<table>
<thead>
<tr>
<th>Nature and Severity of Injurious Stimuli</th>
<th>Cellular Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Altered Physiologic Stimuli</td>
<td>Cellular Adaptations</td>
</tr>
<tr>
<td>Increased demand, trophic stimulation</td>
<td>Hyperplasia, hypertrophy</td>
</tr>
<tr>
<td>Decreased nutrients, stimulation</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Chronic irritation (chemical or physical)</td>
<td>Metaplasia</td>
</tr>
<tr>
<td>2. Reduced O2; Chemical Injury; Microbial Infection</td>
<td>Cell Injury</td>
</tr>
<tr>
<td>Acute and self-limited</td>
<td>Acute reversible injury</td>
</tr>
<tr>
<td>Progressive and severe (incl. DNA damage)</td>
<td>Irreversible injury (\rightarrow) cell death (necrosis, apoptosis)</td>
</tr>
<tr>
<td>Mild chronic injury</td>
<td>Subcellular alterations in various organelles</td>
</tr>
<tr>
<td>3. Metabolic alterations, genetic or acquired</td>
<td>Intracellular accumulations; calcifications</td>
</tr>
<tr>
<td>4. Prolonged life span with cumulative sublethal injury</td>
<td>Cellular aging</td>
</tr>
</tbody>
</table>
Hyperplasia
1. Physiologic
   • Hormonal
   • Compensatory
2. Pathologic
   • Excessive hormonal stimulation or GFs
   • Fertile soil for cancer

Hypertrophy
1. Physiologic
   • Functional demand
   • Specific hormonal stimulation
2. Pathologic
3. Genes that induce hypertrophy
   a. Genes that encode transcription factors
c-fos; c-jun
   b. Growth factors
      TGF-β; IGF-1; FGF
   c. Vasoactive agent
      α-adrenergic agonist; endothelin-1; angiotensin II

Atrophy (Physiologic or Pathologic)
1. Decreased workload
2. Loss of innervation
3. Diminished blood supply
4. Inadequate nutrition
5. Loss of endocrine stimulation
6. Aging (senile atrophy)
7. Pressure

Metaplasia
1. Reversible change
2. Most common = columnar to squamous
3. Vitamin A deficiency
4. May induce malignant transformation
Causes of Cell Injury
1. Oxygen deprivation
2. Physical agents
3. Chemical agents and drugs
4. Infectious agents
5. Immunologic reactions
6. Genetic derangements
7. Nutritional imbalances

Reversible Cell Injury — the HALLMARK of reversible injury is:
1. Reduced oxidative phosphorylation
2. ATP depletion
3. Cellular swelling

Irreversible Injury and Cell Death
1. Morphologic changes – cell death
2. Necrosis – always pathologic
3. Apoptosis – normal function; not necessarily assoc. with cell injury
Table 1-2 Features of Necrosis and Apoptosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Necrosis</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Pyknosis, karyorrhexis, karyolysis</td>
<td>Fragmentation; nucleosome size (180-200bp)</td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact; altered structure</td>
</tr>
<tr>
<td>Cellular contents</td>
<td>Enzymatic digestion; may leak out of cell</td>
<td>Intact; released in apoptotic bodies</td>
</tr>
<tr>
<td>Adjacent inflammation</td>
<td>Frequent</td>
<td>No</td>
</tr>
<tr>
<td>Physiologic or pathologic role</td>
<td>Pathologic</td>
<td>Often physiologic</td>
</tr>
</tbody>
</table>
1. Cellular response to injury depends on:
   - type of injury
   - its duration
   - its severity

2. Consequences of cell injury depend on:
   - cell type
   - cell state
   - cell adaptability

3. Cell injury results from functional / biochemical abnormalities in:
   - aerobic respiration
   - integrity of cell membranes
   - protein synthesis
   - the cytoskeleton
   - the integrity of the genetic apparatus

Mechanisms of Cell Injury:
1. Depletion of ATP
2. Mitochondrial damage
3. Influx of intracellular Ca++; loss of Ca++ homeostasis
4. Accumulation of O2-derived free radicals (oxidative stress)
5. Defects in membrane permeability
Depletion of ATP

