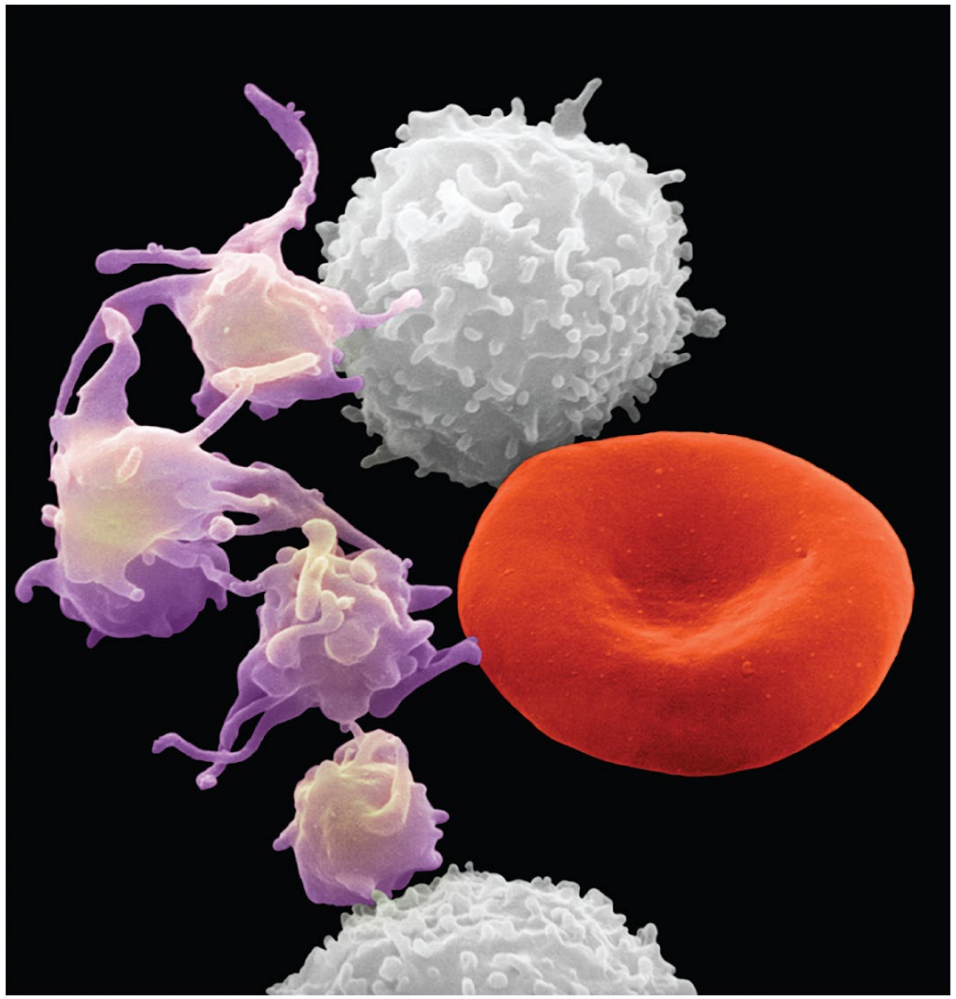
Chapter 18.4

Hemostasis



Hemostasis

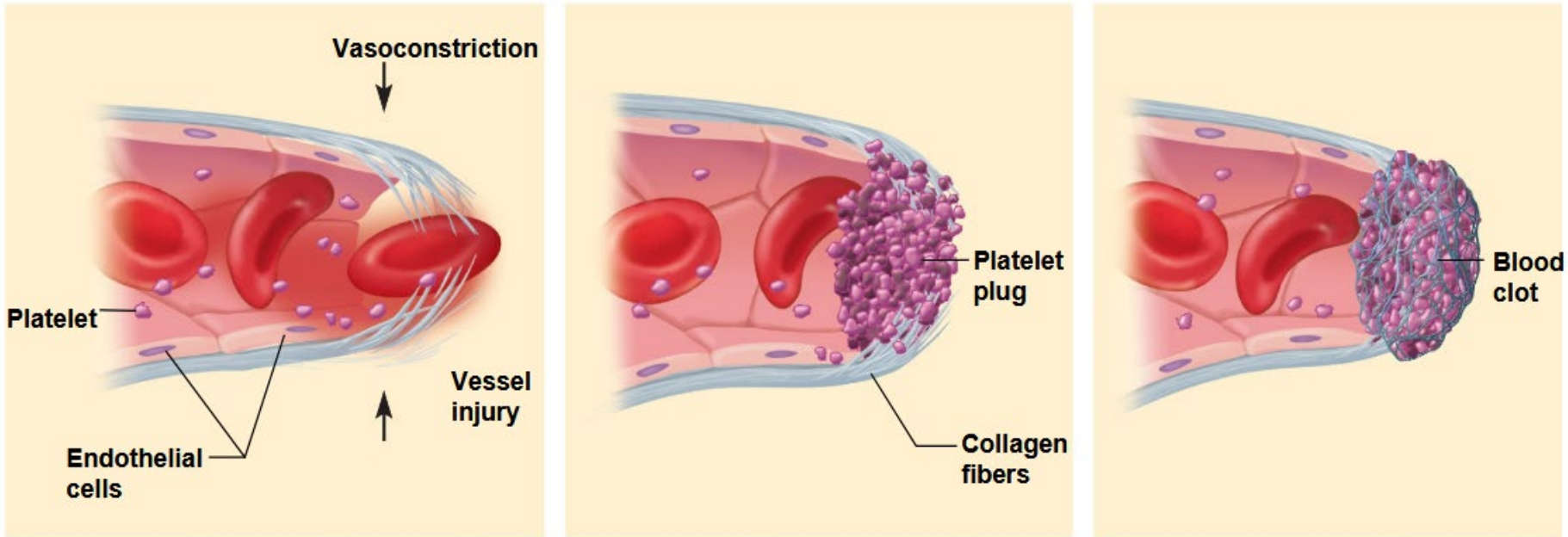
Hemostasis = the cessation of bleeding

- ability to stop potentially fatal leaks
- only in small blood vessels (capillaries)
- not effective in cases of hemorrhage occurring in large artery
- initiated by platelets

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!



(a) Vascular spasm (b) Platelet plug formation (c) Coagulation

each stage involves platelet function

Platelet Functions

Platelets 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

Platelets secrete **procoagulants** or clotting factors to promote proteins circulating in blood to form a “clot”

Platelets initiate formation of **clot-dissolving enzyme** immediately after stopping the loss of blood

Platelets attract neutrophils and monocytes to sites of blood vessel damage // inflammation

Platelets phagocytize and destroy bacteria

Platelets excrete **growth factors** that stimulate mitosis to repair blood vessels

