Introduction to atherosclerosis

Dorian O. Haskard

Vascular Sciences Section

National Heart and Lung Institute

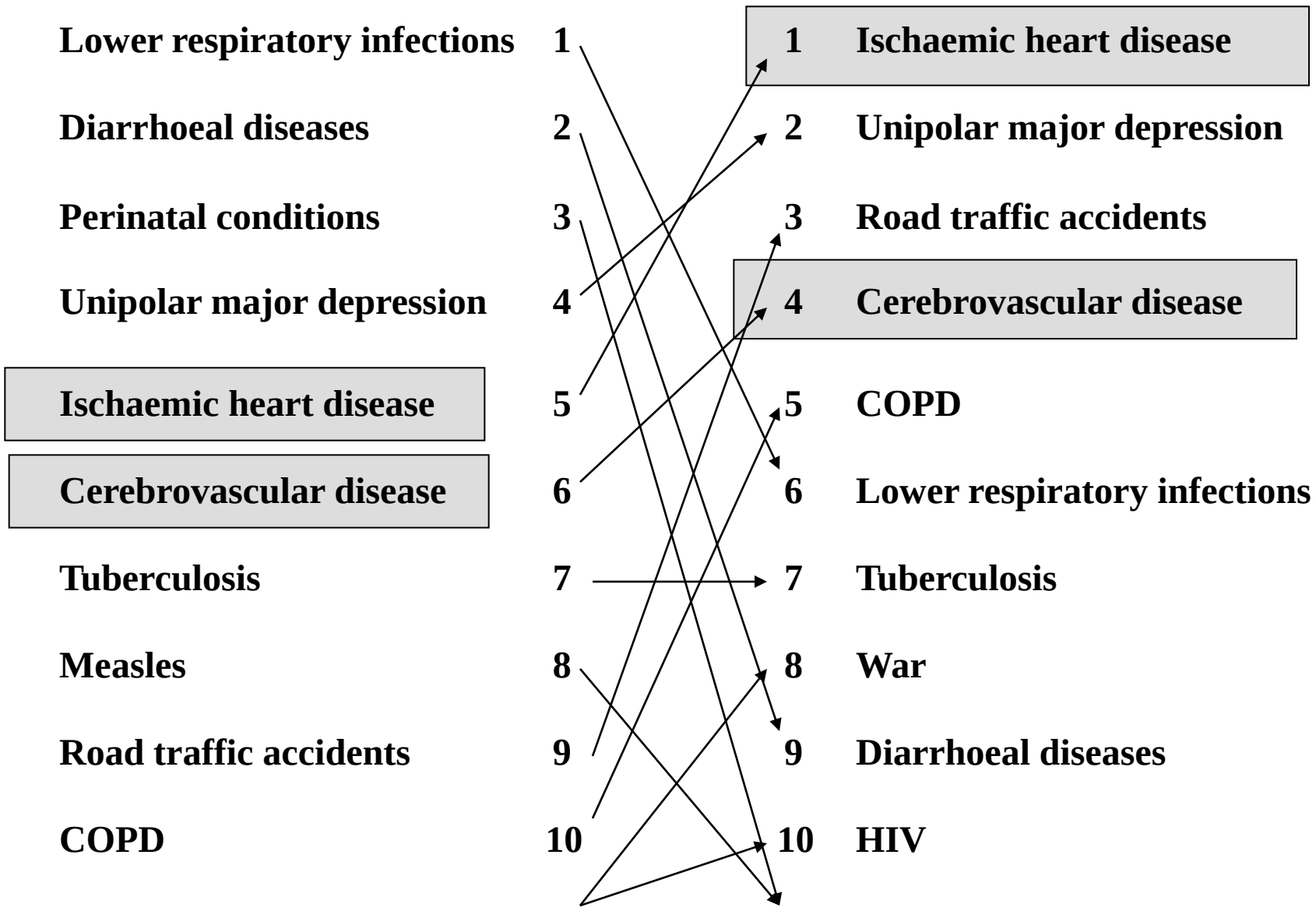
British Heart Foundation

Imperial College London

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

The DEATHS preceding were caused by Diseases and Casualties as follows, viz.

Abscesses	1	Hernia, or Rupture	3
Aneurism	1	Jaundice	10
Apoplexy	13	Inflammation of the bowels	1
Burns or Scalds	6	——— of the stomach	1
Cancer	5	Killed by lightning	1
Casualties	15	Insanity	1
Childbed	14	Intemperance	2
Cholera Morbus	6	Locked jaw	2
Colic	2	Mortification	11
Consumption	221	Old Age	26
Convulsions	36	Palsy	12
Cramp in the stomach	2	Pleurisy	8
Croup	1	Quinsy	15
Debility	28	Rheumatism	1
Decay	20	Rupture of blood vessels	1
Diarrhœa	15	Small-Pox,(at Rainsford's Island)	2
Drinking cold water	2	Sore throat	1
Dropsy	21	Spasms	2
——— in the head	23	Stillborn	49
Drowned	13	Suicide	1
Dysentery	14	Sudden death	25
Dispepsia or Indigestion	15	Syphilis	12
Fever, bilious	7	Teething	15
——— pulmonic	46	Worms	11
——— inflammatory	24	Whooping Cough	14
——— putrid	6	White swelling	2
——— typhus	33	Diseases not mentioned	48
Flux infantile	57		
Gout	3	Total,	942
Hoemorrhage	4		

Causes of Death in 1811. Abstract of the Bill of Mortality for the Town of Boston.

Jones et al 2012 NEJM 366:2333

Firefox | atherosclerosis - Google Scholar | atherosclerosis - Google Search | New Tab | atherosclerosis - Google Search

www.google.co.uk/search?tbm=isch&q=atherosclerosis&hl=en&biw=1600&bih=757&sei=qqFDUNWAD6rE0QXvxIH4DQ&gbv=2

google

Search the Web | Web Search | skype | Email Notifier | facebook | ebay | mapquest | Lyric Watcher | BBC | App

+You Search Images Maps Play YouTube News Gmail Documents Calendar More

Google

atherosclerosis

Sign in

Search

About 1,740,000 results (0.22 seconds)

SafeSearch moderate

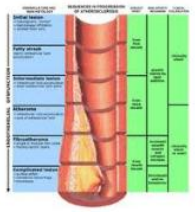
Web
Images
Maps
Videos
News
Shopping
Books
More

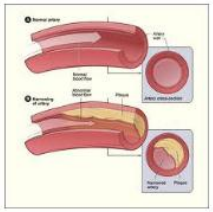
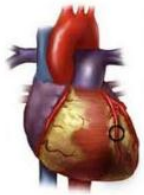
Any time
Past 24 hours
Past week
Custom range...

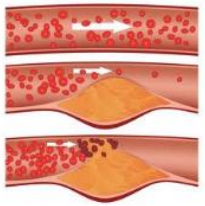
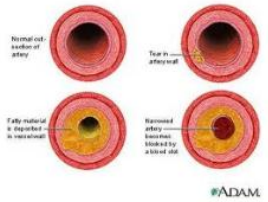
All results
By subject

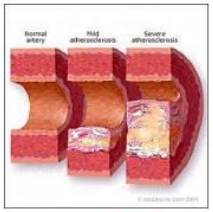
Any size
Large
Medium
Icon
Larger than...
Exactly...

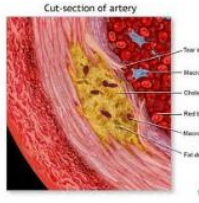
Related searches: atherosclerosis plaque | stages of atherosclerosis | atherosclerosis process | development of atherosclerosis | atherosclerosis progression

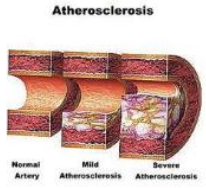


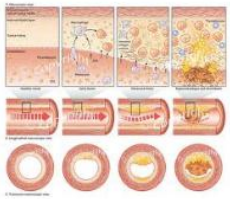
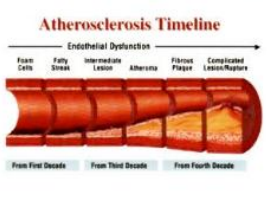



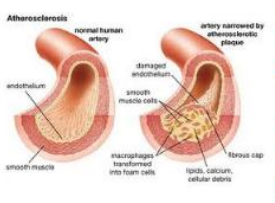



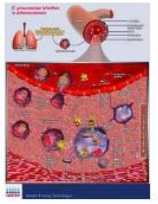
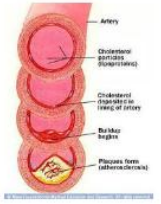


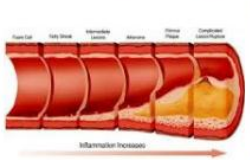


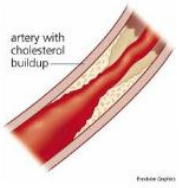


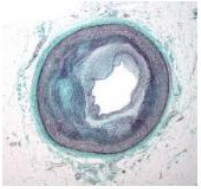
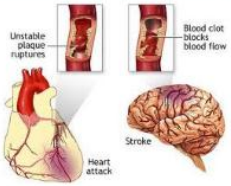







