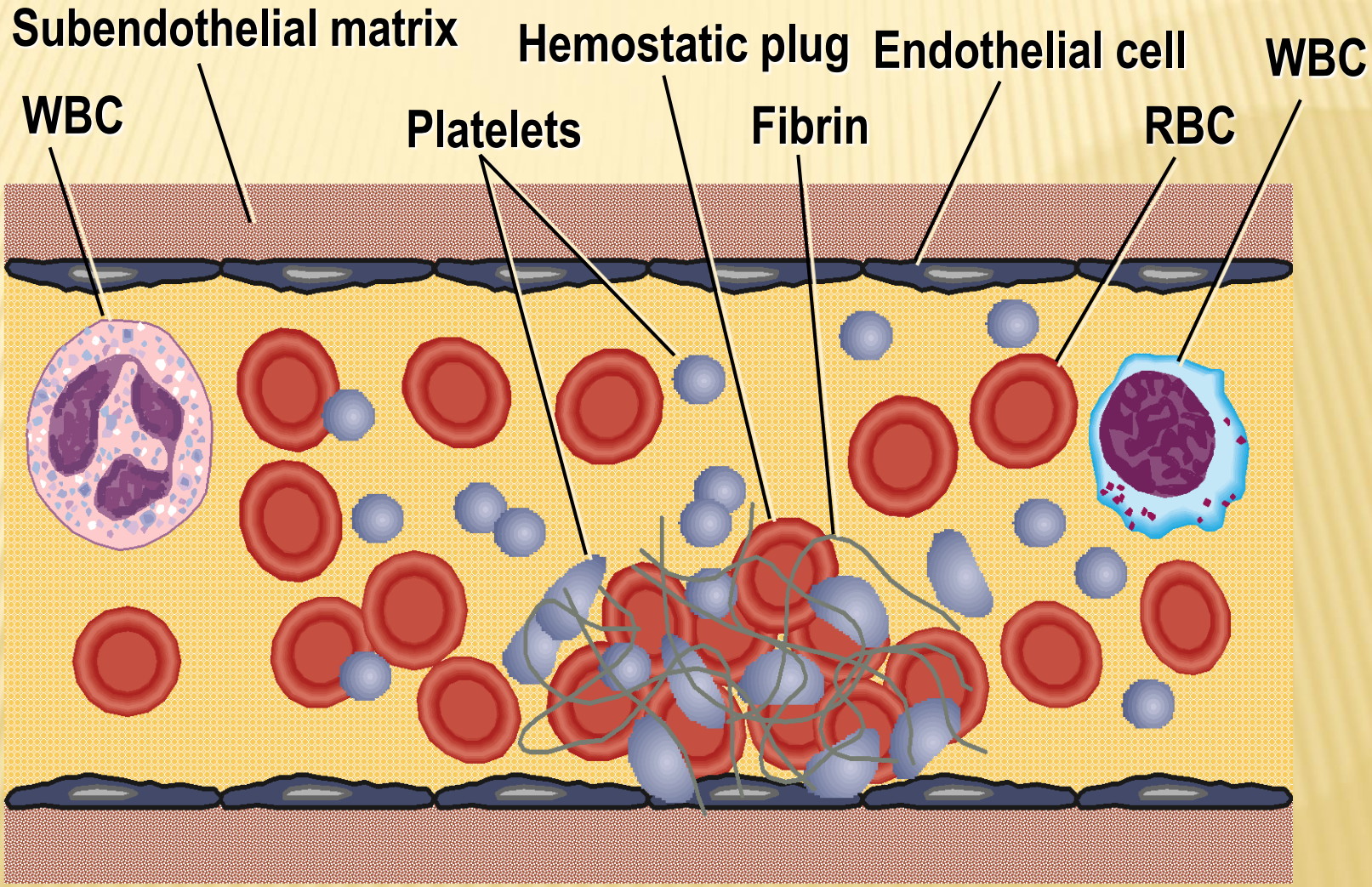
PATHOPHYSIOLOGY OF PRIMARY AND SECONDARY HEMOSTASIS. FIBRINOLYSIS.

November 7, 2017

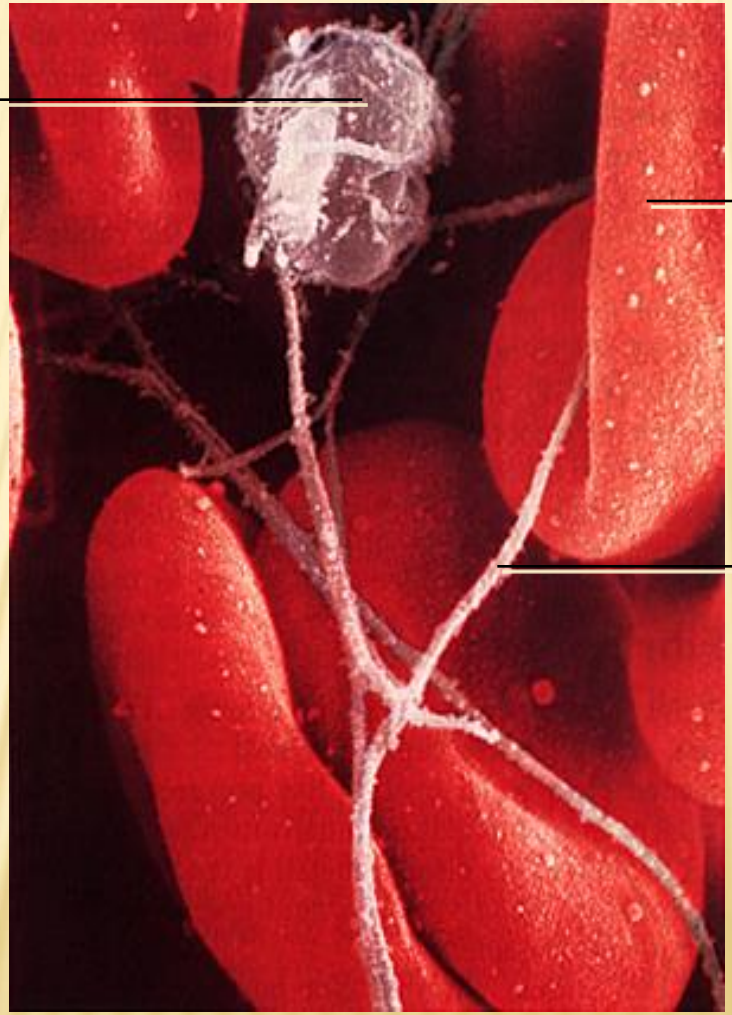
HEMOSTASIS

- The normal physiological response that prevents significant blood loss following **vascular injury** is called **haemostasis**.6 Familiarity with **haemostasis** lays the groundwork for a thorough understanding of the major disease states associated with thrombosis, such as **venous thromboembolism** (VTE), atherothrombosis (thrombosis triggered by plaque rupture), and cardioembolic stroke.

HEMOSTASIS


Subendothelial matrix
Hemostatic plug
Endothelial cell
WBC
WBC
Platelets
Fibrin
RBC

CLOT FORMATION



ABNORMAL HAEMOSTASIS

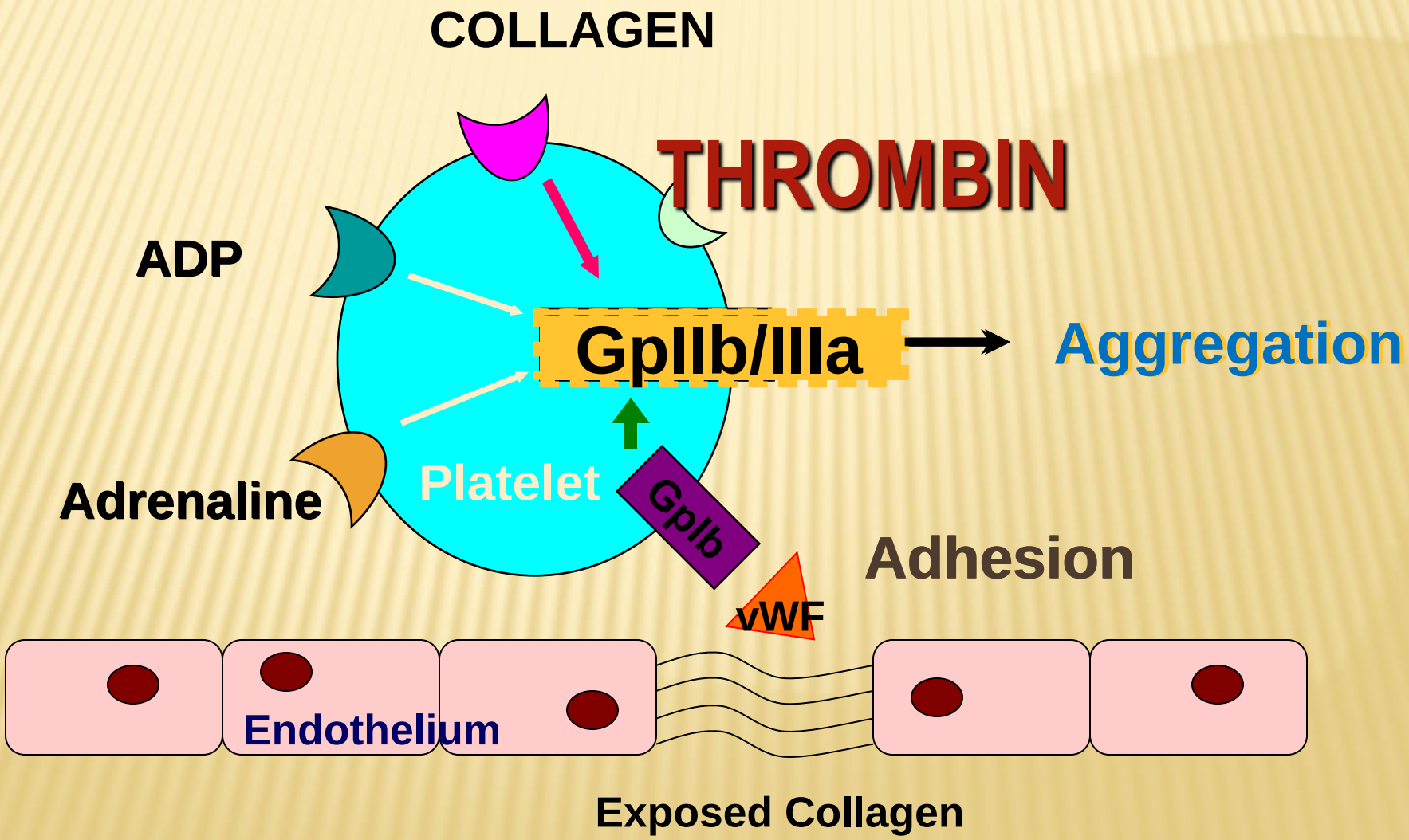
- Excessive coagulation leads to the formation of a thrombus, potentially obstructing blood flow. This is a common problem, especially in hospitalised or immobilised patients.
- Venous thromboembolic disease, for example, is a major problem in the European Union, where it causes more than one million events or deaths every year.
  Excessive bleeding results when certain coagulation factors are lacking, as in patients with haemophilia.

