BIRZEIT UNIVERSITY

FACULTY OF NURSING, PHARMACY AND HEALTH PROFESSIONS

Pathophysiology for Pharm D Course # PHARM 35
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1) **Name the differences Between Extracellular (ECF) and Intracellular (ICF),**
   - The body fluids volume is 60% of body weight.
   - ICF = 40%.
   - ECF = 20%:
     - 80% of ECF is interstitial Fluid (the fluid between cells in tissues)-
     - 20% of ECF is blood plasma.
   - ECF = large amounts of *sodium, chloride, calcium and bicarbonate ions.*
   - ICF = large amounts of *potassium, magnesium,* and *phosphate ions*

2) **Describe the free radicals & their mechanism of action of in cellular injury**
   - Free radicals (ROS) are generated as *by-products of normal cell metabolism*
   - Free radicals have *one or more unpaired electrons* in their outer shell.
   - Exogenous sources include *tobacco smoke, organic solvents, pollutants, radiation, bacterial infections and pesticides.*
   - Examples of free radicals include Superoxide (O_2^-) , hydroxyl radicals (OH^-) , hydrogen peroxide(H_2O_2) and Hydroperoxyl radicals
   - Free radicals are inactivated by *antioxidant enzymes* within the body such as *catalase, glutathione peroxidase (Gpx) and superoxide dismutase (SOD).*
   - Free radicals can injure cells through:
     - Peroxidation of membrane lipids (free radicals "steal" electrons from the lipids in cell membranes, resulting in cell damage)
     - Damage of cellular proteins
     - Mutation of cellular DNA

3) **Describe the cell cycle.**

   - The *cell cycle is a repeating series of events* that cells go through.
   - It includes *growth, DNA synthesis, and cell division.*
   - There are two growth phases (G1 & G2), and cell division includes *mitosis.*
   - The cell cycle is *controlled by regulatory proteins* at three key checkpoints (G1, G2 & M) in the cycle.
   - These checkpoints signal the cell *to either start or delay the next phase of the cycle.*
   - *Cancer is a disease that occurs when the cell cycle is no longer regulated*. Cancer *cells grow rapidly* and may form a mass of abnormal cells called a *tumor.*

4) Describe the Growth regulatory genes & "Drivers" of Cancer.

- The *genetic changes* that contribute to cancer tend to affect *three main types of genes* that involved in *regulation of cell proliferation & growth; proto-oncogenes*, *tumor suppressor genes* and *DNA repair genes*.
- These *changes "mutations"* are sometimes called ***"drivers" of cancer.***
    - **Proto-oncogenes** are involved in *normal cell growth and division.* When mutated they may become *cancer-causing genes (or oncogenes)*, allowing cells to grow and survive when they should not.
    - **Tumor suppressor genes** *restrain* **(تقيد)** *cell growth and division;* loss of function results in unregulated growth and may divide in an uncontrolled manner.
    - **DNA repair genes** are involved in *fixing damaged DNA.* DNA repair genes – when *mutated, become faulty* and tend to develop additional mutations in other genes.
- Together, ***these altered, or "mutated," Genes*** may cause the cells to become *cancerous.*

5) Describe the role of the adenomatous polyps in colorectal cancers.

- There are 2 types of polyps:
    - Sessile: Base is attached to the wall
    - Pedunculated: Mucosal stalk from polyp to wall
- Between 70 and 90 % of colorectal cancers arise from *adenomatous polyps* (Adenomas), and 10 to 30 % arise from ***sessile adenomas.***
- The *larger the polyp, the greater the potential for malignancy.*
- Diminutive polyps (5 mm or less in diameter) have a *negligible malignant potential.*
- Polyps with a diameter of 5 to 10 mm are considered small, whereas polyps greater than 10 mm in diameter are considered large.
- ***Polyps larger than 2 cm in diameter have a 50 percent chance of becoming malignant over time.***
- If polyps are not removed, they continue to grow and can become cancerous.

6) Describe the Blood coagulation

- Blood coagulation is the process in which *fibrin* protein strands wrap around (يلتف حول) the platelet plug to form an insoluble clot.
- The process of blood coagulation occurs through two separate, but related pathways called :
    - The *intrinsic coagulation pathway* and
    - The *extrinsic coagulation pathway*
- Intrinsic coagulation pathway:
    - Initiated by protein factors ***found circulating in the blood.***

- Activation of initial clotting factor *XII* (Hageman factor) ***occurs after Vessel Injury*** through contact with ***exposed collagen or damaged endothelium***
- Extrinsic coagulation pathway:
  - Initiated by protein factors ***located in the tissues***.
  - Activation of extrinsic pathway occurs when factor *III* (thromboplastin) is ***released from tissues*** to activate clotting factor *VII*.

