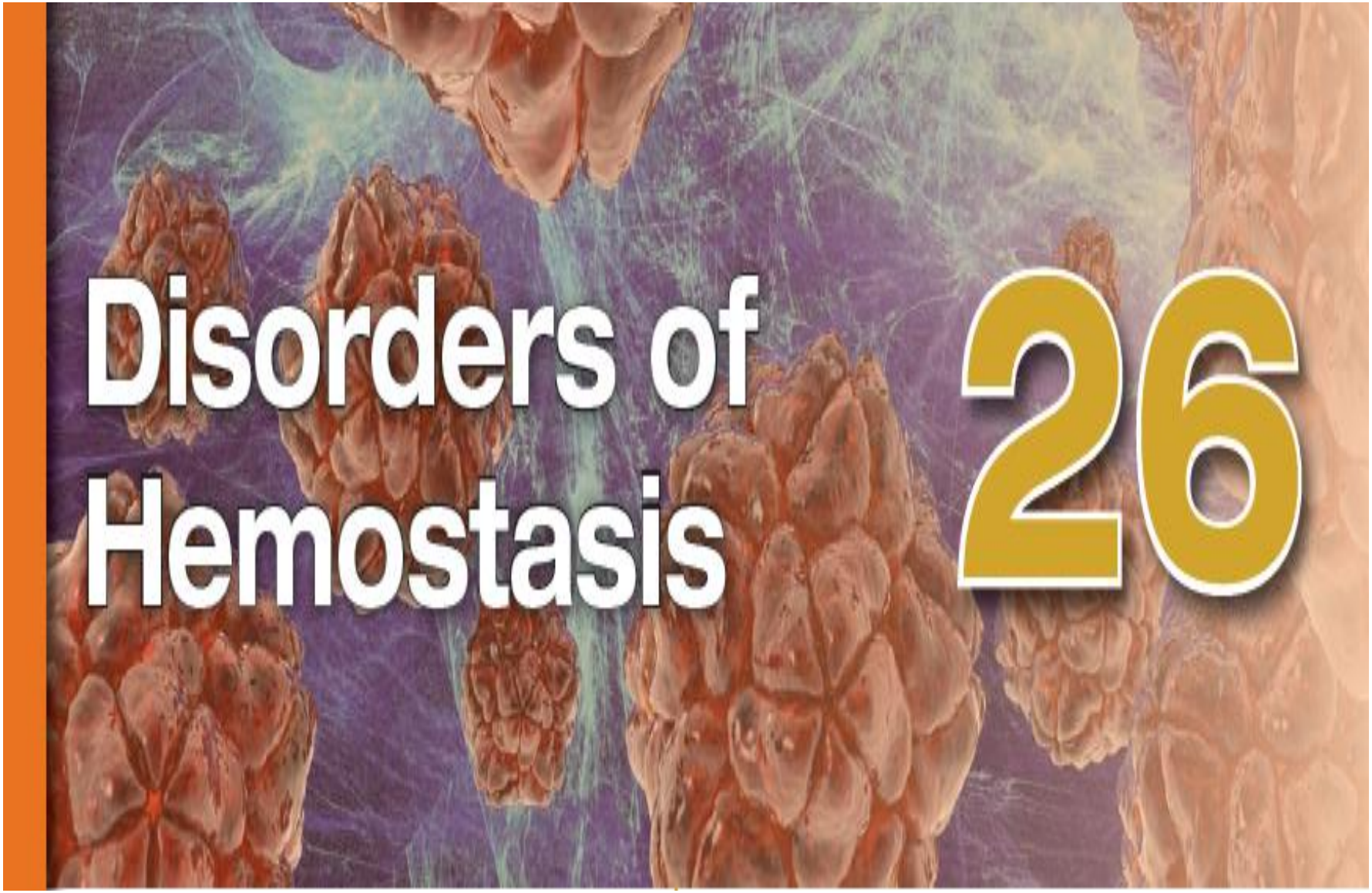

Disorders of Hemostasis
26

Disturbances of Homeostasis

1. Disturbances of Body Water and electrolytes

2. Disturbances of Haemostasis

3. Disturbances of Blood Flow

HYPEREMIA AND CONGESTION

- In both cases there is an increased volume and pressure of blood in a given tissue with associated capillary dilation and a potential for fluid extravasation.
- Hyperemia is an *active process* resulting from augmented (increased) blood flow due to arteriolar dilation (e.g., at sites of inflammation or in skeletal muscle during exercise). The affected tissue is redder and hotter than normal because of engorgement (filled/ swollen) with oxygenated blood.
- Congestion is a *passive process* resulting from impaired venous return out of a tissue. It may occur systemically, as in cardiac failure, or it may be local, resulting from an isolated venous obstruction. The tissue has a blue-red color *(cyanosis ازرقاق),* especially as worsening congestion leads to accumulation of deoxygenated hemoglobin in the affected tissues.

HYPEREMIA

CONGESTION

Abscess

Cellulitis

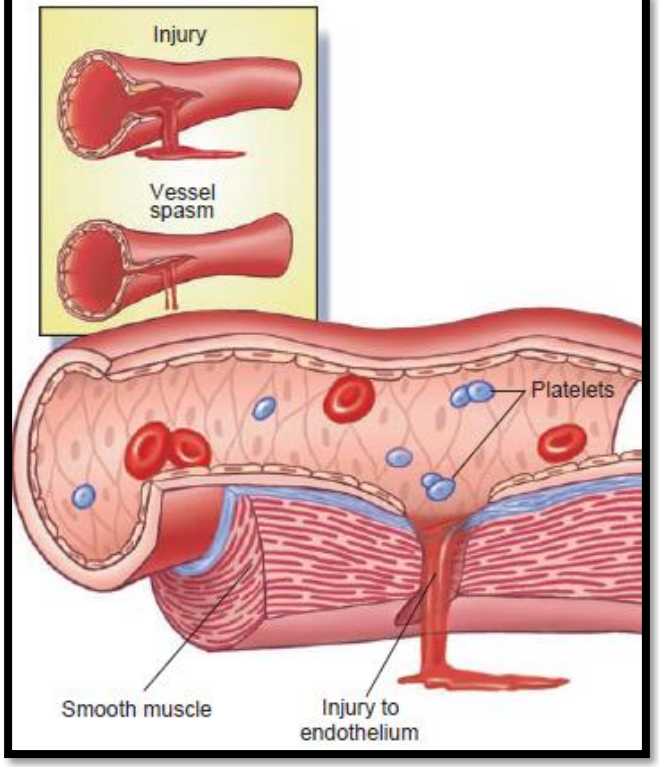
Hemostasis

- ***Hemostasis*** refers to the stoppage of blood flow.
- **Normal process of hemostasis** is regulated by a complex array of activators and inhibitors that maintain blood fluidity and prevent blood from leaving the vascular compartment (blood loss and hemorrhage) while inducing the rapid of a localised hemostatic plug at the site of vascular injury.

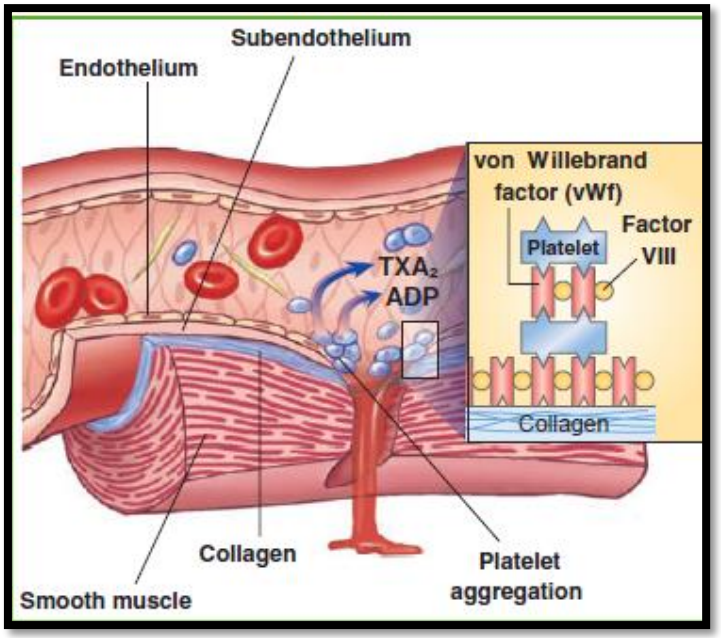
- Hemostasis is designed to maintain the integrity of the vascular compartment and is divided into three stages:

