Arteriosclerosis & Atherosclerosis

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Arteriosclerosis

Literally, "hardening of the arterie"; A generic term for thickening and loss of elasticity of arterial walls. Four patterns of arteriosclerosis are recognized:

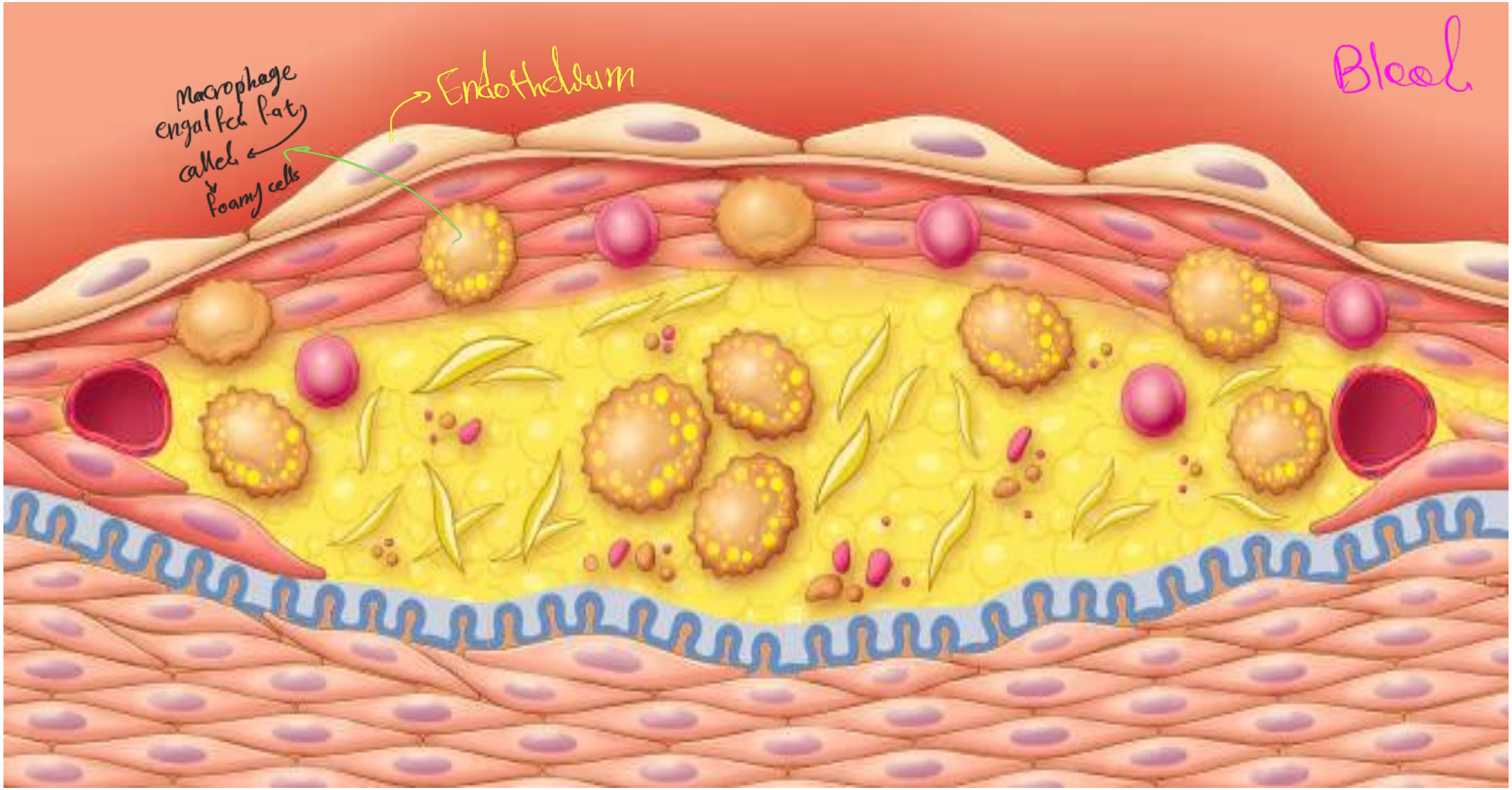
1. Arteriolosclerosis: Small arteries & arterioles, may cause ischemic:
    a. hyaline type
    b. hyperplastic type. ⇒ Associated w/ Severe HT.
2. Monckberg medial calcification.
3. Fibromuscular intimal hyperplasia: thickened vascular wall with luminal narrowing.
4. Atherosclerosis..

Atherosclerosis

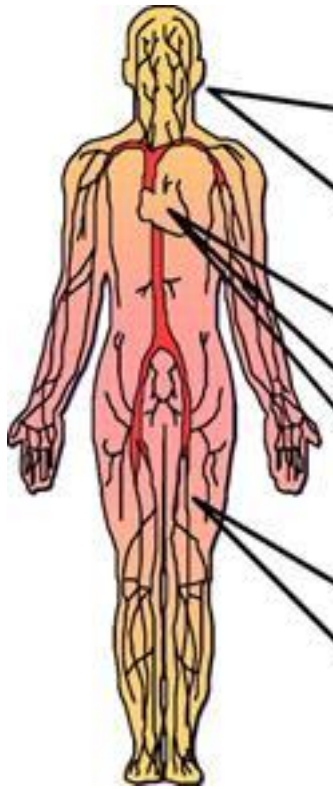
in Tunica Intima (in lumen)

- Atherosclerosis is characterized by intimal lesions called *atheromas* (or *atheromatous* or *atherosclerotic plaques*)
- They form raised lesions composed of soft friable lipid cores (contain cholesterol & cholesterol esters + necrotic debris) covered by fibrous caps.

Structure of an atheromatous plaque



- underlies the pathogenesis of **coronary, cerebral, and peripheral vascular disease**
- causes more morbidity & mortality (roughly half of all deaths) in the Western world than any other disorder



Ischaemic stroke

Transient ischaemic attack

Myocardial infarction

Angina pectoris (stable, unstable)

Sudden death

Intermittent claudication

Critical limb ischaemia, gangrene, necrosis

@ Stenosis + occlusion in popliteal area.

