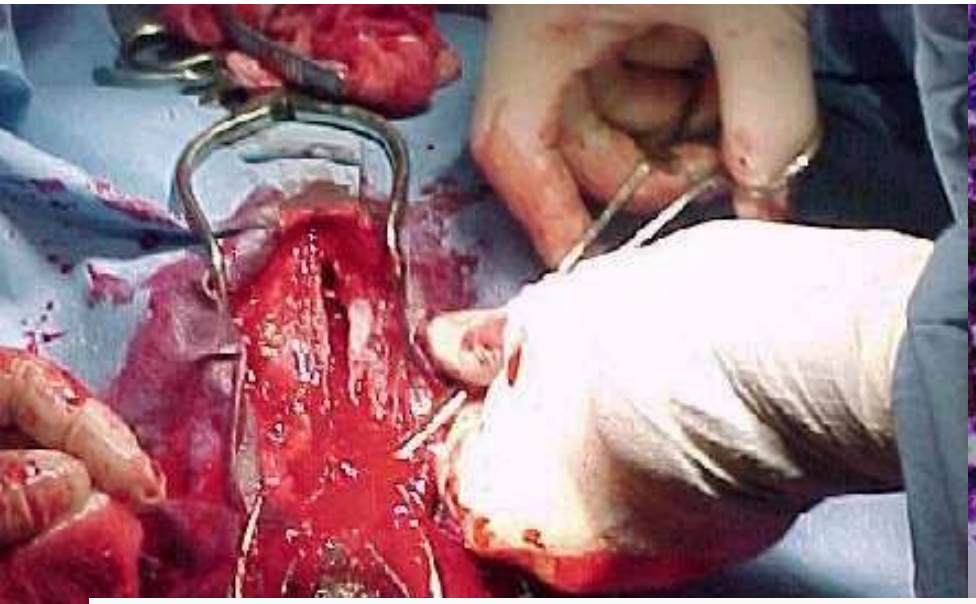
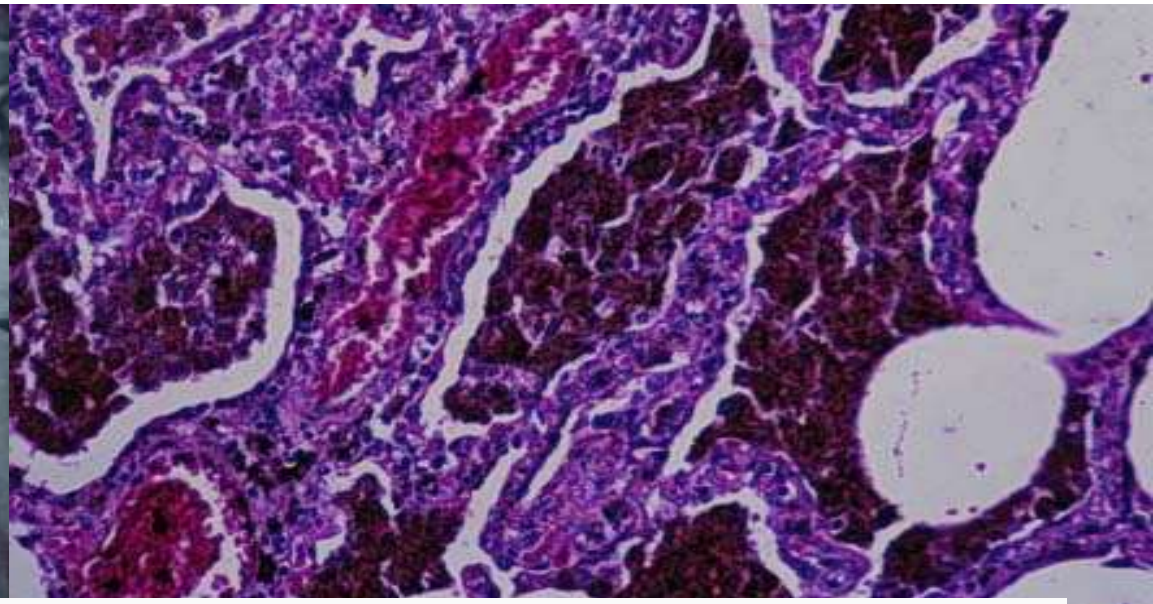
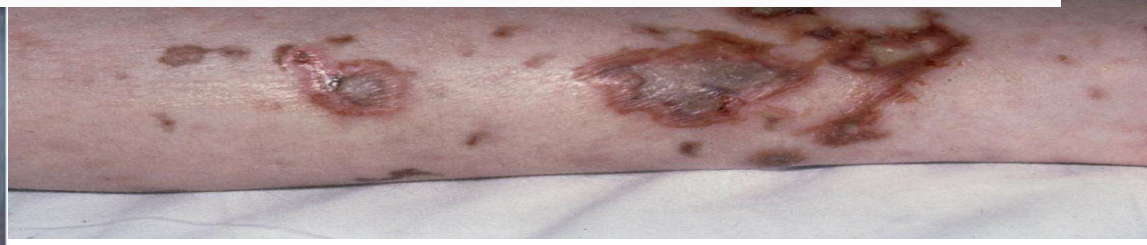




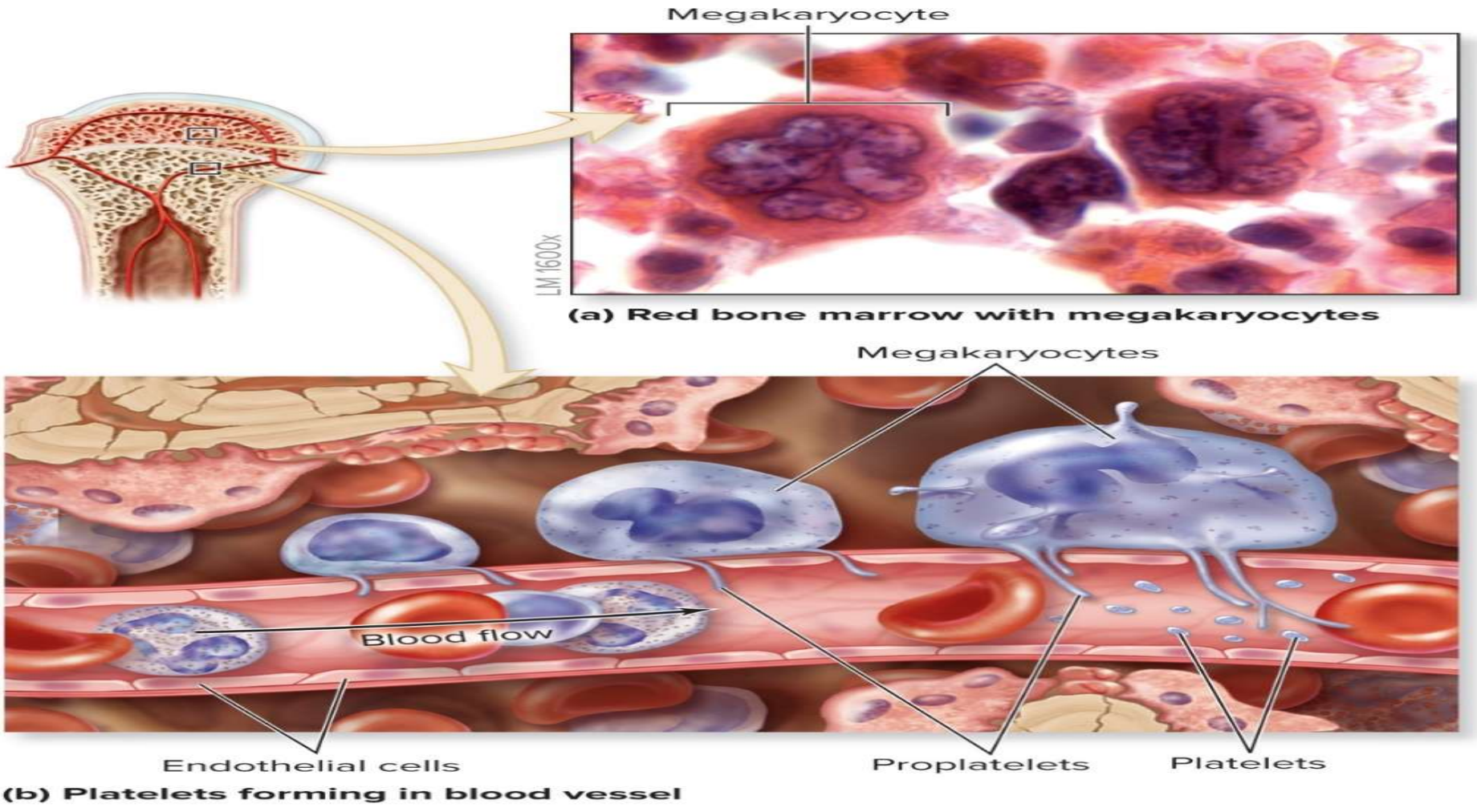
Hemostasis and coagulation



Danil Hammoudi.MD

UPDATE 2025

Figure 18.4



(a) ©McGraw-Hill Education/Al Telser

- **Hemostasis** is the physiological process that **prevents and stops bleeding**.
- It involves a **complex interplay between:**
  - **The vascular endothelium,**
  - **Platelets**
  - **Coagulation cascade.**
- **Maintaining a balance**
  - **Coagulation**
  - **Fibrinolysis**

Hypocoagulation: excessive bleeding (inherited or acquired)

Hypercoagulation (thrombosis) inadequate activation of the fibrinolytic system

HEMOSTASIS & THROMBOSIS

- Platelets
- Coagulation Cascade
- Regulation of Coagulation
- Disseminated Intravascular Coagulation

HEMOSTATIC DISORDERS

Suspicions

- Spontaneous bleeding
- Prolonged or excessive bleeding after procedures or trauma
- Simultaneous bleeding from multiple sites

HEMOSTASIS

Primary vs. Secondary vs. Tertiary

- Primary Hemostasis
  - Platelet Plug Formation
  - Dependent on normal platelet number & function
  - Initial Manifestation of Clot Formation

Secondary Hemostasis

- Activation of Clotting Cascade ⊠ Deposition & Stabilization of Fibrin

Tertiary Hemostasis

- Dissolution of Fibrin Clot
- Dependent on Plasminogen Activation

Time Frame for Hemostasis

Platelets	Coagulation Factors	Fibrinolytic Proteins
Primary Hemostasis	**Secondary Hemostasis**	**Fibrinolysis**
• Vessel constriction occurs immediately • Platelet adhesion occurs in seconds • Platelet aggregation takes minutes	• Activation of coagulation factors occurs in seconds • Fibrin forms in minutes	• Activation of fibrinolytic proteins happens immediately • Dissolving the thrombus requires hours

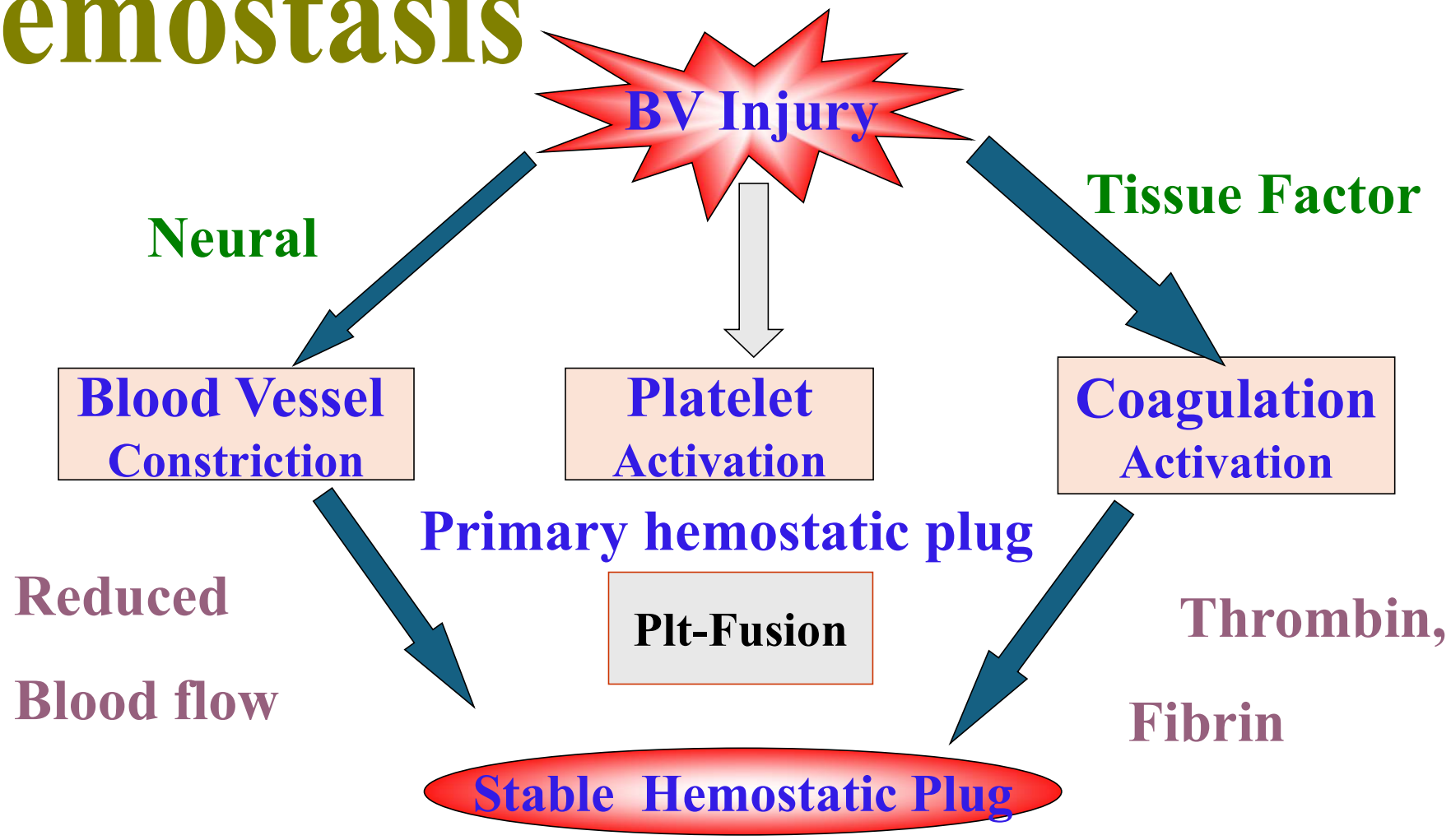
Systems Involved in Hemostasis

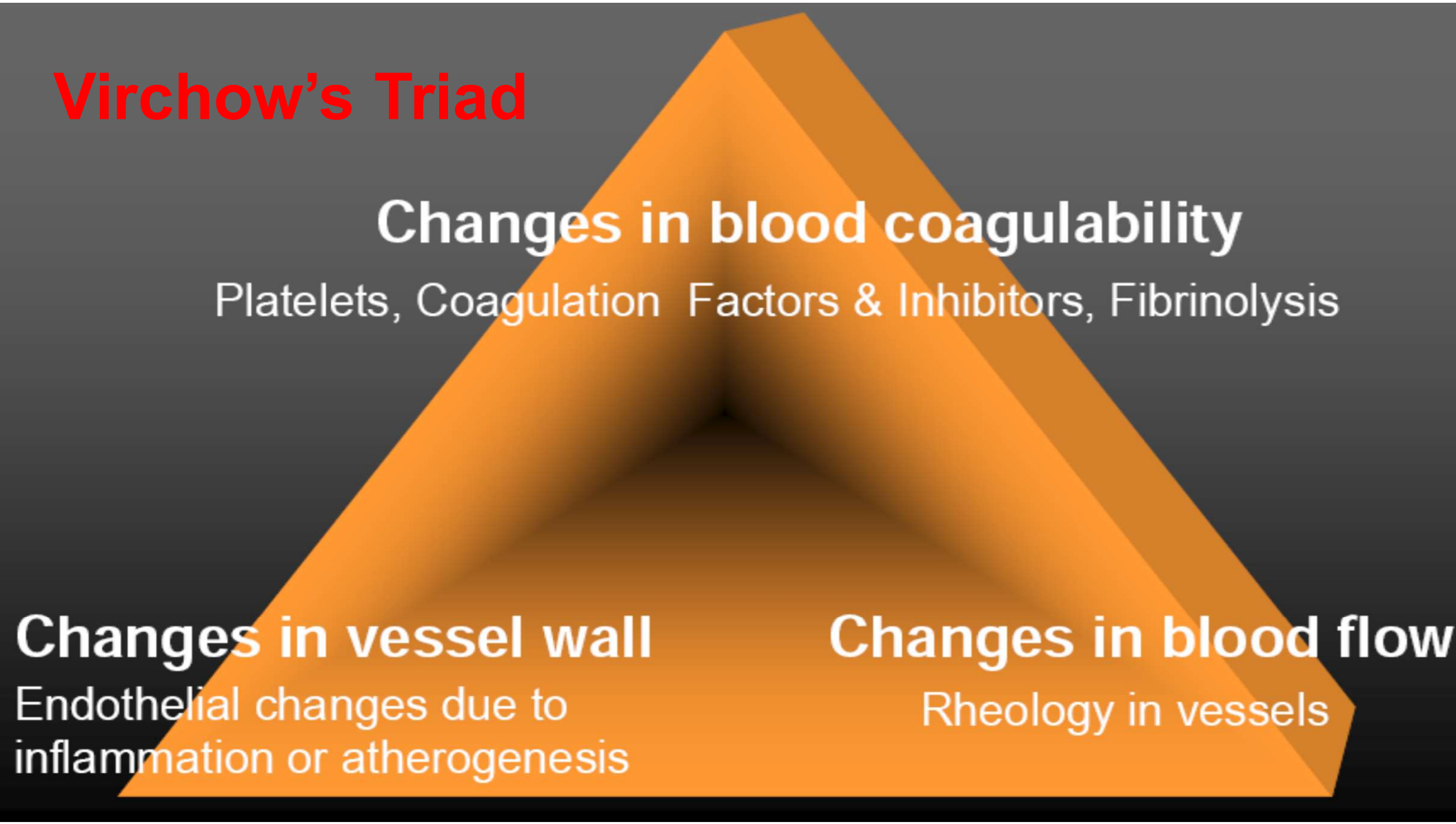
- **Vascular system**
  - Injured vessel initiates vasoconstriction
- **Platelet System**
  - Injured vessel exposes collagen that initiates platelet aggregation and help form plug
- **Coagulation System**
  - protein factors of intrinsic and extrinsic pathways produce a permanent fibrin plug

HEMOSTASIS — Physiologic Process to Stop Bleeding

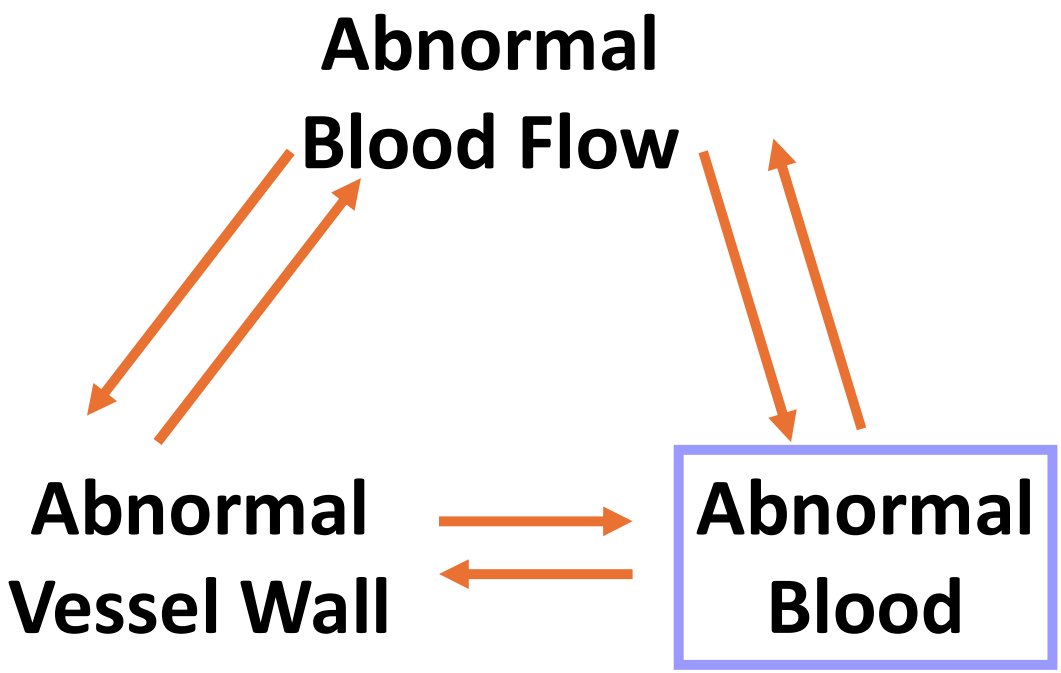
Phase	Key Events	Molecules Involved
1. Vasoconstriction	Immediate response to injury	Endothelin, neural reflex
2. Primary Hemostasis	Platelet adhesion, activation, aggregation → platelet plug	vWF, GPIb, GPIIb/IIIa, TXA_2, ADP
3. Secondary Hemostasis	Activation of coagulation cascade → fibrin mesh stabilizes plug	Thrombin (IIa), fibrinogen → fibrin
4. Clot Stabilization and Retraction	Fibrin crosslinking	Factor XIIIa
5. Fibrinolysis	Breakdown of clot	tPA, plasmin, D-dimers

Hemostasis


BV Injury
Neural
Tissue Factor
Blood Vessel Constriction
Platelet Activation
Coagulation Activation
Primary hemostatic plug
Plt-Fusion
Reduced
Blood flow
Thrombin,
Fibrin
Stable Hemostatic Plug


Virchow's Triad
Changes in blood coagulability
Platelets, Coagulation Factors & Inhibitors, Fibrinolysis
Changes in vessel wall
Endothelial changes due to inflammation or atherogenesis
Changes in blood flow
Rheology in vessels

Dr. Rudolph Virchow
1821-1902



The Hypercoagulable State

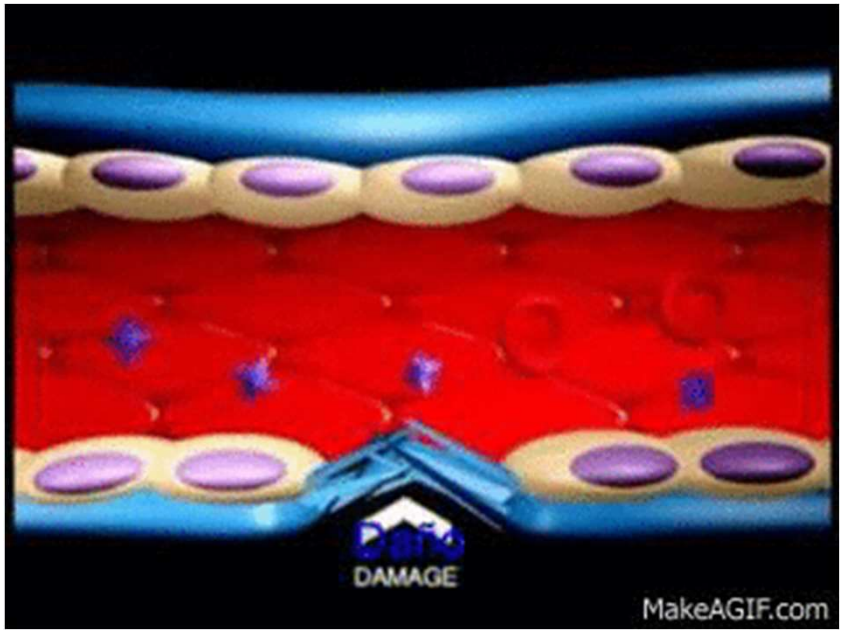
Virchow's Triad – 3 Major Risk Factors

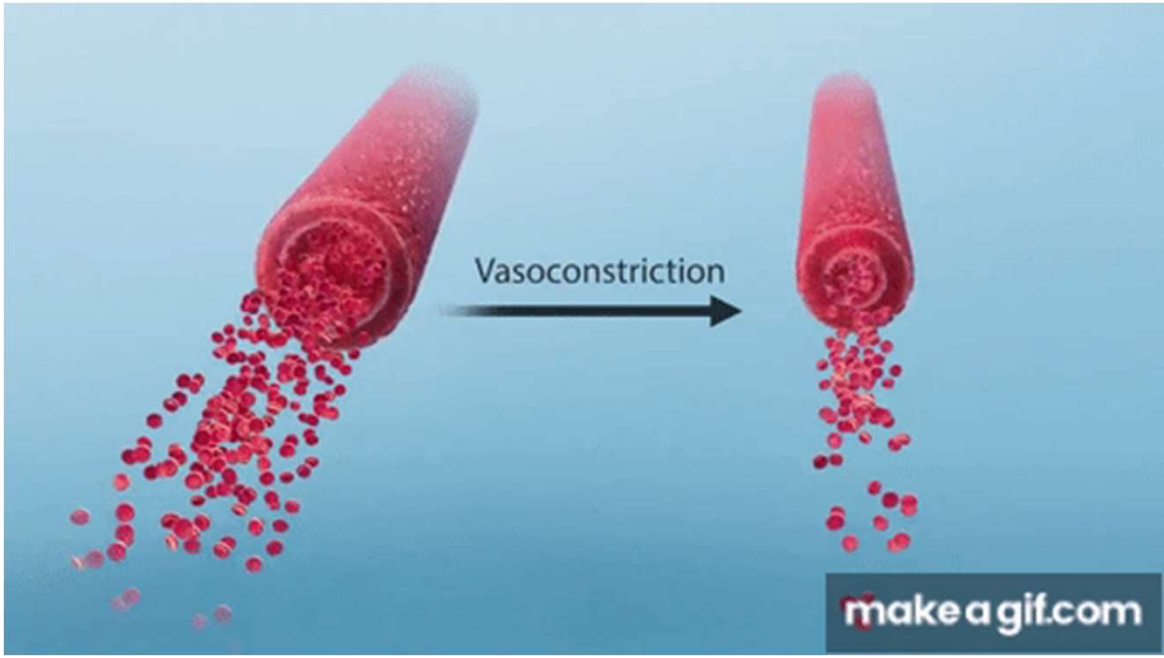
Factor	Example
1. **Endothelial injury**	Atherosclerosis, vasculitis, surgery
2. **Abnormal blood flow**	Stasis (immobilization, AFib), turbulence
3. **Hypercoagulability**	Inherited (e.g. Factor V Leiden) or acquired (e.g. cancer, antiphospholipid syndrome)