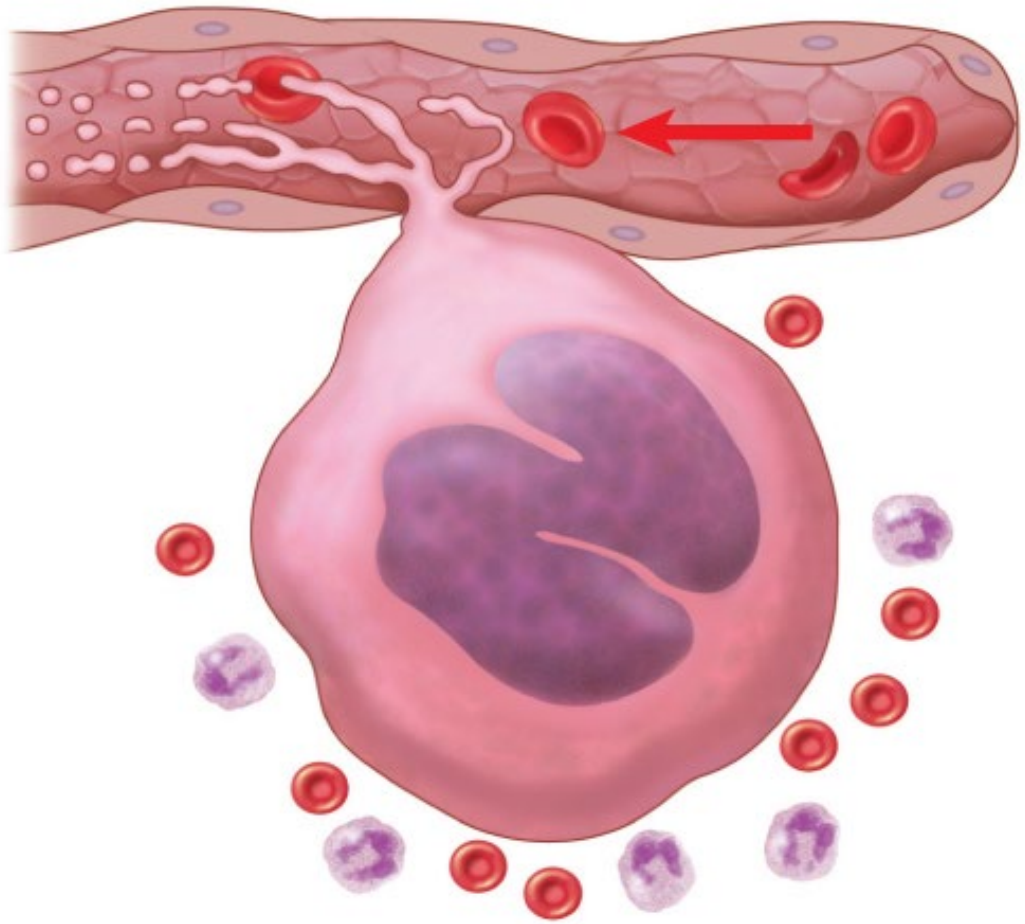
Platelet Production = Thrombopoiesis

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

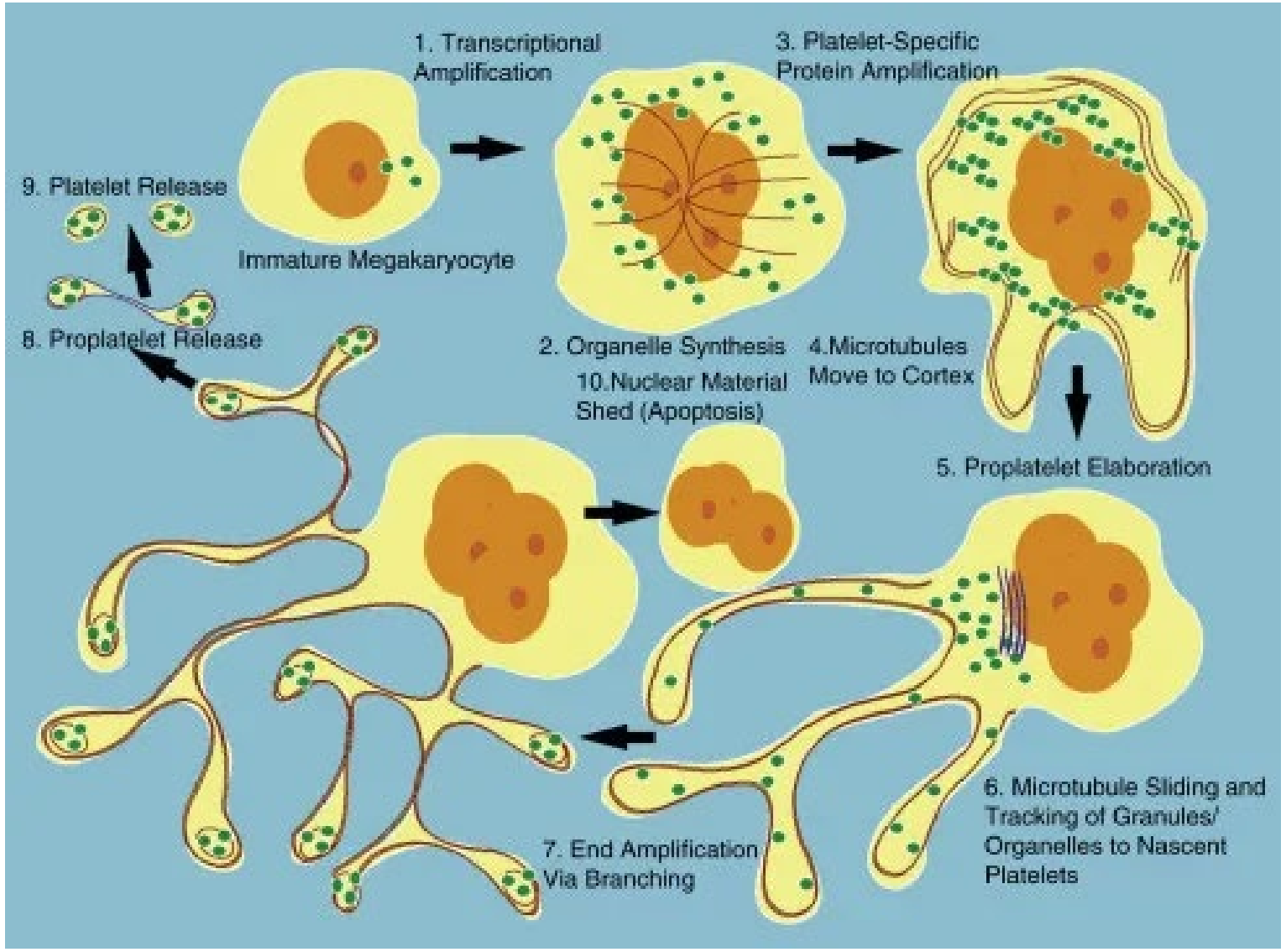
- Megakaryoblasts // repeatedly replicate DNA without dividing // forms gigantic cell called megakaryocyte with a multilobed nucleus // 100 μm in diameter, remains in bone marrow

- 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.



Megakaryocytes are in the red bone marrow with other blood formed elements. The plasma membrane of the Megakaryocyte pass through special sinusoidal capillaries. Fragments of the plasma membranes “pinch off” to become the platelets.


1. Transcriptional Amplification
3. Platelet-Specific Protein Amplification
9. Platelet Release
Immature Megakaryocyte
8. Proplatelet Release
2. Organelle Synthesis
10.Nuclear Material Shed (Apoptosis)
4.Microtubules Move to Cortex
5. Proplatelet Elaboration
7. End Amplification Via Branching
6. Microtubule Sliding and Tracking of Granules/ Organelles to Nascent Platelets

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

Vascular spasm 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

Endothelium (lining of blood vessels) coated with prostacyclin = a platelet repellant // protects against spontaneous activation of platelets and formation of blood clots

Prostacyclin mechanism must be reversed /// another molecule, thromboxane is secreted which makes the surface of endothelium sticky

Platelets now adhere to lining of blood vessel and start to form the platelet plug

More About the Platelet Plug – Second Event

Broken vessel exposes collagen (collagen becomes a trigger)

Platelet's 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 created

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

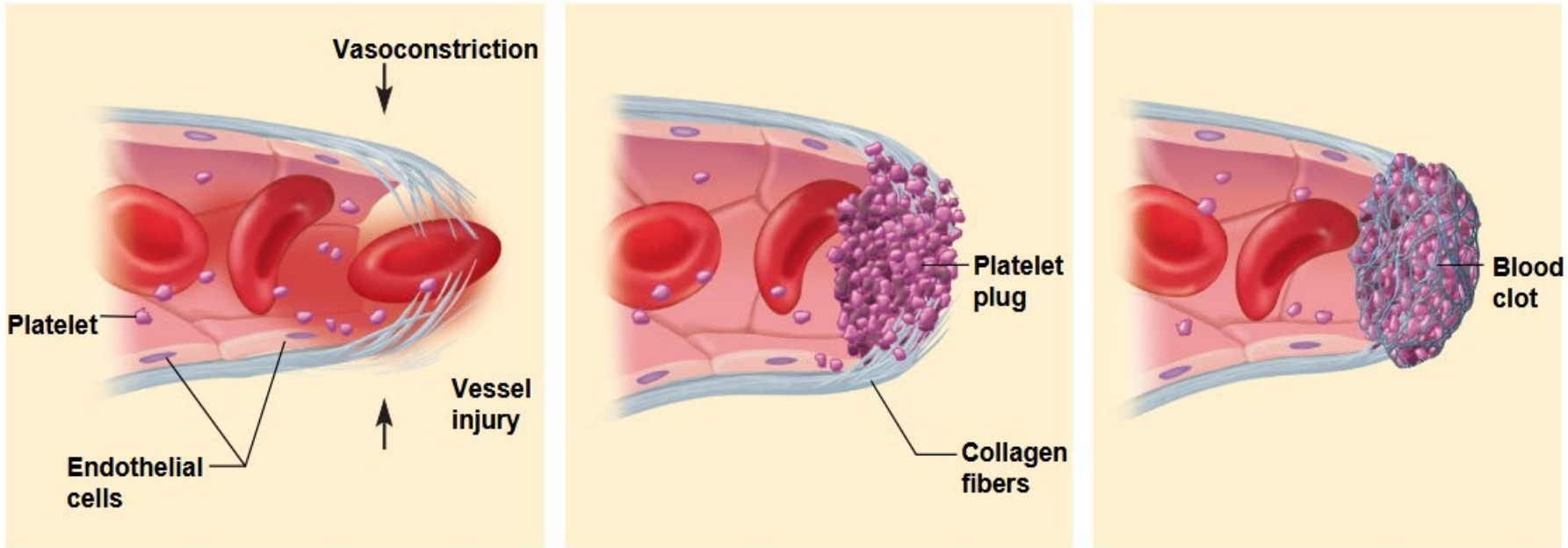
- Activate one factor and it will activate the next to form a reaction cascade

