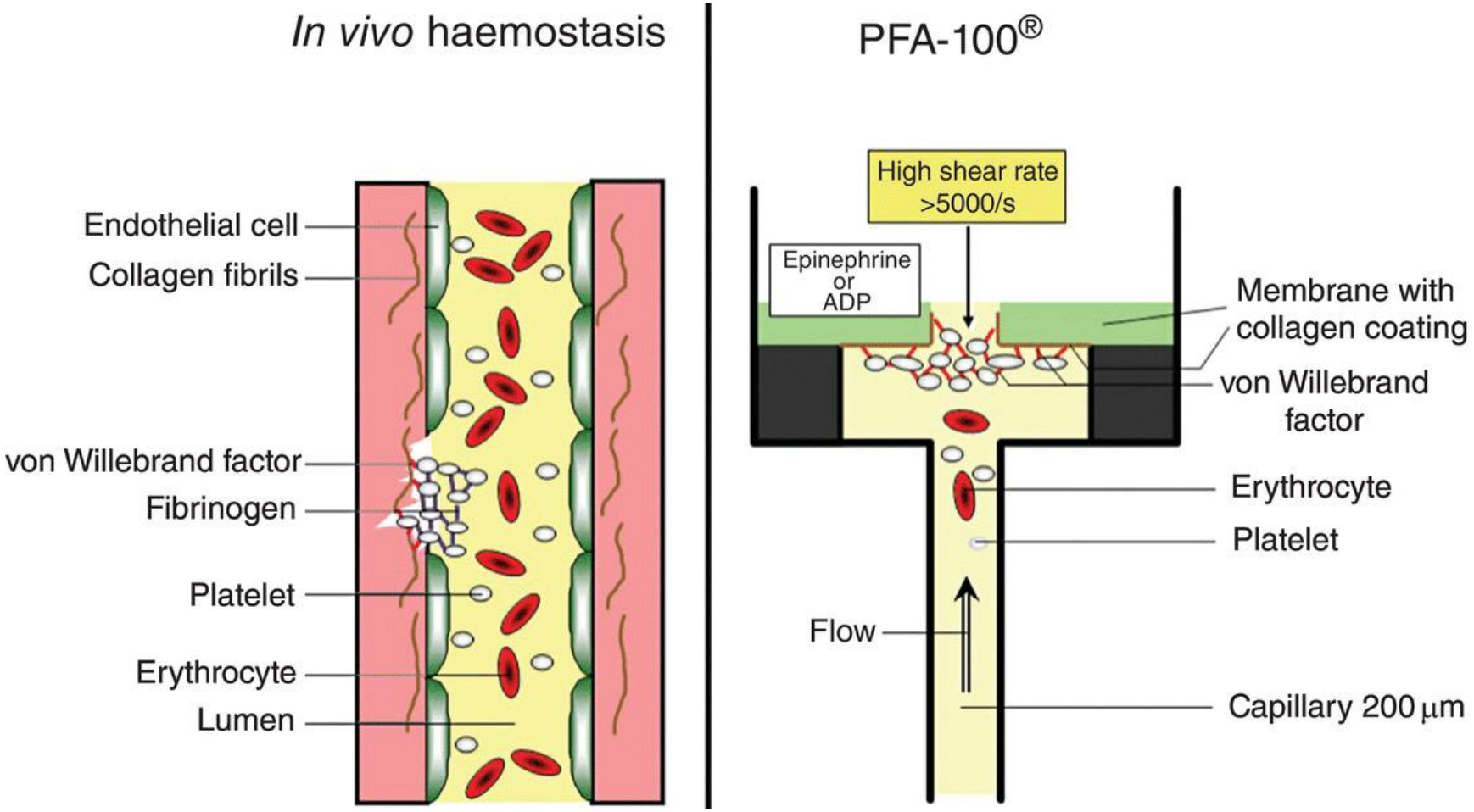
HEME 10
Bleeding Disorders

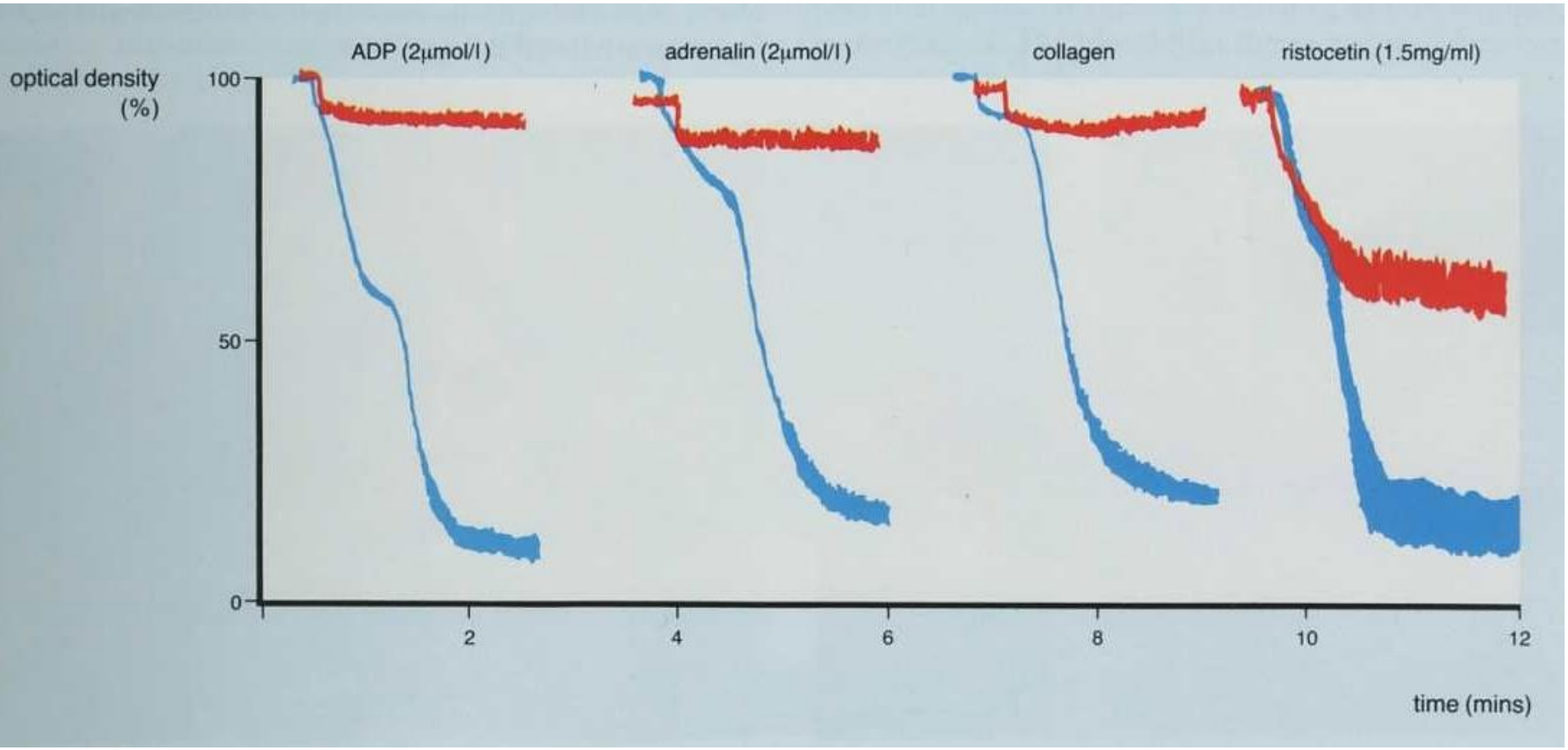
- When injury occurs, three mechanisms occur
  - Blood vessels
  - Primary hemostasis
  - Secondary hemostasis

- Diseases of the blood vessels
- Platelet disorders
  - Thrombocytopenia
  - Functional disorders
- Clotting factor deficiency

Let’s talk about some tests

- Platelet count (150,000-450,000)
  - Does not mean bleeding will occur if slightly decreased
- Platelet function:
  - Bleeding time: old and outdated
  - PFA
  - Aggregation studies

