HAEMODYNAMIC DISORDERS, THROMBOEMBOLIC DISEASE, and SHOCK

TOPIC 2
HAEMOSTASIS
&
THROMBOSIS

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HOD, Pathology
MCWH

References:

- Robbins & Cotran Pathologic Basis of Disease- 9th edition
- Walter & Israel GENERAL PATHOLOGY 7th edition
- Davidson's Principles and Practice of Medicine-23rd edition
- IMAGES- Above mentioned books & internet

CONTENTS

- Definition
- Factors playing role in thrombus formation
- Pathogenesis of thrombus formation
- Morphology of thrombus
- Fate of a thrombus
- Clinical effects of thrombus

HAEMOSTASIS

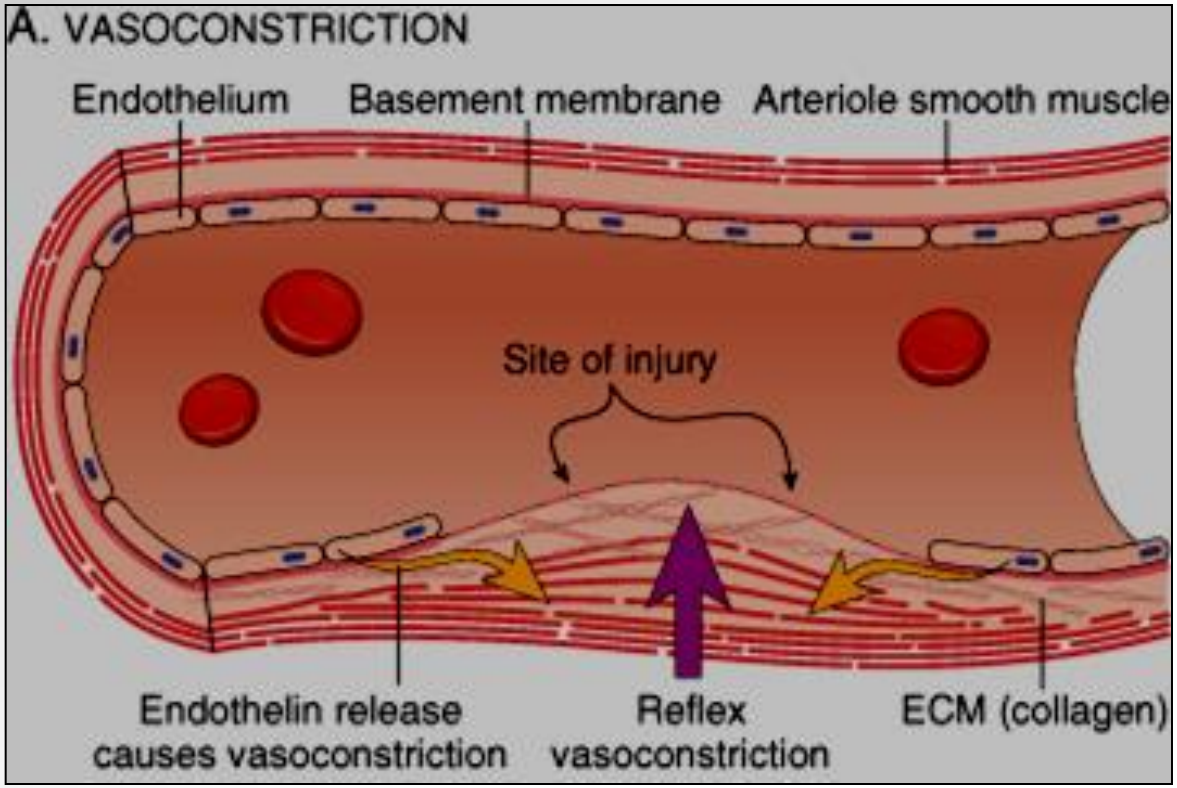
- Physiological process
- Defined simply as the process by which blood clot forms at sites of vascular injury
- Without this process bleeding would have never stopped
- **It is essential for life**

HAEMOSTASIS

- That occurs at the **site of vascular injury**
- Results in the formation of **blood clot**
- This **prevents or limit extent of bleeding**

