

General pathology

Haemodynamics

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MSc pathology

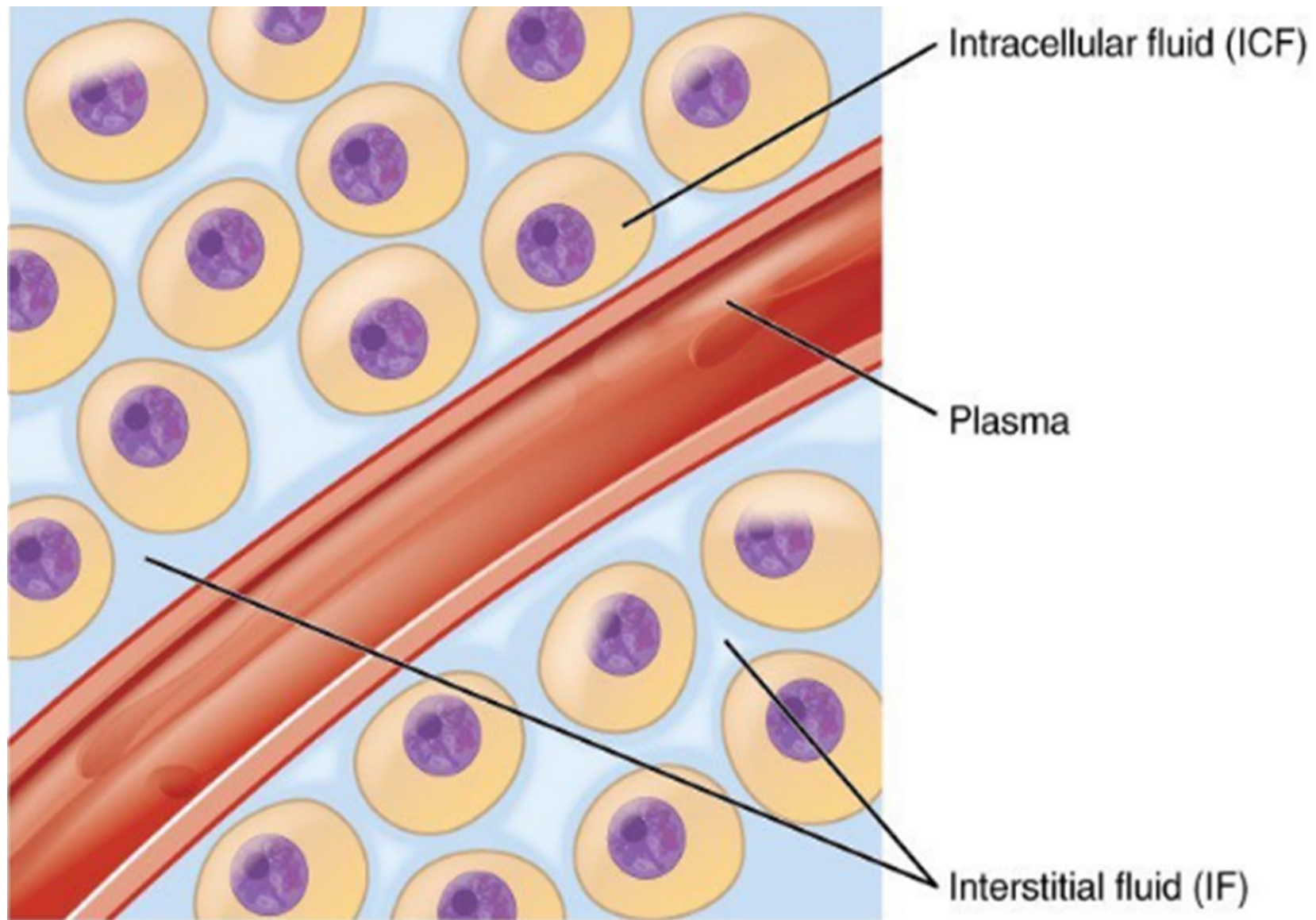
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Q. Define oedema. Write briefly on its types.

Oedema is defined as abnormal and excessive accumulation of fluid in interstitial

tissue spaces and serous cavities.

Approximately, **60% of body weight** is water-two-thirds of which is **intracellular** and one-third **extracellular**. The extracellular space is divided into **interstitial and intravascular** compartments. Bulk of the extracellular water is formed by interstitial fluid and only **5%** of the body's water is present as blood plasma. If the net influx of fluid exceeds the lymphatic drainage, the excessive volume of fluid may accumulate either within the interstitial matrix (interstitial oedema) or in the serous body cavities (effusion).



Examples of Oedema/Effusion.

- Periorbital oedema.
- Dependent oedema.
- Generalized oedema or anasarca.
- Hydrothorax or pleural effusion.
- Hydropericardium or pericardial effusion.
- Hydroperitoneum or ascites.

Oedema causes a palpable swelling and may be the result of either too much pressure or too little protein within the blood vessels.

Classification of Oedema

- **Localized or generalized oedema**, based on the distribution and extent of involvement. Localized oedema is limited to a small area, eg, an organ (organ-specific oedema) or a limb (elephantiasis, oedema due to venous obstruction as seen in deep vein thrombosis, allergic laryngeal oedema as seen in anaphylaxis and localized inflammatory oedema).

Generalized oedema, on the other hand, may involve the entire body (oedema due to congestive cardiac failure, nephrotic syndrome and nutritional deficiency).

- **Transudative or exudative oedema/effusion**, based on the composition of the fluid. The differences between transudative and exudative effusion are summarized

Consequences of Oedema

Oedema may compromise cellular function in the following ways:

- Due to expansion of the interstitial space, there is an increase in the diffusion distance for oxygen and other nutrients, which hampers cellular metabolism, eg, impaired gas exchange due to pulmonary oedema.
- Expansion of the interstitial space also interferes with the removal of toxic by-products of cellular metabolism.

Q. Enumerate the differences between exudate and transudate.

Ans. Differences between exudate and transudate are tabulated in [Table 4.1](#).

TABLE 4.1. Differences between exudate and transudate		
Features	Exudate	Transudate
Definition	Oedema associated with increased vascular permeability	Filtrate of blood or plasma; no increase in vascular permeability observed
Nature	Inflammatory oedema	Noninflammatory oedema
Protein content	1. High (more than 4 g/dl) 2. Has high fibrinogen and tendency to coagulate	1. Low (less than 3 g/dl) 2. Mainly albumin, low fibrinogen
Specific gravity	High (more than 1.018)	Low (less than 1.015)
pH	>7.3	<7.3
LDH	High Fluid LDH/serum LDH ratio is >0.6	Low Fluid LDH/serum LDH ratio is <0.6
Cells	Highly cellular; rich in polymorphs	Few, mainly mesothelial cells
Example	Pus seen in pyogenic infections	Fluid in congestive cardiac failure

Q. What are the factors affecting fluid balance across capillaries?

Factors affecting fluid balance across capillaries can be summarized as follows:

(a) Plasma colloid oncotic pressure (which tends to drive water and salts into the vessels)

(b) Capillary hydrostatic pressure (which tends to drive water and salts out of the vessels

into the interstitial space)

(c) Lymphatic drainage (which tends to drain the interstitial space)

(d) Sodium balance (sodium retention increases hydrostatic pressure and causes a dilutional decrease in the colloid osmotic pressure)

• Oedema occurs when there are

(a) Abnormalities in the hydrostatic and oncotic pressures acting across the vessel walls

(b) Alterations in the endothelial wall structure

(c) Alterations in the lymphatic outflow system

- Normally, at the arteriolar end of the capillary bed, the hydrostatic pressure exceeds the plasma oncotic (colloid osmotic) pressure pushing the water and electrolytes out from the vessels into the interstitial tissue. At the venous end of the capillary bed, osmotic pressure is more than the hydrostatic pressure and hence the fluid is reabsorbed from the interstitial tissue into the vessels at this end. The interstitial fluid is drained by the lymph vessels and this eventually returns to the veins via the thoracic duct.

