Alteracion de la coagulacion en el paciente critico
Thursday 25 Sep 9:30

Coagulation Problems in Critically Ill Patients

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Chair, Conventional Components Committee
Biomedical Excellence for Safer Transfusion Collaborative

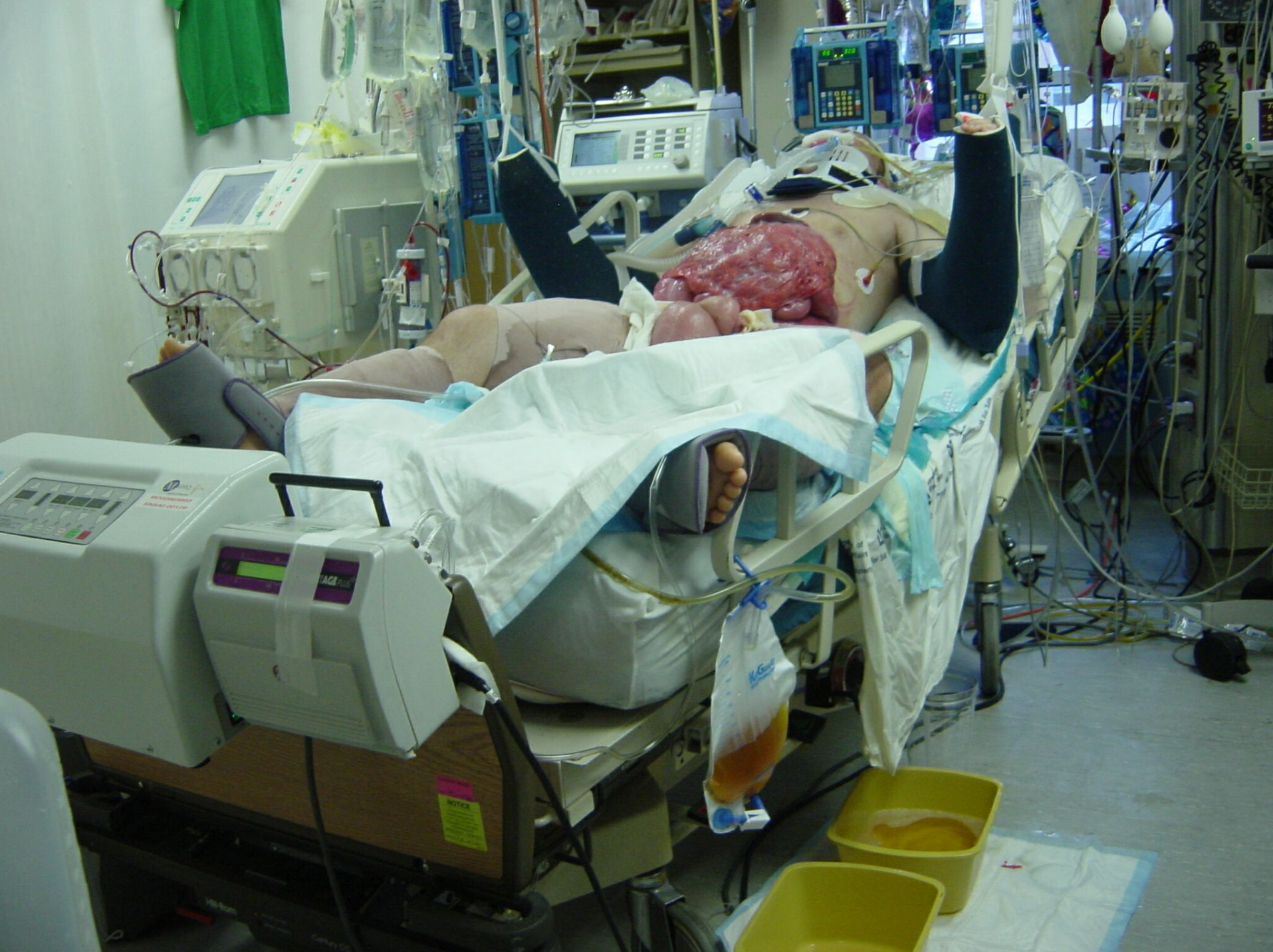
WHO Expert Panel, Blood Transfusion Medicine

an 18 y.o. honors student with a soccor scholorship

Coagulopathic bleeding as a late complication of trauma treatment

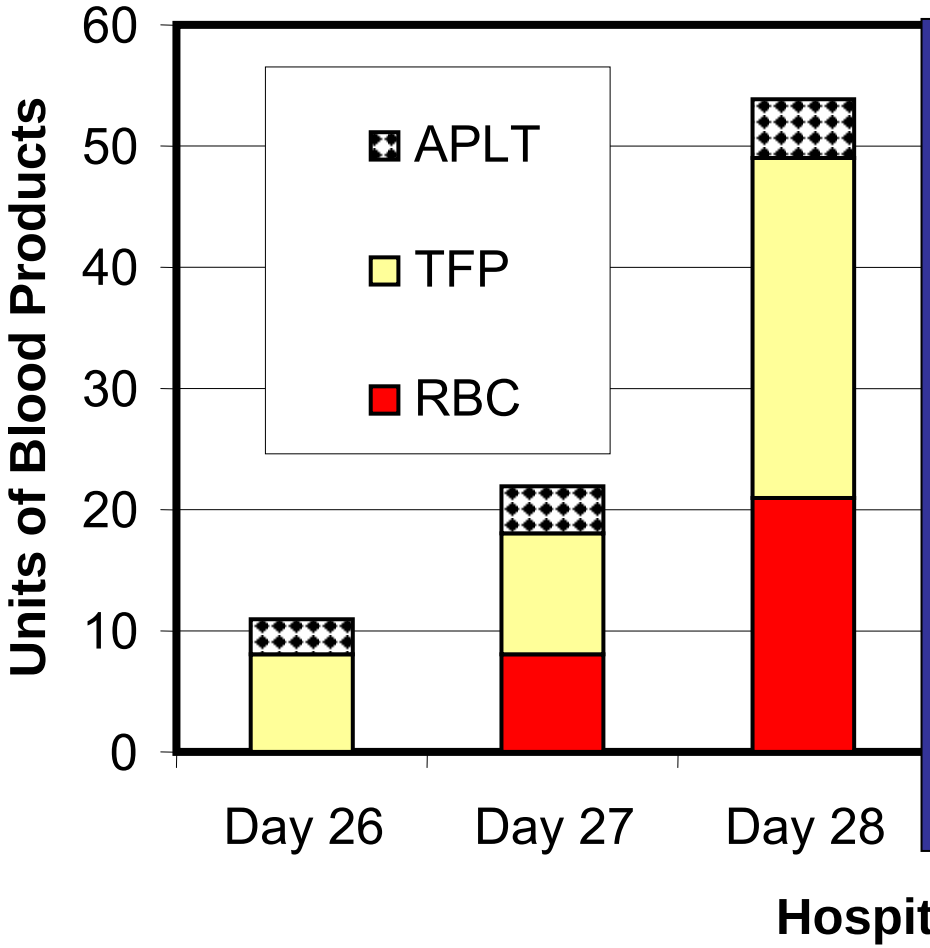
- An 18 yo man received head injuries in an MVA

- High ICP was treated with hypertonic saline and a decompressive lap
- Fluid administration led to muscle compartment syndromes with myoglobin >120 mg/L Fasciotomies were performed with control of compartment pressures
- On day 26, the open surgical wounds oozed



$12,200 of Blood Product Use in Patient in 3 Days

18 yo with coagulopathic bleeding from fasciotomomy sites



	Day 26	Day 27
PT	14	14.8
PTT	29	28
Fib	363	196
Plts	72	82

Perform simple measures first:

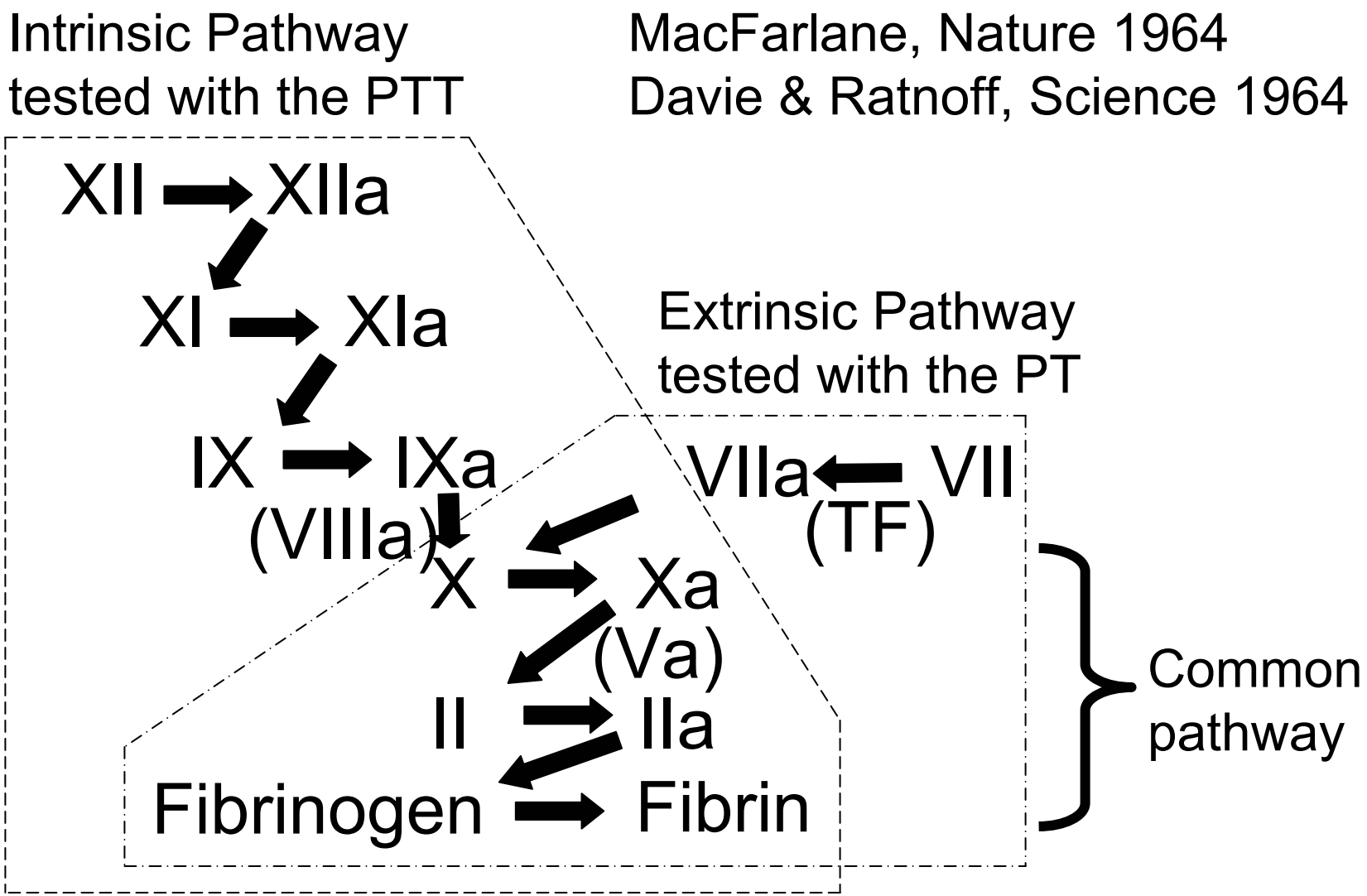
- PT
- PTT
- Fibrinogen
- Platelet count
- Fibrin split products

Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006; 10:222

PT prolonged, aPTT normal	Factor VII deficiency
	Mild vitamin K deficiency
	Mild liver insufficiency
	Low doses of vitamin K antagonists
PT normal, aPTT prolonged	Factor VIII, IX, or XI deficiency
	Use of unfractionated heparin
	Inhibiting antibody and/or anti-phospholipid antibody
	Factor XII or prekallikrein deficiency (no relevance for *in vivo* coagulation)
Both PT and aPTT prolonged	Factor X, V, II or fibrinogen deficiency
	Severe vitamin K deficiency
	Use of vitamin K antagonists
	Global clotting factor deficiency
	Synthesis: liver failure
	Loss: massive bleeding
	Consumption: DIC

aPTT, activated partial thromboplastin time; PT, prothrombin time.

The Classic Coagulation Cascade



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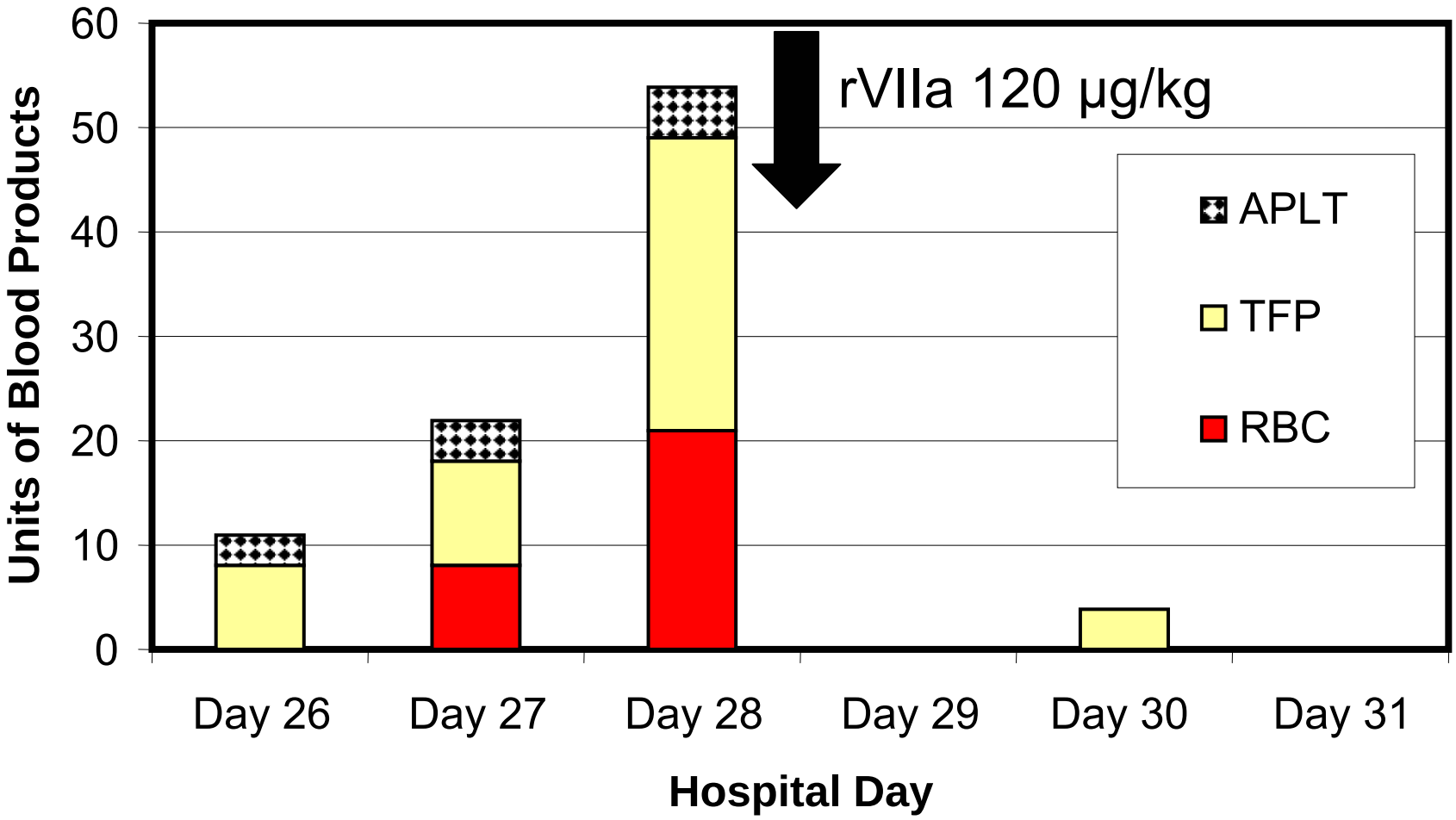

Massive bleeding with minimal laboratory evidence of coagulopathy

	Day 26	Day 27	Day 28	Day 29	Day 30	Day 31
PT	14	14.8	9.3	14.1	14.8	14.2
PTT	29	28	27	31	27	28
FIB	363	196	204	382	456	497
Plts	70	82	62	59	64	82

