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Author(s): Steven Pipe, M.D., 2009

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Acquired Bleeding Disorders

M2 Hematology/Oncology Sequence

Steven Pipe, MD

Winter 2009

Acquired Bleeding Disorders

- Can be a recognized manifestation of a known disorder

or

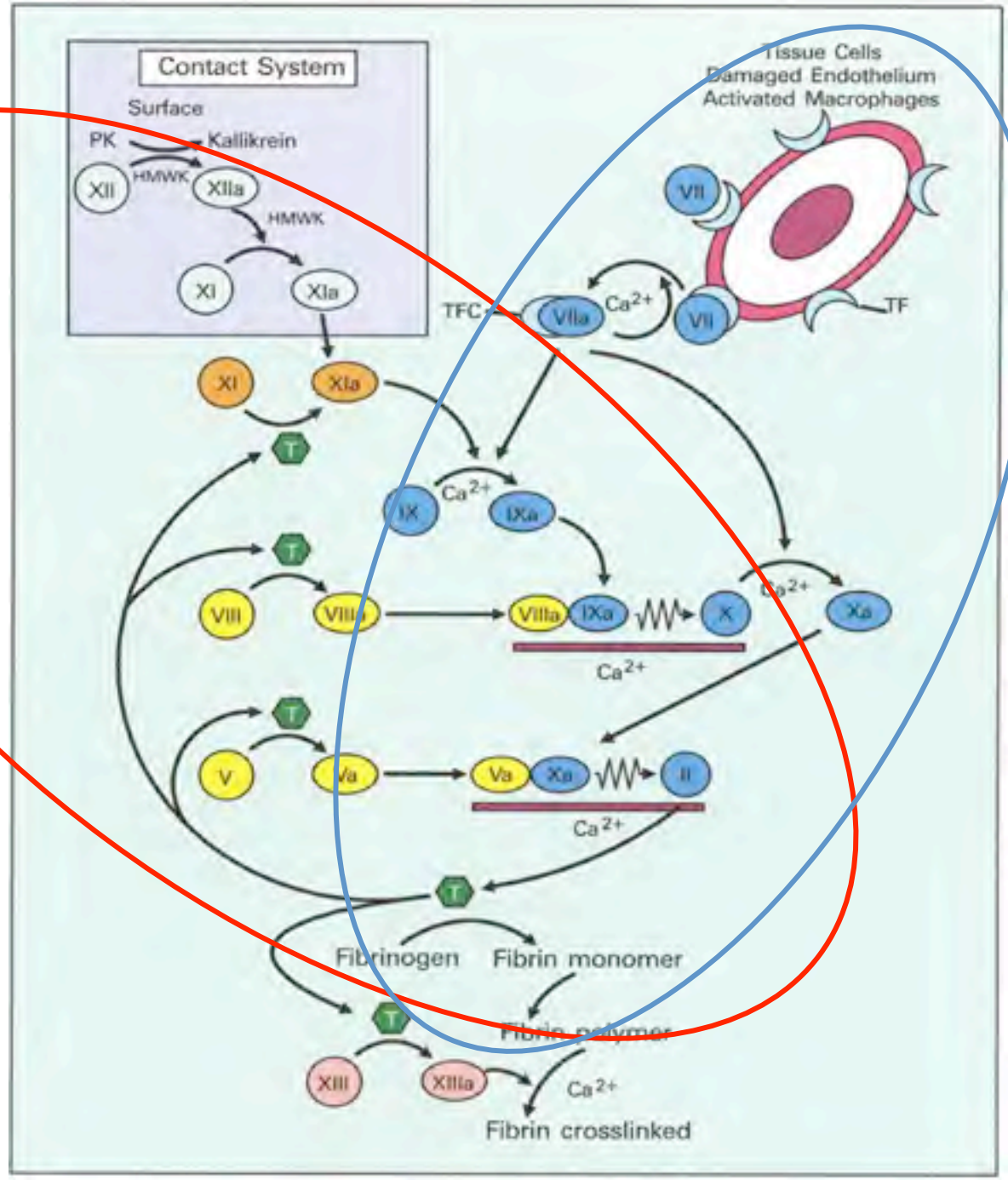
- Can prompt a differential diagnosis to identify an underlying disease

