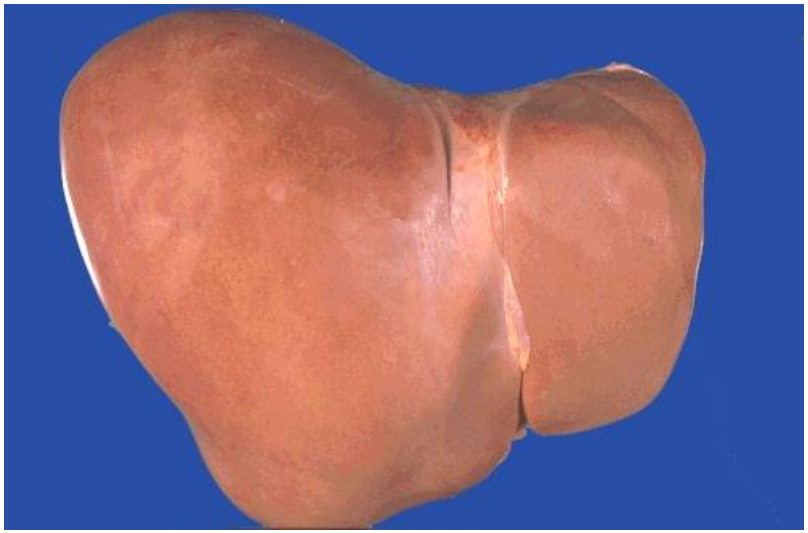
- In the early stages there are small fat vacuoles around the nucleus.
- with progression the vacuoles fuse together creating large clear space that displaces the nucleus to the periphery (in contrast with hydropic changes).

Fatty change may also be seen within **myocardial cells**

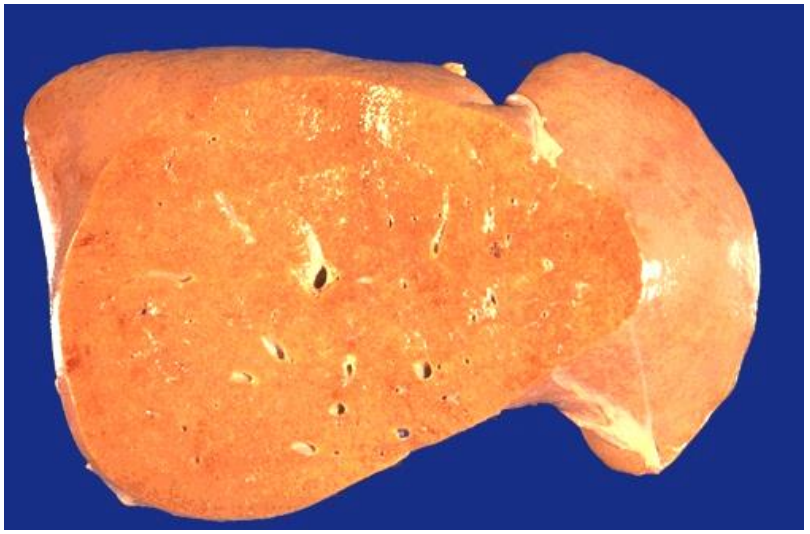
e.g. in ischemia and myocarditis. The latter may be seen as a complication of diphtheria.


Free fatty acids
UPTAKE
Acetate
Fatty acids
Oxidation to ketone bodies, CO_2
α-Glycero-phosphate
Phospholipids
Cholesterol esters
CATABOLISM
Triglycerides
Apoprotein
Lipoproteins
SECRETION
Lipid accumulation
A

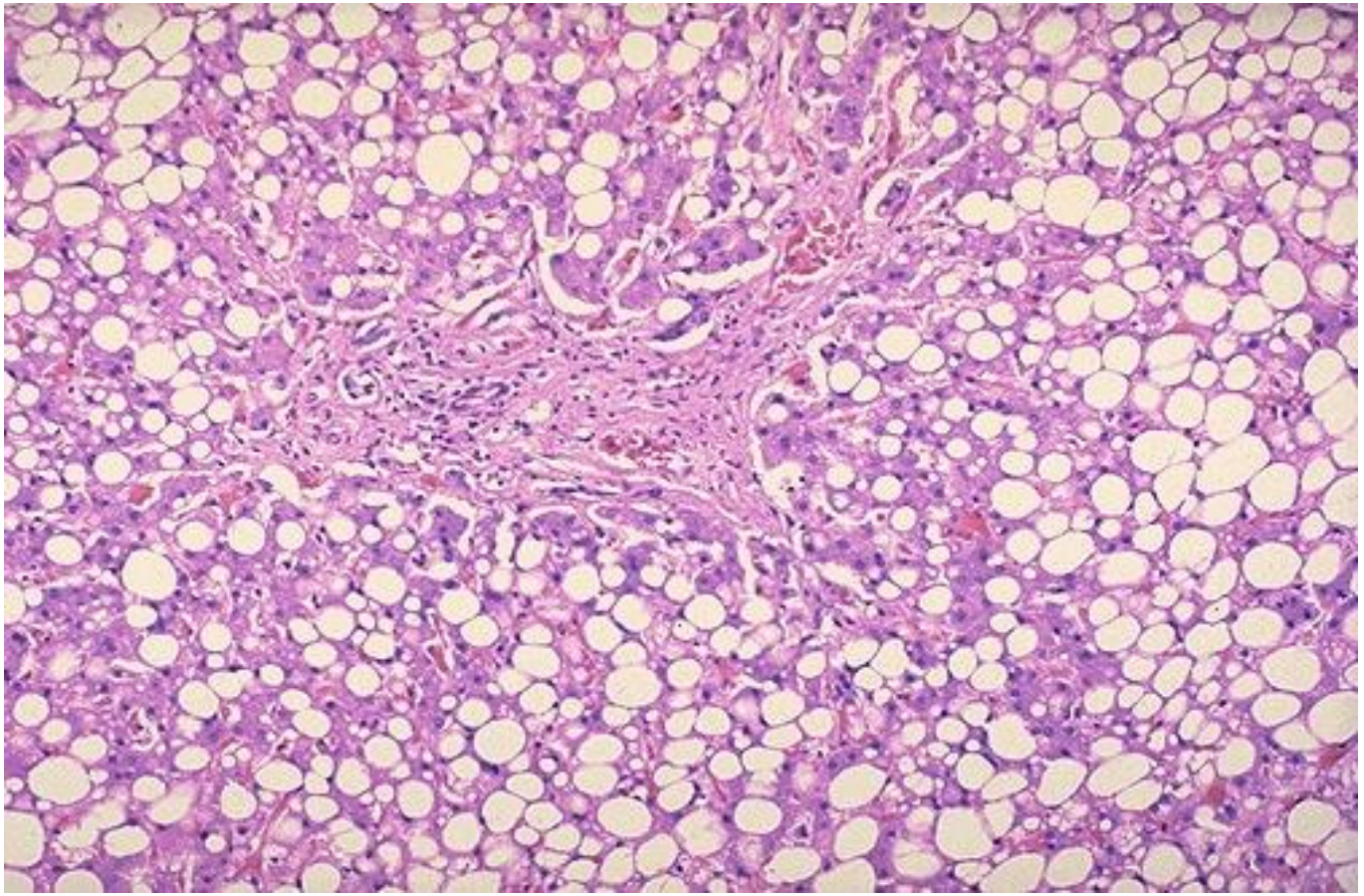
Fatty change liver



Normal



Fatty change



Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is **fatty metamorphosis (fatty change) of the liver** in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes

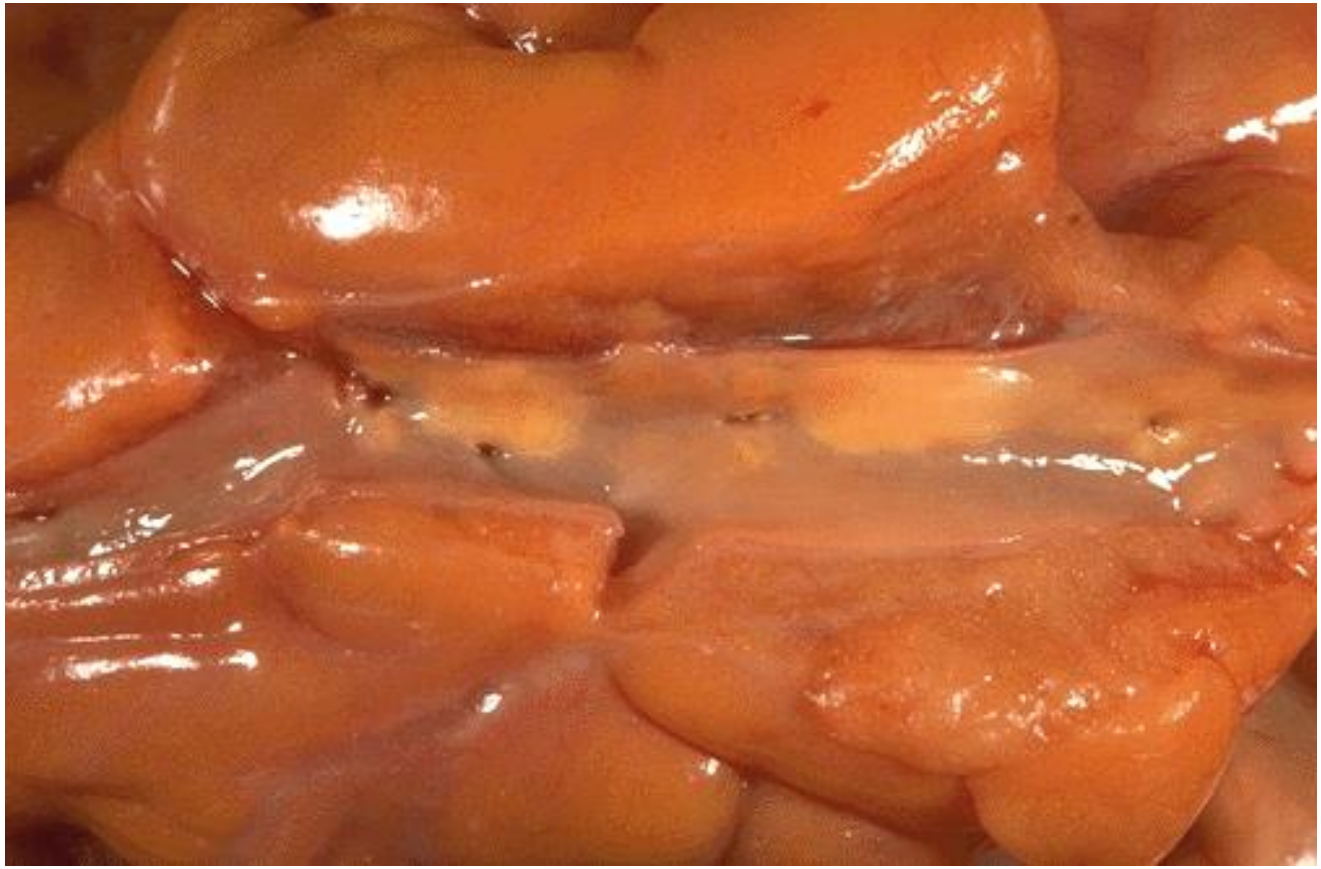
In addition to fatty changes

Accumulations may involve cholesterol and its esters:

a. Within smooth muscle cells and macrophages that are located the intima of arteries in **atherosclerosis.**

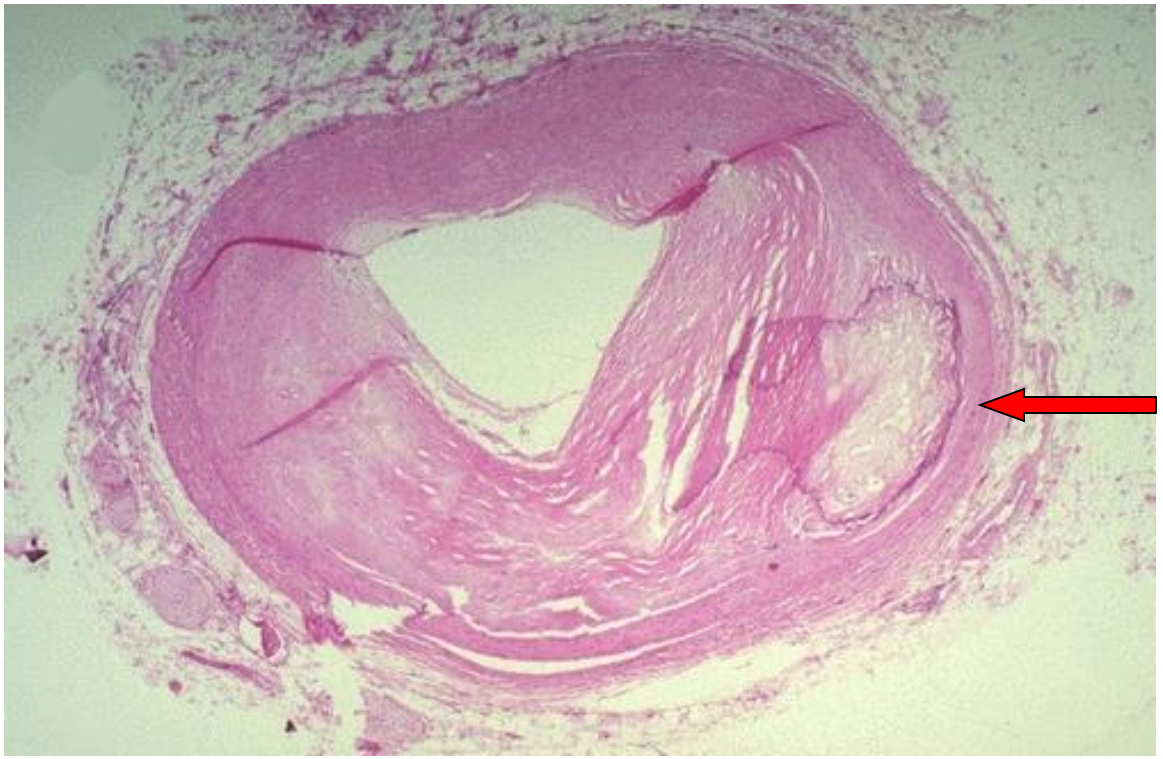
b. within Macrophages in the acquired and hereditary hyperlipidemias: in such cases the accumulations are usually seen within the subcutaneous connective tissues of the skin and in tendons producing masses known as **xanthomas.**

