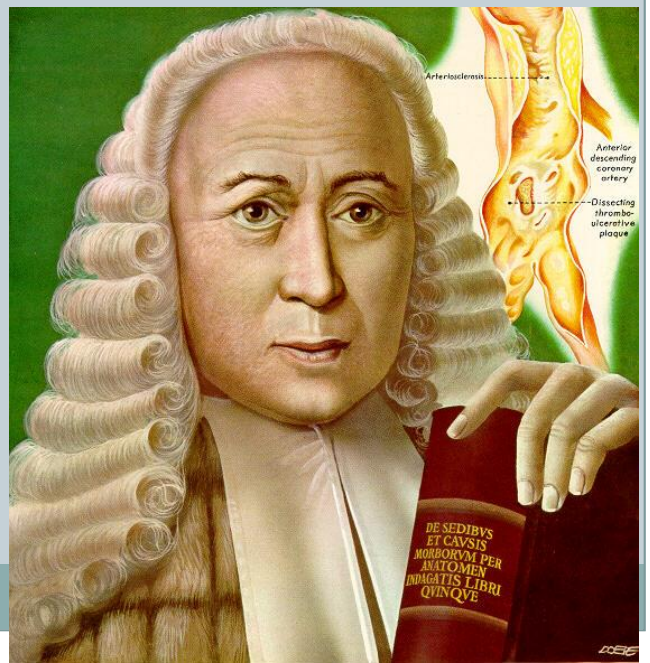
Hypercoagulable States and DVT

History

- Susruta (Ayurveda physician and surgeon, 600-1000 B.C.) – patient with a “swollen and painful leg that was difficult to treat”
- Giovanni Battista Morgagni, 1761 – recognized clots in pulmonary arteries after sudden death, but didn’t make the connection to DVT



Virchow Strikes Again

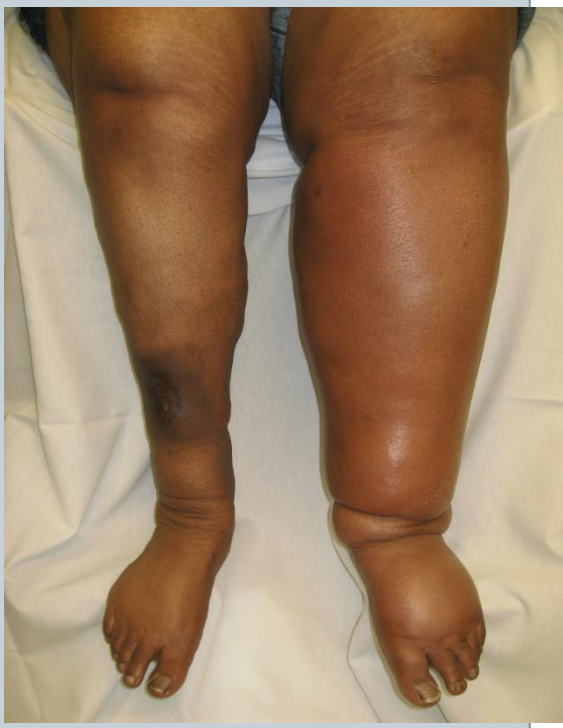
- “Discovered” PE in 1846 – “the detachment of larger or smaller fragments from the end of a softening thrombus which are carried along the current of blood and driven into remote vessels. This gives rise to the very frequent process on which I have bestowed the name Embolia”

Deep Venous Thrombosis - Epidemiology

- 1969 paper by Kakker
  - 30% of post-op patients develop clot in calf veins
  - 35% of these lysed within 72 hrs
  - 15% of pts with persistent thrombosis developed PE
- Recent studies put incidence at 50 per 100,000 person years
- Incidence greatly increases with age, 18% of 80yr old patients have asymptomatic DVT

DVT Diagnosis

- Wells clinical prediction rules
- D dimer ELISA assay >90% sensitive, but 40-50% specific
- When D dimer is negative and clinical suspicion low, further studies are unwarranted
- Ultrasound most sensitive and specific (>90%) for symptomatic, proximal vein
- US only 50-70% sensitive for asymptomatic pts
- Sens. And spec. much lower for symptomatic arm DVT (60-90%)



