HEMOSTASIS AND THROMBOSIS

HEMOSTASIS AND THROMBOSIS

- *Normal haemostasis:*
  - a consequence of tightly regulated processes that:
    - maintain blood in a fluid, clot-free state in normal vessels
    - inducing the rapid formation of a localized *hemostatic plug* at the site of vascular injury

HEMOSTASIS AND THROMBOSIS

- *Thrombosis:*
  - the **pathologic** form of hemostasis
  - involves blood clot (*thrombus*) formation in uninjured vessels (or after relatively minor injury)
- Thrombosis can only occur during life
- Clotting can also occur after death or in a test tube

HEMOSTASIS AND THROMBOSIS

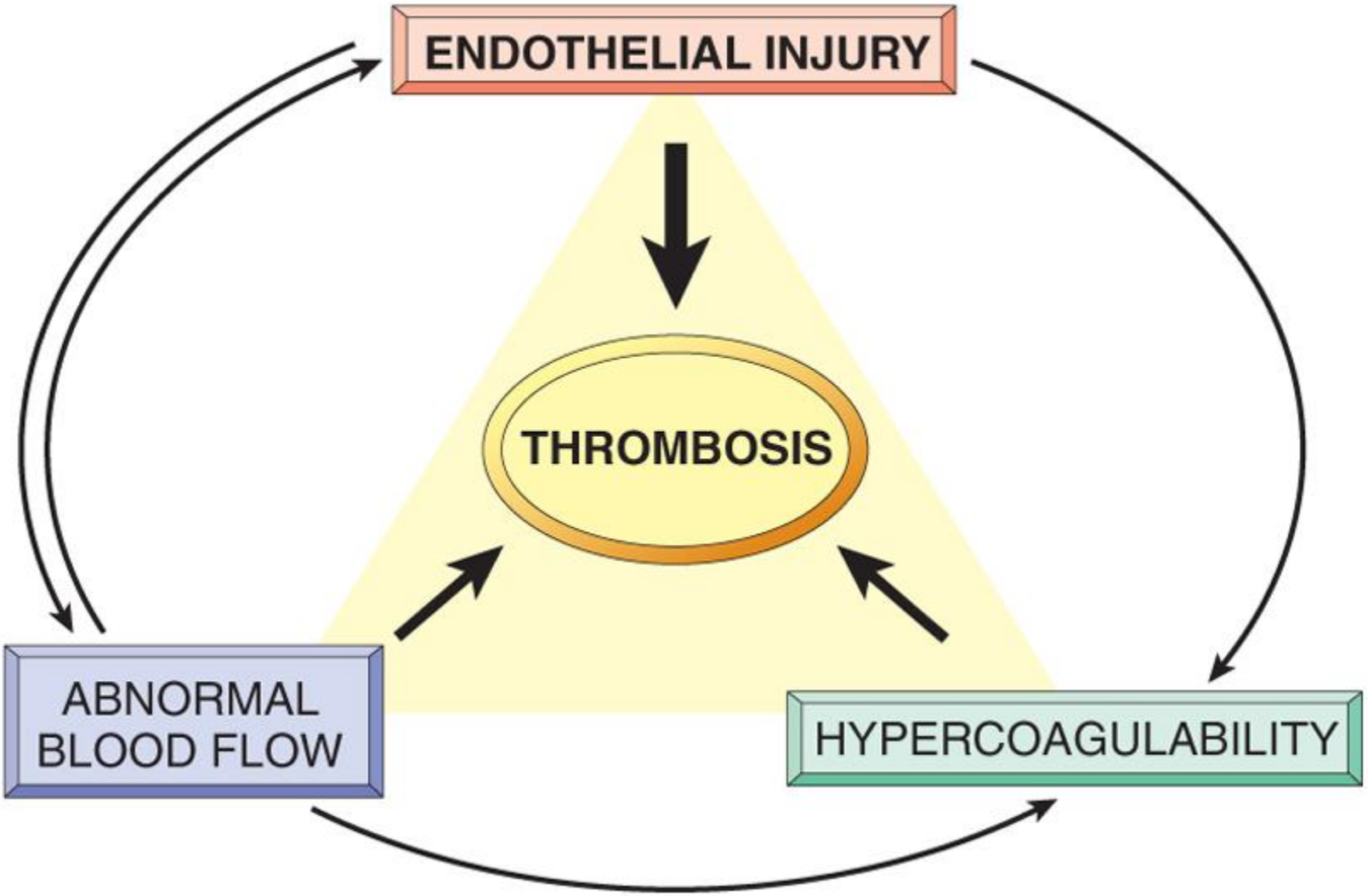
- Hypercoagulability:
  - loosely defined as:

    any alteration of the coagulation pathways that predisposes to thrombosis

HEMOSTASIS AND THROMBOSIS
Hypercoagulable States

- Primary (Genetic)
  - Common
    - Mutation in factor V gene (factor V Leiden)
    - Mutation in prothrombin gene
  - Rare
    - Protein C deficiency
    - Protein S deficiency
  - Very rare
    - Fibrinolysis defects

- Secondary (Acquired)
  - High risk for thrombosis
    - Prolonged bed rest or immobilization
    - Myocardial infarction
    - Atrial fibrillation
    - Tissue damage (surgery, fracture, burns)
    - Cancer
    - Prosthetic cardiac valves
    - Disseminated intravascular coagulation
    - Heparin-induced thrombocytopenia
    - Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)
  - Lower risk for thrombosis
    - Cardiomyopathy
    - Nephrotic syndrome
    - Hyperestrogenic states (pregnancy)
    - Oral contraceptive use
    - Sickle cell anemia
    - Smoking



Virchow's triad in thrombosis. Integrity of endothelium is the most important factor. Injury to endothelial cells can also alter local blood flow and affect coagulability. Abnormal blood flow (stasis or turbulence), in turn, can cause endothelial injury. The factors may act independently or may combine to promote thrombus formation

HEMOSTASIS AND THROMBOSIS

- Both hemostasis and thrombosis involve three structural and molecular components:
  - *the vascular wall*
  - *platelets*
  - *the coagulation cascade*

HEMOSTASIS AND THROMBOSIS

- ***The vascular wall***
  - Intact endothelial cells maintain liquid blood flow by actively:
    - inhibiting platelet adherence
    - preventing coagulation factor activation
    - lysing blood clots that may form
  - Endothelial cell stimulation results in expression of procoagulant proteins (e.g., tissue factor and vWF) that contribute to local thrombus formation
  - Loss of endothelial integrity exposes underlying vWF and basement membrane collagen, both substrates for platelet aggregation and thrombus formation
  - Dysfunctional endothelial cells can produce more procoagulant factors (e.g., platelet adhesion molecules, tissue factor) or may synthesize less anticoagulant effectors (e.g., thrombomodulin, PGI_2, t-PA)

