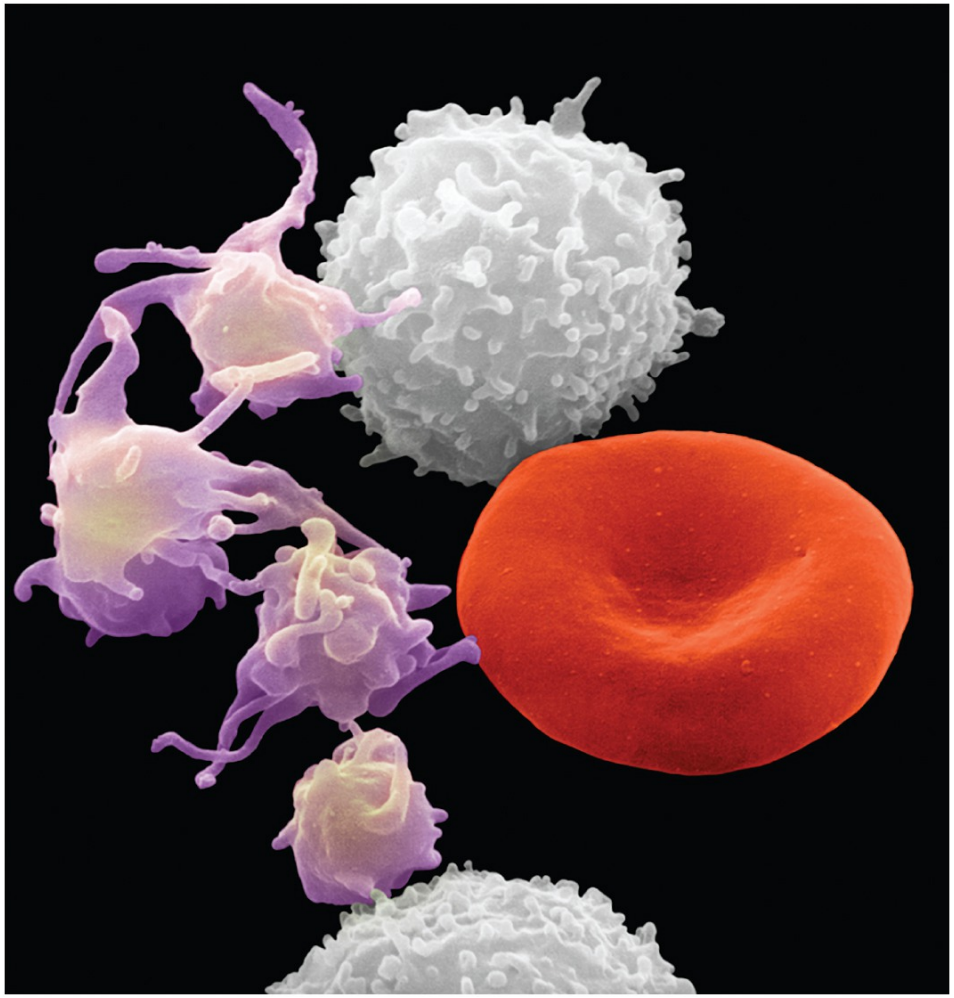
Chapter 18.4

Hemostasis



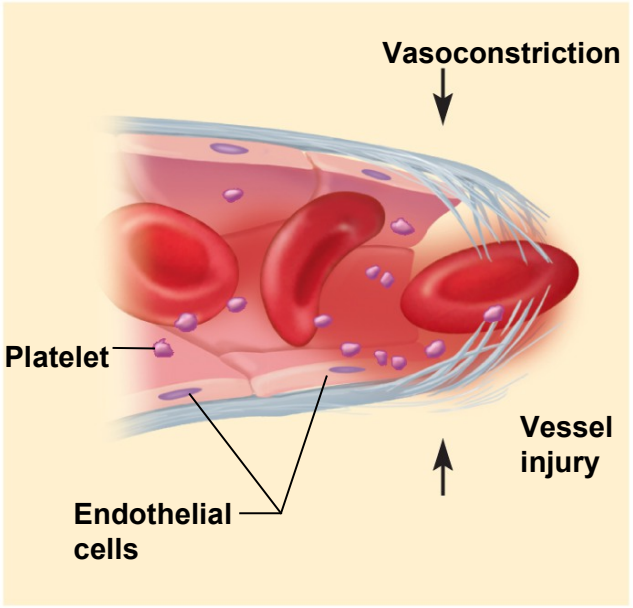
Hemostasis

- Hemostasis = the cessation of bleeding
  - ability to stop potentially fatal leaks
  - only in small blood vessels (capillaries)
  - not effective in cases of hemorrhage occuring in large artery
  - initiated by platelets in blood or thromboplastin secreted by cells not in blood

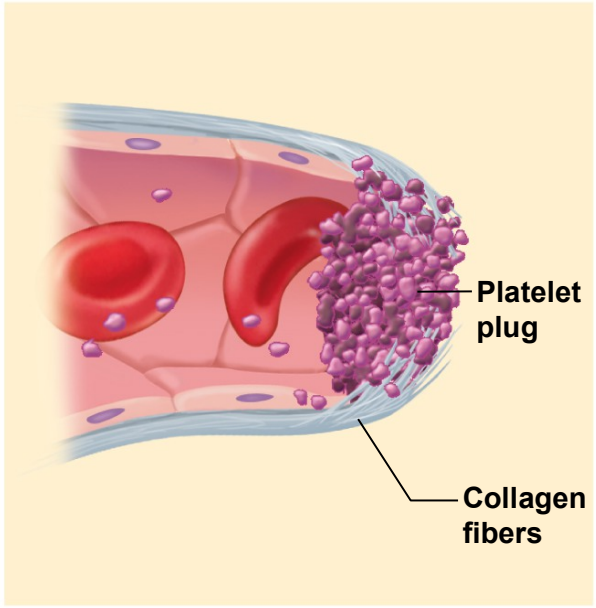
- Three events (mechanisms) must occur to achieve hemostasis
  - #1 - vascular spasm
  - #2 - platelet plug formation
  - #3 - blood clotting (coagulation)

- Platelets play an important role in all three of these mechanisms!

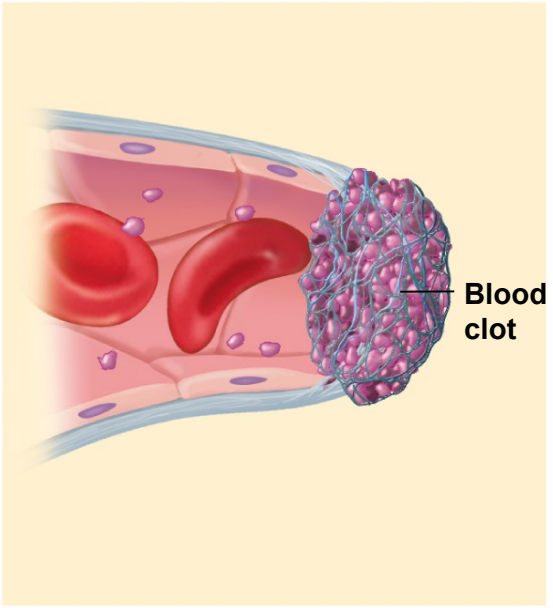
Hemostasis



(a) Vascular spasm



(b) Platelet plug formation

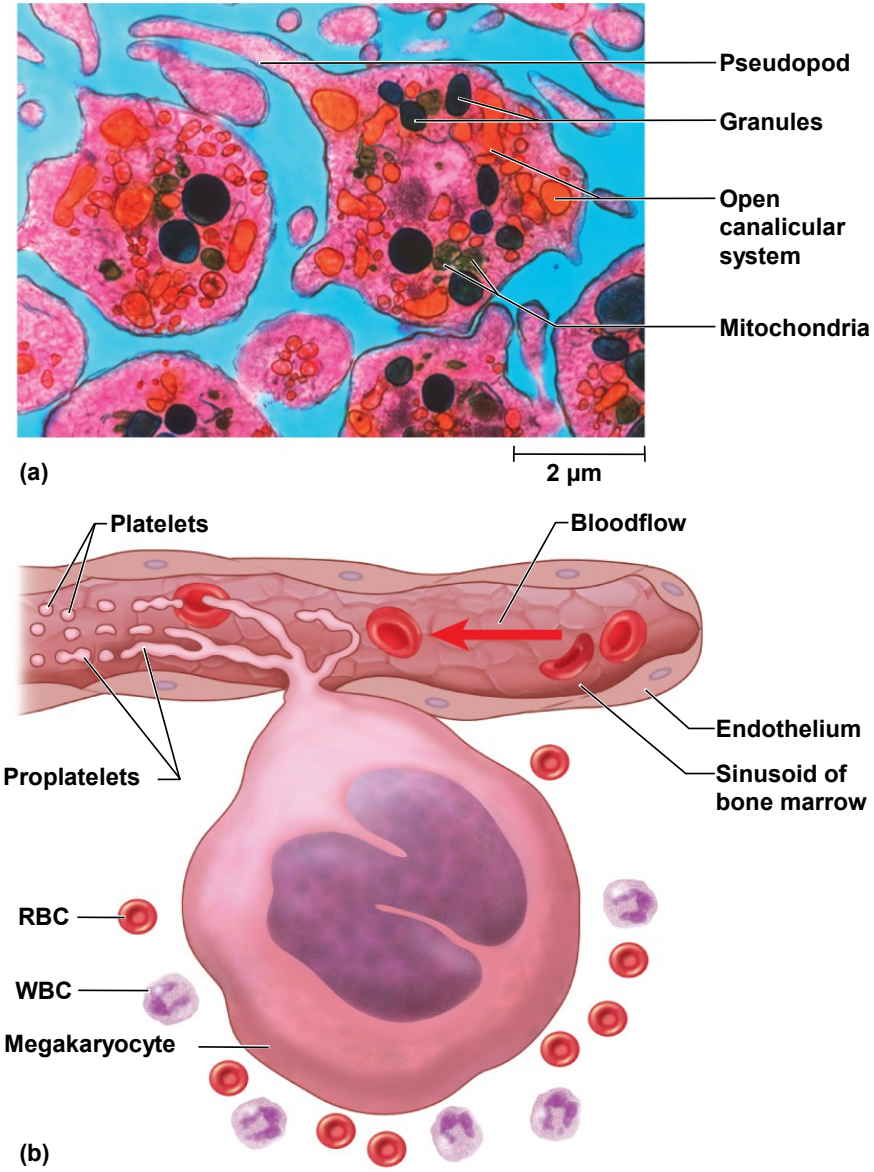


(c) Coagulation

each stage involves platelet function

Platelets – Major Role in Hemostasis

- Platelets (also called thrombocytes) are small fragments of another cell called a megakaryocyte cells
  - platelets are 2-4 μm diameter; contain "granules"
  - complex internal structure and open canalicular system
  - capable of amoeboid like movement and phagocytosis
- normal platelet count = 130,000 to 400,000 platelets/μL



a: NIBSC/Science Photo Library/Photo Researchers, Inc.

