MORPHOLOGY OF CELL INJURY

When the cell gets injured, there will be morphological changes in the cell. Depending upon the severity of cell injury, degree of damage and residual effects on cells and tissues are variable.

MORPHOLOGY OF REVERSIBLE CELL INJURY

The morphological forms of reversible cell injury are,

- Hydropic change (cloudy swelling, or vacuolar degeneration)
- Fatty change
- Hyaline change
- Mucoid change

MORPHOLOGY OF IRREVERSIBLE CELL INJURY

Autolysis

Apoptosis

Necrosis

Gangrene

Calcification

Reversible injury

Hydropic change (cloudy swelling / vacuolar degeneration)

- It means accumulation of water within the cytoplasm of the cell.
- It is the commonest and earliest form of cell injury from almost all causes.
- The causes of it include acute and subacute cell injury.

Impaired regulation of Na and K at the level of cell membrane

↓

Intracellular accumulation of Na and escape of K

↓

Rapid flow of water into the cell (to maintain the iso-osmotic condition)

↓

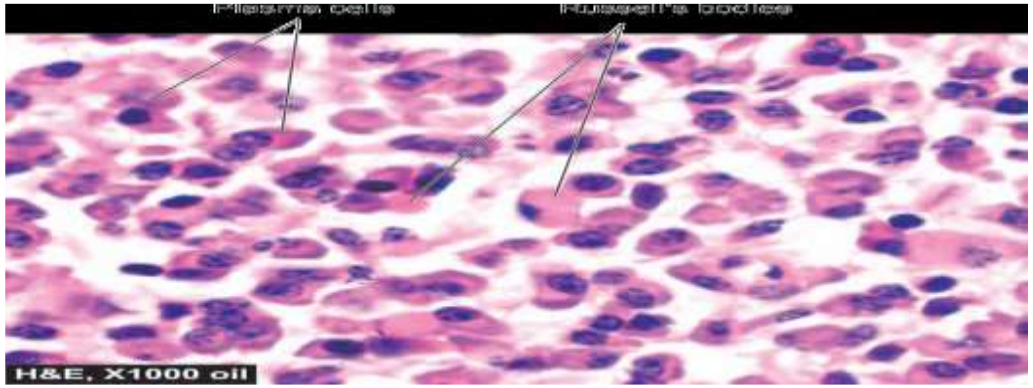
Cellular swelling

Hyaline change *(hyalos* = glass)

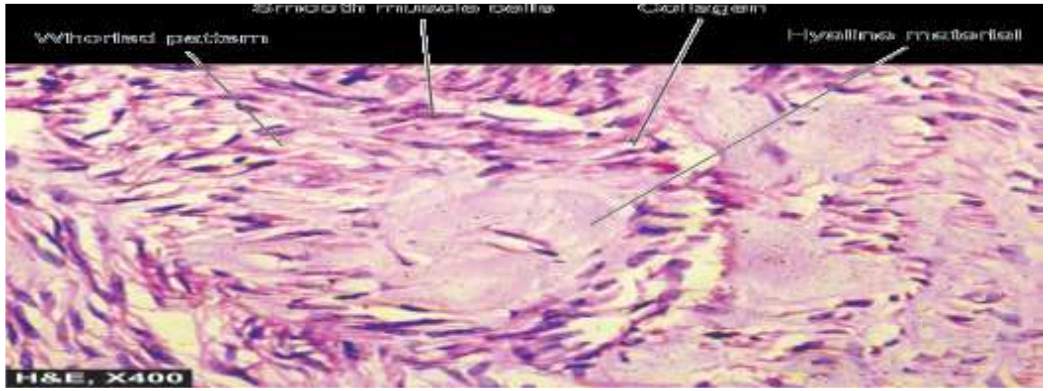
- Hyaline is a descriptive histologic term for glassy, homogeneous, eosinophilic appearance of material in haematoxylin and eosin-stained sections and does not refer to any specific substance. It is associated with heterogeneous pathologic conditions. It may be intracellular or extracellular.

  Intracellular hyaline is seen mainly in epithelial cells. E.g. hyaline droplets, Russell's bodies.