Mild coronary atherosclerosis



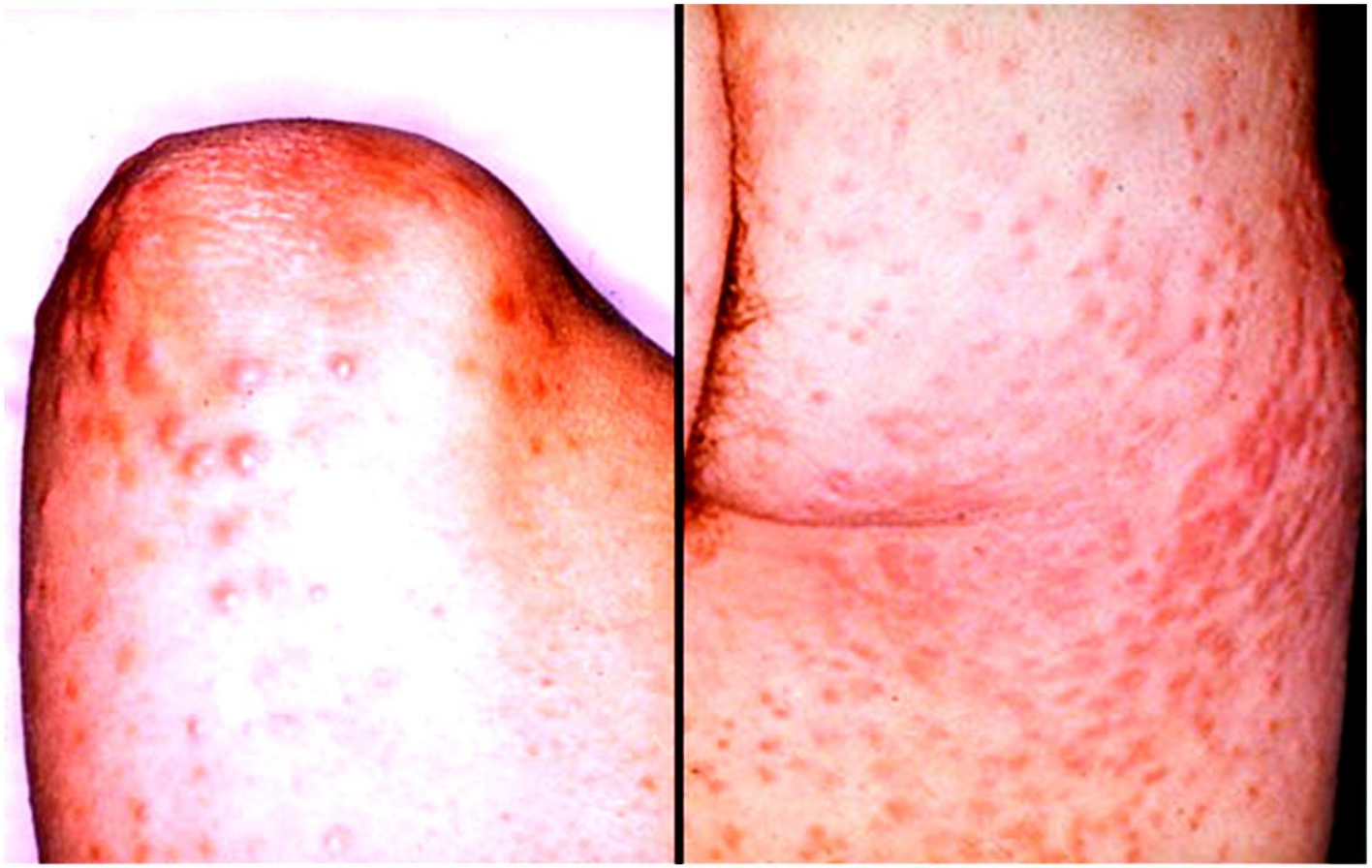
A few scattered yellow lipid plaques are seen on the intimal surface of the opened coronary artery traversing the epicardial surface of a heart. The degree of atherosclerosis here is not significant enough to cause disease .

Atherosclerosis



The degree of atherosclerosis is much greater in this coronary artery, and the lumen is narrowed by half. A small area of calcification is seen in the plaque at the right.

Cutaneous xanthomas



Eruptive xanthomas are seen over the elbow at the left and the buttocks at the right. These yellow papules may be seen in patients with hyperlipidemia. The lesions get their color from the numerous lipid-laden macrophages that are present in them.

Accumulation of Protein

This occurs principally in the:

1. Epithelial cells of proximal convoluted renal tubules,

e.g. in cases of proteinuria.

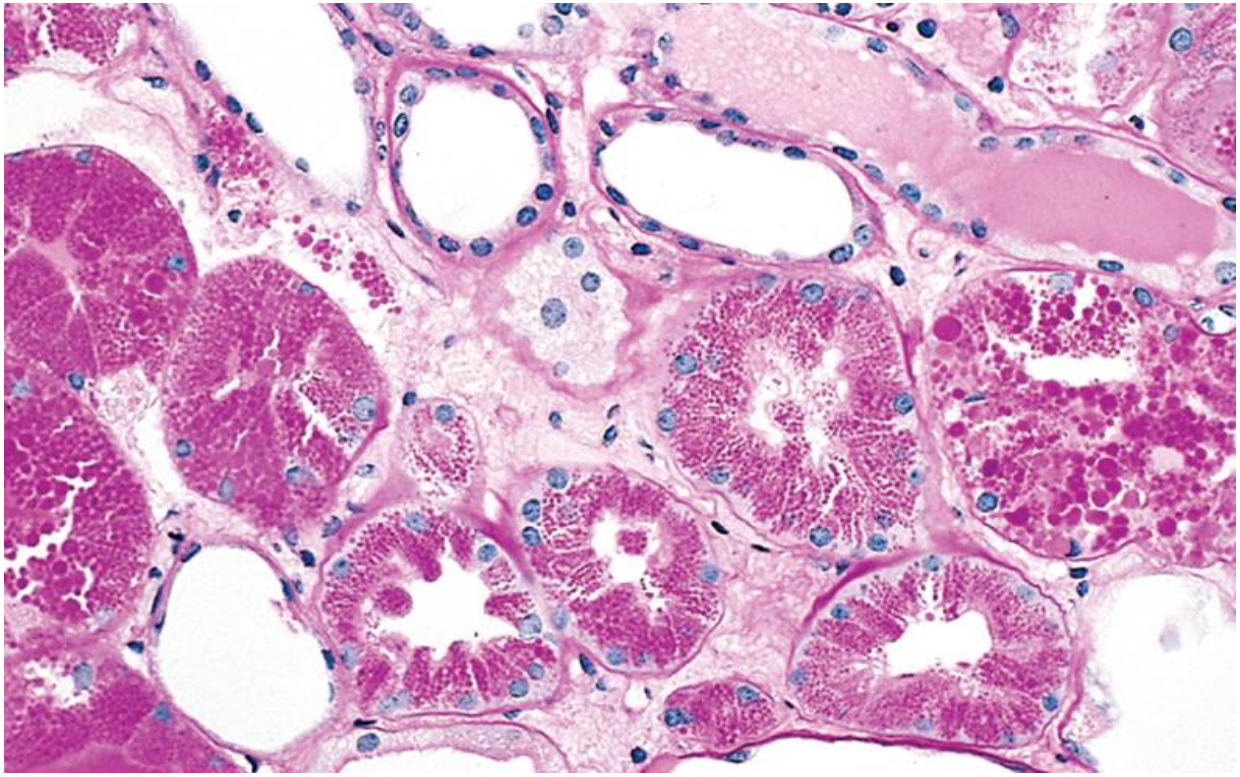
2. Plasma cells, these cells are actively engaged in immunoglobulin synthesis (antibody-formation) and may become overloaded with its own products **(Russell bodies).**

Glycogen accumulations:

Accumulation of glycogen within the cytoplasm is seen as clear cytoplasmic vacuoles. PAS (periodic acid-Schiff reagent) stain is routinely used for its demonstration (appears as red to violet in color).

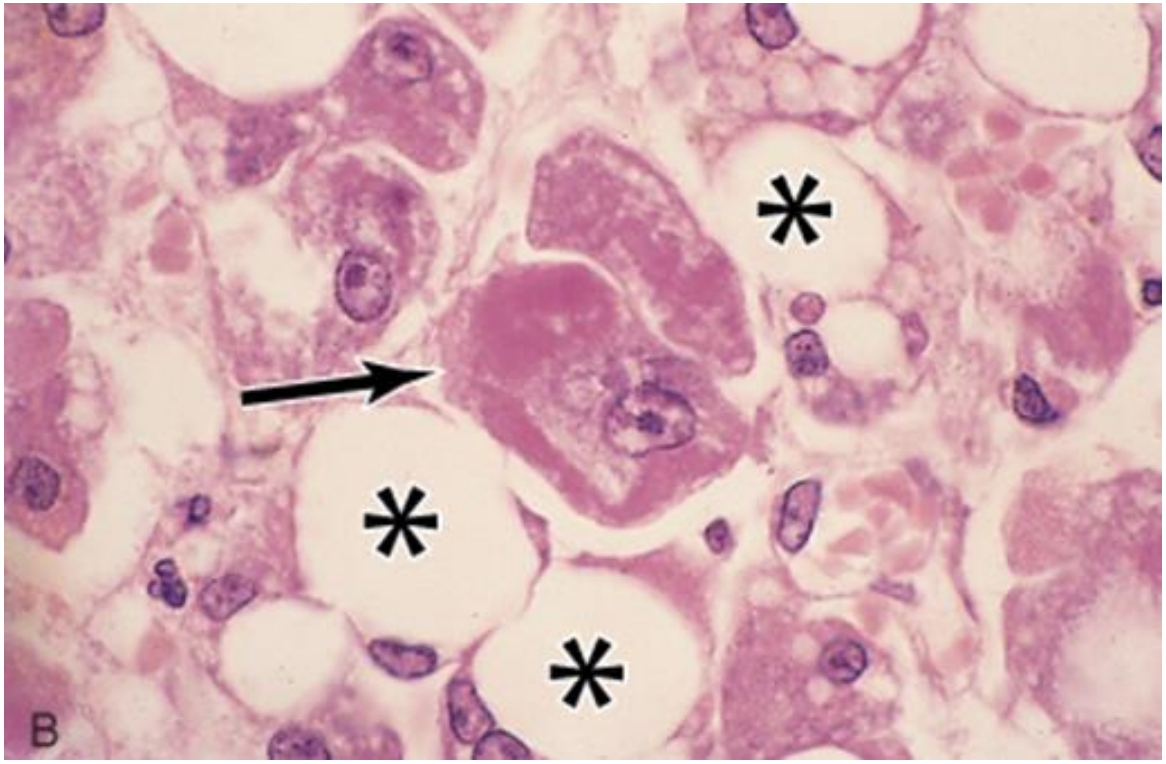
Diabetes mellitus: causes glycogen accumulation within the epithelial cells of distal renal tubules producing virtual clearing of their cytoplasm. Similar accumulations occur in the cells of the liver, heart and islet cells of Langerhans within the pancreas.

Protein reabsorption droplets in the renal tubular epithelium .
the droplets are contained within pinocytic vacuoles and within lysosomes.



