HEMATOLOGY
&LYMPH SYSTEM

physiology sheet

Number	11
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Correction	
Doctor	

Revision of sheet 10

Factors which 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 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).

They are either endogenous or exogenous:

- **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 production of plasmin from plasminogen.

Clot retraction time:

Assume we have a sample of untreated blood (blood with no anti- coagulants) which 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 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 which play a vital role in clot retraction:

a. Platelets

b. Calcium

Clot retraction measures the normal platelet count and the normal calcium present in 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 remained , this clot sometimes -by the effect of blood flow- is removed from its attachment site and moved throughout the circulation, this condition is called embolism, and the circulating clot is called 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 heart or lungs.

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

General causes of thrombus:

1. Injury to a blood vessel by a trauma, this will activate intrinsic or extrinsic pathways which start a coagulation cascade, which in turn will lead to formation of a thrombus.
2. Infection, this 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 blood stream , after major surgery or childbirth there is an increased risk of developing thrombosis and embolism. This may be due to the fact that the flow of blood in veins becomes sluggish

- Changes in blood composition and slowing of the blood stream might occur during delivery or after a major surgery, since both sleep for a long time and sometimes they cannot move.
- Doctors' advise the patients to walk after a 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 formation of a blood clot or a circulating thrombus (embolus).

Hemostatic Defects:

- **Causes of hemostatic defects:**
  1. **Vascular disorder.**
  2. **Platelets *count* disorder. (Thrombocytopenia)**
  3. **Platelets *function* disorder. (Thrombocytopathia)**
  4. **Coagulation factors disorders.**
  5. **Excessive fibrinolytic system.**

Which of these causes is the most common cause?

First is platelets count abnormality , then comes coagulation factors abnormality , platelets function abnormality comes last.

1) Vascular disorder:

The problem here is in the blood vessel itself where the blood vessel becomes fragile and easily bruised (called purpura) , thus blood vessels will rupture, and bleeding will ensue. (This disorder becomes serious in old age)

This disorder is either genetic (inherited) or acquired.

- **Genetic**: usually appears mild during childhood and then becomes more numerous (more vessels affected) during adulthood. It is characterized by microvascular swelling with minor bleeding.
- **Acquired (latent)**: examples:

1. Senile purpura: easily bruised fragile blood vessels because of advancing age. This occurs due to atrophy of supporting tissues of the cutaneous blood vessels and is seen mainly in the dorsal aspects of the forearm and hands.

2. Purpura associated with infection especially viral infections

3. Scurvy: vitamin C deficiency, it causes purpura.

4. Steroid purpura: a result of prolonged steroid therapy such as cortisol.

2) Platelets number disorder:

- Most commonly thrombocytopenia: low platelets count characterized by continues skin bruising (purpura) . Platelets maintain the integrity of the blood vessel and when there is a low count of platelets this will affect their integrity.
- **Thrombocytopenia is characterized by spontaneous skin purpura , mucosal hemorrhage and prolonged bleeding after trauma.**

Causes of thrombocytopenia:

- Failure of platelets 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.
- Splenomegaly: enlarged spleen which captures a lot of platelets (abnormal distribution of platelets).
- Dilutional loss of platelets by massive blood transfusion to bleeding patients.

Thrombocytopenic purpura: It is a purpura due to low platelets count, when platelets' count is low, clot retraction is deficient, so there is poor constriction or ruptured blood vessels . It is characterized by higher susceptibility to bruising and multiple subcutaneous hemorrhages.

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

3) Platelet function disorder :

Thrombocytopathia: Platelet function abnormality. It means that there is a problem in the function of the platelets.

It's either:

- **Genetic:** deficiency in any of the platelet's components contents 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.
- **Acquired:** Aspirin therapy; very high doses of aspirin

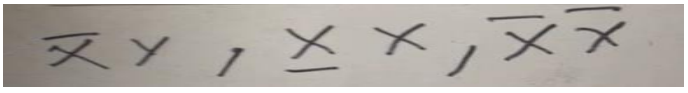
Thrombasthenic purpura; easily bruising due to problem in the platelets function. Purpura may occur when the count of the platelet is normal but the circulating platelets are abnormal.

4) Coagulation factors disorder:

- Inherited deficiencies of most of coagulation factors have been described.
- An Inherited deficiency of a coagulation factor, such as Hemophilia A (deficiency of factor VIII "8"), Hemophilia B (a deficiency of factor IX "9"), von Willebrand's Diseases all are uncommon, but the other factors disorders are rare!

- **Hemophilia A**:

- The most common inherited coagulation defect among the uncommon.
- Incidence 1:10,000.
- Factor VIII:C is deficient, but Factor VIII:AG (related antigen) is intact. **That will lead to coagulation defect only**. {see the figure below}
- Sex-linked (still 30-35% of patients don't have a family history)
- Appears in Males.
- Females are only carriers (a female could become diseased 2 abnormal genes (Homozygous), but it would be Fatal).



