



PATHOLOGY

Lecture 2

Cellular Injury and cell death

Learning Objectives

By the end of this lecture, the student should be able to:

- Define cellular adaptation and describe atrophy, hypertrophy, hyperplasia, metaplasia and dysplasia.
- List the main causes of cell injury.
- Differentiate reversible from irreversible cell injury, and explain the role of hypoxia and ATP depletion.
- Describe intracellular accumulations (fat, cholesterol, proteins, glycogen, pigments) and pathologic calcification.
- Explain the mechanisms of free radical injury.
- Differentiate necrosis from apoptosis and recognize the nuclear changes and the types of necrosis.

1. Introduction

The environment around cells is dynamic and constantly changing. In this fluid environment, cells are exposed to numerous stimuli, some of which may be injurious. To survive, cells must be able to adapt to variable conditions.

When a cell is exposed to an injurious agent, there are three possible outcomes:

- **Adaptation:** the cell adapts to the situation.
- **Reversible injury:** the cell acquires an injury from which it can recover.
- **Irreversible injury:** the cell cannot recover and dies, either by **necrosis** or by **apoptosis**.

Cellular Response to Injury: The Continuum

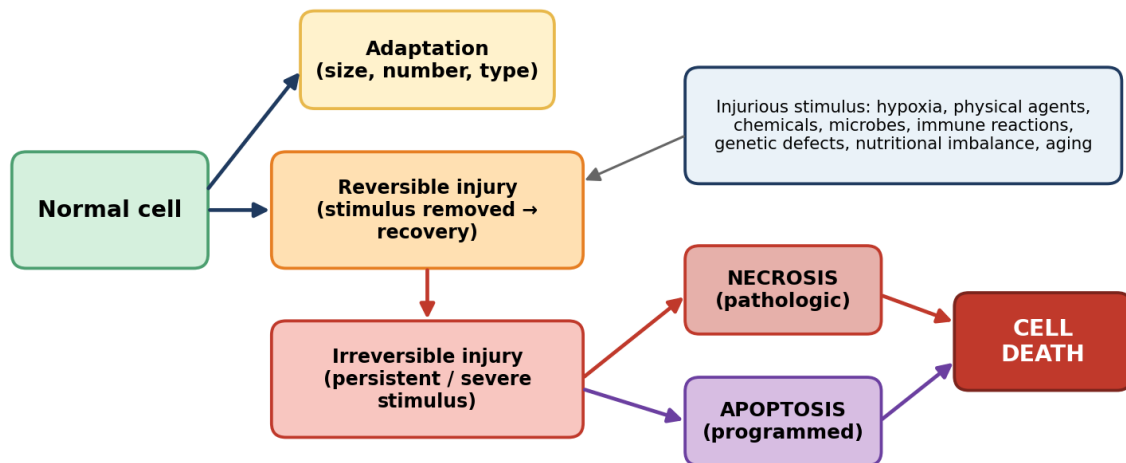


Figure 1. The continuum of cellular response to injury.

2. Types of Cellular Adaptation

Adaptation involves changes in cellular size, number or type.

