PATHOLOGY

Chapter: CELL INJURY

(for first year medical students in 3 lectures)

[Topics in 3 lectures: cell injury, free radical injury, necrosis and apoptosis, cellular accumulations, pathological calcification, adaptation to cell injuries]

(lecture 1)

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REFERENCE: ROBBINS & COTRAN PATHOLOGY AND RUBIN'S PATHOLOGY

Objectives for Cell Injury Chapter (in 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/adapting their structure and function to accommodate changing demands.
- When cells face physiologic or pathologic stress/stimuli, they undergo adaptation.
- The principal adaptive responses are
  - hypertrophy,
  - hyperplasia,
  - atrophy,
  - metaplasia.

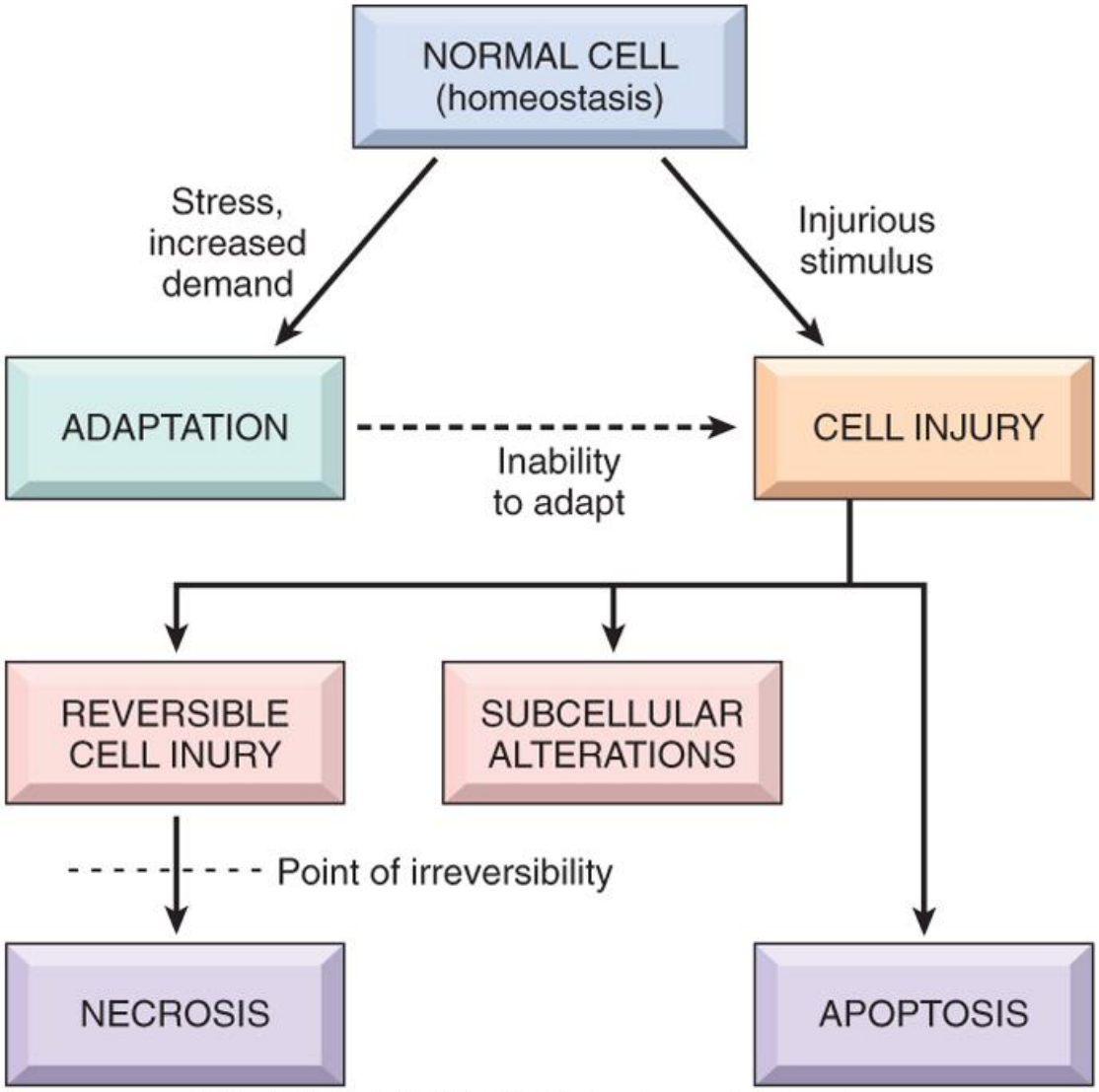

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Figure 1-1 Stages in the cellular response to stress and injurious stimuli.

If the adaptive capability of the cell is exhausted or if the external stress is too harmful, cell injury develops.

