

Hypercoagulable States

Dr. Nervana Mostafa

MB BS, MD, PhD (UK)

Assistant Professor of Physiology

Consultant Molecular Biology

Director of Academic Quality Unit

College of Medicine, KKUH, KSU

Objectives:

Normal Hemostasis:

- **Coagulation cascade**
- **Fibrinolysis**
- **Natural anti-coagulants**
- **Haemostatic balance**

Hypercoagulability:

- **Definition.**
- **Types.**
- **Causes**
- **Laboratory testing**

Hemostasis:

the spontaneous arrest of bleeding from ruptured blood vessels.

Mechanisms:

- 1. Vessel wall**
- 2. Platelet**
- 3. Blood coagulation**
- 4. Fibrinolytic system**

Clotting Factors

Factors	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Labile factor
VII	Stable factor
VIII	Antihemophilic factor
IX	Antihemophilic factor B
X	Stuart-Power factor
XI	Plasma thromboplastin antecedent
XII	(PTA)
XIII	Hagman factor
	Fibrin stabilizing factors

Intrinsic Pathway

FXII → **FXIIa**

FXI → **FXIa**

FIX → **FIXa**

FVIII

X → **Xa**

Prothrombin → **Thrombin**

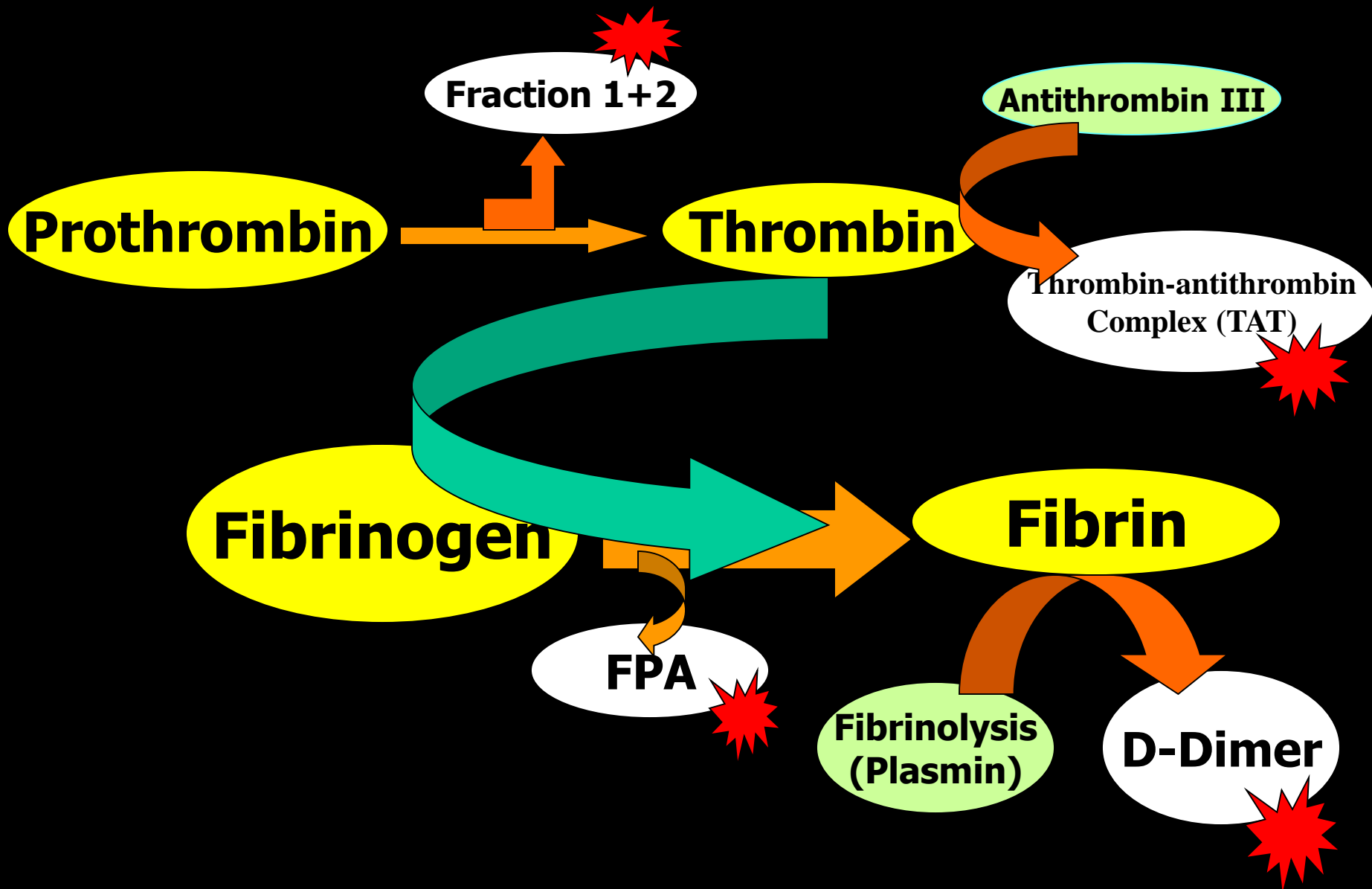
Extrinsic pathway

Tissue factor

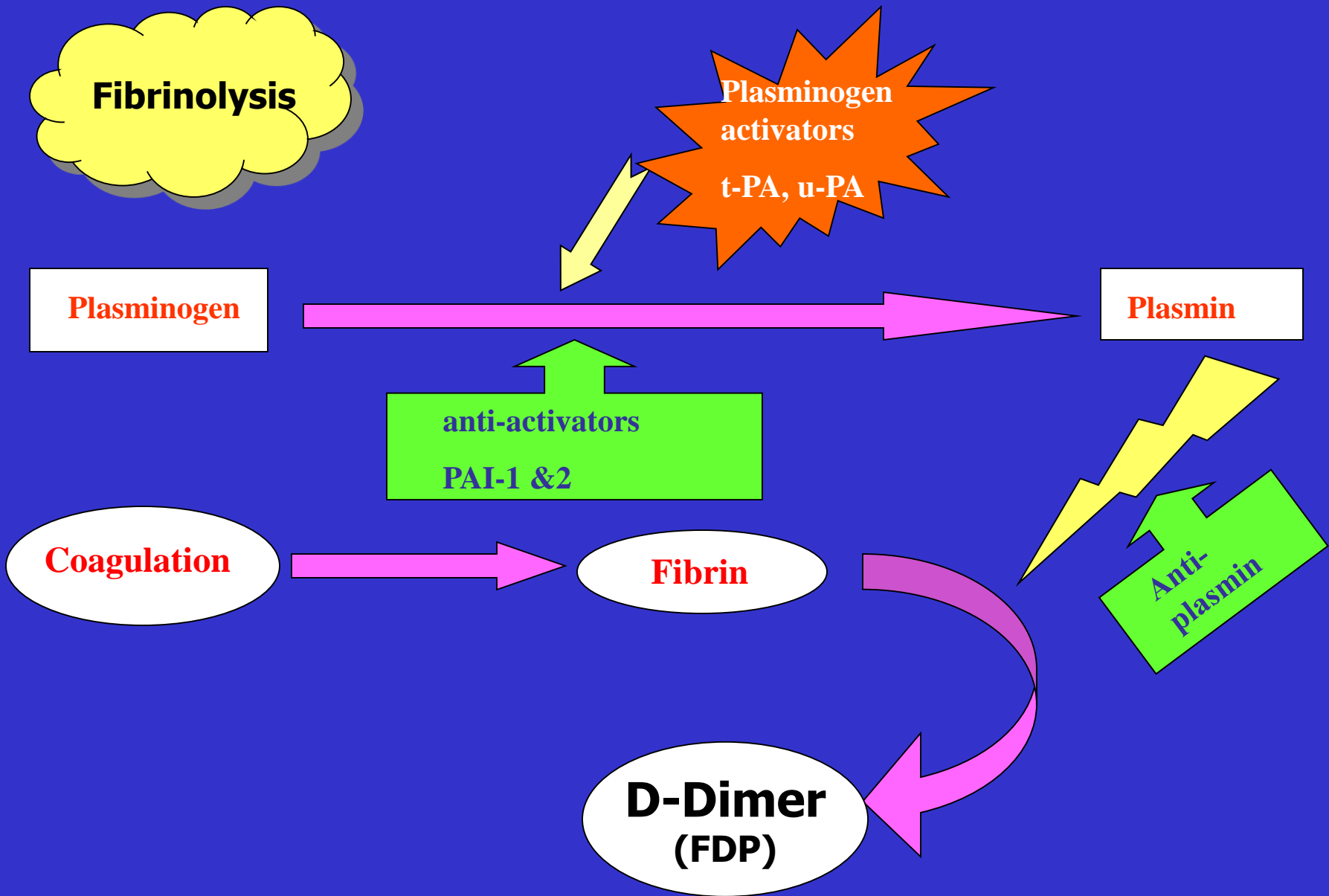
**Factor VII
& Ca⁺⁺**

FV+ Ca+P

The Coagulation Cascade



Haemostatic Activation Markers



Enzymatic activation products of coagulation and fibrinolytic mechanisms such as :

prothombin 1+2 (F1+2)

thrombin-antithrombin complex (TAT)

