Cell injury and adaptation

Normally cells of the body are in equilibrium with the external micro-environment this is called **Homeostasis**. The equilibrium between cells and their microenvironment includes both **Chemical** (electrolytes, glucose, pH, etc.) and **Physical** (e.g. temperature) states. **Stress** is any insult disturbances of cellular chemical and physical states. Internal regulatory mechanisms counteract stress and lead to cellular changes, these changes are called cellular **adaptations** that aim to preserve cell viability and prevent cell injury. If the adaptive ability of the cell is exceeded or the stress inherently harmful (e.g. high temperature), **cell injury** occurs.

**Cellular adaptation:**

Cellular changes that aim to preserve cell viability and prevent cell injury. The adaptive responses include:

1. Atrophy
2. Hypertrophy
3. Hyperplasia
4. Metaplasia
5. Hypoplasia
6. dysplasia

**1. Atrophy**: decrease in cell size by loss of cell substances. When sufficient numbers of cells are involved, the entire organ decreases in size. The cells become smaller with diminished function and reduced metabolic needs to escape injury.

Causes:

1. Decrease workload e.g. muscular atrophy due to immobilization in fracture limb.
2. Denervation (loss of nerve supply) as in paralysis.
3. Ischemia (decrease of blood supply)as in aging
4. Malnutrition as in starvation
5. Loss of endocrine stimulation eg atrophy of uterus and endometrium after menopause.

2. Hypertrophy: increase in the size of the cells which may lead to increase of the size of the tissue or organ. Hypertrophy occurs due to synthesis of more structural components within the cells (more enzymes, mitochondria, filaments … etc) to compensate the increased demand. it could be:

1. Physiological: eg uterus during pregnancy and skeletal muscles in athlete.
2. Pathological: left ventricle hypertrophy due to systemic hypertension.

3. Hyperplasia: increase in number of cells. Hypertrophy and hyperplasia are closely related and often occur together. Not all cell type has the same capacity for division and hyperplasia and accordingly cells are divided to:

1. Labile cells: include epidermis, mucosal surface, hepatocytes, fibroblasts and bone marrow cells.
2. Permanent cells: include nerve cells, myocardium and skeletal muscle fibers
3. Intermediate cells: include bone, cartilage and smooth muscle cells.

Hyperplasia could be:

1. Physiologic: either Hormonal as hormonal effect on breast during puberty and pregnancy or Compensatory when part of tissue is removed: kidney, liver
2. Pathological: eg endometrial hyperplasia after excessive hormonal therapy and prostatic hyperplasia

4. Metaplasia: replacement of one mature cell type by another mature cell type. It may represent replacement of cells sensitive to stress by another cells which are more resistant. It is a genetic “reprogramming” of stem cells and not changing of already differentiated cells. examples for metaplasia include:

1. Squamous metaplasia of laryngeal and bronchial respiratory epithelium due to habitual smoking.
2. Squamous metaplasia of urothelium of urinary bladder due to bilharzia or stone.
3. Columnar metaplasia of esophageal squamous epithelium as aresult of gastric juice reflex (**Barrett esophagus**).

**5. hypoplasia:** Incomplete development of an organ so that it fails to reach adult size. It can occur at any organ in the body especially paired organs.eg hypoplastic kidney or hypoplastic ovary.

**6.** **Dysplasia**: Disturb organization and orientation of the cells. Sever dysplasia equal intraepithelial neoplasia. Chronic irritation by radiation, inflammation considered the major cause.

**Cell injury**

Occur in two situations:

1. The limits of adaptive response are exceeded.
2. When there is no enough time for adaptive responses to take place as in sever injurious agent.

Cell injury divided to:

1. **Reversible cell injury**: cellular changes will regress and disappear when the injurious agent is removed i.e. cells return to normal both morphologically and functionally e.g. cellular swelling (hydropic changes) and fatty changes.

2. **Irreversible cell injury (cell death):** in which cell death is inevitable e.g. mitochondrial damage and autolysis by lysosomal enzymes.