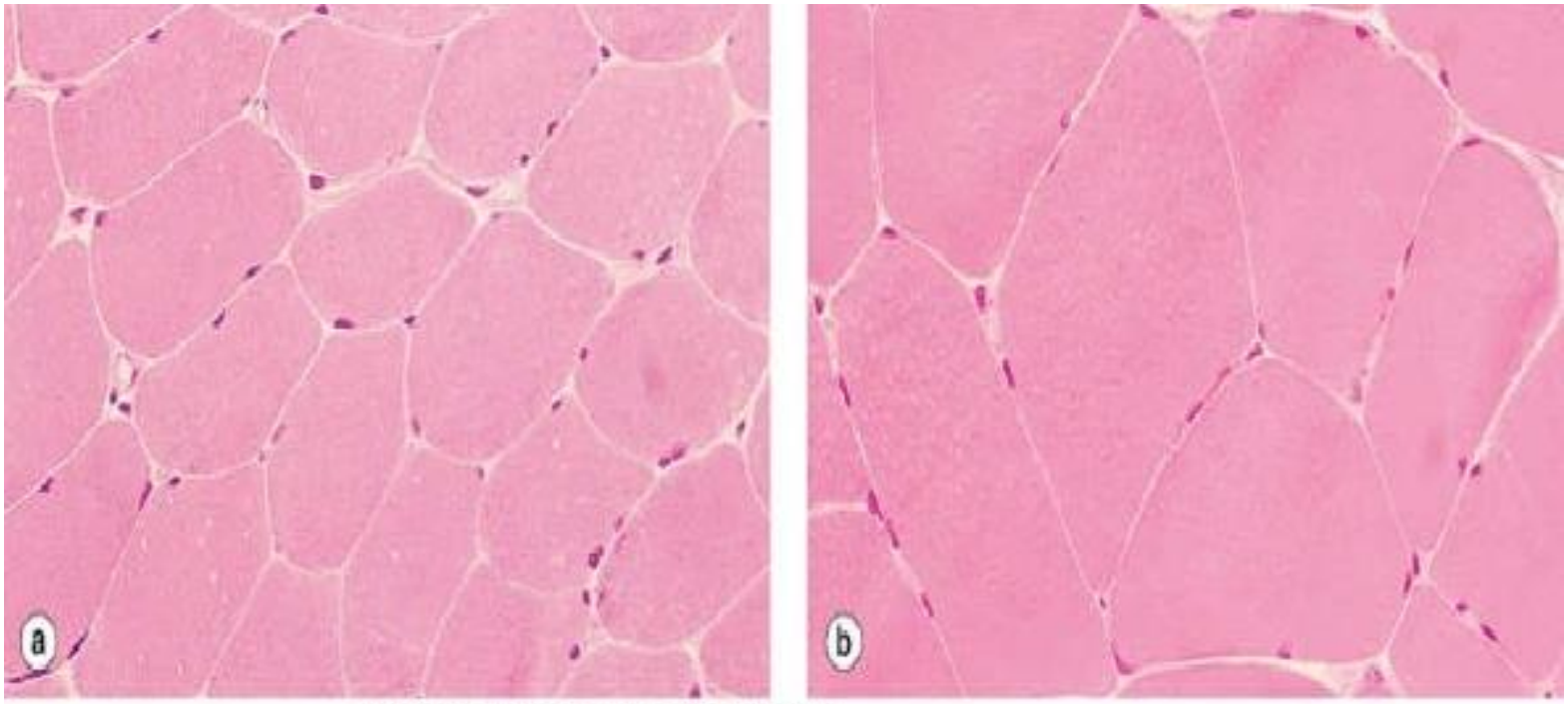
Within certain limits injury is reversible and cells return to normal.

But, in severe or persistent stress the injury becomes irreversible and leads to cell death.

Hypertrophy

- Is an **increase in the size of the cells.**
- 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 usually takes place in cells that are not capable of dividing/replication 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:
    - ✓ Cardiomyocytes are cells of the heart (myocardium), they undergo hypertrophy in heart failure (e.g. in hypertension or aortic valve disease).

Hypertrophy



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Hypertrophy of skeletal muscle fibers. Taken at the same magnification (a) shows transverse section of skeletal muscle fibers with no hypertrophy and (b) shows skeletal muscle fibers with hypertrophy (notice the increase in size of the fibers).

