"Congratulations on getting to the part of your medical school education where you learn about things that actually kill people."

ARTERIOSCLEROSIS

APPROVED

arteriosclerosis- hardening of the arteries. arterio- artery sclerosis- fibrosis

ATHEROSCLEROSIS

athero- implies that there is a fatty component along with the thickening and fibrotic component

MONCKEBERG'S MEDIAL CALCIFIC SCLEROSIS

where someone may calcify the media of their arteries. usually not pathologic because it doesn't impinge on the lumen.

ARTERIOLOSCLEROSIS

in smaller vessels.

Objectives

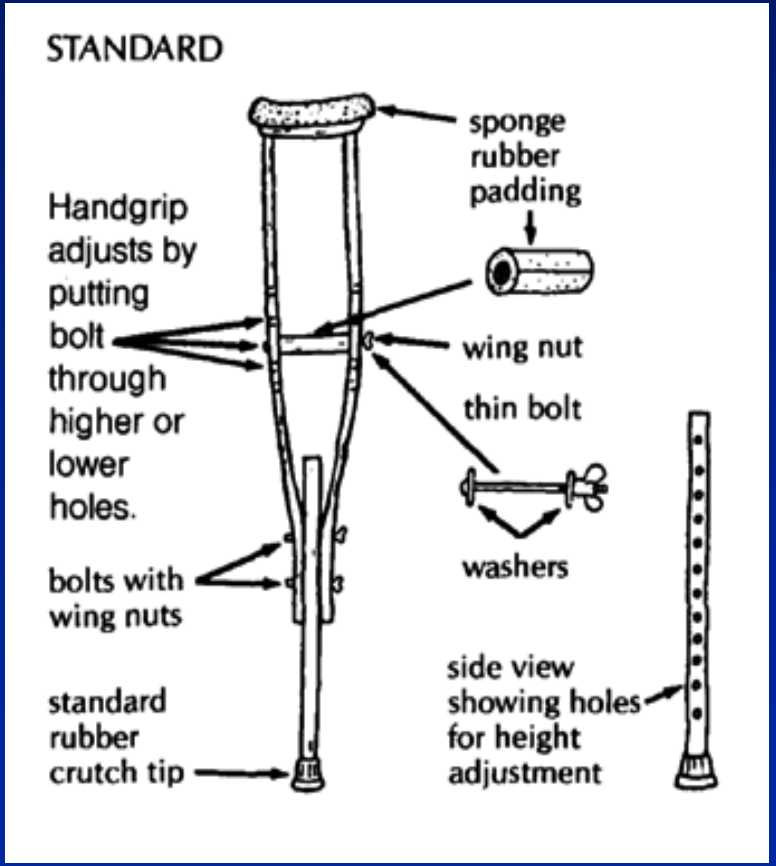
crutch for everybody who needs an objective slide..

- **Discuss the etiology of atherosclerosis and plaque enlargement**

- **Enumerate the clinical presentations of atherosclerosis in the following organ systems:**
  - **Heart**
  - **Central Nervous System**
  - **Peripheral vasculature/Extremities**
  - **Kidneys**
  - **Intestines**

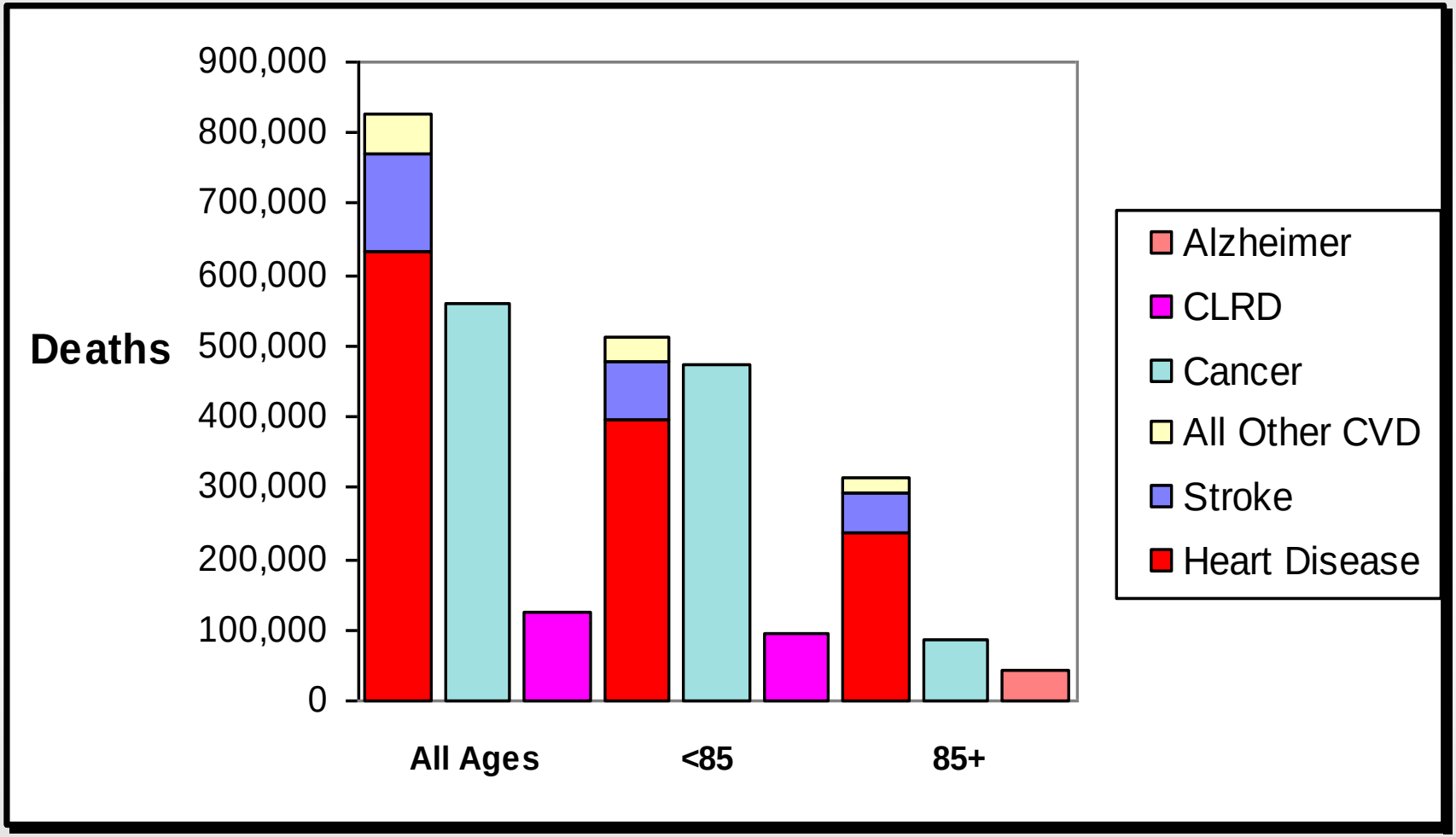
Define and discuss the concepts of "Critical Stenosis" and "Plaque Rupture and Thrombosis" in relation to the above.

- **Compare and contrast thoracic and abdominal aortic aneurysms including dissections on the basis of:**
  - **Etiologic factors**
  - **Incidence**
  - **Complications**



Comparison of heart disease vs. other causes of death.

American Heart Association
Learn and Live

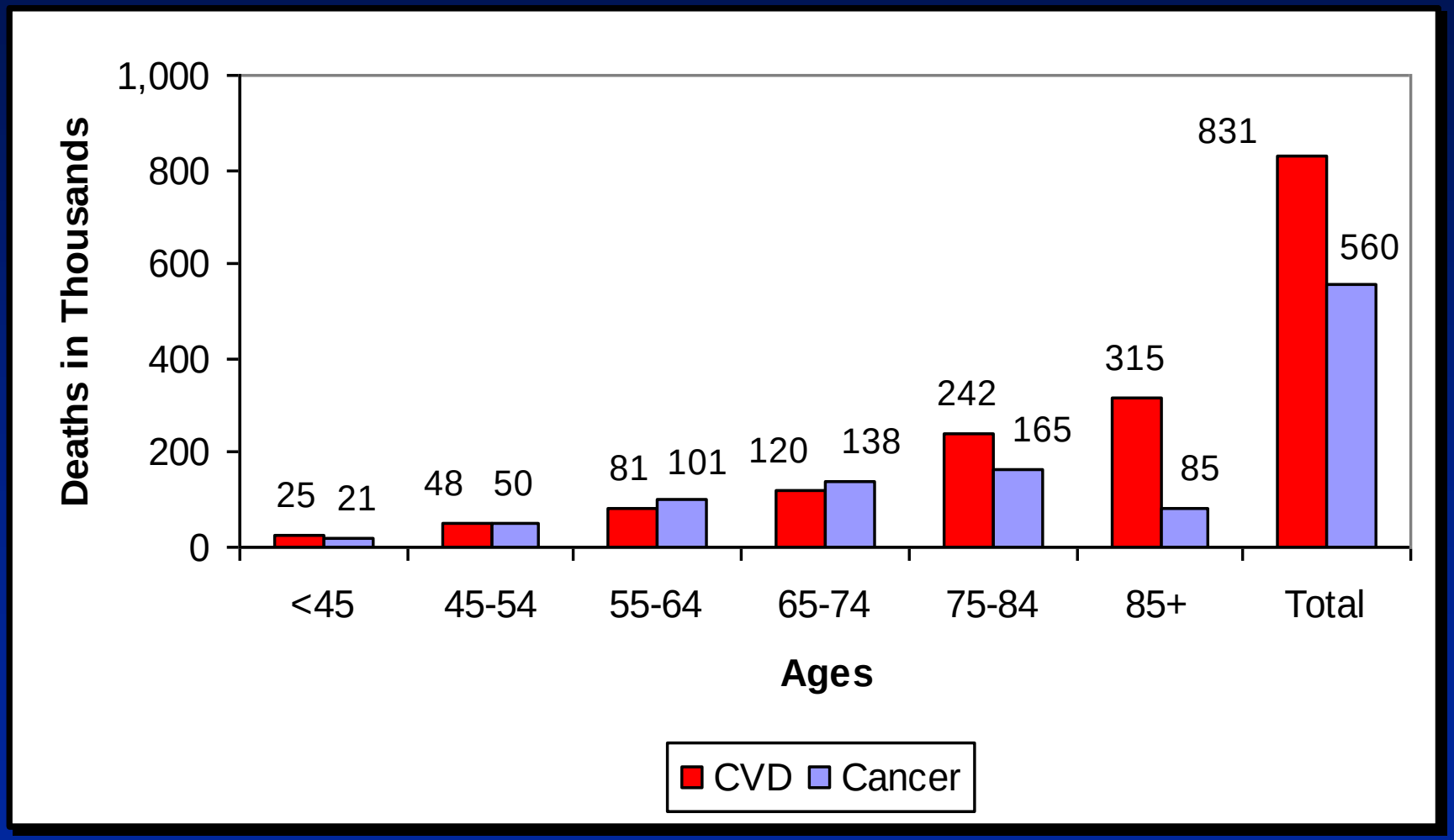


CVD and other major causes of death: both sexes.
(United States: 2006). Source: NCHS and NHLBI.

Cardiovascular Disease Deaths vs. Cancer Deaths by Age

United States: 2006

American Heart Association®
Learn and Live℠



under 45 there are still thousands of deaths. both cancer and cvd increase with age

Source: NCHS

3rd leading cause of death in males, but 5th in females. He thinks it's because women drivers are usually the ones who hit you when you're on the road.

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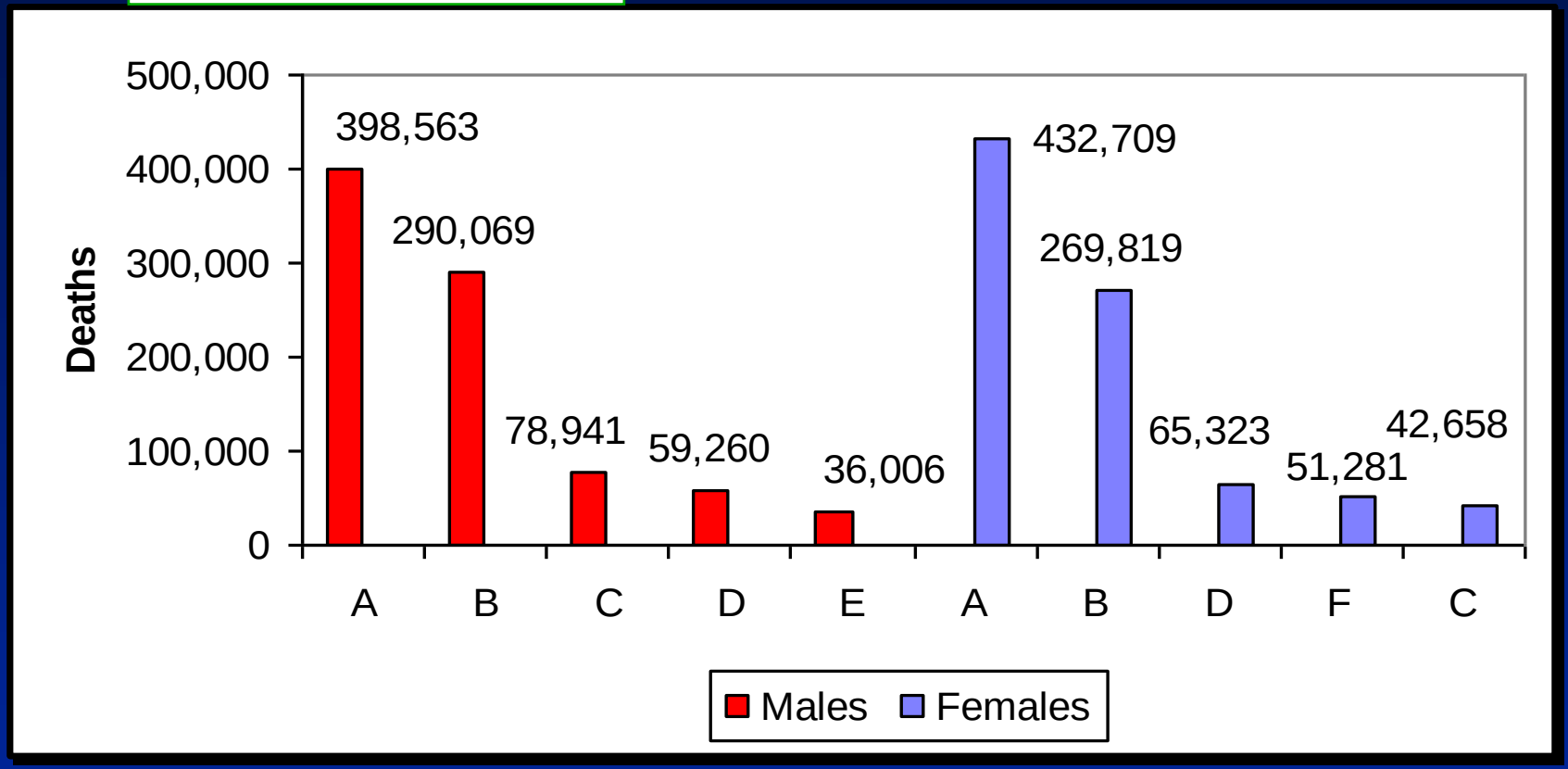

A CVD (I00-I99; Q20-Q28)
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer's Disease

CVD and other major causes of death for all males and females (United States: 2006). Source: NCHS and NHLBI.

Percentage Breakdown of Deaths From Cardiovascular Diseases

United States:2003*

American Heart Association®
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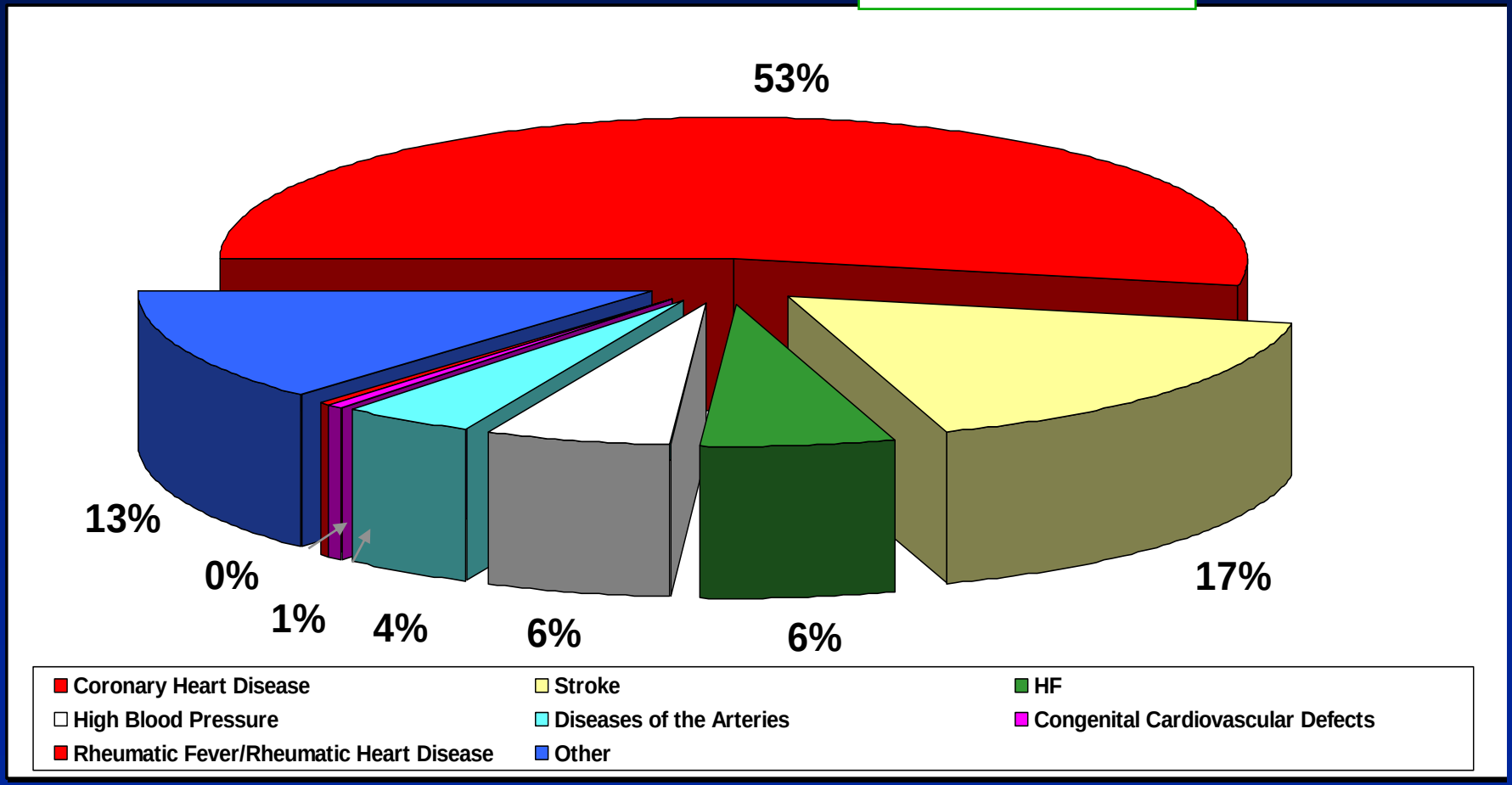
CVD is mostly coronary heart disease.