PHASES OF HEMOSTASIS

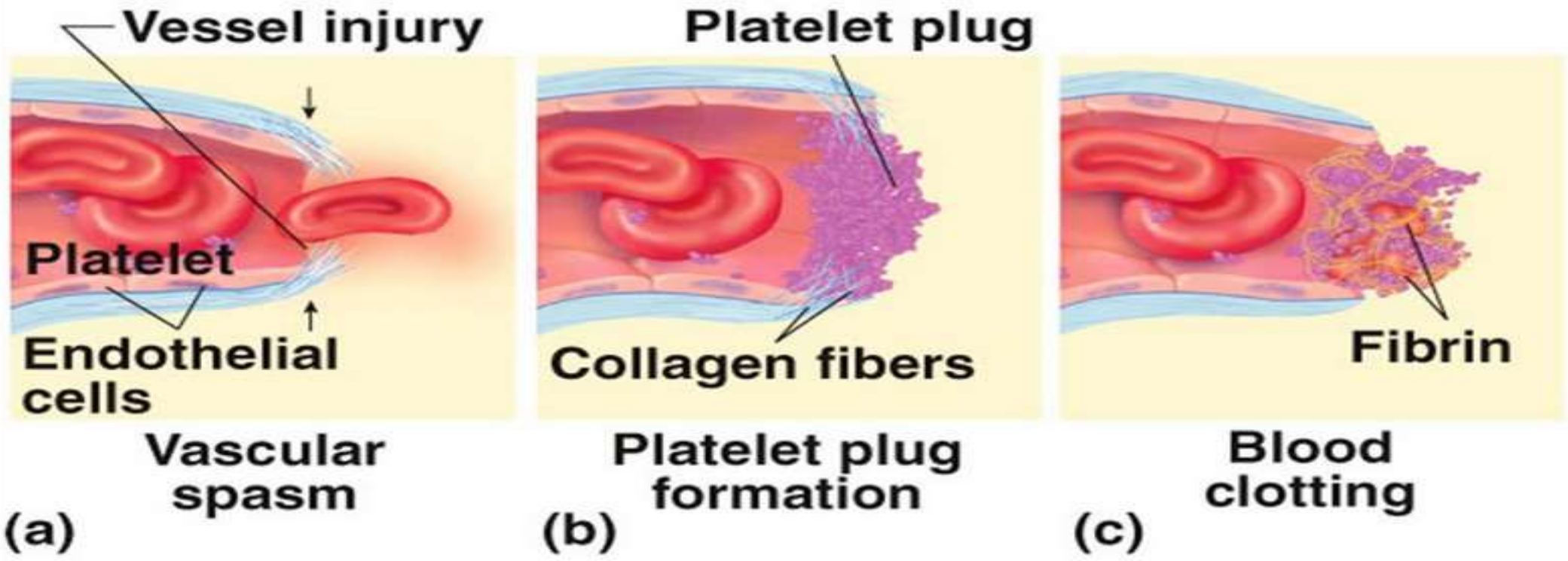
1. Vascular Spasm (Vasoconstriction)

- **Trigger**: Endothelial injury → transient vasoconstriction
- **Mediators**: Endothelin (vasoconstrictor), neural reflexes
- **Purpose**: Minimize blood loss





Steps of Hemostasis



https://www.youtube.com/watch?v=HFNWGCx_Eu4

2. Primary Hemostasis: Platelet Plug Formation

A. Platelet Adhesion

•Injury exposes **subendothelial collagen** and **von Willebrand factor (vWF)**

•Platelets bind to **vWF via GP Ib receptor**

B. Platelet Activation

•**Platelet shape change:** disc → spiky

•**Degranulation:**

- **Dense granules**: ADP, Ca^{2+}, serotonin
- **Alpha granules**: vWF, fibrinogen, PF4

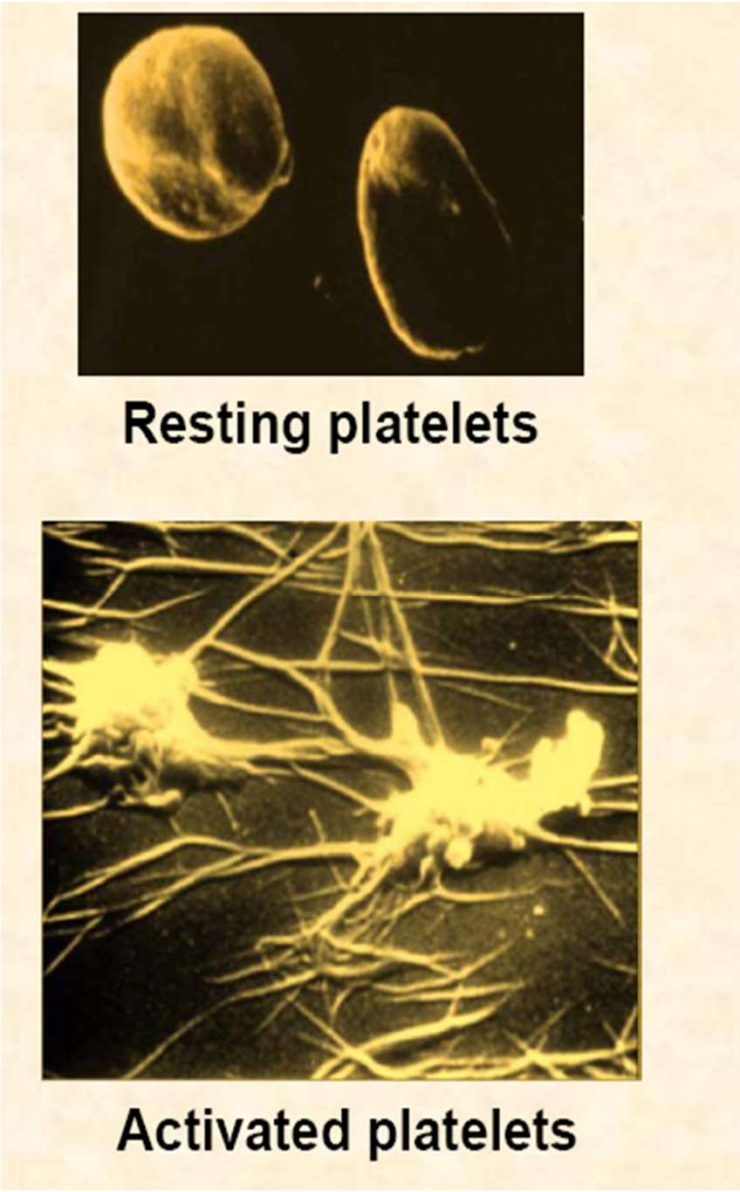
•ADP → ↑ GPIIb/IIIa expression

•**Thromboxane A2 (TXA2)**: vasoconstriction, platelet aggregation

C. Platelet Aggregation

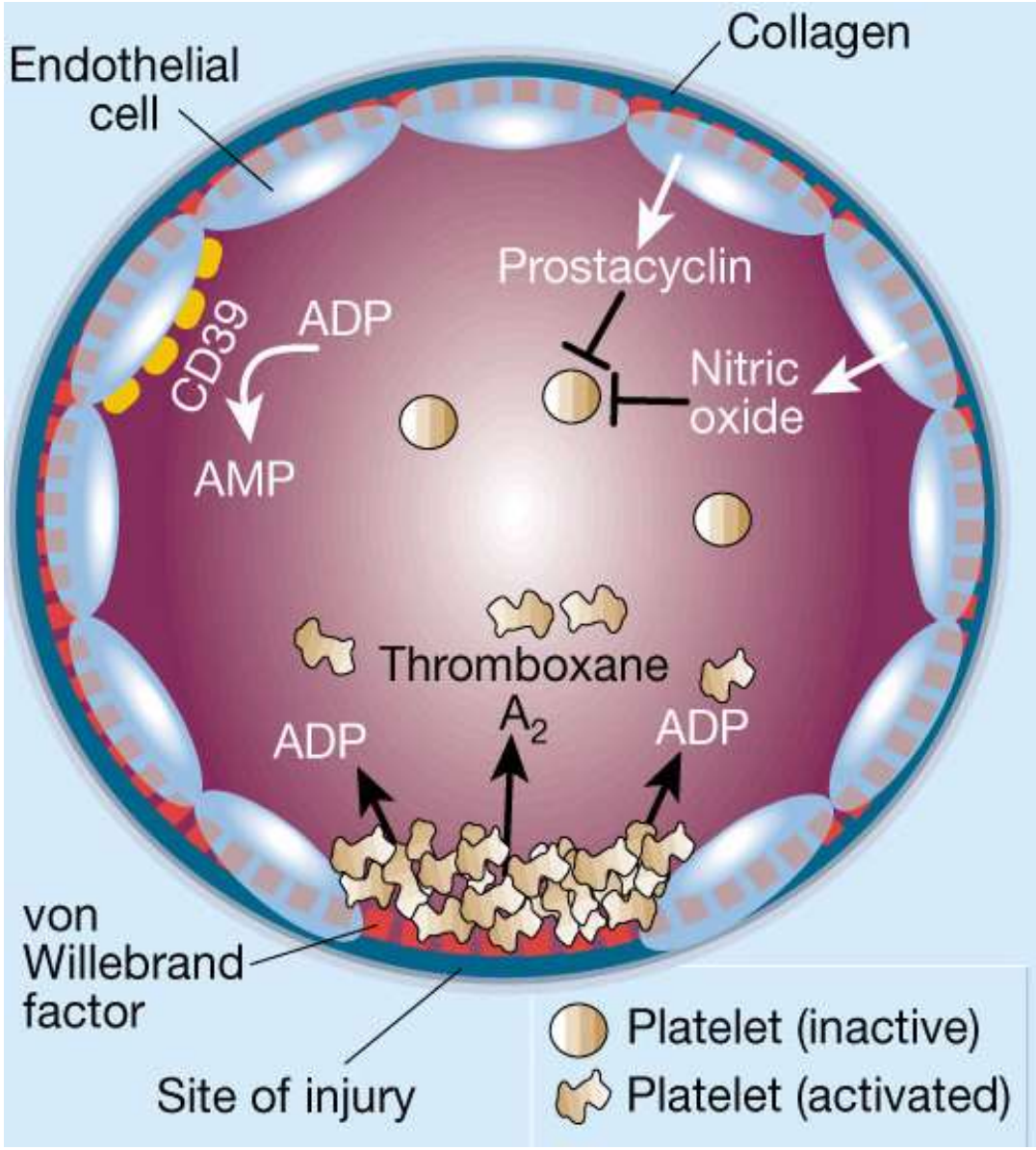
•Platelets bind via **fibrinogen bridges** using **GPIIb/IIIa** receptors

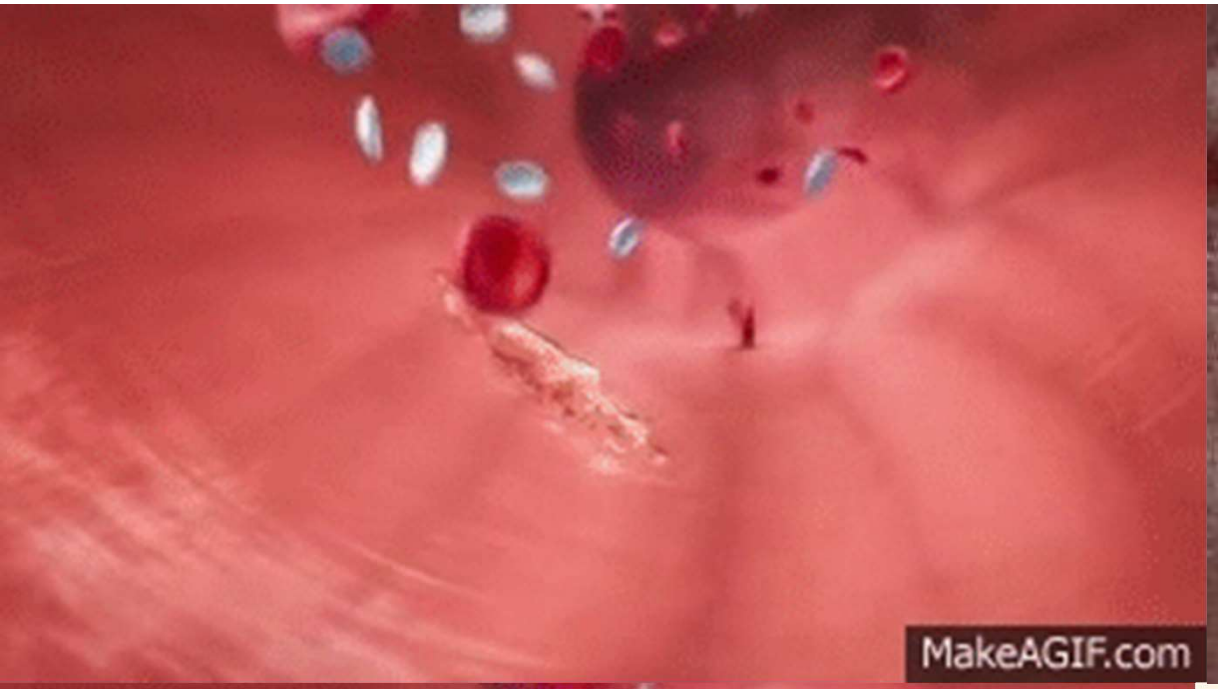
Result: **Unstable platelet plug**



Platelet Plug Formation

- Platelets do not stick to each other or to blood vessels
- Upon damage to blood vessel endothelium platelets:
  - **With the help of von Willebrand factor (VWF) adhere to collagen**
  - **Are stimulated by thromboxane A2**
  - **Stick to exposed collagen fibers and form a platelet plug**
  - **Release serotonin and ADP, which attract still more platelets**
- ***The platelet plug is limited to the immediate area of injury*** by **prostacyclin**

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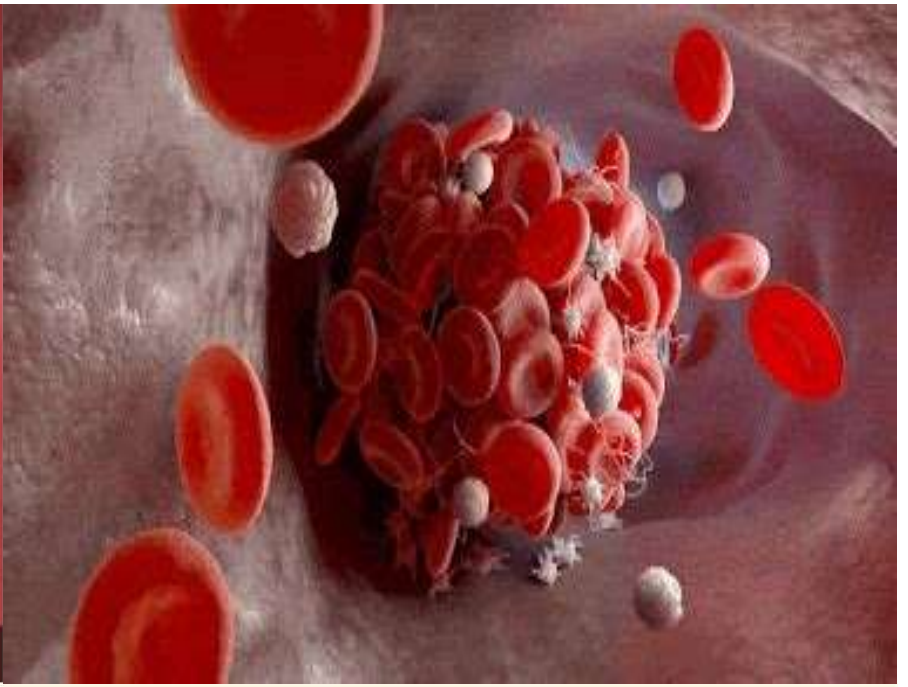
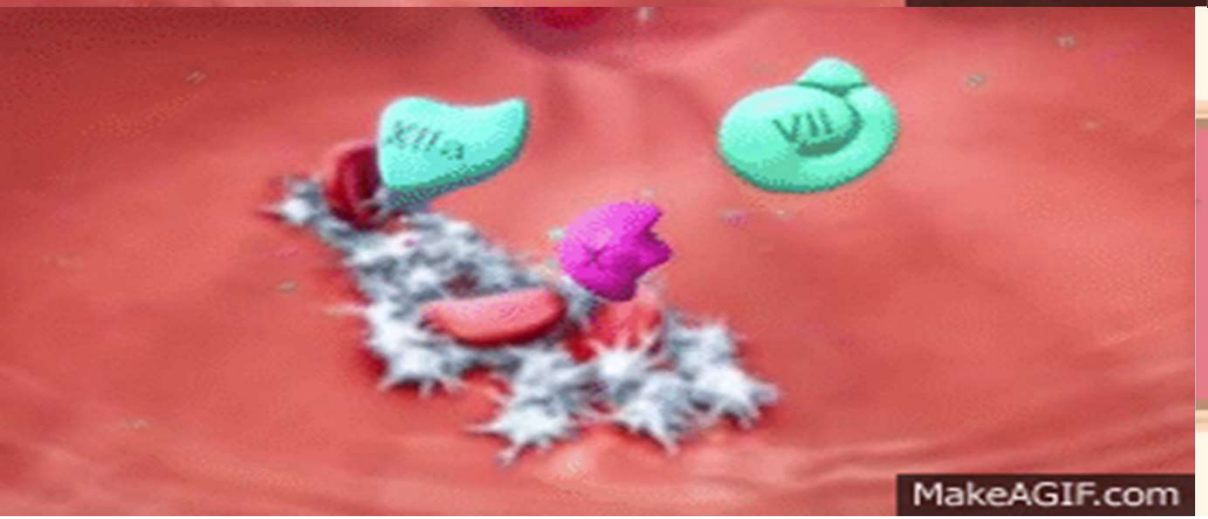
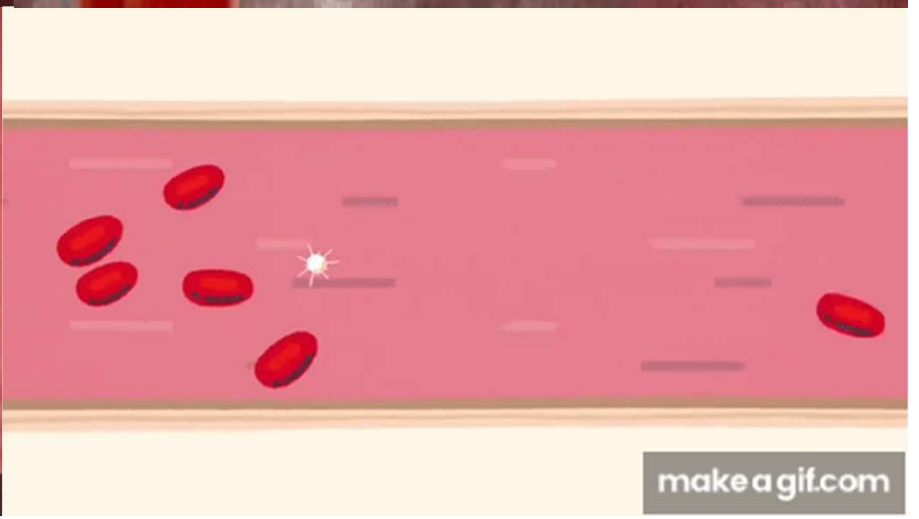