Acute Factor VII Deficiency

- Low doses of Factor VIIa work well
  - Stein DM, Dutton RP, Hess JR, Scalea TM. Low dose recombinant factor VIIa for trauma patients with coagulopathy. Injury 2008; 39:1054-61.
- Low doses only correct for a few hours
  - Ilyas C, Beyer GM, Dutton RP, Scalea TM, Hess JR. Recombinant factor VIIa for warfarin associated intracranial bleeding. J Clin Anesth 2008; 20:276-279

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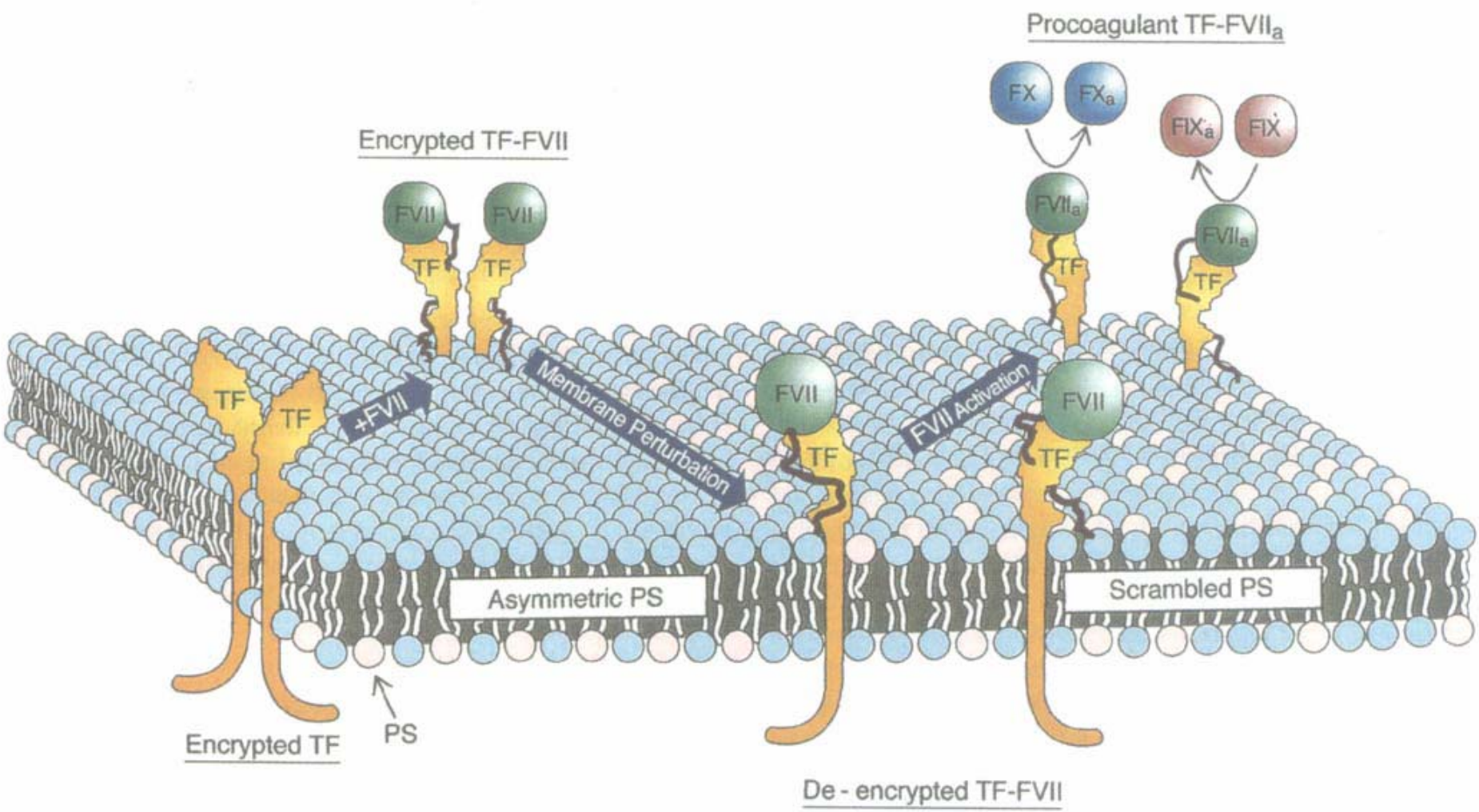
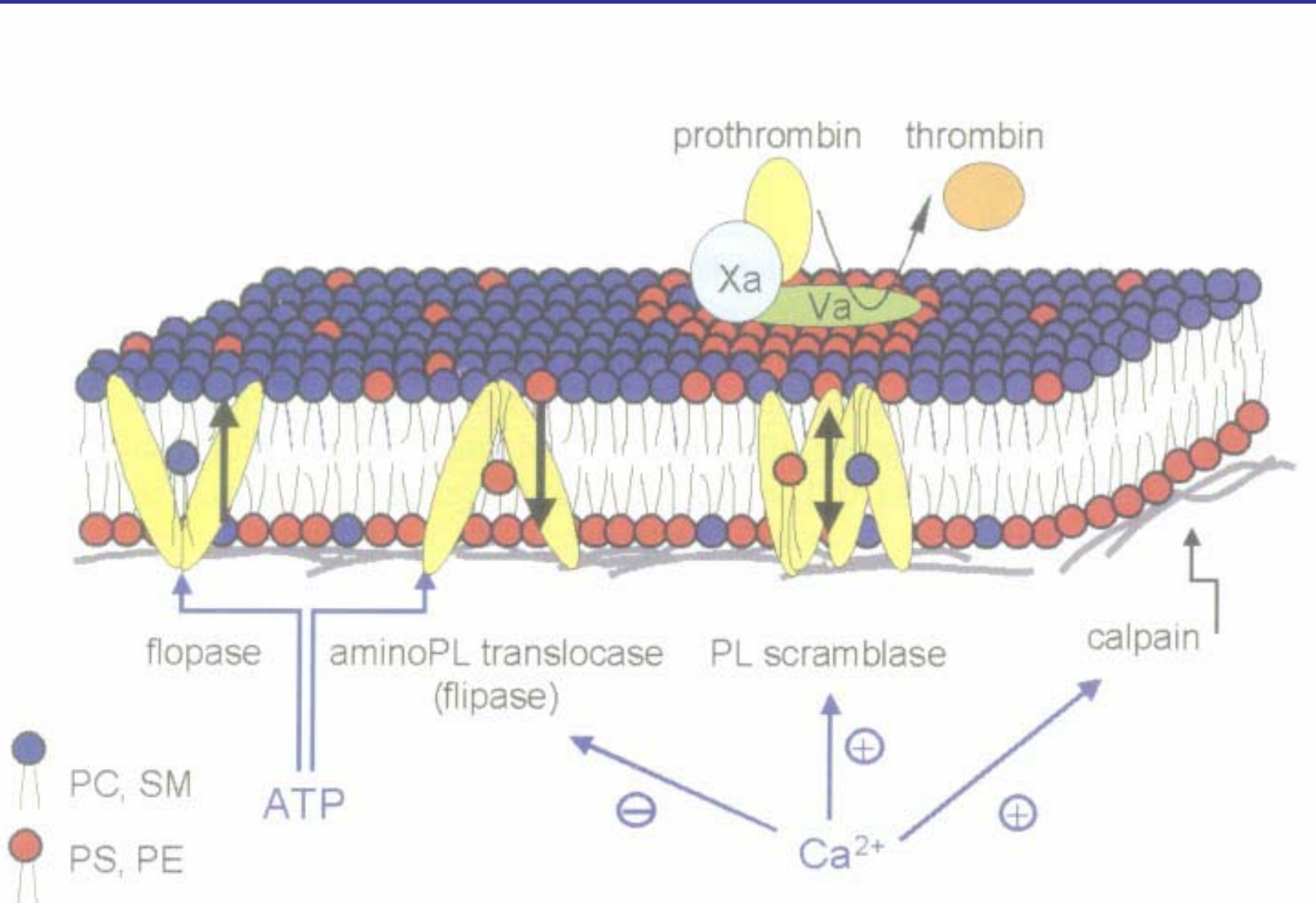
Quick Review of Plasma Coagulation

- Factor VIIa and Tissue Factor initiate coagulation
- Intermidiate factors amplify the response
- Thrombin is the central enzyme activating V, VIII, XI, TAFI and through thrombomodulin protein C
- Fibrinogen is the critical substrate. You have 10 grams of fibrinogen in your blood

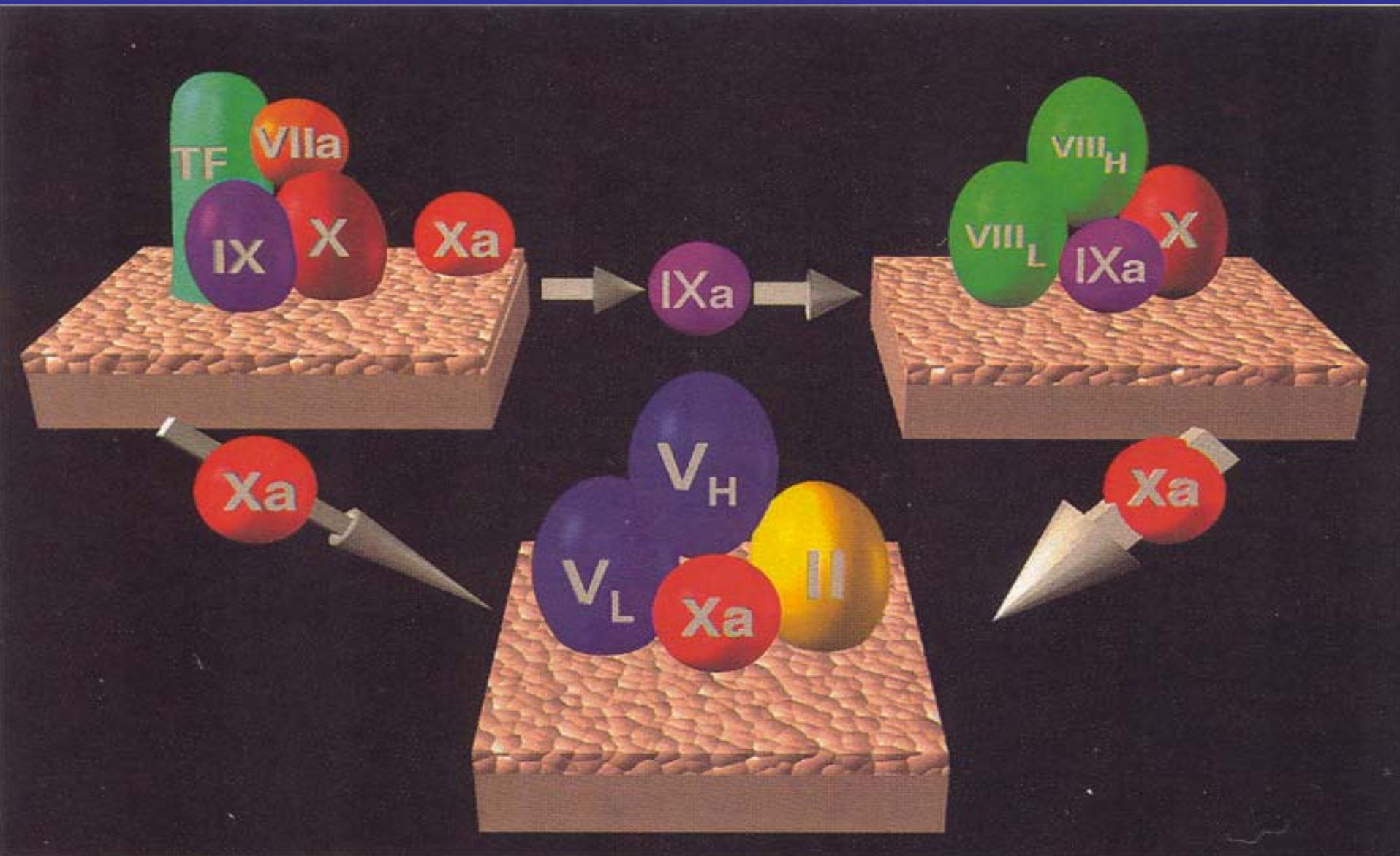
Activation of tissue factor (TF) and Factor VIIa on the cell surface



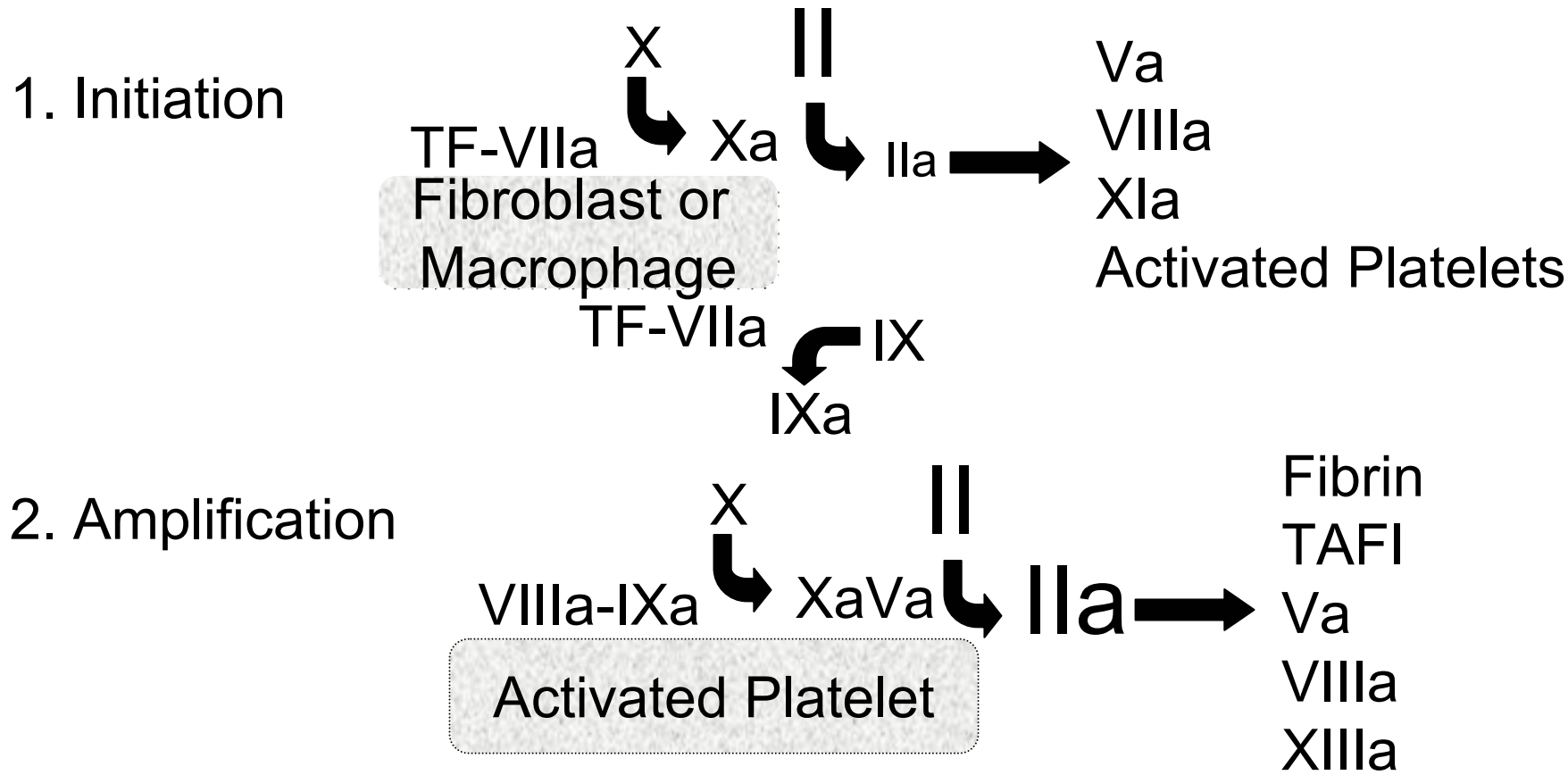
PS scrambling produces negatively charged “rafts” which bind Ca^{++} and vitamin K dependent factors



