Tutorial on mechanisms of coagulation bleeding and clotting disorders

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Objectives

1. Recognize different stages of hemostasis
2. Describe formation and development of platelet
3. Describe the role of platelets in hemostasis
4. Recognize different clotting factors
5. Describe the cascade of clotting
6. Describe the cascade of intrinsic pathway
7. Describe the cascade of extrinsic and common pathways
8. Recognize the role of thrombin in coagulation
9. Recognize process of fibrinolysis and function of plasmin

Haemostasis

Hemostasis: The spontaneous arrest of bleeding from ruptured blood vessels, (prevention of blood loss after injury)

Mechanisms: hemostasis have 4 stages

Dr's note: you should know the difference between Haemostasis and Homeostasis

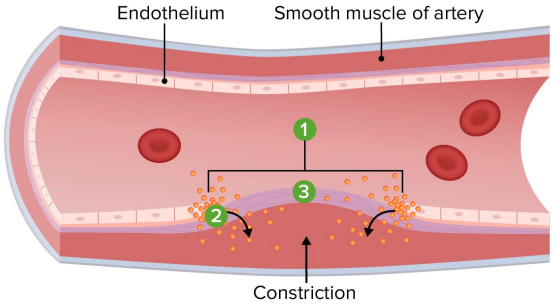
1. Vessel wall Constriction
2. Platelet: temporary hemostatic plug
3. Blood coagulation: Conversion of the temporary plug into a definitive clot by fibrin threads
4. Fibrinolytic system (Clotting is prevented (controlled) over the normal endothelium)

Vessel wall

Vessel wall:

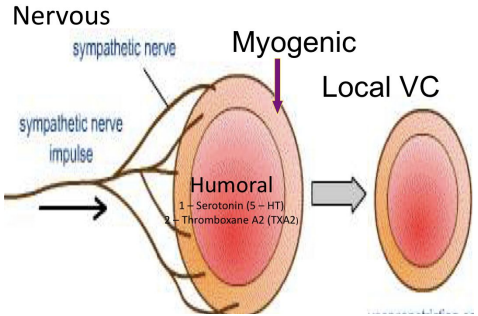
Immediately After injury a localized (transient response)

Vasoconstriction (VC) it reduces the amount of blood loss



Mechanism:

- Myogenic spasm: smooth muscle contraction
- Nervous factors
- Humoral factors: hormones and substances in the blood
  - Systemic release (away from the site of injury) of adrenaline (epinephrine)
  - Local release of thromboxane A2(TxA2) and Serotonin



Platelets (PLT)

Thrombocytes (Platelets): are fragments of megakaryocytes in the bone marrow

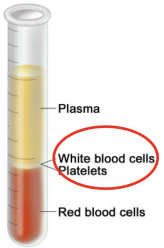
Shape: Small disc shaped granulated, Non nucleated structures

Count: 150x10^3-300x10^3/ml

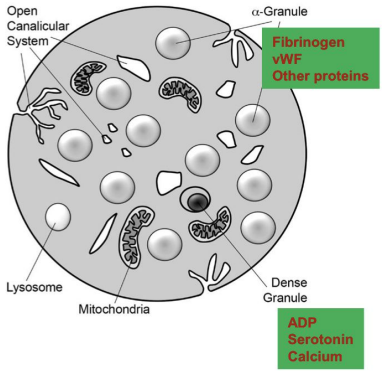
Life span: 8-12 days (mnemonic: pl8lets)

Contain:

- High calcium content
- Rich in ADP



Active cells contain: contractile protein: actin and myosin



α Granule:

- Fibrinogen , VWF (Von Willebrand Factor)

Dense Granules:

- ADP , Serotonin 5-HT , Calcium

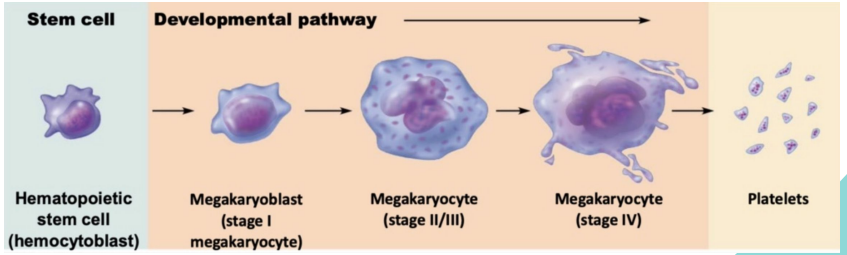
Open canalicular system: canals for release substances and entrance for stimuli