Coagulation – Third Event

Coagulation can be initiated by activating one of two pathways

Extrinsic pathway // factors released by damaged tissues begin cascade // 15 sec

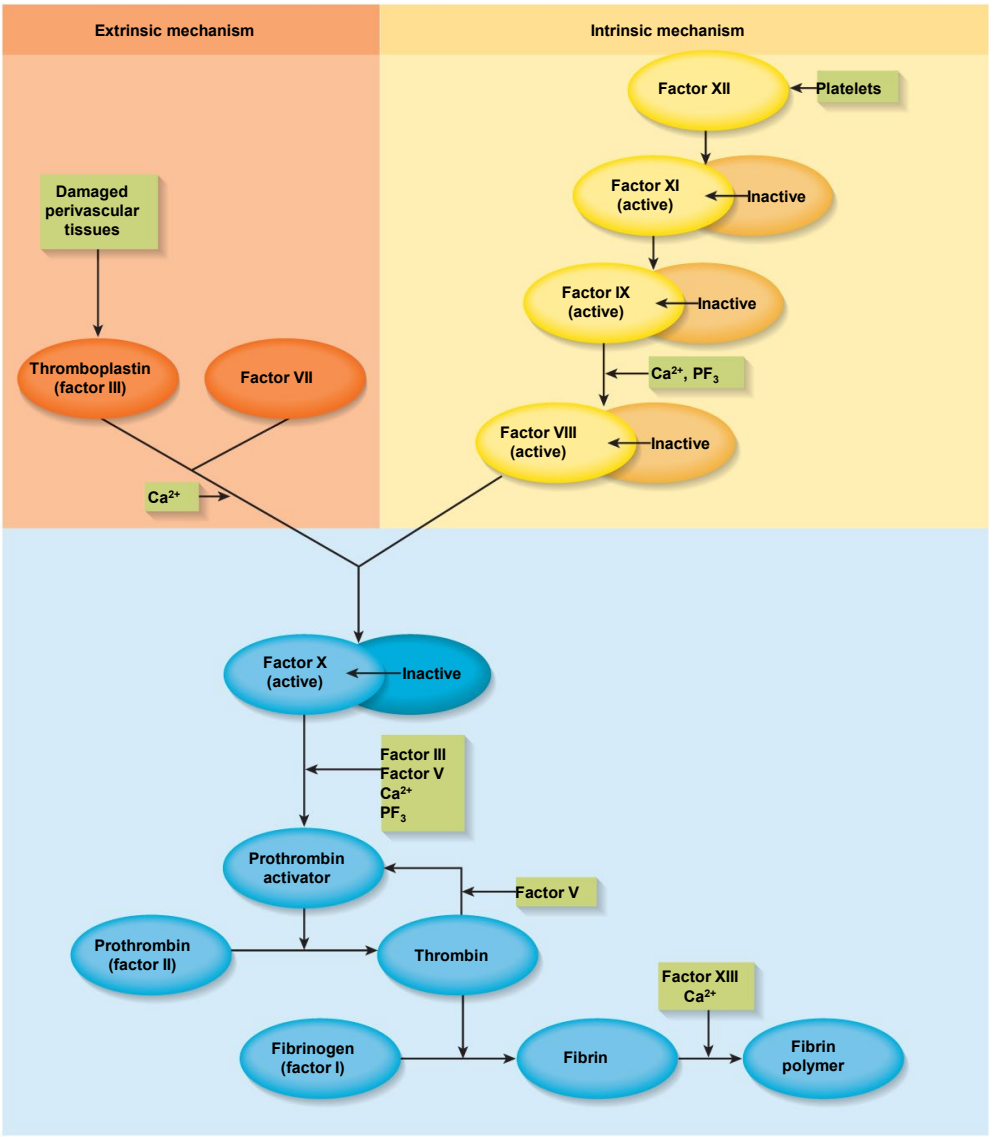
Intrinsic pathway // factors found in blood begin cascade (the platelet degranulation) // 3 to 6 minutes



(a) Vascular spasm (b) Platelet plug formation (c) Coagulation

each stage involves platelet function

Coagulation Pathways



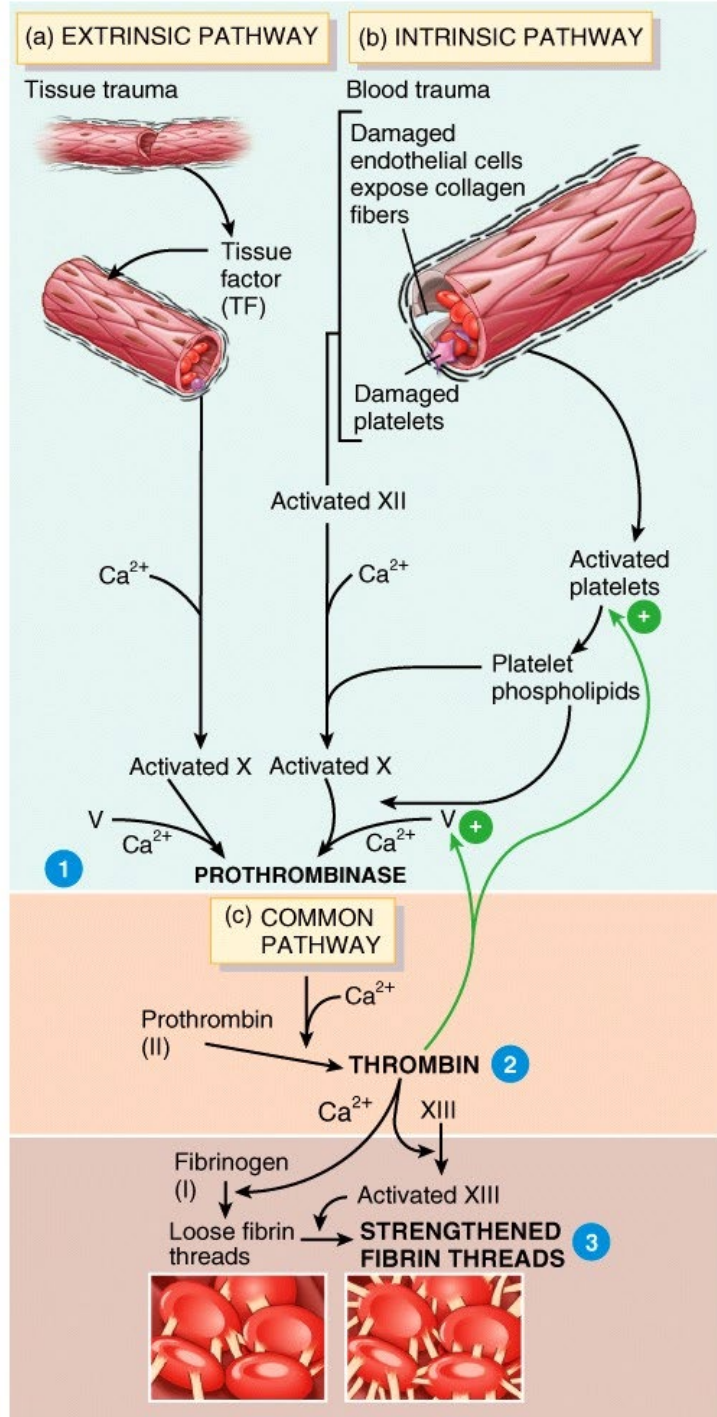
Extrinsic pathway

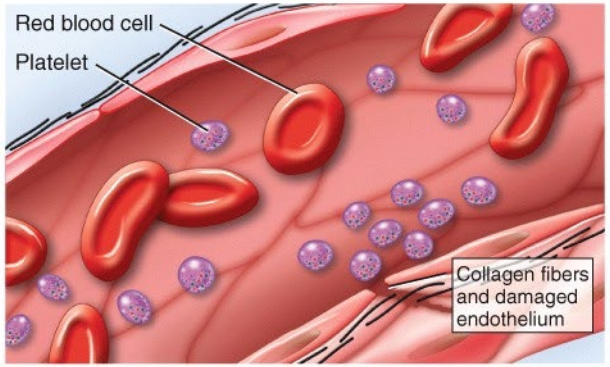
–Initiated by release of **tissue thromboplastin** (factor III)
–From damaged tissue
–Cascade to factor VII, V and X (fewer steps)
–Clot forms in 15 seconds

Intrinsic pathway

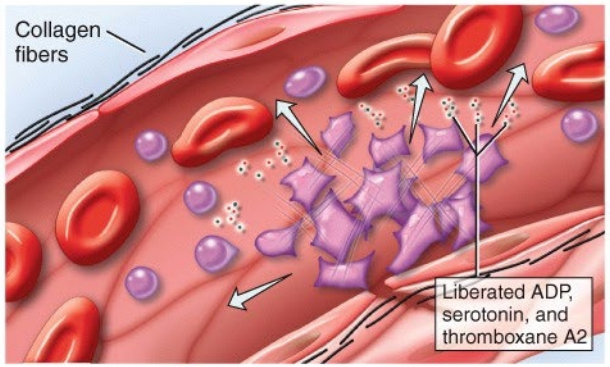
–Initiated by platelets releasing **Hageman factor** (factor XII)
–Cascade to factor XI to IX to VIII to X
–Clot forms in 3 to 6 minutes

Calcium required for both pathways

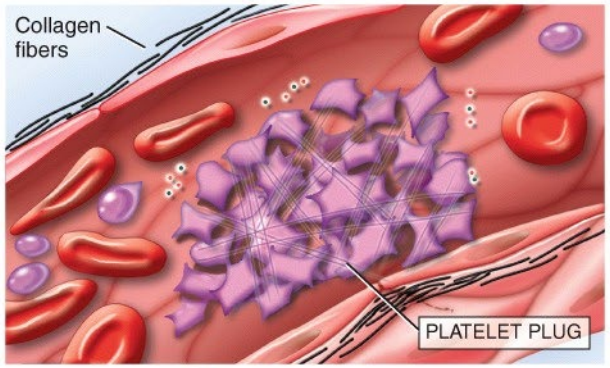

(a) EXTRINSIC PATHWAY
(b) INTRINSIC PATHWAY
Tissue trauma
Blood trauma
Damaged endothelial cells expose collagen fibers
Tissue factor (TF)
Damaged platelets
Activated XII
Ca2+
Ca2+
Activated platelets
Platelet phospholipids
Activated X
Activated X
V
Ca2+
V
Ca2+
1
PROTHROMBINASE
(c) COMMON PATHWAY
Ca2+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