On activated surfaces the complexes are more active than the free enzymes



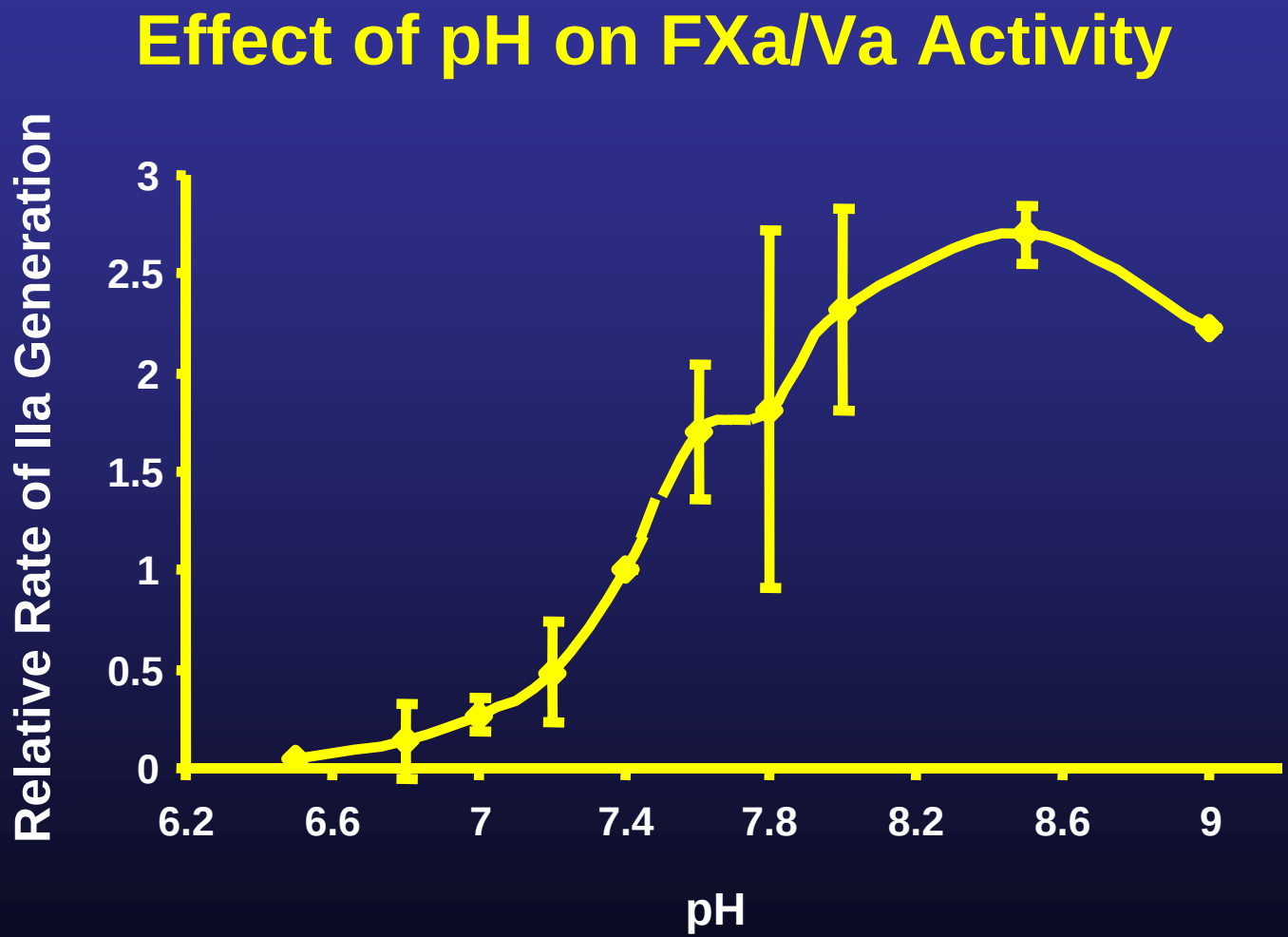
The Modern Kinetic View of Coagulation



3. Propagation – More platelets, activated by **IIa**, the thrombin burst, propagate coagulation

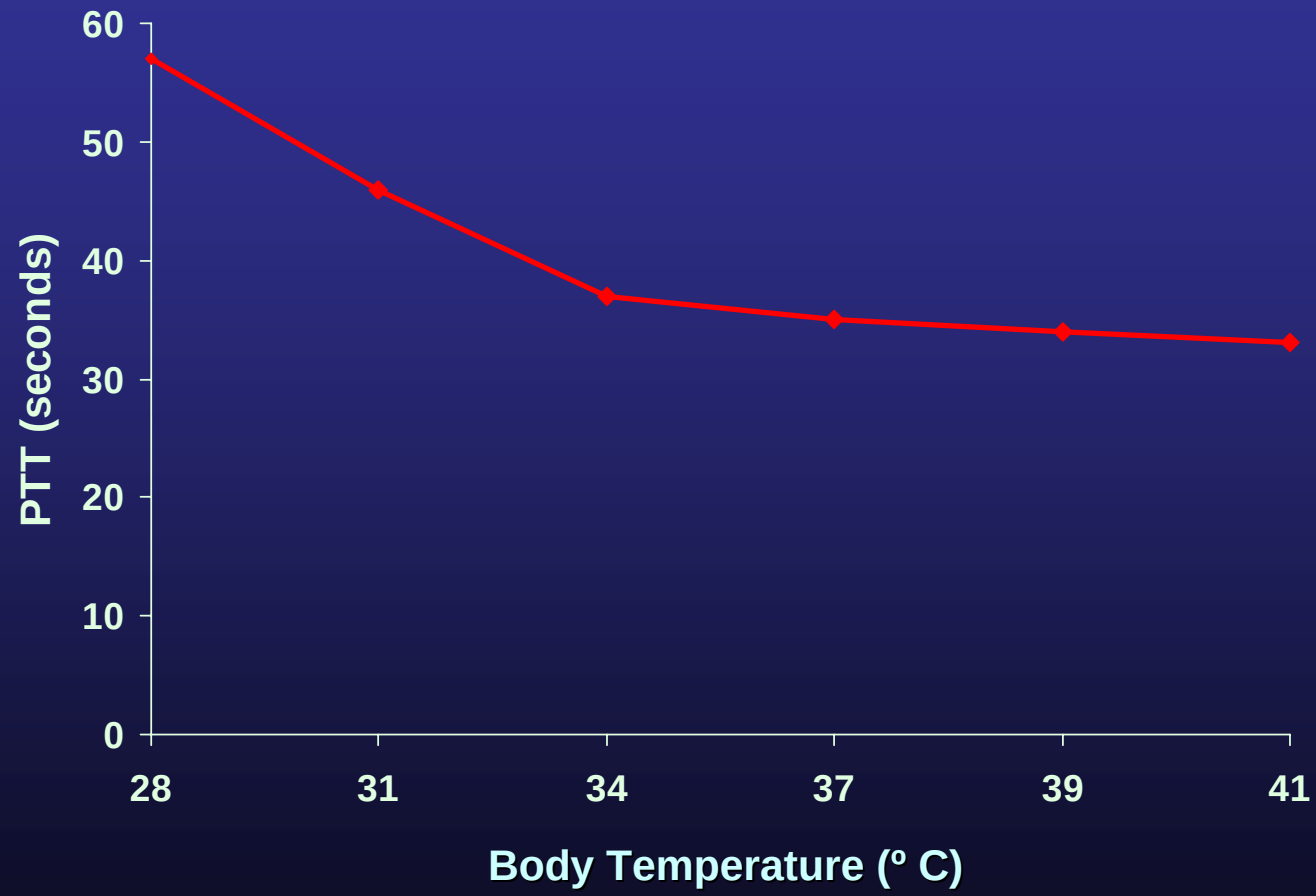
After M Hoffman

The coagulopathy of acidosis



Meng et al, J Trauma, 55:886-91, 2003

Effect of Body Temperature on Coagulation



Rohrer MJ, Natale AM. *Crit Care Med* 1992;20:1402-5.

Effect of dilution of plasma with saline on PT

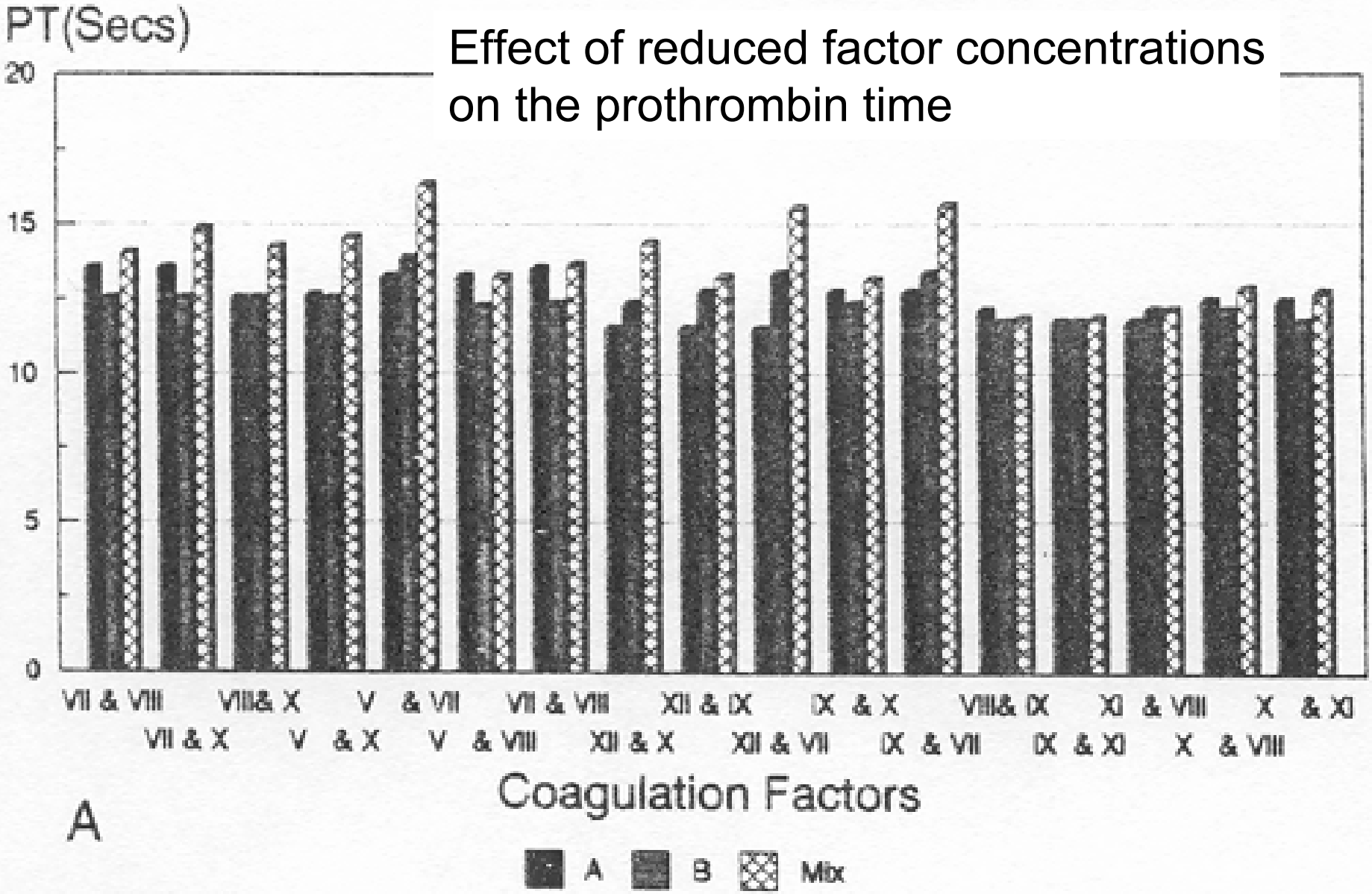
Table 1 The Prothrombin Time Dilution Curve

Original Plasma Fraction (%)	Mean PT (s)	PT Range (s)
100	11.8	11.6–12.1
90	12.2	12.1–12.4
80	12.6	12.5–12.7
70	13.5	13.4–13.6
60	14.6	14.1–15.0
50	15.9	15.6–16.0
40	18.6	18.0–19.5
30	24.9	23.8–27.2
20	34.2	32.4–35.9
10	58.0	56.1–61.9**
5	No clotting	No clotting

** Two of the five specimens with this dilution did not clot.

Hirshberg. J Trauma 2003; 54:454-463.

Effect of reduced factor concentrations on the prothrombin time

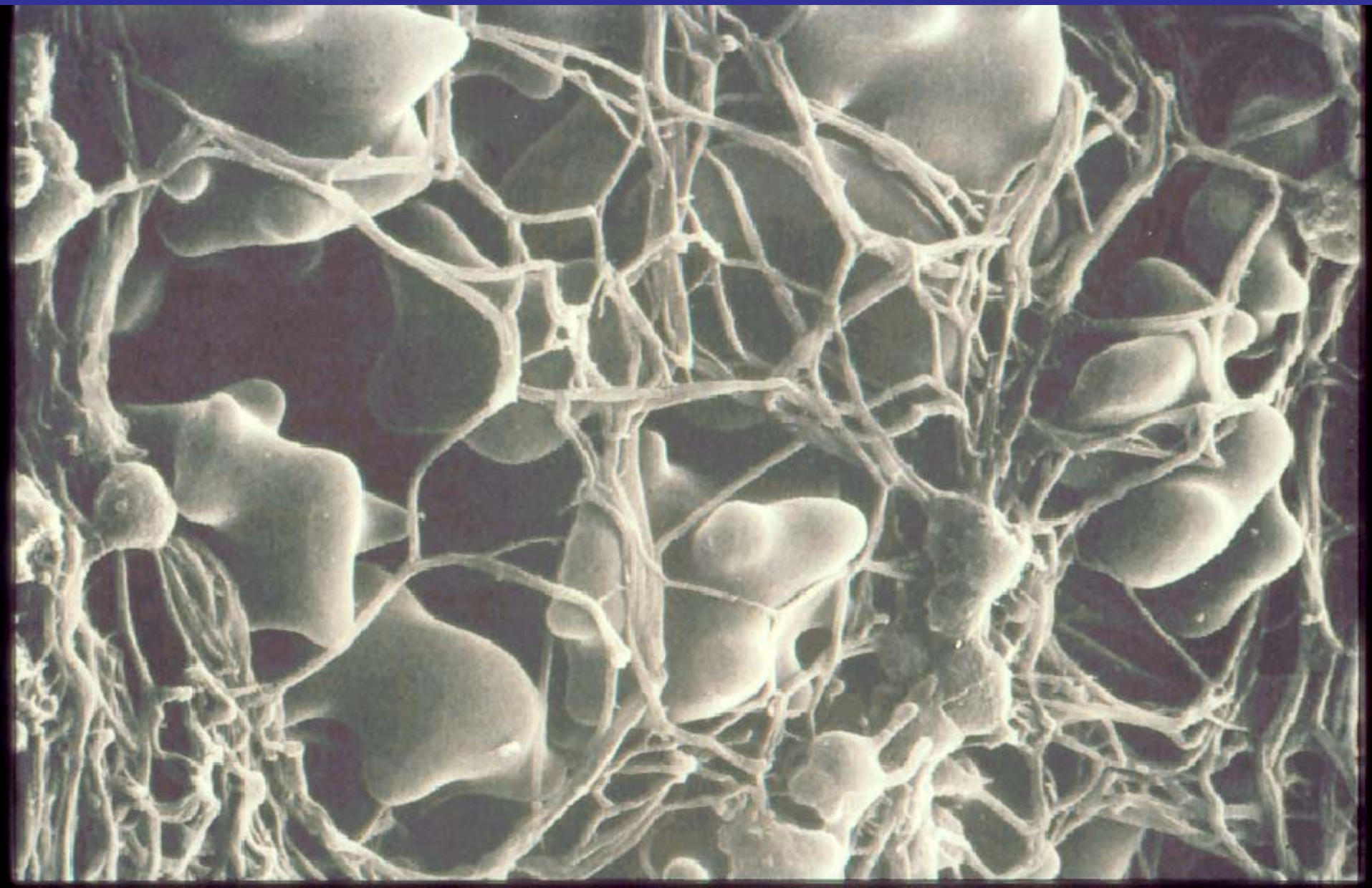


Burns et al. Am J Clin Pathol 1993; 100:94-98

Fibrinogen is the weak link in the clotting system

- It is present in small amounts to begin with
- It is required for both plasma coagulation and platelet aggregation
- It is the first clotting factor to run out in bleeding and blood replacement situations
- The kinetics of its activation are critical to the formation of stable fibrin clot
- Its assembly is susceptible to blocking by its own activation and inactivation products in DIC