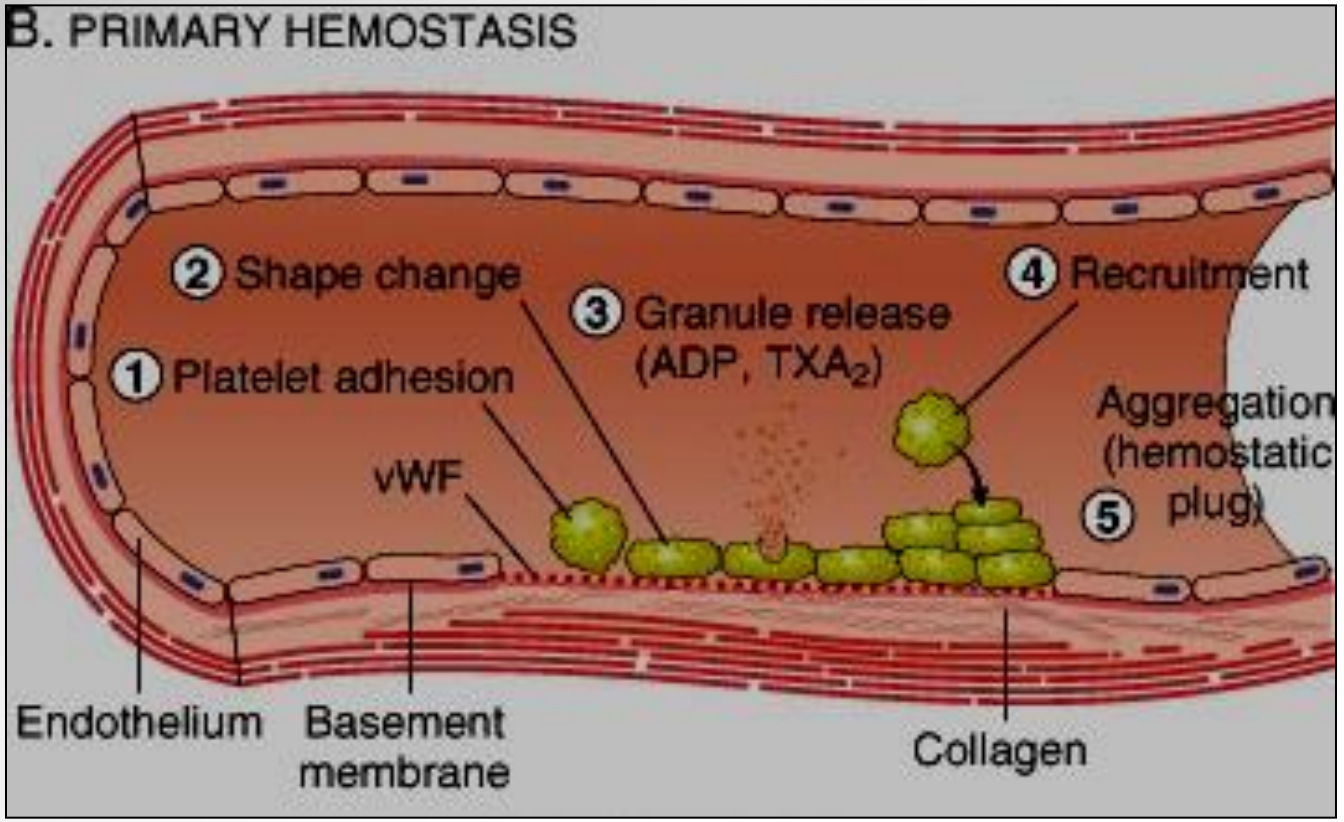
Normal Haemostasis

Arteriolar vasoconstriction



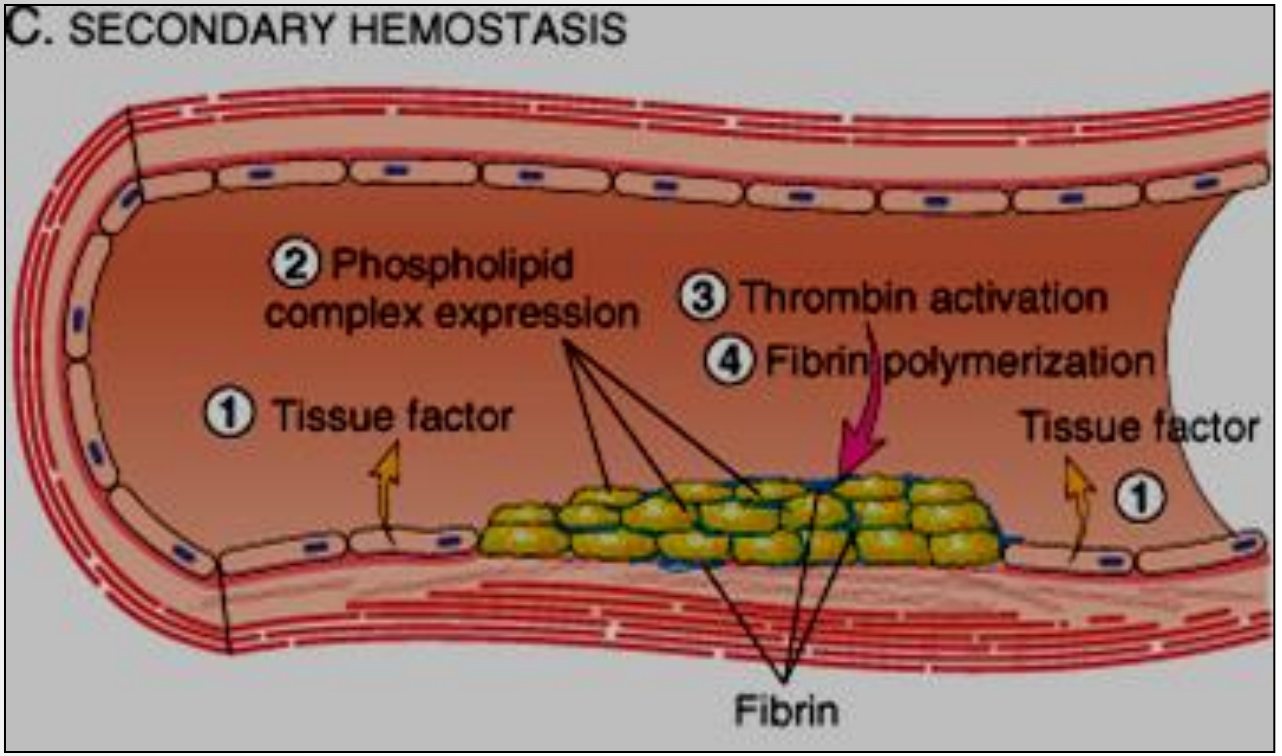
Normal Haemostasis

Primary haemostasis- formation of the platelet plug



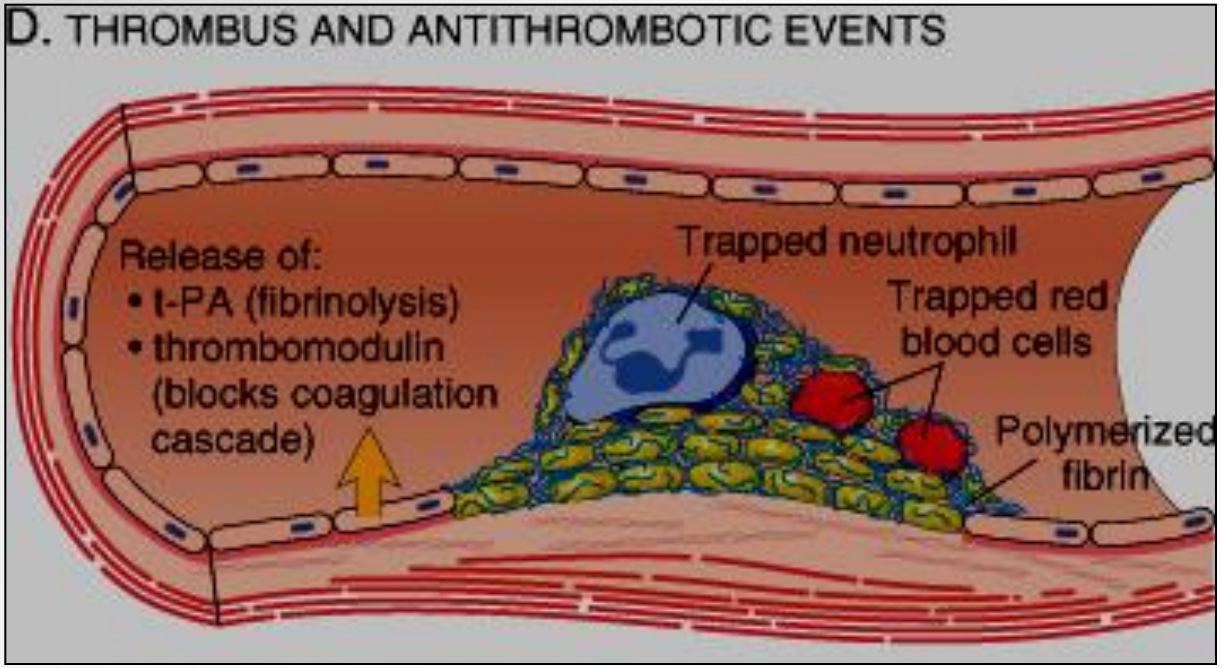
Normal Haemostasis

Secondary haemostasis- deposition of fibrin



Normal Haemostasis

Clot stabilization and resorption



Disorders of haemostasis

- **Haemorrhagic disorders-** haemostatic mechanisms are insufficient- excessive bleeding
- **Thrombotic disorders-** blood clots (thrombi)

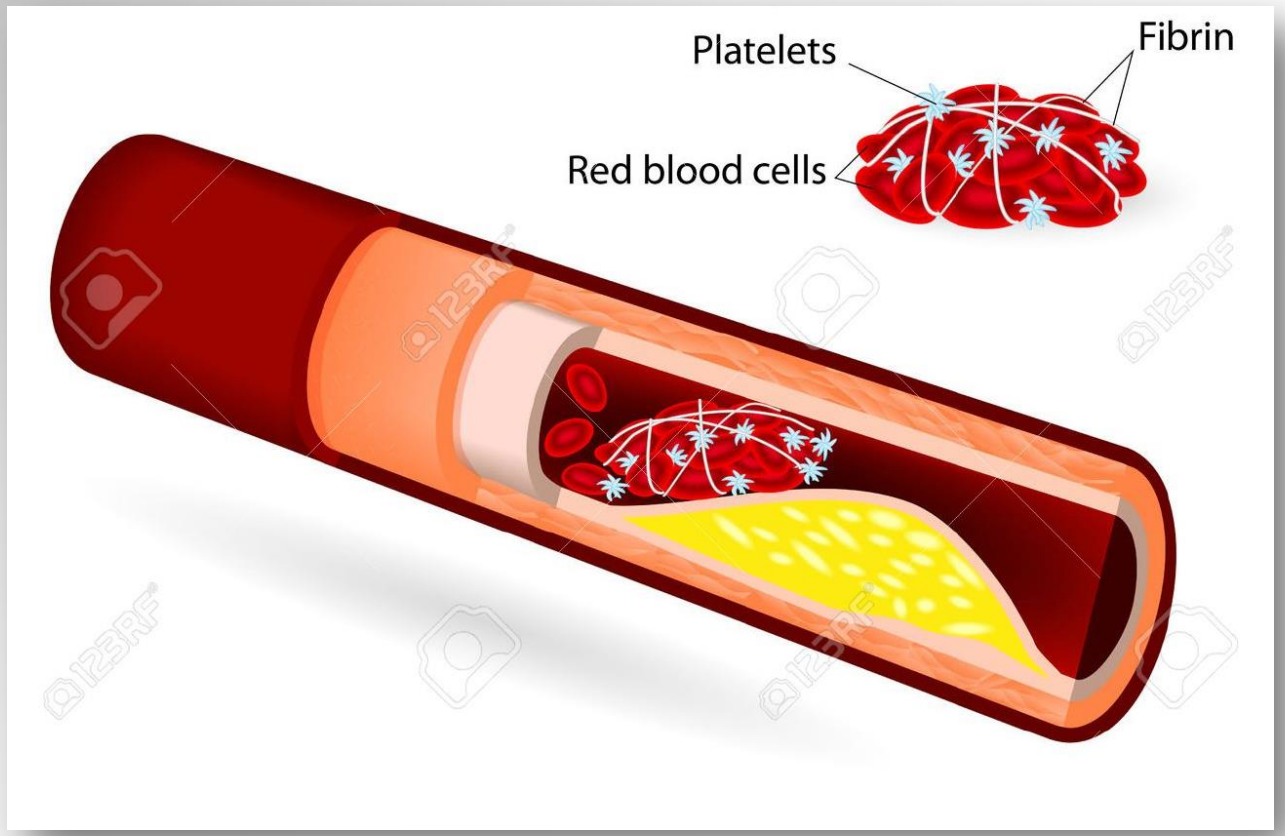
Thrombosis- definition

Formation of a clotted mass of blood within <u>NONINTERRUPTED</u> vascular system

Formation of a solid mass in the circulation from the constituents of streaming blood

<u>The resultant mass is known as a THROMBUS</u>

Thrombus



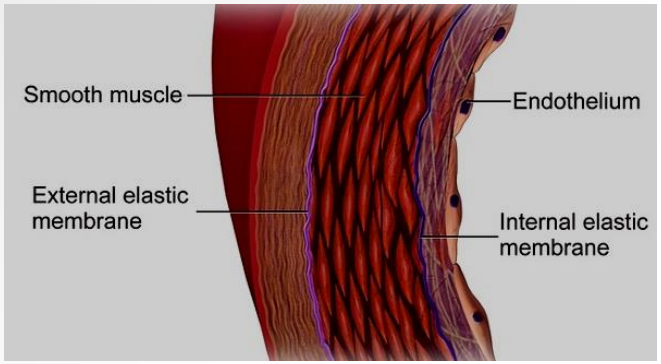
Thrombosis

Haemostasis & thrombosis depend on

- *Vascular wall- mainly endothelium*
- *Platelets*
- *Coagulation system*

Role of endothelium

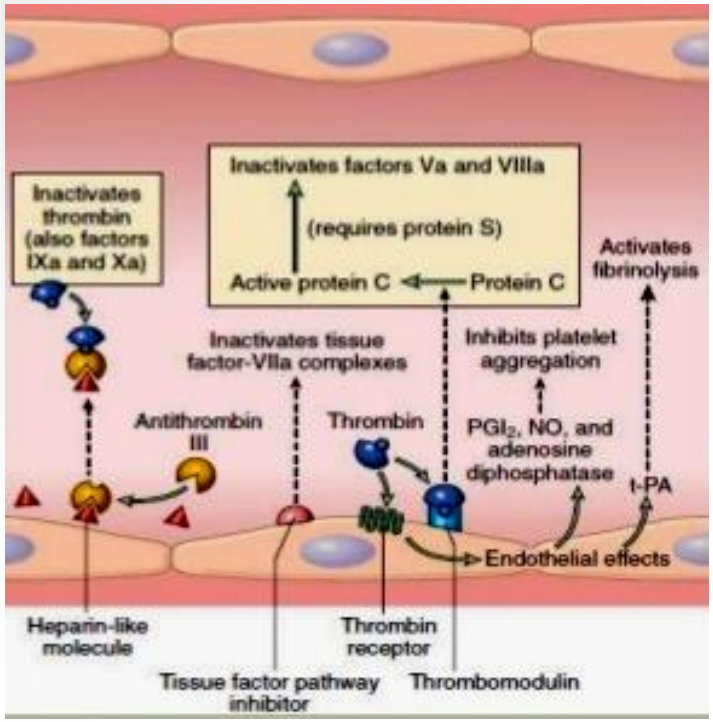
- **NORMALLY (antithrombotic)**
  - **Antiplatelet Properties**
  - **Anticoagulant Properties**
  - **Fibrinolytic Properties**
- **IN INJURY (prothombotic)**
  - **Pro-coagulant Properties**



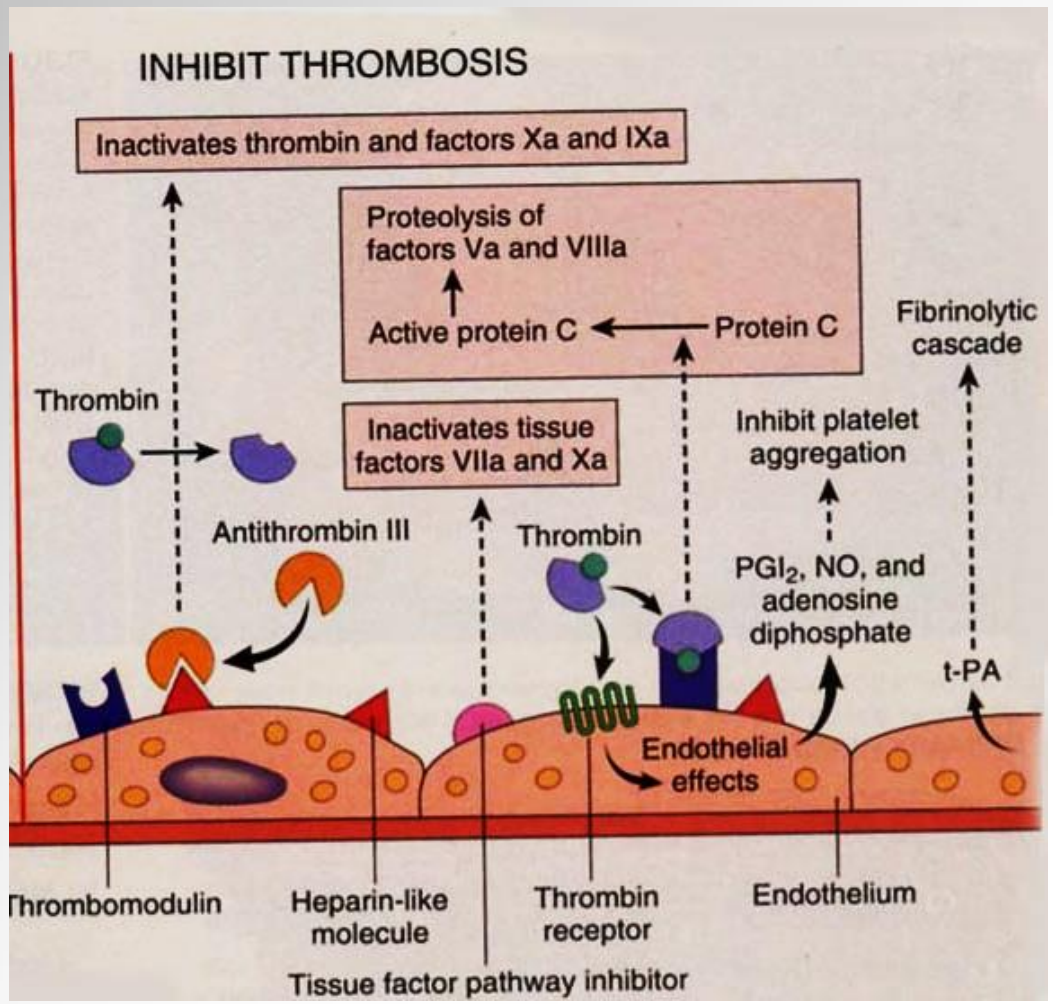
The **balance** between the **anticoagulant** and **procoagulant** activities of the endothelium often determines whether clot formation, propagation or dissolution occurs