XII-a
VII
MakeAGIF.com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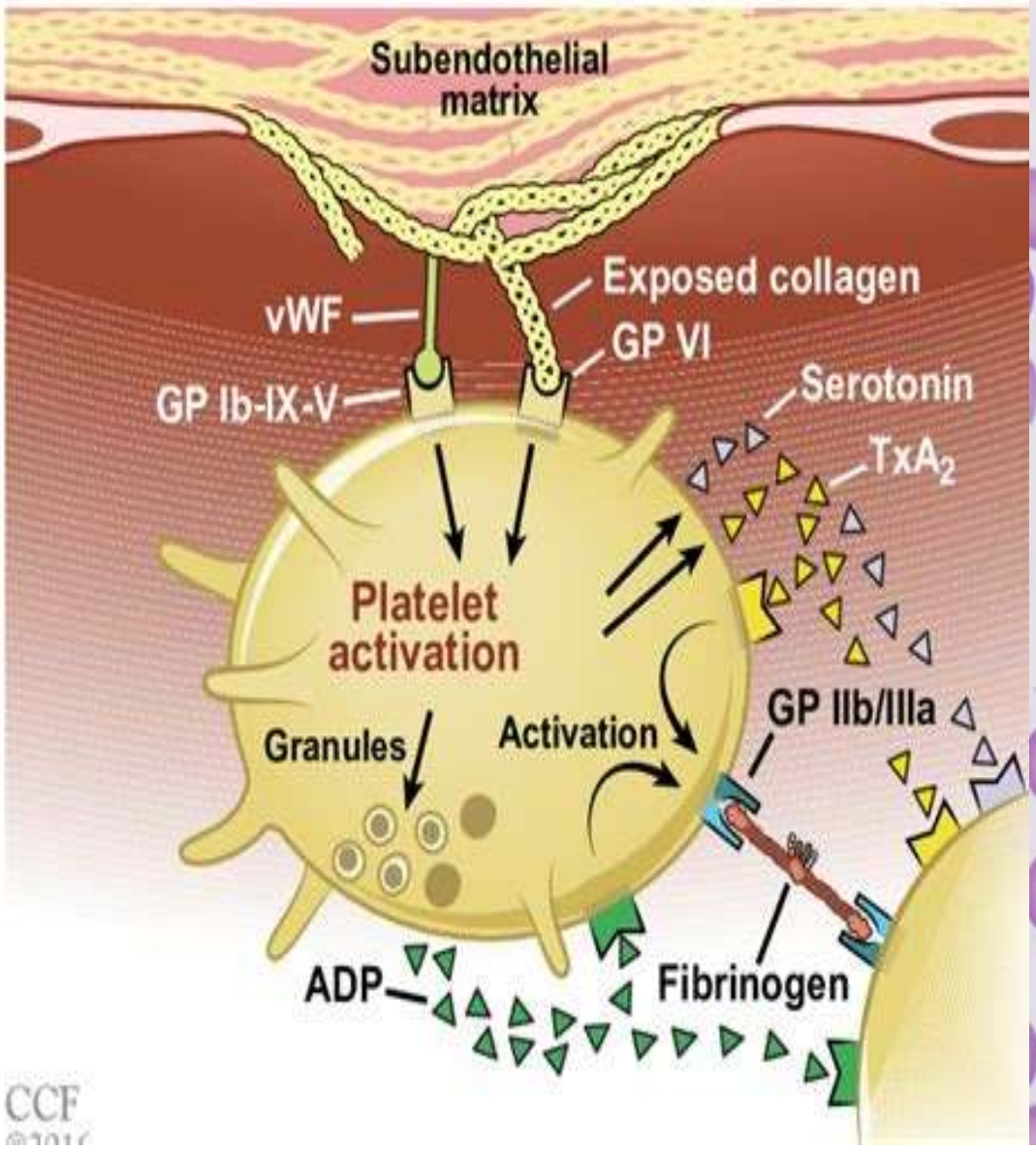
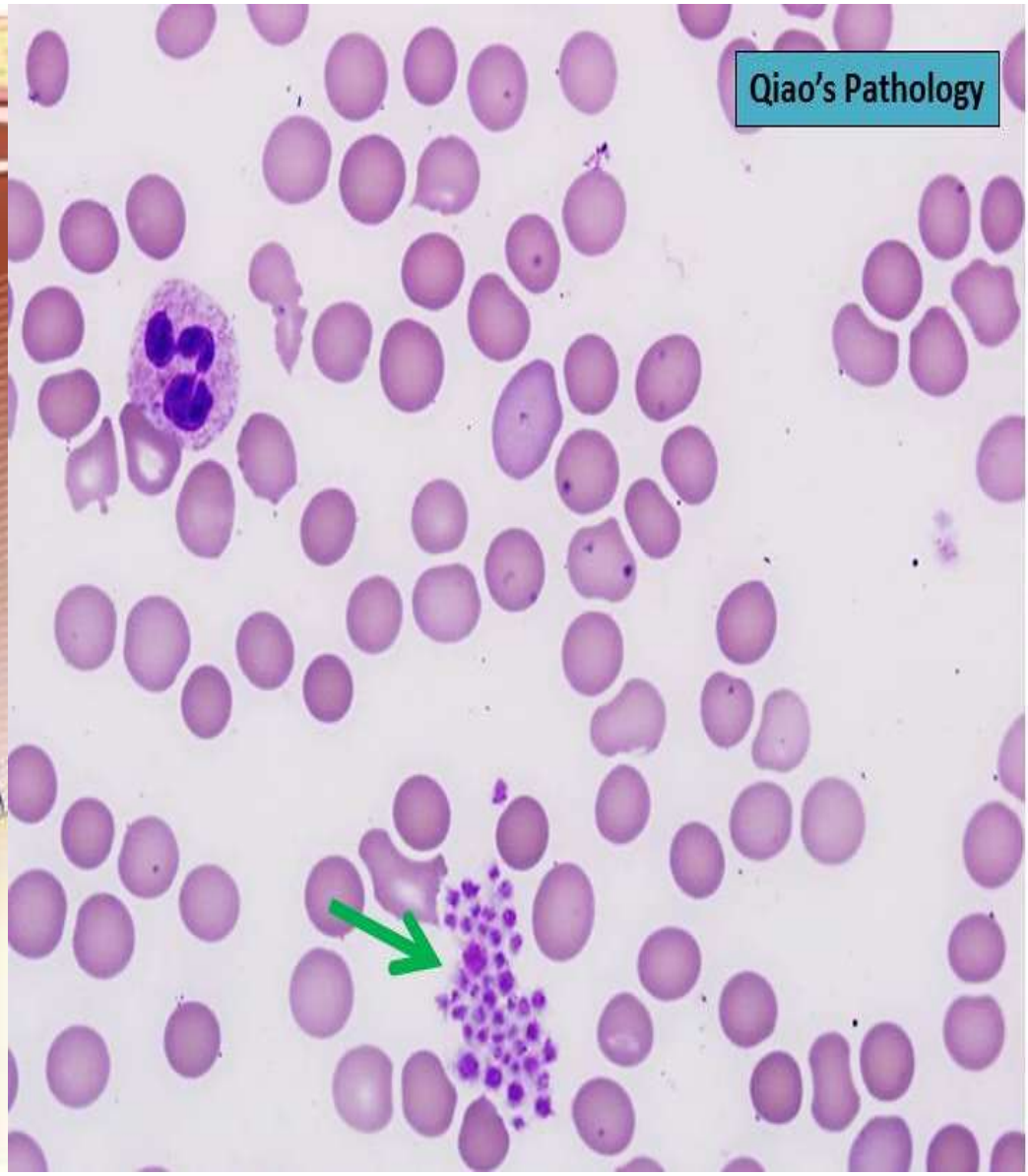
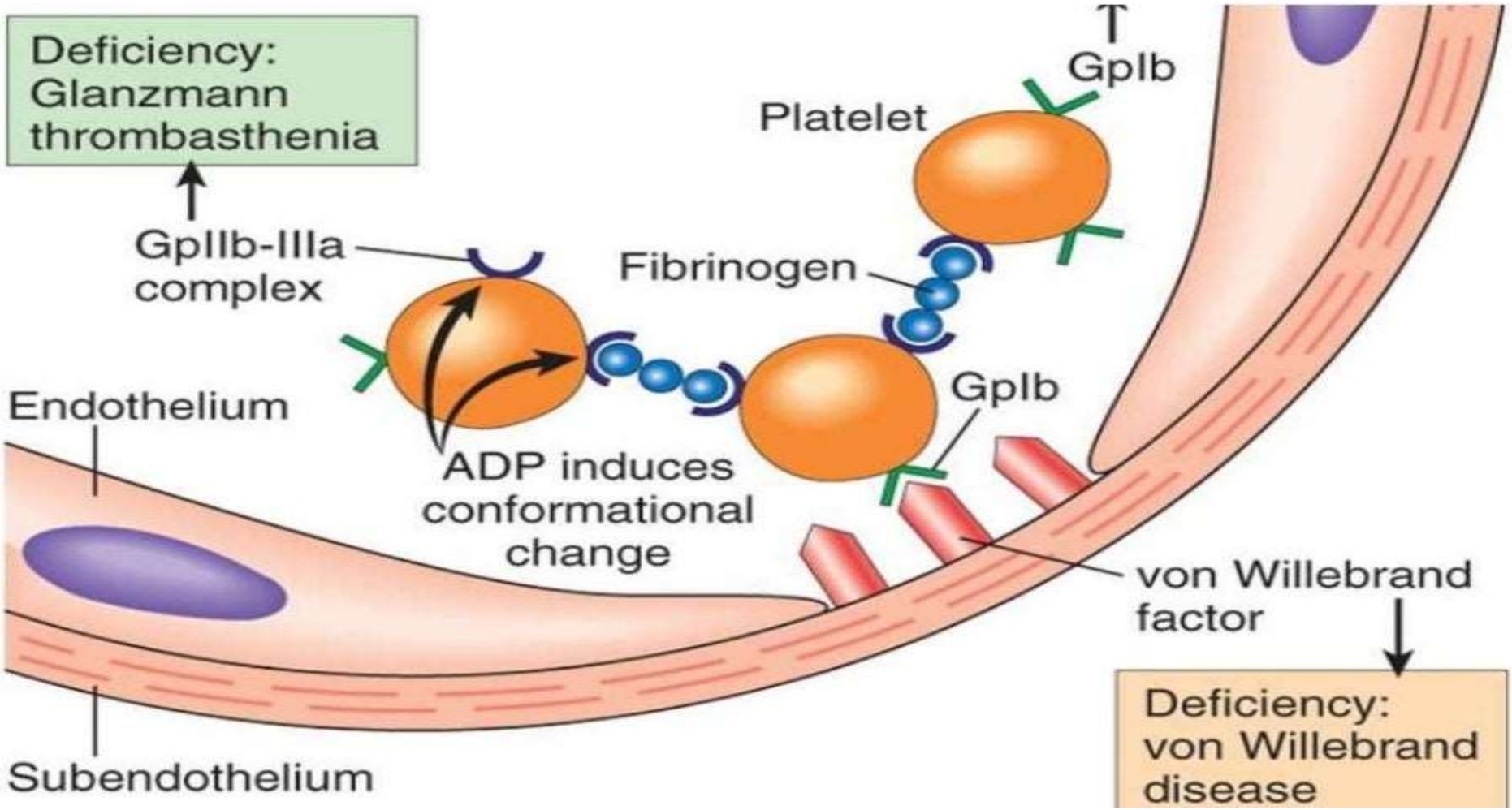
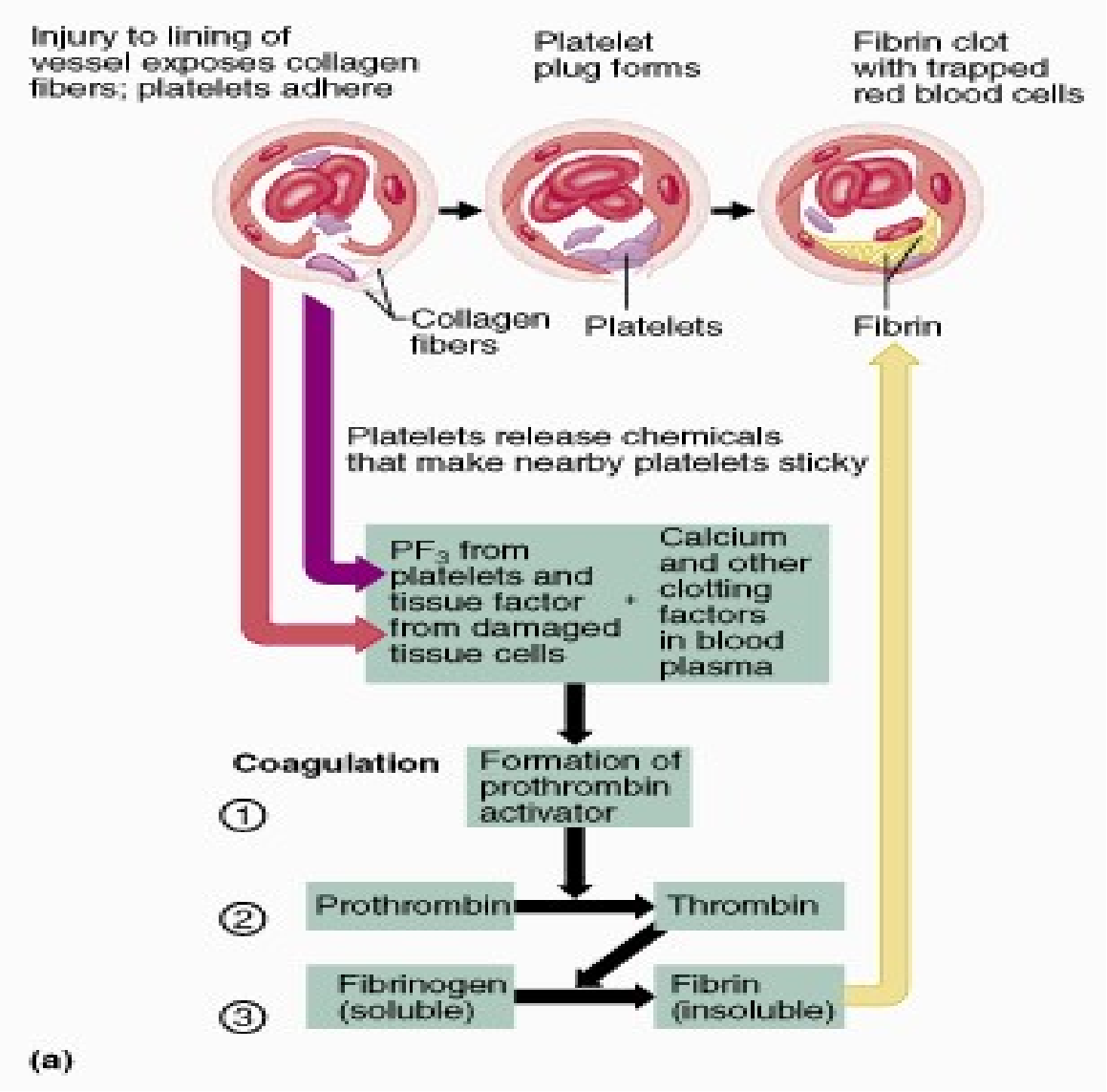

Subendothelial matrix
vWF
Exposed collagen
GP VI
GP Ib-IX-V
Serotonin
TxA_2
Platelet activation
Granules
Activation
GP IIb/IIIa
ADP
Fibrinogen
CCF


Qiao's Pathology

Gp IIb-IIIa complex on platelet surfac



PF3 is **crucial for intrinsic and common pathway efficiency**.



Platelets release

↓

PF3

(**exposed or released by activated platelets** upon stimulation (e.g., by collagen, thrombin).

tissue factor other clotting factors

↓

Prothrombin activator is formed,

↓

Activator transforms prothrombin

↓

Prothrombin becomes thrombin

↓

catalyzes fibrinogen activates factor XIII

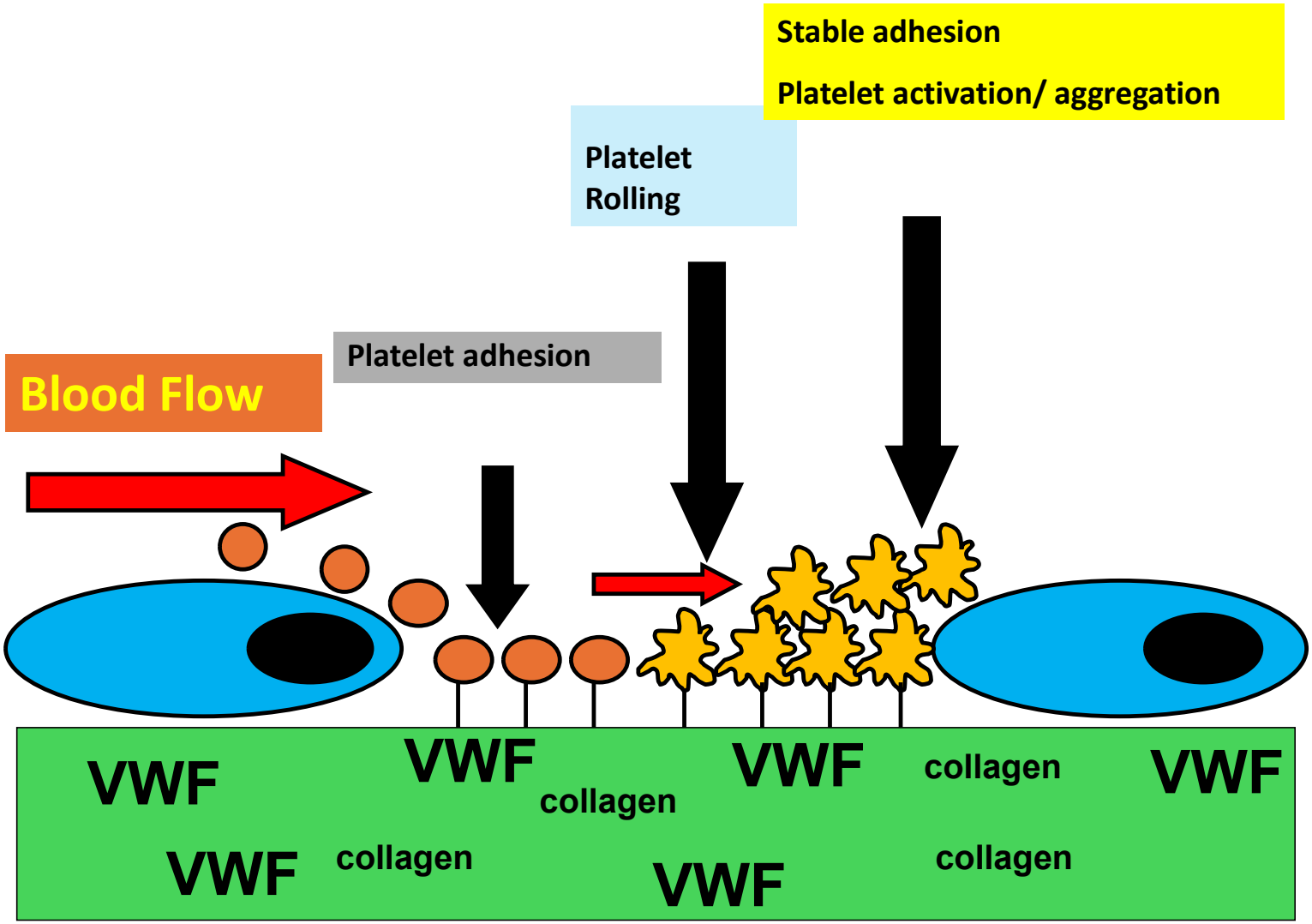
↓

fibrinogen becomes fibrin

fibrin stabilizing factor

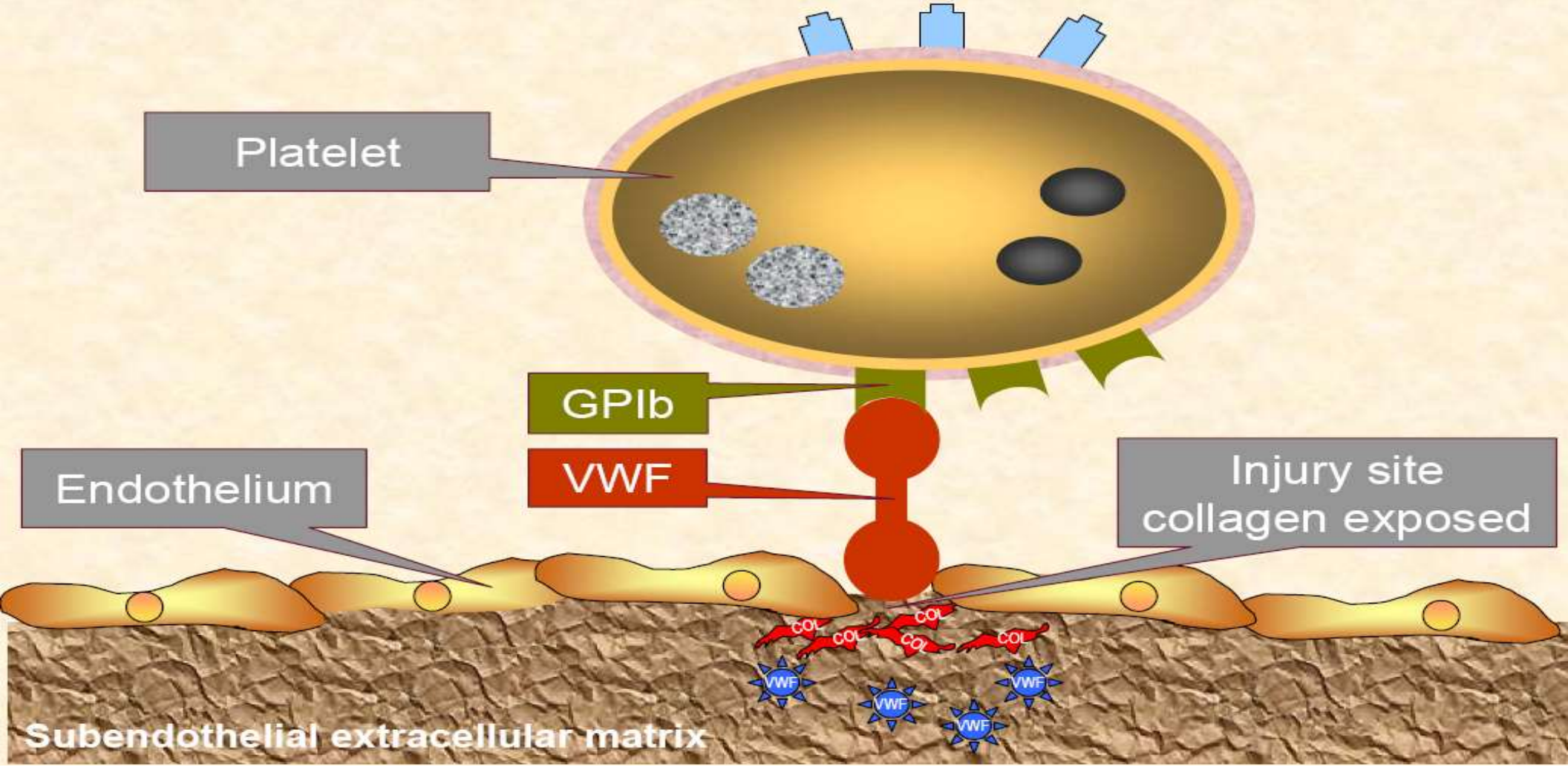
Fibrin Mesh Forms

Clot Forms


Stable adhesion
Platelet activation/ aggregation
Platelet
Rolling
Platelet adhesion
Blood Flow
VWF
VWF
collagen
VWF
collagen
VWF
VWF
collagen
VWF
collagen

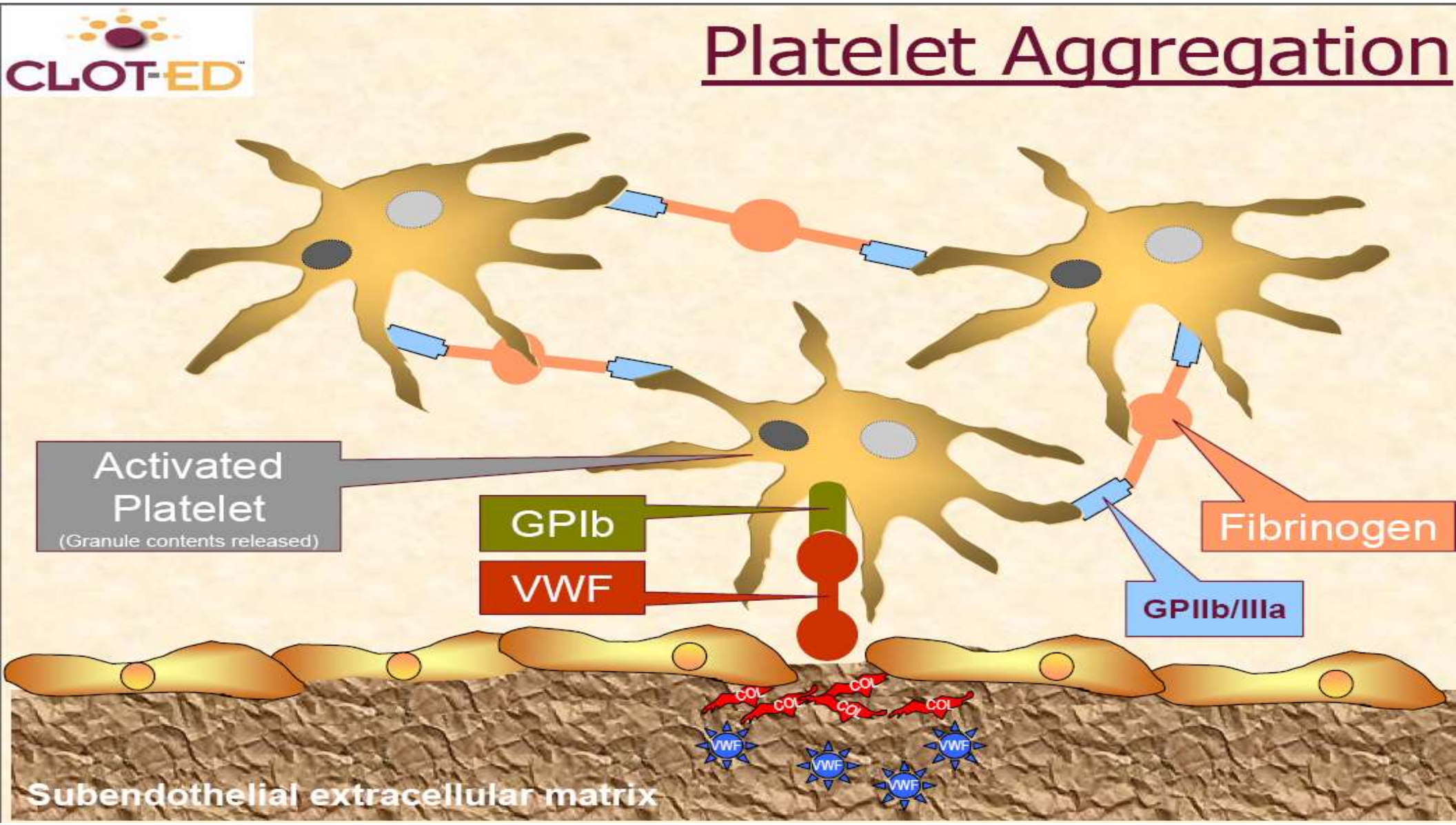
CLOT-ED

Platelet Adhesion



CLOT-ED

Platelet Aggregation



Hemostasis: Vasoconstriction & Plug Formation

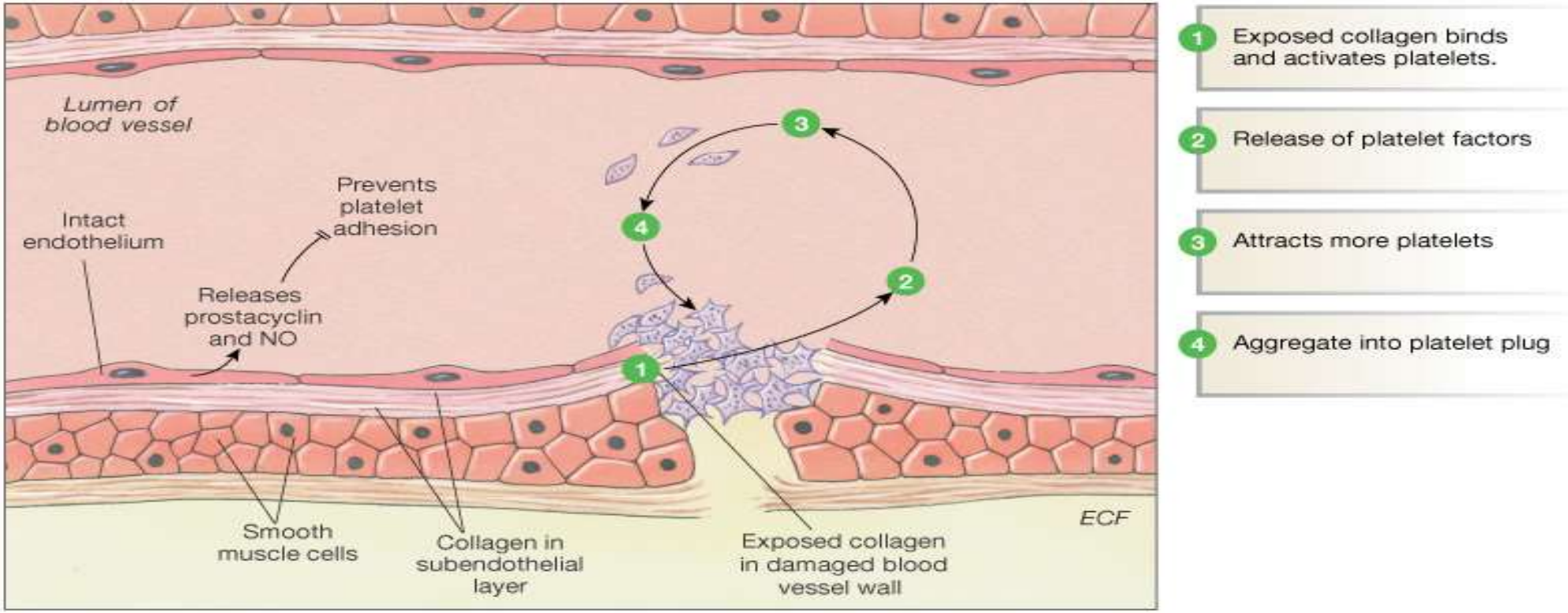
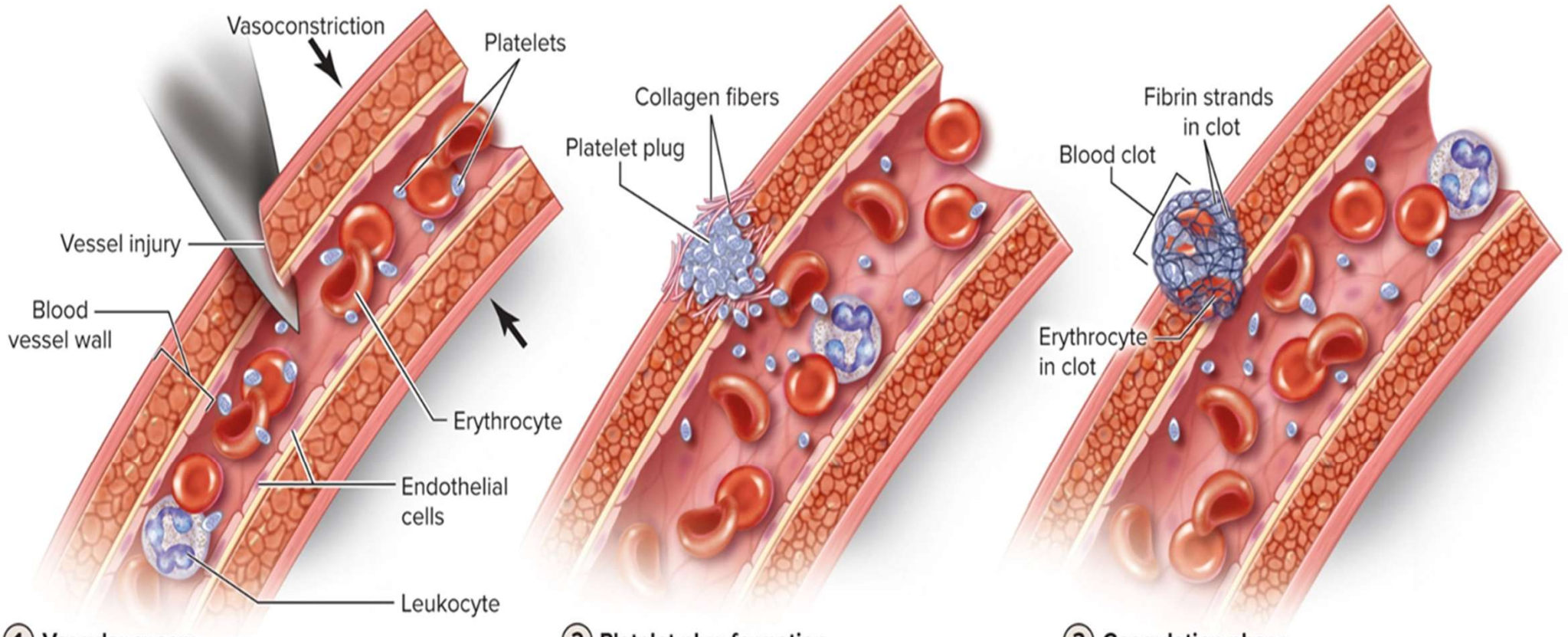