HEMOSTASIS AND THROMBOSIS

- Endothelial dysfunction can be induced by a wide variety of insults, for example:
  - Hypertension
  - turbulent blood flow
  - bacterial endotoxins
  - radiation injury
  - metabolic abnormalities such as homocystinemia or hypercholesterolemia, and toxins absorbed from cigarette smoke

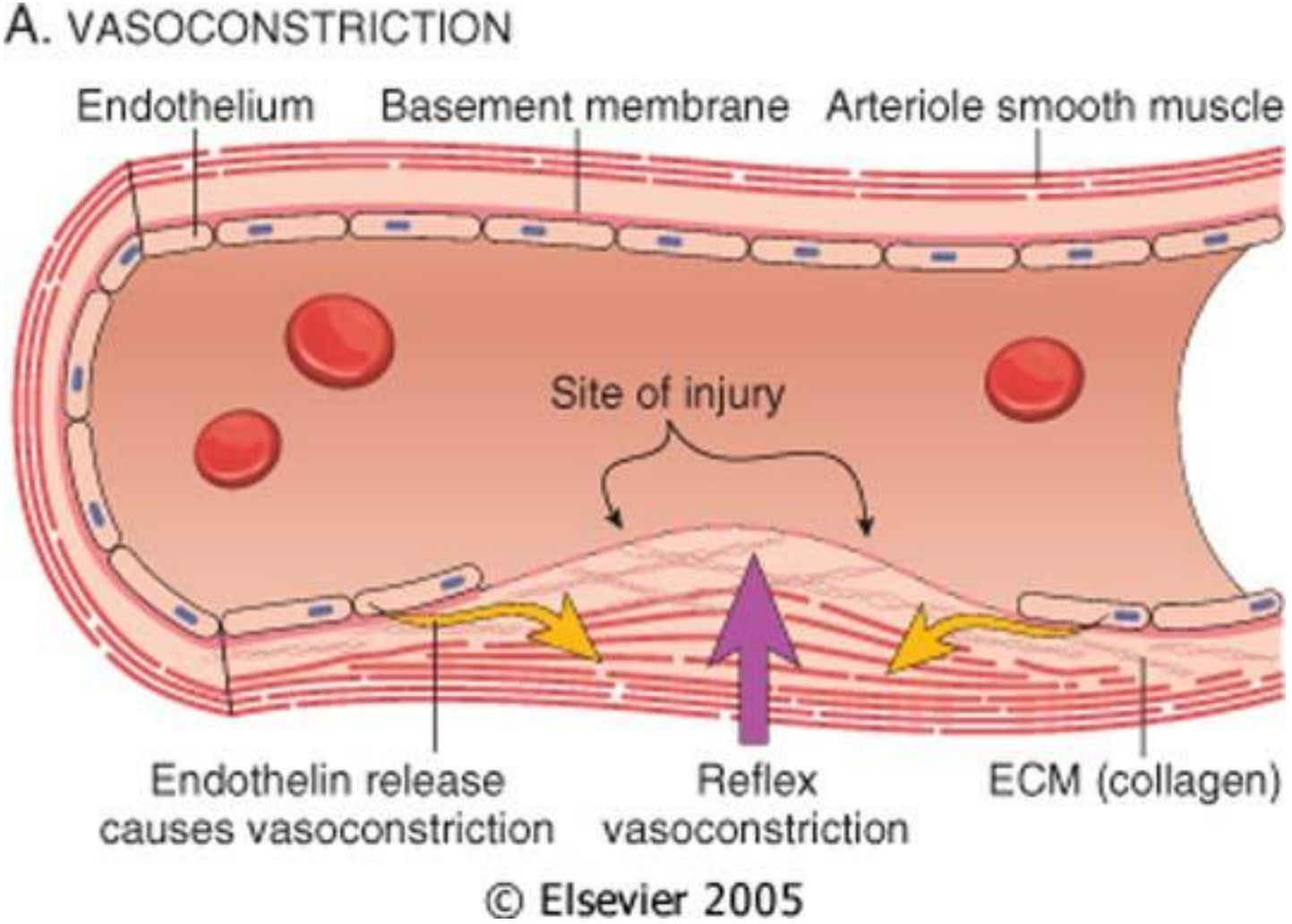
HEMOSTASIS AND THROMBOSIS

- **Platelet Aggregation:**
  - Endothelial injury exposes the underlying basement membrane ECM

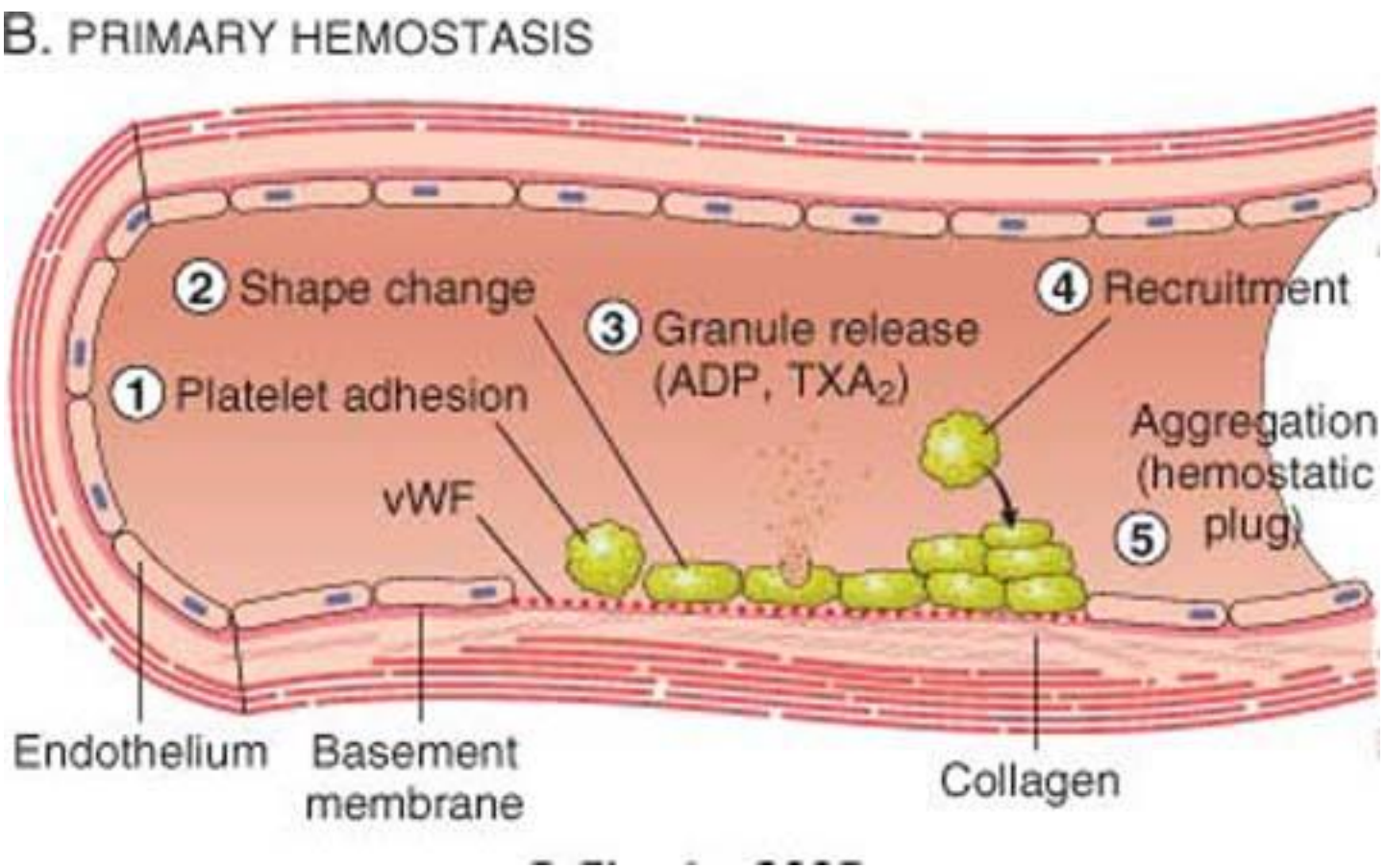
  → platelets adhere to the ECM → become activated by binding to vWF through GpIb platelet receptors→Upon activation, platelets:
    - Secrete granule products that include calcium (activates coagulation proteins)
    - Secrete ADP (mediates further platelet aggregation and degranulation),
      → Released ADP stimulates formation of a primary hemostatic plug by activating platelet GpIIb-IIIa receptors that in turn facilitate fibrinogen binding and cross-linking
    - Secrete TXA_2 (increases platelet activation and causes vasoconstriction)
    - expose phospholipid complexes that provide an important surface for coagulation-protein activation.
    - The formation of the definitive secondary hemostatic plug requires the activation of thrombin to cleave fibrinogen and form **polymerized fibrin** via the coagulation cascade

