HLS

Sub: Physiology

Done by: Mofeed Obeidat

Lec no: 5

Title: Blood Coagulation

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Designed by: MO

الموضوع بسيط بدنا نحكي عن العوامل الي
بتسبب التجلط والمادة بسيطة ان شاء الله

MODULE
HLS (HEMO & LYMPH)

Physiology Lectures
Lecture No. (4+5)
Slides By: Malek Hassan
Notes By:

Hayat Batch-Scientific Team

PLATELETS (THROMBOCYTES)

HEMOSTASIS

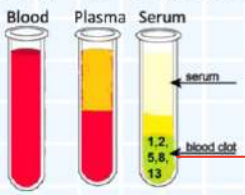
The Hemostatic process consists of the following:

C. **Fibrin Blood Clot Formation** to stabilize the temporary platelet plug.

Clotting Factors were given numbers to simplify the description of the clotting mechanisms. They are given an "a" when they are activated.

هذا factor
يعني XII هذا inactive بس
active form هذاXIIa

1. **Fibrinogen Group :**
   - I , V, VIII & XIII (13 = 8+5 ,1) .
   - Activated by Thrombin.
   - Not present in Serum.
2. **Prothrombin Group :**
   - II, VII, IX & X (1972) .
   - Need Vitamin K for synthesis
   - Prothrombin is Not present in serum.
3. **Contact Group :**
   - XI and XII.
   - Present in serum



Fibrinogen is formed in the liver, and liver disease can decrease the concentration of circulating fibrinogen, as it does the concentration of pro- thrombin, pointed out earlier.

الدكتورة حكت ان اسماء الـ factors مش حفظ الا الي محدد

Table 36-1 Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight kininogen)
Platelets	

General Mechanism of blood coagulation: Clotting takes place in three essential steps: (1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical cal reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation of a complex of activated substances collectively called prothrombin activator. (2) The prothrombin activator catalyzes conversion of prothrombin into thrombin. (3) The thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form the clot.

Let us discuss first the mechanism by which the blood clot itself is formed, beginning with conversion of prothrombin to thrombin; then we will come back to the initiating stages in the clotting process by which prothrombin activator is formed.

PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

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The Clotting Mechanism :

The loose platelet plug changes to a definitive blood clot by conversion of soluble fibrinogen to insoluble fibrin.

Fibrinogen forms loose fibrin which becomes a dense fibrin clot by forming cross-linkages. **This reaction is Catalyzed by factor XIII and Ca^{2+}**

Activated by Either Intrinsic or Extrinsic pathways.

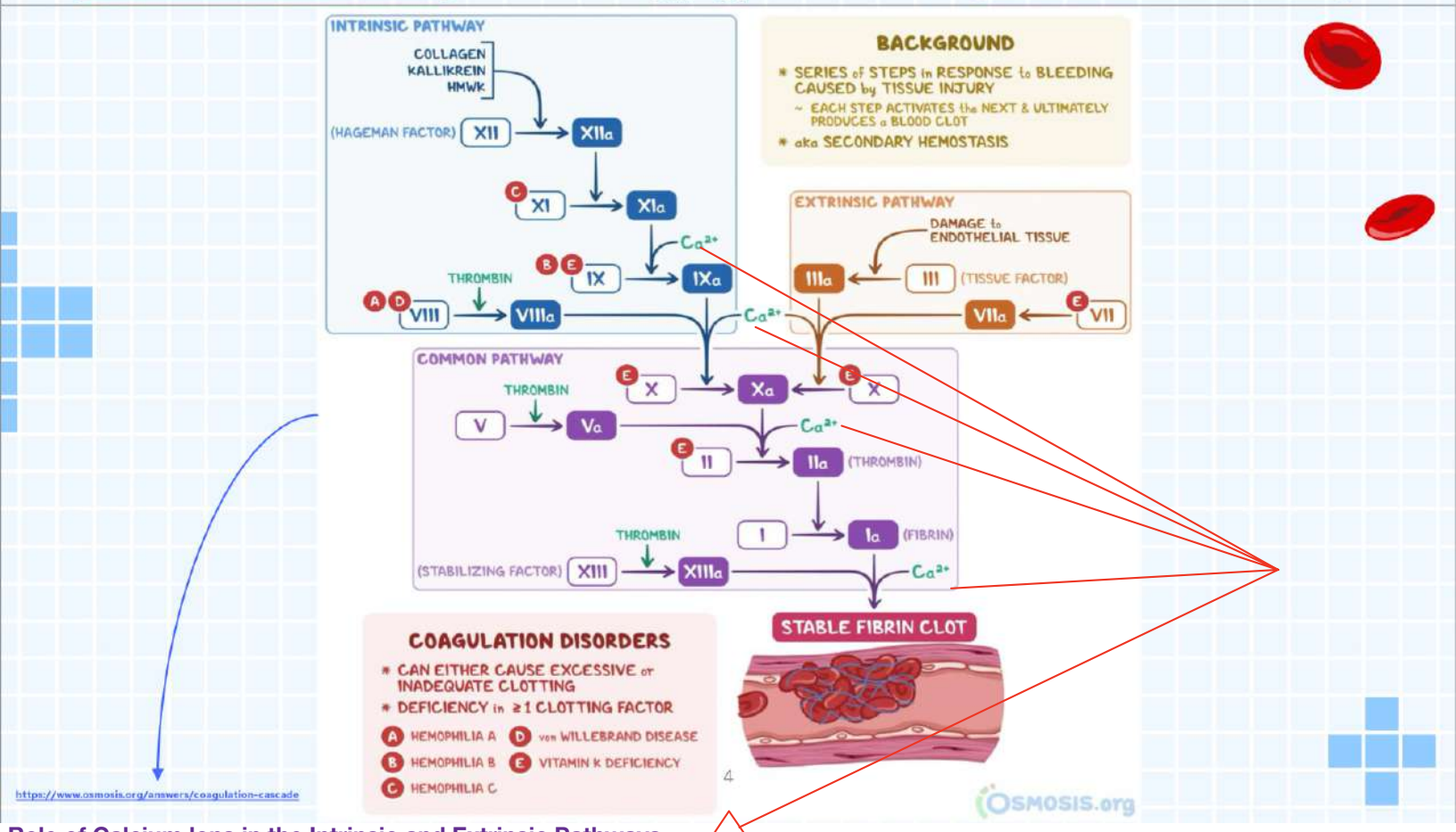
Prothrombin → (Xa) → **Thrombin**

The Conversion of Fibrinogen to Fibrin is Catalyzed by Thrombin, which is formed from Prothrombin in the presence of Active factor X.

Fibrinogen → **Fibrin Monomer + 2 pairs of polypeptide chains**

Fibrin Monomers Polymerize → **Loose Mesh of Fibrin**

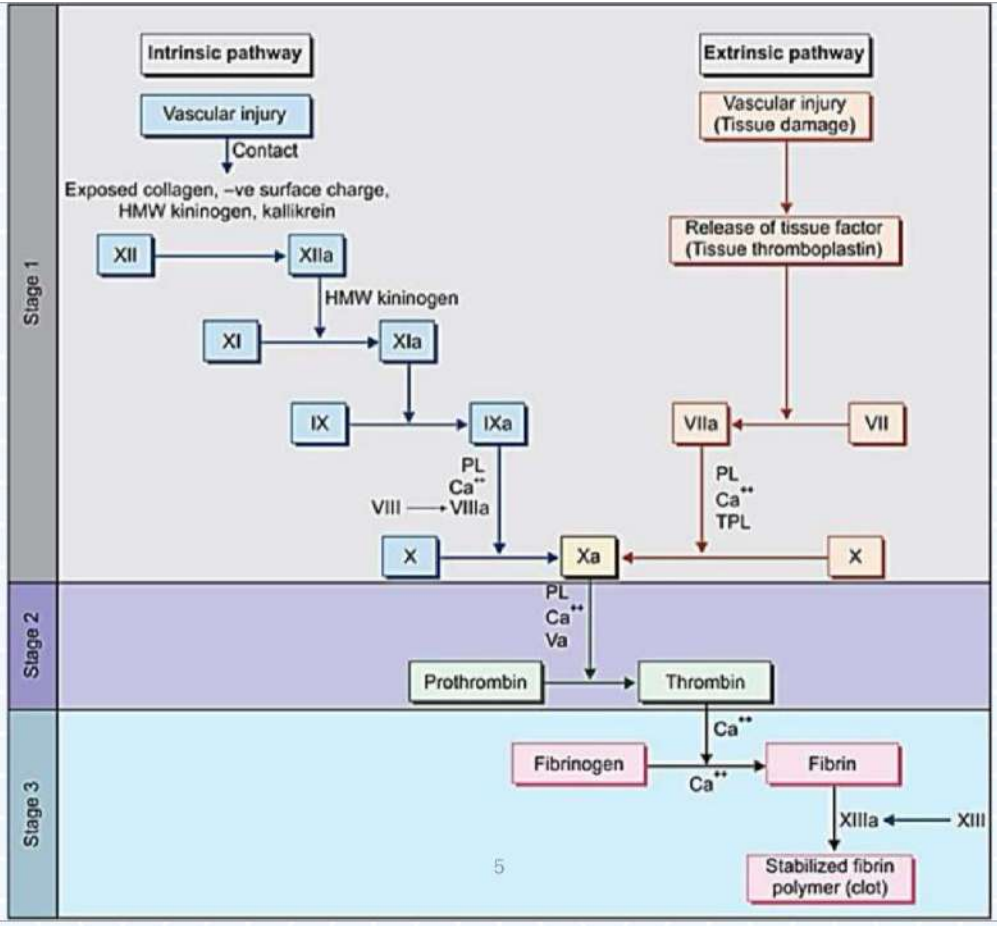
Loose Mesh of Fibrin → (Cross Linkage, XIII + Ca^{2+}) → **Thrombin**