  Extracellular hyaline is seen in connective tissue. E.g. leiomyomas, hyaline arteriosclerosis.



Intracellular hyaline as Russell's bodies in the plasma cells. The cytoplasm shows pink homogeneous globular material due to accumulated immunoglobulins



Extracellular hyaline deposit in leiomyoma uterus. The centres of whorls of smooth muscle and connective tissue show pink homogeneous hyaline material (connective tissue hyaline).

Mucoid Change

Mucus secreted by mucous glands is a combination of proteins complexed with mucopolysaccharides. *Mucin*, a glycoprotein, is its chief constituent. Mucin is normally produced by epithelial cells of mucous membranes and mucous glands, as well as by some connective tissues like in the umbilical cord. By convention, connective tissue mucin is termed myxoid (mucus like).

e.g. functional excess of epithelial mucin:

1. Catarrhal inflammation of mucous membrane (e.g. of respiratory tract, alimentary tract, uterus).
2. Obstruction of duct leading to mucocele in the oral cavity and gallbladder.

disturbances of connective tissue mucin:

1. Mucoid or myxoid degeneration in some tumours e.g. myxomas, neurofibromas, fibroadenoma, soft tissue sarcomas
2. Dissecting aneurysm of the aorta due to Erdheim’s medial degeneration and Marfan’s syndrome.

Intracellular accumulation

Intracellular accumulation of substances in abnormal amounts can occur within the cytoplasm (especially lysosomes) or nucleus of the cell. Intracellular accumulation of the substance in mild degree causes reversible cell injury while more severe damage results in irreversible cell injury. Such abnormal intracellular accumulations can be divided into 3 groups:

i) *Accumulation of constituents of normal cell metabolism produced in excess* e.g. accumulations of lipids (fatty change, cholesterol deposits), proteins and carbohydrates. In addition, deposits of amyloid and urate.

ii) *Accumulation of abnormal substances* produced as a result of abnormal metabolism due to lack of some enzymes e.g. storage diseases or inborn errors of metabolism.

iii) *Accumulation of pigments* e.g. endogenous pigments under special circumstances, and exogenous pigments due to lack of enzymatic mechanisms to degrade the substances or transport them to other sites.

Irreversible cell injury (cell death)

Cell death is a state of irreversible injury. It may occur in the living body as a local or focal change (i.e. autolysis, necrosis and apoptosis) and the changes that follow it (i.e. gangrene and pathologic calcification), or result in end of the life (somatic death).

- **Autolysis**

Autolysis (i.e. *self-digestion*) is disintegration of the cell by its own hydrolytic enzymes liberated from lysosomes. Autolysis can occur in the living body when it is surrounded by inflammatory reaction. Autolysis is *rapid* in some tissues rich in hydrolytic enzymes such as in the pancreas, and gastric mucosa; *intermediate* in tissues like the heart, liver and kidney; and *slow* in fibrous tissue.

- **Necrosis**

Necrosis is defined as a localised area of death of tissue followed by degradation of tissue by hydrolytic enzymes liberated from dead cells; it is invariably accompanied by inflammatory reaction. Necrosis can be caused by various agents such as hypoxia, chemical and physical agents, microbial agents, immunological injury, etc. Two essential changes characterize irreversible cell injury in necrosis of all types:

i) Cell digestion by lytic enzymes

ii) Denaturation of proteins.

- **Apoptosis**

Apoptosis is a form of ‘coordinated and internally programmed cell death’ having significance in a variety of physiologic and pathologic conditions The term was first introduced in 1972 as distinct from necrosis by being a form of cell death which is controlled and regulated by the rate of cell division; when the cell is not needed, pathway of cell death is activated (‘cell suicide’) and is unaccompanied by any inflammation and collateral tissue damage.

Contrasting Features of Apoptosis and Necrosis.

