

血 Hematology 血



- Histology
- Biochemistry
- Pathology
- **Pharmacology**
- Physiology
- Microbiology

● Handout

● **Slide 2**

● Sheet



● Dr. name :
Dr Munir Gharaibeh

● Lecture number :
2 - Heparin

● Done BY :



Drugs used in Thromboembolic Disease

Munir Gharaibeh, MD, PhD, MHPE

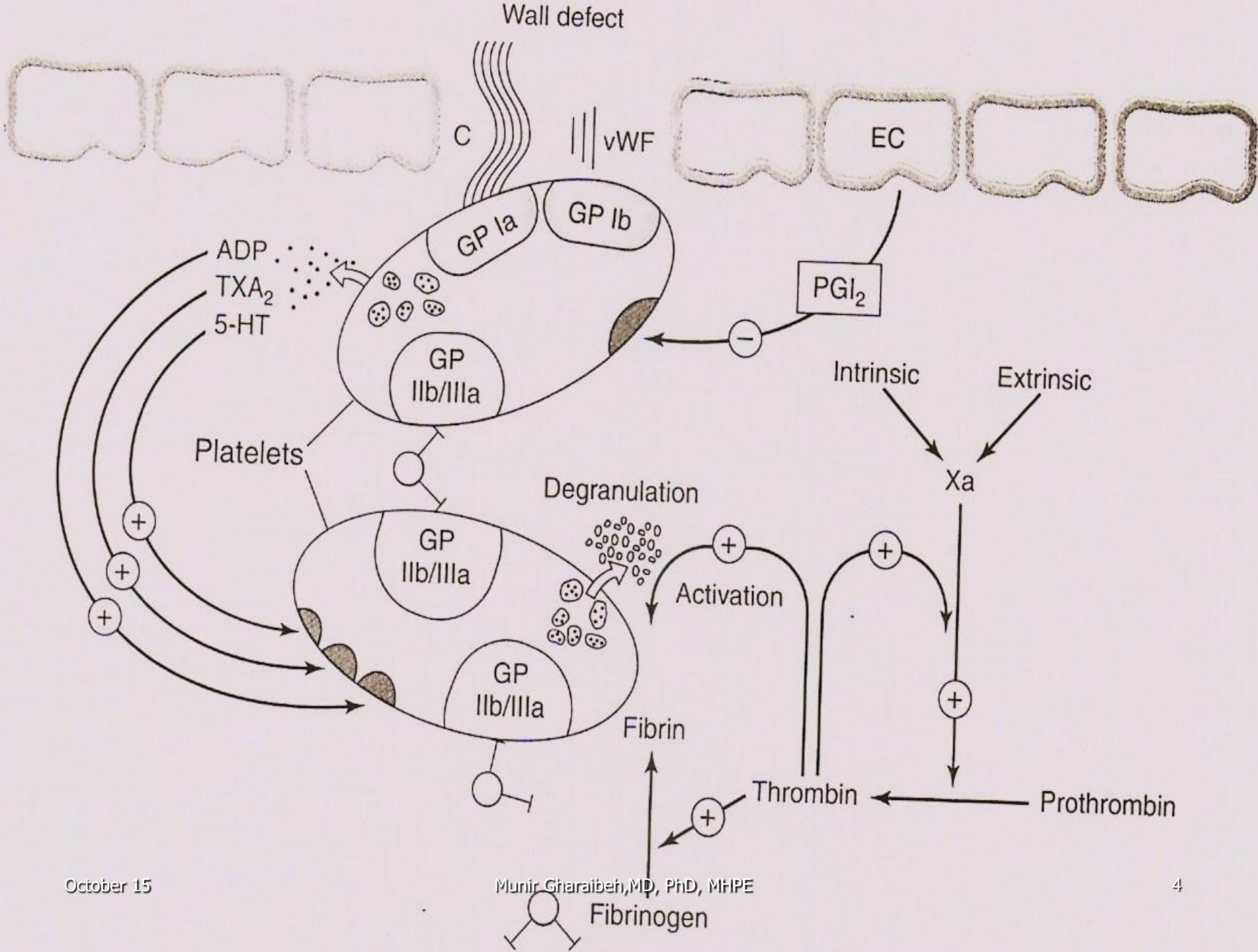
Department of Pharmacology