1. **Vascular constriction:** which constricts the size of the vessel and reduces blood flow (via both local nervous reflexes and local humoral factors).
2. **Formation of the platelet plug:** platelet adherence and formation of the platelet plug.
3. **Blood coagulation:** Blood coagulation is a complex process involving the sequential activation of various factors in the blood including the formation of fibrin which hold the platelet plug together.
4. **Clot retraction and clot dissolution**

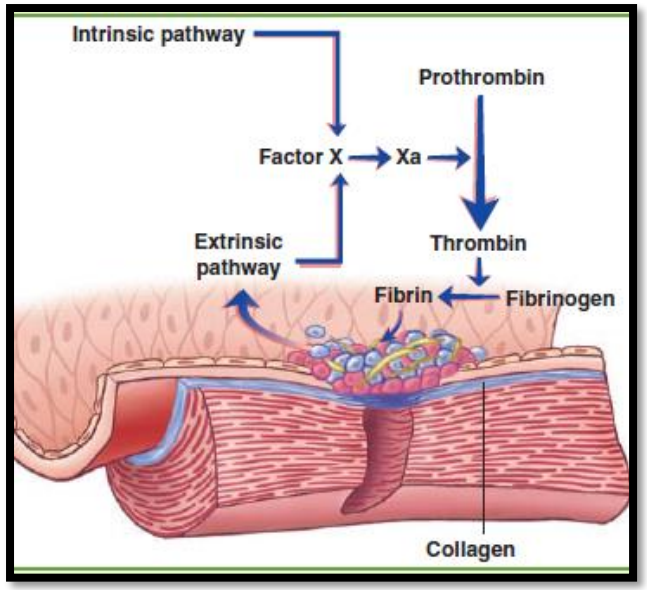
1.


Injury
Vessel spasm
Platelets
Smooth muscle
Injury to endothelium

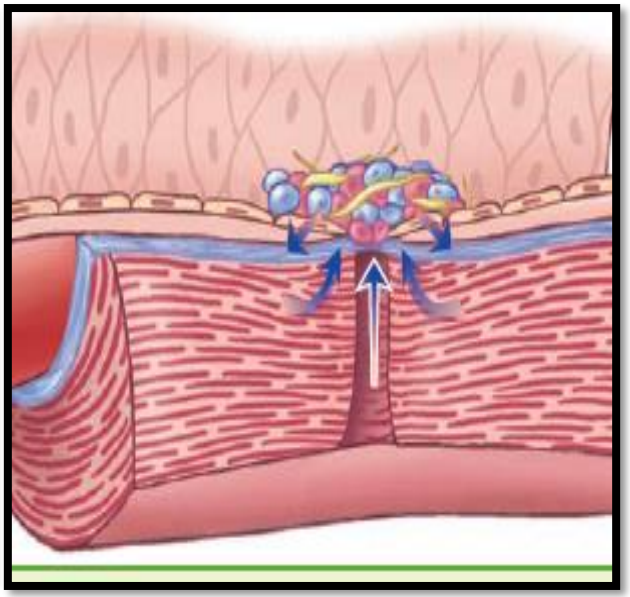
2.

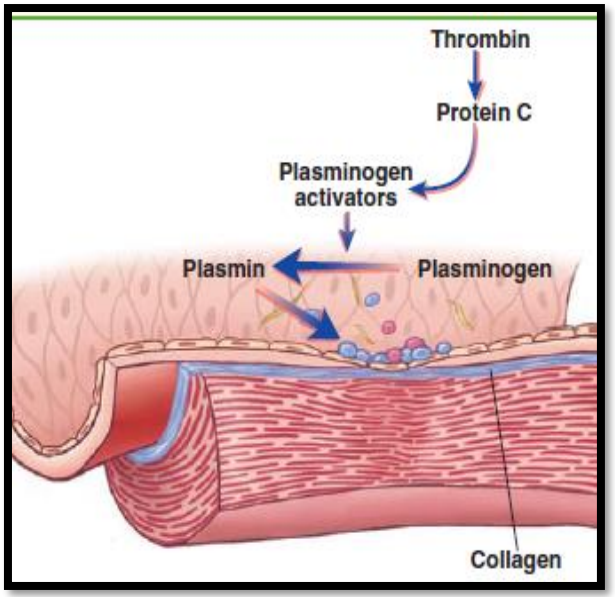

Subendothelium
Endothelium
von Willebrand factor (vWf)
Platelet
Factor VIII
TXA_2
ADP
Collagen
Collagen
Platelet aggregation
Smooth muscle

3.


Intrinsic pathway
Prothrombin
Factor X
Xa
Extrinsic pathway
Thrombin
Fibrin
Fibrinogen
Collagen

4.




Thrombin
Protein C
Plasminogen activators
Plasmin
Plasminogen
Collagen

Disturbances of Hemostasis

- **Hemostasis** is **abnormal** when it causes inappropriate blood clotting or when clotting is insufficient to stop the flow of blood from the vascular compartment. In other words, disorders of hemostasis fall into two main categories:

1. The failure of blood to clot in response to an appropriate stimulus **(bleeding).**
2. The inappropriate formation of clots within the vascular system **(thrombosis)** in uninjured vessels or thrombotic occlusion of a vessel after relatively minor injury.

Hemorrhage

Thrombosis

(1) Hemorrhage

Definition: loss of blood from circulation or extravasation of blood from blood vessels into the extravascular space.

Causes:

A. **Traumatic Injuries** (causes rupture of large artery or vein resulting in sever hemorrhage)

B. **Pathological Injuries** (bleeding associated with platelets disorders including number and function, coagulation factors and blood vessels integrity)

1. **Petechia** (plural: petechiae) is a small (1 - 2 mm) red or purple spot which appears on the skin and mucous membrane, caused by a minor/ minute hemorrhage (broken capillary blood vessels).

Causes

1. The most common cause of petechiae is through **physical trauma due to excessive pressure** (e.g., a hard bout of coughing, holding breath, vomiting or crying, which can result in facial petechiae, especially around the eyes or when a tourniquet is applied to an extremity)
2. Petechiae may be a sign of thrombocytopenia (low platelet counts not function)
3. Sign of certain infections (e.g., HIV which may suppress the production of megakaryocytes, the platelet precursors.)
4. Clotting factor deficiencies.
5. **Petechiae on the face and conjunctiva** (eyes) can be a sign of a death by asphyxiation (result from an increase of pressure in the veins of the head and hypoxicdamage to endothelia of blood vessels)

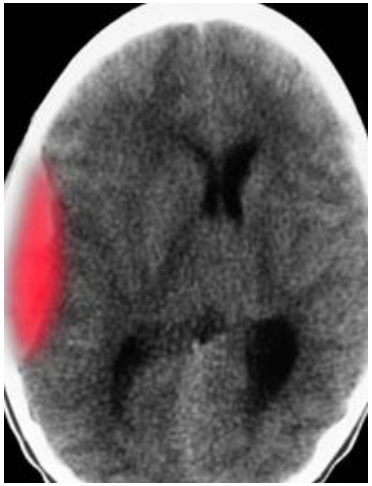
kidney

3. Ecchymosis (bruises) is a small hemorrhagic spot, larger than a petechia, in the skin or mucous membrane caused by the extravasation of blood into the subcutaneous tissues.

- It is purple at first, then turns green, then yellow before resolving.The erythrocytes in the local hemorrhage are phagocytosed and degraded by macrophages. The release hemoglobin is red-blue in colour, which is enzymatically converted into bilirubin (blue-green colour) and eventually into hemosiderin (golden-brown) accounting for the characteristic colour changes in a hematoma

- A good example of an ecchymosis is a black eye.

2. Hematoma is a localized collection of extravasated blood trapped in an organ, space or tissue (i.e., hemorrhage confined within tissue or cavity), resulting from a break in the wall of a blood vessel.



