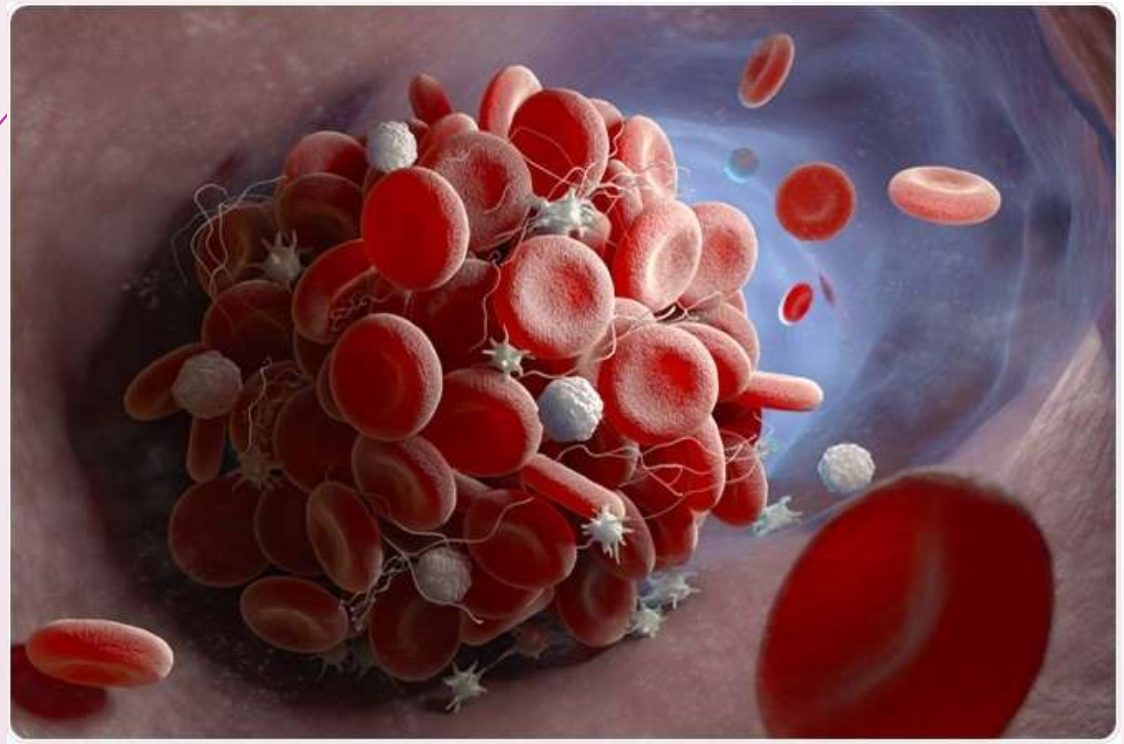
Hemodynamic Disorders, Thromboembolism, and Shock



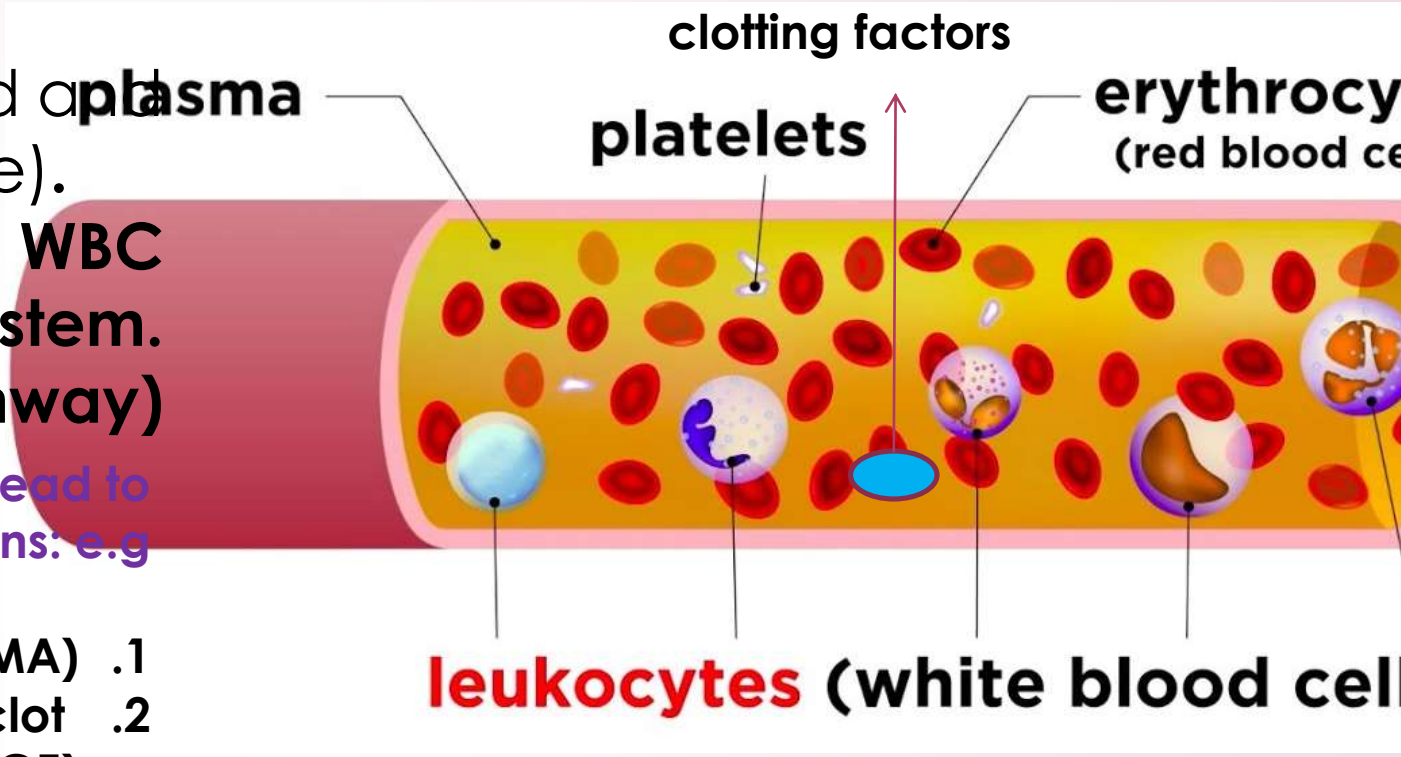
Izzat Al Jaberi ,M.D.

Composition of blood

1. plasma protein (Fluid and electrolyte).

2. RBC. Platelets, WBC

3. Haemostatic system. (clotting pathway)



So any disturbances in these processes lead to pathological conditions: e.g

Defect in Fluid and electrolyte balance(EDEMA) .1

damage to blood vessels or defective clot formation (HEMORRHAGE) .2

Disturbance in clotting pathway led to either : .3

- **Hemorrhage.**
- **thromboembolism**

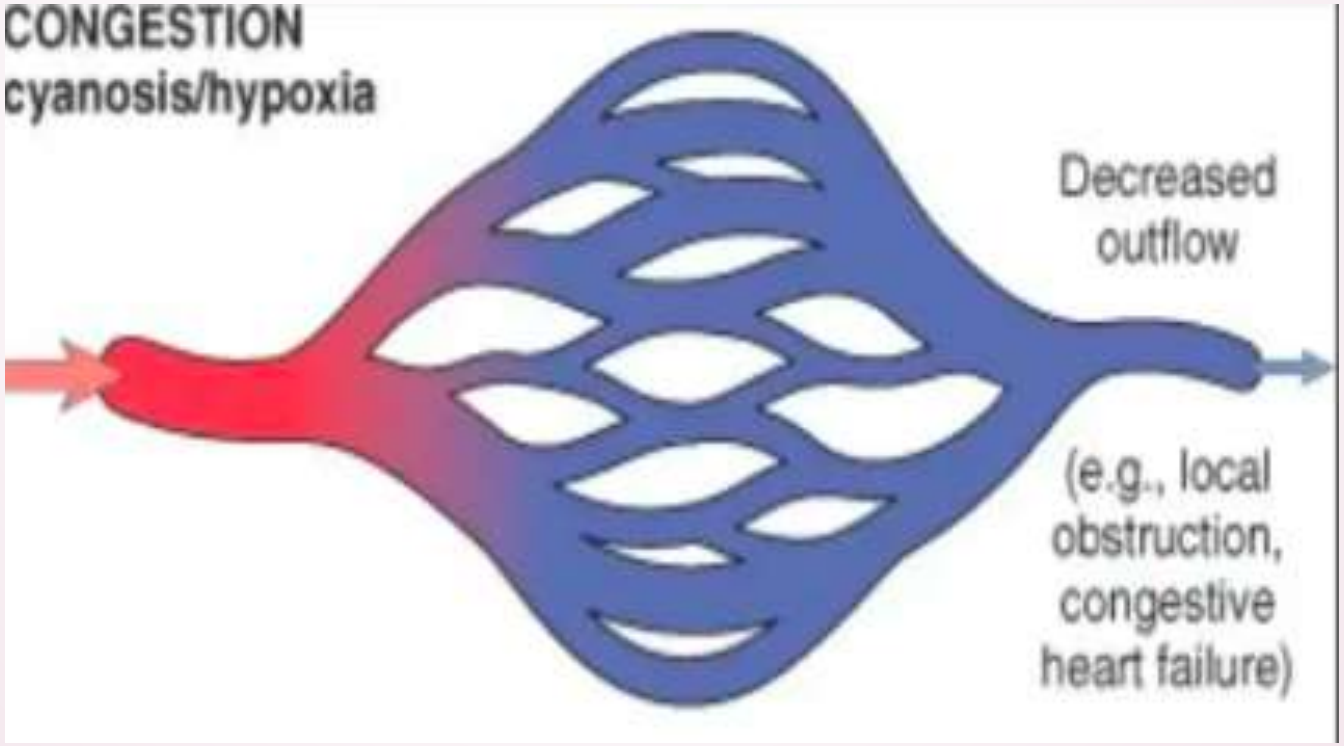
So clinically we have:

- 1. fluid and electrolytes disturbance :
  - increased volume : **HYPEREMIA AND CONGESTION**
  - abnormal distribution : **EDEMA**
  - Decreased volume:
    - **INFARCTION.**
    - **Shock**
- 2. Inadequate hemostasis :
  - **HEMORRHAGE**
  - **THROMBOSIS and EMBOLISM**
- 3. disturbance in RBC:
  - extravasation from vessels: **HEMORRHAGE.**

1. HYPEREMIA AND CONGESTION

- **Hyperemia and congestion both refer to an increase in blood volume within a tissue.**
- **Hyperemia is an active process resulting from arteriolar dilation and increased blood inflow, as occurs at sites of inflammation or in exercising skeletal muscle.**

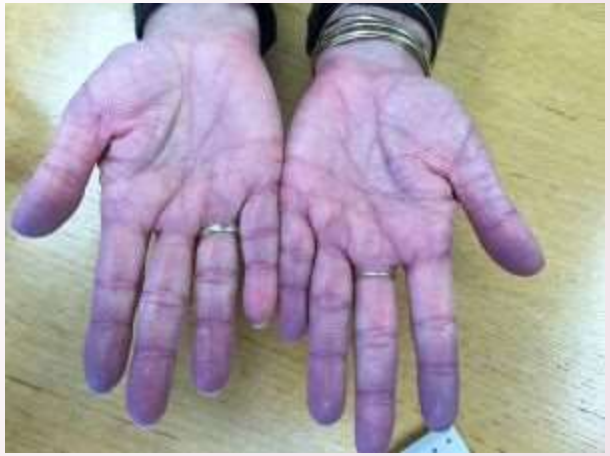
- Congestion is a passive process resulting from impaired outflow of venous blood from a tissue.
- It can occur systemically, as in cardiac failure, or locally as a consequence of an isolated venous obstruction.



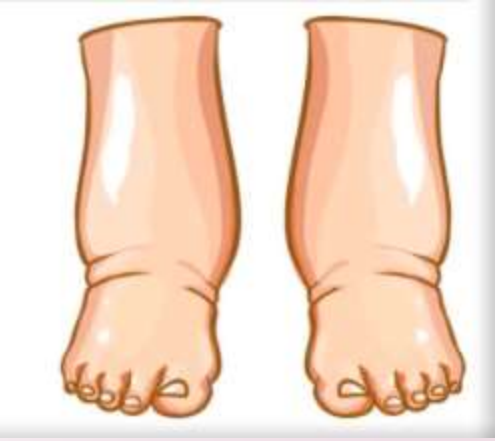
Clinically

Hyperemic tissues are redder than normal because of engorgement with oxygenated blood

Congested tissues have an abnormal blue-red color (cyanosis) that stems from the accumulation of deoxygenated hemoglobin in the affected area.



2.

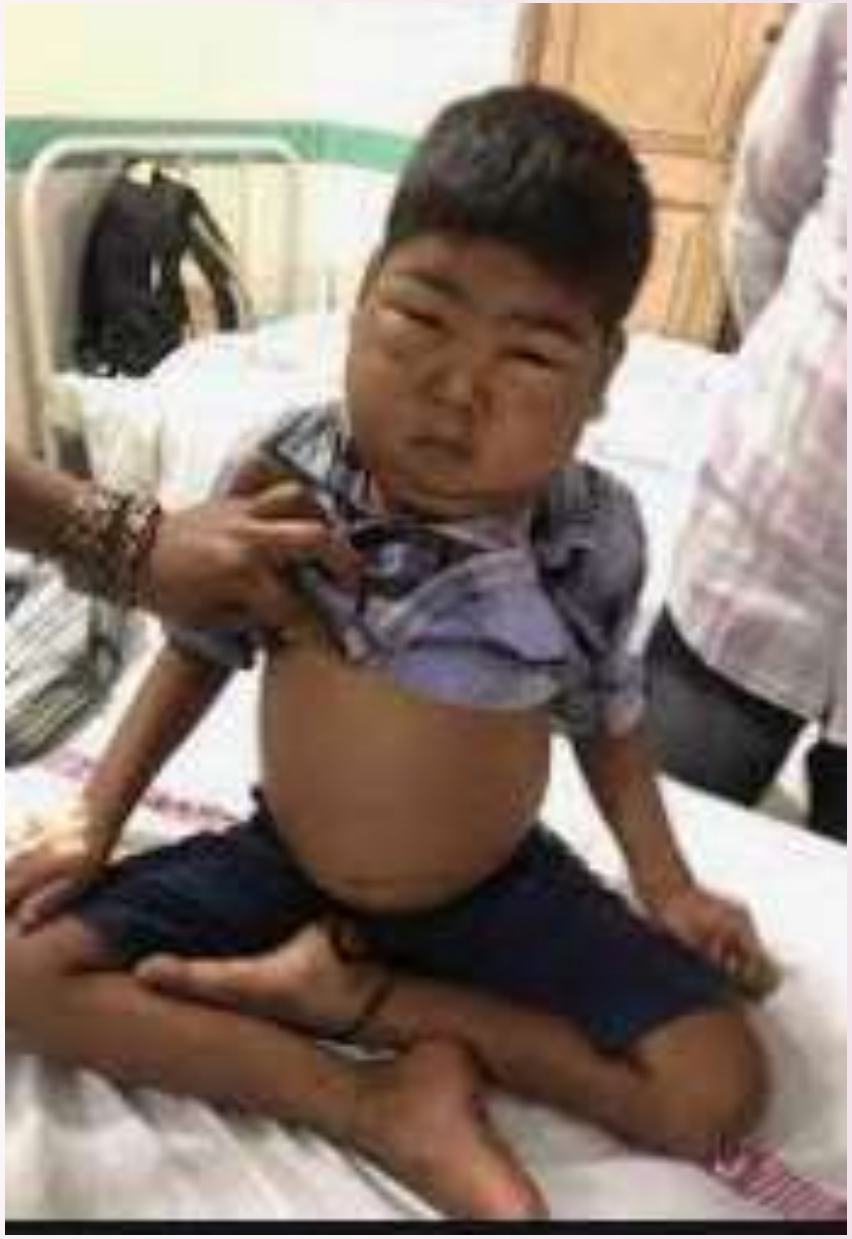


- is an accumulation of interstitial fluid within **tissues** and **subcutaneously**.
- Extravascular fluid can also collect in **body cavities** and such accumulations are often referred to collectively as effusions.