Major Risk Factors for Atherosclerosis

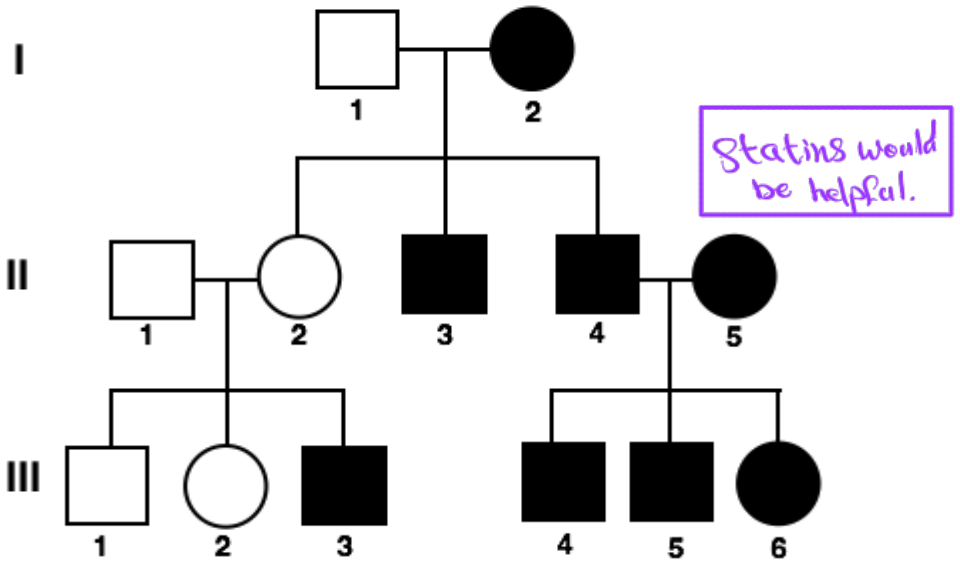
Nonmodifiable (Constitutional)
Genetic abnormalities
Family history
Increasing age
Male gender
Modifiable
Hyperlipidemia
Hypertension
Cigarette smoking
Diabetes
Inflammation

These risk factors have roughly multiplicative effects.

- **GENETIC FACTORS**

Hereditary genetic derangements of lipoprotein metabolism predispose the individuals to high blood lipid level (eg, familial hypercholesterolemia).

Not related to Diet.



- **FAMILIAL AND RACIAL FACTORS**

Familial predisposition: multifactorial traits that go hand-in-hand with atherosclerosis, including hypertension & diabetes.

The most important independent risk factor for atherosclerosis.

- **Age**

Atherosclerosis usually remains clinically silent until lesions reach a critical threshold in middle age.

The incidence of myocardial infarction increases 5-fold between 40 and 60 years of age.

- **Gender**

→ Because of estrogen (Protective)

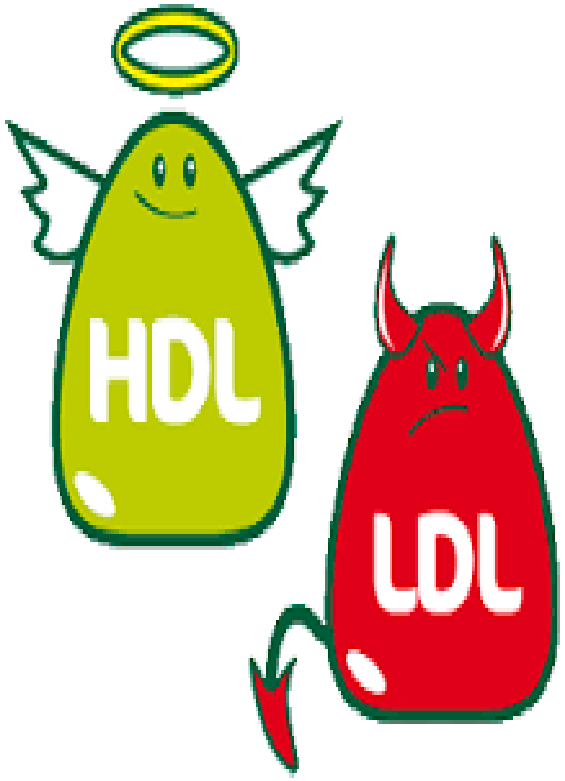
Premenopausal women are relatively protected against atherosclerosis & its consequences compared with age-matched men.

After menopause, however, the incidence of atherosclerosis-related disease increases and can even exceed that in men..

Modifiable Major Risk Factors - Hyperlipidemia

- Prefer Dyslipidemia , specifically, hypercholesterolemia.
- A major risk factor for development of atherosclerosis & is sufficient to induce lesions in the absence of other risk factors.
- Two cholesterol components:

1. Low-density lipoprotein (LDL) cholesterol ("bad cholesterol"); LDL distributes cholesterol to peripheral tissues. Increase risk for atherosclerosis.
2. High-density lipoprotein (HDL) cholesterol ("good cholesterol") mobilizes cholesterol from the periphery (including atheromas) & transports it to the liver for biliary excretion. HDL correlate with reduced risk.



This Recognition has spurred the development of dietary & pharmacologic interventions that lower total serum cholesterol or LDL and/or raise serum HDL

- ✓ High dietary intake of cholesterol & saturated fats (egg yolks, animal fats, & butter) raises plasma cholesterol levels, diets low in cholesterol &/or containing higher ratios of polyunsaturated fats, lower plasma cholesterol levels.
- ✓ Omega-3 fatty acids (fish oils) are beneficial,
- ✓ Exercise & moderate consumption of ethanol raise HDL levels, while obesity & smoking lower them.
- ✓ Statins are a widely used class of drugs that lower circulating cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis.

Modifiable Major Risk Factors - Hypertension

- ✓ Major risk factor for development of atherosclerosis.
- ✓ On its own, hypertension can increase the risk for IHD by approximately 60% .
- ✓ Hypertension also is the major cause of left ventricular hypertrophy (LVH), which also can contribute to myocardial ischemia

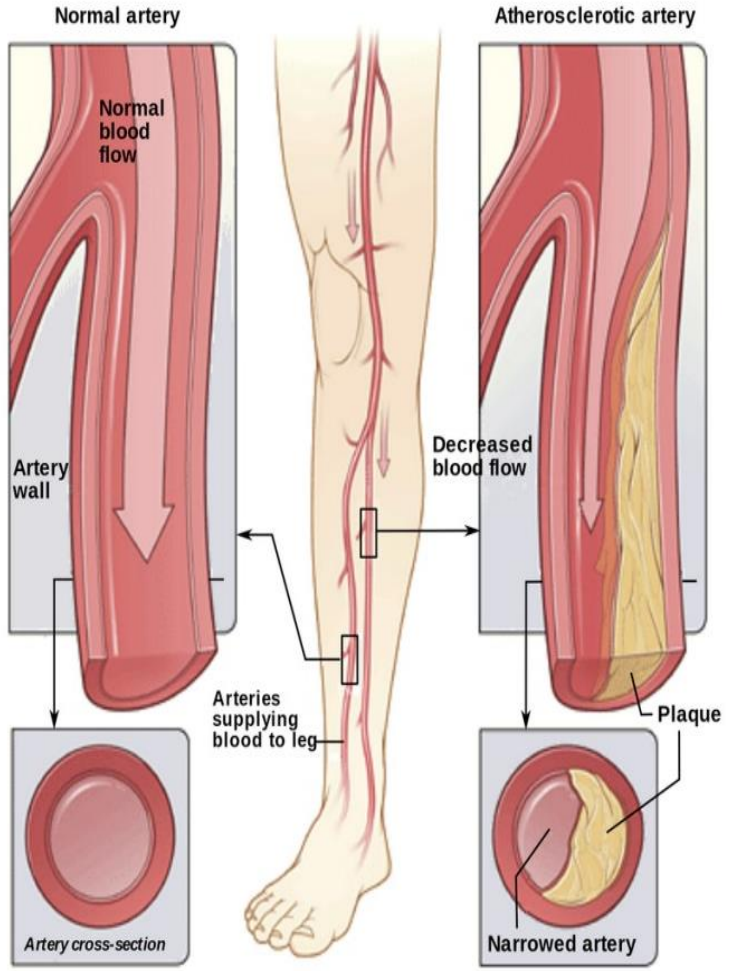
Modifiable Major Risk Factors - Cigarette smoking

- ✓ Well-established risk factor in men, & accounts for the increasing incidence & severity of atherosclerosis in women.
- ✓ Prolonged (years) smoking of one or more packs of cigarettes per day doubles the rate of IHD-related mortality.
- ✓ While smoking cessation reduces the risk.