Figure 16-12: Platelet plug formation

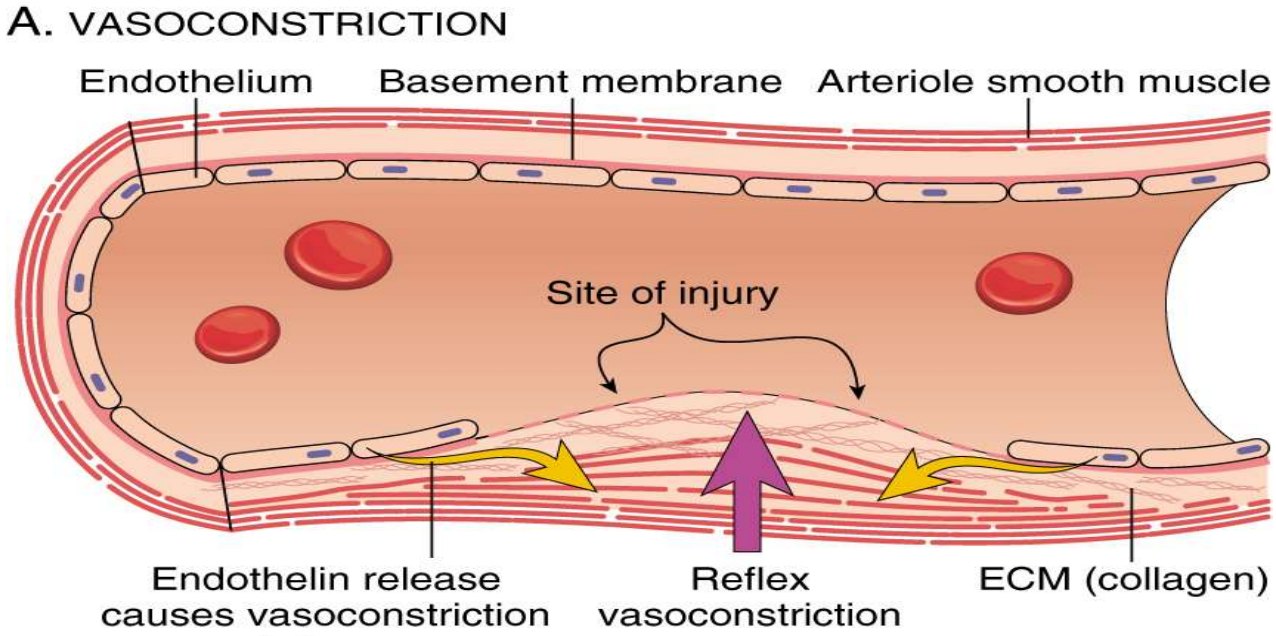
Hemostasis

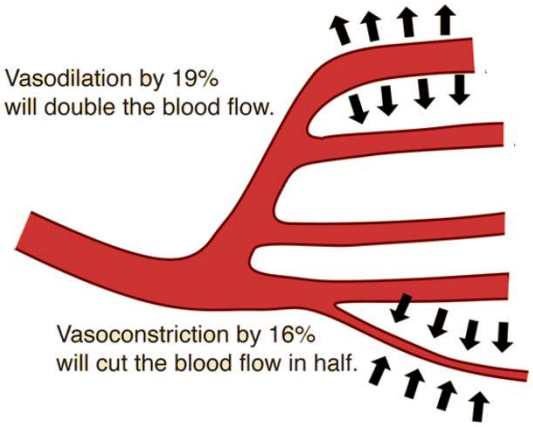


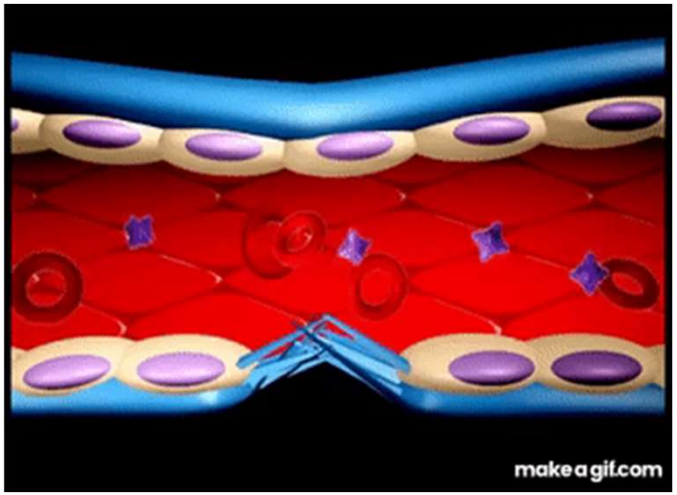
1 Vascular spasm
Blood vessel constricts to limit blood escape.

2 Platelet plug formation
Platelets arrive at site of injury and stick to exposed collagen fibers.

3 Coagulation phase
Coagulation cascade converts inactive proteins to active forms, which ultimately forms fibrin strands of a blood clot.


A. VASOCONSTRICTION
Endothelium
Basement membrane
Arteriole smooth muscle
Site of injury
Endothelin release causes vasoconstriction
Reflex vasoconstriction
ECM (collagen)


Vasodilation by 19% will double the blood flow.
Vasoconstriction by 16% will cut the blood flow in half.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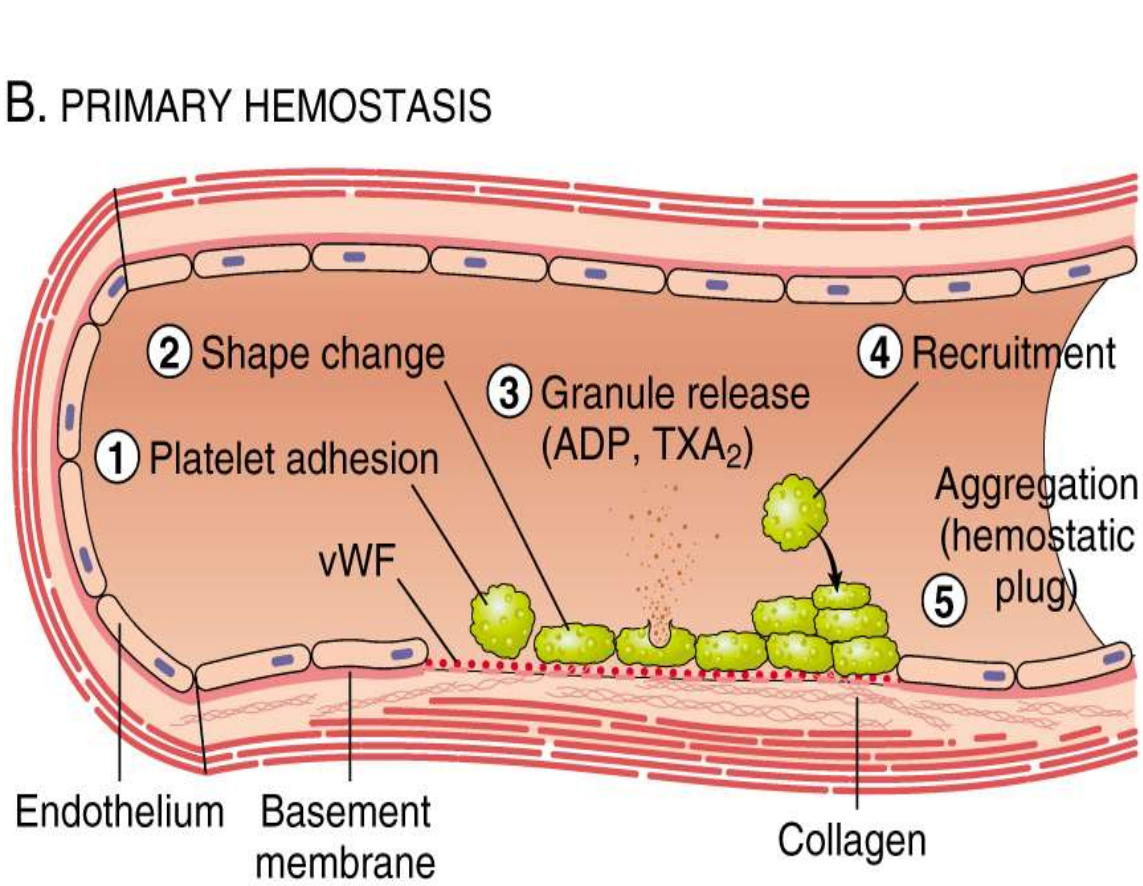
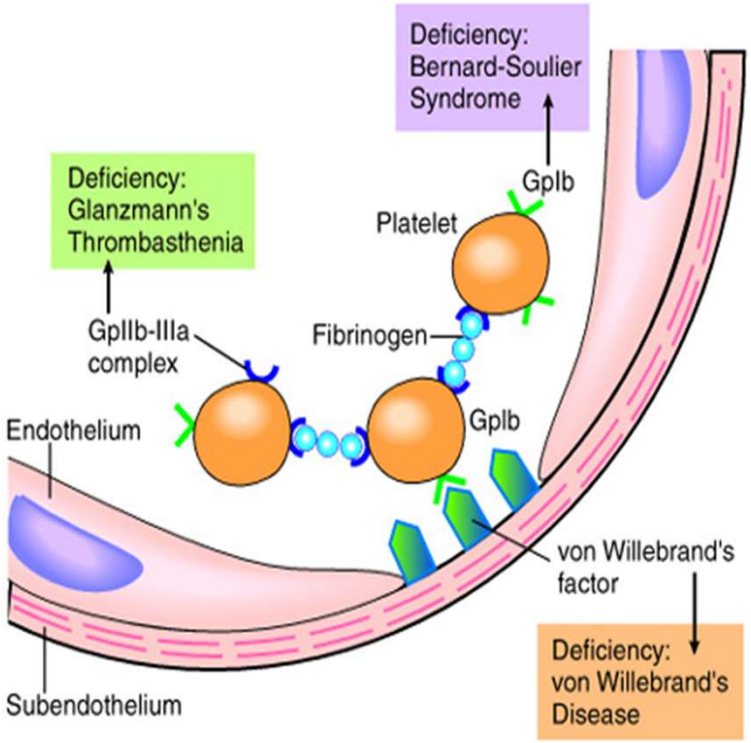
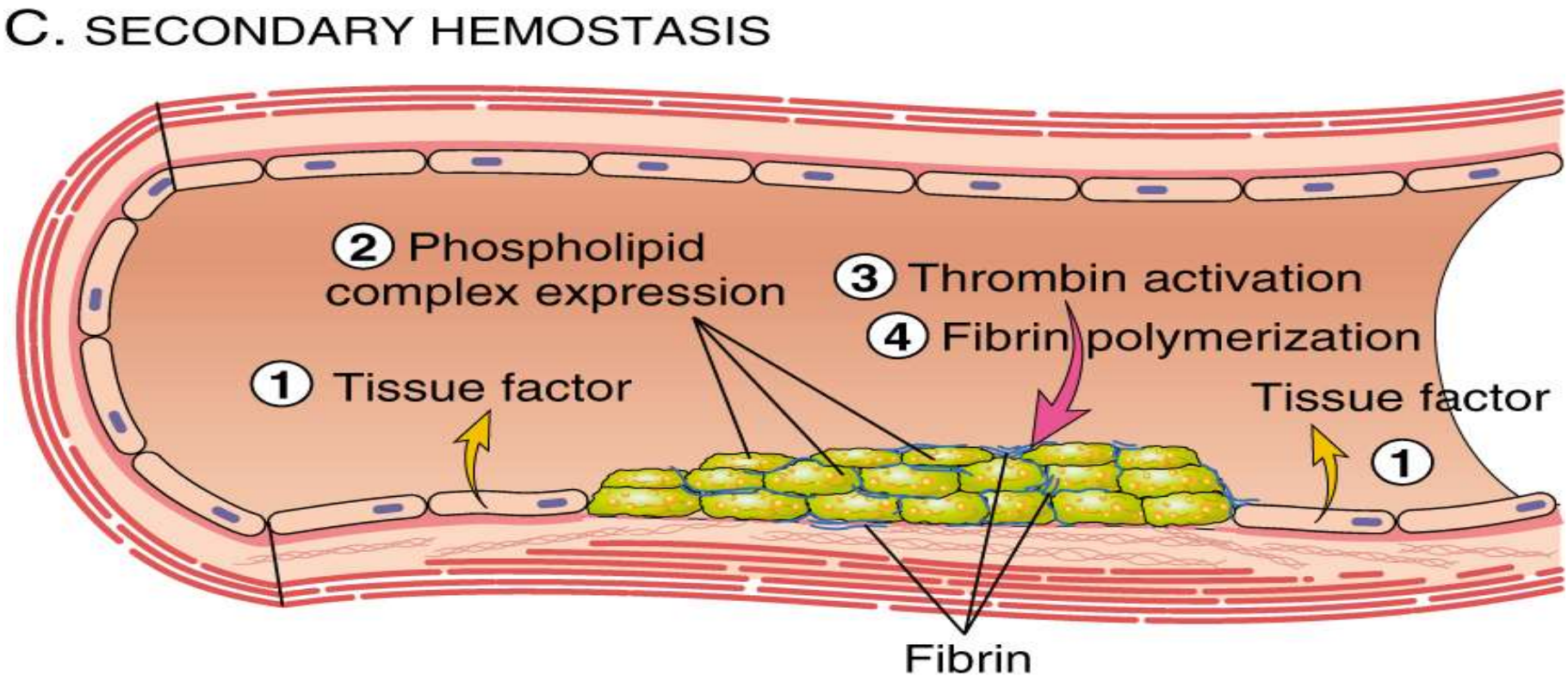
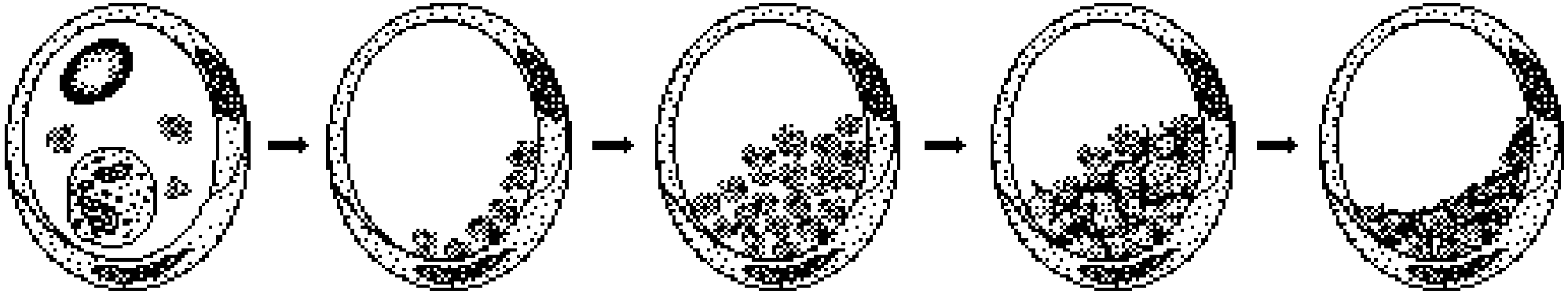




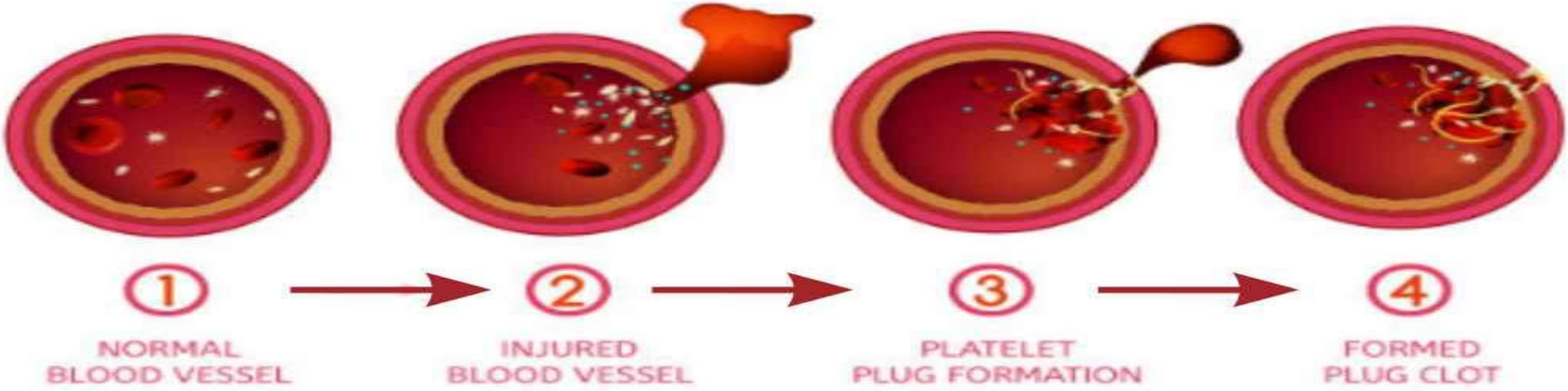
https://www.youtube.com/watch?v=R8JMfbYW2p4



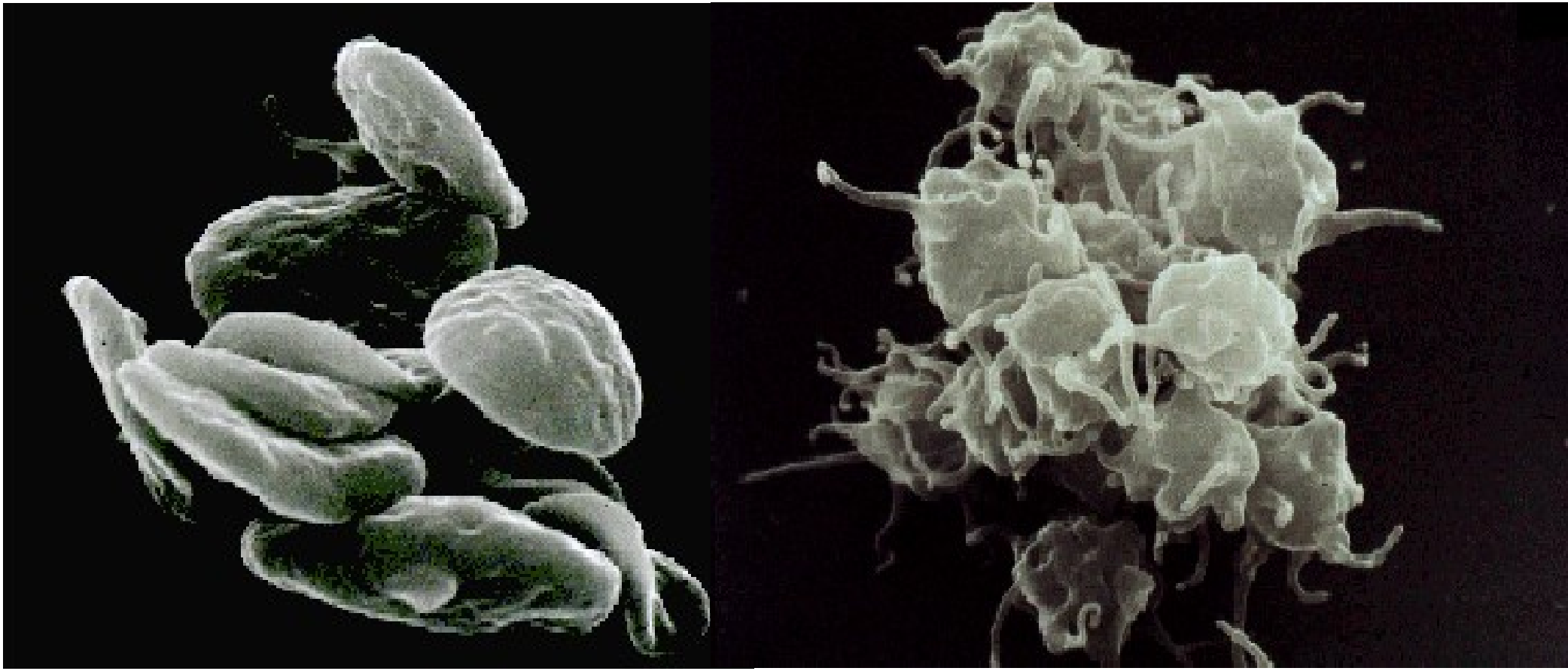
https://www.cast-pharma.com/portfolio/hemophilia/

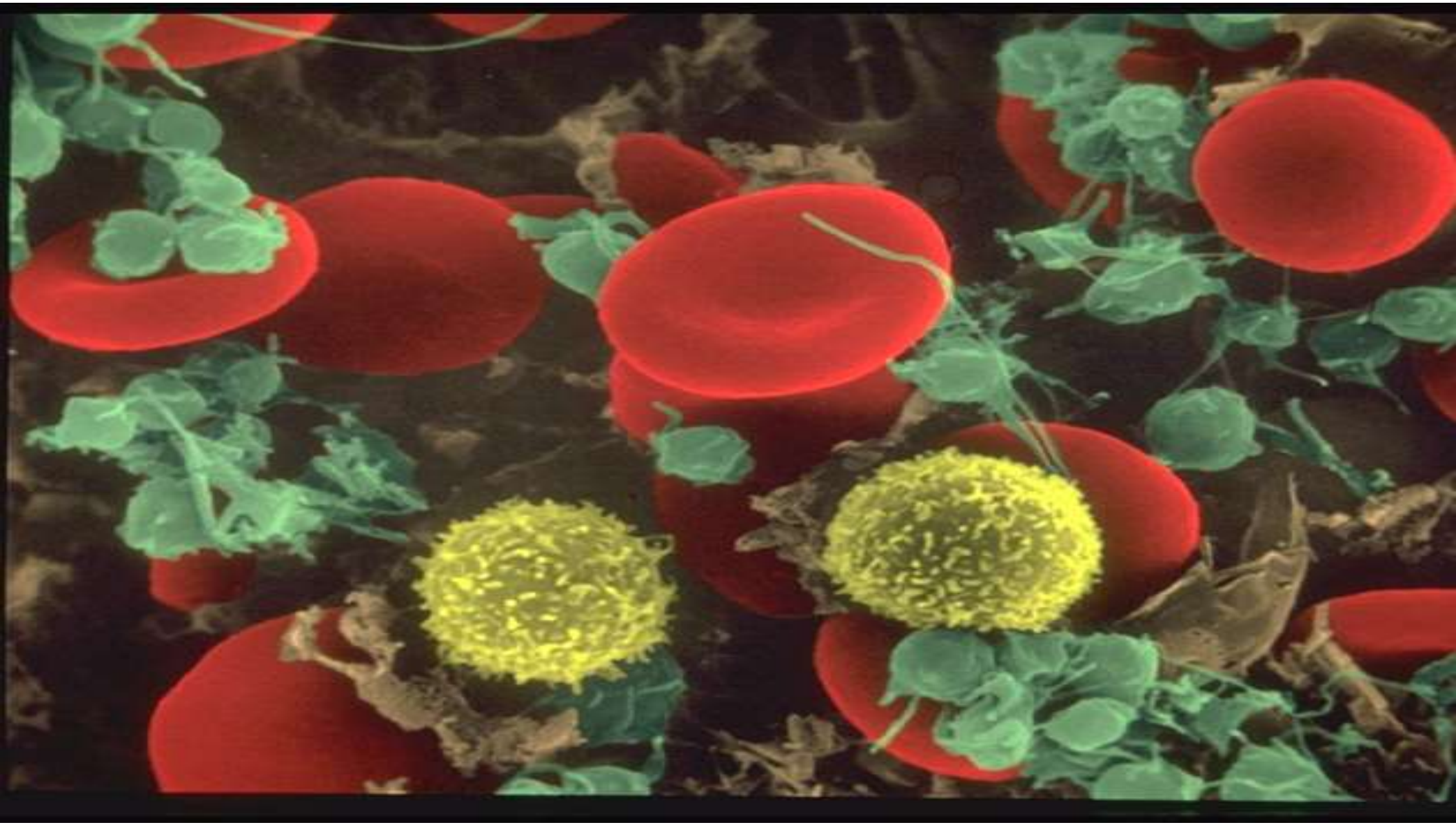


Process of Coagulation



Inactive ***Active***

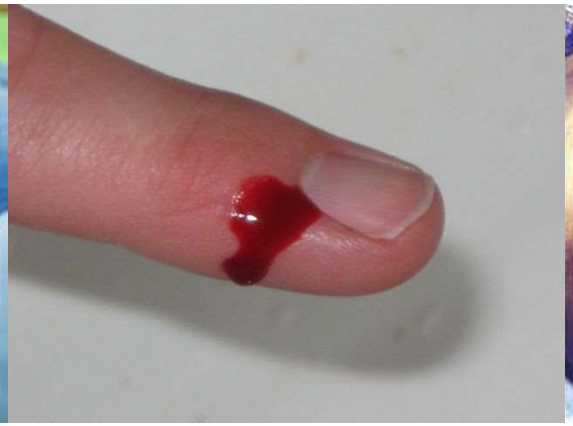
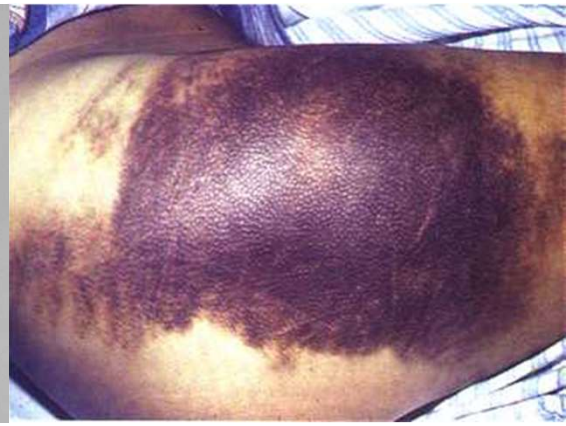