Feature	Apoptosis	Necrosis
1. *Definition*	Programmed and coordinated cell death	Cell death along with degradation of tissue by hydrolytic enzymes
2. *Causative agents*	Physiologic and pathologic processes	Hypoxia, toxins
3. *Morphology*	i) No Inflammatory reaction ii) Death of single cells iii) Cell shrinkage iv) Cytoplasmic blebs on membrane v) Apoptotic bodies vi) Chromatin condensation vii) Phagocytosis of apoptotic bodies by macrophages	i) Inflammatory reaction always present ii) Death of many adjacent cells iii) Cell swelling initially iv) Membrane disruption v) Damaged organelles vi) Nuclear disruption vii) Phagocytosis of cell debris by macrophages
4. *Molecular changes*	i) Lysosomes and other organelles intact ii) Genetic activation by proto-oncogenes hydrolytic enzymes and oncosuppressor genes, and cytotoxic iii) Initiation of apoptosis by intra- and extracellular stimuli, followed by activation of caspase pathway (FAS-R, BCL-2, p53)	i) Lysosomal breakdown with liberation of ii) Cell death by ATP depletion, membrane T cell-mediated target cell killing damage, free radical injury

healthy cell

necrosis

- increase in cell volume
- loss of plasma membrane integrity
- leakage of cellular contents

apoptosis

- cell shrinkage
- plasma membrane blebbing
- formation of apoptotic bodies

- **Gangrene**

Gangrene is a form of necrosis of tissue with superadded putrefaction. The type of necrosis is usually coagulative due to ischaemia (e.g. in gangrene of the bowel, gangrene of limb). On the other hand, *gangrenous or necrotising inflammation* is characterised by primarily inflammation provoked by virulent bacteria resulting in massive tissue necrosis. Thus, the end-result of necrotising inflammation and gangrene is the same but the way the two are produced, is different. The examples of necrotising inflammation are: gangrenous appendicitis, gangrenous stomatitis (noma, cancrum oris).

There are 2 main forms of gangrene—dry and wet, and a variant form of wet gangrene called gas gangrene. In all types of gangrene, necrosis undergoes liquefaction by the action of putrefactive bacteria.

- **PATHOLOGIC CALCIFICATION**

Deposition of calcium salts in tissues other than osteoid or enamel is called pathologic or heterotopic calcification. Two distinct types of pathologic calcification are recognised:

- *Dystrophic calcification*, which is characterised by deposition of calcium salts in dead or degenerated tissues with normal calcium metabolism and normal serum calcium levels. Dystrophic calcification may occur due to 2 types of causes:
  - Calcification in dead tissue
  - Calcification of degenerated tissue
- *Metastatic calcification*, on the other hand, occurs in apparently normal tissues and is associated with deranged calcium metabolism and hypercalcaemia. Since metastatic calcification occurs in normal tissues due to hypercalcaemia, its causes would include one of the following two conditions:
  - Excessive mobilisation of calcium from the bone.
  - Excessive absorption of calcium from the gut.

CELLULAR ADAPTATIONS

On exposure to stress for the sake of survival, the cells make adjustments with the changes in their environment (i.e.adapt) to the physiologic needs *(physiologic adaptation)* and to non-lethal pathologic injury *(pathologic adaptation)*. Such physiologic and pathologic adaptations occur by following processes,

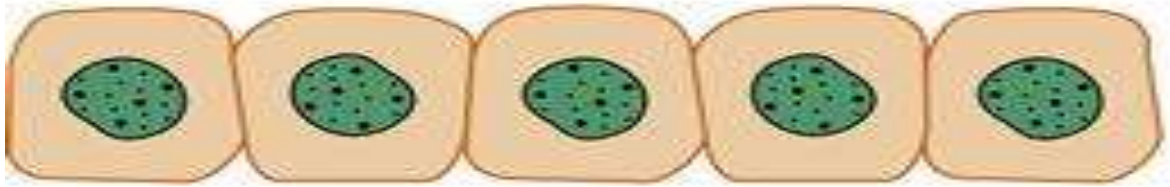
- Decreasing or increasing their size i.e. *atrophy* and *hypertrophy* respectively, or by increasing their number i.e. *hyperplasia* (postfix word -*trophy* means nourishment; -*plasia* means growth of new cells).
- Changing the pathway of phenotypic differentiation of cells i.e. *metaplasia* and *dysplasia* (prefix word *meta*- means transformation; *dys*- means bad development).

