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## CELLULAR ADAPTATION AND INJURY Introduction

Cell injury underlies all diseases. So, to understand diseases one, has to start by knowing what cell injury is. When a cell is exposed to an injurious agent (i.e., the causes of diseases discussed in chapter one), the possible outcomes are:

1. The cell may adapt to the situation or
2. They cell may acquire a reversible injury or
3. The cell may obtain an irreversible injury & may die. The cell may die via one of two ways: either by necrosis or by apoptosis.

Which of these outcomes occur depends on both the injurious agent & on cellular factors. In other words, the result depends on the type, severity, & duration of the injury & on the type of the cell.

This chapter covers the types of cellular adaptation, reversible cell injury, & cell death in that order.



### Types of cellular adaptation

The types of cellular adaptation include hypertrophy, atrophy, hyperplasia, & metaplasia.

### A. Hypertrophy

Hypertrophy is increase in the size of cells. Increased workload leads to increased protein synthesis & increased size & number of intracellular organelles which, in turn, leads to increased cell size. The increased cell size leads to increased size of the organ.

Examples: the enlargement of the left ventricle in hypertensive heart disease & the increase in skeletal muscle during sternous exercise.

**B. Hyperplasia**

Hyperplasia is an increase in the number of cells. It can lead to an increase in the size of the organ. It is usually caused by hormonal stimulation. It can be physiological as in enlargement of the breast during pregnancy or it can pathological as in endometrial hyperplasia.

**C. Atrophy**

Atrophy is a decrease in the size of a cell. This can lead to decreased size of the organ. The atrophic cell shows autophagic vacuoles which contain cellular debris from degraded organelles.

Atrophy can be caused by:

- Disease
- Undernutrition
- Decreased endocrine stimulation
- Denervation
- Old age



**D. Metaplasia**

Metaplasia is the replacement of one differentiated tissue by another differentiated tissue. There are different types of metaplasia. Examples include:

1. Squamous metaplasia

This is replacement of another type of epithelium by squamous epithelium. For example, the columnar epithelium of the bronchus can be replaced by squamous epithelium in cigarette smokers

2. Osseous metaplasia This replacement of a connective tissue by bone, for example at sites of injury.

**Reversible cellular changes & accumulations**

Even though there are many different kinds of reversible cellular changes & accumulations, here we will only mention fatty change & accumulation of pigments.

**1. Fatty change**

This is accumulation of triglycerides inside parenchymal cells. It is caused by an imbalance between the uptake, utilization, & secretion of fat. Fatty change is usually seen in the liver, heart, or kidney. Fatty liver may be caused by alcohol, diabetes mellitus, malnutrition, obesity, & poisonings. These etiologies cause accumulation of fat in the hepatocytes by the following mechanisms:

a. Increased uptake of triglycerides into the parenchymal cells.

b. Decreased use of fat by cells.

c. Overproduction of fat in cells.

d. Decreased secretion of fat from the cells.

**2. The accumulations of pigments**

Pigments can be exogenous or endogenous. Endogenous pigments include melanin, bilirubin, hemosiderin, & lipofuscin. Exogenous pigments include carbon. These pigments can accumulate inside cells in different situations.

**a. Melanin**

Melanin is a brownish-black pigment produced by the melanocytes found in the skin. Increased melanin pigmentation is caused by suntanning & certain diseases e.g. nevus, or malignant melanoma. Decreased melanin pigmentation is seen in albinism & vitiligo. **b. Bilirubin**

Bilirubin is a yellowish pigment, mainly produced during the degradation of hemoglobin. Excess accumulation of bilirubin causes yellowish discoloration of the sclerae, mucosae, & internal organs. Such a yellowish discoloration is called jaundice.

Jaundice is most often caused by

1. Hemolytic anemia Hemolytic anemia is characterized by increased destruction of red blood cells.

2. Biliary obstruction

This is obstruction of intrahepatic or extrahepatic bile ducts. It can be caused by gallstones.

3. Hepatocellular disease This is associated with failure of conjugation of bilirubin.

**C. Hemosiderin**

Hemosiderin is an iron-containing pigment derived from ferritin. It appears in tissues as golden brown amorphous aggregates & is identified by its staining reaction (blue color) with the Prussian blue dye. Hemosiderin exists normally in small amounts within tissue macrophages of the bone marrow, liver, & spleen as physiologic iron stores. It accumulates in tissues in excess amounts in certain diseases. This excess accumulation is divided into 2 types:

1. Hemosiderosis When accumulation of hemosiderin is primarily within tissue macrophages & is not associated with tissue damage, it is called hemosiderosis.