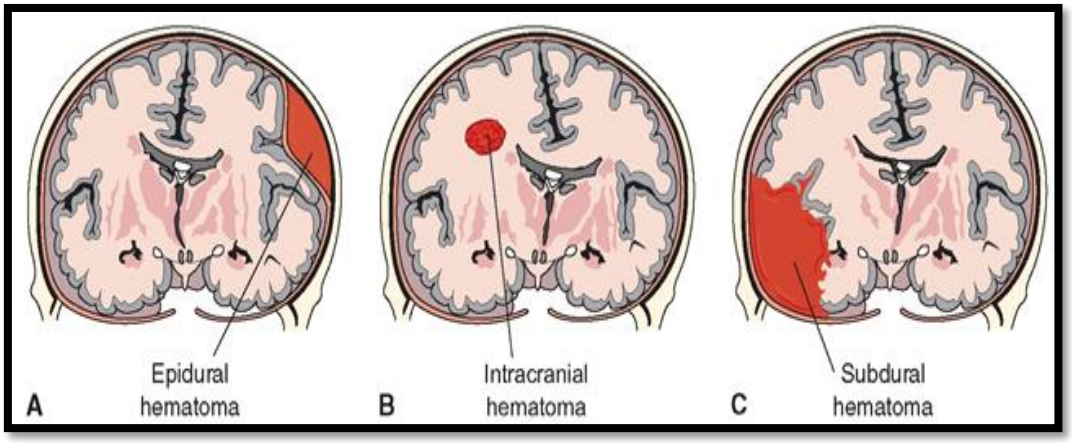
Intra Cranial Hemorrhage

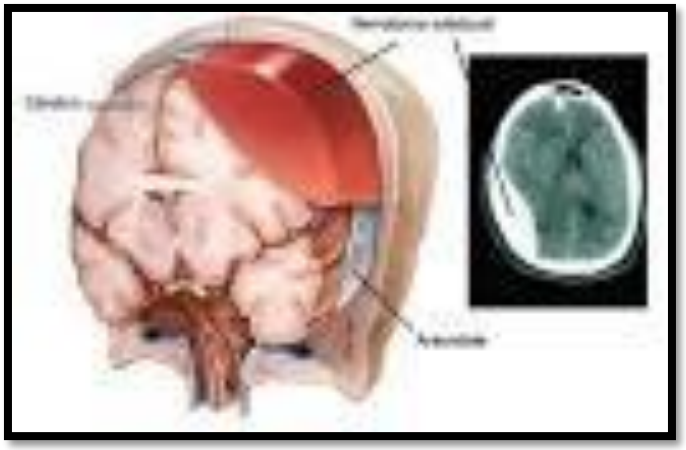
Nail Hemorrhage

Intracranial hemorrhage (bleeding within skull) occurs when blood vessels within the skull ruptured or leaks. It results from physical trauma (as in head injury) or non-trauma (like (a) ruptured aneurysm (formed in weakened blood vessels wall), (b) excessive usage of anticoagulant therapy or (c) disorder with blood clotting).

Intracranial hemorrhage can lead to increased intracranial pressure, which may crush the delicate brain tissue and decrease its blood supply.

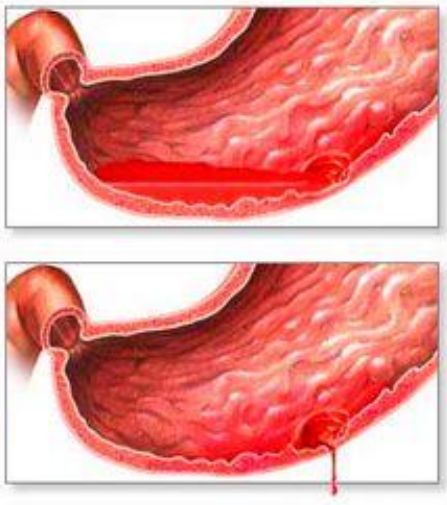
X-ray CT scan (computed tomography) is the definitive tool for accurate diagnosis of an intracranial hemorrhage.





4. Hematoemesis is the vomiting of blood. It is a regurgitation (ارتجاع) of blood from the upper GI tract, and the most common cause of the upper gastrointestinal intestinal tract bleeding are **peptic ulcer, gastritis and esophagitis**.

The color of the vomitus depends on the contact time with the hydrochloric acid of the stomach, if vomiting occurs early after the onset of bleeding, it appears **red**; with delayed vomiting, it becomes **dark red, brown or black**. If blood has been retained in the stomach the digestive processes changes the hemoglobin to a brown pigment, which gives the vomitus a **coffee-ground appearance.** The vomited blood might be mixed with food particles.



Bleeding Gastric Ulcer

Bleeding Esophageal Varices

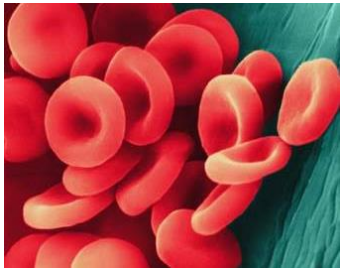
5. Hemoptysis: Coughing of Fresh Blood ?

Hemoptysis means blood in sputum combined with cough or expectoration of blood from the larynx, trachea, bronchi and the lungs. Causes include TB , bronchititis, and lung neoplasm (in smoker). In these conditions, the blood vessels are eroded.

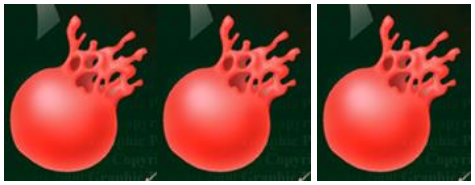
Table 1: Comparison between *hemoptysis* and *hematemesis*

Features	Hemoptysis	Hematemesis
Sputum features	-bright red or pink-frothy -pH: alkaline -consistency: liquid with clotted look -content: mixed in with sputum	-dark red or brown if lower in GI tract, bright red if higher up-usually not frothy -pH: acidic -consistency: ground coffee, stale blood appearance -content: may have food particles
History	-no nausea or vomiting-may have history of lung disease -may be associated with coughing or gurgling	-presence of nausea or vomiting -may have history of gastrointestinal or hepatic disease

6. Hematuria: Blood in Urine caused by bleeding in Urinary Tract



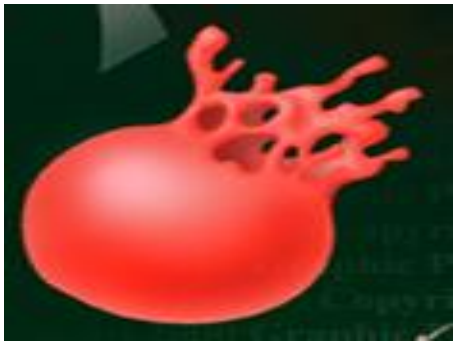
7. Hemoglobinuria: Hemoglobin in Urine caused by Hemolysis



6. Hematuria is the presence of red blood cells (erythrocytes) in the urine it may be a sign of a kidney stone or a tumor in the urinary tract. If white blood cells are found in addition to red blood cells, then it is a signal of urinary tract infection.
Microscopic hematuria the urine contains small amount of blood that is too low to change the color of the urine, so it can be seen only with microscope.
Otherwise it is called **macroscopic or " frank" or "gross" hematuria** when the urine can be seen in the urine as reddish in color.

7. Hemoglobinuria is a condition in which the hemoglobin is found in abnormally high concentrations in urine. The conditions is usually associated with hemolytic anemia, where there is increased plasma hemoglobin (due to (RBCs) are destroyed, thereby releasing free hemoglobin into the plasma) some of which is filtered by the kidneys which excrete into the urine giving urine a **purple color**. Causes also include glomerulonephritis , burns, sickle cell anemia. Colored urine can results also after eating beets (شمندر) or from drugs like rifampicin and phenazopyridine.

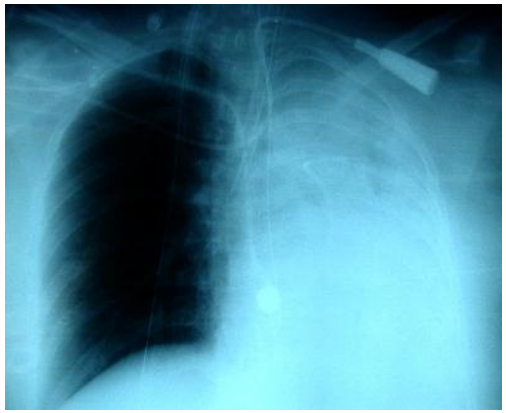
Favism describes clinical presentation of acute hemolytic crises as a consequence of eating broad beans (which contain oxidant substances) in a subgroup of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD supplies NADPH which in turn maintains glutathione in its reduced form and subsequently highly efficient antioxidant. Thus, in those patients the level of glutathione is low making red cell highly vulnerable to oxidative damage and thus liable to hemolysis (oxidative destruction of RBCs) particularly in the presence of high levels of oxidants.