Coagulation

- Coagulation involves a **cascade** of **serine proteases** and cofactors that sequentially activate each other to convert **fibrinogen (Factor I)** to **fibrin**, forming a stable clot.
- **Coagulation follows intrinsic and extrinsic pathways**
- The final three steps of this series of reactions are:
  - **Prothrombin activator is formed**
  - **Prothrombin is converted into thrombin**
  - **Thrombin catalyzes the joining of fibrinogen into a fibrin mesh**



Primary Hemostasis: *Normal physiology, disorders, and clinical findings*

Authors:
Mina Mina
Reviewers:
Parker Lieb
Mao Ding
Kareem Jamani*
**MD at time of publication*

Normal physiology:

Injury to blood vessels from trauma (blunt or penetrating injury)

Collagen and microfibrils (subendothelial elements that are normally protected) are exposed to circulating blood due to vessel injury

Storage granules in endothelial cells release large multimers of clotting factor von Willebrand (vWF) when damaged

Platelet adhesion: vWF binds to collagen and interacts with the platelet surface receptor glycoprotein Ib (GpIb) allowing platelet adhesion

Platelet activation: mediated by agonists like ADP, thrombin and collagen

Platelets change shape and release substances from their granules

ADP

Fibrinogen, vWF, and other substances

Thromboxane A2 (see note)

Induces aggregation

Conformational changes in platelet cell surface glycoprotein IIb/IIIa

↑Affinity for fibrinogen through GpIIb/IIIa

Platelet aggregation: fibrinogen forms bridges between adjacent platelets by binding to activated glycoprotein IIb/IIIa

Interaction with coagulation factors: platelets provide a scaffold that allows the activation of phospholipid-dependent coagulation factors

Primary hemostasis
(formation of a platelet plug)

Secondary hemostasis *(see slide for normal physiology)*

Disorders of primary hemostasis:

Acquired or inherited reduction in vWF quantity or quality *(see vWF deficiency slide)*

von Willebrand Disease

Defect in expression of GpIb interferes with platelet ability to bind to vWF

Bernard-Soulier syndrome

Defect in platelet membrane glycoproteins IIb and IIIa

Glanzmann's Thrombasthenia

Insufficient platelets to form a platelet plug

Thrombocytopenia (low platelet count)

Disorders of primary hemostasis: problems with formation of a platelet plug

Mucocutaneous bleeding (bleeding of the skin and mucous membrane)

↑ Closure time, ↑ bleeding time

Epistaxis | **Menorrhagia** | **Petechiae**

Note:
Drugs like Aspirin and NSAIDs inhibit Thromboxane A2 synthesis (by inhibiting cyclooxygenase) and thereby inhibit platelet aggregation

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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Coagulation Proteins

Coagulation proteins are designated by **Roman numerals (I–XIII)** except for factors IV (Ca^{2+}) and VI (not used anymore)

- Zymogens
  - enzyme precursors II, VII, IX, X, XI, XII, Prekallkrein
  - When activated become serine proteases
- Cofactors
  - Nonenzymatic V, VIII, HMWK, Tissue factor(thromboplastin)

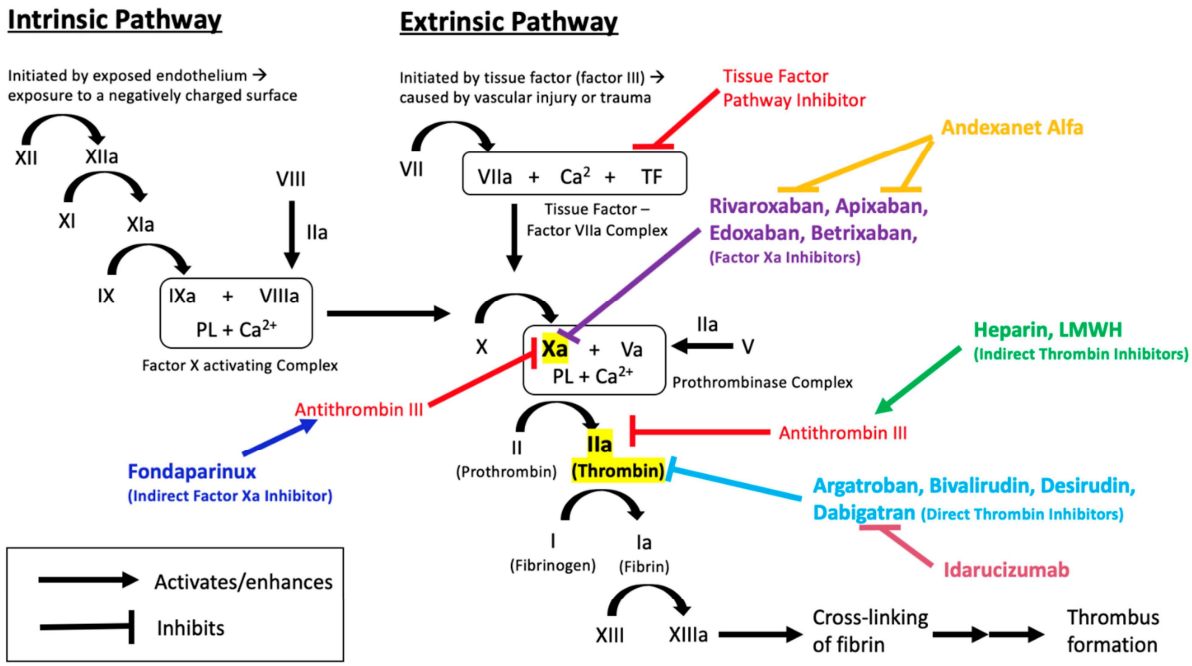
- Kinin factors prekallikrein, kallikrein, HMWK
  - Roles include coag activation as well as fibrinolytic activation

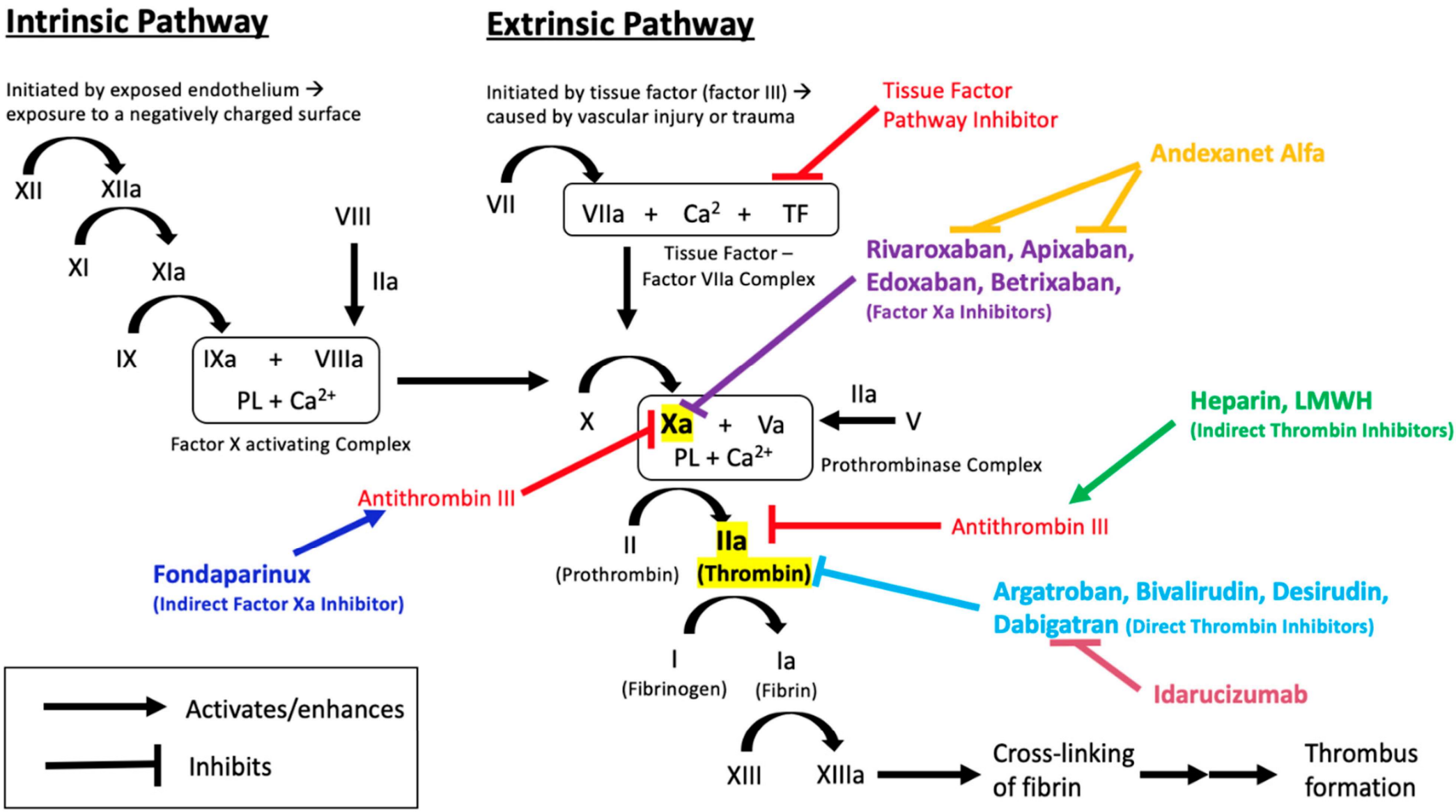
Factor	Name	Nature	Function
I	Fibrinogen	Soluble plasma glycoprotein	Converted to fibrin by thrombin
II	Prothrombin	Serine protease zymogen	Activated to thrombin (IIa)
III	Tissue Factor (TF) / Thromboplastin	Membrane glycoprotein (not plasma protein)	Co-factor for VIIa; starts extrinsic pathway
IV	Calcium (Ca^{2+})	Ion	Required for many steps (II, VII, IX, X)
V	Labile factor	Glycoprotein cofactor	Cofactor for X activation of II
VII	Stable factor	Serine protease	Activates IX and X with TF
VIII	Anti-hemophilic A	Glycoprotein cofactor	Cofactor for IXa activation of X
IX	Christmas factor (B)	Serine protease	Intrinsic activation of X
X	Stuart-Prower	Serine protease	Common pathway activation of II
XI	Plasma thromboplastin antecedent	Serine protease	Activates IX
XII	Hageman factor	Serine protease	Activates XI, kallikrein, plasminogen
XIII	Fibrin-stabilizing factor	Transglutaminase	Crosslinks fibrin (stabilizes clot)

Coagulation Cascade (Simplified)

"Foolish People Try Climbing Long Slopes After Christmas Some People Have Fallen"

Factor	Name
I	Fibrinogen
II	Prothrombin
III	Tissue Factor
IV	Calcium (Ca^{2+})
V	Labile factor
VII	Stable factor
VIII	Anti-hemophilic A
IX	Christmas factor (B)
X	Stuart-Prower
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor




Intrinsic Pathway
Initiated by exposed endothelium → exposure to a negatively charged surface
XII
XIIa
XI
XIa
IX
VIII
IIa
IXa + VIIIa
PL + Ca2+
Factor X activating Complex
Extrinsic Pathway
Initiated by tissue factor (factor III) → caused by vascular injury or trauma
VII
VIIa + Ca2 + TF
Tissue Factor – Factor VIIa Complex
Tissue Factor Pathway Inhibitor
Andexanet Alfa
Rivaroxaban, Apixaban, Edoxaban, Betrixaban,
(Factor Xa Inhibitors)
X
Xa + Va
PL + Ca2+
IIa
V
Prothrombinase Complex
Heparin, LMWH
(Indirect Thrombin Inhibitors)
Antithrombin III
Fondaparinux
(Indirect Factor Xa Inhibitor)
II
(Prothrombin)
IIa
(Thrombin)
Antithrombin III
Argatroban, Bivalirudin, Desirudin, Dabigatran (Direct Thrombin Inhibitors)
Idarucizumab
I
(Fibrinogen)
Ia
(Fibrin)
XIII
XIIIa
Cross-linking of fibrin
Thrombus formation
Activates/enhances
Inhibits

Secondary Hemostasis: Coagulation Cascade Activation

To **stabilize** the platelet plug with an insoluble **fibrin mesh** to stop bleeding.

Coagulation factors = Proteins (mostly liver-made) that circulate as zymogens

Activated in a cascade = Amplified enzymatic steps

Converts **fibrinogen → fibrin** to stabilize the plug.

Pathways:

Intrinsic Pathway (Contact activation)

- Trigger: Collagen, basement membrane, platelets
- **Factors: XII → XI → IX → VIII → X**
- Measured by: **aPTT**

Extrinsic Pathway (Tissue factor)

- Trigger: **Tissue factor (TF)** from damaged tissue
- **Factor: VII → X**
- Measured by: **PT**

Common Pathway:

- **X → Xa → Converts prothrombin (II) → thrombin (IIa)**
- **Thrombin:**
  - Converts **fibrinogen → fibrin (Ia)**
  - Activates factors: V, VIII, XI, XIII
- **Fibrin crosslinking by Factor XIIIa**

1. Intrinsic Pathway (PTT)

- Factors: **XII, XI, IX, VIII**
- Trigger: **Contact with negatively charged surfaces**
- Clinical: **Hemophilia A (VIII), B (IX), C (XI)**

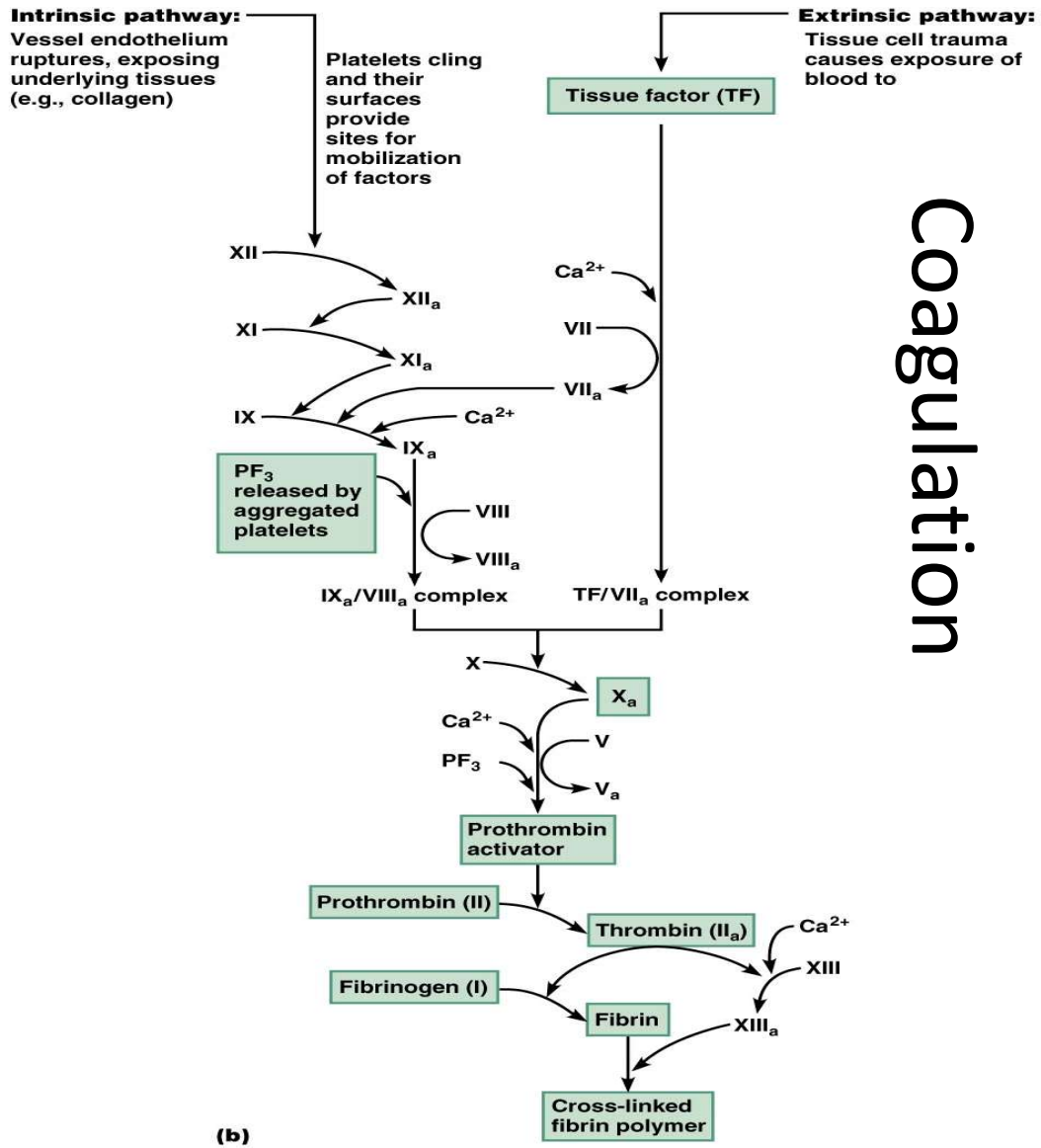
2. Extrinsic Pathway (PT)

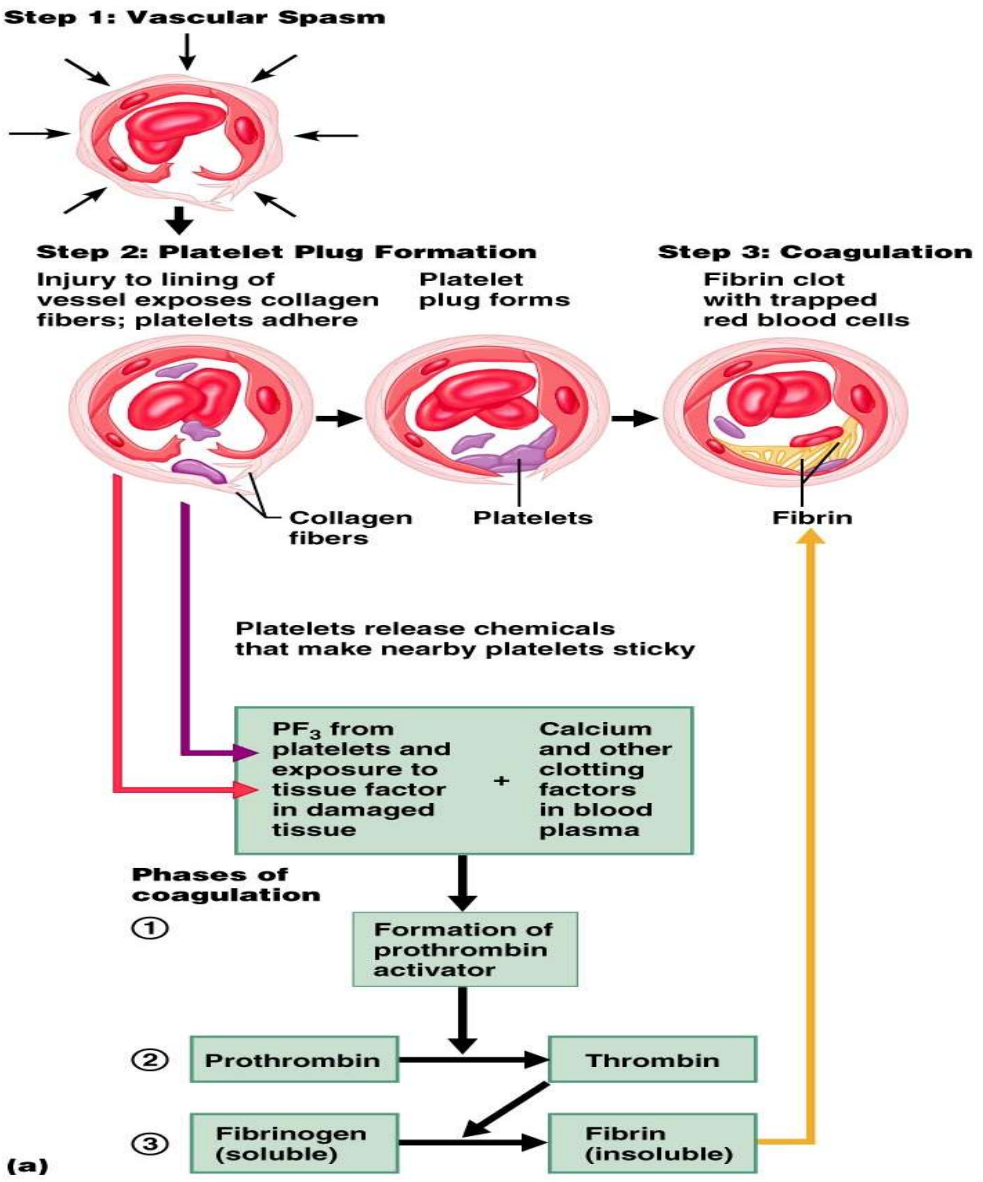
- Factors: **III (TF), VII**
- Trigger: **Tissue injury**
- Clinical: **Sensitive to Warfarin**

3. Common Pathway

- Factors: **X, V, II, I, XIII**
- Final event: **Thrombin converts fibrinogen to fibrin**

Coagulation





Coagulation = Secondary Hemostasis

- The prothrombin time (PT) and its derived measures of **prothrombin ratio** (**PR**) and **international normalized ratio** (**INR**) are measures of the ***extrinsic pathway* of coagulation**.
- They are used to determine the **clotting tendency of blood**, in the measure of
  - **warfarin dosage,**
  - **liver damage,**
  - **vitamin K status.**
- The reference range for prothrombin time is usually around 12–15 seconds;
- the normal range for the INR is 0.8–1.2. PT **measures factors I, II, V, VII, and X.**
- It is used in conjunction with the activated partial thromboplastin time (aPTT) which measures the *intrinsic pathway*.

A. Extrinsic Pathway *("External trauma")*
•Trigger: **Tissue factor (TF or Factor III)**
•Components: **Factor VII → Factor X**
•Test: **PT/INR (Prothrombin Time)**

B. Intrinsic Pathway *("Internal vessel trauma")*
•Trigger: **Collagen, basement membrane, platelets**
•Components: **XII → XI → IX + VIII → X**
•Test: **aPTT (Activated Partial Thromboplastin Time)**

C. Common Pathway
•Trigger: **Factor X → Xa**
•Cascade: **Xa + Va → II (Prothrombin) → IIa (Thrombin)**
→ **Thrombin**: Converts **fibrinogen (I) → fibrin (Ia)**
→ **XIIIa** cross-links fibrin

Pathway	Factors	Trigger	Test
Intrinsic	XII, XI, IX, VIII	Endothelial damage, collagen	aPTT
Extrinsic	VII	Tissue factor (injury)	PT/INR
Common	X, V, II, I, XIII	Amplification loops	PT & aPTT

- *Factors II, VII, IX, X – Vitamin K–dependent (liver-synthesized)*
  Warfarin blocks synthesis; Heparin enhances antithrombin

PT & aPTT – Coagulation Screening Tests

Test	Pathway Assessed	Factors Tested	Used To Monitor
PT (Prothrombin Time)	**Extrinsic** + Common	I, II, V, **VII**, X	**Warfarin**
aPTT (Activated Partial Thromboplastin Time)	**Intrinsic** + Common	I, II, V, VIII, IX, X, XI, XII	**Heparin**

PT (Prothrombin Time) and **PTT/aPTT (Partial Thromboplastin Time)**

EXTRINSIC
|
Tissue Factor — FVII
↓
COMMON PATHWAY
↓
FX → FII (Thrombin)
↓
Fibrinogen → Fibrin

INTRINSIC PATHWAY: FXII → FXI → FIX → FVIII → FX → ...

