CHAPTER ONE

Disturbance in Growth & Circulation

Hypertrophy:

Definition:

 increase in cell size accompanied by an increase in functional capacity

Appearance:

 Cells are bigger than normal which makes the organ look bigger than normal

This refers to an increase in the size of cells those results in enlargement of their relevant organ. Hypertrophy can be **physiologic** or **pathologic** and is caused either by increased functional demand or by specific hormonal stimulation. Examples of physiologic hypertrophy include that of skeletal muscles in athletes and mechanical workers & the massive physiologic enlargement of the uterus during pregnancy due to estrogen-stimulated smooth muscle hypertrophy (and hyperplasia) Pathologic hypertrophy is exemplified by cardiomegaly secondary to hypertension .The stimuli of hypertrophy turn on signals that lead to the induction of a number of genes, which in turn stimulate synthesis of numerous contractile myofilaments per cell. This leads to improved performance to house the excessive demand imposed by the external burden. There is, however, a limit for the adaptation beyond which injury occurs; as for e.g. in the heart, where several degenerative changes occur in the myofilaments that culminate in their loss. This limitation of cardiac hypertrophy (an adaptation) may be related to the amount of available blood to the enlarged fibers. The net result of these regressive changes is ventricular dilation and ultimately cardiac failure. This means that an adaptation can progress to dysfunction if the stress is not relieved.

Hyperplasia refers to an increase in the number of cells. It takes place only if the cells are capable of replication; it may occur with hypertrophy and often in response to the same stimuli. Hyperplasia can be physiologic or pathologic.

Physiologic hyperplasia: this is of two types

1. Hormonal hyperplasia, exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy. The enlargement of the gravid uterus is due to a combination of hypertrophy & hyperplasia.

2. Compensatory hyperplasia, which occurs when a portion of the tissue is removed or diseased. For example, when a liver is partially resected, mitotic activity in the remaining cells begins that eventually restore the liver to its normal weight. The stimuli for hyperplasia in this setting are growth factors produced by remaining hepatocytes & other cells within the organ. After restoration of the liver mass, cell proliferation is "turned off" by various growth inhibitors.

Pathologic hyperplasia: is mostly caused by excessive hormonal or growth factor stimulation. Examples include

1. Endometrium hyperplasia: this results from persistent or excessive estrogen stimulation of the endometrium. This hyperplasia is a common cause of abnormal uterine bleeding.

2. Skin warts: these are caused by Papilloma viruses, and are composed of masses of hyperplastic epithelium. The growth factors responsible may be produced by the virus or by the infected cells. In all the above situations, the hyperplastic process remains controlled; if hormonal or growth factors stimulation subsides, the hyperplasia disappears. It is this response to normal regulatory control mechanisms that distinguishes pathologic hyperplasias from cancer, in which the growth control mechanisms become ineffective. However, some types of pathologic hyperplasias may become a fertile soil for the development of carcinoma.

Atrophy:

Cellular Atrophy is a decrease in cell size caused by loss of sub-cellular organelles and substances.

Organ Atrophy is a decrease in the tissue mass of an organ due to either a decrease in size of individual cells (**cellular atrophy**), a decrease in number of cells, or both.

This refers to shrinkage in the size of the cell due to loss of its constituent substances. This situation is exactly opposite to hypertrophy. When a sufficient number of cells are involved, the entire tissue or organ diminishes in size i.e. becomes atrophic . Causes of atrophy include

1. A decreased workload, which is the most common form of atrophy; it follows reduced functional demand. For example, after immobilization of a limb in a cast as treatment for a bone fracture or after prolonged bed rest. In these situations the limb's muscle cells atrophy and muscular strength is reduced. When normal activity resumes, the muscle's size and function return.
2. Denervation of a limb as in poliomyelitis and traumatic spinal cord injury
3. Diminished blood supply e.g. decreased blood supply to a limb or brain due to narrowing of the lumina of the relevant artery (or arteries) by atherosclerosis. 4. Inadequate nutrition as in starvation and famines
5. Loss of endocrine stimulation as in postmenopausal endometrial atrophy (due to decrease in the levels of estrogen after menopause) and testicular atrophy (due to decrease in the production of LH & FSH as in hypopituitarism

