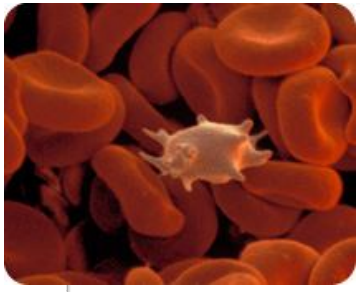


# Hemostasis

## hemo= blood +stasis = stop, cease

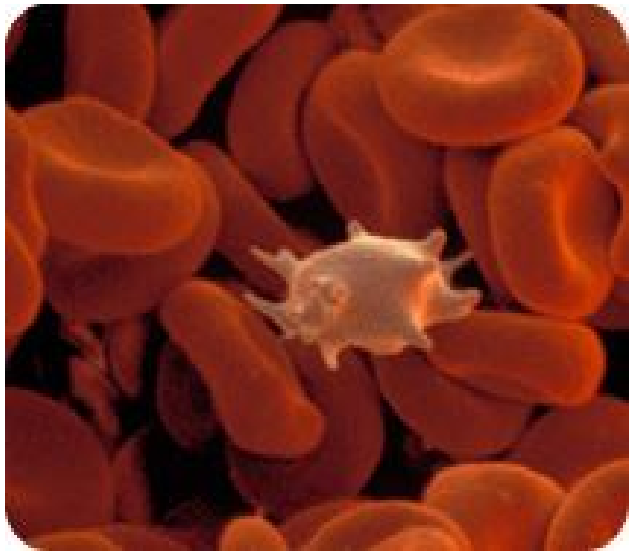
Hemostasis is the maintenance of circulating blood in the liquid state and retention of blood in the vascular system by preventing blood loss

**THE BODY'S RESPONSE IS FAST, LOCALIZED,CONTROLED**

**IT INVOLVES MANY COAGULATION FACTORS AND**

**THREE SEQUENCIAL STEPS**

1. **VASCULAR SPASM**
2. **PLATELET PLUG FORMATION**
3. **COAGULATION**



# VASCULAR SPASM

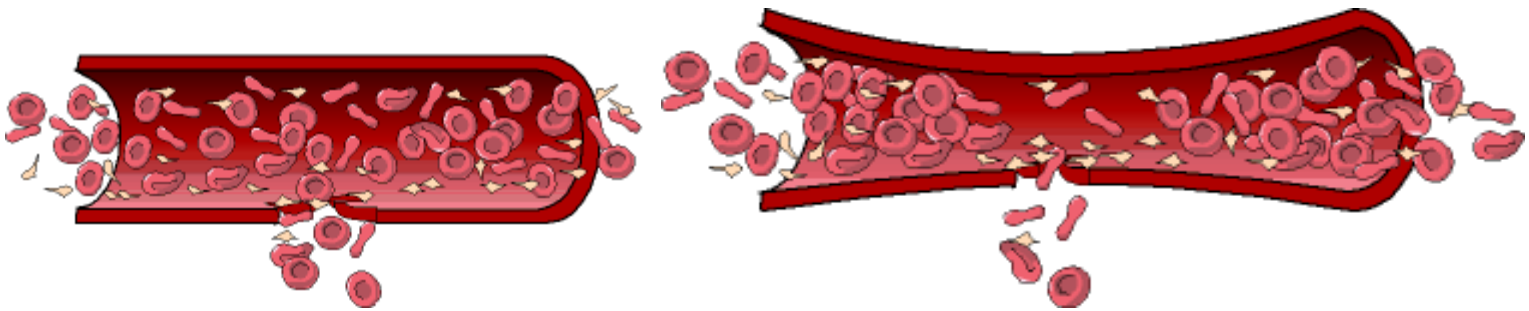
Immediate response is constriction of damaged blood vessels due to…

- **Direct injury to vascular smooth muscle**
- **Chemicals released by the endothelial cells and platelets**

**The more tissue damage the greater the response**

(positive feedback system)

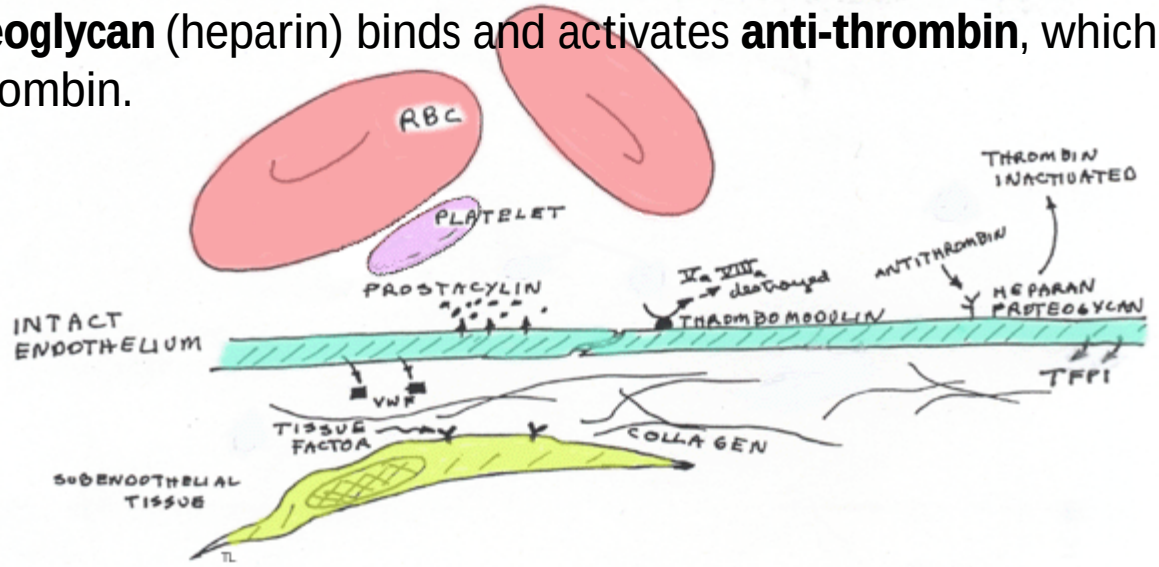
**This reflex allows time for the platelet plug to form and clotting to occur**

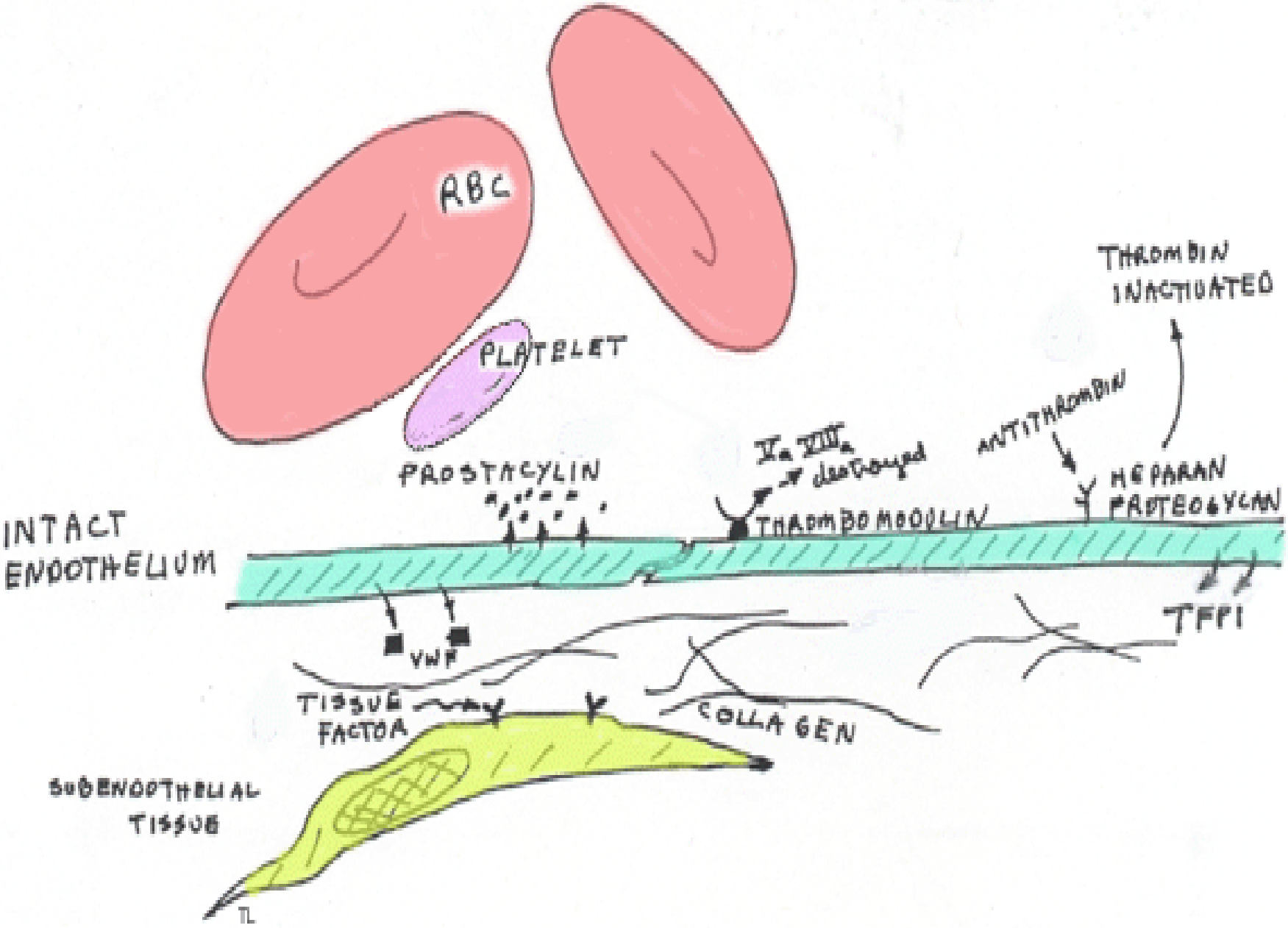


# Intact Endothelium

When the endothelium is intact and healthy, a clot should not form.
A number of factors keep a clot from forming under these circumstances.