- Examples include:
- effusions in the pleural cavity (hydrothorax).
- the pericardial cavity (hydropericardium).
- the peritoneal cavity (hydroperitoneum, or ascites).

- Anasarca is severe, generalized edema marked by profound swelling of subcutaneous tissues and accumulation of fluid in body cavities.

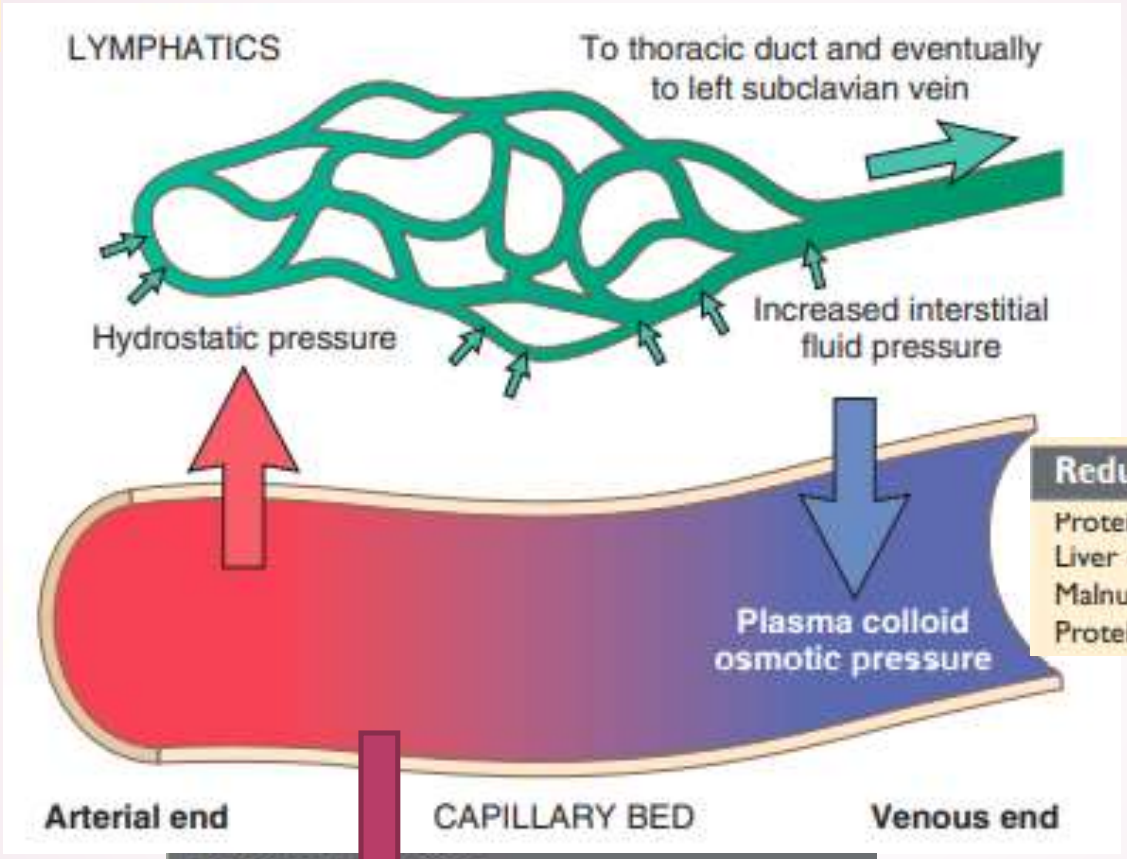
Anasarca is a medical condition that leads to general swelling of the whole body



Causes of Edema❖

Lymphatic Obstruction

Inflammatory
Neoplastic
Postsurgical
Postirradiation



Reduced Plasma Osmotic Pressure (Hypoproteinemia)

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

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

Sodium Retention

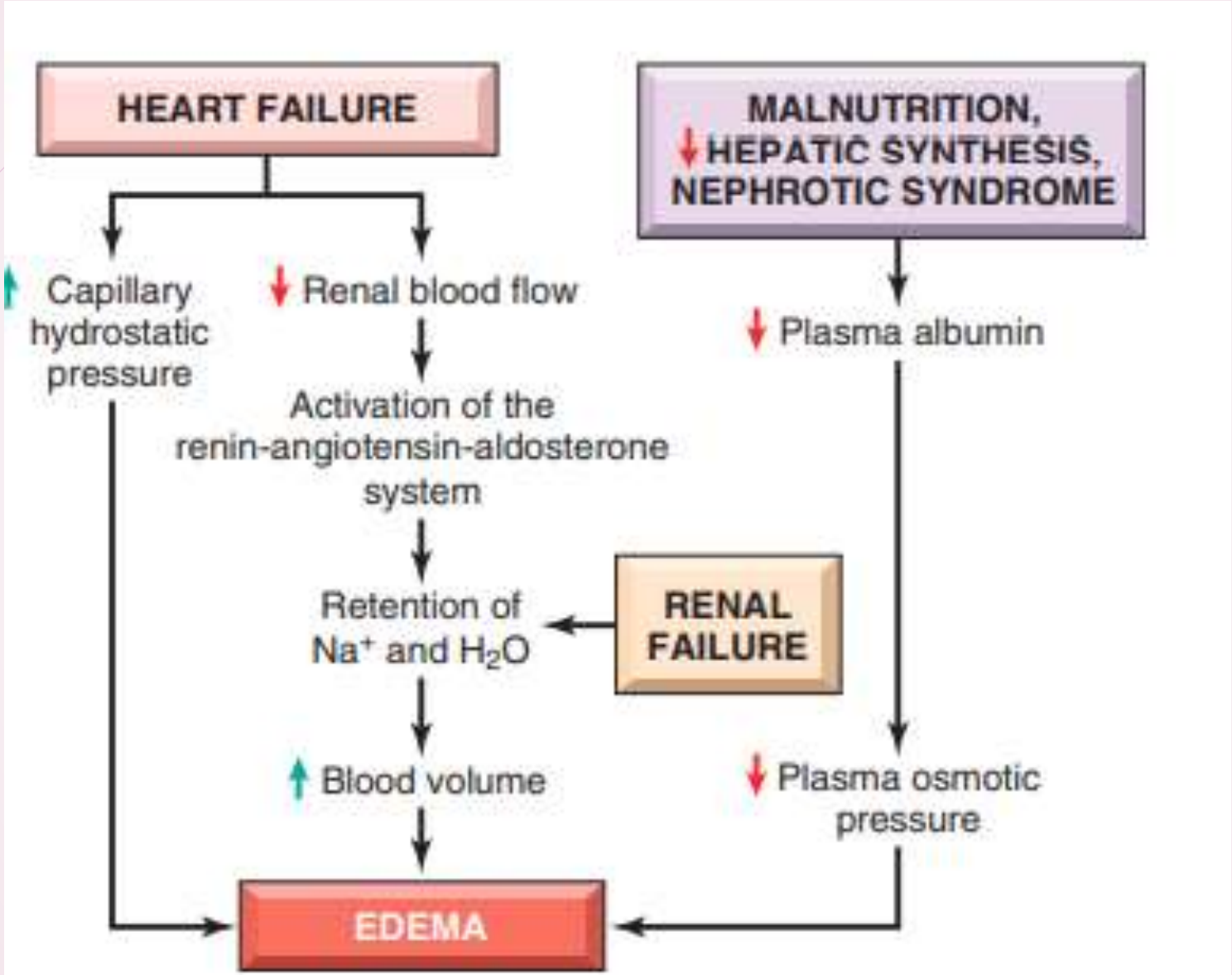
Excessive salt intake with renal insufficiency
Increased tubular reabsorption of sodium
Renal hypoperfusion
Increased renin-angiotensin-**aldosterone** secretion

Table 4.1 Causes of Edema

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
Sodium Retention
Excessive salt intake with renal insufficiency
Increased tubular reabsorption of sodium
Renal hypoperfusion
Increased renin-angiotensin-**aldosterone** secretion
Inflammation
Acute inflammation
Chronic inflammation
Angiogenesis

Mechanisms of edema

- **1. Increased Hydrostatic Pressure:**
- Increases in hydrostatic pressure are mainly caused by disorders that impair venous return, either :
- Localized: e.g deep venous thrombosis.
- Generalized increases in venous pressure: e.g congestive heart failure.


HEART FAILURE
MALNUTRITION,
↓HEPATIC SYNTHESIS,
NEPHROTIC SYNDROME
↑ Capillary hydrostatic pressure
↓ Renal blood flow
↓ Plasma albumin
Activation of the renin-angiotensin-aldosterone system
Retention of Na^+ and H_2O
RENAL FAILURE
↑ Blood volume
↓ Plasma osmotic pressure
EDEMA

Increased Hydrostatic Pressure ❖

reduced cardiac output leads to ➨

systemic venous congestion ➨

lead to increase in capillary hydrostatic pressure. ➨

reduction in cardiac output results in ➨

hypoperfusion of the kidneys, ➨

triggering the renin-angiotensin-aldosterone axis ➨

and inducing sodium and water retention (secondary ➨ hyperaldosteronism

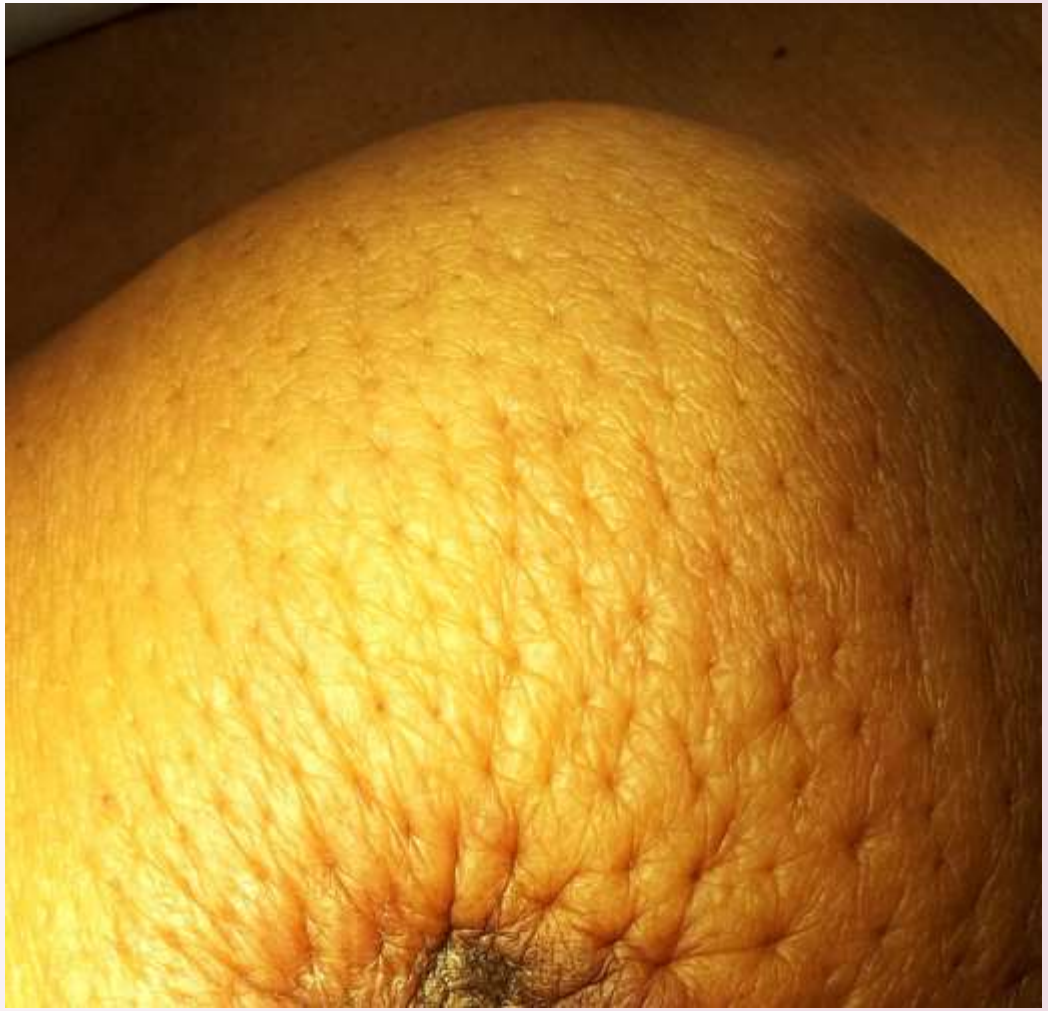
2. **Reduced Plasma Osmotic Pressure**

- Reduction of plasma albumin concentrations leads to decreased colloid osmotic pressure of the blood and loss of fluid from the circulation.
- albumin accounts for almost half of the total plasma protein.
- common causes of reduced plasma osmotic pressure:
  - lost from the circulation: e.g Nephrotic syndrome
  - synthesis of inadequate amounts: e.g severe liver disease (e.g., cirrhosis) and protein malnutrition.

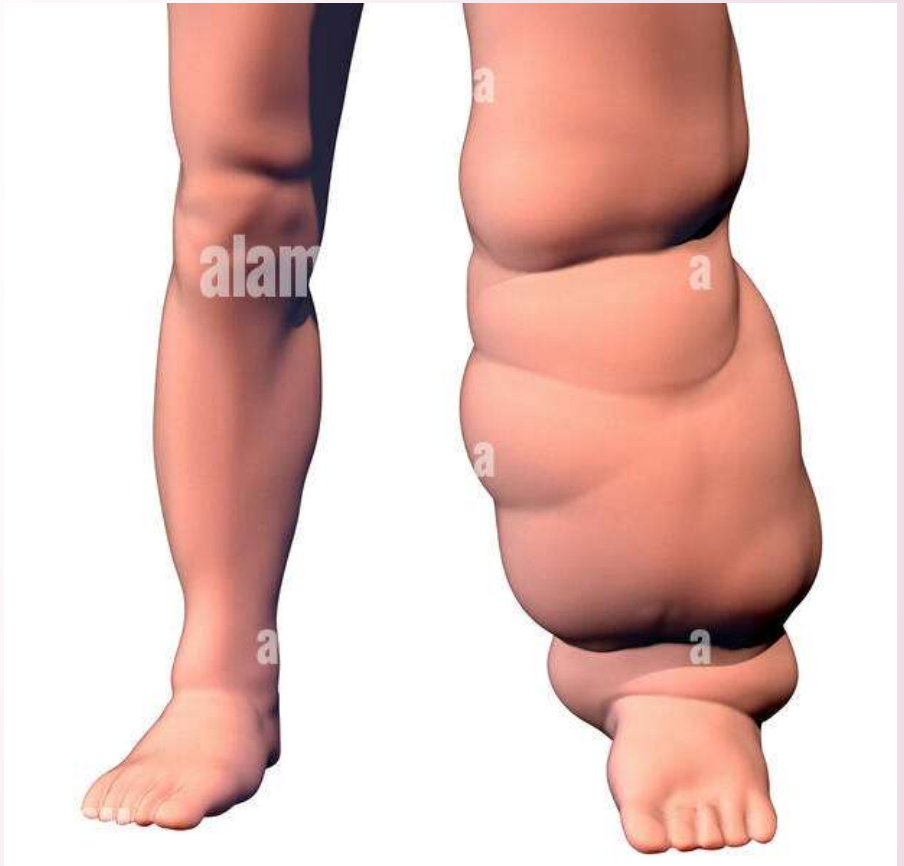
3. Lymphatic Obstruction

- Edema may result from lymphatic obstruction that compromises resorption of fluid from interstitial space.
- results from a localized obstruction caused by an inflammatory or neoplastic condition.