BLOOD VESSEL INJURY

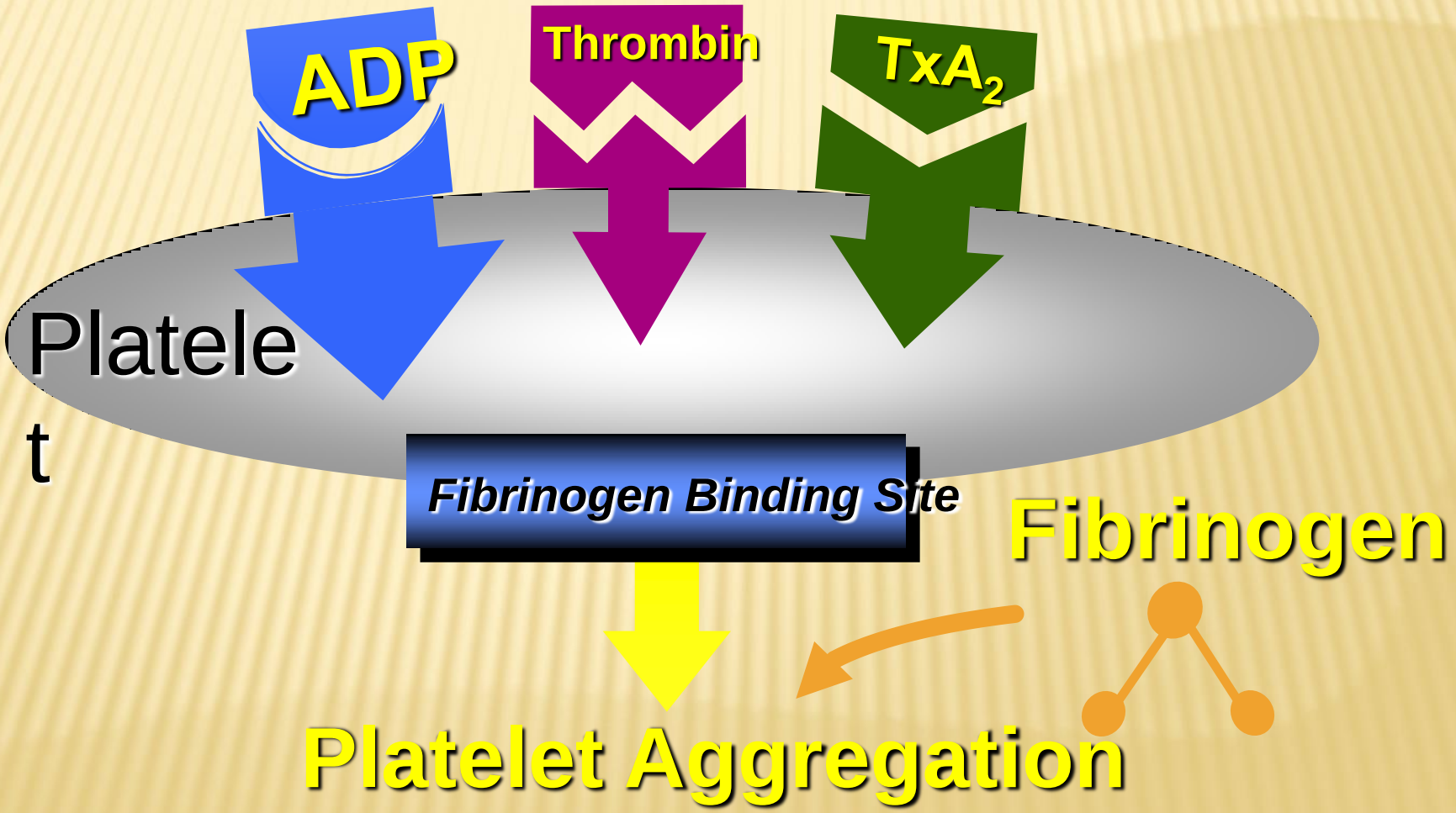
- Blood vessel injury triggers the following sequence:

- The vessel constricts to reduce blood flow
- Circulating platelets adhere to the vessel wall at the site of trauma
- Platelet activation and aggregation, coupled with an intricate series of enzymatic reactions involving coagulation proteins, produces **fibrin** to form a stable haemostatic plug
- This finely tuned process serves to maintain the integrity of the circulatory system.However, the process can go out of balance, leading to significant morbidity and mortality.

PLATELET ACTIVATION PATHWAYS (1)



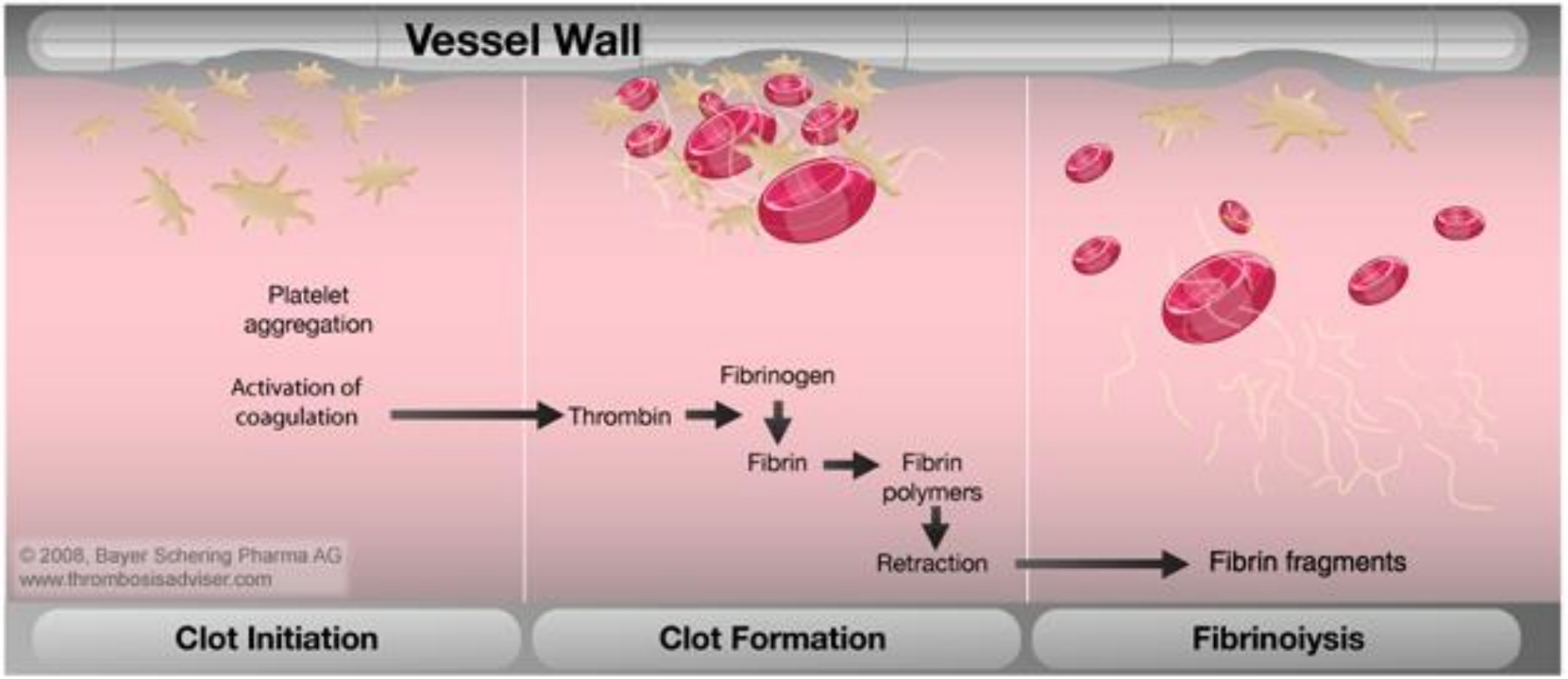
Platelet Activation Pathways (2)



Herbert. Exp Opin Invest Drugs 1994;3:449-455.

THE COAGULATION CASCADE

- Coagulation involves a complex set of protease reactions involving roughly 30 different proteins.
- The final result of these reactions is to convert fibrinogen, a soluble protein, to insoluble strands of **fibrin**. Together with platelets, the **fibrin** strands form a stable blood clot.


Vessel Wall
Platelet aggregation
Activation of coagulation
Thrombin
Fibrinogen
Fibrin
Fibrin polymers
Retraction
Fibrin fragments
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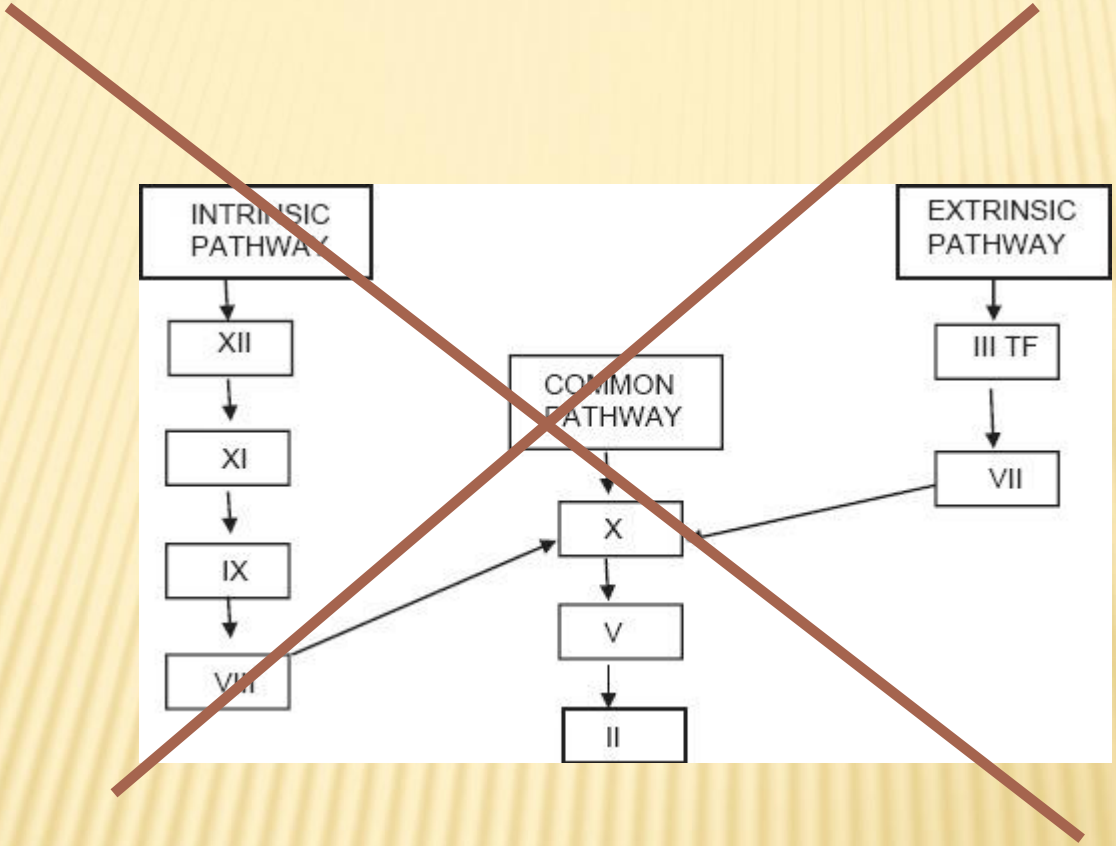
Clot Initiation
Clot Formation
Fibrinoiysis

Site	Thrombogenic	Antithrombogenic
Vessel wall	Exposed endothelium	Heparin
	TF	Thrombomodulin
	Collagen	Tissue plasminogen activator
Circulating elements	Platelets	Antithrombin
	Platelet activating factor	Protein C and S
	Clotting factor	Plasminogen
	Prothrombin	
	Fibrinogen	
	vWF	

vWF – Von Willebrand factor; TF – Tissue factor



Palta S et al., Indian J Anaesth, 58:515-523, 2014

„CELL-BASED MODEL“

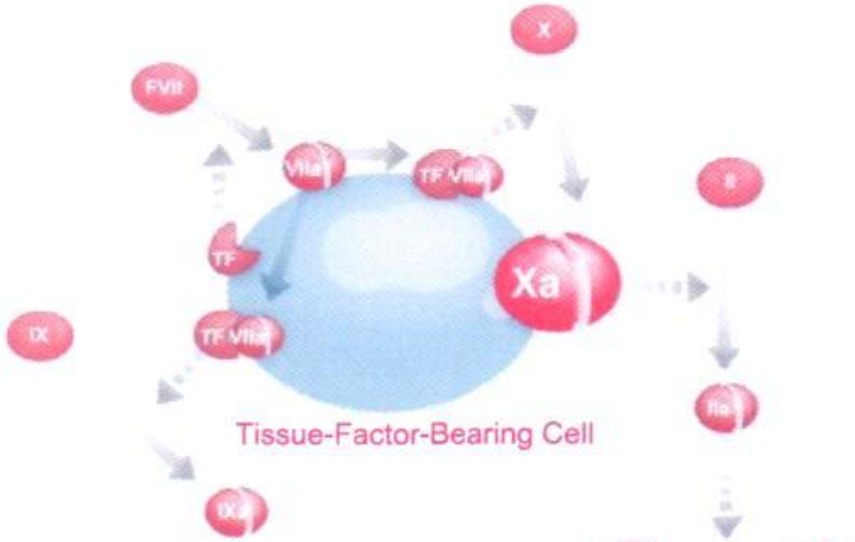
- This model identifies membranes of cell presenting tissue factor)TF) and a surface of platelets as places of activation of specific coagulation factors.
- The model supposes the model of zhree phases: initiation, amplificatopn (propagation) and the proper action of thrombin- thrombus formation.
- Initiation = formation of complex TF-FVIIa which is leading to avtivation of a small amount of thrombin.
- Propagation = activation of platelets by thrombin and formation of complex FIXa-FVIIIa with subsequent activation of factor Xa.
- Thrombus formation = formation of prothrombinase complex anf of large amount of thrombin which is leading to formation of thrombus.