Hyperplasia

- 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

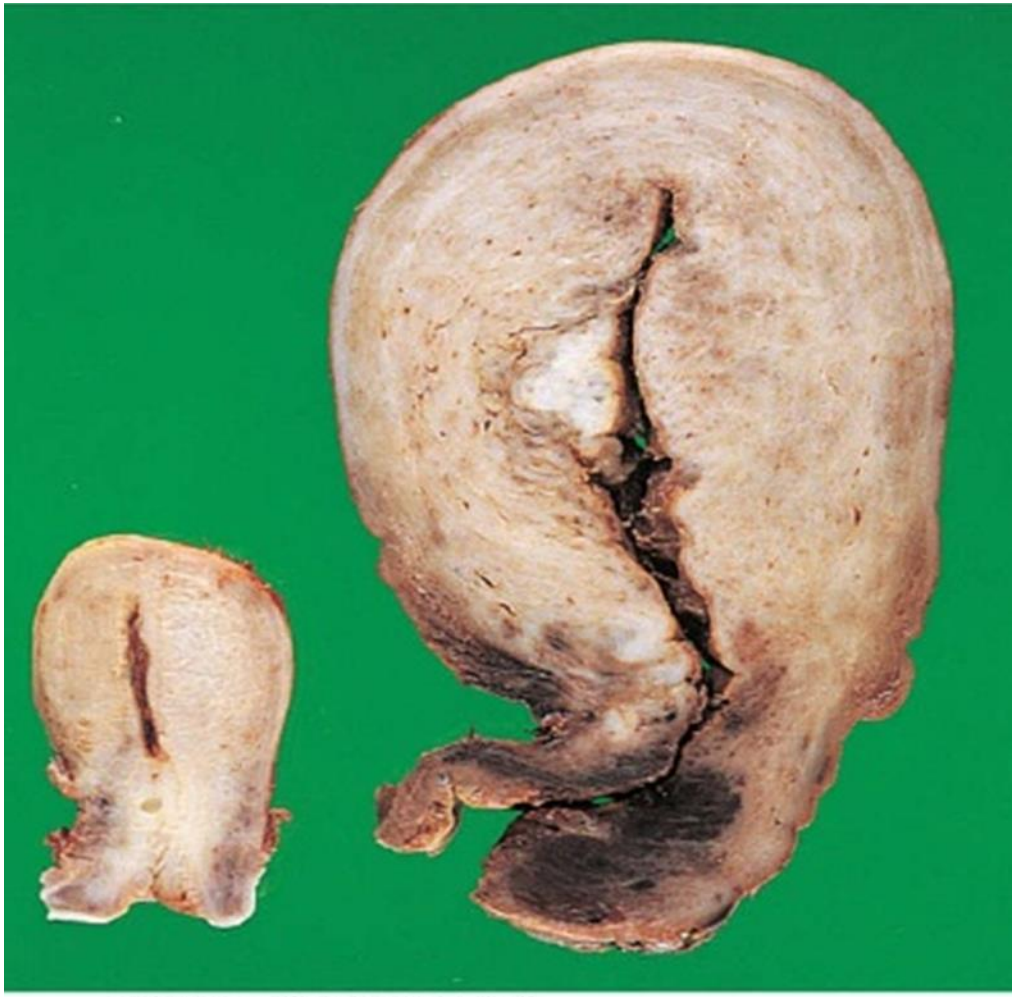
1. Hormonal hyperplasia e.g. the proliferation of the glands of the female breast at puberty and during pregnancy
2. Compensatory hyperplasia e.g. when a portion of liver is partially resected, the remaining cells multiply and restore the liver to its original weight.

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

Hypertrophy and hyperplasia occurring simultaneously:

- Hypertrophy and hyperplasia can occur together, e.g.
  - Uterus during pregnancy: there is both hypertrophy and hyperplasia of the smooth muscle of the uterus.
  - Prostate in elderly: there is both hypertrophy and hyperplasia of the prostate gland and stroma. This condition is called “benign nodular prostatic hyperplasia”.

Hypertrophy and hyperplasia of uterus during pregnancy



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

Atrophy

- 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)

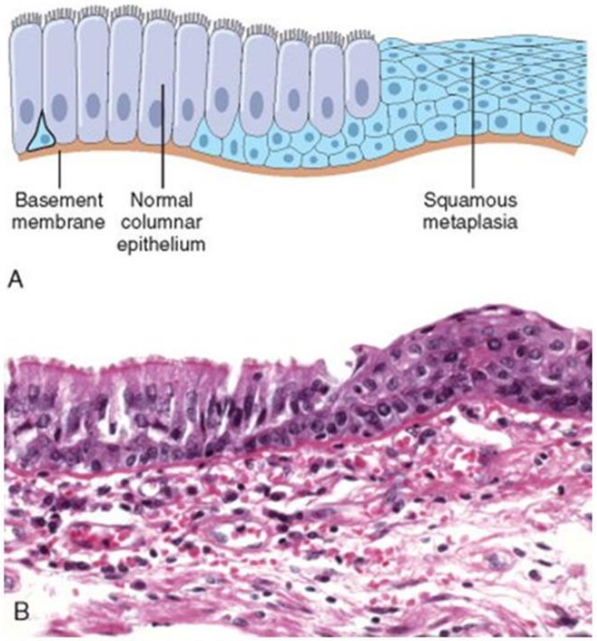
- Involution: it is the reduction in the cell number.

