Cell Injury

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بسم الله الرحمن الرحيم

وَالطَّيِّبَاتُ لِلطَّيِّبِينَ وَالطَّيِّبُونَ لِلطَّيِّبَاتِ

And women of purity are for men of purity
and men of purity are for women of purity

THE QURAN 24:26
(SURAH AN-NUR)

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Introduction

- PATHOLOGY IS THE STUDY OF DISEASE.
- IT DESCRIBES THE MANIFESTATIONS OF THE DISEASE, ITS PROCESS AND SEQUELAE AND ATTEMPTS TO DETERMINE THE CAUSE (ETIOLOGY) AND UNDERLYING MECHANISM (PATHOGENESIS).

- IT FORMS A BRIDGE BETWEEN BASIC SCIENCE AND CLINICAL PRACTICE.

What is the Disease?

- **It is the** "state in which an individual exhibits an anatomical, physiological, or biochemical deviation from the normal".

Disease may be defined as :

an abnormal alteration of structure or function in any part of the body.

Learning Pathology:

- **General Pathology**
  - Common changes in all tissues. e.g.. Inflammation, cancer, ageing, edema, hemorrhage ….etc.
- **Systemic Pathology**
  - Discussing the pathologic mechanisms in relation to various organ systems e.g. CVS, CNS, GIT…..etc.

What should we know about a Disease?

- Definition.
- Epidemiology – Where & When.
- Etiology – What is the cause?
- Pathogenesis - Evolution of dis.
- Morphology - Structural Changes
- Functional consequences

Pathology

- Management
- Prognosis
- Prevention

Pathology focuses on 4 aspects of disease:

- ***ETIOLOGY:*** **Cause of disease.**

- ***PATHOGENESIS:***

Mechanisms of development of disease.

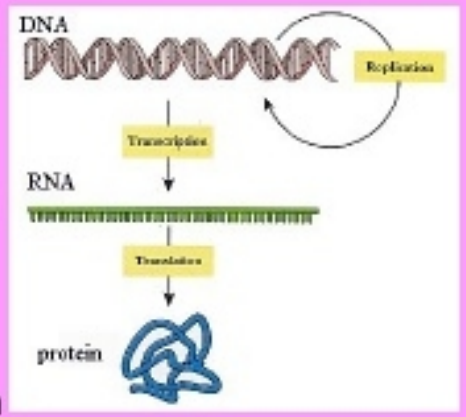
- ***MORPHOLOGY:***

The structural alterations induced in cell and tissues.

- ***FUNCTIONAL CONSEQUENCES:***

ETIOLOGY

Knowledge or discovery of the primary etiology remains the backbone on which a diagnosis can be made and a disease process can be best understood so that a treatment can be prescribed.



THE ETIOLOGICAL FACTORS ARE:

- ENVIRONMENTAL FACTORS
- GENETIC FACTORS
- IINDIRECT CAUSES

ENVIRONMENTAL FACTORS ARE:

- PHYSICAL AGENTS – radiation, trauma or mechanical injury, thermal changes, electrical, nuclear or X-rays, changes in atmospheric pressure
- CHEMICAL AGENTS – chemicals, poisons like venoms or toxins, corrosive agents like strong acids and alkalis
- NUTRITIONAL DEFICIENCES AND EXCESSES
- INFECTIONS AND INFESTATIONS
- ABNORMAL IMMUNOLOGICAL REACTIONS
- PSYCHOLOGICAL FACTORS

GENETIC FACTORS: ABNORMAL GENES

INDIRECT CAUSES: pertain to the predisposing factors like age, age, sex, environment, race, climate, state of nutrition, habits

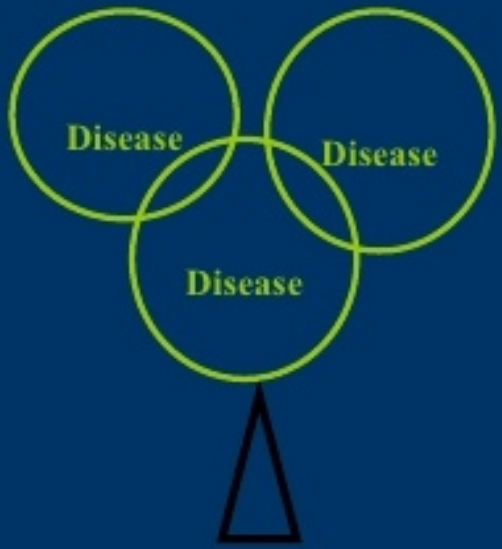
Etiology

- One etiologic agent

→ - one disease, as Malaria.

- Several etiologic agents

→ one disease, as diabetes .



- One etiologic agent several diseases, as smoking.

Pathogenesis

The sequence events in the response of the cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease,"from the time it is initiated to its final conclusion in recovery or death"

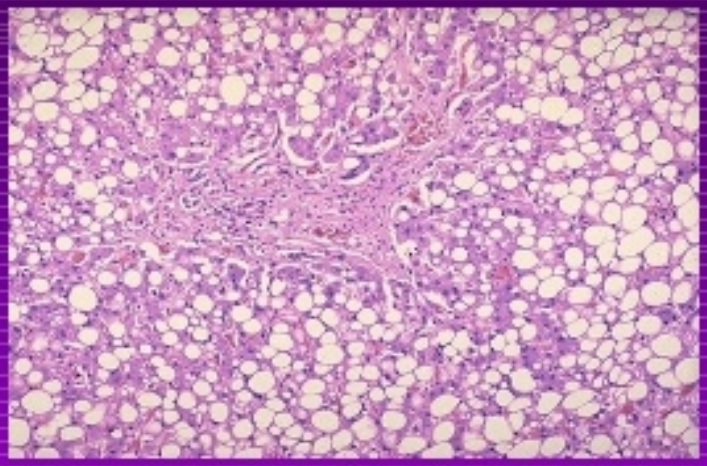
The core of the science of pathology —

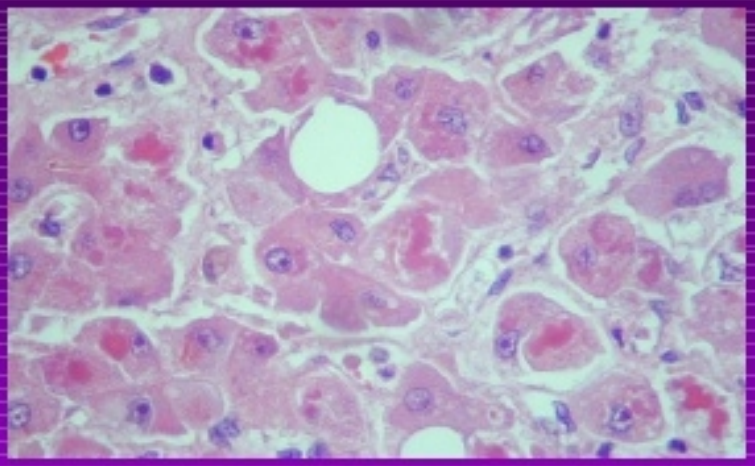
the study the

pathogenesis of the disease.

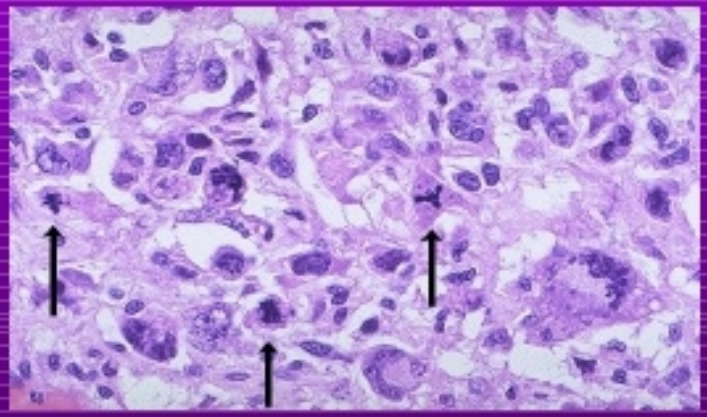
METHODS OF STUDYING PATHOLOGY

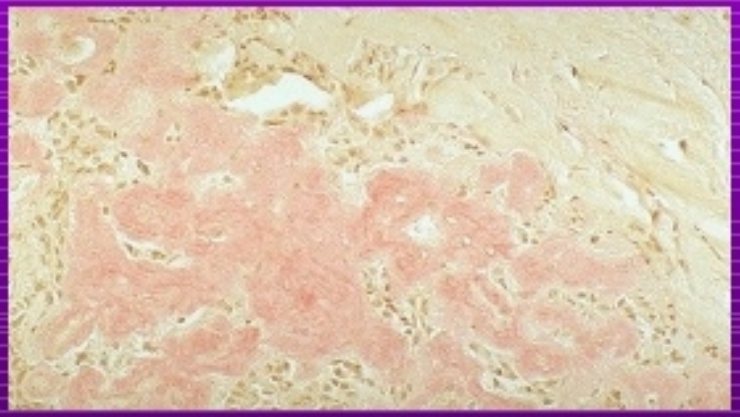
- GROSS EXAMINATION
- LIGHT MICROSCOPY
- IMMUNOCHEMISTRY
- ELECTRON MICROSCOPY
- MOLECULAR BIOLOGY



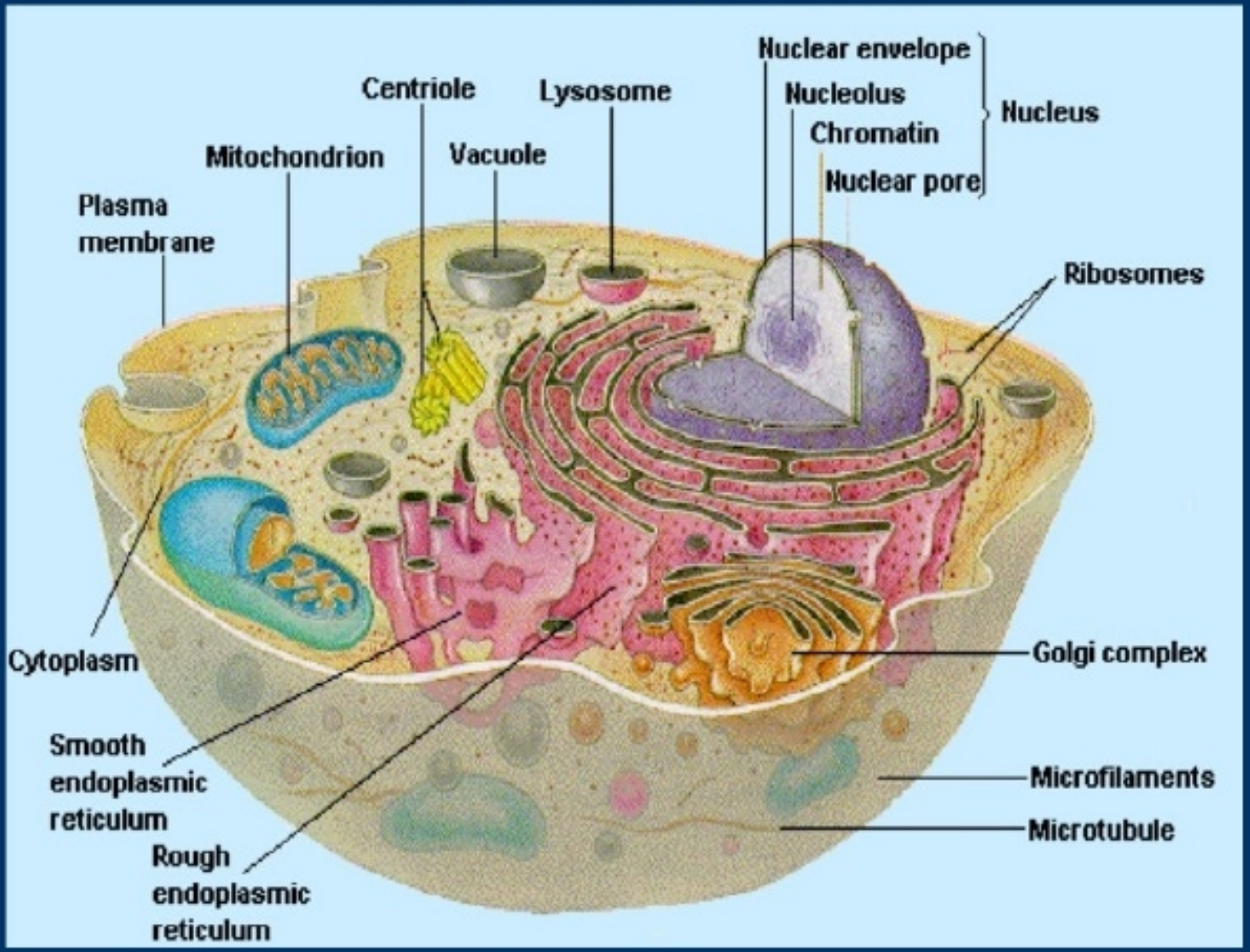


CELL INJURY





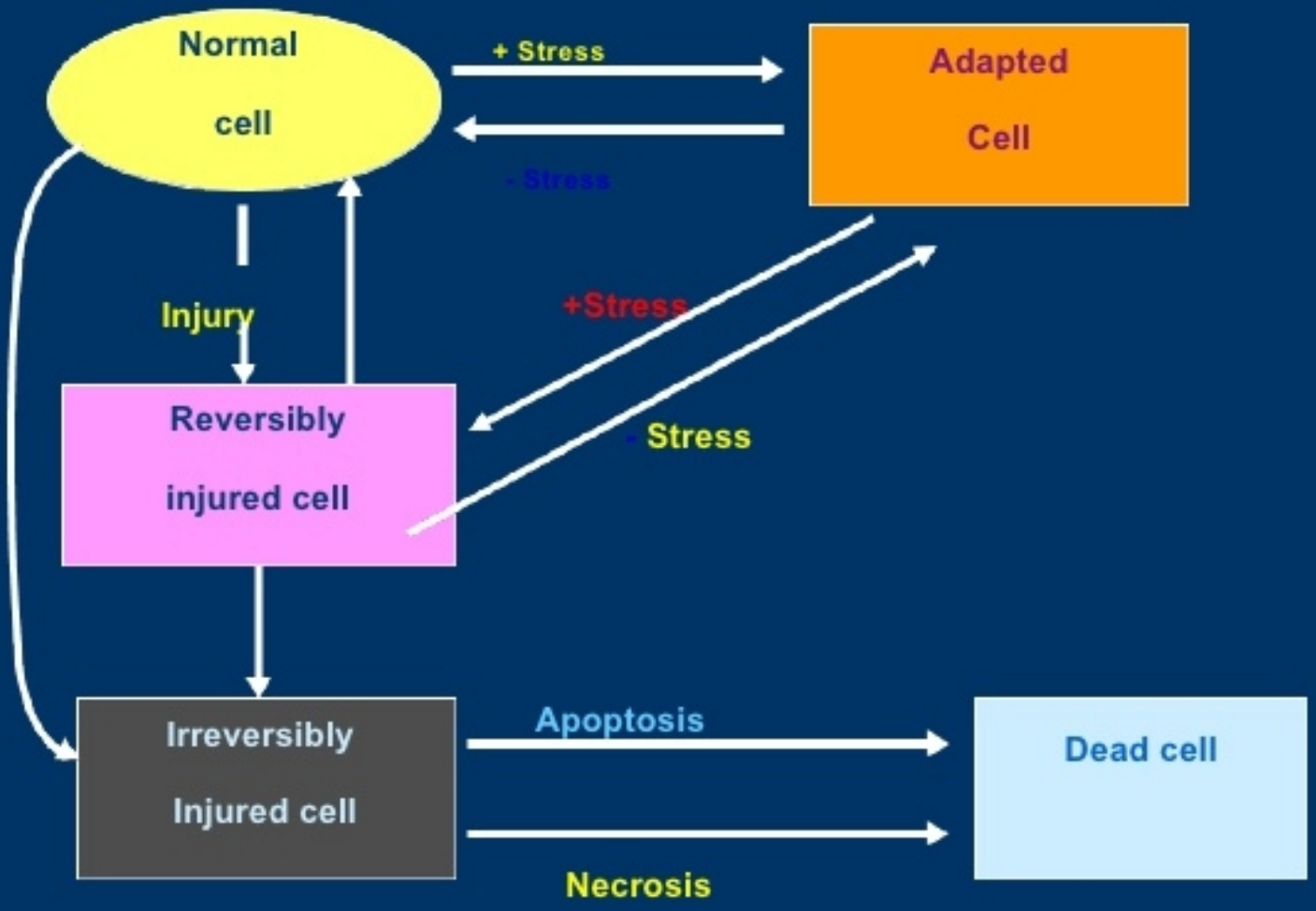
The Normal Cell



What is cell injury?