Modifiable Major Risk Factors - Diabetes mellitus

- ✓ Associated with raised circulating cholesterol levels & markedly increases the risk for atherosclerosis.
- ✓ Incidence of myocardial infarction is twice as high in diabetics as in non-diabetics.
- ✓ This disorder is associated with an increased risk for stroke and a 100-fold increase in atherosclerosis-induced gangrene of the lower extremities.

↳ Diabetic foot.



Additional minor risk factors..

- **Inflammation, CRP levels independently predict the risk for myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals.**
- **Hyperhomocysteinemia, ass. with early onset vascular disease.**
- **Metabolic syndrome, ass. with central obesity this clinical entity is characterized by insulin resistance, hypertension, dyslipidemia , hypercoagulability, and a pro-inflammatory state.**
- **Other factors associated with difficult-to-quantify risks include lack of exercise and living a competitive, stressful lifestyle ("type A personality").**

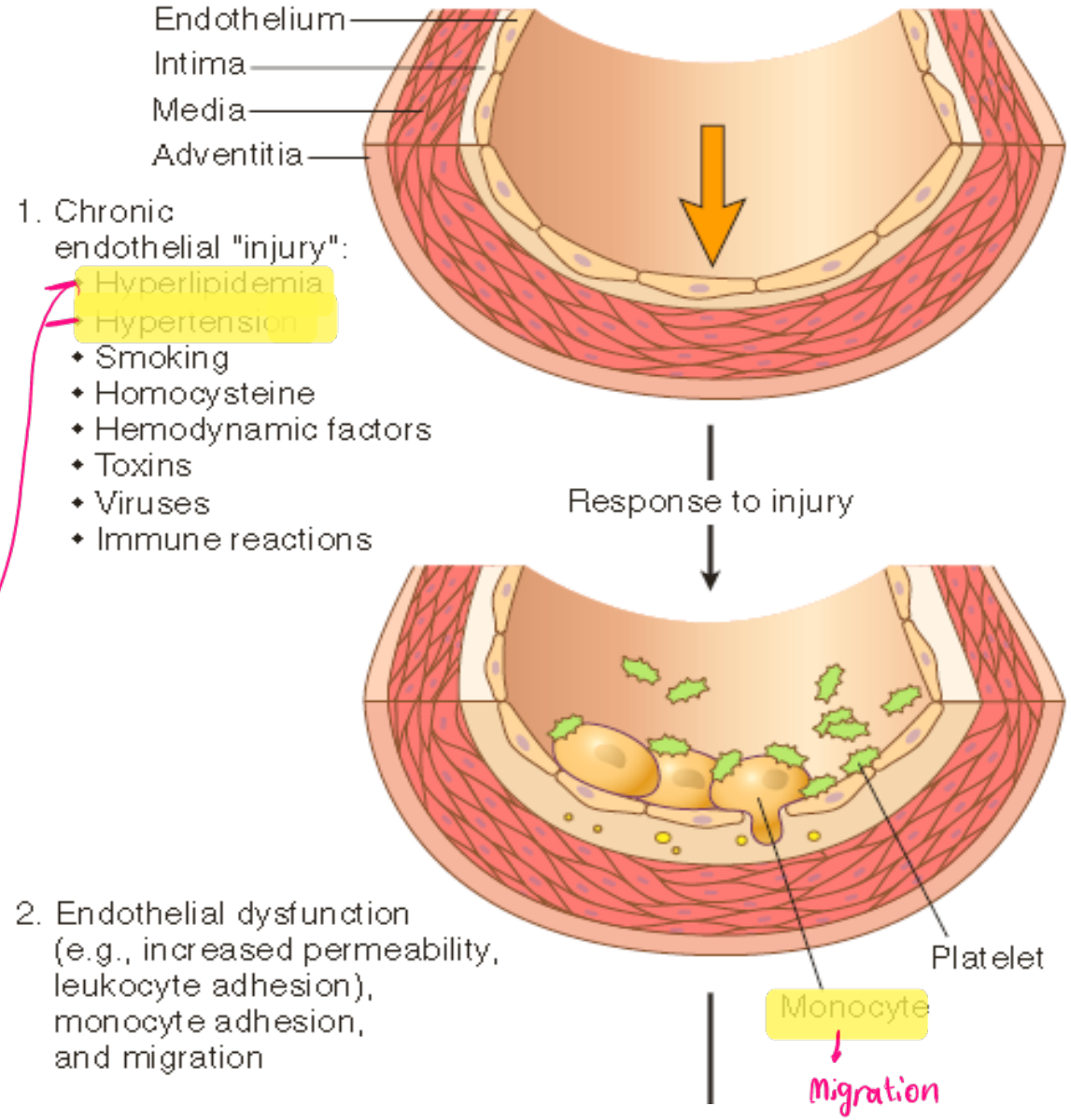
Pathogenesis: *response-to-injury hypothesis.*

- ✓ Atherosclerosis is a chronic inflammatory & healing response of the arterial wall to endothelial injury.
- ✓ Occur through interaction of modified lipoproteins, monocyte derived macrophages, T lymphocytes, & the cellular constituents of the arterial wall, Events:

1. Endothelial injury & **dysfunction** leading to increased permeability, leukocyte adhesion & thrombosis.
2. Accumulation of lipoproteins (mainly oxidized LDL) in the vessel wall.
3. Platelet adhesion.
4. Monocyte adhesion to the endothelium, migration into the intima, & differentiation into macrophages & foam cells.
5. Lipid accumulation within macrophages, which respond by releasing inflammatory cytokines.
6. SMC recruitment due to factors released from activated platelets, macrophages, & vascular wall cells.
7. SMC proliferation and ECM production.