Coagulation Cascade

Text size A A A

- Coagulation Cascade
  - Initiation Phase
  - Propagation Phase
  - Clot Formation
- Anticoagulation Drugs
- Natural Inhibitors
- Fibrinolysis

INITIATION



Legend:

= inactive factor

= active factor

= transformation

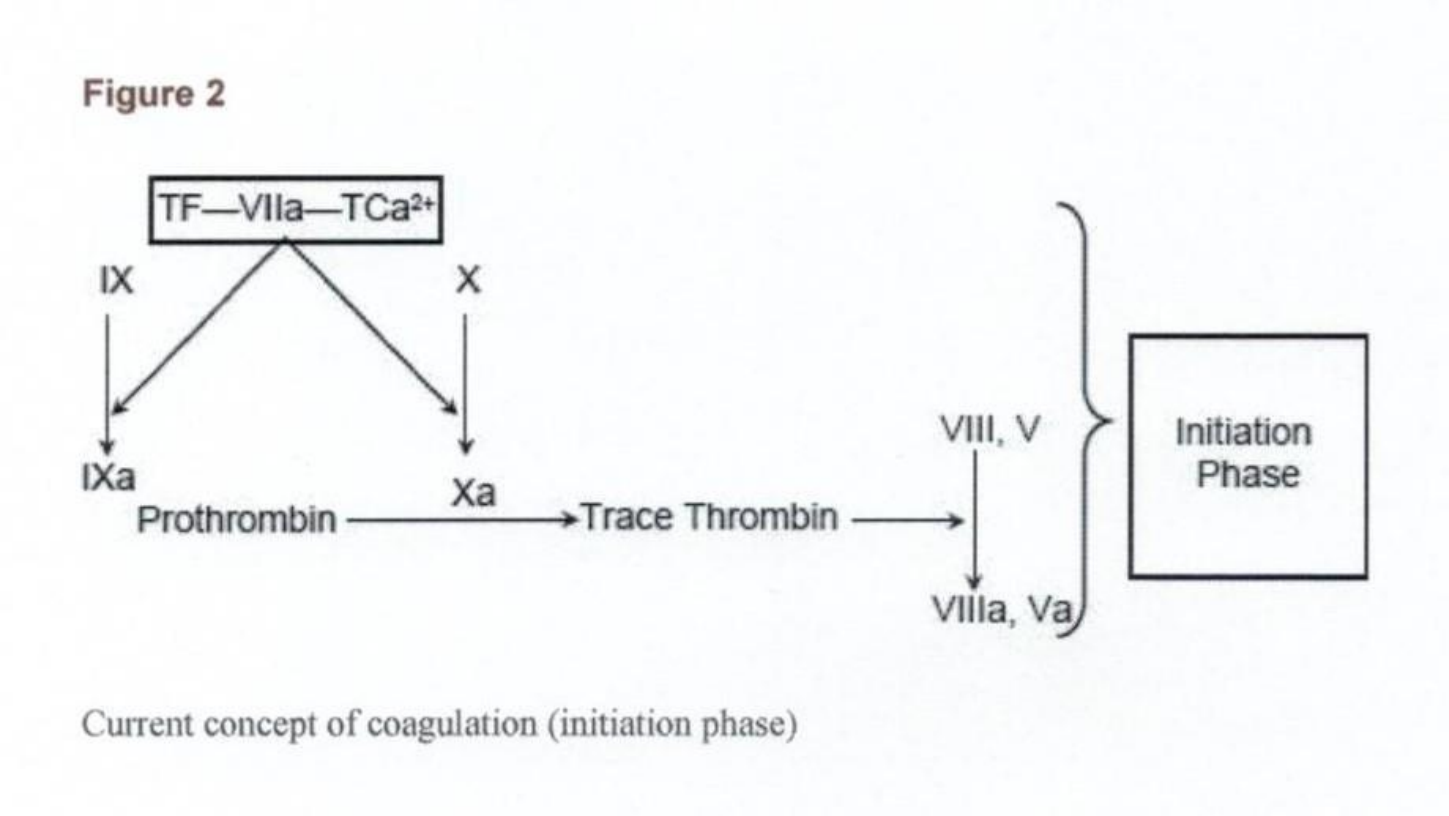
= catalysis

- Membrane-bound tissue factor (TF) activates Factor VII to Factor VIIa, leading to formation of the TF-VIIa complex.

- Membrane-bound TF-VIIa activates both Factor IX and Factor X.

- Factor Xa converts small amounts of prothrombin (Factor II) to thrombin (Factor IIa), which then activates Factor V and Factor VIII.

INICIATION PHASE OF COAGULATION

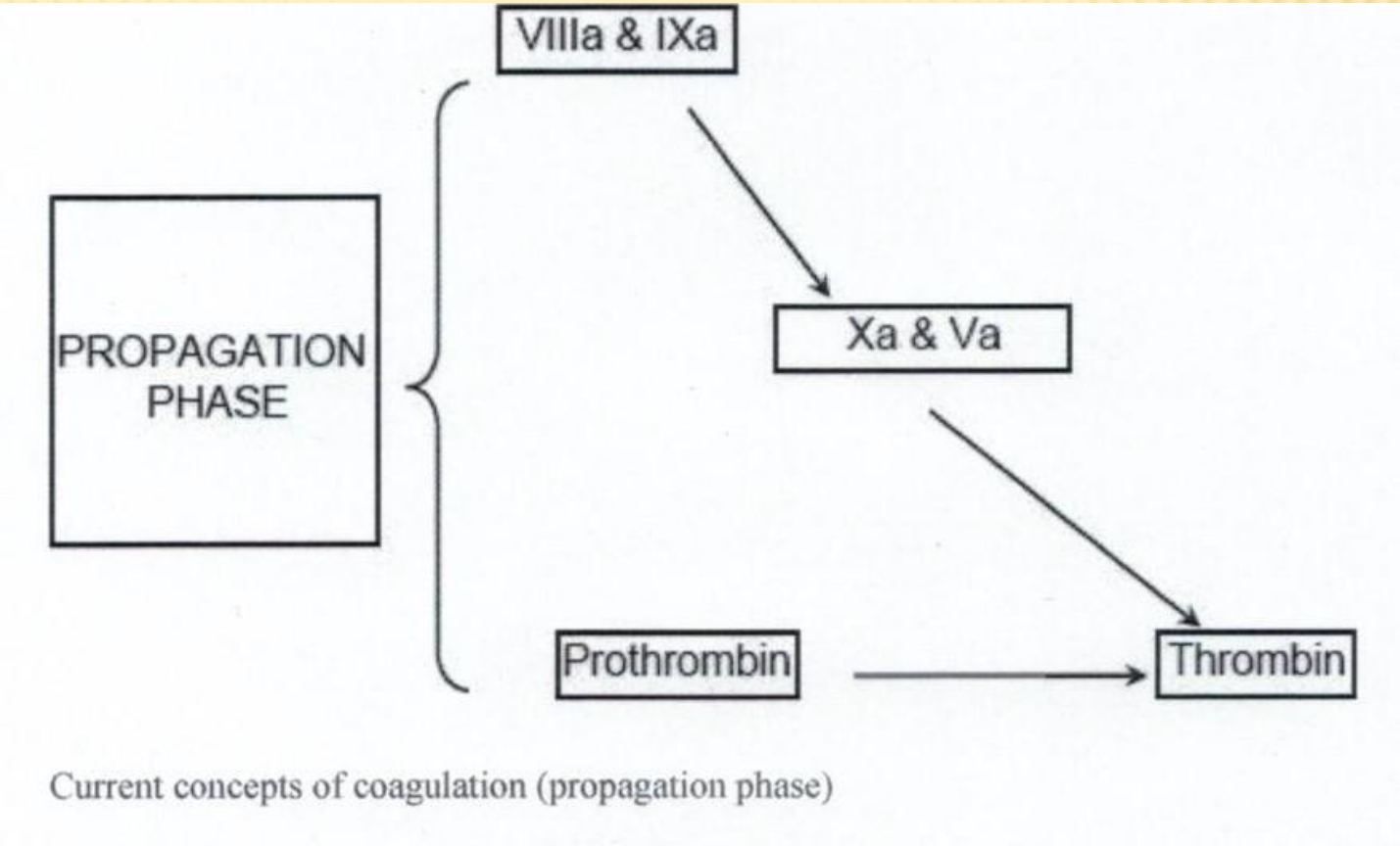


Palta S et al., Indian J Anaesth, 58:515-523, 2014

INITIATION PHASE OF COAGULATION

- Coagulation cascade is activated when defect of vessel wall enables contact of the blood with cells with TF.
- Platelets membrane bound tissue factor TF activates FVII to VIIa which is leding to formation of complex TF-VIIa.
- The complex binding on platelets membranes activates Factor IX(a) and Factor X(a).
- Factor Xa converts small amount of prothrombin (Faktor II) on trombin (Factor IIa) which can activate Factor V on FVa and Factor VIII on FVIIIa.

PROPAGATION PHASE OF COAGULATION



Current concepts of coagulation (propagation phase)

