# Hemodynamic Disorders

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# Objectives of hemodynamics

- Hyperemia
- Congestion and Odema
- Types and causes of odema
- Hemorrhage (types of hemorrhage)
- Thrombosis & DIC
- Embolism. (Types of Embolism )
- Infarction.(Types of Infarction)
- White infarction
- Red infarction
- Shock(Types of shock )
- Hypovolemic shock , Septic Shock
- Anaphylactic shock
- Neurogenic shok
- Cardiogenic shock

# Introduction

- **Hemodynamic disorders** are very common & extremely important cause of clinical illnesses.
- The health of cells & tissues depends on the circulation of blood , which delivers oxygen & nutrients and removes wastes generated by cellular metabolism .
- Under normal conditions, as blood passes through capillary beds, proteins in the plasma are retained within the vasculature and there is little movement of water & electrolytes into the tissues .
- This balance is often disturbed by pathologic conditions that alter endothelial cells function, increase vascular pressure, or decrease plasma protein content, all of which promote **edema** i.e. accumulation of fluid in extra vascular spaces.

- **Hemostasis** is the process of **blood clotting** that prevents excessive bleeding after blood vessel damage.
- Hemostasis is the mechanism that leads to cessation of bleeding from a blood vessel. It is a process that involves multiple interlinked steps. This cascade culminates into the formation of a "plug" that closes up the damaged site of the blood vessel controlling the bleeding
- Inadequate hemostasis may result in **hemorrhage** which can affect tissue perfusion & if its massive and rapid; it may lead to hypotension, shock & death.
- Conversely, inappropriate clotting i.e. **thrombosis** or migration of clot called **embolism** can obstruct blood vessels causing ischemic cell death i.e. **Infarction.**
- **Thrombo-embolism** lies at the heart of three major causes of morbidity & death in developed countries, **myocardial infarction**, **pulmonary embolism** & cerebro-vascular accidents **(CVA) or stroke.**

# HYPEREMIA & CONGESTION

- Both terms, hyperemia & congestion, indicate increased local blood volume in a particular tissue.
- But **Hyperemia** is *an active process*, resulting from increased blood flow due to arteriolar dilation, at sites of inflammation or in skeletal muscle during exercise, & the hyperemic tissue is red .
- **Congestion** is *a passive process* , resulting from impaired venous return from a tissue . The congested tissue is cyanotic, bluish-red in color because congestion leads to accumulation of deoxygenated hemoglobin in the congested tissues.

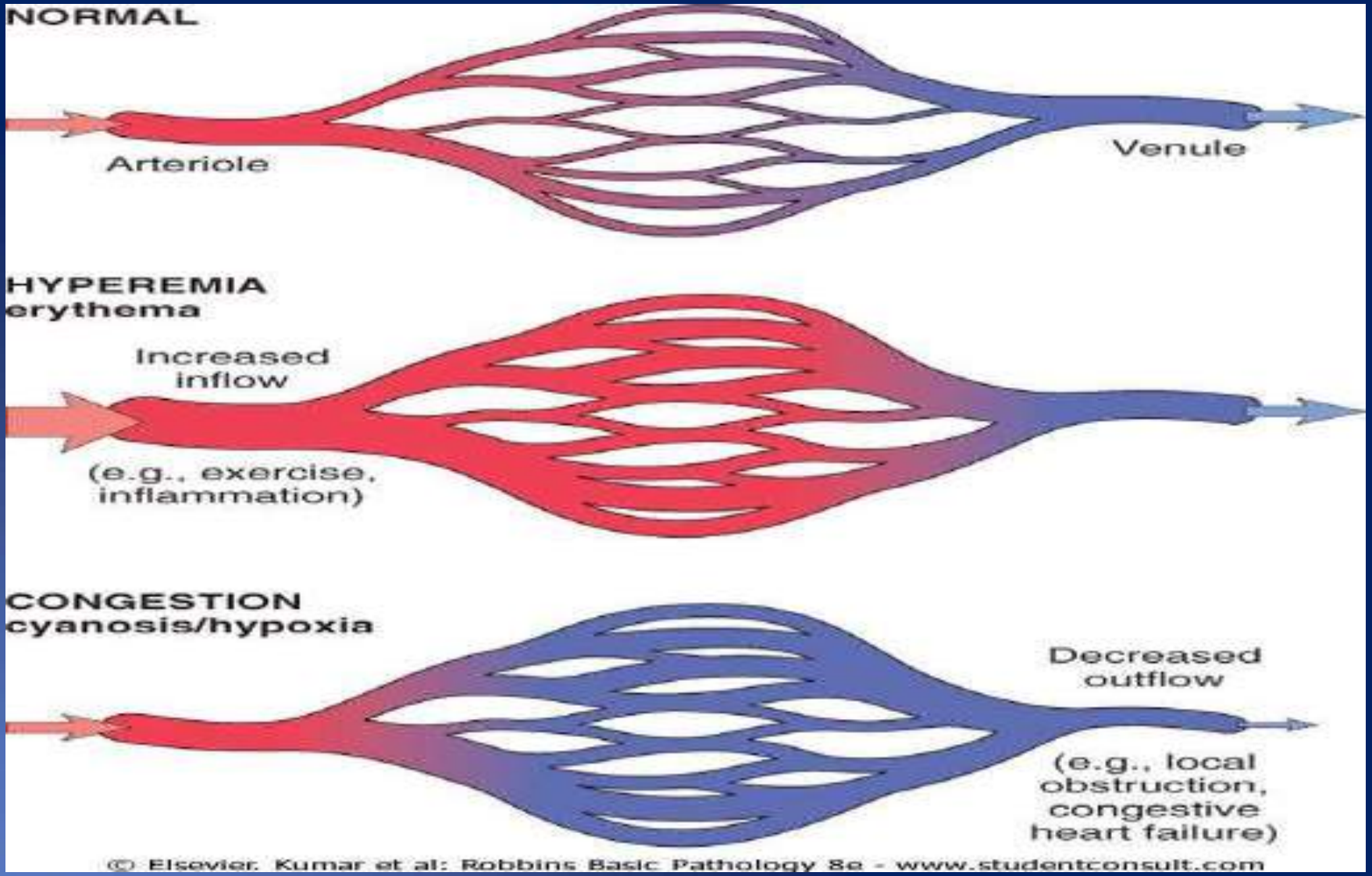



**Figure : Diagrammatic view of normal arterio-venous anastomosis , hyperemia & congestion ..**

**Figure : Photographic appearance of hyperemia of the inflammed conjunctiva of eye .**

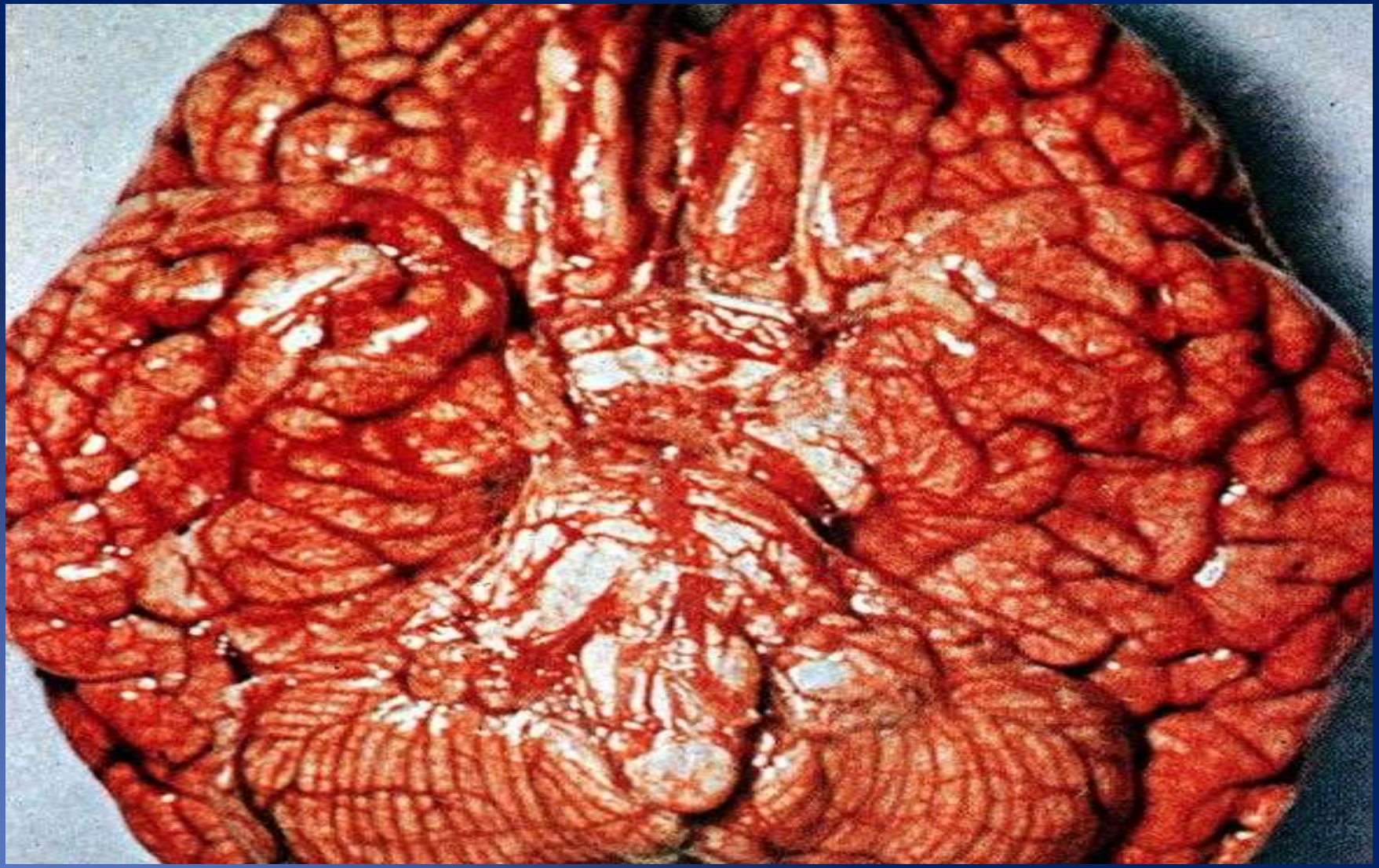


**Figure : Gross view of hyperemia of the brain , brain looks reddish .**

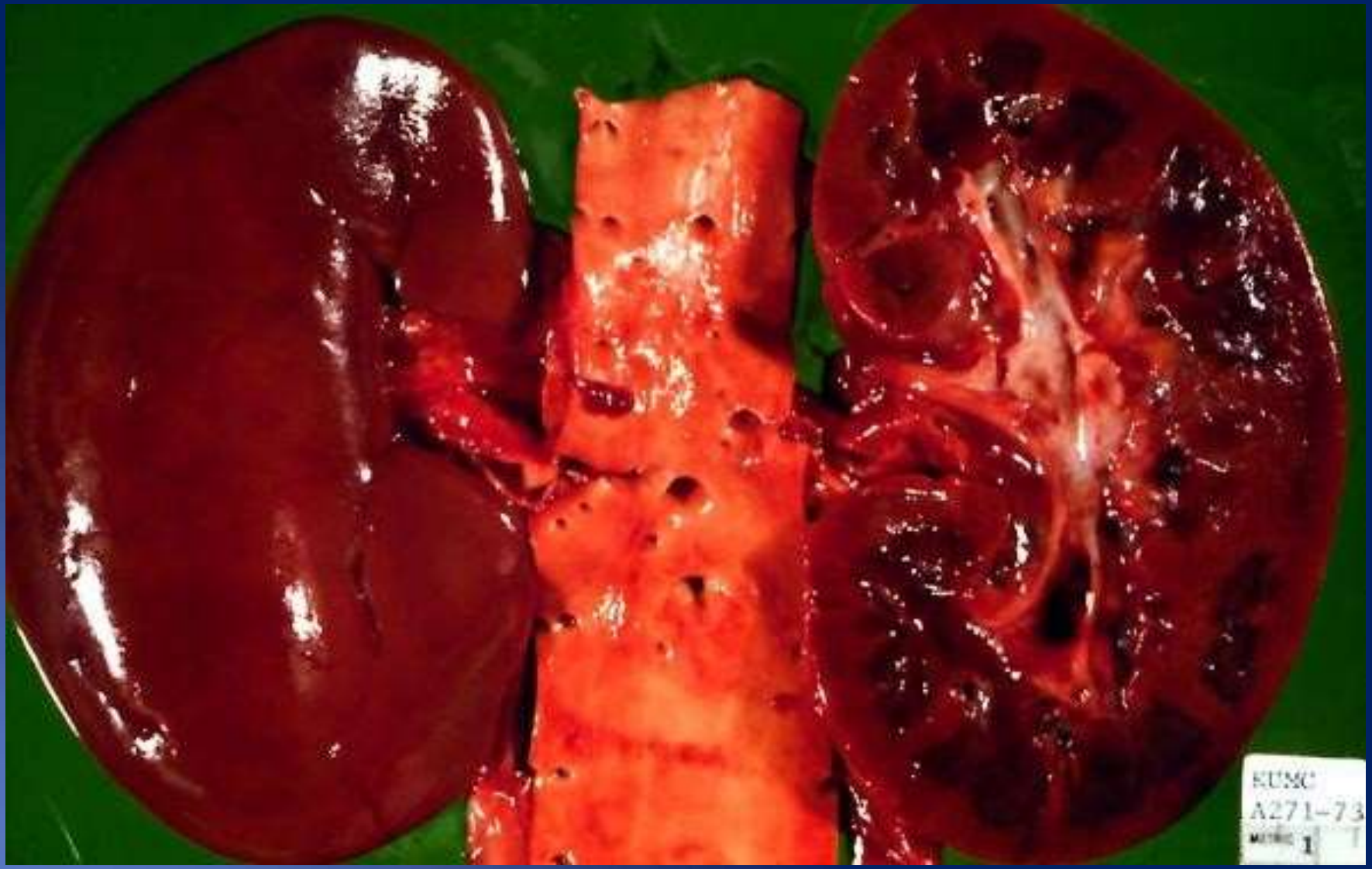



**Figure : Gross view of both kidneys showing hyperemia .**

## Congestion may be

- systemic, as in Congestive heart failure, or localised resulting from an isolated venous obstruction.
- Congestion & edema commonly occur together.
- In long- standing chronic venous congestion (CVC) , the stasis of poorly oxygenated blood causes chronic hypoxia , which can result in paranchymal cell degeneration or death, & subsequent tissue fibrosis.
- Capillary rupture at sites of CVC may also cause small foci of hemorrhage.

# Pulmonary congestion :

- **Grossly :** The congested lung is heavy ,dark red in color when squeezed a frothy air-containing fluid or blood stained fluid will be squeezed out .
- **Microscopically :**

- **Acute pulmonary congestion** is characterized by alveolar capillaries distension with blood ,alveolar septal edema and/or focal minute intra-alveolar hemorrhage.
- While in **chronic pulmonary congestion** , the alveolar septa become thickened & fibrotic & the alveolar spaces may contain numerous hemosiderin - laden macrophages, so-called *("heart failure cells").*

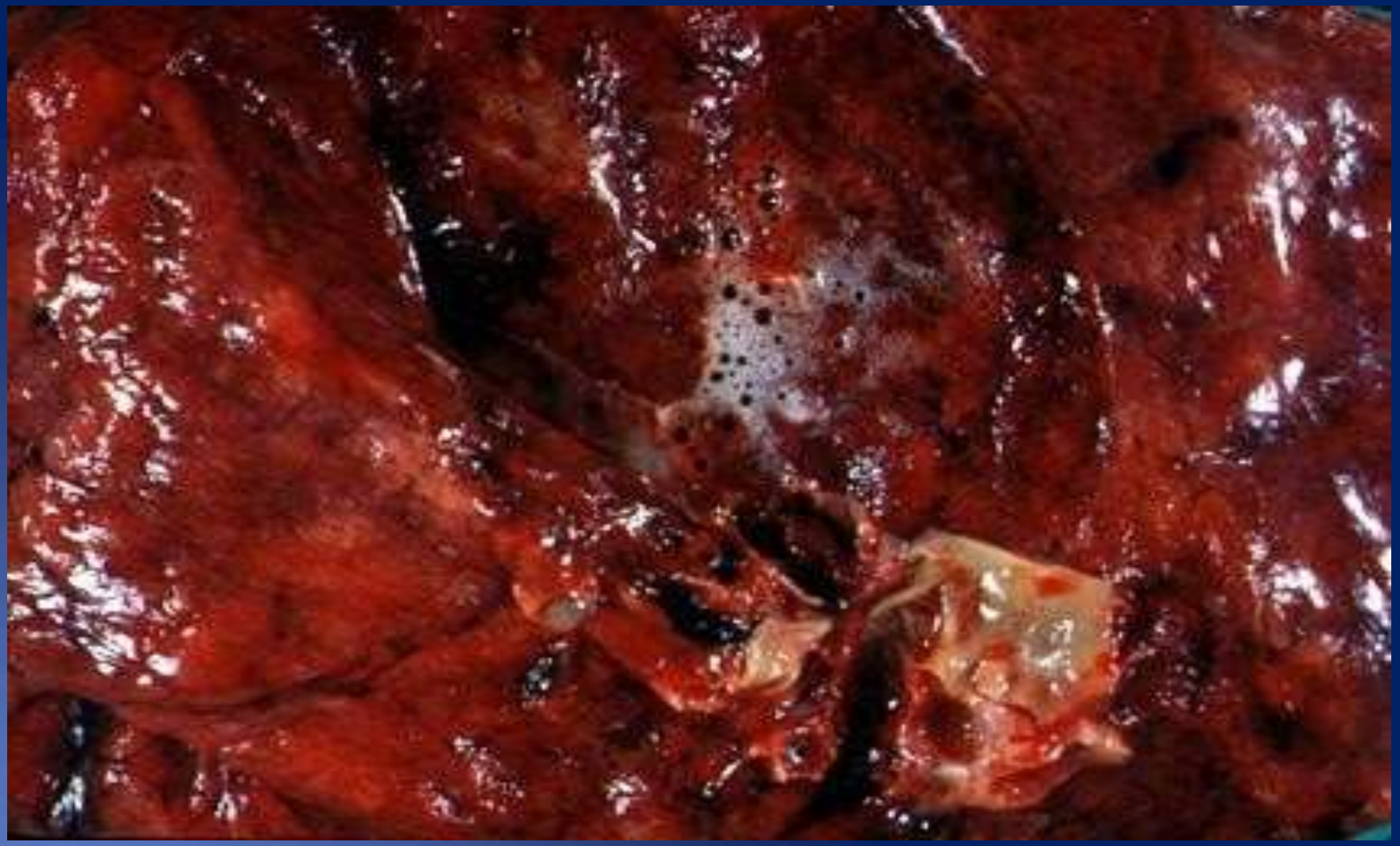


**Figure - Gross view of acute lung congestion , lung tissue is dark red with frothy fluid comes out during cutting .**

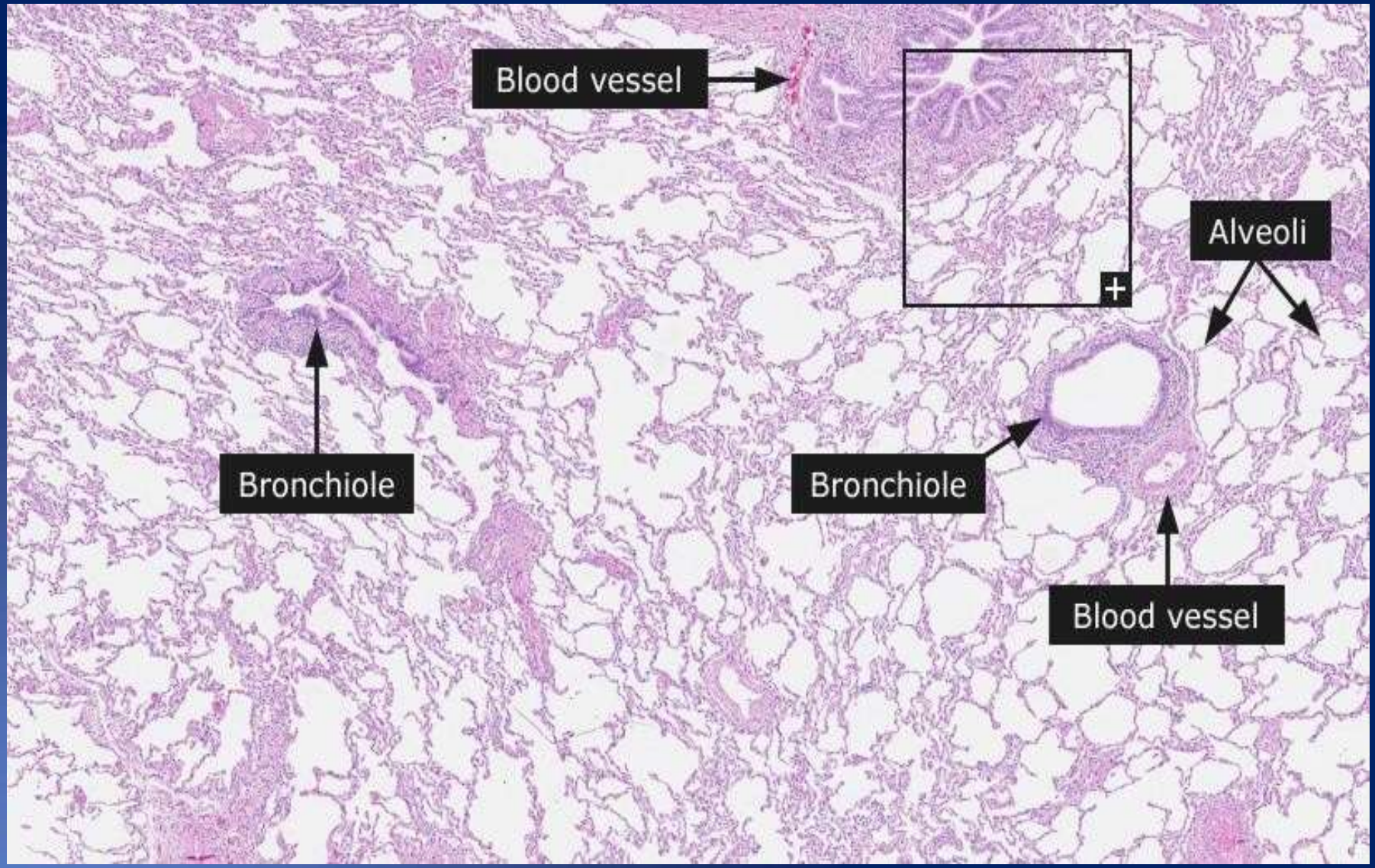



**Figure : Normal lung histology .**

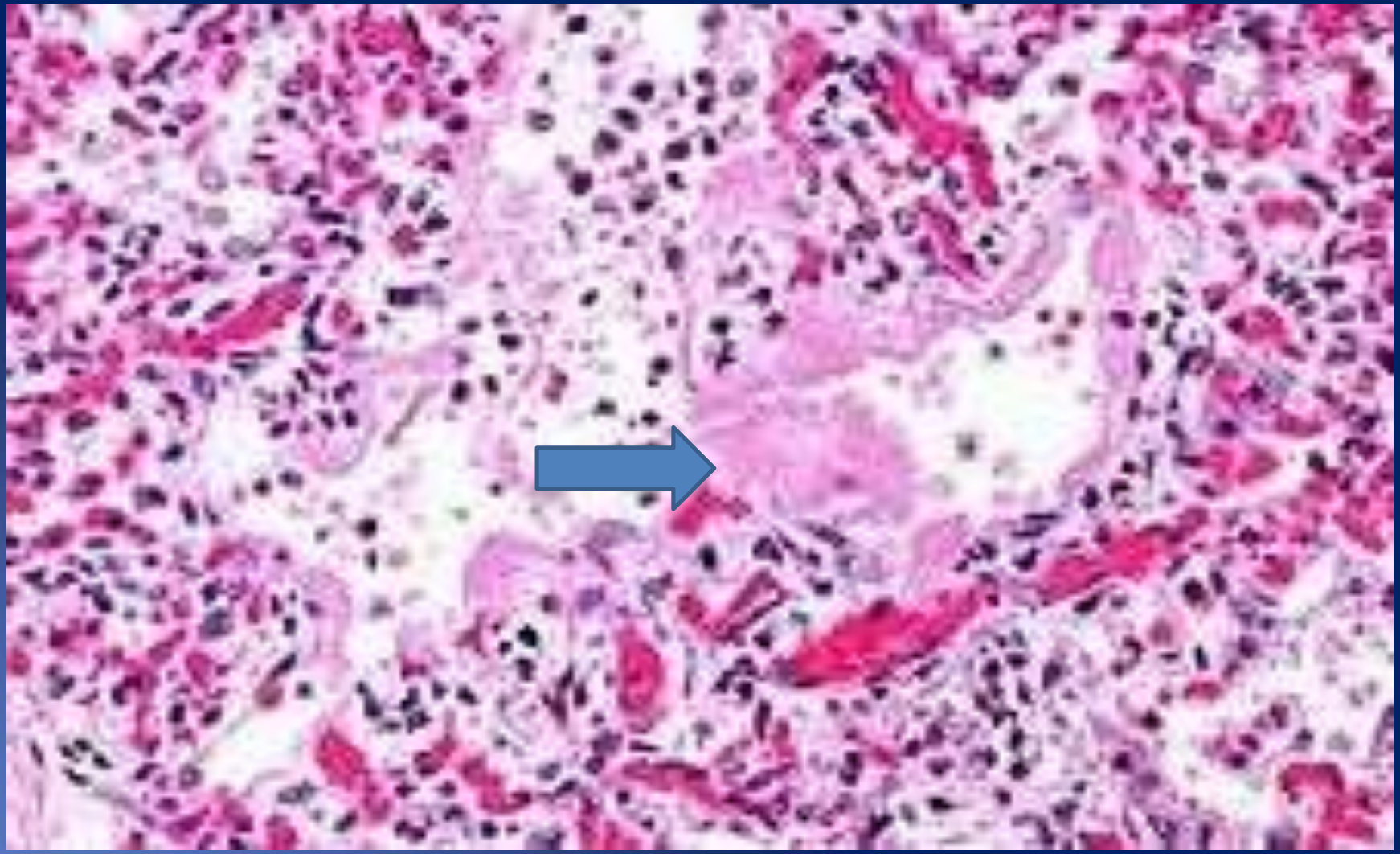


**Figure : Microscopic view of acute pulmonary congestion,showing congested capillaries in alveolar septa with intra alveolar edema (arrow).**

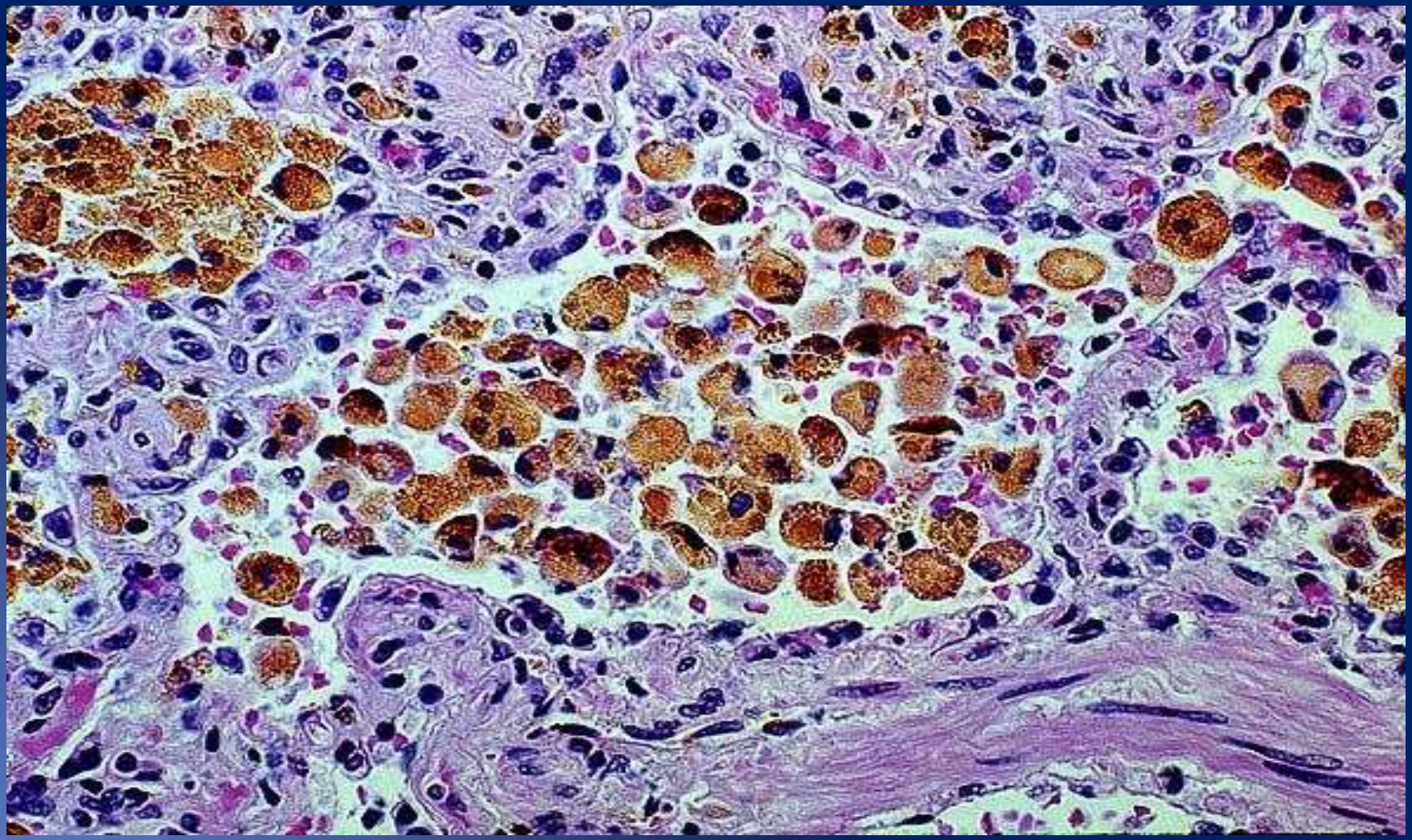


**Figure – Chronic pulmonary congestion showing golden-yellow appearance of hemosiderine –laden macrophages i.e. ( Heart-failure cells) & fibrosis of alveolar septa .**

# Liver Congestion

## Grossly : Microscopically

- There is centri lobular hepatic cell necrosis & hemorrhage, with hemosiderin-laden macrophages , alternating with a pale peripheral zones of fatty change in peripheral hepatocytes .

- In severe & long-standing hepatic Central Venous Congestion (commonly due to heart failure ), there may even be grossly evident hepatic fibrosis, so-called **"cardiac cirrhosis".**
- In chronic venous congestion the liver have **the nut- meg –like appearance,** because the central portions of the hepatic lobule is the last to receive blood from both portal vein & hepatic artery, so they tend to undergo early necrosisdue to ischemic injury , whenever there is reduced hepatic blood flow with hemorrhage thus look dark red & peripheral zone look pale ,due to fat necrosis .

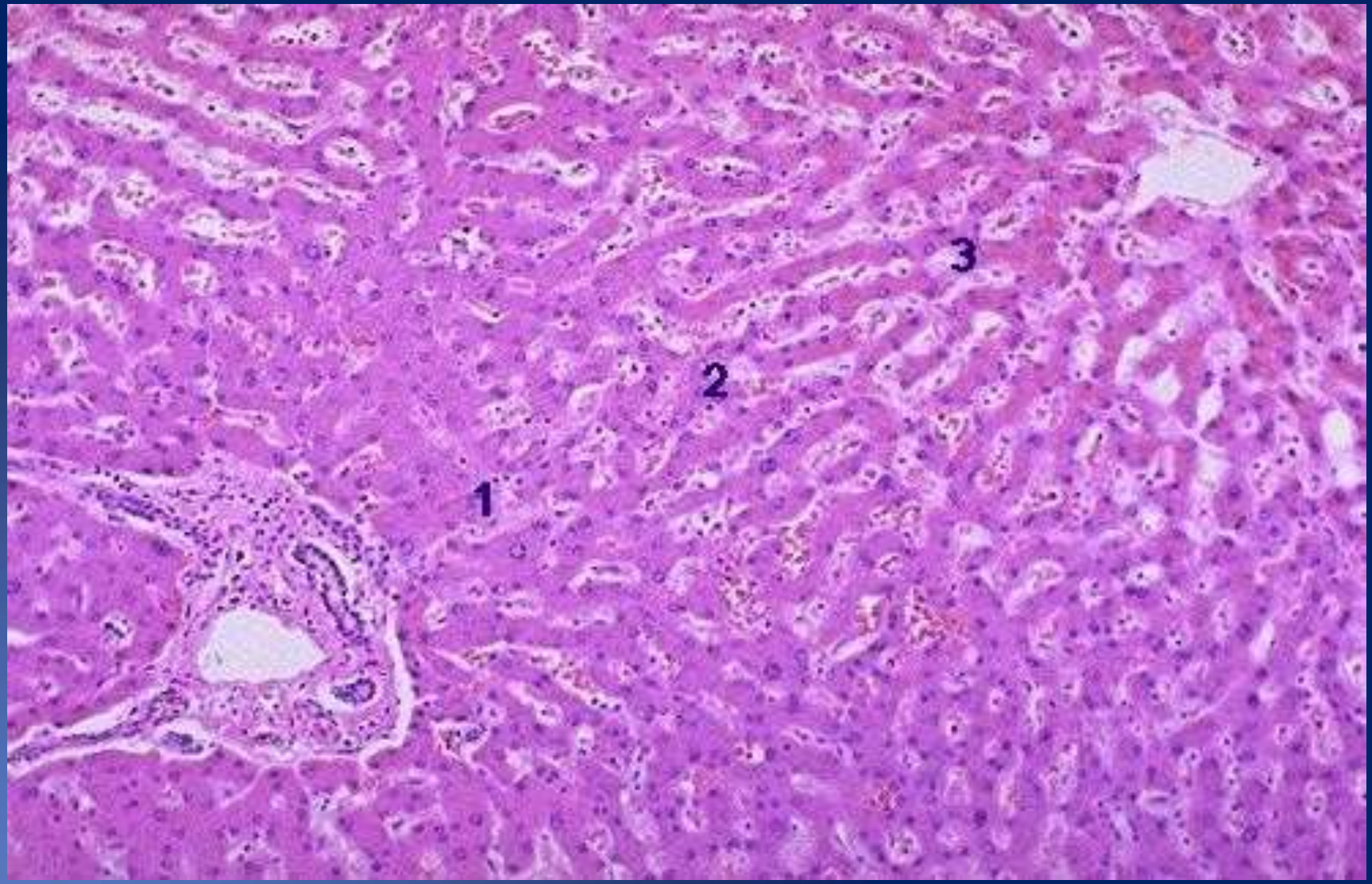



**Figure : Normal liver ,microscopic view .**


**Figure : Nut meg liver in chronic venous congestion due to heart failure .A- Nut meg grain .**

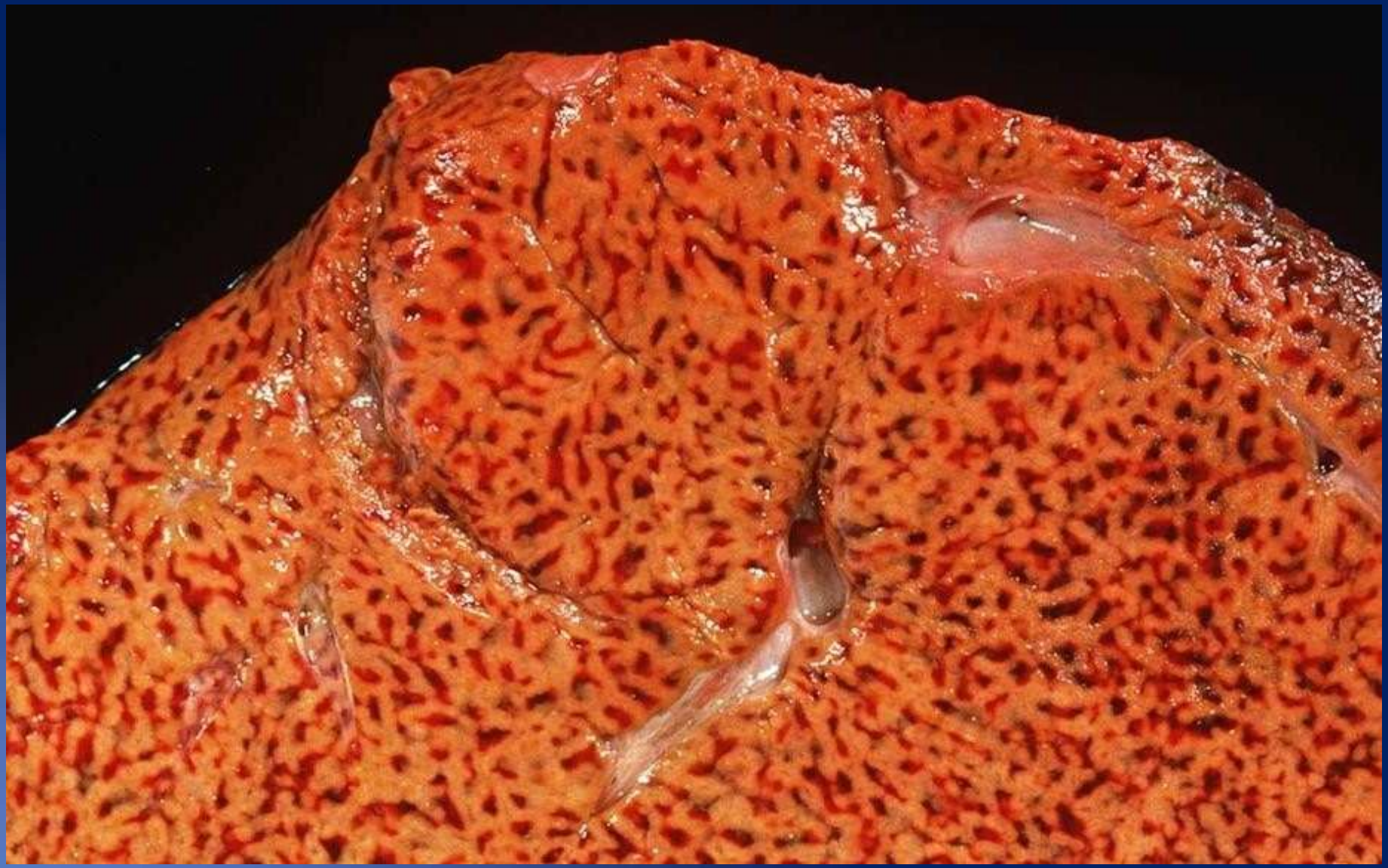


**Figure : Nut meg liver in CVC , gross view.**

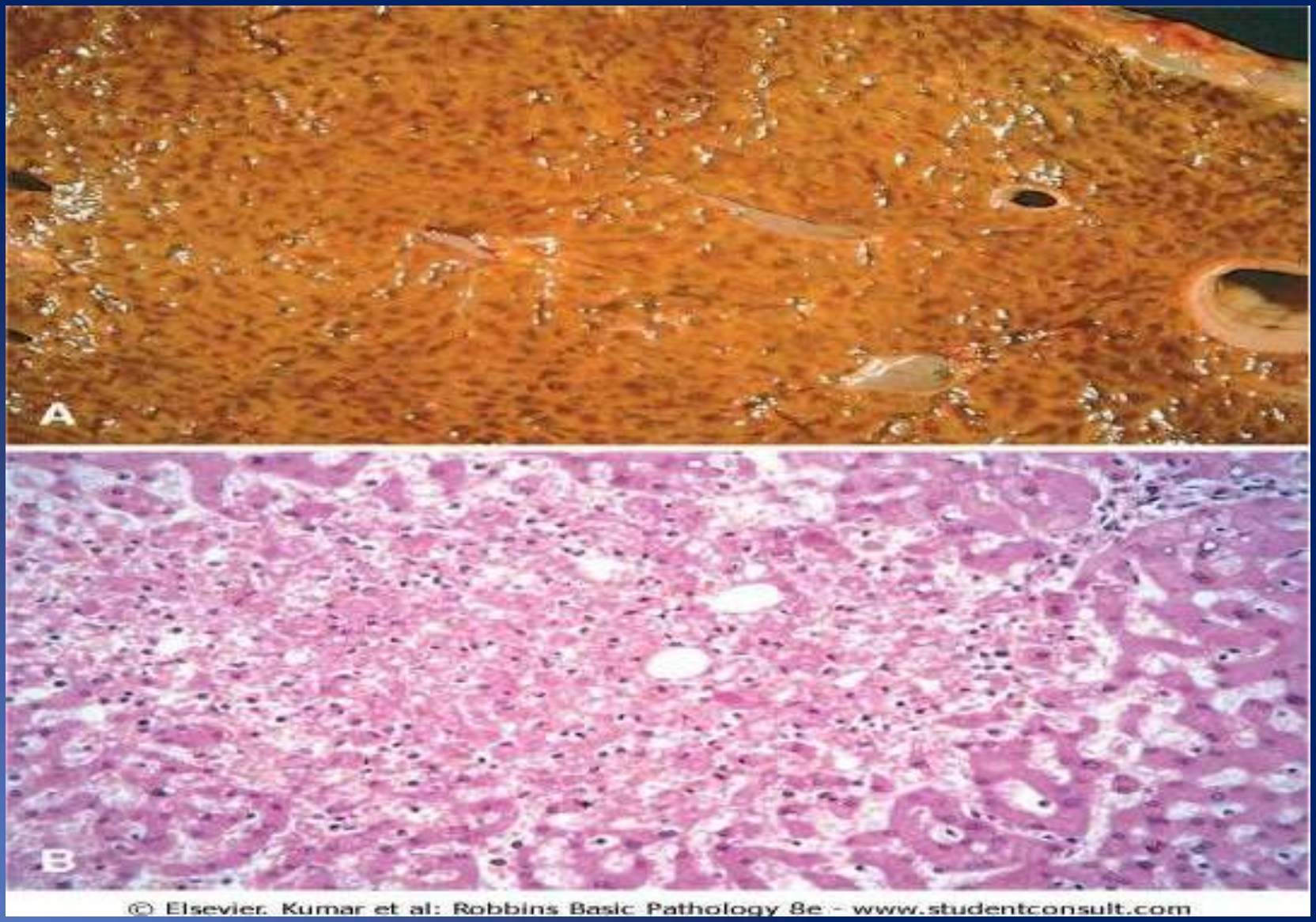



**Figure : Gross & microscopic appearances of liver in CVC.**

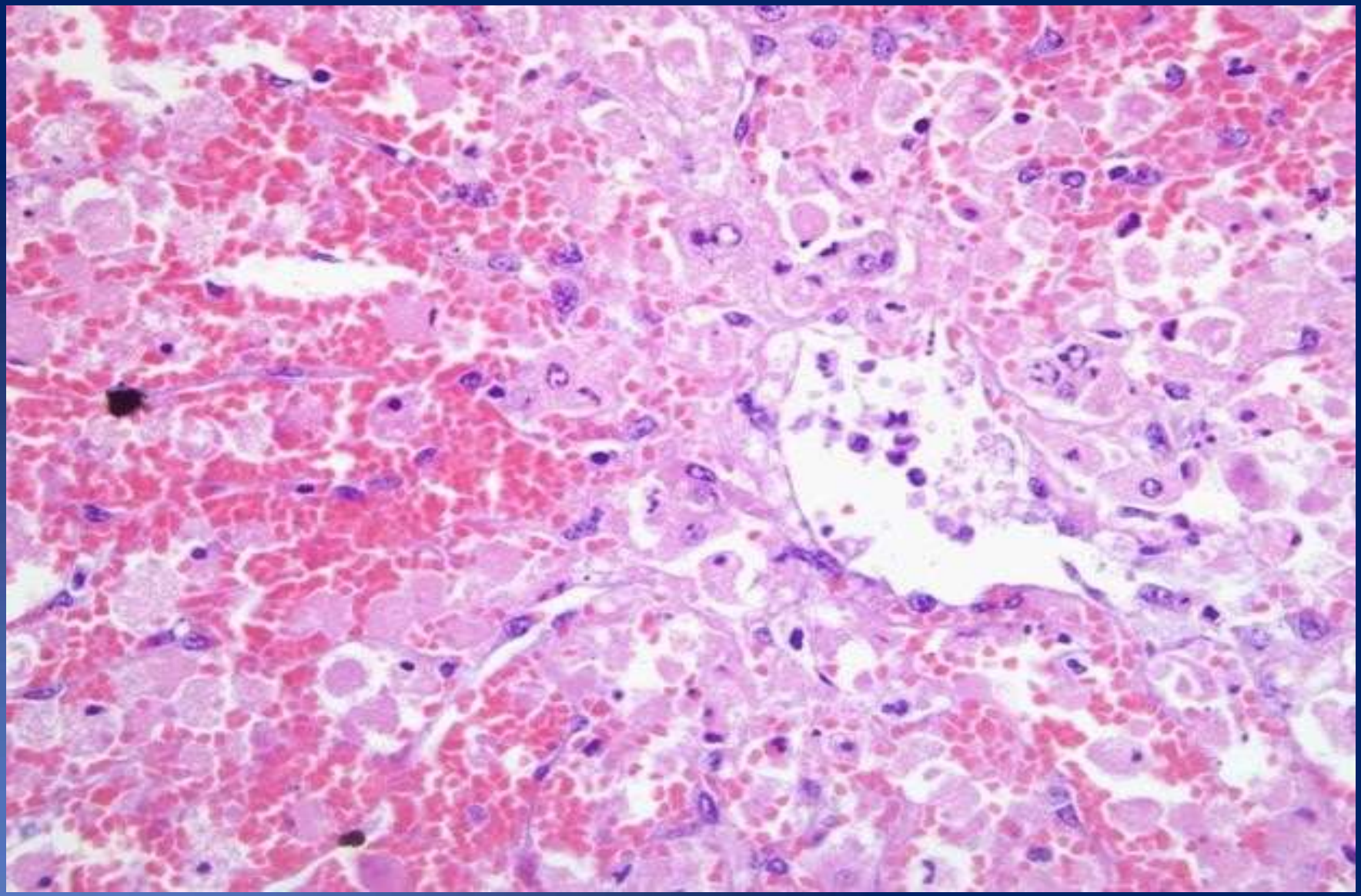


**Figure : microscopic view of liver in CVC (nut meg liver )showing necrotic hepatocytes & hemorrhage around central vein giving red color to this area.**

# EDEMA

- 60% of the lean (without fat) body weight is water, with: 2/3 intracellular (within cells); &1/3 extracellular (out side the cells), mostly as interstitial fluid .
- 5% of total body water only is in the intravascular compartment, i.e. in the blood plasma .
- The term edema refers increased fluid in the interstitial tissue spaces .
  - Fluid collections in different body cavities are refered to as :

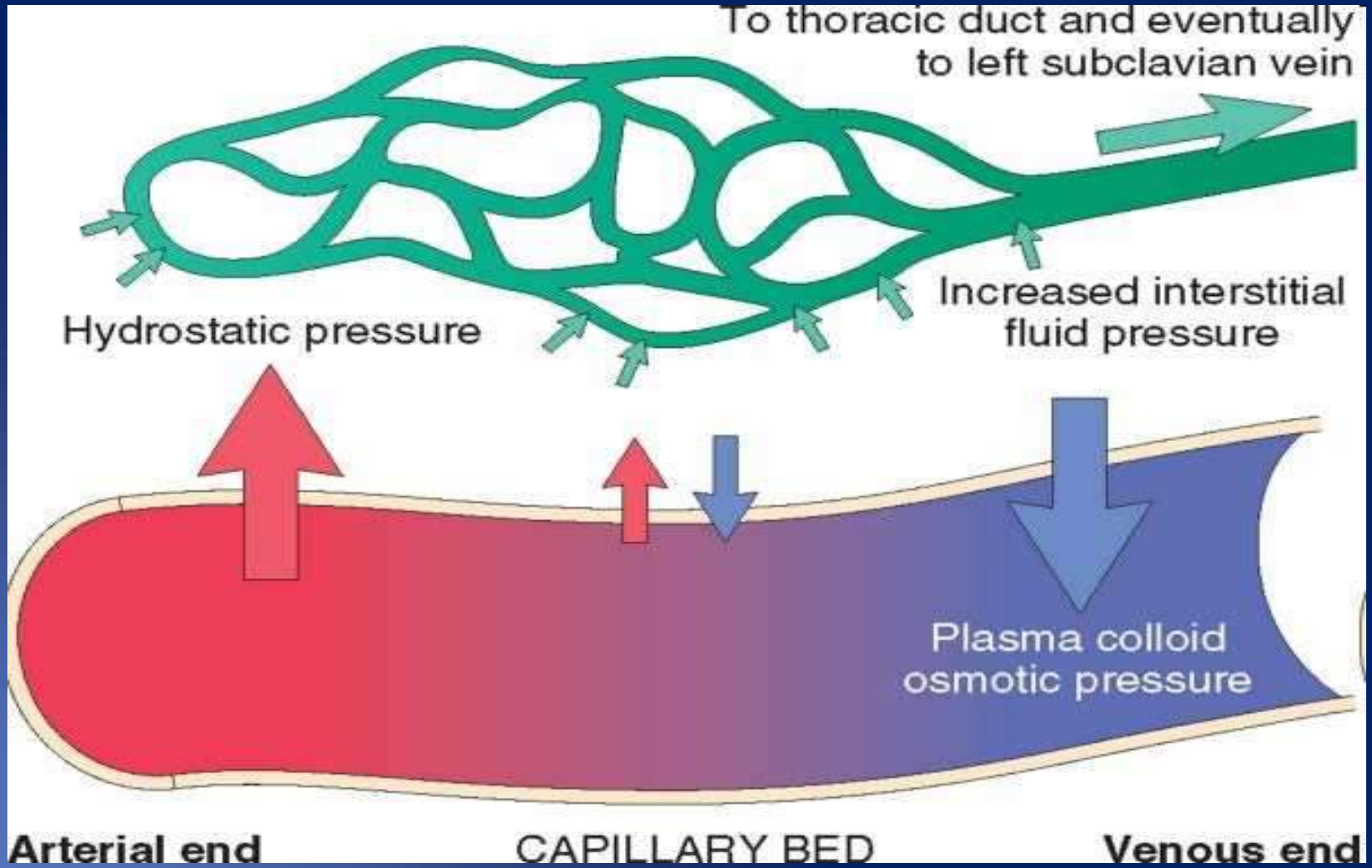
Hydrothorax : in pleural cavity.
Hydropericardium : in pericardial cavity.
Hydroperitoneum : in peritoneal cavity also called ascites Anasarca : Is a severe generalized edema with a profound subcutaneous swelling .

# Edema

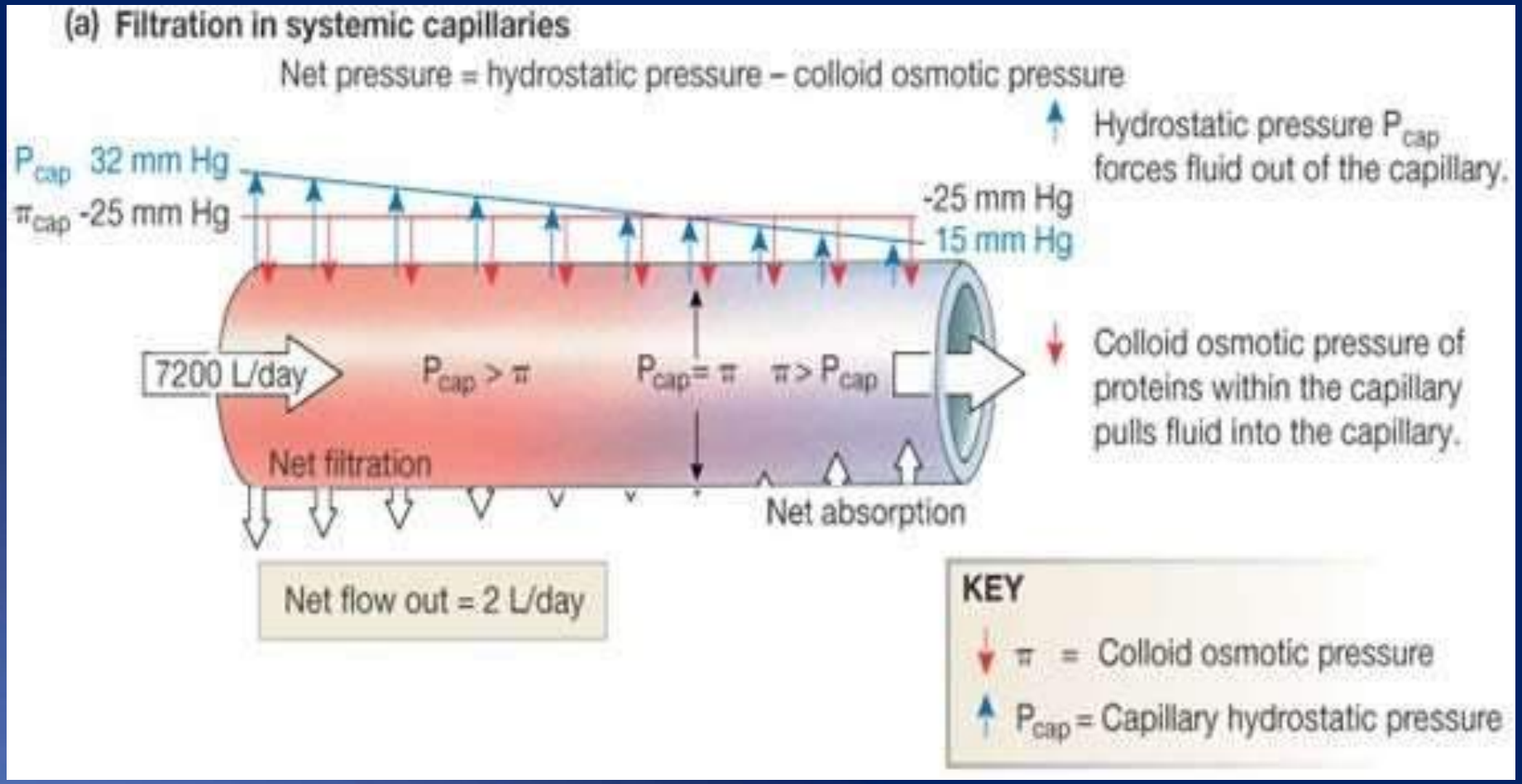
- Fluid movement between the vascular & interstitial spaces is governed by two opposing forces, **the vascular hydrostatic pressure and the colloid osmotic pressure produced by plasma proteins .**
- Normally the outflow of fluid produced by hydrostatic pressure at the arteriolar end of the micro circulation is balanced by the inflow due to the slightly elevated osmotic pressure at the venular end , hence , there is only a small net outflow of fluid into the interstitial spaces, which is drained by the lymphatic vessels .
- Either increased hydrostatic pressure or decreased osmotic pressure causes increased movement of water into the interstitium .
- Excess edema fluid is removed by the lymphatic drainage & returned to the blood stream by the way of the thoracic duct. .

- Edema can be divided into many types based on the mechanisms causing edema:
  - increased capillary hydrostatic pressure
  - decreased plasma oncotic pressure,
  - enhanced permeability of capillary walls(inflammation)
  - lymphatic obstruction.
  - Each of the types can be further divided into generalized and local forms.

# Fluid transit




Note: (Wikipedia)- Oncotic pressure, or colloid osmotic pressure, is a form of osmotic pressure exerted by proteins, notably albumin, in a blood vessel's plasma (blood/liquid) that usually tends to pull water into the circulatory system. It is the opposing force to capillary filtration pressure and interstitial colloidal osmotic pressure.




