

PATHOLOGY

Chapter: CELL INJURY

(for first year medical students in 3 lectures)

[Topics: cell injury, free radical injury, necrosis and apoptosis, cellular accumulations, pathological calcification, adaptation to cell injuries]

(lecture 1)

Dr. Sufia Husain
Associate Prof & Consultant
Department of Pathology
College of Medicine, KSU, Riyadh.
September 2019

Reference: Robbins & Cotran Pathology and Rubin's Pathology



Objectives for Cell Injury Chapter (3 lectures)

The students should:

- A. Understand the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical manifestations.
- B. Is aware of the concept of hypoxic cell injury and its major causes.
- C. Understand the definitions and mechanisms of free radical injury.
- D. Knows the definition of apoptosis, tissue necrosis and its various types with clinical examples.
- E. Able to differentiate between necrosis and apoptosis.
- F. Understand the causes of and pathologic changes occurring in fatty change (steatosis), accumulations of exogenous and endogenous pigments (carbon, silica, iron, melanin, bilirubin and lipofuscin).
- G. Understand the causes of and differences between dystrophic and metastatic calcifications.

Lecture 1 outline

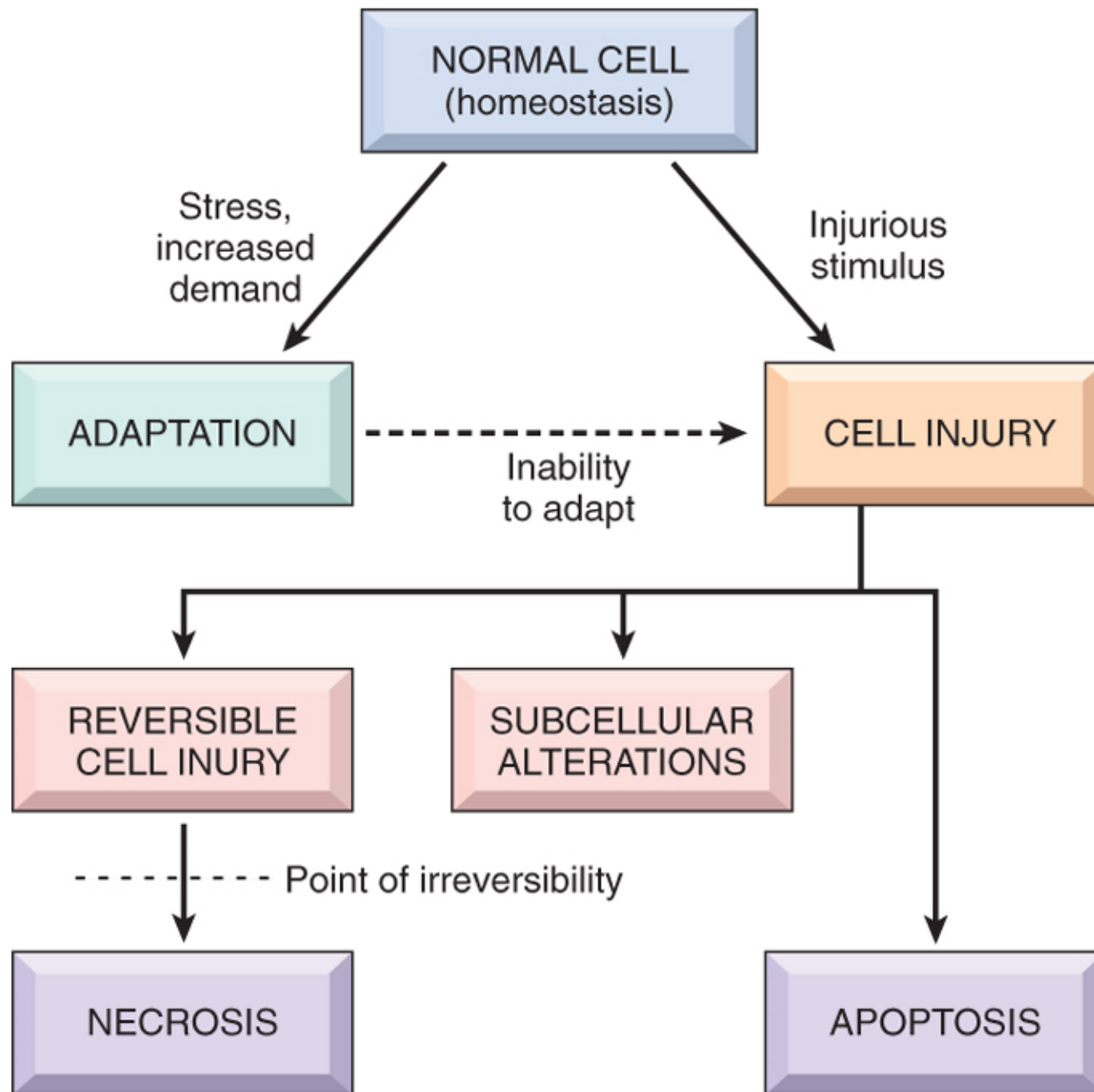
- › **Adaptation to environmental stress/cell injury:** hypertrophy, hyperplasia, atrophy, squamous metaplasia, osseous metaplasia and myeloid metaplasia.
- › **Cell injury**
 - **Hypoxic cell injury** and its causes (ischaemia, anaemia, carbon monoxide poisoning, decreased perfusion of tissues by oxygen, carrying blood and poor oxygenation of blood).
 - **Free radical injury:** definition of free radicals, mechanisms that generate free radicals, mechanisms that degrade free radicals.
 - **Reversible and irreversible cell injury**