7) Name the risk factors for Breast cancer in women

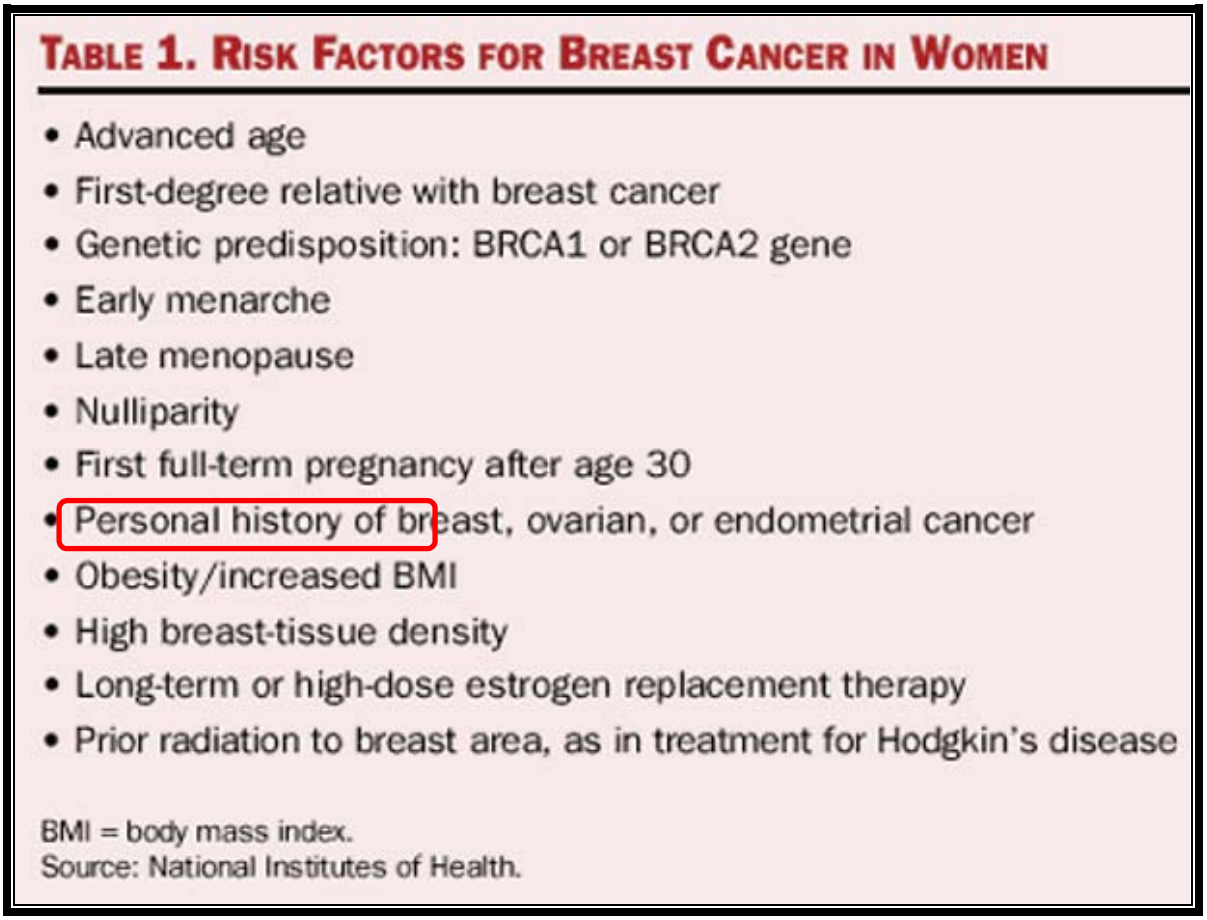

TABLE 1. RISK FACTORS FOR BREAST CANCER IN WOMEN

- Advanced age
- First-degree relative with breast cancer
- Genetic predisposition: BRCA1 or BRCA2 gene
- Early menarche
- Late menopause
- Nulliparity
- First full-term pregnancy after age 30
- Personal history of breast, ovarian, or endometrial cancer
- Obesity/increased BMI
- High breast-tissue density
- Long-term or high-dose estrogen replacement therapy
- Prior radiation to breast area, as in treatment for Hodgkin's disease

BMI = body mass index.
Source: National Institutes of Health.