The movement of water and low molecular weight solutes such as salts betw
the intravascular and interstitial spaces is controlled primarily by the opposin
effect of vascular hydrostatic pressure and plasma colloid osmotic pressure

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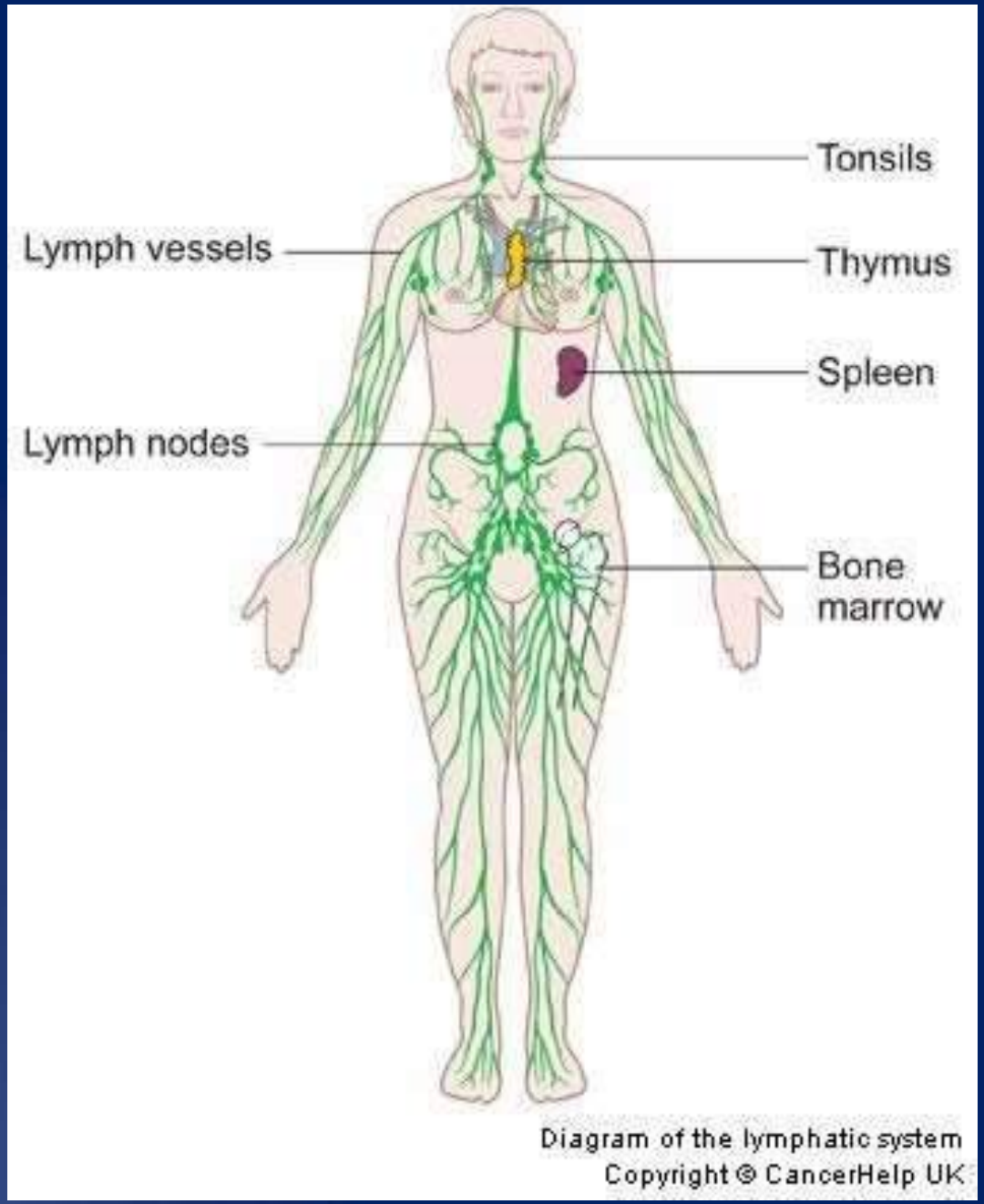
- If the movement of water into tissues (or body cavities) exceeds lymphatic drainage, fluid accumulates.
- An abnormal increase in interstitial fluid within tissues is called edema.I



# Appearance of edema

- Swollen tissues (not cells—fluid is outside the cells)
- Heavy tissues
- Wet tissues
- Widening of fascial planes or interlobular septa
- Filled cavities

# Pathophysiological causes of odema

## INCREASED HYDROSTATIC PRESSURE

- **Impaired venous return**
  - Congestive heart failure
  - Constrictive pericarditis
  - Ascites (liver cirrhosis)
  - Venous obstruction or compression
  - Thrombosis
  - External pressure (e.g., mass)
  - Lower extremity inactivity with prolonged dependency

- **Arteriolar dilation**
  - Heat
  - Neurohumoral dysregulation

## REDUCED PLASMA OSMOTIC PRESSURE (HYPOPROTEINEMIA)

Protein-losing glomerulopathies (nephrotic syndrome) Liver cirrhosis (ascites)
Malnutrition
Protein-losing gastroenteropathy

## LYMPHATIC OBSTRUCTION

Inflammatory
Neoplastic
Postsurgical
Postirradiation

## INFLAMMATION

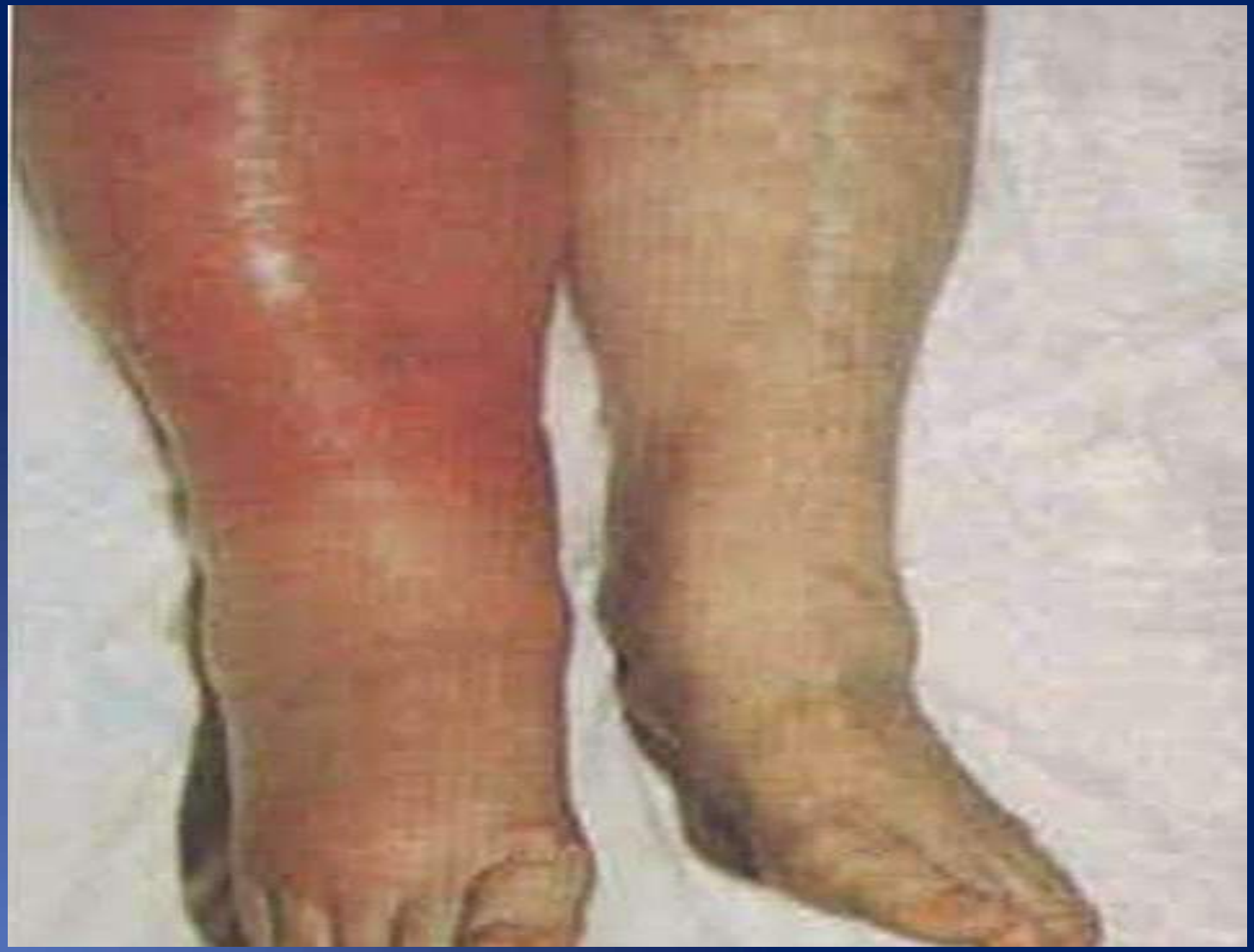
Acute inflammation
Chronic inflammation
Angiogenesis

## SODIUM RETENTION

Excessive salt intake with renal insufficiency
Increased tubular reabsorption of sodium
Renal hypoperfusion
Increased renin-angiotensin-aldosterone secretion

# Increased hydrostatic pressure :

- **Local edema** : increase in intravascular pressure can result from impaired venous return , for example in deep venous thrombosis in the lower extremities can cause edema in the distal part of the affected limb.
- **Generalized edema :** In normal heart , the reduced cardiac output leads to hypoperfusion of the kidneys thus triggering **the rennin-angiotensin- aldosterone axis** , renin is secreted by specialized cells in renal tubules due to hypoxia renin will stimulate angiotensin that enhances tubular reabsorption of Na & water thus inducing Na& water retention , this will increase the intravascular blood volume & improves the cardiac output to restore the renal perfusion and it is called **secondary aldosteronism , .**
- **In congestive heart failure** , the heart cannot improve cardiac output and this leads to increased venous hydrostatic pressure and resulting in edema .



**Figure; Photographic view of swollen edematous right leg due to deep vein thrombosis ( local edema ) .**

## Reduced plasma osmotic pressure:

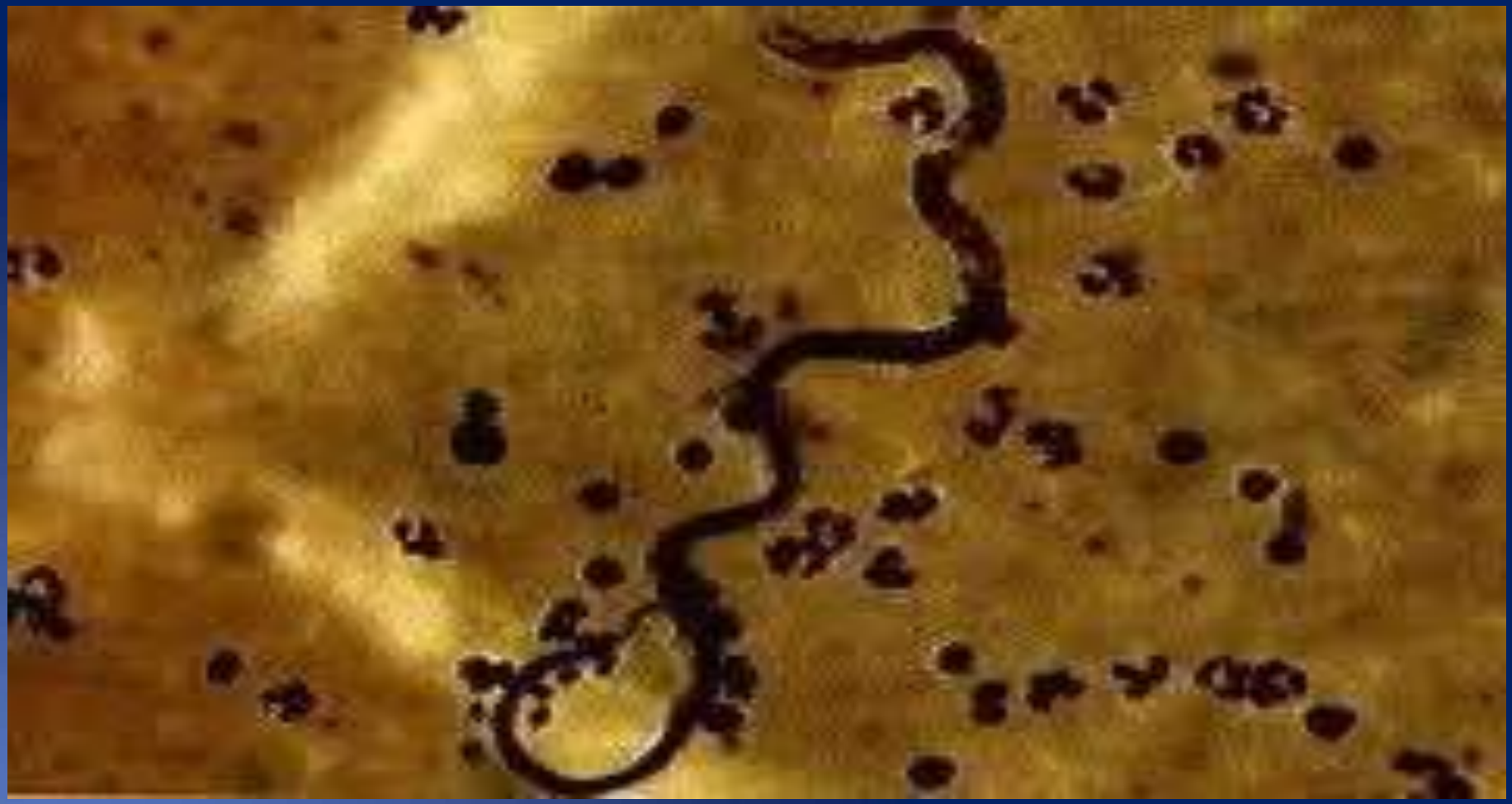
- Albumin is the serum protein most responsible for maintaining intravascular colloid osmotic pressure
- Reduced osmotic colloid pressure occurs when diffuse albumin is inadequately synthesized as in liver diseases , or in protein deficiency in mal nutrition or is lost from circulation through the glomerular capillaries which become leaky as in nephrotic syndrome .

# Lymphatic obstruction :

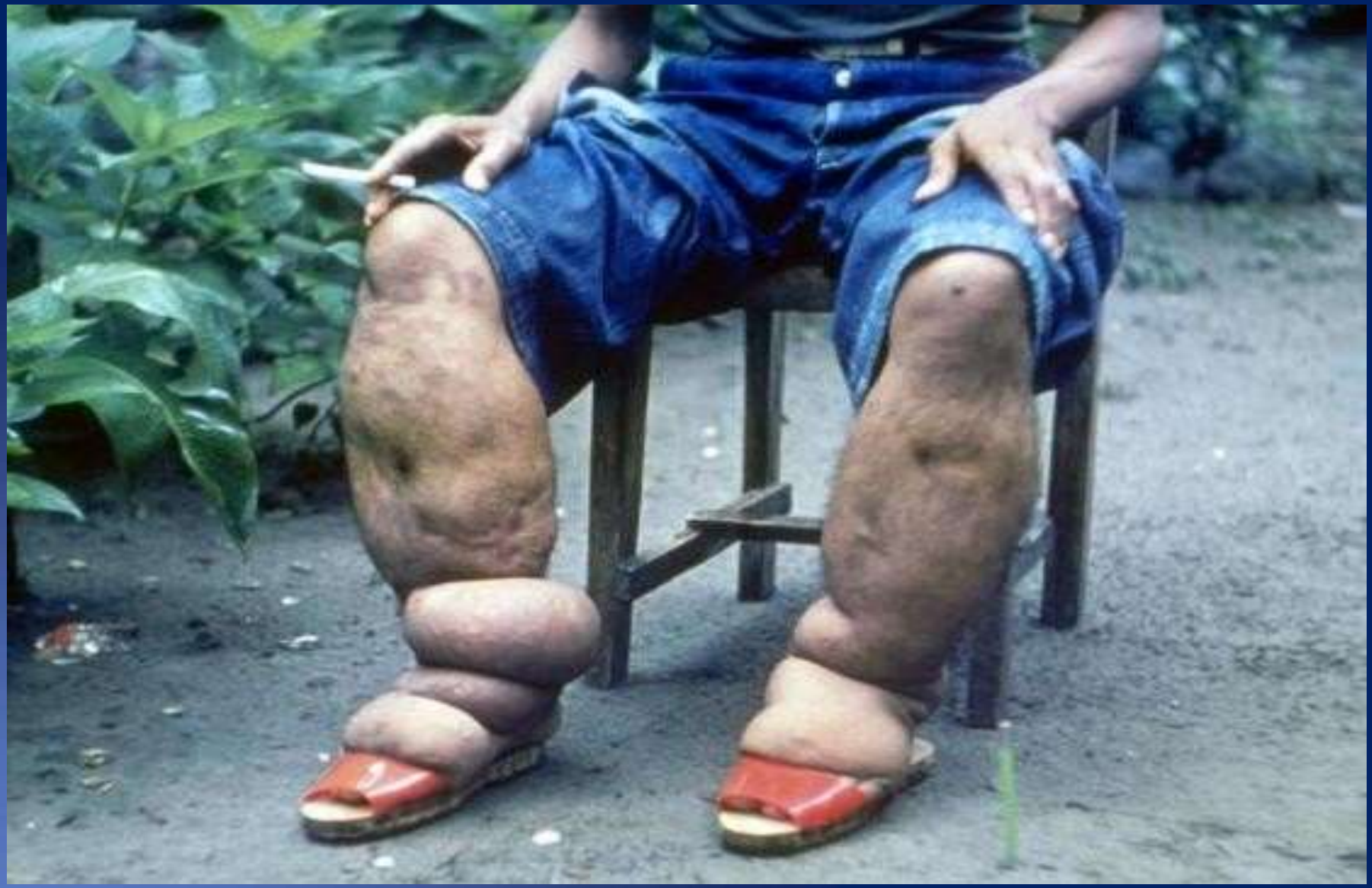
- Normally , excess interstitial fluid is removed by lymphatic drainage returning it to the blood stream via thoracic duct

  (Normally 800 to1000 ml of lymph/per day).

  - Impaired lymphatic drainage & consequent lymph edema can result from inflammatory or neoplastic obstruction or post-irradiation scarring .
  - Parasitic infestation by *filariasis* which involves the inguinal lymphatics causing lymphatic obstruction and lymph nodes fibrosis with resultant progressive edema of the external genitalia and the lower limbs can be so massive to be called *elephantiasis*



**Filaria Bancrufti .The parasite that causes Elephantiasis due to lymphadenitis , obstructing the lymphatic drainage resulting in extensive edema in** lower limbs & the external genitalia .



Photograph of elephantiasis , sever edema in lower limbs .

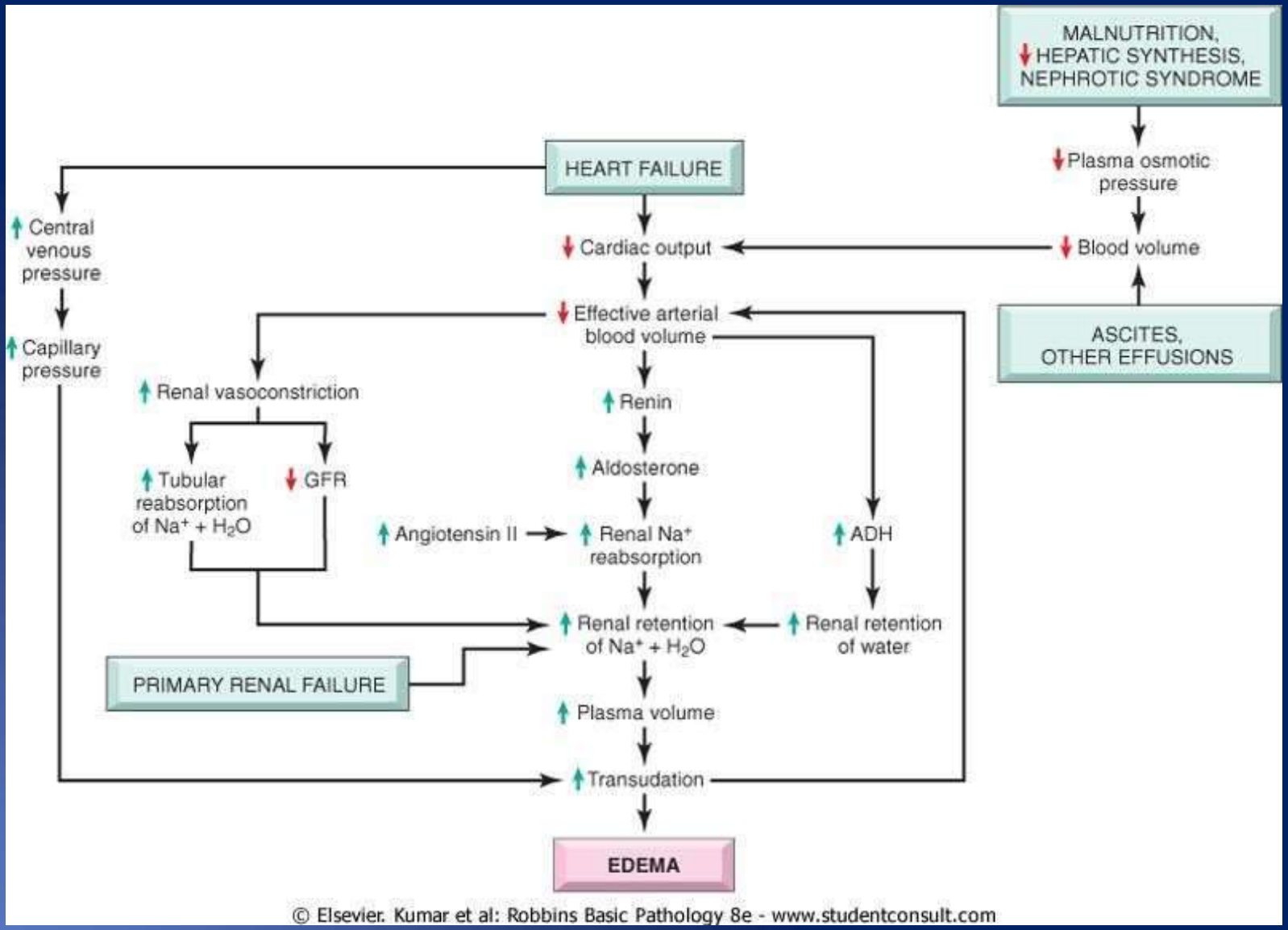



**Diagram showing mechanism of edema .**

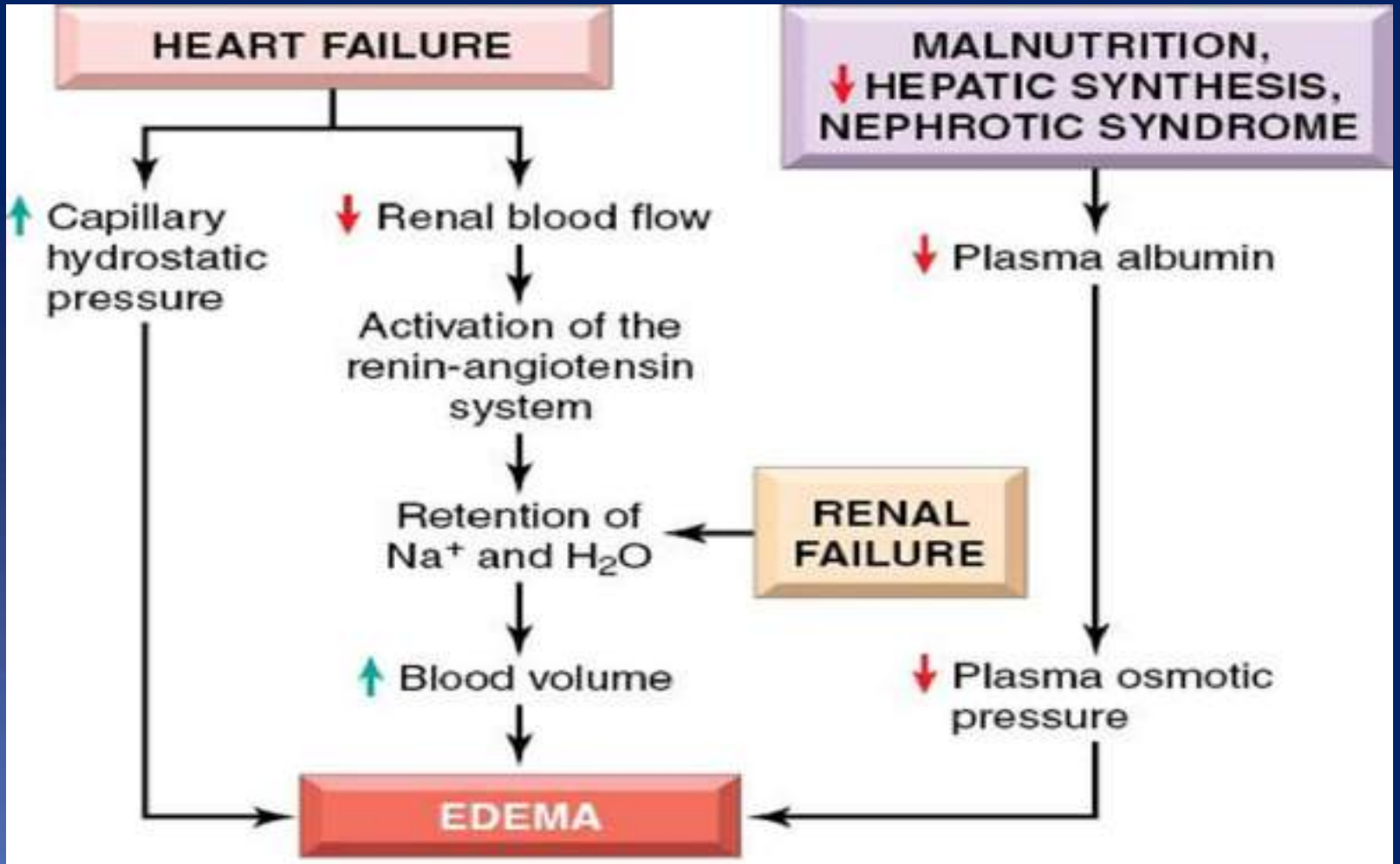



**FIGURE 4–2** Pathways leading to systemic edema from primary heart failure, primary renal failure, or reduced plasma osmotic pressure (e.g., from malnutrition, diminished hepatic synthesis, or protein loss from nephrotic syndrome).

# Morphology of edema :

- The *edema fluid is typically a protein-poor, called transudate, with a specific gravity below 1012.*
- **In inflammatory edema**, *the increased vascular permeability result in a protein-rich edematous fluid called exudate with A specific gravity over 1020.*
- **Grossly;** Edema is most easily recognized, causing swelling and increased weight of the affected organ.

- **Histologically :**

Edema is manifest as clearing & separation of the extracellular matrix elements and cell swelling .

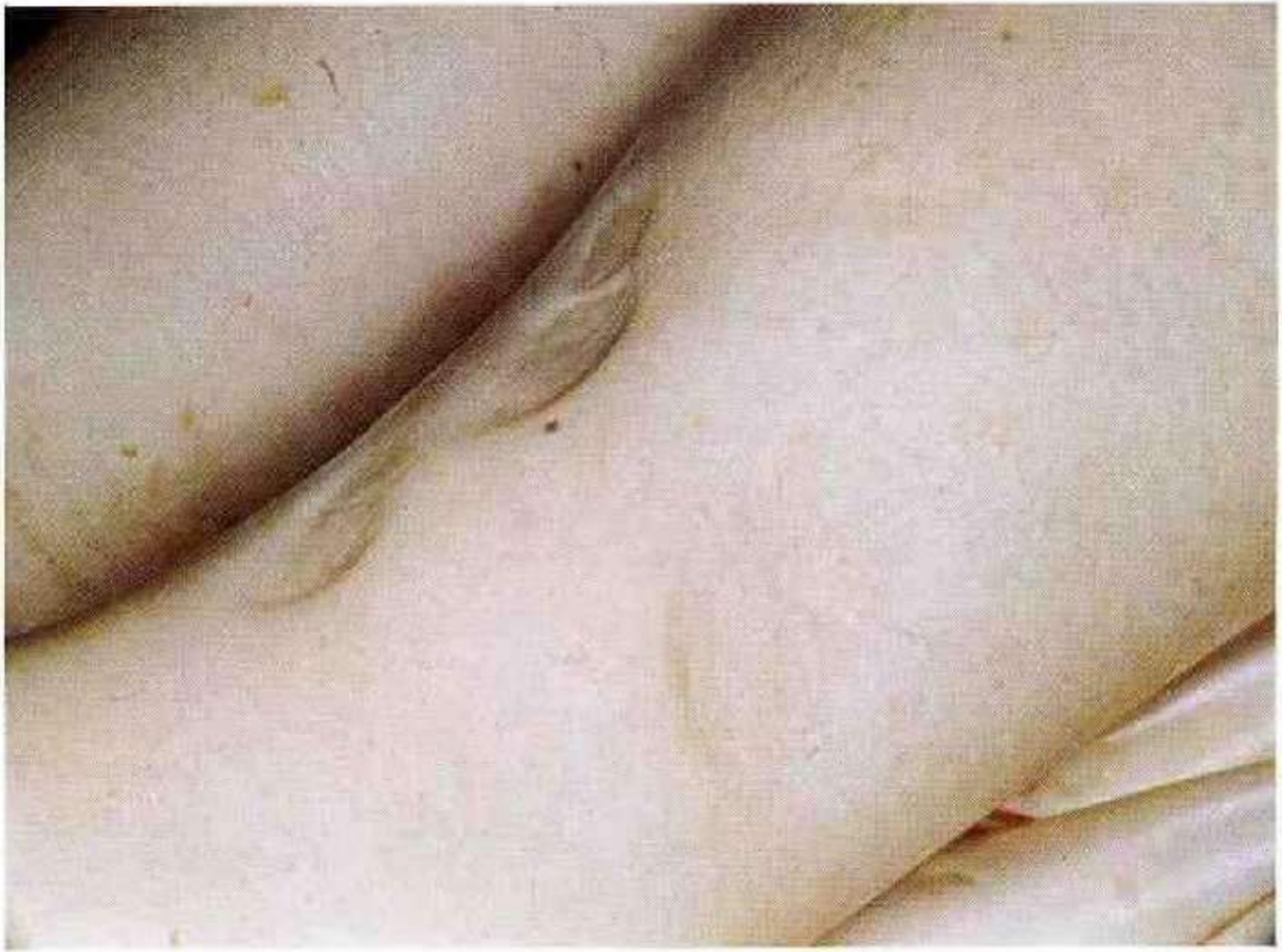
Edema is most commonly encountered in subcutaneous tissues can be *diffuse* may affect different locations depending on the cause of edema.

- **Localised edema :** can involve any organ or tissue in the body may be involved the lungs, & brain are especially affected .
- Glottic or laryngeal edema may be fatal by obstructing the air passages specially in children.

- **Diffuse systemic edema :**

- is usually more prominent in certain areas as result of the effect of gravity ,which is called *dependant edema* , involving the legs when standing & sacrum when recumbent
- This is a feature of heart failure especially right ventricular failure.
- Edema due to renal failure or nephrotic syndrome is generally more sever than cardiac edema tends to affect many parts of the body equally.However, it may be initially appears in tissues with a loose connective tissue matrix, such as the eyelids, causing perior*bital edema*.

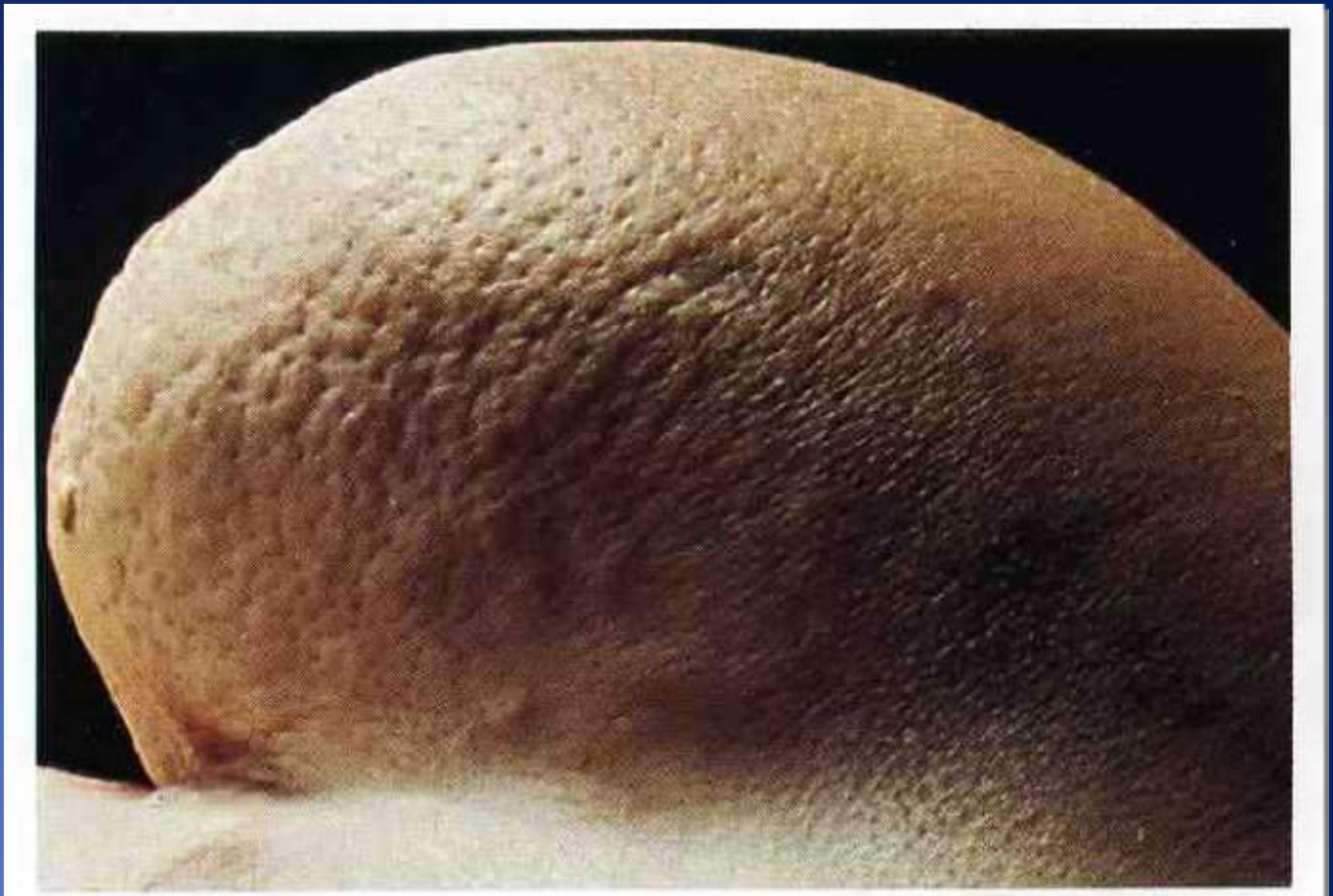
- An important sign of edema is **pitting sign** If finger pressure is applied over edematous subcutaneous tissue, it displaces the interstitial fluid & leaves a finger- shaped depression so **called pitting edema** .
- In breast cancer the skin shows a **Peau d' orange appearance** of the its skin , produced by cutaneous edema causing bulging of the skin (following occlusion of the skin lymphatics by malignant cells around the hair follicles& sweat glands .



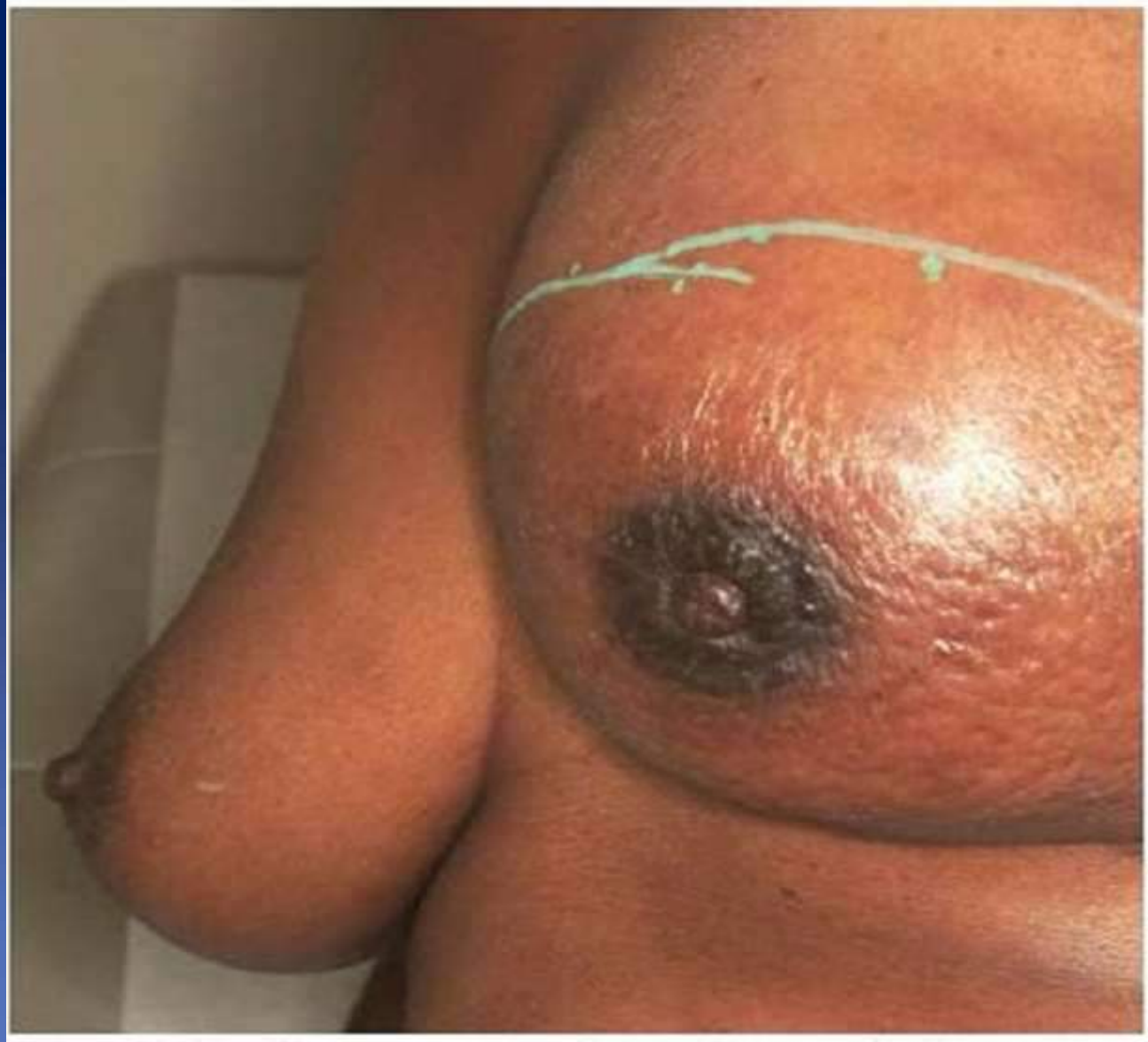
14.15 Oedema: skin

**Photograph showing pitting edema of skin & subcutaneous tissue .**

**Photograph of breast showing Peau d' orange appearance of the breast seen in breast cancer.**



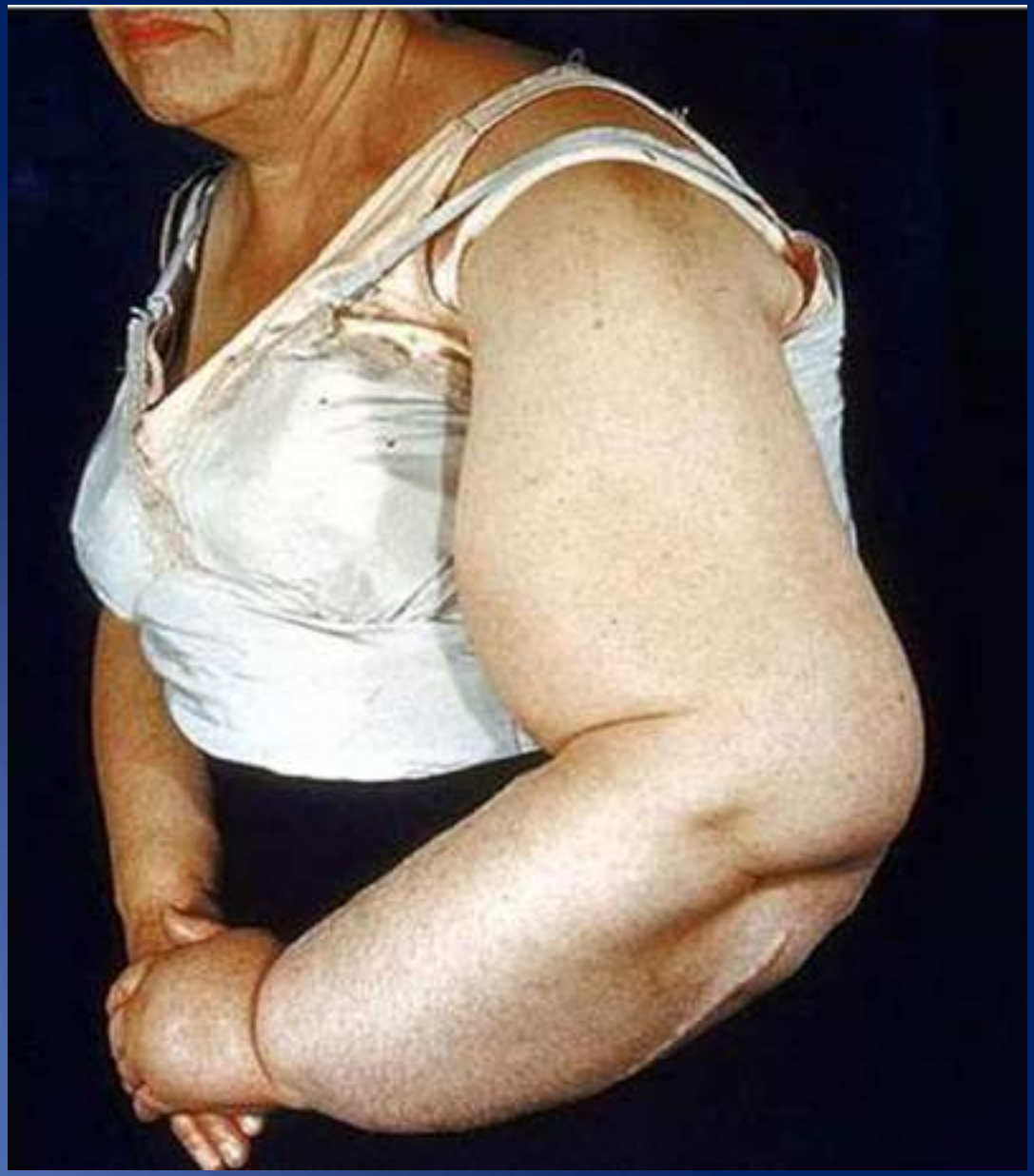
12.11 Carcinoma: breast



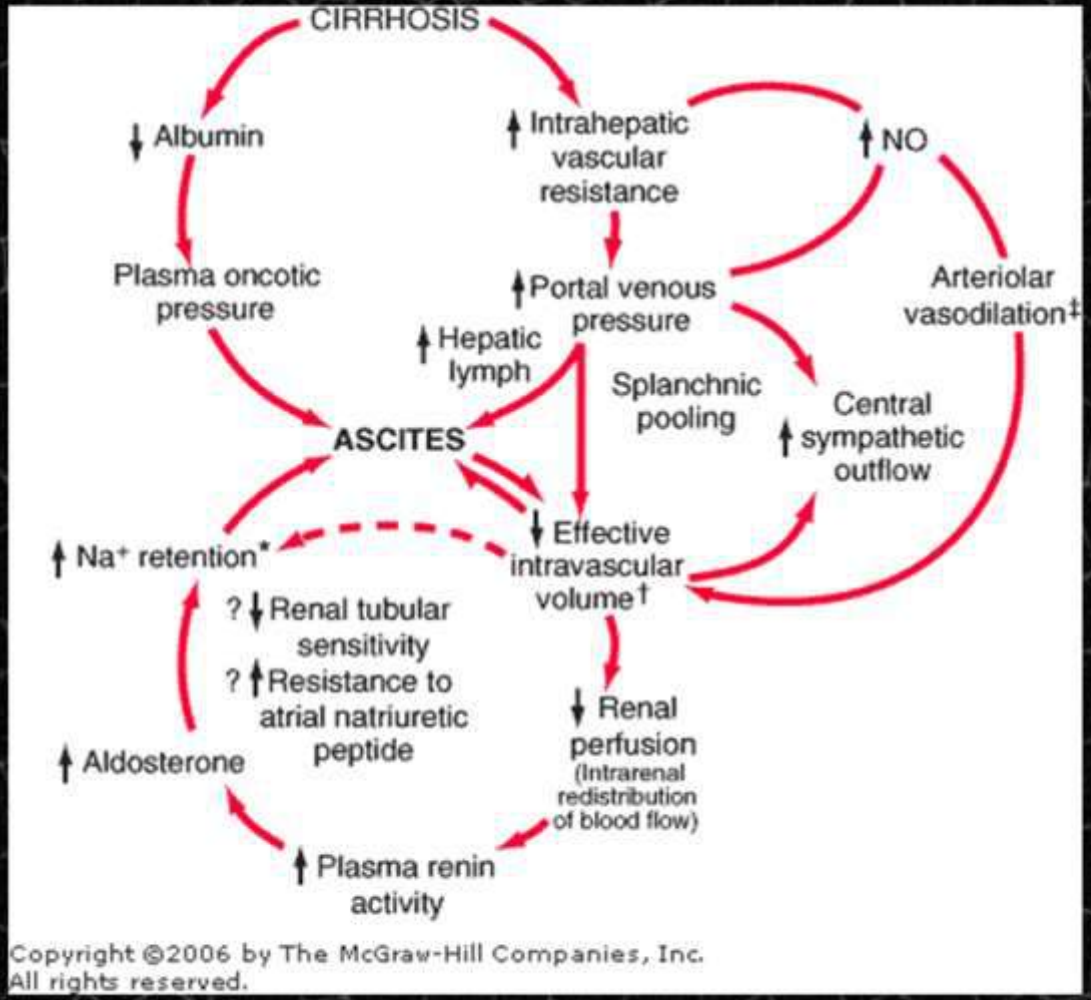
Courtesy of Dr. Eric Strom, M. D. Anderson Cancer Center

**FIGURE 1.** Erythema, edema, and peau d'orange—all classic signs—are seen in a woman with inflammatory breast cancer

# Peau d’orange and post-mastectomy lymphedema



# Ascites

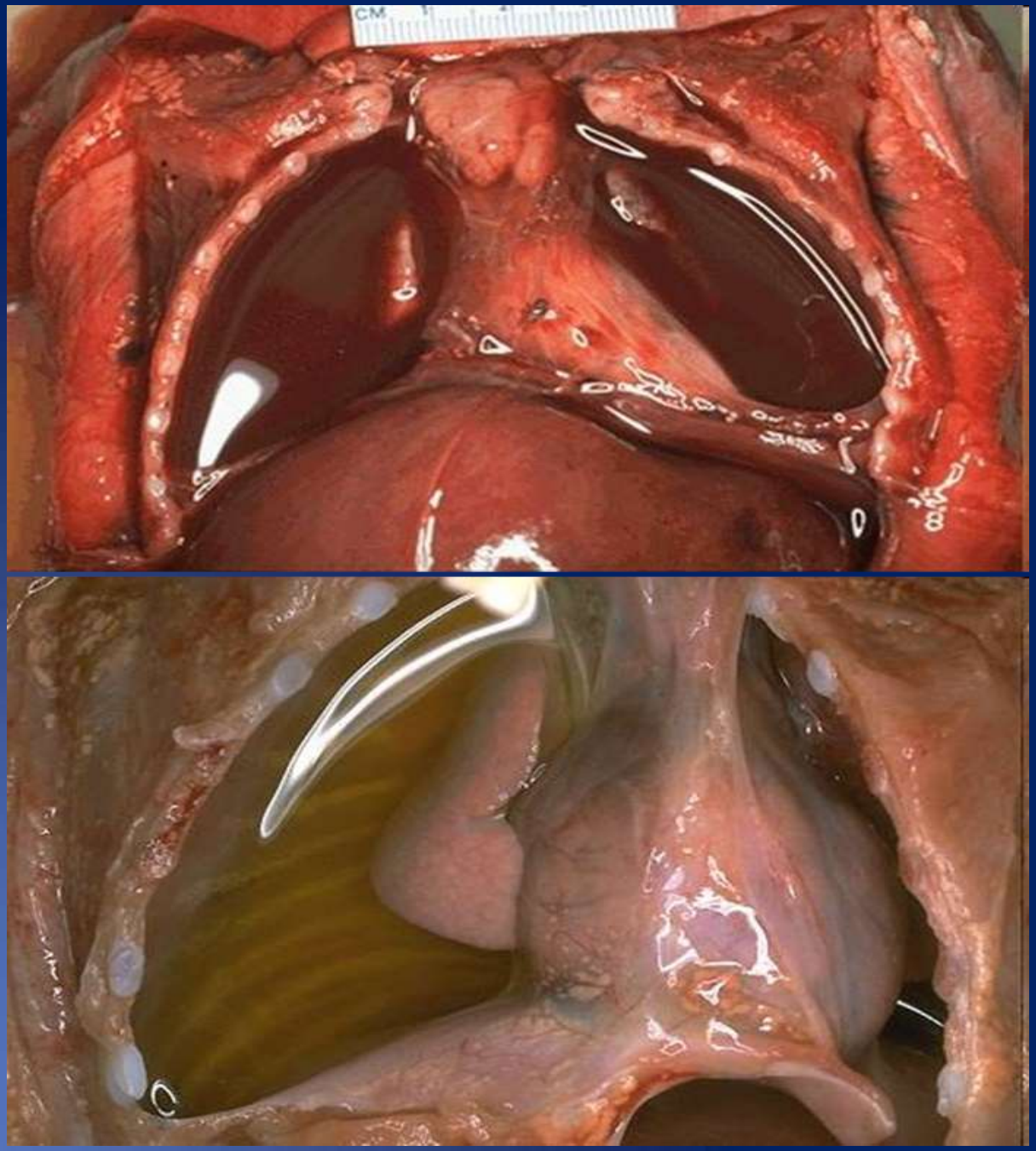




**The accumulation of ascitic fluid represents a state of total- body sodium and water excess, but the event that initiates this imbalance is unclear.**

# Effusion

- Extravascular fluid collections can be classified as follows:
  - Exudate: extravascular fluid collection that is rich in protein and/or cells. Fluid appears grossly cloudy.
  - Transudate: extravascular fluid collection that is basically an ultrafiltrate of plasma with little protein and few or no cells. Fluid appears grossly clear.
- Effusions into body cavities can be further described as follows:
  - Serous: a transudate with mainly edema fluid and few cells.
  - Serosanguinous: an effusion with red blood cells.
  - Fibrinous (serofibrinous): fibrin strands are derived from a protein-rich exudate.
  - Purulent: numerous PMN's are present. Also called "empyema" in the pleural space.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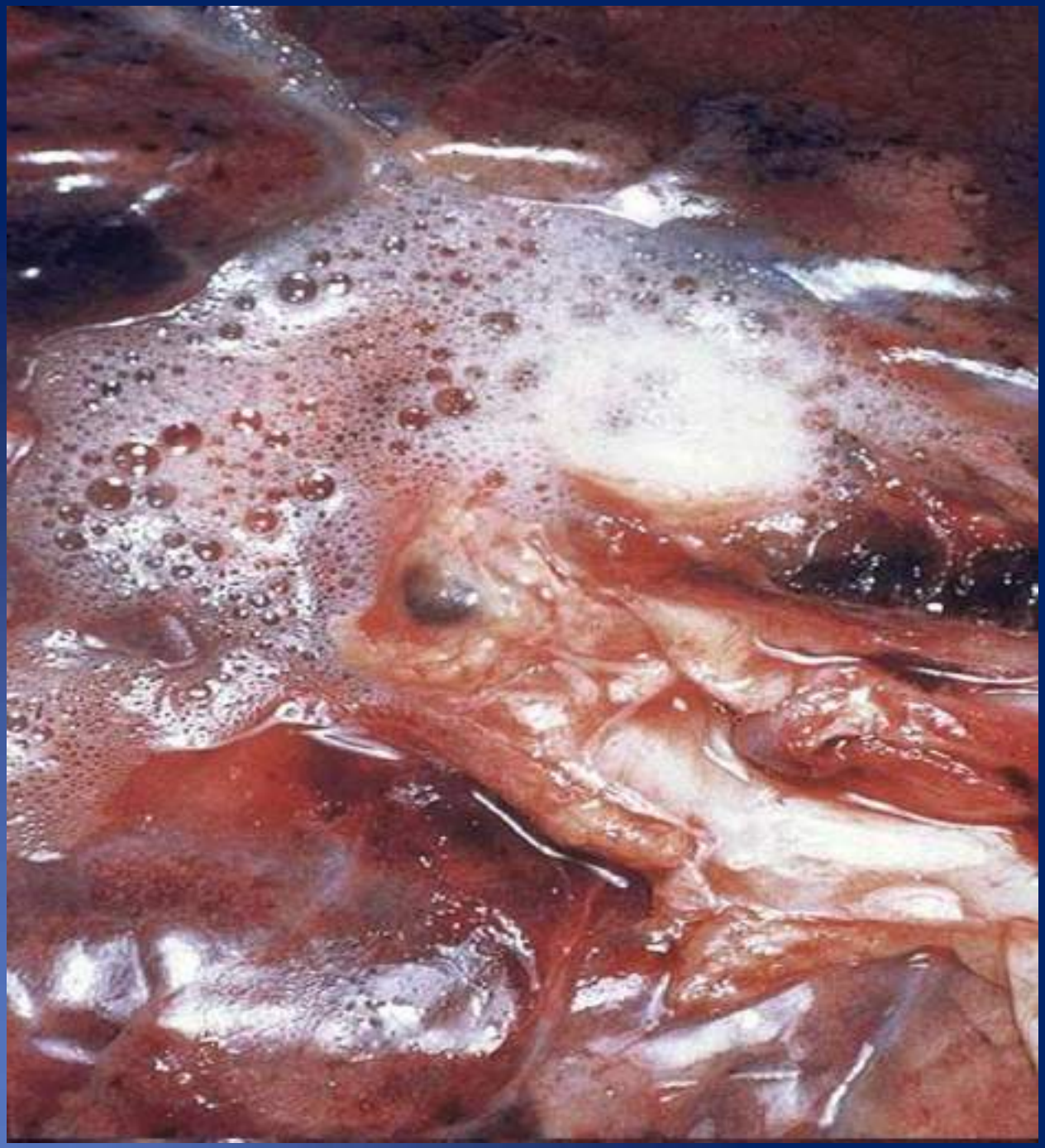
# Pulmonary edema :

- Is a common clinical problem seen in left ventricular failure(LVF), renal failure (RF), adult respiratory distress syndrome (ARDS), pulmonary infections, & hypersensitivity reactions.
- The edematends to involve the lower lobes of both lungs .
- Grossly : The lungs are heavy (2 to 3 times their normal weight, which is 350g) & on sectioning it reveals frothy, or blood-stained fluid, consisting of air + edema fluid + extravasated RBC mixture.
- Clinically :Pulmonary edema causes dyspnea , interference with normal ventilatory functions of the lungas hypoxia and cyanosis & may be fatal .