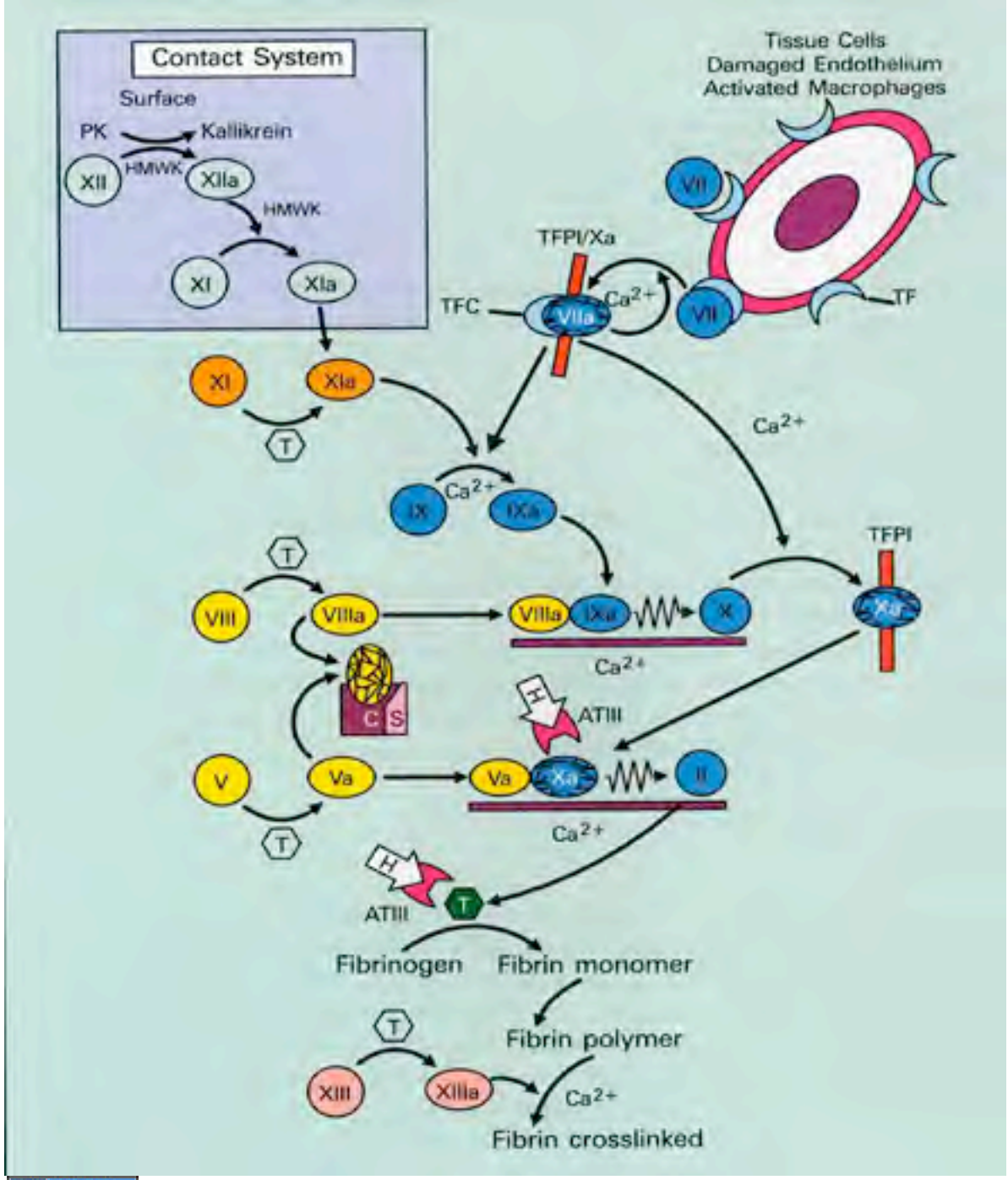
Promoters and Inhibitors of Coagulation

- Coagulation cascade
  - Tissue factor (Extrinsic) Pathway
  - Intrinsic Pathway
  - Fibrinogen, Factor XIII and Fibrinolysis
- Inhibitors
  - Physiologic
  - Acquired
  - Therapeutic

PTT

PT


Contact System
Surface
PK
Kallikrein
XII
HMWK
XIIa
HMWK
XI
XIa
Tissue Cells
Damaged Endothelium
Activated Macrophages
VII
TFC
VIIa
Ca2+
VII
TF
XI
XIa
T
IX
Ca2+
IXa
T
VIII
VIIIa
VIIIa
IXa
X
Ca2+
Xa
Ca2+
T
V
Va
Va
Xa
II
Ca2+
T
Fibrinogen
Fibrin monomer
T
XIII
XIIIa
Ca2+
Fibrin crosslinked


Contact System
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PK
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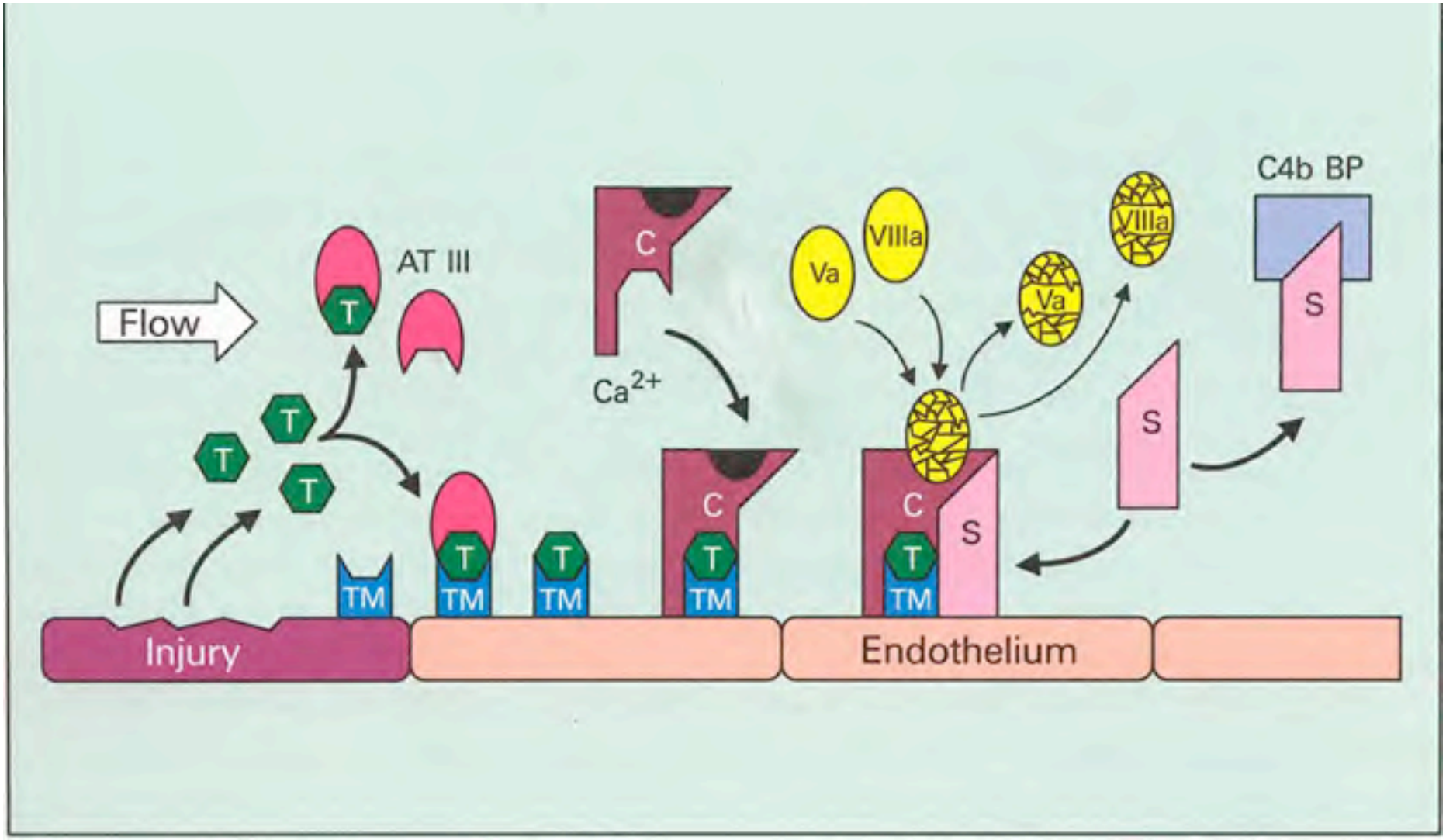
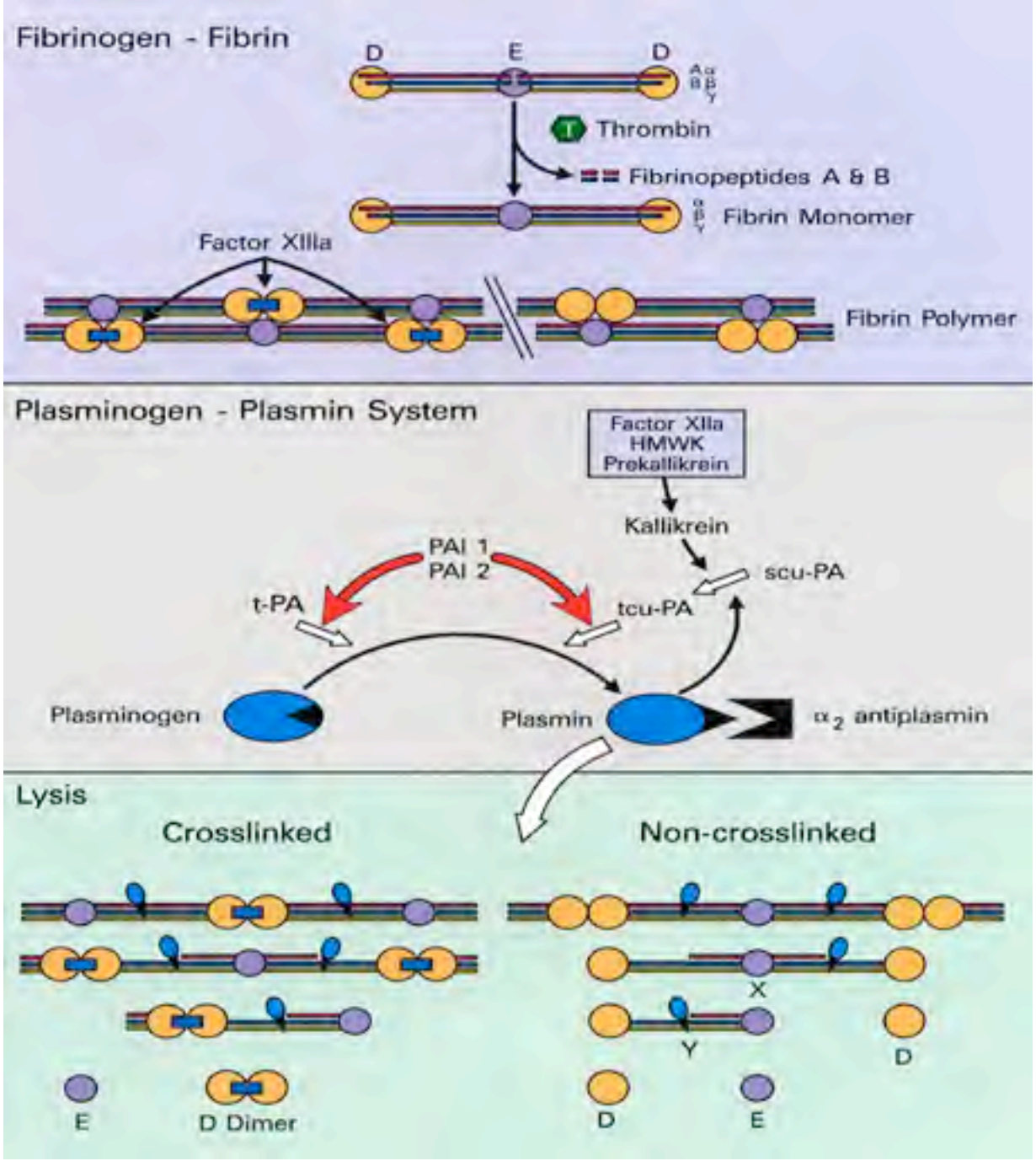
HMWK
XII
XIIa
HMWK
XI
XIa
Tissue Cells
Damaged Endothelium
Activated Macrophages
VII
TFPI/Xa
TFC
VIIa
Ca2+
VII
TF
XI
XIa
T
Ca2+
IX
Ca2+
IXa
TFPI
T
VIII
VIIIa
VIIIa
IXa
X
Xa
Ca2+
C S
H
ATIII
V
Va
Va
Xa
II
Ca2+
T
H
ATIII
T
Fibrinogen
Fibrin monomer
T
Fibrin polymer
XIII
XIIIa
Ca2+
Fibrin crosslinked