ADAPTATION TO ENVIRONMENTAL STRESS

Adaptation to environmental stress

- › Cells are constantly adjusting their structure and function to accommodate changing demands i.e. they adapt within physiological limits.
- › As cells encounter physiologic stresses or pathologic stimuli, they can undergo adaptation. The principal adaptive responses are
 - hypertrophy,
 - hyperplasia,
 - atrophy,
 - metaplasia.

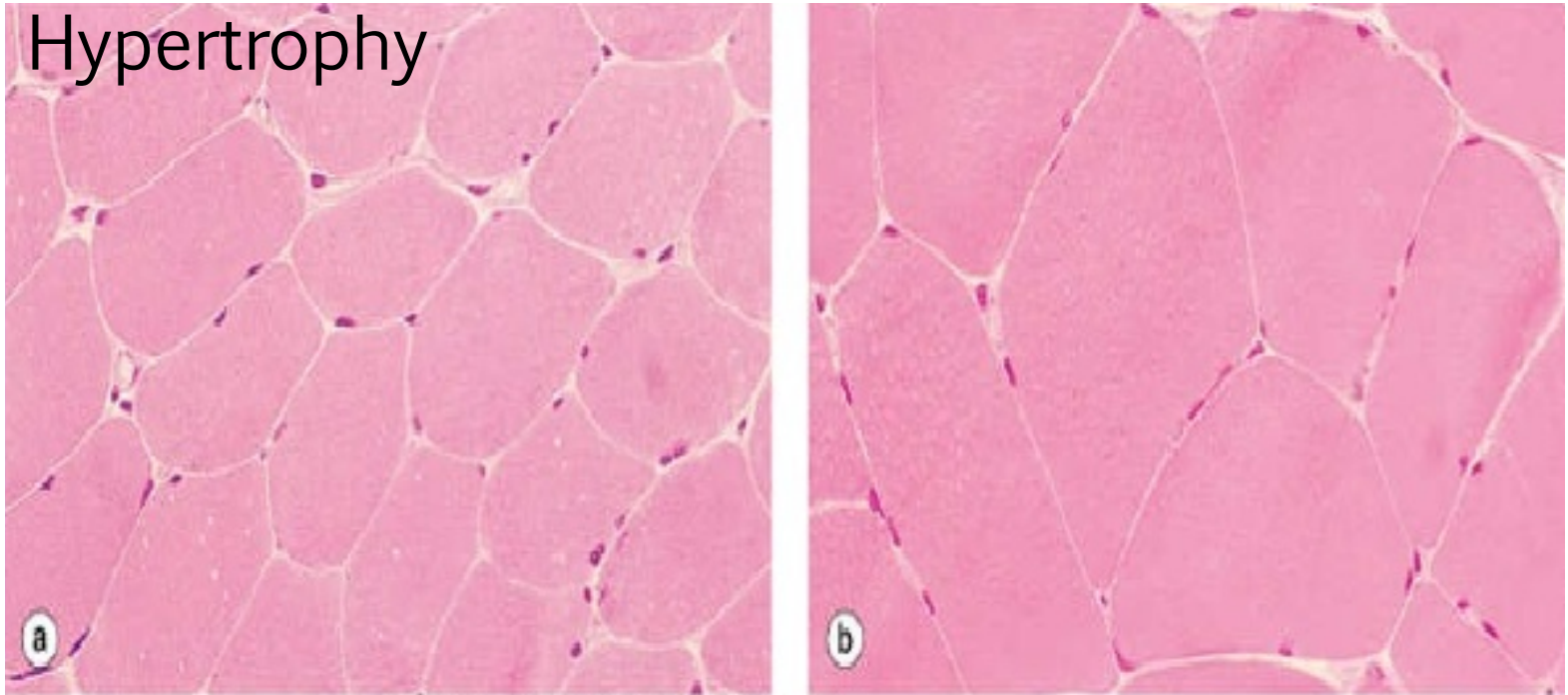
(NOTE: If the adaptive capability is exceeded or if the external stress is too harmful, cell injury develops. Within certain limits injury is reversible, and cells return to normal but severe or persistent stress or injury results in irreversible injury and death of the affected cells.)



