Principle of blood coagulation and approach to bleeding disorder

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Objectives

- อธิบายกลไกการแข็งตัวและการละลายของเลือดในภาวะปกติได้
- บอกสาเหตุของภาวะเลือดออกผิดปกติมา 3 อย่างได้
- บอกชนิดของการทดสอบที่ใช้ในการตรวจความผิดปกติของเลือดได้ 3 อย่าง
- บอกอาการทางคลินิกที่สัมพันธ์กับชนิดของการมีเลือดออกผิดปกติได้ 3 อย่าง

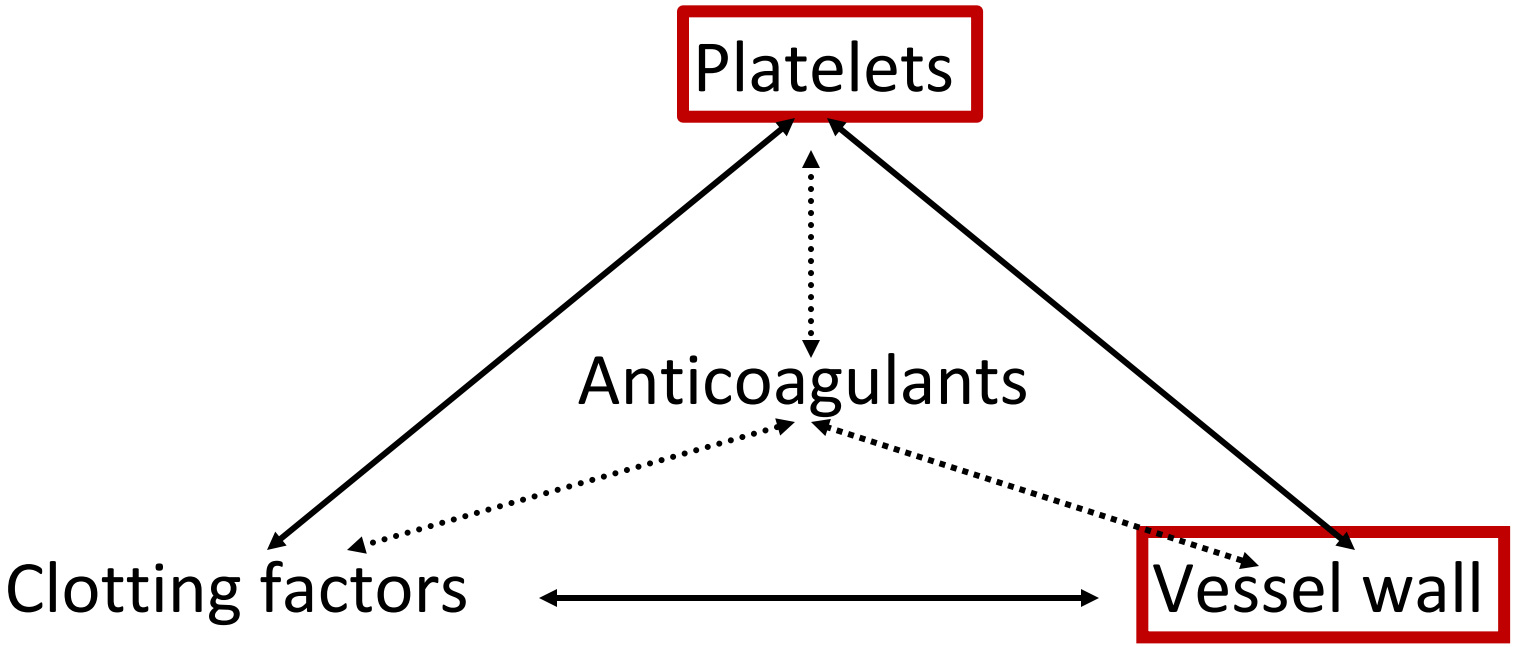
Contents

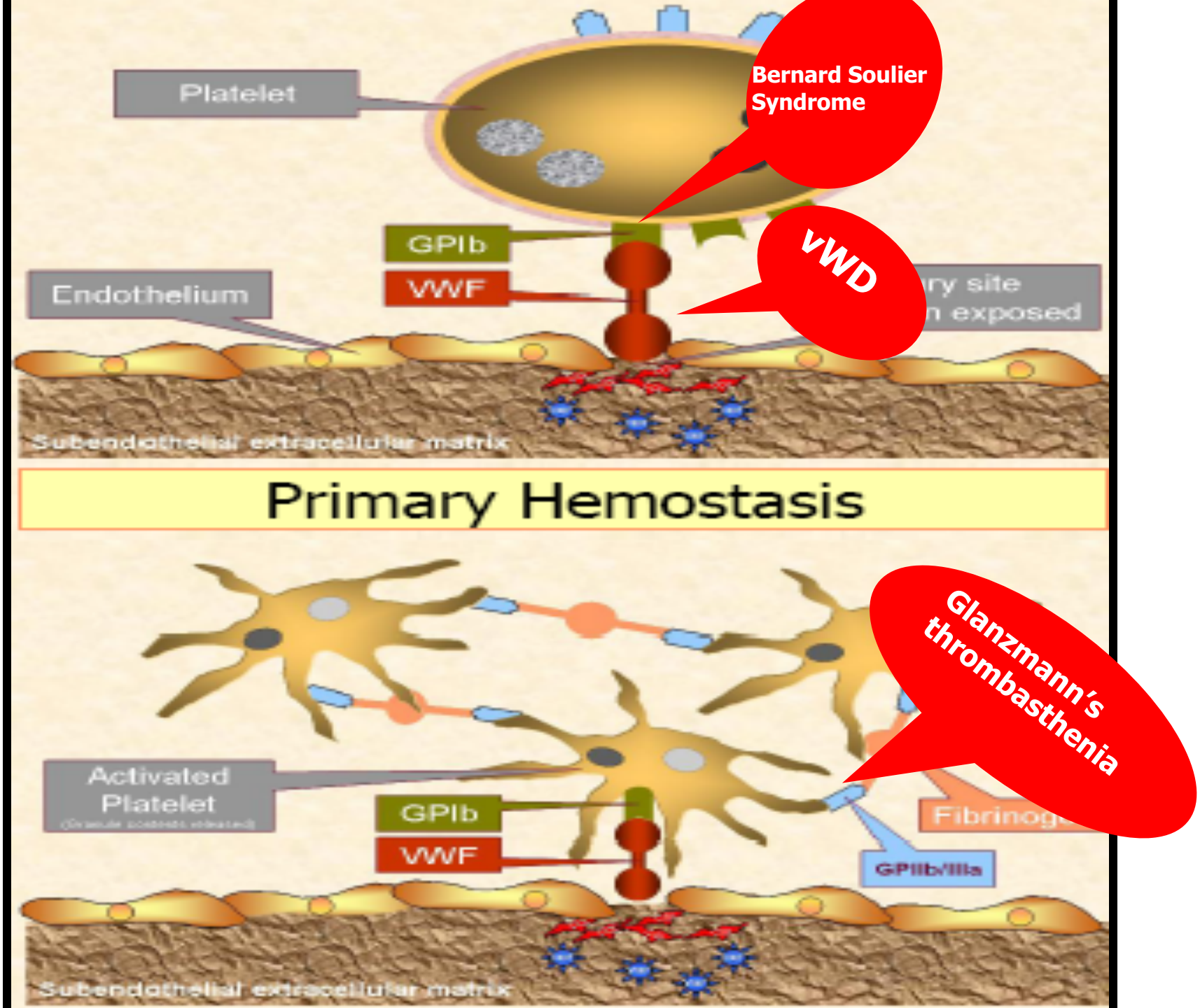
- ***Primary hemostasis***
  - Vessels
  - Platelet
- ***Secondary hemostasis***
  - Coagulation proteins
- ***Fibrinolysis***
- ***Anticoagulant protein***

