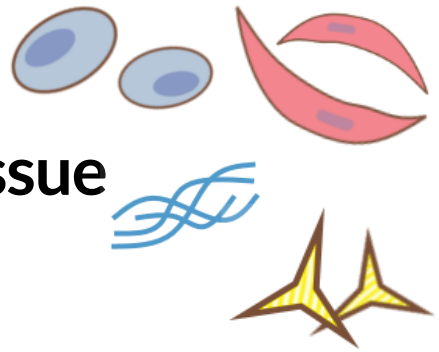
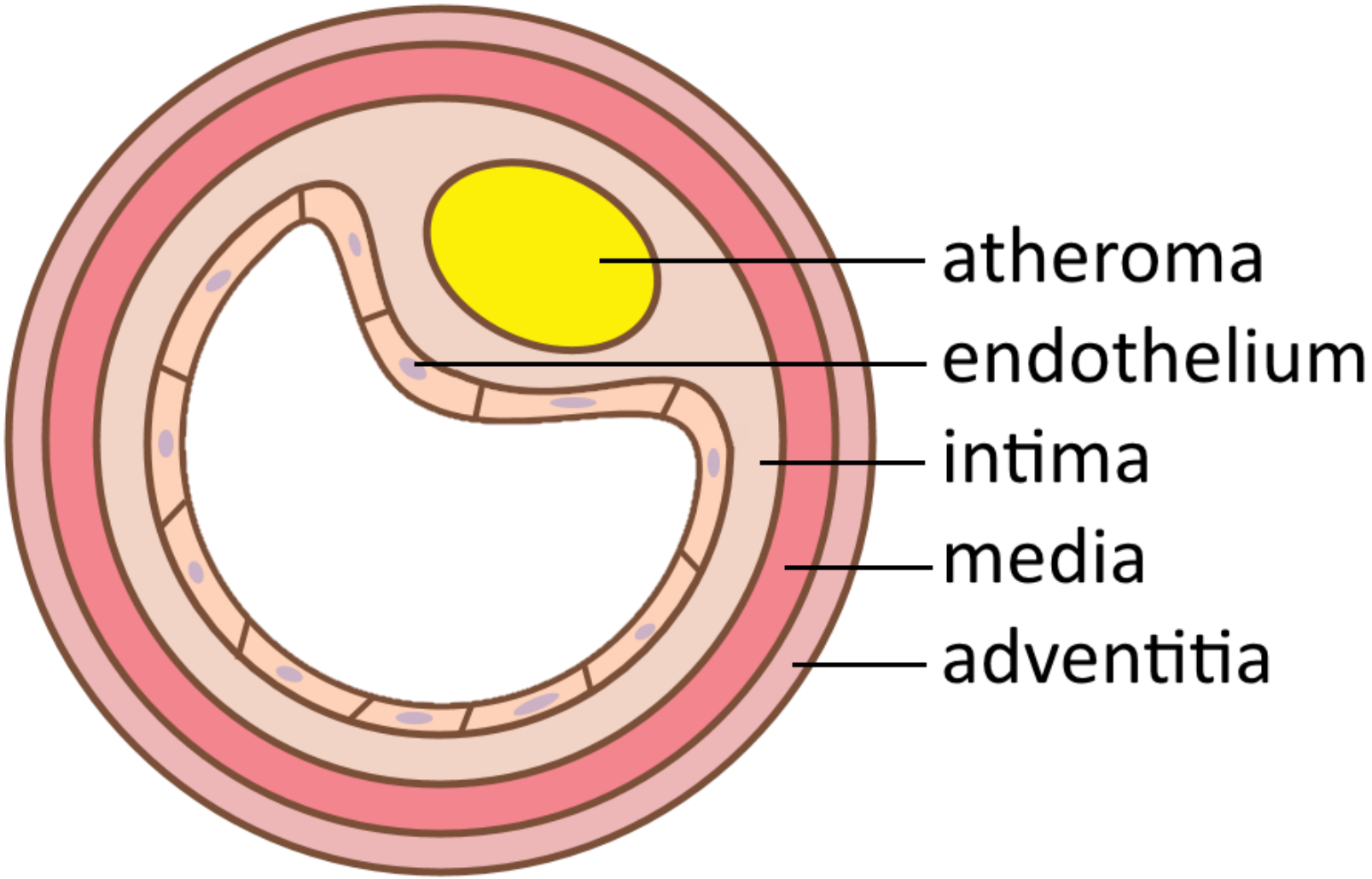
Definition

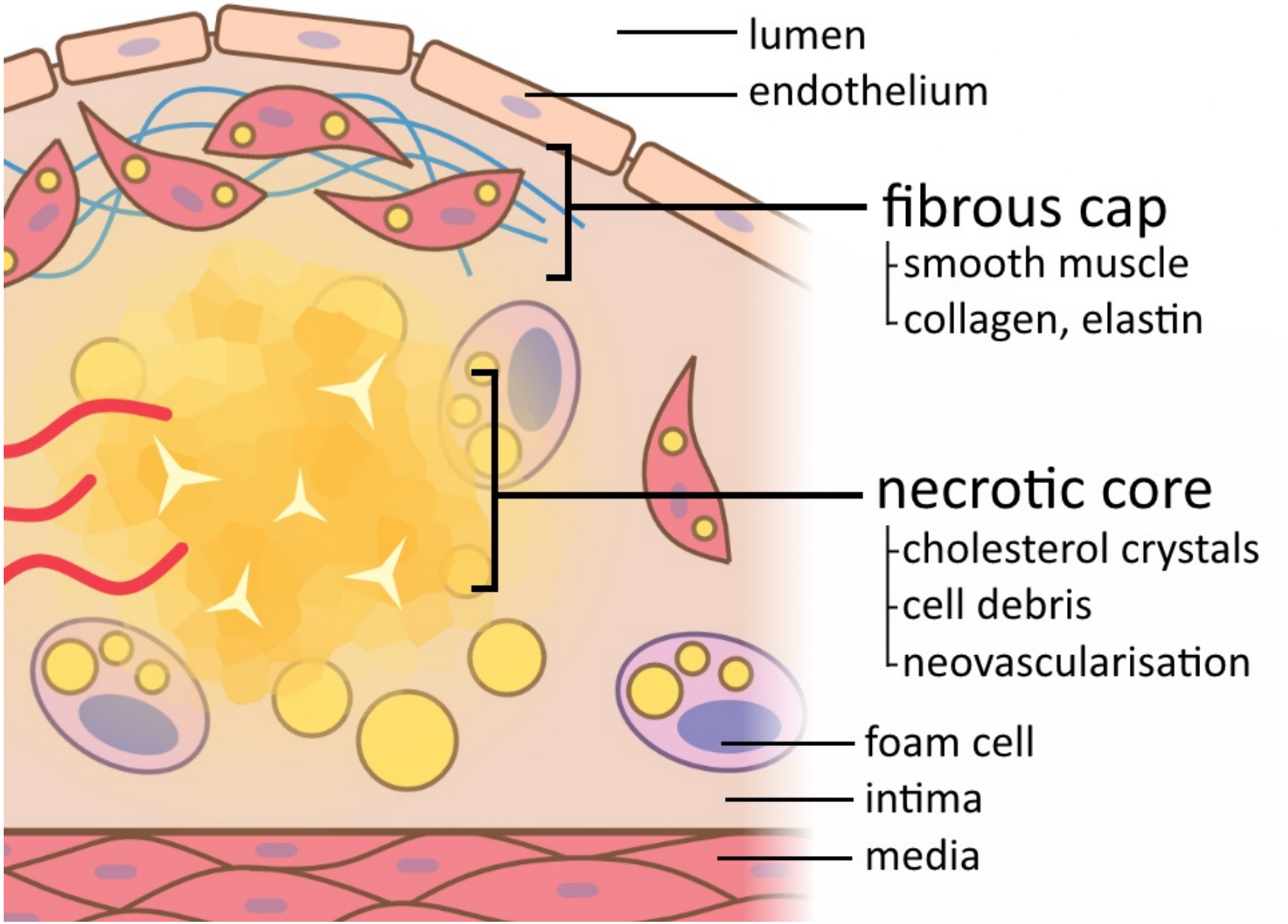
- The **development** of **lesions** in vessel intimal wall
- Known as ***atherosclerotic plaques*** or ***atheromas***
- Within **intima** of **large** and **medium-sized vessels**

