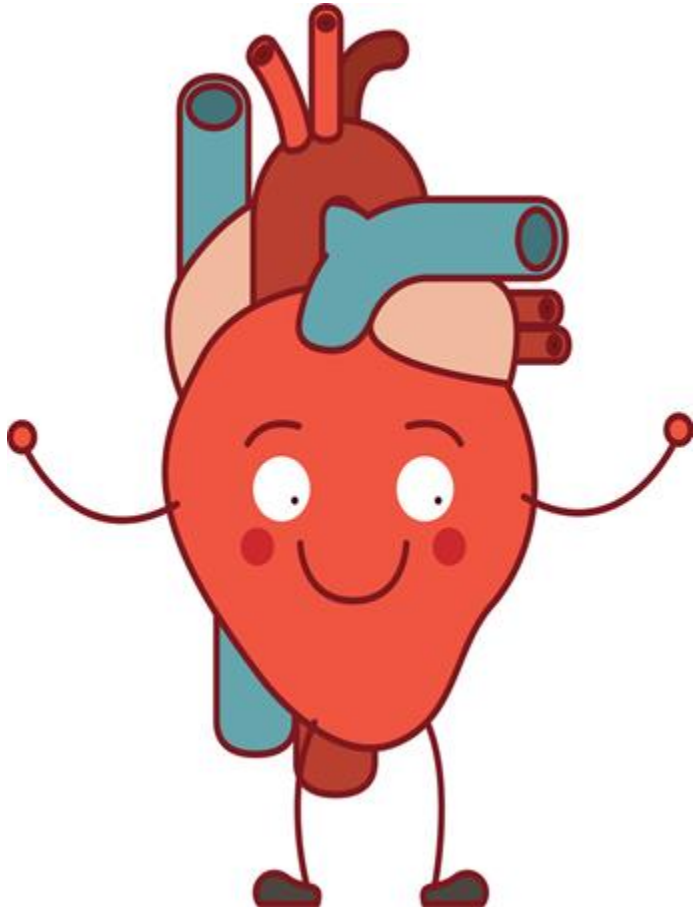

Arteriosclerosis
Cardiovascular Module 2024

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2024

Pathogenesis of atherosclerosis

- **Starts with chronic EC injury:** resulting in increased endothelial permeability. Also, dysfunctional injured endothelial cells **express adhesion molecules, e.g., (VCAM-1)** that binds **monocytes & T cells,** followed by their migration into the intima.

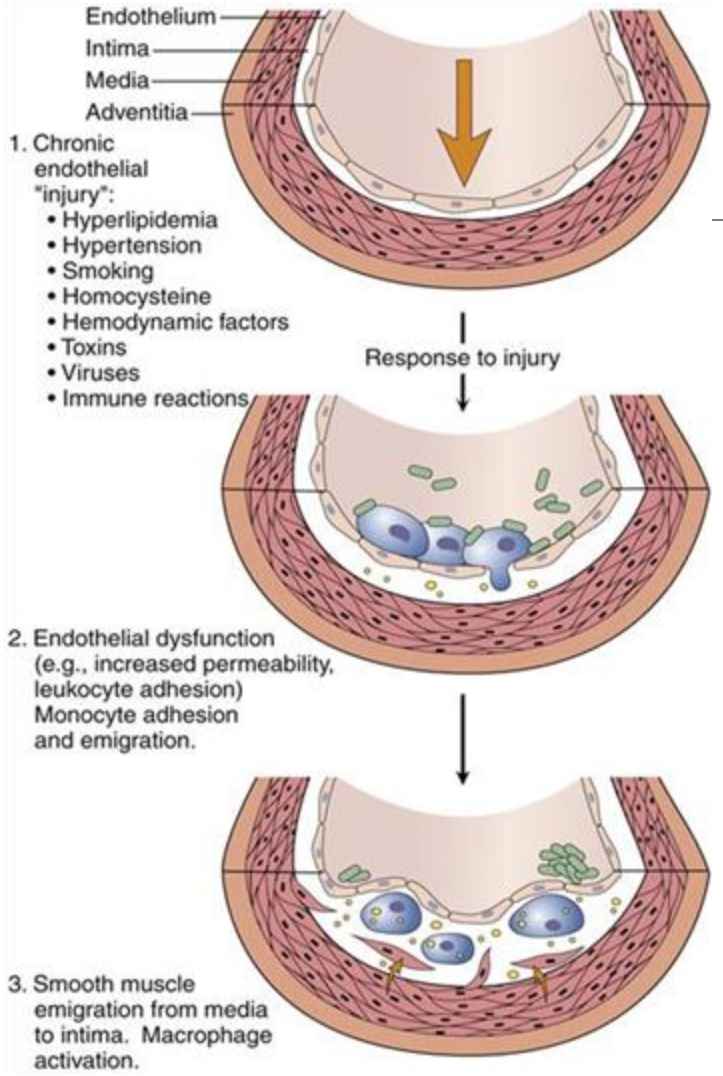
- **Accumulation of the lipoproteins**: **LDL and oxidized forms of LDL**

- **When monocytes** migrate into the intima, they transform into macrophages & foam cells (foam cells are macrophages engulfing oxidized LDL)

- Factors released during this process **induces SMC recruitment from media**

Pathogenesis of atherosclerosis

- Lipid (oxidized LDL) accumulation in both cells macrophages & SMCs → **fatty streaks**
- Some of which die, releasing lipid & necrotic debris
- Activated macrophages produce **free radicles**, thus, aggravating LDL oxidation
- The **activated T lymphocytes** elaborate INF-γ, which → **stimulate macrophages, ECs & SMCs** to release **growth factors GF**
- **GF** promote SMC proliferation & ECM synthesis (mainly collagen) → **stabilizes the atheroma, and produces a fibrous cap** covering the central core of lipid-laden cells & fatty debris



Atherosclerosis

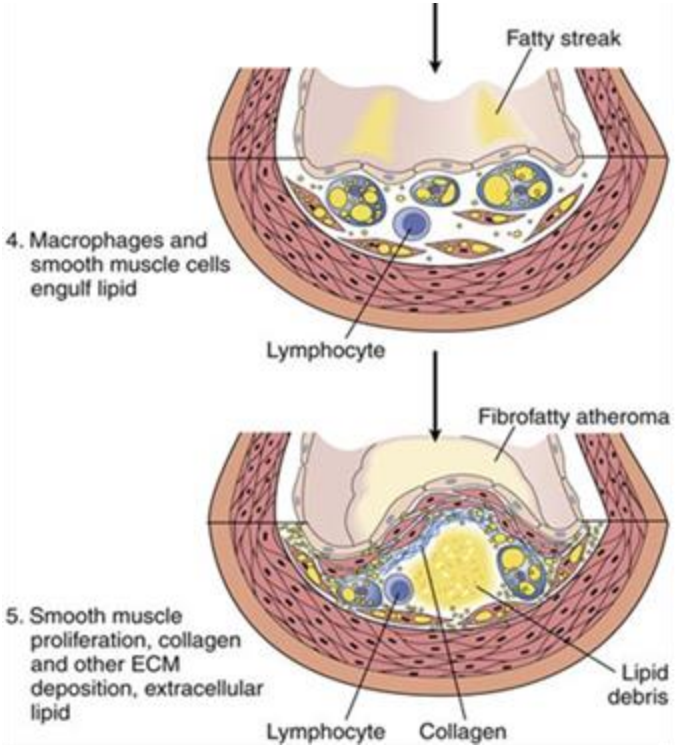
Evolution of arterial wall changes in the **response to injury hypothesis**.