Types of Cellular Adaptation

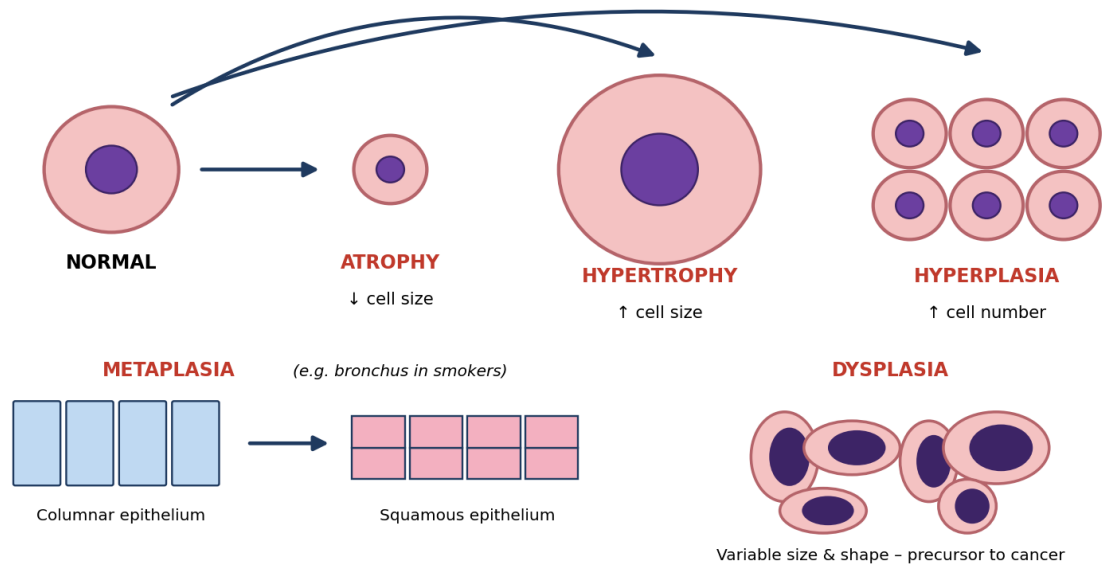


Figure 2. Cellular adaptations compared with a normal cell (schematic).

Adaptation	Definition / mechanism	Examples & causes
Atrophy	Decrease in size of a cell or tissue; reduces oxygen consumption and metabolic needs and may increase the overall efficiency of cell function.	Causes: disuse, under-nutrition, decreased endocrine stimulation, denervation, old age.
Hypertrophy	Increase in cell size. Increased workload → increased protein synthesis and increased size and number of intracellular organelles → larger cells → larger organ.	Left ventricular enlargement in hypertensive heart disease; skeletal muscle increase with strenuous exercise.
Hyperplasia	Increase in the number of cells; may increase organ size. Usually caused by hormonal stimulation.	Physiological: breast enlargement in pregnancy. Pathological: endometrial hyperplasia.
Metaplasia	Replacement of one differentiated tissue by another differentiated tissue.	Squamous metaplasia: bronchial columnar epithelium replaced by squamous epithelium in cigarette smokers.

Adaptation	Definition / mechanism	Examples & causes
Dysplasia	Derangement of cell growth producing tissue with cells of varying size, shape and appearance.	May be a strong precursor to cancer, e.g. in the cervix or respiratory tract.

3. Cell Injury

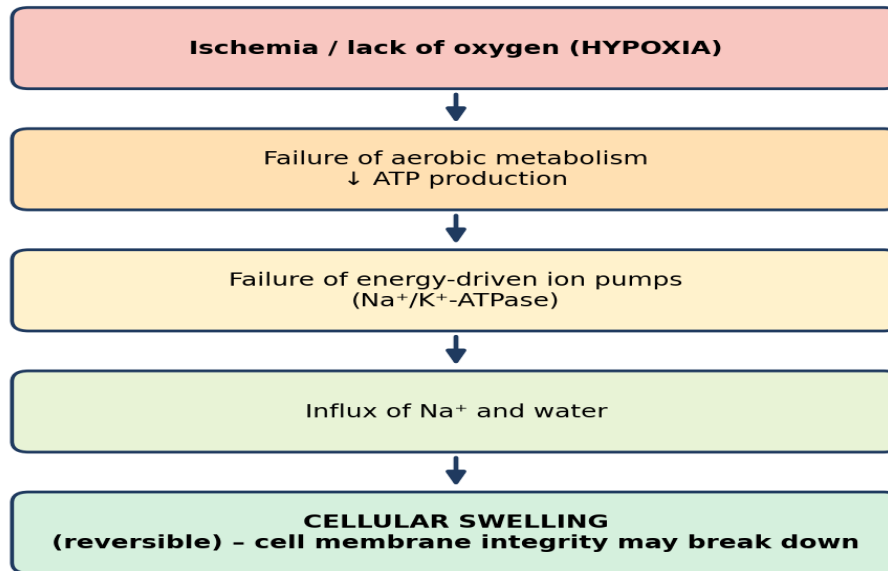
Injury is manifested as functional and morphologic changes. It is **reversible** if the damaging stimulus is removed; with continuing damage it becomes **irreversible**, at which point the cell cannot recover and dies.

