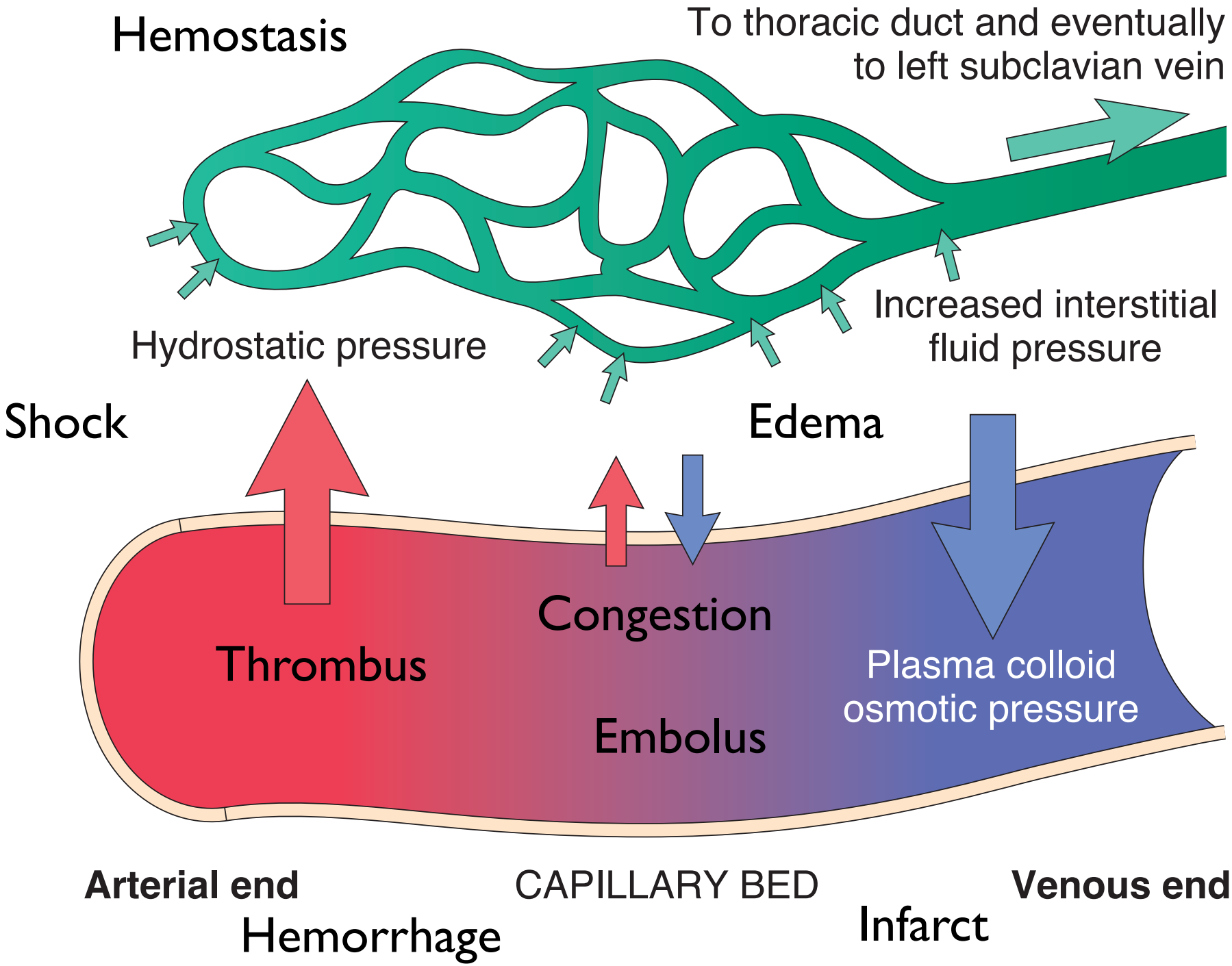
Fluid & Hemodynamic Derangements I & II

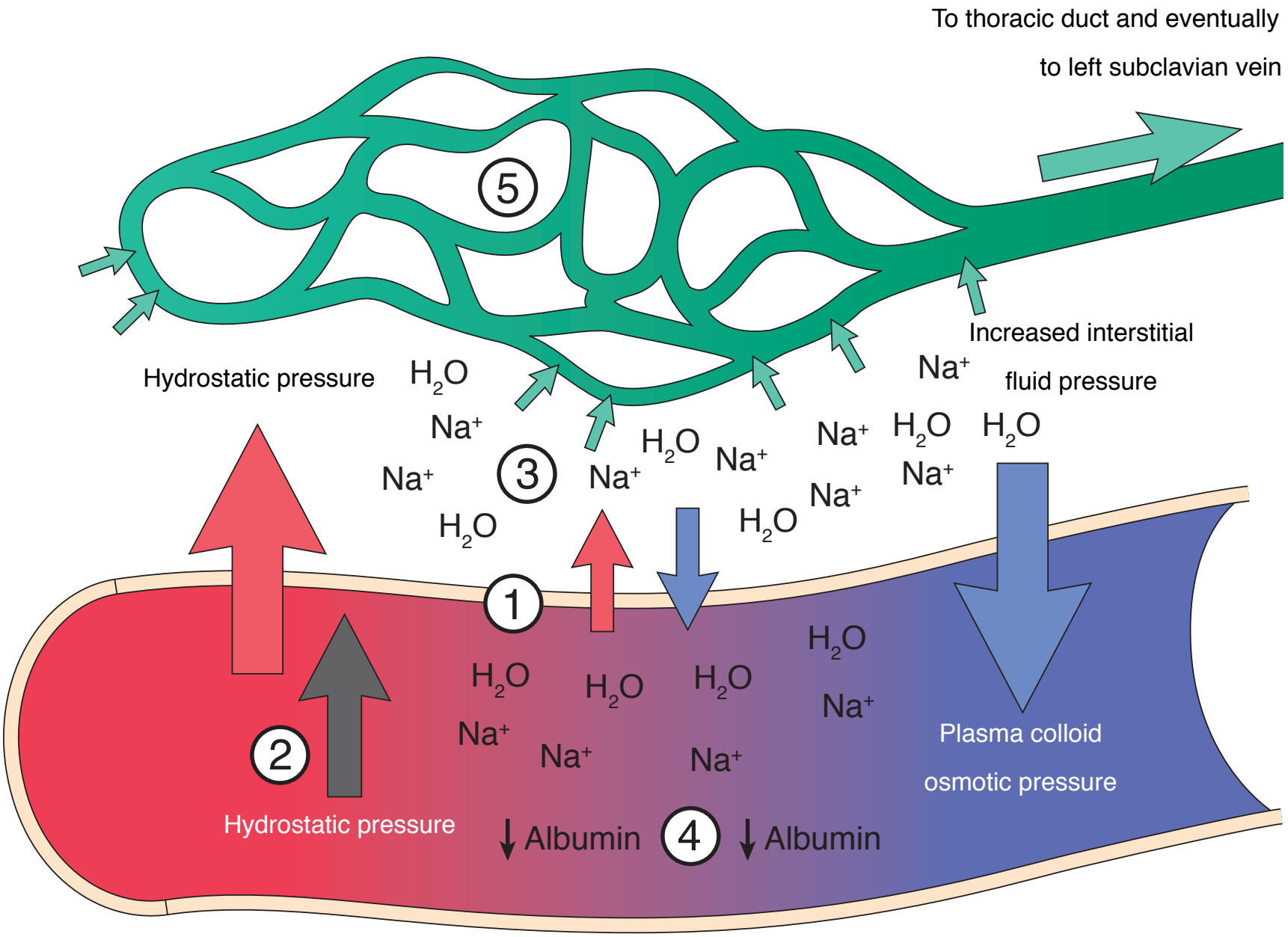
Dr. Henry Sánchez, M.D.


Hemostasis
To thoracic duct and eventually to left subclavian vein
Hydrostatic pressure
Increased interstitial fluid pressure
Shock
Edema
Congestion
Thrombus
Embolus
Plasma colloid osmotic pressure
Arterial end
CAPILLARY BED
Venous end
Hemorrhage
Infarct

Edema

- Injury to endothelial cells/blood vessel wall
- Increase hydrostatic pressure
- Increase interstitial sodium
- Decrease colloid osmotic pressure (albumin)
- Lymphatic obstruction

Edema Formation

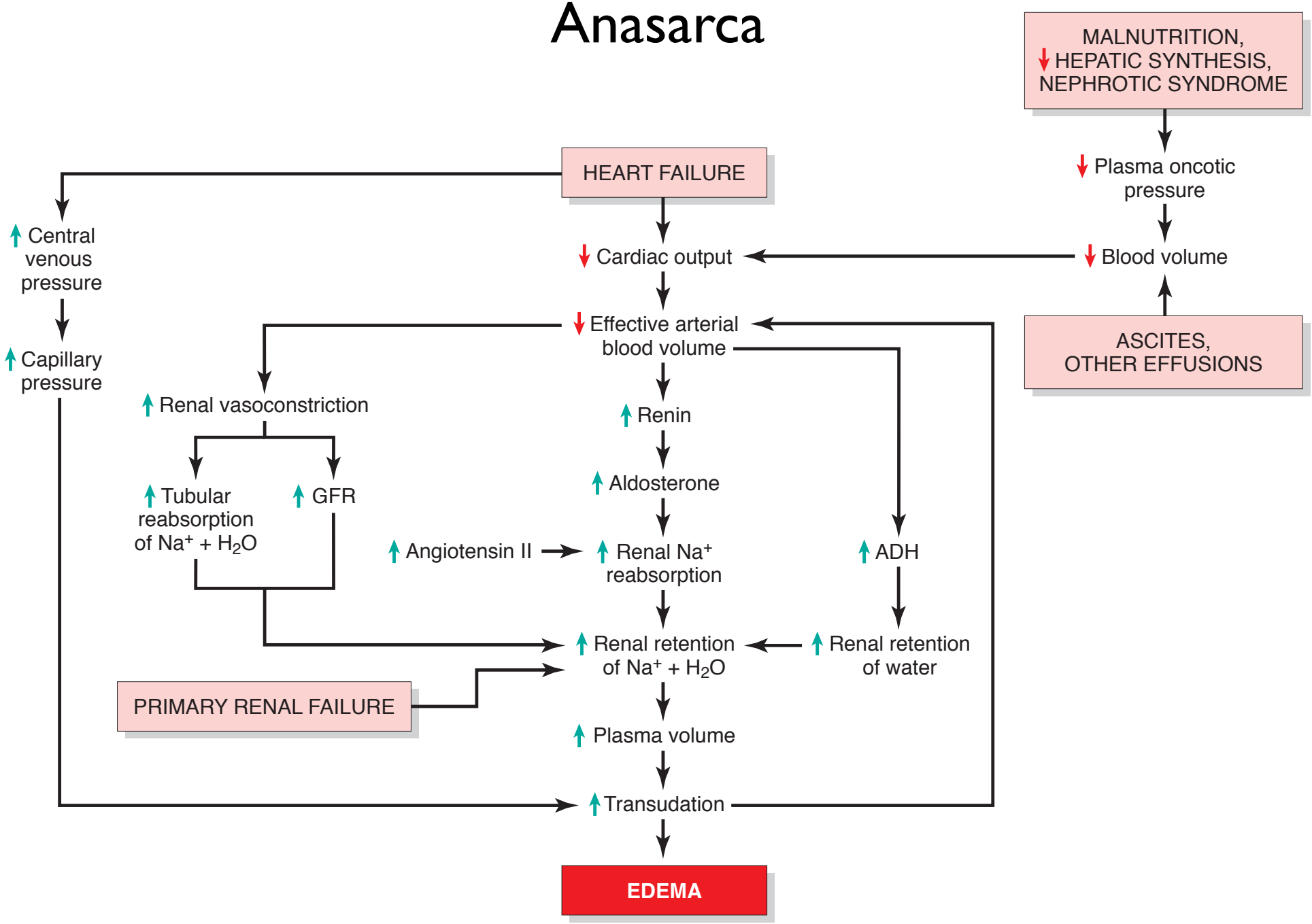


Arterial end CAPILLARY BED **Venous end**

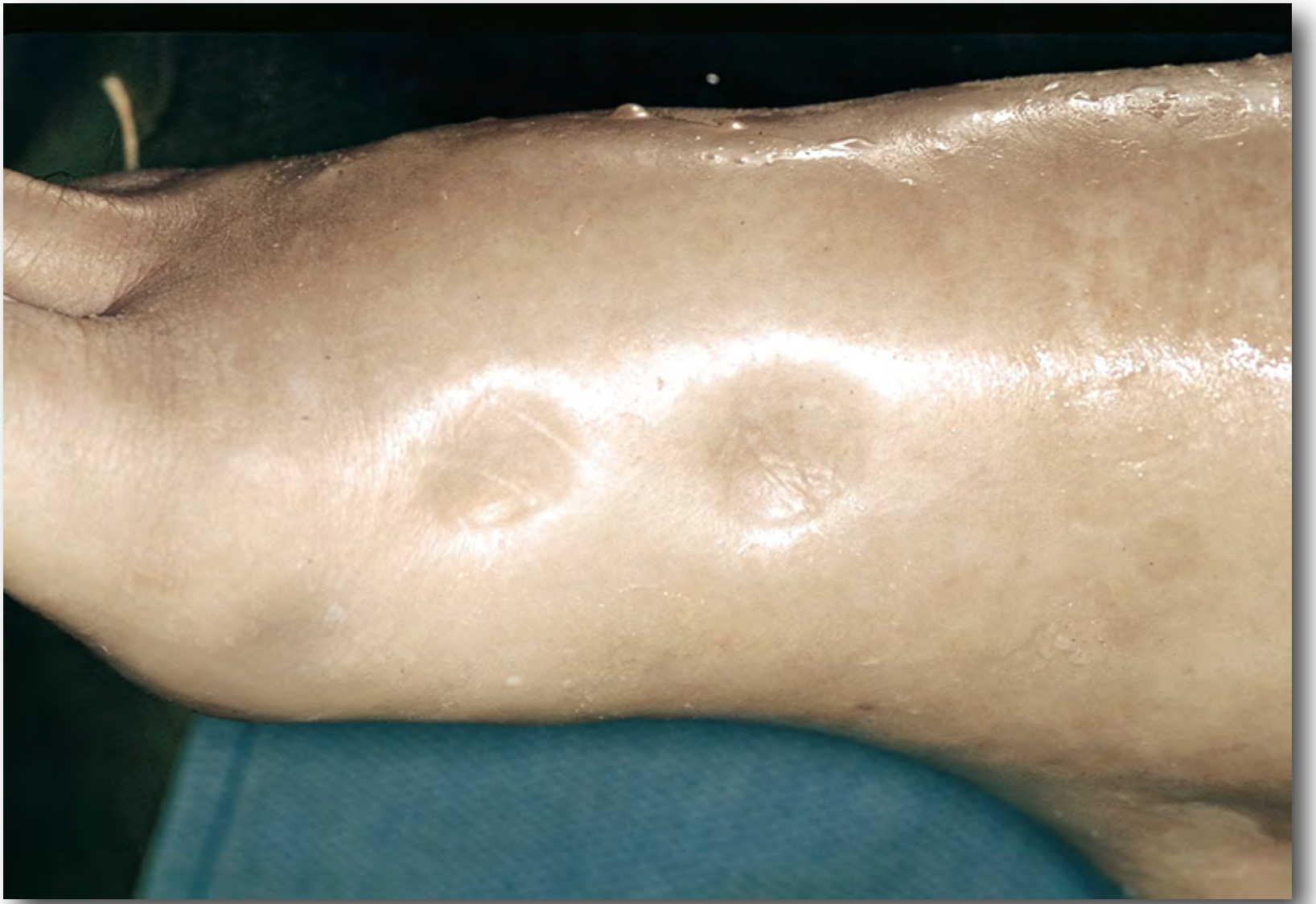
Edema

- Local
  - Acute inflammation, urticaria, venous thrombosis, left-sided heart failure
- Systemic (Anasarca)
  - Heart - congestive heart failure
  - Liver - cirrhosis
  - Kidney - nephrotic syndrome
  - Iatrogenic - fluid resuscitation

Anasarca


MALNUTRITION,
↓ HEPATIC SYNTHESIS,
NEPHROTIC SYNDROME
↓ Plasma oncotic pressure
↓ Blood volume
ASCITES,
OTHER EFFUSIONS
HEART FAILURE
↑ Central venous pressure
↑ Capillary pressure
↓ Cardiac output
↓ Effective arterial blood volume
↑ Renal vasoconstriction
↑ Renin
↑ Aldosterone
↑ Tubular reabsorption of Na+ + H2O
↑ GFR
↑ Angiotensin II
↑ Renal Na+ reabsorption
↑ ADH
↑ Renal retention of Na+ + H2O
↑ Renal retention of water
PRIMARY RENAL FAILURE
↑ Plasma volume
↑ Transudation
EDEMA

Congestive Heart Failure



Pitting Edema

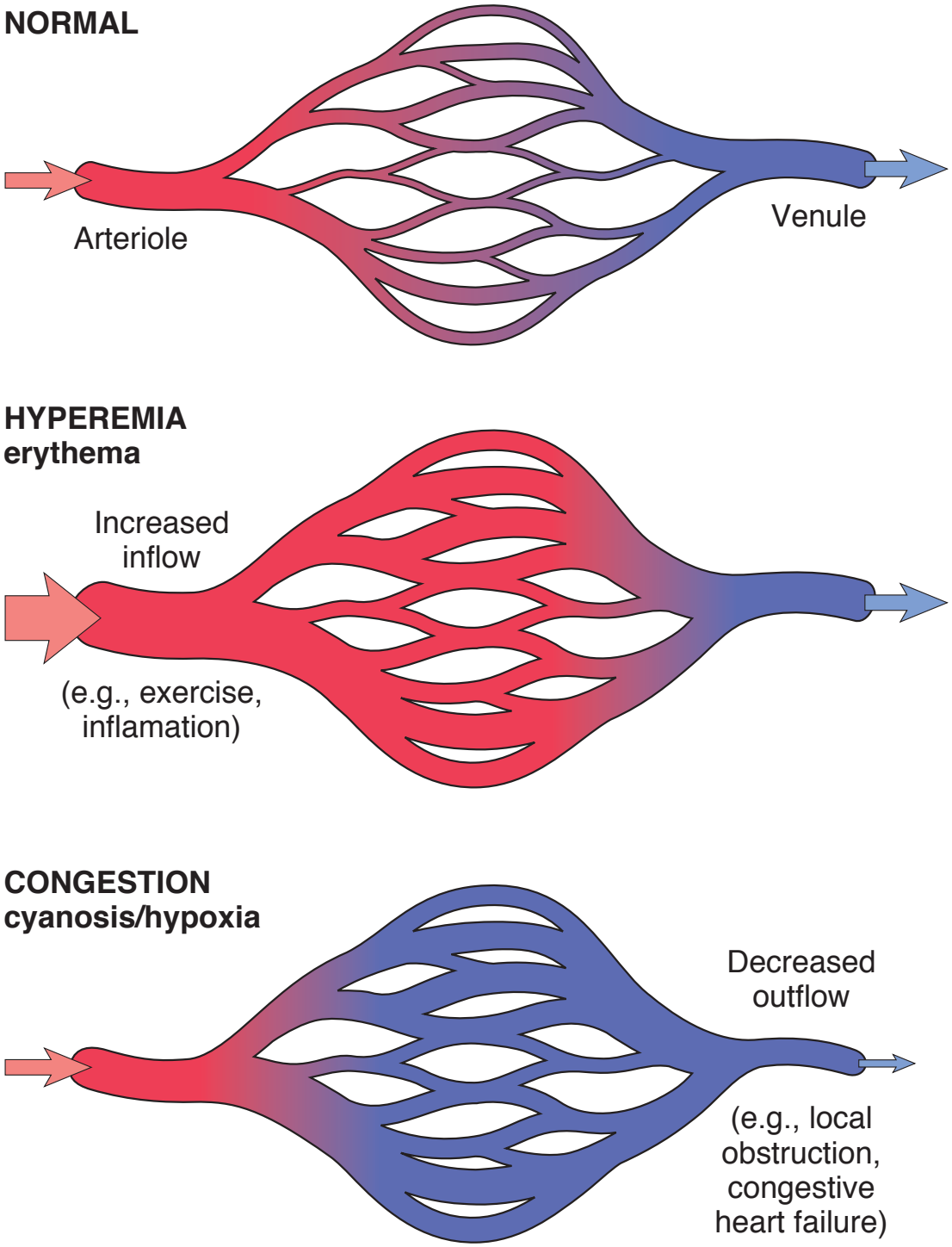
Circulation Pathology

- Effusion: fluid within the body cavities
- Transudate versus exudate
- Transudate - edema fluid with low protein content
  - Specific gravity <1.020
- Exudate - Edema fluid with high protein content and cells
  - Specific gravity >1.020
  - Types of exudates
    - Purulent (pus)
    - Fibrinous
    - Eosinophilic
    - Hemorrhagic

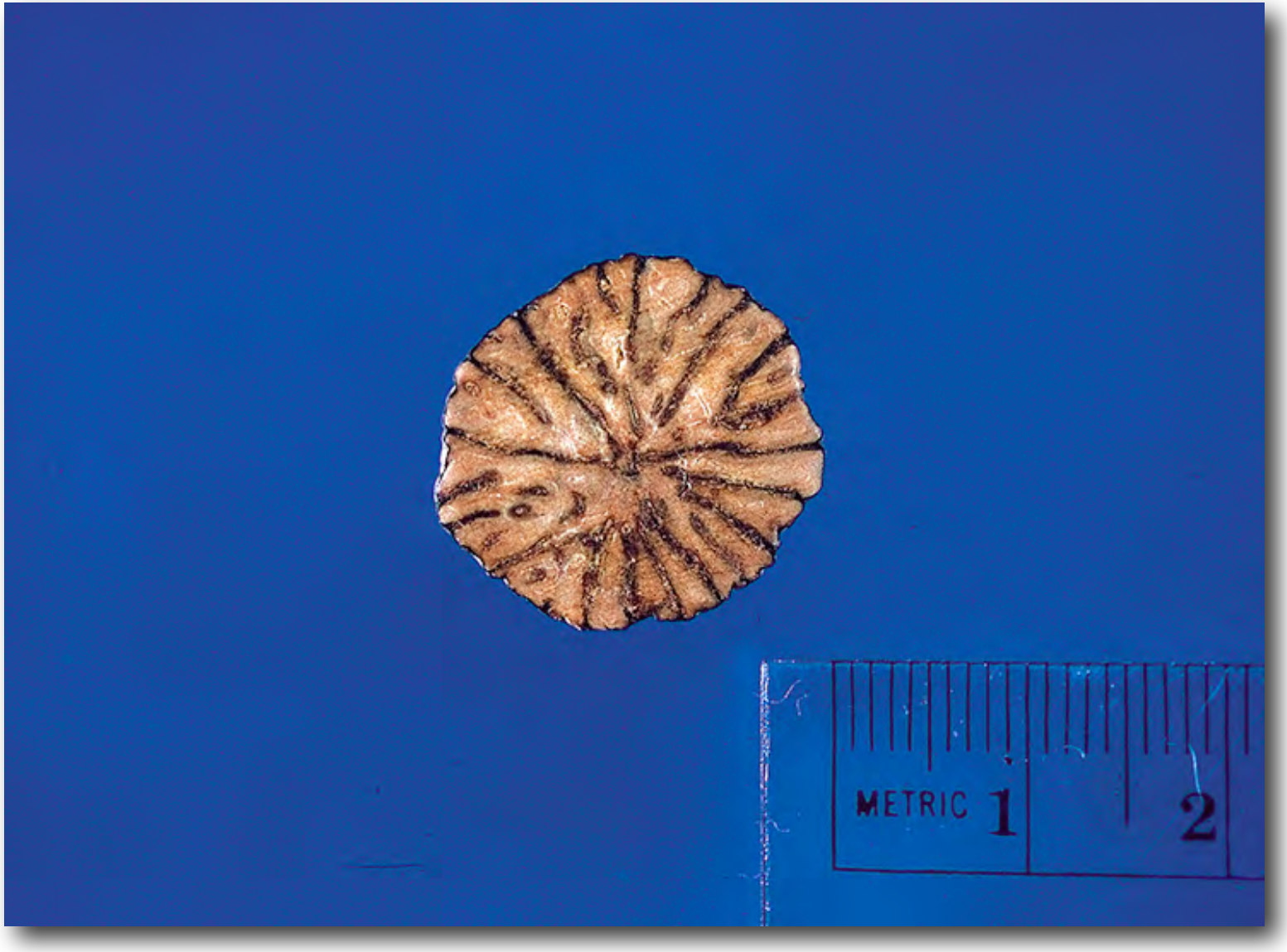
Congestion

- Definition: Dilated blood vessel
- Passive congestion (e.g., mechanical effect - congestive heart failure, venous thrombosis)
- Active congestion (hyperemia) - acute inflammation, hypersensitivity reaction type I