Protein C - Protein S System




Fibrinogen - Fibrin
D
E
D
Thrombin
Fibrinopeptides A & B
Fibrin Monomer
Factor XIIIa
Fibrin Polymer
Plasminogen - Plasmin System
Factor XIIa
HMWK
Prekallikrein
Kallikrein
PAI 1
PAI 2
scu-PA
t-PA
tcu-PA
Plasminogen
Plasmin
α_2 antiplasmin
Lysis
Crosslinked
Non-crosslinked
X
Y
D
E
D Dimer
D
E

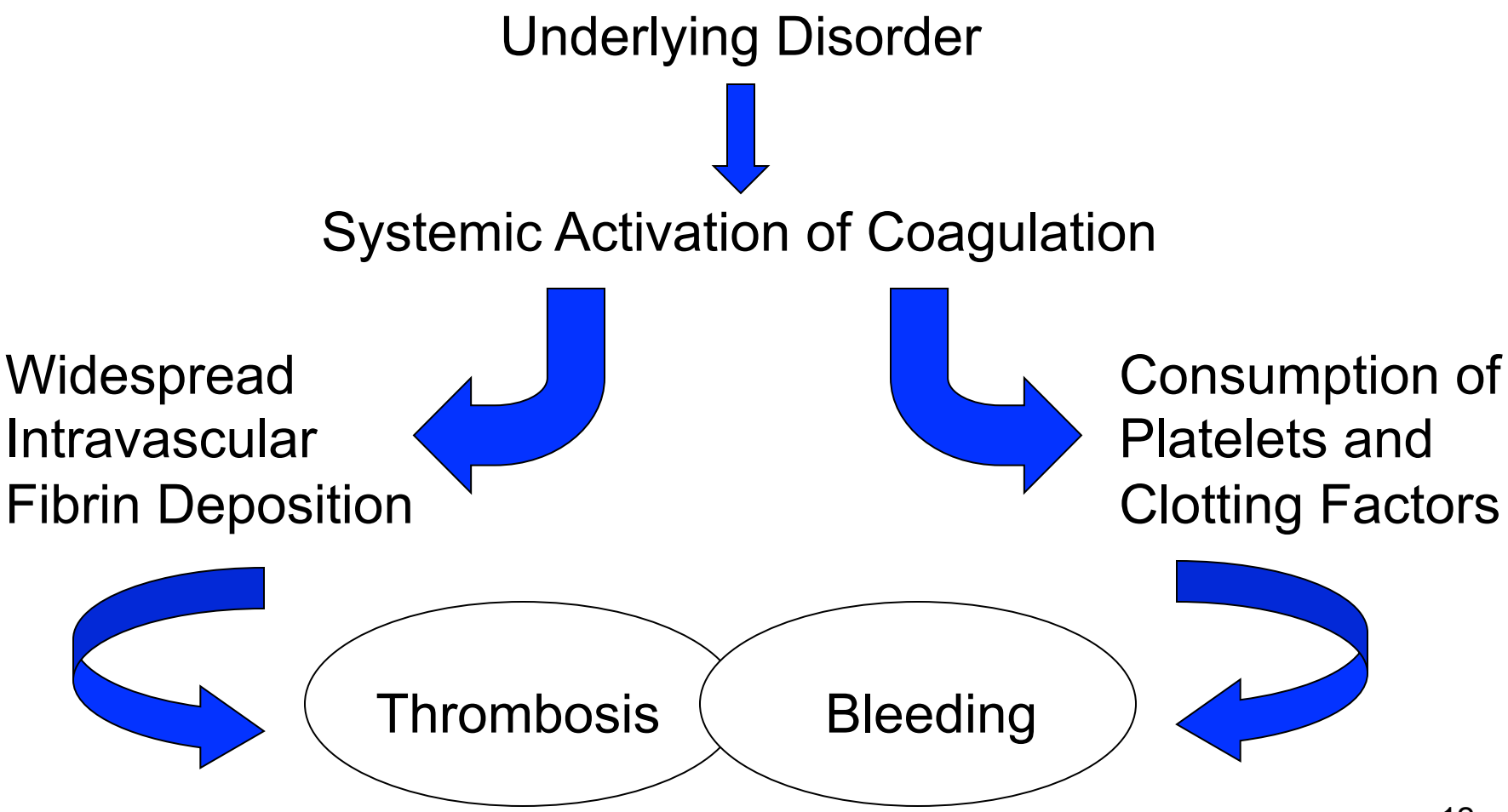
Acquired Bleeding Disorders associated with ↑PT and aPTT