Metaplasia

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

Metaplasia

1) Squamous metaplasia



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

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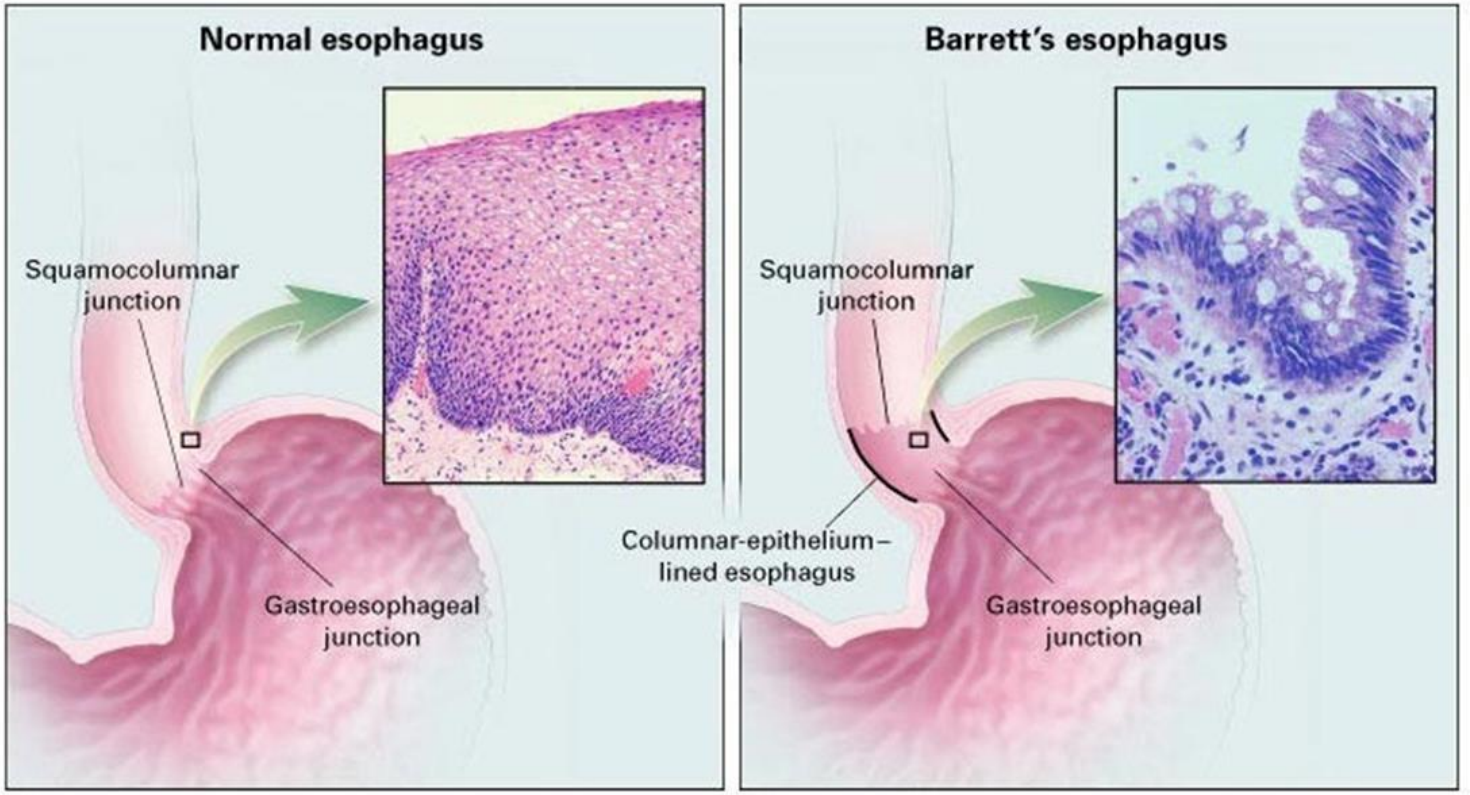
- **In squamous metaplasia, the columnar cells are replaced by squamous cells.** Examples of squamous metaplasia are seen in:
  - **the respiratory tract**: the columnar cells lining the bronchus are replaced by squamous cells following chronic injury in smokers. The squamous epithelium is able to survive the toxicity of tobacco better than the columnar epithelium. Although the metaplastic squamous epithelium will survive better, the important protective functions of columnar epithelium are lost, such as mucus secretion and ciliary action.
  - **the cervix** at the squamocolumnar junction: columnar cells are replaced by squamous cells following chronic irritation and inflammation.
- If the causative agent persists, it may predispose to or provide a platform for cancer to develop. In fact, it is thought that cigarette smoking initially causes squamous metaplasia and later squamous cell cancer arise from it.
- Similarly squamous cell carcinoma of cervix may arise from the squamous metaplasia of cervix.

Metaplasia

2) Columnar cell metaplasia: it is the replacement of squamous cells by columnar cells. It is seen in the esophagus in chronic gastro-esophageal acid reflux disease. The normal stratified squamous epithelium of the lower esophagus cannot handle the acidity of reflux disease and 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.



N Engl J Med 2002; 346:836-842
DOI: 10.1056/NEJMcp012118

Metaplasia

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 then the bone marrow such as liver or spleen.