- Grows over decades to **physically obstruct vessels**
- Prone to **thrombogenic rupture**
- Weakens vessel wall, leads to **aneurysm**

- Composition:
  - **inflammatory** and **immune** cells
  - **smooth muscle** cells, **connective tissue**
  - **lipid**, **cholesterol**




atheroma
endothelium
intima
media
adventitia


lumen
endothelium
fibrous cap
smooth muscle
collagen, elastin
necrotic core
cholesterol crystals
cell debris
neovascularisation
foam cell
intima
media

Prevalence

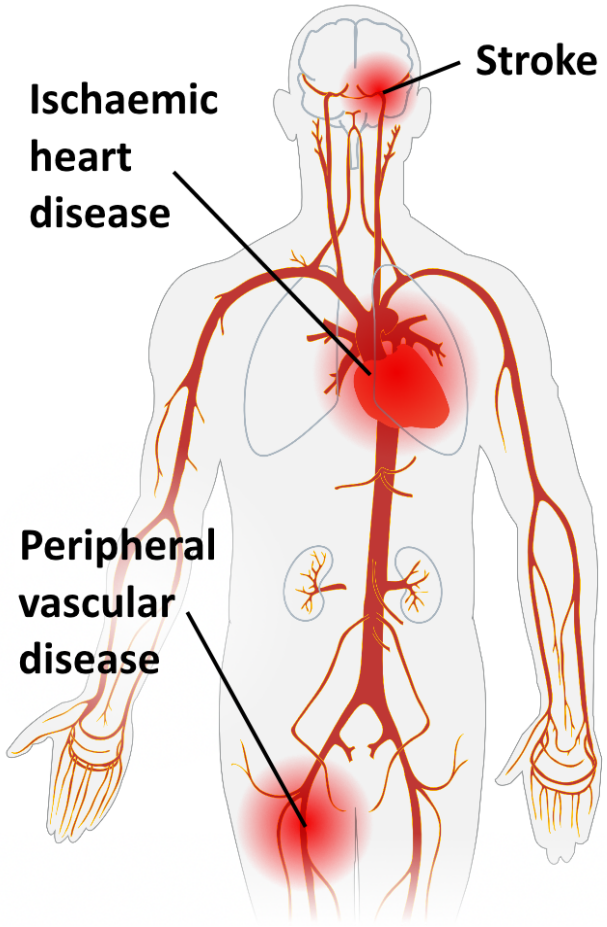
- Extremely common in the **Western world**
- **Leading cause** of **morbidity** and **mortality**

- Incidence increasing for past 50 years
- Now **peaked** and **declining** in some areas (e.g. US)
- Still rising elsewhere (e.g. Japan)

Morbidity

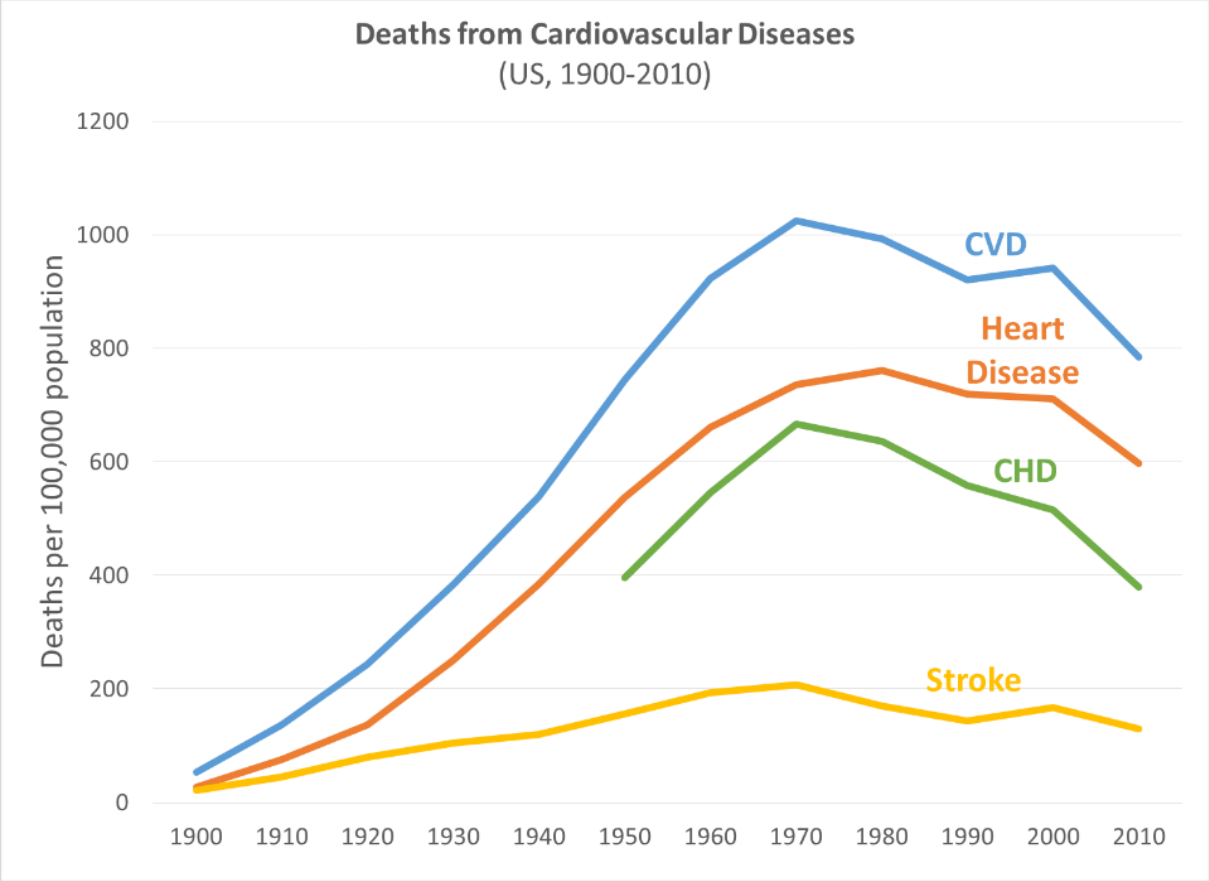
- Responsible for **18% of all DALYs** lost in the West