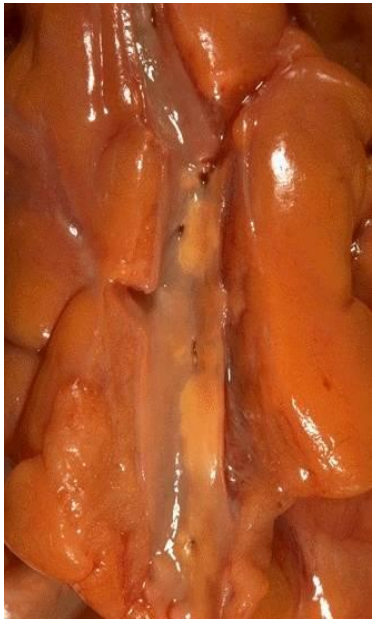
19:21
02/09/2012

Risk Factors

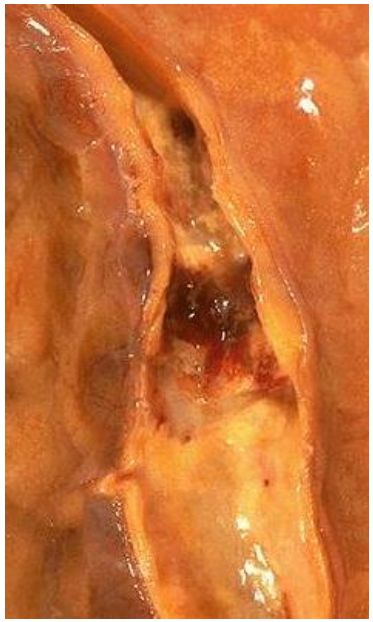
Modifiable	Not modifiable
dyslipidaemia	Age
smoking	Sex
hypertension	Genetics
diabetes mellitus	
visceral obesity	
lack of exercise	
raised homocysteine	

PATHOLOGY

fatty streaks

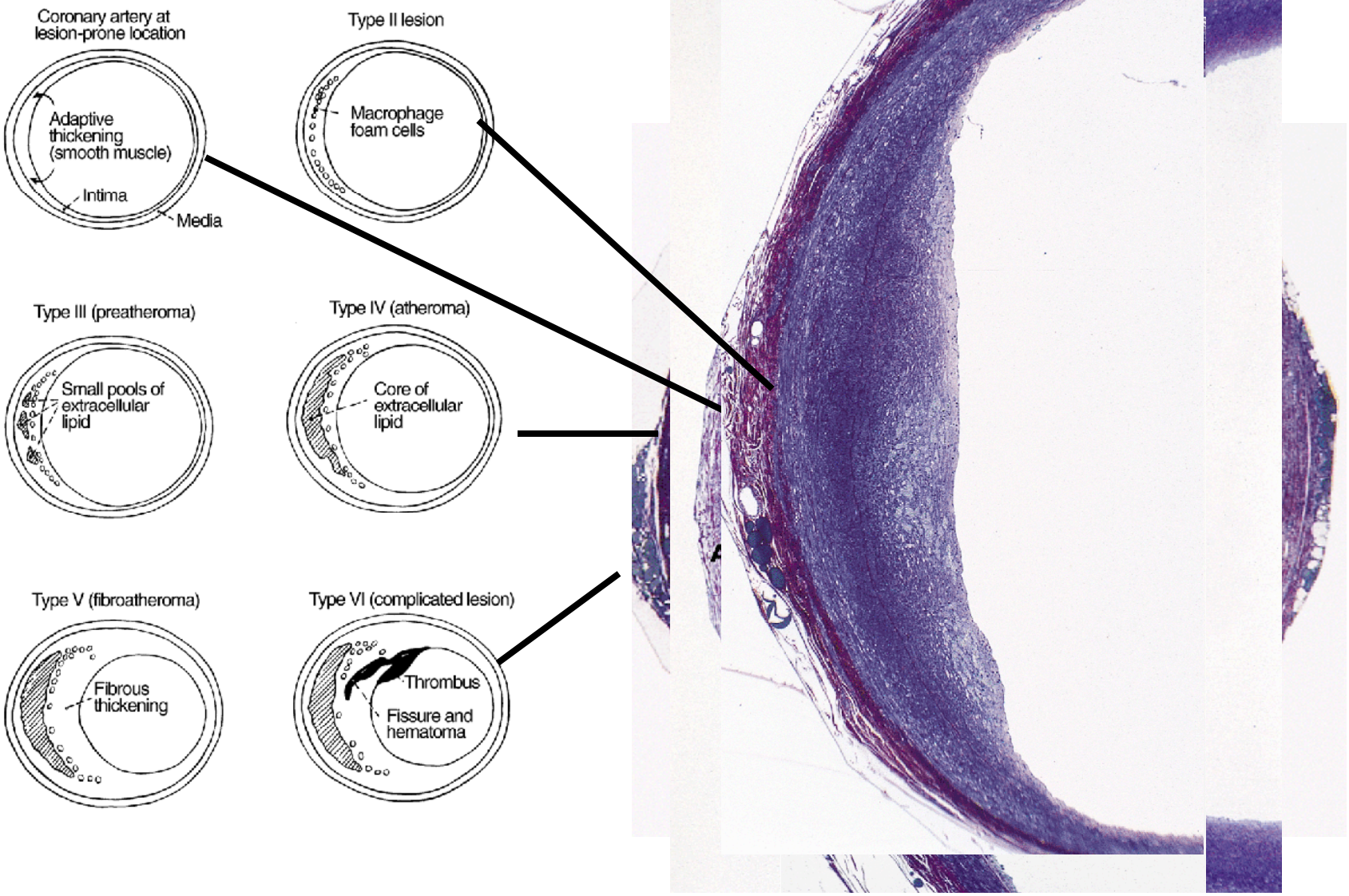


intermediate lesion



ulcerated plaque

Type II lesion



Debris (eg modified lipoproteins, apoptotic cells)