1 Normal.

2. Endothelial injury with adhesion of monocytes & platelets to sites where endothelial has been lost

3. Migration of monocytes & smooth muscle cells (SMC) into intima.

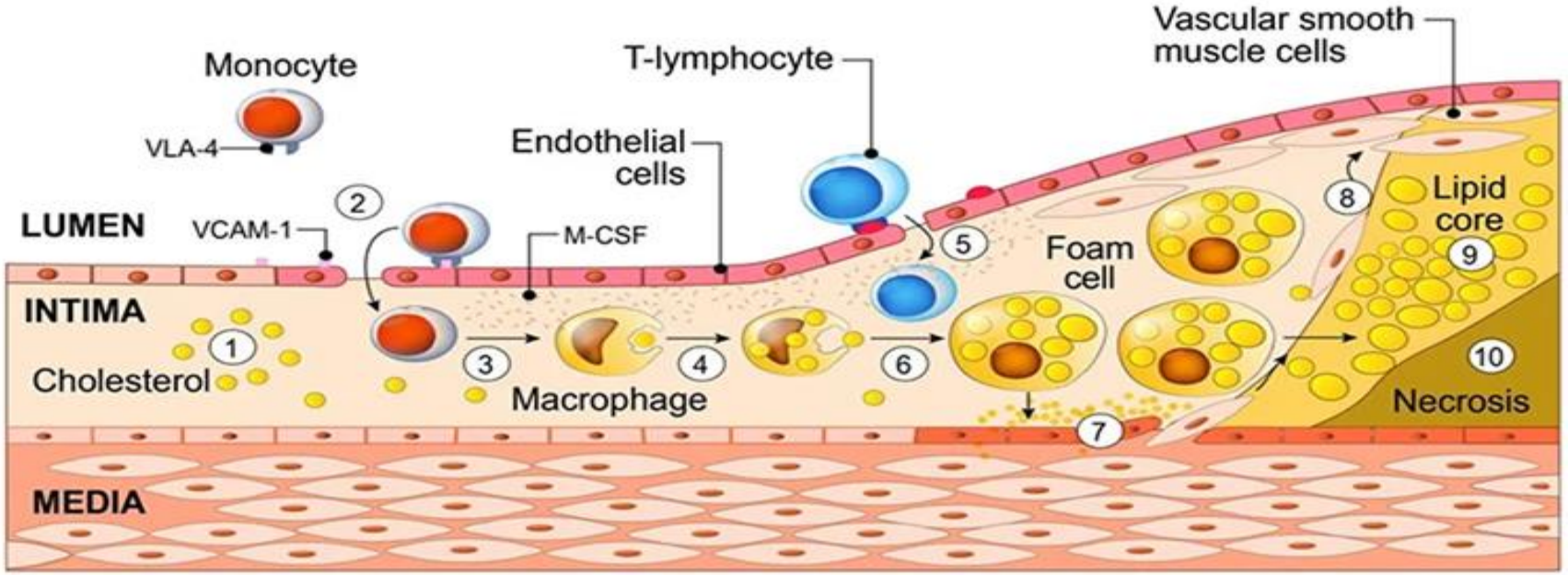
Atherosclerosis



4. SMC proliferation in intima with extracellular matrix (ECM) elaboration

5. Well-developed atheromatous plaque

Pathogenesis of atherosclerosis



Pathogenesis of atherosclerosis

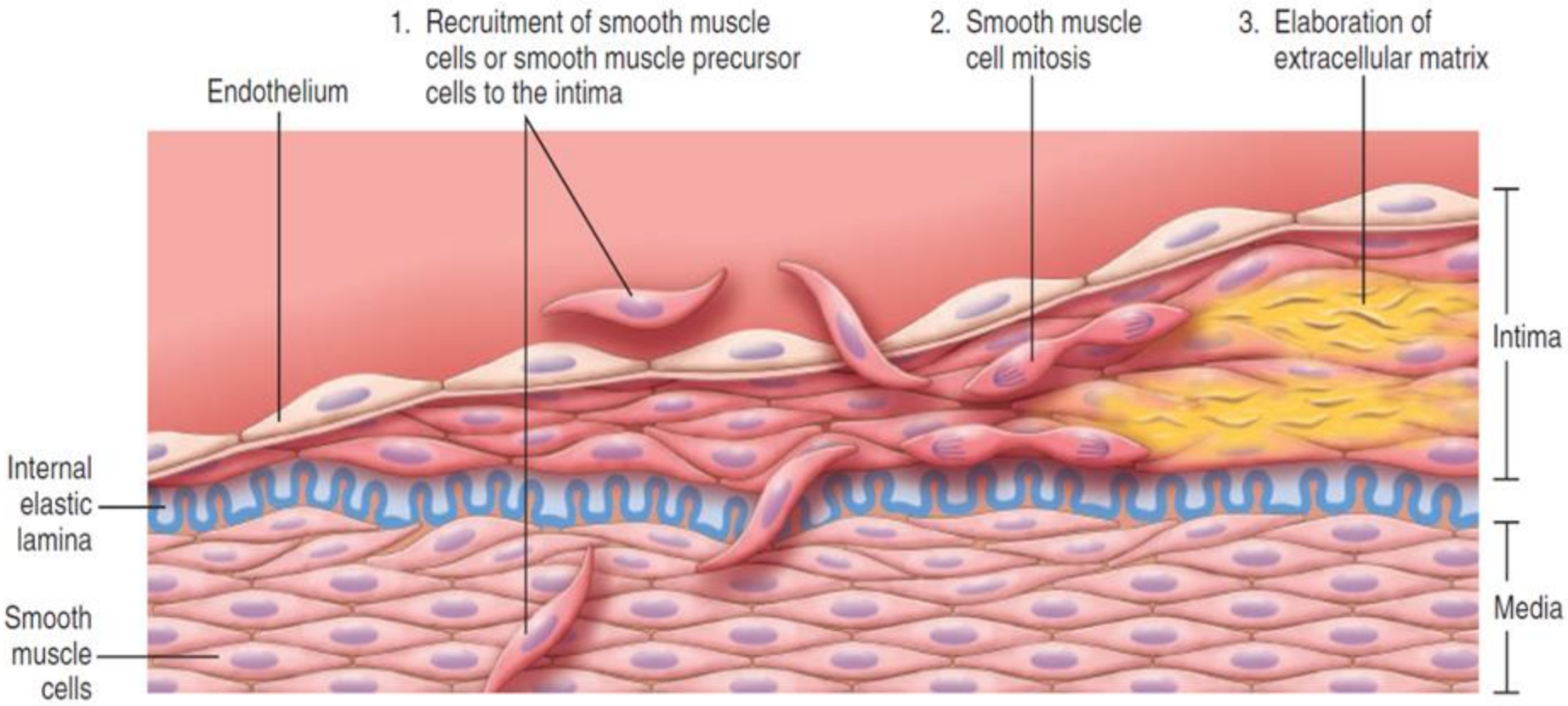
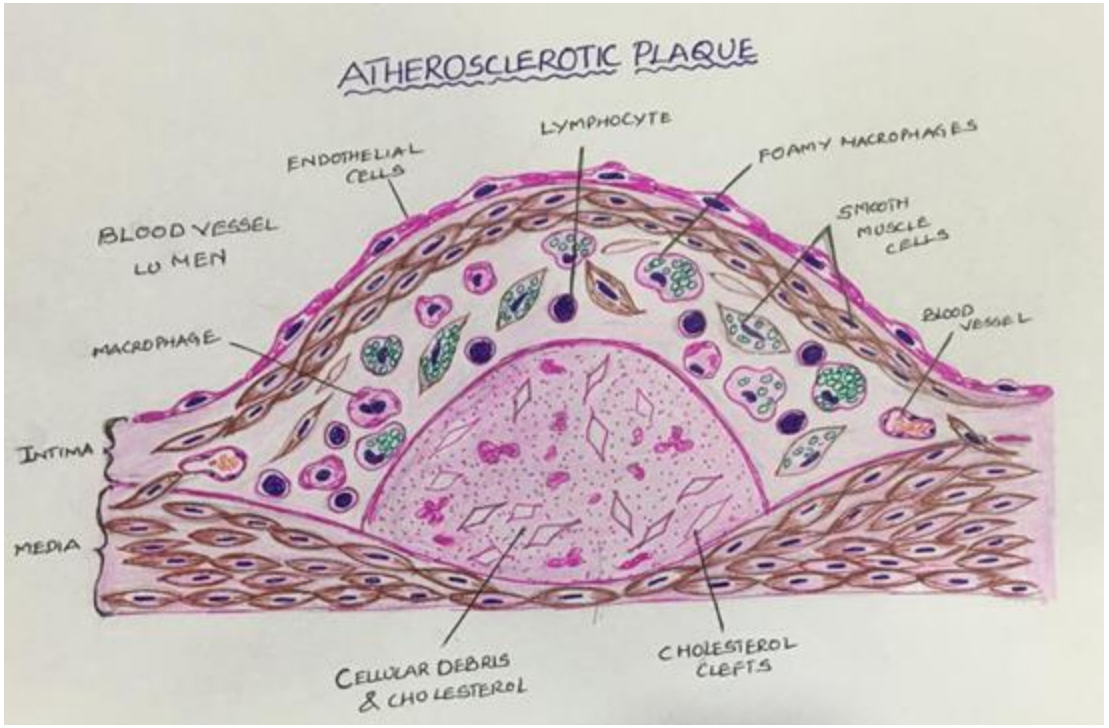


Fig. 10.6 Stereotypical response to vascular injury. Schematic diagram of intimal thickening, emphasizing intimal smooth muscle cell migration and proliferation associated with extracellular matrix synthesis. Intimal smooth muscle cells may derive from the underlying media or may be recruited from circulating precursors; they are depicted in a color different from that of the medial smooth muscle cells, to emphasize their distinct phenotype.

Pathogenesis of atherosclerosis Summary



A plaques have three principal components;

- ✓ **Cells =** SMCs + macrophages + T lymphocytes cells;
- ✓ **ECM =** collagen + elastic fibers
- ✓ **Lipids:** mainly oxidized LDL

AND COMPOSED MAINLY OF

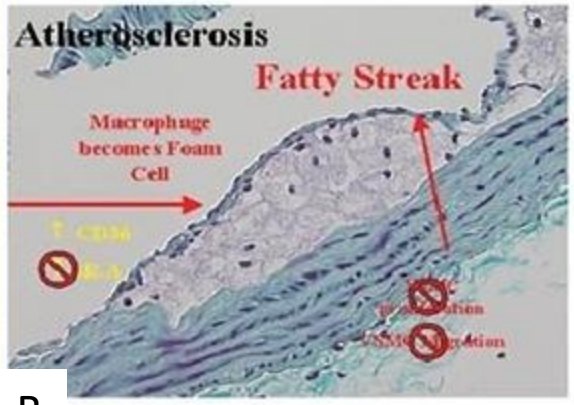
(1) **Fibrous cap (**SMCs & collagen).

