# The pathogenesis of atherosclerosis

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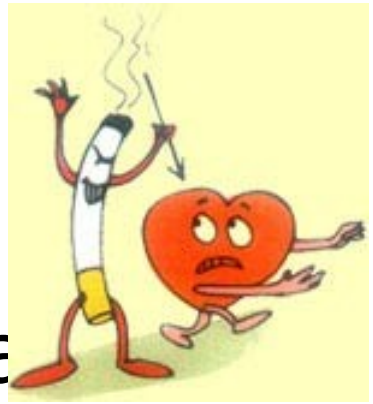
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# Introduction

- Atherosclerosis is a pathological condition characterised by the development of arterial plaques
- Most common pathology of arteries
- Causes heart disease, stroke, aneurysm, peripheral vascular disease
- Accounts for 30% of female & 40% of male deaths in <75yrs

# Risk Factors

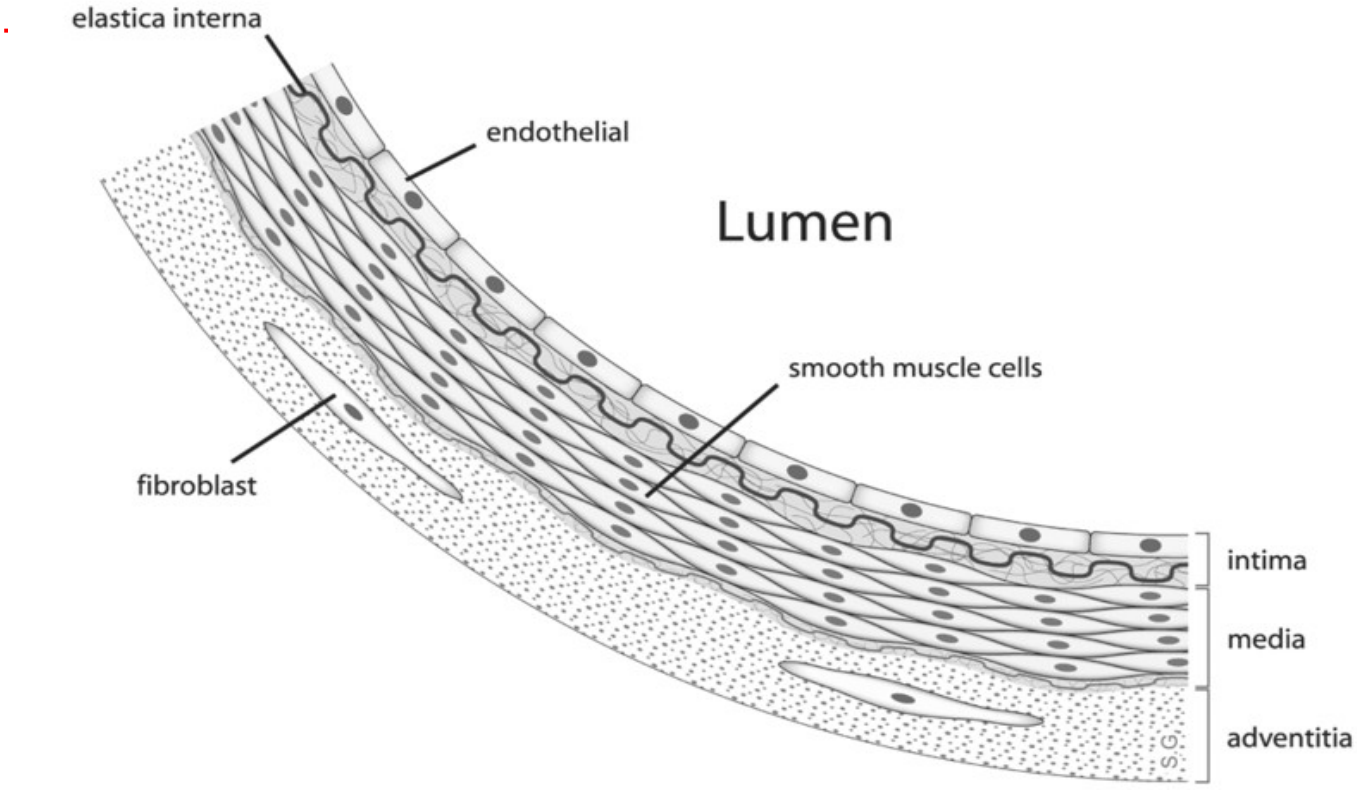
- Age
- Smoking
- Hypercholesterolaemia
- Hypertension
- Diabetes
- Family history of atherosclerotic diseases



# Normal Arterial Anatomy

- **Intima** – single layer endothelium + connective tissue
- Internal elastic lamina separates intima from media
- **Media** – mainly smooth muscle (aorta – elastic)
- **Adventitia** – fibrous connective tissue