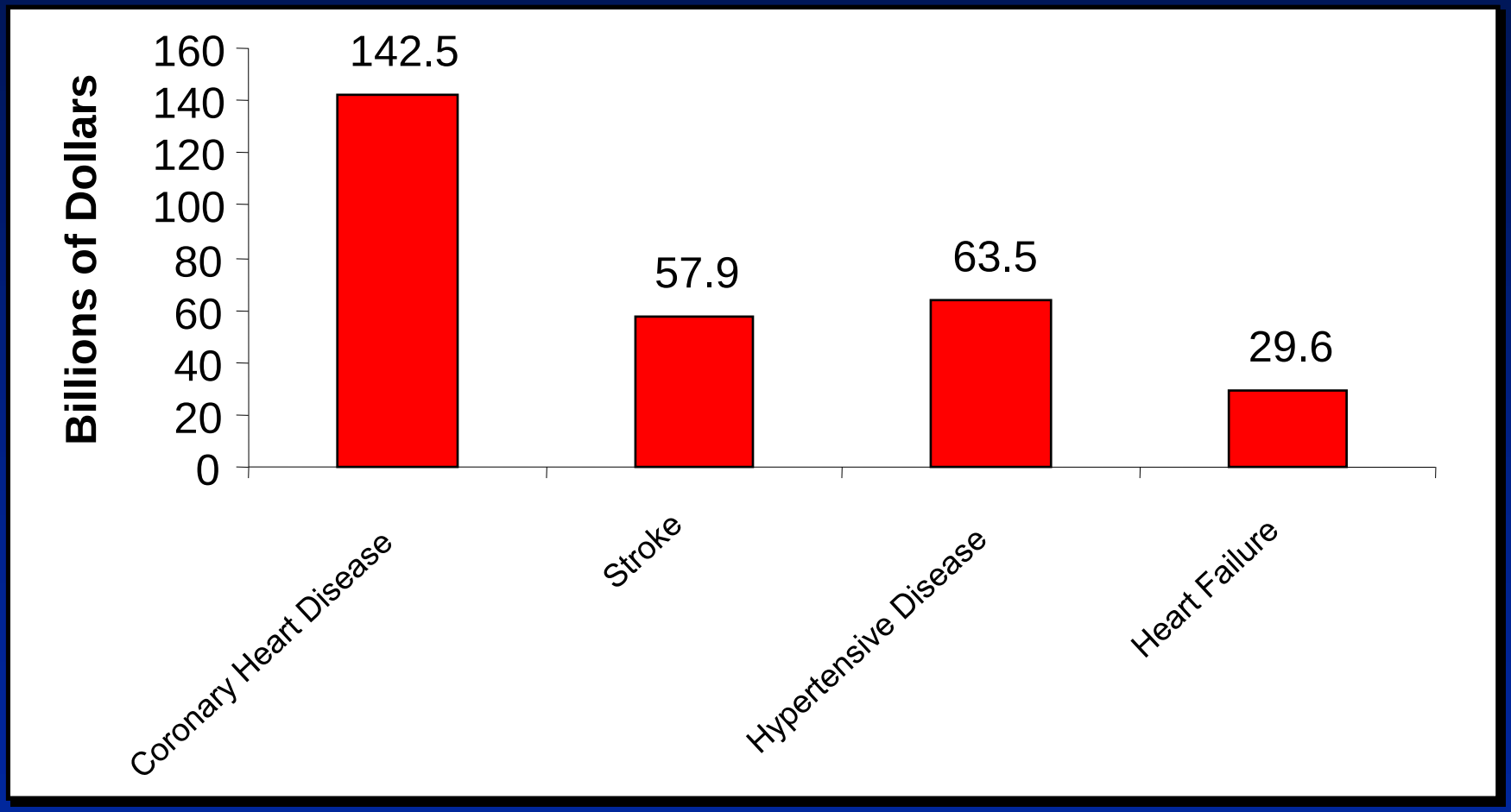


*Source: CDC/NCHS and NHLBI. *Preliminary*

Estimated Direct and Indirect Costs of Major Cardiovascular Diseases and Stroke

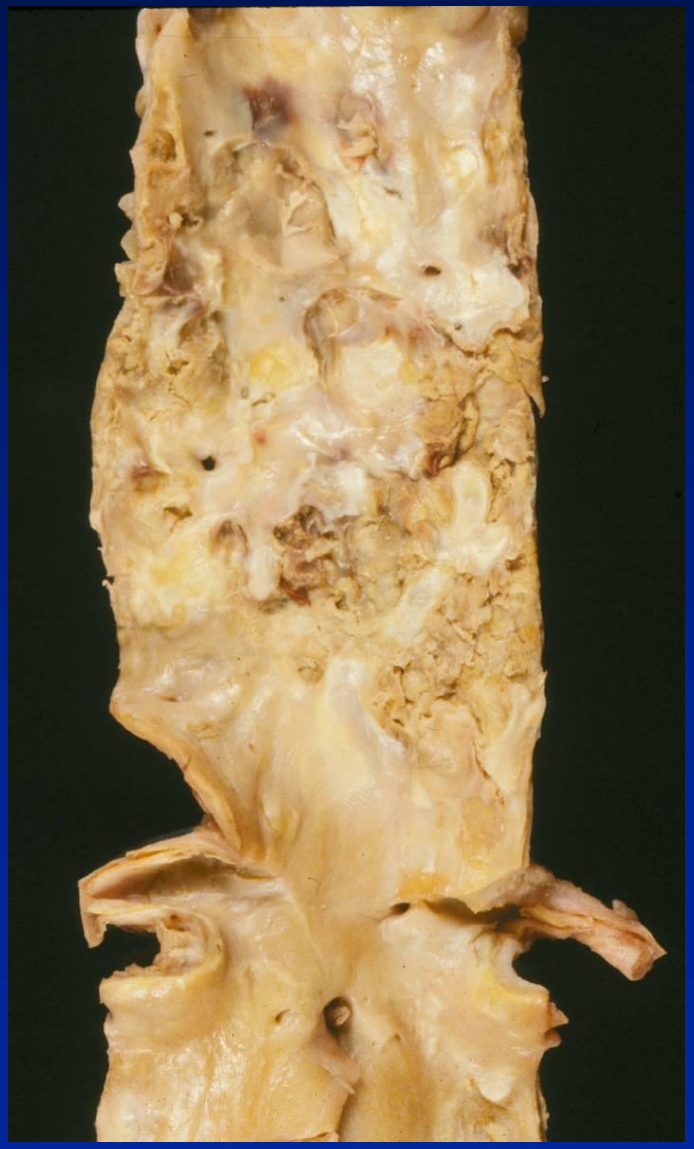
United States: 2006

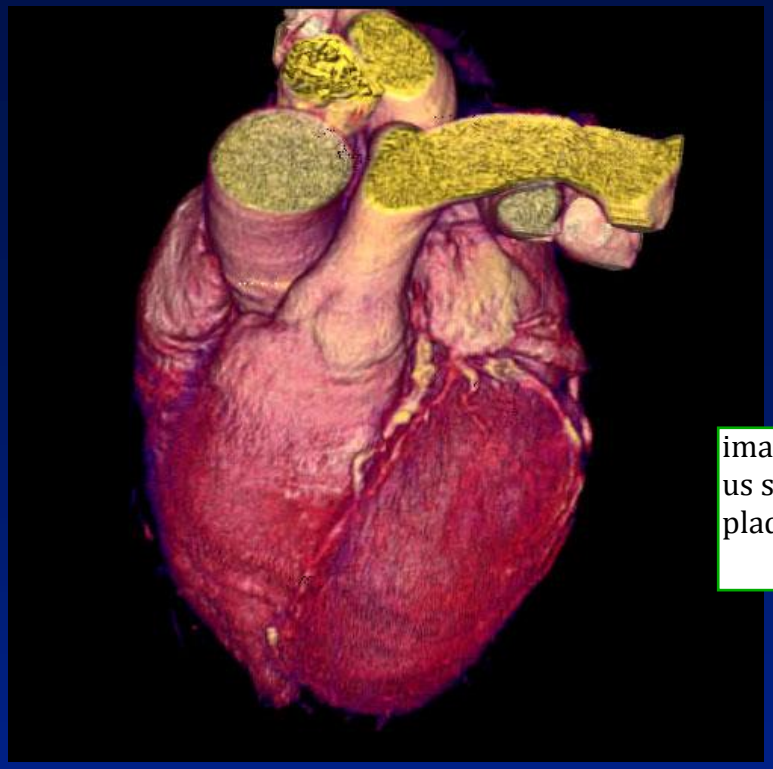
Huge costs related to CAD. If you add what we put into prevention...



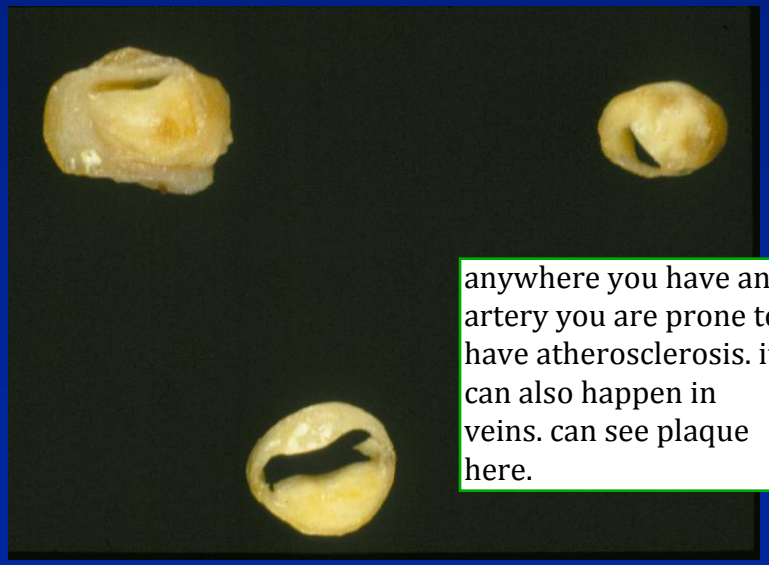
Source: Heart Disease and Stroke Statistics – 2006 Update.

Atherosclerosis





imaging let's us see plaques.



anywhere you have an artery you are prone to have atherosclerosis. it can also happen in veins. can see plaque here.

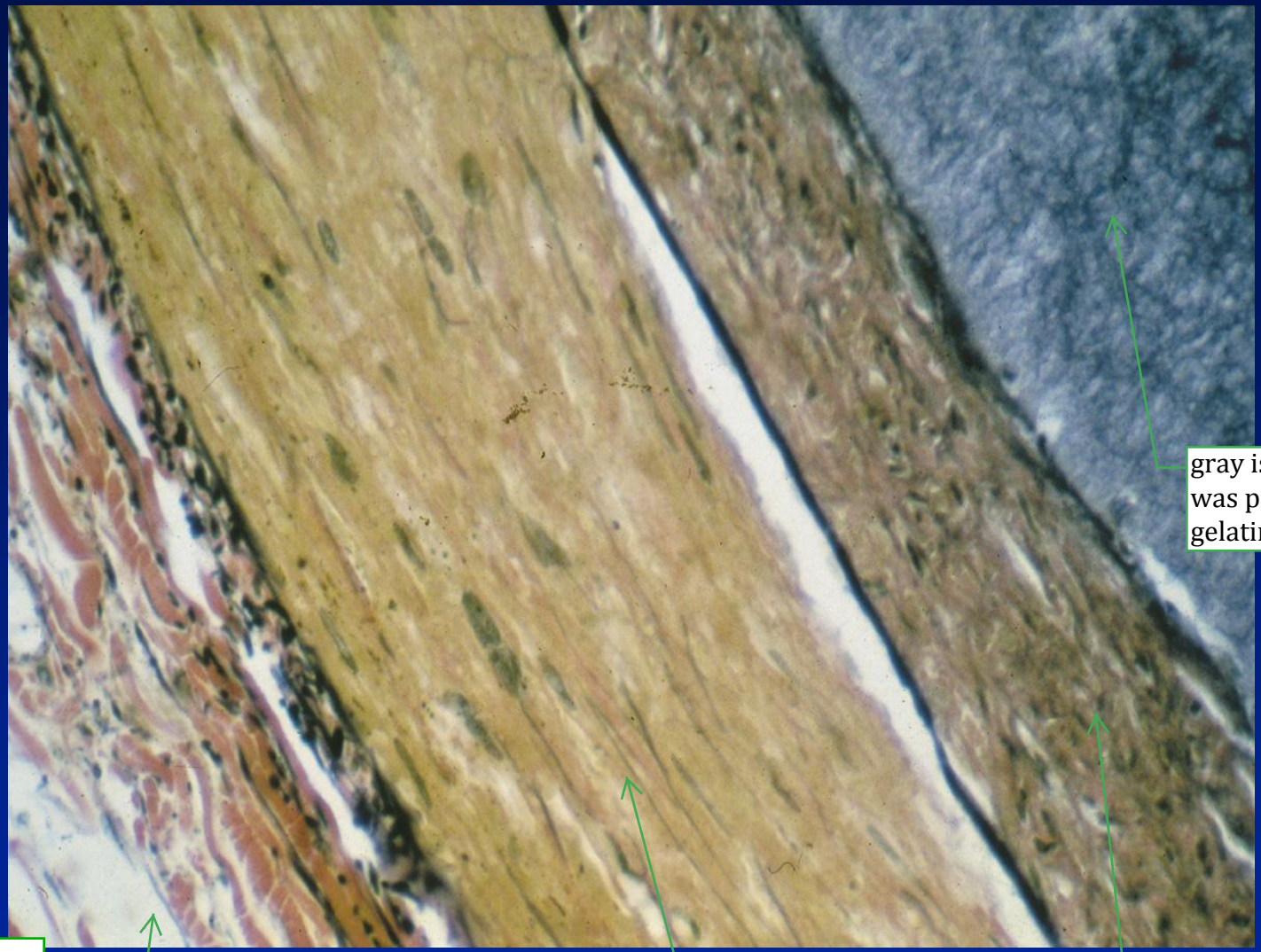
Atherosclerotic Lesions

athero- fatty,
sclerosis- fibrosis.

atherosclerosis starts as somewhat benign lesion called fatty streak: this is when you first get injury in your blood vessels. usually in your second decade of life. end up getting into a vicious cycle in which you collect the plaque and response to injury adds fibrosis. Once you get to fibrous stage you have it for life.

- **Progression**
  - **Fatty Streaks**
    - ►**Lipid filled myointimal cells**
    - ►**Starts in second decade – Intimal Process**
  - **Fibrous Plaques**
    - ►**Subendothelial fibrous cap over extracellular lipid pool**
  - **Complicated Plaques**
    - ►**Fibrous plaque with erosion, intramural hemorrhage, thrombus, calcification**

if you bleed into the plaque it will grow more rapidly and will calcify. complicated just means that something happened and now it grows more quickly not necessarily a clinical complication.



gray is because it was perfused with gelatin solution

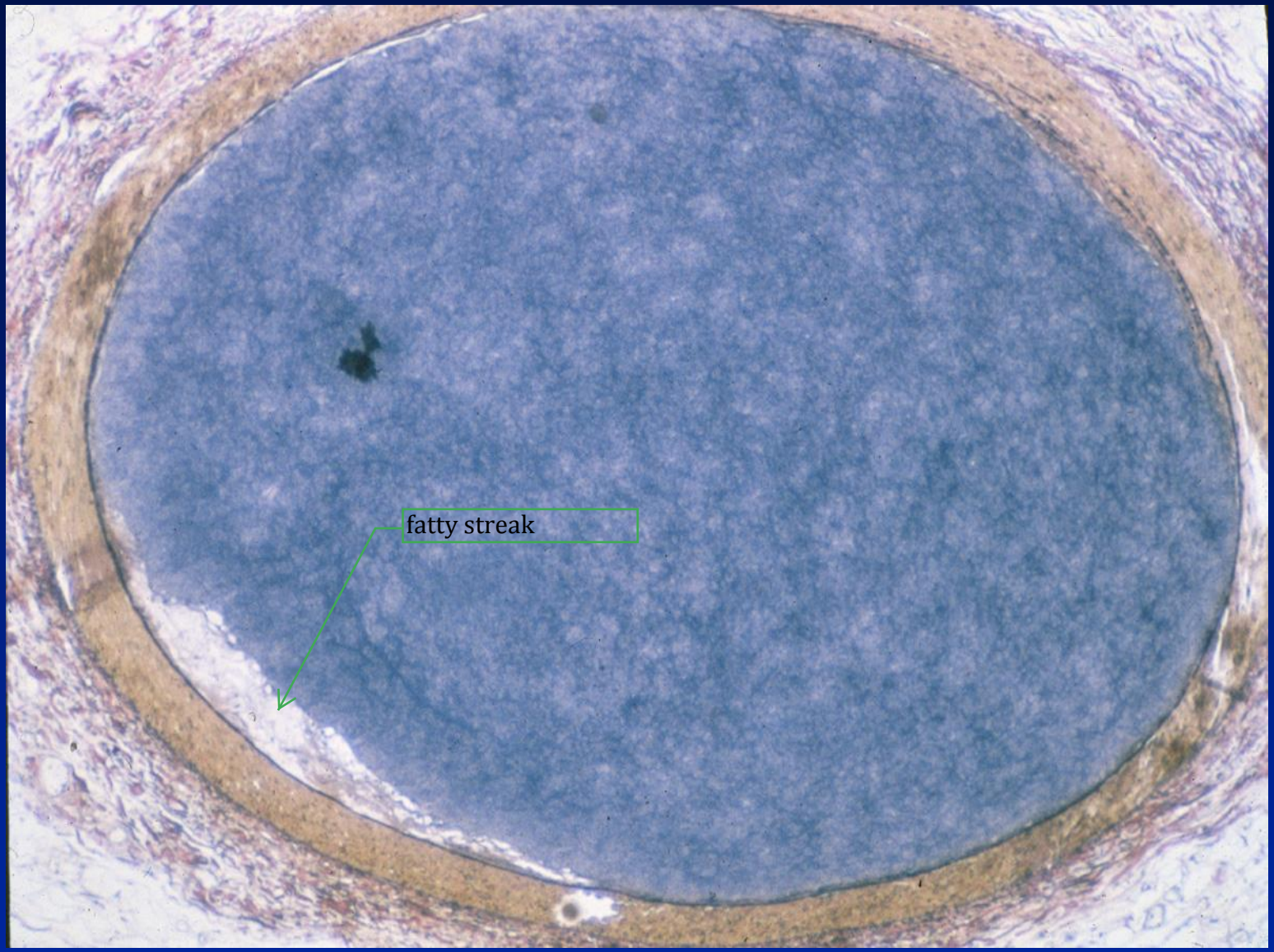
rabbit artery.

adventitia

tunica media- contains muscle and elastin

intima thicker than humans (usually 1-3 cell layers thick)

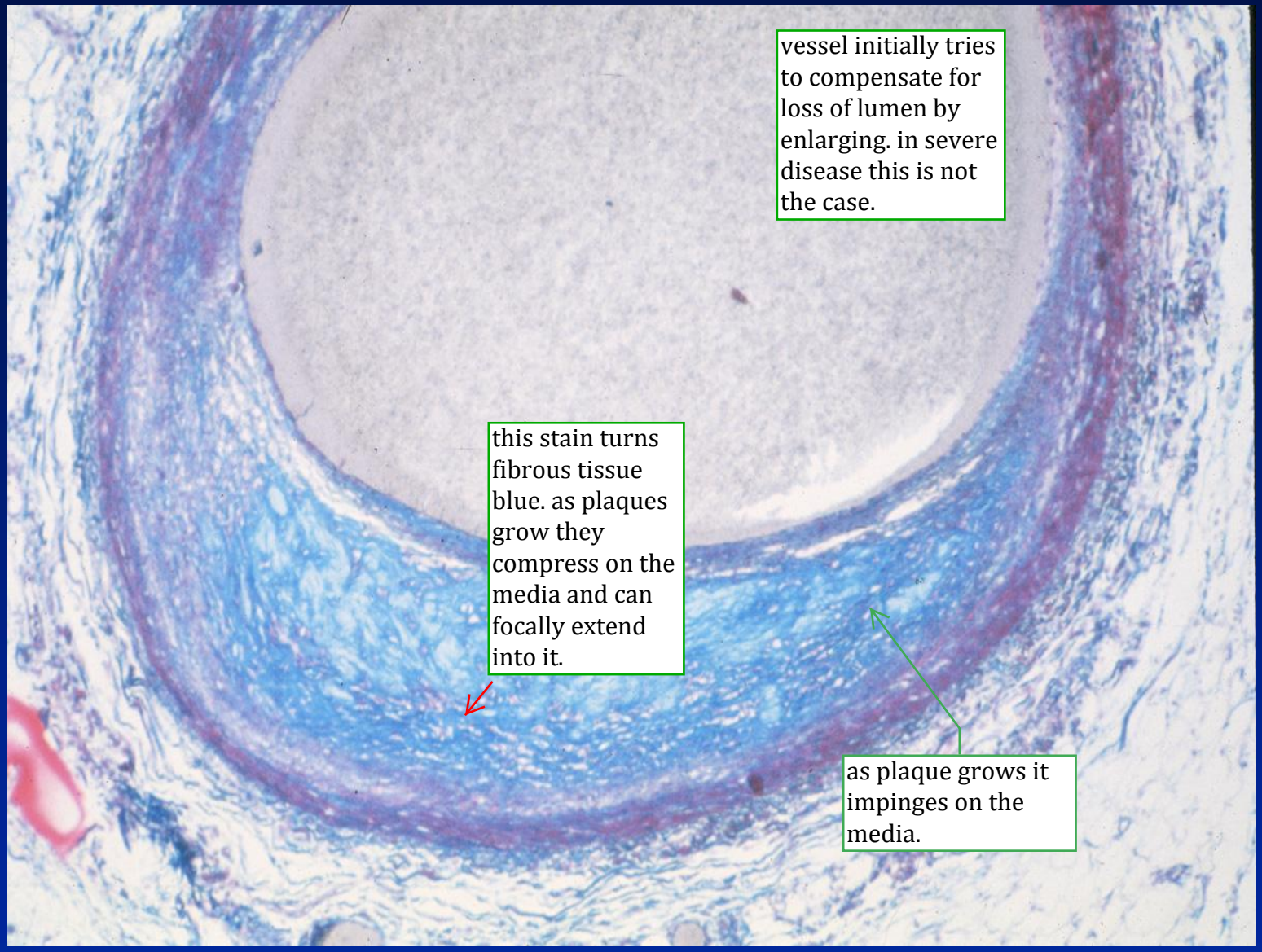
Relatively Normal Muscular Artery



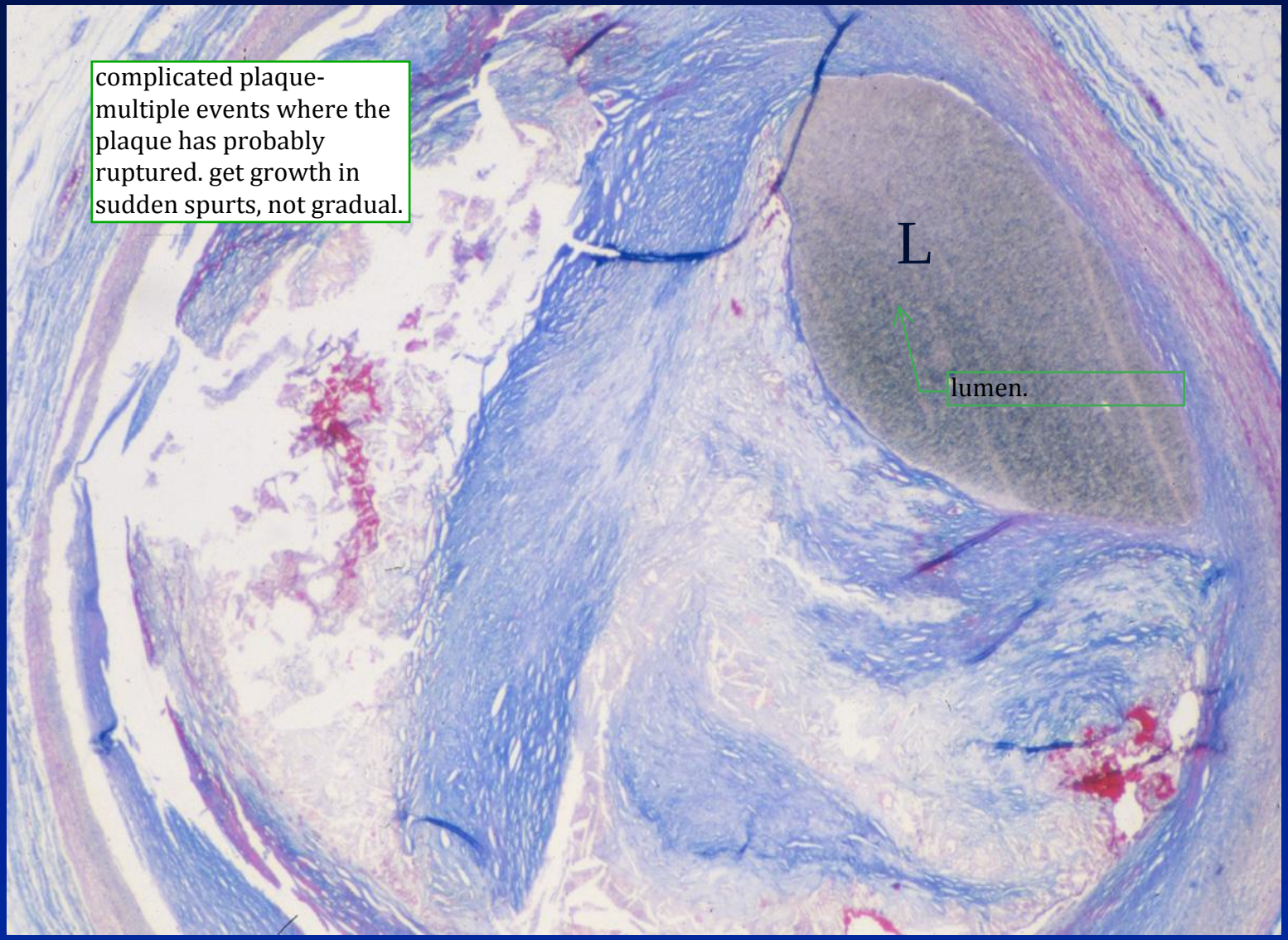
rabbit on human diet.