⇩

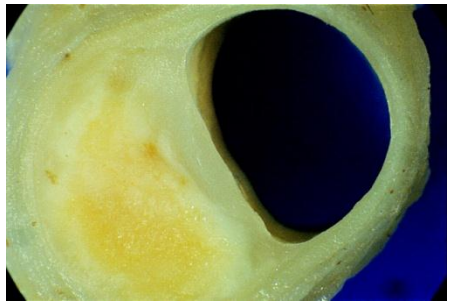
Reversible fatty lesions

⇩

Irreversible remodelling

wound healing

Stable plaques



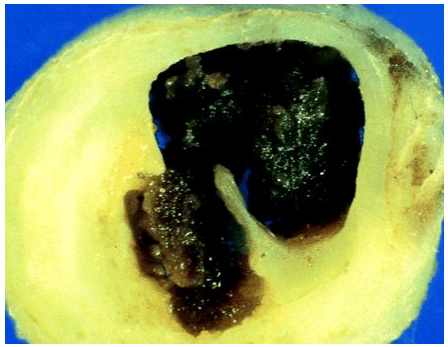
Ischaemia

Angina
Intermittant claudication

⇔

inflammation/thrombosis

Unstable plaques

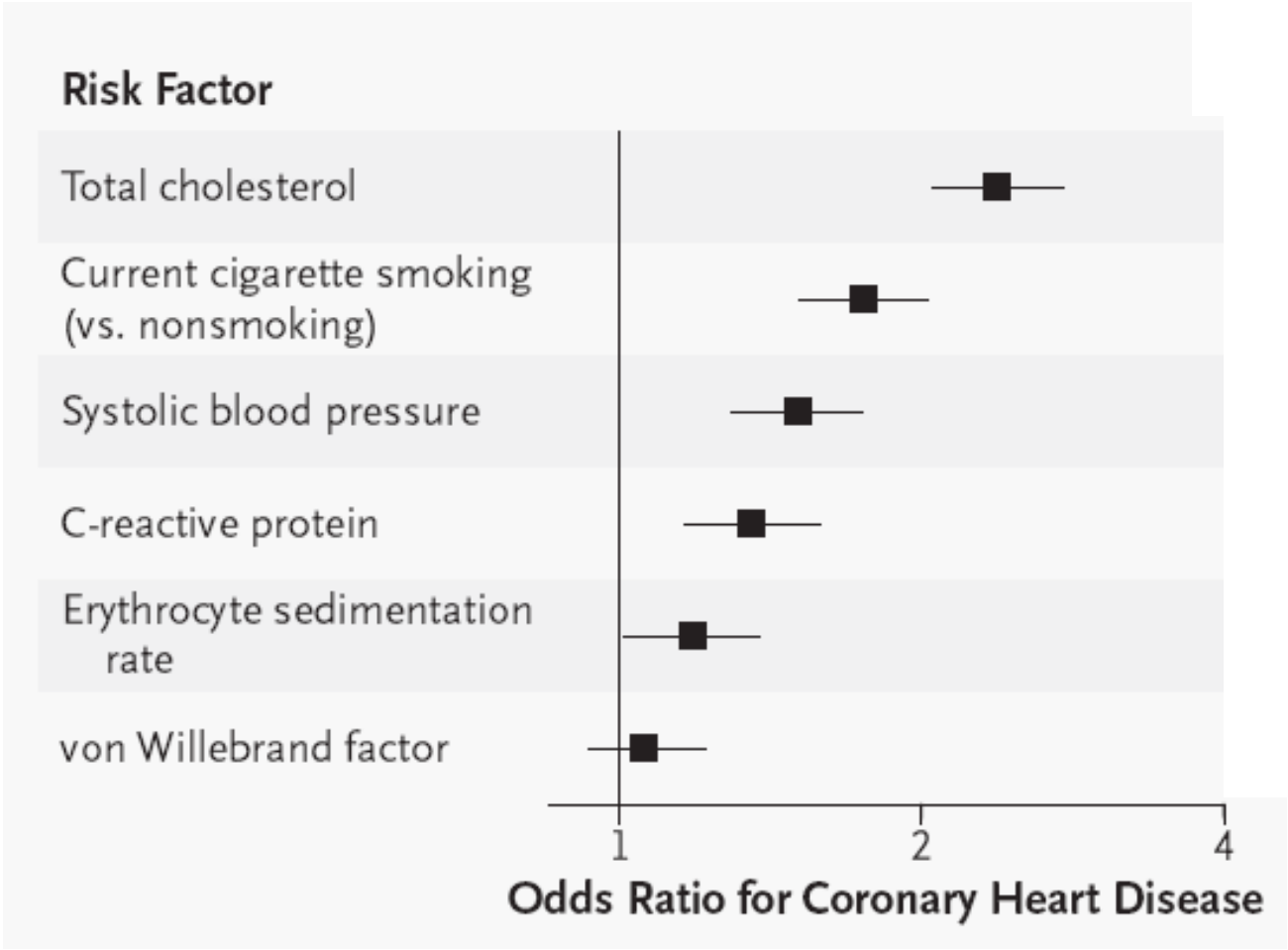


Thrombosis and infarction

Acute coronary syndromes
Stroke
Peripheral gangrene

CHOLESTEROL AND INFLAMMATION

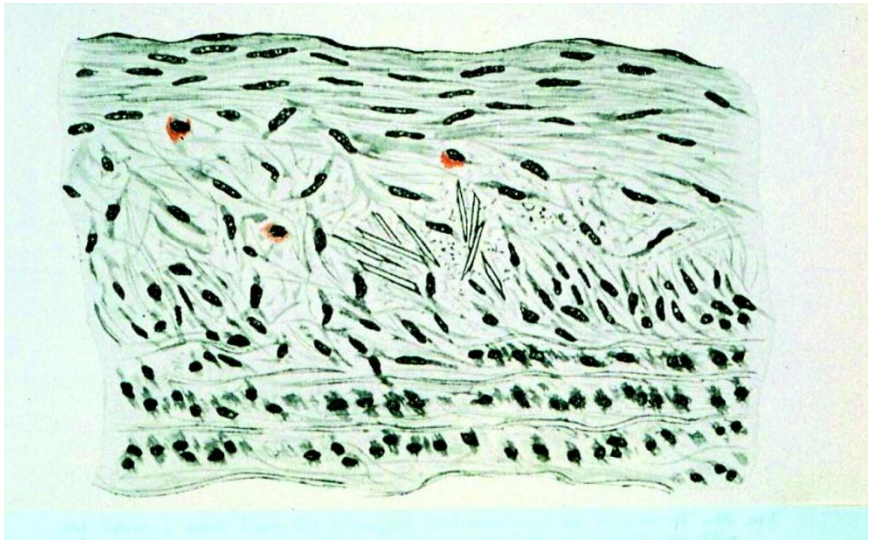
Relative importance of risk factors



Danesh et al 2004 N Engl J Med 350:1387

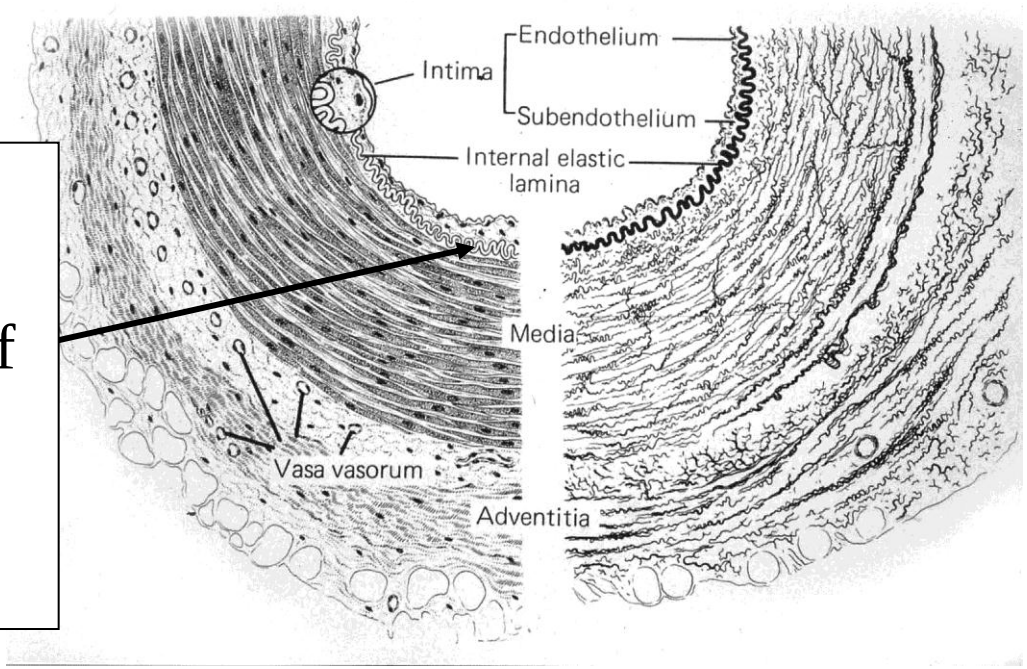
History – the cholesterol hypothesis

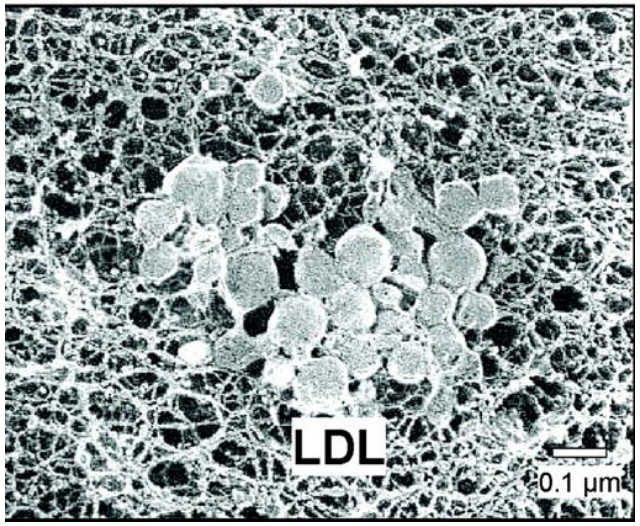
N. N. Anitschkow
Military Medical Academy of St Petersburg
(circa 1904)



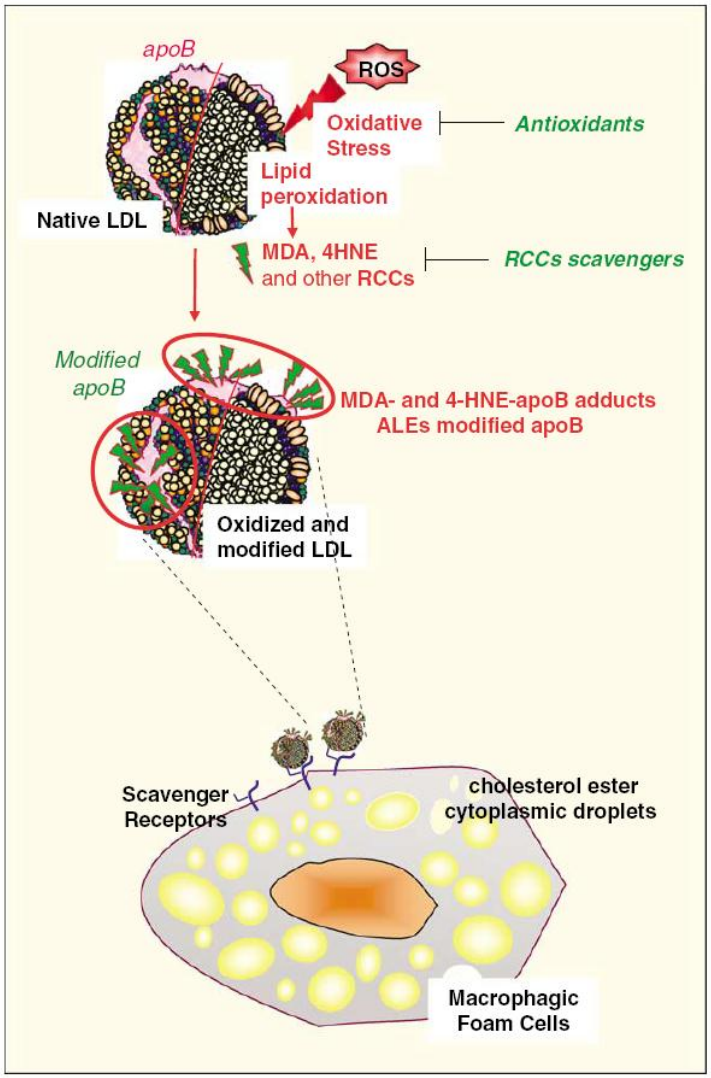
Plaque from a rabbit fed cholesterol for 106 days and then chow for >2 years