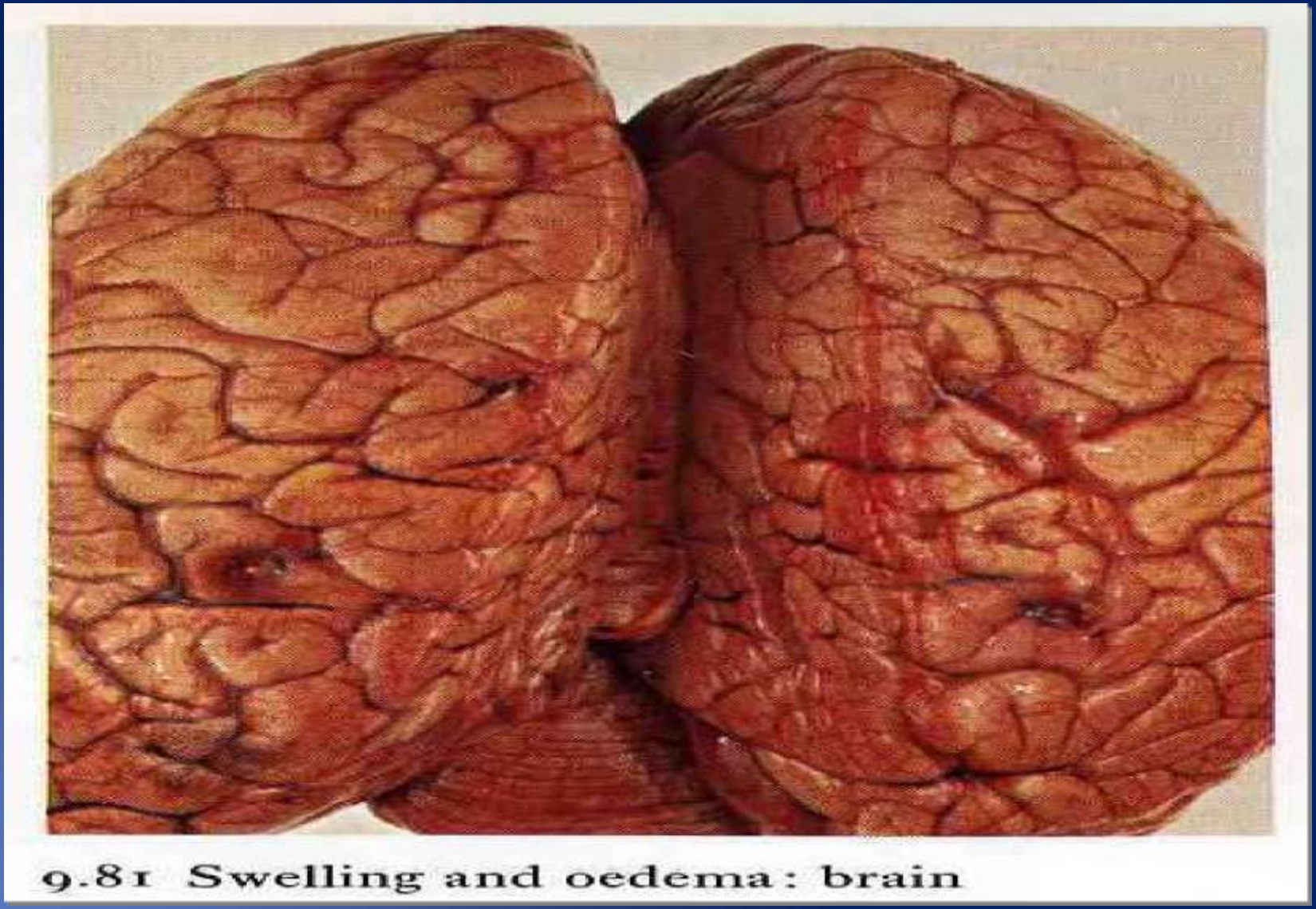


# Brain edema

- May be localized at sites of focal injury as in infarct ,abscess or neoplasm.
- Or generalized as in encephalitis , hypertensive crises ,or obstruction of the venous outflow
- Trauma may result in local or generalized brain edema depending on the nature & extent of the injury.
- Grossly : In generalized brain edema, the brain is grossly swollen, flattened against the unyielding skull , heavier than normal weight , showing narrowed sulci & distended gyri.

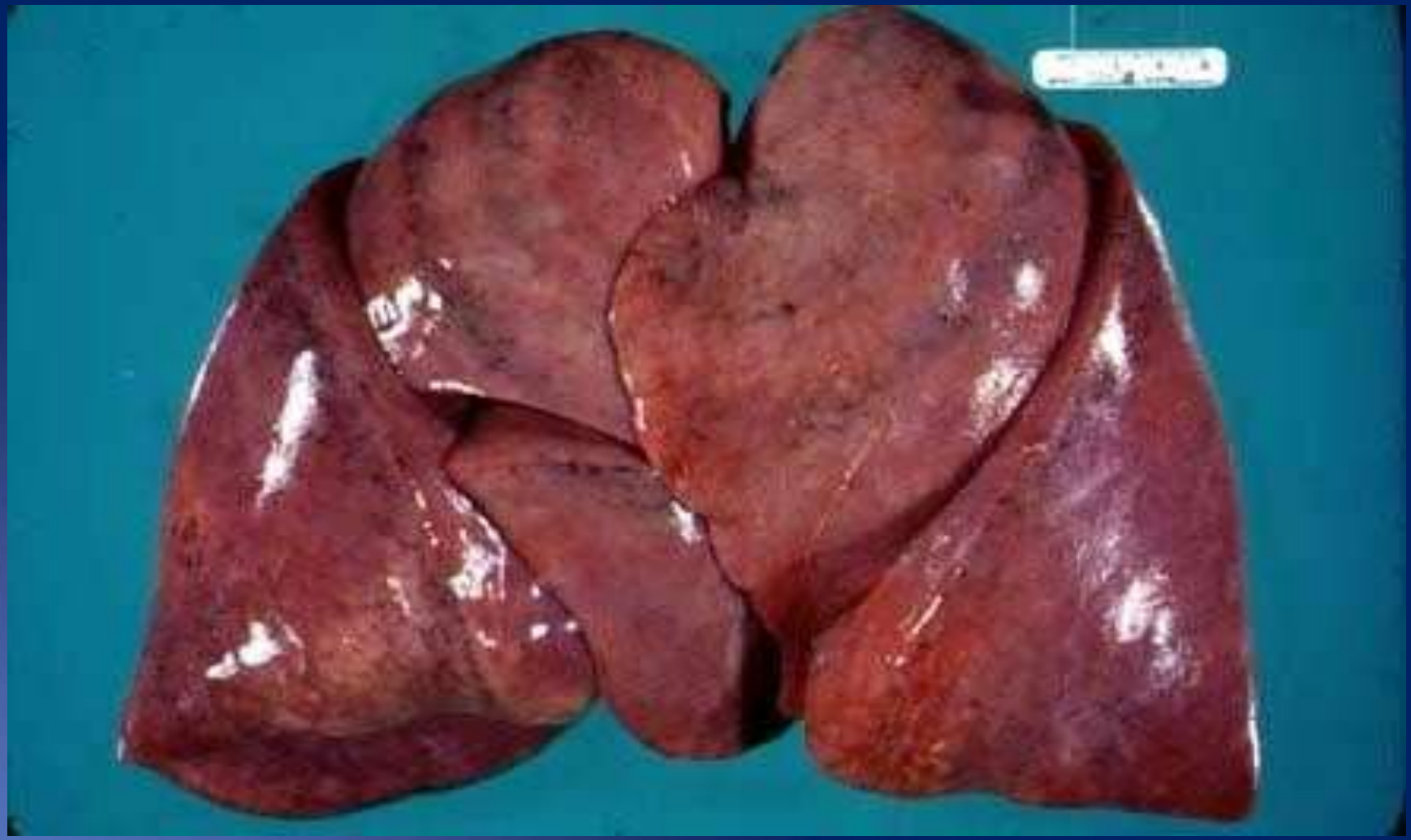
- Clinically :

Brain edema is very serious, & can be rapidly fatal as it causes increased intracranial pressure (ICP) & herniation or extrusion of brain stem through foramen magnum , result in compression of blood supply to medullary vital centres causing sudden death.



9.81 Swelling and oedema: brain

**Gross appearance of edema of the brain.**



Gross appearance of lung edema .Lungs are heavy& swollen.

# HEMORRHAGE (H)

- Is extravasation of blood, due to rupture of blood vessels.
- Capillary H can occur

(1) in chronic venous congestion (CVC) &

(2)in hemorrhagic diatheses, as in Hemophilia a disorders characterized by increased tendency to hemorrhage from usually insignificant injury.

- Hemorrhage or bleeding from ruptured large artery or vein_is almost always due to trauma, other causes include ruptured aneurysms, inflammatory, ulcerative or neoplastic erosion of the vessel wall by tumors .

**Hemorrhage** is either:

*External H:* in which bleeding occurs to the out side from:

Normal cycle uterine bleeding = menstrual bleeding

Excessive or abnormal uterine bleeding = menorrhagia.

Nose = epistaxsis

lung = hemoptysis

Stomach = hematamesis ,

Urinary tract = hematuria

Colon or rectum = bleeding per rectum

**Malena** is a term used to denote a slow bleeding from upper gastro-intestinal tract as in peptic ulcer leading to passage of black stool.

*Internal H .* is enclosed within a

(a) tissue called hematoma .body cavities, as peritoneum, pleura & pericardial sacor joints .

## Hematoma

- is hemorrhage or blood accumulation in tissue.
- Hematomas may be small & insignificant (as in a skin bruise) or may accumulate excessive amount of blood e.g., rupture Atheromatous Abdominal Aortic Aneurysm resulting in massive retroperitoneal hematoma) which is usually usually fatal.

**Skin hematomas are of three types:**

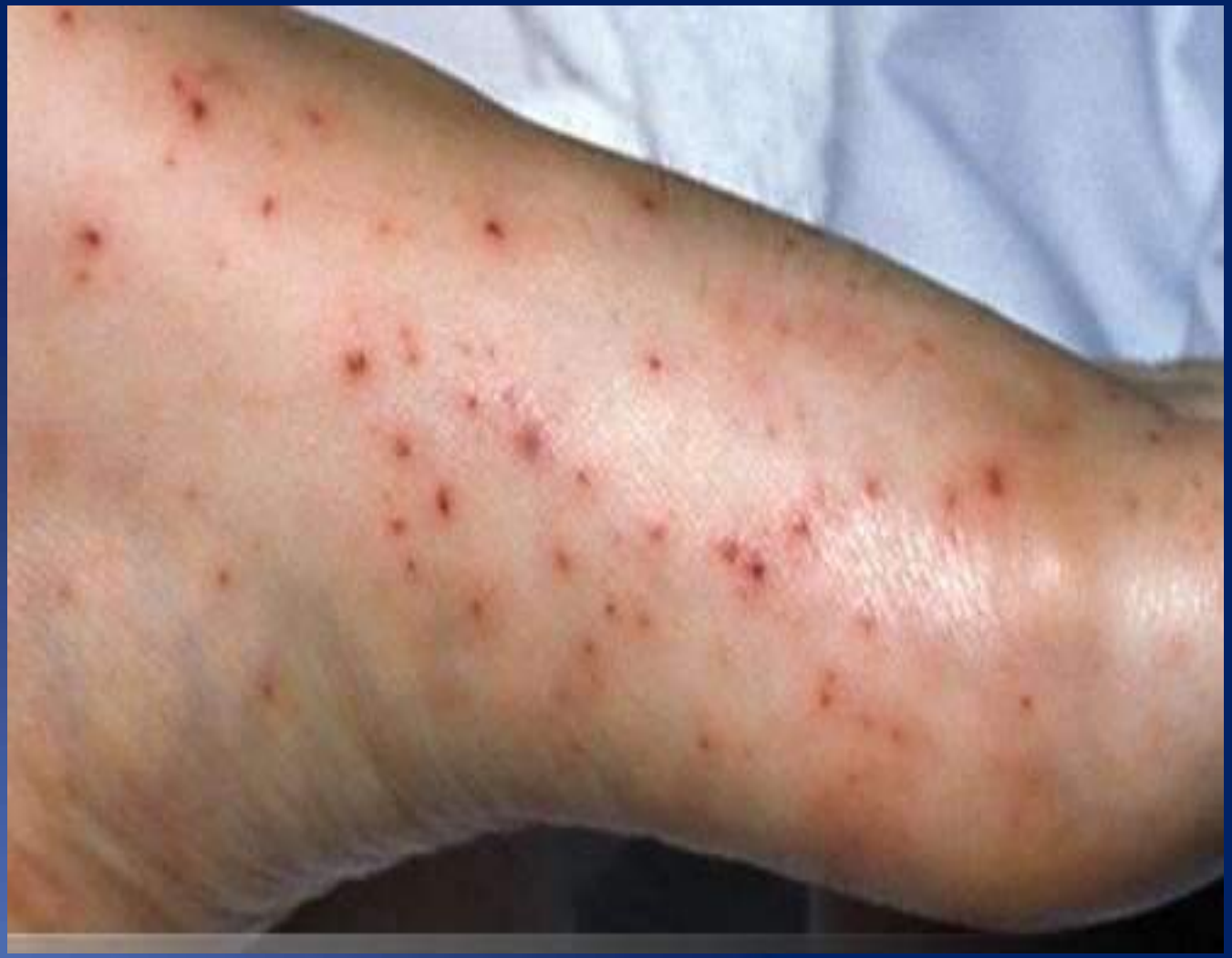
**(I)Petechiae: are minute (1- to 2mm in diameter) hemorrhages into skin, mucous membranes, or serosal surfaces typically associated with :**

**(1) Locally increased intravascular pressure .**

**(2) Low platelet counts(thrombocytopenia) .**

**(3) Defective platelet function .**

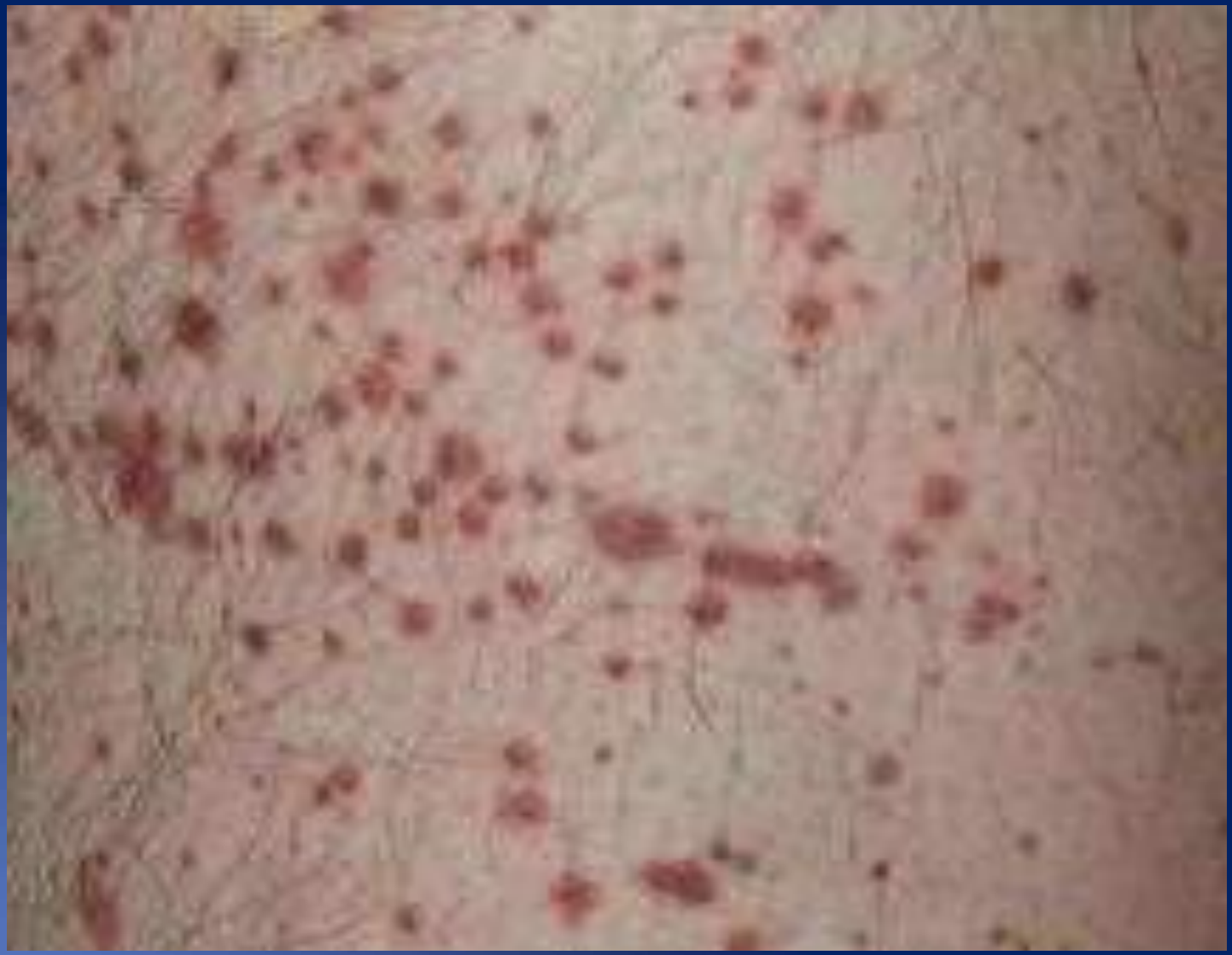
**(4) Clotting factor deficiencies .**



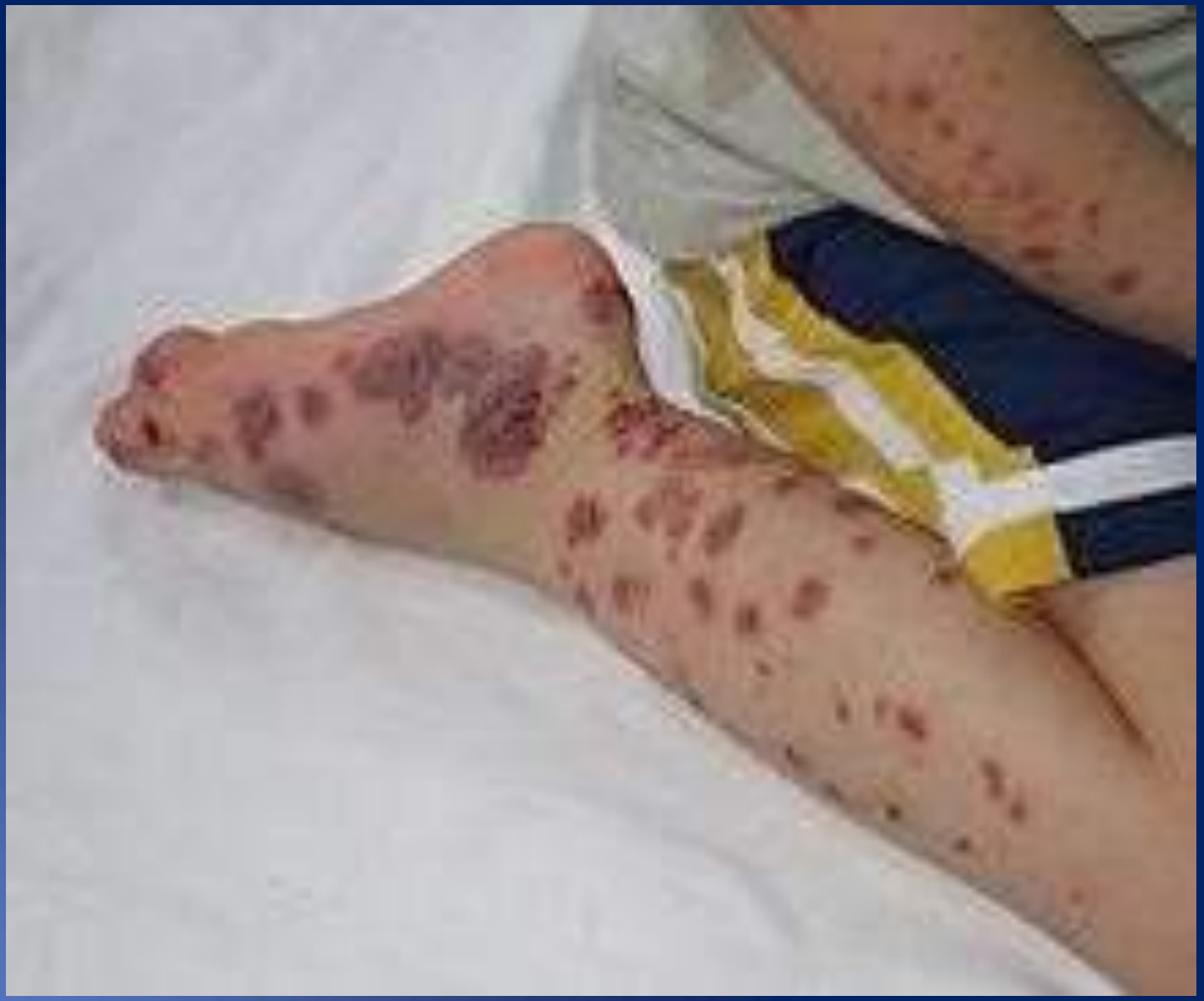
**Petichiae ,skin**

( II) Purpuras : are slightly larger hemorrhagic spots (3- to 5mm in diameter) , may be associated with many of the same disorders that cause petechiae, as well as in the settings of trauma, vasculitis , or increased vascular fragility.

(III) Ecchymoses : or bruises, are larger (10- to 20mm in diameter ) or even larger subcutaneous hematomas.



**Purpura .**



ecchymoses .

- The RBCs in all the above three skin hematomas are degraded & phagocytosed by macrophages, & the hemoglobin (red-blue color) is enzymatically converted into **biliverdin ( green ),** then to **bilirubin** (blue- green color) & eventually into **hemosiderin** (golden-brown) to yellow color.
- The above accounts for the characteristic color changes in hematomas seen, e.g., following **improper I.V. puncture**.

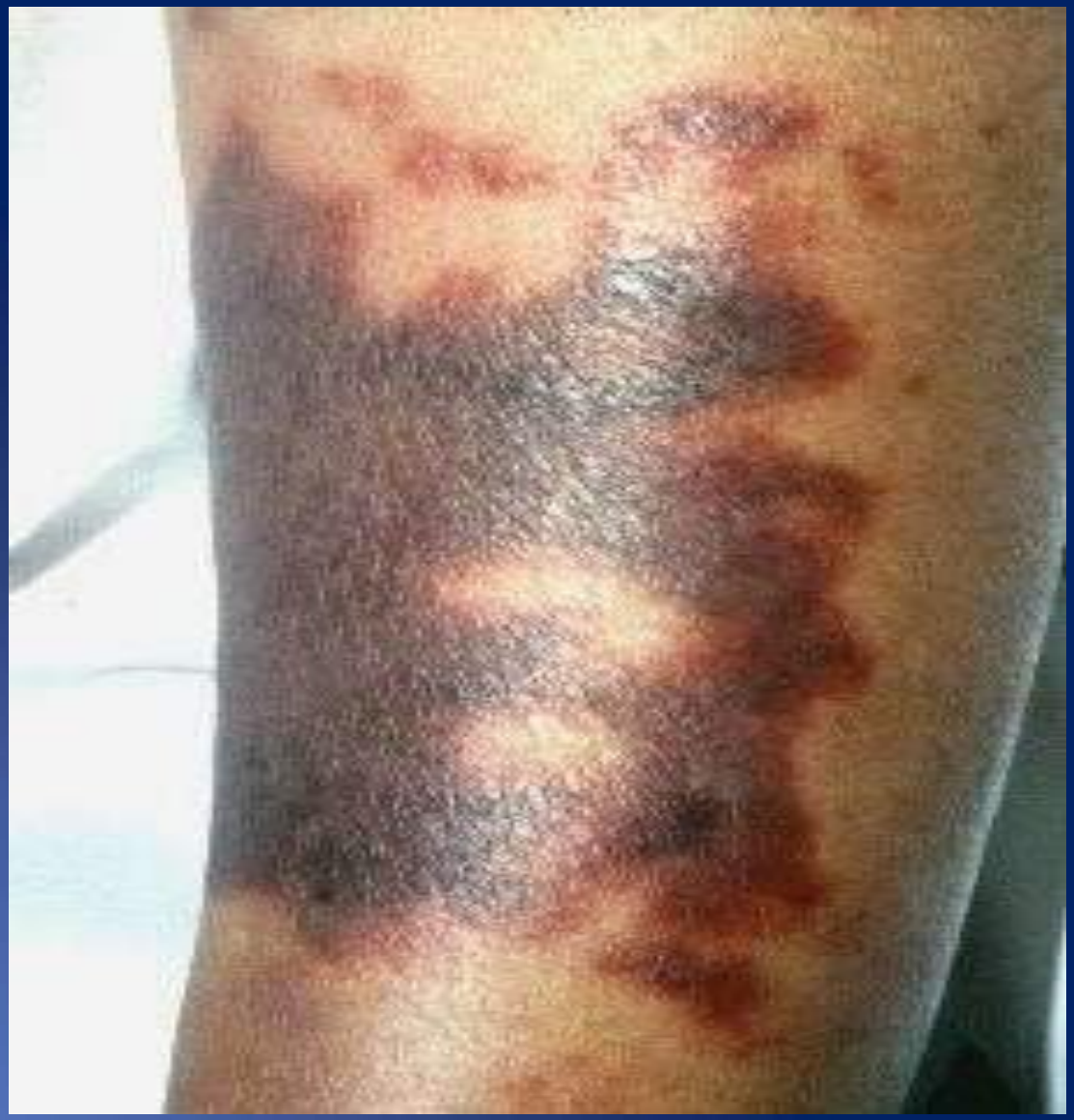


**Figure : Ecchymoses .**

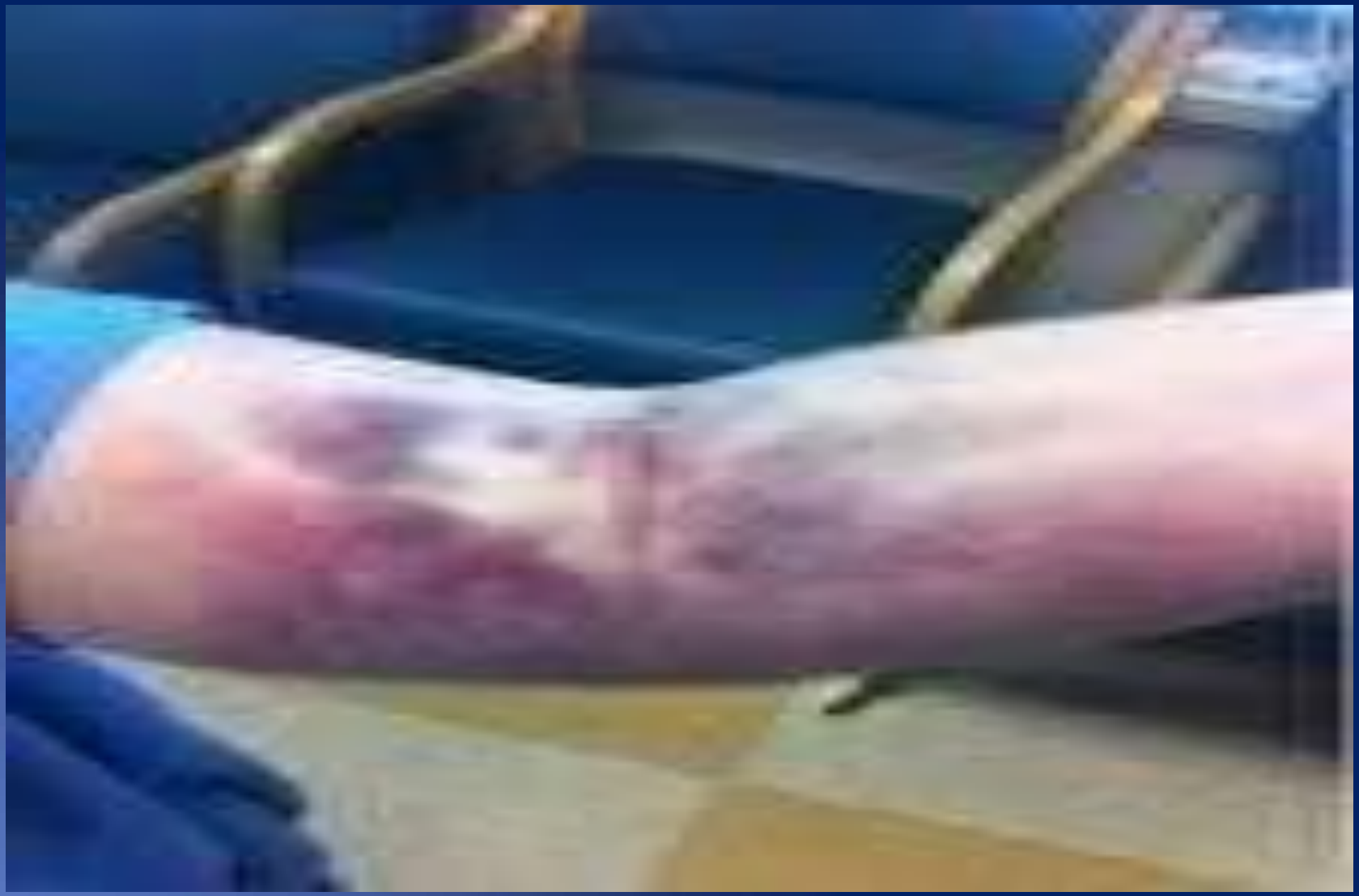
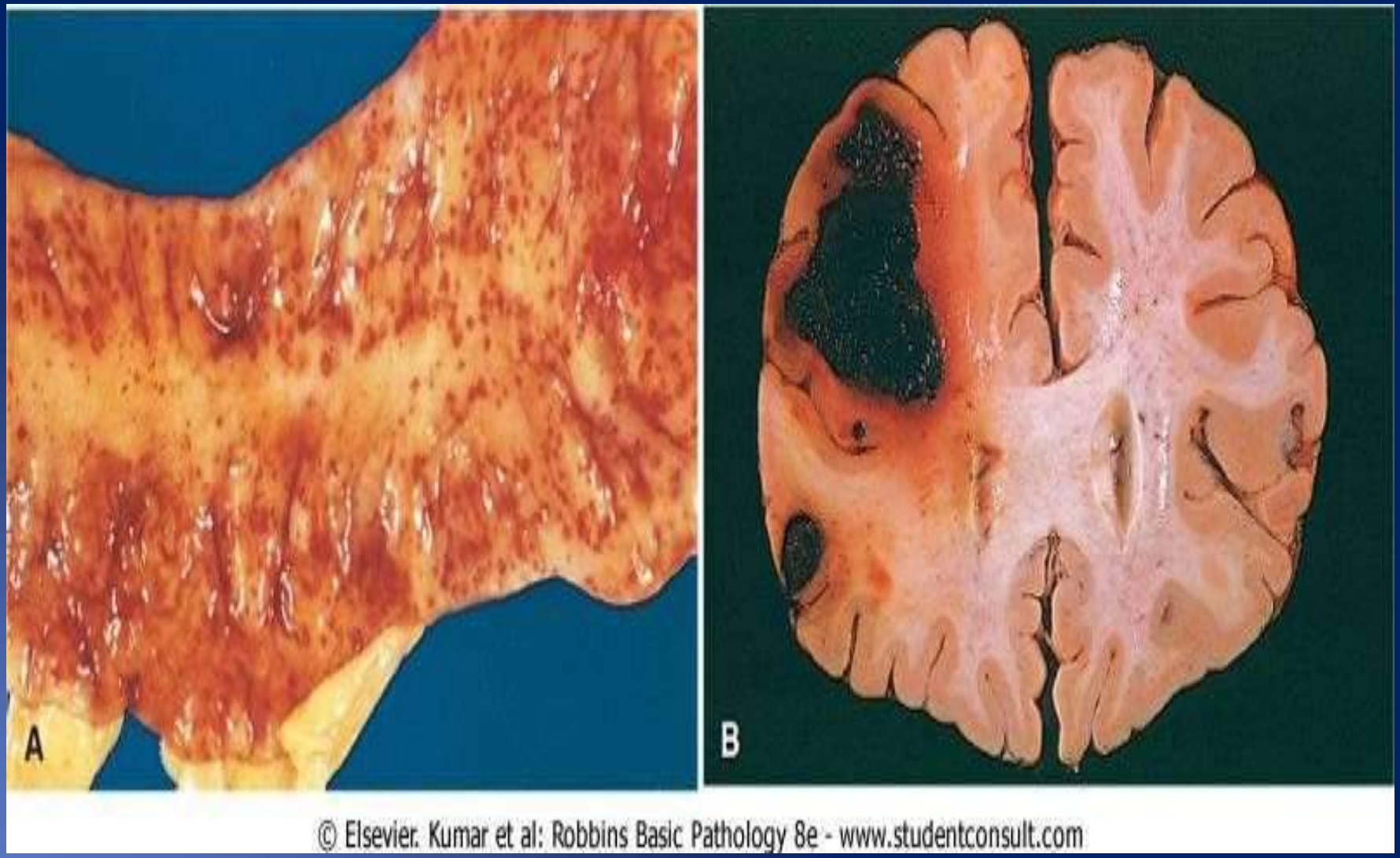


**Figure : Ecchymosis caused by improper I.V. puncture .**

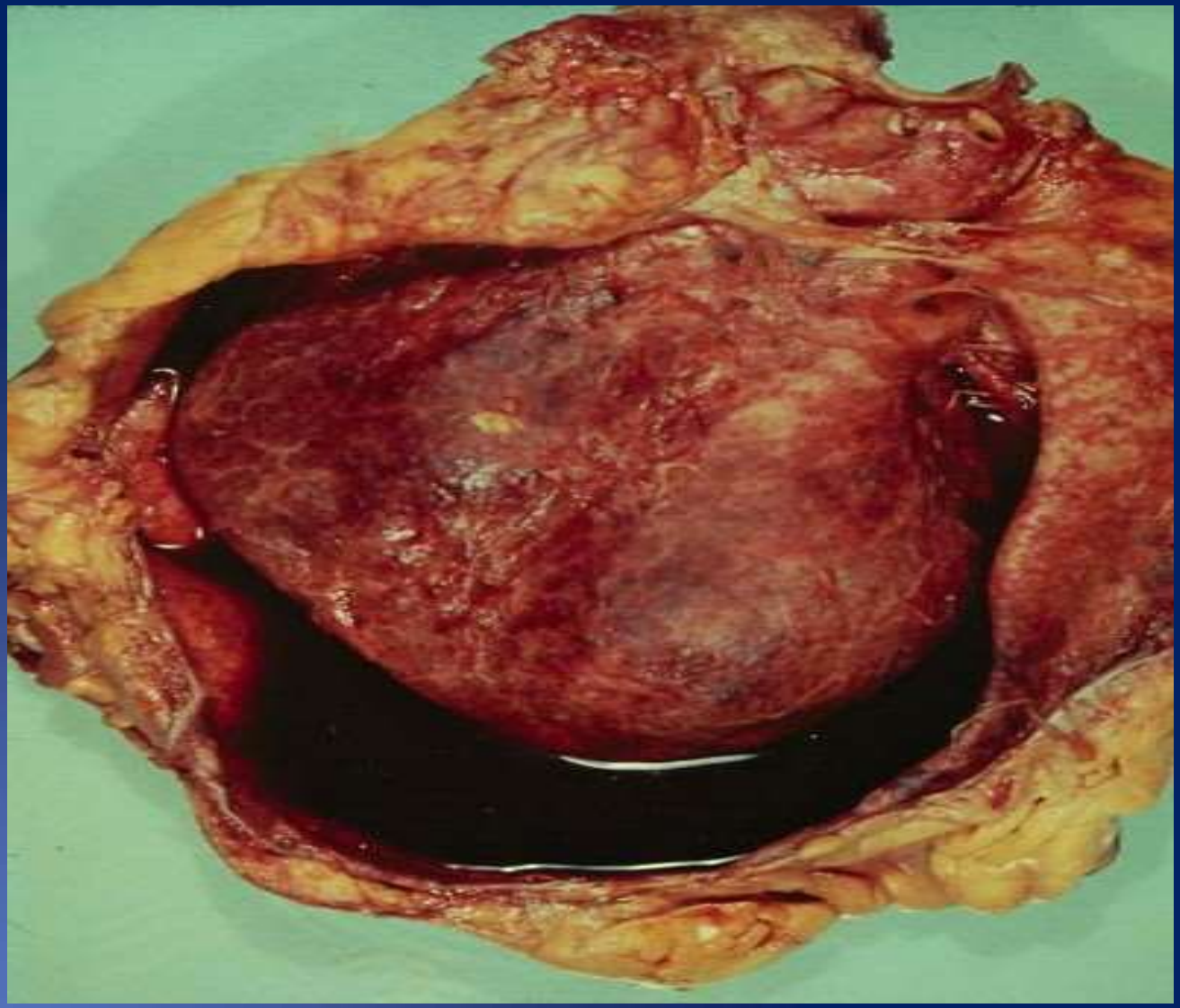





**A-Peticheal hemorrhages in colonic mucosa .**
**B- Fatal intracerebral hemorrhage .**

(b) **Hemothorax, hemopericardium , hemoperitoneum, & hemarthrosis**

are accumulations of blood in the pleural, pericardial, peritoneal & joint cavities respectively.



**Hemopericardium, blood in pericardial cavity .**

**Clinical significance of hemorrhage depends on the:**

**(I) Rate & volume of blood loss;**

**Rapid removal of up to 20% of blood volume or, slow losses of even larger amounts may have little impact in healthy adults; while greater losses, however, may result in hypovolemic shock .**

**(II) Site of hemorrhage is important;**

**Bleeding of about 40 ml of blood, which is considered trivial in the subcutaneous tissues, is rapidly fatal if located in the cerebellum or pons & midbrain .**

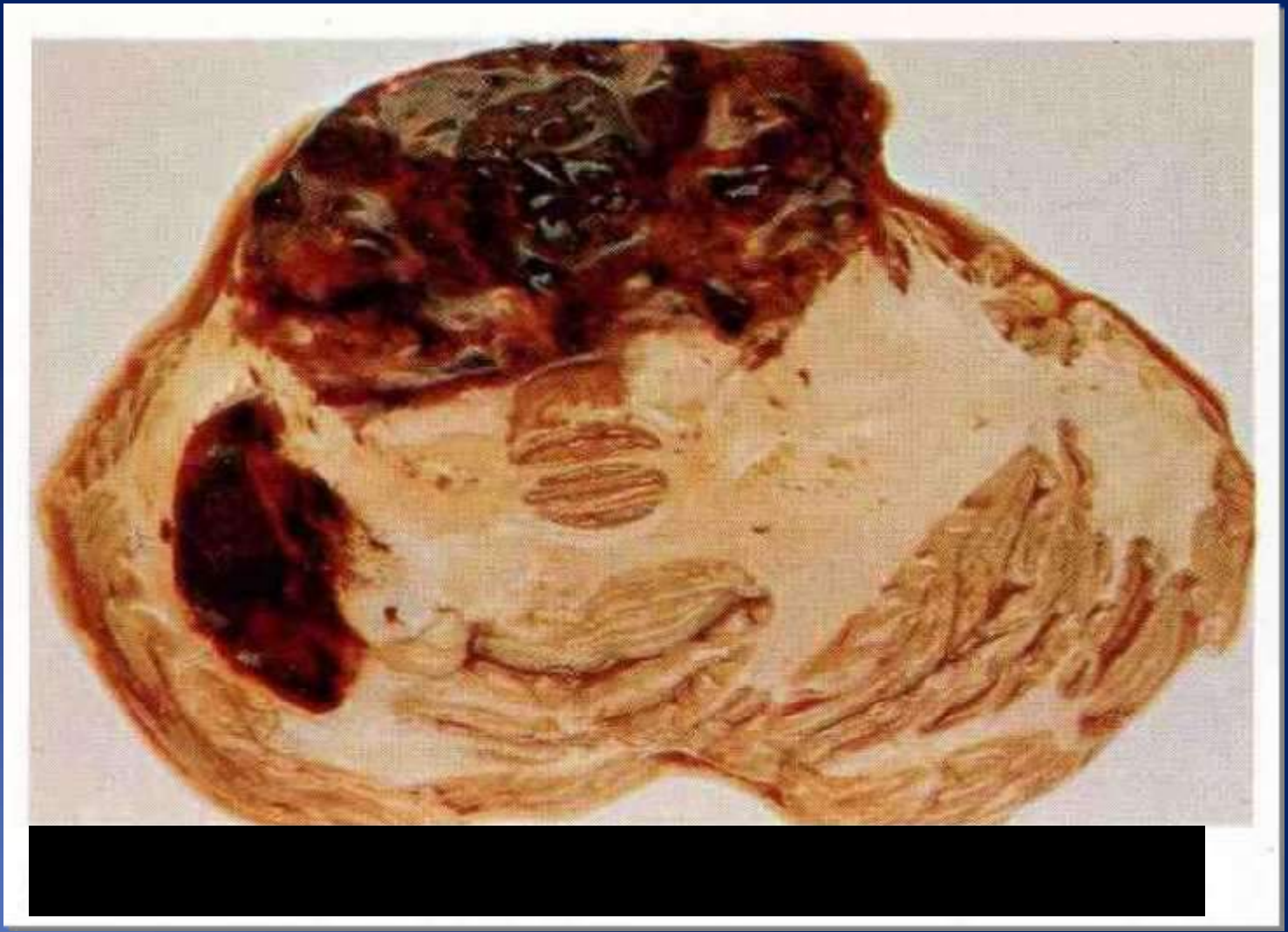


**Figure : Photograph of the hemorrhage in the pons which is rapidly fatal .**

## (III) Recurrent or chronic external hemorrhages

- (e. g., menorrhagia or chronic peptic ulcer) cause loss of iron, with **subsequent iron deficiency anemia.**
- In contrast, when RBCs are retained, as in hemorrhage into body cavities or tissues, the iron can be reutilized for hemoglobin synthesis.

# Thank you and good luck ☺☺☺

# Hemodynamics lecture 3 +4

Dr. Ghada AL-Jussani
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2023
Audio 3

# Hemostasis and Thrombosis

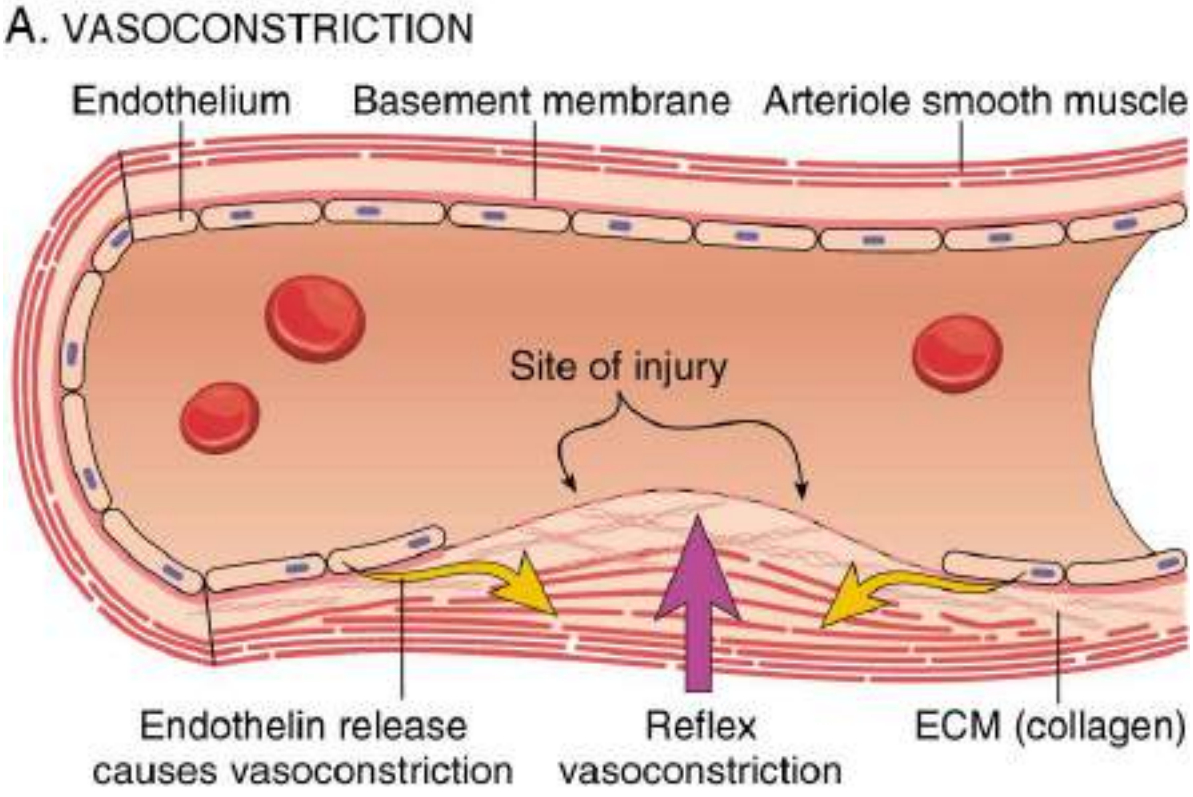
- Hemostasis: physiologic process, maintains blood in fluid condition and clot-free state in normal vessels, and inducing a rapid and localized hemostatic plug at sites of vascular injury.
- It control bleeding at the site of injury , blood loss stop by formation of blood clot that seals the blood vesseles
- Thrombosis: pathologic process, formation of intra-vascular solid mass (thrombus) from the elements of circulating blood. The vessel may be uninjured or with minor injury.

# Hemostasis

- Hemostasis depends on the integrity of
  - Blood vessels
  - Platelets
  - Coagulation factors

# STEPS IN HEMOSTASIS

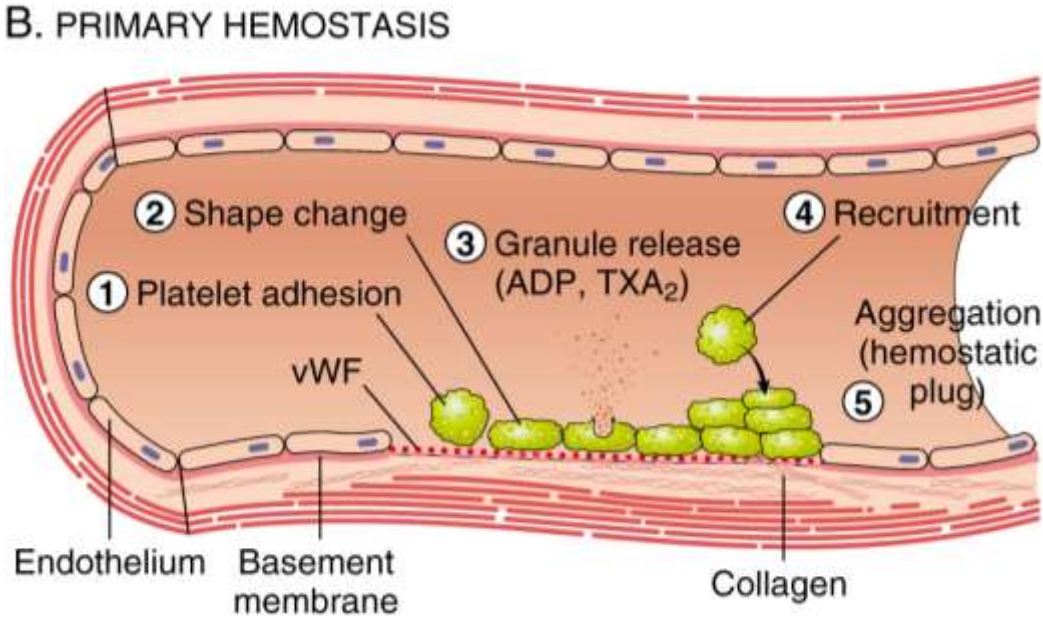
## (1) Transient arteriolar vasoconstriction due to reflex neurogenic mechanism and secretion of endothelin.



# STEPS IN HEMOSTASIS

## (2)Formation of primary platelet plug due to adhesion of platelets to collagen and traces of thrombin.

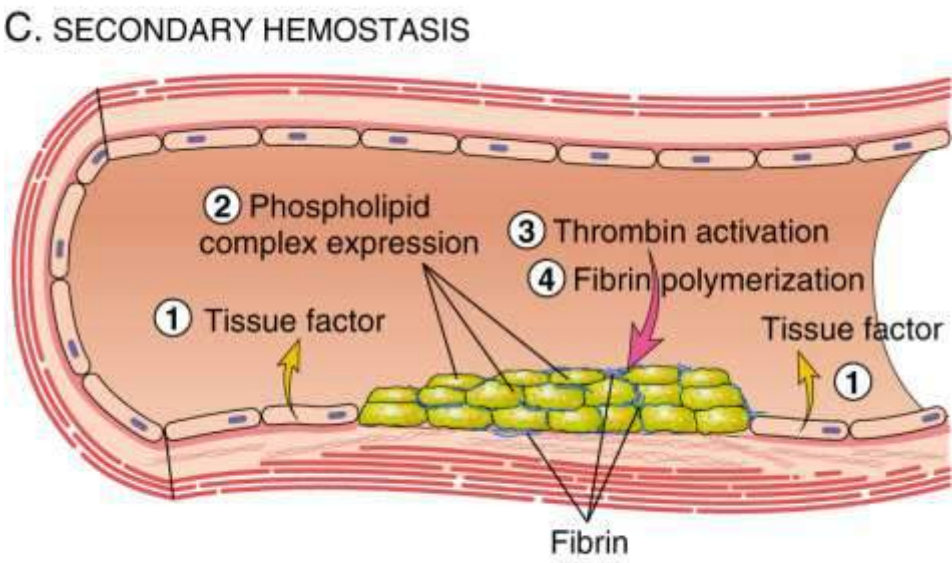
- Adhesion of platelets to the subendothelial ECM via (vWF: von Willebrand factor) then activation of platelets and release of its contents like ($TXA_2$: thromboxane $A_2$) and ADP leading to platelets aggregation and formation of hemostatic plug (primary hemostasis)

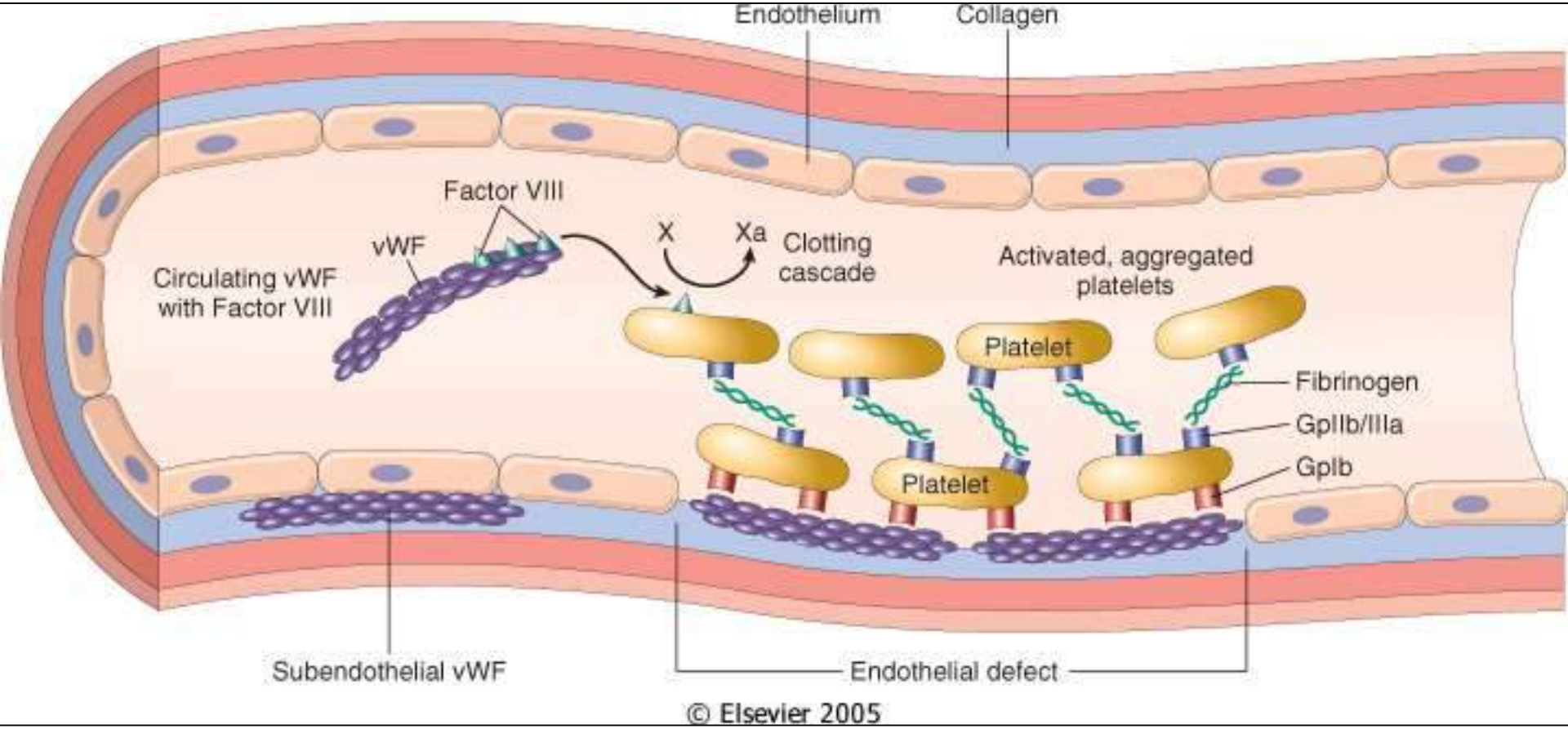


# STEPS IN HEMOSTASIS

(3) Conversion into permanent plug supported by fibrin clot, which is formed by activation of the **coagulation cascade**.

- At sites of injury: release of Tissue factor and activation of **extrinsic** coagulation cascade leading to formation of thrombin which converts fibrinogen into insoluble fibrin which binds to the platelet aggregate and stabilize it and this is called **secondary haemostasis.**

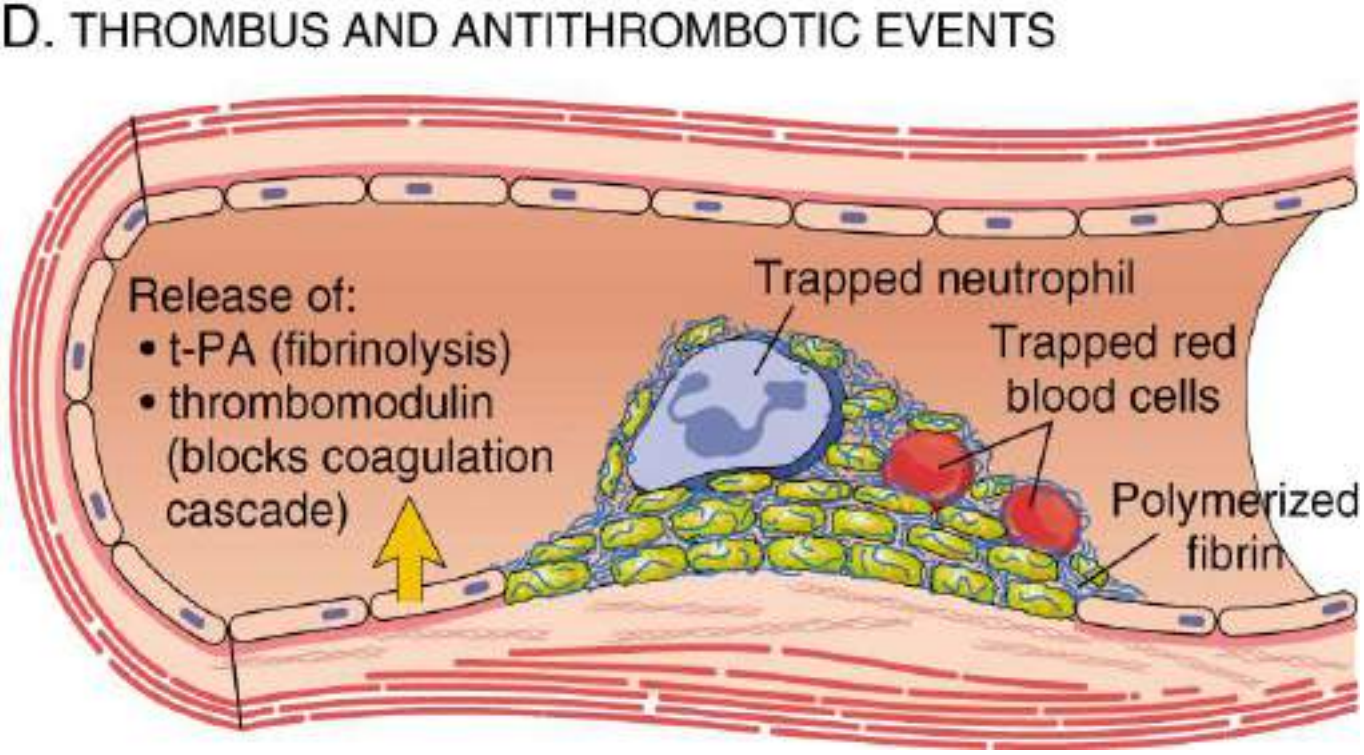




# Antithrombotic Functions
# Fibrinolytic Effects

(4) Lysis of fibrin and confinement of clot to the site of injury.