Infiltration and obstruction of superficial lymphatics by breast cancer may cause edema of the overlying skin; the characteristic finely pitted appearance of the skin of the affected breast is called peau d'orange (orange peel).



the parasitic infection filariasis can cause massive edema of the lower extremity and external genitalia (so-called “elephantiasis.

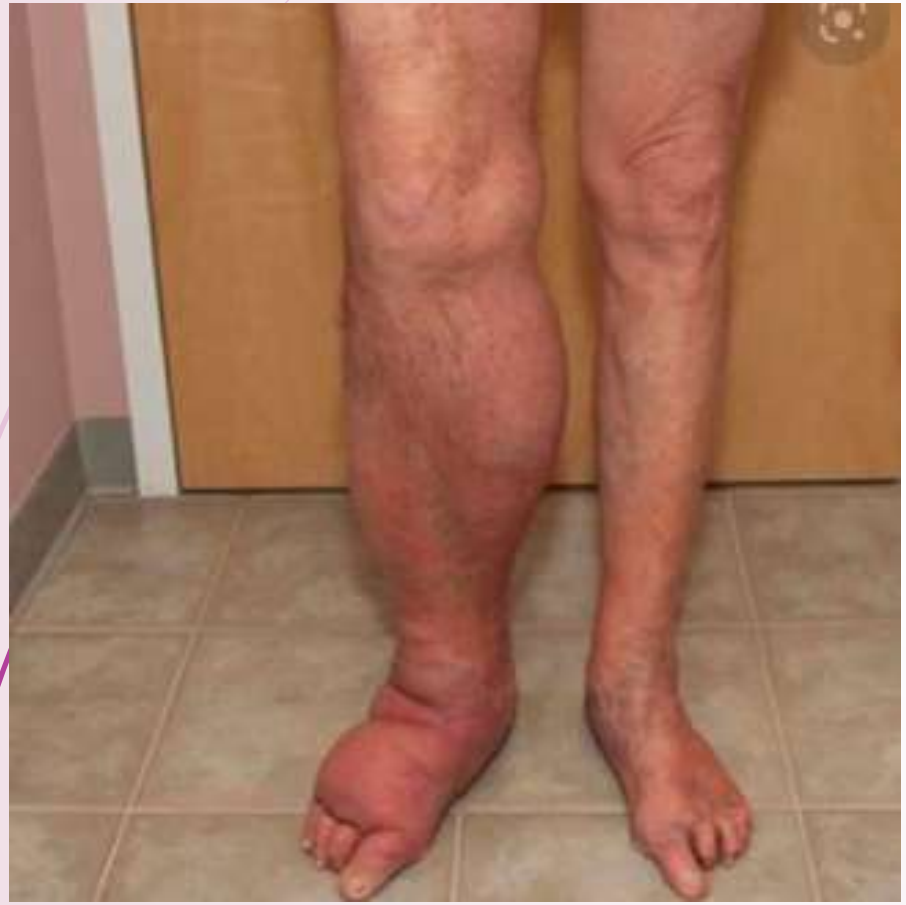


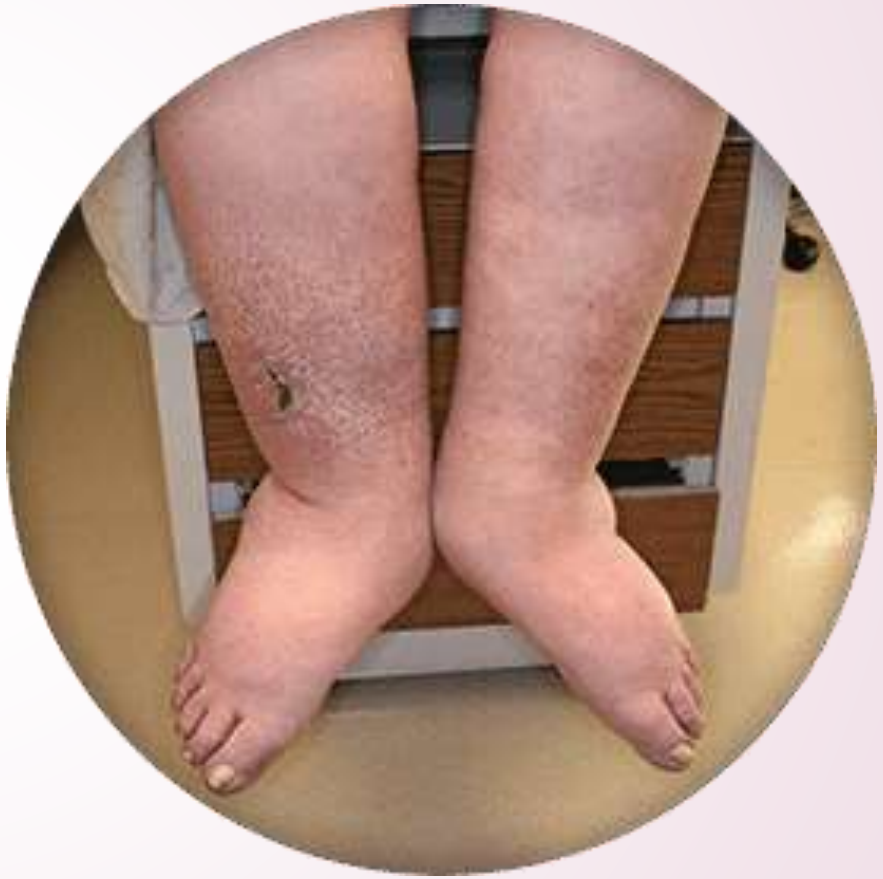
4. Sodium and Water Retention

- Excessive retention of salt lead to edema by increasing hydrostatic pressure (because of expansion of the intravascular volume) and reducing plasma osmotic pressure.

- Excessive salt and water retention are seen in a wide variety of diseases that compromise renal function, including poststreptococcal glomerulonephritis and acute renal failure.

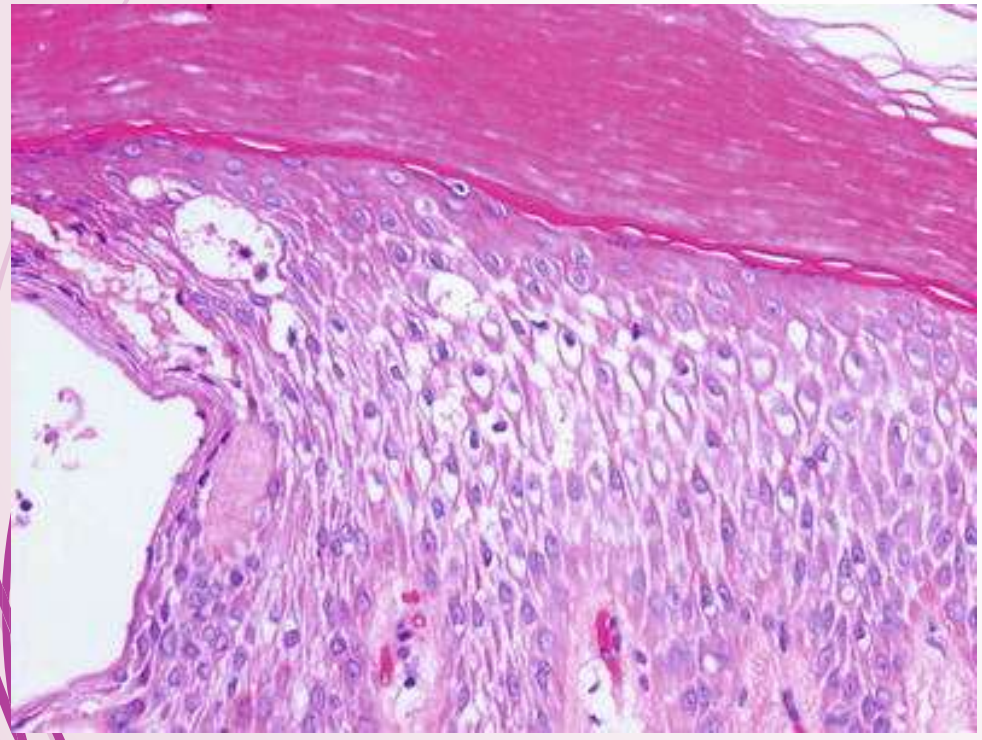
Edema is easily recognized on gross inspection;

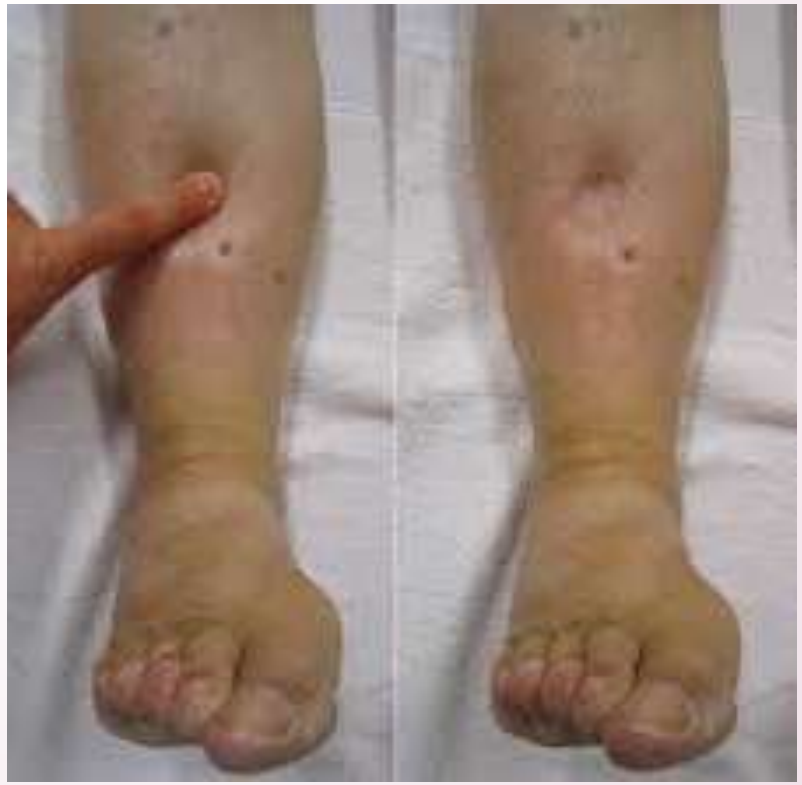




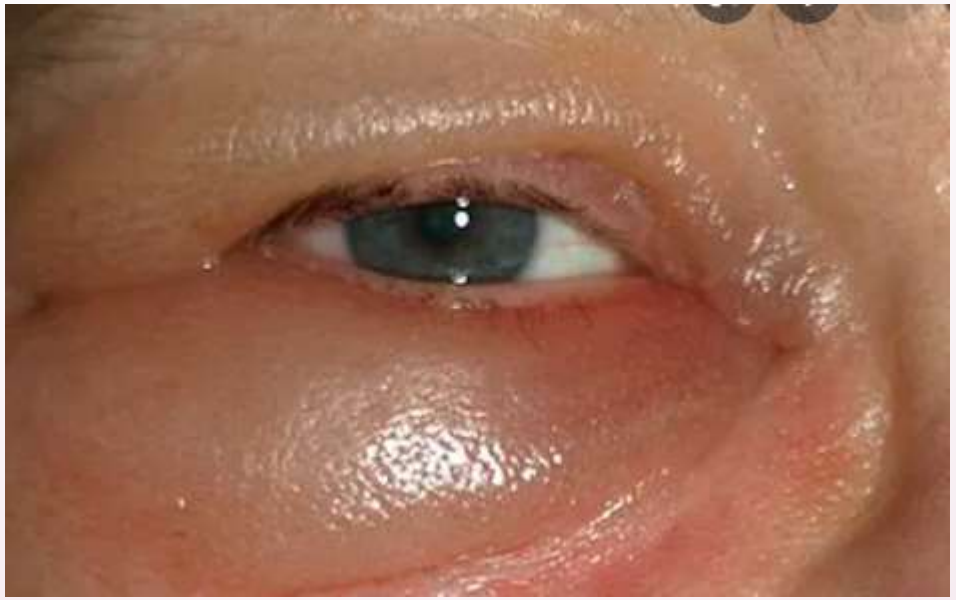
microscopic examination:

- 1.skin : clearing and separation of the extracellular matrix
- Subcutaneous edema can be diffuse but usually accumulates preferentially in the legs with standing and the sacrum with recumbency, a relationship termed dependent edema.
- Finger pressure over edematous subcutaneous tissue displaces the interstitial fluid, leaving a finger-shaped depression; this appearance is **called pitting edema**





- Edema resulting from renal dysfunction or nephrotic syndrome often manifests first in loose connective tissues (e.g., the eyelids, causing periorbital edema).



Clinical Features

Subcutaneous edema :

- is important to recognize primarily because it signals potential underlying cardiac or renal disease.
- when significant, it also can impair wound healing and the clearance of infections.

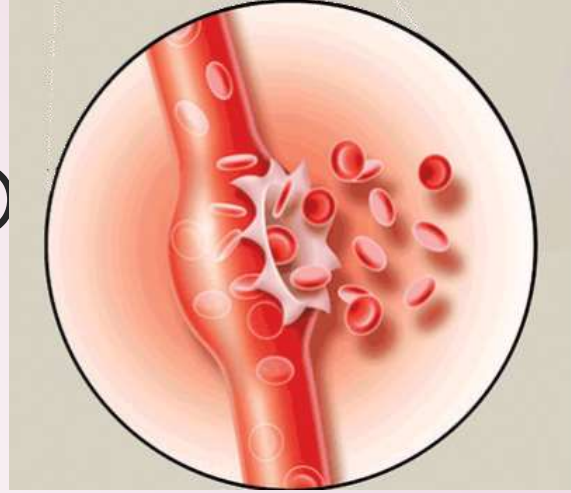
Pulmonary edema:

- It can cause death by interfering with normal ventilatory function; besides impeding oxygen diffusion, alveolar edema fluid also creates a favorable environment for infections..

Brain edema:

- Is life threatening; if the swelling is severe, the brain can herniate (extrude) through the foramen magnum pressure, the brain stem vascular supply can be compressed, leading to death due to injury to the medullary centers controlling respiration and other vital functions .

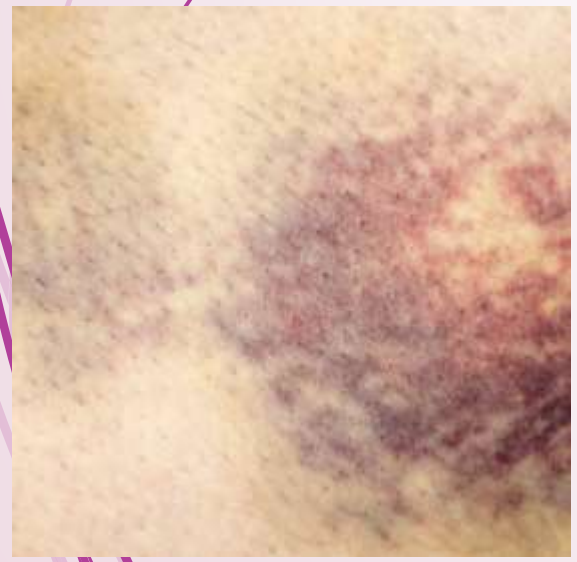
II. HEMO



- extravasation of blood from vessels, is most often the result of damage to blood vessels or defective clot formation.
- Trauma, atherosclerosis, or inflammatory or neoplastic erosion of a vessel wall also may lead to hemorrhage,
- hemorrhagic diatheses:

Hemorrhage may be manifested by different appearances and clinical consequences.