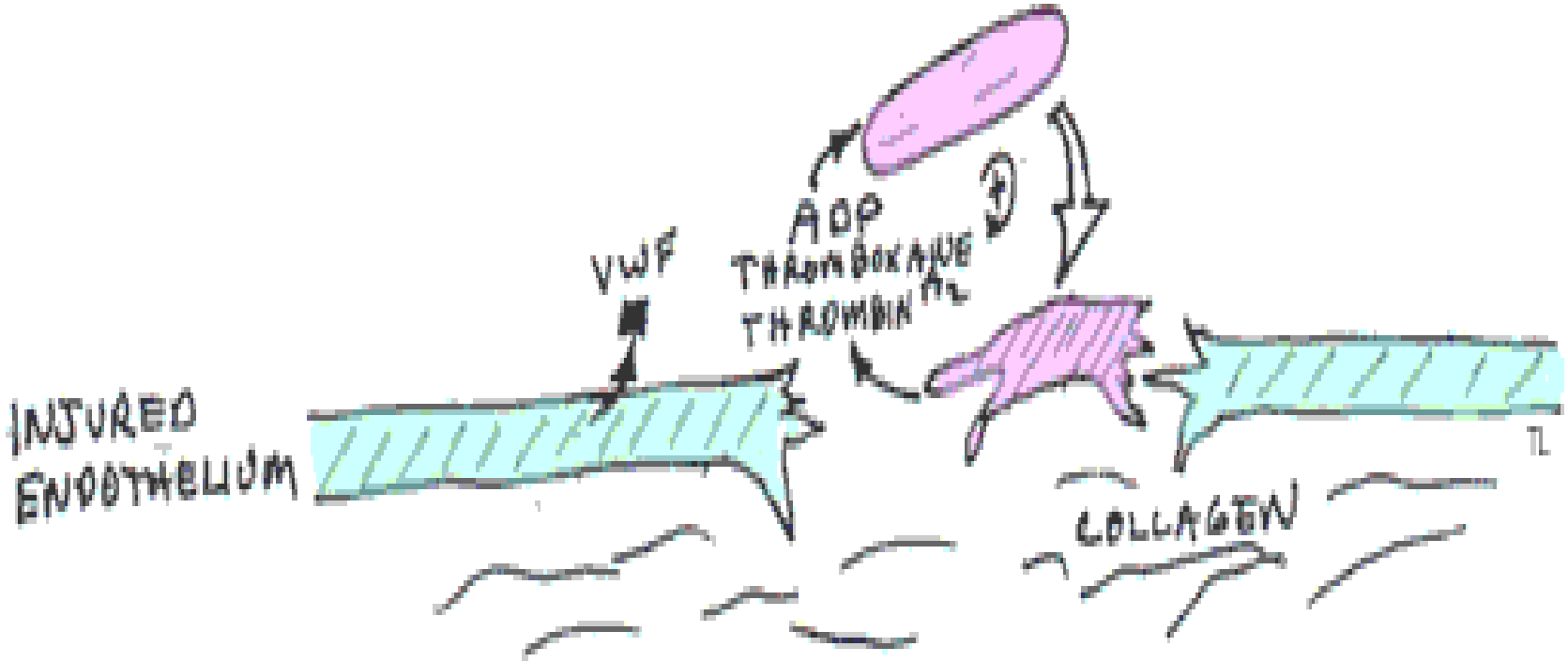
- **Collagen**, **tissue factor** and **VWF** remain out of contact the blood due to the intact endothelium.
- **Prostacyclin** (prostaglandin I2) is synthesized by the intact endothelium and prevents platelet activation.
- **Nitric oxide** is also released under these conditions, which keeps the blood vessels dilated
- **TFPI** (tissue factor pathway inhibitor, which is released from the endothelium, binds to tissue factor and keeps it inactive.
- **Thrombomodulin** binds thrombin and protein C, which activates protein C, which in turn inactives important clotting factors in the blood.
- **heparan proteoglycan** (heparin) binds and activates **anti-thrombin**, which in turn inactivates thrombin.

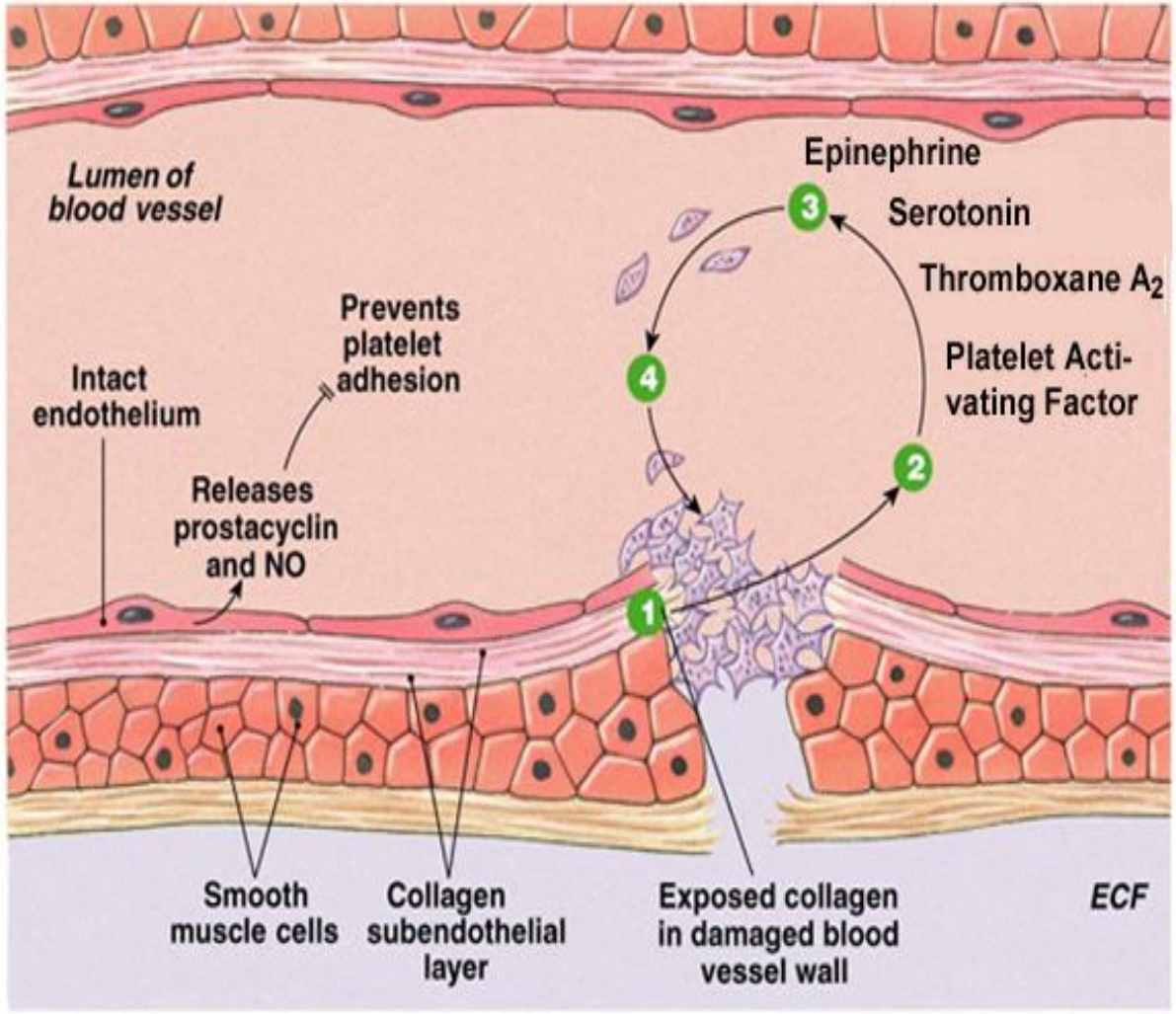



RBC
PLATELET
THROMBIN
INACTIVATED
ANTITHROMBIN
PROSTACYLIN
Xa XIIIa
deactivated
HEPARAN
PROTEOGLYCAN
INTACT
ENDOTHELIUM
THROMBOMODULIN
TFPI
VWF
TISSUE
FACTOR
COLLAGEN
SUBENDOTHELIAL
TISSUE