- Cell injury is a sequence of events that occur if the limits of adaptive capability are exceeded or no adaptive response is possible.
- Most common causes are: ischemia, hypoxia, chemical injury, and injury produced by infectious agents

Overview


Normal
cell
+ Stress
- Stress
Adapted
Cell
Injury
+Stress
- Stress
Reversibly
injured cell
Irreversibly
Injured cell
Apoptosis
Necrosis
Dead cell

ADAPTIVE RESPONSES OF CELLS:

- Atrophy
- Hypertrophy
- Hyperplasia
- Metaplasia
- Storage

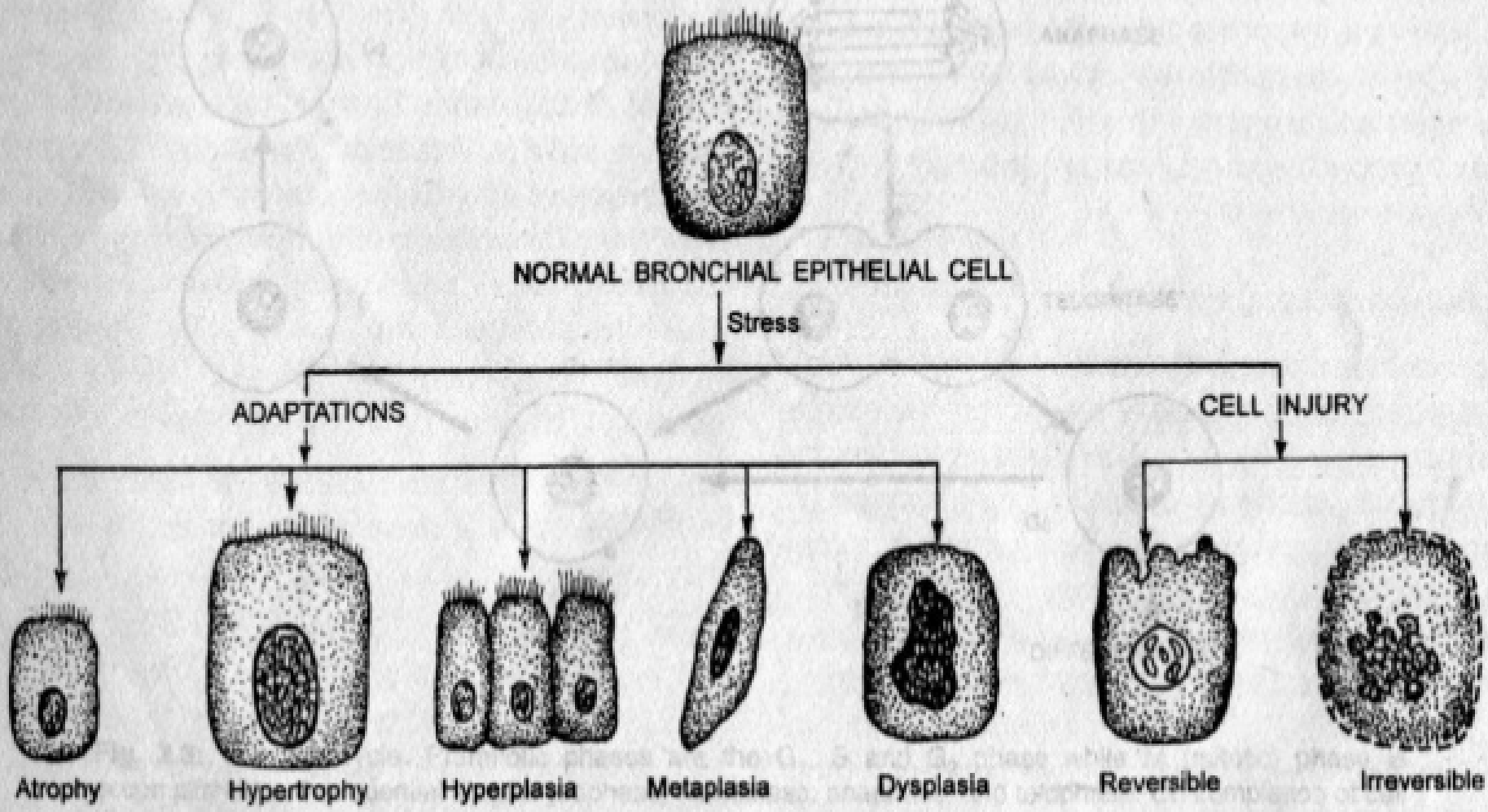
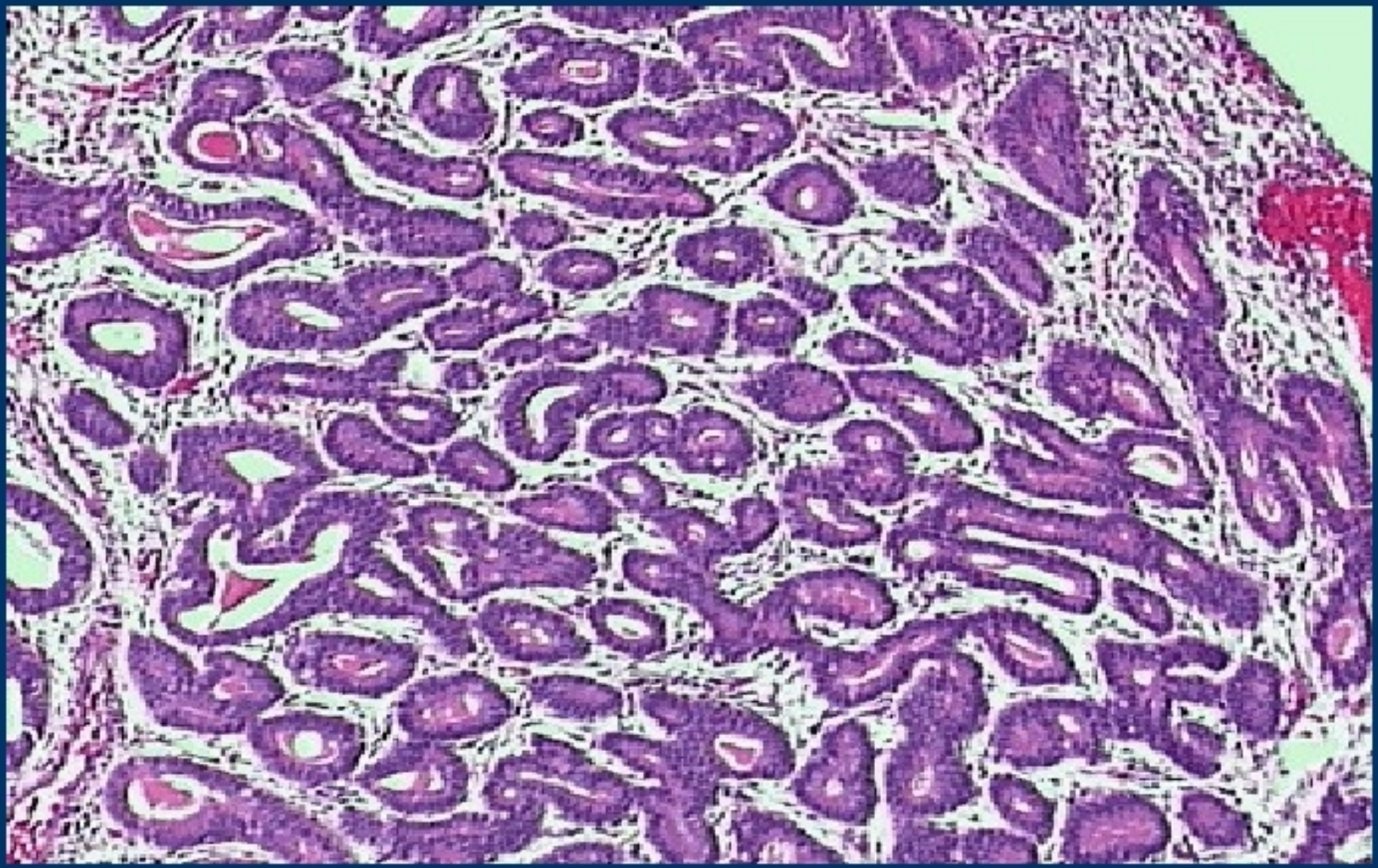
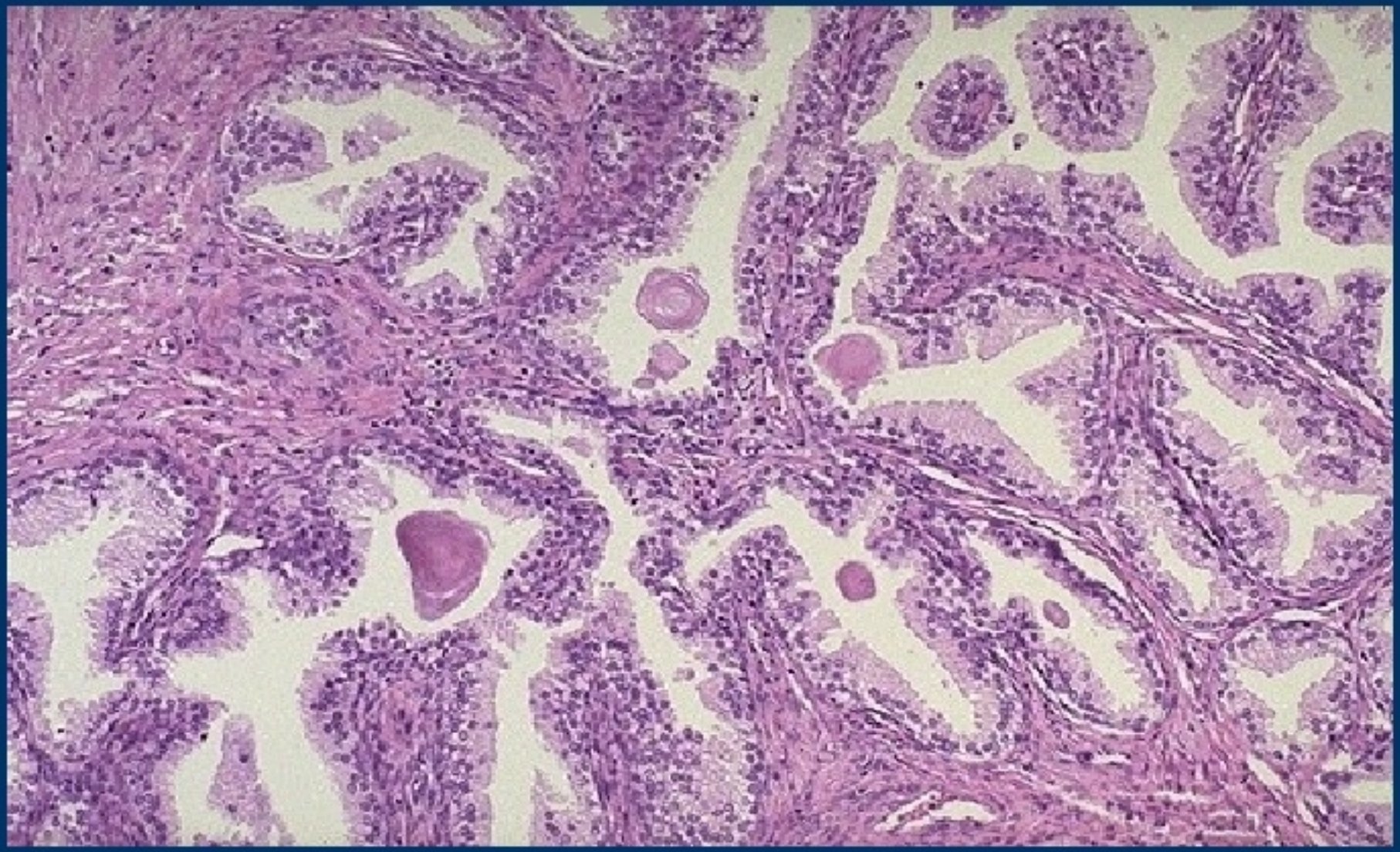


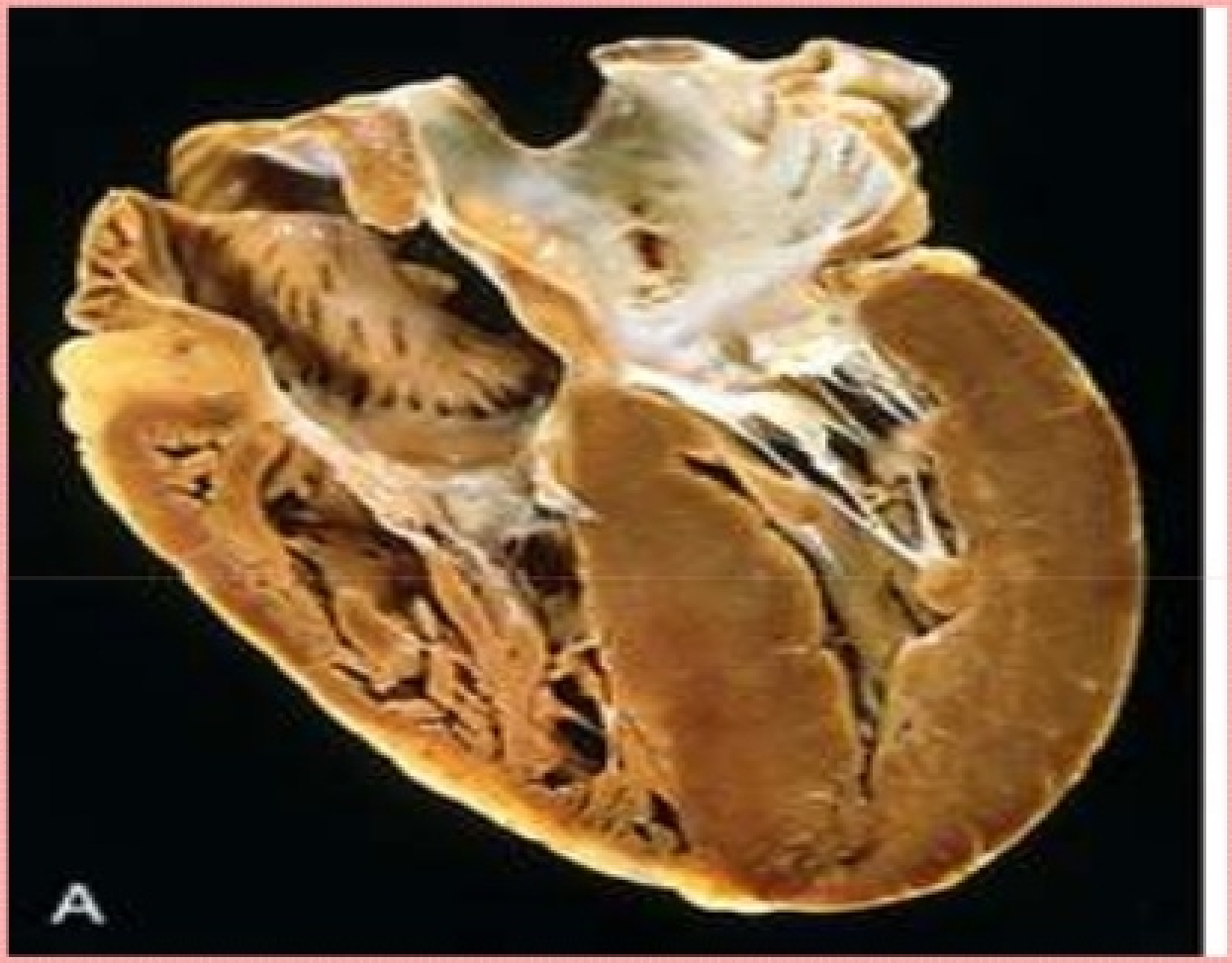
Fig. 4.1: Cellular responses to cell injury.

