Over view of cell injury and cell death:
Cell injury results when:

a. cells are stressed so severely that they are no longer able to adapt or
b. when cells are exposed to inherently damaging agents or
c. suffer from intrinsic abnormalities.

Different injurious stimuli affect many metabolic pathways and cellular organelles at the same time. Injury may progress through a reversible, then to irreversible stages and culminate in cell death.

Causes of cell injury
1. Hypoxia, or oxygen deficiency, interferes with aerobic oxidative respiration and is an extremely important and is the common cause of cell injury and death. Hypoxia should be distinguished from ischemia, which is a loss of blood supply in a tissue due to impeded arterial flow or reduced venous drainage. Causes of hypoxia are;
   a. While ischemia is the most common cause of hypoxia, oxygen deficiency can also result from Inadequate oxygenation of the blood, as in pneumonia, or
   b. reduction in the oxygen-carrying capacity of the blood, as in blood loss anemia or carbon monoxide (CO) poisoning. (CO forms a stable complex with hemoglobin that prevents oxygen binding).
2. Chemical agents; An enormous number of chemicals can injure the cells;
   a. even innocuous substances such as glucose or salt, if sufficiently concentrated, can so derange the osmotic environment that cell injury or death results.
   b. Oxygen at sufficiently high partial pressures is also toxic.
   c. Agents commonly known as poisons cause severe damage at the cellular level by altering membrane permeability, osmotic homeostasis, or the integrity of an enzyme or cofactor, and exposure to these poisons can culminate in the death of the whole organism.
   d. Other potentially toxic agents are encountered daily in our environment; these include air pollutants, insecticides, CO, asbestos, and social "stimuli" such as ethanol.
   e. Even therapeutic drugs can cause cell or tissue injury in a susceptible patient or if used excessively or inappropriately.
3. Infectious agents; these range from submicroscopic viruses to meter-long tapeworms; in between are the rickettsiae, bacteria, fungi, and protozoa can cause cell injury.
4. **Immunological reaction**; although the immune system defends the body against pathogenic microbes, immune reactions can also result in cell and tissue injury. Examples include:
   a. autoimmune reactions against one's own tissues.
   b. allergic reactions against environmental substances in genetically susceptible individuals.

5. **Genetic defects**; can result in pathologic changes as conspicuous as the congenital malformations associated with Down syndrome or as subtle as the single amino acid substitution in hemoglobin S giving rise to sickle cell anemia. Genetic defects may cause cell injury because of deficiency of functional proteins, such as enzymes in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair. Variations in the genetic makeup can also influence the susceptibility of cells to injury by chemicals and other environmental insults.

6. **Nutritional imbalances** includes:
   a. nutritional deficiencies remain a major cause of cell injury. Protein-calorie insufficiency among underprivileged populations is only the most obvious example; specific vitamin deficiencies are not uncommon even in developed countries with high standards of living.
   b. Excesses of nutrition are also important causes of morbidity and mortality. Obesity markedly increases the risk for type 2 diabetes mellitus, and diets rich in animal fat are strongly implicated in the development of atherosclerosis as well as in increased vulnerability to many disorders, including cancer.

7. **Physical agents**; include:
   a. Trauma.
   b. extremes of temperatures.
   c. Radiation.
   d. electric shock.
   e. sudden changes in atmospheric pressure.

8. **Aging**; cellular senescence leads to alterations in replicative and repair abilities of individual cells and tissues. All of these changes result in a diminished ability to respond to damage and, eventually, the death of cells and of the organism.

**Morphology of cells and tissue injury**
1. All stresses and noxious influences exert their effects first at the molecular or biochemical level.

2. **Cellular function may be lost long before cell death occurs, and the morphologic changes of cell injury (or death) lag far behind both.** For example, in myocardial muscle fibers after ischemic injury;
   a. myocardial cells become non-contractile after 1 to 2 minutes of ischemia.
   b. although they do not die until 20 to 30 minutes of ischemia have elapsed (cell death).
   c. These myocytes do not appear dead by electron microscopy until 2 to 3 hours after cell death.
   d. The myocytes do not appear dead by light microscopy until 6 to 12 hours after cell death.
   e. The myocytes do not appear dead grossly (by naked eye) until 24 hours or more after cell death.