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

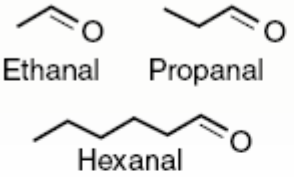




From: Tabas, I. et al. Circulation 2007;116:1832-1844

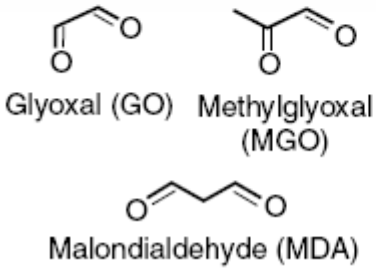


Saturated Aldehydes

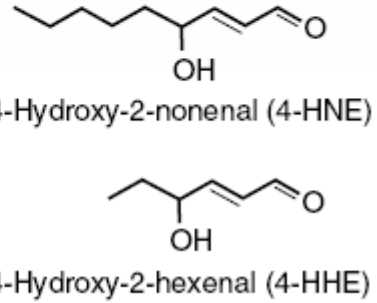


Unsaturated Aldehydes

Dicarbonyls

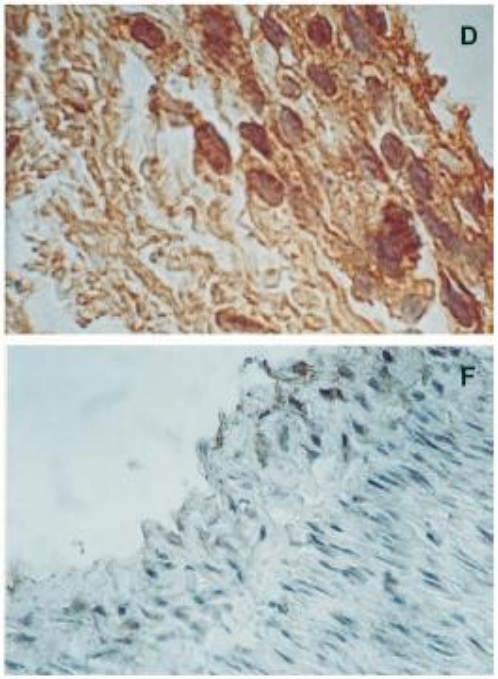


4-Hydroxy-2-alkenals



LDL modification in the arterial wall happens before macrophage infiltration

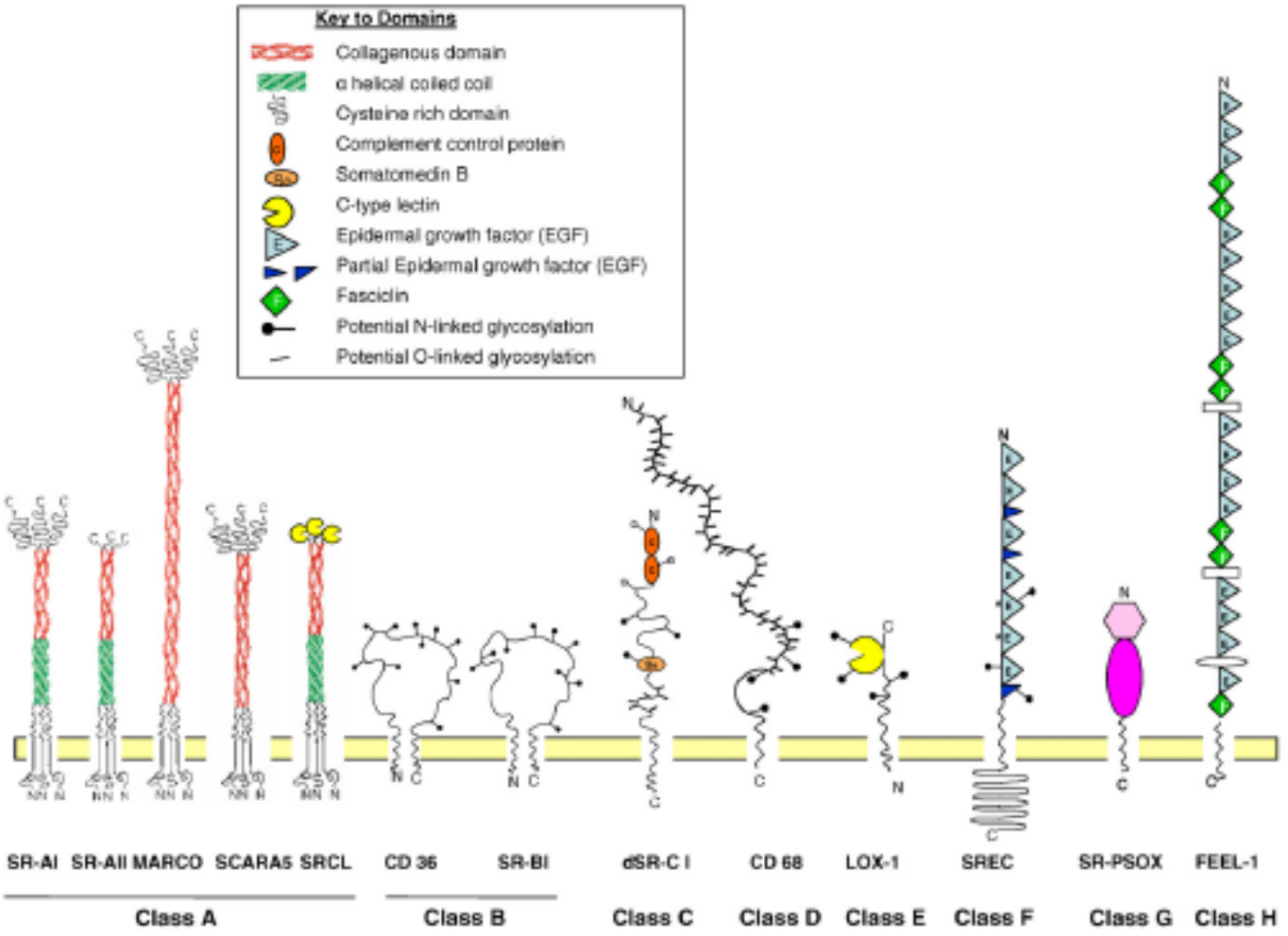
MDA-lysine
(oxidised LDL)



monocyte/møs

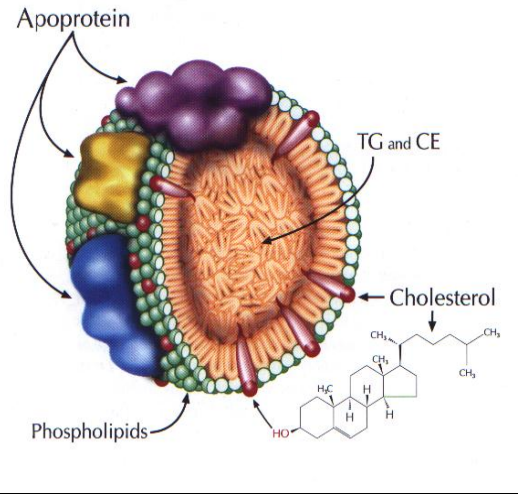
Napoli et al 1997 J Clin Invest 100:2680

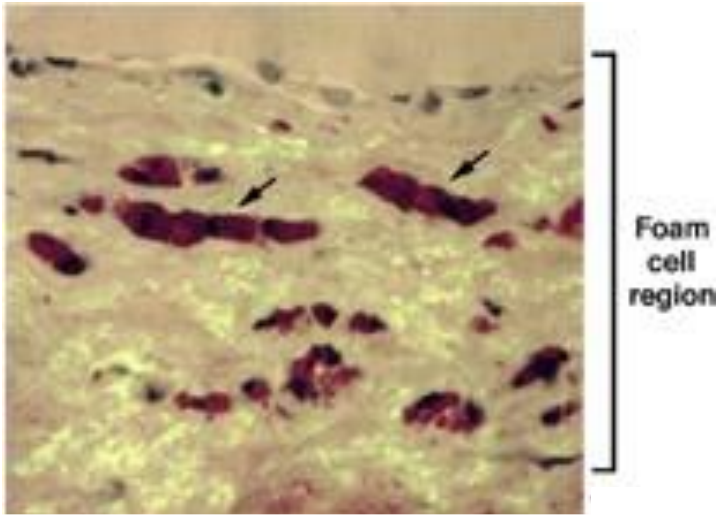
Macrophage scavenger receptors



from Pluddemann et al (2007) Methods 43:207

Foam cells

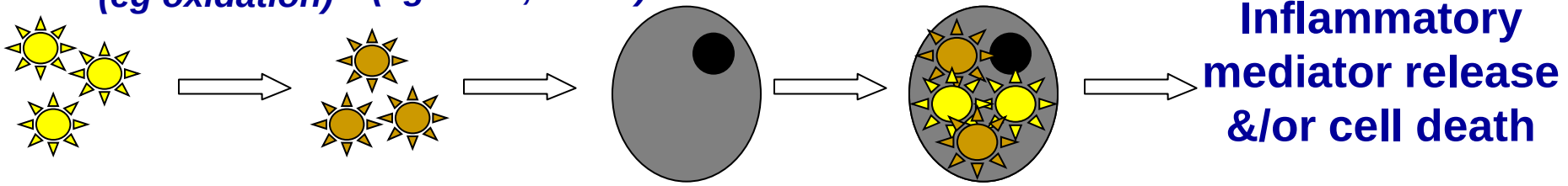




from Dr Howard K

lipoprotein modification (eg oxidation)

via scavenger receptors (eg SR-A, CD36)

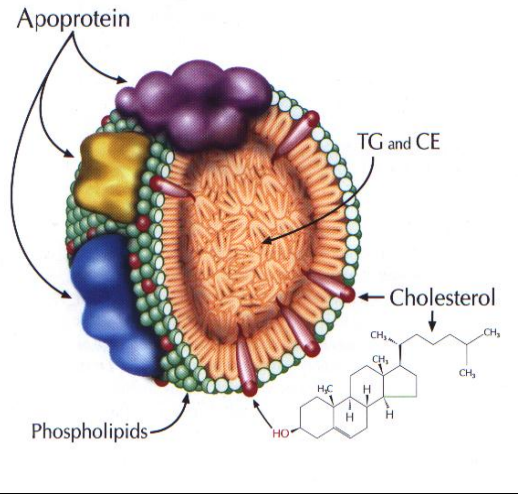


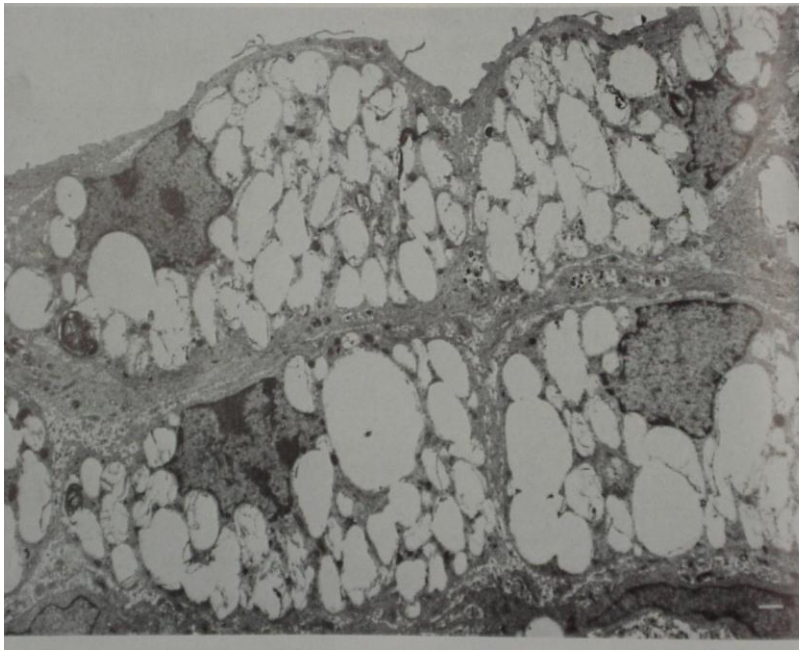
Macrophage

"foam cells"