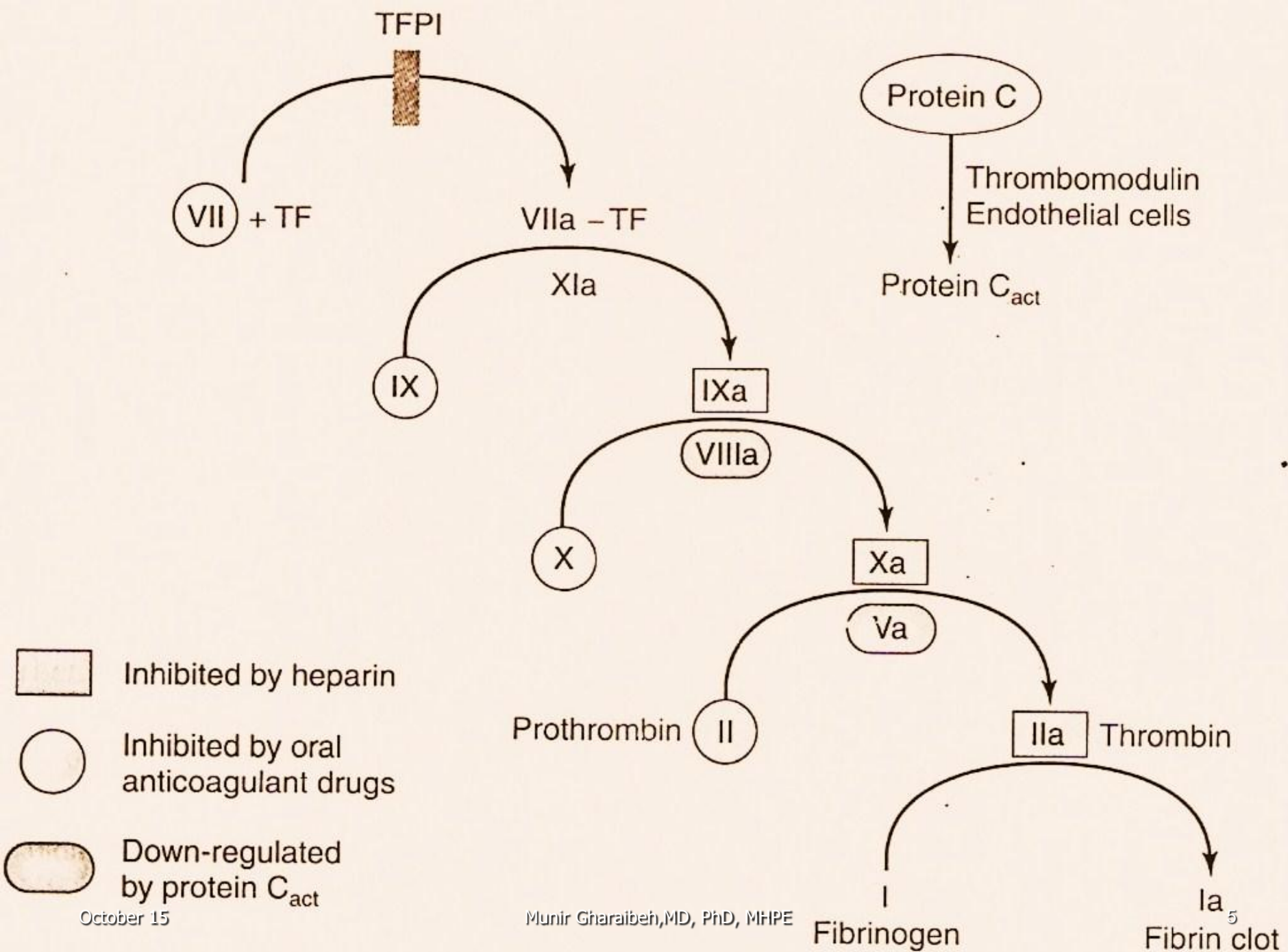
Faculty of Medicine

October 2014

Drugs used in Thromboembolic Disease

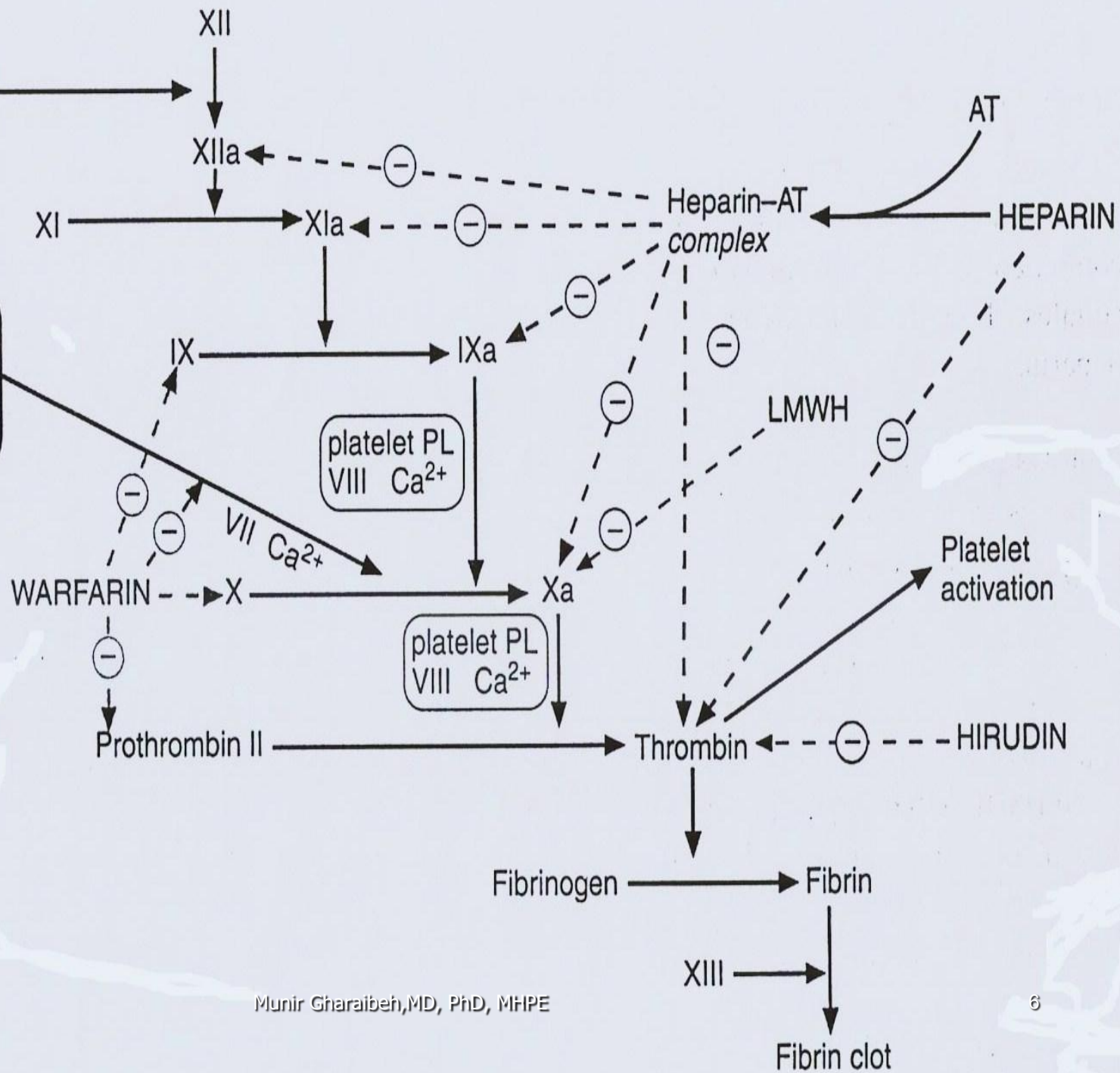
- **Anticoagulants:**
 - Heparin.
 - Oral anticoagulants.
- **Fbrinolytic Drugs:**
 - Streptokinase.
 - ASPAC
 - Rt-PA.
 - Urokinase.
 - Scu-PA.
- **Antiplatelet Drugs:**
 - Aspirin.
 - Dipyridamole.
 - Sulphinpyrazone.