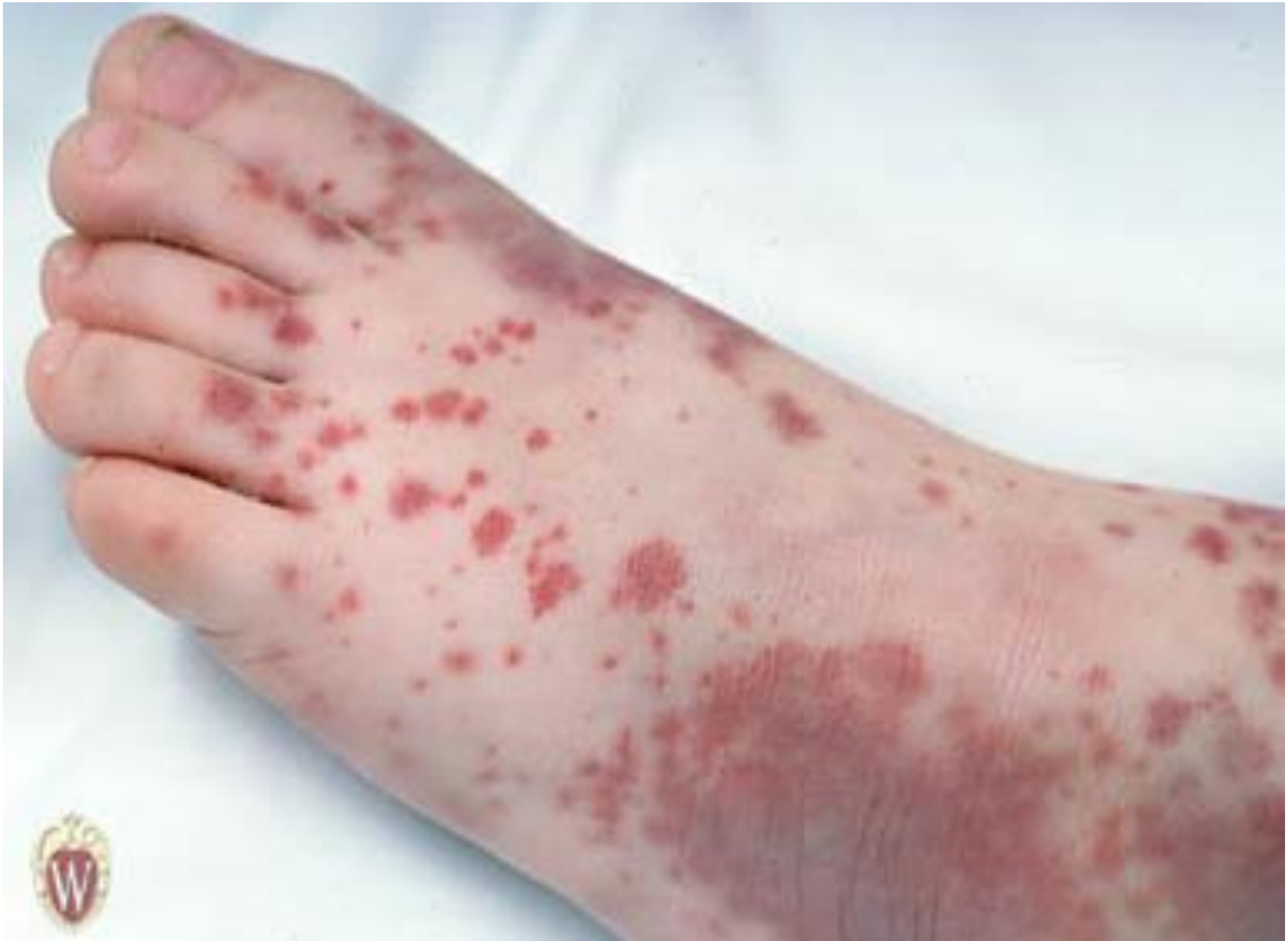

In vivo haemostasis
PFA-100®
Endothelial cell
Collagen fibrils
von Willebrand factor
Fibrinogen
Platelet
Erythrocyte
Lumen
High shear rate
>5000/s
Epinephrine
or
ADP
Membrane with
collagen coating
von Willebrand
factor
Erythrocyte
Platelet
Flow
Capillary 200 μm