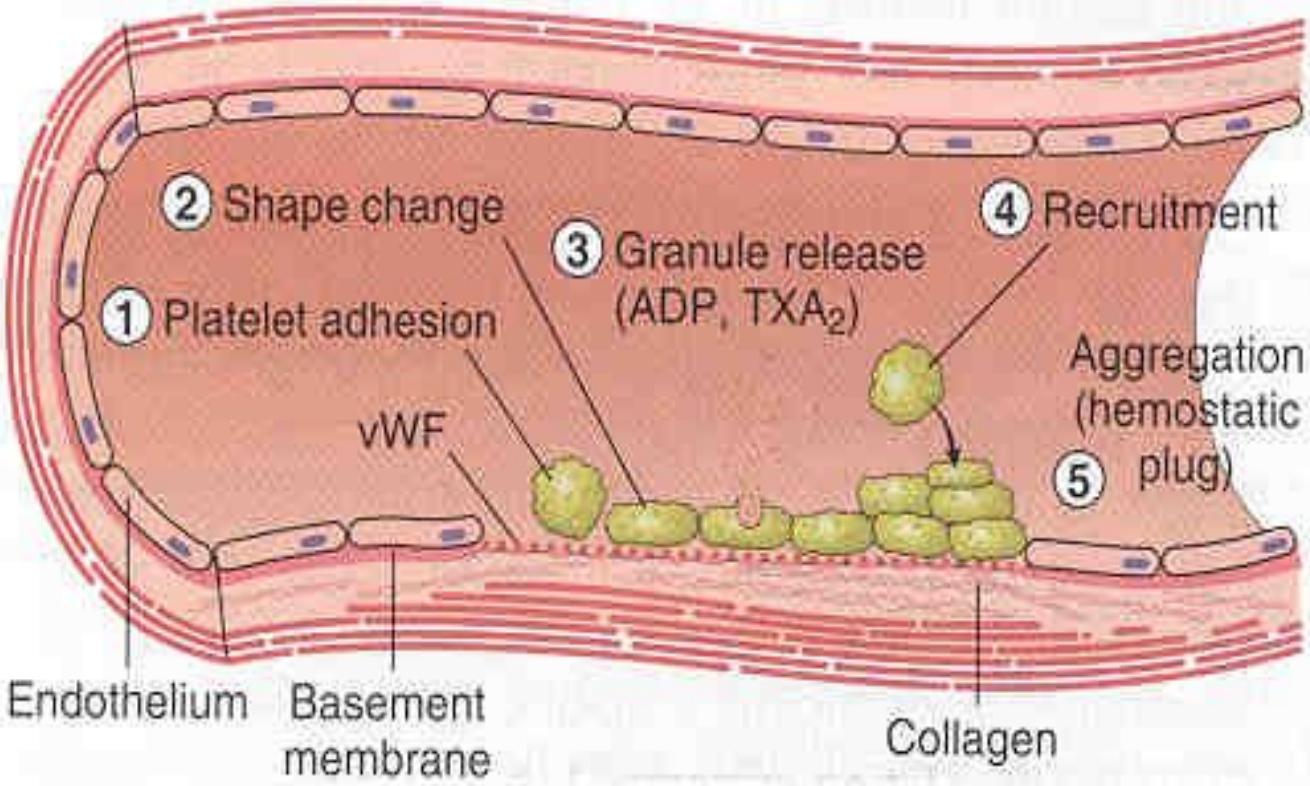
# Platelet Plug Starts to Form

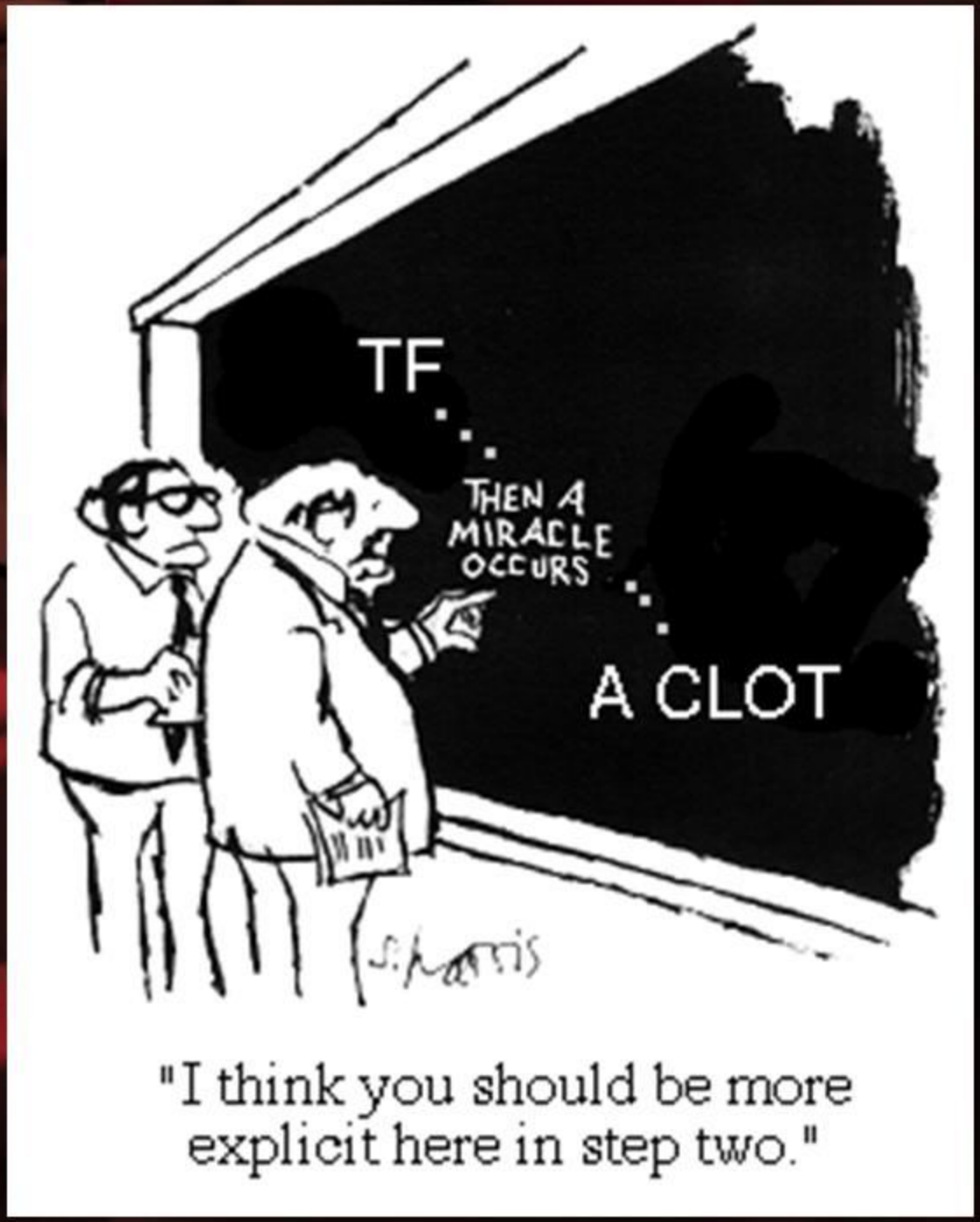
A break in the endothelium allows platelets to contact collagen and the other factors that activate platelets. Platelets begin adhering to one another and the subendothelial tissue via **fibrinogen and VWF receptors**. If the break is small, this **platelet plug** may be adequate to seal the break.





B. PRIMARY HEMOSTASIS



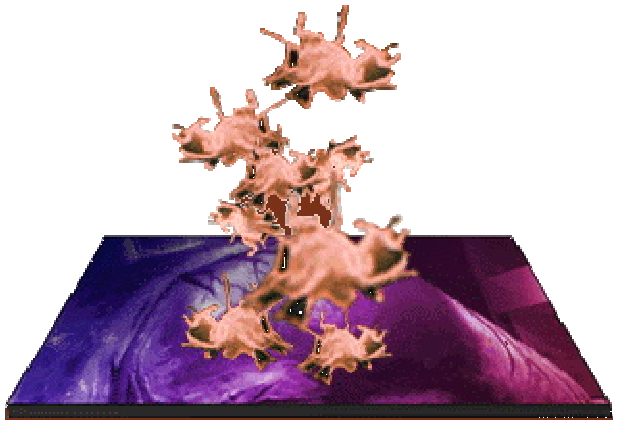



**A good model should also be complicated enough to reflect the realities of the biological system.**

With apologies to Sidney Harris.

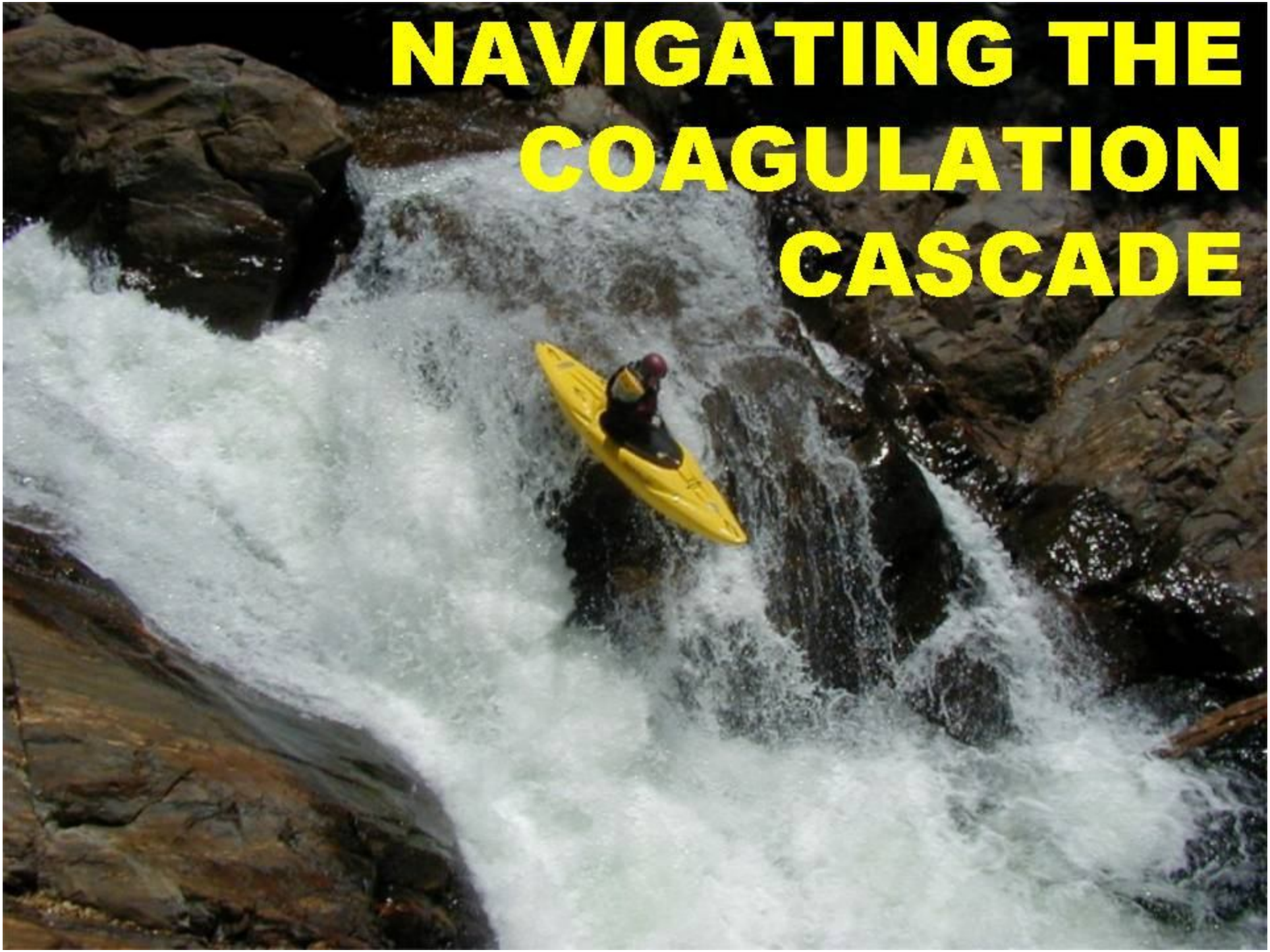
**Platelets remain disc shaped and inert in a normal environment, when epithelium is disrupted**
**Exposing collagen, platelets become ACTIVATED the following sequence occurs...**

- ADHESION
- ACTIVATION
- PRIMARY AGGREGATION
- SECRETION
- SECONDARY AGGREGATION



## Factors that will cause platelet activation are:

- **Exposure to collagen from vascular injury**
- **ADP (causes the platelet membrane to shift and expose receptor sites)**
- **Platelet activation factor (released by monocytes and macrophages)**
- **Thrombin ( is activated prothrombin)**
- **Epinephrine (platelet aggregation)**
- **Thromboxane A (prostiglandin=platelet aggregation)**


NAVIGATING THE
COAGULATION
CASCADE

# COAGULATION IS A MULTISTEP PROCESS

**GOAL:**

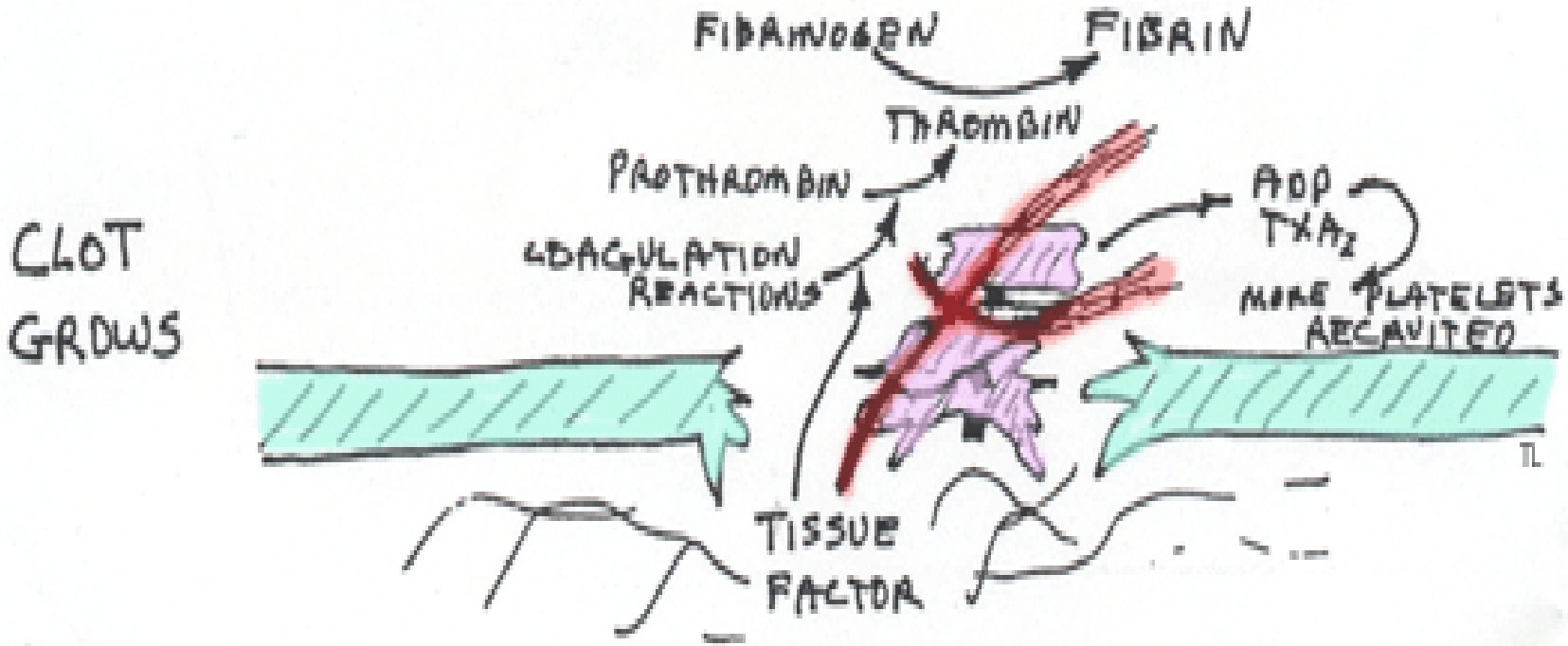
**IS TO SEAL THE BREAK IN THE BLOOD VESSEL WALL WITH A FIBRIN MESH TO ALLOW PERMAMENT REPAIR OF VESSEL WALL TO OCCUR**