1 Platelet adhesion

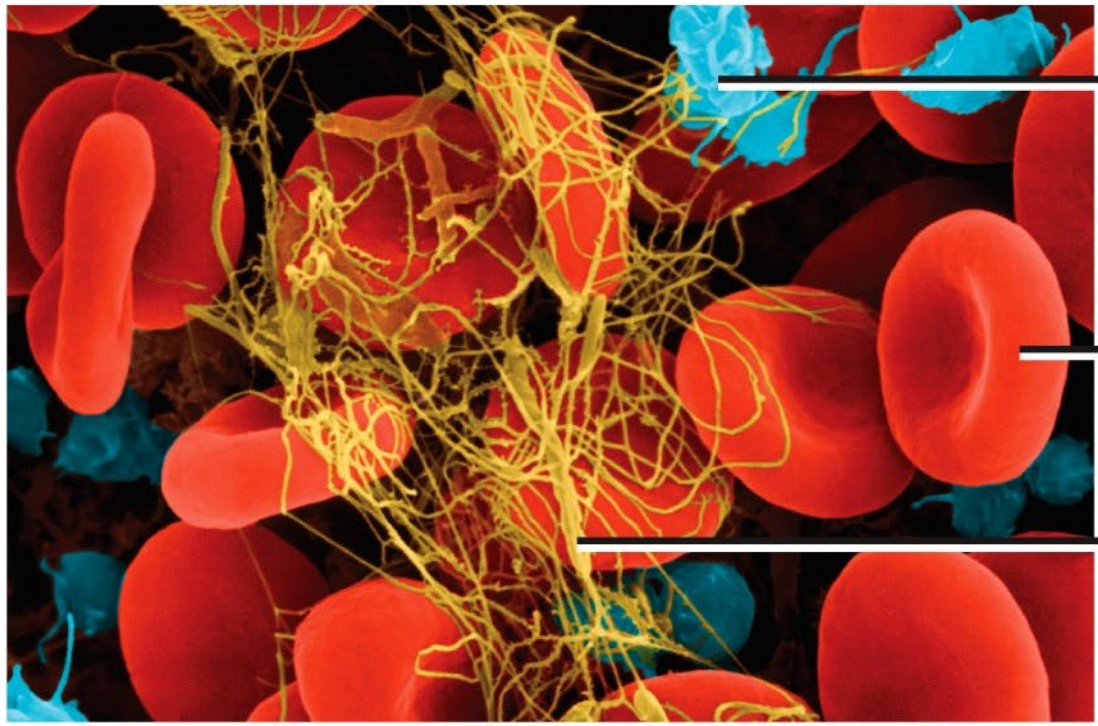


2 Platelet release reaction



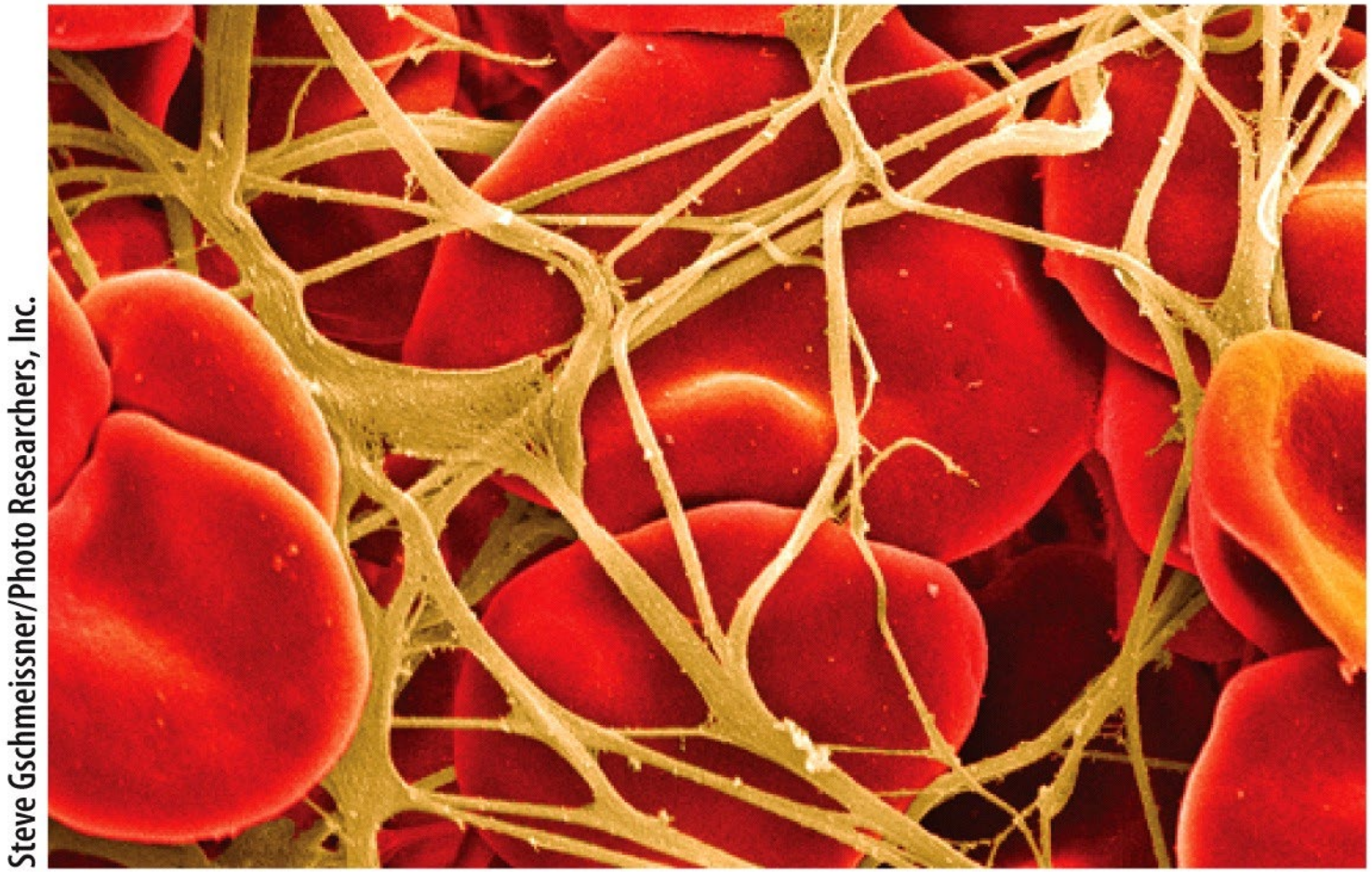
3 Platelet aggregation

Dennis Kunkel Microscopy, Inc./Phototake



SEM 1,445x

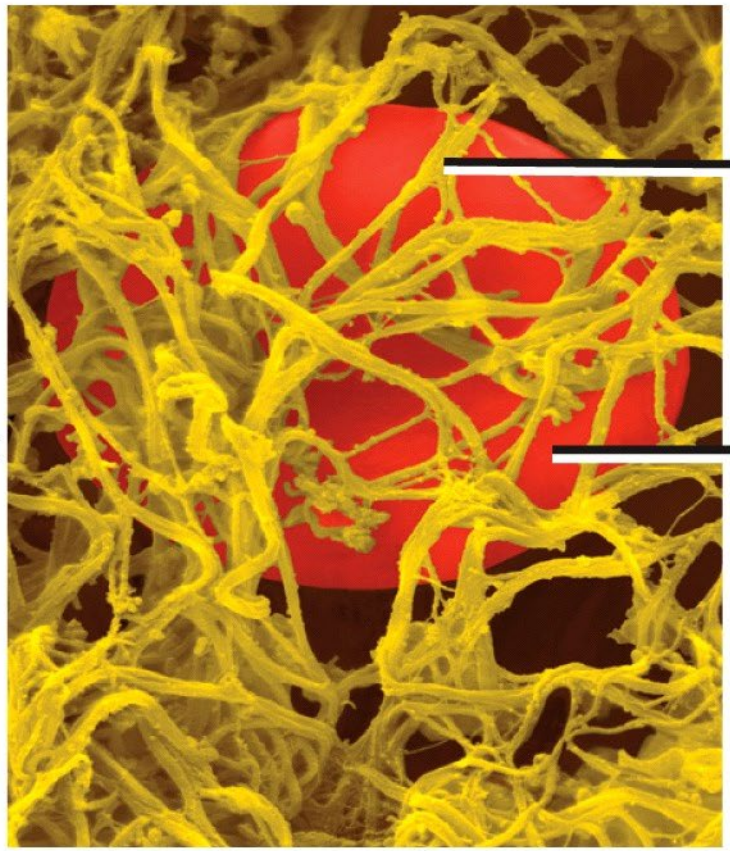
(a) Early stage



Steve Gschmeissner/Photo Researchers, Inc.

