Introduction to atherosclerosis

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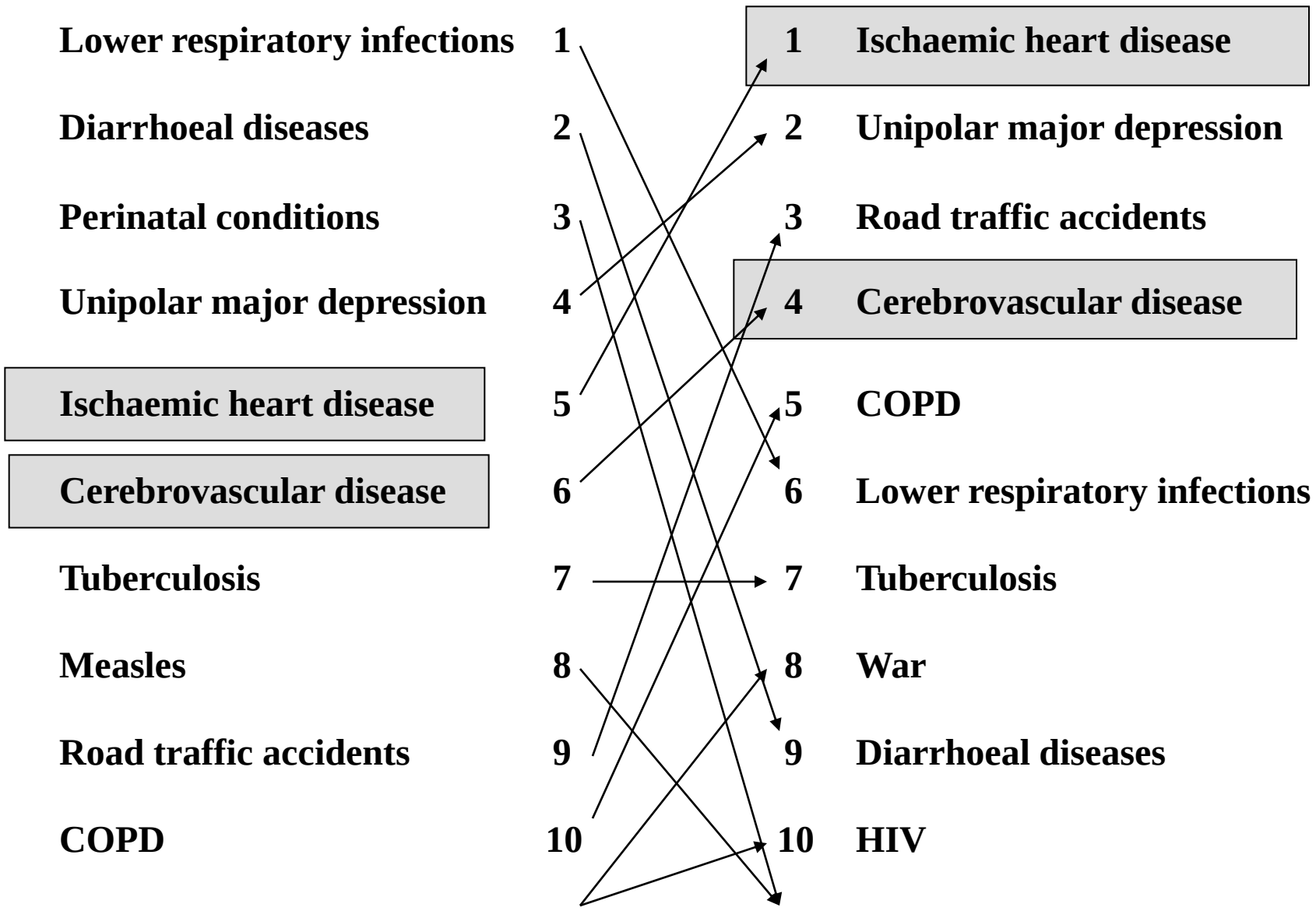
Atherosclerosis – plan of talk/learning objectives

- Importance of atherosclerosis to human health
- Cellular pathology of atherosclerosis
- Link between cholesterol and inflammation
- Importance of blood flow
- Investigating molecular mechanisms

World disease burden



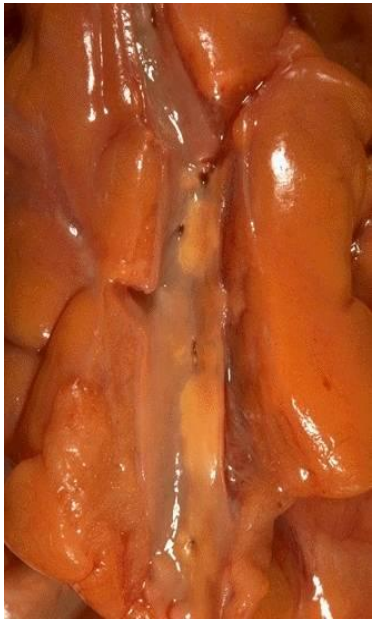
Adapted from Lopez and Murray (1998) Nature Med 4: 1241

Risk Factors

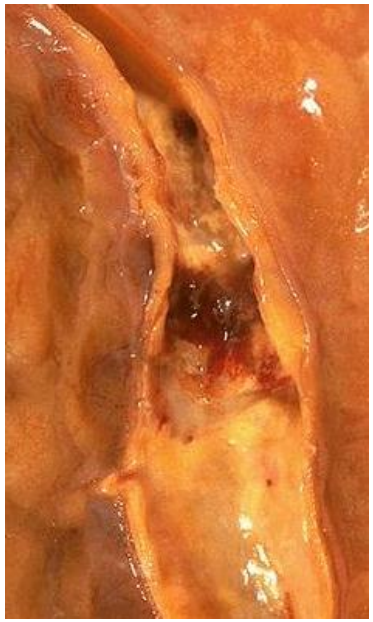
Modifiable	Not modifiable
dyslipidaemia	Age
smoking	Sex
hypertension	Genetics
diabetes mellitus	
visceral obesity	
lack of exercise	
raised homocysteine	

PATHOLOGY

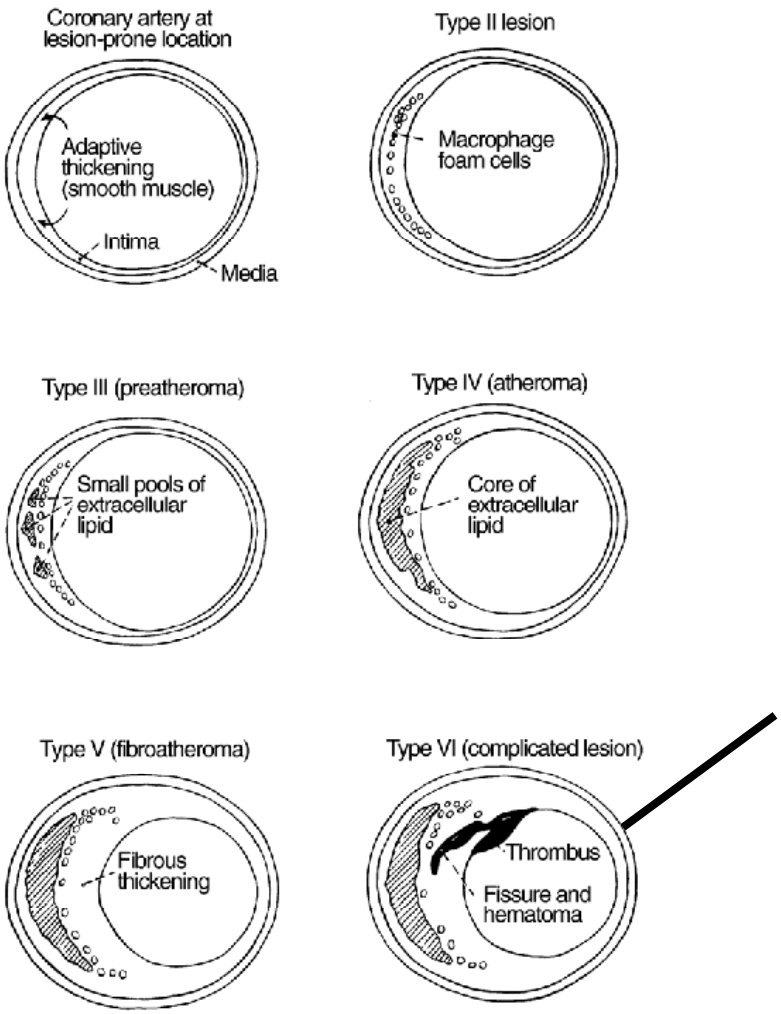
fatty streaks



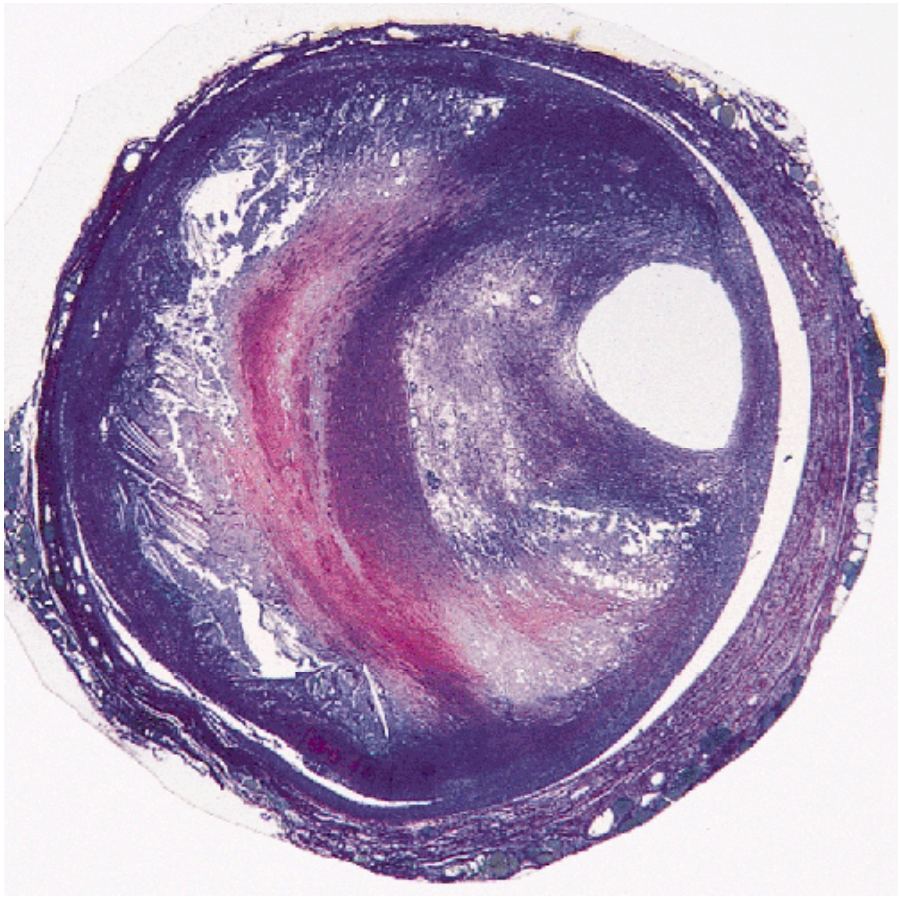
intermediate lesion



ulcerated plaque



Type VI lesion



Debris (eg modified lipoproteins, apoptotic cells)

⇩

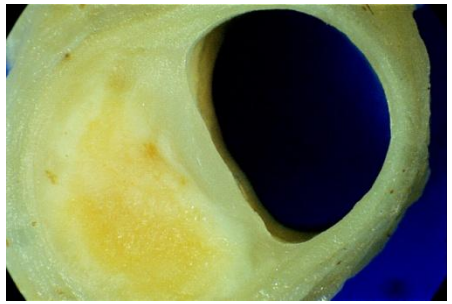
Reversible fatty lesions

⇩

Irreversible remodelling

wound healing

Stable plaques



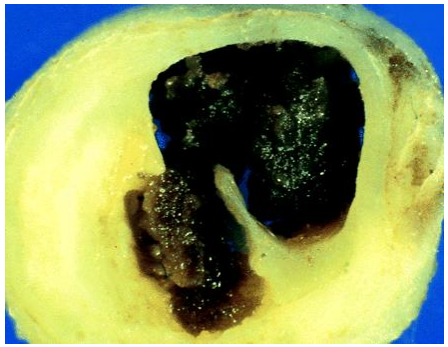
Ischaemia

Angina
Intermittant claudication

⇔

inflammation/thrombosis

Unstable plaques



Thrombosis and infarction

Acute coronary syndromes
Stroke
Peripheral gangrene

Debris (eg modified lipoproteins, apoptotic cells)

⇩

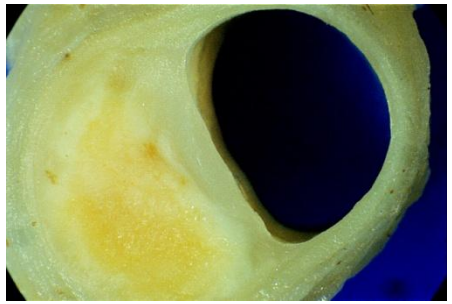
Reversible fatty lesions

⇩

Irreversible remodelling

wound healing

Stable plaques



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Angina
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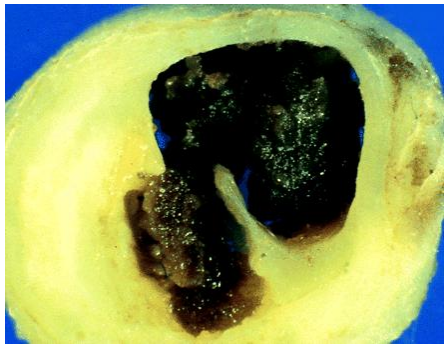
inflammation/thrombosis

