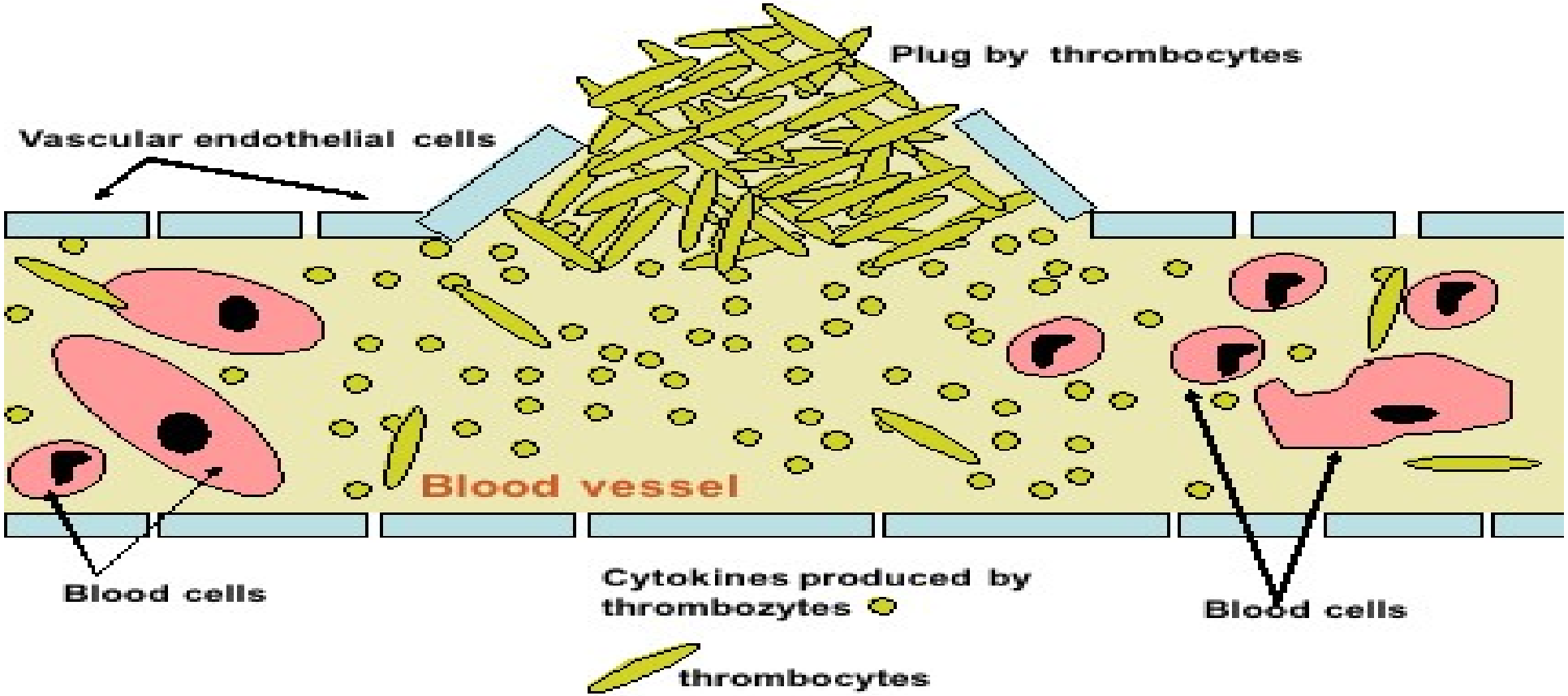
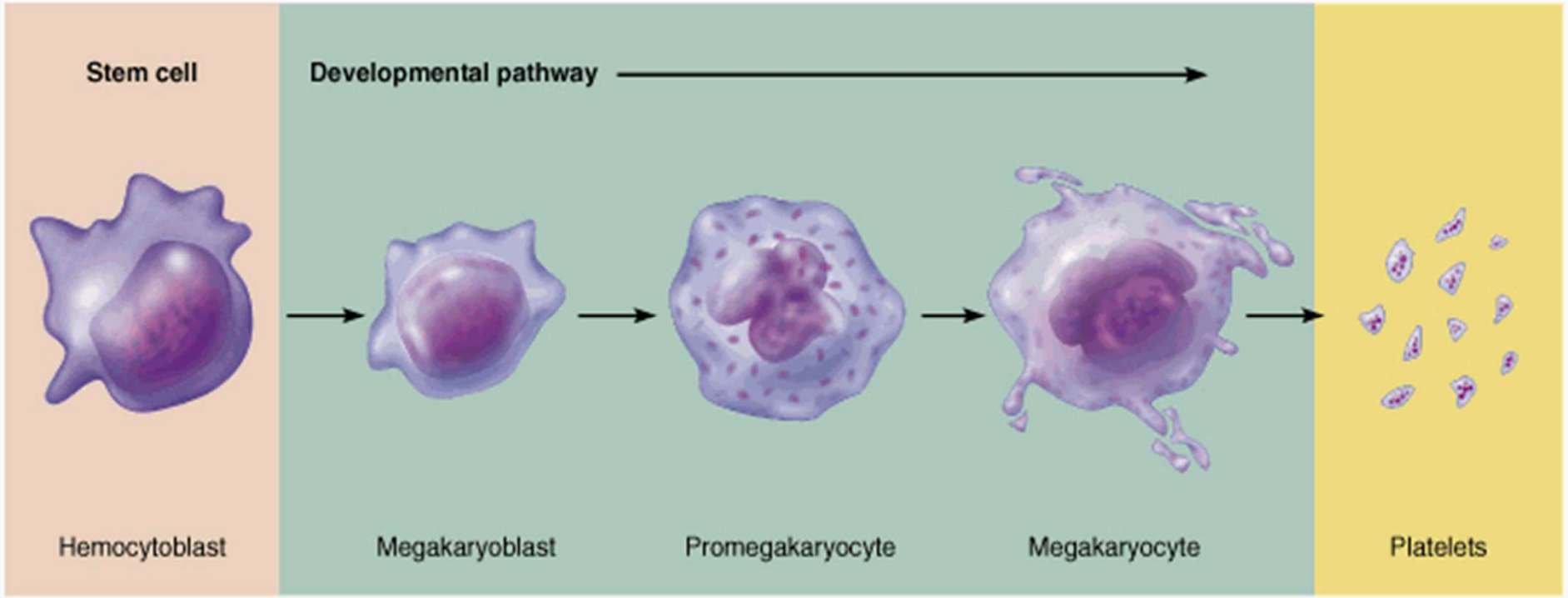
PLATELETS (THROMBOCYTES)



Platelets are the smallest of the cellular elements of blood. They are non-nucleated, granulated bodies, 2-4 micrometers in diameter. Their normal concentration in blood ranges from 150,000 to 400,000 per microliter. They are formed in the bone marrow from giant cells, the megakaryocytes, which fragment into platelet which are extruded into the circulation.

The platelet production is regulated by multiple factors including IL-1, IL-3, IL-6, and GM-CSF that control the production of megakaryocytes.

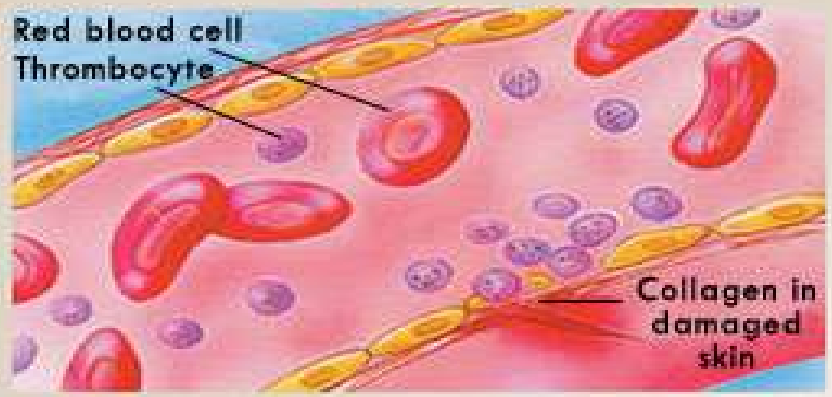
Their life span is 7-10 days, then they are eliminated from the circulation mainly by the tissue macrophage system.



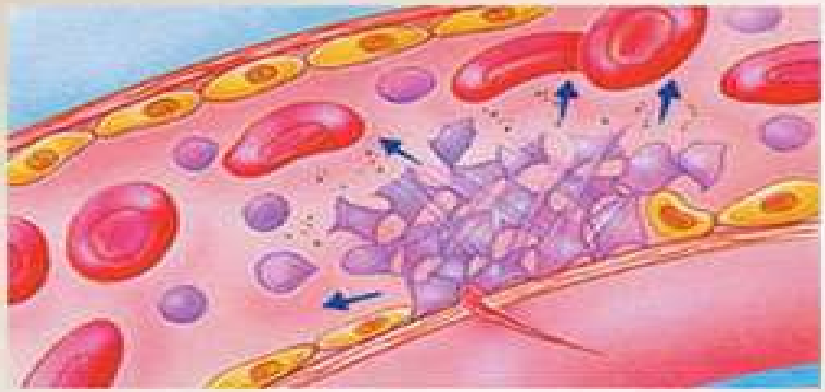
The membranes of platelets contain receptors for collagen, vessel wall von Willebrand factor and fibrinogen. Their cytoplasm contain actin, myosin, glycogen, lysosomes, and 2 types of granules:

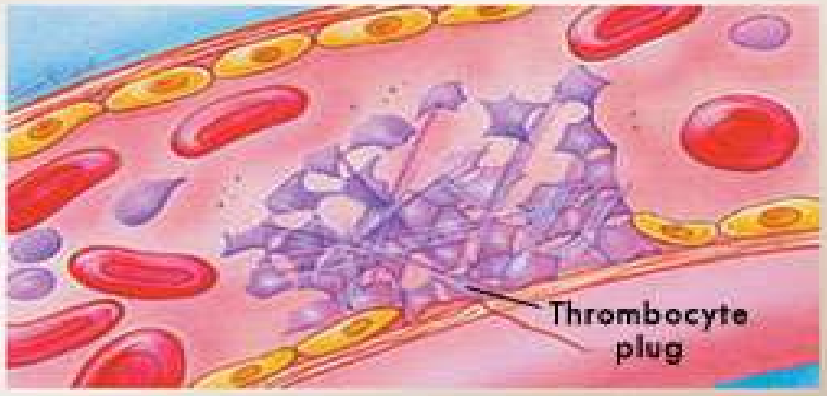
1. Dense granules containing nonprotein substances such as ADP, ATP, serotonin.
2. α–granules containing protein substances such as clotting factors and platelet-derived growth factor which stimulates wound healing. In addition, the platelet membrane contains large amounts of phospholipids that play several activating roles at multiple points in the blood clotting process.

Their most important function is in hemostasis and blood coagulation.