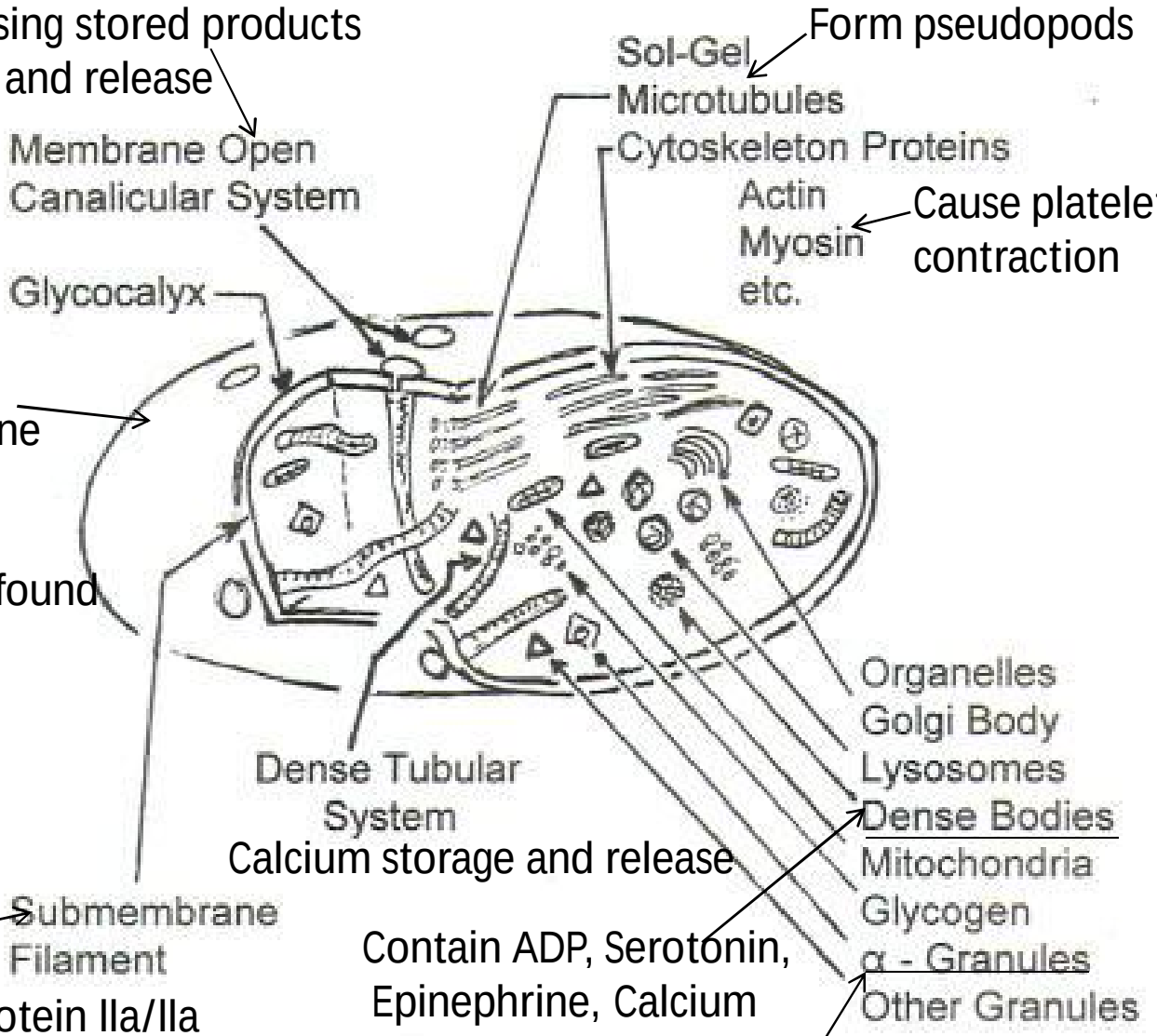
**OVER 30 DIFFERENT SUBSTANCES INVOLVED:**
**FACTORES THAT ENHANCE CLOTTING FORMATION ARE CALLED PROCOAGULANTS FACTORS THAT INHIBIT CLOTTING ARE CALLED ANTICOAGULANTS**

**NOTE: THERE IS MORE ANTICOAGULANTS THAN COAGULANTS AND CLOTTING IS PREVENTED.**
**WHEN VESSELS RUPTURE PROCOAGULANT ACTIVITY INCREASES DRAMATICALY TO PREVENT BLOOD LOSS.**

# Coagulation Reactions Begin at Surface of Platelet

Coagulation reactions begin occuring more rapidly since tissue factor is exposed and the surface of activated platelets provides the environment for the activation of the cascade that ultimately converts prothrombin to thrombin. The developing clot consists of interlaced fibrin fibrils and activated platelets.



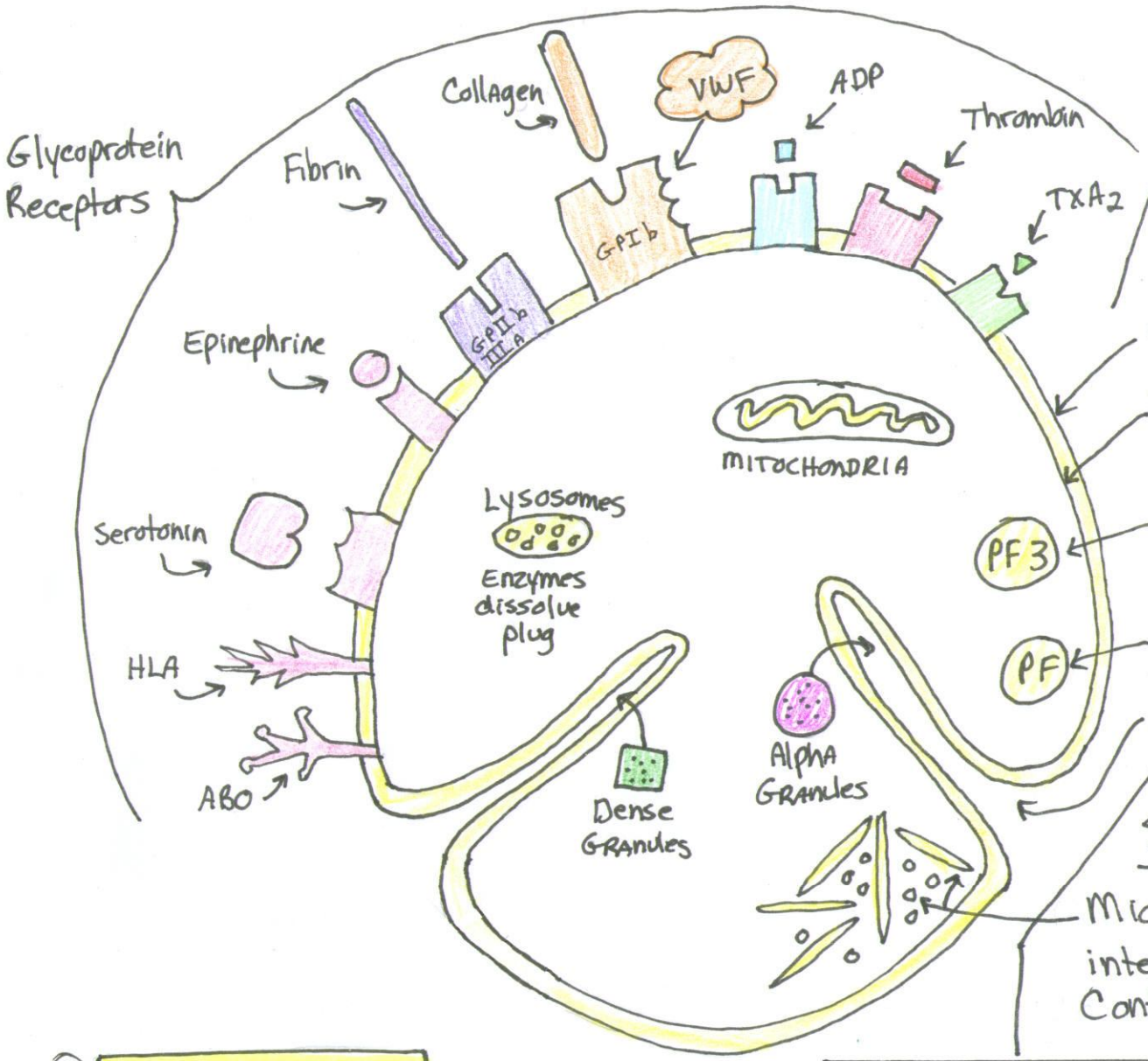



Receptor sites for:
Fibrinogen, fibronectin
vonWillebrand F, epinephrine
thrombin ,ADP, serotonin.
platelet factors PF1-PF7 &
coagulation FV and VIII are found
on membrane

Contains Glycoprotein Ib,
Receptor for vWF &Glycoprotein IIa/IIa
Receptor for fibrinogen

Contain ADP, Serotonin,
Epinephrine, Calcium

Contains Platelet fact.1-7, platelet derived growth factor, fibrinogen, vWF, Factor V,
B-thromboglobulin, fibronectin, Plasminogen, proteinS, IgG, thrombospodin




## Peripheral Zone (Adhesi interac

Glycocalyx (exterior coA

Phospholipid Membrane (reg c
For F10 and prothrombin ac

PF-3 moves membrane to ex
phospholipids to Vit K cofa

Various other platelet fa

OCS = Open canicular sys

## Sol-Gel Zone (cytoskele

Microtubules of Actin and my
interwoven throughout cell.
Contraction = shape change