3.1 Causes of Cell Injury

Cause	Details
1. Hypoxia	Lack of oxygen in cells and tissues, generally resulting from ischemia. Aerobic metabolism fails, causing a dramatic decrease in ATP production.
2. Physical agents	Trauma, extremes of temperature, radiation, electric shock, sudden changes in atmospheric pressure.
3. Chemicals and drugs	Injure by altering membrane permeability, osmotic homeostasis or the integrity of enzyme cofactors.
4. Microbiologic agents	Ranging from viruses to tapeworms.
5. Immunologic reactions	The immune system may itself injure cells, e.g. anaphylactic reaction.
6. Genetic defects	e.g. Down's syndrome, sickle cell anaemia.
7. Nutritional imbalances	Protein-calorie insufficiency, vitamin deficiencies; diets rich in animal fat are implicated in atherosclerosis.
8. Aging	Progressive cellular change with age.

3.2 Reversible Cell Injury

Hypoxia → Reversible Cell Injury



If injury persists → irreversible injury and cell death

Figure 3. Sequence of events from hypoxia to reversible cellular swelling.

Cellular swelling is caused by accumulation of water due to failure of energy-driven ion pumps. Breakdown of cell membrane integrity and accumulation of cellular electrolytes may also occur. Cellular swelling is considered a **reversible** change.

3.3 Intracellular Accumulations

Normal cells may accumulate abnormal substances, transiently or permanently, in the cytoplasm or nucleus. The substance may be synthesized by the affected cell or produced elsewhere. Accumulations fall into three categories:

- A normal endogenous substance produced at a normal or increased rate, with an inadequate rate of metabolism – e.g. fatty change of the liver.
- A normal or abnormal endogenous substance that cannot be metabolized because of a genetic enzymatic defect – these diseases are called storage diseases.
- An abnormal exogenous substance deposited because the cell has neither the enzymatic machinery nor the ability to transport it to other sites.

Fatty change (steatosis)

Fatty change is an abnormal accumulation of triglycerides within parenchymal cells. It is most often seen in the liver and is reversible, but may also occur in the heart, skeletal muscle, kidney and other organs.

- **Causes:** toxins, diabetes mellitus, protein malnutrition, obesity and anoxia. Excess triglyceride may result from defects at any step from fatty-acid entry to lipoprotein synthesis.
- **Effect:** mild change may have no effect on function; severe change may transiently impair it.
- **Gross:** the liver enlarges and becomes progressively yellow.
- **Microscopic:** small cytoplasmic vacuoles around the nucleus first appear; they coalesce into clear spaces that push the nucleus to the periphery.

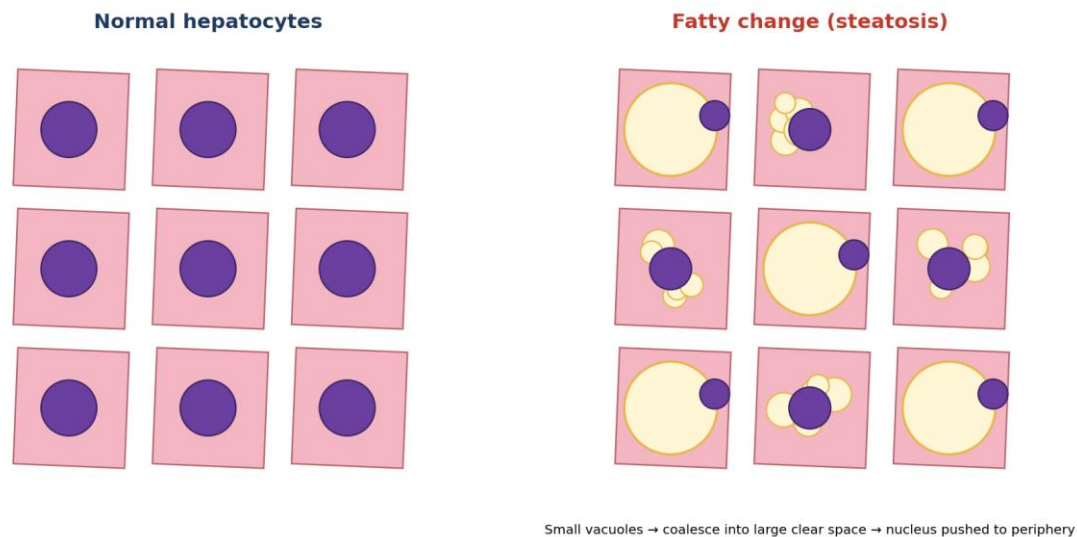


Figure 4. Normal hepatocytes versus fatty change (schematic).