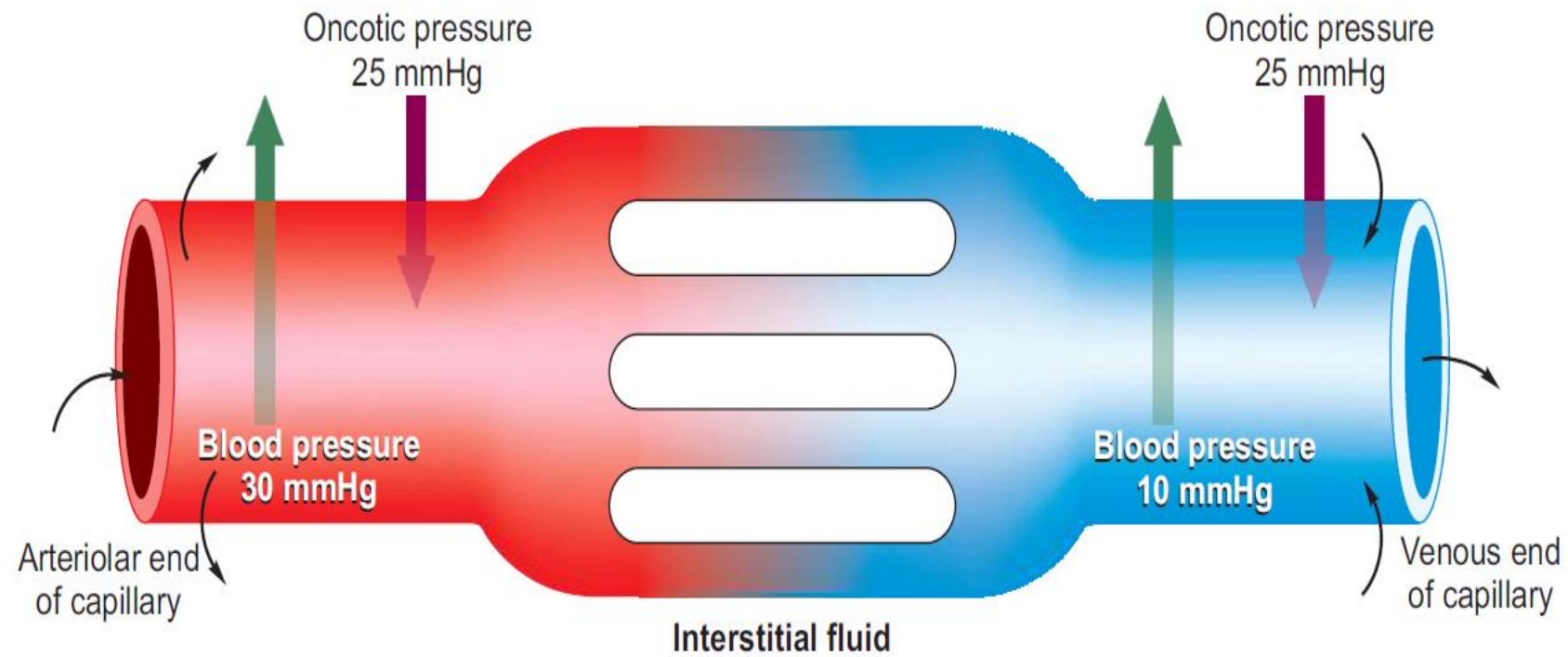


FIGURE 4.1. Factors affecting fluid balance across capillaries.

Q. What are the pathophysiologic categories of oedema?

Important pathophysiologic categories of oedema are enumerated below:

1. Increased hydrostatic pressure

(a) Hydrostatic pressure of capillaries is the force that tends to drive fluid through capillary wall into interstitial space.

(b) A rise in hydrostatic pressure at venular end of a capillary to a level more than plasma oncotic pressure results in oedema.

(c) Increased hydrostatic pressure may be due to

(i) Impaired venous return

- Congestive heart failure
- Constrictive pericarditis
- Ascites (liver cirrhosis)
- Venous obstruction
- Thrombosis
- External pressure due to a mass

(ii) Arteriolar dilatation

- Heat
- Neurohumoral dysregulation

2. Reduced plasma oncotic pressure

- (a) Normally, plasma oncotic pressure is exerted by plasma proteins and drives fluid into the vessels.
- (b) Reduced oncotic pressure causes increased movement of fluid into interstitial space.
- (c) Decreased plasma oncotic pressure may be due to
 - (i) Protein-losing glomerulopathies (nephrotic syndrome)
 - (ii) Reduced synthesis of proteins (liver cirrhosis)
 - (iii) Decreased intake of proteins (malnutrition as in famine oedema)
 - (iv) Protein-losing gastroenteropathies and malabsorption

3. Lymphatic obstruction

- (a) Normally, interstitial fluid escapes via lymphatic system. Lymphatic obstruction causes accumulation of fluid in interstitial space.
- (b) Lymphatic obstruction may be
 - (i) Inflammatory
 - (ii) Neoplastic
 - (iii) Post-surgical
 - (iv) Post-irradiation
 - (v) Due to congenital absence of lymphatics

4. Sodium retention:

Increased sodium retention is invariably associated with water retention, which leads to increased plasma volume as well as hydrostatic pressure.

Dilutional effect on albumin leads to decreased plasma colloid oncotic pressure.

Causes of sodium retention include

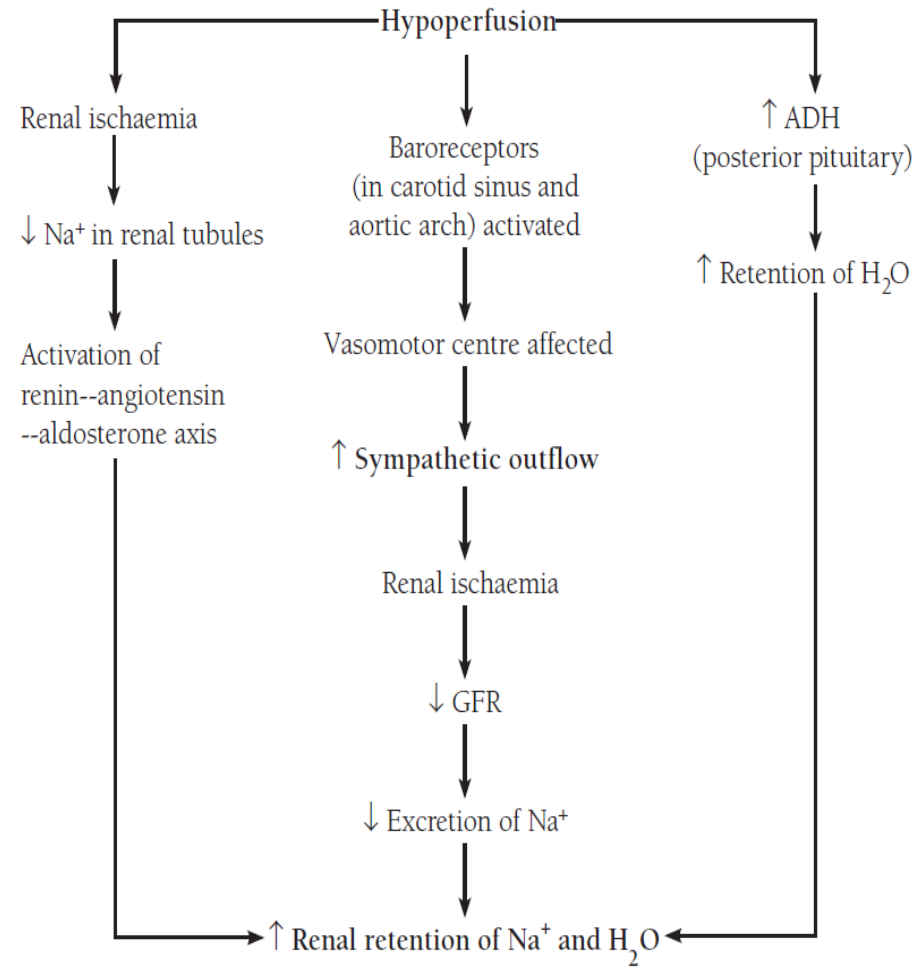
- (a) Excessive salt intake with renal insufficiency
- (b) Increased tubular reabsorption of sodium
- (c) Renal hypoperfusion
- (d) Increased renin–angiotensin–aldosterone secretion

5. Inflammation:

Endothelial lining may be injured by toxins and their products, eg, histamine, anoxia, venoms, drugs and chemicals. Endothelial damage leads to

increased vascular permeability and leakage of plasma proteins into the interstitial tissue resulting in oedema.

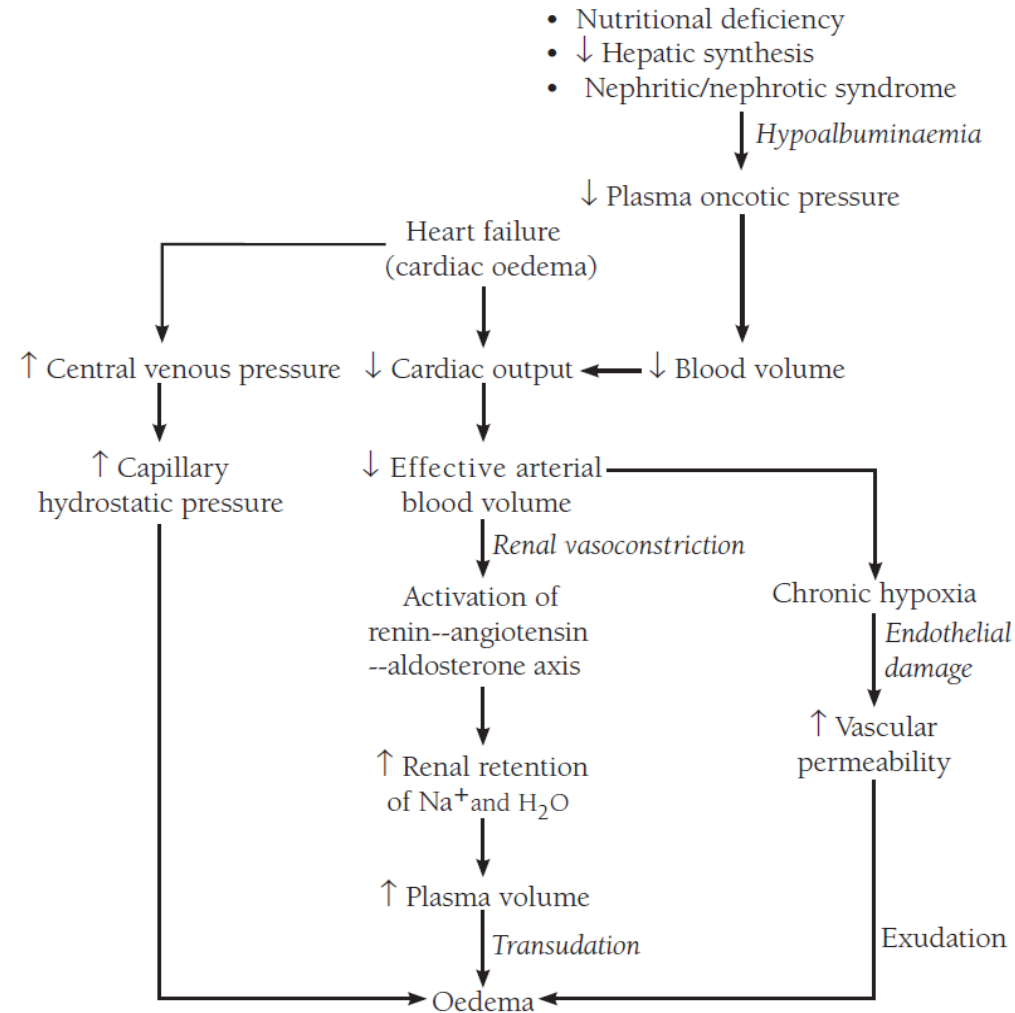
Q. Write briefly on normal regulatory mechanisms responsible for maintaining sodium and water balance. Eighty percent of sodium is reabsorbed by proximal convoluted tubule under the influence of intrinsic and extrinsic renal mechanisms (Flowchart 4.1).



