SHEET 8

Physiology

Hematolymphatic System

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Revision of the last sheet

Factors that cause normal fluidity of the blood:

1. Heparin

2. Clotting factors circulate as proenzymes in the blood (prothrombin and fibrinogen), some of these factors are removed by the liver. Maintaining the normal amount of clotting factors is done either by being inactive unless needed or by removal of the active form from the circulation by the liver.

3. Minor clotting (fibrin degradation products act as anticoagulants).

4. Protein S and protein C

5. Normal fibrinolytic system

Fibrinolytic system

- It means the production of plasmin from plasminogen to lyse clots in the blood vessel, **how?**

1. Tissue plasminogen activator and contact phase of coagulation are plasminogen activators.

2. Plasminogen activators cause the conversion of plasminogen to plasmin.

3. Plasmin causes proteolysis of fibrinogen, fibrin, factor V and factor VIII.

- This will result in fibrin degradation products which function to inhibit the polymerization of fibrin and platelet aggregation.

Plasminogen activators

- Promote the conversion of plasminogen (inactive form) to plasmin (active form).
- <u>They are either endogenous or exogenous:</u>

• **Endogenous**, such as **tissue plasminogen activators (TPA)** or **contact phase of coagulation**, the exposure of the blood to the medium

• **Exogenous**, such as **streptokinase**, produced normally by certain types of bacteria, and enzyme **Urokinase** that is present in plasma.

- All of this will lead to the production of plasmin from plasminogen.

Clot retraction time

Assume we have a sample of untreated blood (blood with no anti-coagulants) that is left in the lab. We will notice that a clot was formed. The untreated blood will shrink either partially or completely and extrude the entrapped fluid inside as a serum. The time needed for this is called

"clot retraction time", and it's used in the diagnosis of hemorrhagic indices such as Purpura, in which the clot retraction time is greatly increased. In severe cases, there is no retraction of the blood clot, even after 24 hours!

■ Two factors play a vital role in clot retraction:

a. Platelets

b. Calcium

■ Clot retraction measures the normal platelet count and the normal calcium present in the blood.

Thrombosis

• Sometimes, an unwanted clot (thrombus) is formed in the blood vessel. This condition is called thrombosis. The thrombus usually dissolves but sometimes it remains

• If the blood clot remains, this clot sometimes -by the effect of blood flow- is removed from its attachment site and moved throughout the circulation, this condition is called an embolism, and the circulating clot is called an embolus. An embolus is not always a blood clot; it could be an air bubble, fat, a piece of a broken bone, or might be debris of an injured tissue

• This embolus will continue circulating in the blood vessels until it faces a narrow or a small blood vessel and lodges there, thus obstructing that vessel. This will cause problems such as tissue ischemia. This happens usually in blood vessels supplying the heart or lungs.

■ Important note: an embolus in arteries is much more dangerous than in veins, especially in arteries supplying vital organs such as the Heart (leads to heart infarction) and Brain (leads to stroke).

General causes of thrombus:

1. Injury to a blood vessel by trauma, will activate intrinsic or extrinsic pathways which start a coagulation cascade, which in turn will lead to the formation of a thrombus
2. Infection, induces platelet adhesion to the inner endothelium cells of the blood vessel, which leads to ADP release and platelet aggregation
3. Changes in blood composition such as high fibrinogen which causes the platelets to stick to the inner surface of the blood vessel and aggregate forming a clot
4. Slowing of the bloodstream, after major surgery or childbirth there is an increased risk of developing thrombosis and embolism. This may be since the flow of blood in veins becomes sluggish

✨ Changes in blood composition and slowing of the bloodstream might occur during delivery or after major surgery, since both sleep for a long time and sometimes they cannot move

✨ Doctors advise the patients to walk after major surgery, otherwise they will need anti-coagulants.

Arteriosclerosis and Atherosclerosis

- Arteriosclerosis: It is a condition where a blood vessel loses its elasticity and flexibility, either because of a disease or aging, and it is the most common underlying cause of heart attacks.