Human blood clot: RBCs, platelets, and fibrin



NEJM 327:494

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Antiphospholipid Syndrome

- Clinical situation
  - One or more episodes of thrombosis in any organ
  - Pregnancy morbidity: spontaneous abortion, fetal death, early birth
- Lab tests
  - Anti-cardiolipin
  - Anti-β2 Glycoprotein-1
  - Anti-phosphotidyl serine

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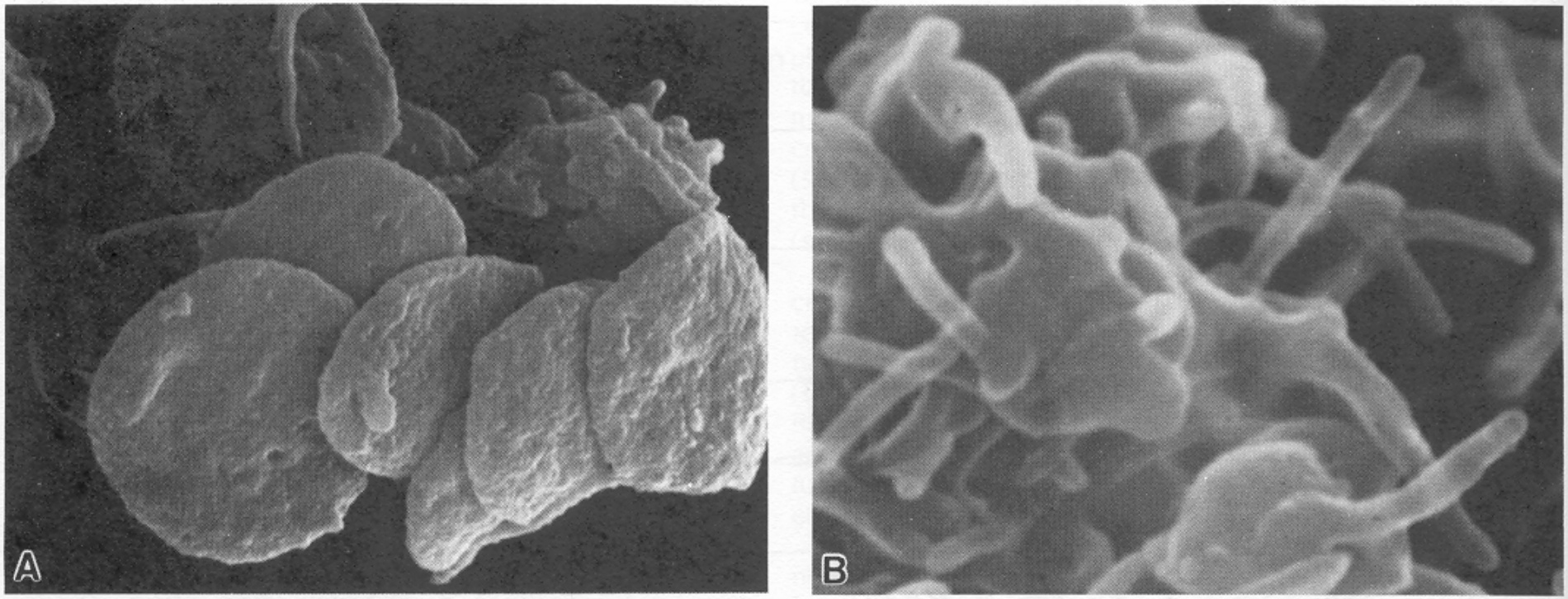
Liver Disease

- Bleeding is common because of
  - Decreased production and dysfunction of coagulation factors
  - Hyperfibrinolysis (low PAI)
- Clotting is common because of
  - Low flow
  - Inflammed vessels
  - Hypercoagulation (low AT & PC)

Disease sate	Possible contributing etiologies
Portal vein thrombosis	Obstruction of flow Prothrombotic predisposition Infectious nidus from gastrointestinal tract Local inflammatory mediators
Deep vein thrombosis or pulmonary embolism	Imbalance in clotting cascade favoring coagulation Immobility of end-stage liver disease Infection and systemic inflammation
Progression of cirrhosis	Parenchymal extinction
Vascular prosthesis and extracorporeal circuit thrombosis	Mechanical obstruction Inflammatory mediators Abnormal platelet adhesion
Portopulmonary hypertension	Pulmonary endothelial dysfunction Microvascular pulmonary thrombosis Altered shear stress in the pulmonary vessels
Metabolic syndrome and non-alcoholic fatty liver disease	Venulitis and microthrombi with remodeling Atherosclerotic vascular changes Inflammation related to metabolic syndrome Factor level alteration with insulin resistance

There are many interactions of liver disease and coagulation. Liver disease makes coagulation worse and coagulation is often involved in the progression of liver disease.

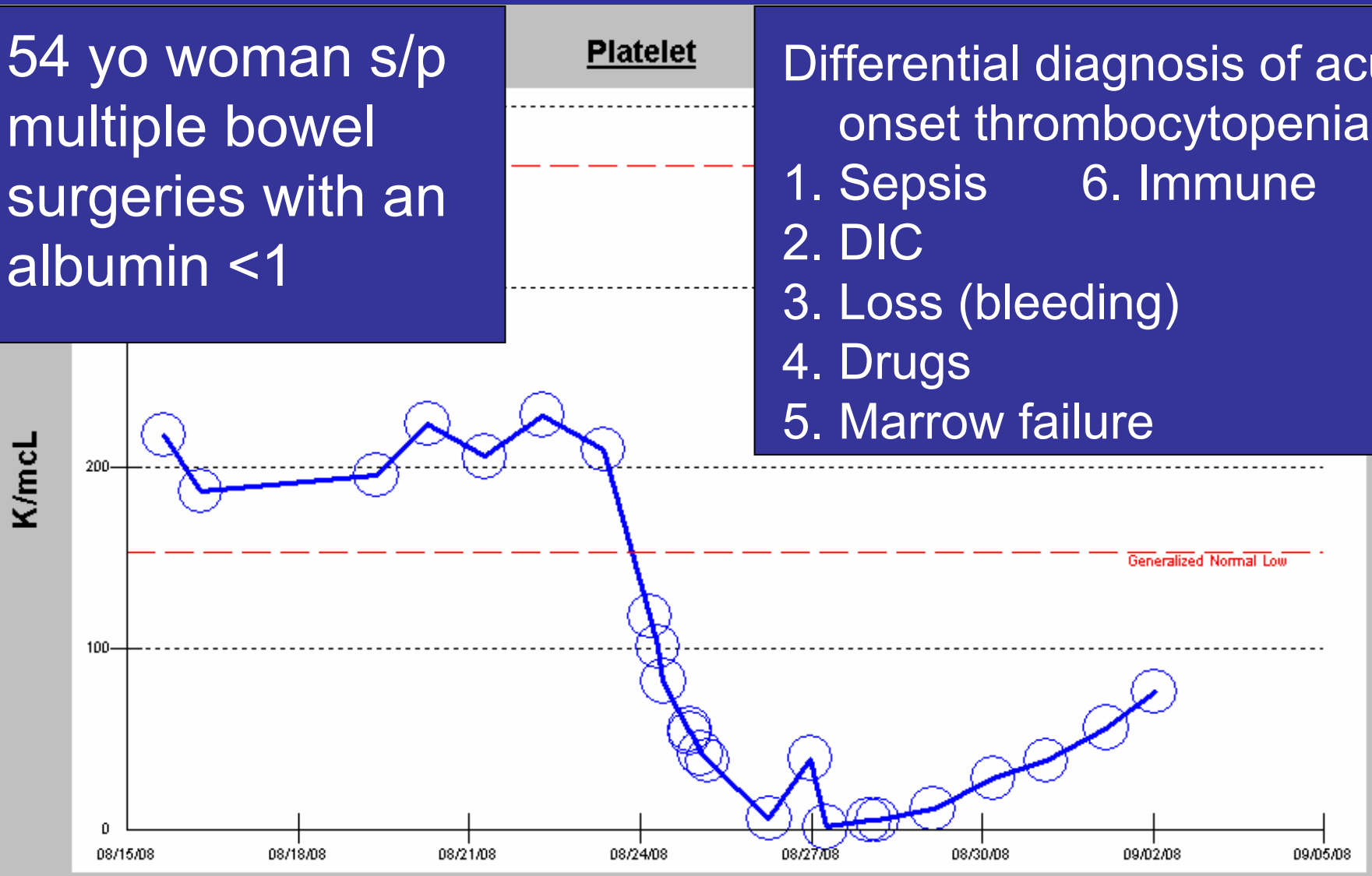
Platelets



Hoffman et al. *Hematology,* 1991, page 1162

Thrombocytopenia

54 yo woman s/p multiple bowel surgeries with an albumin <1

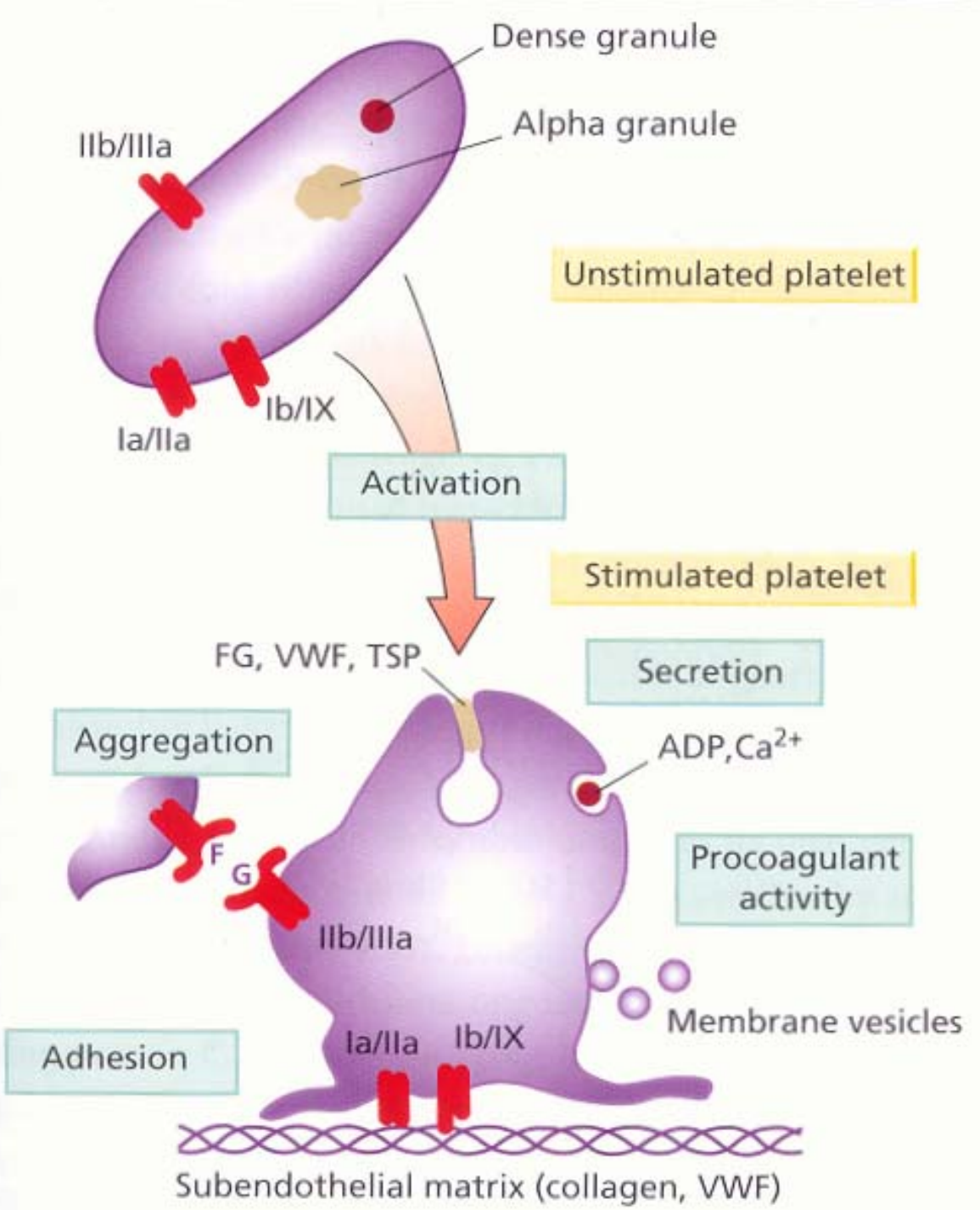


Differential diagnosis of acute onset thrombocytopenia:

1. Sepsis
2. DIC
3. Loss (bleeding)
4. Drugs
5. Marrow failure
6. Immune

Quick Review of Platelet Function

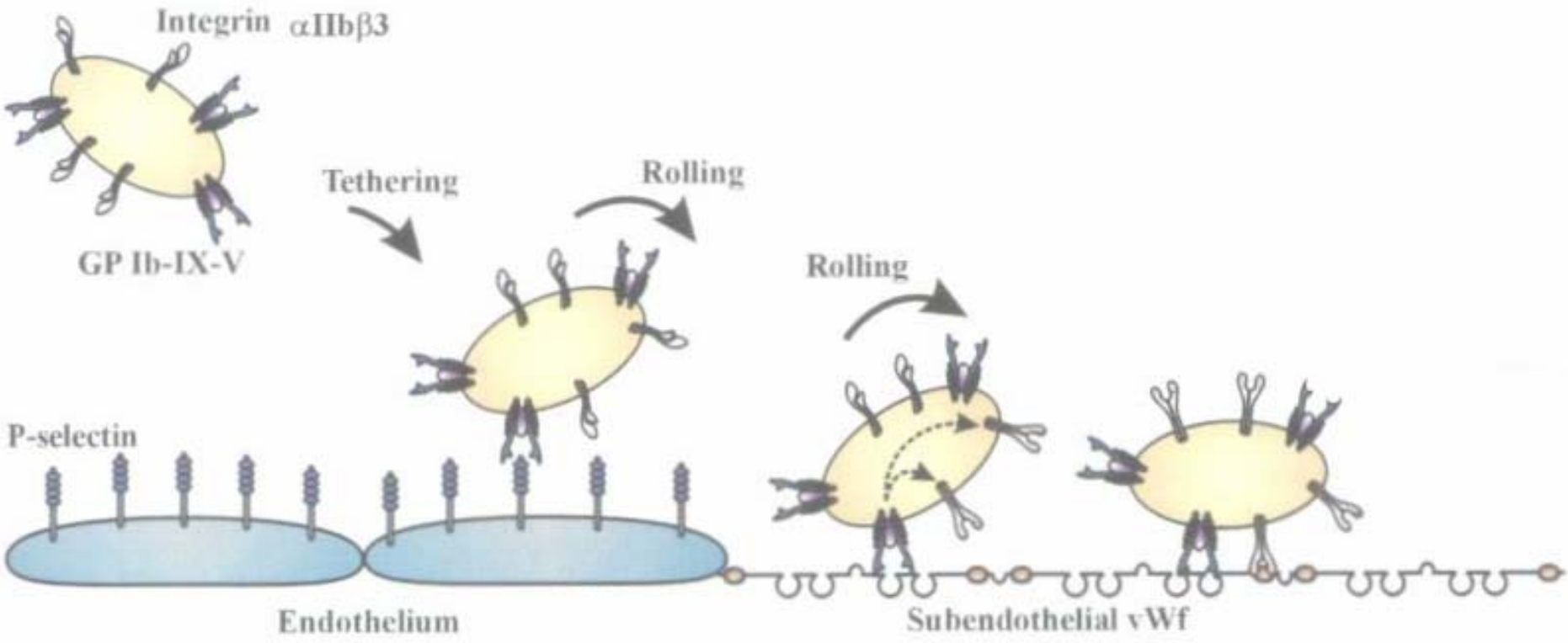
- Platelets adhere to exposed collagen through von Willebrand's factor and GP Ib/IX
- Adherence leads to activation with formation of active surfaces, secretion of procoagulants and shedding of active microvesicles
- Activated platelets aggregate through binding fibrinogen with Gp IIb/IIIa



Platelets adhere, activate, secrete and aggregate.