# Normal Arterial Anatomy

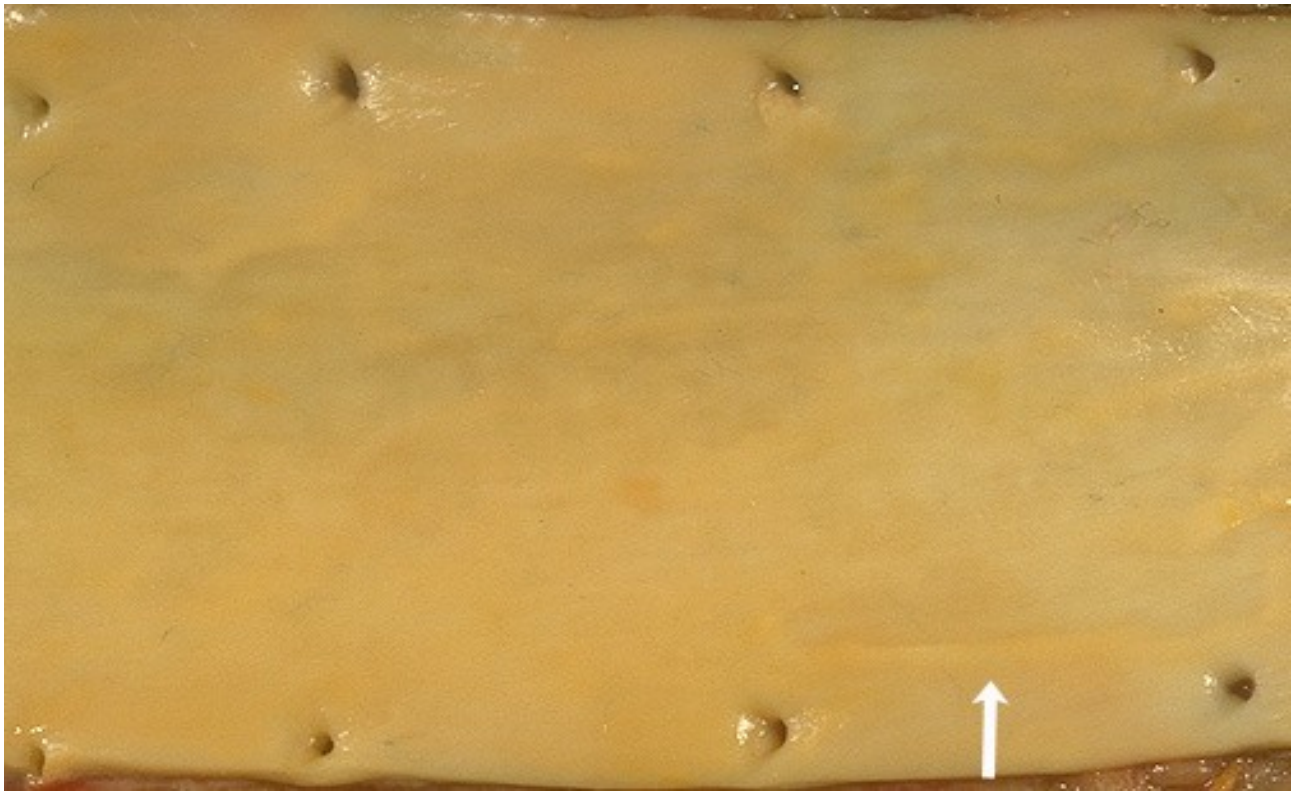


# Morphology

- Fatty streaks – linear lesions of foam cells & T-lymphocytes in intima

  Present in children
- Transitional plaque – as above plus migration of smooth muscle cells (SMC) into intima