Platelet plug formation

Clot Formation

Hemostasis



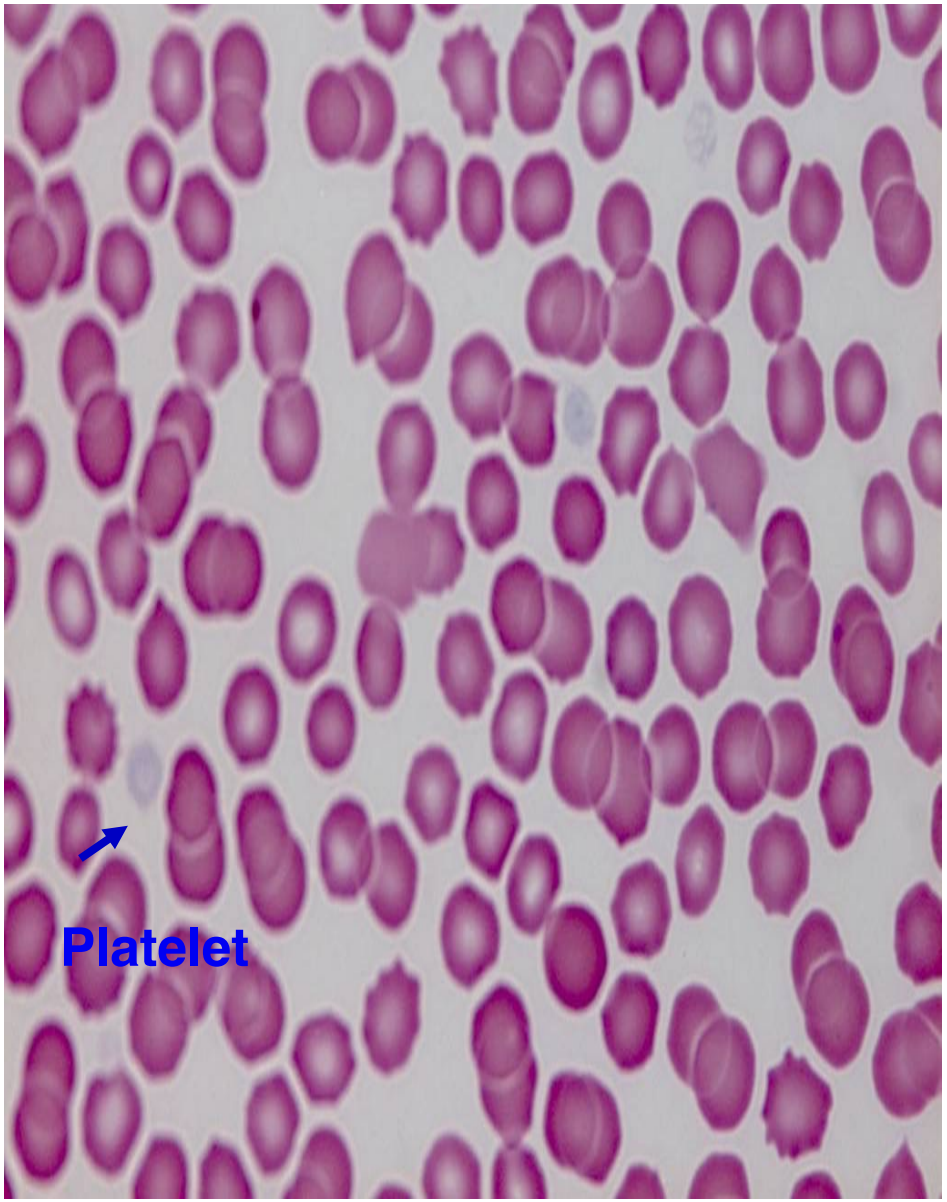

Platelet
Bernard Soulier Syndrome
GPIb
VWF
vWD
Endothelium
ry site
n exposed
Subendothelial extracellular matrix
Primary Hemostasis
Activated Platelet
GPIb
VWF
Glanzmann's thrombasthenia
Fibrinog
GPIIb/IIIa
Subendothelial extracellular matrix

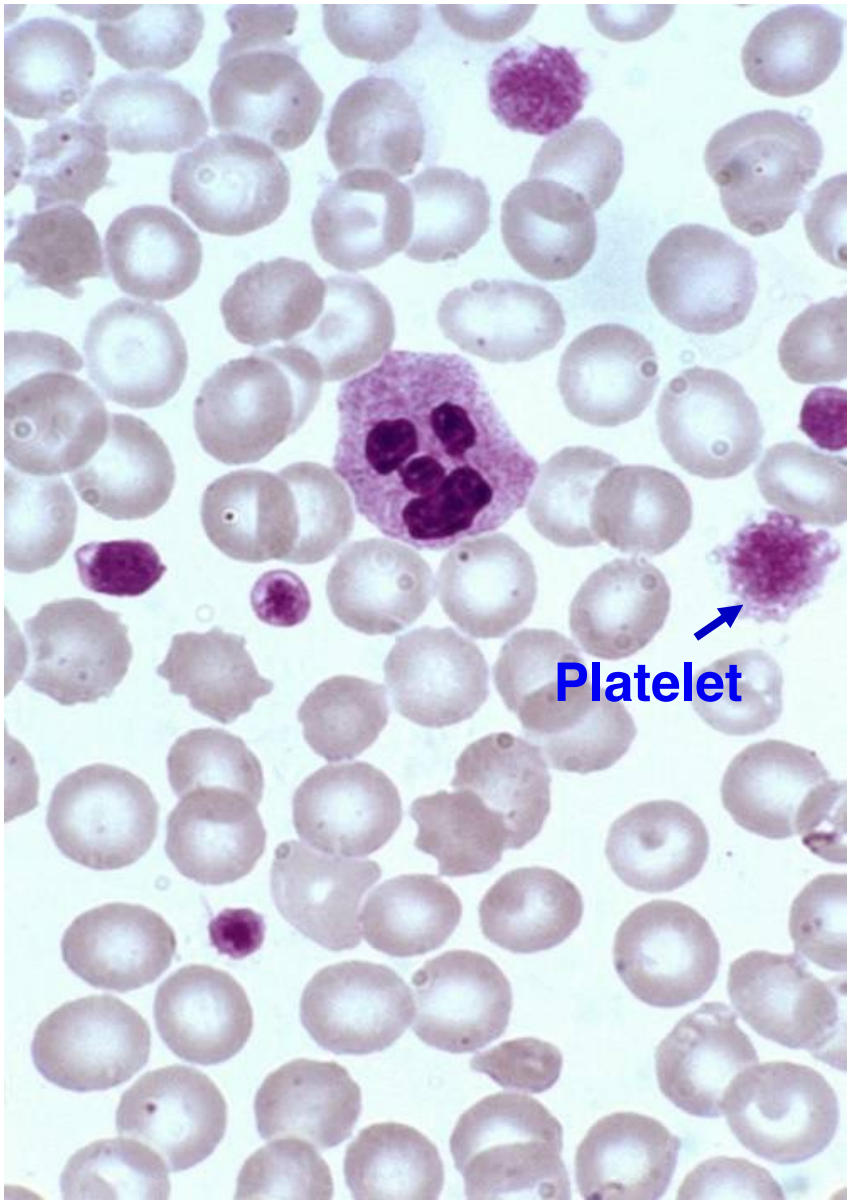
CBC: Platelet count / PBS

- Number of platelet
- Size / Shape / Stain

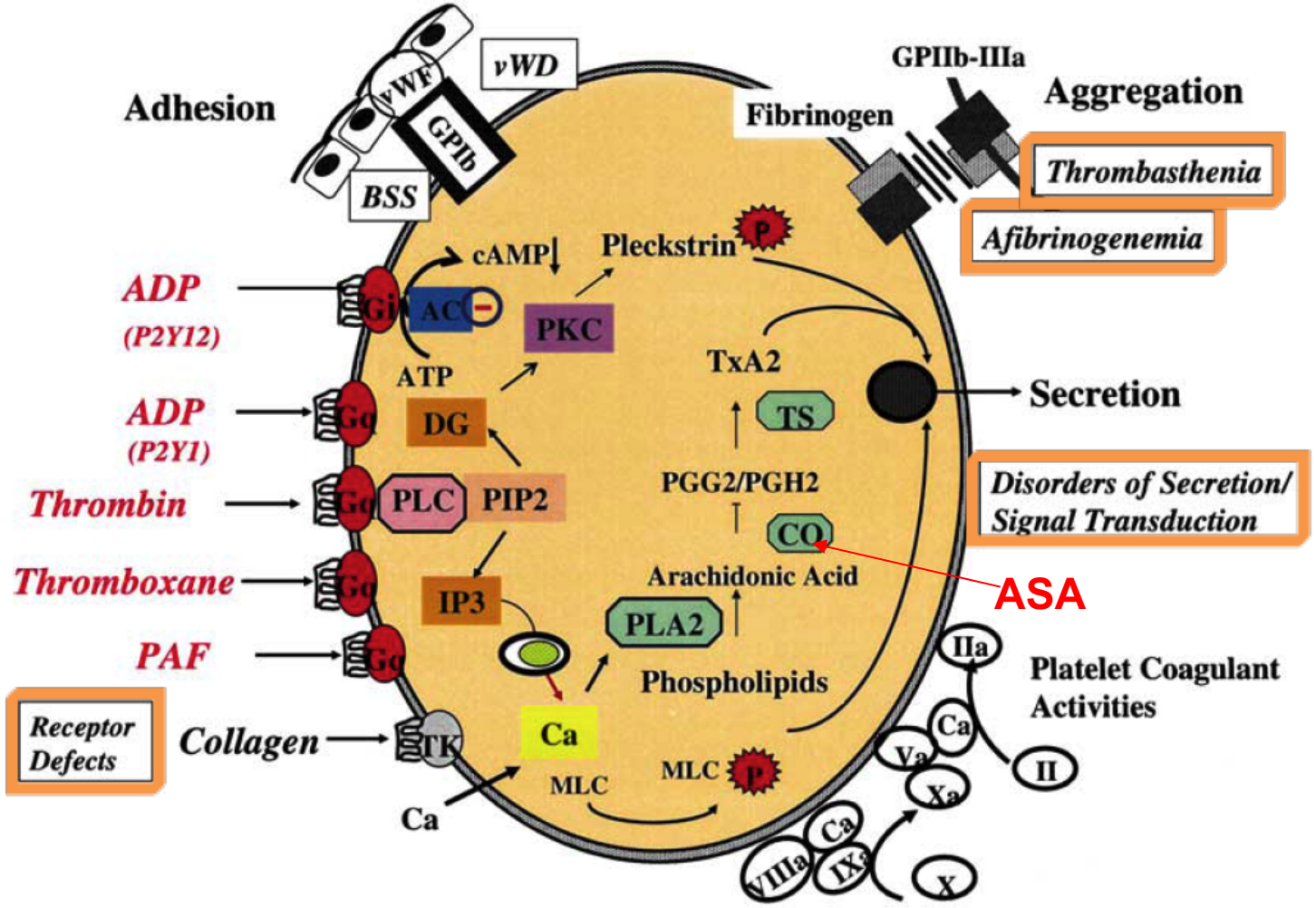
If the number is LOW, ***CHECKING the PBS is a MUST***

- ***Pseudothrombocytopenia***
  - EDTA induce platelet agglutination
  - Pre-analytical error:
    - Refrigerated blood, poor mixing after collection