Hypertrophy

- › Is an **increase in the size of the cells** and when many cells undergo hypertrophy it leads to an increase in the size of the tissue/organ.
- › An increased demand on cells can lead to hypertrophy.
- › Hypertrophy takes place in cells that are not capable of dividing e.g. striated muscles.
- ***Hypertrophy can be physiologic or pathologic***
 - Physiological:
 - ✓ breast during lactation
 - ✓ pregnant uterus
 - ✓ the skeletal muscles undergo only hypertrophy in response to increased demand by exercise.
 - Pathologic:
 - ✓ the cardiomyocytes (muscle cells of the heart i.e. myocardium) undergo hypertrophy in heart failure (e.g. hypertrophy in hypertension or aortic valve disease).

Hypertrophy



Stevens et al: Core Pathology, 3rd Edition.

Copyright © 2009 by Mosby, an imprint of Elsevier, Ltd . All rights reserved.

- › Hypertrophy of skeletal muscle in response to exercise. Hypertrophy in the absence of hyperplasia is typically seen in muscle where the stimulus is an increased demand for work. Taken at the same magnification (a) shows muscle fibers in the transverse section from the soleus muscle of a normal 50 year old man, and (b) shows fibers from the same muscle in a veteran marathon runner. Note the dramatic increase in size of the fibers in response to the demands of marathon running.

Hyperplasia

π

- › Is an **increase in the number of cells**
- › It may lead to an increase in the size of an organ/ tissue.
- › An increased demand on cells can lead to hyperplasia.
- › Hyperplasia takes place in the cells capable of replication.

Hyperplasia can be physiologic or pathologic.

A) Physiologic hyperplasia are of two types

1. Hormonal hyperplasia e.g. the proliferation of the glands of the female breast at puberty and during pregnancy
2. Compensatory hyperplasia e.g. when a portion of liver is partially resected, the remaining cells multiply and restore the liver to its original weight.

B) Pathologic hyperplasia is caused by abnormal excessive stimulation of cells by hormones or growth factors e.g. excess estrogen leads to endometrial hyperplasia which causes abnormal menstrual bleeding. Sometimes pathologic hyperplasia acts as the base for cancer to develop from. Thus, patients with hyperplasia of the endometrium are at increased risk of developing endometrial cancer.

Hypertrophy and hyperplasia

- › Hypertrophy and hyperplasia can occur together, e.g.
 - the uterus during pregnancy in which there is smooth muscle hypertrophy and hyperplasia.
 - Benign prostatic hyperplasia

Hypertrophy and hyperplasia of uterus during pregnancy



Hypertrophy and hyperplasia of uterine myometrium during pregnancy. On the left is a normal uterus normal smooth muscle wall. On the right is the uterus of a recently pregnant woman in which there is marked increase in the smooth muscle wall thickness. This is due to the hypertrophy and hyperplasia of uterine smooth muscle.

Atrophy

π

- › Atrophy is shrinkage in the size of cells.
- › A reduced demand on cells can lead to atrophy.
- › When a sufficient number of cells are involved, the entire organ decreases in size, becoming atrophic.
- › Atrophic cells are not dead but have diminished function. In atrophic cells there is decreased protein synthesis and increased protein degradation.
- › Causes of atrophy include
 - decreased workload or disuse (e.g. immobilization of a limb in fracture),
 - loss of innervation (lack of neural stimulation to the peripheral muscles caused by injury to the supplying nerve causes atrophy of that muscle)
 - diminished blood supply,
 - inadequate nutrition
 - loss of endocrine stimulation (e.g. the loss of hormone stimulation in menopause)
 - aging: senile atrophy of brain can lead to dementia.
- › Some of these stimuli are physiologic (the loss of hormone stimulation in menopause) and others pathologic (denervation)

π

Involution

- › It is the reduction in the cell number.

The term “hypoplasia” and “aplasia” are not adaptation responses to environmental stress

- › Hypoplasia refers to an organ that does not reach its full size. It is a developmental disorders and not an adaptive response.
- › Aplasia is the failure of cell production and it is also a developmental disorders e.g. during fetal growth aplasia can lead to agenesis of organs.