- Various Medical Conditions
  - Anticoagulation
  - Disseminated Intravascular Coagulation
  - Vitamin K Deficiency
  - Liver Disease
  - Massive Transfusion
- Dysfibrinogenemias
- Acquired Inhibitors to Factors V, II & X

Disseminated Intravascular Coagulation (DIC)

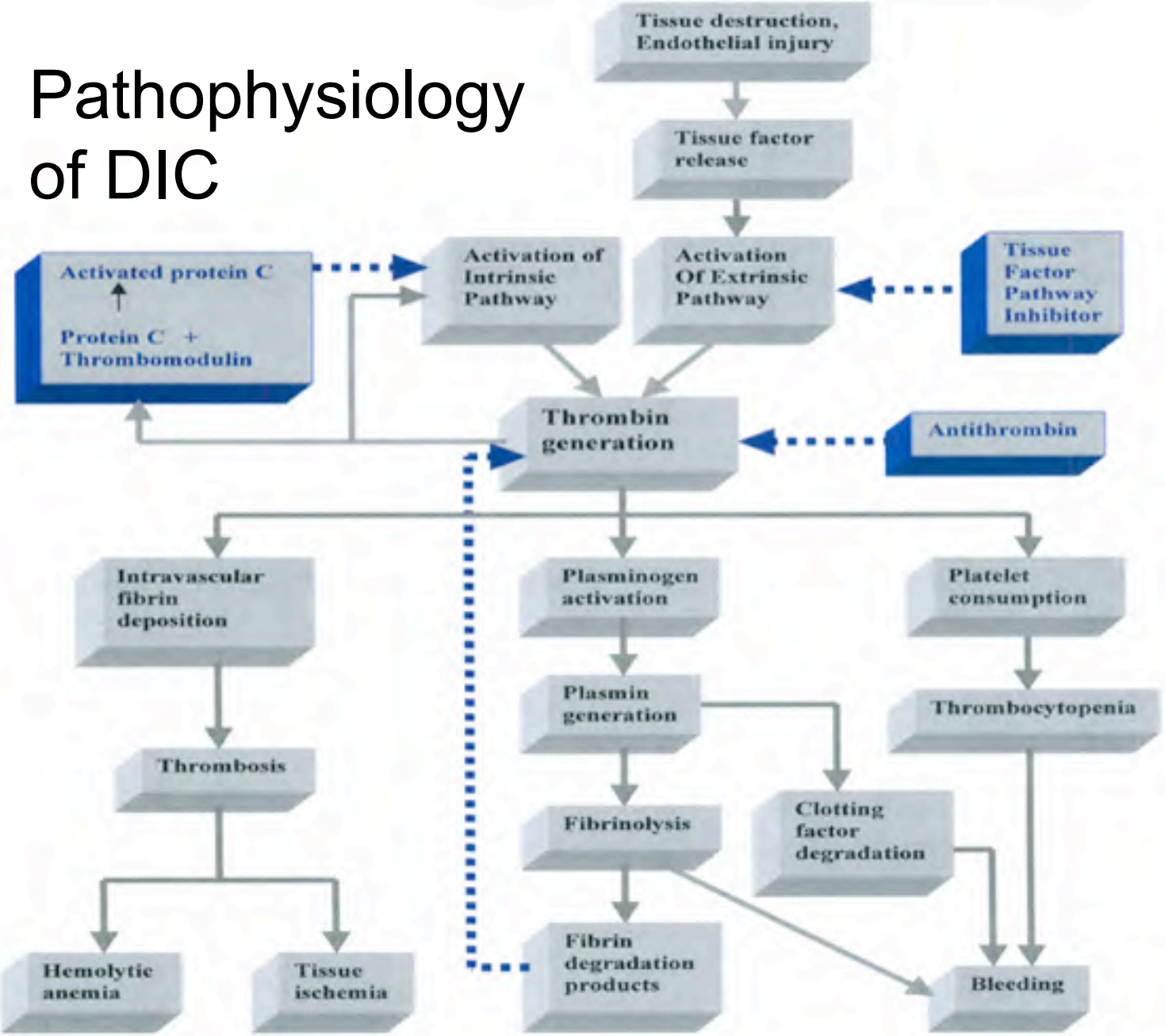
- DIC is evidence for the simultaneous presence of:
  - thrombin(procoagulation)
  - plasmin(fibrinolysis)
- Presentations:
  - an acute hemorrhagic disorder
  - an indolent, subacute thrombotic disorder