Platelet


Platelet

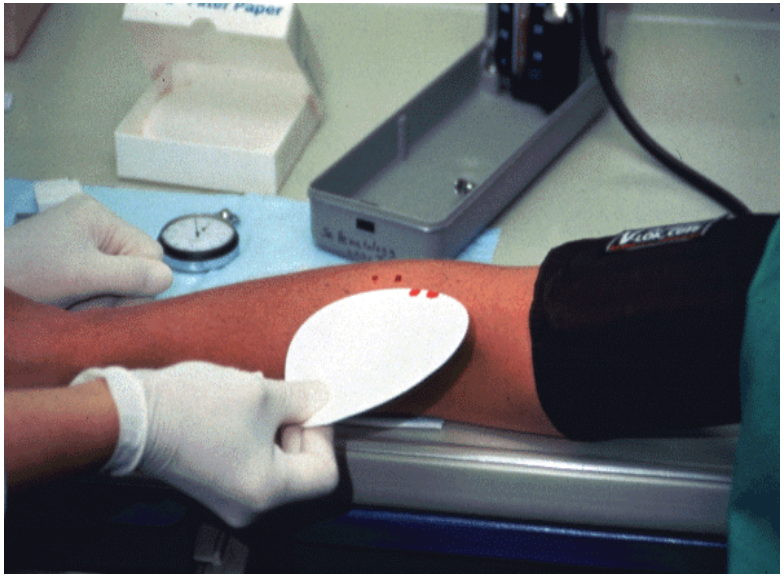
Platelet Function



Rao AK J Thromb Haemost 2003 ; 1 :671-681

Bleeding Time

- Normal range up to 10 mins
- ***Prolongation in***
  - Plt. dysfunction
  - VWD (aPTT prolonged)
  - Thrombocytopenia (<60 x 109/L)
  - Hypofibrinogenemia (TT prolonged)
  - Vascular defect



<u>NOT</u> recommend for <u>Pre-operative evaluation</u>

Poor sensitivity and reproducibility

Most preferred method: Modified Ivy method

Platelet Aggregation Test

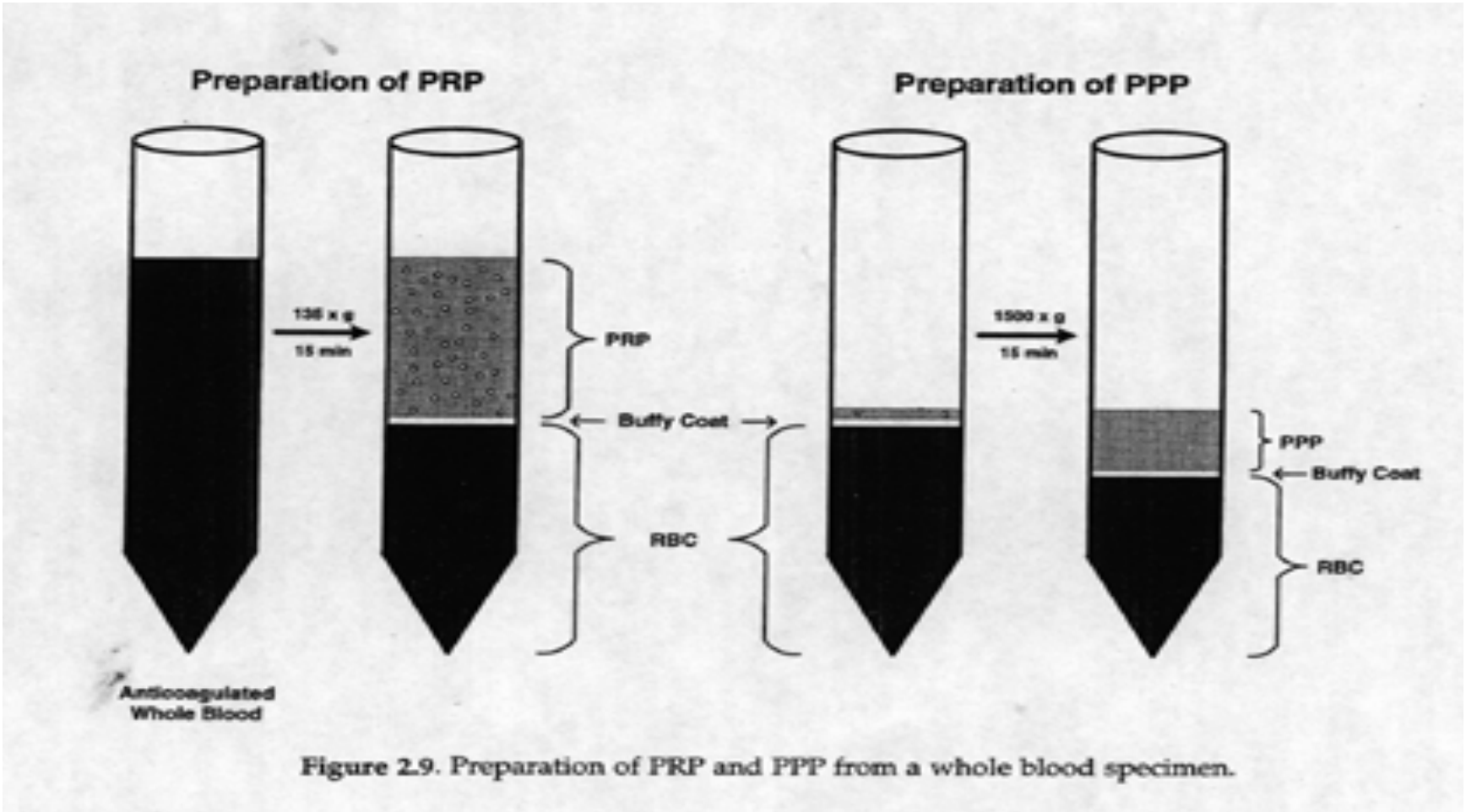
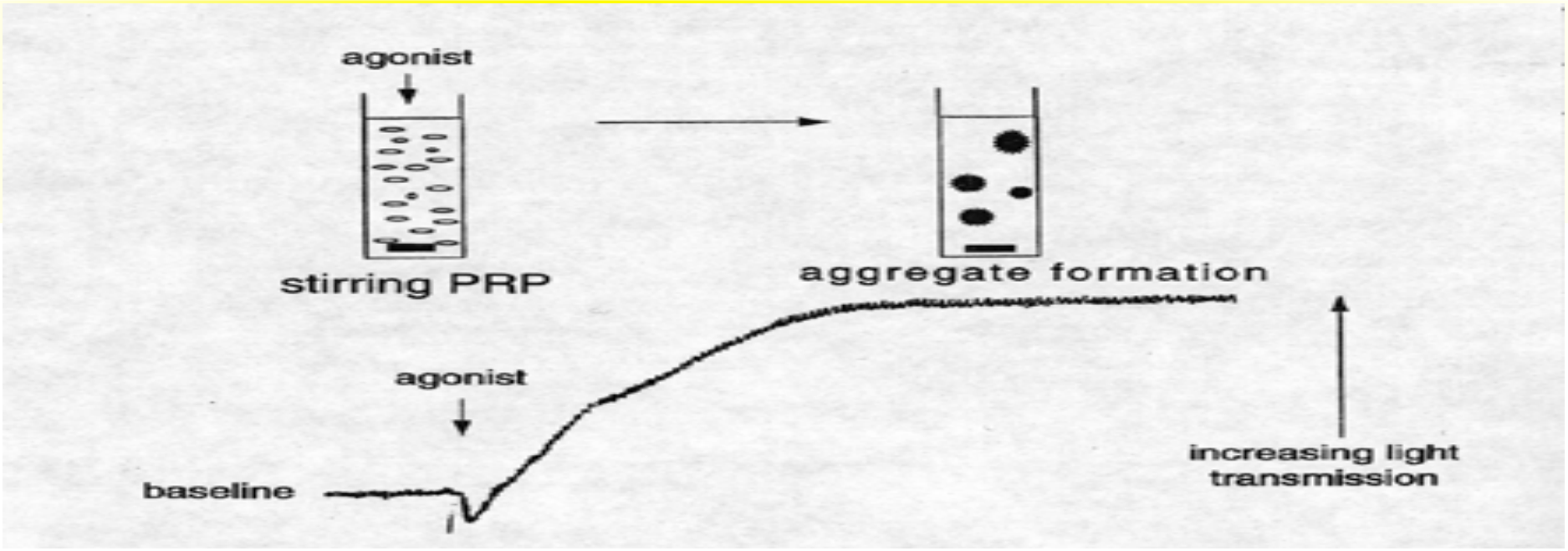
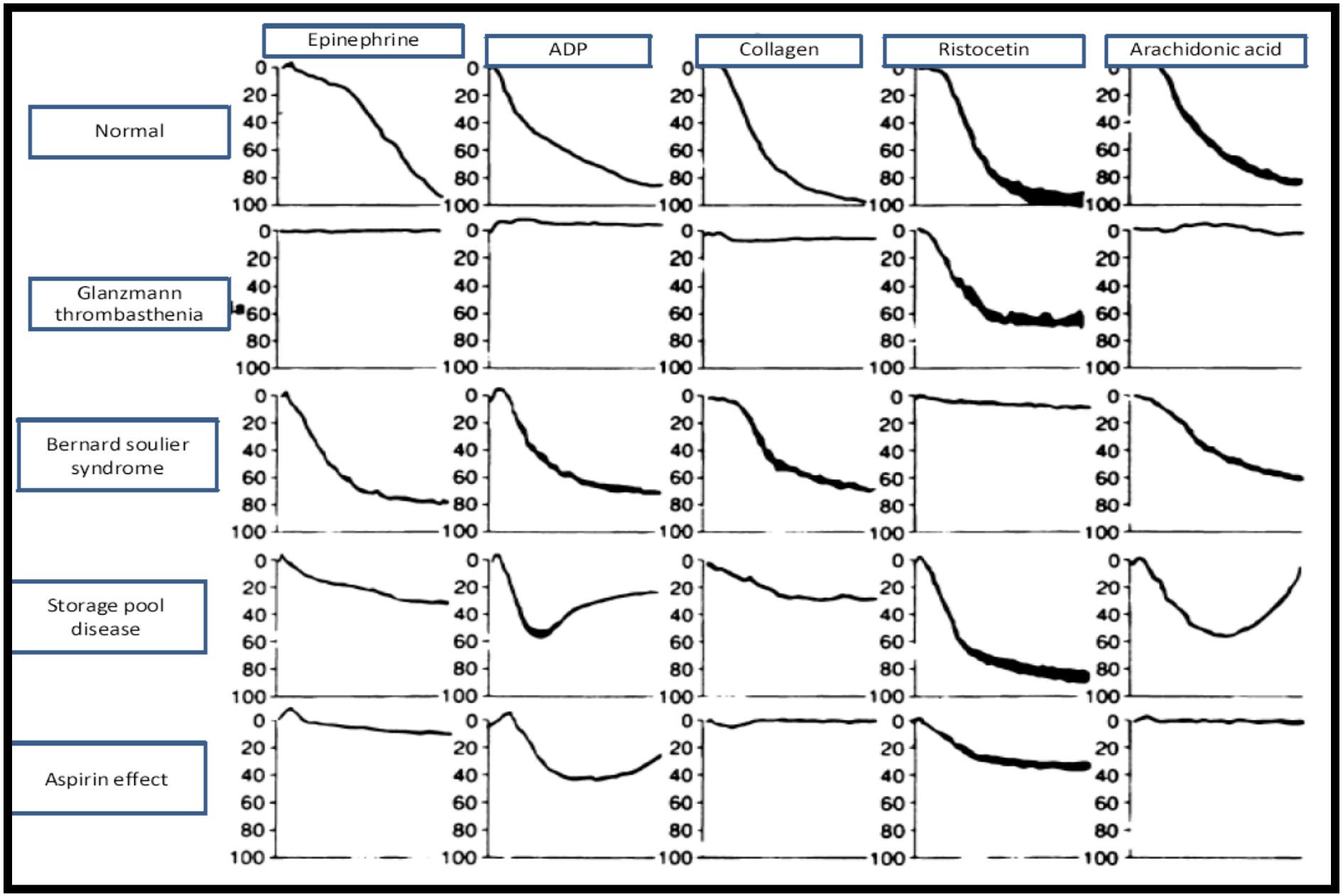