Antithrombotic activities of endothelial cell

INHIBITION OF PLATELET AGGREGATION
➢PGI_2 ➢NO ➢ADPase
ANTICOAGULANT – BINDING & INHIBITION OF THROMBIN
➢ Heparin – like molecules ➢Thrombomodulin ➢Tissue factor pathway inhibitor (TFPI)
FIBRINOLYSIS
➢Tissue plasminogen activator (t-PA)



Antithrombotic activities of endothelial cell



Prothrombotic activities of endothelial cell

STIMULATION OF PLATELET AGGREGATION & ADHESION

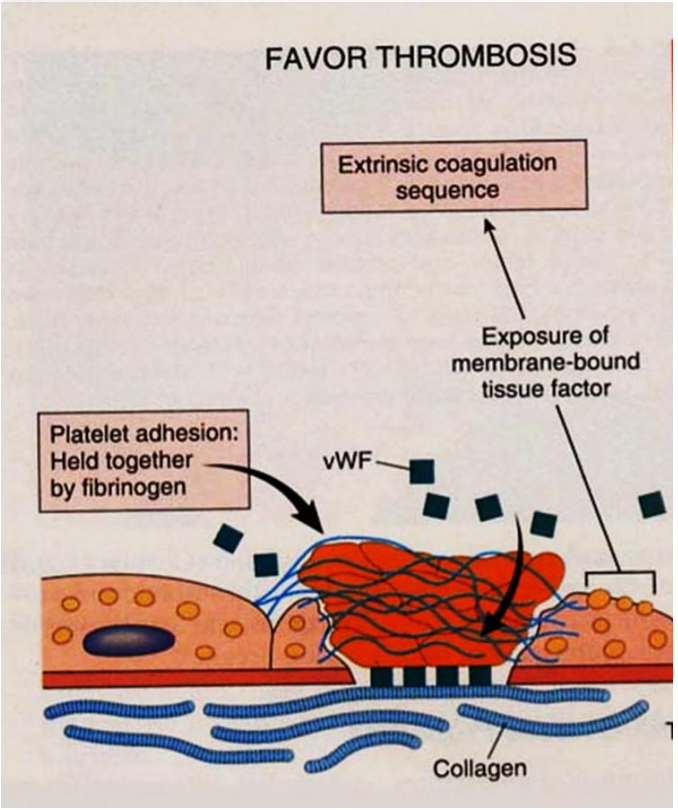
- Von Willebrand's factor
- PAF

PROCOAGULANT CHANGES

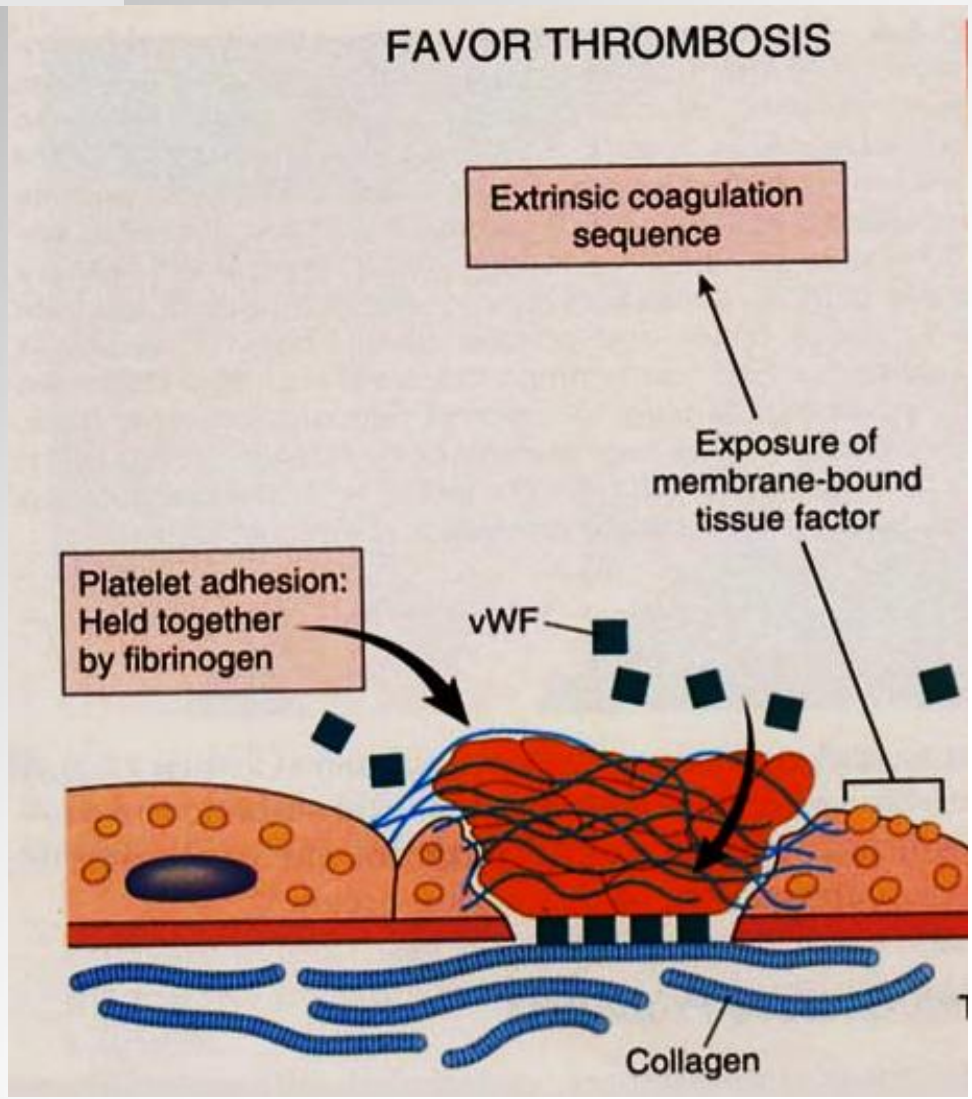
- Thrombomodulin expression is decreased by cytokines
- Tissue Factor
- Binding factors IXa, Xa

INHIBITION OF FIBRINOLYSIS

t-PA inhibitor (PAIs)



Prothrombotic activities of endothelial cell



Prothrombotic – antithrombotic balance

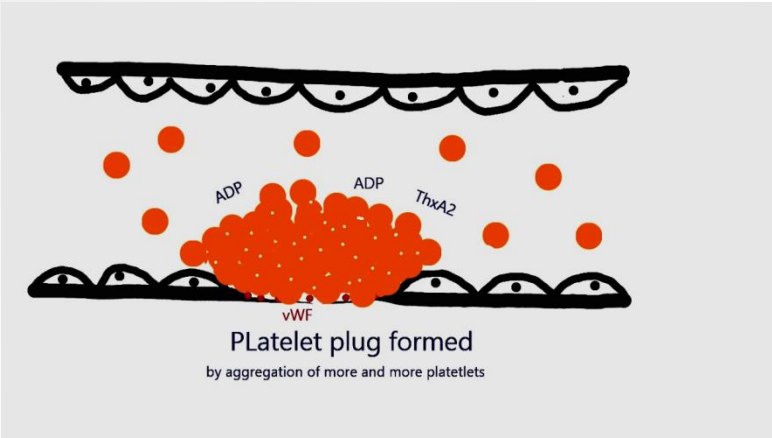
ANTITHROMBOTIC	PROTHROMBOTIC
INHIBITION OF PLATELET AGGREGATION ➢ PGI_2 ➢ NO ➢ ADPase	STIMULATION OF PLATELET AGGREGATION & ADHESION ➢ Von Willebrand's factor ➢ PAF
ANTICOAGULANT – BINDING & INHIBITION OF THROMBIN ➢ Antithrombin III acceleration by heparin – like molecules ➢ Thrombomodulin activation of protein C/S ➢ Tissue factor pathway inhibitor (TFPI)	PROCOAGULATION FACTORS ➢ Tissue Factor ➢ Binding factors IXa, Xa ➢ Factor V
FIBRINOLYSIS ➢ Tissue plasminogen activator (t-PA)	INHIBITION OF FIBRINOLYSIS ➢ t-PA inhibitor

PLATELETS

Disc shaped anucleated cells

Platelets

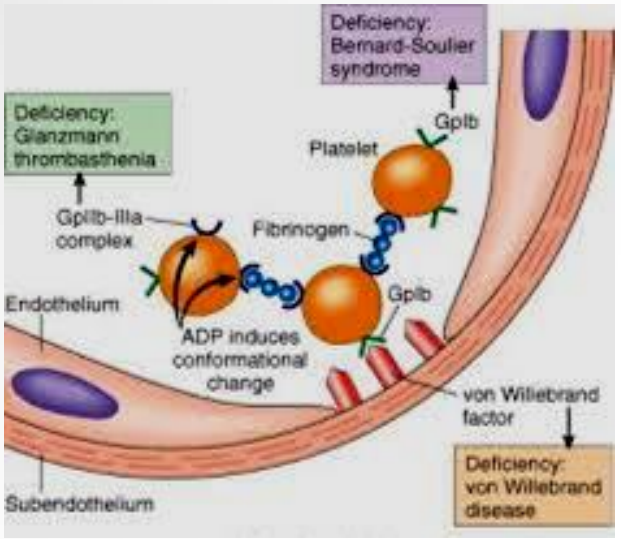
- Platelets have a **critical** role in haemostasis
- **Primary platelet plug seals** the vascular defects
- **Provides a surface** that binds and concentrate activated coagulation factors