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

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SUMMARY

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

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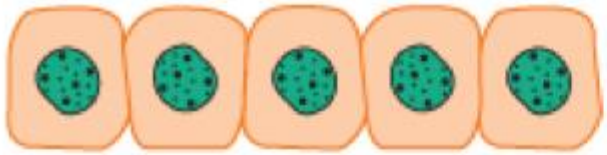
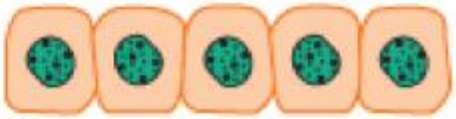
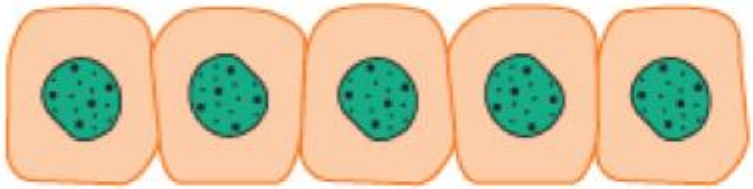


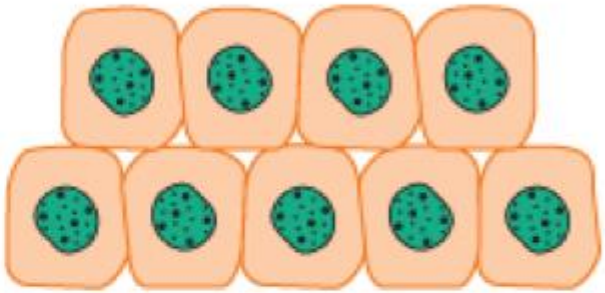
Normal



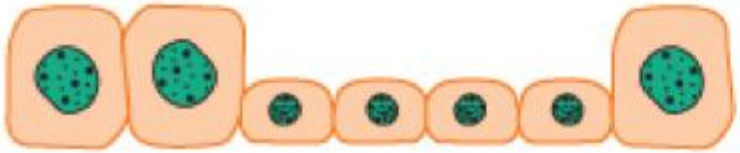
Atrophy
(decreased cell size)



Hypertrophy
(increased cell size)



Hyperplasia
(increased cell number)



Metaplasia
(conversion of one cell
type to another)

Dysplasia
(disorderly growth)

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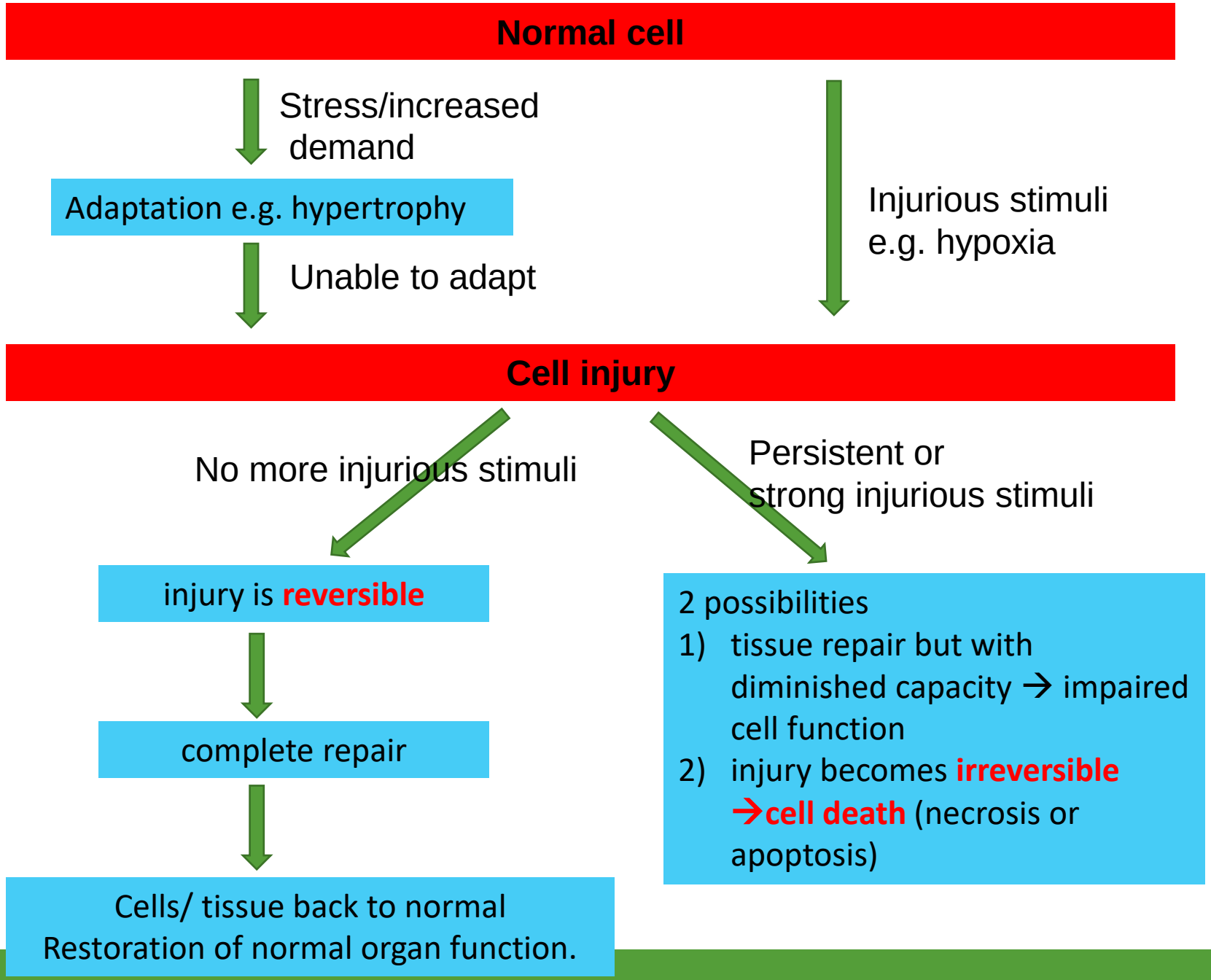
NOTE: the term “hypoplasia” and “aplasia” are not adaptations