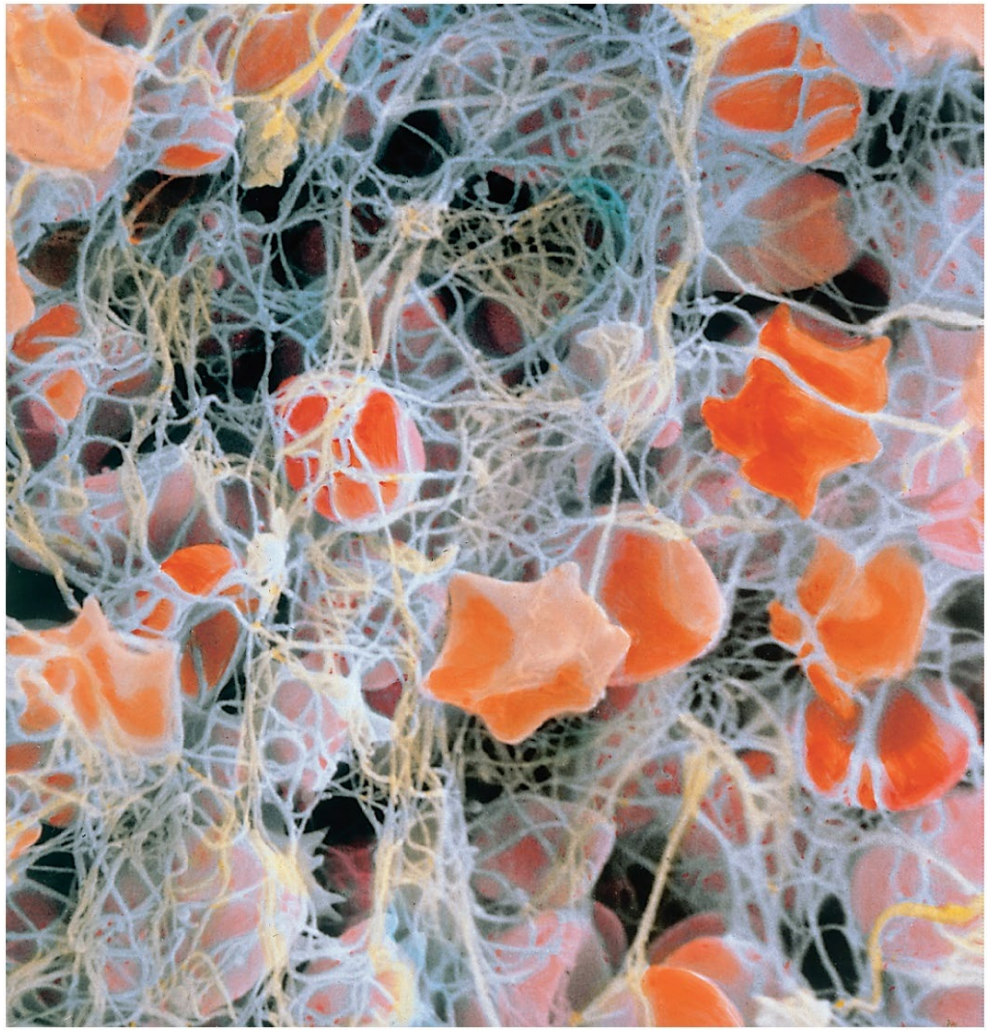
SEM 900x

(b) Intermediate stage

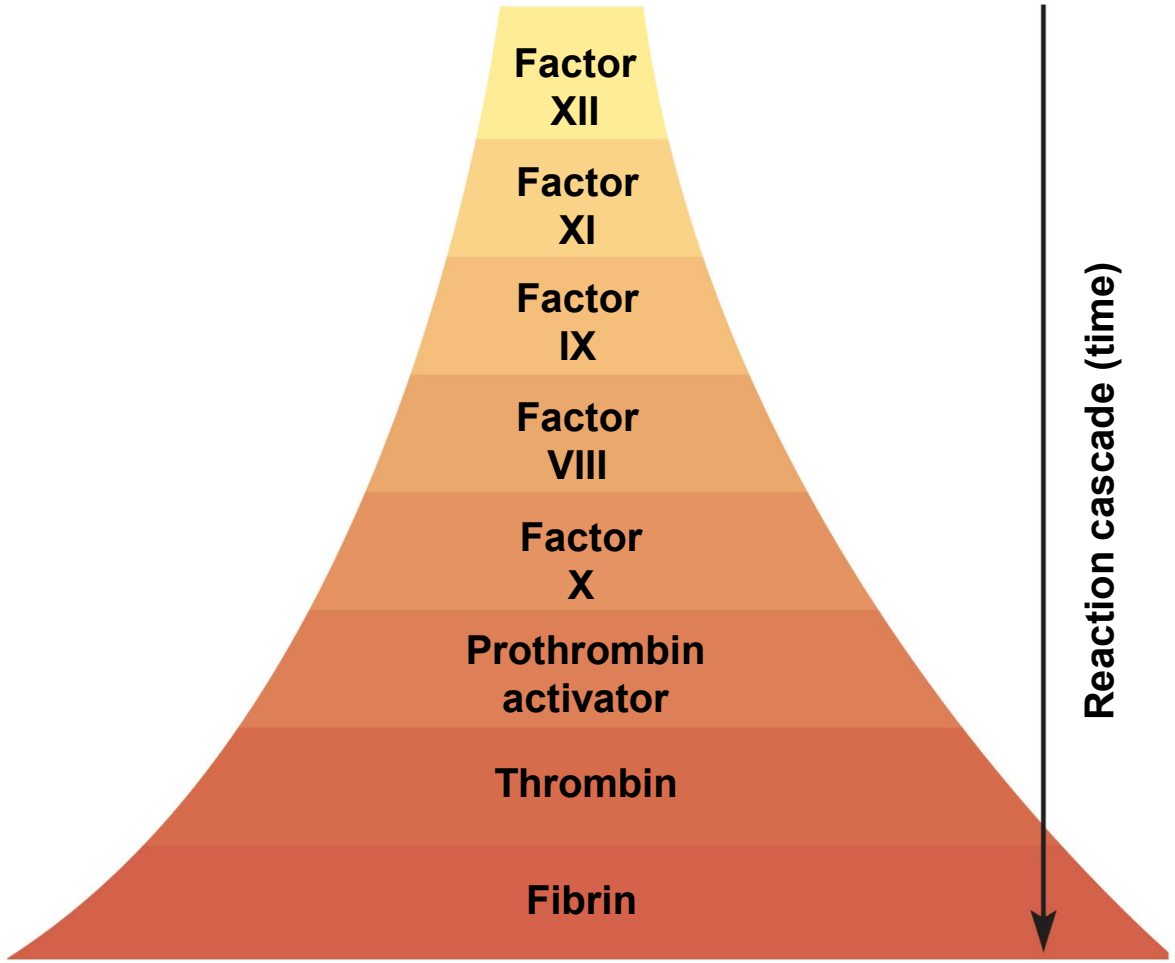


(c) Late stage showing red blood cells trapped in fibrin threads

Scanning Electron Microscope
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

Note: Eliquis blocks Factor X // prevents blood clot formation

After Blood Clot Forms

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

Platelet-derived growth factor secreted by platelets and endothelial cells

this stimulates mitosis // stimulates fibroblasts and smooth muscle to multiply // together they help to repair damaged vessel

After Blood Clot Forms

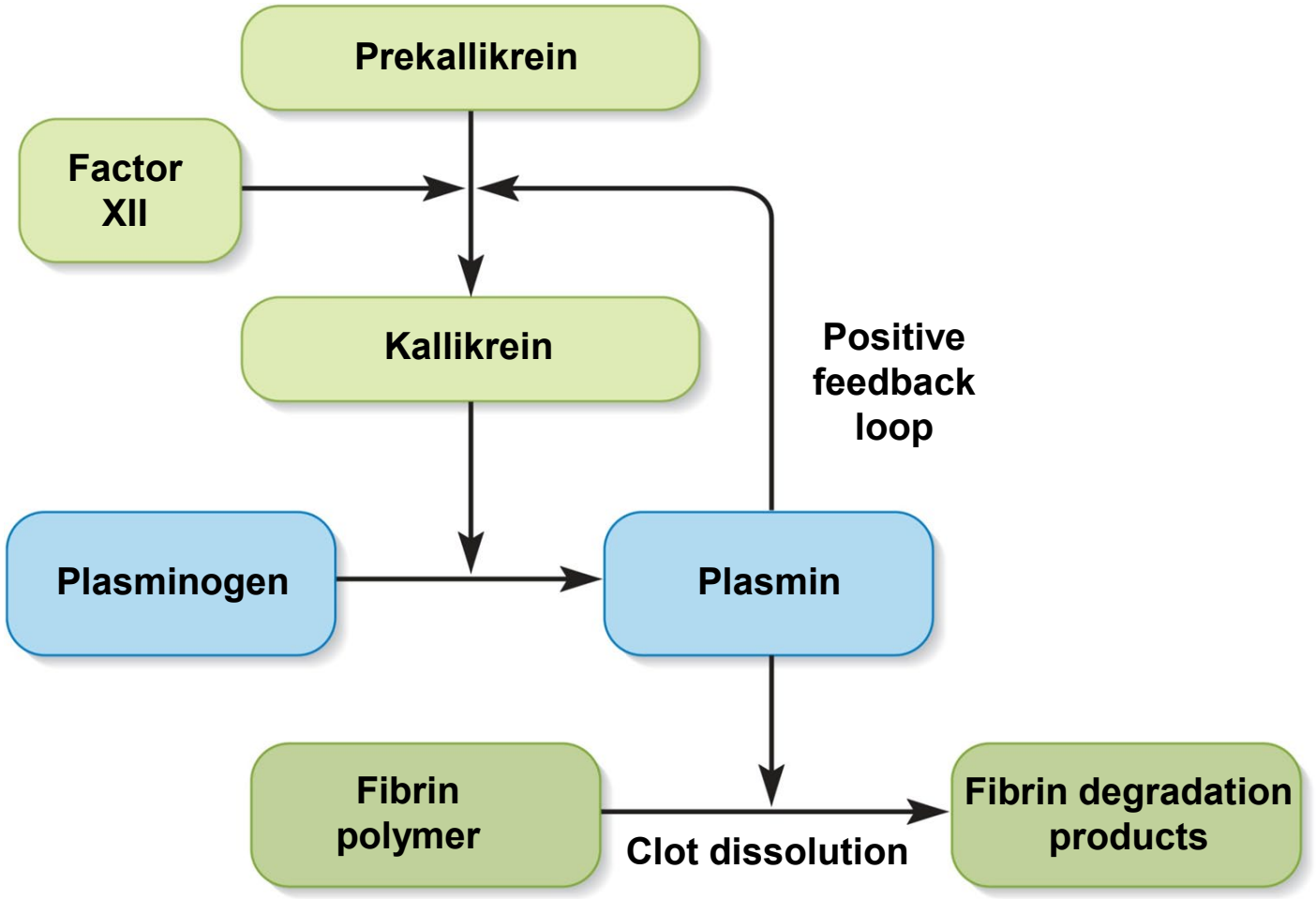
Fibrinolysis // enzyme that breaks apart the blood clot

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 // increased number of platelets
- Thrombocytopenia // decreased number of platelets

Clinical Management of Clotting

Goal is to prevent spontaneous formation of clots or to dissolve existing clots

Preventing clots by:

–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 blood clots be “dissolved” ?