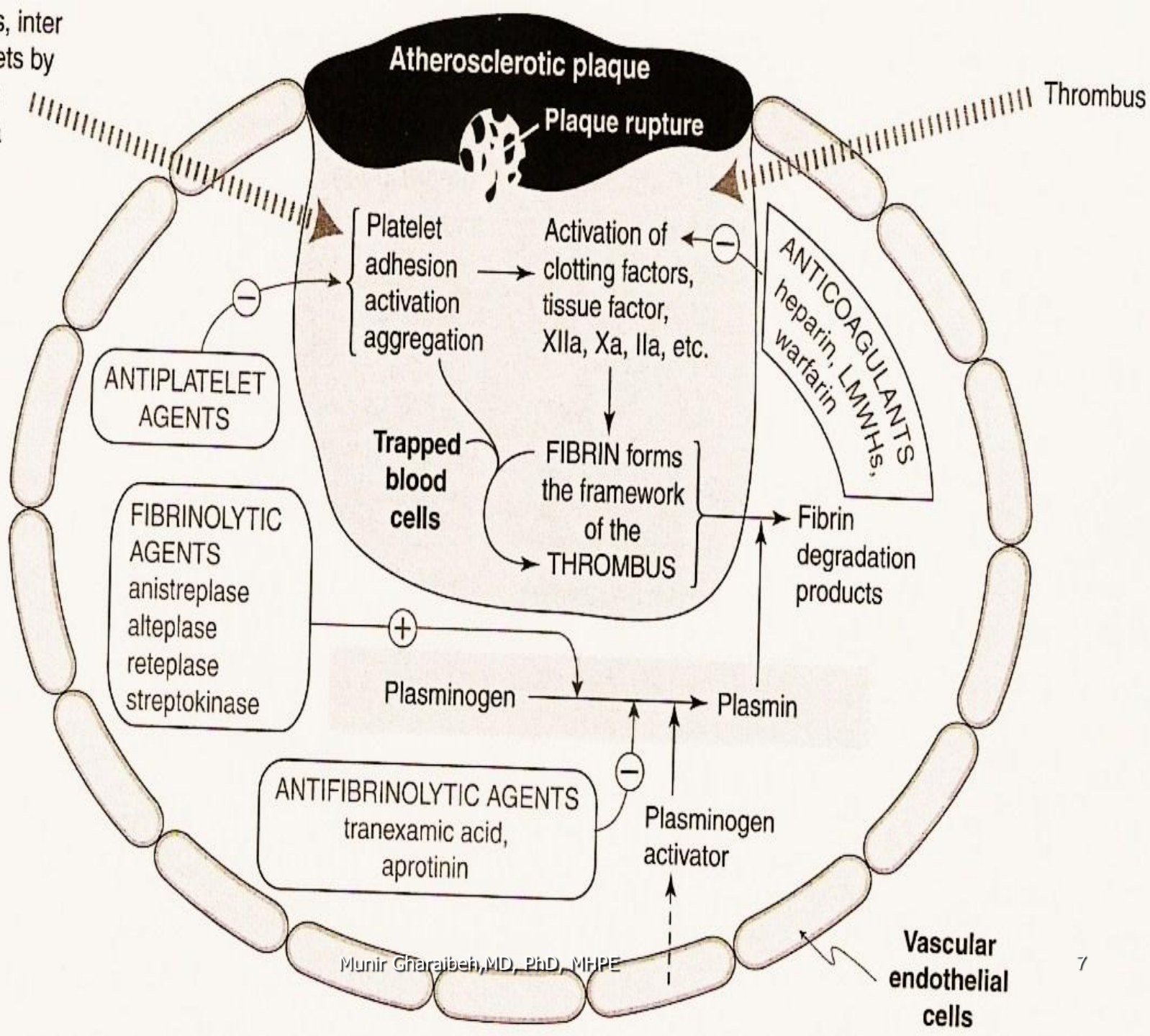


INTRINSIC PATHWAY
exposed collagen
kallikrein

EXTRINSIC PATHWAY
tissue damage
thromboplastin
platelet PL



Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)