EC (Endothelial cell) injury

- ✓ **EC injury is the cornerstone of the response to injury hypothesis.**
- ✓ **Dysfunctional ECs exhibit increased & permeability, enhanced leukocyte adhesion, & altered gene expression, all contribute to the development of atherosclerosis.**
- ✓ **The two most important causes of endothelial dysfunction are hemodynamic disturbances & hypercholesterolemia.**
- ✓ **Hemodynamic factors in atherogenesis → plaques tend to occur at ostia of exiting vessels (branch points) also along the**



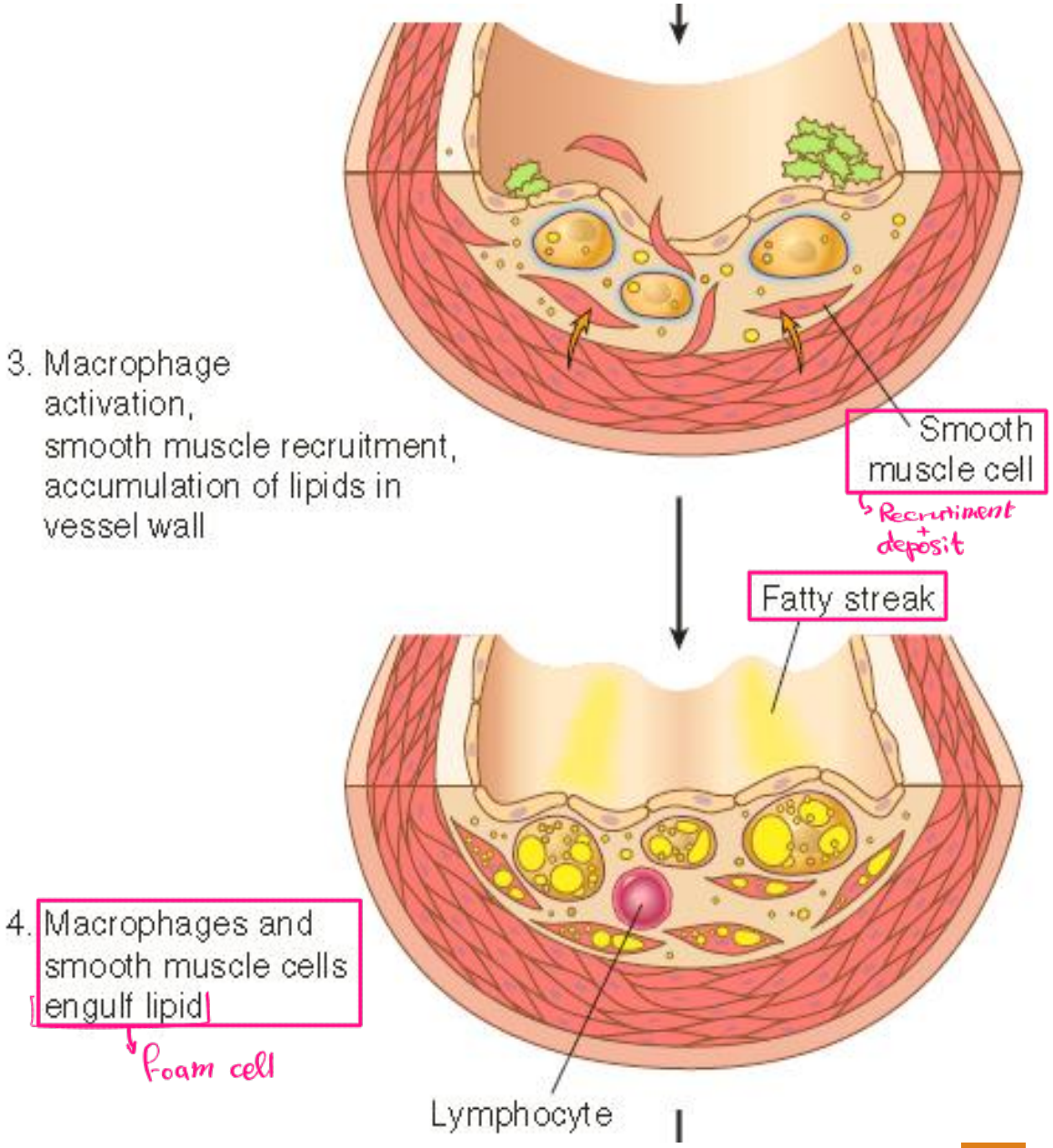
Lipids

- **Lipids transported in the bloodstream bound to specific apoprotei-ns (forming lipoprotein complexes).**
- **Common lipoprotein abnormalities in the general population:**

(1)Increased LDL cholesterol levels.

(2)Decreased HDL cholesterol levels.

(3)Increased levels of abnormal lipoprotein.



The mechanisms by which dyslipidemia contributes to atherogenesis

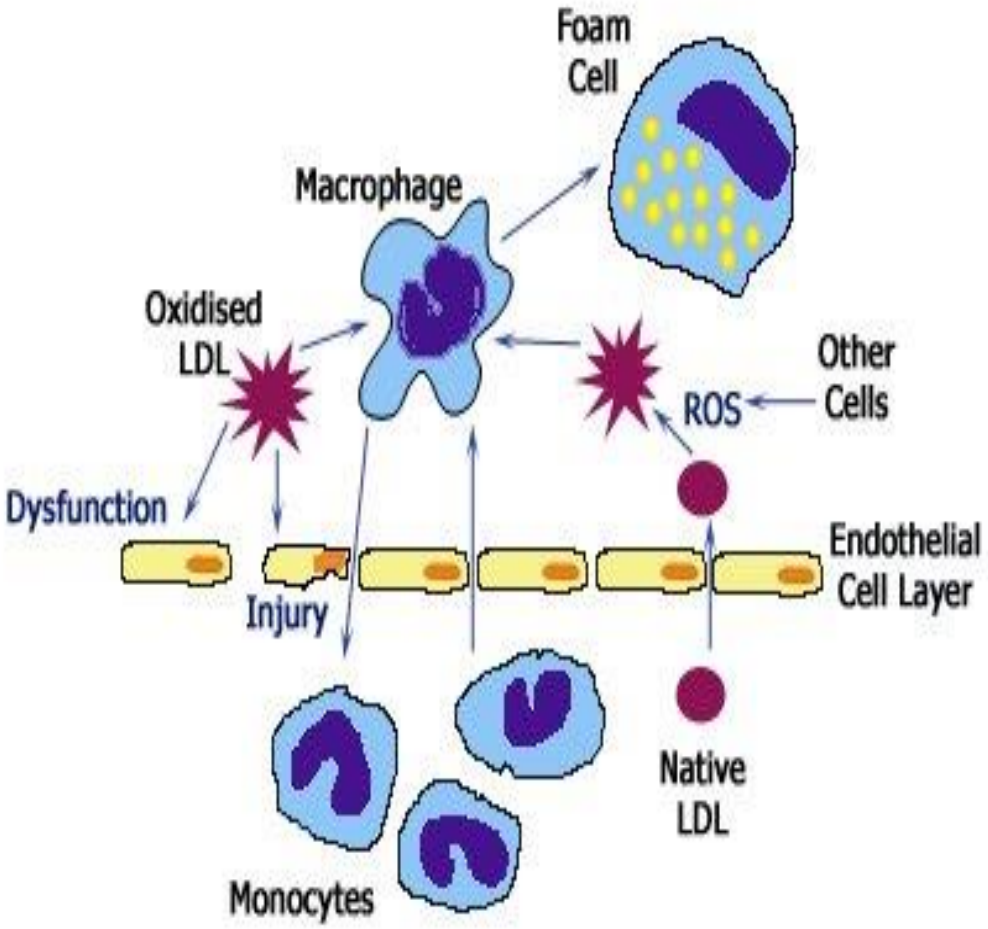
a. Hypercholesterolemia → impair EC function by increasing local oxygen free radical production → free radicals accelerate NO decay → ↓ its vasodilator activity.

Endothelial activation

b. Lipoproteins accumulate within the intima → generate oxidized LDL. (LDL is oxidized through the action of oxygen free radicals generated locally by macrophages or ECs), then ingested by macrophages through the scavenger receptor, resulting in foam cell formation.