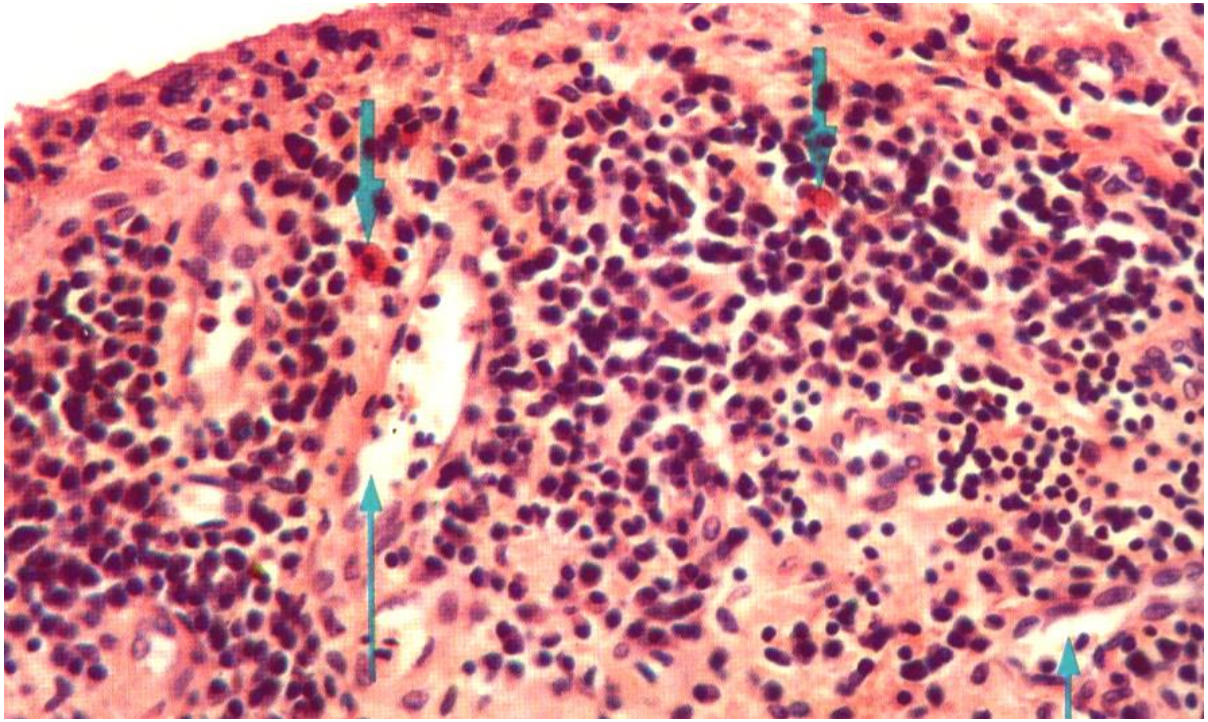
PAS (periodic acid-Schiff reagent)

Alcoholic Mallory bodies & fatty changes



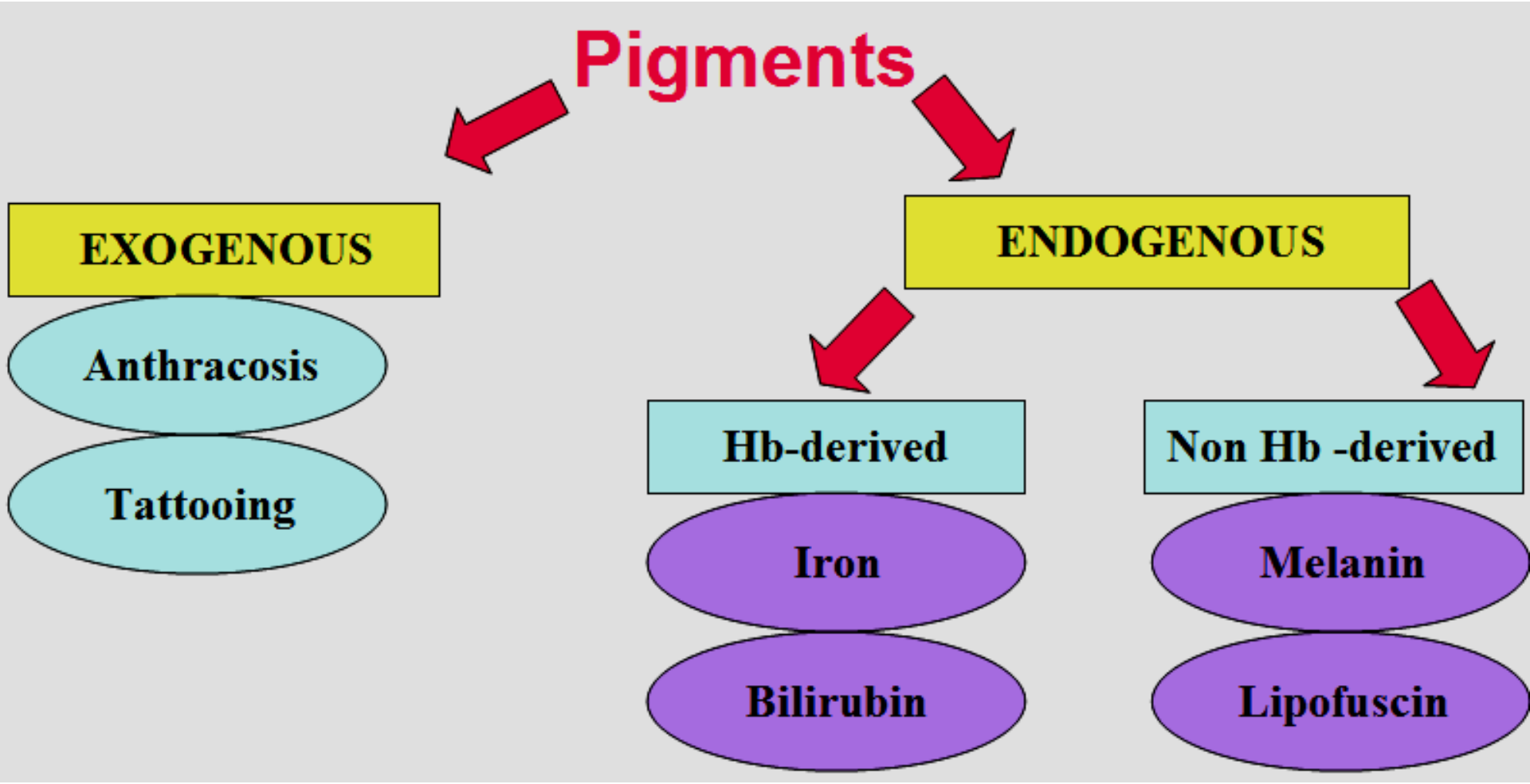
B- Alcoholic hyalin *(arrow)* (also called Mallory bodies), composed of aggregated intermediate filaments in hepatocytes from an individual with chronic alcohol abuse. Also note the intracellular fat accumulation *(asterisks)*, associated with acute alcohol intake.

Russell bodies



Rheumatoid arthritis. The connective tissue is vascular, with numerous dilated small blood vessels (thin arrows), and its stroma is heavily infiltrated with chronic inflammatory cells, many of which are mature plasma cells. **Two Russell bodies (thick arrows), effete plasma cells with red-stained cytoplasm, are present.**

Pigments


Pigments
EXOGENOUS
Anthracosis
Tattooing
ENDOGENOUS
Hb-derived
Iron
Bilirubin
Non Hb -derived
Melanin
Lipofuscin

Pigments

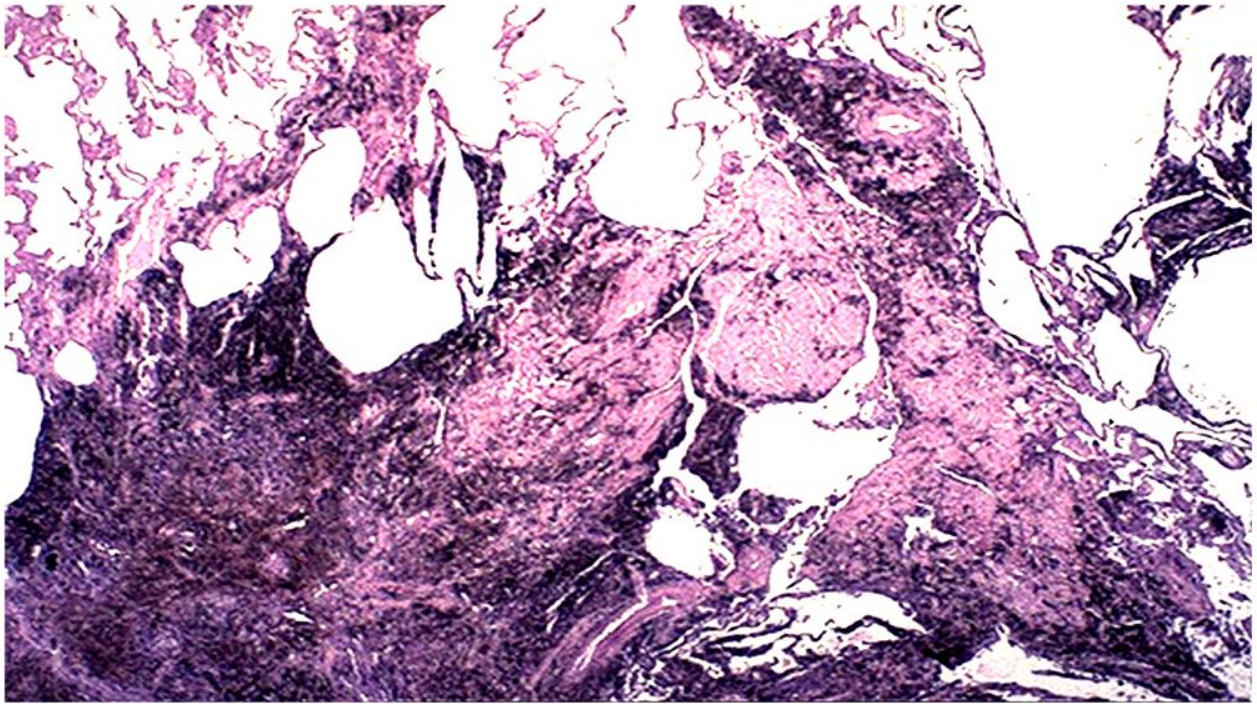
- **Either exogenous or endogenous.**
- **The endogenous either normal constituents of the body** e.g. **melanin or abnormal that accumulate under certain situations**.

A- Exogenous pigment is **carbon** (coal dust).

When this is inhaled, it is picked up by macrophages within the alveoli then transported via lymphatics to regional lymph nodes in the hila of the lungs. Accumulation of this carbon pigment causes black discoloration of lung tissue, a condition called **anthracosis, in coal miners** and in those living in heavily polluted atmosphere the deposition may be very marked and associated with fibrosis and emphysema (coal worker's pneumoconiosis).

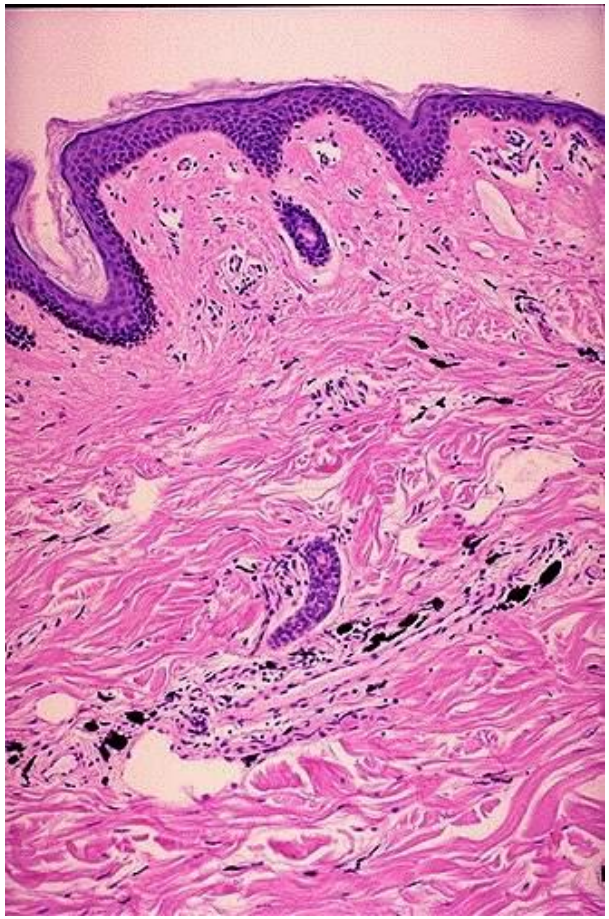
Tattooing is a form of exogenous pigmentation of the skin. The pigment inoculated is taken up by dermal macrophages.

Lung coal worker's pneumoconiosis



Anthracotic pigment in small quantities does not lead to fibrosis, but in massive amounts (as in "black lung disease" in coal miners) it is associated with excessive collagenous fibrosis that is impregnated with the black pigment.

Skin tattoo



Lt. Tattoo. Tattooing is a practice that is thousands of years old. The pigment in tattoos is transferred to the **dermis** with a needle.

Rt. This is the microscopic appearance of tattoo pigment (black) in the dermis. Note that this pigment is well within the dermis and, therefore, difficult to remove.

B- Endogenous pigments

1 . Lipofuscin.
2. Melanin.
3. Derivatives of hemoglobin.

1- Lipofuscin (lipochrome pigment):

This is a yellow-brown (fuscus = brown), intra-cytoplasmic pigment, which is seen in cells undergoing slow atrophy:

a. Particularly prominent in the cells of the liver and heart of the elderly. (Brown atrophy of the heart).

b. Patients with severe malnutrition and cancer cachexia.