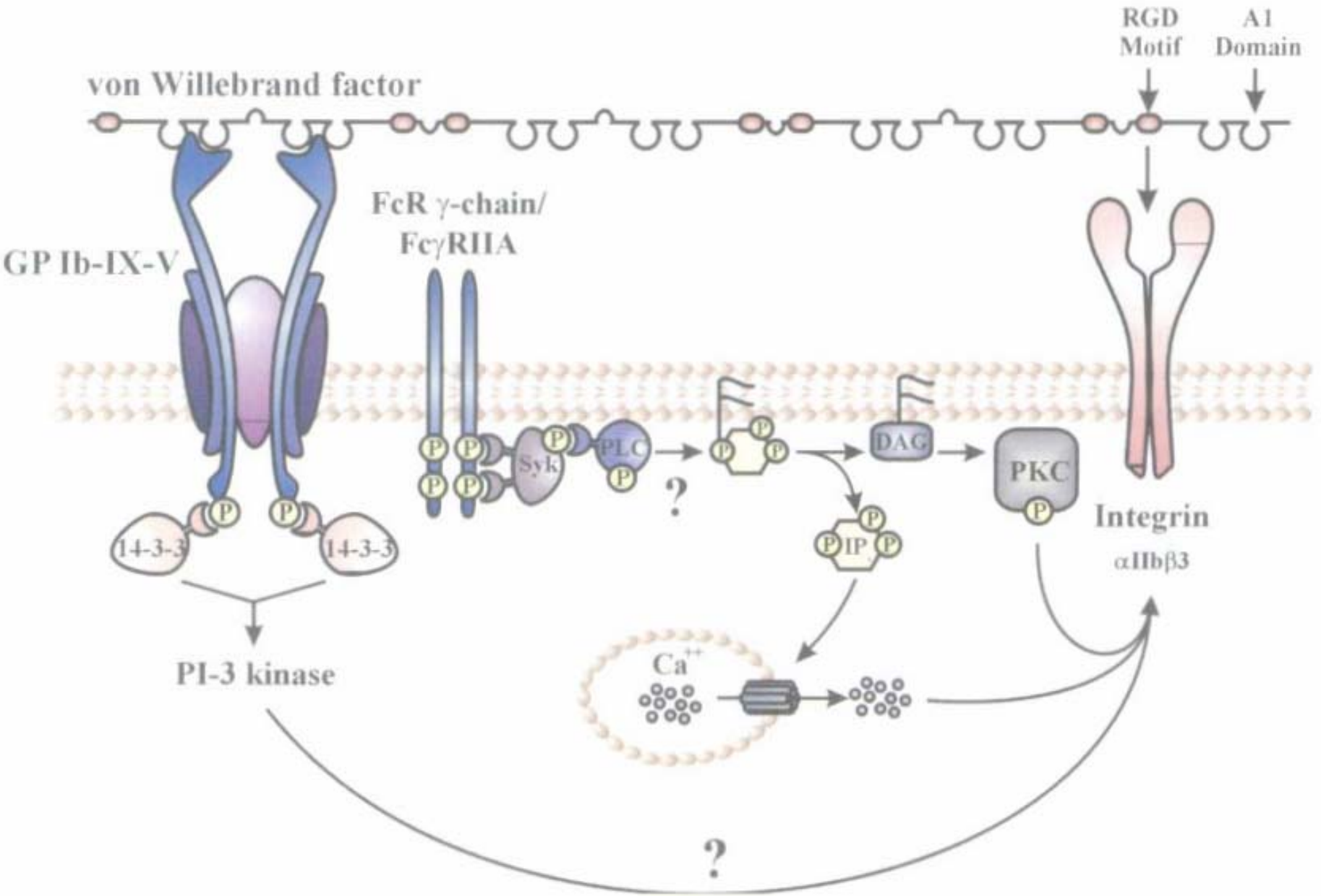
Adherence and activation are coupled by vWF pulling on GPIb-IX. Activation, secretion, and aggregation are coupled by Ca^{++} signaling

The critical role of vWF in platelet adhesion

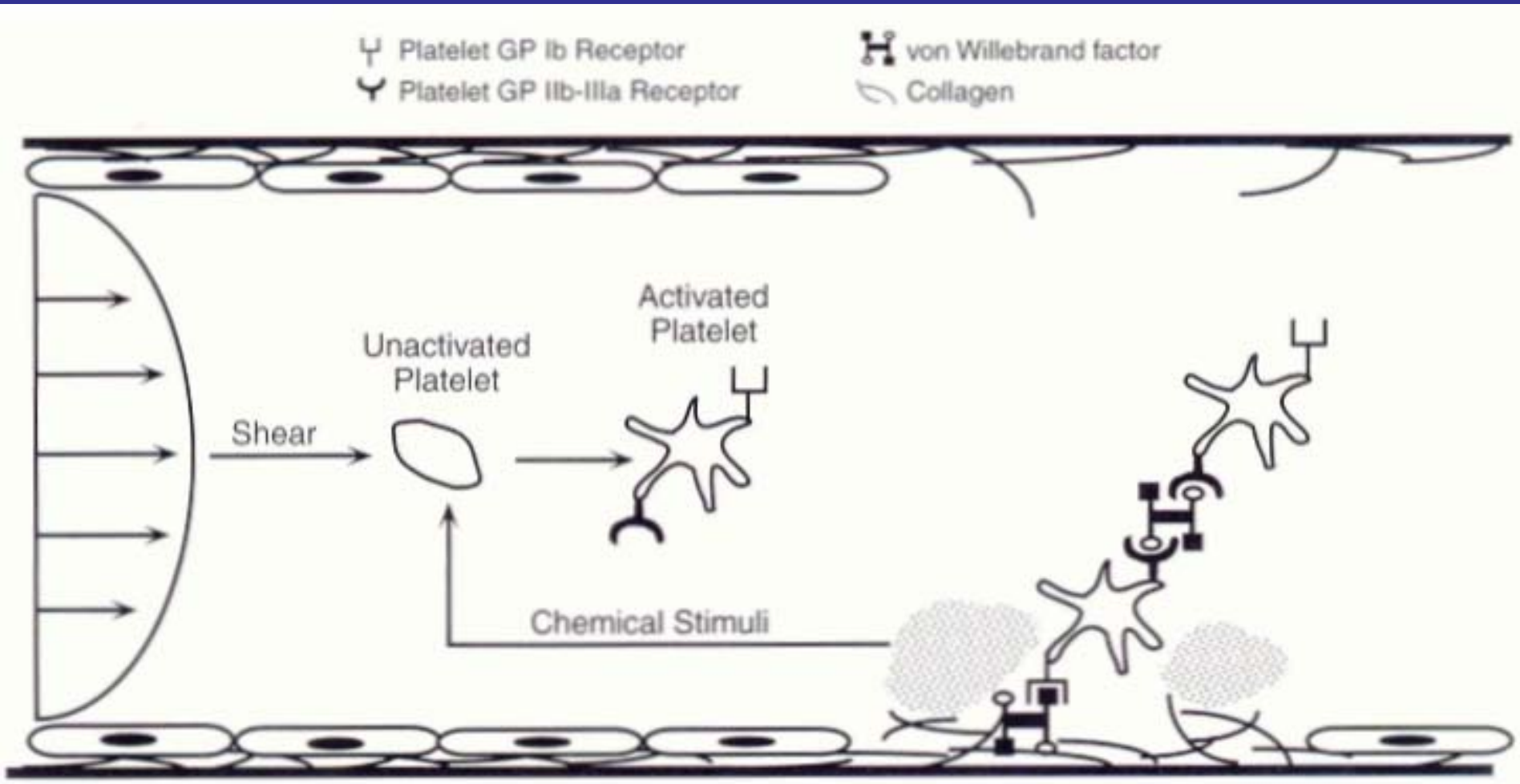


Berndt et al. Thromb Haemostas 2001, 86:178-188

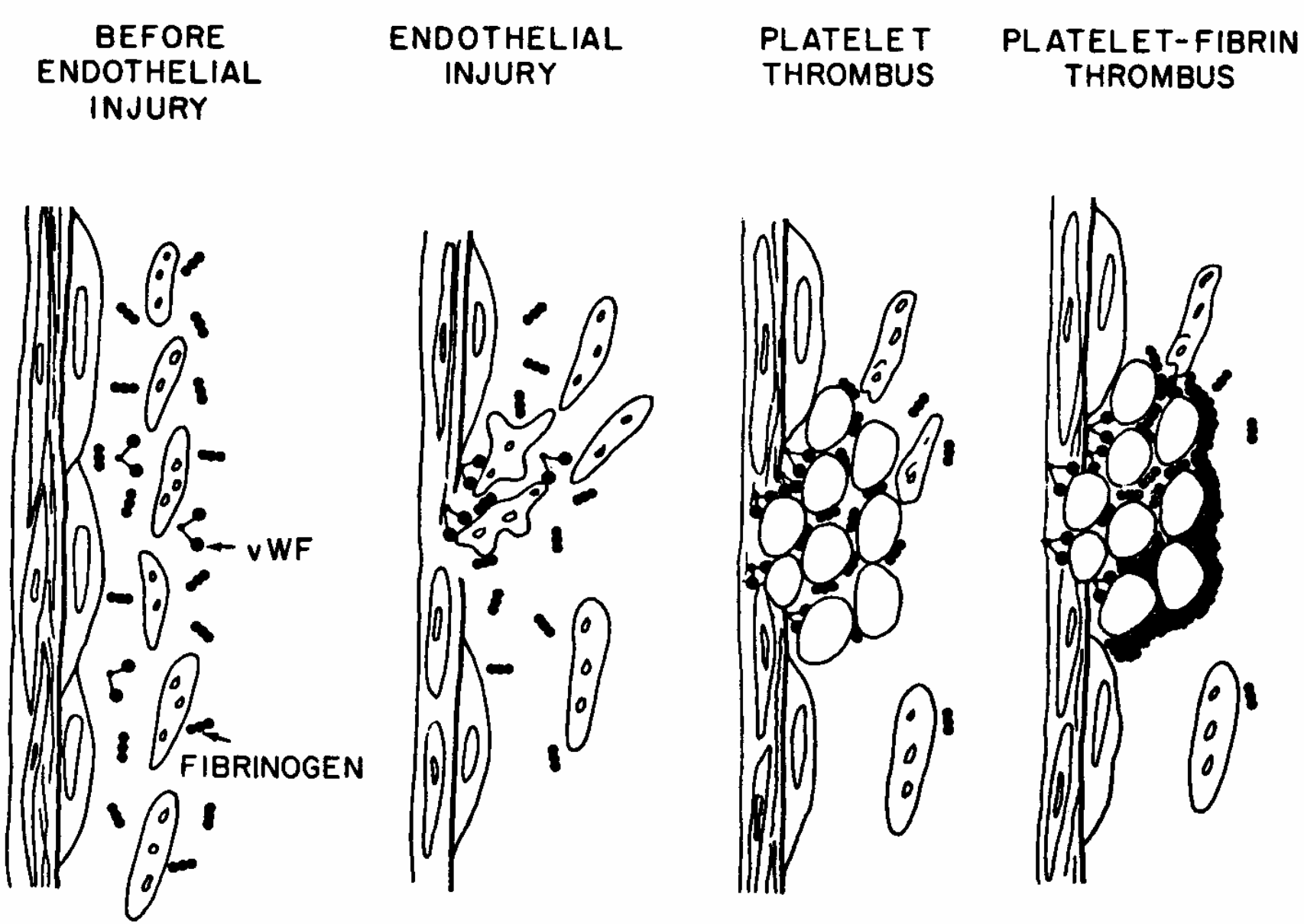
Platelet signal transduction for activation



Platelet recruitment and aggregation

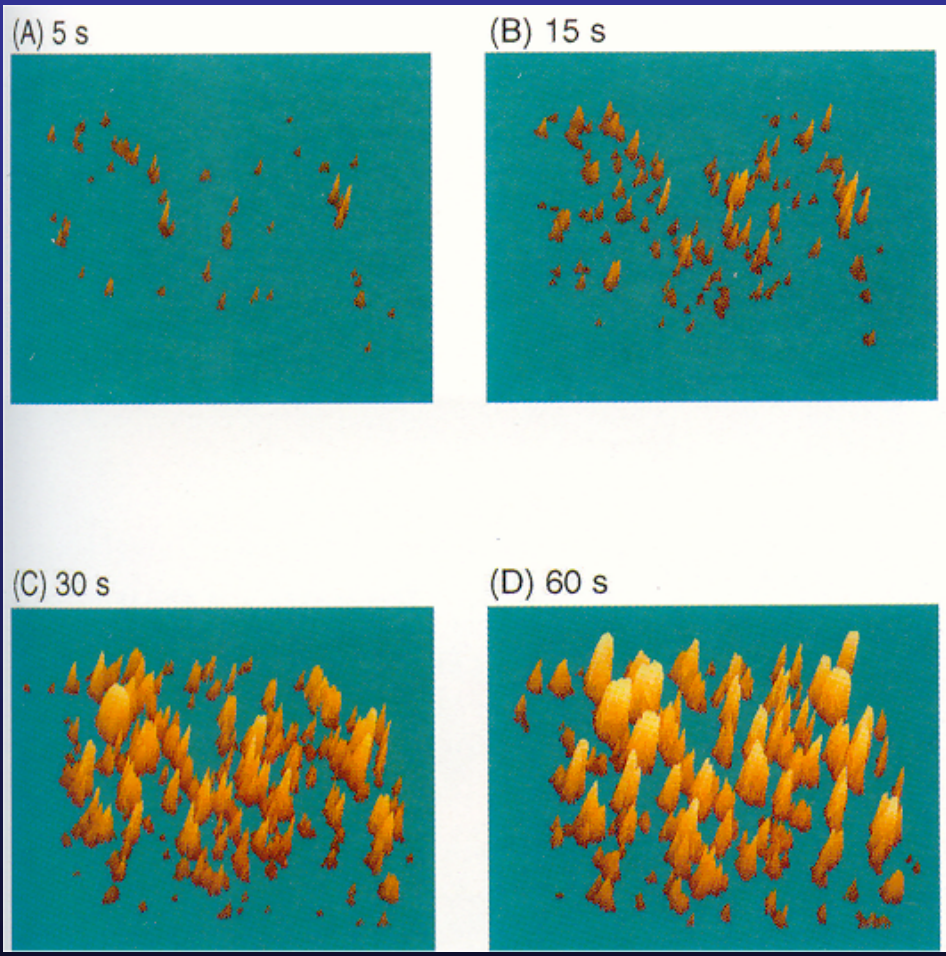


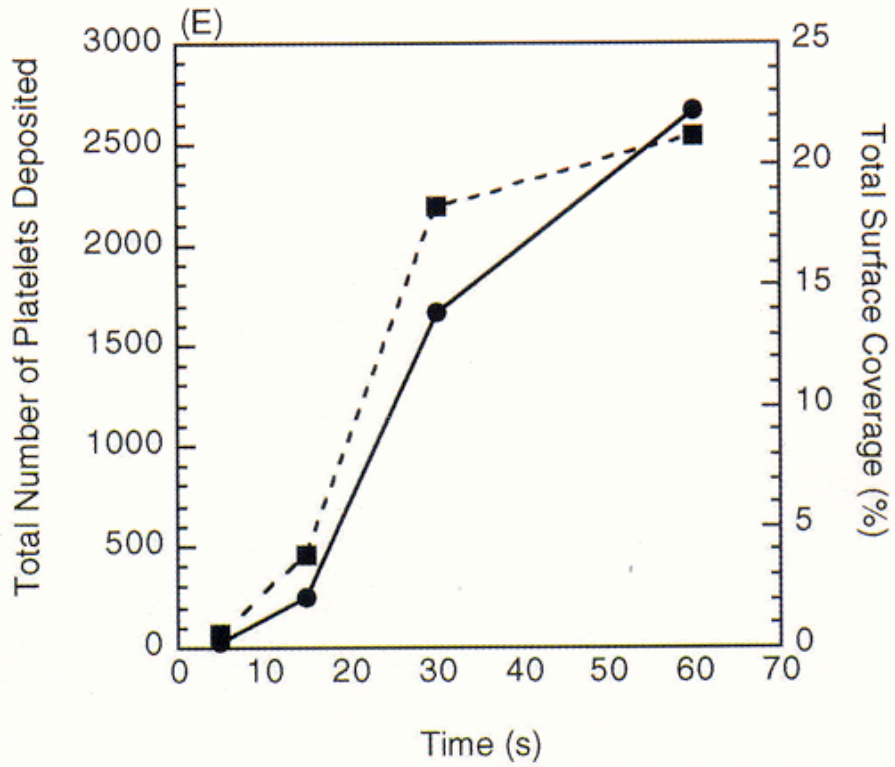
Colman et al. *Hemostasis & Thrombosis* 4th Ed., 2001, p632