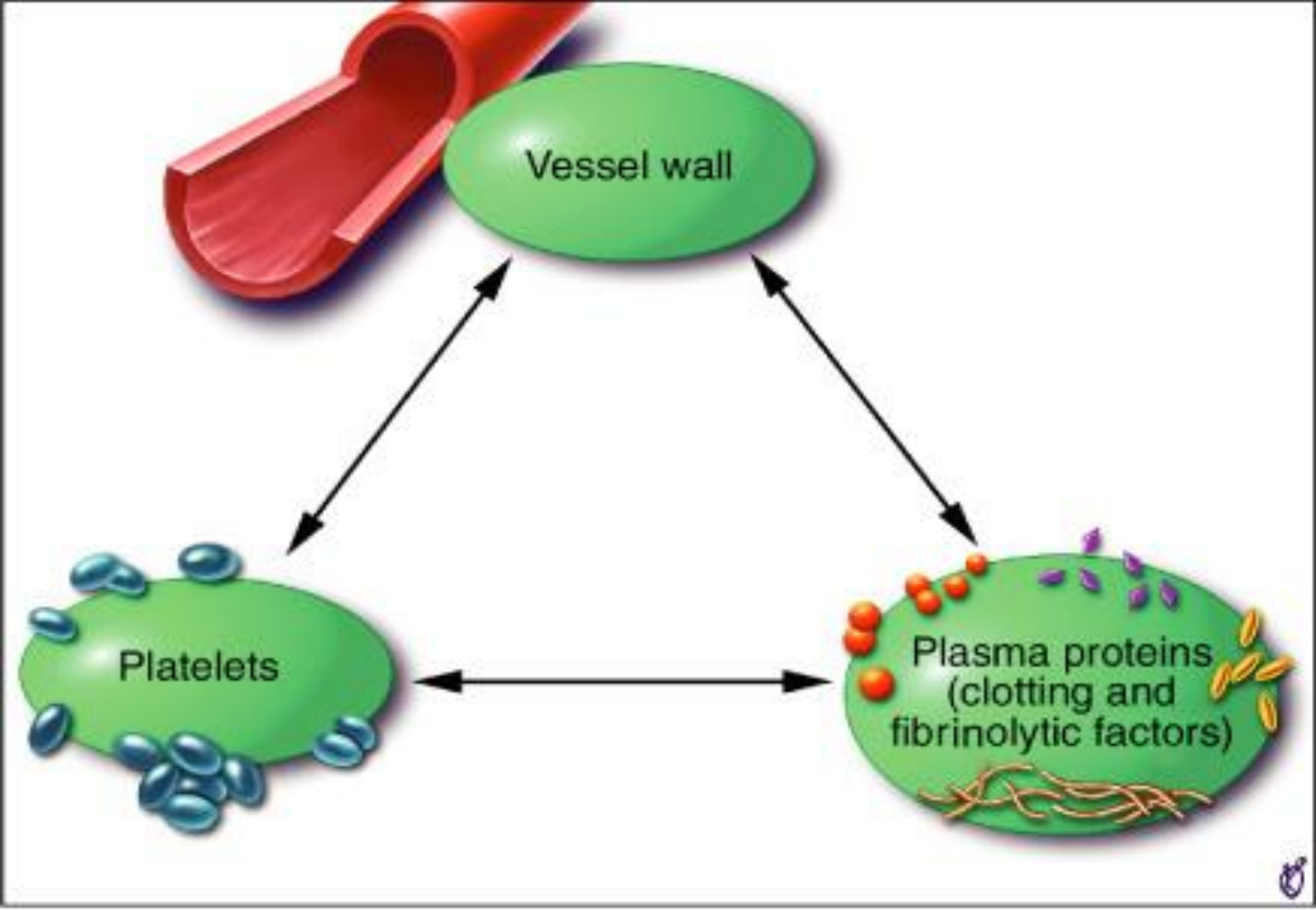
Wells Clinical Prediction Rule

Clinical Feature	Points
Active cancer (treatment ongoing or within previous 6 months or palliative	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Unilateral calf swelling of greater than 3 cm (below tibial tuberosity)	1
Unilateral pitting edema	1
Collateral superficial veins	1
Previous Hx DVT	1
Alternative diagnosis as likely as or more likely than DVT	-2
Total Points	

