CHS 2413
(Pathology and Physiopathology)

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Hemodynamic Disorders

Pathology of Hemodynamics

1. Edema (increased fluid in the ECF)
2. Hyperemia (INCREASED flow)
3. Congestion (INCREASED backup)
4. Hemorrhage (extravasation)
5. Shock (circulatory failure/collapse)
6. Hemostasis (keeping blood as a fluid)
7. Thrombosis (clotting blood)
8. Embolism (downstream travel of a clot)
9. Infarction (death of tissues w/o blood)

Hemostasis

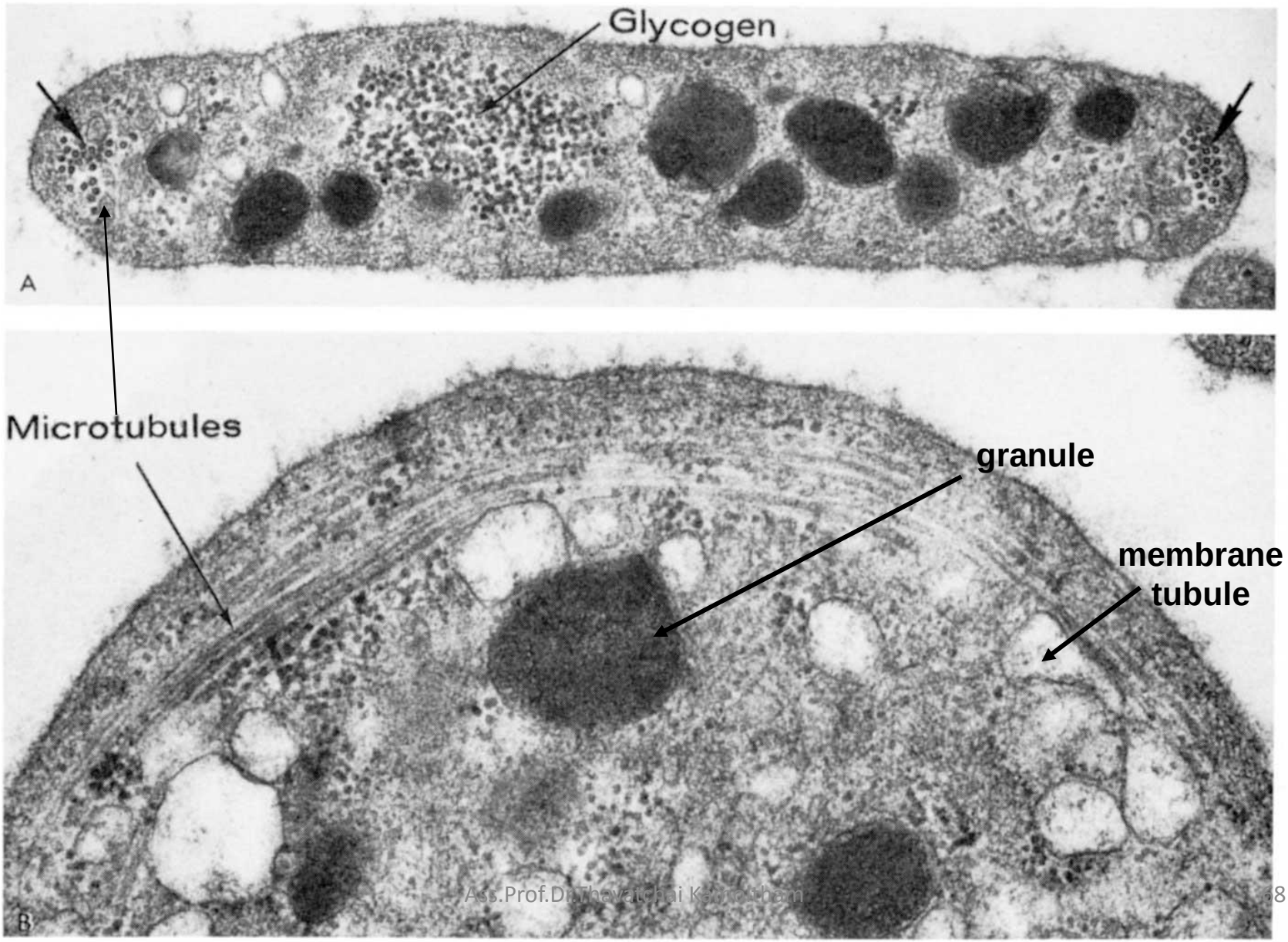
Sequence of events following vascular injury that results in the formation of a clot (stasis)

Key regulators are **endothelial cells** and **platelets**

Platelets (thrombocytes)

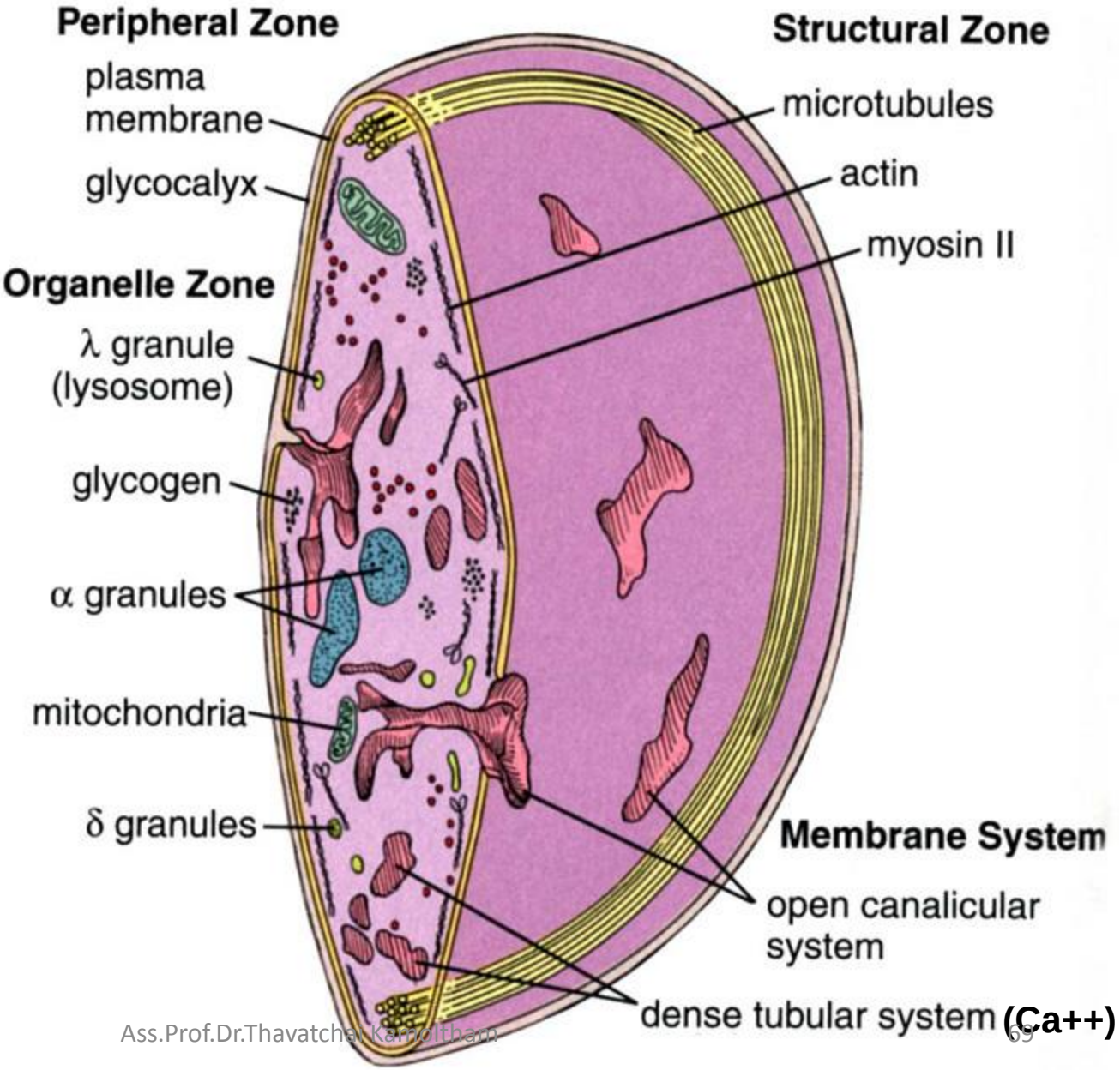
1. **Life Span:** about 10 days
2. **Shape, size, and origin:** Small, biconvex disks, 2-3 µm in diameter. Non-nucleated cell fragments derived from cytoplasm of a very large cell, the megakaryocyte, in bone marrow. Platelets have a life span of about 10 days.
3. **LM appearance in smears:** Small basophilic fragments, often appearing in clusters.
4. **TEM appearance:** The platelet is bounded by a plasma membrane, and has a bundle of microtubules around the margin of the disk (which maintains the disk shape). There are three types of granules, containing fibrinogen, plasminogen, thromboplastin and other factors for clotting. There are also membrane tubules and glycogen.
5. **Function:** Platelets initiate blood clots.

Transmission electron micrographs of a platelet seen in cross section (above) and in a section in the plane of the disk (below)