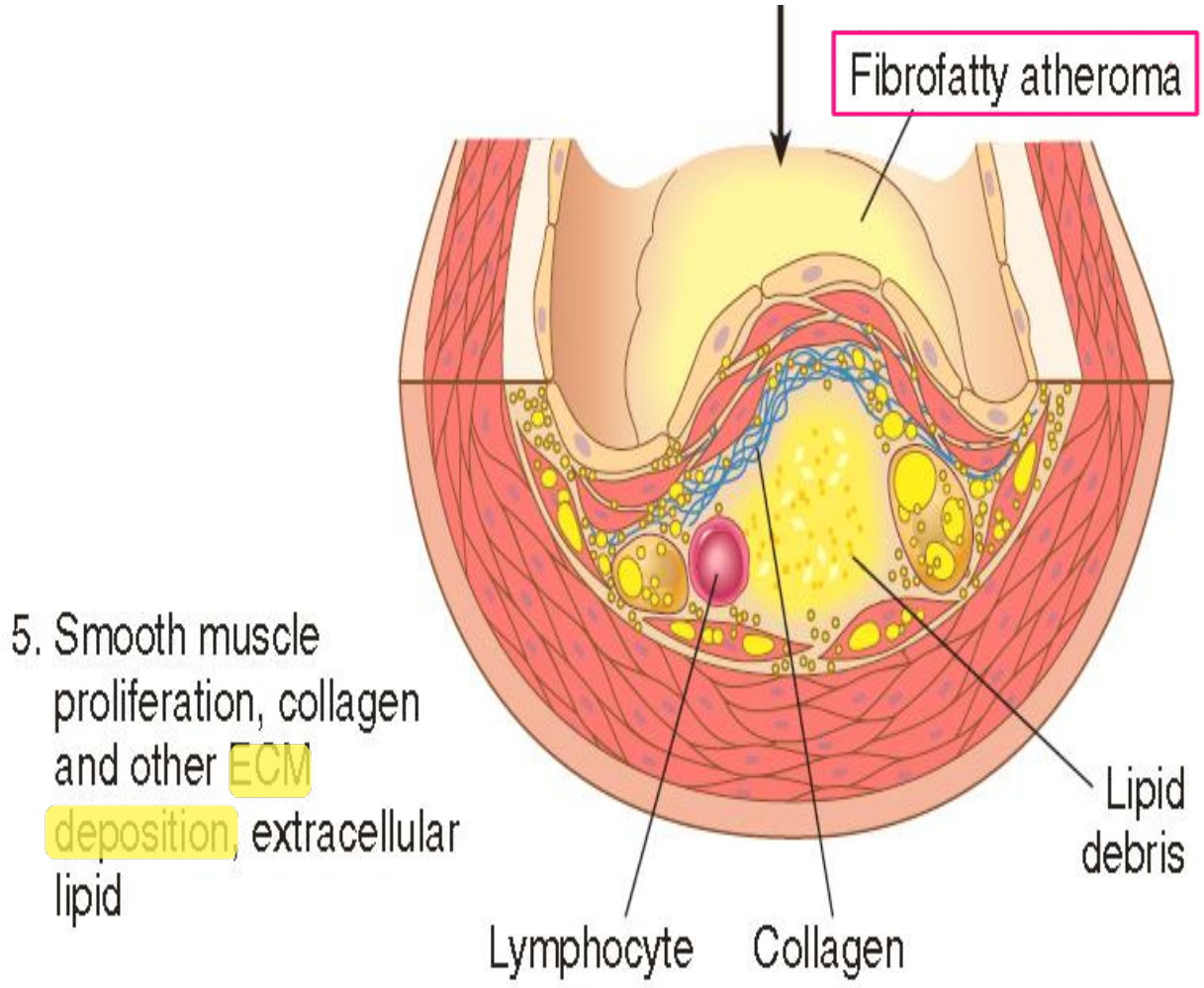
c. Oxidized LDL stimulates release of growth factors, cytokines, & chemokines → increase monocytes recruitment + cytotoxic to ECs & SMCs.

d. Extracellular cholesterol crystals found in early atherosclerotic lesions serve as “danger” signals → activate innate immune cells.