Metaplasia refers to a reversible change in which there is “replacement of normal mature epithelium at a given site by another mature benign epithelium inappropriate to that site.” In this type of cellular adaptation, cells sensitive to a particular stress are replaced by other cell types that are more capable of resisting the adverse environment. Metaplasia is thought to arise by genetic "reprogramming" of stem cells. Epithelial metaplasia is exemplified by the squamous change that occurs in the respiratory epithelium in habitual cigarette smokers. The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or extensively replaced by stratified squamous epithelial cells. Although the metaplastic squamous epithelium is more resistant to the injurious environemen, it has its adverse effects that include

1. Loss of protective mechanisms, such as mucus secretion and ciliary clearance of particles. 2. Predisposition to malignancy. In fact, squamous cell carcinoma of

the bronchi often coexists with squamous metaplasia. Squamous metaplasia is also seen in the urinary bladder harboring Shistosomal ova. When there persistent regurgitation of the gastric contents in to the esophagus (chronic gastroesophageal reflux disease [GERD]), the normal stratified squamous epithelium of the lower esophagusmay be replaced by a metaplastic intestinal-type columnar epithelium. The latter is more resistant to the highly acidic regurgitating gastric contents.

Dysplasia: abnormally develop tissue also refer to organization of the tissue which cause unknown cell may diffuse or focal mostly in malignant cancer also adenocarcenama.

Causes: chronic irritation in cigar smoking

Aplasia : reduce or absence of the cell lead to reduce in tissue

Aplastic : not tendency to form new tissue as failure to regenerated bone marrow eg. Aplastic anemia.

Atresia : absence of normal opening eg atresia of anus

Agenesis: absence of normal organ e.g absence of uterus

Anaplasia : poorly differentiated cell mostly seen in highly malignant tumor.

HEMODYNAMIC DISORDERS

THROMBOEMBOLIC DISEASE AND SHOCK

Haemostasis is the process that keeps blood in its fluid state and within the confines of the vasculature.

Successful haemostasis depends on:

- Vessel wall (constrict to limit blood loss)
- Platelets (formation of platelet plug)
- Coagulation system (via thrombin)
- Fibrinolytic system (breakdown of fibrin)

I. Edema and **Effusion**

1. **Edema** generally refers to *fluid accumulation in interstitial tissue*. When due to purely hemodynamic changes the fluid is a ***transudate***.

2. **Anasarca** - systemic edema and effusions due to hemodynamic cause(s).

3. **Ascites** - generally refers to *fluid accumulation in the peritoneal cavity*; clinically may refer to a transudate type of fluid (hemodynamic).

4. **Effusion** refers to fluid accumulation in a body cavity.

Pathogenesis of transudate:

1. Increased intravascular hydrostatic pressure. Increased intravascular pressure in capillaries and venules "pushes" water, electrolytes and a small amount of low Molecular Weight (MW) protein molecules out of the vessels and into adjacent interstitial tissue and/or body cavities.

Example: Increased pressure in the left ventricle of the heart (left-sided heart failure) is transmitted backwards to the left atrium, pulmonary veins and then to the pulmonary capillaries. The result is the formation of transudate in the septal and then in the alveolar spaces; called **pulmonary edema**. The causes include:

- Impaired venous return
- Congestive heart failure
- Constrictive pericarditis
- Ascites (liver cirrhosis)
- Venous obstruction or compression
- Thrombosis
- External pressure (e.g., mass)
- Lower extremity inactivity with prolonged dependency
- Arteriolar dilation

2. Reduced intravascular osmotic pressure. Most often this is due to hypoalbuminemia.

Examples:

- Liver disease (e.g. cirrhosis) results in a marked reduction in albumin synthesis.
- Renal disease (e.g. nephrotic syndrome) results in a marked loss of albumin.
- Malnutrition
- Protein-losing gastroenteropathy

3. Increased pressure in lymphatic vessels

Example*:* Radical mastectomy in which the excision of axillary lymph nodes blocks the normal drainage of lymph and results in the accumulation of fluid in the patient's arm. Also, could be:

- Inflammatory
- Neoplastic
- Postsurgical
- Postirradiation

4. Sodium Retention

- Excessive salt intake with renal insufficiency
- Increased tubular reabsorption of sodium
- Renal hypoperfusion
- Increased renin-angiotensin-aldosterone secretion

II. HYPEREMIA or CONGESTION

In hyperemia.

Increased inflow leads to engorgement with oxygenated blood, resulting in erythema.