PT (Prothrombin Time)

- **Measures**: Time to form a clot after adding tissue factor and calcium to **plasma**
- **Sensitive to**: **Factor VII deficiency**, as it's part of the extrinsic pathway
- **Normal range**: ~11–15 seconds
- **Reported as INR** (International Normalized Ratio) in warfarin monitoring:
  - INR target for DVT/PE/AFib: **2.0–3.0**
  - For mechanical valves: **2.5–3.5**

Prolonged PT

Cause	Notes
Warfarin use	↓ Vitamin K-dependent factors
Vitamin K deficiency	Affects factor VII early
Liver disease	↓ production of clotting factors
DIC (late)	Consumption of factors
Factor VII deficiency	Isolated ↑ PT
Early Coumadin effect	PT rises first due to short t½ of factor VII

aPTT (Activated Partial Thromboplastin Time)

- **Measures**: Time to clot after adding **kaolin**, **phospholipid**, and **calcium**
- **Tests intrinsic and common pathways**
- **Normal range**: ~25–35 seconds

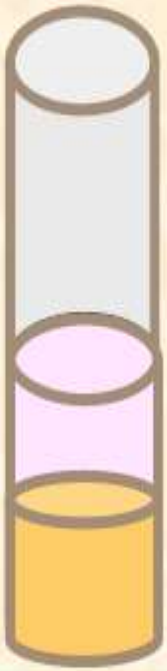
Prolonged aPTT

Cause	Notes
Heparin therapy	Activates antithrombin → inhibits thrombin, FXa
Hemophilia A/B (VIII/IX deficiency)	Severe bleeding with ↑ aPTT only
Lupus anticoagulant	↑ aPTT but paradoxical hypercoagulability
vWD	Can prolong aPTT (Factor VIII relies on vWF)
DIC	Consumes factors VIII, IX, XI
Factor XI or XII deficiency	XII prolongs aPTT but not clinically significant bleeding

- **PT** ↑ **first** in Vitamin K deficiency or warfarin use (factor VII has shortest half-life)
- **aPTT** ↑ **first** in heparin use or intrinsic factor deficiency
- **Liver failure**: both PT and aPTT prolonged; **factor V** ↓ (not vitamin K dependent)
- **vWD**: ↑ bleeding time, possible ↑ aPTT (↓ FVIII), normal platelet count
- **Lupus anticoagulant**: ↑ aPTT, **increased thrombosis risk** (not bleeding)
- **DIC**: ↑ PT, ↑ aPTT, ↓ platelets, ↓ fibrinogen, ↑ D-dimer

CLOT-ED

Prothrombin Time (PT)



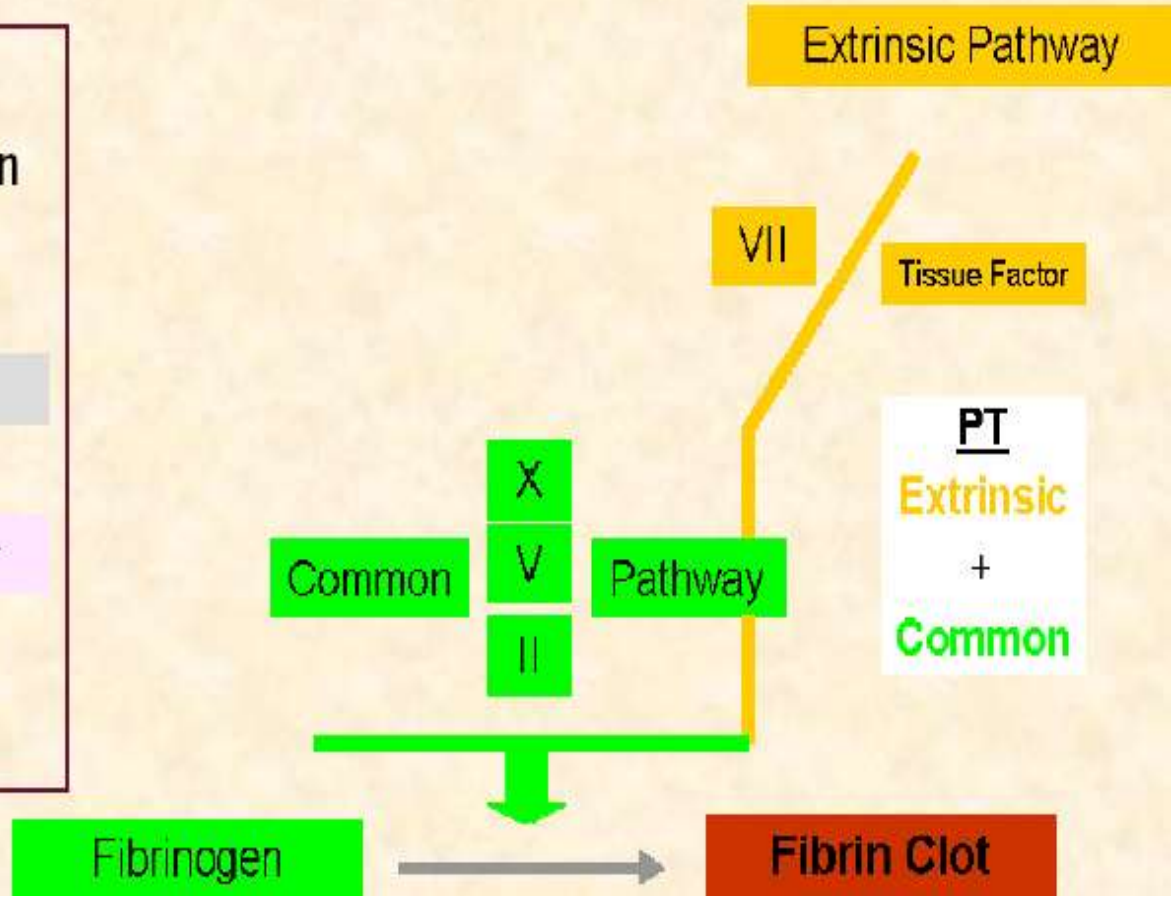
Time for clot formation

~ 12 seconds

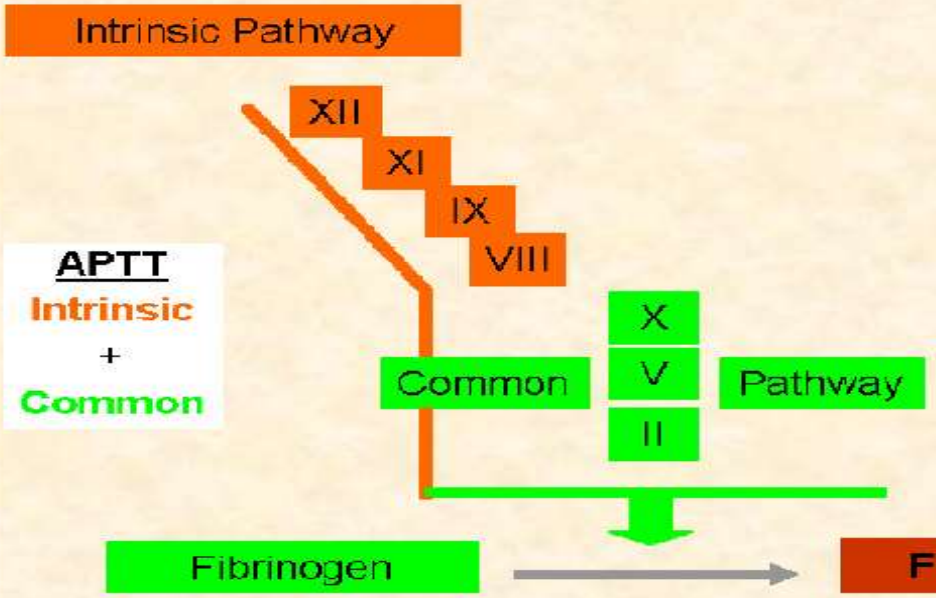
Incubate at 37 °C for ~3 minutes

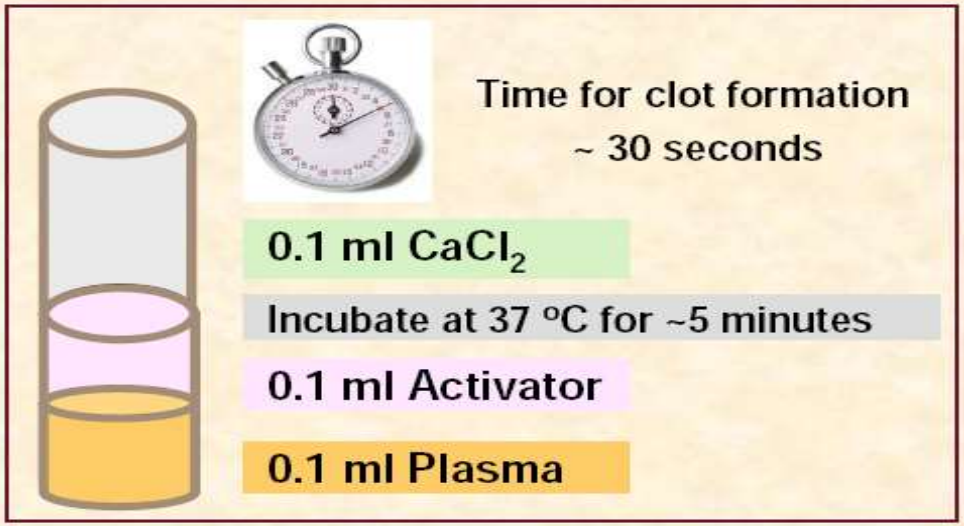
0.1 ml Thromboplastin + Ca^{++}

0.1 ml Plasma



Activated Partial Thromboplastin Time

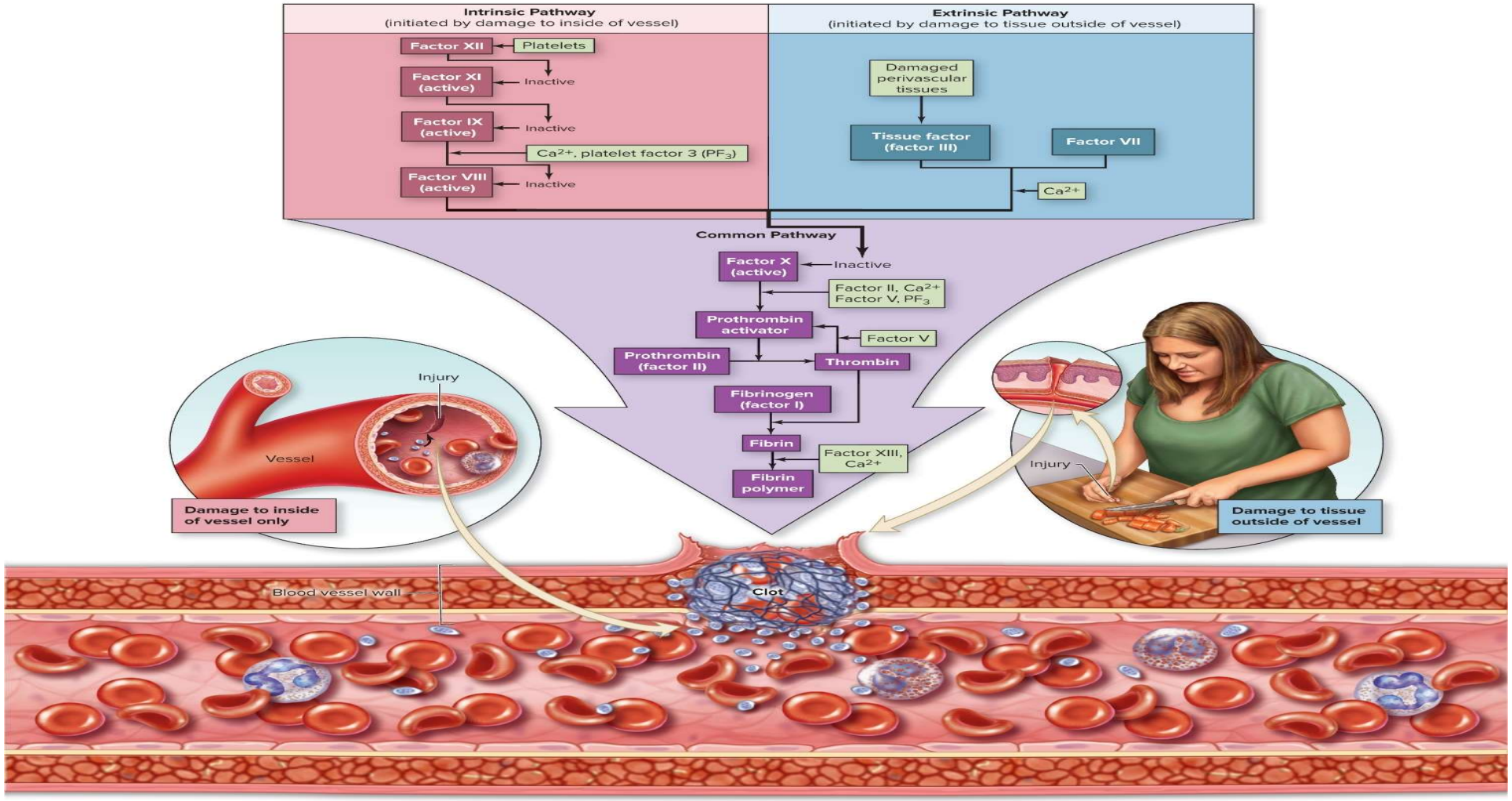


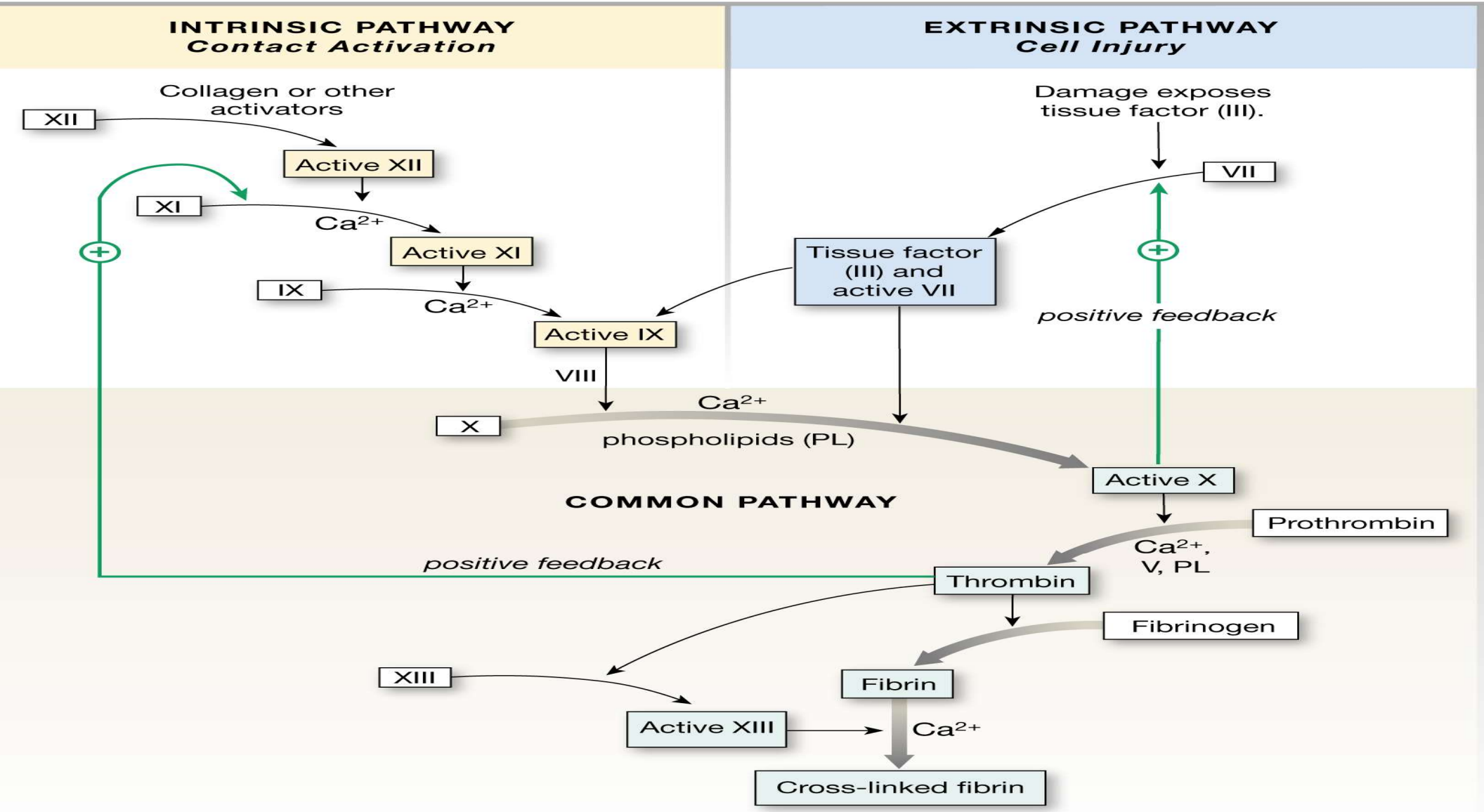


APTT Reagent Composition

- Activator to convert FXII to FXIIa
- Phospholipid (replaces "in vivo" platelet surface on which coagulation reactions occur)
- $CaCl_2$ – used to reintroduce calcium ions that were chelated by sodium citrate
- Referred to as "partial thromboplastin" since no Tissue Factor is used
  - Two-stage assay (activation and re-calcification)

Figure 18.13




INTRINSIC PATHWAY
Contact Activation
EXTRINSIC PATHWAY
Cell Injury
Collagen or other activators
XII
Active XII
XI
Ca2+
Active XI
IX
Ca2+
Active IX
VIII
Damage exposes tissue factor (III).
VII
Tissue factor (III) and active VII
positive feedback
X
Ca2+
phospholipids (PL)
Active X
COMMON PATHWAY
Prothrombin
Ca2+, V, PL
positive feedback
Thrombin
Fibrinogen
XIII
Fibrin
Active XIII
Ca2+
Cross-linked fibrin

Secondary Hemostasis: *Coagulation Cascade*

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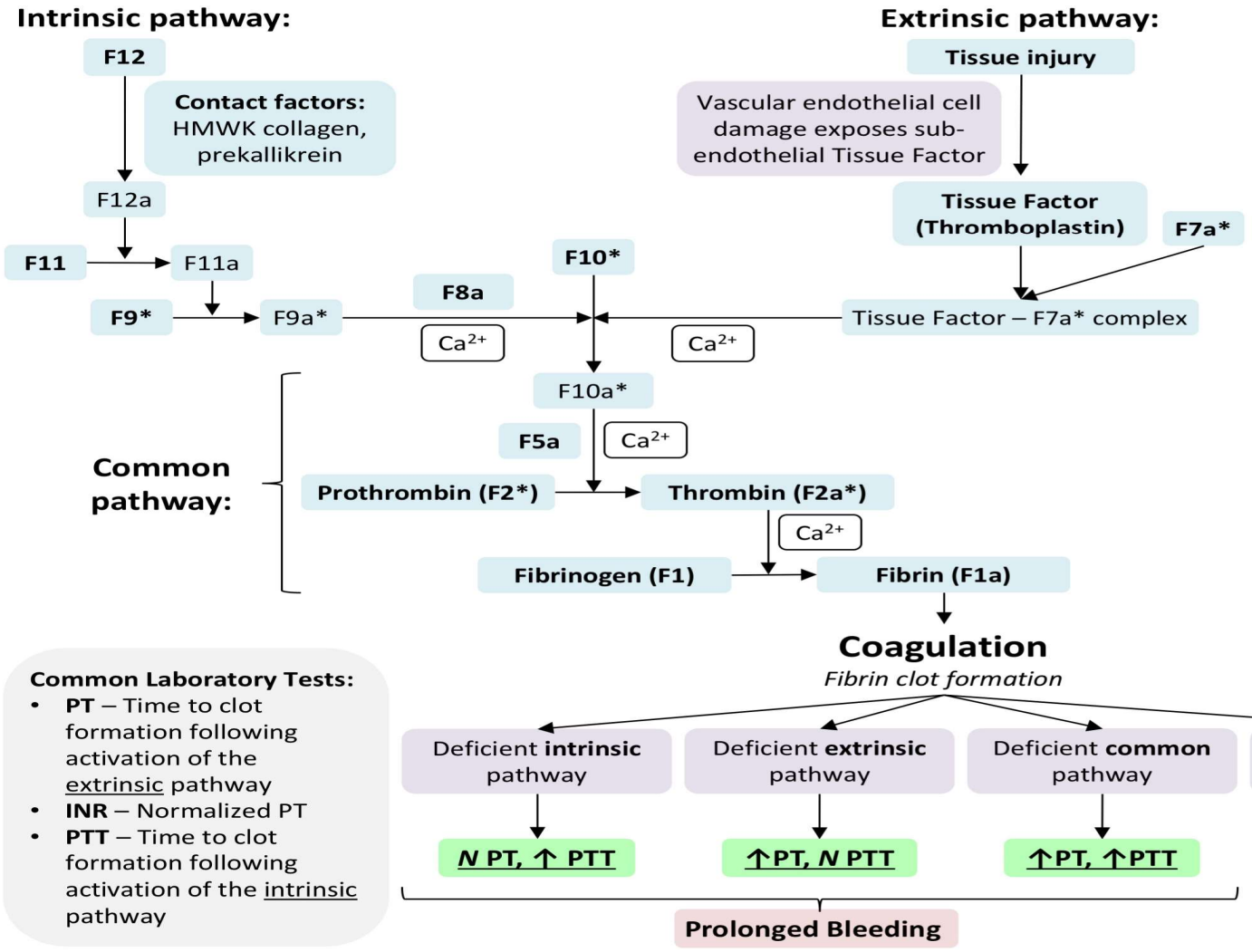

Abbreviations:
- **PT** – Prothrombin Time
- **INR** - International Normalized Ratio
- **PTT** – Partial Thromboplastin Time
- **F** – Coagulation Factor
- **a** – Activated coagulation factor
- ***N*** – Normal
- **HMWK** – High molecular weight kininogen
- * – Vitamin K dependent (for more information, see *Vitamin K Deficiency* slide)

Memory Aids:
- PT = Extrinsic: Play Tennis outside
- PTT = Intrinsic: Play Table Tennis Inside
- Intrinsic factors – TENET: Twelve, Eleven, Nine, Eight, Ten
- Common pathway factors – 10/5=2, 2/2=1 (F10, 5, 2, 1)
- Vitamin K dependent factors – 1972 (the year Canada won the Summit Series in hockey vs. the USSR): F10, 9, 7, 2

Common Laboratory Tests:
- **PT** – Time to clot formation following activation of the extrinsic pathway
- **INR** – Normalized PT
- **PTT** – Time to clot formation following activation of the intrinsic pathway

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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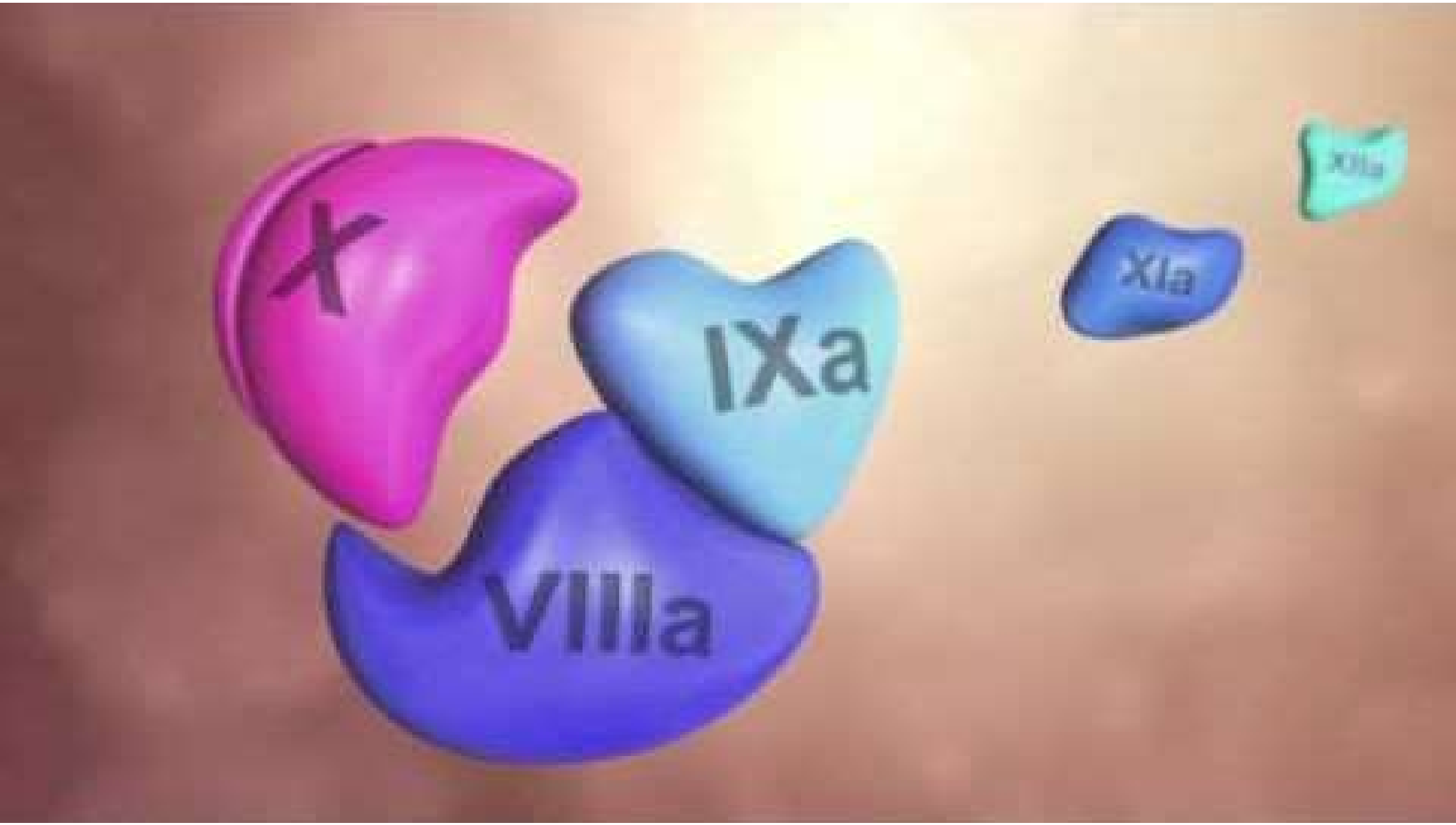
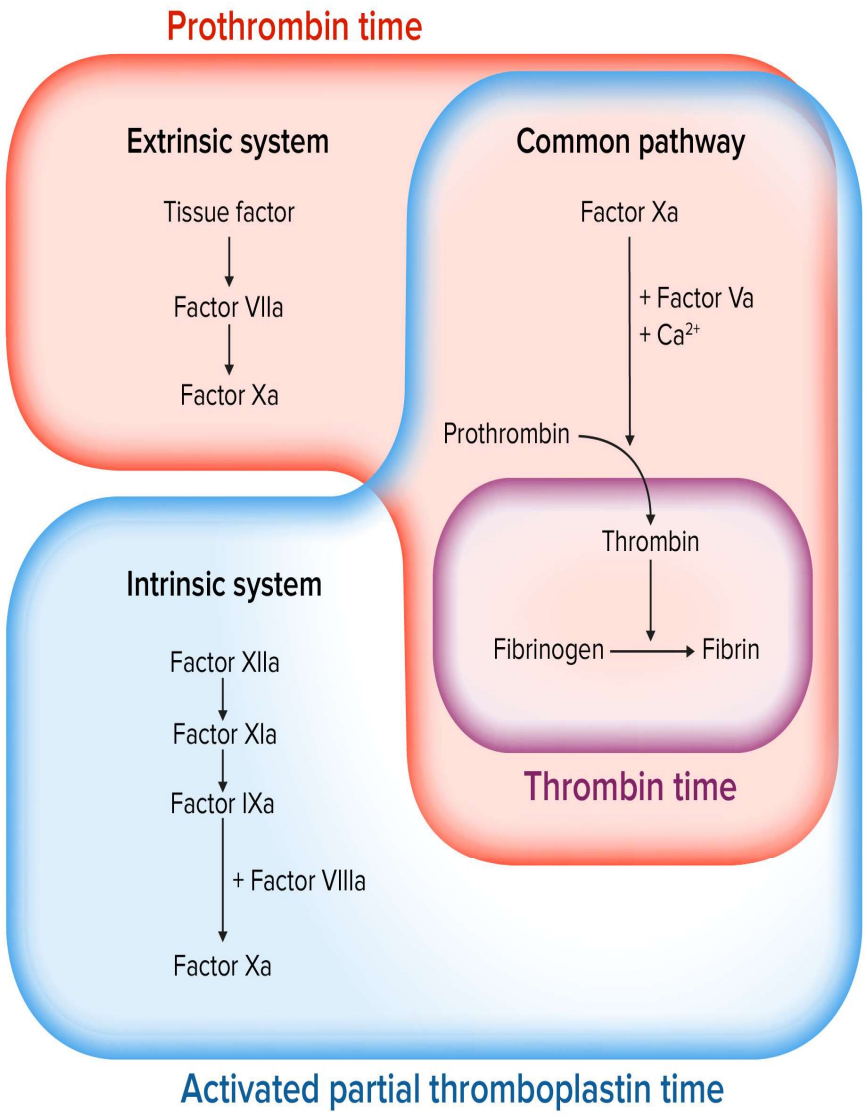