FLOWCHART 4.1. Normal regulatory mechanisms responsible for maintaining sodium and water balance.

Q. Write briefly on the pathogenesis of oedema.

Ans. Pathogenesis of oedema is shown in [Flowchart 4.2](#).



FLOWCHART 4.2. Pathogenesis of oedema.

Q. Write briefly on renal oedema.

Oedema due to renal dysfunction typically appears first in loose connective tissue, eg, the eyelids (periorbital oedema).

- **Causes of renal oedema** include nephrotic syndrome, glomerulonephritis (acute glomerulonephritis, rapidly progressive glomerulonephritis) and acute tubular injury.

Nephrotic syndrome is characterized by persistent and heavy proteinuria causing a reduced plasma oncotic pressure leading to generalized severe oedema.

- Also, a reduction in the plasma volume causes activation of the renin–angiotensin–aldosterone mechanism, thereby causing retention of sodium and water.

- **Nephritic oedema** is mainly due to excessive reabsorption of sodium and water in the renal tubules and not due to protein loss. It is milder as compared to nephrotic oedema.

- **In acute tubular injury**, which is due to shock or toxic chemicals, tubules lose their capacity for selective renal concentration of the glomerular filtrate resulting in increased reabsorption and oliguria.

Q. Write briefly on cardiac oedema.

Cardiac oedema is mostly a manifestation of congestive heart failure, and occurs due to activation of a series of mechanisms that increase venous capillary pressure, promote sodium and water retention by the kidneys and expansion of the extracellular fluid

Q. Write briefly on pulmonary oedema.

Defined as fluid accumulation in the air spaces and parenchyma of the lungs, pulmonary oedema may lead to respiratory failure due to impaired gas exchange. It is mainly of two types:

1. **Cardiogenic pulmonary oedema**

caused by congestive cardiac failure or left ventricular failure which lead to inadequate removal of blood from the pulmonary Circulation.

2. **Noncardiogenic pulmonary oedema**

caused by injury to lung parenchyma or vasculature of the lung.

Q. Write briefly on subcutaneous oedema.

Subcutaneous oedema can be diffused or localized to the most dependent part of

the body positioned at the greatest distance below the heart (legs while standing and the sacrum while recumbent). This type of oedema is called dependent oedema and is pitting in nature (ie, pressure over oedematous subcutaneous tissue displaces the interstitial fluid, leaving a finger-shaped depression).

Q. Write briefly on cerebral oedema.

Cerebral oedema can be localized (eg, due to a space occupying intracranial lesion like an abscess or tumour) or generalized (due to extensive brain pathology or injury). The latter causes narrowing of the sulci while the gyri are swollen and flattened against the skull.



Table 4.1 Pathophysiologic Categories of Edema

Increased Hydrostatic Pressure
<i>Impaired Venous Return</i>
Congestive heart failure Constrictive pericarditis Ascites (liver cirrhosis) Venous obstruction or compression Thrombosis External pressure (e.g., mass) Lower extremity inactivity with prolonged dependency
<i>Arteriolar Dilation</i>
Heat Neurohumoral dysregulation
Reduced Plasma Osmotic Pressure (Hypoproteinemia)
Protein-losing glomerulopathies (nephrotic syndrome) Liver cirrhosis 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

Modified from Leaf A, Cotran RS: *Renal Pathophysiology*, ed 3, New York, 1985, Oxford University Press, p 146.

Q. Differentiate between cardiac and renal oedema.

TABLE 4.2.

Contrasting features of cardiac and renal oedema

Features	Cardiac oedema	Renal oedema
Causes	CHF and right-sided heart failure	Nephritic and nephrotic syndrome/acute tubular injury/necrosis
Mechanism	Decreased cardiac output	Hypoalbuminemia and decreased plasma oncotic pressure
Clinical	• Dependent oedema, the distribution of which changes with posture • Mainly pedal or sacral; later generalized	First observed around face, eyes, ankle and genitalia
Serum albumin	Normal	Decreased
Proteinuria	Absent	Present

Q. Define and compare hyperaemia and congestion.

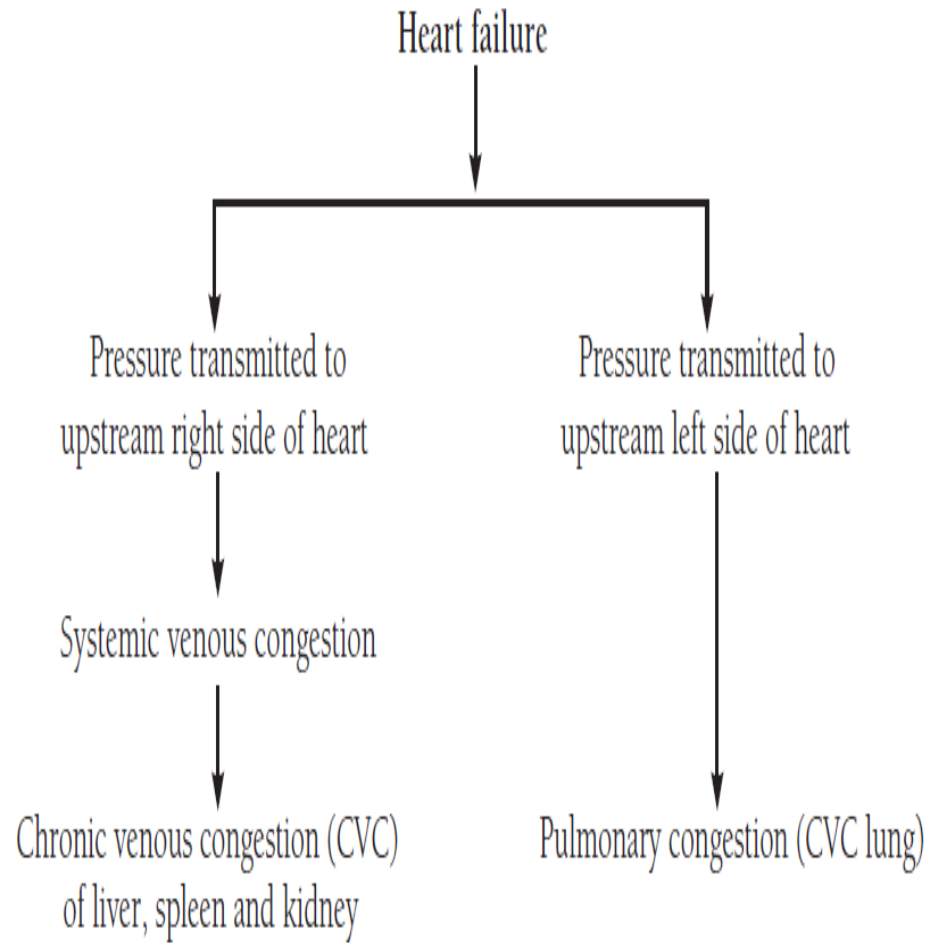
Hyperaemia is defined as local increase in volume of blood in a particular tissue due to arteriolar dilatation, eg, **increased inflow** in skeletal muscle during exercise.

Congestion is a passive process resulting from **impaired outflow** from a particular organ/tissue. It may occur systemically (in cardiac failure) or locally (in an isolated venous obstruction). Congestion and oedema can occur together since capillary blood congestion can lead to increased fluid transudation causing oedema. The contrasting features of hyperaemia and congestion are summarized in Table 4.3 given below.

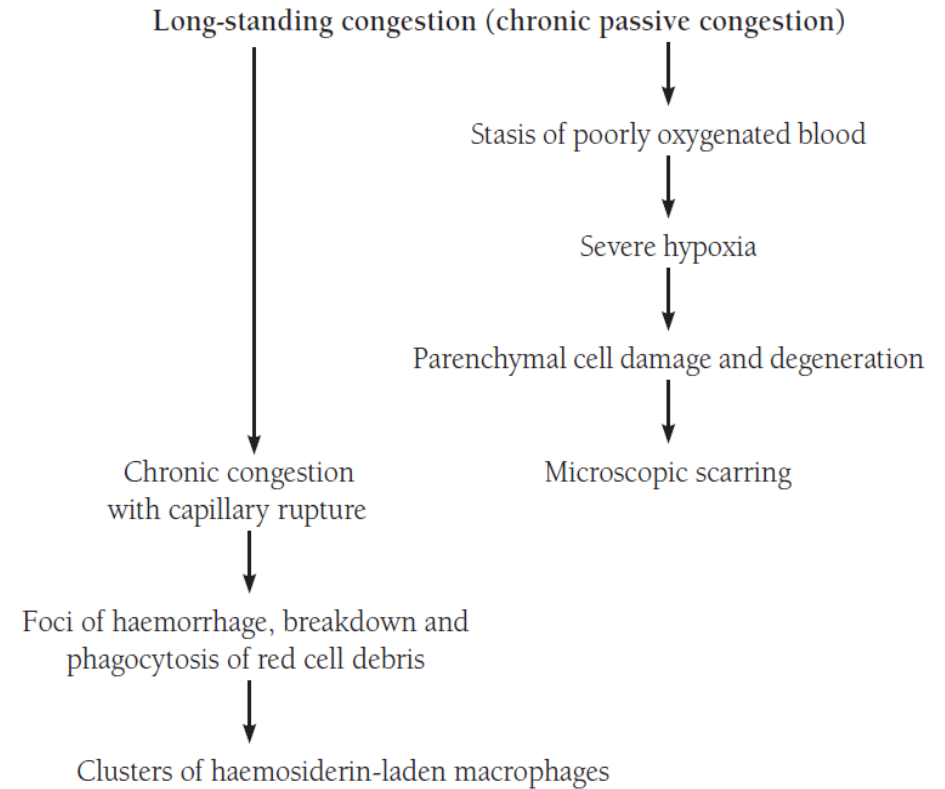
TABLE 4.3.