Metaplasia

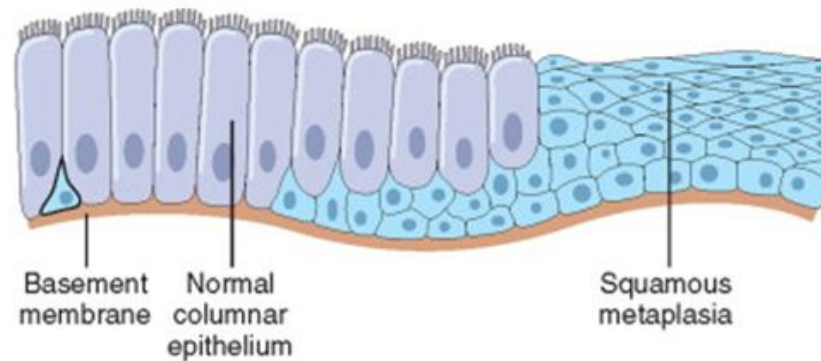
- › In metaplasia the cells adapt by changing (differentiating) from one type of cell into another type of cell. This is known as metaplasia.
- › Here the cells sensitive to a particular causative/toxic agent are replaced by another cell types better able to tolerate the difficult environment.
- › Metaplasia is usually a reversible provided the causative agent is removed.
- › Examples include:
 1. Squamous metaplasia:
 2. Columnar cell metaplasia
 3. Osseous metaplasia
 4. Myeloid metaplasia

Metaplasia

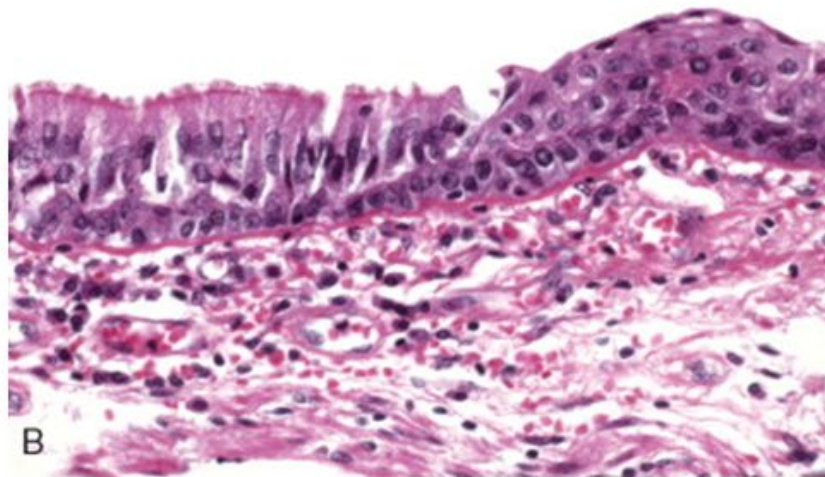
1) Squamous metaplasia

- **In it the columnar cells are replaced by squamous cells.** It is seen in:
 - **In respiratory tract:** the columnar epithelium of the bronchus is replaced by squamous cell following chronic injury in chronic smokers. The squamous epithelium is able to survive better under circumstances that the more fragile columnar epithelium would not tolerate. Although the metaplastic squamous epithelium will survive better, the important protective functions of columnar epithelium are lost, such as mucus secretion and ciliary action.
 - **In cervix:** replacement takes place at the squamocolumnar junction.
- If the causative agent persists, it may provide the base for (or predispose to) malignant transformation. In fact, it is thought that cigarette smoking initially causes squamous metaplasia and later squamous cell cancers arise from it.
- Similarly squamous cell carcinoma of cervix also arises from the squamous metaplasia in the cervix.

Squamous metaplasia



A



B

Metaplasia of columnar to squamous epithelium. A , Schematic diagram. B , Metaplasia of columnar epithelium (left) to squamous epithelium (right) in a bronchus.

Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death
Perkins, James A., MS, MFA, Robbins and Cotran Pathologic Basis of Disease, Chapter 1, 3-42