# Fatty streaks



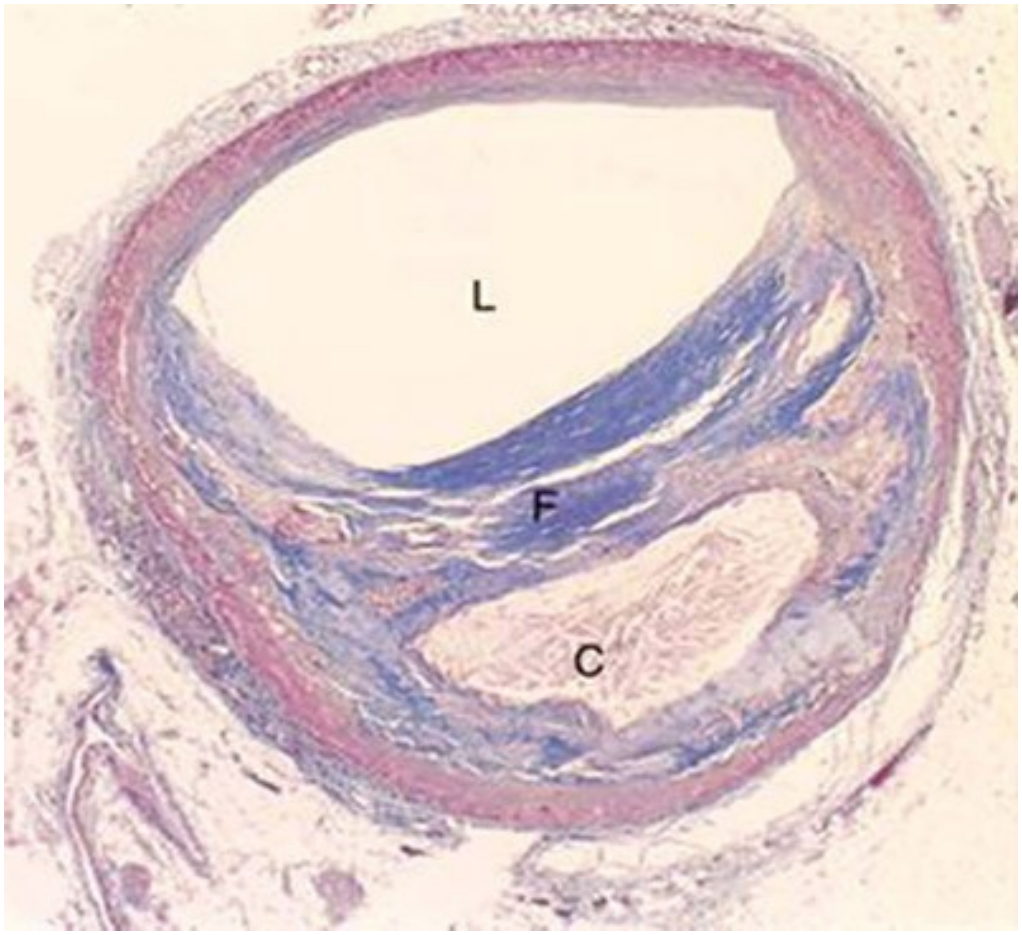
# Morphology cont'd

- Advanced plaques – dense fibrous cap of connective tissue and SMC overlying necrotic core with lipids

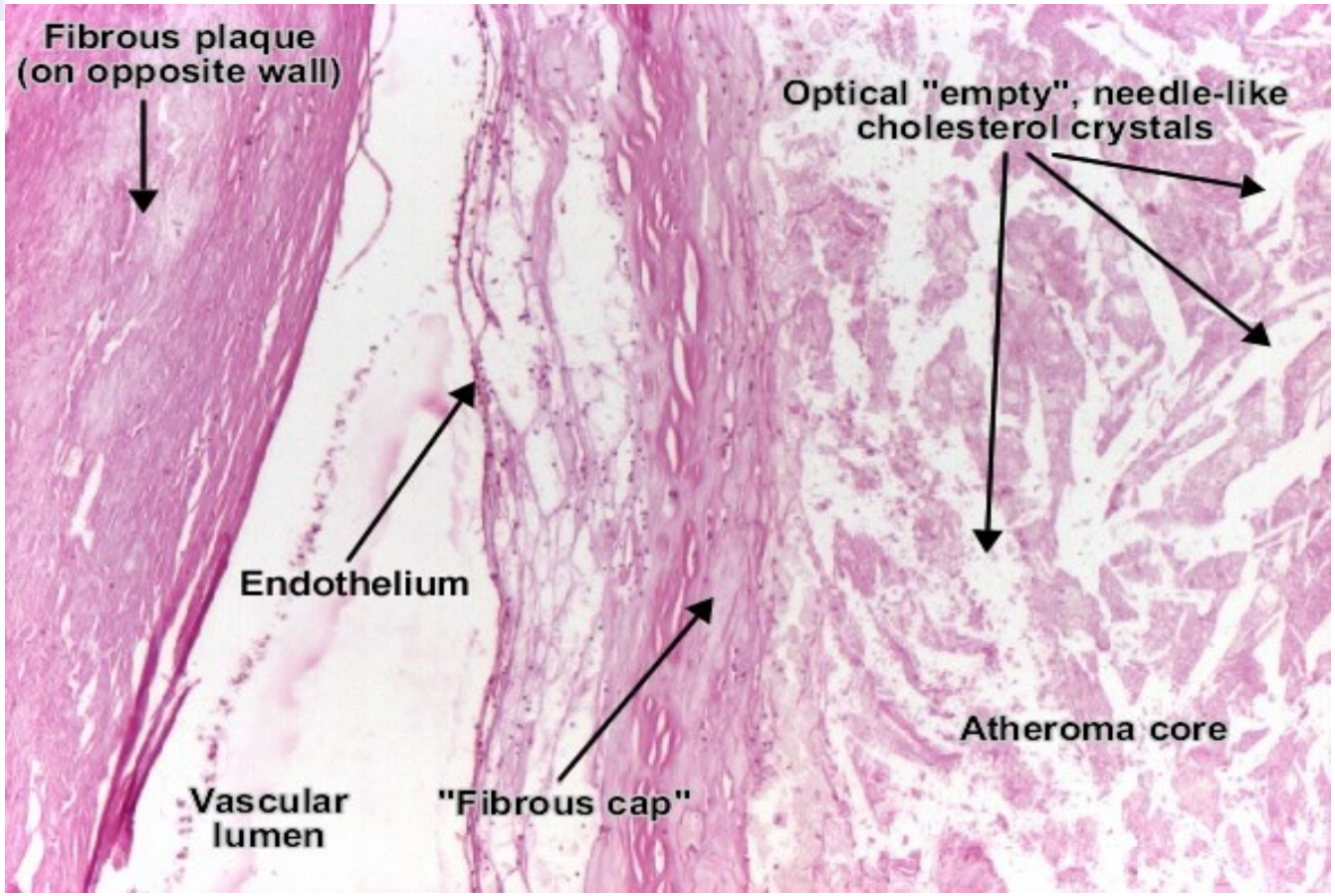
  Large number foam cells, SMC & T cells