Platelet Functions

- secrete vasoconstrictors that help reduce blood loss
- when activated platelets become sticky and adhere together to form **platelet plugs** // **this starts tp** seal small breaks
- secrete **procoagulants** or clotting factors to promote clotting proteins circulating in blood
- at same time platelets initiate formation of **clot-dissolving enzyme**
- chemically attract neutrophils and monocytes to sites of blood vessel damage // inflammation
- phagocytize and destroy bacteria
- secrete **growth factors** that stimulate mitosis to repair blood vessels

Platelet Production = Thrombopoiesis

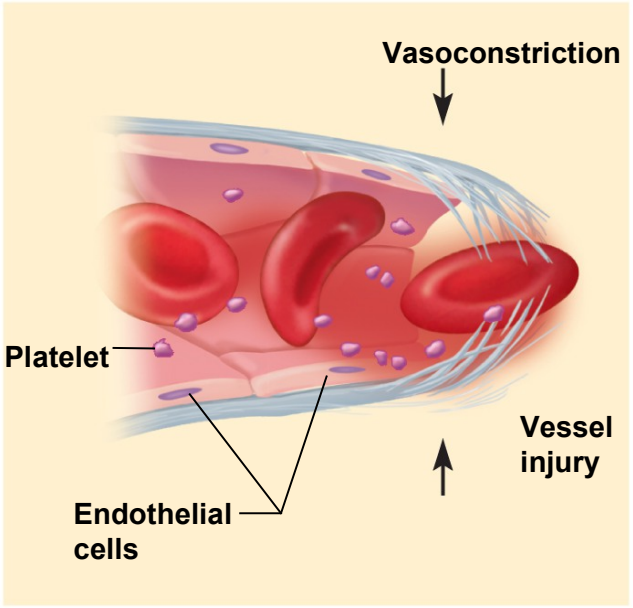
- stem cells develop receptors for thrombopoietin // these cells become megakaryoblasts

- megakaryoblasts // repeatedly replicate DNA without dividing // forms gigantic cell called megakaryocyte with a multilobed nucleus // 100 μm in diameter, remains in bone marrow

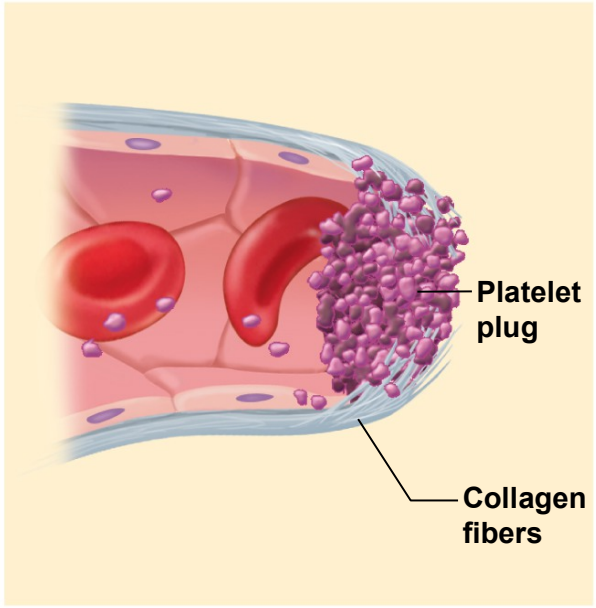
- Megakaryocytes // live in bone marrow adjacent to blood sinusoids // long tendrils of cytoplasm (proplatelets) protrude into the blood sinusoids – blood flow splits off fragments called platelets // platelets are also called throbocyes

- platelets circulate freely for 10 days // 40% are stored in spleen // the spleen filters blood and the spleen is like a sponge holding a reserve volume of blood // If you hemorrhage then the spleen "contracts" to help replace lost blood and restore blood pressure as well as flood circulation with platelets to aid hemostasis.

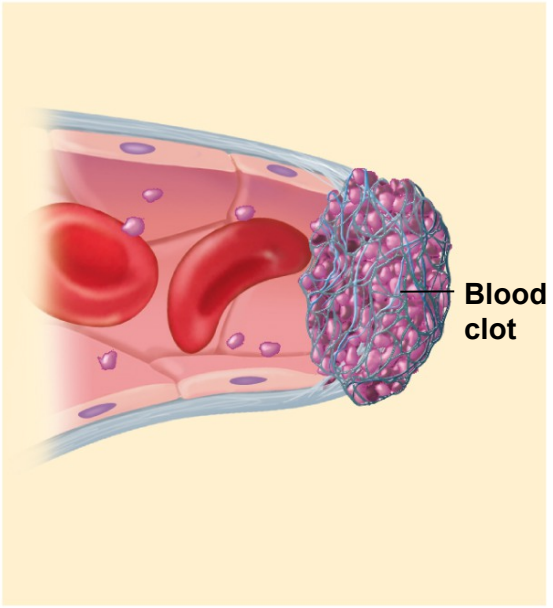
Hemostasis



(a) Vascular spasm



(b) Platelet plug formation



(c) Coagulation

each stage involves platelet function

Vascular Spasm – First Event

- vascular spasm (two spasm events) = prompt constriction of a broken vessel // most immediate protection against blood loss // the first spasm is independent of platelets

  - First spasm event // smooth muscle injury response // pain receptors // some directly innervate blood vessels to constrict // minor factor

  - Second spasm // platelets release serotonin (vasoconstrictor) to *augment vascular spasm!* // second vascular spasm event

- **Overall effect:**

  - prompt vaso-constriction of a broken vessel // pain receptors - short duration (minutes) // smooth muscle injury - longer duration

  - initial vascular spasmt provides time for other two clotting events to develop

Platelet Plug – Second Event

- Under normal conditions endothelium surface needs to be smooth to inhibit activation of platelets

- However, after vessel damage mechanism to make inner lining of blood vessels “sticky” must be activated

  - under normal conditions endothelium coated with prostacyclin // a platelet repellant // protects against spontaneous activation of platelets and formation of blood clots

  - to complete hemostasis the prostacyclin mechanism must be reversed /// another molecule, thromboxane is secreted which makes the surface of endothelium sticky

  - platelets now may adhere to lining of blood vessel and start to form the platelet plug

Platelet Plug – Second Event

- Platelet plug formation
  - broken vessel exposes collagen (collagen becomes a trigger)
  - platelet pseudopods stick to damaged vessel
  - platelets pseudopods contract to draw walls of vessel together /// this is the formation of the platelet plug
  - platelets degranulate releasing a variety of substances
    - Serotonin = vasoconstrictor
    - ADP attracts and degranulates more platelets
    - thromboxane A_2, an eicosanoid, promotes platelet aggregation, degranulation and more vasoconstriction
  - positive feedback cycle is active until break in small vessel is sealed

Coagulation – Third Event

- Coagulation = blood clotting = last step and most effective defense against bleeding

- Conversion of plasma protein fibrinogen into insoluble fibrin threads to form framework for the clot // conversion needs the enzyme thrombin (note: this discovery was made in the 1940s at Wayne State University by Dr. Seager PhD)

- Forming a blood clot is a many step sequence that involves plasma proteins and plasma enzymes (also called clotting factors) /// positive feedback mechanism

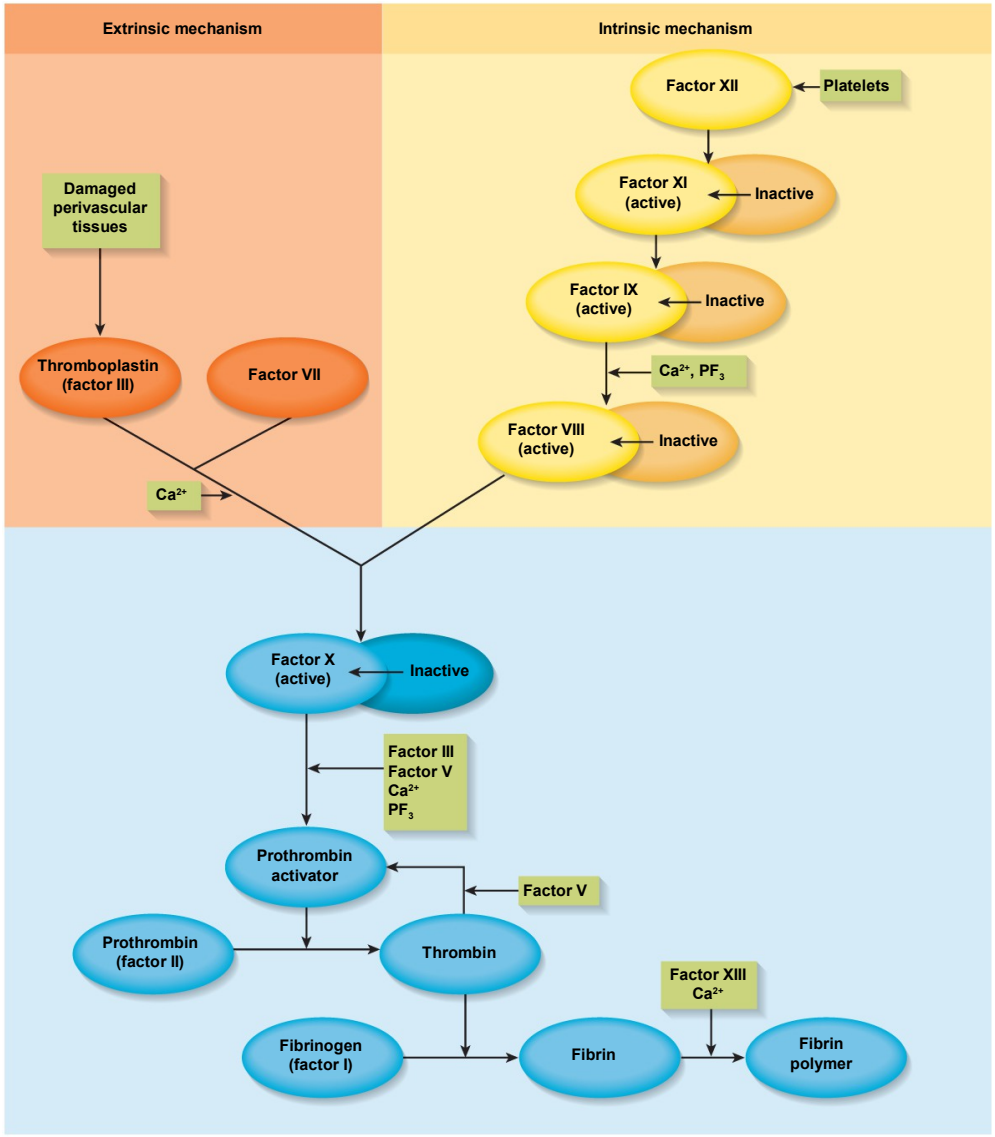
- procoagulants (clotting factors) // produced by the liver // circulating in plasma

