Hemostasis and Coagulation

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HEMATOLOGY PART 2

Hemostasis

Process by which blood is maintained in a fluid state and confined to the circulatory system

Goal is to stop bleeding and to do so only at the site of injury
Components

– Platelets

• Involved in Primary Hemostasis

– Coagulation system

• Involved in Secondary Hemostasis

– Fibrinolytic system

– Inflammatory processes

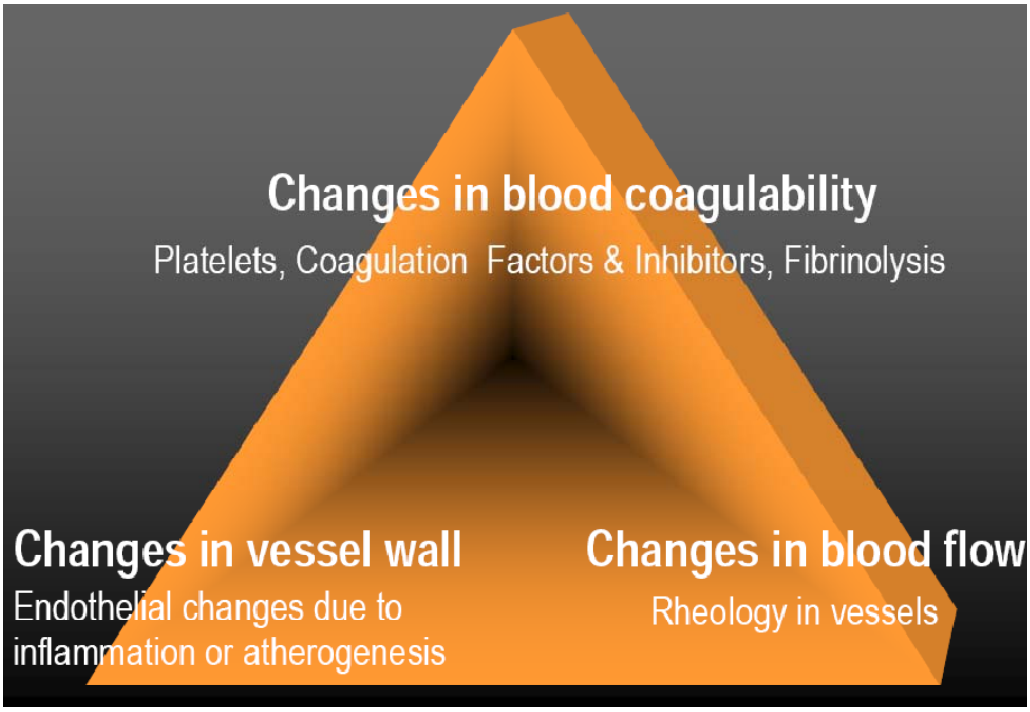
– Wound healing processes

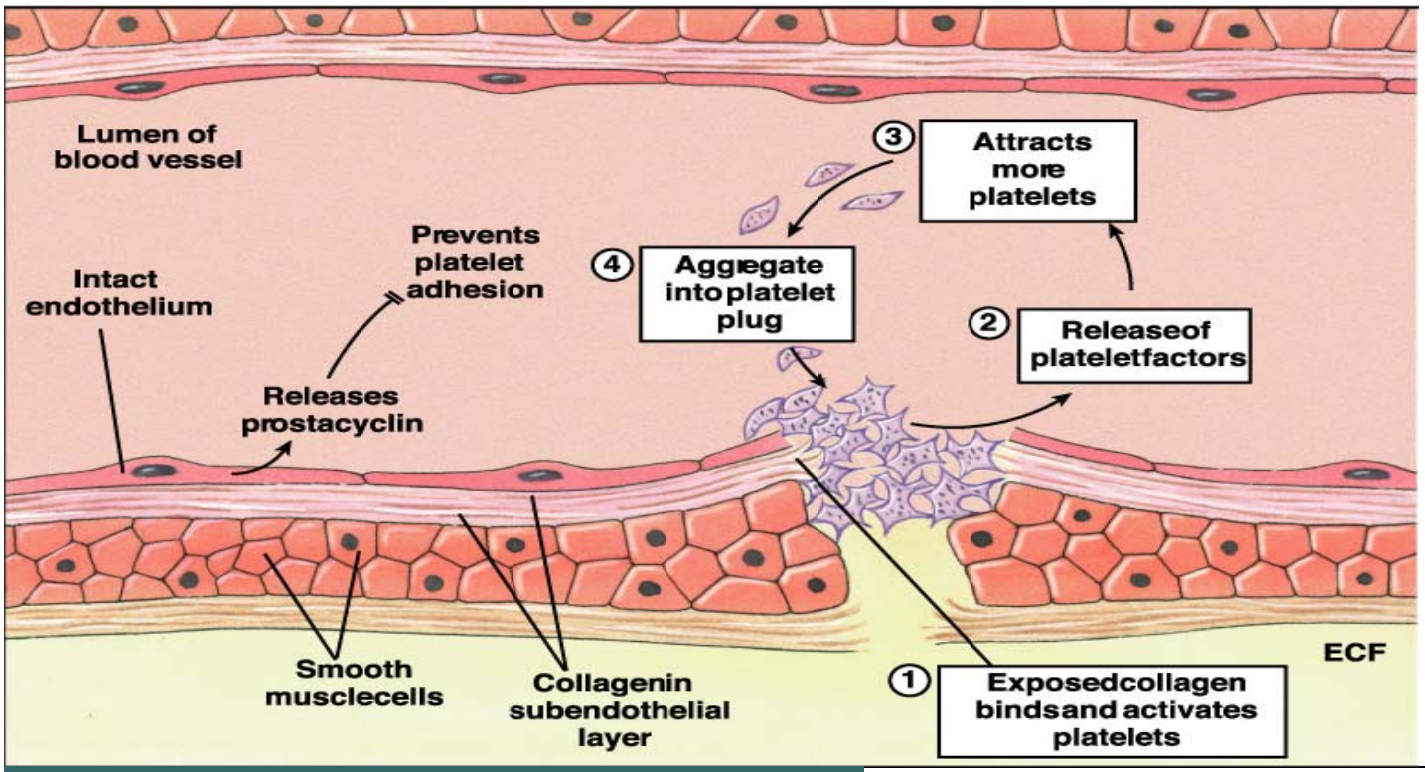
Platelets -
small, anuclear cytoplasmic disks. In an unstimulated state, the shap is discoid.