- Atherosclerosis: The accumulation of fat in the inner surface of the blood vessel resulting in its narrowing, this will lead to the formation of a blood clot or a circulating thrombus (embolus).

Now let's start our lecture :)

Hemostatic defects

1. Vascular disorder

- The problem here is in the blood vessel itself or the connective tissue around it. The blood vessel becomes fragile and easily bruised (called purpura), thus blood vessels will rupture, and bleeding will occur (becomes serious in old age)

- This disorder is either:

1. **Genetic**: usually appears mild during childhood and then becomes moderate or severe and numerous (more vessels affected) during adulthood. It is characterized by microvascular swelling with minor bleeding.

2. **Acquired** (latent): examples:

- Senile purpura ➔ easily bruised blood vessels because of advancing age. This occurs due to connective tissue damage or atrophy in the dermis and is seen mainly in the dorsal aspects of the forearm and hands.
- Purpura associated with chronic infection especially viral infection ➔ due to microbial damage of the vessels.
- Scurvy ➔ vitamin C deficiency, it causes purpura.
- Steroid purpura ➔ a result of prolonged steroid therapy.

(Purpura refers to purplish cutaneous or mucosal lesions caused by hemorrhage)

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2. Platelet count disorder (thrombocytopenia)

- The MOST COMMON hemostatic disorder.

- Thrombocytopenia is characterized by spontaneous skin purpura, mucosal hemorrhage and prolonged bleeding after trauma.

REMEMBER: Platelets maintain the integrity of the blood vessel and when there is a low count of platelets this will affect their integrity

- Causes of thrombocytopenia:

  - Failure of platelet production due to some drugs, chemicals, or viral infections.
  - Bone marrow failure due to Leukemia, Aplastic anemia, and megaloblastic anemia.
  - Increased destruction of platelets because of high concentration of heparin.
  - Disseminated Intravascular Coagulation (DIC); characterized by excessive clots formation thus, causing a depletion in platelets, which will eventually lead to unhealed bruises → Purpura Formation
  - Abnormal distribution of platelet such as in Splenomegaly (enlarged spleen which captures **a lot** of platelets)
    The spleen normally sequesters little amount of the body's platelets, but this amount can rise when the spleen is enlarged
  - Massive blood transfusion to bleeding patients causing dilutional loss of platelets
    (Because of the short half-life of WBCs and platelets, we can't donate them frequently)

- Thrombocytopenic purpura: It is purpura due to low platelets count, when platelets count is low, clot retraction is deficient, so there is the poor repair of the injured blood vessels. This leads to higher susceptibility to bruising and multiple subcutaneous hemorrhages.

- Clot retraction is very important because when the clot shrinks it releases the entrapped platelets and fibrin. This helps the injured blood vessel to repair the damage.

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3. Platelet function disorder

- Thrombocytopathia: characterized by abnormal platelet function and normal platelet count.

- <u>This disorder is either:</u>

  1. Genetic: deficiency in any of the platelet components such as deficiency in VWf or deficiency in glycoprotein-1 on the platelet or failure in thromboxane synthesis or failure of the release of ADP and serotonin.
  2. Acquired: Aspirin therapy; very high doses of aspirin
     (**REMEMBER**: Aspirin is an inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A2)

SO, Thrombasthenic purpura; due to a defect in platelets function

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4. Coagulation factors disorders

- The second most common hemostatic disorder.
- Most of coagulation factor deficiencies are inherited problems.
- Hemophilia A (a deficiency of factor VIII "8"), Hemophilia B (a deficiency of factor IX "9") and von Willebrand's Diseases all are **uncommon**

1 Hemophilia A (factor 8 deficiency)

- The most common inherited coagulation defect among the uncommon.
- Incidence 1:10000
- Factor VIII: C is deficient, but Factor VIII: AG (related antigen) is intact, which will lead to coagulation defect only.
- Sex-linked, 2 abnormal genes are needed to consider the individual diseased.
- **Appears in males only and females are only CARRIERS** (30-35% of patients don't have a family history).
- **Female patients usually do NOT survive, even newborns usually die IMMEDIATELY after birth**.