HYPERPLASIA-UTERUS



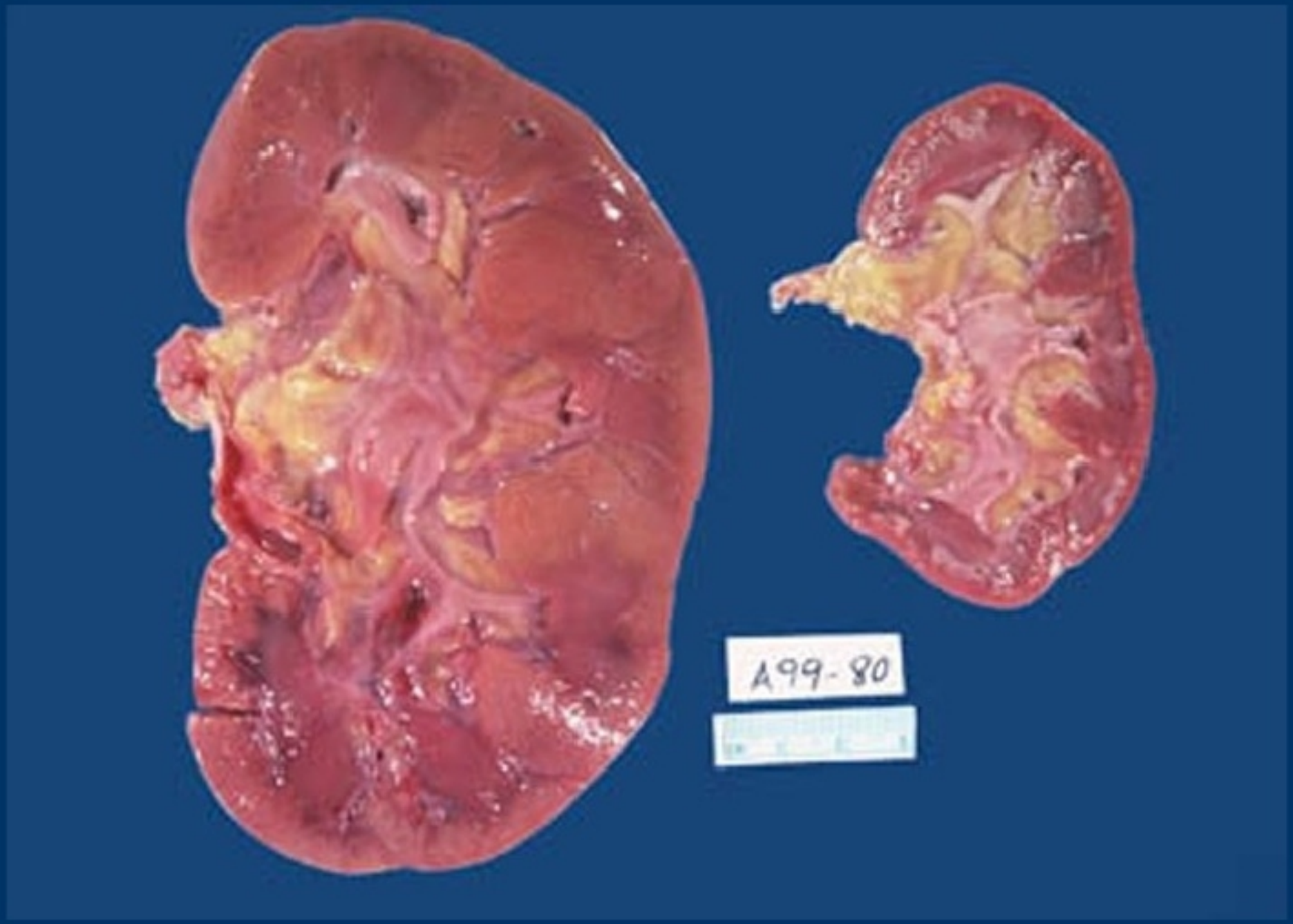
HYPERPLASIA-PROSTATE GLAND





Hypertrophied heart

（From ROBBINS BASIC PATHOLOGY，2003）


A99-80

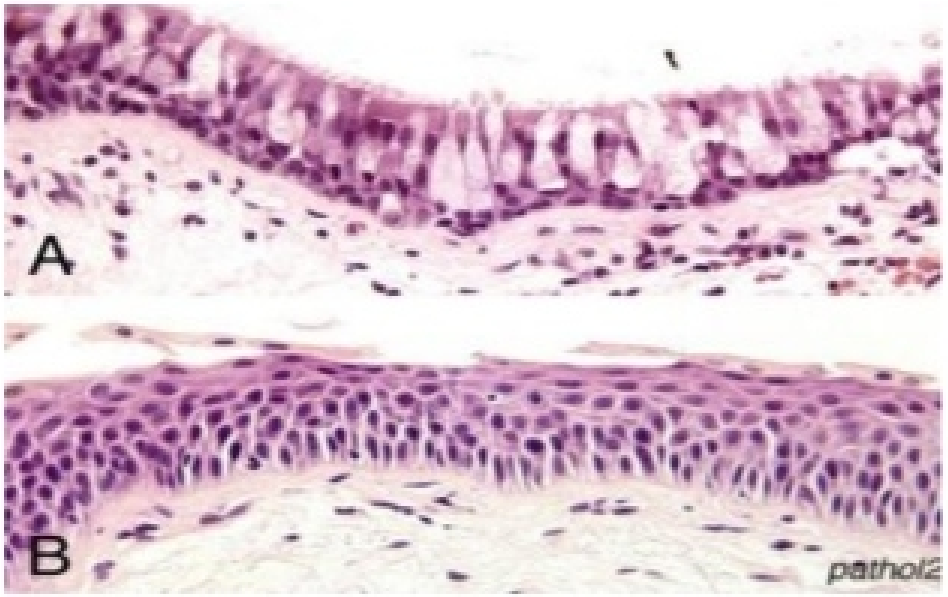
Metaplasia

- Types:
  1) ***Epithelial metaplasia***
  2) ***Connective tissue metaplasia***

1- Epithelial metaplasia

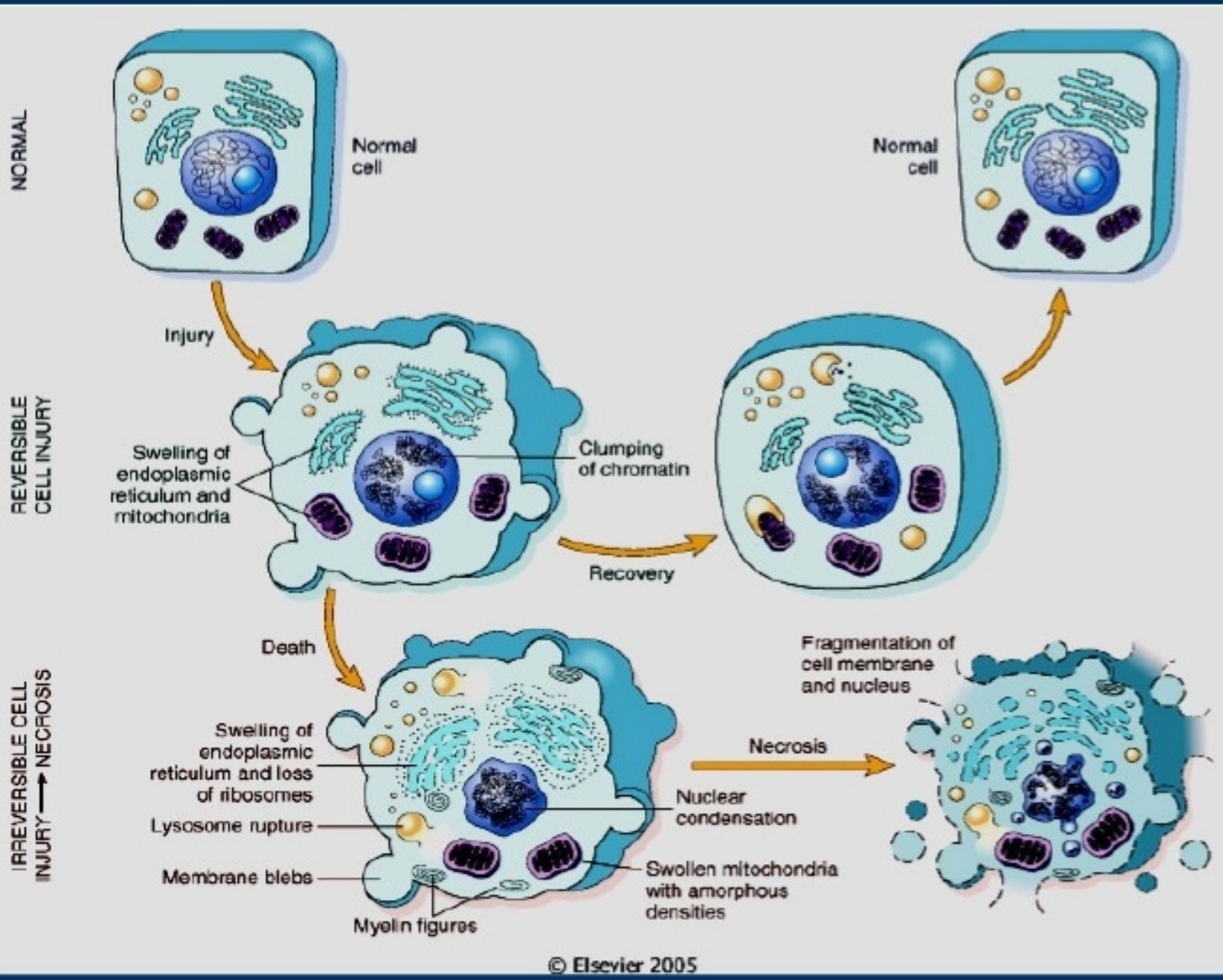
Squamous metaplasia

- In the respiratory epithelium of habitual cigarette smokers & in vitamin A deficiency



Cell Injury and Death

- **Reversible Injury**
  - Cell swelling develops when cells are incapable of fluid an ion homeostasis (↓ed function of ATP dependant pumps).
  - Fatty change the accumulation of lipid vacuoles in the cytoplasm.
- **Irreversible injury (Necrosis)**
  - Two basic processes underlie the morphologic changes of necrosis
    - Denaturation of protein
    - Enzymatic digestion of cell components


NORMAL
Normal cell
Normal cell
REVERSIBLE CELL INJURY
Injury
Swelling of endoplasmic reticulum and mitochondria
Clumping of chromatin
Recovery
IRREVERSIBLE CELL INJURY → NECROSIS
Death
Swelling of endoplasmic reticulum and loss of ribosomes
Lysosome rupture
Membrane blebs
Myelin figures
Nuclear condensation
Swollen mitochondria with amorphous densities
Necrosis
Fragmentation of cell membrane and nucleus
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Morphology of Cell Injury

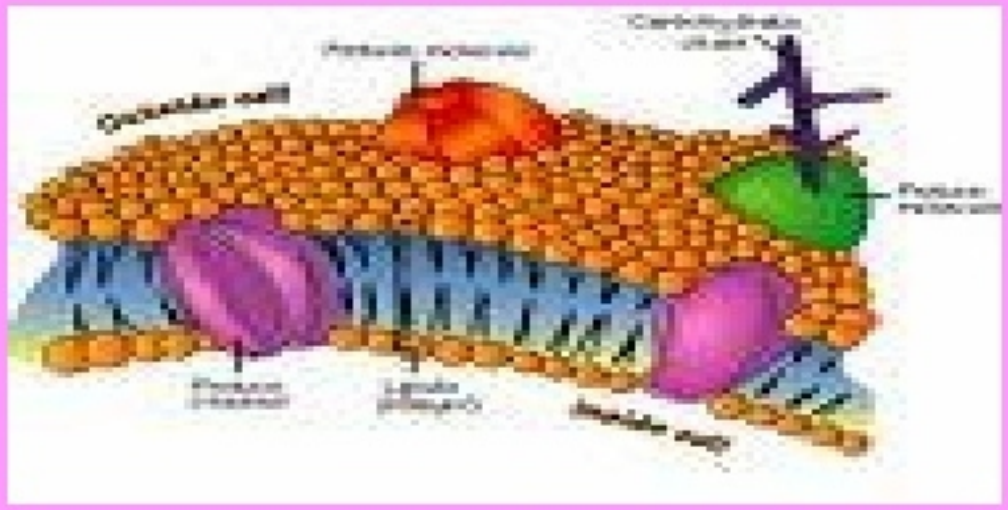
Reversible Injury

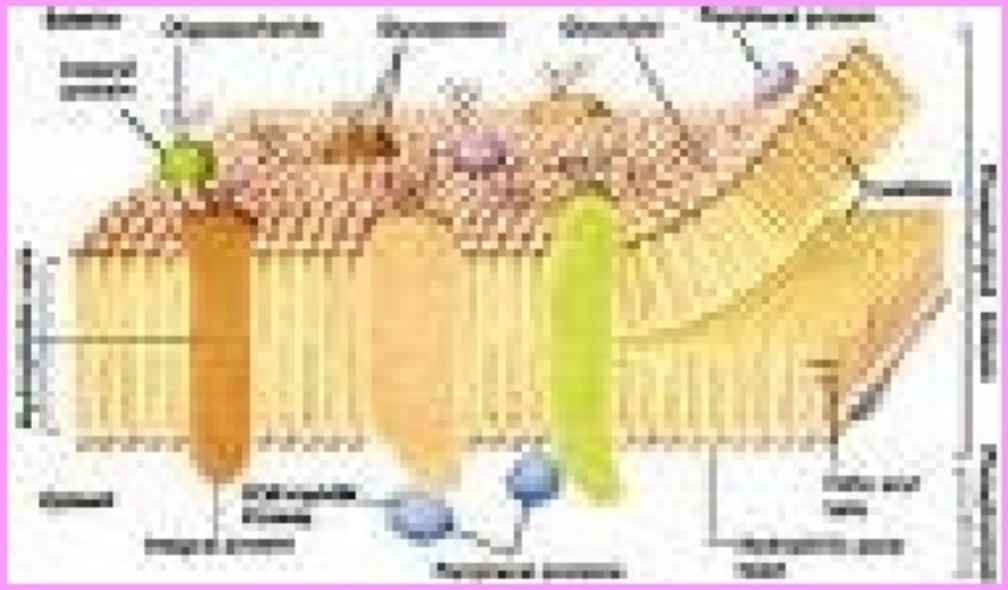
Cellular swelling

Fatty change

- Plasma membrane alteration
- Mitochondrial Changes
- Dilation of Endoplasmic reticulum
- Nuclear Alteration

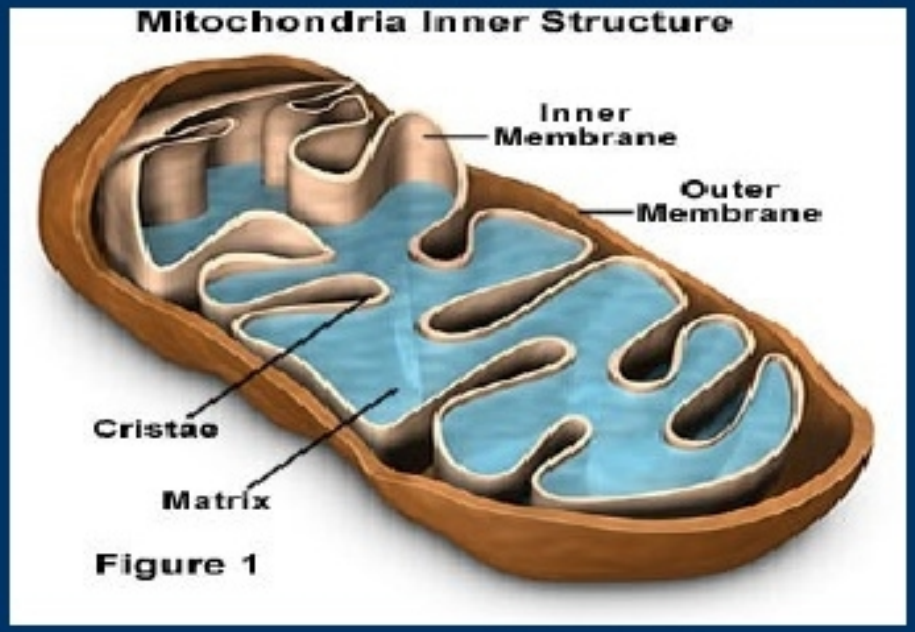
Alteration in the Plasma Membrane

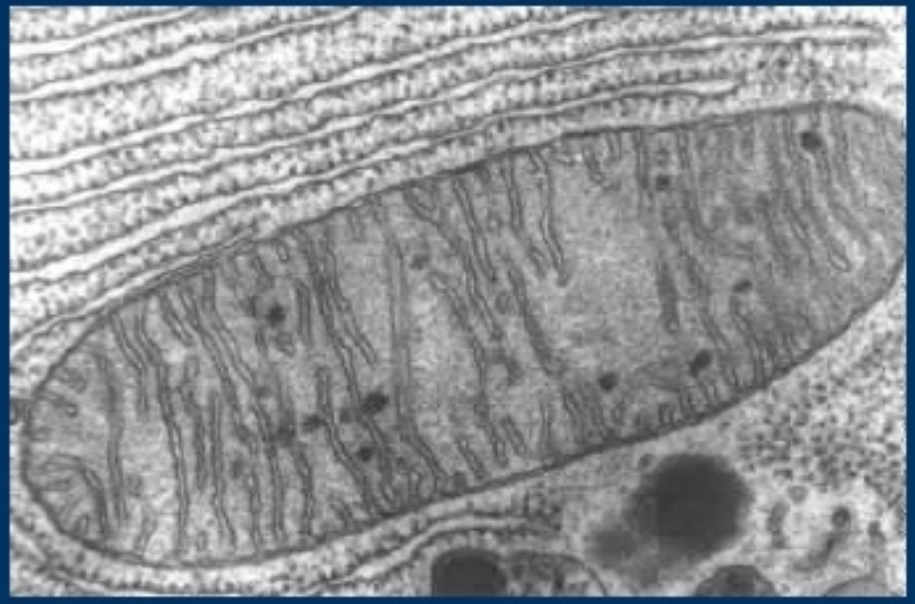




- Cellular swelling
- Formation of cytoplasmic blebs
- Blunting and distortion of microvilli
- Creation of myelin figures
- Deterioration and loosening of intercellular attachments