The types of cell injury are;

1. **Reversible cell injury;** characterized by
   a. Occurs early stages of cell injury or
   b. in cases of mild forms of injury.
   c. functional and morphologic changes are reversible if the damaging stimulus is removed.
   d. Although there may be significant structural and functional abnormalities, the injury has typically not progressed to *severe membranes damage, severe mitochondrial damage,* and *nuclear dissolution.*

**Morphology of cells and tissue injury**

A. **Morphology of cells and tissues with reversible cell injury**

1. **Gross morphology of organ with reversible cell injury are;**
   a. *Increased pallor, turgor, and weight of the organ affected by cellular swelling due to* failure of energy-dependent ion pumps in the plasma membrane.
   b. Enlargement, yellowish discoloration, and organ becomes greasy on touching due to fatty changes. It is seen mainly in cells involved in and dependent on fat metabolism, such as hepatocytes and myocardial cells.
Gross appearance of normal (left) and fatty liver (right)

2. **Light microscopic findings in reversible cell injury are;**
   a. Cellular swelling (hydropic or vacuolar degeneration).
   b. Fatty changes.
   c. Increased cytoplasmic eosinophilia.
   d. Surface blebbing of affected cells.

A- Fatty change of liver (hepatocytes are

B- Cellular swelling of liver (hepatocytes
filled by various sized lipid vacuoles). cytoplasm is clear and dilated).

Morphologic changes in reversible and irreversible cell injury (necrosis). A, Normal kidney tubules with viable epithelial cells. B, Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. C, Necrotic (irreversible) injury of epithelial cells, with loss of nuclei and fragmentation of cells and leakage of contents.

3. Ultrastructural changes of reversible cell injury are:
   a. plasma membrane alterations such as blebbing, blunting or distortion of microvilli, and loosening of intercellular attachments.
   b. mitochondrial changes such as swelling and the appearance of phospholipid-rich amorphous densities.
   c. dilation of the ER with detachment of ribosomes and dissociation of polysomes.
   d. nuclear alterations, with clumping of chromatin.
2. **Irreversible cell injury**: with continuing damage cell injury becomes irreversible and end in cell death. *There are two types cell death which differ in their morphology, mechanisms, and roles in disease and physiology.*

   a. **Cell death by necrosis**: characterized by;
      
      I. Severe damage to membranes, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell.
      
      II. Cellular contents also leak out through the damaged plasma membrane and elicit a host reaction (inflammation).
      
      III. Necrosis is the major pathway of cell death in ischemia, exposure to toxins, various infections, and trauma.

   b. **Cell death by apoptosis**: characterized by;
      
      I. nuclear dissolution without complete loss of membrane integrity.
      
      II. Apoptosis is an active, energy-dependent, tightly regulated type of cell death that is seen in some specific situations.
      
      III. *Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury.*
      
      IV. Apoptosis is seen in cell deprived of growth factors or the cell's DNA or proteins are damaged beyond repair, and in viral infected cells.
Features of necrosis and apoptosis

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<thead>
<tr>
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<th>Necrosis</th>
<th>Apoptosis</th>
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<tr>
<td>Cell size</td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
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<td>Nucleus</td>
<td>Pyknosis – Karyorrhexis - Karyolysis</td>
<td>Fragmentation into nucleosome size fragments</td>
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<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact; altered structure, especially orientation of lipids</td>
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<tr>
<td>Cellular contents</td>
<td>Enzymatic digestion, may leak out of cell</td>
<td>Intact; may be released in apoptotic bodies</td>
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<tr>
<td>Adjacent inflammation</td>
<td>Frequent</td>
<td>No</td>
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<td>Physiologic or pathologic role</td>
<td>Invariably pathologic (culmination of irreversible Cell injury</td>
<td>Often physiologic, means of eliminating unwanted cells, may be pathologic after some form of cell injury, especially DNA damage</td>
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**Morphology of necrosis**

**Cytoplasmic changes of necrotic cells are:**
1. Light microscopic
   a. *Increased cytoplasmic eosinophilia* in (H & E) stains, attributable in part to the loss of cytoplasmic RNA (which binds the blue dye, Hematoxlin) and in part to the fact that (denatured cytoplasmic proteins bind strongly to the red dye eosin).
   b. The necrotic cell may have a glassier and homogeneous appearance than do normal cells, mainly as a result of the loss of glycogen particles.
   c. When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears moth-eaten.
   d. Dead cells may be replaced by large, whorled phospholipid masses called **myelin figures** that are derived from damaged cell membranes.
   e. Dead cells may ultimately have calcified (dystrophic calcification).

2. By electron microscopy;
   a. necrotic cells are characterized by discontinuities in plasma and organelle membranes.
   b. marked dilation of mitochondria with the appearance of large amorphous densities.
   c. intracytoplasmic myelin figures, amorphous debris, aggregates of fluffy materials which probably representing denatured protein.
   d. Profound nuclear changes culminating in nuclear dissolution.