FPA

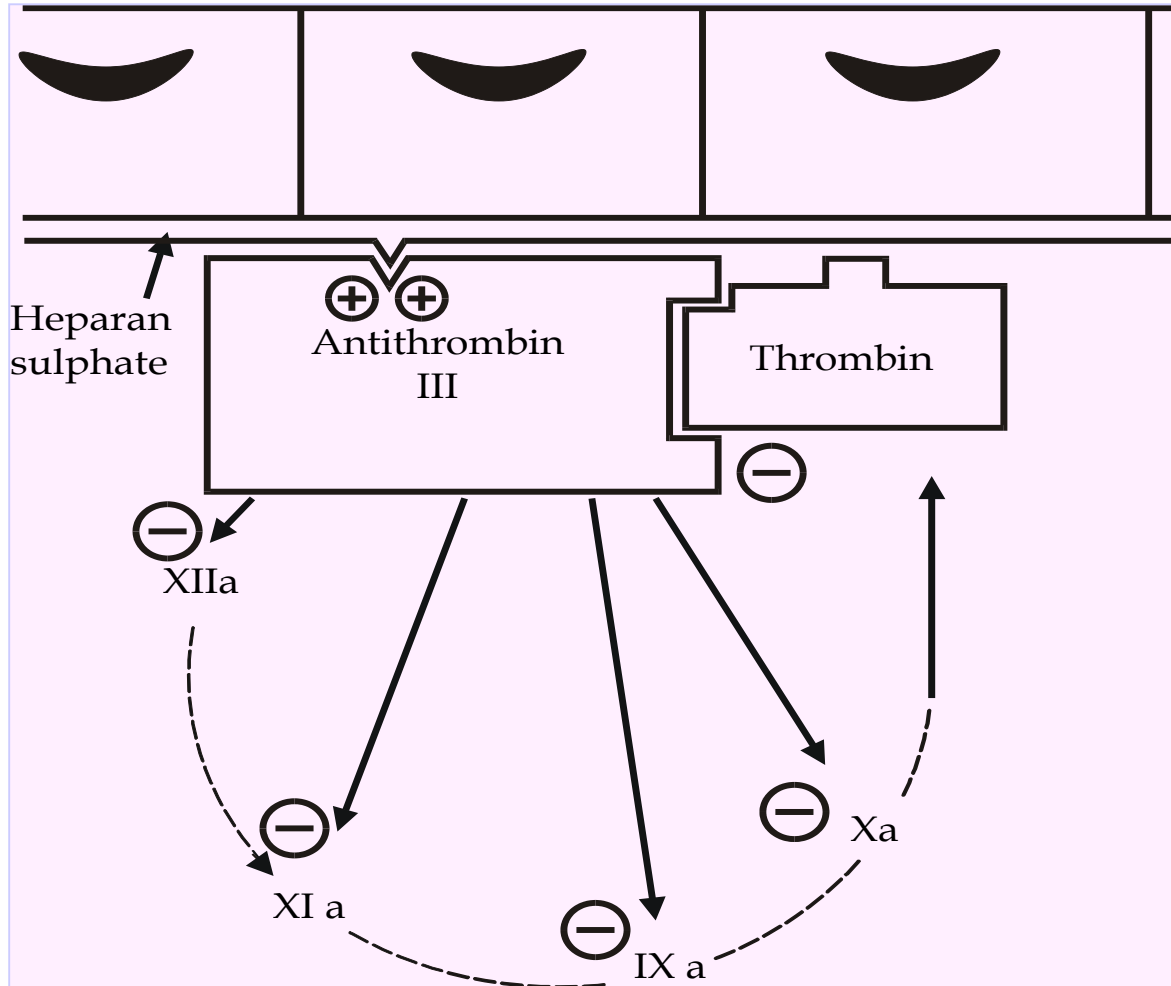
D-dimer

are not coded for by specific genes, and their concentrations reflect the overall activation of the coagulation and fibrinolytic systems.

Natural anticoagulants :

- Anti-thrombin III (AT-III)
- Protein C (inhibits Va & VIIIa)
- Protein S (cofactor for protein C)