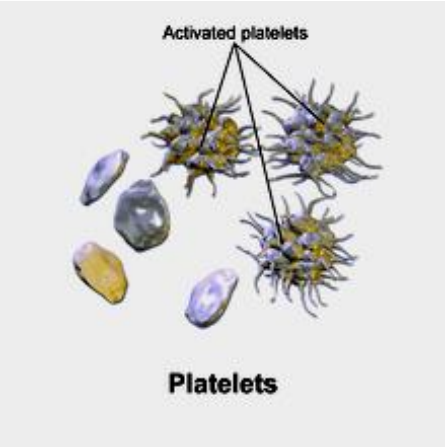


Platelets-sequence of reactions

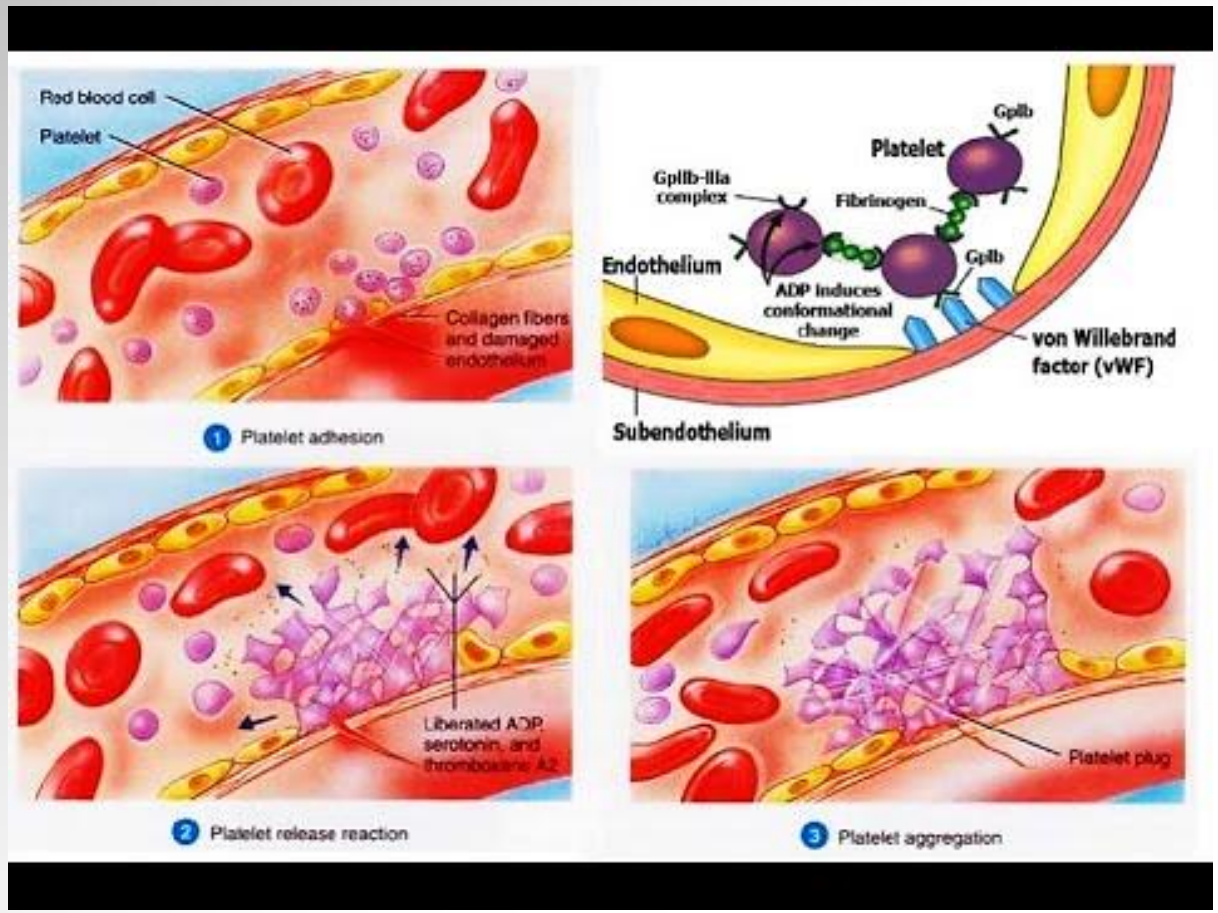
- **Platelet adhesion**
- **Shape change**
- **Secretion** (release reaction) **of granule contents**

Shape change and release reaction- called **platelet activation**





Role of platelets



Role of platelets

Platelet aggregation

- Three important stimuli -
  - ADP
  - TXA_2
  - THROMBIN
- Primary haemostatic plug
- Secondary haemostatic plug

COAGULATION SYSTEM

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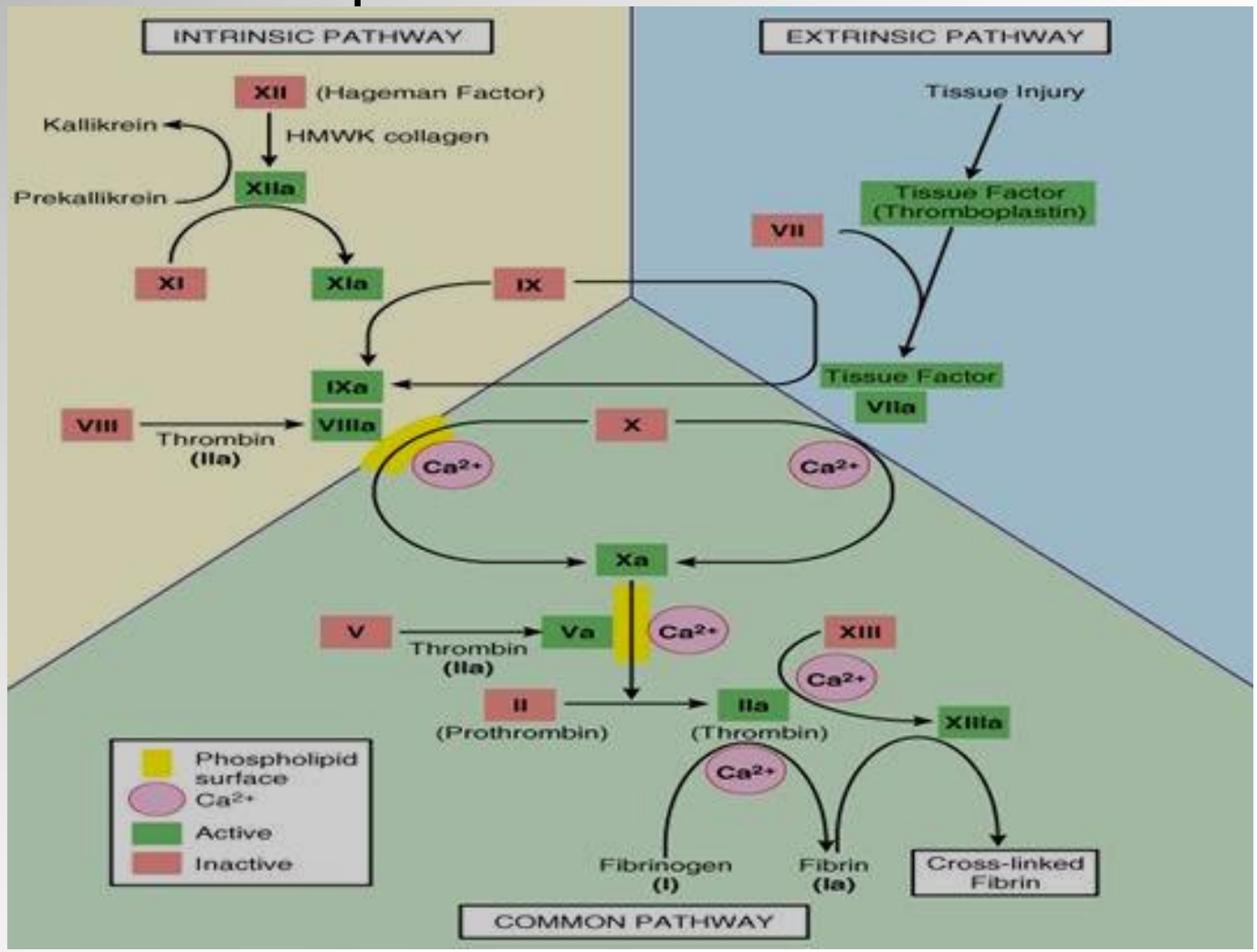
The coagulation cascade

Is series of amplifying enzymatic reactions that lead to deposition of an insoluble fibrin clot



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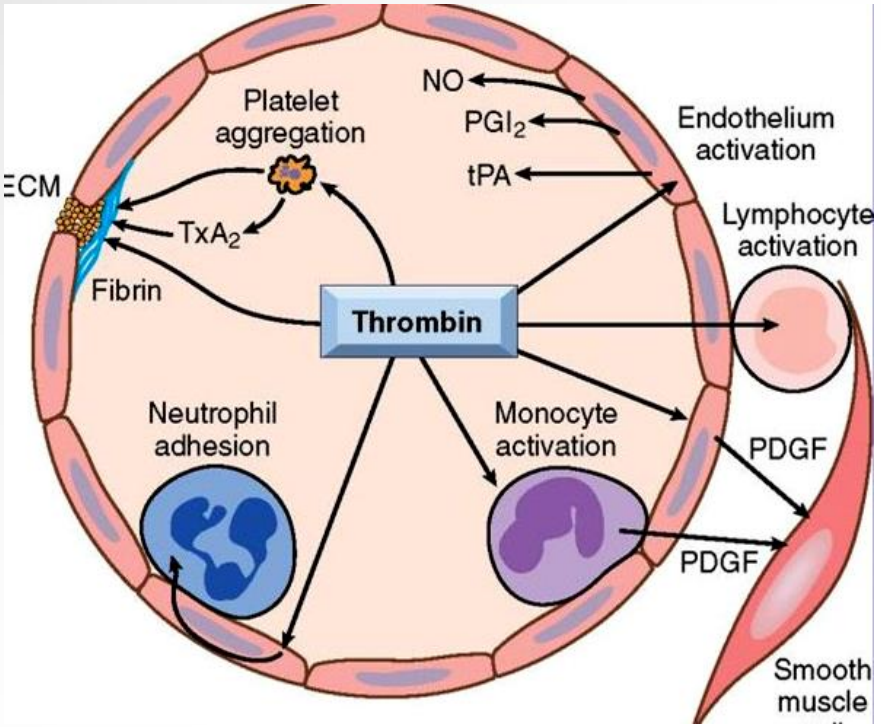
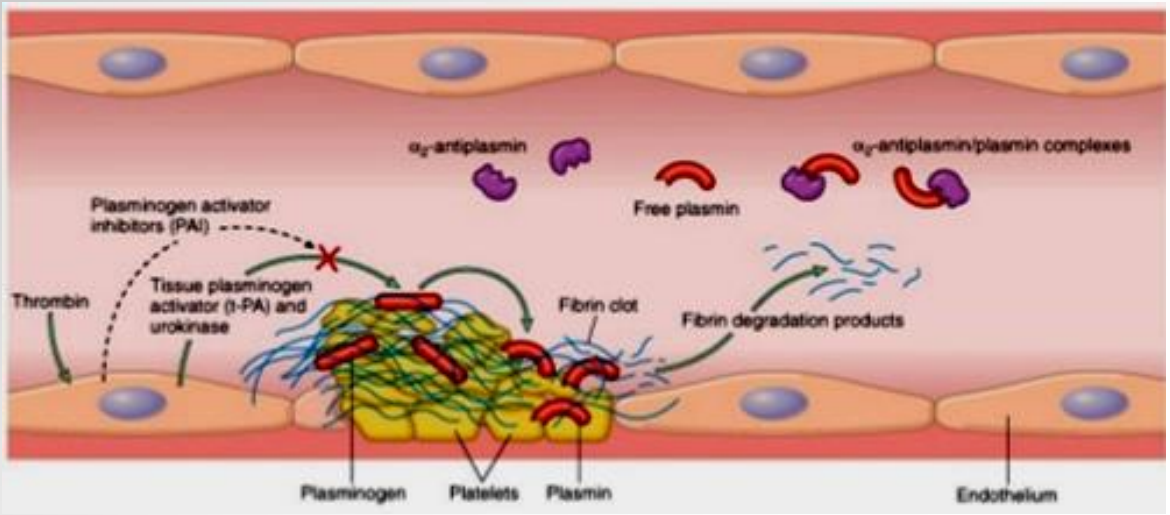
Thrombin- functions