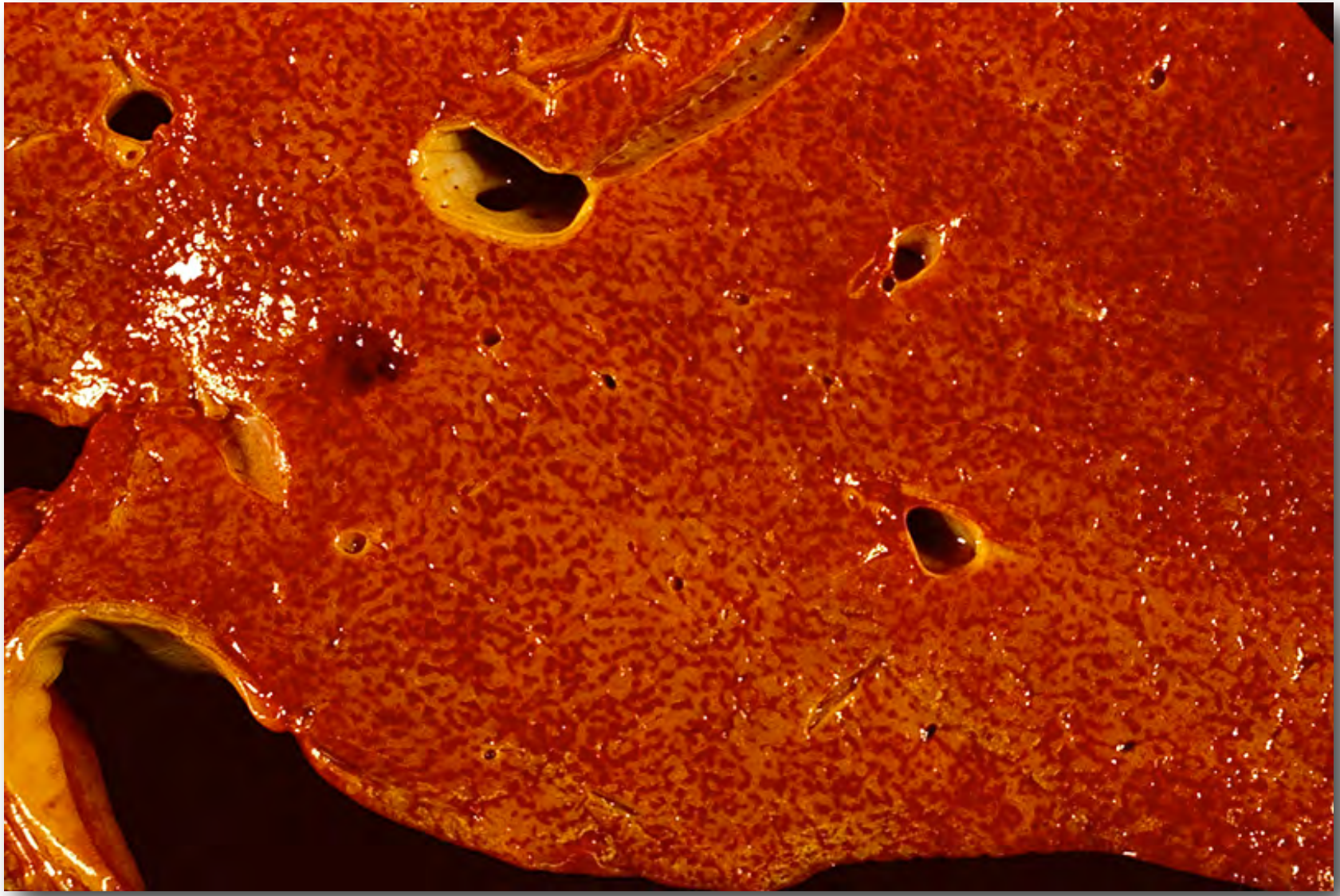
Congestion


NORMAL
Arteriole
Venule
HYPEREMIA
erythema
Increased
inflow
(e.g., exercise,
inflamation)
CONGESTION
cyanosis/hypoxia
Decreased
outflow
(e.g., local
obstruction,
congestive
heart failure)

Nutmeg

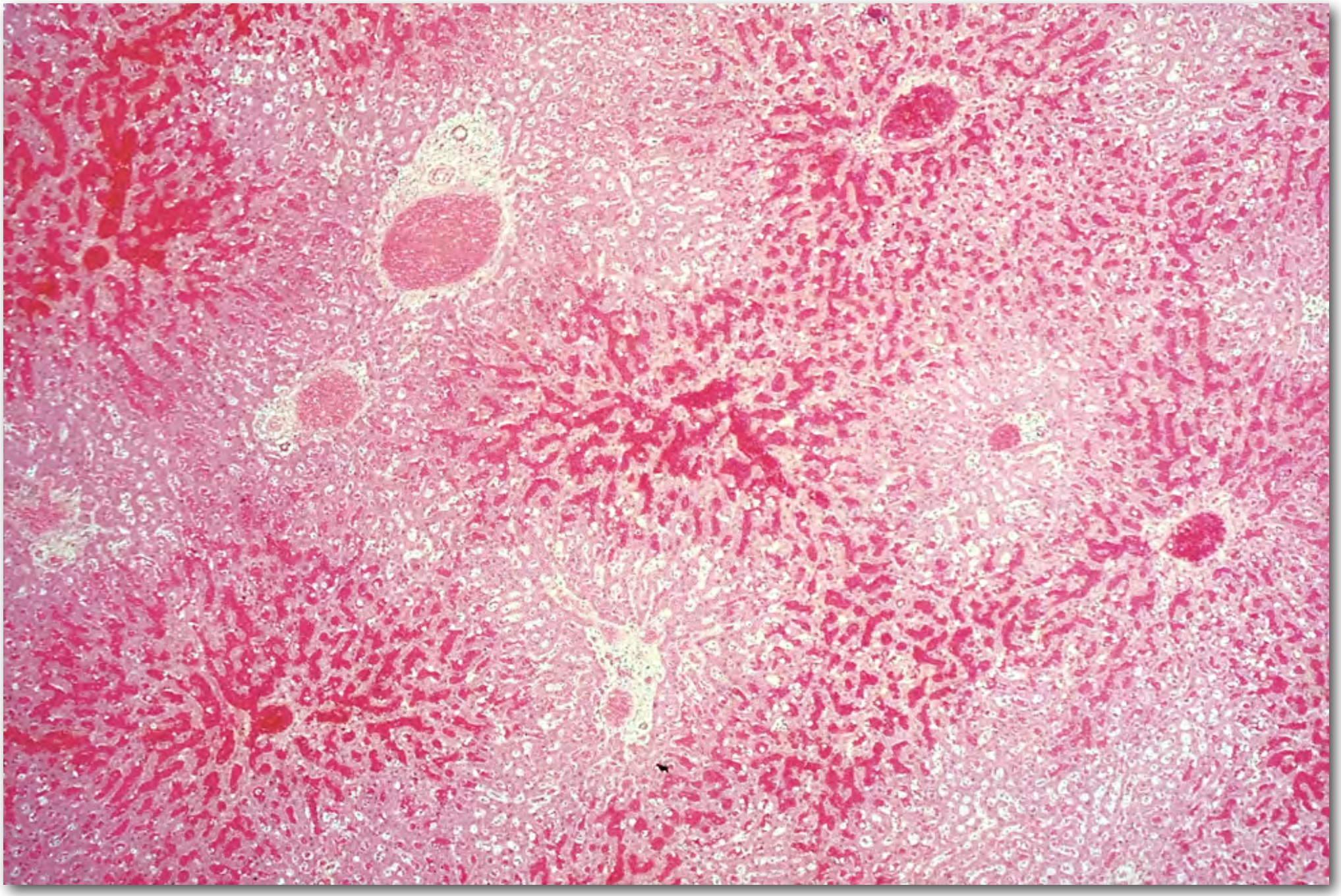


Chronic Passive Congestion



"Nutmeg liver"

Chronic Passive Congestion

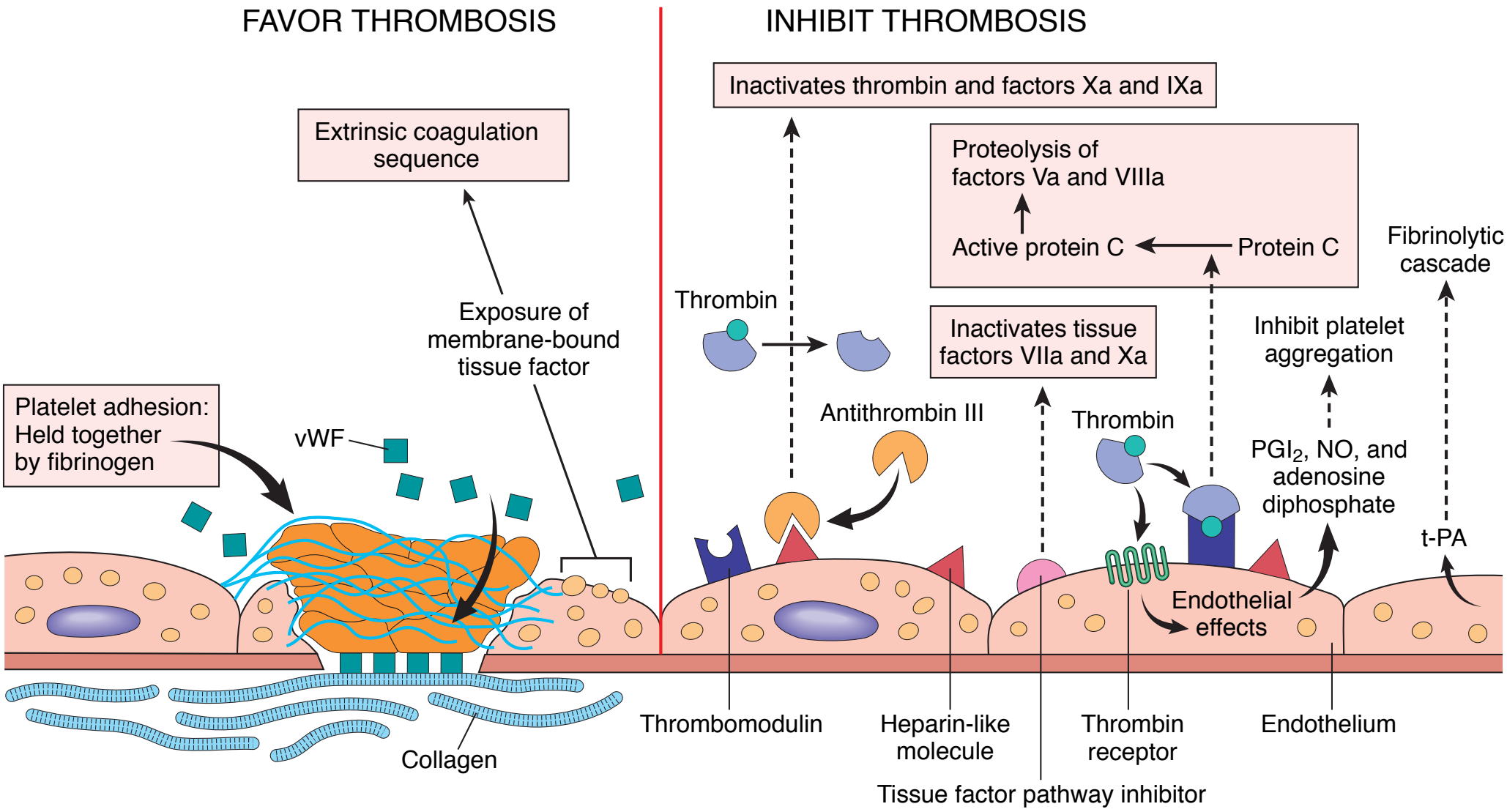


Hemostasis

- Definition: sequence of events leading to the cessation of bleeding by the formation of a stable fibrin-platelet hemostatic plug
- Vascular Wall
- Platelets
- Coagulation cascade

Hemostasis

- Vascular Wall
  - Endothelial lining - endothelial cells contain:
    - Potent thrombogenic factors - tissue factor (tissue thromboplastin), von Willebrand's factor causing platelet adhesion to subendothelial collagen, thromboxane A_2
    - Anti-thrombogenic substances - tissue plasminogen activator, anti-platelet aggregating prostaglandin (prostacyclin - PGI_2), thrombomodulin (binds thrombin and activates protein C (cofactor protein S) leading to enzymatic cleavage of activated factors Va and VIIIa, nitric oxide


FAVOR THROMBOSIS
INHIBIT THROMBOSIS
Inactivates thrombin and factors Xa and IXa
Extrinsic coagulation sequence
Proteolysis of factors Va and VIIIa
Active protein C
Protein C
Fibrinolytic cascade
Thrombin
Exposure of membrane-bound tissue factor
Inactivates tissue factors VIIa and Xa
Inhibit platelet aggregation
Platelet adhesion: Held together by fibrinogen
vWF
Antithrombin III
Thrombin
PGI2, NO, and adenosine diphosphate
t-PA
Endothelial effects
Thrombomodulin
Heparin-like molecule
Thrombin receptor
Endothelium
Collagen
Tissue factor pathway inhibitor

Hemostasis

- Vascular Wall
  - Subendothelial connective tissue
  - Promotes platelet adherence and release reactions

Hemostasis

- Vascular Wall
  - Muscular layer
    - Constriction of blood vessels induced by pain reflexes and vasoactive amines (histamine and serotonin)
    - Dependent upon the amount of muscular tissue composing the vascular wall

Hemostasis

- Platelets
  - Circulating platelets = 150k to 400k per mm3
  - Derived from megakaryocytes in the bone marrow
  - Thrombocytopenia = decreased number of platelets
    - Decreased production
    - Increased destruction

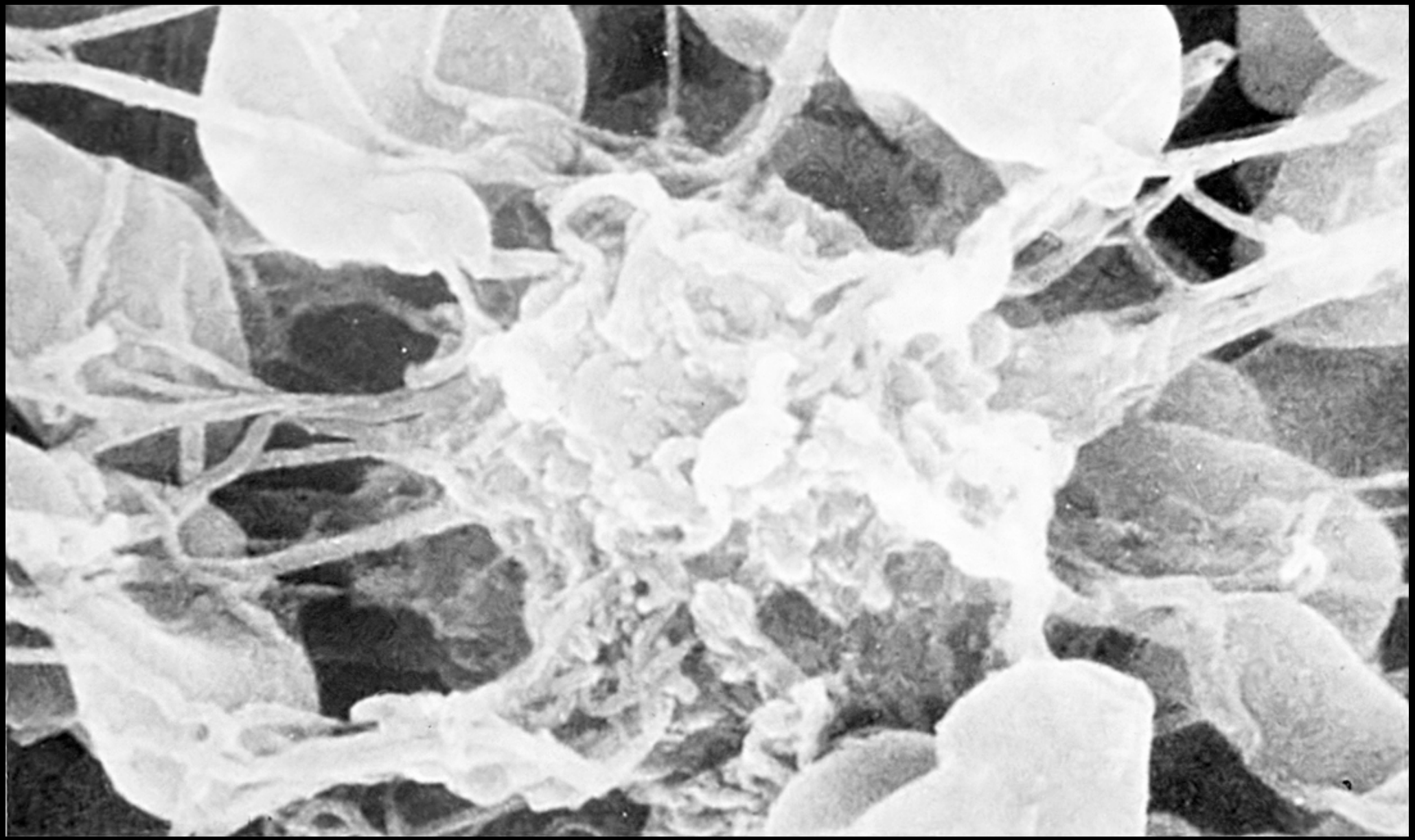
Platelets

- Derived from megakaryocytes in the bone marrow
- Step 1: platelet adhesion
  - First vWF adheres to subendothelial collagen
  - Platelets then adhere to vWF by glycoprotein Ib
- Step 2: platelet activation
  - Platelets undergo a shape change and degranulation occurs
  - Platelet synthesis of thromboxane A2
  - Membrane expression of the phospholipid complex, which is an important platform for the coagulation cascade
- Step 3: platelet aggregation
  - Additional platelets are recruited from the blood stream ADP and thromboxane A2 are potent mediators of aggregation
  - Platelets bind to each other by binding to fibrinogen using Gp IIb-IIIa

Table 5-2. Contents of Platelet Alpha Granules and Dense Bodies

Alpha Granules	Dense Bodies
• Fibrinogen	• ADP (potent platelet aggregator)
• Fibronectin	• Calcium
• Factor V and vWF	• Histamine and serotonin
• Platelet factor 4	• Epinephrine
• Platelet-derived growth factor (PDGF)	

Fibrin-Platelet Thrombus

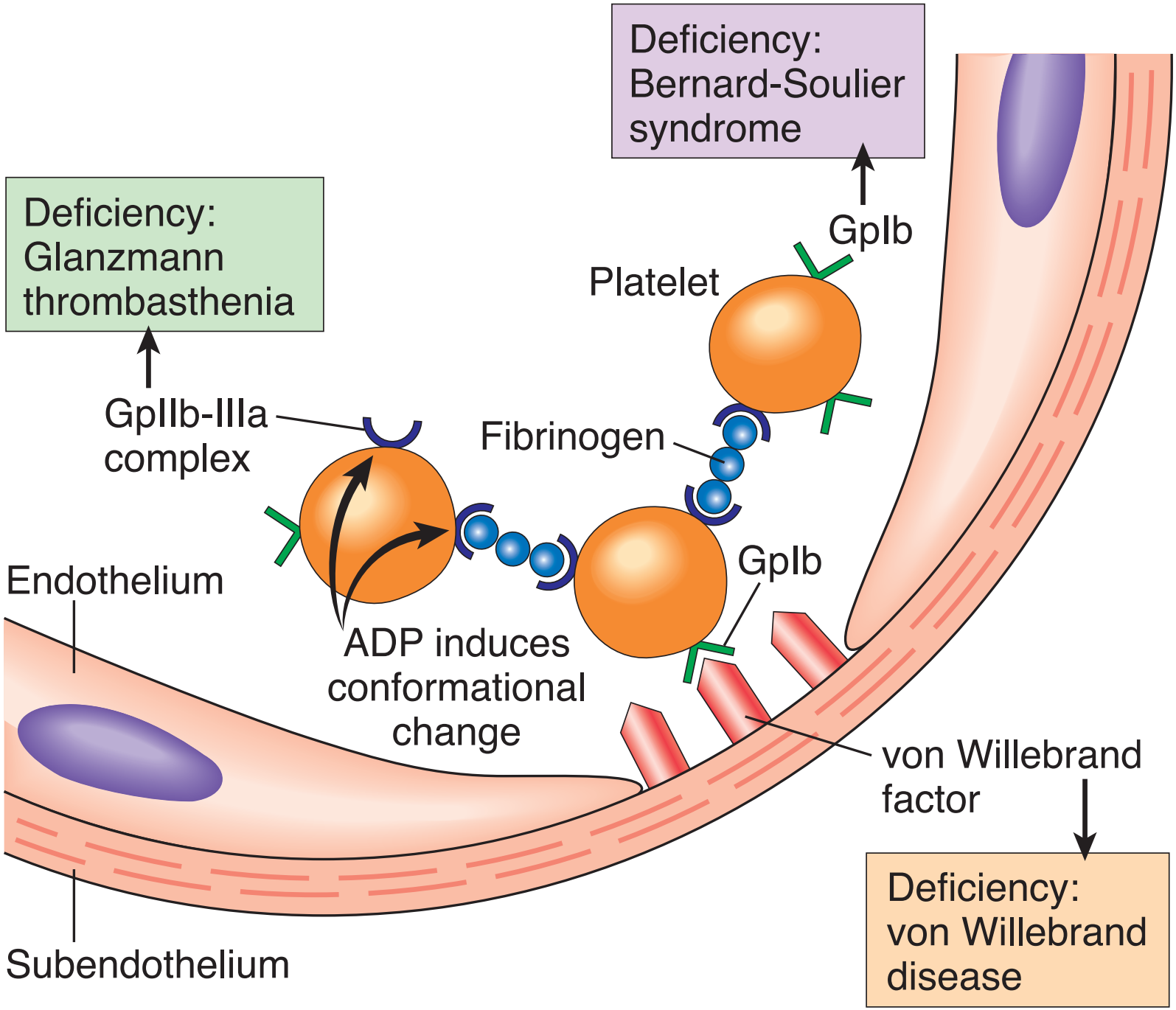


Laboratory Tests for Platelets

- Platelet count (normal 150 to 400K/mm^3)
- Bleeding time test (normal 2 to 7 minutes)
- Platelet aggregometry

Table 5-3. Common Platelet Disorders

Thrombocytopenia	Qualitative Defects
Decreased production • Aplastic anemia (drugs, virus, etc.) • Tumor	• von Willebrand disease • Bernard-Soulier syndrome • Glanzmann thrombasthenia • Drugs (aspirin) • Uremia
Increased destruction • Immune thrombocytopenia (ITP) • Thrombotic thrombocytopenia purpura (TTP) • Disseminated intravascular coagulation (DIC) • Hypersplenism	


Deficiency:
Bernard-Soulier
syndrome
GpIb
Platelet
Deficiency:
Glanzmann
thrombasthenia
GpIIb-IIIa
complex
Fibrinogen
GpIb
Endothelium
ADP induces
conformational
change
von Willebrand
factor
Deficiency:
von Willebrand
disease
Subendothelium

Hemostasis

- Laboratory Tests for Platelets
  - Bleeding time = skin puncture (normal range: 2-7 minutes)
  - Platelet count (normal range: 150k to 400k per mm^3)

Immune Thrombocytopenia Purpura (ITP)

- Etiology
  - Antiplatelet antibodies against platelet antigens such as Gp IIb-IIIa and Gp Ib-IX
  - Antibodies are made in the spleen
  - Platelets are destroyed peripherally in the spleen by macrophages, which have Fc receptors that bind IgG-coated platelets

Purpura (“purple”)

Immune Thrombocytopenia Purpura (ITP)

- Forms of ITP
  - Acute ITP
    - Seen in children following a viral infection
    - Self-limited disorder
  - Chronic ITP
    - Usually seen in women in their childbearing years
    - May be the first manifestation of systemic lupus erythematosus (SLE) and AIDS
    - Petechiae, ecchymoses, menorrhagia, and nosebleeds

Immune Thrombocytopenia Purpura (ITP)

- Lab
  - Decreased platelet count and prolonged bleeding time
  - Normal prothrombin time (PT) and partial thromboplastin time (PTT)
  - Peripheral blood smear shows thrombocytopenia with enlarged immature platelets (megathrombocytes)
  - Bone marrow biopsy shows increased numbers of megakaryocytes with immature forms

Immune Thrombocytopenia Purpura (ITP)

- Treatment
  - Corticosteroids, which decrease antibody production
  - Immunoglobulin therapy, which binds Fc receptors on splenic macrophages
  - Splenectomy, which removes the site of platelet destruction and antibody production