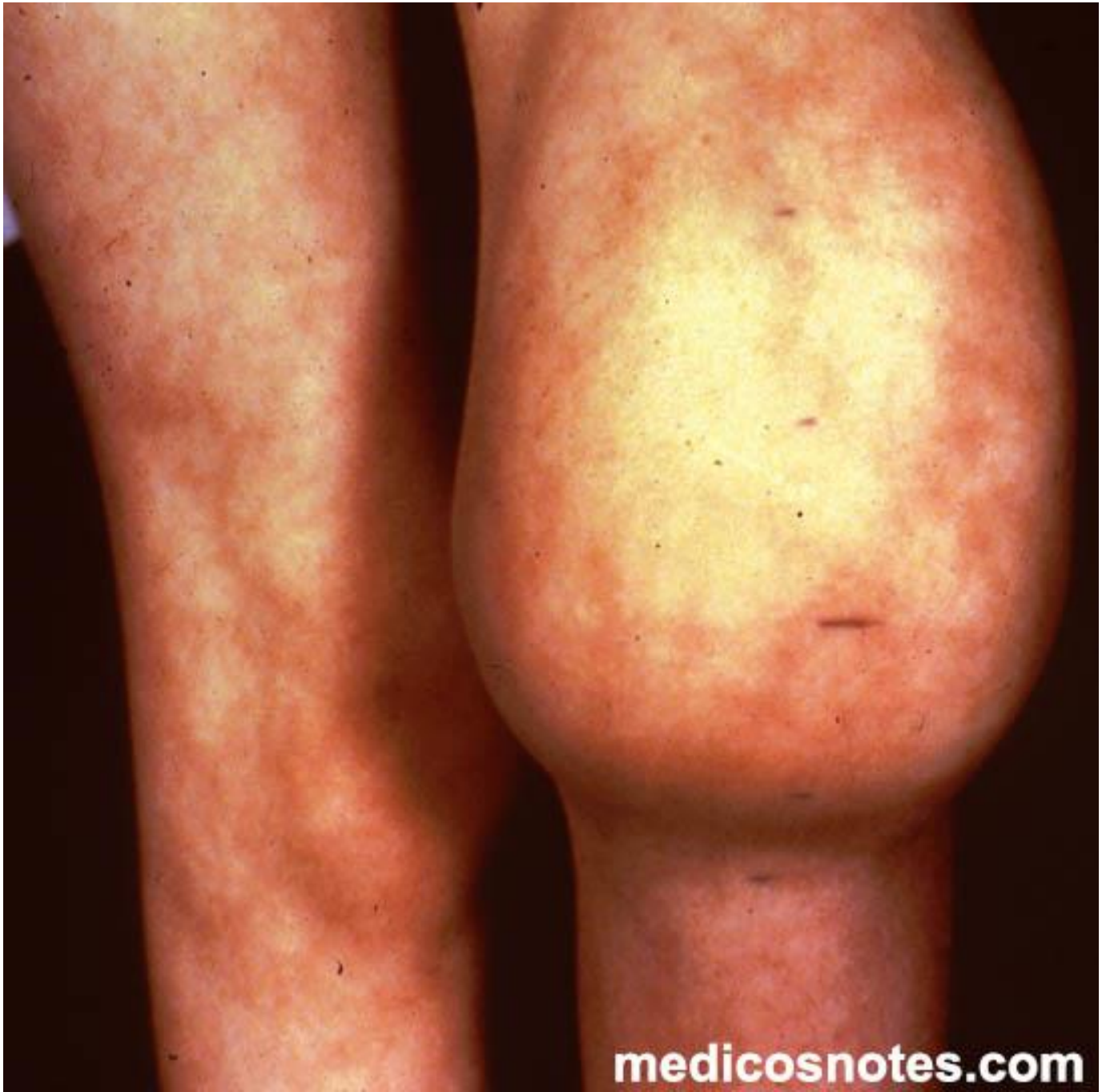

optical density (%)
100
50
0
ADP (2μmol/l)
adrenalin (2μmol/l)
collagen
ristocetin (1.5mg/ml)
2
4
6
8
10
12
time (mins)

- PT: prothrombin time: extrinsic and common pathways
- PTT: partial thrombopalstin time: intrinsic and common pathways
- D dimer and fibrin split products
  - Sensitive for DIC but not specific

Two major clinical types of bleeding

- Mucocutaneous seen in disorders of the vessels and platelets
  - Petechiae and ecchymosis
- Deep bleeding in muscles and joints seen in clotting factor deficiency

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Disorders related to blood vessles

- Increased vascular fragility
- Endothelial damage

Increased vascular fragility

- Vitamin C deficiency
- Amyloidosis
- Chronic steroid use
- Vasculitis
- Normal platelet count, function, PT and PTT

- Endothelial damage
  - DIC
  - overwhelming damage to the endothelial cells converting them to prothrombotic surfaces
    - Consumption of platelets and coagulation factors (consumptive coagulopathy)

DIC

- **DIC occurs as a complication of a wide variety of disorders; it is caused by the systemic activation of coagulation and results in the formation of thrombi throughout the microcirculation, consumption of platelets and coagulation factors and severe bleeding**

