In case you are comparing to your own slides:
- I switched the placement of 3 Slides
- I consolidated notes on big picture ideas like atherosclerosis and differentiating clot types on a few slides - see below for slide numbers (not necessarily at the slide that she mentioned it)

# Mechanisms of Thrombosis

APPROVED

Blood clotting where it shouldn't or when you don't want it to

Maureane Hoffman, MD, PhD

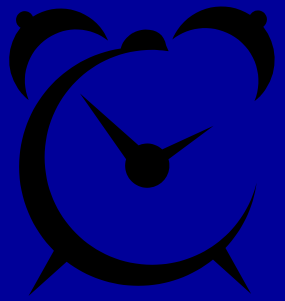
Professor of Pathology

Things You Should Know:
(1) Arterial (and sometimes venous) Thrombosis and Atherosclerosis (Plaque Rupture) - I consolidated things she said throughout the lectures on Slides 2 & 30
(2) Venous Thrombosis and Pulmonary Embolism - Slides 4, 5 & 8
(3) Thrombosis and Cancer - Slide 9
(4) Differentiating Pre-Mortem and Post-Mortem Clots: Slides 6 & 7
(5) Virchow's Triad (especially inflammation and hypercoagulability): Slides 10-21, 25

ARTERIAL THROMBOSIS

# Thrombosis

One of the leading causes of morbidity and mortality in developed countries via MI and Stroke



- Formation of a blood clot in an artery or vein of a living person
- Arterial thrombosis denies oxygen and nutrition to an area of the body
  - Thrombosis of an artery leading to the heart causes a myocardial infarction
  - Thrombosis of an artery leading to the brain causes a stroke
- Acute arterial thrombosis often results from the deposition of atherosclerotic material in the wall of an artery, which gradually narrows the channel, precipitating clot formation

Narrowing of channel leads to TURBULENCE which precipitates clot formation. Details on atheroscleroris-thrombosis relationship Slides 30-32.

# Thrombosis

- Extends into vessel without blocking it completely - mural thrombus
- Blocks it completely - occlusive thrombus
- Extends along the blood vessel - propagative thrombus

After MI, clot may form at site of damage along wall of ventricle

common in patients with DEEP-VEIN THROMBOSIS can create a cast of the venous system

VENOUS THROMBOSIS

# Thrombosis

Getting blood from legs to heart is difficult - physical (muscle) inactivity can lead to stasis in veins in legs BUT after clot is formed, activity can break the clot leading to major complications (like pulmonary embolism)

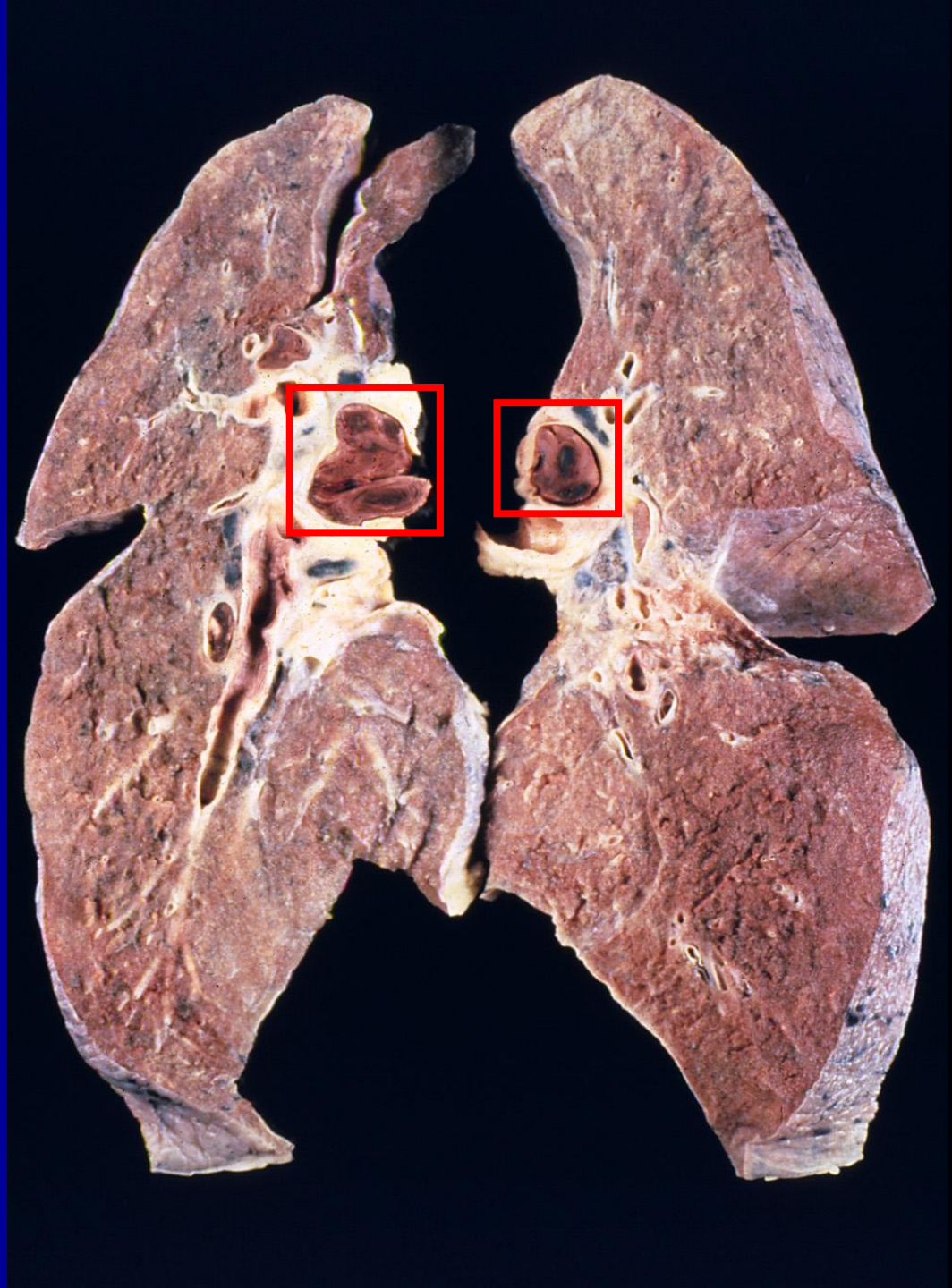
- Venous thrombosis blocks return of deoxygenated blood to the heart
- Venous thrombosis is quite common in the lower extremities, but can also occur in the upper extremeties
- Symptoms include swelling, bluish discoloration and pain.
- The most feared complication of venous thrombosis is pulmonary embolism

Symptoms depend on type / location of vein - superficial veins (probably less pain) vs. deep veins

Inflammation, trauma (SURGERY or CATHETERIZATION) in limbs increases the risk for thrombosis - a lot of patients in the hospital will have some degree of venous thrombosis.