Inflammatory mediator release &/or cell death

Foam cells

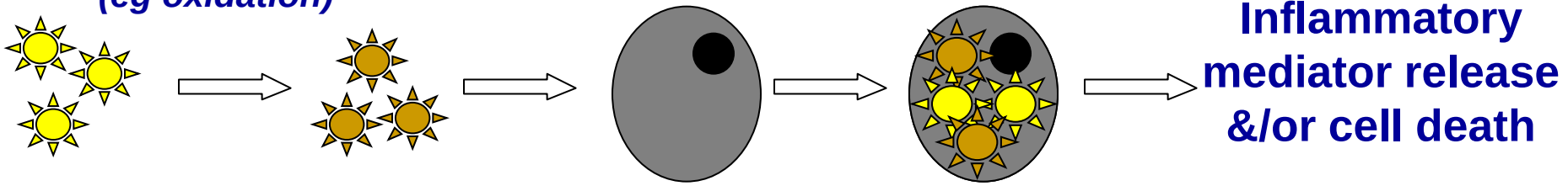




Faggiotto et al 1984 Arteriosclerosis 4:323

lipoprotein modification (eg oxidation)

via scavenger receptors (eg SR-A, CD36)

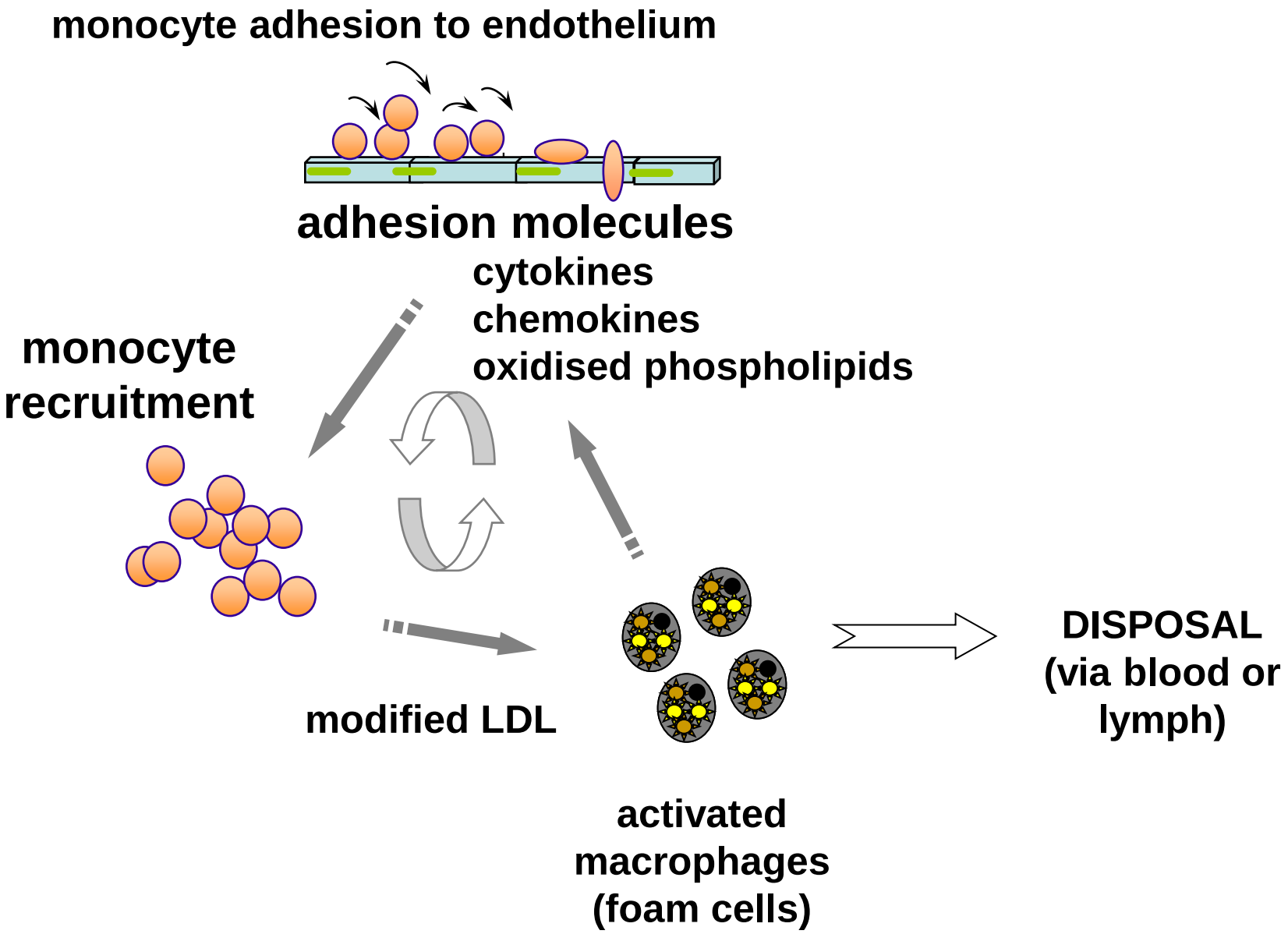


Macrophage

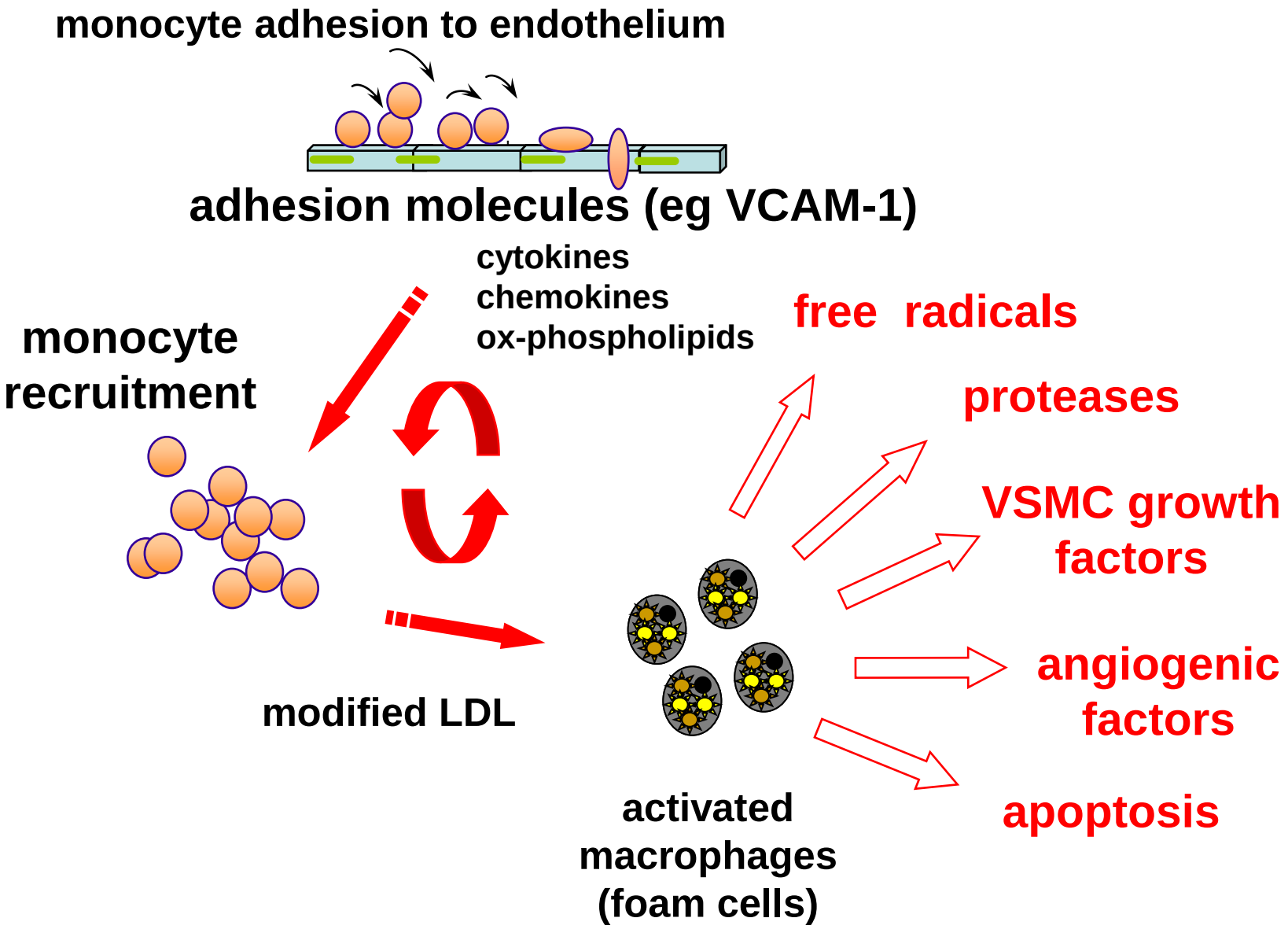
"foam cells"