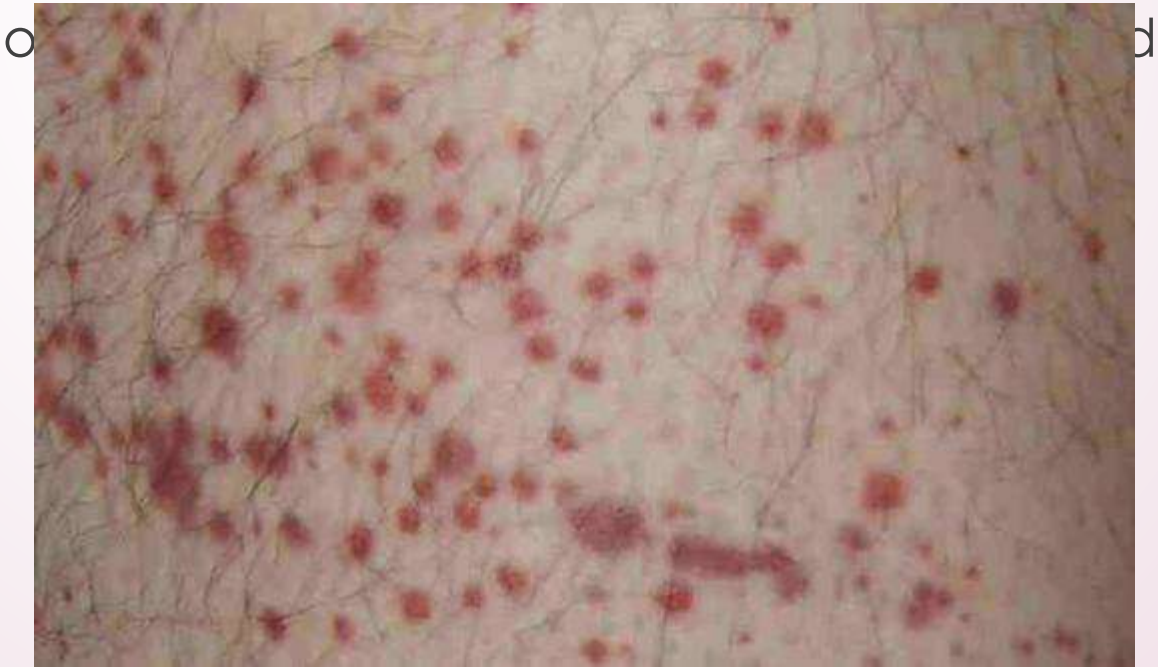
- Hemorrhage may be external or accumulate within a tissue as a hematoma,
- May ranges in significance from trivial (e.g., a bruise) to fatal (e.g., a massive retroperitoneal hematoma resulting from rupture of a dissecting aortic aneurysm.
- Extensive hemorrhages can occasionally result in jaundice from the massive breakdown of red cells and hemoglobin.



Subcutaneous bleeding my present as

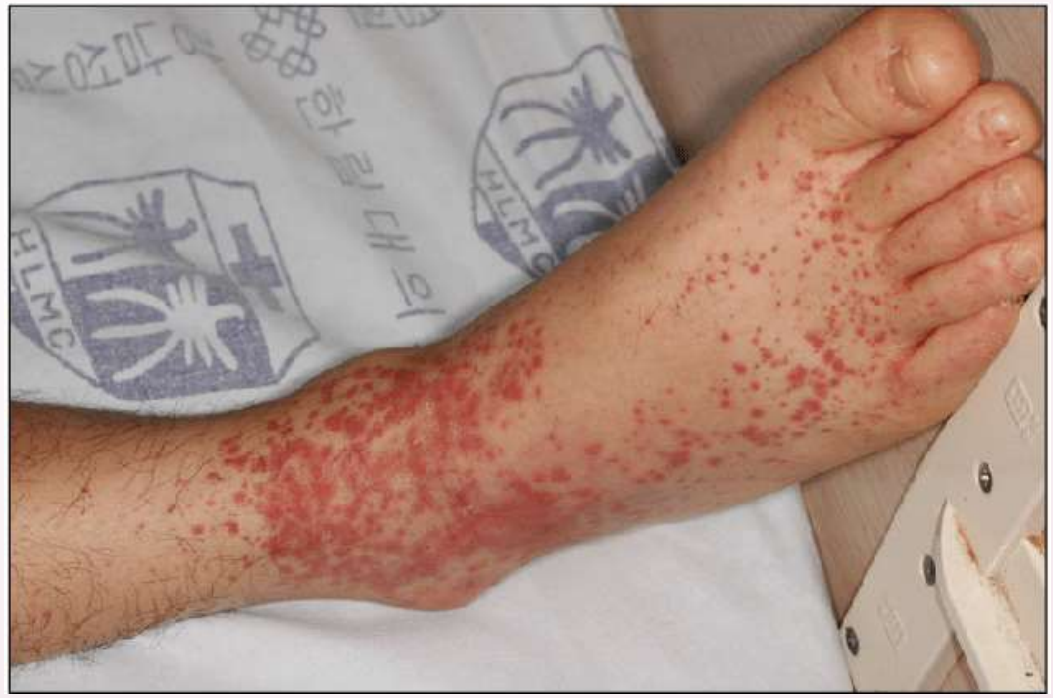
Defects in primary hemostasis:

- **1. Petechiae :**
- are minute (1 to 2 mm in diameter) hemorrhages into skin, mucous membranes, or serosal surfaces
- Causes
- low platelet counts (thrombocytopenia).
- defective platelet function.
- lo deficiency.



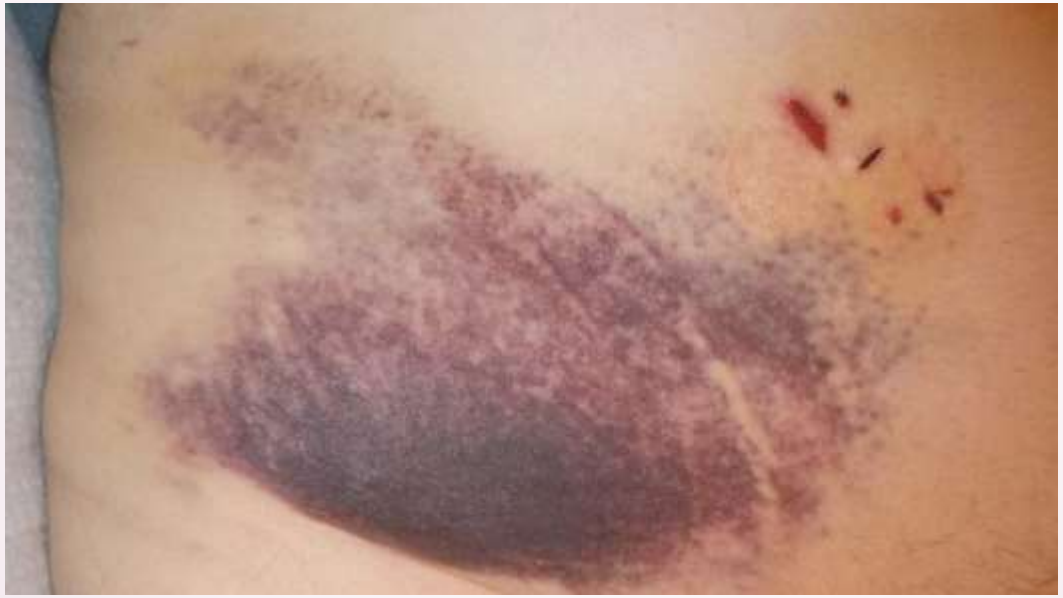
2. Purpura

- are slightly larger (3 to 5 mm) hemorrhages.
- Purpura can result from the same disorders that cause petechiae, as well as:
- trauma.
- vascular inflammation (vasculitis).
- increased vascular fragility.



3.Ecchymoses:

- are larger (1 to 2 cm) subcutaneous hematomas (also called bruises).
- Extravasated red cells are phagocytosed and degraded by macrophages; the characteristic color changes of a bruise result from the enzymatic conversion of hemoglobin (red-blue color) to bilirubin (blue-green color) and eventually hemosiderin (golden-brown)



- The clinical significance of any particular hemorrhage depends on:
  - the volume of blood that is lost. ✓
  - the rate of bleeding. ✓

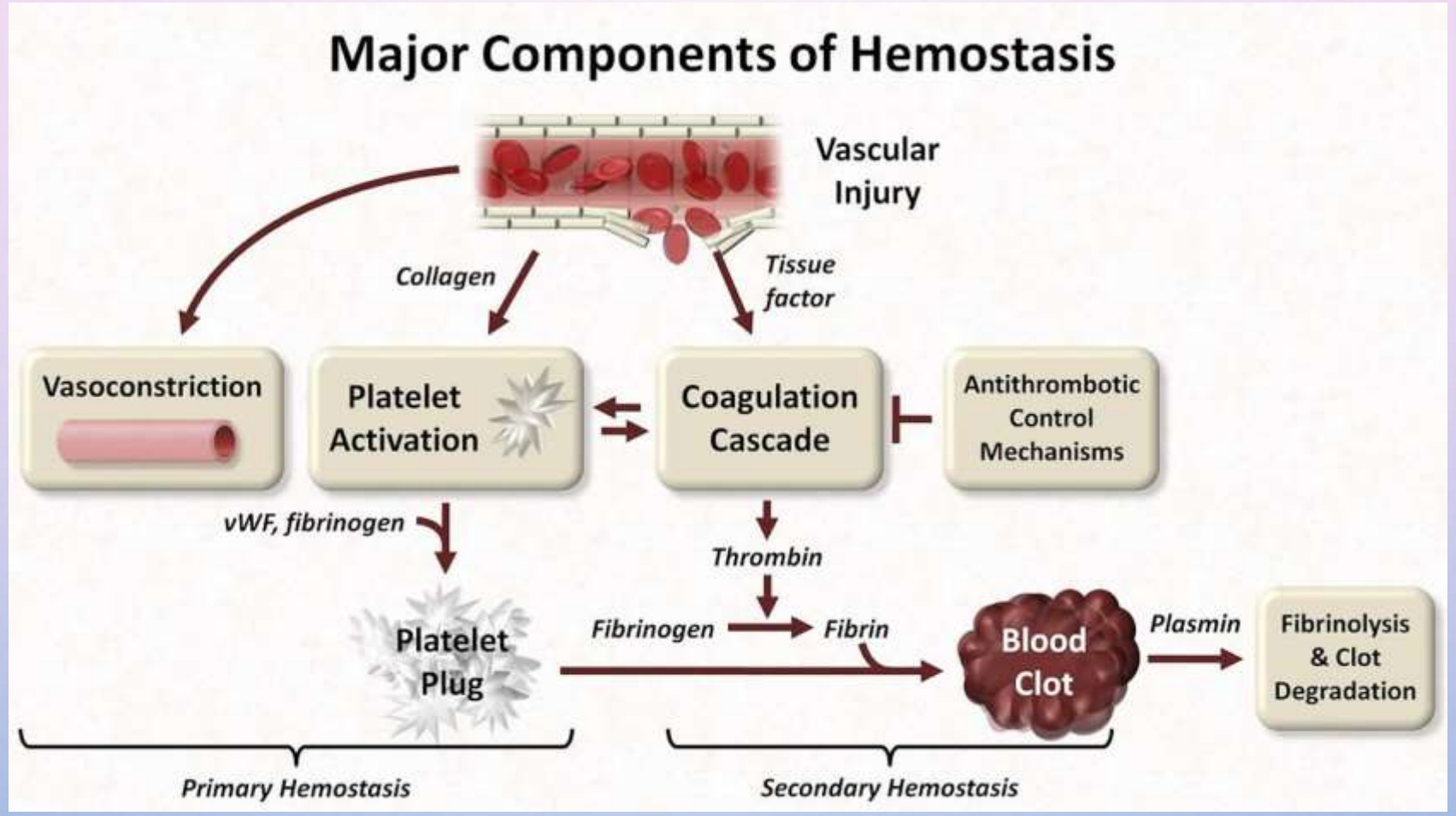
HEMOSTASIS AND THROMBOSIS

- NORMAL HEMOSTASIS COMPRISES A SERIES OF REGULATED PROCESSES THAT CULMINATE IN THE FORMATION OF A BLOOD CLOT THAT LIMITS BLEEDING FROM AN INJURED VESSEL.

- THE PATHOLOGIC COUNTERPART OF HEMOSTASIS IS THROMBOSIS, THE FORMATION OF BLOOD CLOT (THROMBUS) WITHIN NON-TRAUMATIZED, INTACT VESSELS.

NORMAL HEMOSTASIS

- HEMOSTASIS IS PROCESS INVOLVING PLATELETS, CLOTTING FACTORS, AND ENDOTHELIUM THAT OCCURS AT THE SITE OF VASCULAR INJURY AND CULMINATES IN THE FORMATION OF A BLOOD CLOT, WHICH SERVES TO PREVENT OR LIMIT THE EXTENT OF BLEEDING.