1

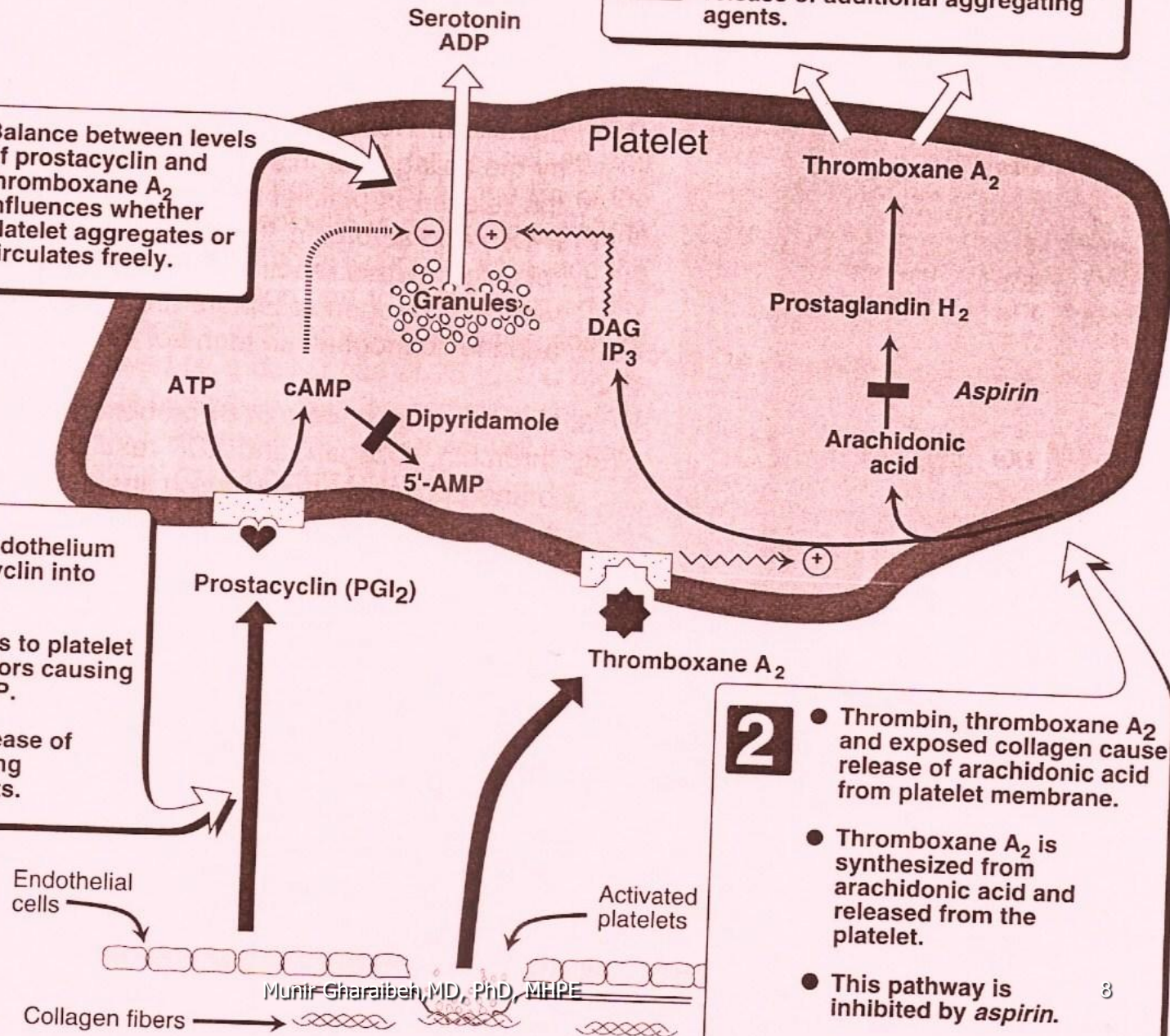
- Healthy, intact endothelium releases prostacyclin into plasma.
- Prostacyclin binds to platelet membrane receptors causing synthesis of cAMP.
- cAMP inhibits release of granules containing aggregating agents.

3

Thromboxane A₂ binds to receptors on other platelets thereby initiating release of additional aggregating agents.

4

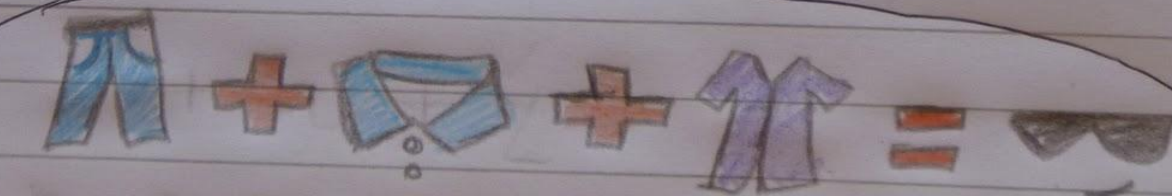
Balance between levels of prostacyclin and thromboxane A₂ influences whether platelet aggregates or circulates freely.

**2**

- Thrombin, thromboxane A₂ and exposed collagen cause release of arachidonic acid from platelet membrane.
- Thromboxane A₂ is synthesized from arachidonic acid and released from the platelet.
- This pathway is inhibited by aspirin.

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, aminocaproic acid

<u>I</u>	Fibrinogen	Freshers	Foolish
<u>II</u>	Prothrombin	Party	People
<u>III</u>	Tissue Thromboplastin	Tonights	Try
<u>IV</u>	Calcium ions	Come	Climbing
<u>V</u>	Labile factor	Lets	Long
<u>VII</u>	Stable factor	Sing	Slopes
<u>VIII</u>	Antihemophilic factor	And	After
<u>IX</u>	Christmas factor	Call	Christmas
<u>X</u>	Stuart Prower factor	Seniors	Some
<u>XI</u>	PTA	Please	People
<u>XII</u>	Hageman factor	Have	Have
<u>XIII</u>	Fibrin stabilizing factor	Fun	Fallen