(2) **Necrotic core,** deep to the fibrous cap containing lipids + foam cells + debris from dead cells

MORPHOLOGY OF ATHEROMAS
Fatty Streaks

Fatty streak

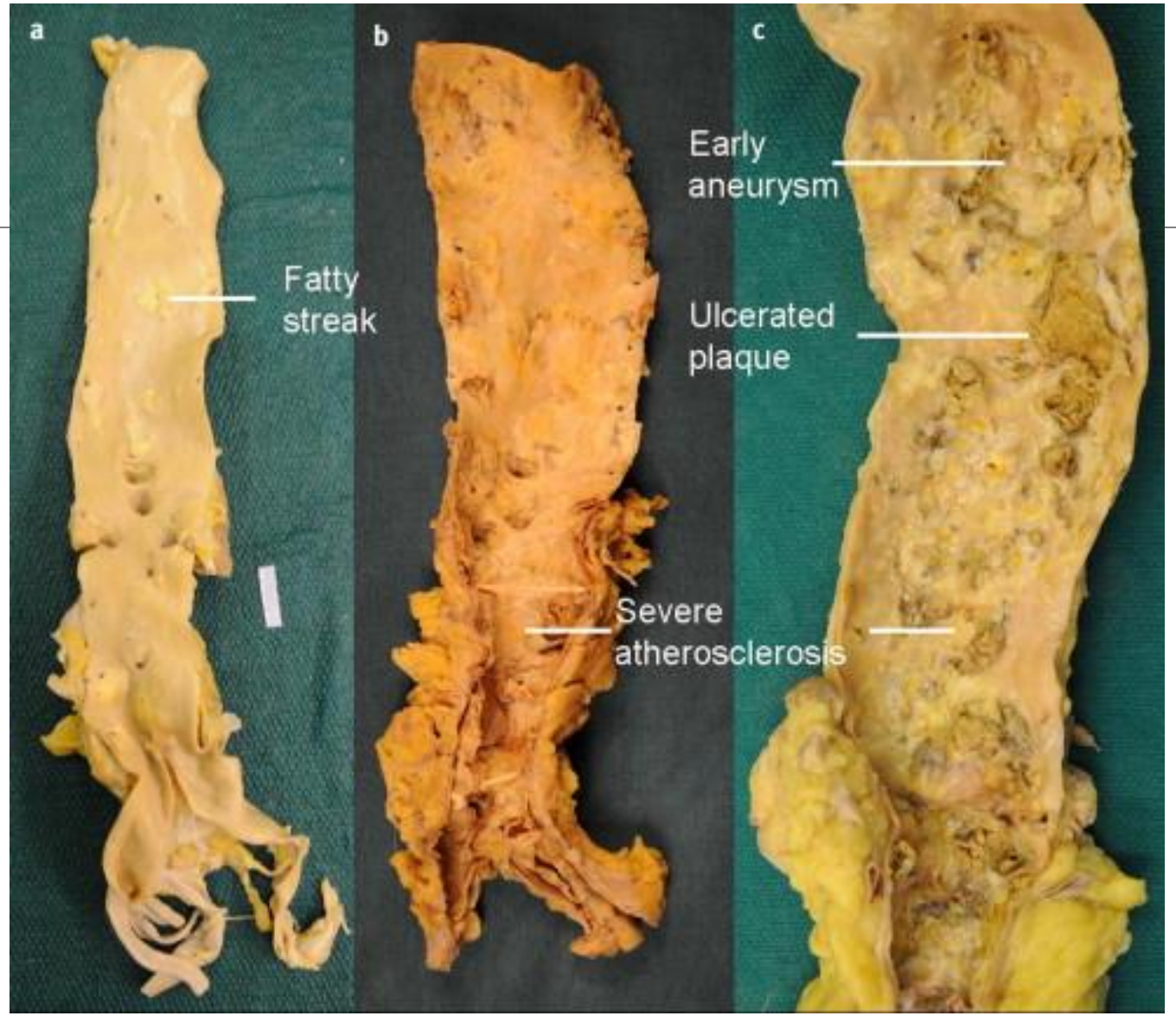
A



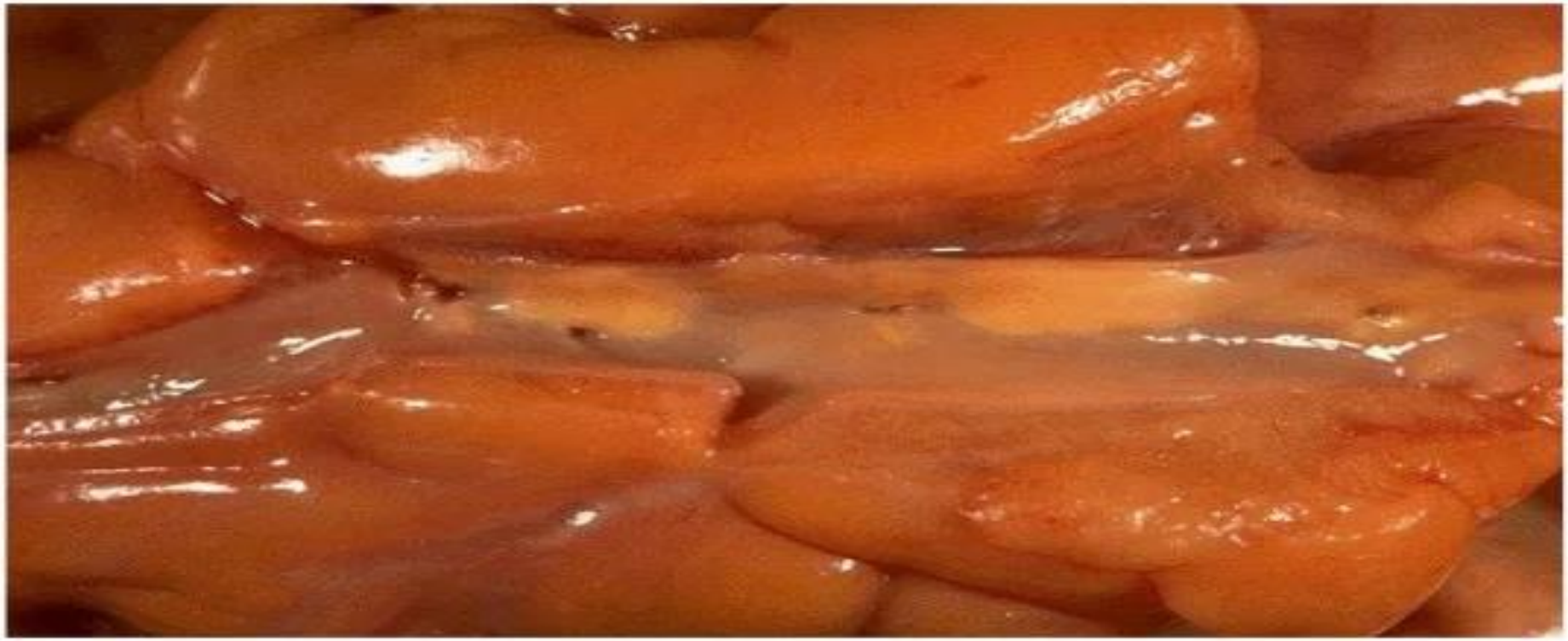
B

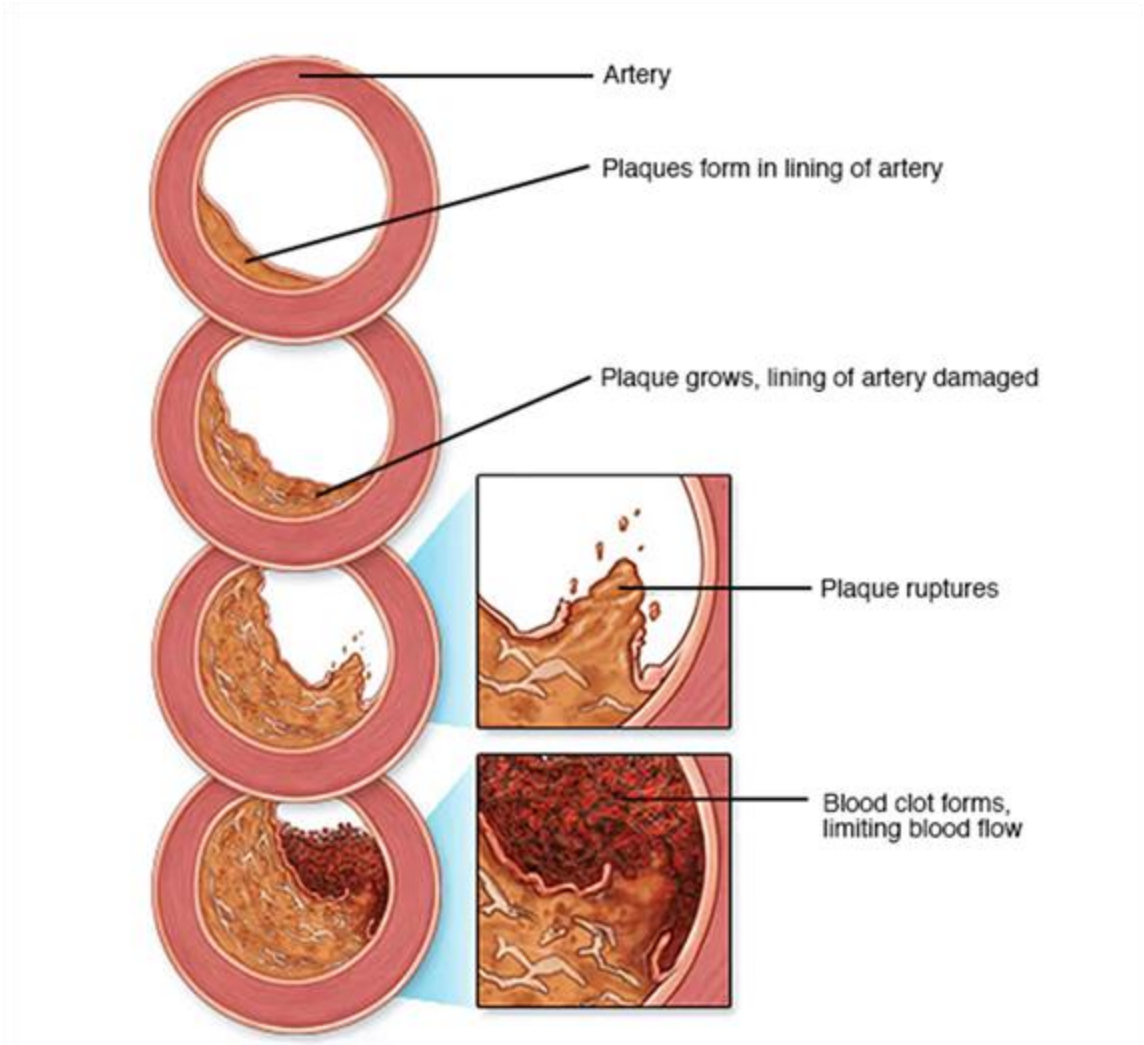
A. Grossly, the fatty streaks are multiple, minute **yellow flat spots**

B. Histology, fatty streaks are composed of **lipid-filled foam cells only**


a
b
c
Fatty streak