Role of Calcium Ions in the Intrinsic and Extrinsic Pathways

Except for the first two steps in the intrinsic pathway, calcium ions are required for promotion or acceleration of all the blood-clotting reactions. Therefore, in the absence of calcium ions, blood clotting by either pathway does not occur.

In the living body, the calcium ion concentration seldom falls low enough to significantly affect the kinetics of blood clotting. But, when blood is removed from a person, it can be prevented from clotting by reducing the calcium ion concentration below the threshold level for clotting, either by deionizing the calcium by causing it to react with substances such as citrate ion or by precipitating the calcium with substances such as oxalate ion.



PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

C. Fibrin Blood Clot Formation to stabilize the temporary platelet plug.

Factor X is Activated by Either Intrinsic or Extrinsic pathways.

A. Intrinsic Pathway :

Platelets factor 3

This System is called Intrinsic, as the Phospholipids involved in the reactions arise from platelets (PF3), i.e., it is present in plasma.

Initiation of the pathway may occur either:

i. **In Vivo: by contact of blood with Subendothelial Collagen of the damaged vessel.**

ii. **In Vitro: by contact of blood with:**

- **Electronegative charged wet surfaces, e.g., a glass of a test tube.**
- **Collagen Fibers**

1. **Any of the previously mentioned factors activates factor XII.**
2. **XIIa activates factor XI, which in turn activates IX.**
3. **IXa forms a complex with VIIIa and activates factor X in the presence of phospholipids (PL) and Ca^{2+}**

PLATELETS (THROMBOCYTES)

Factor X is Activated by Either Intrinsic or Extrinsic pathways.

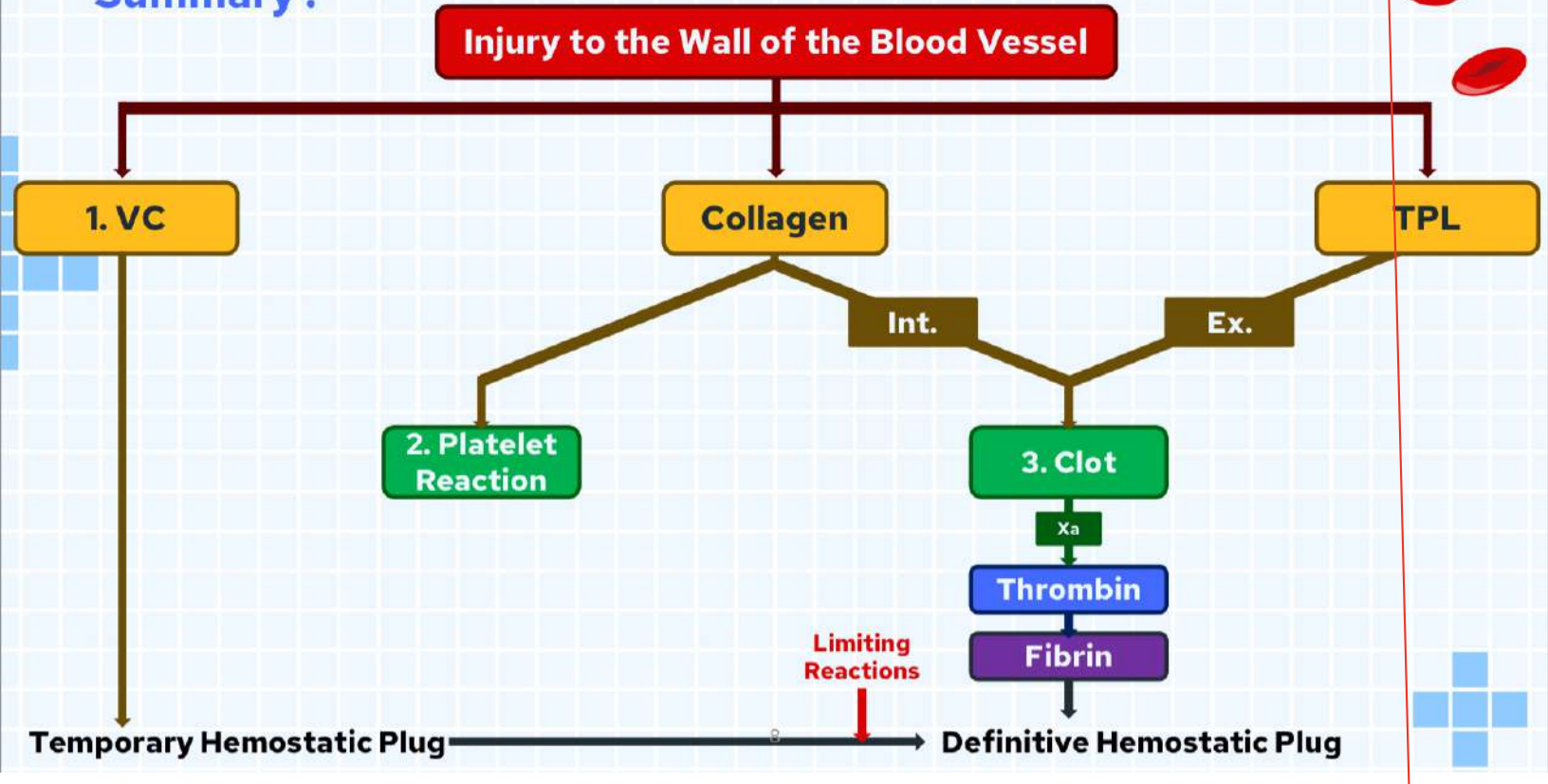
B. Extrinsic Pathway : الشرح تحت

- This system is called Extrinsic as it requires the presence of phospholipids from outside blood vessels.
- It is initiated Only in Vivo by factor III : Tissue Thromboplastin (TPL) released from damaged tissues. (Tissue factor)
- TPL activates factor VII, which directly activates factor X in the presence of Ca^{2+}, TPL and PL, and indirectly through the activation of factor IX.

Common Part in Both Pathways :

- Xa (activated by intrinsic and extrinsic pathways) catalyzes the conversion of Prothrombin to Thrombin in the presence of factor V, PL, and Ca^{2+}.
- Finally, Thrombin transforms Soluble Fibrinogen into Insoluble Fibrin.
- Thrombin in the presence of Ca^{2+} also activates factor XIII, which stabilizes the Fibrin Clot. Platelets, Blood Cells and Plasma become entangled in the clot.
- Contraction of the Platelets in the Fibrin Mesh causes clot retraction and squeezes serum out.
- The Serum is devoid of Fibrinogen, Prothrombin and factors V, VIII and XIII which become consumed during clotting.