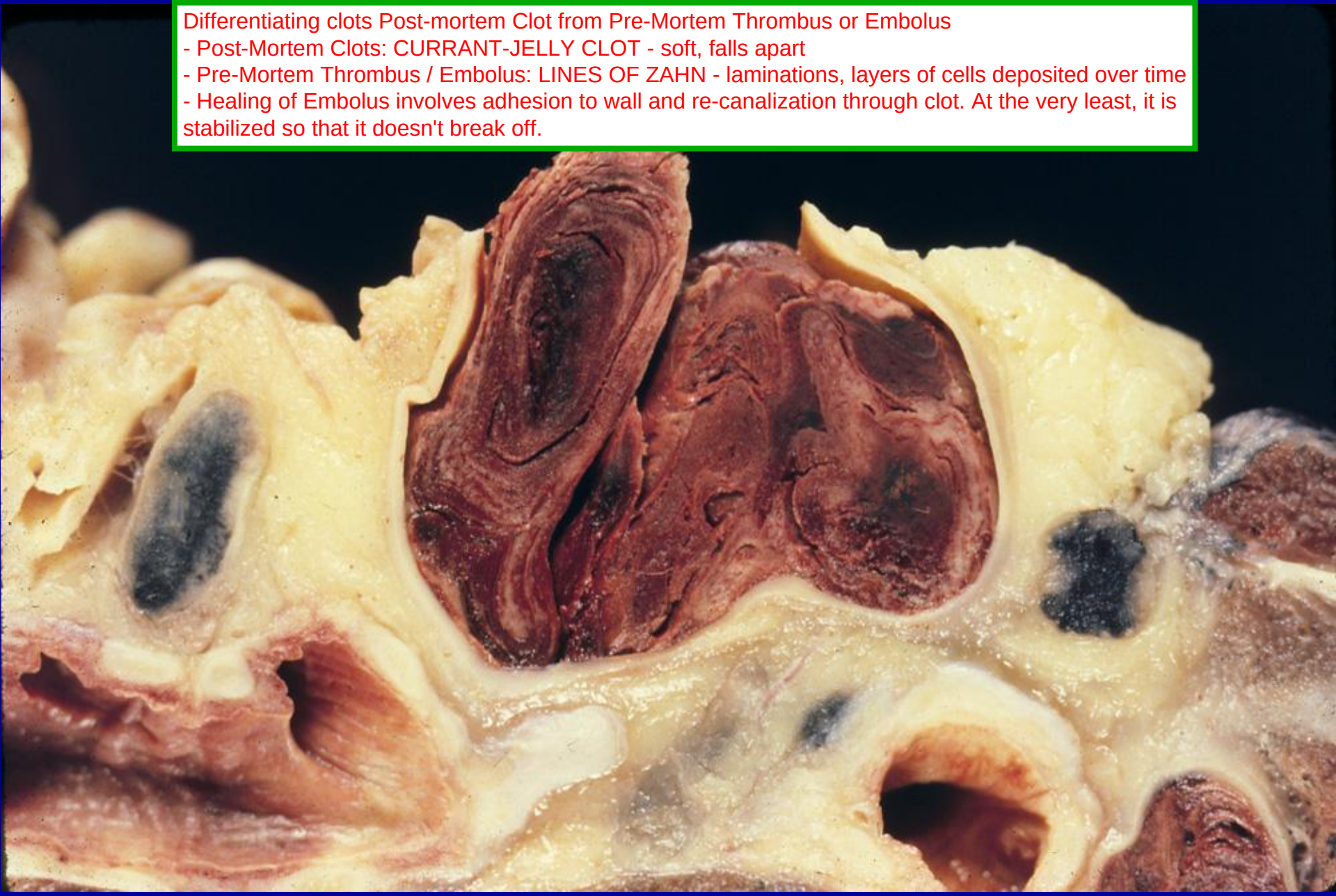
# Pulmonary Emboli

Clot travels from venous circulation to pulmonary artery and death can occur RAPIDLY



# Lines of Zahn in a pulmonary embolus

Differentiating clots Post-mortem Clot from Pre-Mortem Thrombus or Embolus
- Post-Mortem Clots: CURRANT-JELLY CLOT - soft, falls apart
- Pre-Mortem Thrombus / Embolus: LINES OF ZAHN - laminations, layers of cells deposited over time
- Healing of Embolus involves adhesion to wall and re-canalization through clot. At the very least, it is stabilized so that it doesn't break off.

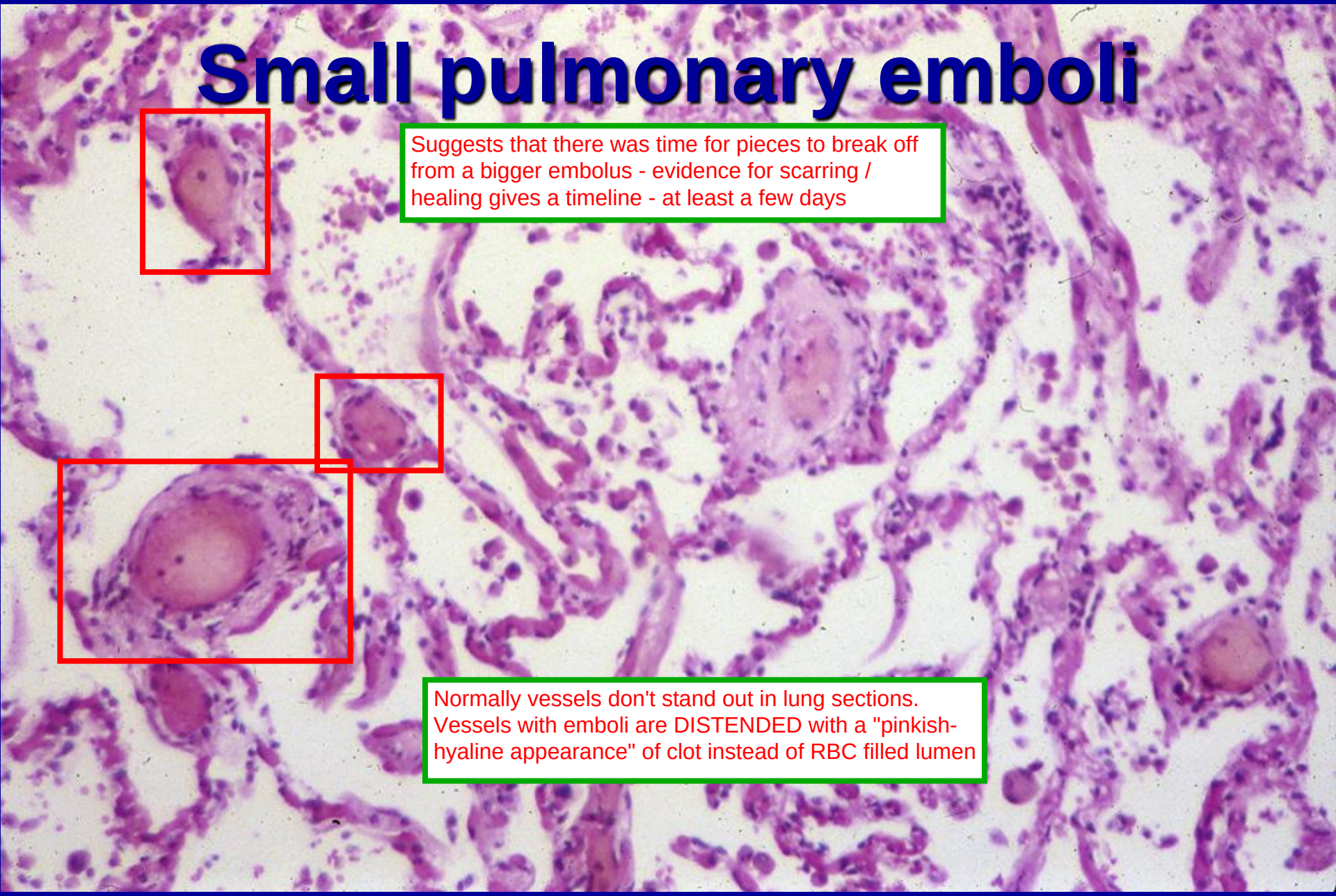


# Is it thrombus or post-mortem clot?

- Thrombus adheres to the vessel wall
- May be red, white, or mixed
- Is crumbly and layered

When Thrombus leads to quick death (i.e. via MI), it can be hard to tell pre-mortem from post-mortem clots. In these cases, pre-mortem clots may simply be mixed in with atherosclerotic plaque