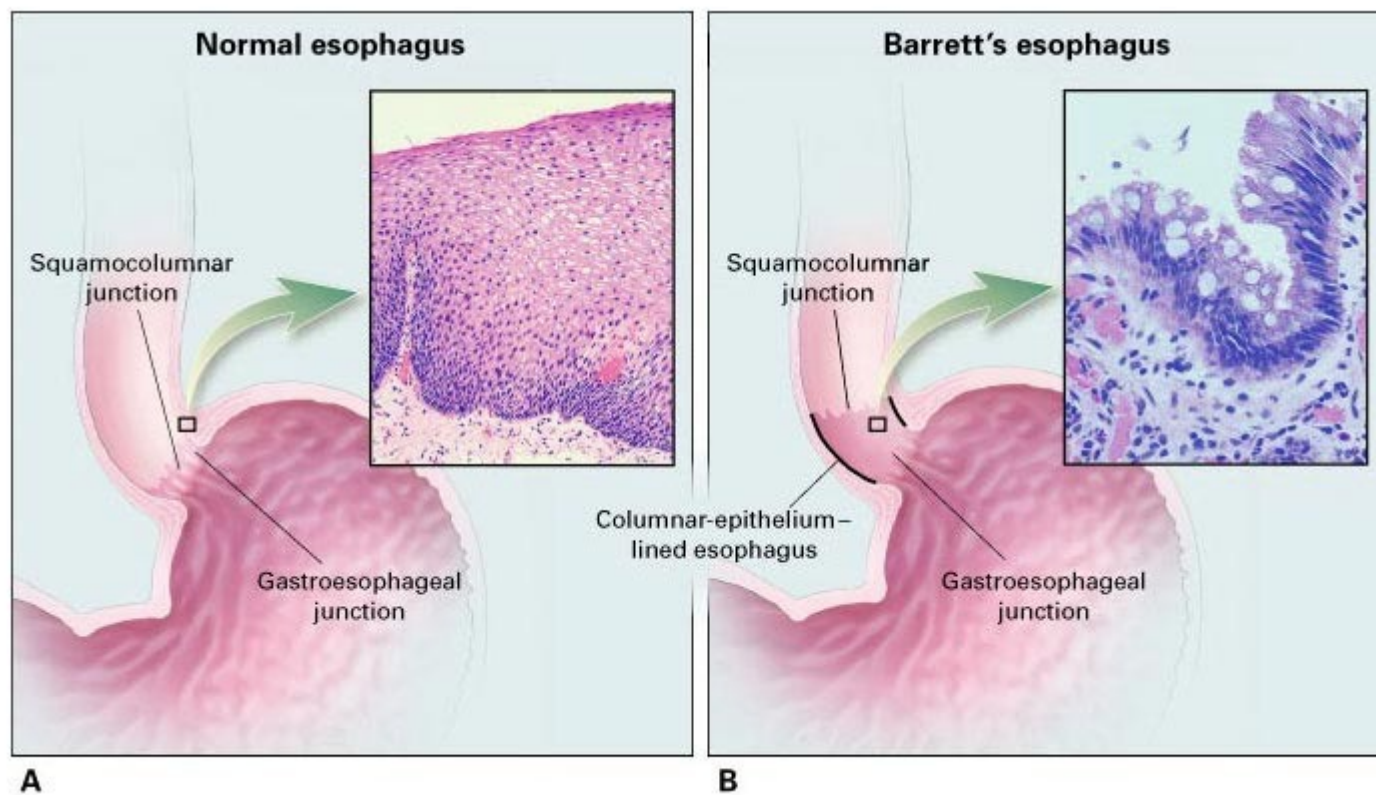
Copyright © 2010 Copyright © 2010 by Saunders, an imprint of Elsevier Inc.

Metaplasia

- 2) Columnar cell metaplasia:** it is the replacement of the squamous lining by columnar cells. It is seen in the esophagus in chronic gastro-esophageal reflux disease. The normal stratified squamous epithelium of the lower esophagus undergoes metaplastic transformation to columnar epithelium. This change is called as **Barrett's oesophagus** and it can be precancerous and lead to development of adenocarcinoma of esophagus.
- 3) Osseous metaplasia:** it is the formation of new bone at sites of tissue injury. Cartilagenous metaplasia may also occur.
- 4) Myeloid metaplasia (extramedullary hematopoiesis):** is the proliferation of hematopoietic tissue in sites other than the bone marrow such as liver or spleen.

Columnar cell metaplasia

Barrett's oesophagus



π

Examples of metaplasia

Original tissue	Stimulus	Metaplastic tissue
Ciliated columnar epithelium of bronchial tree	Cigarette smoke	Squamous epithelium
Transitional epithelium of bladder	Trauma of bladder calculus	Squamous epithelium
Columnar epithelium in gland ducts	Trauma of calculus	Squamous epithelium
Fibrocollagenous tissue	Chronic trauma	Bone (osseous) tissue
Esophageal squamous epithelium	Gastric acid	Columnar epithelium
Columnar glandular epithelium	Vitamin A deficiency	Squamous epithelium

Stevens et al: Core Pathology, 3rd Edition.

Copyright © 2009 by Mosby, an imprint of Elsevier, Ltd . All rights reserved.

Change in size of cells

Atrophy

Reduction in the size of cells

Hypertrophy

Increase in the size of cells

Change in number of cells

Involution

Decrease in the number of cells

Hyperplasia

Increase in the number of cells

Change in differentiation of cells

Metaplasia

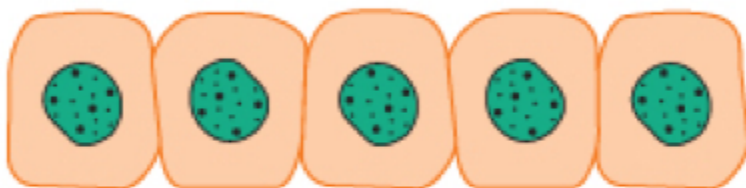
Stable change to another cell type



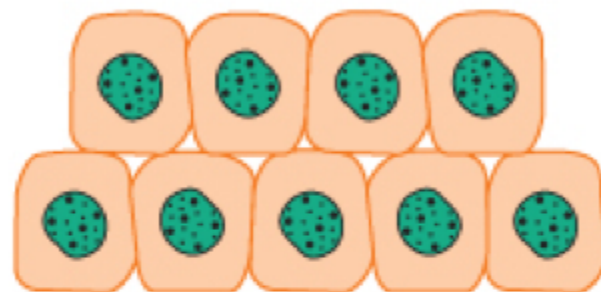
Normal



Atrophy
(decreased cell size)