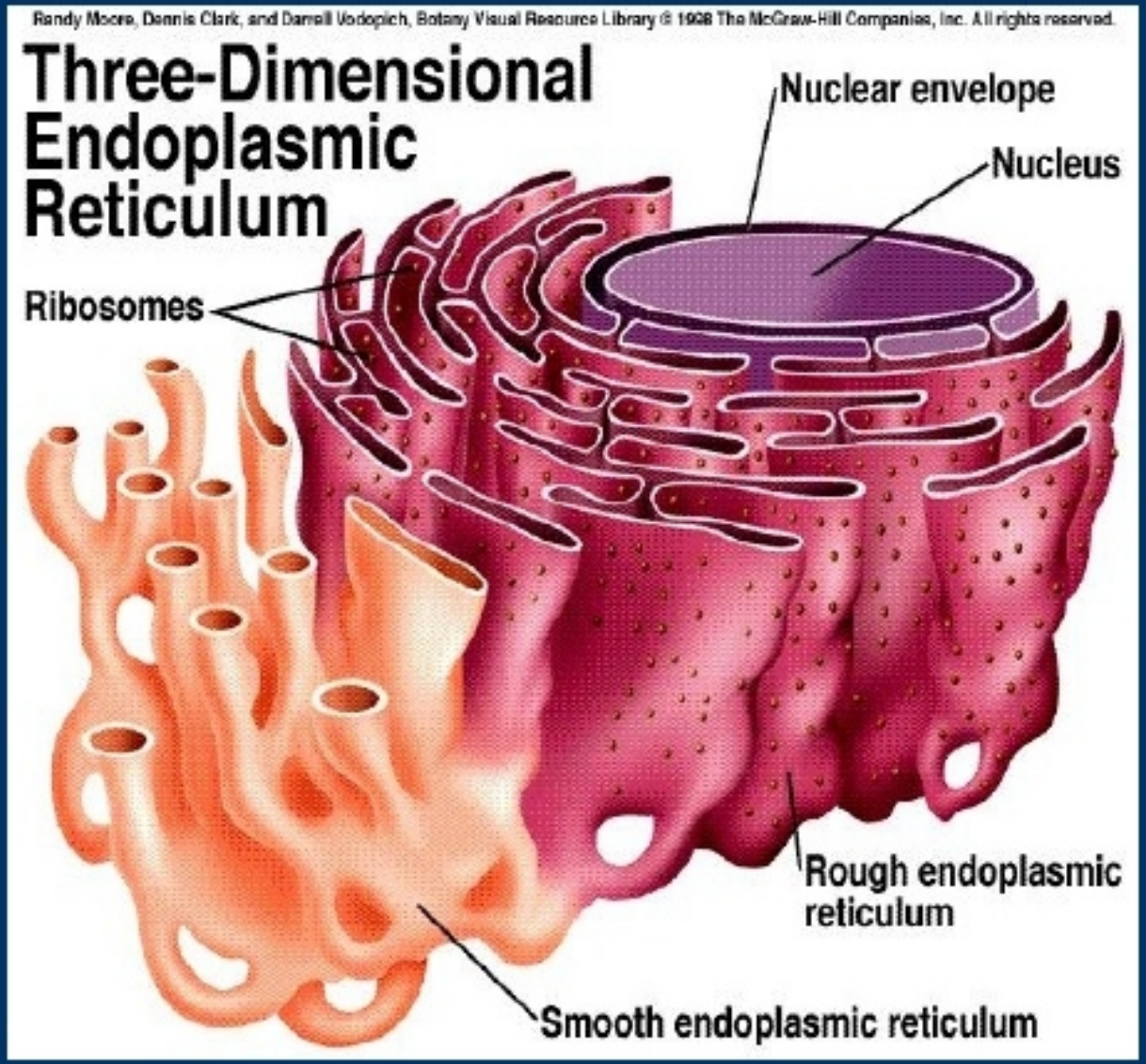
Mitochondrial Changes





- Early, appears condensed as a result of loss of matrix protein following loss of ATP
- Followed by swelling due to ionic shifts
- Amorphous densities which correlate with the onset of irreversibility
- Finally, rupture of membrane followed by progressing increased calcification

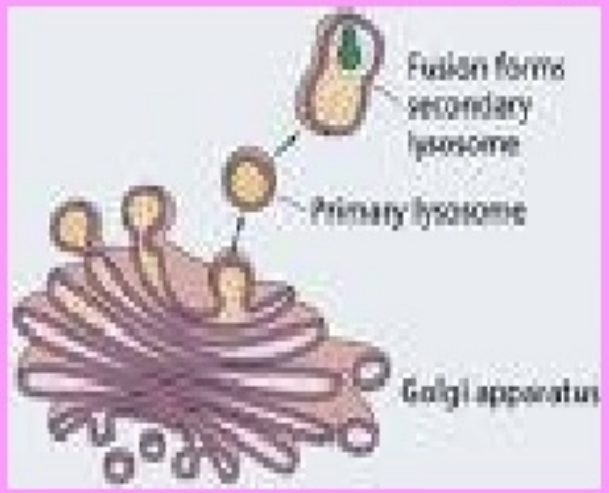
Endoplasmic reticulum changes

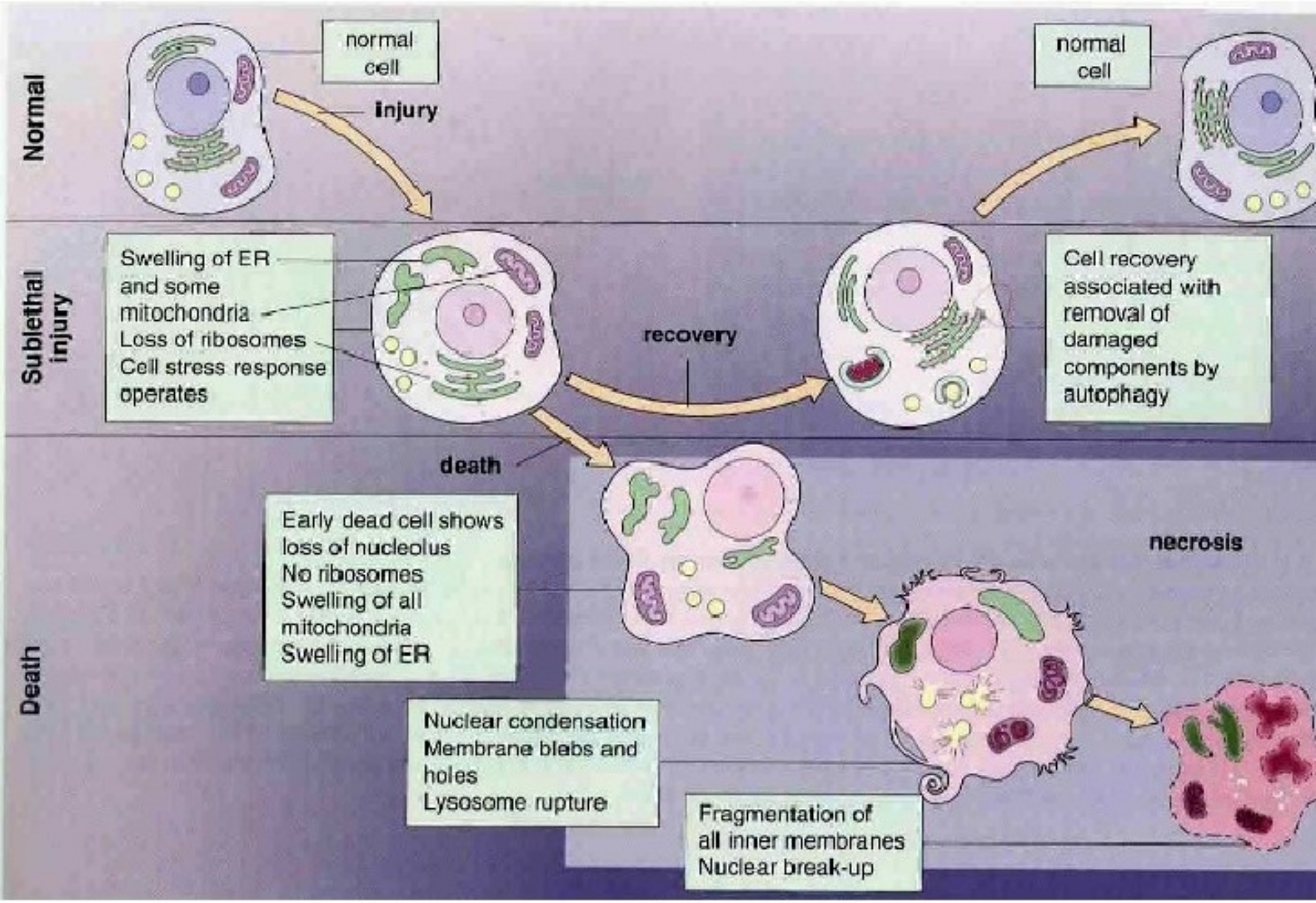


- Dilatation
- Detachment of ribosomes and disaggregation of polysomes with decreased protein synthesis
- Progressive fragmentation and formation of intracellular aggregates of myelin figures

Changes in the Lysosomes

- Generally appear late
- Swelling → rupture → disappear
- some fused with the autohagic vacuoles (phagosomes) which become apparent within damaged cells




Normal
Sublethal injury
Death
normal cell
injury
normal cell
Swelling of ER and some mitochondria
Loss of ribosomes
Cell stress response operates
recovery
Cell recovery associated with removal of damaged components by autophagy
death
Early dead cell shows loss of nucleolus
No ribosomes
Swelling of all mitochondria
Swelling of ER
necrosis
Nuclear condensation
Membrane blebs and holes
Lysosome rupture
Fragmentation of all inner membranes
Nuclear break-up

Reversible Injury

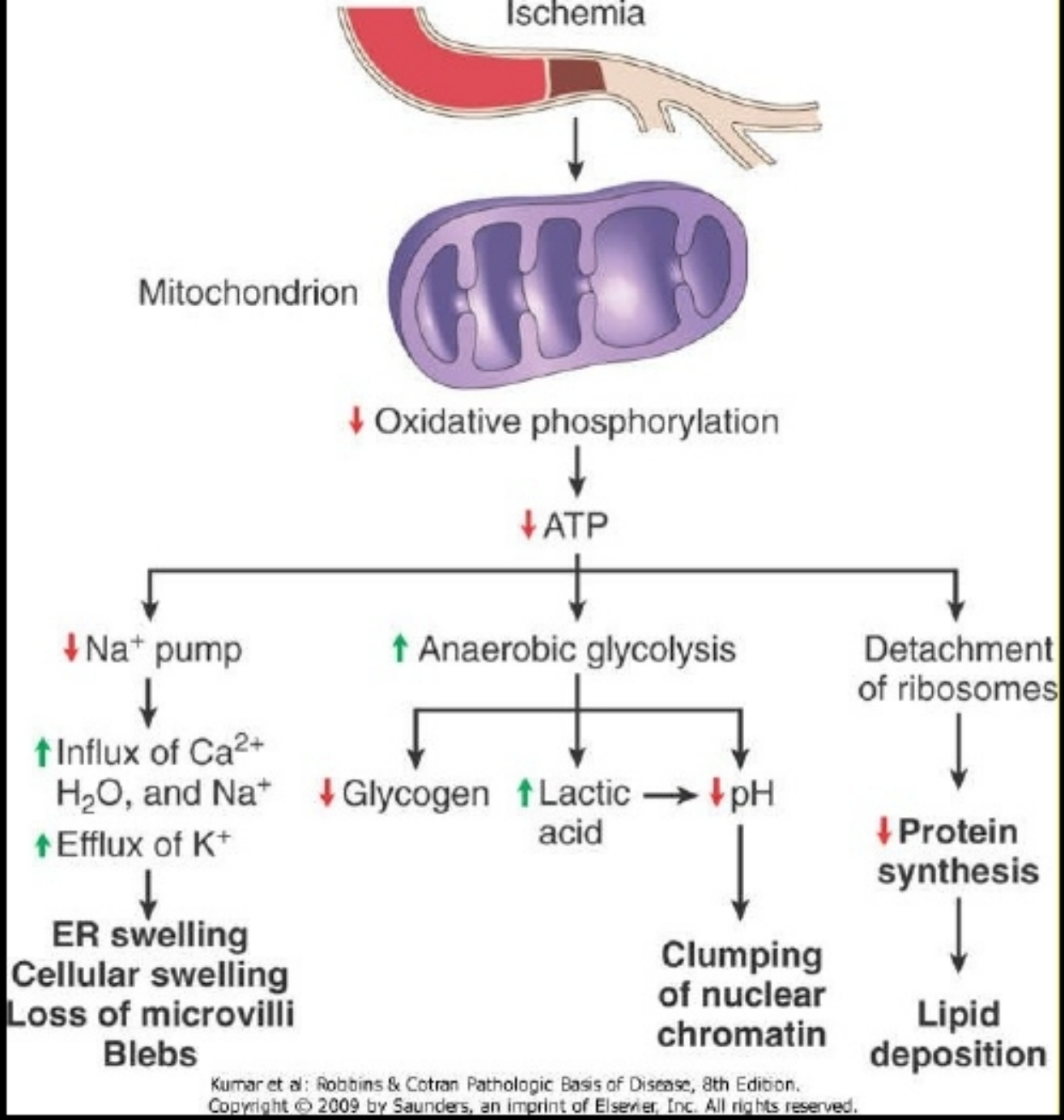
- Mitochondrial oxidative phosphorylation is disrupted first → Decreased ATP →
  - Decreased Na/K ATPase → gain of intracellular Na → cell swelling
  - Decreased ATP-dependent Ca pumps → increased cytoplasmic Ca concentration
  - Altered metabolism → depletion of glycogen
  - Lactic acid accumulation → decreased pH
  - Detachment of ribosomes from RER → decreased protein synthesis
- End result is cytoskeletal disruption with loss of microvilli, bleb formation, etc