Unstable plaques

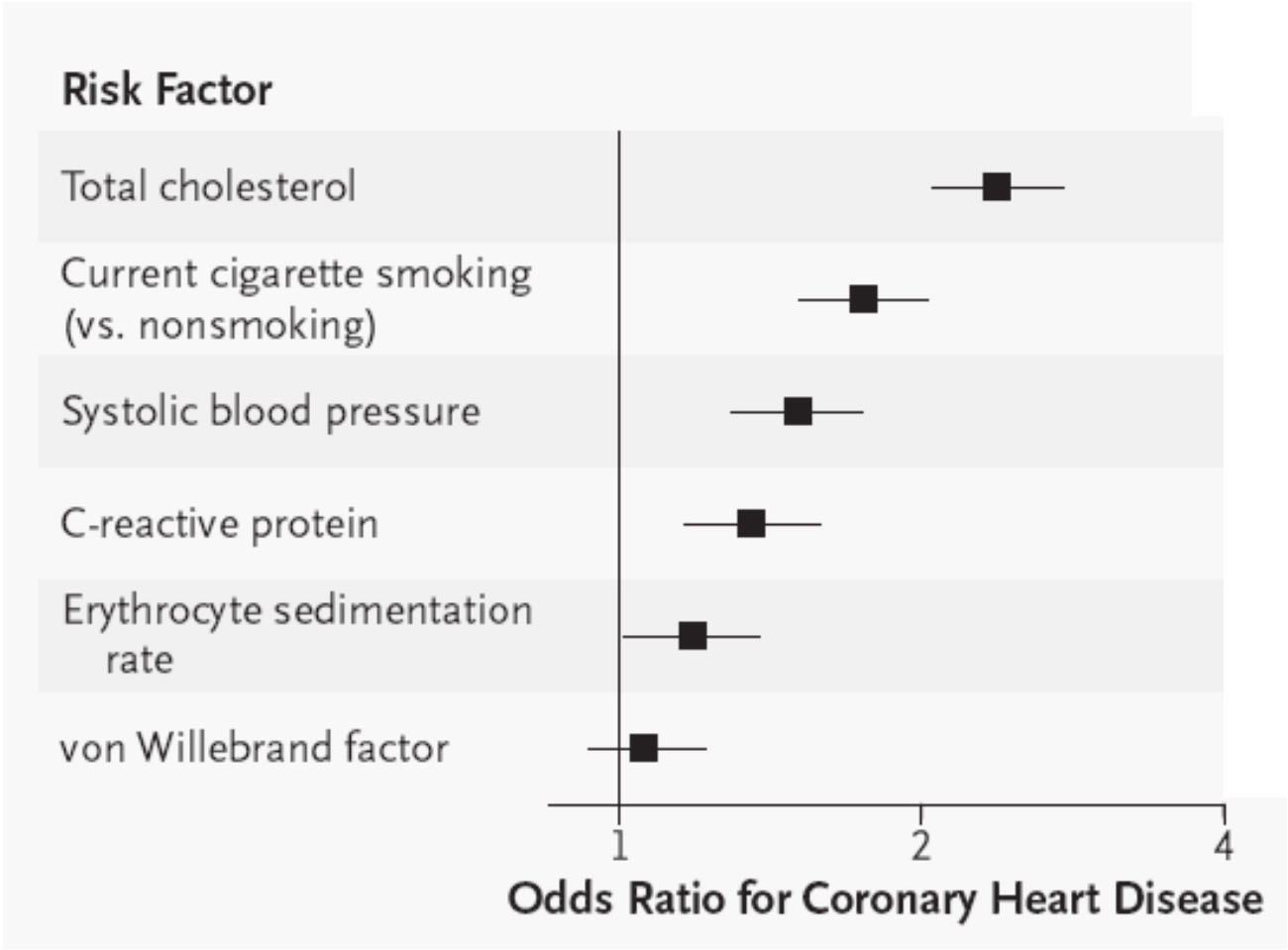


Thrombosis and infarction

Acute coronary syndromes
Stroke
Peripheral gangrene

CHOLESTEROL AND INFLAMMATION

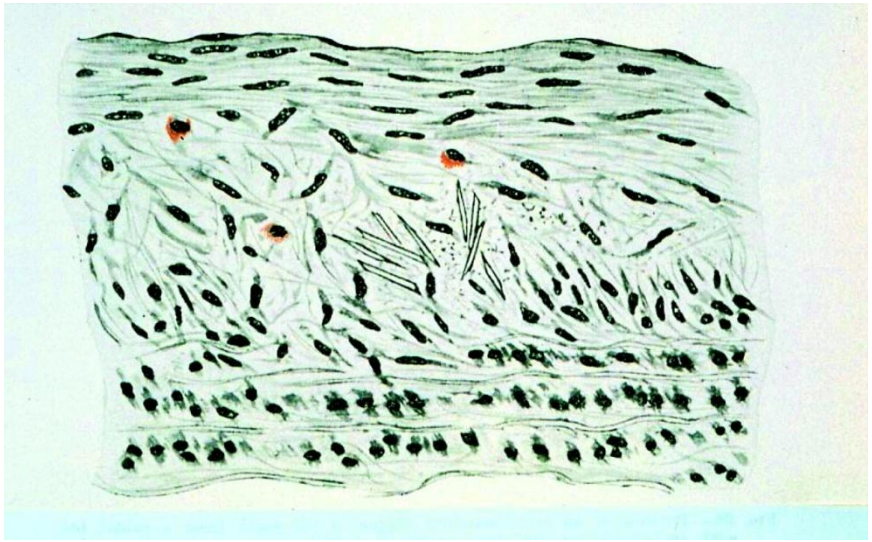
Relative importance of risk factors



Danesh et al 2004 N Engl J Med 350:1387

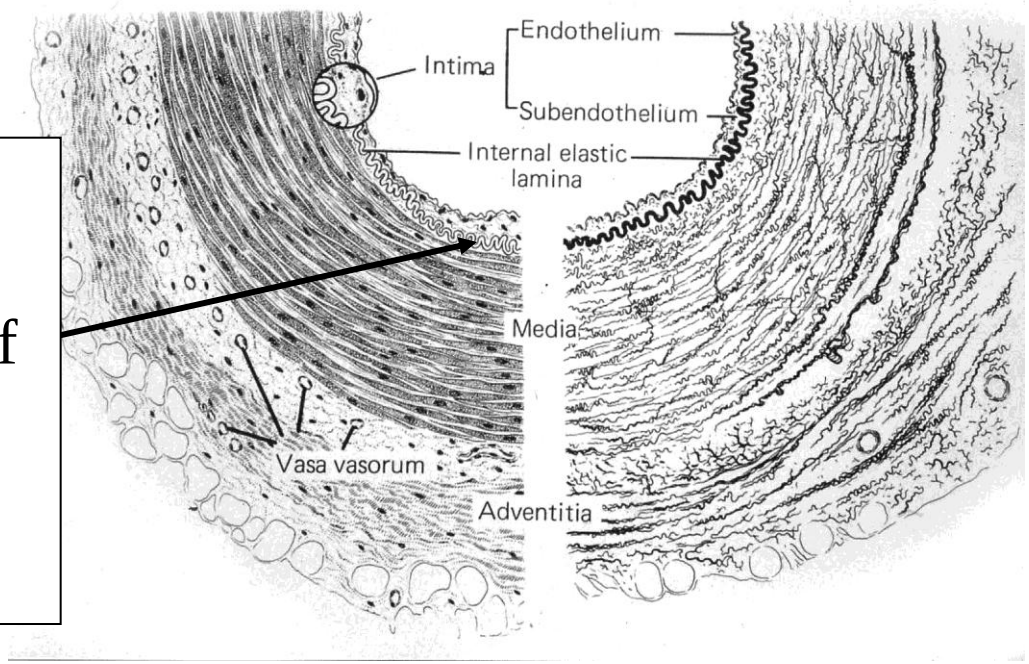
History – the cholesterol hypothesis

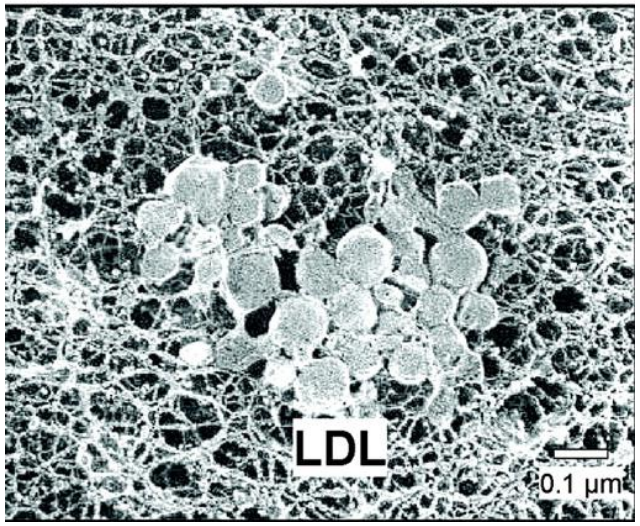
N. N. Anitschkow
Military Medical Academy of St Petersburg
(circa 1904)



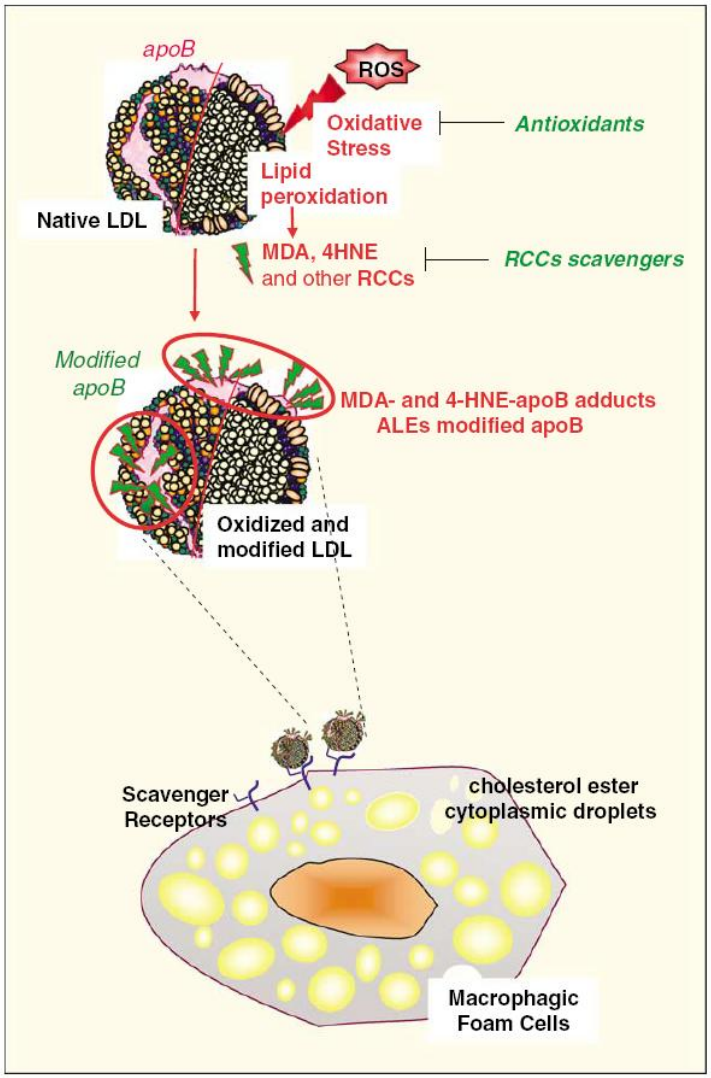
Plaque from a rabbit fed cholesterol for 106 days and then chow for >2 years

Low density lipoproteins (LDL) deposit in the subintimal space at sites of low/complex flow, and bind to matrix proteoglycans