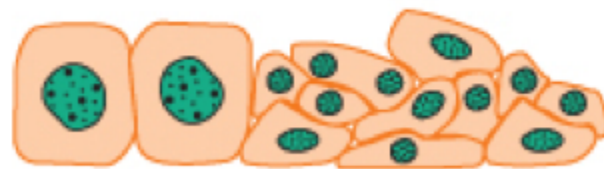
Hypertrophy
(increased cell size)



Hyperplasia
(increased cell number)



Metaplasia
(conversion of one cell
type to another)



Dysplasia
(disorderly growth)

CELL INJURY

- › When the cell is exposed to an injurious agent or stress, a sequence of events follows that is loosely termed cell injury. Cell injury is reversible up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell reaches a point of no return and suffers irreversible cell injury and ultimately cell death.
- › Cell death, is the ultimate result of cell injury
- › There are two principal patterns of cell death, necrosis and apoptosis.

CELL DEATH

- › ***Necrosis*** is the type of cell death that occurs after ischemia and chemical injury, and it is always pathologic.
- › ***Apoptosis*** occurs when a cell dies through activation of an internally controlled suicide program.
- ›

π

Normal cell

↓ Stress/increased demand

Adaptation e.g. hypertrophy

↓ Unable to adapt

↓ Injurious stimuli e.g. hypoxia

Cell injury

↓ No more injurious stimuli

injury is **reversible**

↓

complete repair

↓

Cells/ tissue back to normal
Restoration of normal organ function.

↓ Persistent or strong injurious stimuli

2 possibilities
1) tissue repair but with diminished capacity → impaired cell function
2) injury becomes **irreversible** → **cell death** (necrosis or apoptosis)

Causes of Cell Injury

Causes of injury (both reversible and irreversible) are:

1) Oxygen Deprivation (*hypoxic cell injury*). It is a common cause of cell injury and cell death. Hypoxia can be due to:

- i. Ischemia (obstruction of arterial blood flow), E.g. in myocardial infarction and atherosclerosis.
- ii. Inadequate oxygenation of the blood e.g. lung disease and carbon monoxide poisoning
- iii. Decreased oxygen-carrying capacity of the blood e.g. anemia
- iv. Inadequate tissue perfusion due to cardiorespiratory failure, hypotension, shock etc

Depending on the severity of the hypoxia, cells may adapt, undergo injury or die. Also some cell types are more vulnerable to hypoxic injury than others e.g. neurons are most susceptible followed by cardiac muscle, hepatocytes and then skeletal muscles.

Causes of Cell Injury cont.

2) Physical Agents e.g. mechanical trauma, burns and deep cold, sudden changes in atmospheric pressure, radiation, and electric shock

3) Chemical Agents and Drugs e.g. oxygen in high concentrations, *poisons*, pollutants, insecticides, industrial and occupational hazards, alcohol and narcotic drugs and therapeutic drugs.

4) Infectious Agents

5) Immunologic agents e.g. thyroid damage caused by autoantibodies.

6) Genetic Derangements eg sickle cell anemia.

7) Nutritional Imbalances

MECHANISM OF CELL INJURY

- 1. Depletion of ATP**
- 2. Cell membrane damage/defects in membrane permeability:**
- 3. Mitochondrial damage:**
 - It is seen specially in hypoxic injury and cyanide poisoning.
- 4. Ribosomal damage:**
 - It is seen in alcohol damage of liver cells and with antibiotic use.
- 5. Nuclear and DNA damage:**
- 6. Influx of intracellular calcium leading to loss of normal calcium balance:** ischemia causes an increase in intracellular calcium concentration. Increased Ca^{2+} in turn activates a number of enzymes which cause damage.
- 7. Free radical injury: see details in the next 2 slides**

Free radical injury

π

Free radical injury is due to excess accumulation of oxygen-derived free radicals (oxidative stress). **Free radicals** are highly reactive and harmful atoms that have a single unpaired electron in the outer orbit. They are referred to as reactive oxygen species/free radicals. The free radicals are produced in our cells through several ways, called as the free radical generating systems. They are produced via:

- i. Normal metabolism/ respiration: Small amounts of harmful reactive oxygen is produced as a bi-product of mitochondrial respiration during normal respiration (reduction-oxidation reactions that occur in normal metabolism).
- ii. Ionizing radiation injury e.g. UV light, x-rays result in production of free radicals.
- iii. Chemical toxicity: enzymatic metabolism of exogenous chemicals or drugs.
- iv. Oxygen therapy and reperfusion injury
- v. Immune response or inflammation (neutrophilic oxidative burst)
- vi. Transition metals such as iron and copper can trigger production.