Causes

- 1- widespread endothelial damage
- 2- Release of tissue factor or thromboplastic

1- obstetric complication, placental damage

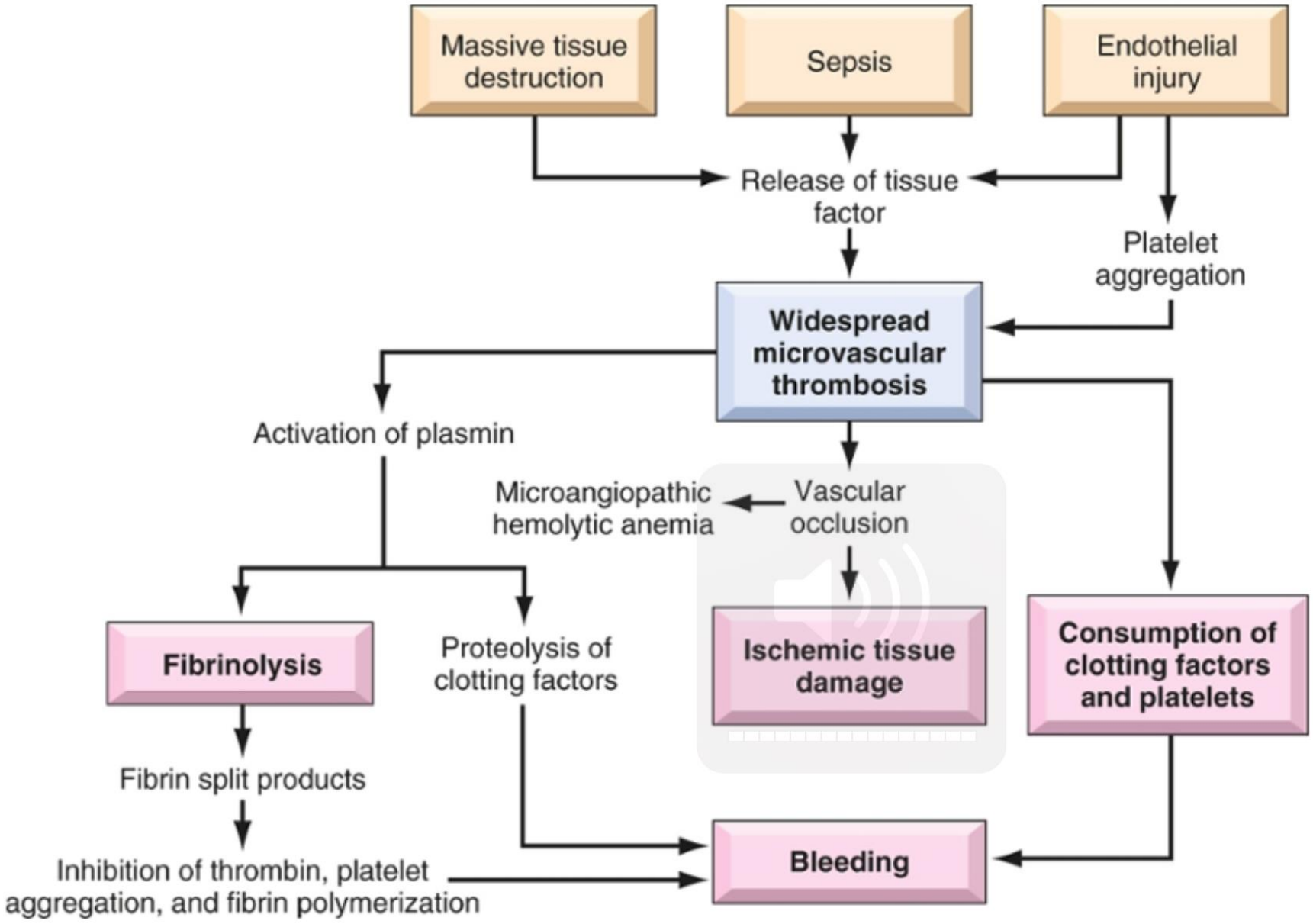
2- cancer: APL and adenocarcinomas

- Releasing proteolytic enzymes
- Releasing tissue factor

3- bacterial sepsis

- Endotoxins trigger release of tissue factors from monocytes
  - Monocytes also release IL1 and tumor necrosis factors
    - Both increase tissue factor and decrease thrombomodulin