Inactivation of coagulation by antithrombin III

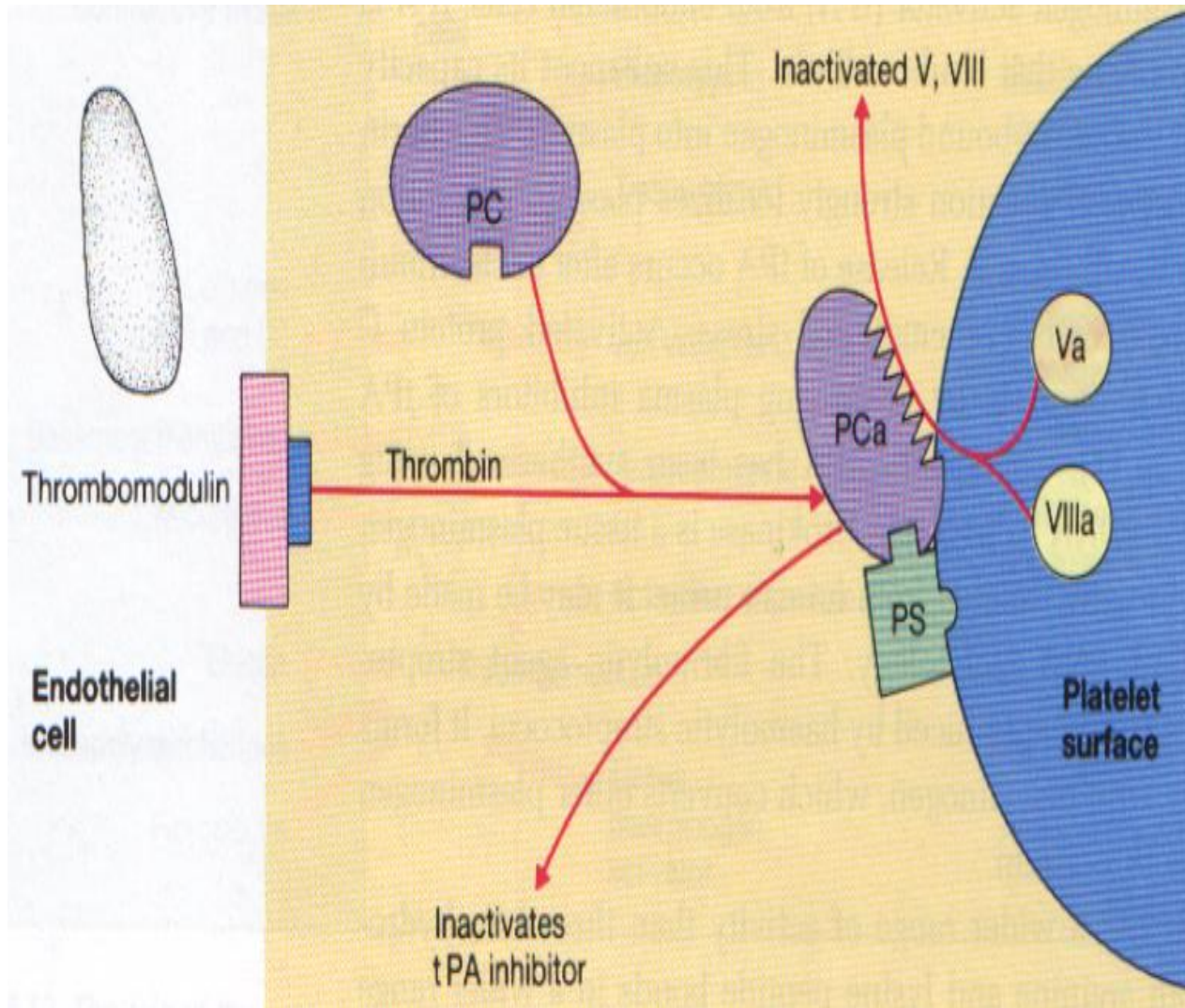


/// **Synthesis:**
hepatocytes &
endothelial cells.

/// **Action:**
ATIII + thrombin
→ thrombin-ATIII
complex.

/// **Heparin**
dramatically
enhances this
action .

Action of Protein C & S

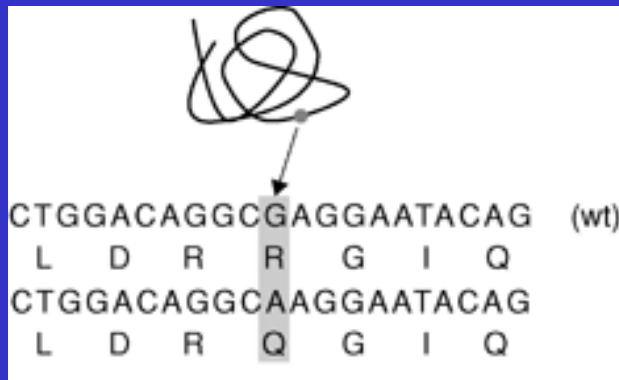