In general, the adaptive responses are reversible on withdrawal of stimulus. However, if the irritant stimulus persists for long time, the cell may not be able to survive and may either die or progress further e.g. cell death may occur in sustained atrophy; dysplasia may progress into carcinoma.

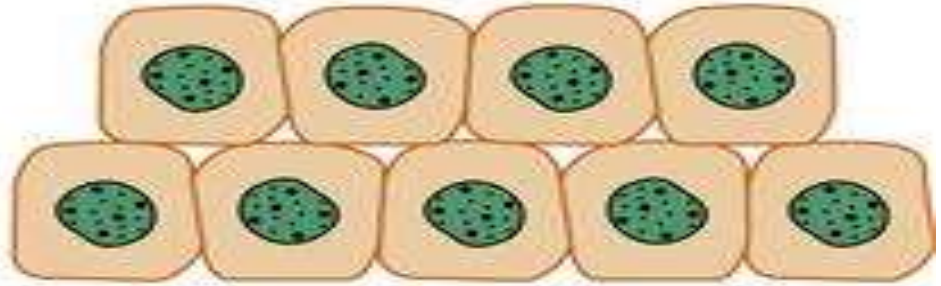
- **ATROPHY-**Reduction of the number and size of parenchymal cells of an organ or its parts which was once normal is called atrophy.
- **HYPERTROPHY-***Hypertrophy* is an increase in the size of parenchymal cells resulting in enlargement of the organ or tissue, without any change in the number of cells.
- **HYPERPLASIA-**Hyperplasia is an increase in the number of parenchymal cells resulting in enlargement of the organ or tissue. Quite often, both hyperplasia and hypertrophy occur together.
- **METAPLASIA-**Metaplasia is defined as a reversible change of one type of epithelial or mesenchymal adult cells to another type of adult epithelial or mesenchymal cells, usually in response to abnormal stimuli, and often *reverts back to normal on removal of stimulus*. However, if the stimulus persists for a long time, epithelial metaplasia may transform into cancer.
- **DYSPLASIA-** Dysplasia means ‘disordered cellular development’, often accompanied with metaplasia and hyperplasia, it is therefore also referred to as *atypical hyperplasia*. Dysplasia occurs most often in epithelial cells.

Normal

Atrophy
(decreased cell size)

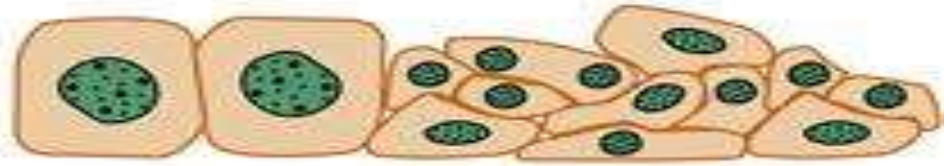


Hypertrophy
(increased cell size)



Hyperplasia
(increased cell number)

Metaplasia
(conversion of one cell
type to another)



Dysplasia
(disorderly growth)

ELECTROLYTE IMBALANCE

- Electrolytes are nutrients that are important for a variety of essential functions in our body including brain, nerve and muscle function.
- Keeping our electrolyte levels balanced is necessary for our health and well-being.
- Electrolytes include sodium, potassium, magnesium, calcium, chloride and other minerals. Each plays a specific role in our body.
- Sodium – helps to maintain fluid balance, nerve signaling, blood pressure and muscle contractions.
- Potassium – helps with stable blood pressure, muscle functions, bone health, nerve impulses and regulating heart contractions.
- Magnesium – helps with muscle contraction, nerve functioning, bone building, bone strength, regulating heart rhythms, maintain blood glucose levels, sustaining a stable protein-fluid balance.
- Calcium – helps our body with muscle contractions, muscle movement, cell division, nerve signaling, blood clotting and by forming and maintaining bones & teeth.
- Chloride – helps to maintain fluid balance and a healthy pH.
- Phosphate – helps to strengthen your bones and teeth and production of energy for tissue growth and repair.