- 4- deposition of antigen-antibody complex such as in SLE
- 5- extremes of temperature
- 6- major trauma such as severe head trauma


Massive tissue destruction
Sepsis
Endothelial injury
Release of tissue factor
Platelet aggregation
Widespread microvascular thrombosis
Activation of plasmin
Microangiopathic hemolytic anemia
Vascular occlusion
Fibrinolysis
Proteolysis of clotting factors
Ischemic tissue damage
Consumption of clotting factors and platelets
Fibrin split products
Inhibition of thrombin, platelet aggregation, and fibrin polymerization
Bleeding

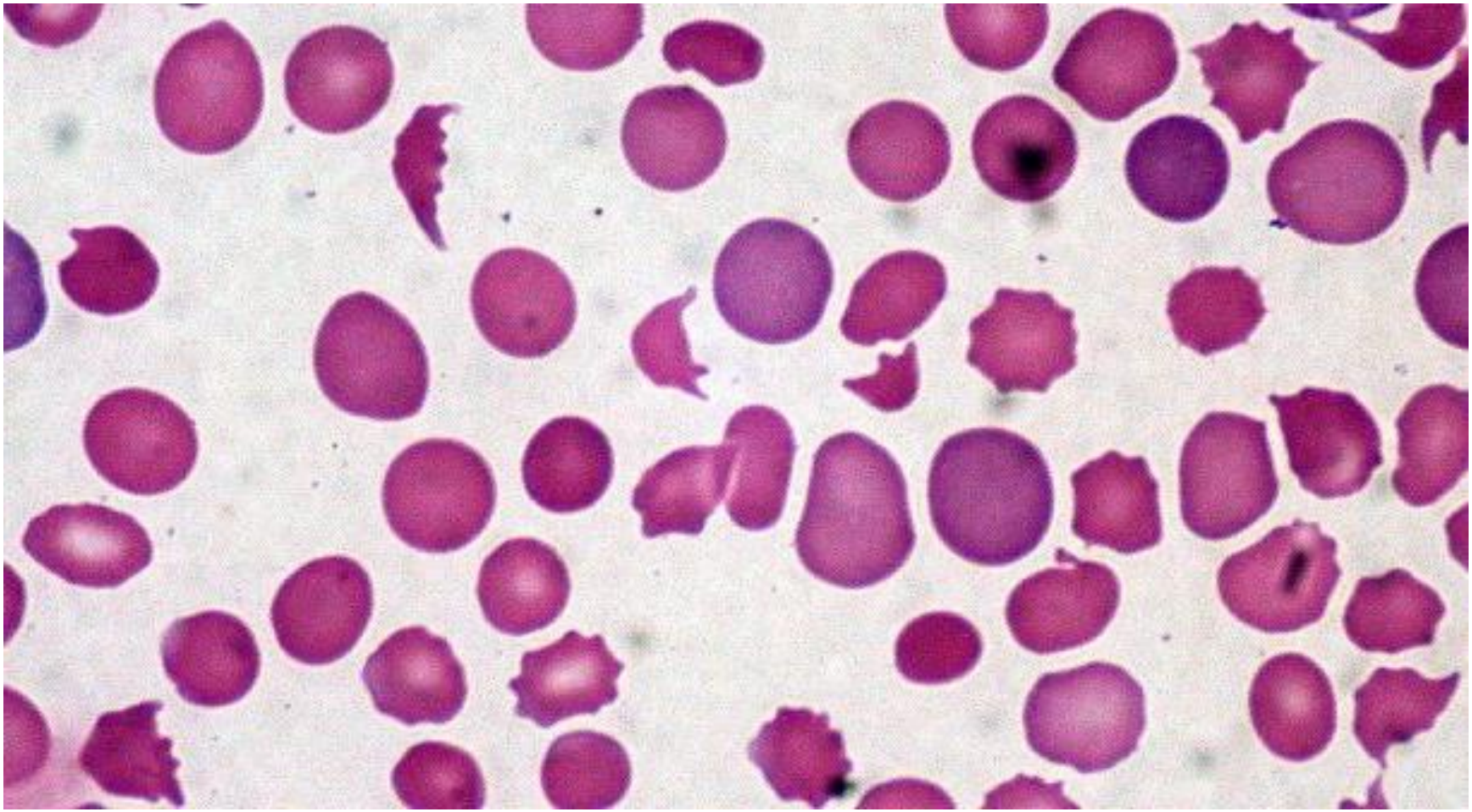
Obstetric Complications
Abruptio placentae Retained dead fetus Septic abortion Amniotic fluid embolism Toxemia
Infections
Sepsis (gram-negative and gram-positive) Meningococcemia Rocky Mountain spotted fever Histoplasmosis Aspergillosis Malaria
Neoplasms
Carcinomas of pancreas, prostate, lung, and stomach Acute promyelocytic leukemia
Massive Tissue Injury
Trauma Burns Extensive surgery
Miscellaneous
Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease

Consequences

- Widespread microthrombi and fibrin deposition
  - Ischemic infarcts
  - Microangiopathic hemolytic anemia
- Bleeding tendency due to
  - Consumption of platelets and clotting factors
  - Widespread activation of plasmin which cleaves factors V and VIII
  - Release of FDP which inhibit platelets and fibrinogen polymerization

Morphology

- Intravascular hemolysis with schistocytes
- Microthrombi in the small vessels and capillaries



Clinical manifestaitons

- Variable
- Could be acute (a in postpartum DIC) or chronic as in cancer
- Can be minimal or severe
  - Shock, acute renal failure, dyspnea, cyanosis, convulsions, and coma.

- Lab findings
  - Low platelets
  - High PT and PTT
  - Elevated FDP
- Prognosis depends on the severity of presentation and the underlying condition
  - Treatment with heparin or replacement of coagulation factors

Thrombocytopenia

- Low platelet count
  - Less than 15000
- Bleeding occurs when 20000-50000
  - 20000-50000 posttraumatic bleeding
  - Less than 5000 spontaneous bleeding
- Mucocutaneous bleeding
  - Brain hemorrhage is a major factor for mortality

Decreased Production of Platelets
Generalized Bone Marrow Dysfunction
Aplastic anemia: congenital and acquired Marrow infiltration: leukemia, disseminated cancer
Selective Impairment of Platelet Production
Drug-induced: alcohol, thiazides, cytotoxic drugs Infections: measles, HIV infection
Ineffective Megakaryopoiesis
Megaloblastic anemia Paroxysmal nocturnal hemoglobinuria
Decreased Platelet Survival
Immunologic Destruction
Autoimmune: ITP, systemic lupus erythematosus Isoimmune: posttransfusion and neonatal Drug-associated: quinidine, heparin, sulfa compounds Infections: infectious mononucleosis, HIV infection, cytomegalovirus infection
Nonimmunologic Destruction
Disseminated intravascular coagulation TTP Giant hemangiomas Microangiopathic hemolytic anemias
Sequestration
Hypersplenism
Dilutional
Multiple transfusions (e.g., for massive blood loss)

- ITP
- HIT
- TTP and HUS

ITP

- Immune thrombocytopenic purpura
  - Acute: children after a viral infection, self-limiting
  - Chronic: affects women 20-40 years of age
- Antibodies against platelet antigens (IIb/IIIa and IB/IX)
  - Spleen causes damage to those antibody coated platelets
    - Benefits of splenectomy
  - Steroids, immunosuppressive therapy or splenectomy

Clinical

- Mucocutaneous bleeding
  - Brain hemorrhage is rare
- Lab results
  - Low platelets
  - Normal PT
  - Normal PTT
  - Bone marrow shows megakaryocytic hyperplasia

HIT (heparin induced thrombocytopenia)

- Occurs in 3-5% of patients using unfractionated heparin
  - Develops after 1-2 weeks of therapy
  - Results in thrombosis associated with low platelets
  - IgG antibodies against platelet factor 4 (PF4)
  - Cessation of heparin breaks the cycle
  - Use of low molecular weight heparin

TTP and HUS

- THROMBOTIC THROMBOCYTOPENIA PURPURA
- HEMOLYTIC UREMIC SYNDROME

TTP

- FIVE FINDINGS
  - Fever
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia
  - Neurological manifestations
  - Renal failure

HUS

- Fever
- Thrombocytopenia
- Renal failure
- NO neurologic manifestations
- Frequently in children secondary to E. coli infection