Palta S et al., Indian J Anaesth, 58:515-523, 2014

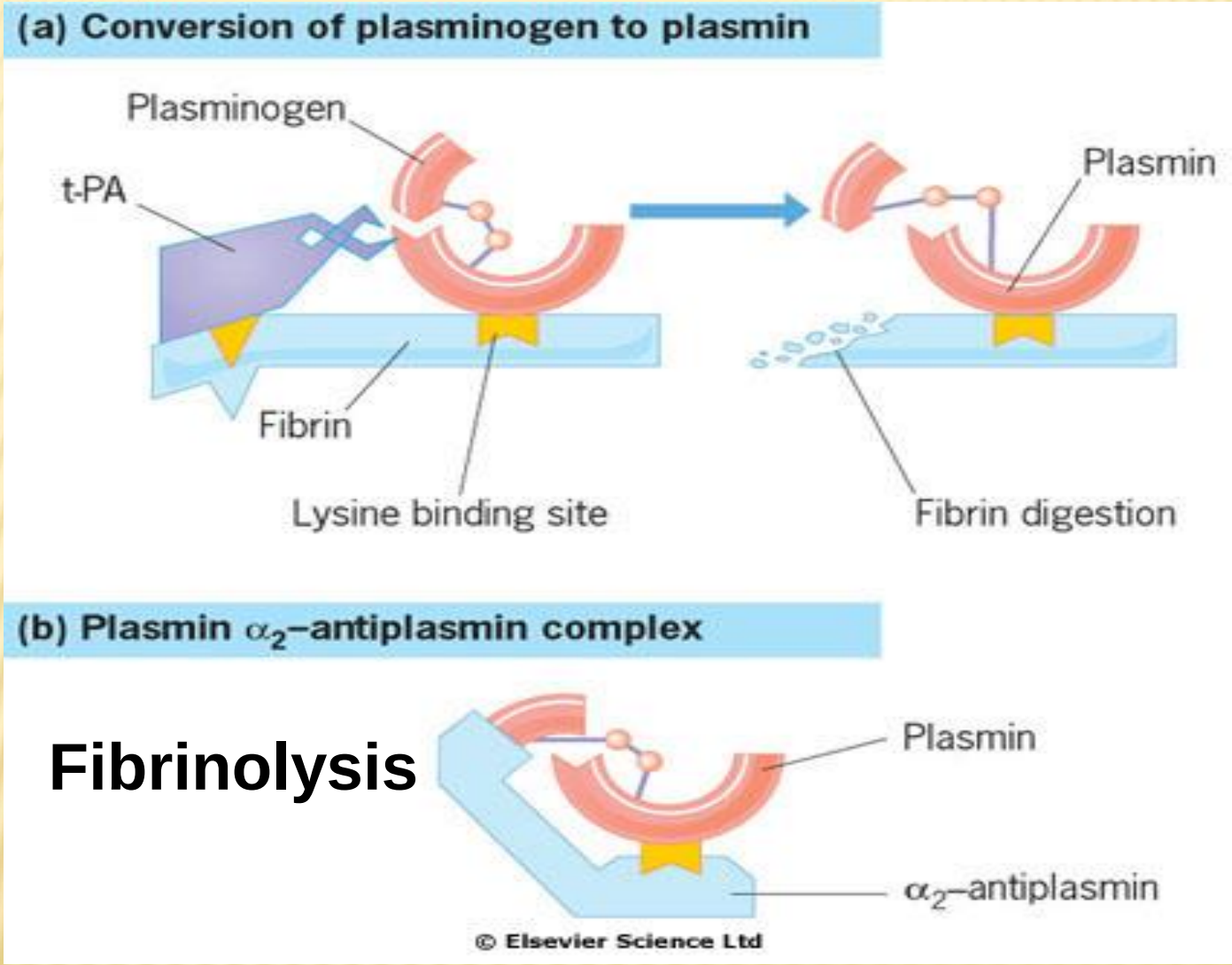
PROPAGATION OF COAGULATION: CENTRAL ROLE FOR FACTOR XA

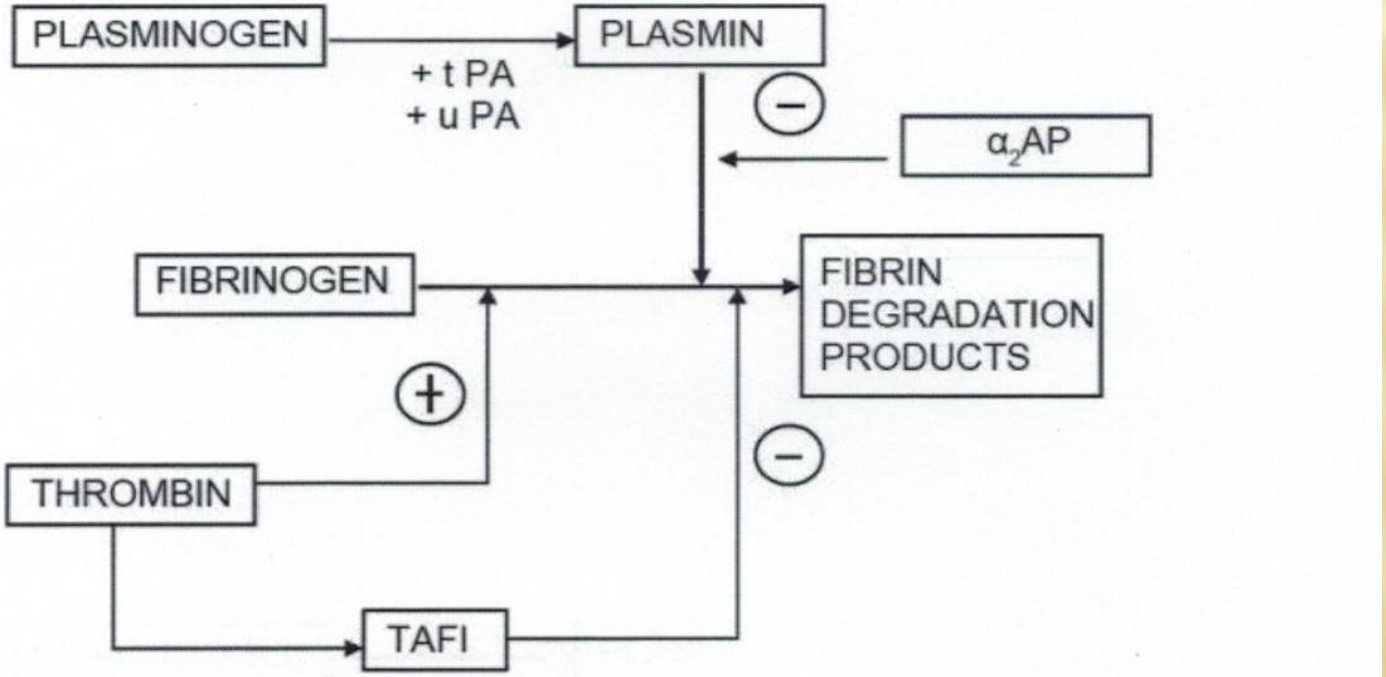
- **Factor Xa together with activated** Factor V (Va) as cofactor support coagulation by thrombin formation (Factor IIa) from prothrombin (Factor II).
- **Factor Xa** is primary pount for propagation of the porcess; one molecule of **Factor Xa** catalyses formation of about 1,000 molecules of thrombin.

FINAL STEP: FIBRIN FORMATION

- In the final step, sequence of serin proteinases reactions which lead to formation of blood clot, thrombin will convert soluble fibrinogen to insoluble **fibrin**.
- **Thrombin** also activates Factor XIII (stabilizing fibrin) which can stabilize clot by crosslinking of fibrin.
- Stabilized fibrin is able to retain cellular components (red blood cells, platelets or both).

Fibrinolysis





Regulation of the fibrinolytic system

Palta S et al., Indian J Anaesth, 58:515-523, 2014

Coagulation Cascade

Text size A A A

- Coagulation Cascade
- Anticoagulation Drugs
- Natural Inhibitors
- Fibrinolysis

TFPI
Tissue factor pathway inhibitor (TFPI) from endothelial and other cells forms a complex with Factor Xa to inactivate it. The TFPI-Xa complex then inactivates the membrane-bound TF-VIIa complex.

APC
Activated protein C (APC) inactivates Factors Va and VIIIa with protein S as a cofactor. APC is converted from protein C by a complex of thrombin and thrombomodulin. Thrombomodulin is bound to the membranes of endothelial cells.

AT
Antithrombin (AT) binds activated coagulant Factors (IIa, IXa, Xa, XIa and XIIa) that are not clot-bound or in the prothrombinase complex. AT is activated by endothelial heparan sulfate.

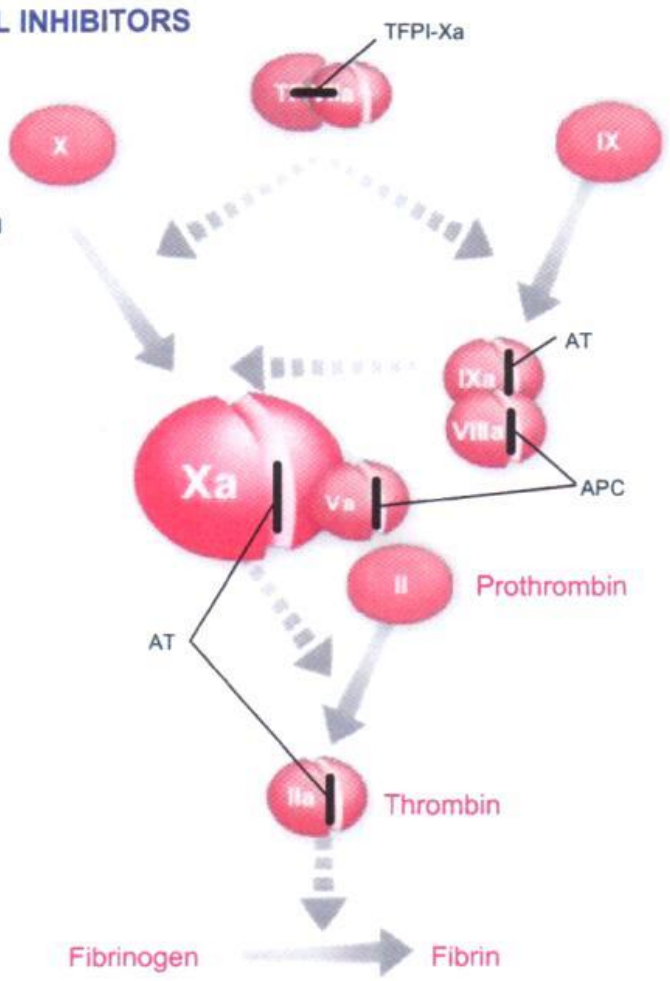
Legend:

= inactive factor

= active factor

= transformation

= catalysis



Coagulation inhibitors

- Adequate coagulation will develop only on surface of activated cells (platelets and endothelial cells). Non- activated cells distally of the injury exprime another inhibitory systems - tissue factor pathway inhibitor (TFPI), heparansulphate (HS), thrombomodulin (TM) and protein C (PC).
- TFPI prevents thrombin formation on the surface of endothelial cells by inhibition of FXa an FVIIa formed by cells producing TF (monocytes). By this, activity of Xa is even in initiation phase strongly controlled.
- Endothelial cells produce HS binding plasma AT and accelerate its inhibitory activity. As result, inactivation of thrombin and other activated factors (FXa, FIXa, FXIa, FXIIa) from the space of coagulum formation can be expected. Heparin is functioning like HS. Formatted thrombin will bind on TM and the complex thrombin-TM quickly activates PC on activated PC (APC). APC together with its cofactor protein (PS) irreversibly cleaves FVa and FVIIIa. This step limits formation of thrombin in propagation phase. Endothelial cells produce ADPase on their luminal surface which blocks proaggregation effect of ADP releasing from activated platelets.

NATURAL INHIBITORS OF COAGULATION

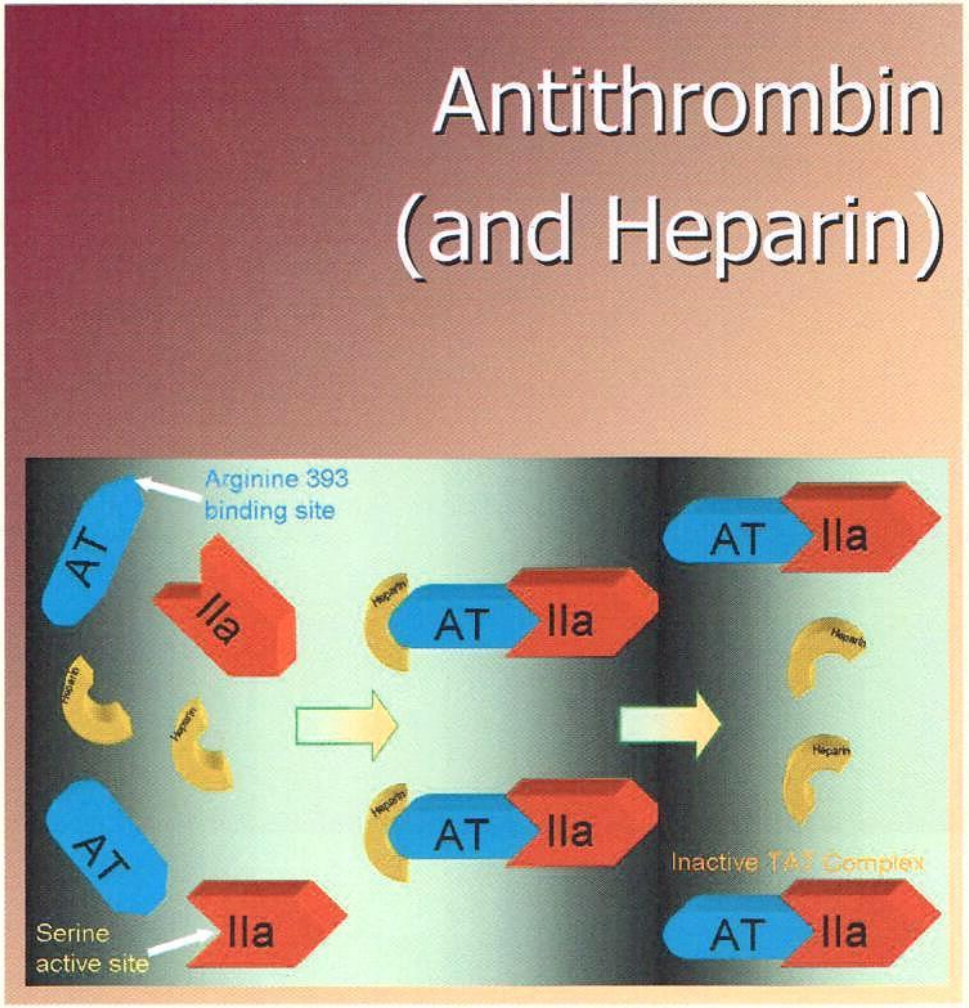
- „Tissue factor pathway inhibitor“ –produced by endothelial celllls. It inhibits complex TF-VIIa.
- Antithrombin (previously AT III) – binds activated vitamin K dependent coagulation factors (can be activated by heparin which increases its binding capacity)
- „Protein Z dependent protease inhibitor/ protein Z (PZI)“ produced by liver. It inhibits FXa in presence PZ and Ca++.