Figure 2.9. Preparation of PRP and PPP from a whole blood specimen.

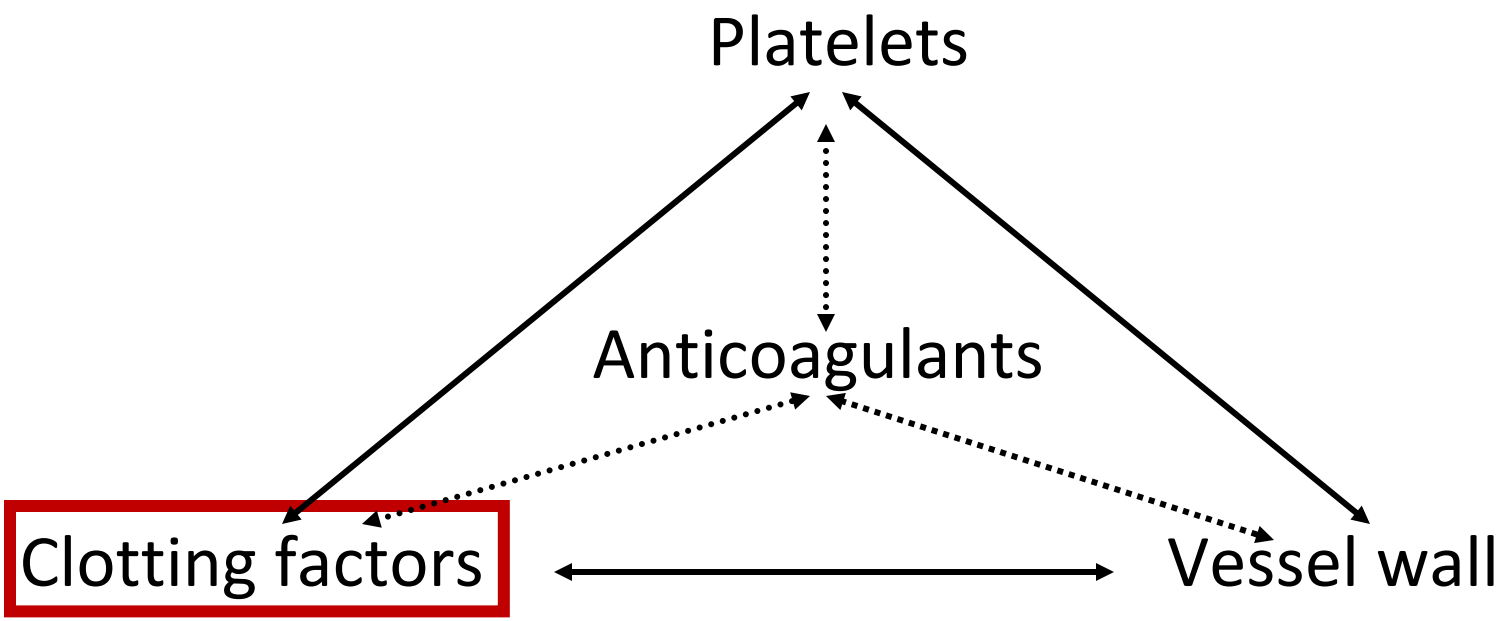


Agonist	Concentration	Pathway
ADP	5-10 umoL	ADP receptor and cyclooxygenase or G-protein pathway
Epinephrine	2-10 umoL	Epinephrine receptor and cyclooxygenase or G-protein pathway
Collagen	5-10 ug/mL	Membrane receptor and cyclooxygenase or G-protein pathway
Thrombin	0.3 U/mL	Protease activated factor (PAR) 1 and PAR 4
Ristocetin	1.0 mg/mL	GPIb/IX integrin and aggregation with vWF
Arachinodic acid	1 mM	Cyclooxygenase pathway

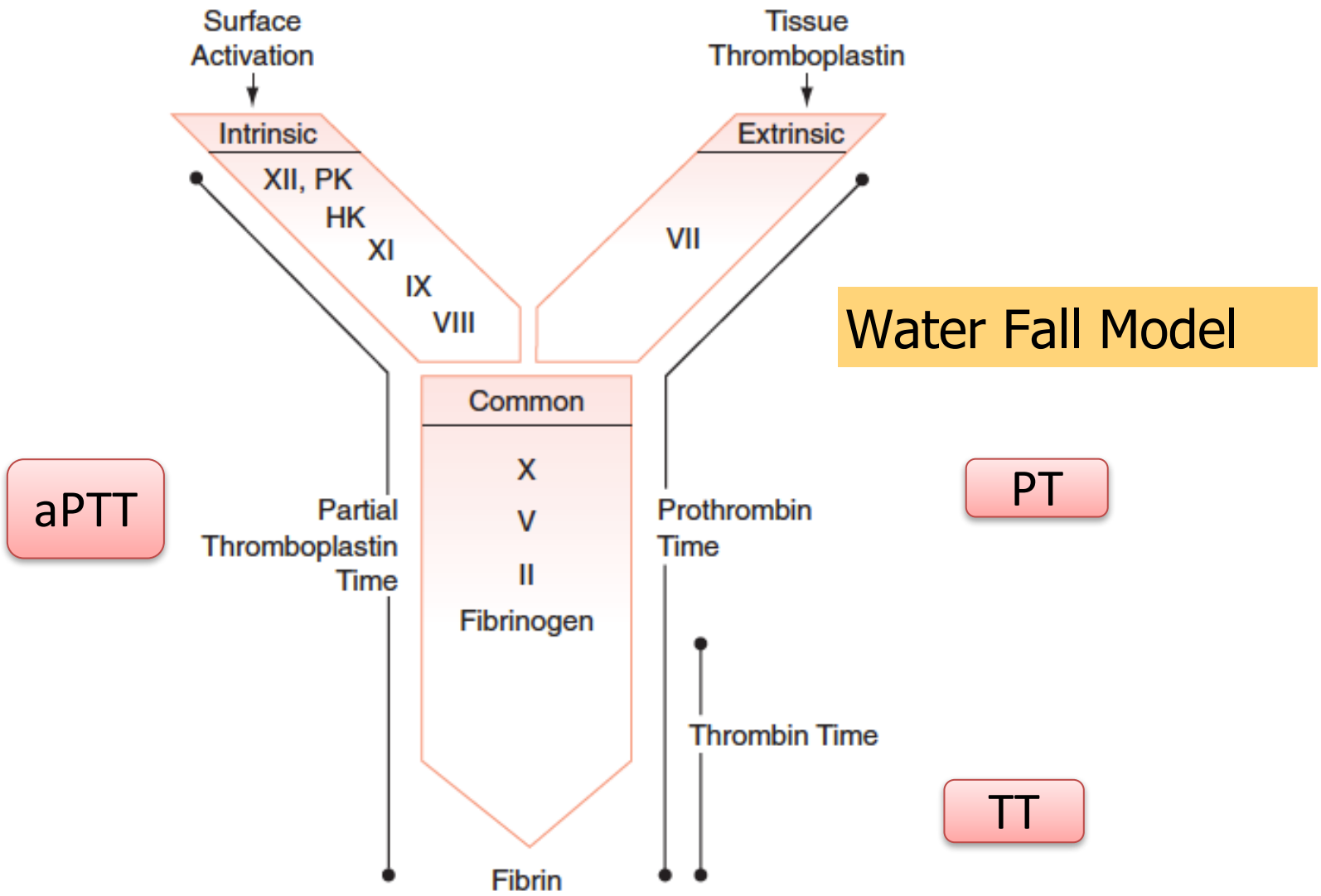


(Shapiro A.D. Haemophilia 2000;6 (suppl.1): 120-7)