- **Ischaemic heart disease**
  - angina
  - myocardial infarction
- **Stroke**
  - severe, long-term disability
- **Peripheral arterial disease**
  - pain, cyanosis
  - ulceration, gangrene



Mortality

- **Most common cause** of Western death
- Implicated in 50% of all deaths



Data: NHLBI

Cost

Coronary heart disease costs: Germany, 1996 (Ref: WHO)

Direct costs: primary care, clinical care, rehabilitation	$26 billion
Indirect costs: lost productivity due to death and disability	$48 billion
Average cost per case	$82,000

Pathogenesis

- A lesion slowly developing over 20-30 years
- May see initial stages (fatty streaks) in childhood

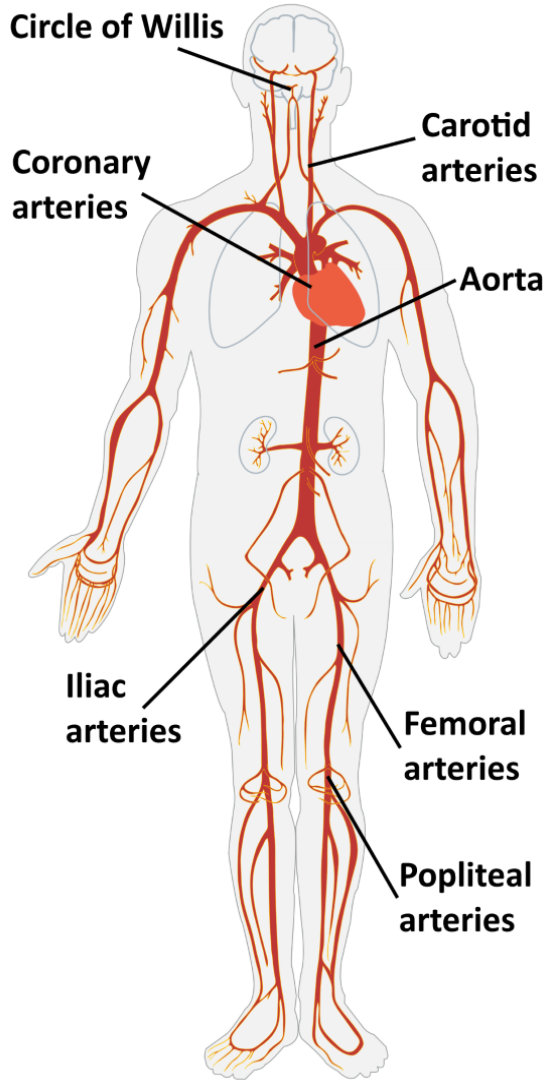
- Risk factors accelerate progression
- Chronic pathogenesis with acute complications

Distribution

- **Large** and **medium** arteries *only*
- Often at turbulent **branch points**

<u>Common sites:</u>

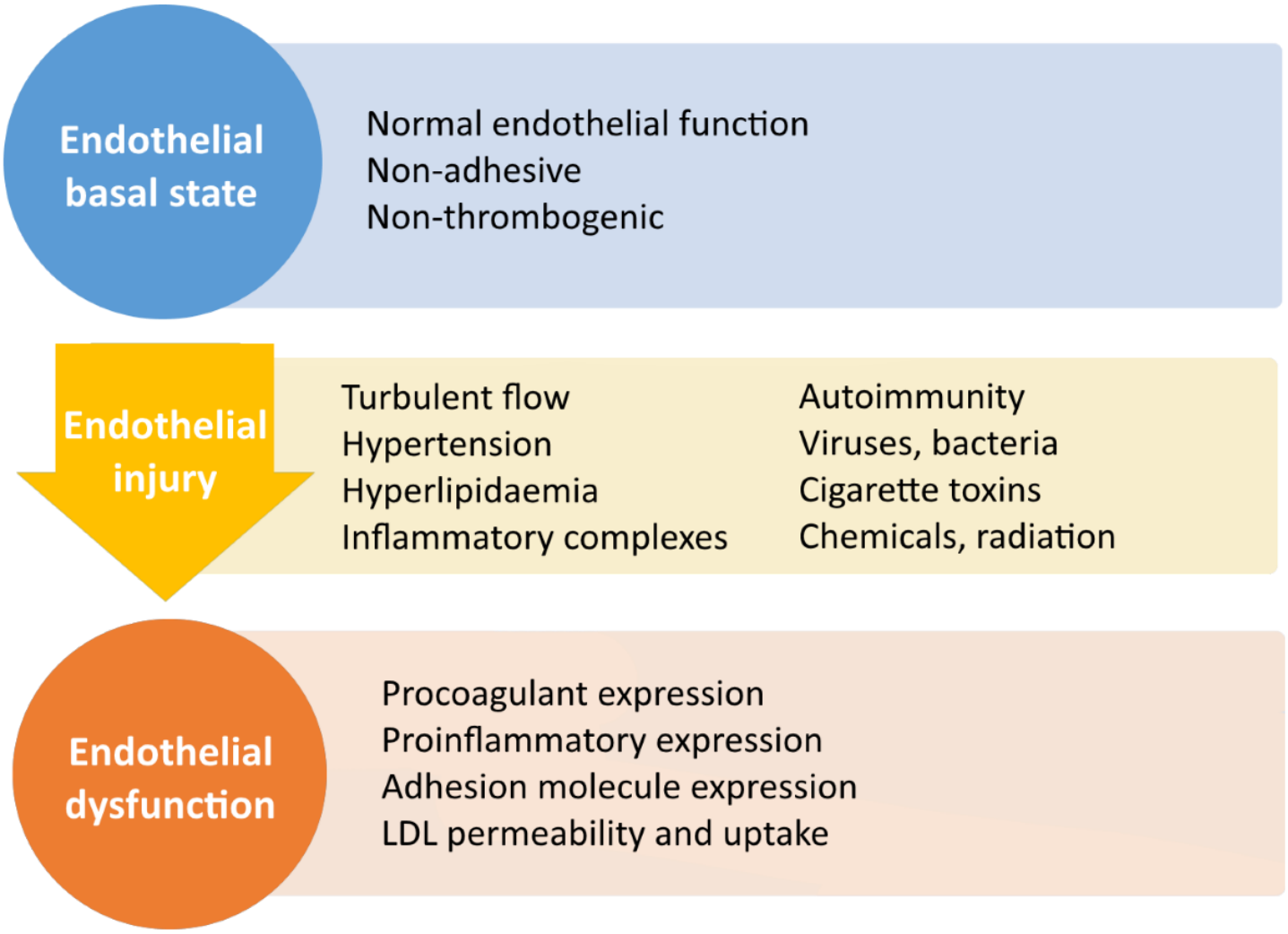
- Aorta
- Coronary arteries
- Iliac, femoral, popliteal arteries
- Carotid arteries
- Circle of Willis