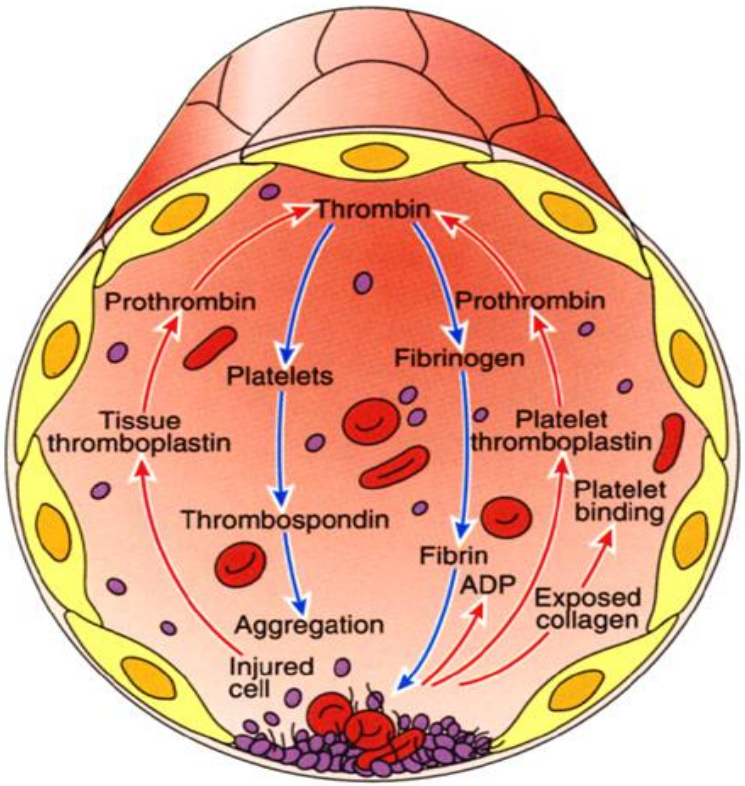


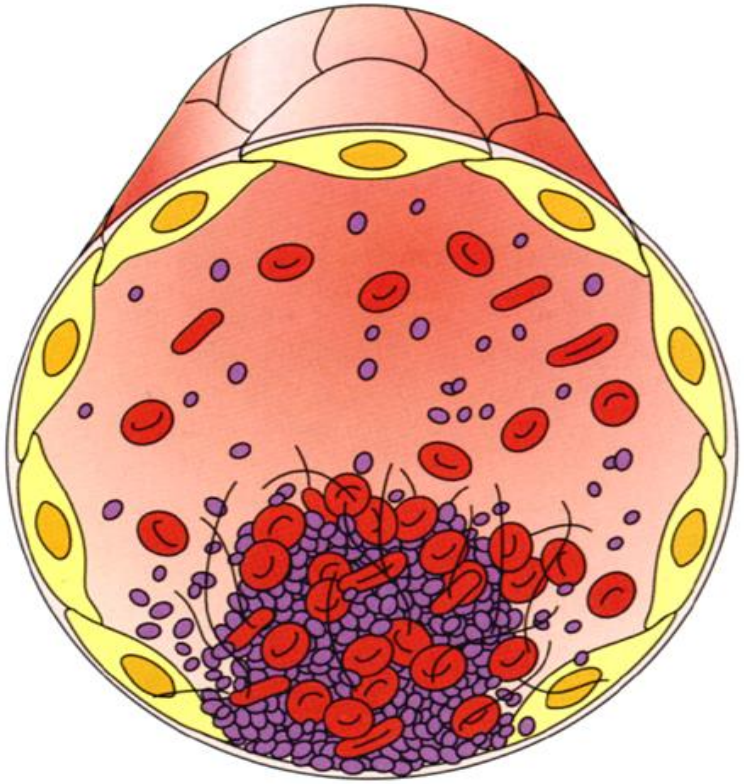
Cutaway diagram of a platelet

1. Peripheral microtubule bundle (maintains shape)
2. Actin and myosin (clot contraction)
3. Organelles facilitate clotting:
   - Mitochondria for ATP production
   - Granules contain clotting factors
   - Dense tubular system sequesters Ca^{++} for signaling (similar to SR in skeletal muscle)
   - Open canalicular system facilitates signaling and secretion



Platelets and blood clot formation





When a blood vessel wall is damaged, factors from the damaged endothelial cells and the ECM induce the clotting cascade. Platelets aggregate and release proteins for clot formation and resolution:

1. Vasoconstriction –via release of **endothelin (from endothelium)**
2. Further platelet aggregation –mediated via **thromboxane A_2** and **ADP**
3. Fibrin polymerization –initiated by **thromboplastin** and free **Ca^{++}**

$$\text{Prothrombin} \xrightarrow{\text{thromboplastin}} \text{Thrombin}$$

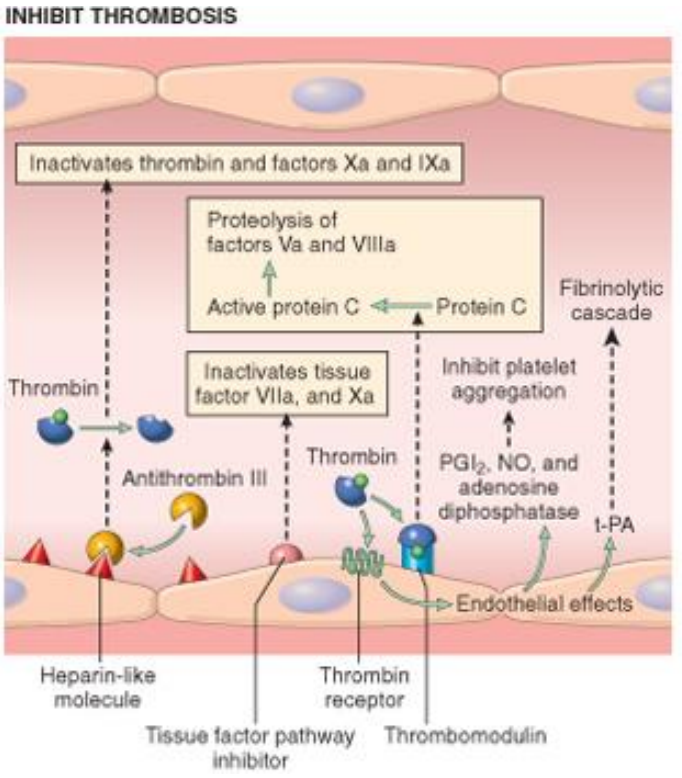
$$\text{Fibrinogen} \xrightarrow[Ca^{++}]{\text{thrombin}} \text{Fibrin} \longrightarrow \text{Fibrin polymerization}$$

4. Clot contraction –via **actin**, **myosin**, and **ATP** released into the matrix of the clot
5. Clot resolution –**platelet plasminogen activator** (**pPA**, converts **plasminogen** into active fibrinolytic **plasmin**)
6. Tissue repair –**platelet derived growth factor** (**PDGF**, stimulates smooth muscle and fibroblast proliferation)

Endothelial modulation of clotting

Antithrombotic properties

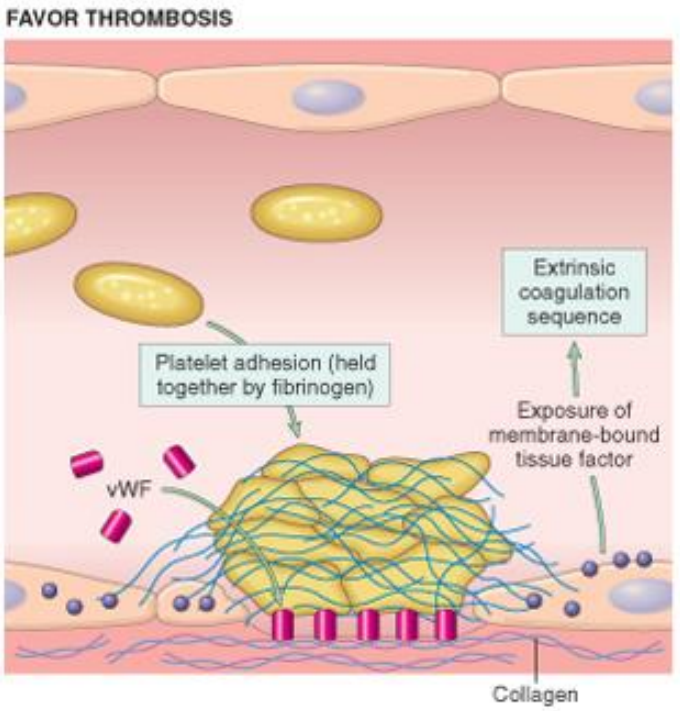
- Antiplatelet effects:
  - Endothelial prostacyclin (PGI_2) and Nitric Oxide inhibit platelet aggregation
  - ADPase: degrades ADP thus inhibiting platelet aggregation
- Anticoagulant effects:
  - Heparin-like co-factors mediate *antithrombin III* inactivation of thrombin
  - *Thrombomodulin* binds and converts thrombin to an anticoagulant enzyme that activates protein (which then inactivates downstream clotting factors)
- Fibrinolytic effects:
  - *tissue plasminogen activator* (tPA) activates plasmin which promotes lysis of clots



Endothelial modulation of clotting

Prothrombotic properties

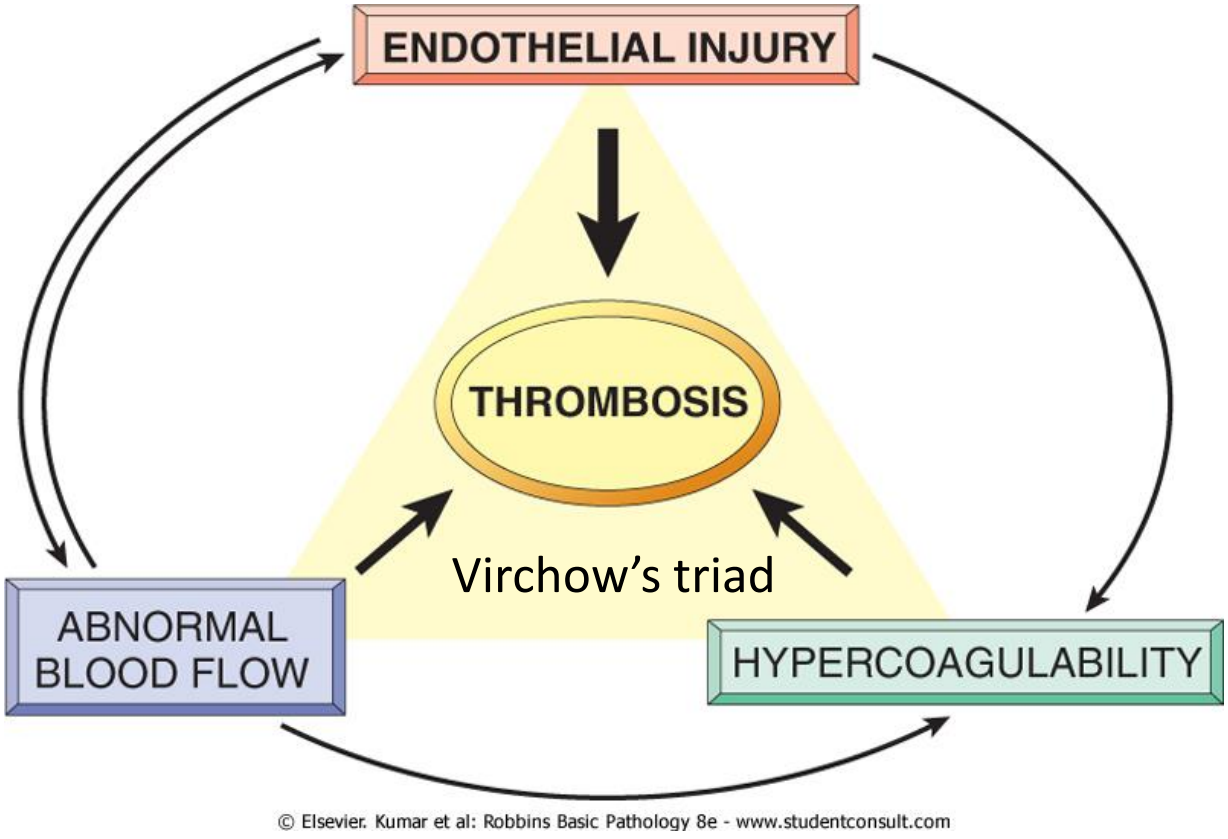
- von Willebrand Factor:
  - Cofactor made by endothelial cells and bound to underlying collagen; when exposed allows platelets to bind to collagen and start to aggregate
- Tissue factor:
  - Activates clotting cascade
  - Induced by proinflammatory cytokines such as IL-1 and TNF
- Plasminogen activator inhibitors (PAIs):
  - **Prevents** cleavage of plasminogen into active plasmin, thus inhibiting fibrinolysis