CLOT-ED

Antithrombin (AT) is a serine protease inhibitor (SERPIN) that inhibits factors XIa, IXa, Xa, FVIIa/TF, and Thrombin (IIa)

AT inhibitory activity is increased 1000 fold by heparin

Plasma half-life is 60-70 hours



PC and PS Deficiencies

Protein C

- Classification
  - Type I (quantitative)
  - Type II (qualitative)
- Relative risk for thrombosis ~6.5
- Onset of thrombosis is before middle age (<45 years)
- Homozygous deficiency is associated with neonatal purpura fulminans

Relative risk is ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the non-exposed population

Protein S

- PS either circulates freely as Free PS (40%) or bound to C4b-Binding Protein (60%)
  - Free form is active
  - C4b-BP is acute phase reactant
- Relative risk for thrombosis ~2 but difficult to predict since in some families the risk is substantial (possible interaction with other defects)

Type	PS Activity	Free PS Antigen	Total PS Antigen
I	Low	Low	Low
II	Low	Normal	Normal
III	Low	Low	Normal

Acquired Deficiencies: PC, PS, AT

- Acquired deficiencies of Protein C and Protein S
  - Oral anticoagulants (warfarin) or Vitamin K deficiency
  - Liver disease
  - Post-operatively
  - Disseminated Intravascular Coagulation (DIC)
  - Consumption during an acute thrombotic event
  - PS also reduced in nephrotic syndrome and pregnancy
- Acquired deficiencies of Antithrombin
  - Heparin therapy
  - L-asparaginase therapy
  - Liver disease
  - Nephrotic syndrome

COAGULATION FACTORS -STATE

- Non activated-after their synthesis in liver
- Posttranslationally modified –vitamin K dependent coagulation factors = serin proteázy
- Activated –activated serin proteases, other activated factors (Va, VIIIa)

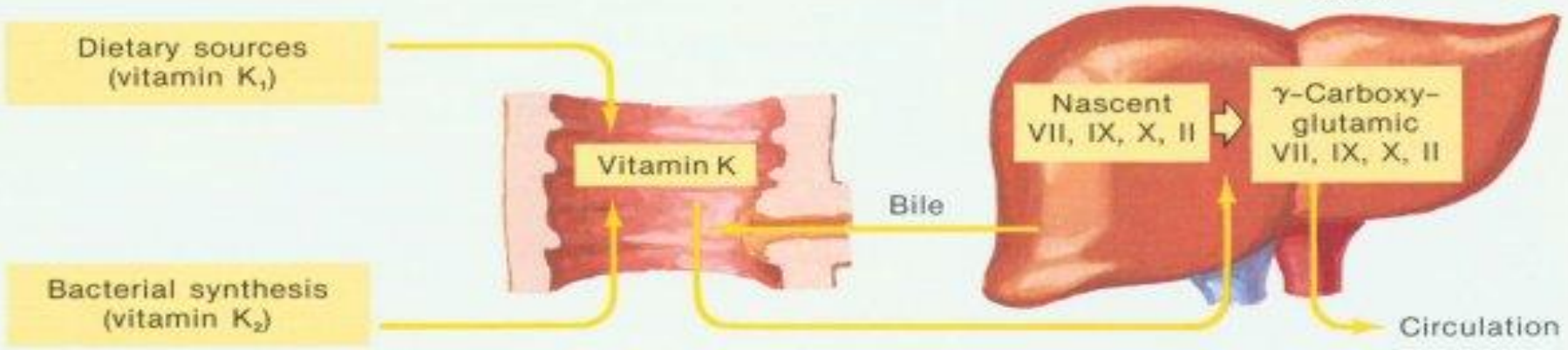
Role of Liver in Hemostasis

- Site for synthesis
  - All coagulation factors (except VWF)
  - Regulators of coagulation proteins (Antithrombin, Protein C, Protein S)
  - Fibrinolytic proteins (Plasminogen, Antiplasmin, Thrombin Activatable Fibrinolysis Inhibitor [TAFI])
- Site for carboxylation of vitamin K-dependent proteins
  - Procoagulant factors: II, VII, IX, X and anticoagulant proteins: Protein C, Protein S
  - Process allows these proteins to bind to cellular membranes and participate in macromolecular complex formation on these surfaces resulting in Thrombin formation
- Site for clearance
  - Activated coagulation factors, enzyme-inhibitor complexes (ie, thrombin-anthithrombin complexes), & fibrin degradation products

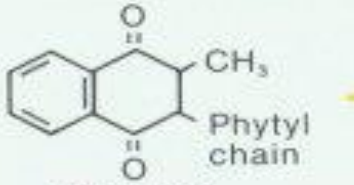
Synthesis of Vitamin K-Dependent Coagulation Factors

JOHN A. CRAIG, MD

Vitamin K absorption and metabolism

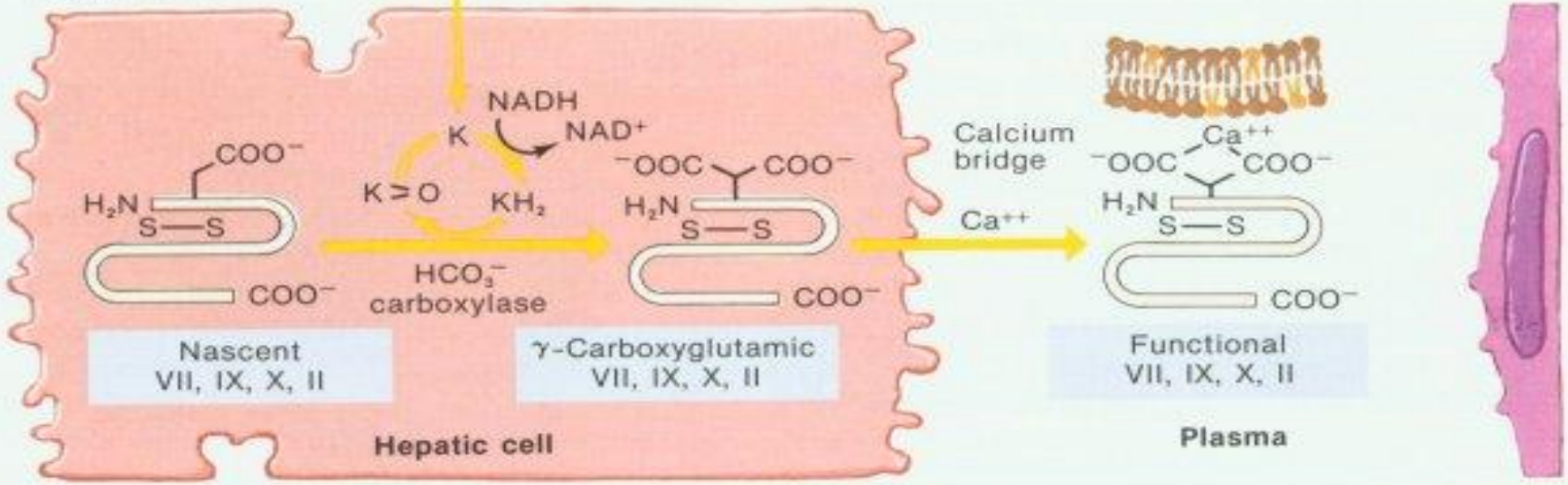


Vitamin K mechanism of action



Vitamin K

Synthesis of functional forms of VII, IX, X and II depends on vitamin K, the cofactor for a carboxylase enzyme that adds γ-carboxyl groups to glutamic acids in nascent coagulation proteins VII, IX, X and II



ANTICOAGULATION THERAPY

- Vitamin K antagonists (warfarin) block recyclation of oxidased K to reduced KH2 in liver. Vitamin KH_2 is a cofactor of carboxylation of glutamate residua in N-terminal regions of vitamin K dependent coagulation factors (serin proteinases). This limits binding of non carboxylated coagulation using Ca++ on phospholipid surfaces, especially on surface of activated plateles and endothelial cells.
- Optimal doses of warfarin has great interindividual variability. They are dependnt on diet, treatment, age, body weight and important genetic factors [VKORC1 and cytochrom P450 (CYP) 2C9].
-

TESTS

- Screening tests
- Bleeding time
- Platelet count
- Prothombin time (PT)
- Partial thromboplastin time (PTT)
- Thrombin time (TT)
- More specific tests

SAMPLING

- Venous blood
- Excessive stress and exercise cause changes in blood clotting. and fibrinolysis.
- Whenever possible, venous samples should be collected without a pressure cuff (to avoid haemoconcentration, increase of fibrinolysis, platelet release, and activation of some clotting factors.
- To minimize the effect of contact activation plastic or polypropylene, siliconized glass, syringes and containers should be used.
- Thoroughly mixing the blood with the anticoagulant by inverting the containers several time.
- The sample should be brought to the laboratory as soon as possible.
- Labeling the patient sample is very important.

SAMPLING

- Anticoagulant trisodium citrate 3.2 % in a ratio of 1 : 9.
- Time of sample collection is very important factor in the interpretation of results.
- Centrifugation and preparation of platelets poor plasma - 4000 rpm in a cooling centrifuge.
  - **P.T & Factor VII → kept at room temperature.**
  - **Other assays → at 4°C.**

  - Testing should preferably be completed within 2 hours of the collection.

BLEEDING TIME

- **Time** taken for bleeding to cease from a small superficial wound

- **Affected by**
  - Platelet count and function
  - Vessel wall

  - **Normal range** Ivy's method: 2-7 **min**

PLATELET COUNT

- Normal platelet count = 150-400x10^9/L
- A part of complete blood picture (CBC)
- Performed by electronic counters or manually (inherent error)

PROTHROMBIN TIME

- Indicates the overall efficiency of extrinsic pathway of blood coagulation (FVII, FII, FV, X)
- Normal range: 10-14 sec

PROTHROMBIN TIME

- **Causes of prolonged PT**
- Liver disease
- Vit K deficiency (FII, V, VII, IX are Vit k dependent)
- Deficiency of factors involved in extrinsic pathway
- DIC
- **Oral anticoagulants**

PARTIAL THROMBOPLASTIN

- Indicates the overall efficiency of intrinsic pathway of blood coagulation (FVIII, FIX, FXI, FXII, FII, FV, X)

- Normal range: 30-40 sec

PARTIAL THROMBOPLASTIN

- **Causes of prolonged PTT**
- Deficiency of factors involved in intrinsic pathway (coagulation factors other than FVII)
- Liver disease
- DIC
- Massive transfusion (labile FV, FVIII)
- **Heparin**

PT & PTT

- **Prolonged PT** + normal PTT= **ex**trinsic pathway defect
- **Prolonged PTT** + normal PT= **in**trinsic pathway defect
- **Prolonged PT and PTT**= **common** pathway defect or **combined** factor deficiencies

THROMBOCYTOPENIA

- Platelet count below $150x10^9/L$
- Causes:
- - Congenital
- Acquired
- failure of production
- Increased destruction *(ITP)*
- - Splenic sequestration *(hypersplenism)*

IDIOPATHIC THOMBOCYTOPENIC PURPURA

- **ITP** is immune thrombocytopenia due to formation of **antibodies** against platelets and BM megakaryocytes.