- Intracelluar compartment has higher concentration of potassium, calcium, magnesium and phosphate ions than the blood, while extracellular fluid (including serum) has higher concentration of sodium, chloride, and bicarbonate ions.
- In health, for *electrolyte homeostasis*, the concentration of electrolytes in both these compartments should be within normal limits.
- Normal serum levels of electrolytes are maintained in the body by a careful balance of 4 processes: their intake, absorption, distribution and excretion.
- Disturbance in any of these processes in diverse pathophysiologic states may cause *electrolyte imbalance*.
- Among the important components in electrolyte imbalance, abnormalities in serum levels of sodium (hypo and hypernatraemia), potassium (hypo- and hyperkalaemia), calcium (hypo- and hypercalcaemia) and magnesium (hypo and hypermagnesaemia) are clinically more important.
- A few general principles on electrolyte imbalances are as under:

1. Electrolyte imbalance in a given case may result from one or more conditions.

2. Resultant abnormal serum level of more than one electrolyte may be linked to each other. For example, abnormality in serum levels of sodium and potassium; calcium and phosphate.

3. Generally, the reflection of biochemical serum electrolyte levels is in the form of metabolic syndrome and clinical features rather than morphological findings in organs.

4. Clinical manifestations of a particular electrolyte imbalance are related to its pathophysiologic role in that organ or tissue.

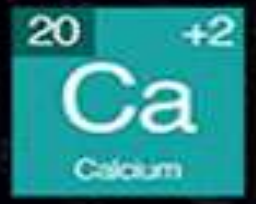
Normal Ranges and Disturbances for Common Electrolytes

Normal Range of Sodium: 134 to 145 mEq/L
Hypernatremia: when sodium is **higher** than the normal range.
Hyponatremia: when sodium is **lower** than the normal range.

Normal Range of Magnesium: 0.70 to 0.95 mmol/L
Hypermagnesemia: when magnesium levels are **higher** than the normal range.
Hypomagnesemia: when magnesium levels are **lower** than the normal range.

Normal Range of Phosphate: 0.8 to 1.3 mmol/L
Hyperphosphatemia: when phosphate levels are **higher** than the normal range.
Hypophosphatemia: when phosphate levels are **lower** than the normal range.

Normal Range of Potassium: 3.5 to 5.0 mmol/L
Hyperkalemia: when the concentration of potassium in the blood is **higher** than the normal range.
Hypokalemia: when the concentration of potassium in the blood is **lower** than the normal range.



Normal Range of Calcium: 2.20 to 2.55 mmol/L
Hypercalcemia: when serum calcium levels are **higher** than the normal range.
Hypocalcemia: when serum calcium levels are **lower** than the normal range.

Sodium

- Sodium, or *Na*, is one of the most important electrolytes in the body and is responsible for a number of important functions, mostly related to fluid and water regulation. T**he normal accepted range for sodium** is 134 to 145 mEq/L.

- *Hyponatraemia* is considered to be a serum sodium below 134 mEq/L.
- Etiology:

  A common cause of hyponatraemia is water retention due to cardiac or renal or hepatic failure.

  Other causes of hyponatraemia include some medicines,

  psychogenic polydipsia (excessive water intake),

  syndrome of inappropriate ADH (antidiuretic hormone) secretion,

  chronic or severe vomiting and diarrhoea.
- Clinical manifestations:

  Confusion, agitation, nausea and vomiting, muscle weakness, spasms or cramps.

- *Hypernatraemia* is defined as a serum sodium greater than 145 mEq/L.
- Etiology:

Anything that leads to excessive water loss or salt gain. For example, water depletion or dehydration may be caused by vomiting or diarrhoea.

Excessive ingestion of sodium is rare, but the administration of infusions containing sodium such as sodium chloride or sodium bicarbonate may lead to hypernatraemia.

- Clinical manifestations:

fever, irritability, drowsiness, irritability, lethargy and confusion.