Causes of cell injury:

1. Hypoxia: oxygen deprivation
2. Physical agents: trauma, heat, cold and radiation
3. Chemical: poisons (cyanide), pollutants, alcohol, smoking
4. Infectious agents: bacteria, viruses, fungi and parasites.
5. Immunological: hypersensitivity reactions and autoimmune diseases.
6. Genetic derangements: chromosomal genetic defect eg downs syndrome or single gene defect sickle cell anemia.
7. Nutritional imbalance: include both excess and deficiency

Injurious agents induce cell injury through their effect on one or more of the following five cellular targets:

1. Aerobic respiration
2. Cell membranes
3. Protein synthesis
4. Cytoskeleton
5. Genetic apparatus (chromosomes)

**Mechanisms of cell injury:**

**First: ATP depletion:**

Hypoxia and toxic chemicals are the main causes for ATP depletion. Depletion of ATP produces the followings:

**A. Reduction of the activity of energy dependent plasma membrane sodium pump.** This causes Na+ to be restricted inside the cell and K+ outside. An increased intracellular Na+ results in water retention that leads to cell edema.

**B.** **Switch to anaerobic glycolysis.** If ATP depletion due to hypoxia, this will block oxidative phosphorylation for ATP production and cells undergo anaerobic glycolysis to maintain energy and ATP production. This anaerobic glycolysis will produce lactic acid that decreases intracellular PH (acidic cytoplasm) which interferes with the optimal activity of many cellular enzymes.

**C. increase in intracellular Ca+:** failure of Ca+ pump leads to influx of Ca+ that have damaging effect on many cellular components.

**D. Structural disruption of the protein synthesis apparatus.** With prolong ATP depletion there will be reduction in protein synthesis due to:

1. Detachment of ribosomes from rough endoplasmic reticulum rough ER.
2. Dissociation of polysomes to monosomes.

**E. Unfolded protein response.** A protein is initially a linear polymer of amino acids linked together by peptide bonds synthesized within ribosomes. Then these linear proteins are drawn into ER where they acquire their folded configuration. They are transported by vesicles to Golgi apparatus. ATP depletion leads to misfolded or unfolded proteins. These abnormally configured protiens cannot be mobilized and this leads to their accumulation within the ER.

**Second: Loss of cell membranes permeability and cell membrane damage.**

The damage is not limited to the cell membrane only but may also involve that of mitochondria, ribosomes and lysosomes. Cell membrane damage in cell injury result from activation of intracellular enzymes that include: ATPase, phospholipases, proteinases and endonucleases which occur due to increase in intracellular Ca+. Some bacteria like bacteria of gas gangrene can directly damage cell membrane by phospholipase enzyme that elaborated from these bacteria.

**Third: accumulation of oxygen derived free radicals (oxidative stress).**

Oxygen-derived free radicals (OFR) are produced as a byproduct of mitochondrial respiration. These are chemically reactive, having single unpaired electron in the outer orbit. OFR include: o2- (superoxide), H2O2 (hydrogen peroxide), OH- (hydroxyl radicle) and 1 O (singlet oxygen). OFR can damage lipids, proteins and nucleic acids leading to various forms of cell injury. Cells normally have defense against OFR by **antioxidan**t materials like glutathione, vit C and others. An imbalance between generation of OFR and level of antioxidant materials in the body called **oxidative stress**.

* + ***Mechanisms of Cell Injury by(FREE RADICALS*)**
* ***Free radicals* can be injured the cells *by the following mechanisms.***

1. **Lipid Peroxidation.**
   * ***Free radicals* attack the *double bonds of polyunsaturated lipid in the membrane*, which result in the formation of *Peroxide* (free radical causes cell injury).**
2. **DNA Fragmentation.**

* ***Free radicals* attack the *Thymine base* in the DNA of nucleus & mitochondria which result in *Single Strand Breaks (SSB).***
* **These (SSB) are implicated in cell killing & the malignant transformation of the cells**

1. **Gross – Linkage of Proteins.**

* ***Free radicals* promote sulfhydryl mediated proteins cross linkage (SH- SH) which result in degradation & loss of enzymatic activities.**
  + ***Inactivation of Free Radicals.***

**Inactivation of free radicals can achieve by the following mechanisms.**

1. **Enhancement the rate of spontaneous decay of free radicals by SuperOxide Dismutase (SOD) which is present in many cell types of body**

**SOD**

**2O2 .-  2H H2O2 + O2**

1. **Glutathione (GSH) Peroxide, which catalyzing the free radicals by the following equation**

**2OH.-  + 2GSH H2O2 + GSSG**

1. **Catalase, which direct the degradation of hydrogen superoxide as the following equation**

**2H2O2  2H2O + O2**

1. **Endogenous or Exogenous antioxidants (Vitamins A, E,C, Beta Carotene), these act either by block the formation of free radicals or removed them as they are formed.**
2. **Plasma Transporting proteins e.g. *Transferrin, Ceruloplasmin,* these will sequestrate the free radicals.**

**Fourth: mitochondrial damage.**

It is the reliable cause for irreversible cell injury. Mitochondria can be damaged by:

1. Increase in cytoplasmic Ca+
2. Oxidative stress
3. Breakdown of mitochondrial membrane phospholipid by activated phospholipases.