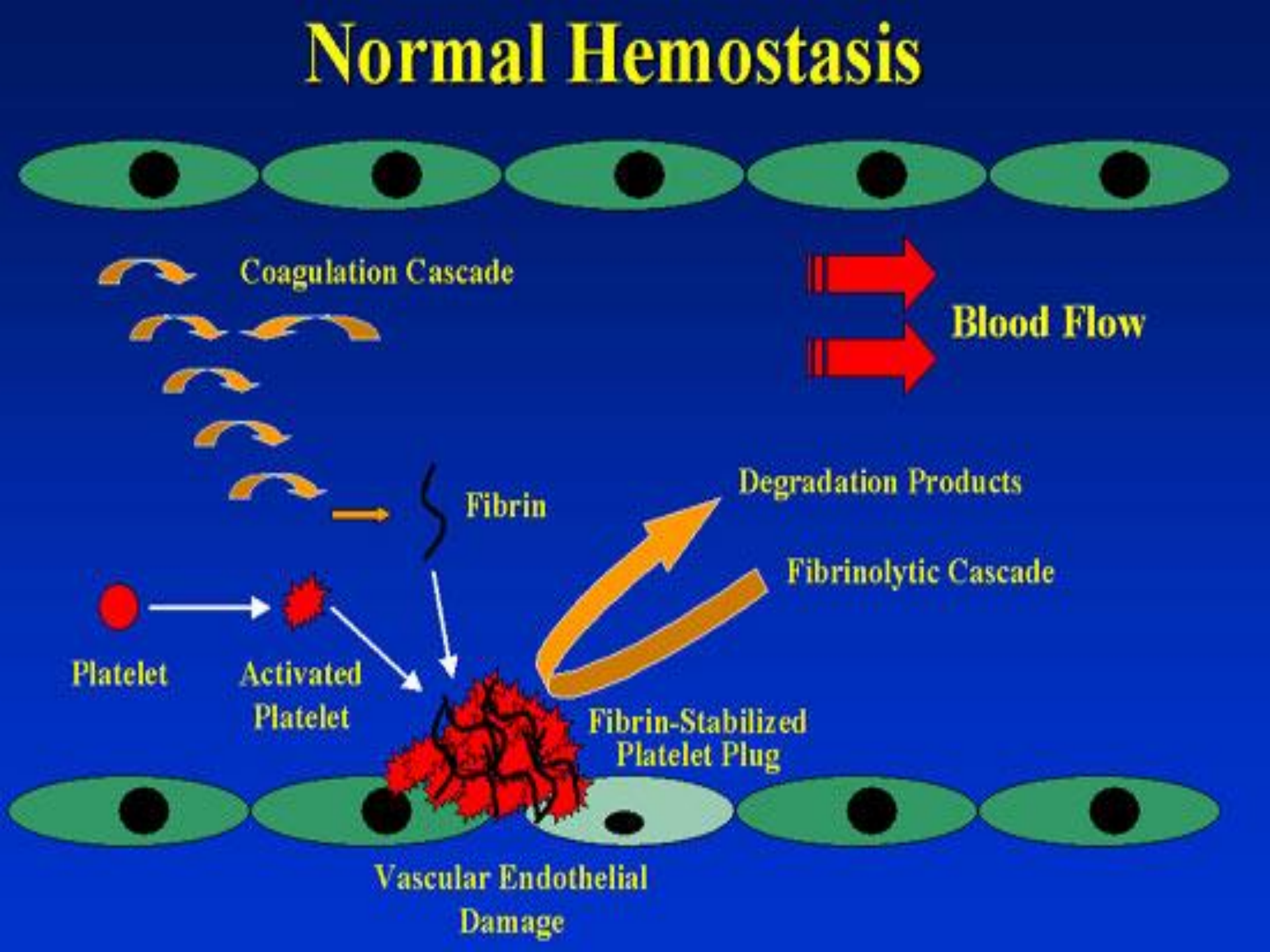
physiological hemostasis

The major components of the hemostatic system are :

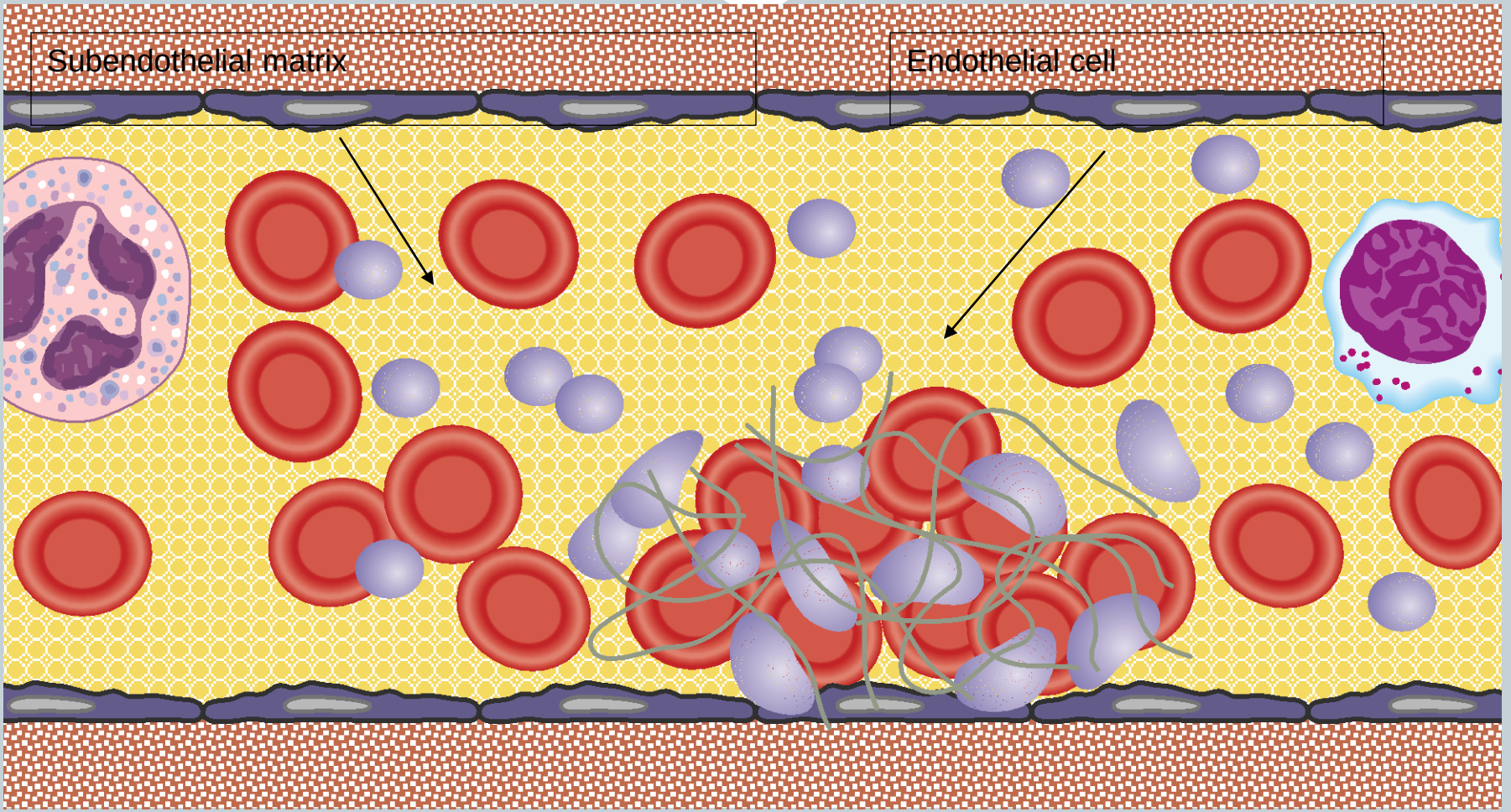
1. The vessel wall.
2. Platelets (and other blood elements).
3. Plasma proteins (coagulation and fibrinolytic factors).