Depletion of ATP to <5-10% of normal levels has effects on many critical cellular systems:

1. Plasma membrane energy-dependent Na\(^{++}\) pump
   - Na\(^{++}\) accumulates intracellularly
   - K\(^{+}\) diffuses out of the cell
   - osmotic pull \(\rightarrow\) cell swelling

2. Cellular energy metabolism is altered
   - increased rate of anaerobic glycolysis
   - glycogen stores rapidly depleted
   - lactic acid accumulation \(\rightarrow\) dec. intracellular pH

3. Failure of the Ca\(^{++}\) pump \(\rightarrow\) influx of Ca\(^{++}\)

4. Depletion of ATP \(\rightarrow\) structural disruption of the protein synthetic pathway \(\rightarrow\) detachment of ribosomes \(\rightarrow\) reduced protein synthesis

5. Irreversible damage to mitochondrial and lysosomal membranes

6. Proteins may become misfolded \(\rightarrow\) trigger the “unfolded protein response” that may lead to cell injury or death
Mitochondria can be damaged by:
1. Increased cytosolic Ca++
2. Oxidative stress
3. Breakdown of phospholipids
   - phospholipase A2
   - sphingomyelin pathways
   - lipid breakdown products

Mitochondrial damage results in:
1. Formation of high-conductance channel (mitochondrial permeability transition) (MPT)
2. Reversible in the early stages
3. MPT can become permanent with continued stimulus
4. Irreversible MPT \( \rightarrow \) death blow to cell

1. Most intracellular Ca++ is sequestered in the mitochondria and ER
2. Ischemia and toxins increase cytosolic Ca++
   - influx of Ca++ across the plasma membrane
   - release of Ca++ from the mitochondria and ER
3. Increased Ca++ activates a number of enzymes:
   - ATPases \( \rightarrow \) hasten ATP depletion
   - phospholipases \( \rightarrow \) membrane damage
   - proteases \( \rightarrow \) breakdown membrane and cytoskeletal proteins
   - endonucleases \( \rightarrow \) DNA and chromatin fragmentation
Accumulation of Oxygen-Derived Free Radicals
(Oxidative Stress)

1. Absorption of radiant energy
2. Enzymatic metabolism of exogenous chemicals or drugs
3. Reduction-oxidation reactions
   - superoxide anion radical (O2-)
   - hydrogen peroxide (H2O2)
   - hydroxyl ions (OH)
4. Transition metals
5. Nitric Oxide (NO)

Effects of Reactive Species:
1. Lipid peroxidation of membranes
2. Oxidative modification of proteins
3. Lesions in DNA

Mechanisms to Remove Free Radicals

1. Antioxidants
   - Vitamin E
   - Vitamin A
   - Ascorbic acid
   - Glutathione
2. Storage and transport proteins
   - Transferrin
   - Ferritin
   - Lactoferrin
   - Ceruloplasmin
3. Enzymes
   - Catalase
   - Superoxide dismutase
   - Glutathione peroxidase
Defects in Membrane Permeability Result In:

1. Mitochondrial dysfunction
2. Loss of membrane phospholipids
3. Cytoskeletal abnormalities
4. Reactive oxygen species
5. Lipid breakdown products → detergent effect on membranes
Two phenomena consistently characterize irreversibility:
1. Inability to reverse mitochondrial dysfunction
2. Development of profound disturbances in membrane function

Histological Reversible Cell Injury:
1. Cellular swelling
2. Fatty change

Ultrastructural Reversible Cell Injury:
1. Plasma membrane alterations
   - blebbing, blunting, distortion of microvilli, creation of myelin figures, loosening of intercellular attachments
2. Mitochondrial changes
   - swelling, rarefaction, small amorphous densities
3. Dilation of the ER
   - detachment and disaggregation of polysomes
4. Nuclear alterations
   - disaggregation of granular and fibrillar elements

Figure 1-17 Morphologic changes in reversible and irreversible cell injury.
A, Electron micrograph of a normal epithelial cell of the proximal kidney tubule. Note abundant microvilli (mv) lining the lumen (L). N, nucleus; V, apical vacuoles (which are normal structures in this cell type).

