Thrombosis (lec#1)

* Pathogenesis (called Virchow's triad): Endothelial Injury (Heart, Arteries), Stasis (abnormal blood flow), Blood Hypercoagulability.

* Endothelial cells can be stimulated by direct injury or by various cytokines that are produced during inflammation.

* Pathologic effect of vascular healing → Excessive thickening of the intima → luminal stenosis & blockage of vascular flow

*Stasis: a major factor in venous thrombi.

* Hypercoagulability

  A. Genetic (primary):
  - Mutations in the factor V gene and the prothrombin gene are the most common

  B. Acquired (secondary):
  - Multifactorial and is therefore more complicated

* Morphology of thrombi:
  - Can develop anywhere in the CVS, focally attached to the underlying vascular surface.

  - Arterial or cardiac thrombi → begin at sites of endothelial injury or turbulence; and are usually superimposed on an atherosclerotic plaque.

  - Venous thrombi → occur at sites of stasis. Most commonly the veins of the lower extremities (90%).

* lines of Zahn

  - Thrombi can have grossly (and microscopically) apparent laminations called lines of Zahn; these represent pale platelet and fibrin layers alternating with darker erythrocyte-rich layers.

  - Such lines are significant in that they represent thrombosis of flowing blood.

  - Postmortem blood clots are bland non-laminated clots (no lines of Zahn).

* Mural thrombi: thrombi occurring in heart chambers or in the aortic lumen.

* Vegetations: Thrombi on heart valves

  - Types:
    1- infectious (Bacterial or fungal blood-borne infections) → (e.g. infective endocarditis,).
    2- Non-bacterial thrombotic endocarditis occur on sterile valves.

* Venous thrombi: (veins of the legs) are most common

  a. Superficial: e.g. Saphenous veins, can cause local congestion, swelling, pain, and tenderness along the course of the involved vein, but they rarely embolize.

  b. Deep: e.g. Popliteal, Femoral and iliac vein, more serious because they may embolize, can occur with stasis or in a variety of hypercoagulable states.
Embolism (Lec#2)
- 99% due to dislodged thrombus.

* Types:

1. Thromboembolism (99%)
   - Emboli result in partial or complete vascular occlusion.

   A. Pulmonary Thromboembolism
      - 95% originate from deep veins of lower limb
      - Saddle embolus: at bifurcation of Pulmonary artery
      - Paradoxical embolus: Passage of an embolus from venous to systemic circulation through IAD, IVD
      - Most pulmonary emboli (60% to 80%) are clinically silent because they are small.

   B. Systemic thromboembolism
      - 80% due to intracardiac mural thrombi.
      - The major targets are: Lower limbs 75%, Brain 10%

2. Fat embolism
   - Causes: Skeletal injury (fractures of long bones ), Adipose tissue Injury
   - In skeletal injury, fat embolism occurs in 90% of cases, but only 10% or less have clinical findings.
   - Fat embolism syndrome is characterized by: Pulmonary Insufficiency, Neurologic symptoms, Anemia, Thrombocytopenia, Death in 10% of the case.

3. Air embolism
   - Causes: Obstetric procedures, Chest wall injury, Decompression sickness
   * Caisson disease: gas emboli in the bones leads to multiple foci of ischemic necrosis, usually the heads of the femurs, tibias, and humeri.

4. Nitrogen embolism
5. Cholesterol embolism
6. Amniotic fluid embolism
   - Due to infusion of amniotic fluid into maternal circulation via tears in placental membranes and rupture of uterine veins.
   - Finding: squamous cells, languo hair, fat, mucin within the pulmonary microcirculation.
INFARCTION

- 99% of all infarcts result from thrombotic or embolic events
- **The dominant histologic characteristic of infarction is ischemic coagulative necrosis**.
- Most infarcts are ultimately replaced by scar. The brain is an exception, it results in **liquefactive necrosis**.

1- **Red infarcts** occur in: **venous occlusions** (such as in ovarian torsion), **loose tissues** (like lung) that allow blood to collect in the infarcted zone, **tissues with dual circulations** (lung and small intestine), **previously congested tissues** because of sluggish venous outflow, when flow is re-established to a site of previous arterial occlusion and necrosis.

2- **White infarcts** occur with **arterial occlusions**, **solid organs** (such as heart, spleen, and kidney).

3- **Septic infarctions** occur when bacterial vegetations from a heart valve embolize or when microbes seed an area of necrotic tissue.
- The infarct is converted into an abscess, with a correspondingly greater inflammatory response

*Factors That Influence Development of an Infarct*: **nature of the vascular supply, rate of development of the occlusion (collateral circulation), vulnerability to hypoxia, the oxygen content of blood**.
Veins and lymphatics (Lec#3)

* Pathology of veins

A) Varicose Veins
- More common in females
- The superficial veins of the leg are most typically involved
- **RISK FACTORS**: Obesity, Female gender, Pregnancy, Familial tendency (premature varicosities results from imperfect venous wall development)
- **Microscopic Morphology**: spotty medial calcifications (phlebosclerosis), venous valve deformities (rolling and shortening),
- Embolism is very rare complication

B) Thrombophlebitis And Phlebothrombosis
- **Inflammation + thrombosis of veins**
- The deep leg veins account for more than 90% of cases
- The most important clinical **predispositions** are: congestive heart failure, neoplasia, pregnancy, obesity, the postoperative state, and prolonged bed rest or immobilization
- **Thrombophlebitis of upper limb veins** are usually associated with local risk factors like: catheter or canula site; or in some cases can be associated with systemic hypercoagulabilities.