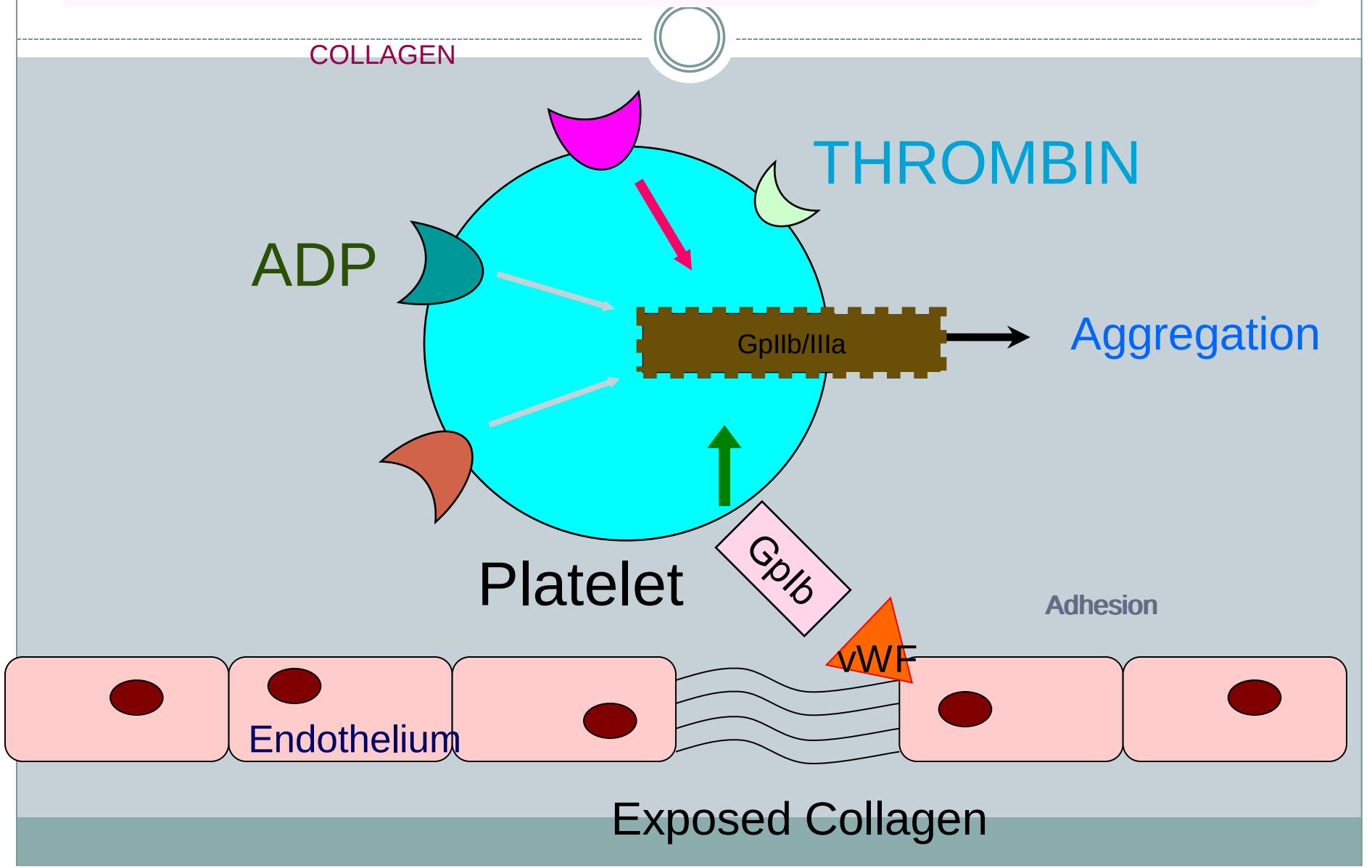
Normal Hemostasis

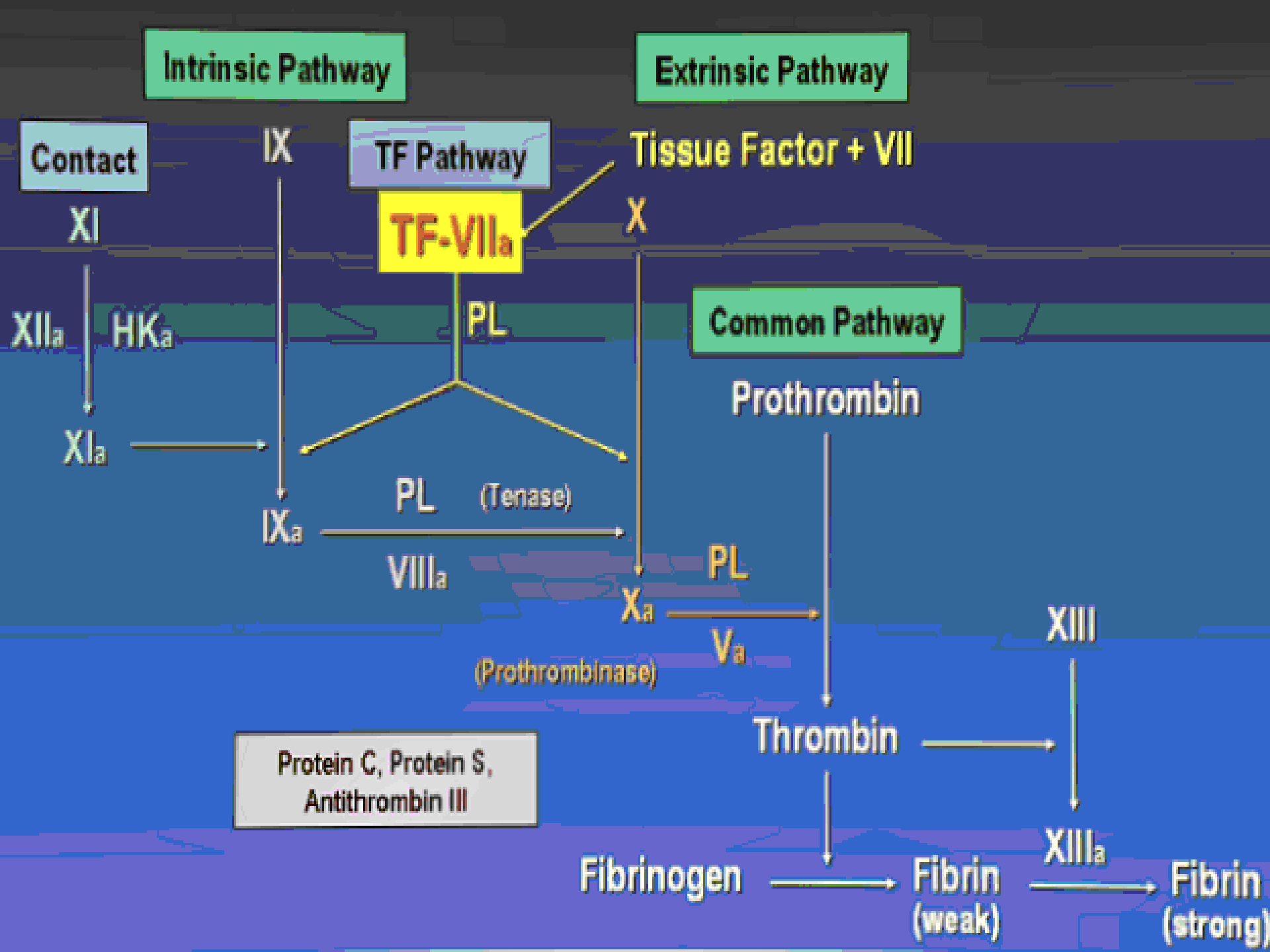


Vascular Phase



Platelet Activation Pathways




Intrinsic Pathway
Extrinsic Pathway
Contact
XI
XIIa
HKa
XIa
IX
IXa
TF Pathway
TF-VIIa
Tissue Factor + VII
X
PL
PL (Tenase)
VIIIa
Xa
PL
Va
(Prothrombinase)
Common Pathway
Prothrombin
Thrombin
XIII
XIIIa
Fibrinogen
Fibrin (weak)
Fibrin (strong)
Protein C, Protein S, Antithrombin III

Coagulation Factors

I. Fibrinogen.
II. Prothrombin.
III. Thromboplastin.
IV. Calcium.
V. Proaccelerin (Labile factor).
VII. Proconvertin (Stable factor).
VIII. Antihemophilic globulin A.