- Conversion of fibrinogen to **crosslinked fibrin**
- Platelet actvation
- Pro inflammatory effects
- Anticoagulant effects



Fibrinolytic system



Factors that limit coagulation

Pathogenesis of Thrombus Formation

THROMBOGENESIS

THROMBOGENESIS- VIRCHOW TRIAD

- **Rudolf Virchow** (13 October 1821 – 5 September 1902)
- **German** physician, anthropologist, pathologist, prehistorian, biologist, writer, editor, and politician.
- He is known as "the father of modern pathology" and as the founder of social medicine
- To his colleagues, he was known as the "Pope of medicine"

THROMBOGENESIS

Three major influences (*Virchow triad*)

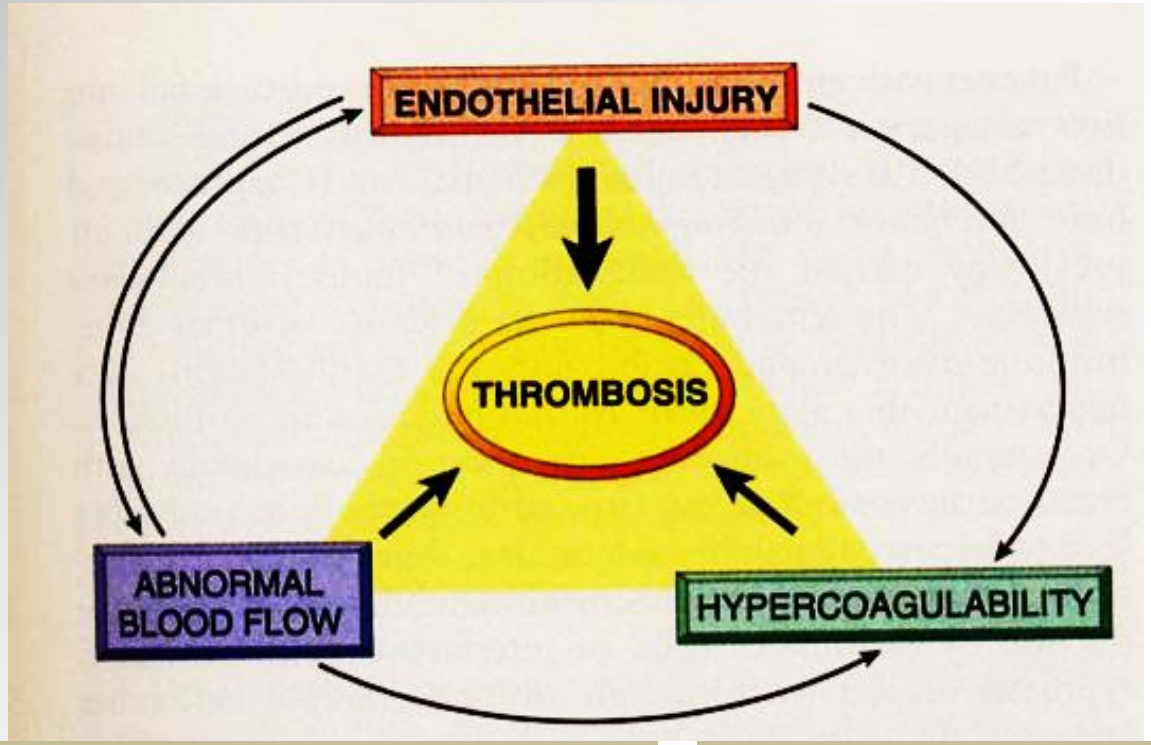
(1) Endothelial injury

(2) Alteration in normal blood flow

(3) Alteration in the blood

Virchow Triad

Hypercholesterolemia
Inflammation



Stasis – (e.g., atrial fibrillation, bed rest)
Turbulence – (e.g., atherosclerosis)

Inherited- (e.g., factor V mutation)
Acquired- (e.g., disseminated cancer)

ENDOTHELIAL INJURY

ENDOTHELIAL "INJURY"

- Any perturbation in the dynamic balance of the pro- and antithrombotic effects of endothelium
- Not only physical "damage"
- Plays role In the heart and arterial circulation

Endothelial Injury

Activated by

- **Physical injury**
- **Infectious agents**
- **Abnormal blood flow**
- **Inflammatory mediators**

Endothelial Injury

Causes :

- Myocardial Infarction
- Ulcerated atherosclerotic plaque
- Cardiac Surgery
- Myocardial infection
- Inflammatory valve disease
- Prosthetic valves
- Hypertension
- Radiation injury
- Chemicals - cigarette smoke
  hypercholesterolaemia
- Bacterial toxins
- Immunologic injuries - transplant rejection
  & immune complex deposition

ALTERATION IN NORMAL BLOOD FLOW

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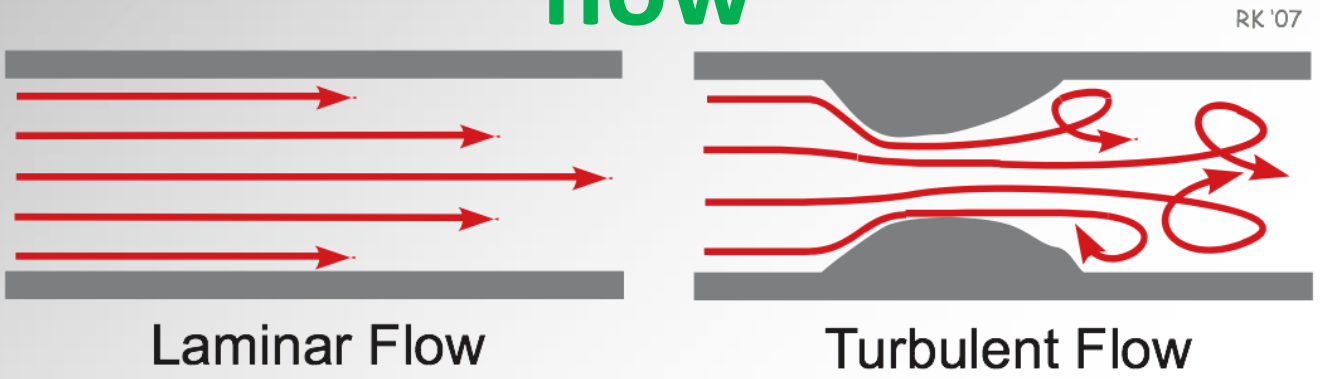
Normal Blood Flow

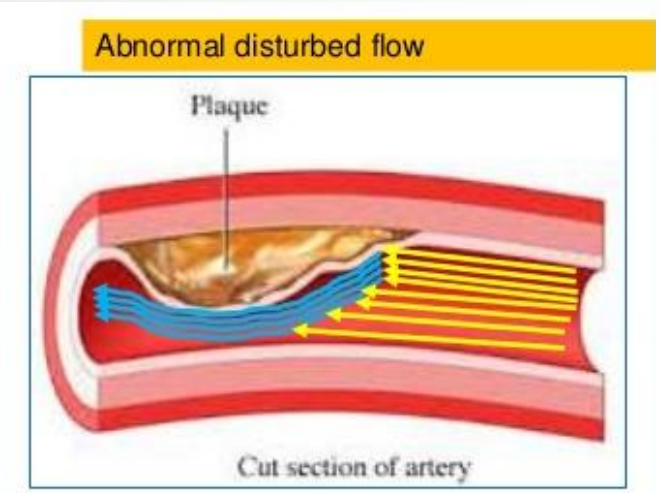
Normal laminar flow

Axial stream → **All formed elements**

Periphery → **Free from all formed elements**

Alteration in normal blood flow





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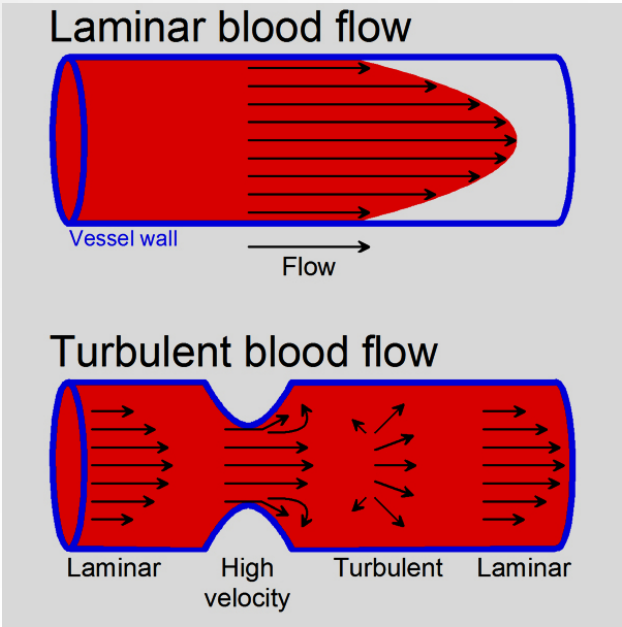
Alteration in normal blood flow

- High velocity
- Sharp turns in circulation
- Rough surfaces in circulation
- Narrowing in the circulation

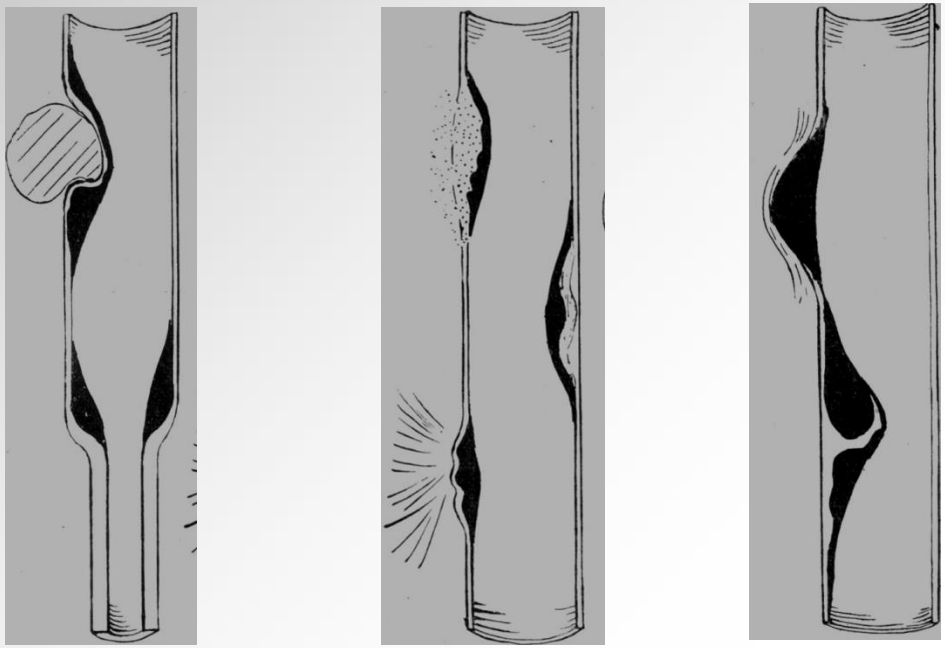


Alteration in normal blood flow

Turbulence - Development of arterial or cardiac thrombi

Stasis - Contributes to venous thrombi

Causes of disruption of normal blood flow



a b c

(a) External pressure or spasm (b) inflammation, atheroma (c) aneurysm and a sclerotic rigid valve