- 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.

CELL INJURY


Normal cell
Stress/increased demand
Adaptation e.g. hypertrophy
Unable to adapt
Injurious stimuli e.g. hypoxia
Cell injury
No more injurious stimuli
Persistent or strong injurious stimuli
injury is reversible
complete repair
Cells/ tissue back to normal
Restoration of normal organ function.
2 possibilities
1) tissue repair but with diminished capacity → impaired cell function
2) injury becomes irreversible →cell death (necrosis or apoptosis)

CELL INJURY

- When the cell is exposed to an injurious agent/stress/stimulus, and it leads to injury of the cell, it is termed cell injury.
- Cell injury is reversible up to a certain point, but if the stimulus persists or is severe from the start, the cell reaches a point of no return and suffers irreversible cell injury and ultimately cell death.
- Cell death is death of a cell as a 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 due to disease, injury, or failure of the blood supply (ischemia) and it is always pathologic.
- ***Apoptosis*** occurs when a cell dies through activation of an internally controlled suicide program.

Causes of Cell Injury

Causes of injury (are the same for both reversible and irreversible):

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 then 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 Ca2+ in turn activates a number of enzymes which cause damage.
7. **Free radical injury: see details in the next 2 slides**

Free radical injury

Free radical injury (oxidative stress): is due to excess accumulation of oxygen-derived free radicals
Free radicals: are highly reactive and harmful atoms that have a single unpaired electron in the outer orbit. These atoms are called reactive oxygen species/free radicals. The free radicals are produced in our cells by various mechanisms (called free radical generating systems). They are produced by:

i. Normal metabolism/ respiration: produce free radicals 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 produce free radicals.

iv. Oxygen therapy and reperfusion injury produce free radicals.

v. Immune response or inflammation (neutrophilic oxidative burst)

vi. Transition metals such as iron and copper can trigger production of free radicals.

The names of the common free radicals are:

- superoxide anion radical (O2-),
- hydrogen peroxide (H2O2),
- 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.

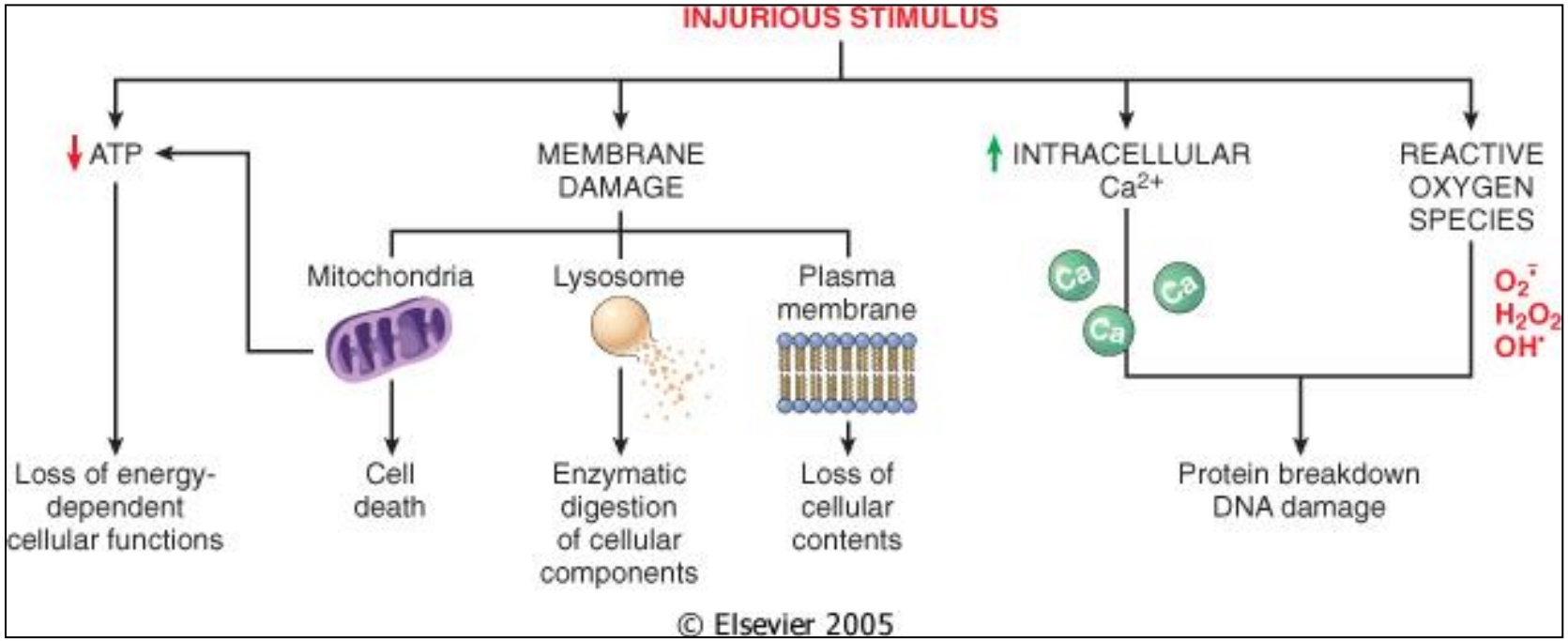
Free radicals cause damage to lipids, proteins, and nucleic acids:

