**LECTURE 5**

**METHODS & PRINCIPLES OF DIAGNOSIS**

***Aspects of Pathology and methods of studying* pathology** involves 4 steps/aspects;-

1. studying the injury cause
2. Pathogenesis or progression from the injury
3. Alterations of structures & morphology from the injury on cells
4. Functional alterations of the cells

**CELLULAR RESPONSE TO INJURY**

**Non lethal changes**

A. ***Cell swelling***

1. Initial response to metabolic disruptions.
2. Cellular hypoxia causes decreased ATP production.
3. Na-k pump cannot remove intracellular Na; therefore, Extracellular fluid enters cell.
4. Organs can be affected
5. Reversible.

B. ***Intracellular accumulations***

 (a) Lipid accumulation

1. Fatty changes occur in cytoplasm of parenchymal cells.
2. Can lead to necrosis, fibrosis, scarring, and functional impairment of organ.
3. Fatty liver common in alcoholism (triglycerides).
4. Occassionally, in heart its due to hypoxia, in kidney due to poisons, and in intestine its due to obesity.

 (b) Glycogen depositions

* Genetic disorders (e.g. glycogen storage diseases).
* Diabetes mellitus. Proximal tubules and liver store glycogen.

 (c) Pigmentation

 1). Lipofuscin.- wear & tear pigment. Accumulates with age in injured cells. Also, brain, liver heart and ovaries of elderly. No associated dysfunction.

Causes includes:- aging, malnutrition, wasting illness, pts receiving radiotherapy.

2). Melanin.- Absorbs light and protects skin from sun.

* Addison's disease. Excess deposits
* Melanomas. Arise from melanocytes

 Aging. Decreased activity and pale skin. Also hyperpigmentation of lentigines (liver spots)

 (d). Hemosiderin, formed from excess iron.

* Increased dietary iron or impaired use.
* Hemoglobin derived (e.g. bruise).
* Hemosiderosis. Deposits in organ and tissues. Usually no dysfunction.

 (e). Calcification. Abnormal accumulation in skin, soft tissues, blood vessels, heart, and kidneys.

* Dystrophic calcification. Calcium forms in areas of unresolved healing.
* Metastatic calcification.
* Calcium-phosphorous imbalance with increased circulating calcium.

 (f). Hyaline infiltration. Homogeneous, glassy, pink inclusion or staining.

* Intracellular hyaline changes. Excess protein, Immunoglobin, viral nucleoproteins, and fibrils.
* Extrcellular hyaline. Precipitated plasma proteins and other proteins across a cell membrane (e.g. arterioles and renal glomeurli).

C. ***Adaptation***

Definition. Return of the internal environment of the body to normal balance after exposure to some alteration. Adaptive cellular responses include:

Increase normal cellular constituents.

Accumulate abnormal substances.

Change cell size or number.

a) Atrophy. Decrease in cell size due to reduction in cell substance

1. Physiologic atrophy. Survival of cells with decreased functions due to aging (e.g. thymus, uterus).
2. Pathologic atrophy. Examples include

 Decreased workload of muscles results in decreased size (e.g. casted limb), disuse atrophy

 Spinal cord injury resulting in loss of nervous enervation to muscles, denervation injury

 Chronic ischemia to lower limbs.

b) Dysplasia.

1. Atypical changes due to chronic irritation.
2. Epithelial cells usually (e.g. bronchi of smokers and cervical epithelium)
3. Closely related to malignancy.

c) Hypertrophy

Increased cell size, tissue mass and functional capacity without an increased in cell number.

1. Can occur due to increased workload, organelles increased in number (e.g. mitochondria).
2. Physiologic hypertrophy (uterus increase in size due to increase of oestrogen at puberty, )
3. Pathologic hypertrophy (e.g. myocardium)

d) Hyperplasia.

1. Increase in tissue mass due to an increase in number of cells. Cells divide.
2. Physiologic hyperplasia. Puberty and pregnancy
3. Compensatory hyperplasia. Abnormal stimulation of organ (e.g. thyroid and parathyroid)

e) Metaplasia

-Change of fully differentiated cell type to another type.

-Reversible change in which one mature type of cell is replaced by another mature type of cell that is more suited to the environment.

*Causes of metaplasia include:*

* Tobacco smoke, which may lead to conversion of pseudostratified

ciliated columnar epithelium to stratified squamous epithelium

in the bronchi

* Chronic infection of the endocervix, which may cause conversion

of simple columnar epithelium to stratified squamous epithelium

* Chronic reflux of gastric acid into the esophagus, which may

lead to replacement of the stratified squamous epithelium of

the esophagus with simple columnar surface mucous cells of

the stomach (Barrett epithelium); Barrett’s also includes columnar

cells of the intestinal type

* Chronic gastritis, which may cause replacement of the surface

mucous cells of the stomach by simple columnar absorptive

and goblet cells of the small intestine -*intestinal metaplasia*

* Chronic inflammation of the bladder, which may cause conversion

of transitional epithelium to simple columnar epithelium

* In chronic bronchitis, Columna-ciliated goblet cell is replaced by stratified squamous epithelium cells.

-Closely related to malignancy.

**Lethal Changes/Cell Death**

The injured cell may undergo a lethal change.