Differences between hyperaemia and congestion

Features	Hyperaemia	Congestion
Definition	Characterized by increased blood flow due to <i>arteriolar dilatation</i>	Characterized by blood pooling due to impaired outflow/drainage from tissue
Nature of process	Active	Passive
Appearance	Red	Bluish-red/cyanosed
Type of blood	Oxygenated	Deoxygenated; tissue hypoxia present
Oedema	Absent	Present
Examples	Menopausal flush, muscular exercise, high-grade fever, etc.	Local: portal venous obstruction in cirrhosis of liver; systemic: right-sided heart failure



FLOWCHART 4.3A. Pathogenesis of chronic venous congestion.



FLOWCHART 4.3B. Outcomes of chronic congestion.

Q. Write briefly on the pathogenesis and clinicopathological features of pulmonary congestion.

Pulmonary congestion is defined as accumulation of fluid within the pulmonary interstitium as well as alveoli. It may be classified into 'acute or chronic' types based on duration.

Acute Pulmonary Congestion This may be cardiogenic or noncardiogenic in origin.

Gross morphology

Lungs are enlarged; cut section shows frothy, blood-stained fluid (air in combination with oedema fluid and red cells).

Microscopic Features

The main histopathological features of acute pulmonary congestion are:

- Alveolar septal oedema
- Engorged septal capillaries
- Focal intra-alveolar haemorrhages

Chronic venous congestion (CVC) lung (Fig. 4.2)

Long-standing pulmonary venous congestion occurs due to left-sided heart failure (eg, rheumatic mitral stenosis), which results in increased pulmonary venous pressure.

Gross morphology

- The lungs are heavier and firmer than normal.
- Cut surface is dark brown in colour (brown induration) with oozing of frothy, blood-tinged material.

Microscopic features

- Dilatation and congestion of septal capillaries
- Intra-alveolar haemorrhage (occurs due to rupture of congested capillaries)
- RBC breakdown produces hemosiderin which is taken up by alveolar macrophages.

These hemosiderin-laden macrophages present in alveolar lumina are called heart failure cells (siderophages).

- Thickening and fibrosis of alveolar septae is eventually seen.

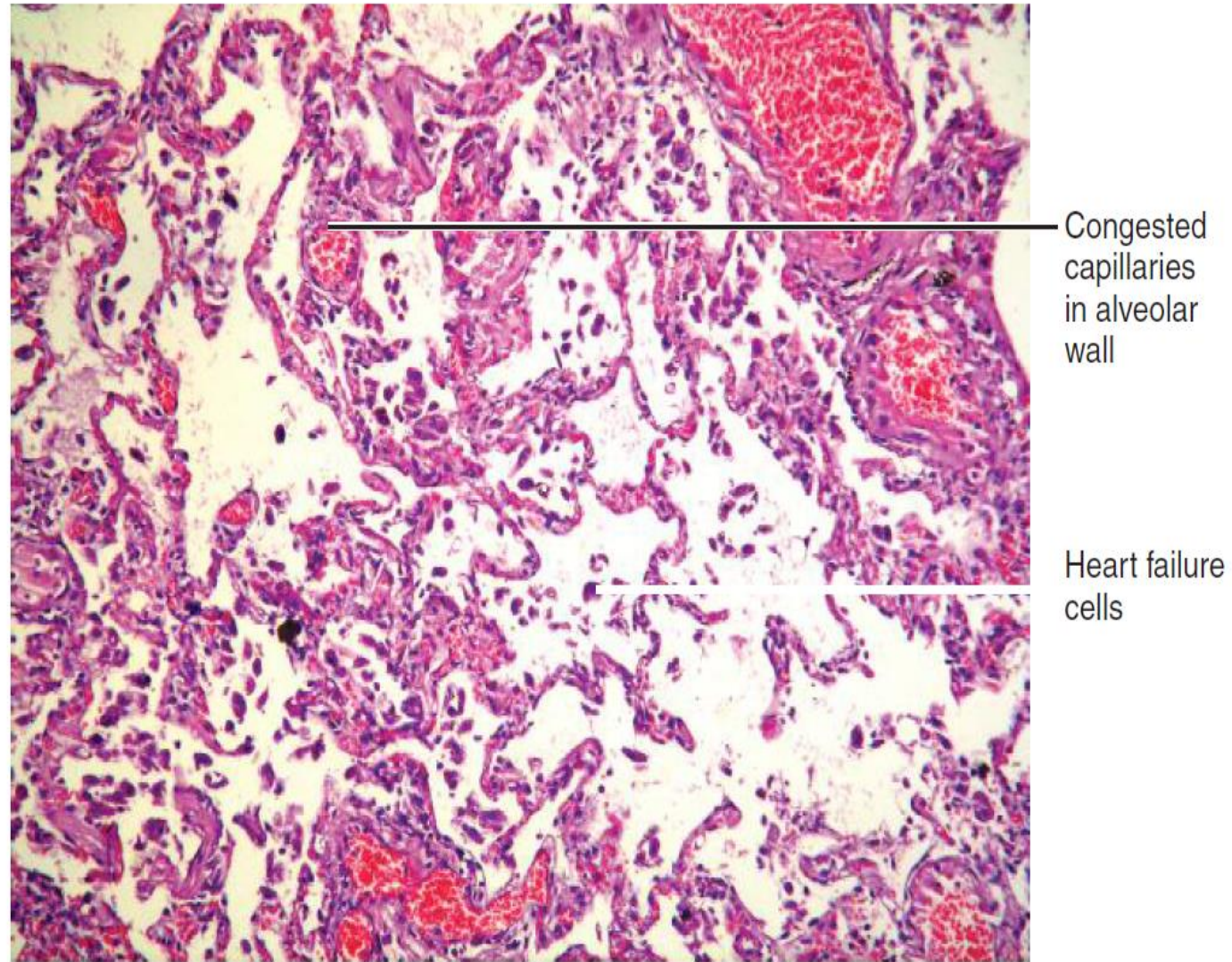


FIGURE 4.2. CVC lung showing congested and widened alveolar septae with hemosiderin-laden macrophages in the alveolar spaces (H&E; 200X).

Q. Write briefly on the pathogenesis and clinicopathological features of hepatic congestion.

Congestive hepatopathy refers to hepatic manifestations attributable to right-sided heart failure, Budd-Chiari syndrome, hepatic sinusoidal obstruction syndrome, hepatic infarction and ischaemic hepatitis. Passive congestion often coexists with reduced cardiac output.

Acute hepatic congestion is characterized by:

- Dilated, distended central vein and sinusoids
- Central hepatocyte degeneration
- Fatty change in periportal hepatocytes (periportal hepatocytes experience less hypoxia because of proximity to hepatic arterioles, and therefore develop fatty change only)

In chronic passive congestion of liver (Fig. 4.4), the central region of hepatocytic lobules appears grossly red-brown and slightly depressed with surrounding zones of uncongested liver (nutmeg appearance). Central portion of hepatocytes being least perfused, undergoes centrilobular necrosis with loss or drop out of hepatocytes. Severe long-standing congestion may lead to grossly evident hepatic fibrosis (cardiac cirrhosis).