Thrombotic Thrombocytopenic Purpura (TTP)

- Pathology
  - Widespread formation of fibrin-platelet thrombi (hyaline thrombi)
  - Deficiency of a plasma metalloprotease (ADAMTS13)
- Clinical presentation
  - Most often affects adult women
  - Pentad of characteristic signs
    - Fever
    - Thrombocytopenia
    - Microangiopathic hemolytic anemia
    - Neurologic symptoms
    - Renal failure

Thrombotic Thrombocytopenic Purpura (TTP)

- Labs
  - Decreased platelet count and prolonged bleeding time
  - Normal PT and PTT
  - Peripheral blood smear shows thrombocytopenia and schistocytes, and reticulocytosis

Hemolytic Uremic Syndrome (HUS)

- Example of thrombotic microangiopathy
- Occurs most commonly in children
- Follows a gastroenteritis with bloody diarrhea
- Organism: verotoxin-producing *E. coli* 0157:H7
- Similar clinical pentad

Hemostasis

- Coagulation
  - Intravascular transformation of fluid blood into a gel matrix entrapping cellular constituents (red blood cells and white blood cells)

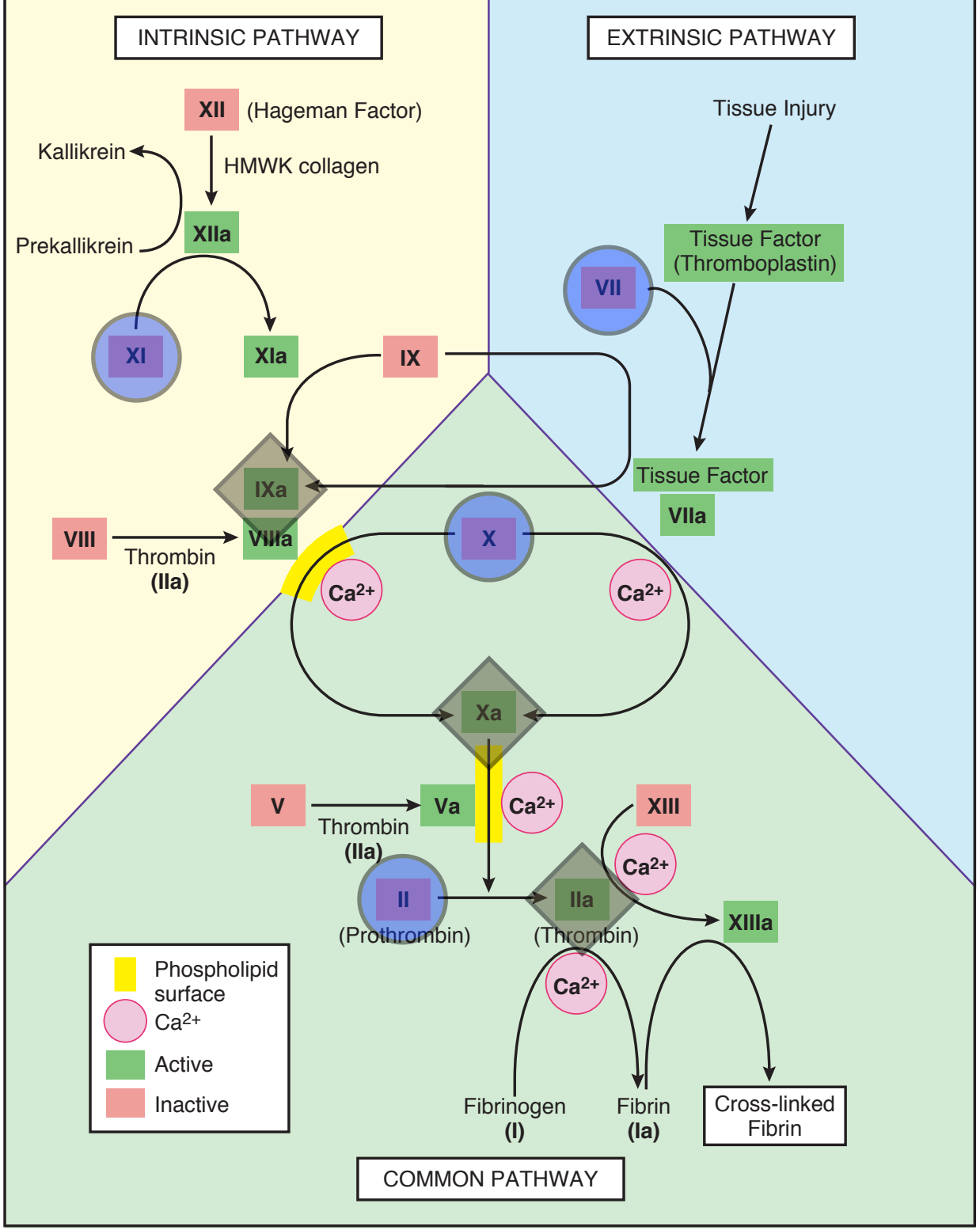
Hemostasis

- Coagulation
  - Intrinsic system
    - All substrates necessary for clotting are present within the circulating blood
    - Activated by contact with a foreign surface - usually collagen, Ag-Ab complexes, glass, etc.
    - Contact-sensitive protein is Hageman factor (factor XII)

Hemostasis

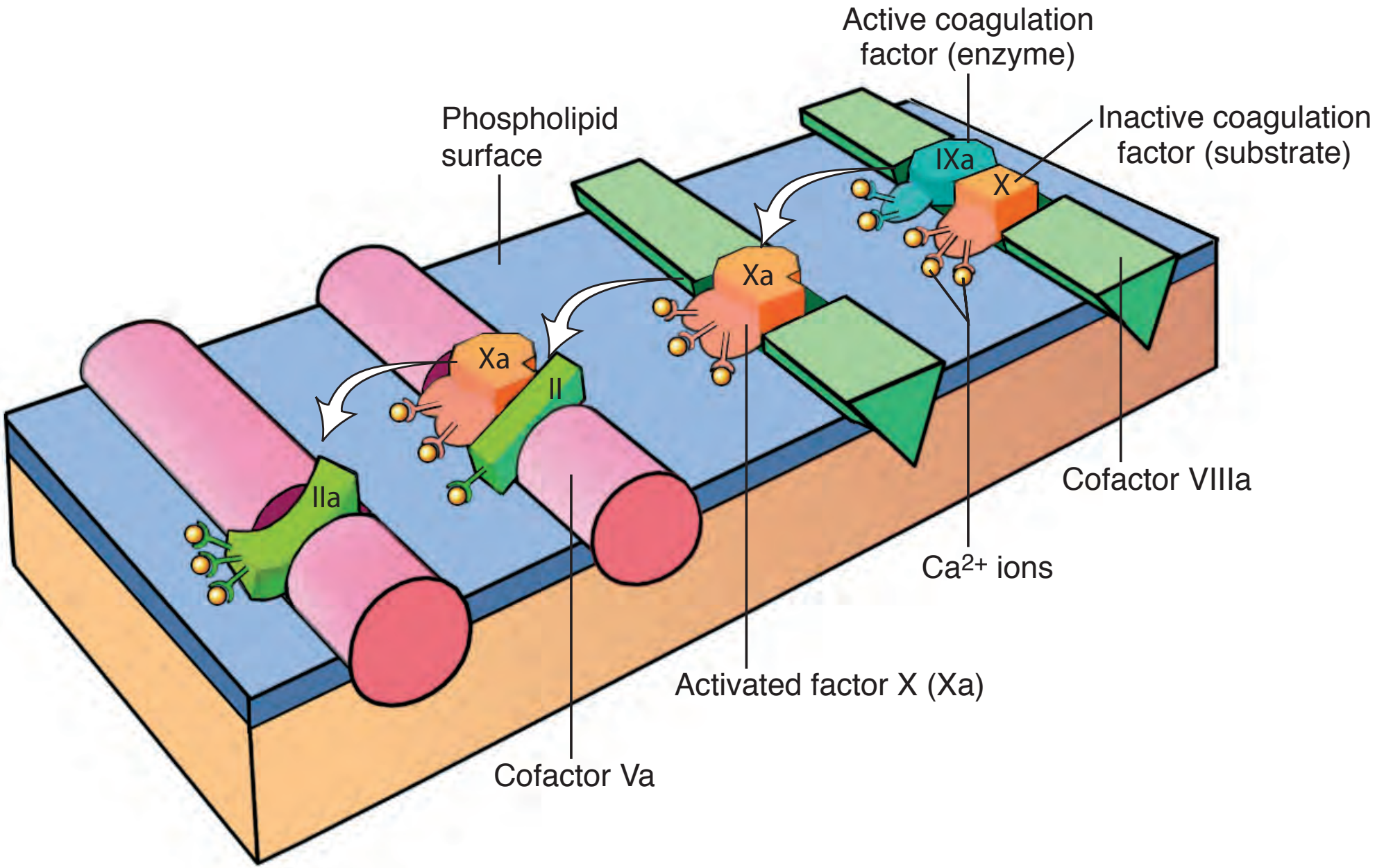
- Coagulation
  - Extrinsic system
    - After tissue injury, phospholipid protein complex (tissue thromboplastin) is released into the circulating blood
    - Activating the extrinsic pathway (inactive factor VII to active factor VII)

Coumadin



Heparin

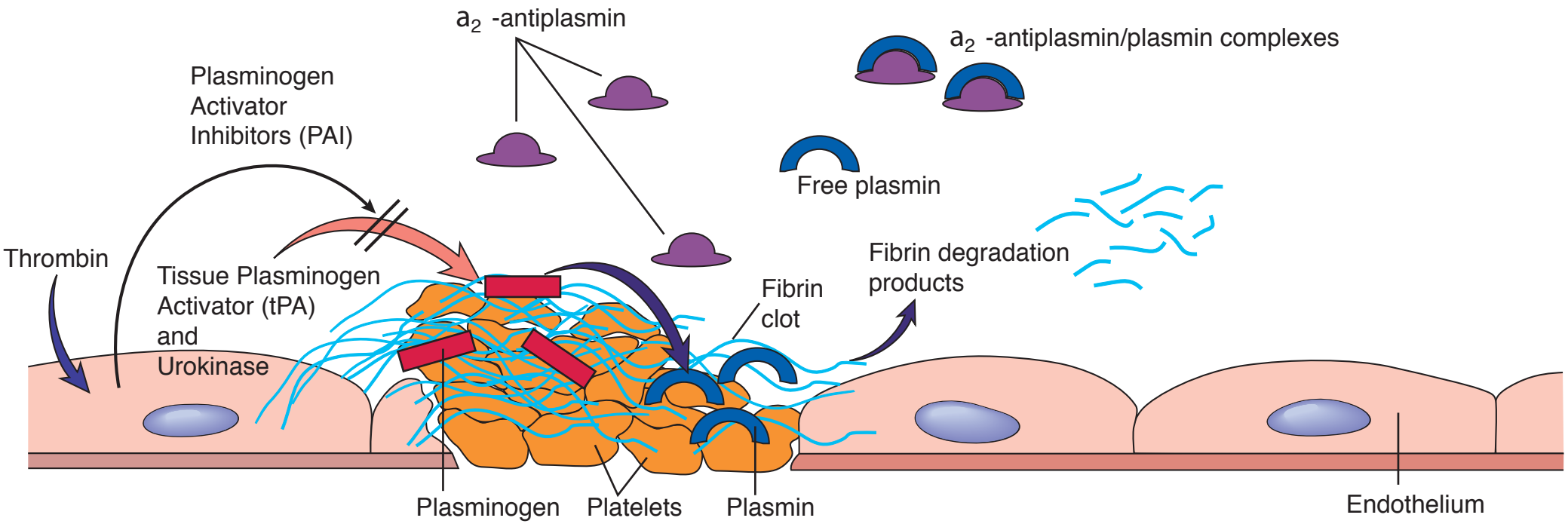
Coagulation



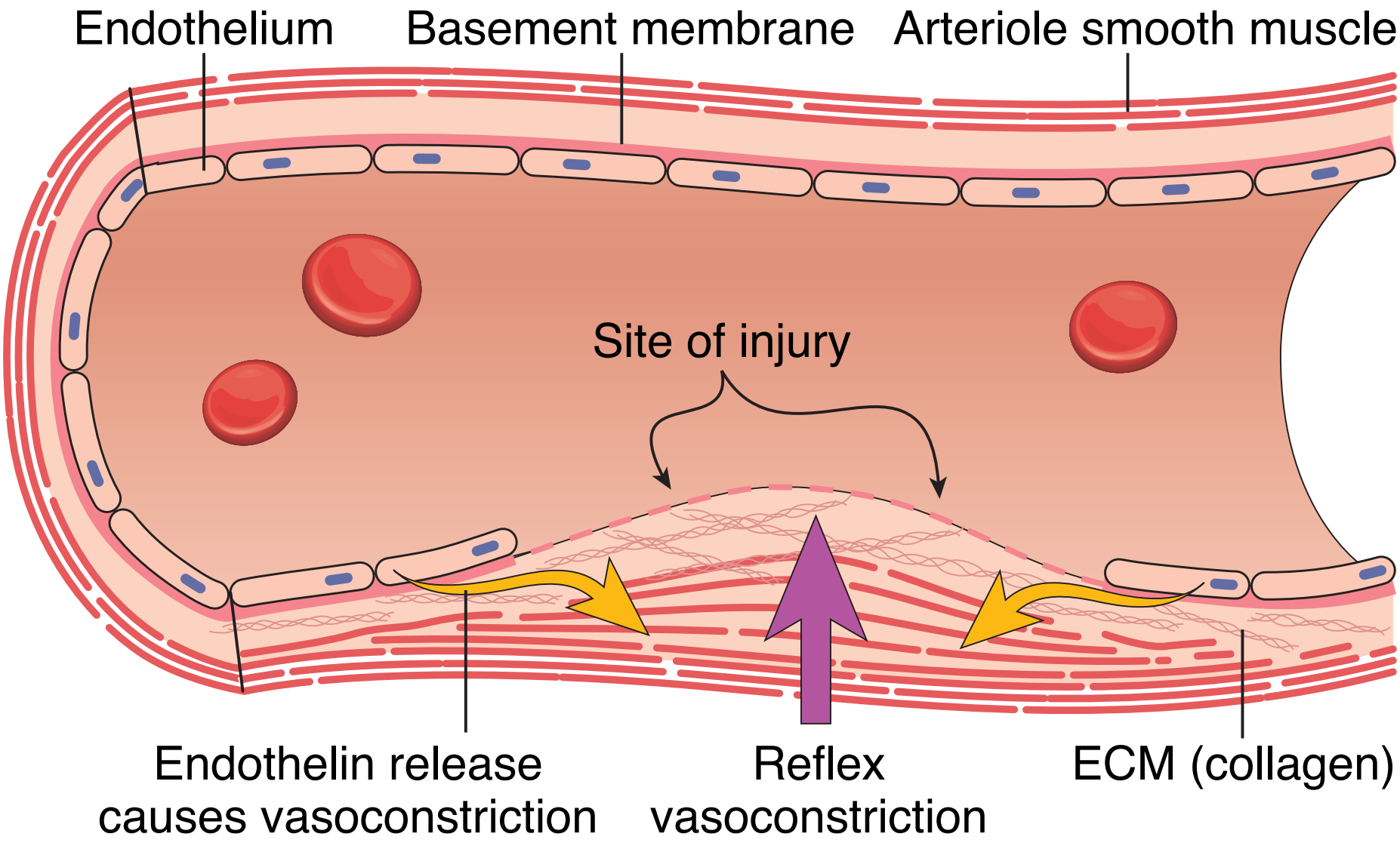
Laboratory Tests for Coagulation

- Prothrombin time (PT) - (normal range: 10-15 seconds)
  - Tests the extrinsic and common coagulation pathways - VII, X, V, prothrombin, fibrinogen
- Partial thromboplastin time (PTT) - (normal range: 25-35 seconds)
  - Tests the intrinsic and common coagulation pathways - XII, XI, IX, VIII, X, V, prothrombin, fibrinogen
- Thrombin time (TT) tests for adequate fibrinogen levels - (normal range: 9-13 seconds)
- Fibrin degradation products (FDP) tests the fibrinolytic system (increased with DIC)

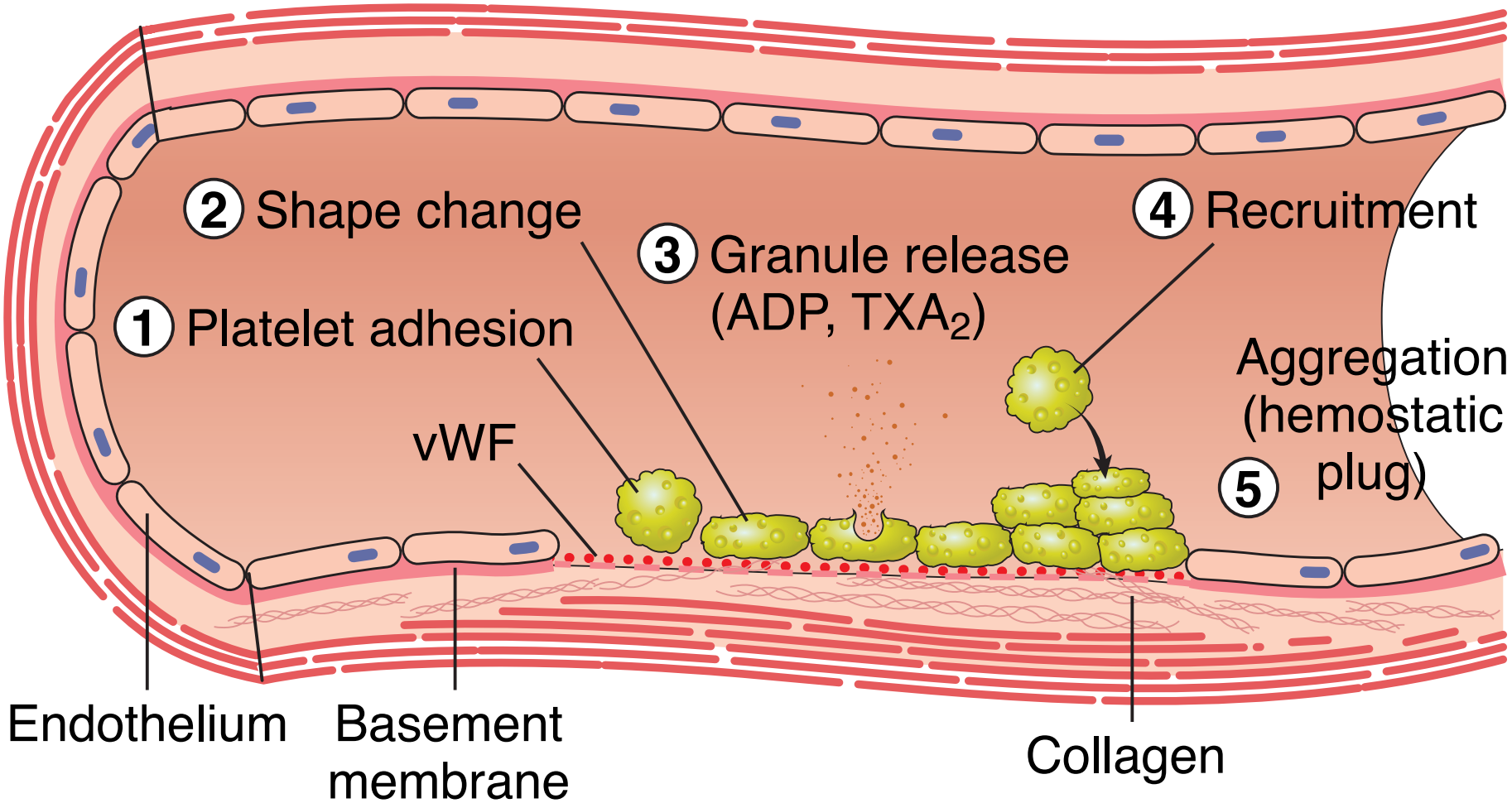
Fibrinolytic Pathway



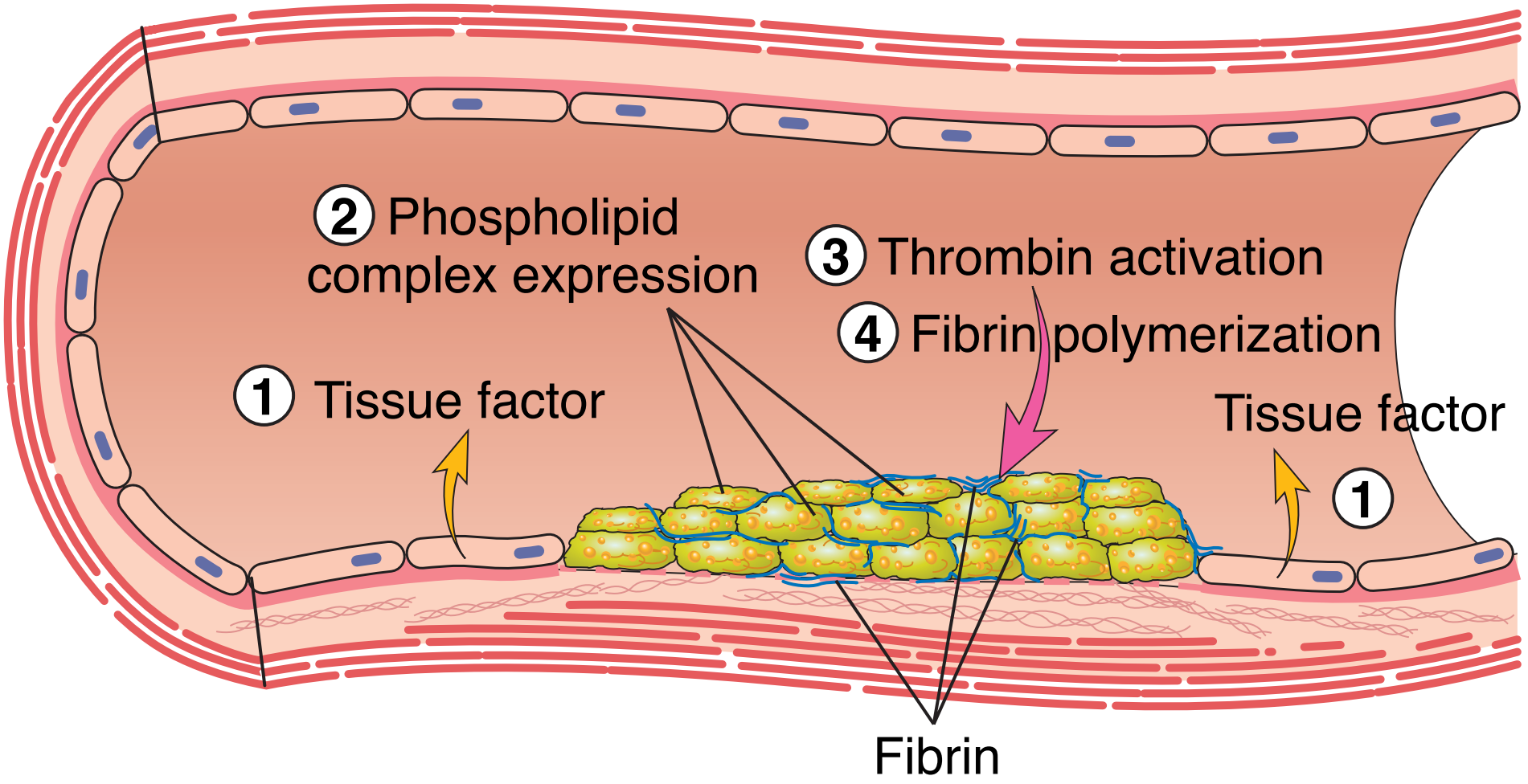
VASOCONSTRICTION



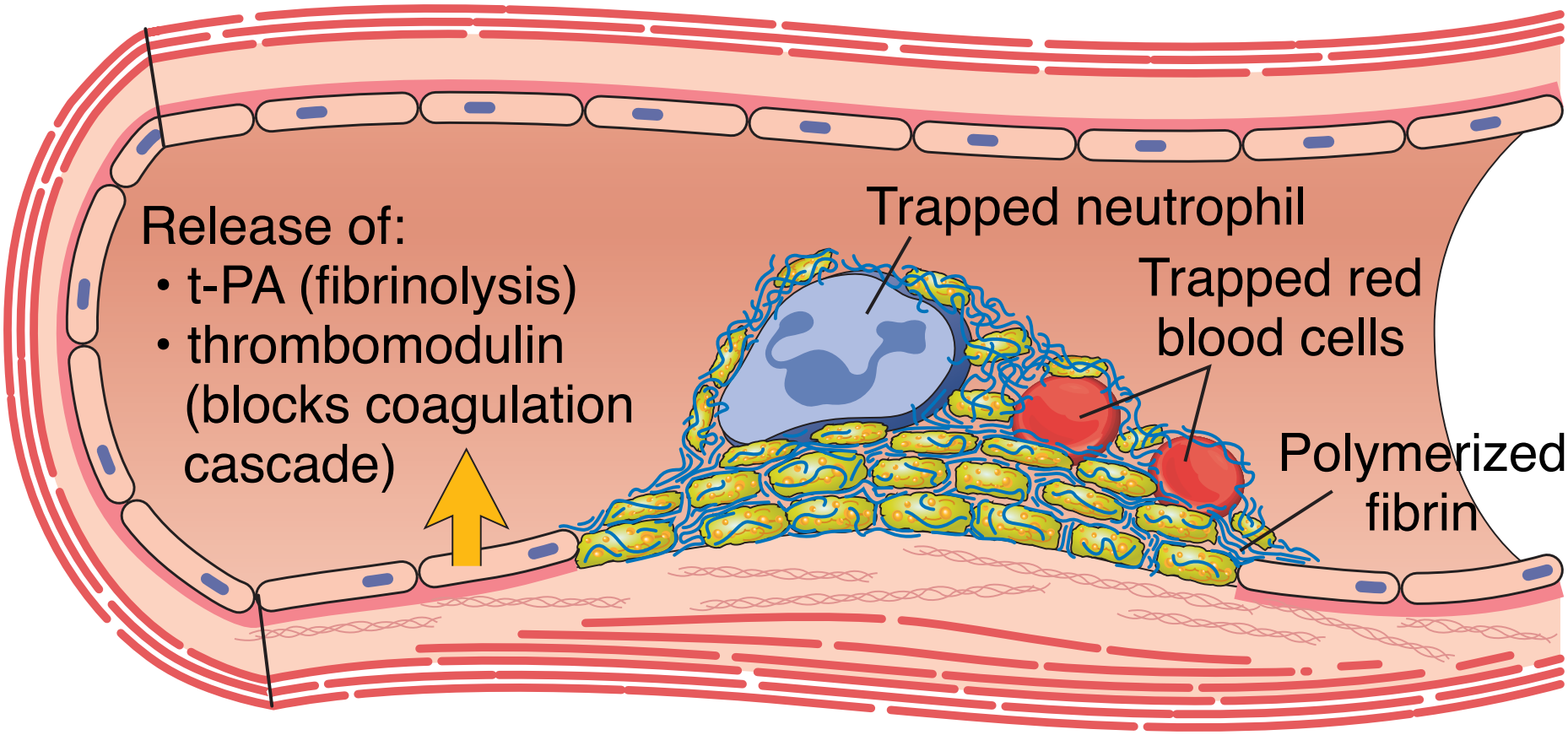
PRIMARY HEMOSTASIS



SECONDARY HEMOSTASIS



THROMBUS AND ANTITHROMBOTIC EVENTS



Hemophilia A (classic hemophilia)