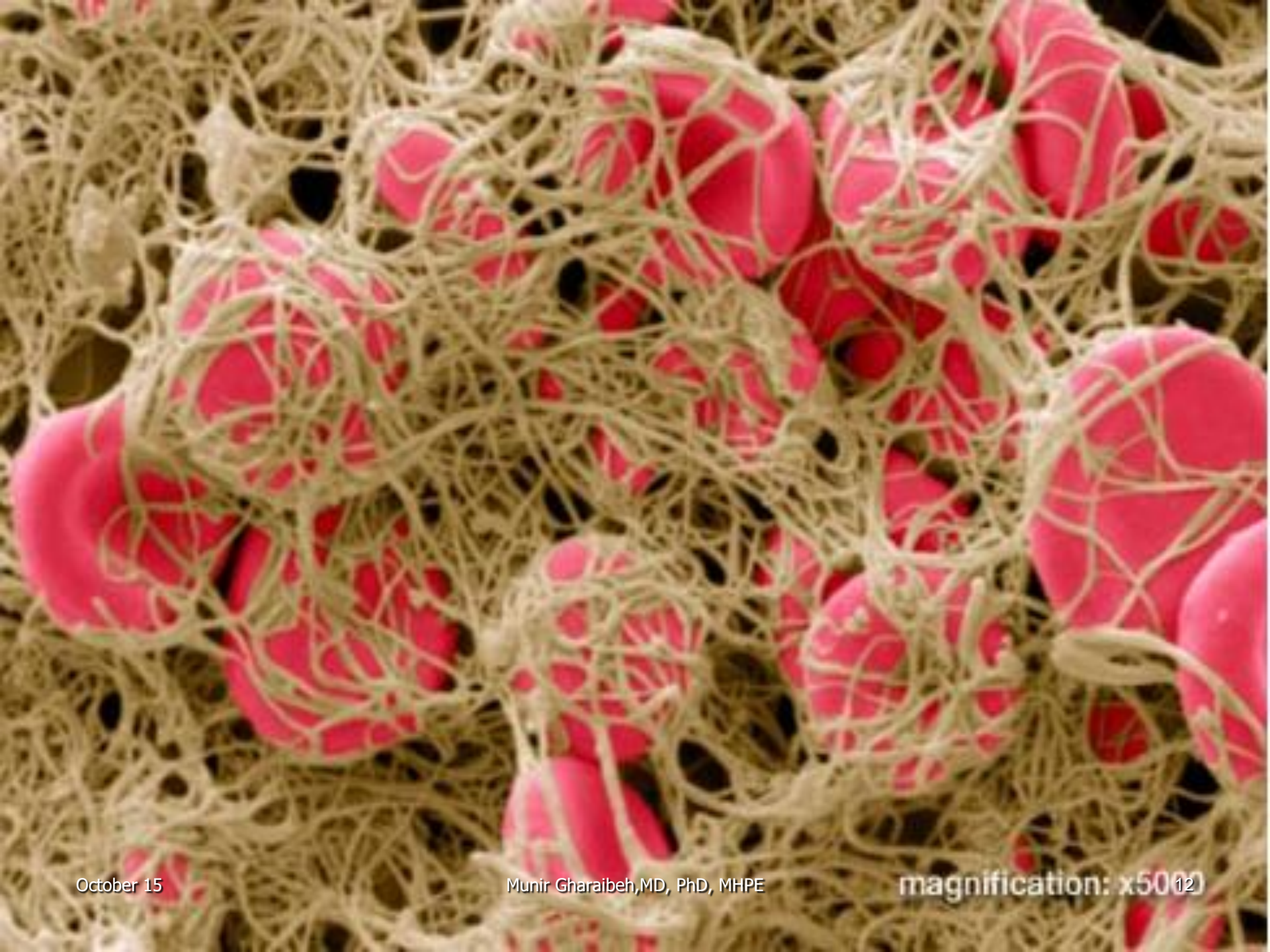
Fit Pants, Tight Collars, Loose
American Shirts Are Cool Says
Pretty Heroine, Farah



Table 28-1. Blood Coagulation Factors

Factor*	Synonyms	Synthesis	In vivo half-life
I	Fibrinogen	Liver	4–5 days
II	Prothrombin	Liver; K-dependent	3–5 days
III	Thromboplastin, tissue factor	—	—
IV	Ca ²⁺	—	—
V	Accelerator globulin, labile factor	Liver	12–36 hr
VII	Serum prothrombin conversion accelerator (SPCA), proconvertin	Liver; K-dependent	4–6 hr
VIII:C	Antihemophilic globulin (AHG), anti-hemophilic factor (AHF)	Liver; endothelium	10–18 hr
IX	Plasma thromboplastin component (PTC), Christmas factor	Liver; K-dependent	15–30 hr
X	Stuart factor, Stuart-Prower factor	Liver; K-dependent	20–80 hr
XI	Plasma thromboplastin antecedent (PTA)	?	60–70 hr
XII	Hageman factor	Liver?	60–70 hr
XIII	Fibrin-stabilizing factor	?	3–4 days
Protein C	Autoprothrombin II-A	Liver; K-dependent	—

* Roman numerals are international designations. There is no factor VI.



Risk Factors for Thromboembolism

- **Abnormalities of Blood Flow:**
 - **Atrial fibrillation.**
 - **Left ventricular dysfunction.**
 - **Bed rest/immobilization/paralysis.**
 - **Venous obstruction.**

Risk Factors for Thromboembolism

- **Abnormalities of Surface Contact with blood:**
 - **Vascular injury/trauma.**
 - **Heart valve disease and replacement.**
 - **Atherosclerosis.**
 - **Acute myocardial infarction.**
 - **Indwelling catheters.**
 - **Previous DVT/PE.**
 - **Fractures.**
 - **Chemical irritation (K+, hypertonic solutions, chemotherapy).**
 - **Tumor invasion.**

Risk Factors for Thromboembolism

- **Abnormalities of Clotting Components:**
 - Protein C, Protein S, Antithrombin deficiency.
 - Prothrombin G20210A mutation.
 - Antiphospholipid antibody syndrome.
 - Estrogen therapy.
 - Pregnancy, malignancy.
 - Homocystenemia, dysfibrinogenemia,
 - Polycythemia, thrombocytosis.
 - Myeloproliferative disorders.