*Morphological patterns of tissue necrosis*
1. **Coagulative necrosis:**
   a. seen in solid organs.
   b. affected tissues grossly are firm texture.
   c. general architecture of dead tissues is preserved at least some days but with loss of cellular details because injury denatures not only structural proteins but also lysosomal enzymes and so blocks the proteolysis of the dead cells.
   d. localized area of coagulative necrosis is called an **infarct**.
Coagulative necrosis. A, wedge-shaped kidney infarct (yellow). B, Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate.

2. **Liquefactive necrosis is seen in two situations:**
   
   a. hypoxic death of cells within the central nervous system.
   
   b. pyogenic bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells. Liberation of enzymes from these leukocytes will digest the dead cells.

Liquefactive necrosis characterized grossly by;

a. In brain infarction digestion of the dead cells, resulting in transformation of the dead tissue into a liquid viscous mass.

b. In pyogenic infection necrotic material is frequently creamy yellow because of the presence of dead leukocytes and is called pus.
3. **Gangrenous necrosis;** is not a distinctive pattern of cell death, term is commonly used in clinical practice. Lower leg, that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers. Two types of gangrene are present;
   a. **Dry gangrene;** when there is no bacterial infection, line of demarcation is clear between dead and viable tissues.
   b. **Wet gangrene;** when bacterial infection is superimposed causing liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes. Line of demarcation is not seen.

4. **Caseous necrosis;** seen in tuberculous infection. The term “caseous” is a gross description of (cheese-like) of the friable white appearance of necrotic tissues. Microscopic examination, the **tuberculoid granuloma** is composed of necrotic area of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border composed of epithelioid macrophages with **Langhan’s giant cells**
and outer rim of small lymphocytes. The lesion is the result of infection *tuberculous bacilli*.

Gross appearance of tuberculous lesion showing caseation

Microscopic appearance of tuberculous granuloma showing central caseous necrosis surrounded by epitheloid macrophages, Langhan’s giant cell and peripheral rim of lymphocytes.
5. **Fat necrosis**; is a term that does not in reality denote a specific pattern of necrosis, it is a focal areas of fat destruction. Either from release of activated pancreatic enzyme “lipases” in acute pancreatitis or due trauma in traumatic fat necrosis of the breast in large pendulous breasts. The released lipases split the triglyceride esters contained within fat cells. The derived fatty acids combine with calcium to produce grossly visible chalky-white areas (**fat saponification**). Histologic examination of necrotic tissues shows shadow of necrotic fat cells, with basophilic calcium deposits, surrounded by an inflammatory reaction.

![Fat necrosis; areas of white chalky deposits represent foci of fat necrosis (saponification)in the mesentery.](image1.png)

![Shadows of necrotic fat cells with calcium deposition.](image2.png)

6. **Fibrinoid necrosis**; is a special form of necrosis usually seen in immune reactions involving blood vessels (vasculitis), when complexes of antigens and antibodies are deposited in the walls of arteries. It is amorphous bright pink in H&E stains, called “fibrinoid” (fibrin-like) by pathologists.
Subcellular response to injury

1. Autophagy

Autophagy refers to lysosomal digestion of the cell's own components, while heterophagy, in which a cell (usually a macrophage) ingests substances from the outside for intracellular destruction. Autophagy is thought to be a survival mechanism in times of nutrient deprivation, such that the starved cell lives by eating its own contents. Lysosomes with undigested debris may persist within cells as residual bodies or may be extruded, such as Lipofuscin pigment.
2. **Induction (Hypertrophy) of Smooth ER:** Smooth ER (SER) is involved in the metabolism of various chemicals. Cells exposed to these chemicals show hypertrophy of the ER as an adaptive response. Patients taking phenobarbital for epilepsy increase their alcohol intake, they may have subtherapeutic levels of the anti-seizure medication because of induction of SER in response to the alcohol.

3. **Mitochondrial alteration:** Mitochondrial dysfunction plays an important role in acute cell injury and death (it is the main source of energy in the cell). In some nonlethal pathologic conditions, however, there may be alterations in the number, size, shape, and presumably function of mitochondria. For example, hypertrophy giant mitochondria (*megamitochondria*), as seen in hepatocytes in various nutritional deficiencies and alcoholic liver disease. Mitochondria decreases in number in atrophic cells.

4. **Cytoskeletal abnormalities:** The cytoskeleton consists of actin and myosin filaments, microtubules, and various classes of intermediate filaments. Abnormality may result in (*Kartagener, or the immotile cilia, syndrome*).

5. **Nuclear changes:**
   - *(Karyolysis)*, a change that reflects loss of DNA because of enzymatic degradation by endonucleases (DNases).
   - **Pyknosis,** characterized by nuclear shrinkage and increased basophilia.
c. **karyorrhexis**, the pyknotic nucleus undergoes fragmentation.