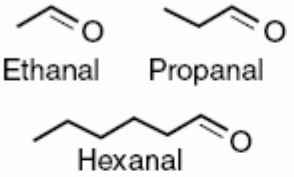




From: Tabas, I. et al. Circulation 2007;116:1832-1844

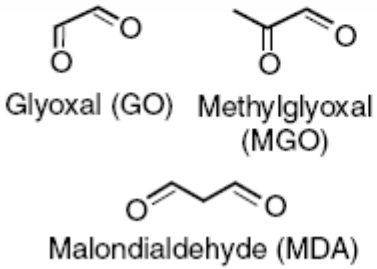


Saturated Aldehydes

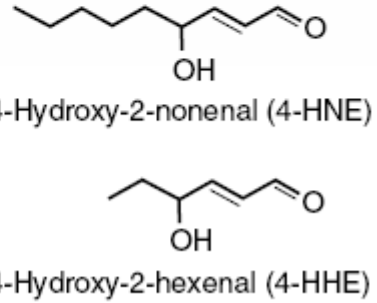


Unsaturated Aldehydes

Dicarbonyls

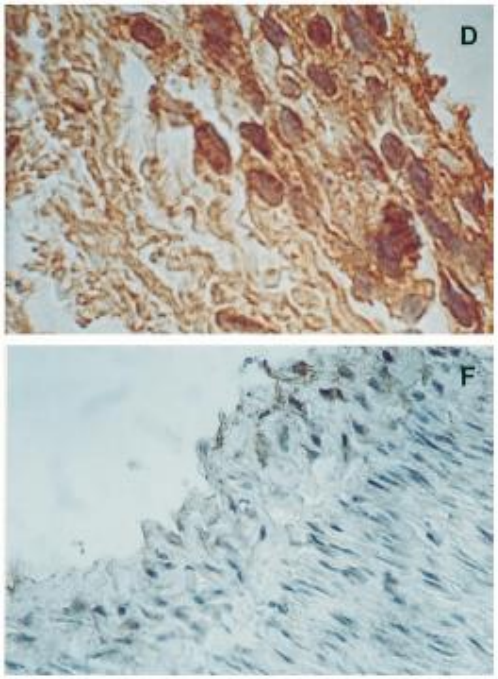


4-Hydroxy-2-alkenals



LDL modification in the arterial wall happens before macrophage infiltration

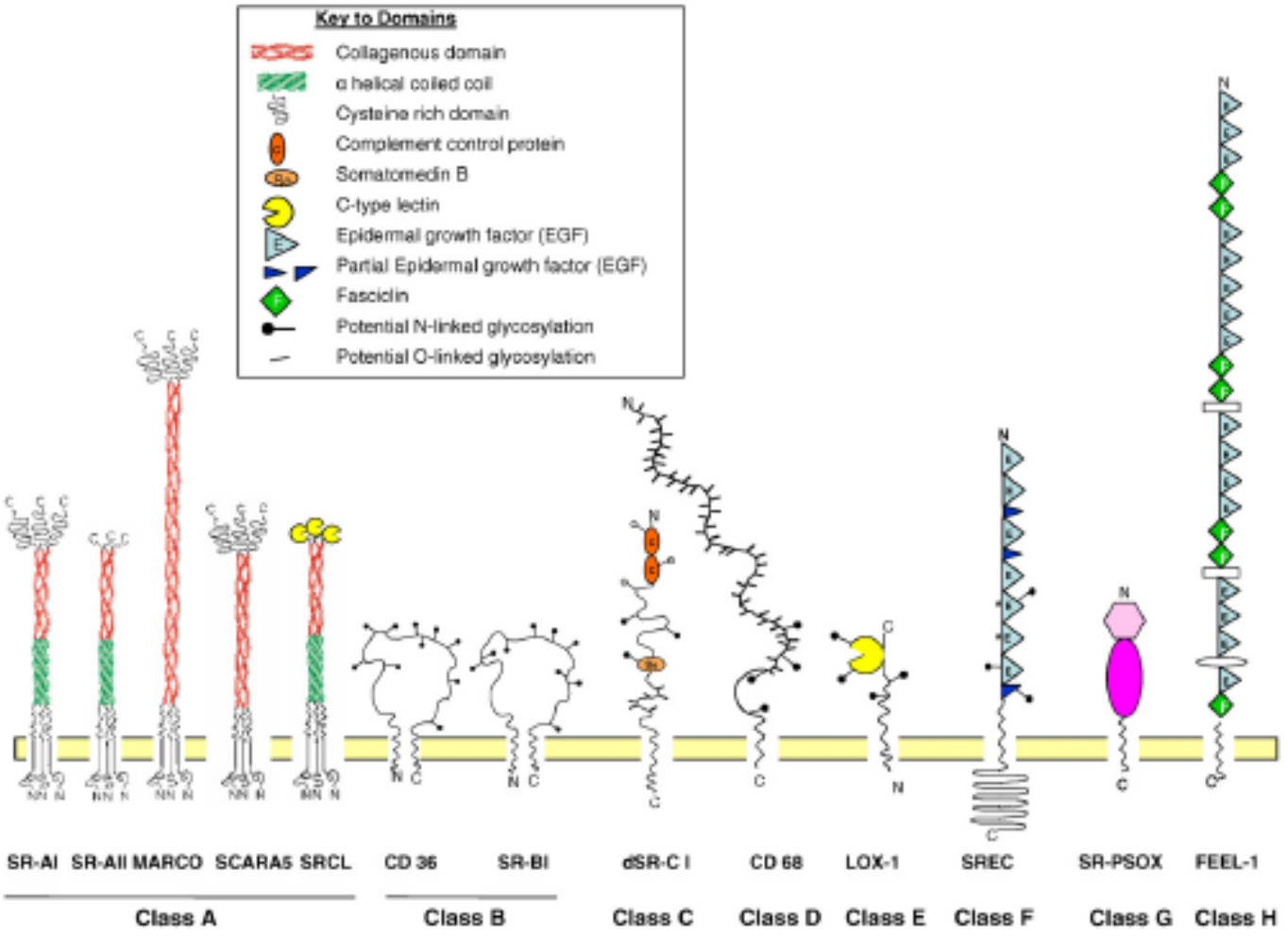
MDA-lysine
(oxidised LDL)



monocyte/møs

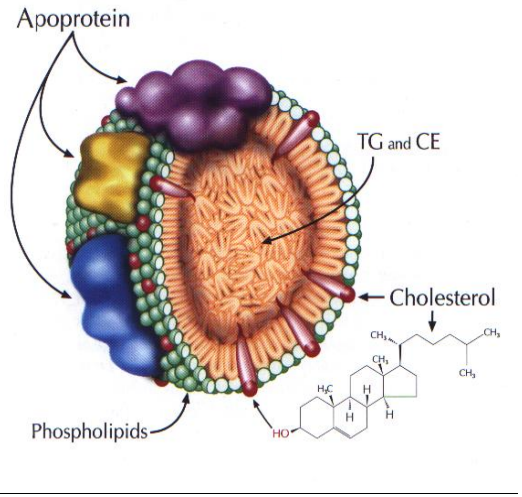
Napoli et al 1997 J Clin Invest 100:2680

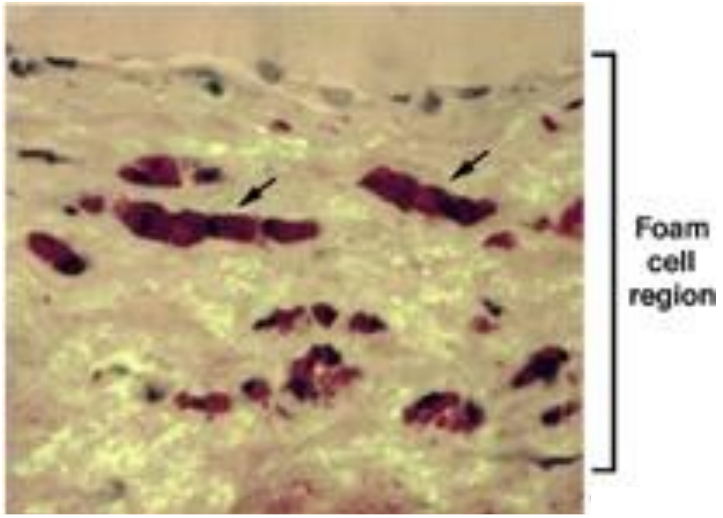
Macrophage scavenger receptors



from Pluddemann et al (2007) Methods 43:207

Foam cells

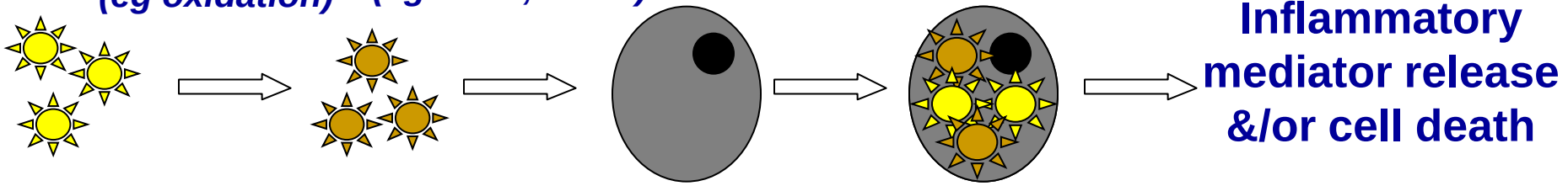




from Dr Howard K

lipoprotein modification (eg oxidation)

via scavenger receptors (eg SR-A, CD36)

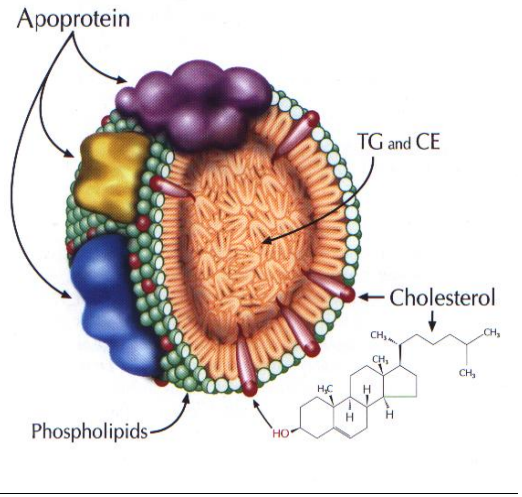


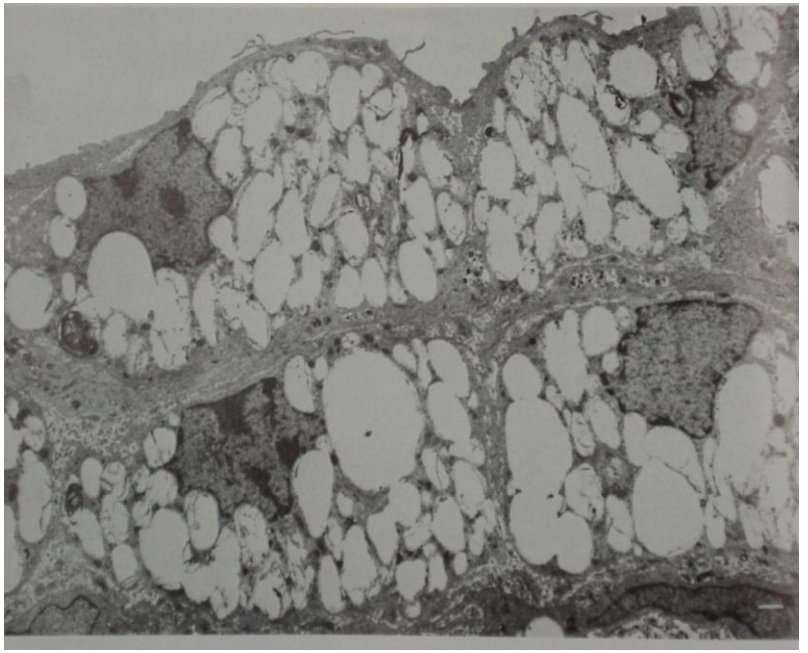
Inflammatory mediator release &/or cell death

Macrophage

"foam cells"

Foam cells

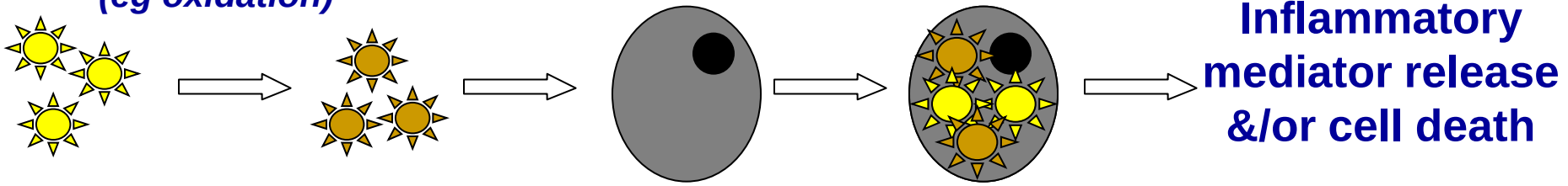




Faggiotto et al 1984 Arteriosclerosis 4:323

lipoprotein modification (eg oxidation)

via scavenger receptors (eg SR-A, CD36)

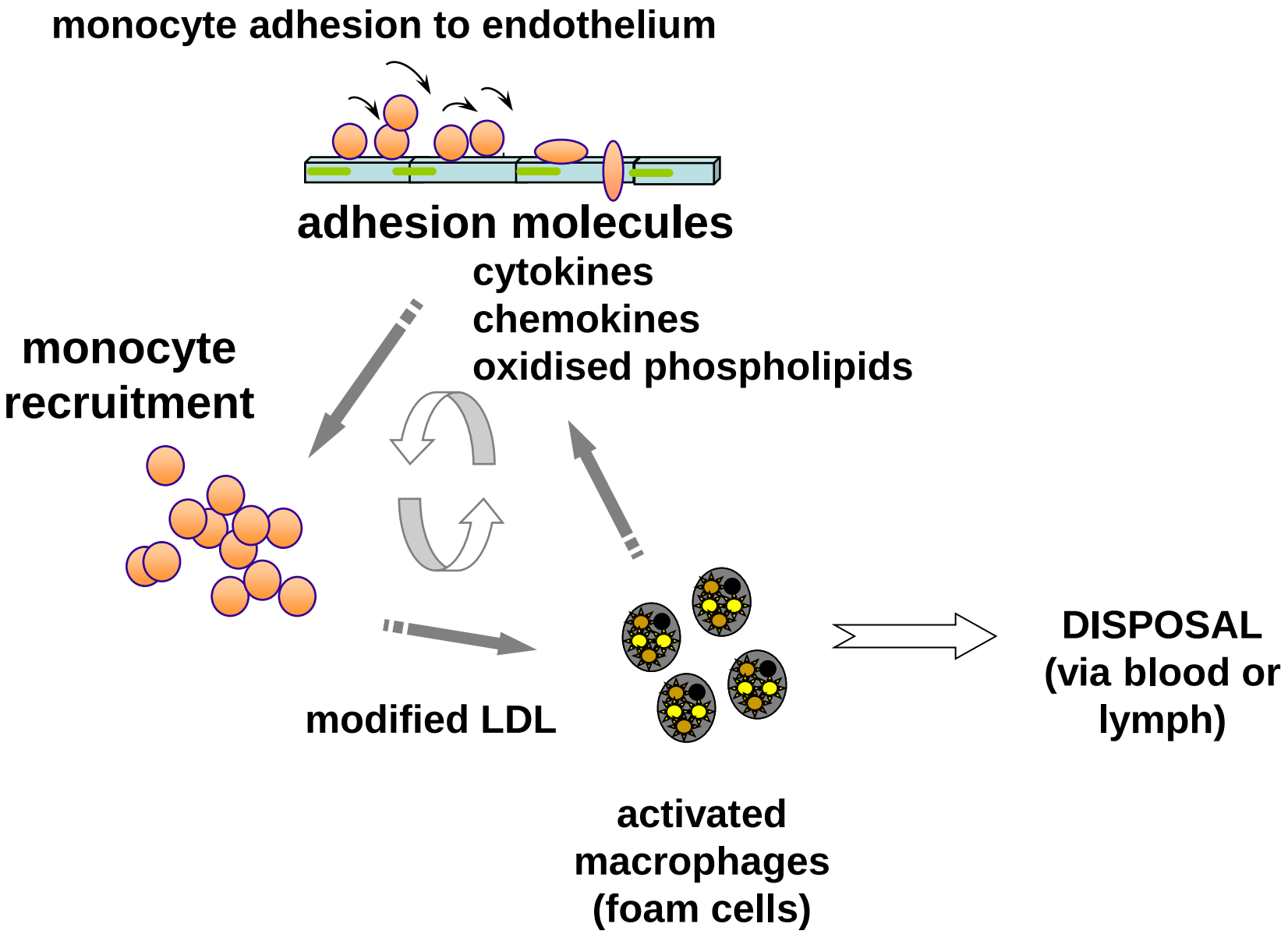


Macrophage

"foam cells"