Risk of Thromboembolism in Hospital Patients

Risk	Procedure
Low	<p>Minor surgery, no other risk factor</p> <p>Major surgery, age < 40 years, no other risk factors</p> <p>Minor trauma or illness</p>
Moderate	<p>Major surgery; age ≥ 40 years or other risk factor</p> <p>Heart failure, recent myocardial infarction, malignancy, inflammatory bowel disease.</p> <p>Major trauma or burns</p> <p>Minor surgery, trauma or illness in patient with previous deep vein thrombosis or pulmonary embolism.</p>
High	<p>Fracture or major orthopaedic surgery of pelvis, hips or lower limb</p> <p>Major pelvic or abdominal surgery for cancer</p> <p>Major surgery, trauma or illness in patient with previous deep vein thrombosis or pulmonary embolism.</p> <p>Lower limb paralysis.</p> <p>Major lower limb amputation.</p>

Non Thrombogenic Mechanisms in Blood Vessels

- **Transmural negative electrical charges.**
- **Plasminogen activation.**
- **Protein C activation.**
- **Production of heparin-like proteoglyans.**
- **Release of PGI_2 .**

Inhibitors of Clotting Mechanisms

<i>Inhibitor</i>	<i>Target</i>
Antithrombin	Inhibits factor IIa, IXa and Xa.
Protein C	Inactivates factor Va and VIIIa
Protein S	Cofactor for activation of factor C
Tissue factor pathway inhibitor (TFPI)	Inhibits activity of factor VIIa.
Plasmin	Lyse fibrin into fibrin degradation products.

Indirect Thrombin Inhibitors

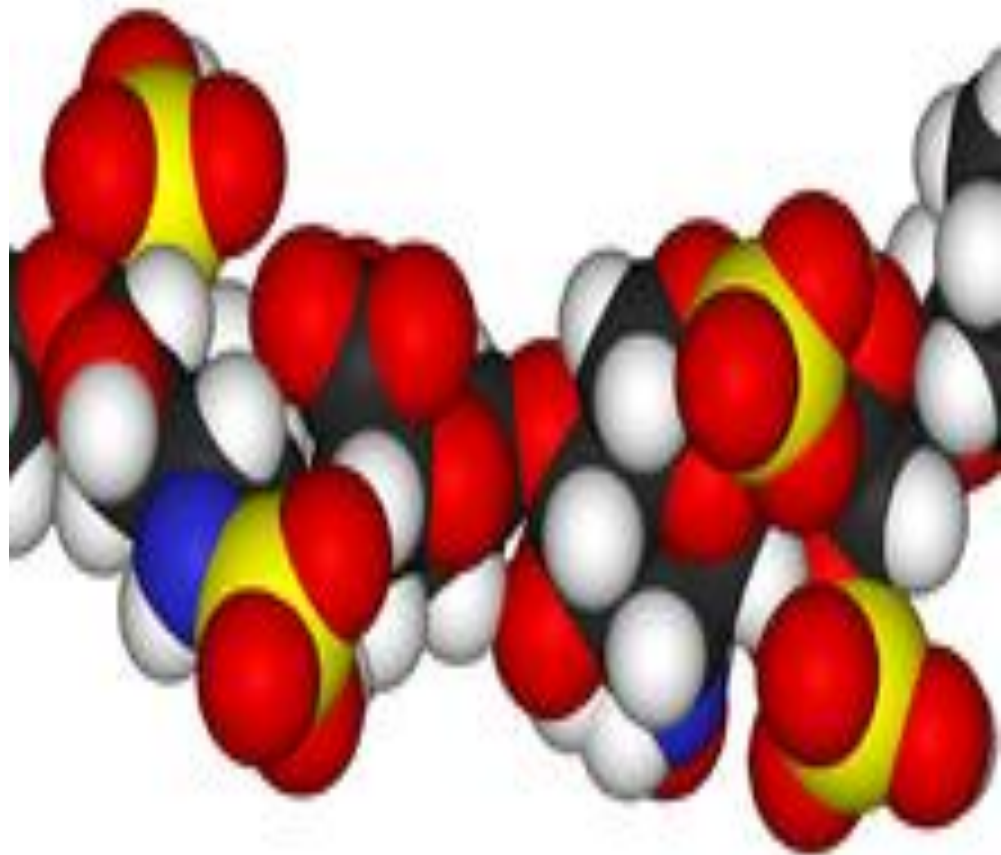
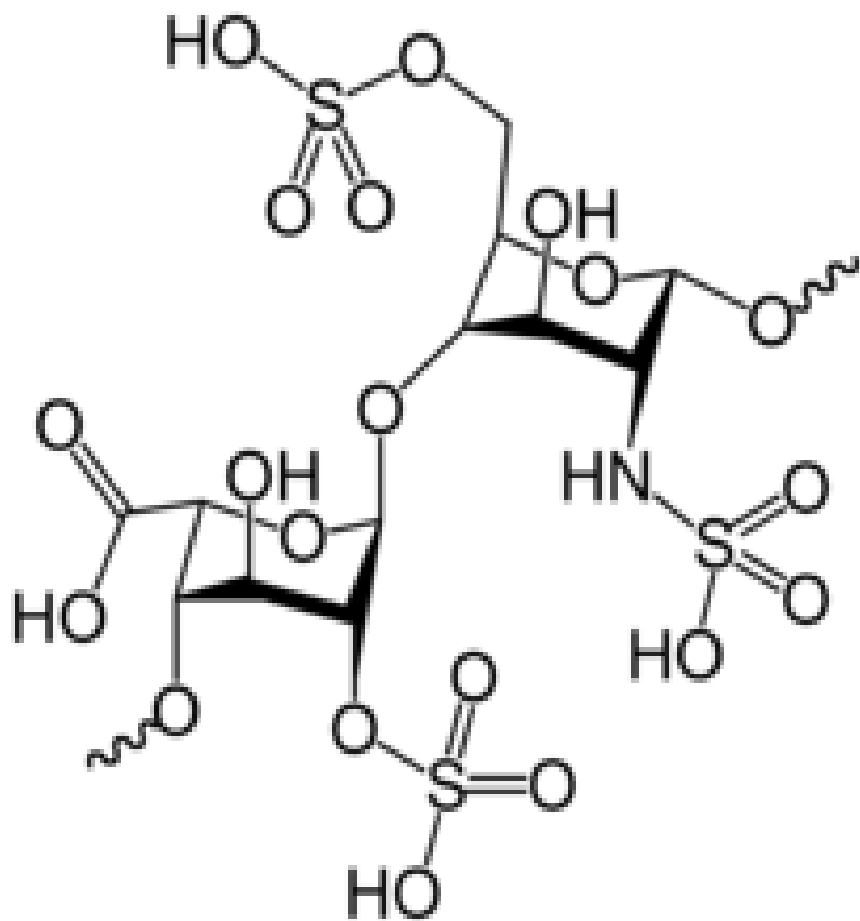
- **HEPARIN:**