Hemostasis



Laboratory assessment of coagulation



Prothrombin Time (PT / INR)

Principle

- ***Patient plasma is mixed with optimal concentration of thromboplastin (tissue factor and phospholipid) calcium is added and time taken to produced gel clot is measured***
- Results are standardized to INR (to facilitate management of oral anticoagulation)
- Used to assess the integrity of **the extrinsic system** (primarily factor VII)
- ***Two "functions" of PT***
  - ***Clotting factor concentration (Factor VII)***
  - ***Assessment of oral anticoagulation***

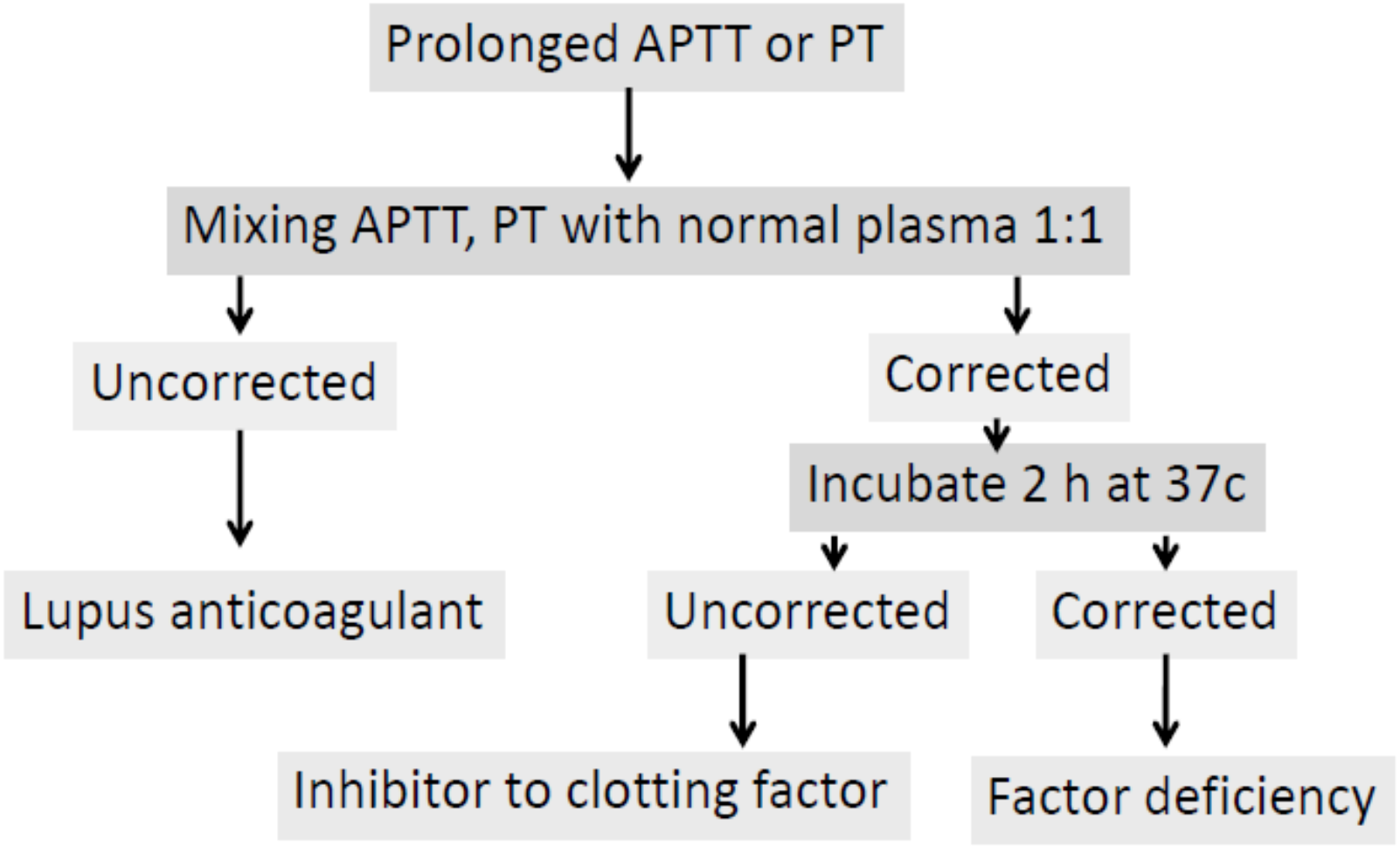
Activated partial thromboplastin time (aPTT / PTT)

- Principle
  - Patient plasma is incubated with an activation agent (e.g. silica, clay) with ***a phospholipid*** (e.g. animal or recombinant phospholipid), calcium is added and the time taken for a gel clot to form is detected
  - Results of patients are compared to normal (normal ranges)
  - Used to assess the integrity of the ***intrinsic coagulation system (factors XII XI IX VIII, vWF)***
  - ***Three "functions" of aPTT***
    - ***Monitor heparin***
    - ***Factor level concentrations***
    - ***Detection of lupus anticoagulants***

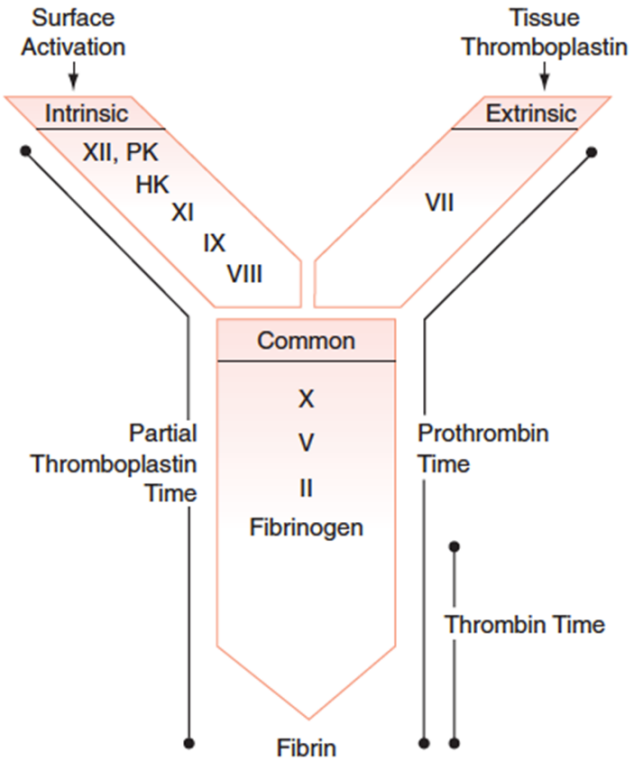
When Screening Coagulation Test is Abnormal…

Coagulation factors deficiency ?
Coagulation factors inhibitor ?
Antiphospholipid antibody ?

What is "Mixing study"



Thrombin Time (TT)

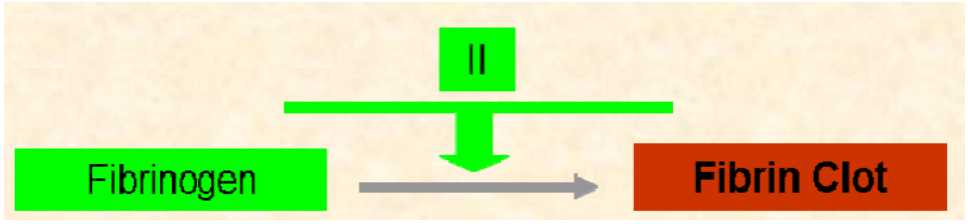


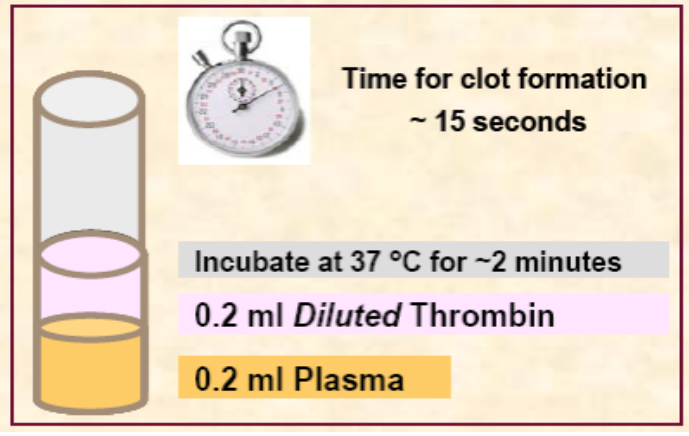
Thrombin Time (TT)