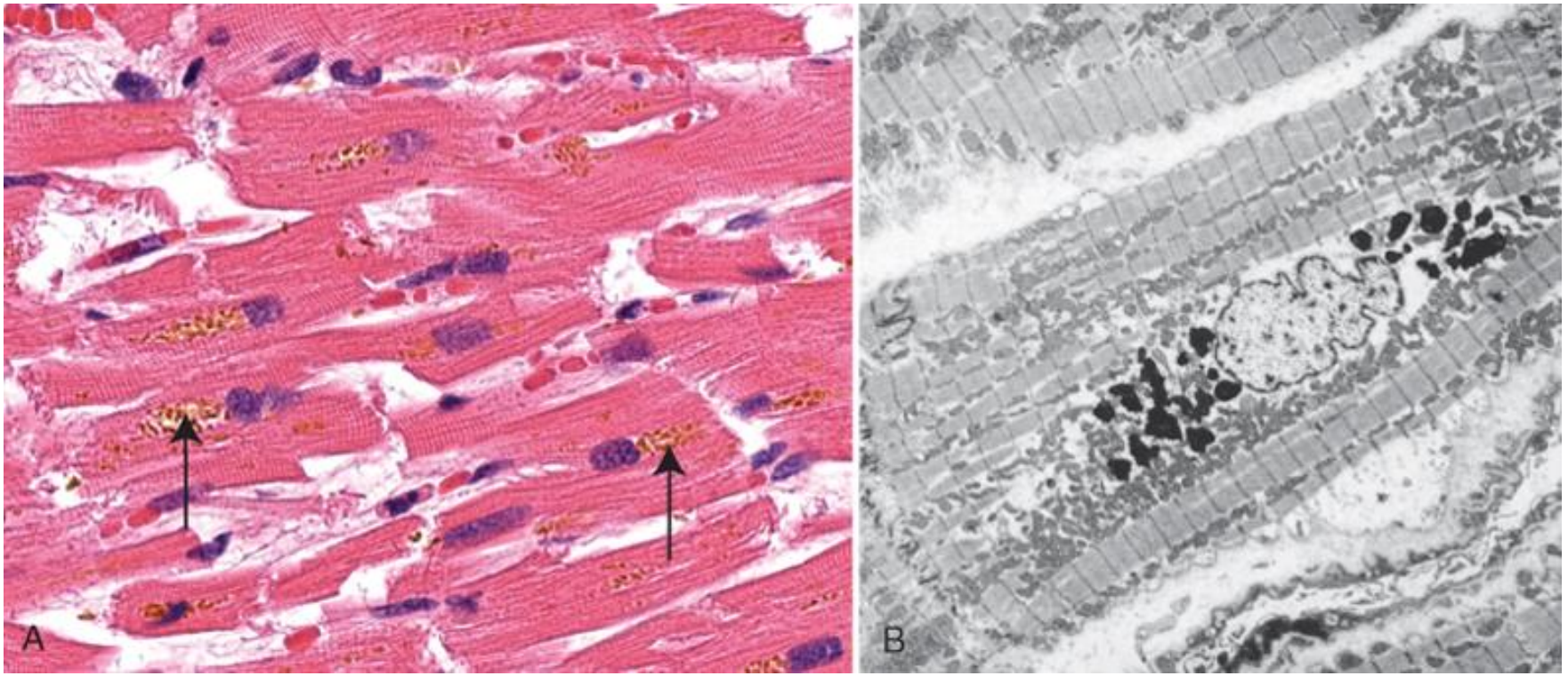
2- Melanin:

This is an endogenous, nonhemoglobin-derived, brown-black pigment (melas = black). This skin pigment is produced by the oxidation of tyrosine through the help of the enzyme tyrosinase within melanocytes.

Lipofuscin pigment

- A brown pigment in cytoplasm of cells, represents residue of oxidized lipid derived from digested membranes of organelles.
- It is called “wear and tear”pigment accumulates as a part of the aging process and atrophy,in which lipid peroxidation take part in it.
- It is harmless to the cell.
- Large amounts in atrophic organs gives rise to “Brown atrophy” e.g brown atrophy of the heart.

Lipofuscin granules in a cardiac myocyte

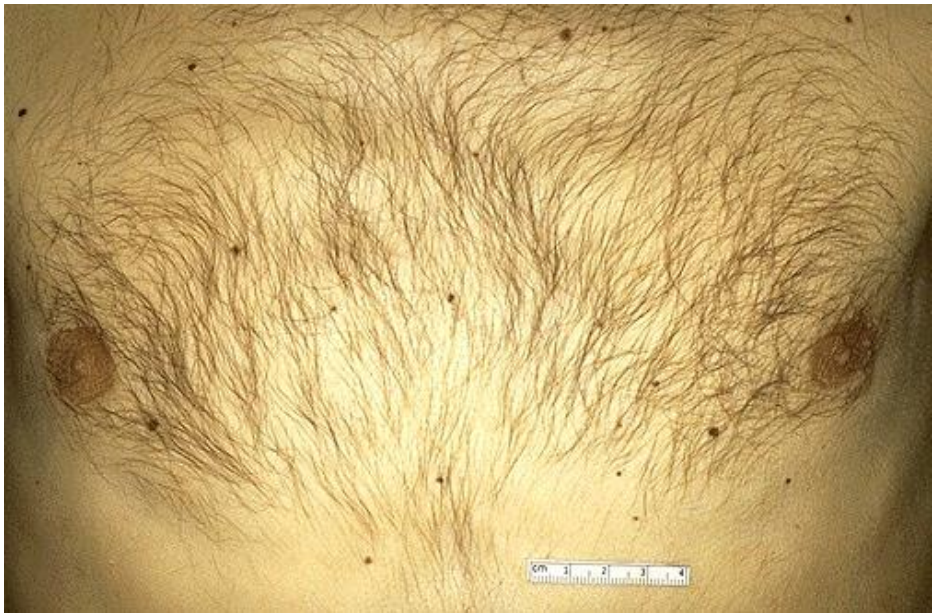


A, Light microscopy (deposits indicated by *arrows*).

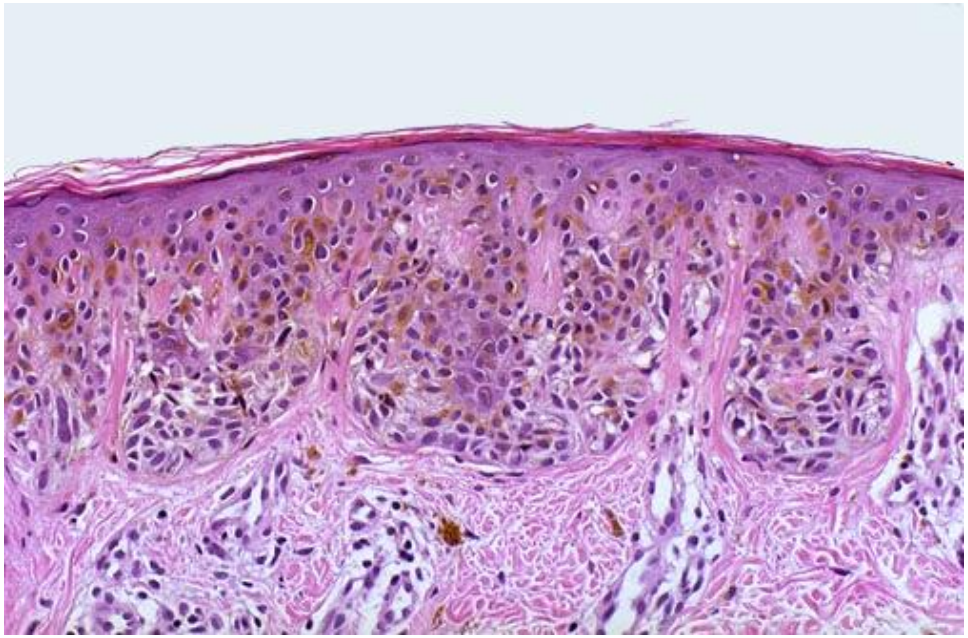
B, Electron microscopy. Note the perinuclear, intralysosomal location.

Pigmented nevi

These are benign nevi; small, brown, flat to slightly raised nevi are quite common. They are usually less than a centimeter in diameter.



The nevus cells are seen here in nests within the lower epidermis. They show brownish melanin pigment.



3- Hb. derivatives : **A- Hemosiderin** **B- Bilirubin**

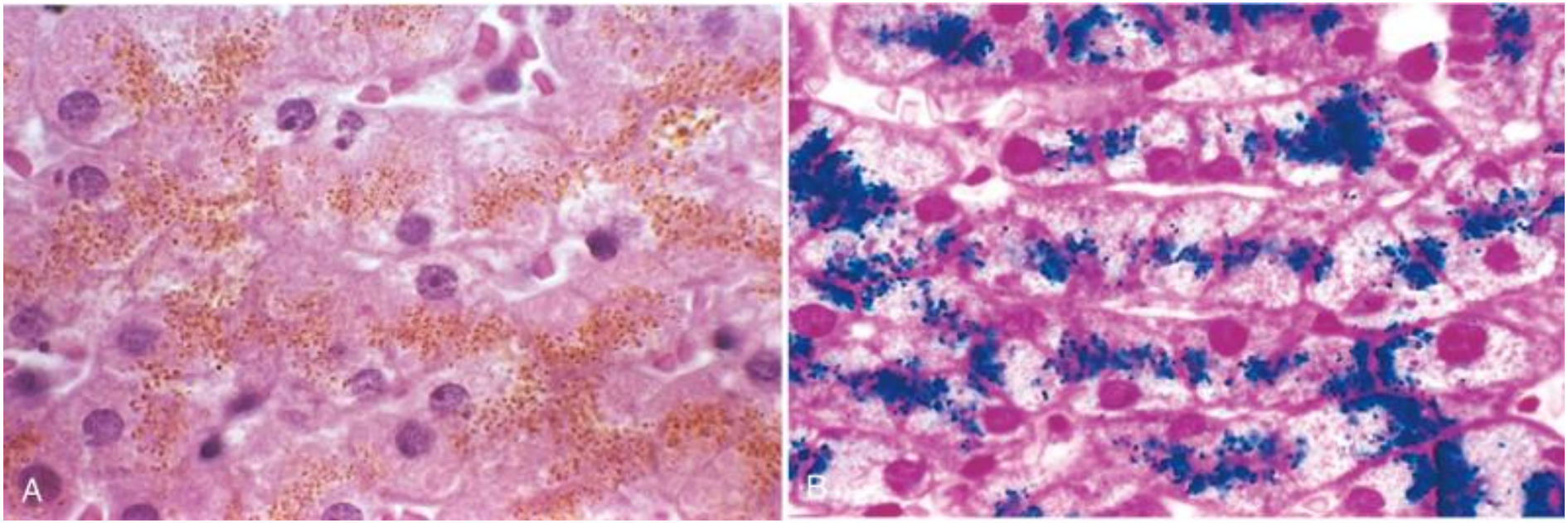
A- Hemosiderin: This is a hemoglobin-derived, golden-yellow to brown granules. Excess iron in the body causes hemosiderin to accumulate within cells. Excess deposition of hemosiderin is termed **hemosiderosis.**
Hemosiderosis is either localized or systemic (generalized).

Localized hemosiderosis result from local hemorrhage e.g. the common bruise, pulmonary or cerebral hemorrhage.
Systemic hemosiderosis occurs whenever there is systemic iron overload. Here the deposition is seen in many organs and tissues such as the liver, pancreas & endocrine glands.
This is associated with:

1. Increased absorption of iron.
2. Impaired utilization of iron .
3. Hemolytic anemias.
4. Excessive blood transfusion

One pint of whole blood - 450 ml- contain 225 mg of iron

Hemosiderin granules in liver cells



A- H&E section showing golden-brown, finely granular pigment.

B- Prussian blue reaction, specific for iron.

In systemic hemosiderosis, hemosiderin accumulates first within the reticuloendothelial cells of various organs and tissues.

With progression accumulation is seen in the parenchymal cells principally of the liver, pancreas, heart and endocrine organs.

In most instances the accumulated hemosiderin does not damage the parenchymal cells.

However, in the more extreme accumulations **(hemochromatosis)** there are associated liver and pancreatic damage, resulting in liver cirrhosis and diabetes mellitus.