Regulation of thrombopoiesis (Thrombocytes synthesis) By: Thrombopoietin (Glycoprotein hormone produced in the liver)

Site of formation: Bone marrow

Steps:

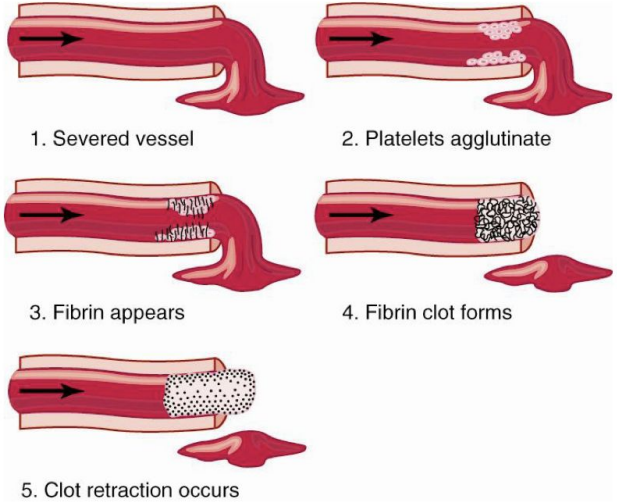
Stem cell ➜ Megakaryoblast ➜ Megakaryocyte ➜ Platelets



Platelet functions

Platelet Activation:

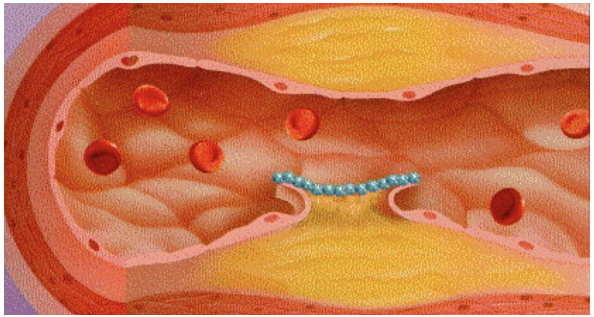
- Adhesion
- Activation (Shape change)
- Release reaction
- Aggregation
- Fusion
- Clot Retraction



HELPFUL VIDEO !!

Platelet Adhesion

Exposed collagen attracts platelets



Platelets stick to Von WilleBrand Factor VWF released from the damaged endothelial cells in the exposed subendothelial collagen tissue underlying damaged endothelial cells in vessel wall

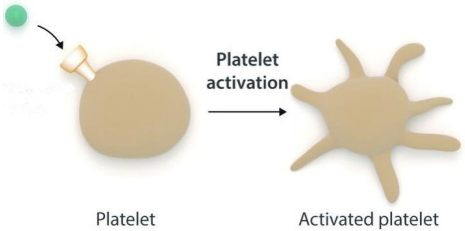
Intact (uninjured) endothelium secret prostacyclin (PGI2) and nitric oxide ➜ inhibit platelet aggregation

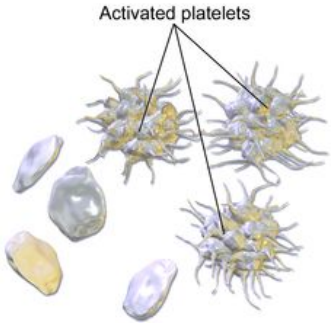
Mnemonic: Prosta**cyclin** keeps the blood **cyclin**

vWf stick to collagen -> platelets stick to vWf

Platelet Activation

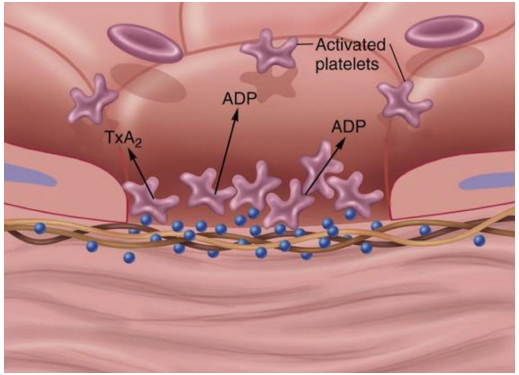
Platelet activate by adhesion.
- Extend projection to make contact with each other (med441:Shape change)
- Platelets become sticky