Protein C:

- Vitamin K-dependent.
- Synthesized by the hepatocytes

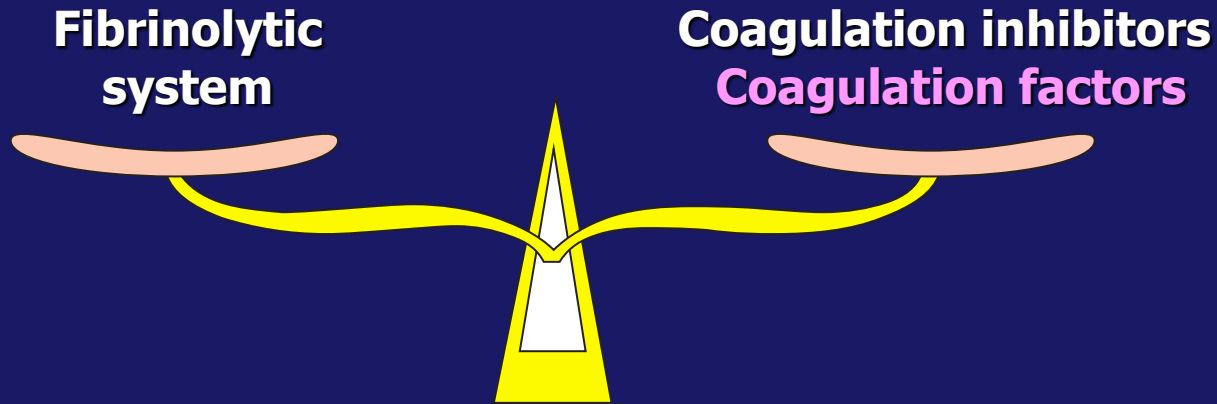
Activated protein C resistance (APC-R):

is mainly due to a genetic abnormality of clotting factor V called (factor V Leiden mutation).



point mutation in the factor V gene,
G1691A in exon 10, leading to
Arg506Gln.