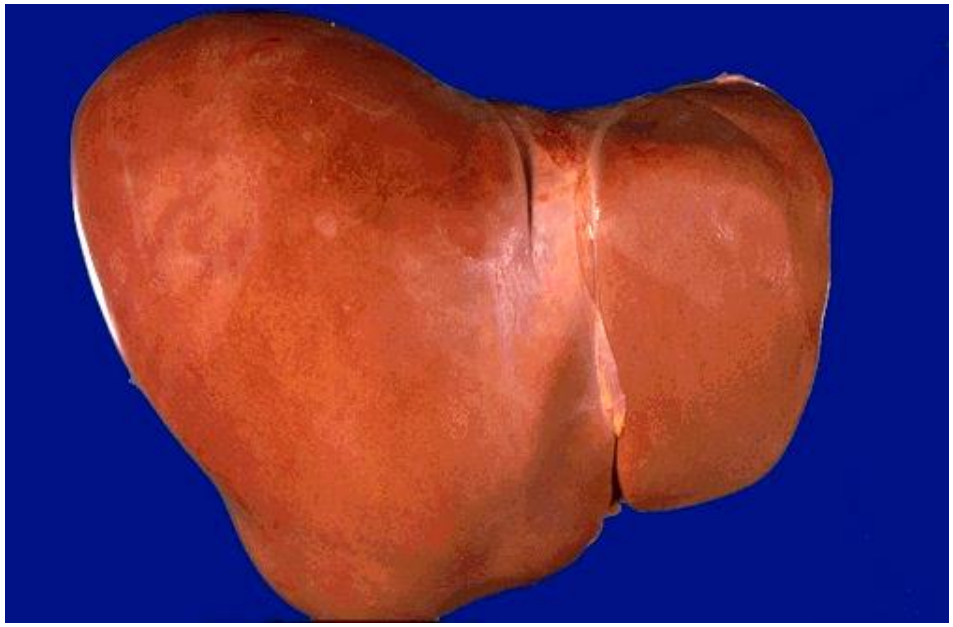
Hemochromatosis liver pancreas and lymph node

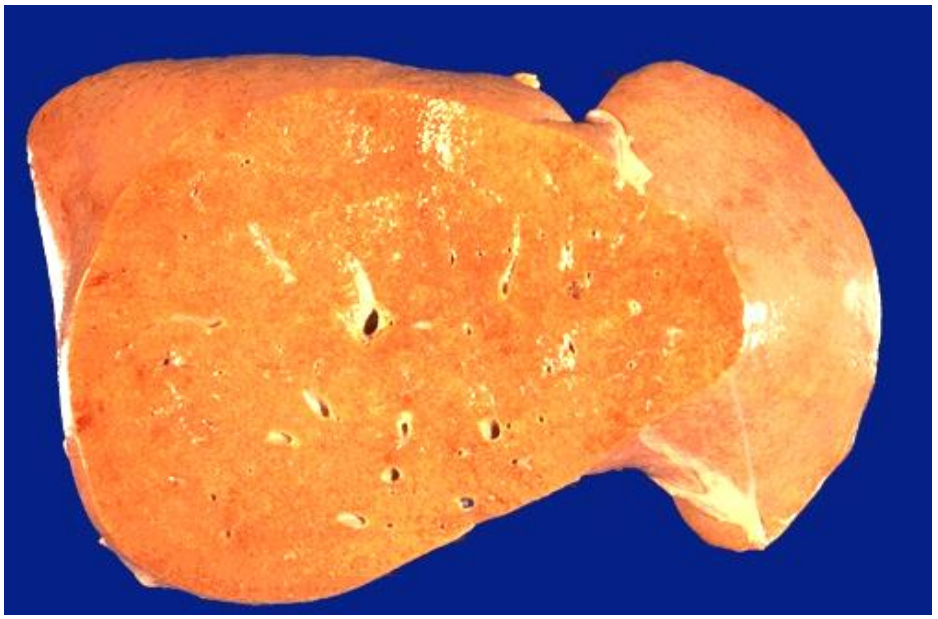
The abnormal dark brown color of the liver, as well as the pancreas (bottom center) and lymph nodes (bottom right) on sectioning is due to extensive iron deposition in a middle-aged man with hereditary hemochromatosis. About 1 in 10 persons of European ancestry carries the recessive gene for this disorder, but only about 3 to 5 persons per 1000 are affected.

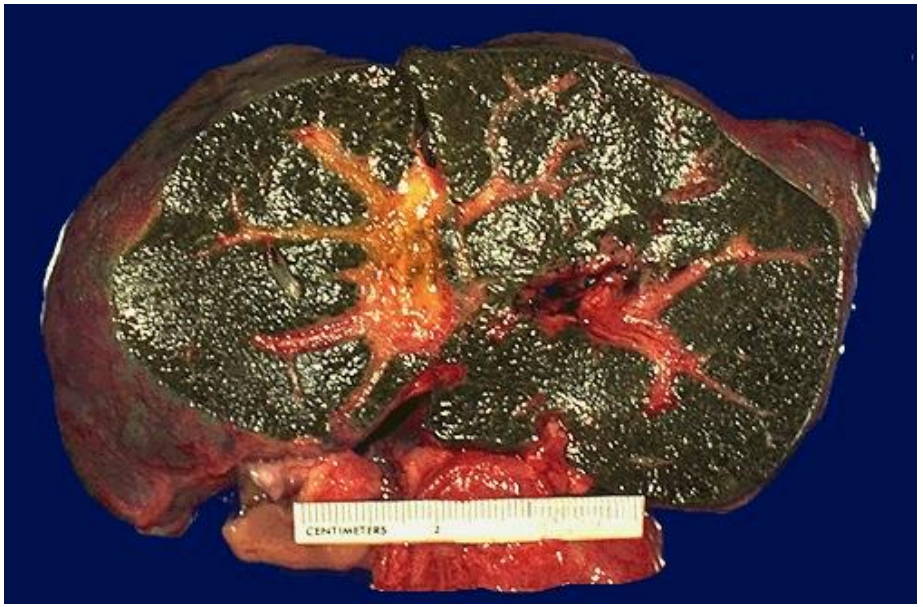
B- Bilirubin:

This is a normal major pigment of bile, which is derived from hemoglobin (but contains no iron). The conversion to bile occurs within hepatocytes.

Jaundice results from excess bilirubin pigment that is distributed throughout all tissues and body fluids. In the liver, particularly when there is obstruction to the bile flow (e.g. obstruction of the common bile duct by a stone, tumor or biliary atresia) and the bilirubin is seen within bile canaliculi, Kupffer cells and hepatocytes as green-brown globular deposits. **This imparts greenish color to the liver grossly.**






CENTIMETERS

Degenerative changes

Degenerative changes

Calcification & Hyaline change

Calcification abnormal deposition of calcium salts.

There are two forms of calcification:

1. Dystrophic calcification; refers to calcium deposition in nonviable or dying tissue that occurs despite normal serum calcium levels and the absence of any derangement of calcium metabolism. It is noted in:

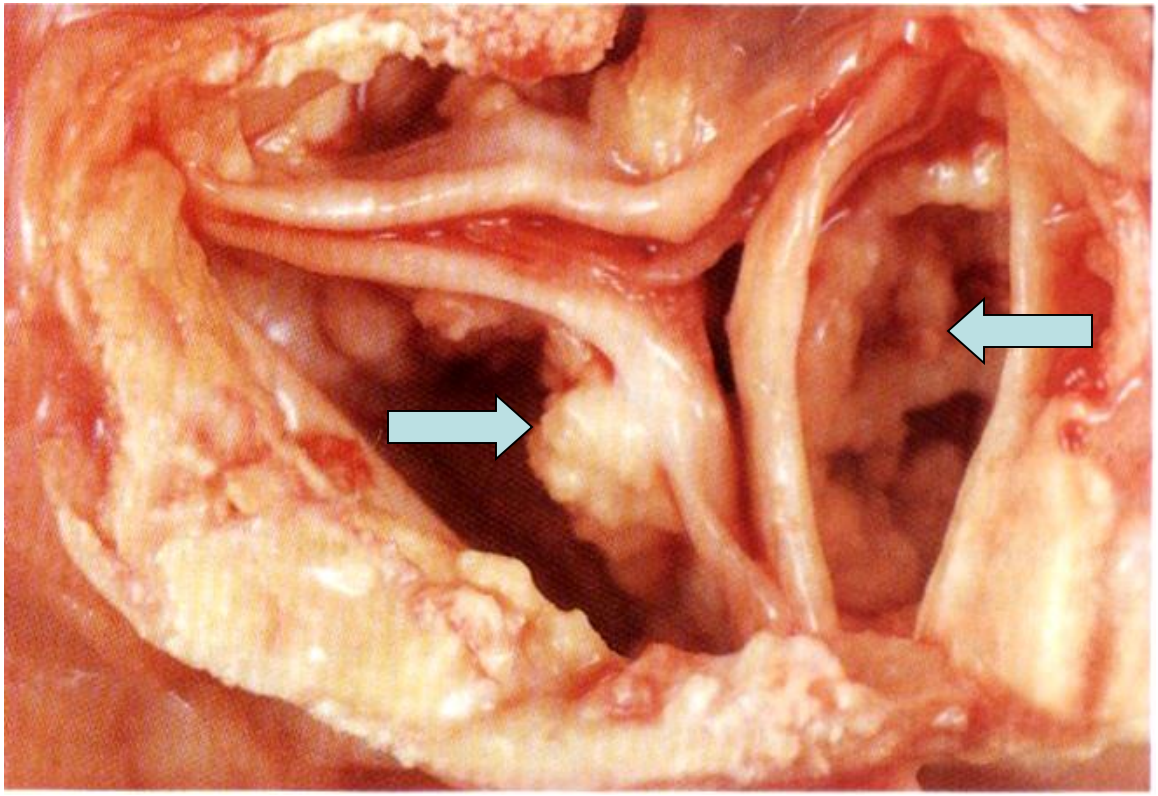
a. Areas of necrosis (whether coagulative, caseous, liquefactive or fat necrosis).

b. Advanced atherosclerosis.

c. Damaged or aging heart valves.

The calcification **is seen grossly** as fine, white granules or clumps giving gritty feeling.

Dystrophic calcification aortic valve



Aortic valve viewed from above; the semilunar cusps are thickened and fibrotic. Behind each cusp are large irregular masses of dystrophic calcification **(arrows)** that prevents normal opening of the cusps.

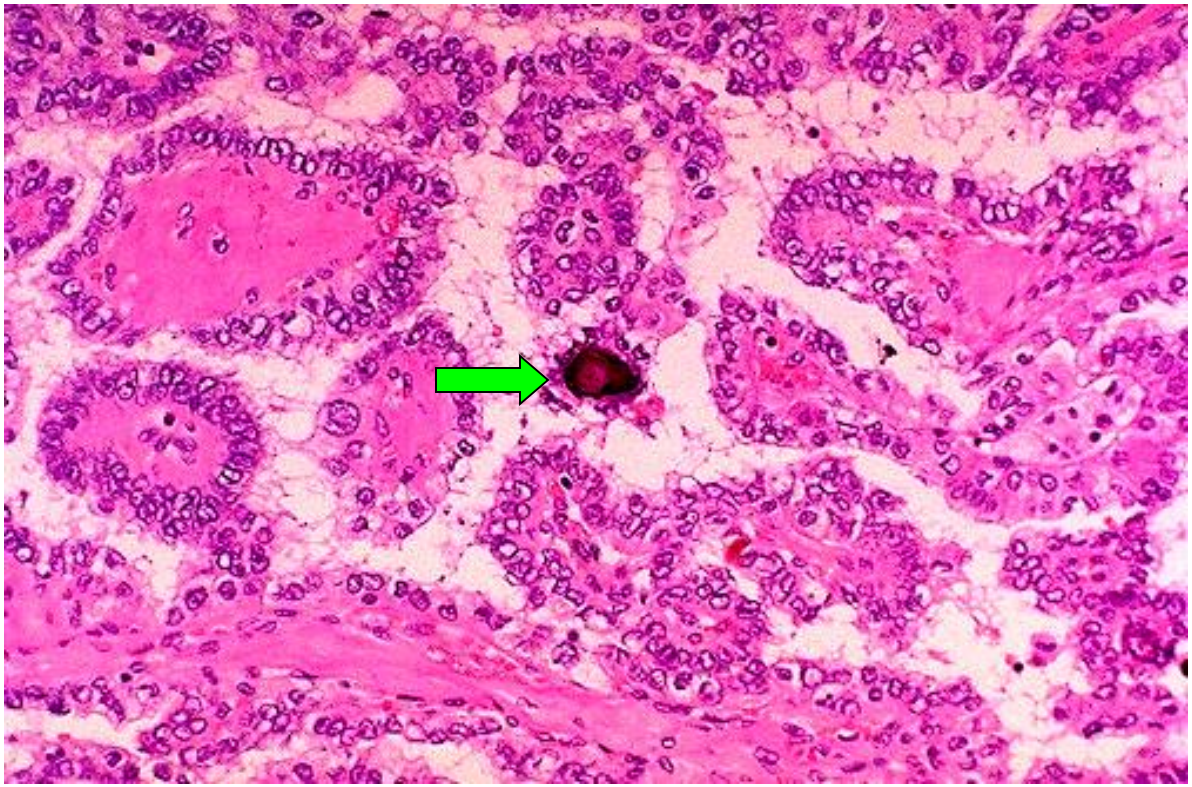
Microscopically (with H & E stains) it appears as basophilic (bluish), amorphous granules that may coalesce to form larger clumps. Sometimes calcium deposition occurs in a rounded lamellar fashion at anidus of necrotic cells. These structures are called **psammoma bodies.** This is seen in some tumors such as papillary carcinomas of the thyroid and ovary as well as in some meningioma.

2. Metastatic calcification; signifies deposition of calcium in viable tissue, almost always a reflection of some derangement of calcium metabolism that leads to hypercalcemia.

Metastatic calcification is seen in cases of hypercalcemia of any cause.

It principally affects blood vessels, kidneys, lungs and gastric mucosa.

Papillary carcinoma of thyroid Psammoma body



Note the small psammoma body in the center (arrow). The tumor cells show fingerlike projections (papillary).

Hyaline change:

This refers to intra- or extra-cellular homogeneous, pinkish alteration in sections stained with H& E.

Intracellular hyaline change include:

1. Hyaline droplets within renal tubular epithelium in cases of proteinuria.
2. Russel bodies in plasma cells.
3. Viral inclusions (nuclear or cytoplasmic).
4. Alcoholic hyaline in liver cells (Mallory bodies).

Extracellular hyalinization may be encountered in:

1. Collagen in old scar.
2. Hyalinization of arteriolar walls associated with hypertension and diabetes.
3. Amyloid deposition .