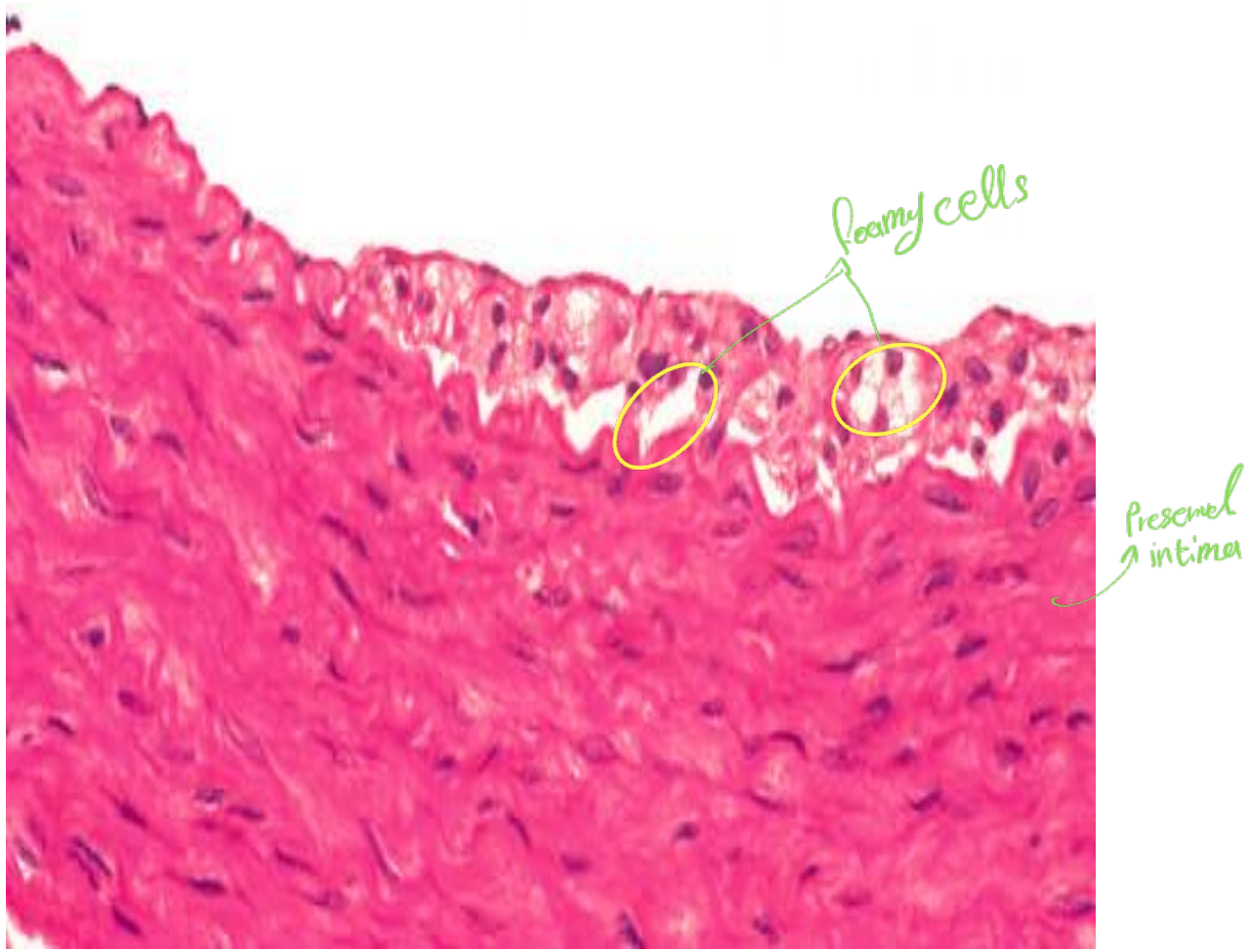


SMC Proliferation and Matrix Synthesis

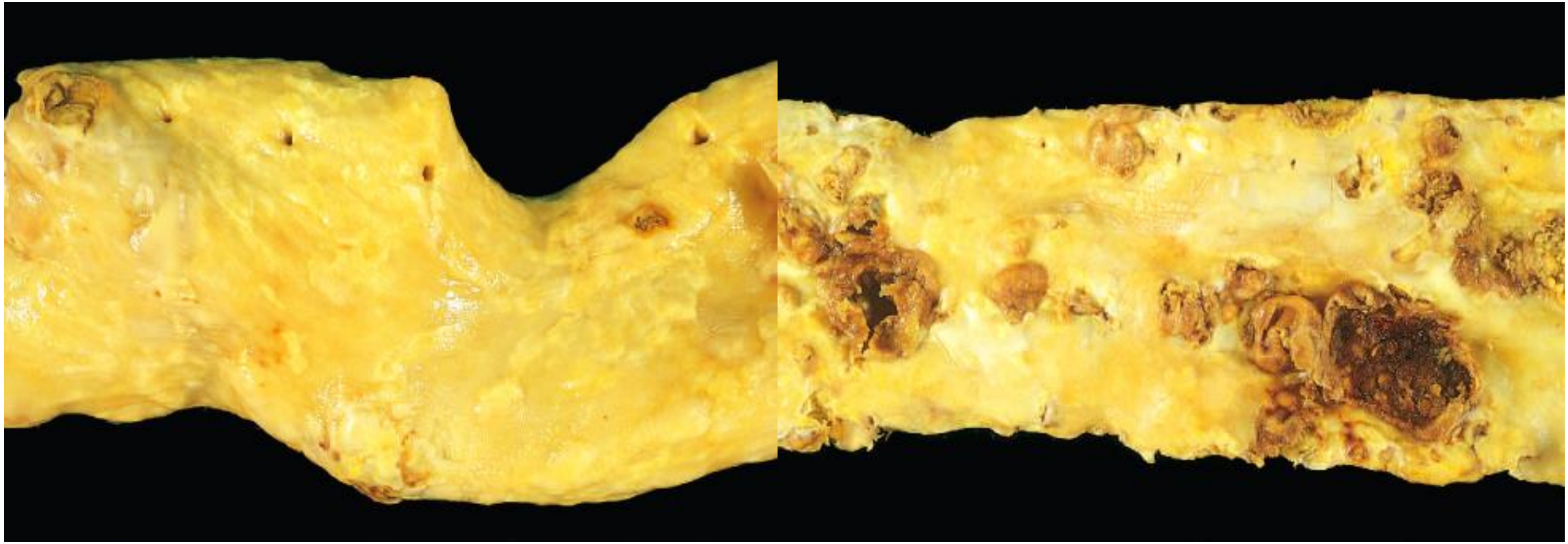
- **Intimal SMC proliferation & ECM deposition lead to conversion of the earliest lesion(a fatty streak) into a mature atheroma →contributing to the progressive growth of atherosclerotic lesions.**
- **SMC proliferation & matrix synthesis Growth factors: platelet-derived growth factor (released by locally adherent platelets, macrophages, ECs, & SMCs), fibroblast growth factor, & TGF-α.**
- **The recruited SMCs synthesize ECM (most notably collagen), which stabilizes atherosclerotic plaques.**
- **But activated inflammatory cells in atheromas also can cause intimal SMC apoptosis & breakdown of matrix, leading**



Morphology



Fatty streaks: minute yellow, flat macules → coalesce into elongated lesions,> 1 cm. Composed of lipid-filled foamy macrophages. No flow disturbance. Aortas of infants can exhibit them, & present in all adolescents, regardless of genetic, clinical, or dietary risk factors. Not all fatty streaks progress to atherosclerotic plaques.