Early aneurysm
Ulcerated plaque
Severe atherosclerosis

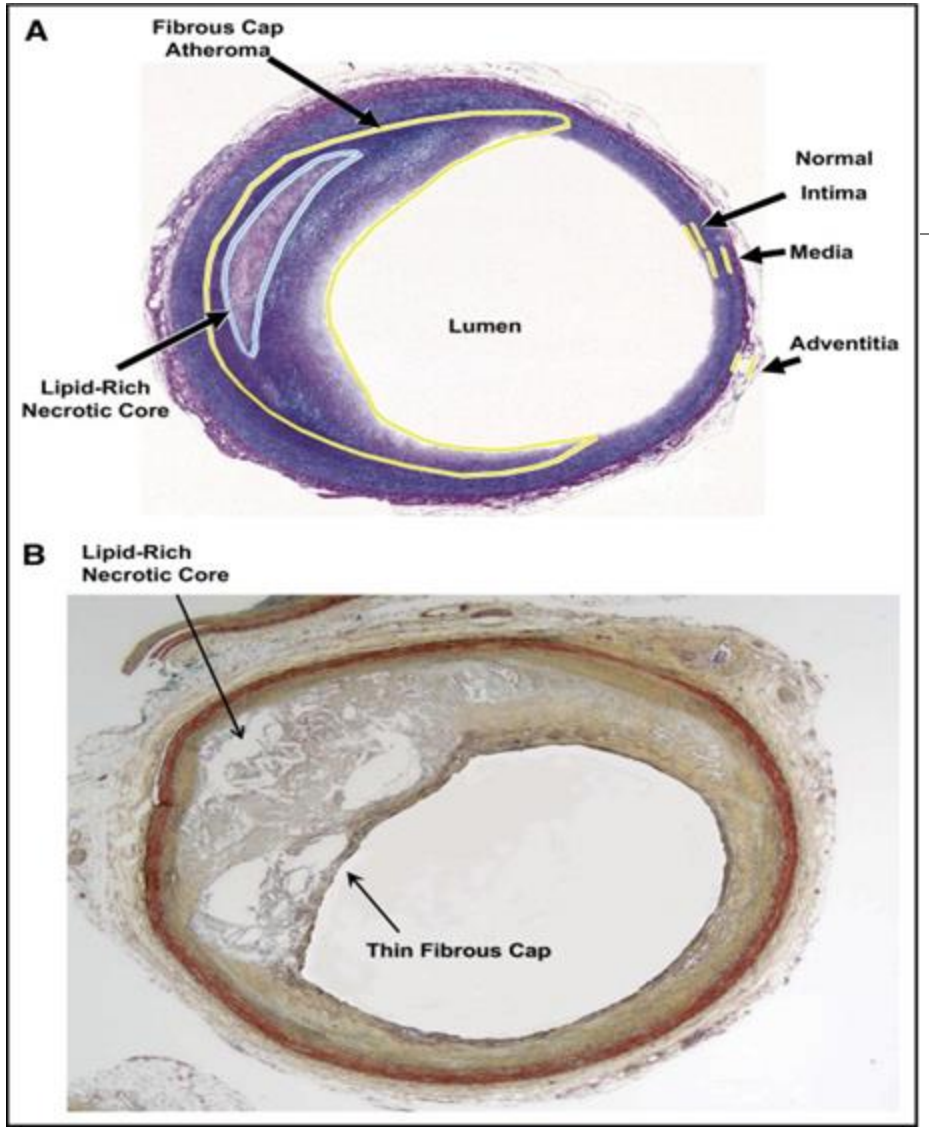
Fatty Streaks, Coronary Artery with Increased Fat



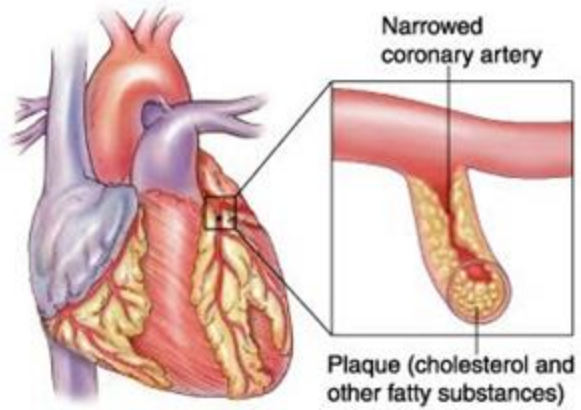


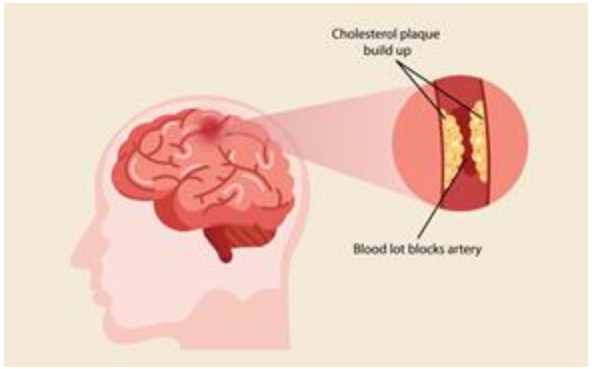
Pathogenesis of atherosclerosis

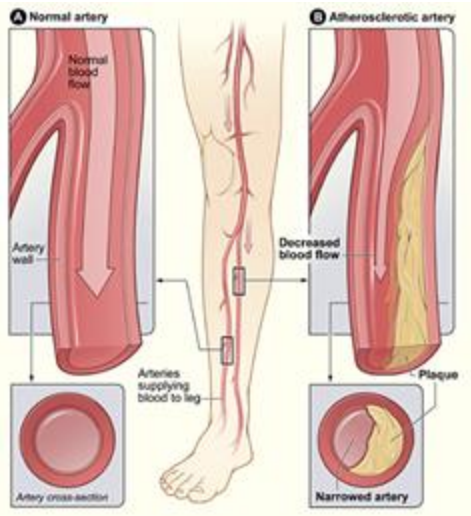
Rupture of the fibrous cap → superimposed thrombus → leads to catastrophic consequences (sudden occlusion of the vessel or thromboembolism)