The names of the common free radicals are:

- superoxide anion radical (O_2^-),
- hydrogen peroxide (H_2O_2),
- and hydroxyl ions (OH).
- Nitric oxide (NO) is an important chemical mediator generated by various cells and it can also act as a free radical.

Free radical injury contd.

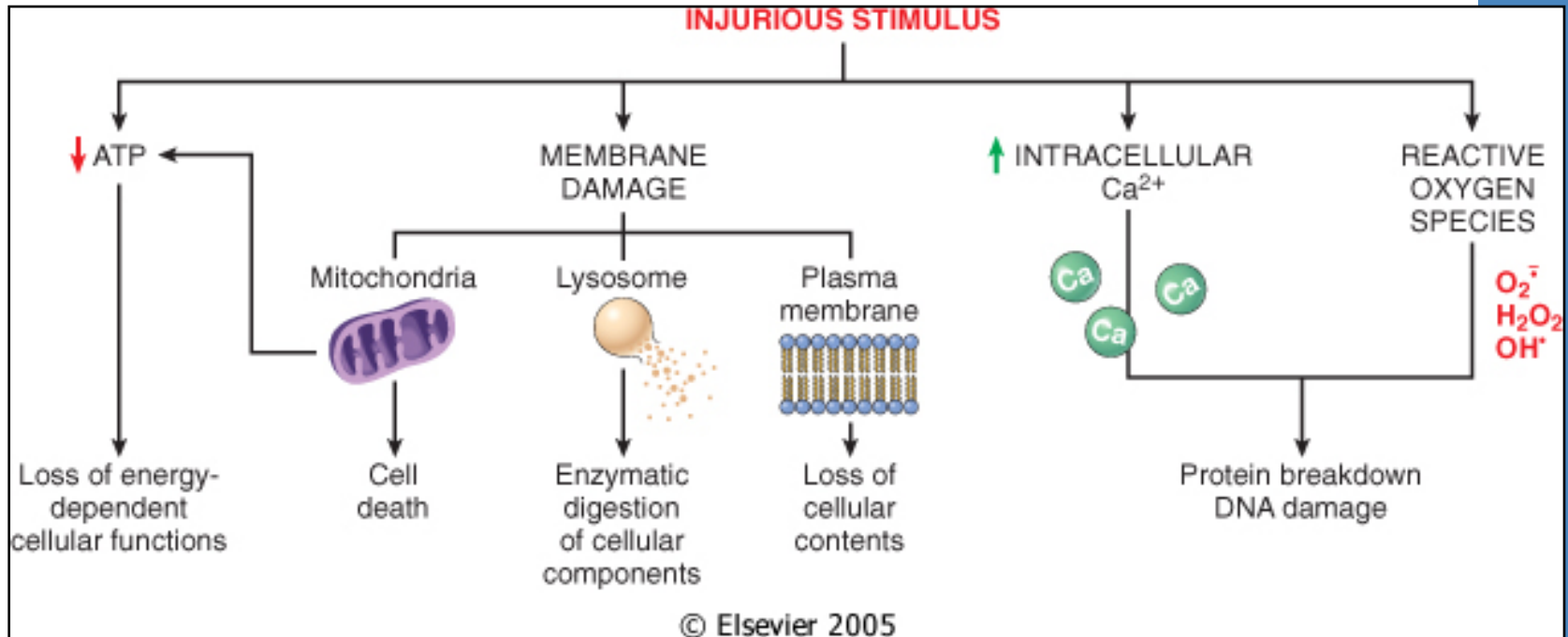
Free radicals cause damage to lipids, proteins, and nucleic acids:

1. **Lipids:** lipid peroxidation of membranes → damage of cell membranes & organelles etc.
2. **Proteins:** oxidative modification of proteins → protein fragmentation.
3. **Nucleic acid:** DNA damage → cell aging & malignant transformation of cells.

How does our body fight the free radicals? Certain substances in the cells remove or inactivate the free radicals in order to minimize injury caused by them. They form the free radical scavenging system. These substances are:

- **Antioxidants:** e.g. **vitamins E, A and C** (ascorbic acid).
- **Enzymes:** which break down hydrogen peroxide and superoxide anion e.g. **Catalase, Superoxide dismutases, Glutathione peroxidase and mannitol.**