Hemostasis -
the process in circulation where the blood is maintained fluid in vessels and without major loss in case of injury.

Coagulation factors -
Components that exist in the circulation and supply the necessary constituents for clot formation.

Virchow's Triad





Overview of Hemostasis: Clot Formation & Vessel Repair

Figure 16-11: Overview of hemostasis and

Hemostasis

- A series of reactions for stoppage of bleeding
- During hemostasis, three phases occur in rapid sequence
  - Vascular spasms – immediate vasoconstriction in response to injury
  - Platelet plug formation
  - Coagulation (blood clotting)

Coagulation *in vitro*

	Clotting time

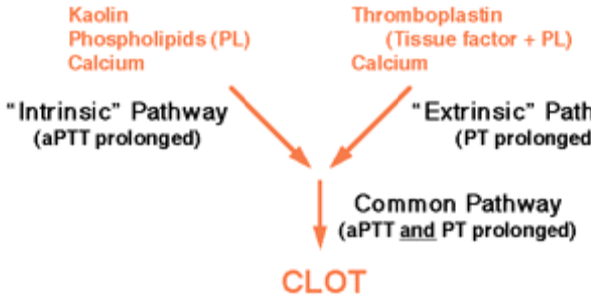
Platelet Plug Formation

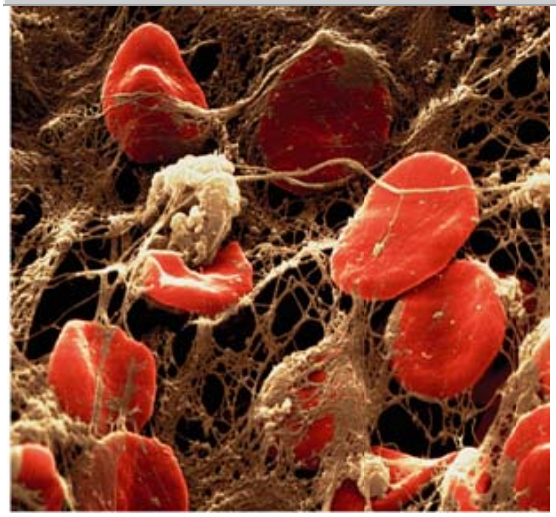
- Platelets do not stick to each other or to blood vessels
- Upon damage to blood vessel endothelium platelets:
  - With the help of von Willebrand factor (VWF) adhere to collagen
  - Are stimulated by thromboxane A2
  - Stick to exposed collagen fibers and form a platelet plug
  - Release serotonin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

Coagulation

- A set of reactions in which blood is transformed from a liquid to a gel
- 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

Whole blood	4-8 min
Whole blood + EDTA or citrate	infinite
Citrated platelet-poor plasma + Ca^{++}	2-4 min
Citrated platelet-poor plasma + PL + Ca^{++}	60-85 sec
Citrated platelet-poor plasma + kaolin + PL + Ca^{++}	21-32 sec (aPTT)
Citrated platelet-poor plasma + thromboplastin + Ca^{++}	11-12 sec (PT)





Coagulation
Detailed Events of Coagulation

Coagulation Phase 1: Two Pathways to Prothrombin Activator

- May be initiated by either the intrinsic or extrinsic pathway
  - Triggered by tissue-damaging events
  - Involves a series of procoagulants
  - Each pathway cascades toward factor X
- Once factor X has been activated, it complexes with calcium ions, PF_3, and factor V to form prothrombin activator

Coagulation Phase 2: Pathway to Thrombin

- Prothrombin activator catalyzes the transformation of prothrombin to the active enzyme thrombin

Coagulation Phase 3: Common Pathways to the Fibrin Mesh

- Thrombin catalyzes the polymerization of fibrinogen into fibrin
- Insoluble fibrin strands form the structural basis of a clot
- Fibrin causes plasma to become a gel-like trap
- Fibrin in the presence of calcium ions activates factor XIII that:
  - Cross-links fibrin
  - Strengthens and stabilizes the clot

Clot Retraction and Repair

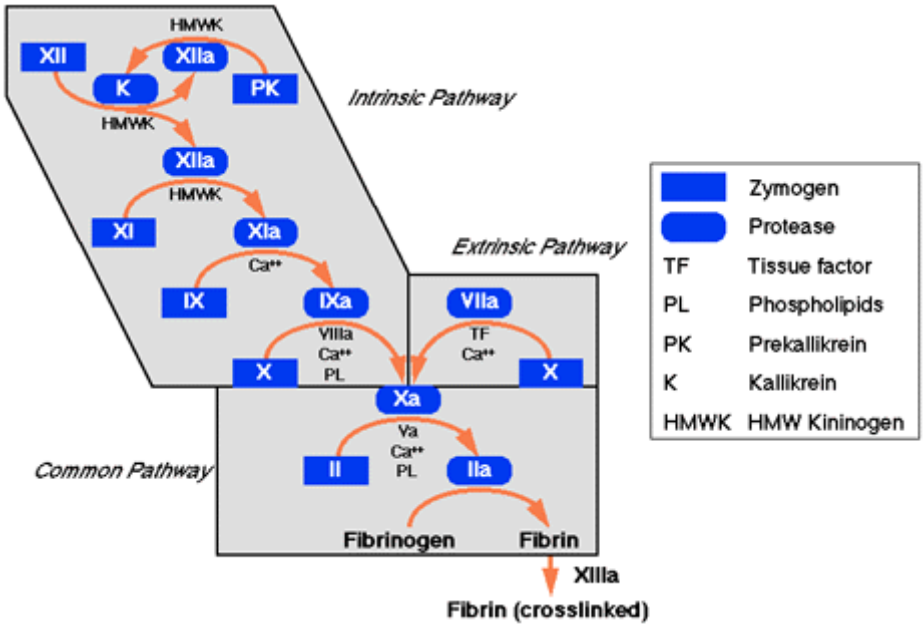
- Clot retraction – stabilization of the clot by squeezing serum from the fibrin strands
- Repair
  - Platelet-derived growth factor (PDGF) stimulates rebuilding of blood vessel wall
  - Fibroblasts form a connective tissue patch
  - Stimulated by vascular endothelial growth factor (VEGF), endothelial cells multiply and restore the endothelial lining