HEMOSTASIS AND THROMBOSIS

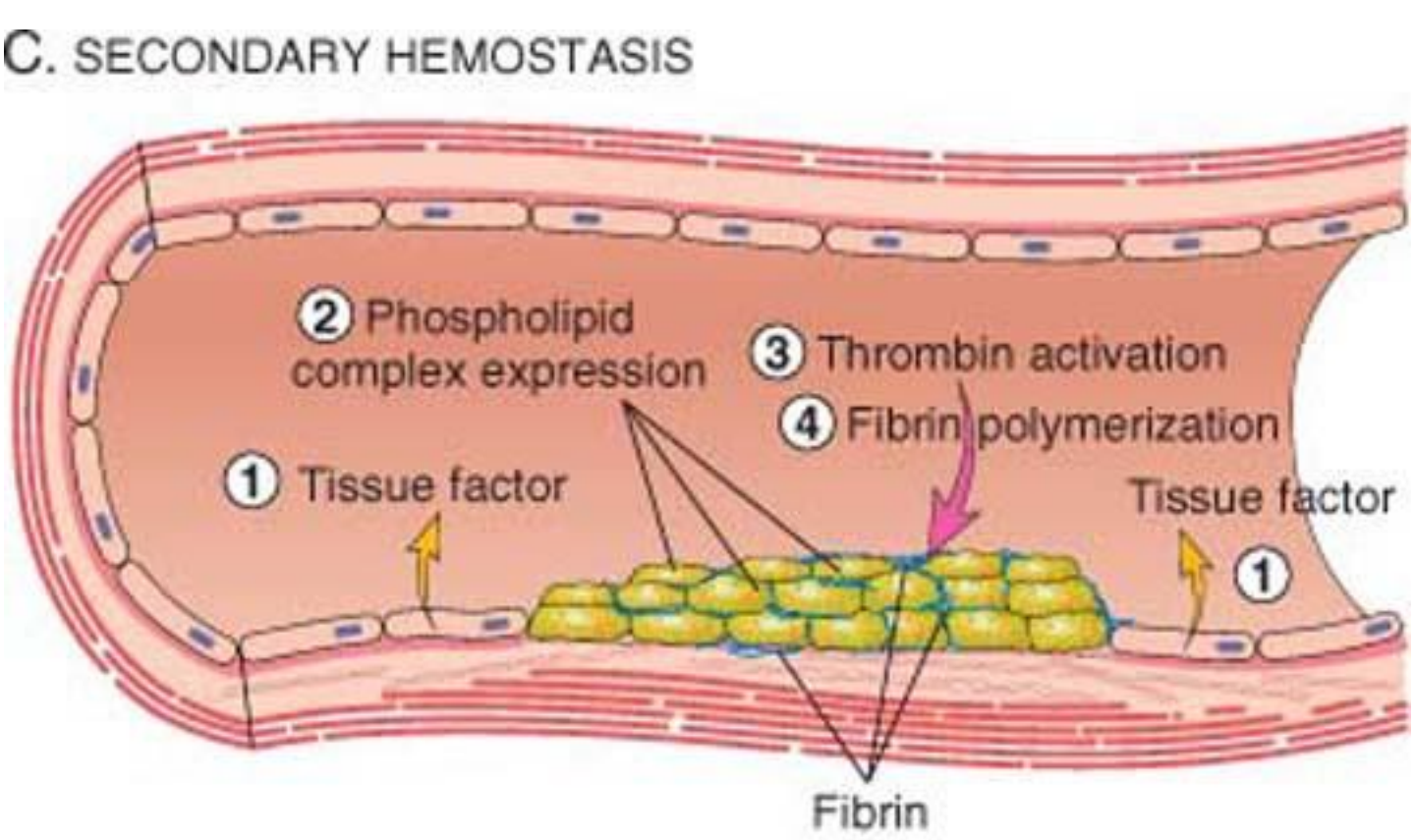
- **Coagulation Factors:**
  - Coagulation occurs via the sequential enzymatic conversion of a cascade of circulating and locally synthesized proteins
  - Tissue factor elaborated at sites of injury is the most important initiator of the coagulation cascade
  - At the final stage of coagulation, thrombin converts fibrinogen into insoluble fibrin, which helps to form the definitive hemostatic plug
  - Coagulation is normally constrained to sites of vascular injury by:
    - Limiting enzymatic activation to phospholipid complexes provided by activated platelets
    - Natural anticoagulants elaborated at sites of endothelial injury or during activation of the coagulation cascade
    - Induction of fibrinolytic pathways involving plasmin through the activities of various PAs