Inflammatory mediator release &/or cell death

Homeostatic debris disposal



flow

Juvenile rabbit

Courtesy of Peter Weinberg, Imperial College

Early lesions can move – ie they are reversible

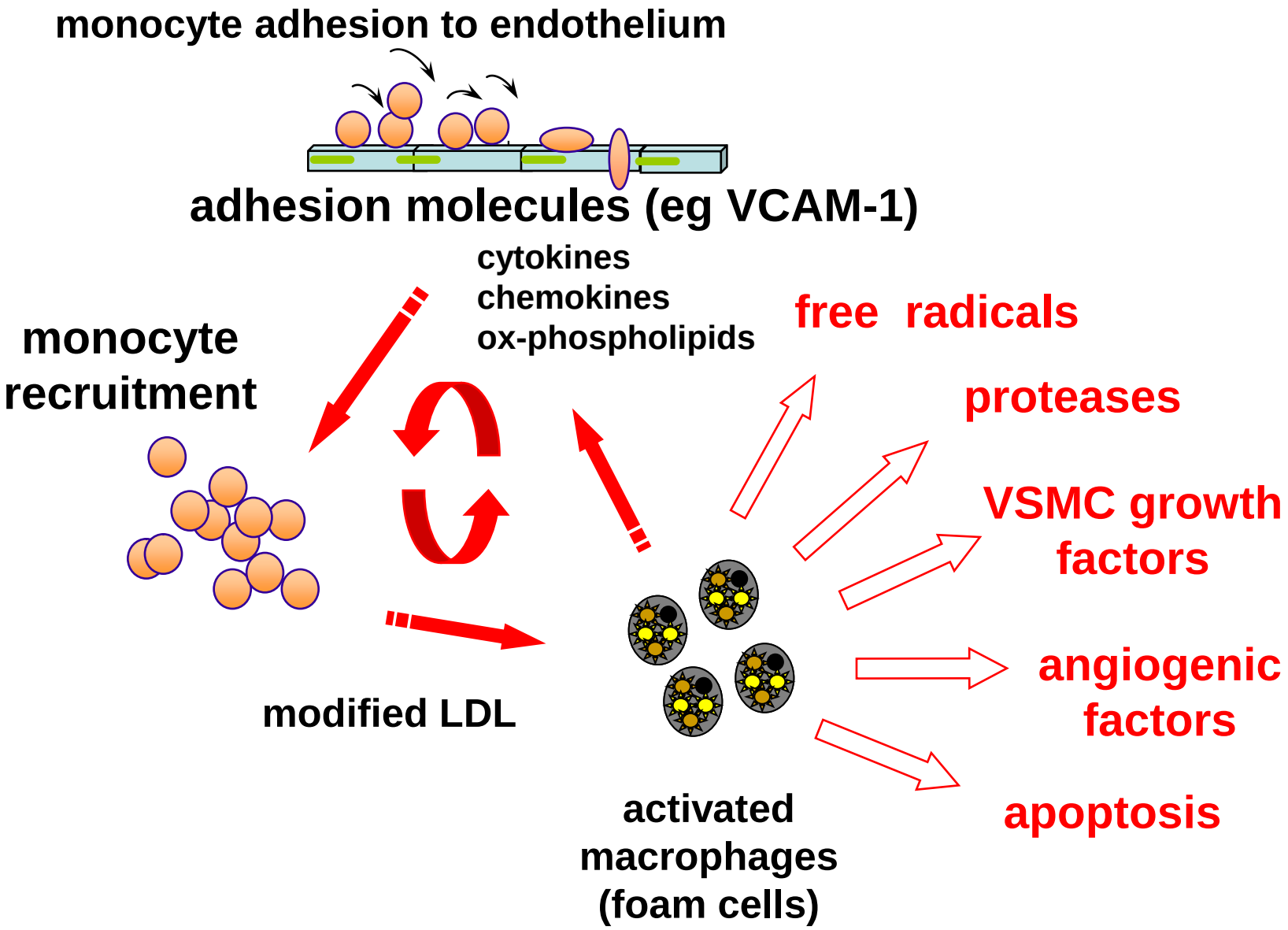
flow

Juvenile rabbit

Adult rabbit

Courtesy of Peter Weinberg, Imperial College

Inflammatory basis of atherosclerosis



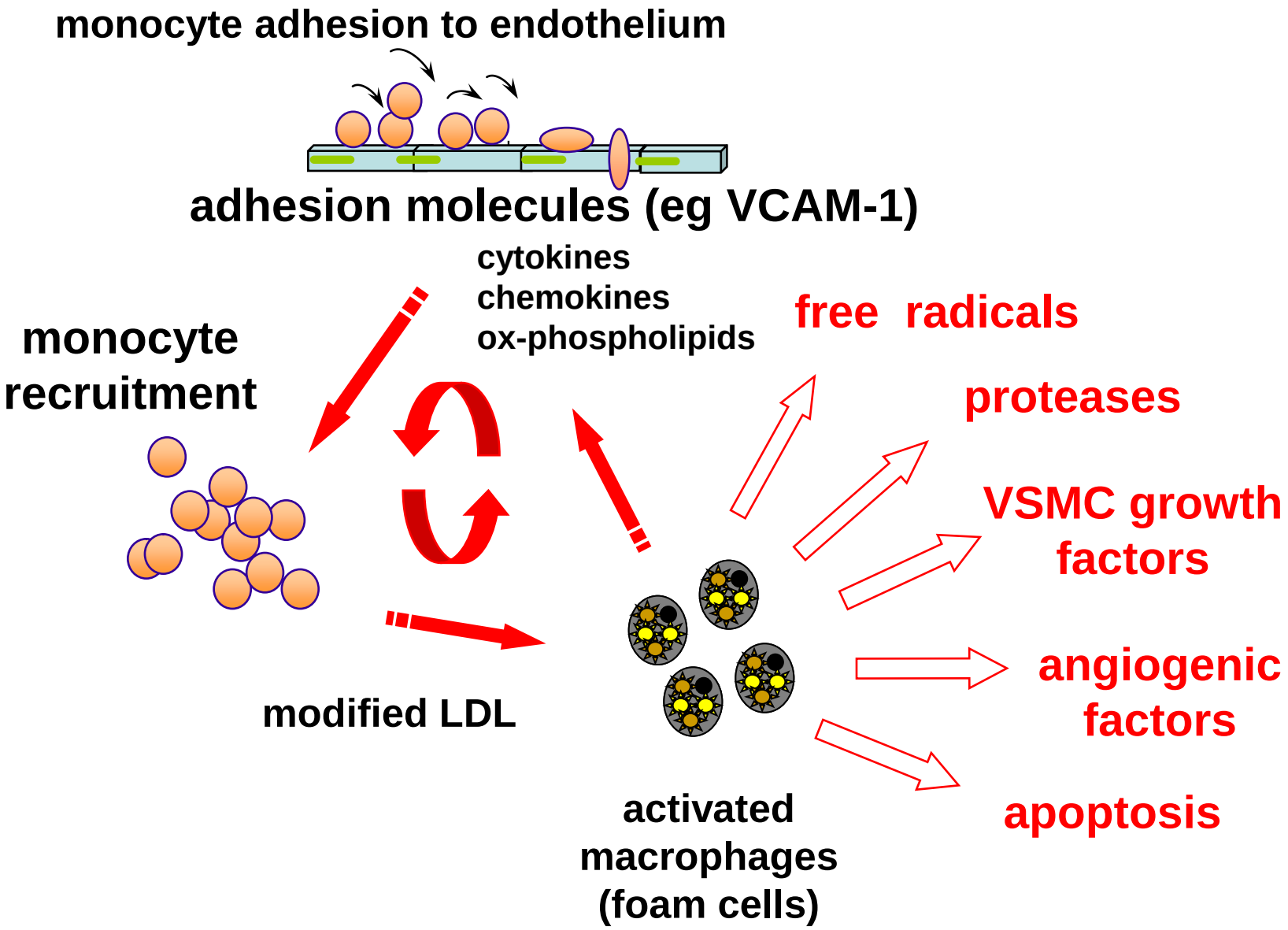
Macrophage uptake of LDL

- Physiological uptake of LDL via LDL controlled by receptor down-regulation
- Uptake of oxidised LDL by scavenger receptors is not regulated and results in “foam cell” formation.
- Cholesterol-laden macrophages release cytokines (eg IL-1, TNF) and growth factors (eg PDGF), and die by apoptosis or necrosis

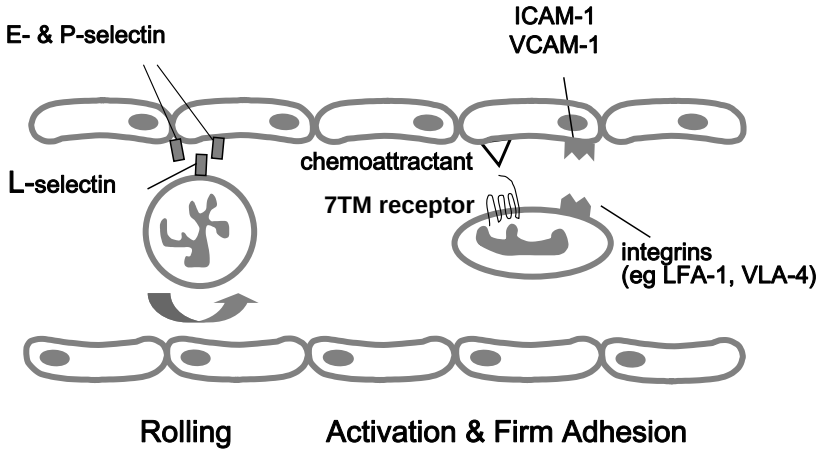
Main cellular players

- **Vascular endothelial cells**
  - Barrier function (eg to lipoproteins)
  - Leukocyte recruitment
- **Platelets**
  - Thrombus generation
  - Cytokine and growth factor release
- **Monocyte-macrophages**
  - Foam cell formation
  - Cytokine and growth factor release
  - Major source of free radicals
  - Metalloproteinases
- **T lymphocytes**
  - Macrophage activation
- **Vascular smooth muscle cells**
  - Migration and proliferation
  - Collagen synthesis
  - Remodelling and fibrous cap formation

Inflammatory basis of atherosclerosis

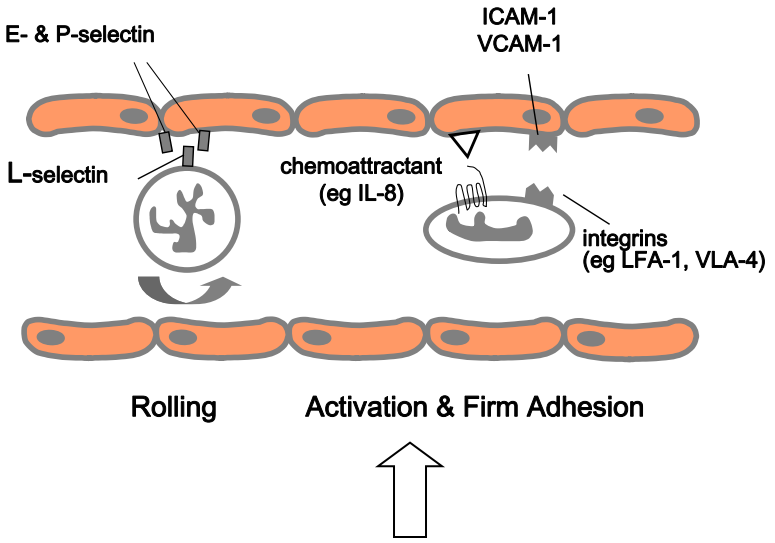


Leukocyte-endothelial cell interactions



Courtesy of Prof Sussan Nourshargh

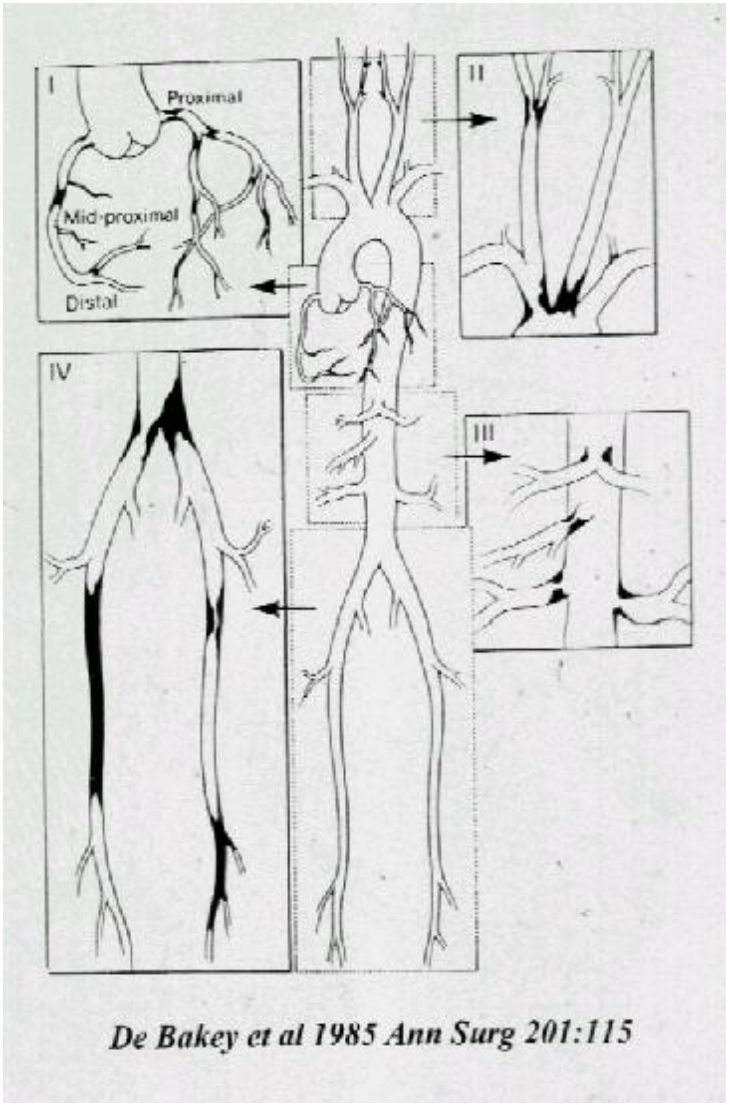
Leukocyte-endothelial cell interactions



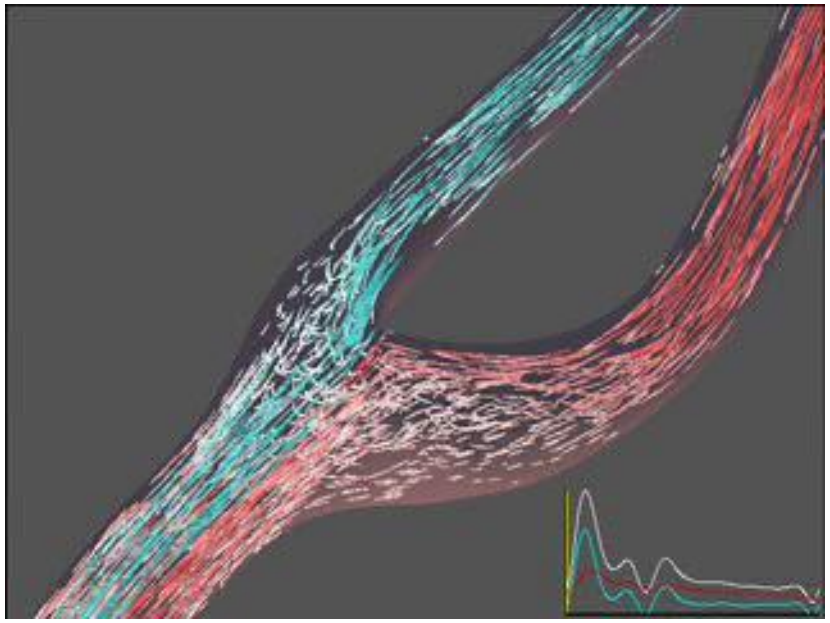
137 endothelial cell genes regulated more than 4-fold by IL-1
De Martin et al (2004) ATVB 24:1192