Cellular adaptations

Cellular adaptations

- The cells are able to handle normal **(physiological)** and sometimes, abnormal **(pathological)** demands without get injured; to achieve this,

- a number of changes inside the cells occur that eventually lead to a new but altered steady state.

- These induced changes are referred to as **adaptations.**

- The aim of adaptations is to preserve cell viability i.e. prevent cell injury.

Cellular adaptations

include:

1. **Atrophy**.
2. **Hypertrophy.**
3. **Hyperplasia.**
4. **Metaplasia**.

1- Atrophy:

- **a decrease in the size of the cell by loss of cell substance**.

When sufficient numbers of cells are involved, the entire organ or tissue decreases in size, i.e. become atrophic.

Causes of atrophy include:

1. Decrease workload e.g. muscular atrophy due to immobilization as in fractured limb.

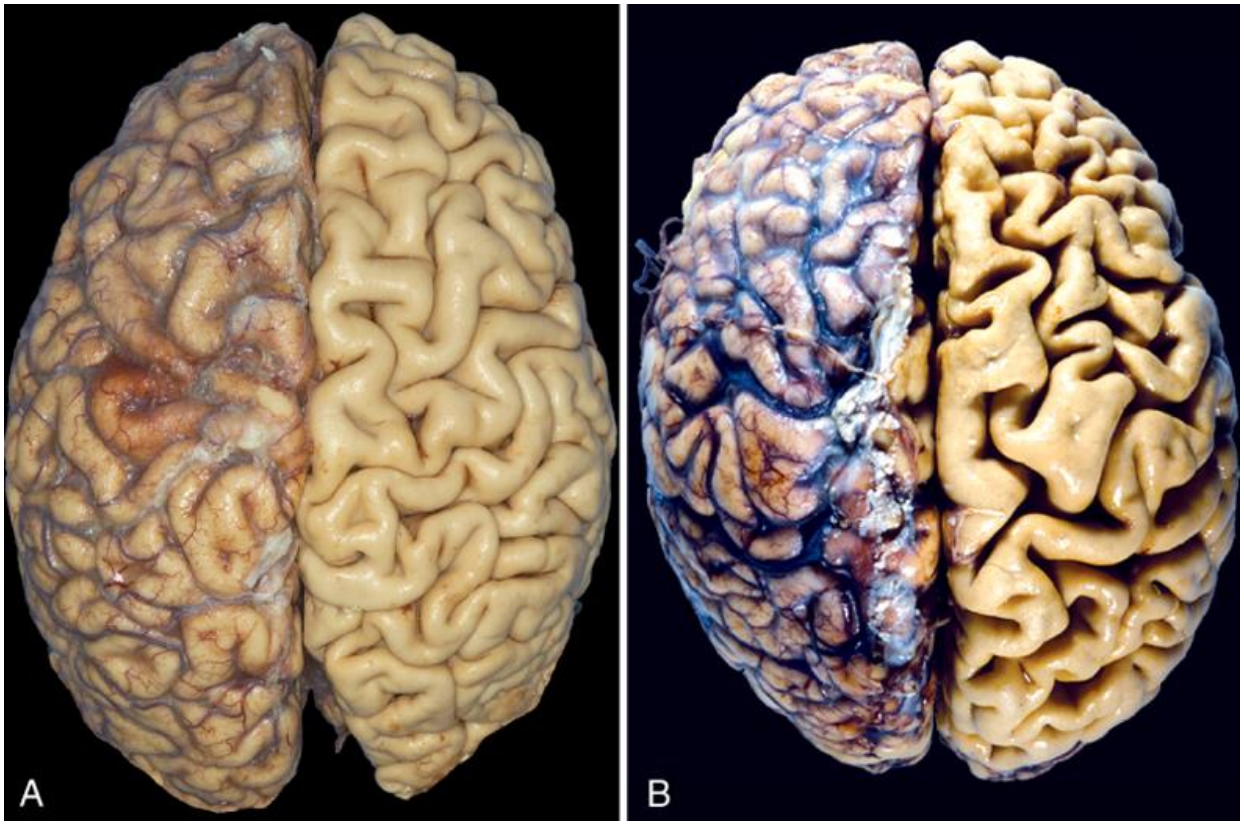
2. Denervation (loss of nerve supply) e.g. paralysis of a limb due to nerve injury or poliomyelitis.

3. Ischemia e.g. brain atrophy as an ageing phenomenon due to atherosclerosis**.**

4. Under nutrition, as in starvation and Kwashiorkor.

5. Loss of endocrine stimulation e.g. atrophy of the gonads in hypopituitarism and senile endometrial atrophy (decrease estrogen secretion from the ovary).

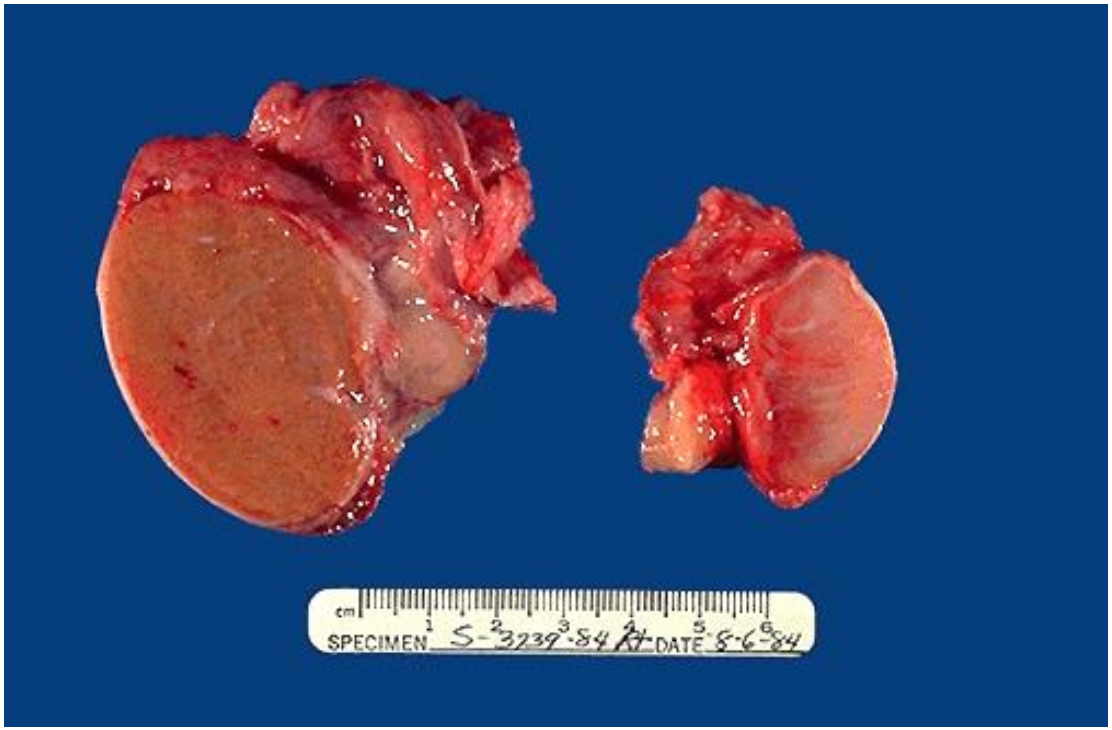
The reduction in size is due to reduction in the number of its structural components e.g. mitochondria, myofilaments, endoplasmic reticulum etc. The aim is to achieve equilibrium between the demand and the cell's functional capacity.



Normal **Atrophy**

Atrophy of the brain is due to aging and reduced blood supply. Note that loss of brain substance **narrows the gyri and widens the sulci**. The meninges have been stripped from the right half of each specimen to reveal the surface of the brain.

Normal **Atrophy**



On the left is a normal testis.

On the right is a testis that has undergone atrophy.

Bilateral atrophy may occur with a variety of conditions including chronic alcoholism, hypopituitarism, atherosclerosis, chemotherapy or radiation, and severe prolonged illness. A cryptorchid testis will also be atrophic. Inflammation may lead to atrophy.

2- Hypertrophy: (opposite to atrophy).

This Refers to **increase in the size of cells and as a consequence the size of the organ or tissue** containing them.

The aim is to achieve equilibrium between the demand and the cell's functional capacity.

If the burden persists the hypertrophy reaches a limit beyond which the enlarged muscle is no longer able to compensate for the increased work and cardiac failure ensues.

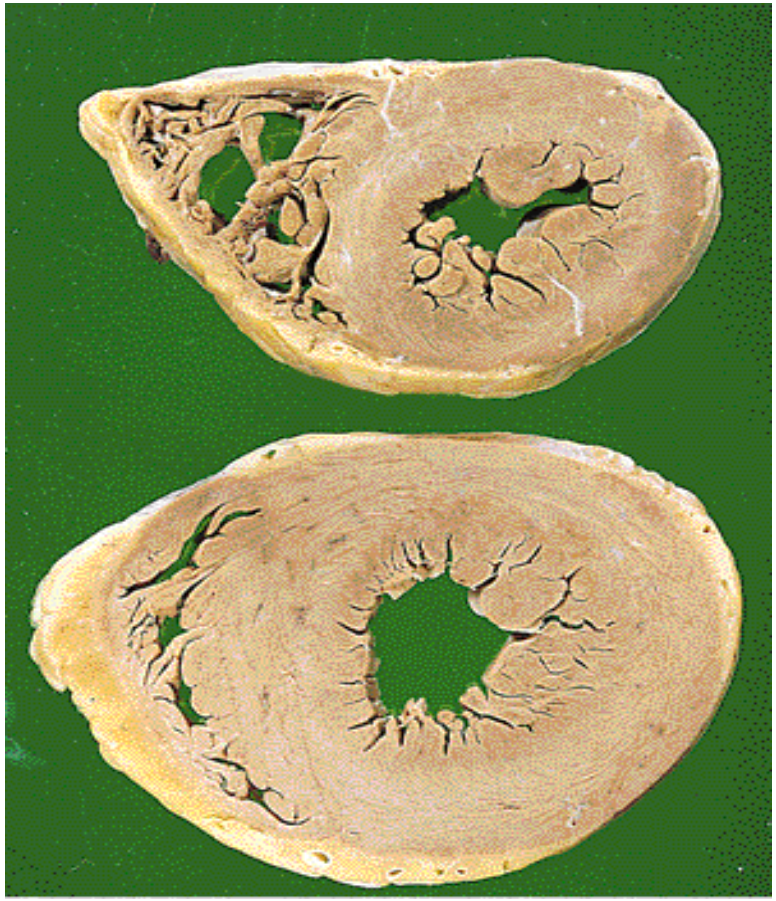
At this point there is lysis and loss of myofibrils' contractile elements.

It can be physiological or pathological.

1. Uterus in pregnancy (**physiological**: hormonal)
2. Skeletal muscles in athletes (**physiological**: increased workload).
3. Left ventricle in systemic hypertension (**pathological**: increased workload) the ventricle has to contract against increased pressure in the aorta) **.**

Athletes as an example of physiological muscular hypertrophy

pathological Left ventricular hypertrophy

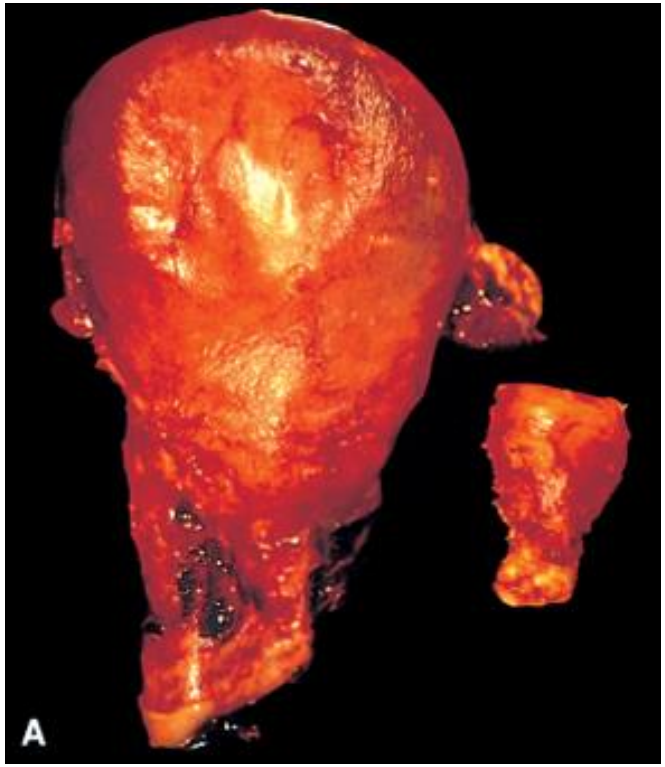


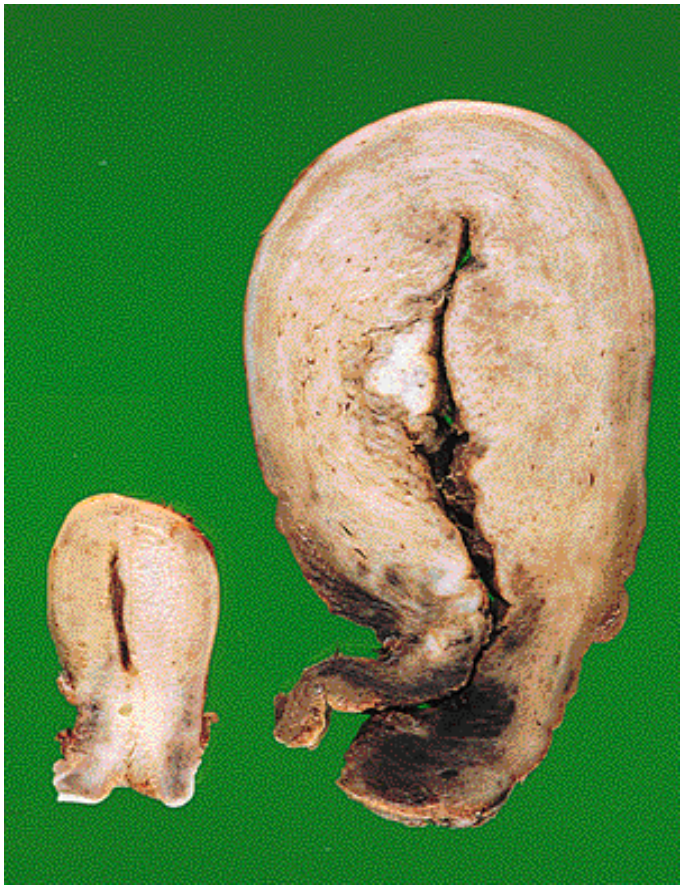
The **upper** specimen demonstrates the normal thickness of the Lt ventricular wall **(normal, 1-1.5 cm)** for comparison with the greatly thickened wall in the **lower** specimen. The increased mass of the Lt ventricle is due to enlargement of cardiac muscle cells as a result of **hypertrophy**.