Obesity is associated with a *twofold increase* in the risk of breast cancer in *postmenopausal women* whereas among *premenopausal women* it is associated with a *reduced incidence.*

8) Describe the Natural inhibitors (Anticoagulants)

- Antithrombin III – inhibits factor X and thrombin
- Heparin from basophils and mast cells potentiates effects of antithrombin III (together they inhibit IX, X, XI, XII and thrombin)
- Antithromboplastin (inhibits „tissue factors" – tissue thromboplastins)
- Protein C and S – activated by thrombin; degrade factor Va and VIIIa

9) Describe the process of Erythropoiesis.

- Erythropoiesis is the part of hematopoiesis that deals with the *production of RBCs*.
- A major regulator of *red blood cell* production is the hormone *erythropoietin* (Epo) *which is a* glycoprotein.
- The major site of Epo production is the kidney, while the *liver* is the main *extrarenal site of Epo* production.
- Epo secretion is stimulated by hypoxia (O2 deficiency), which is detected by an *oxygen sensor located in the kidney.*
- The erythropoietin that is produced acts directly on stem cells in the bone marrow to promote the proliferation, maturation and release of *immature red cells* (Reticulocytes)

10) Define and describe the manifestations of Polycythemia

- Polycythemia = number of *RBC in circulation* is greatly increased.
- Manifestations
  - Increased blood volume and viscosity
  - Increased risk of thrombus
  - Occlusion of small blood vessels
  - Hepatosplenomegaly from pooling of blood
  - Impaired blood flow to tissues (ischemia)
  - Headache , Dizziness, Weakness ,Increased blood pressure, Itching / sweating

11) Describe the pathophysiology of leukemia

- The pathophysiology of leukemia isn't completely understood, but like other types of cancer; it is due to the **mutation in the DNA** of the ***Hematopoietic stem cells (HSCs)*** of the bone marrow.
- Once a mutation in DNA occurs that can't be repaired, the ***abnormal or immature form white blood cells*** can freely ***replicate and become essentially "immortal".***
- These abnormal white blood cells **no longer function normally**.
- **Over time**, these leukemic cells ***multiply*** and ***crowd out* (تزاحم)** the normal cells of the bone marrow that do function properly. ***This increases the risk of infections*** – one of the most common causes of death in people with leukemia.
- This overabundance of abnormal white blood cells also ***reduces the number of red blood cells and platelets,*** leading to anemia and bleeding problems.
- The **abnormal and immature (blast) Leukemic cells** *spill out* into the blood and invade other tissues such as the ***spleen, liver, lymph nodes and bone*** and cause tissue destruction.

12) Describe shortly the 4 types of leukemia.

- ALL most common type of childhood leukemia (**80%**)
- AML is the ***most common adult leukemia***. Auer rods seen *in the leukemic blasts* of AML.
- CLL is caused by an *abnormal proliferation* of lymphocytes. Hypogammaglobulinemia *occurs in > 50% of patients. Low IgM (patients are predisposed to infections).*
- CML is a proliferation of *primitive hematopoietic stem cells*(*hypercellular*). ***Philadelphia chromosome*** *(*Chromosome 22 containing the fused BCR-ABL gene) *leads* to the *production of an abnormal protein with tyrosine kinase activity causing proliferation of the myeloid mass, which leads to CML,*

13) Describe the types of Immunity

Innate or Natural or Nonspecific Immunity — Adaptive or Acquired or Specific

NONSPECIFIC DEFENSE MECHANISMS		SPECIFIC DEFENSE MECHANISMS (IMMUNE SYSTEM)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic white blood cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes • Antibodies

14) Describe the Cells of the Immune System

- **The myeloid progenitors** develop into the cells that *respond early and nonspecifically to infection.*
  - **Monocytes** turn into **Macrophages** *in body tissues* and gobble up foreign invaders.
  - **Neutrophils** engulf bacteria upon contact and send out warning signals.
  - Granule-containing cells such as **eosinophils** *attack parasites*, while basophils release granules containing histamine and other allergy-related molecules.
- **Lymphoid precursors** develop into lymphocytes.
  - **Lymphocytes** *respond later in infection*. They mount a more specifically tailored attack after *antigen-presenting cells* such as dendritic cells or macrophages, display their catch in the form of antigen fragments.