- Deficiency of factor VIII
- X-linked recessive
- Clinical features
  - Predominately affects males and symptoms are variable dependent on the degree of deficiency
  - Spontaneous hemorrhages into joints (hemarthrosis)
  - Easy bruising and hematoma formation after minor trauma
  - Severe prolonged bleeding after surgery or lacerations
  - Petechiae or ecchymoses can occur

Hemophilia A

- Labs
  - Normal platelet count and bleeding time
  - Normal PT and prolonged PTT
- Treatment: factor VIII concentrate

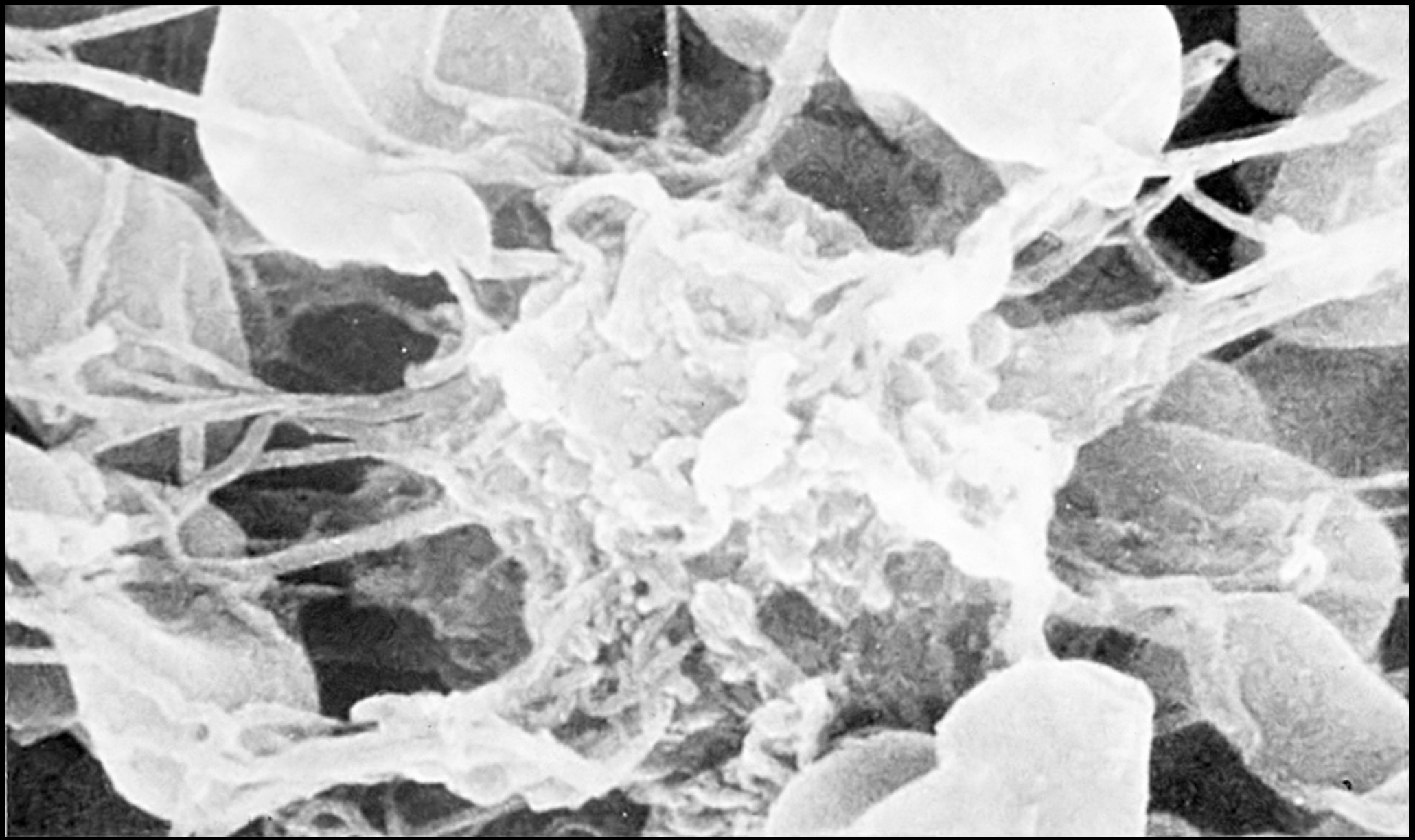
Acquired Coagulopathies

- Vitamin K deficiency: decreased synthesis of factors II, VII, IX, X, and protein C & S
- Liver disease: decreased synthesis of virtually all clotting factors

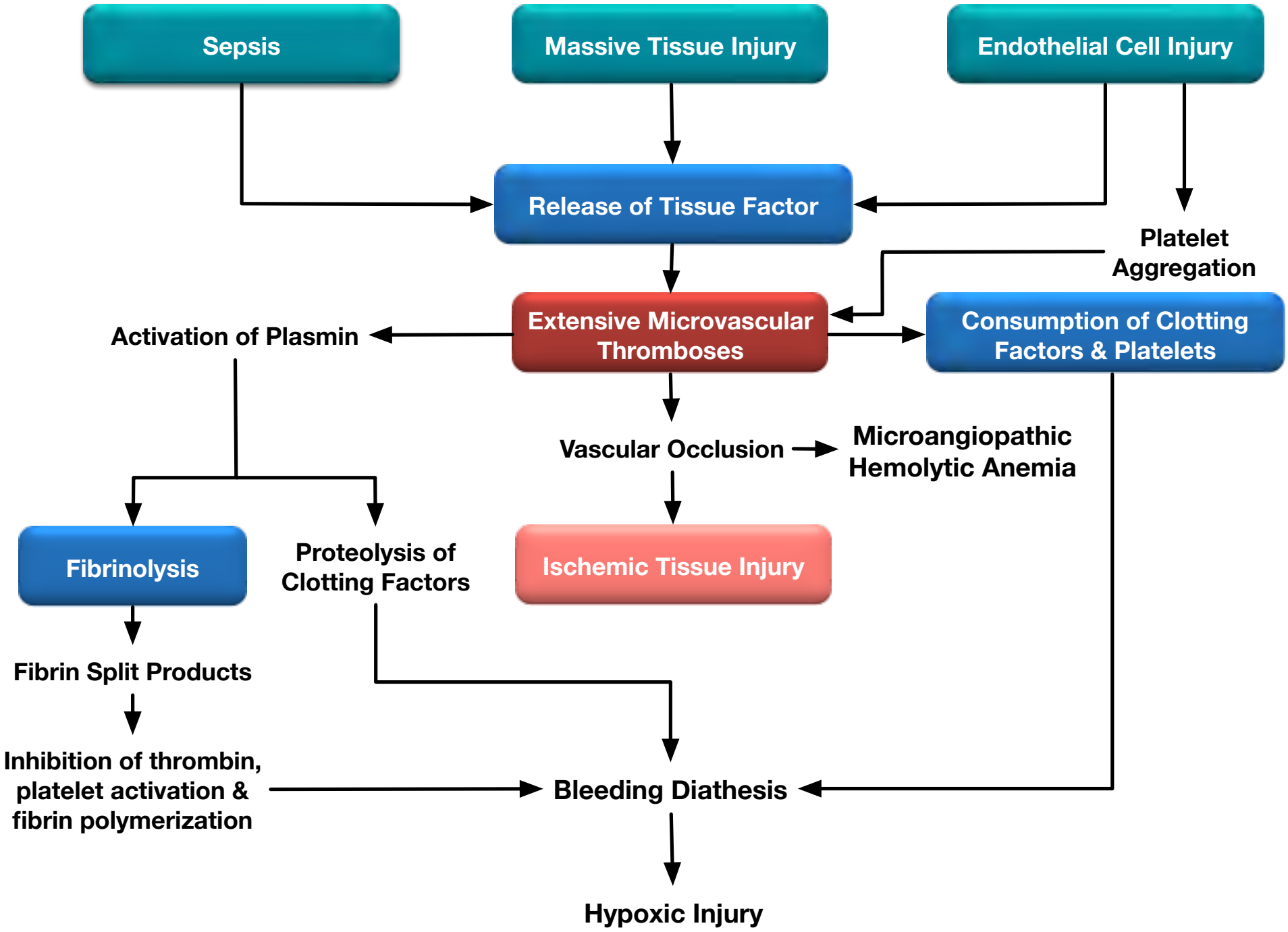
Disseminated Intravascular Coagulation (DIC)

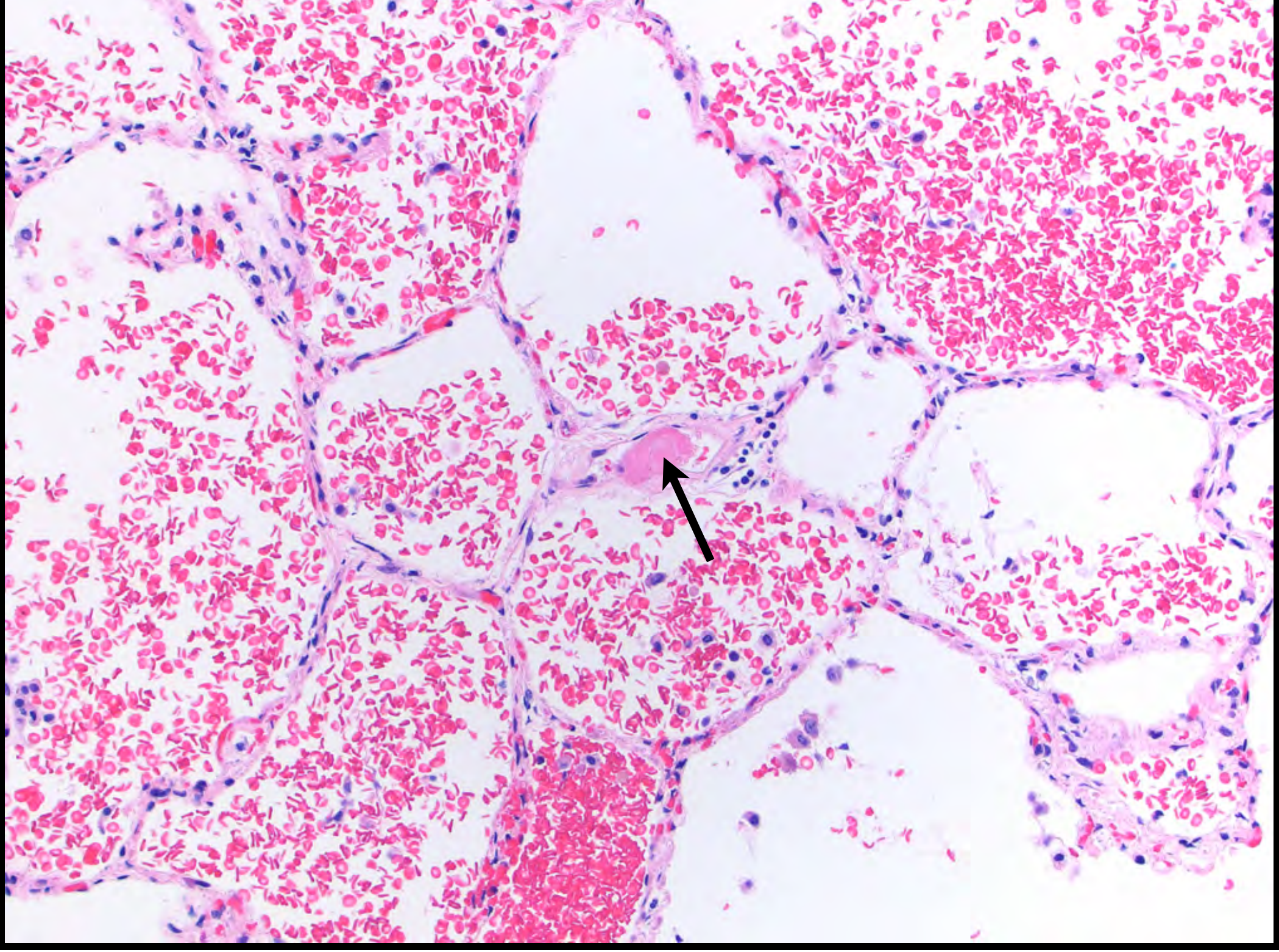
- DIC is always secondary to another disorder
- Causes
  - Obstetric complications (placental tissue factor activates clotting)
  - Gram-negative sepsis (tumor necrosis factor [TNF] activates clotting)
  - Micro-organisms (especially meningococcus and rickettsia)
  - AML M3 (cytoplasmic granules in neoplastic promyelocytes activate clotting)
  - Adenocarcinomas (mucin activates clotting)

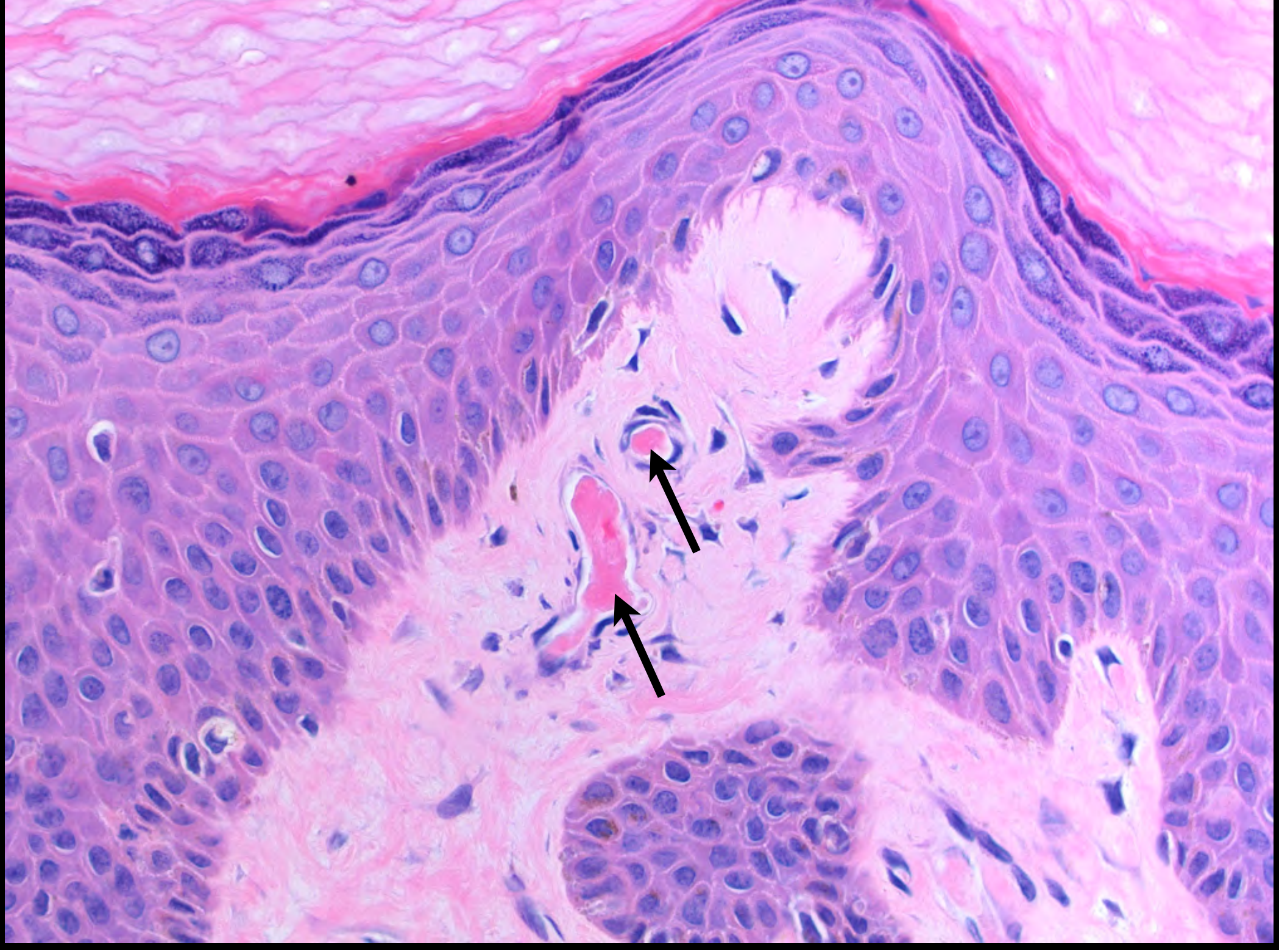
Fibrin-Platelet Thrombus



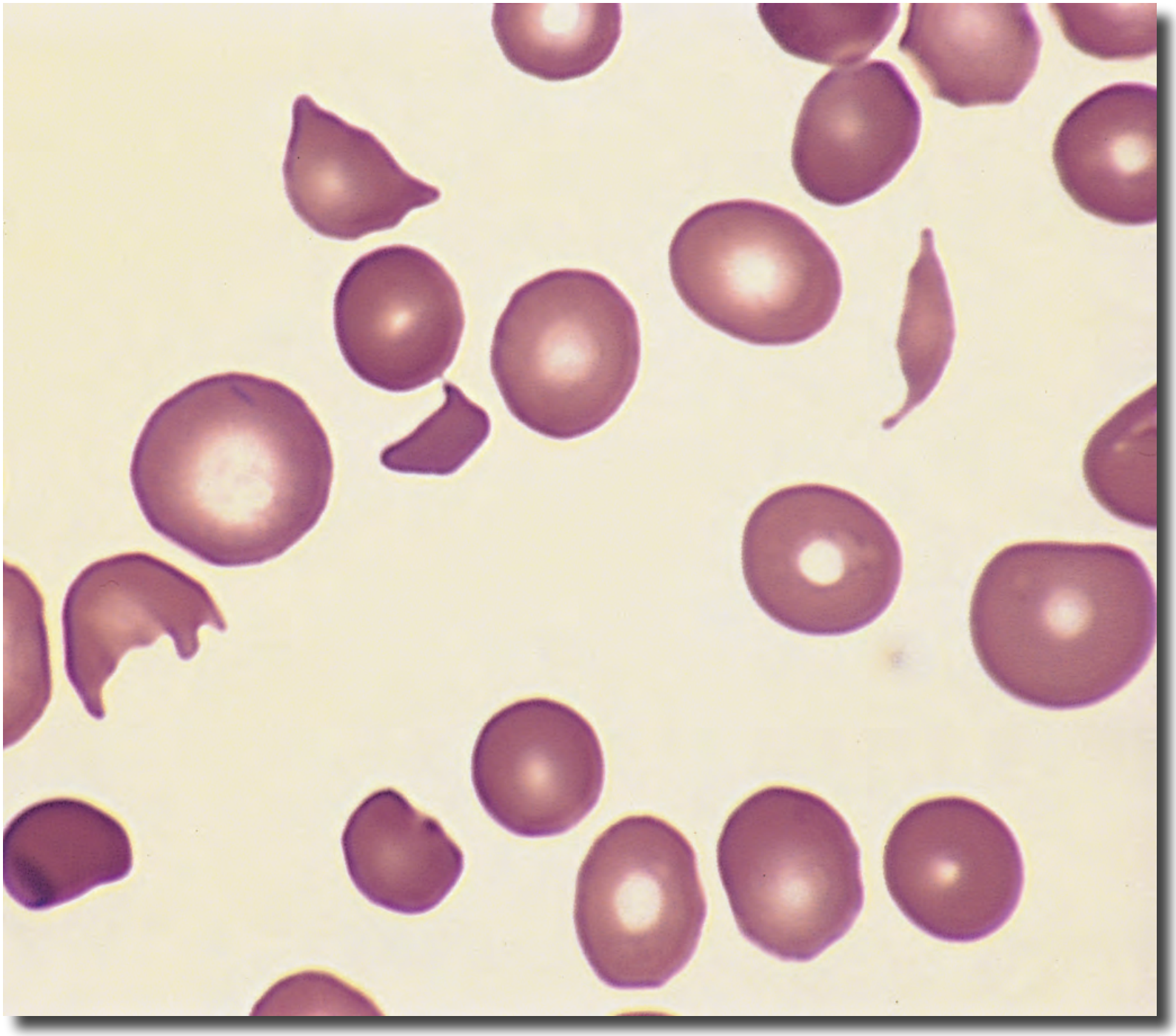
Pathogenesis of Disseminated Intravascular Coagulation