2. Hemochromatosis When there is more extensive accumulation of hemosiderin, often within parenchymal cells, which leads to tissue damage, scarring & organ dysfunction, it is called hemochromatosis.

## Cell death

Cells can die via one of the following two ways:

1. Necrosis

2. Apoptosis

| Feature | Necrosis | Apoptosis |
|---|---|---|
| Cell size | Enlarged (swelling) | Reduced (shrinkage) |
| Nucleus | Pyknosis → karyorrhexis → karyolysis | Fragmentation (round nucleosome) |
| Plasma membrane | Disrupted | Intact |
| Cellular contents | Enzymatic digestion; may leak out of cell | Intact; may be released in apoptotic bodies |
| Adjacent inflammation | Frequent | No |
| Physiologic or pathologic role | Pathologic | Physiologic and Pathologic |



### 1. Necrosis

In necrosis, excess fluid enters the cell, swells it, & ruptures its membrane which kills it. After the cell has died, intracellular degradative reactions occur within a living organism. Necrosis does not occur in dead organisms. In dead organisms, autolysis & heterolysis take place.

Necrosis occurs by the following mechanisms:

A. Hypoxia B. Free radical–induced cell injury C. Cell membrane damage D. Increased intracellular calcium level

### A. Hypoxia

Hypoxia is decreased oxygen supply to tissues. It can be caused by:

1. Ischemia  Ischemia is decreased blood flow to or from an organ.

Ischemia can be caused by obstruction of arterial blood flow – the most common cause, or by decreased perfusion of tissues by oxygencarrying blood as occurs in cardiac failure, hypotension, & shock.

2. Anemia  Anemia is a reduction in the number of oxygen-carrying red blood cells.

3. Carbon monoxide poisoning  CO decreases the oxygen-capacity of red blood cells by chemical alteration of  hemoglobin.

4. Poor oxygenation of blood due to pulmonary disease.

The cell injury that results following hypoxia can be divided into early & late stages:

1. Early (reversible) stages of hypoxic cell injury  At this stage, hypoxia results in decreased oxidative phosphorylation & ATP  synthesis. Decreased ATP leads to:

a. Failure of the cell membrane Na – K pump, which leads to increased intracellular Na & water, which cause cellular & organelle swelling. Cellular swelling (hydropic change) is characterized by the presence of large vacuoles in the cytoplasm. The endoplasmic reticulum also swells. The mitochondria show a low amplitude swelling. All of the above changes are reversible if the hypoxia is corrected.

b. Disaggregation of ribosomes & failure of protein synthesis.

2. Late (irreversible) stages of hypoxic cell injury.  This is caused by severe or prolonged injury. It is caused by massive calcium

influx & very low pH, which lead to activation of enzymes, which damage the cell membrane& organelle membranes. Irreversible damage to the mitochondria, cell membranes, & the nucleus mark the point of no return for the cell, that is after this stage, the cell is destined to die.

Release of aspartate aminotransferase (AST), creatine phosphokinase(CPK), & lactate dehydrogenase (LDH) into the blood is an important indicator of irreversible injury to heart muscle following myocardial infarction.

**B. Free radical-induced injury**

Free radical is any molecule with a single unpaired electron in the outer orbital. Examples include superoxide & the hydroxyl radicals. Free radicals are formed by normal metabolism, oxygen toxicity, ionizing radiation, & drugs & chemicals, & reperfusion injury. They are degraded by spontaneous decay, intracellular enzymes such as glutathione peroxidase, catalase, or superoxide dismutase, & endogenous substances such as ceruloplasmin or transferrin. When the production of free radicals exceeds their degradation, the excess free radicals cause membrane pump damage, ATP depletion, & DNA damage. These can cause cell injury & cell death.

a. Cell membrane damage

Direct cell membrane damage as in extremes of temprature, toxins, or viruses, or indirect cell membrane damage as in the case of hypoxia can lead to cell death by disrupting the homeostasis of the cell.

b. Increased intracellular calcium level Increased intracellular calcium level is a common pathway via which different causes of cell injury operate. For example, the cell membrane damage leads to increased intracellular calcium level. The increased cytosolic calcium, in turn, activates enzymes in the presence of low pH. The activated enzymes will degrade the cellular organelles.