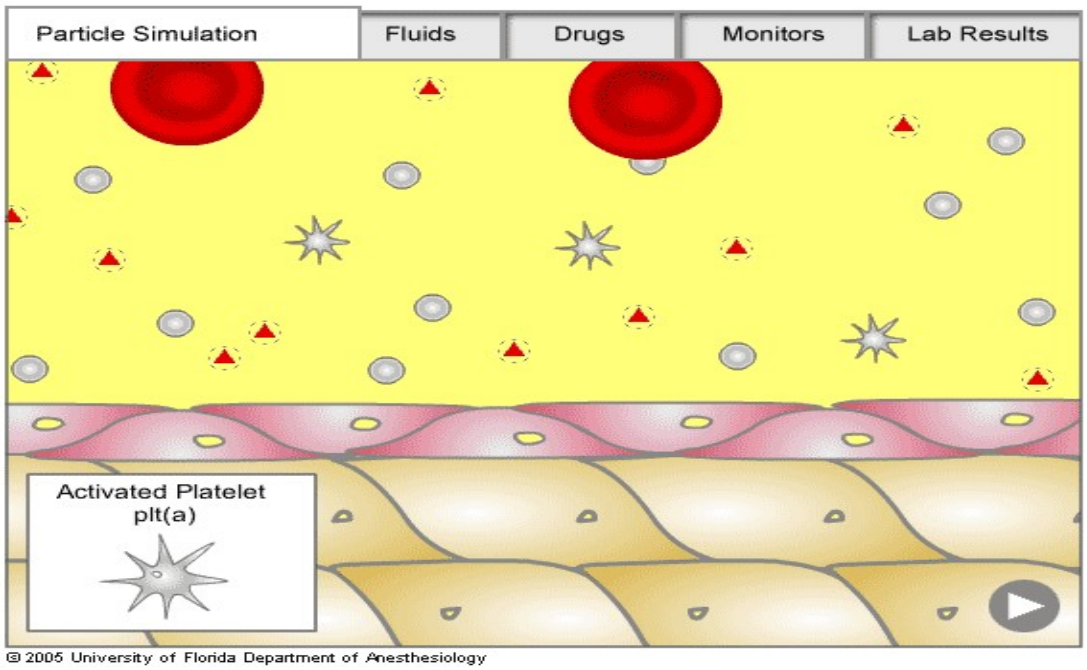
a) Thrombocyte plug

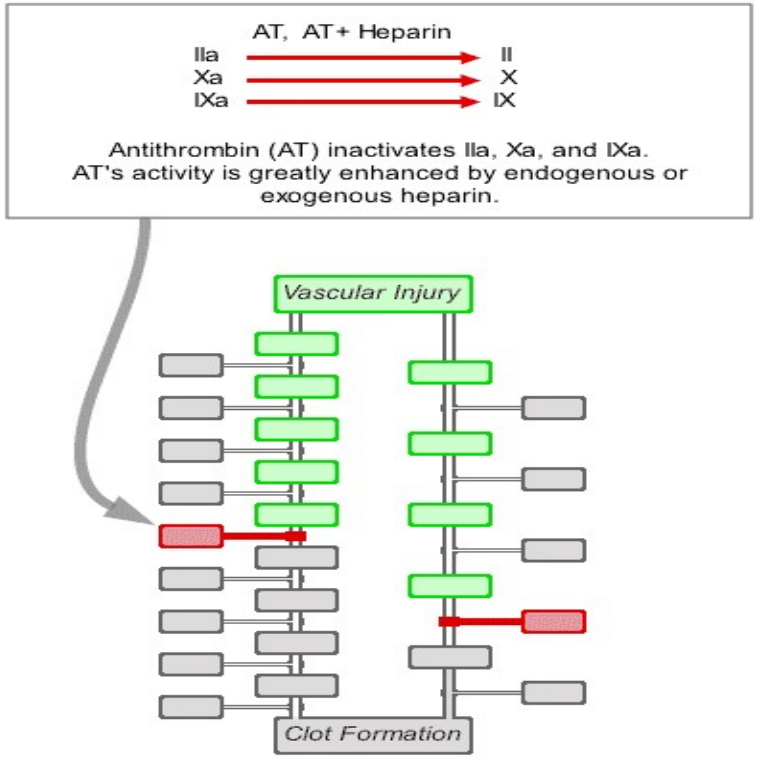

b) Thrombocyte movement



c) Thrombocytes collecting together

HEMOSTASIS AND BLOOD COAGULATION

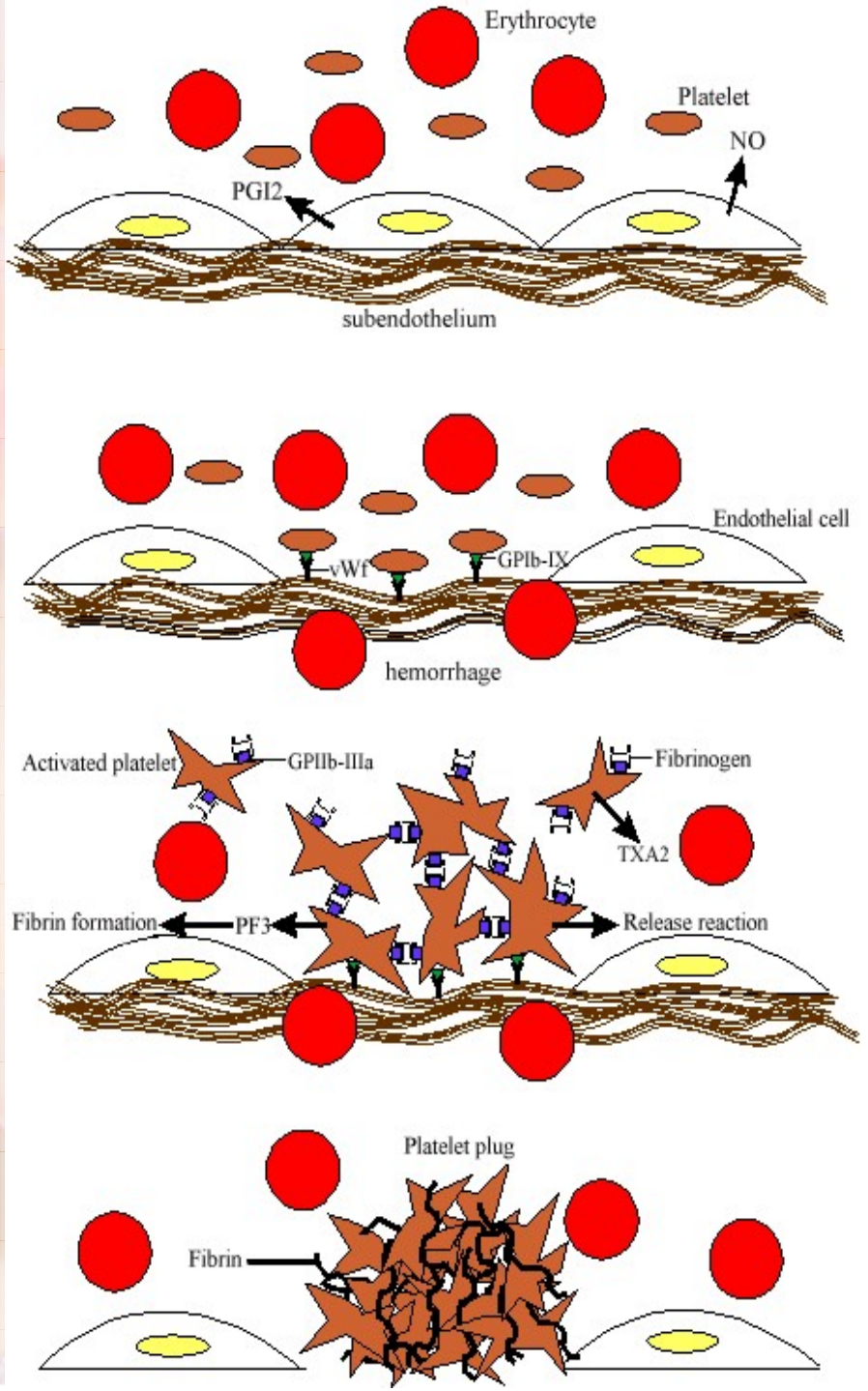


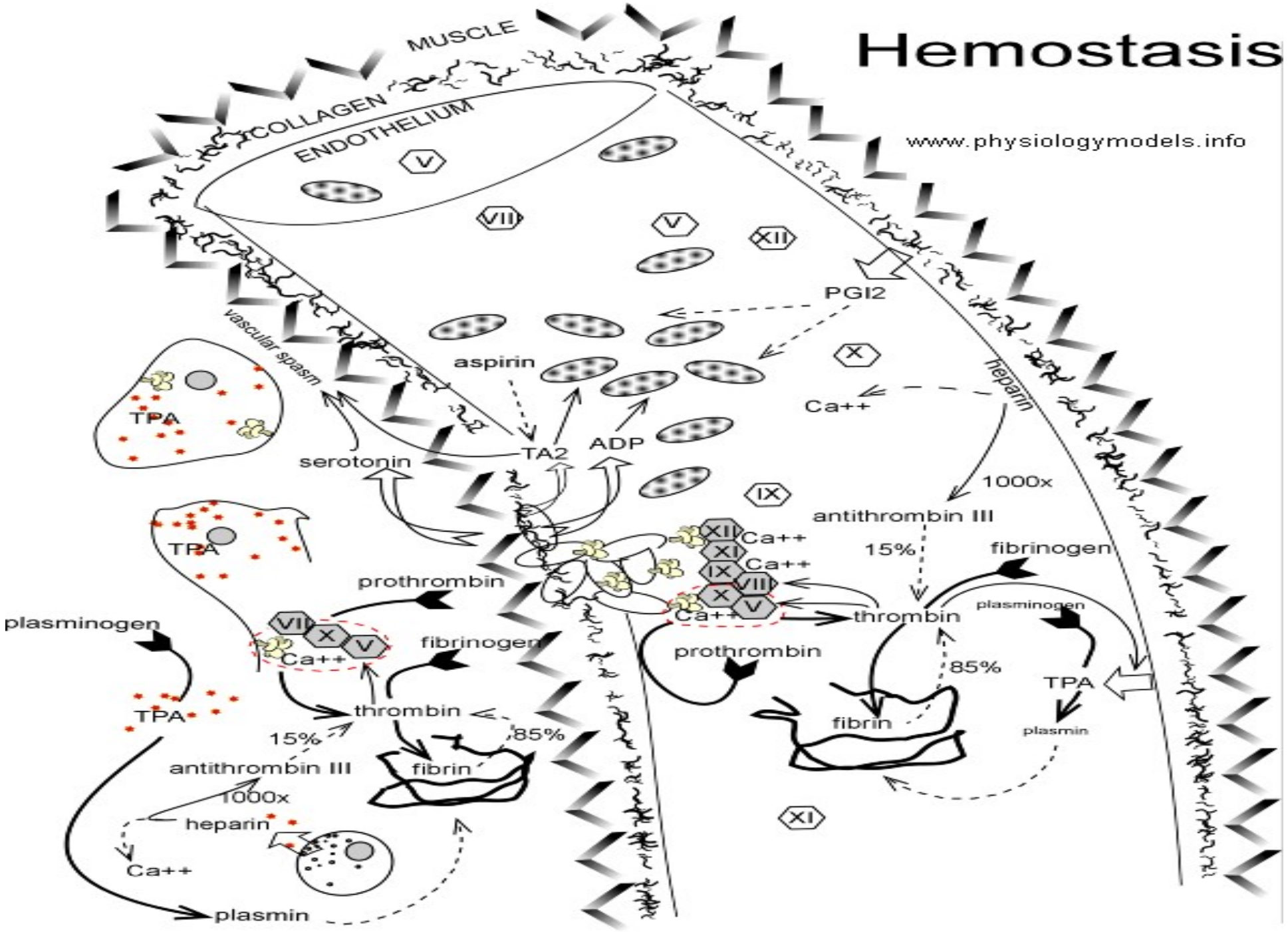


When a small blood vessel is transected or injured, a spontaneous and natural process occurs to arrest bleeding, this process is called "hemostasis". It involves a series of events which leads to clot formation and prevention of further blood loss.

These include:

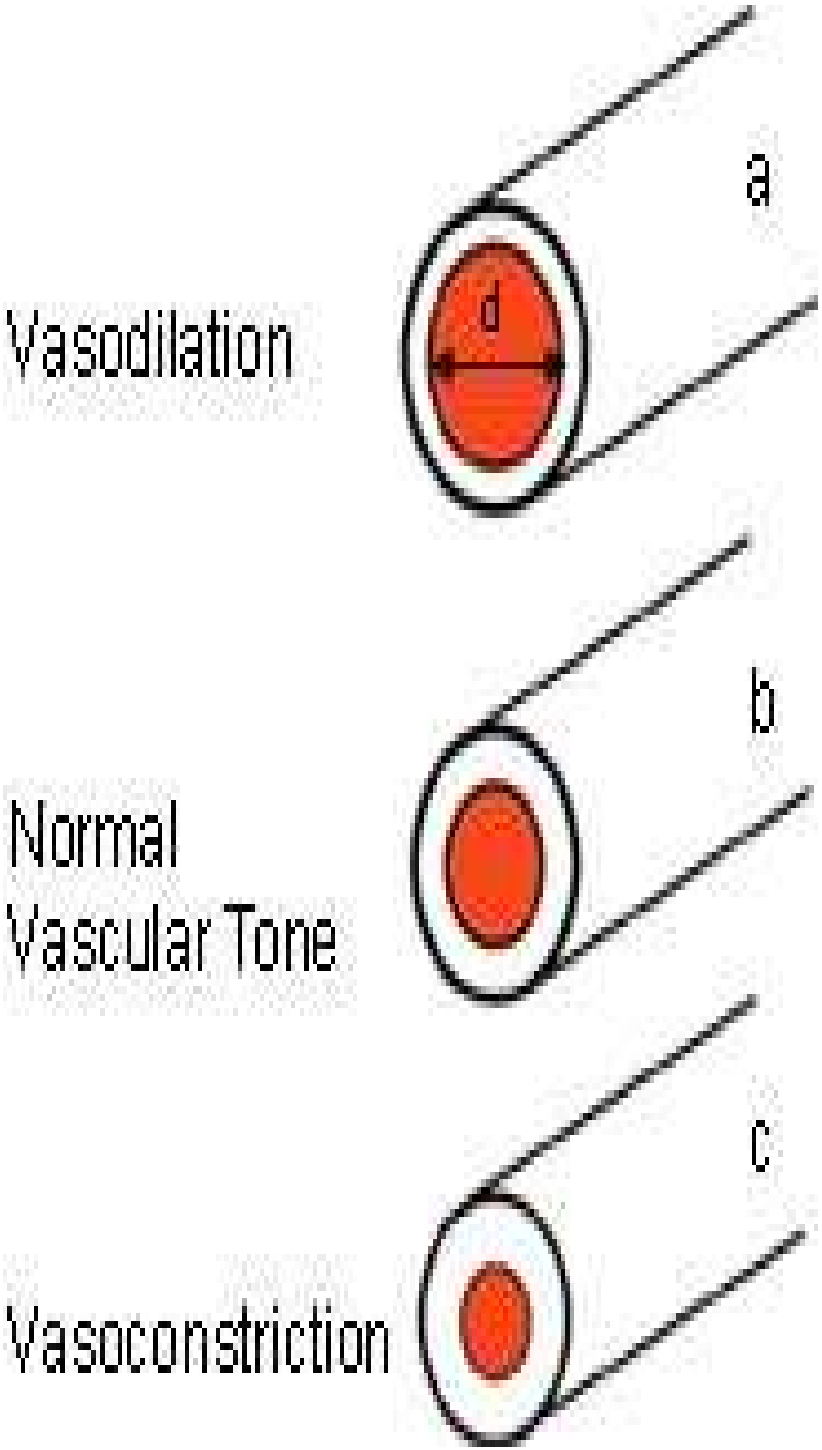
- **Contraction of the injured vessel,**
- **Formation of platelet plug at the site of injury,**
- **Activation of blood coagulation,**
- **Activation of the fibrinolytic system which gradually dissolves away the fibrin clot as tissue repair is taking place.**



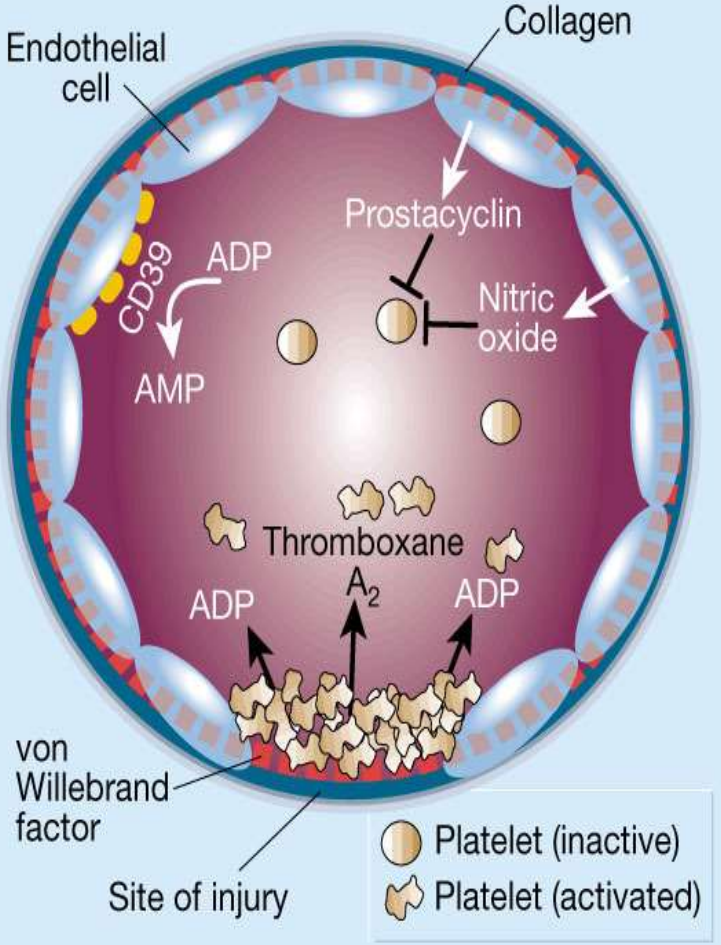

Hemostasis
www.physiologymodels.info
MUSCLE
COLLAGEN
ENDOTHELIUM
VII
V
XII
PGI2
vascular spasm
aspirin
X
Ca++
heparin
TPA
TA2
ADP
serotonin
1000x
IX
antithrombin III
15%
fibrinogen
XII
Ca++
XI
Ca++
IX
VII
X
V
Ca++
thrombin
plasminogen
prothrombin
plasminogen
VII
X
V
Ca++
fibrinogen
prothrombin
85%
TPA
TPA
thrombin
fibrin
plasmin
15%
85%
antithrombin III
fibrin
1000x
heparin
Ca++
plasmin
XI

Repair of the vessel wall occurs by the proliferation of smooth muscle cells and fibroblasts, the deposition of new connective tissue matrix, and the ingrowth of a new luminal lining of endothelial cells.

[1] Contraction of the vessel wall (vasoconstriction): This reduces the flow of blood from the vessel rupture. Most of vasoconstriction results probably from direct effect of injury upon vascular smooth muscle cells. Vasoconstrictor substances released from the platelets also contribute to this vasoconstriction.



[2] Formation of a platelet plug: when platelets come in contact with the exposed collagen of the damaged blood vessel, they become activated, they begin to swell, put out pseudopodia, become sticky and adhere to collagen and release different substances such as *serotonin*, and *ADP*. Their enzymes form *thromboxane A2*. Serotonin and thromboxane A2 enhance vasoconstriction. ADP and thromboxane A2 activate other nearby platelets and increase their stickiness and this causes circulating platelets to adhere to the platelets already attached to the collagen, so platelets will aggregate (platelets stick to each other) and form platelet plug at the site of the injury.