IX. Christmas factor.
X. Stuart- Prower factor.

XI. Plasma thromboplastin antecedent.

XII. Hageman factor.

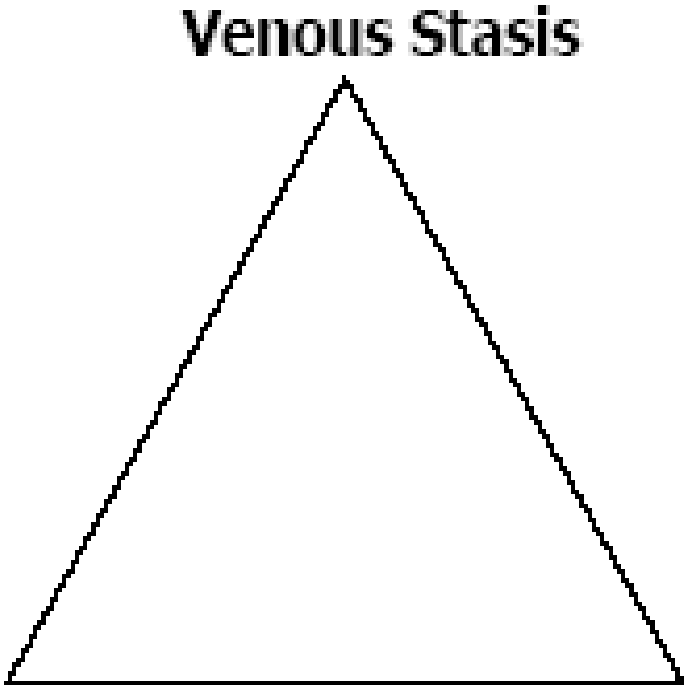
XIII. Fibrin Stabilizing factor.

Risk factors for Thrombosis

- In 1856, Rudolf Virchow postulated a triad of factors that leads to intravascular coagulation :

1. Local trauma to the vessel wall.
2. Hypercoagulability (Thrombophilia).
3. Stasis.

Virchow's Triad



Zed PJ, Advances in the Acute Management of Pulmonary Embolism, VGH EM Pharmacology Rounds, Sept 17, 2003

A) Stasis:

- Immobility.
- Paralysis (e.g. CVA).
- Obesity.
- Postoperative & casting.
- Heart & Respiratory Failure.