- **Clinical picture**: spontaneous bleeding purpuric eruptions.

- **BT**: prolonged
- **Platelet count**: thrombocytopenia
- **PT,PTT**: normal
- **BM:** increased megakaryocytes with poor platelet separation

QUALITATIVE PLATELET DEFECT

- Platelet function defect + normal plt count
- Causes:

- Hereditary (Glanzmann's disease, Bernard-Soulier syndrome)
- Acquired (drugs as *aspirin*, uremia)

QUALITATIVE PLATELET DEFECT

- **Clinical picture**: spontaneous bleeding purpuric eruptions.

- **BT**: prolonged
- **Platelet count:** normal or slightly decreased
- **PT,PTT, TT**: normal
- **Platelet function**: abnormal depending on the defect (defective aggregation in Glanzmann's disease and Bernard-Soulier syndrome)

HEREDITARY THROMBOPHILIA

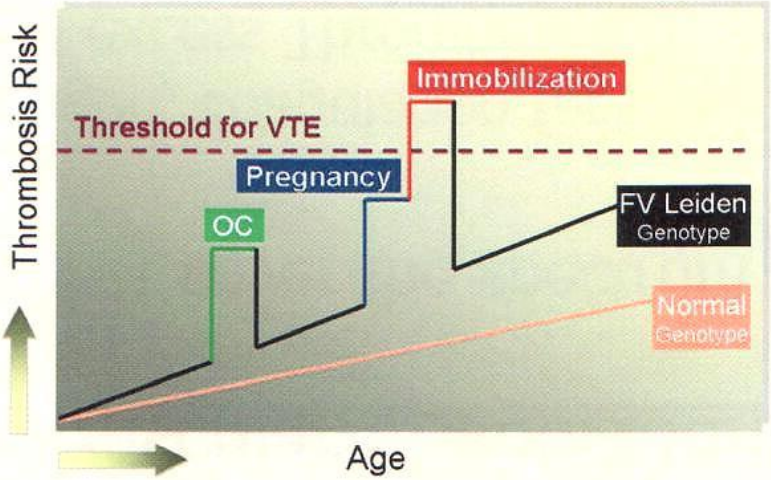
- Hereditary thrombofilia
- AT deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Prothrombin polymorphism (G/A 20210 in 3´ area of the gene)

ACQUIRED THROMBOTIC DISORDERS

- Sy of antiphospholipid antibodies
- Increased levels of factors VIII, IX, XI and fibrinogen
- Fibrinolysis defects

Thrombophilia

- Tendency to develop thrombi in veins (venous thrombosis) or arteries (arterial thrombosis)
  - Thrombophilia in western countries is frequently used in the context of venous thrombosis
- Thrombosis is a complex (multicausal) disease in which many different pathways can contribute to the risk of developing disease
  - Singularly, inherited and acquired risk factors have may have only a moderate effect
  - Risk is greatly increased when two or more risk factors combine
    - Genetic and genetic
    - Genetic and environmental



Acquired Thrombophilia

- Risk factors for thrombosis - Disorders
  - Antiphospholipid Syndrome (APS)
  - Underlying malignancy
  - Pregnancy/postpartum
  - Heparin-Induced Thrombocytopenia (HIT)
  - Paroxysmal Nocturnal Hemoglobinuria (PNH)
  - Disseminated Intravascular Coagulation (DIC)
- Risk factors for thrombosis - Environmental
  - Stasis due to prolonged immobilization, obesity
  - High risk surgeries (orthopedic)
  - Trauma
  - Previous thrombosis
  - Oral contraception (OC) and hormone replacement therapy (HRT)

HEPARIN/LMWH—ADVERSE EFFECTS

- **Heparin**
  - **Bleeding**
  - **Thrombocytopenia**
  - **Osteoporosis**
  - **Hypersensitivity**
- **LMWH**
  - **Bleeding**
  - **Thrombocytopenia**
  - **Hypersensitivity**

WARFARIN—ADVERSE EFFECTS

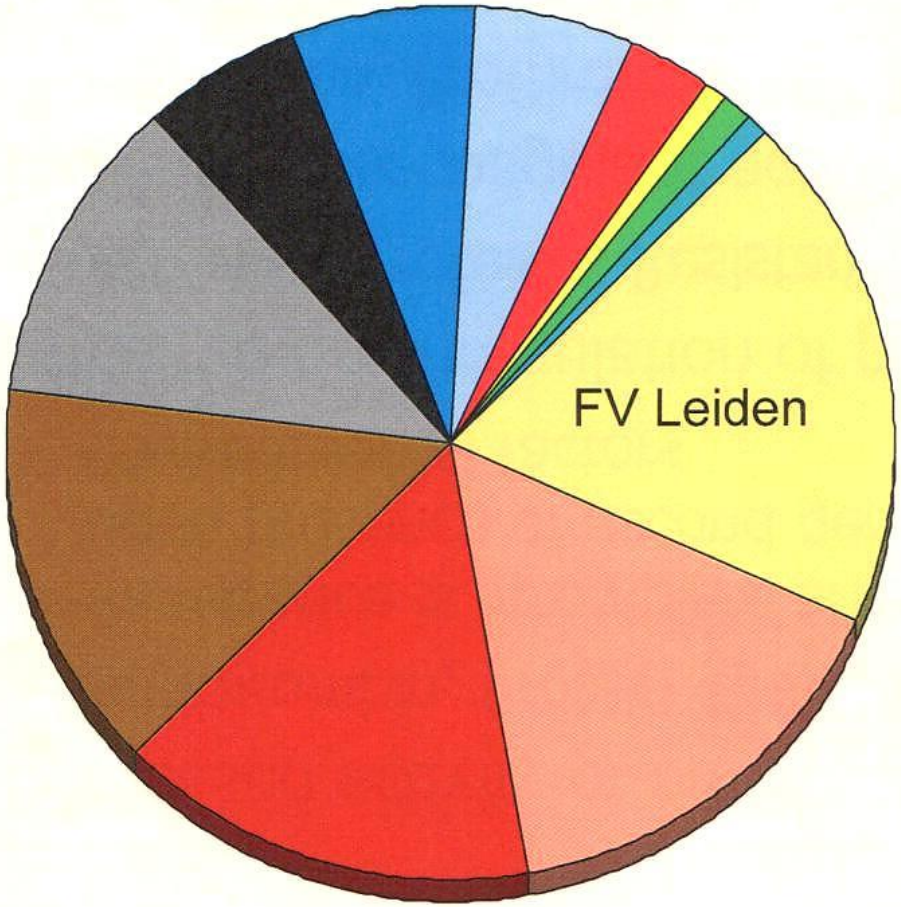
- Fatal or non-fatal hemorrhage from any tissue or organ
- Necrosis of skin and other tissues
- Other adverse reactions reported less frequently include:
  - Systemic cholesterol microembolization
  - Alopecia
  - Purple toes syndrome, urticaria, dermatitis including bullous eruptions

CLOT-ED

Venous Thrombosis

- Venous system: low flow & pressure
- Thrombi are fibrin rich
- Function of age, biologic conditions, genetic & environmental factors, and their interactions
- Venous thromboembolism (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
  - Superficial, portal, cerebral, or retinal vein thrombosis
- Reasons for coagulation testing
  - Risk for recurrence of thrombosis
  - Treatment considerations (duration & intensity)
  - Genetic counseling for affected family members
  - Prophylaxis for high risk situations

Prevalence for Venous Thrombosis



- FV Leiden 20%
- Surgery/Trauma 16%
- FVIII (>150U/ml) 16%
- Immobilization 15%
- Malignancy 10-15%
- APS 2-14%
- HyperHyc 5-10%
- PT 20210 6%
- Protein C 3%
- Protein S 1%
- Antithrombin 1%
- Dysfibrinogenemia <1%

HyperHyc: Hyperhomocysteinemia

Prevalence: proportion of persons with disease

CLOT-ED

Genetic Risk Factors

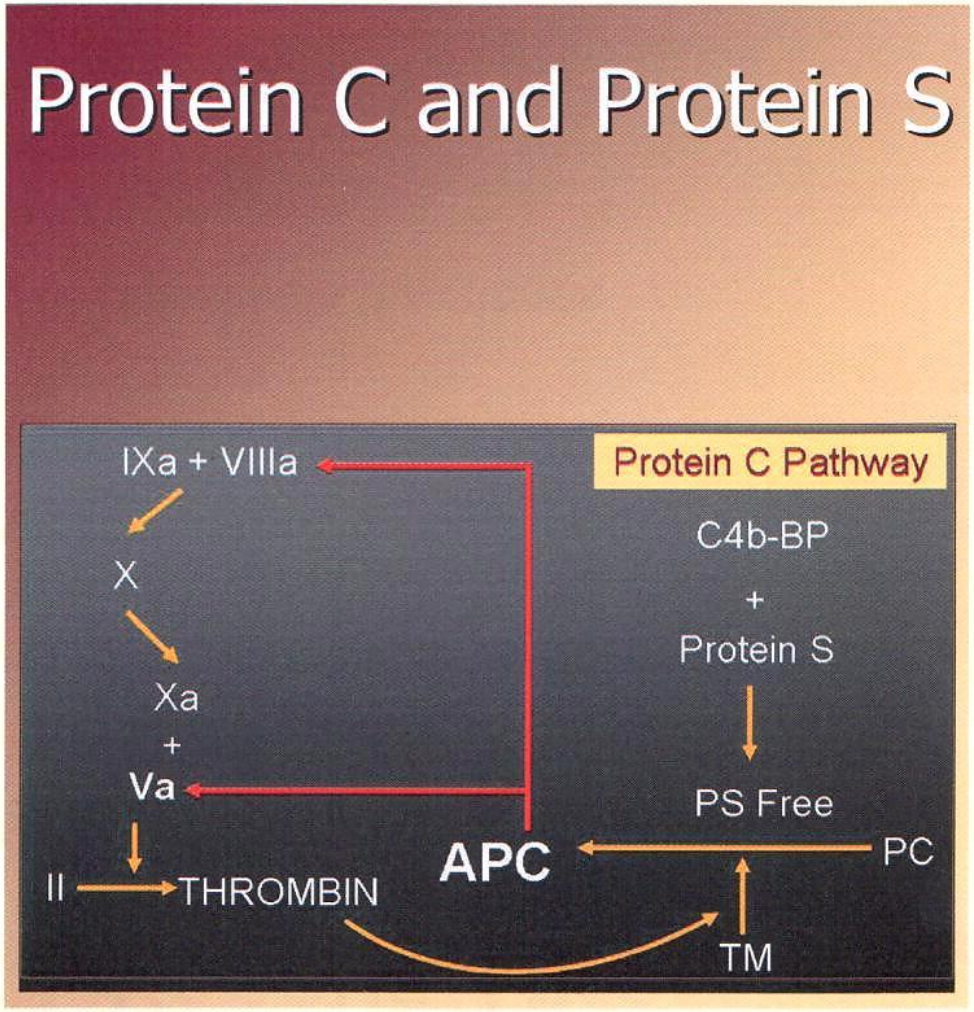
- Decreased activity of natural anticoagulants
  - Antithrombin, Protein C, and Protein S
  - Penetrance is incomplete and expression is dependent upon presence of second genetic defect and environmental factors
- Impaired downregulation of procoagulant activity
  - Activated Protein C Resistance (Factor V Leiden)
- Increased procoagulant activity of plasma proteins
  - Fibrinogen, Prothrombin (PT 20210), factors VIII, IX, XI
- Impaired fibrinolysis (weak association)
  - Plasminogen (deficiency), FXIII polymorphisms

CLOT-ED

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)