Artery with Fatty Streak

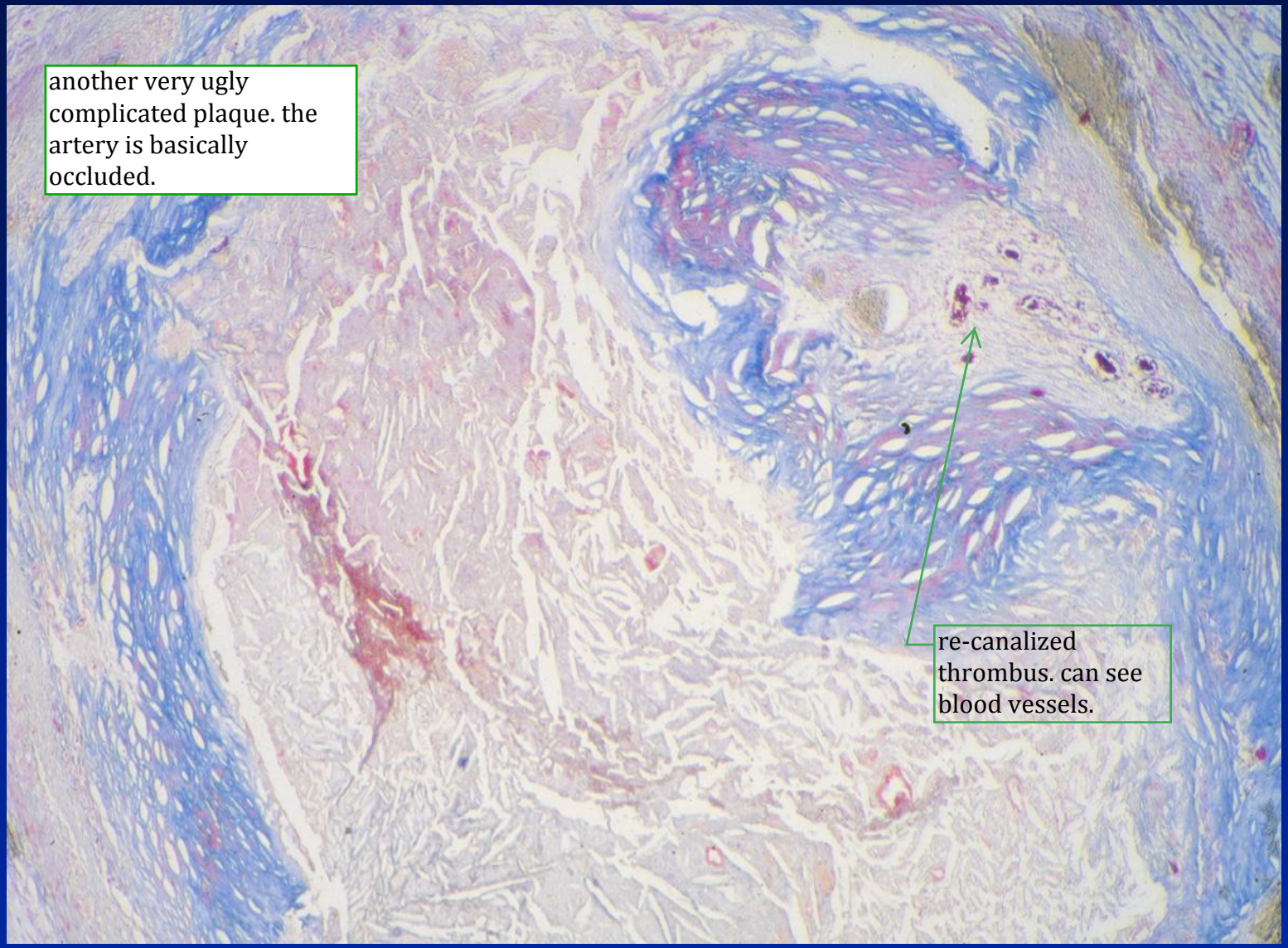
Fatty Streak

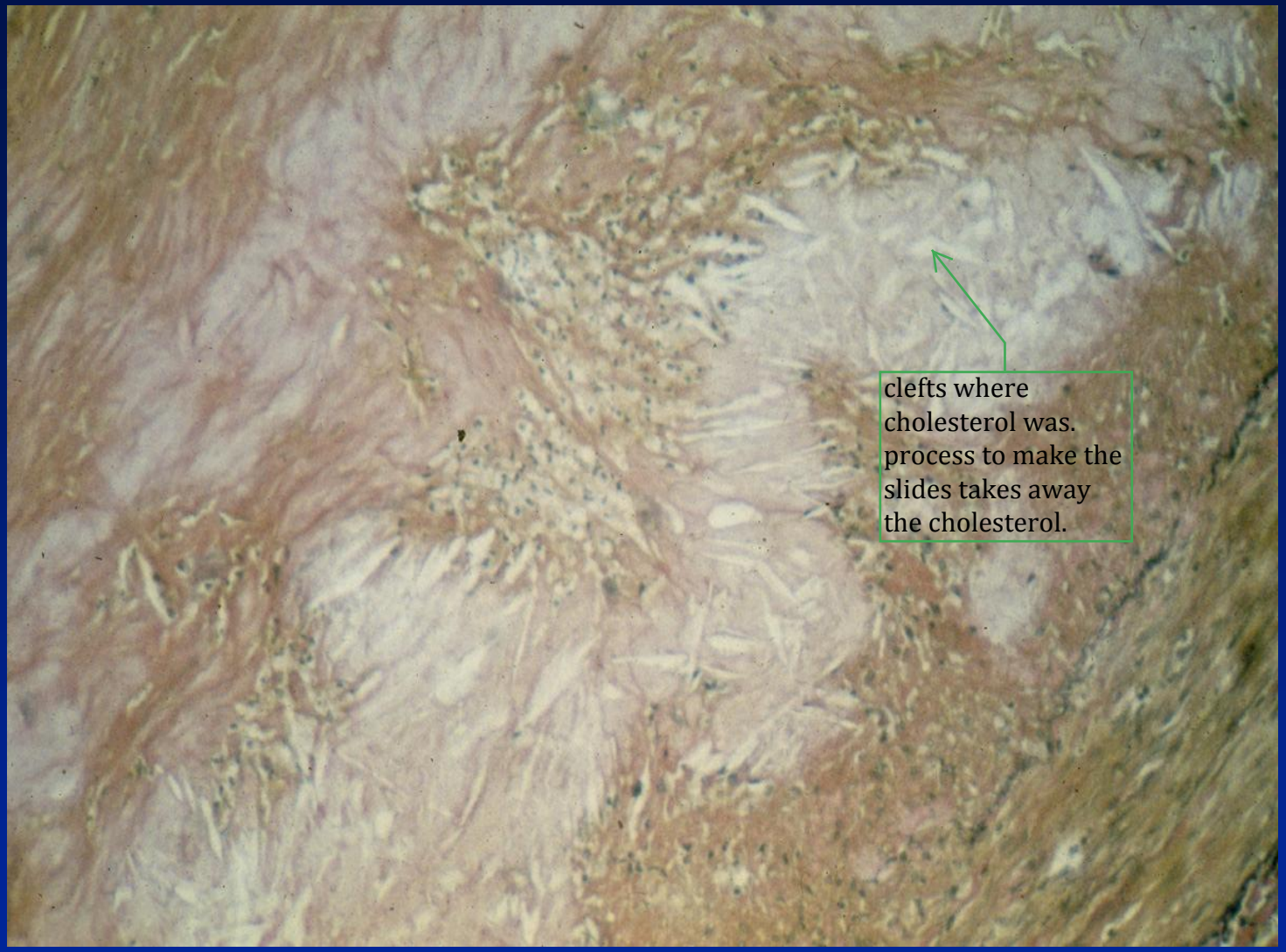


Fibrous Plaque

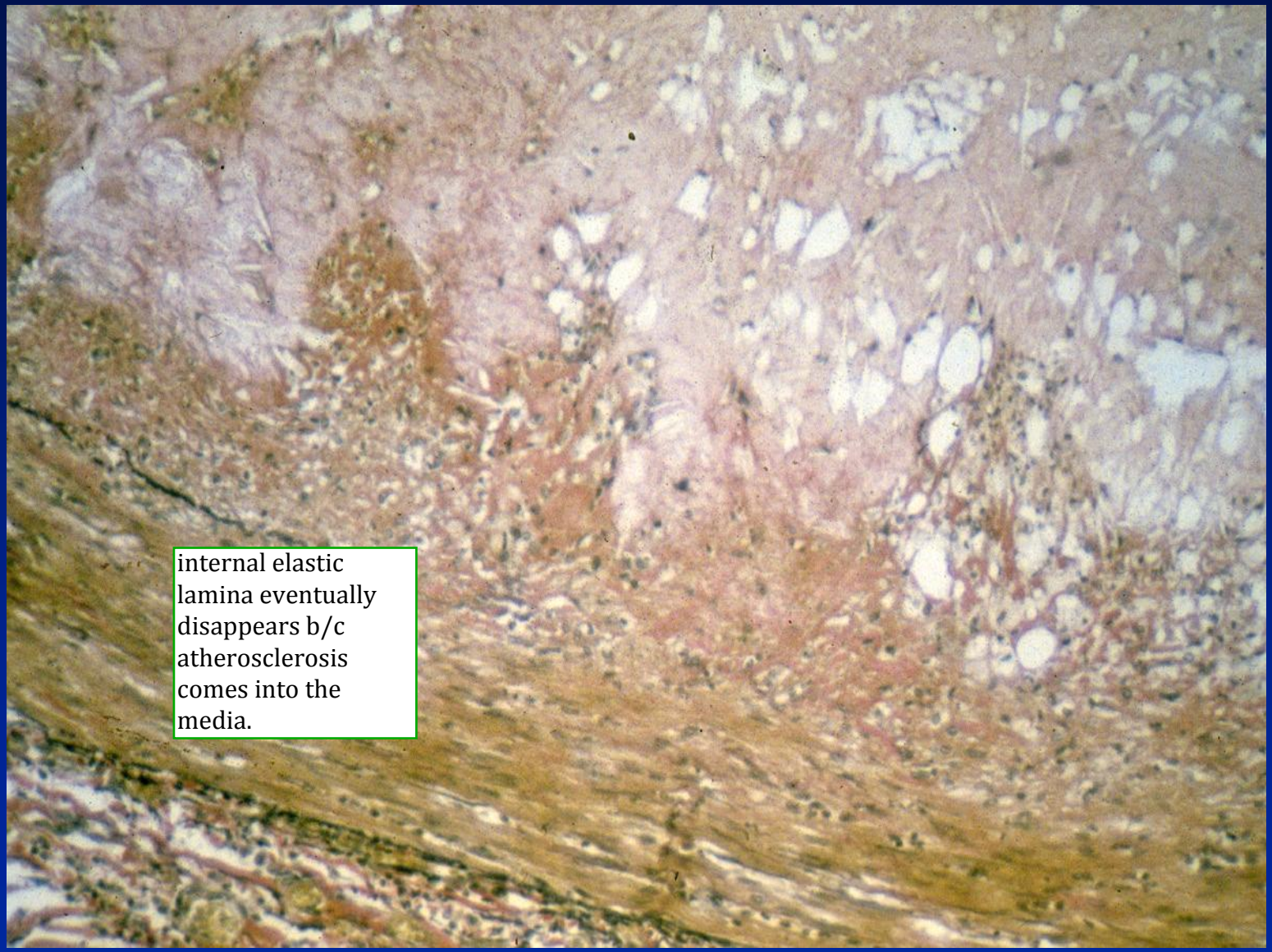


Complicated Plaque


another very ugly complicated plaque. the artery is basically occluded.
re-canalized thrombus. can see blood vessels.



Cholesterol Clefts in Atherosclerotic Plaque Atheromatous Core



Focal disruption of internal elastic lamina

Prevalence of Cardiovascular Diseases in Americans Age 20 and Older by Age and Sex NHANES 2003-2006

American Heart Association®
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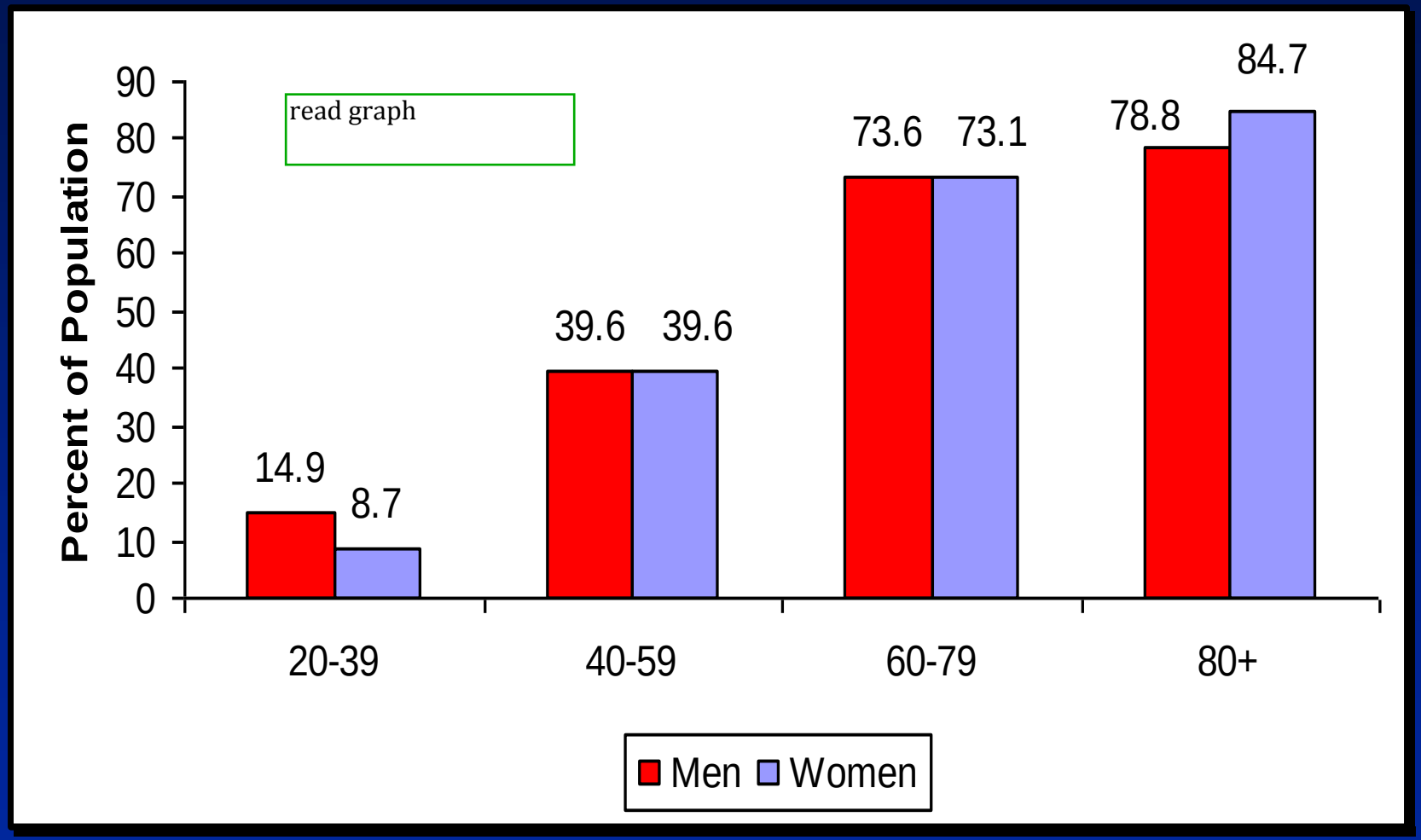
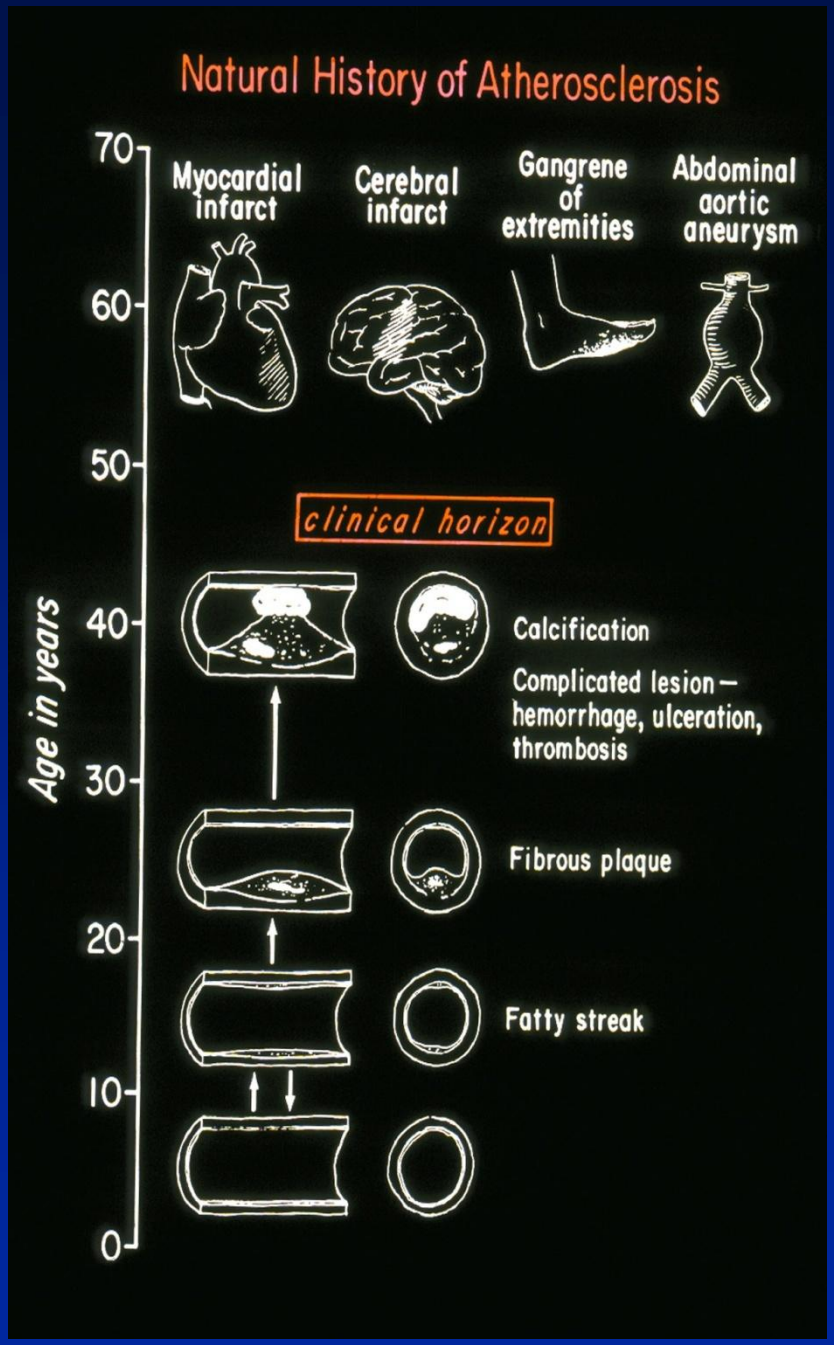
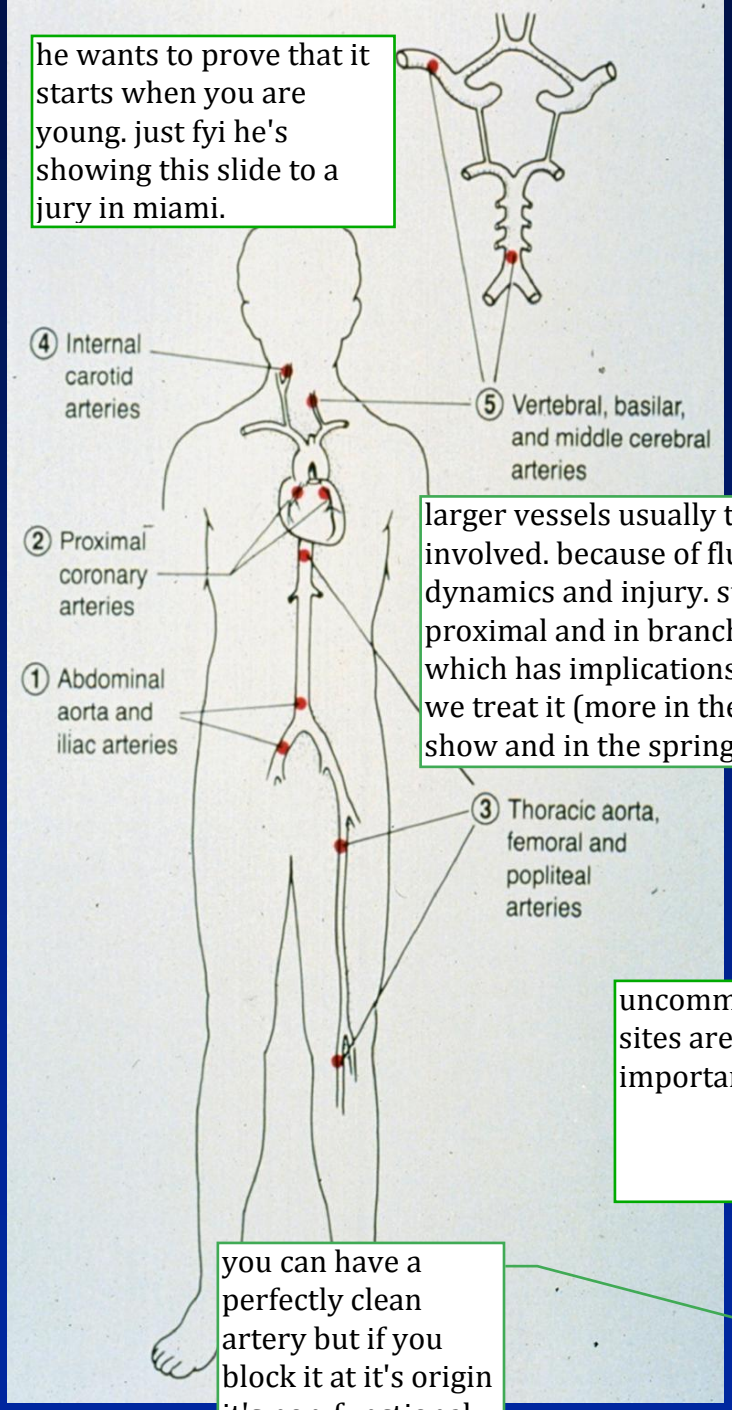


Source: CDC/NCHS and NHLBI. These data include coronary heart disease, heart failure, stroke and hypertension.

start in teens, progresses, see clinical phase in 30s - 40s.



he wants to prove that it starts when you are young. just fyi he's showing this slide to a jury in miami.



Common Sites of Atherosclerotic Plaques

→ Larger vessels, branch pt.s

Abdominal aorta and iliacs

Proximal Coronaries

Thoracic Aorta , Distal LE's

Internal Carotid and Cerebral

larger vessels usually the 1st involved. because of fluid dynamics and injury. starts proximal and in branch points which has implications on how we treat it (more in the road show and in the spring)

Uncommon Sites:

Subclavian arteries

Axillary arteries

Renal arteries

Superior Mesenteric and Celiac

(Not incl. aortic origin)

uncommon sites are also important.

you can have a perfectly clean artery but if you block it at it's origin it's non-functional