Colman et al. *Hemostasis & Thrombosis, 4th Ed.*, 2001, p647

Platelet deposition occurs rapidly





Colman et al. *Hemostasis & Thrombosis* 4th Ed., 2001, p780

Low platelets can make weak clots

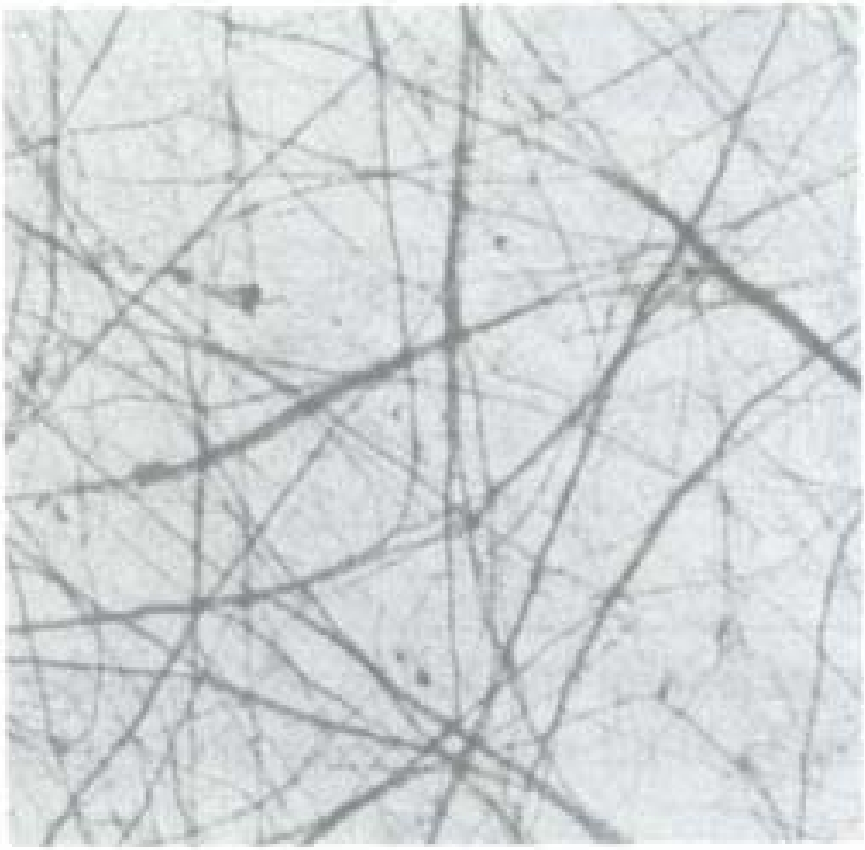


Fig. 1 a

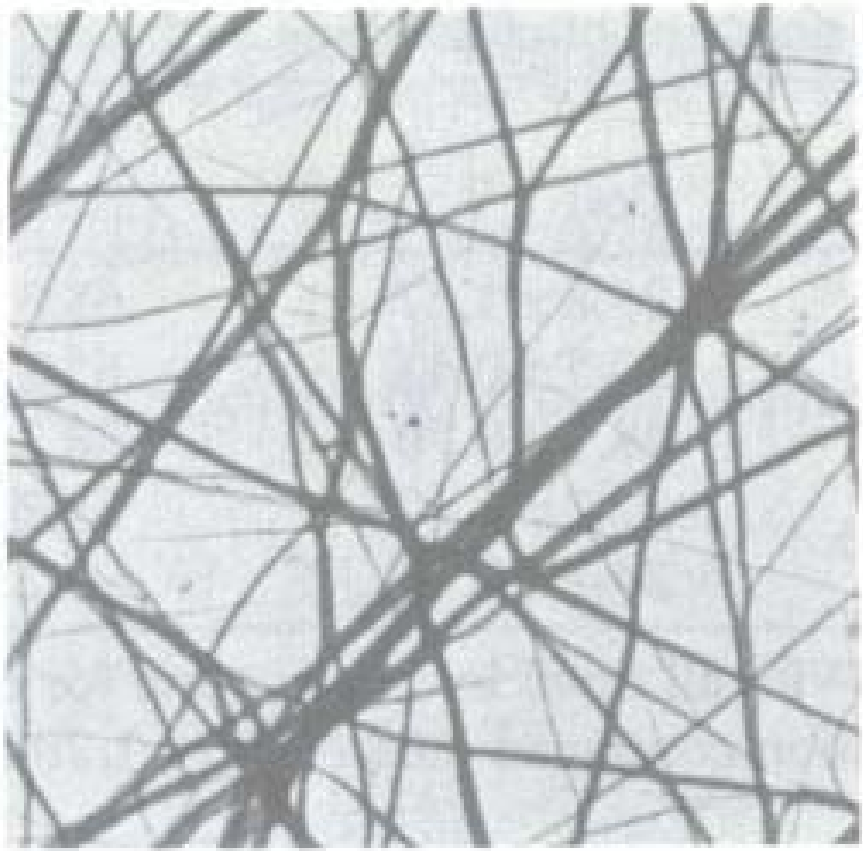


Fig. 1 b

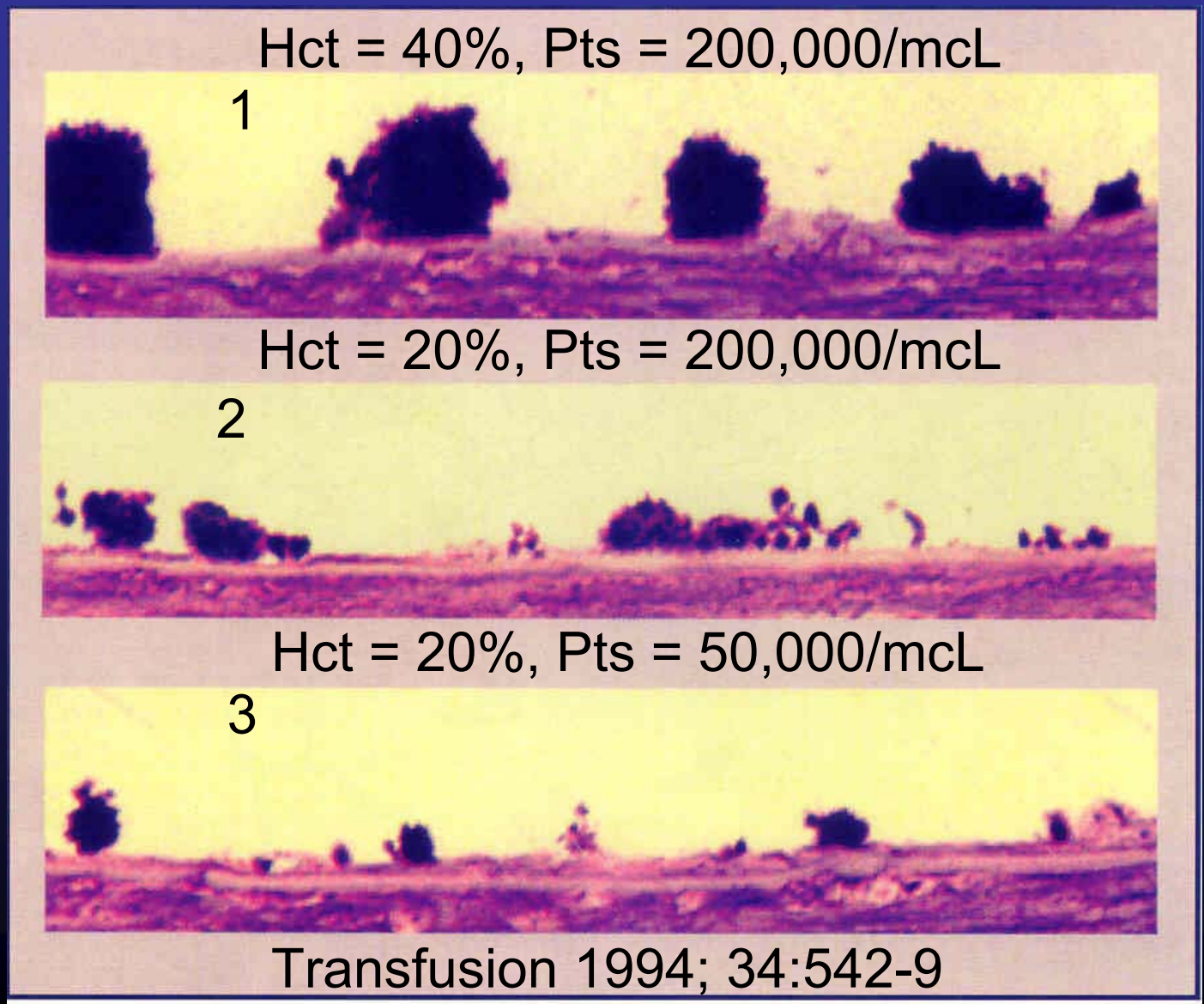
Fig. 1 Electron micrographs of platelet-poor plasma clots made with (a) and without (b) the addition of platelet extract.

Dhall et al. Thromb Haemostas 1983; 49:42-6

Two roles of platelets in hemostasis

- Form multicellular aggregates, linked by fibrinogen, to create a physical barrier that limits blood loss.
- Accelerate the rate at which coagulation proteins are activated to facilitate thrombin generation and fibrin strand formation.
- Both roles are necessary for normal hemostasis.

Effect of hematocrit on platelet deposition on damaged arterial segments



Thinking about low platelets in the ICU

Differential diagnosis of thrombocytopenia in the intensive care unit

Differential diagnosis	Approximate relative incidence	Additional diagnostic clues
Sepsis	52%	Positive (blood) cultures, positive sepsis criteria, hematophagocytosis in bone marrow aspirate
DIC[a]	25%	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	8%	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	1%	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurological symptoms, renal insufficiency
Heparin-induced thrombocytopenia	1%	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin-platelet factor IV antibodies), rebound of platelets after cessation of heparin
Immune thrombocytopenia	3%	Anti-platelet antibodies, normal or increased number of megakaryocytes in bone marrow aspirate, thrombopoeitin decreased
Drug-induced thrombocytopenia	10%	Decreased number of megakaryocytes in bone marrow aspirate or detection of drug-induced anti-platelet antibodies, rebound of platelet count after cessation of drug

Seven major causes of thrombocytopenia (platelet count $<150 \times 10^9$/l) are listed. Relative incidences are based on two studies in consecutive intensive care unit patients [1,6] but may vary depending on the population studied. Patients with hematological malignancies were excluded.
[a]Patients with sepsis and disseminated intravascular coagulation (DIC) are classified as DIC. aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; PT, prothrombin time.

Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006; 10:222

Thrombocytopenia

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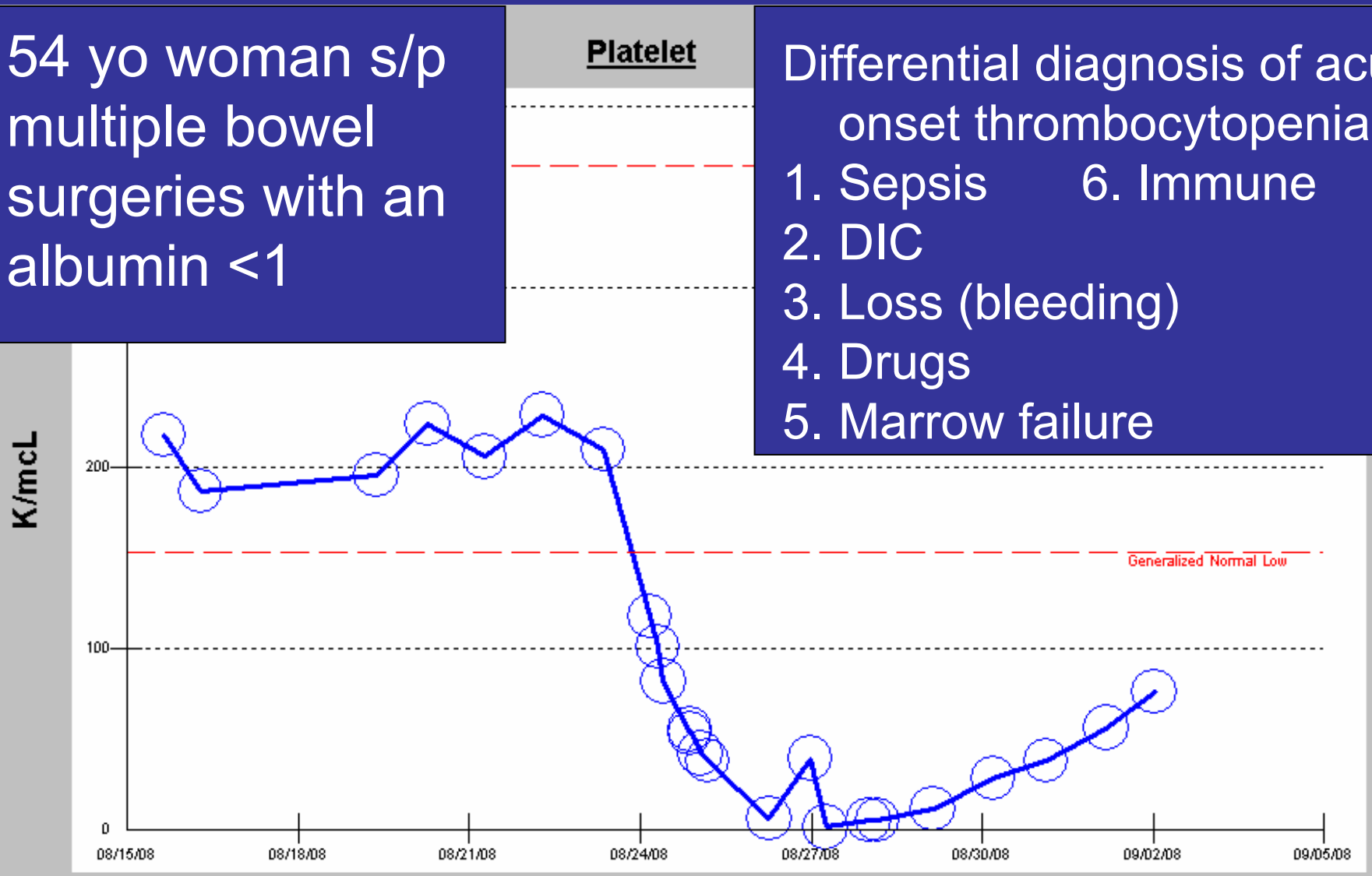

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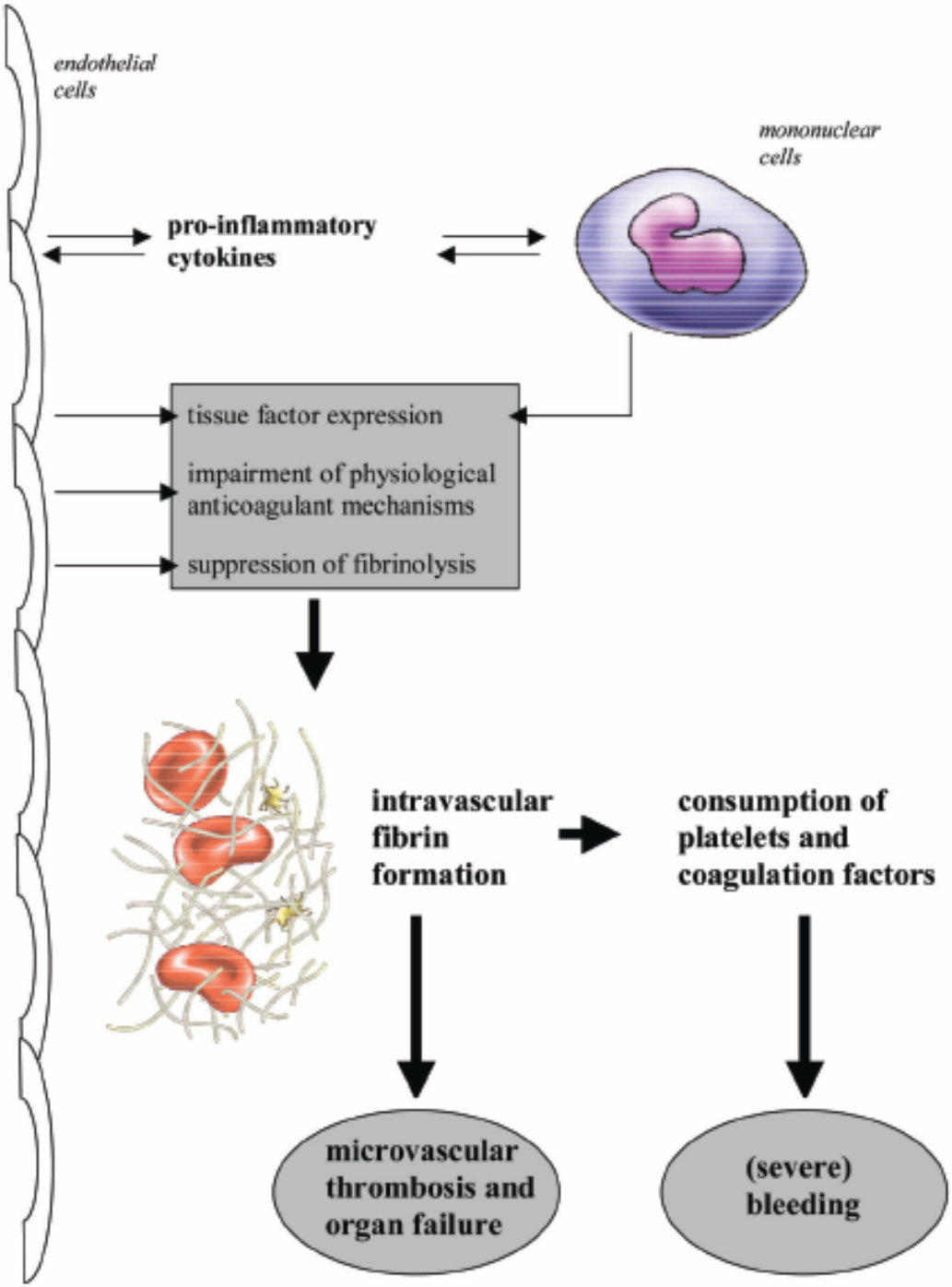
2. DIC
3. Loss (bleeding)
4. Drugs
5. Marrow failure
6. Immune