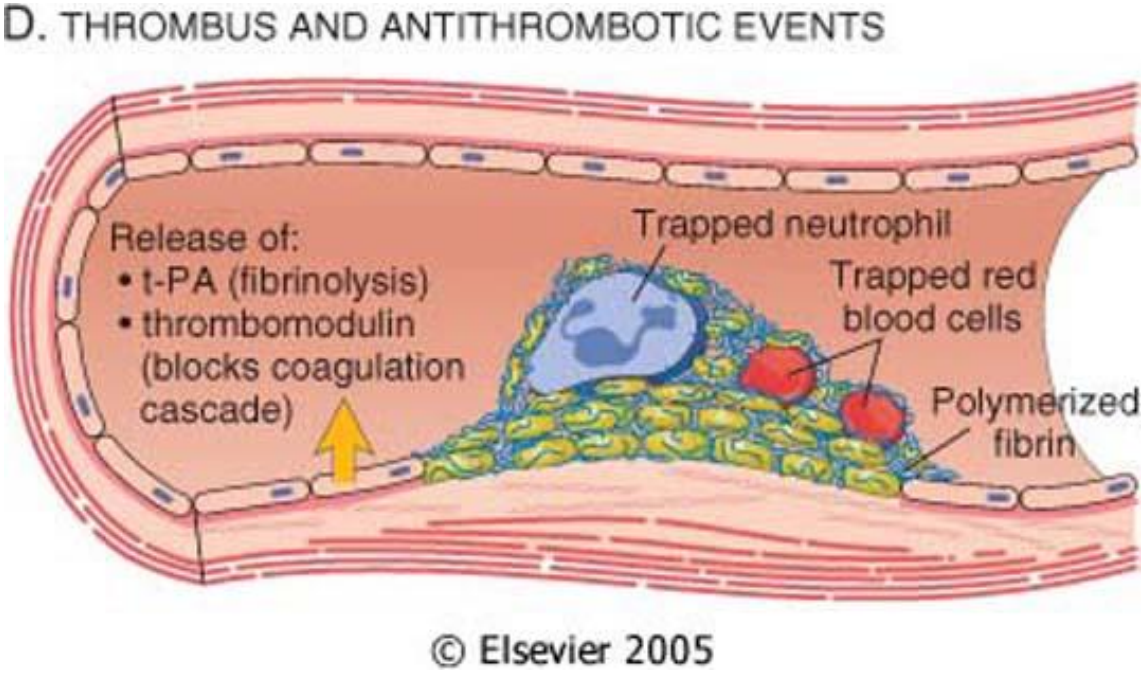
- After vascular injury, local neurohumoral factors induce a transient vasoconstriction



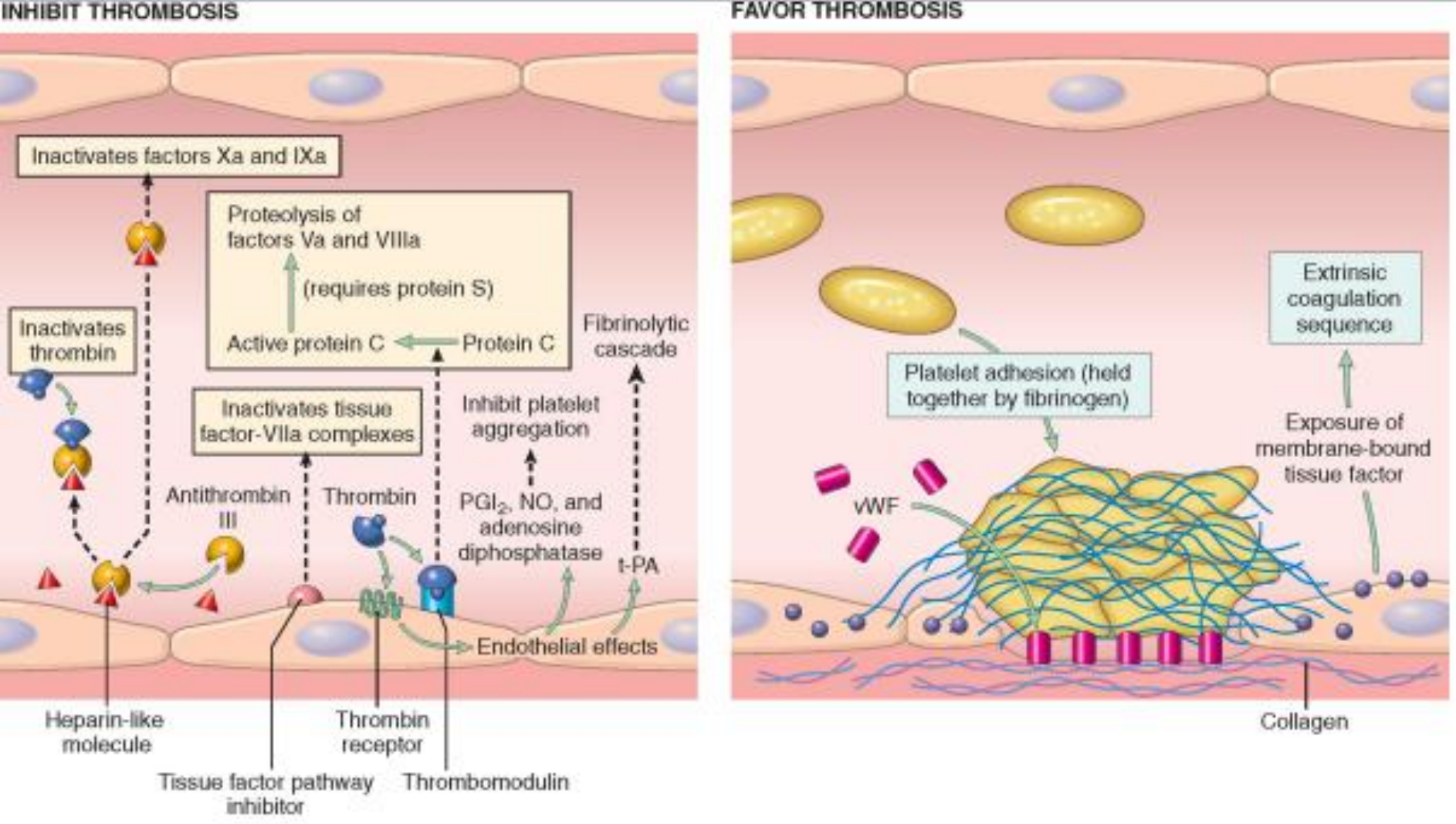
- Platelets adhere (via GpIb receptors) to exposed extracellular matrix (ECM) by binding to von Willebrand factor (vWF) and are activated, undergoing a shape change and granule release. Released adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2) lead to further platelet aggregation (via binding of fibrinogen to platelet GpIIb-IIIa receptors), to form the primary hemostatic plug.