Potassium

- Potassium, or *K*, is responsible for the functioning of excitable tissues such as skeletal and cardiac muscle and nerves. **The normal range for potassium** is 3.5 to 5.0 mmol/L.
- *Hypokalaemia* is defined as a serum potassium less than 3.5 mmol/L.
- Etiology:

Decreased oral intake, increased renal or gastrointestinal loss of potassium, or a shift of potassium within the body's fluid compartments (from outside the cell where it should be, to inside the cell).

- Clinical manifestations:

Range from muscle weakness and ileus (lack of peristalsis), to serious cardiac arrhythmias such as ventricular tachycardias.

- *Hyperkalaemia* is defined as a serum potassium greater than 5.0 mmol/L.
- Etiology:

excessive intake, tissue damage from burns or trauma, medicines such as potassium sparing diuretics, and most commonly, due to renal failure.

- Clinical manifestations:

muscle weakness, hypotension, bradycardia and loss of cardiac output, and ECG changes may include peaked T waves and flattened P waves.

Magnesium

- Magnesium, or *Mg*, is another element that has a strong effect on muscle contractions. **The normal plasma range for magnesium** is 0.70 to 0.95 mmol/L.
- *Hypomagnesaemia*, is as a plasma magnesium level less than 0.70 mmol/L.
- Etiology:

  decreased intake or increased loss of magnesium.
- Clinical manifestations:

  confusion, irritability, delirium, muscle tremors and tachyarrhythmias.

- *Hypermagnesaemia* is when the level of magnesium in the blood is above the normal range (0.95 mmol/L) Fortunately, this is uncommon.
- Etiology:

  excessive administration of magnesium and lithium therapy, often in the presence of renal failure.
- Clinical manifestations:

  poor reflexes,low BP, respiratory depression, and cardiac arrest.

Calcium

- Calcium, or *Ca*, is an important element in the body as it helps to control nerve impulses, muscle contractions and has a role in clotting. **The serum calcium range** should be between 2.20 to 2.55 mmol/L when normal.
- *Hypocalcaemia*, is defined as low serum calcium levels (less than 2.20mmol/L).
- Etiology:

  It is relatively rare because the bones always act as a reservoir for this electrolyte.

  Parathyroid disease, vitamin D deficiency, septic shock and acute pancreatitis can cause this problem.
- Clinical manifestations:

  tetany (involuntary muscle contraction), mental changes and decreased cardiac output.

- *Hypercalcaemia,* is elevated levels of calcium in the blood (serum calcium level above 2.55 mmol/L)
- Etiology:

  It again arises from parathyroid problems and vitamin D issues.
- Clinical manifestations:

  nausea, vomiting, polyuria, muscular weakness and mental disturbance.

Phosphate

- Phosphate, or *P*, is an electrolyte used in several functions throughout the body. Although a phosphate imbalance isn't as well known as some of the other imbalances, it can still cause problems with the patient's condition.
- **The normal range of phosphate in the plasma** is generally between 0.8 to 1.3 mmol/L.
- *Hypophosphataemia*, is when levels of phosphate in the blood are below the normal range(0.8mmol/L)
- Clinical manifestations:

  muscle weakness, heart failure, seizure, and coma.

- Etiology:

  Vitamin D deficiency, hyperparathyroidism, or alcoholism. Hypophosphataemia may also be present, in addition to other electrolyte disturbances, in re-feeding syndrome, which is associated with the commencement of total parental nutrition (TPN).

- *Hyperphosphataemia,* is levels of phosphate in the blood above the normal range (1.3mmol/L)
- Etiology:

  Kidney disease, parathyroid issues, and metabolic or respiratory acidosis.

- Clinical manifestations:

  Symptoms are usually not present, and they are related to hypocalcaemia. Renal patients can experience hardened calcium deposits when this condition goes untreated.

Management of electrolyte imbalance:

First identify the cause or etiology of the electrolyte imbalance. After that we have to remove that cause of the imbalance if possible. If it is not possible we have to correct the level of elctrolytes with medications or any other medical interventions (e.g.dialysis).

If there is low level of electrolytes we can correct it with the diet supplements.