## Organelle Zone (metabolic activities)

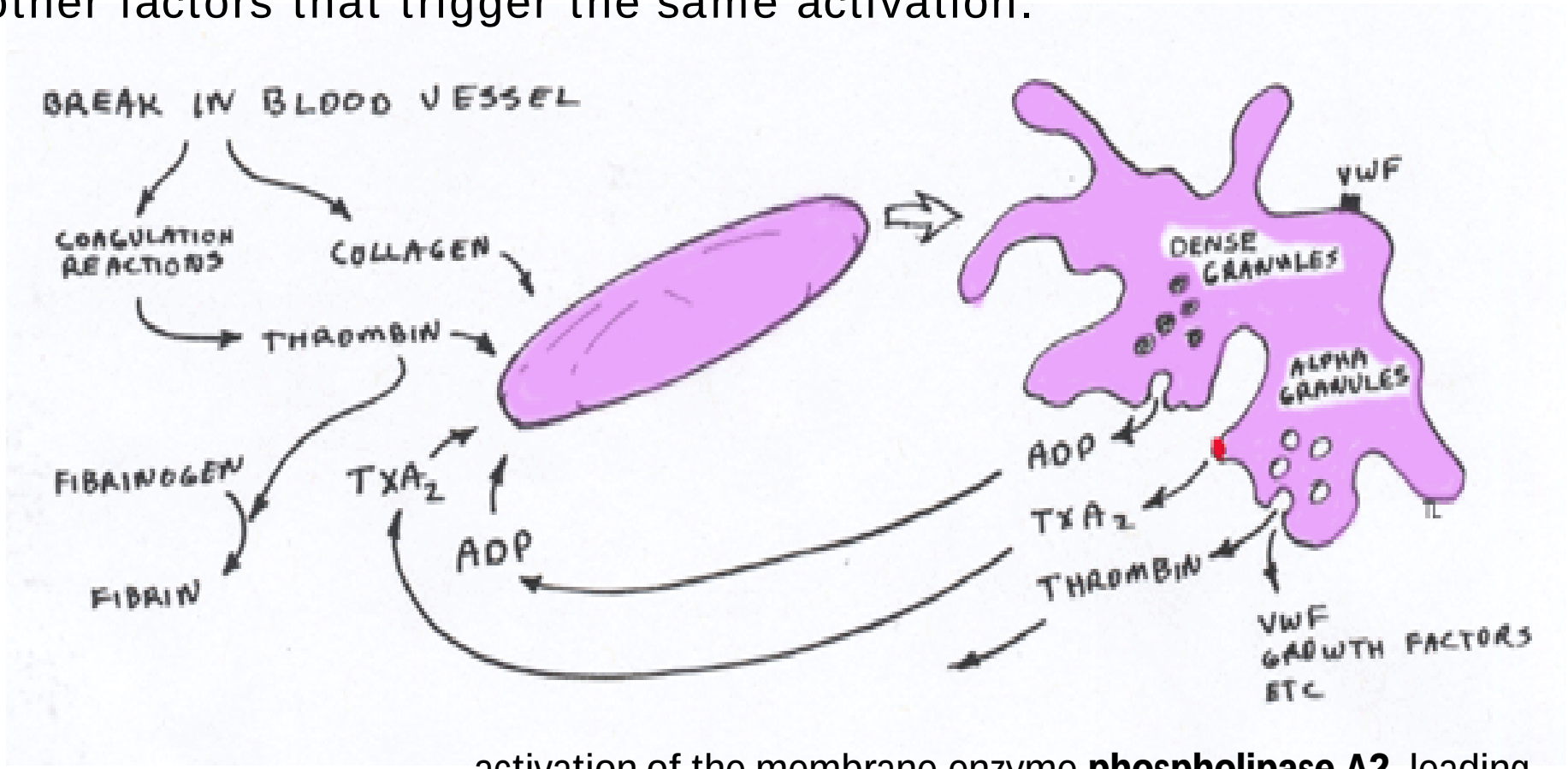
* No Nucleus

1) Dense Granules: ADP ATP $Ca^{++}$ Serotonin, Phosph

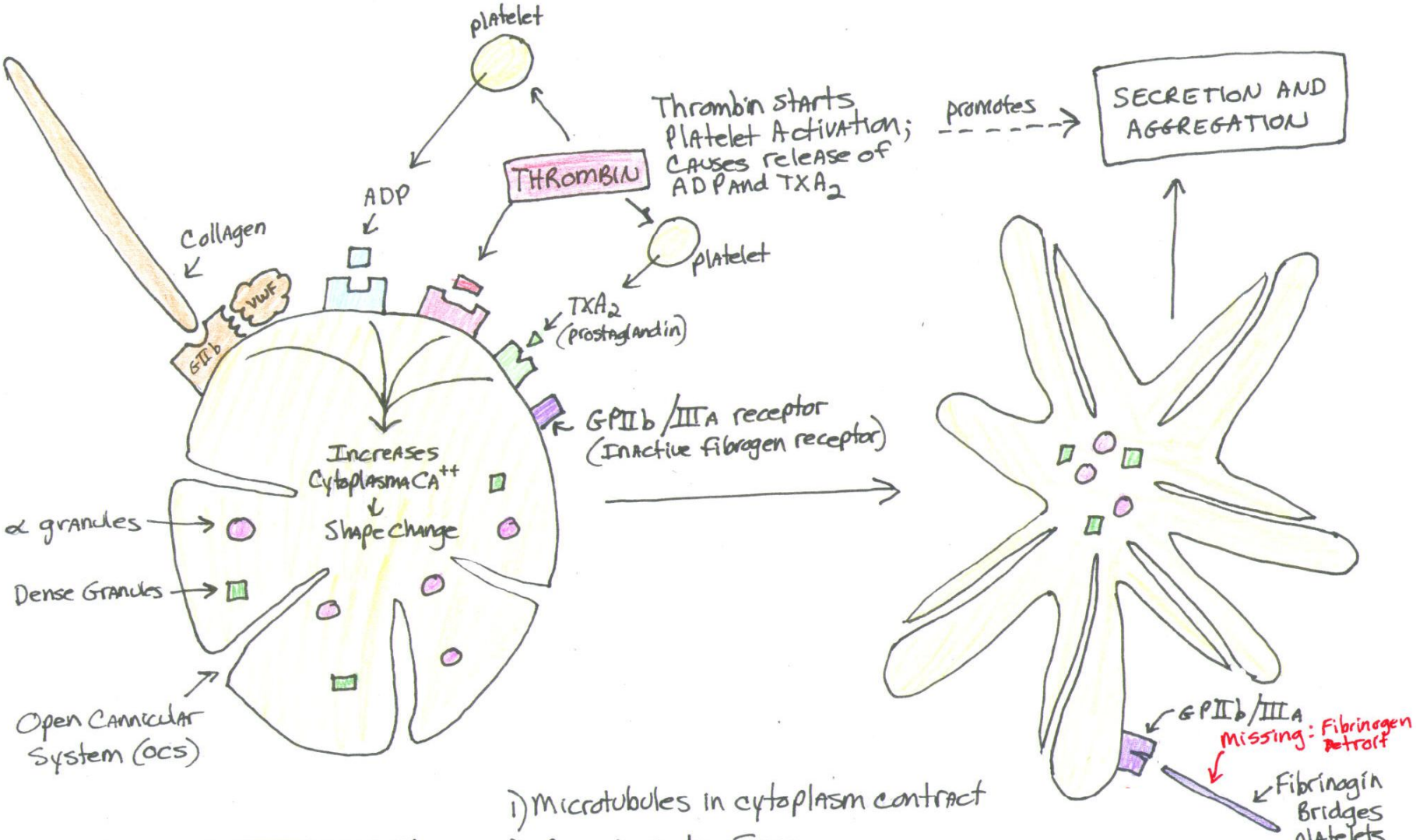
(2) PLATELET MORPHOLOGY

# Platelet Activation

When a platelet encounters a break in the endothelium, it encounters molecules that trigger its activation. One such molecule is **collagen**, which is characteristically found almost everywhere except inside a blood vessel. In addition, **thromboxane A2**, **ADP** and **thrombin** are other factors that trigger the same activation.



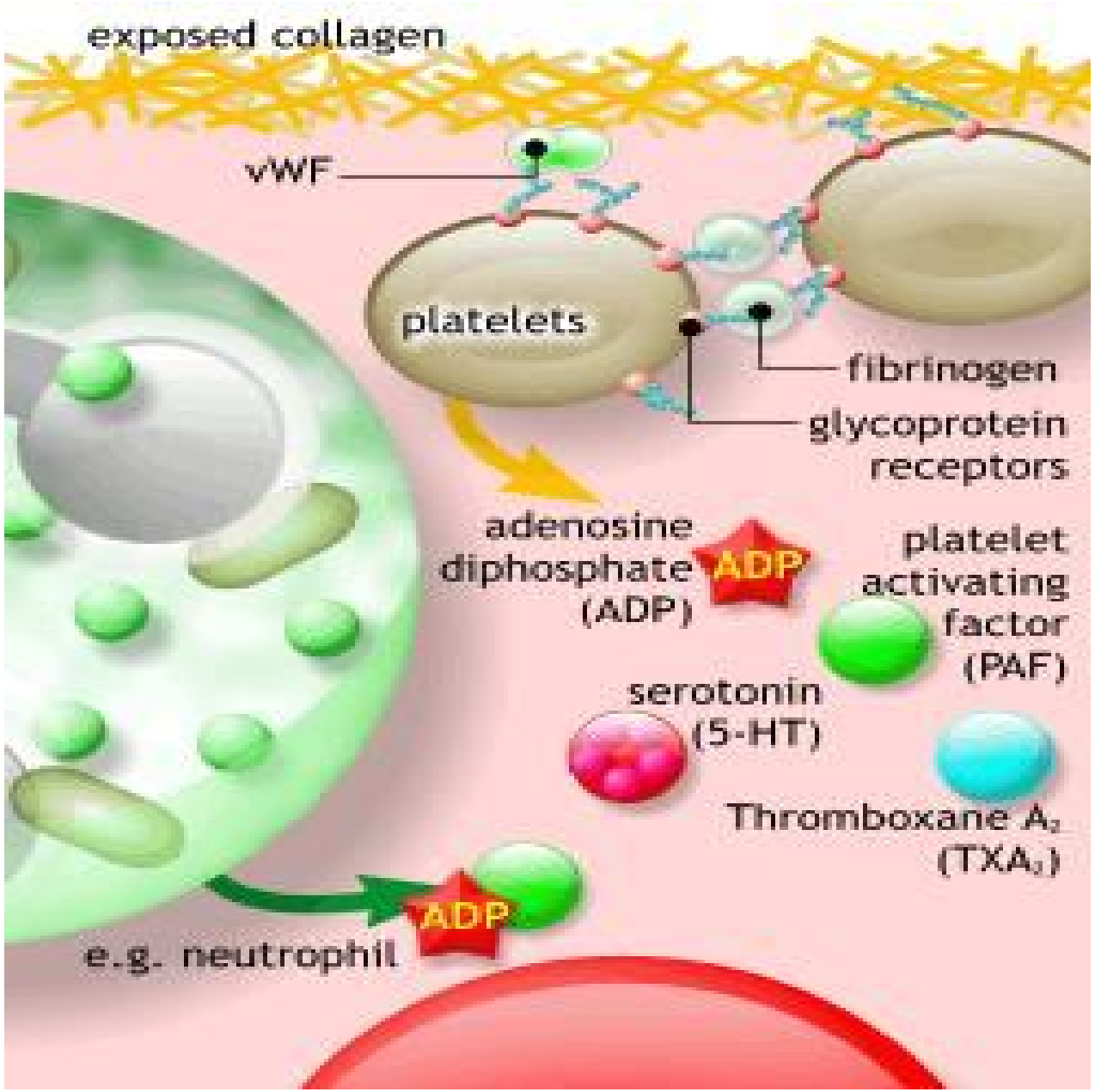

activation of the membrane enzyme **phospholipase A2**, leading to the formation of **thromboxane A2 (TXA2)**




1) Microtubules in cytoplasm contract
2) Pseudo pods form
3) Organelles move to center of platelet
4) Fibrinogen receptor changes shape And can now bind to fibrinogin