***Apoptosis:*** - also known as programmed cell death. Physiological cell death involves the activation of an internal suicide mechanism/ program, which results in cell death.

*-Apoptosis sequence* may be initiated by receptor-ligand interactions at the cell membrane. When transmembrane receptors for TNF and *Fas* are activated, *‘‘death domain’’* sequences in the receptors cytoplasmic ends serve as docks for proteins that lead to a cascade of *caspase proteases* that initiate cell death

-Apotposis can as well be initiated by opening of MPTP which in turn results into leakage of cytochrome cinto cytoplasm leading to apoptosis..

-It can also be activated by p53,which is due to accumulation of p53 as a result from severe cell stress(hypoxia…) . p53 acts as a tumor suppressor gene and is crucial in downregulation or upregulation in cell cycles.

Apoptosis is important in;-

1. Apoptosis is important in development, and is often activated for the detection and removal of damaged or infected cells.
2. It is important in deletion of mutant cells or those with DNA defects
3. Important in elimination of infected cells by viruses.
4. Elimination of self-recognizing lymphocytes clones in immunological processes.

However ***necrosis***, or pathological cell death, is not regulated and is injurious to the cell, and is caused by exogenous stress.

Injury and death of cells due to lack of oxygen is a common cause of cellular injury and death. This kind of Cell or tissue death is referred to as necrosis.

There are two main types of necrosis; -coagulative and liquefactive necrosis. Other types of necrosis involve combinations or predominance of these main types.

**Types of necrosis:**

1. Coagulative; - Mainly seen in areas of lack of blood supply (eg heart and kidney). The architectural outline of cell is preserved, nucleus lost. Phagocytozed. protein denaturization is predominant than enzymatic breakdown.
2. Liquefactive; - Release of lysosomes causes liquefaction of cell (eg brain infarct or
bacterial lesion). The tissue is enzymatically digested by the released enzymes.
* *Caseous.* A type of liquefactive necrosis with a soft central area of necrosis surrounded by cheesy, crumply appearance. Cellular architecture is destroyed and may be surrounded by calcium (eg tuberculosis).
* *Fat*. Mainly in fat rich tissues and organs and involves the lipase enzyme. Lipase enters fat storage area (eg pancreatic necrosis). There is enzyme digestion of lipids and the released fatty acids combine with calcium to form a chalky substance.
* *Fibrinoid necrosis*is characterized by the fibrinlike accumulation of eosinophilic plasma proteins in the walls of injured blood vessels and may be associated with immune-mediated arteritis.

 c)Gangrene; - Combination of coagulative and liquefactive necrosis.

* Dry gangrene. Coagulative pattern dominates.
* Wet gangrene. Liquefactive pattern dominates.
* Gas gangrene. Due to clostridia (gram-positive anaerobe), for example tetanus, botulism, and food poisoning. Bubbles and blue black appearance. If enter bloodstream, shock and DIC

*Differences between Necrosis & Apoptosis*

**Necrosis Apoptosis**

1. No gene activation or protein signaling - Engages signaling cascades of cell
2. Usually involves large area of -Usually involves one or small

tissue or organ groups of cells

1. Cell and organelle swelling -Nuclear fragmentation and pyknosis
2. Usually elicits inflammatory response -inflammatory response unusual

1. Injurious to organism -Important in organism development
2. Cell death results in pathology -Cell death crucial in cell number regulations
3. DNA fragmented irregularly -DNA cleaved into regular fragments

**D. Somatic death**

***Biological Aging*;-** functional and structural changes accompany aging.

Reduced nerve conduction, reduced gfr, cardiac contractility, vascular degeneration and general muscle decrease kin vitality, genetic and environmental factors contribute ultimately in aging.

In genetics, every time a cell divides, it losses some telomeres. Telomeres prevents the ends of chromosomes from attaching each other and prevent chromosomes from losing their base pair sequences. When the telomeres become too short ,the chromosomes can nolonger replicate resulting to apoptosis. Telomere shrinkage is one of factors that determine cell lineage longetivity to final death.

***Somatic death*** Involves cessation of respiratory and cardiac function as well as cessation of neuronal activity

***Postmortem changes.***

1. *Rigor mortis*. Depletion of ATP causes stiffening of muscles.(myosin molecules adheres to actin filaments causing muscle rigidity. Occurs within 1-6hrs after death and can last upto 48-60hours)

ATP is required for separation of actin-myosin cross-bridges during muscle relaxation.

Without oxygen, the body may produce ATP via anaerobic glycolysis until it diminishes rendering body unable to break those bridges. Later muscle stiffness is broken by enzymes or decomposition

*There are 4 stages of rigor mortis*🡪autolysis,bloat,active decay, and skeletonization

*Rigor mortis starts with eyelids,neck, and jaw then spreads to the other muscles.*

1. *Livor mortis.* Red-blue discoloration due to blood pooling.
2. *Algor mortis*. Cooling of body.
3. *Intravascular clotting*. Layered clots non adherent to vasculature.
4. *Autolysis.* Digestion of tissues from enzymes and lysosomes.
5. *Putrefactions*. Saprophytic organism from intestine enters body, causing greenish discoloration of tissues and organ.

***-----------------------END OF LECTURE--------------------***