  Vascularisation → access inflammatory cells
- Complicated lesion – develops from advanced, thin cap at shoulders/margins of lesion may contain ulcerations, erosions, fissures

# Advanced plaque in X-section



# Advanced plaque



# Pathogenesis

- Initially a response to injury hypothesis
- Spectrum from endothelial disjunction to altered permeability/growth factor secretion
- Chronic inflammatory process
- Dynamic

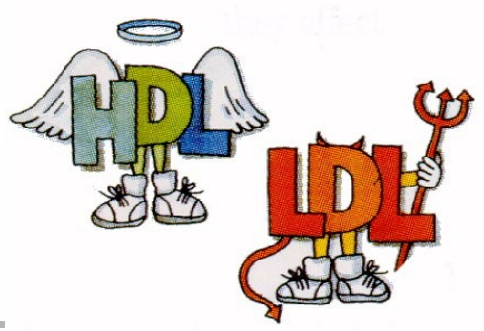
# Endothelium involvement

- Affected by tobacco smoke toxins, modified LDL, hypertension, diabetes
- Alters normal homeostasis
  - Increased expression of adhesion molecules (ICAM-1, E-selectin) & growth promoting factors (PDGF)
  - Monocytes & T-cells adhere to endothelium

    Produce GFs, cytokines, and chemoattractants

    Adherent WCCs migrate into intima, SMC from media
- Repeated injury/repair →accumulates →plaque

# LDL

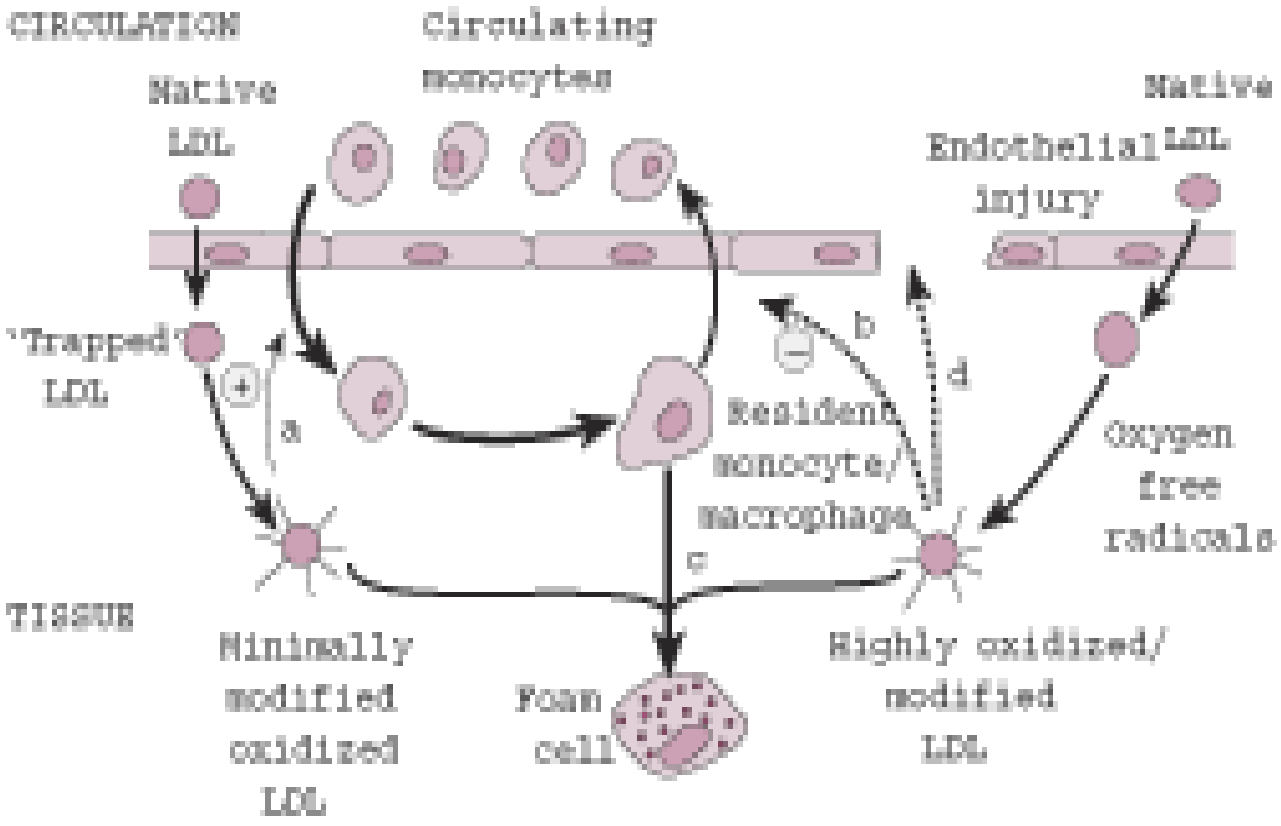



- Enters intima through damaged endothelium or by transcytosis via LDL receptor
- Minimally modified by oxidative free radicals
- Stimulates release of macrophage colony stimulating factor & monocyte chemotactic protein 1 from endothelium
- Mod. LDL adheres to proteins of arterial wall → extensive oxidation by free radicals from macrophages and nitric oxide derived from endothelium