  - activate one factor and it will activate the next to form a reaction cascade

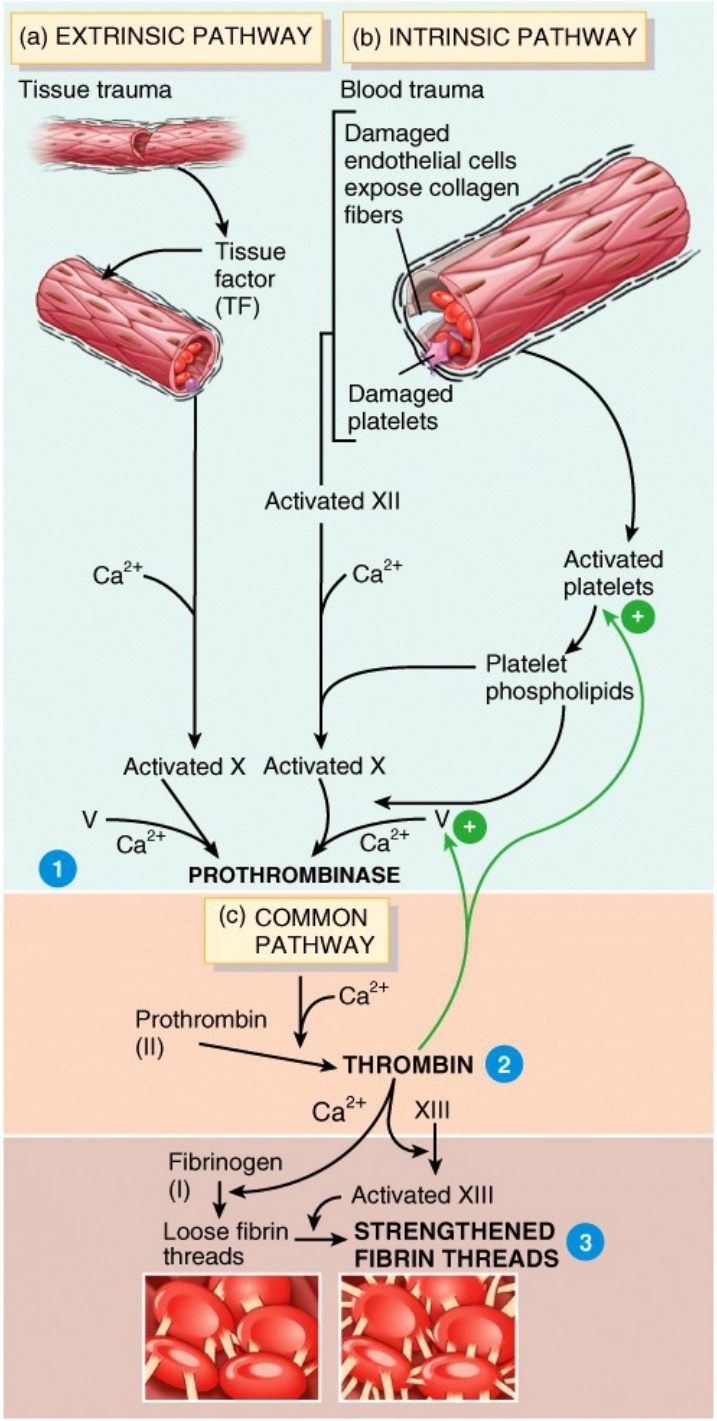
Coagulation – Third Event

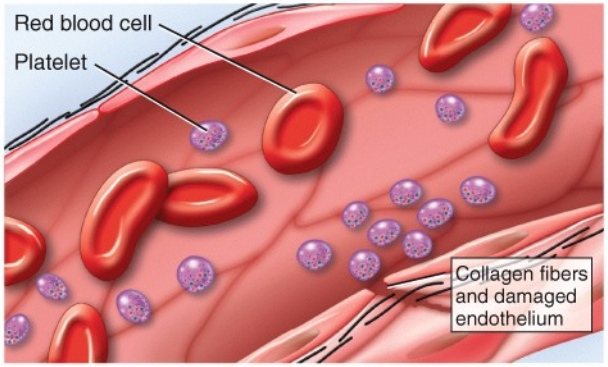
- Coagulation can be initiated by activating one of two pathways
  - extrinsic pathway // factors released by damaged tissues begin cascade // 15 sec
  - intrinsic pathway // factors found in blood begin cascade (the platelet degranulation) // 3 to 6 minutes

Coagulation Pathways

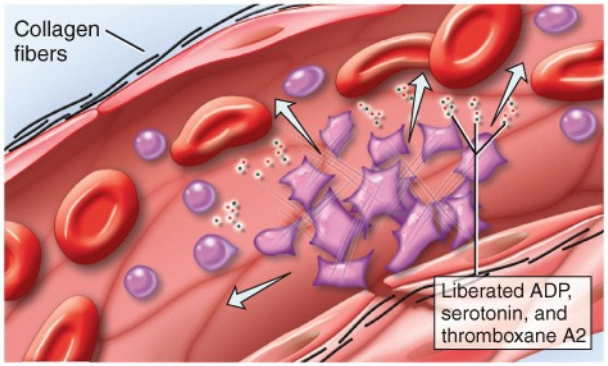


- **extrinsic pathway**
  - initiated by release of **tissue thromboplastin** (factor III) from damaged tissue
  - cascade to factor VII, V and X (fewer steps)
  - Clot forms in 15 seconds
- **intrinsic pathway**
  - initiated by platelets releasing **Hageman factor** (factor XII)
  - cascade to factor XI to IX to VIII to X
  - Clot forms in 3 to 6 minutes
- **calcium** required for both pathways

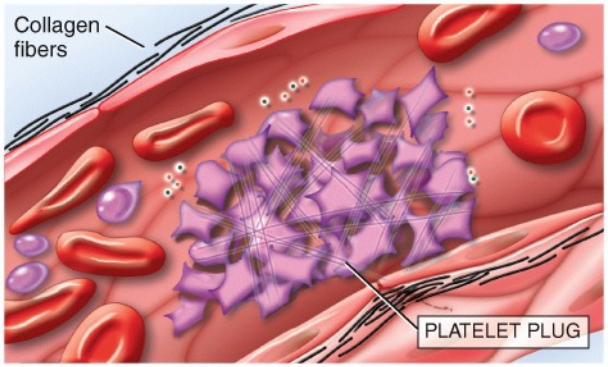

(a) EXTRINSIC PATHWAY
(b) INTRINSIC PATHWAY
Tissue trauma
Blood trauma
Damaged endothelial cells expose collagen fibers
Tissue factor (TF)
Damaged platelets
Activated XII
Ca2+
Ca2+
Activated platelets
+
Platelet phospholipids
Activated X
Activated X
V
Ca2+
Ca2+
V
+
1
PROTHROMBINASE
(c) COMMON PATHWAY
Ca2+
Prothrombin (II)
THROMBIN
2
Ca2+
XIII
Fibrinogen (I)
Activated XIII
Loose fibrin threads
STRENGTHENED FIBRIN THREADS
3