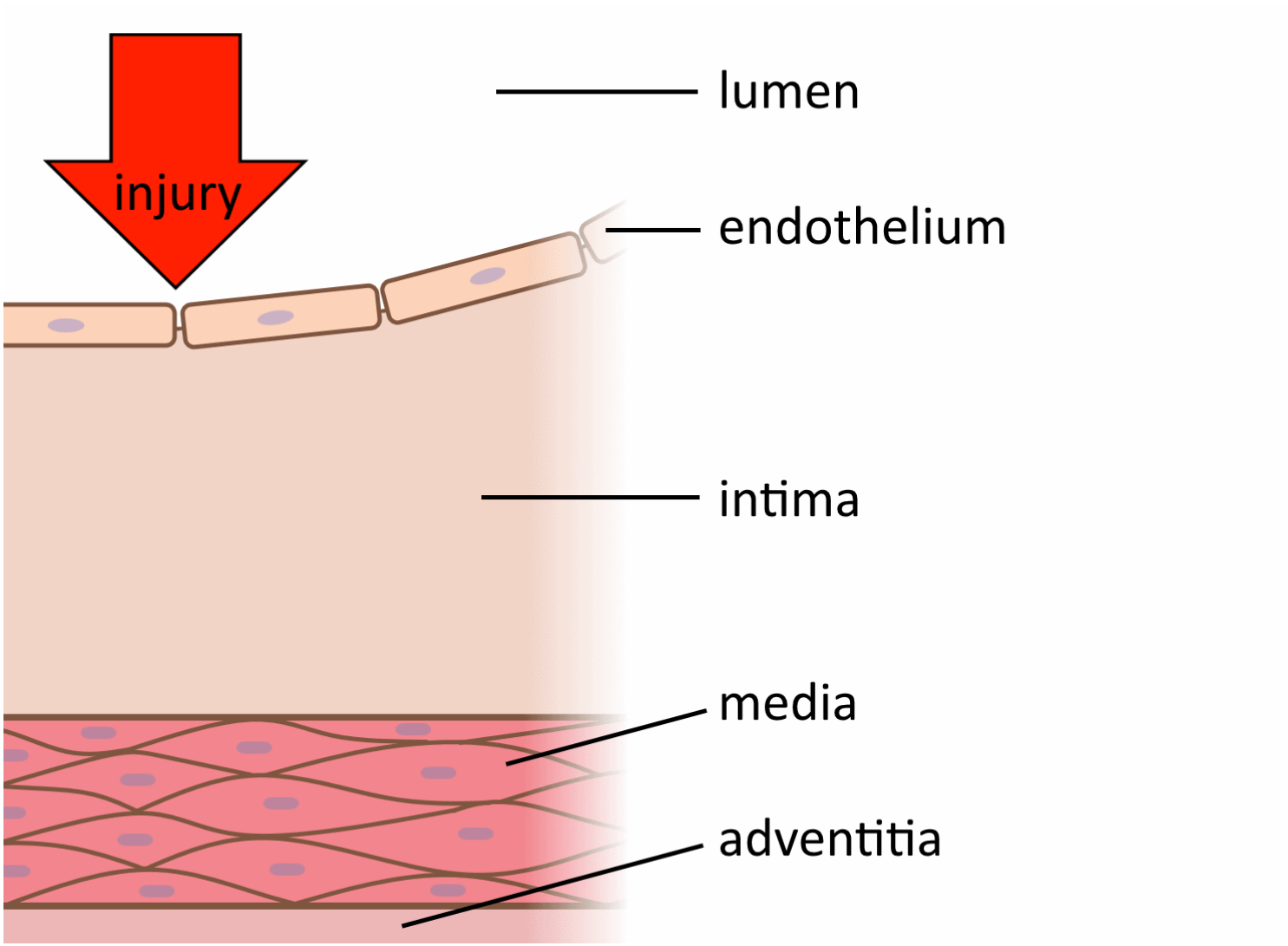
Summary of Events

- Endothelial **injury**
- Endothelial **dysfunction**
  - monocyte and platelet adhesion
  - LDL permeability and uptake
- **Engulfment**
  - of lipids by monocytes and smooth muscle
  - foam cell formation
- **Proliferation** of smooth muscle cells
  - fibrous cap generation
  - increasing size, vessel stenosis
- **Neovascularisation**
  - potential for haemorrhage