Platelet Release Reaction

- Activated platelets release their contents which stored in the granules Serotonin, ADP & Thromboxane A2
- (Aspirin blocks Thromboxane A2)
- Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel
- ADP & Thromboxane A2 (TxA2) → the stickiness of platelets (Activate the platelets) → Platelets aggregation → plugging of the cut vessel



TxA2 is prostaglandin in the cell membrane, it's not stored in the granules

Girls slides only

Platelet Release Secrete

1. 5-HT Serotonin , TxA2 → vasoconstriction
2. ADP → activate the platelets
3. Platelet phospholipid (PF3) → clot formation
4. Thromboxane A2 (TxA2) is a prostaglandin formed from arachidonic acid (cell membrane)

Function:

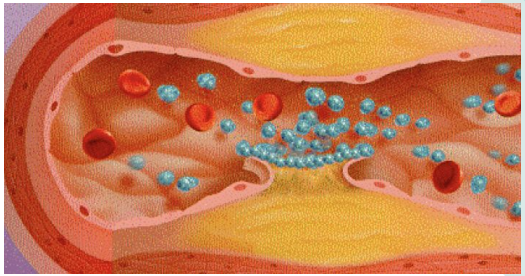
- vasoconstriction
- Platelet aggregation

(TXA2 inhibited by aspirin)

Platelet Aggregation

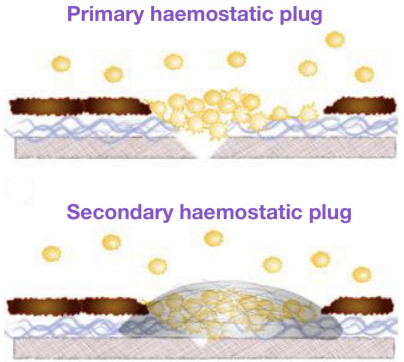
Activated platelets stick together and activate new platelets to form a mass called a platelet Plug (Primary haemostatic plug)

Plug reinforced by fibrin threads formed during clotting process (Secondary haemostatic plug)



Platelet Plug formation Cont..

- The platelet plug is a loose plug that is usually successful in blocking the blood loss if the vascular opening is small
- Then, during the process of blood coagulation, the stronger fibrin threads are formed that will strengthen the platelet plug



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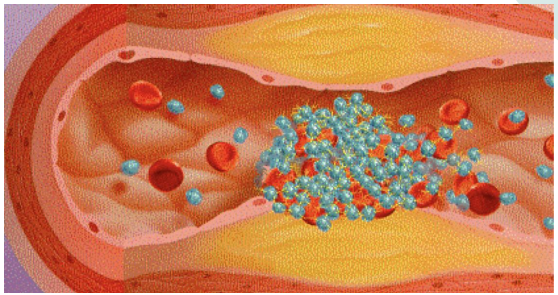
Clot Retraction

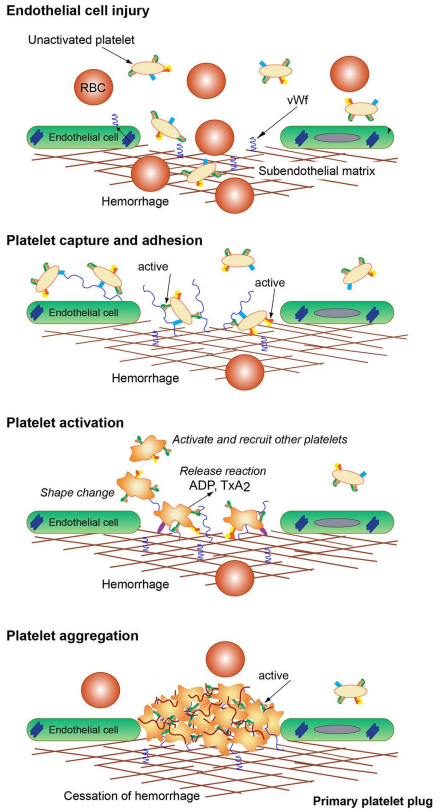
Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.