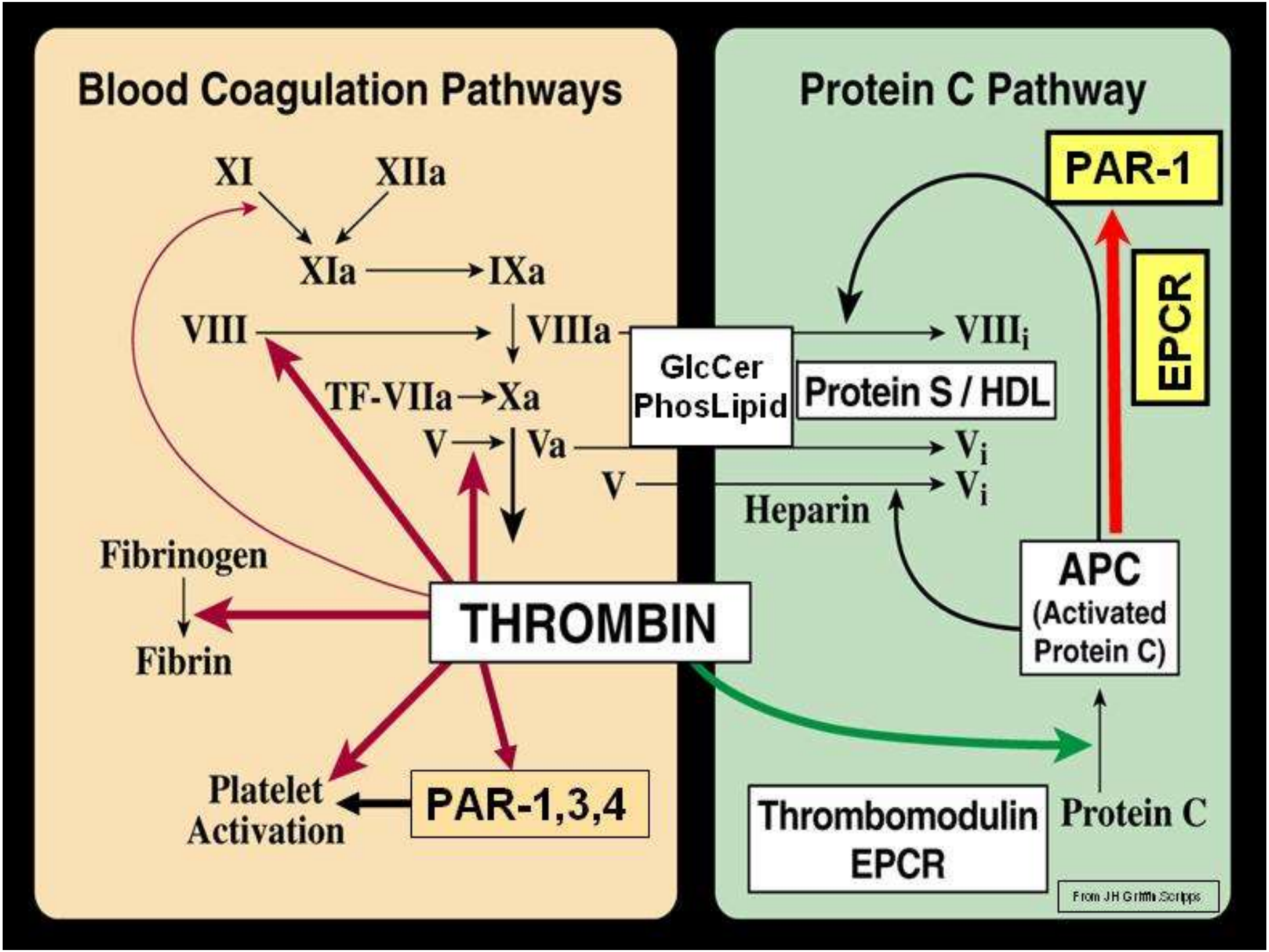


[3] Blood coagulation: platelet plug is converted into the definitive clot by formation of *fibrin*. The clotting mechanism responsible for the formation of fibrin involves a cascade of reactions in which inactive enzymes are activated, and the activated enzymes in turn activate other inactive enzymes. Most of the various clotting factors are designated by Roman numerals.

Coagulation is initiated through *extrinsic* or *intrinsic pathways* or mechanisms.

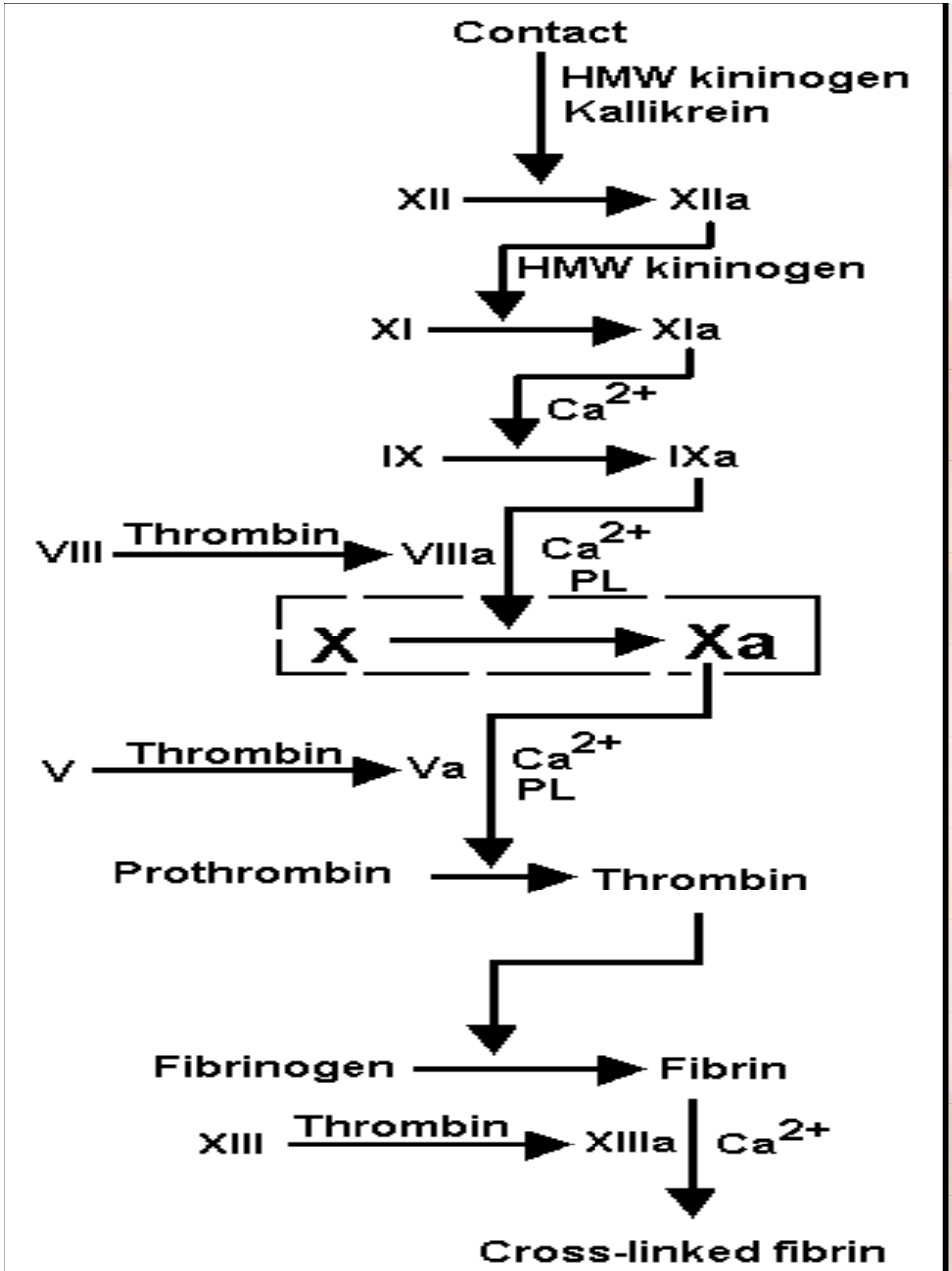
Factors	Names
I	Fibrinogen
II	Prothrombin
III	Tissue thromboplastin
IV	Calcium
V	Proaccelerin
VII	Proconvertin
VIII	Antihaemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor
HMW-K	High momecular weight kininogen (Fitzgerald factor)
Pre-K	Prekallikrein (Fletcher factor)
Ka	Kallikrein
PL	Platelet phospholipid

System for naming blood-clotting factors

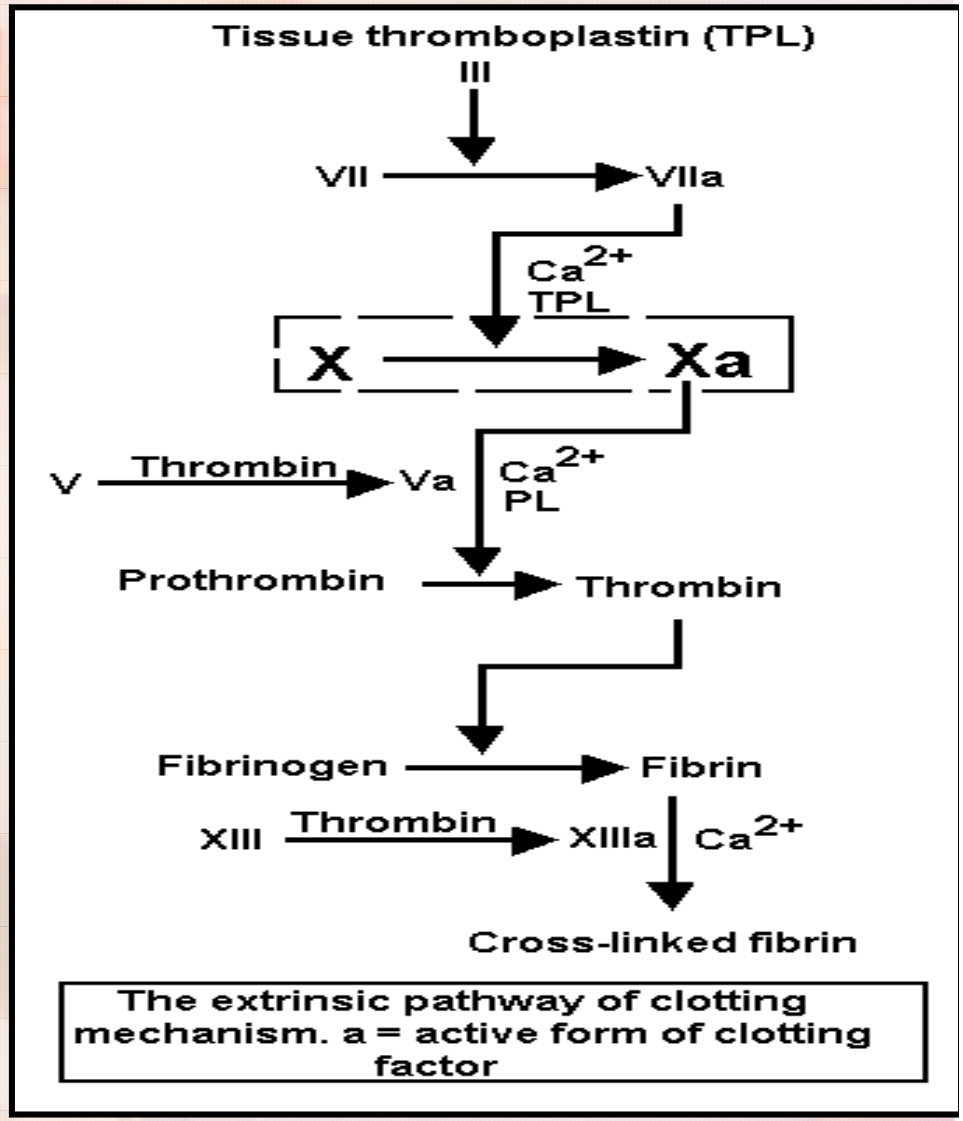

Blood Coagulation Pathways
Protein C Pathway
XI
XIIa
XIa
IXa
VIII
VIIIa
TF-VIIa
Xa
V
Va
Fibrinogen
Fibrin
THROMBIN
Platelet Activation
PAR-1,3,4
GlcCer PhosLipid
Protein S / HDL
VIII$_i$
V$_i$
V$_i$
V
Heparin
PAR-1
EPCR
APC (Activated Protein C)
Thrombomodulin EPCR
Protein C
From JH Griffin Scripps

Extrinsic mechanism **results from the entry into the blood of certain phospholipoproteins released from damaged tissues and are called tissue factor or tissue thromboplastin, they are not found normally in the circulation (they are extrinsic to the circulation). Tissue thromboplastin activates factor VII, tissue thromboplastin and activated factor VII (VIIa), in the presence of Ca2+, activate factor X.**

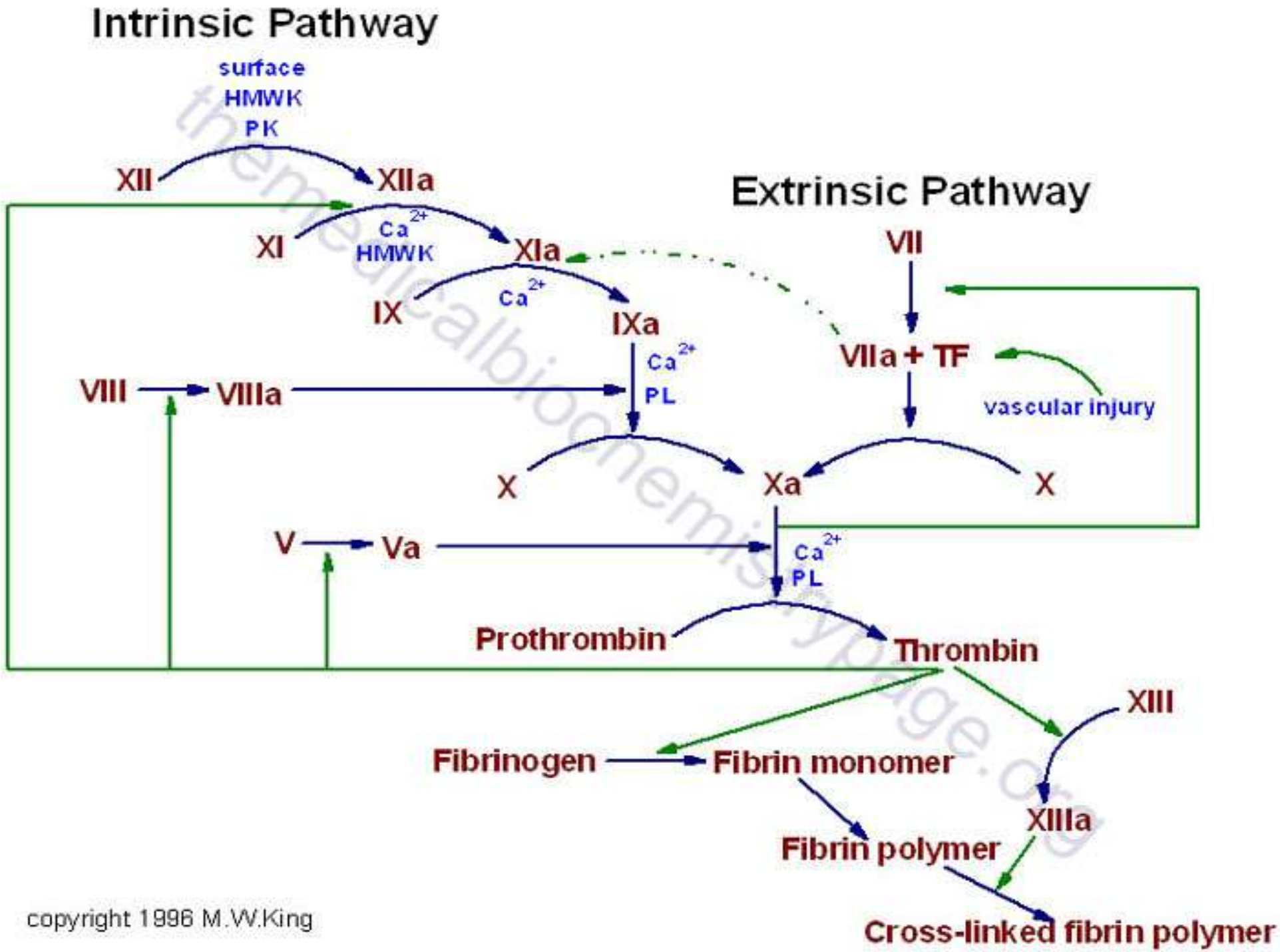
Intrinsic mechanism **begins when blood comes in contact with collagen underlying the endothelium in the blood vessels or in vitro when blood comes in contact with negatively charged surfaces such as glass. This alters factor XII and the platelets. Factor XII will be activated and this activation is catalyzed by high molecular weight (HMW) kininogen and plasma kallikrein. Also platelet phospholipid is released and plays a role in subsequent clotting reactions. Activated factor XII (XIIa) then activates factor XI, this reaction also requires HMW kininogen. Activated factor XI (XIa) forms a complex with active factor VIII (factor VIII is activated by thrombin). The complex of IXa and activated factor VIII (VIIIa) activate factor X. Phospholipids from platelets, and Ca2+ are necessary for full activation of factor X.**