1 Platelet adhesion

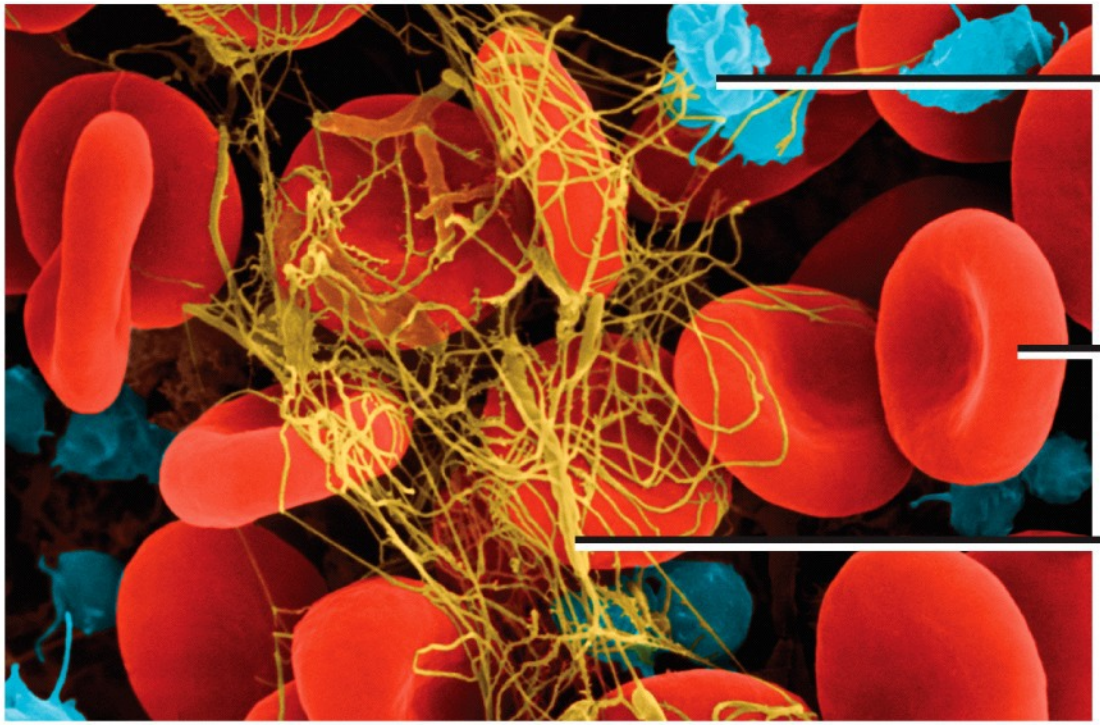


2 Platelet release reaction

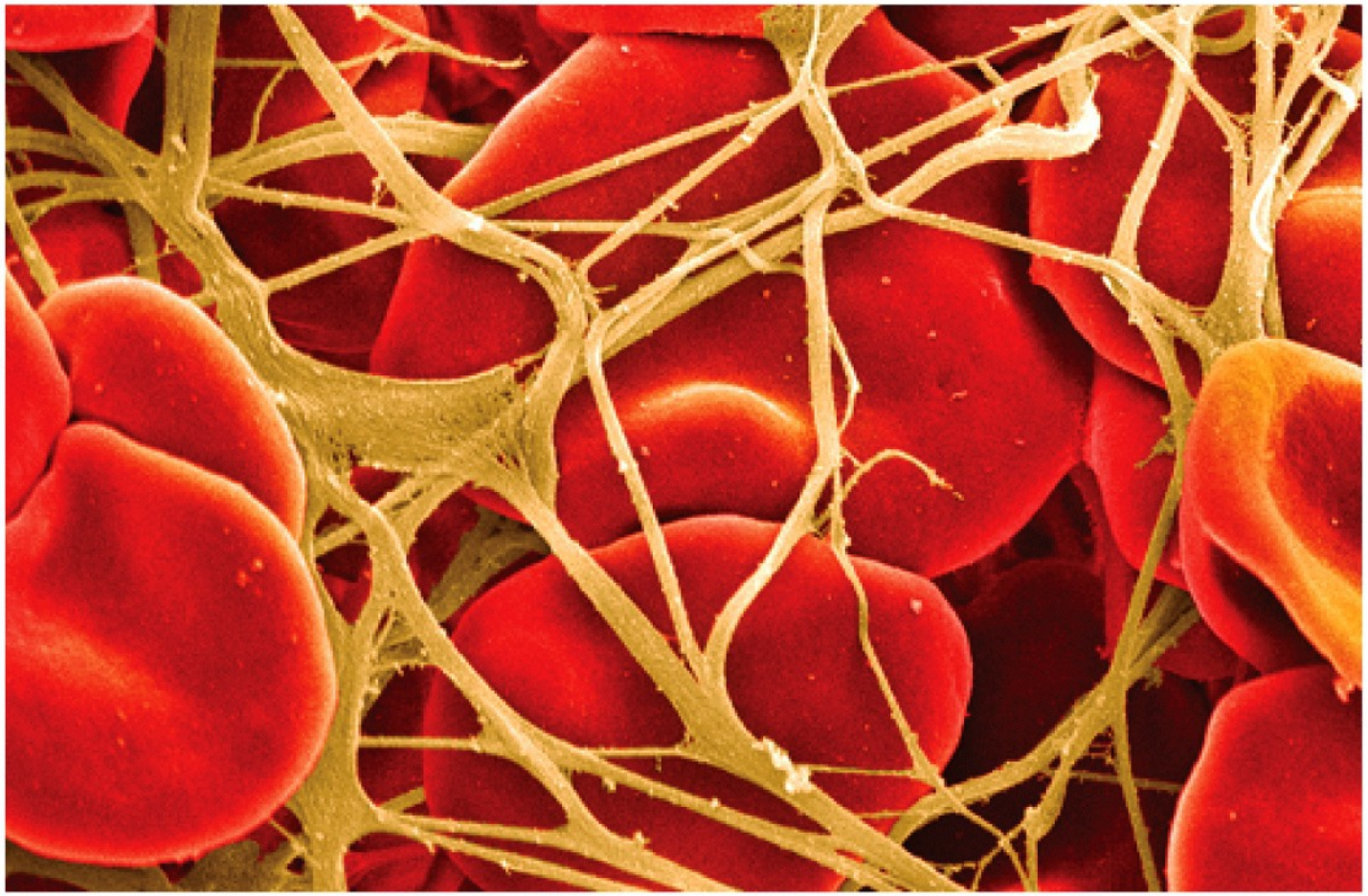


3 Platelet aggregation

Dennis Kunkel Microscopy, Inc./Phototake



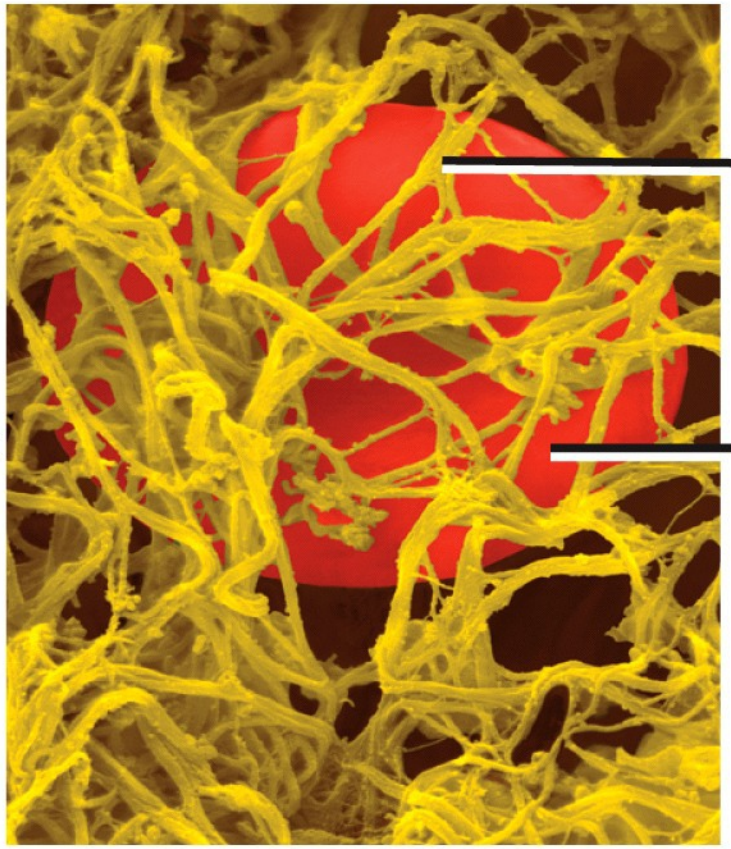
(a) Early stage



Steve Gschmeissner/Photo Researchers, Inc.