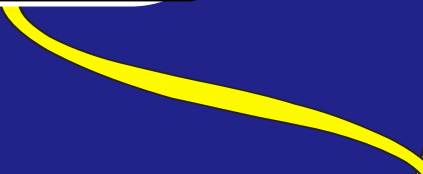
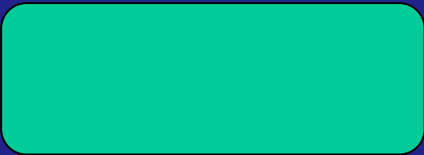
Hemostatic Balance



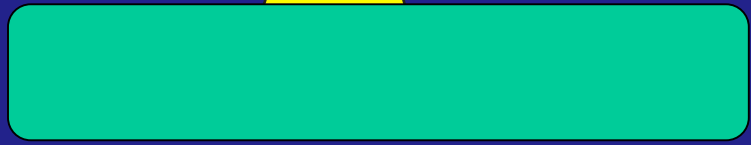
Homeostasis of the clotting system

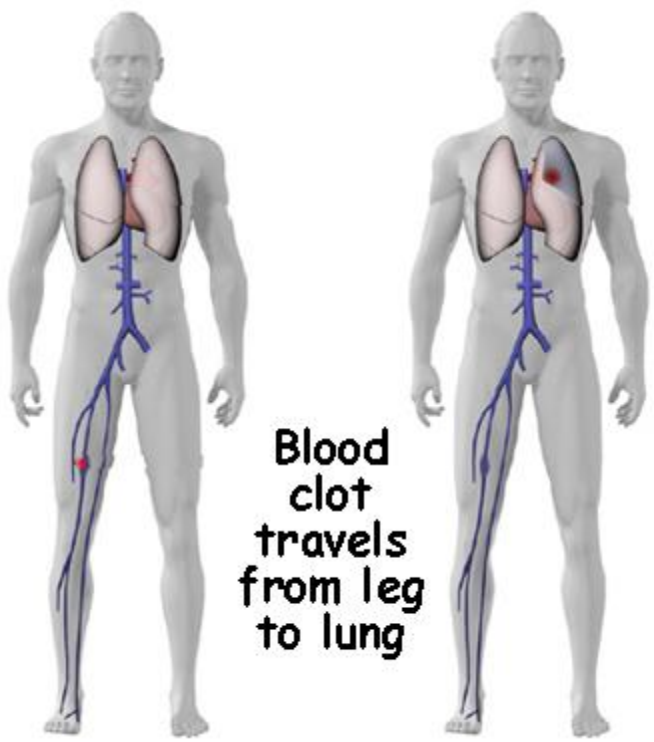
A crucial physiological balance exists between factors favoring clotting and factors that oppose it.

Disturbances in this balance can lead to thrombotic diseases or bleeding.



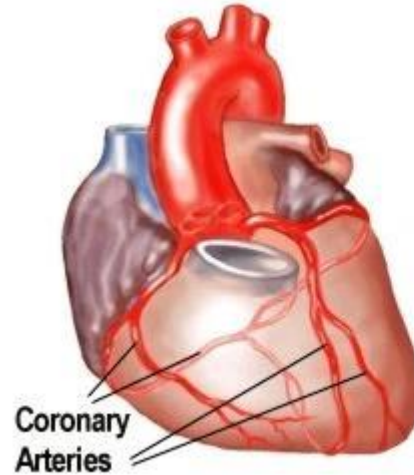
↓ Coagulation inhibitors
(ATIII, Pc, Ps)
↑ clotting factors