8. **Hemothorax**: presence of blood in pleural cavity

- **Hemothorax** (haemorrhgical pleural effusion (escape from the blood vessels into the tissues or cavity)) in which blood accumulate in the pleural cavity (between chest wall and lung). Its cause is usually traumatic, from a blunt or penetrating injury to the thorax. (The pleura is a thin, double-layered serous membrane that encases the lungs).

Normal chest



Blood in pleura (hemothorax)

- **Pneumothorax** is an abnormal collection of air or gas in the pleural space. It can be caused by a blunt or penetrating chest injury (stab or gunshot), certain medical procedures, or damage from underlying lung disease.
- **An empyma** is a collection of pus within a naturally existing naturally anatommical cavity. For example pleural empyema is empyema of pleural cavity. It must be differentiated from an abscess which is a collection of pus in a newly formed cavity.

- **Pulmonary edema** is a fluid accumulation in the air spaces and parenchyma of lungs.

9. **Menorrhagia** is abnormally heavy and prolonged menstrual period at regular intervals. A blood lose of greater than 80 ml or lasting for more than 7 days constitute menorrhagia. It can be caused by abnormal blood clotting, or disorders of the endometrial lining of the uterus. It may be associated with abnormally painful periods (dysmenorrhea).

10. **Metrorrhagia** is uterine bleeding at irregular intervals which occurs between periods. It can be a sign of hormone imbalance, endometriosis, uterine fibroids or cancer of the reproductive organs.

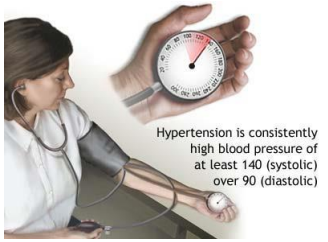
- Endometriosis occurs as endometrium that normally grows inside the uterus grows outside the uterus like on the ovaries, fallopian tubes, bowels, or bladder, so that the displaced endometrial tissue continues to act as it normally would — it thickens, breaks down and bleeds with each menstrual cycle. Because this displaced tissue has no way to exit your body, it becomes trapped.
- Uterine fibroids are muscular tumors that grow in the wall of the uterus. Fibroids are almost always benign (not cancerous).

- Due to repeated excessive bleeding, it can cause significant iron deficiency anemia.

Endometrial Bleeding

11. Epistaxis (nosebleed) is hemorrhage from the nose usually associated with rupture of a blood vessel within the richly perfused nasal mucosa.

- Cause could be trauma, an increased blood pressure tends to increase the duration of massive spontaneous epistaxis (an early sign of hypertension). Spontaneous epistaxis is more common in elderly as the nasal mucosa lining become dry and thin and blood pressure tends to be higher.



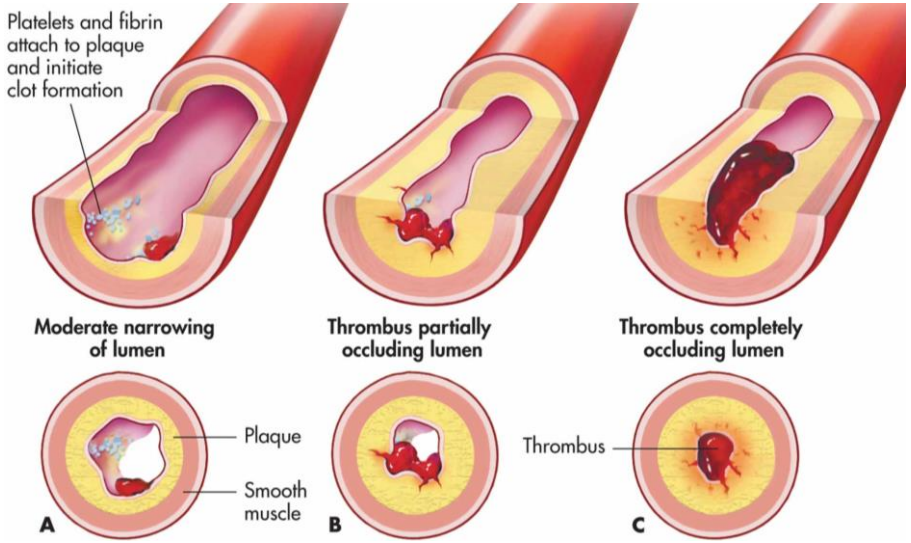
12. Melena: refers to the black **"tarry" feces** that are associated with **upper GI bleeding (blood in stomach due to peptic ulcer or in duodenum due to duodenal ulcer)**. The black color is caused by the hemoglobin in blood altered by digestive chemicals and intestinal bacteria. Only blood that originates from a high source (such as the small intestine) or bleeding from a lower source that occurs slowly enough to allow for enzymatic breakdown is associated with melena.

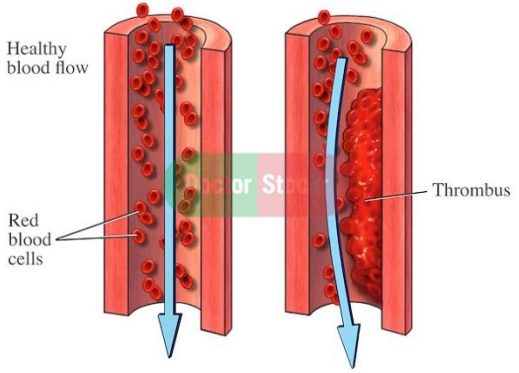
- **Iron supplements** may cause a grayish-black stool that should be distinguished from the black, tarlike stool that occurs from bleeding ulcers.

- **Hematochezia** Is bleeding originate from the lower GIT tract (such as the sigmoid colon and rectum) are generally associated with the passage of bright red blood or hematochezia, particularly when brisk (quick).

(2)Pathological Thrombosis

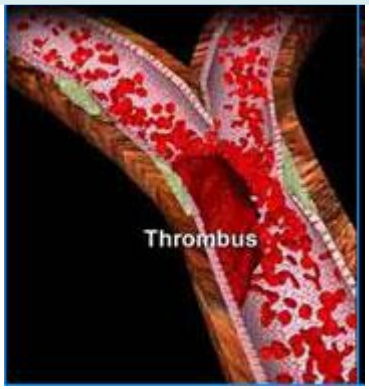
Definition: is a gradual formation of semi-solid mass called thrombus from the blood constituents (platelets + fibrin) inside cardio-vascular system during life.

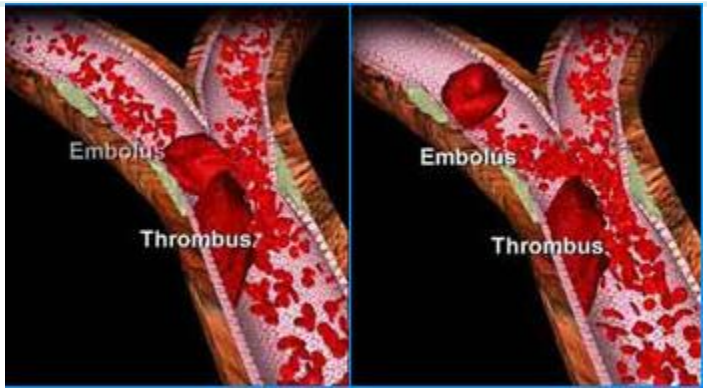




Pathological thrombosis can be classified into: venous arterial or cardiac (endocardium) thrombosis

Useful Thrombus to Arrest Bleeding





Harmful Thrombus leads to vascular occlusion

There are three primary influences on thrombus formation called Virchow's triad (ثلاثي) :