Perturbations in hemostasis result in **thrombosis**

Endothelial injury:
- Direct injury
- Depletion of anticoagulants (e.g. PGI_2 by Cox-2 inhibitors)
- Upregulation of procoagulants (e.g. inflammation)

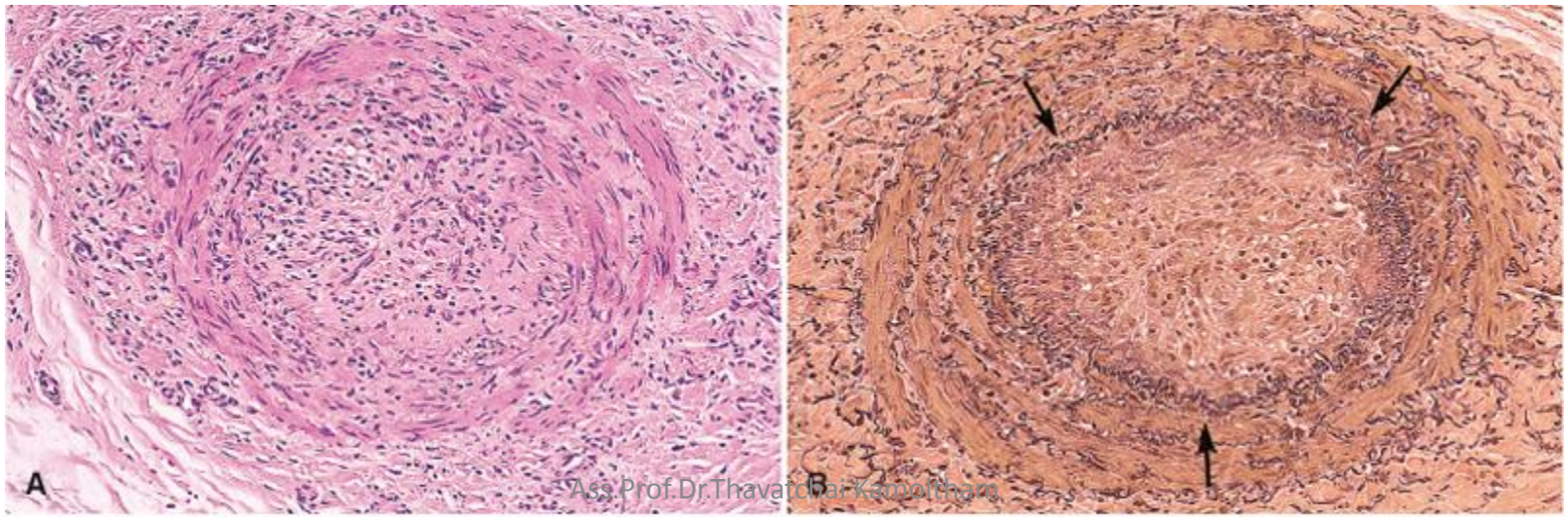
Abnormal blood flow:
- Aneurismal dilation of vessels create local stasis
- Hyperviscosity (too many erythrocytes in blood)
- Sickle cell anemia
- Turbulence at branchpoints



Hypercoagulability:
- **Protease-resistant clotting factors** (e.g. *factor V Leiden*): resistant to cleavage and therefore more active
- **Hormonal:** estrogen **increases** production of clotting factors and **reduces** anticoagulant factors
- **Heparin-induced thrompocytopenia:** administration of full-length heparin causes antibodies to develop that inactivate its antithrombotic activities
- **Antiphospholipid antibody syndrome:** often seen in autoimmune disease (e.g. lupus), Abs activate platelets and inhibit PGI_2 synthesis, thus promoting hypercoagulable state.

Fate of a thrombus

- Dissolution: fibrinolytic activity completely clears thrombus
- Organization and recanalization or incorporation: thrombi in vessels induce inflammation and fibrosis (organization); these can **recanalize** (shown below) or they can become **incorporated** into the vessel wall
- Propagation: thrombus stimulates further platelet aggregation and growth that may eventually occlude vessel lumen
- Embolization: thrombi may break off and plug a distant site



Venous vs. arterial thromobosis

Venous thrombosis

- Superficial (varicosities): cause local edema, pain, and perhaps ulceration; rarely embolize
- Deep (i.e. “DVT”): rarely cause local pain due to collaterals, but often embolize with significant consequences

Arterial thrombosis

- Atherosclerosis: rupture of plaques induces clotting and occlusion of vessels
- Mural thrombosis: post-infarction or post-infection damage to lining of heart induces formation of clots that can break off and plug a distant site.

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Embolism

Embolus = detached mass that is carried to a site distant from its origin, for example:

Fat: bone marrow or soft tissue trauma releases adipocytes into blood that can plug distant sites

Air: rapid depressurization causes gas to bubble out of solution; these bubbles block blood vessels causing infarction in muscles, brain, and other organs

Amniotic fluid: trauma during childbirth may allow amniotic fluid (and its non-fluid contents such as dead skin cells, mucus, etc.) to enter maternal circulation and cause remote blockages.

Thromboembolism

Embolism causing blockage is derived from a thrombus

Pulmonary thromboembolism: thrombus (usually from a DVT) breaks off and goes to right ventricle. From there it is pumped out to the lungs and blocks pulmonary arteries. The problem at first is not the ischemia per se, but instead that this blood is not oxygenated and does not return to the heart (thus eventually causing systemic ischemia).

Systemic thromboembolism: thrombus originates in left ventricular wall or wall of aorta breaks off and causes infarction at a distant site (brain, kidney, spleen).