All the above causes lead to increase mitochondrial membrane permeability and release of H+ ion and cytochrome-C. H+ ion essential for oxidation phosphorylation and ATP synthesis so leakage of H+ ion depletes ATP. Release of cytochrome-C triggers cell death by apoptosis.

Cell death

There are two modes of cell death:

A. Necrosis B. Apoptosis

**Necrosis: cell death due to degrading action of enzymes on irreversibly damaged cells with denaturation of cellular proteins. cellular swelling and presence of inflammation are characteristic features. It include cytoplasmic as well as nuclear changes**

**Cytoplasmic changes:** in hematoxylin-eosin stain (H&E stain) hematoxylin stains the acidic cell materials (nucleus) blue whereas eosin stains alkaline cell materials (cytoplasm) pink. Necrotic cells cytoplasm becomes more alkaline and stains deeply with eosin (eosinophilic) than viable cells because: Loss of cytoplasmic RNA (RNA acidic material) and increase binding of eosin to denatured protein.

**Nuclear changes:** include

**chromatin clumping** (chromatin aggregation) which is the earliest nuclear changes.after that nucleus

**Either** shrinks and transformed to a wrinkled mass **(pyknosis)** with subsequent disintegration of chromatin and disappearance of nucleus **(karyolysis).**

**Or** the nucleus breaks into many clumps **(karyorrhexis).**

**Types of cell Necrosis:**

**A/Coagulative necrosis:** result from sudden sever ischemia in organs such as heart kidney….

**B/Liquefactive necrosis:** characterized by complete digestion of dead cells by enzymes and the lesion converted into cyst filled with debris. It was seen in two situations:

1. Brain infarct: ischemic destruction of brain tissue.
2. Abscess that occur after suppurative bacterial infection.

**C/Fat necrosis:** specific pattern of cell death seen in adipose tissue due to action of lipase enzyme as in acute pancreatitis. Also can be seen after trauma of fatty tissue e.g. of trauma of female breast.

**D/Caseous necrosis (caseation):** have the combined features of both coagulative and liquefactive necrosis seen in the center of TB granuloma.The **term caseous** is derived from the cheesy white gross appearance of the area of necrosis.

**E/Gangrenous necrosis:** it is surgical term represents combination of coagulative necrosis (ischemia) of tissue followed by liquefactive necrosis by liquefactive action of enzymes derived from bacteria and inflammatory cells.

* Gangrene is classified into 3 types -  
  **1. Dry gangrene  
  2. Wet gangrene  
  3. Gas gangrene**

**A. Dry Gangrene**

* occurs in the distal part of the limb **due to ischemia**,
* Typical examples of a dry gangrene are **on the toes and feet of an old patient due to Atherosclerosis.**
* Usually initiated at the toe region which is farthest from the bloody region, and **contains very less blood where invading bacteria to grow into the necrosed tissue.**
* This gangrene **slowly grows** upwards and reaches a point where the blood supply is adequate enough to keep the whole tissue viable.
* The affected part is **dry, shrunken and dark black, resembling** [**mummified**](http://en.wikipedia.org/wiki/Mummification) **flesh. The dark coloration is due to liberation of** [**hemoglobin**](http://en.wikipedia.org/wiki/Hemoglobin) **from hemolyzed red blood cells which is converted by** [**hydrogen sulfide**](http://en.wikipedia.org/wiki/Hydrogen_sulfide) **(H2S) produced by the bacteria, resulting in formation of black iron sulfide that remains in the tissues**
* A **“Line of separation”** is well formed between the gangrenous part and the viable part.

**B. Wet gangrene**

* Usually occurs in the **moist tissues and organs such as the Mouth, Bowel, Lung, Cervix, and Vulva** etc.
* **Diabetic leg** & **Bedsores** are other examples with high sugar contents in the necroses tissue which is favorable for the bacteria to grow.
* Wet gangrene usually **develops rapidly due to blockage of venous and less commonly arterial blood flow from thrombosis or embolism.**
* At the affected part, **stuffed blood encourages the formation and growth of the invading bacteria. And the toxic products formed by the bacteria are absorbed causing the systemic manifestations of septicaemia, and then finally to death.**
* There is **no clear demarcation of any line of separation**.