Boys slides

Platelet plug formation

Steps	Substances involved	Characters
Platelet adhesion	Subendothelial collagen and Von Willeberand factor. ??	Occurs to the subendothelial tissue.
Platelet activation	ADP and Thrombin	Platelets enlarge and forms pseudopodia.
Release reaction	Calcium ions	Calcium dependent process
Platelet aggregation	ADP Thromboxane A2 (TXA2). Fibrinogen	This process is inhibited by Aspirin which inhibits the formation of TXA2.
Platelet fusion	ADP	Irreversible process
Clot retraction	Actin and myosin contract to strengthen the plug.	Causes stabilization of the formed blood clot.

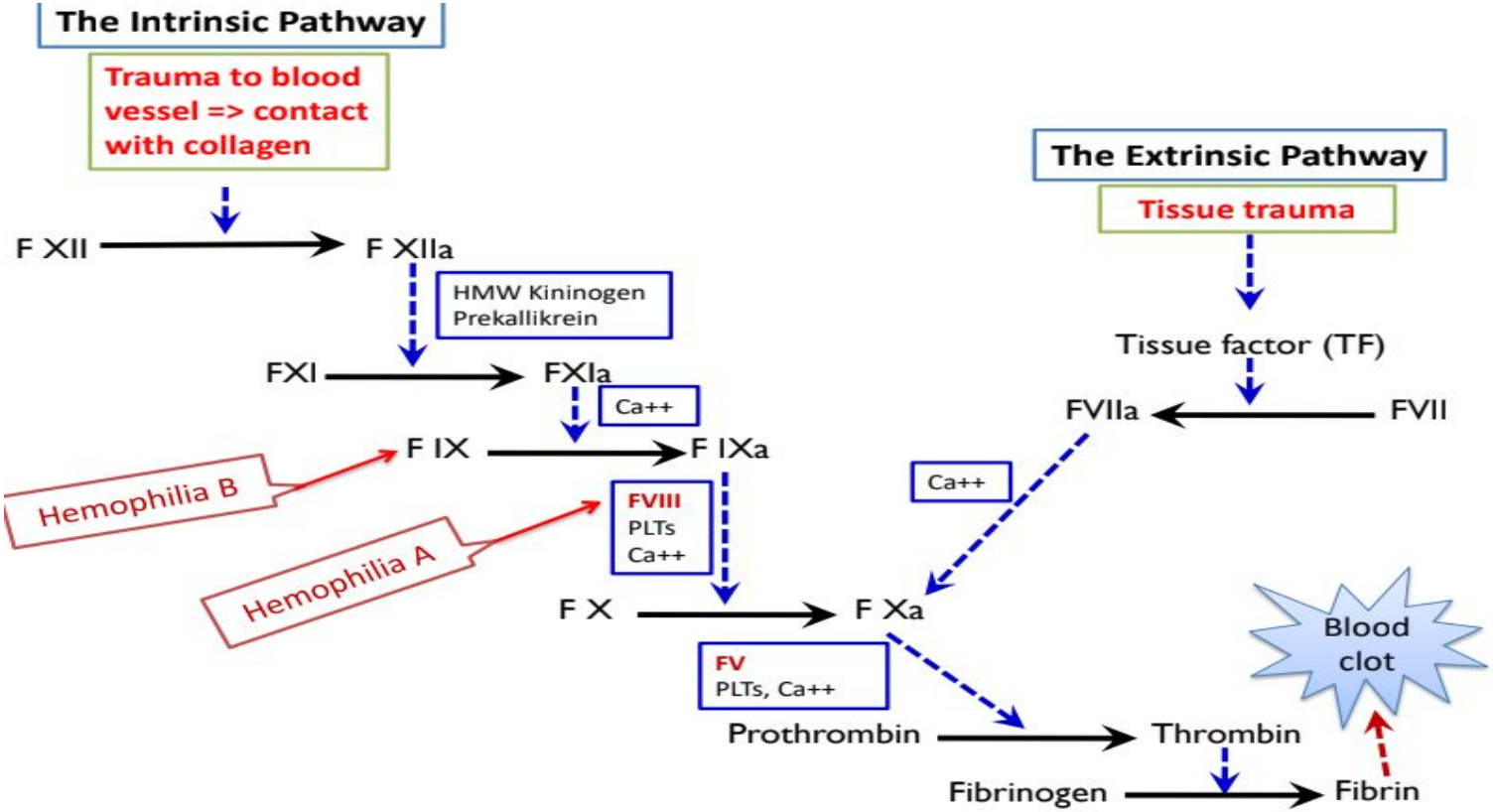


Blood Coagulation

Initiation on blood coagulation occurs by two ways:

1. The extrinsic pathway: initiated by trauma to the tissue.

2. The intrinsic pathway: initiated by injury to the blood vessel.

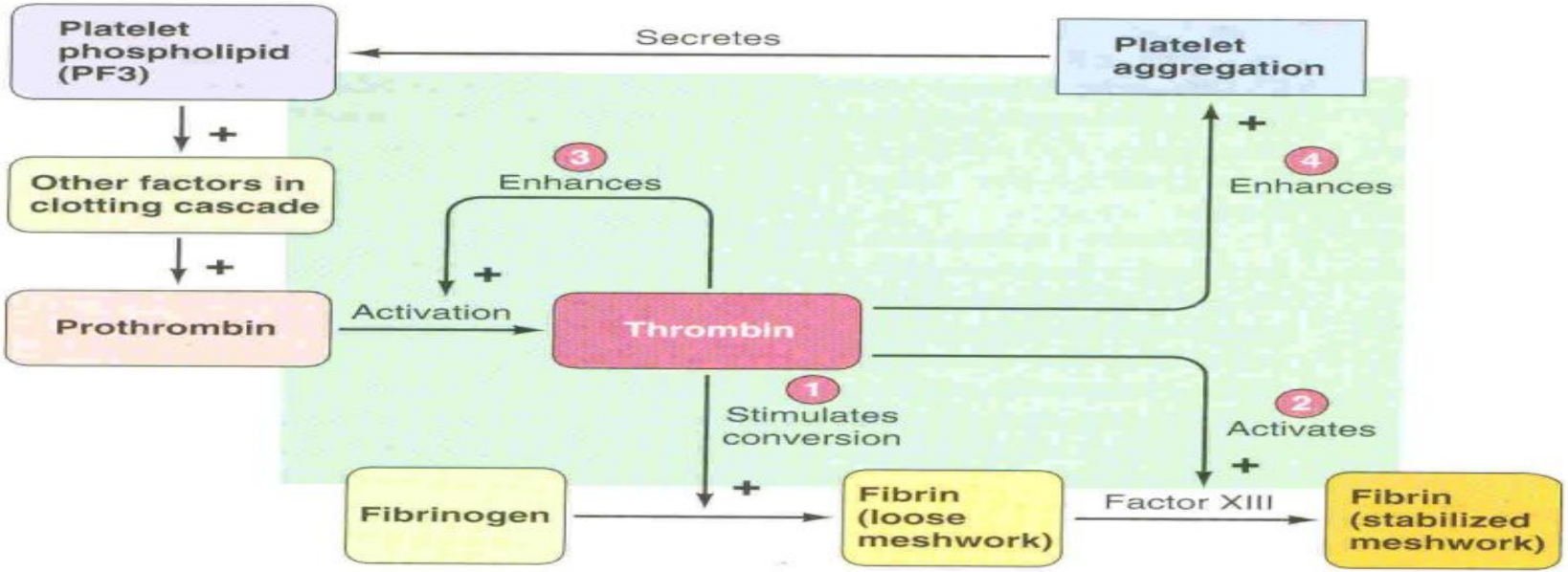

The Intrinsic Pathway
Trauma to blood vessel => contact with collagen
F XII
F XIIa
HMW Kininogen
Prekallikrein
FXI
FXIa
Ca++
F IX
F IXa
Hemophilia B
Hemophilia A
FVIII
PLTs
Ca++
F X
F Xa
FV
PLTs, Ca++
Prothrombin
Thrombin
Fibrinogen
Fibrin
Blood clot
The Extrinsic Pathway
Tissue trauma
Tissue factor (TF)
FVIIa
FVII
Ca++