Risks and Etiology

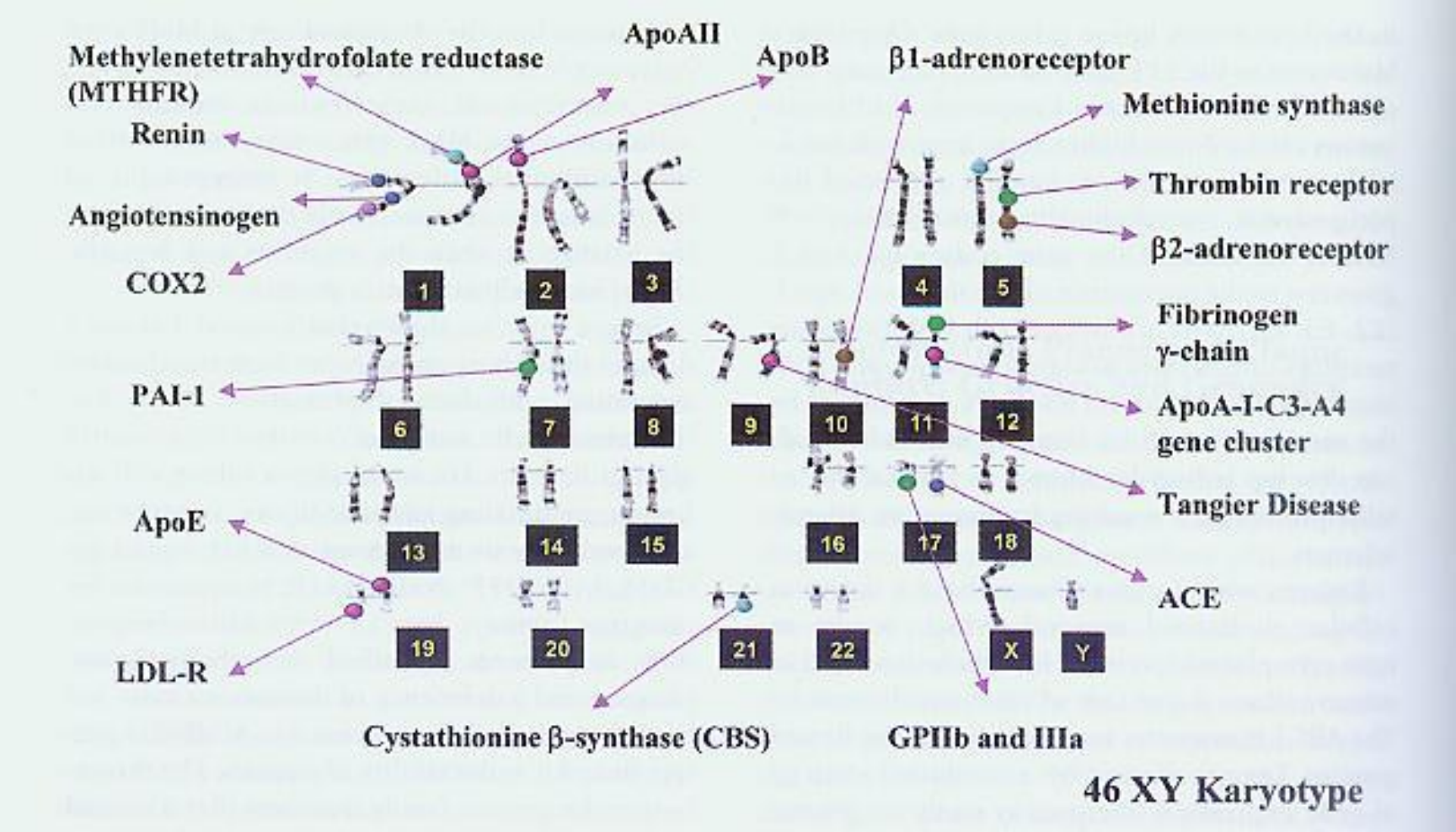
- **Major – Can Not Be Changed:**
  - **Genetic** — strongest risk factor. tons of genes are involved in atherosclerosis. ask for family history.
  - **Male Gender**
  - **Age** — older than 55.
- **Major – Can Be Changed/Managed**
  - **Tobacco use**
  - **Hypertension**
  - **Lipidemias**
  - **Diabetes Mellitus**

these we can do something about

- **Contributing Factors:**
  - **Obesity, Sedentary Life, Stress**

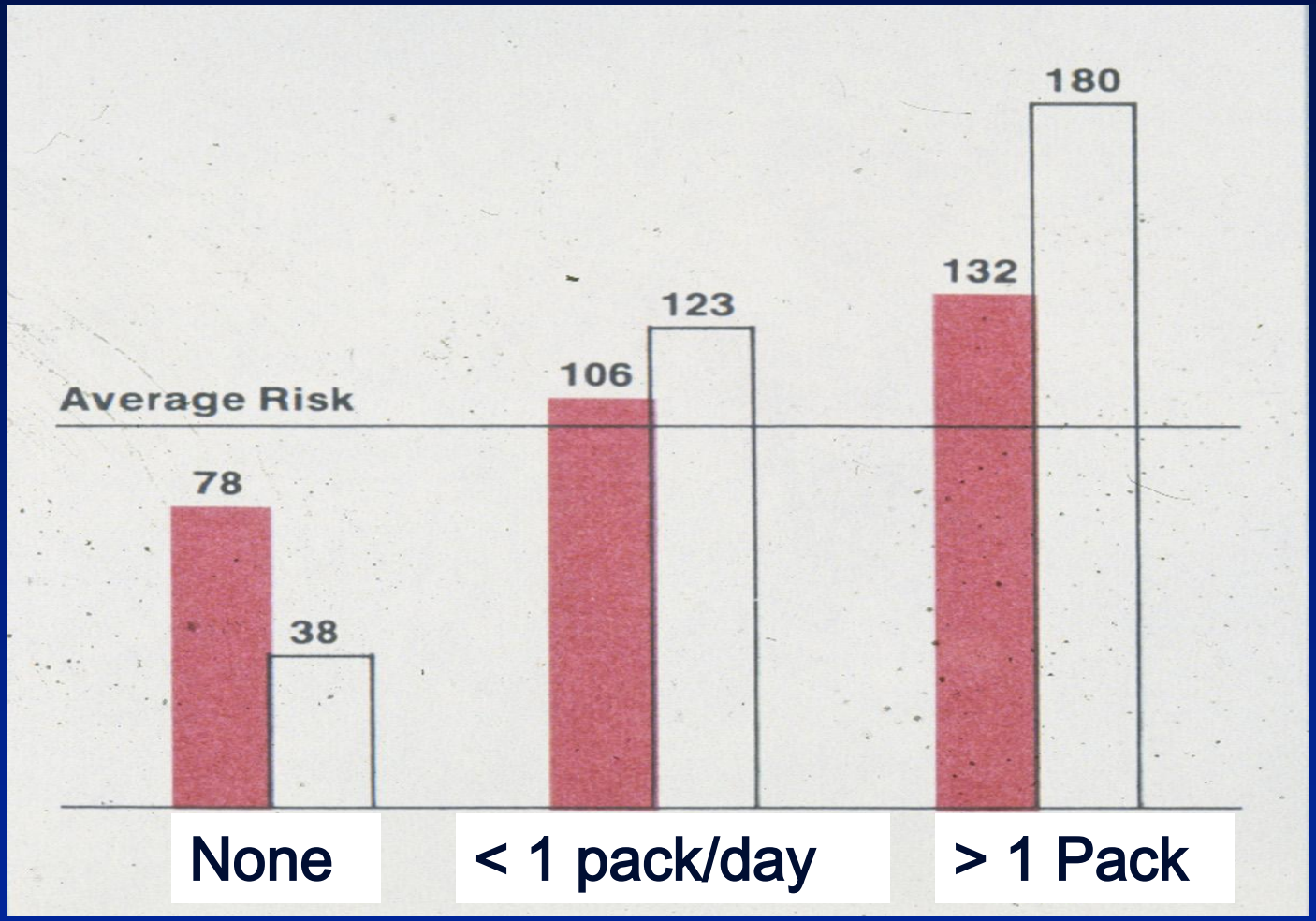
obesity contributes but is not a MAJOR risk factor.

Atherosclerosis: Genetics



very complicated b/c multiple genes are involved.

Tobacco Use: Smoking



Red bars are myocardial infarcts

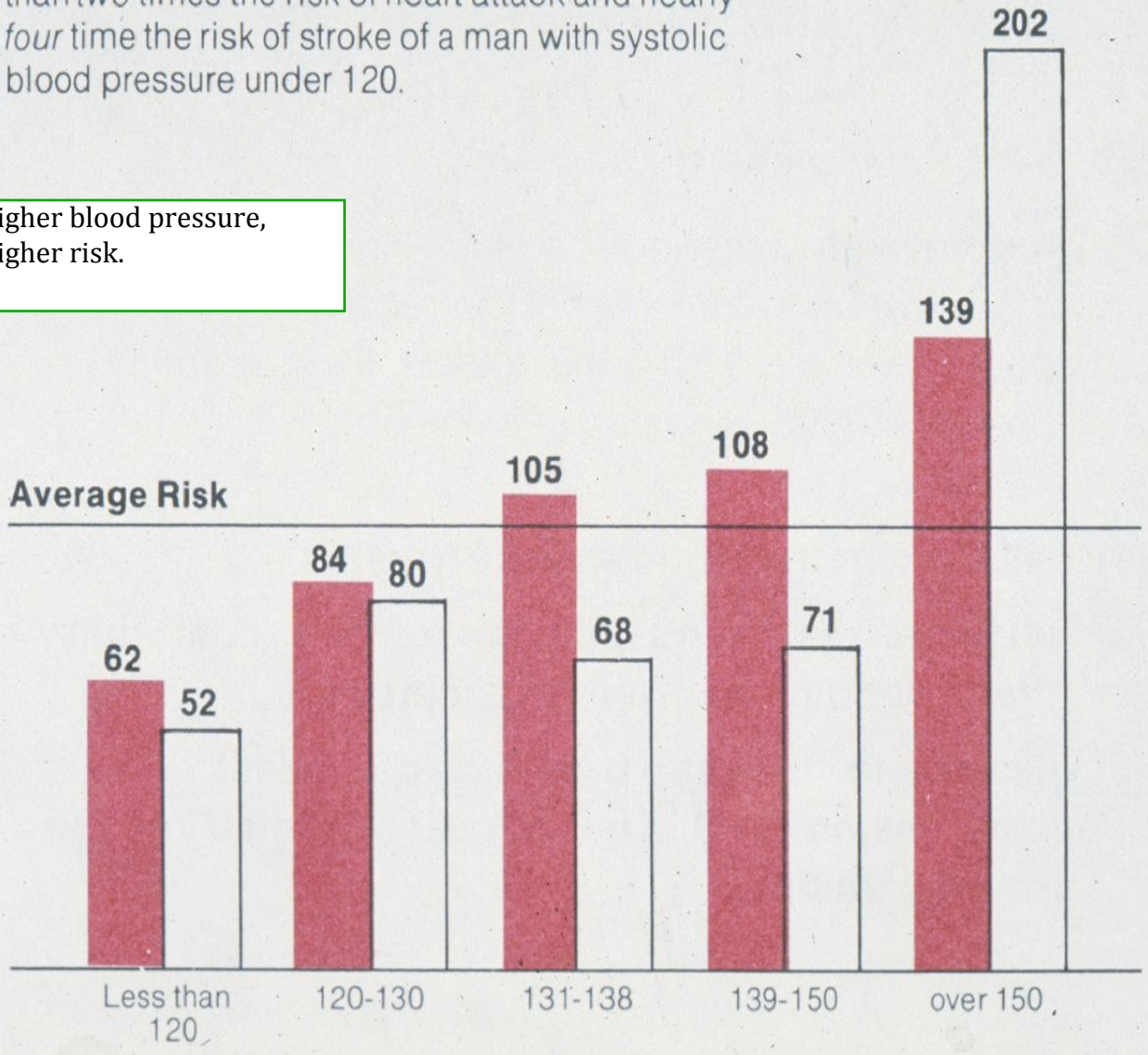
White bars are strokes

more you smoke the higher your risk.

Blood Pressure

A man whose blood pressure at systole (the moment the heart contracts) is over 150 has more than *two* times the risk of heart attack and nearly *four* time the risk of stroke of a man with systolic blood pressure under 120.

higher blood pressure,
higher risk.



in general they keep becoming more stringent on where they want your cholesterol levels to be, depending on your risk factors.

Cholesterol and Atherosclerosis

In adults, total cholesterol > 240 mg/dL is high risk

LDL cholesterol > 130 mg/dL is associated with increased risk of coronary artery disease

HDL cholesterol < 40 mg/dL is associated with increased risk of coronary artery disease

basically read slide.

Inflammation

how do we explain these people w/ normal cholesterol levels? started looking at inflammatory responses.

- > 50% of deaths from CAD have normal cholesterol levels
- Is there an overall "hyper-inflammatory" state?

YES.

- C-Reactive Protein (CRP) – Acute phase reactant - indicates ongoing inflammation

CRP- ongoing inflammation.

  - hs-CRP - Easily measured by blood test, low cost

elevated CRP important in both short and long term.

  - Correlates with risk of adverse coronary events
    - ► Short and long term risk
  - Medications can reduce levels and risk
    - ► Statins (HMG-CoA reductase inh) – dual role also reduces CRP levels.

aspirin also reduces inflammatory state.

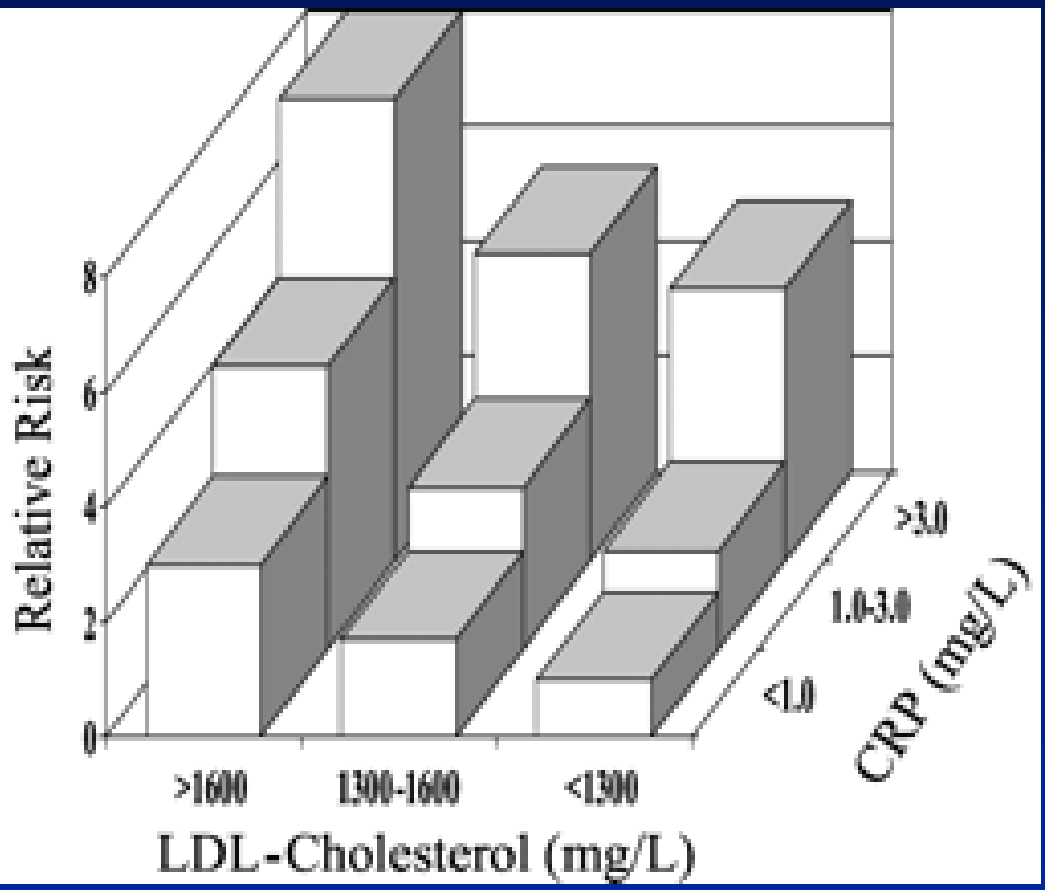
- Other Markers being developed
  - PlacentalGF – less influenced by ongoing inflammation

more specific markers that are specific to arteries and vascular inflammationbeing developed

paper looked at stratified risk in patients w/ both high cholesterol and high CRP. if patients controlled their levels of cholesterol and had elevated CRP they were still at risk. **elevated CRP is a stronger predictor for CAD than lipids.**

Inflammation

LDL-Cholesterol (mg/L)	CRP (mg/L) <1	1-3	>3
<1300	1.0	1.7	4.7
1300-1600	1.7	2.8	5.3
>1600	3.0	4.9	8.0



- **Rifai and Ridker, Clinical Chemistry. 2003;49:666-669**

Pathogenesis of Atherosclerosis

Intimal Injury and Repair
(The Response to Injury Hypothesis)

model that is now focused on.

Mural Thrombosis and Organization
(The Thrombogenic or Encrustation Hypothesis)

ppl thought it was a thrombus.

Monoclonal Proliferation
(The Monoclonal Hypothesis)

mini tumor- this idea is gone.

Injury and Repair

- **Injury Mechanisms:**
  - **Hyperlipidemia**
  - **Hypertension/Shear Stress**
  - **Tobacco Abuse**
  - **Inflammatory State**
  - **Microorganisms/ Viruses: CMV, Adenovirus**
- **Effects – Vicious Cycle**
  - **Lipid Accumulation/ Free Radicals**
  - **Cytokines/Chemotaxis**
  - **Necrosis/Apoptosis/Thrombosis**
  - **Fibrosis**
- **Players:**
  - **Smooth Muscle Cells (medial and circulating), Macrophages, Endothelial Cells, White Cells and Platelets**

flow dynamics, high bp extends and distends the vessel. remember blood is viscous.

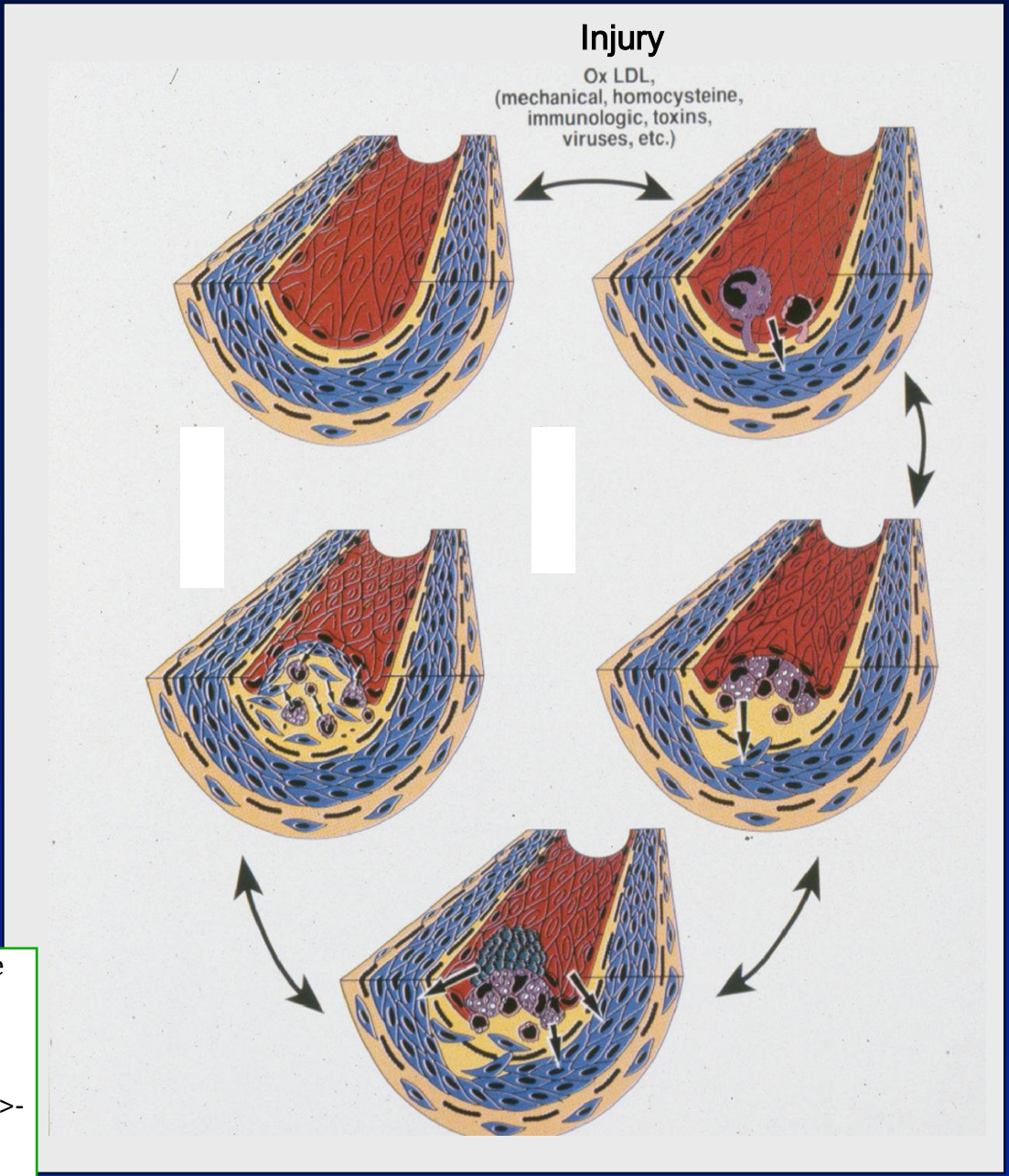
chemicals in bloodstream

once this process starts it's difficult to stop.

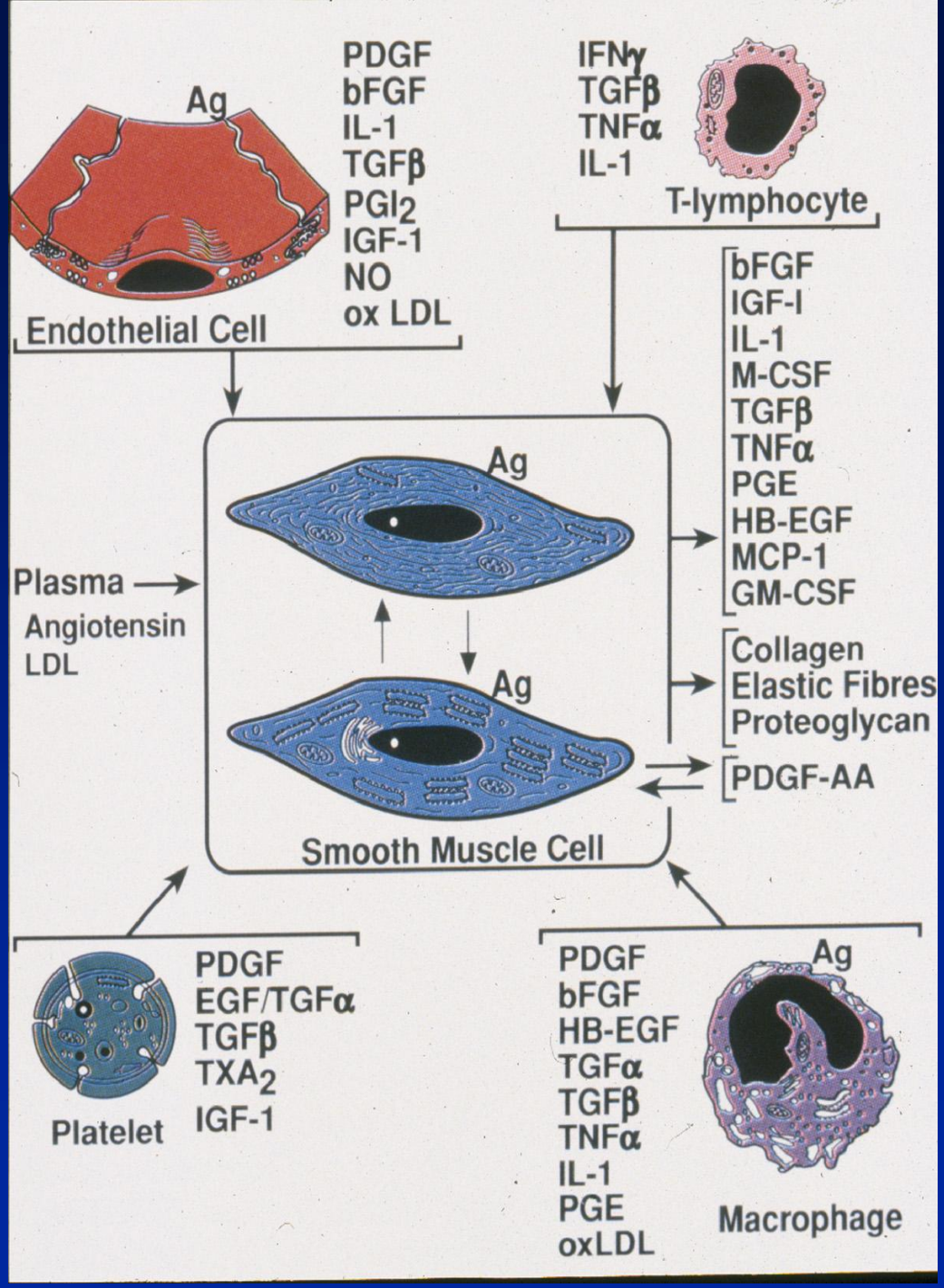
generate free radicals when lipids are oxidized.

especially problematic in peds- immunosuppressed patients, there seems to be a problem in heart arteriosclerosis when they get these viruses.

smooth muscle cells are VERY important because they are pluripotent here- can become secretory cells, cells that take up the fatty component, and can also be in our circulation and settle down in areas of injury and join the "riot". these and all the above-mentioned are involved.