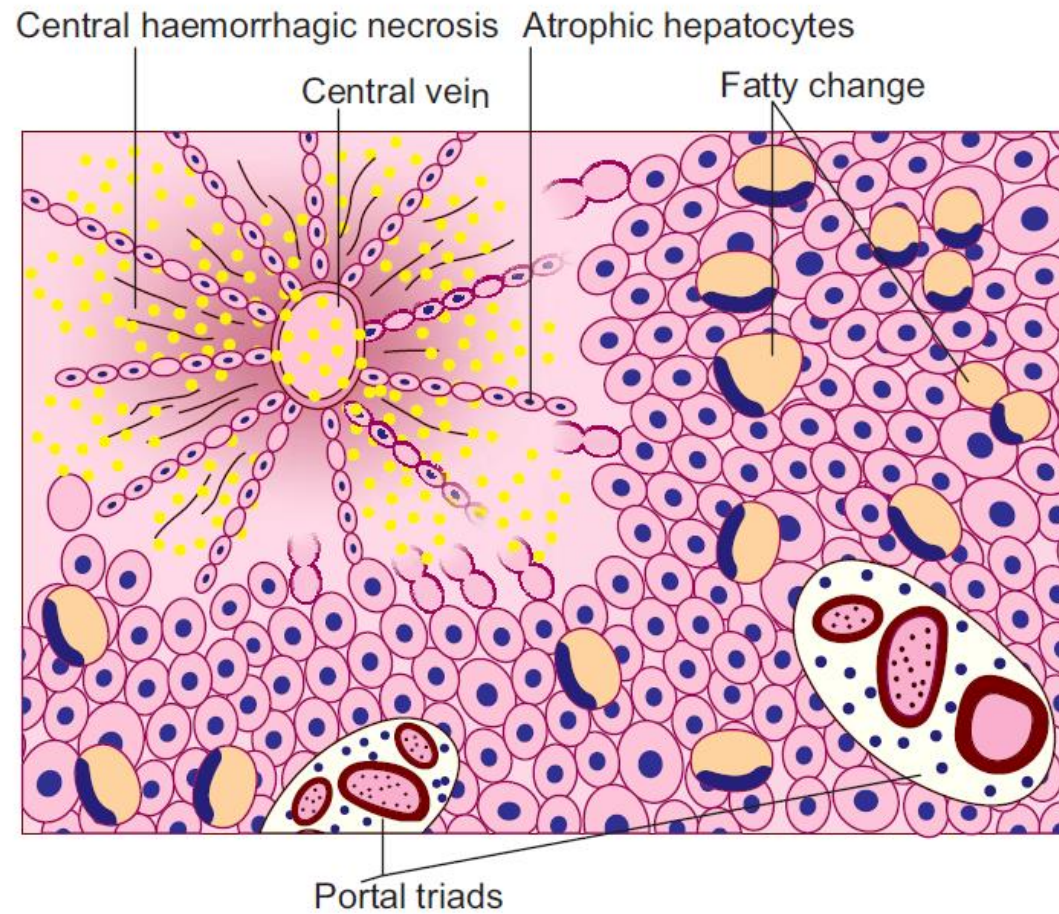
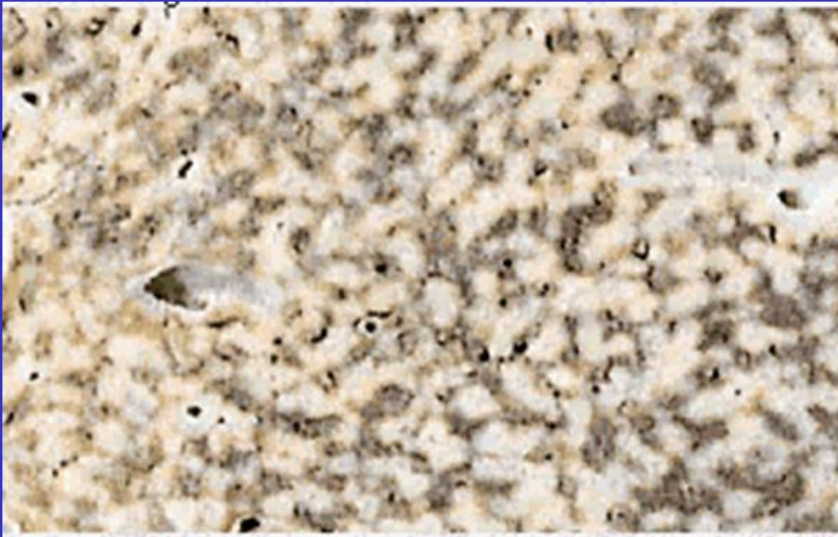


FIGURE 4.4. Photomicrograph of chronic passive congestion of liver showing centrilobular necrosis with loss or drop out of hepatocytes and peripheral fatty change.

Chronic venous (passive) congestion liver



The liver is enlarged and firm. The cut surface mottled dark/pale, simulating cut surface of a nutmeg-“nutmeg liver”. If the congestion is unrelieved, there will be necrosis of central zones with replacement by fibrosis (cardiac cirrhosis).

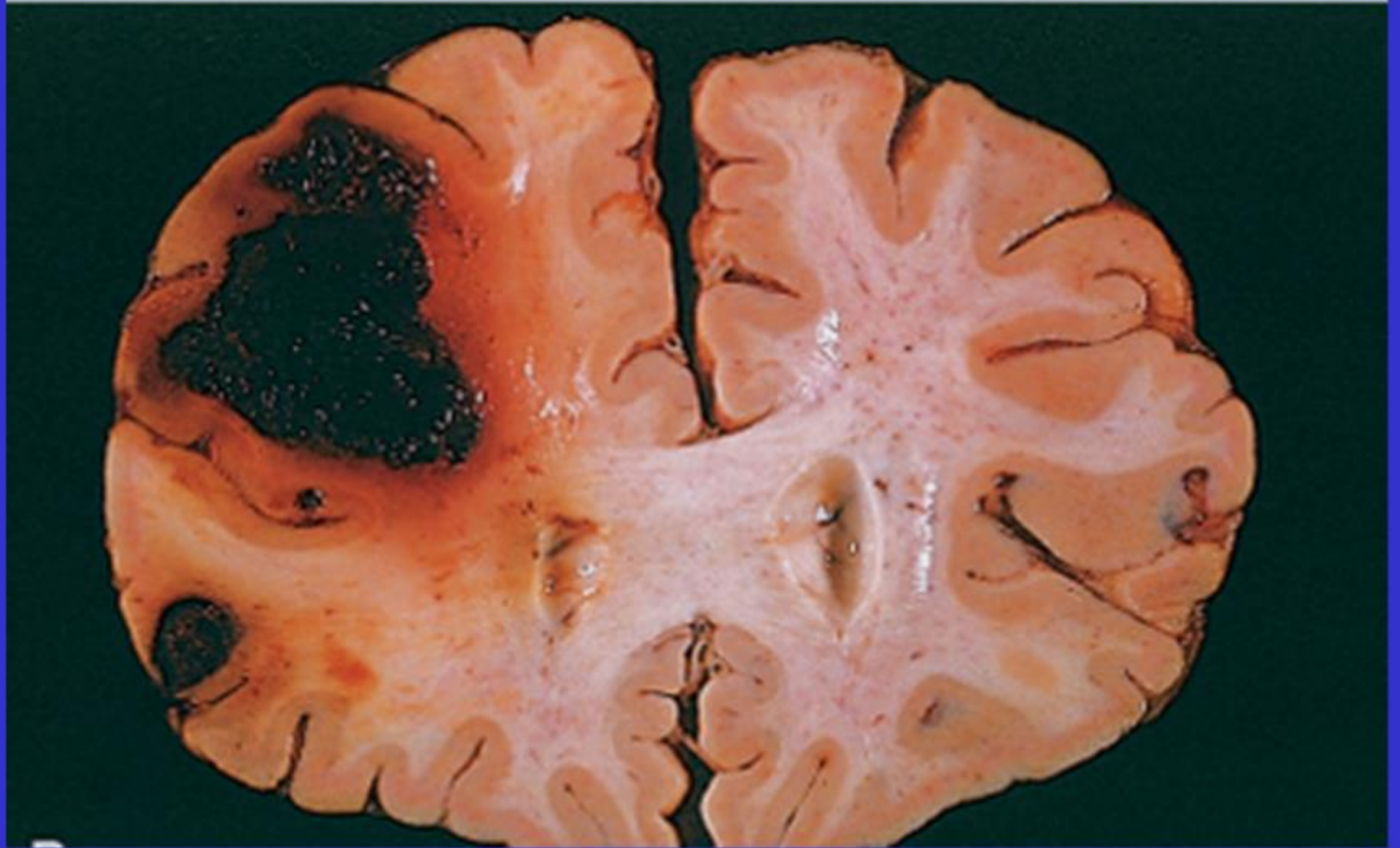


Q. Define and describe types of haemorrhage.

Extravasation of red cells due to vessel rupture is called haemorrhage.

- It may be external (external haemorrhage) or enclosed within the tissue (when it is called a haematoma).
- Haematoma may be insignificant (bruise) or large enough to cause fatality, eg, a large retroperitoneal haematoma or an internal (visceral) haematoma.
- Minute 1–2 mm haemorrhages into the skin, mucous membranes or serosal surfaces are denoted as petechiae (typically seen with locally increased intravascular pressure, low platelet counts and defective platelet function).
- Larger >3 mm haemorrhages are called purpura (associated with the same disorders as petechiae and also occur secondary to trauma, vasculitis or increased vascular fragility).
- Still larger >1–2 cm subcutaneous haematomas or bruises are called ecchymoses (generally seen after trauma).
- Accumulation of blood in body cavities may be called haemothorax, haemopericardium, haemoperitoneum and haemarthrosis (joints) depending on the cavity involved.

Hematomas can be relatively insignificant (e.g., a bruise) or can be due to massive bleeding as to cause death (e.g., a massive retroperitoneal hematoma resulting from rupture of a dissecting aortic aneurysm).





Write in detail on haemostasis.

Haemostasis is the mechanism which maintains the integrity of the circulatory system after vascular damage.

Normal haemostatic mechanism of the body has three components:

1. Vascular component: This involves a reflex spasm of the injured vessel (vasoconstriction), which minimizes the blood loss.

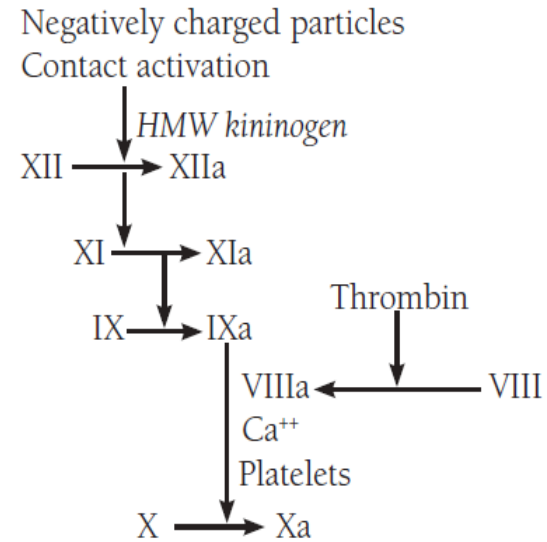
2. Platelet component: Platelets are anucleate discoid structures derived from marrow megakaryocytes. The cytoplasm of platelets contains three major types of storage granules:

- (i) Alpha granules containing a variety of proteins like fibrinogen and vonWillebrand factor
- (ii) Dense granules containing serotonin, ADP and calcium
- (iii) Lysosomal granules containing acid hydrolases

Following vessel constriction, platelets adhere to the vessel wall and also aggregate to form a platelet plug which seals off the vascular breach and arrests haemorrhage (primary haemostasis). This is followed by activation of the coagulation cascade and fibrin deposition (secondary haemostasis).