The intrinsic pathway of clotting mechanism. a = active form of clotting factor



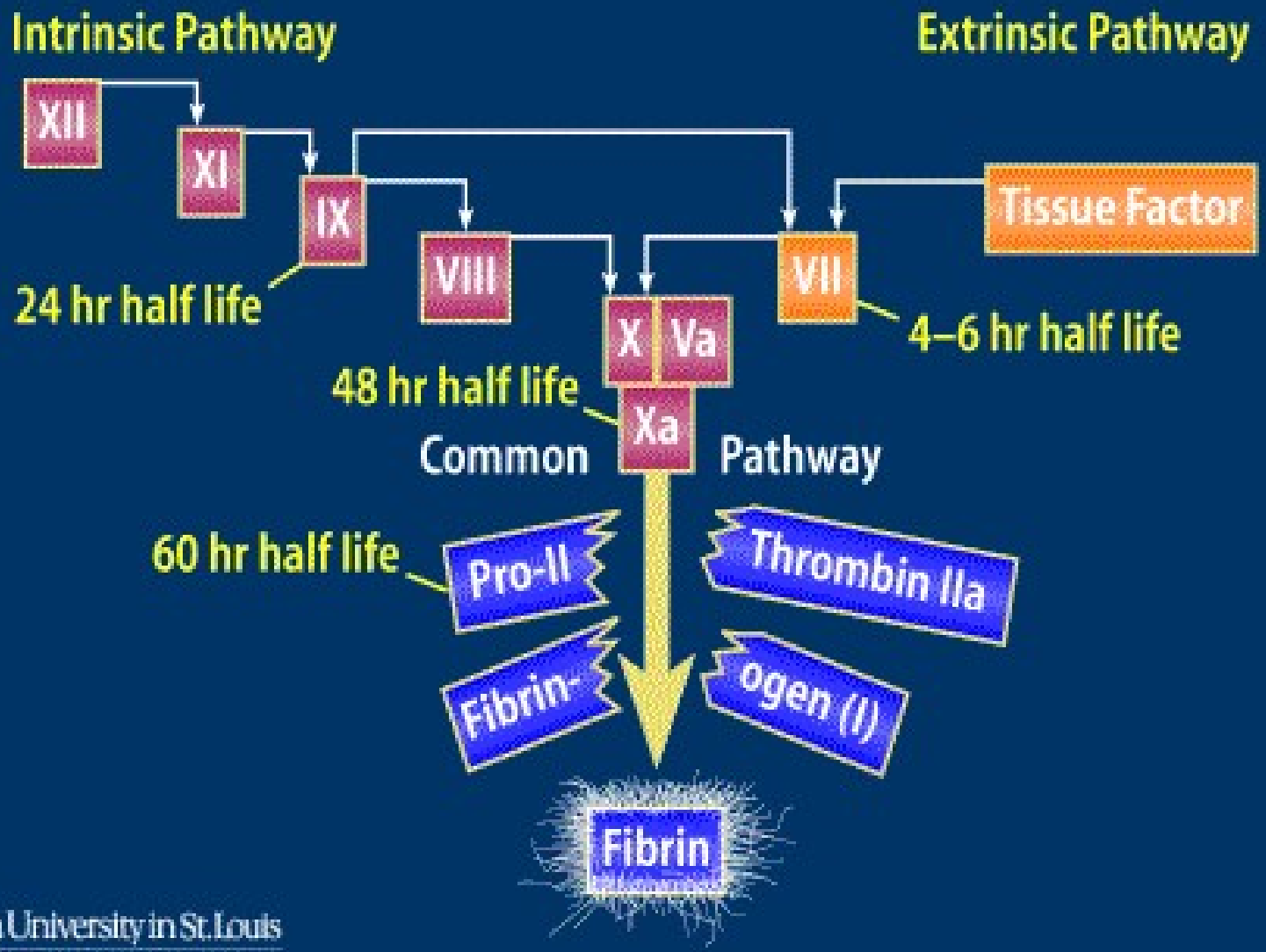
The extrinsic pathway of clotting mechanism. a = active form of clotting factor


Intrinsic Pathway
surface
HMWK
PK
XII
XIIa
XI
Ca2+
HMWK
XIa
IX
Ca2+
IXa
VIII
VIIIa
Ca2+
PL
X
Xa
V
Va
Ca2+
PL
Prothrombin
Thrombin
Extrinsic Pathway
VII
VIIa + TF
vascular injury
X
XIII
Fibrinogen
Fibrin monomer
XIIIa
Fibrin polymer
Cross-linked fibrin polymer
copyright 1996 M.W.King

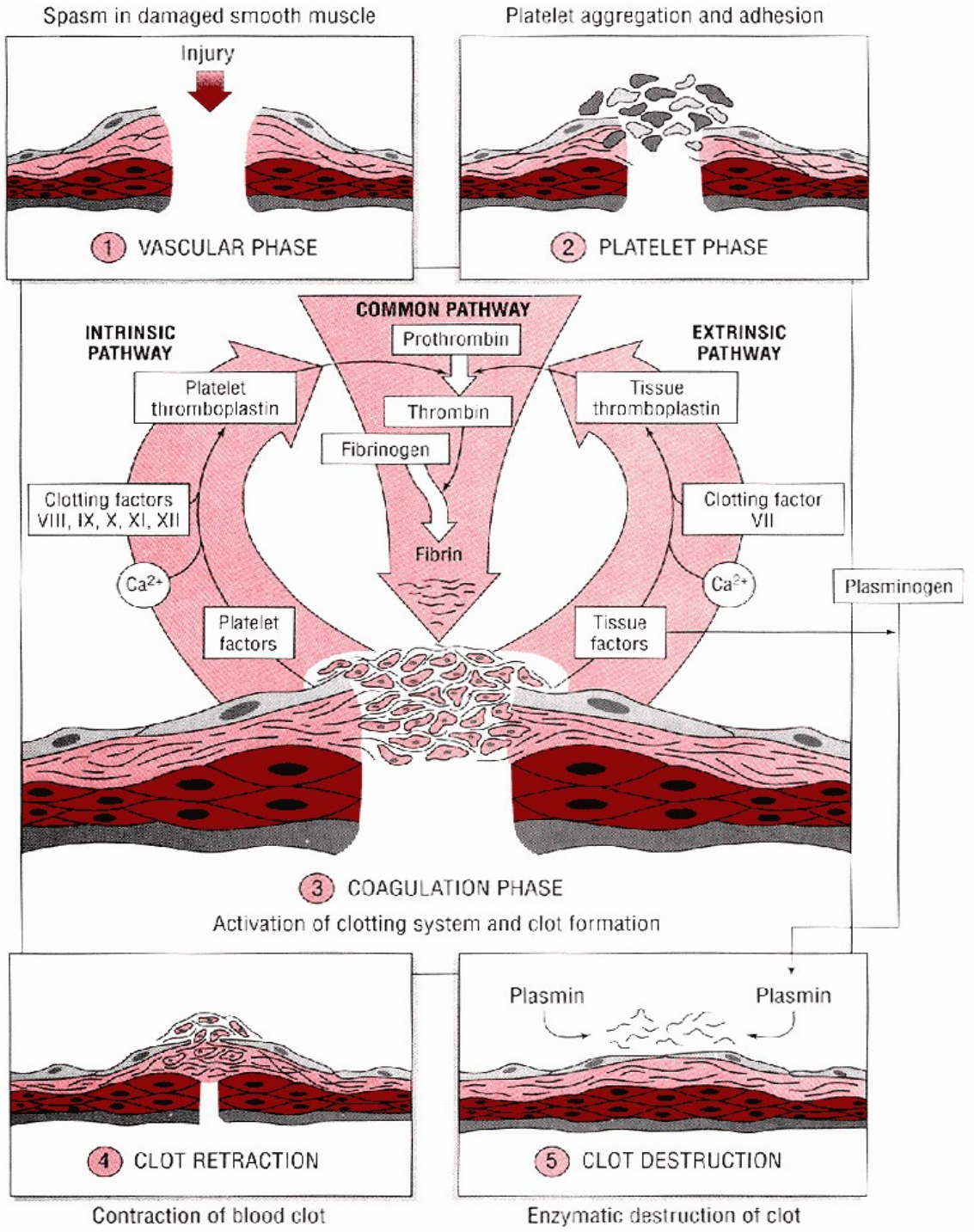
After activation of factor X either by extrinsic of intrinsic mechanisms, both pathways proceed by a common pathway: Activated factor X (Xa), in the presence of tissue phospholipids (which are part of the tissue factor) or platelet phospholipids, plus Ca2+ and factor V, catalyzes the conversion of prothrombin to thrombin. Prothrombin is a plasma protein (α2 globulin) formed by the liver. At first, factor V is inactive, but once thrombin begins to form, the proteolytic action of thrombin activates factor V. Activated factor V (Va) greatly accelerates the protease activity of Xa. Thrombin catalyzes the conversion of the soluble plasma protein fibrinogen to insoluble fibrin. The process involves the removal of 2 pairs of polypeptides from fibrin. The fibrin is initially a loose mesh of interlacing strands, it is converted by the formation of covalent cross-linkages to a dense, tight aggregate. This reaction is catalyzed by active factor XIII (the fibrin-stabilizing factor) and requires Ca2+. Factor XIII is present normally in plasma globulins in small amounts but is also released from the platelets entrapped in the clot and is activated by thrombin.

The blood clot is composed of fibrin network entrapping RBCs, WBCs, platelets, and plasma. Fibrin fibers adhere to damaged surface of blood vessels therefore blood clots become adherent to any vascular opening and thereby prevent blood loss.

Clotting Cascade



Clot retraction: Within few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the colt within 20-60 minutes. The fluid expressed is called serum. Serum differs from plasma in that it cannot clot because all its fibrinogen and most other clotting factors have been removed and also serum has higher serotonin content because of breakdown of platelets during clotting.



Platelets are necessary for clot retraction to occur, and as follows:

[1] They become attached to the fibrin fibers in such a way that they actually bond different fibers together.

[2] Platelets entrapped in the clot continue to release procoagulant substances (substances promoting coagulation), one of which is factor XIII which cause more and more cross-linking bonds between the adjacent fibrin fibers.

[3] Platelets themselves contribute directly to clot contraction by activating platelet thrombosthenin, actin and myosin molecules, which are contractile proteins in the platelets and cause strong contraction of platelet spicules attached to the fibrin. This also helps compress the fibrin meshwork into a smaller mass. The contraction is activated or accelerated by thrombin and by calcium ions released from the calcium stores in the mitochondria, endoplasmic reticulum and Golgi apparatus of the platelets.

As the clot retracts, the edges of the broken blood vessel are pulled together.

When the number of platelets in the circulating blood is low, there will be failure of clot retraction.

Other action of thrombin: In addition to those mentioned above thrombin also has a direct proteolytic effect on prothrombin tending to convert this into still more thrombin. Thrombin also accelerates the actions of factors IX, X, XI, and XII, and causes aggregation of platelets.

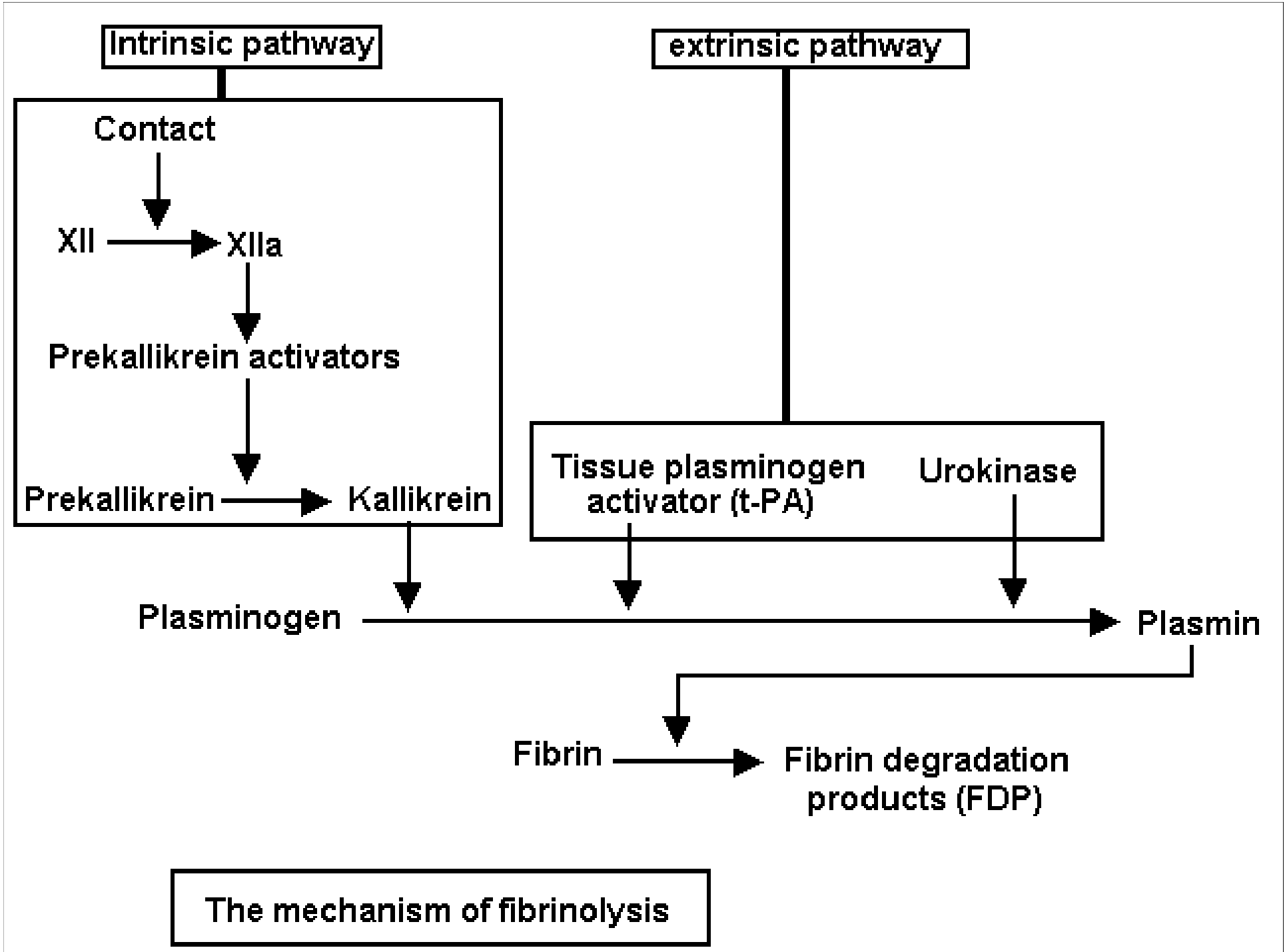
[4] Fibrinolysis: The components of the fibrinolytic system are:

[A] Plasminogen and plasmin: Plasminogen is the inactive precursor of the active fibrinolytic enzyme; plasmin (fibrinolysin). Plasminogen is a glycoprotein synthesized in the liver and present in the plasma.