* Special thrombophlebitis types:
1. **Migratory thrombophlebitis (Trousseau sign)**: colon cancer
2. The **superior vena caval syndrome**: lung cancer
3. The **inferior vena caval syndrome**: hepatocellular carcinoma and renal cell carcinoma

* Pathology of Lymphatics

A) **Lymphedema** can occur as:
1. **Primary (A congenital defect)**, resulting from lymphatic agenesis or hypoplasia.
2. **Secondary or obstructive lymphedema**

B) **Lymphangitis**
- Most common are group A β-hemolytic streptococci.
- Red, painful subcutaneous streaks (the inflamed lymphatics), with painful enlargement of the draining lymph nodes (**acute lymphadenitis**).

C) **Chylous**
- Milky accumulations of lymph in various **body cavities**
- Caused by rupture of dilated lymphatics, typically obstructed secondary to an infiltrating tumor mass
- **Types**: **chylous ascites** (abdomen), **Chylothorax** (chest), **Chylopericardium** (pericardium)
ARTERIOSCLEROSIS (LEC#4)

* Patterns:

1-Arteriolosclerosis: affects small arteries and arterioles, most often associated with hypertension and/or diabetes mellitus.

2-Mönckeberg medial calcific sclerosis: characterized by calcific deposits in muscular arteries, typically in persons older than age 50, often palpable calcifications, do not encroach on the vessel lumen and are usually not clinically significant.

3-Atherosclerosis: most frequent and clinically important pattern, characterized by intimal lesions called atheromas (also called atherosclerotic plaques).

- Pathogenesis: initiation of inflammatory process => LDL particles and their content are susceptible to oxidation by free radicals => endothelial activation.

- Epidemiology: Multiple risk factors have a multiplicative effect: 2 risk factors increase the risk 4X. E.g. if 3 risk factors are present (e.g., hyperlipidemia, hypertension, and smoking), the rate of myocardial infarction is increased 7X.

- Major Constitutional Risk Factors for atherosclerosis:

A) Major Risks (Nonmodifiable):
1) Increasing age: between ages 40 and 60, the incidence of myocardial infarction in men increases 5 times, Death rates from IHD rise with each decade.
2) Male gender
- Premenopausal women are relatively protected against atherosclerosis compared with age-matched men unless they are otherwise predisposed by diabetes, hyperlipidemia, or severe hypertension.
3) Genetic abnormalities
- Familial predisposition to atherosclerosis and IHD is multifactorial either familial clustering of other risk factors such as (hypertension or diabetes) or well-defined genetic derangements in lipoprotein metabolism, e.g. familial hypercholesterolemia that result in excessively high blood lipid levels.
4) Family history

B) Potentially Controllable/modifiable: Hyperlipidemia, Hypertension, Cigarette smoking, Diabetes.
**Hypertensive Vascular Disease (LEC#5)**

- Cutoffs in diagnosing hypertension in clinical practice ➔ sustained diastolic pressures > 90 mm Hg, and/or sustained systolic pressures > 140 mm Hg.
- **Malignant hypertension**: rapidly rising blood pressure, most commonly is superimposed on preexisting benign hypertension, **systolic pressures > 200 mm Hg or diastolic pressures > 120 mm Hg**

*Types of hypertension:*

**A- Essential Hypertension**
- Most cases (95%) are idiopathic.

**Pathogenesis:**
- **Genetic factors**: linked to specific angiotensinogen polymorphisms and angiotensin II receptor variants; polymorphisms of the renin-angiotensin system, Susceptibility genes for essential hypertension: genes that control renal sodium absorption.
- **Environmental factors**: stress, obesity, smoking, physical inactivity, dietary sodium intake

**Morphology:** HTN is associated with arteriolosclerosis (small arterial disease)
- **Two forms of small blood vessel disease are hypertension-related:**

1. **Hyaline arteriolosclerosis**
   - Associated with benign hypertension.
   - Marked by homogeneous, pink hyaline thickening of the arteriolar walls, and luminal narrowing.
   - Results from leakage of plasma components across injured endothelial cells into vessel walls.
   - Most significant in the kidneys ➔ nephrosclerosis (glomerular scarring).

2. **Hyperplastic arteriolosclerosis**
   - Associated with severe (malignant) hypertension.
   - **Onionskin appearance**: laminated thickening of arteriolar walls consist of smooth muscle cells and thickened reduplicated basement membrane.
   - In malignant hypertension these changes are accompanied by fibrinoid deposits and vessel wall necrosis (**necrotizing arteriolitis**), which are particularly prominent in the kidney.

**B- Secondary Hypertension:**
- Due to renal disease, or renal artery narrowing (**renovascular hypertension**).
EDEMA

- Extravascular fluid collection in body cavities: pleural cavity (hydrothorax), the pericardial cavity (hydropericardium), peritoneal cavity (hydroperitoneum, or ascites).

- **Mechanisms of edema**: Increased Hydrostatic Pressure, Reduced Plasma Osmotic Pressure (Hypoproteinemia), Lymphatic Obstruction, Sodium Retention, Inflammation

1) **Subcutaneous edema**: the most common, signals potential underlying cardiac or renal disease, Can impair wound healing or the clearance of infections.

2) **Pulmonary edema**
   - Common causes: left ventricular failure, renal failure, Acute Respiratory Distress Syndrom (ARDS), inflammatory and infectious disorders of the lung.
   - Can cause death by interfering with normal ventilatory function & impeding oxygen diffusion.

3) **Brain edema**
   - Life-threatening→ brain herniation (extrude) through the foramen magnum.