X
IXa
VIIIa
XIa
XIIa

https://youtu.be/SGzp9wqeu84

https://youtu.be/cy3a__OOa2M

Test	Pathway	Affected Factors
PT (Prothrombin Time)	Extrinsic	VII, X, V, II, I
INR	Normalized PT	Warfarin monitoring
aPTT	Intrinsic	XII, XI, IX, VIII, X, V, II, I
TT (Thrombin Time)	Final step	Conversion of fibrinogen to fibrin
Mixing Study	Distinguishes deficiency vs inhibitor	Corrects = deficiency, No correction = inhibitor
D-dimer	Clot degradation product	DIC, PE, DVT



VITAMIN K–DEPENDENT FACTORS

Vitamin K Needed For:	II, VII, IX, X, Protein C, Protein S
Site	Liver
Inhibited by	**Warfarin**
Deficiency causes	↑ PT > PTT; bleeding tendency

REGULATORY ANTICOAGULANT PROTEINS

Protein	Function	Clinical Notes
Antithrombin III	Inhibits IIa, Xa, IXa, XIa, XIIa	↑ by Heparin
Protein C	Inhibits Va, VIIIa (with S)	Activated by thrombin-thrombomodulin
Protein S	Cofactor for C	Free form active; ↓ in pregnancy, OCP use
TFPI (Tissue Factor Pathway Inhibitor)	Inhibits VIIa-TF complex	Natural brake of extrinsic path

LIVER & SYNTHESIS

- Most clotting factors made in the **liver**
- **Exceptions**:
- **vWF**: Made in **endothelium & megakaryocytes**
- **Factor VIII**: Made in **endothelial cells**

Disease	Deficient Factor	Inheritance	Presentation
Hemophilia A	VIII	X-linked recessive	Hemarthroses, ↑ aPTT
Hemophilia B (Christmas disease)	IX	X-linked recessive	Same as above
Hemophilia C	XI	AR, Ashkenazi Jews	Mild bleeding
Factor V Leiden	Factor V resistant to Protein C	AD	Hypercoagulability, DVT
DIC	Consumption of all factors	Acquired	↑ PT/PTT, ↓ fibrinogen, ↑ D-dimer
Vitamin K Deficiency	II, VII, IX, X, C, S	Acquired	Bleeding, ↑ PT > PTT
Liver Disease	Global ↓ synthesis	Acquired	↑ PT and PTT, ↓ fibrinogen

Termination and Regulation of Coagulation

- **Antithrombin III (ATIII)**: Inhibits thrombin, Xa, IXa, XIa, XIIa
- **Protein C & S**: Inactivate Factors Va and VIIIa
- **TFPI (Tissue Factor Pathway Inhibitor)**: Blocks extrinsic pathway
- **Endothelial factors:** NO, prostacyclin (PGI_2), heparan sulfate

Fibrinolysis

- **Plasminogen → Plasmin** (via tPA)
- Plasmin breaks down **fibrin** into **D-dimers**
- Inhibited by: α2-antiplasmin

Injury → Vasoconstriction (Endothelin)
↓
vWF exposure + Collagen
↓
Platelet Adhesion (GPIb)
↓
Activation (ADP, TXA2, Ca^{2+})
↓
Aggregation (GPIIb/IIIa + fibrinogen)
↓
Plug + Coagulation cascade → Fibrin
↓
Stable clot
↓
Fibrinolysis (tPA → Plasmin)

FIBRINOLYTIC SYSTEM

The **fibrinolytic system** dissolves fibrin clots once hemostasis has stabilized, **preventing pathological thrombosis and maintaining vessel patency.**

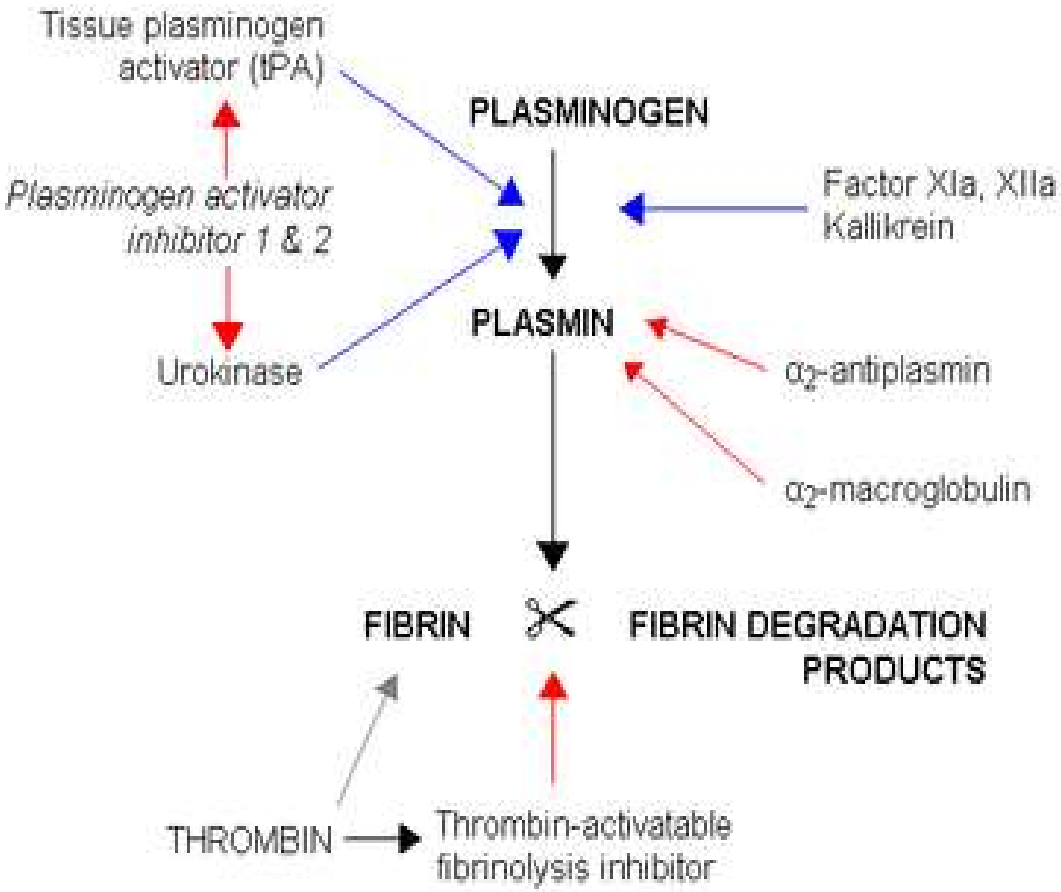
•Opposes the coagulation cascade

•Balances clot **formation** and **removal**

- Definition: **<u>temporary fibrin clot systematically and gradually dissolved as the vessel heals</u>**
- Key components
  - Plasminogen (inactive form)
  - Plasminogen activators
  - Plasmin
  - Fibrin
  - Fibrin Degradation Products (FDP)
  - Inhibitors of plasminogen activators and plasmin

Inhibitors of Fibrinolysis

- Plasminogen Activator Inhibitors (PAI)
- α_2 –antiplasmin
- α_2 -macroglobulin



Component	Type	Function
Plasminogen	Inactive zymogen	Circulates in plasma, incorporated into clots
Plasmin	Active serine protease	Degrades fibrin and fibrinogen → FDPs
tPA (Tissue Plasminogen Activator)	Activator	Endothelial-derived, activates plasminogen → plasmin on fibrin
uPA (Urokinase Plasminogen Activator)	Activator	Works in ECM remodeling and pathology
α2-Antiplasmin	Inhibitor	Inhibits free plasmin in plasma
PAI-1 (Plasminogen Activator Inhibitor-1)	Inhibitor	Inhibits tPA and uPA; prevents premature fibrinolysis
Fibrin Degradation Products (FDPs)	Fragments	Includes **D-dimer** – marker of clot breakdown

Coagulation	Fibrinolysis
Forms clot	Removes clot
Fibrinogen → Fibrin (via thrombin)	Fibrin → FDPs (via plasmin)
Stabilized by Factor XIIIa	Dissolved by plasmin
Promotes hemostasis	Prevents thrombosis

Test	Use
D-dimer	Indicates recent fibrin clot **formation AND breakdown**
↑ D-dimer	DIC, DVT, PE, MI, post-surgery, COVID-19
Euglobulin lysis time	Assesses fibrinolytic activity (rarely used clinically)

- Prolonged APTT may indicate:

1. use of heparin (or contamination of the sample)
2. antiphospholipid antibody (especially lupus anticoagulant, which paradoxically increases propensity to thrombosis)
3. coagulation factor deficiency (e.g. hemophilia)

LAB TESTS

Test	Pathway	Prolonged In...
PT (Prothrombin Time)	Extrinsic (VII) + common	Warfarin, liver disease
aPTT (Activated Partial Thromboplastin Time)	Intrinsic (XII, XI, IX, VIII) + common	Heparin, hemophilia
INR	Normalized PT	Used to monitor **warfarin**
D-dimer	Fibrin degradation	↑ in **DIC, PE, DVT**
Bleeding Time	Platelet function	↑ in vWD, thrombocytopenia

Tests for Primary Hemostasis

Bleeding Time: The time taken for **bleeding to stop** after a standardized skin incision — assesses **primary hemostasis** (platelet plug formation).

NORMAL RANGE

- **2–7 minutes** (depending on technique — e.g., Ivy method)

– Assesses all components of Virchow's triad

WHAT DOES IT MEASURE?

- **Platelet function**, not number
- **Vascular integrity**
- **Interaction between platelets and endothelium**
- ❗Does **not** measure coagulation cascade or fibrin formation (secondary hemostasis)

Bleeding time tests:

- **Platelet adhesion (via vWF)**
- **Platelet aggregation**
- **Initial platelet plug formation**

Condition	Mechanism
Thrombocytopenia	↓ Platelet count
von Willebrand Disease (vWD)	↓ Platelet adhesion (vWF defect)
Bernard-Soulier syndrome	Defective GpIb → ↓ platelet adhesion
Glanzmann thrombasthenia	Defective GpIIb/IIIa → ↓ aggregation
Uremia (kidney failure)	Platelet dysfunction due to toxins
NSAIDs, Aspirin	Inhibit COX → ↓ TxA2 → ↓ aggregation
Leukemias, Myelodysplasia	Marrow failure → ↓ platelet production
Scurvy	Defective collagen → ↑ capillary fragility

Platelet Aggregation studies

– **Measure ability of platelets to aggregate**, in vitro, when subjected to various stimulators (agonists)

– Predominantly assesses function **of platelet glycoprotein IIb/IIIa receptor**

WHY DO WE STUDY THIS?

- Diagnose inherited platelet disorders
- Identify acquired dysfunctions (drugs, systemic disease)
- Complement bleeding time, platelet count, and PFA-100 findings (PFA (Platelet Function Assay)

Von Willebrand Factor (VWF) assays

– Measure amount and function of VWF, a protein that works with platelets so that they adhere to site of injury

– Assesses function of VWF ligand in its interaction with **platelet glycoprotein Ib receptor**

Role of vitamin K

What is Vitamin K?

•**Fat-soluble vitamin (K_1 = phylloquinone from plants; K_2 = menaquinone from gut flora)**

•Essential **cofactor** in **γ-carboxylation** of certain glutamate residues on clotting factors

Play key roles in the regulation of three physiological processes:

•**Blood coagulation:**

- (prothrombin (factor II),
- factors VII,
- IX,
- X,
- protein C,
- protein S, and protein Z).

•**Bone metabolism:**

- osteocalcin, also called bone Gla-protein (BGP), and matrix gla protein (MGP).

•**Vascular biology.**

Like other liposoluble vitamins (A, D, E), **vitamin K is stored in the fat tissue of the human body.**

VITAMIN K-DEPENDENT COAGULATION FACTORS

Factor	Function
II (Prothrombin)	Converts to thrombin → fibrin formation
VII	Initiates extrinsic pathway
IX	Activates factor X in intrinsic pathway
X	Final common pathway activator
Protein C & Protein S	**Natural anticoagulants** – degrade Va and VIIIa

•Enables calcium (Ca^{2+}) binding → essential for membrane interaction and activation of clotting factors

- First lab abnormality in vitamin K deficiency = ↑ **PT**
- **Protein C** is depleted faster than procoagulant factors → **hypercoagulable state** early in warfarin therapy
- **Warfarin-induced skin necrosis** = due to Protein C depletion
- **INR monitoring** for patients on warfarin
- **Vitamin K does NOT reverse heparin** (use protamine sulfate instead)

Drug	Target	Use
Aspirin	Irreversible COX-1 inhibition → ↓ TXA_2	Antiplatelet
Clopidogrel / Ticagrelor	ADP receptor (P2Y12) blocker	Antiplatelet
Abciximab	GPIIb/IIIa inhibitor	Acute coronary syndrome
Heparin	Activates ATIII → ↓ thrombin/Xa	Anticoagulation
LMWH (e.g., enoxaparin)	Preferentially inhibits Xa	Anticoagulation
Warfarin	Inhibits epoxide reductase → ↓ Vit K factors	Long-term anticoagulation
tPA (alteplase)	Plasminogen activator	Thrombolysis
Aminocaproic acid	Inhibits fibrinolysis	Antidote to tPA

Defect	Associated Factor	Key Features	Test
Hemophilia A	Factor VIII	X-linked recessive, ↑ aPTT	aPTT ↑
Hemophilia B (Christmas disease)	Factor IX	Same as A	aPTT ↑
von Willebrand Disease	vWF (and low VIII)	Mucosal bleeding, ↑ bleeding time, ↑ aPTT	BT ↑, aPTT ↑
Vitamin K Deficiency	Factors II, VII, IX, X, protein C/S	Bleeding, neonates, warfarin	PT ↑ first, then aPTT
DIC	All factors consumed	↑ PT/PTT, ↓ fibrinogen, ↑ D-dimer	All abnormal
Immune Thrombocytopenic Purpura (ITP)	Autoantibodies to GPIIb/IIIa	↓ Platelets, normal PT/PTT	Isolated thrombocytopenia
Bernard-Soulier Syndrome	GPIb defect	Large platelets, platelet adhesion defect	BT ↑
Glanzmann Thrombasthenia	GPIIb/IIIa defect	Platelet aggregation defect	BT ↑

Role of PT, PTT: Warfarin, Heparin Monitoring

Anticoagulant	PT	PTT
Low dose Heparin	Normal	Prolonged
High dose heparin	Prolonged	Prolonged
Low dose warfarin	Prolonged	Normal
High dose warfarin	Prolonged	Prolonged

THROMBOSIS — Pathologic Clot Formation

Thrombosis = inappropriate activation of hemostatic mechanisms **inside intact vessels**

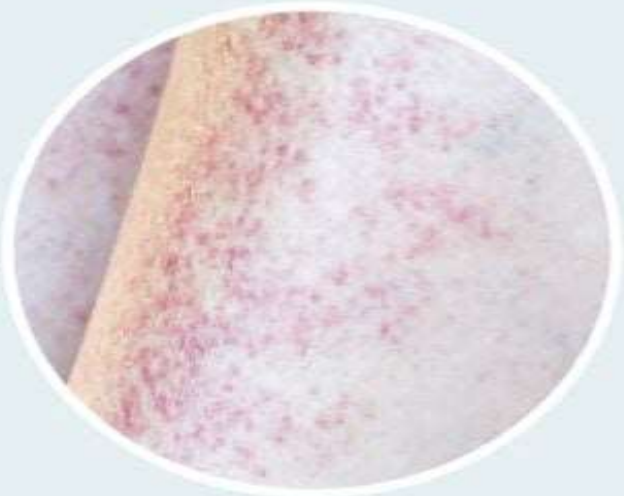
Type	Description	Key Features
Arterial thrombi	High shear stress; platelet-rich	Pale, grow **retrograde**
Venous thrombi	Stasis; fibrin + RBC-rich	Red/stasis thrombi, grow **toward heart**
Mural thrombi	Occur in heart or large arteries post-MI	Risk of embolism
Vegetations	On heart valves	Infective endocarditis

Fates of a Thrombus

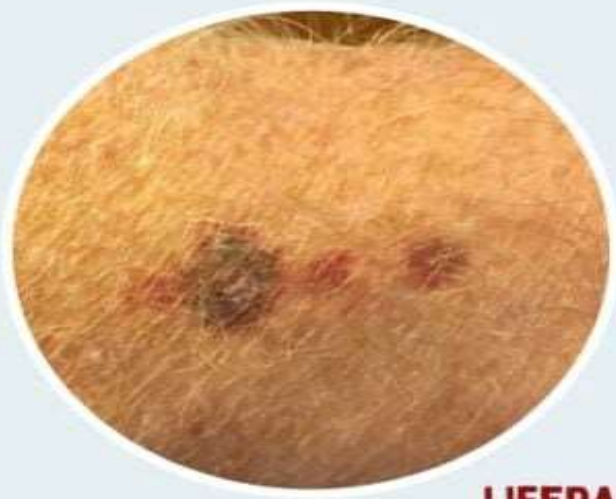
- **Propagation** (extends)
- **Embolization** (dislodges → distant site)
- **Dissolution** (fibrinolysis via tPA)
- **Organization & recanalization** (ingrowth of cells/fibroblasts)

PETECHIAE VS. PURPURA VS. ECCHYMOSIS

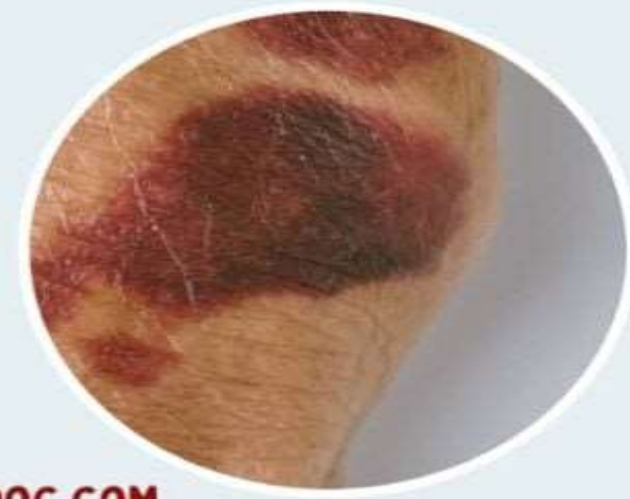
Petechiae
Less than 2 mm



Purpura
2 mm to 1 cm



Ecchymosis
More than 1 cm



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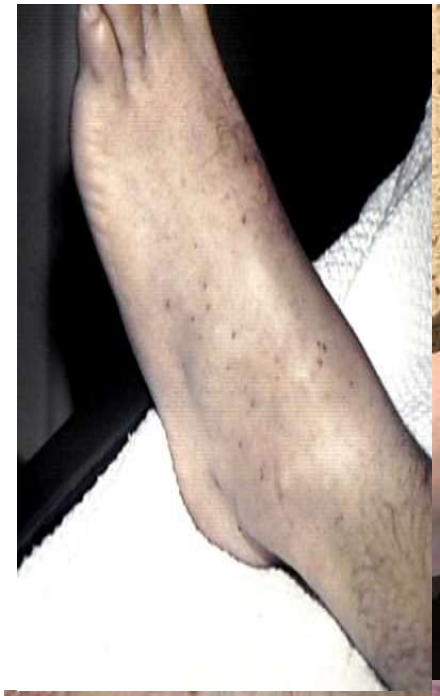
- Examination Platelet Disease

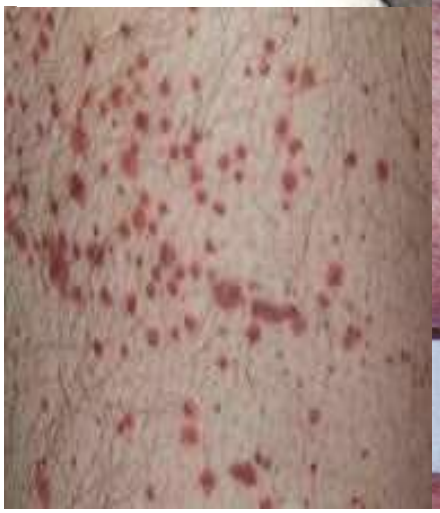
Mucosal/cutaneous bleeding
Lack vessel protection by submucosal tissue
Bleed immediately after vascular trauma

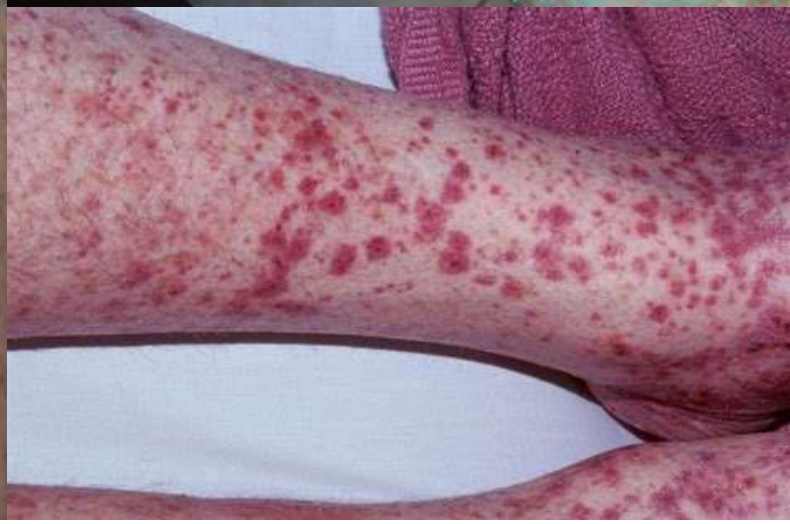
- **Petechiae**
  - From small capillary
  - In areas of increased venous pressure (dependent parts of the body)
  - Asymptomatic and not palpable
  - D/D small telangiectasias

    (Angiomas, Vasculitic purpura, Wiskott-Aldrich Syndrome, Leukemia, Vit K deficiency



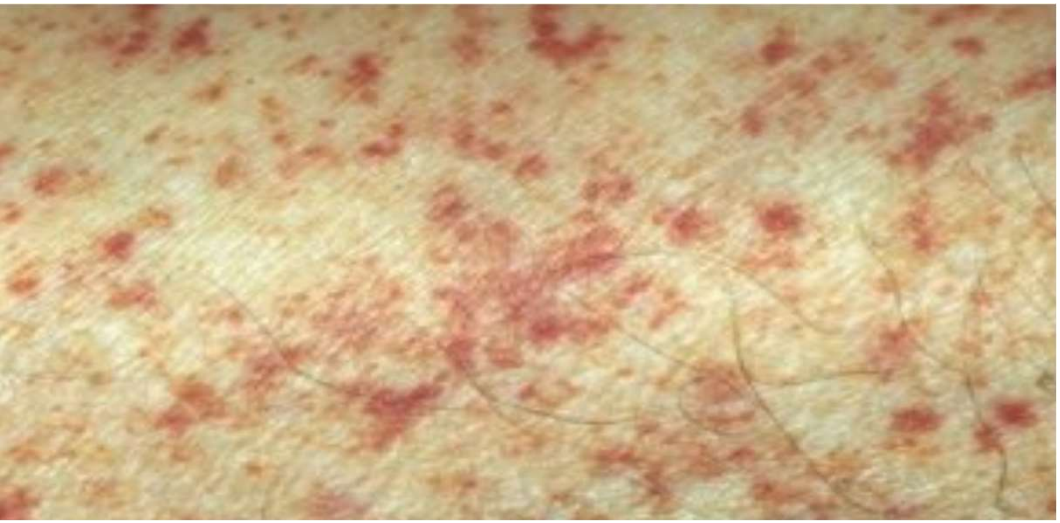
- **Purpura**
  - Characteristically purple in colour
  - Small, multiple, and superficial in location
  - Develop without noticeable trauma / not spread into deeper tissues
  - Seen in – (Acute / Chronic leukemia, Vitamin K deficiency)