   Necrosis comes from the Greek origin nekrosis meaning “death” and later moved to modern Latin to necrosis. Necrosis can be described

As a pathological process of cell death which could have been resulted from infections, hypoxia, trauma or toxins. Unlike apoptosis, necrosis is uncontrolled and release lots of chemicals from the dying cell to which causes damage to surrounding cells. Inflammation is often initiated due to necrosis. There are many types of morphological patterns that necrosis can present itself. These are coagulative, liquefactive, caseous, gangrenous which can be dry or wet, fat and fibrinoid.

Necrosis can start from a process called “oncosis”. Oncosis comes from the Greek origin ónkos, meaning swelling. Oncosis occurs when the mitochondria within a cell are damaged beyond recovery by toxins or hypoxia. ATP is thus not

being made, which ch dysregulate the ionic concentration within the cell as the ionic pumps are no longer functioning. Sodium moves into the cell and water follow, making the cell explode. The content that has been released will attract immune cells which will initiate inflammation and release reactive oxygen species (ROS) and enzymes such as proteases. The surrounding tissues may be damaged, and therefore organs may fail to work. In a way, necrosis alerts the immune system to clean through phagocytosis and start local inflammation. However, if the collateral damage is more significant than the process of healing, necrosis will thus increase in size, killing more healthy cells and decrease surrounding body function, which may cause organ failure. Decomposing tissue will increase in number, and micro-organisms may start to replicate and dominate as the immune system struggle to contain the necrosis. Surgery is thus utilised to remove the necrotic tissue by a procedure called debridement and let the healthy tissue take over and heal. Depending on the severity, time, type and extent of the necrosis, the tissues may never heal back to its original function and integrity.

NECROSIS (COMPARED TO APOPTOSIS)

- Occurs less frequently, involves many cells, may not be localised.
- Abnormal and uncontrolled cell death that is associated with a
- Pathological condition. Caused by external and internal injuries.
- Caspase independent pathway.
- Inflammation is present. Cell swells and burst, releasing its content at once.
- Swelling of the mitochondria and endoplasmic reticulum occurs.
- Leakage and enzymatic digestion of neighbouring cellular contents.
- Disrupted plasma membrane structure.
- Eosinophilia cell-like present (cells presenting pink on a histology slide).
- Nuclear changes: pyknosis, karyorrhexis and karolysis

## Types of necrosis

Depending on where (such as which org and what type of damage occurred in the body, necrosis will have a specific morphological pattern. There are six distinct patterns that are identifiable, and by identifying the pattern, an underlying cause could be identified. Let’s have a look at: coagulative, liquefactive, caseous, gangrenous, fat and fibrinoid necrosis.

## Coagulative

Coagulative necrosis generally occurs due to an infarct (lack of blood flow from an obstruction causing ischaemia) and can occur in all the cells of the body except the brain. The heart, kidney, adrenal glands or spleen are good examples of coagulative necrosis. Cells that undergo coagulative necrosis can become dry, hard, and white. What is interesting is that gel-like appearance occurs in dead tissues, but the architecture of the cells is maintained for at least some days. Coagulation occurs as the proteins are degraded and denatured, and an opaque film starts to form.

Gross appearance: a pale segment may be seen in contrast to surrounding healthy tissues. The segment may be hard to the touch.

Microscopic appearance: in an H&E staining tissue, eosinophilia like cell (cells presenting pink on a histology slide) will be noticeable. Anucleated cells (cells without a nucleus) should be observable with preserved cell outlines.

## Liquefactive

Liquefactive necrosis can be associated from bacterial, viruses, parasites fungal infections. Unlike coagulative necrosis, or liquefactive necrosis forms a viscous liquid mass as the dead cells are being digested. The micro-organisms can release enzymes to degrade cells and initiate an immune and inflammatory response. Cellular dissolution and digestion of dying cells may also release further enzymes, which speeds up the liquefying process. The micro-organisms stimulate the leukocyte to home-in on the necrotic area and release powerful hydrolytic enzymes (such as lysozymes) which causes local damage and cells to be lysed, causing a fluid phase. The enzymes responsible for liquefaction are derived from either bacterial hydrolytic enzymes or

lysosomal hydrolytic enzymes. These are proteases (collagenases, elastases), DNases and lysosomal enzymes.

A creamy yellow liquid should be p”esen’ as lots of leukocytes are found to be dead, this is generally called pus. Interestingly, an infarct that involves the nervous system (such as the brain) should present as coagulative necrosis but does not occur, instead liquefactive necrosis is present. It is not fully explained why the nervous system displays liquefactive necrosis without the cause of an infection, but it is suggested that the nervous system does hold a higher amount of lysosomal content, which leads to autolysis and an increased opportunity for these enzymes to digest the cells in the brain.