SEM 900x

(b) Intermediate stage

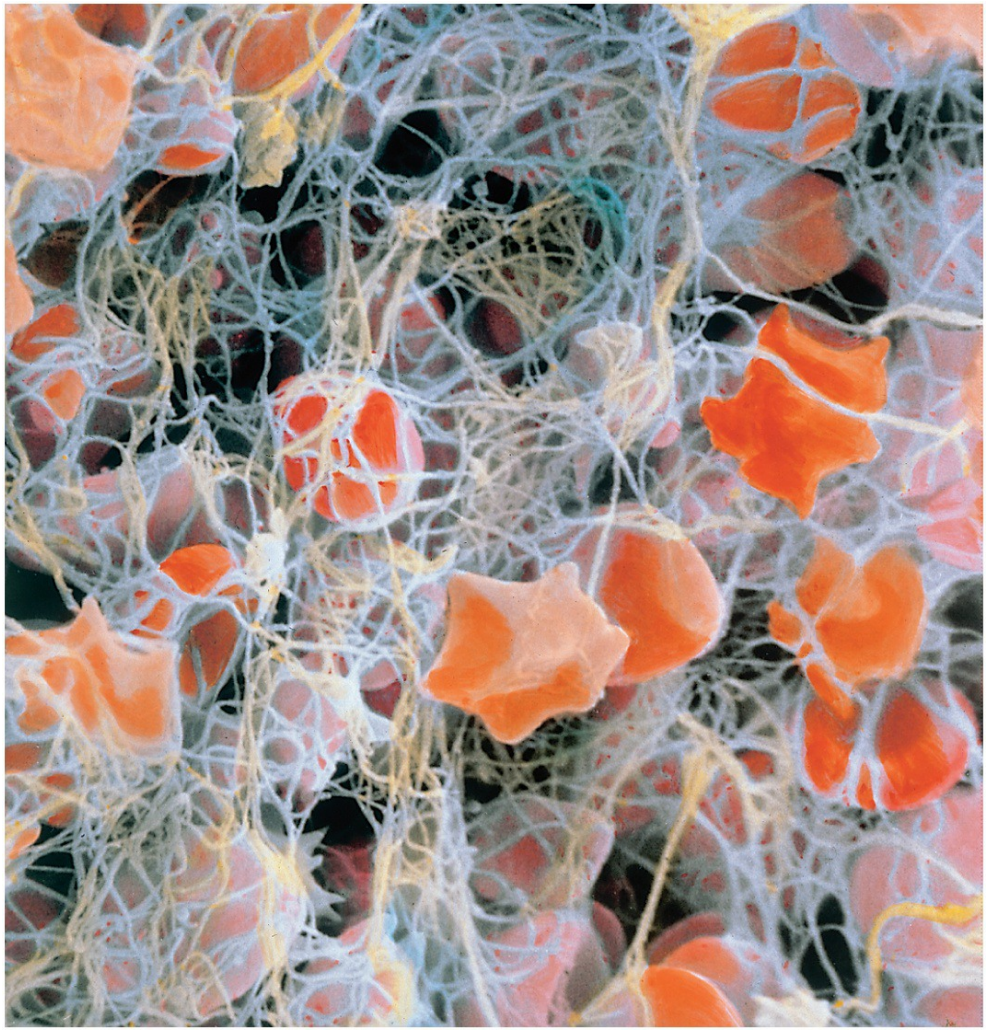


Dennis Kunkel Microscopy, Inc./Phototake

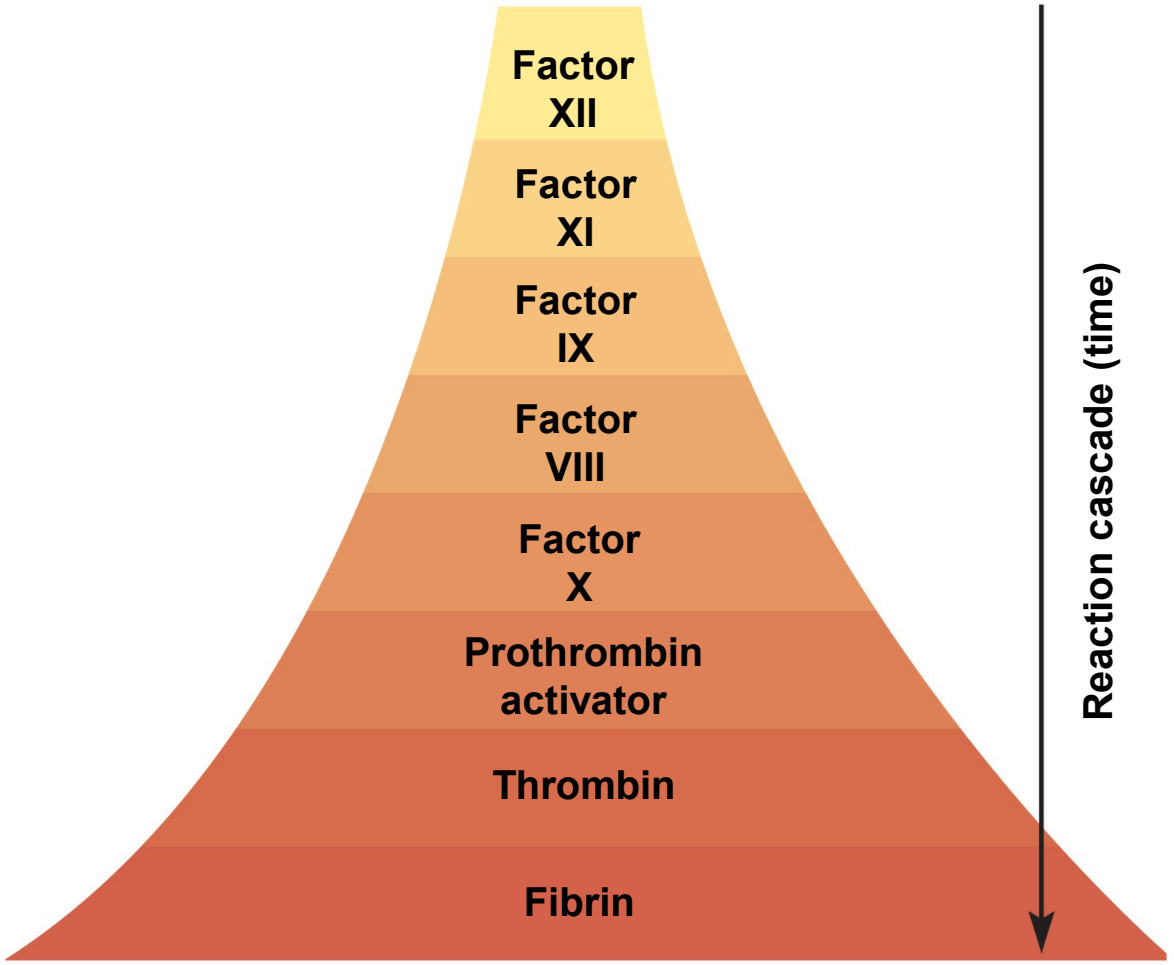
SEM 900x

(c) Late stage showing red blood cells trapped in fibrin threads

SEM of Blood Clot



Enzyme Amplification in Clotting



rapid clotting - each activated cofactor activates many more molecules in next step of sequence / positive feedback

Key Step in Coagulation

- activation of factor X // leads to production of prothrombin activator // key step!
- prothrombin activator // converts prothrombin to thrombin
- thrombin // converts fibrinogen into fibrin
- positive feedback - thrombin speeds up formation of prothrombin activator

Fate of Blood Clots

- **Clot retraction** occurs within 30 minutes /// you can actually see this if you exam a small cut on the cutaneous membrane!

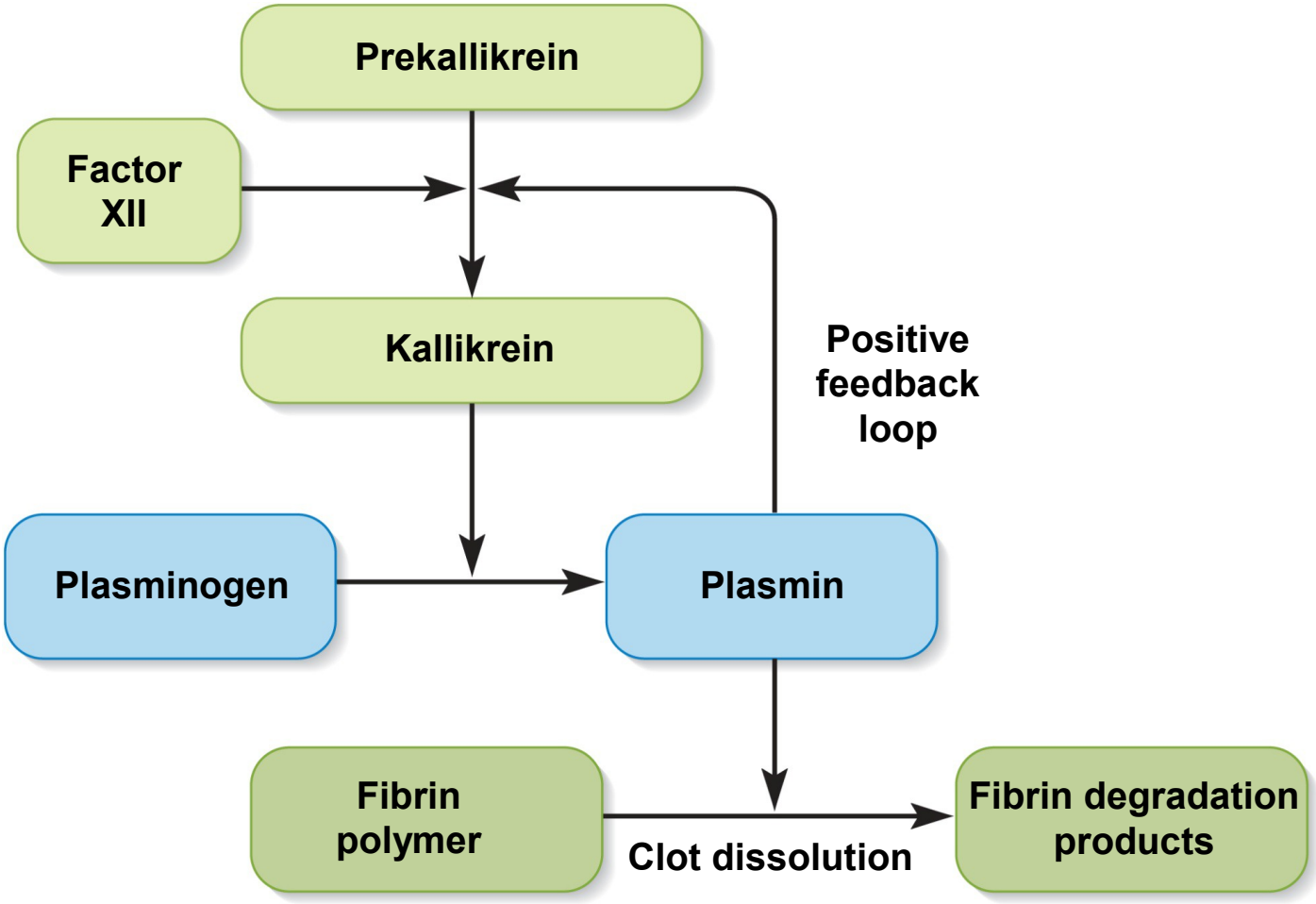
- **Platelet-derived growth factor** secreted by platelets and endothelial cells

  - this is a mitotic stimulant // stimulates fibroblasts and smooth muscle to multiply // together they help to repair damaged vessel

Fate of Blood Clots

- Fibrinolysis // enzyme that breaks apart the blood clot
  - factor XII speeds up formation of kallikrein enzyme (also initiates clot formation!!!)
  - kallikrein converts plasminogen into plasmin
  - Plasmin = a fibrin-dissolving enzyme that breaks up the clot

Blood Clot Dissolution



- This is also a positive feedback event!