# Small pulmonary emboli

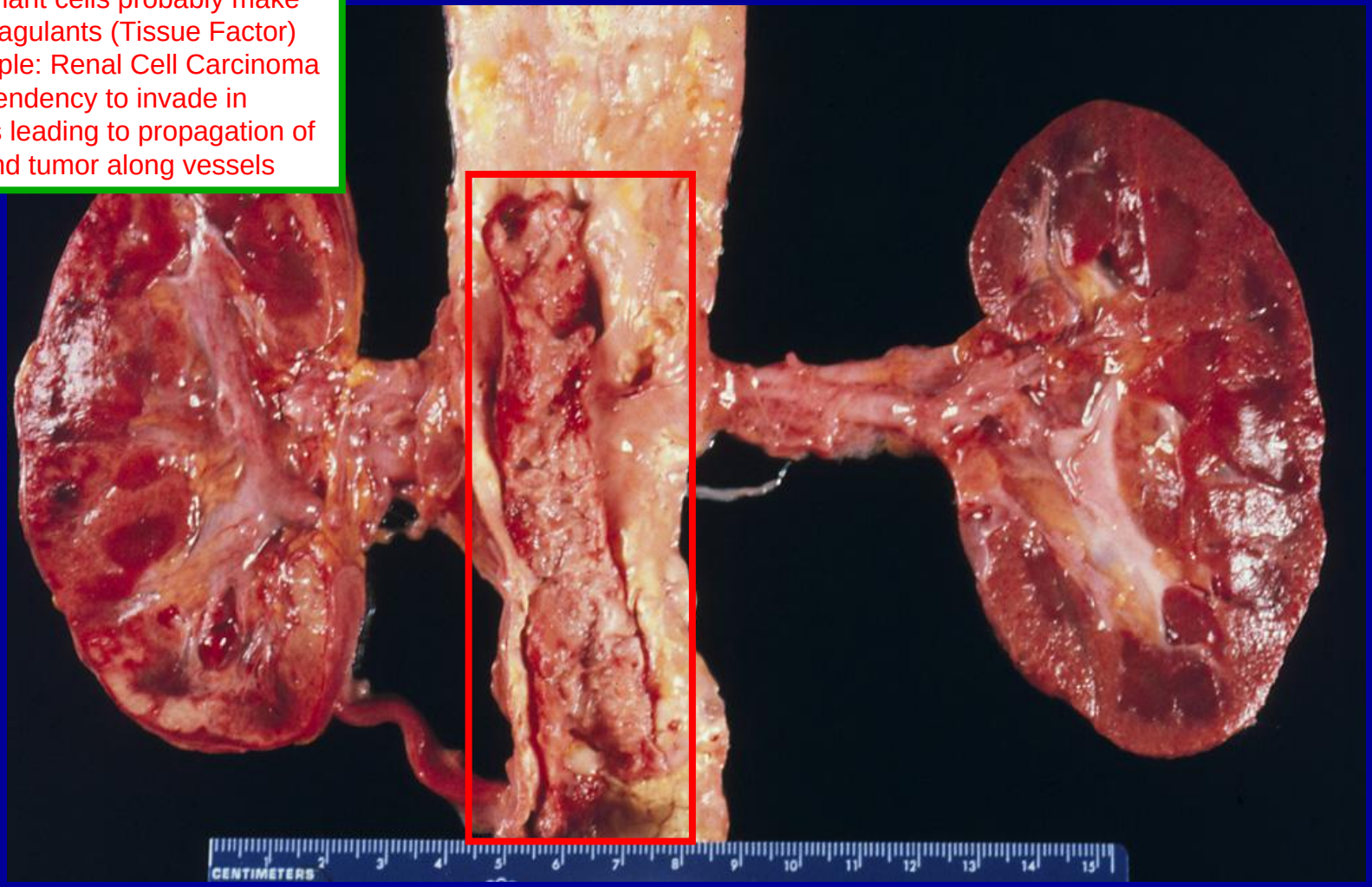


Suggests that there was time for pieces to break off from a bigger embolus - evidence for scarring / healing gives a timeline - at least a few days

Normally vessels don't stand out in lung sections. Vessels with emboli are DISTENDED with a "pinkish-hyaline appearance" of clot instead of RBC filled lumen

# Thrombosis in the Aorta

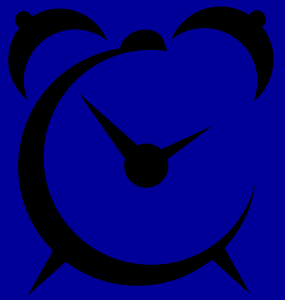
Thrombosis and Cancer:
- Malignant cells probably make Pro-Coagulants (Tissue Factor)
- Example: Renal Cell Carcinoma has a tendency to invade in vessels leading to propagation of clots and tumor along vessels



# What Causes Thrombosis?

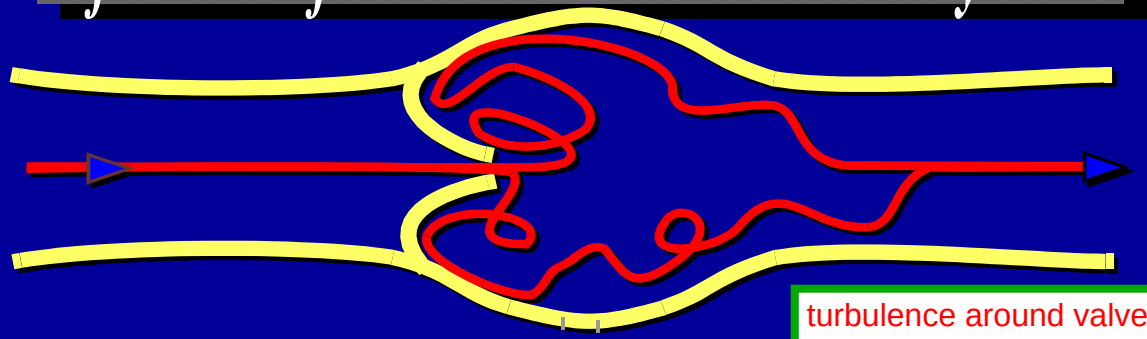
**Virchow's Triad:**

- **Stasis**
- **Vascular Injury**
- **Hypercoagulability**

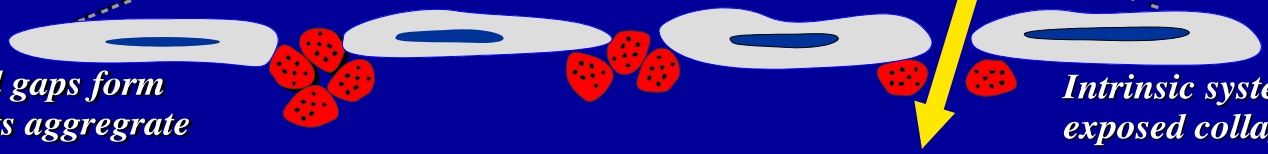


# STASIS

*Loss of laminar flow with turbulence and eddy currents*



turbulence around valves when there is low flow rate (STASIS)