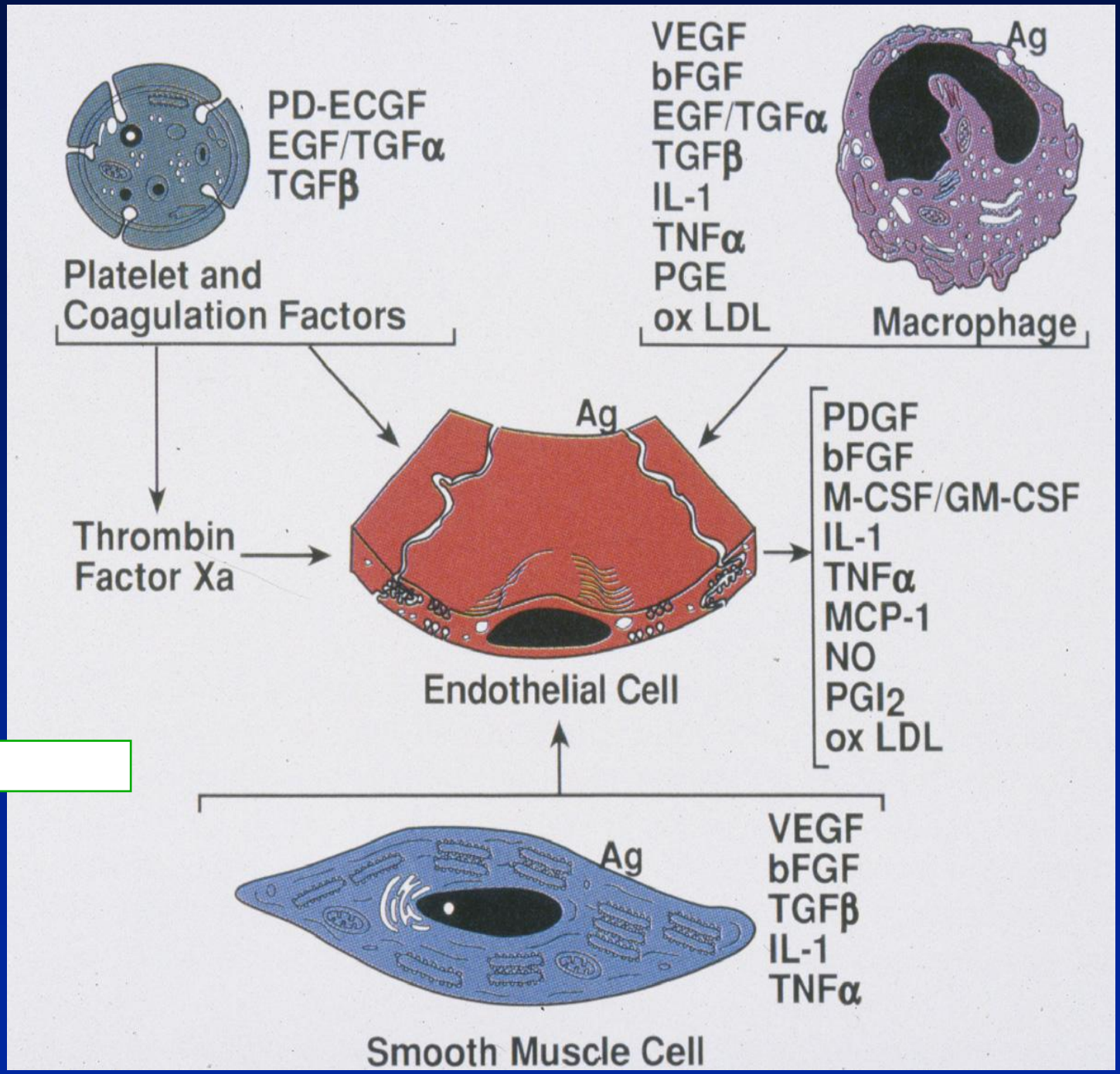


as plaque forms we get smooth muscle cells, platelet aggregation, more cell recruitment->->-> accumulation on blood vessels

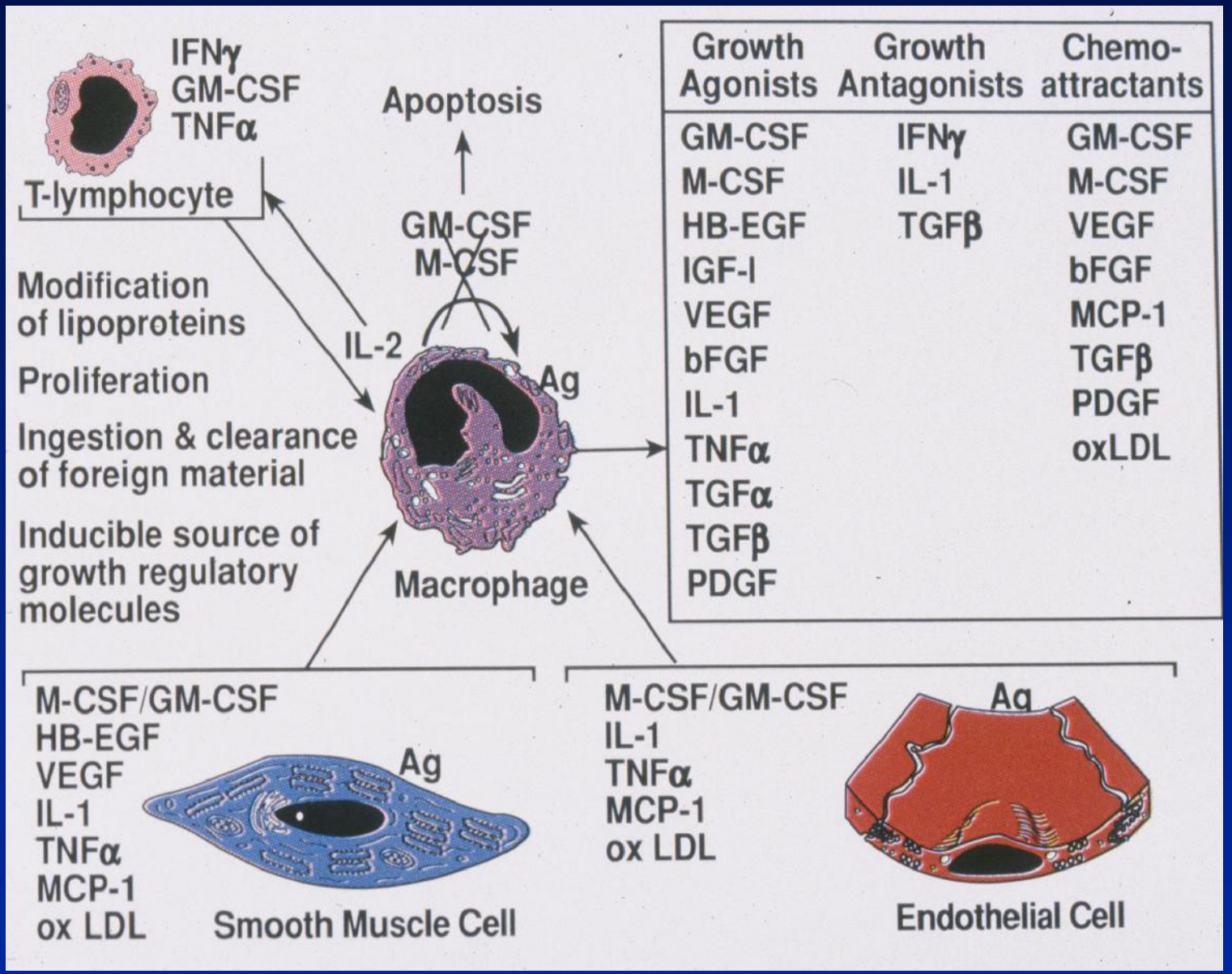


chemokines are involved. just remember it's a COMPLICATED process with a lot of players that interact with each other.

Growth Agonists	Growth Antagonists	Chemo-attractants
GM-CSF	IFNγ	GM-CSF
M-CSF	IL-1	M-CSF
HB-EGF	TGFβ	VEGF
IGF-I		bFGF
VEGF		MCP-1
bFGF		TGFβ
IL-1		PDGF
TNFα		oxLDL
TGFα		
TGFβ		
PDGF		


PD-ECGF
EGF/TGFα
TGFβ
Platelet and
Coagulation Factors
VEGF
bFGF
EGF/TGFα
TGFβ
IL-1
TNFα
PGE
ox LDL
Ag
Macrophage
Thrombin
Factor Xa
Ag
Endothelial Cell
PDGF
bFGF
M-CSF/GM-CSF
IL-1
TNFα
MCP-1
NO
PGI2
ox LDL
Ag
VEGF
bFGF
TGFβ
IL-1
TNFα
Smooth Muscle Cell

skipped


IFNγ
GM-CSF
TNFα
T-lymphocyte
Apoptosis
GM-CSF
M-CSF
IL-2
Ag
Modification of lipoproteins
Proliferation
Ingestion & clearance of foreign material
Inducible source of growth regulatory molecules
Macrophage
Growth Agonists
GM-CSF
M-CSF
HB-EGF
IGF-I
VEGF
bFGF
IL-1
TNFα
TGFα
TGFβ
PDGF
Growth Antagonists
IFNγ
IL-1
TGFβ
Chemo-attractants
GM-CSF
M-CSF
VEGF
bFGF
MCP-1
TGFβ
PDGF
oxLDL
M-CSF/GM-CSF
HB-EGF
VEGF
IL-1
TNFα
MCP-1
ox LDL
Ag
Smooth Muscle Cell
M-CSF/GM-CSF
IL-1
TNFα
MCP-1
ox LDL
Ag
Endothelial Cell

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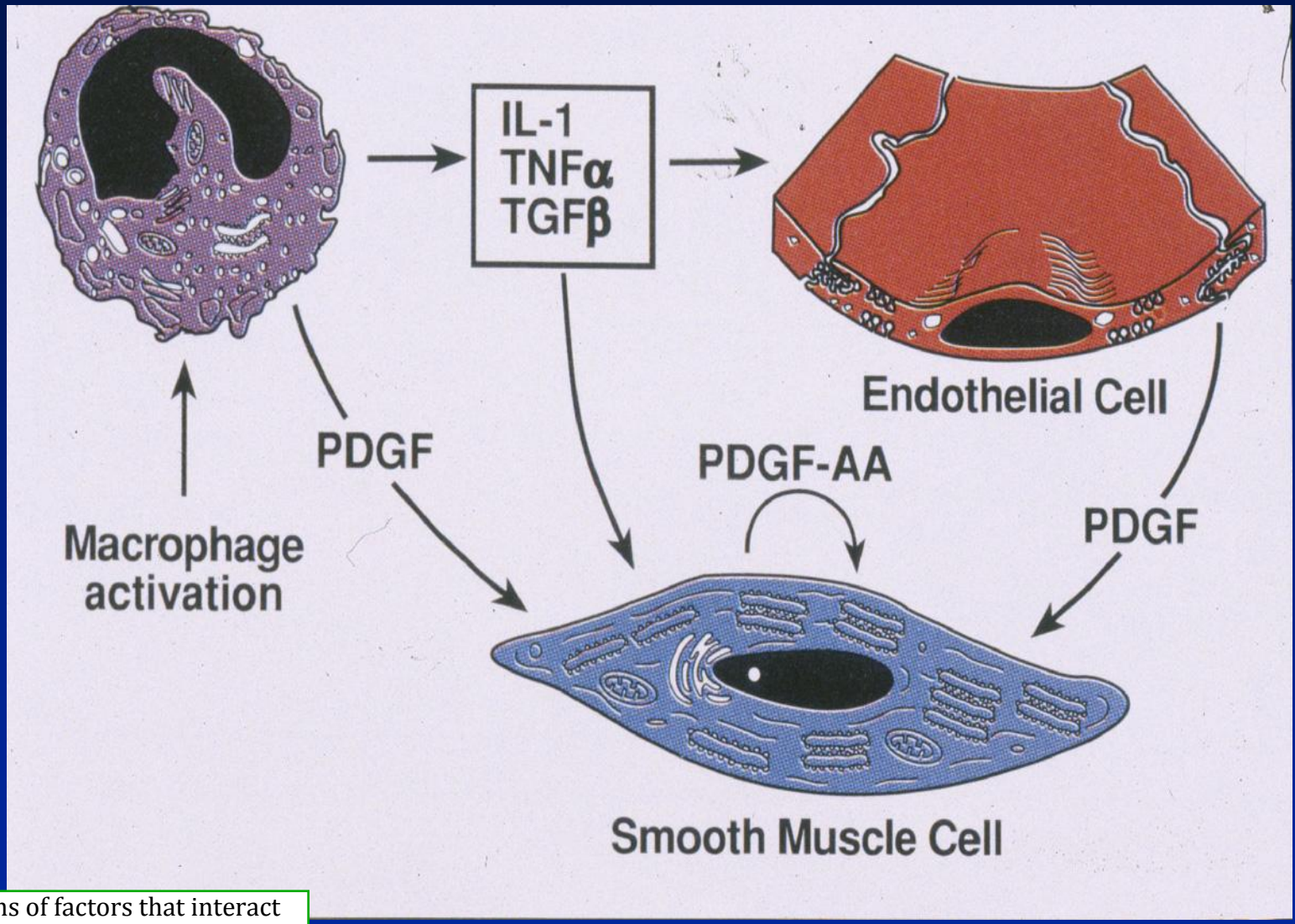


tons of factors that interact with each other.

Read slide

Inflammation: Toll-Like Receptors

TLRs are present in your intima. React to pathogens and thus can trigger advanced atherosclerosis.

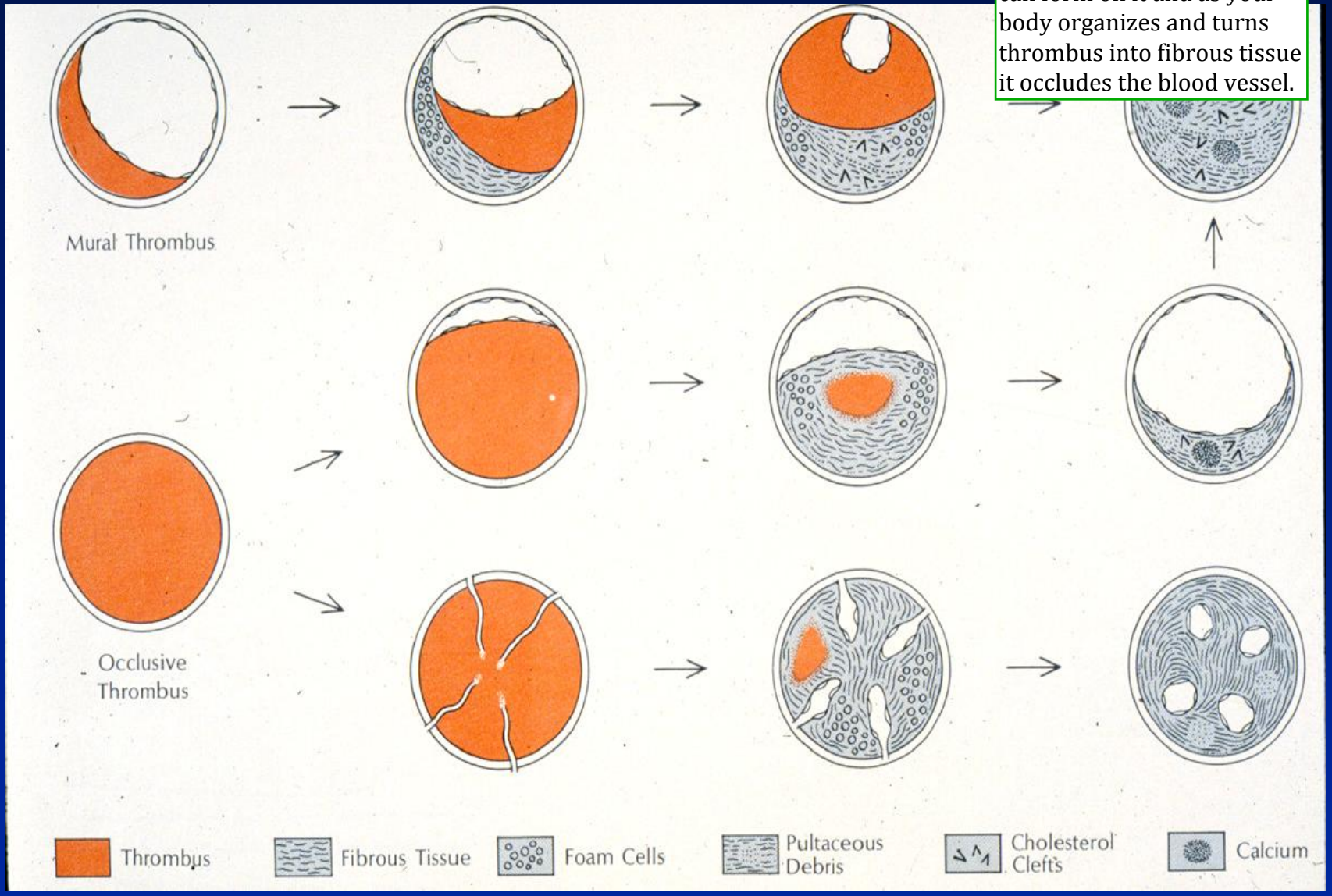
- Immune functions
  - React to pathogens
  - Endogenous ligand stimulation
- Responses
  - Affects lipid transport and macrophage uptake and release (cholesterol)
  - Interact with oxidized lipoproteins
  - Cytokine upregulation
- Cycle
  - Injury can further activate TLR's
- Remodeling
  - May also stimulate arterial remodeling to accommodate progressing atherosclerosis

ongoing topic:it's a CYCLE.

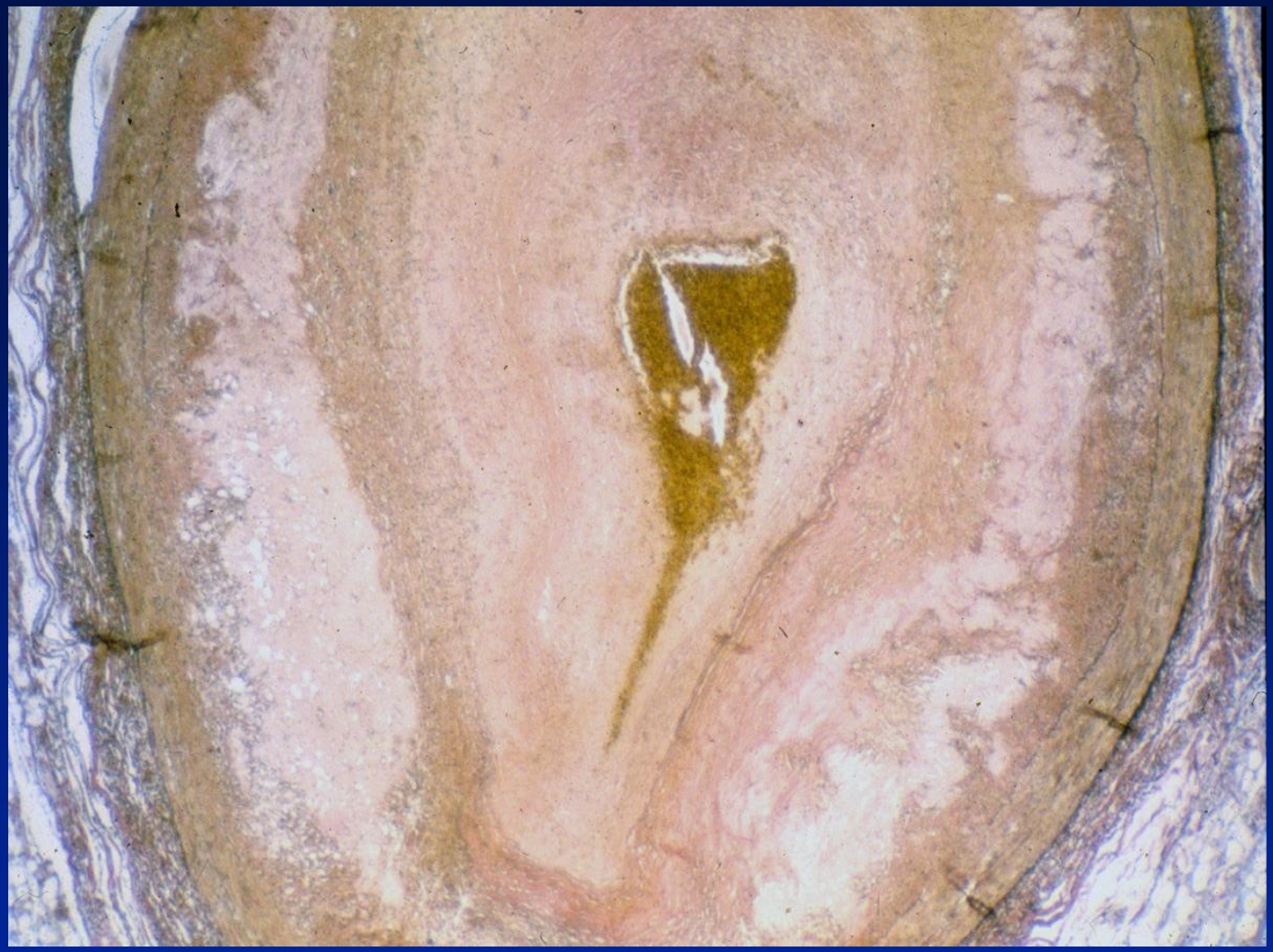
initially they might try to help the artery.

Thrombotic Theory

doesn't speak to how plaque begins to form but once plaque forms a thrombus can form on it and as your body organizes and turns thrombus into fibrous tissue it occludes the blood vessel.



Atherosclerotic plaque with organized mural thrombus



Concentric atherosclerotic plaque, central organized thrombus, small central lumen

had plaque, it became complicated and the process, which included thrombosis, led to severe blockage.

2 "ends of the spectrum"- 1. critical stenosis.

Clinical Atherosclerosis: Luminal Narrowing

Critical Stenosis: Supply < Demand

Symptoms related to flow restriction

- **Episodic** Ischemia

when you require higher blood flow (exercise) you feel symptoms.

  - Heart: Angina Pectoris

chest pain

  - Brain: Transient Ischemic Attacks (± emboli)

further discussed in road show.

  - Extremities: Intermittent Claudication

patients cramp when they walk.

  - Kidneys: Renovascular Hypertension
  - Intestines: Mesenteric Ischemia

not as common.

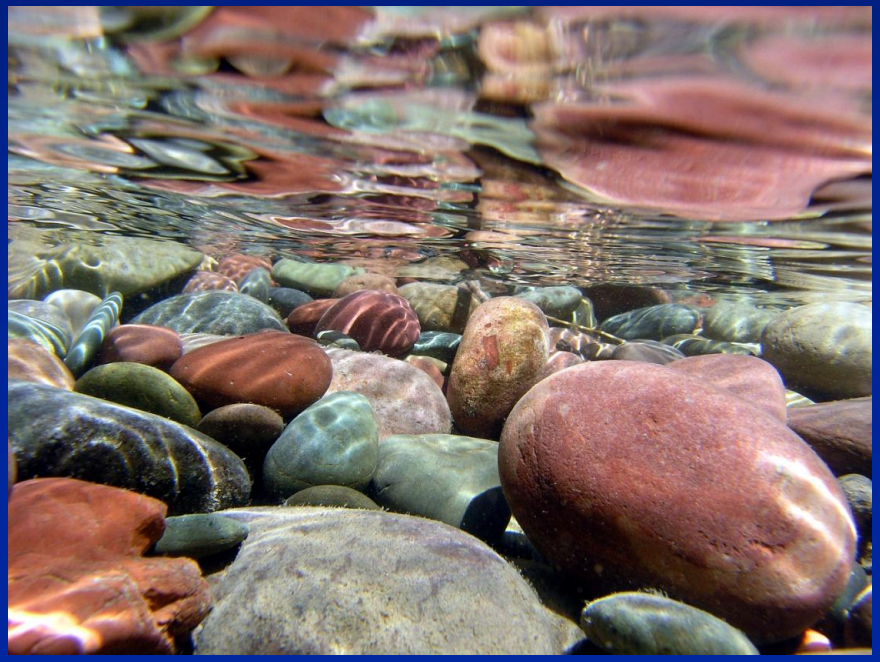
2. acute arterial occlusion

Clinical Atherosclerosis: Plaque Rupture and Thrombosis

Acute Arterial Occlusion - leads to sudden significant or total obstruction of lumen

Most Common Cause: Thrombus superimposed over plaque rupture/erosion site

most important event in atherosclerosis.



usually occurs because of plaque rupture. thrombus occludes lumen.

plaques sit in a dynamic setting like rocks in a stream.