Factors to Prevent Inappropriate Clotting

- platelet repulsion // platelets do not adhere to prostacyclin
- prostacyclin coats inside of endothelium // note thromboxane is an antagonist to prostacyclin
- thrombin dilution // by rapidly flowing blood // however, if heart slows with drop in blood pressure and shock then this can result in clot formation
- natural anticoagulants
  - heparin (from basophils and mast cells) interferes with formation of prothrombin activator
  - antithrombin (from liver) deactivates thrombin before it can act on fibrinogen

Terminology

- thrombosis - abnormal clotting in unbroken vessel
- thrombus = clot // most likely to occur in leg veins of inactive people
- pulmonary embolism - clot breaks free from inside blood vesel, travel from veins to lungs
- embolus – anything that can travel in the blood and block blood vessels (like a blood clot)
- infarction (tissue death) may occur if clot blocks blood supply to an organ (MI or stroke) // 650,000 Americans die annually of thromboembolism – traveling blood clots
- thrombocytosis // increase number of platelets
- thrombocytopenia // decrease number of platelets

Clinical Management of Clotting

- goal to prevent formation of clots or dissolve existing clots
- preventing clots
  - vitamin K is required for formation of clotting factors // coumarin (Coumadin) is a vitamin K antagonist
  - aspirin suppresses thromboxane A_2
  - other anticoagulants discovered in animal research
    - medicinal leeches used since 1884 (hirudin)
    - snake venom from vipers (Arvin)

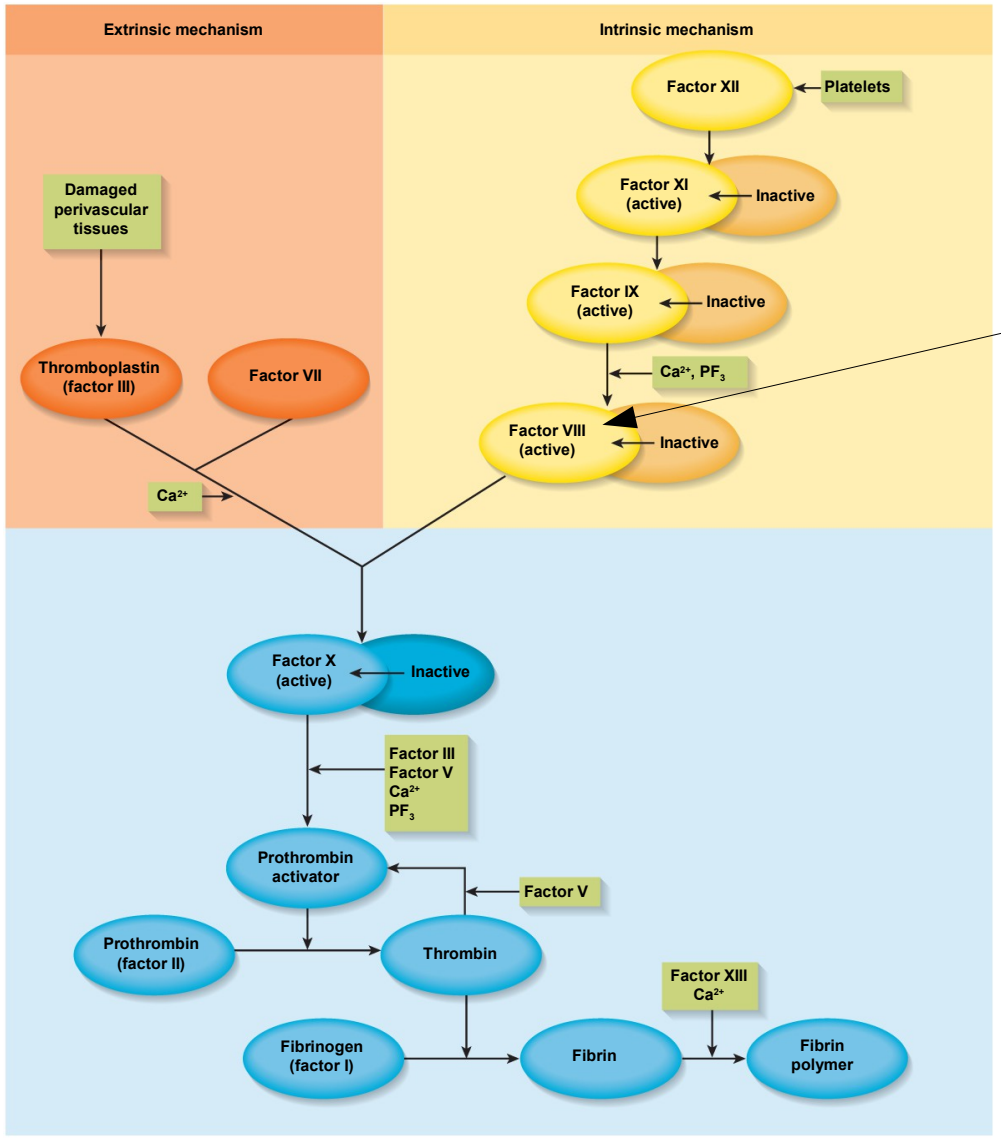
Clinical Management of Clotting

- How may we dissolve clots?
  - streptokinase – enzyme make by streptococci bacteria
    - used to dissolve clots in coronary vessels
    - digests almost any protein not selective for blood clots
  - tissue plasminogen activator (TPA) – works faster, is more specific, and now made by transgenic bacteria
  - hementin – produced by giant Amazon leech

Clotting Disorders - Hemophilia

- deficiency of any clotting factor can shut down the coagulation cascade
- **hemophilia** – family of hereditary diseases characterized by deficiencies of one factor or another
- sex-linked recessive (on X chromosome)
  - **hemophilia A** missing factor VIII (83% of cases)
  - **hemophilia B** missing factor IX (15% of cases)
- physical exertion causes bleeding and excruciating pain
  - Treatment - transfusion of plasma or purified clotting factors
  - Treatment - factor VIII produced by transgenic bacteria
- **hematomas** – masses of clotted blood in the tissues

Coagulation Pathways



Hemophilia A caused by missing factor VIII

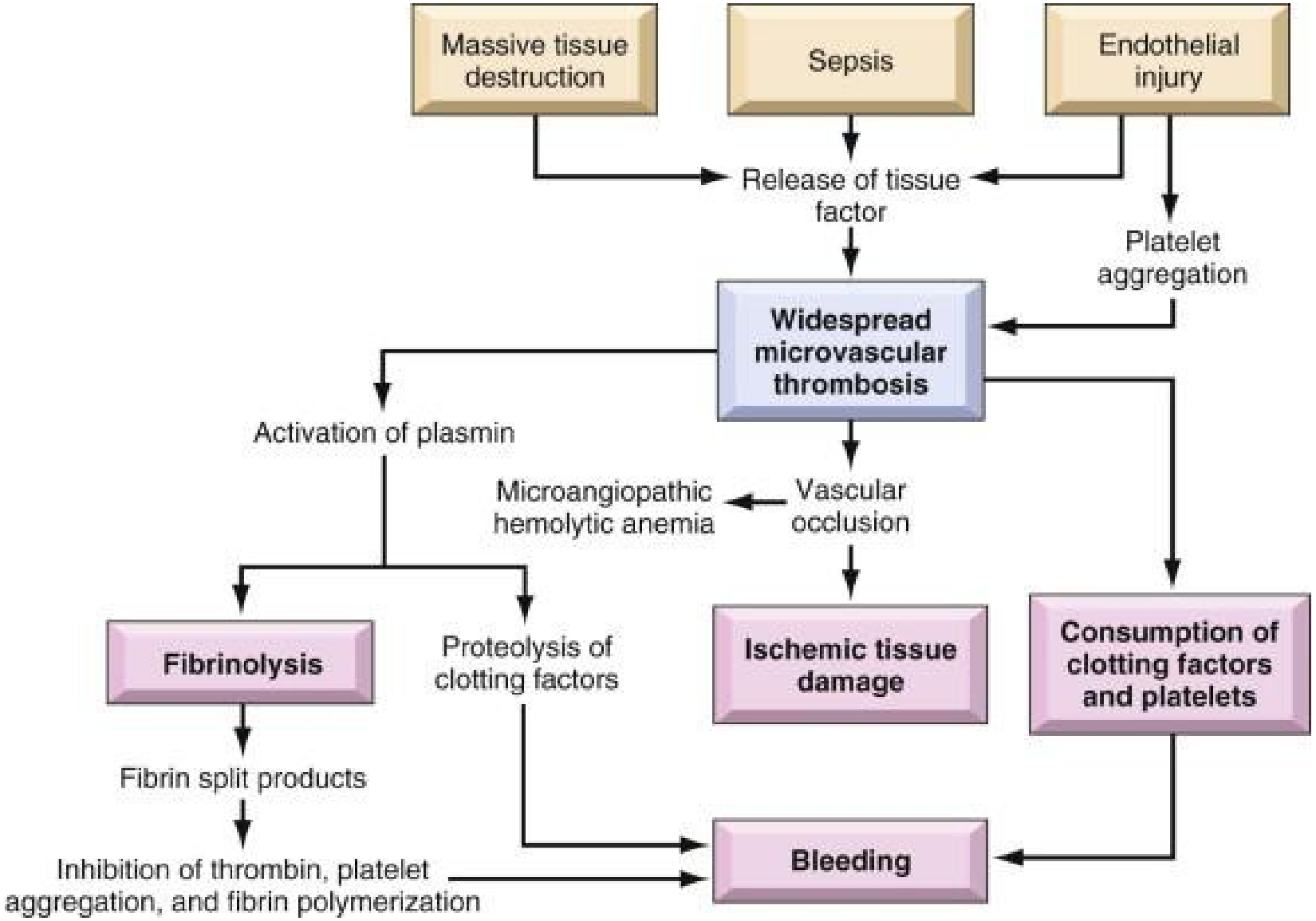
Responsible for 83% of hemophilia cases

Factor VIII is an enzyme.

Why is this called a genetic disease?

How would you cure this disease?