1. Endothelial injury.
2. Stasis or turbulence of blood flow.
3. Blood hypercoagulability.

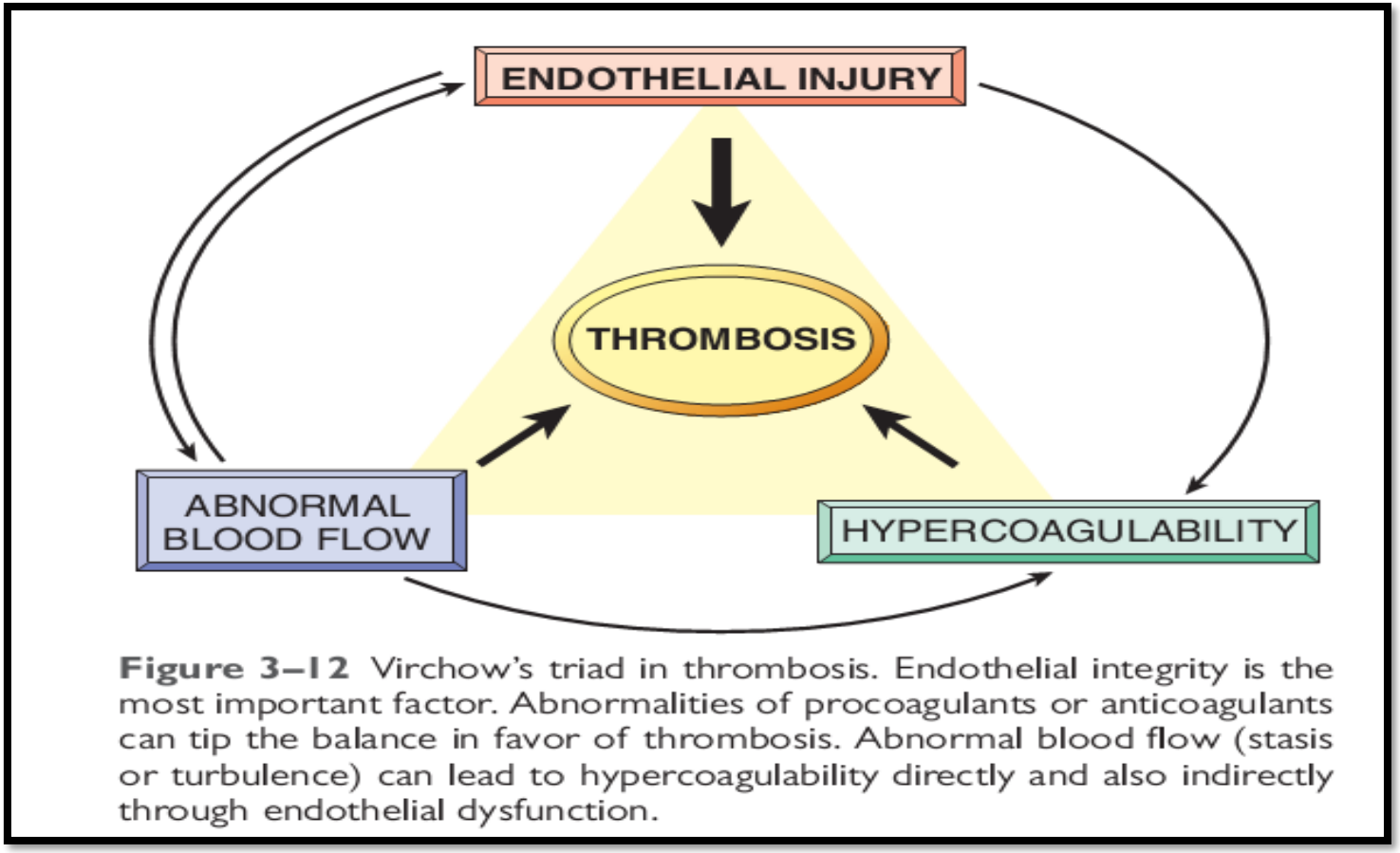


Figure 3–12 Virchow's triad in thrombosis. Endothelial integrity is the most important factor. Abnormalities of procoagulants or anticoagulants can tip the balance in favor of thrombosis. Abnormal blood flow (stasis or turbulence) can lead to hypercoagulability directly and also indirectly through endothelial dysfunction.

Causes of Thrombosis

1. Endothelial injury (leads to endothelial loss)

Is an important cause of thrombosis especially in the heart and the arteries **why???** (because of the normally high flow rates of blood in these compartments which accordingly prevents clotting by preventing platelet adhesion or diluting coagulation factor).

- **Loss** of **endothelium** exposes sub-endothelial ECM (connective tissue) **leading to** **(1)** platelets adhesion, **(2)** release of tissue factor, and **(3)** reduces local production of PGI2 and plasminogen activators. **Examples of thrombosis related to endothelial damage** are **(1)** the formation of thrombi in cardiac chamber after myocardia infarction, **(2)** over ulcerated plaques in atheroscleortic arteries allows the exposure of subendothelial cells to platelets, or **(3)** at sites of traumatic or inflammatory vascular injury (vasculitis).

- The **dysfunctional** **endothelium** stimulates greater amounts of pro-coagulant factors (platelets adhesion molecules, tissue factors) and synthesizes lesser amount of anticoagulant molecules such as (PGI2) and nitric oxide (both mediators are vasodilator and inhibitors of platelet aggregation). In other words, endothelial dysfunction is associated with imbalance between prothrombotic and antithrombotic activities of endothelium. Endothelial dysfunction (in the absence of endothelial cells loss) can be induced by: **(1)** hypertension, **(2)** turbulent (sudden and violent changes) blood flow, **(3)** bacterial products, **(4)** radiation injury, **(5)** hypercholesterolemia, and **(6)** toxins absorbed from cigarette smoke.

Causes of Thrombosis

2. Alterations in normal blood flow:

- **Normal blood flow** allows platelets to flow centrally separated them from the endothelium by a slower moving zone of plasma. Thus, stasis and turbulences cause the following: **(1)** Allow the platelet to contact with endothelium. **(2)** Prevent dilution of activated clotting factors by fresh-flowing blood. **(3)** Retard the inflow of clotting factor inhibitors and permit the build up of thrombi. **(4)** Promote endothelial cells activation resulting in local thrombosis and leukocytes adhesion.
- **Turbulence** contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction.
- **Stasis** is a major contributor to the development of venous thrombi.
- **Examples of conditions causes blood stasis** which consequently permits the formation of clot: **(1) Myocardial infarction** results in noncontractile myocardium. **(2) Atrial fibrillation (>200,300,400 beats per min)** a type of cardiac arrhythmia, or irregular heartbeat. When the atria beat improperly, blood doesn't flow through the heart as it should. This can cause blood to pool in the heart's chambers, possibly resulting in blood clots. **(3) Varicose veins** occurs most often between the knee and foot. They're caused when the tiny valves in the vein that push blood along begin to weaken. As the valves leak, blood that should be headed back up the leg to the heart and lungs instead seeps backward into the vein. This backflow pools in the vein and may encourage clot formation.

Causes of Thrombosis

3. Thrombophilia or hypercoagulability:

- **Definition:** is an abnormality of blood coagulation that increases the risk of thrombosis.
- The most common **conditions** associated with thrombophilia are: (a) Deep vein thrombosis (DVT) and (b) Pulmonary embolism (PE).
- It can be divided into: (1) Congenital (inheritable). (2) Acquired.

Congenital	Acquired
• **Common causes** which results in overactivity of coagulation factors: 1. Mutation in factor V Leiden gene. 2. Mutation in prothrombin gene.	• **High risk** for thrombosis: 1. Prolonged bedrest. 2. Myocardial infarction. 3. Cancer.
• **Rare causes** which results in deficiency in anticoagulants: 1. Antithrombin deficiency. 2. Protein C deficiency.	• **Low risk** for thrombosis: 1. Oral contraceptive use (containing estrogen). 2. Hyperestrogenic states (pregnancy)

Other risk factors for a blood clot in a vein include: (stasis and genetic errors in the clotting mechanism)

❖ Differentiate between the **cause** and the **risk factor**

- A previous blood clot
- Obesity
- Immobility
- Surgery increase the coaguability of blood in addition to immobility.
- Significant injury or trauma
- During and after pregnancy (due to increased levels of estrogen)

The risk factors for a blood clot in an artery include: (turbulence and injury in endothelium)

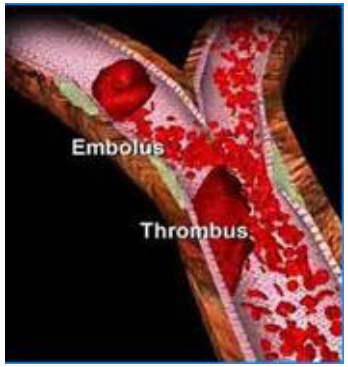
- High-fat diet
- Smoking
- Alcohol
- Obesity
- Lack of exercise (decreases HDL) leads to arthrosclerosis.
- Diabetes (both type 1 diabetes and type 2 diabetes)
- Hypertension

Fate of Thrombosis

1. **Resolution (dissolution)** by Fibrinolysis.