Inflammatory mediator release &/or cell death

Homeostatic debris disposal



Inflammatory basis of atherosclerosis



Macrophage uptake of LDL

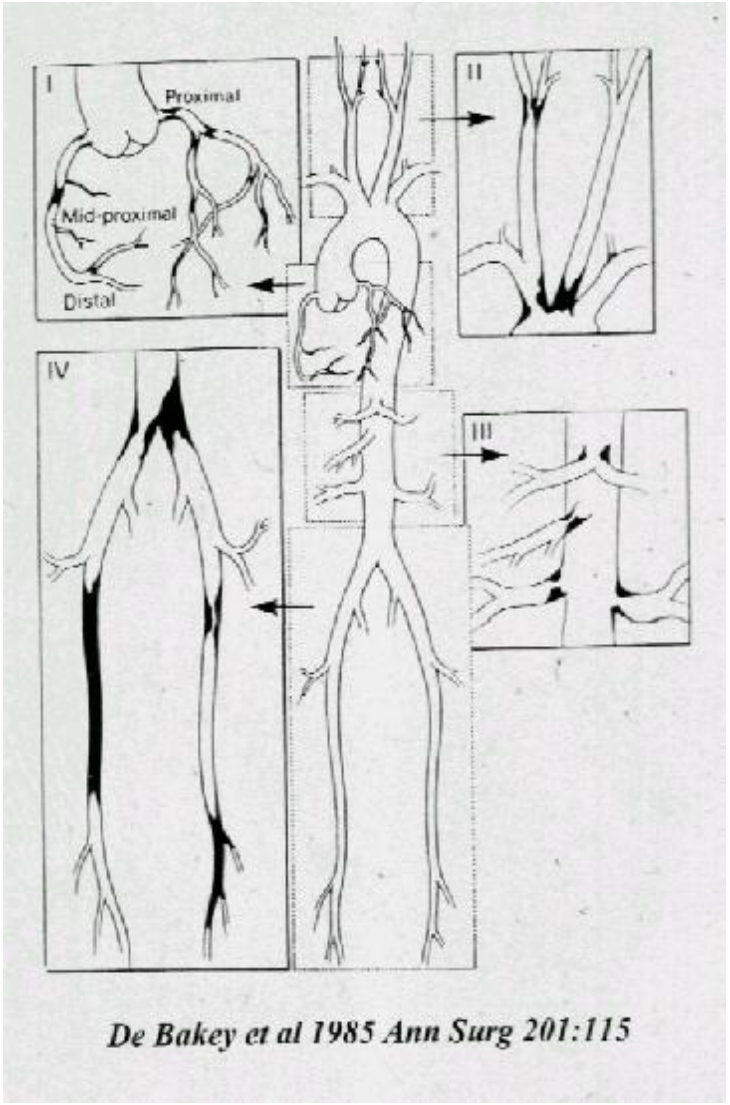
- Physiological uptake of LDL via LDL controlled by receptor down-regulation
- Uptake of oxidised LDL by scavenger receptors is not regulated and results in “foam cell” formation.
- Cholesterol-laden macrophages die by apoptosis or necrosis and release proinflammatory cytokines and growth factors.

Main cellular players

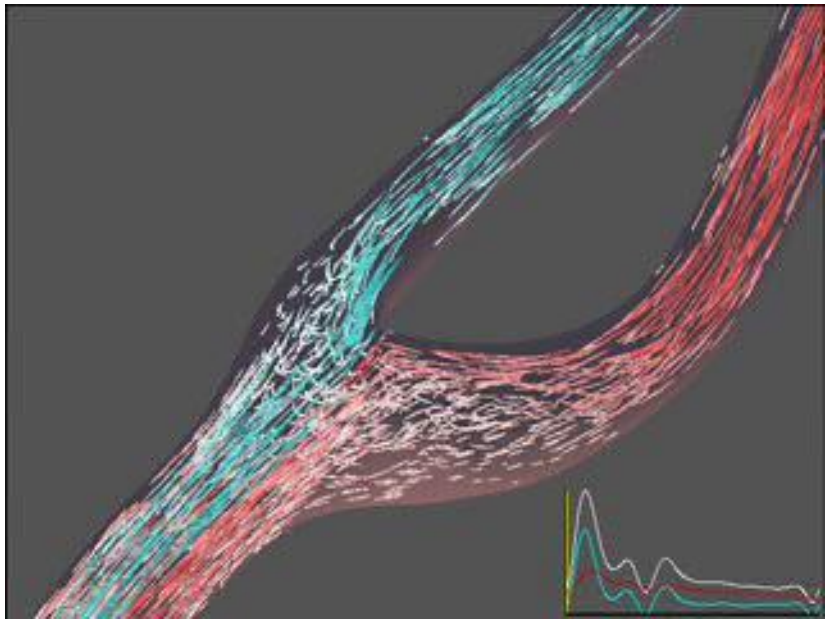
- **Vascular endothelial cells**
  - Barrier function (eg to lipoproteins)
  - Leukocyte recruitment
- **Platelets**
  - Thrombus generation
  - Cytokine and growth factor release
- **Monocyte-macrophages**
  - Foam cell formation
  - Cytokine and growth factor release
  - Major source of free radicals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

IMPORTANCE OF BLOOD FLOW

Flow-related susceptibility of branch points and curvatures

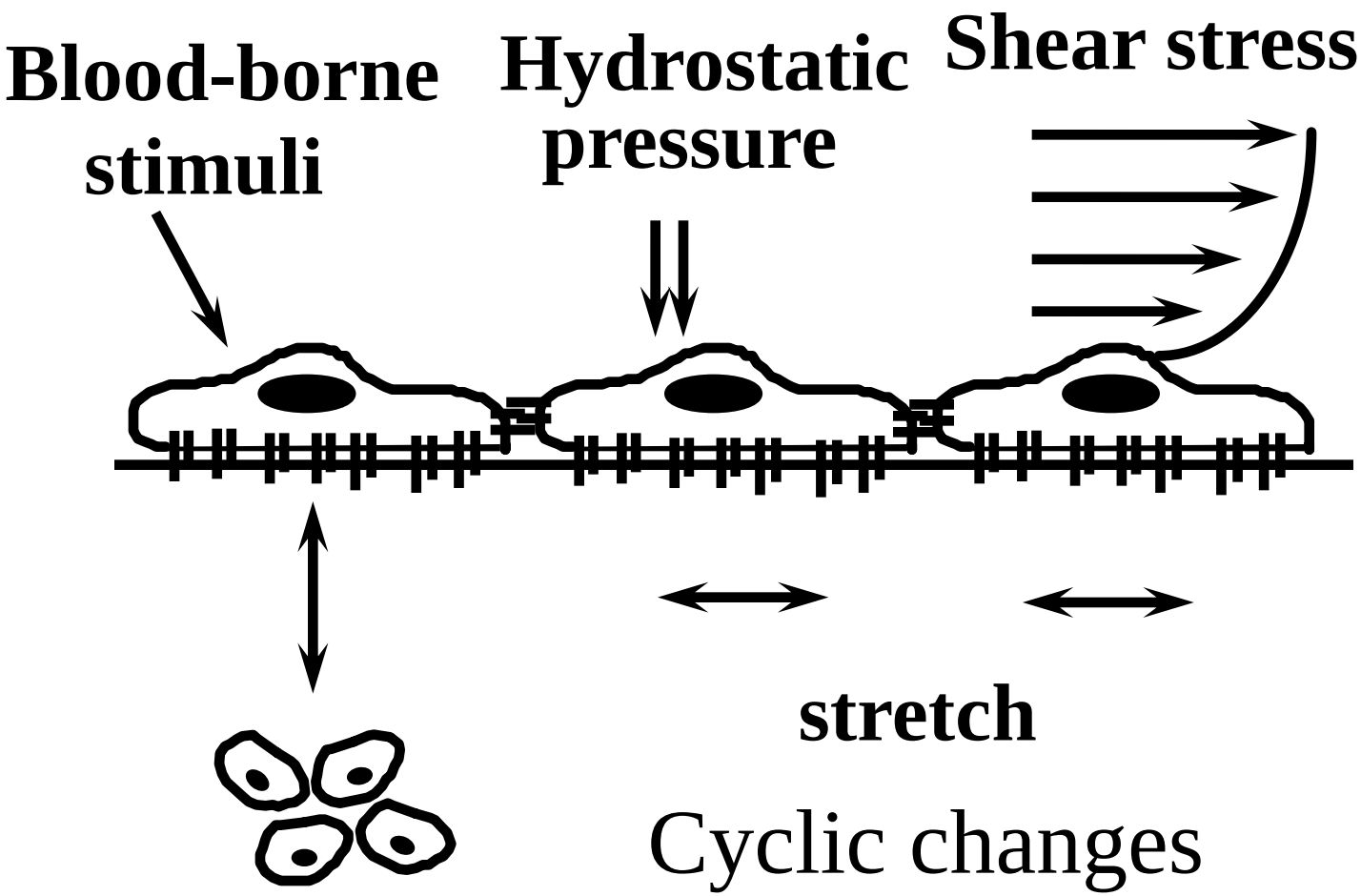


Risk factors are general but atherosclerosis is focal

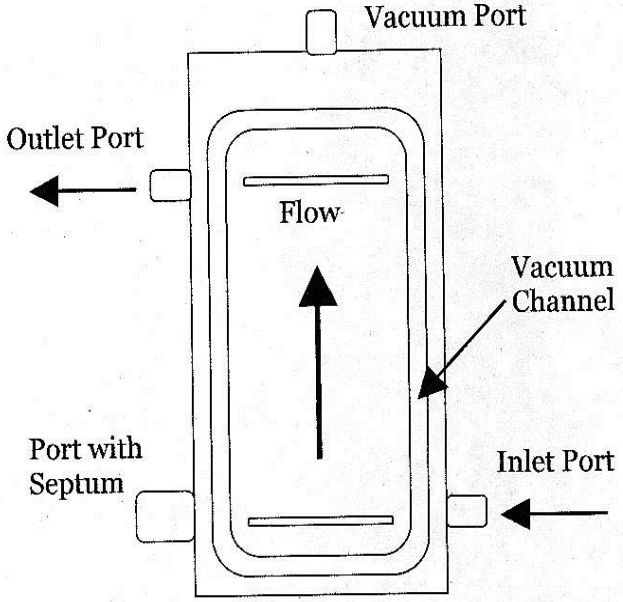


Courtesy of David Steinman
University of Western Ontario

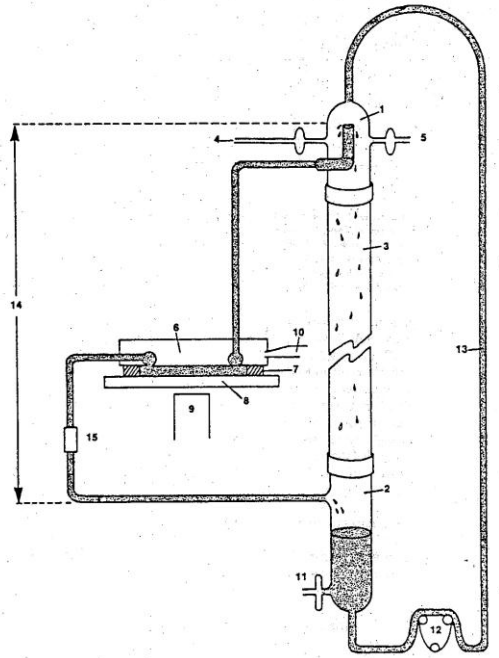
Effects of mechanical forces on endothelial function