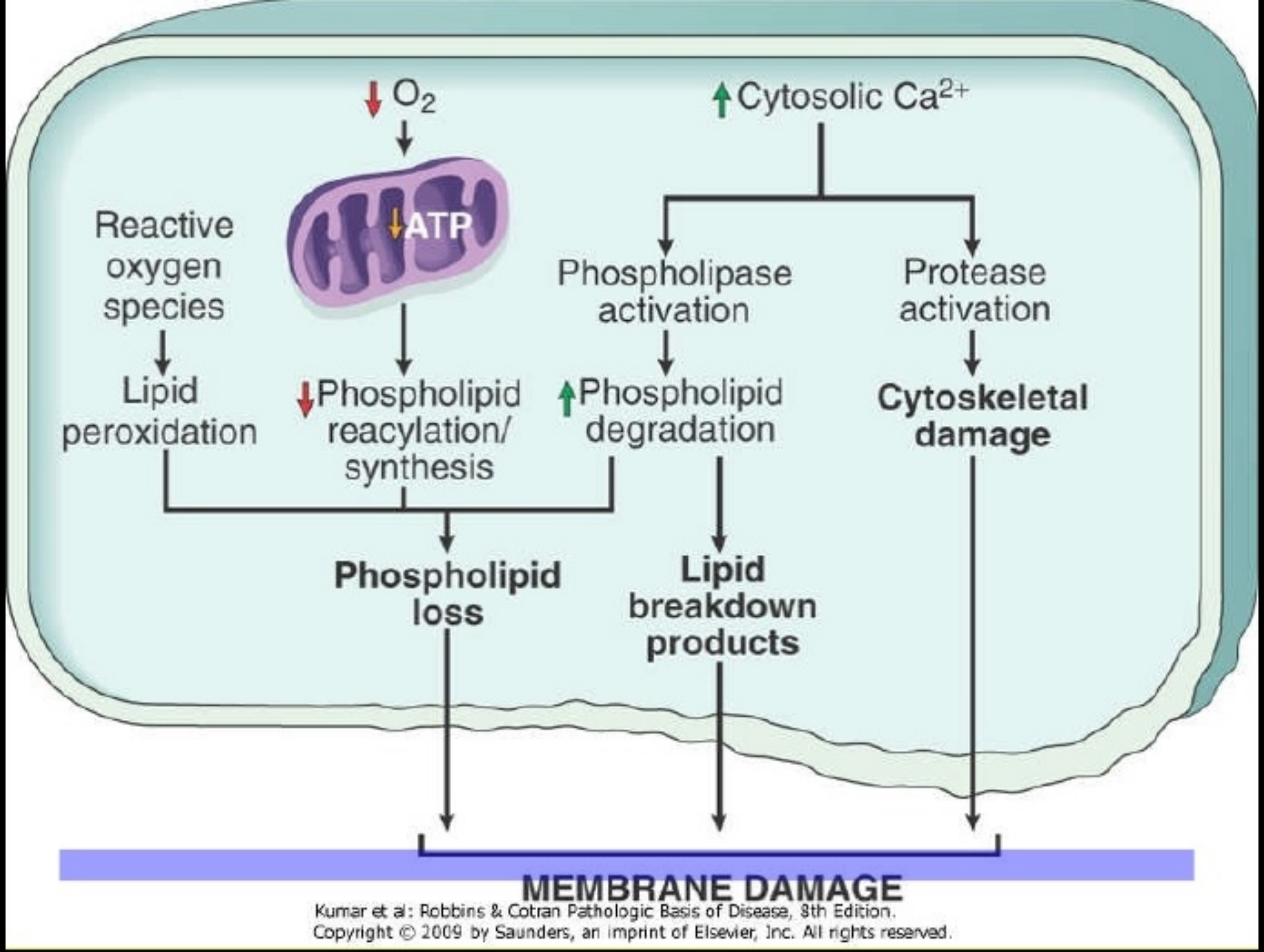
Irreversible Injury

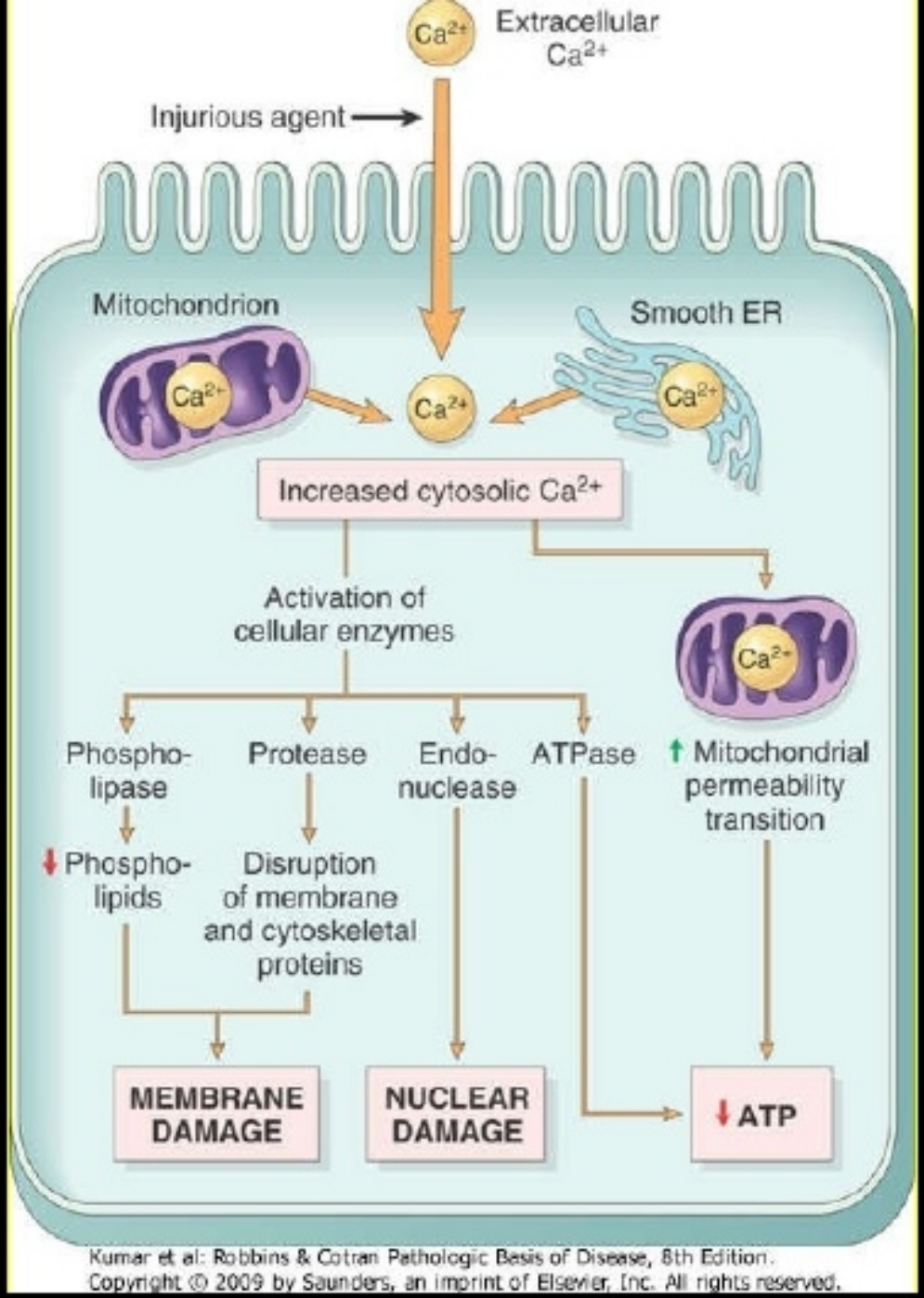
- Mitochondrial swelling with formation of large amorphous densities in matrix
- Lysosomal membrane damage → leakage of proteolytic enzymes into cytoplasm
- Mechanisms include:
  - Irreversible mitochondrial dysfunction → markedly decreased ATP
  - Severe impairment of cellular and organellar membranes

Irreversible Injury – Nuclear Changes

- Pyknosis
  - Nuclear shrinkage and increased basophilia
- Karyorrhexis
  - Fragmentation of the pyknotic nucleus
- Karyolysis
  - Fading of basophilia of chromatin







Clinical Correlation

- Injured membranes are leaky
- Enzymes and other proteins that escape through the leaky membranes make their way to the bloodstream, where they can be measured in the serum

Free Radicals

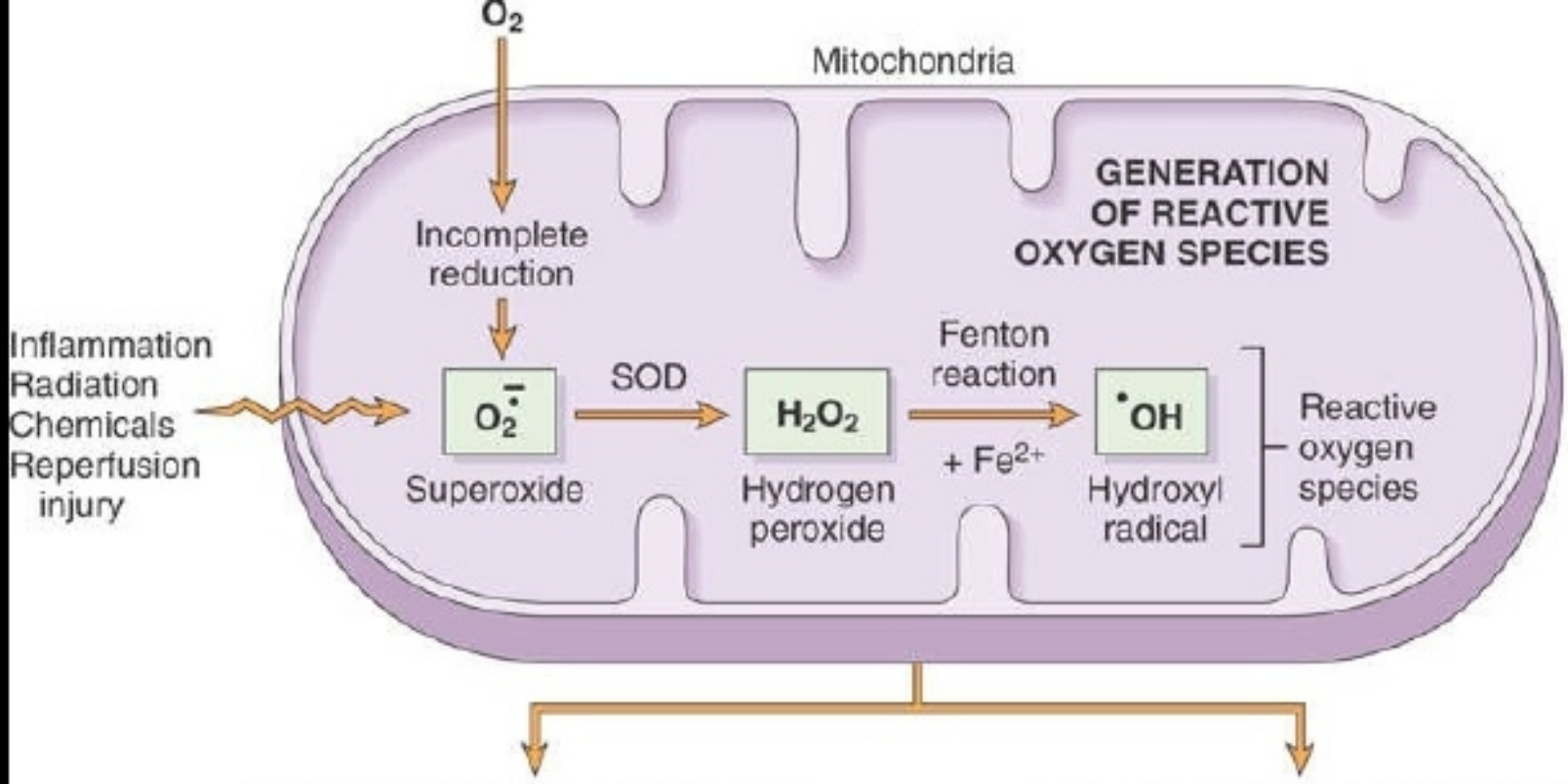
- Free radicals have an unpaired electron in their outer orbit
- Free radicals cause chain reactions
- Generated by:
  - Absorption of radiant energy
  - Oxidation of endogenous constituents
  - Oxidation of exogenous compounds

Examples of Free Radical Injury

- Chemical (e.g., CCl_4, acetaminophen)
- Inflammation / Microbial killing
- Irradiation (e.g., UV rays → skin cancer)
- Oxygen (e.g., exposure to very high oxygen tension on ventilator)
- Age-related changes

Mechanism of Free Radical Injury

- Lipid peroxidation → damage to cellular and organellar membranes
- Protein cross-linking and fragmentation due to oxidative modification of amino acids and proteins
- DNA damage due to reactions of free radicals with thymine



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

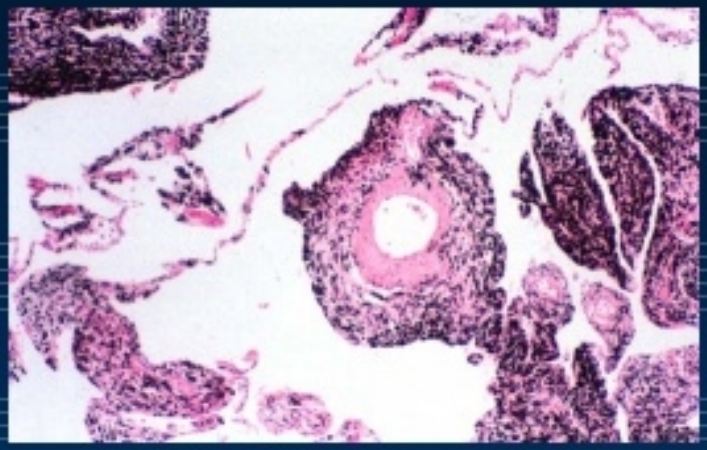
REMOVAL OF FREE RADICALS

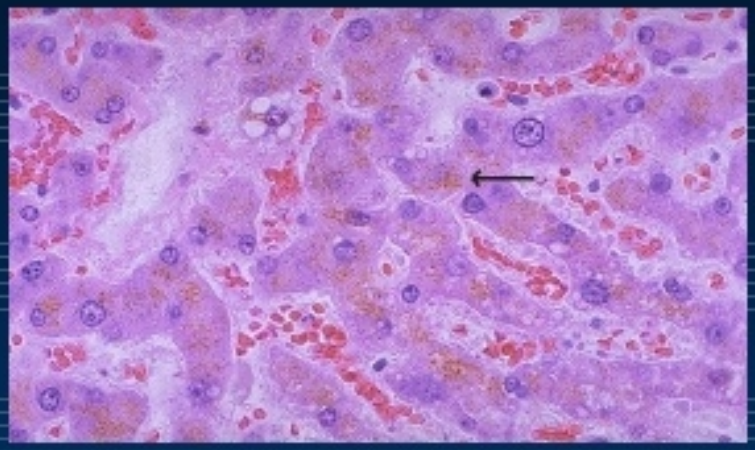
Antioxidant mechanisms:

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

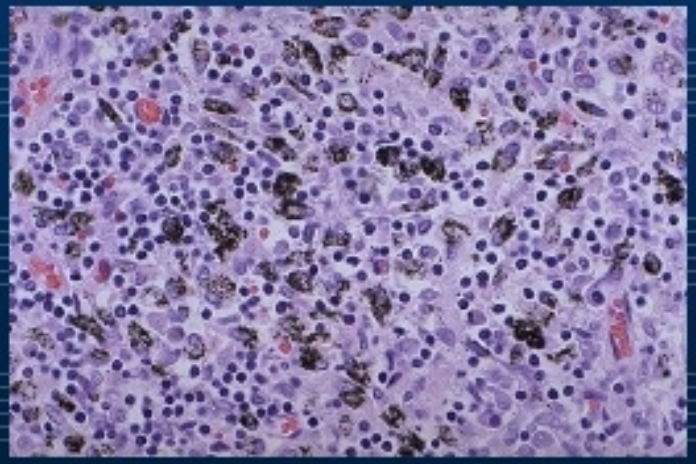
Types of Cell Death

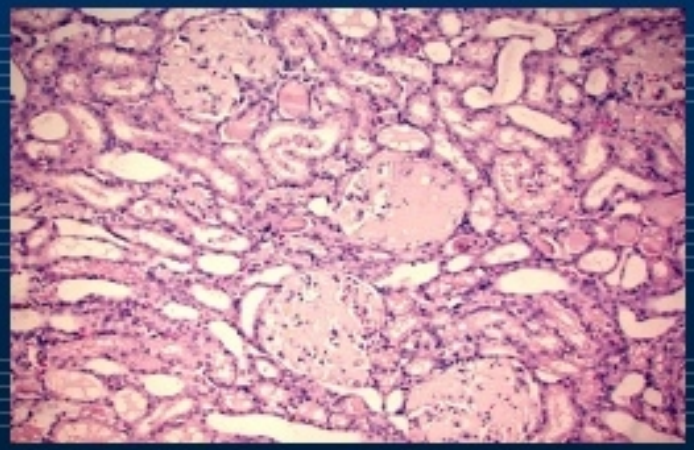
- Apoptosis
  - Usually a regulated, controlled process
  - Plays a role in embryogenesis
- Necrosis
  - Always pathologic – the result of irreversible injury
  - Numerous causes





ABNORMAL ACCUMULATIONS





TYPES OF ACCUMULATIONS

There are 2 basic types of accumulations:

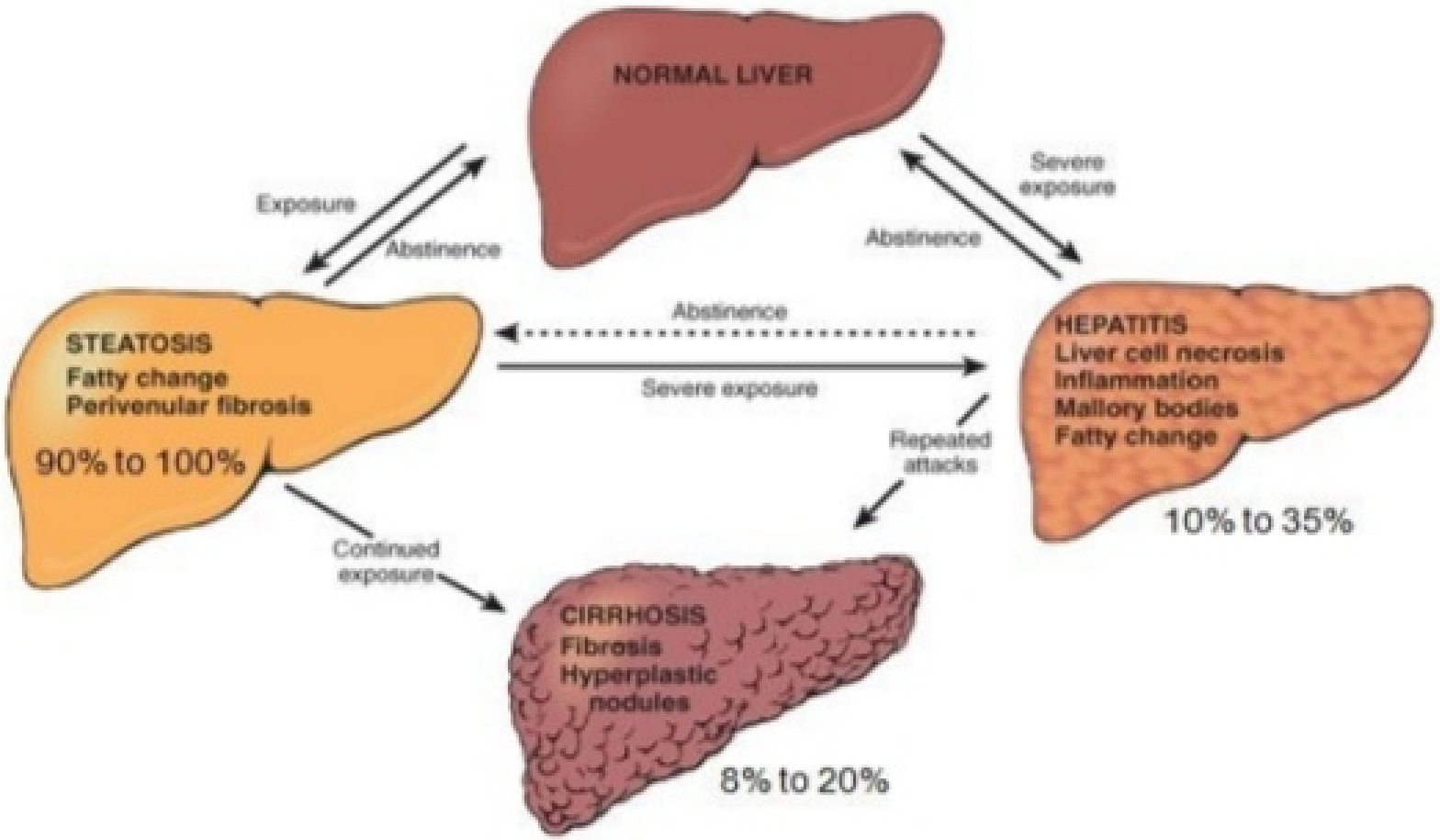
1. Excess of substances normal to the particular cell, and
2. Abnormal substances in three mechanisms: (a) decrease in normal metabolic removal, (b) inability to metabolize the substance, and (c) deposition of abnormal exogenous substance in which the cell has no mechanism to metabolize it.