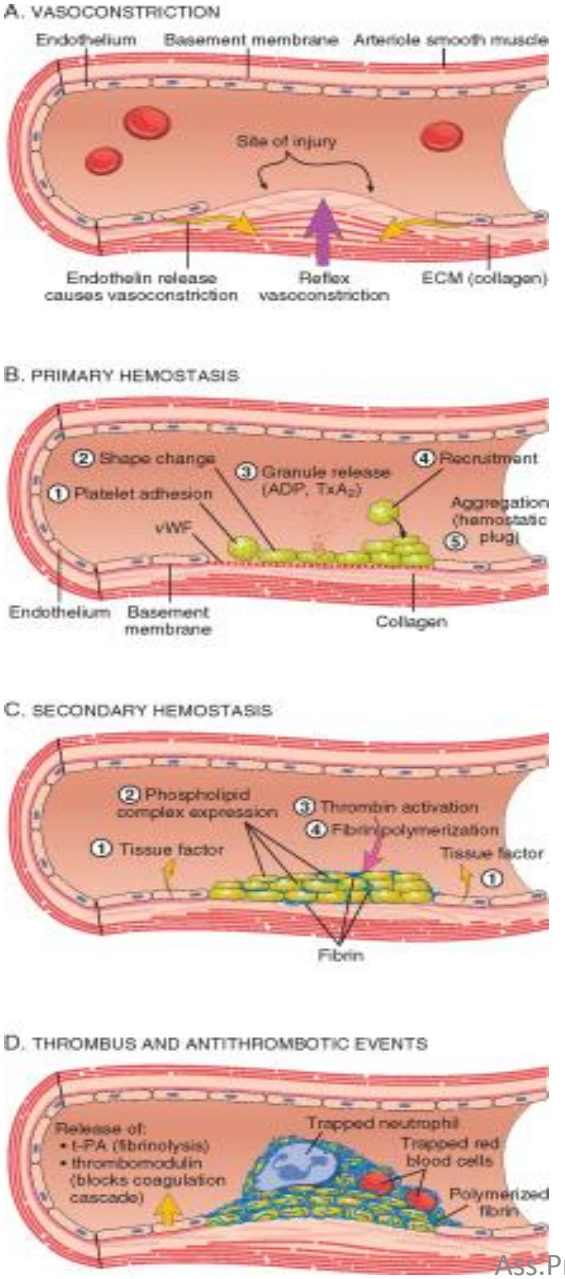
HEMOSTASIS & THROMBOSIS

Normal hemostasis

- Maintain blood in a fluid, clot-free state
- Localized hemostatic plug

<>**Thrombosis**

Blood clot (thrombus) formation in cardiovascular system of a living body



HEMOSTASIS

Three components

- Vascular wall
- Platelets
- Coagulation cascade

Events in hemostasis

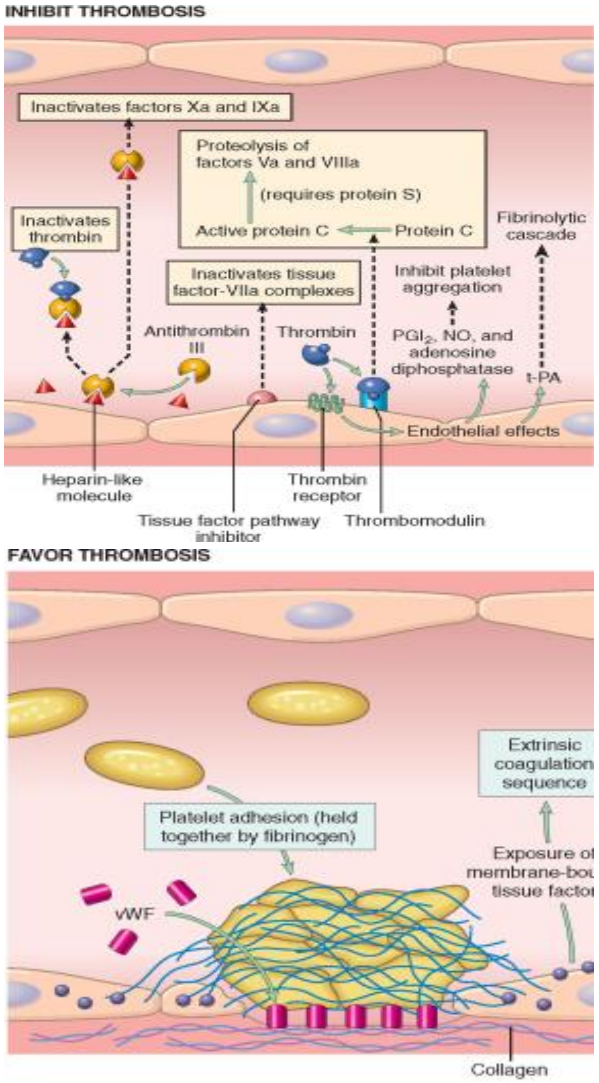
vasoconstriction

primary hemostasis

secondary hemostasis

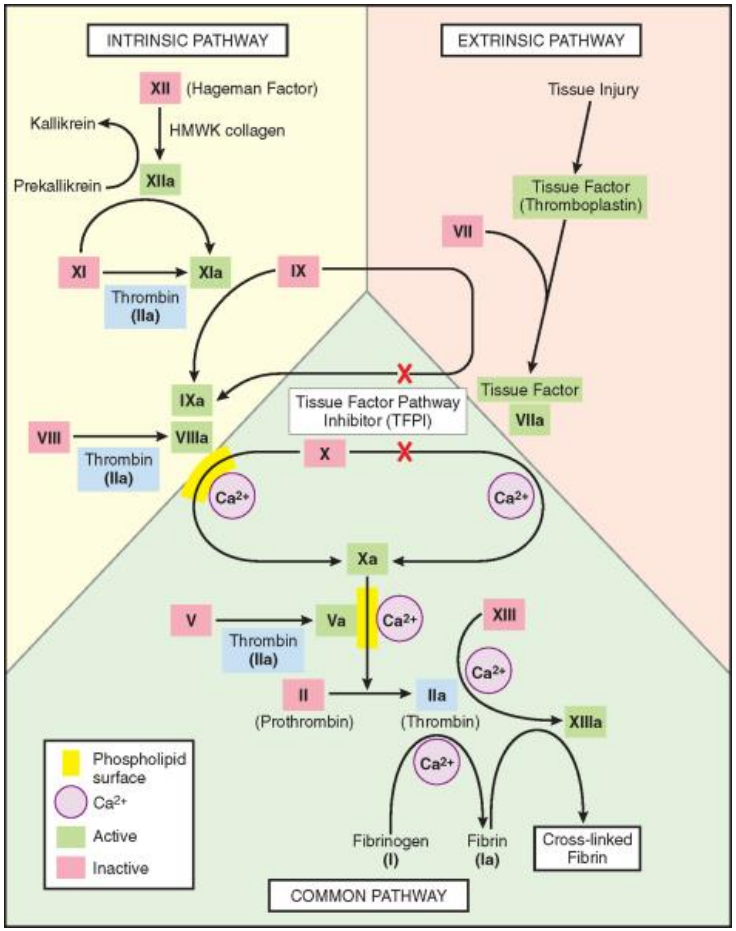
antithrombotic counter-regulation

HEMOSTASIS & THROMBOSIS



- Endothelium
  - Antithrombotic
    - Antiplatelet
    - Anticoagulant
    - fibrinolytic
  - Prothrombotic

HEMOSTASIS & THROMBOSIS



- Platelet
  - Adhesion
  - Secretion
  - Aggregation
- Coagulation casecade

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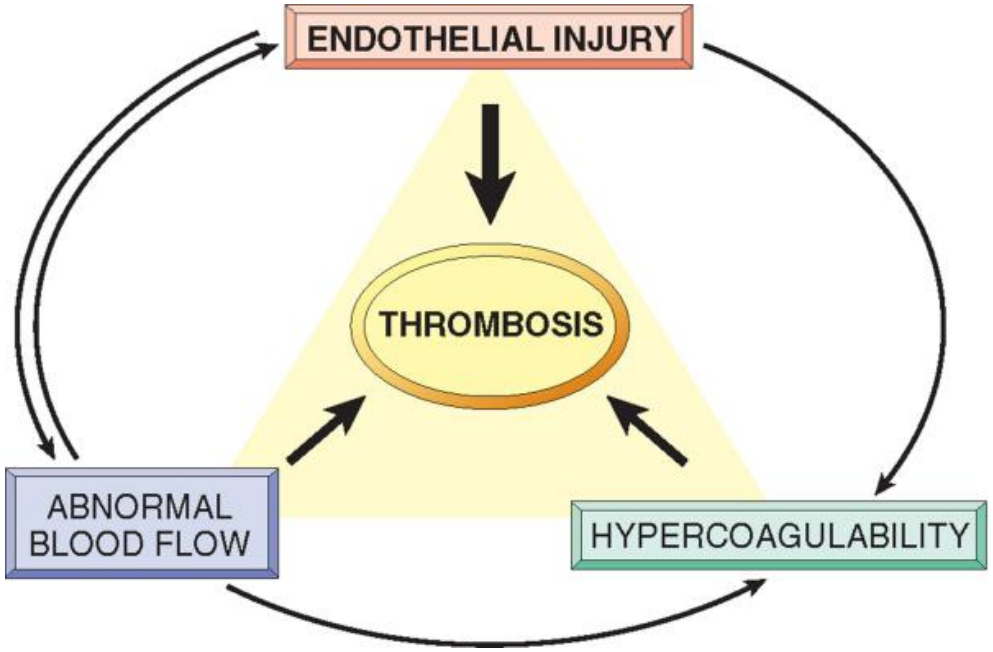
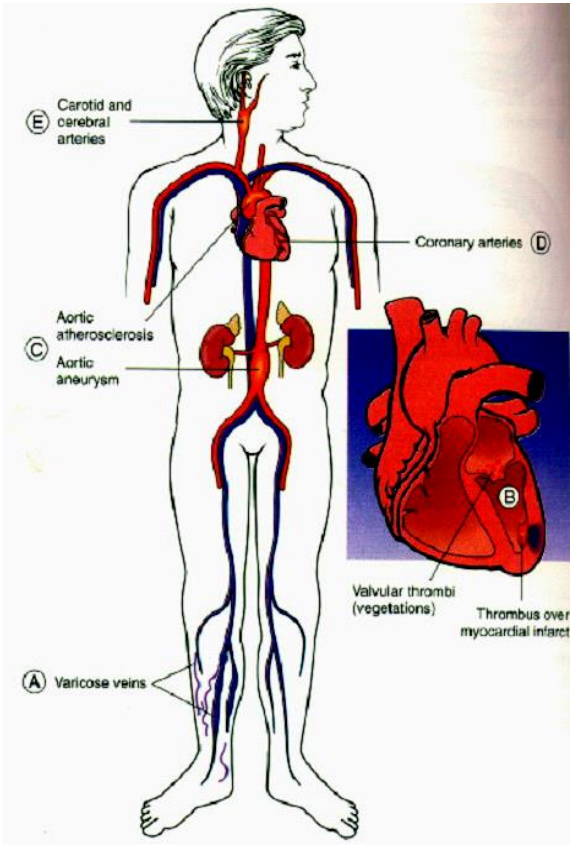
THROMBOSIS



Pathogenesis

- Endothelial injury
- Turbulence of blood flow
- Hypercoagulability

THROMBOSIS



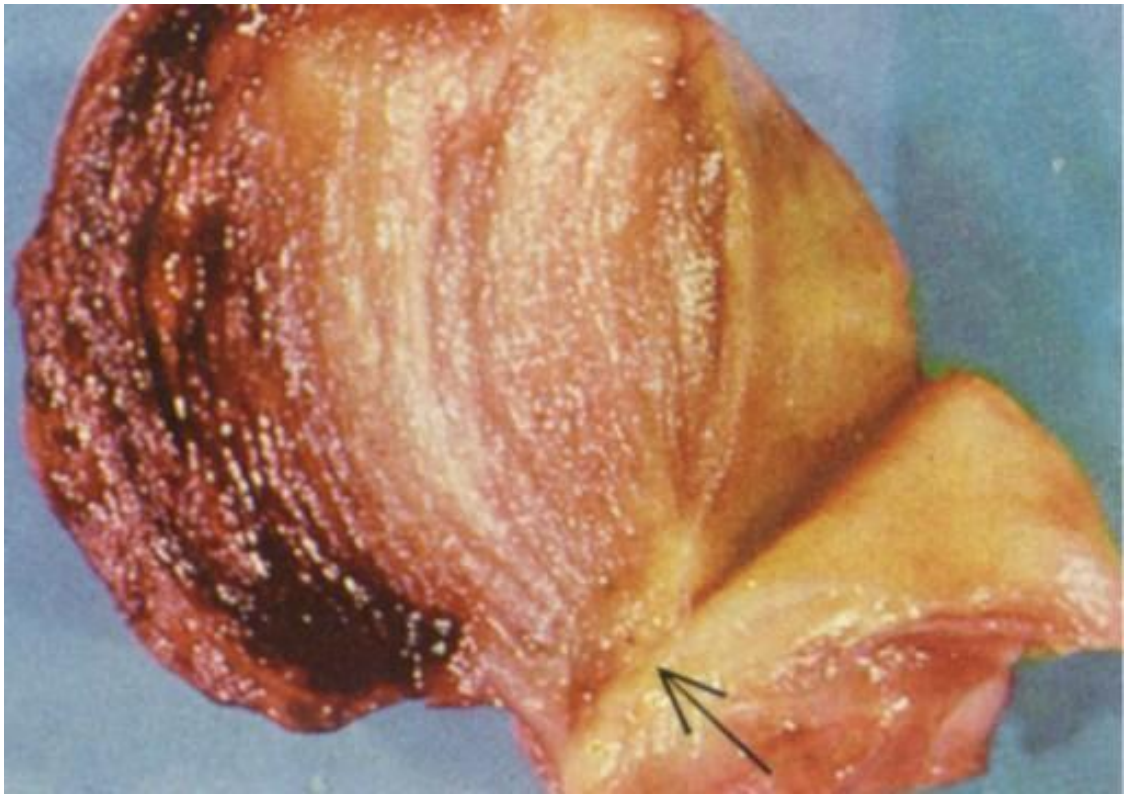
Morphology

- Arterial thrombi
  - Originate from injury sites
- Venous thrombi (phlebothrombi)
  - Originate from the sites of stasis