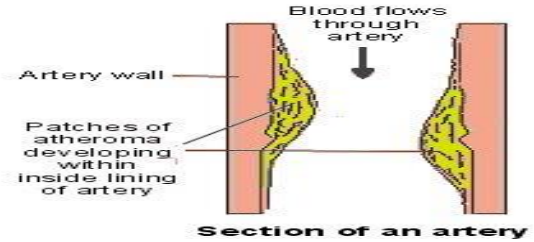
2. **Propagation** resulting in local **occlusion** of blood vessels (Gradual Process due to accumulation of additional platelets and fibrin resulting in tissue injury)

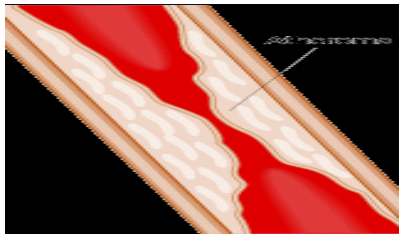
3. **Embolism** (Sudden Process, distal part, resulting in tissue injury)



Clinical Correlations: Venous versus Arterial Thrombosis

- Atheroscelerosis (in which atheroma is fomed) is a major initiator of thromboses in arteries because it is associated with loss of endothelial integrity and abnormal vascular flow. **Atheroma** is a fatty mass that develop within the inside lining of arteries. Patches of atheroma can become larger and thicker making an artery narrower. This can reduce the blood flow through the artery. Sometimes, a blood clot (thrombosis) forms over a patch of atheroma and completely blocks the blood flow causing a heart attack, a stroke, etc....





- Venous thrombi can cause congestion and edema in vascular beds distal to an obstruction, but they are most worrisome for their capacity to embolise to the lungs and cause death (**upstream)**.

Embolism

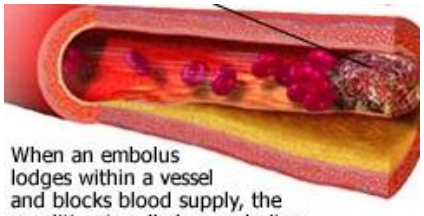
- **Definition**: sudden transference of foreign substance (called **embolus**) inside the cardiovascular system causing sudden occlusion of an artery and consequently infarction of the downstream tissues.
- **Embolus** is a detached intravascular solid, liquid or gaseous mass that is carried by the 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.
- **Types of embolism:**

➢ FAT EMBOLISM (embolus as fatty marrow) e.g., bone fracture: Most of the bone marrow in adults is fatty one (yellow). Fat enters circulation by rupture of the marrow vascular sinusoids or rupture of venules in injured tissues.

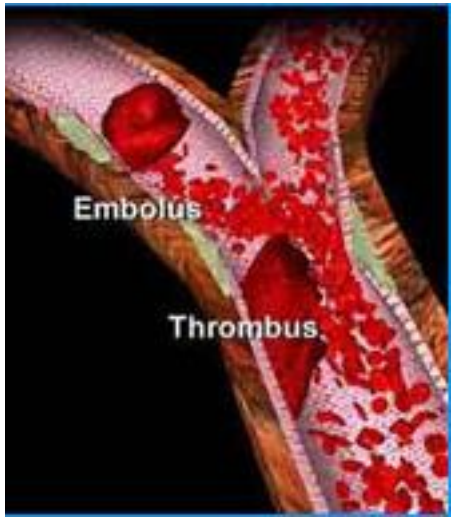
➢ AIR EMBOLISM (embolus as gas bubble) e.g., diving and sudden change in atmospheric pressure (during deep-diving, the solubility of nitrogen increases and upon rapidly ascending to the surface, the nitrogen solubility will rapidly decrease leading to formation of air bubble).

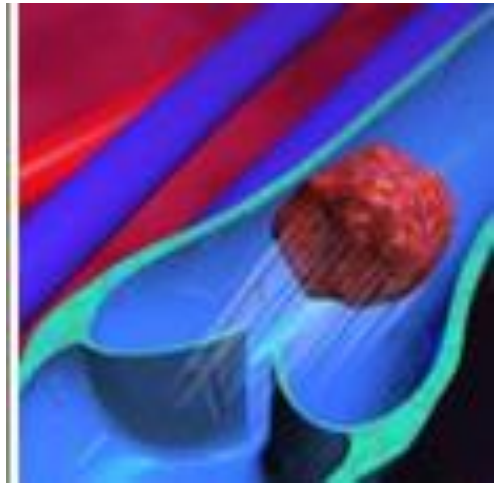
➢ THROMBOEMBOLISM e.g., DVT (deep venous thrombosis)

EMBOLISM



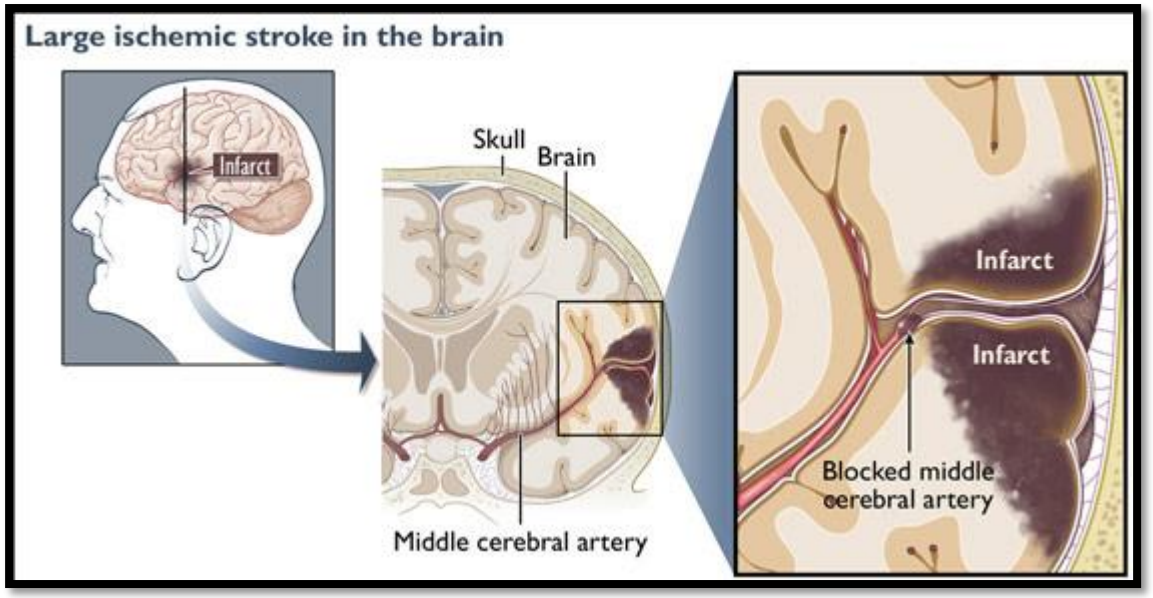
When an embolus lodges within a vessel and blocks blood supply, the condition is called an embolism.