Assesses the ***functionality of fibrinogen in plasma***

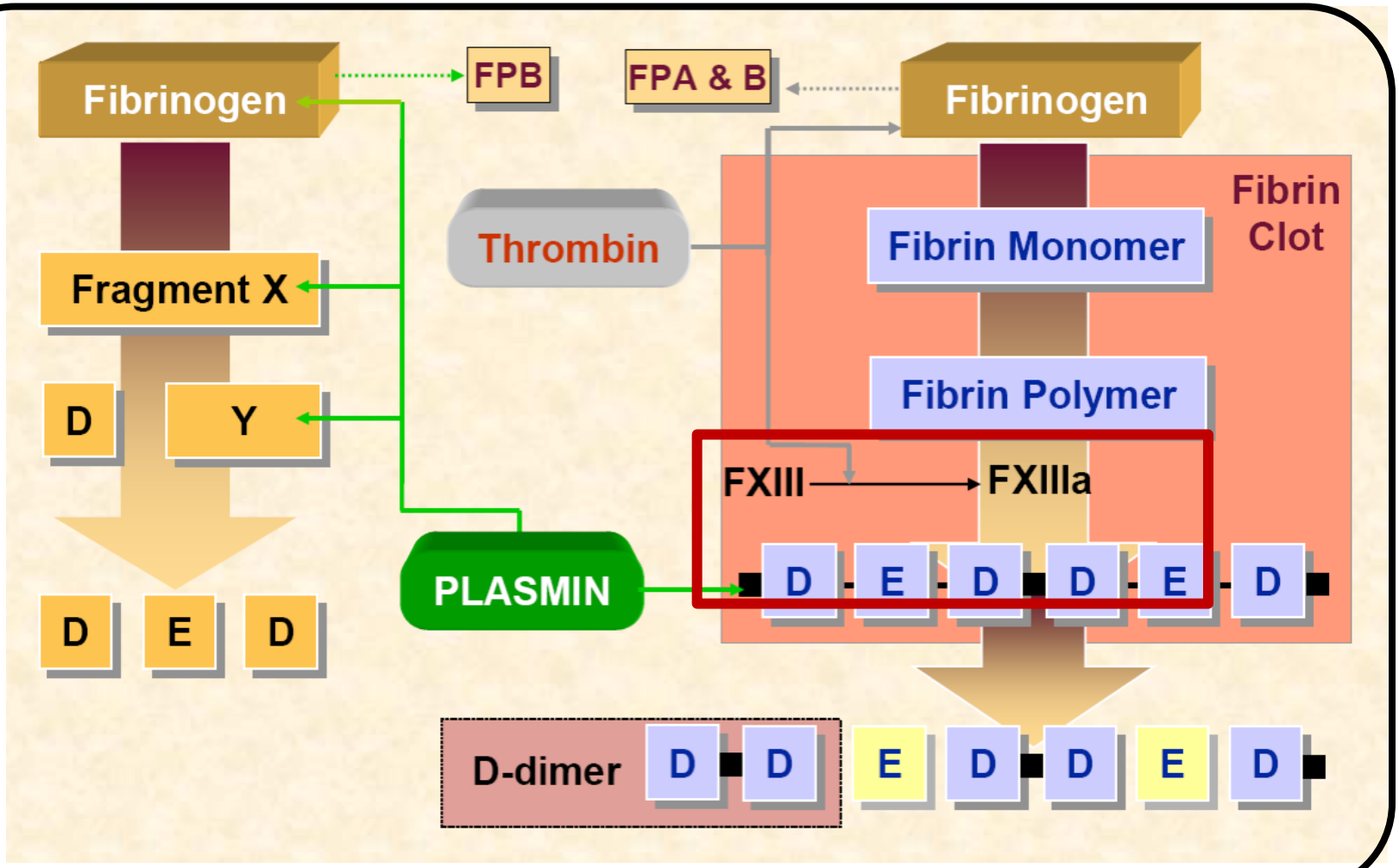
TT clotting time prolonged

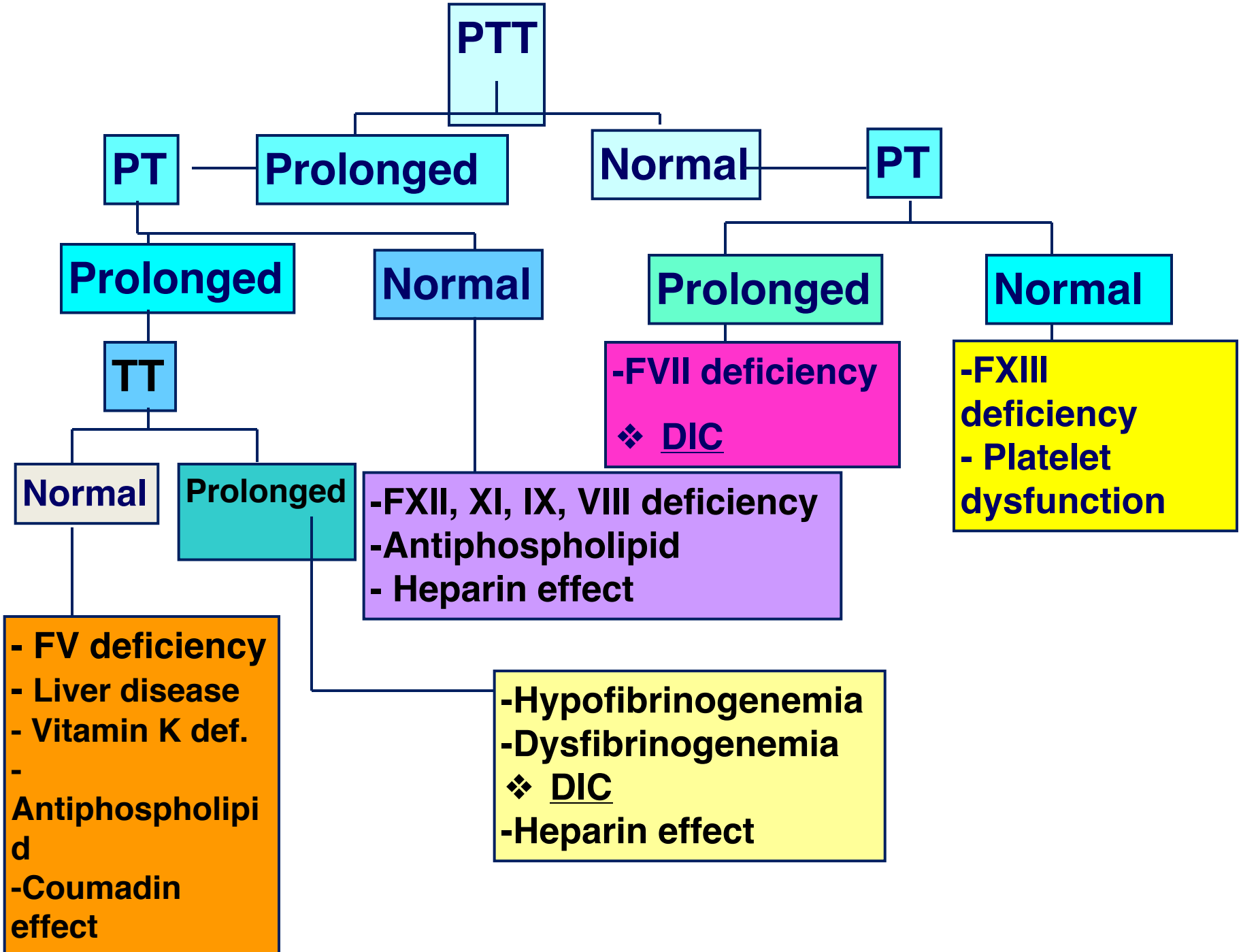
- HEPARIN
- Hypofibrinogenemia
- Dysfibrinogenemia





Breakdown of Fibrin(ogen)

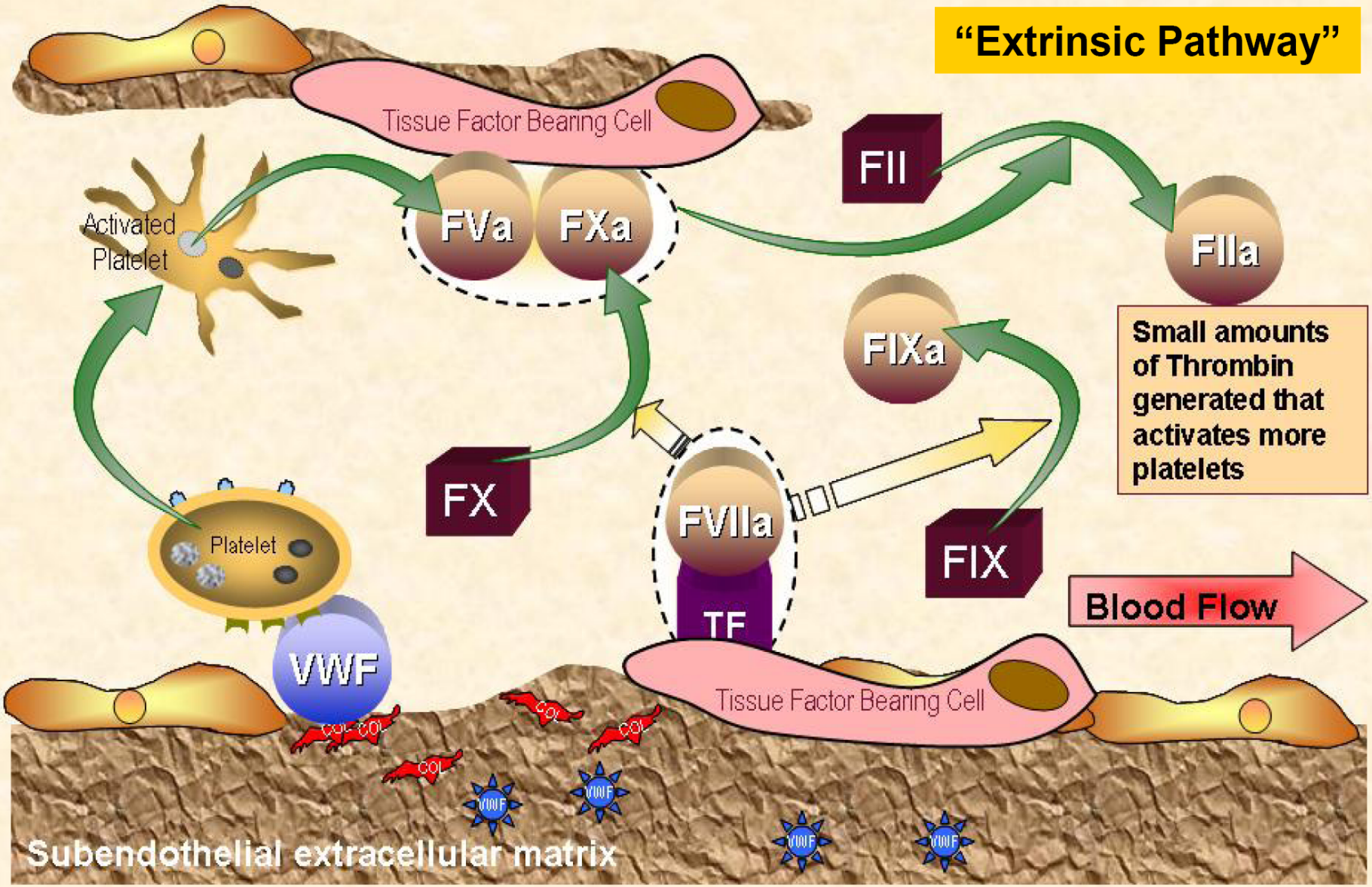



PTT
PT
Prolonged
Normal
PT
Prolonged
Normal
Prolonged
Normal
TT
-FVII deficiency
❖ DIC
-FXIII deficiency
- Platelet dysfunction
Normal
Prolonged
-FXII, XI, IX, VIII deficiency
-Antiphospholipid
- Heparin effect
- FV deficiency
- Liver disease
- Vitamin K def.
- Antiphospholipid
-Coumadin effect
-Hypofibrinogenemia
-Dysfibrinogenemia
❖ DIC
-Heparin effect