Primary Events in DIC



 K. McInerny. American Academy of Pediatrics textbook of pediatric care. 2009

Pathophysiology of DIC



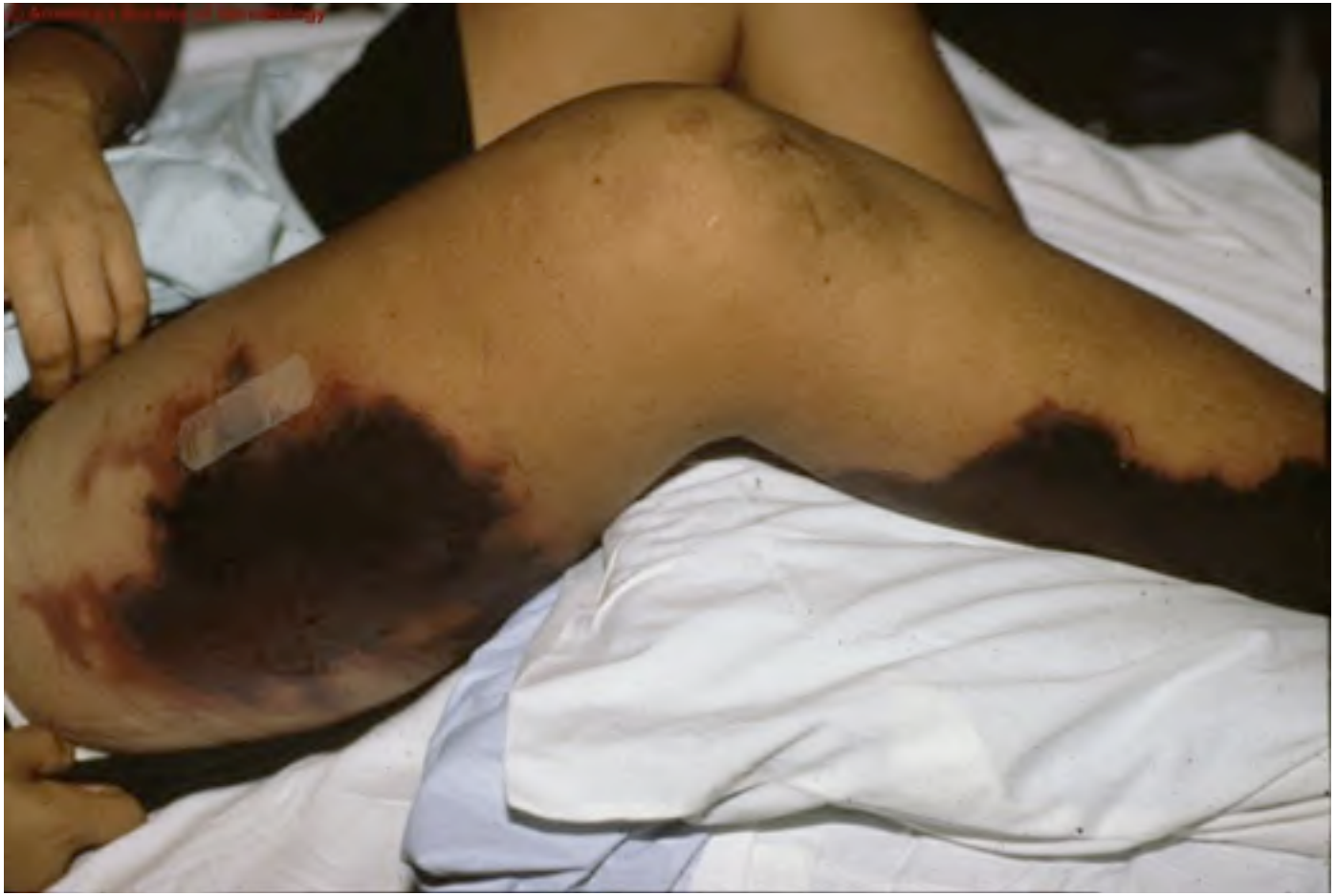
Blue (dotted) indicates inhibitors of coagulation

 K. McInerny. American Academy of Pediatrics textbook of pediatric care. 2009

Etiology of DIC

- Acute DIC
  - **Infection:** Gram -ve sepsis, viremia, parasitic
  - **Obstetric:** Abruption, amniotic fluid embolism, eclampsia
  - **Malignancy:** Acute promyelocytic leukemia
  - **Trauma:** Crush injury, freshwater drowning, heat stroke, snakebite
  - **Other:** Homozygous protein C and S deficiency (infants), severe liver disease, HIT
- Subacute DIC
  - **Malignancy:** mucinous adenocarcinoma (Trousseau syndrome)
  - **Obstetric:** retained dead fetus
  - **Vascular:** hemangioendothelioma (Kasabach-Merritt), venous thromboembolic disease, chronic renal failure