In congestion. Diminished out flow leads to a capillary bed swollen with deoxygenated venous blood and resulting in cyanosis

1. **Active**. Dilatation of **arteries/arterioles** results in increased blood flow (perfusion) of a tissue or organ. The tissue appears red. This was the mechanism

for the "redness" of acute inflammation. Hot ,gray red in color without fluid causes by bacterial disease, physiological.

2. **Passive**. Impaired **venous** drainage results in stasis and the accumulation of deoxygenated blood. The tissue has a bluish color due to the accumulation of deoxygenated hemoglobin. Cold doughy and swollen ,accompanied by oozing of fluid .causes by any disease

Either of these may be acute or chronic. The term "**congestion**" is sometimes used to describe a hyperemic organ or tissue.

Example: Passive hyperemia resulting in acute or chronic passive congestion of the liver or spleen. The organs are enlarged and the liver may be tender.

III. HEMORRHAGE:

Extra vacation of blood from BVs. These are the most important lesions related to coagulation disorders:

Occur by tow way

a- **diapedsis** in which RBCs escape one by one in infection

b- **rhexis** escape of RBCs due to cutting of BVs

Types of hemorrhage.

1. **Petechiae** - pinhead size; **Purpura** - up to 1 cm.; **Ecchymoses** - larger

2. **Hematoma** - a mass composed of blood infiltrating soft tissue.

3. **Hemothorax / hemopericardium / hemoperitoneum** - blood within the respective body cavity.

IV. THROMBUS (The process is called thrombosis)

Thrombosis is the solidification of a formed mass of blood components within the circulatory system. It requires the interaction of all cells within the vasculature and endothelial cells, as well as circulating elements, such as platelets and the clotting cascade. Clotting is a balance between two opposing forces: those favoring the formation of a stable thrombus, and those factors causing breakdown of the clot.

Type of thrombus

1- **Occluding thrombus:** in which the clot closes compeletly the entire lumen of artery.
2- **Obturating thrombus:** in which the clot is partial closes the arterial lumen**.**
3- **Canalized thrombus:** there is many canals (opining) in the thrombus so the oxygenated blood became circulated.

Patho-physiology of thrombus formation

Injury to the vascular endothelium causes factors that facilitate and inhibit thrombus.

a. Facilitation

Exposure of tissue factor from injured cells activates factor VII

Exposure of the thrombogenic subendothelial collagen activates factor XII

Platelets deposit and aggregate due to collagen exposure and generation of thrombi

b. Inhibition

Increased prostacyclin (PGI2) and nitryl (NO2) inhibit platelet aggregation

Synthesis of plasminogen activator promotes fibrinolytic activity

predisposing factors

- **Abnormalities of the vessel wall**: Damage to the endothelium/vascular wall e.g. atherosclerosis, vascular trauma.

- **Abnormalities of blood flow**: Stasis of blood flow (varicose veins, prolonged bed rest).

- **Abnormalities of the blood constituents**: Hypercoagulable state, and increased blood viscosity (dehydration).

Features:

1. Intravascular

2. Adherent to the luminal surface of the vessel.

3. Mass of coagulated blood composed of platelets, fibrin and entrapped cells and other plasma proteins. Early lines of **Zahn** are present: alternating layers of platelets and fibrin.

Distinguish from:

1. *In vitro* clot

2. Postmortem clot - does not adhere to the vessel wall.

3. Clotting of a hematoma or hemorrhagic exudate.

Outcome: Consequences of thrombosis

1. **Lysis**. The role of fibrinolytic agents in the blood.

2. **Propagation**. Enlargement and extension of the thrombus.

3. **Organization**. Fibrosis of the thrombus.

4. **Recanalization**. During organization new channels may form within the thrombus; these may allow renewed blood flow through the obstructed vessel.

Complications:

1. Reduced blood flow to a tissue/organ resulting in ischemic injury or infarction.

2. Fragments of thrombus break off and result in thromboembolization.

Clinical consequences

1. arterial thrombosis (tissue infarction distally)

2. venous thrombosis (oedema, due to impaired venous drainage)

3. embolism

Emboli &Embolism:

Emboli: foreign body circulated in blood**.**

Embolism: the process of formation of foreign body.

is the occlusion of a vessel (either artery or vein) by a mass. Most commonly, they are thrombi that have dislodged from their site of formation and have lodged in a distal lumen occluding blood flow.

