Degenerative changes, Intracellular accumulations and pathologic calcification.

- Cells tend to maintain their intracellular milieu within a fairly narrow range of physiologic parameters; they maintain homeostasis.
- As cells encounter physiologic stresses or pathologic stimuli, they undergo adaptation achieving a new steady state and preserving viability and function.
- The principle adaptive responses are **hypertrophy, hyperplasia, atrophy and metaplasia**
- If the adaptive capability is exceeded or if the external stress is inherently harmful, cell injury develops.
- Within certain limits injury is reversible, and cells return to a stable baseline; severe or persistent stress results in irreversible injury and death of the affected cells
- Cell death is one of the most crucial events in the etiology and morphologic changes of pathology.

- Cell death is also a normal and essential process in embryogenesis, development of organs and the maintenance of homeostasis.
- Reversible injury occurs in the early stages when the injury is mild.
- Cell death - with continuing damage, the injury becomes irreversible and cell death results; 2 types of cell death: **apoptosis and necrosis**.

- When severe damage of membrane occur, enzymes leak out of the lysosomes, enter the cytoplasm and digestion of the cell, resulting in necrosis.
- Cellular contents also leak out through a damaged plasma membrane eliciting a host reaction (inflammation).
- Necrosisis a major pathway of cell death in commonly countered injuries, such as ischemia, exposure to toxins, various infections and trauma.
- When a cell is deprived of growth factors or the cell`s DNA or proteins are damaged beyond repair, the cell kills itself by apoptosis, which is characterized by nuclear dissolution without loss of membrane integrity.

- Apoptosis is an active, energy-dependent, tightly regulates type cell death. Whereas necrosis is always a pathologic process, apopotosis serves many normal functions and is not necessarily associated with pathologic chnges.

Causes of cell injury

- Oxygen deprivation
  Hypoxia or oxygen deficiency in ischaemia and infarction.
- Chemical agents.
- Infectious agents e.g. Rickettsial, bacterial, fungal, protozoal etc.
- Immunologic reactions; autoimmune diseases or allergic diseases causing cell death.
- Genetic defects
  Enzyme deficiencies and inborn errors of metabolism or accumulation of damaged DNA or misfolded proteins-trigger cell death
- Nutritional imbalances: excesses or deficiencies

- Physical agents e.g. trauma, extreme of temperatures, radiation, electric shock, sudden changes in atmospheric pressure.
- Aging

  Cellular senescence leads to alteration of replicative and repair abilities of individual cells and tissues.

  These changes result in diminished ability to respond to damage and eventually the death of cells and of the organism.

REVERSIBLE CELL INJURY

- 2 main features:
  - Cellular swelling - as a result of failure of energy dependent pumps in the plasma membrane leading to inability to maintain ionic and fluid homeostasis.
  - Fatty change.

- The ultrastructural changes in reversible injury;
  Plasma membrane alterations such as blebbing, blunting or distortion of microvilli and loosening of intracellular attachments
  Mitochondrial changes as swelling and the appearance of phospholipid-rich amorphous densities
  Dilatation of the ER with detachment of polysomes
  Nuclear alterations, with clumping of chromatin

Necrosis

- Increased eosinophilia
- Nuclear shrinkage, fragmentation and dissolution
- Breakdopwn of the plasma mebrane and organellar membranes
- Myelin figures
- Leakage and enzymatic digestion of cellular contents

Apoptosis

- Nuclear chromatin condensation
- Formation of apoptotic bodies.

Morphology

- **Coagulative necrosis** - is a form of tissue necrosis in which the component cells are dead but the basic tissue architecture is preserved
- **Coagulative necrosis** is characteristic of infarcts (areas of ischemic necrosis) in all solid organs except the brain.
- **Liquefactive necrosis** is seen in focal bacterial or occassionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest (liquefy) the tissue.