Factors Limiting Clot Growth or Formation

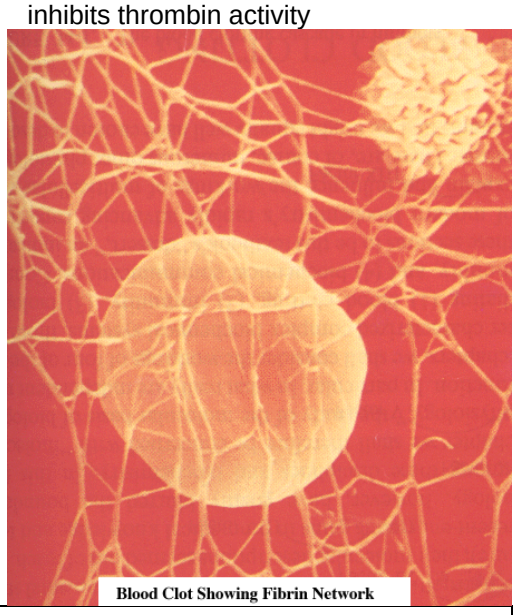
- Two homeostatic mechanisms prevent clots from becoming large
  - Swift removal of clotting factors
  - Inhibition of activated clotting factors

Inhibition of Clotting Factors

- Fibrin acts as an anticoagulant by binding thrombin and preventing its:
  - Positive feedback effects of



coagulation
  - Ability to speed up the production of prothrombin activator via factor V
  - Acceleration of the intrinsic pathway by activating platelets
- Thrombin not absorbed to fibrin is inactivated by antithrombin III
- Heparin, another anticoagulant, also inhibits thrombin activity


Blood Clot Showing Fibrin Network

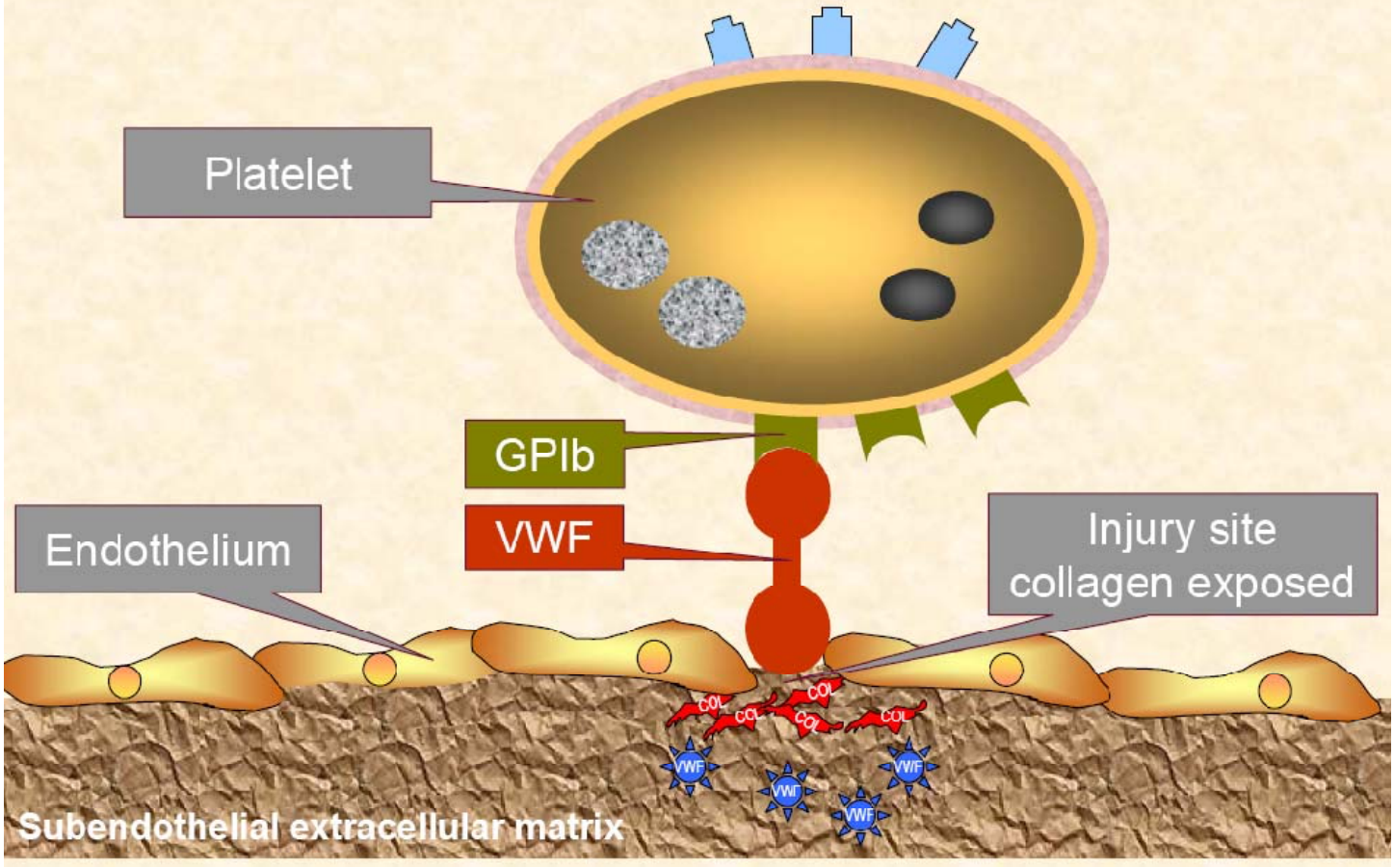
Factors Preventing Undesirable Clotting

- Unnecessary clotting is prevented by endothelial lining the blood vessels
- Platelet adhesion is prevented by:
  - The smooth endothelial lining of blood vessels
  - Heparin and PGI_2 secreted by endothelial cells
  - Vitamin E quinone, a potent anticoagulant

Primary Hemostasis	**Secondary Hemostasis**
First physiological response to vascular injury, which is mediated by platelets, in order to arrest bleeding Mechanism – Activation of platelets via stimulators such as thrombin – Adhesion of platelets to subendothelium via interaction between GPIb and von Willebrand Factor (VWF) – Release of platelet granule products in order to recruit more platelets to the injured site – Aggregation of platelets via interaction between **GPIIb/IIIa (αIIbβ3) and fibrinogen to form the initial plug** Triggers secondary hemostasis (coagulation proteins) Affected by medications, platelet function status, and vessel wall status	Process of blood coagulation Mechanism – Coagulation proteins work in concert to generate thrombin – Thrombin converts fibrinogen to fibrin – Fibrin consolidates the platelet plug made in primary hemostasis such that a thrombus (secondary hemostatic plug) is formed Prevents further blood loss from the injury site Credit: Weisel JW. University of Pennsylvannia