Turbulence and stasis

- **Promote endothelial activation**, enhances procoagulant activity, leukocyte adhesion etc.
- **Disrupt laminar flow** & bring platelets into contact with endothelium
- **Prevent washout and dilution** of *activated coagulation factors due to reduced inflow of fresh blood*
- **Retard inflow** of clotting factors **inhibitors**

Alteration in normal blood flow

Clinical settings

- Ulcerated atherosclerotic plaque- turbulance
- Aneurysm- stasis
- M I- stasis
- Rheumatic mitral valve stenosis-stasis
- Polycythemia - stasis
- Sickle cell anemia- stasis

HYPERCOAGULABILITY

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Hypercoagulability

- Also called thrombophilia
- Any alteration in the blood coagulation pathways that predisposes to thrombosis

Hypercoagulability

Primary

(genetic)

Secondary

(acquired)

Hypercoagulability – Primary (genetic)

Common

- Mutations in factor V gene- resistant to action of protein C
- Mutation in prothrombin gene
- Increased levels of factor VIII, IX XI or fibrinogen

Hypercoagulability- Secondary (acquired)

High risk for thrombosis

- **Prolonged bed rest or immobilization**
- **Myocardial infarction**
- **Atrial fibrillation**
- **Tissue damage (surgery, fracture burns)**

Lower risk for thrombosis

- **Cardiomyopathy**
- **Use of oral contraceptives**
- **Smoking**

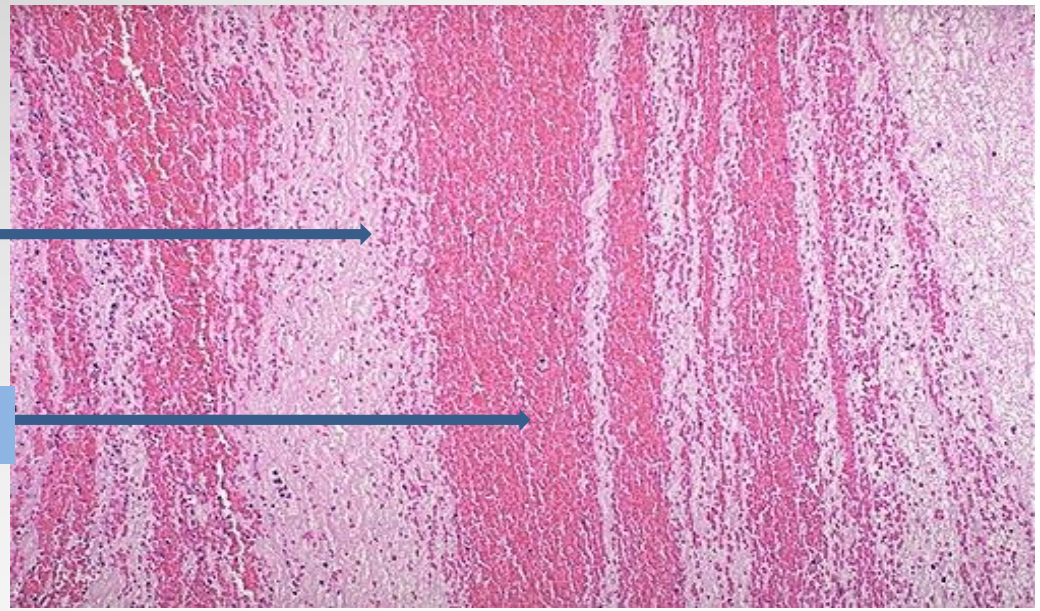
Morphology of thrombi

Can occur anywhere in C V S

Size & Shape are variable

When formed in CARDIAC CHAMBER or AORTA ⟶ *Lines of Zahn* are found

"**LINES OF ZAHN**" are the **alternating pale pink bands of platelets with fibrin and darker red bands of RBC's** forming a true thrombus.



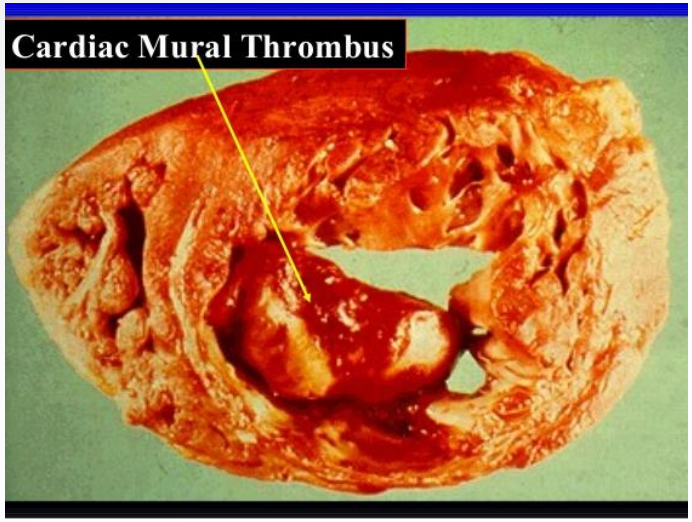
Such laminations signify that a thrombus has formed in flowing blood

Differentiates from post mortem clot

Morphology of thrombi

Thrombi applied to one wall of an underlying structure (Cardiac chambers & Aorta)

Mural Thrombi



Morphology of thrombi

Thrombi deposited on heart valves

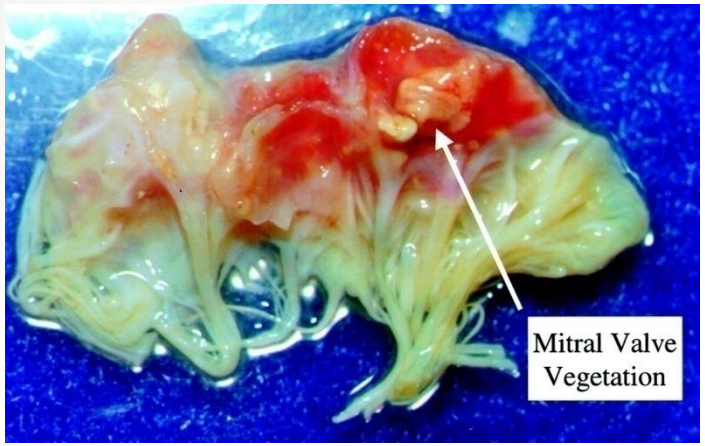
(a) Bacterial/infective endocarditis

(b) Non infective

- **S L E**
- **older patient with terminal Ca**
- **chronic disease**

Vegetation

fibrin *vegetation* on the mitral valve



Common sites of thrombus formation

- Arterial thrombi
- Venous thrombi (phlebothrombosis)
- Thrombus in heart

Differences between arterial thrombi and venous thrombi

Features	Arterial thrombi	Venous thrombi
Blood flow	Rapidly flowing	Slow moving blood
Sites	Aorta, coronary , cerebral arteries	Deep veins of leg, superficial varicose veins
Thrombogenesis	Endothelial injury	Venous stasis
Type	Usually mural	Usually occlusive
Microscopy	Lines of Zahn, fibrin , RBCs & WBCs	Lines of Zahn with more abundant RBCs
Effects	Ischemia leading to infarct	Thromboembolism, edema, skin ulcers

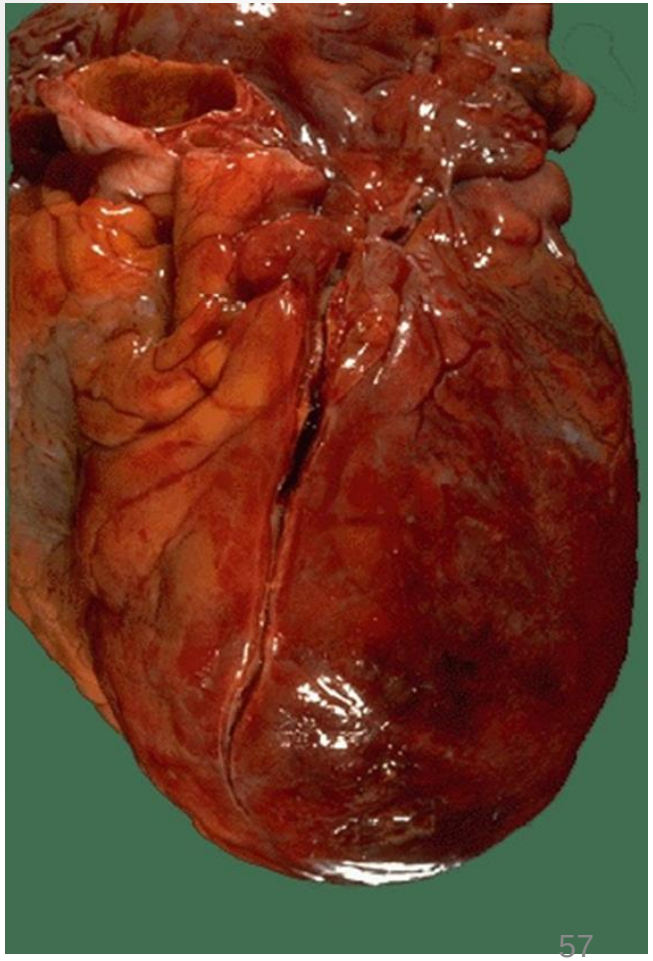
Arterial thrombi

- Usually occlusive,
- Firm attachment
- Superimposed on AS lesion
- When formed in heart chambers or aorta they adhere to the wall of underlying structure and termed **mural thrombus**
- *Coronary, cerebral & femoral arteries are involved in decreasing order of frequency*