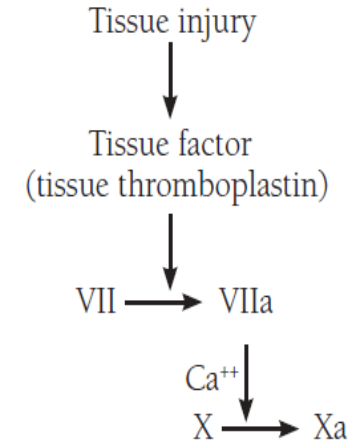
3. Components of the coagulation cascade: Coagulation cascade includes three pathways, namely, the **intrinsic** (Flowchart 4.4), **extrinsic** and the **common pathways** (Flowcharts 4.5 and 4.6). Intrinsic pathway is assessed in vitro by the activated partial thromboplastin time (aPTT). Extrinsic pathway is assessed by the prothrombin time (PT).

Intrinsic pathway



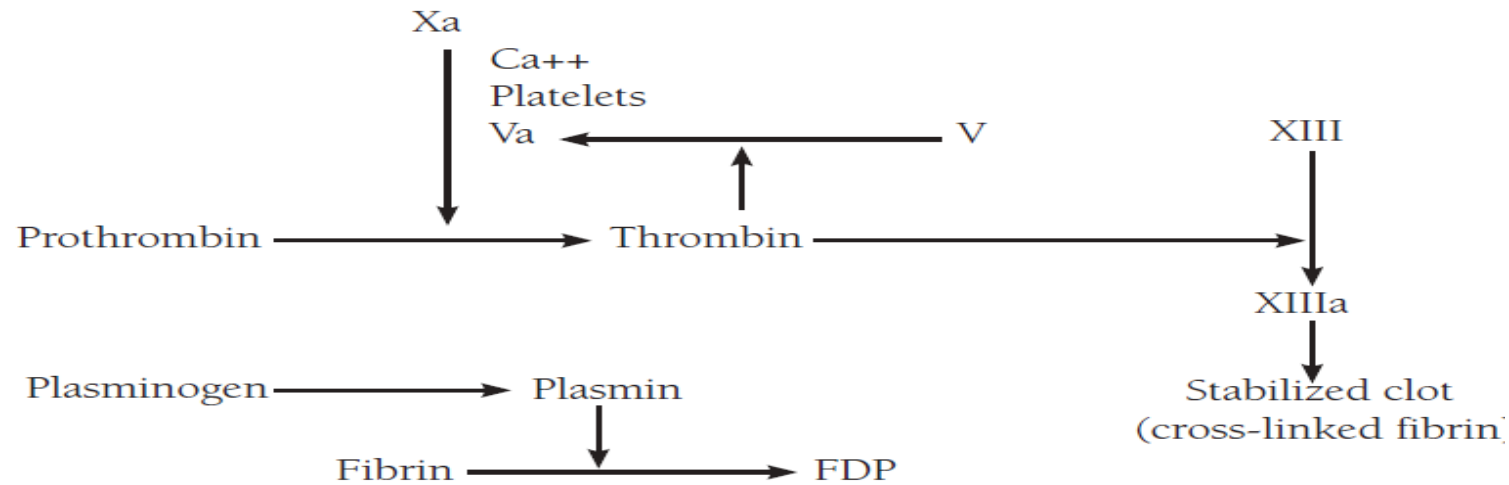
FLOWCHART 4.4. Intrinsic pathway of coagulation.

Extrinsic pathway



FLOWCHART 4.5. Extrinsic pathways of coagulation.

Common pathway



FLOWCHART 4.6. Common pathways of coagulation.

TABLE 4.4.**Coagulation factors**

I	Fibrinogen
II	Prothrombin
V	Proaccelerin
VII	Proconvertin
VIII	Anti-haemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma Thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin stabilizing factor

Prekallikrein: Fletcher factor

HMW kininogen: Fitzgerald factor

Inhibitors of Coagulation

The natural inhibitors of coagulation include

- Anti-thrombin III
- α -macroglobulin
- Heparin cofactor II
- Protein C and protein S

Fibrinolytic System

The physiological function of the fibrinolytic system is to digest deposits of fibrin (thrombi).

Q. Write briefly on the factors contributing to thrombus formation.

Thrombosis is the process of formation of a solid mass in the circulation constituted by platelets, fibrin and other entrapped blood elements. Vessel wall injury induces rapid recruitment of the circulating platelets to the site of injury, where they initiate formation of a thrombus.

There are three major contributors to thrombus formation:

1. **Endothelial injury**, which may be secondary to:

- (a) Myocardial infarction
- (b) Ulcerated atherosclerotic plaques
- (c) Cardiac surgery
- (d) Myocarditis
- (e) Infected valve disease
- (f) Prosthetic valves
- (g) Radiation injury
- (h) Chemical agents (smoking, hypercholesterolaemia, homocysteineamia, bacterial toxins and endotoxins).

2. Alteration in normal blood flow (stasis or turbulence):

Stasis is typically seen in hyperviscosity syndromes and polycythemia; where as, turbulence is commonly associated with hypertension. Alterations in normal flow result in:

- (a) Disruption of laminar flow
- (b) Decreased hepatic clearance of activated coagulation factors
- (c) Damage to endothelium

3. Conditions predisposing to hypercoagulability:

(a) Genetic:

- (i) Deficiency of antithrombotic factors like AT III, proteins C and S, Methylene tetrahydrofolate reductase (MTHFR) gene mutation and defects in fibrinolysis.
- (ii) Increased prothrombotic factors as in Factor V mutation/factor V Leiden (activated protein C resistance); prothrombin G20210A mutation (excessive levels of prothrombin); high levels of factors VII, XI, IX, VIII, von Willebrand factor and fibrinogen and homocysteinuria.

(b) Acquired:

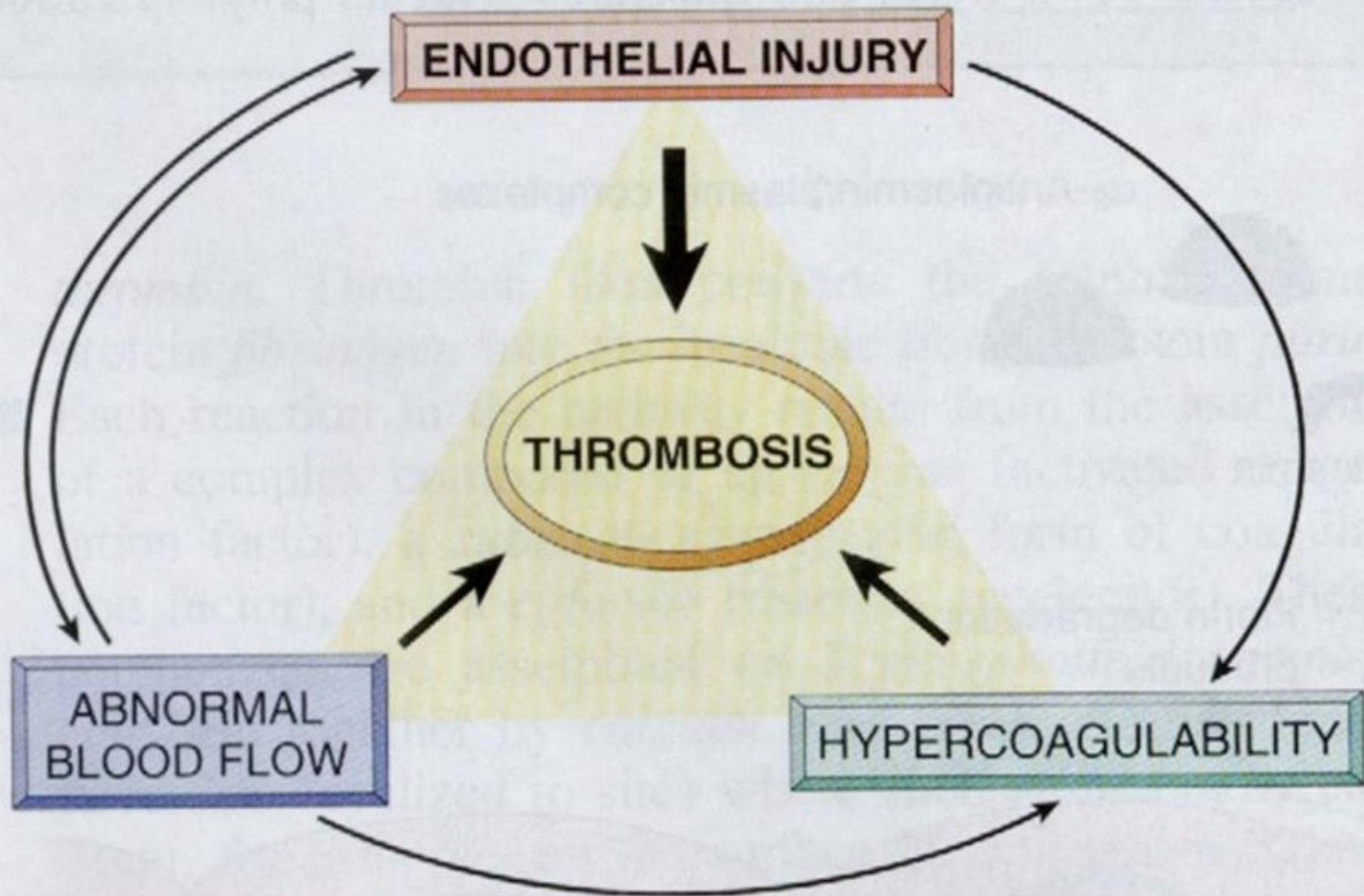
(i) **Venous stasis:** Prolonged immobilization and congestive cardiac failure

(ii) **Increased platelet activation:** Cancers, acute leukaemias, myeloproliferative disorders, paroxysmal nocturnal haemoglobinuria, prosthetic cardiac valves, atrial fibrillation, myocardial infarction and thrombotic thrombocytopenic purpura

(iv) **Increased hepatic synthesis** of coagulation factors or reduced anticoagulant synthesis: Oral contraceptives, pregnancy, etc.