Clinical Atherosclerosis: Plaque Rupture and Thrombosis

Vulnerable Plaque

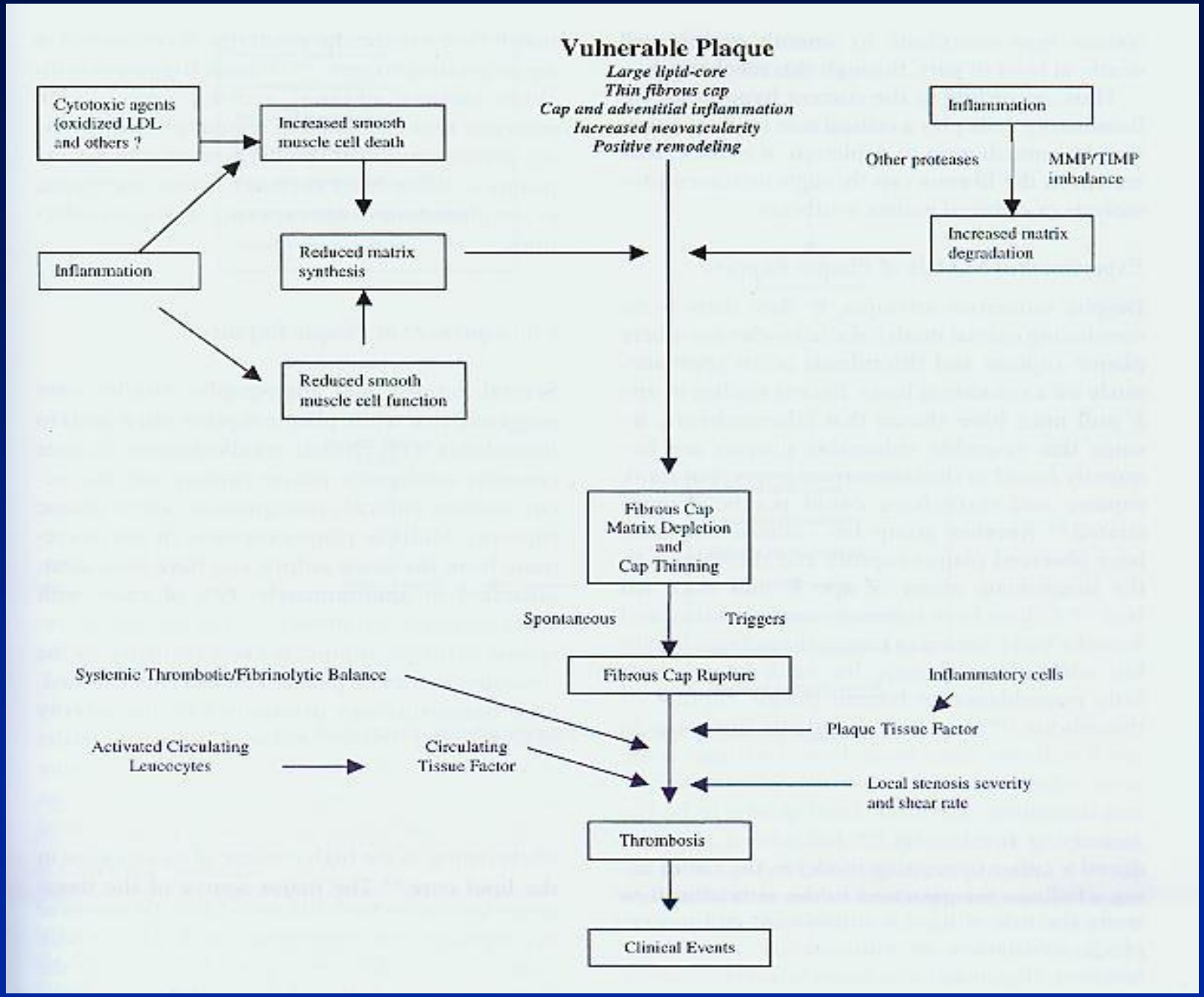
plaques more likely to rupture.

Vulnerability to Plaque Rupture

these are more likely to rupture. _>>>>>>

- Large Atheromatous Core
- Thin Fibrous Cap/Increased Cap Tension
- Inflammation or Foam Cells in Fibrous Cap
- Matrix Metalloproteases
- Cap Fatigue

cap- cells degrading can losen the cap, so do inflammation and foam cells.


Vulnerable Plaque
Large lipid-core
Thin fibrous cap
Cap and adventitial inflammation
Increased neovascularity
Positive remodeling
Cytotoxic agents (oxidized LDL and others ?
Increased smooth muscle cell death
Inflammation
Reduced matrix synthesis
Reduced smooth muscle cell function
Inflammation
Other proteases
MMP/TIMP imbalance
Increased matrix degradation
Fibrous Cap Matrix Depletion and Cap Thinning
Spontaneous
Triggers
Fibrous Cap Rupture
Systemic Thrombotic/Fibrinolytic Balance
Inflammatory cells
Plaque Tissue Factor
Activated Circulating Leucocytes
Circulating Tissue Factor
Local stenosis severity and shear rate
Thrombosis
Clinical Events

Acute Manifestations of Coronary Artery Disease

Angina Pectoris

Myocardial Infarction

Sudden Cardiac Death

Prevalence - 13,000,000

Deaths/Year - 600,000

half of them are sudden. difficult because we are not able to treat for their CAD.

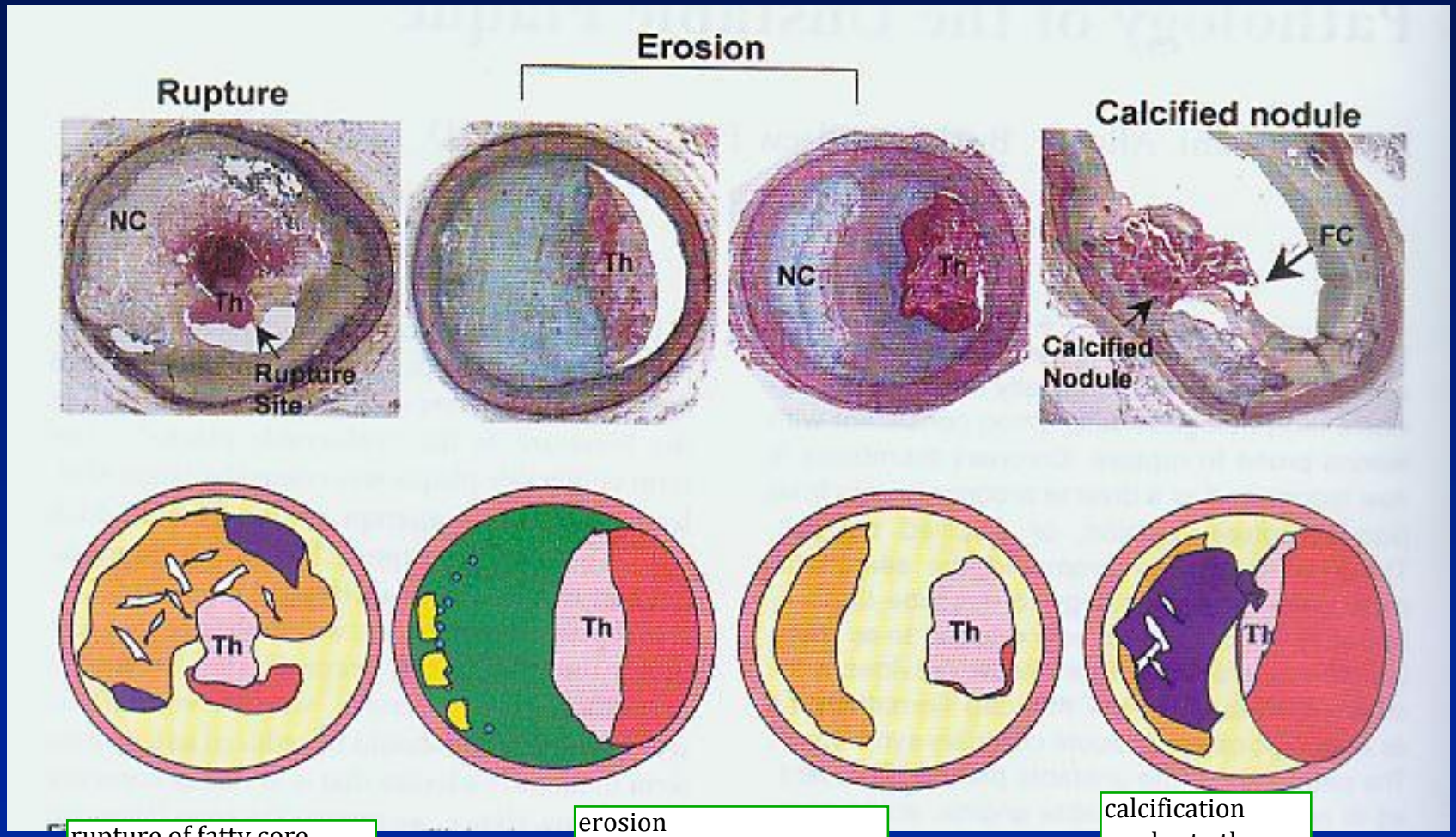
from 600,000 - 800,000 in the US

50% of Deaths are Sudden Cardiac Death (SCD)

50-60% of SCD are First Clinical Manifestation of CAD

10% of Patients with CAD First Present as SCD

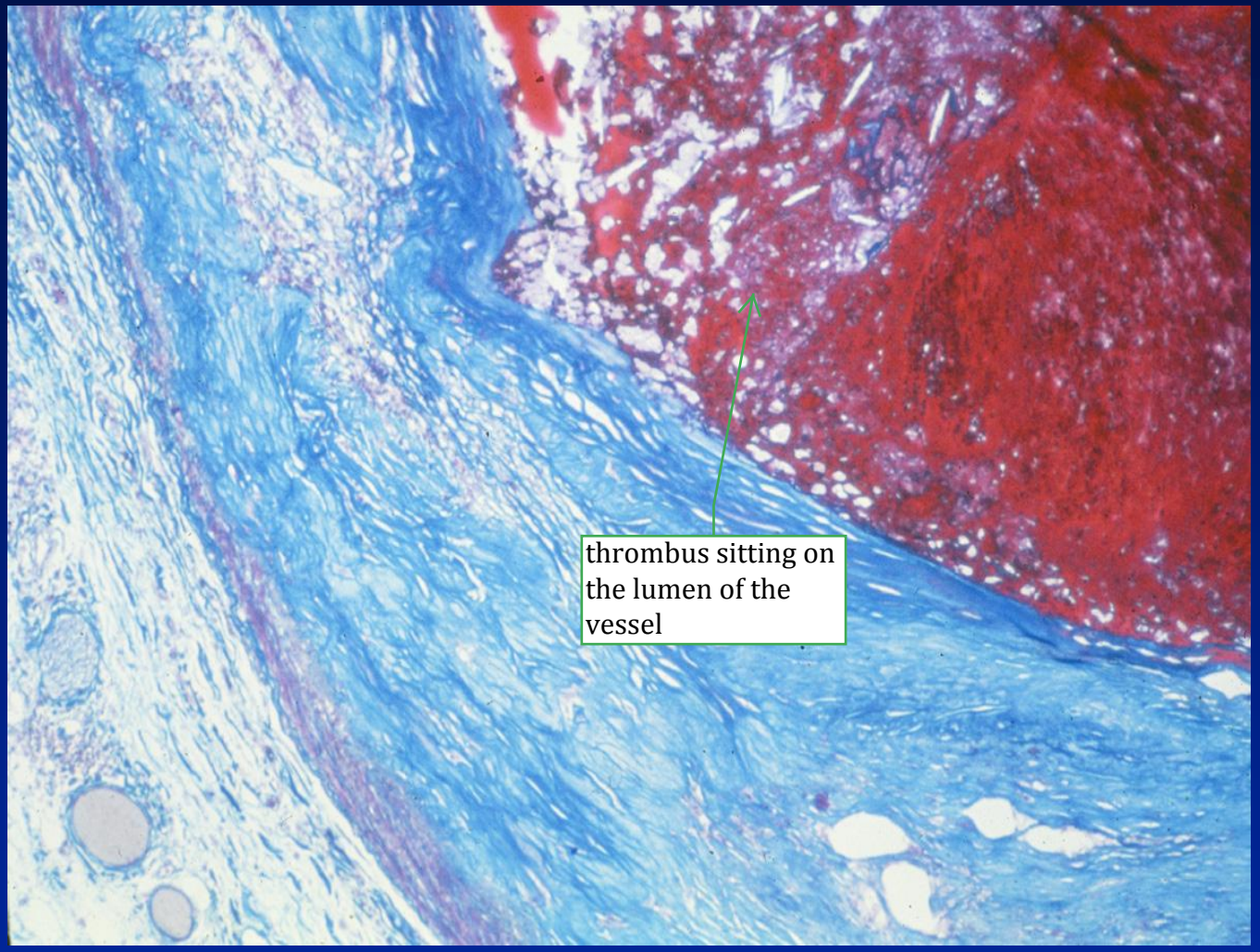
Plaque Rupture



rupture of fatty core

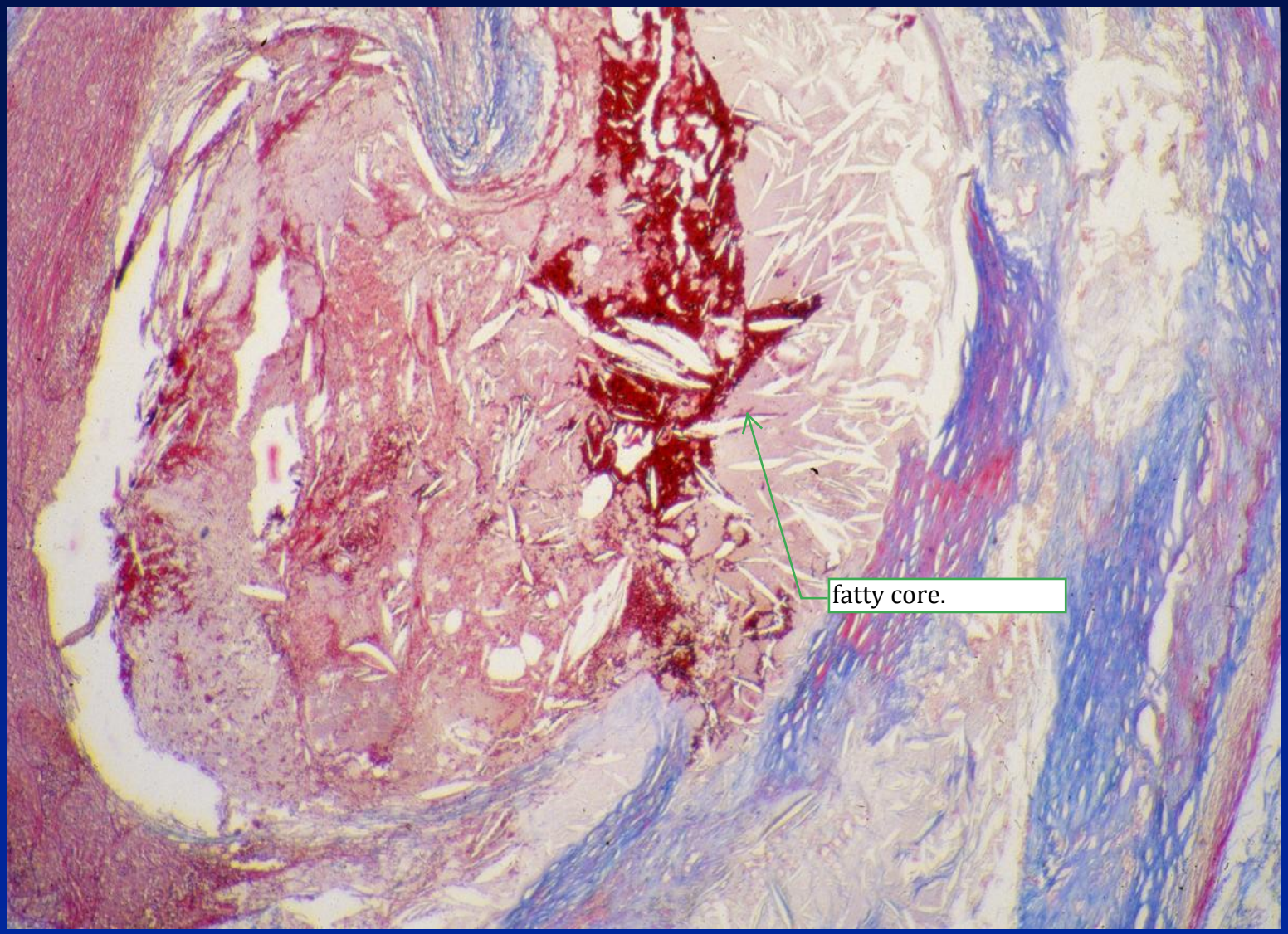
erosion

calcification erodes to the surface-> vulnerable plaque

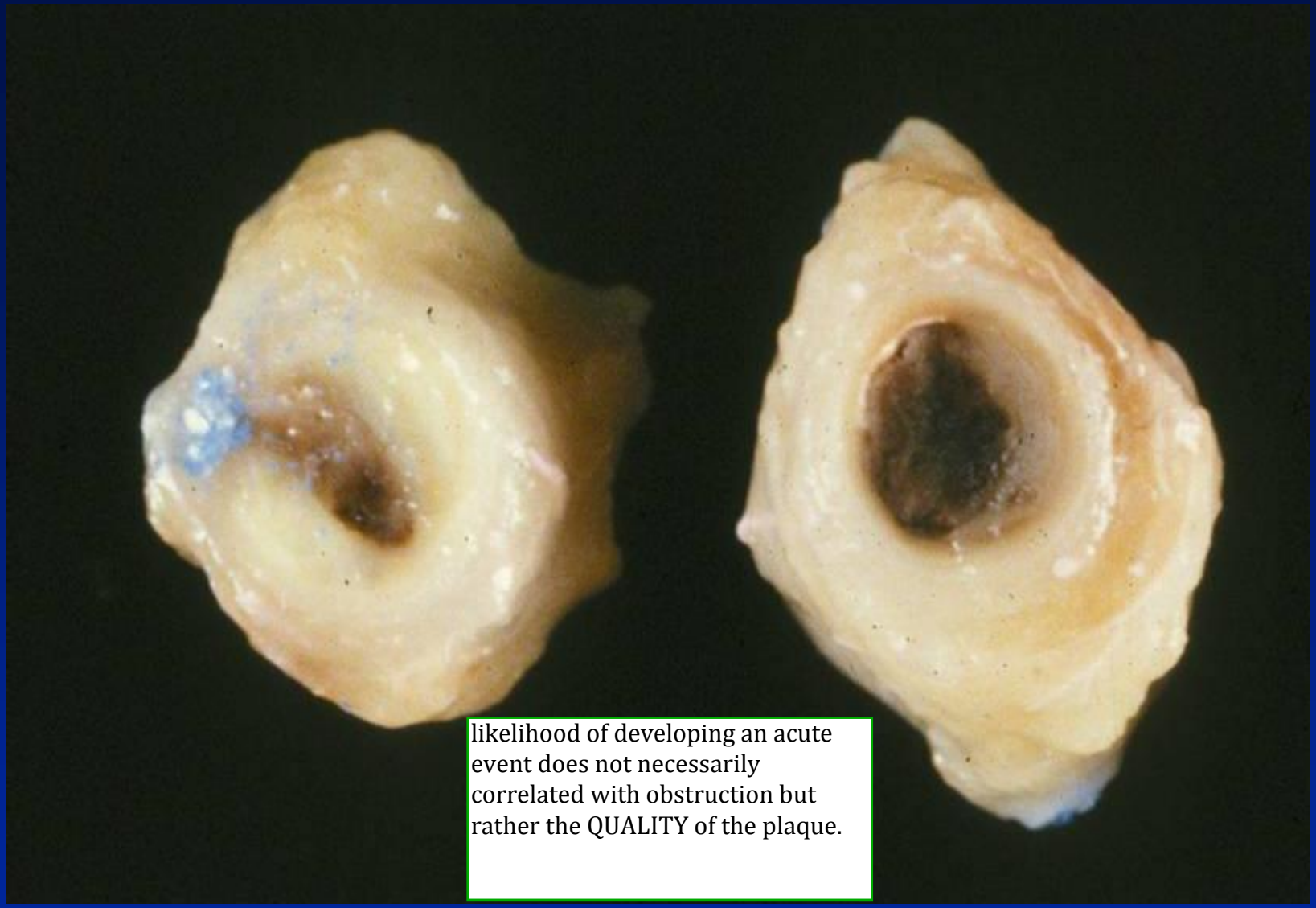


Atherosclerotic Plaque with Acute Thrombus

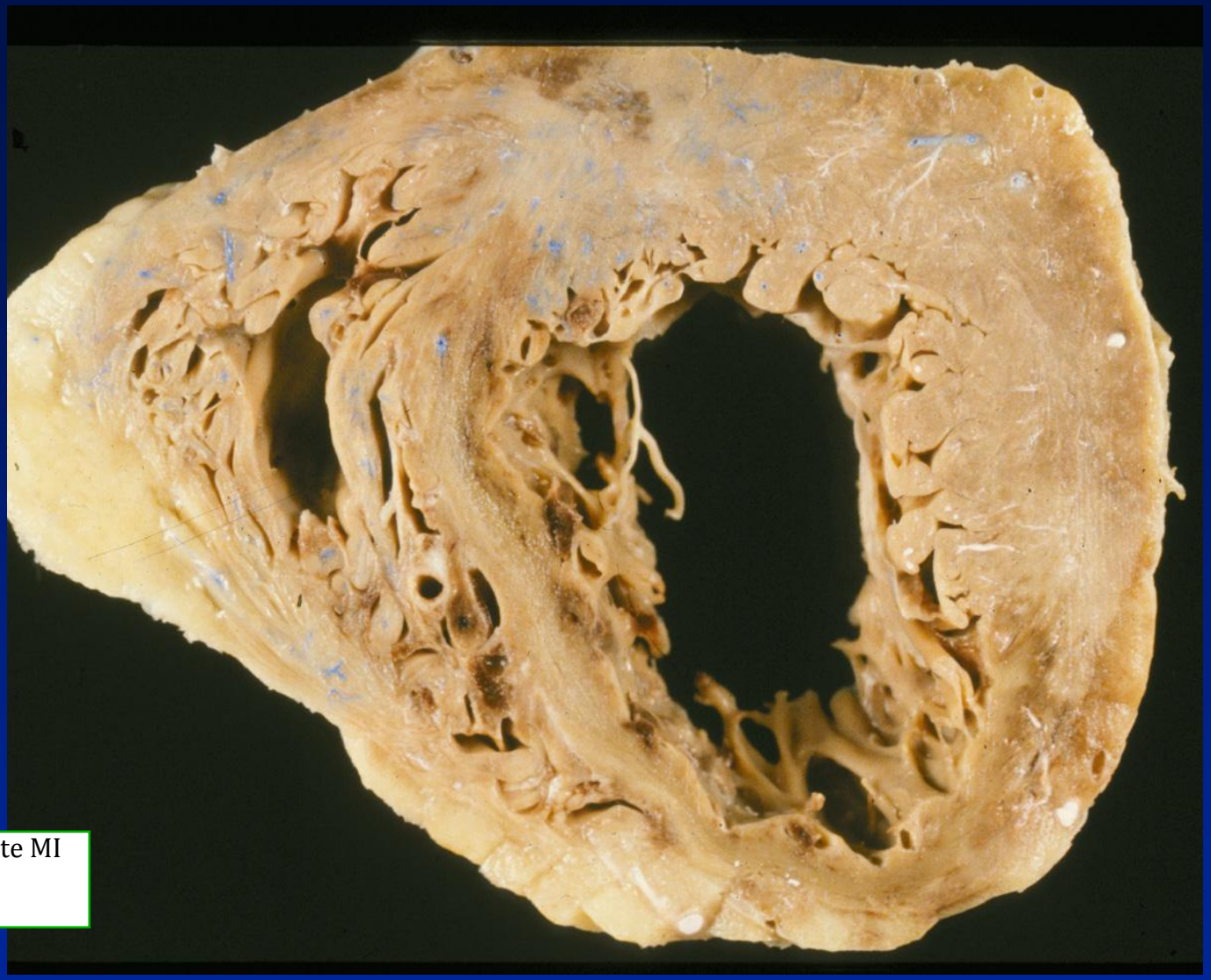
(Plaque Rupture, with lipid debris on left, inducing thrombosis)



Ruptured atherosclerotic plaque (right), superimposed thrombus (left)