- Fibrinolytic Effect: synthesize tissue-type plasmimogen activator (t-PA) that clears fibrin deposits from endothelial surfaces.



# Endothelium

Antithrombotic Properties of Normal Endothelium:

- **Inhibitory Effects on Platelets*:***

- Intact endothelium prevents platelets from engaging the highly thrombogenic subendothelial ECM.
- Prostacyclin and nitric oxide produced by endothelium are potent vasodilators and inhibitors of platelet aggregation
- Endothelial cells produce adenosine diphosphatase, which degrades adenosine diphosphate (ADP)

**Inhibitory Effects on Coagulation Factors:**

- **The heparin-like molecules**: Activates **antithrombin**
- **Thrombomodulin:** activates **protein C (anticoagulant)**
- **Tissue factor pathway inhibitor** (TFPI)

**Fibrinolysis.**

- Endothelial cells synthesize tissue-type plasminogen activator, a protease that cleaves plasminogen to plasmin
- Plasmin cleaves fibrin.

# Prothrombotic Properties of Injured or Activated Endothelium

- **Activation of Platelets.**

- Endothelial injury brings platelets into contact with the von Willebrand factor (vWF), a large multimeric protein that is synthesized by EC.

- vWF binds tightly to Gp1b, a glycoprotein found on the surface of platelets.

- **Activation of Clotting Factors.**

- Endothelial cells produce tissue factor

- **Antifibrinolytic Effects.**

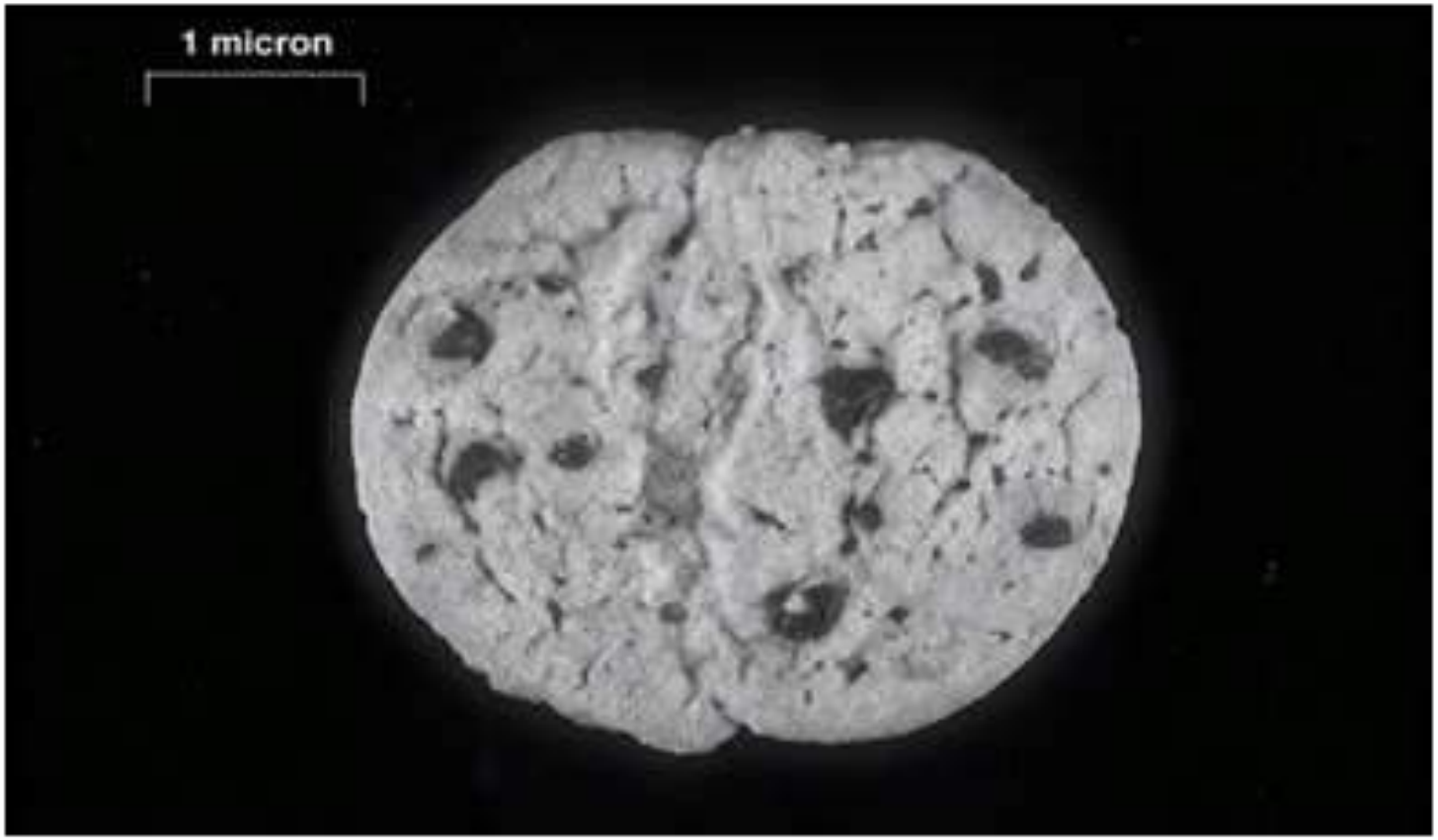
- Activated endothelial cells secrete plasminogen activator inhibitors (PAIs)

# Platelets

- anucleate cell fragments shed into the bloodstream by marrow megakaryocytes.
- Two types of cytoplasmic granules:

- α granules
- Dense bodies (δ granules): contain adenine nucleotides (ADP and ATP), ionized calcium, histamine, serotonin,and epinephrine

Here is an actual electron micrograph of a platelet. Note that this platelet bears a striking resemblance to a chocolate chip cookie. The chocolate chips are the alpha and dense granules that contain a variety of mediators such as ADP.



# After vascular injury:

1- Platelet **Adhesion**

- Depends on vWF and platelet glycoprotein **Gp1b.**

2- Platelet **Activation**

- Irreversible shape change and secretion of both granule types.
- Calcium and ADP released
- **Calcium is required by several coagulation factors**
- Activated platelets also synthesize TxA2

# After vascular injury:

3- Platelet **Aggregation**

- Stimulated by TxA2.
- Promoted by bridging interactions between **fibrinogen and GpIIb/IIIa** receptors on adjacent platelets .
- Rare inherited deficiency of GpIIb/IIIa (Glanzmann thrombasthenia)

# coagulation cascade

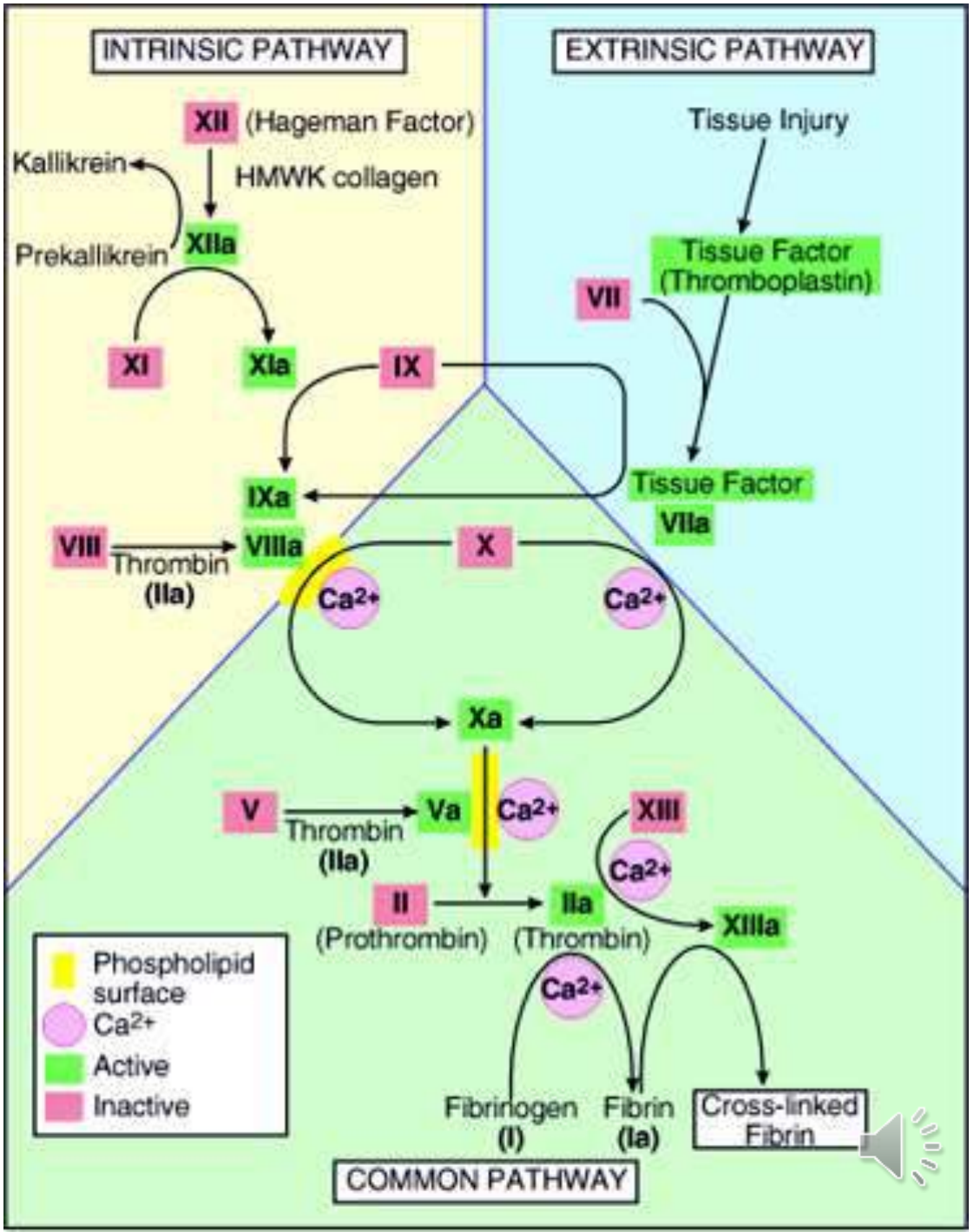
- Coagulation components typically are assembled on a phospholipid surface (provided by endothelial cells or platelets)
- Coagulation components are held together by interactions that depend on **calcium ions**
- The ability of coagulation factors **II, VII, IX, and X** to bind to calcium requires that additional γ-carboxyl groups be enzymatically appended to certain glutamic acid residues on these proteins.

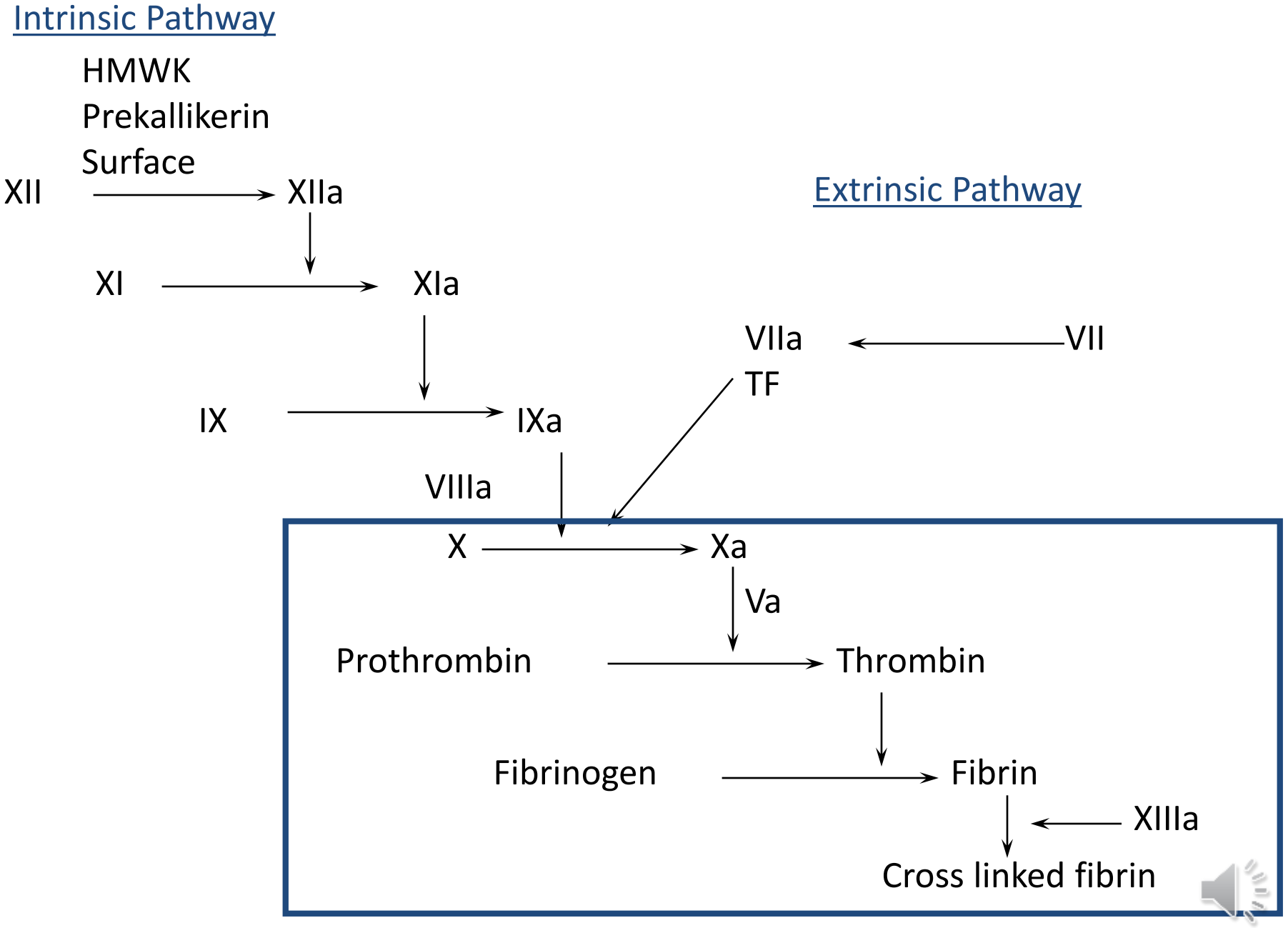
- This reaction requires vitamin K as a cofactor

- Blood coagulation divided into **extrinsic** and **intrinsic** pathways, converging at the **activation of factor X** .
- Several interconnections between the two pathways exist.
- The **extrinsic** pathway is the most physiologically relevant pathway for coagulation occurring after vascular damage; it is activated by **tissue factor**.

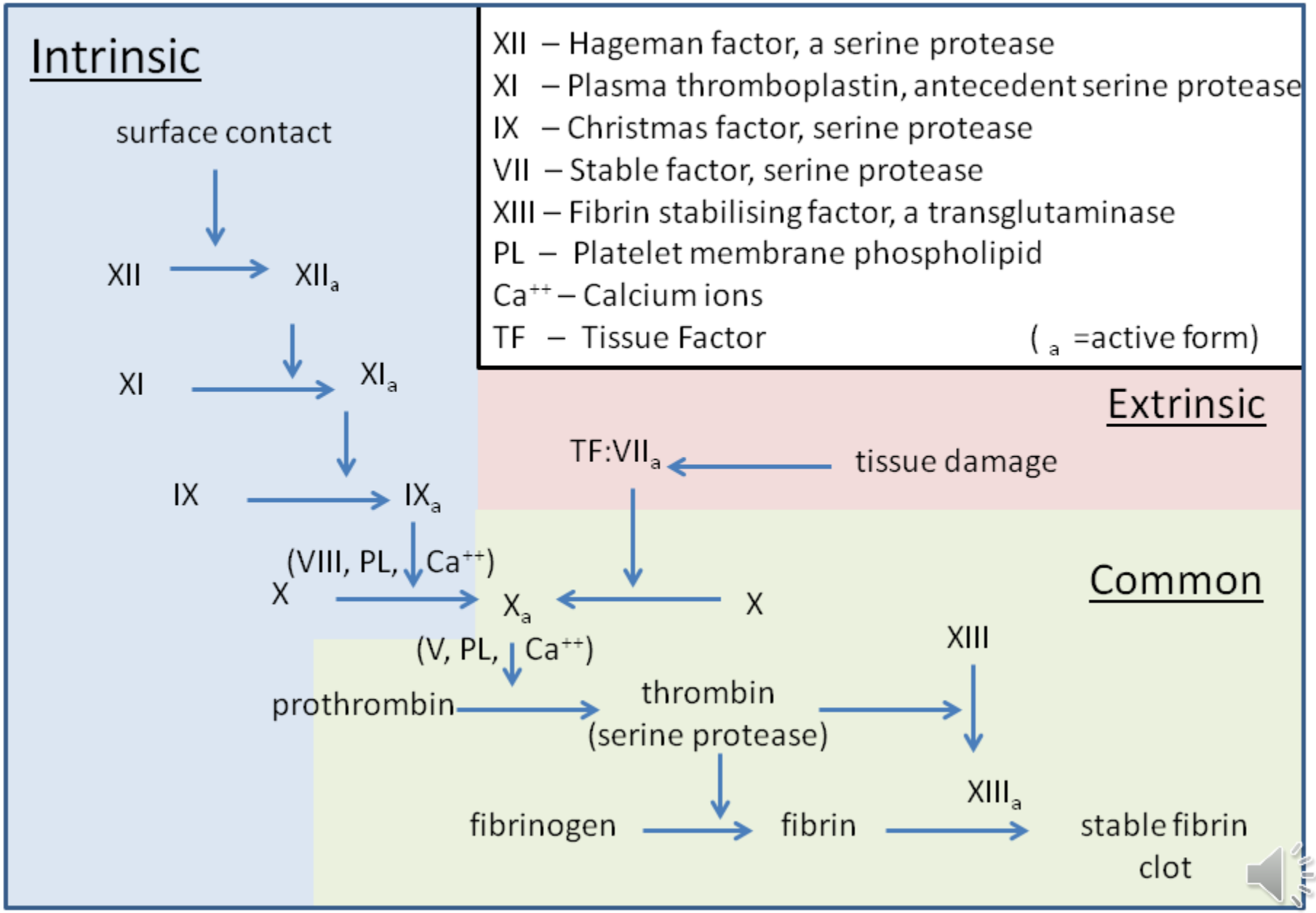
# The coagulation cascade

- 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).




Intrinsic Pathway
HMWK
Prekallikerin
Surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Extrinsic Pathway
VIIa
VII
TF
X
Xa
Va
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
Cross linked fibrin

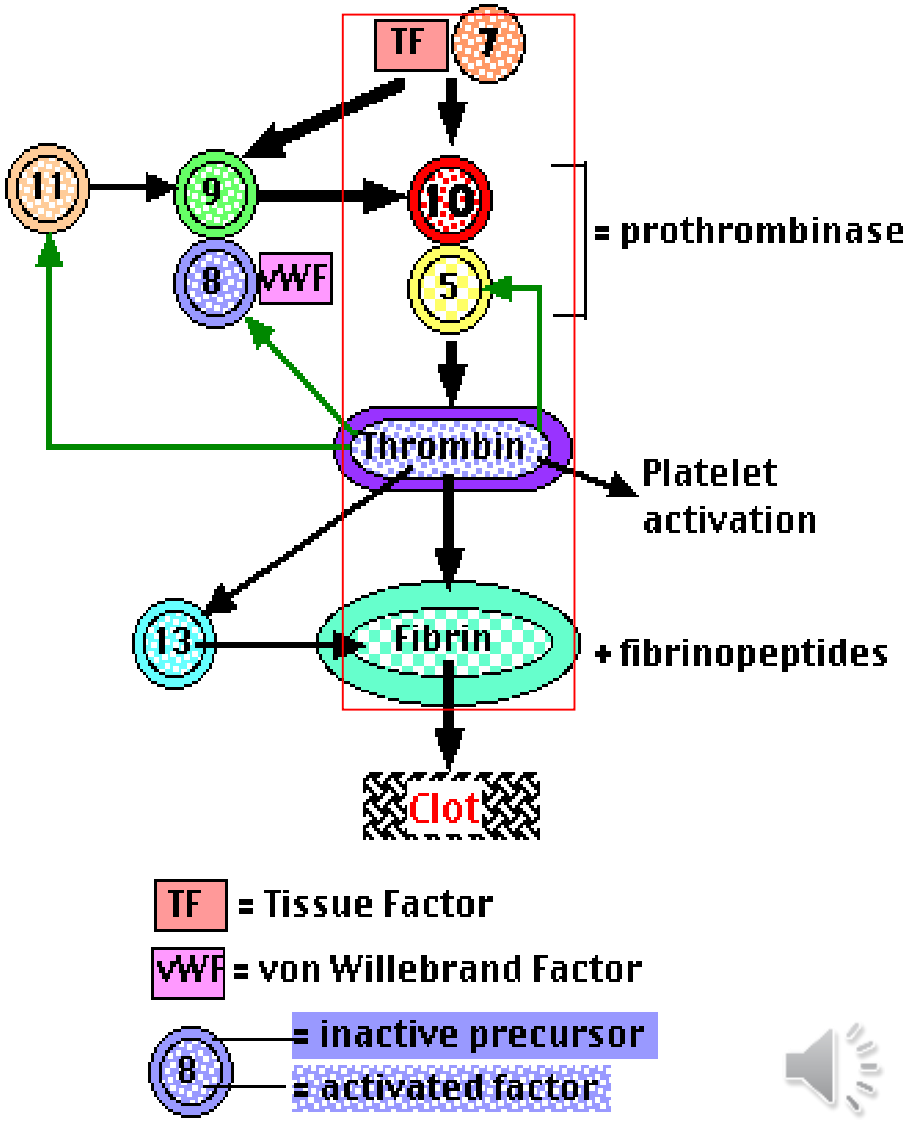
# The three pathways that makeup the classical blood coagulation pathway



# Coagulation cascade

1. Damaged cells (extrinsic pathway) display a surface protein (tissue factor: TF) that binds to activated Factor 7 (TF-7) to cleave: Factor 10

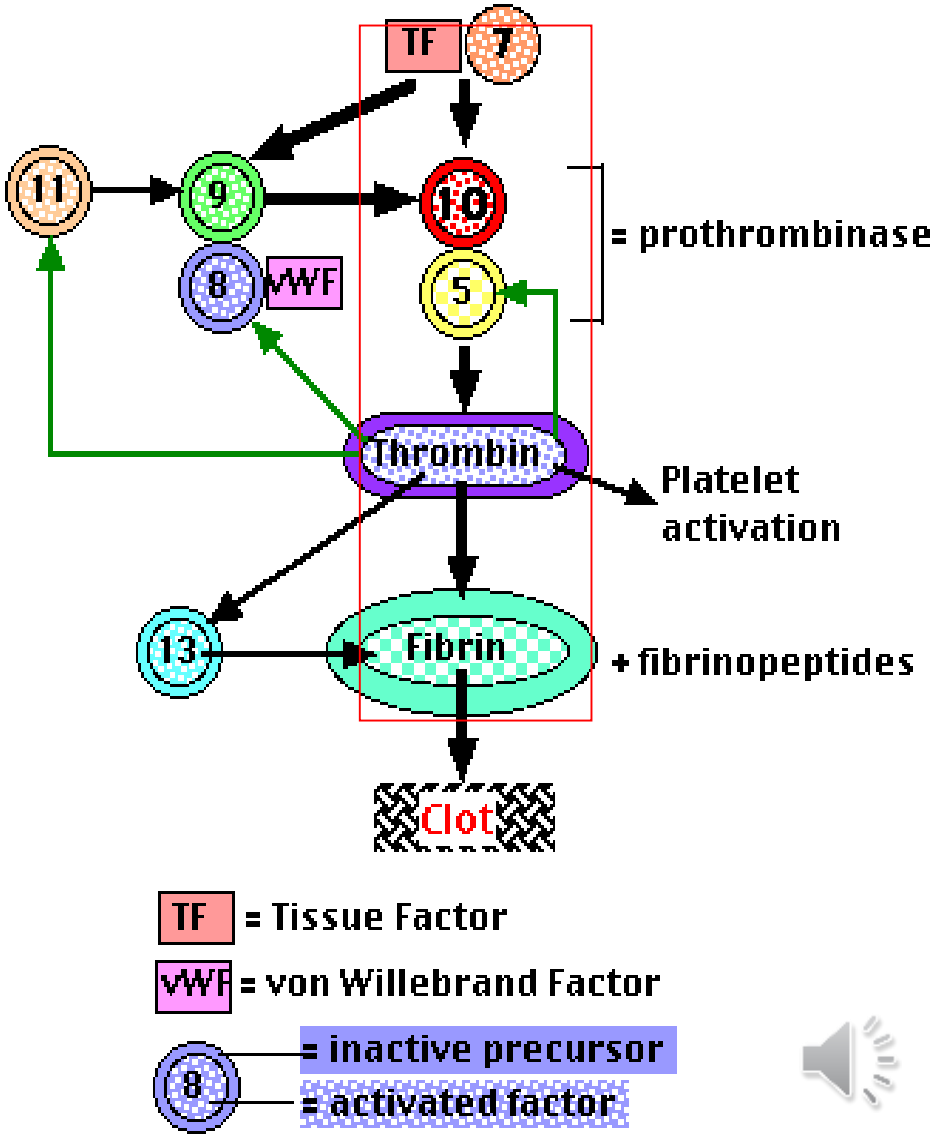
2. Factor 10 binds and activates Factor 5 (prothrombinase) converting prothrombin (also known as Factor II) to thrombin



# Coagulation cascade

3. Thrombin proteolytically cleave fibrinogen (Factor I) to fibrin.

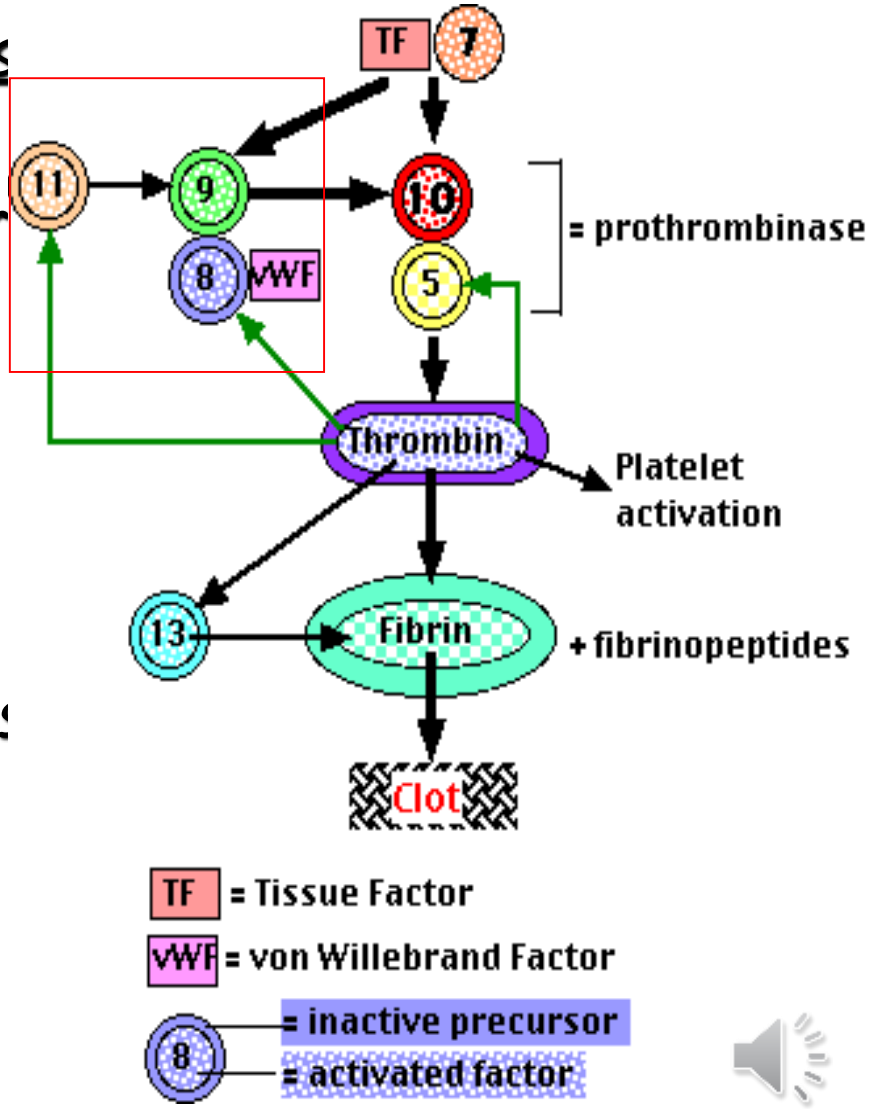
4. Factor 13 forms covalent bonds between the soluble fibrin molecules converting them into an insoluble meshwork — the clot.



# Coagulation cascade

## Amplifying the Clotting Process

- The TF-7 complex & factor 11 activates Factor 9.
- Factor 9 binds to factor 8, a protein that circulates in the blood stabilized by another protein (vWF).
- Complex 9-8-vWF activates more factors: 5,10



# Coagulation factors and related substances

| Number and/or name | Function |
|---|---|
| I (fibrinogen) | Forms clot (fibrin) |
| II (prothrombin) | Its active form (IIa) activates I, V, VIII, XI, XIII, protein C, platelets |
| III (Tissue factor or thromboplastin | Co-factor of VIIa |
| IV (Calcium) | Required for coagulation factors to bind to phospholipid |
| V (proaccelerin, labile factor) | Co-factor of X with which it forms the prothrombinase complex |
| VI | Unassigned – old name of Factor Va |
| VII (stable factor) | Activates IX, X |
| VIII (antihemophilic factor) | Co-factor of IX with which it forms the tenase complex |
| IX (Christmas factor) | Activates X: forms tenase complex with factor VIII |
| X (Stuart-Prower factor) | Activates II: forms prothrombinase complex with factor V |
| XI (plasma thromboplastin antecedent) | Activates IX |
| XII (Hageman factor) | Activates factor XI and prekallikrein |
| XIII (fibrin-stabilizing factor) | Crosslinks fibrin |
| von Willebrand factor | Binds to VIII, mediates platelet adhesion |

# Coagulation factors and related substances

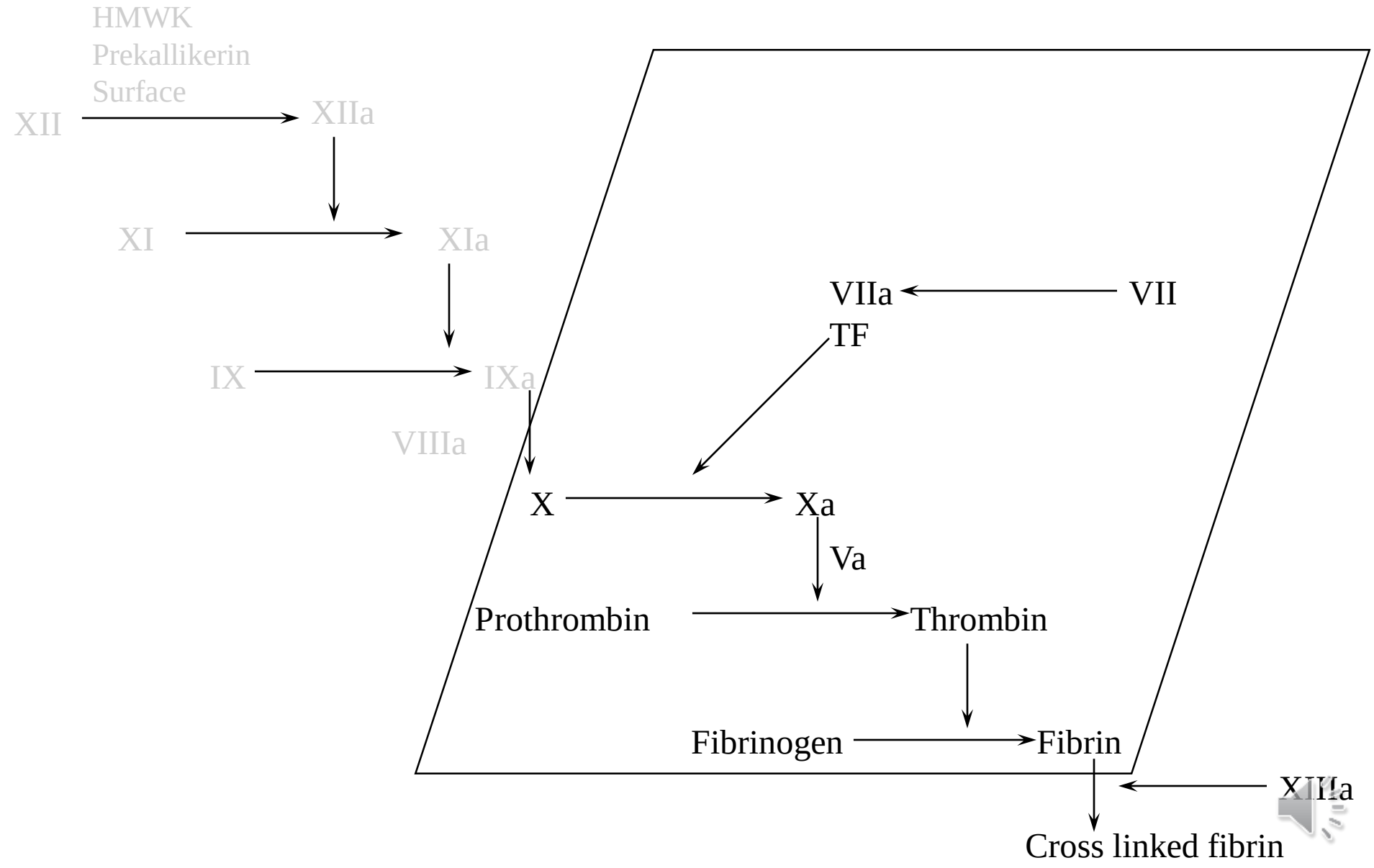
| | |
|---|---|
| prekallikrein | Activates XII and prekallikrein; cleaves HMWK |
| high molecular weight kininogen (HMWK) | Supports reciprocal activation of XII, XI, and prekallikrein |
| fibronectin | Mediates cell adhesion |
| antithrombin III | Inhibits IIa, Xa, and other proteases; |
| heparin cofactor II | Inhibits IIa, cofactor for heparin and dermatan sulfate ("minor antithrombin") |
| protein C | Inactivates Va and VIIIa |
| protein S | Cofactor for activated protein C (APC, inactive when bound to C4b-binding protein) |
| protein Z | Mediates thrombin adhesion to phospholipids and stimulates degradation of factor X by ZPI |
| Protein Z-related protease inhibitor (ZPI) | Degrades factors X (in presence of protein Z) and XI (independently) |
| plasminogen | Converts to plasmin, lyses fibrin and other proteins |
| alpha 2-antiplasmin | Inhibits plasmin |
| tissue plasminogen activator (tPA) | Activates plasminogen |
| urokinase | Activates plasminogen |
| plasminogen activator inhibitor-1 (PAI1) | Inactivates tPA & urokinase (endothelial PAI) |
| plasminogen activator inhibitor-2 | Inactivates tPA & urokinase (placental PAI) |

# Clinical labs assessment

- **Prothrombin time (PT):**

- Screens for the activity of the proteins in the **extrinsic** pathway (factors **VII**, X, II, V, and fibrinogen).
- The PT is performed by adding phospholipids and tissue factor to a patient's citrated plasma (sodium citrate chelates calcium and prevents spontaneous clotting), followed by calcium, and the time to fibrin clot formation (usually 11 to 13 seconds) is recorded.

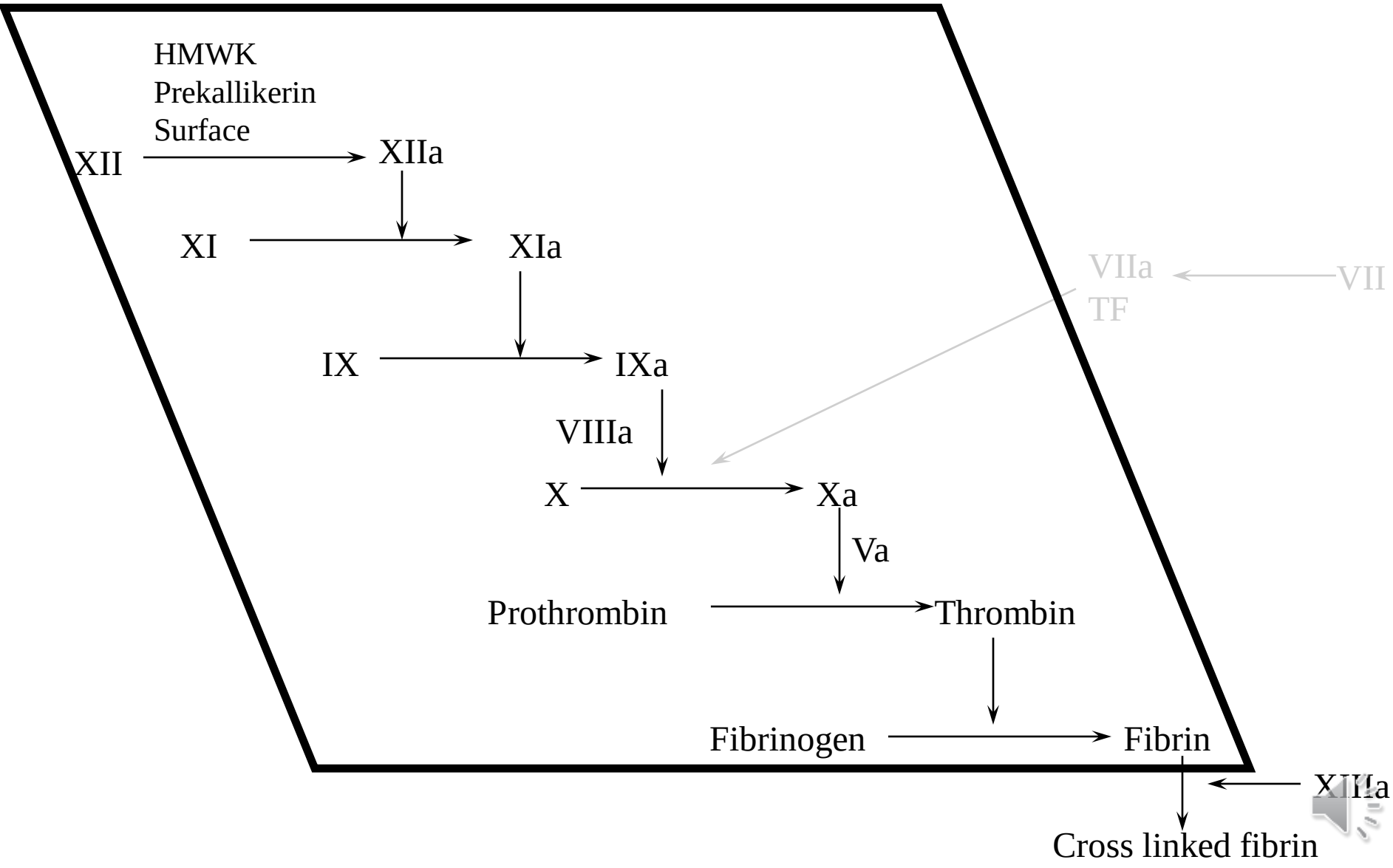
# Prothrombin Time(PT)



- **Partial thromboplastin time (PTT):**

- Screens for the activity of the proteins in the **intrinsic** pathway (factors **XII, XI, IX, VIII**, X, V, II, and fibrinogen).
- The PTT is performed by adding a negatively charged activator of factor XII and phospholipids to a patient's citrated plasma, followed by calcium, and recording the time required for clot formation (usually 28 to 35 seconds).

# Partial Thromboplastin Time

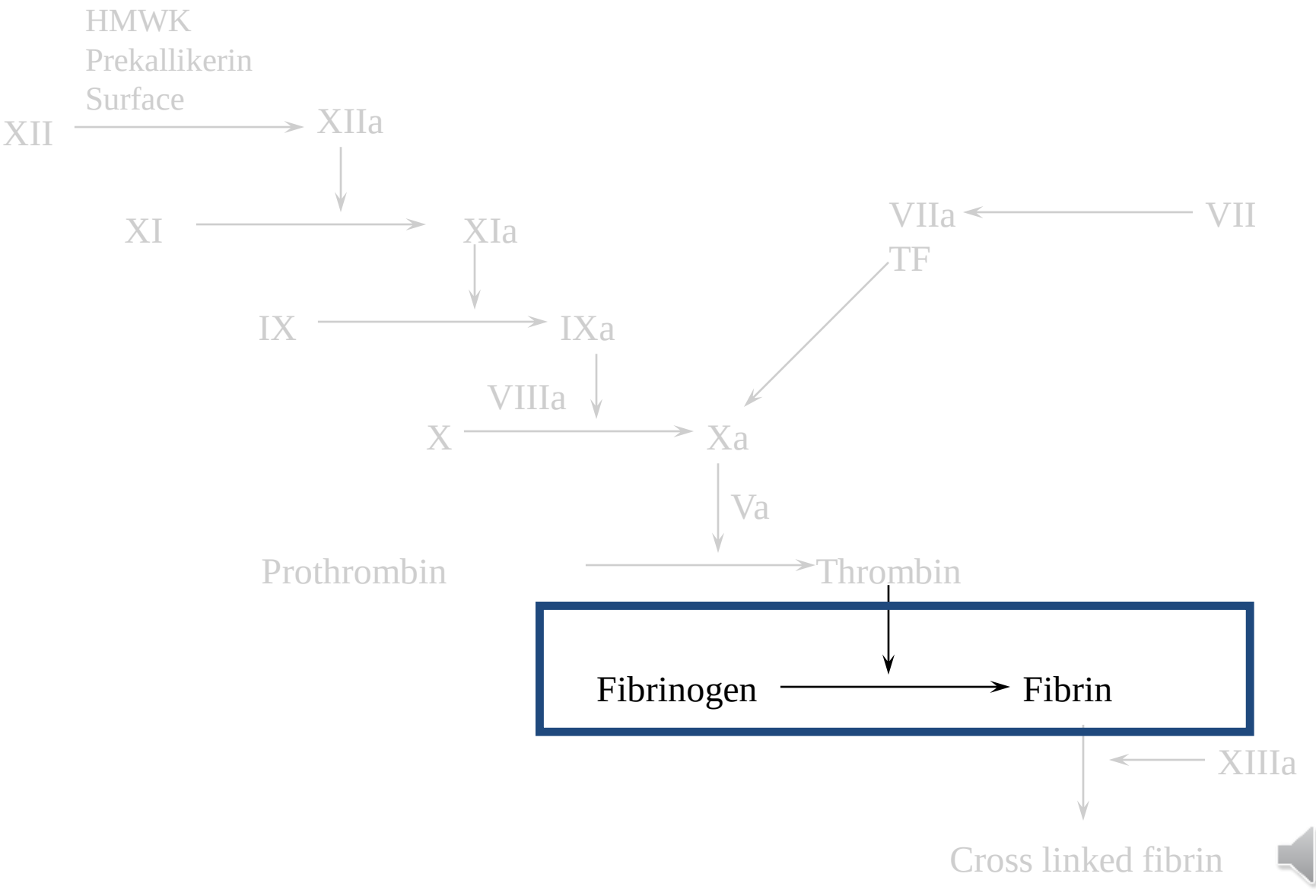


- **Thrombin Time:**

- screen for reduction of fibrinogen concentration and presence of fibrin split products.

- Thrombin is added to plasma. Time needed to clot is measured as TT.

# Thrombin Time



# Regulation of clotting

1- **Antithrombins** (e.g., antithrombin III) :

- Inhibit the activity of thrombin and factors **IXa, Xa, XIa, and XIIa**.
- Activated by binding to **heparin-like molecules**

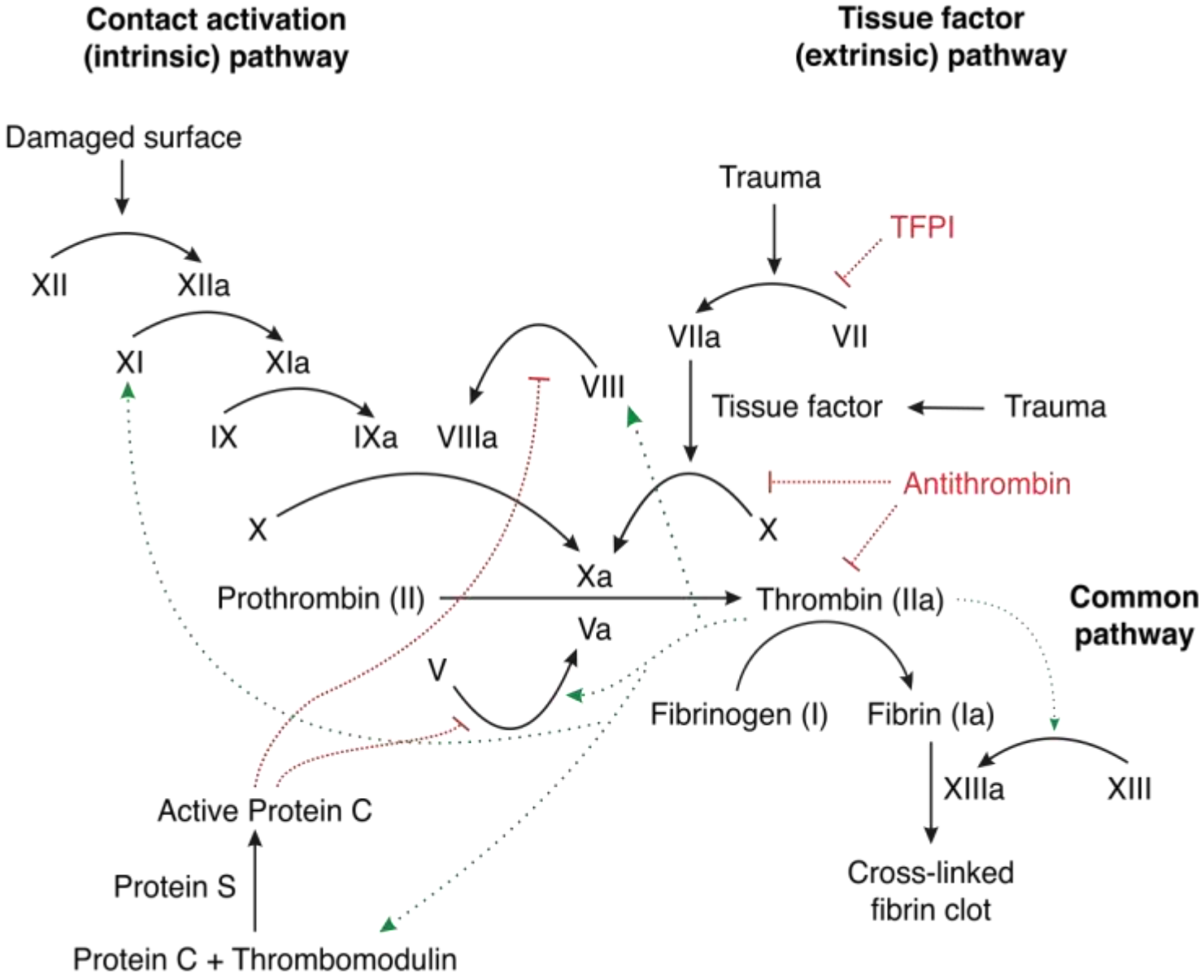
**2**- **Protein C and protein S**:

- Two vitamin K–dependent proteins that act in a complex to proteolytically **inactivate cofactors Va and VIIIa**.
- Protein C **activated by thrombomodulin**
- protein S is a cofactor for protein C activity

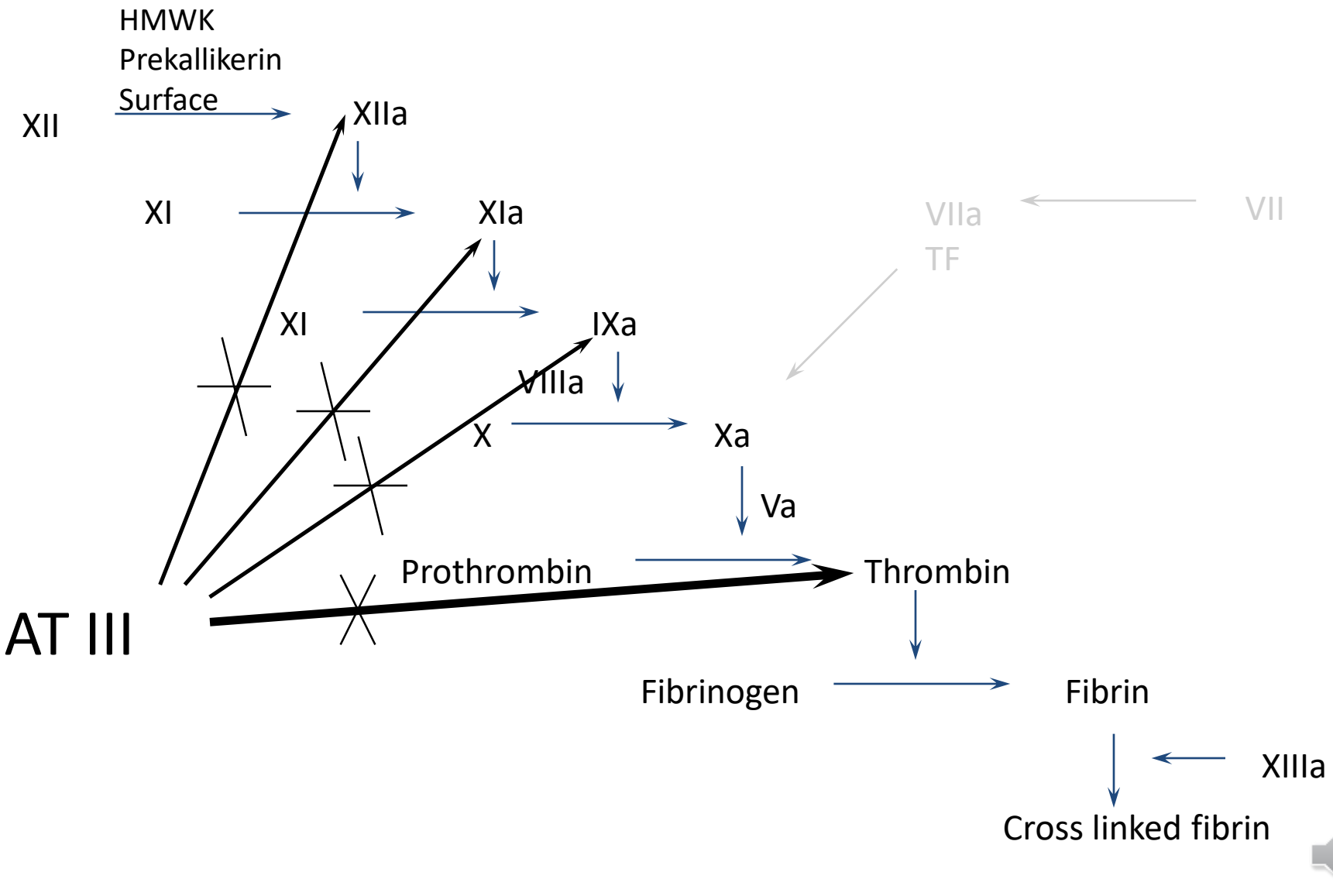
**3-Tissue factor pathway inhibitor (TFPI):**

- I**nactivates factor Xa and tissue factor–factor VIIa complexes**

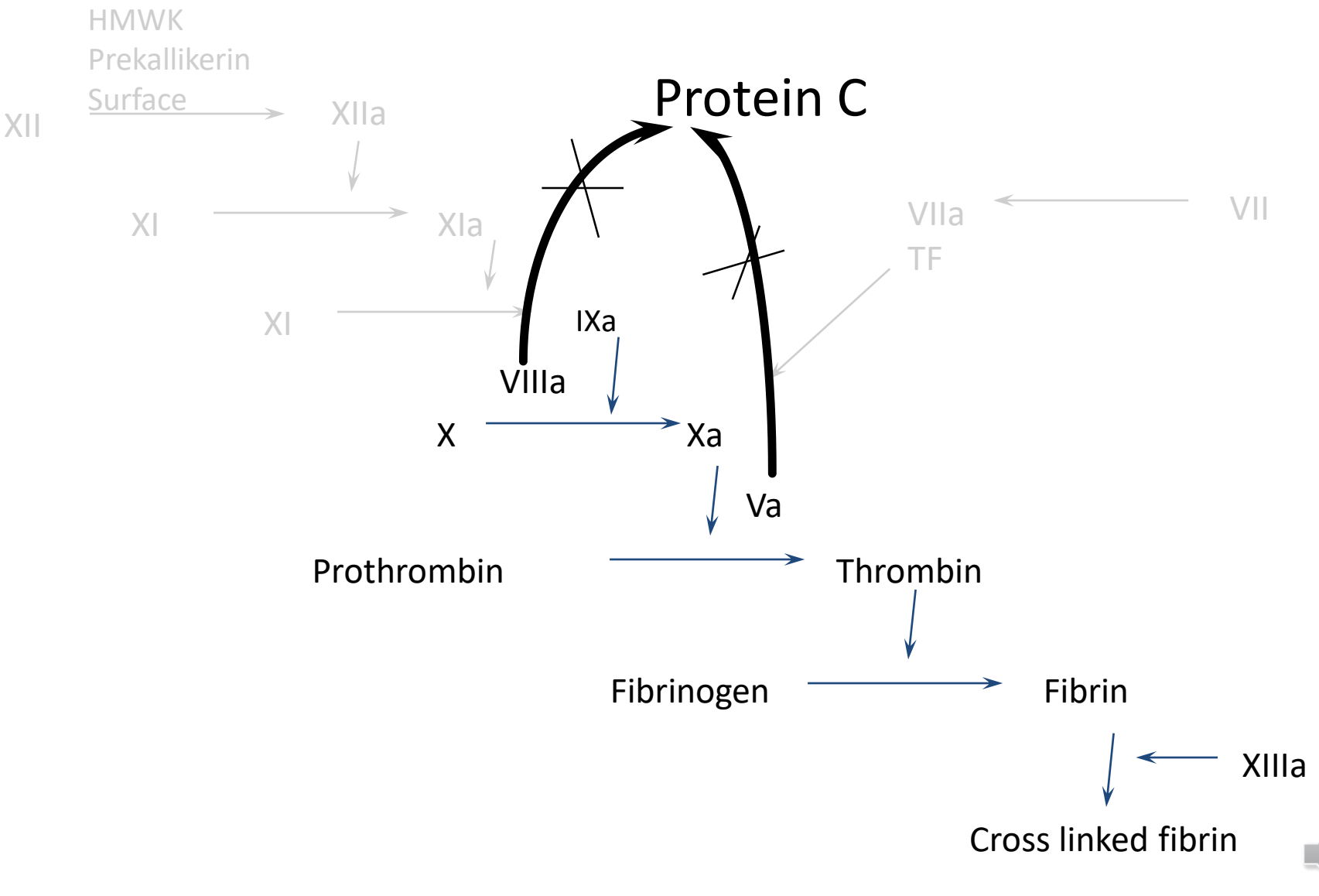
**4- Plasmin**


Contact activation
(intrinsic) pathway
Tissue factor
(extrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
X
Xa
Prothrombin (II)
Thrombin (IIa)
Common
pathway
Va
V
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked
fibrin clot
Active Protein C
Protein S
Protein C + Thrombomodulin