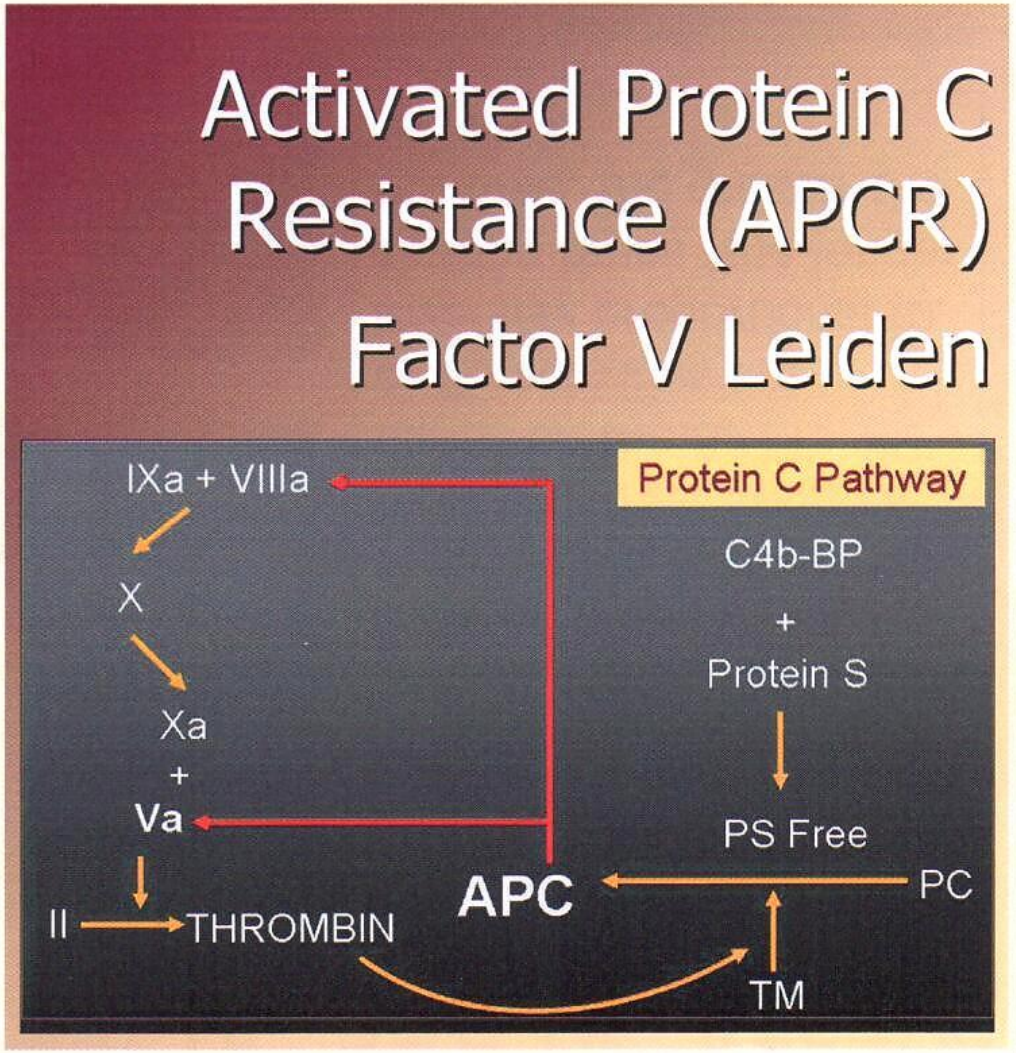
APC downregulates coagulation cofactors, VIIIa and Va



CLOT-ED

A single base mutation (guanine to adenine at position 1691 of the *FV gene*) is responsible for the Arg506Gln mutation known as FV Leiden

Phenotype is characterized by a reduced anticoagulant response to APC (FV Leiden is inactivated 10 fold slower than normal FV)

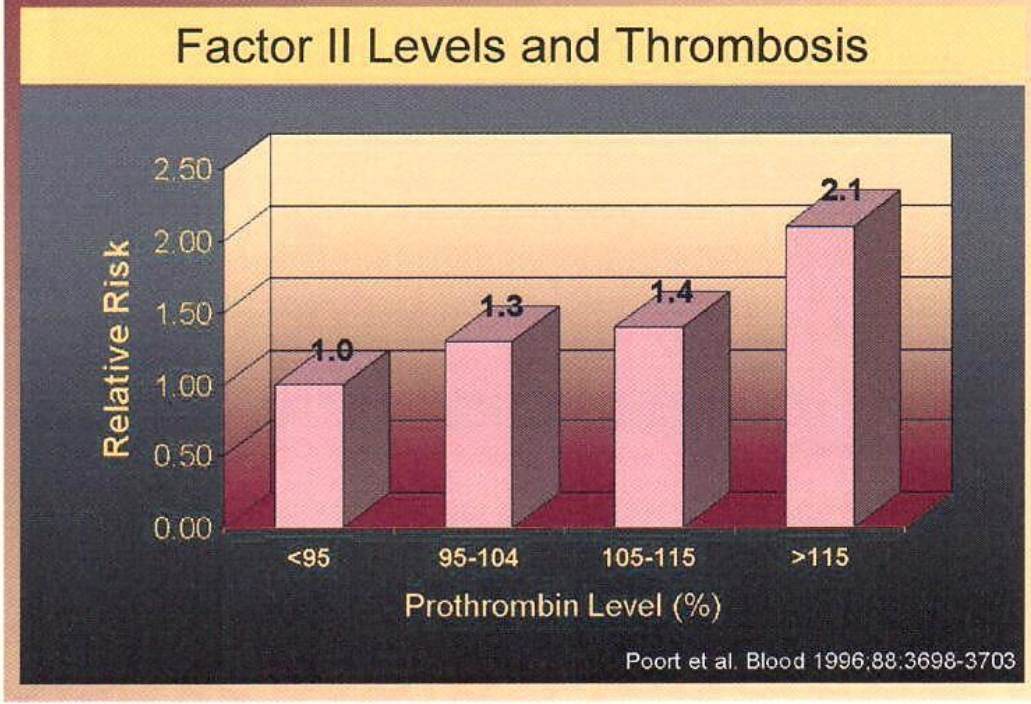


CLOT-ED

Polymorphism (adenine substituted for guanine at nucleotide 20210) in the 3′-untranslated region of the gene encoding for Factor II (Prothrombin)

Patients heterozygous for the mutation have elevated levels of Prothrombin but activity levels can not be used to exclude genetic defect

Prothrombin 20210



Acquired Thrombophilia

- Risk factors for thrombosis - Disorders
  - Antiphospholipid Syndrome (APS)
  - Underlying malignancy
  - Pregnancy/postpartum
  - Heparin-Induced Thrombocytopenia (HIT)
  - Paroxysmal Nocturnal Hemoglobinuria (PNH)
  - Disseminated Intravascular Coagulation (DIC)
- Risk factors for thrombosis - Environmental
  - Stasis due to prolonged immobilization, obesity
  - High risk surgeries (orthopedic)
  - Trauma
  - Previous thrombosis
  - Oral contraception (OC) and hormone replacement therapy (HRT)

CLOT-ED

Venous Thrombosis

- Venous system: low flow & pressure
- Thrombi are fibrin rich
- Function of age, biologic conditions, genetic & environmental factors, and their interactions
- Venous thromboembolism (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
  - Superficial, portal, cerebral, or retinal vein thrombosis
- Reasons for coagulation testing
  - Risk for recurrence of thrombosis
  - Treatment considerations (duration & intensity)
  - Genetic counseling for affected family members
  - Prophylaxis for high risk situations

THROMBOSIS AND AF

- AF is the most common **arrhythmia** seen in clinical practice.
- Without appropriate anticoagulant treatment, most patients with AF are at increased risk of cardioembolic stroke.

THROMBOSIS AND CORONARY ARTERY DISEASE

- Cardiovascular disease is the leading cause of death in industrialised countries. **Coronary artery disease** (CAD) is the most common form of cardiovascular disease. In CAD, atherosclerosis damages the coronary artery wall, predisposing to thrombus formation. The symptoms and severity of acute coronary syndromes (unstable **angina** and myocardial infarction) vary depending on the degree to which thrombi occlude the coronary arteries.

VASCULAR DISORDERS

- Pattern of bleeding: purpura

- Causes……

- Screening tests for hemostasis:
- BT: prolonged
- Platelet count: normal
- - PT, PTT, TT: normal

Table 8.22
Vascular disorders

Congenital
Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease)
Connective tissue disorders (Ehlers–Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, Marfan's syndrome)

Acquired
Severe infections:
- Septicaemia
- Meningococcal infections
- Measles
- Typhoid

Allergic
Henoch–Schönlein purpura
Autoimmune disorders (SLE, rheumatoid arthritis)

Drugs
Steroids
Sulphonamides

Others
Senile purpura
Easy bruising syndrome
Scurvy
Factitious purpura

Table 8.24
Causes of thrombocytopenia

Impaired production	Excessive destruction
Bone marrow failure	**Immune**
Megaloblastic anaemia	AITP
Leukaemia	Secondary immune (SLE, CLL, viruses, drugs, e.g. heparin)
Myeloma	Alloimmune neonatal thrombocytopenia
Myelofibrosis	Post-transfusion purpura
Solid tumour infiltration	
Aplastic anaemia	**Sequestration**
drugs	Hypersplenism
chemicals	
viruses	**Dilutional**
paroxysmal nocturnal haemoglobinuria	Massive transfusion
	Other
	Disseminated intravascular coagulation
	Thrombotic thrombocytopenic purpura
	Haemolytic uraemic syndrome

BLEEDING DISORDERS

- Abnormal bleeding may result from
  - Vascular disorders
  - Thrombocytopenia (↓ platelet count)
  - Defective platelet function (qualitative defect)
  - Coagulation disorders

HEREDITARY BLEEDING DISEASES

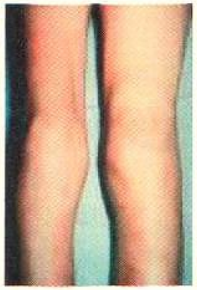
- Von Willebrand´s disease
- Hemophilia A
- Hemophilia B
- Hemophilia C
- Factor V deficiency
- Factor VII deficiency
- Factor XIII deficiency
- Prothrombin deficiency
- Afibrinogenemia

ACQUIRED BLEEDING DISORDERS

- Consumption coagulopathies
- DIC-diseminated intravascular coagulation
- Microangiopathic hemolytic anemia
- Vitamin K deficinecy
- Liver diseases

Hemophilia A and B

- Inheritance is X-linked
- Severity of bleeding depends on levels of FVIII or FIX
  - Mild: activity levels between 5-25%
    - Have significant bleeding after major trauma or surgery but generally go undetected until abnormal APTT is found
  - Moderate: activity levels between 2-5%
    - Bleeding is precipitated by trauma or surgery
  - Severe: less than 1% activity
    - Present with recurrent hemorrhages that occur spontaneously or after minor trauma/surgery
- Clinical presentation
  - 90% of bleeding episodes occur into the joints (knees and elbows predominantly)
  - Intramuscular, intracranial, & gastrointestinal



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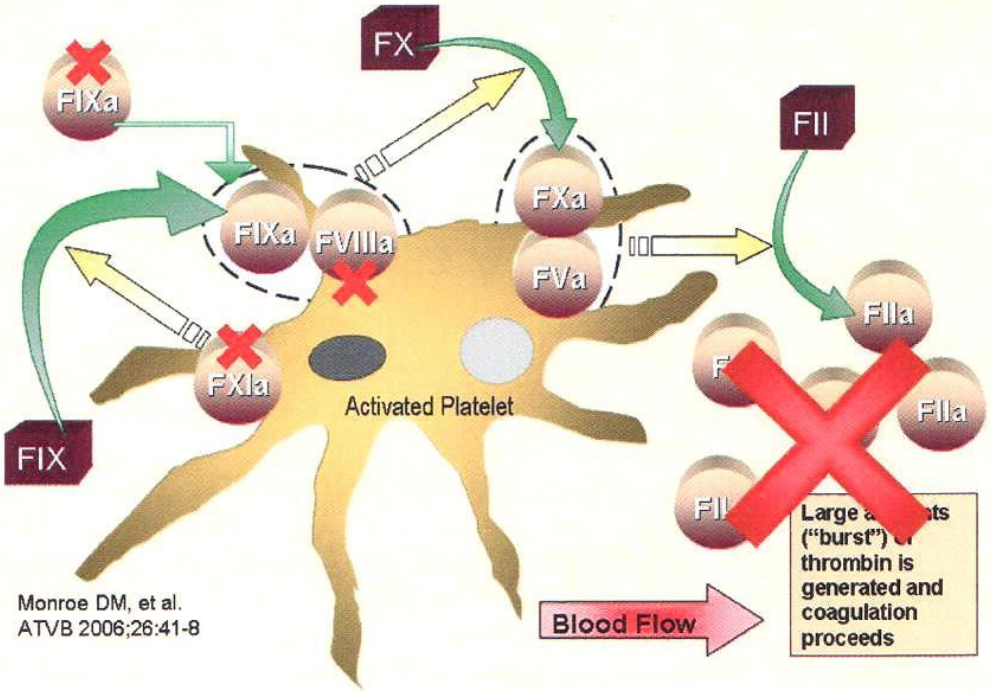
The Defect in Hemophilias