both extends to the heart

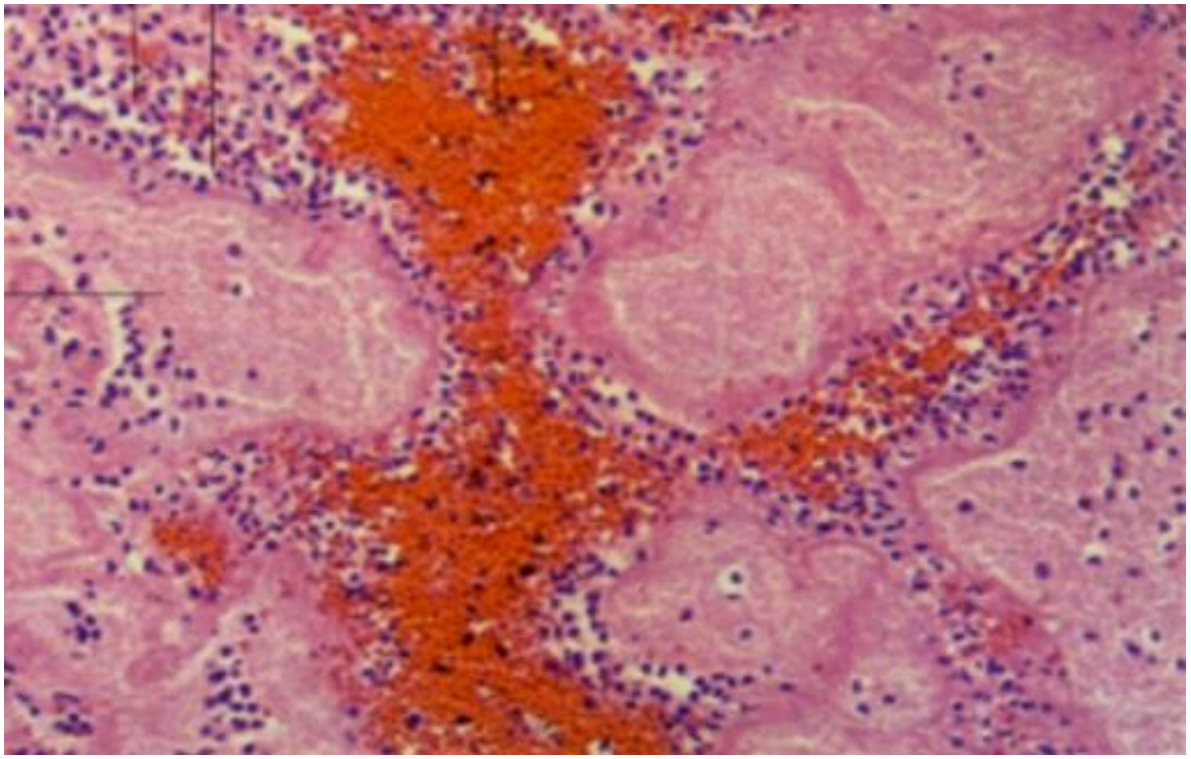
Lines of Zahn
- pale platelet and fibrin layers
- dark erythrocyte-rich layers

THROMBOSIS



Lines of Zahn

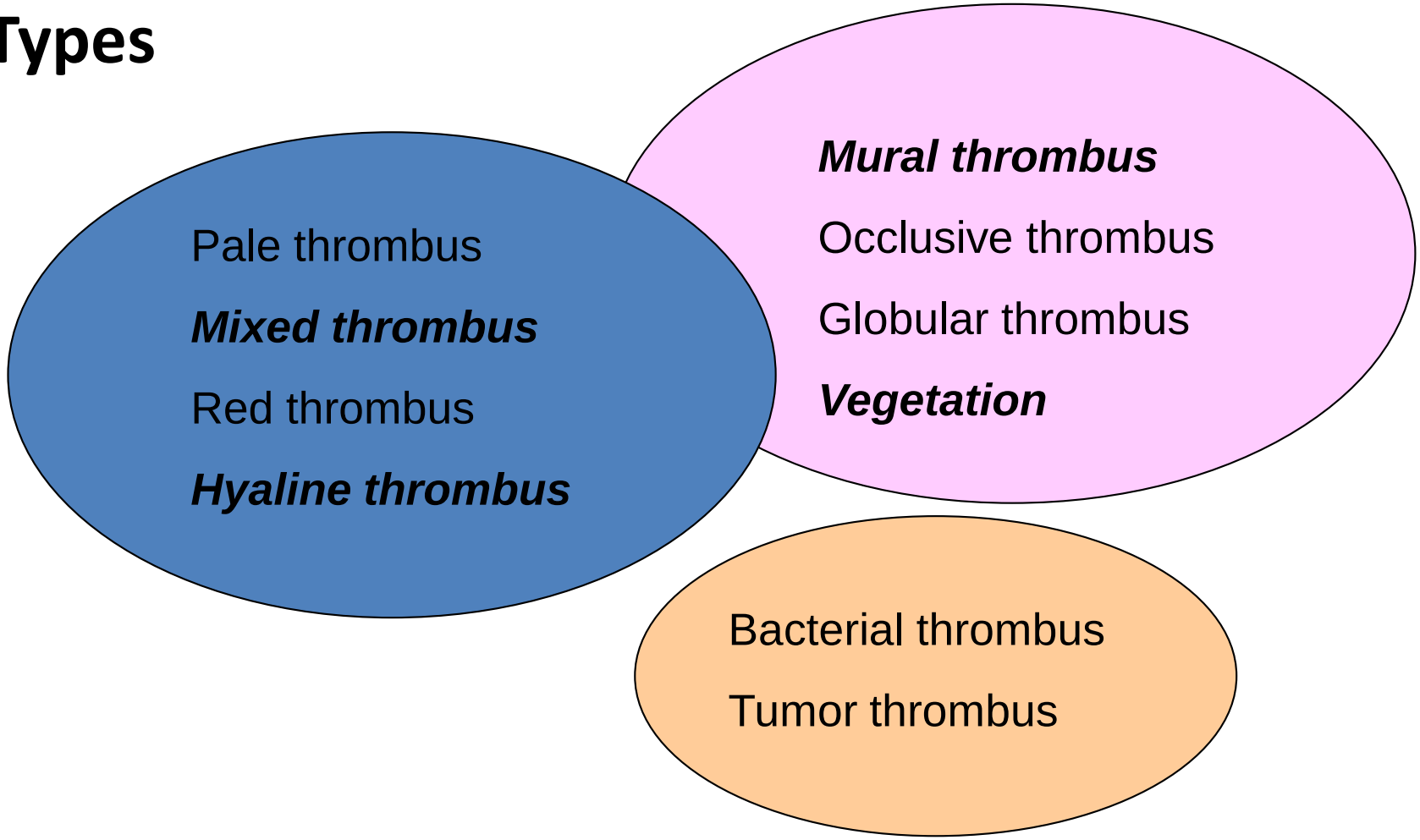
THROMBOSIS



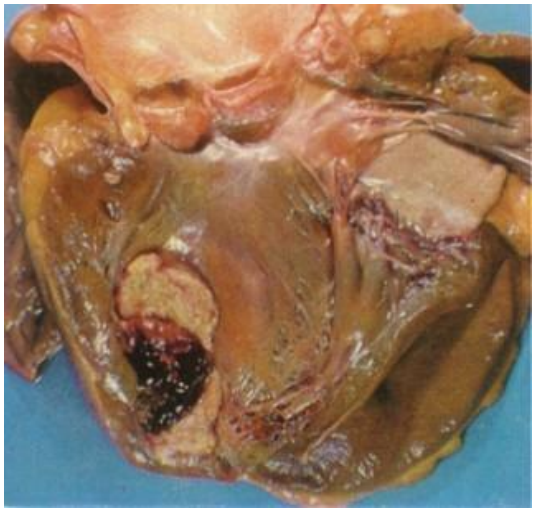
LM: Platelets Trabeculae + Neutrophil
fibrin + red cells

THROMBOSIS

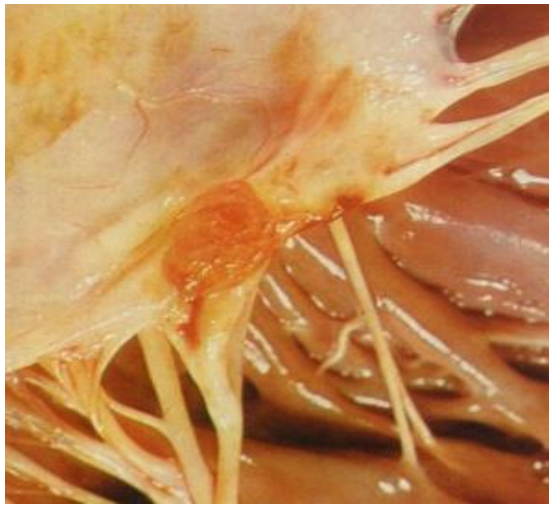
Types



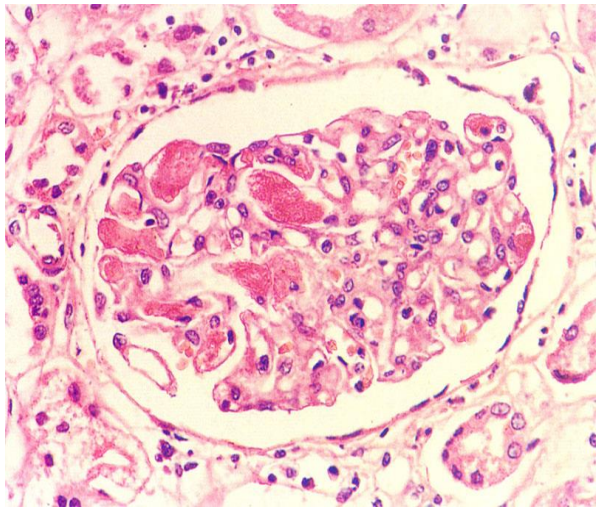
THROMBOSIS



Mural thrombus



Vegetation



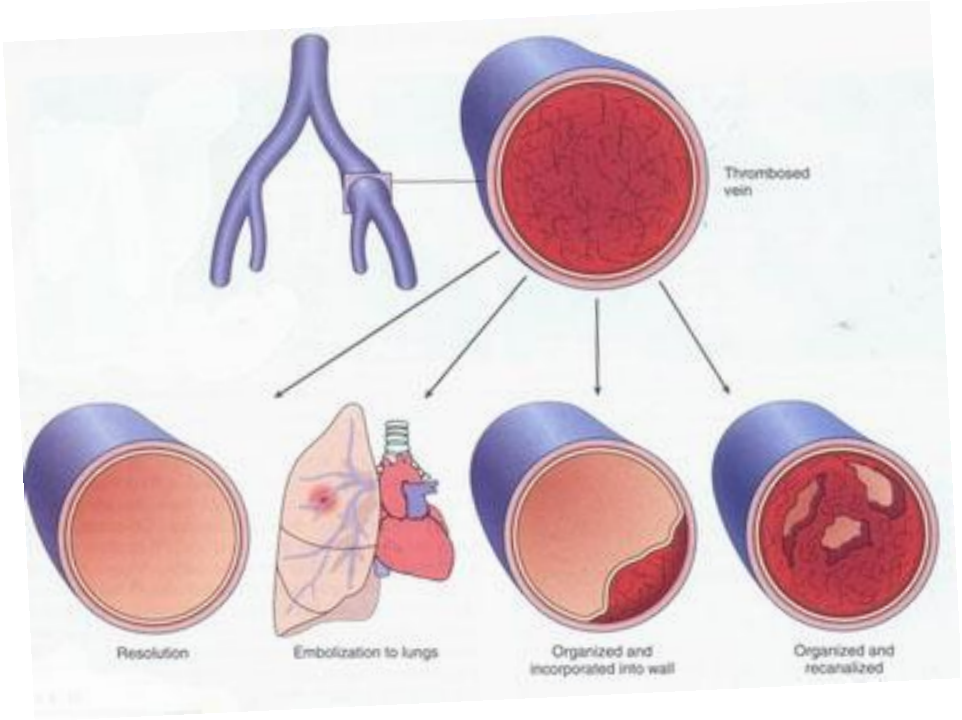
Hyaline thrombus

THROMBOSIS

Differentiation between thrombus from ***postmortem clot***

	Thrombus	Postmortum clots
干	Dry	wet and gelatinous “chicken fat” supernatant
糙	Rough surface	Smooth surface
硬	Hard	Soft
脆	Friable	Gelatinous
层	Lines of Zahn	Homogenous
紧	Firmly attached	No attachment
裂	Slit due to contraction, fragmentation, generate embolus	No slit