LIPID ACCUMULATION

- Abnormal lipid accumulation in cell. It may be of fatty acid (steatosis) & cholesterol .

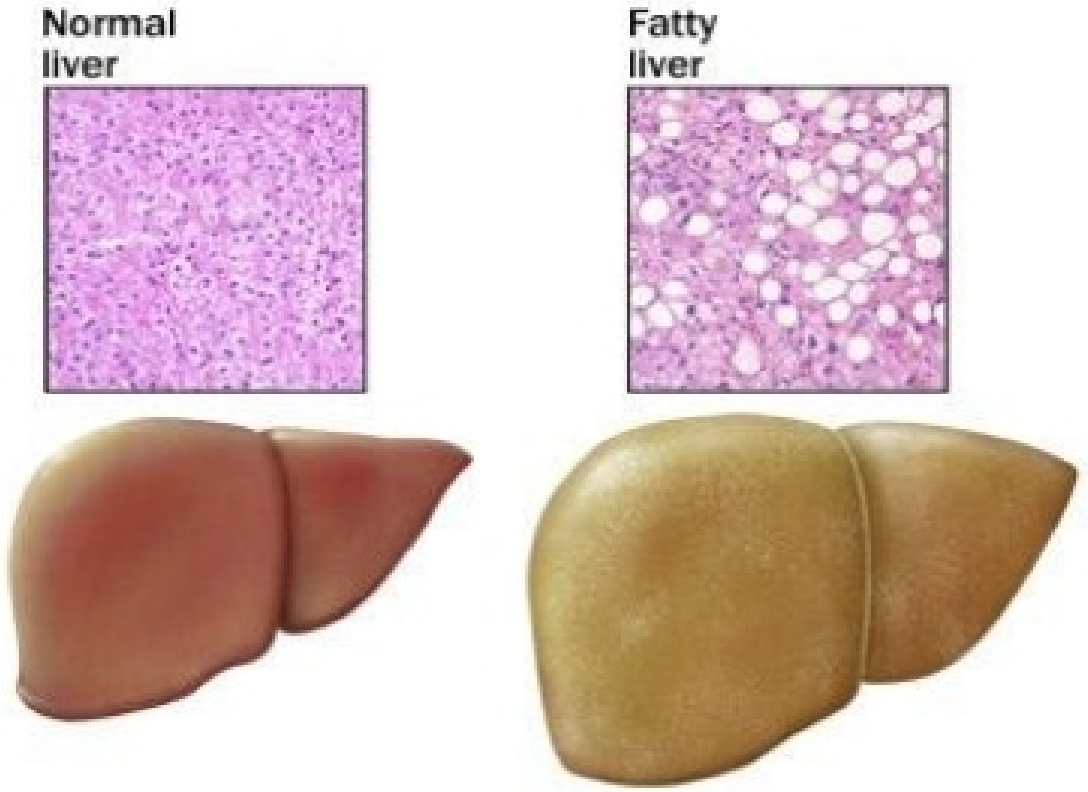
❑ ***Steatosis (Fatty change):***

- Abnormal accumulation of triglycerides within parenchymal cells.
- *Sites:* liver (commonly), heart, muscles, kidney.
- *Causes:* toxins, protein malnutrition, diabetes mellitus, obesity, anoxia & alcohol.
- *Example:* fatty liver.


NORMAL LIVER
Exposure
Abstinence
Severe exposure
Abstinence
STEATOSIS
Fatty change
Perivenular fibrosis
90% to 100%
Abstinence
Severe exposure
HEPATITIS
Liver cell necrosis
Inflammation
Mallory bodies
Fatty change
10% to 35%
Repeated attacks
Continued exposure
CIRRHOSIS
Fibrosis
Hyperplastic nodules
8% to 20%

Morphology:

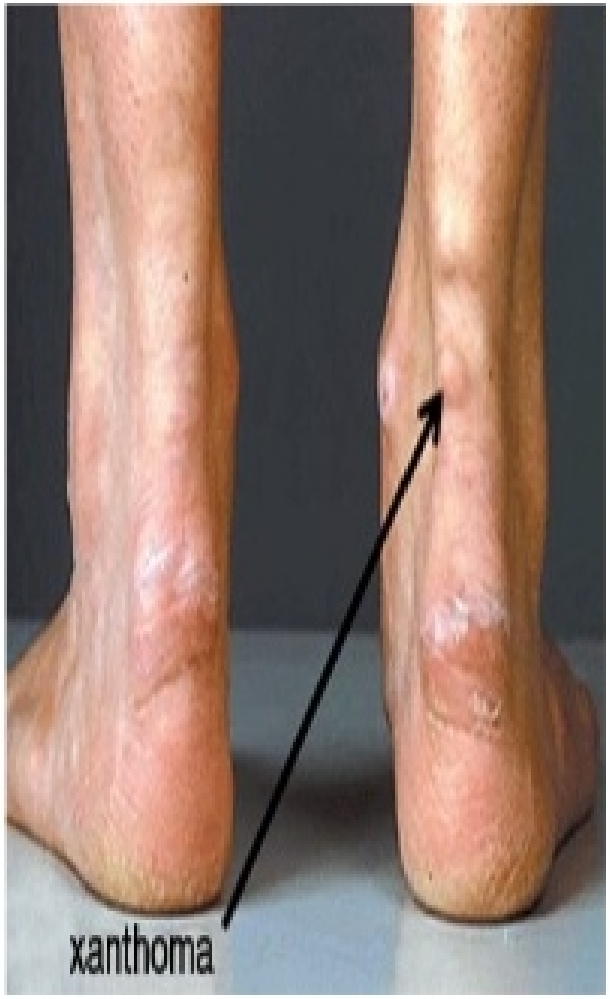
- *L*ight microscopy; vacuoles in the cytoplasm displacing the nucleus to the periphery of the cell.
- Rarely cell rupture & enclosed fat globules coalesce & forming fatty cyst.
- Grossly; fatty liver will be enlarged bright yellow soft greasy.

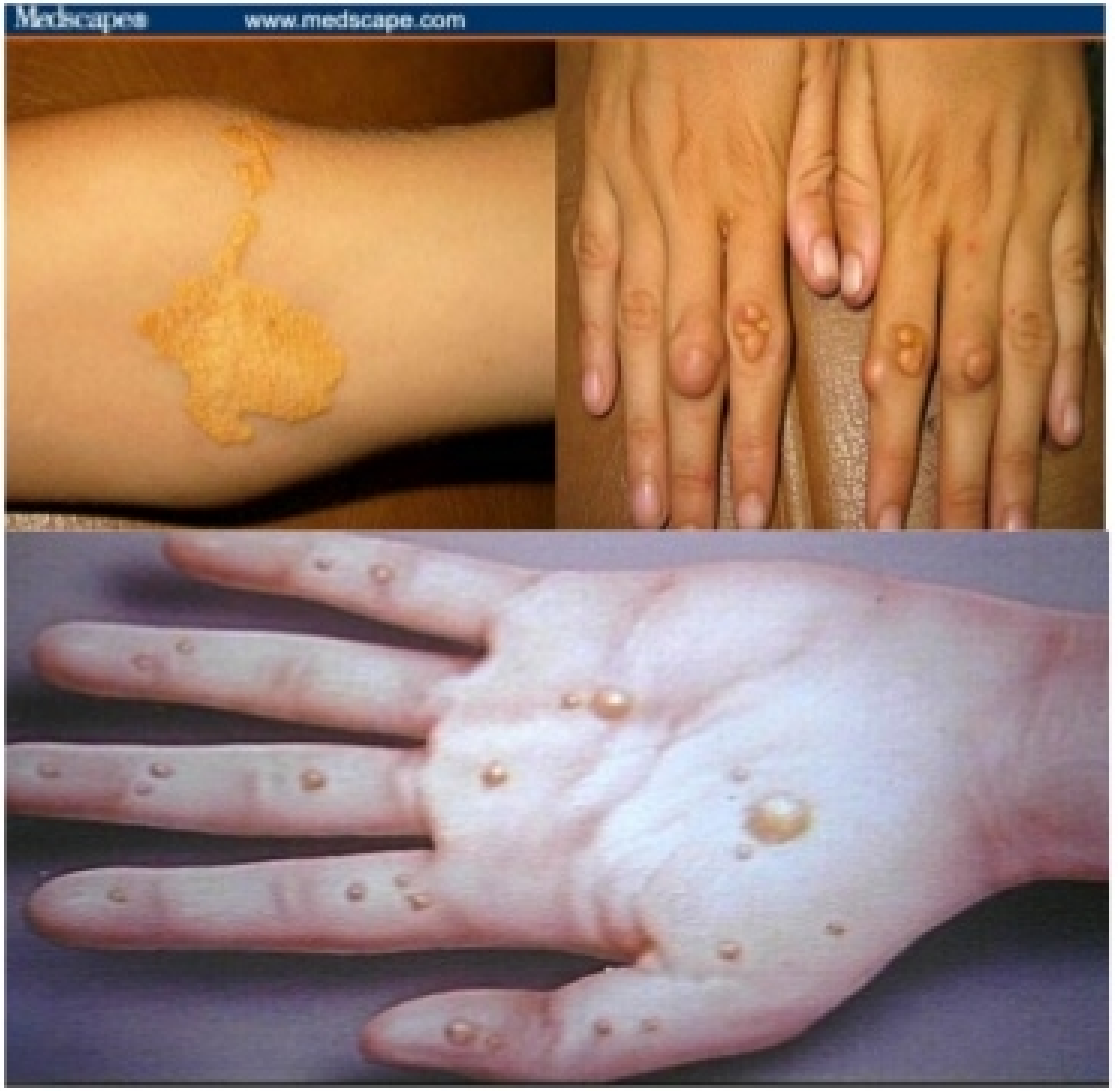

Normal
liver
Fatty
liver

- ***Cholesterol & Cholesterol Esters:***

- Accumulations in the form of intracellular vacuoles, are seen in several pathologic processes.

1. *Atherosclerosis:* Smooth muscles cells & macrophages filled with cholesterol & cholesterol ester forming foam cells within intima layer of vessels.
2. *Xanthomas:* Cluster of *f*oam cells in subepithelial connective tissues of skin & in tendons producing tumorous masses.


xanthoma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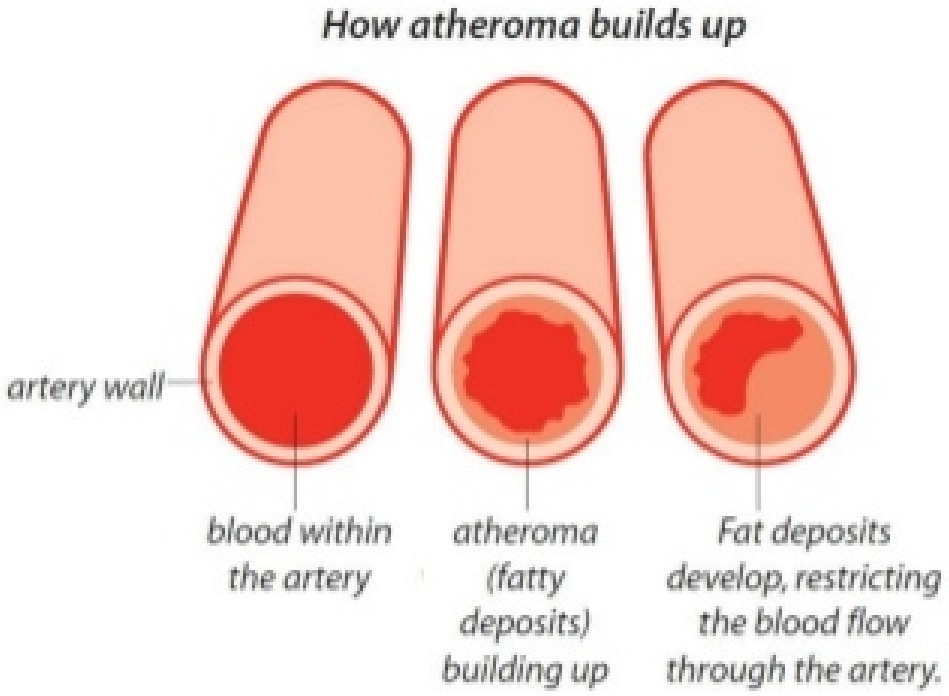
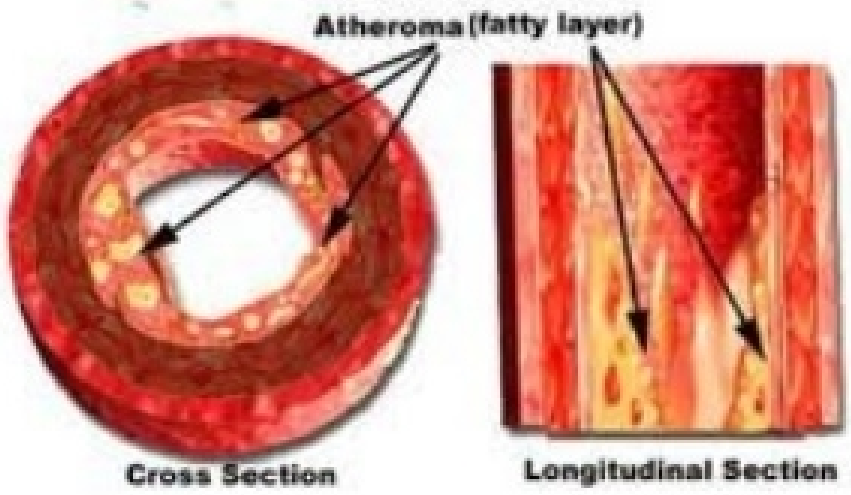
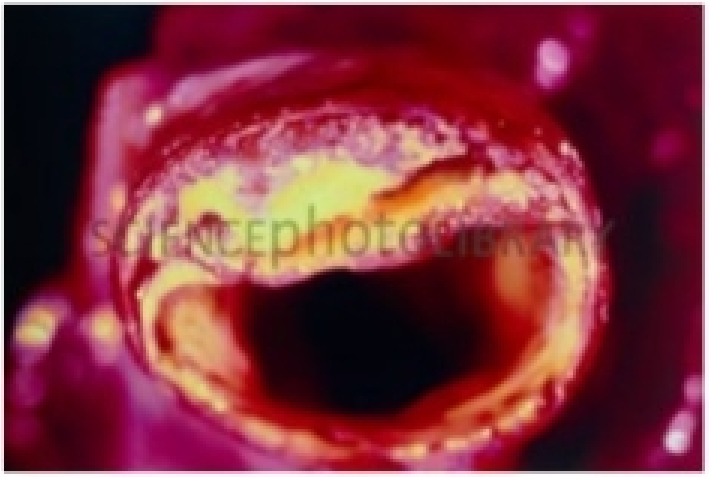

How atheroma builds up
artery wall
blood within the artery
atheroma (fatty deposits) building up
Fat deposits develop, restricting the blood flow through the artery.


Atheroma (fatty layer)
Cross Section
Longitudinal Section



PROTEIN ACCUMULATION

- Accumulation of protein droplets in proximal renal tubules; in renal disease with heavy protein leakage across the glomerular filter.
- Defect in protein folding;

- defect in intracellular transport & secretion
- ER stress induced by unfolded & missfolded protein accumulation in ER
- aggregation of abnormal or missfolded proteins in tissues

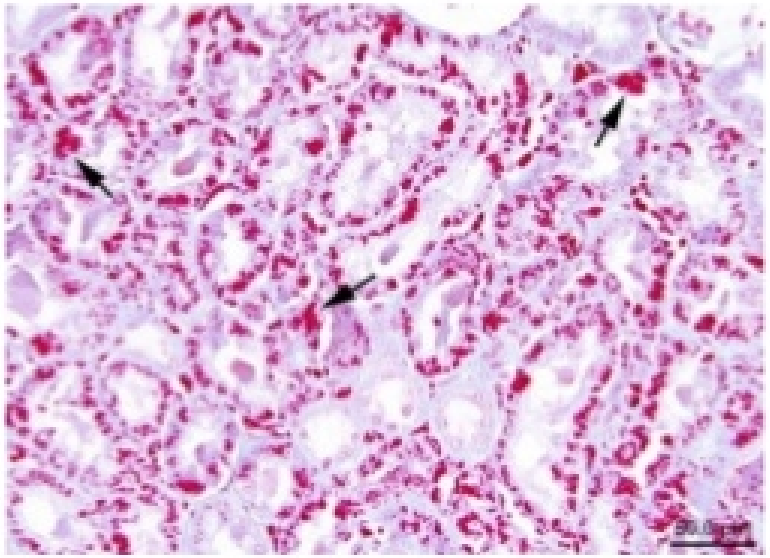
- ***Morphology :***

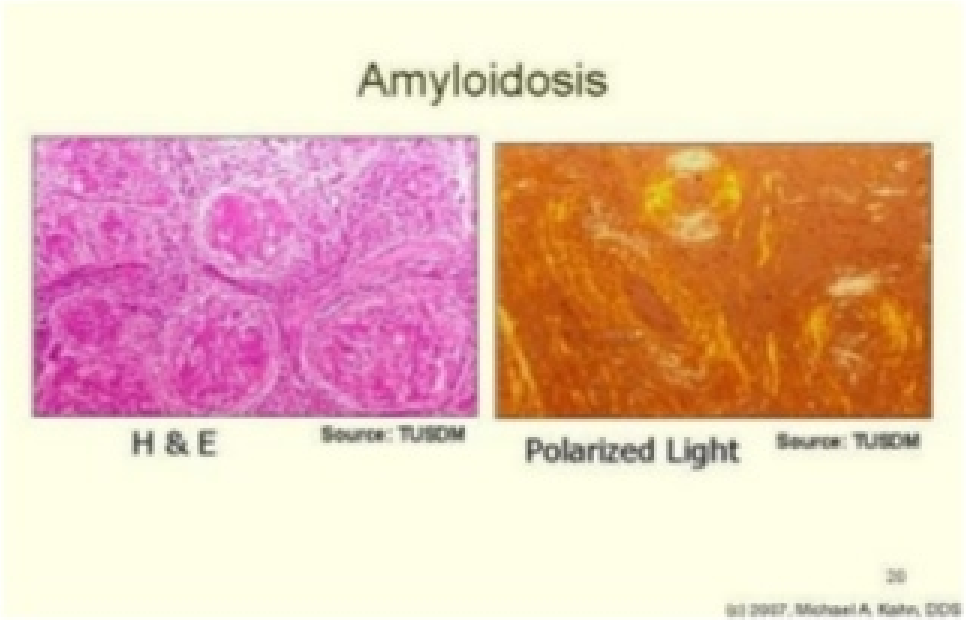
  Round eosinophilic droplets, vacuoles or aggregates in cytoplasm.