Summary :



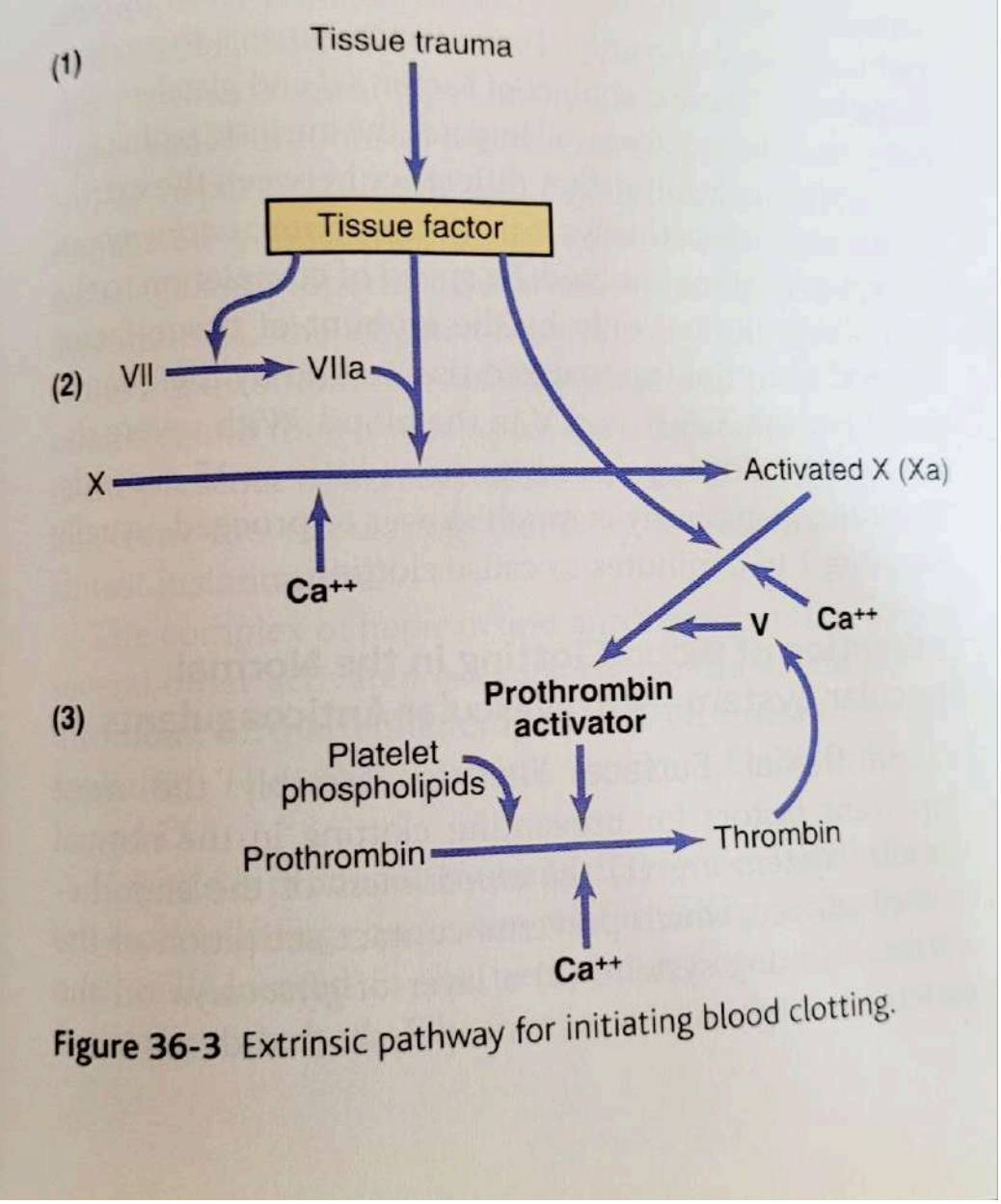


Figure 36-3 Extrinsic pathway for initiating blood clotting.

1 Release of tissue factor.

هاي المعلومات في منها بالشرح والباقي للاستزادة

Traumatized tissue releases a complex of several factors called tissue factor or tissue thromboplastin. This factor is composed especially of phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme

2 Activation of Factor X-role of Factor VII and tissue factor. The lipoprotein complex of tissue factor further complexes with blood coagulation Factor VII and, in the presence of calcium ions, acts enzymatically on Factor X to form activated Factor X (Xa).

3.Effect of Xa to form prothrombin activator-role of Factor V. The activated Factor X combines immediately with tissue phospholipids that are part of tissue factors or with additional phospholipids released from platelets, as well as with Factor V to form the complex called prothrombin activator. Within a few seconds, in the presence of calcium ions (Ca++), this splitsprothrombin to form thrombin, and the clotting process proceeds as already explained. At first, the Factor V in the prothrombin activator complex is inactive, but once clotting begins and thrombin begins to form, the proteolytic action of thrombin activates Factor V. This then becomes an additional strong accelerator of prothrombin activation. Thus, in the final prothrombin activator complex, activated Factor X is the actual protease that causes splitting of prothrombin to form thrombin; activated Factor V greatly accelerates this protease activity, and platelet phospholipids act as a vehicle that further accelerates the process. Note especially the positive feedback effect of thrombin, acting through Factor V, to accelerate the entire process once it begins

PLATELETS (THROMBOCYTES)

Important Notes :

- Von Willebrand factor (vWF) is a glycoprotein crucial to Primary Hemostasis through Platelet and Subendothelial Collagen Adhesion and the Intrinsic Coagulation Cascade, through factor VIII stabilization. It resides in the Plasma, Subendothelial Matrix & Storage Granules within Endothelial cells & Platelets.

- During Primary Hemostasis, vascular injury exposes vWF bound to Subendothelial Collagen. Then, Glycoprotein 1b (GP1b) receptors on the surface of nearby platelets adhere to the exposed vWF, triggering Platelet Activation and a Cascade of Events which includes the release of platelet storage granule content such as vWF from alpha granules and the recruitment of more platelets to form a plug at the site of damaged Endothelium.

- Plasma vWF supports the Intrinsic Coagulation Cascade by stabilizing factor VIII, thereby increasing its circulating half-life. During the Intrinsic Coagulation Pathway, Thrombin cleaves the factor VIII binding site with vWF, allowing the release (activation) of factor VIIIa to continue the clotting process. By serving as a carrier for factor VIII, vWF influences the Common Coagulation Pathway and the generation of Thrombin and Fibrin.

PLATELETS (THROMBOCYTES)

Important Notes :

- The Extrinsic Pathway is Very Rapid (15 sec.), while the Intrinsic Pathway is Slow (1-6 min.).

- Injury of a Blood Vessel will trigger both the Intrinsic System (by Collagen) and the Extrinsic System (by TPL).

- In the test tube, clotting occurs Only by the Intrinsic system (glass or addition of collagen).

- In Intravenous Thrombosis, blood clotting occurs via the Intrinsic System, which is initiated by The Exposure of Clotting Factors to Collagen.

Thrombin functions :

- Activates Fibrinogen to Fibrin.
- Activates the other factors of the Fibrinogen group (V, VIII, and XIII)
- Accelerates the actions of factors IX, X, and XI
- Accelerates the formation of more Thrombin from Prothrombin (Positive Feedback).
- Accelerates Platelet Aggregation and Fusion.

Therefore, as soon as a small amount of Thrombin is formed, the clotting reactions are markedly enhanced by Thrombin, and the clot continues to grow until this process is Stopped by Limiting Reactions.

PLATELETS (THROMBOCYTES)

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PLATELETS (THROMBOCYTES)

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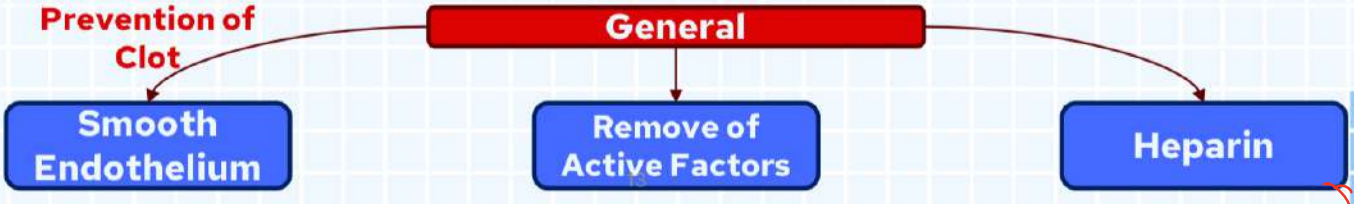
Anticlotting Mechanisms = Limiting Reactions

The Tendency of blood to clot is balanced in Vivo by limiting reactions that prevent blood clotting in healthy Blood vessels and break down any clots already formed.

A. **General Limiting Reactions:**

1. **Smooth Vascular Endothelium** prevents activation of platelets & factor XII.
2. **Rapid Blood flow Removes Activated Clotting Factors and inactivates them in the liver.** So, slow blood flow favors Intravascular Thrombosis.
3. **Heparin** is a natural Anticoagulant present in the blood.



HEMOSTASIS

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B. Specific limiting reactions:

1. **Thromboxane A2 and Prostacyclin:** The formation of Thromboxane A2 at the site of Blood vessel injury allows clot formation, while the synthesis of Prostacyclin by healthy Endothelium prevents the spread of the blood clot to neighboring healthy areas and obstruction of the lumen of blood vessels.
2. **Antithrombin III:**
   This Circulating Inhibitor of Blood Coagulation binds to active factors II, IX, X, XI, and XII, blocking their activity. This binding is facilitated by Heparin.
3. **The Fibrinolytic System:**

- **Thrombomodulin** is produced by most Endothelial cells. This protein binds Thrombin to form the Thrombomodulin-Thrombin complex, which activates protein C.
- **Activated protein C** (APC) causes:
  - Inactivation of factors Va and VIIIa, and
  - Inactivation of the inhibitor of tissue Plasminogen activator (tPA)=(TPA-I), increases the formation of plasmin.
- **Plasmin** (fibrinolysin) lyses Fibrin and Fibrinogen, forming Fibrinogen Degradation Products (FDP), inhibiting Thrombin.