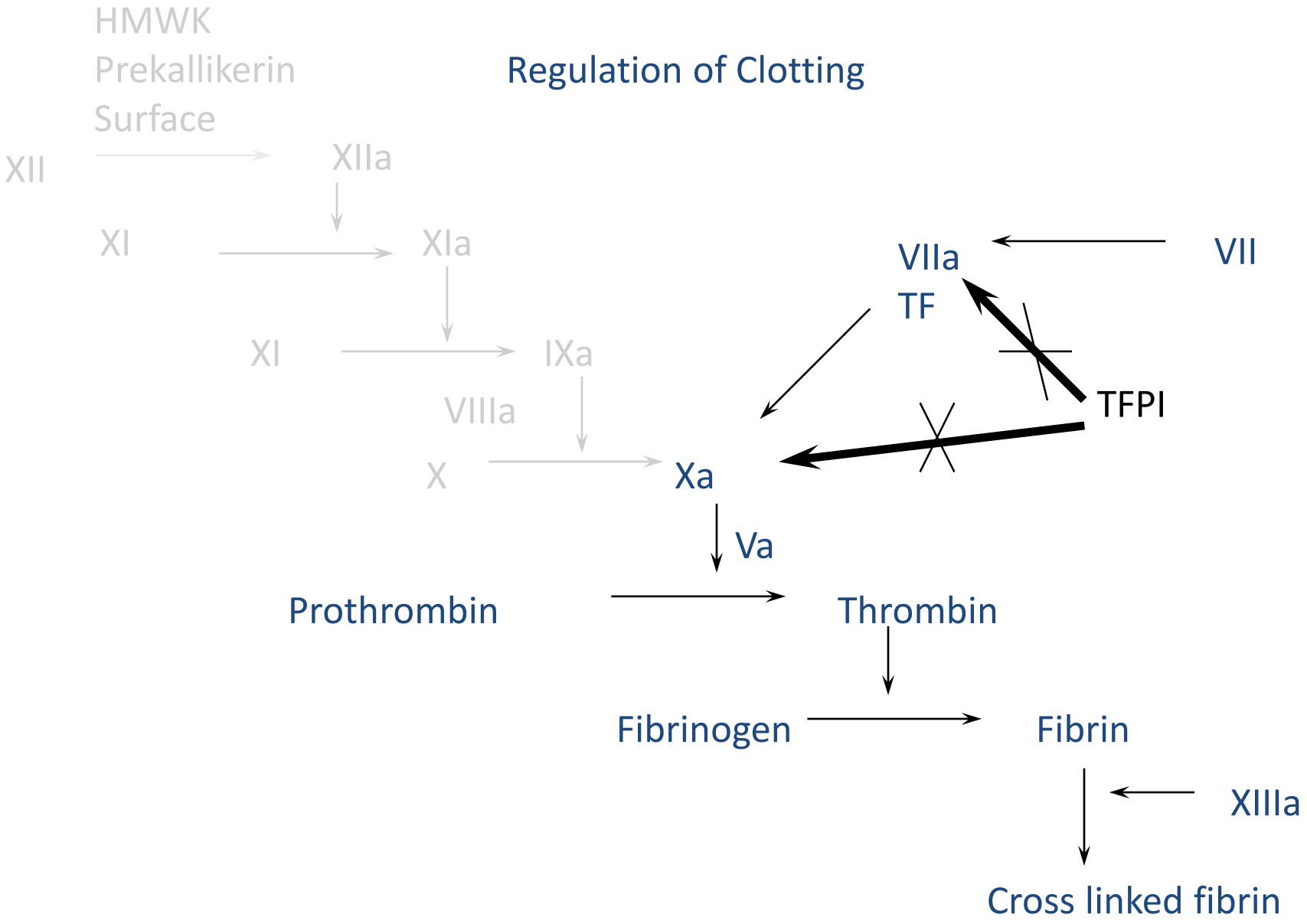
# Antithrombin III



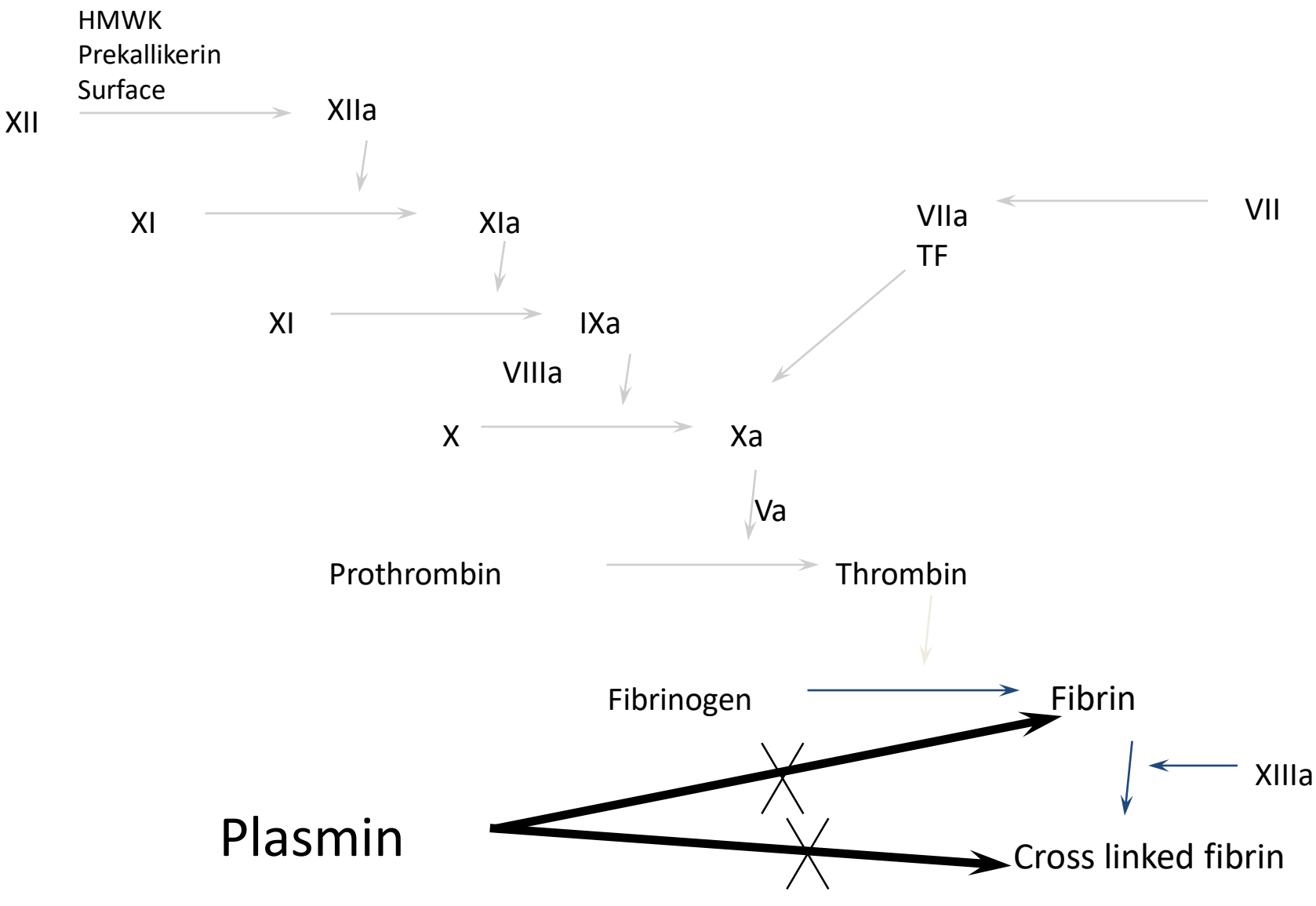
# Protein C


HMWK
Prekallikerin
Surface
XII
XIIa
XI
XIa
XI
IXa
VIIIa
X
Xa
Va
Protein C
VIIa
TF
VII
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
Cross linked fibrin

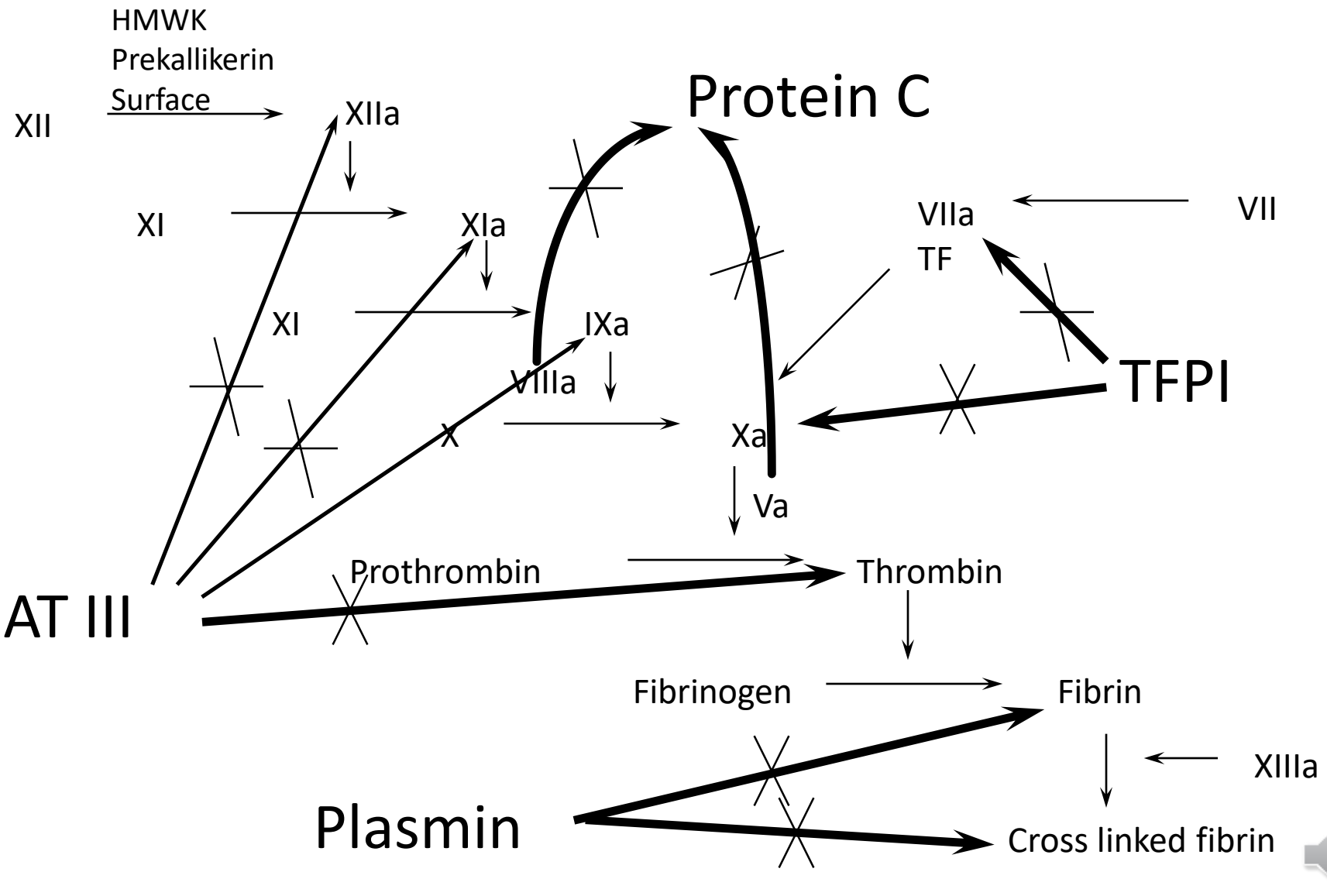
# Regulation of Clotting



# Plasmin


HMWK
Prekallikerin
Surface
XII
XIIa
XI
XIa
XI
IXa
VIIIa
VIIa
TF
VII
X
Xa
Va
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
Plasmin
Cross linked fibrin

# Regulation of Clotting



# Hemodynamics lecture 5
# Ischemia , thrombosis, arterial , venous

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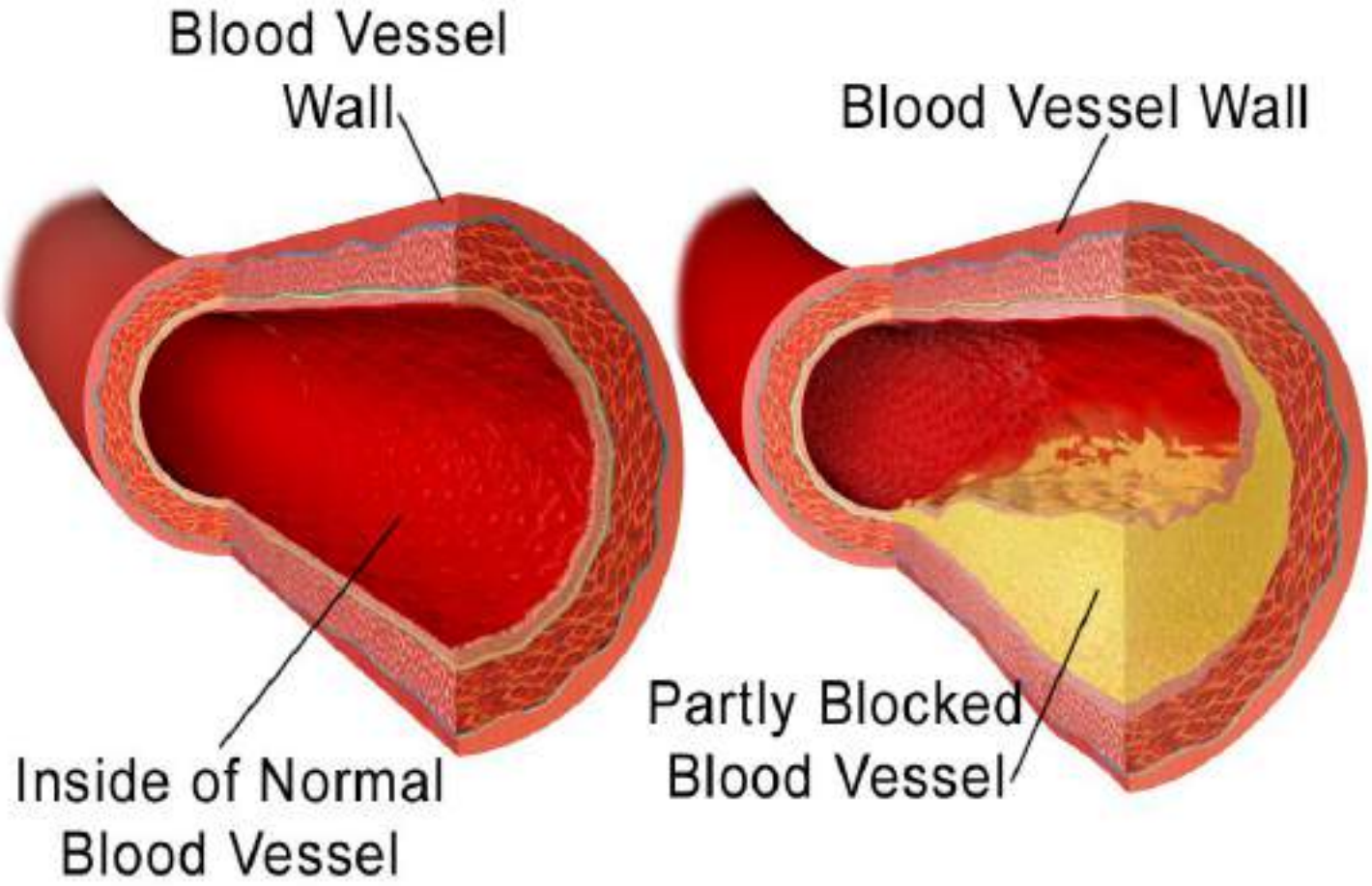
MBCHB,PhD ,FRCPath (UK)

2023-2024

Audio 4

# Causes of ischemia

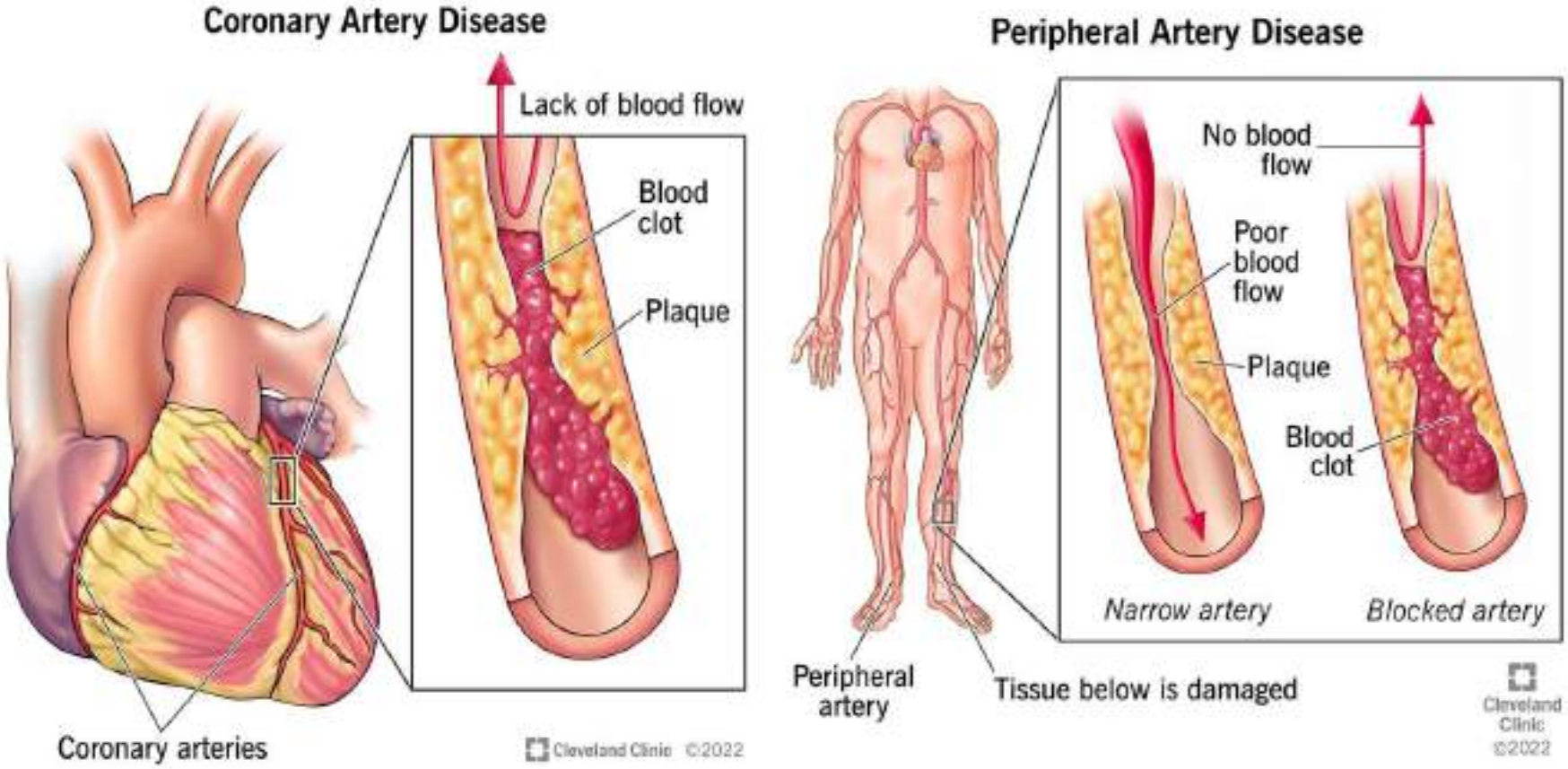
- Ischemia is decrease blood supply to the tissue and organ due to complete or partial obstruction of blood vessels might be caused by many factors
- Sudden Complete obstruction cause by ;
- 1- thrombosis
- 2- embolisim
- 3-ligation (surgical )
- Partial Gradual obstruction caused by
- 1- inflammation as in endarteritis obliterance ( syphilis)
- 2-degenerative disease (atherosclerosis )
- 3- Spasm (as in coronary arteries which lead to angina or myocardial infarction ) or raynauds phenomena as in peripheral vessels of the hands and feet in cold weather
- pressure by tumour from outside blood vessels




**Normal and Partly Blocked Blood Vessel**

# Effect of Obstruction of blood supply

- If obstruction Sudden , Complete obstruction it will lead to infarction (dead of tissue ) if there is NO EFFICENT COLLATERALS
- Or gangrene if associated with tissue putrefaction ( by bacterial action of saprophyte bact))
- IF there is Collaterals ( anastomosis )--- No effect (no tissue damage )
- If Obstruction Partial ,gradual without collaterals --- degenerative changes ,atrophy , fibrosis
- Partial with collateral No tissue damage


Coronary Artery Disease
Lack of blood flow
Blood clot
Plaque
Coronary arteries
Cleveland Clinic ©2022
Peripheral Artery Disease
No blood flow
Poor blood flow
Plaque
Blood clot
Narrow artery
Blocked artery
Peripheral artery
Tissue below is damaged
Cleveland Clinic ©2022

# Thrombosis

**Thrombosis is Formation of undissoved mass compsed of blood constituent formed during life inside the blood vessels.**

**كتله غير قابله للذوبان مكونه من مكونات الدم خلال الحياة تتكون داخل الوعاء الدموي**

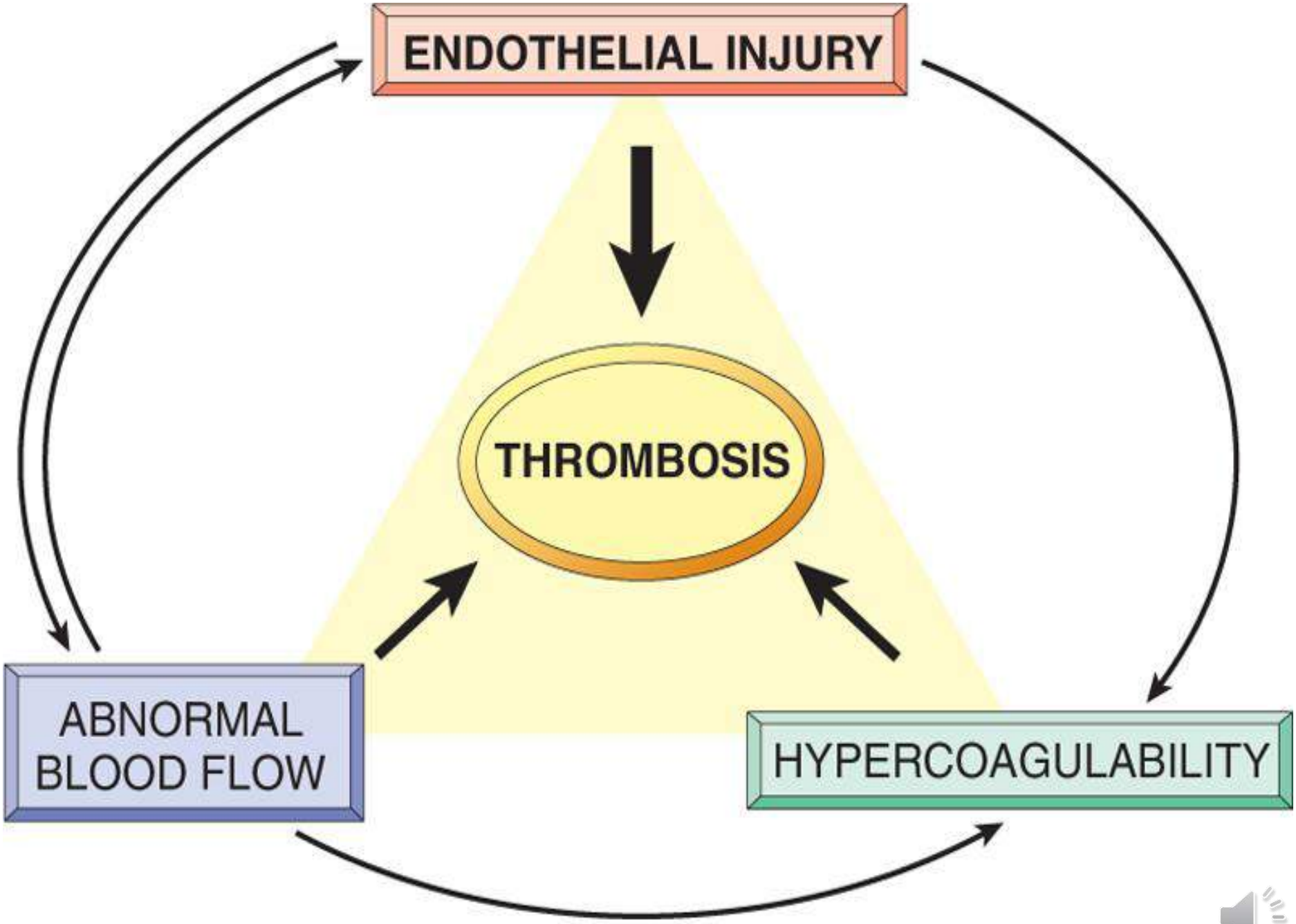
## Causes of thrombosis

***Virchow's triad*:**

(1) Endothelial injury

(2) Stasis *or* turbulence of blood flow

(3) Blood hypercoagulability

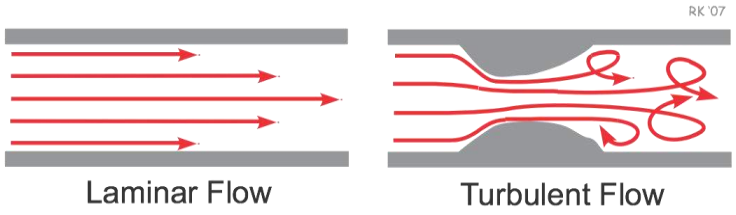


# 1- Endothelial injury

- The commonest cause of thrombus formation, **mainly in the heart and arterial circulation**.
- Loss of endothelium exposes subendothelial ECM, releases tissue factor, and reduces local production of PGI2 and plasminogen activators.
- **Any dynamic imbalance** of the prothrombotic and antithrombotic effects of endothelium can influence clotting locally.

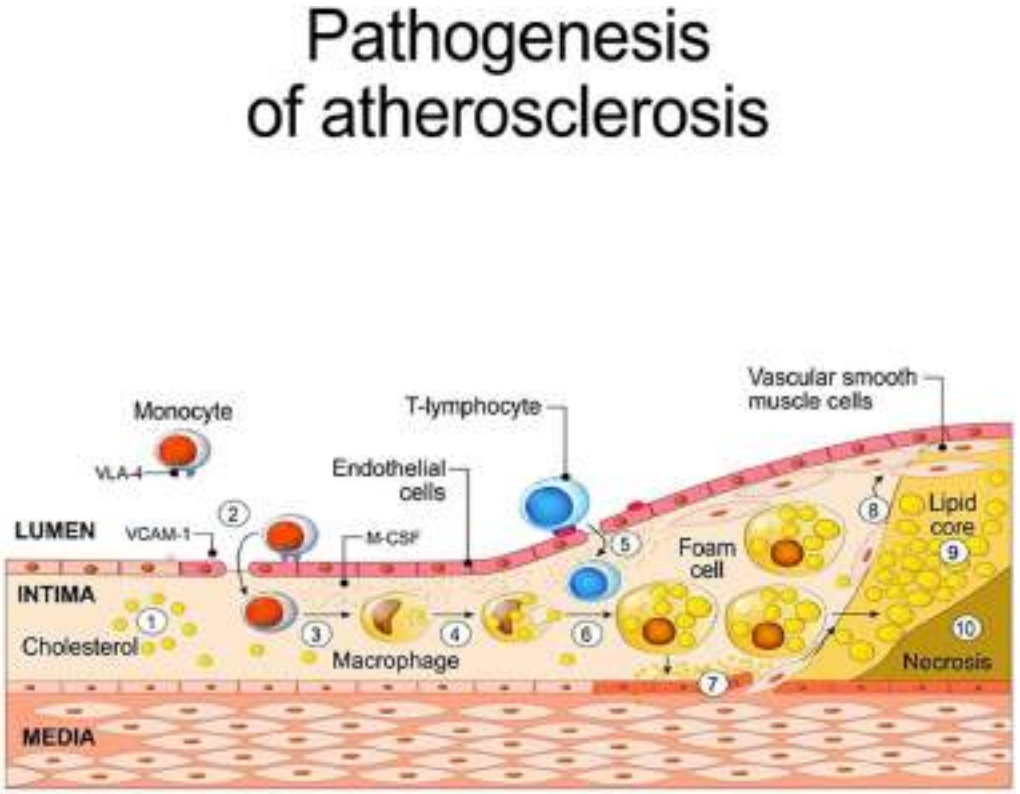
Chronic endothelial dysfunction can be induced by a variety of insults:

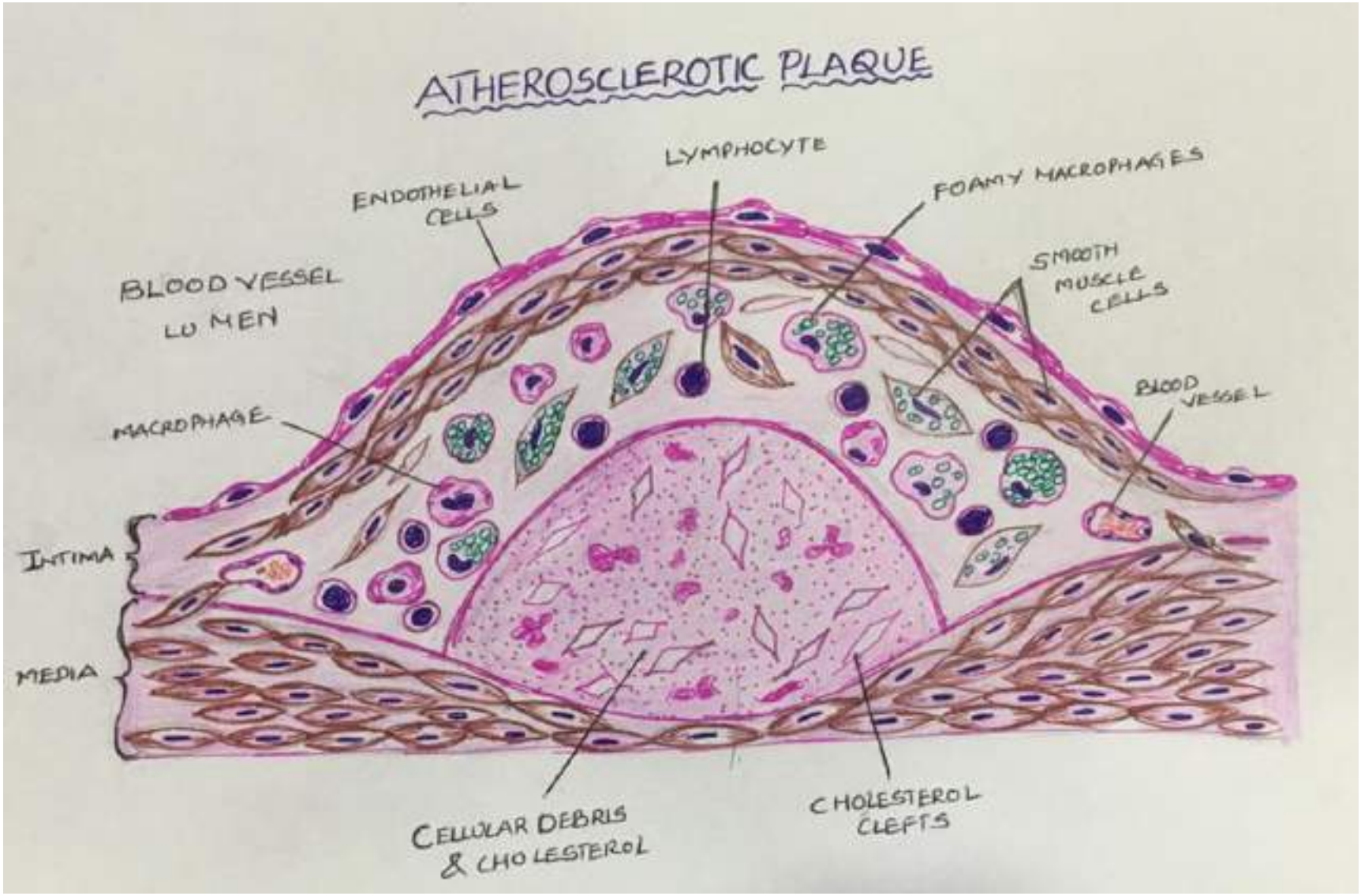
- ✓ Hypertension
- ✓ Turbulent blood flow
- ✓ Bacterial products
- ✓ Radiation injury
- ✓ Metabolic abnormalities such as hypercholesterolemia
- ✓ Toxins absorbed from cigarette smoke



# Atherosclerosis is a result of chronic endothelial injury

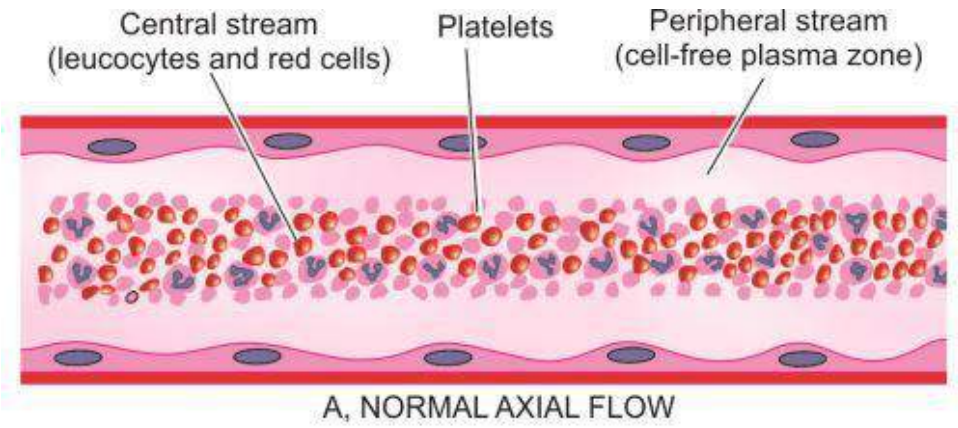
- Atherosclerosis is a chronic inflammatory disease of the inner wall of large- and medium-sized arteries.
- Its basic pathogenic mechanisms are inflammation and oxidative stress involving interactions with multiple genetic, epigenetic and environmental factors.




ATHEROSCLEROTIC PLAQUE
LYMPHOCYTE
ENDOTHELIAL CELLS
FOAMY MACROPHAGES
BLOOD VESSEL LUMEN
SMOOTH MUSCLE CELLS
BLOOD VESSEL
MACROPHAGE
INTIMA
MEDIA
CELLULAR DEBRIS & CHOLESTEROL
CHOLESTEROL CLEFTS

# 2- Alterations in Normal Blood Flow

- Normal laminar blood flow: platelets (and other blood cells) are found mainly in the center of the vessel lumen, separated from the endothelium by a slower-moving layer of plasma
- **Turbulence** contributes to **arterial and cardiac thrombosis** by causing endothelial injury or dysfunction.
- **Stasis** is a major contributor to the development of **venous thrombi.**



**Turbulence** contributes to **arterial and cardiac thrombosis** by causing endothelial injury or dysfunction.

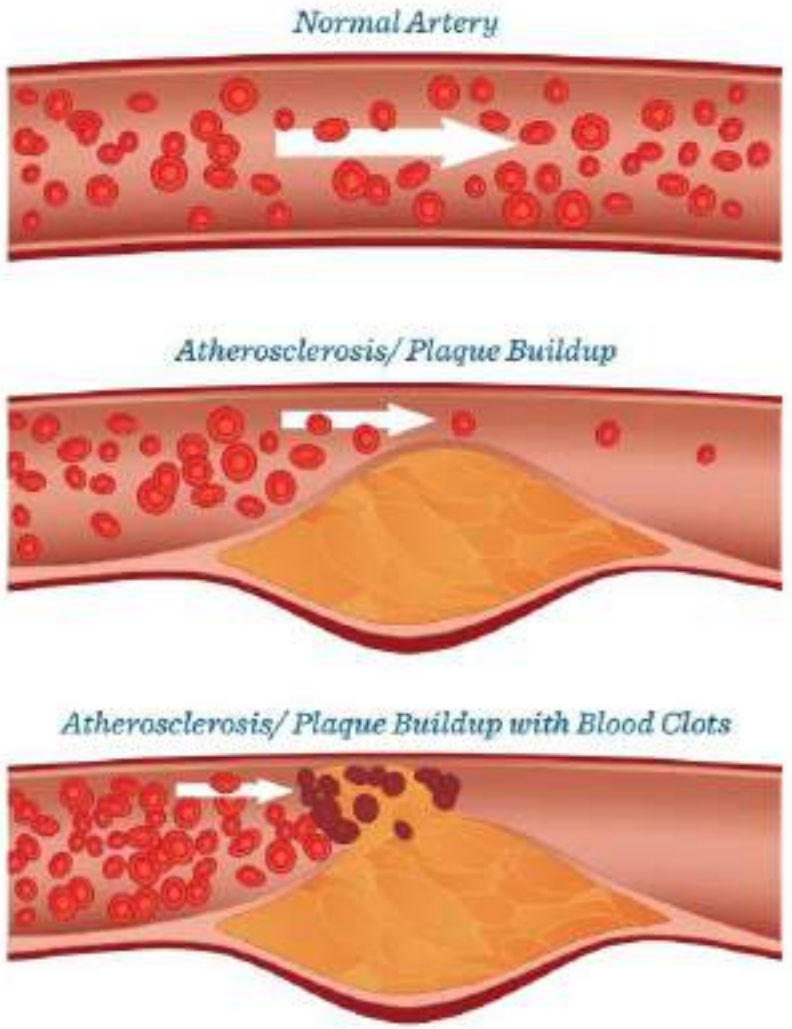
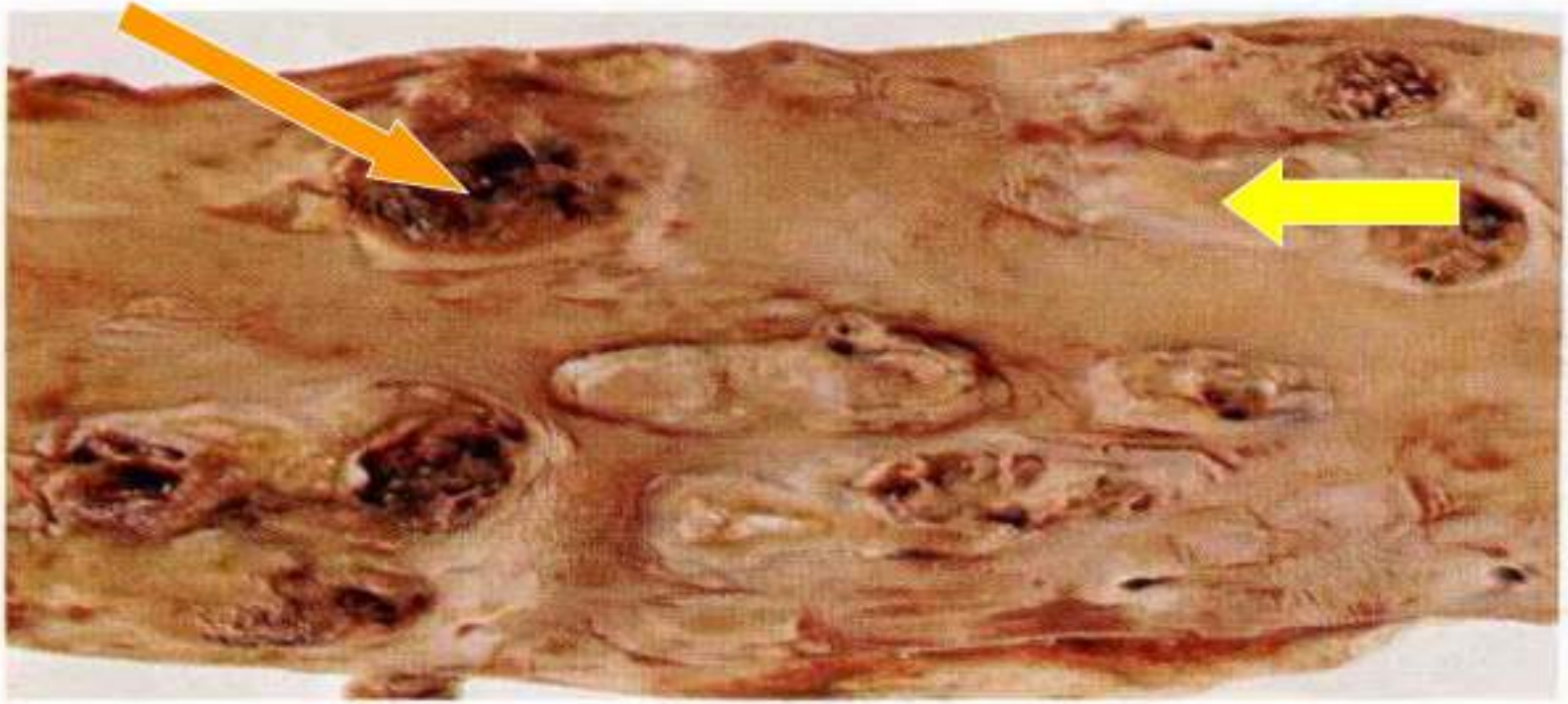


Figure 36 : Complicated atheromatous plaques, most show central ulceration, the **yellow fatty debris** is seen in the plaque at the top right. The brown color of the ulcerated plaques on the left is due to **mural thrombosis**, an important source of **thromboemboli.**



6.59 Atherosclerosis: aorta

Stasis and turbulent (chaotic) blood flow have the following effects:

- ✓ Both promote endothelial cell activation and enhanced procoagulant activity.
- ✓ Stasis allows platelets and leukocytes to come into contact with the endothelium when the flow is sluggish.
- ✓ Stasis slows the washout of activated clotting factors and impedes the inflow of clotting factor inhibitors.

# Can be seen in several clinical settings:

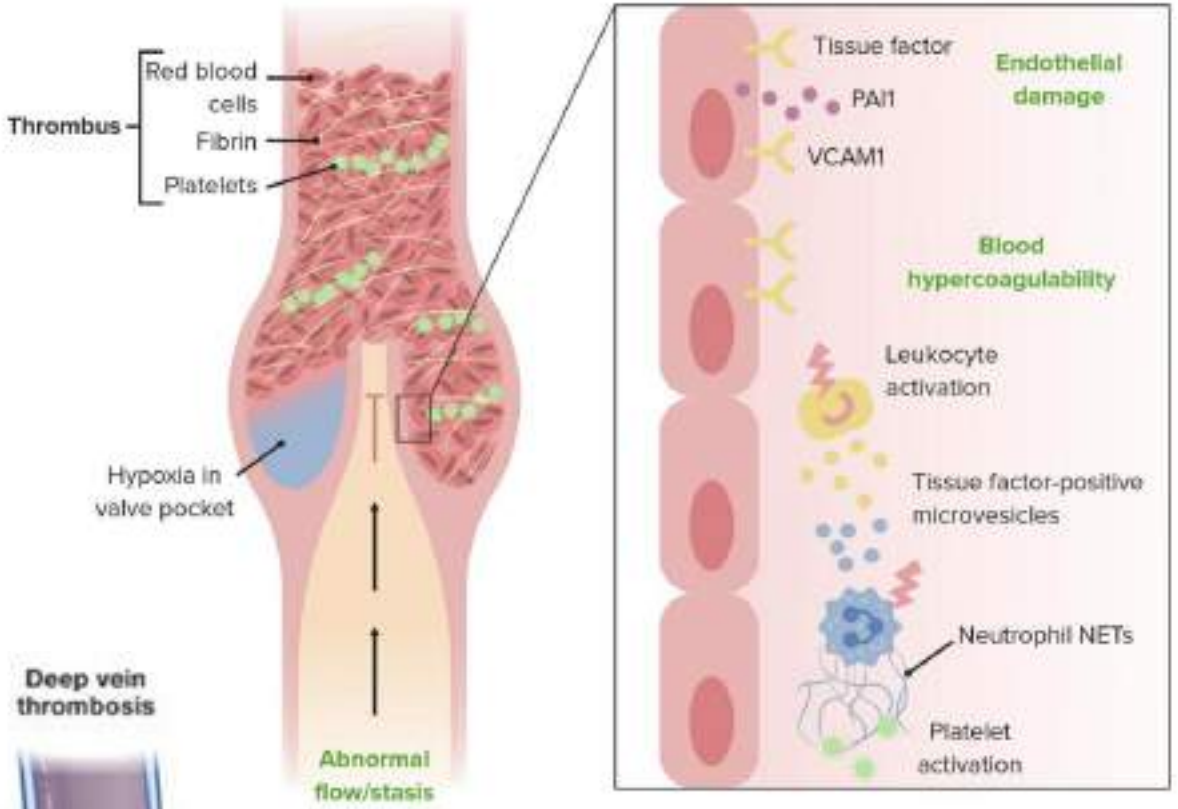
1- Ulcerated atherosclerotic plaques (**turbulent**)

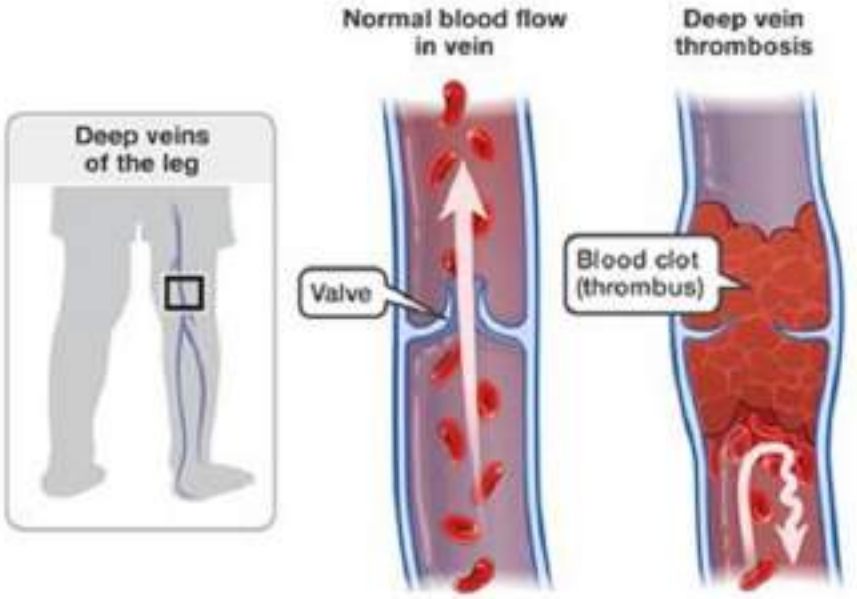
2- Abnormal aortic and arterial dilations, called aneurysms (**stasis**)

3- Hyperviscosity syndromes (such as polycythemia;) increase resistance to flow and cause small vessel **stasis**.

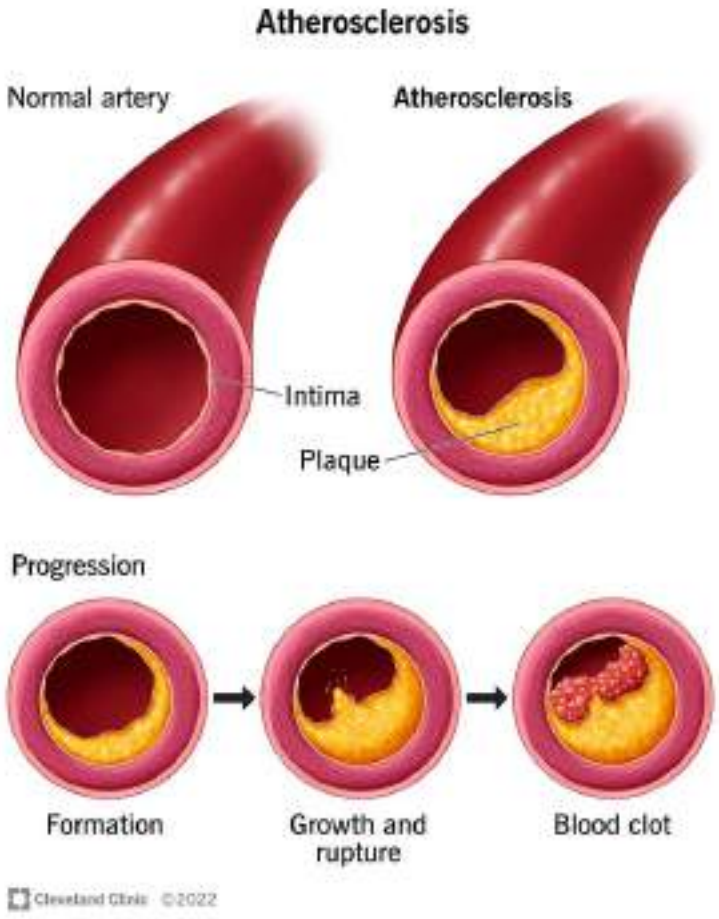
4- Deformed red cells in sickle cell anemia cause vascular occlusions, with the resultant **stasis**

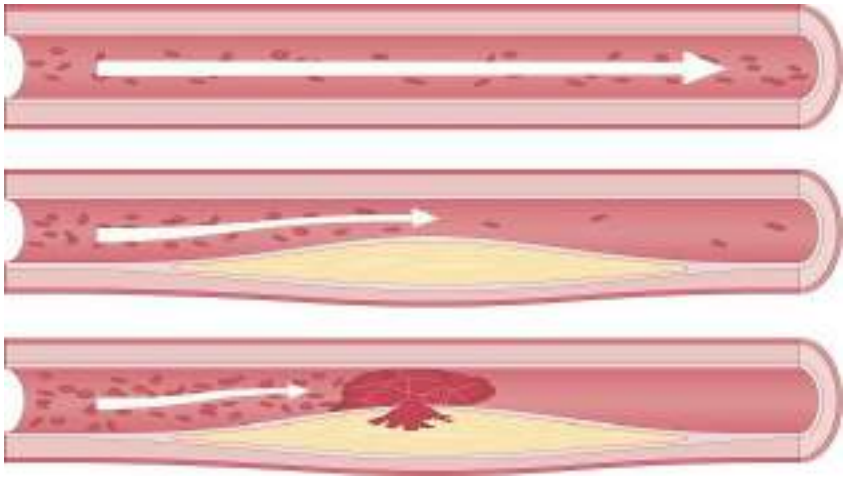
**Stasis** is a major contributor to the development of **venous thrombi**



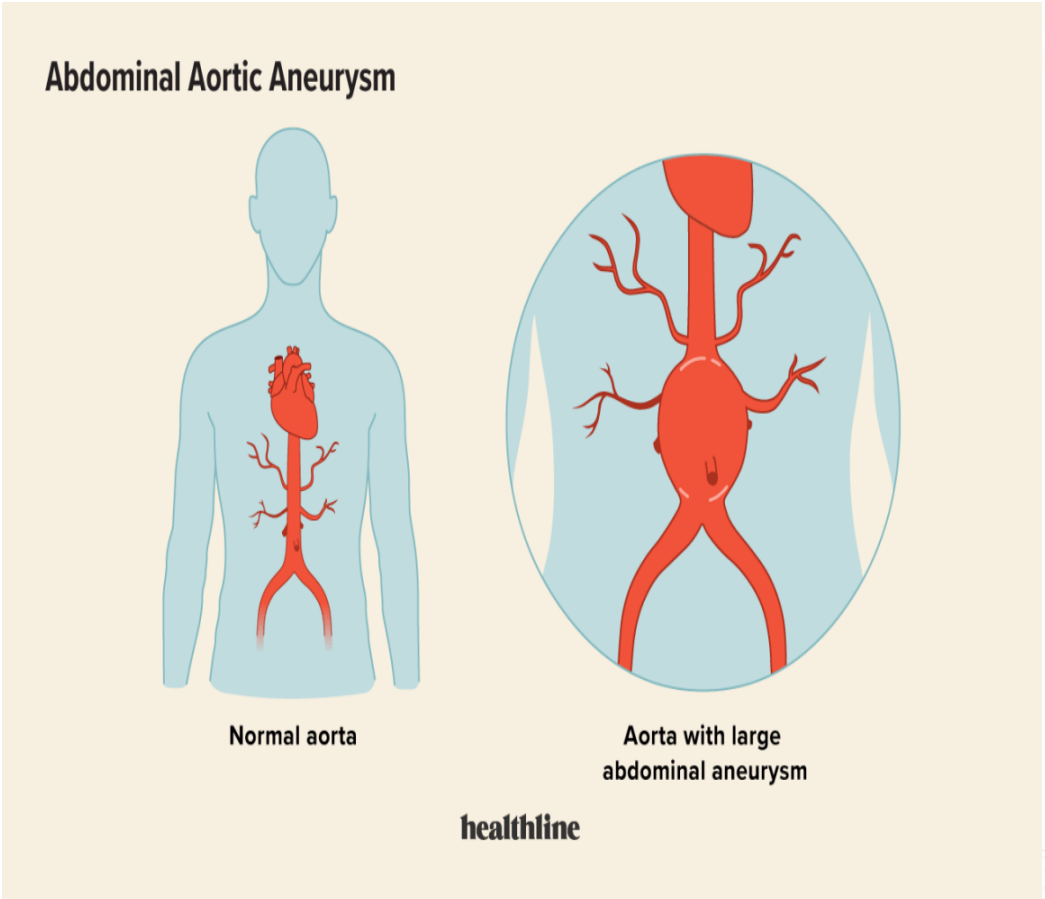



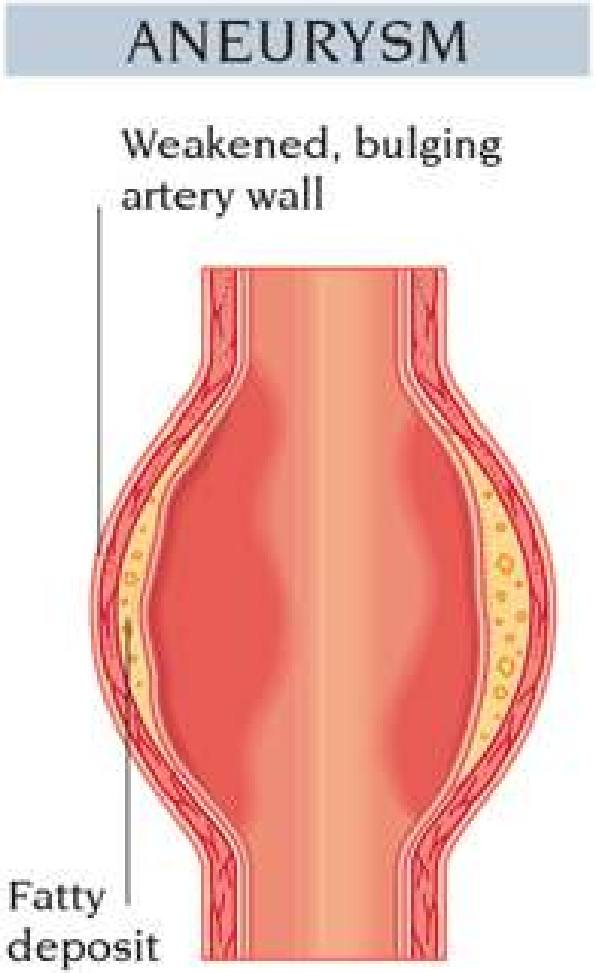
# 1- Ulcerated atherosclerotic plaques (turbulent)



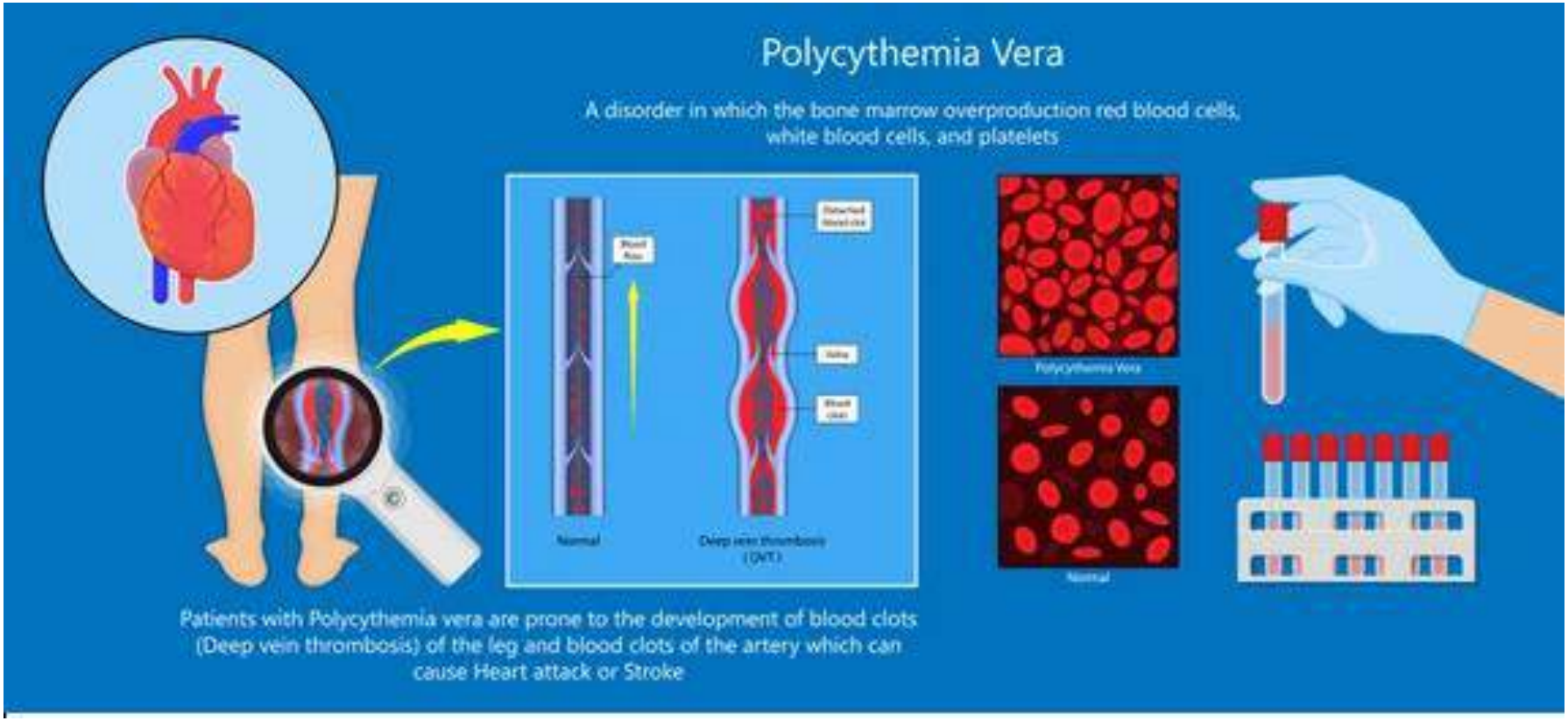



# 2- Abnormal aortic and arterial dilations, called aneurysms (stasis)

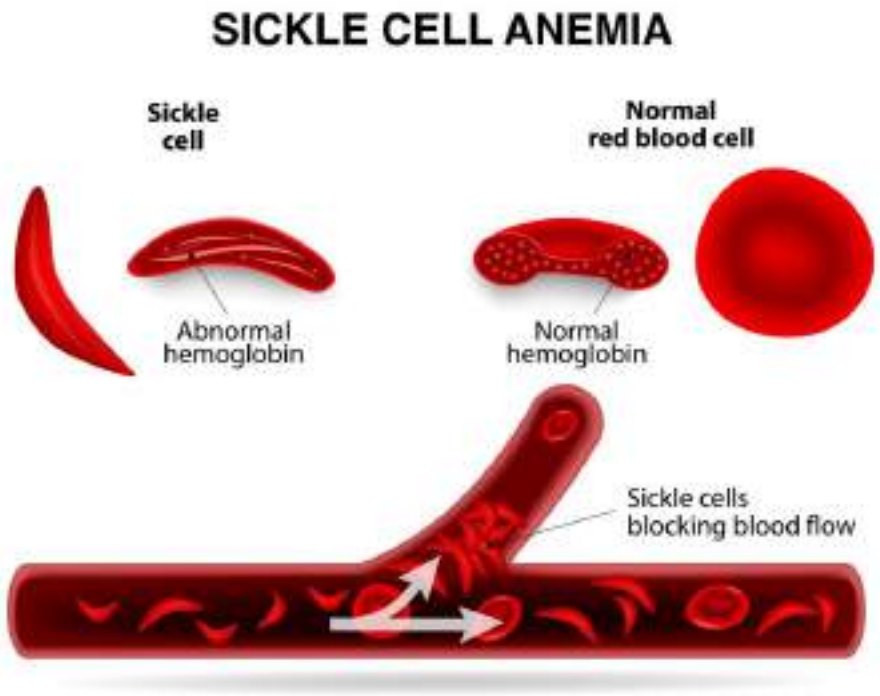


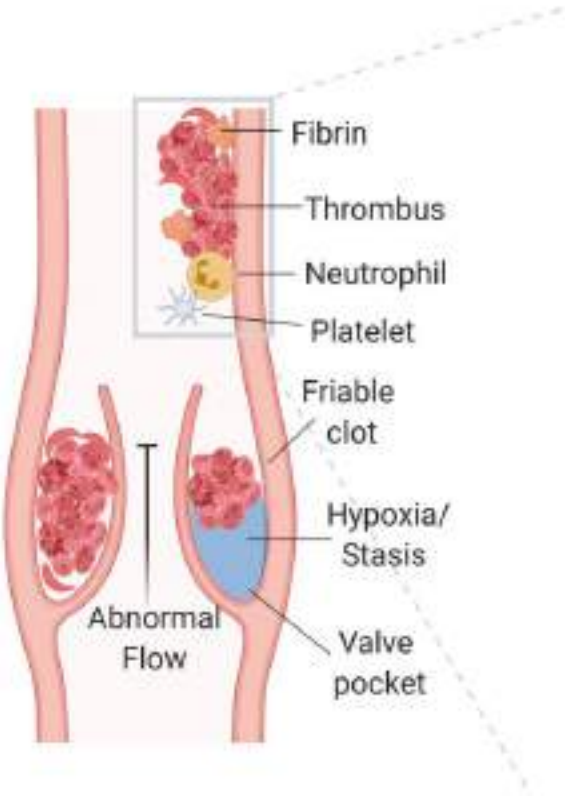



# 3-Hyperviscosity syndromes (such as **polycythemia**) increase resistance to flow and cause small vessel **stasis**



# 4- Deformed red cells in **sickle cell anemia** cause vascular occlusions, with the resultant **stasis**



# 3- Hypercoagulability

- An important underlying risk factor for **venous thrombosis**
- Primary (genetic) and secondary (acquired) disorders .