Major Components of Hemostasis
Vascular Injury
Collagen
Tissue factor
Vasoconstriction
Platelet Activation
Coagulation Cascade
Antithrombotic Control Mechanisms
vWF, fibrinogen
Thrombin
Platelet Plug
Fibrinogen
Fibrin
Blood Clot
Plasmin
Fibrinolysis & Clot Degradation
Primary Hemostasis
Secondary Hemostasis

MAJOR COMPONENT OF HEMOSTASIS

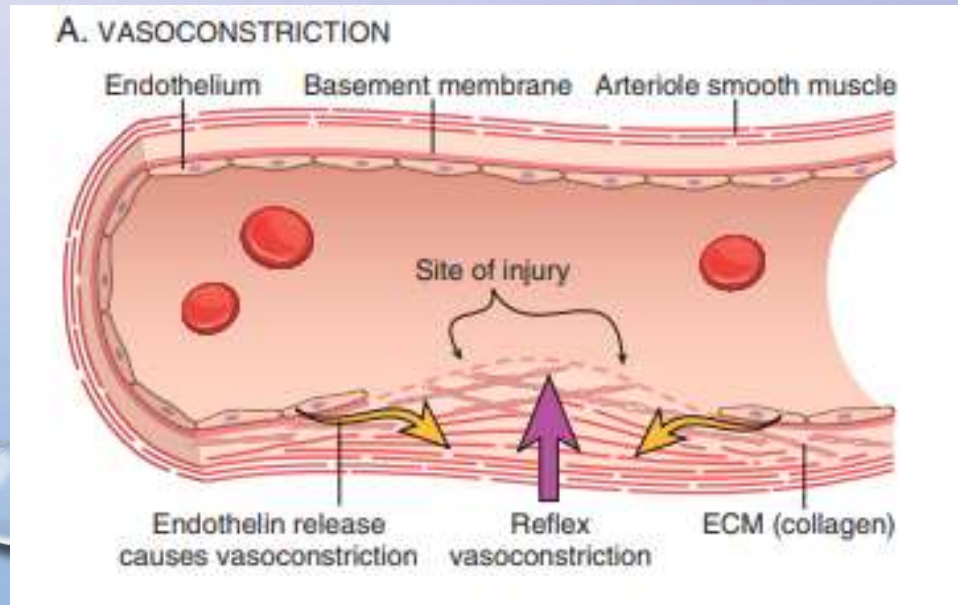
1.platelates

2.Clotting factors

3.Endothelium

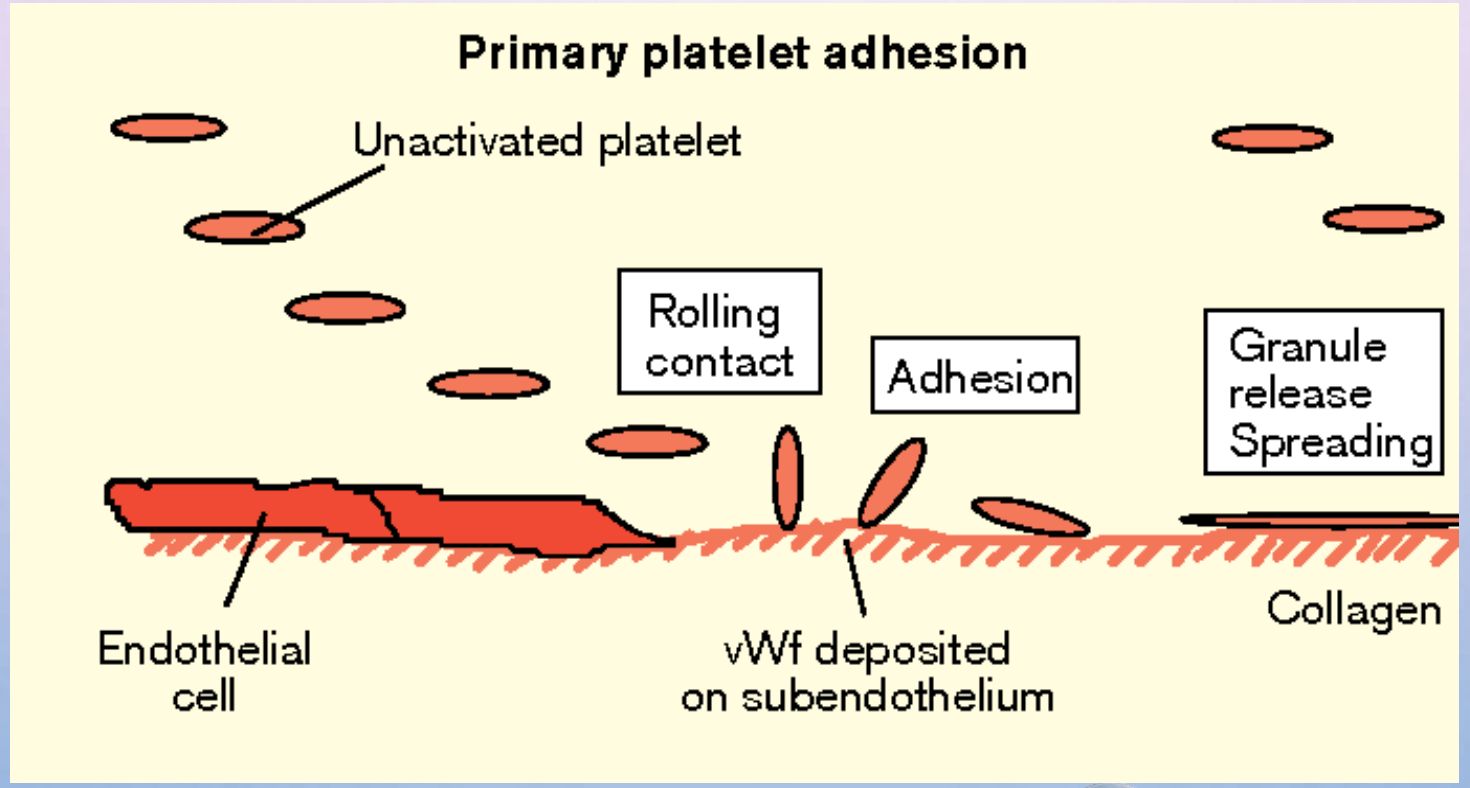
THE GENERAL SEQUENCE OF EVENTS LEADING TO HEMOSTASIS AT A SITE OF VASCULAR INJURY INCLUDE: I . PRIMARY HEMOSTASIS

- 1. ARTERIOLAR VASOCONSTRICTION :
- occurs immediately and markedly reduces blood flow to the injured area.
- it is mediated by reflex neurogenic mechanisms.
- it is augmented by endothelin, a potent endothelium-derived vasoconstrictor.
- this effect is transient, however, bleeding would resume if not followed by activation of platelets



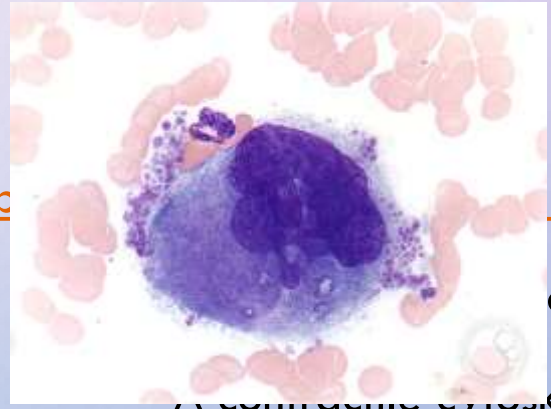
2. PLATELET ACTIVATION

- THE FORMATION OF THE PLATELET PLUG.



PLATELETS

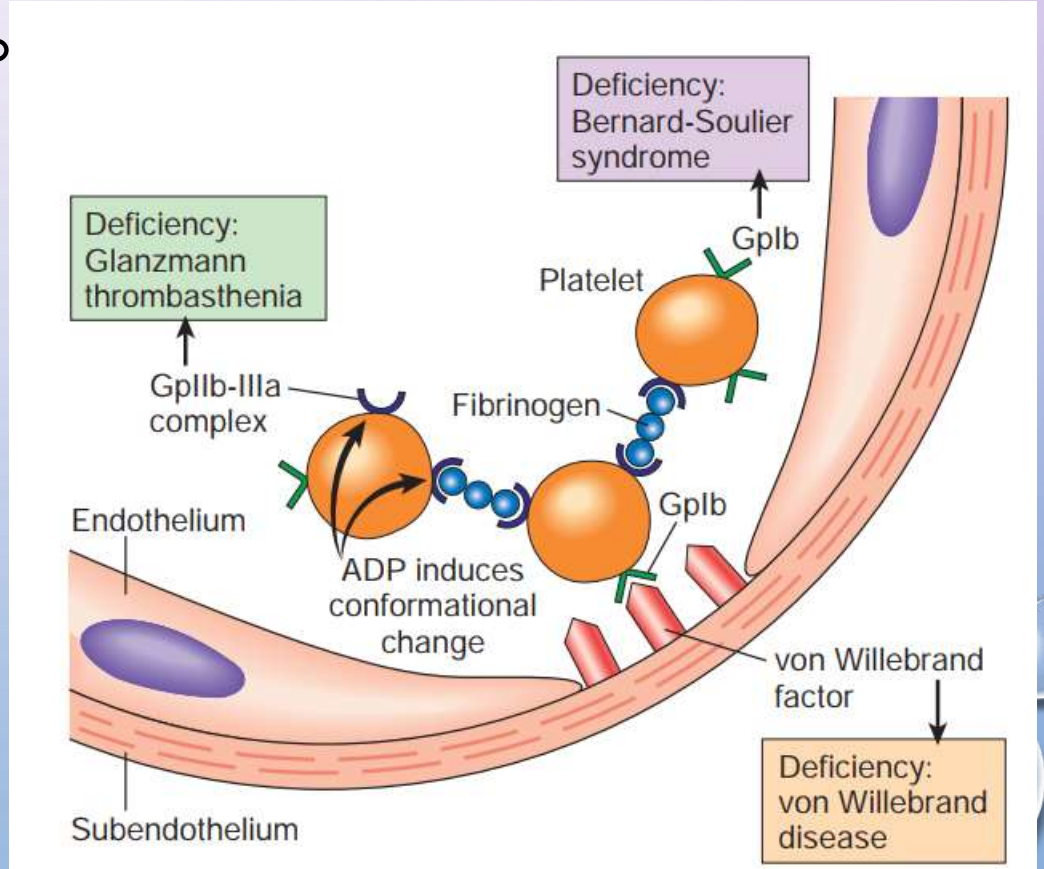
- platelets play a critical role in hemostasis by forming the primary plug that initially seals vascular defects and by providing a surface that binds and concentrates activated coagulation factors.
- platelets are disc-shaped anucleate cell fragments that are shed from megakaryocytes in the bone marrow into the bloodstream.



- Their function dep luding:
- eptors.
- keleton
- Awo types of cytoplasmic granules.
- α-granules have the adhesion molecule p-selectin, and contain proteins involved in coagulation.
- dense (or δ) granules contain ADP and ATP , ionized calcium, serotonin, and epinephrine.

PLATELETS UNDERGO A SEQUENCE OF REACTIONS AFTER A TRAUMATIC VASCULAR INJURY THAT CULMINATE IN THE FORMATION OF A PLATELET PLUG

- 1. PLATELET ADHESION:
- is mediated via interactions with vwf, which acts as a bridge between the platelet surface receptor glycopro



A. CHANGES IN SHAPE from smooth discs to spiky “sea urchins” with greatly increased surface area.

- alterations in glycoprotein iib/iiia that increase its affinity for fibrinogen
- the translocation of negatively charged phospholipids to the platelet surface

B. SECRETION OF GRANULE CONTENTS, e.g:

- ADP: CREATE AN ADDITIONAL ROUNDS OF PLATELET ACTIVATION. ✓
- THROMBOXANE A2 (TXA2): A POTENT INDUCER OF PLATELET AGGREGATION. ✓

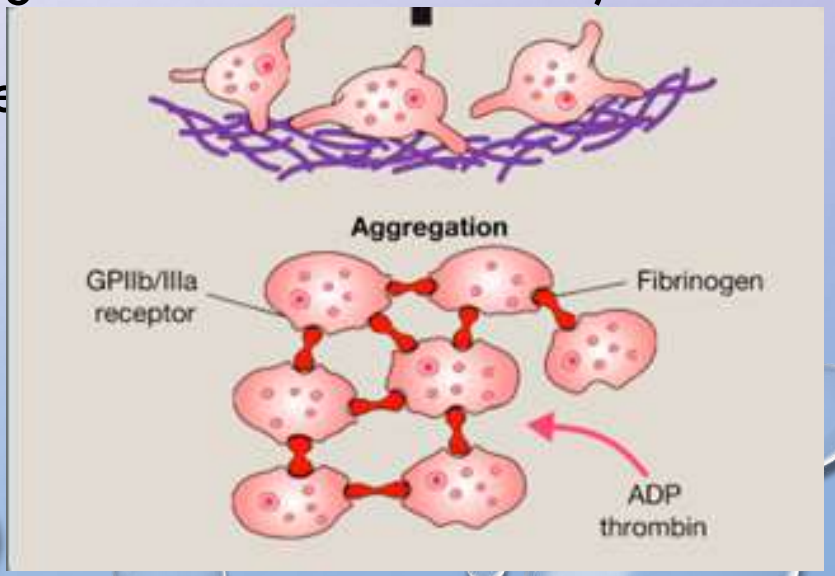
3. PLATELET AGGREGATION FOLLOWS THEIR ACTIVATION.

- The conformational change in glycoprotein iib/iiia allows binding of fibrinogen that forms bridges between adjacent platelets, leading to their aggregation.

fibrinogen cause reversible aggregation✓

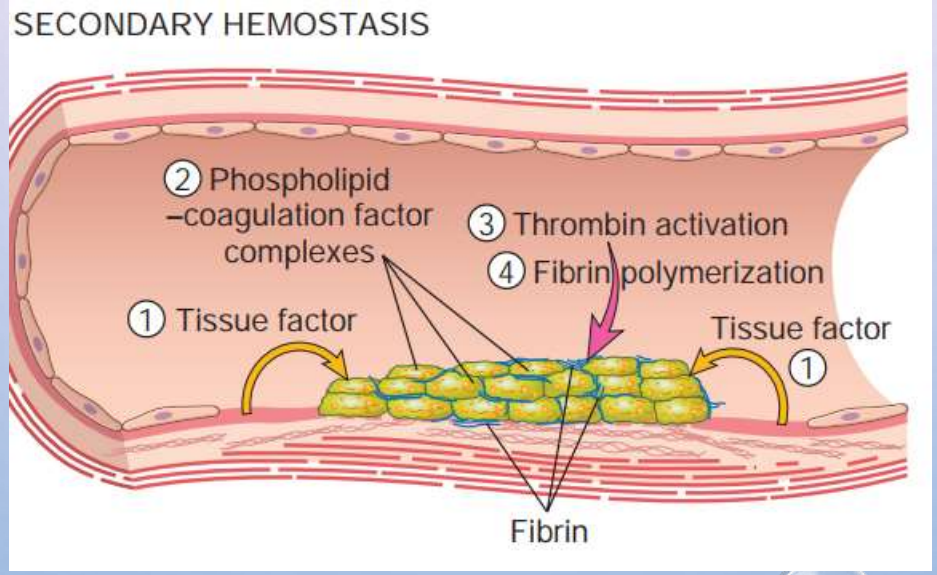
thrombin cause irreversible aggregation (converts fibrinogen into insoluble fibrin).✓

cytoskeleton cause



II .SECONDARY HEMOSTASIS:

- DEPOSITION OF FIBRIN.
- VASCULAR INJURY EXPOSES TISSUE FACTOR AT THE SITE OF INJURY.
- TISSUE FACTOR BINDS AND ACTIVATES FACTOR VII , SETTING IN MOTION A CASCADE OF REACTIONS THAT CULIMINATES IN THROMBIN GENERATION.