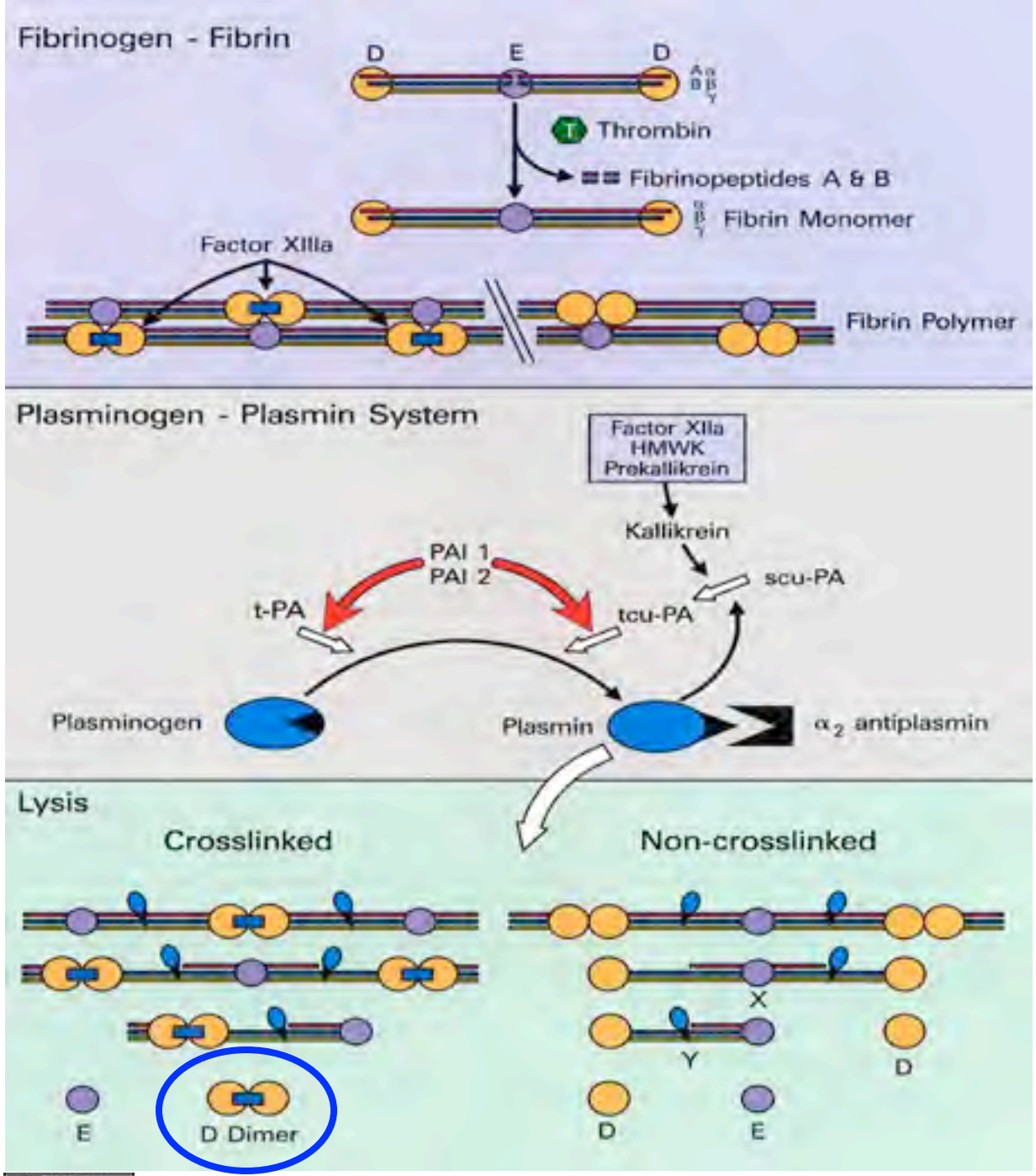
Post-varicella purpura fulminans



 DeLoughery, ASH Image Bank, 2004

Diagnosis of DIC

- Screening tests:
  - Activated partial thromboplastin time (prolonged)
  - Prothrombin time (prolonged)
  - Fibrinogen (decreased)
  - Platelet count (decreased)
- Confirmatory tests:
  - D-dimer (elevated)
  - Fibrin degradation products (elevated)


Fibrinogen - Fibrin
D
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Fibrin Monomer
Factor XIIIa
Fibrin Polymer
Plasminogen - Plasmin System
Factor XIIa
HMWK
Prekallikrein
Kallikrein
PAI 1
PAI 2
scu-PA
t-PA
tcu-PA
Plasminogen
Plasmin
α_2 antiplasmin
Lysis
Crosslinked
Non-crosslinked
X
Y
D
E
D Dimer
D
E

Value of the D-dimer

- Measure of D-dimers liberated from fibrin by action of plasmin
  - Evidence of prior thrombin activity followed by fibrinolysis
- Should be part of evaluation of DIC
- Also now an important screening and prognostic tool in venous thromboembolic disease
  - Good positive predictive value for DVT and PE
  - Very high negative predictive value

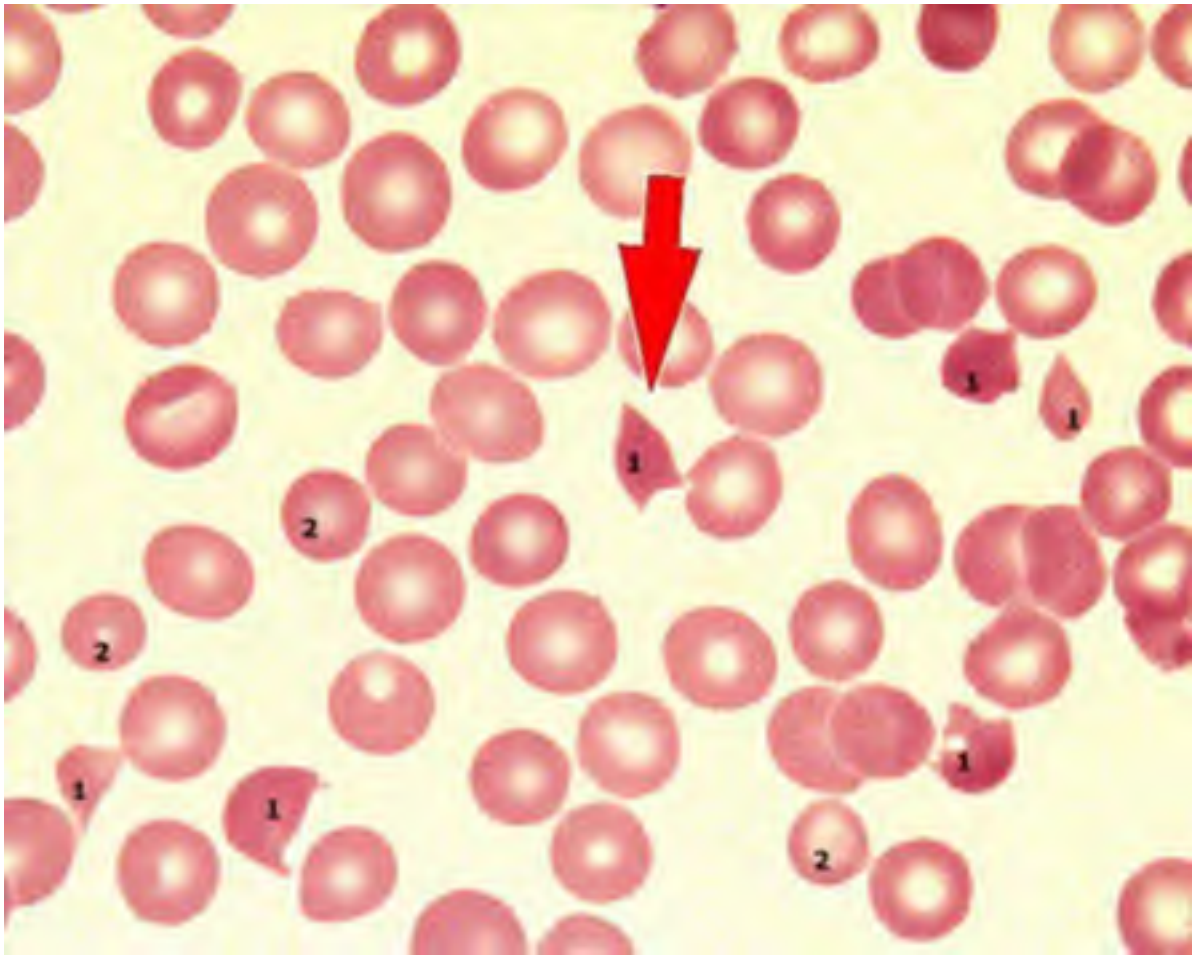
Source: Wells et al., NEJM, 2003;349:1227-1235
Eichinger et al., JAMA, 2003;290:1071-1074