CLOT-ED

Monroe DM, et al. ATVB 2006;26:41-8

Initiation Phase



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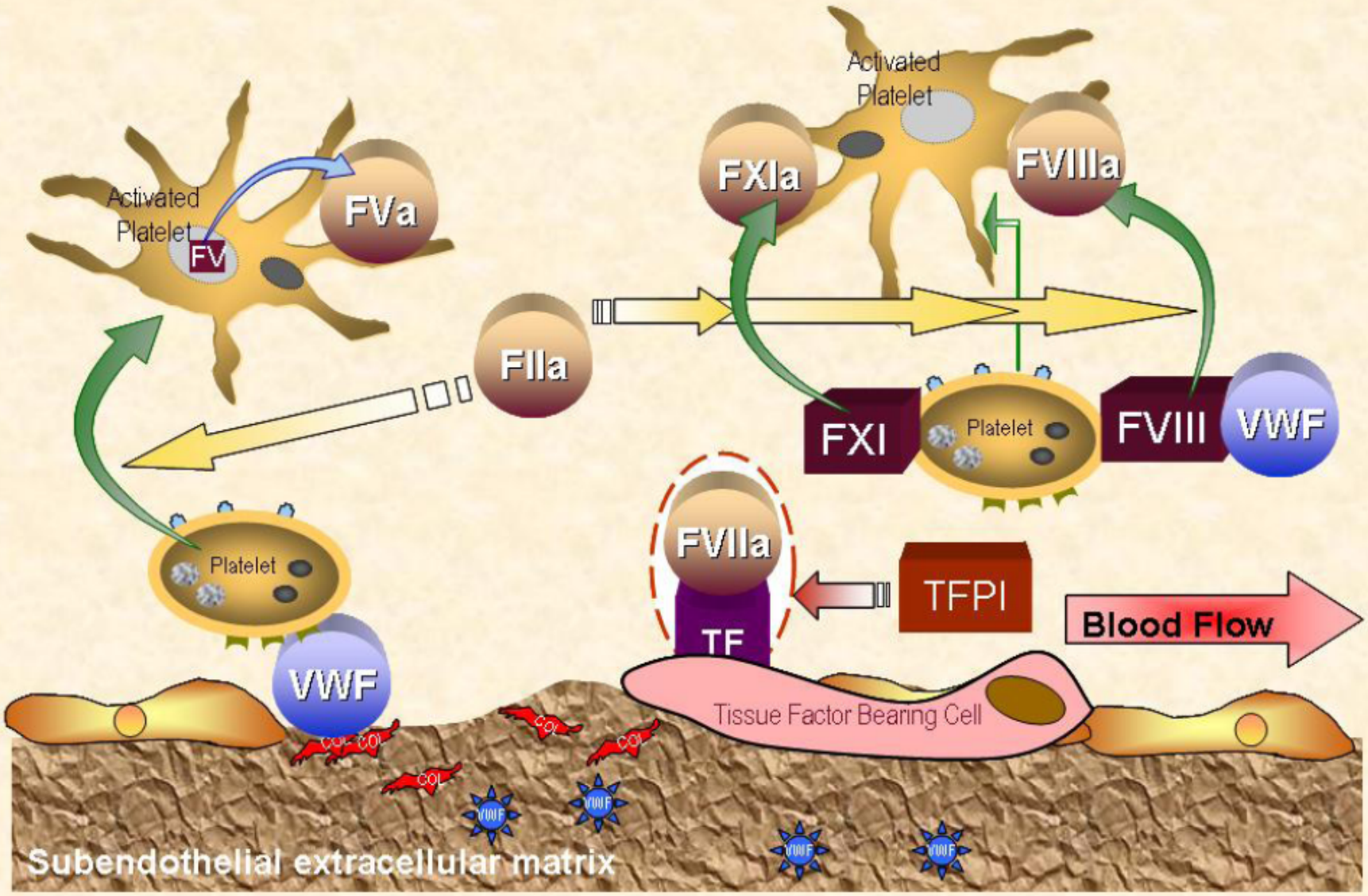
Amplification Phase