B) Endothelial injury :

Trauma & major syrgery.

Central venous catheters.

C) Hypercoagulable states (Thrombophilias) :

- Definition:

- Conditions that predispose to an increased risk for thrombosis either venous (most common), arterial or both.
- These conditions are being identified more frequently and may be classified as inherited or acquired.

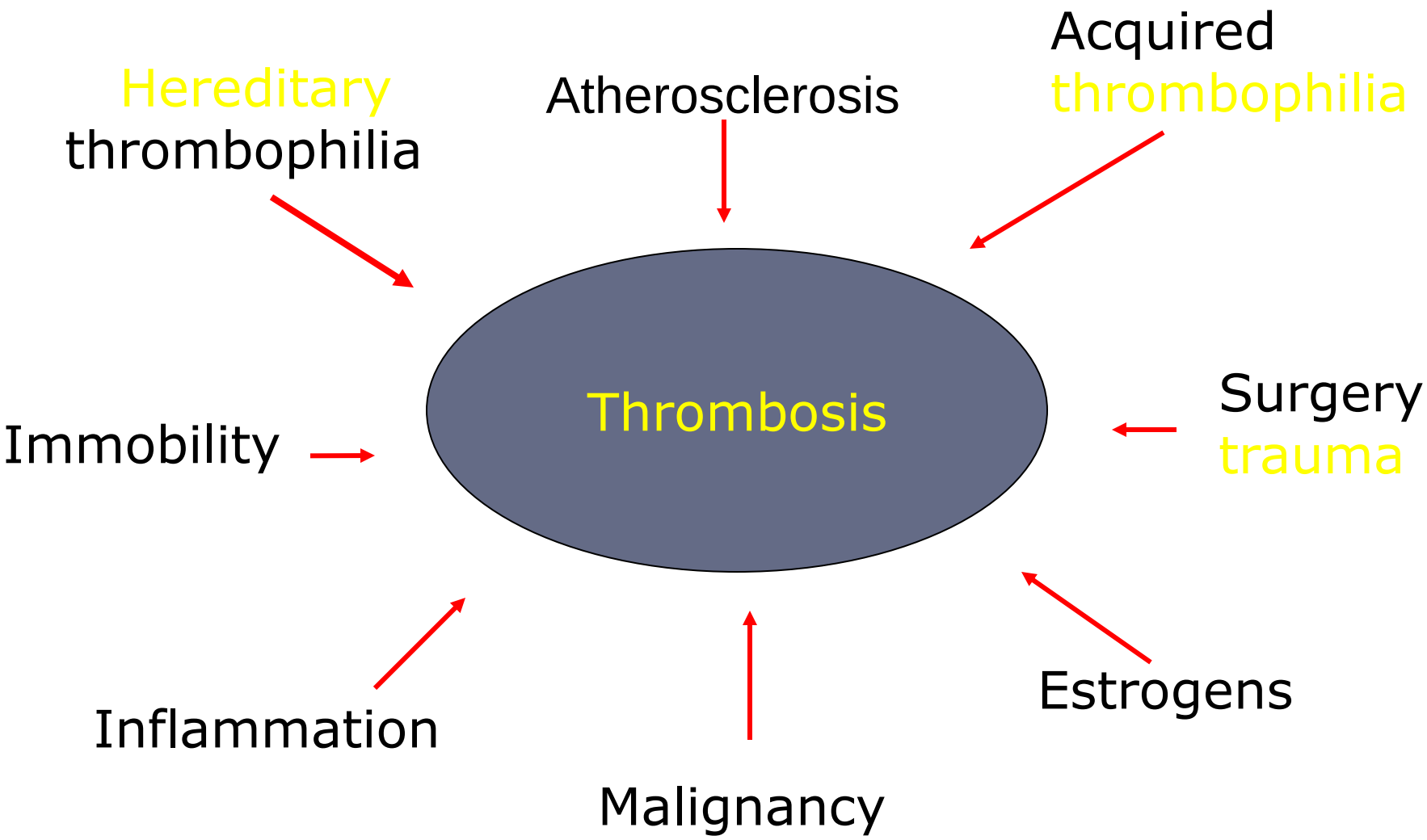
- Inherited

Venous	Arterial and venous
Factor V Leiden mutation	Homocystinuria
Prothrombin G20210A	Hyperhomocystinemia
Protein C & Protein S deficiency	Dysfibrinogenemia
Antithrombin deficiency	
Elevated Factor VIII activity	

• Acquired

Venous	Arterial and venous
Age	Malignancy
Previous thrombosis	Antiphospholipid antibodies syndrome
Immobilization	Hormonal therapy (CCP)
Major surgery	Polycythemia vera
Pregnancy & Puerperium	Essential thrombocythemia
Hospitalization	Hyperhomocystinemia
Activated Protein C	Paroxysmal nocturnal hemoglobinuria.