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 are called "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.

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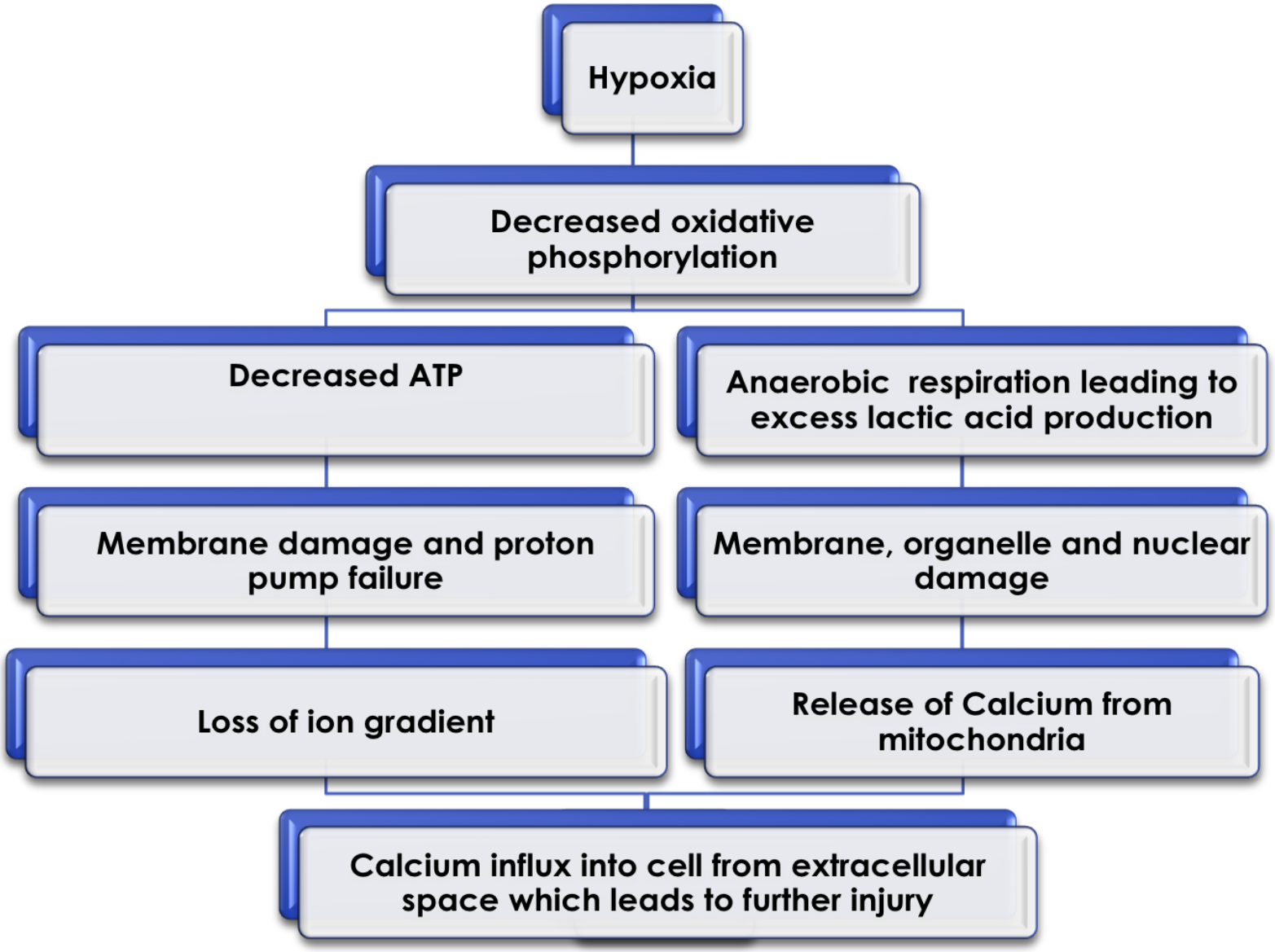
Mechanism in hypoxic cell injury