B, Epithelial cell of the proximal tubule showing reversible ischemic changes. The microvilli (mv) are lost and have been incorporated in apical cytoplasm; blebs have formed and are extruded in the lumen (L). Mitochondria are slightly dilated. (Compare with A.)

C, Proximal tubular cell showing irreversible ischemic injury. Note the markedly swollen mitochondria containing amorphous densities, disrupted cell membranes, and dense pyknotic nucleus. (Courtesy of Dr. M.A. Venkatachalam, University of Texas, San Antonio, TX.)
**Types of Necrosis**

1. **Coagulative necrosis** – preservation of the basic outline of the coagulated cells
2. **Liquefactive necrosis** – transformation of tissue into a viscous mass
   - Gangrenous necrosis – a limb that has lost its blood supply and undergone coagulative necrosis
3. **Caseous necrosis** – a distinctive form of coagulative necrosis; most often a foci of tuberculous infection
4. **Fat necrosis** – focal areas of fat destruction

**Ischemic and Hypoxic Injury**

1. Ischemia tends to injure tissues faster than does hypoxia
2. If O2 is restored, all of the disturbances are reversible
3. If ischemia persists, irreversible injury and necrosis ensue

**Ischemia-Reperfusion Injury**

1. Damage may be initiated during reoxygenation by increased generation of oxygen free radicals
2. Reactive oxygen species can further promote the MTP → may lead to cell death
3. Ischemic injury is associated with inflammation; production of cytokines; increased expression of adhesion molecules
4. Activation of Complement pathway

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**Figure 1-22**

![Diagram illustrating reversible and irreversible injury processes](https://example.com/figure122.png)
Chemical Injury
1. Some chemical can act directly by combining with some critical molecular component or cellular organelle
2. Others must be converted to reactive toxic metabolites
   - P45 mixed function oxidase in SER

Examples:
- Carbon tetrachloride: $\text{CCl}_4 \rightarrow \text{CCl}_3 + \text{Cl}^-$
- Acetaminophen is detoxified by interaction with GSH
Causes of Apoptosis

Physiologic:
1. The programmed destruction of cells during embrogenesis
2. Hormone-dependent involution in the adult
3. Cell deletion in proliferating cell populations
4. Acute inflammatory reaction; immune response
5. Elimination of potentially harmful self-reactive lymphocytes
6. Cell death induced by cytotoxic T cells

Pathologic:
1. Injurious stimuli – radiation, cytotoxic chemotherapy
2. Viral diseases
3. Pathologic atrophy in parenchymal organs after duct obstruction
4. Cell death in tumors

Morphology of Apoptosis
1. Cell shrinkage
2. Chromatin condensation
   - the MOST CHARACTERISTIC feature of apoptosis is chromatin condensation with chromatin aggregates at the periphery
3. Cytoplasmic blebs and apoptotic bodies
4. Phagocytosis of apoptotic cells or cell bodies

Biochemical Features of Apoptosis
1. Protein cleavage
   - cysteine proteases (caspases)
2. DNA breakdown
   - formation of oligonucleosomes (180-200 bp)
3. Phagocytic recognition
   - apoptotic cells express phosphatidylserine in the outer layers of the membrane
   - cells may also express thrombospondin, an adhesive glycoprotein
   - these are recognized by MØ
Bcl-2 Family Members
1. Pro-apoptotic
   Bak
   Bax
   Bim

2. Anti-apoptotic
   Bcl-2
   Bcl-x

Caspases
1. Initiator caspases
   caspase-8
   caspase-9

2. Executioner caspases
   caspase-3
   caspase-6

Examples of Apoptosis
1. GF deprivation
2. DNA damage-mediated apoptosis
3. TNF family of receptors
4. Cytotoxic T-lymphocyte-mediated
   - perforin
   - granzyme B

Figure 1-28 Mechanisms of apoptosis.

(1) are some of the major inducers of apoptosis. These include specific death ligands (tumor necrosis factor [TNF] and Fas ligand), withdrawal of growth factors or hormones, and injurious agents (e.g., radiation). Some stimuli (such as cytotoxic cells) directly activate execution caspases (right). Others act by way of adapter proteins and initiator caspases, or by mitochondrial events involving cytochrome c.