- **Caseous necrosis** is encountered most often in foci of TB infection
- **Fat necrosis** - focal areas of fat destruction
- **Fibrinoid necrosis** is a special form of necrosis usually seen in immune reactions involving blood vessels

Intracellular accumulations

- The substance may be located in the cytoplasm or in the organelles (typically lysosomes) or in the nucleus and it may be synthesised within the cell or may be exogenous substances produced elsewhere.

MECHANISMS

- A normal substance is produced at a normal rate or an increased rate but the metabolic rate is inadequate to remove it e.g. fatty change in the liver.
- A normal or abnormal endogenous substance accumulates because of genetic or acquired defects in its folding, packaging, transport or secretion e.g. in alpha anti-trypsin deficiency .
- An inherited defect in an enzyme may result in failure to degrade a metabolite resulting in storage disorders.
- An abnormal exogenous substance is deposited and accumulates because the cell has neither the enzymatic machinery to degrade the substance nor to transport it to to other sites.

Fatty change/steatosis

- Refers to any abnormal accumulation of triglycerides within parenchymal cells
- Most often seen in the liver but may also occur in heart, skeletal muscle, kidney and other organs
- Caused by toxins, protein malnutrition, DM, obesity and anoxia
- The significance of fatty change depends on the severity and cause of the accumulation; when mild it may have no effect on cellular function
- Most severe fatty change may transiently impair cell function

Cholesterol and cholesteryl esters

- Phagocytic cells may become overloaded with lipids in several different pathologic processes.
- In atherosclerosis, smooth muscle cells and macrophages are filled with lipid vacuoles composed of the above; these give atherosclerotic plaques their characteristic yellow and contribute to the pathogenesis of the lesion.
- In hereditary and acquired hyperlipidemic syndromes, macrophages accumulate intracellular cholesterol; when present in the sub-epithelial conective tiissue of skin or in tendons, clusters of theses foamy macrophages for masses called **xanthomas**

Protein accumulation

- Much less common than lipid accumulations
- In disordes with heavy proteinuria e.g. nephroptic syndrome, pinocytic vesicles containing this protein fuse with lysosomes, resulting in the histologic appearance of pink, hyaline cytoplasm droplets
- Another example is the marked accumulation of newly synthesized immunoglobulins that may occur in some plasma cells forming rounded eosinophilic **Rusell bodies**
- The **Mallory body/alcoholic hyalin** is an eosinophilic cytoplasm inclusion in liver cells that is highly characteristic of alcoholic liver disease
- The neurofibrillary tangle found in the brain in Alzheimer`s disease is an aggregated protein inclusion that contains microtubule-associated proteins and neurofilaments, a reflection of a disrupted neuronal cytoskeleton.

Glycogen

- In poorly controlled DM, glycogen accumulates in the renal tubular epithelium, cardiac myocytes and the beta cells of the islets of langerhans
- Glycogen accumulates within cells in **GSDs** or **glycogenoses**

Pigments

- Pigments are colored substances that are either endogenous or exogenous (carbon is the most common)
- When the carbon is inhaled it is phagocytosed by alveolar macrorphages and transported to regional tracheobronchial lymph nodes.
- Aggregates of the pigment blacken the draining lymph nodes and pulmonary parenchyma (**anthracosis**)
- Heavy accumulations may induce **emphysema** or a fibroblastic reaction that can result in **coal worker`s pneumoconiosis.**
- Endogenous pigments include lipofuchsin, melanin and certain derivatives of hemoglobin

Calcificaton

- It implies the anbormal deposition of calcium salts together with smaller amounts of magnesium, iron etc.
- **Dystrophic calcification** occurs within dead or dying tissues; in the absence of calcium metabolic derangements.
- The deposition of calcium salts in normal tissue is known as **metastatic clacification** and almost always reflects some derangement in calcium metabolism (hypercalcemia).

ASSIGNMENT: Amyloidosis

- Definition
- Pathogenesis
- Classification and types
- Presentation
- Complication