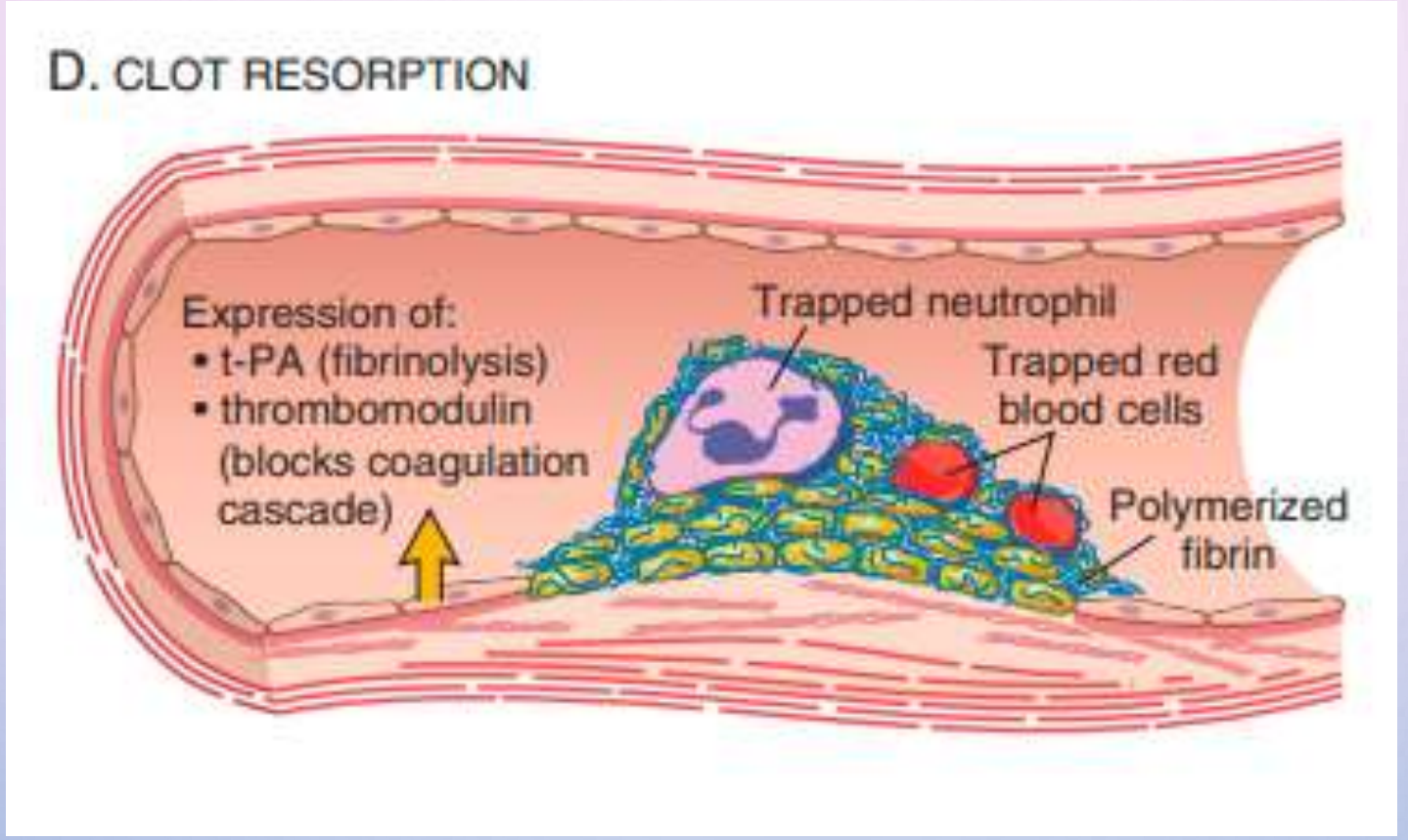


III. CLOT STABILIZATION AND RESORPTION:

- POLYMERIZED FIBRIN AND PLATELET AGGREGATES UNDERGO CONTRACTION TO FORM A SOLID, PERMANENT PLUG THAT PREVENTS FURTHER HEMORRHAGE.

- ENTRAPPED RED CELLS AND LEUKOCYTES ARE ALSO FOUND IN HEMOSTATIC PLUGS, IN PART DUE TO ADHERENCE OF LEUKOCYTES TO P-SELECTIN EXPRESSED ON ACTIVATED PLATELET

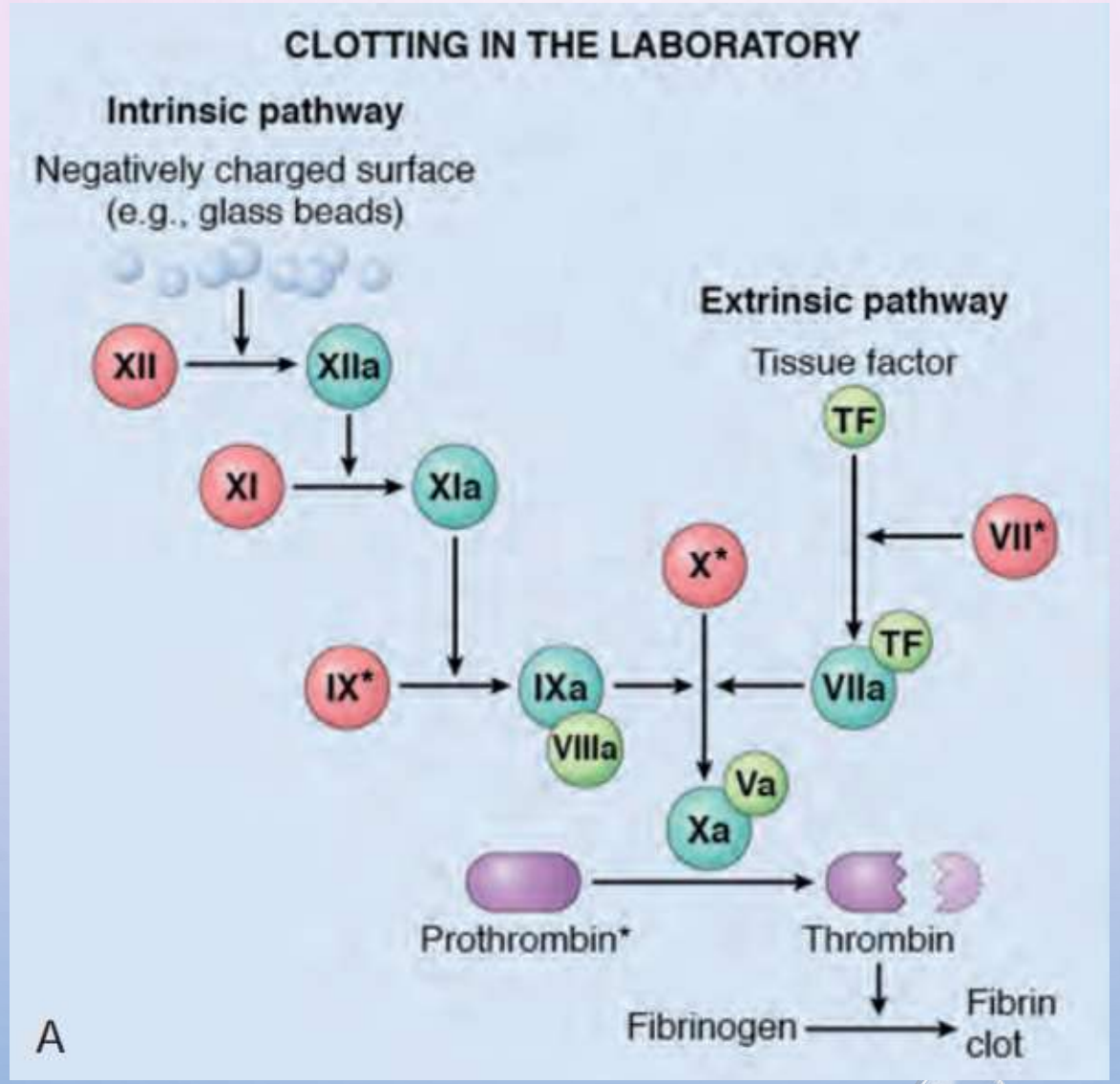
- AT THIS STAGE, COUNTERREGULATORY MECHANISMS (E.G., TISSUE PLASMINOGEN ACTIVATOR, T-PA MADE BY ENDOTHELIAL CELLS) ARE SET INTO MOTION THAT LIMIT CLOTTING TO THE SITE OF INJURY , AND EVENTUALLY LEAD TO CLOT RESORPTION AND TISSUE REPAIR.


D. CLOT RESORPTION
Expression of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

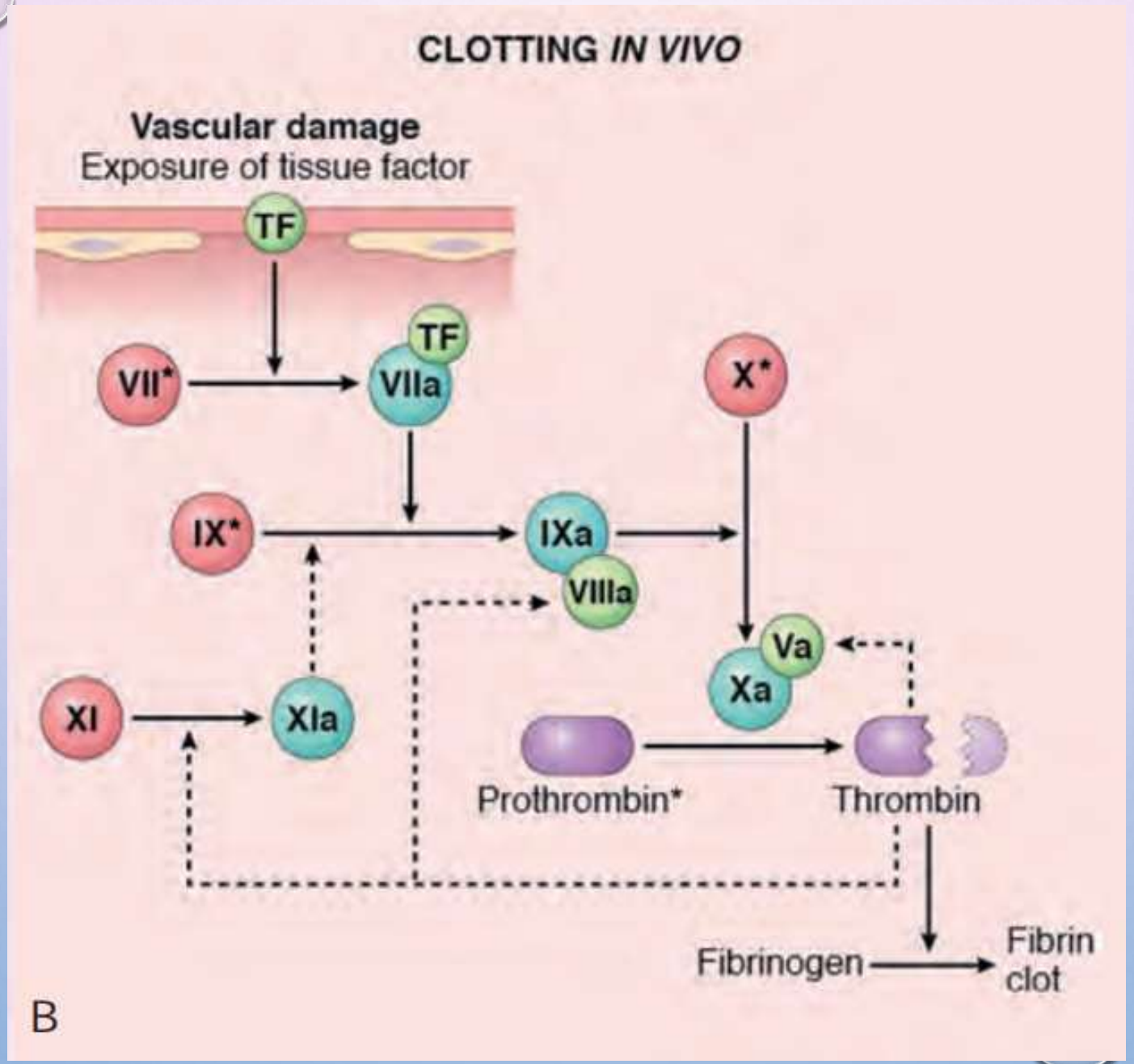
COAGULATION CASCADE

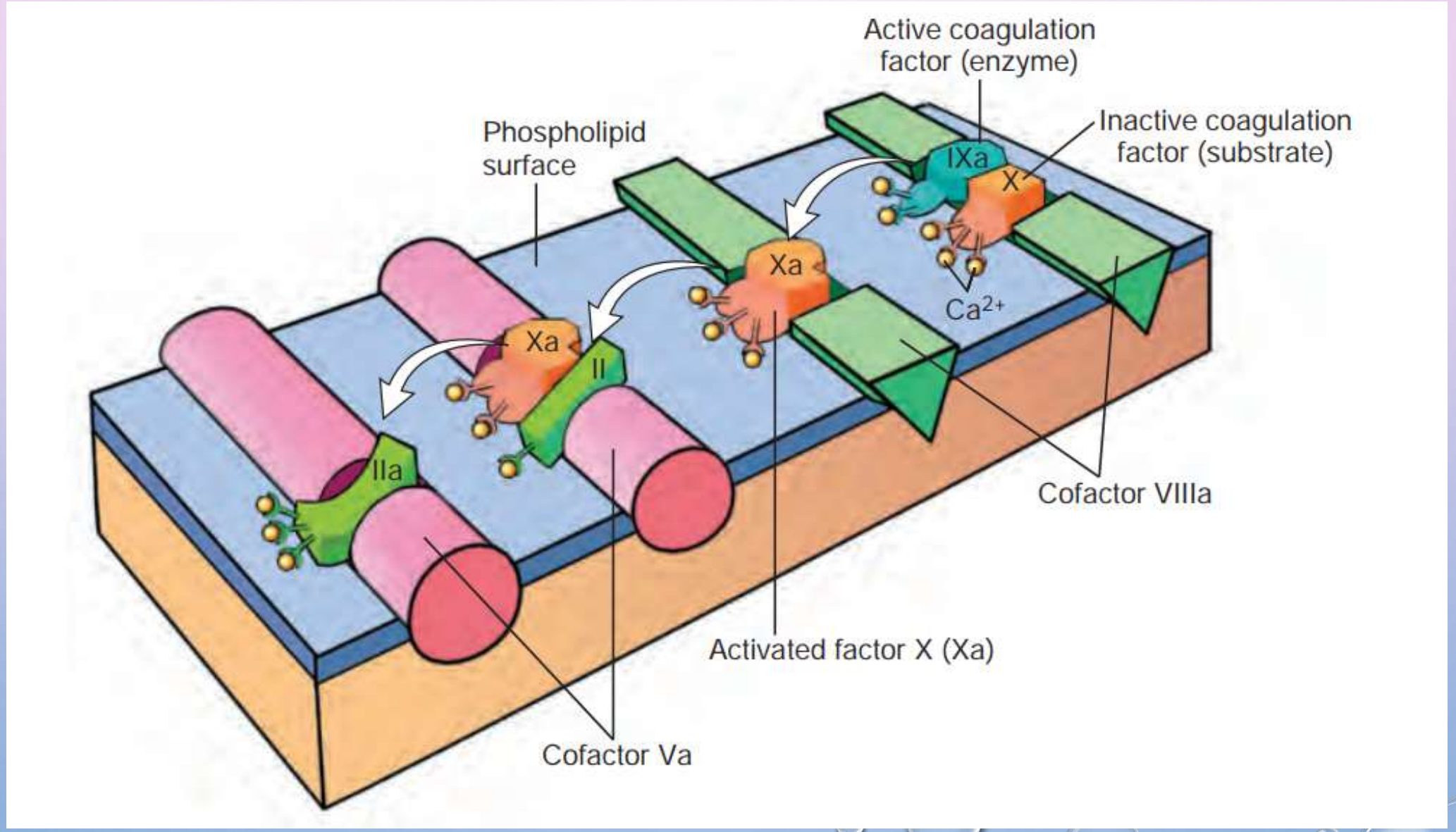
- the coagulation cascade is a series of amplifying enzymatic reactions that lead to the deposition of an insoluble fibrin clot.
- each reaction step involves an enzyme (an activated coagulation factor), a substrate (an inactive proenzyme form of a coagulation factor), and a cofactor (a reaction accelerator).
- these components are assembled on a negatively charged phospholipid surface, which is provided by activated platelets. assembly of reaction complexes also depends on calcium

PTT


CLOTTING IN THE LABORATORY
Intrinsic pathway
Negatively charged surface
(e.g., glass beads)
XII
XIIa
XI
XIa
IX*
IXa
VIIIa
Extrinsic pathway
Tissue factor
TF
VII*
X*
TF
VIIa
Va
Xa
Prothrombin*
Thrombin
Fibrinogen
Fibrin clot
A

PT


CLOTTING IN VIVO
Vascular damage
Exposure of tissue factor
TF
VII*
TF
VIIa
X*
IX*
IXa
VIIIa
Va
Xa
XI
XIa
Prothrombin*
Thrombin
Fibrinogen
Fibrin clot
B


Active coagulation factor (enzyme)
Inactive coagulation factor (substrate)
Phospholipid surface
IXa
X
Xa
Ca2+
Xa
II
IIa
Cofactor VIIIa
Activated factor X (Xa)
Cofactor Va

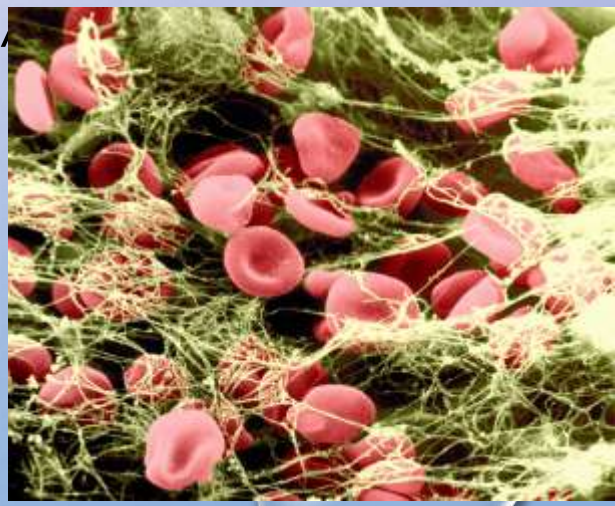
vitamin K antagonists

Coagulation cascade has traditionally been div
the extrinsic and intrinsic

- 1.THE PROTHROMBIN TIME (PT)
- ASSAY ASSESSES THE FUNCTION OF THE PROTEINS IN THE EXTRINSIC PATHWAY (FACTORS VII, X, V, II (PROTHROMBIN), AND FIBRINOGEN).
- THE PARTIAL THROMBOPLASTIN TIME (PTT)
- ASSAY SCREENS THE FUNCTION OF THE PROTEINS IN THE INTRINSIC PATHWAY (FACTORS XII, XI, IX, VIII, X, V, II, AND FIBRINOGEN.