Disseminated Intravascular Coagulation

Levi M, Ten Cate H.
NEJM 1999; 341:586

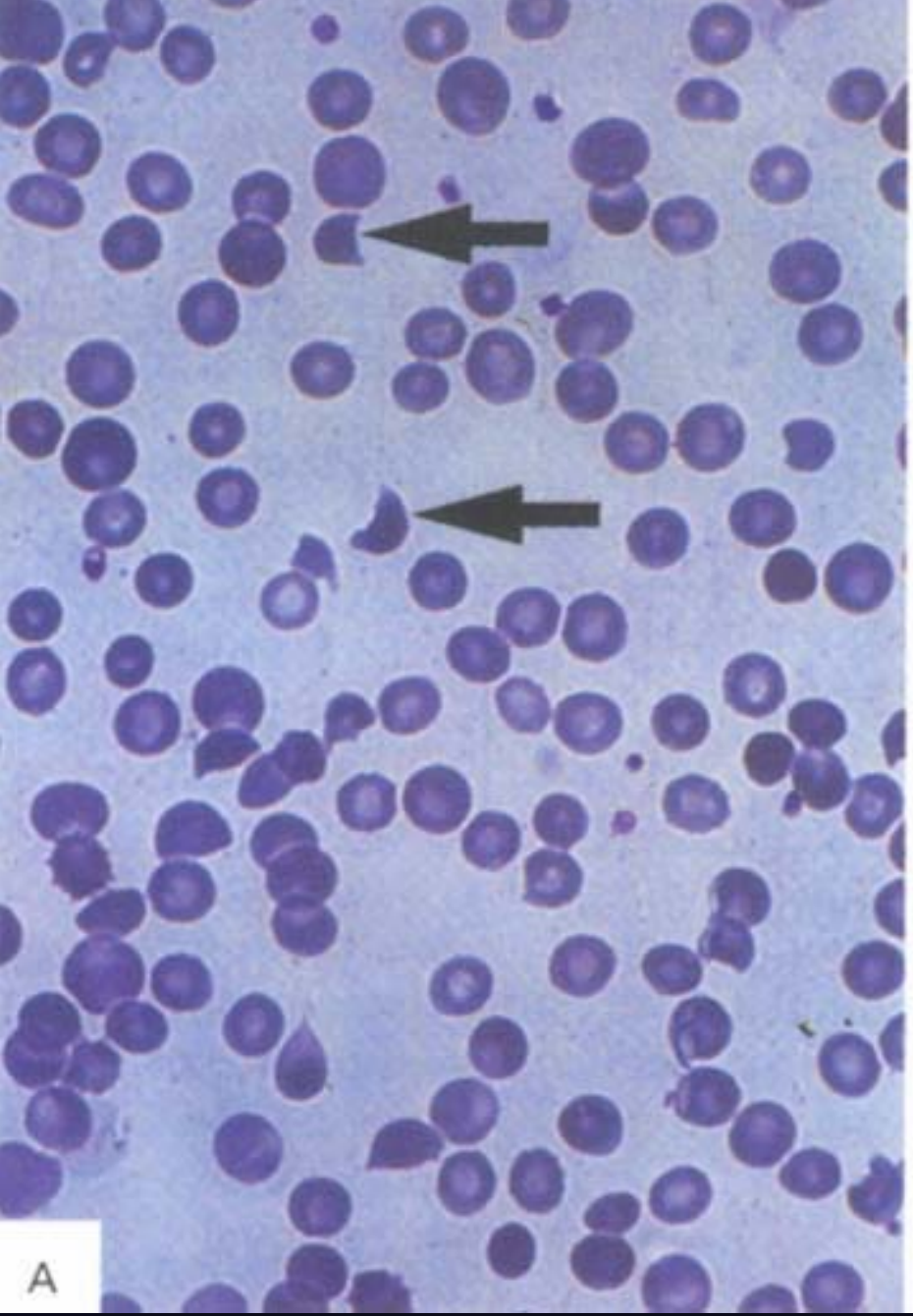
- Sepsis
- Trauma
  - Crush, Head injury, Fat embolism
- Cancer
  - MPD, Pancreas, Prostate
- OB complications
  - Amniotic-fluid embolism, Abruptio
- Vascular disorders
  - Giant hemangioma, Aortic aneurism
- Toxins
  - Snake venoms, amphetamines
- Immunologic disorders
  - Allergic reactions, transfusion reactions



Thinking about DIC:

1. Endotoxin causes mononuclear cells to express tissue factor and secrete TNF-α and IL-1
2. TNF-α causes endothelial cells to express TF, & loss thrombomodulin and heparins

Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006; 10:222



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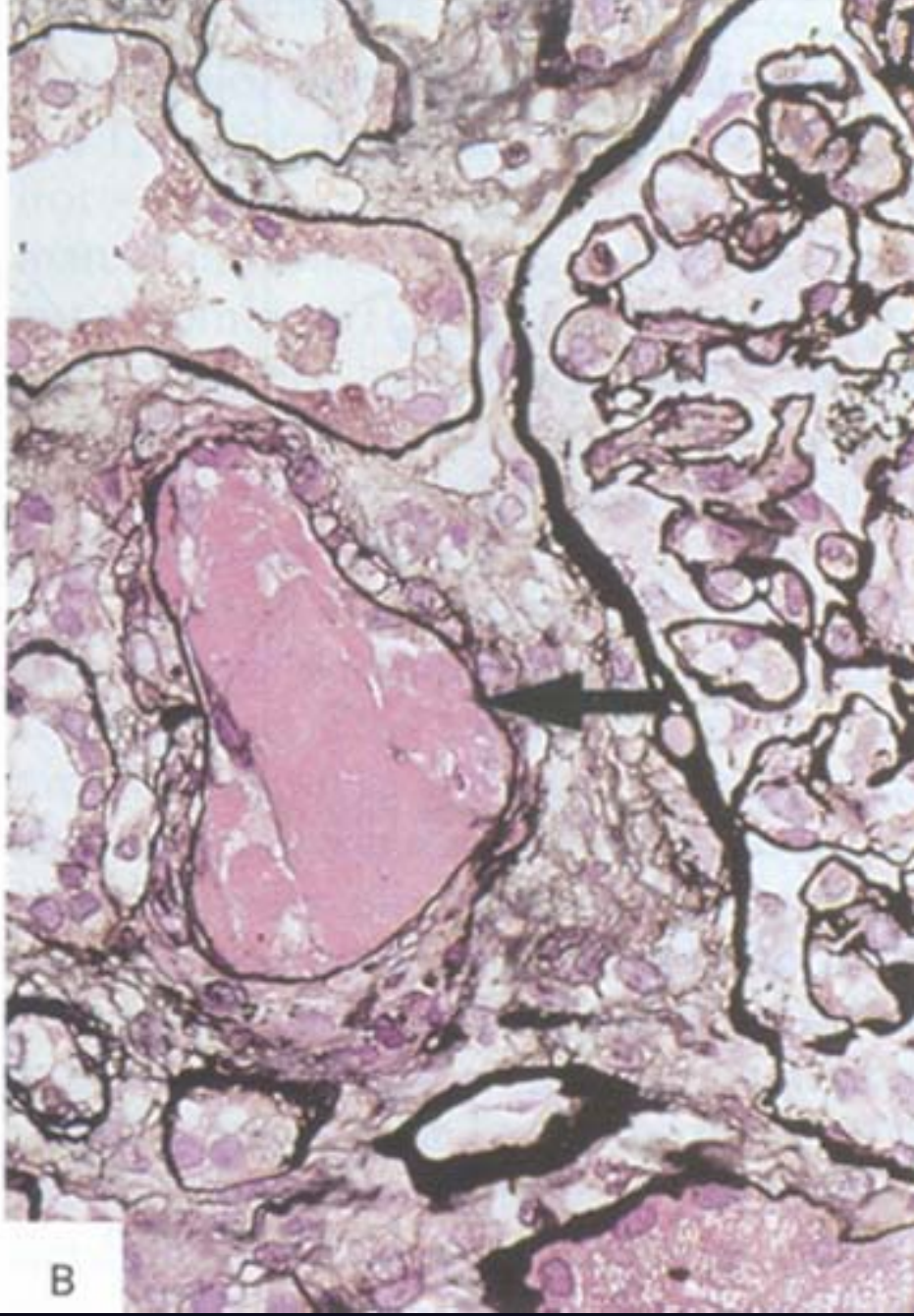
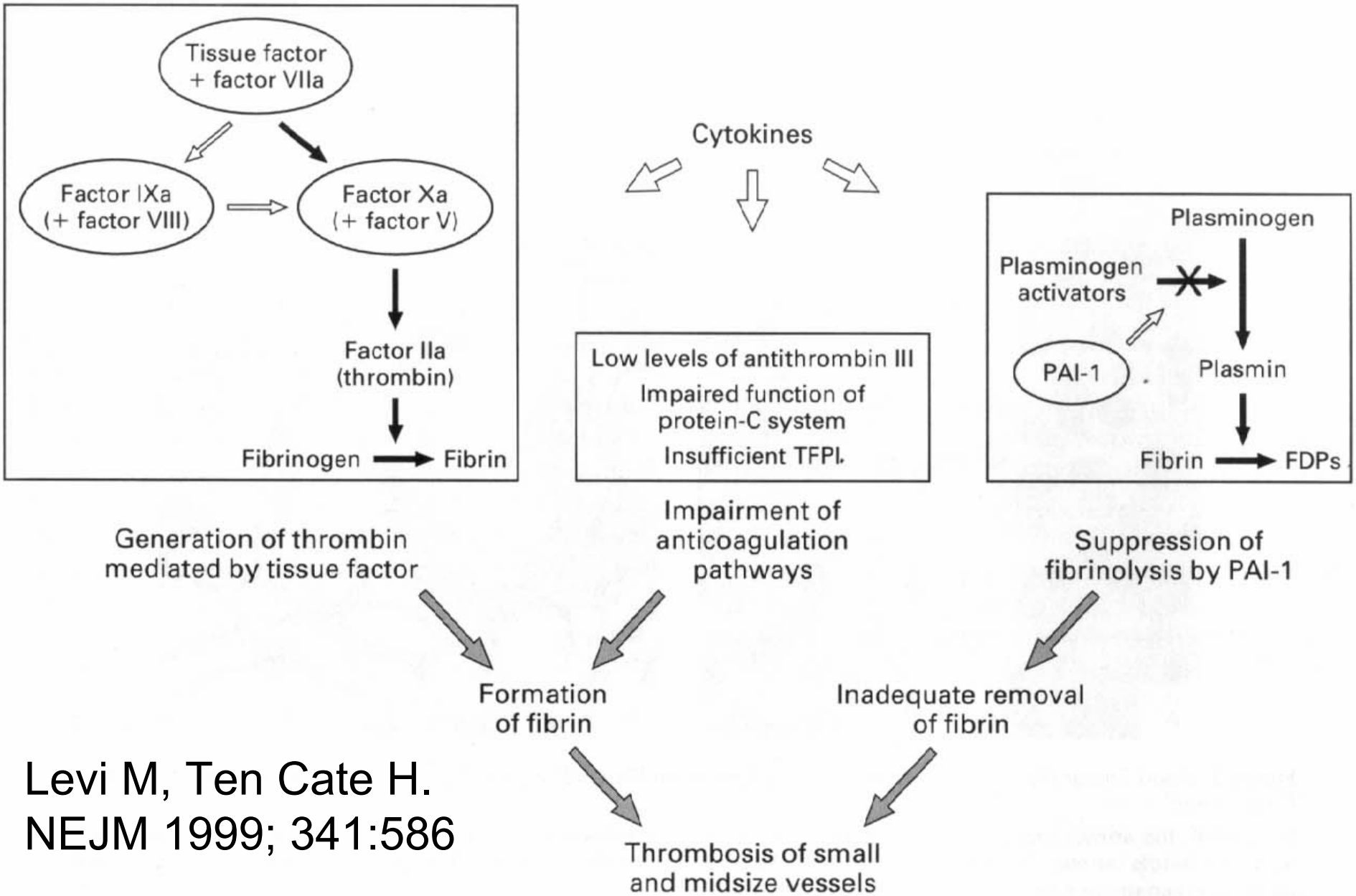


B

Levi M, Ten Cate H. NEJM 1999; 341:586

Disseminated Intravascular Coagulation



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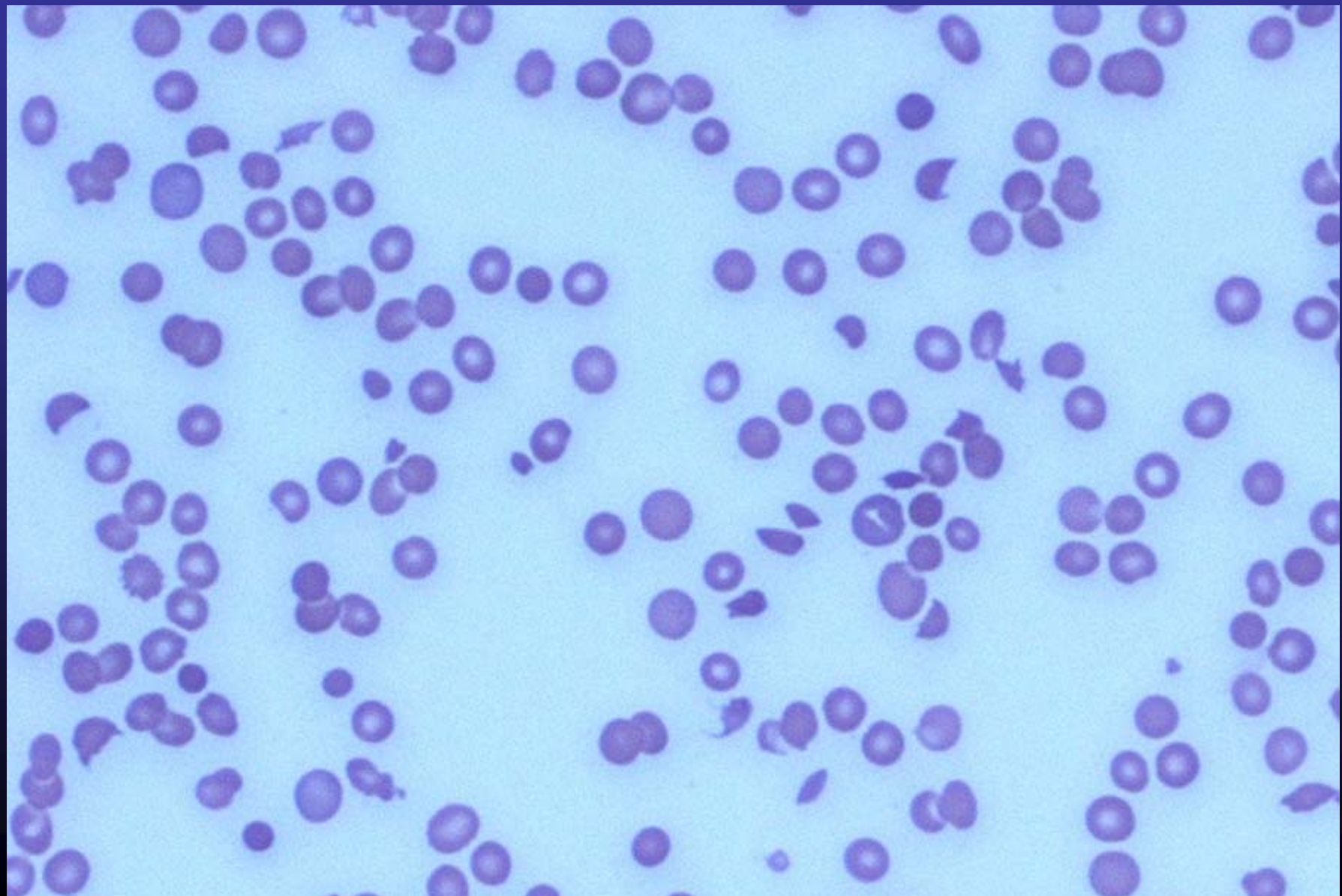
33 yo woman with HUS, machine reads 20K plts, but no platelets on the smear