Other accumulations

Substance	Key points
Cholesterol & cholesterol esters	Macrophages in contact with lipid debris of necrotic cells become stuffed with lipid and appear as foamy cells. In atherosclerosis, smooth-muscle cells and macrophages are filled with lipid vacuoles. Xanthomas: accumulation of fat within macrophages of subcutaneous connective tissue, appearing as white nodules.
Proteins	Less common; e.g. glomerular diseases with proteinuria, with accumulation in proximal convoluted tubules.
Glycogen	Seen in abnormal metabolism of glucose or glycogen; appears as vacuoles under the light microscope.

Substance	Key points
Pigments – Melanin	Endogenous; accumulates in basal cells of the epidermis (freckles) or in dermal macrophages.
Pigments – Haemosiderin	Haemoglobin-derived, golden-brown granular pigment; accumulates with local or systemic iron excess.
Pigments – Bilirubin	Derived from haemoglobin but contains no iron. Excess within cells and tissues causes jaundice.

Pathologic calcification

Abnormal accumulation of calcium salts, with smaller amounts of iron, magnesium and other minerals. When deposited in dead or dying tissue it is called **dystrophic calcification** – it occurs despite normal serum calcium and without any derangement of calcium metabolism.

- Seen in areas of necrosis anywhere, in atheromas of advanced atherosclerosis (intimal injury of large arteries), in aging, and in aortic valves.
- Appears as intracellular or extracellular basophilic deposits; heterotopic bone may sometimes form.

3.4 Irreversible Cell Injury

Features

- Severe vacuolization of mitochondria and accumulation of calcium particles.
- Extensive damage of the plasma membrane.
- Swelling of lysosomes.
- Reperfusion with oxygen results in calcium-mediated injury.
- Continued loss of proteins, coenzymes and RNA through hyperpermeable membranes; lysosomal enzymes leak into the cytoplasm, are activated by the reduced pH and degrade cytoplasmic components.
- Dead cells may be replaced by whorled masses of phospholipids (myelin figures).

Mechanisms

- **Progressive loss of membrane phospholipids.**

- **Cytoskeletal abnormalities:** activation of proteases and increased calcium may detach the cell membrane.
- **Toxic oxygen free radicals:** generated after reperfusion of ischaemic areas and released by influxed neutrophils.
- **Lipid breakdown products:** have detergent effects.

4. Free Radical Injury

Free radicals are highly reactive chemical species with one or more unpaired electrons in their outer shell. Examples: superoxide ($O_2^{\bullet-}$), hydroxyl radical ($\bullet OH$) and hydrogen peroxide (H_2O_2).

- They are generated as by-products of normal cell metabolism and inactivated by scavenging enzymes such as catalase and glutathione peroxidase.
- Injury occurs when excess free radicals form from exogenous sources, or when the protective mechanisms fail.
- Exogenous sources: tobacco smoke, organic solvents, pollutants, radiation and pesticides.
- They injure cells through peroxidation of membrane lipids, damage to cellular proteins and mutation of cellular DNA.
- Implicated in normal aging and in diabetes mellitus, cancer, atherosclerosis, Alzheimer's disease and rheumatoid arthritis.