2 Hemophilia B (factor 9 deficiency)

- less common than Hemophilia A.
- Sex-linked with similar symptoms to Hemophilia A. (appears only in males)
- Deficiency in coagulation factor IX (9), SO no coagulation

3 Von Willebrand's disease

- Somatic (autosomal) inheritance, so the occurrence is equal in both males and females.
- No problem in the X chromosome of the factor 8-c, but there is a problem in the Factor8-related Antigen, and this results in rapid destruction of Factor8-c.
- NO ADHESION → NO ACTIVATION of platelets → NO AGGREGATION → NO COAGULSTION

	Hemophilia A	Hemophilia B	Von Willebrand's disease
Inheritance	Sex-linked (recessive)	Sex-linked (recessive)	Somatic (Dominant)
Platelets count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Factor VIII:C	Low	Normal	Low
Factor VIII:AG	Normal	Normal	Low
Aggregation	Normal	Normal	Impaired

■ Clinical features of patients with these defects:

Severely affected infants may suffer from profuse post-circumcision hemorrhage. Prolonged bleeding occurs after dental extraction. Operative and post-traumatic hemorrhage are life-threatening in both severely and mildly affected patients

4 Hereditary disorders of other coagulation factors

- Extremely rare, and their mode of inheritance is somatic (autosomal).
- **Factor XII (12) deficiency** is not associated with abnormal bleeding (the deficiency of factor XII (12) does not cause severe bleeding, because platelets can directly activate Factor XI (11))
- **Factor XI (11) deficiency**: not that serious problem, mild symptoms (stimulated directly by platelet).
- **Factor 13 deficiency** causes severe bleeding because the coagulation isn't "stable". Factor 13 (fibrin stabilizer) is activated under the effect of thrombin and Ca++, it stabilizes fibrin
- Vitamin K-dependent factor: Factor 2, 7, 9, 10, Protein C and S, these factors aren't synthesized properly **in case of vitamin K deficiency**
- There is usually a good correlation between the patient's symptoms and the severity of the coagulation deficiency.

Anticoagulants

■ Anticoagulants are used in medication (in vivo) and in lab experiments (in vitro) to prevent blood clotting and coagulation.

■ They are grouped into three groups:

Coumarin- like anticoagulants	Non-Wettable surface	Substances that capture the Ca++
-They are called in vivo Warfarin-like anticoagulants. -They prevent coagulation by preventing the formation of prothrombin and delaying the conversion of prothrombin into thrombin by limiting the activity of thrombokinase.	We put the blood in a tube covered by wax, silicon or polystyrene. In this way, we inhibit the formation of Thrombokinase.	-Oxalate, citrate, EDTA; block the action of Ca++. -Ca++ (Coagulation factor 4) is present in the whole intrinsic pathway, EXCEPT the first two steps.

- We also have Heparin, Hirudin and the stirring method

(1) Heparin → It inhibits the whole intrinsic pathway by binding to anti-coagulant 3
(2) Hirudin → It's a chemical found in leeches, and it inhibits the action of thrombin
(3) Stirring (mechanical method) →fibrin is removed and thus coagulation is inhibited.

- In medications we mostly use Heparin and Warfarin.

Warfarin	Heparin
Plant origin	Animal source (already present in our bodies). Secreted by basophils
Slow acting (takes up to one day for it to start its function)	Acts rapidly
Its effect lasts for days, longer duration (duration of action)	Shorter duration of action
*It inhibits the formation of vitamin k dependent factors. *Therefore, it is used in vivo, since there is no VITAMIN K synthesis in vitro (mechanism of action)	*Disturb the formation of thrombokinase and it may inhibit the reaction between thrombin and fibrinogen. *It's used in vivo and vitro (Mechanism of action)