ROLE OF CALCIUM IONS IN CLOTTING

No Ca++ ⟶ No Clotting

- Blood samples are prevented from clotting by adding:
  - Citrate ions ⟶ Deionization of Ca++
  - Oxalate ions ⟶ Precipitate the Ca++

ROLE OF THROMBIN IN HEMOSTASIS



Coagulation Defects

Hepatic (liver) Disease

e.g. Hepatitis, Cirrhosis
Decreased formation of clotting factors
Increased clotting time

II. Vitamin K deficiency

required for Factor's II (prothrombin), VII, IX, and X

III. Hemophilia
Factor VIII (hemophilia A , 1/10,000), (Mnemonic: Hemophilia A = factor 8 (Aight)
Factor IX (hemophilia B, 1/100,000)

IV. Thrombocytopenia
Low number of platelets

COAGULATION PROFILE

Blood Parameters	Conditions
Bleeding Time (BT)	Thrombocytopenia Von Willebrand Disease
Clotting Time (CT)	Hemophilia A & B
Prothrombin Time (PT)	Vitamin K Deficiency (Vitamin K dependent factors deficiency)
Activated Partial Thromboplastin Time (aPTT)	Hemophilia A & B
International Normalization Ratio (INR)	Warfarin Monitoring

HEMOPHILIA (types)

HEMOPHILIA - A
– Classic Hemophilia
– 85 % cases
– Def. Of factor VIII

HEMOPHILIA – B or CHRISTMAS DISEASE
– 15 % cases
– Deficiency of factor IX OR Christmas Factor
(It is named after the first person to be diagnosed with the disorder in 1952, Stephen Christmas)

HEMOPHILIA

Genetic disorders

- Transmitted by female chromosome as recessive trait, it is X linked.
- Occurs exclusively in male. Females are carriers.
- Clinical Features

Easy bruising, massive bleeding after trauma or operation, hemorrhages in joints.

– Rx

- Replacement of factor VIII (Hemophilia A)
- Replacement of factor IX (Hemophilia B)

THROMBOCYTOPENIA

- PLT count upto 50,000 ul
- Less than 10,000 ------ Can be Fatal
- ETIOLOGY
- Decreased production

– Aplastic anemia
– Leukemia
– Drugs
– Infections (HIV, Measles)

DRUGS CAUSING THROMBOCYTOPENIA

Heparin is the most common cause of drug-induced immune thrombocytopenia.

Other medicines that cause drug-induced thrombocytopenia include:

- Furosemide
- Gold, used to treat arthritis
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Penicillin
- Quinidine
- Quinine
- Ranitidine
- Sulfonamides
- Linezolid and other antibiotics
- Statins
- Chemotherapeutic agents.
- Valproic acid

THROMBOCYTOPENIA

Clinical Features
– Easy brusability
– Epistaxis
– Gum bleeding
– Hemorrhage after minor trauma
– Petechiae/Ecchymosis

THROMBOCYTOPENIA

Diagnosis
– PLT decreased
– Bleeding Time increased
▪ Rx
– Rx of the underlying cause
– PLT concentrates
– Fresh whole blood transfusion
– Splenectomy

MCQs

1- Which of the following stimulates Hemostasis?			
A)hypoxia	B)exposed collagen	C)bacterial infection	D)malnutrition
2- Exposed collagen attracts?			
A)Factor X	B)Platelet	C)F VII	D)ADP
3- Which one of the following inhibits platelet aggregation:			
A)serotonin	B)interleukin	C)thromboxane A2	D)prostacyclin
4- Which one of the following stimulate platelet aggregation:			
A)serotonin	B)interleukin	C)thromboxane A2	D)prostacyclin

SAQ

1)List 4 substances released from platelets and mention one function for each:

2)Define Platelet Aggregation:

1)
- 5-HT (Serotonin) —> Vasoconstriction
- Thromboxane A2 —> Vasoconstriction & platelet aggregation
- ADP —> Platelet aggregation
- Thrombin —> Activate factors (I, V, VIII, XIII) & platelet activation
- PF3 —> clot formation

2)
Activated platelets stick together and activate new platelets to form a mass called platelet plug.

1-B
2-B
3-D
4-C

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