IMPORTANCE OF BLOOD FLOW

Flow-related susceptibility of branch points and curvatures

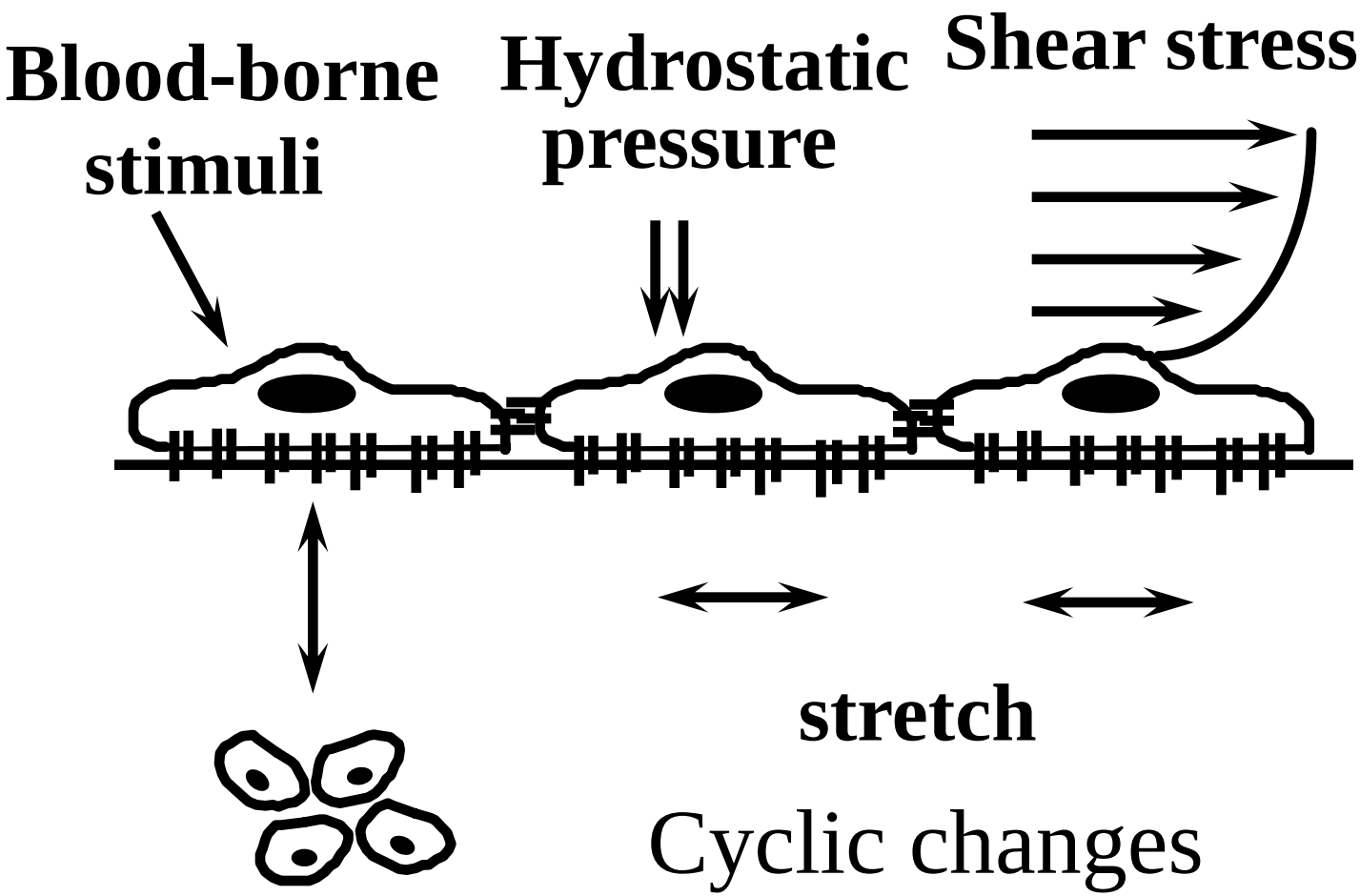


Risk factors are general but atherosclerosis is focal

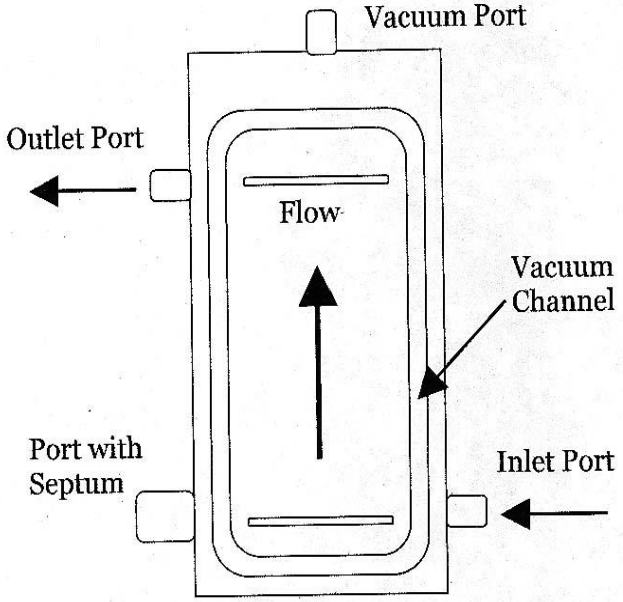


Courtesy of David Steinman
University of Western Ontario

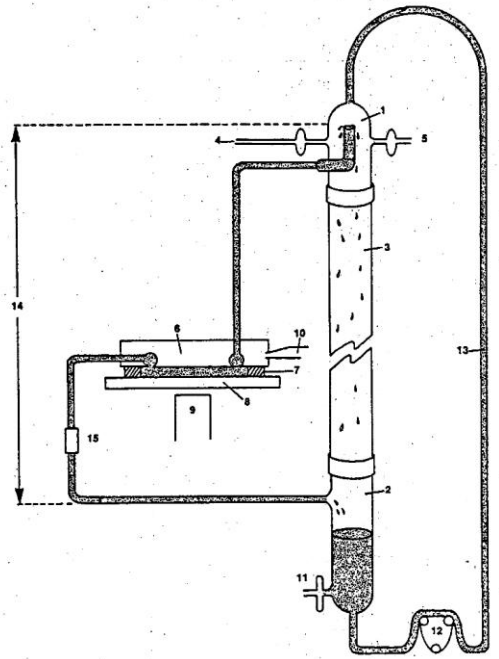
Effects of mechanical forces on endothelial function

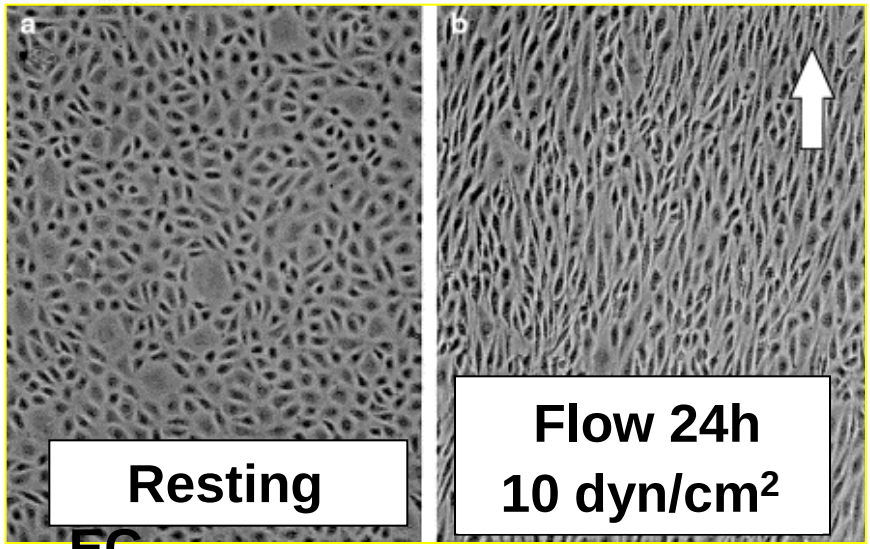


Use of parallel plate flow chamber for studying endothelial cells under flow



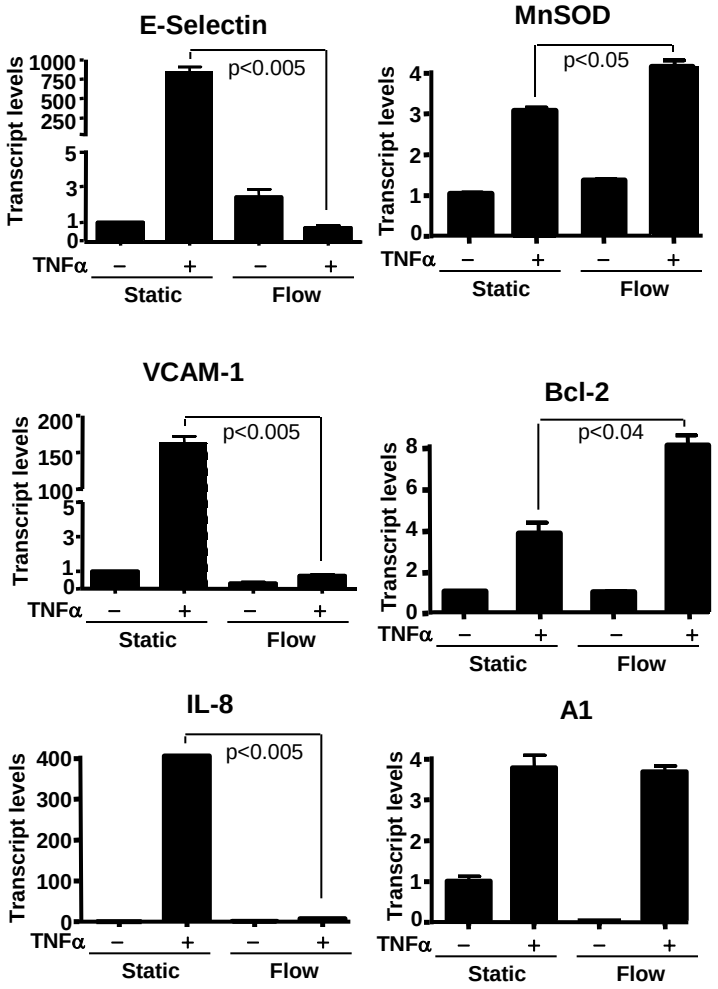
Flow Chamber





EC

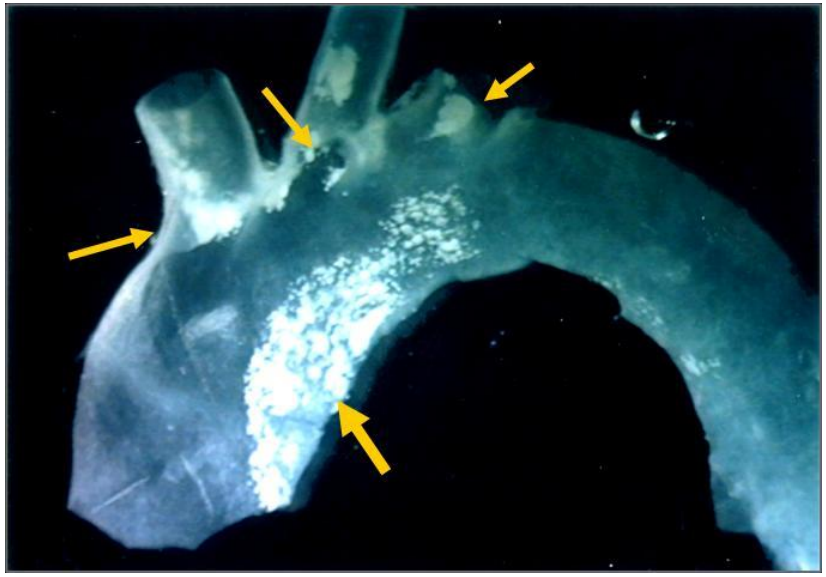
Laminar flow suppresses proinflammatory gene expression but sustains cytoprotective responses in response to TNFα