*Endothelial gaps form and platelets aggregrate*

*Intrinsic system activated on exposed collagen in gaps*

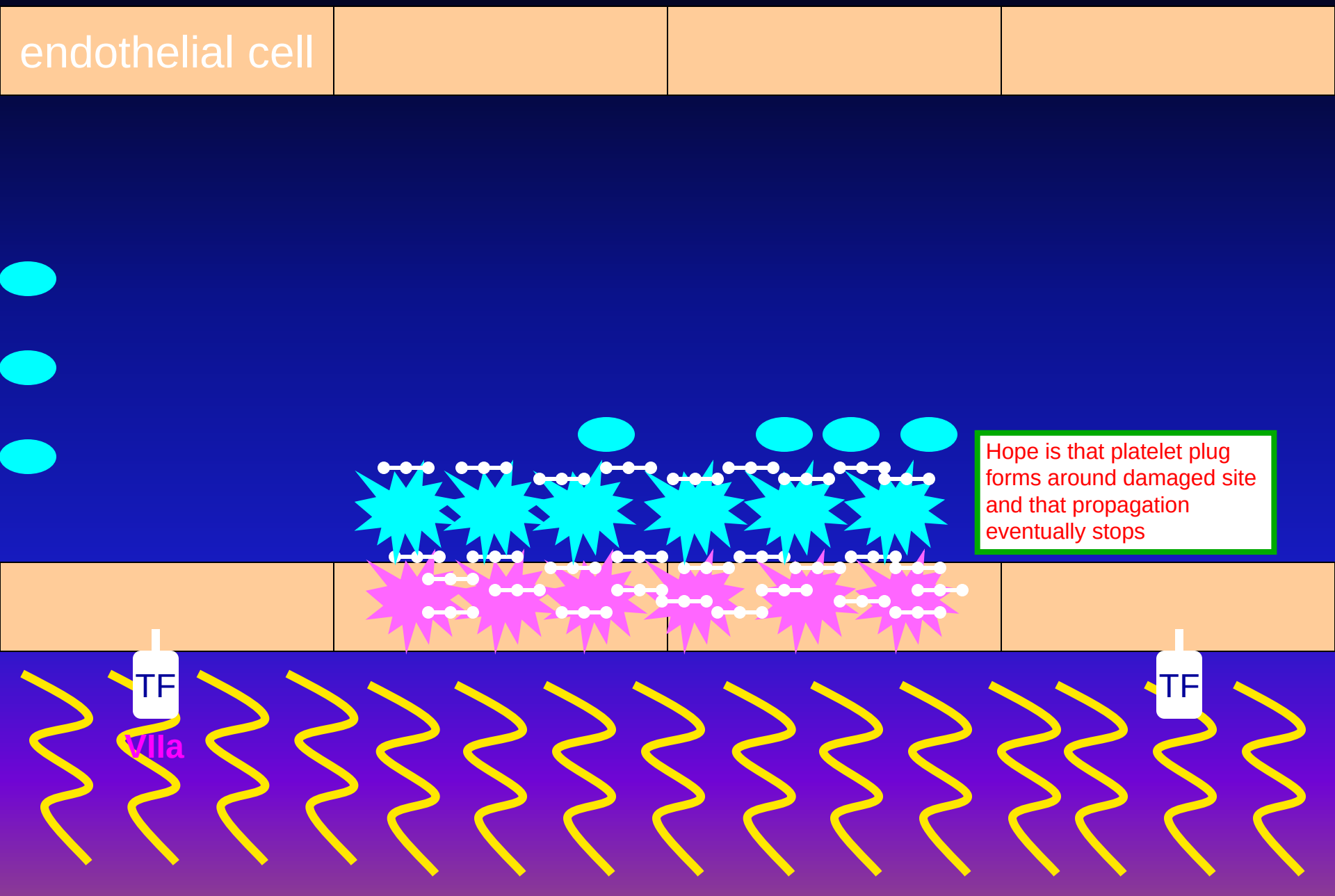
*Tissue factor released and extrinsic system activated*

*Heparinoids lost decreasing AT III reactivity*

*Prostacyclin synthesis is decreased*

# Vascular Injury

examples: catheterization, external trauma, surgery



INFLAMMATION can be key driver for this (especially at local vascular beds)

# Hypercoagulability

The coagulant/anticoagulant proteins and the cells each play a role

# Evolution of the Paradigm

sometimes - in these cases we can test blood

**Old:** Hypercoagulable State = Systemic Disorder

**New:** Vascular Bed-Specific Disorders

local factors like inflammation may determine hypercoagulability

[Rosenberg & Aird, N Engl J Med, 340:1555, 1999]

- Vascular-Bed Specific Signals
- Vascular-Bed Specific Cell Subtypes
- Vascular-Bed Specific Transcriptional Regulation

**How do we test vascular bed function?**

hard because lab test may not always pick up the local vascular-bed specific factors

**Hypercoagulability is multifactorial**

Lifestyle and environmental factors play critical roles

**Hypercoagulability is multifactorial**

This is different from hemorrhagic disorders which are often single gene defects

# Hypercoagulability

SYSTEMIC DISORDERS that are detectable by blood test

- Gene defect
  - AT deficiency
  - Protein C/S deficiency

AT - Anti-Thrombin: inhibitor of coagulant factors
-Heterozygotes: develop clotting problems as young adults
-Homozygotes: develop problems as infants
Anti-Thrombin can be replaced

Vitamin K dependent factors (anti-coagulant system)
(1) Deficiency due to Mutation
(2) Deficiency due to Activated Protein C Resistance
- mutation in Factor V

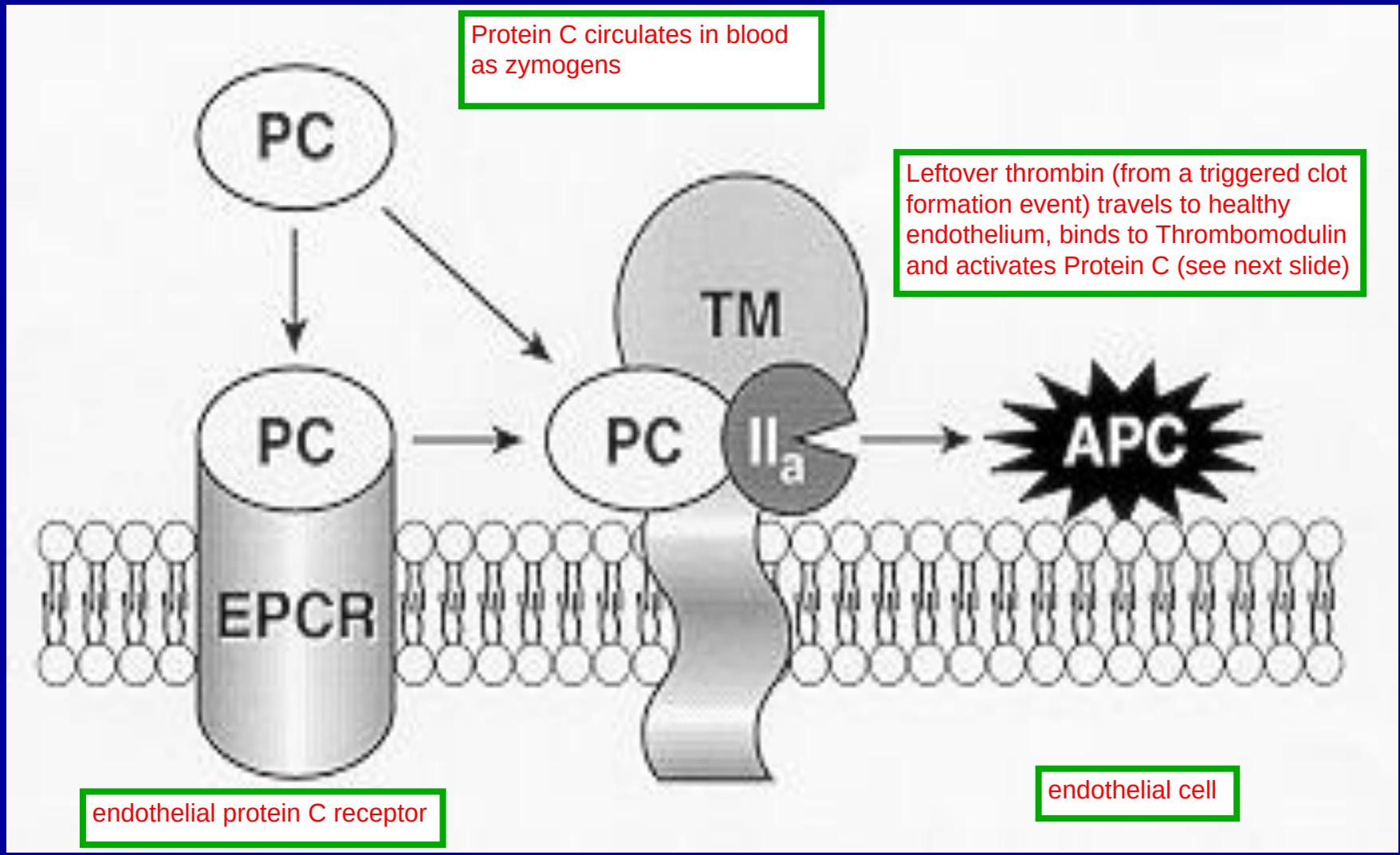
Activated Protein C Resistance

Mechanism shown on slide 20

## – APC resistance/factor V Leiden

- Gene prevalence about 7% in Caucasians
- Not Blacks or Asians
- Up to 10% in some European populations

something that is tested


Protein C circulates in blood as zymogens
PC
Leftover thrombin (from a triggered clot formation event) travels to healthy endothelium, binds to Thrombomodulin and activates Protein C (see next slide)
TM
PC
PC
IIa
APC
EPCR
endothelial protein C receptor
endothelial cell