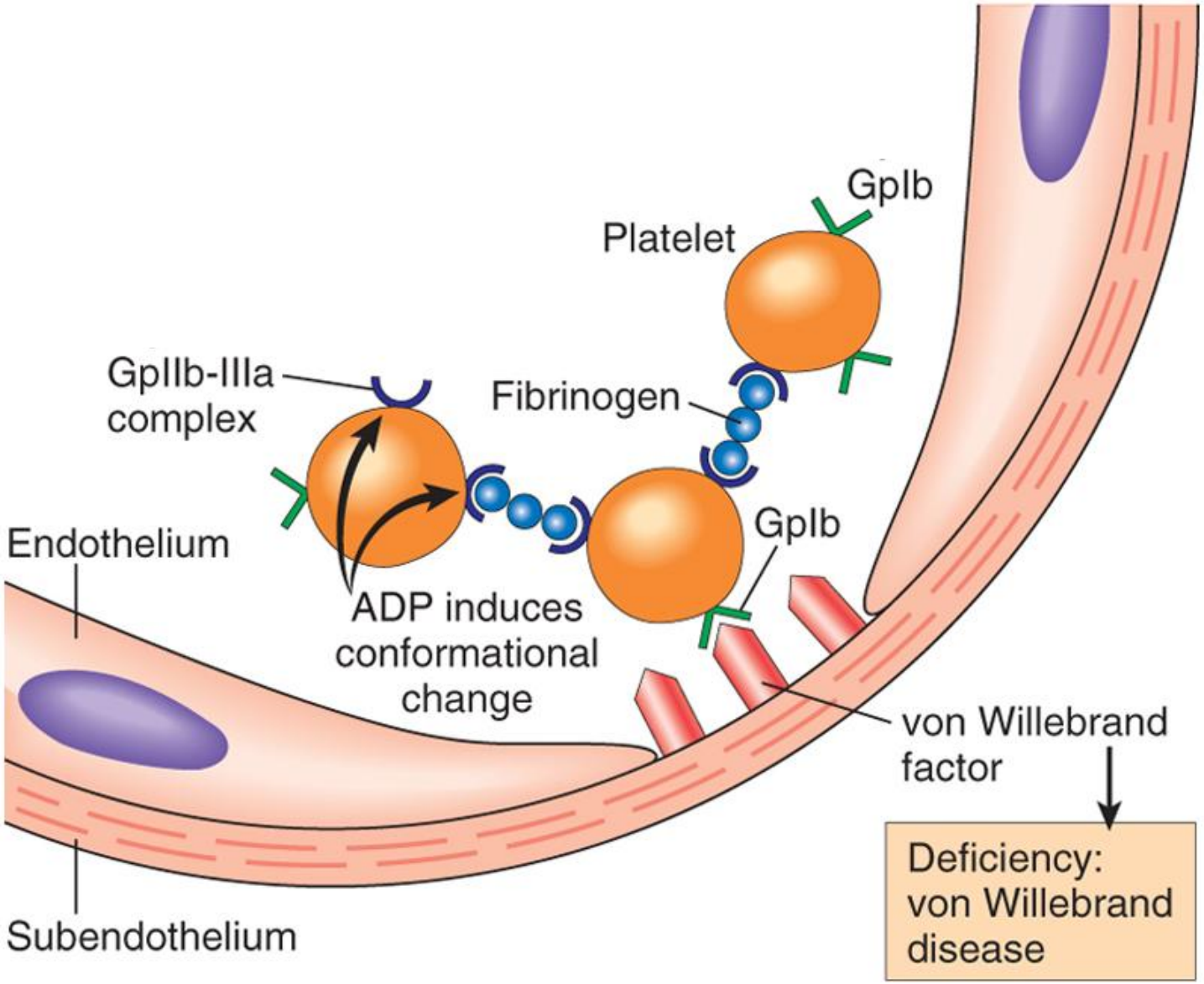
- Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing" the platelets into a definitive secondary hemostatic plug



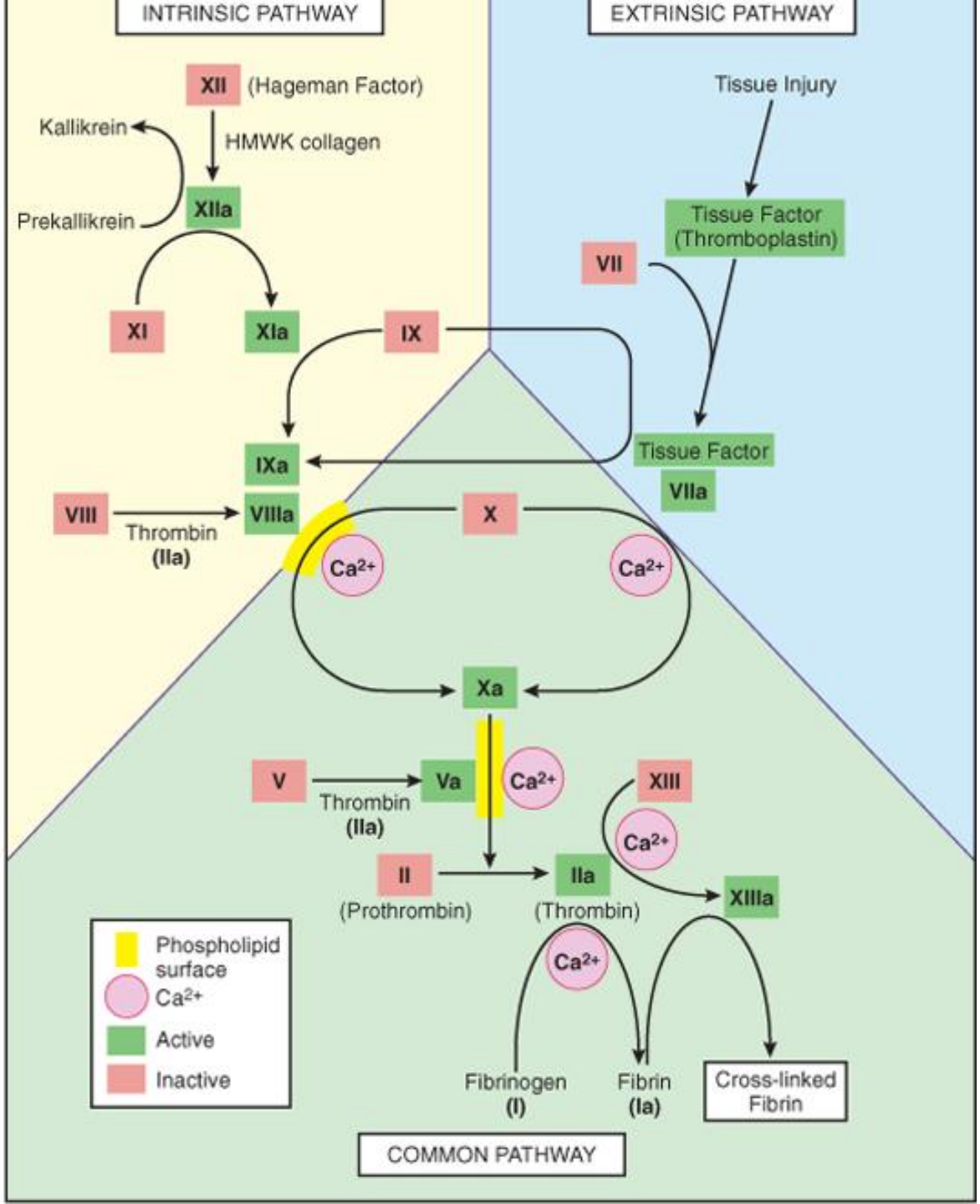
Counter-regulatory mechanisms, such as release of t-PA (tissue plasminogen activator, a fibrinolytic product) and thrombomodulin (interfering with the coagulation cascade), limit the hemostatic process to the site of injury