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Hemophilic male , carrier female , Hemophilic female (fatal)

- **Von Willebrand's disease**:
  - Inheritance is autosomal {somatic}
  - No problem in the X chromosome of the factor VIII:C , but there is a problem in the Factor VIII:AG , and this results in rapid destruction of Factor VIII:C which leads to **platelets adhesion and coagulation defect.** {figure2 }

- **Hemophilia B**:
  - Sex-linked.
  - Similar symptoms to Hemophilia A, but less common.
  - Factor IX is deficient.

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.

Remember that:

- Factor 8-related Antigen : for Aggregation
- Factor 8 (VWF) : for Adhesion
- Factor 8-c : for Clotting.

The Doctor compared between them, study the table below.

Table 13.2 Main clinical and laboratory findings in haemophilia A, factor IX deficiency (haemophilia B, Christmas disease) and von Willebrand's disease.

	Haemophilia A	Factor IX deficiency	Von Willebrand's disease
Inheritance	Sex-linked	Sex-linked	Dominant
Platelet 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

Hereditary disorders of other coagulation factors

1) All these disorders are rare.
2) In most , inheritance is autosomal (somatic).
3) There is usually a good correlation between the patients symptoms and the severity of the coagulation deficiency.
4) Factor XII is not associated with abnormal bleeding.
5) Factor XI deficiency produces mild symptoms (Hemophilia C).
6) Factor XIII deficiency produces severe bleeding tendency because fibrin threads are not stabilized.