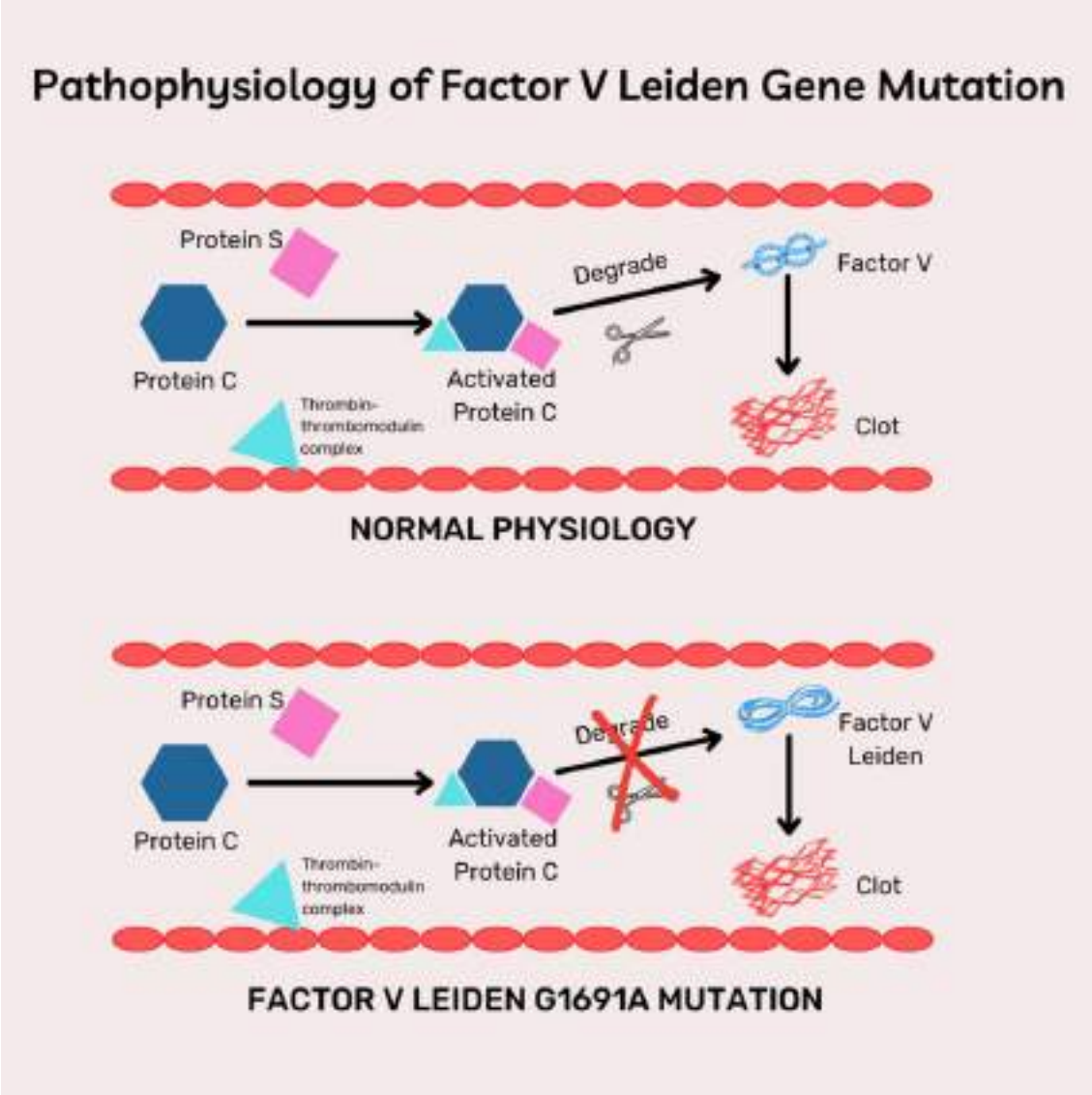
## A- Inherited causes of hypercoagulability:

- Mutations in the **factor V gene** and the **prothrombin gene** are the most common.

- Approximately 2% to 15% of whites carry a specific factor V mutation (called the Leiden mutation). The mutation alters an amino acid residue in factor V and renders it resistant to protein C.

- Deficiencies of anticoagulants such as **protein C or protein S (rare) and antithrombin III**

# Factor v Leiden mutation

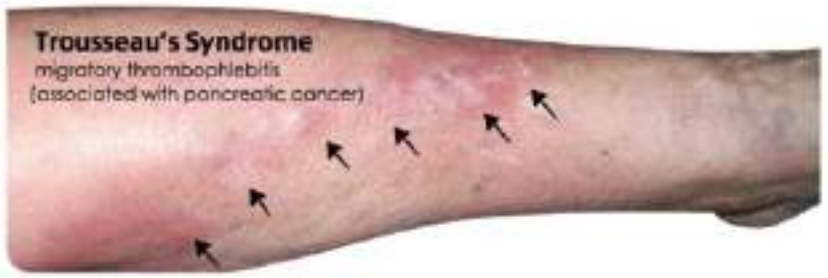


## B. Acquired hypercoagulability

1. Oral contraceptive use and hyperestrogenic state of pregnancy may be related to increased hepatic synthesis of coagulation factors and reduced synthesis of antithrombin III .
2. Prolonged bed rest or immobilization
3. Disseminated cancers, release of mucin in adenocarcinoma predisposes to thrombus formation (migratory thrombophlebitis or Trousseau's syndrome).
4. Advancing age: due to increased platelet aggregation and reduced release of PGI2 from endothelium

# Migratory thrombophlebitis or Trousseau's syndrome


Trousseau syndrome is an acquired blood clotting disorder that results in migratory thrombophlebitis (inflammation of a vein due to a blood clot) in association with an often-undiagnosed malignancy. Most associated with **pancreatic cancer.**



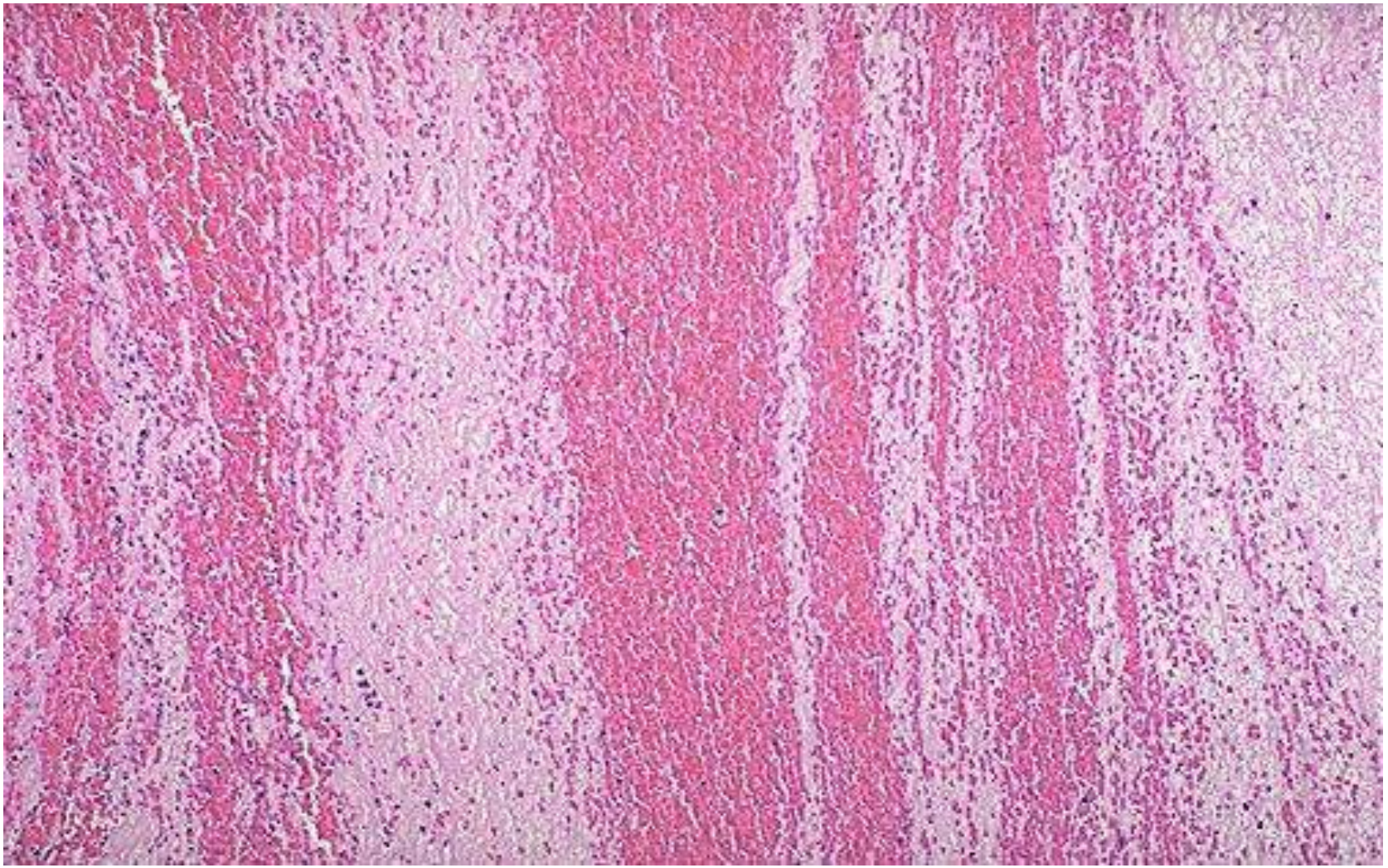
# Thrombi

- Thrombi can have grossly (and microscopically) apparent laminations called **lines of Zahn:**
- **Lines of Zahn are characteristic of thrombus formed at the site of rapid arterial blood flow, with laminations produced by successive deposition of platelets and fibrin (pale layers) alternating with red blood cells (dark layers).**

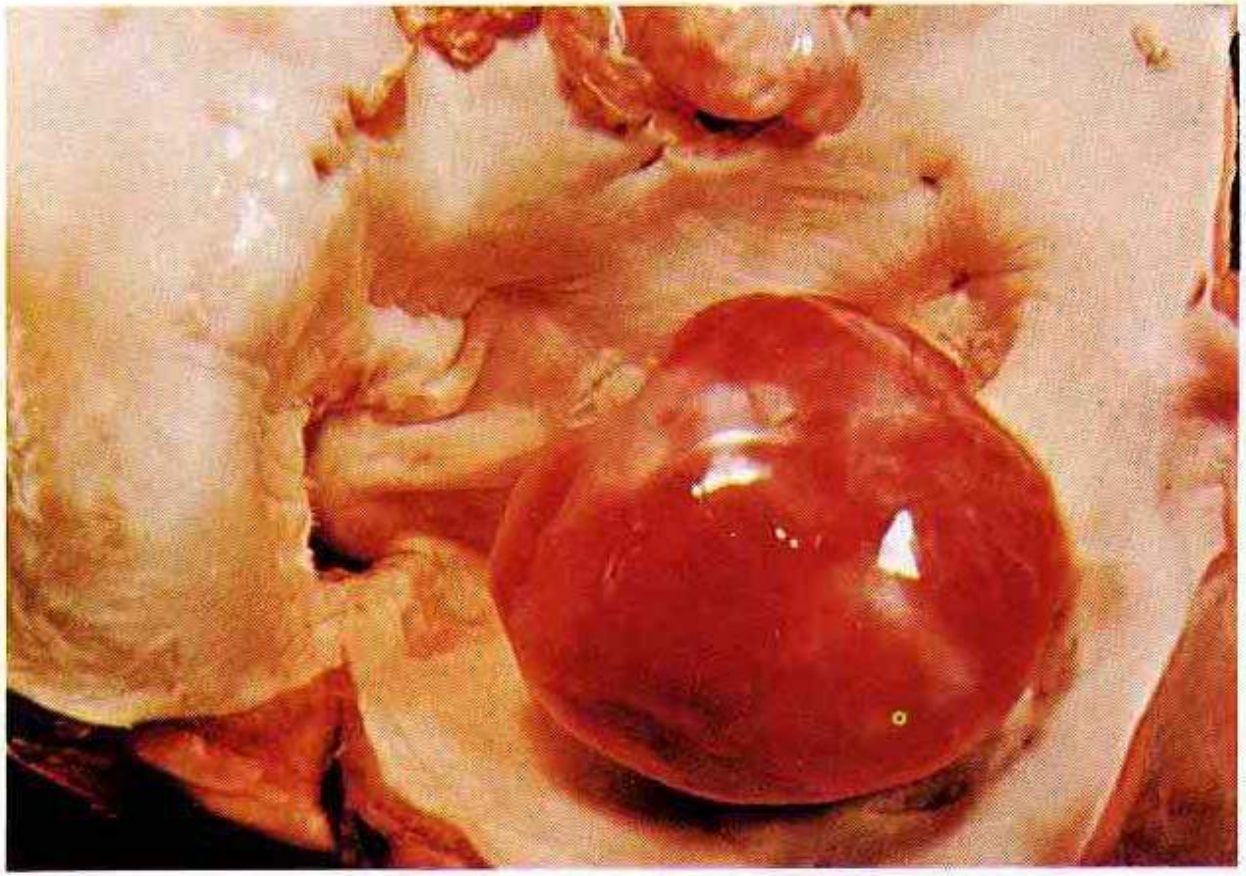
**- Only found in thrombi that form in flowing blood**

- Can distinguish antemortem thrombosis from the **bland nonlaminated** clots that form in the **postmortem state**.
- Thrombi occurring in heart chambers or in the aortic lumen are designated as **mural thrombi.**

These are "lines of Zahn" which are the alternating pale pink bands of platelets with fibrin and red bands of RBC's forming a true thrombus.



**Ball thrombus (mural thrombus):** left atrium. The dilated, thick-walled left atrium is viewed from above, showing stenosed mitral valve . A globular red thrombus ball thrombus) lies free within the atrial lumen, & obstructing the mitral valve orifice intermittently.

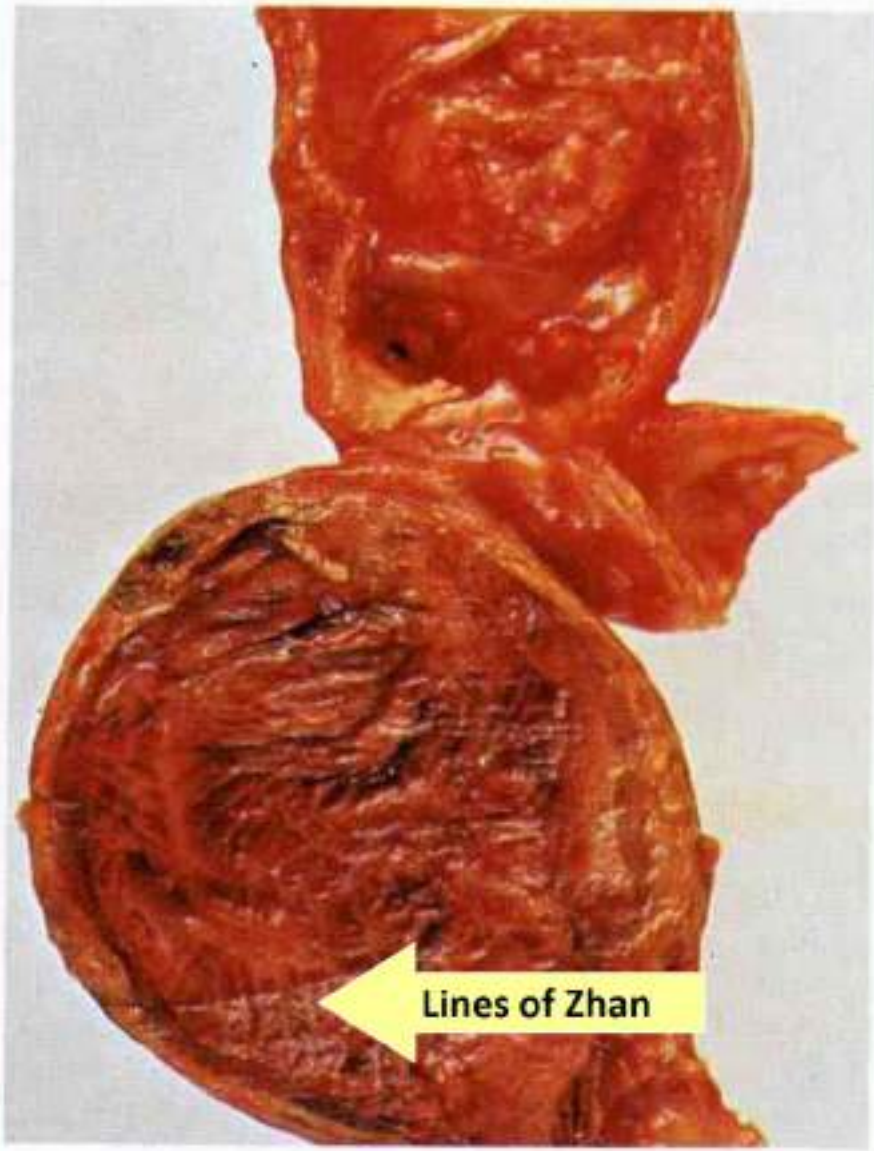


6.45 Ball thrombus: left atrium

# Arterial vs. venous thrombi

- **Arterial thrombi: relatively rich in platelets,** as the processes underlying their development (e.g., endothelial injury) lead to platelet activation.
- **Venous thrombi (phlebothrombosis):** tend to contain more enmeshed red cells because these thrombi form in the sluggish venous circulation, leading to the **red** color.

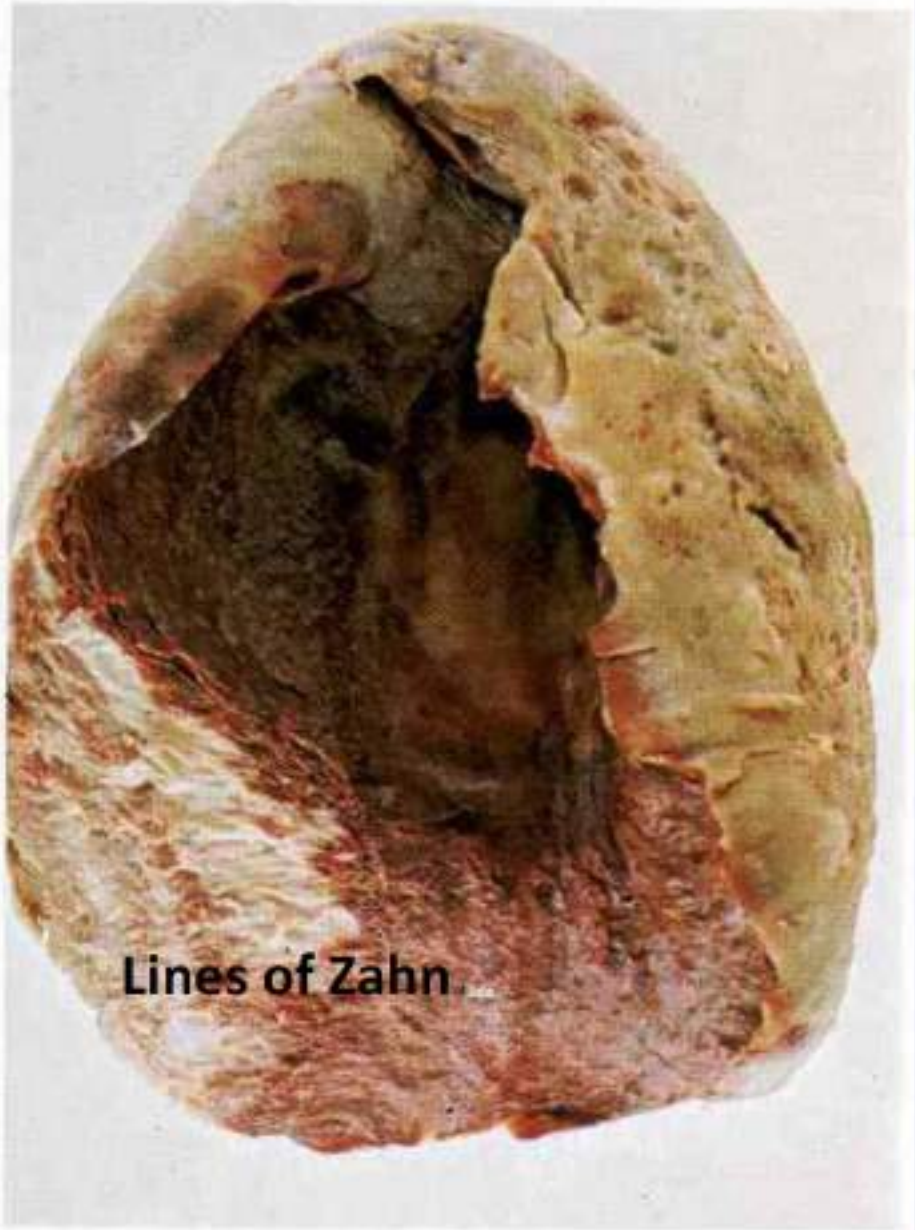
| | Arterial thrombi | Venous thrombi |
|---|---|---|
| Etiology | Endothelial damage or turbulence | Stasis and hyperco-agulable states |
| Lines of Zahn | Prominent | Less prominent |
| Color | Gray | Red |
| Occlusive | Yes | Yes |
| Location | Heart; coronary, cerebral, aorta | Lower limb veins |




6.65 Aneurysm: iliac arteries

**Fig. 37 : Saccular aneurysm** of the iliac artery.

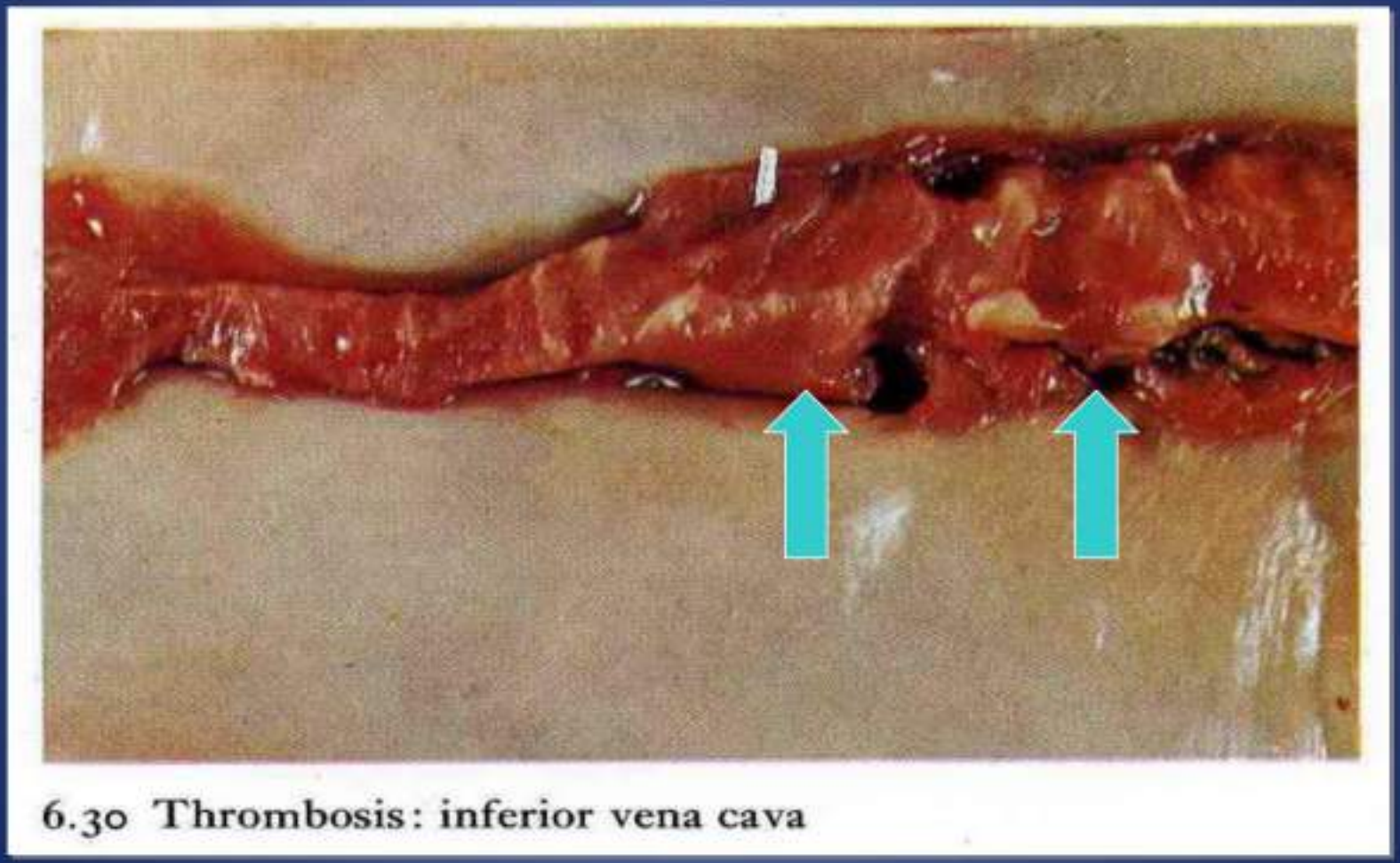
The lumen is filled with arterial thrombus, which is reddish-brown & shows greyish-white **lines of Zhan.**




6.66 Thrombus from aneurysm

**Fig. 38 : Large thrombus,** (measuring **20X12X12** cm) removed from an atheromatous abdominal aortic aneurysm (AAAA). The laminated structure **(lines of Zahn**) of the thrombus is clearly evident (lower left).

**F 39 : Venous Thrombosis.** The **inferior vena cava contains** a long pale tapering thrombus .Thrombus is mural & firmly attached to the vein wall.



6.30 Thrombosis: inferior vena cava

# Fate of the Thrombus

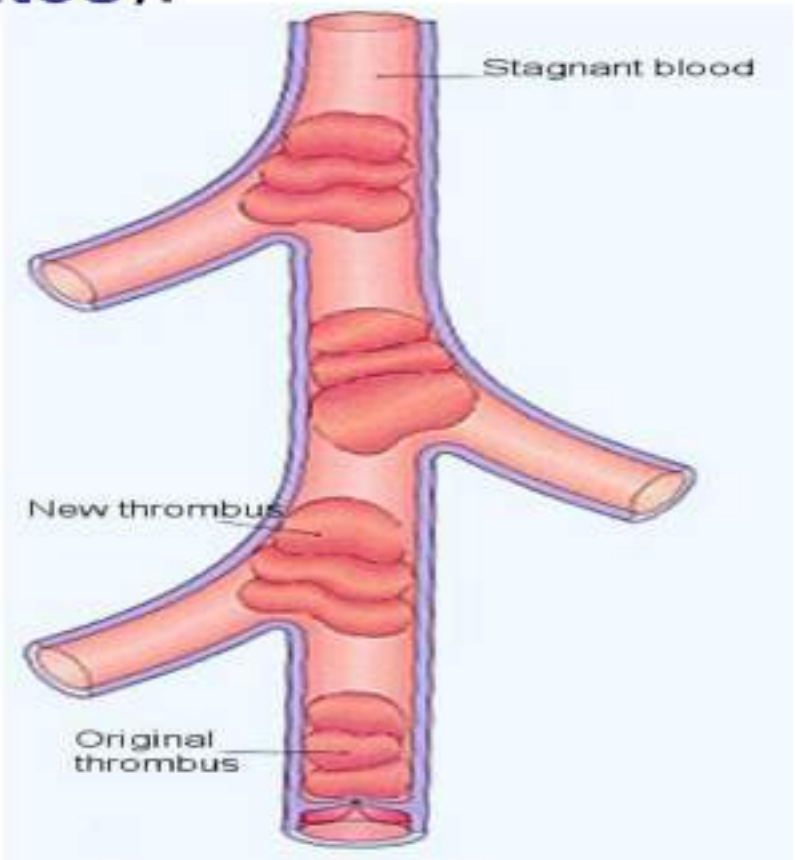
1. **Propagation:** Thrombus enlargement by accumulation of additional platelets and fibrin.

Propagation of a thrombus occurs towards the direction of the heart and involves the accumulation of additional platelets and fibrin. This means that it is anterograde in veins or retrograde in arteries.

2. **Embolization:** Fragment of thrombus is transported elsewhere in the vasculature.
3. **Dissolution**: In newly formed thrombus, activation of fibrinolysis may lead to its rapid shrinkage and complete dissolution.

# Outcomes of thrombosis ( Fates):

- **Propagation**
  - progressive spread of thrombosis
  - distally in arteries
  - proximally in veins



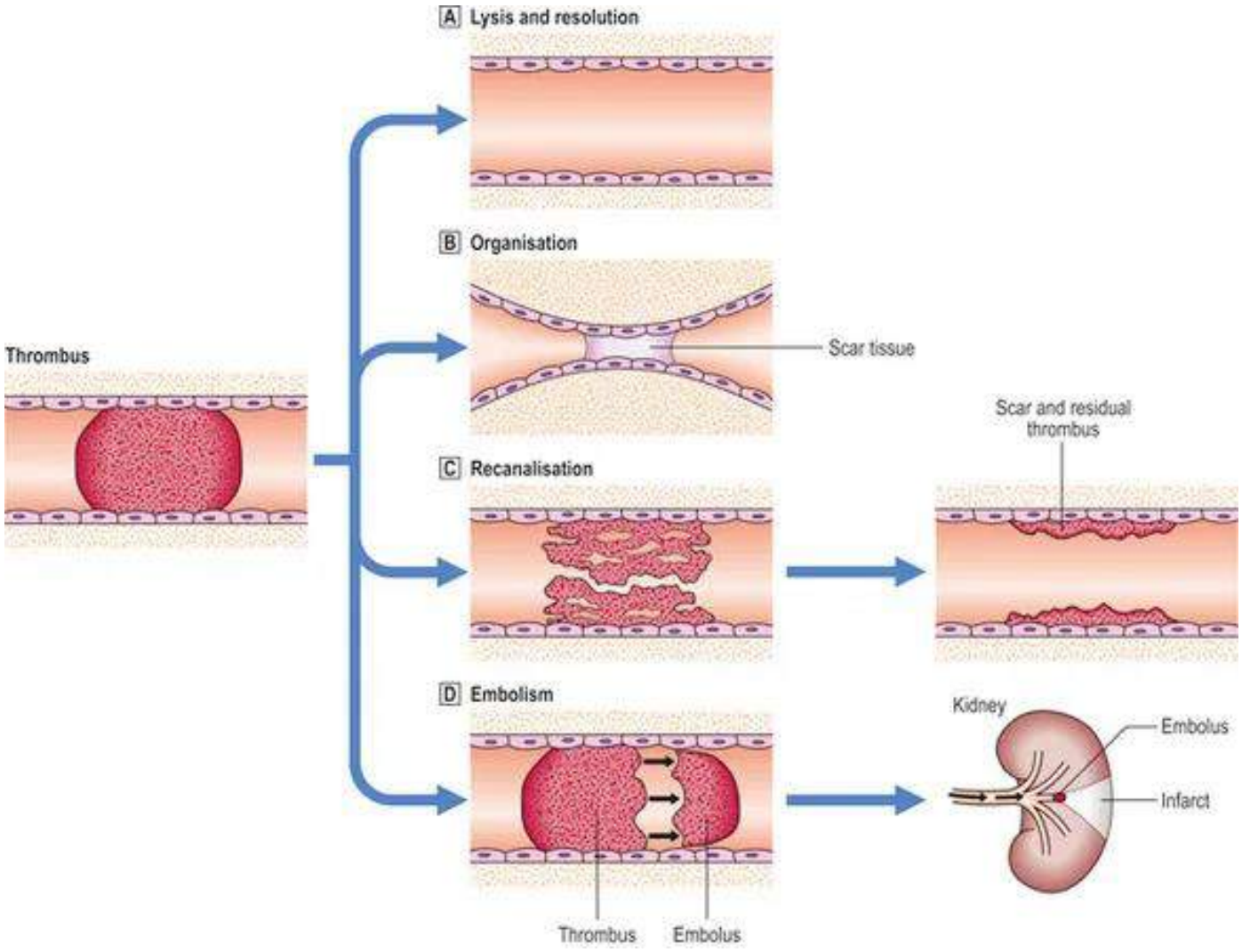
# Fate of the Thrombus

**4. Organisation and recanalization**:

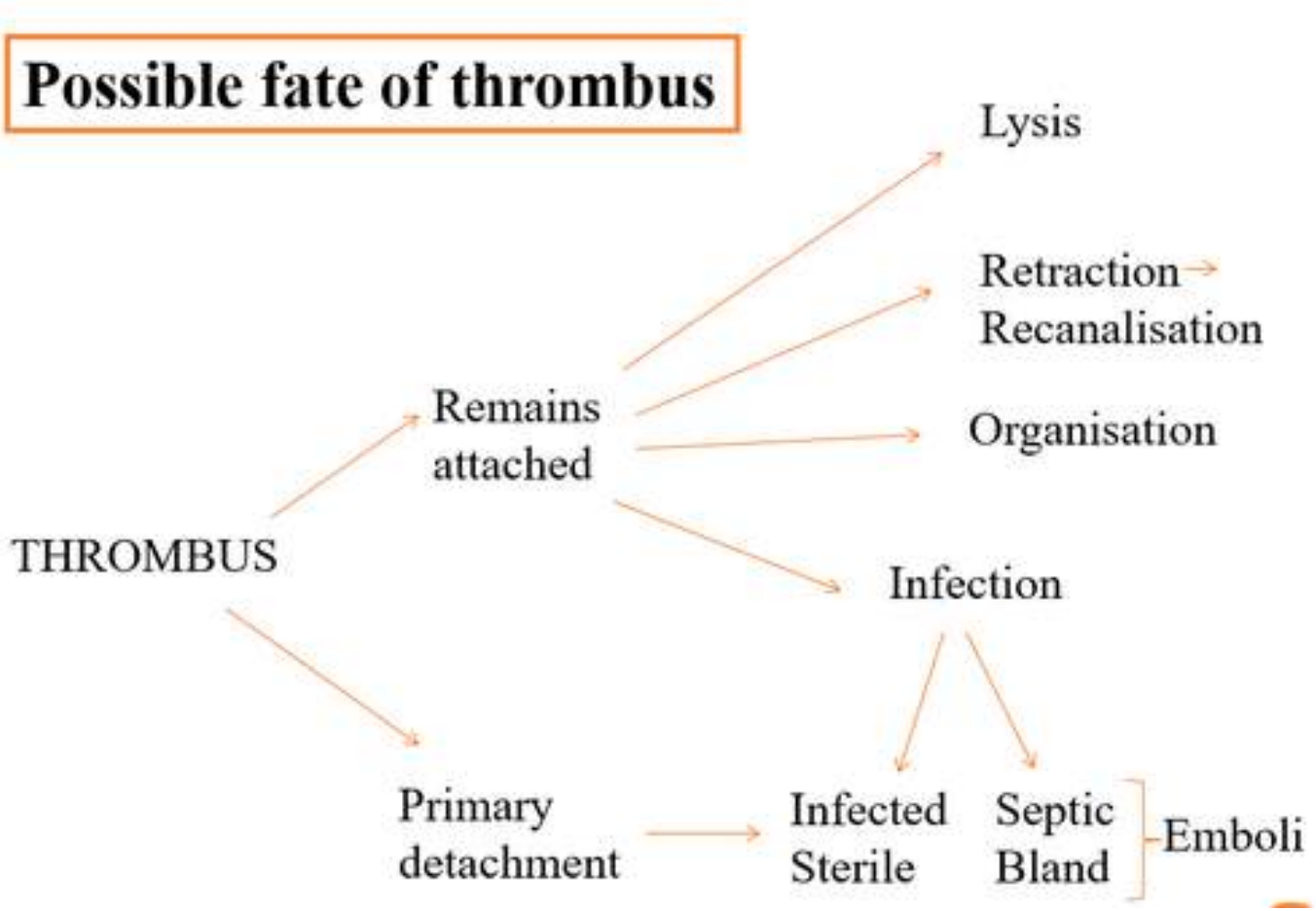
- Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin-rich thrombus
- In time, capillary channels are formed and create conduits along the length of the thrombus, thereby reestablishing the continuity of the original lumen.

**5. Bacterial seeding of thrombus:** serve as a culture medium, and the resulting infection may weaken the vessel wall, leading to formation of a **mycotic aneurysm**.

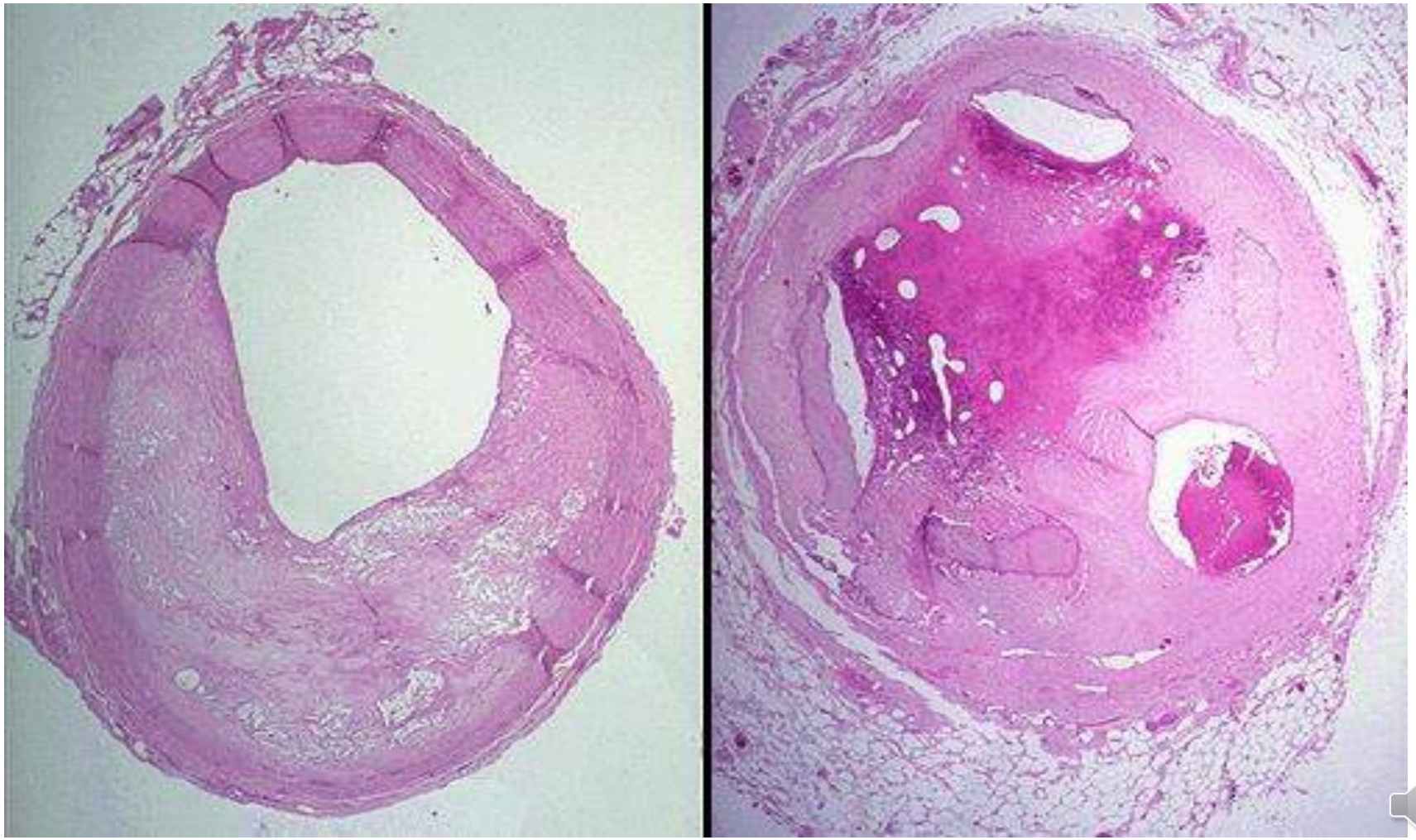
# Fate of the Thrombus



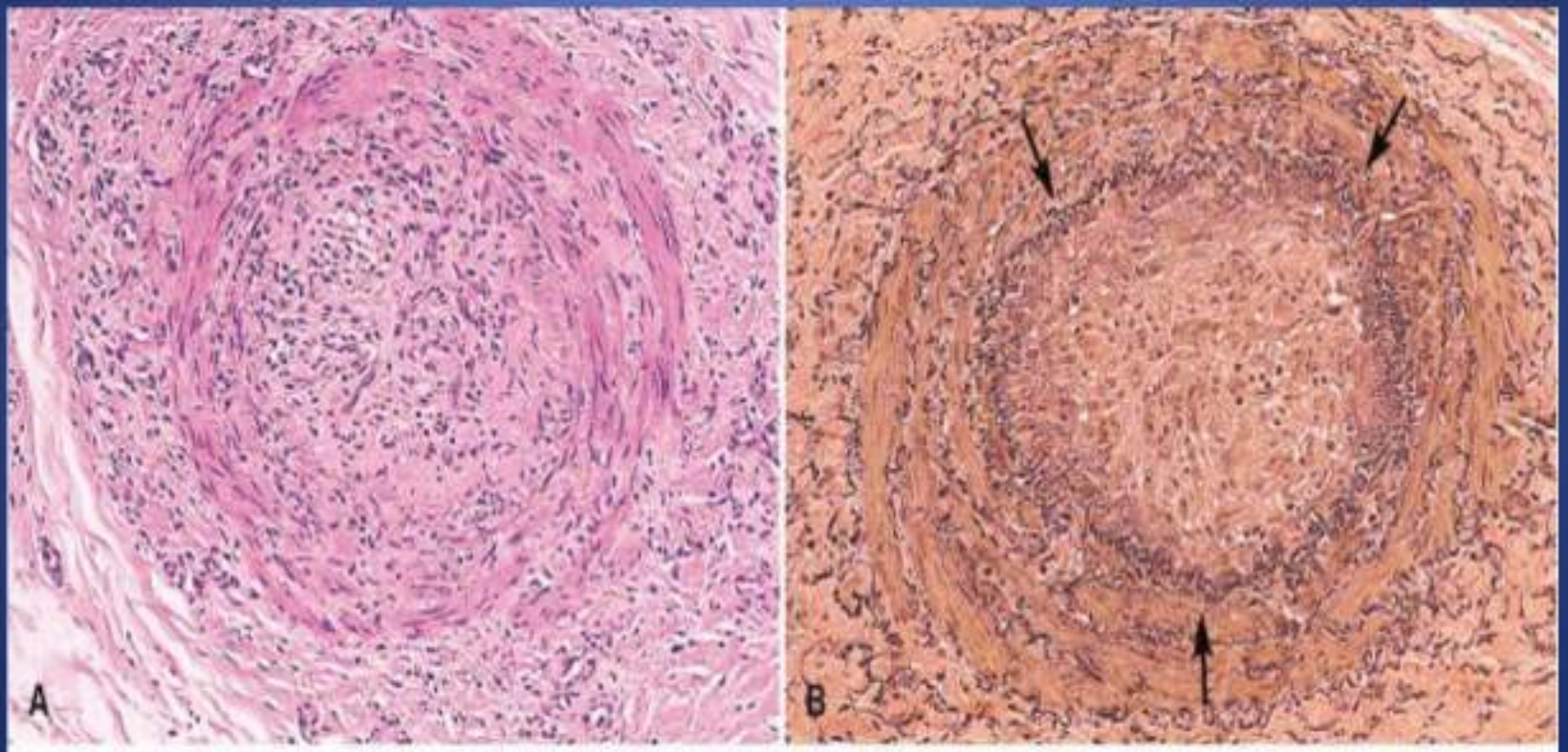
# Fate of the Thrombus



Here is occlusive coronary atherosclerosis. The coronary at the left is narrowed by 60 to 70%. The coronary at the right is even worse with evidence for previous thrombosis with organization of the thrombus and recanalization such that there are three small lumens remaining.



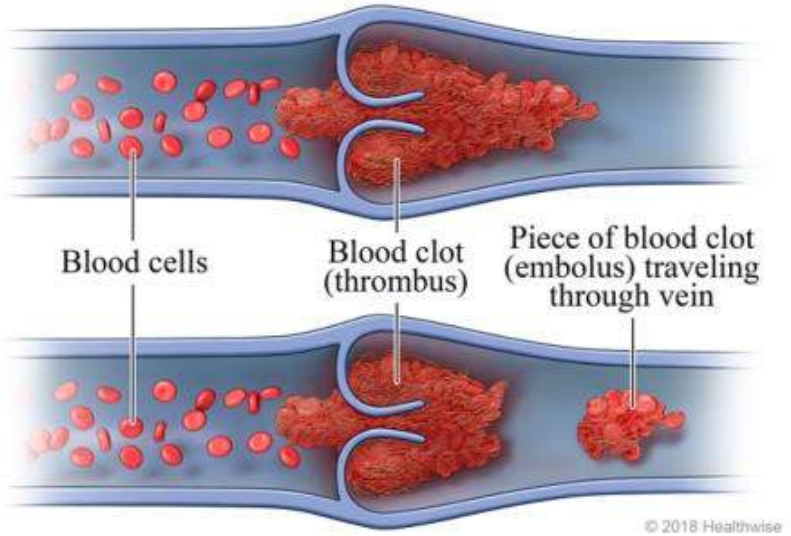
F 41 : **Artery with an old thrombus. A,** H&E stained section. **B,** Stain for **elastic tissue (black)**. The original lumen is delineated by the **internal elastic lamina** (**3 arrows**) & is totally filled with organized thrombus .



# Complications of Thrombi

- Occlusion (Obstruction) of blood vessels
  - Veins: Congestion and edema distal to obstruction
  - Arteries: Ischemia and infarcts in areas supplies by the vessel.