Endothelial Injury



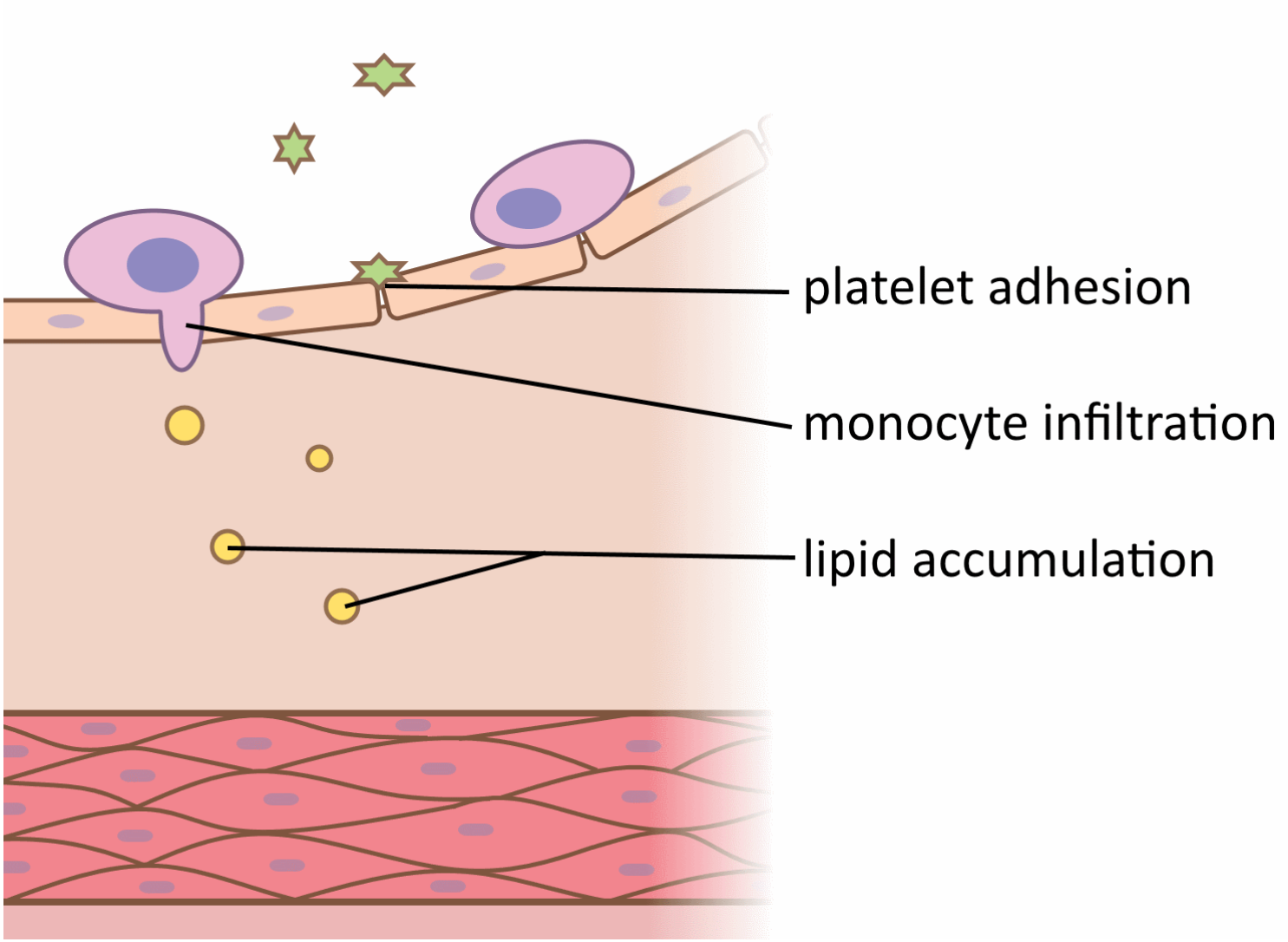
Endothelial Injury



Endothelial Dysfunction

- Endothelium becomes 'sticky' with **adhesion molecules**
- **Platelet** adhesion → thrombogenicity
- **Monocyte** infiltration
- Increased **LDL permeability** and **uptake**

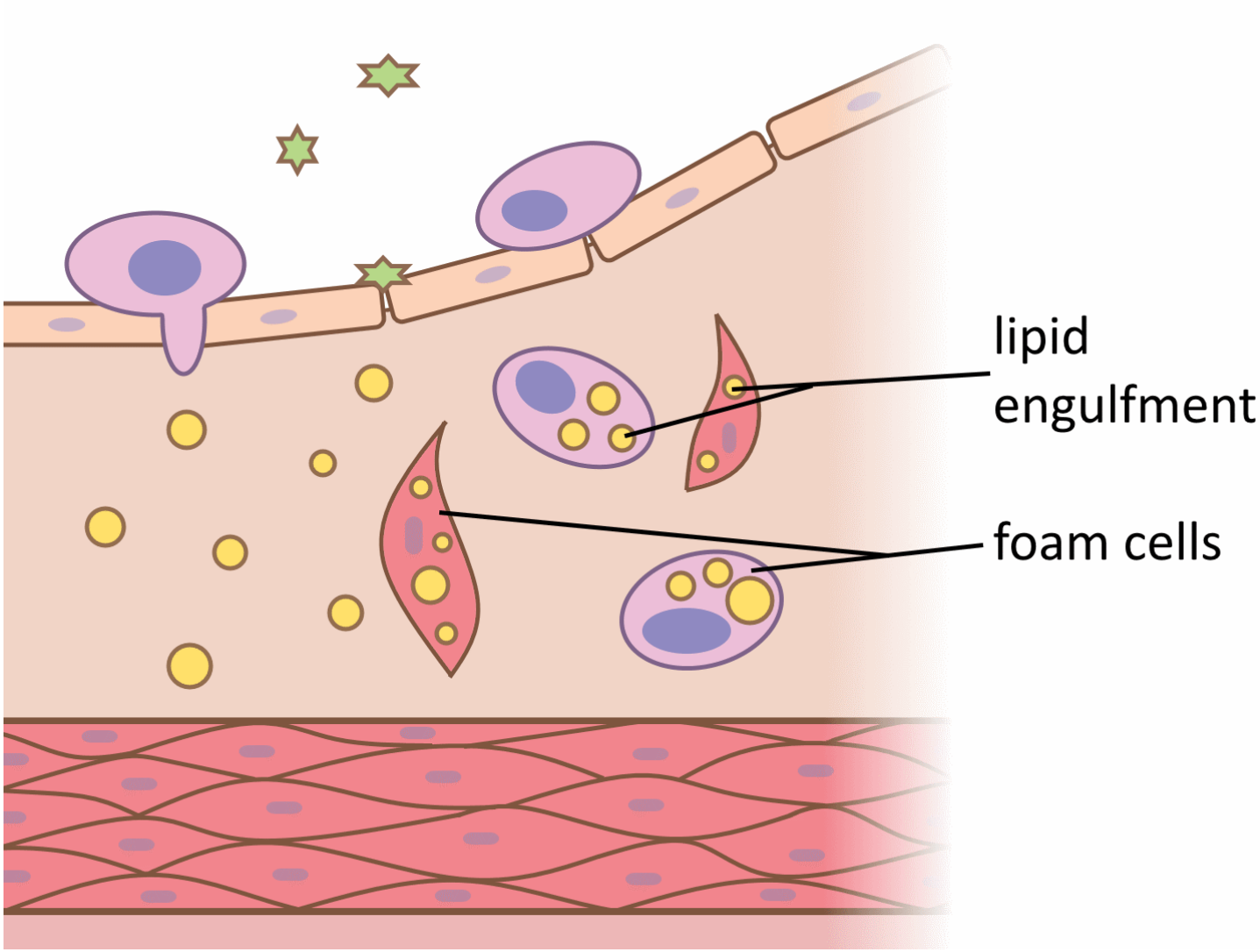
Endothelial Dysfunction



Proliferation, Oxidation, Engulfment

- **Smooth muscle** cells **proliferate**
  - in response to **growth factors**
  - from platelets and macrophages
- Accumulated **LDL is oxidised**
  - **by free radicals** released from macrophages and stressed endothelial cells
  - oxLDL stimulates release of growth factors, cytokines, chemokines and **recruits monocytes**
  - oxLDL is **cytotoxic** to endothelial and smooth muscle cells
- **Macrophages** and smooth muscle cells **engulf oxLDL**
  - become **foam cells**