Atheromas: histology





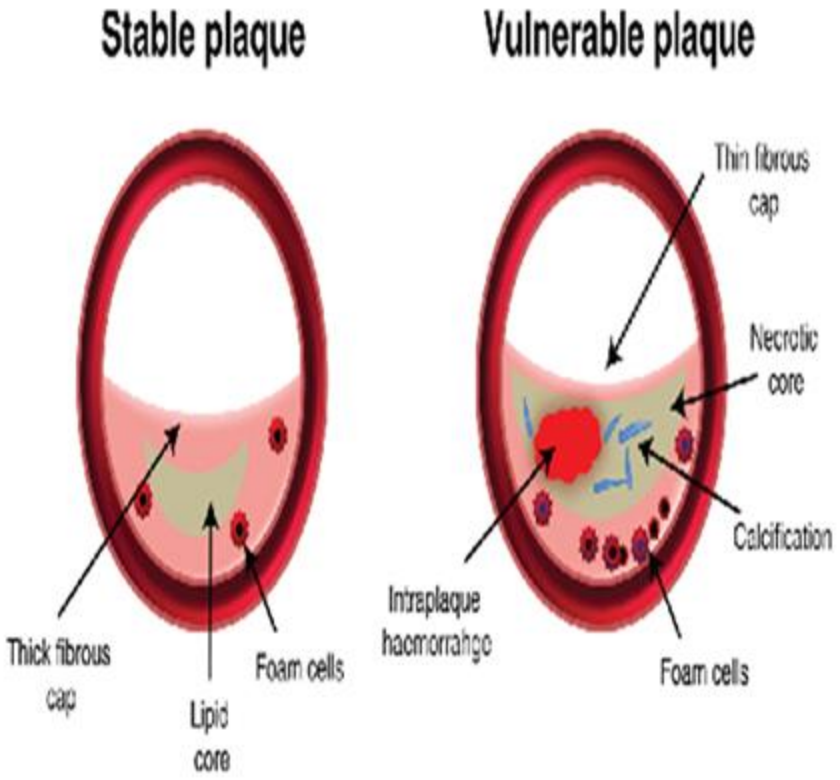


Atherosclerosis (Vessels involved)

Most common vessels involved by atherosclerosis are:

1. Coronary arteries (IHD)
2. Infrarenal abdominal aorta (aneurysms)
3. Popliteal arteries (gangrene)
4. Internal carotid arteries (stroke)
5. The vessels of the circle of Willis (stroke)

Types of Plaque



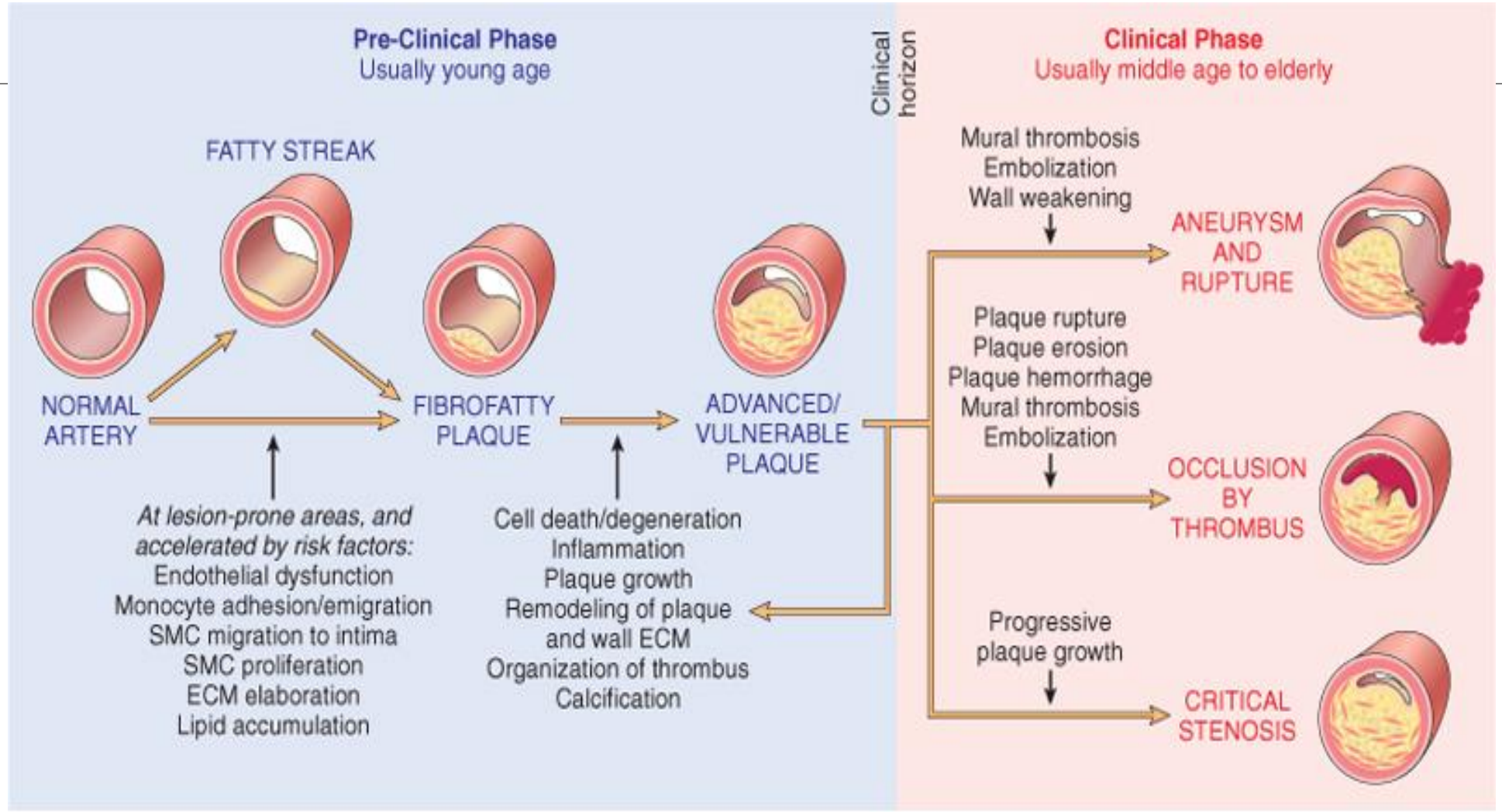
Vulnerable plaques: leads to dramatic and fatal ischemic complications

- Large numbers of foam cells and abundant extracellular lipid
- Thin fibrous caps
- Clusters of inflammatory cells.

Stable Plaques: leads to chronic ischemia

- Minimal lipid accumulation
- Dense collagen, thick fibrous cap
- Minimal inflammation
- **The factors involved to promote either a vulnerable plaque or a stable plaque are not clear yet, however, the major differences between a vulnerable and stable plaque are that vulnerable plaques have a "rich-lipid core" and a "thin fibrous cap" in comparison with the "thick fibrous cap" and the "poor lipid**
- **Whereas stabilized atherosclerotic lesions progress slowly, vulnerable plaques suddenly rupture and cause thrombosis, resulting in acute coronary syndrome (ACS).**

Natural history, morphologic features, main pathogenic events, & clinical complications of atherosclerosis.



Effects and complications of atherosclerotic plaques

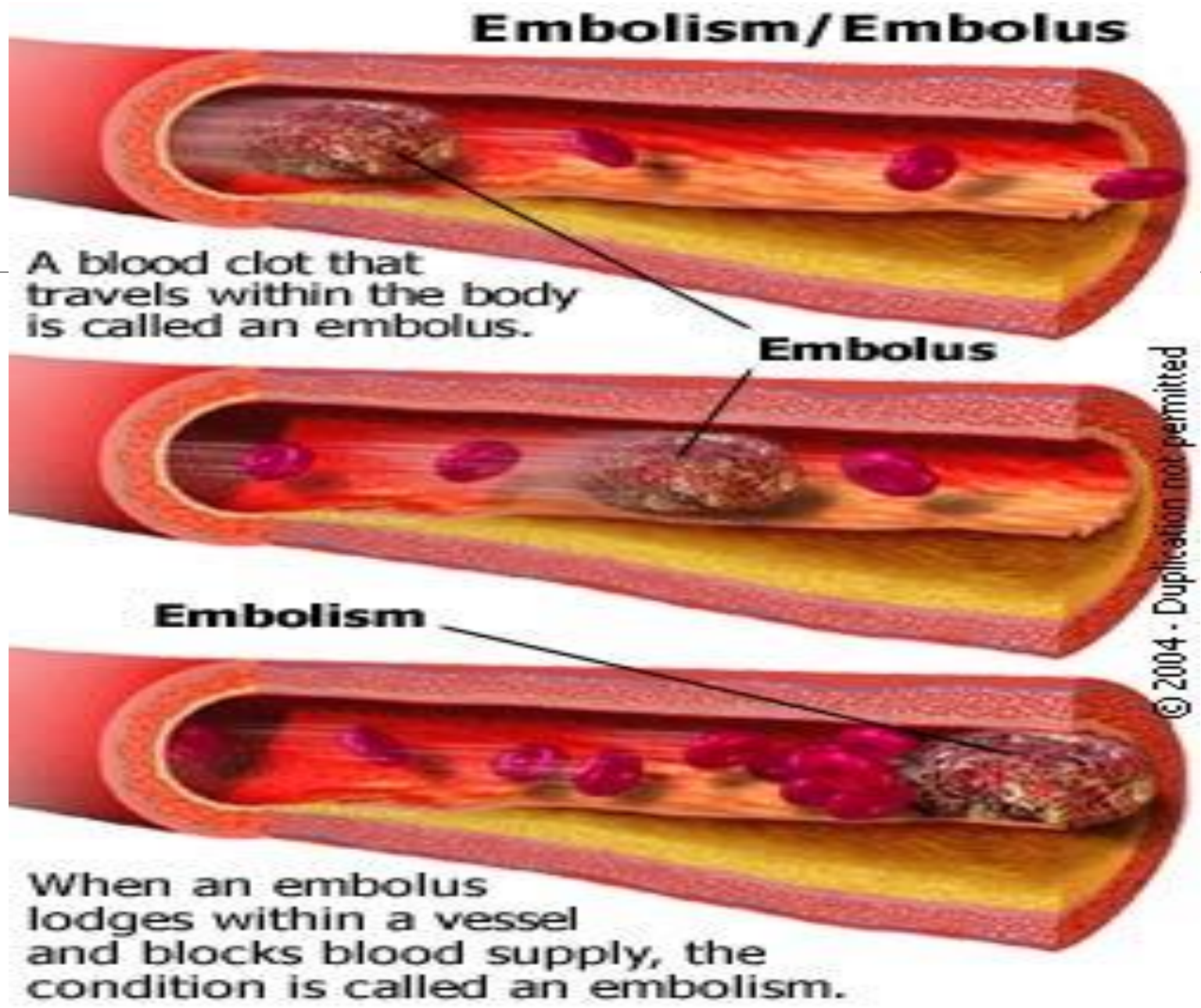
- **Narrowing**, or even complete occlusion of the arterial lumen, by progressively enlarging plaque causing ischemic injury