# Thrombin on an Endothelial Surface has Anti-coagulant Activity

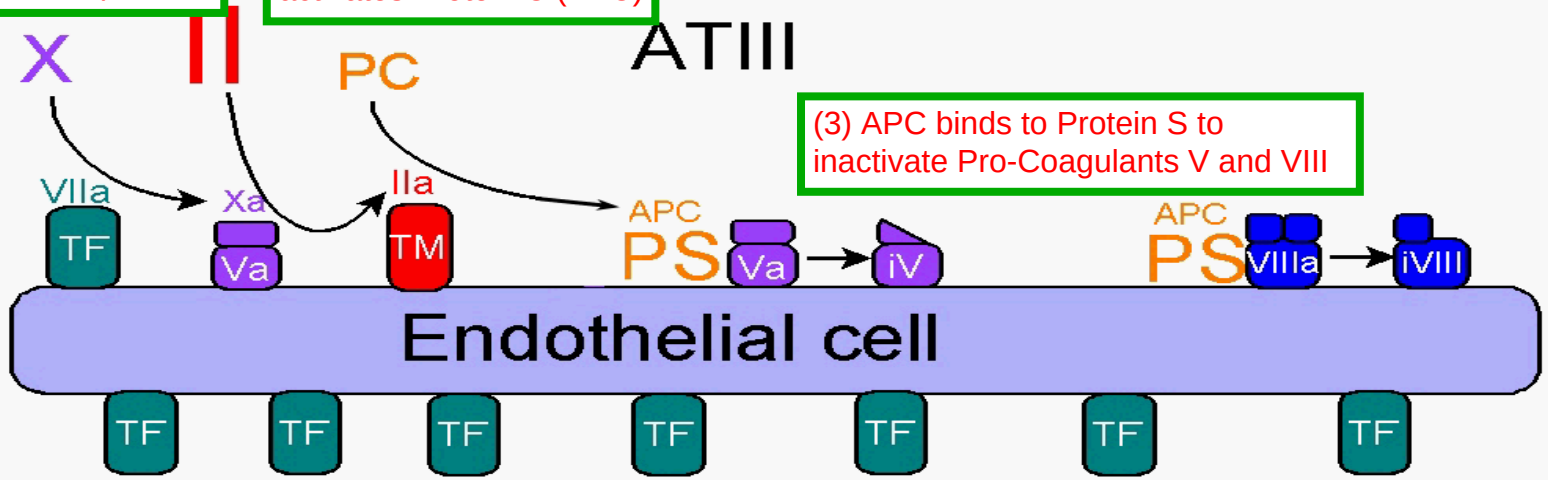
-Inflammation causes shedding of Thrombomodulin (TM) - inflammation promotes thrombosis

MUTATIONS AFFECTING THIS PATHWAY:
-Mutations in Protein C and S
-Mutations in Factor V that prevents its cleavage by APC / PS complex
-Mutation in Prothrombin

(1) Pro-Coagulant Activity generates Thrombin (COAGULANT)

(2) Thombin binds to Thrombomodulin on a healthy cell (ANTI-COAGULANT) and activates Protein C (APC)

(3) APC binds to Protein S to inactivate Pro-Coagulants V and VIII



# Hypercoagulability

in promoter region

- Prothrombin G20210A Mutation
  - Prevalence 1-2% in Caucasians
  - Results in elevated prothrombin level
  - Synergistic with FV Leiden

see next slide

# Relative Risk of Thrombosis

testing for people with family histories of thrombosis

| | |
|---|---|
| Normal | 1 |
| Oral contraceptive | 4 |
| Factor V Leiden, *heterozygous* | 5-7 |
| FV Leiden, *hetero* + OC | 30-35 |
| FV Leiden, *homozygous* | 80 |
| FV Leiden, *homo* + OC | ?>100 |
| Prothrombin 20210AT, *heterozygous* | 3 |
| Prothrombin 20210AT, *hetero* + OC | 16 |

synergistic

with age, risk of thrombosis increases dramatically

# "Anti-phospholipid" antibodies aka "Lupus Anticoagulants"

often associated with Lupus, autoimmune disease

- Mildly prolong clotting assays, especially aPTT, by interfering with coagulation complex assembly on phospholipid surface

# "Anti-phospholipid" Antibodies

something to look for in patients with thrombosis

- Are usually associated with thrombosis, not hemorrhage
- May be associated with autoimmune disease or may be primary
- Syndrome of recurrent fetal loss

recurrent, spontaneous early term abortions - thrombosis of vessels in placenta

# Inflammation can also Promote a Hypercoagulable State

Increases Pro-Coagulant Factors, Reduces Anti-Coagulant Factors

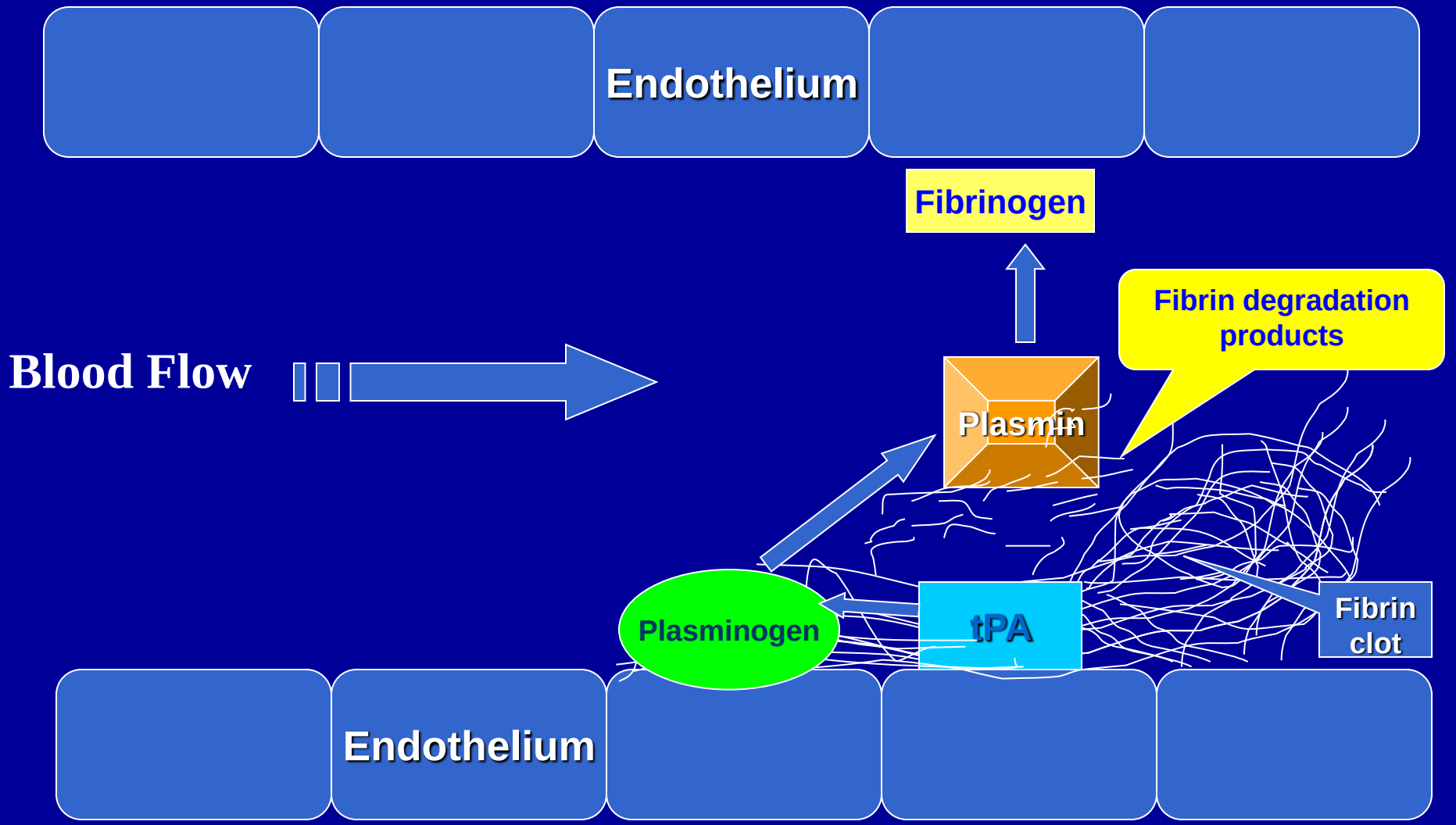
- "Activates" endothelial cells
  - Enhances TF expression
  - Reduces TM and heparan sulfate expression
  - Enhances expression of endothelial adhesion molecules