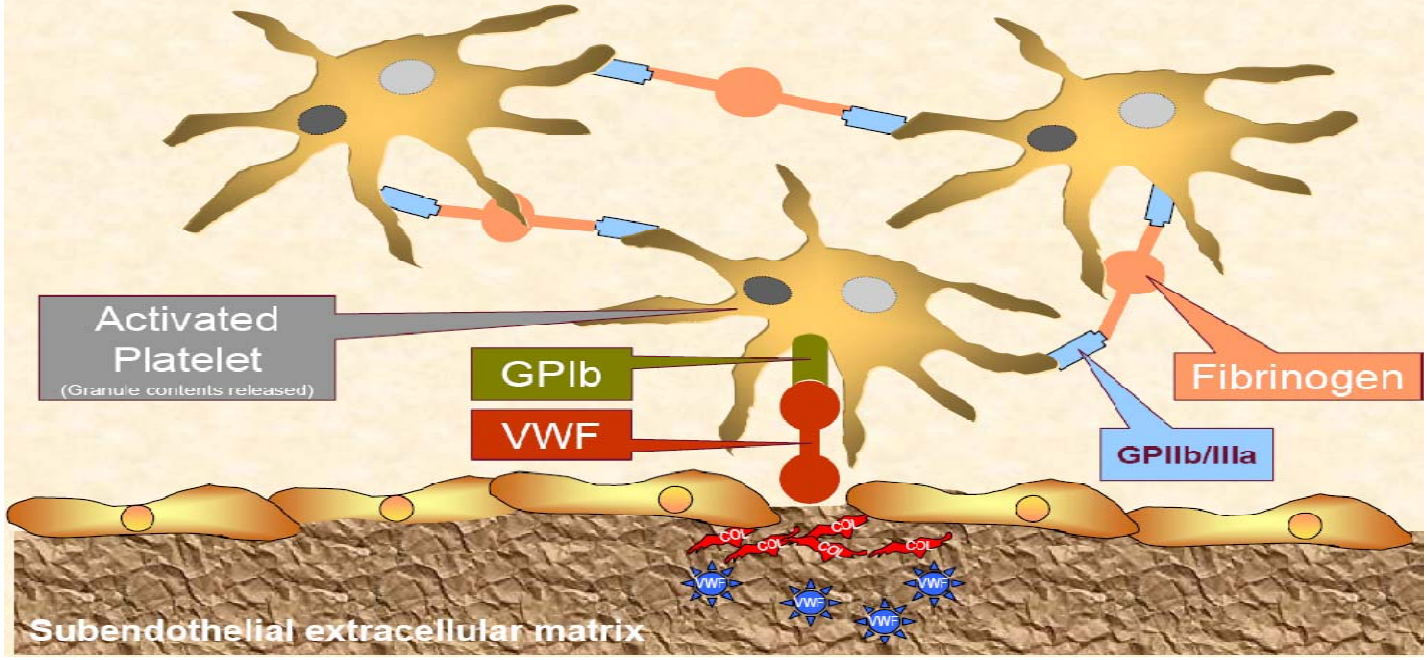
CLOT-ED

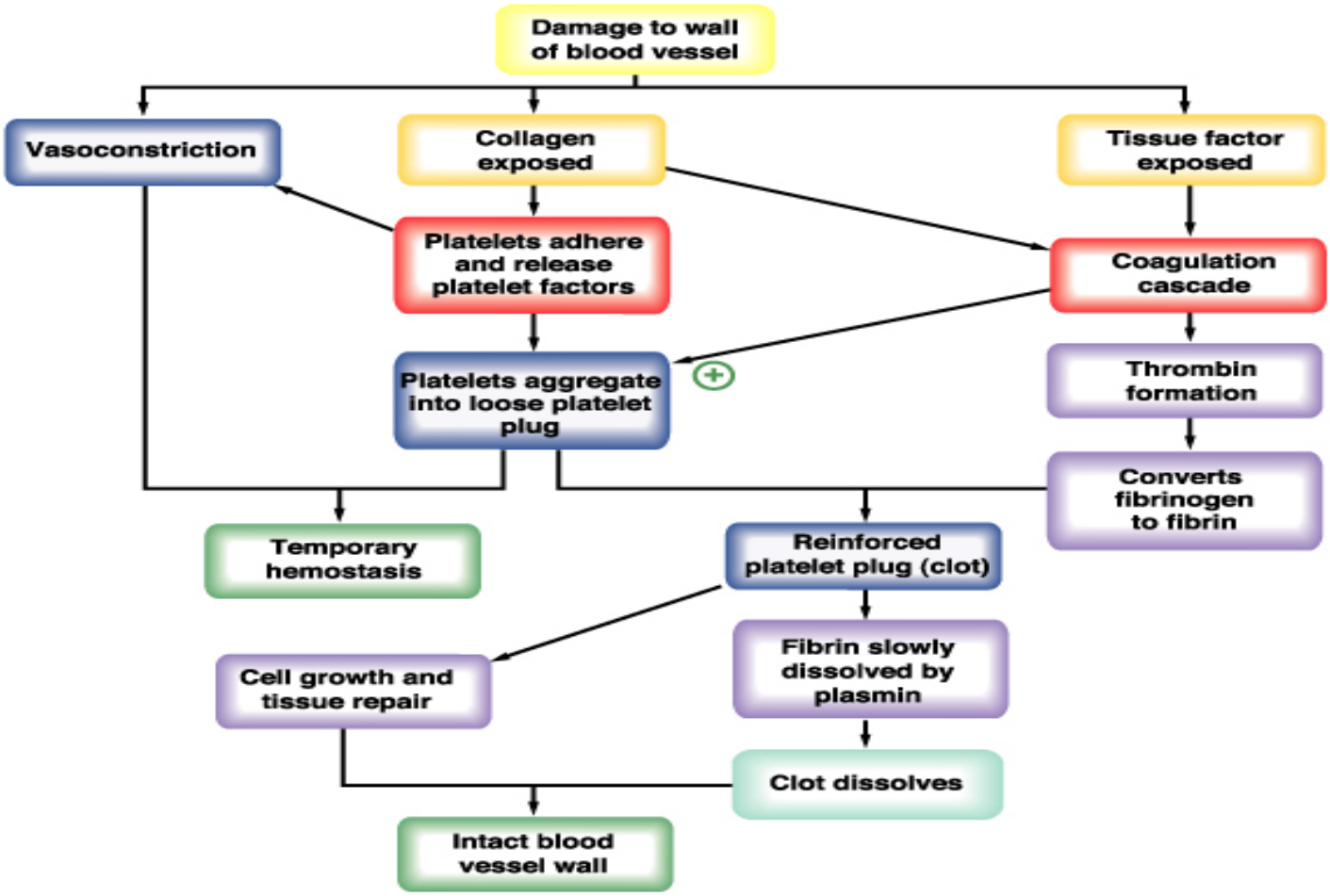
Platelet Adhesion



CLOT-ED

Platelet Aggregation





Extrinsic Pathway

Enzyme:

- **Organic compound, frequently a protein, capable of accelerating or producing by catalytic action some change in a substrate for which it is often specific.**

Extrinsic pathway:

- **Pathway in which fibrin is formed as the result of the release of tissue thromboplastin into the circulation.**

Prothrombin time:

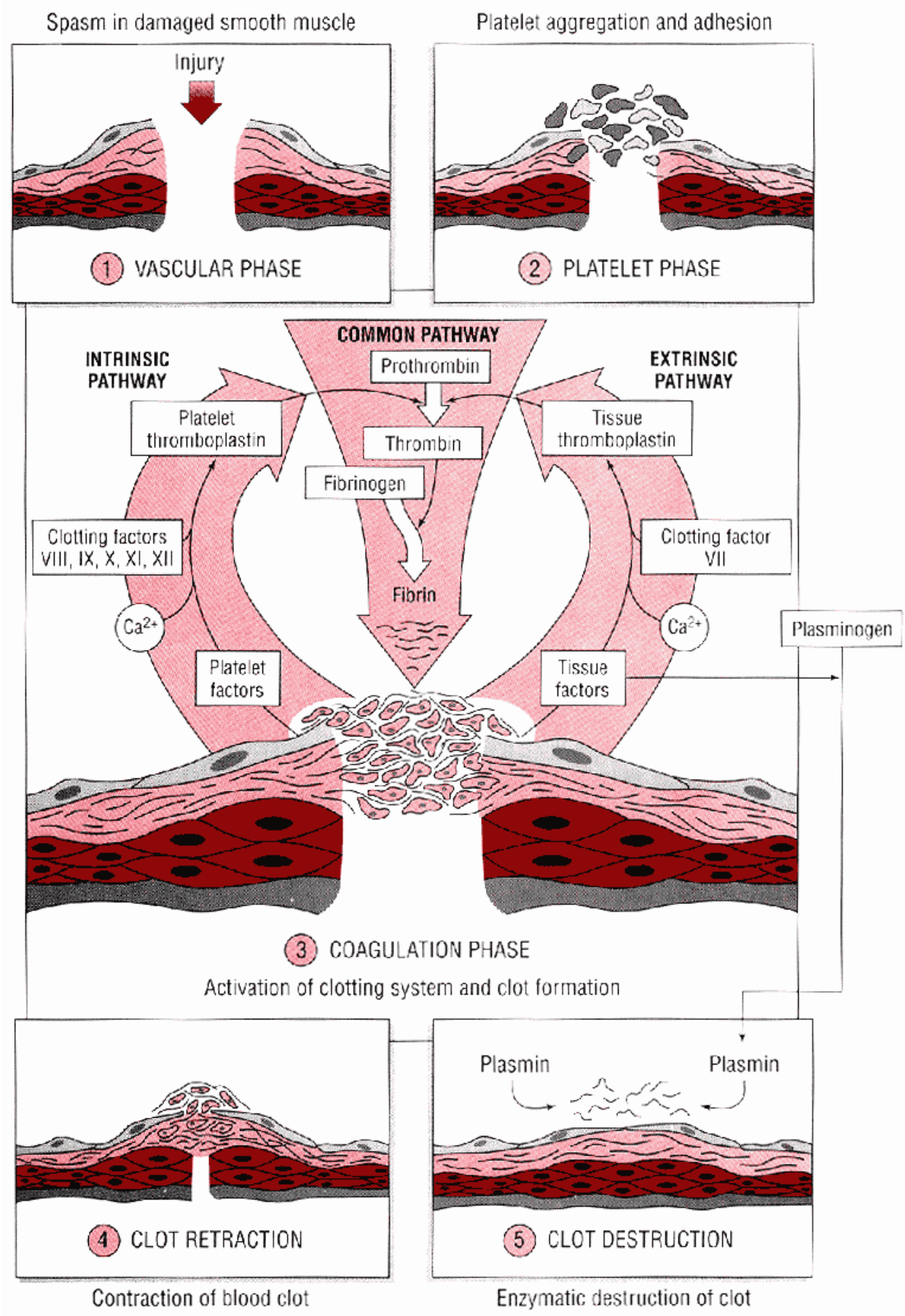
- **A laboratory coagulation test which measures the general level of clottability of a plasma sample. It is sensitive to the factors of the extrinsic clotting system.**

INR:

- **International Normalized Ratio which provides a convenient method for standardizing the monitoring of Warfarin therapy.**

- **Routine Coagulation Assays**

Prothrombin Time (PT)
Activated Partial Thromboplastin Time (APTT)
Quantitative Fibrinogen (FIB)
Thrombin Time (TT)
Assays for specific coagulation factors
– Factors assessed by a PT-based test system: FVII, FV, FX, and FII
– Factors assessed by an APTT-based test system: FXII, FXI, FIX, and FVIII


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

$$INR = \left[\frac{PT\ (patient)}{PT\ (control\ mean)}\right]^{ISI}$$

Platelets are small fragments of bone marrow cells and are therefore not really classified as cells themselves.

Platelets have the following functions:

1. Secrete vasoconstrictors which constrict blood vessels, causing vascular spasms in broken blood vessels
2. Form temporary platelet plugs to stop bleeding
3. Secrete procoagulants (clotting factors) to promote blood clotting
4. Dissolve blood clots when they are no longer needed
5. Digest and destroy bacteria
6. Secrete chemicals that attract neutrophils and monocytes to sites of inflammation
7. Secrete growth factors to maintain the linings of blood vessels

The first three functions listed above refer to important haemostatic mechanisms in which platelets play a role in during bleeding - Vascular spasms, Platelet plug formation and Blood clotting (coagulation).