– streptokinase – enzyme make by streptococci bacteria /// used to dissolve clots in coronary vessels /// digests protein and not selective for blood clots

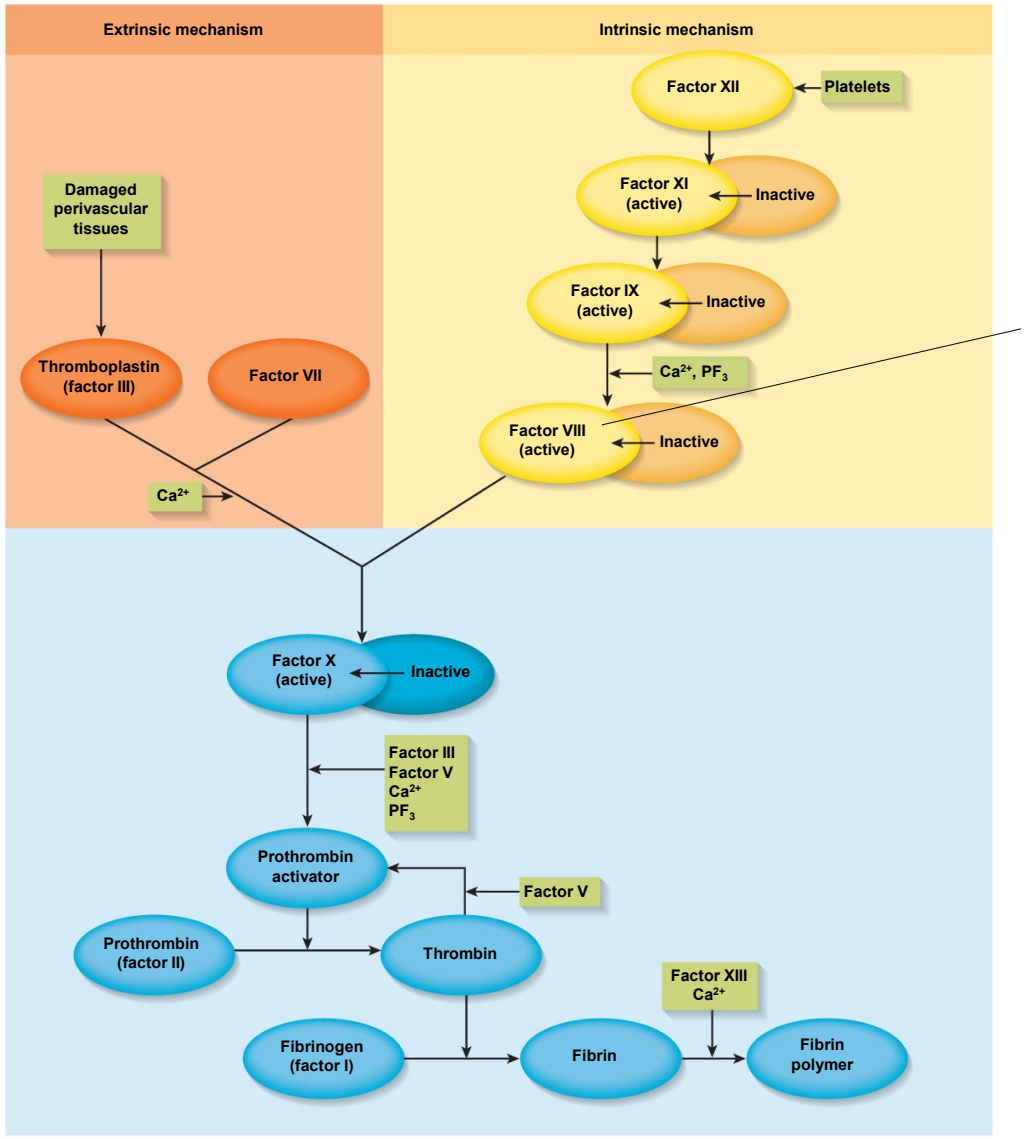
– tissue plasminogen activator (TPA) – works faster, is more specific, and now made by transgenic bacteria

– 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

- This is a clinical complication from a gram-negative bacterial infection. Molecules released by the bacteria cause three events: fever, vaso-dilation with drop in blood pressure, and spontaneous blood clot formation throughout circulatory system. The coagulation is major problem.

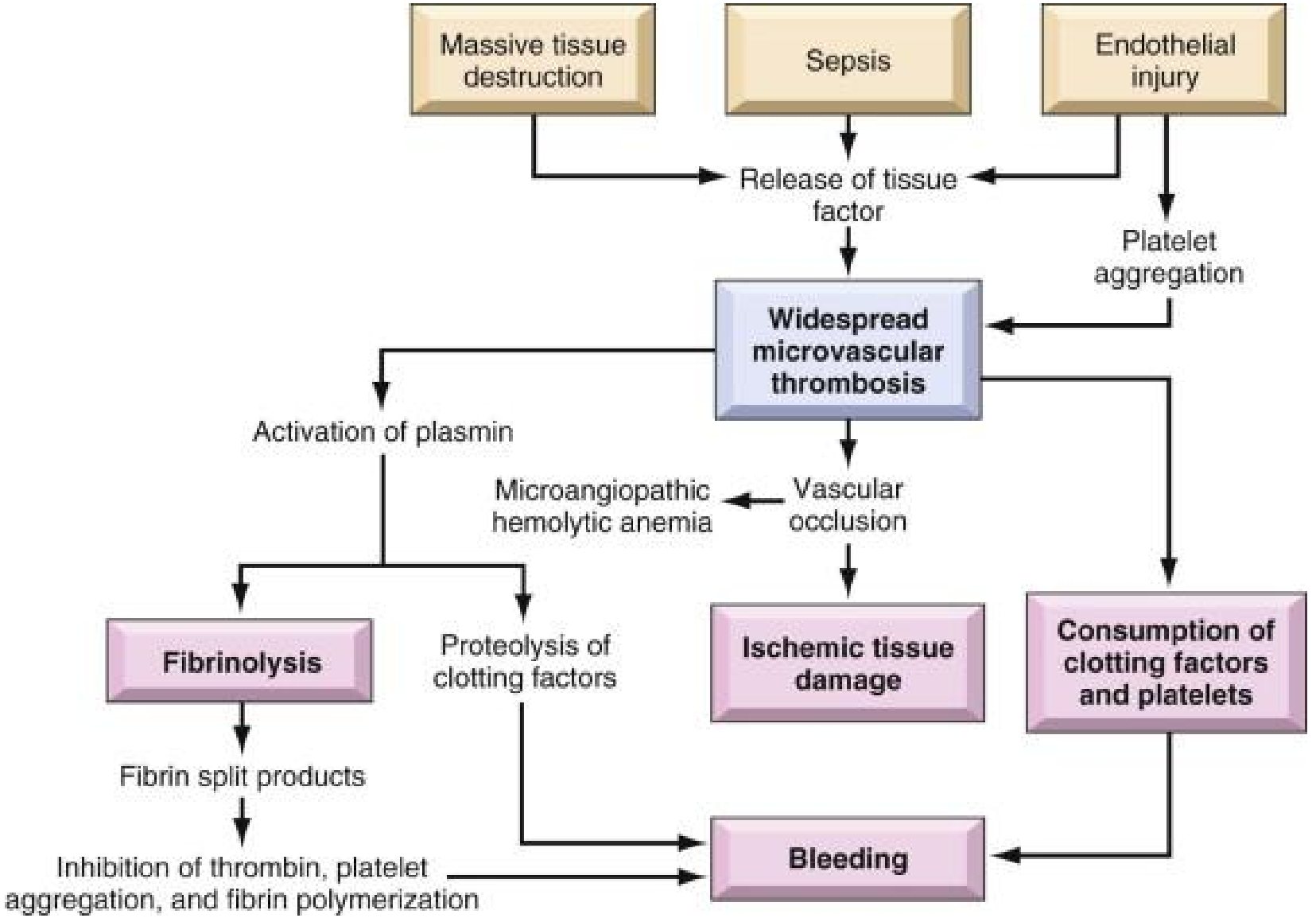
- First event: Excessive clotting in circulation // Results in thromus formation, embolisms, and infarction. (e.g. lipopolysacharide shed by gram negative bacteria stimulate monocytes to release cytokines which cause several outcomes including blood clotting)