Anticoagulant for clinical use

Heparin

Commercial heparin is extracted from several different animal tissues and prepared in almost pure form. Injection of relatively small quantities, about 0.5 to 1 mg/kg of body weight, causes the blood-clotting time to increase from a normal of about 6 minutes to 30 or more minutes. Furthermore, this change in clotting time occurs instantaneously, thereby immediately preventing or slowing further development of a thromboembolic condition.

The action of heparin lasts about 1.5 to 4 hours. The injected heparin is destroyed by an enzyme in the blood known as heparinase.

Coumarins as Anticoagulants

When a coumarin, such as warfarin, is given to a patient, the amounts of active prothrombin and Factors VII, IX, and X, all formed by the liver, begin to fall. Warfarin causes this effect by inhibiting the enzyme, vitamin K epoxide reductase complex 1 (VKOR c1). As discussed previously, this enzyme converts the inactive, oxidized form of vitamin K to its active, reduced form. By inhibiting VKOR c1, warfarin decreases the available active form of vitamin K in the tissues. When this occurs, the coagulation factors are no longer carboxylated and are biologically inactive. Over several days the body stores of the activecoagulation factors degrade and are replaced by inactive factors. Although the coagulation factors continue to be produced, they have greatly decreased coagulant activity. After administration of an effective dose of warfarin,

the coagulant activity of the blood decreases to about 50 percent of normal by the end of 12 hours and to about 20 percent of normal by the end of 24 hours. In other words, the coagulation process is not blocked immediately but must await the degradation of the active prothrombin and the other affected coagulation factors already present in the plasma. Normal coagulation usually returns 1 to 3 days after discontinuing coumarin therapy.

Lysis of Blood Clots-Plasmin (slide 16)

The plasma proteins contain a euglobulin called plasminogen (or profibrinolysin) that, when activated, becomes a substance called plasmin (or fibrinolysin). Plasmin is a proteolytic enzyme that resembles trypsin, the most important proteolytic digestive enzyme of pancreatic secretion. Plasmin digests fibrin fibers and some other protein coagulants such as fibrinogen, Factor V, Factor VIII, prothrombin, and Factor XII. Therefore, whenever plasmin is formed, it can cause lysis of a clot by destroying many of the clotting factors, thereby sometimes even causing hypocoagulability of the blood.

HEMOSTASIS

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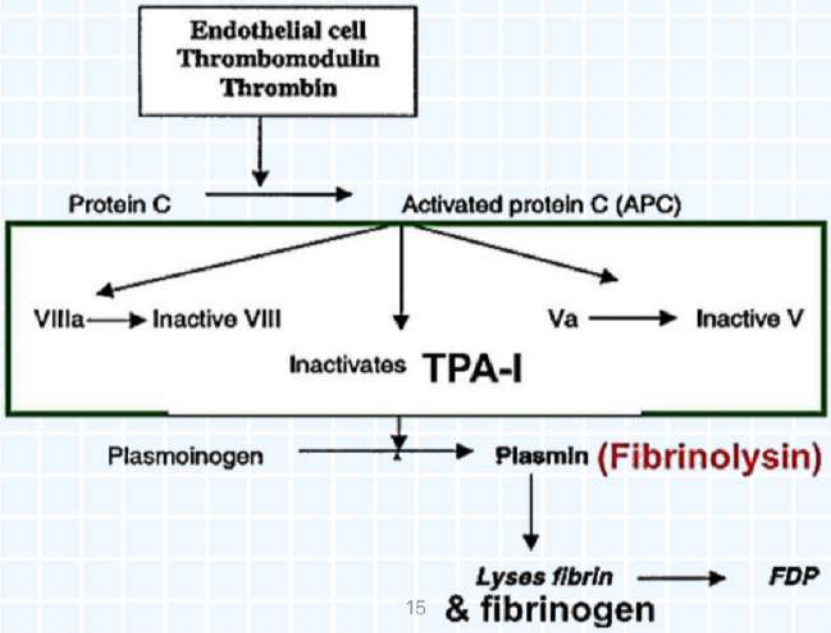

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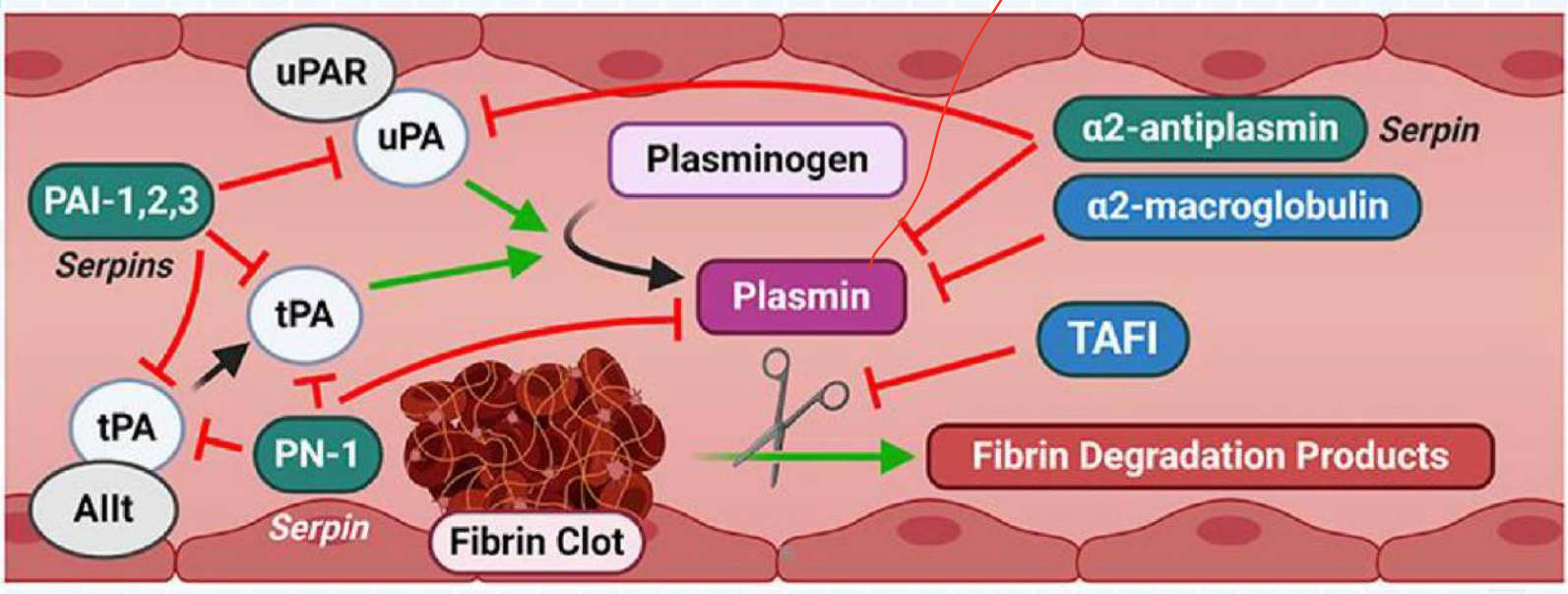

PLATELETS (THROMBOCYTES)