- Unfractionated heparin (UFH).
- Low Molecular Weight Heparins (LMWHs):
 - Enoxaparin.
 - Dalteparin.
 - Tinzaparin(Innohep).
 - Danaparoid.

- **FONDAPARINUX**

HEPARIN(1922)

- **Heterogenous mixture of sulfated mucopolysacharides.**
- **Composed of sulfated glucosamine and D-glucuronic acid connected by sulfaminic bridges.**
- **It is a normal physiological anticoagulant.**
- **Normally found in mast cells(in heart, liver, intestine, and lungs), in an inactive form, but has an obscure function.**
- **Released with anaphylaxis.**
- **Obtained from cow lung and pig intestinal mucosa.**



HEPARIN

- **Molecular weight varies:**
 - **Commercial Unfractionated(UFH):5,000-30,000.**
 - **High Molecular Weight Heparin (HMWH):2/3rds of UFH**
 - **Low Molecular Weight Heparin (LMWH)**
- **$T_{1/2} = 1$ hr.**
- **Distribution limited to the intravascular compartment.**
- **Does not cross the placenta and not excreted in breast milk.**
- **Eliminated by rapid metabolism by heparinase enzyme in the liver, renal excretion, and uptake by the RES .**

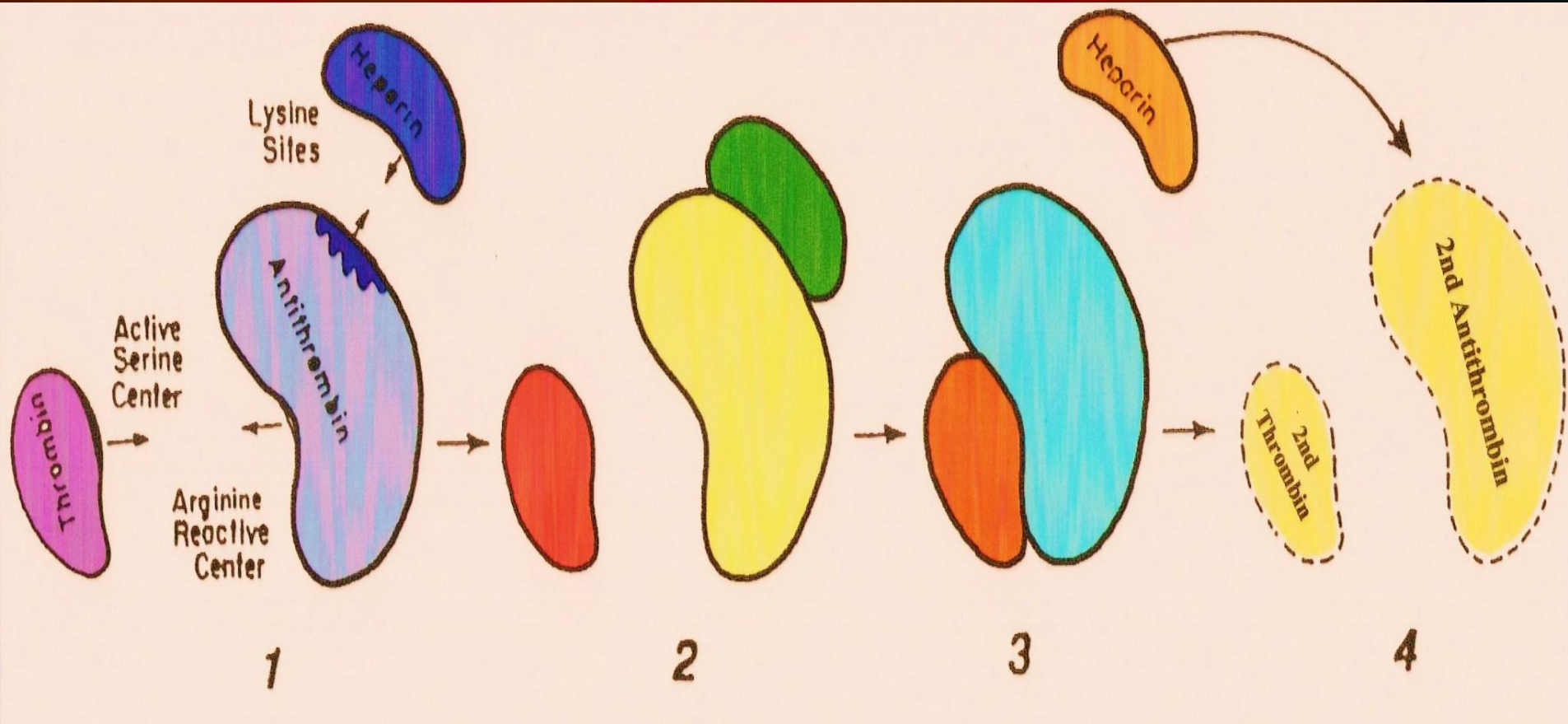
HEPARIN

- **Acts directly in peripheral blood.**
- **Does not affect the biosynthesis or plasma levels of any coagulation factor.**
- **Taken up by the endothelium where it increases the electronegative potential of the vessel wall.**
- **Binds to a variety of plasma proteins, mainly antithrombin.**
- **Causes the release of Tissue Factor Pathway Inhibitor (TFPI), which works on Xa, platelets and endothelium.**
- **UFH inhibits platelets aggregation.**
- **Activates Lipoprotein Lipase which reduces platelets adhesiveness.**