- **Ulceration, fissuring, erosion or rupture,** of the plaques fibrous cap exposes the bloodstream to highly thrombogenic substances and causes **thrombus formation**.

Such thrombi can: (I) occlude the lumen, partially or completely (II) dislodged, resulting in systemic thromboembolism.

Note: If the patient survives the initial vascular occlusion, the thrombi may become organized & incorporated into the growing plaque.

- **Intra-plaque hemorrhage**


Embolism/Embolus
A blood clot that travels within the body is called an embolus.
Embolus
Embolism
When an embolus lodges within a vessel and blocks blood supply, the condition is called an embolism.
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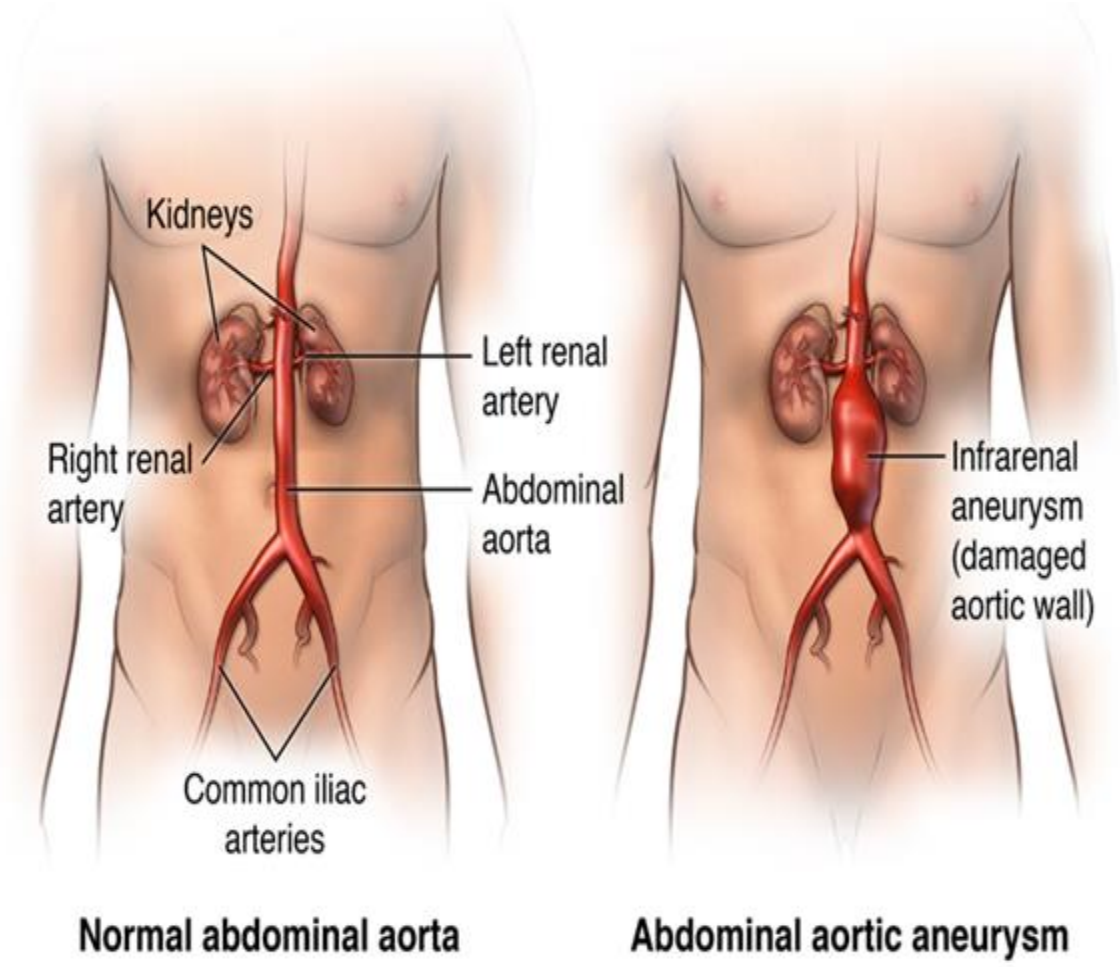


Effects and complications of atherosclerotic plaques

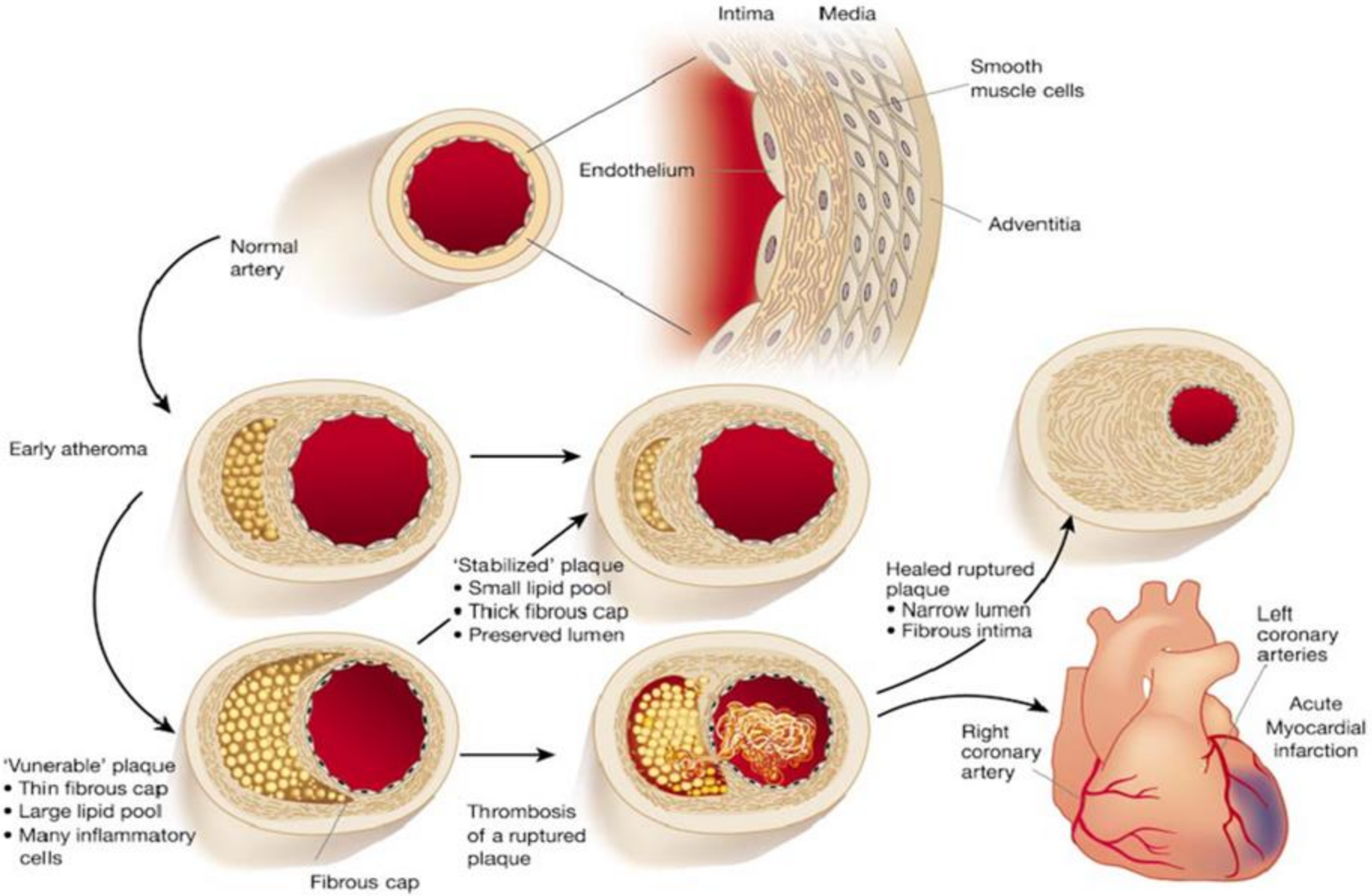
- **Aneurysm formation: atheroma** induce **pressure or ischemic atrophy of the underlying media**, with loss of elastic tissue in large arteries, this causes **weakness** of the arterial wall & development of **atheromatous aneurysms (commonest type of aneurysm) that may rupture.**