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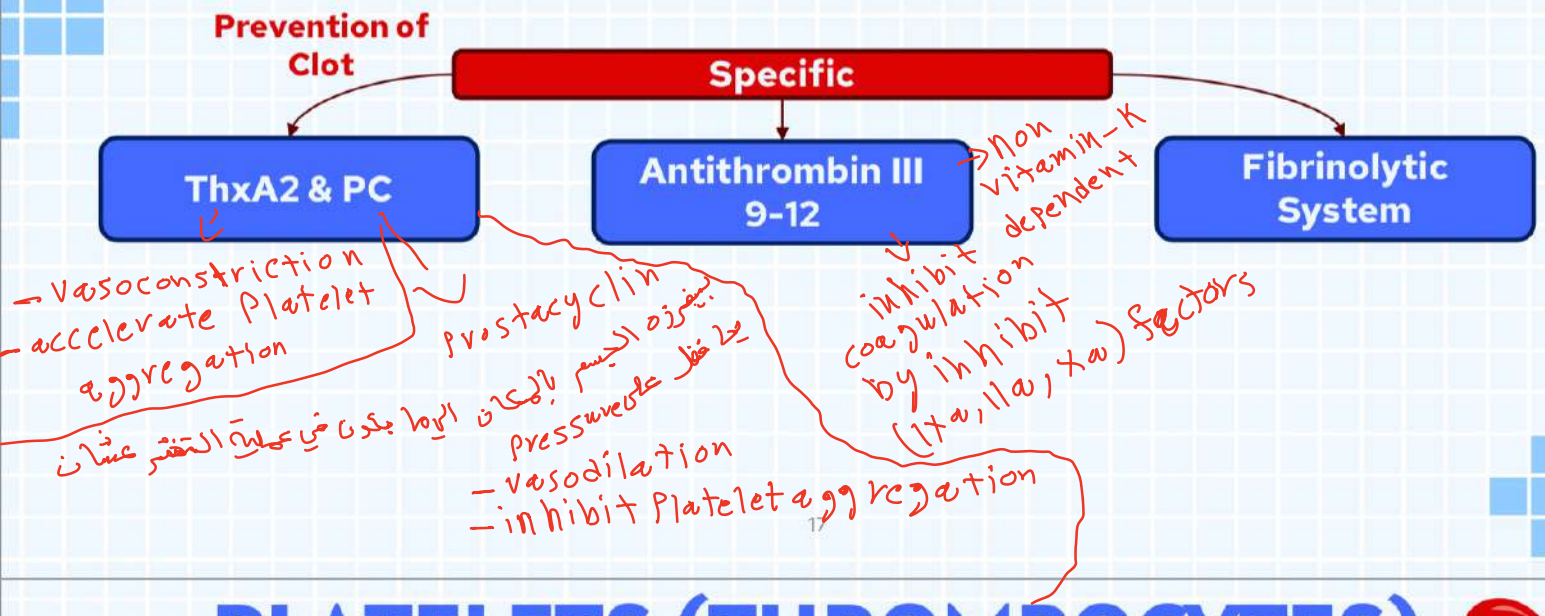


PLATELETS (THROMBOCYTES)

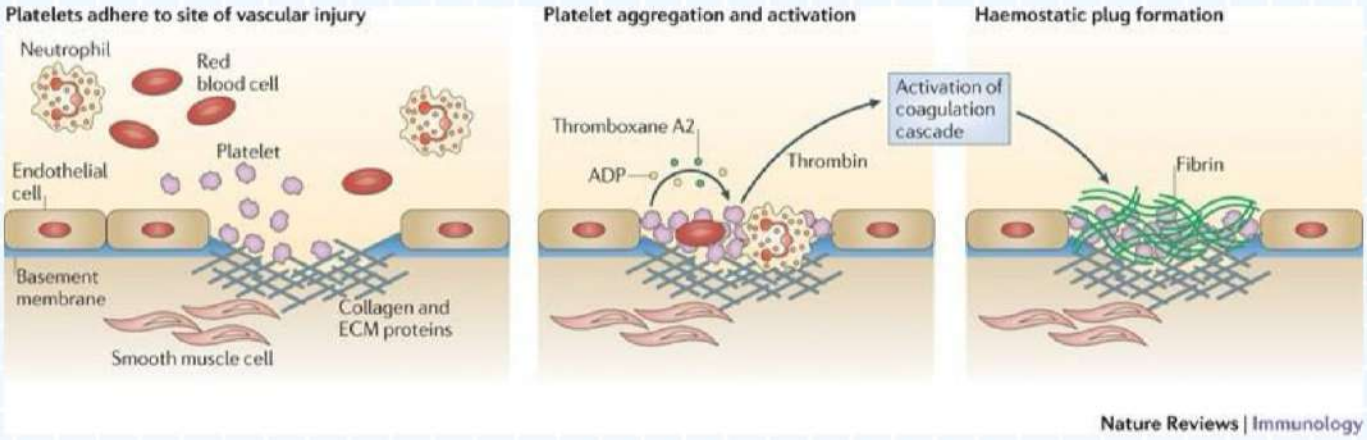
Anticoagulants:

B. In Vivo Anticoagulants:

They prevent Blood clotting **inside the body**.

	Heparin	Dicumarol
Origin	Mast Cells & Basophils.	Plants
Mode of Action	Facilitates action of Antithrombin III (Inactivates II, IX, X, XI, XII)	Competitive Inhibition of Vitamin K on its receptors in the liver → inhibits the formation of II, VII, IX, X.
Site of Action	In Vivo and in Vitro	Only in Vivo
Onset	Rapid	Slow
Duration	Short	Long
Administration	Intravenous (IV) and Subcutaneously (SC)	Orally
Antidote	Protamine Sulfate 1% Fresh Blood transfusion	Vitamin K Fresh Blood transfusion

PLATELETS (THROMBOCYTES)



PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

- **Complete Blood Count (CBC)**
- **Bleeding & Clotting Time**
- **Prothrombin Time (PT)**
- **International Normalised Ratio (INR)**
- **Active Partial Thrombin Time (aPTT)**
- **Platelet Count (PC)**

Bleeding Time

When a sharp-pointed knife is used to pierce the tip of the finger or lobe of the ear, bleeding ordinarily lasts for 1 to 6 minutes. The time depends largely on the depth of the wound and the degree of hyperemia in the finger or ear lobe at the time of the test. Lack of any one of several of the clotting factors can prolong the bleeding time, but it is especially prolonged by lack of platelets

Clotting Time

Many methods have been devised for determining blood clotting times. The one most widely used is to collect blood in a chemically clean glass test tube and then to tip the tube back and forth about every 30 seconds until the blood clotted. By this method, the normal clotting time is 6 to 10 minutes. Procedures using multiple test tubes have also been devised for determining clotting time more accurately.
Unfortunately, the clotting time varies widely, depending on the method used for measuring it, so it is no longer used in many clinics. Instead, measurements of the clotting factors themselves are made, using sophisticated chemical procedures.

Prothrombin Time and International Normalized Ratio

Prothrombin time gives an indication of the concentration of prothrombin in the blood. Figure 36-5 shows the relation of prothrombin concentration to prothrombintime. The method for determining prothrombin time is the following

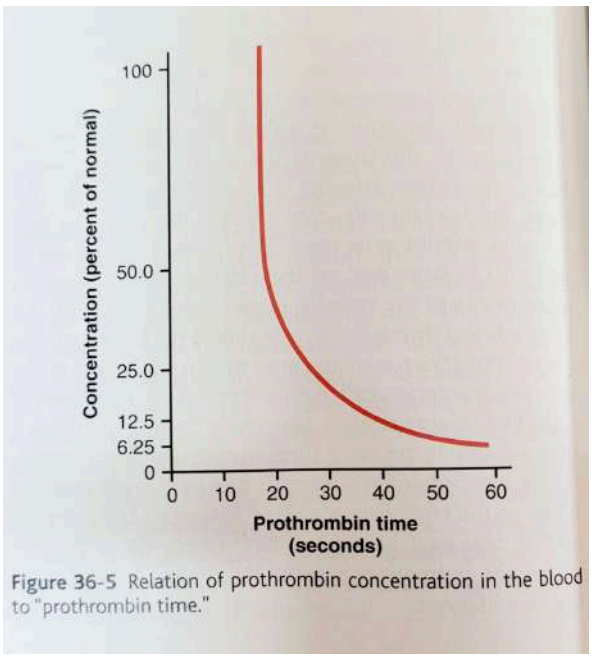


Figure 36-5 Relation of prothrombin concentration in the blood to "prothrombin time."