  May be amorphous or crystaline.

- Example : amyloidosis

Protein droplets in proximal renal tubules





GLYCOGEN ACCUMULATION

- ***Diabetes mellitus:*** disorder of glucose metabolism, glycogen found in renal tubular epithelial cells.
- ***Glycogen storange disorder or glycogenoses:*** genetic disorder result in enzymatic defect in synthesis & breakdown of glycogen.

Teacher to Paul: “Wake up, Paul! You can’t sleep in class!”

Paul to teacher: “I could actually, it’s just that you’re a bit loud.”

DEFINITION

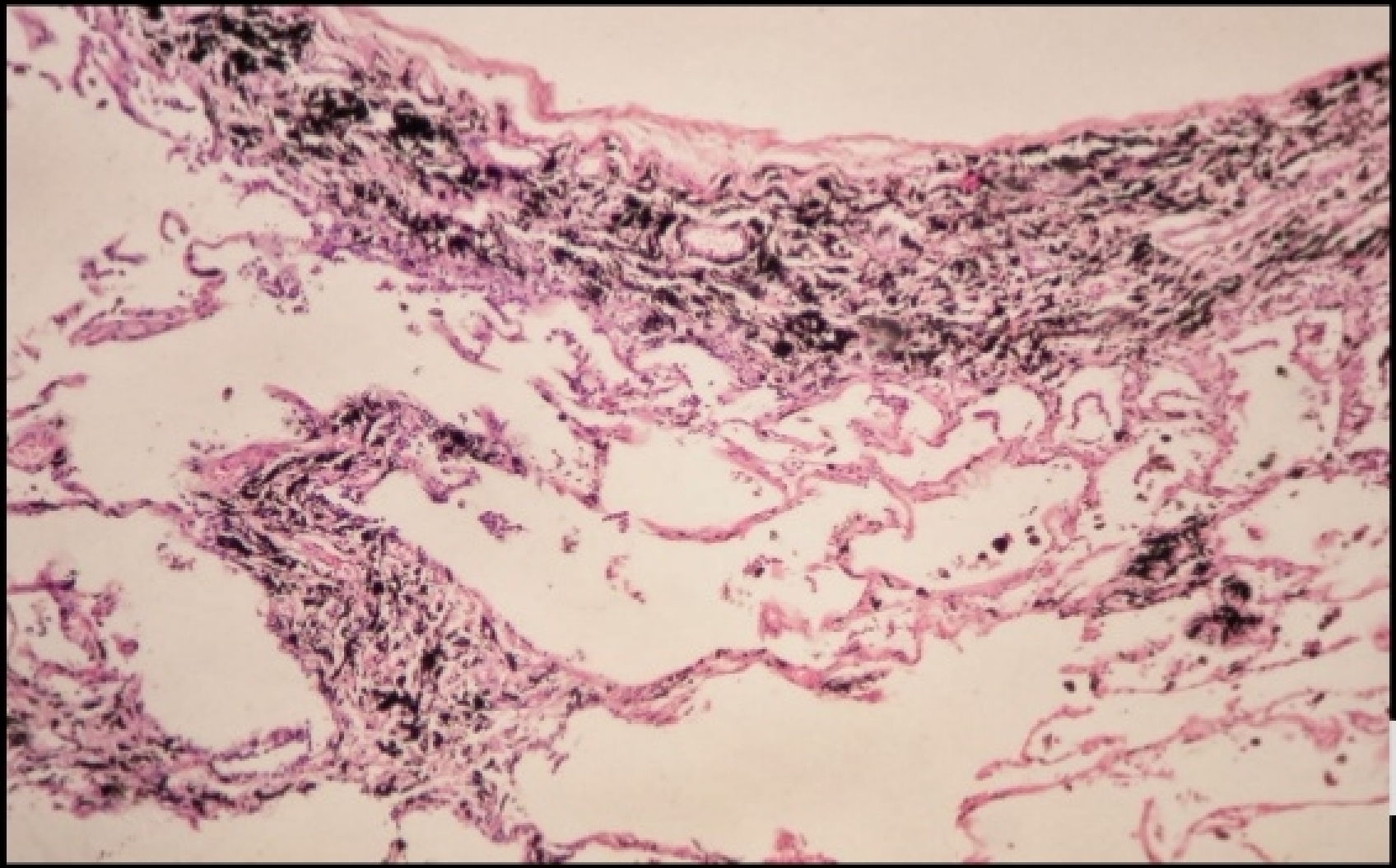
- Pigments are coloured substances, some of which are normal constituents of cells (e.g., melanin), whereas others are abnormal and accumulate in cells only under special circumstances

- Pigments can be **exogenous**, coming from outside the body, or **endogenous**, synthesized within the body itself.

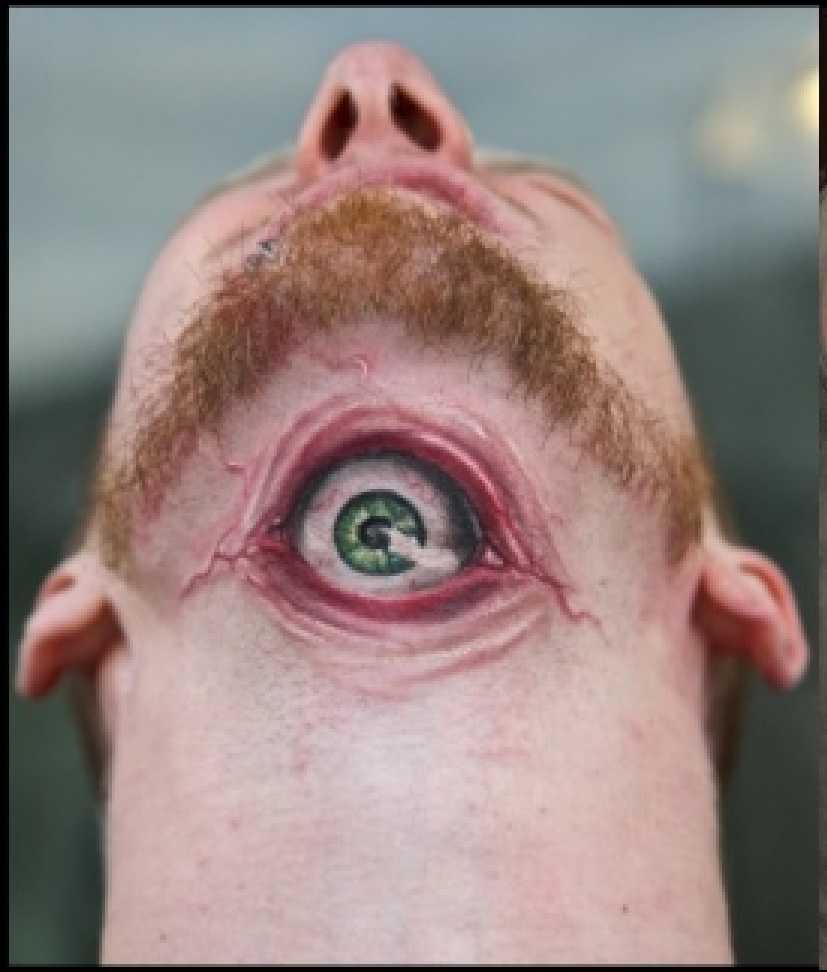
EXOGENOUS PIGMENTS

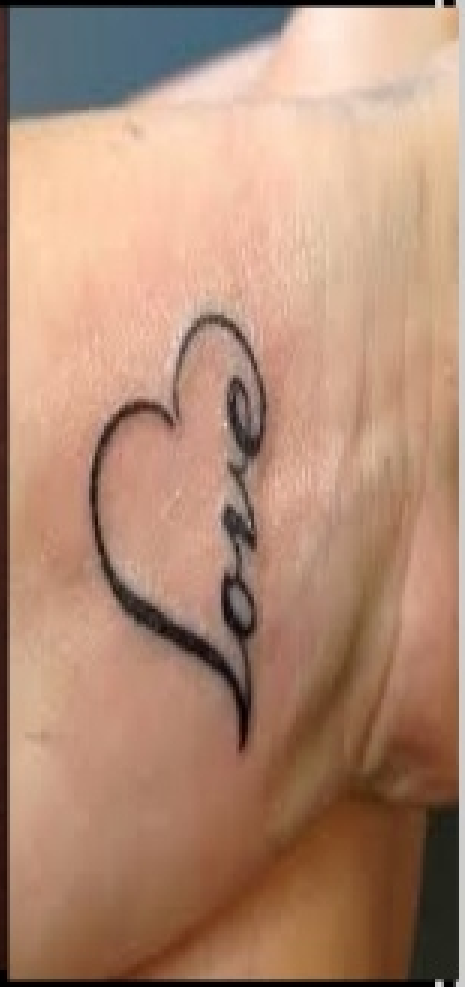
- Carbon (coal dust),air pollutant & tattooing.
- Mechanism:
- Inhaled → macrophages (alveoli) → transported to lymph node (tracheobronchial region).
- Black color of lungs (anthracosis) & lymph node.
- In coal miners → carbon dust induce fibroblastic reaction or emphysema → coal worker's pneumoconiosis.
- Tattooing → phagocytosis by dermal macrophages.