- *Additional reading*
  - Anti- and procoagulant activities of endothelium. NO, nitric oxide; PGI_2, prostacyclin; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. The thrombin receptor is also called a protease-activated receptor (PAR).

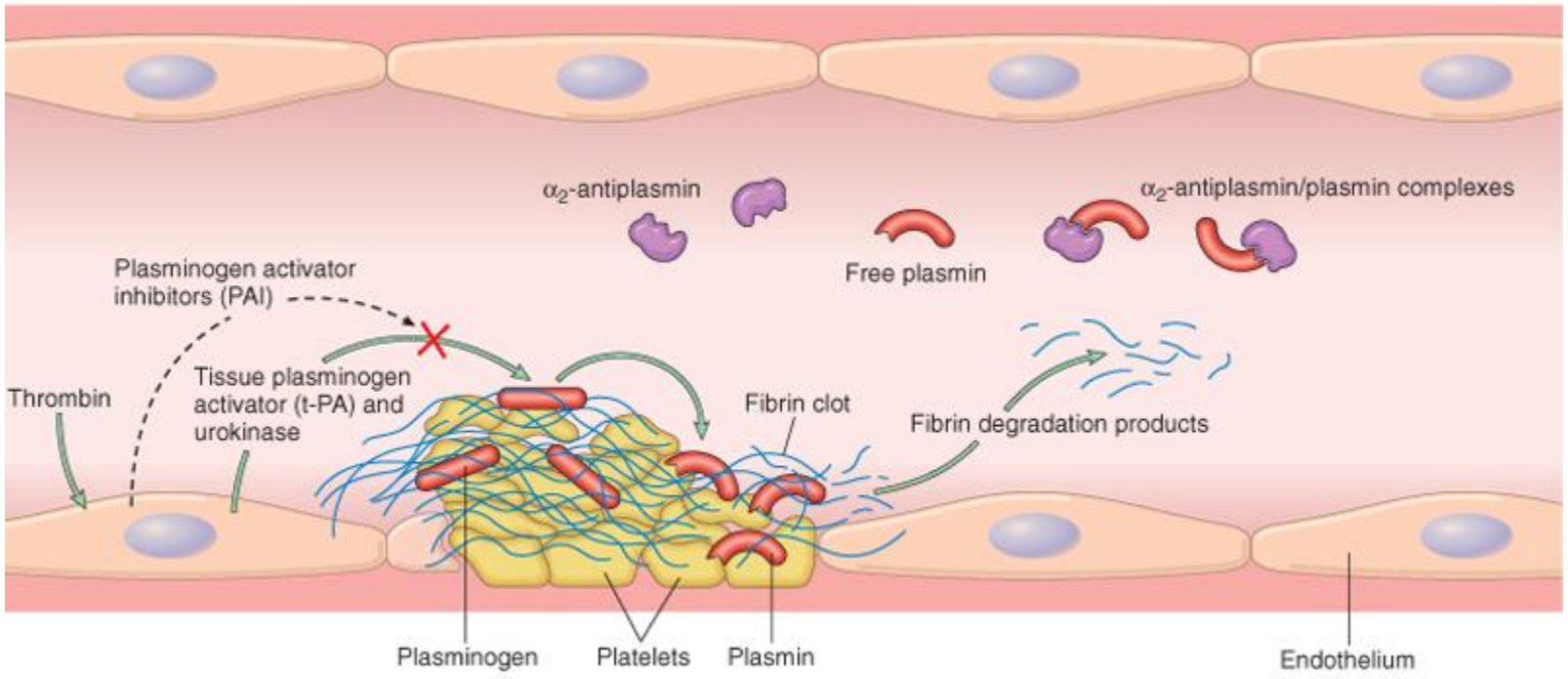


- Platelet adhesion and aggregation. Von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor. Aggregation is accomplished by binding of fibrinogen to platelet GpIIb-IIIa receptors and bridging many platelets together. ADP, adenosine diphosphate.



- The classical coagulation cascade. Note the common link between the intrinsic and extrinsic pathways at the level of factor IX activation. Factors in red boxes represent inactive molecules; activated factors are indicated with a lower-case *a* and a green box. HMWK, high-molecular-weight kininogen
- This reaction requires vitamin K as a cofactor

The details of the diagram is additional reading



- The fibrinolytic system, illustrating various plasminogen activators and inhibitors, major players include t-PA

HEMOSTASIS AND THROMBOSIS

- So formation and outcome of a thrombus:
  - Platelet plug + fibrin mesh → RBCs and other cells entrapped → the thrombus may →
    - Grow in layers in the direction of the blood (PROPAGATION)
    - Be removed by fibrinolysis
    - Be organized and recanalized
    - Embolize

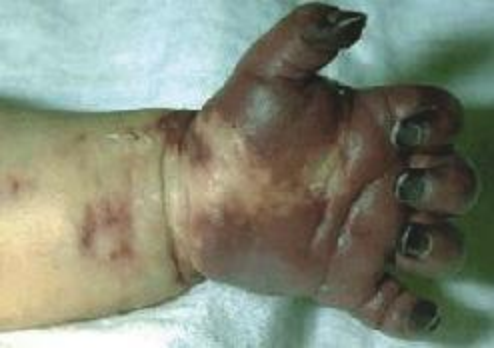
HEMOSTASIS AND THROMBOSIS

- **Factor V Leiden:**
  - an autosomal dominant condition which exhibits incomplete dominance
- In this disorder the Leiden variant of factor V cannot be inactivated by activated protein C
- The most common thrombophilic genotypes found in various populations
- Only a moderately increased risk of thrombosis (when otherwise healthy, patients are free of thrombotic complications)
- However, mutations in factor V and prothrombin are frequent enough that homozygosity and compound heterozygosity are not rare
  - individuals with such mutations have a significantly increased frequency of venous thrombosis in the setting of other acquired risk factors