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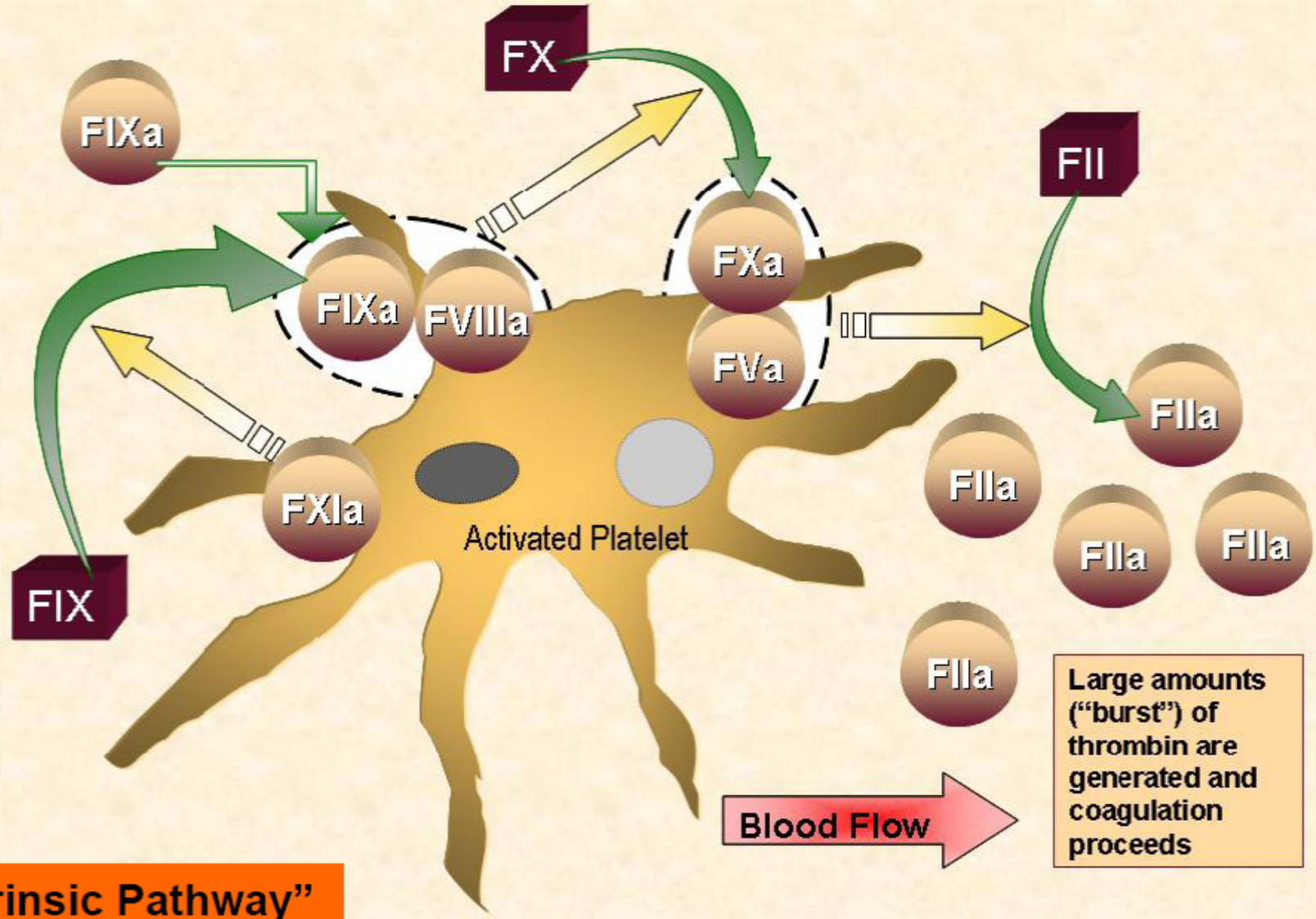
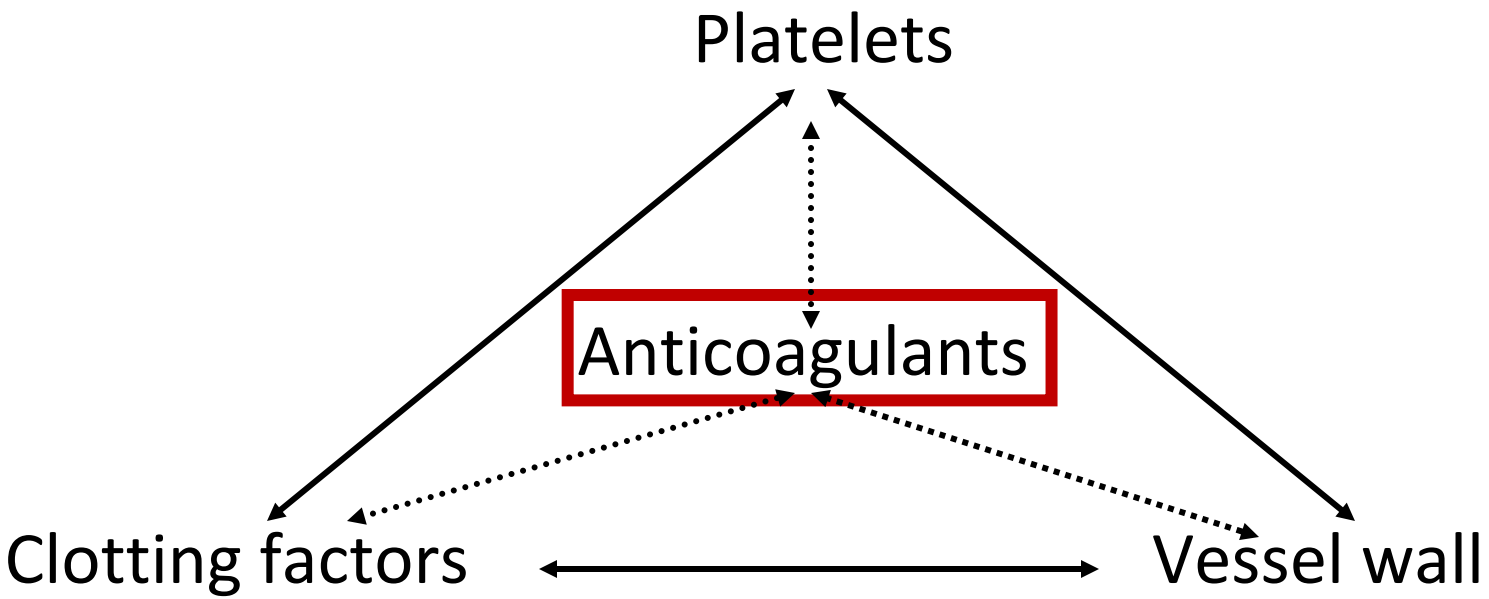
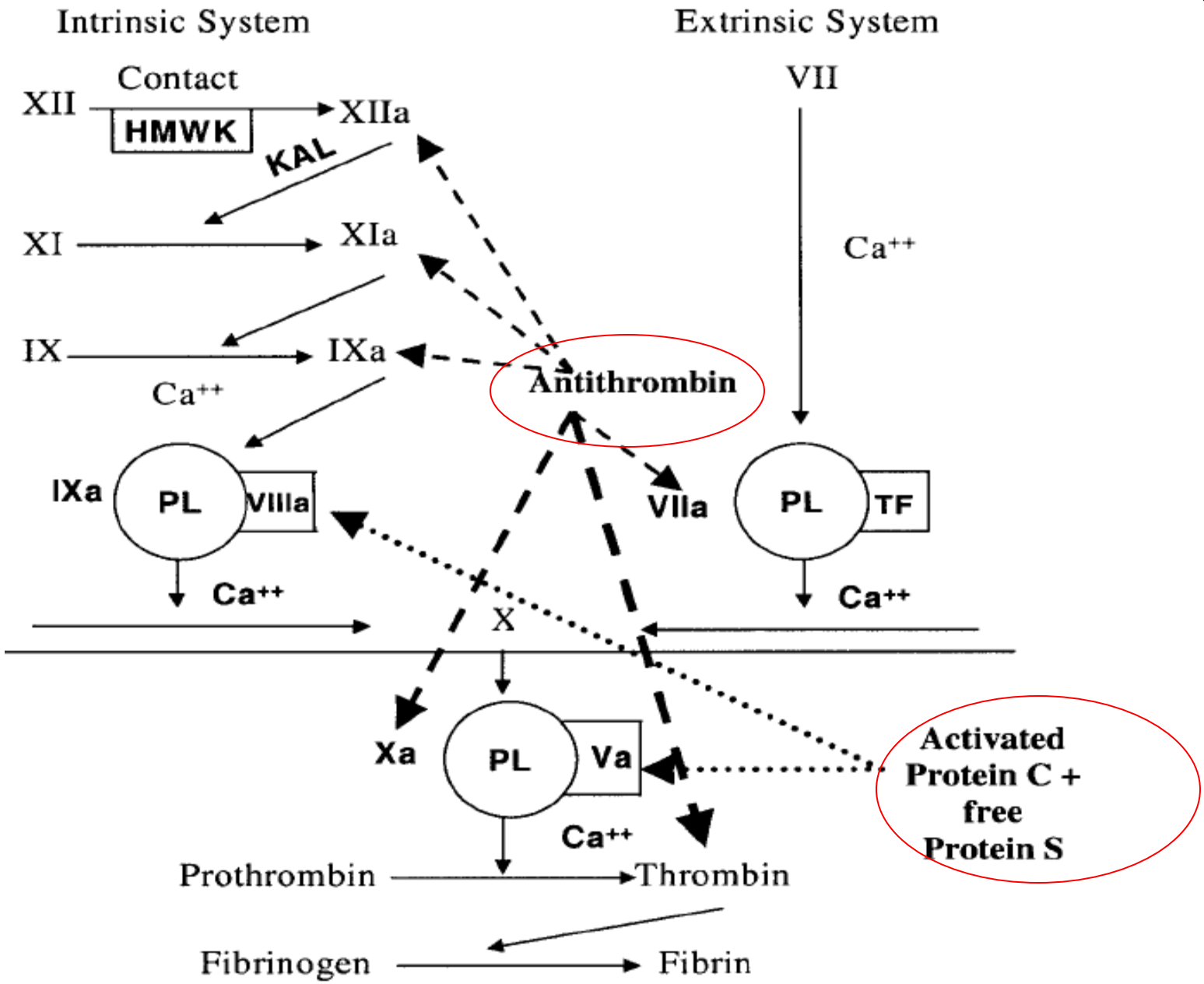
Propagation Phase



"Intrinsic Pathway"

Hemostasis



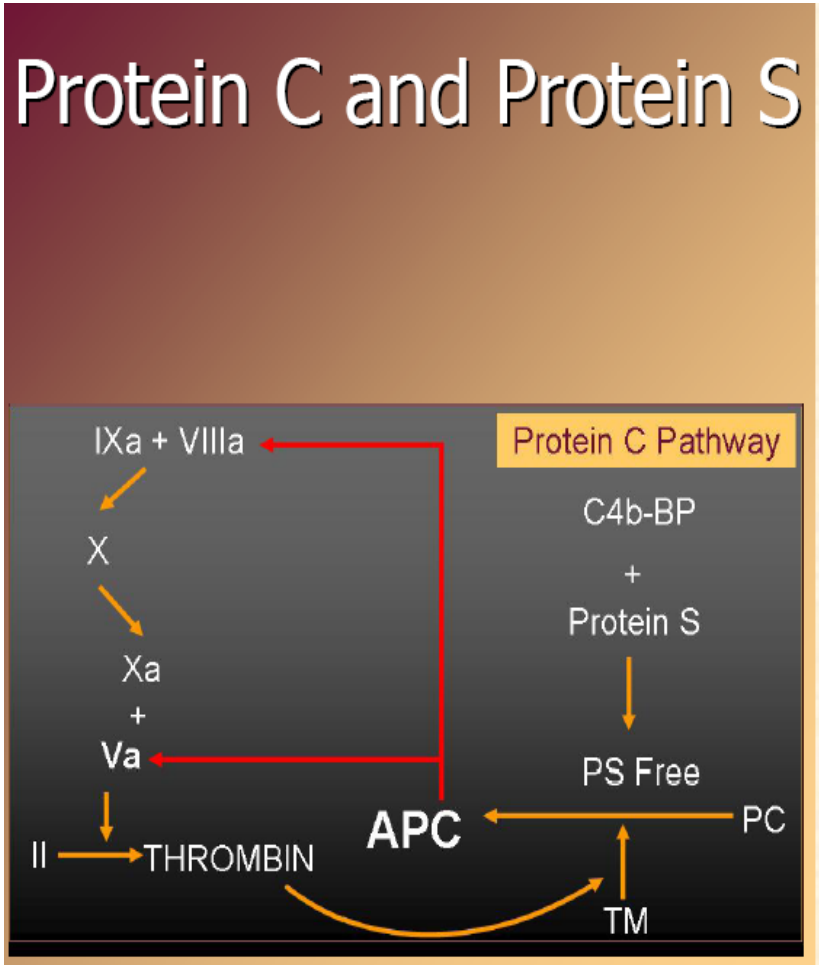

Intrinsic System
Extrinsic System
Contact
XII
HMWK
XIIa
KAL
VII
XI
XIa
Ca++
IX
IXa
Antithrombin
Ca++
IXa
PL
VIIIa
VIIa
PL
TF
Ca++
Ca++
X
Xa
PL
Va
Activated Protein C + free Protein S
Ca++
Prothrombin
Thrombin
Fibrinogen
Fibrin

Protein C & S

- Protein C (PC) and Protein S (PS) are ***Vitamin K dependent natural anticoagulants***

- Thrombin in the presence of ***Thrombomodulin (TM)*** "modulates" its own procoagulant activities to those of anticoagulant by ***activating PC, in the presence of its cofactor PS, to Activated PC (APC)***

- APC downregulates ***coagulation cofactors, VIIIa and Va***



Example Case

Take Home Message

- **Primary Hemostasis**
    - Platelet , vWF , Endothelium
- **Secondary**
    - Coagulation factors
- **Investigations**
    - History taking and Physical examination
    - CBC
    - Platelet aggregation study
    - Coagulogram

THANK YOU
for your attention