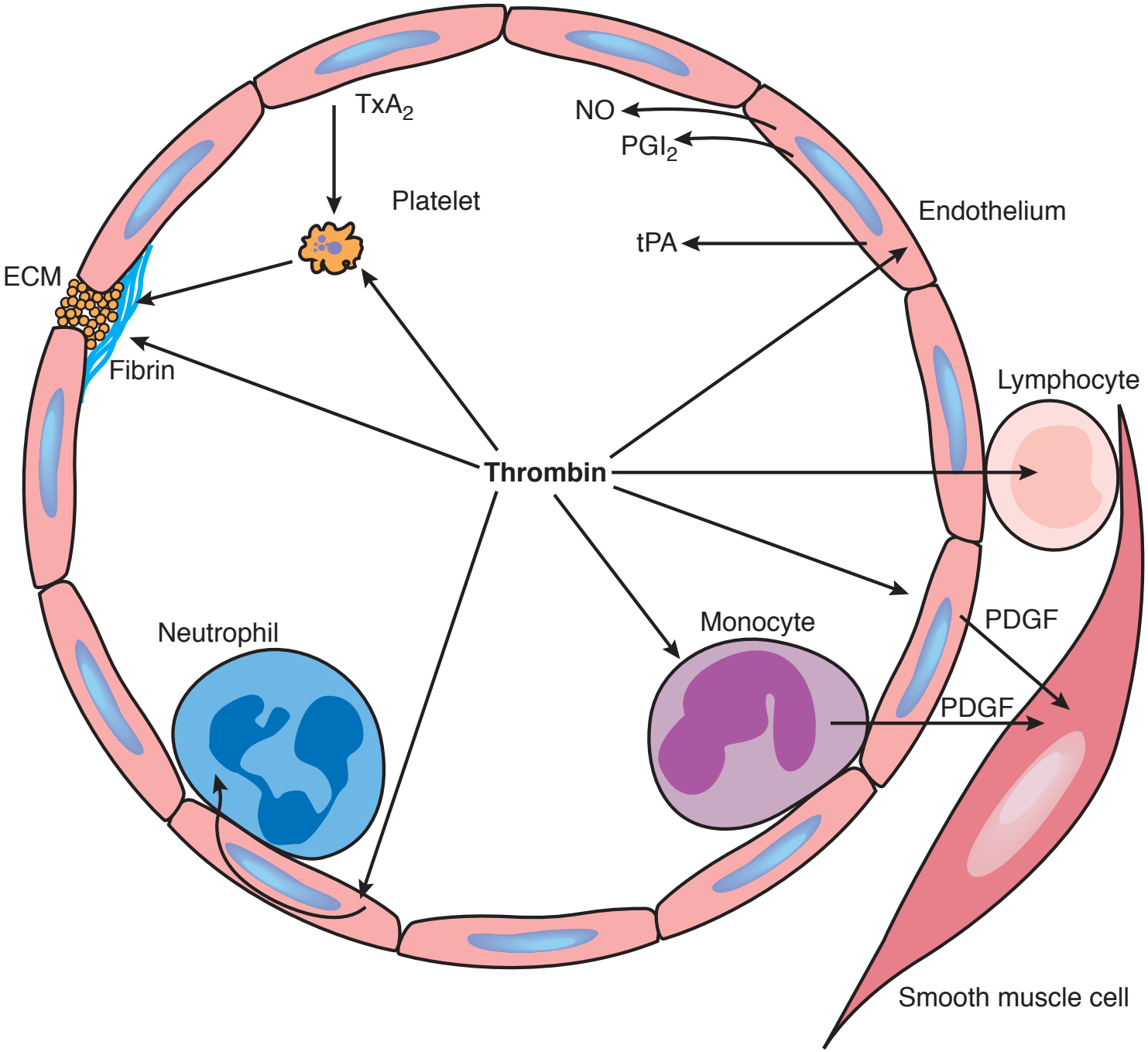
Peripheral Blood Smear: Schistocyte



Disseminated Intravascular Coagulation (DIC)

- Pathology
  - Results in widespread fibrin-platelet thrombi
  - Consumption of platelets and clotting factors leads to a bleeding diathesis
- Labs
  - Platelet count is decreased
  - Prolonged PT/PTT
  - Decreased fibrinogen
  - Elevated fibrin split products (D-dimers)
- Treatment: treat the underlying disorder

Effects of Thrombin



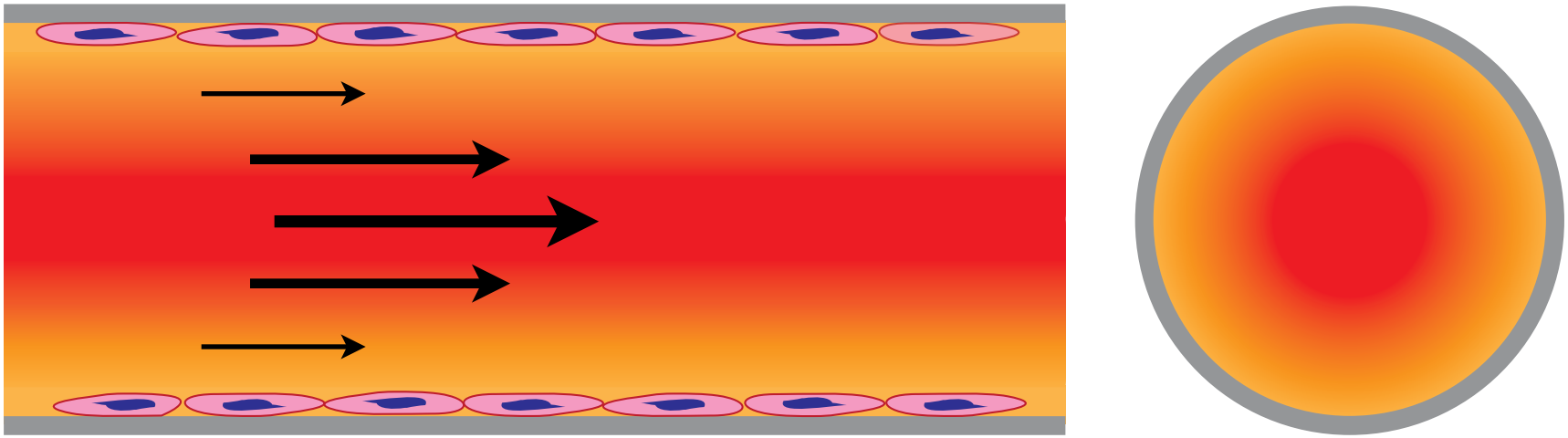
Hemostasis

- Interaction between Clotting, Fibrinolytic and Inflammatory Systems
  - Hageman factor is a common activator in all three systems
  - Platelets contain clotting factors, vasoactive agents, and other activators of inflammation
  - Fibrin split products are vasoactive agents
  - Plasmin activates complement
  - Fibrin plays an important role in acute inflammation

Thromboembolism

- Three Predisposing Factors Leading to Abnormal Thrombosis
  - Injury to vascular endothelium - atherosclerosis
  - Changes in laminar flow of blood - increased viscosity (polycythemia), stasis of blood (deep leg veins), and turbulence (aneurysms)
  - Hypercoagulability - increased level of platelets or clotting factors, decreased fibrinolytic activity (pregnancy)

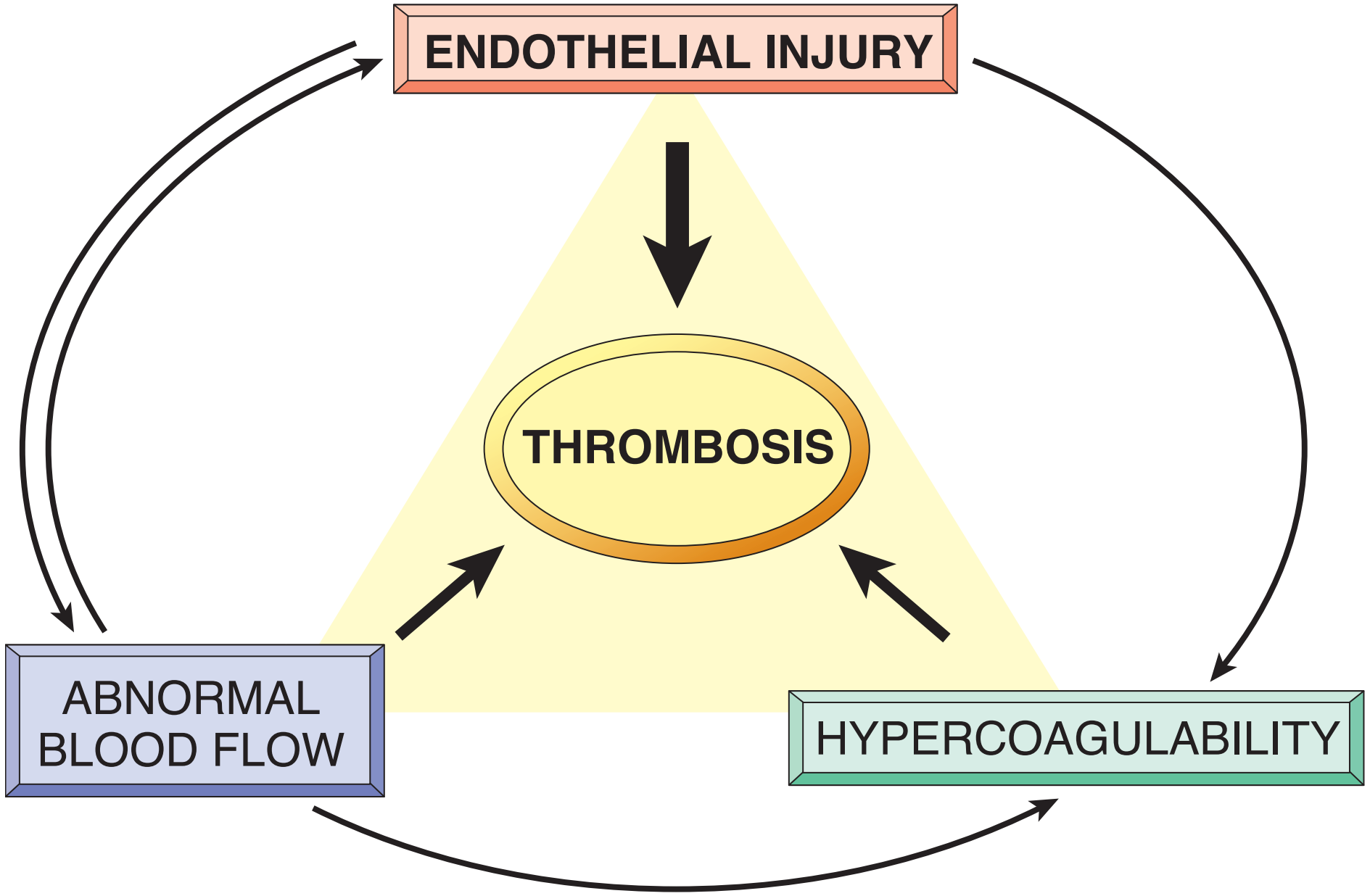
Laminar Flow of Blood



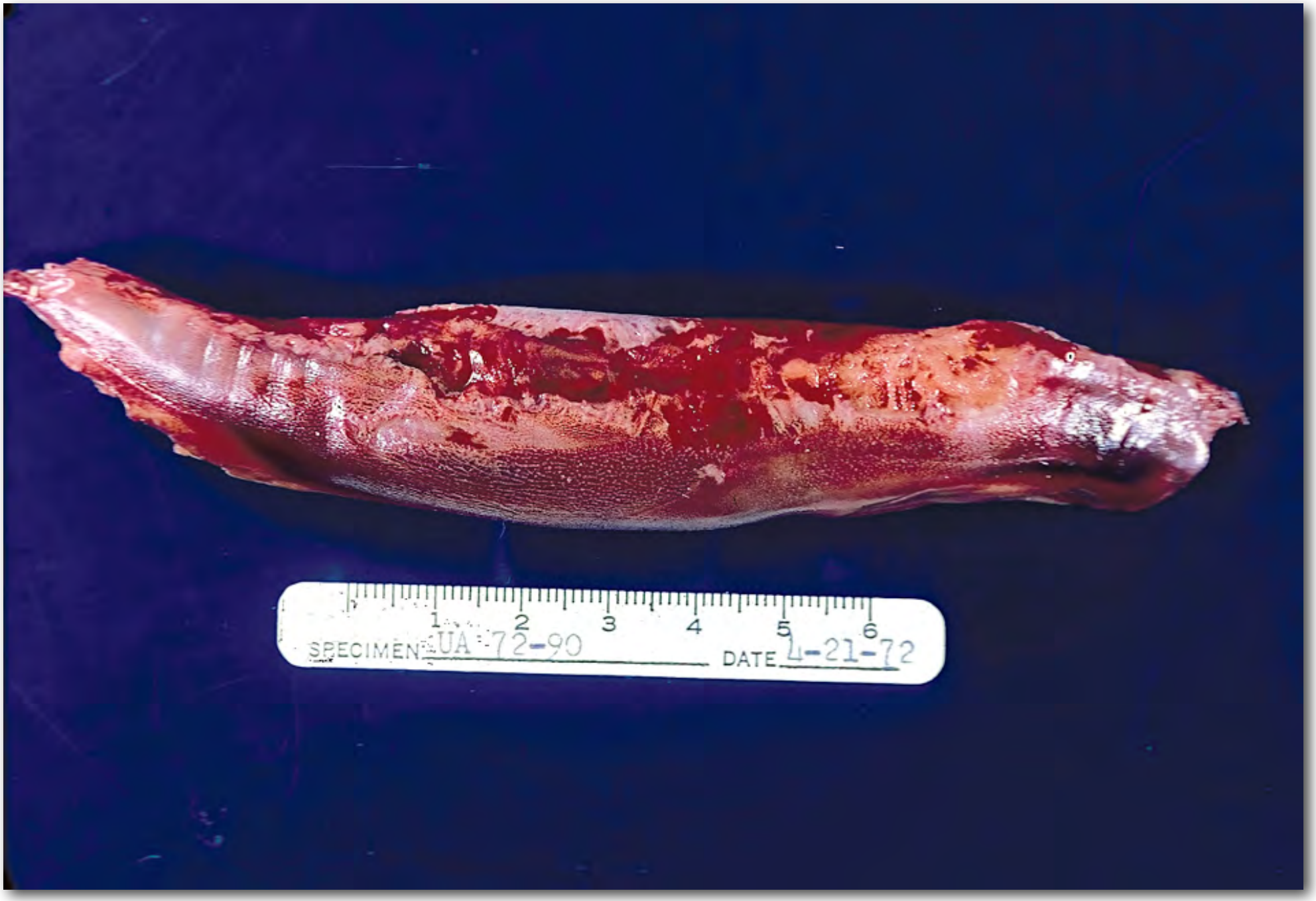
Hypercoagulable States

Primary (Genetic)
Common - Factor V mutation (factor V Leiden), Prothrombin mutation (increased prothrombin levels, Increased levels of factors VIII, IX, XI, or fibrinogen
Rare - Antithrombin III deficiency, Protein C deficiency, Protein S deficiency
Very Rare - Fibrinolysis defects, Homozygous homocystinuria (deficiency of cystathione beta-synthetase

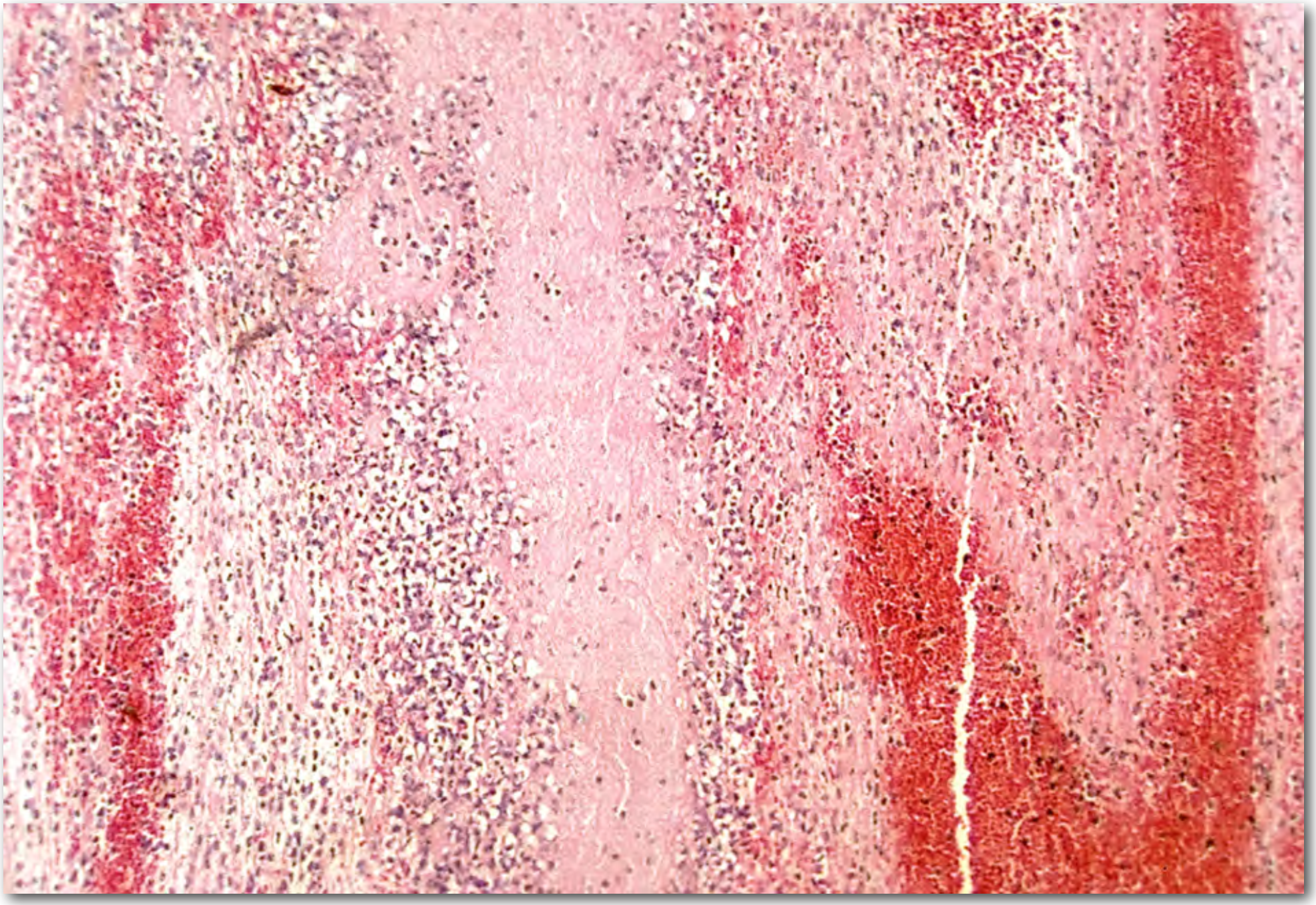
Secondary (Acquired)
High Risk for Thrombosis - Prolonged bed rest or immobilization, Myocardial infarction, Atrial fibrillation, Tissue injury (surgery, fracture, burn), Cancer, Prosthetic cardiac valves, Disseminated intravascular coagulation, Heparin-induced thrombocytopenia, Anti-phospholipid antibody syndrome
Low Risk for Thrombosis - Cardiomyopathy, Nephrotic syndrome, Hyperestrogenic states (pregnancy and postpartum), Oral contraceptive use, Sickle cell anemia, Smoking


ENDOTHELIAL INJURY
THROMBOSIS
ABNORMAL BLOOD FLOW
HYPERCOAGULABILITY

Thrombus



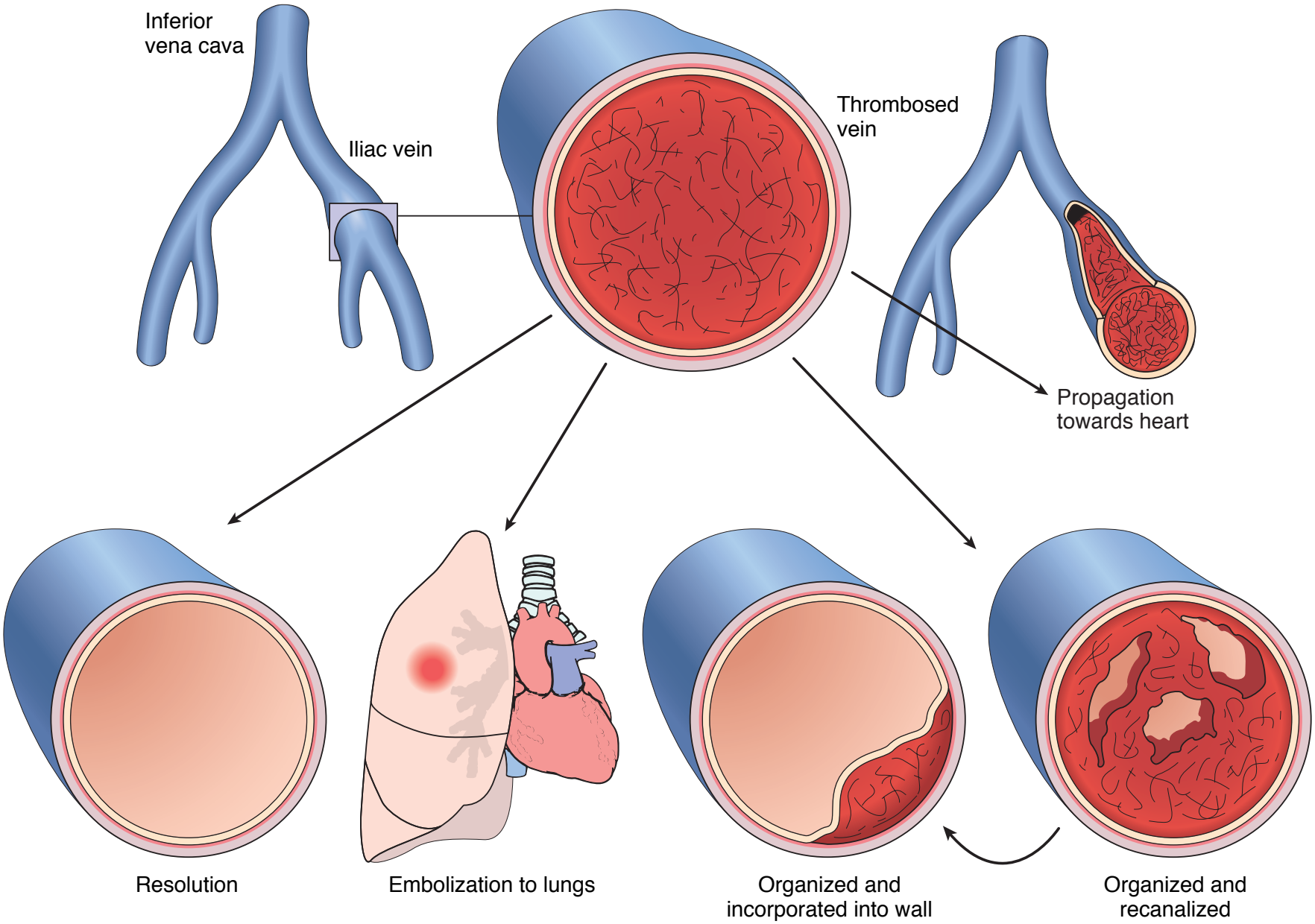
Thrombus ("Lines of Zahn")



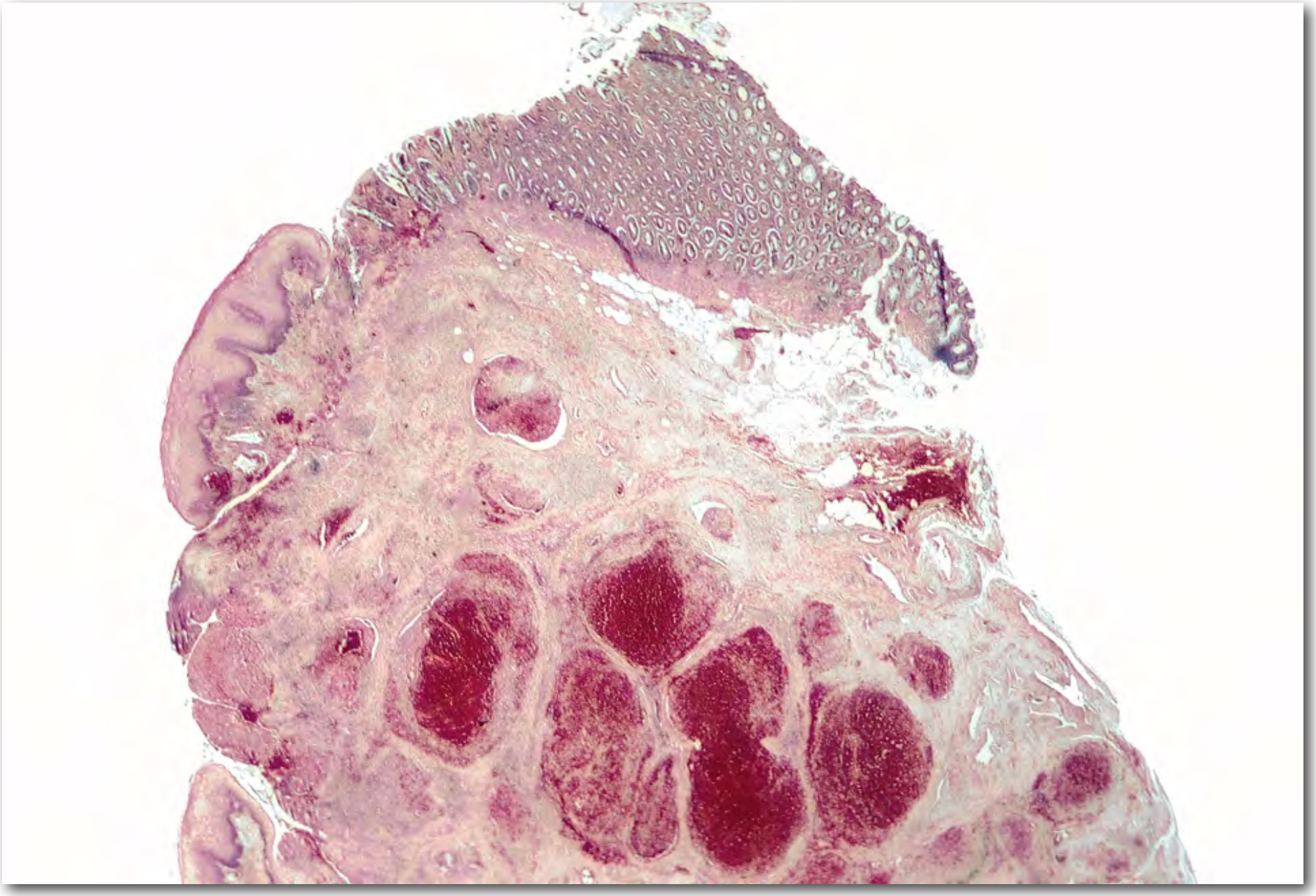
Thromboembolism

- Evolution of a Thrombus
  - Enlarge and cause obstruction with the formation of Lines of Zahn (early)
  - Give rise to an embolus
  - Be removed by fibrinolytic action (small thrombi) or
  - Become organized leading to recanalization (large thrombi)