Complete dominance occurs when the phenotype of the heterozygote is completely indistinguishable from that of the dominant homozygote

HEMOSTASIS AND THROMBOSIS

- ***Antiphospholipid antibody syndrome***
  - *Clinically, the findings include:*
    - recurrent thromboses
    - repeated miscarriages
    - cardiac valve vegetations
    - Thrombocytopenia
  - Fetal loss is attributable to antibody-mediated inhibition of t-PA activity necessary for trophoblastic invasion of the uterus
  - The name *antiphospholipid antibody syndrome* is a bit of a misnomer, as it is believed that the most important pathologic effects are mediated through binding of the antibodies to epitopes on plasma proteins (e.g., prothrombin) that are somehow induced or “unveiled” by phospholipids
  - Antiphospholipid antibody syndrome can be:
    - *primary*, only the manifestations of a hypercoagulable state and lack evidence of other autoimmune disorders
    - *Secondery*, Individuals with a well-defined autoimmune disease, such as SLE



HEMOSTASIS AND THROMBOSIS

- **DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**
  - Sudden or insidious onset of widespread fibrin thrombi in the microcirculation
  - Although these thrombi are not grossly visible, they are readily apparent microscopically
  - Can cause diffuse circulatory insufficiency, particularly in the brain, lungs, heart, and kidneys
  - It can evolve into a bleeding catastrophe:
    - platelet and coagulation protein consumption (hence the synonym *consumption coagulopathy*)
    - At the same time, fibrinolytic mechanisms are activated
  - *It should be emphasized that DIC is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin*

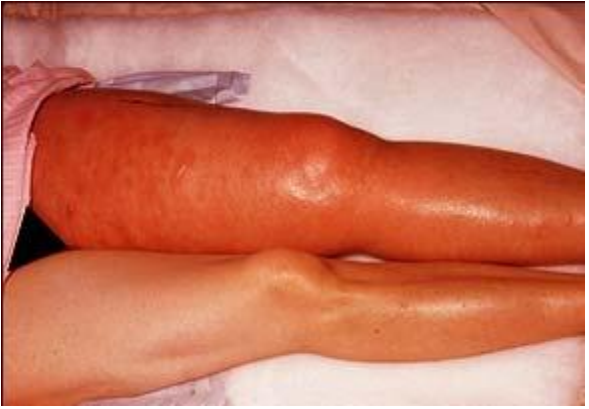
HEMOSTASIS AND THROMBOSIS
Thrombi

- Thrombi are focally attached to the underlying vascular surface
- Thrombi often have grossly and microscopically apparent laminations called **lines of Zahn** these represent pale platelet and fibrin deposits alternating with darker red cell–rich layers.
  - Such laminations signify that a thrombus has formed in flowing blood → indicate antemortem thrombsosis
  - **Postmortem clots** can sometimes be mistaken for antemortem venous thrombi:
    - gelatinous
    - Have a dark red dependent portion where red cells have settled by gravity and a yellow “chicken fat” upper portion
    - usually not attached to the underlying wall
  - In comparison, red thrombi are firmer and are focally attached, and sectioning typically reveals gross and/or microscopic lines of Zahn
- Thrombi on heart valves are called **vegetations**

HEMOSTASIS AND THROMBOSIS

- **Arterial thrombi:**
  - frequently occlusive
  - the most common sites in decreasing order of frequency are:
    - Coronary
    - Cerebral
    - Femoral
  - Although these are usually superimposed on a ruptured atherosclerotic plaque, other vascular injuries (vasculitis, trauma) may be the underlying cause.
  - Arterial or cardiac thrombi usually begin at sites of turbulence or endothelial injury

- **Venous thrombosis (phlebothrombosis):**
  - almost invariably occlusive
  - venous thrombi characteristically occur at sites of stasis
  - Because these thrombi form in the sluggish venous circulation, they tend to contain more enmeshed red cells (and relatively few platelets) and are therefore known as **red**, or **stasis, thrombi**
  - The veins of the lower extremities are most commonly involved (90% of cases)
  - Upper extremities, periprostatic plexus, or the ovarian and periuterine veins can also develop venous thrombi
  - Under special circumstances, they can also occur in the dural sinuses, portal vein, or hepatic vein.