(2) Control and regulation are influenced by members of the Bcl-2 family of proteins, which can either inhibit or promote the cell's death.

(3) Executioner caspases activate latent cytoplasmic endonucleases and proteases that degrade nuclear and cytoskeletal proteins. This results in a cascade of intracellular degradation, including fragmentation of nuclear chromatin and breakdown of the cytoskeleton.

(4) The end result is formation of apoptotic bodies containing intracellular organelles and other cytosolic components; these bodies also express new ligands for binding and uptake by phagocytic cells.
The Extrinsic (Death Receptor-Initiated) Pathway
FasL binds to Fas \(\rightarrow\) 3+ Fas come together and form a binding site for an adaptor protein (FADD- Fas-associated death domain) \(\rightarrow\) this then binds to the inactive caspase-8 \(\rightarrow\) multiple caspase-8 are brought together and they cleave one another \(\rightarrow\) active caspase-8 \(\rightarrow\) this then triggers a cascade of caspase activation \(\rightarrow\) activation of executioner caspases

This pathway is INHIBITED by a protein FLIP which binds to pr-caspase-8 But cannot cleave and activate it

The Intrinsic (Mitochondrial) Pathway
Increased mitochondrial permeability \(\rightarrow\) release of pro-apoptotic molecules (AIF-apoptosis inducing factor) and cytochrome c

Cytochrome c binds to Apaf-1 (apoptosis activating factor-1) \(\rightarrow\) this complex activates caspase-9

AIF enters the cytosol and binds to and neutralizes various inhibitors of apoptosis

Bcl-2 and Bcl-x directly INHIBIT Apaf-1 activation
Primary lysosomes contain:
1. Acid phosphatase
2. Glucoronidase
3. Sulfatase
4. Ribonuclease
5. Collagenase

Lipofuscin pigment = granules of undigested material derived from intracellular lipid peroxidation

Subcellular Responses to Injury
1. Lysosomal catabolism
2. Induction (hypertrophy) of SER
3. Mitochondrial alterations
4. Cytoskeletal abnormalities
   - thin filaments
   - microtubules
   - intermediate filaments (keratin, vimentin, desmin, GFAP, neurofilaments)
Intracellular accumulation of abnormal amounts of substances:
1. a normal cellular constituent accumulates
2. an abnormal substance – exogenous or endogenous
3. a pigment

Three types of abnormalities:
1. normal endogenous substance; rate of metabolism is inadequate
2. normal or abnormal endogenous substance accumulates; genetic or acquired defect in metabolism, packing, transport, secretion
3. abnormal exogenous substance is deposited and accumulates

Types of Accumulations:
1. Lipids
   - steatosis and fatty change (LIVER, HEART, MUSCLE, KIDNEY)
   - cholesterol and cholesterol esters (atherosclerosis, xanthomas, inflammation and necrosis, cholesterolosis, Niemann-Pick disease type C
2. Proteins
   - reabsorption droplets in PCT kidneys
   - synthesis of excessive amounts
   - defects in protein folding ➔ may lead to “unfolded protein response”
3. Hyaline change
4. Glycogen
   - glycogen storage diseases
   - DM
5. Pigments
   - exogenous pigments (carbon, tattoo)
   - endogenous pigments (lipofuscin, melanin, hemosiderin)

**Systemic overload of iron, hemosiderin is deposited in many organs and tissues; a condition called hemosiderosis and is seen with:**
1. increased absorption of dietary iron
2. impaired use of iron
3. hemolytic anemias
4. transfusions
**Pathologic Calcification**
1. Dystrophic calcification – occurs locally in dying tissues; NORMAL serum Ca++ levels

2. Metastatic calcification – occurs in normal tissues; almost always results from HYPERCALCEMIA
   - increased secretion of PTH
   - destruction of bone tissue
   - vitamin D-related disorders
   - renal failure

**Metastatic calcification occurs in the following:**
1. Gastric mucosa
2. Kidneys
3. Lungs
4. Systemic arteries
5. Pulmonary veins

**Cellular Aging**
1. Telomere shortening ultimately results in cell cycle arrest
2. Telomerase = lengthens the telomeres by nucleotide addition