- Both has widespread microthrombi

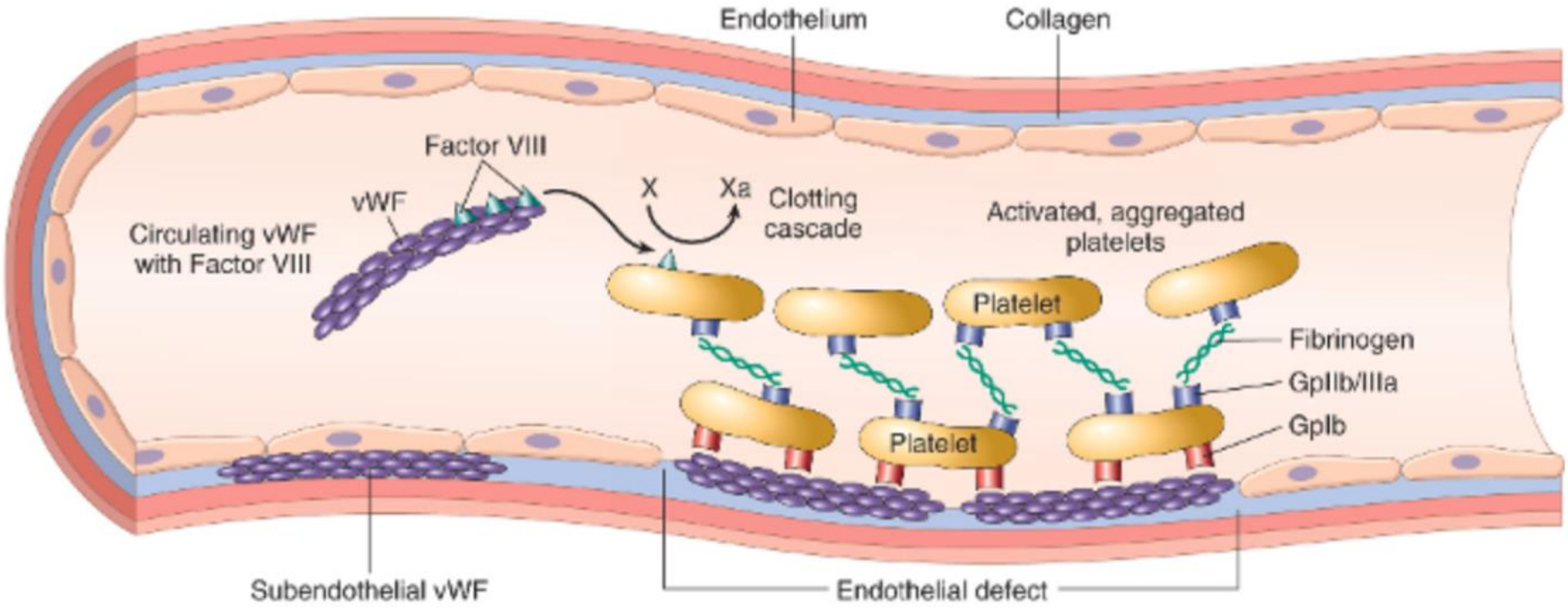
So how are they different from DIC???

- No significant consumption of clotting factor
  - Normal PT and PTT

Coagulation disorders

- Hereditary or acquired
- Acquired is more common
  - Vitamin K deficiency
    - Factors II, VII, IX, and X
    - Newborns
    - Patients with fat malabsorption such as cystic fibrosis
  - Liver disease
  - DIC

- Hereditary
  - Von-Willebrand disease
  - Hemophilia A
  - Hemophilia B


Endothelium
Collagen
Factor VIII
vWF
Circulating vWF
with Factor VIII
X
Xa
Clotting
cascade
Activated, aggregated
platelets
Platelet
Fibrinogen
GpIIb/IIIa
GpIb
Platelet
Subendothelial vWF
Endothelial defect

Von-Willebrand disease

- Autosomal dominant
- Mucocutaneous bleeding
- The most common inherited bleeding disorder
- 1% of the US population
- Frequently asymptomatic and under recognized

- Labs
  - Normal platelet count
  - Abnormal platelet aggregation studies
  - Elevated PTT
  - Normal PT

Hemophilia A

- Deficiency in factor VIII
- X-linked disorder affects males
- Deep muscle and joint hemorrhage
- Most cases are associated with low factor VIII level
  - 10% are associated with normal level but reduced activity

- Lab results
  - Normal platelet count and function
  - Normal PT
  - Elevated PTT that corrects with mixing studies

Hemophilia B

- Also called Christmas disease
- Factor IX deficiency
- Deep muscle and joint bleeding (hemarthrosis)
- X-linked disorder
- Affects males

- Lab results same as hemophilia A
- It is less common than hemophilia A
- Distinguish by doing specific assays for factors VIII, and IX