proinflammatory genes

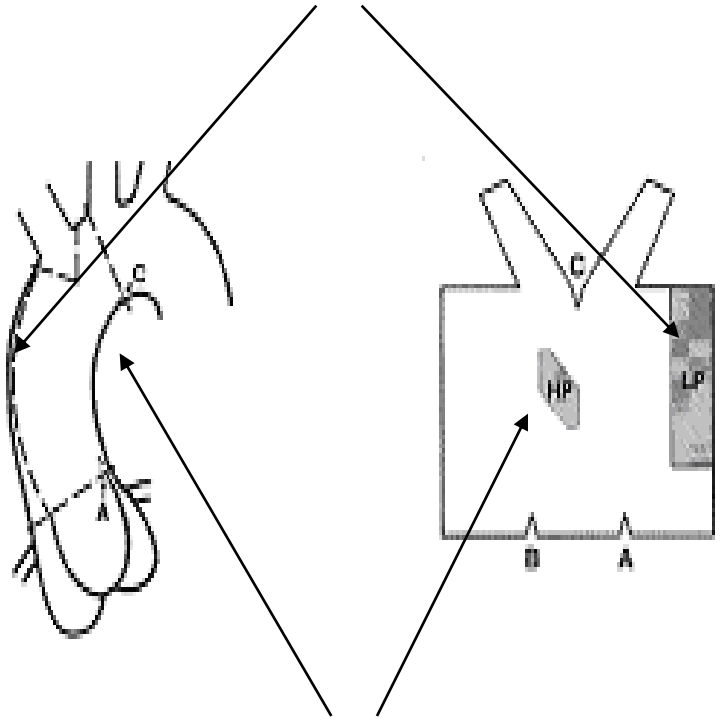
cytoprotective genes

Partridge et al (2007) FASEB J , 21:3553



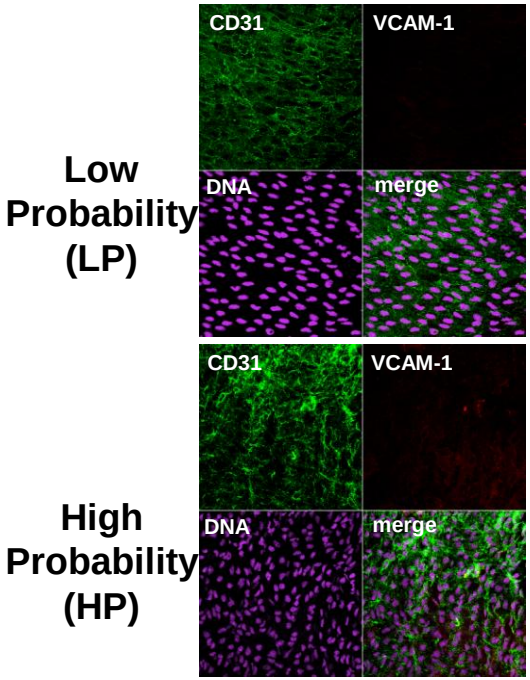
Courtesy of Prof Rob Krams

Low probability (HP)



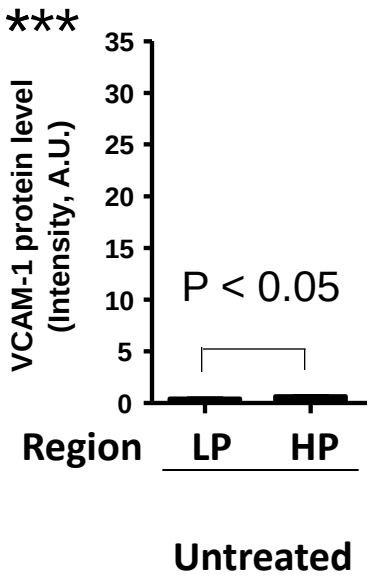
High probability (HP)

Differential adhesion molecule expression in the murine aorta shown by *en face* immunostaining



unstimulated

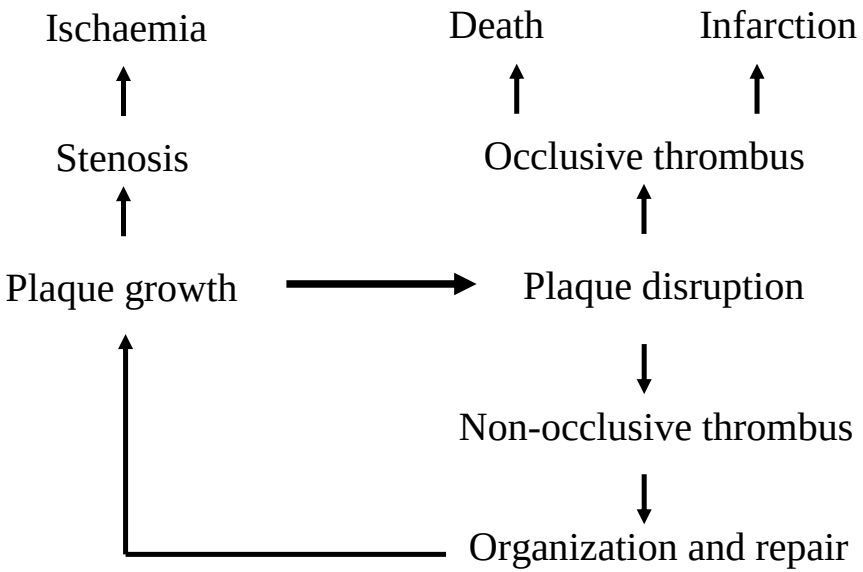
VCAM-1

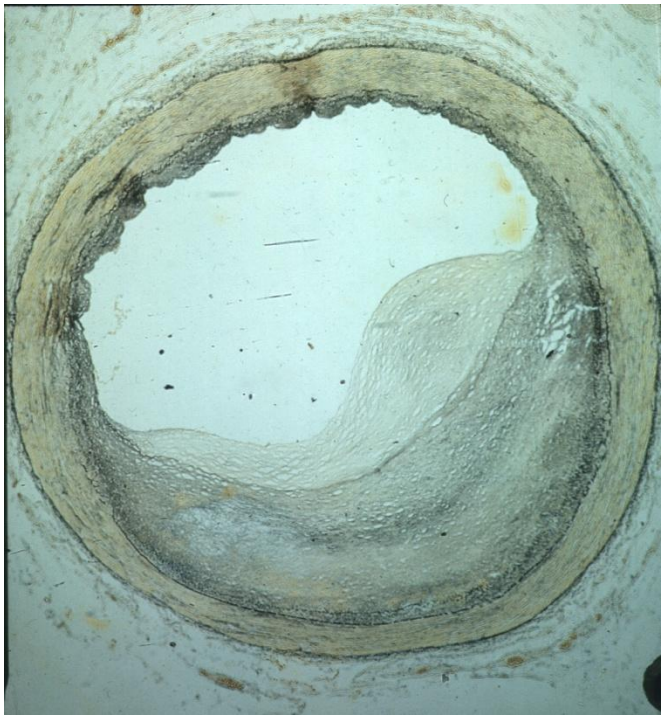


Untreated

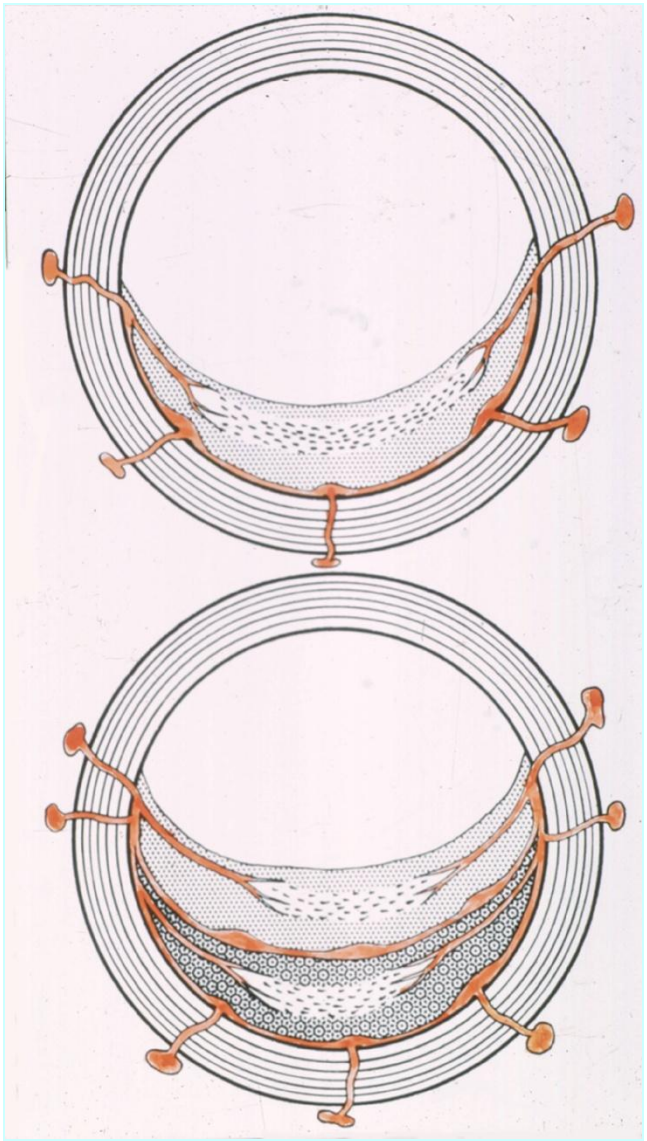
PLAQUE DEVELOPMENT AND ANGIOGENESIS

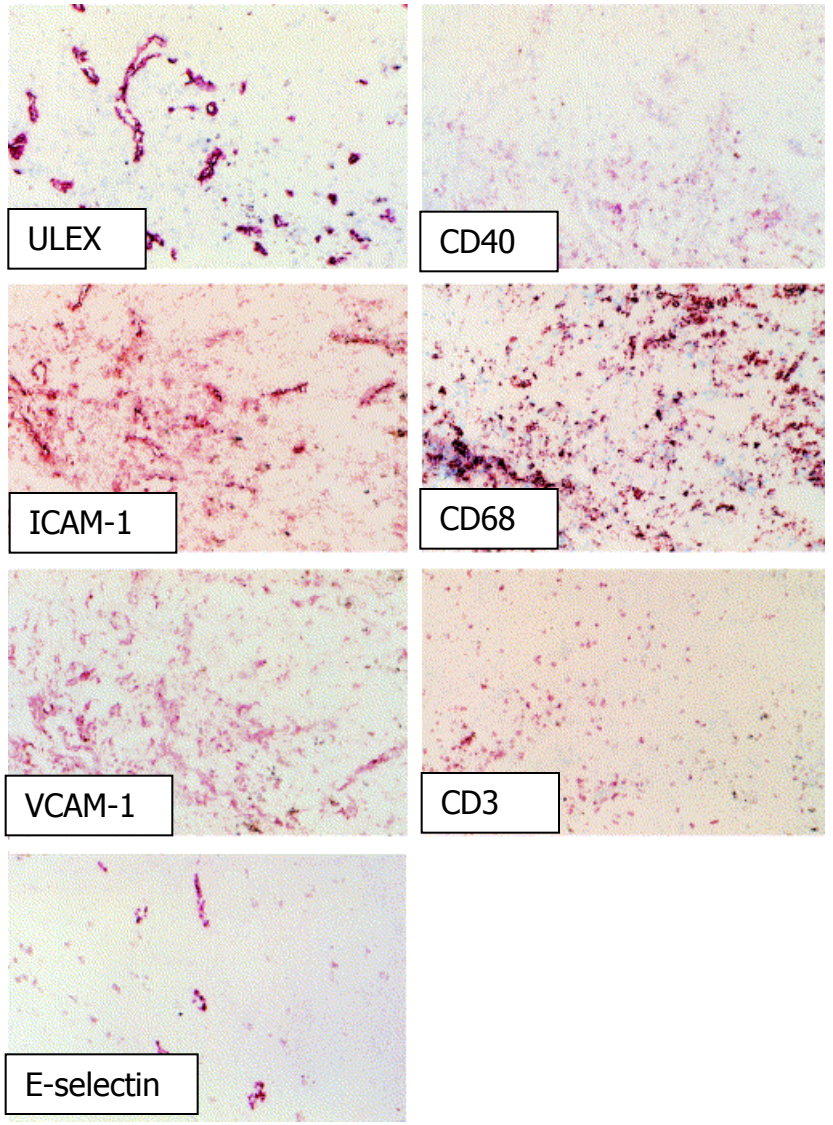
Step-wise progression of atherosclerotic plaques





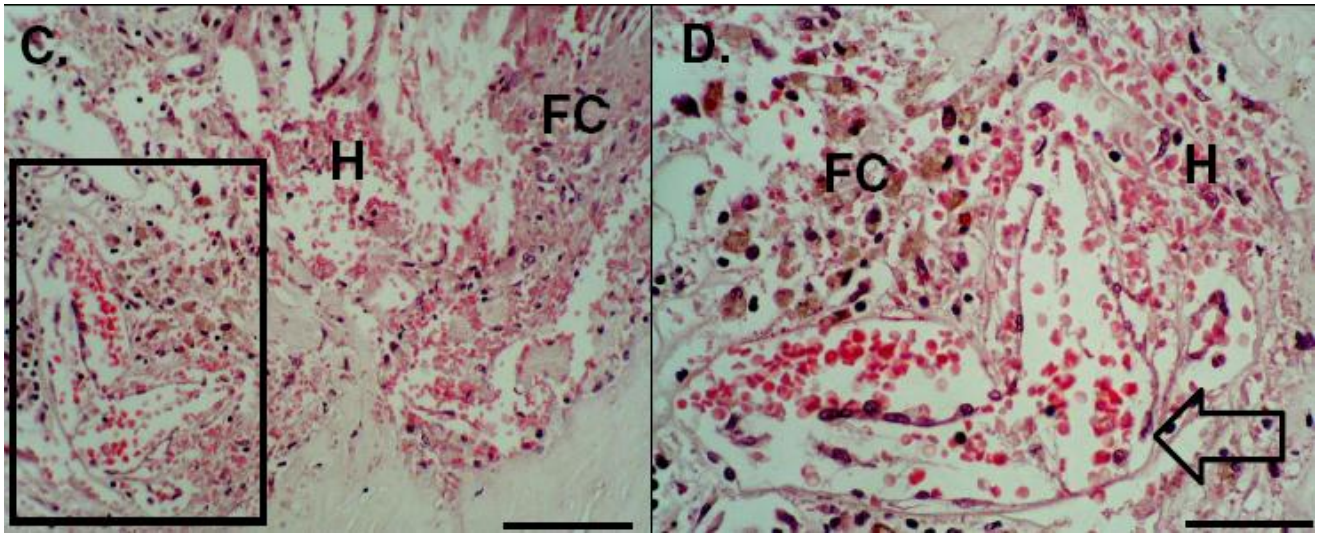
Vasa vasorum are the back-door for leukocyte recru

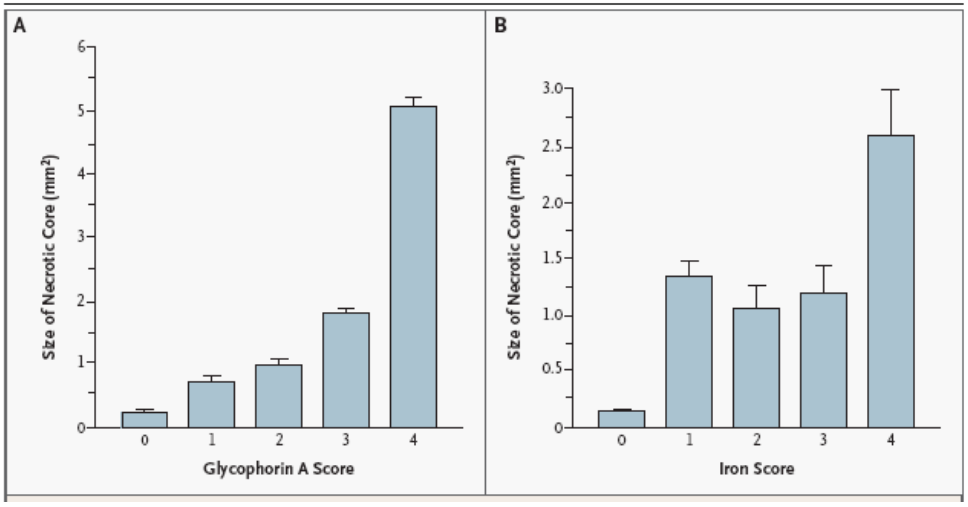




De Boer et al (1999) Cardiovasc Res 41:443.