# Impaired Fibrinolysis can Lead to Thrombosis

- Small clots probably form all the time in the vasculature and are lysed by the fibrinolytic system

# tPA Release Initiates Fibrinolysis

tissue plasminogen activator



# tPA and THROMBOSIS

- Deep vein thrombosis and pulmonary emboli occur in patients with depressed endothelial tPA stores
- Many factors lead to decreased endothelial synthesis of tPA including:
  - Obesity
  - Sedentary life style
  - Smoking
  - Birth Control Pills

# PAI-1 AND THROMBOSIS

plasminogen activator inhibitor

- Vascular smooth muscle and fat cells (and maybe others, too) synthesize an inhibitor of tPA called plasminogen activator inhibitor 1 (PAI-1)
- Some patients have elevated PAI-1
  - Inflammation
  - Hyperhomocysteinemia
  - Obesity

adipose tissue makes a lot of PAI

- PAI-1 levels are associated with thromboembolic disease

# Thrombosis is Associated with ATHEROSCLEROSIS

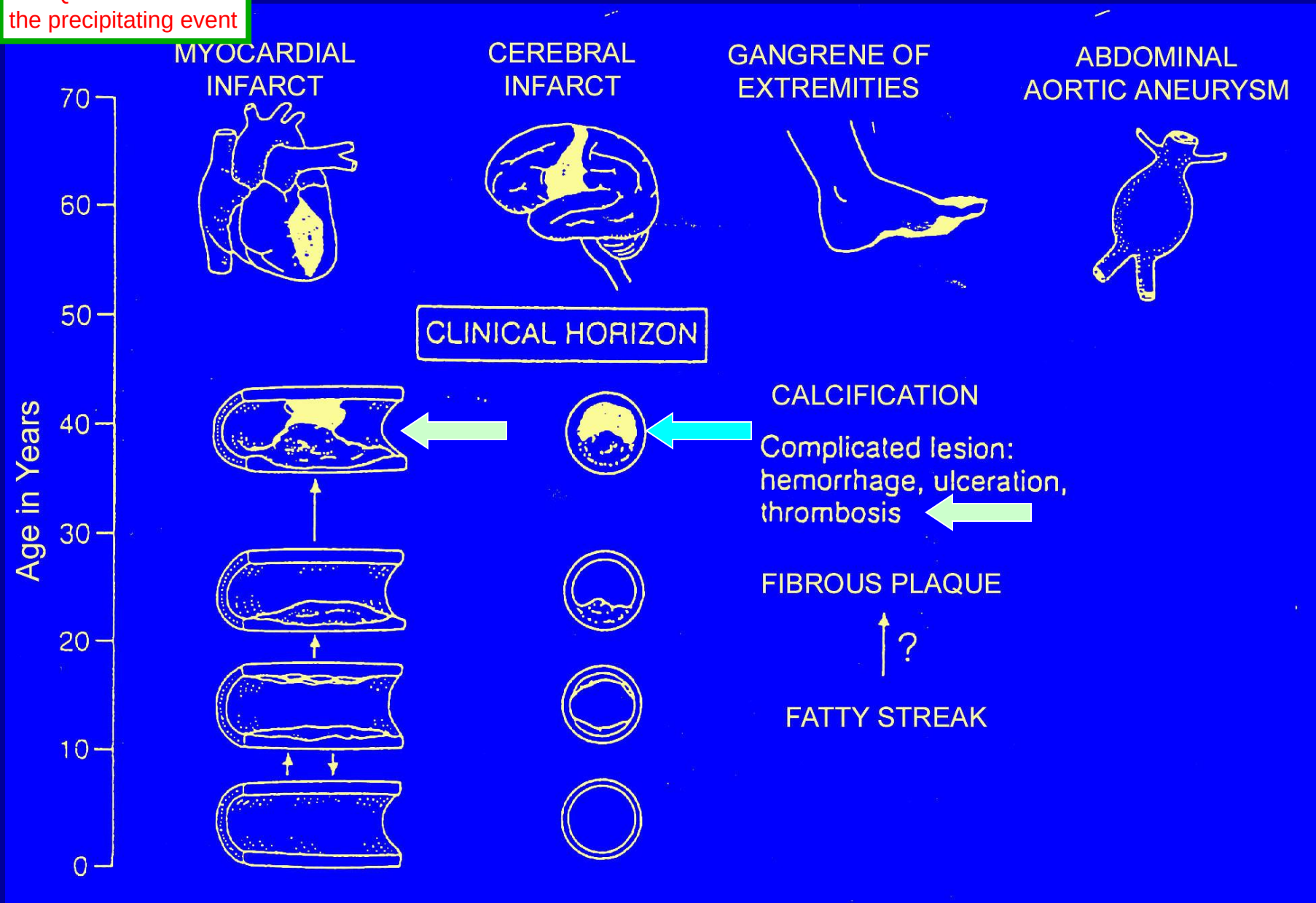
atherosclerosis leads to thrombosis, thrombosis leads to atherosclerosis

- Thrombosis can occur on atherosclerotic plaques - especially if a plaque ruptures
- Deposition of fibrin and activation of platelets intravascularly is associated with development of atherosclerotic lesions
- Sites of vascular injury – including turbulence – are sites of plaque development