Vascular Spasm

This is a prompt constriction of the broken blood vessel and is the most immediate protection against blood loss. Injury stimulates pain receptors. Some of these receptors directly innervate nearby blood vessels and cause them to constrict. After a few minutes, other mechanisms take over. Injury to the smooth muscle of the blood vessel itself causes a longer-lasting vasoconstriction where platelets release a chemical vasoconstrictor called serotonin. This maintains vascular spasm long enough for the other haemostatic mechanisms to come into play.

Platelet plug formation

Under normal conditions, platelets do not usually adhere to the wall of undamaged blood vessels, since the vessel lining tends to be smooth and coated with a platelet repellent. When a vessel is broken, platelets put out long spiny extensions to adhere to the vessel wall as well as to other platelets. These extensions then contract and draw the walls of the vessel together. The mass of platelets formed is known as a platelet plug, and can reduce or stop minor bleeding.

Coagulation

This is the last and most effective defence against bleeding. During bleeding, it is important for the blood to clot quickly to minimise blood loss, but it is equally important for blood not to clot in undamaged vessels. Coagulation is a very complex process aimed at clotting the blood at appropriate amounts. The objective of coagulation is to convert plasma protein fibrinogen into fibrin, which is a sticky protein that adheres to the walls of a vessel. Blood cells and platelets become stuck to fibrin, and the resulting mass helps to seal the break in the blood vessel. The forming of fibrin is what makes coagulation so complicated, as it involved numerous chemicals reactions and many coagulation factors.

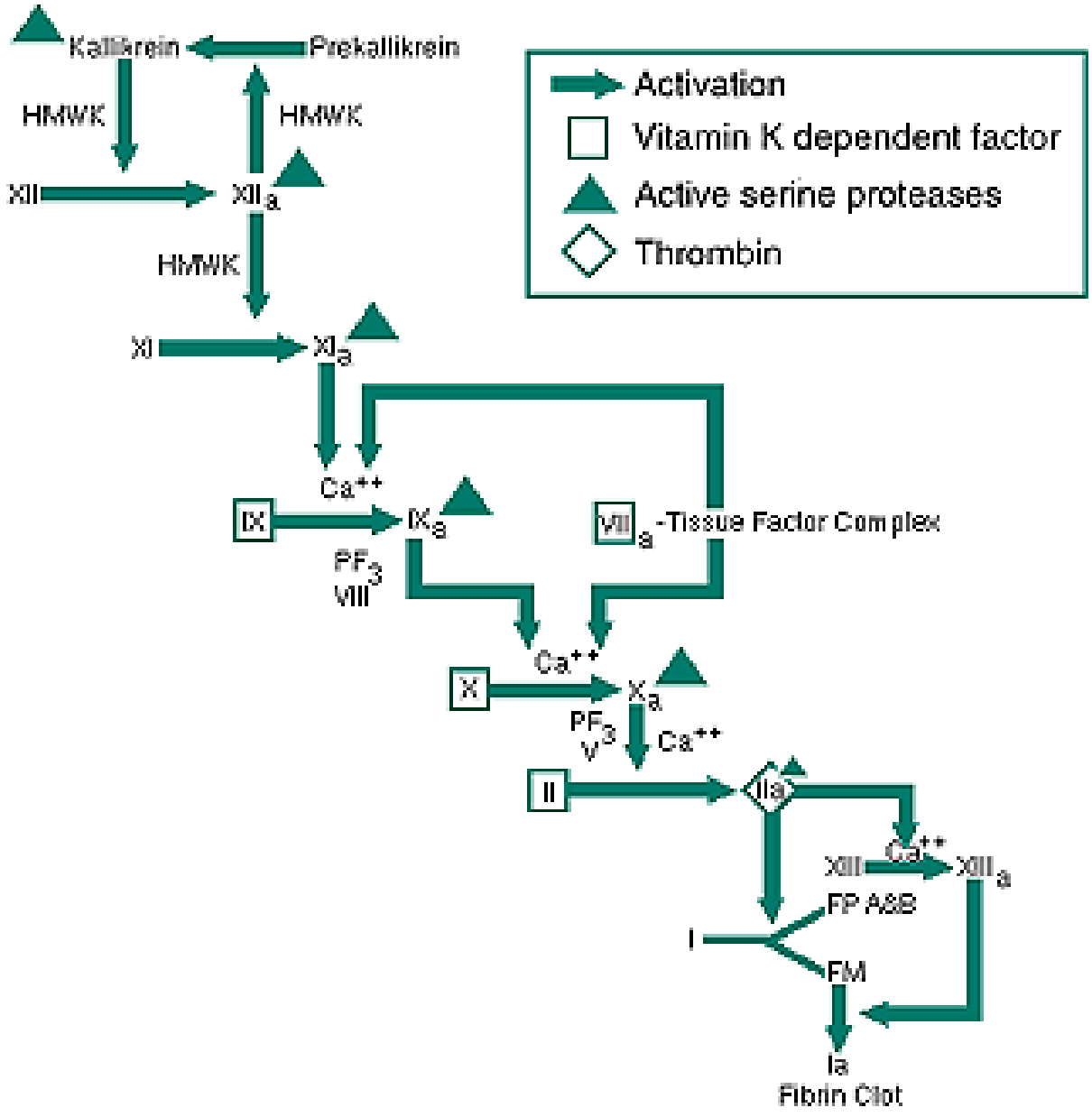
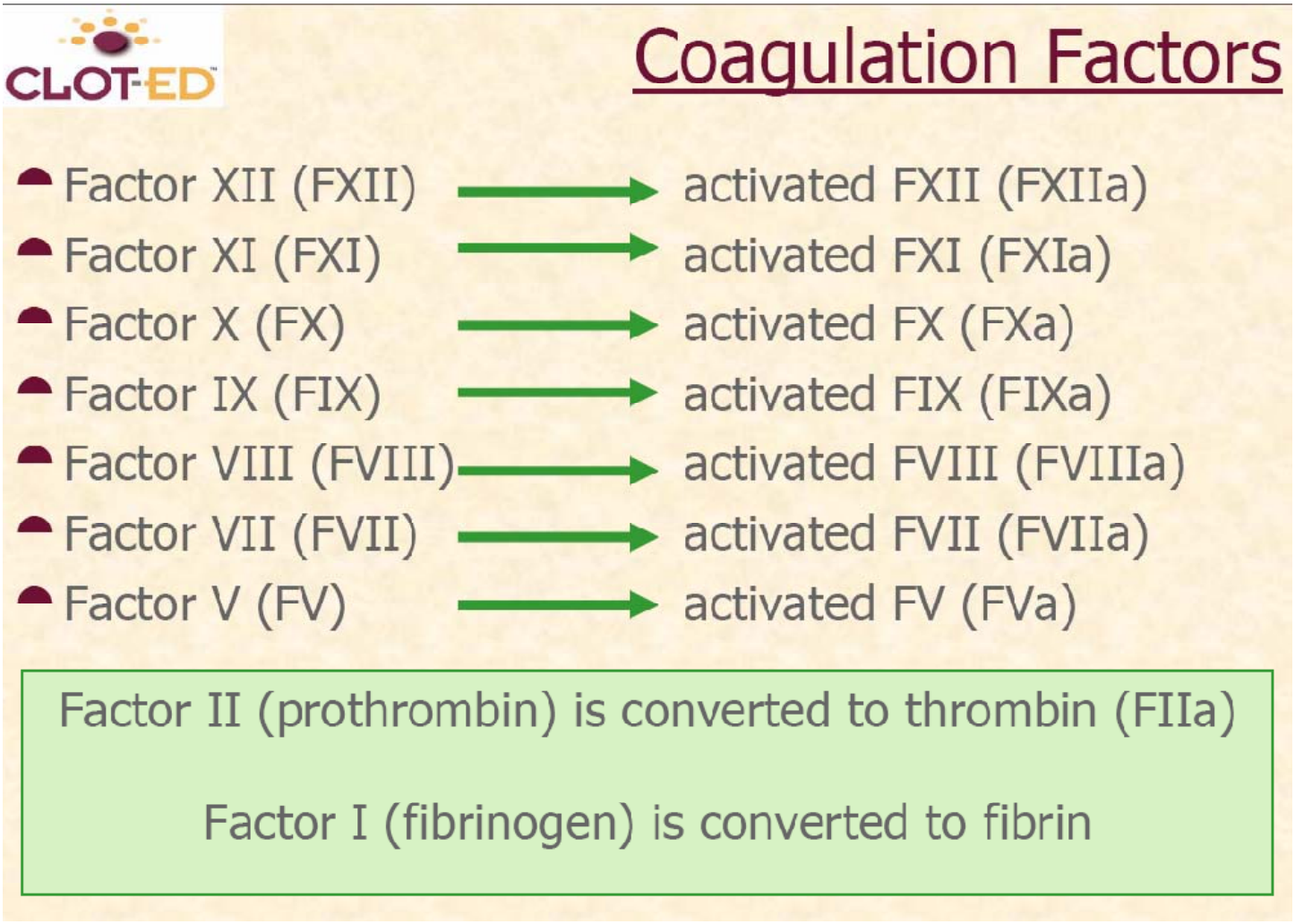