AMONG THROMBIN'S MOST IMPORTANT ACTIVITIES ARE THE FOLLOWING:

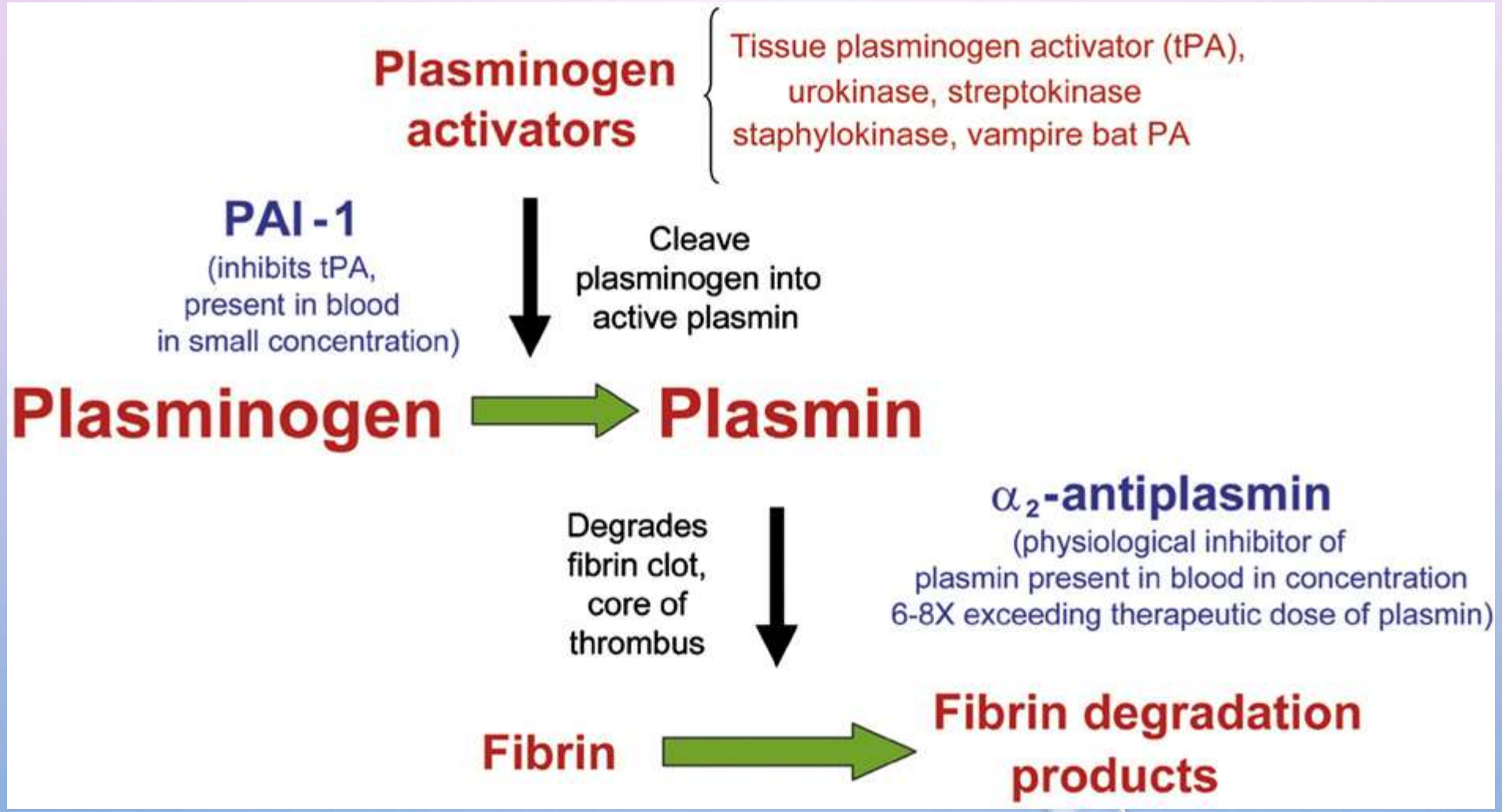
- 1. CONVERSION OF FIBRINOGEN INTO CROSSLINKED FIBRIN.
- THROMBIN DIRECTLY CONVERTS SOLUBLE FIBRINOGEN INTO FIBRIN MONOMERS THAT POLYMERIZE INTO AN INSOLUBLE FIBRIL.
- 2.PLATELET ACTIVATION.
- 3. PRO-INFLAMMATORY EFFECT (CONTRIBUTE TO TISSUE REPAIR AND ANGIOGENESIS)
- 4. ANTI-COAGULANT EFFECTS.
- ENCOUNTERING NORMAL ENDOTHELIUM, THROMBIN CHANGES FROM A PROCOAGULANT TO AN ANTICOA



FACTORS THAT LIMIT COAGULATION.

- COAGULATION MUST BE RESTRICTED TO THE SITE OF VASCULAR INJURY TO PREVENT DANGEROUS CONSEQUENCES THROUGH:
- 1.SIMPLE DILUTION:
- BLOOD FLOWING AT THE SITE OF INJURY WASHES OUT ACTIVATED COAGULATION FACTORS, WHICH ARE RAPIDLY REMOVED BY THE LIVER.
- 2.REQUIREMENT FOR NEGATIVELY CHARGED PHOSPHOLIPIDS
- 3. FIBRINOLYTIC CASCADE:
- THROUGH THE ENZYMATIC ACTIVITY OF PLASMIN, WHICH BREAKS DOWN FIBRIN AND INTERFERES WITH ITS POLYMERIZATION.

fibrinolytic cascade



ENDOTHELIUM

- THE BALANCE BETWEEN THE ANTICOAGULANT AND PROCOAGULANT ACTIVITIES OF ENDOTHELIUM OFTEN DETERMINES WHETHER CLOT FORMATION, PROPAGATION, OR DISSOLUTION OCCURS.

- 1.PLATELET INHIBITORY EFFECTS:

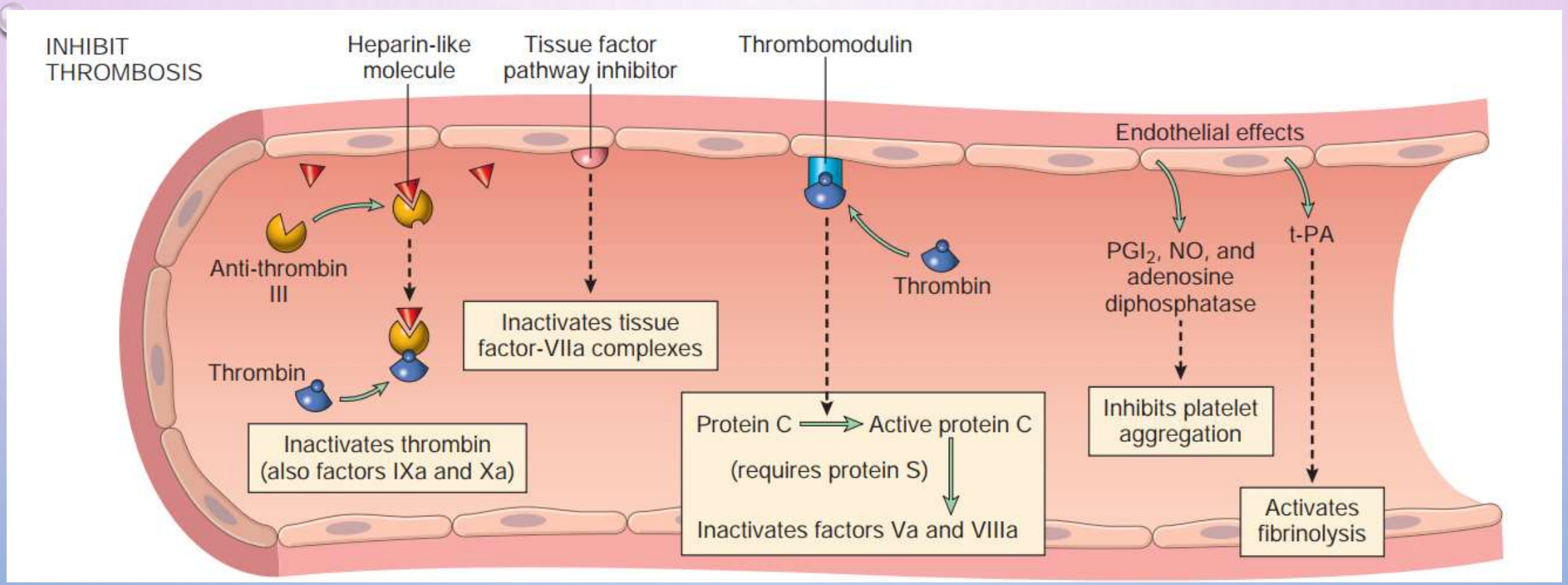
SERVE AS A BARRIER THAT SHIELDS PLATELETS FROM SUBENDOTHELIAL VWF AND COLLAGEN. ✓

RELEASES A NUMBER OF FACTORS THAT INHIBIT PLATELET ACTIVATION AND AGGREGATION. AMONG THE MOST IMPORTANT ARE PROSTACYCLIN (PGI2), NITRIC OXIDE (NO), AND ADENOSINE DOPHOSPHATASE. ✓

ENDOTHELIAL CELLS BIND AND ALTER THE ACTIVITY OF THROMBIN, WHICH IS ONE OF THE MOST POTENT ACTIVATORS OF PLATELETS. ✓

- 2. ANTICOAGULANT EFFECTS.
- NORMAL ENDOTHELIUM SHIELDS COAGULATION FACTORS FROM TISSUE FACTOR IN VESSEL WALLS AND EXPRESSES MULTIPLE FACTORS THAT ACTIVELY OPPOSE COAGULATION: MOST NOTABLY THROMBOMODULIN, ENDOTHELIAL PROTEIN C RECEPTOR, HEPARIN-LIKE MOLECULES, AND TISSUE FACTOR PATHWAY INHIBITOR.

3. FIBRINOLYTIC EFFECTS. SYNTHESIZE T.PA


INHIBIT THROMBOSIS
Heparin-like molecule
Tissue factor pathway inhibitor
Thrombomodulin
Endothelial effects
Anti-thrombin III
Thrombin
Inactivates tissue factor-VIIa complexes
Thrombin
Inactivates thrombin (also factors IXa and Xa)
Protein C
Active protein C
(requires protein S)
Inactivates factors Va and VIIIa
PGI2, NO, and adenosine diphosphatase
Inhibits platelet aggregation
t-PA
Activates fibrinolysis

All are true about blood coagulation except:

A: Factor X is a part of both intrinsic and extrinsic pathway.

B. Extrinsic pathway is activated by contact of plasma with a negatively charged surfaces.

C. Calcium is very important for coagulation.

D. Intrinsic pathway can be activated in vitro

Edema in nephrotic syndrome occurs due to : •

A: Na and water restriction. •

B. Increased venous pressure. •

C: Decreased serum albumin. •

D: Decreased fibrinogen. •

- Thrombomodulin thrombin complex prevents clotting because :

- A: Inhibits prothrombin activator.
- B: Activates antithrombin.
- C: The complex activates heparin.
- D: It activates protein C which inactivates the activated factor V and VIII

Extrinsic pathway of clotting factors is measured by:

A: Prothrombin time. (PT)

B: Activated partial thromboplastin time (PTT)

C: Bleeding time.

D: All of the above.

- Platelet adhesion to collagen is mediated by which of the following:

- A: Factor VIII
- B: Factor IX
- C: Von willebrand factor.
- D: Fibonectin

LAB•

HEPATIC CONGESTION.