Clinical Consequences of Atherosclerotic Disease

- ✓Signs and symptoms related to ischemia in the heart, brain, kidneys, and lower extremities
- ✓Myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral vascular disease (gangrene of extremities)
- ✓**Atheroembolism:** ruptured plaque can discharge debris into the blood, producing microemboli composed of plaque contents.
- ✓Outcomes depends on **size of the affected vessel, size and stability of the plaques**

Atherosclerotic Stenosis

- **At early stages:** remodeling of the media tends to preserve the luminal diameter by increasing the vessel circumference.
- **Critical stenosis:** chronic occlusion limits flow so severely that tissue demand exceeds supply.
- **Arterial remodeling** is currently being recognized as an important determinant in vascular pathology in which narrowing of the lumen is the predominant feature. Not only expansive remodeling (enlargement), but also constrictive remodeling (shrinkage) is observed.
- **What is Remodeling in atherosclerosis?**
- Vascular remodeling is an active process of structural change that involves changes in at least four cellular processes: cell growth, cell death, cell migration, and the synthesis or degradation of extracellular matrix.
- With development of atherosclerotic plaque, outward remodeling may preserve size of lumen. However, necessary degradation of matrix by metalloproteinases may increase risk of plaque rupture. Healing process after plaque rupture may result in inward remodeling.
- Mechanisms involved in arterial remodeling include fibrosis, hyperplasia of the arterial intima and media, changes in vascular collagen and elastin, endothelial dysfunction, and arterial calcification. Migration and proliferation of vascular smooth muscle cells (VSMCs) contribute to thickening of the arterial intima.


Intima
Media
Smooth muscle cells
Endothelium
Adventitia
Normal artery
Early atheroma
'Stabilized' plaque
• Small lipid pool
• Thick fibrous cap
• Preserved lumen
Healed ruptured plaque
• Narrow lumen
• Fibrous intima
'Vunerable' plaque
• Thin fibrous cap
• Large lipid pool
• Many inflammatory cells
Fibrous cap
Thrombosis of a ruptured plaque
Left coronary arteries
Acute Myocardial infarction
Right coronary artery

Prevention of atherosclerosis

Primary prevention programs:

Aim to delay atheromatous plaque formation in persons who have not yet suffered a serious complication. These involve cessation of cigarette smoking + control of hypertension + weight loss + exercise, & lowering total & LDL blood cholesterol levels while increasing HDL

Secondary prevention programs:

It aims to **prevent recurrence** of IHD or stroke in symptomatic patients, involving medications (**aspirin** antiplatelet agent), **statins, & beta-blockers** (to limit cardiac demand).

What is the gold standard diagnostic test for atherosclerosis?

It is invasive coronary angiography (ICA) has remained the gold standard upon which other diagnostic tests are measured.

Arteriosclerosis

Arteriosclerosis **is hardening of arterial wall**

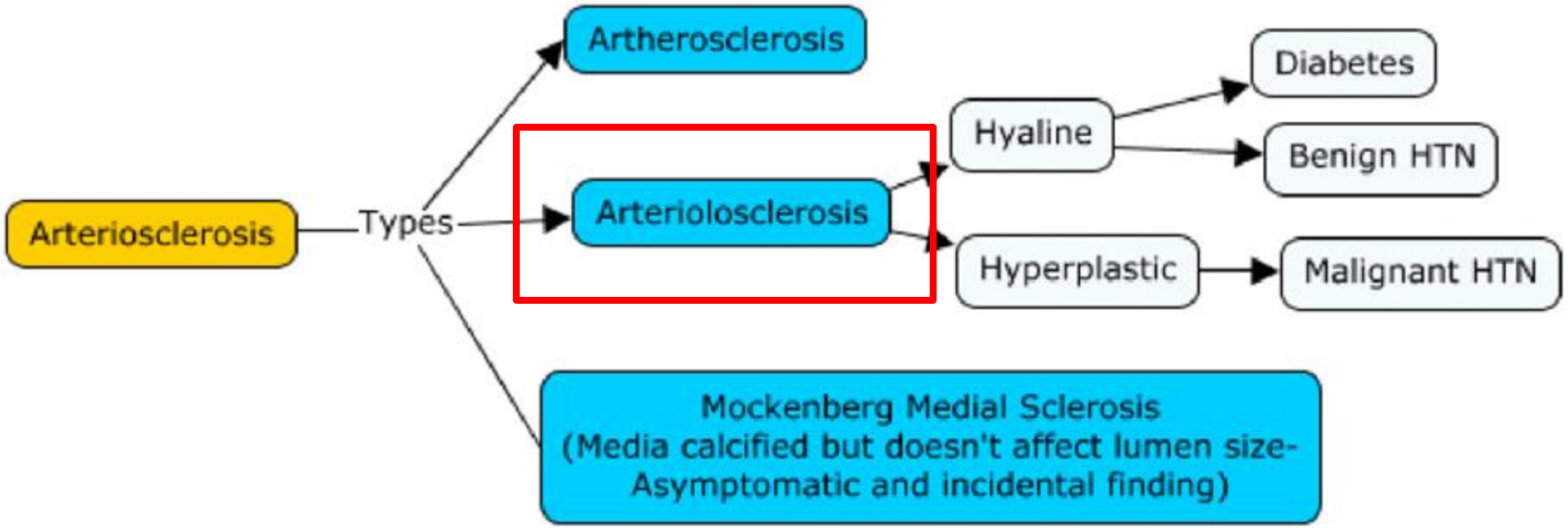
Three patterns

1. Atherosclerosis

1. **Arteriolosclerosis - thickening of small vessels. Wall thickens due to protein deposition (hyaline arteriolosclerosis) or hyperplasia of smooth muscle (hyperplastic arteriolosclerosis)**

1. Monckeberg medial sclerosis

Arteriosclerosis

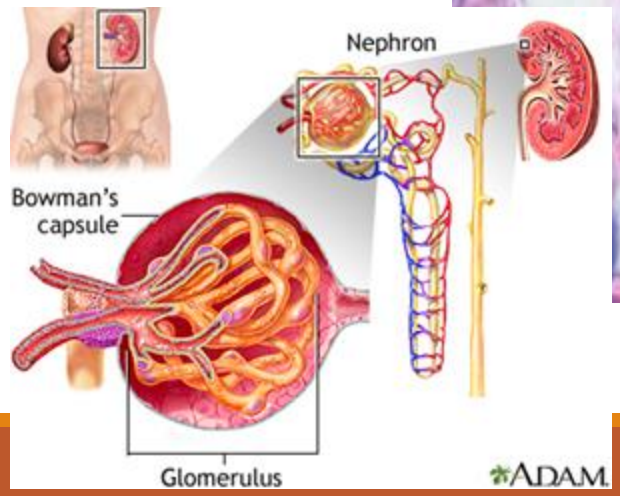


Artherosclerosis

Arteriolosclerosis

1. Hyaline arteriolosclerosis:

- Seen in benign hypertension and DM.
- Pink hyaline thickening of the arteriolar walls, and luminal narrowing
- In the kidneys: narrowing leads to diffuse vascular compromise and **nephrosclerosis (glomerular scarring).**
- Seen in **elderly** patients (normo- or hypertensive)
- Common in **diabetic microangiopathy**