Arterial thrombi

- ***Coronary,***
- ***Cerebral &***
- ***Femoral arteries***

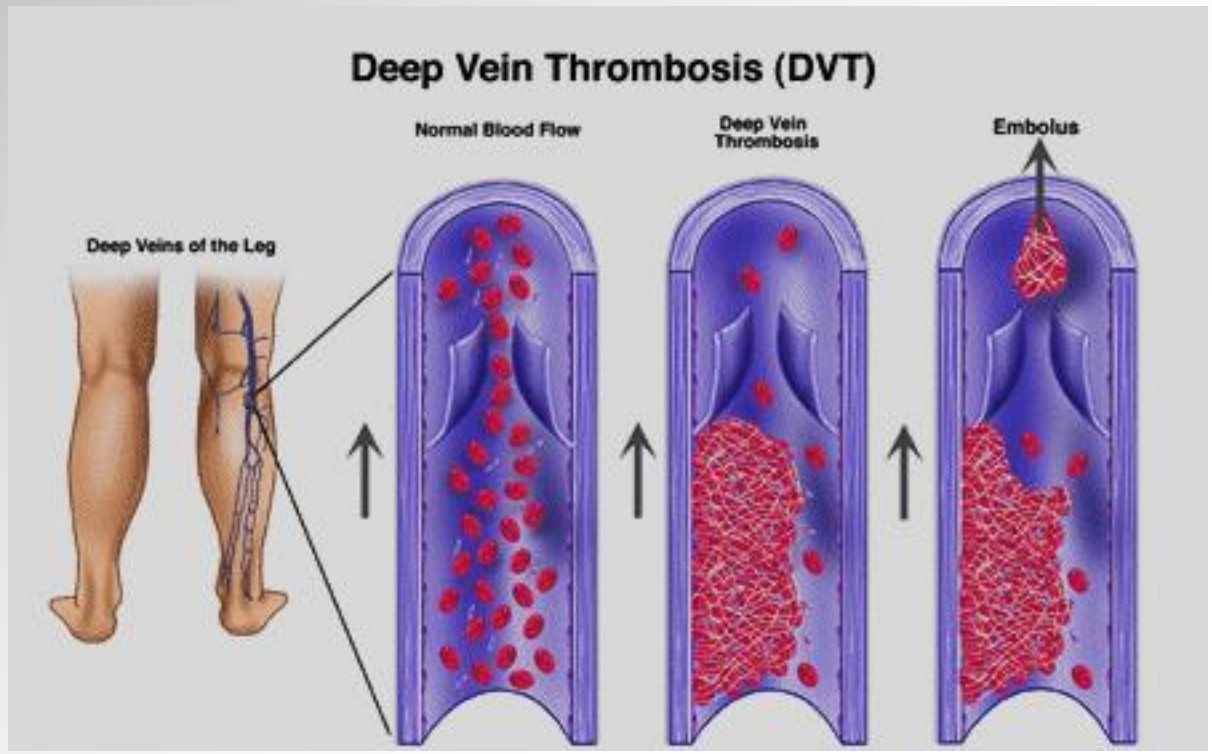
are involved in decreasing order of frequency



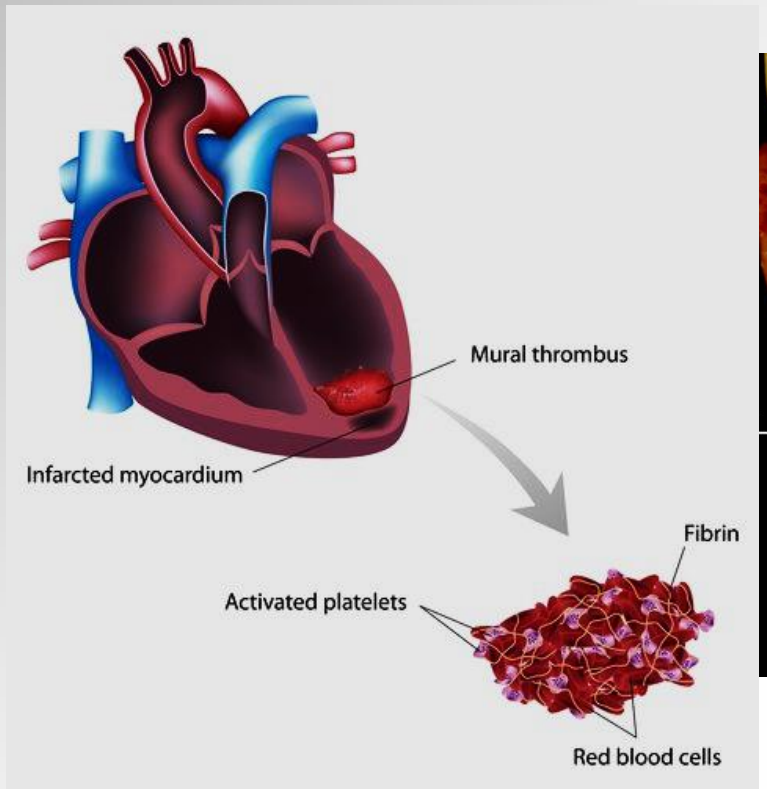
Venous thrombosis (phlebothrombosis)

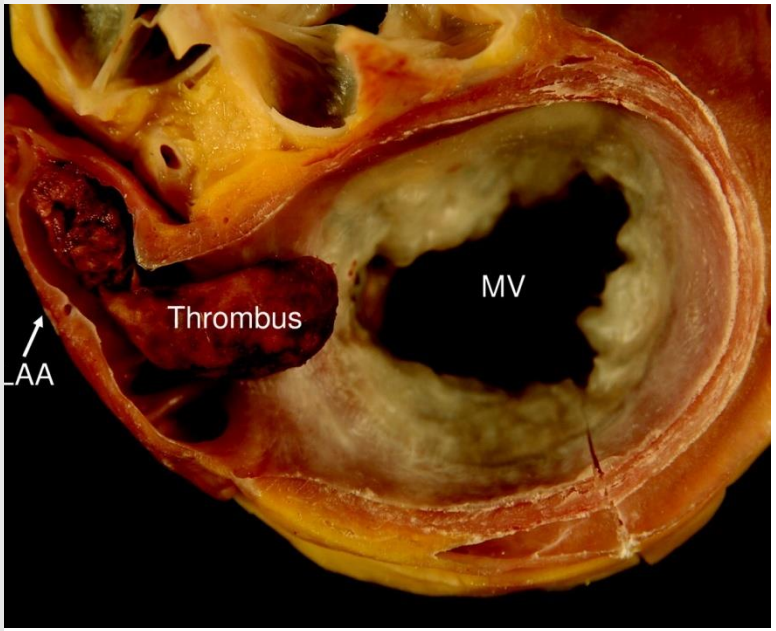
- **Red** or **stasis** thrombi- as **sluggish flow**; contain **more RBCs**
- Firm, focally attached to the vessels
- **Lines of Zahn present**
- In 90% of cases lower extremities are involved
- Upper extremity, periprostatic plexus, ovarian veins can develop

Venous thrombi



Cardiac thrombi





Pathogenesis of Deep Vein Thrombosis

Five stages can be recognized

- **Primary platelet thrombus**
- **The coralline thrombus**
- **Occluding thrombus**
- **Consecutive clot**
- **Propagated clot**

(Ref: Walter and Israel General Pathology 7th ed)

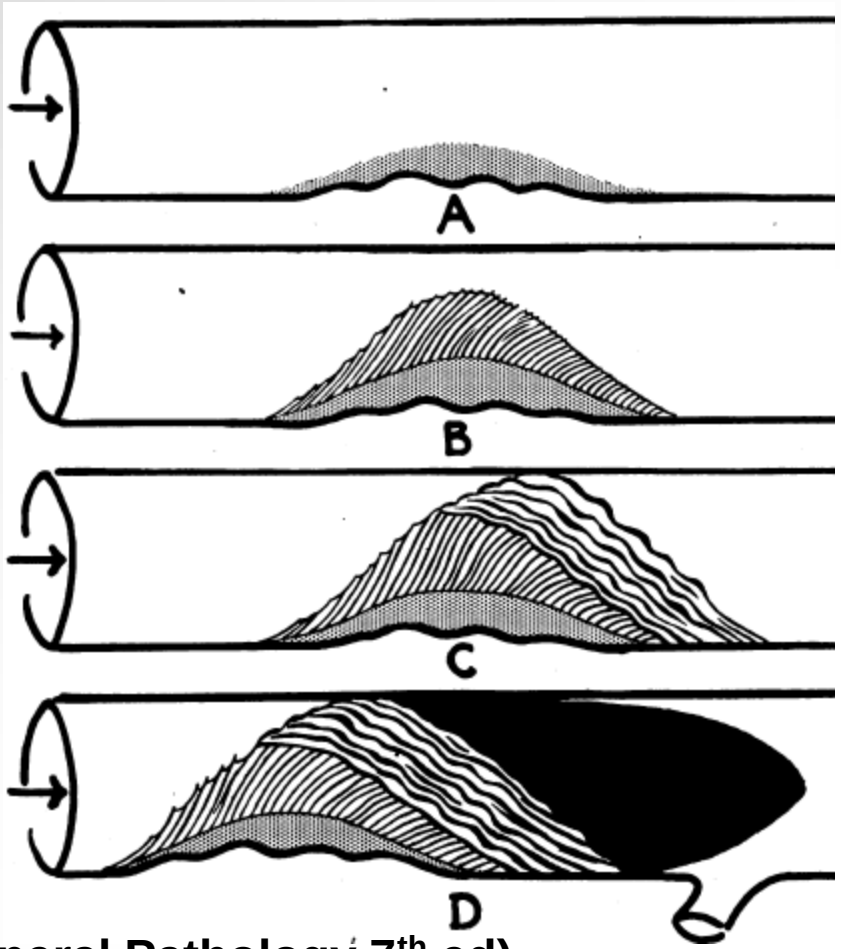
Pathogenesis of Phlebothrombosis

A. Primary platelet thrombus

B. Coralline thrombus

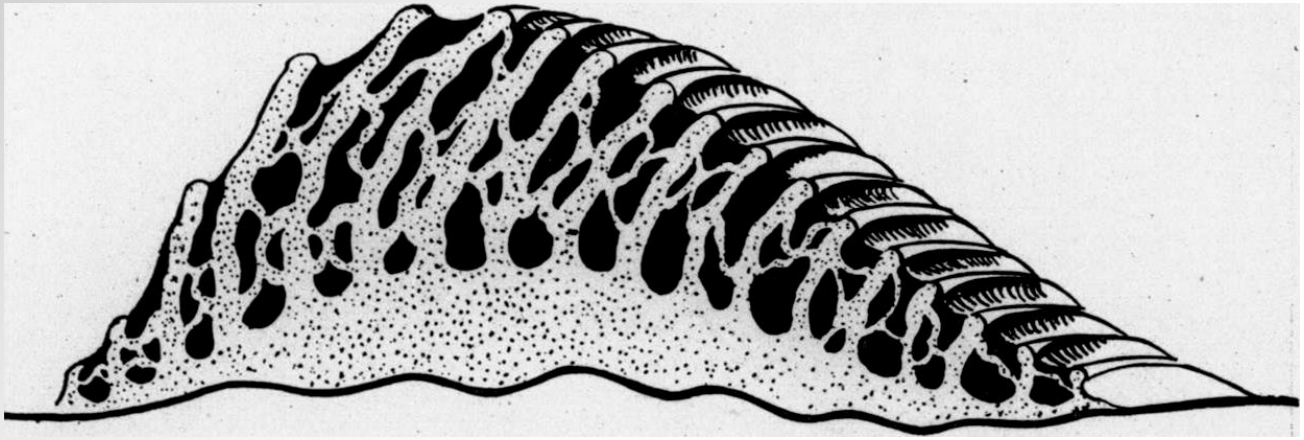
C. Occluding thrombus

D. Consecutive clot to the next venous tributary



(Ref: Walter and Israel General Pathology 7th ed)