[B] Plasminogen activators: Which are of two types:

***Intrinsic (blood) activators* (derived from plasma or blood cells): Fibrinolytic activity is generated during contact activation stage of blood coagulation and is generally attributed to kallikrein. On contact activation of factor XII and formation of prekallikrein activators from XIIa, prekallikrein is converted to kallikrein by the prekallikrein activators. Kallikrein stimulates fibrinolysis by acting as plasminogen activator. Red blood cells and granulocytic leukocytes also synthesize plasminogen activators, which may be released in certain pathological states.**

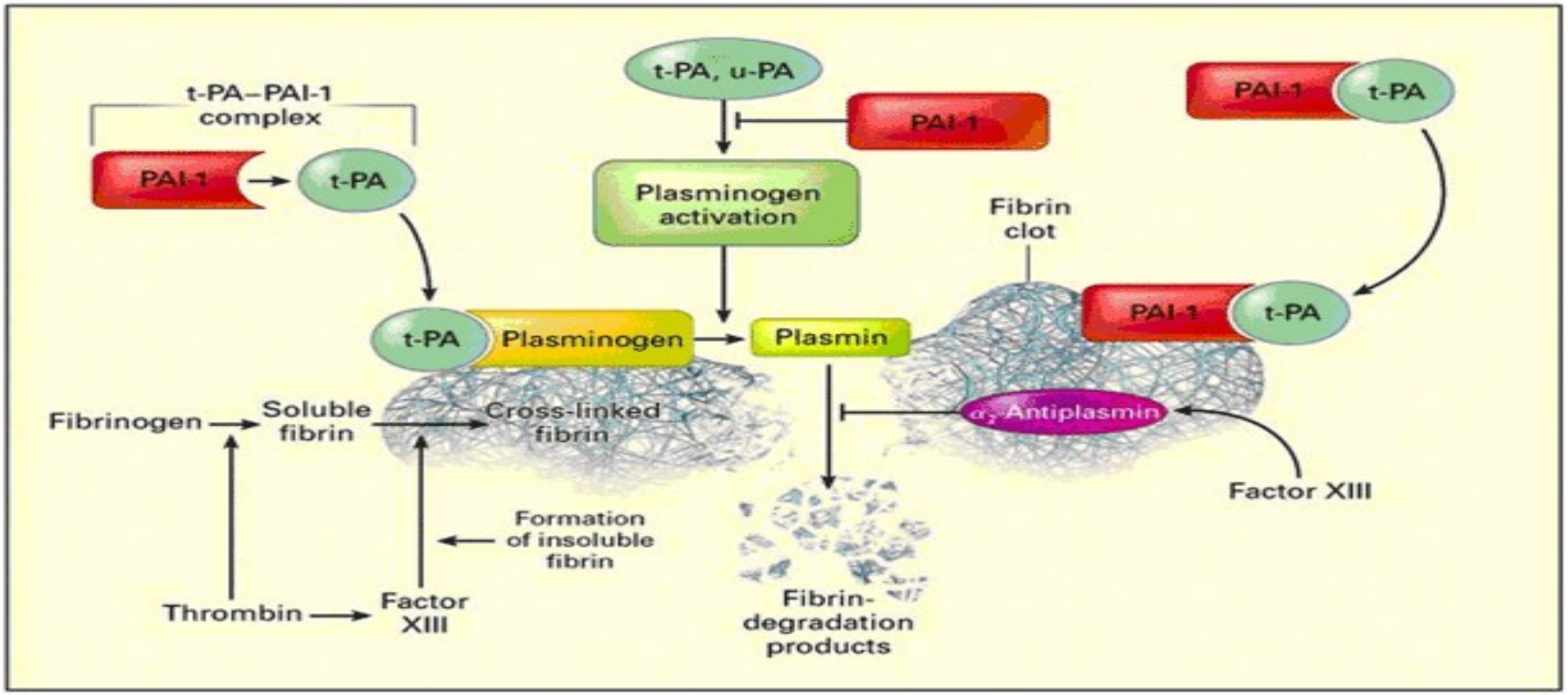
***Extrinsic activators*: Two immunologically distinct plasminogen activators are released from cells and are the tissue plasminogen activator (t-PA) (synthesized mainly by endothelial cells) and urokinase (synthesized mainly by kidney). These proteases are also synthesized in almost all organs of the boy, except the liver. Normal plasma has a very low concentration of these activators, most of which are complexed with plasminogen activator inhibitors.**



The mechanism of fibrinolysis

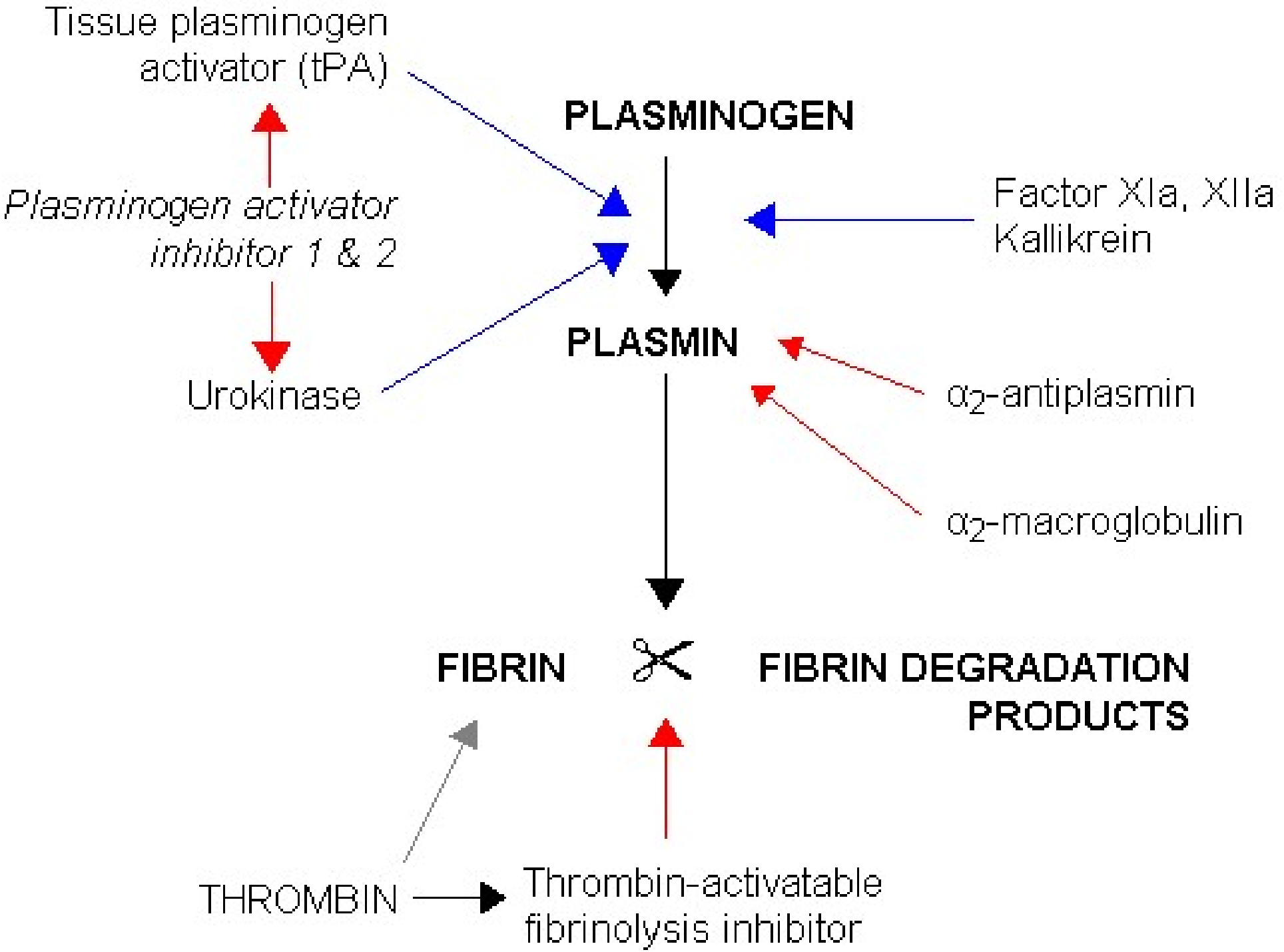
[C] Inhibitors of fibrinolytic activity:

1. ***α2 -antiplasmin (α2 AP)*** **is the principal and most important physiologic inhibitor of plasmin, and is synthesized in the liver and present in the plasma.**
2. ***Plasminogen activator inhibitors*** **(inhibitors of t-PA and urokinase) are synthesized by endothelial cells and by placenta. They are present in the plasma in low concentrations.**



When a clot is formed, a large amount of plasminogen is bound to fibrin, t-PA released slowly from endothelial cells by the action of thrombin is adsorbed on fibrin surface and activates the adsorbed plasminogen and plasmin is generated at the clot surface, and begins to dissolve the fibrin clot with the production of fibrin degradation products, which inhibit thrombin. Free plasmin released into the circulation, from the digested fibrin, is inactivated by α2 AP. Plasmin can also attack other proteins such as fibrinogen and other clotting factors, but this non-specific proteolysis is normally prevented by inactivation of plasmin in blood by α2AP.

The fibrinolytic system removes clots from intravascular and extravascular sites. An especially important function of the fibrinolytic system is to remove minute clots that form in tiny peripheral vessels which otherwise would become occluded.

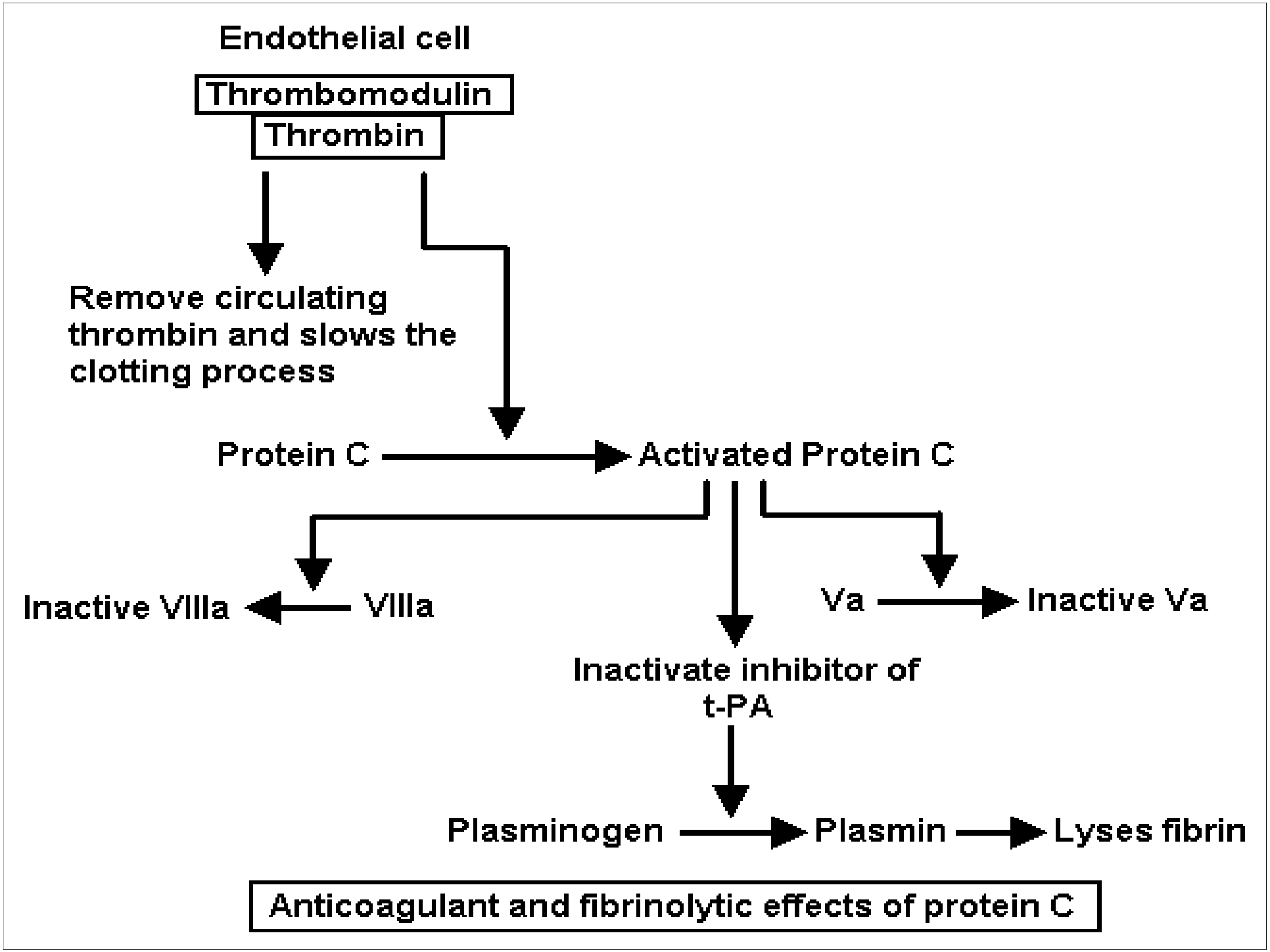

Tissue plasminogen activator (tPA)
PLASMINOGEN
Factor XIa, XIIa Kallikrein
Plasminogen activator inhibitor 1 & 2
PLASMIN
Urokinase
α2-antiplasmin
α2-macroglobulin
FIBRIN
FIBRIN DEGRADATION PRODUCTS
THROMBIN
Thrombin-activatable fibrinolysis inhibitor

Prevention of Clotting in Normal Vascular System and Anticlotting Mechanisms: The in vivo action of the clotting mechanism is balanced by limiting reactions that tend to prevent clotting in uninjured blood vessels and to break down any clots that do form, and also prevent or limit excessive growth and extension of the clot in the injured vessel. These include:

[1] Smoothness of endothelium prevents contact activation of the intrinsic clotting system.

[2] A thin layer of glycocalyx, a mucopolysaccharide, is adsorbed to the inner surface of the endothelium that repels the clotting factors and platelets, thereby prevent activation of clotting.

[3] All endothelial cells, except those in the cerebral microcirculation, produce thrombomodulin, a thrombin-binding protein, and express it on their surface. The binding of thrombin with thrombomodulin slows the clotting process [A] by removing thrombin and [B] also the thrombomodulin-thrombin complex activates a plasma protein, protein C. Activated protein C along with its cofactor protein S inactivates factors Va and VIIIa, and inactivates an inhibitor of t-PA, increasing the formation of plasmin. So binding of thrombin with thrombomodulin prevents the extension of clots into blood vessels.


Endothelial cell
Thrombomodulin
Thrombin
Remove circulating thrombin and slows the clotting process
Protein C
Activated Protein C
Inactive VIIIa
VIIIa
Va
Inactive Va
Inactivate inhibitor of t-PA
Plasminogen
Plasmin
Lyses fibrin
Anticoagulant and fibrinolytic effects of protein C

[4] The interaction between the platelet-aggregating effect of thromboxane A2 and antiaggregating effect of prostacyclin causes clots to form at the site when blood vessel is injured but keeps the vessel lumen free of clot.