Treatment of DIC

- Treat the underlying condition first!
  - Antibiotics, surgery, chemotherapy, embolization
  - disease-specific therapy
    - APML - all trans-retinoic acid (ATRA)
- Replacement therapy
  - Platelets, FFP, cryoprecipitate
- Heparin
  - May be useful in certain situations
    - Acral cyanosis and digital ischemia, purpura fulminans, retained dead fetus, migratory thrombophlebitis

Microangiopathic Hemolytic Anemia

PD-INEL K. McInerny. American Academy of Pediatrics textbook of pediatric care. 2009



* Note absence of platelets

1. Shistocyte
2. Microcyte

Microangiopathic Hemolytic Anemias
Pathophysiology

- Hallmarks are red cell fragmentation (shistocytes, microcytes) on peripheral blood smear, often accompanied by thrombocytopenia
- Intravascular hemolysis as red cells are damaged traversing small blood vessels with fibrin deposition or platelet aggregates
  - Can also occur in areas of high turbulence (eg. Aortic stenosis)
- Red cell fragments are targeted for destruction in the reticuloendothelial system (eg. spleen)

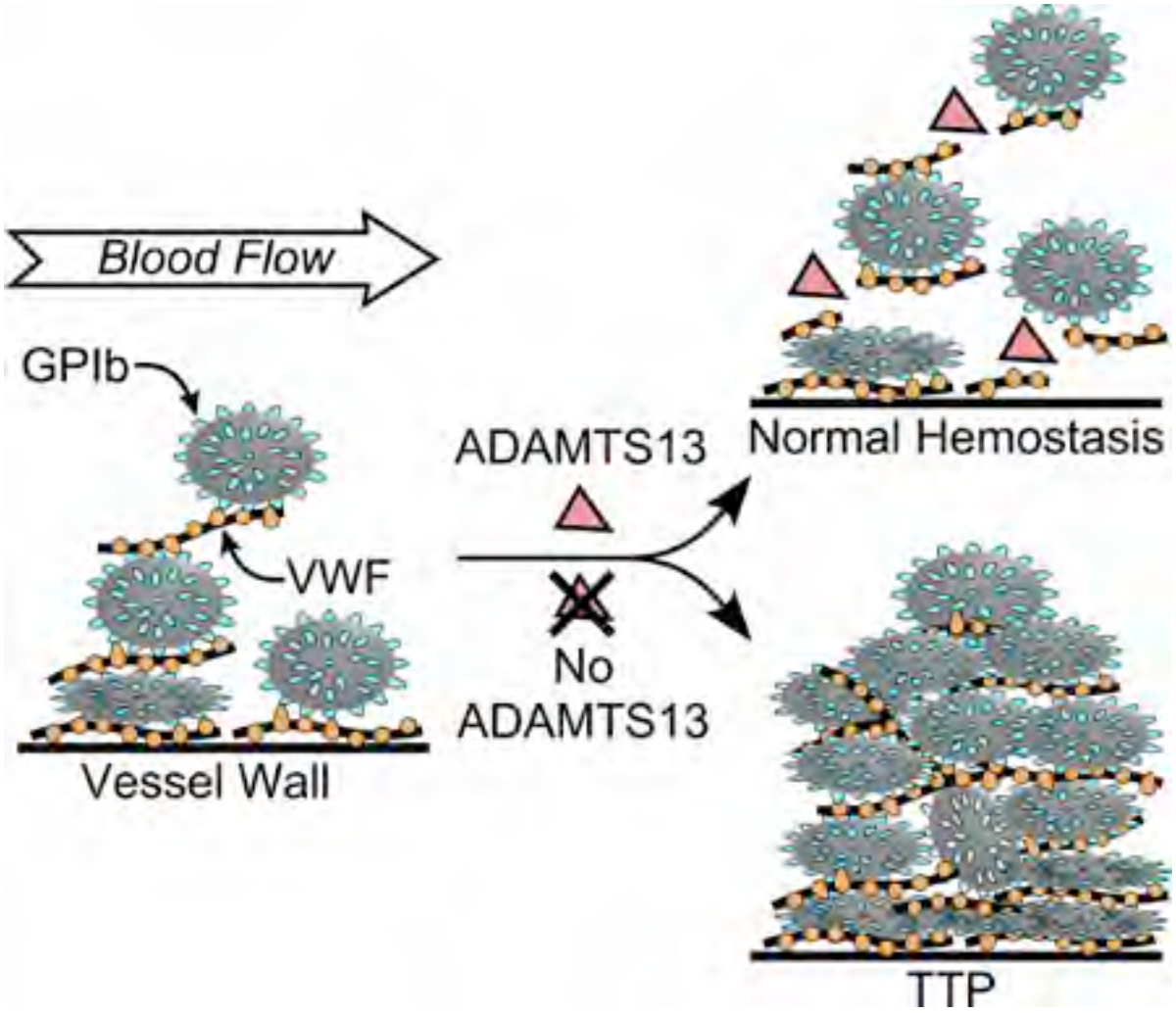
Microangiopathic Hemolytic Anemias
Differential Diagnosis

- Disseminated intravascular coagulation (DIC)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Malignant hypertension
- Aortic stenosis
- HELLP syndrome and eclampsia
- Heparin-induced thrombocytopenia
- Severe glomerulonephritis

Thrombotic Thrombocytopenic Purpura

- Classic pentad:
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - Renal involvement
  - Neurologic signs
  - Fever
- Most cases in adults are caused by acquired autoantibodies that inhibit ADAMTS13, a metalloprotease that cleaves vWF within platelet-rich thrombi
  - Congenital form (Upshaw-Schulman syndrome) is the result of a deficiency of ADAMTS13
- Treatment is plasma exchange +/- immunosuppression

Pathogenesis of Idiopathic TTP caused by ADAMTS13 Deficiency



PD-INEL Sadler, J. E. *Blood* 2008;112:11-18

DIC vs TTP

Abnormality	DIC	TTP
Abnormal PT/ PTT	Y	N
Hemolysis	Y	Y
Thrombocytopenia	Y	Y
Abnormal Renal Tests	N	Y