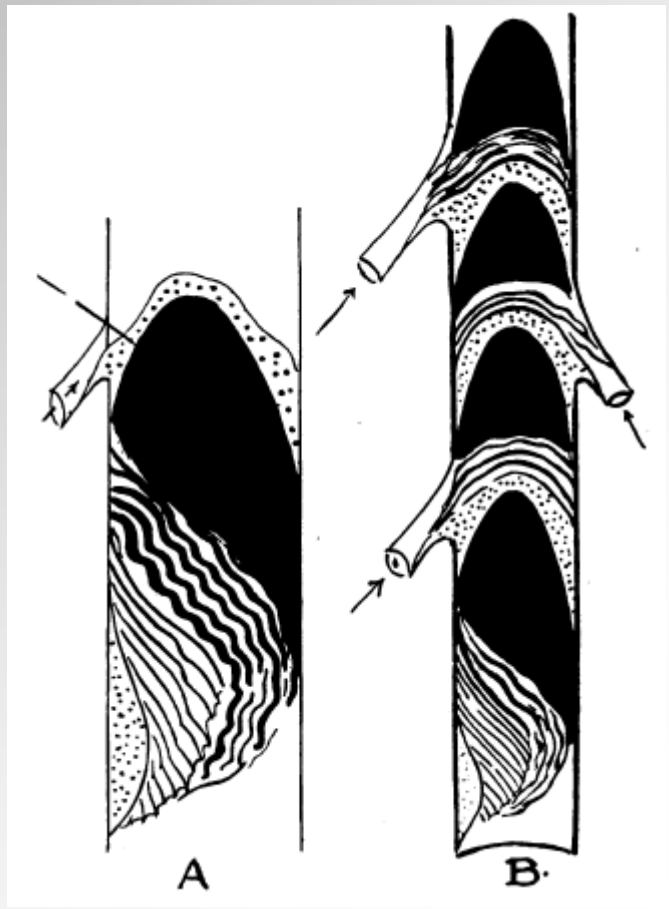
The Coralline thrombus

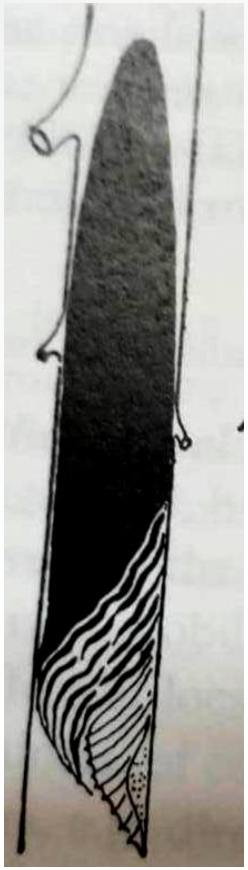


(Ref: Walter and Israel General Pathology 7th ed)

Propagation of a Phlebothrombosis

(Ref: Walter and Israel General Pathology 7th ed)





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Thrombophlebitis

Thrombosis caused by inflammation of vein

Differences between Phlebothrombosis and Thrombophlebitis

(Ref: Walter and Israel General Pathology 7th ed)

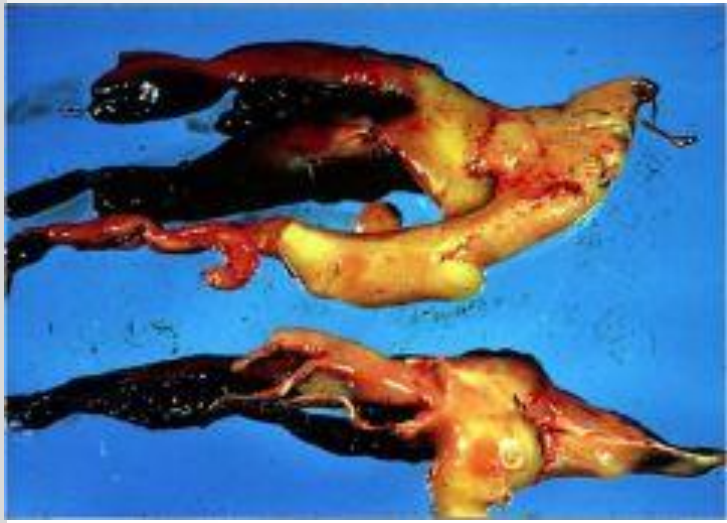
	Phlebothrombosis	Thrombophlebitis
Cause	**Stasis**	Inflammation of vein wall
Size of primary thrombus	**Smaller**	**Larger**
Size of propagated clot	Long & poorly anchored to the vessel wall	Usually none If present is short and well anchored
Emboli	**Common**, massive & sterile	**Rare** except in infective cases
Site	Usually **calf veins**	**Anywhere**
Clinical picture	**Silent** or there are few signs and symptoms	Sign and symptoms of **acute inflammation**

Post mortem clot

- A **post mortem clot** is a **clot** that formed in the heart or a large blood vessel after death, and subsequently discovered during the autopsy.
- Clots are gelatinous
- **Dark dependant portion**

(RBCs settled by gravity)

- **Yellow "chicken fat" upper portion**



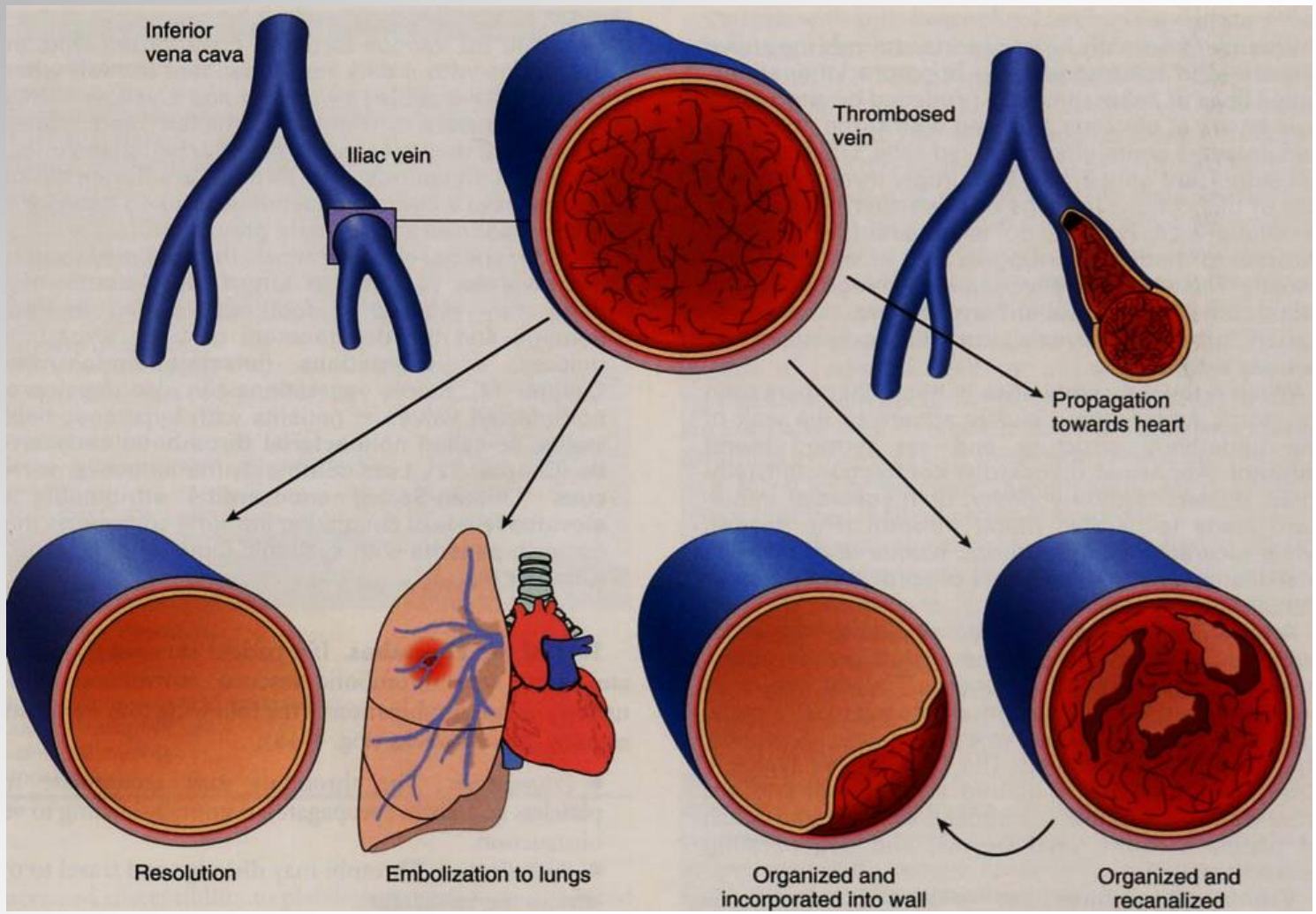
Differences between thrombus and post mortem clot

Thrombus	Post mortem clot
Dry	Wet and gelatinous (chicken fat appearance)
Firm in attachment	No attachment
Lines of Zahn present	Absent
Hard	Soft
Friable	Gelatinous

Fate of a thrombus

- Dissolution- commonest fate
- Propagation (Downstream)
- Embolization
- Organization
- Recanalization
- Calcification

Potential outcomes of venous thrombosis



Clinical effects of thrombosis

Large thrombi in heart cause sudden death by mechanical obstruction to blood flow

Cardiac thrombi

Sudden death through thromboembolism of vital organs

Clinical effects of thrombosis

- **Arterial thrombi**

Infarct

Sudden death following thrombosis of coronary artery

Clinical effects of venous thrombosis

- Thromboembolism
- Edema of the area drained
- Poor wound healing
- Skin ulcer
- Thrombophlebitis

Practice questions

- Define thrombus.
- What is Virchow triad?
- Discuss the prothrombotic role of endothelium in thrombus formation.
- Discuss the antithrombotic role of endothelium in thrombus formation
- What are the causes of endothelial injury?
- Briefly describe the role of platelets in normal haemostasis
- What are the causes of hypercoagulable states?
- What is lines of Zahn? Why it is not found in post mortem clot?

Practice questions

- What are the differences between thrombophlebitis and phlebothrombosis?
- How turbulence and stasis (altered blood flow) play role in thrombus formation?
- What is mural thrombus?
- What is vegetation?
- What are the fates of a thrombus?
- What are the clinical effects of a thrombus?
- What are the differences between venous thrombi and post mortem clot?
- What are the differences between arterial and venous thrombi?

THANK YOU

MCQ

Prothrombotic agents are

a) ADP
b) Prostacyclin
c) Thromboxane A2
d) Plasminogen activator
e) Thrombomodulin

MCQ

Prothrombotic agents are

a) ADP T

b) Prostacyclin F

c) Thromboxane A2 T

d) Plasminogen activator F

e) Thrombomodulin F

MCQ

Predisposing factors to thrombosis are

a) Mutations in factor V gene
b) Thrombomodulin
c) t- PA
d) Lupus anticoagulant
e) Cigarette smoking

MCQ

Predisposing factors to thrombosis are

a) Mutations in factor V gene T

b) Thrombomodulin F

c) t- PA F

d) Lupus anticoagulant F

e) Cigarette smoking T

MCQ

Deep vein thrombosis in leg can cause

a) Pulmonary infarction
b) Coronary artery thrombosis
c) Local pain
d) Varicose vein
e) Death

MCQ

Deep vein thrombosis in leg can cause

a) Pulmonary infarction T

b) Coronary artery thrombosis F

c) Local pain T

d) Varicose vein T

e) Death T

MCQ

Post mortem clot in contrast to antemortem venous thrombosis has

- A point of attachment
- Yellow chicken fat and a dependant red portion
- Lines of Zahn
- Gelatinous consistency
- Friable consistency

MCQ

Post mortem clot in contrast to antemortem venous thrombosis has

- A point of attachment F
- Yellow chicken fat and a dependant red portion T
- Lines of Zahn F
- Gelatinous consistency T
- Friable consistency F

Thank You