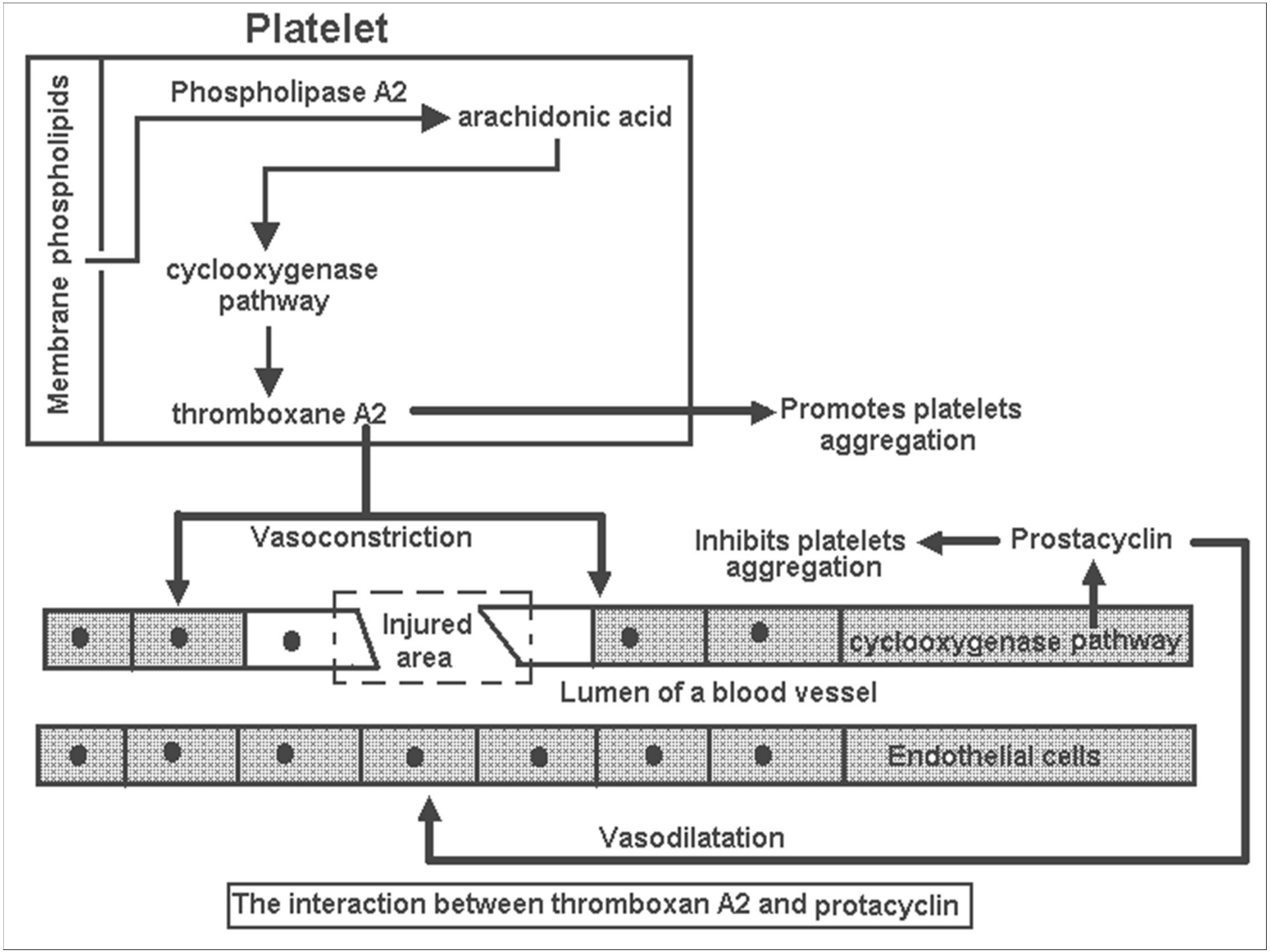
Prostacyclin is produced by endothelial cells and thromboxane A2 by platelets from their common precursor, arachidonic acid (released from membrane phospholipids by phospholipase A2 enzyme), via cyclooxygenase pathway.

Thromboxane A2 promotes platelet aggregation and vasoconstriction.

Prostacyclin inhibits platelet aggregation and promotes vasodilatation.

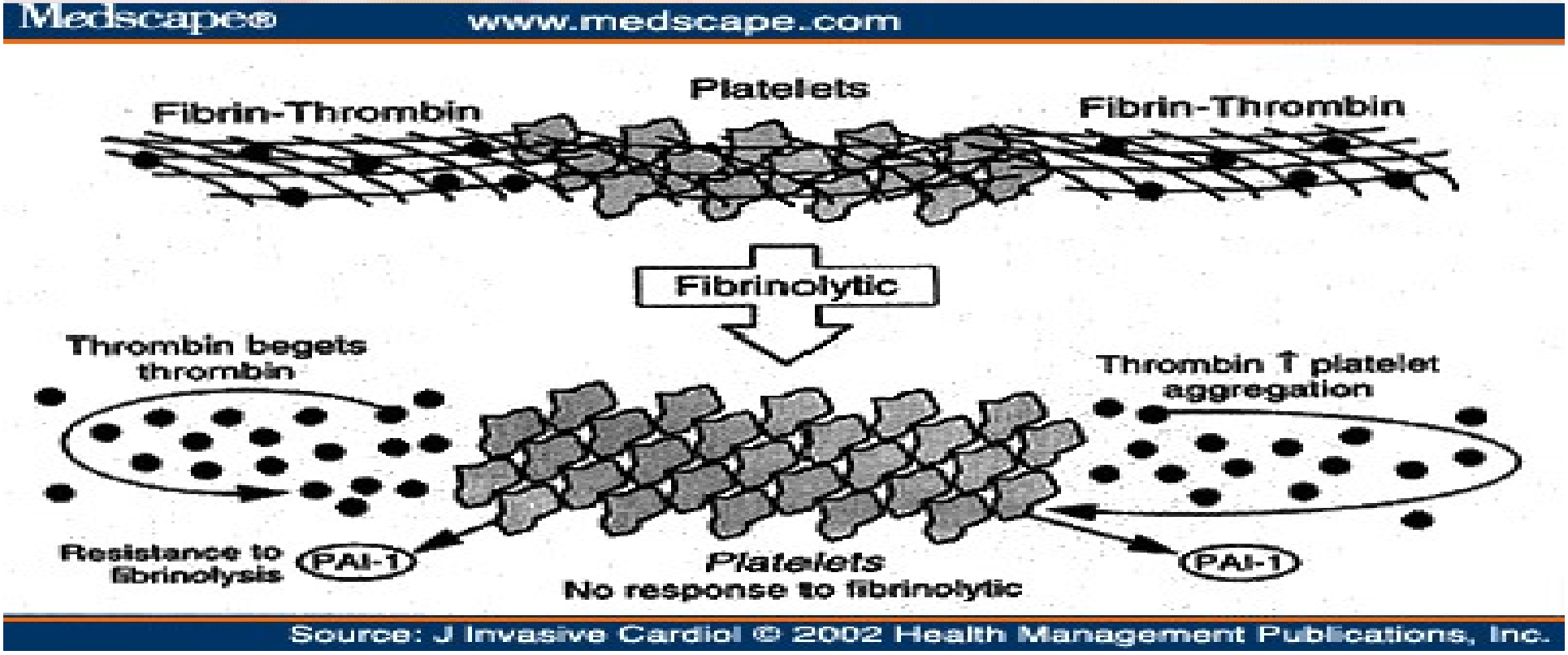
Release of thromboxane A2 by platelets at the immediate site of injury to a blood vessel promotes clot formation whereas prostacyclin formation by endothelial cells around the injury site keeps the clot localized and prevents extensive extension of the clot and maintains the patency of the rest of the vessel.

The thromboxane A2-prostacyclin balance can be shifted toward prostacyclin by administration of low doses of aspirin. Aspirin produces irreversible inhibition of cyclooxygenase, and this reduces production of both thromboxane A2 and prostacyclin. However, endothelial cells produce new cyclooxygenase in a matter of hours whereas platelets cannot manufacture the enzyme and the level rises only as new platelets enter the circulation, which is a slow process. Therefore, administration of small amounts of aspirin for prolonged periods has been shown to be of value in preventing formation of clots in cerebral and myocardial vessels.


Platelet
Membrane phospholipids
Phospholipase A2
arachidonic acid
cyclooxygenase pathway
thromboxane A2
Promotes platelets aggregation
Vasoconstriction
Inhibits platelets aggregation
Prostacyclin
Injured area
cyclooxygenase pathway
Lumen of a blood vessel
Endothelial cells
Vasodilatation
The interaction between thromboxan A2 and protacyclin

[5] Antithrombin action of fibrin and antithrombin III. While a clot is forming, most of thrombin formed from prothrombin becomes adsorbed to the fibrin. This prevents spread of thrombin into the remaining blood and therefore prevents excessive spread of the clot. The thrombin that does not adsorb to fibrin soon combines with antithrombin III (an α2-globulin that circulates in the plasma) and becomes inactivated. Antithrombin III inhibits other factors too (Ixa, Xa, XIa, XIIa). Normally the concentration of heparin, a naturally occurring anticoagulant, in blood is slight. It combines with antithrombin III increasing the effectiveness of antithrombin III in removing thrombin and the clotting factors Ixa, Xa, XIa, XIIa.

[6] The fibrinolytic system



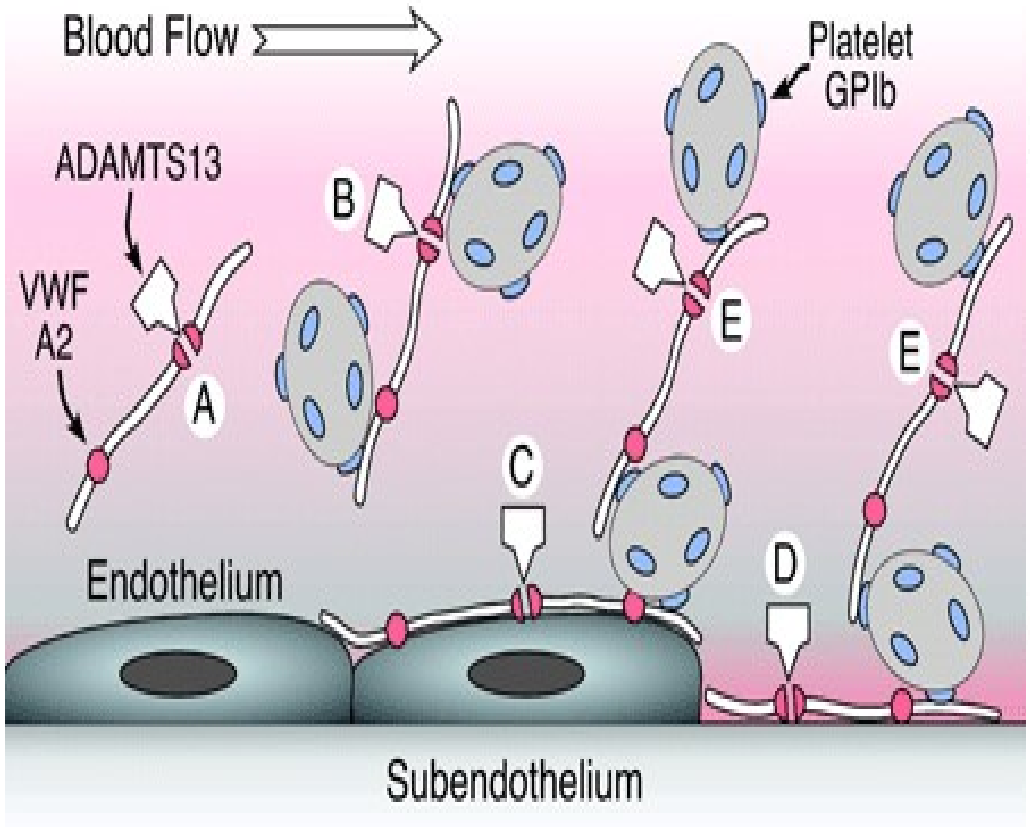
Abnormalities of Hemostasis

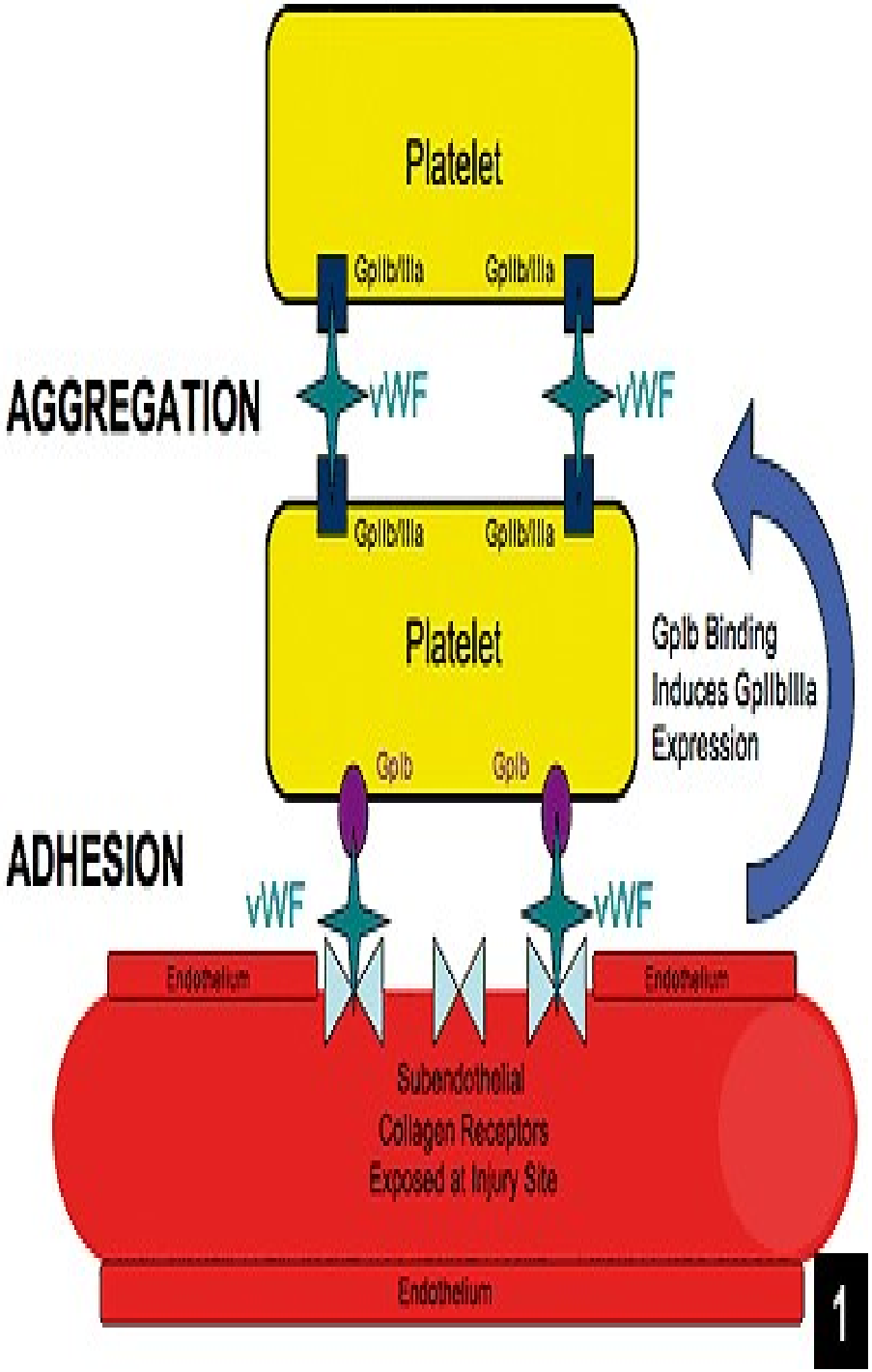
Bleeding tendency: Abnormal bleeding may occur in different conditions. Bleeding can be seen on the skin or mucous membranes as "petechiae", which are pin point purplish hemorrhagic spots, or as "purpura" which are extensive area of red or dark purple discoloration. Bleeding can be in subcutaneous tissue in form of "ecchymosis" (or bruises) and hematomas (collection of blood). Bleeding also can occur in internal organs and from the body orifices.