Disseminated Intra-Vascular Coagulation



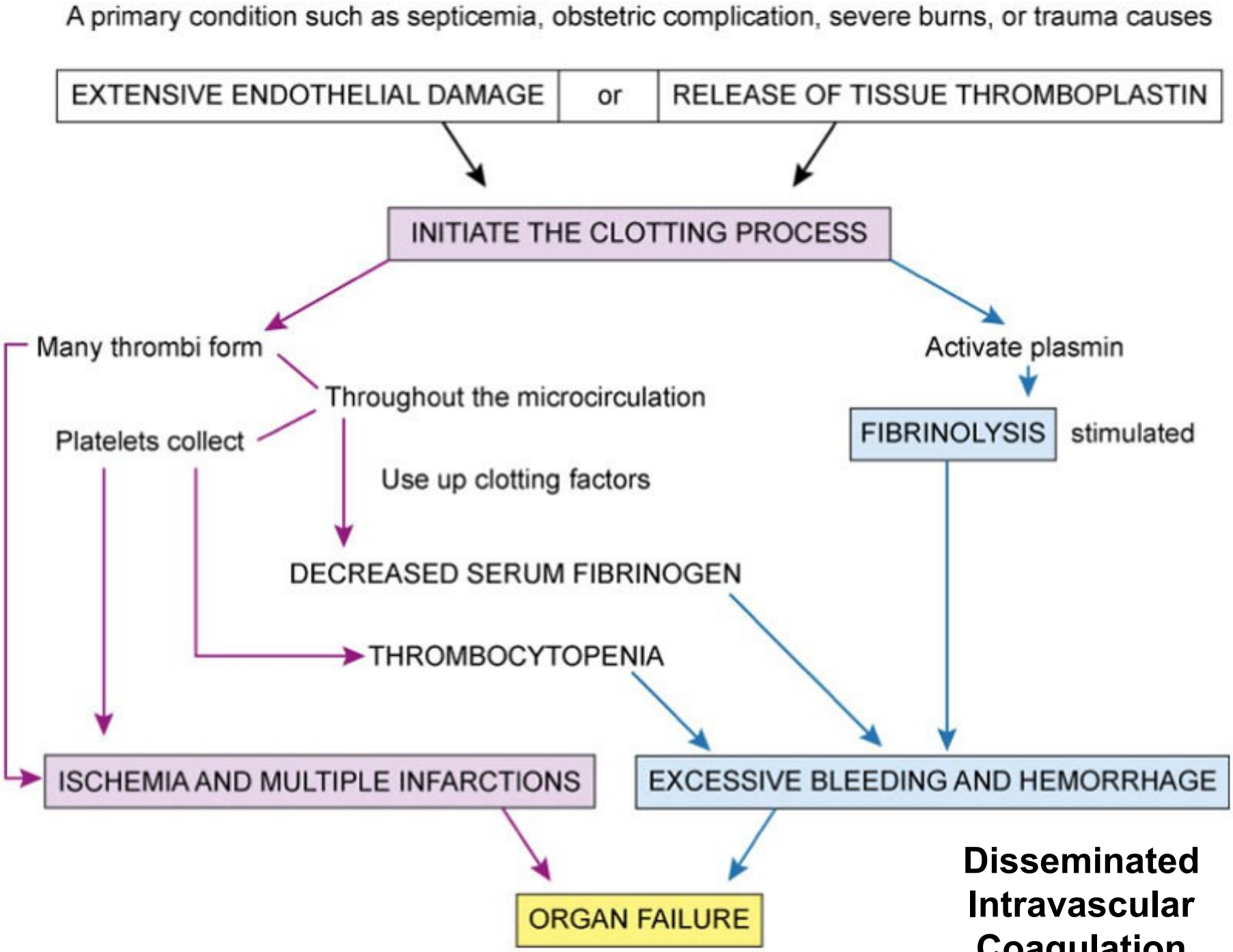
Disseminated Intra-Vascular Coagulation

- First event: Excessive clotting in circulation // Results in thromus formation, embolisms, and infarction. (e.g. lipopolysacharide shed by gram negative bacteria stimulate monocytes to release cytokines which cause several outcomes including blood clotting)

- *Second event:* *Clotting factors are reduced to a dangerous level*. // Widespread, uncontrollable hemorrhage then results. /// followed by excessive bleeding in microcirculation

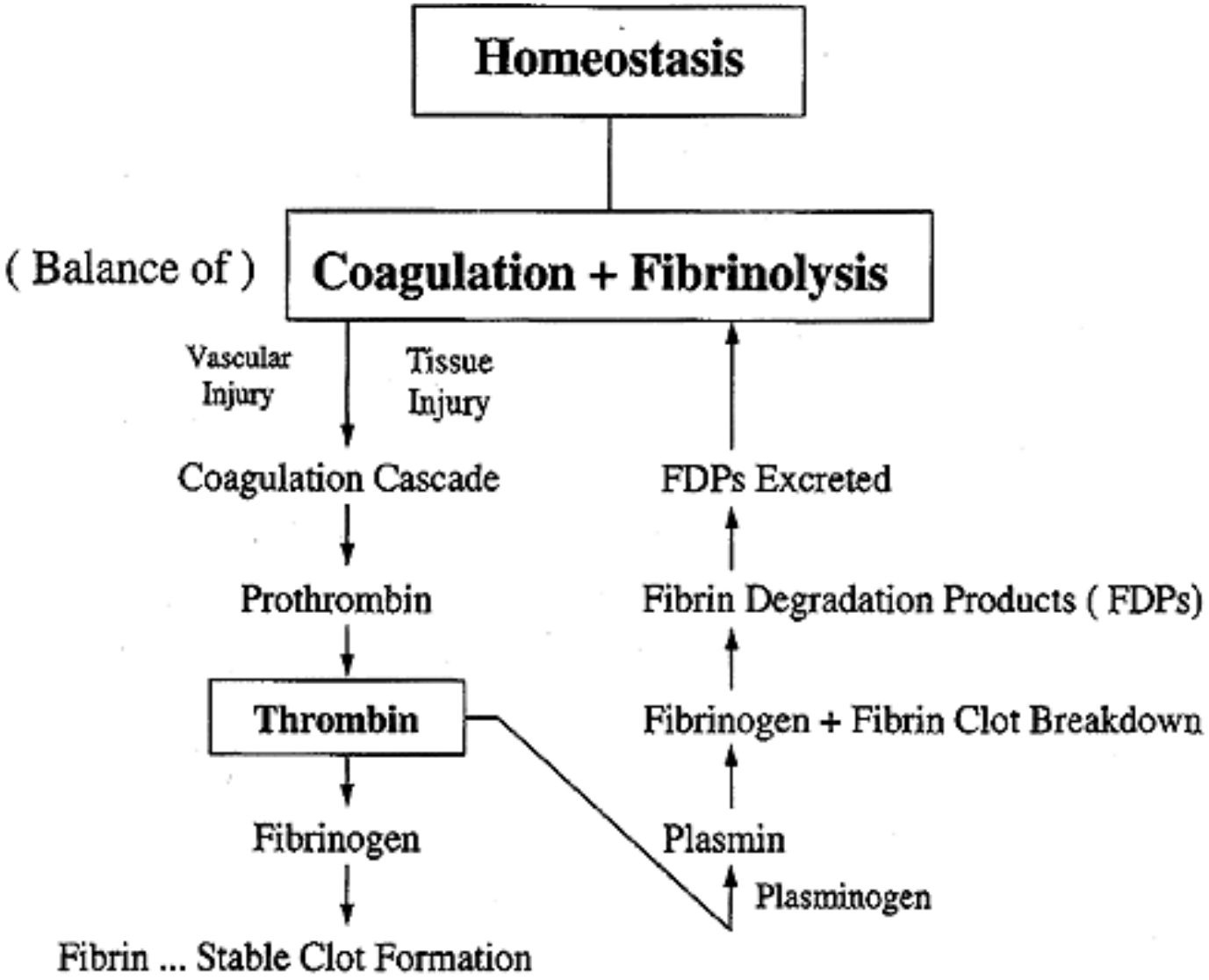
- Very poor prognosis, with high fatality rate

- Complication of many primary problems
  - Obstetrical complications, such as abruptio placentae
  - Infections
  - Carcinomas
  - Major trauma



Disseminated Intravascular Coagulation

Normal Physiologic Condition



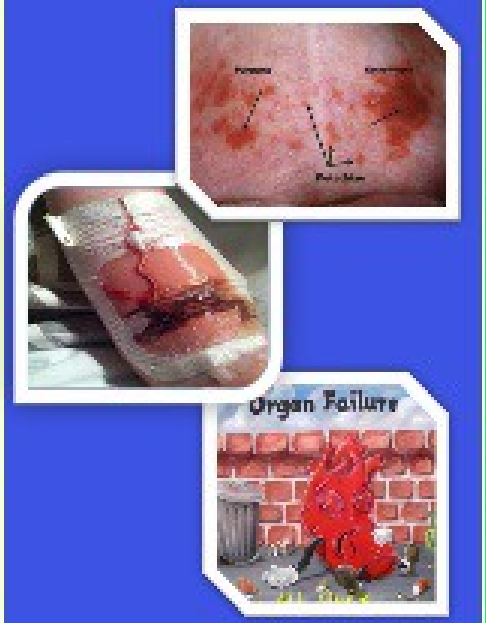
Disseminated intravascular coagulation (DIC)

Pathophysiology

- Hyper-activated coagulation system.
- Hyper-activated fibrin-lytic system, or both simultaneously.
- Coagulation factors and plts consumed as soon as they are made.
- Secondary to an underlying disease or condition. Ex; sepsis, placenta abruption, snake bites, toxin, trauma, graft vs. host disease, and burns.

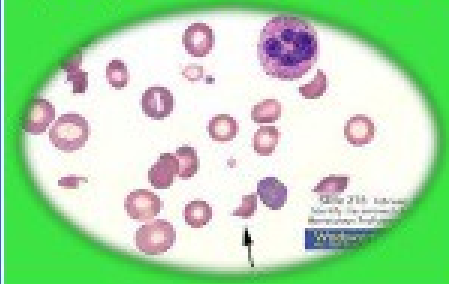
Clinical Finding

- Patients are at risk of bleeding and thrombosis.



Laboratory Finding

- Thrombocytopenia
- Prolonged PT, APTT, thrombin time.
- Decreased fibrinogen.
- Elevated D-dimers.
- Schistocytes on the peripheral blood smear.