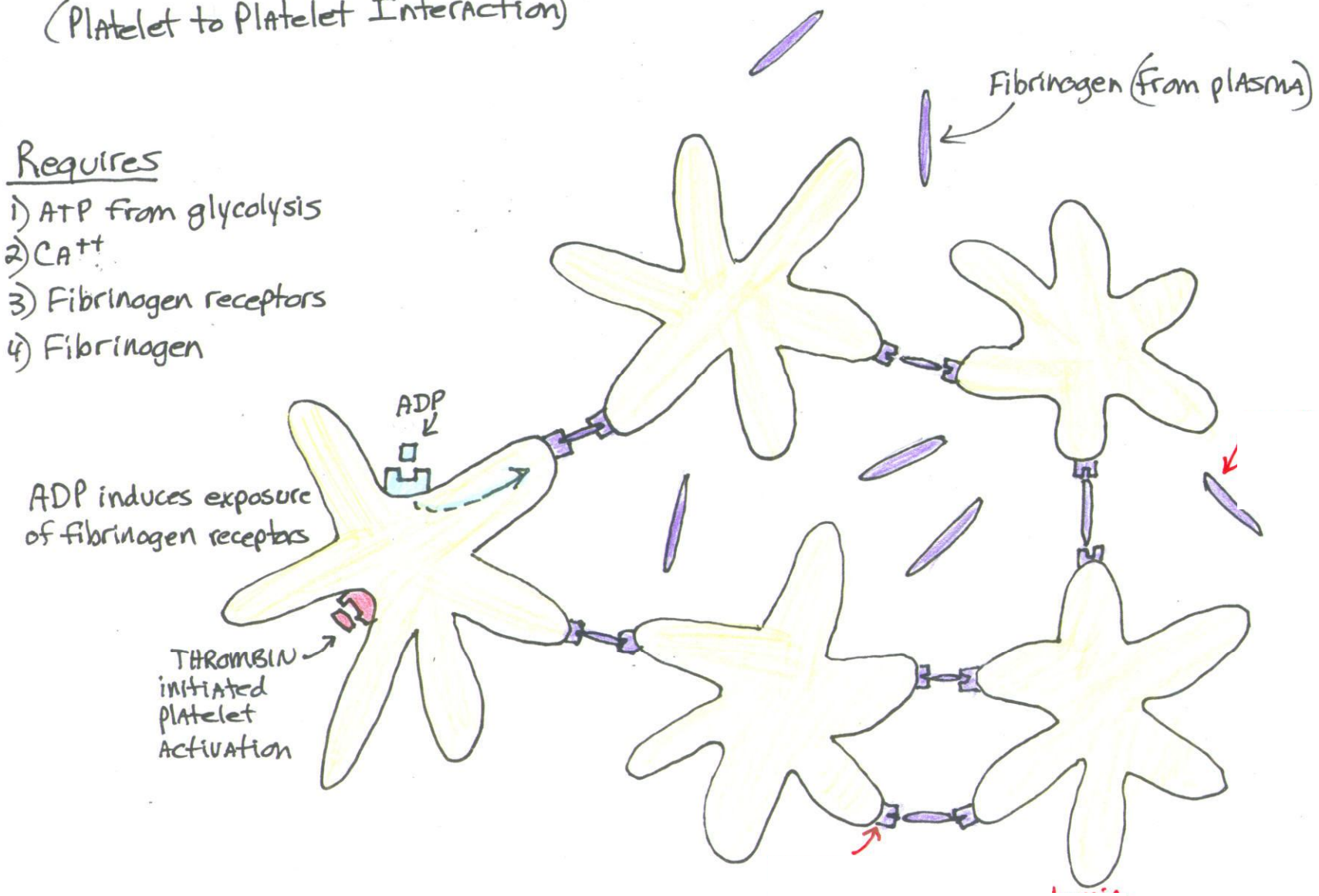
⑤ **SHAPE CHANGE**

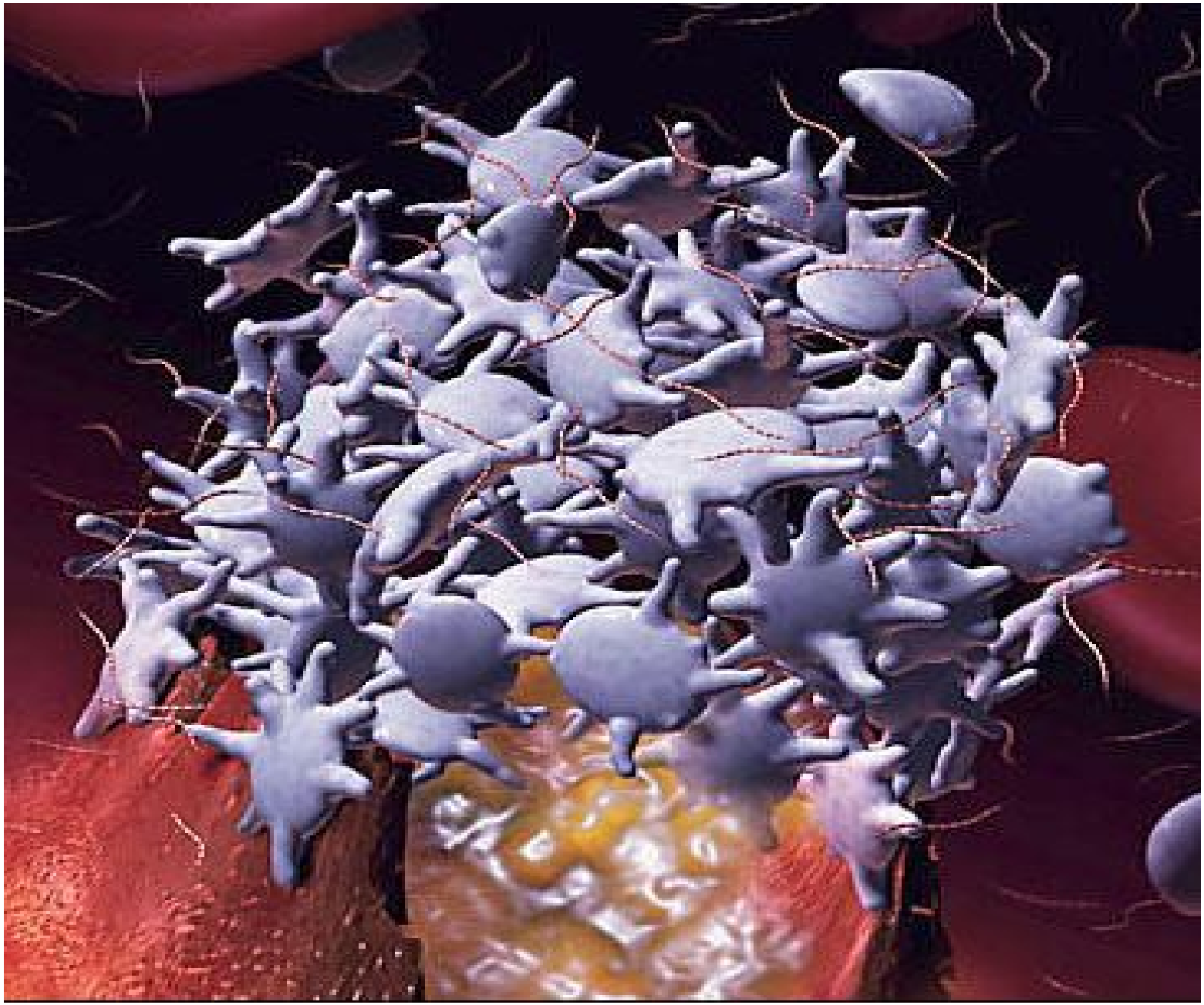
(Increases surface area)


exposed collagen
vWF
platelets
fibrinogen
glycoprotein receptors
adenosine diphosphate (ADP)
ADP
platelet activating factor (PAF)
serotonin (5-HT)
Thromboxane A2 (TXA2)
ADP
e.g. neutrophil

⑦ **AGGREGATION** 10-20 seconds after injury

(Platelet to Platelet Interaction)

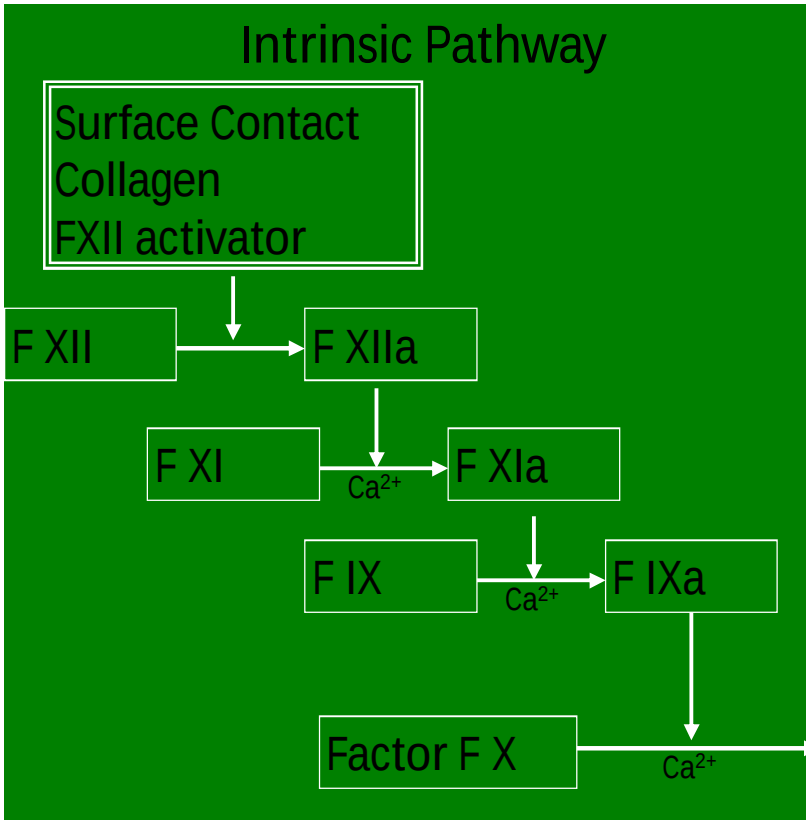




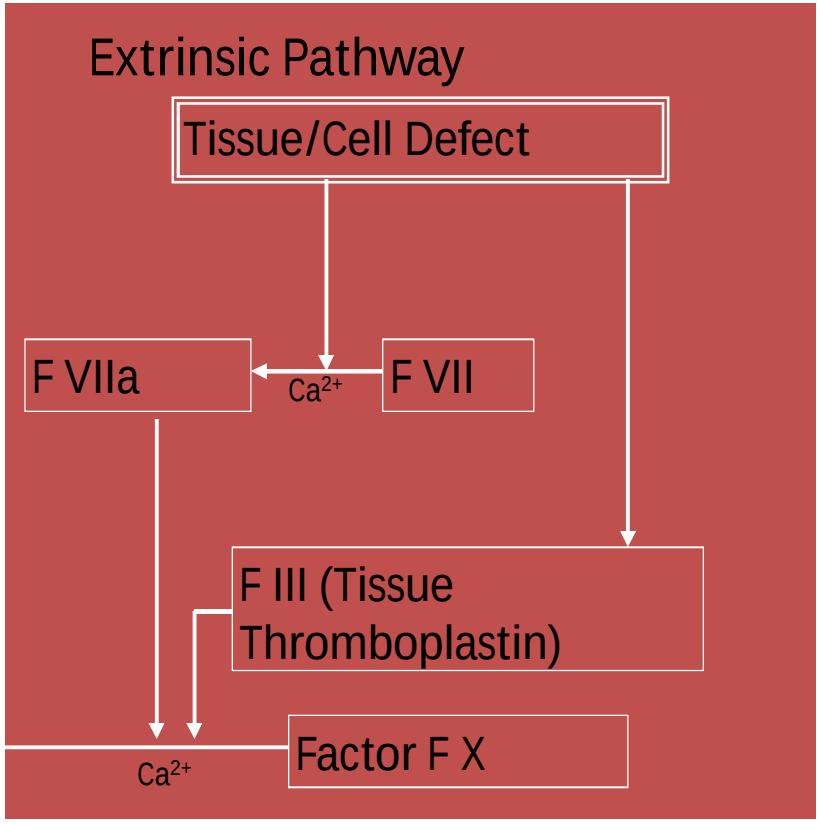
# TWO PATHWAYS TO PROTHROMBIN ACTIVATOR

**PIVITOL COMPONENT IN BOTH PATHWAYS IS NEGATIVELY CHARGED MEMBRANES ESPECIALY THOSE ON THE PLATELETS CONTAINING PLATELET FACTOR PF3**