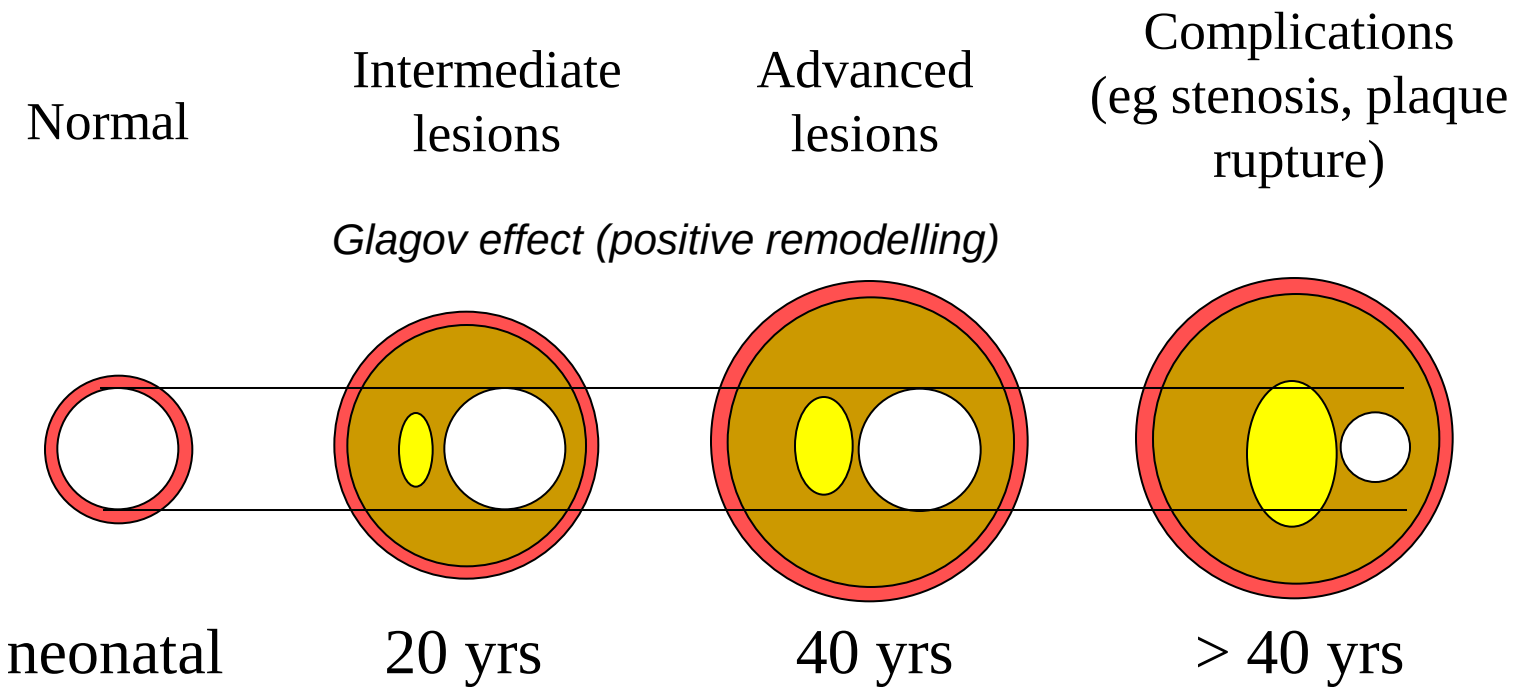
Intraplaque haemorrhage contributes to plaque growth

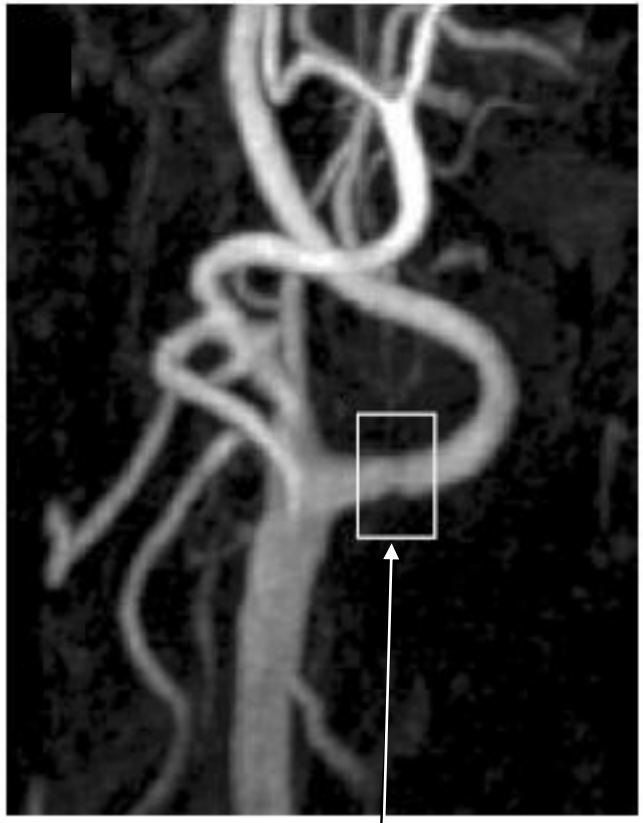


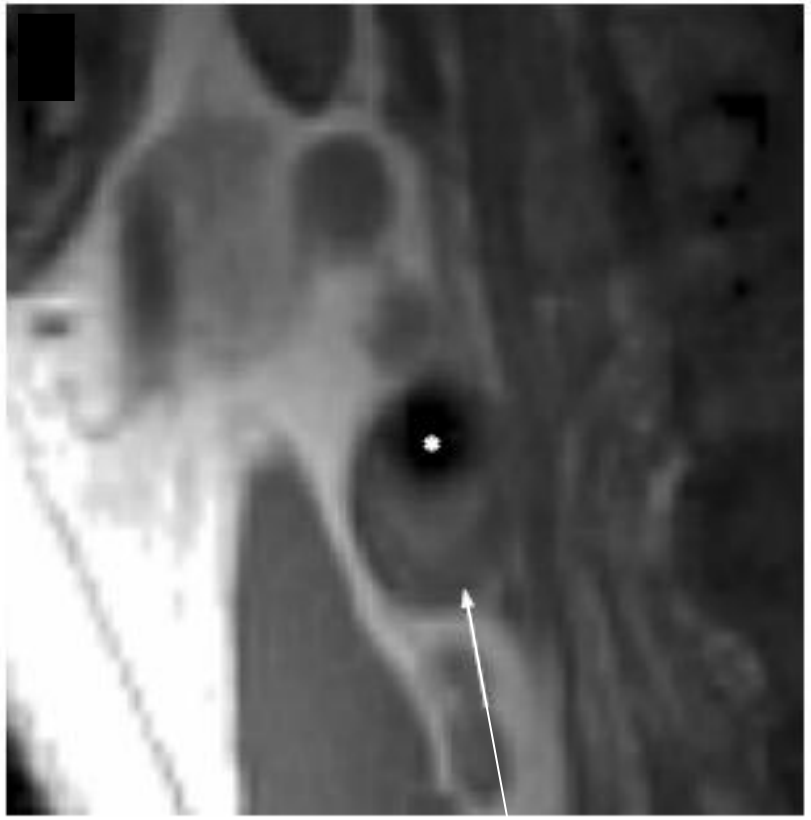


Kolodgie et al 2003 N Eng J Med 349@2316

Natural history of atherosclerosis







Minor (~30%) stenosis of R internal carotid artery

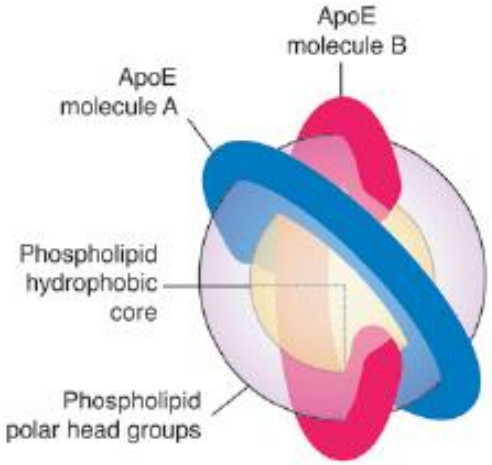
Atherosclerotic plaque occupying ~80% of arterial cross-section

Keenan, N G et al. Heart 2008;94:228

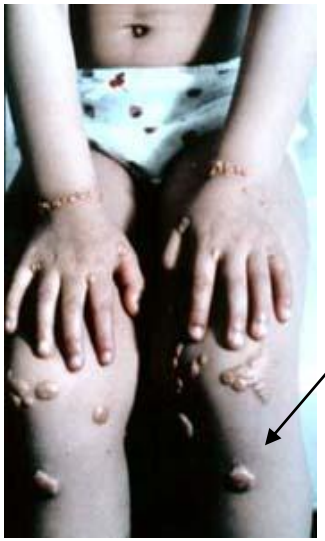
INVESTIGATING MOLECULAR MECHANISMS

Mouse models of atherosclerosis

- **ApoE-/-**
  - 34kd component of VLDL and chylomicrons
  - ligand for LDL receptor

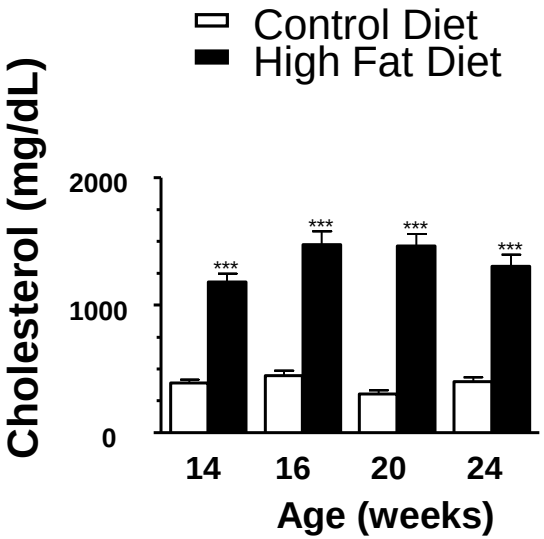


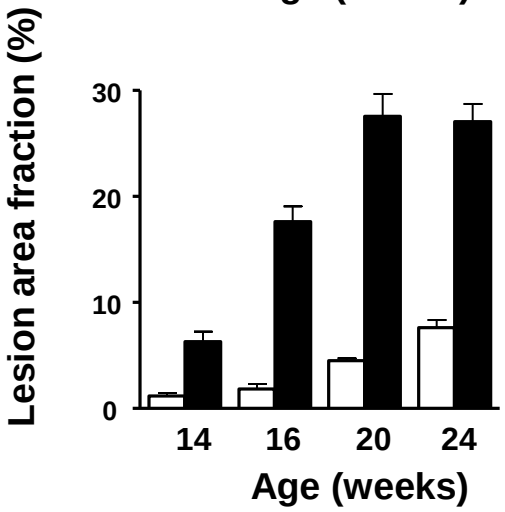
- **LDL receptor -/-**
  - Mutations in familial hypercholesterolaemia