Blood clot travels from leg to lung

DVT & PE



Coronary Arteries



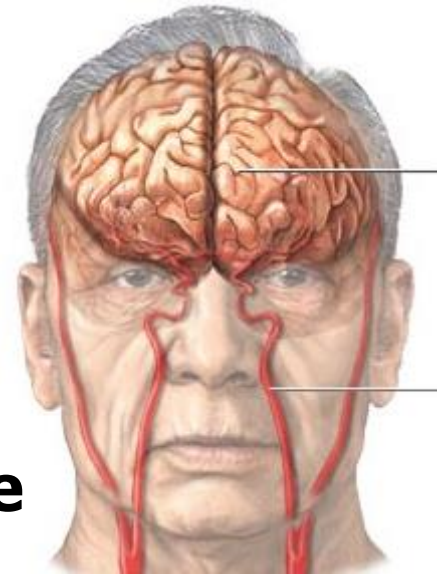
Atherosclerotic Disease

MI

Placental infraction



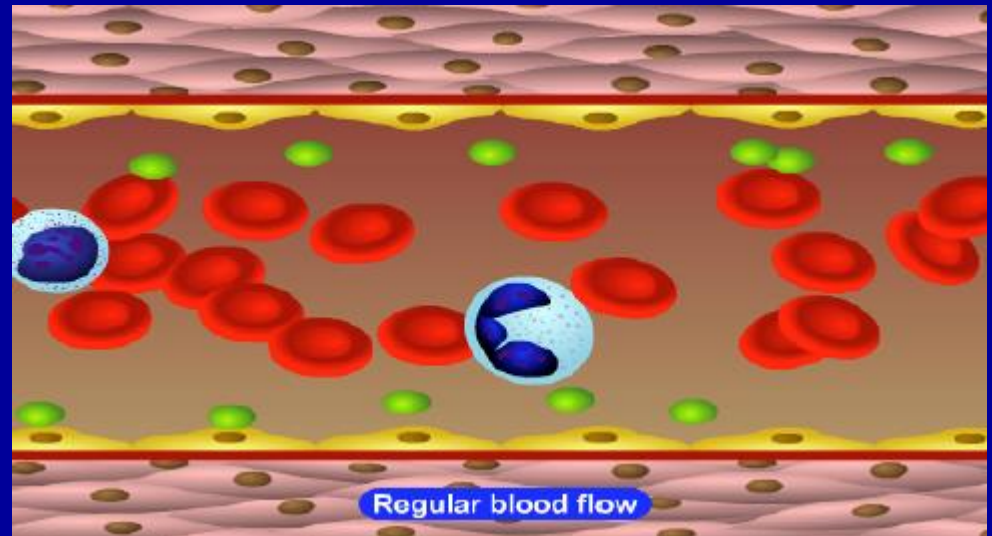
Stroke



Virchow Triads 1845

Aetiological factors for thrombosis:

- Changes in blood flow (stasis)
- Changes in the endothelium
- Changes in blood composition
(Hypercoagulability)



The dynamic balance between procoagulant reactions & their downregulation by natural anticoagulants in conjunction with the fibrinolytic system should function within normal parameters to prevent abnormal thrombus formation or propagation.

However, in some instances, alteration of just one variable in this complex series of interacting components will bring about a significant hypercoagulable (prothrombotic) state, which can manifest itself clinically as arterial and/or venous TE.

Hypercoagulability:

Is a laboratory phenotype whereby activation of the of clotting, fibrinolysis, endothelial cells and platelets are identified.

Hypercoagulability/Prothrombotic States

Hereditary Hemostatic disorders:

Factor V Leiden

Prothrombin G20210A

Hyperhomocysteinaemia

Deficiencies of AT III, Proteins C & S

Increased FVIII

Acquired Hemostatic disorders:

Raised Levels of fibrinogen & FVII

Antiphospholipid Antibodies (LA & ACAs)

Oestrogen therapy

Pregnancy and its complications

Surgery and prolonged immobility

Major Trauma

Malignancy

Nephrotic Syndrome

Hypercoagulability/Prothrombotic States

cont.

Acquired Hemostatic disorders : cont.

**Dehydration, Hyperviscosity, Polycycaemia,
Thrombocytosis**

Sepsis

Smoking

Obesity

Age

Varicose veins

Laboratory tests of hypercoagulability

Natural anticoagulants

ATIII

Protein C

Protein S

Fibrinolysis

PAI-1

FDPs (D-Dimer)

Laboratory tests of hypercoagulability *cont.*

Coagulation activation markers

Thrombin-Antithrombin complexes (TAT)

Prothrombin fraction 1+2

D-Dimer

Activated protein C Resistance (APCR)

Functional Assay

Genetic assay (Factor V Leiden)

Genotyping:

Factor V Leiden

Prothrombin G20210A

Hyperhomocysteinaemia (MTHFR)

Summary:

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