Acquired Bleeding Disorders associated with ↑PT and aPTT

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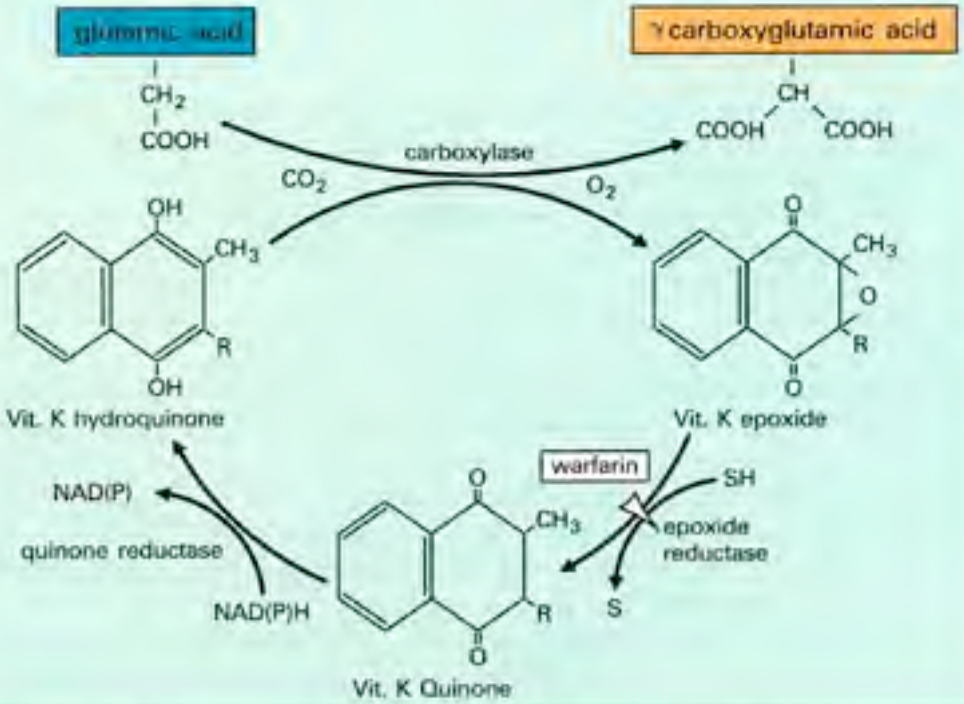
  - Vitamin K Deficiency
  - Liver Disease
  - Massive Transfusion
- Dysfibrinogenemias
- Acquired Inhibitors to Factors V, II & X

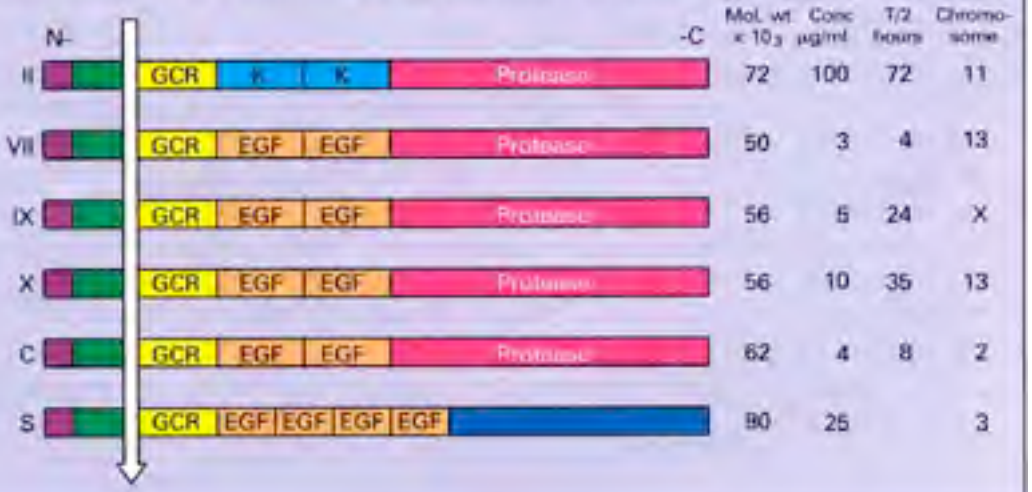
Vitamin K deficiency

- Vitamin K cycle
- Mechanisms of Vitamin K deficiency
- Warfarin action

Vitamin K Cycle



Vitamin K Dependent Coagulation Factors



Mechanisms of Vitamin K deficiency

- Nutritional depletion
  - Alcoholics, long-term IV nutrition
- Antibiotic administration
  - Interfere with bacteria synthesis and absorption
- Warfarin
  - Inhibition of epoxide reductase and (to a lesser degree) quinone reductase

Liver Disease

- Liver synthesizes and clears both procoagulants and inhibitors
- Paradoxically factor VIII is often elevated
  - Likely due to decreased clearance
- Reduced factor V helps distinguish liver synthetic dysfunction from vitamin K deficiency
- Fibrinogen the last to fall
- Structural manifestations of liver disease contribute to bleeding
  - Portal hypertension, varices, gastritis, hemorrhoids

Massive Transfusion

- Defined as transfusion of more than 1.5 times the patient's blood volume in 24 h
- Acquired coagulopathy results from dilution of plasma and platelets and excess anticoagulant
  - 10% of transfusion is anticoagulant
- Prevention:
  - Administer 1 unit FFP and calcium chloride for every 4-6 units PRBC's

Other uncommon acquired coagulation protein defects

- Dysfibrinogenemia
  - Acquired liver disease (EtOH, immunologic, toxic, viral)
- Inhibitors to X, V, II and fibrinogen
- Hypergammaglobulinemia
  - Multiple myeloma (IgG)
  - Waldenstrom macroglobulinemia (IgM)
- Systemic amyloidosis
  - Decreased factor X or IX
- Heparinoids
  - Heparin-like anticoagulants produced in patients with an underlying malignancy
- Factitious
  - Self-administered heparin/warfarin

Acquired bleeding disorders associated with prolonged aPTT only

- Inhibitors to factor VIII
  - Elderly, post-partum, connective tissue disorder, B cell malignancy
  - Prolonged aPTT but normal PT
  - Skin ecchymoses and tissue hematomas
  - Respond to immunosuppressive therapy
  - “bypassing agents” to treat bleeding
    - Activated prothrombin complex concentrates
    - Recombinant factor VIIa (Novoseven)
  - Prognosis generally favorable

Slide 6: Mechanisms In Hematology Israel
Slide 7: Mechanisms In Hematology Israel
Slide 8: Mechanisms In Hematology Israel
Slide 9: Mechanisms In Hematology Israel
Slide 12: K. McInerny. American Academy of Pediatrics textbook of pediatric care. 2009 – From the chapter "Disseminated Intravascular Coagulation"
Slide 13: K. McInerny. American Academy of Pediatrics textbook of pediatric care. 2009 – From the chapter "Disseminated Intravascular Coagulation"
Slide 15: DeLoughery, ASH Image Bank, 2004
Slide 17: Steven Pipe
Slide 20: K. McInerny. American Academy of Pediatrics textbook of pediatric care. 2009 – From the chapter "Disseminated Intravascular Coagulation"
Slide 24: Sadler, J. E. Blood 2008;112:11-18, http://bloodjournal.hematologylibrary.org/cgi/content/full/112/1/11/F2, 2008 American Society of Hematology
Slide 25: Source Undetermined
Slide 28: Mechanisms In Hematology Israel