(v) **Antiphospholipid syndrome**

(vi) **Tissue injury:** Surgery, fracture and extensive burns



Q. Write briefly on the morphology of a thrombus.

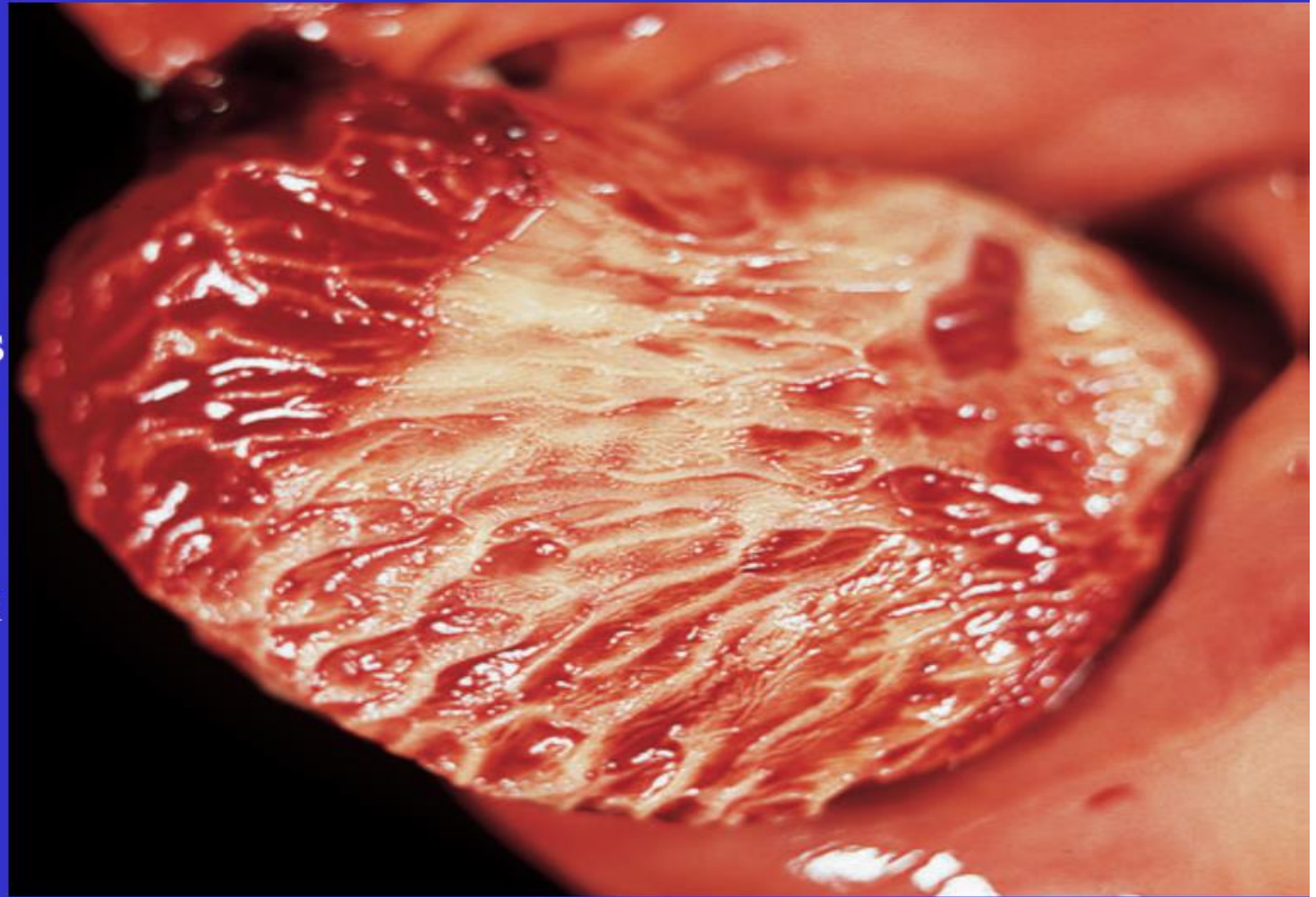
Thrombi are grey-white, friable, tangled strands of fibrin and platelets, which may form anywhere in the cardiovascular system, as in cardiac chambers, arteries and veins and capillaries.

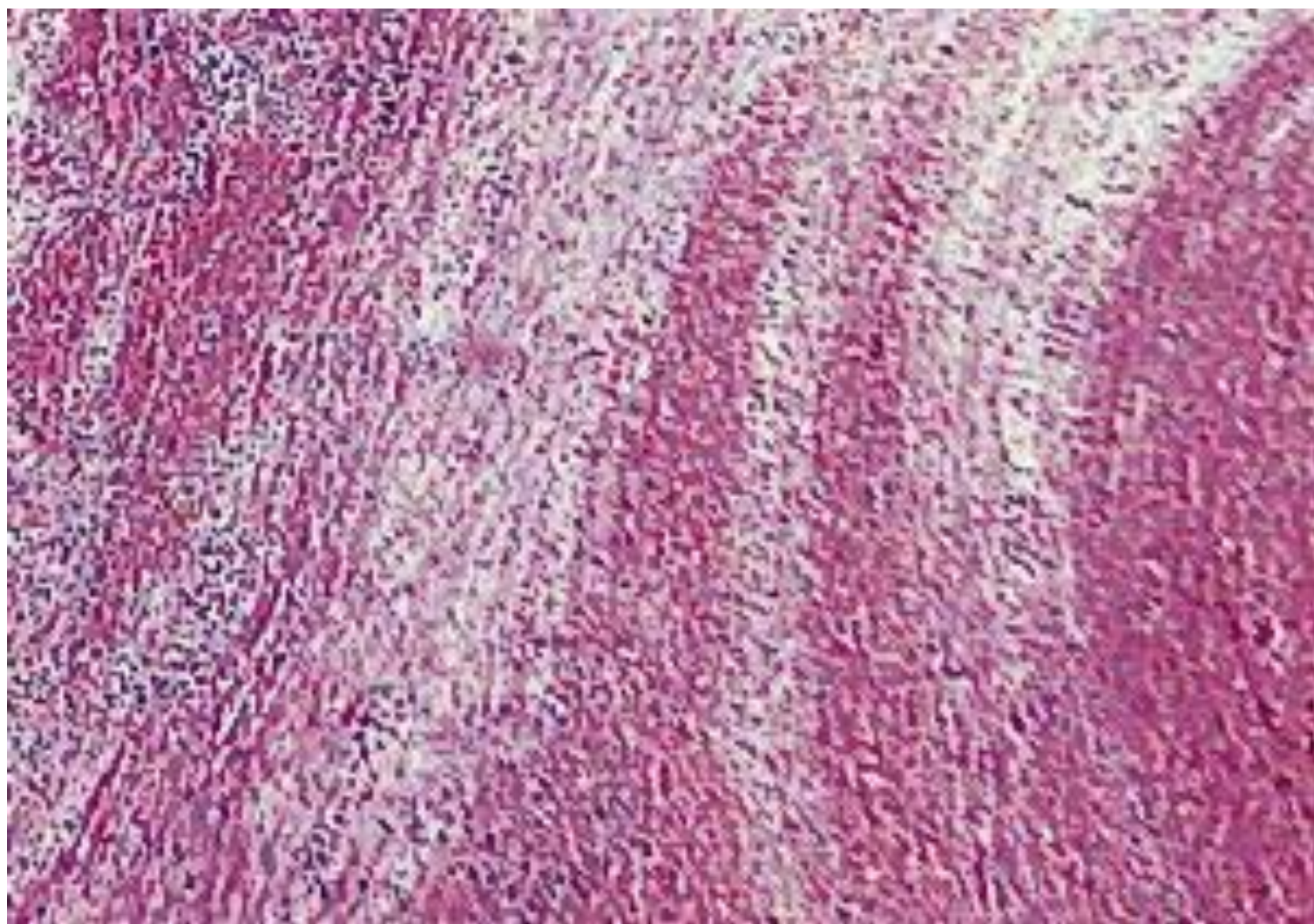
General Features of Thrombi

- Different sizes and shapes of thrombi may be seen, dictated by:
- Site of origin
- Circumstances leading to their development
- Cardiac thrombi mostly develop in the regions of turbulence and at sites of endocardial injury (atrial appendages, endocardial surface of a myocardial infarct and cardiac valves).
- **Thrombi in cardiac chambers or aorta** show the presence of **laminations or lines of Zahn** (paler layers of fibrin and platelets alternating with darker layers of RBCs).
- **Thrombi in smaller arteries or veins** do not show lines of Zahn.
- Mural thrombi are attached to one wall of an underlying structure, usually capacious lumina of heart chambers and aorta.