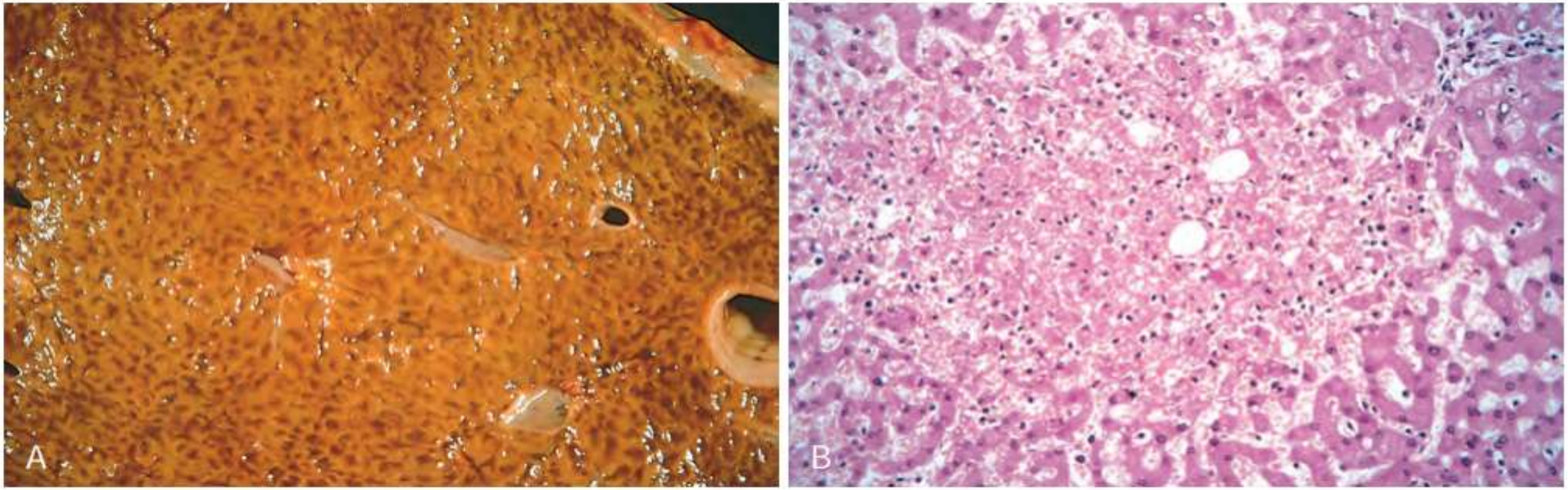
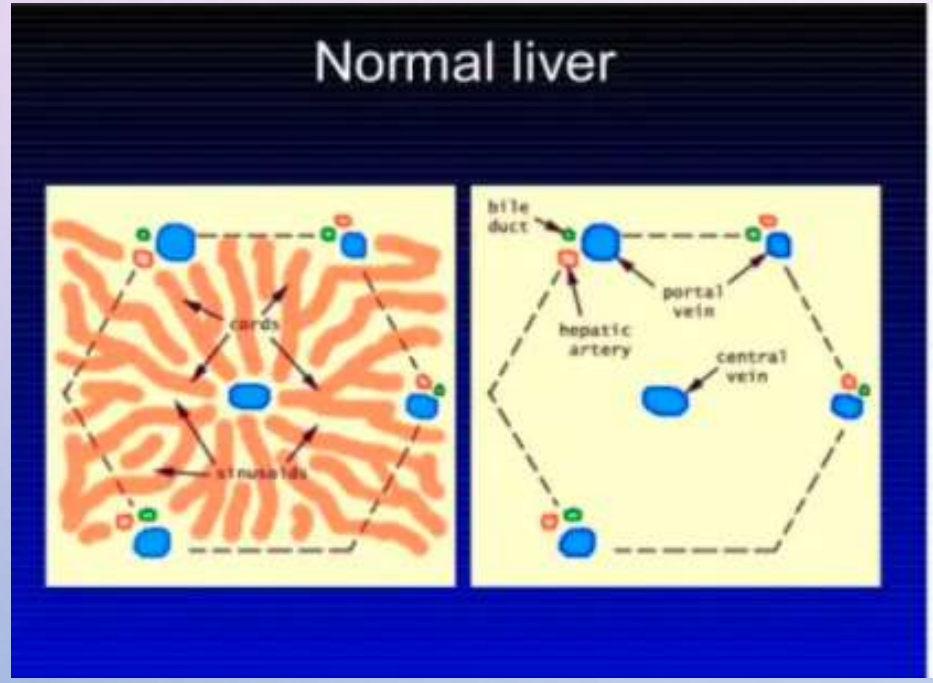
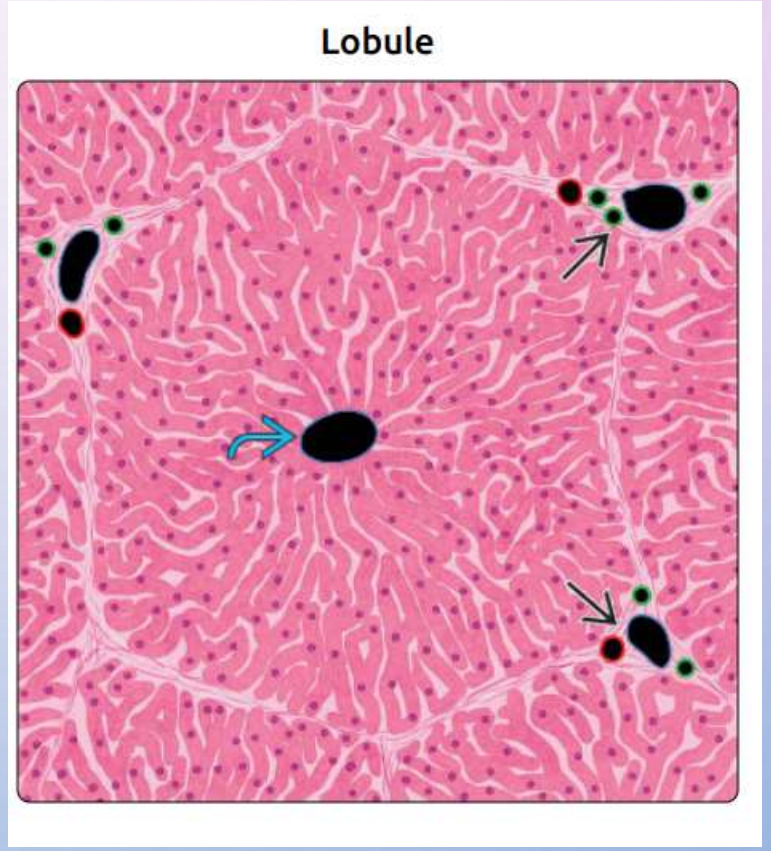


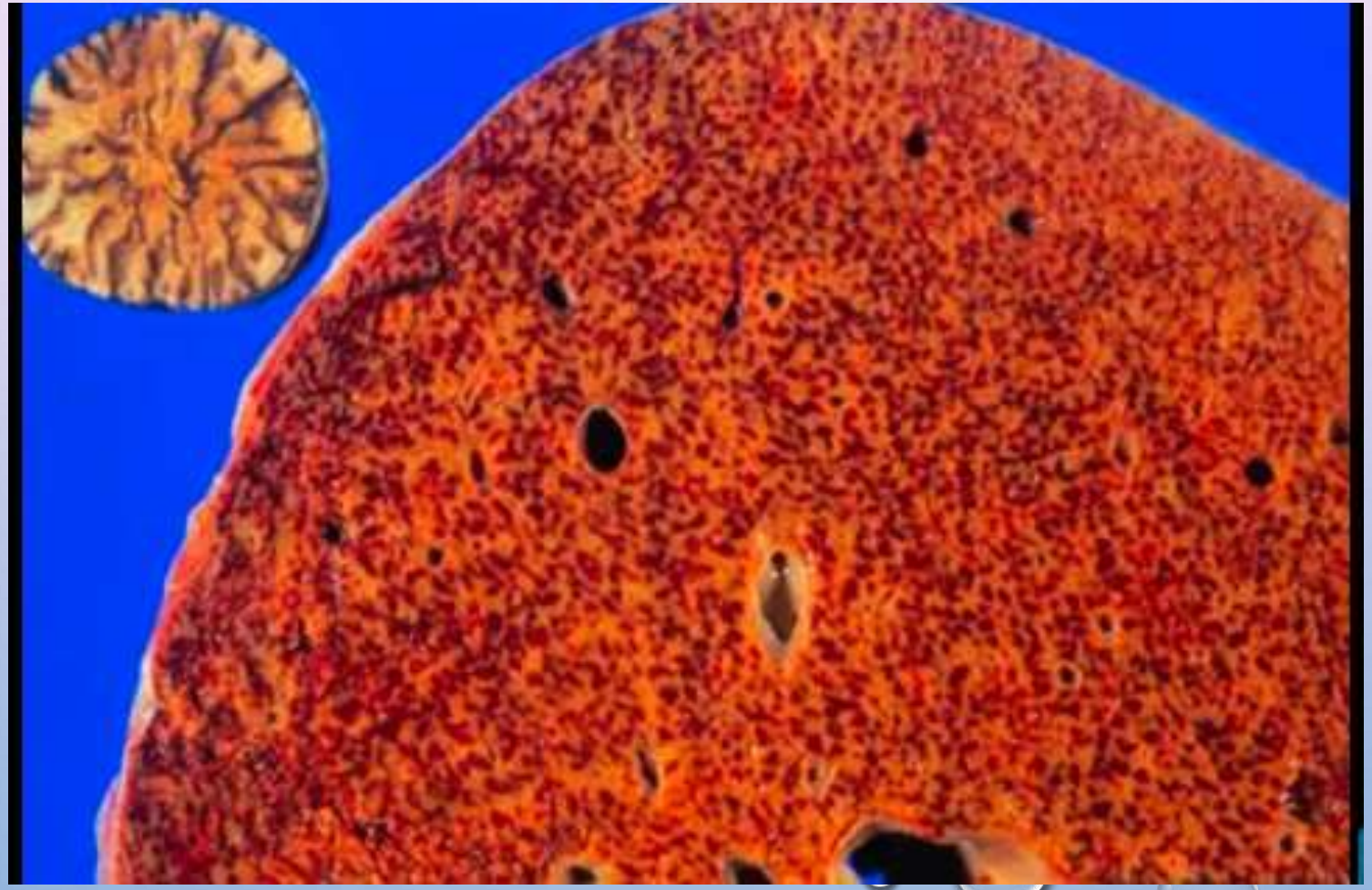
Figure 4.3 Liver with chronic passive congestion and hemorrhagic necrosis. (A) Central areas are red and slightly depressed compared with the surrounding tan viable parenchyma, forming a "nutmeg liver" pattern (so-called because it resembles the cut surface of a nutmeg). (B) Centrilobular necrosis with degenerating hepatocytes and hemorrhage. (Courtesy Dr. James Crawford, Department of Pathology, University of Florida, Gainesville, Fla.)

Centrally located hepatocytes are prone to necrosis more than the periportal hepatocytes which is better oxygenated because of their proximity to hepatic arterioles



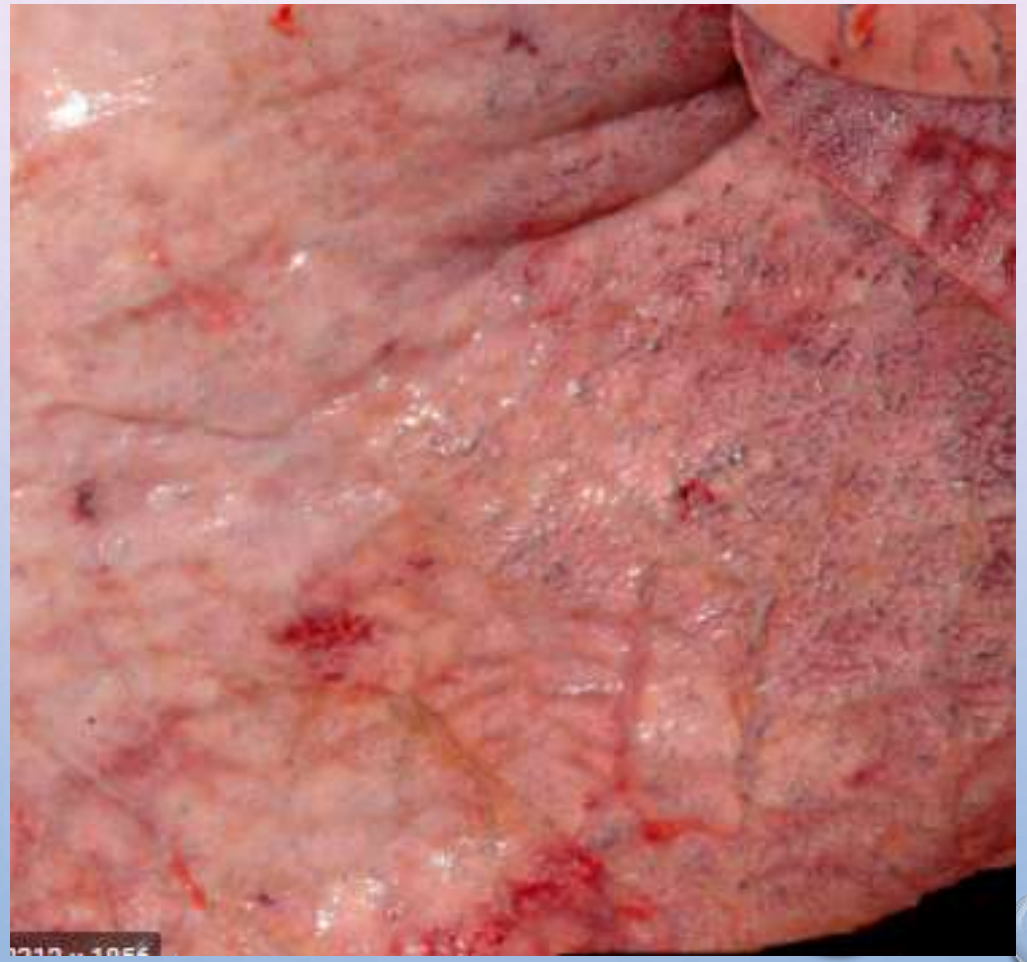


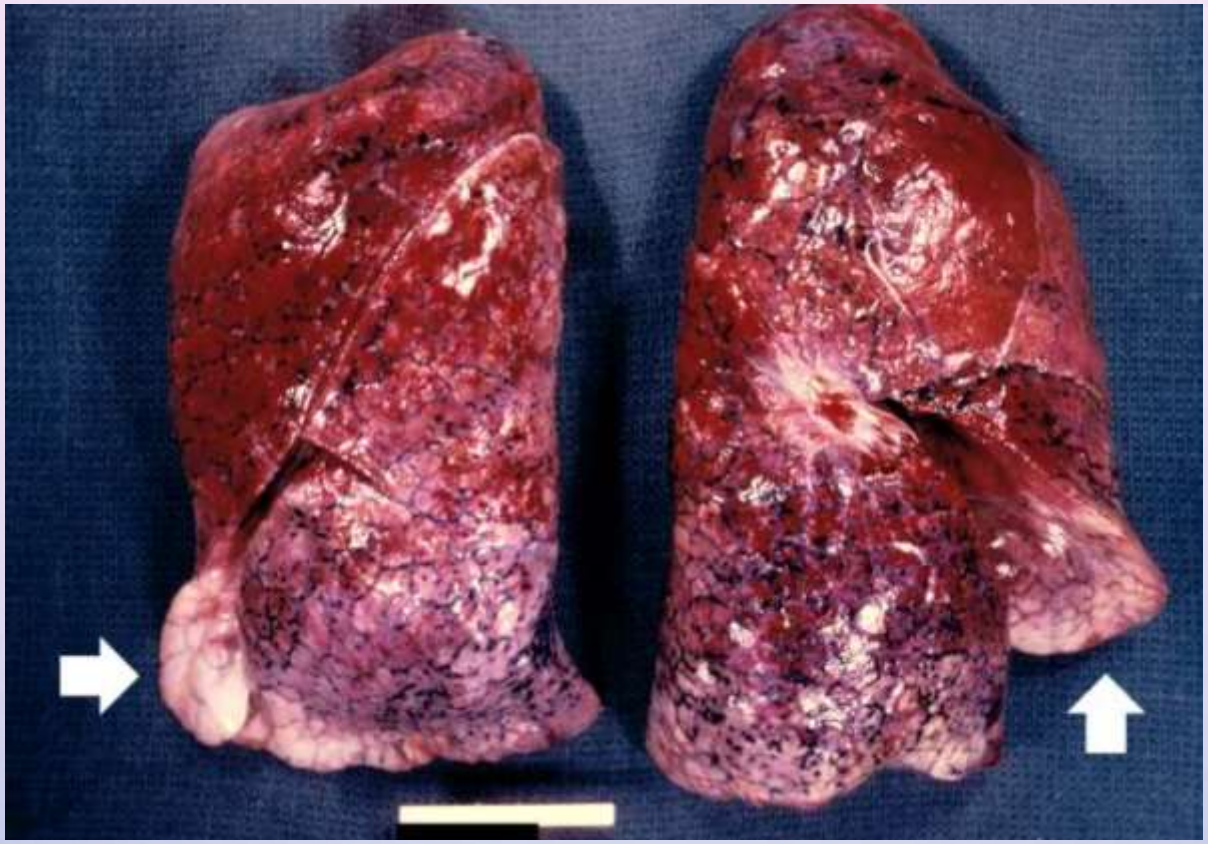
central areas are red and slightly depressed compared with the surrounding tan viable parenchyma, creating “nutmeg liver”



LUNG CONGESTION.

Cut surfaces of hyperemic or congested tissues feel wet and typically ooze blood





The reddish coloration of the tissue is due to congestion. Some normal pink lung tissue is seen at the edges of the lungs (arrows).

Microscopic examination:

acute pulmonary congestion is marked by blood-engorged alveolar capillaries and variable degrees of alveolar septal edema and intraalveolar hemorrhage.

chronic pulmonary congestion, the septa become thickened and fibrotic, and the alveolar spaces contain numerous macrophages laden with hemosiderin ("heart failure cells") derived from phagocytosed red cells.