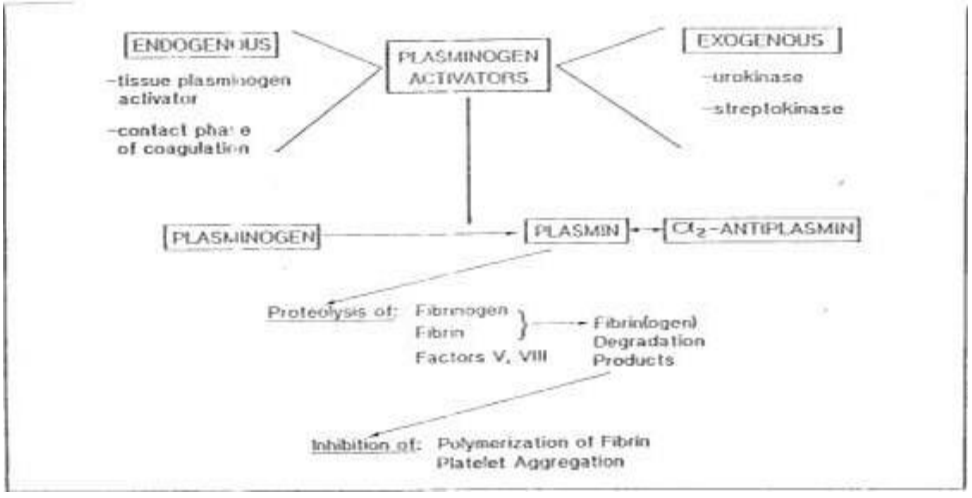


Figure 1

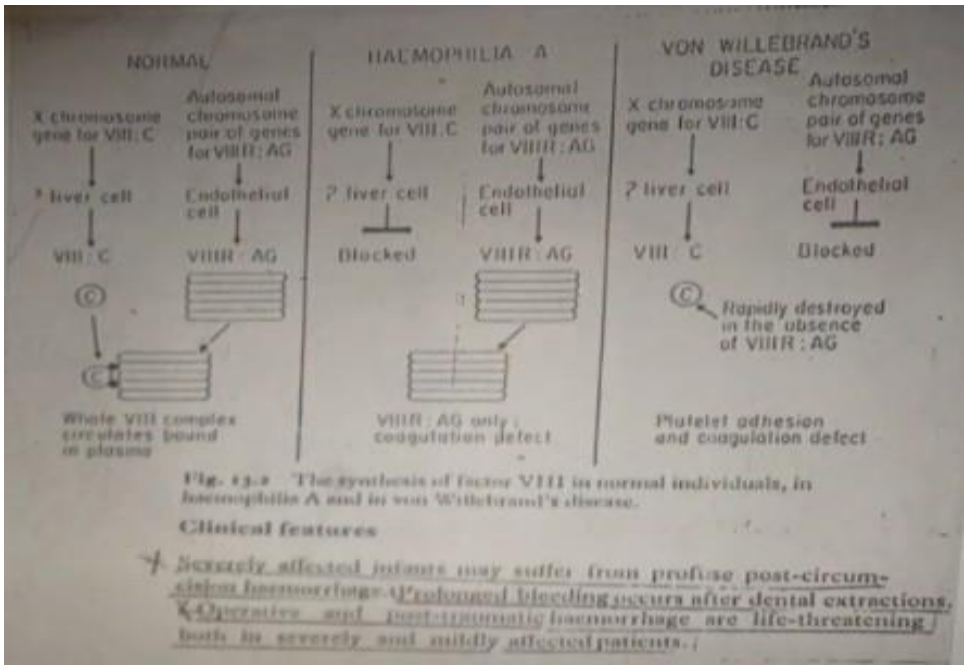


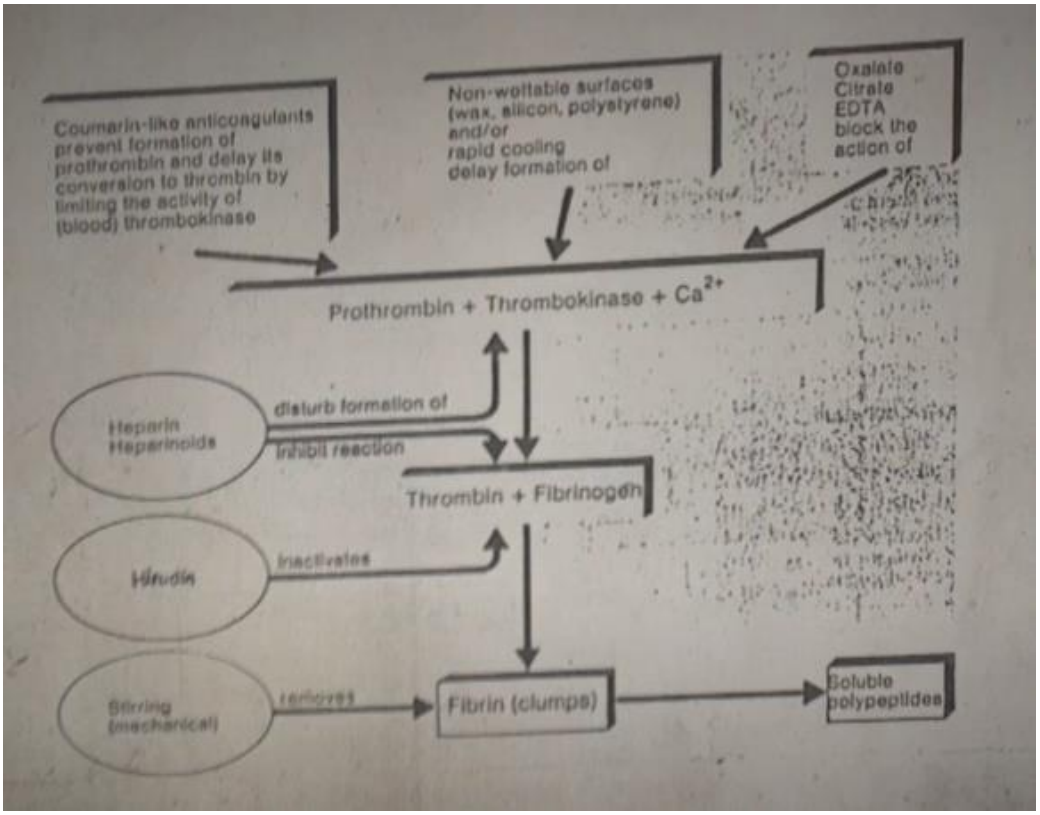
Fig. 13.2 The synthesis of factor VIII in normal individuals, in haemophilia A and in von Willebrand's disease.

Figure 2

Clinical features

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

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:

A. Coumarin-like anticoagulants:
Also called **<u>Warfarin-like</u>** anticoagulant.
They prevent coagulation by preventing the formation of prothrombin and delaying the conversion of prothrombin into thrombin by limiting the activity of thrombokinase.

B. Non-Wettable surfaces:
We put the blood in a tube covered by wax, silicon or polystyrene. Taking the blood "nicely and smoothly" in a tube covered by silicon or wax, by this way we <u>inhibit the formation of Thrombokinase.</u>

C. Substances that capture the Ca++:
- Oxalate, citrate, EDTA; they 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 disturbs the formation of thrombokinase.

It **inhibits the whole intrinsic pathway** by binding to anti-thrombin 3.

(2) Hirudin:

It's a chemical found in **leeches,** and it **inhibits the action of thrombin**.

(3) Stirring: (mechanical method)

By stirring, **fibrin is removed** and thus coagulation is inhibited.

Warfarin :

- Interferes with the **production of vitamin K dependent coagulation factors** (2,7,9,10) by blocking the synthesis of vitamin K.
  SO only used in vivo, since there is no VITAMIN K synthesis in vitro.

In medications we mostly use **Heparin and **Warfarin**:

The following table compares between the two:

Warfarin	Heparin
Of plant origin.	Of animal source (already present in our bodies). Secreted by basophils.
Slow acting (takes up to one day for it to start its action)	Acts rapidly.
Its effect lasts for days, longer duration (duration of action)	Shorter duration in comparison
It inhibit the formation of vitamin k dependent factors therefore its used only in vivo (mechanism of action)	Disturb the formation of thrombokinase and it may inhibit the reaction between thrombin and fibrinogen. It's used in vivo and in vitro. (Mechanism of action).