Severe atherosclerotic narrowing, superimposed thrombus more distally

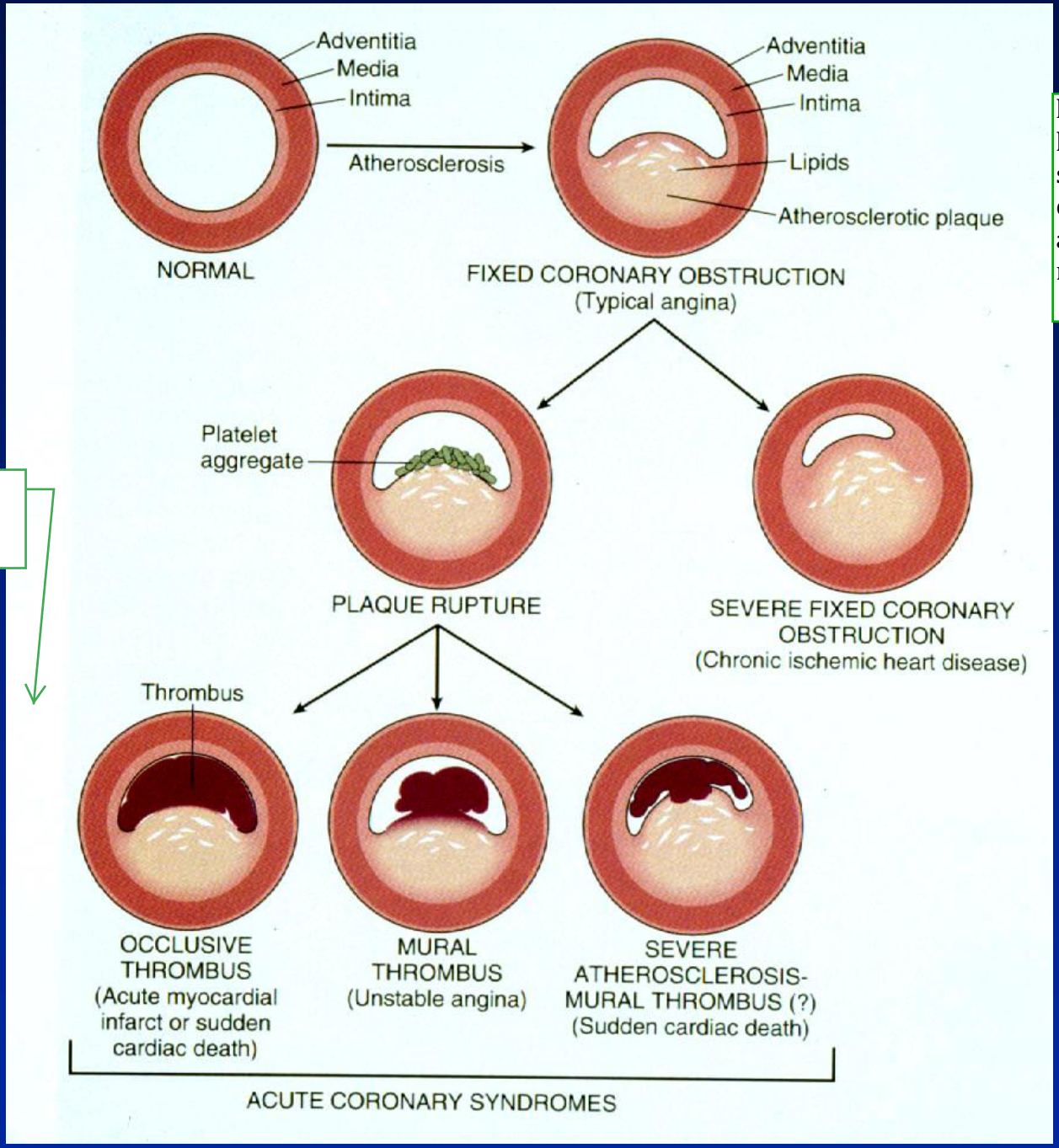


outcomes? acute MI

Anteroseptal Myocardial Infarct due to LAD Thrombus

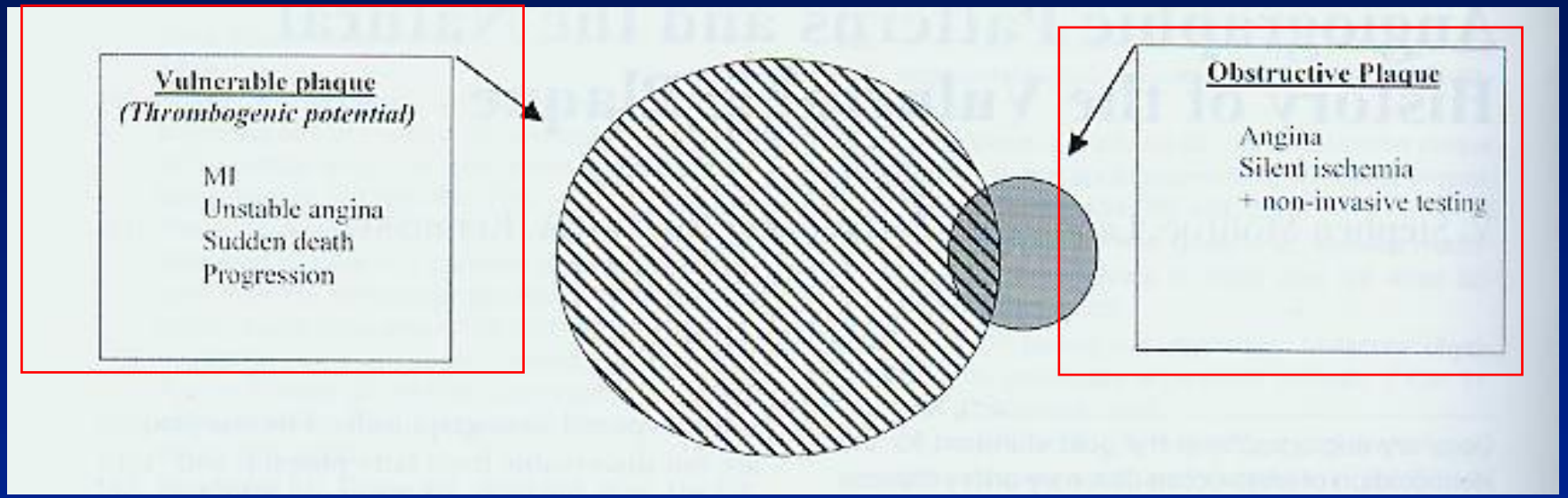
how does plaque lead to symptoms- severe coronary obstruction or acute plaque rupture.

types of thrombi and their clinical correlations



read the slide. but remember severity does not necessarily equal acute event risk.

Clinical Effects



- **Plaque Rupture vs. Obstructive Stenosis**
- **Severity of stenosis does not necessarily equal vulnerability or acute event risk at that focus**

Stress Test Raises Questions About Bank Capital

The Obama administration's announcement that it will begin a series of stress tests on Wednesday on the biggest financial institutions …

Bloomberg.com

Obama Seeks to 'Clean Out the System' with Bank Stress Test

Stress tests: demonstrate symptoms of flow restriction when requirements increased

Designed to demonstrate ischemia due to Critical Stenosis through exercise or pharmacology

Predicts severity of stenosis, not plaque vulnerability

stress test looks at critical stenosis not quality- patient can do great on stress test and drop dead.

Interventional Frontier$

- Reduced Lipid content
- Reduced Inflammation
- Reduced Neovascularity
- Reduced Matrix Metalloproteinase Activity
- Reduced tissue Factor Activity
- Smooth Muscle Cell Activity/death
- Increased collagen content/Strength

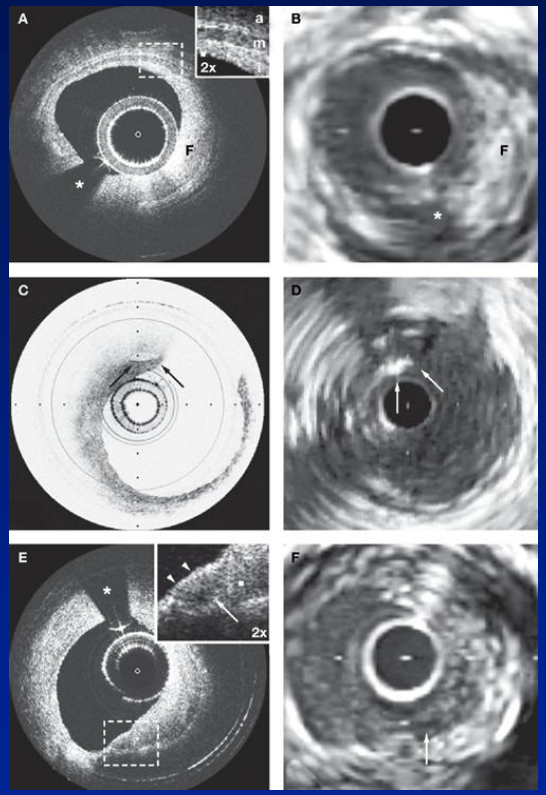
if you interact here you make a lot of $$ $$$$$.

- Identification Techniques: MR, IVUS, OCT

way to see the type of plaque.

Figure 3 *In vivo* optical coherence tomography images of different coronary plaque types compared with intravascular ultrasonography of the corresponding sites

IV ulstrasound and OCT- catheter goes through artery and can look at plaque from inside



ultrasound

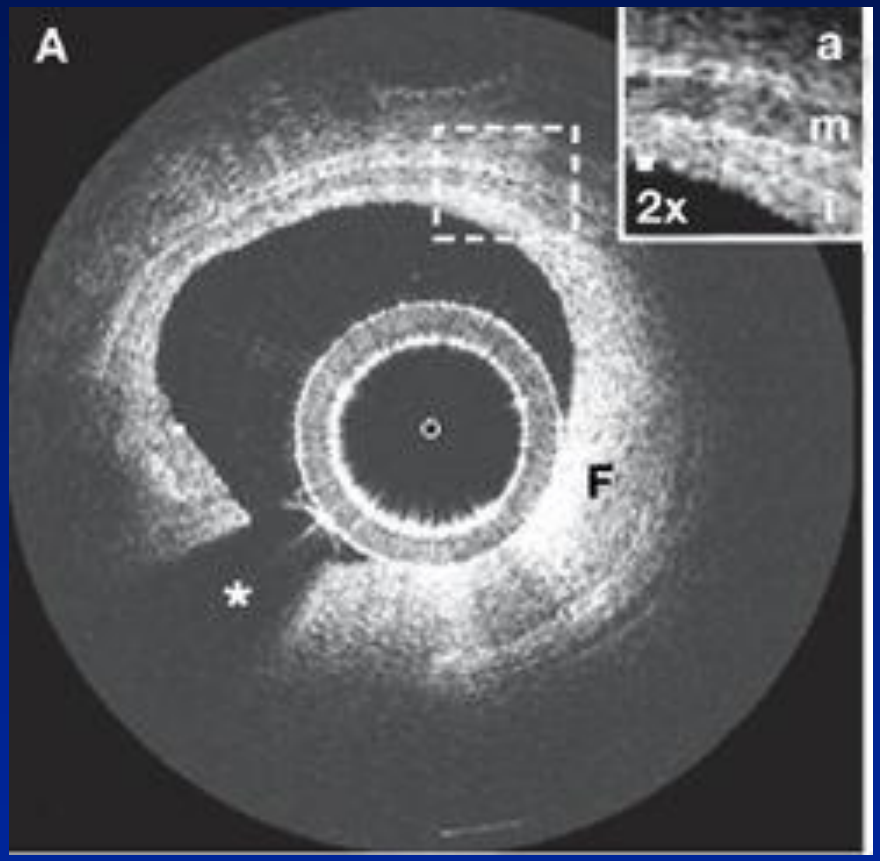
oct

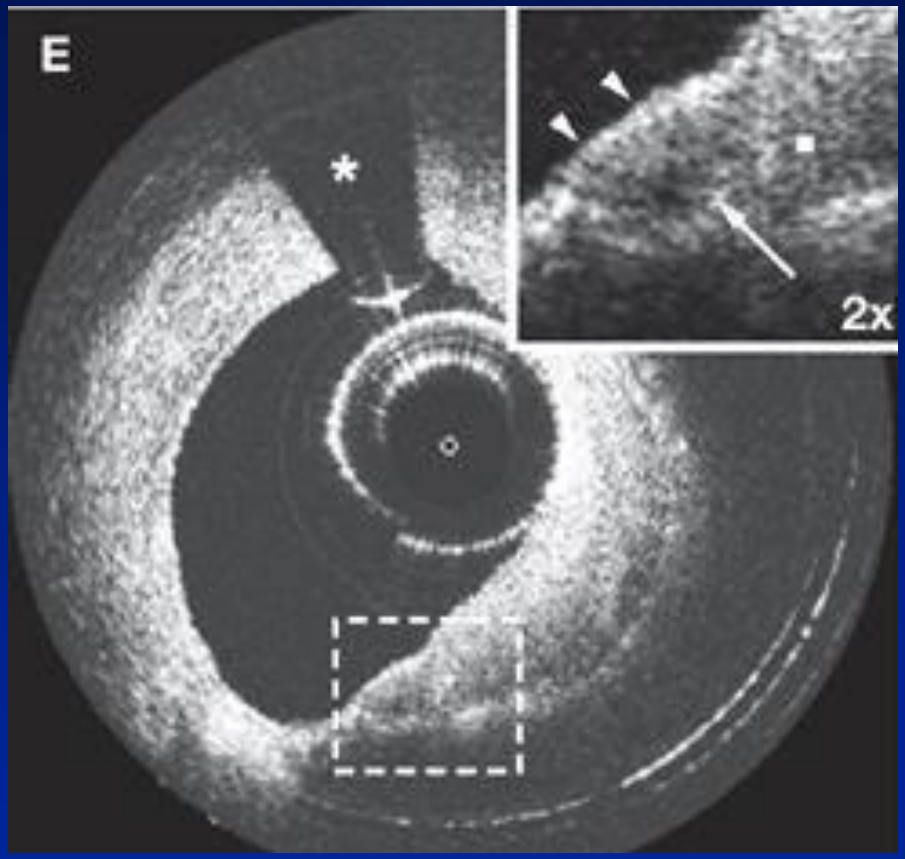
both show you the specific amount of blockage.

from Jang IK *et al*. (2002) Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *J Am Coll Cardiol* **39**: 604–609.

nature CLINICAL PRACTICE CARDIOVASCULAR MEDICINE

OCT





Fibrous Plaque

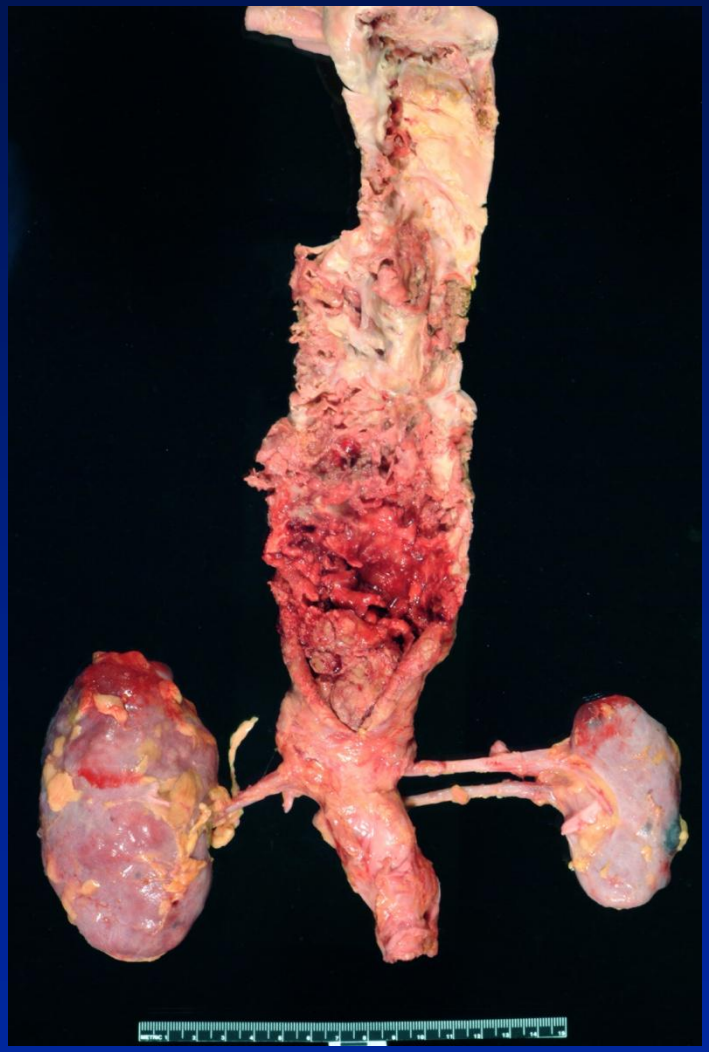
Atheromatous Plaque

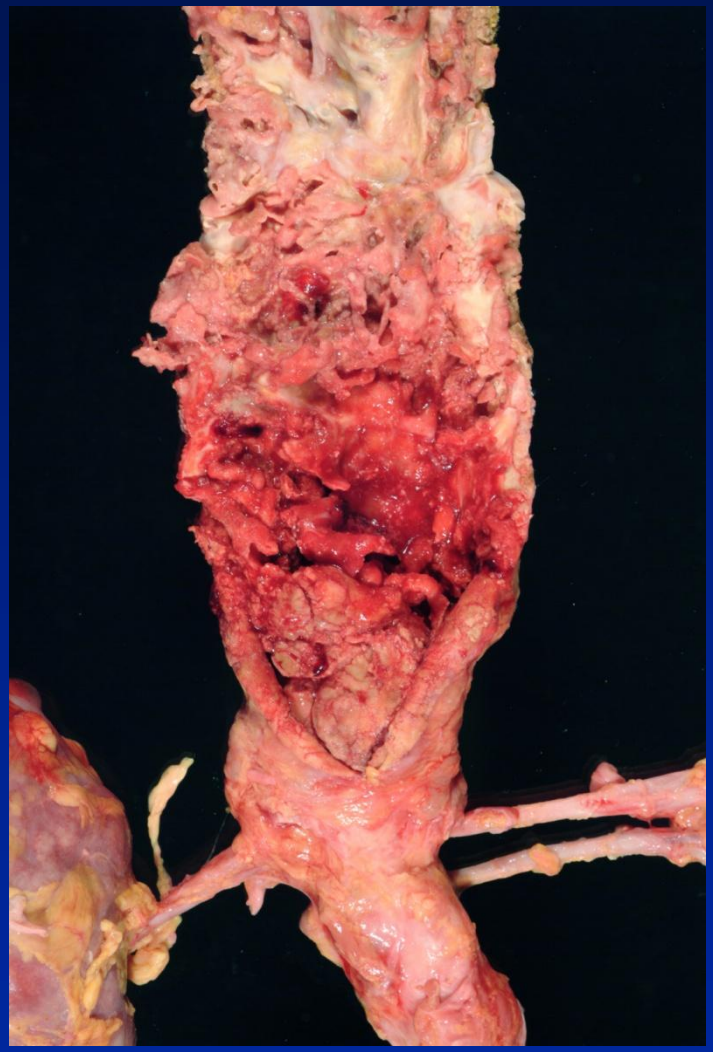
although this plaque is only 40% lesion, it will probably be followed up by intervention

Atherosclerosis:

Other Complications

Thrombosis



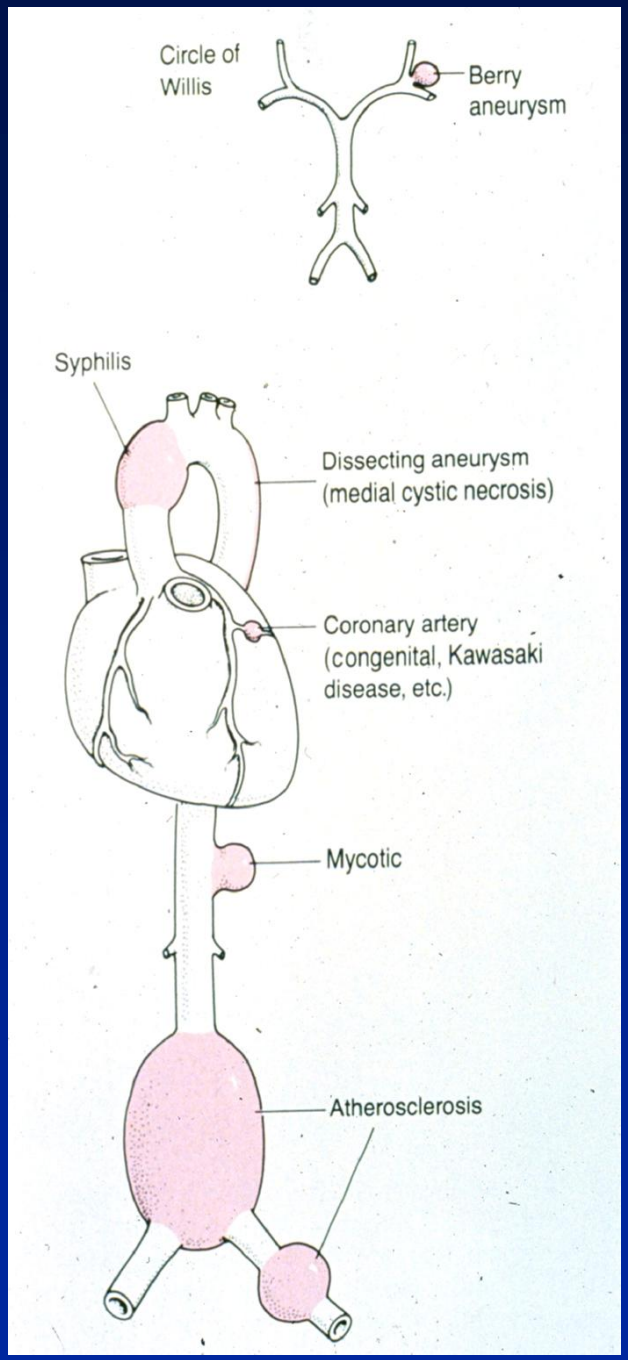


thrombosis in entire aorta. kidneys are "unhappy looking". if disease goes on long enough you can get collateral flow to lower extremities so ppl walk around with this.

Aneurysms

In the vascular system, an aneurysm is an area of weakness in the wall of a blood vessel that typically results in bulging due to arterial blood pressure

in the media.



Etiology: Medial Injury or Weakness

Congenital / Genetic

- Ex: Polycystic Kidney Dz

Marfan's disease, too.

Atherosclerosis

when it goes through the media.