# LDL cont’d

- Highly oxidised LDL is not recognised by the LDL receptor but becomes the major ligand for the scavenger receptor expressed in the accumulating macrophages
- This increases uptake of oxidized LDL by receptors, not regulated by the cholesterol content of the cell
- Causes massive accumulation of cholesteryl esters in the macrophages, cytoplasm appears foamy

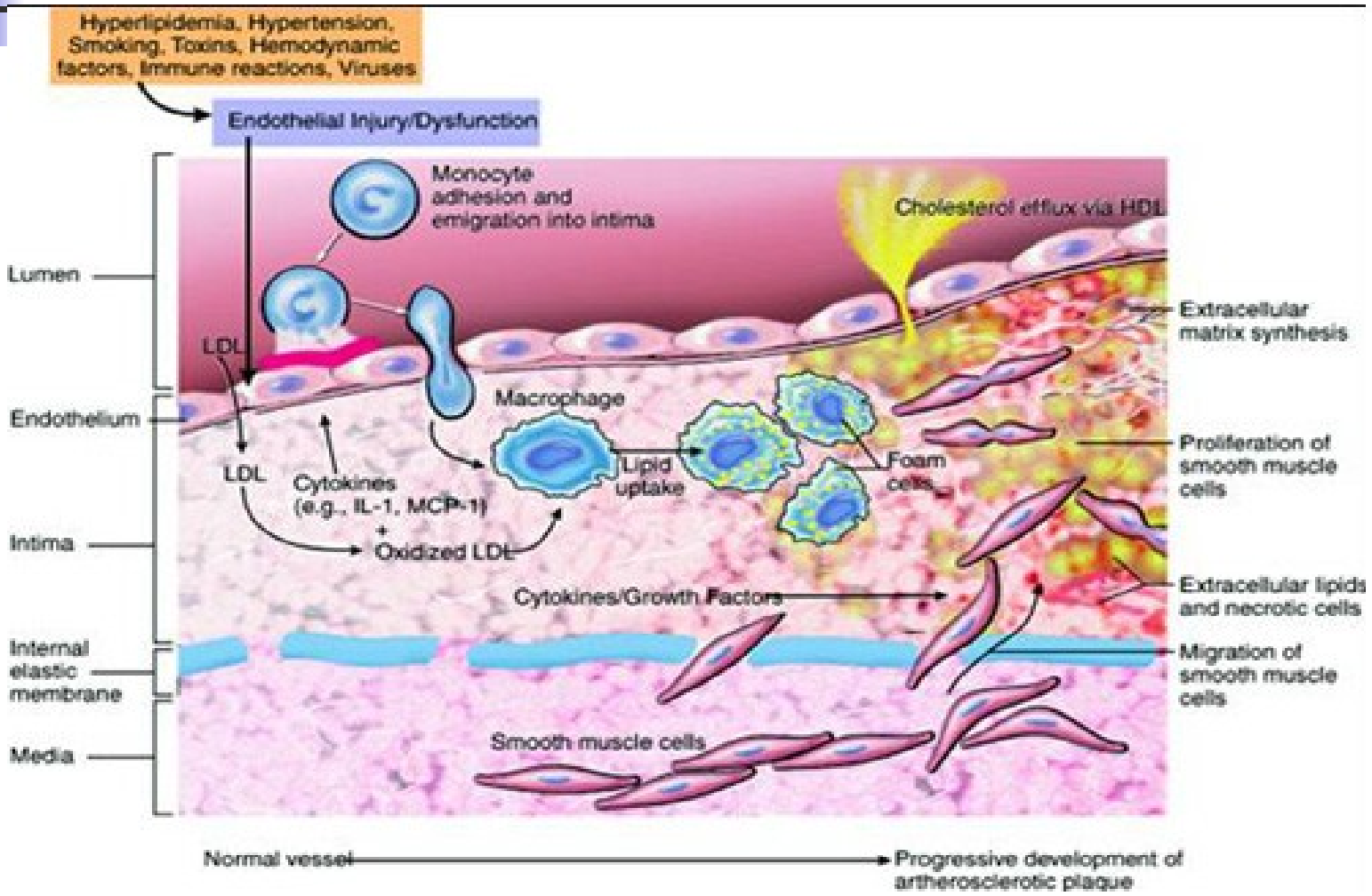
# LDL/macrophage interaction



# Smooth muscle cells

- Contractile type
- Usually respond to vasoregulatory substances – e.g. catecholamines, angiotensin II, prostaglandins
- Act to vasodilate/constrict and maintain ECM by secreting collagen & elastin
- Intimal hyperplasia following endothelial damage
- In presence of proinflammatory cytokines and growth factors (PDGF) become secretory, producing alternative ECM
- Consists of proteoglycans & loose collagen fibrils