The results obtained for prothrombin time may vary considerably even in the same individual if there are differences in activity of the tissue factor and the analytical system used to perform the test. Tissue factor is isolated from human tissues, such as placental tissue, and different batches may have different activity. The international normalized ratio (INR) was devised as a way to standardize measurements of prothrombin time. For each batch of tissue factor, the manufacturer assigns an international sensitivity index (ISI), which indicates the activity of the tissue factor with a standardized sample. The ISI usually varies between 1.0 and 2.0. The INR is the ratio of the per- son's prothrombin time to a normal control sample raised to the power of the ISI:

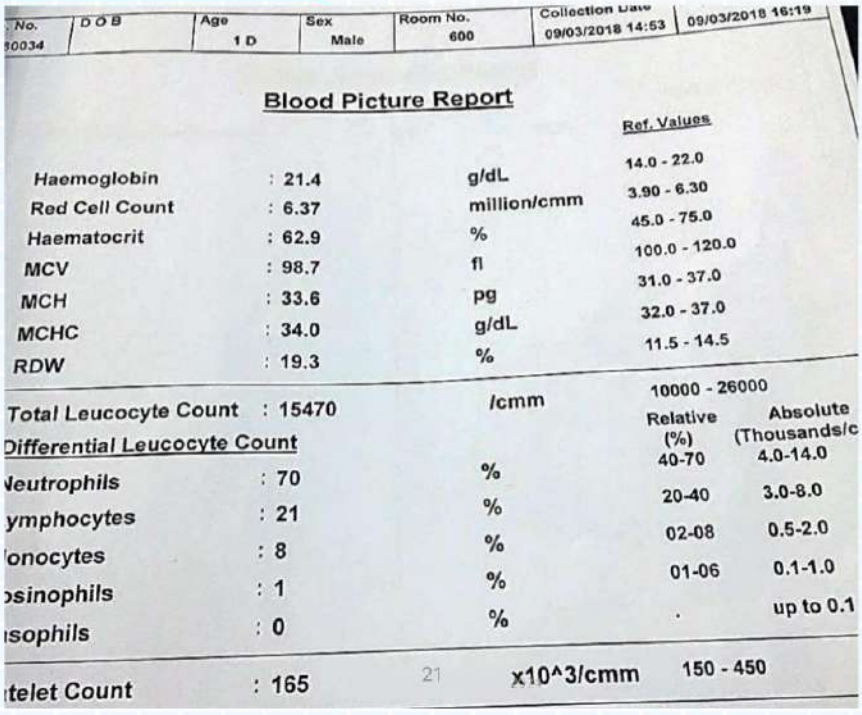
$$INR = \left(\frac{PT_{test}}{PT_{normal}} \right)^{ISI}$$

The normal range for healthy person is 0.9 to 1.3.

Patient on warfarin therapy usually have an INR of 2.0 to 3.0 .

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests



No.	DOB	Age	Sex	Room No.	Collection Date	
30034		1 D	Male	600	09/03/2018 14:53	09/03/2018 16:19

Blood Picture Report

			Ref. Values
Haemoglobin	: 21.4	g/dL	14.0 - 22.0
Red Cell Count	: 6.37	million/cmm	3.90 - 6.30
Haematocrit	: 62.9	%	45.0 - 75.0
MCV	: 98.7	fl	100.0 - 120.0
MCH	: 33.6	pg	31.0 - 37.0
MCHC	: 34.0	g/dL	32.0 - 37.0
RDW	: 19.3	%	11.5 - 14.5
Total Leucocyte Count	: 15470	/cmm	10000 - 26000
Differential Leucocyte Count			Relative (%) / Absolute (Thousands/c
Neutrophils	: 70	%	40-70 / 4.0-14.0
Lymphocytes	: 21	%	20-40 / 3.0-8.0
Monocytes	: 8	%	02-08 / 0.5-2.0
Eosinophils	: 1	%	01-06 / 0.1-1.0
Basophils	: 0	%	. / up to 0.1
Platelet Count	: 165	x10^3/cmm	150 - 450

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PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

1. **Blood Count and Blood Film**

2. **Bleeding Time :**
   It is the Time needed for Bleeding to Stop without blood clotting. The normal bleeding time is 1-3 minutes, depending on platelet count and function. It is prolonged in Thrombocytopenic Purpura.

3. **Tests for Blood Coagulation**
   a. **Clotting time:** It is the Time needed for Blood to Clot. Normally, it is 3-10 minutes at 37° C. It is prolonged in disorders such as Vitamin K deficiency, Hemophilia and Liver Diseases.

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

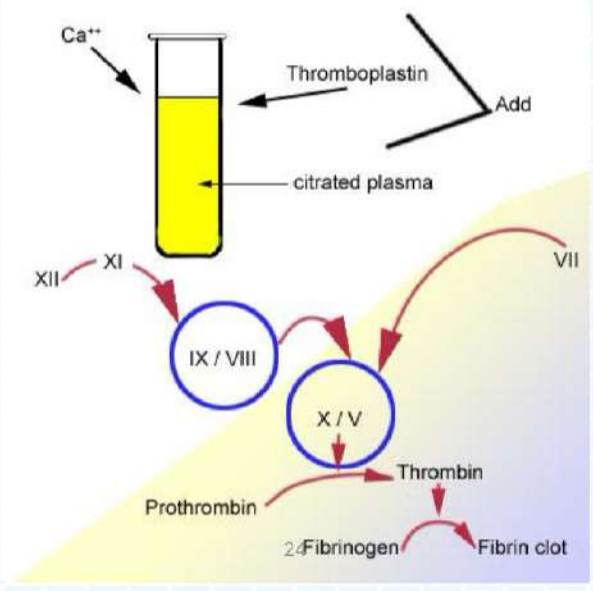
- **Prothrombin Time (PT):** A blood sample is collected in a tube containing Citrate or EDTA to chelate any Calcium and thus inhibit Coagulation, and then the cells are removed by Centrifugation. After the cells are removed, excess Calcium is added with an excess of Thromboplastin to Anticoagulated Plasma to initiate Coagulation. A normal PT is 11.0–12.5 seconds. A PT greater than 20 seconds is indicative of a Coagulation deficit. The result (in seconds) for a Prothrombin Time performed on a normal individual will vary according to the type of Analytical System employed. This is due to the variations between different batches of the manufacturer's tissue factor used in the reagent to perform the test.

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

b. **Prothrombin Time (PT):**



PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

- **International Normalized Ratio (INR):**

The INR was devised to standardize the results.

Each manufacturer assigns an **ISI Value** (**International Sensitivity Index**) for any tissue factor they manufacture. The **ISI value** indicates how a particular batch of tissue factor compares to an international reference tissue factor. **The ISI is usually between 1.0 and 2.0.**

$$INR = \left\{\frac{PT\ (pat)}{Pt\ (n)}\right\}^{ISI}$$

PT (pat)= Patient's prothrombin time

PT (n) = Normal reference range

ISI = International sensitivity index (the optimal ISI is 1.3 to 1.5)

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PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

- **International Normalized Ratio (INR):**

The INR is the ratio of a patient's Prothrombin Time (PT) to a normal (control) sample, Raised to the power of the ISI Value for the Analytical System used.

$$INR = \left\{\frac{PT\ (pat)}{Pt\ (n)}\right\}^{ISI}$$

PT (pat)= Patient's prothrombin time

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ISI = International sensitivity index (the optimal ISI is 1.3 to 1.5)

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A high INR level, such as INR=5, indicates a high chance of bleeding, whereas if the INR=0.5, there is a high chance of having a clot. The Normal INR Range for a Healthy person is 0.9–1.3, and for people on Warfarin therapy, 2.0–3.0. However, the target INR may be higher in particular situations, such as those with a Mechanical Heart Valve

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

- **Activated Partial Thromboplastin Time Test (aPTT):** a test performed to **investigate bleeding disorders** and **to monitor patients taking an anticlotting drug** such as Heparin which inhibits factors X and Thrombin, while activating Anti-Thrombin.
  The Partial Thromboplastin time is the time it takes for a clot to form, measured in seconds. **Normally, the sample will clot in 35 seconds.**

- **Prothrombin Concentration:** **Normally > 70 %.**

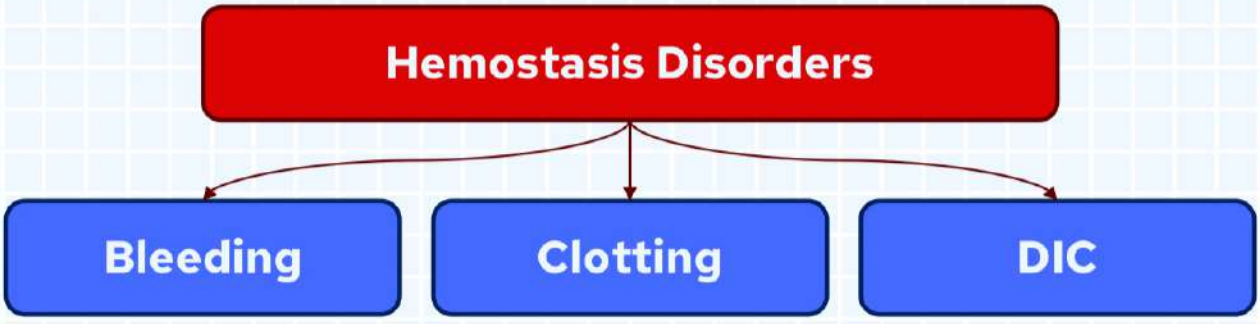
lo.	D O B	Age	Sex	Room No.	Collection Date	Report Date
034		1 D	Male	600	09/03/2018 14:53	09/03/2018 1

Coagulation Report

				Normal Values
Prothrombin Time (PT)	:	17.7	sec	10.1 - 15.9
Prothrombin Activity	:	55.0	%	
INR	:	1.62		Less Than 1.
Partial Thromboplastin Time (PTT)	:	45	sec	31 - 54

PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:



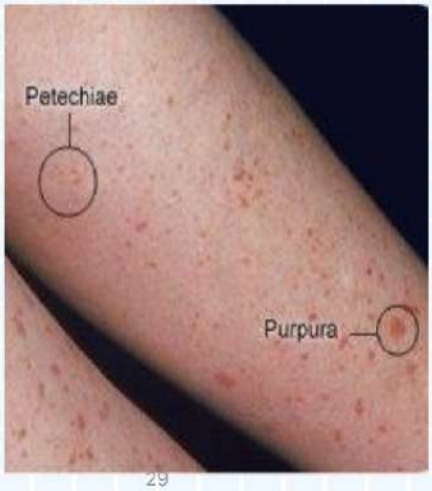
PLATELETS (THROMBOCYTES)

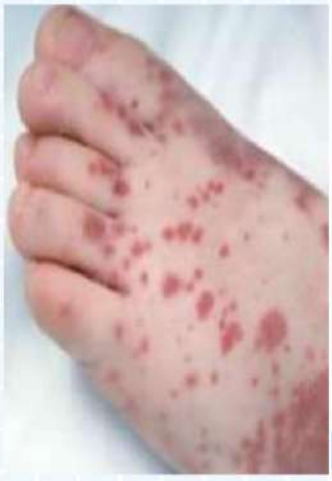
Abnormalities of Hemostasis:

A. **Bleeding:**

1. **Thrombocytopenic Purpura:**

It is due to a **Decreased Platelet Count below 50,000/mm3** . It is characterized by the presence of Subcutaneous Hemorrhages. The Bleeding Time is Prolonged.





PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. **Bleeding:**

2. **Vitamin K Deficiency:**

- **Vitamin K** is essential for forming the **Prothrombin group** (II, VII, IX, and X) in the liver.
- **Vitamin K** is continuously Formed by the Intestinal Flora.
- **Vitamin K** is Fat-Soluble and requires Bile for its Absorption.
- Causes of Vitamin K Deficiency: (associated with prolonged clotting time)
  - ✓ **Absence of Intestinal Flora:** in newborns, Prolonged Oral Antibiotics.
  - ✓ **Absence of Bile:** in Obstructive Jaundice.
  - ✓ **Block of its receptors in the liver by Dicumarol.**

We can summarize the Causes of the Vitamin K Deficiency by:

- Inadequate Intake
- Inadequate Absorption
- Inadequate Utilization
- Vitamin K Antagonist, such as Warfarin

PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

3. Hemophilia:

This is a Congenital Sex-linked Disease carried on the X Chromosome. It is Recessive and is transmitted by Females to their Male sons.

It is characterized by Severe Bleeding, even after mild trauma. Joint Damage (Hemophilia Arthropathy) is the most common complication of bleeding in Hemophilia.

There are three types of hemophilia:

- Hemophilia A: due to the Absence of factor VIII (85% of cases)
- Hemophilia B: due to Deficiency of factor IX (10% of cases)
- Hemophilia C: due to Deficiency of factor XI (5% of cases).

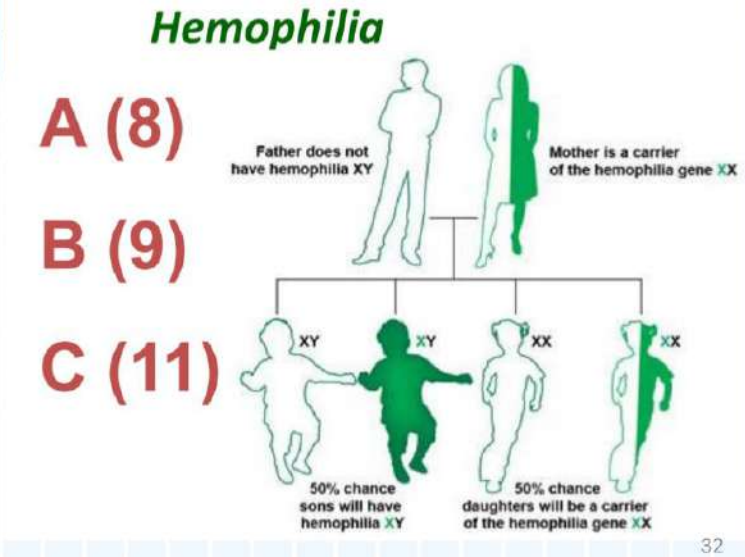
There is prolonged clotting time.

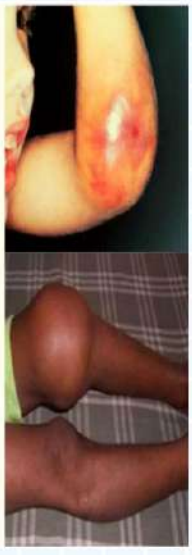
PLATELETS (THROMBOCYTES)

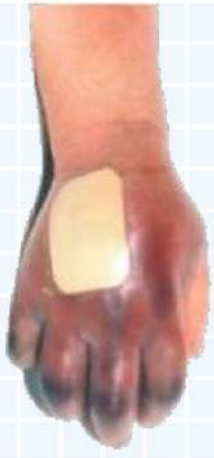
Abnormalities of Hemostasis:

A. Bleeding:

3. Hemophilia:







Decreased Prothrombin, Factor VII, Factor IX, and Factor X Caused by Vitamin K Deficiency

With few exceptions, almost all the blood-clotting factors are formed by the liver. Therefore, diseases of the liver such as hepatitis, cirrhosis, and acute yellow atrophy can sometimes depress the clotting system so greatly that the patient develops a severe tendency to bleed. Another cause of depressed formation of clotting factors by the liver is vitamin K deficiency. Vitamin K is an essential factor to a liver carboxylase that adds a carboxyl group to glutamic acid residues on five of the important clotting factors: prothrombin, Factor VII, Factor IX, Factor X, and protein C. In adding the carboxyl group to glutamic acid residues on the immature clotting factors, vitamin K is oxidized and becomes inactive. Another enzyme, vita- min K epoxide reductase complex 1 (VKOR c1), reduces vitamin K back to its active form.

In the absence of active vitamin K, subsequent insufficiency of these coagulation factors in the blood can lead to serious bleeding tendencies.

Vitamin K is continually synthesized in the intestinal tract by bacteria, so vitamin K deficiency seldom occurs in the normal person as a result of vitamin K absence from the diet (except in neonates before they establish their intestinal bacterial flora). However, in gastrointestinal disease, vitamin K deficiency often occurs as a result of poor absorption of fats from the gastrointestinal tract. The reason is that vitamin K is fat soluble and ordinarily absorbed into the blood along with the fats.

One of the most prevalent causes of vitamin K deficiency is failure of the liver to secrete bile into the gastrointestinal tract (which occurs either as a result of obstruction of the bile ducts or as a result of liver disease). Lack of bile prevents adequate fat digestion and absorption and, there- fore, depresses vitamin K absorption as well. Thus, liver disease often causes decreased production of prothrombin and some other clotting factors both because of poor vita- min K absorption and because of the diseased liver cells. Because of this, vitamin K is injected into surgical patients with liver disease or with obstructed bile ducts before per- forming the surgical procedure. Ordinarily, if vitamin K is given to a deficient patient 4 to 8 hours before the operation and the liver parenchymal cells are at least one-half normal in function, sufficient clotting factors will be produced to prevent excessive bleeding during the operation.

Hemophilia

Hemophilia is a bleeding disease that occurs almost exclusively in males. In 85 percent of cases, it is caused by an abnormality or deficiency of Factor VIII; this type of hemophilia is called hemophilia A or classic hemophilia. About 1 of every 10,000 males in the United States has classic hemophilia. In the other 15 percent of hemophilia patients, the bleeding tendency is caused by deficiency of Factor IX. Both of these factors are transmitted genetically by way of the female chromosome. Therefore, almost never will a woman have hemophilia because at least one of her two X chromosomes will have the appropriate genes. If one of her X chromosomes is deficient, she will be a hemophilia carrier, transmitting the disease to half of her male offspring and transmitting the carrier state to half of her female offspring.

The bleeding trait in hemophilia can have various degrees of severity, depending on the character of the genetic deficiency. Bleeding usually does not occur except after trauma, but in some patients, the degree of trauma required to cause severe and prolonged bleeding may be so mild that it is hardly noticeable. For instance, bleeding can often last for days after extraction of a tooth.

Factor VIII has two active components, a large component with a molecular weight in the millions and a smaller component with a molecular weight of about 230,000. The smaller component is most important in the intrinsic pathway for clotting, and it is deficiency of this part of Factor VIII that causes classic hemophilia. Another bleeding disease with somewhat different characteristics, called von Willebrand's disease, results from loss of the large component.