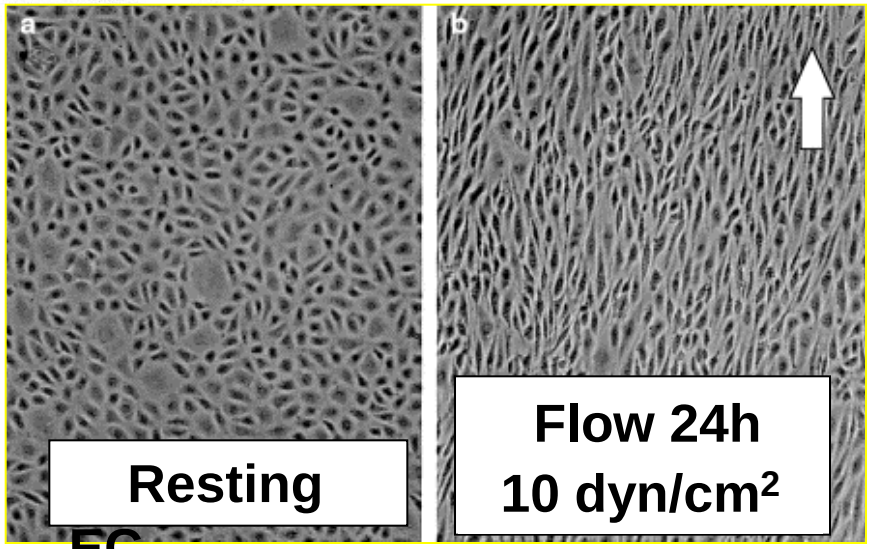


Use of parallel plate flow chamber for studying endothelial cells under flow



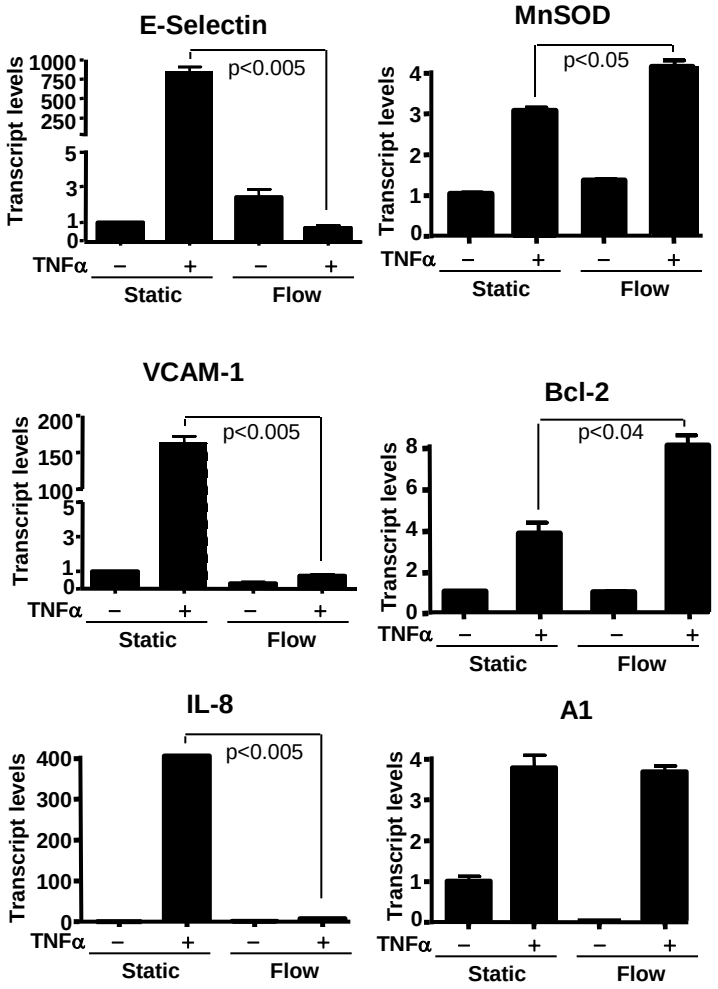
Flow Chamber





EC

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



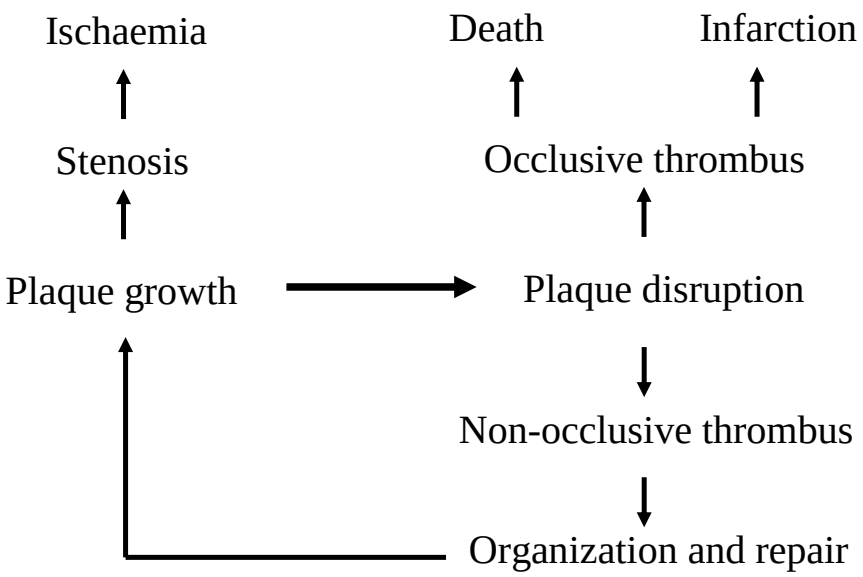
proinflammatory genes

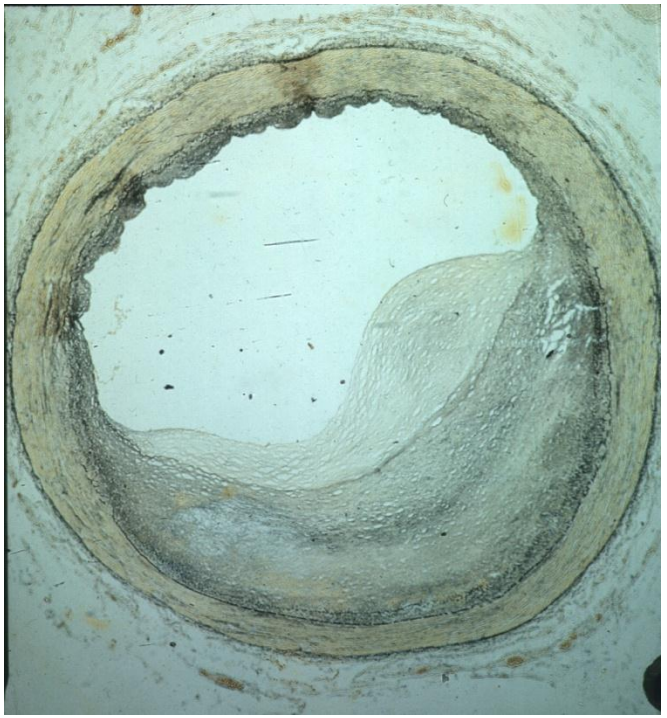
cytoprotective genes

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