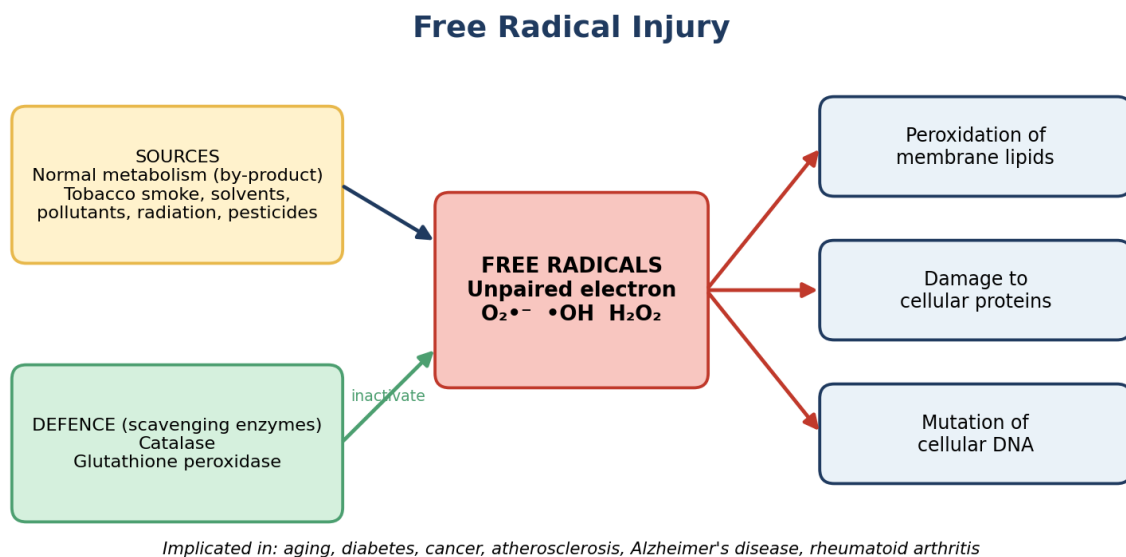


Figure 5. Sources, defences and targets of free radicals.

5. Cell Death

There are two principal patterns of cell death:

	Necrosis	Apoptosis
Nature	Follows exposure to noxious conditions; pathologic	Programmed cell death occurring in normal or physiologic conditions
Features	Cell swelling, protein denaturation, breakdown of organelles	Programmed, regulated cell death

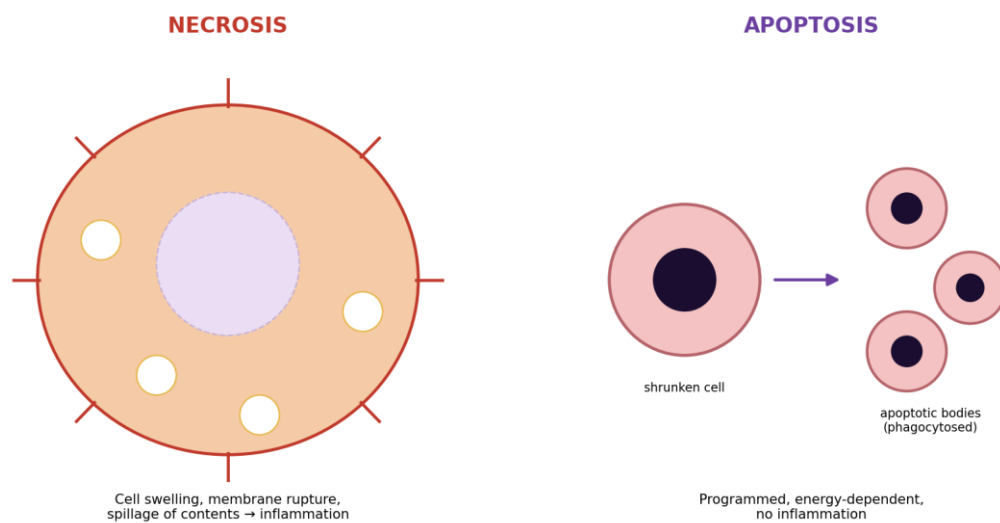


Figure 6. Necrosis compared with apoptosis (schematic).

5.1 Necrosis

Necrosis refers to the sequence of morphologic changes that follow cell death in living tissue; it is the gross and histologic term for cell death in the setting of irreversible exogenous injury. Its appearance results from two processes: enzymatic digestion of the cell and denaturation of proteins. Hydrolytic enzymes may come from the dead cells themselves (autolysis) or from lysosomes of infiltrating leukocytes (heterolysis).

Cytoplasmic changes: increased eosinophilia and glassy appearance due to loss of glycogen, cytoplasmic vacuolation and calcification.

Nuclear changes:

- **Pyknosis:** nuclear shrinkage and increased basophilia (seen mainly in apoptosis).
- **Karyorrhexis:** the pyknotic nucleus fragments.
- **Karyolysis:** fading of the nucleus due to digestion of DNA.