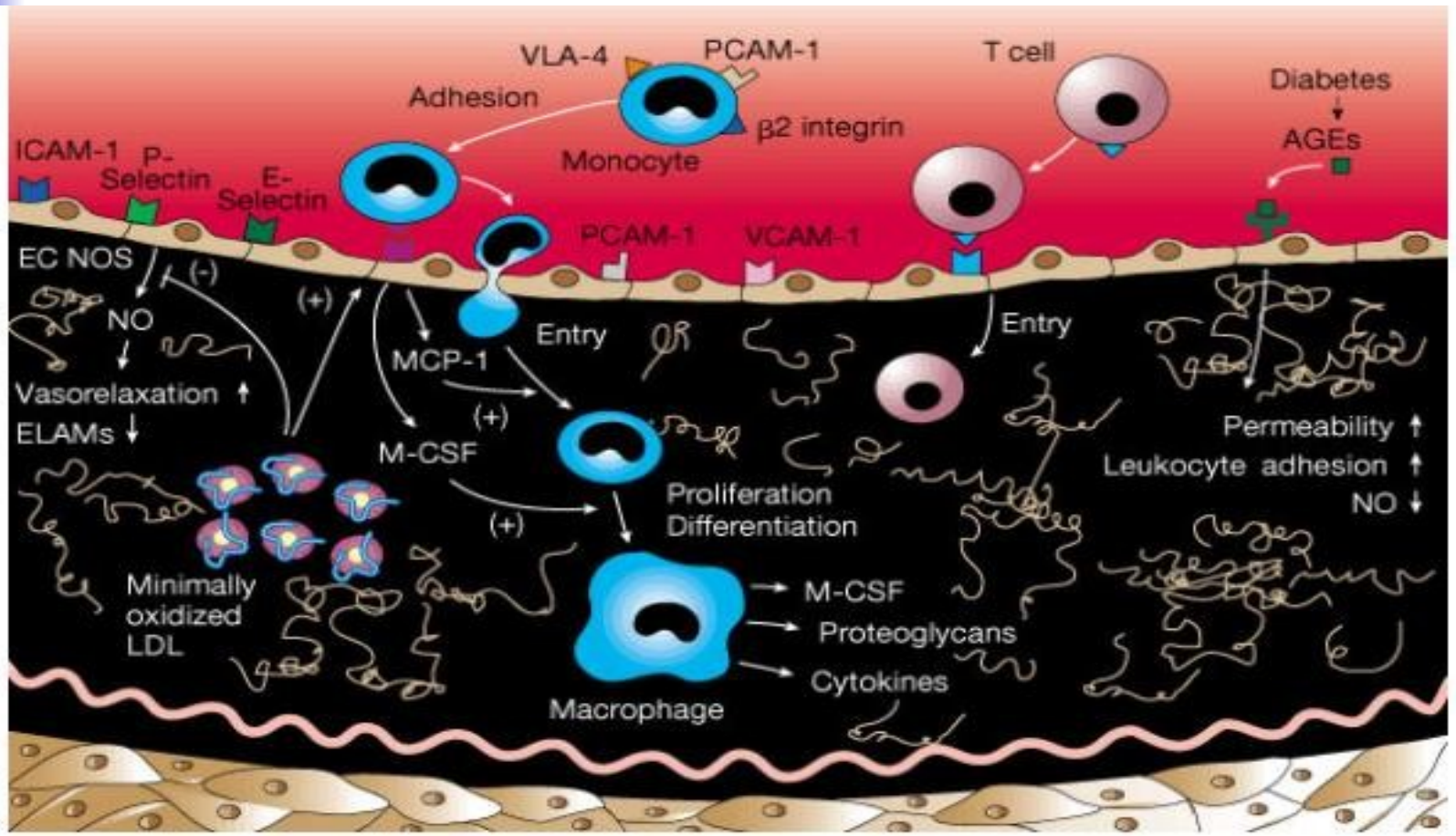
# Smooth muscle cell effects



# T-lymphocytes

- Become activated by antigens presented by macrophages
- Secretion of pro-inflammatory cytokines (e.g. IL-1, interferon-γ, TNF-α and β)
- Amplify the inflammatory response, attracting further macrophages and T lymphocytes and perpetuating endothelial cell activation
- T cells in the plaque become sensitized to new antigens e.g. modified LDL

# Atherosclerosis & inflammation



# Plaque stability

- Size of lipid core
- Size of fibrous cap
- SMC and collagen
- Macrophages and T-cells
- Protease action

# Serum LDL & plaque stability

- High serum LDL increases incidence CVD
- Lower cholesterol diet
- Statins (HMG CoA reductase inhibitors) proven to reduce total and LDL cholesterol and subsequently mortality
- Statins do not reduce plaque size, modifies structure