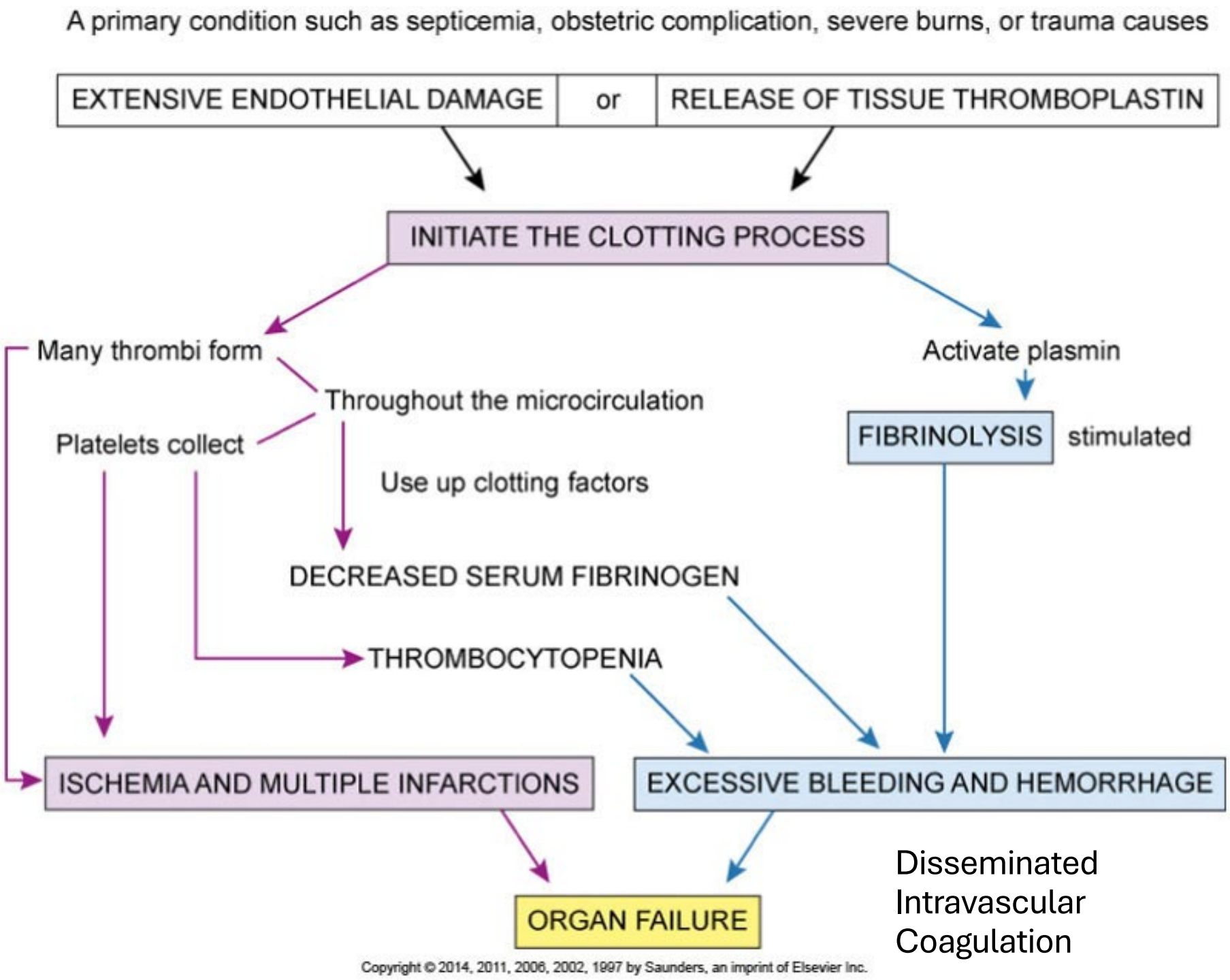
- *Second event:* *Clotting factors are reduced to a dangerous level*. // Widespread, uncontrollable hemorrhage then results. /// followed by excessive bleeding in microcirculation

- Very poor prognosis, with high fatality rate

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

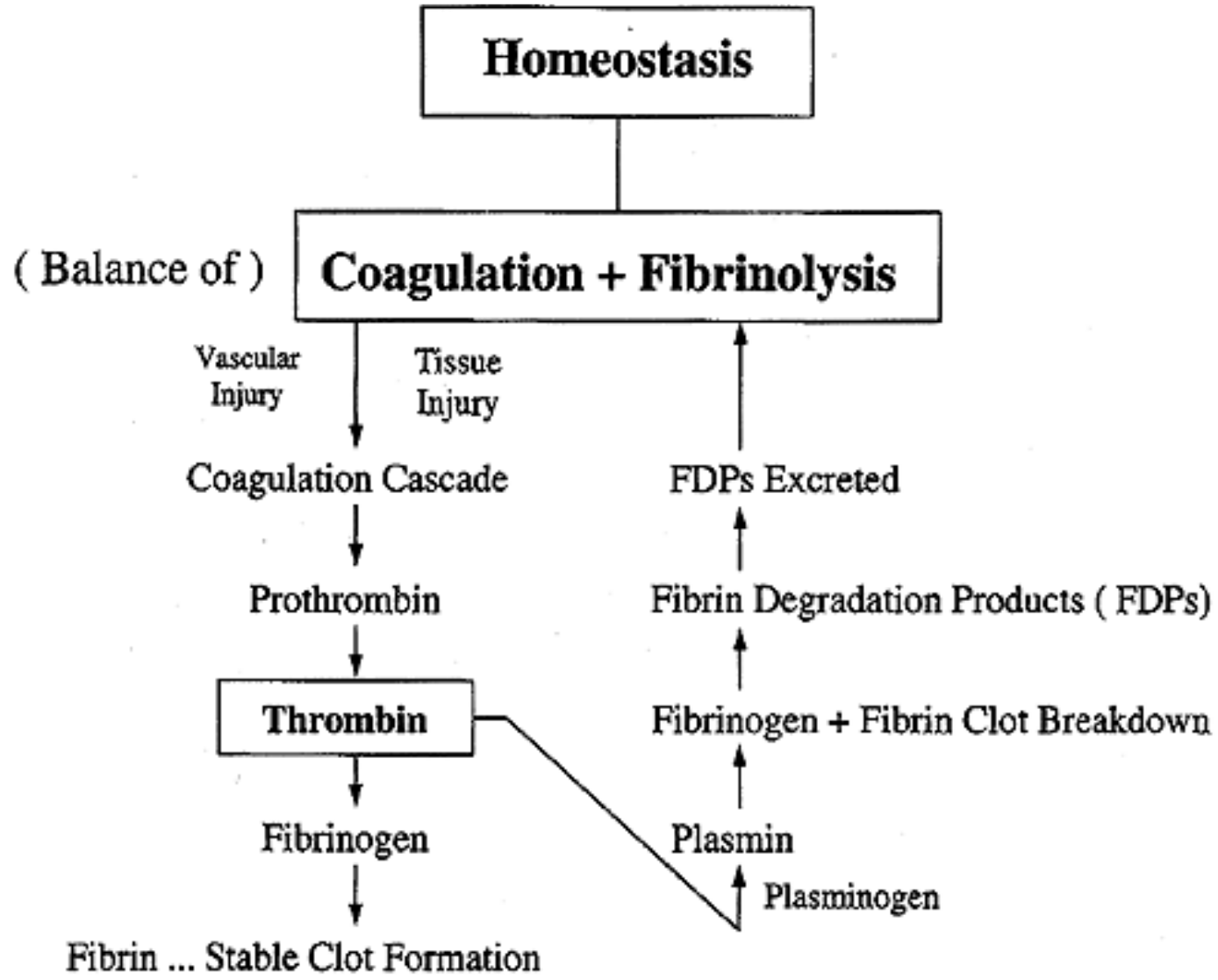
Disseminated Intra-Vascular Coagulation





Disseminated Intravascular Coagulation

Normal Physiologic Condition



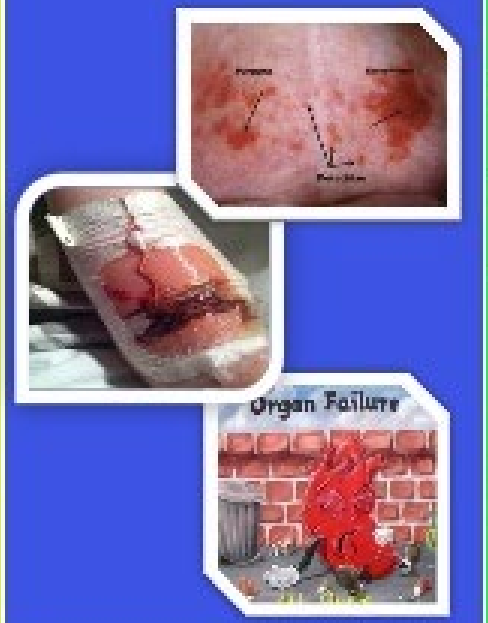
Disseminated intravascular coagulation (DIC)

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.

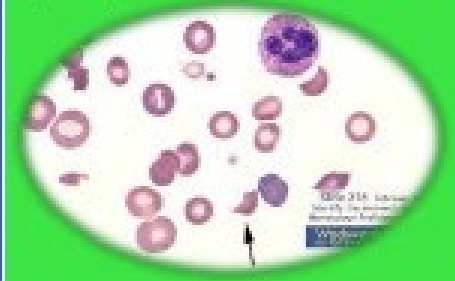
Clinical Finding

- 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.