Hemophilia A (FVIII), Hemophilia B (FIX), and Hemophilia C (FXI) are disorders of the Propagation Phase of coagulation

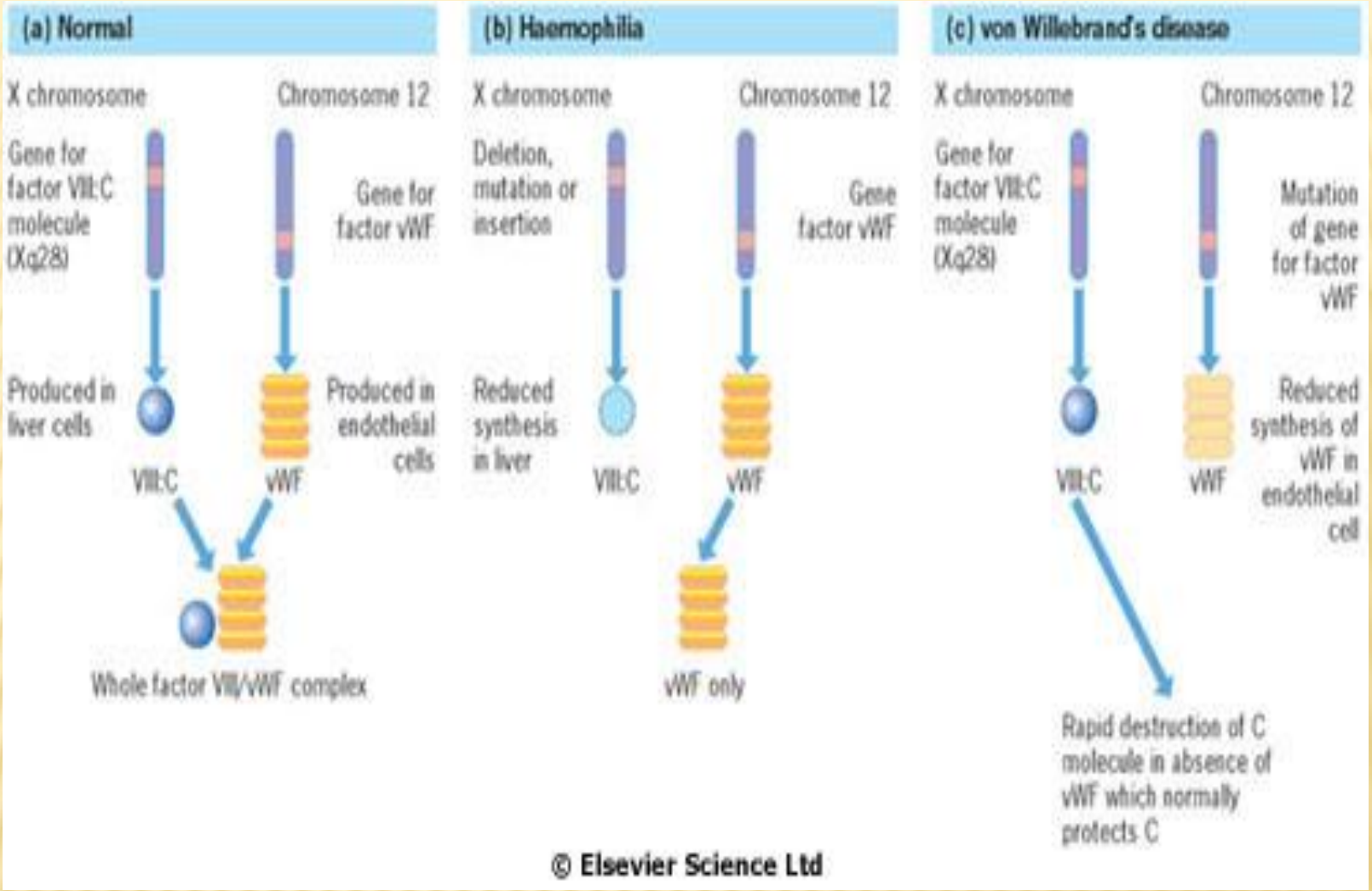
Thrombin is initially generated via the TF/FVIIa Initiation Phase however, the large amounts of Thrombin necessary for adequate secondary hemostasis are not generated



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

HEMOPHILIA A

- X-linked disorder
- Quantitative or qualitative disorder of factor VIII
- Screening tests:
- BT: normal
- Platelet count: normal
- PT: normal
- PTT: prolonged
- Platelet count: normal
- Specific test: FVIII assay: decreased activity



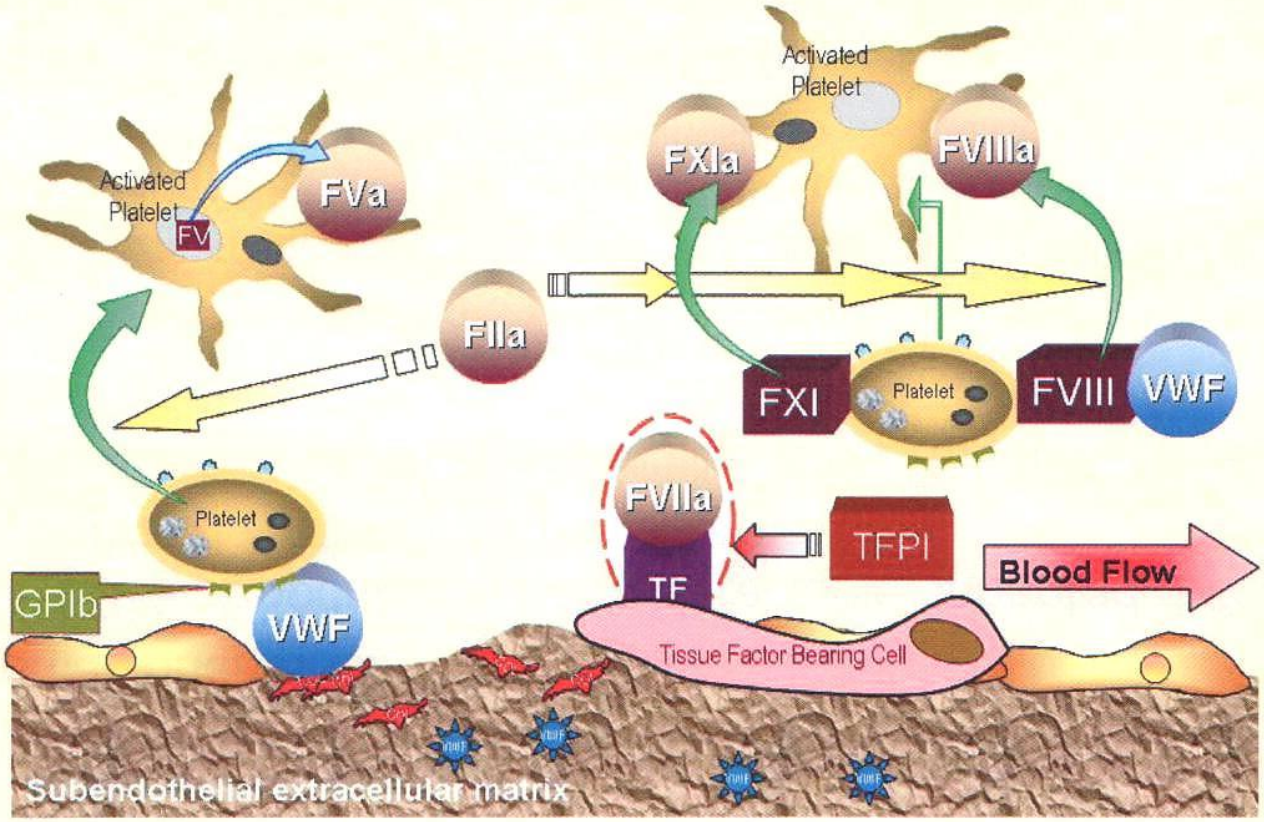
(a) Factor VIII synthesis.
(b) Hemofilia A has a defect synthesis of VIIIc.
(c) von Willebrand ´s disease has a reducted synthesis of vWF

HEMOPHILIA B

- Also called Chritmas disease
- Compared to hemophilia A:
  - Less common
  - same presentation
  - Same screening tests results
  - Specific test: FIX assay: decreased activity

Von Willebrand Factor Roles

Primary Hemostasis
(Adhesion step)



Secondary Hemostasis
(Amplification and Propagation phases)

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

CLOT-ED

Von Willebrand Disease (VWD)

- Most common bleeding disorder in humans
- Autosomal inheritance
- ~ 0.8 - 1.3% of population has a detectable, inherited defect in Von Willebrand Factor (VWF)
  - Low VWF levels, bleeding, and family history (the "holy" three)
- Types of bleeding
  - Mucocutaneous bleeding
    - Epistaxis, menorrhagia, ecchymoses & hematomas, gingival and gastrointestinal bleeding
    - Results from defect in primary hemostasis
  - Soft tissue bleeding (after trauma/injury)
    - Dental extraction, wounds, post-operatively, post-partum
    - Results from defect in secondary hemostasis
      - VWF is carrier (protector) protein for FVIII

VON WILLEBRAND DISEASE

- Autosomal dominant disease
- Quantitative or qualitative disorder of vWF
- Von Willebrand factor acts as a carrier for FVIII
- Acts as an essential cofactor for platelet adhesion and aggregation

VON WILLEBRAND DISEASE

- Screening tests:
- BT : prolonged.
- Platelet count: normal
- PT: normal
- PTT: prolonged

- Specific tests:
- Platelet aggregation: defective with ristocetin
- FVIII assay: decreased activity
- vWF antigen : reduced

Acquired Causes for Bleeding

- Liver Disease
- Immune coagulopathies
  - Inhibitors have been described to each of the coagulation factors
- Disseminated intravascular coagulation (DIC)
- Pharmacologic overdosing
- Primary fibrinogenolysis
  - Plasmin acts on fibrinogen
- Acquired platelet defects due to
  - Uremia, myeloproliferative disorders, antiplatelet antibodies, drugs that inhibit platelet function (administered in excess)

DIC (DISSEMINATED INTRAVASCULAR COAGULATION

- Release of ***tissue factor, TF.***
- TF is expressed on many cell types (endothelial, macrophages, monocytes).
- Contact with blood after damage of vessel wall (the effects of cytokines and endotoxins).
- TF is binding to coagulation factors which is leading to activation of both pathways of coagulation cascades.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- Due to extensive coagulation followed by fibrinolysis with consumption of hemostatic factors.

- Causes:
- infection, malignancy, obstetric complications, liver disease

DIAGNOSIS OF DIC

- BT: prolonged
- Platelet count: decreased
- PT: prolonged
- PTT: prolonged
- TT: prolonged
- Fibrinogen level: reduced
- FDPs (D dimer): increased
- Red cell fragmentation in the blood film

	BT	PT	PTT	Platelet count	Platelet function	Other tests
ITP	P	N	N	↓		
Glanzman	P	N	N	N	Defect aggreg	
Hemoph A	N	N	P	N		FVIII assay
Hemoph B	N	N	P	N		FIX assay
vWD	P	N	P	N	Defect aggreg	FVIII, vWF
DIC	P	P	P	↓		Fibrinogen FDPs

THANK YOU FOR YOUR ATTENTION