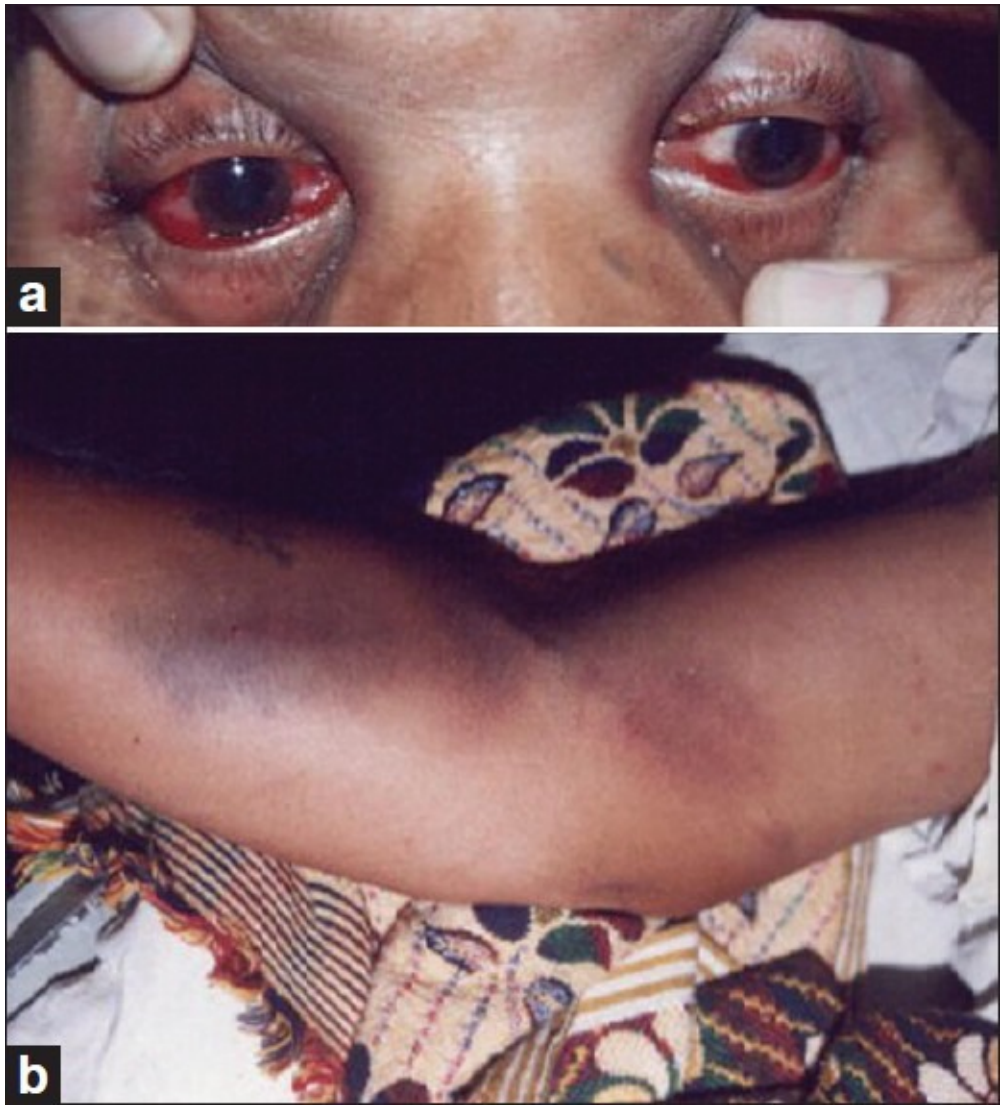


Treatment of DIC

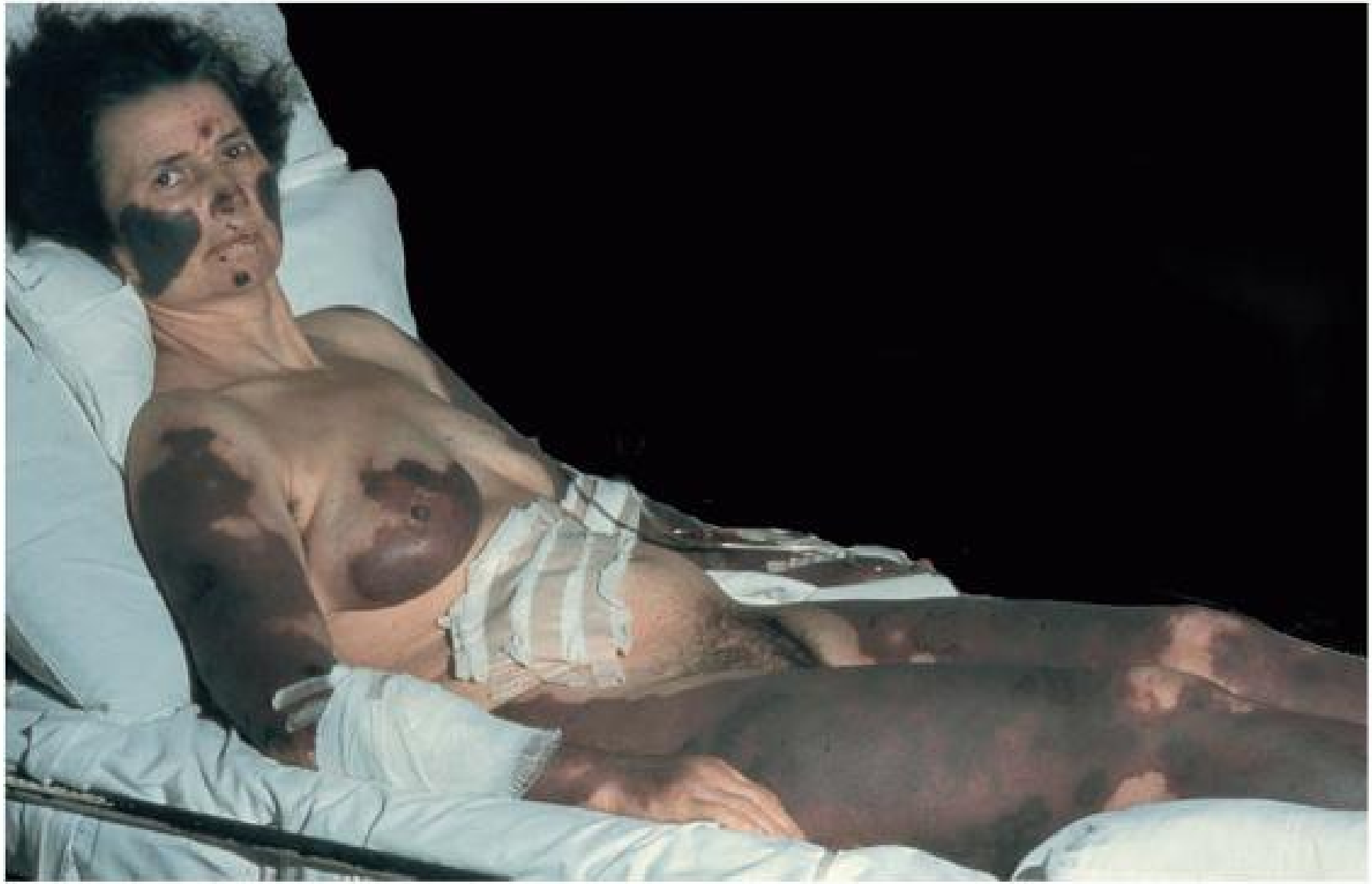
- Treatment of the underlying disorder .
- Transfusion support of Red Blood Cells or Fresh Frozen Plasma (FFP) to replace coagulation factors.

DIC is associated with three conditions: fever, hypotension (i.e. shock), and intravascular coagulation. We can usually control two out of the three conditions, however. Intravascular coagulation is the greatest risk to life.

DIC – Clinical Presentation



DIC – Clinical Presentation



DIC - Spleen

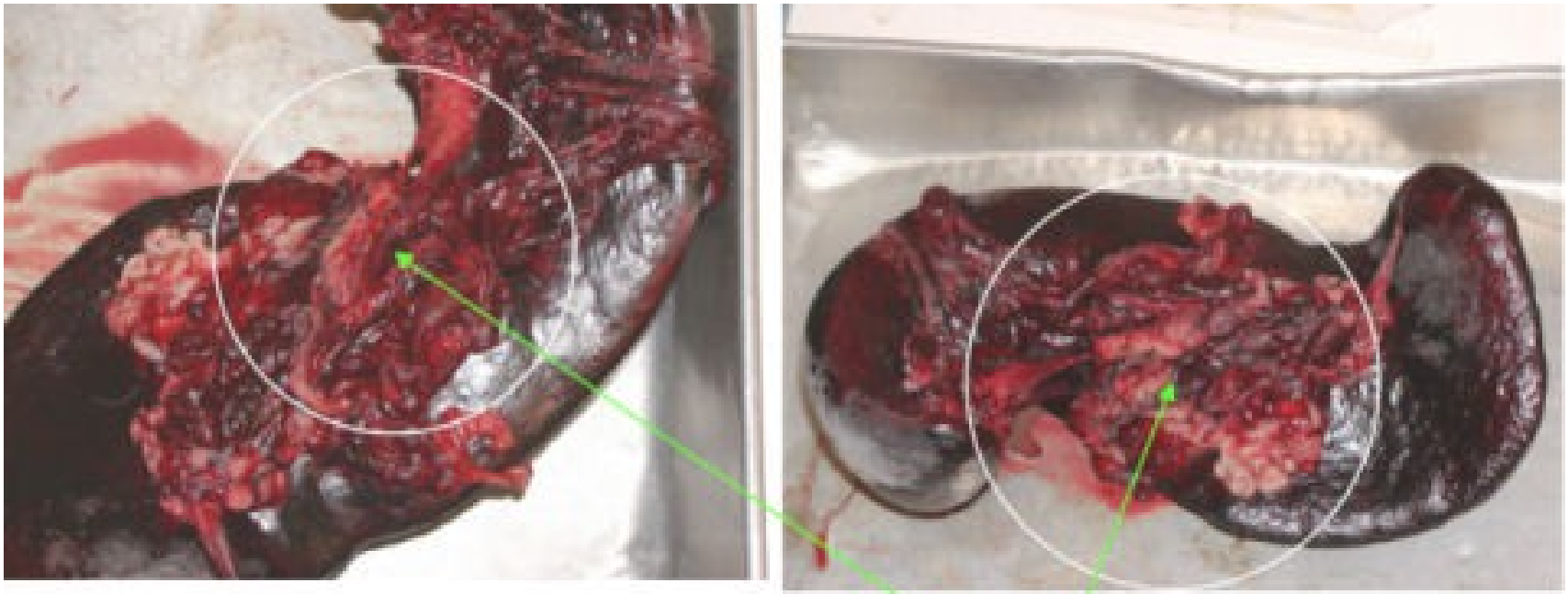


Fig. 2 — This pictures show the spleen after it has been removed due to splenic infarction. The consistency of the spleen normally is fairly spongy while in splenic infarction the spleen feels very "wooden".

Area of splenic infarction at the pedicle of the spleen and greatly enlarged spleen.

DIC – Clinical Presentation