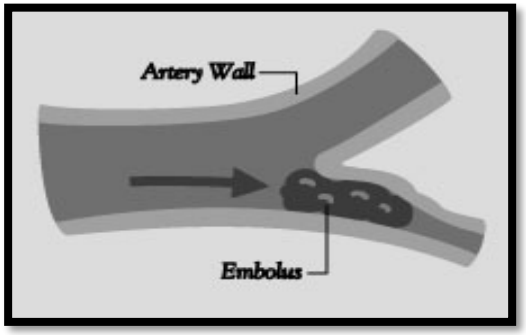




Effects of Embolisms

- Sudden Arterial Occlusion >>> Sudden Tissue Ischemia >>> followed by Tissue Infarction

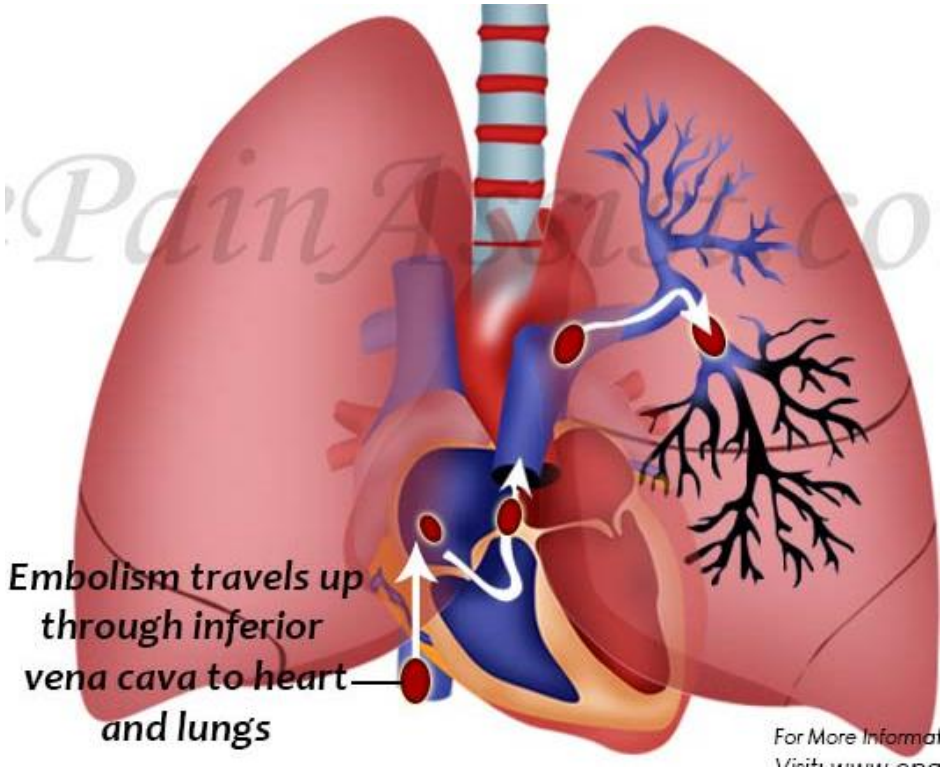




Blocked by embolus>>tissue ischemia>>infarction

1. Pulmonary Embolism (which means the blockage in the pulmonary artery of the lung caused by a blood clot or a foreign material)

Origin of PE	Effects
DVT-leg results in venous emboli formation which passes through right side of heart before entering the pulmonary vasculature/ PVT Via RV (right ventricle)	1. Sudden Occlusion of Pulmonary Artery 2. Sudden Ischemia of lung Tissue affected 3. Right heart failure

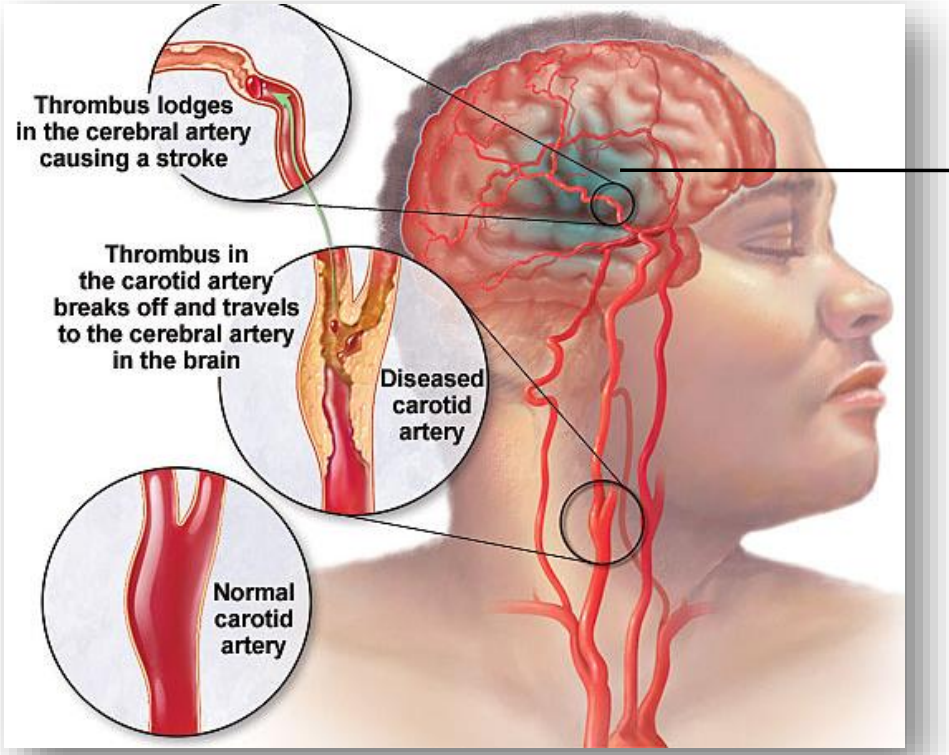


2. Systemic Embolisms (refer to emboli in arterial circulation)

- They arise from thrombi originated in different places.
- The most common cause is intracardiac mural thrombi which occur due to left ventricle infarction.
- Arterial emboli travel to a wide variety of sites (of these sites is brain causing cerebral embolism).
- Cerebral Embolism:

➢ Origin: Left Atrial Thrombosis

➢ Effects: * Cerebral artery Occlusion >>> * Cerebral Tissue Ischemia >>> * Cerebral Tissue Infarction



Embolic stroke>> ischemia>> infarction

Infarction

Infarct: is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue. (small localized area of dead tissue resulting from failure of blood supply). It is a cause of many clinical illnesses.

Causes:

a) Thrombotic and embolic events.

b) Arterial occlusion.

c) Local vasospasm.

d) Extrinsic compression of a vessel (due to tumour or edema)

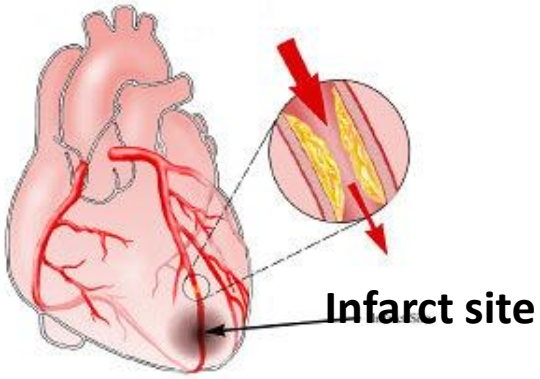
Examples:

a) Myocardial infarction causes cardiovascular diseases leading to death. ⟶

b) Pulmonary infarction.

c) Bowel infarction.

d) Gangrene.



Types:

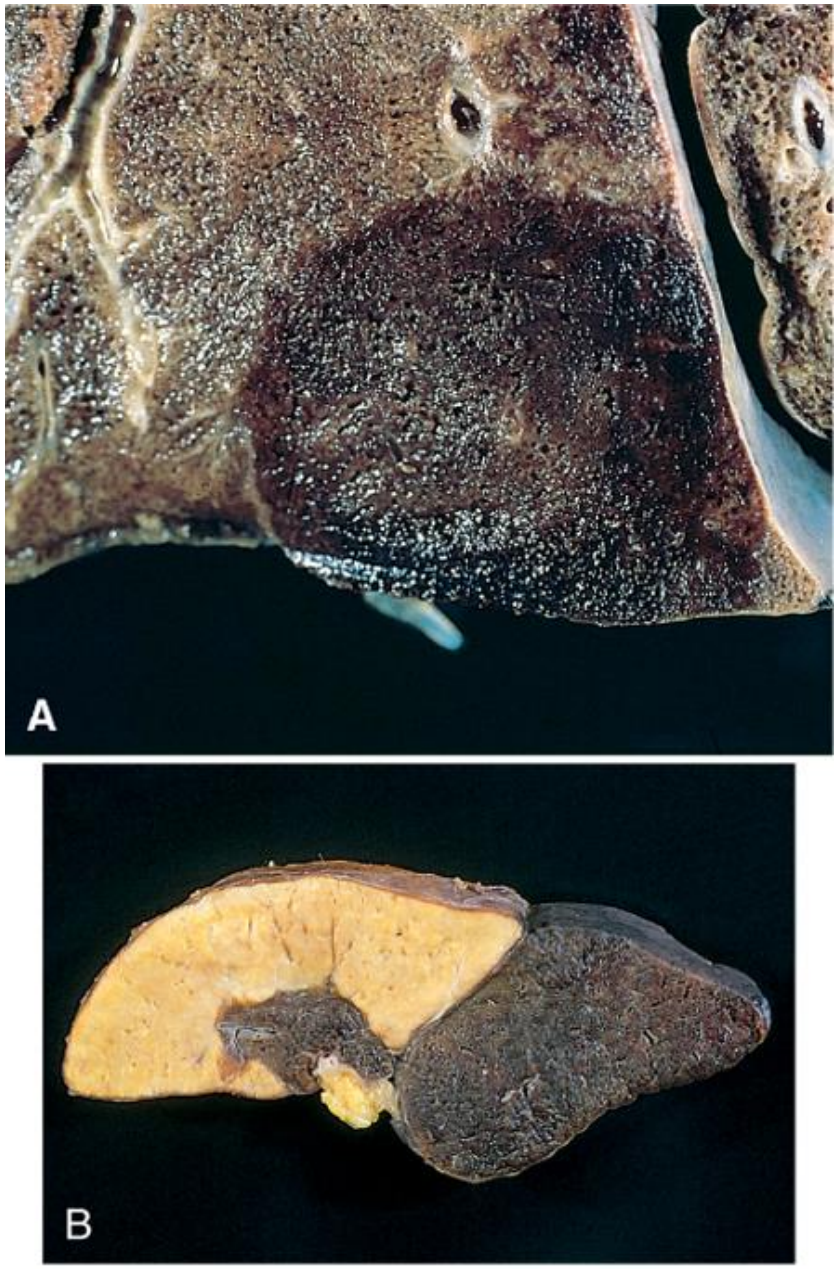
a) Red infarct.
b) White infarcts.

- **A,** Hemorrhagic, roughly wedge-shaped pulmonary infarct (*red infarct*)

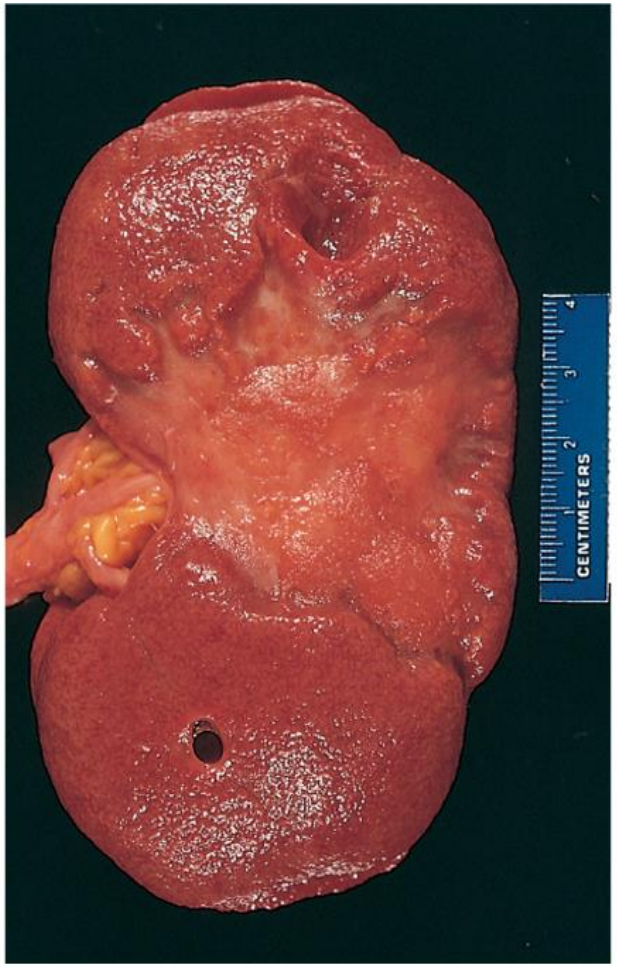
➢ It occurs in tissues with **dual circulations** such as lung and small intestine permitting flow of blood from an unobstructed parallel supply into a necrotic area or **when flow is re-established** to a site of previous arterial occlusion and necrosis.

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

➢ It occurs with **arterial occlusion or in solid organs where the solidity of the tissue** limits the amount of hemorrhage that can seep into the area of ischemic necrosis from adjacent capillaries.



Remote (slight) kidney infarct, now replaced by a large fibrotic scar.



Shock

- **Definition:** It is a sudden severe fall in blood pressure resulting in systemic decrease of blood flow (systemic hypo-perfusion) to the vital body organs such as the brain, heart muscle, liver, kidney and lungs, resulting in multi-organs ischemia. It occurs due to inability of circulatory system to adequately supply the vital organs.

- **One of the most important complications** of the shock is acute renal failure (ischemia in the kidney→ kidney damage→ acute renal failure). This is considered as a normal compensatory mechanism, so that the blood flow to the kidney is to keep enough blood for the vital organs.

- **Causes:**

1. Reduced cardiac output.
2. Reduced effective circulating blood volume due to most commonly severe acute bleeding leading to the loss of large amount of blood in short time (in few hours). On the contrary, if the blood is lost in small amount in longer time (daily basis), it will not lead to shock; instead it will lead to anaemia, because there is a gradual compensation of the lost plasma volume.

- Hypovolemic shock leads to fall in blood pressure and decrease in the pulse. This is accompanied with stimulating the sympathetic nervous system (as homeostatic/reflex responses), thereby increasing the cardiac output and peripheral resistance through stimulating β-receptor and α-receptor, respectively. Increasing the peripheral resistance through vasoconstriction allows the blood pressure to return back to normal since blood pressure = CO X peripheral resistance).

Shock

- **Clinical picture:**

- Ischemia in the brain will give clinical pictures of restlessness and confusion, drowsiness, and finally coma.
- Pale cold extremities (pale due to decreased blood flow, cold due to vasoconstriction)
- Cold sweating (due to sympathetic system stimulation)
- Very low blood pressure.
- Rapid weak pulse: the heart beat is very high but the pulse is very weak.

Types of shock

1. **Cardiogenic shock:** results from failure of the cardiac pump. The most common causes of cardiogenic shock are massive myocardial infarction, severe bradycardia, cardiac arrest due to arrhythmia, ventricular fibrillation (no pumping only fibrillation).
2. **Hypovolemic shock:** results from (a) severe acute hemorrhage (acute loss of whole blood volume), (b) severe acute extensive loss of plasma (due severe widespread burns), or (c) severe dehydration (e.g., massive diarrhea due to cholera →extensive loss of body fluid and severe dehydration).
3. **Septic shock:** is a life-threatening condition in which blood pressure drops to a dangerously low level after a microbial infection.

- In severe wide spread infections as in the case of septicemia, vasodilatation occurs resulting in a high decrease in the peripheral resistance (severe hypotention), red color not pale and fever (which is a common symptom of infection). In contrast to hypovolemic shock in which vasoconstriction due to sympathetic stimulation →Pale cold extremities due to vasoconstriction → decreased blood flow occur.

4. **Anaphylactic shock** due to severe allergic condition.

Anaphylactic shock results from systemic release of mediators from mast cells and basophils. These mediators are either preformed substances stored in the granules of mast cells and basophils such as histamine, tryptase, heparin, chymase, and cytokines), or newly synthesized molecules that are principally derived from the metabolism of arachadonic acid (e.g., prostaglandins and leukotrienes).

Anaphylaxis occurs in an individual after reexposure to an antigen to which that person has produced a specific IgE antibody. These IgE antibodies then bind to the high-affinity IgE receptor on the surface of mast cells and basophils resulting in cellular degranulation and release of histamine which mediates itching, rhinorrhea, tachycardia, and bronchospasm, headache, flushing, and hypotension, vasodilation and increased vascular permeability.

Angioedma seen in anaphylactic shock: includes swelling in eyes, lips, tongue, and if it includes the larynx, this leads to airway obstruction and suffocation. So angioedema should be treated as a medical emergency.