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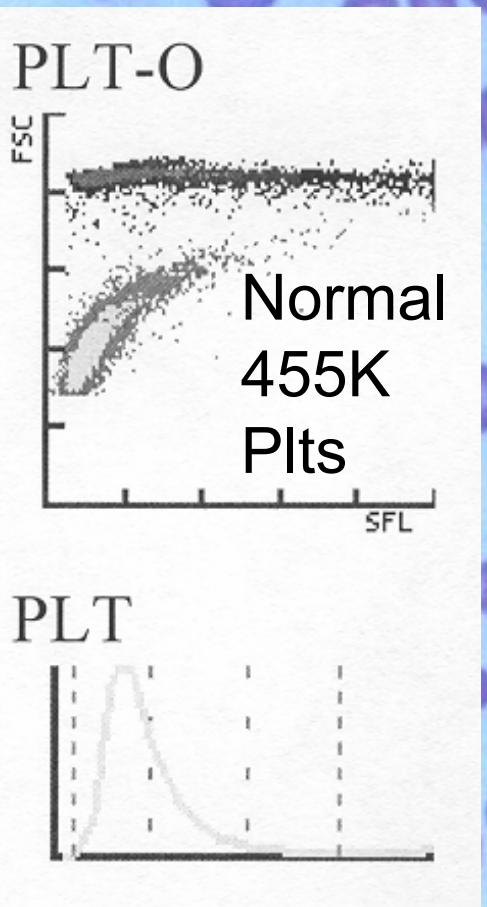
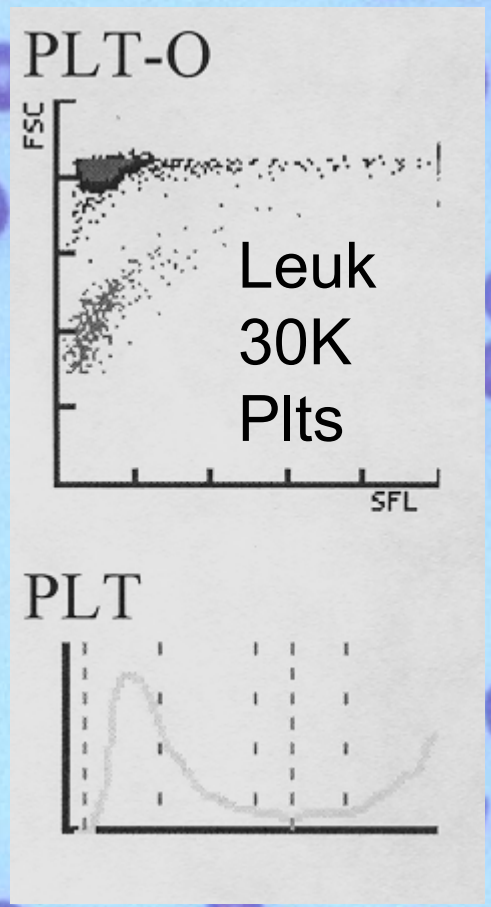
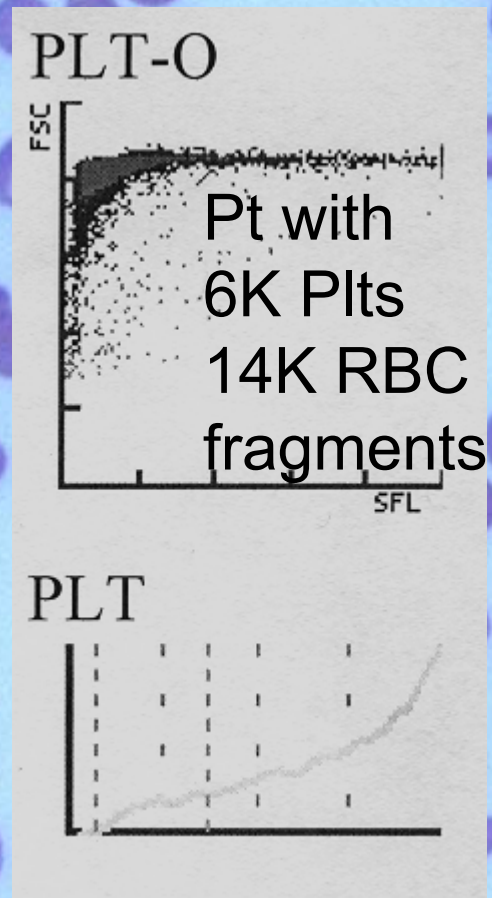






Drugs that effect platelet function

- NSAIDS
- Antimicrobials
- Cardiovascular agents
- Anticoagulants
- Thrombolytic agents
- Psychotropics
- Anesthetics
- Chemotherapeutics
- Dextrans
- Radiographic contrast agents
- Ethanol
- Caffeine
- Spices
- Antiplatelet drugs

Arch Pathol Lab Med 2002 Feb; 126:133-146

Drugs that effect platelet function

- Antimicrobials
  - Quinine
  - Penicillins
  - Cephalosporins
  - Nitrofurantoin
  - Hydroxychloroquine
  - Amphotericin
- Spices
  - Garlic
  - Cumin
  - Turmeric

Arch Pathol Lab Med 2002 Feb; 126:133-146

Perform simple measures first:

- PT
- PTT
- Fibrinogen
- Platelet count
- Fibrin split products

Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006; 10:222

PT prolonged, aPTT normal	Factor VII deficiency
	Mild vitamin K deficiency
	Mild liver insufficiency
	Low doses of vitamin K antagonists
PT normal, aPTT prolonged	Factor VIII, IX, or XI deficiency
	Use of unfractionated heparin
	Inhibiting antibody and/or anti-phospholipid antibody
	Factor XII or prekallikrein deficiency (no relevance for *in vivo* coagulation)
Both PT and aPTT prolonged	Factor X, V, II or fibrinogen deficiency
	Severe vitamin K deficiency
	Use of vitamin K antagonists
	Global clotting factor deficiency
	Synthesis: liver failure
	Loss: massive bleeding
	Consumption: DIC

aPTT, activated partial thromboplastin time; PT, prothrombin time.

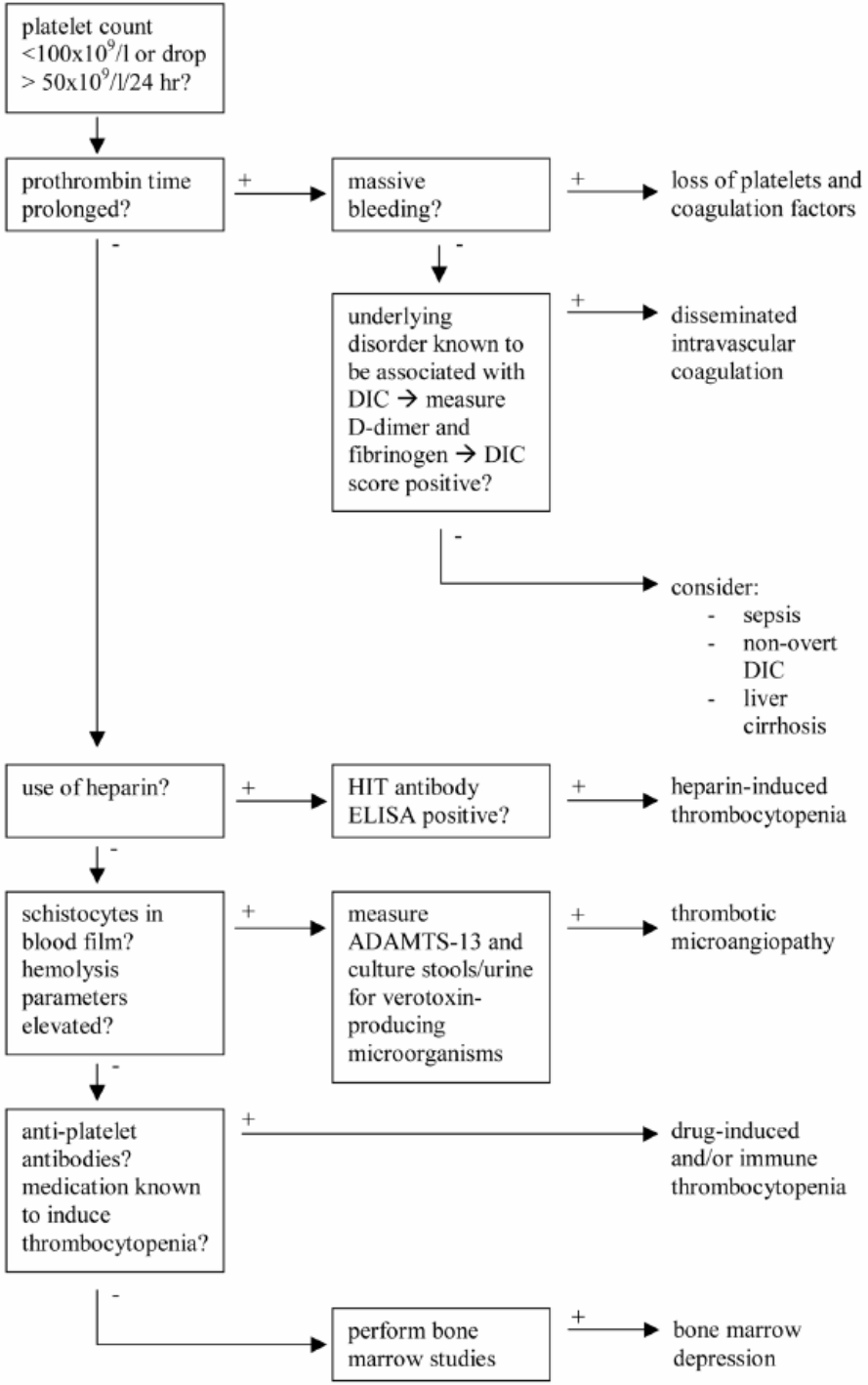
Thinking about low platelets in the ICU

Differential diagnosis of thrombocytopenia in the intensive care unit

Differential diagnosis	Approximate relative incidence	Additional diagnostic clues
Sepsis	52%	Positive (blood) cultures, positive sepsis criteria, hematophagocytosis in bone marrow aspirate
DIC[a]	25%	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	8%	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	1%	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurological symptoms, renal insufficiency
Heparin-induced thrombocytopenia	1%	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin-platelet factor IV antibodies), rebound of platelets after cessation of heparin
Immune thrombocytopenia	3%	Anti-platelet antibodies, normal or increased number of megakaryocytes in bone marrow aspirate, thrombopoeitin decreased
Drug-induced thrombocytopenia	10%	Decreased number of megakaryocytes in bone marrow aspirate or detection of drug-induced anti-platelet antibodies, rebound of platelet count after cessation of drug

Seven major causes of thrombocytopenia (platelet count $<150 \times 10^9$/l) are listed. Relative incidences are based on two studies in consecutive intensive care unit patients [1,6] but may vary depending on the population studied. Patients with hematological malignancies were excluded.
[a]Patients with sepsis and disseminated intravascular coagulation (DIC) are classified as DIC. aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; PT, prothrombin time.

Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006; 10:222

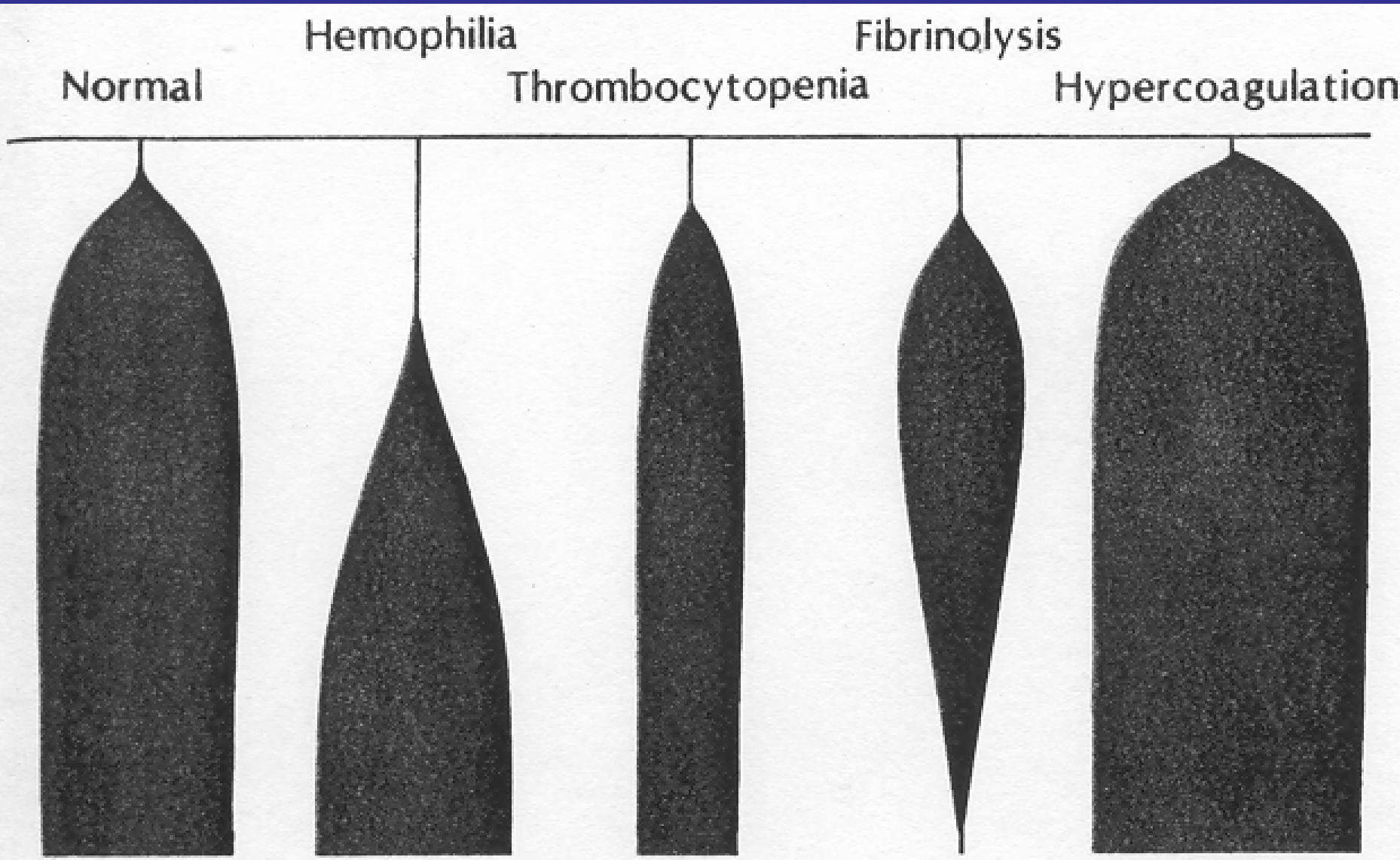


Putting it all together:

1. Take a good history
2. Look at simple screening tests
3. Remember, common things are common
4. Treat the obvious early

Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006; 10:222

TEG Patterns in Pathologic States




Thank you
Gracias