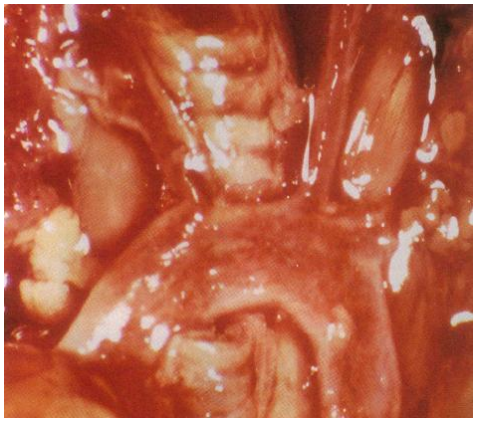


xanthoma

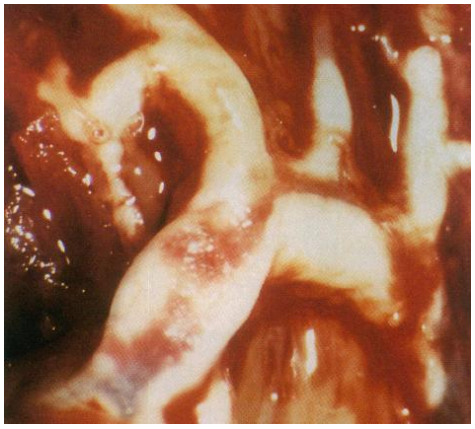
Atherosclerosis in *Ldlr*$^{-/-}$ mice





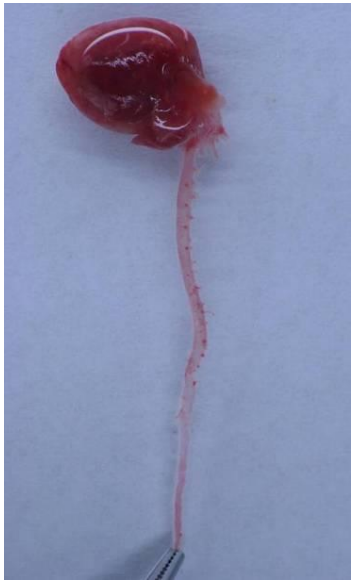


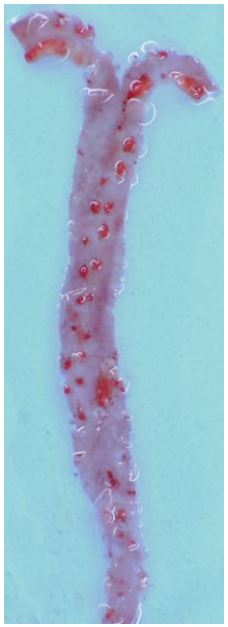
wild-type

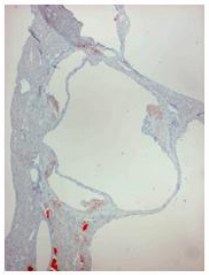
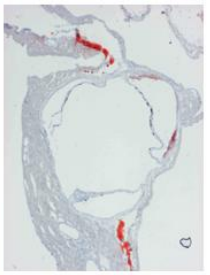
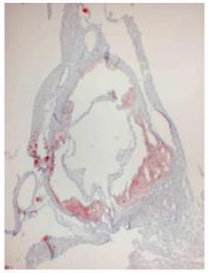
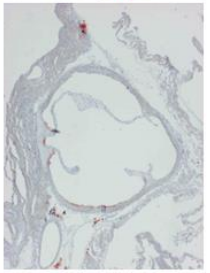
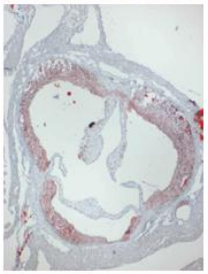
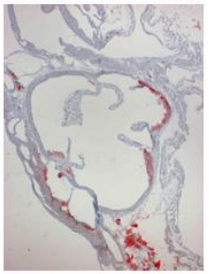
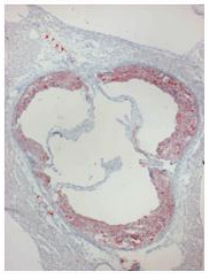
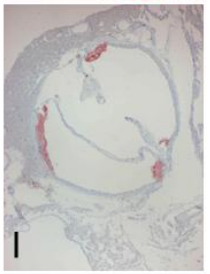


Ldlr-/- high fat 13 mo

Ishibashi et al 1994 JCI 93:1885





	high fat	chow
14		
16		
20		
24		

weeks

Aortic valve

Influence of adhesion molecules, chemokines and cytokines on mouse atherosclerosis

Accelerators

Adhesion molecules
P-selectin
E-selectin
ICAM-1
VCAM-1

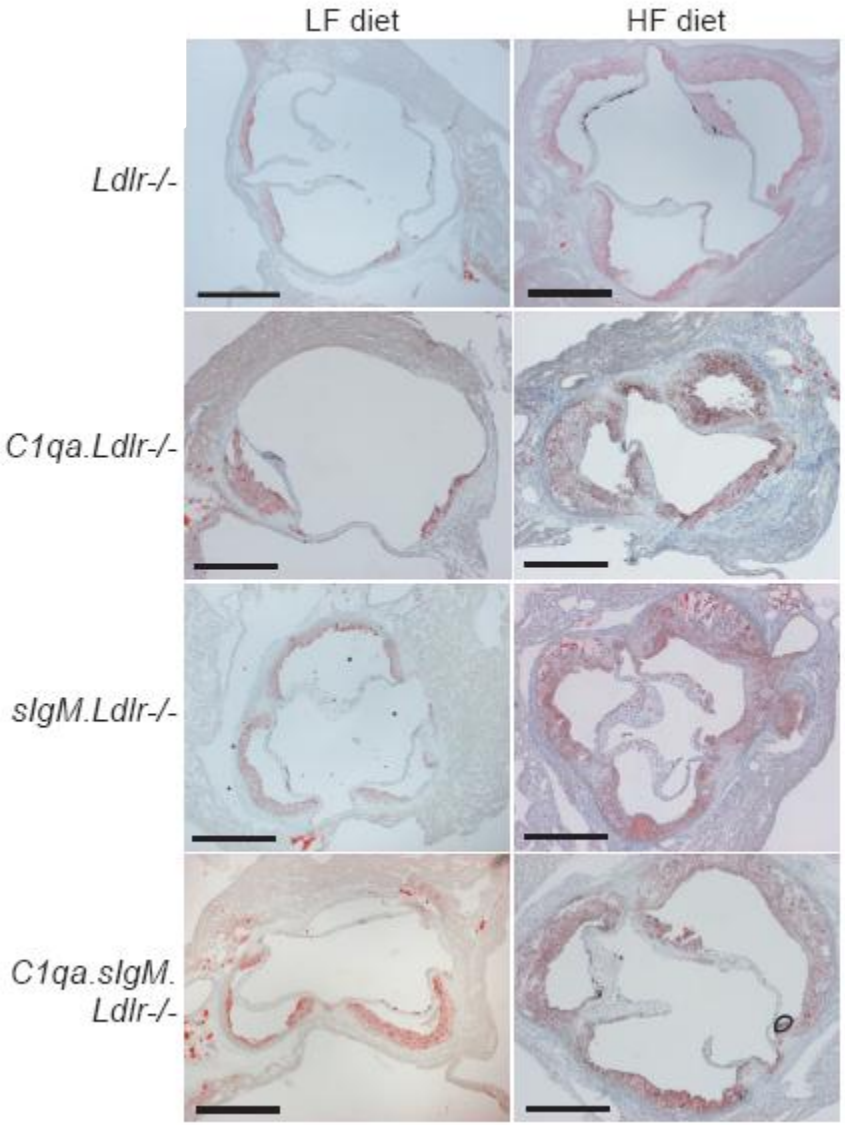
Chemokines & receptors
MCP-1
CCR2
CXCR2
CX3CR1

Cytokines
IL-1
TNFa
IL-4
IL-6
IL-12
IL-18
IFNg

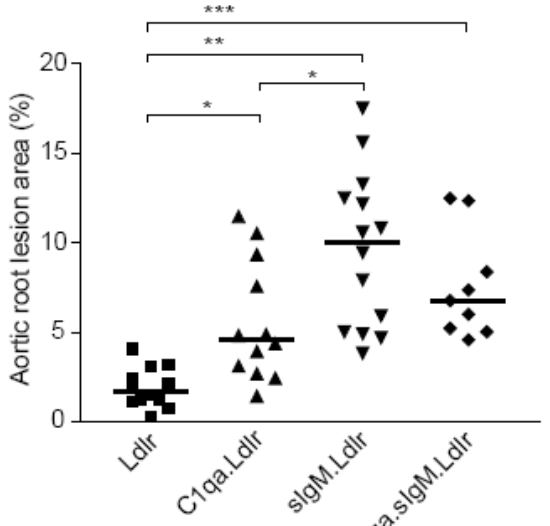
Decelerators

IL1RA
TGFb
IL-10

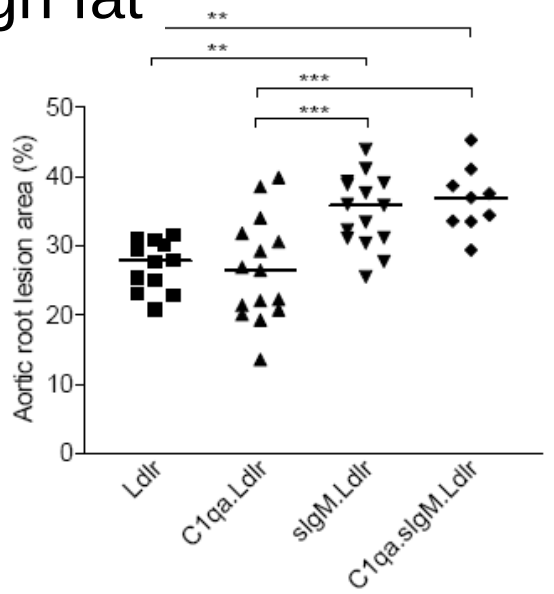
IgM deficiency accelerates atherosclerosis



Low fat

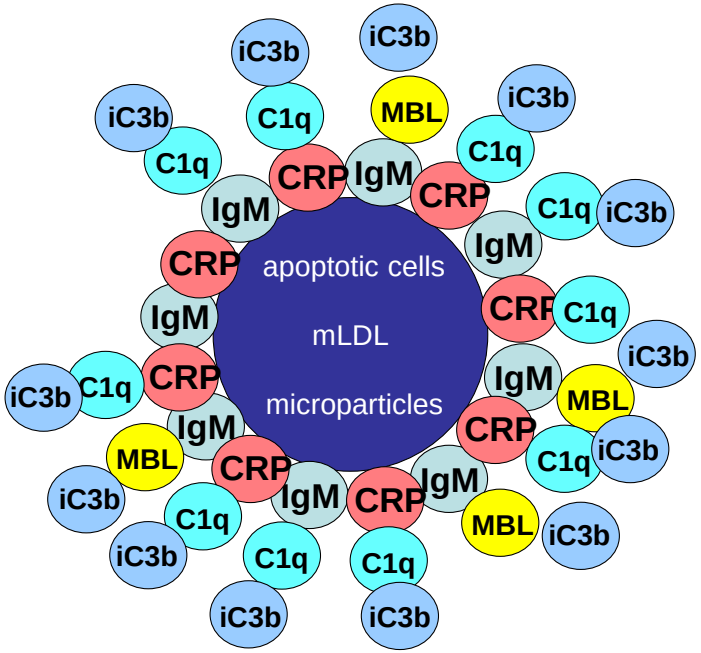


High fat



Lewis et al 2009 Circulation 120:417

Hypothetical model of the role of complement and IgM natural antibodies in atherosclerosis



Homeostatic clearance

Role of T lymphocytes in atherosclerosis

- Atherosclerotic plaques contain MHC Class II positive dendritic cells and T lymphocytes at all stages

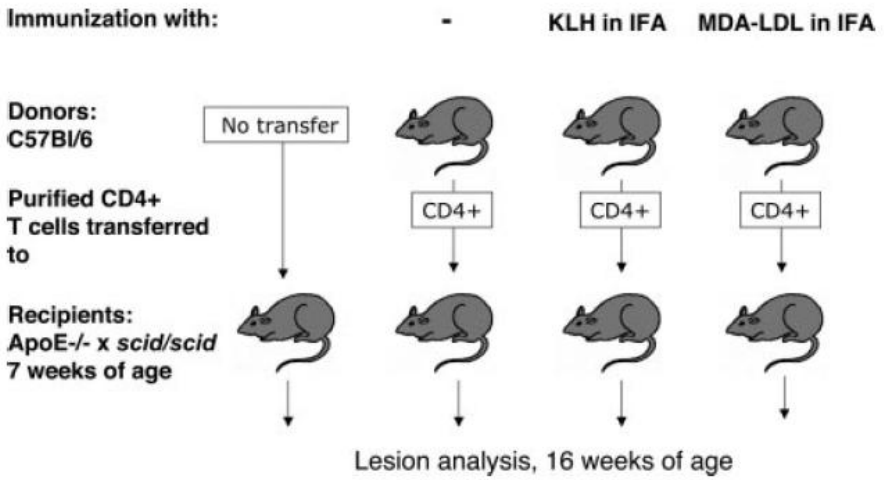
- Plaque T cells show evidence of activation (eg HLA-DR, IFNγ)

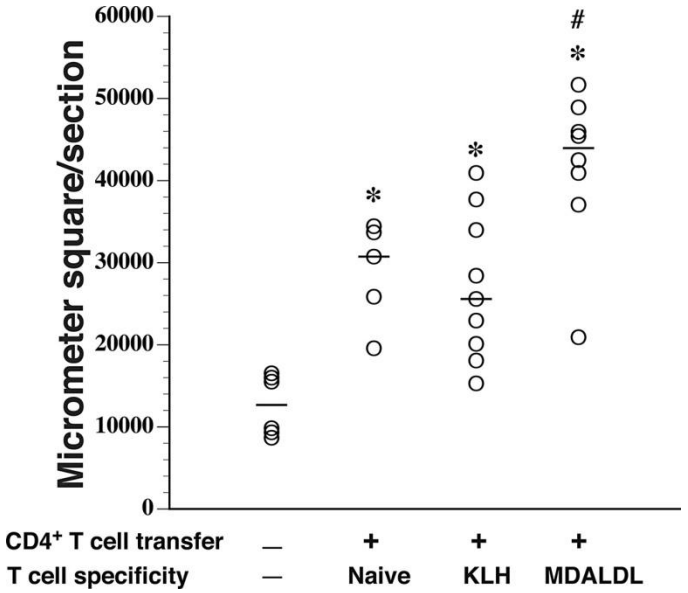
- Plaque T cells are oligoclonal and ~10% react with oxidised LDL

- T cells may activate macrophages and VSMC (eg via CD40L-CD40 contact interactions)

- Activated T cells are present in the circulation during acute coronary syndromes (ie plaque instability)

Effects of CD4 T cell transfer





Zhou et al (2006) ATVB 26:864

Summary

- Atherosclerosis can be viewed as a dynamic chronic inflammatory disease of arteries
- The innate immune system regulates the safe disposal of lipoproteins and other debris from the arterial wall and is intrinsically protective
- Overdrive of the innate immune system leads to irreversible remodelling, and this may be accelerated by adaptive immune mechanisms
- The interplay between proinflammatory and wound healing pathways governs plaque stability