Reversible Cell Injury:

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. If the injurious stimulus is removed the damage can be **reversed.**

Ultrastructural (electron microscopic) changes associated with reversible cell injury are:

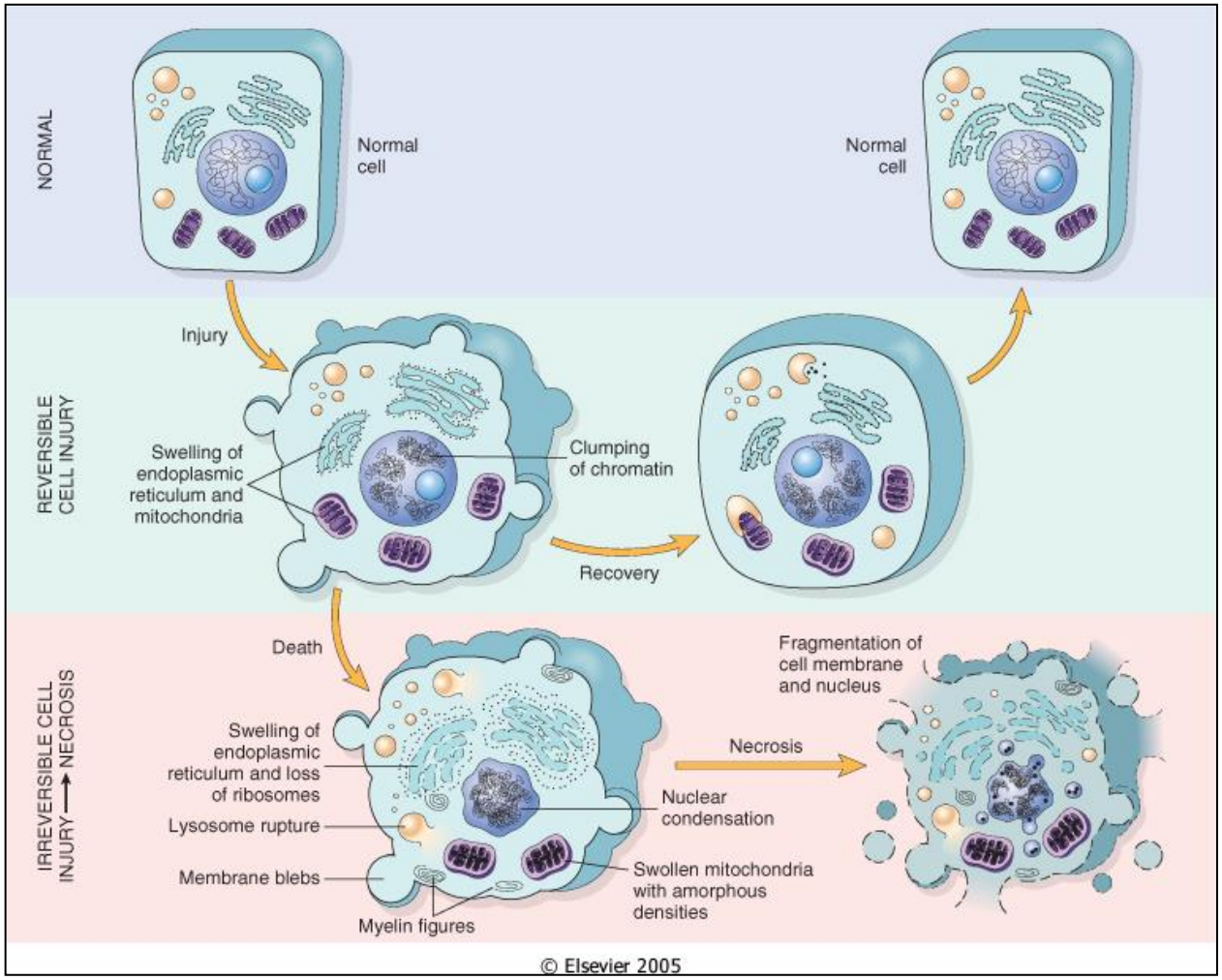
1. Swelling & vacuolization of cytoplasm called "hydropic/ vacuolar degeneration".
2. Mild mitochondrial swelling
3. Mild rough endoplasmic reticulum and plasma membrane damage.
4. Defect in protein synthesis.
5. Mild eosinophilia of cytoplasm (due to decrease in cytoplasmic RNA)

.

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)



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