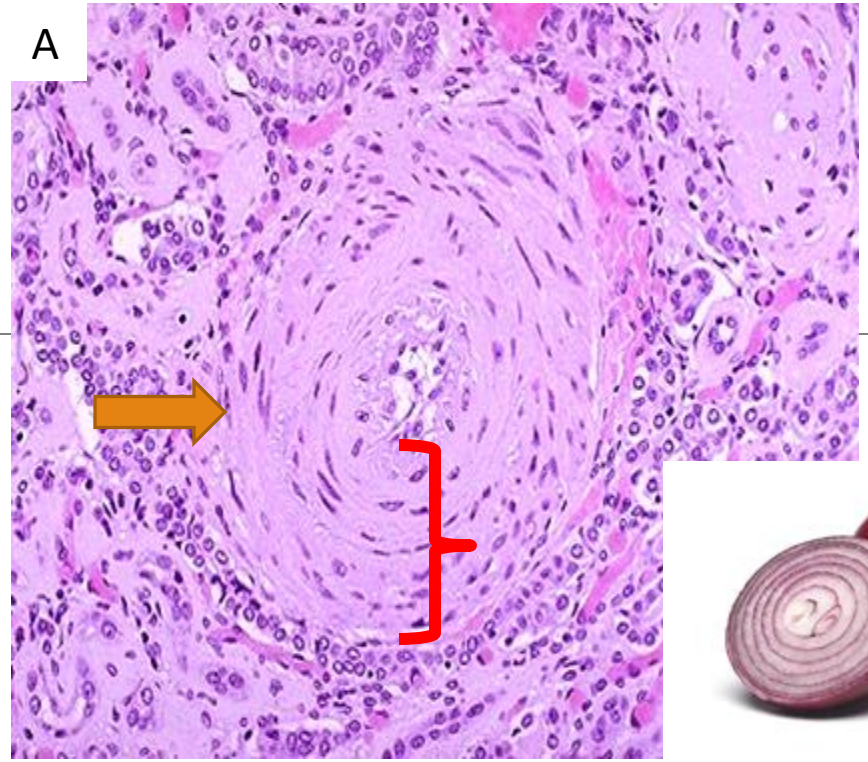


Arteriolosclerosis

2. Hyperplastic arteriolosclerosis :

- **Seen in severe (malignant) hypertension**.
- Onionskin concentric, laminated thickening of walls and luminal narrowing (figure A)
- The laminations consist of smooth muscle cells and thickened, reduplicated BM
- In malignant hypertension: accompanied by fibrinoid deposits and vessel wall necrosis **(necrotizing arteriolitis),** prominent in the kidney (figure B)

A



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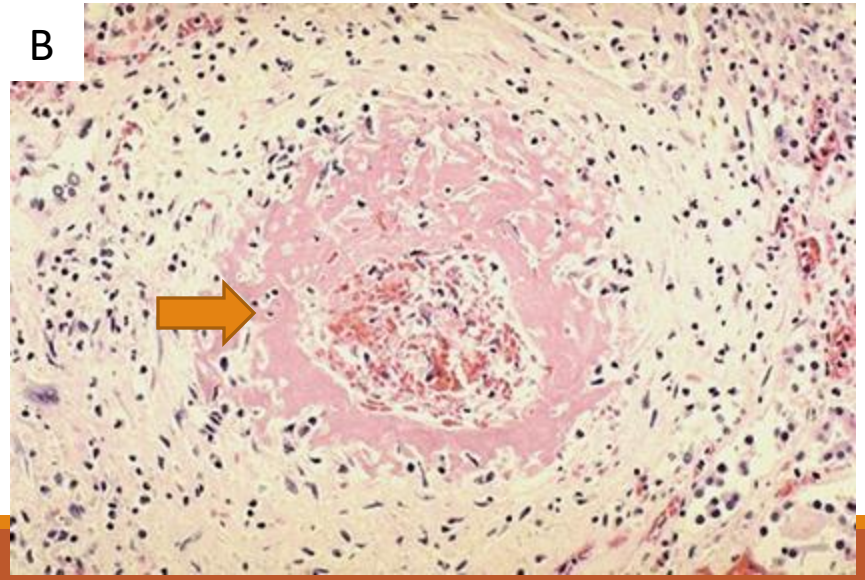


Arteriosclerosis

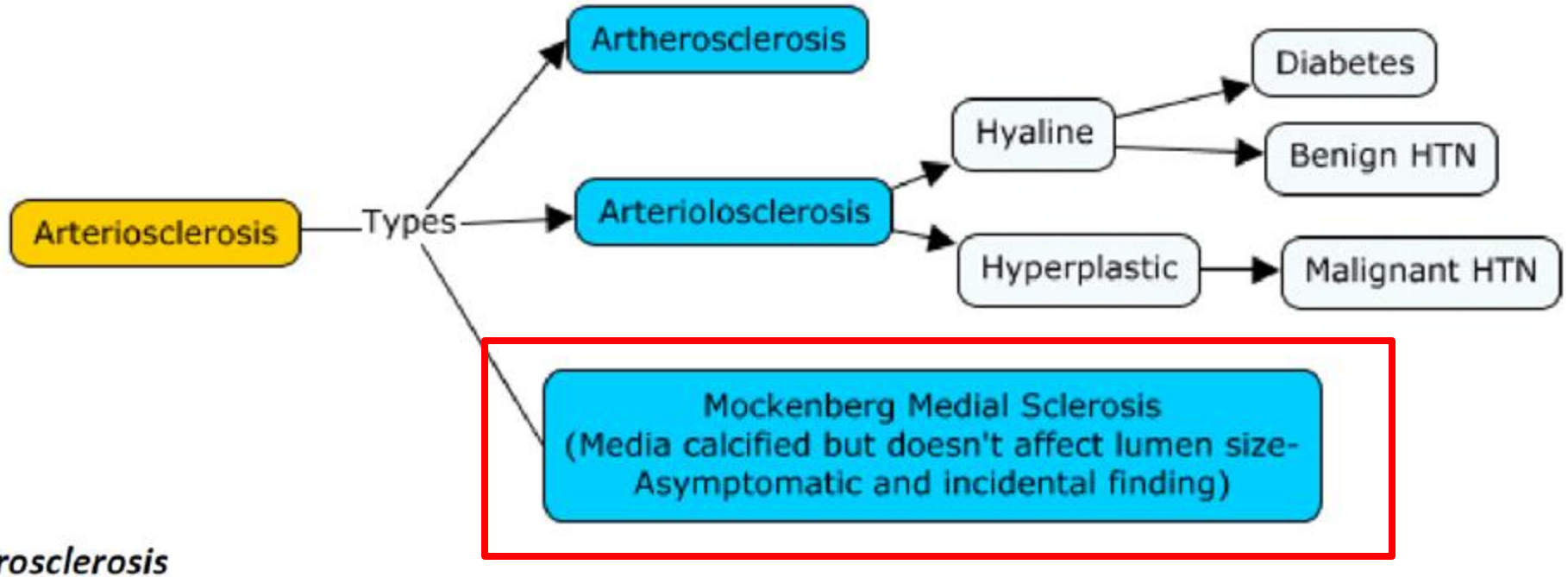
Arteriosclerosis **is hardening of arterial wall**

Three patterns

1. Atherosclerosis
2. Arteriolosclerosis

1. **Monckeberg medial sclerosis - calcification of media. Not very clinically significant**

Arteriosclerosis

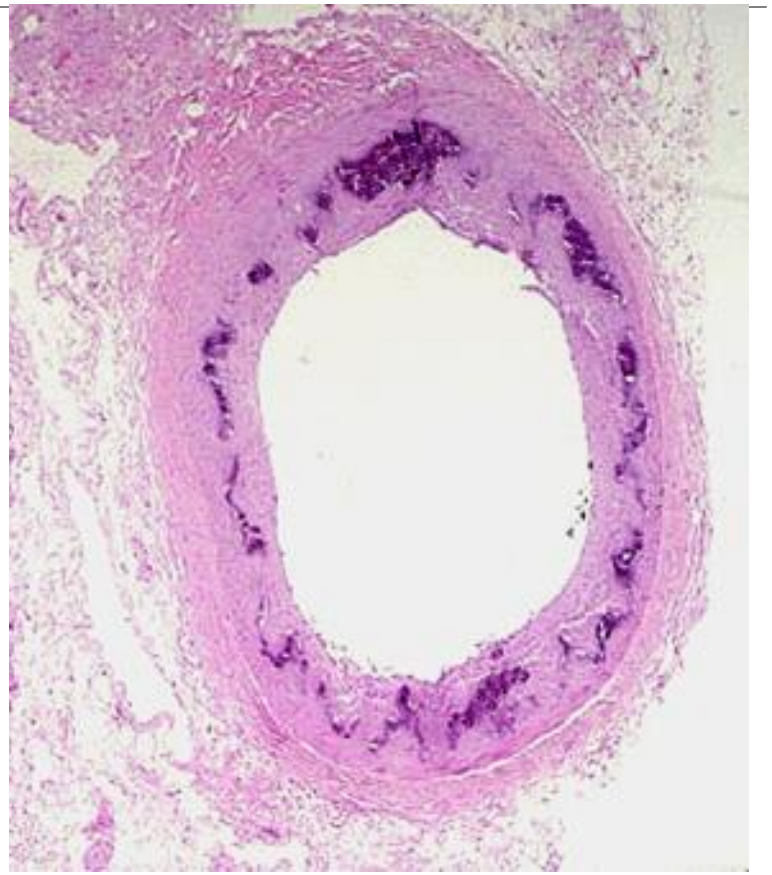


Artherosclerosis

Monckeberg medial sclerosis

Monckeberg medial sclerosis:

- Calcified deposits in muscular arteries
- Seen in adults (older than 50 years)
- Not clinically significant



Monckeberg medial sclerosis

Monckeberg medial sclerosis