Gross appearance: liquid-like layer can be seen; pus should be present. Yellowing, softening or swelling of the tissue should be seen. Malacia (softening, or loss of consistency) should be present. A cystic space should be present for tissue resolution.

Microscopic appearance: macrophages and neutrophils, both dead and alive, should be present. Debris and lysed cells should be seen with inflammation. Partial space should be filled with lipids and debris. There is a loss of neurons and glial cells, with the formation of clear space.

Caseous

Caseous necrosis occurs when the immune system and body cannot successfully remove the foreign noxious stimuli. For example, tuberculosis is a prime example where there is an aberrant immune response (such as the alveolar macrophages are not responding correctly) to the bacteria as the bacteria has infected the macrophages. The immune system seals off the

Foreign matter by using fibroblasts and white blood cells such as lymphocytes, neutrophils, NK cells, dendritic cells and macrophages. A granuloma may form with fibroblast cells (which creates an encasing layer), leukocytes and the formation of Langhans giant cells (fusion of epithelioid cells). The organism is not killed but rather contained.

Gross appearance: a yellow-white soft cheesy sphere that is enclosed by a distinct border.

Microscopic appearance: a granuloma should be present. The core is necrotic and uniformly eosinophilic, which is surrounded by a border of activated macrophages and lymphocytes. The core is structureless and should have debris and lysed cells. Langhans giant cells may be seen, and inflammation should also be noticed and present. There is a fibrous case surrounding and enclosing the core; hence fibroblasts should also be seen.

Gangrenous

Gangrenous necrosis does not demonstrate a specific pattern of cell death but is preferably used in clinical practice to describe the condition. Gangrenous necrosis generally describes the damage that has occurred to the extremities (especially lower) where there is severe ischaemia. These extremities lack in blood supply and oxygen and typically cause coagulative necrosis at different tissue planes (this is also called dry gangrene). Severe frostbite injuries can lead to dry gangrene. If bacterial infection occurred, liquefactive necrosis could also be occurring due to the degrading enzymes and the involvement of the leukocytes. When liquefactive necrosis is present, the term ‘wet’ gangrene is used.

Gross appearance: black skin is generally seen with a degree of putrefaction (the process of decay or rotting in a body or other organic matter). The tissues

may look ‘mummified’, be sure to ascertain if this is dry or wet gangrene. Smelling may give a clue if there is an infection.

Microscopic appearance: due to the ischaemia which would suggest dry gangrene, coagulative necrosis histological traits should be seen. If there is a bacterial infection which would suggest wet gangrene, liquefactive necrosis histological traits should be seen.

Fat

Fat necrosis does not denote a type of necrosis pattern. Instead, it is used to describe the destruction of fat, for example, due to pancreatic lipases that have been released into the surrounding tissues where the pancreas itself is at risk along with the peritoneal cavity. Acute pancreatitis causes the pancreatic enzymes to leak out from the acinar cells. Once the enzymes come into contact with fat cells, their plasma membrane is liquefied, releasing the fats/triglycerides. The fatty acids combine with calcium through a process called saponification. An insoluble salt is created and gives the appearance of a chalky-white area. Infections, viruses, trauma, ischaemia and toxins could be responsible for the pancreas being damaged and releasing its enzymes. Breast tissues can also have fat necrosis triggered by trauma, for example. To clinically diagnoses and manage pancreatitis

Gross appearance: soft chalky-white area should be seen on the pancreas.

Microscopic appearance: basophilic (bluish) calcium deposits are present. Anucleated adipocytes with a cytoplasm that is more pink and contains amorphous mass of necrotic material. Inflammation would be present.

Fibrinoid

Fibrinoid necrosis is associated with vascular damage (caused mainly by autoimmunity, immune-complex deposition, infections) and the exudation of plasma proteins (such as fibrin). This pattern typically occurs due to a type 3 hypersensitivity, where an immune complex is formed between an antigen (Ag) with an antibody (Ab). The Ag-Ab complex may be deposited in the vascular walls causing inflammation, complement being activated, and phagocytic cells are recruited, which could be releasing oxidants and other enzymes causing further damage and inflammation. Fibrin, a non-globular protein involved in the clotting of blood, is leaked out of the vessels. The results create an amorphous appearance that is bright pink in an H&E stain. The pathologists call this appearance 'fribinoid' which means fibrin-like.