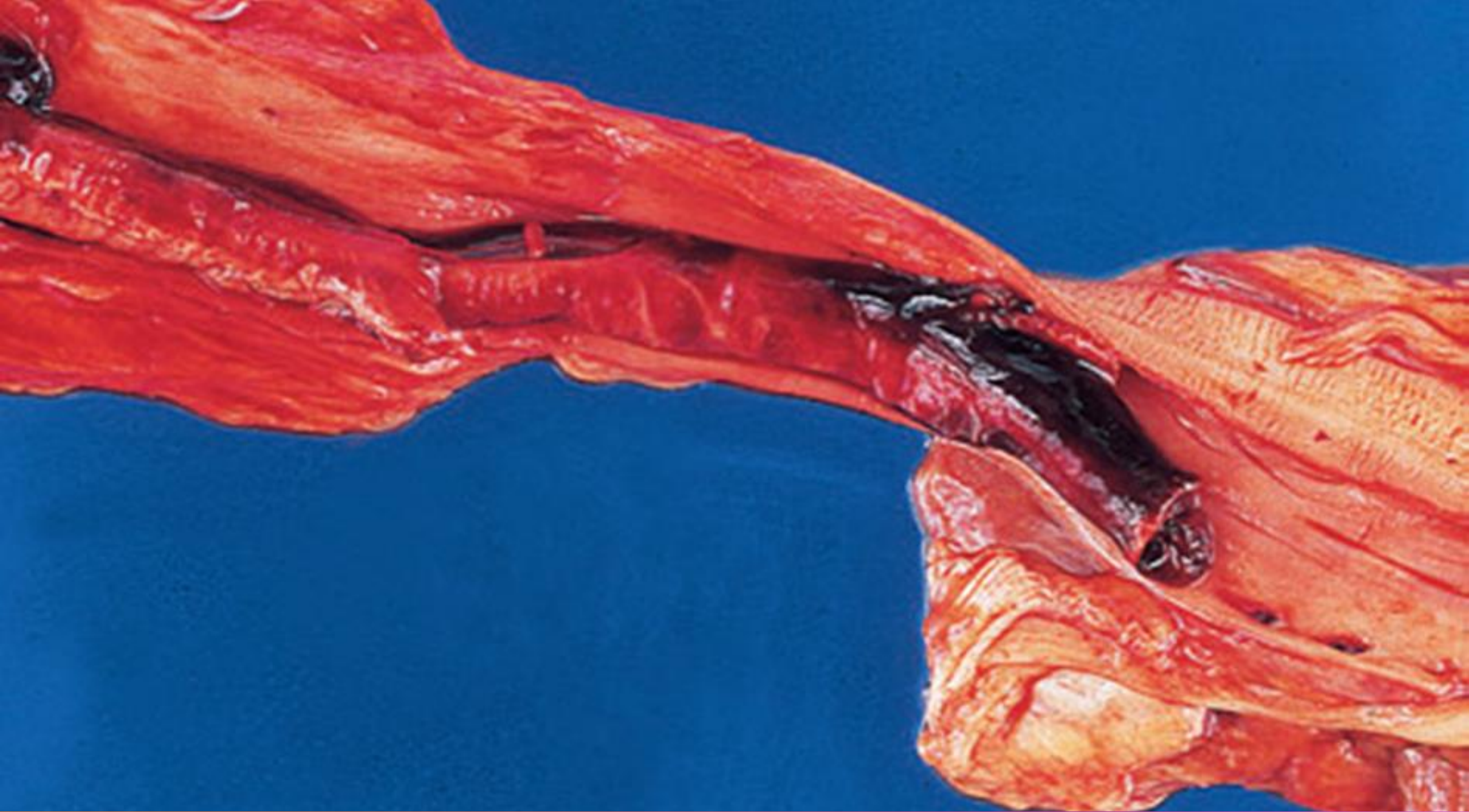
Cardiac auricle thrombus showing lines of Zahn

Thrombi have grossly & microscopically apparent laminations called *lines of Zahn*; these represent pale platelet and fibrin layers alternating with darker RBC-rich layers. Their presence can distinguish ante-mortem thrombi from the non-laminated postmortem clots seen after death. Such lines are less prominent in venous thrombi compared to arterial ones





- **Arterial thrombi** are **usually occlusive** when they involve smaller vessels; large vessels, eg, iliac and common carotid tend to have mural thrombi.
- **Venous thrombi** (phlebothrombosis) are **invariably occlusive and contain a large RBC component**, because these are formed in a relatively static environment. These are also called red or stasis thrombi. Other features of venous thrombi are as follows:
 - **Lines of Zahn are not well developed.**
 - **Mostly affect veins of lower extremity (90% cases).**
 - **May be confused with post-mortem clots.**
 - **Always have a point of attachment to the underlying structure, firmest at the point of origin.**
 - **Contraction of a thrombus gives way to a slit-like lumen which restores blood flow leading to propagation of the thrombus upstream and downstream.**



Q. Differentiate between arterial and venous thrombi.

Ans. Differences between arterial and venous thrombi are tabulated in [Table 4.5](#).

TABLE 4.5. Differences between arterial and venous thrombi		
Features	Arterial thrombi	Venous thrombi
Sites	Common in coronary, cerebral, iliac and femoral arteries (vessels with active blood flow)	Superficial varicose veins and deep veins of leg, eg, femoral and iliac veins (vessels with less active blood flow)
Pathogenesis	Due to endothelial injury (as in atherosclerosis or turbulent blood flow)	Due to venous stasis
Progression	Grows in a retrograde direction from point of attachment	Extends in the direction of blood flow
Occlusion	Do not occlude lumen completely	Invariably occlusive
Gross	Grey-white, friable, prominent lines of Zahn	Dark red with fibrin strands; lines of Zahn less prominent or absent
Microscopy	Lines of Zahn show paler layers of fibrin and platelets alternating with darker layers of RBCs	Constituted by more of RBCs and less of fibrin
Complications	Ischaemia/infarction of vital organs	Embolism, oedema, ulceration

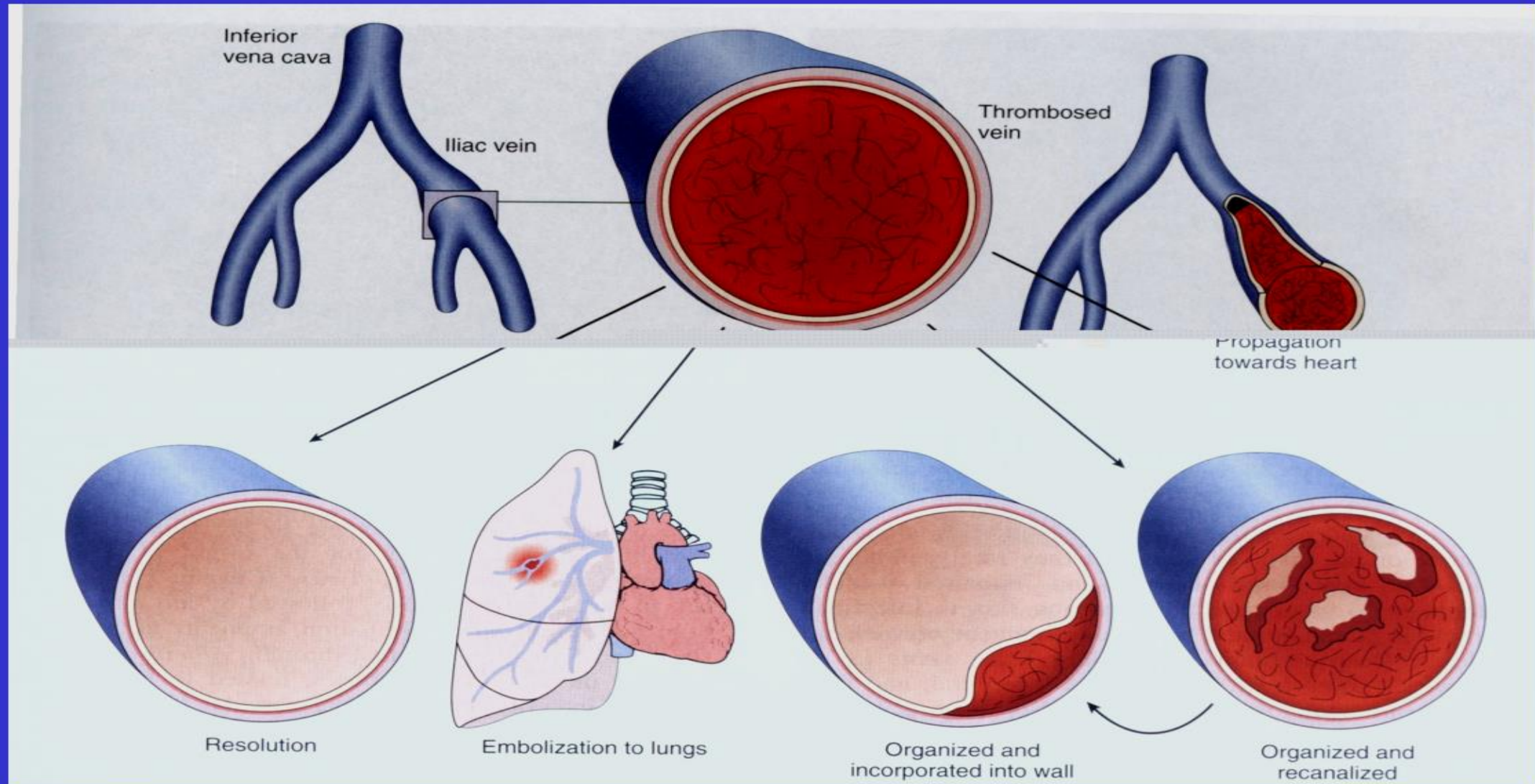
- Q. Differentiate between antemortem and post-mortem clot.

Q. Write briefly on fate of a thrombus.

A thrombus may undergo:

1. **Propagation** (accumulation of additional platelets and fibrin leading to progression)
2. **Embolization** (propagating tail fragments give rise to emboli)
3. **Dissolution** (fibrinolysis usually on the first or second day)
4. **Organization and recanalization** (ingrowth of endothelial cells, smooth muscle and fibroblasts)
5. **Inflammation and fibrosis** (central liquefaction, bacterial seeding and influx of inflammatory cells)

Potential outcomes of venous thrombosis



END