cardiac hypertrophy

The number of myocardial fibers never increases, but their size can increase in response to an increased workload, leading to the marked thickening of the left ventricle in this patient with hypertension.

physiological hypertrophy and hyperplasia





On the left is a normal uterus showing the normal mass of smooth muscle in its wall. On the right is a uterus from a recently pregnant women, in which the striking increase in mass of smooth muscle is evident. At cellular level this is due to both hyperplasia and hypertrophy of uterine smooth muscle.

3- Hyperplasia:

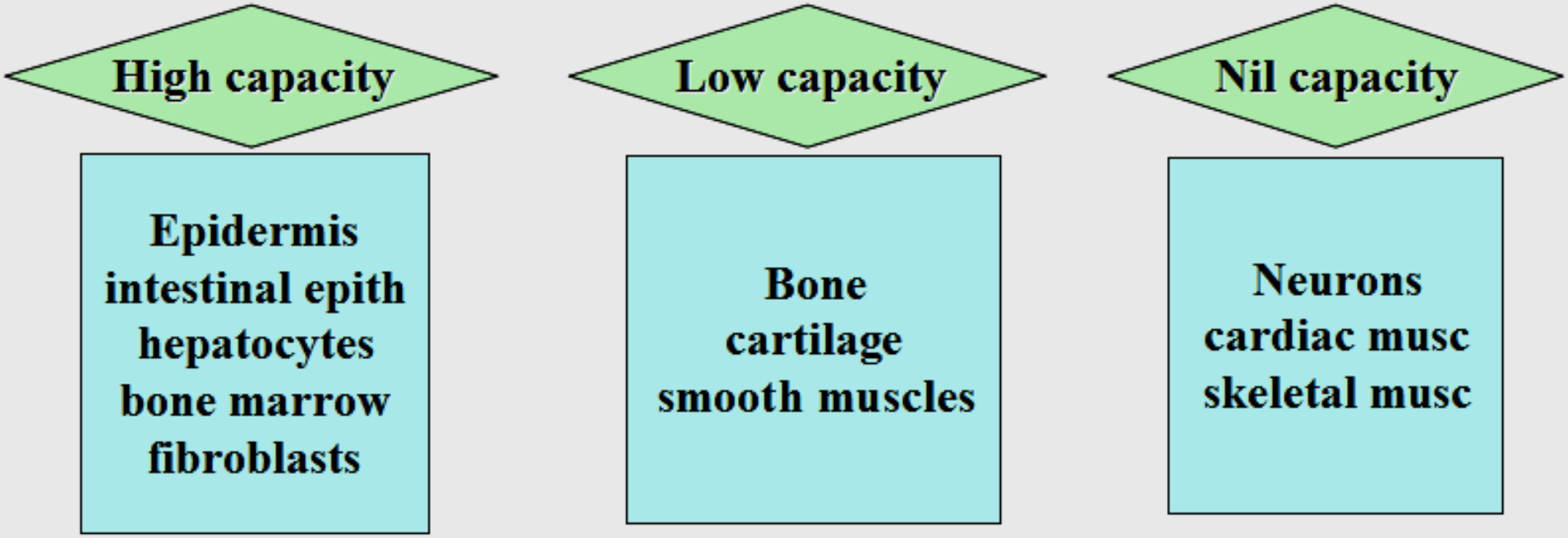
increase in the number of cells in an organ or tissue leading to an increase in its size.
Hyperplasia and hypertrophy are closely related and often occur together (e.g. in estrogen induced enlargement of the uterus during pregnancy; there is both hyperplasia and hypertrophy the myometrium).

Not all adult cell types have the same capacity for hyperplasia.

- **labile cells** can undergo profound hyperplastic growth e.g. those of the epidermis, mucosal surfaces, hepatocytes, fibroblasts and bone marrow cells.
- **permanent cells** : nerve cells and those of the heart (myocardial cells) and skeletal muscle fibers have no capacity for hyperplasia **.**
- **Intermediate** among the above two are those of bone, cartilage and smooth muscle cells.

Hyperplasia

- Increase in the number of cells in an organ or tissue. Cells capable of division.



Hyperplasia is divided into **physiological and pathological**

A. Physiological hyperplasia is either:

1. Hormonal (e.g. proliferation of the breast glandular epithelium in females at puberty or during pregnancy).

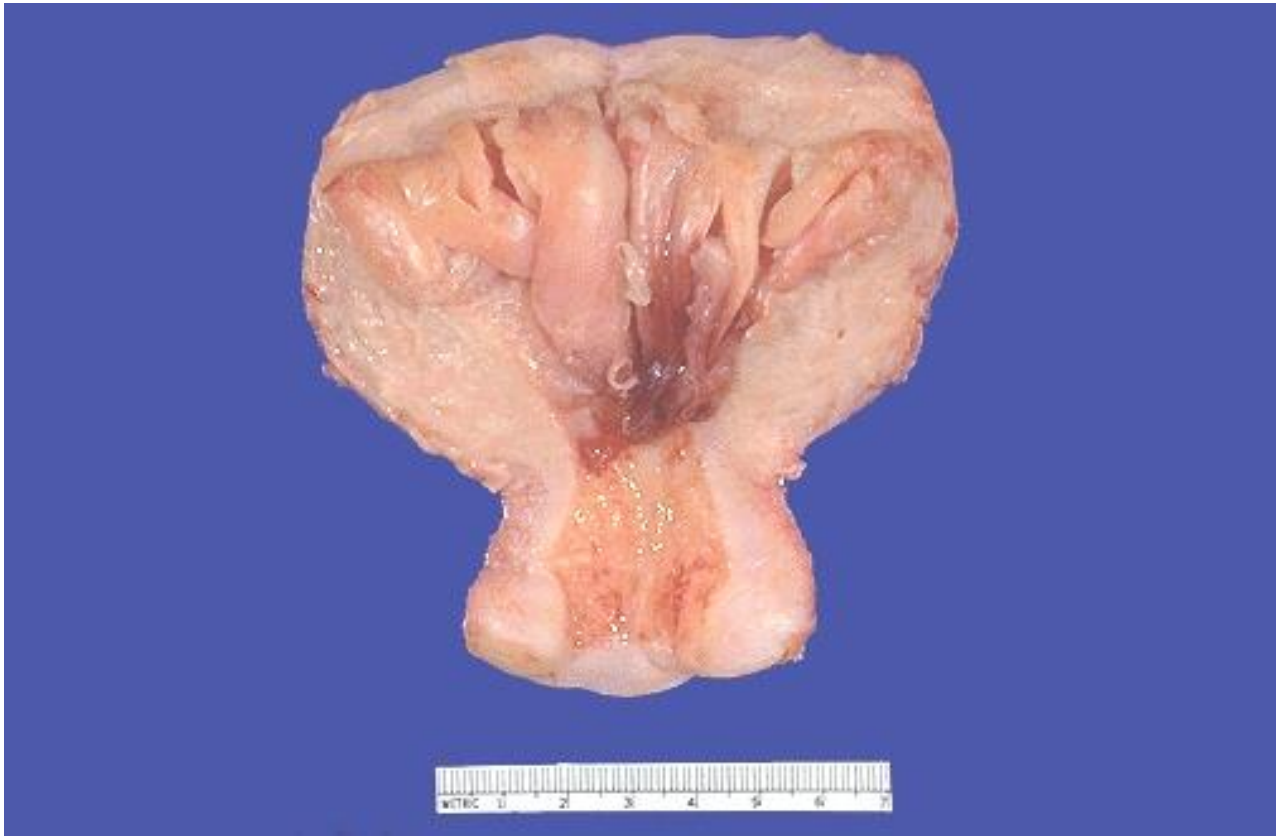
2. Compensatory (e.g. after partial hepatectomy).

B. Pathological hyperplasia is mostly either due to:

1. Excessive hormonal stimulation (e.g. endometrial hyperplasia) **.**

2. The effect of growth factors on target cells (as in wound healing).

Endometrial hyperplasia



The prominent folds of endometrium in this uterus (opened to reveal the endometrial cavity) are an example of hyperplasia. The hyperplasia involves both endometrial glands and stroma.

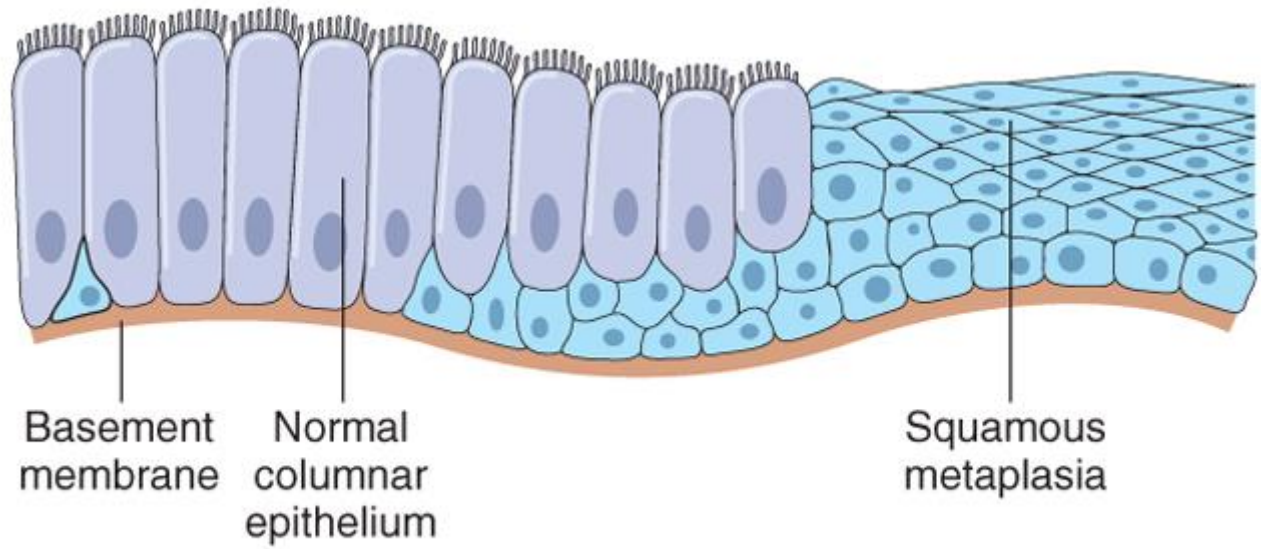
Hyperplasia (cont)

- Physiologic hyperplasaia
  - Female breast in puberty & lactation
  - Compensatory hyperplasia in the liver
- Pathologic hyperplasia
  - excessive hormone stimulation e.g endometrial hyperplasia.
  - Effects of growth factors e.g mitogenic GF in wound healing.