EXOGENOUS PIGMENTS



TATTOOS

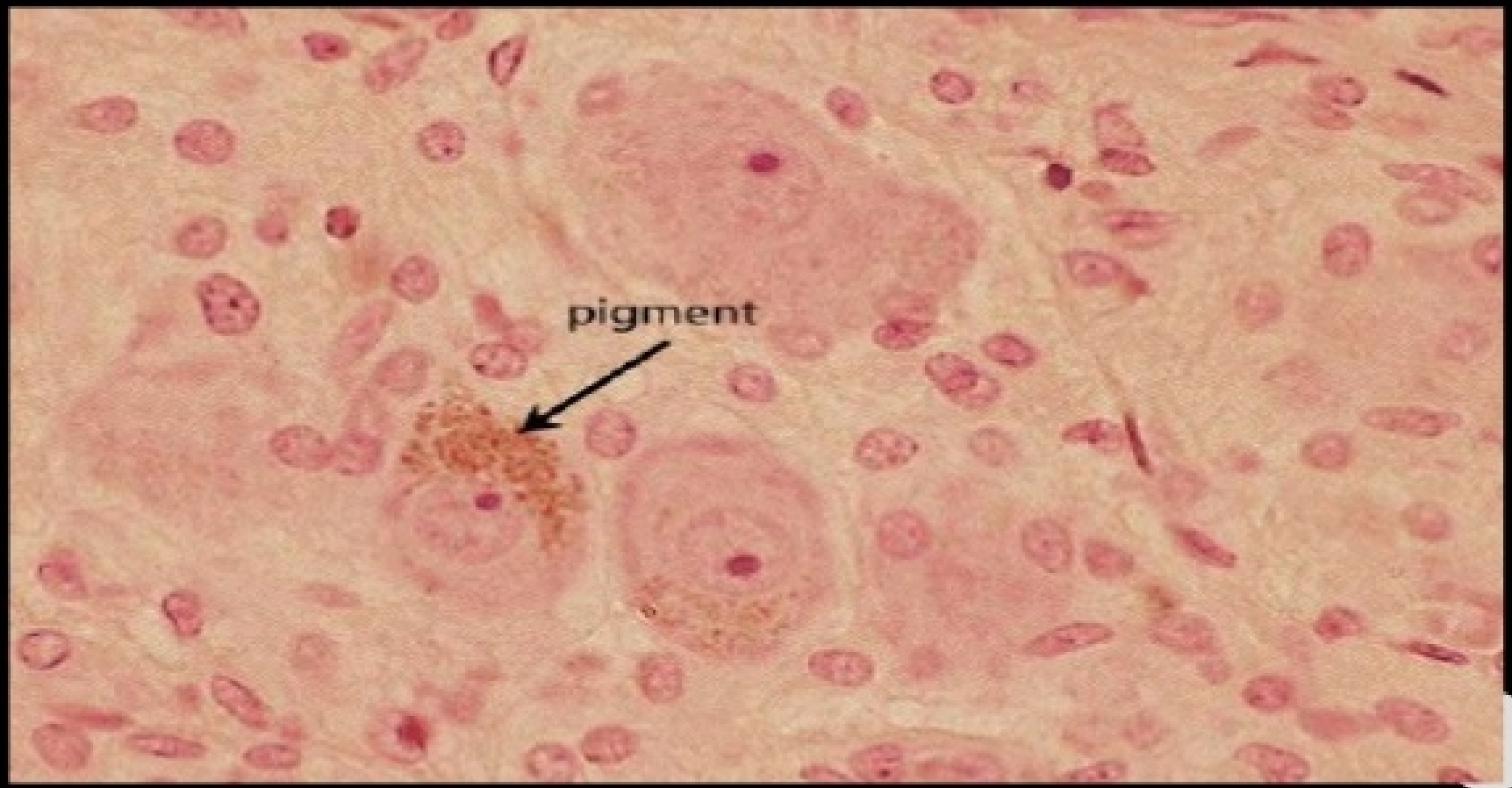


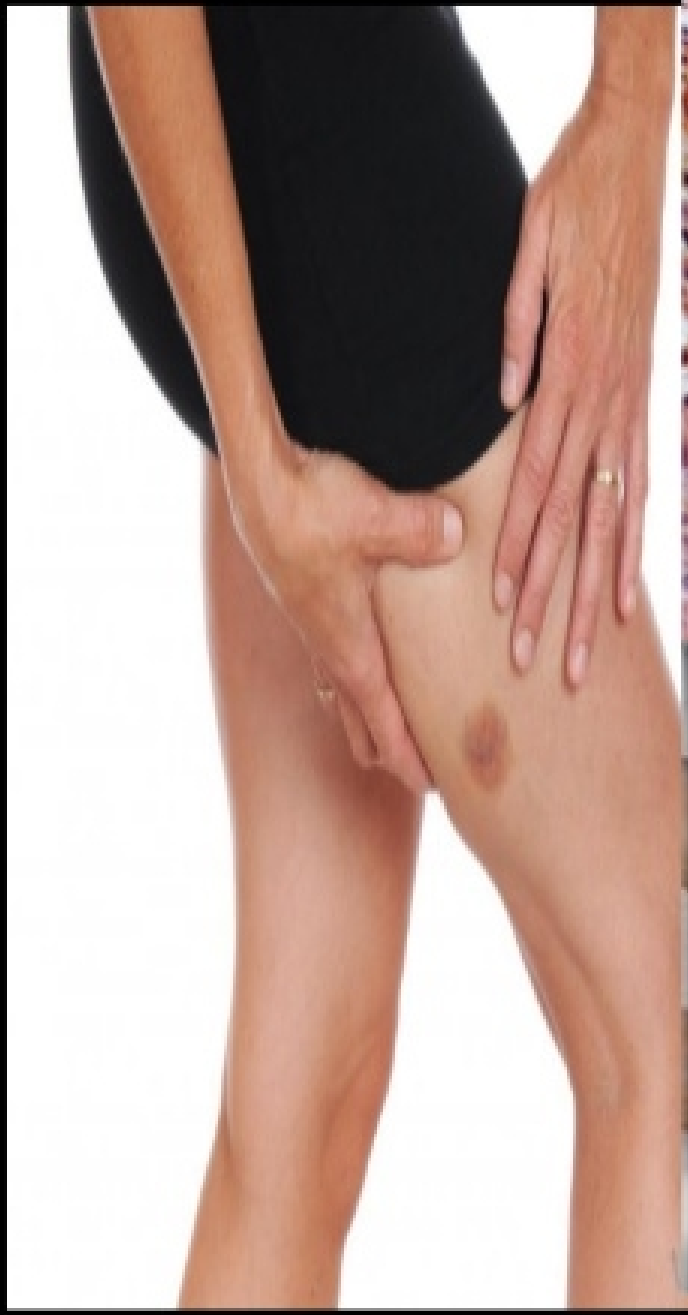


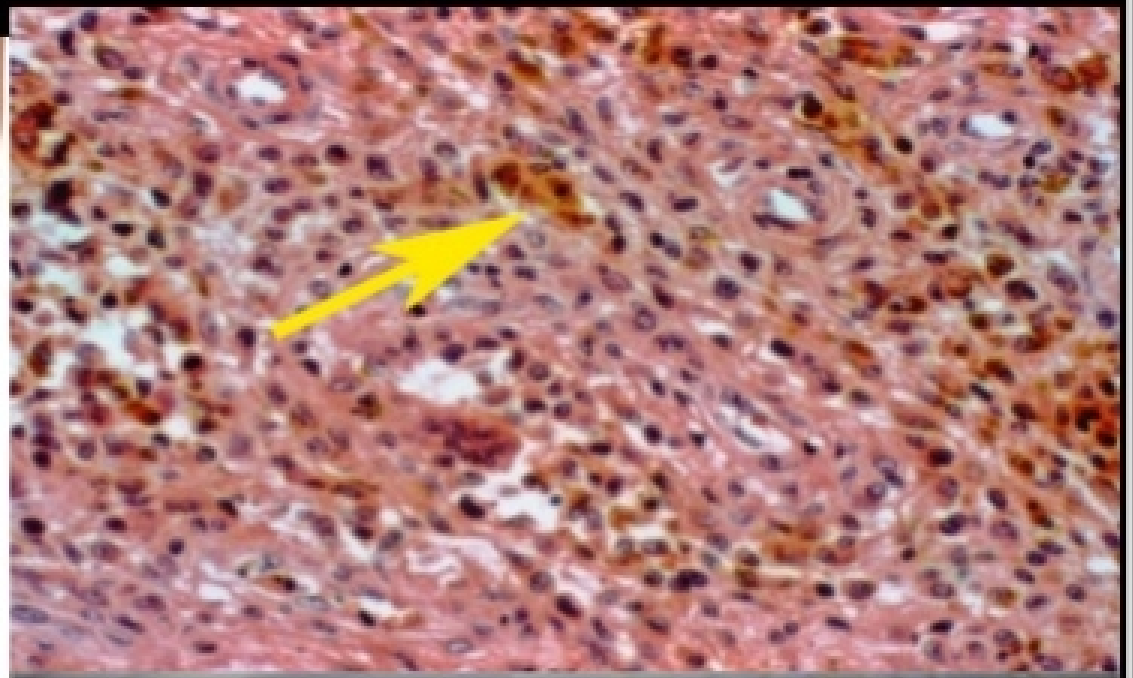
ENDOGENOUS PIGMENTS

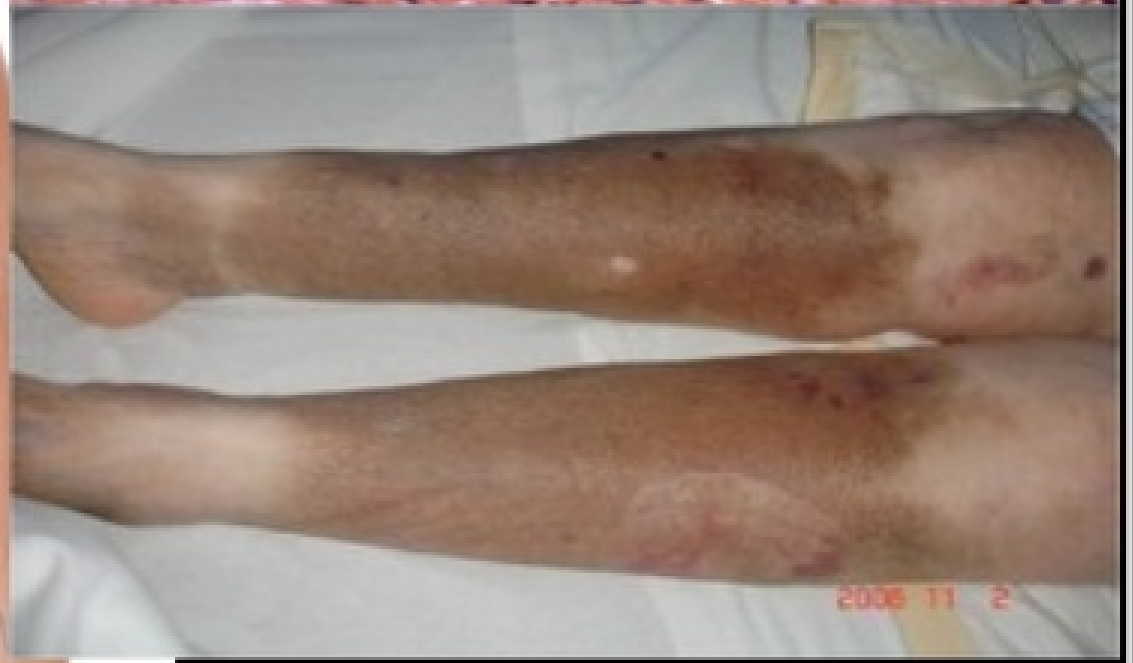
- *Lipofuscin (lipochrome or wear & tear pigment)*
- *Melanin*
- *Hemosiderin*

ENDOGENOUS PIGMENTS










Just chill

Pathologic calcification

Definition: Abnormal deposits of calcium salts occur in any tissues except bones and teeth.

- Two distinct types of pathologic calcification:
  - **Dystrophic calcification:** characterised by deposition of calcium salts in dead or degenerated tissues with normal calcium metabolism and normal serum calcium levels.
  - **Metastatic calcification:** apparently normal tissues and is associated with deranged calcium metabolism and hypercalcaemia.

Morphological Features

- Etiology and pathogenesis of the two are different.
- But morphologically the deposits in both resemble normal minerals of the bone.
- **H and E stained sections,**
  - Calcium salts appear as deeply basophilic, irregular and granular clumps.
  - The deposits may be intracellular, extracellular, or at both locations.
  - Occasionally, heterotopic bone formation (ossification) may occur.
  - Calcium deposits can be confirmed by special stains
    - **Silver impregnation** method of ***von-Kossa*** producing **black colour**,
    - **Alizarin red S** that produces **red staining**.
  - Pathologic calcification is often accompanied by diffuse or granular deposits of iron
    - **Positive Prussian blue reaction in Perl's stain**.

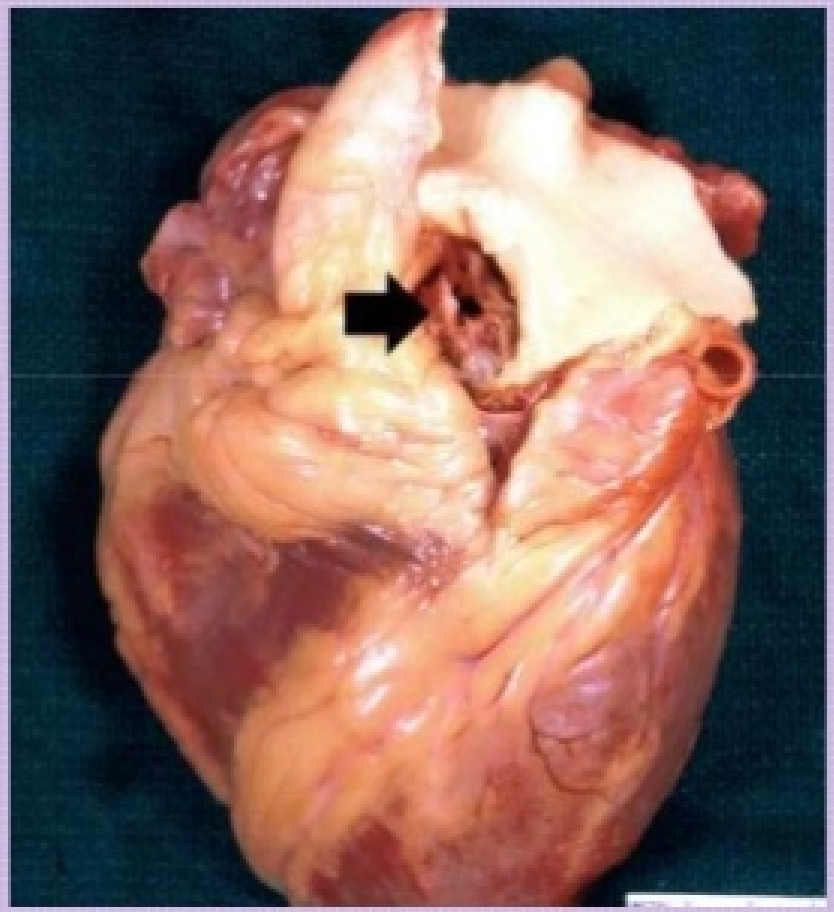
Dystrophic calcification

- Encountered in areas of necrosis of any type
- Although dystrophic calcification may be an incidental finding
- Indicating insignificant past cell injury, it may also be a cause of organ dysfunction
- May occur due to 2 types of causes:
  - Dead tissue
  - Degenerated tissue.

Calcification of the aortic valve

Metastatic calcification

- Calcification in normal tissue whenever there is hypercalcemia.
- These may be due to
  - **Excessive mobilisation of calcium from the bone**
  - **Excessive absorption of calcium from the gut**



Excessive mobilisation of calcium from the bone

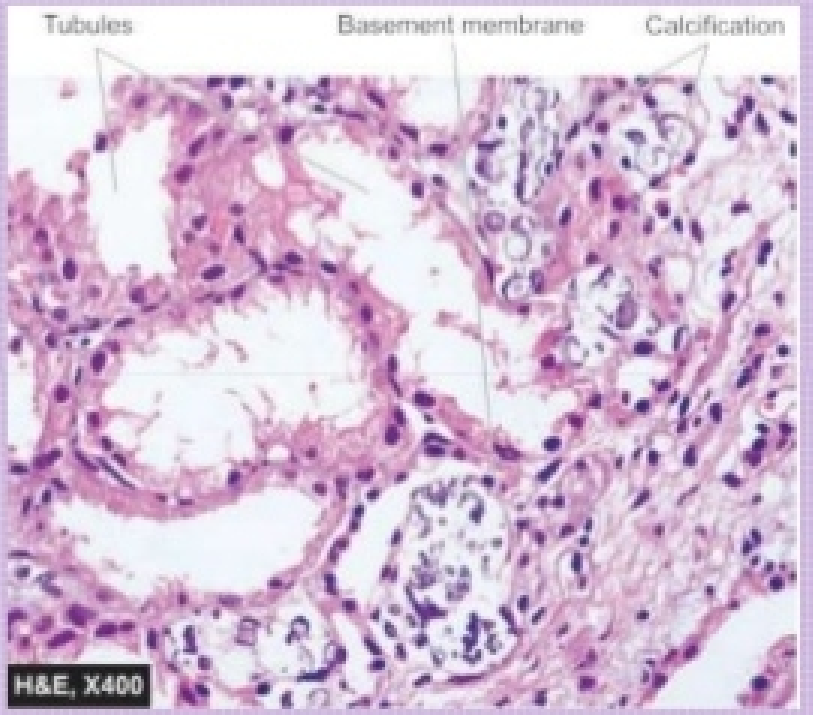
- ***Hyperparathyroidism***
  - **Primary :** parathyroid adenoma,
  - **Secondary:** parathyroid hyperplasia, chronic renal failure
- ***Bony destructive lesions***
  - Multiple myeloma
  - Metastatic carcinoma
  - leukemia
- ***Prolonged immobilisation***
  - Disuse atrophy of the bones and hypercalcaemia.

Excessive absorption of calcium from the gut

- ***Hypervitaminosis D***
- ***Milk-alkali syndrome***
  - Excessive oral intake of calcium in the form of milk
  - And administration of calcium carbonate in the treatment of peptic ulcer.
- ***Hypercalcaemia of infancy***
- ***Sarcoidosis:*** macrophages activate a vitamin D precursor

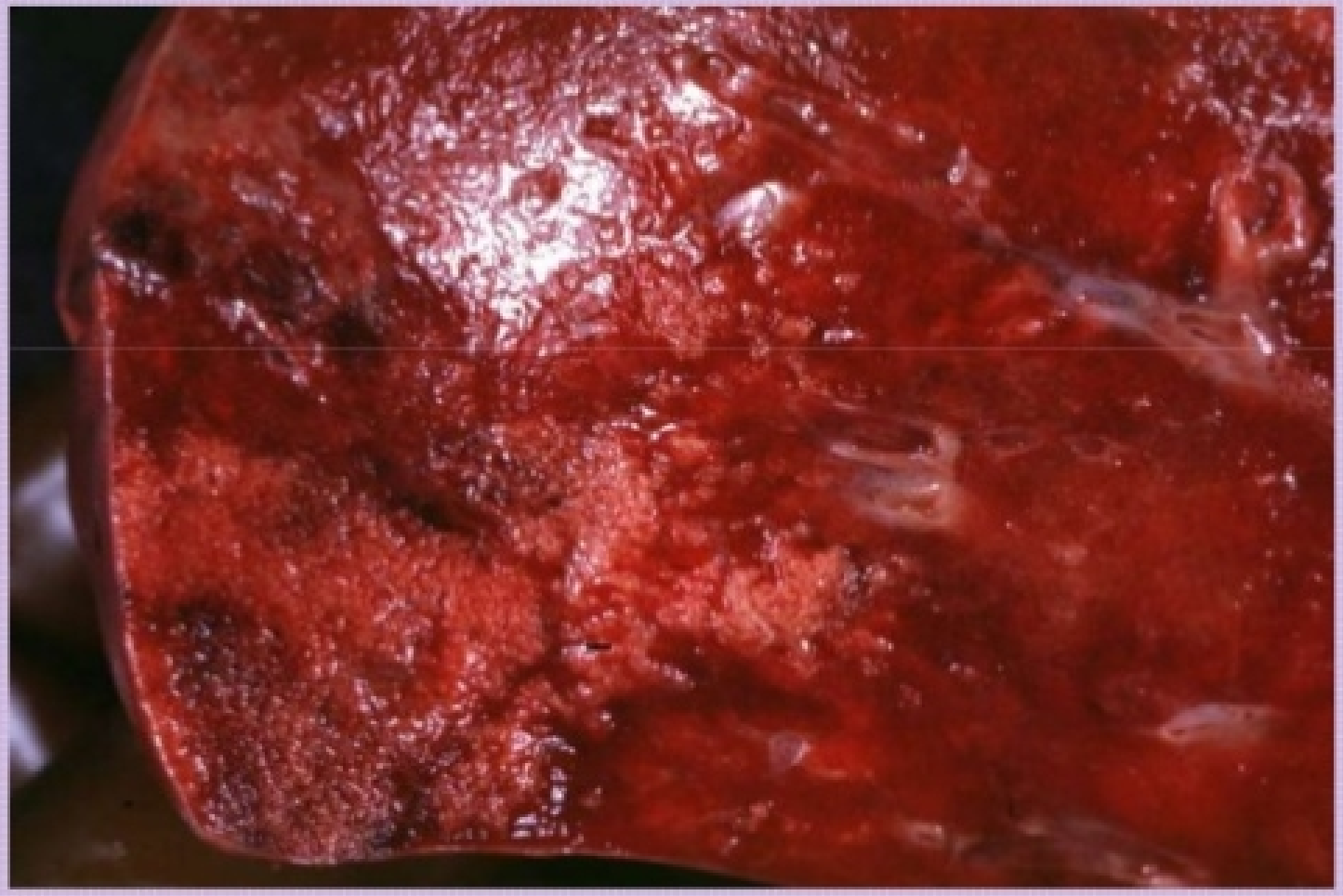
Sites of Metastatic calcification

- May occur in any normal tissue of the body but affects the following organs more commonly:
- ***Kidneys***, especially at the basement membrane of tubular epithelium and in the tubular lumina causing **nephrocalcinosis**
- ***Lungs***, especially in the alveolar walls.
- ***Stomach***, on the acid-secreting fundal glands.
- ***Blood vessels***, especially on the internal elastic lamina.
- ***Cornea:*** another site affected by metastatic calcification.
- ***Synovium*** of the joint causing pain and dysfunction.



Tubular basement membrane in **nephrocalcinosis** due to hypercalcaemia

Metastatic calcification



Lung: Metastatic Calcification

Differences between Dystrophic and Metastatic Calcification

Feature	Dystrophic Calcification	Metastatic Calcification
Definition	Deposits of calcium salts in dead and degenerated tissues	Deposits of calcium salts in normal tissues
Calcium metabolism	Normal	Deranged
Serum calcium level	Normal	Hypercalcaemia
Reversibility	Generally irreversible	Reversible upon correction of metabolic disorder
Causes	Necrosis (caseous, liquefactive, fat), infarcts, thrombi, haematomas, dead parasites, old scars, atheromas, Mönckeberg's sclerosis, certain tumours, cysts, calcinosis cutis	Hyperparathyroidism (due to adenoma, hyperplasia, CRF), bony destructive lesions (e.g. myeloma, metastatic carcinoma), prolonged immobilisation, hypervitaminosis D, milk-alkali syndrome, hypercalcaemia of infancy
Pathogenesis	Increased binding of phosphates with necrotic and degenerative tissue, which in turn binds to calcium forming calcium phosphate precipitates	Increased precipitates of calcium phosphate due to hypercalcaemia at certain sites e.g. in lungs, stomach, blood vessels and cornea


Thank you
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