- Embolization



# Venous Thrombosis (Phlebothrombosis)

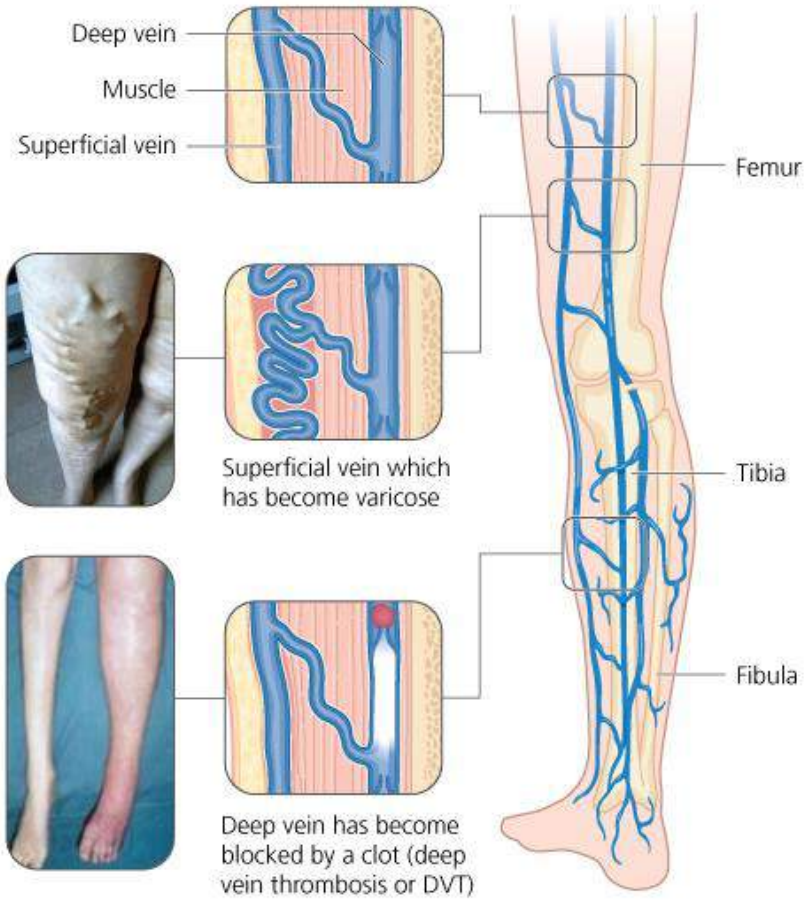
Mostly in **superficial** or **deep veins** of the legs

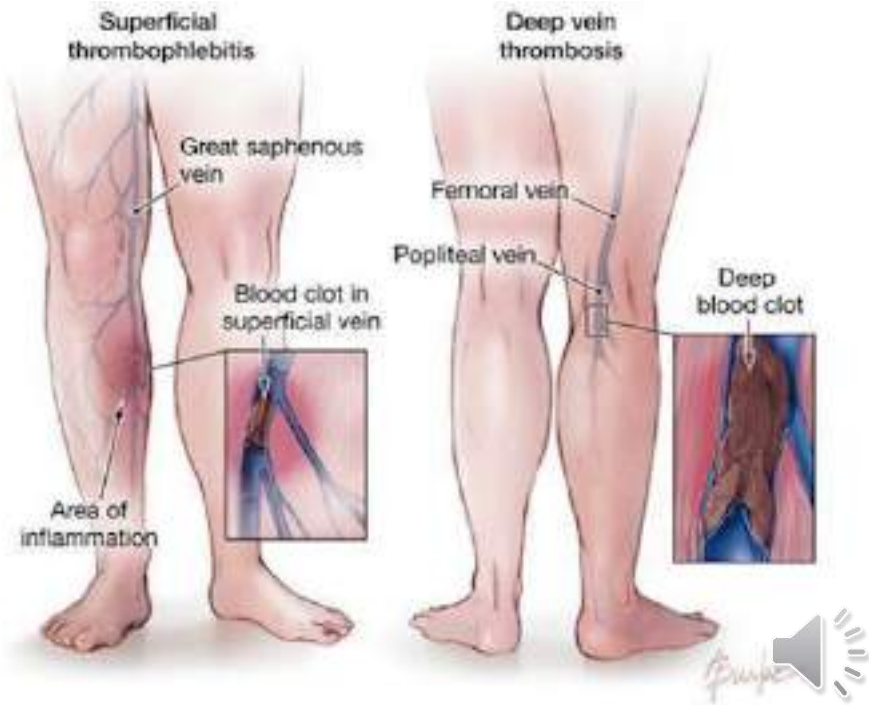
- Superficial vein thrombosis occur in the saphenous system (varicosities).

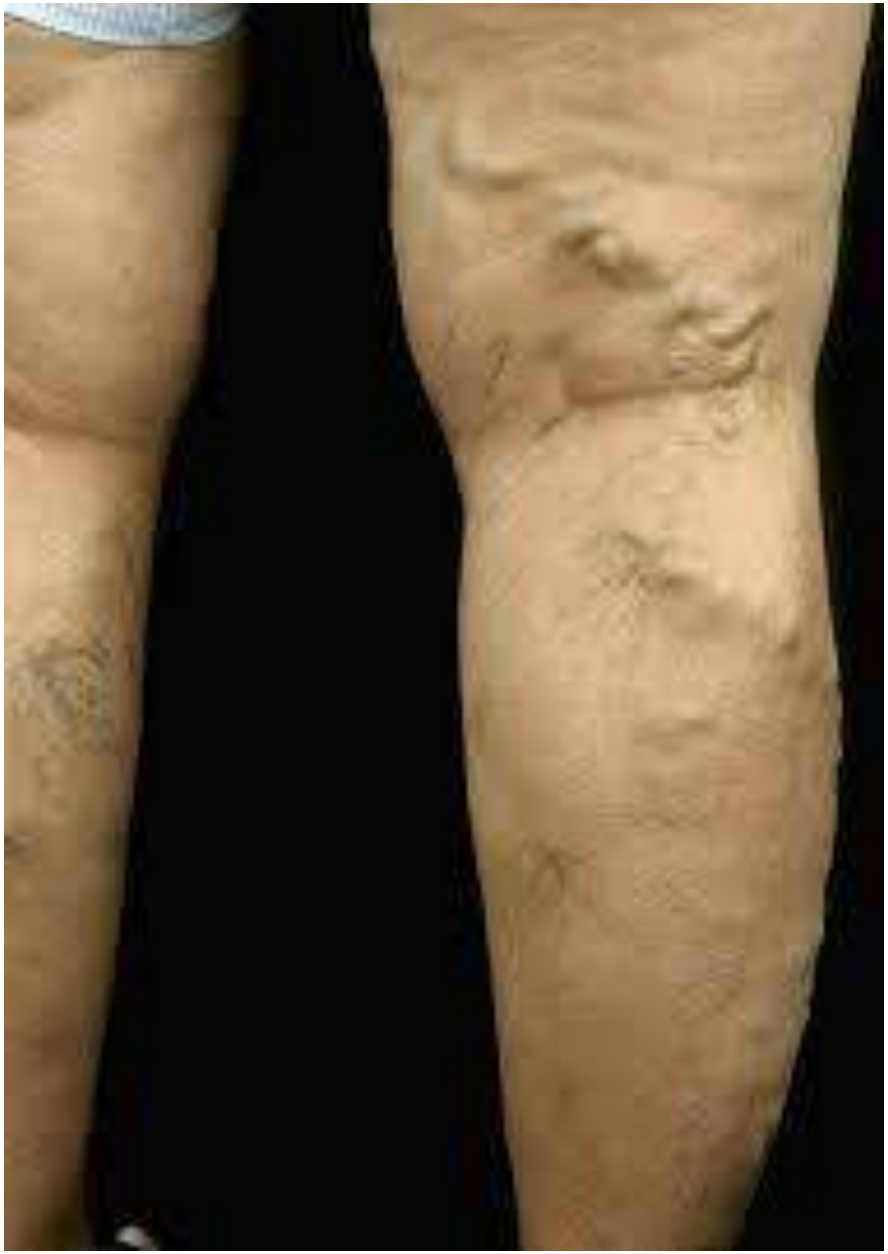
  Manifestations: local congestion, swelling (edema), pain, tenderness, infections of overlying skin and development of varicose ulcers. Rarely embolize

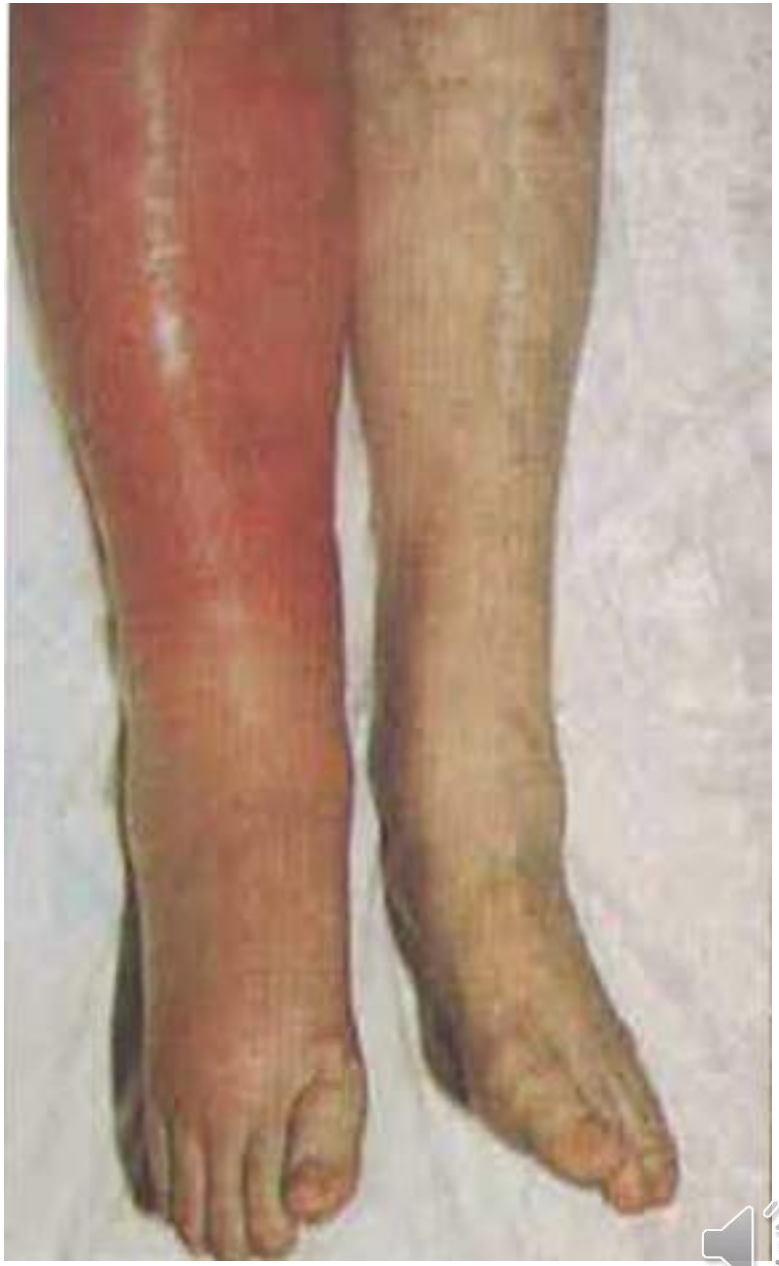
- Deep vein thrombosis(In the larger veins at or above the knee joint) *is more serious*; it may lead to pulmonary emboli, causes edema, pain and tenderness

# Superficial and deep vein thrombosis



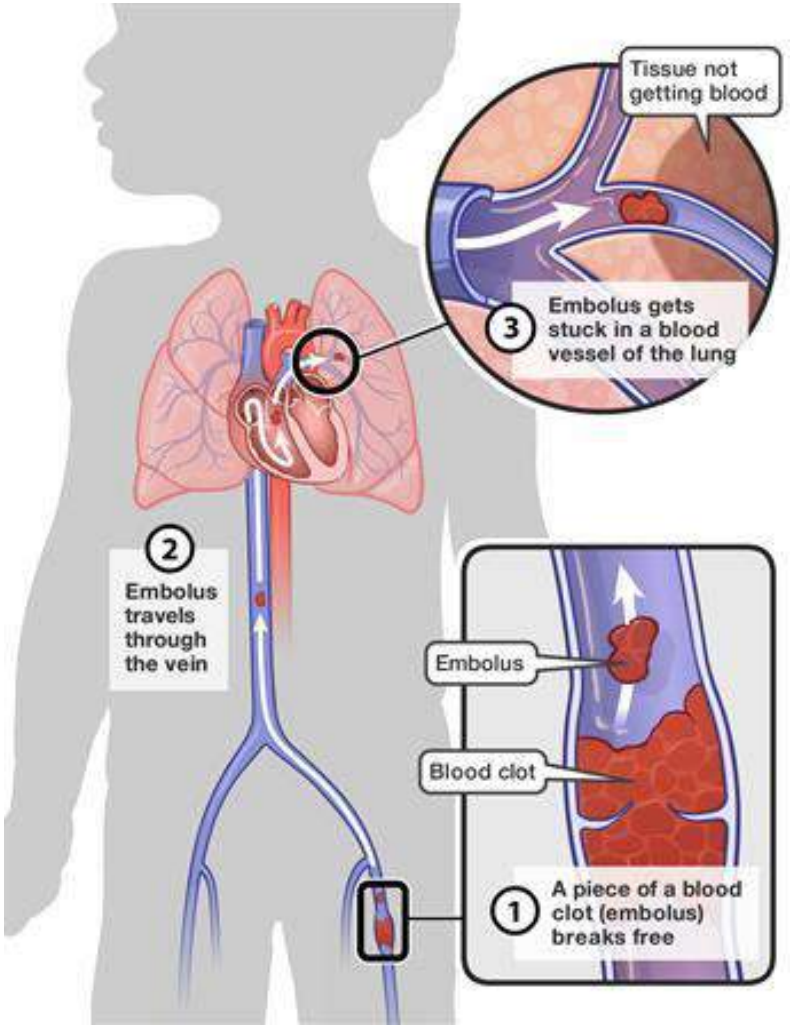







# Venous Thrombosis (Phlebothrombosis)

- Venous obstruction often is circumvented by collateral channels.
- Consequently, DVTs are entirely asymptomatic in approximately 50% of patients and are recognized after they have embolized to the lungs.



# Hemodynamics 6 lectures

Dr. Ghada AL-Jussani
MBCHB,PhD,FRCpath (UK)
2023
Audio 5

# Disseminated Intravascular Coagulation ( DIC)

**DIC is a thrombo-hemorrhagic disorder, characterized by systemic activation of the coagulation cascade by various stimuli , with hundreds of thrombi occluding microcirculation leading to hypoxia and microinfarcts**

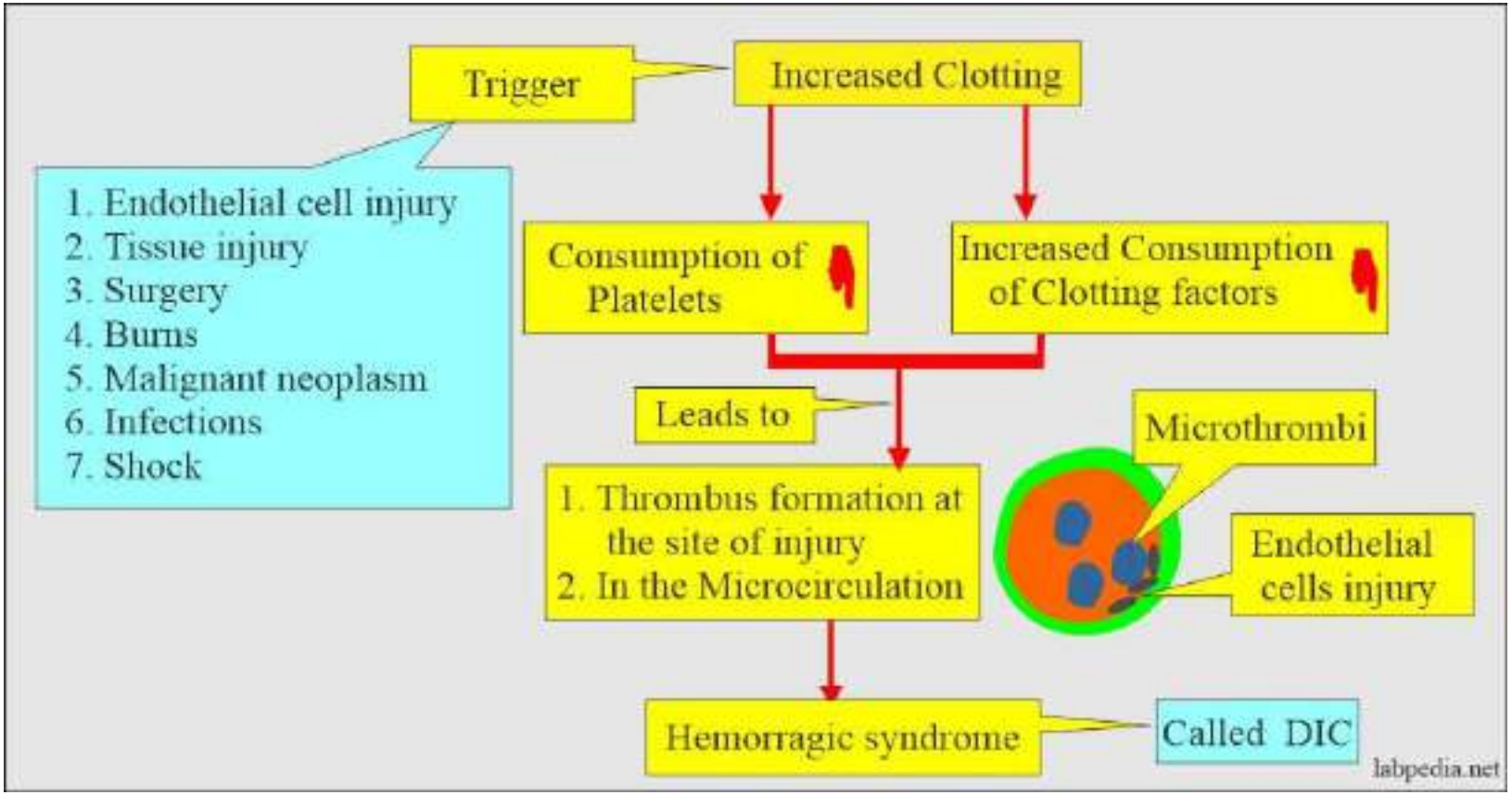
**It is also called consumptive coagulopathy , followed by bleeding due to consumption of platelets & clotting factors in blood**

**Mechanism of DIC;**

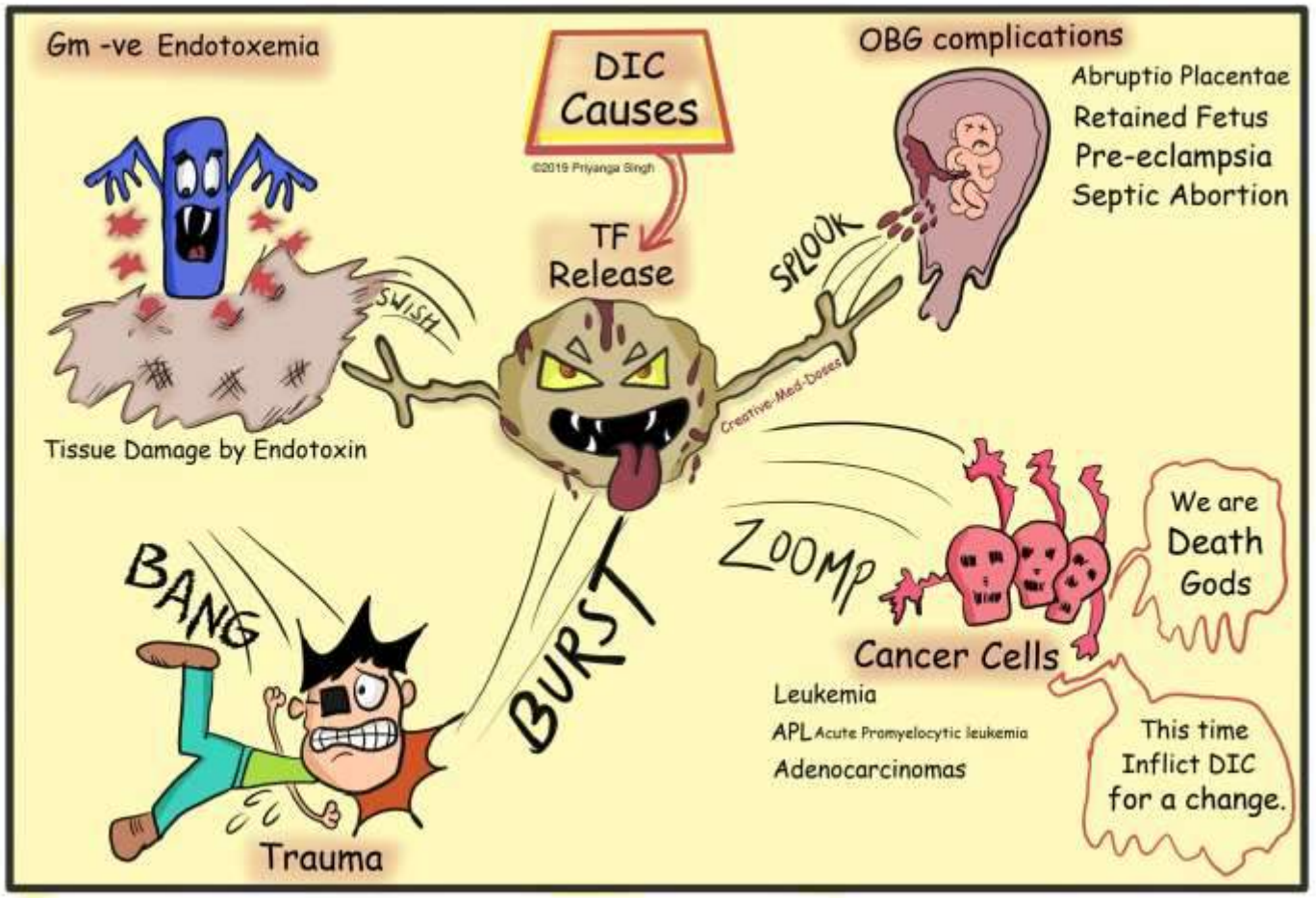
1. **Wide-spread endothelial cell damage**
2. **The release of tissue factor or thromboplastic substances into the circulation**

- ✓ It is characterized by a sudden or gradual onset of widespread fibrin thrombi in the microcirculation.
- ✓ DIC is not a primary disease but rather is a potential complication of any condition associated with widespread activation of thrombin
- ✓ The major causes of which including obstetric complications, infections , neoplasms , massive tissue injury & others .
- ✓ The thrombi can cause widespread & diffuse circulatory insufficiency , especially in the brain, lungs, heart, & kidneys.

- ✓ Thrombin generation in DIC is initiated through the tissue factor/factor VII(a) pathway that activates downstream coagulation factors.
- ✓ Tissue factor may be expressed by activated monocytes, but also by vascular endothelial cells or cancer cells.
- ✓ Histologic studies in patients with DIC show the presence of ischemia and necrosis due to fibrin deposition in small and medium-sized vessels of various organs.
- ✓ The presence of these intravascular thrombi appears to be clearly and specifically related to the clinical dysfunction of the organ.



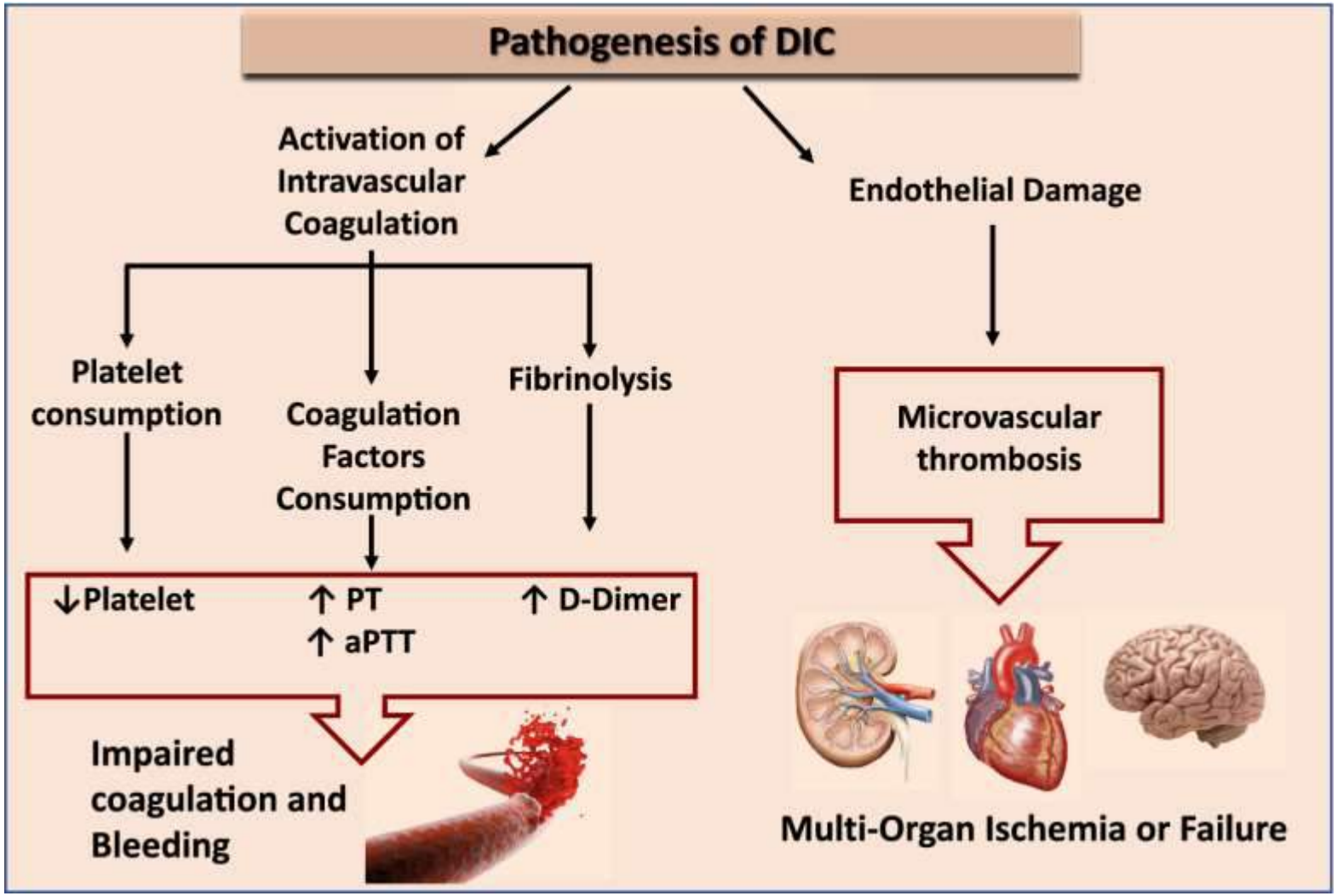
# Disseminated Intravascular Coagulation ( DIC)



# Manifestation of DIC

- **In kidneys**, microthrombi can result in numerous microinfarcts in renal cortex leading to bilateral renal cortical necrosis , then renal failure
- **In brain**, microthrombi & numerous micro infarcts in the brain
- **Lungs and GIT** involvement by microinfarcts
- **The adrenals** involvement leading to extensive bilateral adrenal hemorrhage called (Waterhouse Friedrichsen Syndrome)
- **In the skin** widespread petechiae, and ecchymosis

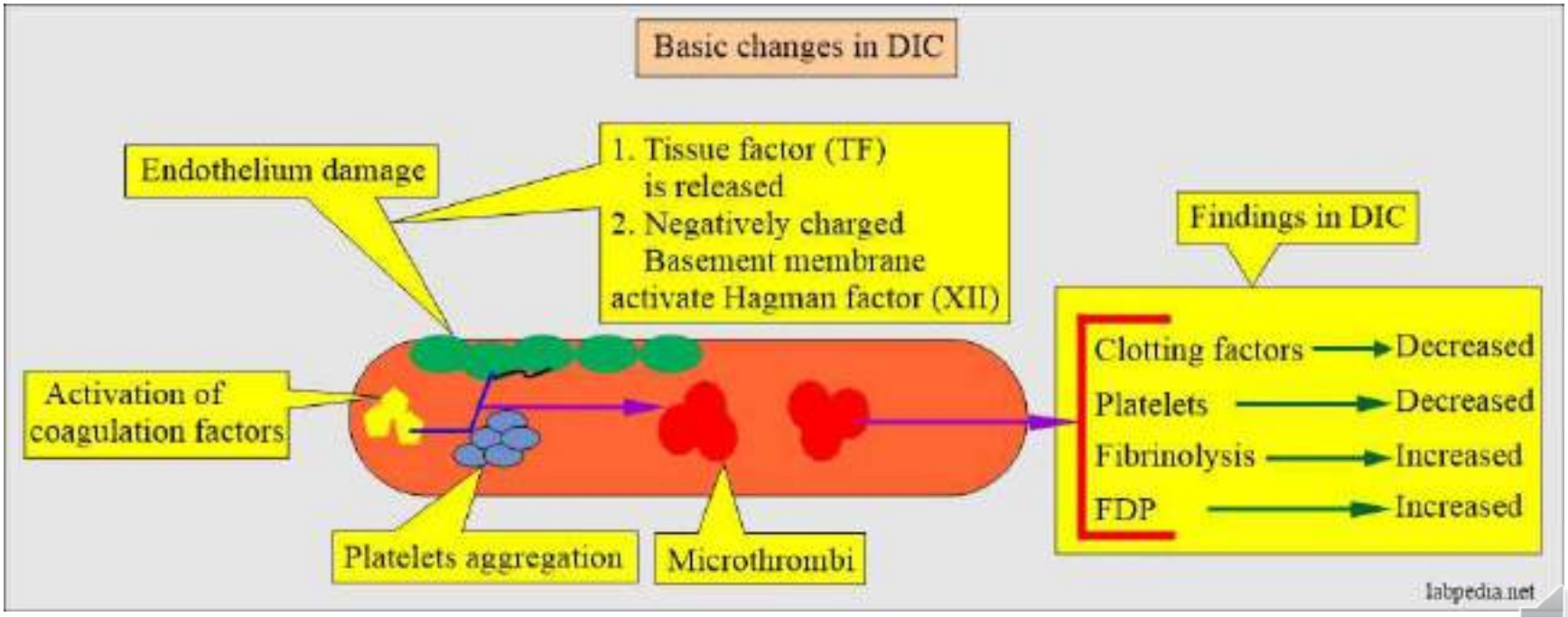
# Disseminated Intravascular Coagulation ( DIC)



**Laboratory tests reveal:**

- **Thrombocytopenia**
- **Prolonged prothrombin time (PT ) & partial thromboplastin time ( PTT)**
- **Increase Fibrin degradation products ( FDPs)**

**Treatment: heparin & fresh frozen plasma, and treat the underlying cause**



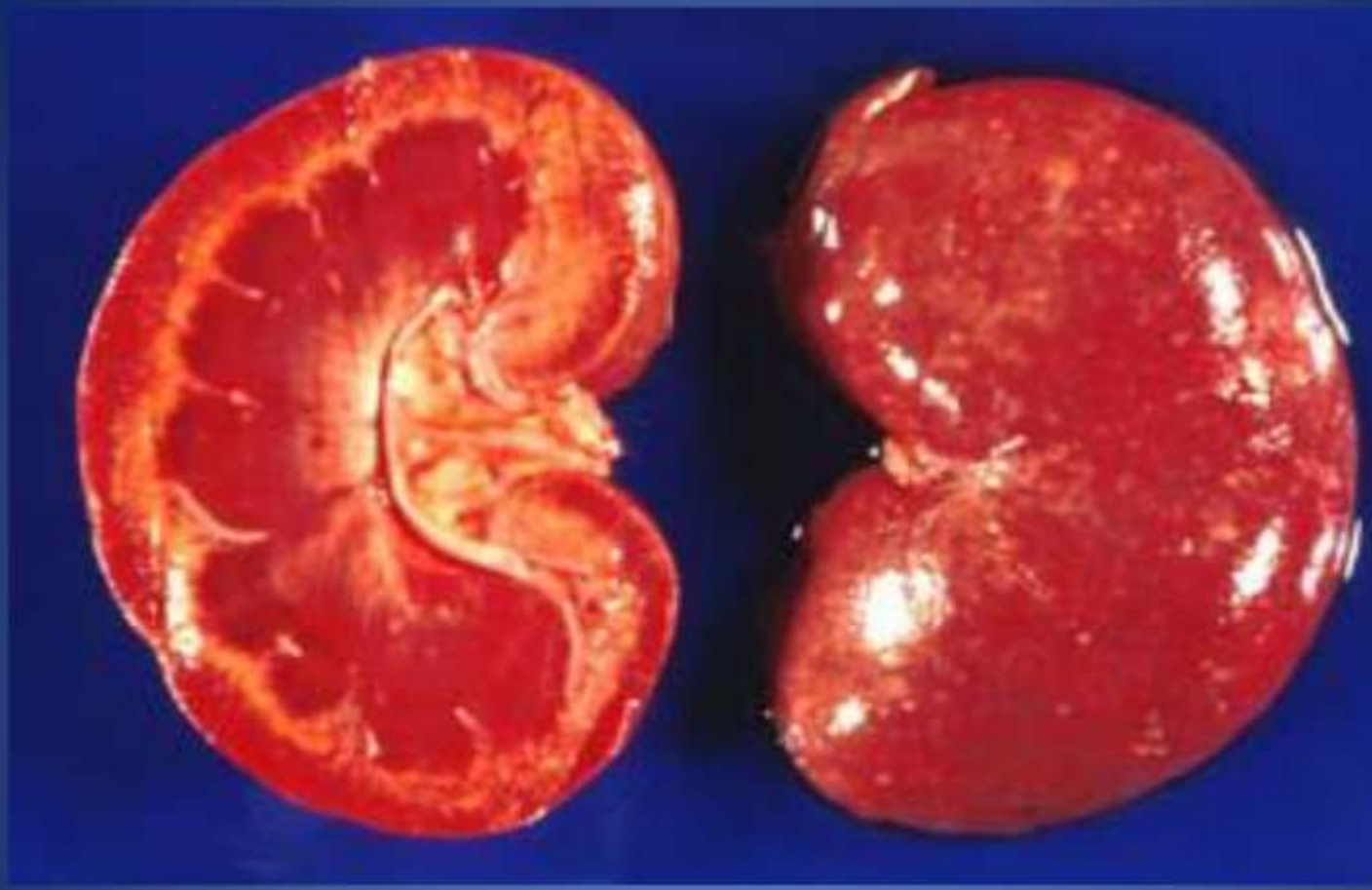


Figure 42 : Gross appearance of kidney showing renal cortical necrosis in DIC .

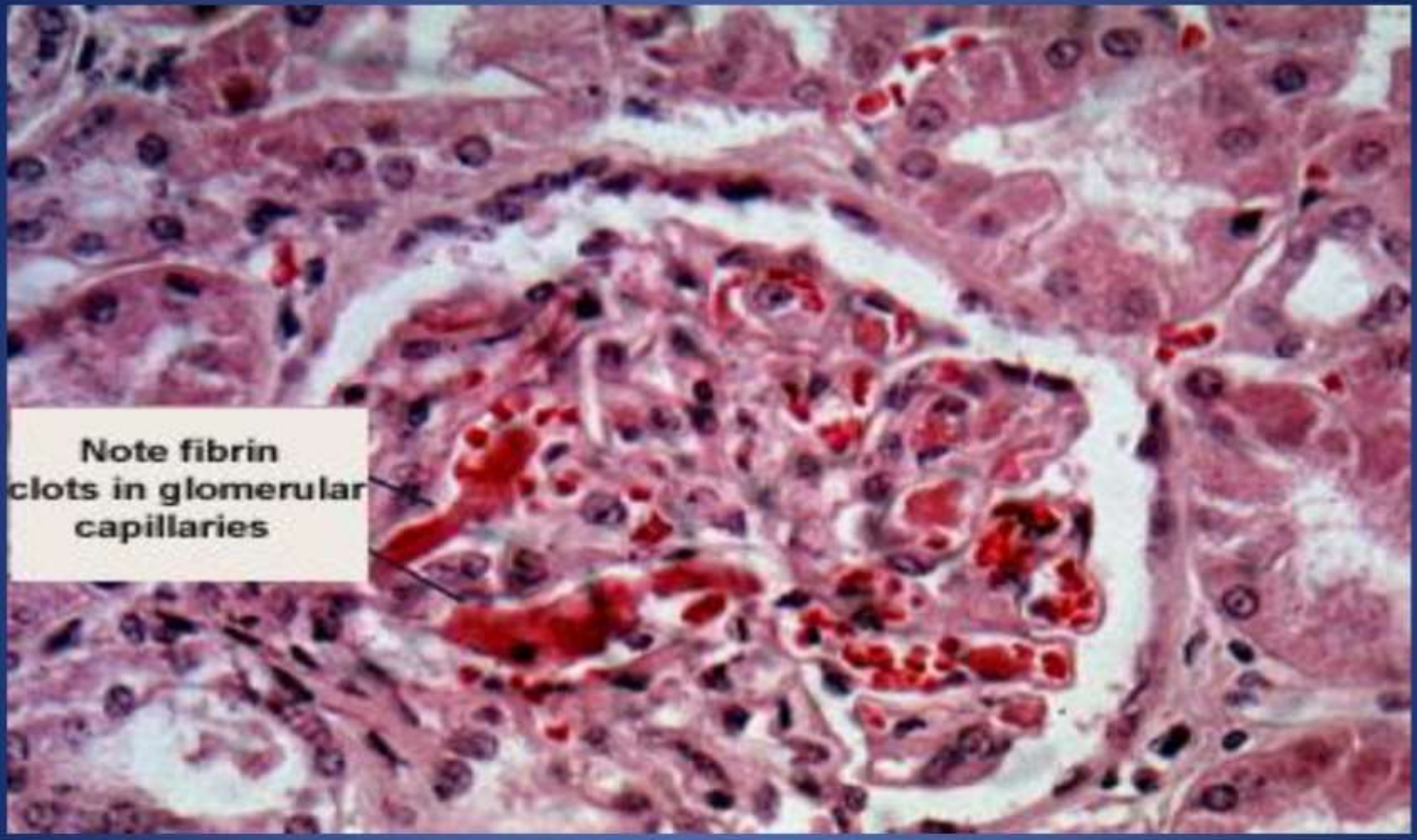



Figure 43 : DIC in kidney : Microscopic view .

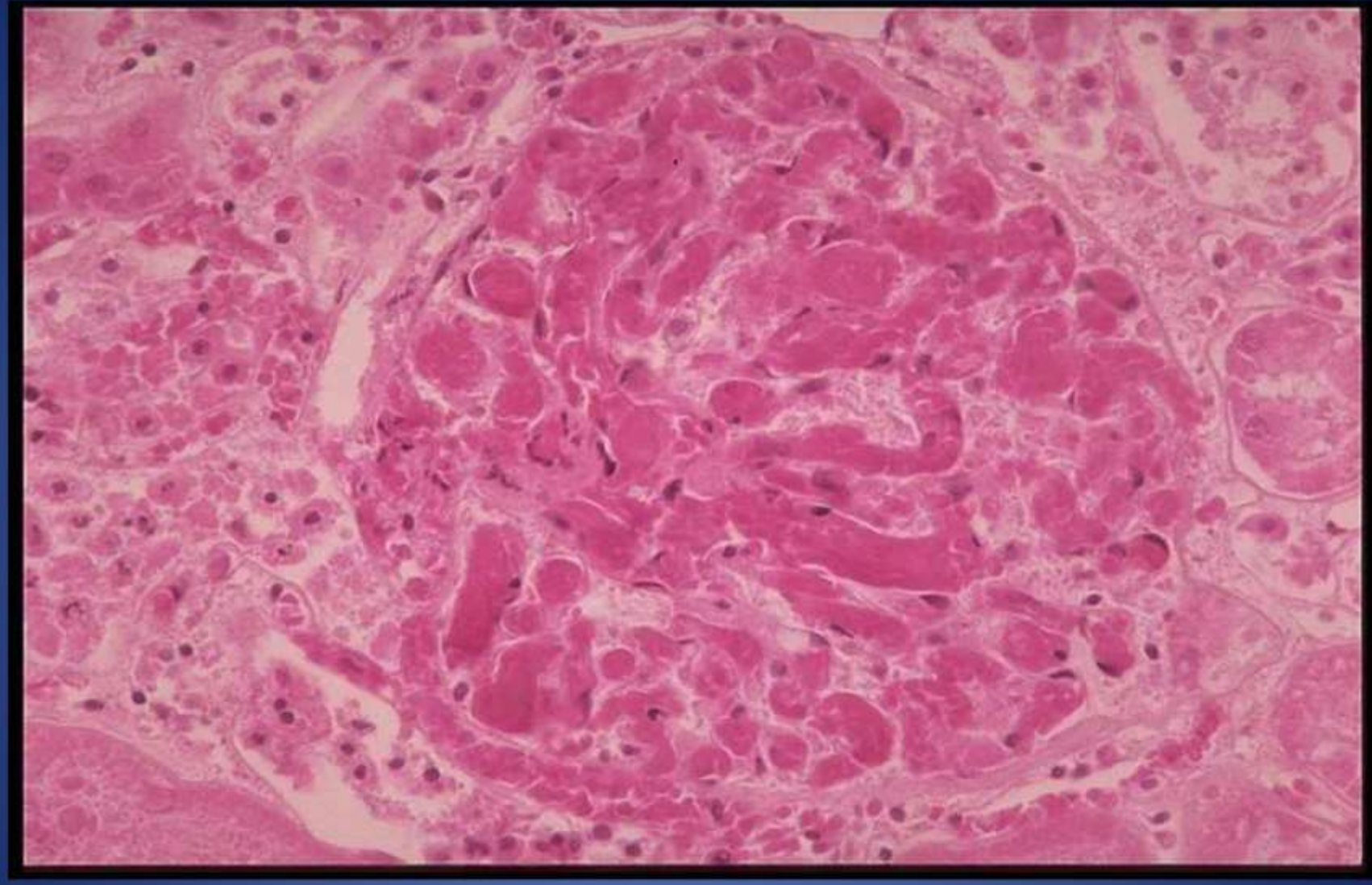


Figure 44 - Microscopic view of renal microthrombi in DIC.

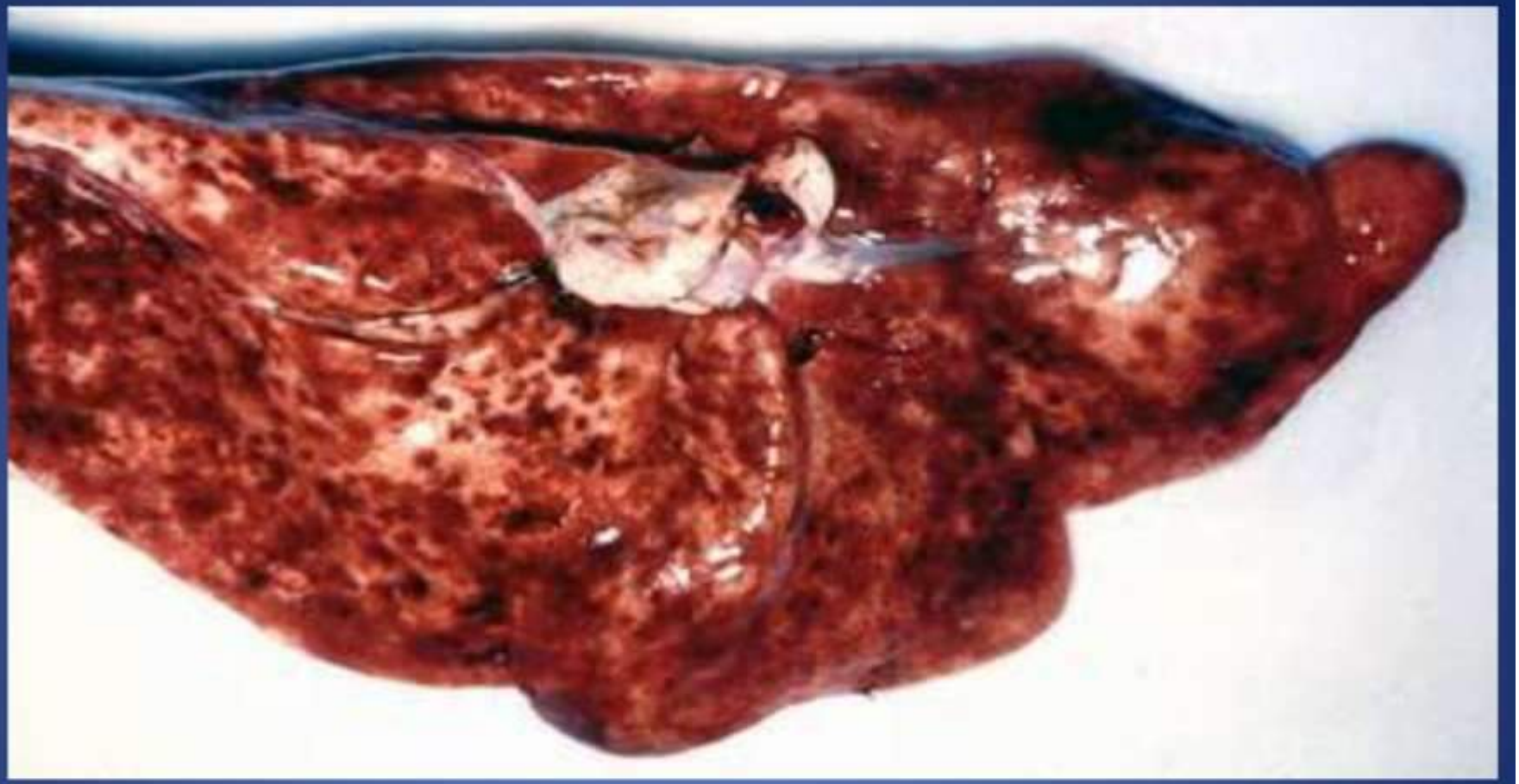


Figure 45 : Gross appearance of lung showing features of DIC , numerous hemorrhagic microinfarcts & hemorrhages .

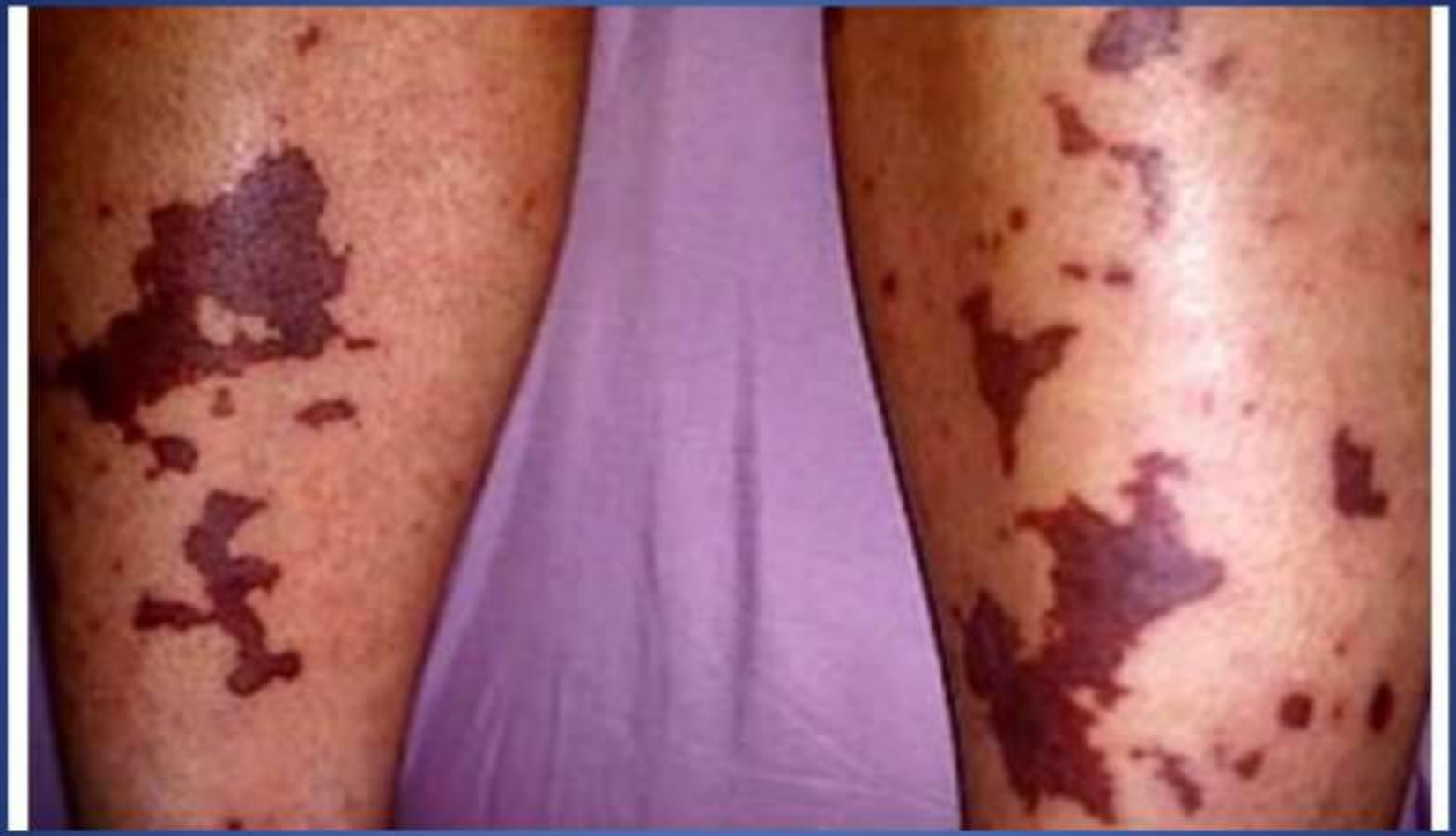


Figure 46 : Skin in DIC,

# Embolism

# Embolism

- An embolus is a detached intravascular **solid, liquid, or gaseous** mass that is carried by the blood to a site distant from its point of origin.
- 99% of all emboli represent some part of a dislodged thrombus, hence the term **thromboembolism**.

**Two forms:**

1. **Pulmonary thromboembolism** leads to hypoxia and right-sided heart failure.
2. **Systemic thromboembolism:** Ischemic necrosis (infarction) of downstream tissue.

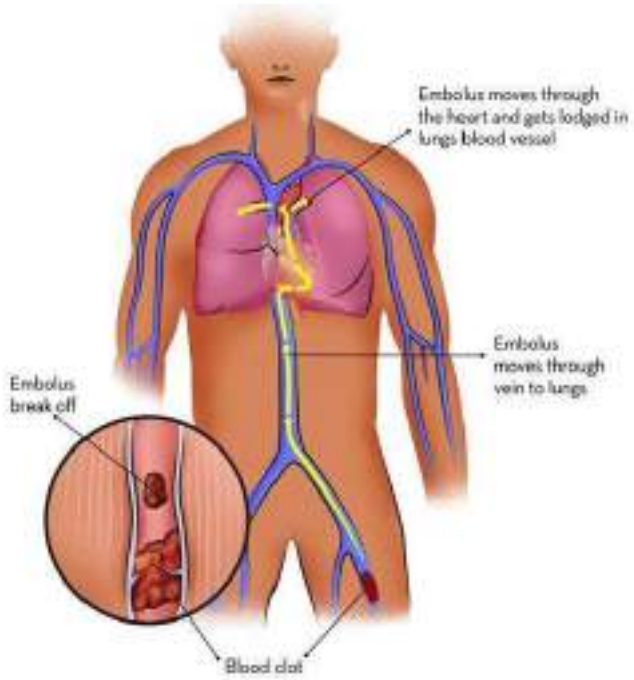
- Rare forms:

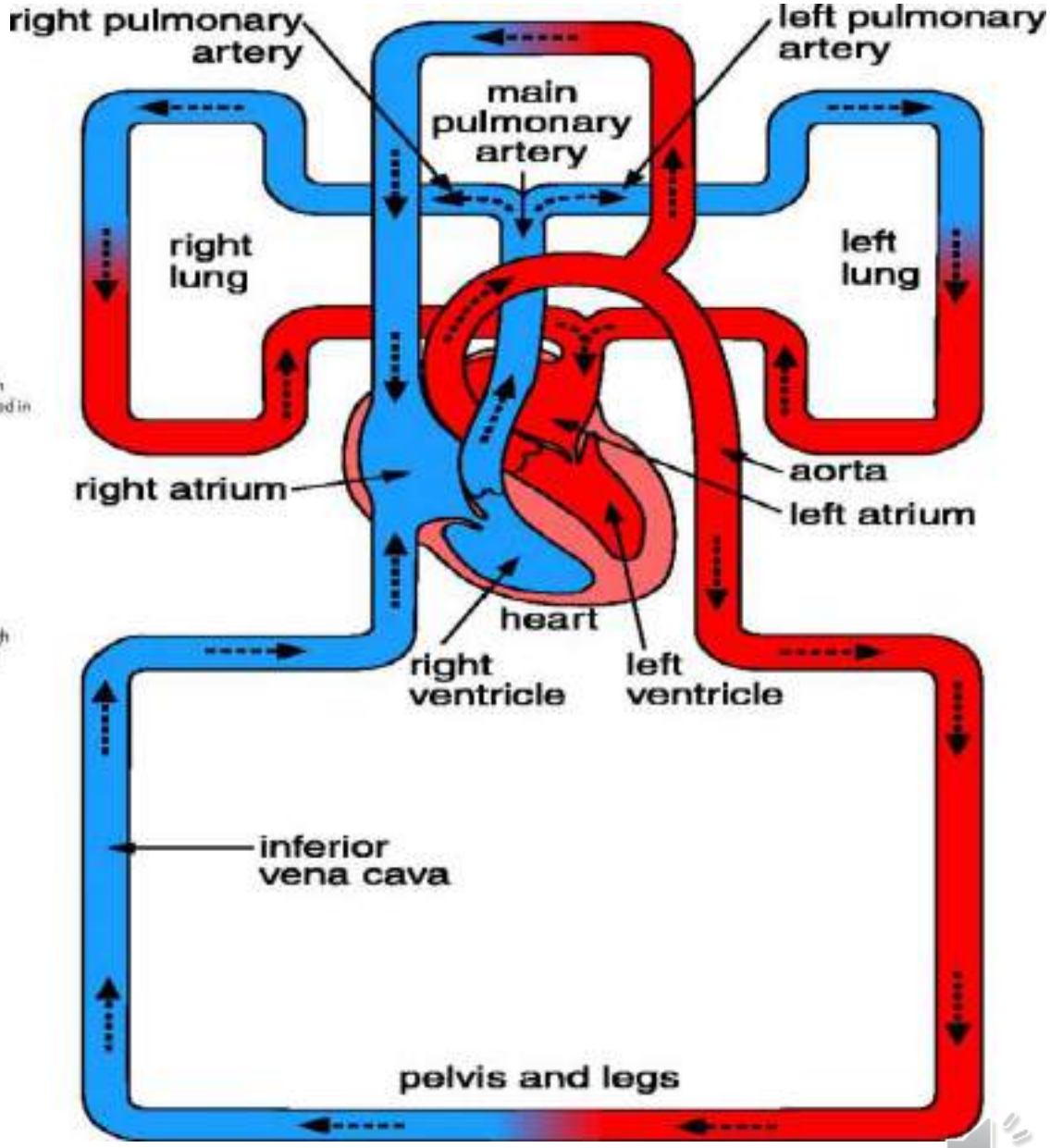
Air embolism, fat embolism, amniotic fluid embolism.

# Pulmonary Thromboembolism

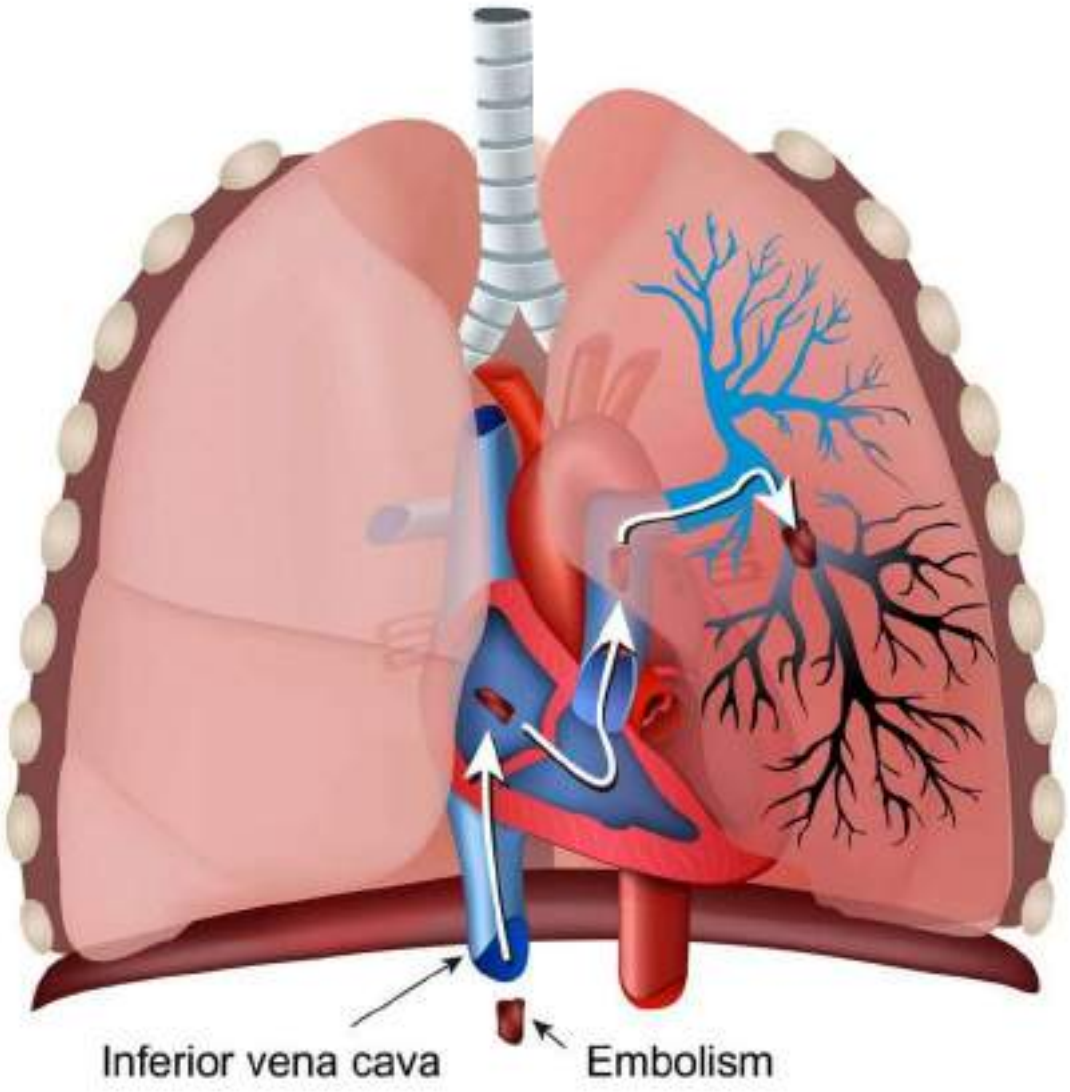
- In 95% of cases, emboli originate from thrombi within deep leg veins, above the knee (DVT).