Risk Factors for Thrombosis



Risk Factors for Venous Thrombosis

- Acquired
- Inherited
- Mixed/unknown

Risk Factors—Acquired

- Advancing age
- Prior Thrombosis
- Immobilization
- Major surgery
- Malignancy
- Estrogens
- Antiphospholipid antibody syndrome
- Myeloproliferative Disorders
- Heparin-induced thrombocytopenia (HIT)
- Prolonged air travel

Risk Factors—Inherited

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden mutation (Factor V-Arg506Gln)
- Prothrombin gene mutation (G→A transition at position 20210)
- Dysfibrinogenemias (rare)

Risk Factors—Mixed/Unknown

- Hyperhomocysteinemia
- High levels of factor VIII
- Acquired Protein C resistance in the absence of Factor V Leiden
- High levels of Factor IX, XI

Prevalence of Defects In Patients with Venous Thrombosis

Thrombophilic Defect	Rel. Risk
Antithrombin deficiency	8 – 10
Protein C deficiency	7 – 10
Protein S deficiency	8 – 10
Factor V Leiden/APC resisance	3 – 7
Prothrombin 20210 A muation	3
Elevated Factor VIII	2 – 11
Lupus Anticoagulant	11
Anticardiolipin antibodies	1.6-3.2
Mild hyperhomocysteinemia	2.5

Risk vs. Incidence of First Episode of Venous Thrombosis

	Risk	Incidence/year (%)
Normal	1	.008
Oral Cont. Pills	4x	.03
Factor V Leiden (heterozygote)	7x	.06
OCP + Factor V L.	35x	.3
Factor V Leiden homozygotes	80x	.5-1

Risk of Recurrent Venous Thromboembolism (VTE) in Thrombophilia Compared to VTE Without a Thrombophilic Defect

Thrombophilic Defect	Rel. Risk
Antithrombin, protein C, or protein S deficiency	2.5
Factor V Leiden mutation	1.4
Prothrombin 20210A mutation	1.4
Elevated Factor VIII:c	6 – 11
Mild hyperhomocysteinemia	2.6 – 3.1
Antiphospholipid antibodies	2 – 9

Antithrombin, Antithrombin Deficiency

- Also known as Antithrombin III
- Inhibits coagulation by irreversibly binding the thrombogenic proteins thrombin (IIa), IXa, Xa, XIa and XIIa
- Antithrombin's binding reaction is amplified 1000-fold by heparin, which binds to antithrombin to cause a conformational change which more avidly binds thrombin and the other serine proteases

Protein C and Protein C Deficiency

- Protein C is a vitamin K dependent glycoprotein produced in the liver
- In the activation of protein C, thrombin binds to thrombomodulin, a structural protein on the endothelial cell surface
- This complex then converts protein C to activated protein C (APC), which degrades factors Va and VIIIa, limiting thrombin production
- For protein C to bind, cleave and degrade factors Va and VIIIa, protein S must be available
- Protein C deficiency, whether inherited or acquired, may cause thrombosis when levels drop to 50% or below
- Protein C deficiency also occurs with surgery, trauma, pregnancy, OCP, liver or renal failure, DIC,or warfarin

Protein S, C4b Binding Protein, and Protein S Deficiency

- Protein S is an essential cofactor in the protein C pathway
- Protein S exists in a free and bound state
- 60-70% of protein S circulates bound to C4b binding proten
- The remaining protein S, called free PS, is the functionally active form of protein S
- Inherited PS deficiency is an autosomal dominant disorder, causing thrombosis when levels drop to 50% or lower

Causes of Acquired Protein S Deficiency

- May be due to elevated C4bBP, decreased PS synthesis, or increased PS consumption
- an acute phase reactant and may be elevated in inflammation, pregnancy, SLE, causing a drop in free PS
- Functional PS activity may be decreased in vitamin K deficiency, warfarin, liver disease
- Increased PS consumption occurs in acute thrombosis, DIC, MPD, sickle cell disease

Activated Protein C (APC) Resistance Due to Factor V Leiden

- Activated protein C (APC) is the functional form of the naturally occurring, vitamin K dependent anticoagulant, protein C
- APC is an anticoagulant which inactivates factors Va and VIIIa in the presence of its cofactor, protein S
- Alterations of the factor V molecule at APC binding sites (such as amino acid 506 in Factor V Leiden) impair, or resist APC' s ability to degrade or inactivate factor Va

Prothrombin G20210A Mutation

- A G-to-A substitution in nucleotide position 20210 is responsible for a factor II polymorphism
- The presence of one allele (heterozygosity) is associated with a 3-6 fold increased for all ages and both genders
- The mutation causes a 30% increase in prothrombin levels.

Antiphospholipid Syndrome

Antiphospholipid Syndrome—Diagnosis

- Clinical Criteria

  -Arterial or venous thrombosis

  -Pregnancy morbidity

- Laboratory Criteria

  -IgG or IgM anticardiolipin antibody-medium or high titer

  -Lupus Anticoagulant

Antiphospholipid Syndrome—Clinical

- Thrombosis—arterial or venous
- Pregnancy loss
- Thrombocytopenia
- CNS syndromes—stroke, chorea
- Cardiac valve disease
- Livedo Reticularis

Antiphospholipid Syndrome—
The Lupus Anticoagulant (LAC)

- DRVVT- venom activates F. X directly;
  prolonged by LAC' s
- APTT- Usually prolonged, does not correct in 1:1 mix
- Prothrombin Time- seldom very prolonged

Antiphospholipid Syndrome—Anticardiolipin Antibodies

- ACAs are antibodies directed at a protein-phosholipid complex
- Detected in an ELISA assay using plates coated with cardiolipin and B2-glycoprotein

Antiphospholipid Syndrome—Treatment

- Patients with thrombosis- anticoagulation, INR 3
- Anticoagulation is long-term—risk of thrombosis is 50% at 2 years after discontinuation
- Women with recurrent fetal loss and APS require LMW heparin and low-dose heparin during their pregnancies

VTE

- Incidence of VTE 2-3 per 1000
- Incidence is higher in men than in women (above the age of 45).
- Overall adjusted incidence in men is 130 : 100,000 vs 110: 100,000 in women(1.2:1)

VTE

- DVT and PE are a single clinical entity
- Risk of early death in DVT + PE is 18 X higher than in DVT alone
- ¼ of PE cases present with sudden death
- Other predictors of poor survival in DVT are older age, male gender, confinement to hospital, CHF, chronic lung disease, neurological disease and active malignancy.