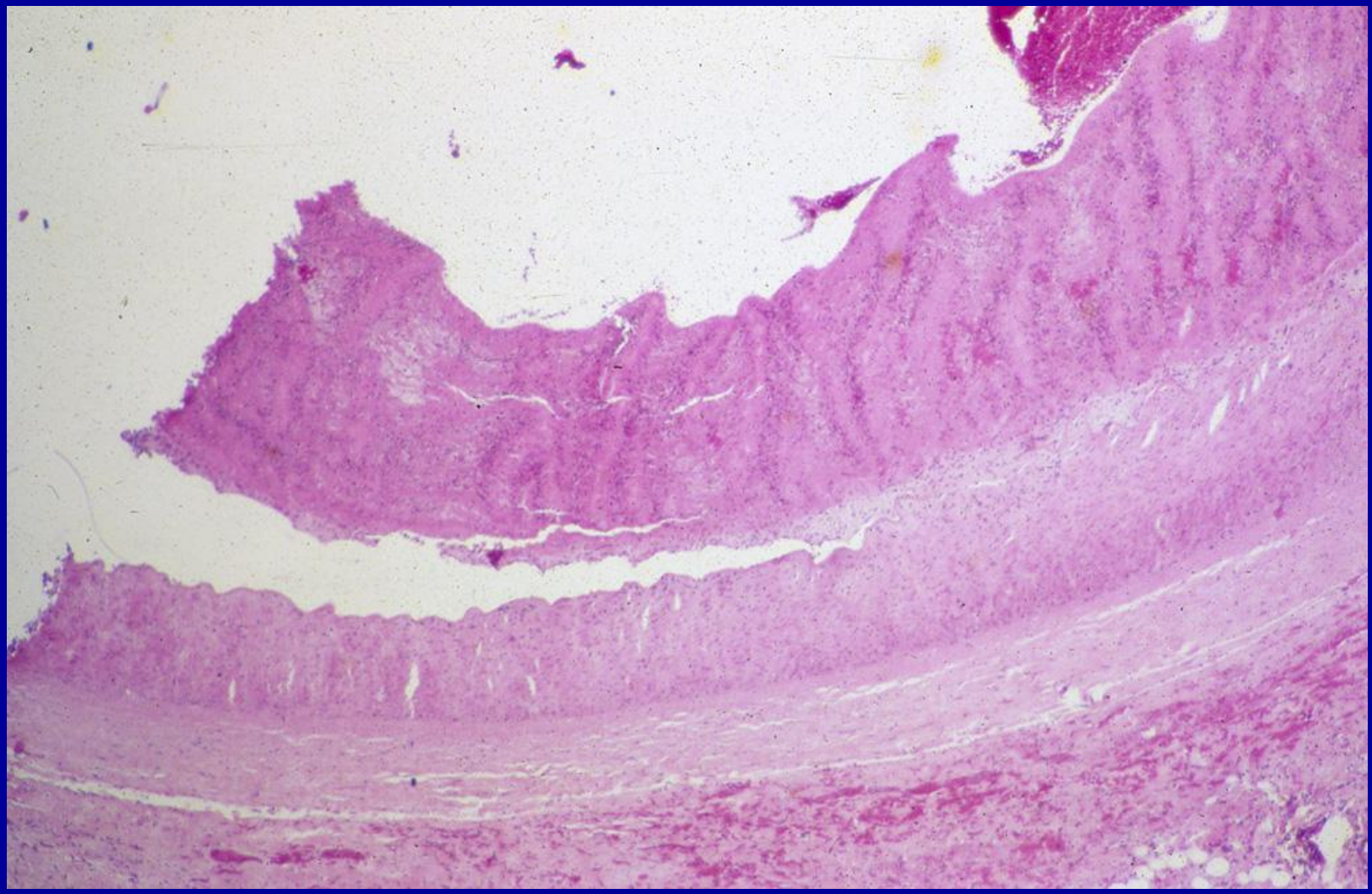
When you're on the wards, the answer is always PLAQUE RUPTURE:
- Plaques are inflexible and won't distend / contract normally in response to systolic / diastolic pressure - inevitably they will break
- Pro-coagulant (Tissue Factor) in necrotic center of plaque is exposed when plaque ruptures. Precipitates a major clot and OFTEN a HEART ATTACK