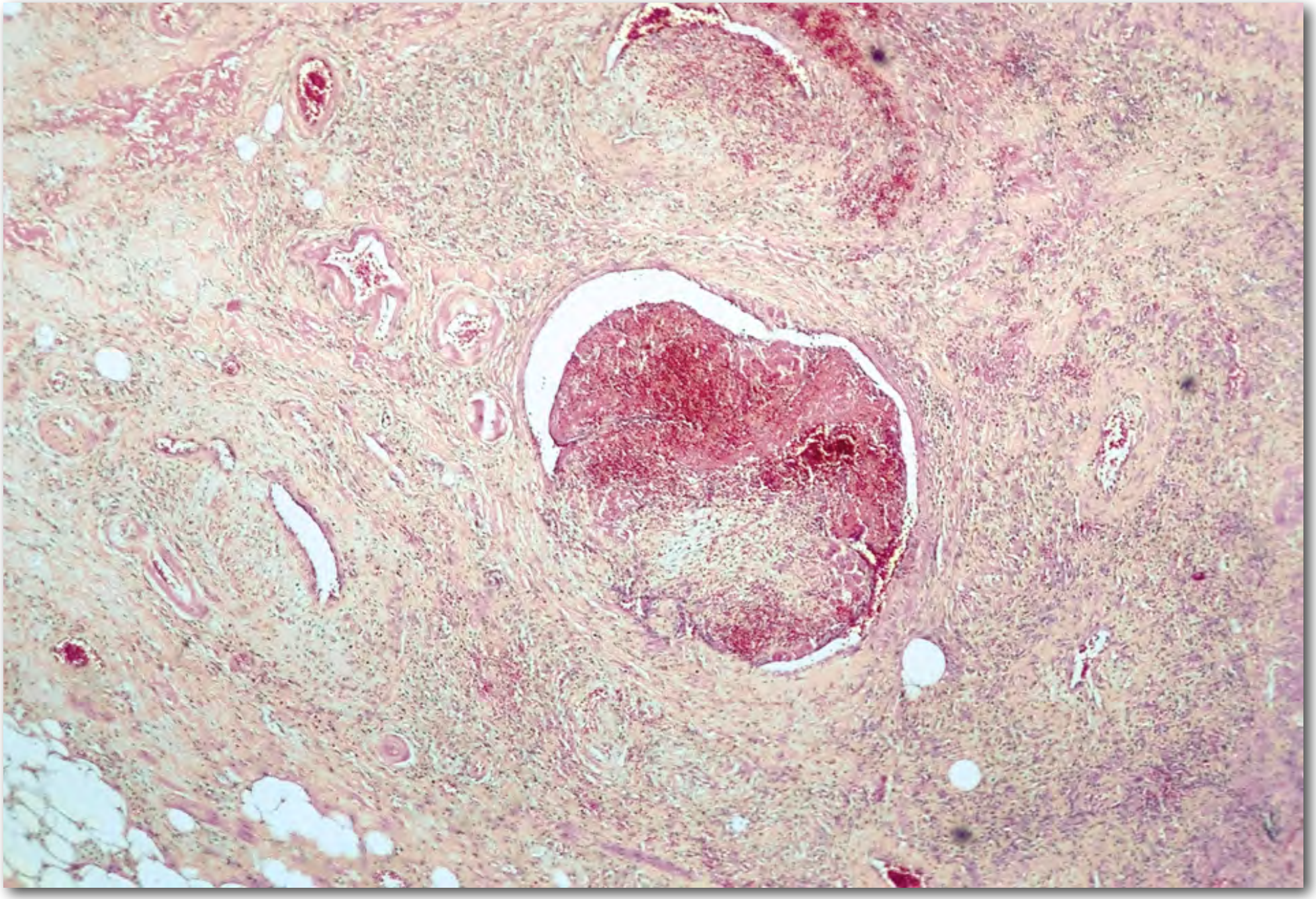
Evolution of a Thrombus



Organizing Thrombosed Hemorroids



Organizing Thrombosed Hemorroids



Thromboembolism

- Thrombus vs Blood Clot
  - Thrombus only occurs within the intravascular space while a blood clot can occur in either intravascular (postmortem), or extravascular compartments
  - Blood clot does not have Lines of Zahn
  - Blood clot contains minimal number of platelets

Blood Clot

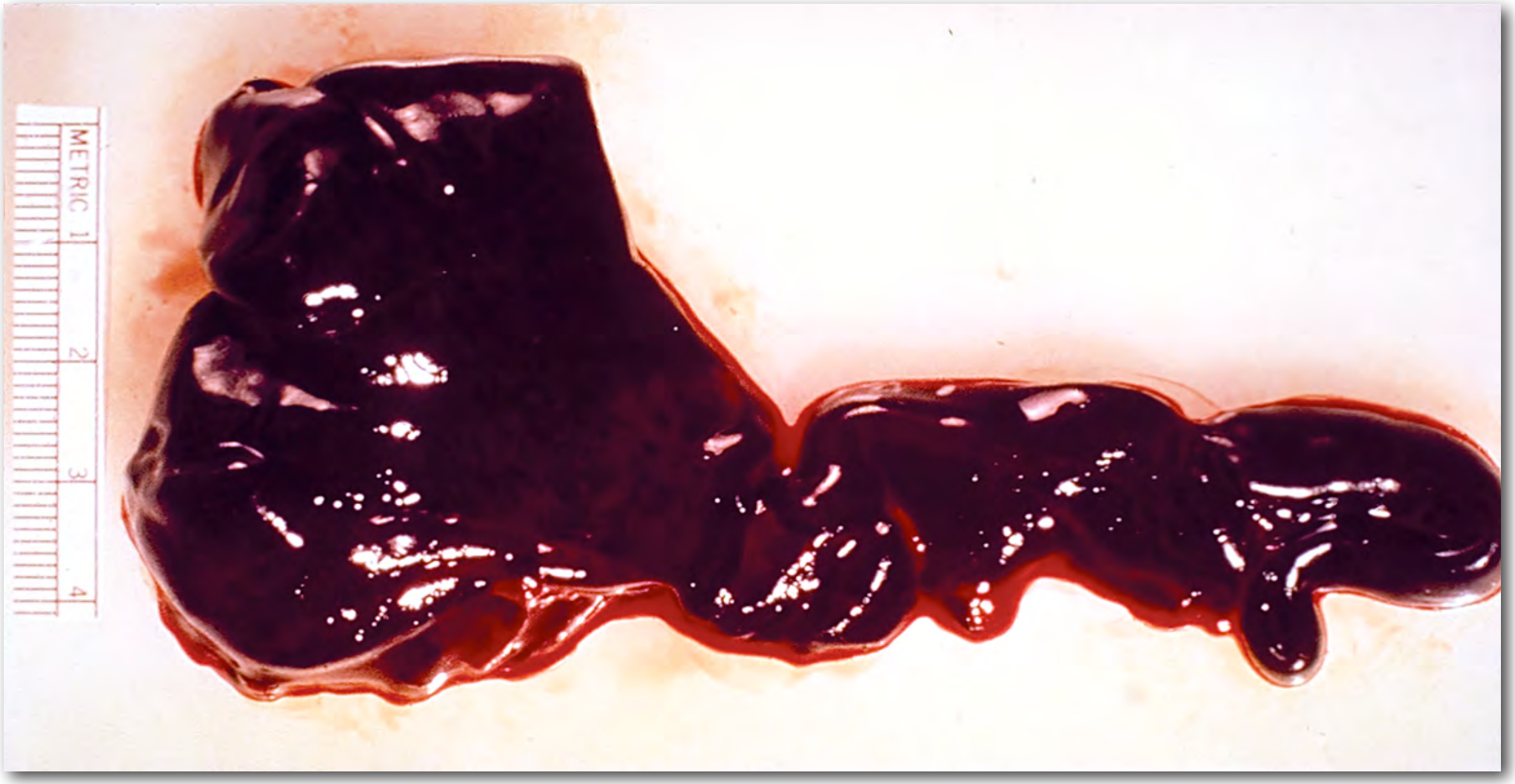


Table 5-4. Comparison of a Thrombus with a Blood Clot

	Thrombus	**Blood Clot**
Location	Intravascular	Extravascular or intravascular (postmortem)
Composition	Platelets Fibrin RBCs and WBCs	Lacks platelets Fibrin RBCs and WBCs
Lines of Zahn	Present	Absent
Shape	Has shape	Lacks shape

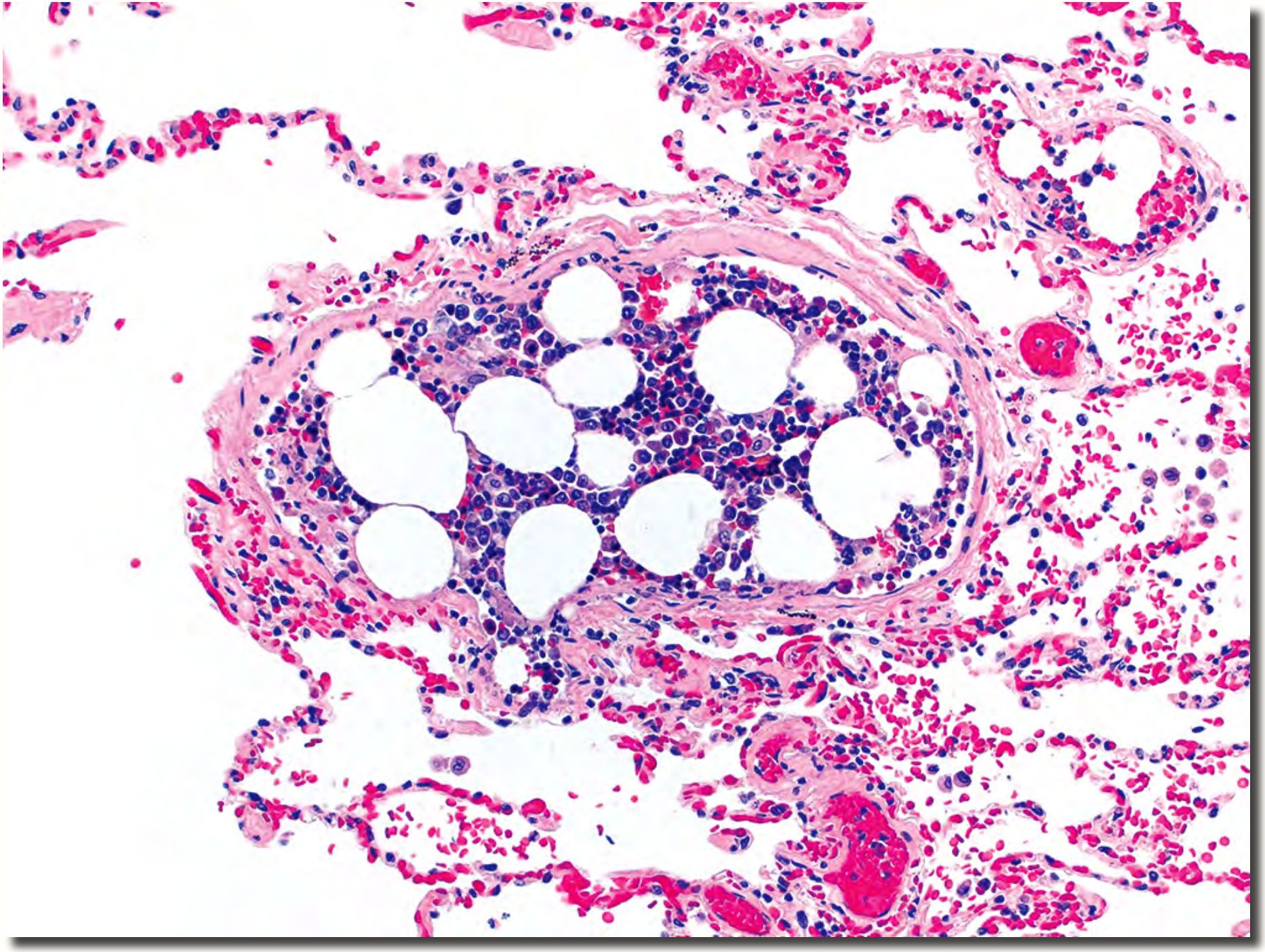
Thromboembolism

- Embolus
  - Definition - a detached intravascular mass (solid, liquid, or gas) that is carried to a site distant from point of origin
- Embolus vs Thrombus
  - Embolus can be composed of "foreign" material (amniotic fluid, bacteria, tumor cells)
  - Embolus may not conform to the shape of a blood vessel
  - Arterial thrombus is usually associated with underlying atherosclerosis while an embolus is typically found overlying a normal vessel until organization occurs

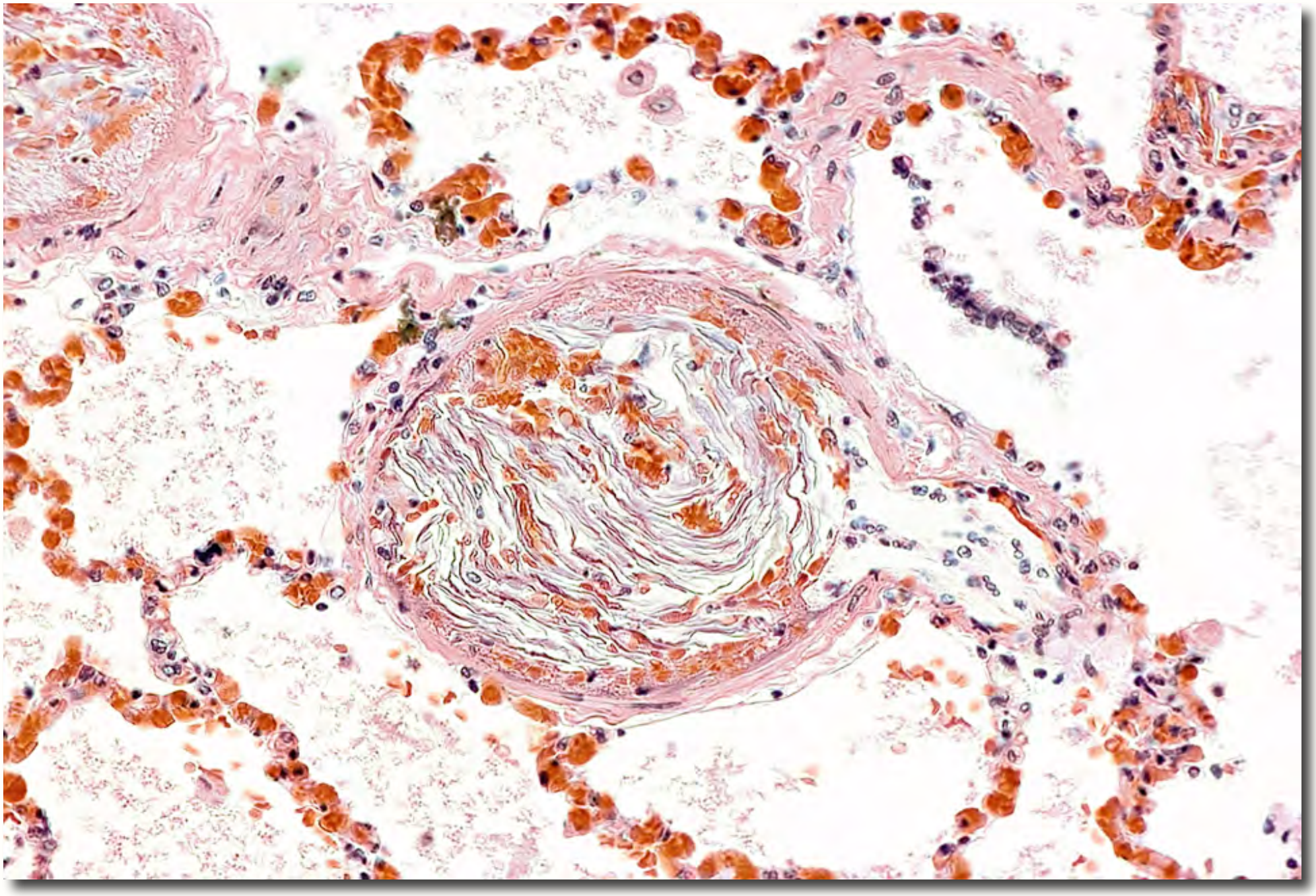
Thromboembolism

- Types of Emboli
  - Thrombus
  - Bone marrow
  - Atheromatous debris
  - Fat
  - Bacteria
  - Tumor cells
  - Amniotic fluid
  - Air - acute and chronic

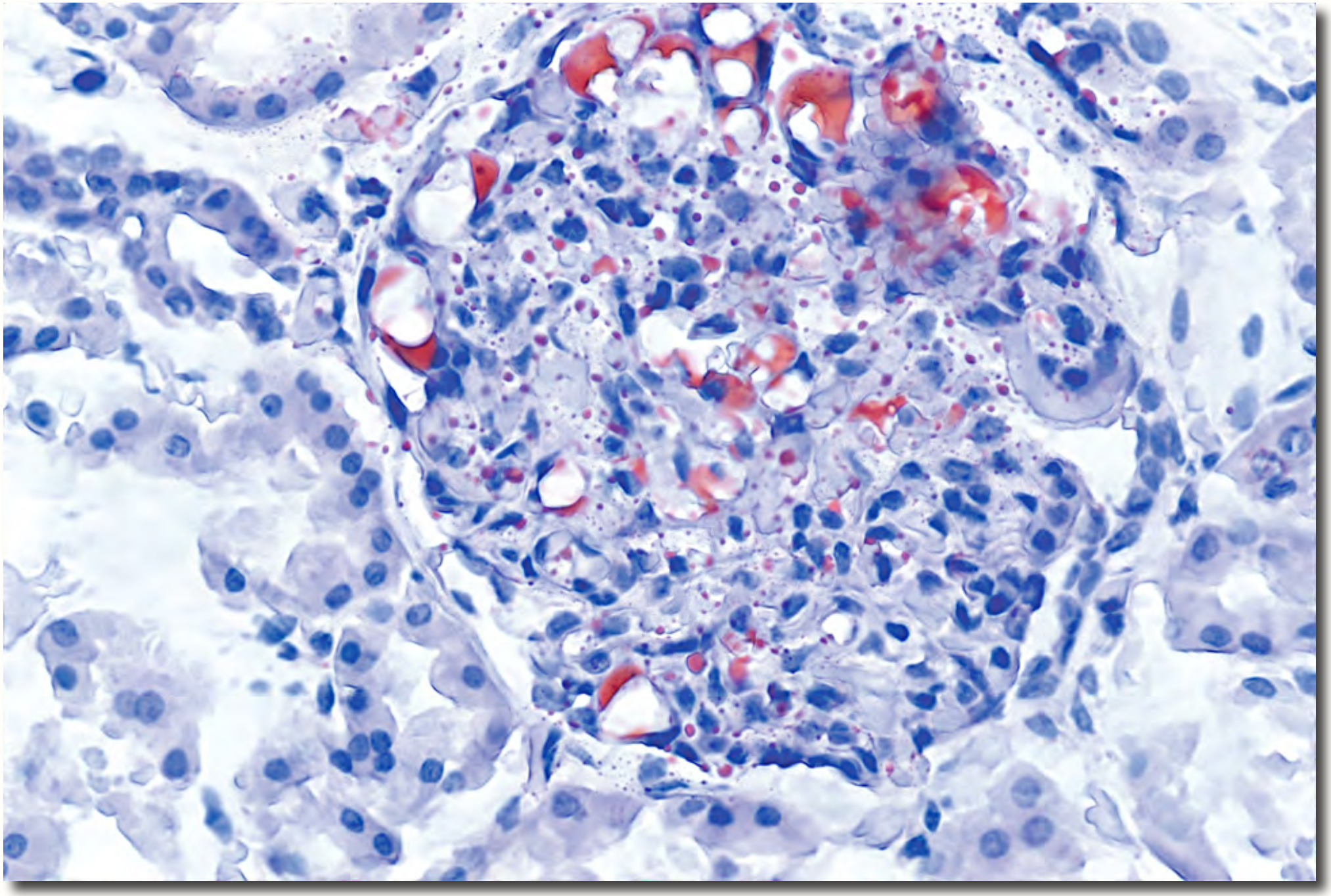
Bone Marrow Embolus



Amniotic Fluid Embolus



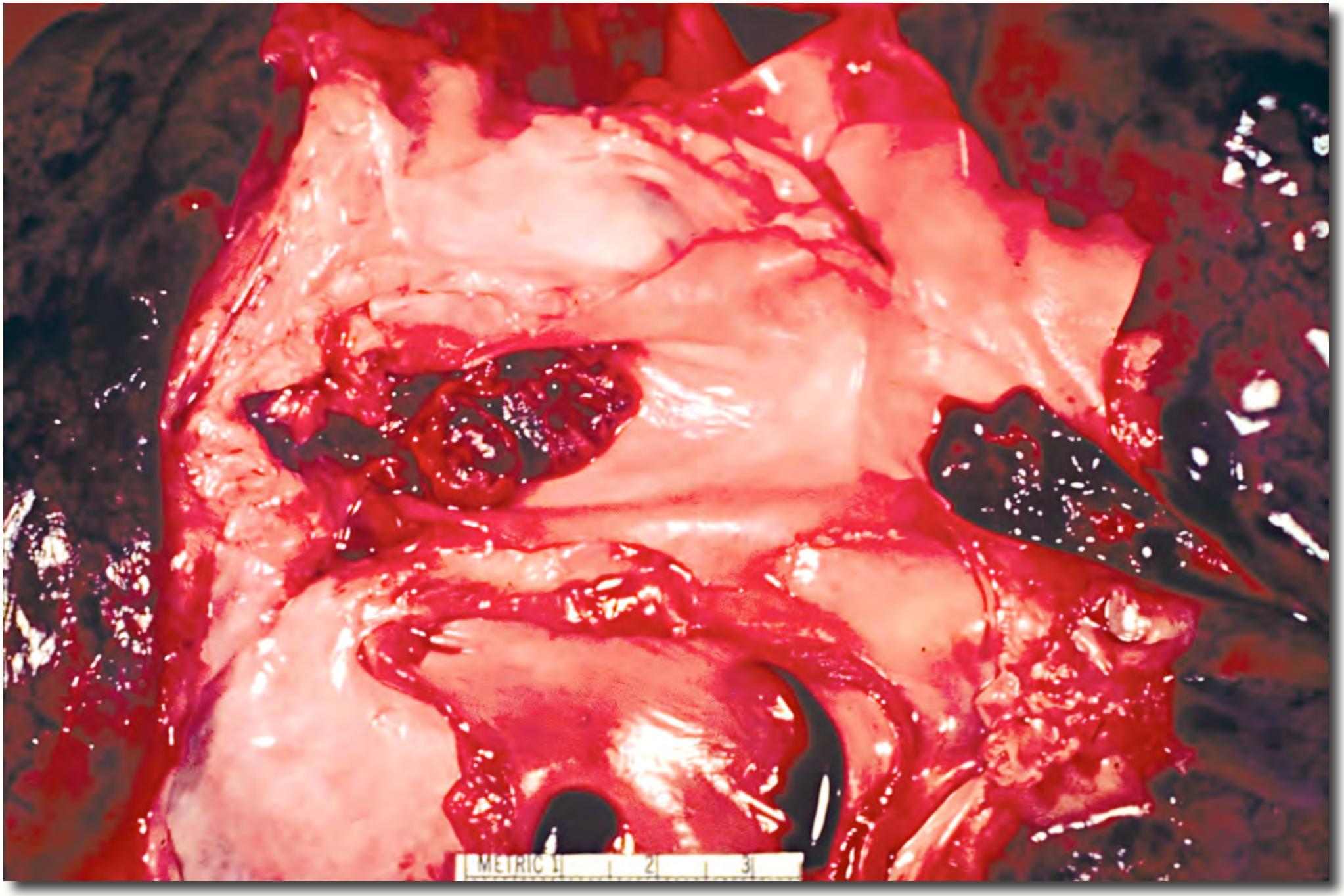
Fat Emboli



Thromboembolism

- Pulmonary Embolus
  - Origin - deep leg veins, prostatic venous plexus
  - Outcome
    - Resolution in 70 to 80%
    - Infarction in 10 to 15%
    - Chronic pulmonary hypertension in 5%
    - Death in 10%