When a person with classic hemophilia experiences severe prolonged bleeding, almost the only therapy that is truly effective is injection of purified Factor VIII. The cost of Factor VIII is high, because it is gathered from human blood and only in extremely small quantities. However, increasing production and use of recombinant Factor VIII will make this treatment available to more patients with classic hemophilia.

PLATELETS (THROMBOCYTES)

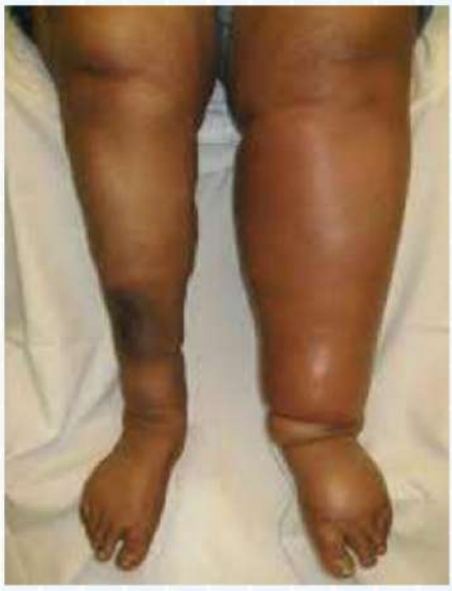
Abnormalities of Hemostasis:

A. **Bleeding:**

3. **Clotting (Thromboembolic Conditions):**

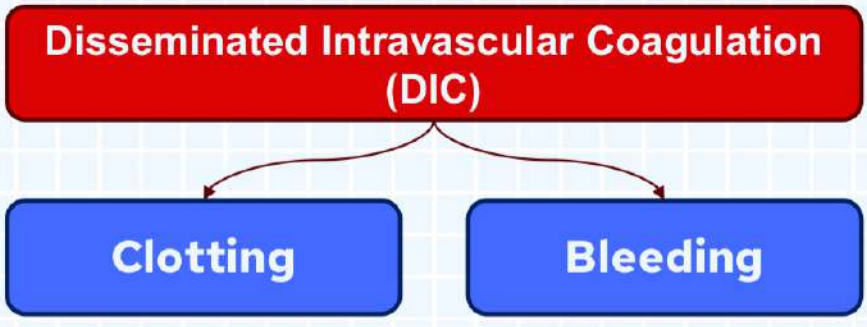
Slow Blood Flow :

- **Long Bed Rest**
- **Varicose Veins**
- **Atherosclerosis**



PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:



PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

4. Disseminated Intravascular Coagulation (DIC):

Definition and Etiology

DIC is a Clinicopathological Syndrome in which there is widespread Intravascular Coagulation that occurs due to Procoagulants that are introduced into or produced by Blood Circulation.

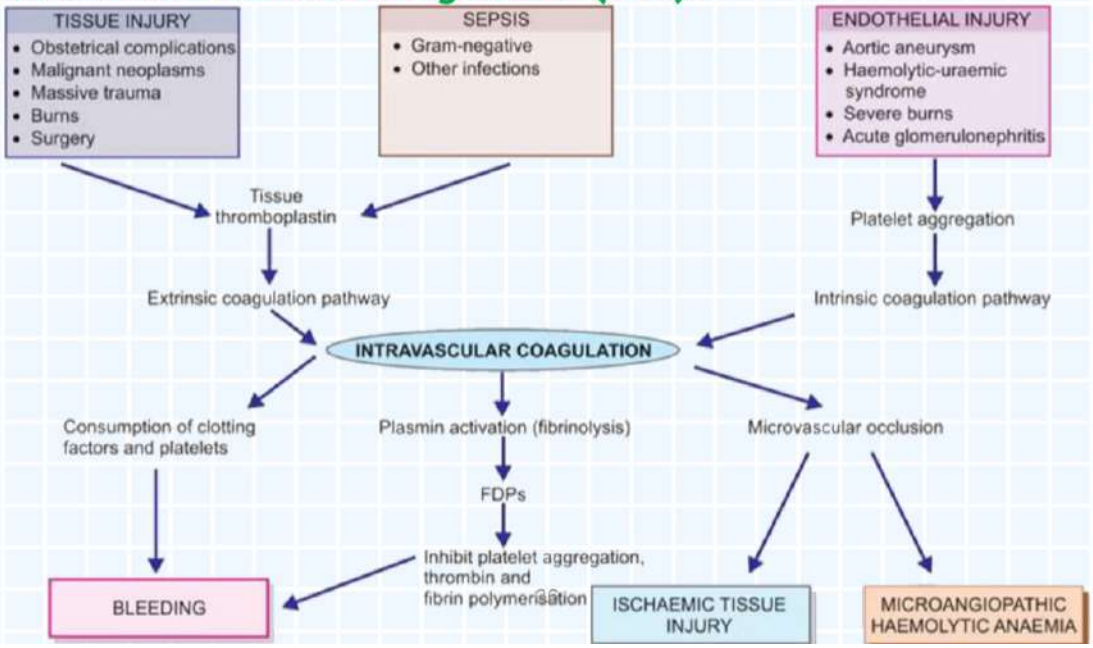
1. The Procoagulant activity overcomes the natural Anti-Coagulant mechanisms. This is also called Consumption Coagulopathy or Defibrination Syndrome.
2. This is a Hemorrhagic Disorder in which diffused Intravascular Coagulation results in defects of Hemostasis.
3. In this Disease, Coagulation factors and Platelets are overutilized. This results in bleeding.
4. The Most Common Procoagulant stimulus is the Tissue Factor (Tissue Thromboplastin) exposure to the blood, that activates Extrinsic pathway of Coagulation

PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

4. Disseminated Intravascular Coagulation (DIC):



Disseminated Intravascular Coagulation (DIC)

Occasionally the clotting mechanism becomes activated in widespread areas of the circulation, giving rise to the condition called disseminated intravascular coagulation. This often results from the presence of large amounts of traumatized or dying tissue in the body that releases great quantities of tissue factor into the blood. Frequently, the clots are small but numerous, and they plug a large share of the small peripheral blood vessels. This occurs especially in patients with widespread septicemia, in which either circulating bacteria or bacterial toxins-especially endotoxins-activate the clotting mechanisms. Plugging of small peripheral vessels greatly diminishes delivery of oxygen and other nutrients to the tissues-a situation that leads to or exacerbates circulatory shock. It is partly for this reason that septicemic shock is lethal in 85 percent or more of patients.

A peculiar effect of disseminated intravascular coagulation is that the patient on occasion begins to bleed. The reason for this is that so many of the clotting factors are removed by the widespread clotting that too few procoagulants remain to allow normal hemostasis of the remaining blood.

Positive Feedback of Clot Formation

Once a blood clot has started to develop, it normally extends within minutes into the surrounding blood. That is, the clot itself initiates a positive feedback to promote more clotting. One of the most important causes of this is the fact that the proteolytic action of thrombin allows it to act on many of the other blood-clotting factors in addition to fibrinogen. For instance, thrombin has a direct proteolytic effect on prothrombin itself, tending to convert this into still more thrombin, and it acts on some of the blood- clotting factors responsible for formation of prothrombin activator. (These effects, discussed in subsequent para- graphs, include acceleration of the actions of Factors VIII, IX, X, XI, and XII and aggregation of platelets.) Once a critical amount of thrombin is formed, a positive feedback develops that causes still more blood clotting and more and more thrombin to be formed; thus, the blood clot continues to grow until blood leakage ceases.

Quiz time

Q1: Which of the following is NOT one of the four major physiologic events of hemostasis?

A. Fibrinolysis

B. Vasodilatation

C. Platelet plug formation

D. Fibrin production

Q2: Which is required for platelet adherence to injured endothelium?

A. Thromboxane A2

B. Glycoprotein (GP) IIb/IIIa

C. Adenosine diphosphate (ADP)

D. Von Willebrand factor (vWF)

Q3: Which of the following clotting factors is the first factor common to both intrinsic and extrinsic pathways?

A. Factor I (fibrinogen)

B. Factor IX (Christmas factor)

C. Factor X (Stuart-Prower factor)

D. Factor XI (plasma thromboplasma antecedent)

Q4: Which congenital factor deficiency is associated with delayed bleeding after initial hemostasis?

A. Factor VII

B. Factor IX

C. Factor XI

D. Factor XIII

Q5: All of the following are true about thrombin functions except?

A. Activate factor I .

B. Accelerates the actions of factors IX,X and XII

C. Accelerates the formation of more Thrombin from prothrombin

D. Accelerates Platelet aggregation and fusion

E. Activates the other factors V,VII and XIII

Answers:

1. B
2. D
3. C
4. D
5. B

Thanks