Gross appearance: usually not grossly discernible.

Microscopic appearance: an amorphous appearance that is bright pink in an H&E stain. The deposition of fibrinoid is surrounding the blood vessels. Inflammation should be present.



**2. Apoptosis**

Apoptosis is the death of single cells within clusters of other cells. (Note that necrosis causes the death of clusters of cells.) In apoptosis, the cell shows shrinkage & increased acidophilic staining of the cell. This is followed by fragmentation of the cells. These fragments are called apoptotic bodies. Apoptosis usually occurs as a physiologic process for removal of cells during embryogenesis, menstruation, etc... It can also be seen in pathological conditions caused by mild injurious agents.

Apoptosis is not followed by inflammation or calcification. The abovementioned features distinguish apoptosis from necrosis.

## VI. Pathologic calcification

Pathologic calcification is divided into 2 types:

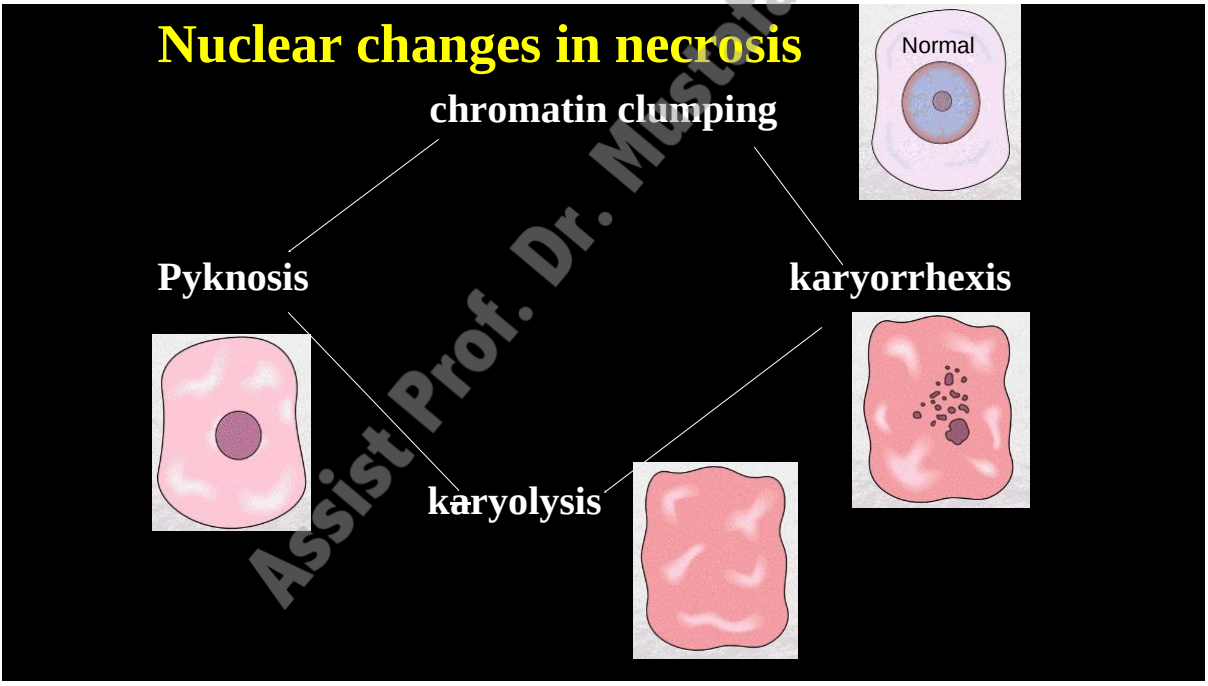
### 1. Metastatic calcification

This is caused by hypercalcemia, resulting from hyperparathyroidism, milk-alkali syndrome, sarcoidosis etc...

## 2. Dystrophic calcification

This occurs in previously damaged tissue, such asareas of old trauma, tuberculous lesions, scarred heart valves, & atherosclerotic lesions.

Unlike metastatic calcification, it is not caused by hypercalcemia. Typically, the serum calcium level is normal.



| 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 |
| Oesophageal squamous epithelium | Gastric acid | Columnar epithelium |
| Columnar glandular epithelium | Vitamin A deficiency | Squamous epithelium |

**هذا الجدول مموجود بالملزمة بس هو شرحة اليوم بالمحاضرة وگال كلش مهم**