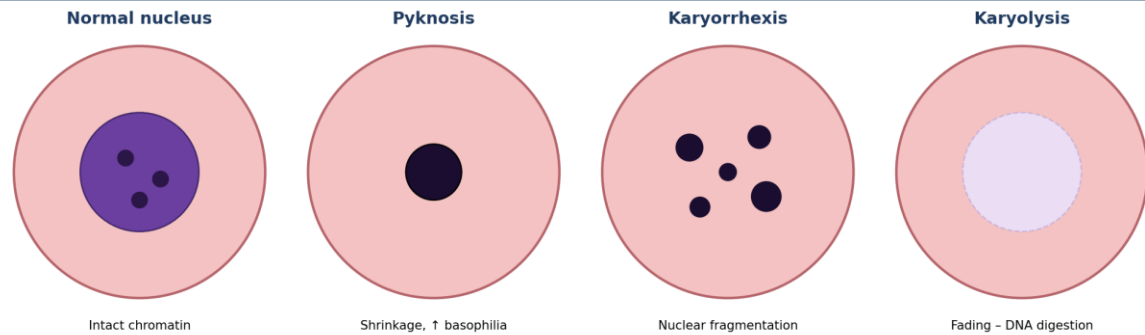


Figure 7. Nuclear changes in necrosis (schematic).

5.2 Types of Necrosis

Types of Necrosis - Key Examples

Coagulative Myocardial infarction (hypoxic death, all tissues except brain)	Liquefactive Bacterial / fungal infection; hypoxic death in the CNS	Gangrenous Ischaemic necrosis + infection ('wet gangrene')
Caseous Tuberculosis – cheesy white amorphous granular debris	Fat necrosis Acute pancreatitis – lipase hydrolyses triglycerides	Fibrinoid Immune vasculitis, e.g. polyarteritis nodosa

Figure 8. Types of necrosis and a key example of each.

Type	Description
Coagulative	Preservation of the structural outlines of the coagulated cell or tissue for days; injury and acidosis denature the enzymes that would cause cellular hydrolysis. Prime example: myocardial infarction (acidophilic, coagulated, anucleate cells). Necrotic cells are removed by fragmentation and phagocytosis by leukocytes. Characteristic of hypoxic death in all tissues except the brain.
Liquefactive	Caused by focal bacterial or fungal infection with accumulation of white cells. Hypoxic cell death in the CNS also produces liquefactive necrosis.
Gangrenous	Not a distinctive pattern, but still used in surgical practice: ischaemic coagulative necrosis with superimposed infection and liquefactive necrosis ("wet gangrene").

Type	Description
Caseous	Seen in tuberculous infection; named for the cheesy, white gross appearance of the central necrotic area. Microscopically: structureless amorphous granular debris within granulomatous inflammation.
Fat necrosis	Focal areas of fat destruction after acute pancreatitis: release of activated pancreatic enzymes causes hydrolysis of triglyceride esters within fat cells of the peritoneal cavity.
Fibrinoid	Seen in immune reactions involving blood vessels: deposition of immune complexes with fibrin leaked from vessels gives a bright pink, amorphous appearance on H&E, e.g. polyarteritis nodosa.

Key Points Summary

- Cells respond to injury by adapting (atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia), by reversible injury, or by irreversible injury leading to death.
- Hypoxia → ↓ ATP → ion-pump failure → cellular swelling (reversible).
- Fatty change is a reversible accumulation of triglycerides, most often in the liver.
- Dystrophic calcification occurs in dead tissue with normal serum calcium.
- Free radicals damage lipids, proteins and DNA; catalase and glutathione peroxidase neutralize them.
- Necrosis: pyknosis → karyorrhexis → karyolysis; six patterns: coagulative, liquefactive, gangrenous, caseous, fat, fibrinoid.

Review Questions

1. List five causes of cell injury.
2. Differentiate hypertrophy from hyperplasia, giving an example of each.
3. Describe the sequence of events by which hypoxia causes cellular swelling.
4. Describe the gross and microscopic appearance of fatty change in the liver.
5. Name the three nuclear changes of necrosis.
6. Which type of necrosis is characteristic of tuberculosis, and which of acute pancreatitis?

Reference:

Kumar, V., Abbas, A. K., Aster, J. C., Debnath, J., & Das, A. (2025). Robbins, Cotran & Kumar pathologic basis of disease (11th ed.). Elsevier.