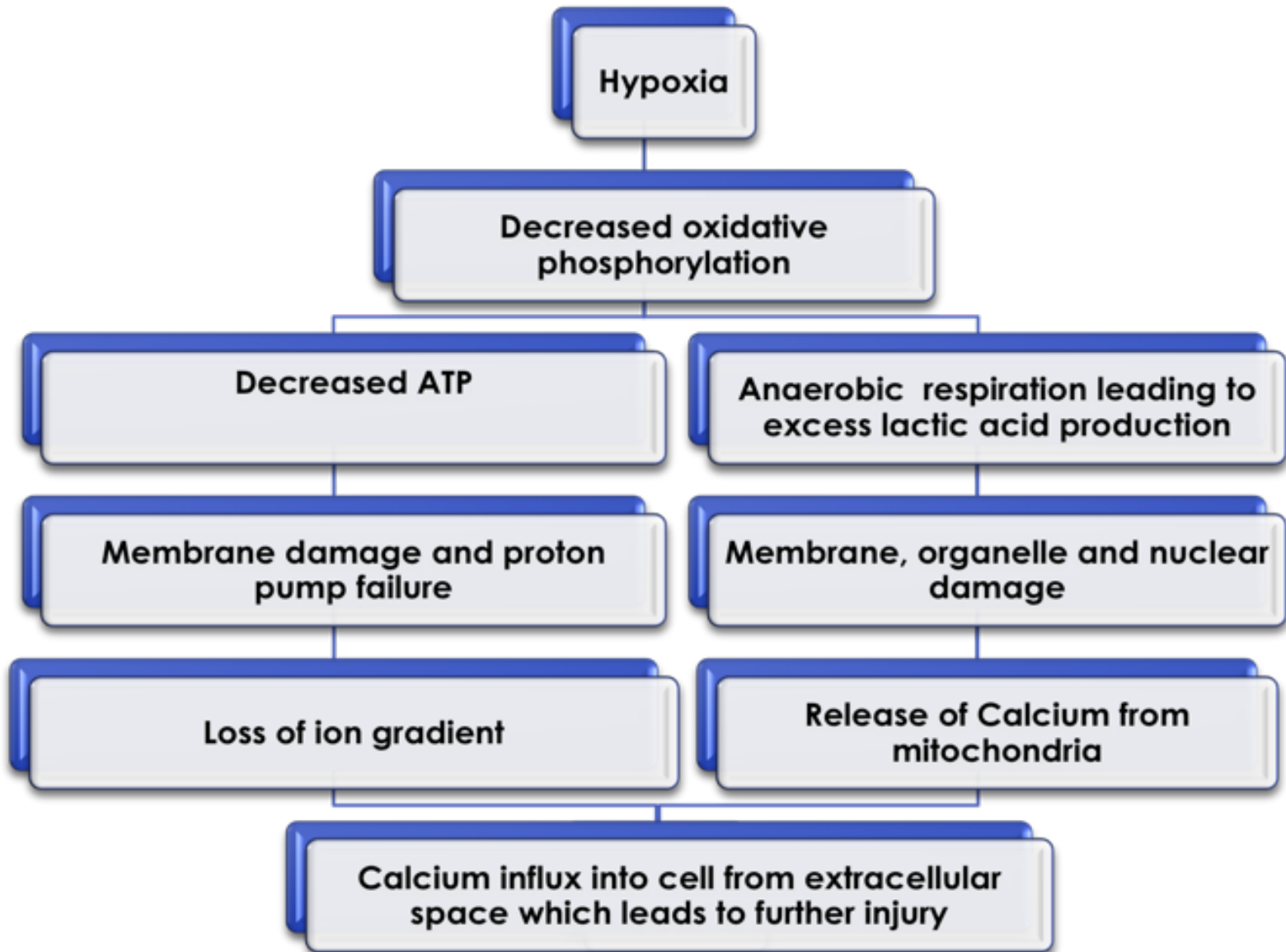
NOTE: Any imbalance between free radical-generating and radical-scavenging systems results in oxidative stress causing cell injury.



Cellular and biochemical sites of damage in cell injury.

Mechanism in hypoxic cell injury

π



Reversible Cell Injury:

π

Cell injury can be reversible or irreversible. The type of injury, the time duration of injury and the severity of injury will determine the extent of cell damage i.e. whether the injury is reversible or irreversible.

Reversible Cell Injury: initially cell injury is reversible. Ultrastructural (electron microscopic) changes associated with reversible cell injury are:

1. Swelling & vacuolization of cytoplasm called hydropic/ vacuolar degeneration.
2. Mild mitochondrial swelling. the rough endoplasmic reticulum and plasma membrane damage.
3. Defect in protein synthesis.
4. Mild eosinophilia of cytoplasm (due to decrease in cytoplasmic RNA)

Within limits, the cell can compensate for these derangements and, if the injurious stimulus is removed the damage can be **reversed**.

Irreversible Cell Injury

Persistent or excessive injury causes cells to pass into **irreversible injury**. Irreversible injury is marked by

1. severe mitochondrial damage with the appearance large, amorphous densities in mitochondria.
2. Severe plasma/cell membrane damage
3. Increased eosinophilia
4. Numerous myelin figures
5. Rupture of lysosomes leakage and enzymatic digestion of cellular contents
6. Nuclear damage:
 - i. pyknosis (shrinkage),
 - ii. karyolysis (dissolution)
 - iii. karyorrhexis (break down or fragmentation)