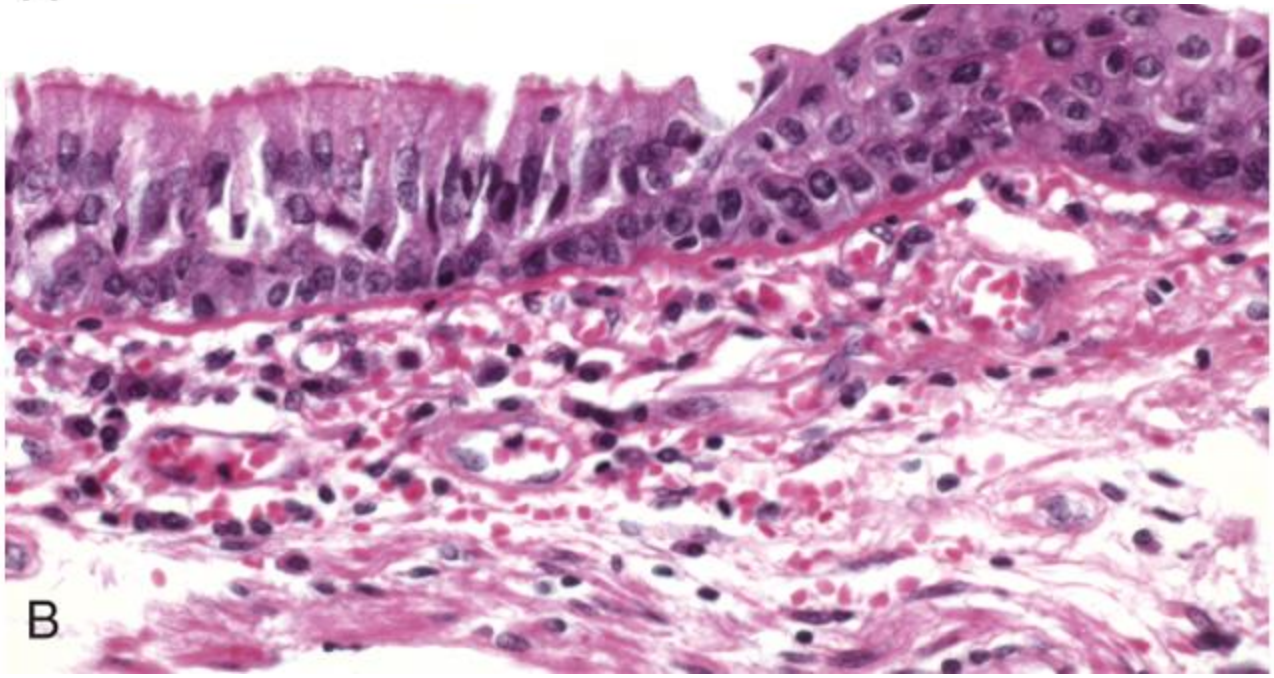
4- Metaplasia:

This refers **to replacement of one mature cell type by another mature cell type**.
It may represent an adaptation of cells more sensitive to stress by other cells that are more resistant to the adverse environment. Examples include:

1. Squamous metaplasia of the laryngeal and bronchial respiratory epithelium due to habitual smoking.
2. Squamous metaplasia of the urothelium in the urinary bladder due to bilharzia or vesical stone.
3. Columnar metaplasia of esophageal squamous epithelium as a result of prolonged reflux of acidic gastric juice into the esophagus..
4. In the mesenchymal cells e.g. formation of bone in long- standing fibrosis of soft tissue as a result of injury.

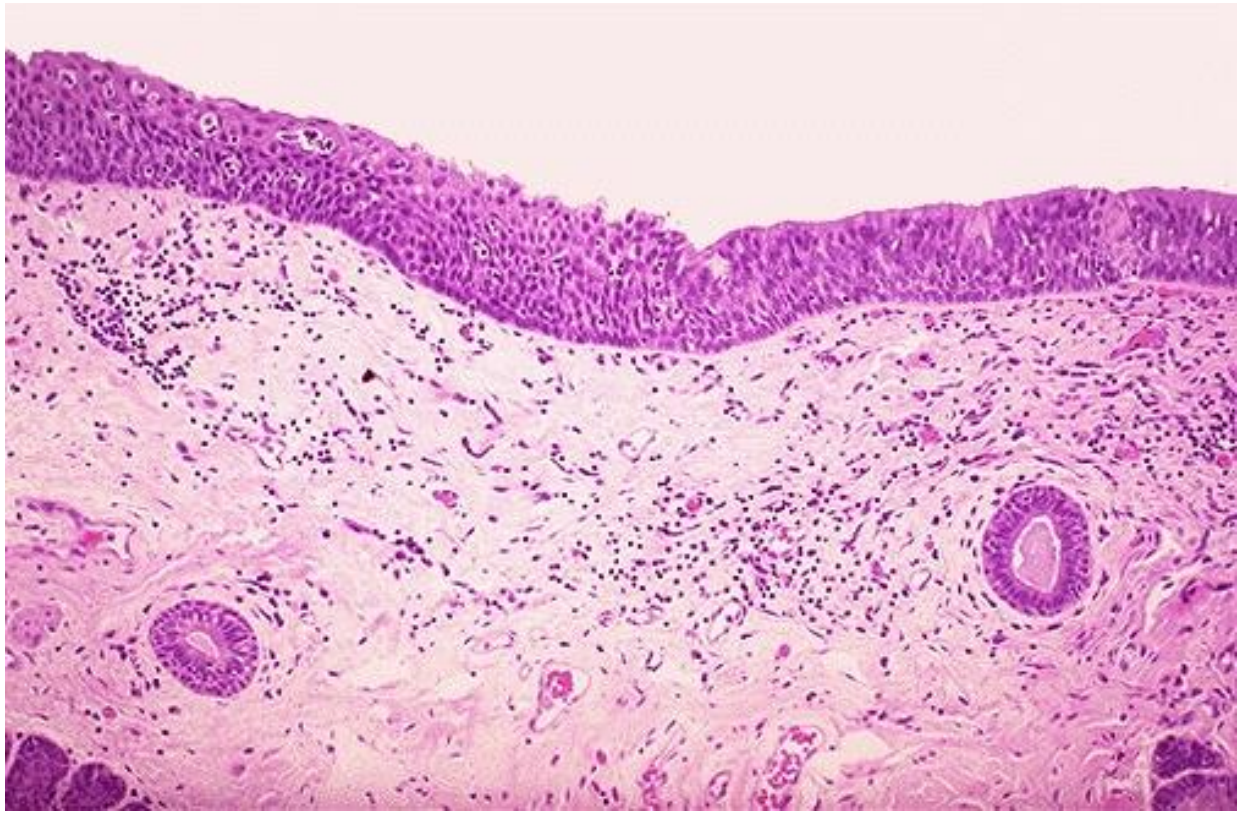

Basement membrane
Normal columnar epithelium
Squamous metaplasia

A



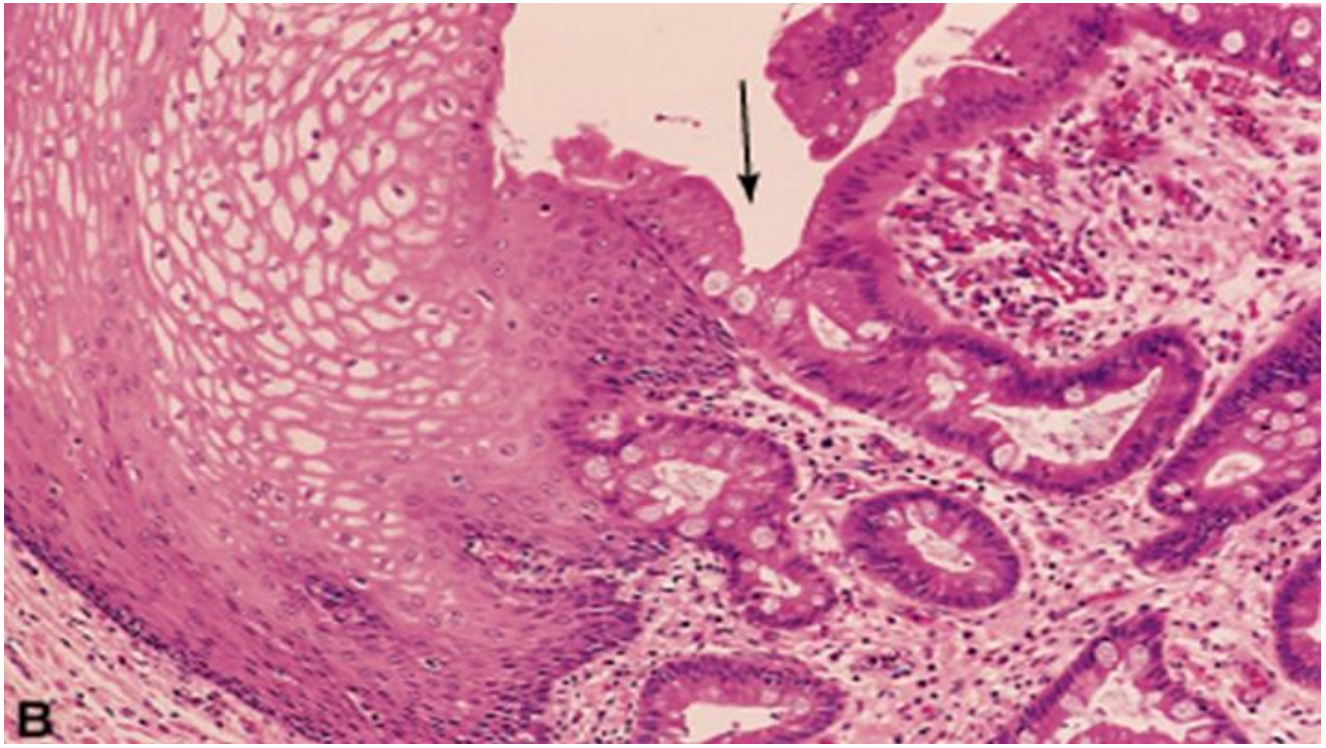
B

Metaplasia of laryngeal respiratory epithelium in smoker



The chronic irritation has led to an exchanging of one type of epithelium (the normal respiratory epithelium at the right) for another (the more resilient squamous epithelium at the left). Metaplasia is not a normal physiologic process and may be the first step toward neoplasia

Barrett metaplasia esophagus



Metaplastic transformation *(arrow)* of the normal adult esophageal stratified squamous epithelium *(left)* to mature columnar epithelium (so-called Barrett metaplasia).

Dysplasia

This refers **to disturbed proliferation of cells associated with atypical cytological changes that involve cell size, shape, and organization**.

It is not an adaptive process but considered here because **of its close relation to hyperplasia**.

It is most commonly encountered in lining epithelia, mostly squamous e.g. that of the uterine cervix, and metaplastic squamous epithelium of the respiratory passages (in habitual smokers).

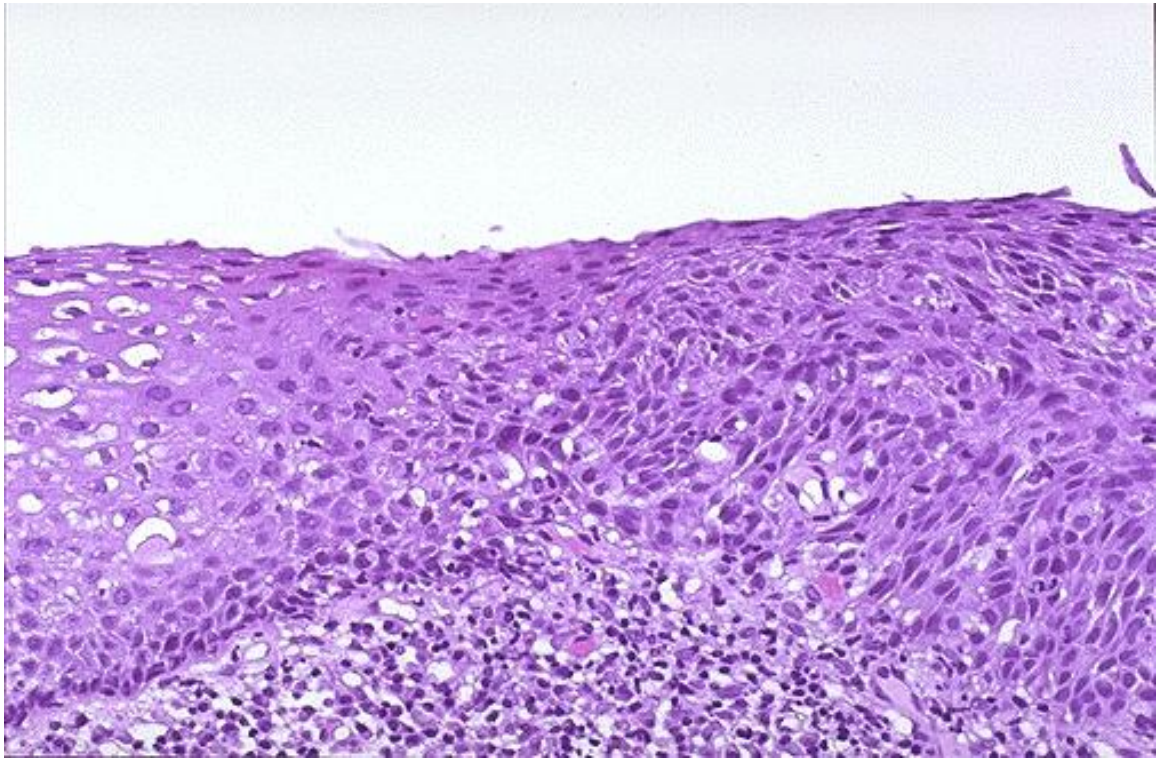
The increased proliferative activity produces greater amounts of DNA and thus the nuclei appear more hyperchromatic.

Although there is an increase in mitotic activity, there are usually no abnormal mitoses. The latter is usually met within cancerous states.

Dysplastic changes are often found adjacent to foci of cancer indicating that it is a stage that precedes development of frank malignancy.

However, dysplasia does not necessarily progress to cancer.

cervical squamous dysplasia



at high magnification extending from the center to the right.
The epithelium is normal at the left. Note how the dysplastic cell nuclei are larger and darker, and the dysplastic cells have a disorderly arrangement.