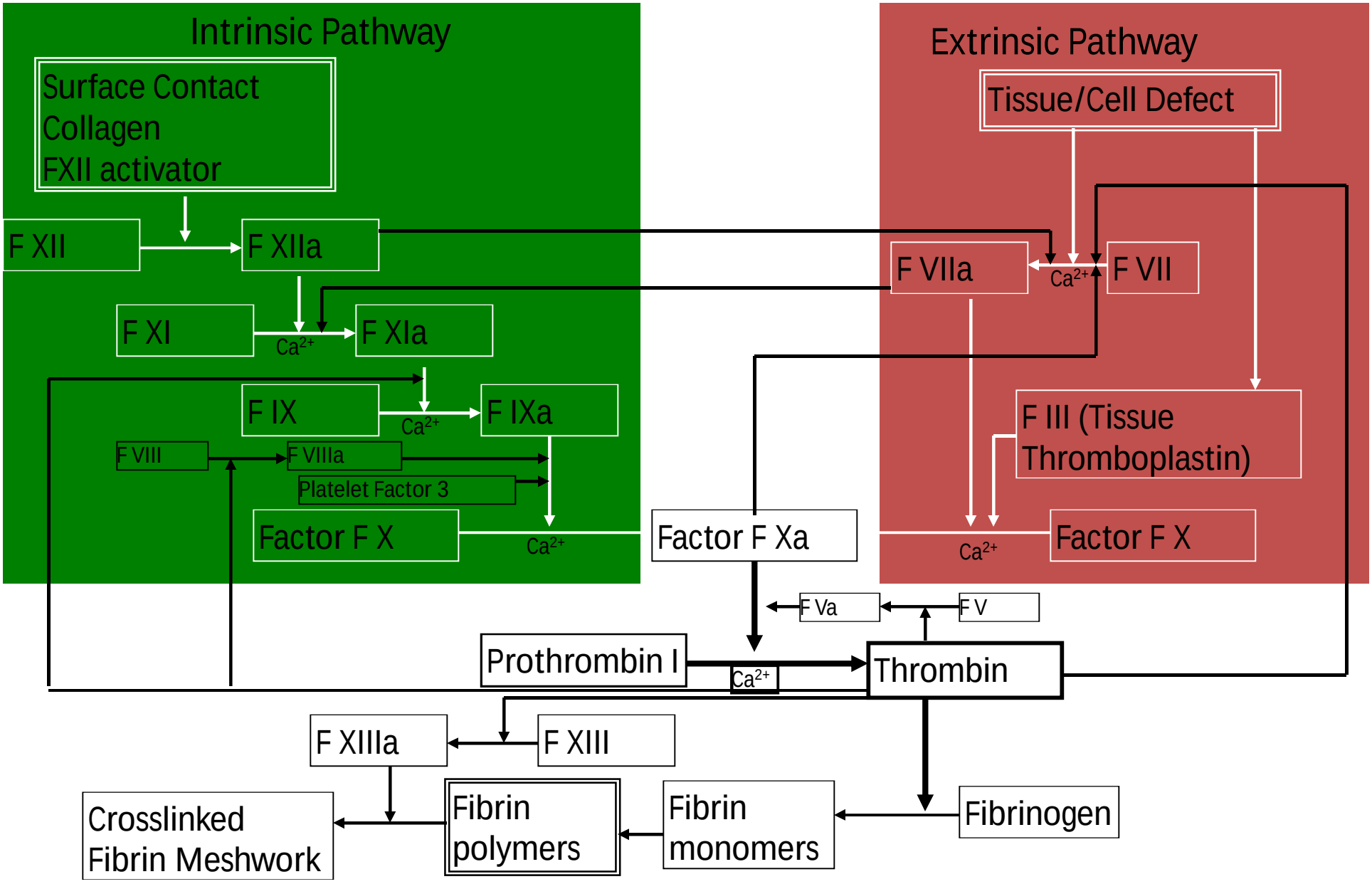
SLOWER PATHWAY ALL FACTORS ARE PRESENT IN THE BLOOD