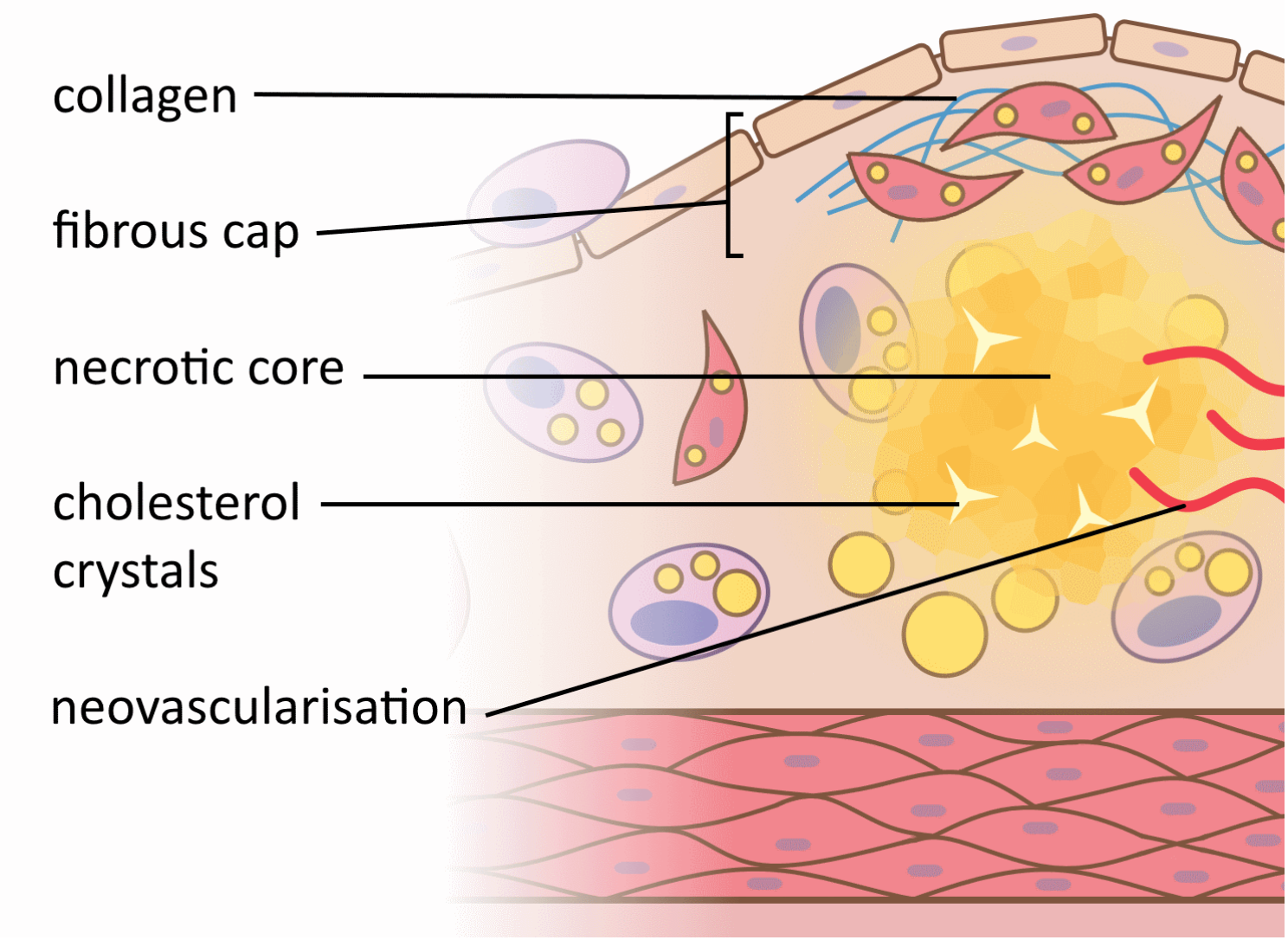
Proliferation, Engulfment



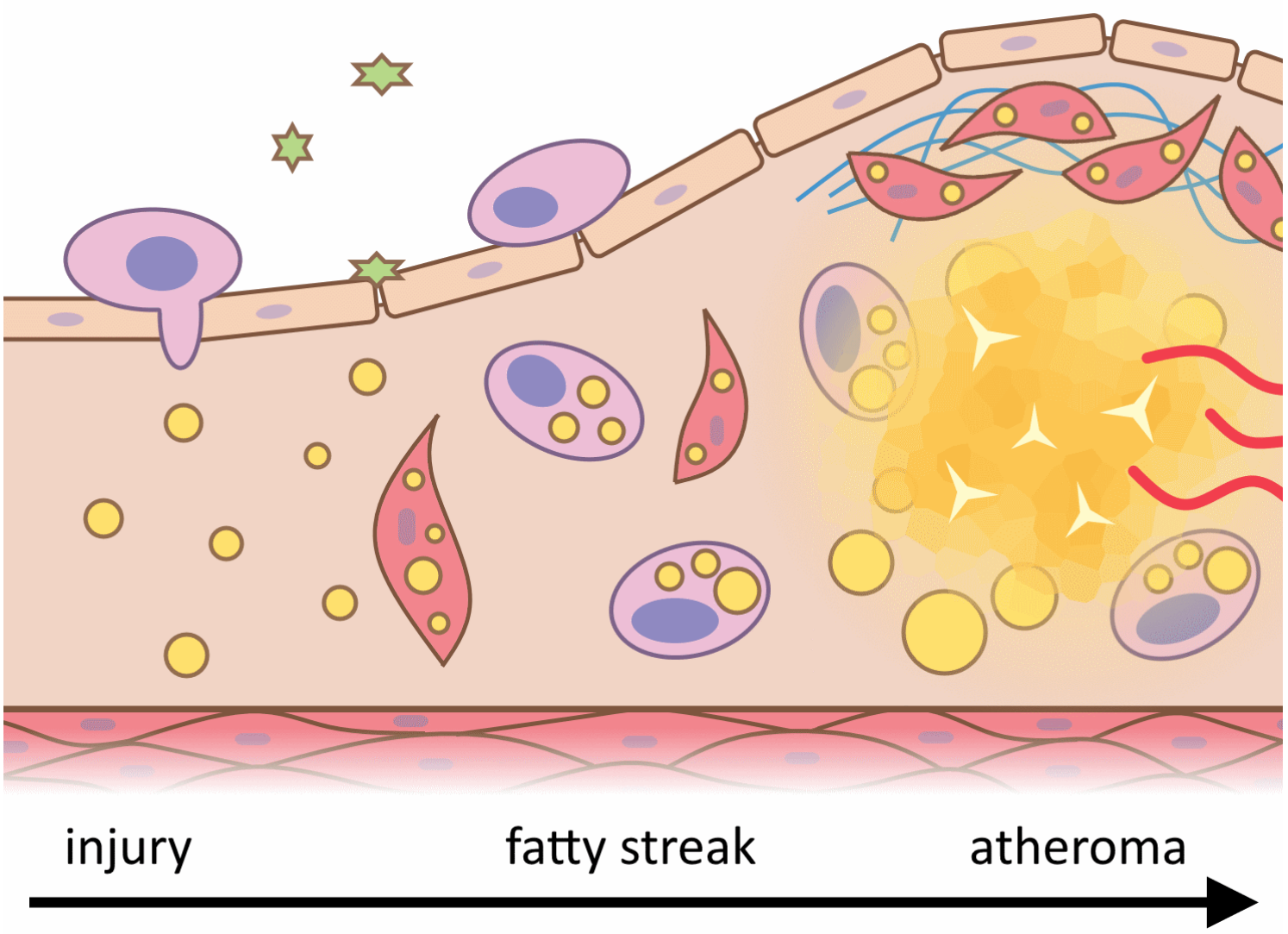
Fibrous Cap, Necrotic Core

- Continued smooth muscle proliferation:
  - **extracellular matrix** generation
  - **collagen** secretion
  - f**ibrous cap** formation
- Increasing size:
  - necrosis of thickening intima → **necrotic core**
  - stimulation of **neovascularisation**

Fibrous Cap, Necrotic Core



Overview: Response to Injury Hypothesis



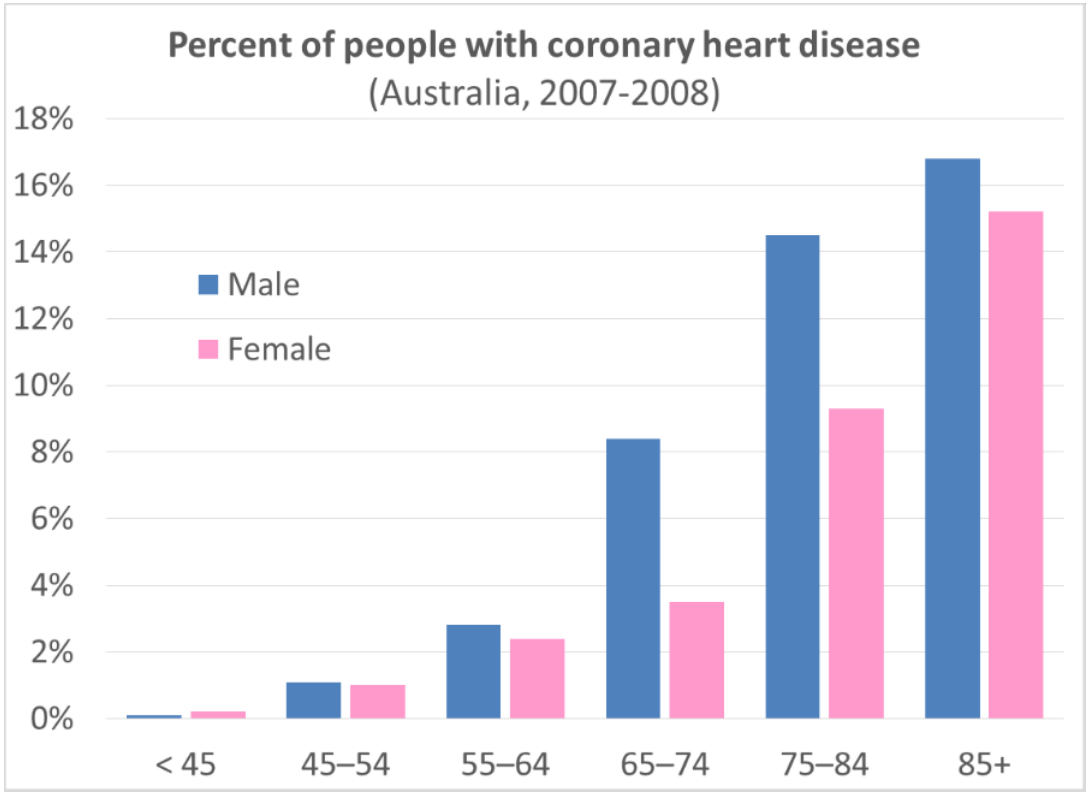
Risk Factors

Constitutional	genetics family history age, gender
Modifiable	hyperlipidaemia hypertension diabetes smoking diet

Risk factors are roughly multiplicative

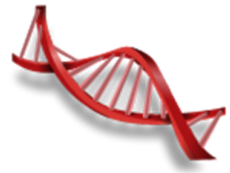
Age, Gender

- **Age:** presentations in middle age and beyond
- **Male gender:** pre-menopausal women protected, risk equalises after menopause



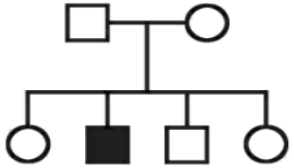
Data: AIHW

Genetics



- some Mendelial disorders
- (e.g. familial hypercholesterolaemia)
- mostly polygenic traits and polymorphisms

Family History

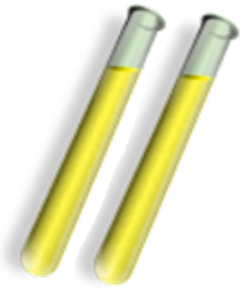


- especially 1st degree heart disease <50 y/o

Hypertension

- Systolic **>140 mmHg**
- Diastolic **>90 mmHg**
- Includes 25% of population

Hypercholesterolaemia



- Risk: **LDL**
  - distributes lipids to tissues
- Protective: **HDL**
  - extracts lipids from atheromas
  - transports to liver for excretion

Lifestyle

- Smoking
- Obesity
- Little exercise

Diet

- Main effect: lipid profile alteration
- Bad: cholesterol, saturated fats
- Good: omega-3 fatty acids, polyunsaturated fats