Complications of DVT

Risk factors for PTS

- Inadequate initial anticoagulation
- Recurrent DVT
- Higher BMI
- Distal vein thrombosis
- Recently, persistently elevated D- dimers
- Not impact for long – term anticoagulation.

Management of VTE

Aim of Management:

- Initially : to prevent propagation of thrombus
- Chronic anticoagulation to allow fibrinolysis and recanalization.

Impact of PTS

- In the US $ 200,000,000 annually to treat PTS and 2 million work days lost
- In Sweden its 75% of cost of DVT ttt
- In developing world major morbidity
- Poorer QOL

Hypercoagulability Work Up

- No consensus on who to test
- Increased likelihood if:
  - Age <50y/o without immediate identifiable risk factors (idiopathic or provoked)
  - Family history
  - Recurrent clots
  - If clot is in an unusual site (portal, hepatic, mesenteric, cerebral)
  - Unprovoked upper extremity clot (no catheter, no surgeries)
  - Patient's with warfarin induced skin necrosis (they may have protein C deficiency

Anticoagulation

- Start during resuscitation phase itself
- If suspicion high, start emperic anticoagulation
- Evaluate patient for absolute contraindication (i.e.: active bleeding)

Anticoagulation (cont'd)

- **HEPARIN**: OR LMWH
  - Lovenox: if hemodynamically stable, no renal function
    - 1mg/kg BID OR 1.5mg/kg QDay
  - Heparin gtt: if hypotension, renal failure
    - 80units/kg bolus then 18units/kg infusion
    - Goal PTT1.5 to 2.5 times the upper limit of normal
- **COUMADIN** , new oral anticoagulant

Duration of Anticoagulation for DVT or PE*

Event	Duration	Strength of Recommendation
First Time event of Reversible cause (surgery/trauma)	At least 3 mos	A
First episode of idiopathic VTE	At least 6 mos	A
Recurrent idiopathic VTE or continuing risk factor (e.g., thrombophilia, cancer)	At least 12 mos	B
Symptomatic isolated calf-vein thrombosis	6 to 12 weeks	A

*From American College of Chest Physicians

IVC Filter

- **Indication**:
  - Absolute contraindication to anticoagulation (i.e. active bleeding)
  - Recurrent PE during adequate anticoagulation
  - Complication of anticoagulation (severe bleeding)
- Also:
  - Pts with poor cardiopulmonary reserve
  - Recurrent P.E. will be fatal
  - Patient's who have had embolectomy
  - Prophylaxis against P.E. in select patients (malignancy)

Embolectomy

- Surgical or catheter
- Indication:
  - Those who present severe enough to warrant thrombolysis
  - In those where thrombolysis is contraindicated or fails

QUESTIONS?

Case scenario 1

John

John: 1

Presentation

John is a 75-year old man with a recent (4 weeks ago) admission to hospital for hip replacement. The procedure was performed under general anaesthetic. During admission, John received the following VTE prophylaxis (to be continued until John no longer had significantly reduced mobility):

- antiembolism stockings
- pharmacological VTE prophylaxis.

John reports that his right leg has been swollen for over 2 weeks. He thought it was healing after the operation, which is why he has not told anyone sooner. He presented to his GP and the GP has referred him to your accident and emergency (A&E) department.

John: 2

1.1 Question

You believe John has symptoms of DVT. What would you do next?

John: 3

1.1 Answer

Carry out an assessment of John's general medical history and a physical examination to exclude other causes.

1.2 Question

John reports that he had a DVT 20 years ago and that he has osteoarthritis.

On admission, he is apyrexial with a temperature of 37° C and his right calf and ankle are red, blotchy and swollen with pitting oedema. His heart rate is 80 beats per minute, respiratory rate 15 breaths per minute, blood pressure is 136/80 mmHg and SpO_2 96% in air.

You suspect DVT: what would you do next?

John: 4

1.2 Answer

Even though John received VTE prophylaxis, the diagnosis of DVT should still be highly considered. Use the two-level DVT Wells score to estimate the clinical probability of DVT.

1.3 Question

John's two-level DVT Wells score is 3 (DVT likely):

- Major surgery within 12 weeks requiring general or regional anaesthesia = 1.
- Pitting oedema confined to symptomatic leg = 1.
- Previously documented DVT = 1.

You do not consider that an alternative diagnosis is at least as likely as DVT.

You suspect DVT: what would you do next?

John: 5

1.3 Answer

Organise a proximal leg vein ultrasound scan. Unfortunately, in your organisation, this scan is not available within 4 hours of being requested. Therefore, you offer a D-dimer test, an interim 24-hour dose of a parenteral anticoagulant and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.

The D-dimer test is positive and the proximal leg vein ultrasound scan is also positive.

1.4 Question

What would you do next?

John: 6

1.4 Answer

Diagnose DVT and start treatment with low molecular weight heparin (LMWH) or anticoagulant as soon as possible and Also start

Thanks