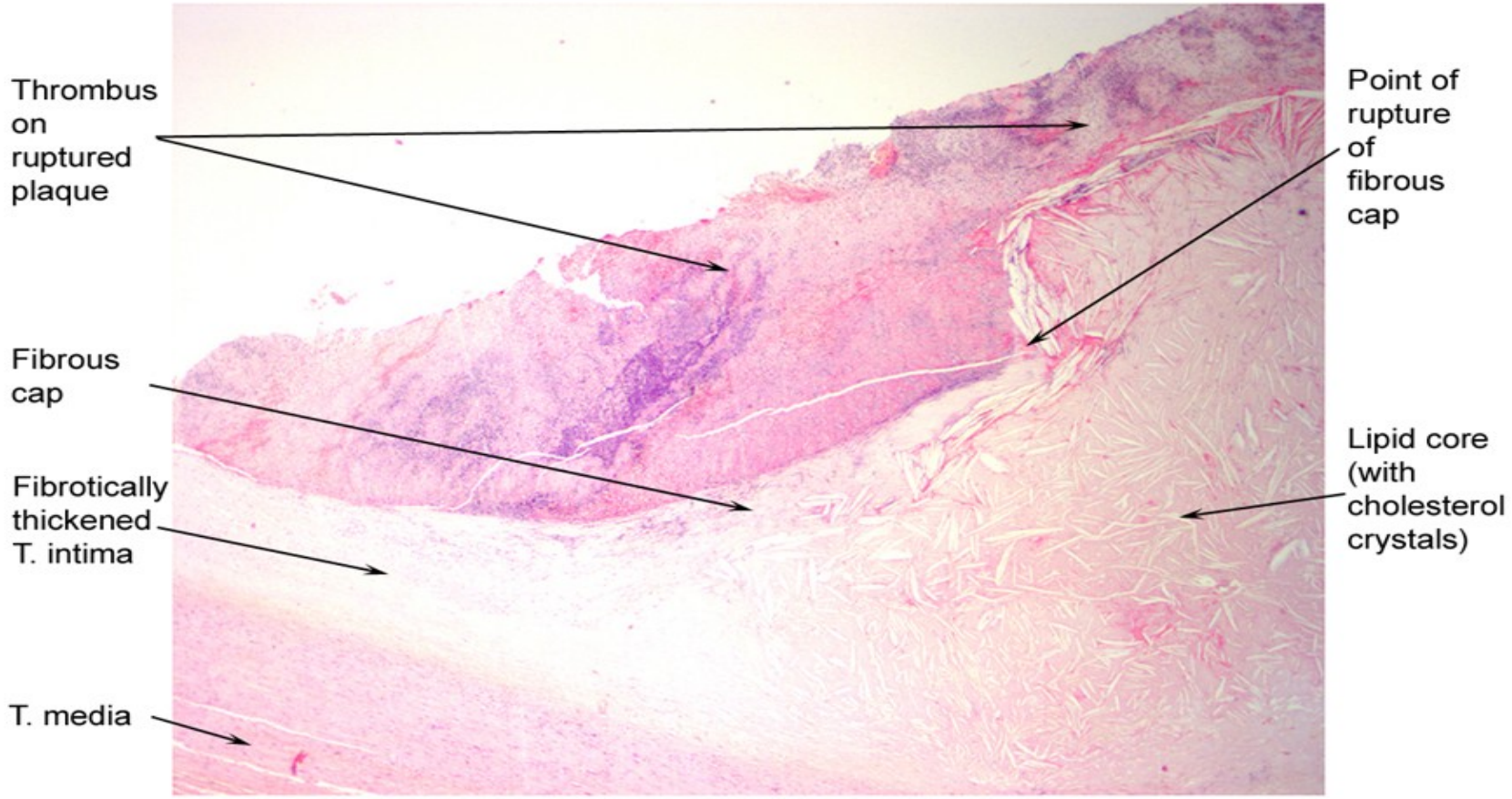
# Plaque rupture & thrombosis

- Exposure of thrombogenic core to luminal blood
- Plasma membrane expression of tissue factor
- Coagulation pathway cascade (VIIa, IX & X)
- Thrombin induces P-selectin and PAF
- Accumulation and activation of platelets
- Release of thromboxane A2, PDGF – potent vasoconstrictors
- E-selectin is induced, acts as a site for leucocyte attachment

# Triggers for plaque rupture (coronary arteries)

- Physical activity
- Emotional stress (anger)
- Environmental (air pollution), smoking
- Circadian variation (increased morning risk)
- Peak on Mondays (for workers)
- Peak in Winter and cold days

# Atherosclerotic plaque rupture



# Clinical manifestation of plaque pathology

- Plaque erosion/minor fissure
- Endothelial dysfunction
- Vascular remodelling
- Organised thrombus
- Residual stenosis
  - Chronic angina
  - Peripheral vascular disease

# Clinical manifestation of plaque pathology 2

- Plaque erosion/fissure
- Platelet activation & aggregation
- Inflammatory cell migration
- Transient occlusion
- Platelet emboli