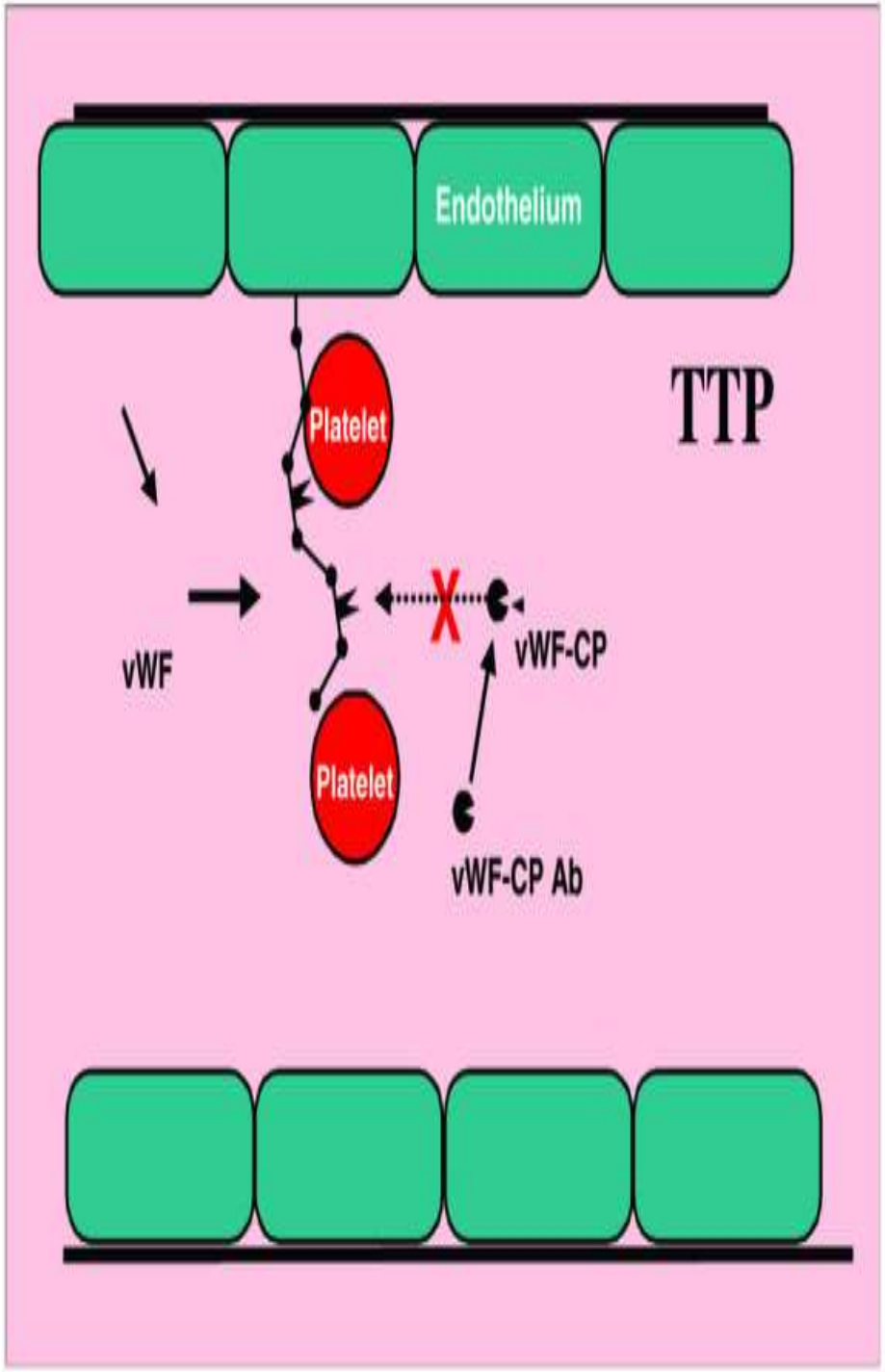
Bleeding tendency can occur due to vascular disorders, platelet disorders or disorders of blood coagulation.

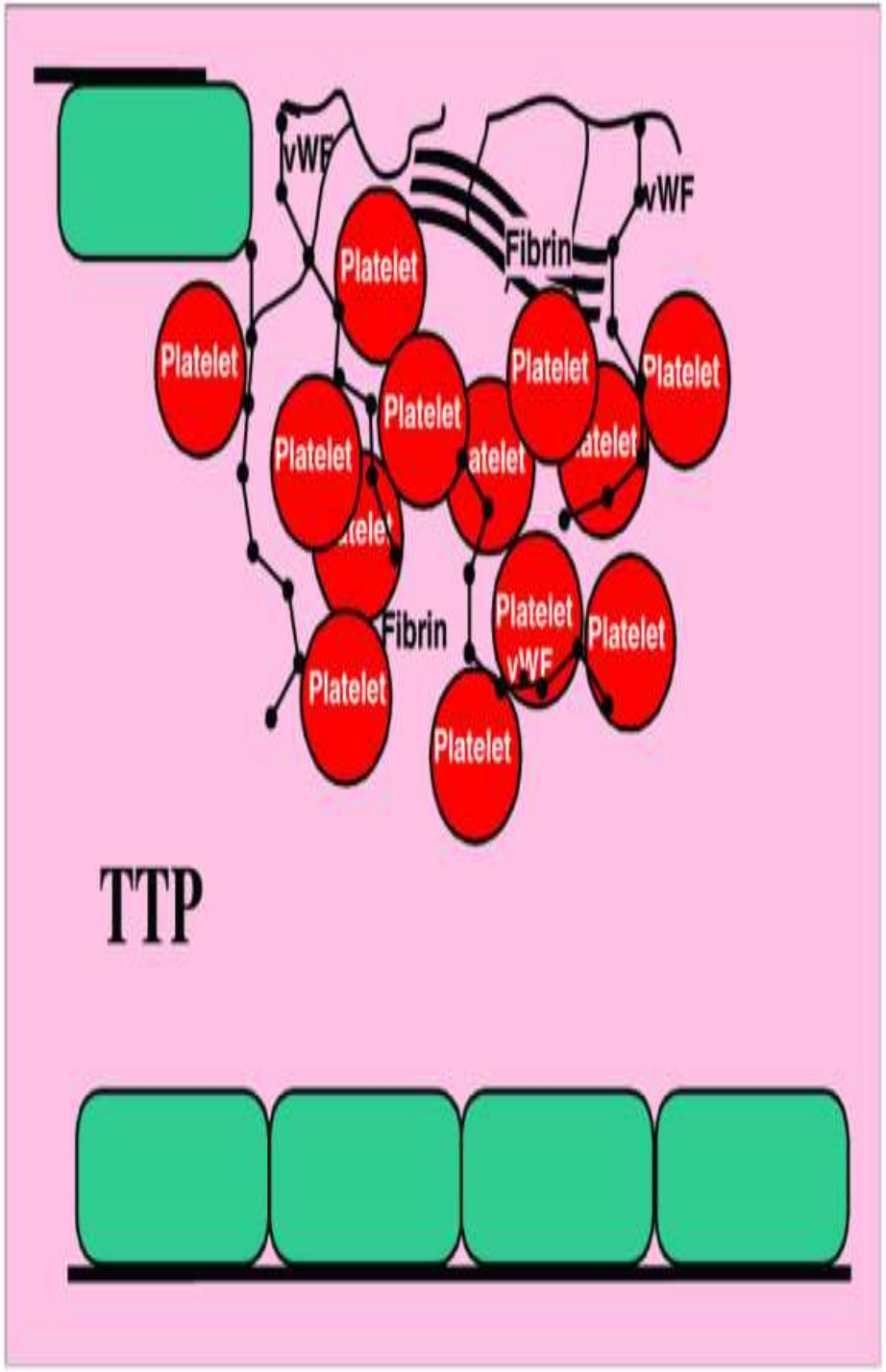
Vascular disorder may be due to damage of connective tissue of vessel wall such as in senility, hereditary disease and scurvy. Or it may be due to damage of endothelium of blood vessel by for example some infections or drugs.

Platelet disorders: Normal platelet number and function is needed for normal hemostasis. Low platelet count is known as "*thrombocytopenia*" and could be due to many causes; such as decreased production of platelets, which occur with folate or B12 deficiency, radiation, chemotherapy or marrow replacement by tumor. Or increased destruction of platelets by some drugs or in a certain condition known as "idiopathic thrombocytopenic purpura" specific Abs are formed and react against the platelets to destroy them. Abnormal platelet function (*thrombocytopathy*) also causes bleeding tendency. Such as in von Willebrand's disease which is an inherited disease, in which platelet count and structure are normal, but platelets cannot adhere to vascular subendothelium because of deficiency of von Willebrand factor (vWF). This factor is a protein synthesized by endothelial cells and megakaryocytes. Platelet adherence requires the presence of vWF because this factor forms bridges between platelets and subendothelial components allowing platelets to adhere to damaged vessel walls. vWF also acts as carrier protein for factor VIII, a deficiency of vWF therefore also results in a secondary reduction in factor VIII level in plasma. In addition, some drugs can also affect platelet function such as aspirin, which impairs aggregation of platelets, as explained earlier.


Blood Flow
Platelet
GPIb
ADAMTS13
VWF
A2
A
B
C
D
E
E
Endothelium
Subendothelium


Platelet
GpIIb/IIIa
GpIIb/IIIa
AGGREGATION
vWF
vWF
GpIIb/IIIa
GpIIb/IIIa
Platelet
GpIb Binding
Induces GpIIb/IIIa
Expression
GpIb
GpIb
ADHESION
vWF
vWF
Endothelium
Endothelium
Subendothelial
Collagen Receptors
Exposed at Injury Site
Endothelium


Endothelium
TTP
Platelet
vWF
vWF-CP
Platelet
vWF-CP Ab


vWF
vWF
Fibrin
Platelet
Platelet
Platelet
Platelet
Platelet
Platelet
Platelet
Fibrin
Platelet
vWF
Platelet
Platelet
TTP

Disorders of blood coagulation could be due to different causes such as:

Deficiency of clotting factors due to hereditary defects as in *classic hemophilia* (factor VIII is deficient) and in *Christmas disease* (factor IX is deficient).

***Deficiency of vitamin K*, which can cause decreased synthesis of prothrombin and factors VII, IX and X in liver, because vitamin K is necessary for formation of these factors in liver.**

***Liver diseases* which cause defective production of coagulation factors (prothrombin, fibrinogen, and factors VII, IX, X... etc) because many or almost all clotting factors are formed by liver. Also liver diseases lead to a fall in plasma concentration of the plasma inhibitor, α2-antiplasmin.**

Thromboembolic conditions: An abnormal clot that develops inside a blood vessel is called a "thrombus". Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment or break off bits of the thrombus to flow along with the blood, such freely flowing clots are known as "emboli". Emboli do not stop flowing until they come to a narrow point in the circulatory system. Thus, emboli that originate in large arteries or in the left side of the heart eventually plug either smaller arteries or arterioles in the brain, kidneys, or elsewhere. Emboli that originate in the venous system and in the right side of the heart flow into the vessels of the lung to cause pulmonary arterial embolism.

The causes of thromboembolic conditions include:

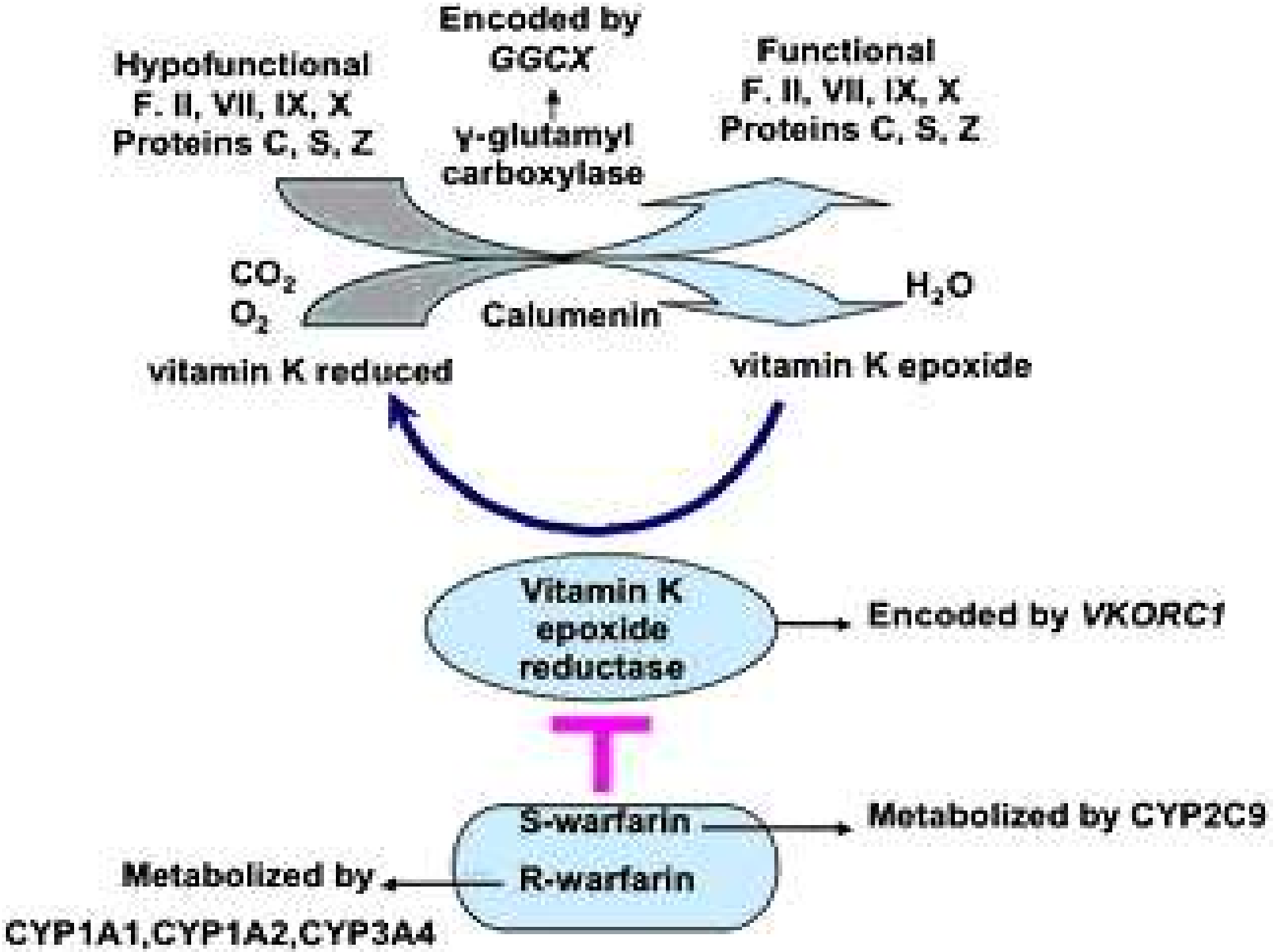
1. **Roughened endothelial surface of a vessel, as may be atherosclerosis, is likely to initiate the clotting process.**
2. **Slow blood flow through blood vessels, because the slow flow permits activated clotting factors to accumulate instead of being washed away.**
3. **Congenital absence of protein C.**
4. **Resistance to activated protein C due to a mutation in the gene for factor V, which prevents activated protein C from inactivating the factor.**
5. **Mutations in protein S and antithrombin III.**

To treat or prevent thromboembolic conditions, anticoagulants can be used clinically to delay coagulation process to a certain degree. These include:

1. *Heparin*, which is commercially extracted from several different animal tissues and prepared in almost pure form, is given as intravenous injection. It binds to antithrombin III increasing its effectiveness in inhibiting thrombin and factors IXa, Xa, XIa, and XIIa.