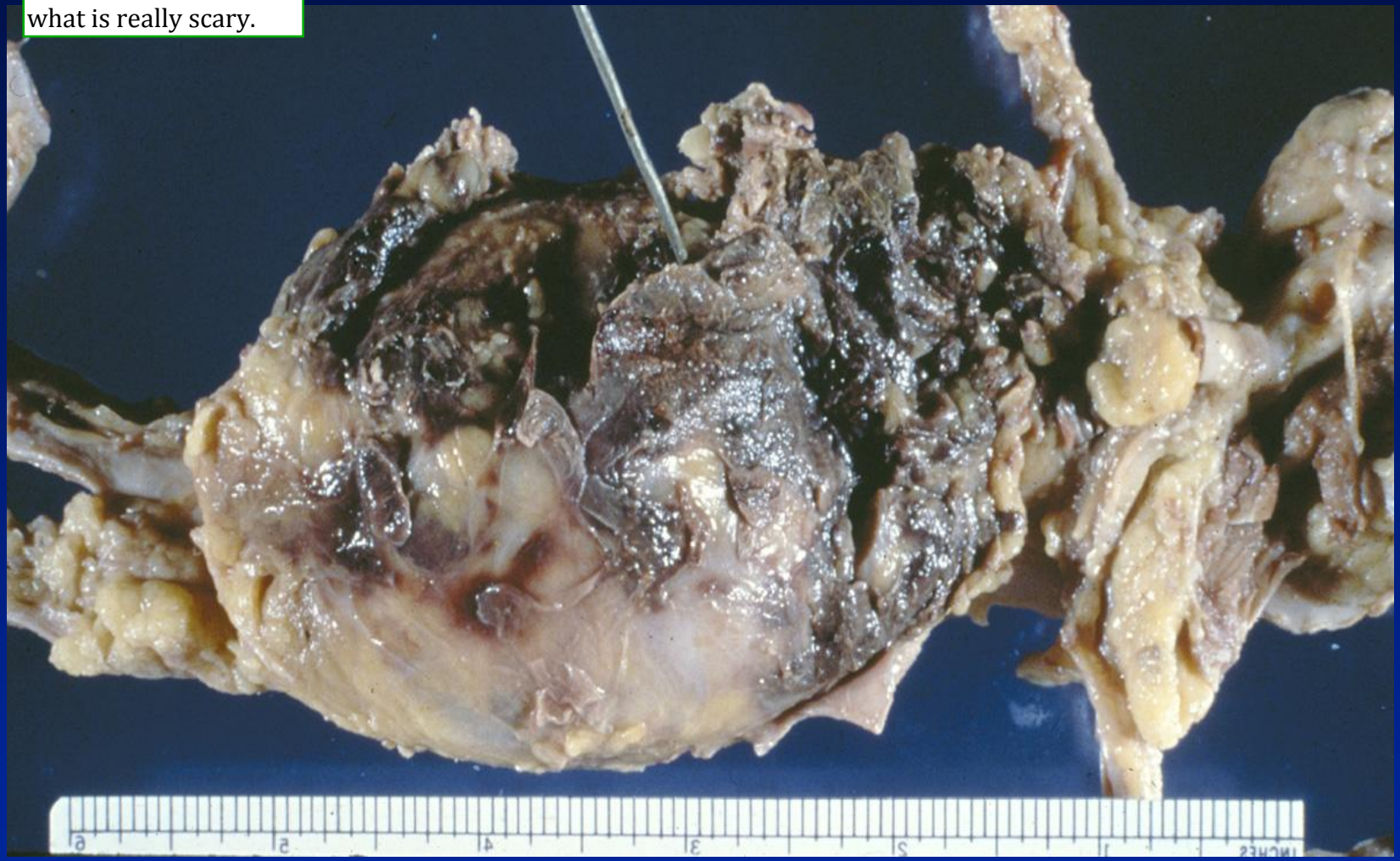
Infectious

Autoimmune

can directly destroy the wall and lead to aneurysm.

connective tissue disorders or lupus, arthritis.

possible rupture is what is really scary.



Atherosclerotic aortic aneurysm (renal arteries on right, bifurcation on left), which has ruptured (see probe)

Syphilitic Aortitis
(Obliterative Endarteritis)

Aortic Aneurysm

Aortic Valve Insufficiency

Coronary Stenosis

*** Late Complications***

syphilis attacks small vessels that supply bigger ones (vaso vasorum). end up with a fibrous scar that over time stretches.

Aortic Dissection

"Dissecting Aneurysm"

dissection- get a tear in a wall and it propagates to the media and adventitia.

when we are out jogging we probably create micro-dissections ever day but our bodies can handle it.

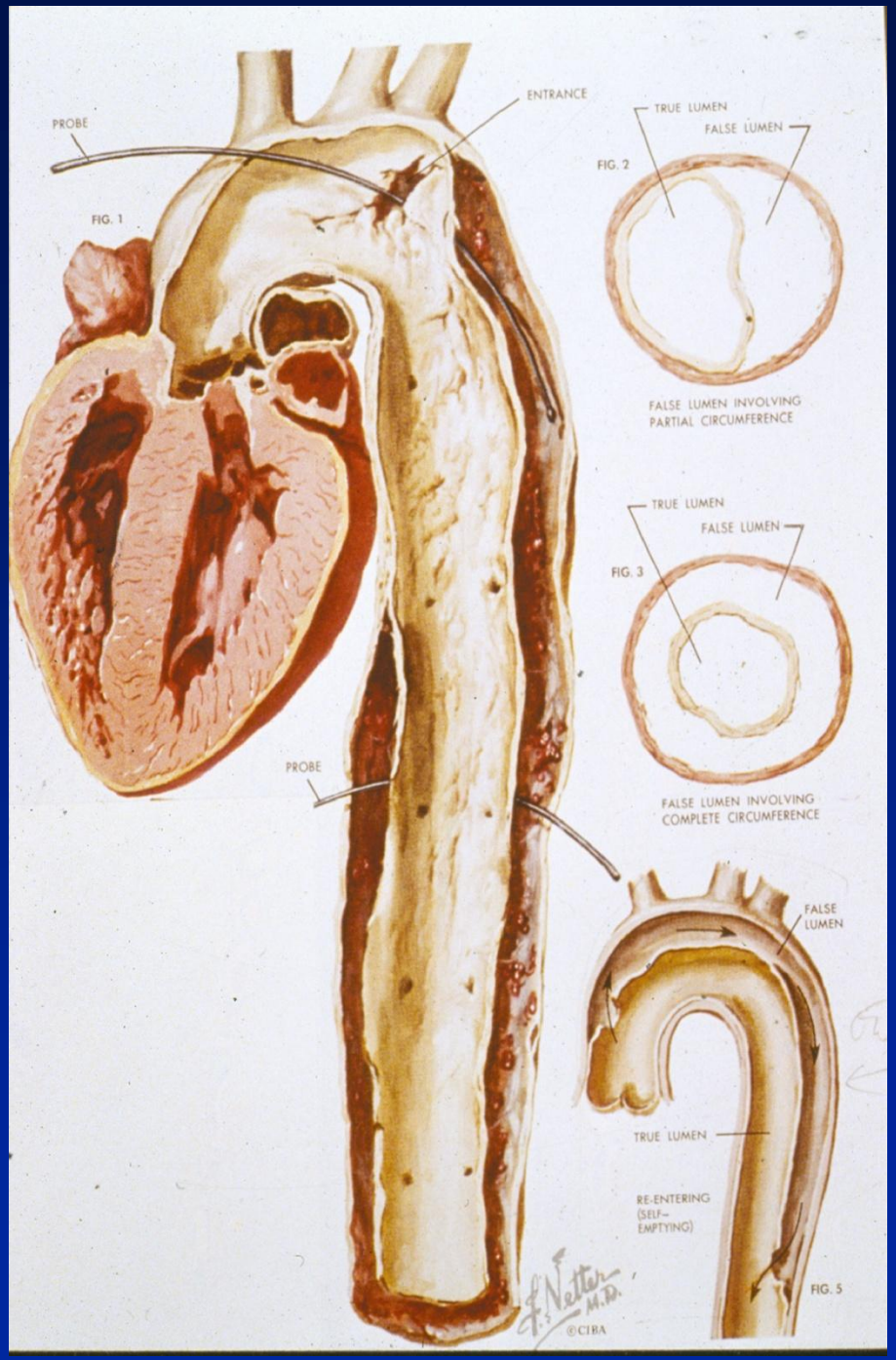
- **Cystic Medial Necrosis (Degeneration)**
  - – Loss of elastin fibers and smooth muscle
  - – Replacement with Ground Substance
  - **Isolated lesions**
  - **Marfan's Syndrome**
    - **– Fibrillin-1 gene on chr 15**

these patients often have a connective tissue disorder.cystic tissue necrosis. replace elastin fibers with ground substance.

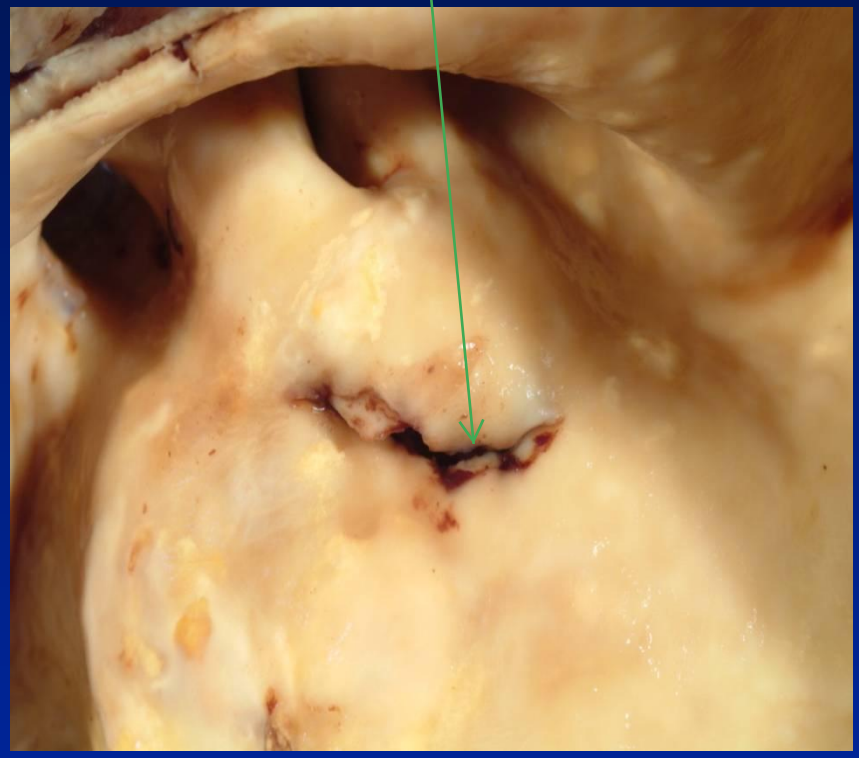
Hypertensive injury

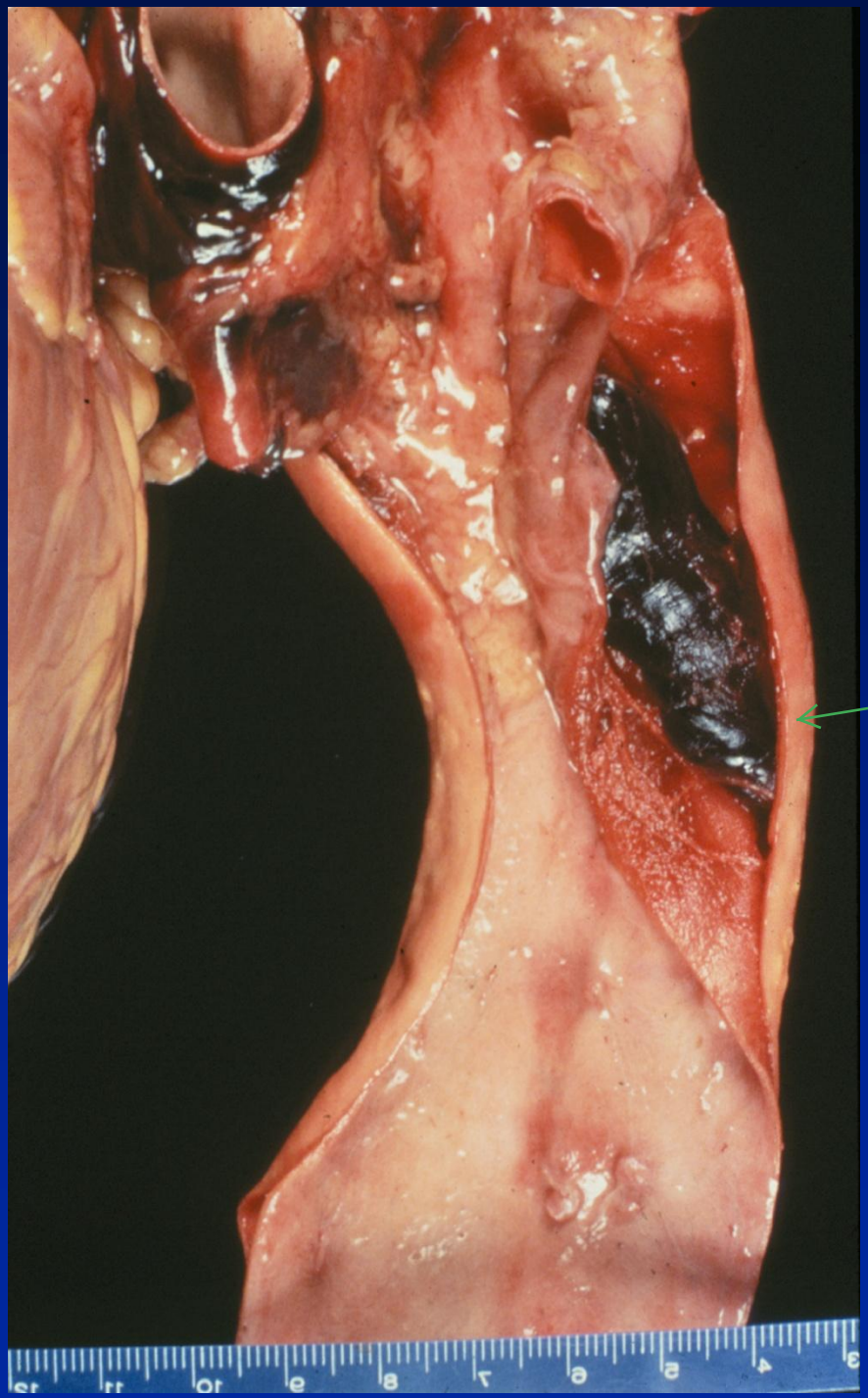
– Essential, "pharmacologic"

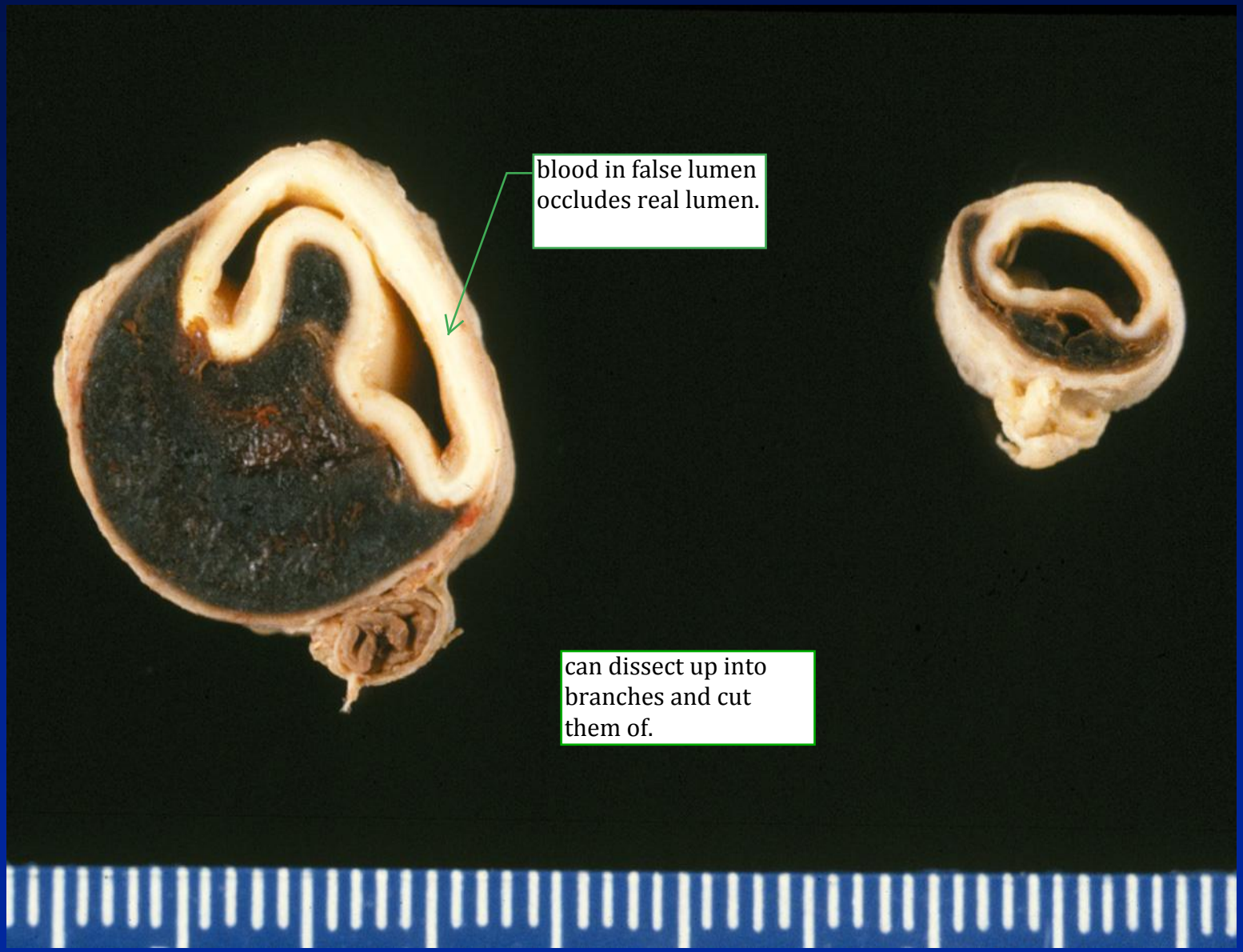
cocaine. high systolic BP leads to tears.



tear lets blood in and dissects through.

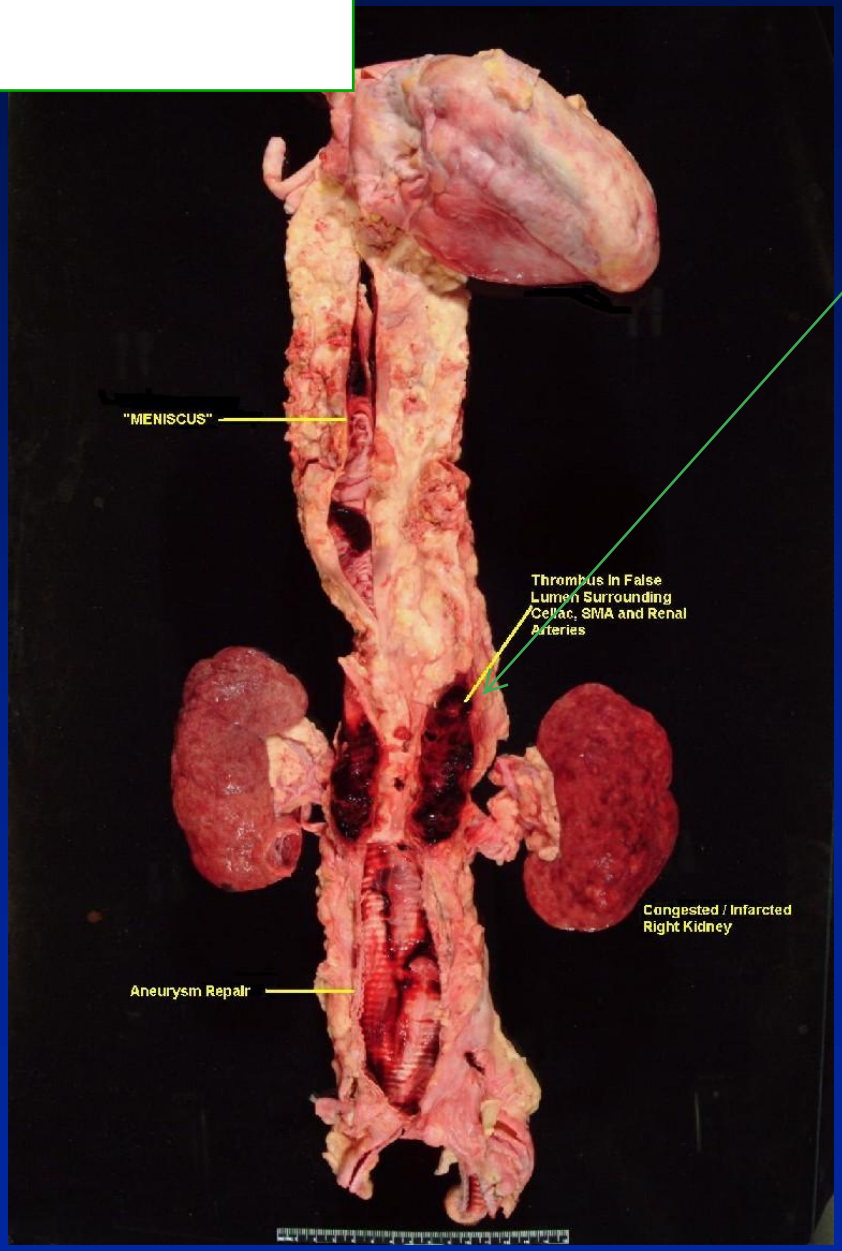



blood in lumen.

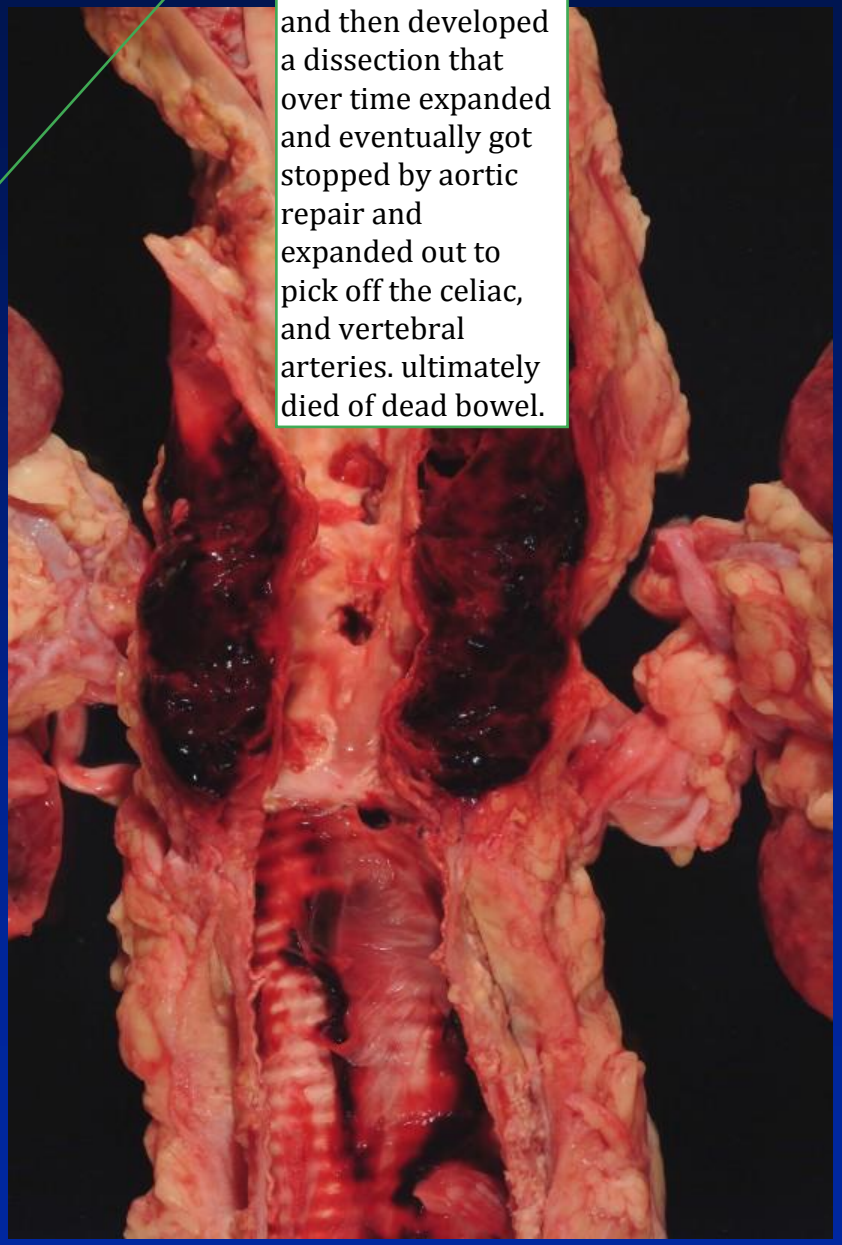

blood in false lumen occludes real lumen.
can dissect up into branches and cut them of.

saw this in road show.

Dissection



abdominal aortic aneurysm was originally repaired and then developed a dissection that over time expanded and eventually got stopped by aortic repair and expanded out to pick off the celiac, and vertebral arteries. ultimately died of dead bowel.



Any Questions?