- The **B cell** turns into a **plasma cell** that produces and releases into the bloodstream *thousands of specific* **antibodies.** *Antibodies attach to a specific antigen* and make it easier for the immune cells *to destroy the antigen.*
- The **T cells** *attack antigens directly* and help control the immune response. They also release chemicals, known as cytokines, which control the entire immune response.

15) Describe Hodgkin's Lymphoma.

- Hodgkin lymphoma is a *malignant proliferation* of *B-cell lymphocyte*, that begins in a single node or group of nodes and *then spread to contiguous (the next in sequence) lymph node, (*rarely skipping areas-*which is more common-* in NHL).
- Involvement of *retroperitoneal lymph nodes*, *spleen*, *liver*, and *bone marrow occurs after the lymphoma becomes generalized.*
- It is characterized by the presence of of ***Reed-Sternberg cells** (RS) in lymph nodes & in Blood.*
- Curability >75% **(NHL** Curability < 25%)

16) Describe the Multiple Myeloma

- Multiple myeloma is a ***plasma cell cancer*** in the ***bone marrow*** (which is found in the big bones of the body, such as the ***skull, pelvis, ribs, and sternum,*** as well as the long bones of the legs ***(femur)*** and arms ***(humerus).***
- Plasma cells are ***B lymphocyte cells*** that secrete ***immunoglobulins (Antibodies).***
- It is called multiple myeloma because myeloma cells can occur in ***multiple bone marrow sites in the body.***
- Accounts for 10% to 15% of all hematologic malignancies.
- It is characterized by the uncontrolled proliferation of an abnormal clone of plasma cells, which secrete huge amounts of *monoclonal proteins (also called M protein or paraprotein such as Bence Jones proteins)* or immunoglobulins mainly IgG, IgA .
- Most patients are **> 40 years;** median age **65** years.

17) Define Atherosclerosis

- Atherosclerosis is a *syndrome affecting arterial blood vessels*, a *chronic inflammatory response* in the walls of arteries starts when high blood pressure, smoking, or high cholesterol ***damage the endothelium***.
- At that point, cholesterol plaque formation begins.
- ***Calcification*** **of plaques** may occur over time.
- *Significant narrowing of the blood vessel lumen* can occur over time.
- Atherosclerosis tends to happen throughout the body.
- Atherosclerosis usually causes *no symptoms until middle or older age*.

18) Describe the pathophysiology of deep vein thrombus (DVT) with examples.

- Three main factors that may contribute to the formation of a thrombus:
  1) Hypercoagulable State (Blood Clots: *Malignancy, trauma or surgery of lower extremities ,hip, abdomen or pelvis*)
  2) Circulatory Stasis (Decreased Blood Flow : *Atrial fibrillation, venous obstruction from tumor ,obesity or pregnancy*)
  3) Vascular Wall Injury (Endothelial Injury : *Heart valve disease or replacement , atherosclerosis*)

19) Describe the Protective actions of Nitric Oxide (NO) and the results of its deficiency

- Endothelial NO has the following actions
  - Smooth muscle relaxation and vasodilatation
  - Essential for regulation of blood pressure
  - Reduces proliferation of vascular smooth muscle
  - Protects blood vessel intima from injurious consequences of platelet aggregation
- **Nitrite oxide** causes the blood vessels to *dilate in order to increase blood flow.*
- Endothelial Dysfunction causes a *reduction in the secretion of nitric oxide.*
- Lack of nitrite oxide causes the blood vessels to constrict →Atherosclerosis → ↑Systemic vascular resistance → Hypertension

20) Describe the role of renal artery stenosis in the secondary hypertension .

- Renal artery disease can cause of narrowing of the vessel lumen (stenosis). This stenosis reduces the pressure at the *afferent arteriole in the kidney*. Reduced arteriolar pressure and reduced renal perfusion *stimulate Renin release* by the kidney *(Juxtaglomerular apparatus)*
- *Reduced arteriolar pressure* and reduced renal perfusion ***stimulate** Renin release* by the kidney.
- This increases circulating angiotensin II (AII) and aldosterone.
- Aldosterone hormones *increase blood volume* by enhancing *renal reabsorption of sodium and water.* ***(Increase Cardiac Output)***
- Increased AII causes *systemic vasoconstriction and enhances sympathetic activity.*
- Chronic elevation of AII promotes cardiac and vascular hypertrophy.
- The net effect of these renal mechanisms is an increase in blood volume *that augments cardiac output* by the *Frank-Starling mechanism.*
- **Therefore, hypertension caused by renal artery stenosis** *results from both an* ***increase in systemic vascular resistance and an increase in cardiac output.***