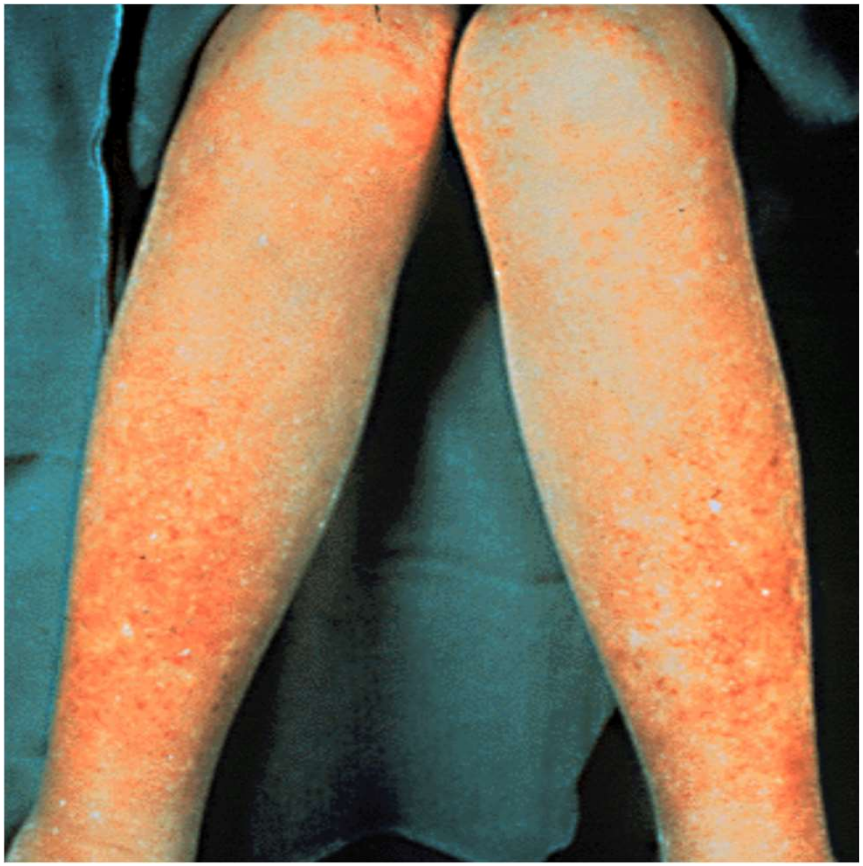




Physical Examination

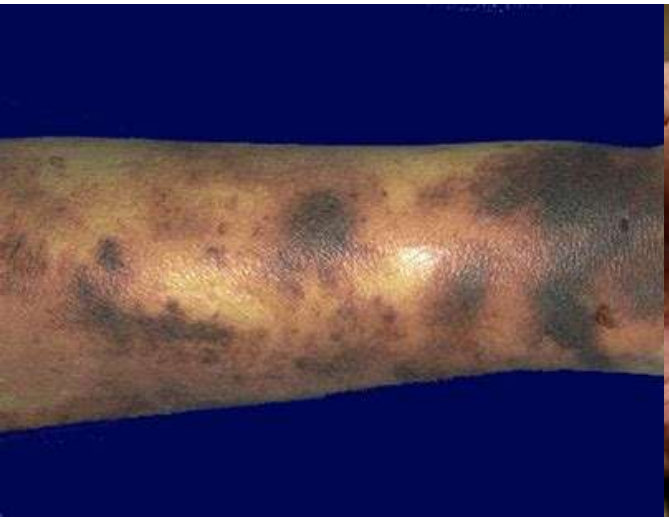
- **Petechiae**

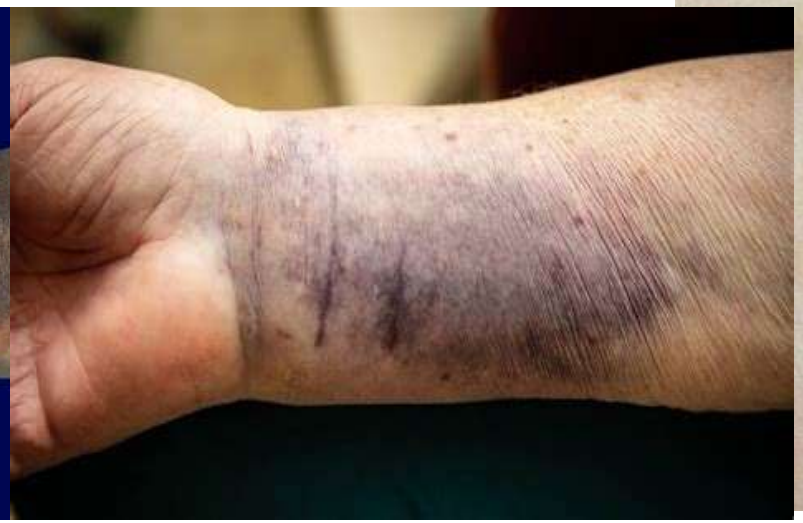


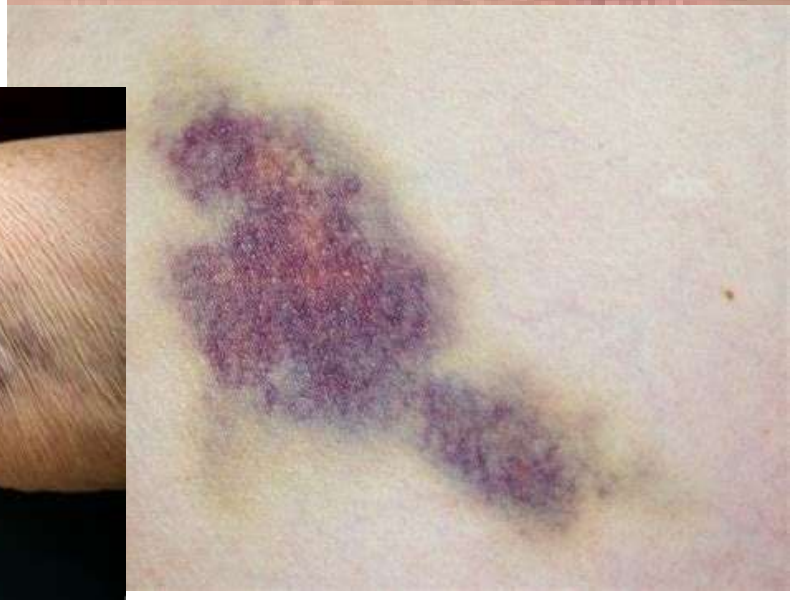


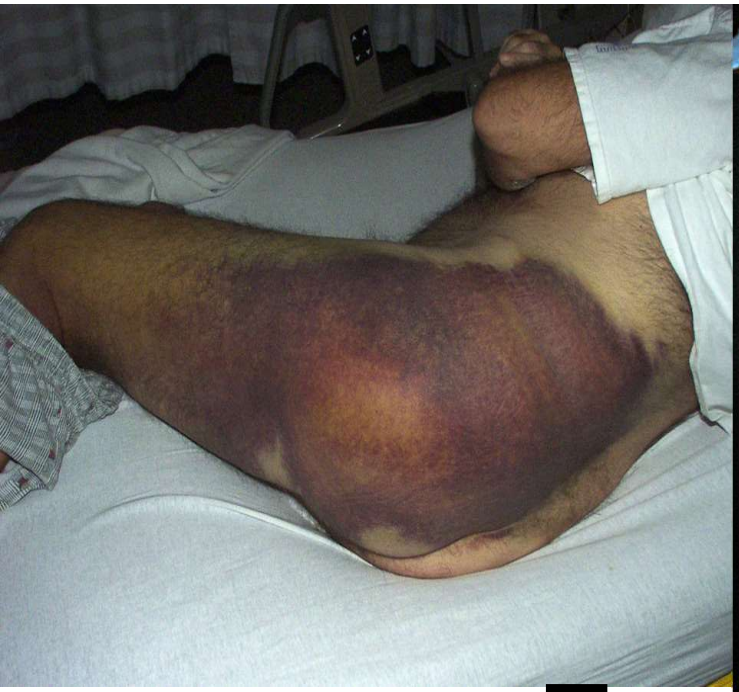
Examination
Coagulation Disorders

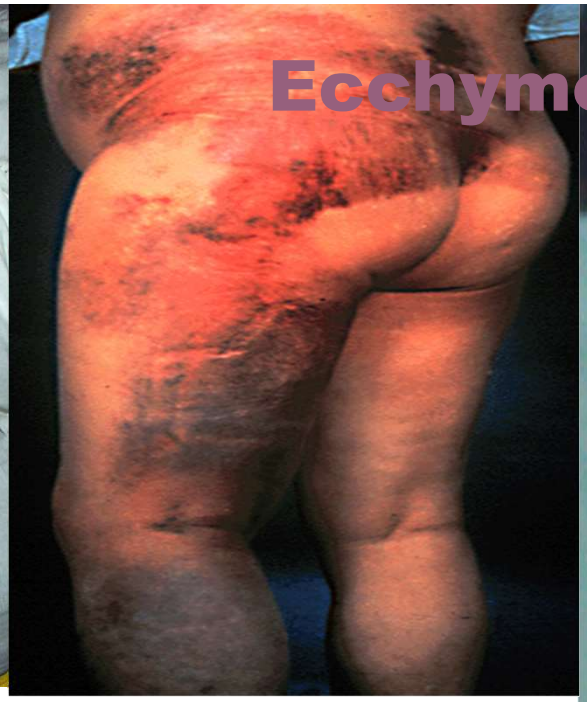
- **Ecchymoses**
  - Large palpable ecchymoses
  - Spreading into deep tissue - haematomas – Hemarthrosis- severe coagulation disorder- haemophilia
  - Coagulation disorder bleeding onset may be delayed after surgery



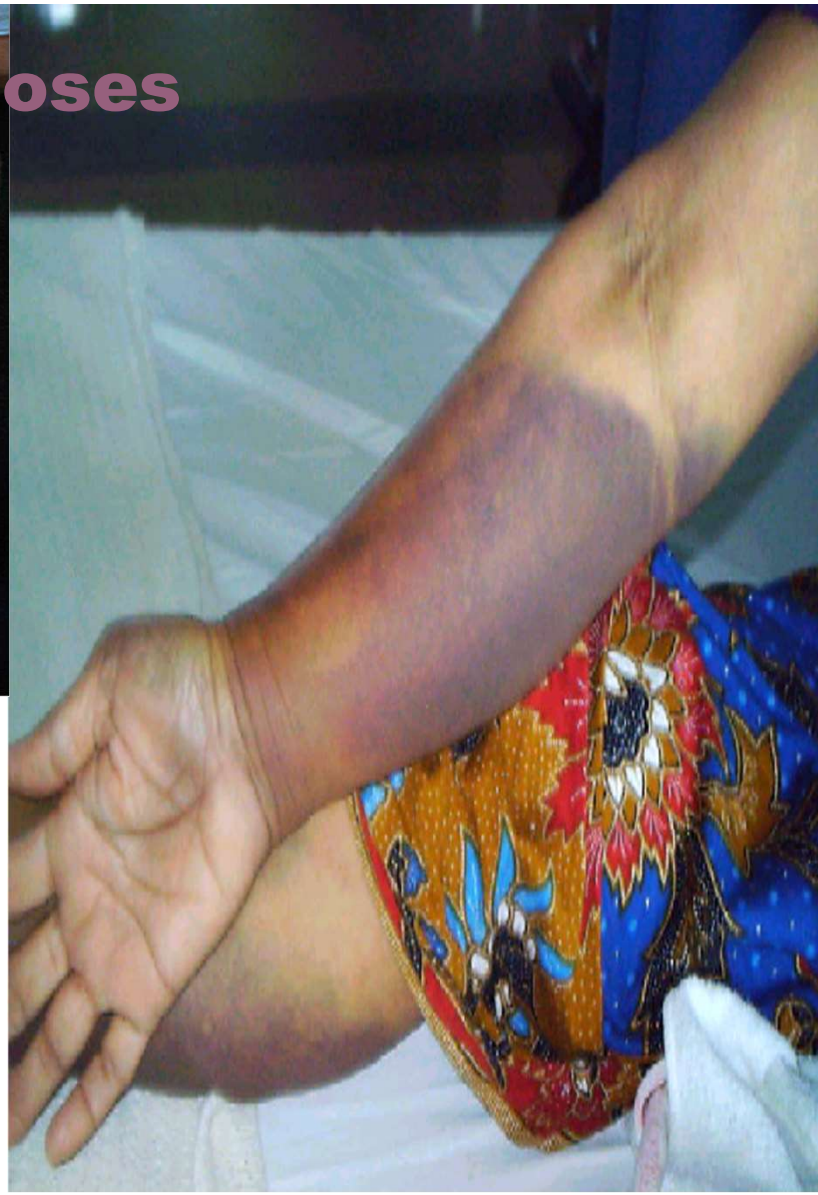


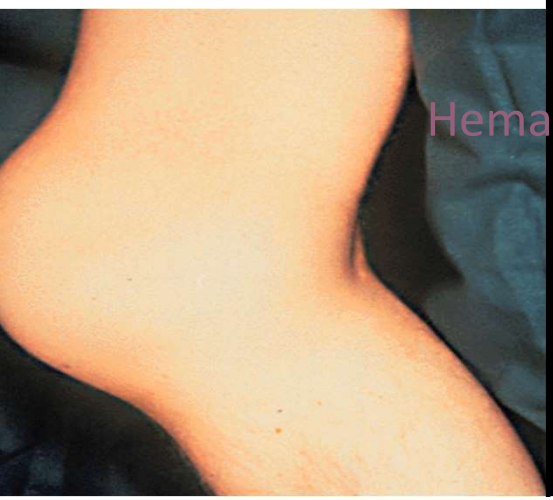




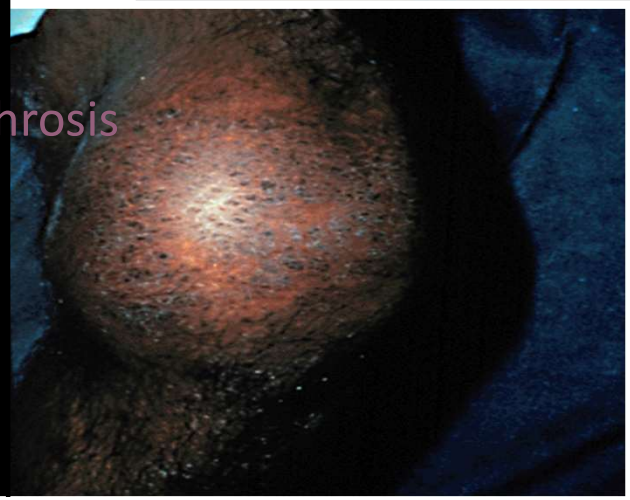


Ecchymoses





Hemarthrosis



52 year old male

Severe Hemophilia

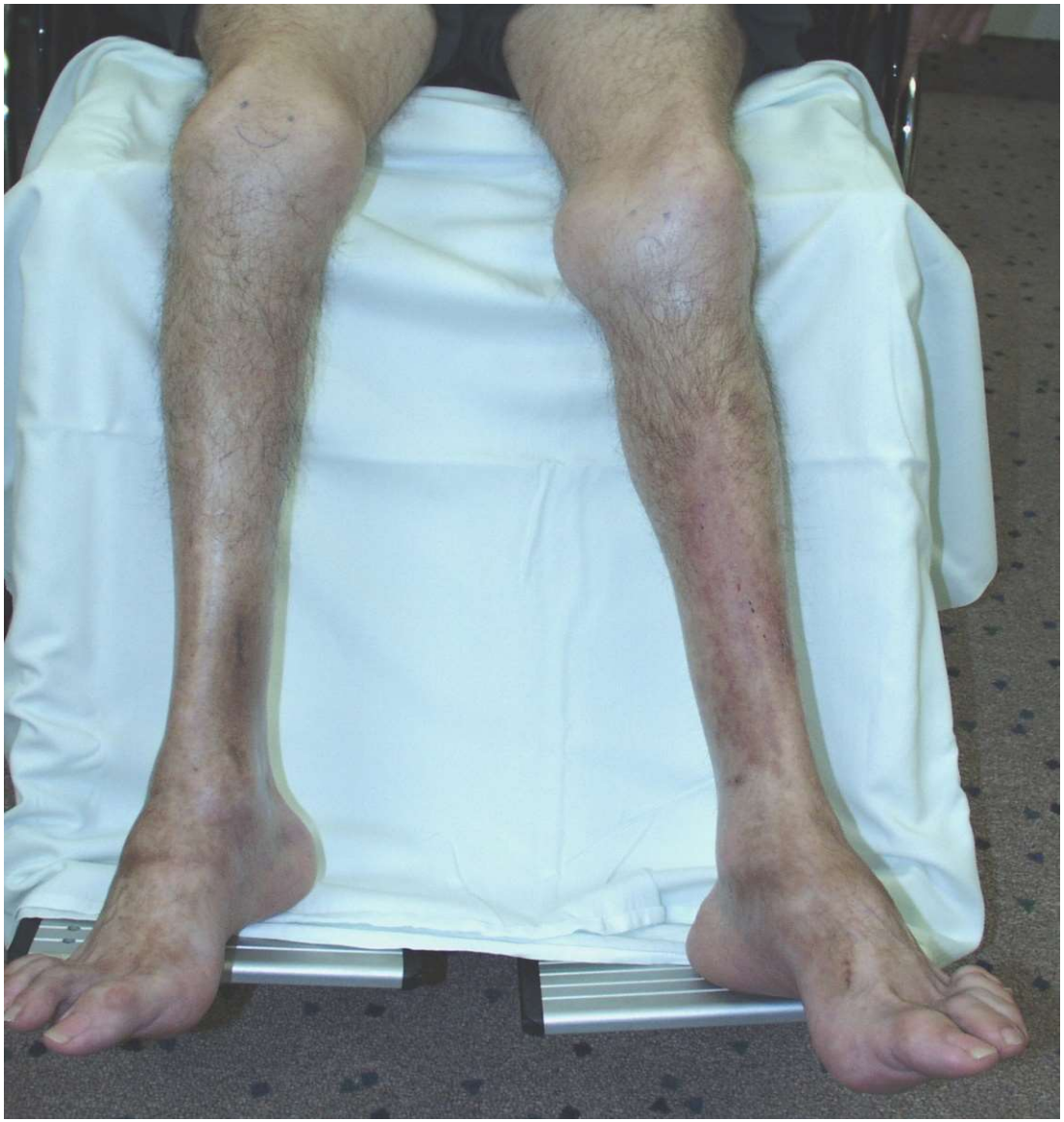
Now bleeds 3x month

Severe muscle wasting

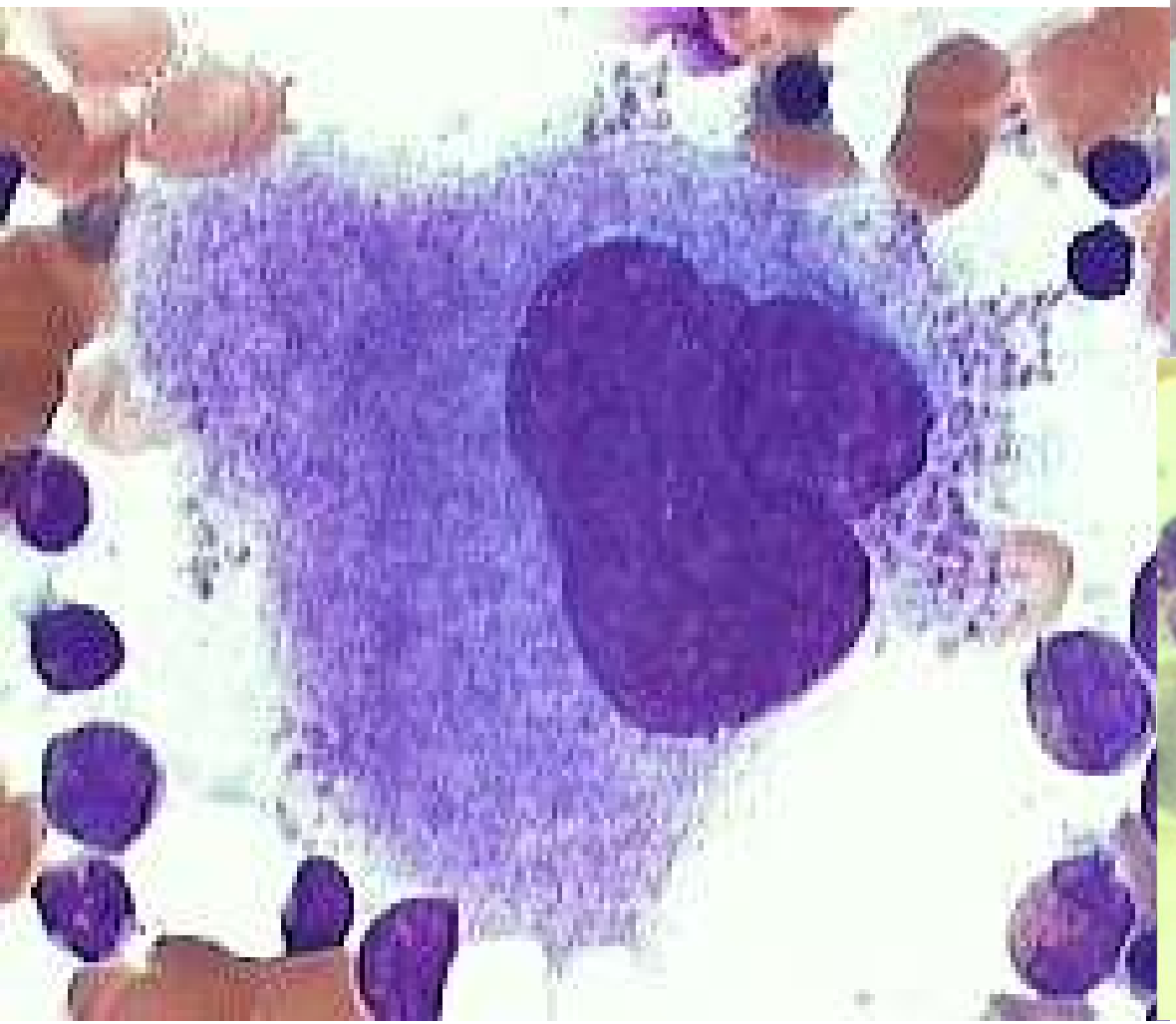
Joint immobility

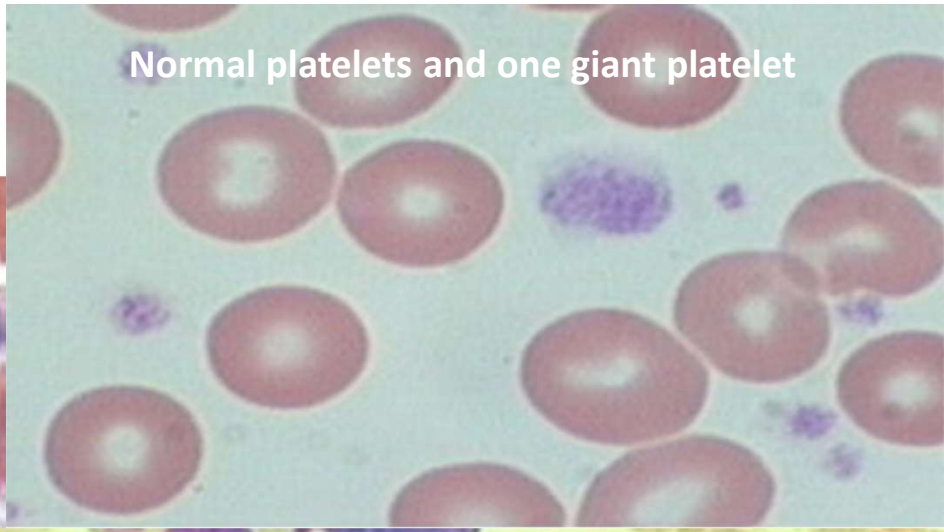
Atrophic skin changes

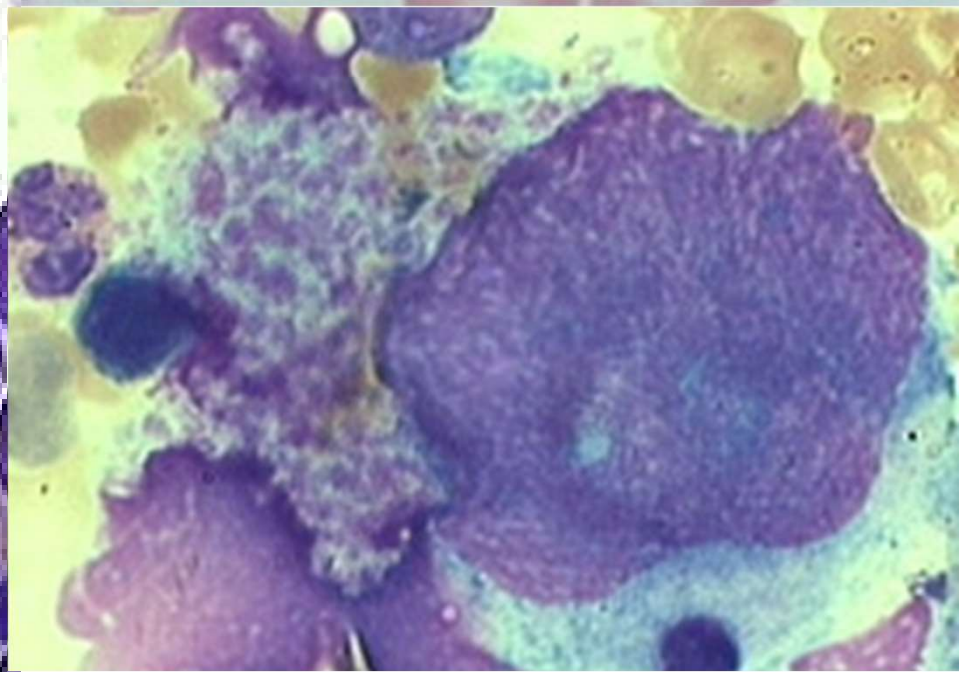
HIV and HCV +ve



Megakaryocyte







Clinical View: Bleeding and Blood Clotting Disorders[1]

Hemophilia: bleeding disorders

- **Hemophilia A** and **hemophilia B** most common
  - Occur in X-linked recessive pattern
  - Males exhibit full-blown disease; females typically carriers
  - Result from deficiency of factor VIII, factor IX, or factor XI (more rare)

Thrombocytopenia: platelet deficiency

- Increased breakdown or decreased production
- May occur in bone marrow infections or cancer

Certain drugs interfere with clotting (can cause bleeding)

- E.g., aspirin, ibuprofen, warfarin, ginkgo

Clinical View: Bleeding and Blood Clotting Disorders 2

Hypercoagulation

- Increased tendency to clot blood
- Can lead to **thrombus,** blood vessel clot
- When dislodged within blood, **embolus**
- If lodges in lungs, **pulmonary embolism**
  - Can cause breathing problems and death
- Can have drug-related, environmental, and genetic causes
  - E.g., birth control pills, prolonged inactivity

. "Teenage boy with joint swelling and prolonged bleeding after dental procedure":

- Likely **Hemophilia A/B**
- Inheritance: **X-linked recessive**
- Labs: **↑ aPTT, normal PT/BT**

Woman with heavy periods, nosebleeds, prolonged bleeding after surgery, and normal platelet count":

- Think: **vWD**
- Labs: **↑ BT**, **↑ aPTT**
- Treatment: **Desmopressin (↑ vWF release)**

"Patient on heparin develops thrombocytopenia and clots":

- Diagnosis: **HIT (Heparin-Induced Thrombocytopenia)**
- Pathogenesis: IgG to **PF4–Heparin** complex → platelet activation
- Switch to: **Argatroban or fondaparinux**