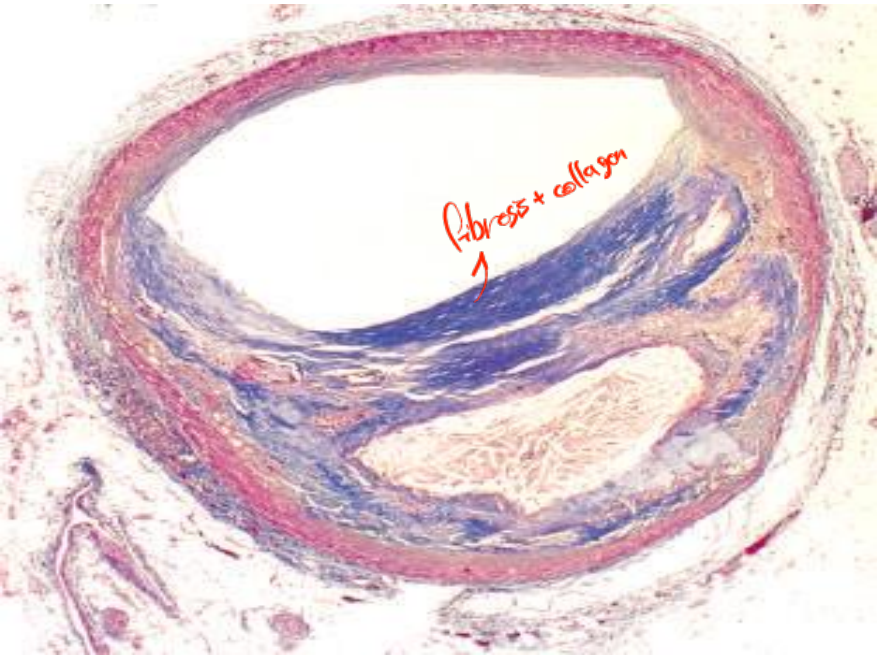


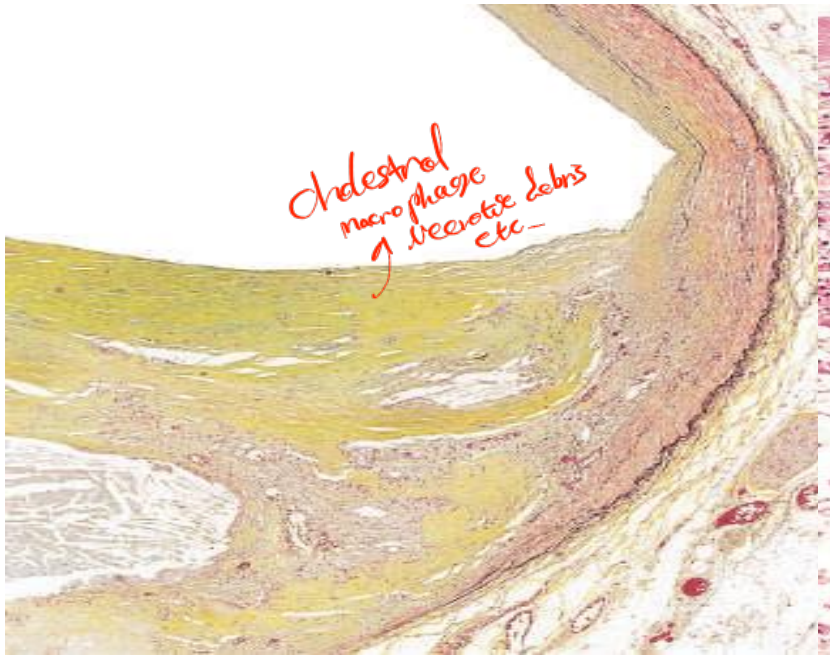
Atherosclerotic Plaque: Intimal thickening and lipid accumulation plaques are white to yellow **raised** lesions; range from 0.3 to 1.5 cm in diameter, can coalesce to form larger masses. Thrombus superimposed on ulcerated plaques imparts a red-brown color

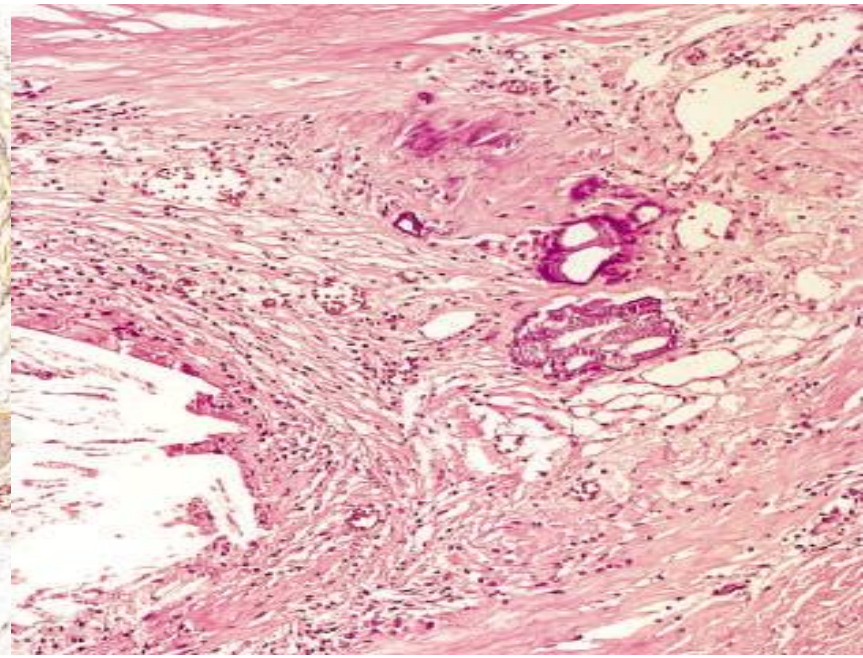
- Atherosclerotic plaques have three principal components:

(1) Cells, including SMCs, macrophages, and T cells.
(2) ECM, including collagen, elastic fibers, and proteoglycans.
(3) Intracellular and extracellular lipid.

- In descending order of severity, atherosclerosis involves the **infrarenal abdominal aorta, the coronary arteries, the popliteal arteries**, the internal carotid arteries, & the vessels of the circle of Willis.







Plaques: (1)A superficial **Fibrous cap** composed of SMCs and relatively dense collagen. Where the cap meets the vessel wall (shoulder) is a more cellular area (macrophages, T cells, & SMCs)

Deep to the fibrous cap is (2) a necrotic **core**, containing lipid, necrotic debris, foam cells, fibrin, variably organized thrombus, & other plasma proteins.

the internal and external elastic membranes are attenuated, & the media of the artery is thinned under the most advanced plaque

Plaques progressively enlarge over time through cell death & degeneration, synthesis & degradation of ECM (remodeling), & thrombus organization. Atheromas also often undergo calcification and neovascularization

Atherosclerotic Stenosis

- **Critical stenosis:** the tipping point at which chronic occlusion limits flow so severely to produce tissue ischemia.
- At early stages, remodeling of the media tends to preserve the luminal diameter by increasing the vessel circumference.
- Remodeling is limited → eventually atheroma may impinge on blood flow. Although this most commonly happens as a consequence of acute plaque change, it can also occur gradually, with critical stenosis which limits flow.

Acute Plaque Change

Plaque erosion or rupture typically triggers thrombosis, leading to partial or complete vascular obstruction & often tissue infarction; three general categories:

- **Rupture/fissuring**, exposing highly thrombogenic plaque constituents.
- **Erosion/ulceration**, exposing the thrombogenic subendothelial basement membrane to blood.
- **Hemorrhage into the atheroma**, expanding its volume.

It is now recognized that plaques responsible for myocardial infarctions & other acute coronary syndromes often are asymptomatic before the acute event. The worrisome conclusion is that large numbers of asymptomatic individuals are at risk for a catastrophic coronary event.