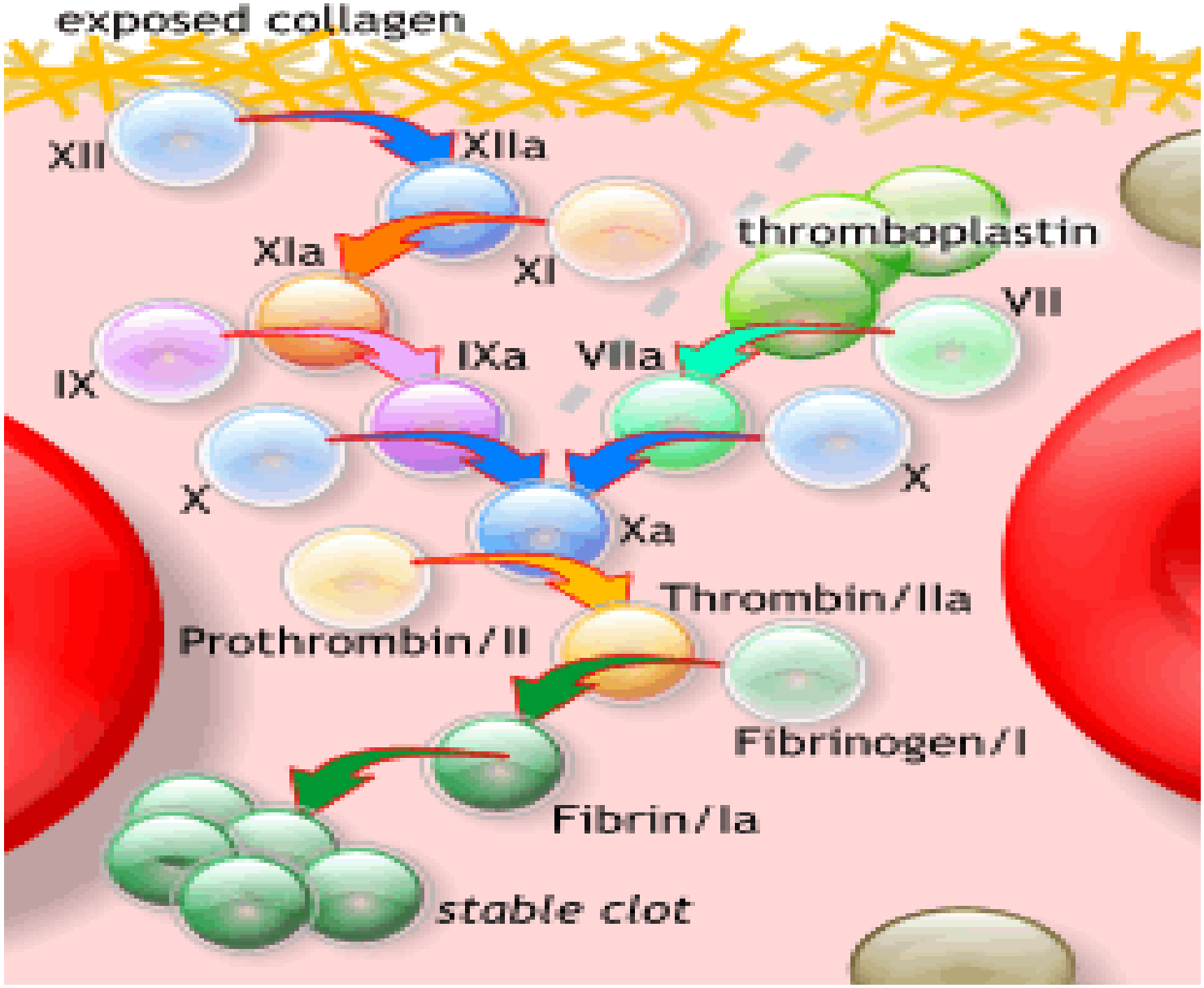


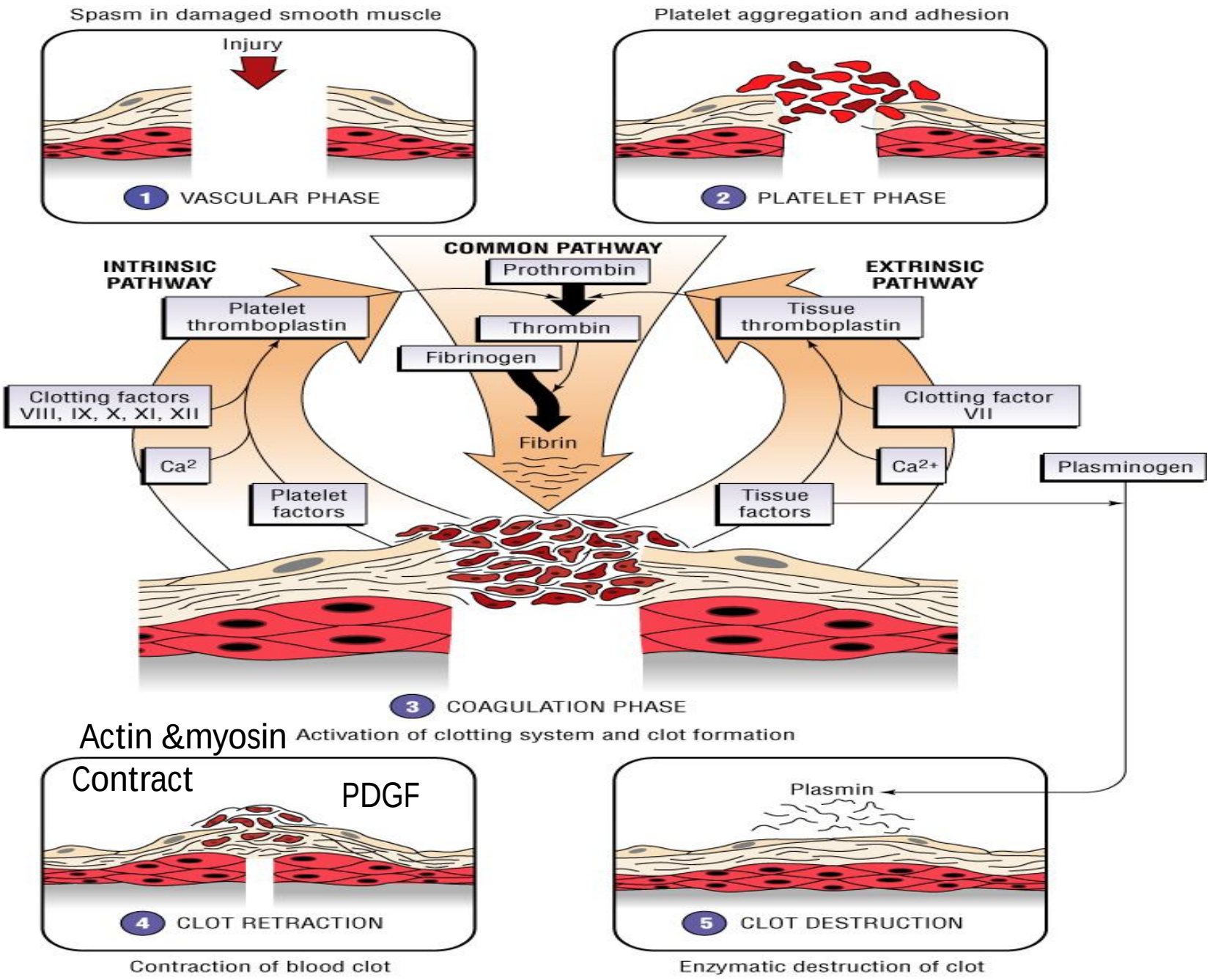

FASTER PATHWAY WHEN **EXPOSED TO TISSUE FACTOR**



# The Clotting Cascade

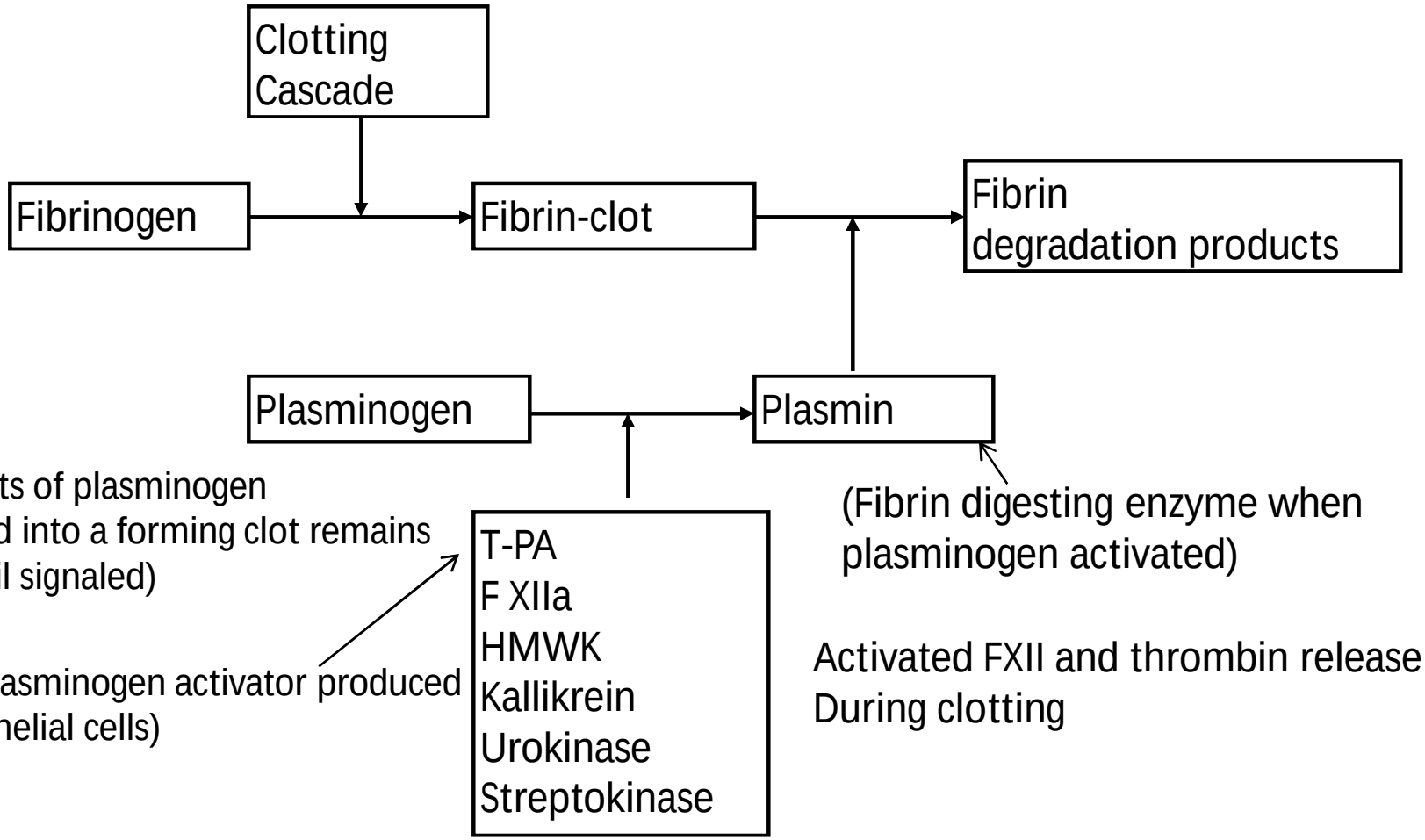



exposed collagen
XII
XIIa
XIa
XI
thromboplastin
VII
IX
IXa
VIIa
X
X
Xa
Thrombin/IIa
Prothrombin/II
Fibrinogen/I
Fibrin/Ia
stable clot

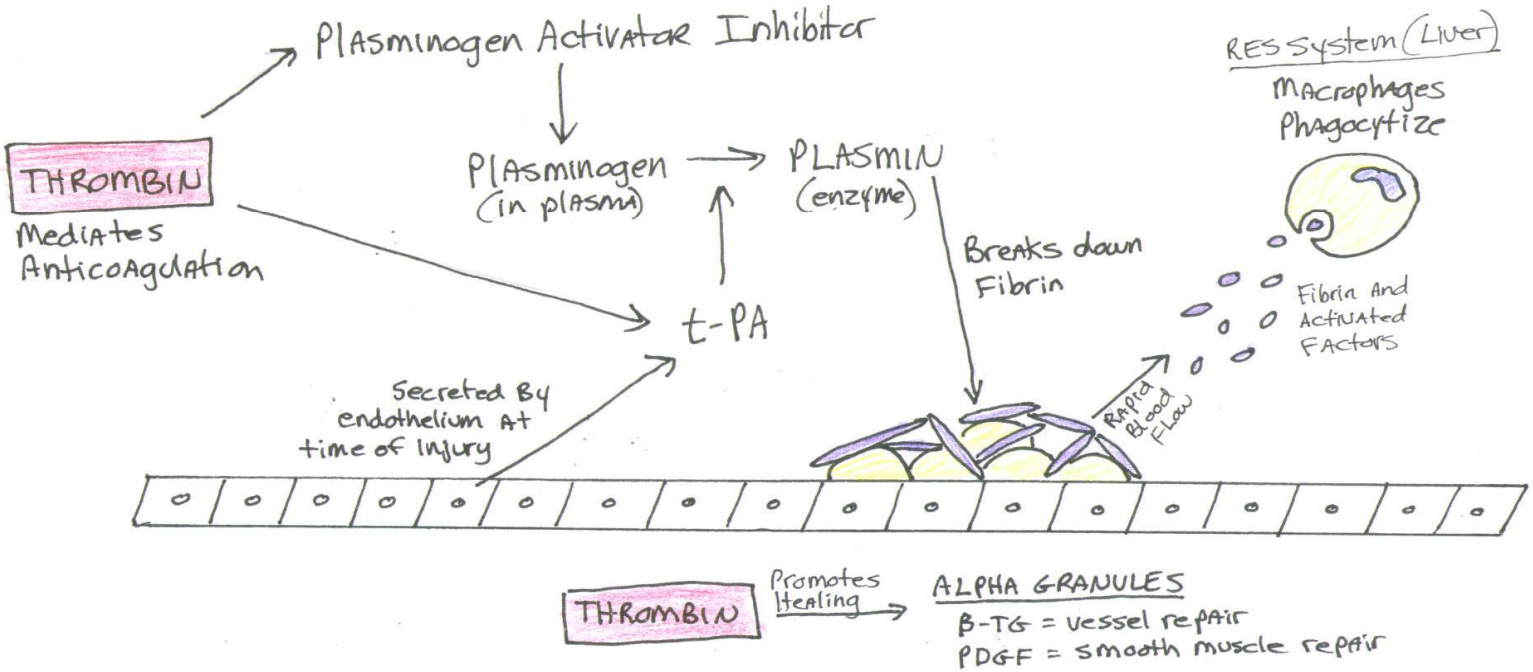

Spasm in damaged smooth muscle
Injury
1 VASCULAR PHASE
Platelet aggregation and adhesion
2 PLATELET PHASE
COMMON PATHWAY
Prothrombin
Thrombin
Fibrinogen
Fibrin
INTRINSIC PATHWAY
Platelet thromboplastin
Clotting factors VIII, IX, X, XI, XII
Ca2
Platelet factors
EXTRINSIC PATHWAY
Tissue thromboplastin
Clotting factor VII
Ca2+
Tissue factors
Plasminogen
3 COAGULATION PHASE
Activation of clotting system and clot formation
Actin &myosin
Contract
PDGF
4 CLOT RETRACTION
Contraction of blood clot
Plasmin
5 CLOT DESTRUCTION
Enzymatic destruction of clot

# The Fibrinolytic System

Begins within two days cont. slowly over several days



# ⑨ FIBRINOLYSIS



# FACTORS LIMITING CLOT FORMATION

**HEOMEOSTATIC MECHANISMS THAT PREVENT CLOTS FROM BECOMING TOO LARGE**

- SWIFT REMOVAL OF CLOTTING FACTORS BY RAPIDLY MOVING BLOOD
- AS A CLOT FROMS ALL THROMBIN IS BOUND BY FIBRIN
- INACTIVATING THROMBIN BY ANTITHROMBIN III & PROTIEN C
- HEPARIN NATURAL ANTICOAGULANT IN BSOPHILS AND MAST CELL GRANULE
- HEPARIN IS ALSO PRODUCED BY ENDOTHELIAL CELL

# Coagulation proteins

## Prothrombin Group

Vit. K dependant produced in the liver

All are Serine proteases

- **Prothrombin FII**
- **Proconvertin FVII**
- **Christmas Factor FIX**
- **Stuart-Prower Factor FX**

## Fibrinogen Group

NOT Vit. K dependant, produced in the liver

- **Fibrinogen FI (substrate)**
- **Proaccelerin FV (co factor)**
- **Antihemophilic Factor FVIII (co factor)**
- **Fibrinogen stabilizing FXIII (serine protease)**

## Contact type coagulation Factors

Involved in the initial activation of the intrinsic coagulation

- **Plasma thomrboplastin antecedent (XI)**
- **Hageman Factor (XII)**
- **Pre-Kallikrein (PK)**
- **High –molecular-weight kininogen (HMWK)**

23 ***LIST FOURTEEN COAGULATION FACTORS, COMMON NAMES, ABBREVIATIONS AND/OR SYNONYMS***.

*factor common name (with known synonyms)*

I Fibrinogen

II Prothrombin

III Tissue Thromboplastin; Tissue Factor

IV Ionized Calcium ($Ca^{++}$)

V Proaccelerin, Labile Factor, Prothrombin Accelerator, Accelerator Globulin (AcG), Thrombogen

VI This designation is now unassigned. It was formerly listed as a clotting factor, it is now known that it was an impure derivative of Factor V. It is now a discarded term and textbooks do not list this factor nor indicate it as being unassigned.

VII Stable Factor, Serum Prothrombin Conversion Accelerator (SPCA), Proconvertin

VIII Antihemophilic Factor (AHF), Antihemophilic Factor A, Antihemophilic Globulin (AHG), Platelet Cofactor 1.

IX Christmas Factor,, Antihemophilic Factor B, Prothrombin II, Platelet Cofactor 2, Plasma Thromboplastin Component (PTC).

X Stuart-Prower Factor, Stuart Factor, Autoprothrombin III, thrombokinase.

XI Plasma Thromboplastin Antecedent (PTA),, Antihemophilic Factor C, Prothrombin Antecedent

XII Hageman Factor, Contact Factor, Glass Factor

XIII Fibrin-Stabilizing Factor (FSF), Transglutaminase, Fibrinoligase, Laki-Lorand Factor (LLF), Fibrinase, Plasma Transglutaminase

Fitzgerald High-Molecular-Weight Kininogen (HMWK), Flaujeac Factor, Contact Activation Factor, Williams Factor, Reid Factor, Washington Factor

Fletcher Prekallikrein (PK)

# QUESTIONS AND ANSWERS

1.WHAT DO ENDOTHELIAL CELLS PRODUCE T0 KEEP PLATELETS FROM BEING ACTIVATED?

PROSTACYLIN, NITRIC OXIDE,

**TFPI** (tissue factor pathway inhibitor

2. WHAT FACTORS WILL ACTIVATE PLATELETS

- **Collagen**, **tissue factor** and **VWF** in contact the blood due to vessel wall

3. What are the three steps that occur in rapid sequence when there is damage to Vessel wall?

1. vascular spasm,
2. platelet plug formation
3.coagulation of blood

4. What are the two pathways to the common pathway

- Intrinsic with the involvement of collagen, PF3, factors: XII, XI, IX, VII with vWF (calcium)
- Extrinsic with the involvement of TF3, FVII (calcium)
- Both leading to the common pathway has factor PF3, V,X,II,I,XIII (calcium)