Figure 3. The coagulation cascade, including both intrinsic and extrinsic pathways.



Intrinsic Pathway

Activated partial thromboplastin time (APTT)

FIGURE 5

ACTIVATED PARTIAL THROMBOPLASTIN TIME

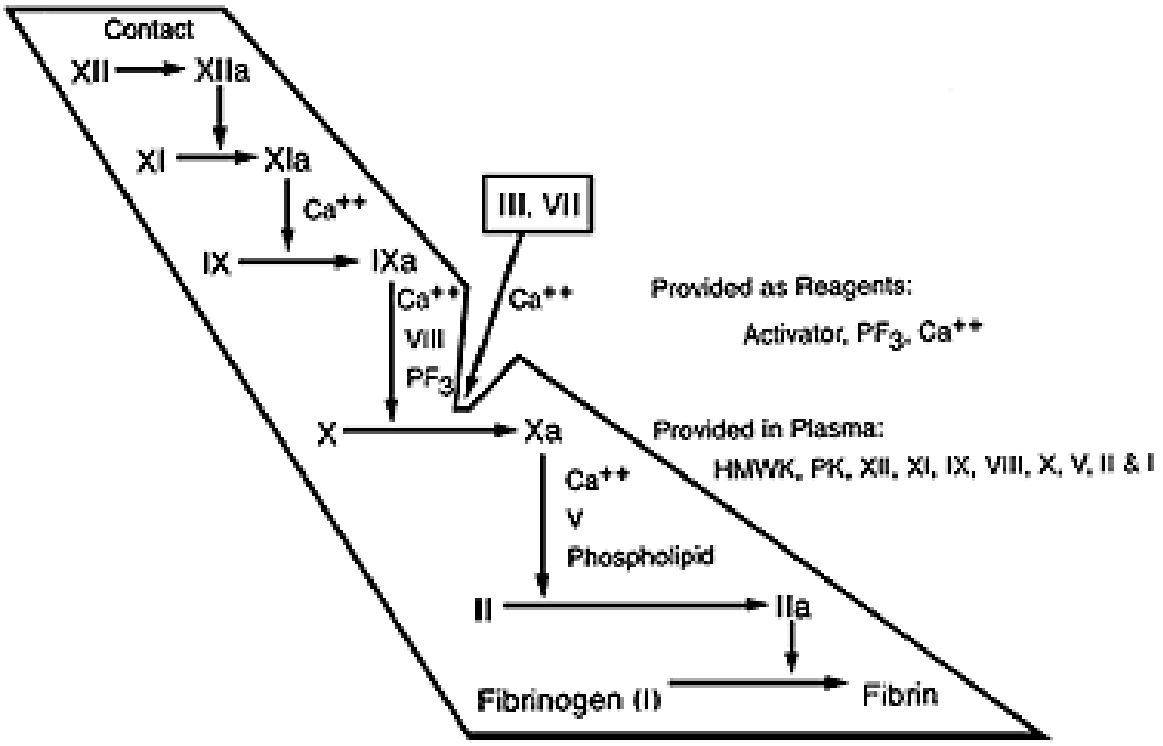
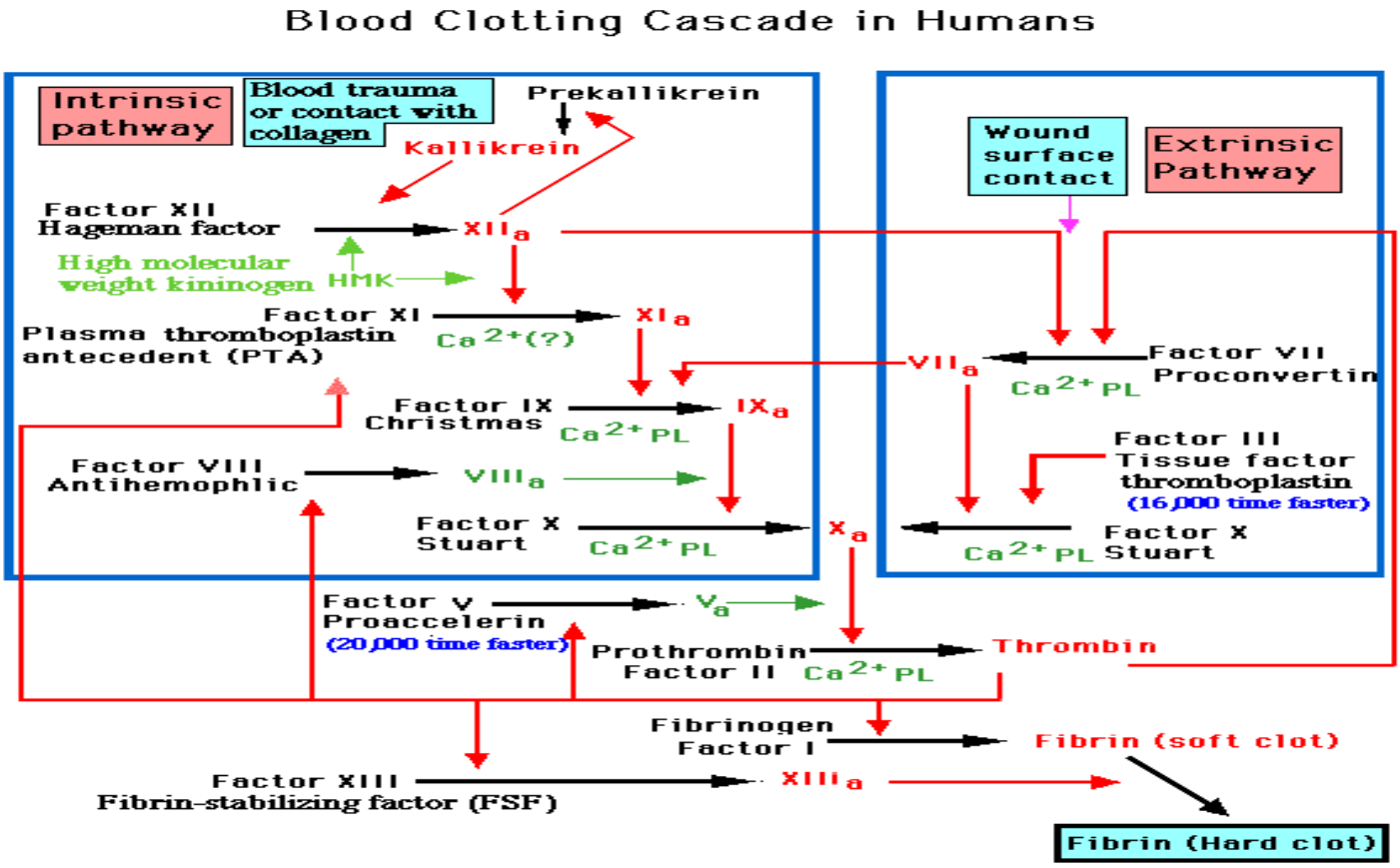
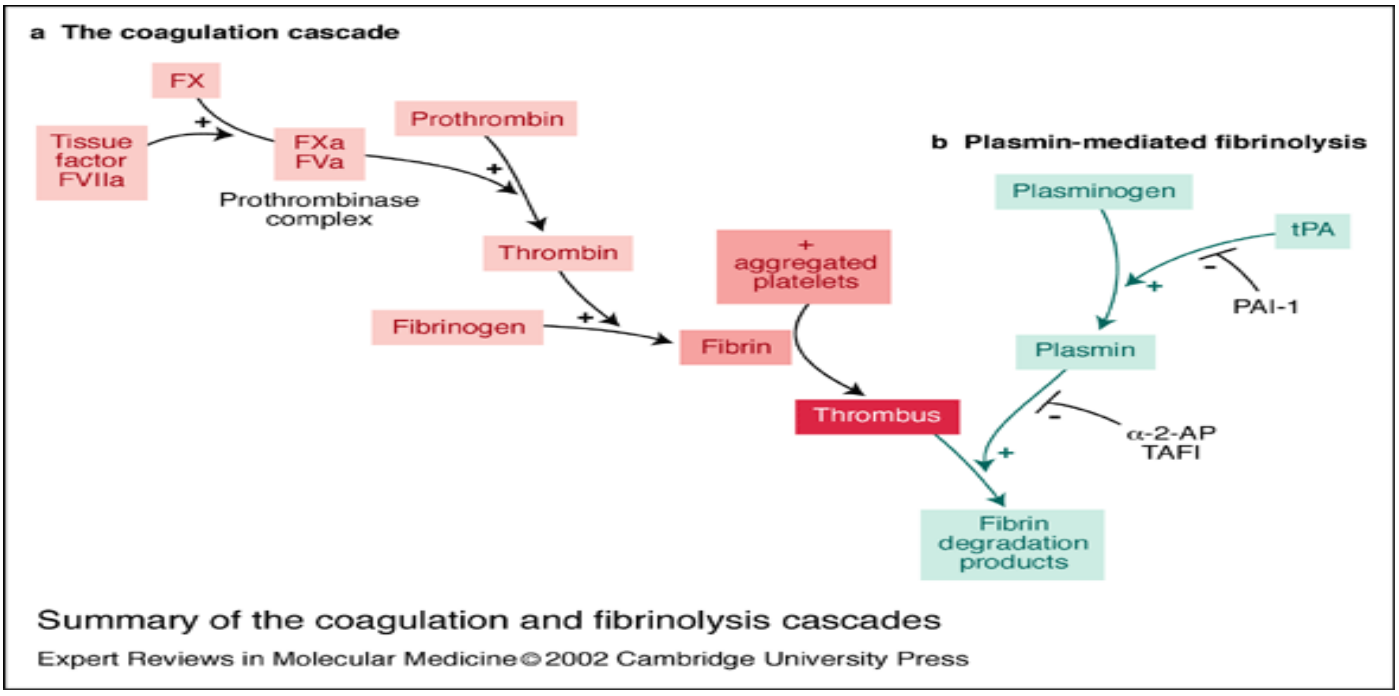


Figure 5. The aPTT is an intrinsic pathway screening test

One of the tests used for screening patients for a bleeding tendency.Specifically, adequate levels of the coagulation factors XII, XI, IX,VIII, X, V and II must be present for the test to be normal. The test also serves as the basis for other test procedures such as certain factor assay tests.

Intrinsic Originating from within





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Alex Munoz notes