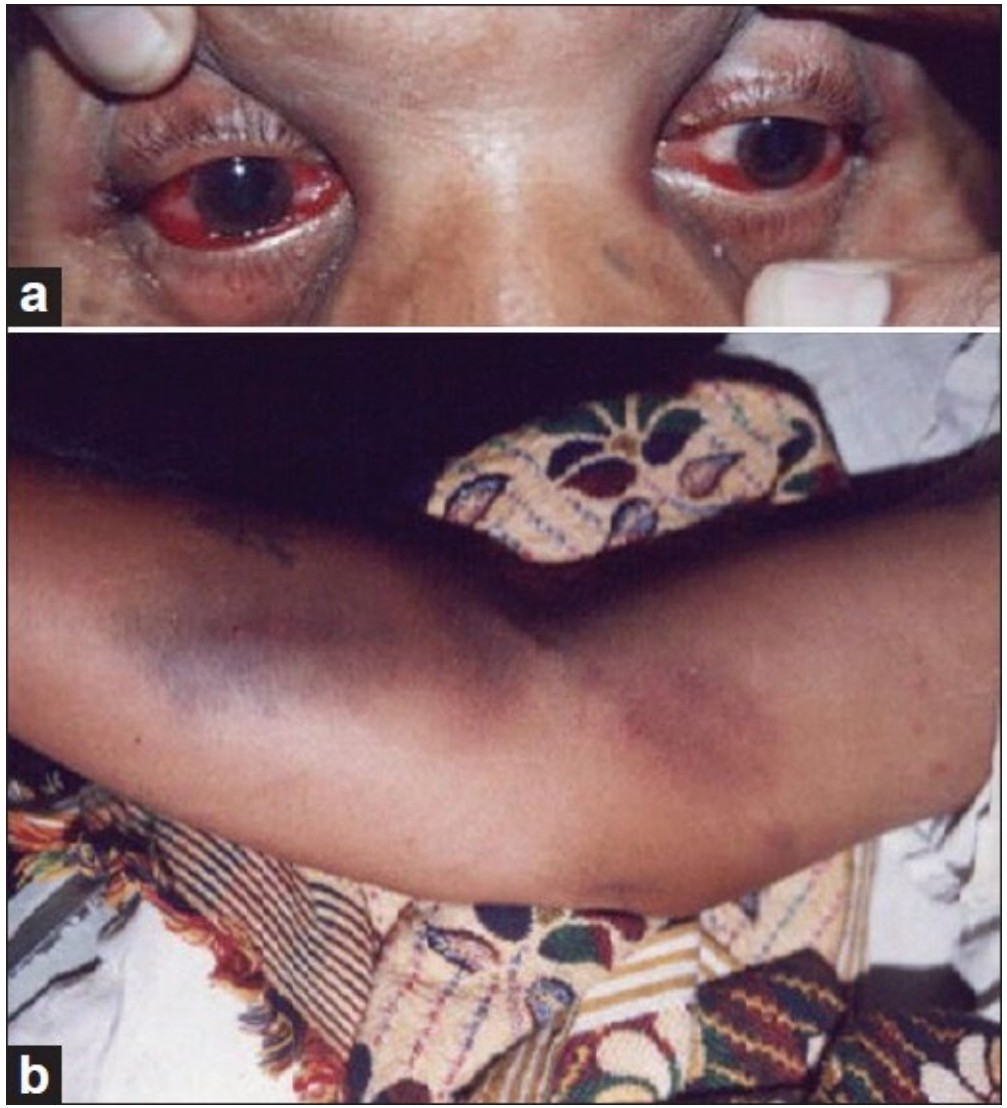


Treatment of DIC

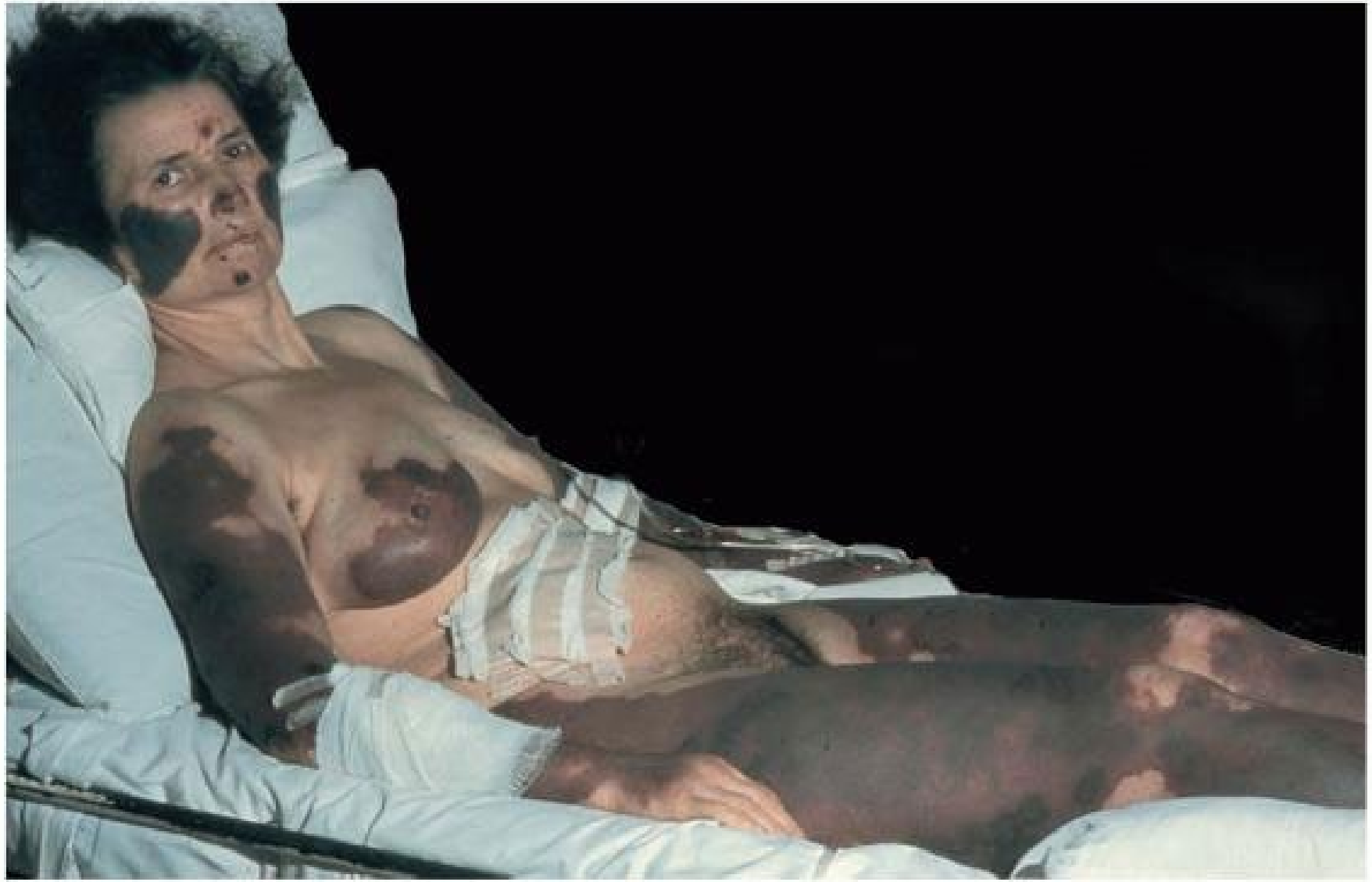
- Treatment of the underlying disorder .
- Transfusion support of Red Blood Cells or Fresh Frozen Plasma (FFP) to replace coagulation factors.

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

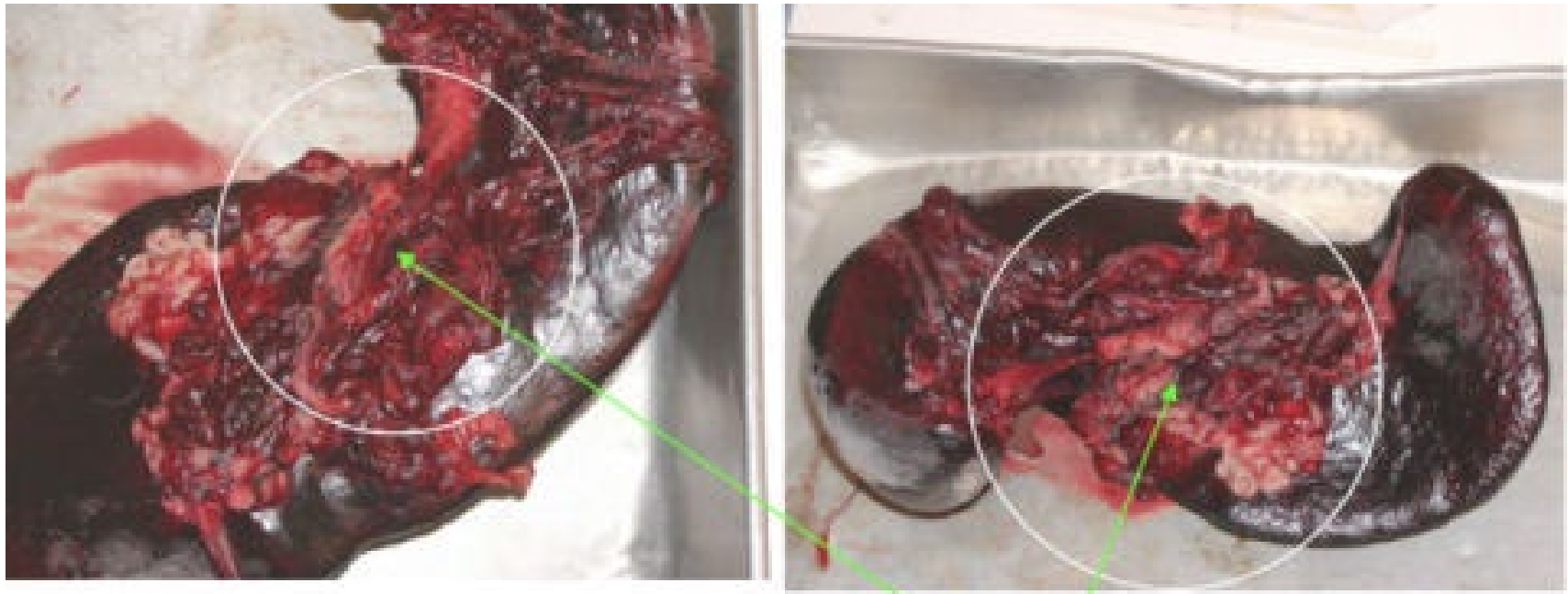


Fig. 2 — This pictures show the spleen after it has been removed due to splenic infarction. The consistency of the spleen normally is fairly spongy while in splenic infarction the spleen feels very "wooden".

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

DIC – Clinical Presentation