HEPARIN

- **Antithrombin(ATIII) inhibits clotting factor proteases, especially thrombin (IIa), IXa and Xa.**
- **Heparin binds tightly to antithrombin and causes a conformational change to expose its active site for more rapid interaction with the proteases.**
- **Heparin accelerates this complexing by 1000 folds.**
- **Heparin functions as a cofactor, it is not consumed.**

HEPARIN



HEPARIN

- **HMWHs have high affinity for antithrombin which will inhibit coagulation by inhibiting all three factors, especially thrombin and factor Xa.**

LMWHs

- 15 Polysaccharide units.
- LMWHs causes factor Xa inhibition, but have less effect on thrombin or endothelial cell-heparin receptors and plasma protein binding sites.
- LMWHs have:
 - Equal efficacy.
 - More predictable effects.
 - More bioavailability from s.c site of injection.
 - Less frequent dosing requirements.
 - Doses specified in milligrams rather than in units.
 - Treatment is not generally monitored (except in renal failure, pregnancy and obesity).

HEPARIN

- **MONITORING:**
- **Activated Partial Thromboplastin Time (aPTT)**
- **Also, Protamine Titration and Anti-Xa units.**
- **Monitoring the response is needed only in patients receiving UFH, but not needed with LMWH.**

HEPARIN

- **TOXICITY:**
- **Bleeding.**
- **Allergic reactions: fever, anaphylaxis.**
- **Alopecia, or loss of hair.**
- **Osteoporosis and ostealgia.**
- **Mineralocorticoid deficiency.**
- **Thrombocytopenia:**
 - **Occurs in 1- 4% of patients taking UFH for 7 days.**
 - **More with UFH from bovine sources.**
 - **Lower with LMWH.**

HEPARIN

● Contraindications:

- Thrombocytopenia ($<75,000$).
- Hypersensitivity.
- Active bleeding.
- Severe hypertension.
- Hemophilia, purpura.
- Infective endocarditis, active TB.
- Ulcerative lesions of GIT.
- Threatened abortion.
- Visceral carcinoma.
- Advanced liver or renal disease.

HEPARIN

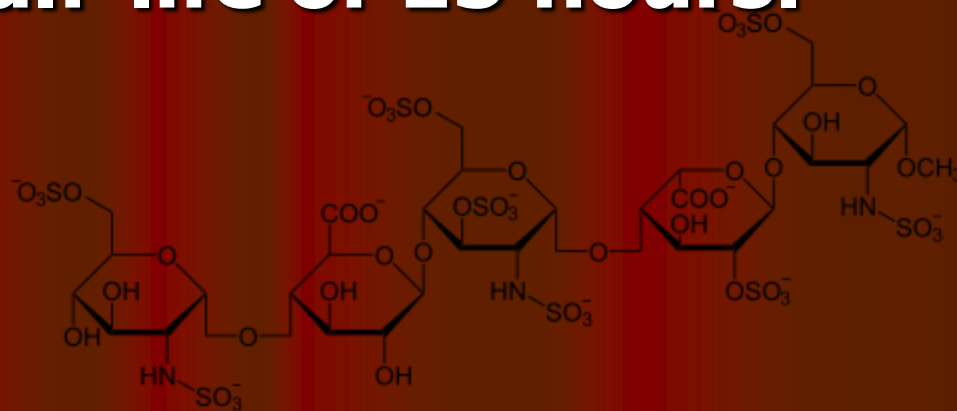
- Administration of UFH:
- Initial bolus injection: 80-100 units/kg.
- Continuous infusion through a pump:
 - 15-22 unit/kg/hr.
 - This usually maintains aPTT at 2-2.5 times of the control.
 - Not by intramuscular injection.
 - Low dose prophylaxis:
 - Subcutaneously 5000 units every 8-12 hrs.
- Antidote:
 - Protamine sulfate: is a highly basic low mol.wt compound.

HEPARIN

- **Administration of LMWHs:**
 - Almost completely absorbed after s.c. injection.
 - Usually given once or twice daily by subcutaneous injection.
 - Monitoring is by Xa inhibition assay which is not routinely carried.
- **Antidote:**
 - Protamine binds poorly and ineffective.
 - No antidote is available nor needed.

Fondaparinux

- **Synthetic pentasaccharide fragment of heparin.**
- **Binds antithrombin with high specific activity, resulting in more selective inactivation of factor Xa.**
- **Has a long half-life of 15 hours.**



Direct Thrombin Inhibitors

- **Hirudine** (from leeches, *Hirudo medicinalis*)
- **Lepirudin**, *recombinant form*.
- **Bivalirudin**.
 - Are bivalent compounds, i.e. they bind at both the catalytic site and the substrate recognition site of thrombin.
 - Eliminated by the kidneys.
 - Can cause allergy and anaphylaxis.

Direct Thrombin Inhibitors

- **Argatroban.**
- **Ximelagatran.**
- **Melagatran.**
 - **Are small molecules that bind only at the active site of thrombin.**
 - **Eliminated by the liver.**

Factor Xa Inhibitors

- **Rivaroxaban "Xarelto"**
- **Apicaban**
- **Edoxaban**
 - **These inhibit factor Xa, in the final common pathway of clotting.**
 - **Given orally at fixed doses and do not require monitoring.**
 - **Used to prevent stroke in atrial fibrillation.**