- They are carried through progressively larger channels and pass through the right side of the heart to the pulmonary vasculature.

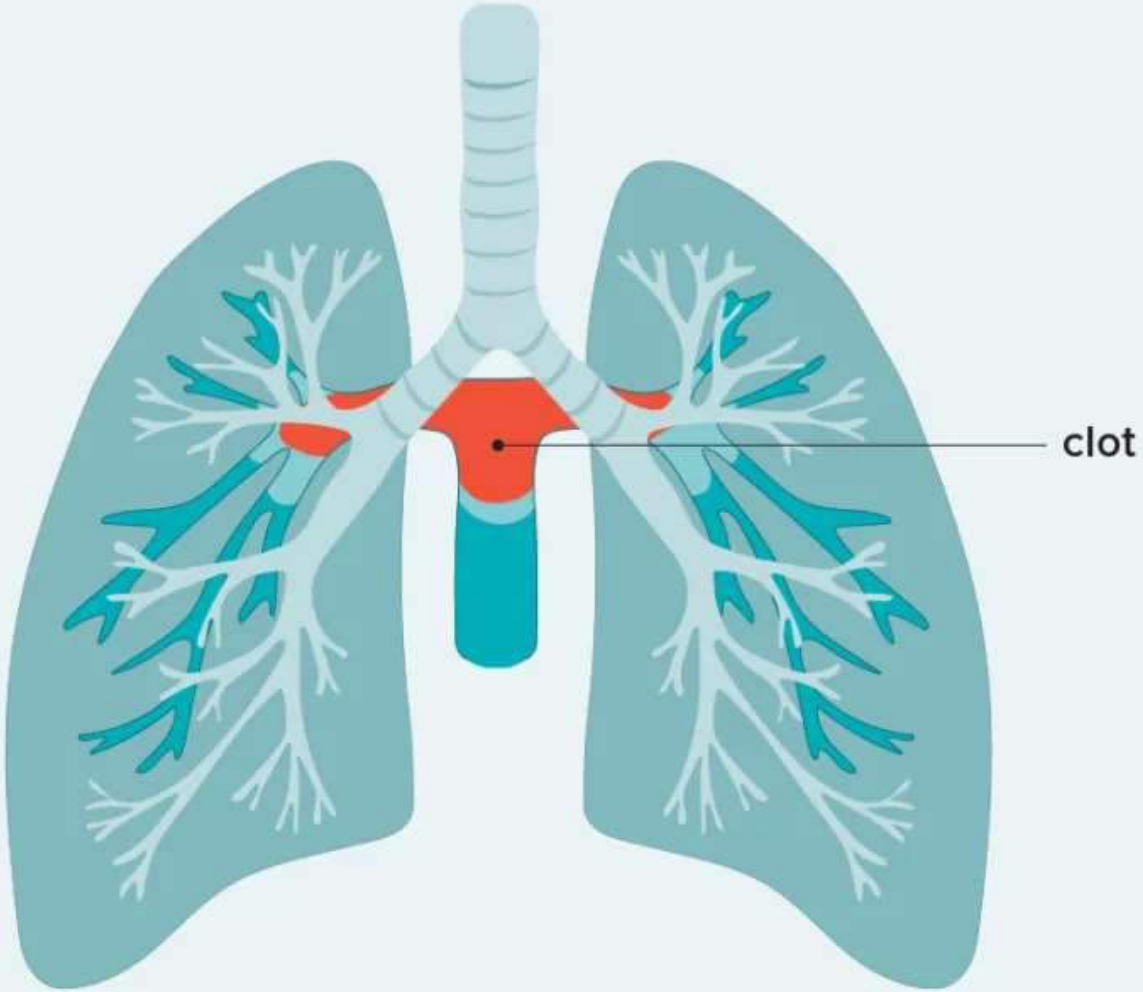

Embolus moves through the heart and gets lodged in lungs blood vessel
Embolus moves through vein to lungs
Embolus break off
Blood clot


right pulmonary artery
left pulmonary artery
main pulmonary artery
right lung
left lung
right atrium
aorta
left atrium
heart
right ventricle
left ventricle
inferior vena cava
pelvis and legs

# Pulmonary Embolism



# Saddle Pulmonary Embolism

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# Thrombophlebitis versus phlebo thrombosis

- Thrombophlebitis is a condition in which inflammation of the vein wall has preceded the formation of a thrombus (blood clot).
- Phlebothrombosis is the presence of a clot within a vein, unassociated with inflammation of the wall of the vein

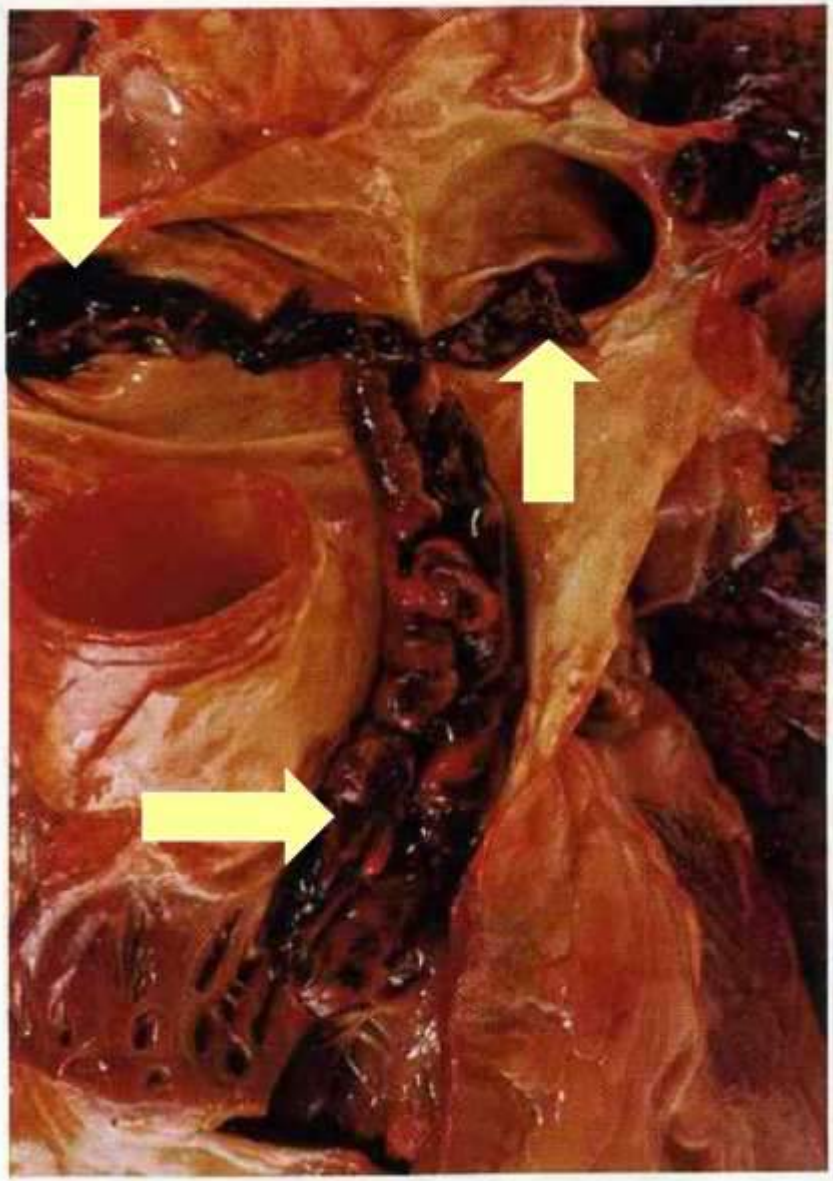
# Effects of Pulmonary Thromboembolism :

- (1) Fatal, Sudden death, acute right heart (ventricular) failure, also called acute cor pulmonale , occur when 60% or more of the pulmonary circulation is obstructed with emboli.
- (2) Embolic obstruction of medium- sized arteries may result in:

(A) Pulmonary hemorrhage : but usually does not causes pulmonary infarction (in normal person) because of blood flow into the area from an intact bronchial circulation ( normally there is double pulmonary blood supply from pulmonary & bronchial arterial circulations), however,

(B) (B) A similar embolus in the setting of left-heart failure (& resultant sluggish bronchial artery blood flow) may result in a large pulmonary infarction

- (3) Embolic obstruction of small end-arteriolar pulmonary branches usually does not result in associated infarction.
- (4) Multiple emboli over time may cause pulmonary hypertension with chronic right heart failure (cor pulmonale).
- (5) Majority (60% to 80%) of pulmonary emboli are clinically silent because they are small. With time, they undergo organization & become incorporated into the vascular wall may undergo fibrosis leading to pulmonary hypertension



6.31 Pulmonary embolism

**F 47 : Fatal pulmonary thrombo-embolism (PTE).**

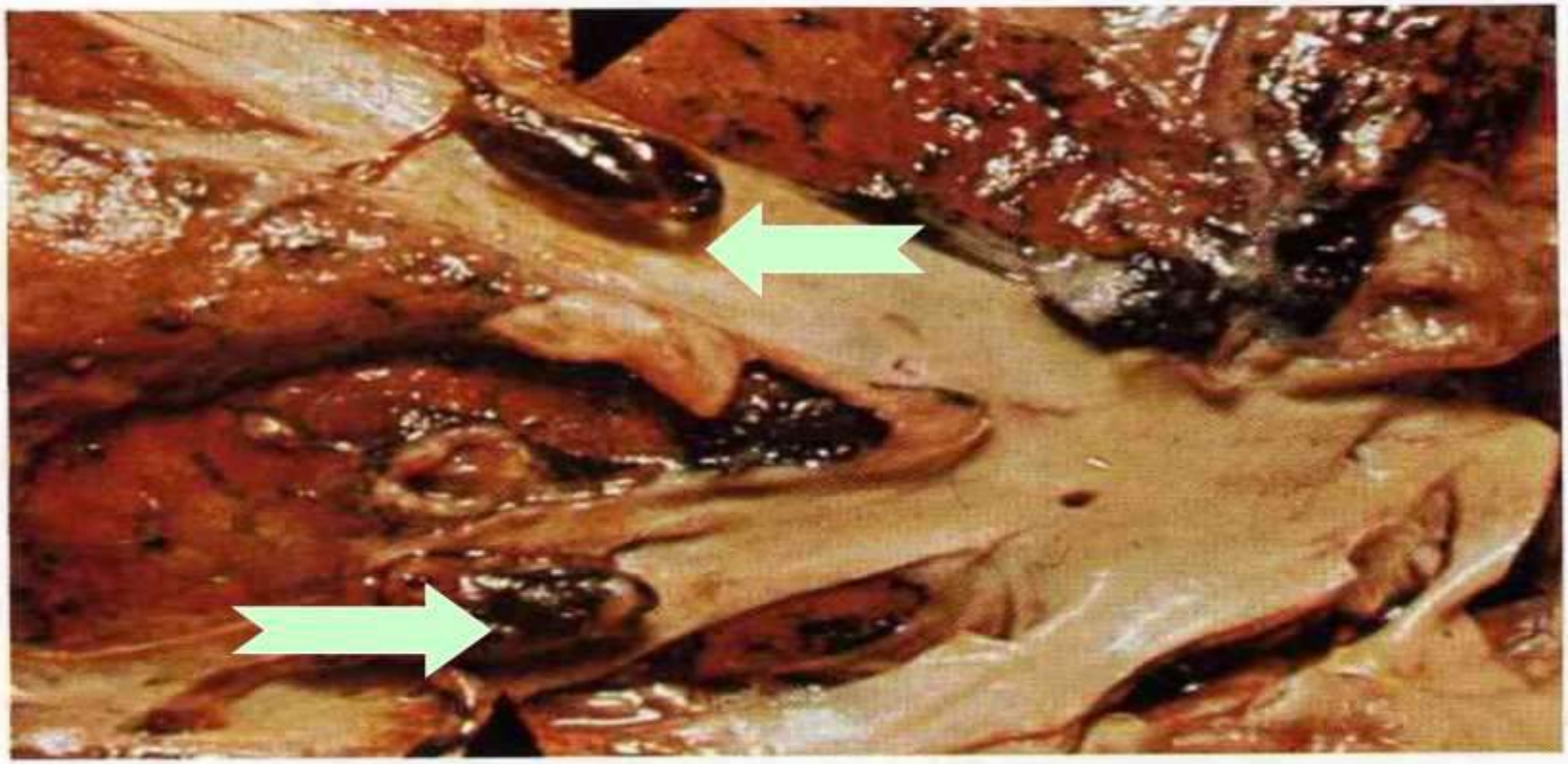
A large coiled-up thrombo-embolus . It lies within the Rt.V. outflow tract, filling the pulmonary trunk & the bifurcation of both Rt & Lt pulmonary arteries **(saddle embolus).**


F 48 : **Pulmonary Thrombo Embolism**: Saddle embolus

**F 49 : Recurrent pulmonary Thromboembolism (PTE).**

The secondary branches of a pulmonary artery have been opened to reveal two small emboli wedged within the vessels.

Both have tapering distal extensions.



6.34 Recurrent pulmonary embolism

# Systemic Thromboembolism

- 80% arise from **intra cardiac thrombi.**
- The remainder (20%) originate from **aortic aneurysms** and thrombi overlying ulcerated atherosclerotic plaques. or from fragmentation of a valvular vegetation (of infective endocarditis);
- only very rarely due to paradoxical emboli (emboli passing from the right heart through atrial or ventricular septal defect into the left heart & then in the aorta)

**Common arteriolar embolization sites :**

**a. The lower extremities (75%).**

b. Central nervous system (10%).

c. Intestines and kidneys.

**Note: Arterial emboli often cause infarction**

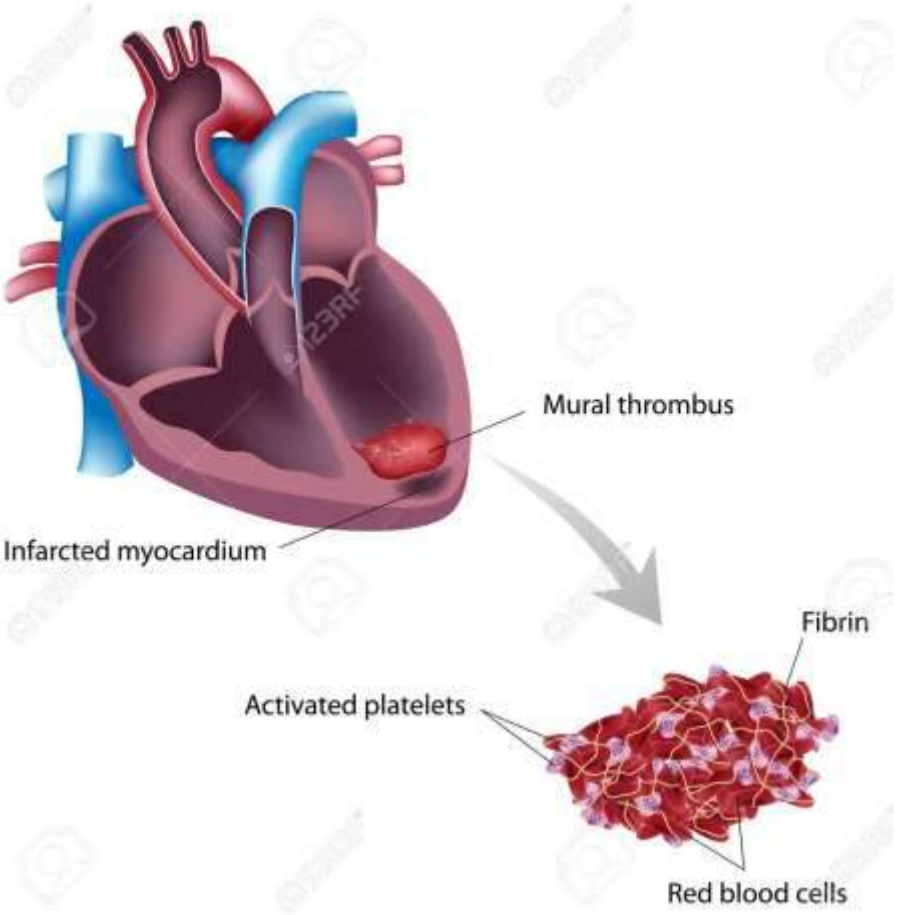
# Effects:

- In contrast to venous emboli, which tend to lodge primarily in one vascular bed only (the lung in systemic venous circulation & the liver in the portal circulation)
- arterial emboli can travel to a wide variety of sites; the site of arrest depends on the point of origin of the thromboembolism

# Major sites for arterial embolization are

- (1) Lower extremities (75%),
- (2) Brain (10%), with the intestines, kidneys, & spleen involved to a lesser extent.
- The consequences of systemic emboli depend on the:
- (1) Collateral's, the extent of collateral vascular supply in the affected tissue,
- (2) Tissue's vulnerability to ischemia,
- (3) Caliber of the arterial BV occluded; in general, however, arterial emboli cause infarction of tissues in the distribution of the obstructed vessel

# Systemic Thromboembolism



# Postmortem Clots

- Postmortem Clots : At autopsy, postmortem (PM) clots may be mistaken for venous thrombi.
- PM clots are gelatinous with a dark red dependent portion where RBCs have settled by gravity, & a yellow chicken fat" supernatant; they are usually not attached to the underlying wall.
- In contrast, red thrombi are firmer, almost always have a point of attachment, & on transaction reveal vague strands of pale gray fibrin.

Post-mortem clot. Typically, a glistening , semi-translucent, homogeneous pale yellow (chicken-fat) clot which formed a cast of the pulmonary trunk & its branches, sometimes, they appear deep red (red current jelly clot). Post-mortem clots do not show lines of Zahn .

6.28 Post-mortem clot

# Fat Embolism

**Caused by:**

- Soft tissue crush injury or long bone fractures, with release of microscopic fat globules into the circulation.
- Presumably, the fat is released by marrow or adipose tissue injury & enters the circulation by rupture of the marrow vascular sinusoids or rupture of venules. Although traumatic fat embolism occurs in some 90% of individuals with severe skeletal injuries , fewer than 10% of such patients show any clinical findings
- **Causes of fat embolism include**

1. **Fracture of long bones**
2. **severe burn**
3. **severe fatty liver causing liver cirrhosis**
4. **oily intravenous injections ( mismanagement )**
5. **surgical operations (liposuction )**

**Fat embolism syndrome:**

**a. Pulmonary insufficiency (**tachypnea, dyspnea)

**b. Neurologic symptoms (**irritability and restlessness to coma)

**c. Anemia, thrombocytopenia.**

**d. Diffuse petechial rash**

**Typically, the symptoms appear 1 to 3 days after injury with sudden onset of symptoms**

# Fat Embolism

**Pathogenesis**:

- Mechanical theory:

➢ Mechanical obstruction by microemboli of neutral fat +platelet &RBC aggregates

- Intravascular coagulation theory:

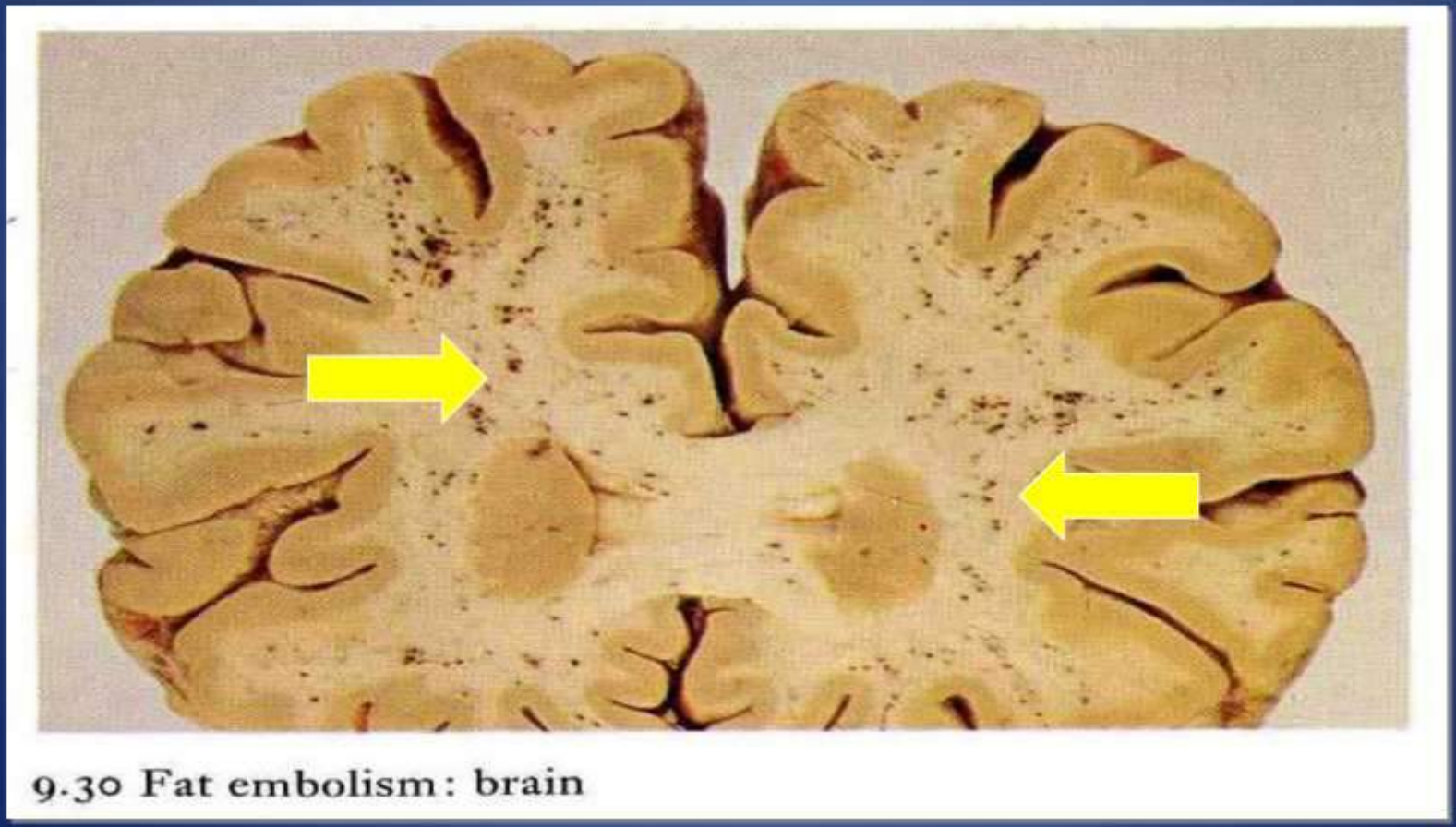
➢ Chemical irritation (local injury to endothelium) from release of fatty acids + platelet activation & recruitment of granulocyyes –release of free radicals,protease &ecosanoids →DIC

- a characteristic petechial skin rash is related to rapid onset of thrombocytopenia, presumably caused by platelets adherence to the myriad (tens of thousands) fat globules & being removed from the circulation.
- Adherence of platelets →

Thrombocytopenia ( low platelet count ) →

Bleeding tendency ( petechial hemorrhage )

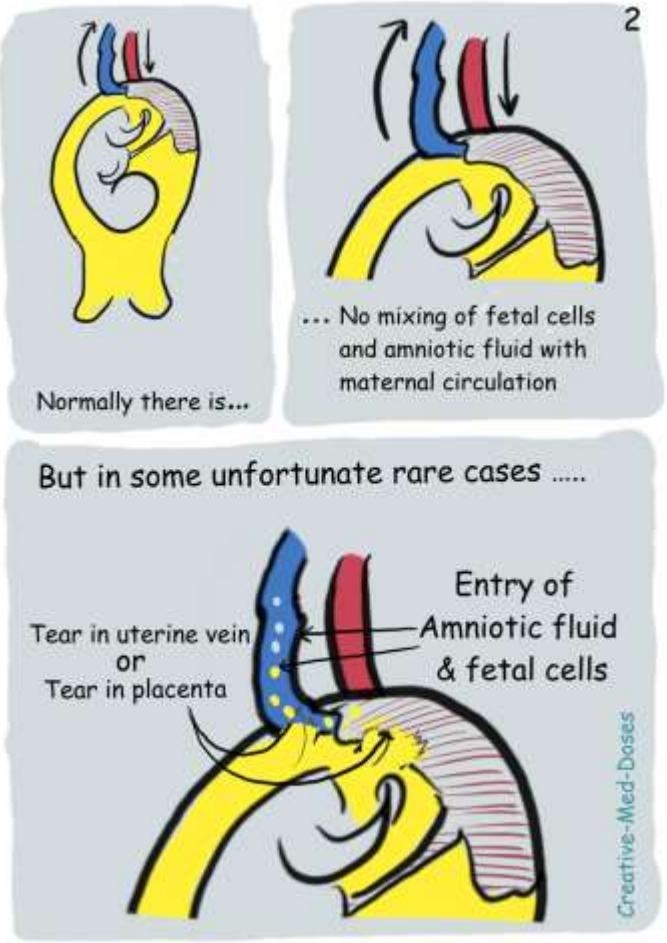
Figure 50 - **Fat embolism: Brain. Before his death, the patient had a fractured femur .At PM, coronal section of the frontal brain region shows multiple small hemorrhagic foci scattered throughout the white matter.**



9.30 Fat embolism: brain

# Amniotic Fluid Embolism

- Introduction of amniotic fluid and its contents to the **maternal circulation** via a tear in the placental membranes and rupture of uterine veins during childbirth
- Rare (1 in 40,000 deliveries), but carries 80% mortality rate
- **Manifestations:** Respiratory failure (sudden severe dyspnea, cyanosis, and hypotensive shock), seizures, and coma
- **Histologic analysis:** squamous cells shed from fetal skin, lanugo hair, and mucin derived from the fetal respiratory or gastrointestinal tracts present in the maternal pulmonary microcirculation




# Amniotic Fluid Embolism

# Air embolism

- Source: air may enter the circulation
- (1) during obstetric procedures (tubal insufflation )
- (2) as a consequence of chest injury (stabbing )or neck stabbing by sharp tool causing puncture of internal jugular vein . Or artificial pneumothorax during operation.
- (3) miss management of intravenous infusion .
- (4) Scuba diving
- Generally, in excess of 30-50 mL of air is required to produce a clinical effect; the air bubbles act like physical obstruction (just as thromboembolism & causing distal ischemic injury), bubbles may coalesce to form frothy masses sufficiently large to occlude major vessel

# Decompression sickness

- Decompression sickness Is a particular form of gas embolism, which occurs when individuals are exposed to sudden changes in atmospheric pressure. Scuba (under water breathing apparatus users) deep sea divers, underwater construction workers, & individuals in unpressurized aircraft in rapid ascent are at risk .

- When air is breathed at high pressure (e.g., during a deep sea dive) → increased amounts of gas (particularly nitrogen) become dissolved in the blood & tissues.
- If the diver then ascends (depressurizes) too rapidly, the nitrogen expands in the tissues & bubbles out of solution in the blood to form gas emboli.
- Clinically, the rapid formation of gas bubbles within skeletal muscles & supporting tissues in & about joints is responsible for the painful arching of the backs, condition called (the bends)

- Gas emboli may also induce focal ischemia in a number of tissues, including brain, heart, & in the lungs where it may leads to respiratory distress, called the chokes.
- Treatment of gas embolism consist of :

1. placing the individual in a compression chamber, where the barometric pressure may be raised, thus forcing the gas bubbles back into solution.
2. Subsequent, slow decompression, theoretically permits gradual resorption & exhalation of the gases so that obstructive bubbles do not reform.

- A more chronic form of decompression sickness is called Caisson disease, in which persistence of gas emboli in the bones leads to multiple foci of ischemic necrosis; the commonest sites are the heads of the femur, tibia, & humeri

# INFARCTION

- Infarct: area of **ischemic necrosis** caused by **occlusion of vascular supply in a particular tissue**.
- **Arterial thrombosis or arterial embolism underlies the vast majority of infarctions.**
- **Venous thrombosis** can cause infarction, but it more often induces venous **obstruction and congestion**.

- Infarcts caused by venous thrombosis thus usually occur only in organs with a single efferent vein (e.g., testis or ovary).

# INFARCTION

- Infarcts are classified on the basis of their **color** (reflecting the amount of hemorrhage) and the presence or absence of microbial infection:

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

# Red infarcts

(1) **With venous occlusions** (such as in ovarian torsion).

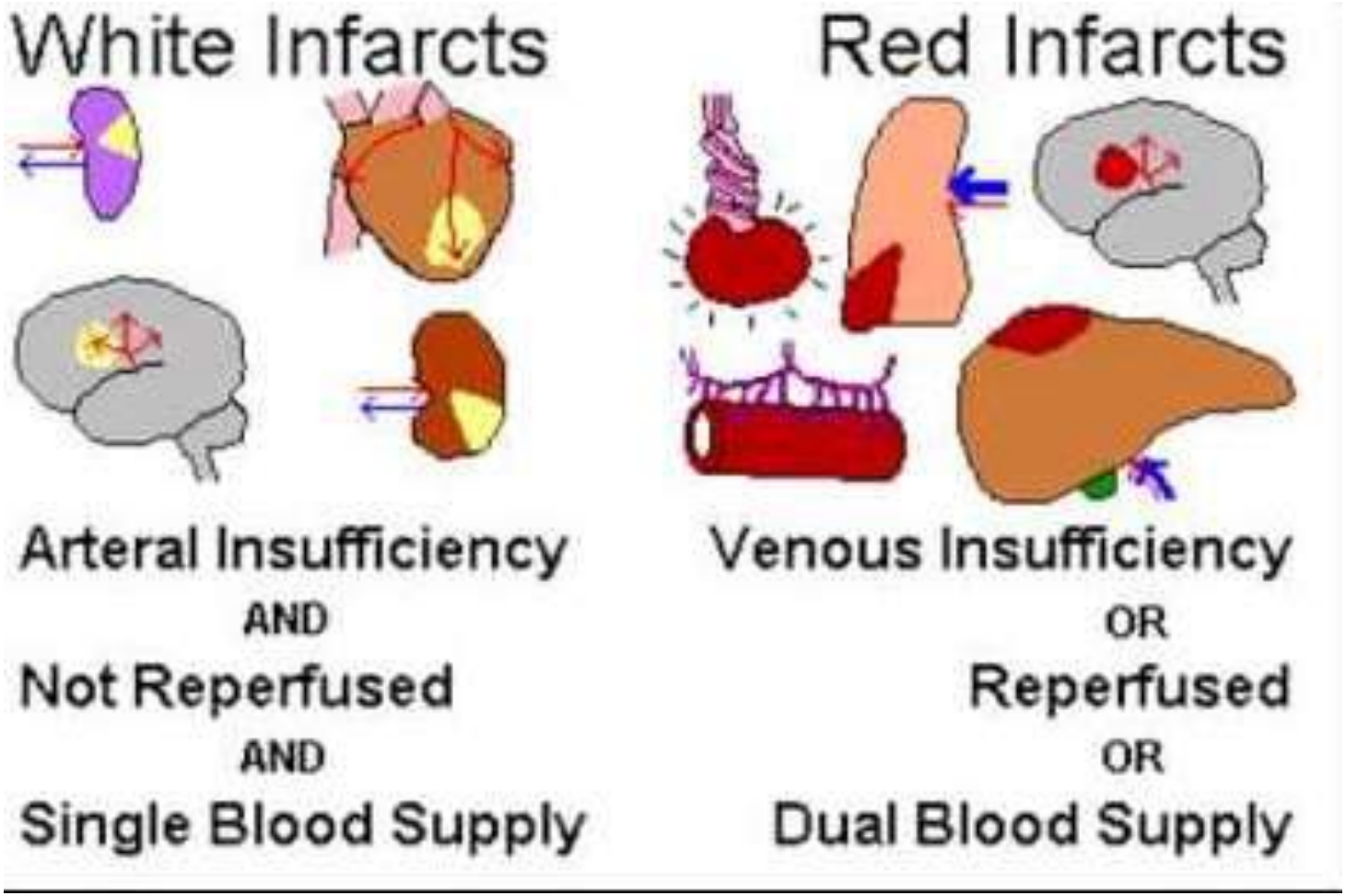
(2) In **loose** tissues (such as lung).

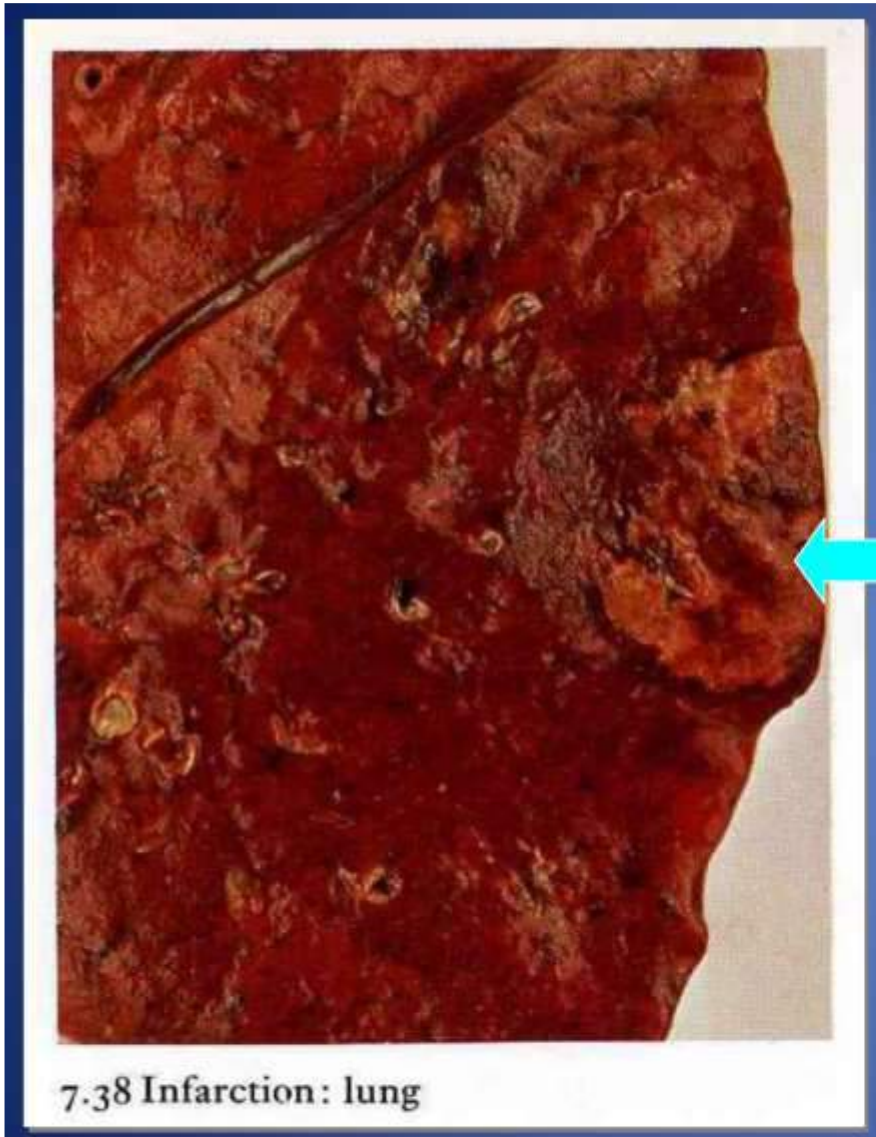
(3) In tissues with **dual** circulations such as lung and small intestine.

(4) In tissues that were previously congested because of sluggish venous outflow.

(5) When flow is **re-established** to a site of previous arterial occlusion.

# Red infarcts





7.38 Infarction: lung

**Figure 54 -Lung infarction.** There is lower lobe,sub-pleura, pale pink, wedge-shaped infarct.

The infarct is swollen, with raised pleural surface over it, & is surrounded by a dark-red congested border.

# White infarcts

- Occur with **arterial occlusions** in **solid organs** with end-arterial circulations (e.g**., heart, spleen, and kidney)**

- Where the solidity of the tissue limits the amount of hemorrhage that can seep into the area of ischemic necrosis from the adjoining capillary beds

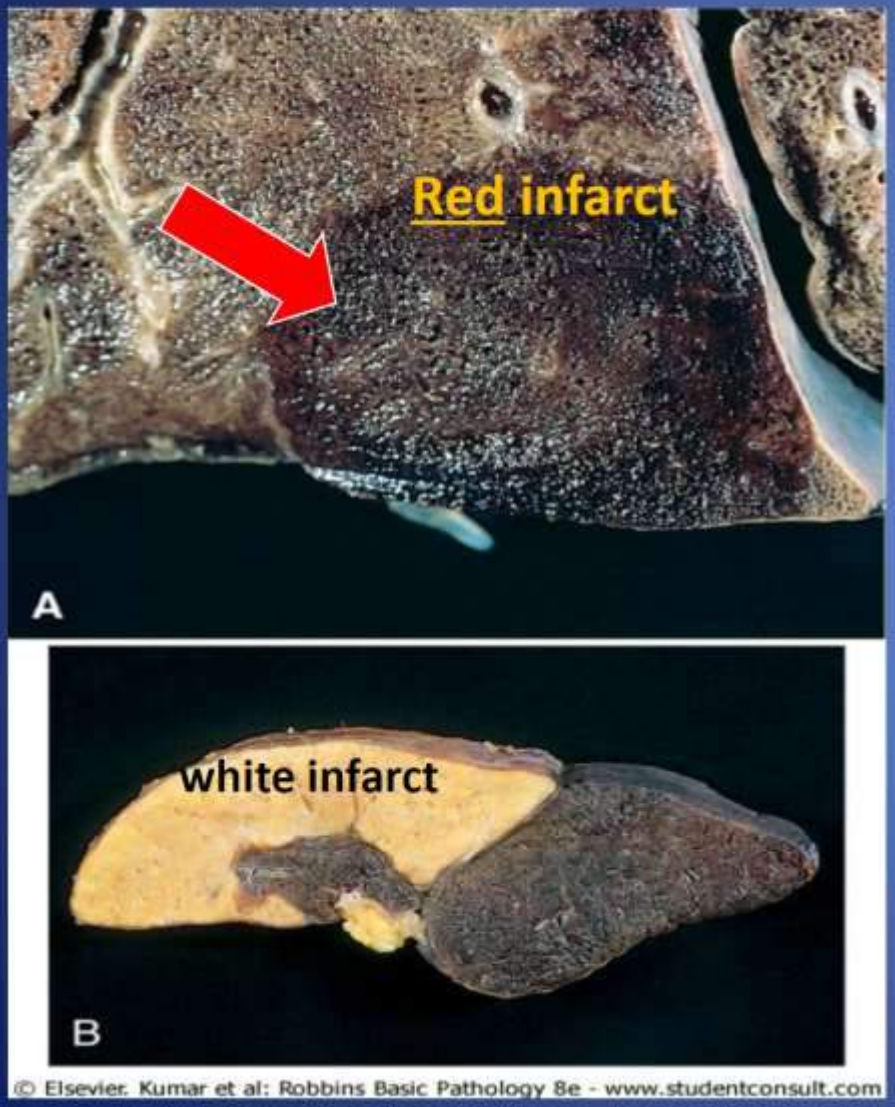



Fig. 55 : A, Hemorrhagic wedge-shaped **pulmonary (red infarct).**

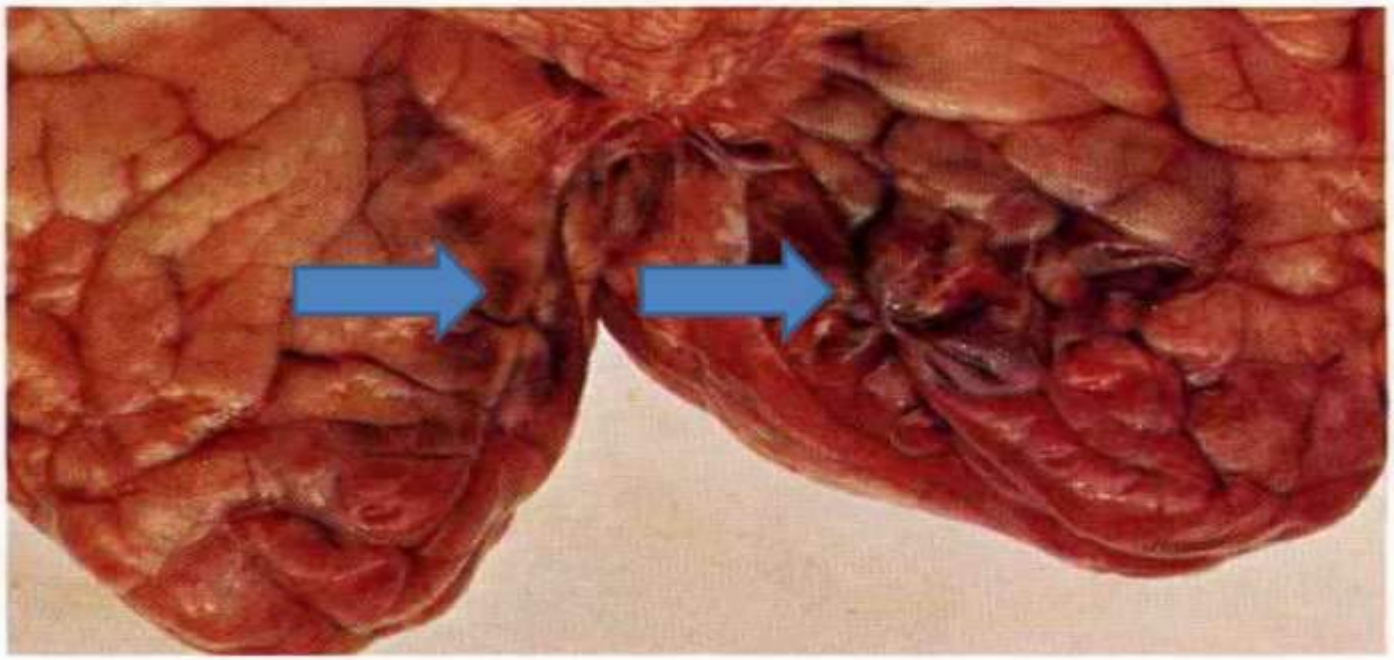
B, Sharply demarcated pale infarct in the **spleen (white infarct).**

# Infarction

- Infarcts tend to be wedge-shaped, with the occluded vessel at the apex and the organ periphery forming the base

- The main histologic finding: **ischemic coagulative necrosis, except the brain, in which liquefactive necrosis occurs.**

F 56 : Infarction: Brain. The patient had tentorial herniation obstructing the posterior cerebral arteries, which results in recent hemorrhagic infarction of the infero-medial aspects of both occipital lobes .



9.47 Infarction: brain

# Shock

- Definition: Systemic hypoperfusion and reduced oxygen delivery due to either reduced cardiac output, or ineffective circulatory blood volume.
- is a life-threatening medical condition and is a medical emergency. If shock is suspected call 911 or get to an emergency department immediately.
- Results of shock:
  - Hypotension,impaired tissue perfusion.cellular hypoxia.
    - The main symptom of shock is low blood pressure. Other symptoms include rapid, shallow breathing; cold, clammy skin; rapid, weak pulse; dizziness, fainting, or weakness.

# Major types of shock

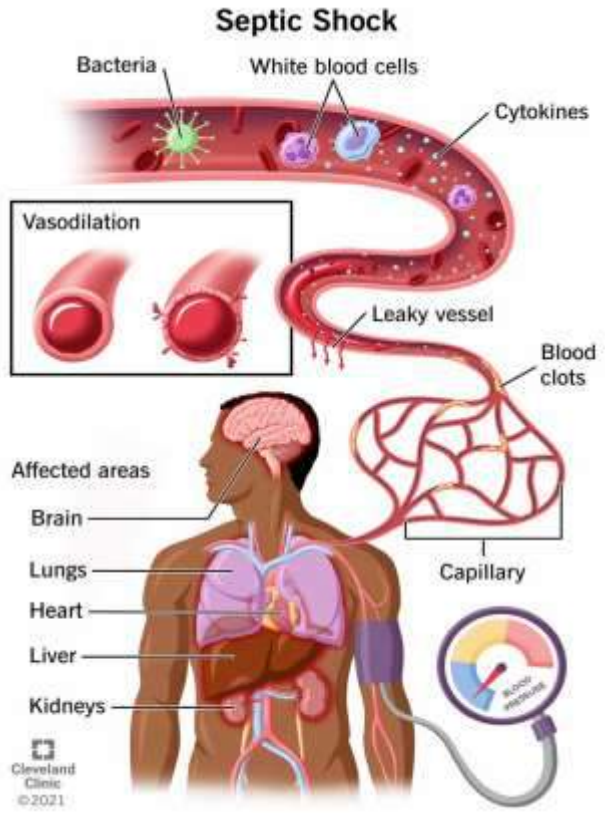
- **Cardiogenic shock:** results from low cardiac output due to myocardial pump failure.
- **Hypovolemic shock:** results from low cardiac output due to loss of blood or plasma volume (e.g., due to hemorrhage or fluid loss from severe burns).
- **Anaphylactic shock ,** caused by hypersensitivity or allergic reaction
- **Neurogenic shock,** **Neurogenic shock** is caused by spinal cord injury, usually as a result of a traumatic accident or injury.
- **Septic shock**

# Vasovagal syncope

- Vasovagal syncope is the most common cause of fainting.
- It happens when the blood vessels open too wide or the heartbeat slows, causing a temporary lack of blood flow to the brain.
- It's generally not a dangerous condition. To prevent fainting, stay out of hot places and don't stand for long periods.

# Septic shock

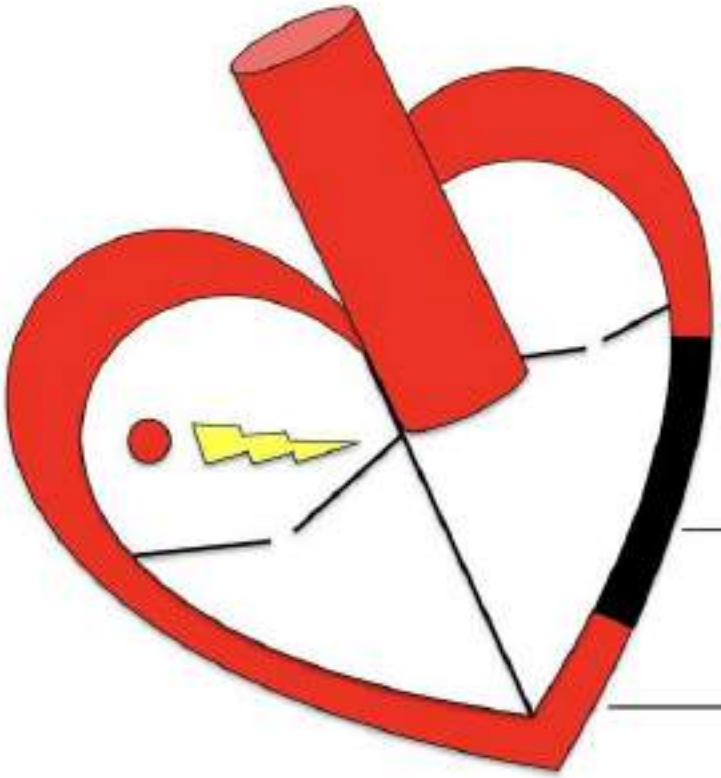
- High mortality rate
- is a life-threatening condition that happens when your blood pressure drops to a dangerously low level after an infection. Any type of bacteria can cause the infection.
- **Gram-positive bacteria** constitute the most common cause of septic shock, followed by gram-negative organisms and fungi.
- **Systemic arterial and venous dilation leads to tissue hypoperfusion**.
- Septic shock is the last and most severe stage of sepsis. Sepsis occurs when your immune system has an extreme reaction to an infection. The inflammation throughout your body can cause dangerously low blood pressure. You need immediate treatment if you have septic shock. Treatment may include antibiotics, oxygen and medication.



# Septic shock

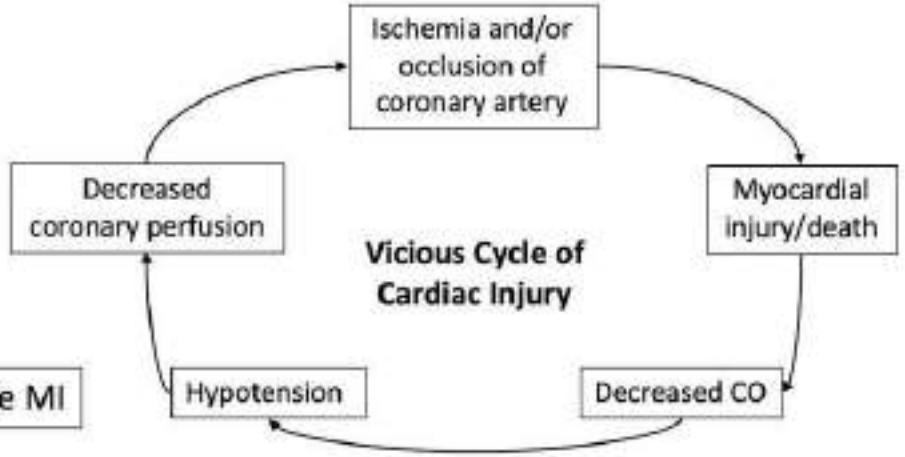
- Pathogenesis :An inflammatory stimulus (eg, a bacterial toxin) triggers production of pro-inflammatory mediators, including tumor necrosis factor (TNF) and interleukin (IL)-1.
- The septic response may accelerate due to continued activation of neutrophils and macrophages/monocytes.
- Upregulation of lymphocyte molecules and rapid lymphocyte apoptosis, delayed apoptosis of neutrophils, and enhanced necrosis of cells/tissues also contribute to the pathogenesis of sepsis.

# Cardiogenic Shock

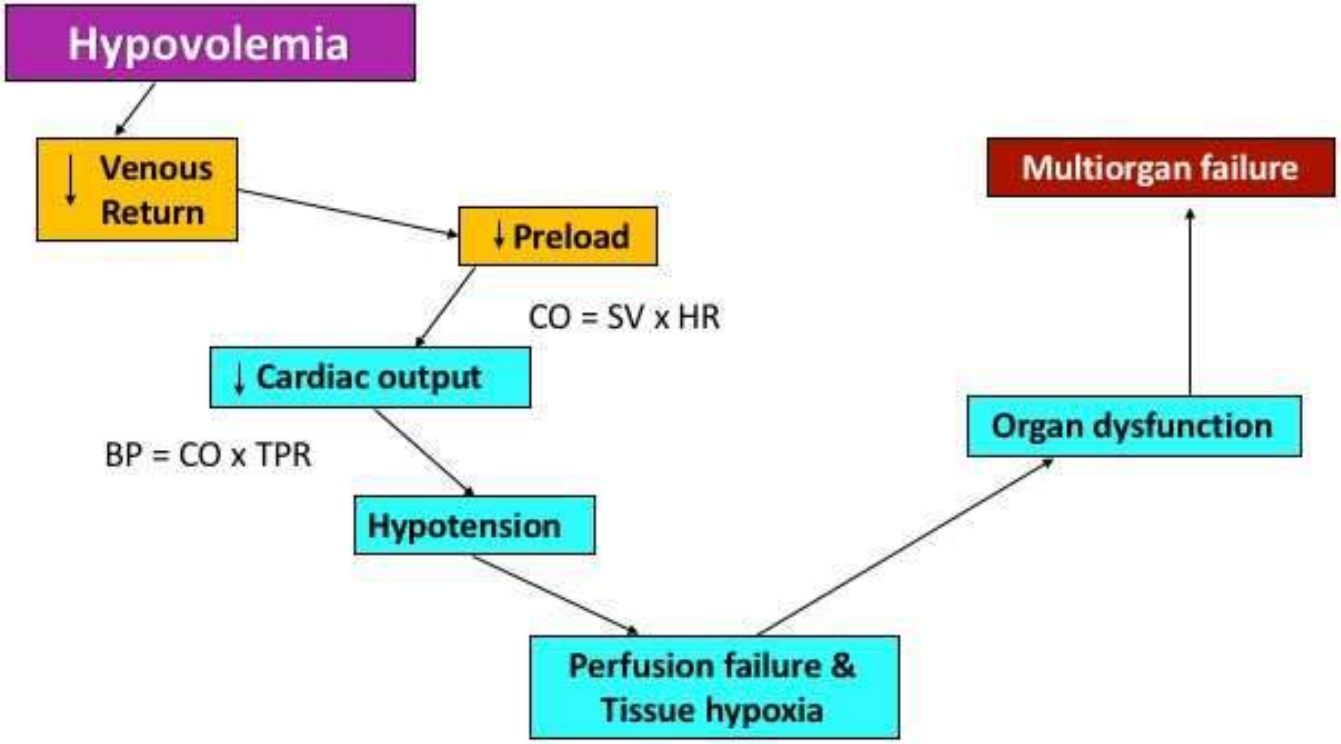


Acute MI

Acute Decompensated HF
Cardiomyopathy
Myocarditis



# Pathophysiology of Hypovolemic shock



# Stages of Shock

Shock is a progressive disorder that leads to death if the underlying problems are not corrected

- **Non-progressive phase: Compensatory mechanisms maintains perfusion of vital organs.**
- **Progressive phase: Tissue hypoperfusion with metabolic and circulatory worsening.**
- **Irreversible stage: Severe irreversible tissue and cellular injury** that even if the hemodynamic defects are corrected, survival is not possible

- The clinical manifestations of shock depend on the precipitating insult.
- **In hypovolemic and cardiogenic shock:** hypotension, a weak rapid pulse, tachypnea, and cool, cyanotic skin.
- **In septic shock:** the skin may be warm and flushed owing to peripheral vasodilation.
- Prognosis varies with the origin of shock and its duration.
- More than 90% of young, healthy patients with hypovolemic shock survive with appropriate management
- Septic or cardiogenic shock is associated with substantially worse outcomes

# Treatment

- Septic shock is treated with antibiotics and fluids.
- Anaphylactic shock is treated with diphenhydramine (Benadryl), epinephrine (an "Epi-pen"), and steroid medications (solumedrol).
- Cardiogenic shock is treated by identifying and treating the underlying cause.
- Hypovolemic shock is treated with fluids (saline) in minor cases, and blood transfusions in severe cases.
- Neurogenic shock is the most difficult to treat as spinal cord damage is often irreversible. Immobilization, anti-inflammatories such as steroids and surgery are the main treatments.
- Shock prevention includes learning ways to prevent heart disease, injuries, dehydration, and other causes of shock.