Pulmonary Saddle Embolus



Infarct

- Definition - A localized area of necrosis resulting from circulatory insufficiency
- Infarcts of the heart, brain, and lungs collectively account for more deaths than all forms of cancer and infectious disease put together in the United States

Infarct

- Etiology
  - Thrombus
  - Embolus
  - Shock

Infarction

- Whether or not infarction occurs depends on several factors
  - Degree of obstruction
  - Rate of occlusion - acuteness
  - Vulnerability of tissue to ischemia
  - Presence or absence of collateral circulation
  - Preexisting disease
  - Length of patient survival

Infarct

- Gross Pathology
  - Wedge-shaped
  - Apex of wedge points to the occlusion

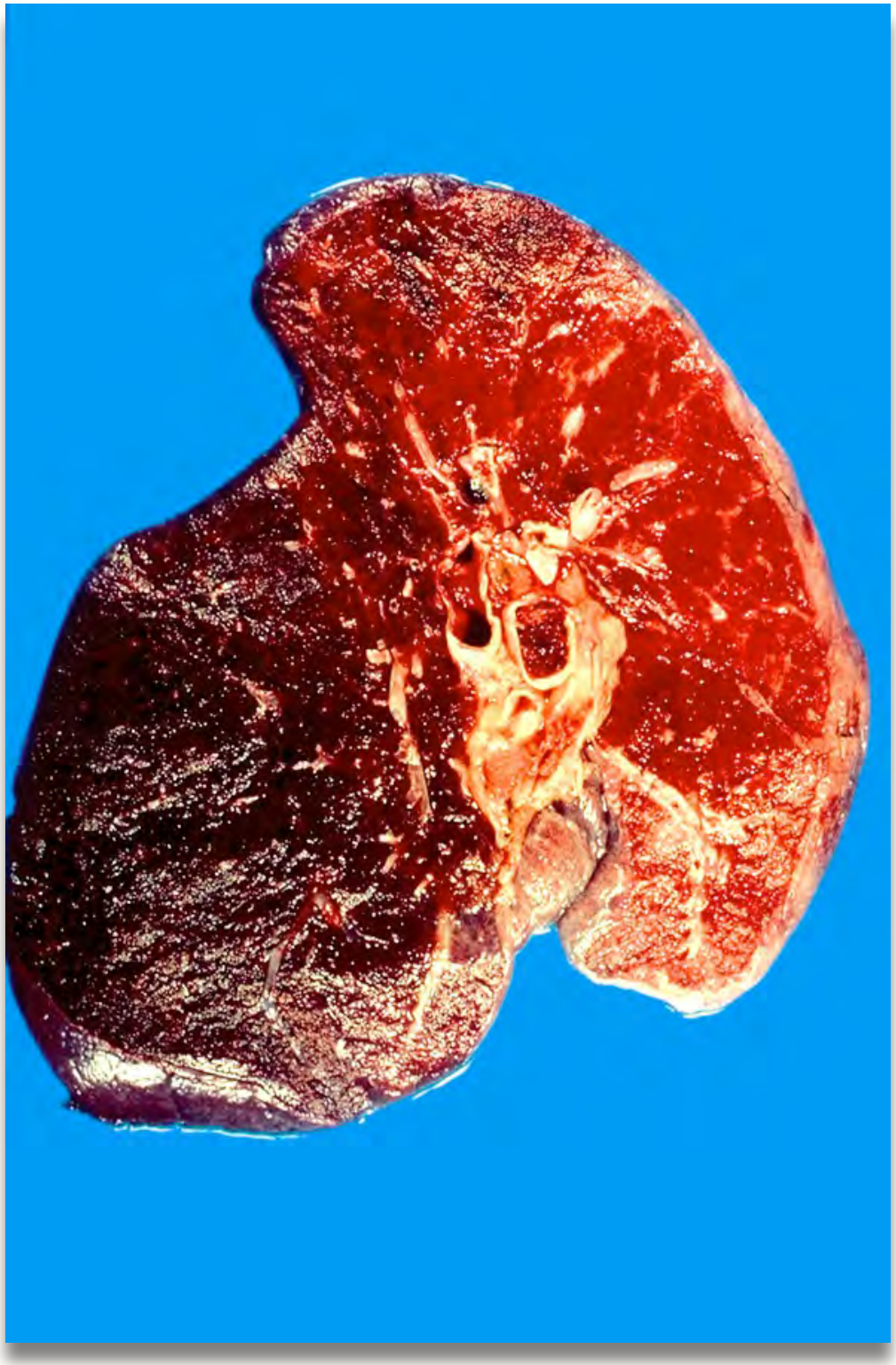
Infarct

Hemorrhagic or Red	Anemic, pale or white
Loose tissues	Solid organs or tissues
Dual blood supply	Single blood supply
Venous occlusion	Arterial occlusion

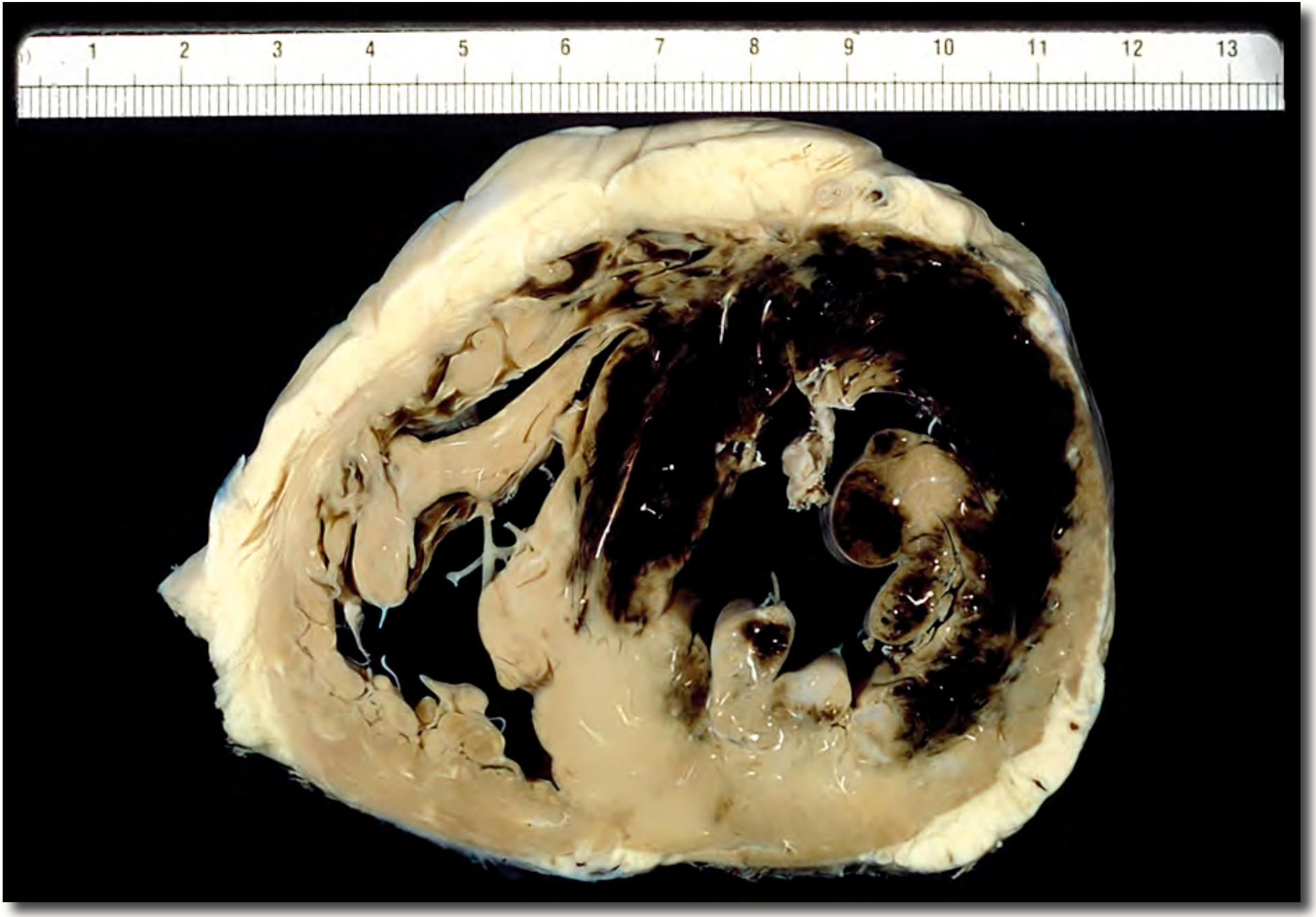
Infarct

- Gross Pathology
  - Heart (usually anemic) - thrombus secondary to underlying atherosclerotic coronary artery
  - Brain (hemorrhagic or anemic) - thrombotic occlusions are usually anemic while embolic occlusions are usually hemorrhagic
  - Lung (hemorrhagic) - usually due to embolism rather than thrombus
  - Intestine (hemorrhagic) - thrombotic or embolic
  - Spleen (anemic) - thrombotic or embolic