- Unstable angina
- Sudden death
- Stroke
- Acute ischaemic PVD

# Clinical manifestation of plaque pathology 3

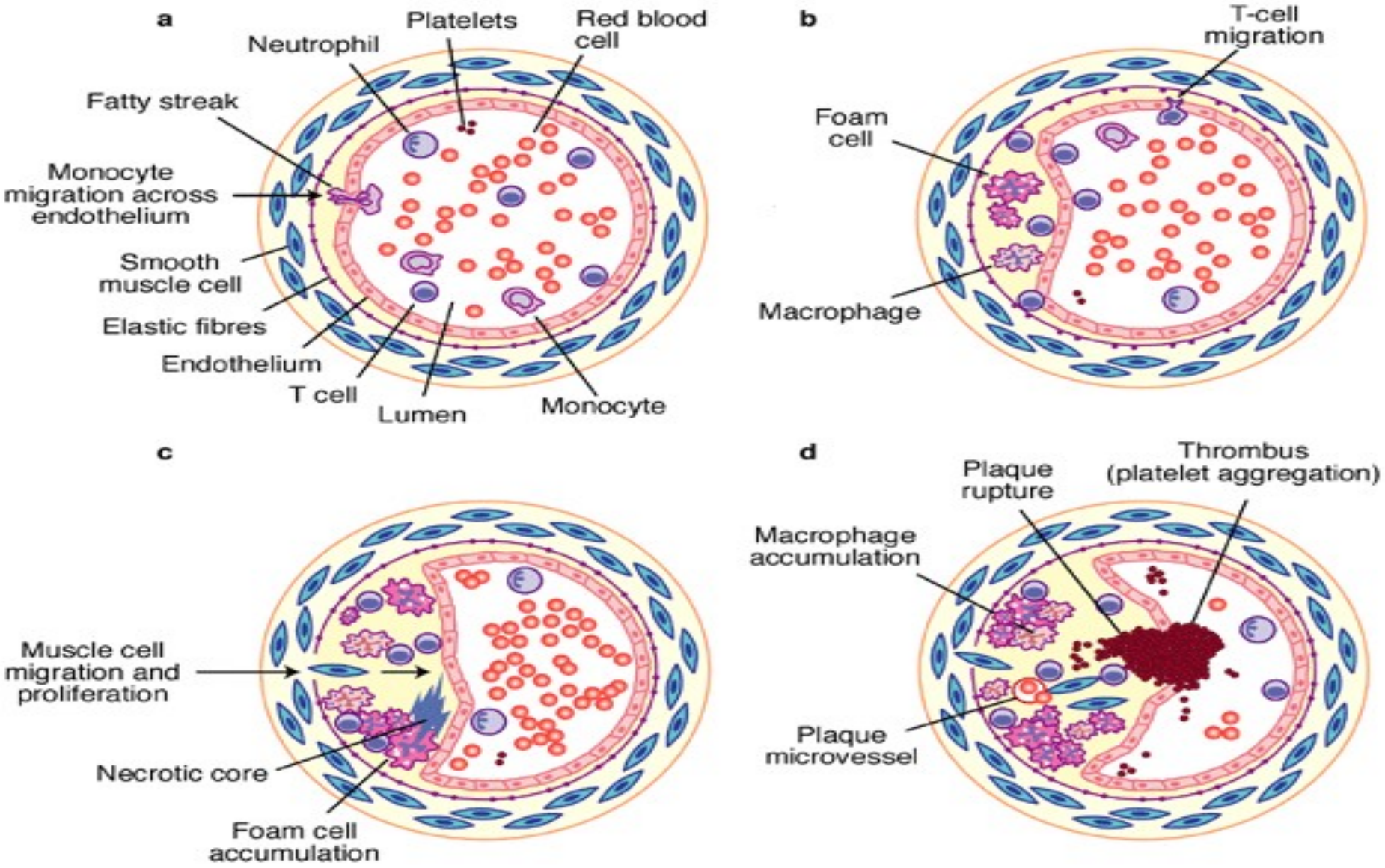
- Plaque erosion/fissure
- Platelet activation & aggregation
- Inflammatory cell migration
- Temporary occlusion (<2 hours)
- Endogenous thrombolysis
  - Non-Q wave MI
  - Stroke

# Clinical manifestation of plaque pathology 4

- Plaque rupture/fissure
- Highly thrombogenic substrate
- Occlusive fibrin rich thrombus
- Abrupt cessation perfusion
- Myocardial necrosis
  - Q-wave or STEMI
  - Sudden death

# Atheromatous plaque with haemorrhage






Stages of atherosclerotic plaque development

# Conclusion

- Atherosclerosis major underlying cause of morbidity and mortality in UK
- Chronic inflammatory process
- Interaction between arterial structure and circulating factors
- Modifiable

# Bibliography


- D Brown (ed) 2002 **Cardiovascular plaque rupture**. Marcel Dekker, New York.
- JCE Underwood (ed) 2000 **General and systematic pathology**, 3rd ed. Churchill Livingstone, Edinburgh.
- D Warrell, TM Cox, JD Firth, EJ Benz (eds) 2004 **Oxford Textbook of Medicine**, 4th ed. Oxford University Press