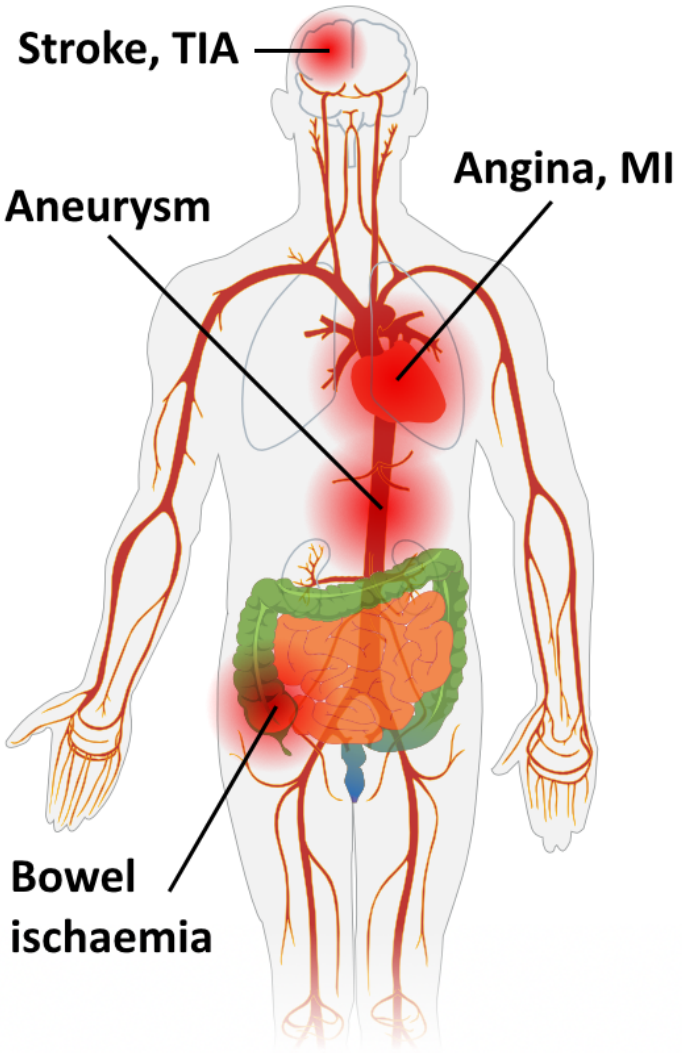
Diabetes Mellitus

- Raised cholesterol levels
- Increased risk of stroke and MI
- Particularly increased risk of atherosclerosis-associated gangrene

Acute Complications

- Weaken wall → **aneurysms**
- Rupture → **thrombosis**, **thromboembolism**
- Obstruct lumen → **stenosis**

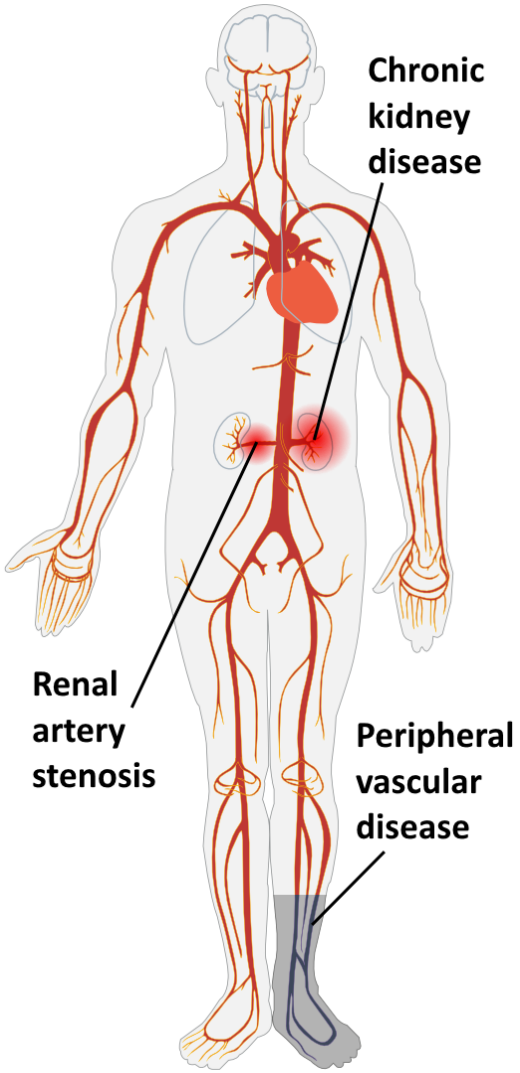
- **Stroke** , transient ischaemic attacks (**TIAs**)
- **Angina** , **MI**
- **Bowel ischaemia**



Chronic Complications

- **Peripheral vascular disease**
  - especially diabetics and elderly
  - pallor, cyanosis, pain
  - intermittent claudication
  - ulceration, gangrene

- **Renal artery stenosis**
- **Chronic kidney disease**



Fatty Streak

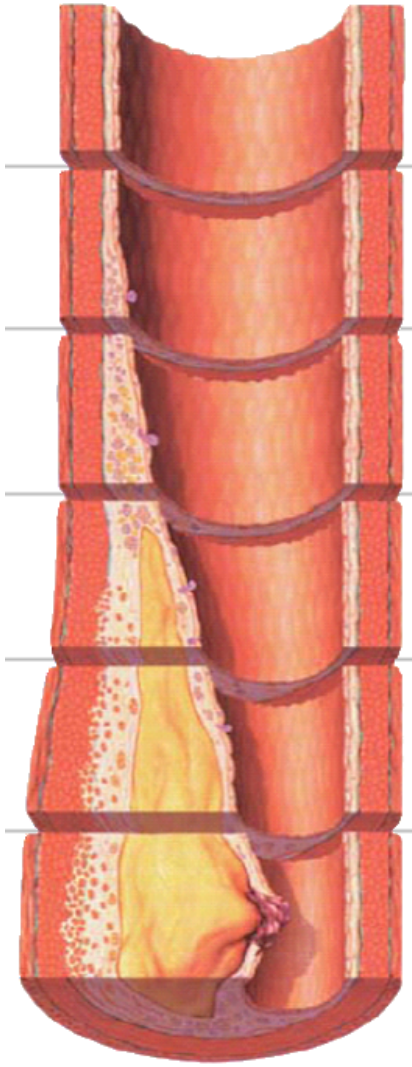
- Fatty streaks form almost **universally** as young as childhood
- Especially at **branch points** and **turbulent zones**
- No clinical significance, don't necessarily progress

Atheroma

- Risk factors accelerate progression
- Protrusion into lumen, **wall remodelling** to compensate
- Decompensation of remodelling **>50% diameter** → **stenosis**

Complicated Plaque

- Surface **ulceration**, **fissuring**
- **Haemorrhage**
- **Aneurysm**
- **Rupture**
  - thomobosis and occulusion
  - thomboembolism



Initial lesion	"normal" histology some foam cells
Fatty streak	intracellular lipid accumulation
Intermediate lesion	extracellular lipid accumulation
Atheroma	lipid core development
Fibroatheroma	fibrotic/calcific layers
Complicated lesion	surface defect thrombosis

Complicated Plaque

Treatment

- Main treatment is to **modify risk factors** for progression
  - **Lifestyle**: diet, exercise, weight loss, smoking
  - **Hypertension**: anti-hypertensives
  - **Hypercholesterolaemia**: statins, fibrates
  - Diabetes control

- Reduce risk of thrombosis: **aspirin**

- **Surgical**: stents, bypasses