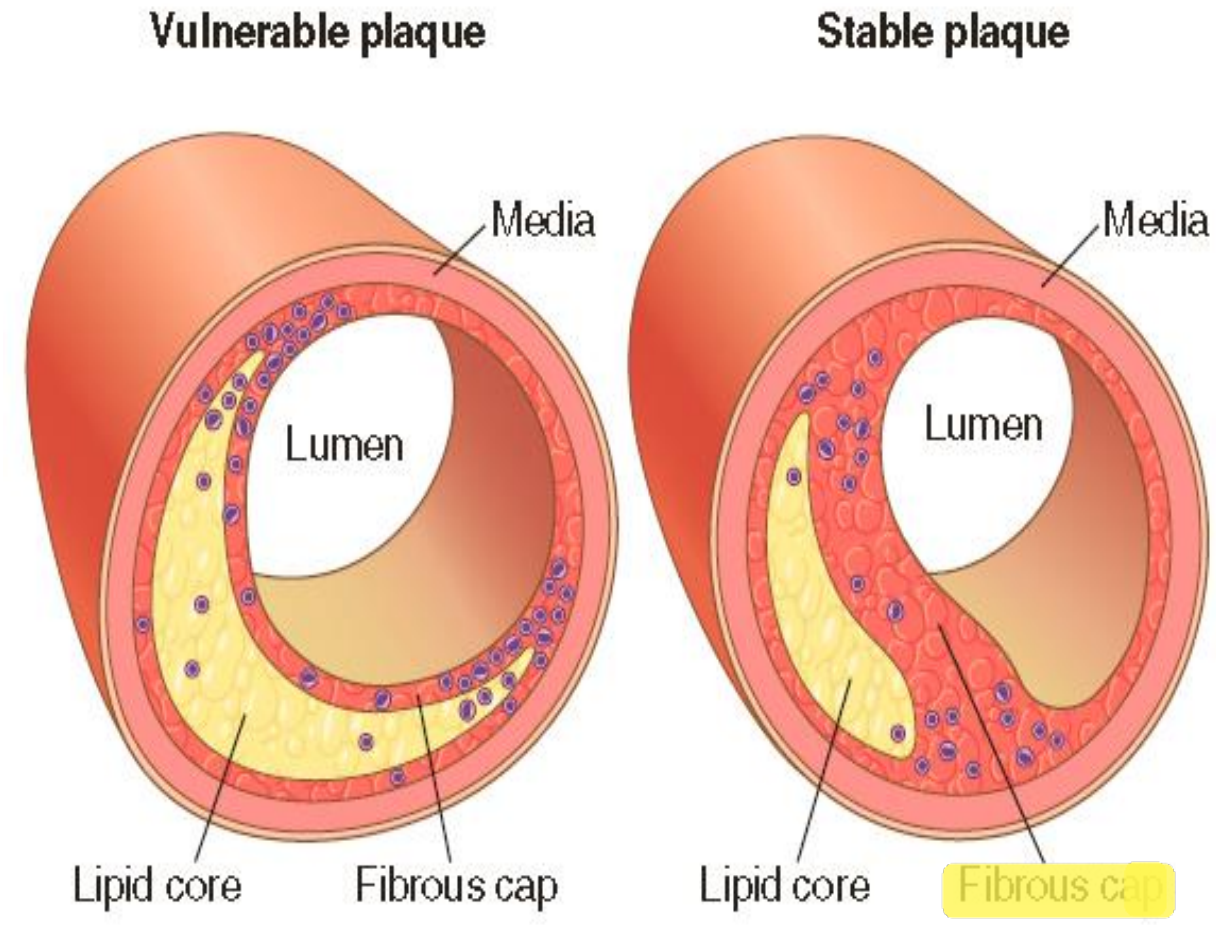
Causes of acute plaque changes

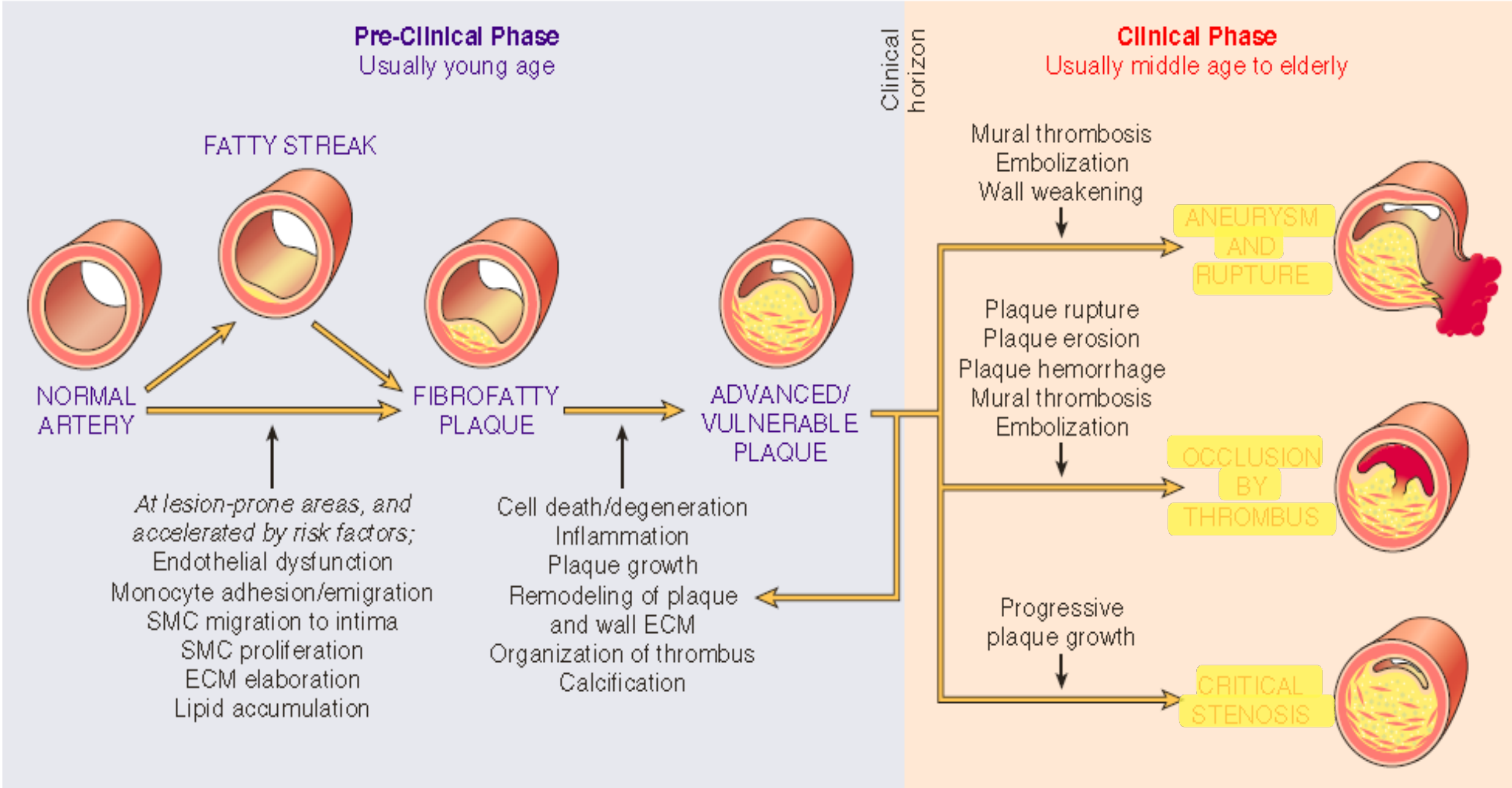
- **Complex but could be divided:**
- **Intrinsic factors:**

Vulnerable plaques: Plaques at high risk for rupture, they contain **large** numbers of **foam cells** & **abundant extracellular lipid**, have **thin fibrous caps** containing **few SMCs**, and contain **clusters of inflammatory cells**.

- **Extrinsic factors:**

Adrenergic stimulation (as with intense emotions) can increase systemic blood pressure or induce local **vasoconstriction**, thereby increasing the mechanical stress on a given plaque.




Pre-Clinical Phase
Usually young age
Clinical horizon
Clinical Phase
Usually middle age to elderly
FATTY STREAK
NORMAL ARTERY
FIBROFATTY PLAQUE
ADVANCED/ VULNERABLE PLAQUE
At lesion-prone areas, and accelerated by risk factors;
Endothelial dysfunction
Monocyte adhesion/emigration
SMC migration to intima
SMC proliferation
ECM elaboration
Lipid accumulation
Cell death/degeneration
Inflammation
Plaque growth
Remodeling of plaque and wall ECM
Organization of thrombus
Calcification
Mural thrombosis
Embolization
Wall weakening
ANEURYSM AND RUPTURE
Plaque rupture
Plaque erosion
Plaque hemorrhage
Mural thrombosis
Embolization
OCCLUSION BY THROMBUS
Progressive plaque growth
CRITICAL STENOSIS