1. **Pulmonary emboli** often originate from deep vein thrombosis in the low legs and less often from deep pelvic veins

2. **Systemic emboli** are formed in the arterial circulation; most arise in the heart

3. **Paradoxical emboli** cross over from the right side to the left side of the heart through septal defects and gain access to the systemic circulation

4. **Other types of emboli** include gas emboli (e.g. Caisson's disease), fat emboli (e.g. associated with bone fractures), amniotic fluid emboli, bone chips, and tumour cells

V. EMBOLISM or **EMBOLUS**

(the process is called embolization)

 A particle/mass which is carried in the blood stream as far as its size will allow. It becomes lodged at that point and obstructs the vessel.

 Thrombo-embolus is the most common type. Thromboemboli arise from thrombi and range in size from microscopic to those which are large enough to occlude major arteries.

 Thromboemboli may occur in either arteries or veins. Like thrombi they may undergo lysis, propagation, organization and/or re-canalization and can result in ischemic injury and infarction.

 The most common type of **venous thromboembolus** arises from a thrombus in the deep leg veins. Fragments of the thrombi travel to the lung where they occlude the pulmonary artery and may result in infarction in the lung. In general the term “embolus” (e.g. pulmonary embolus) is synonymous with “thromboembolus.”

 Systemic

VI. INFARCT (the process is called infarction)

1. An area of ischemic necrosis which typically results from obstruction of the corresponding artery by a thrombus or an embolus. Typically wedge-shaped and

pale ("**white infarct**") - unless there is some associated hemorrhage (e.g. in the lung).

2. Infarction is an irreversible process and healing occurs by fibrosis.

3. Does total arterial obstruction always result in infarction? No - if there is a dual or **collateral blood supply**.

4. Can infarction occur in the absence of total arterial obstruction? Yes - all that is needed for infarction to occur is for the oxygen supply to be insufficient to sustain the life of the affected tissue. This may occur, for example, as the result of partial obstruction ischemic injury exacerbated by hypoxemia and/or by increased needs for oxygen by the tissue. We will say more about this when we discuss myocardial infarction.

5. Infarcts due to systemic venous obstruction are much less common than arterial. Obstruction of a vein allows blood to enter the tissue - but not exit; this leads to severe passive congestion, hemorrhage and infarction. Venous infarcts are typically hemorrhagic ("**red infarct**").

6. Factors which modify the development of an infarct include the type of vascular supply, the rate of development of the obstruction, the vulnerability of the tissue to hypoxia, and the oxygen concentration of the arterial blood supply.

V. SHOCK –

is the systemic hypoperfusion of cells and tissue. It is characterized by marked hypotension (tachycardia) with increased pulse rate. Aerobic cellular metabolism switches to anaerobic with increased lactate production (lactic acidosis).

Four types

1. **Cardiogenic**- reduced cardiac output, e.g. as the result of a large myocardial infarct.

2. **Hemorrhagic / hypovolemic** - reduced blood volume, e.g. massive fluid loss.

3. Septic- most often Gram-negative bacteremia. Endotoxins are mediated by tumor necrosis factor and other chemical mediators results in a frequently irreversible situation of systemic vasodilatation, endothelial damage and direct injury to cells.

4. **Neurogenic**, e.g. anaesthesia with severe widespread peripheral vasodilatation. Very uncommon.

Stages

1. **Non-progressive** - reflex compensatory mechanisms result in the perfusion of vital organs.

2. **Progressive** - hypoperfusion of tissues with increasing circulatory and metabolic imbalances.

3. **Irreversible** - despite temporary interventional correction of hemodynamic defects, cellular and tissue injury are so severe as to preclude survival.

Major sites of injury

- Brain - hypoxic encephalopathy
- Lungs - “shock lung” - adult respiratory distress syndrome (ARDS)
- Kidneys - acute tubular necrosis
- G.I. - hemorrhagic necrosis of the mucosa

Type of Shock	Clinical Examples	Principal Mechanism
Cardiogenic	- Ventricular rupture - Arrhythmia - Cardiac tamponade - Pulmonary	Failure of myocardial pump owing to intrinsic myocardial damage, extrinsic pressure, or obstruction to

	embolism - Myocardial infarction	outflow
Hypovolemic	- Hemorrhage - Fluid loss, e.g., vomiting, diarrhea, burns, or trauma	Inadequate blood or plasma volume
Septic	-Overwhelming microbial infections - Endotoxic shock - Gram-positive septicemia - Fungal sepsis	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; disseminated intravascular coagulation; activation of cytokine cascades