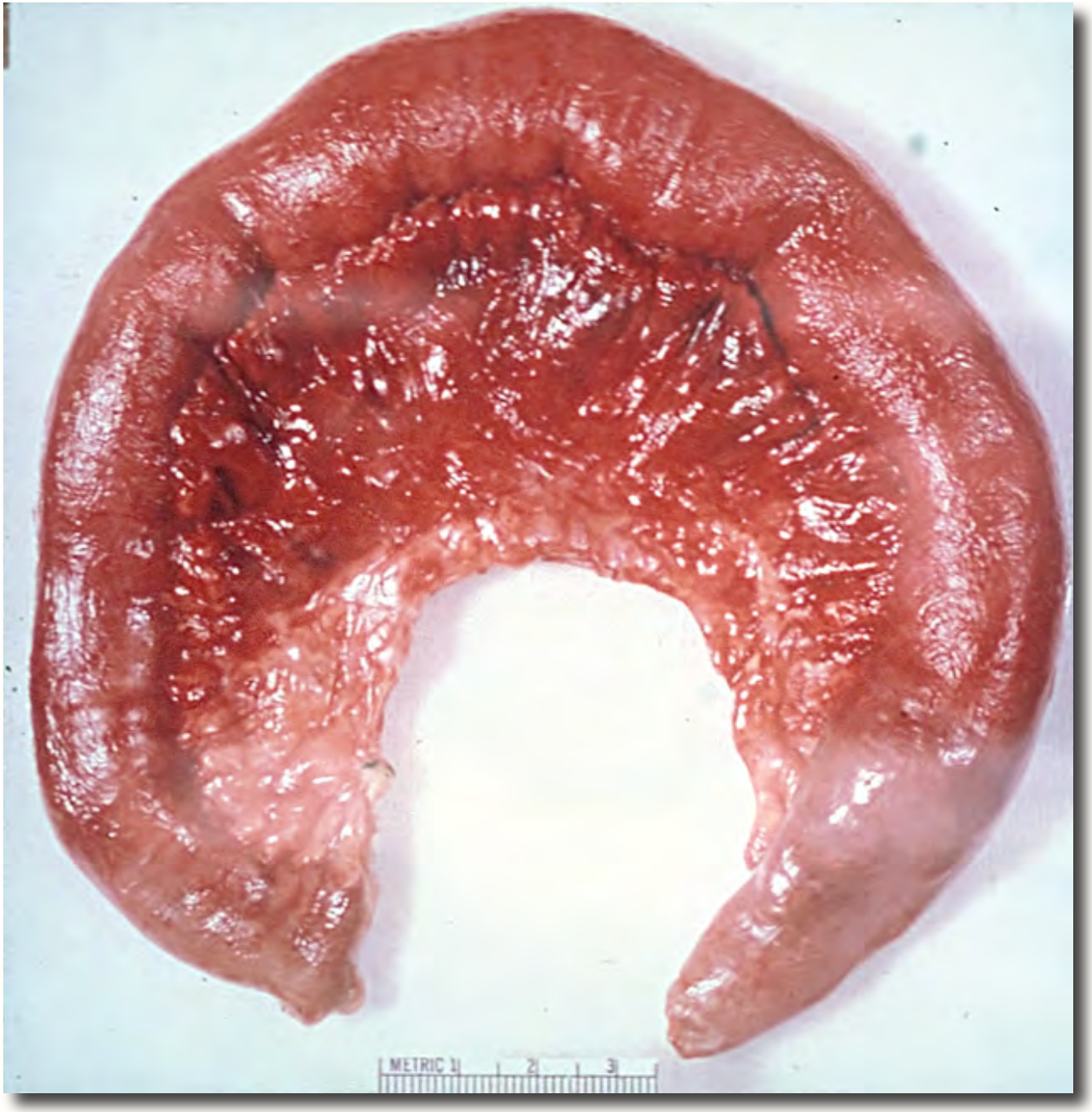
Hemorrhagic Infarct



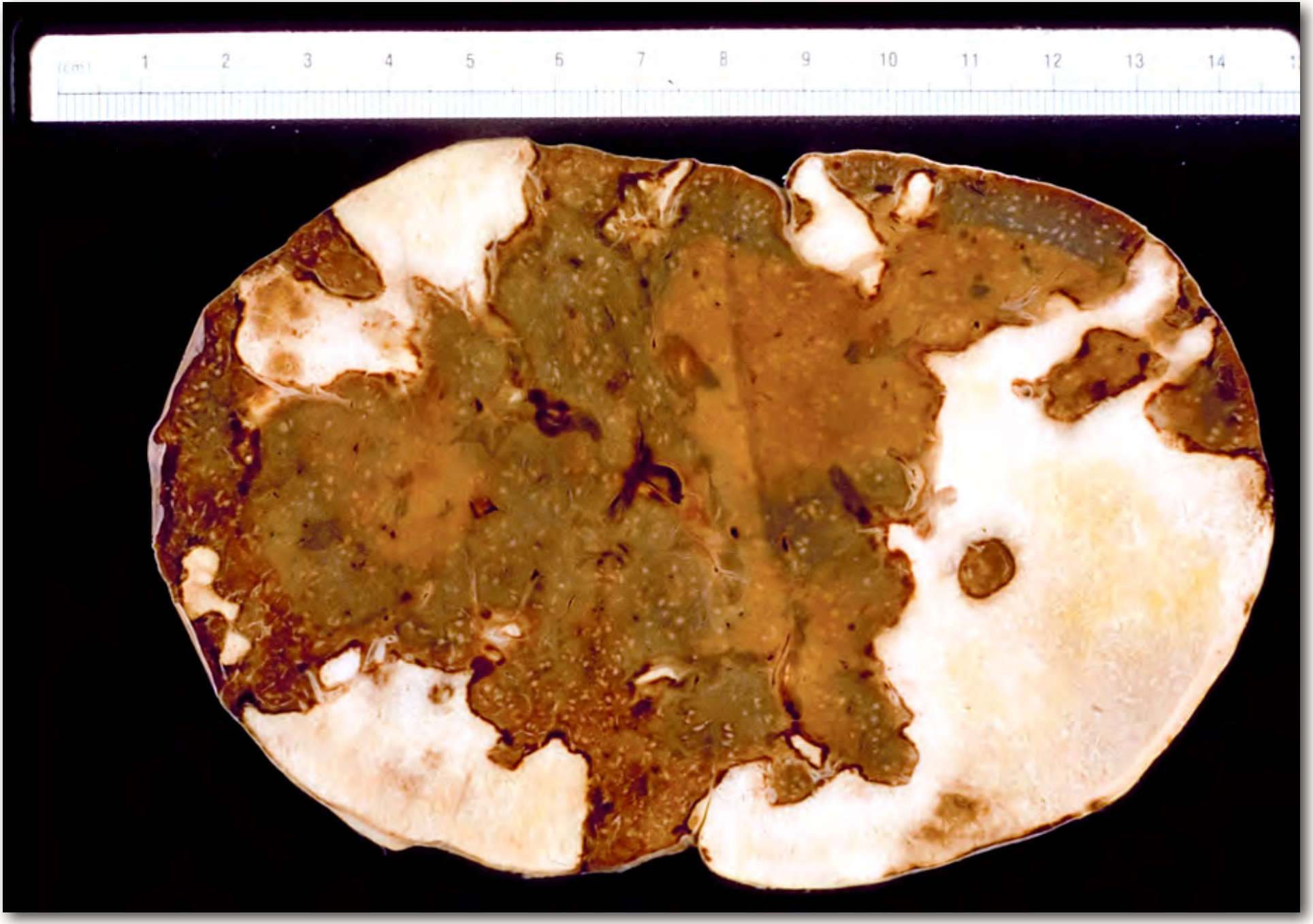
Acute Hemorrhagic Infarct



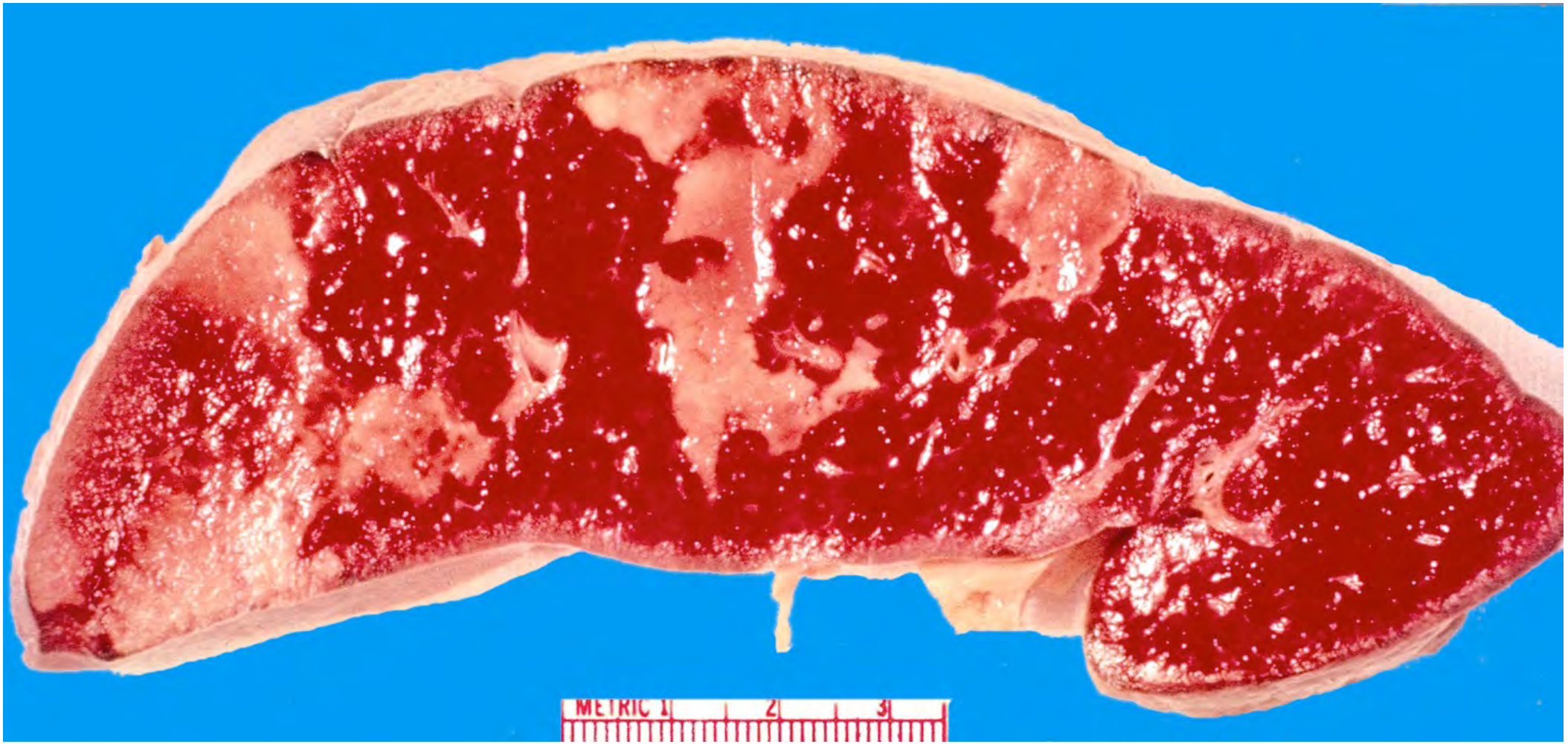
Acute Hemorrhagic Infarct



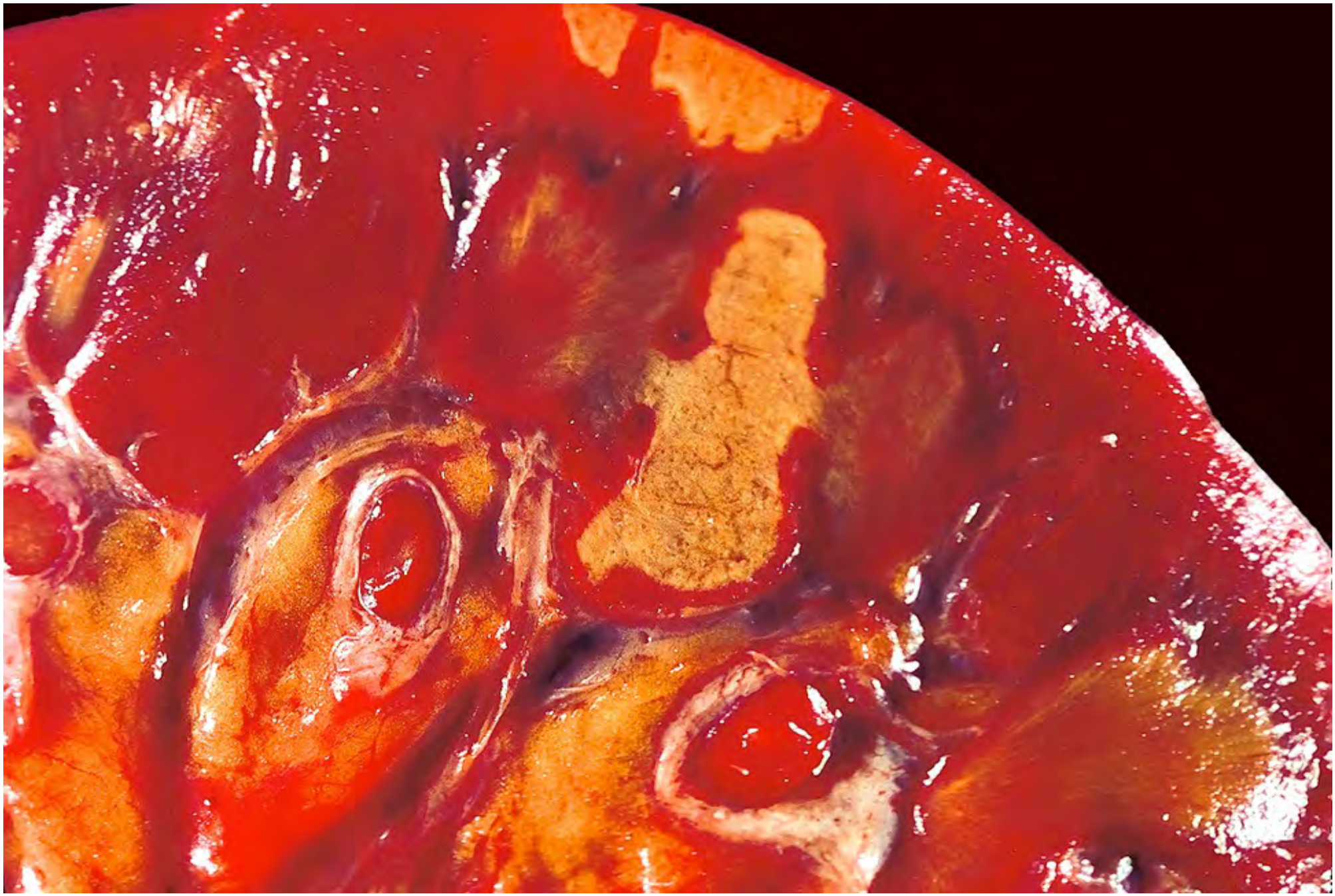
Acute Pale Infarcts



Acute Pale Infarcts



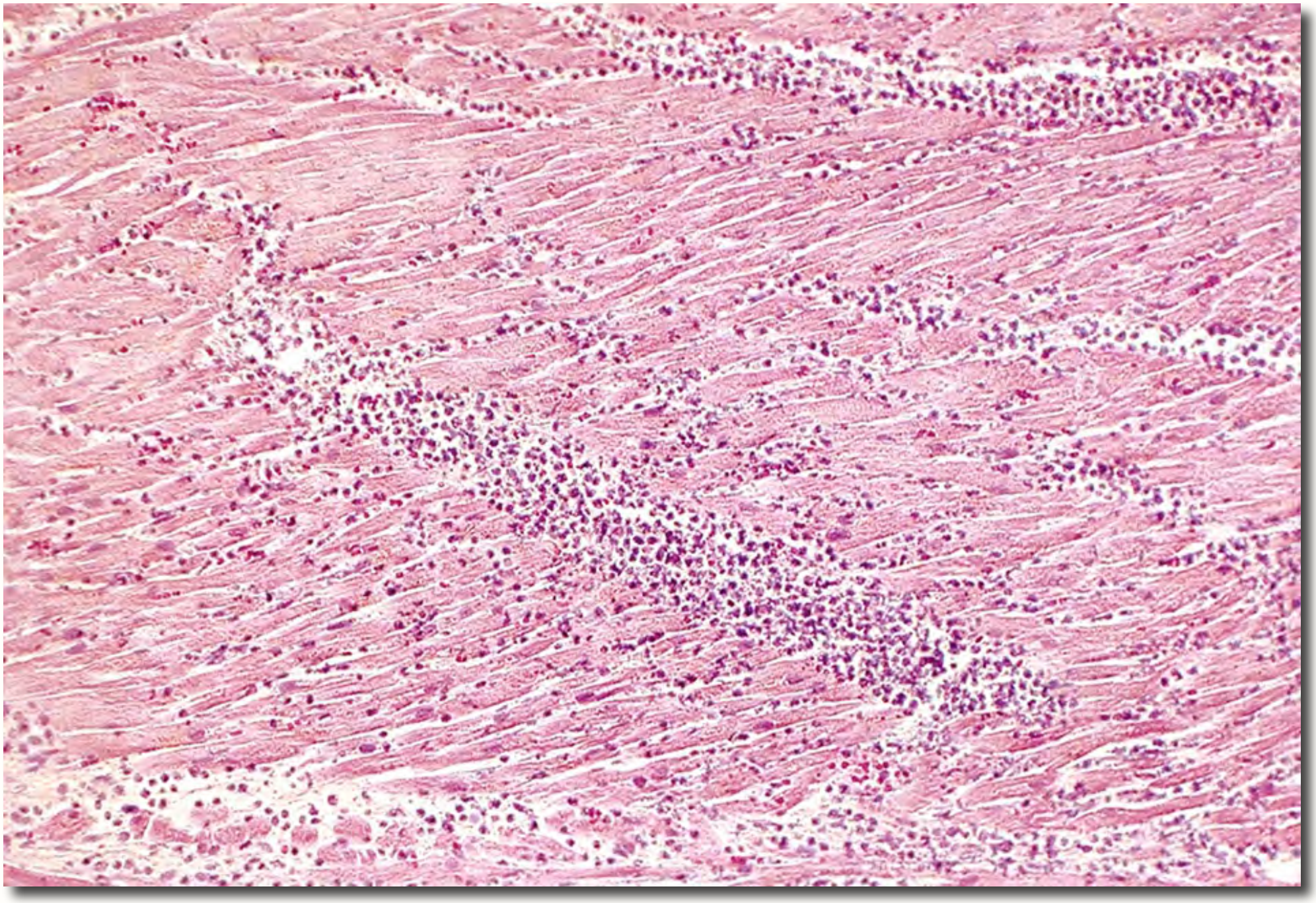
Acute Pale Infarcts



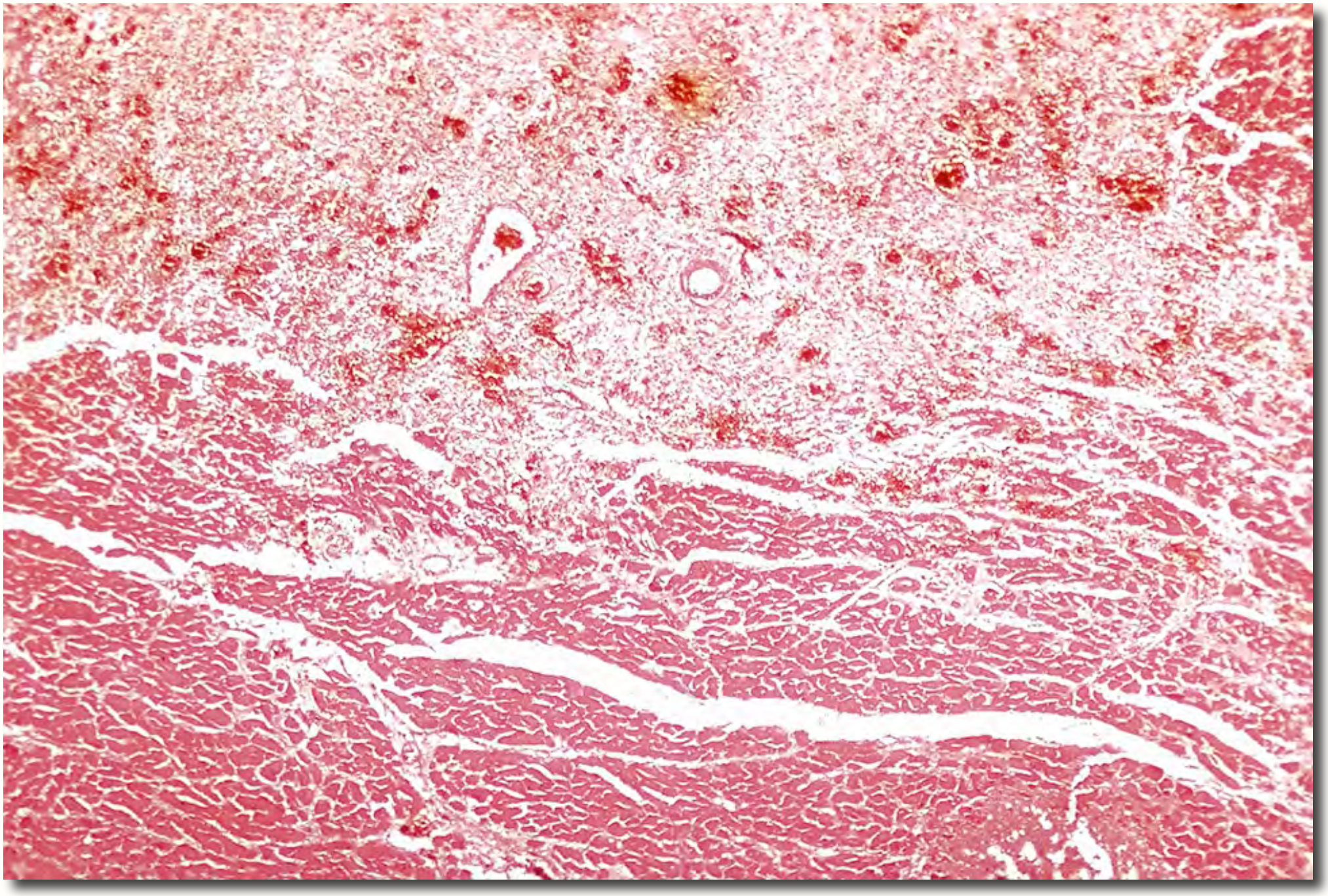
Infarct

- Microscopic Pathology
  - Ischemic coagulative necrosis
    - Brain is the exception with liquefaction necrosis
  - Inflammatory response
  - Granulation tissue (proliferation of blood vessels and fibroblasts) surrounds the infarcted area
  - Fibrosis

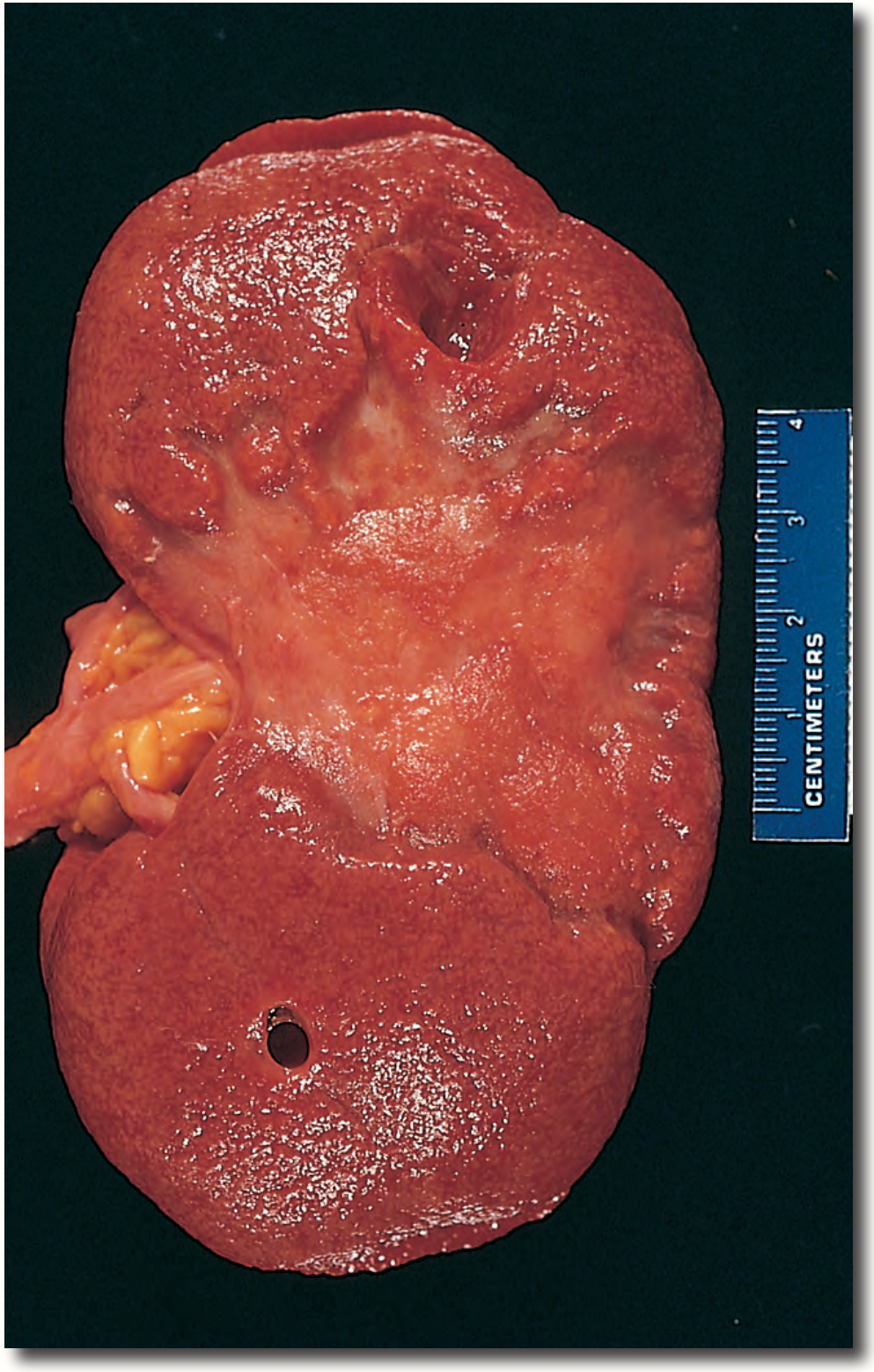
Acute Myocardial Infarct (3-5 Days)



Acute Myocardial Infarct (14 Days)



Remote Infarct



Hemorrhage

- Terminology
  - Petechie
  - Ecchymosis
  - Purpura
  - Epistaxis - bleeding from the nose
  - Hematemesis - vomiting blood

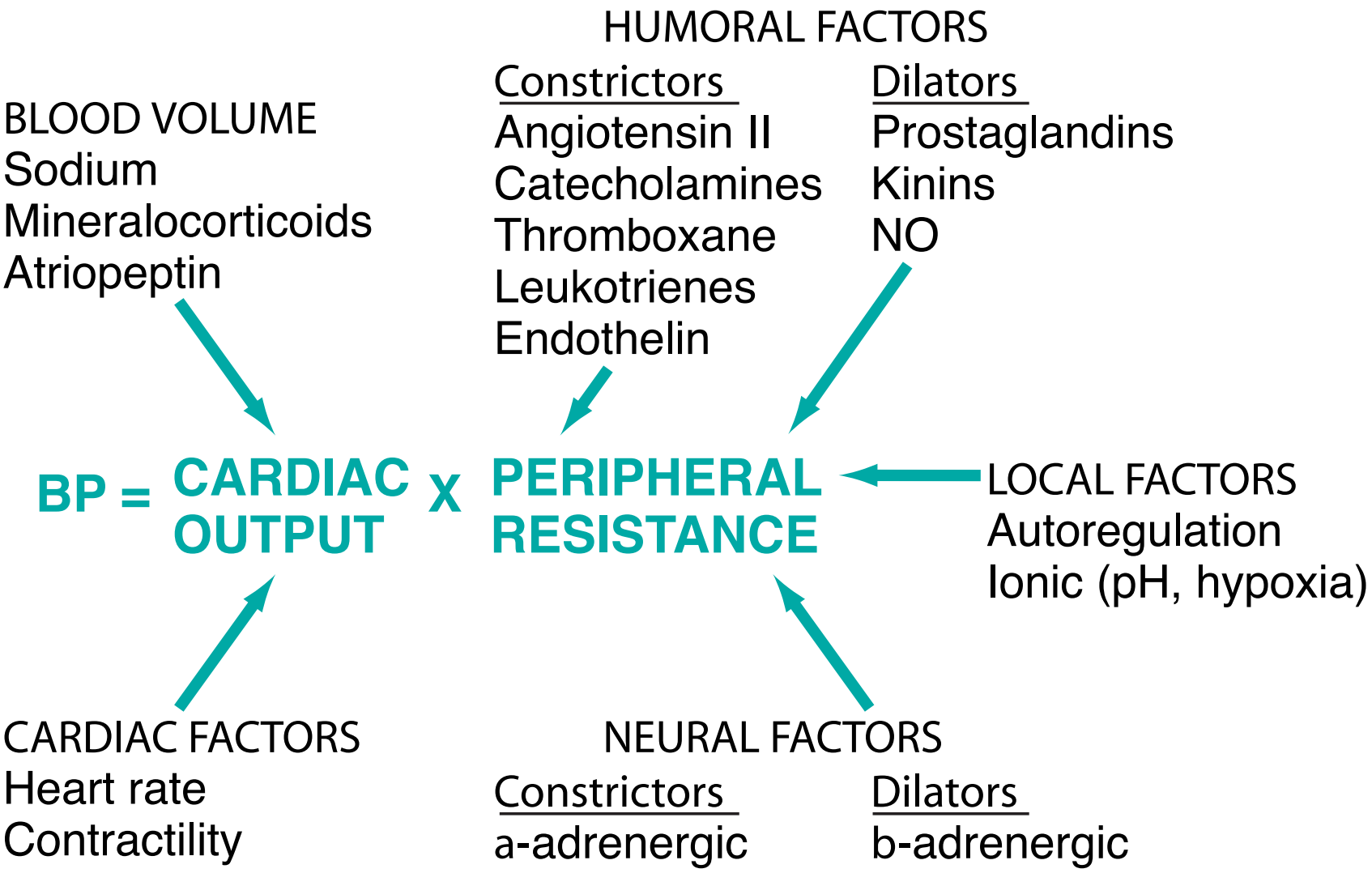
Hemorrhage

- Terminology
  - Hemoptysis - coughing blood
  - Melena - partially digested blood in the stools
  - Hematochezia - passage of bloody stools
  - Hematuria - blood in the urine
  - Hemothorax, hemopericardium, hemoperitoneum - bleeding into the various cavities
  - Hematoma - localized hemorrhage into the tissues or tissue spaces

Shock

- Definition:
  - Widespread hypoperfusion of cells and tissues due to reduction in the blood volume or cardiac output, or redistribution of blood resulting in an inadequate effective circulating volume

Factors Affecting Blood Pressure



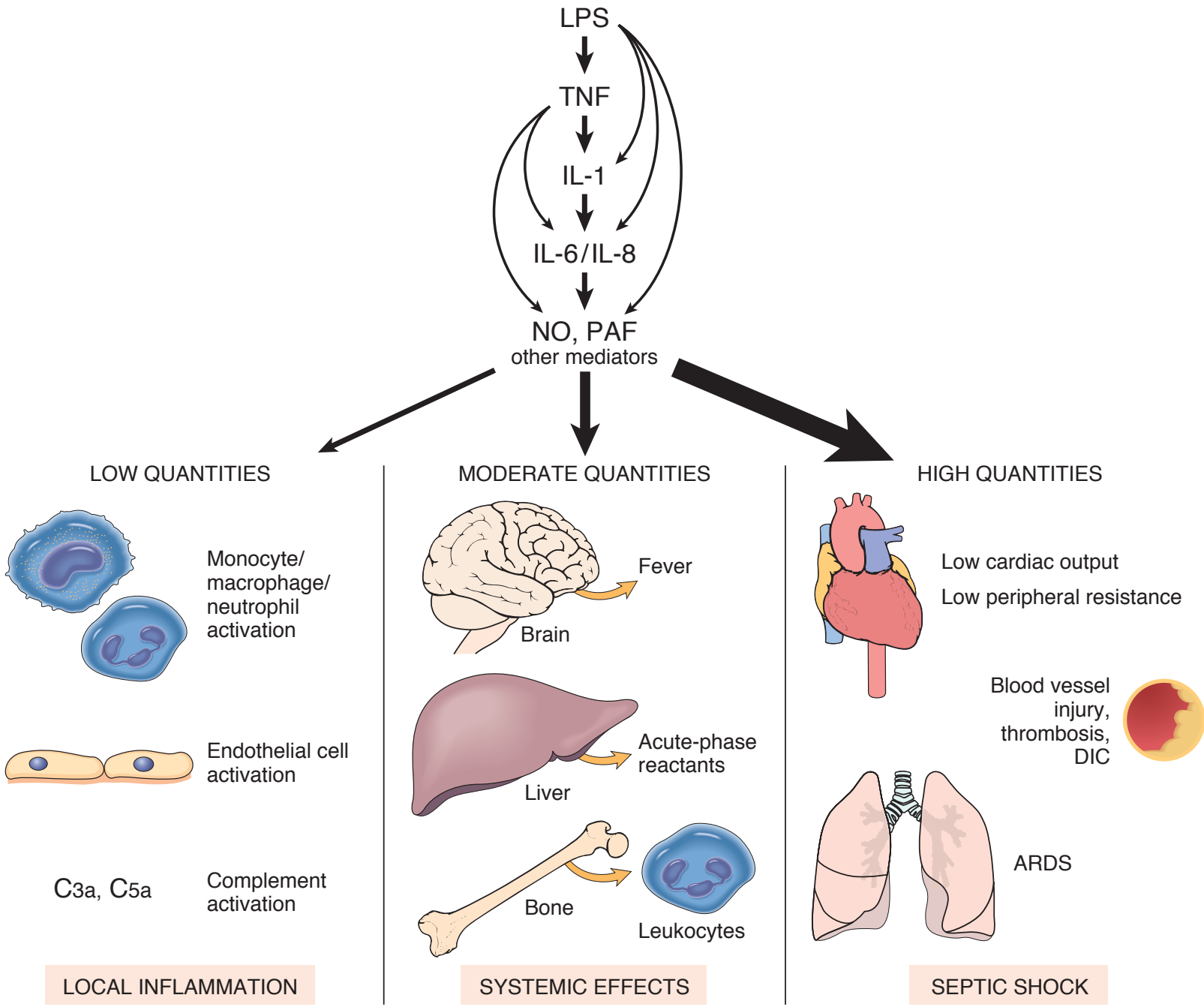
Shock

- Causes
  - Shock may be due to decreased blood volume
    - Loss of whole blood - hemorrhage
    - Loss of plasma (severe burns and peritonitis)
    - Loss of fluids and electrolytes (diarrhea and vomiting; anaphylaxis)

Shock

- Causes
  - Shock may also occur in the presence of a normal blood volume
    - Myocardial infarction, myocarditis, etc.
    - Massive pulmonary embolism
    - Neurogenic shock due to brain trauma or general anesthesia
    - Sepsis
    - Endotoxin shock
      - Vasoconstriction of arterioles and venules
      - Disseminated intravascular coagulation (DIC)
  - Irreversible shock does not respond to therapy

Pathogenesis of Endotoxic Septic Shock



Causes of Shock

Neurogenic

Anaphylactic

Cardiogenic

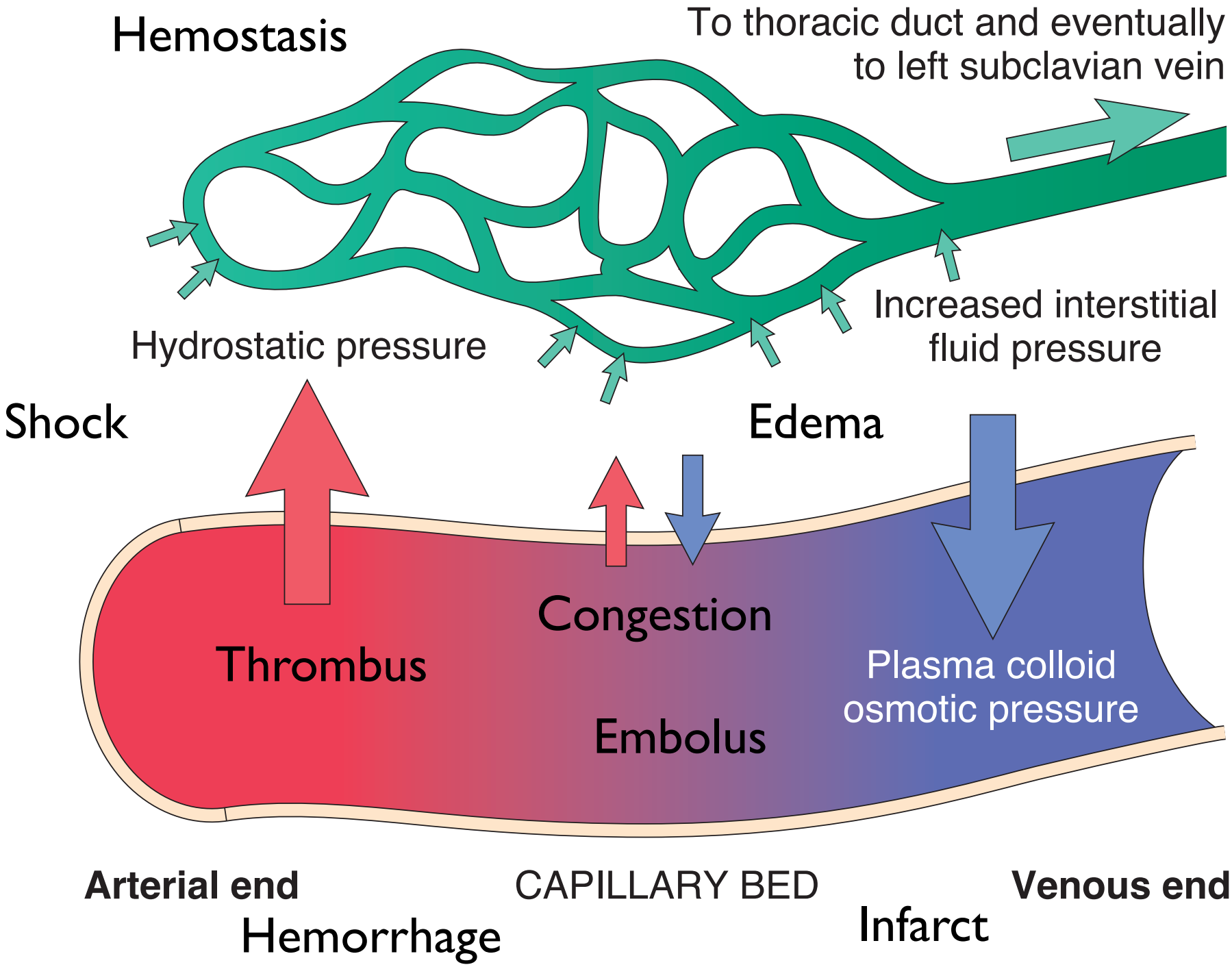
Hypovolemic

Obstructive

Sepsis

Shock

- Pathology - nonspecific
  - Congestion of the viscera
  - Shock kidney - focal tubular necrosis, acute renal injury
  - Shock lung (ARDS) - diffuse alveolar damage, acute lung injury
  - Shock liver - centrilobular hemorrhage and necrosis
  - Thrombotic lesions - more common in endotoxin shock than in shock due to other causes


Hemostasis
To thoracic duct and eventually to left subclavian vein
Hydrostatic pressure
Increased interstitial fluid pressure
Shock
Edema
Congestion
Thrombus
Plasma colloid osmotic pressure
Embolus
Arterial end
CAPILLARY BED
Venous end
Hemorrhage
Infarct