THROMBOSIS



Fate

- Propagation and obstruction
- Dissolution
- Embolization
- ***Organization and recanalization***
- Calcification

THROMBOSIS

Clinical correlations

- Venous thrombosis (phlebothrombosis)
  - Varicosities, embolism (sometimes fatal),
  - DVT, trauma, surgery, post partum
  - Cancer associated thrombosis
- Cardiac and arterial thrombosis
  - Mural thrombus
  - cardiac infarction, rheumatic heart disease
  - Embolize peripherally, brain, kidney, spleen, etc

THROMBOSIS

DIC (*Disseminated intravascular coagulation*)

- **Usually happens in many severe disorders**
  severe bacterial or viral infection, allergic disease, anoxia, trauma, shock, malignancy ,etc.
- **Coagulation System is Activated**
  Microthrombi are Formed in Capillaries of Many Organs Platelets + Fibrin
  (lung ,brain ,kidney,liver,GI tract,adrenal gland,etc.)
- **Consumption of coagulation substance and activation of fibrinolytic system**
  hemorrhage diathesis, mutiorgan dysfunction
  consumption coagulopathy / defibrination syndrome
  消耗性凝血病/ 去纤维蛋白综合征

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EMBOLISM

Occlusion of cardiovascular system by some insoluble mass.

The mass is termed “Embolus”.

Solid, liquid, gaseous mass

- Thromboembolism 99%
- Fat, air, amniotic fluid, tumor fragments, bits of bone marrow, etc

EMBOLISM

Route of emboli

- Arterial emboli —— systemic embolism
- Venous emboli —— pulmonary embolism
- Portal vein emboli —— hepatic embolism
- ***Paradoxical emboli***

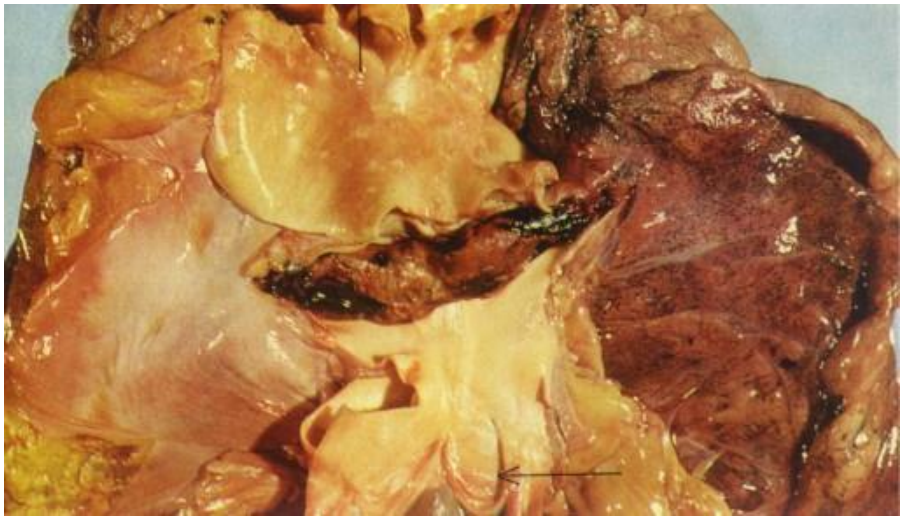
  Emboli from veins of the general circulation pass through an atrial or ventricular septal defect, entering arteries of the general circulation.
- Retrograde emboli

EMBOLISM

Pulmonary Thromboembolism

Incidence: 20-25/100,000 hospitalized patients

Source: >95% from DVT above the knee



EMBOLISM

Results: (depends on the size, number and the clinical setting)

Few Emboli with Small Size :

asymptomatic → infarction (pain and dyspnea)

Numerous Small Emboli :

decrease the volume of pulmonary circulation sharply, pulmonary hypertension and right ventricular failure

Medium Sized Emboli: hemorrhage, infarction

Large Emboli: sudden death, saddle embolus

EMBOLISM

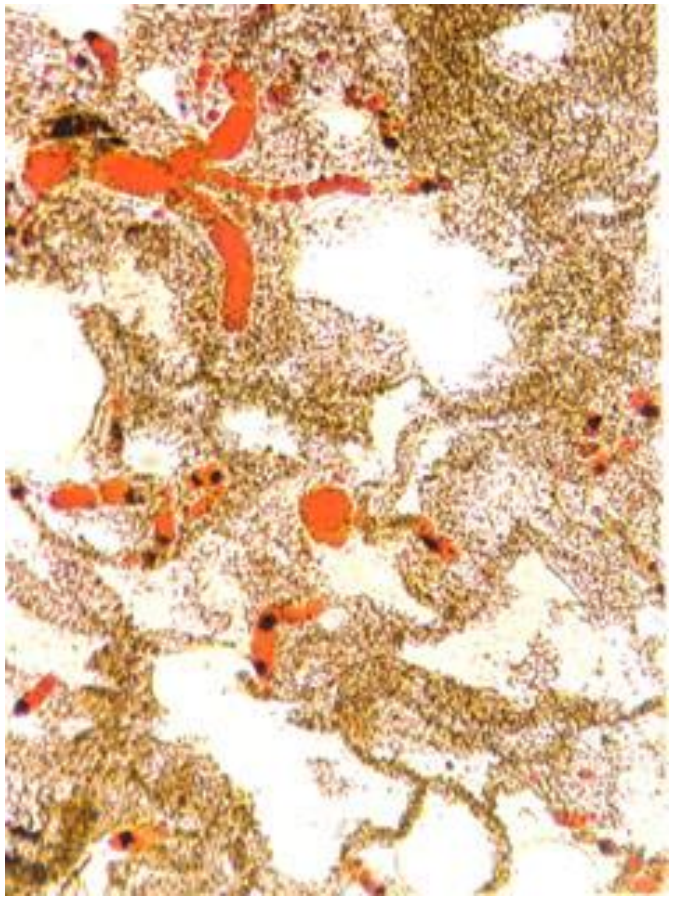
Systemic Thromboembolism

- Source: 80% from intracardiac mural thrombi;
  aortic aneurysms, ulcerated AS plaques, vegetations

- Target sites:
  lower extremities, brain, intestines, kidney, spleen

- Consequences: infarction

EMBOLISM



Fat Embolism

- **Source:**

  Fractures of long bones

  Soft tissue trauma

- **Results:**

  ϕ > 20μm,

  pulmonary embolism

  ϕ < 20 μm,

  cerebral embolism or
  other organ embolism

Special staining (Sudan III)

EMBOLISM

Fat Embolism

- **Pathogenesis**

  obstruction & toxic effect of free fatty acid

- **Symptoms**

  Tachypnea, dyspnea, tachycardia;
  irritability, restlessness, delirium or coma;
  anemia and thrombocytopenia

EMBOLISM

Gas Embolism

- **Source:**

  Exogenic: transfusion,

  operation or trauma in the neck or chest,

  artificial pneumothorax, pneumoperitoneum

  Endogenic: caisson disease or decompression sickness

- **Results:**

  Small amount of gas may be absorbed

  Occupies the heart ventricle, interrupted the blood flow cause death

  Gas embolism in multiple organs (brain, pulmonary)

EMBOLISM

Amniotic Fluid Embolism

Low Incidence (1/10,0000~80, 000) with **high mortality rate** (70%~80%)

Amniotic fluid may enter vascular system through
- Sinusoids which placenta attached
- Torn cervical vessels

Emboli consists squamous epithelial cells, lanugo hair, fat, fetal feces, mucin and TXA2

Cause of death

multiple embolism; reflex vasoconstriction, pulmonary embolism; allergic shock ; DIC

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INFARCTION

The formation of a localized area of ischemic necrosis within a tissue or organ due to impaired arterial supply or the venous drainage

The necrosis area is called “infarct”.

important

An extremely cause of clinical illness:

myocardiac infarction

cerebral infarction

INFARCTION

Causes

- Occlusion of arterial supply or venous drainage

  Thrombosis, embolism, athermanous plaques, external compression

- Functional spasm of arteriole

Types

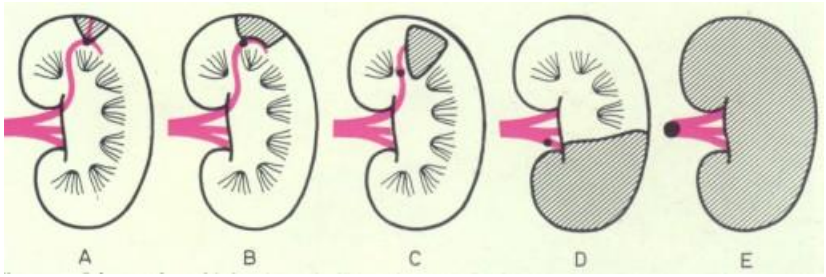
- White infarcts *(anemic infarcts)*
- Red infarcts *(hemorrhagic infarcts)*
- Septic infarcts

Infarction

Area of ischemic necrosis caused by occlusion of arterial supply or venous drainage. Factors that influence development of an infarct and extent of damage is influenced by:

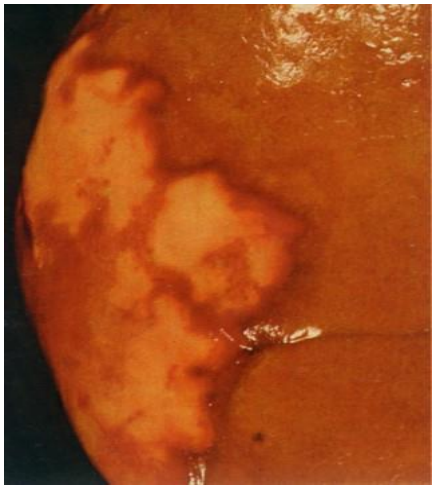
1. **Nature of blood supply:** tissues with dual or collateral blood supply (e.g. lungs, liver, and limbs) are less affected compared to end organs (muscles, brain, kidney, spleen)
2. **Rate of development:** slowly progressing occlusion tolerated because of development of collateral routes
3. **Tissue vulnerability:** neurons can withstand only 3-4 minutes of hypoxia, myocytes ~30 minutes, fibroblasts can survive many hours in low oxygen.
4. **Oxygen content of blood**

INFARCTION



White infarction

- Arterial occlusion
- Solid, compact organs
- Few collateral circulation
- (spleen, kidney, heart, brain, etc.)