2. *Coumarin derivatives* such as warfarin which is given orally and acts by inhibiting the action of vitamin K, so the plasma levels of prothrombin, and factors VII, IX, and X begin to fall due to decreased liver formation of these factors, because vitamin k is required for their synthesis.

Outside the body (in vitro) clotting can be prevented by: 1. Heparin 2. Removal of Ca^{2+} from the blood by addition of substances such as oxalates which form insoluble salts with Ca^{2+}, or citrates, which bind Ca^{2+}.


Encoded by
GGCX
γ-glutamyl
carboxylase
Hypofunctional
F. II, VII, IX, X
Proteins C, S, Z
Functional
F. II, VII, IX, X
Proteins C, S, Z
CO_2
O_2
Calumenin
H_2O
vitamin K reduced
vitamin K epoxide
Vitamin K
epoxide
reductase
Encoded by *VKORC1*
S-warfarin
Metabolized by CYP2C9
Metabolized by
R-warfarin
CYP1A1,CYP1A2,CYP3A4

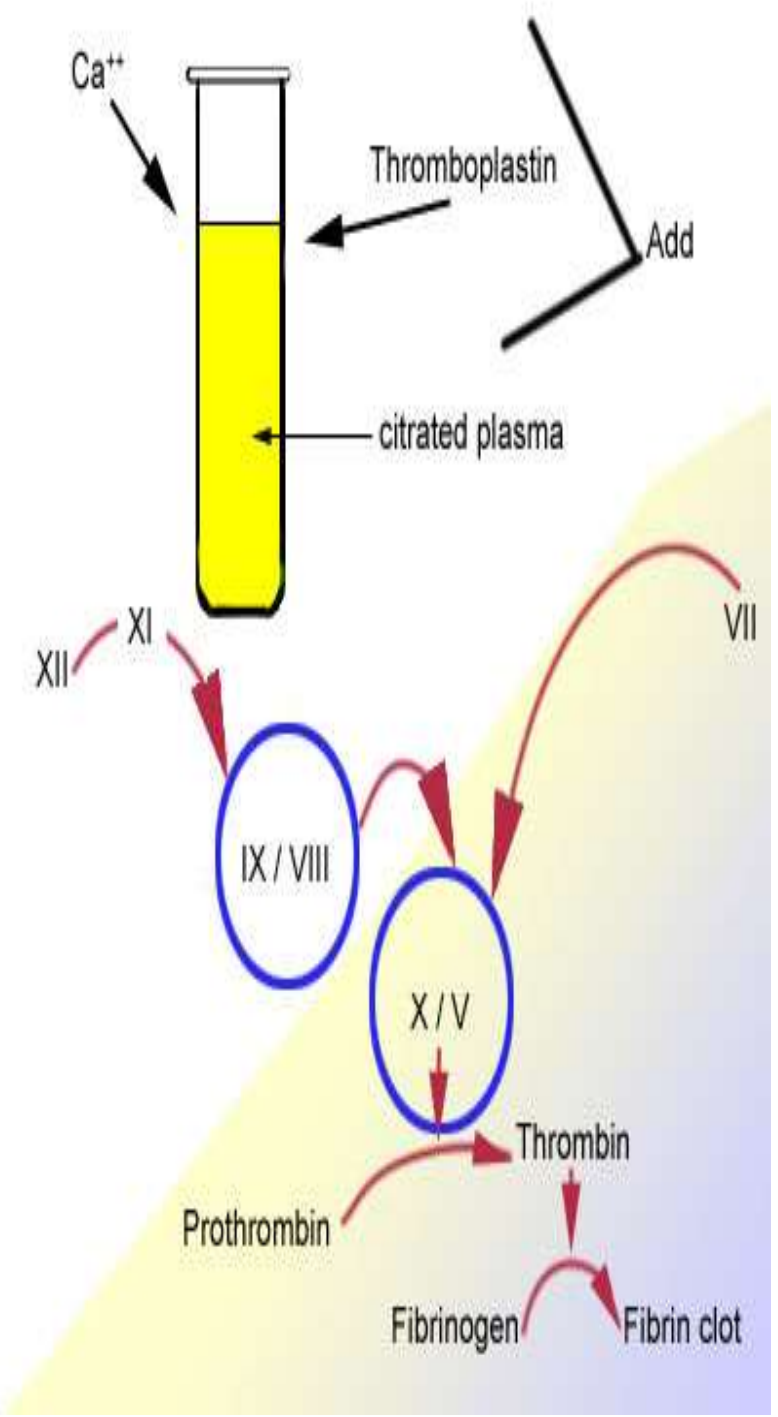
Screening Tests of Hemostasis: Hemostasis function is examined in clinical medicine to evaluate the possibility of abnormal bleeding, and to obtain information for the diagnosis and management of diseases whose manifestations include disturbed hemostasis. The tests, which usually provide a satisfactory screen of hemostatic function, include:

1. Platelets count.
2. Bleeding time.
3. Prothrombin time.
4. Activated partial thromboplastin time.
5. Thrombin time.

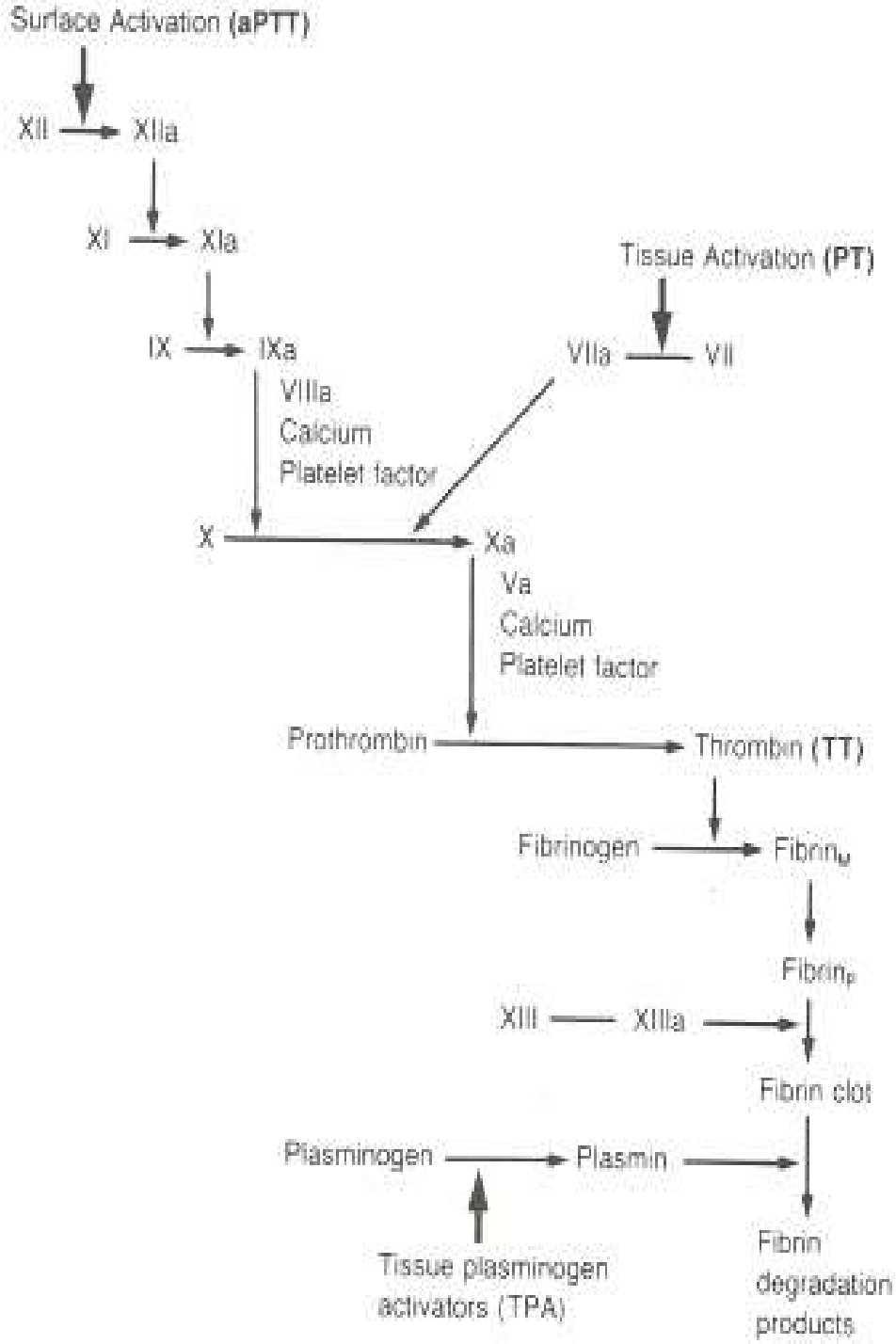
Platelet count: **From this test we can find out if the patient has thrombocytopenia. When platelet count is between 50,000-100,000 per microliter of blood, bleeding may occur after major trauma, and between 20,000-50,000/ microliter, bleeding may occur after minor trauma, and if platelet count is below 20,000/ microliter of blood, spontaneous hemorrhages may occur.**

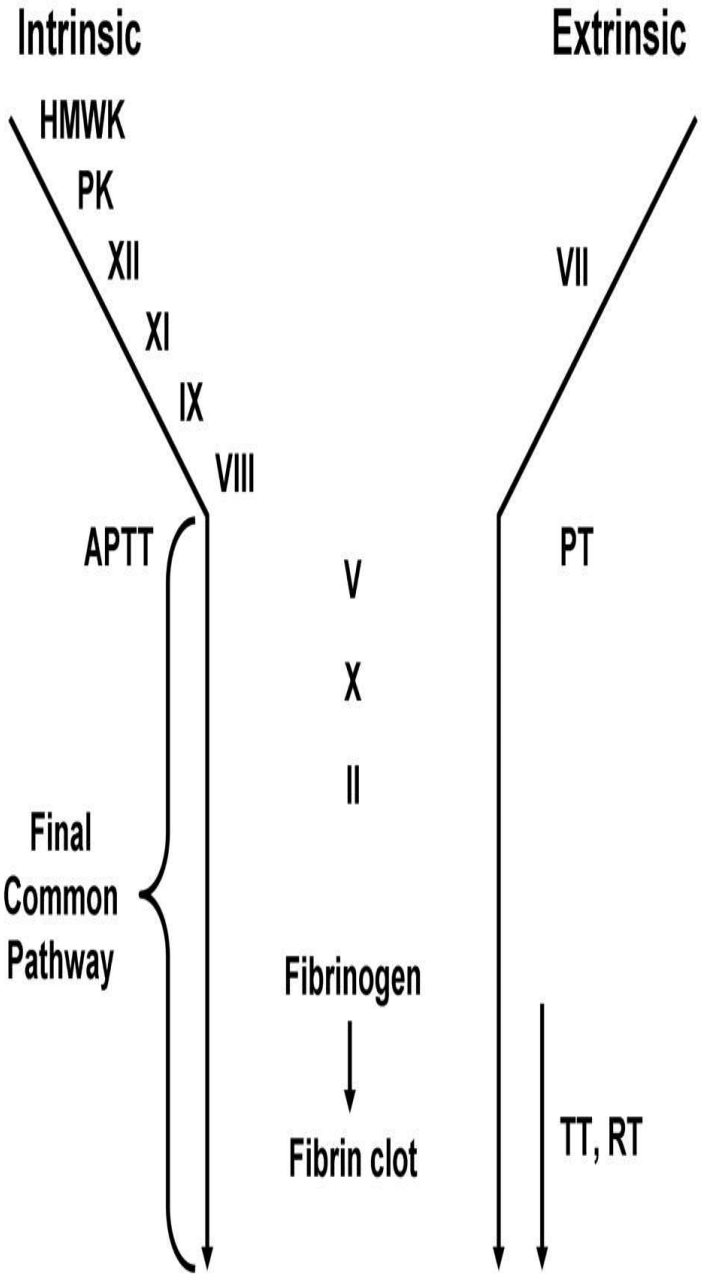
Bleeding time: **This test involves making a small wound in the skin and measuring the time taken for bleeding to cease i.e. measuring the time it takes to form platelet plugs that stop the bleeding. It is a screening test of platelet numbers and function. Normal bleeding time ranges from 2-7 minutes and depends on the method used. It is prolonged in thrombocytopenia, and in disorders of platelet function such as in von Willebrand's disease.**

Prothrombin time (PT): **The PT procedure evaluates the generation of thrombin and formation of fibrin via the extrinsic pathway. Extrinsic tissue thromboplastin and calcium ions are added to the citrated plasma, and the time required for the fibrin clot to form is measured and compared with the time obtained with plasma from a normal subject. Normal value range from 11 to 15 seconds and depend on the exact procedure and reagent used. PT is prolonged by deficiency of one or more factors in the extrinsic pathway: Factors VII, X, V, prothrombin, and fibrinogen. So abnormal PT can be found in conditions such as liver disease and vitamin K deficiency. Clinically, PT is used to control the dose of oral anticoagulants such as warfarin.**



Activated partial thromboplastin time (APTT): **APTT procedure measures the time required for generation of thrombin and formation of fibrin via the intrinsic pathway. In this test, calcium ions, phospholipids (that substitute for platelet phospholipids), and an activator such as kaolin (to optimize contact activation reactions), are added to citrated plasma. The generation of fibrin is the end point. So clotting time is noted and compared with the time obtained with normal plasma. Normal values range from 30 to 40 seconds and depend on the procedure and reagent used. APTT assay reflects the activity of prekallikrein, HMW kininogen, and factors XII, XI, IX, VIII, X, V, prothrombin, and fibrinogen which are involved in the intrinsic pathway of blood coagulation. Abnormal APTT can be found in conditions such as classic hemophilia, Christmas disease, von Willebrand's disease, and liver disease. In practice, APTT is used to control anticoagulant therapy with heparin.**


Surface Activation (aPTT)
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Calcium
Platelet factor
Tissue Activation (PT)
VIIa
VII
X
Xa
Va
Calcium
Platelet factor
Prothrombin
Thrombin (TT)
Fibrinogen
Fibrin$_M$
Fibrin$_P$
XIII
XIIIa
Fibrin clot
Plasminogen
Plasmin
Tissue plasminogen activators (TPA)
Fibrin degradation products


Intrinsic
Extrinsic
HMWK
PK
XII
XI
IX
VIII
VII
APTT
PT
V
X
II
Final Common Pathway
Fibrinogen
Fibrin clot
TT, RT

Thrombin time (TT): **The TT test measures the final reaction of fibrin formation from fibrinogen. A calcium and thrombin mixture is added to citrated plasma and clotting time is measured and compared with the time obtained with normal plasma. Normal values range between 10 to 15 seconds and depend on the method and reagent used. TT is abnormal if fibrinogen concentration is below 100 mg/dl, and in the presence of thrombin inhibitors such as heparin and fibrin degradation products. TT can be used to monitor heparin therapy.**

When screening tests are abnormal, the pattern of abnormality plus the patient's other clinical findings provide the information needed to proceed with more specific tests.

Thank You