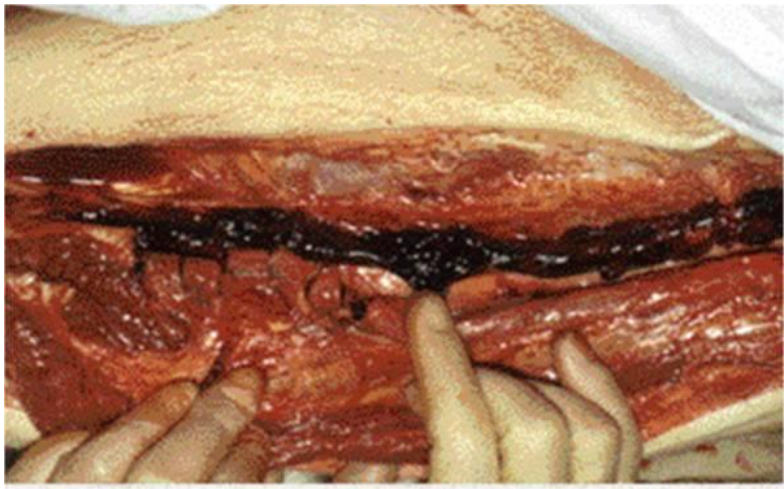


HEMOSTASIS AND THROMBOSIS

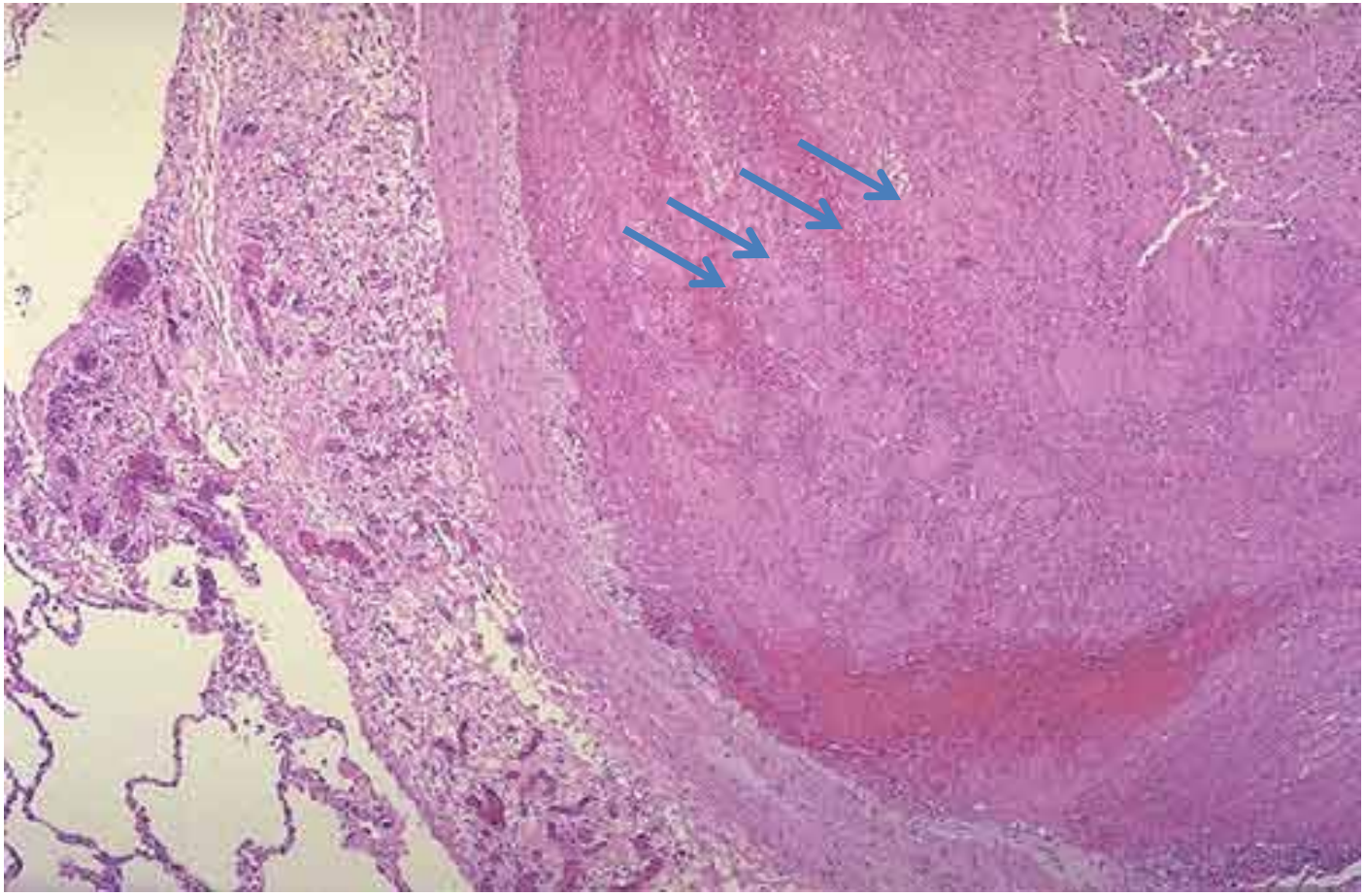
- ***Deep venous thrombosis (DVT):***
  - *in the larger leg veins—at or above the knee* (e.g., popliteal, femoral, and iliac veins)
  - such thrombi more often embolize to the lungs and give rise to pulmonary infarction
  - Although they can cause local pain and edema, venous obstructions from DVTs can be rapidly offset by collateral channels.
  - Consequently, DVTs are asymptomatic in approximately 50% of affected individuals and are recognized only in retrospect after embolization

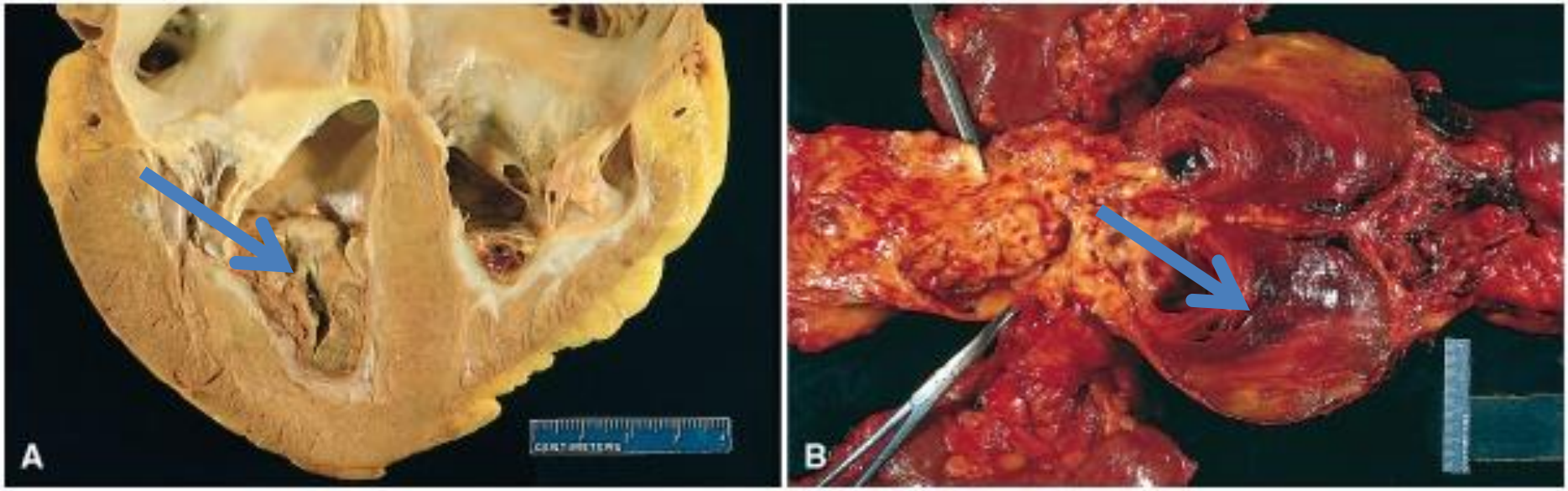
HEMOSTASIS AND THROMBOSIS

- **Common DVT** predisposing factors (these are included within the hypercoagulable statuse table):
  - **Bed rest and immobilization**
  - **Congestive heart failure** (a cause of impaired venous return)
  - **Trauma, surgery, and burns** (immobilize and are also associated with vascular insults, procoagulant release from injured tissues, increased hepatic synthesis of coagulation factors, and altered t-PA production)
  - **Preganancy**:
    - the potential for amniotic fluid infusion into the circulation at the time of delivery
    - late pregnancy and the postpartum period are also associated with systemic hypercoagulability
  - **Tumors**:
    - associated inflammation and coagulation factors (tissue factor, factor VIII)
    - procoagulants (e.g., mucin) release
  - **Advanced age:**
    - Regardless of the specific clinical setting



Lines of Zahn





- Mural thrombi. **A**, Thrombus in the left and right ventricular apices, overlying white fibrous scar. **B**, Laminated thrombus in a dilated abdominal aortic aneurysm. Numerous friable mural thrombi are also superimposed on advanced atherosclerotic lesions of the more proximal aorta *(left side of picture)*.