Morphology

Gross

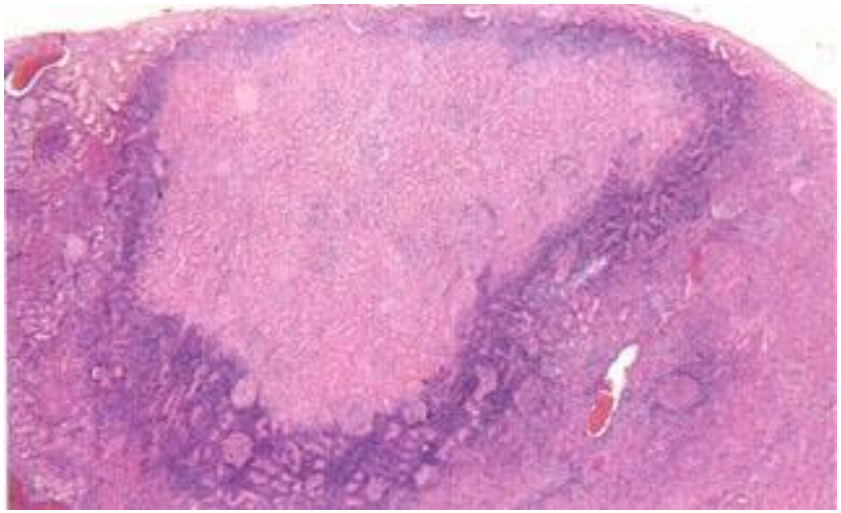
- Dull pale, dry, wedge-shaped necrotic lesion
- A hemorrhagic zone surrounding

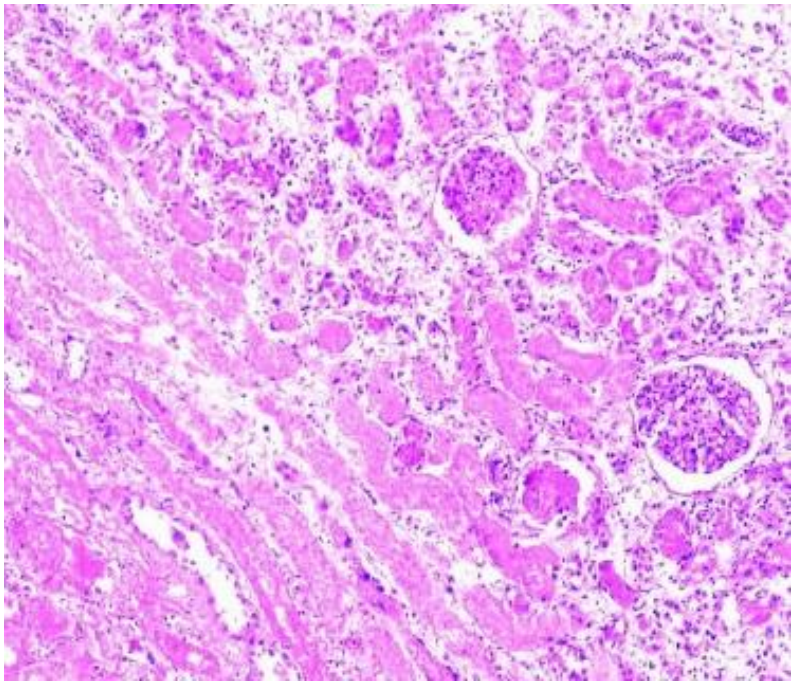
INFARCTION

LM

Ischemic coagulative necrosis

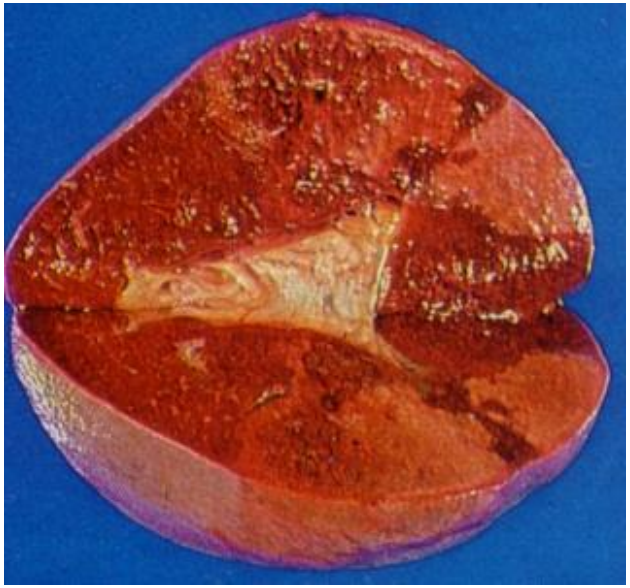
Hemorrhagic zone : inflammatory and granulation tissue.

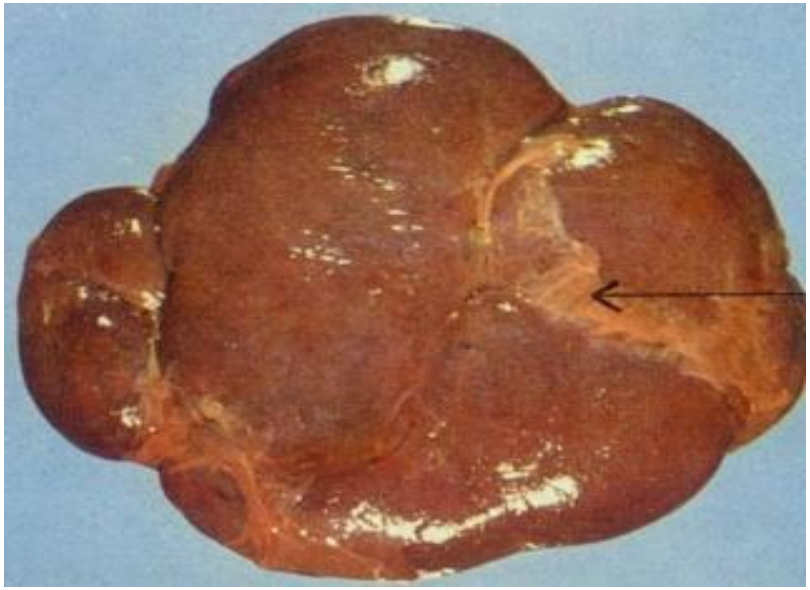




Most undergo organization and scarring in the end.