**C. Gas gangrene**

* is a special form of wet gangrene that is caused by a gas-forming **Clostridia**([Clostridium perfringens](http://en.wikipedia.org/wiki/Clostridium_perfringens)) which is a gram positive anaerobic bacteria) which enters into the tissues through open contaminated wounds, normally in the muscles
* Or this invasion can also occur as a compilcation of operation on colon which usually contains the bacteria Clostridia.
* The bacteria produce many toxins which can produce necrosis and oedema locally and are absorbed producing systemic manifestations.

**Apoptosis:** distinct pattern of cell death differs from necrosis in that it is an internally controlled energy - dependent process for deletion of unwanted cells without damage to the tissue that containing them (**without inflammation**).cells undergo apoptosis showing cytoplasmic membrane blebs and cells fragmented to apoptotic bodies engulfed by phagocytosis. Apoptosis can occur in:

1. During embryogenesis for organ morphogenesis and remodeling.
2. Hormone dependent involution eg shedding of endometrium during menstrual cycle.
3. Physiological Deletion of aged cells of blood, skin, intestinal epithelia
4. Deletion of inappropriately proliferated cells eg tumor cells.

Intracellular accumulation

Under certain circumstances, cells may accumulate abnormal amounts of various substances. The accumulated substances may be:

1. Normal cellular constituents accumulated in excess eg lipid, protein and CHO. they are examples of reversible cell injury and include fatty liver changes and accumulated protein drops in the epithelia of proximal convoluted tubules in case of protein urea.
2. An abnormal molecules produced by abnormal metabolic pathway. This can result from genetic mutation that produce changes in protein folding and transport.
3. Accumulation of pigmets. Colored substances accumulated because cells cannot get rid of it through enzymatic degradation or to transport it to the outside. This can include accumulation of melanin pigment, anthracosis (accumulation of carbon pigment) and tattooing.

Degenerative changes:

I//calcification: abnormal deposition of ca++ salts. There are two types

1. dystrophic calcification: ca++ deposition in nonviable or dying tissue that occur despite normal serum ca++. This type may be seen in:

a. area of necrosis (any type of necrosis)

b. advanced atherosclerosis

c. damaged or aged heart valves

2. metastatic calcification: ca++ deposition in viable tissue. It is almost always reflect serum hypercalcemia.

The FOUR principal causes of hypercalcaemia;  
- Increased PTH  
- Destruction of bone  
- Vit D related disorders  
- Renal failure  
  
METASTATIC calcification may occur widely throughout the body but mainly affects the interstitial tissues of the GASTRIC MUCOSA, KIDNEYS, LUNGS, SYSTEMIC arteries and PULMONARY VEINS. These tissues excrete acid and therefore have an internal alkaline medium that predisposes them to metastatic calcification.

II//hyaline change: this refers to intra or extracellular homogenous pinkish alteration in section stained by hematoxylin and eosin stain.

**Intracellular hyaline changes:**

1. hyaline droplet in renal tubules in patients with proteinuria
2. russel bodies in plasma cells
3. viral inclusions
4. alcoholic hyaline in liver cells (Mallory bodies)

**extracellular hyaline changes**

1. collagen in old scar
2. in arteriolar wall in patients with hypertension and diabetes

In REVERSIBLE injury, there is:  
- CELLULAR swelling   
- ORGANELLE swelling  
- BLEBBING of the plasma MEMBRANE  
- DETACHMENT of RIBOSOMES from the ER   
- nuclear CHROMATIN CLUMPING  
- DECREASED ATP generation  
- loss of cell membrane integrity  
- defects in protein synthesis  
- cytoskeleton damage   
- DNA damage  
  
To enter the "point of no return", or irreversible injury, the cell it goes through the various stages of reversible injury, so features often may overlap. However, nucleus DESTRUCTION in IRREVERSIBLE injury includes PYKNOSIS - KARYORRHEXIS and KARYOLYSIS.   
  
Other features of irreversible cell injury include:   
- LYSOSOMAL rupture  
- DISRUPTION of the cellular MEMBRANES and DEPLETION of ATP.