# Atherosclerosis starts young

PLAQUE RUPTURE - the precipitating event

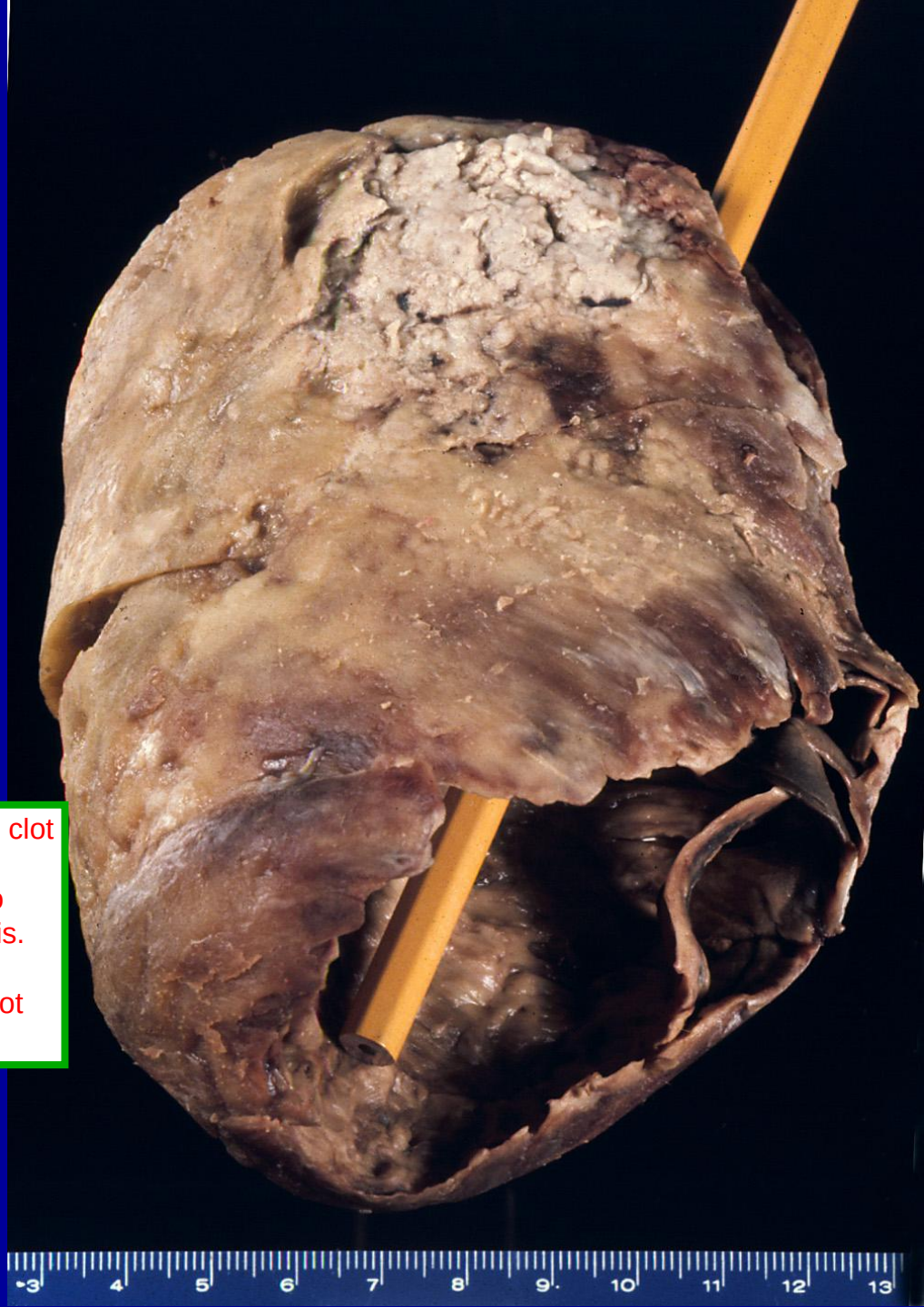


# Atherosl cerosis thickens the vessel wall and reduces the lumen size

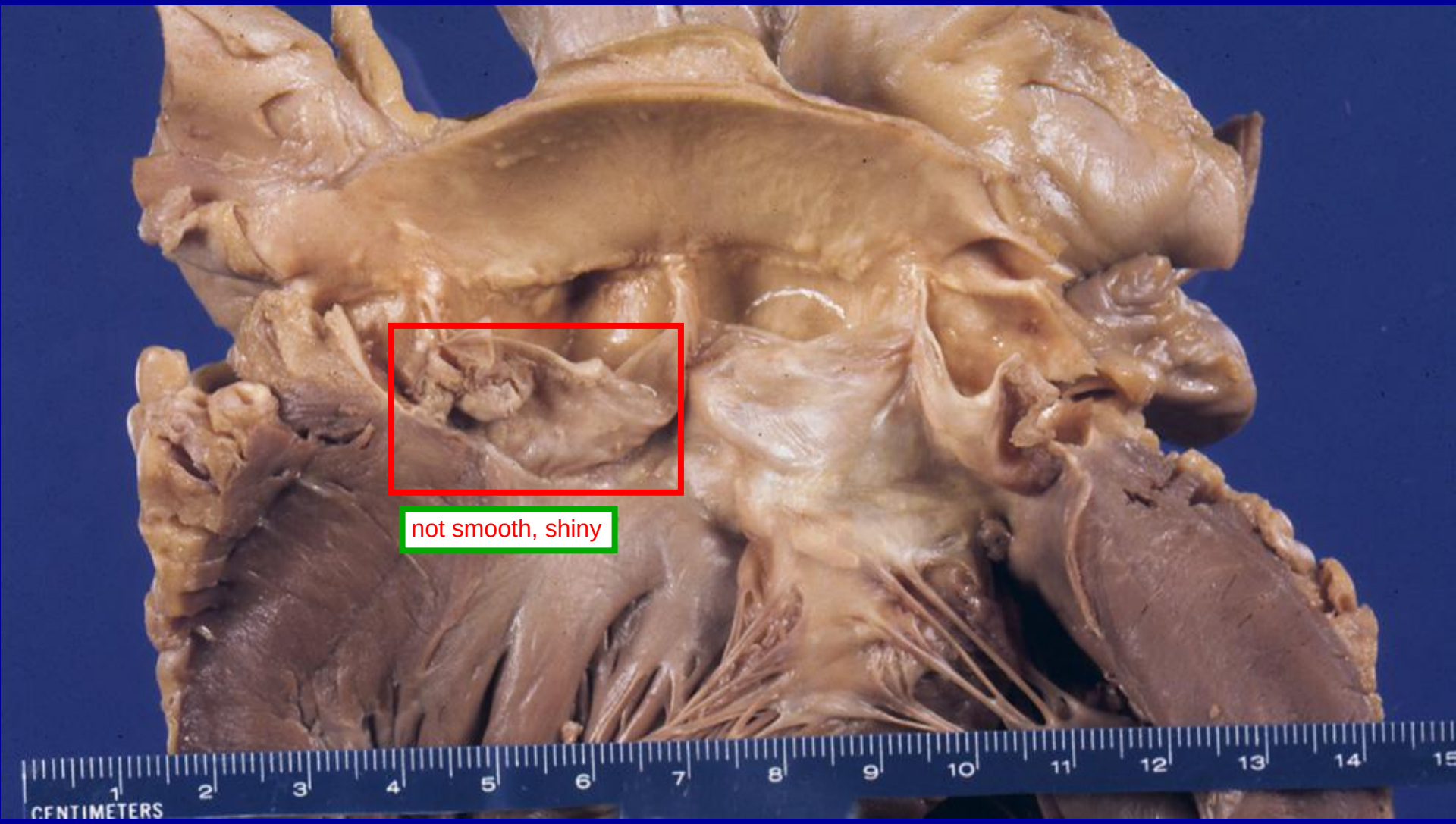


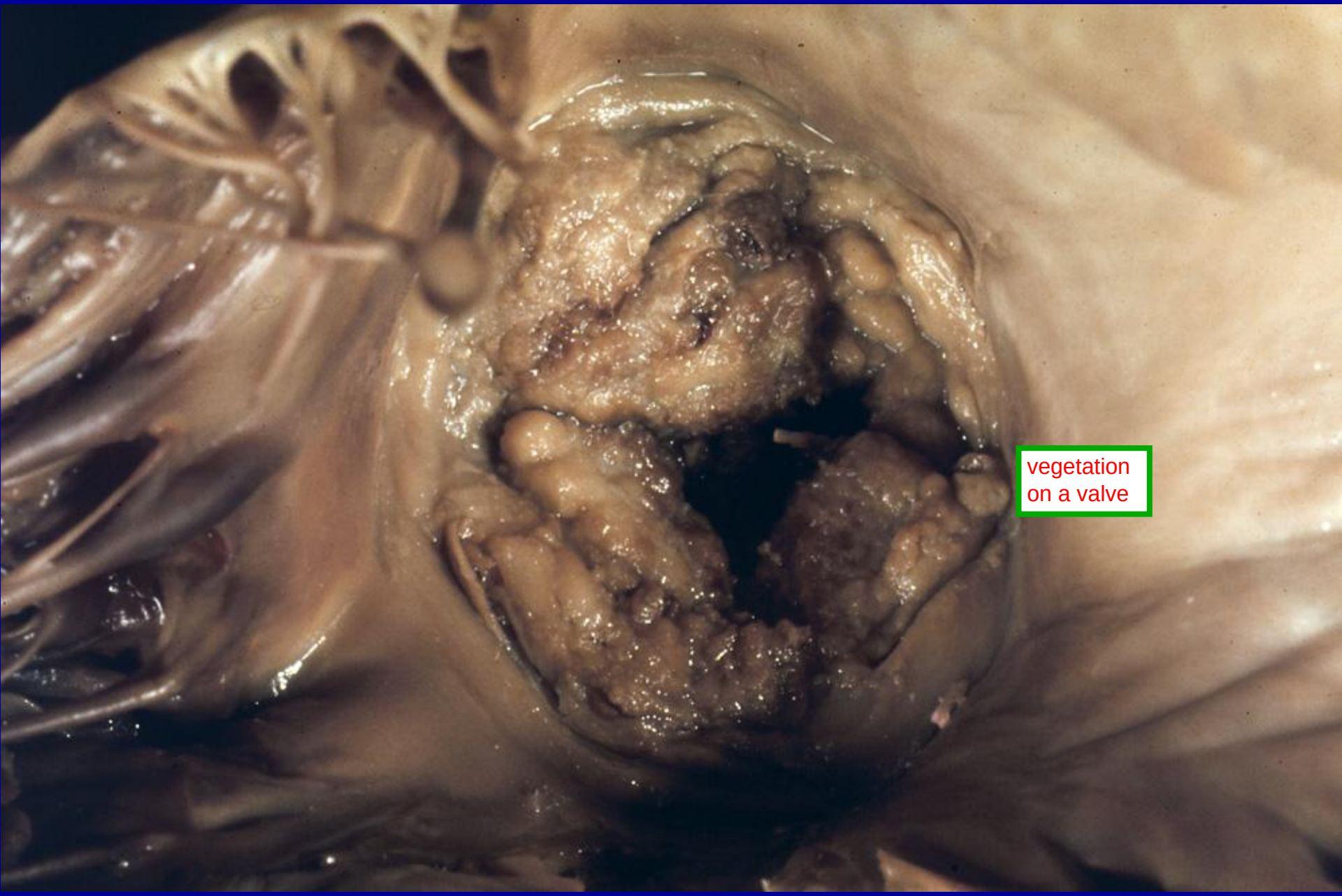
# Thrombus from an aortic aneurysm

an impressive clot - vessel walls balloon due to atherosclerosis. dead tissue precipitates clot formation



# Vegetations on Aortic Valve




vegetation
on a valve

# Mechanical Heart Valve – a good source of emboli

# What do we normally do for someone with a prosthetic heart valve?

ANTICOAGULANTS for life!

# Bottom Line

- Thromboembolism is multifactorial, and risk factors accumulate (or even multiply)
- Thromboembolism can affect any organ/tissue
- Many aspects of modern lifestyle promote thrombosis and atherosclerotic vascular disease

"Go out there and jog, and avoid a pulmonary embolism"