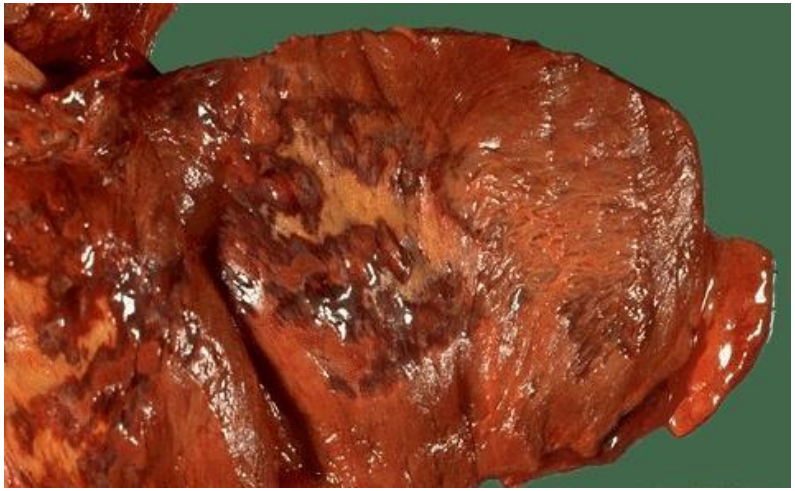
INFARCTION

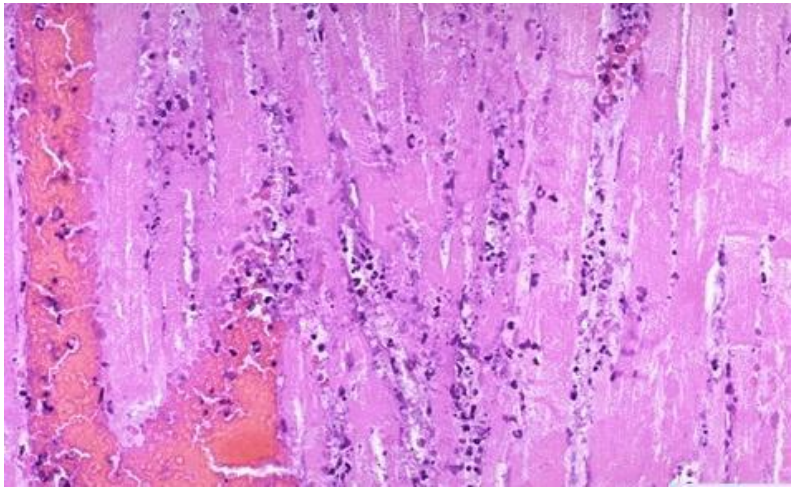




Spleen infarction

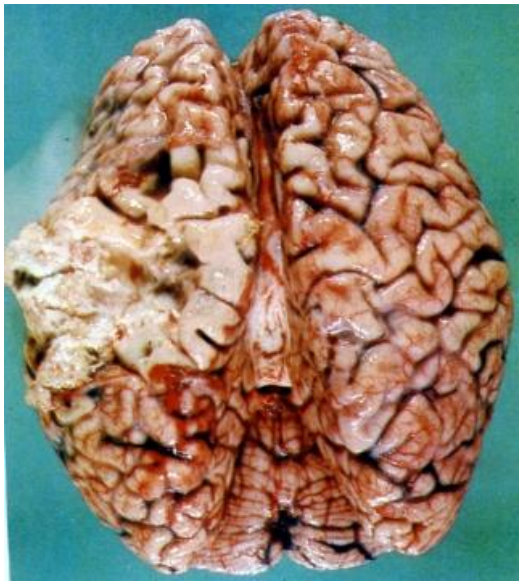
INFARCTION

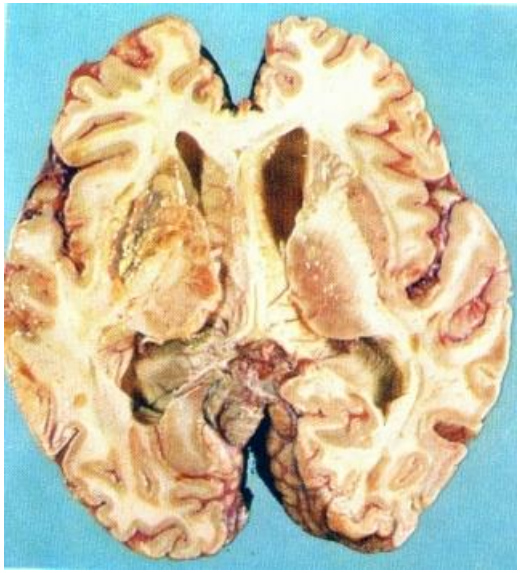


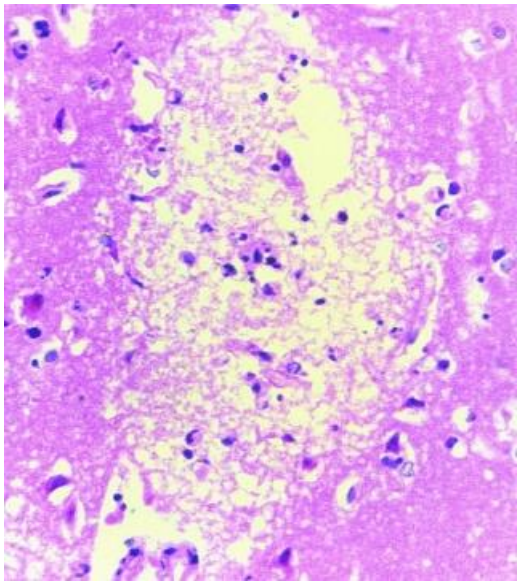


Cardiac infarction

INFARCTION







Brain infarction *(liquefied necrosis)*

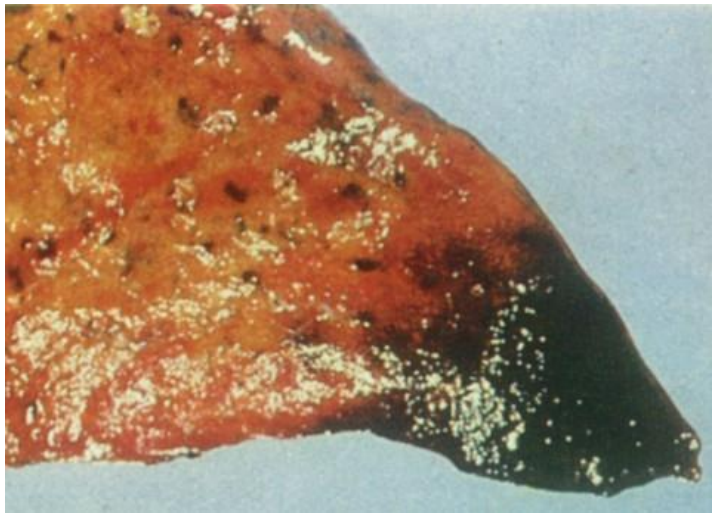
INFARCTION

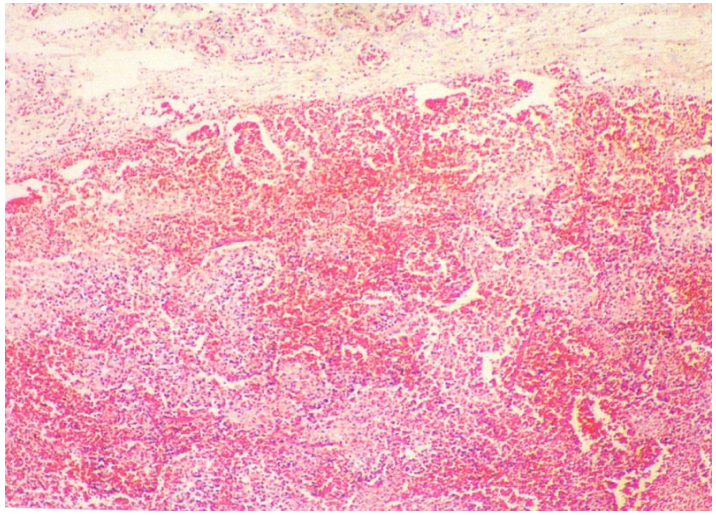
Red infarction

- Arterial occlusion
- Venous occlusion
- Loose tissue
- Dual circulations: *lung , small intestine*

Previously congested
Re-established blood flow to a site of previous arterial occlusion and necrosis

INFARCTION

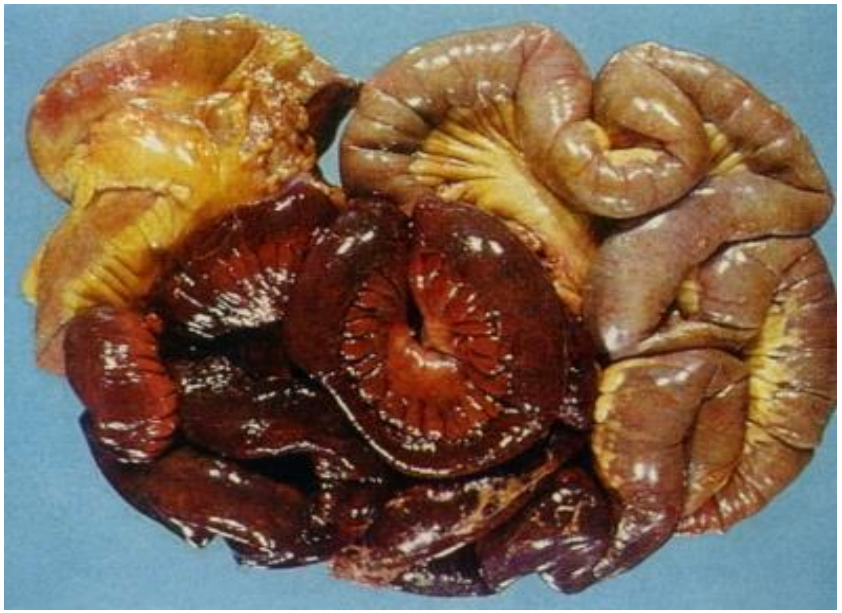




Hemorrhagic infarction of the lung

Gross	Roughly wedged shaped
	Dark red, solid area
	Base beneath the pleura
	Fibrin exudation
LM	Coagulative necrosis
	Large amounts of RBC filled in alveolar space
	Obscure structure

INFARCTION

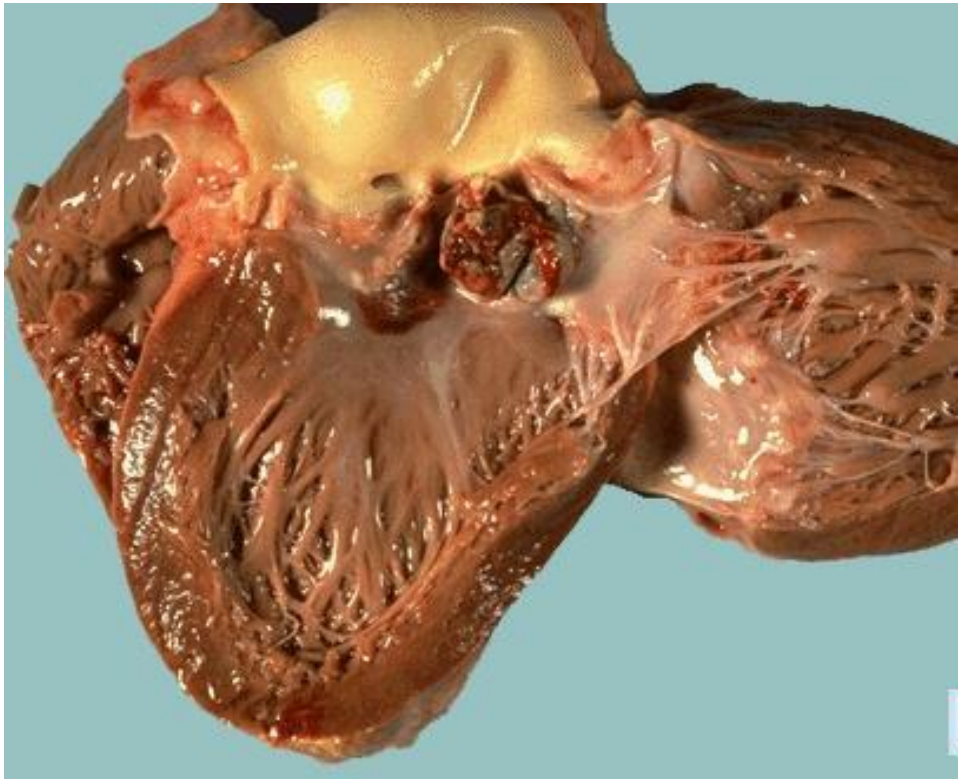


Hemorrhagic infarction of the intestine

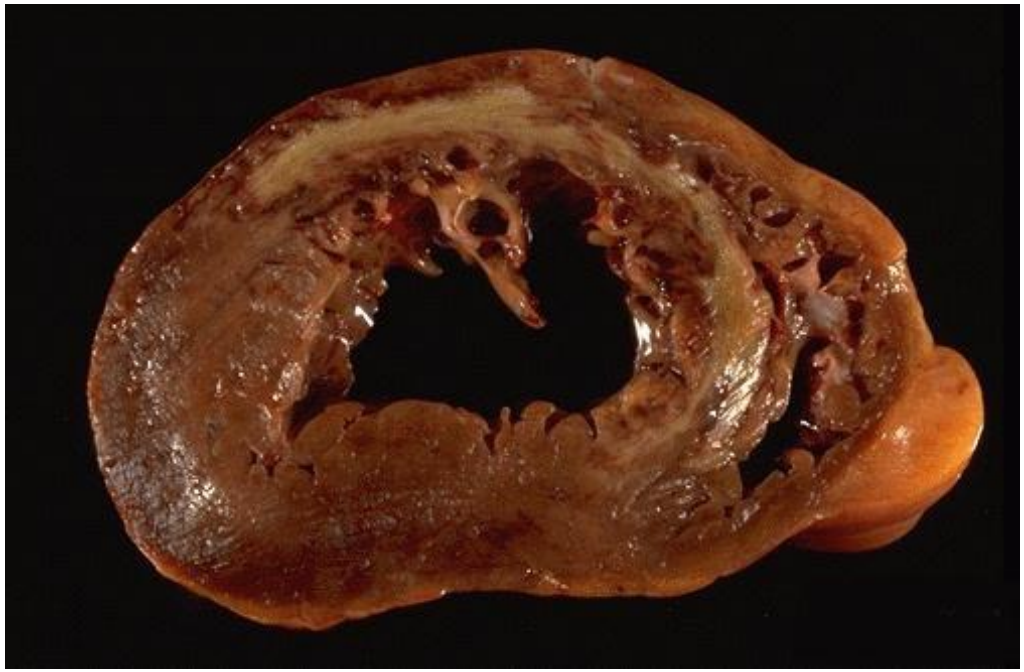
INFARCTION

Septic Infarction

- Bacteria containing emboli
- May form abscess and pus



INFARCTION



Fate of Infarct

- Enzymatic lysis, liquefaction and absorption
- Organization with scar formation
- Encapsulation and Calcification

INFARCTION

Factors that influence development of an infarct

- Nature of the vascular supply
- Rate of development of occlusion
- Vulnerability to hypoxia
- Oxygen content of blood