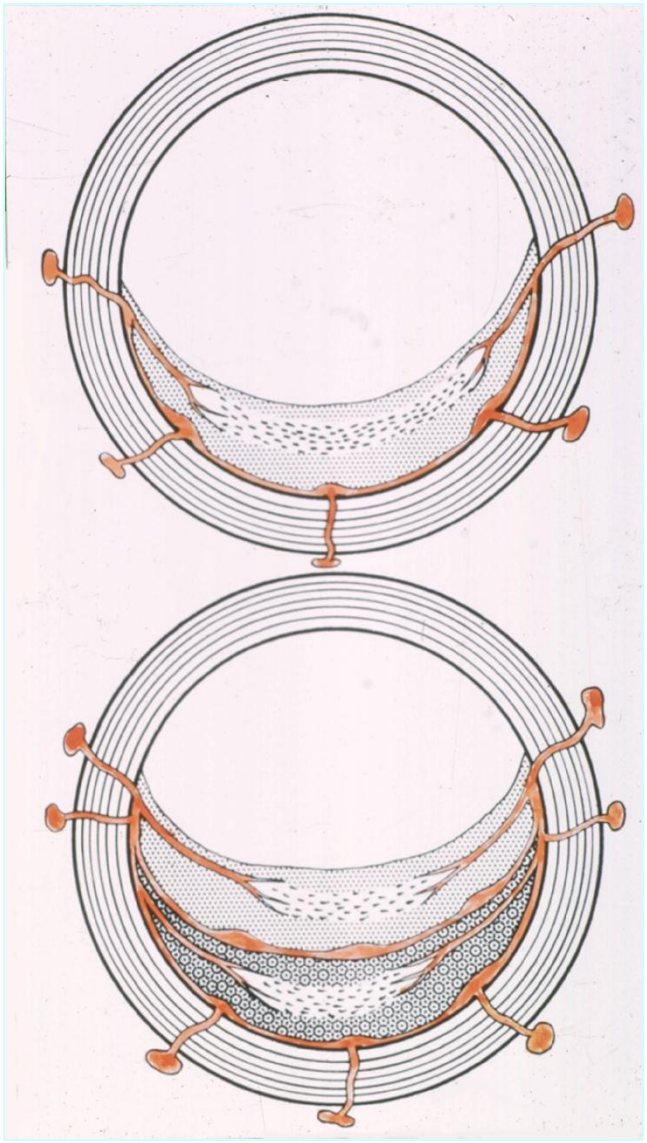
PLAQUE DEVELOPMENT AND ANGIOGENESIS

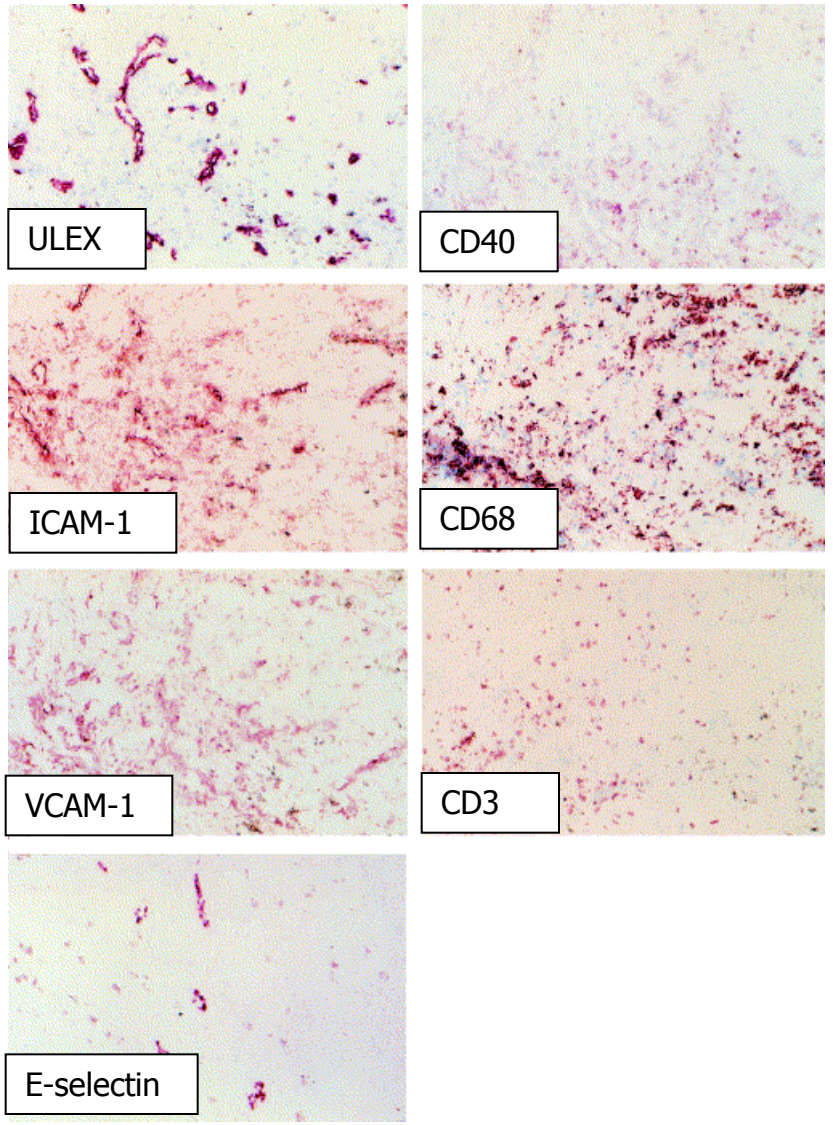
Step-wise progression of atherosclerotic plaques





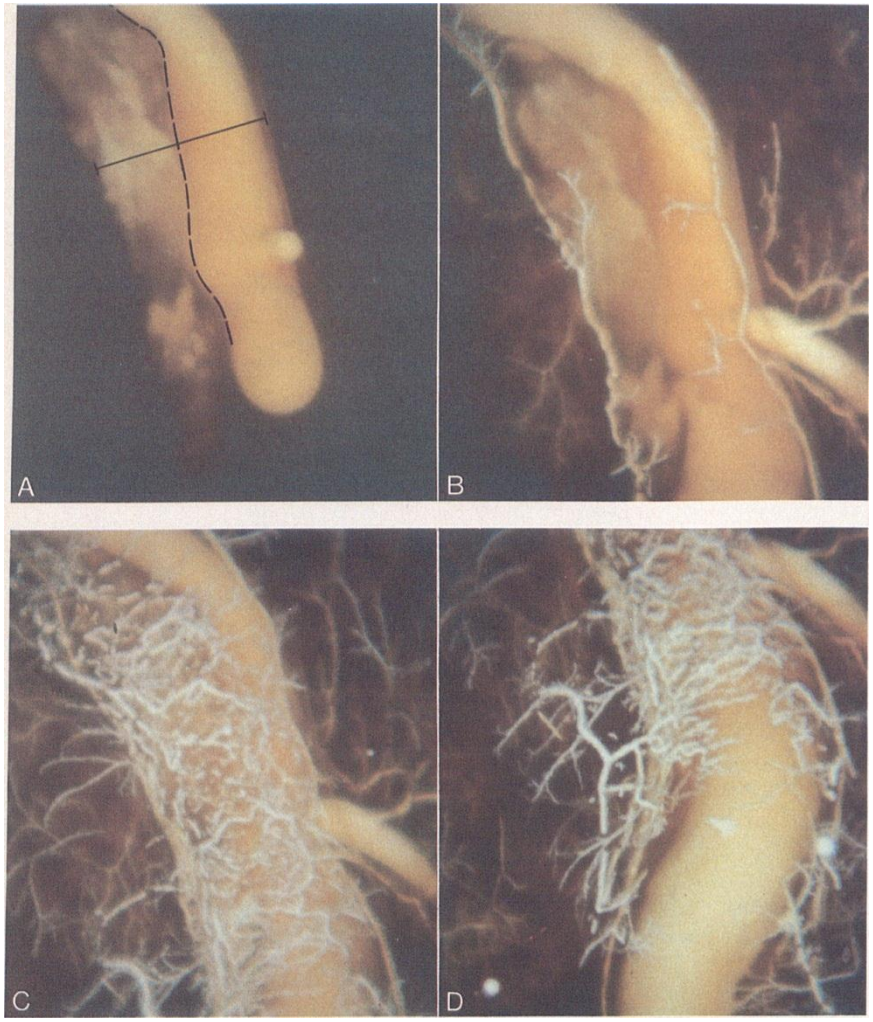
Vasa vasorum are the back-door for leukocyte recru





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

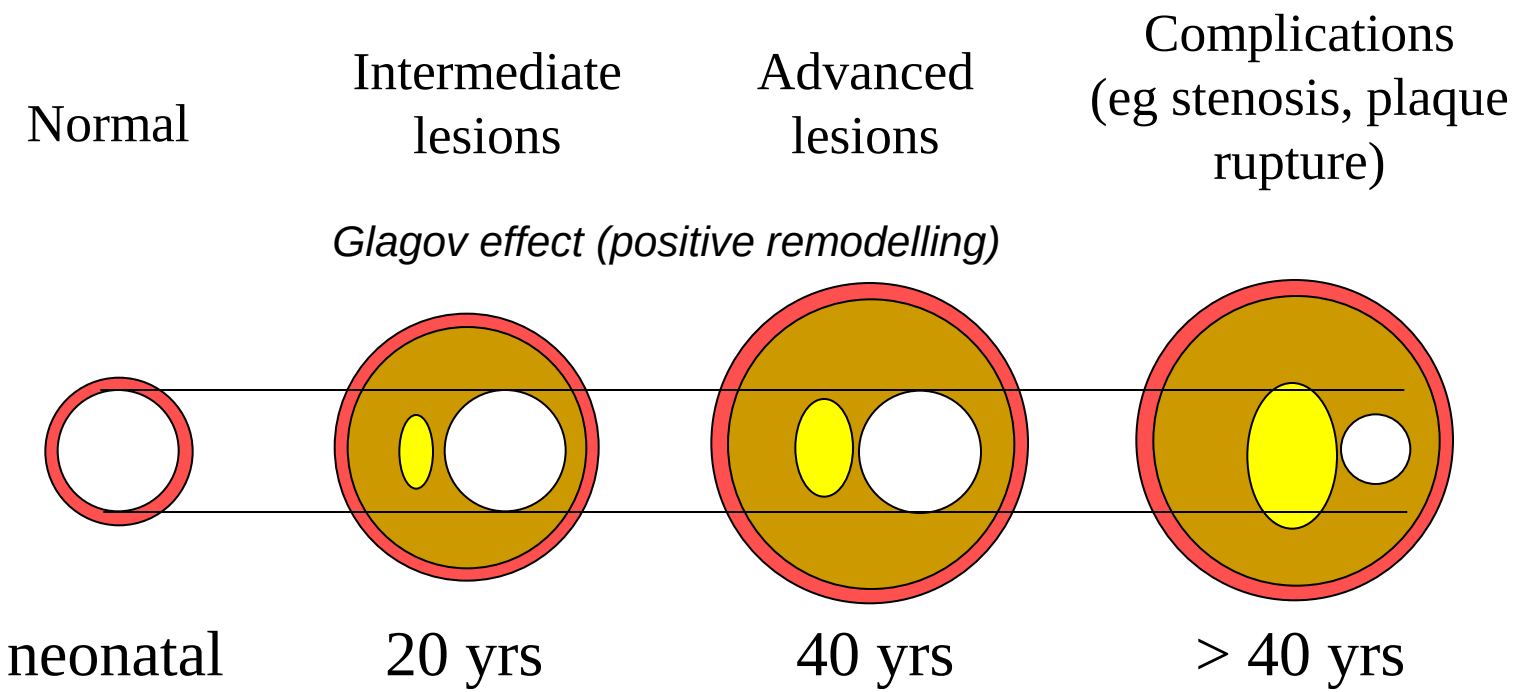
Intra-plaque haemorrhage and lesion progression



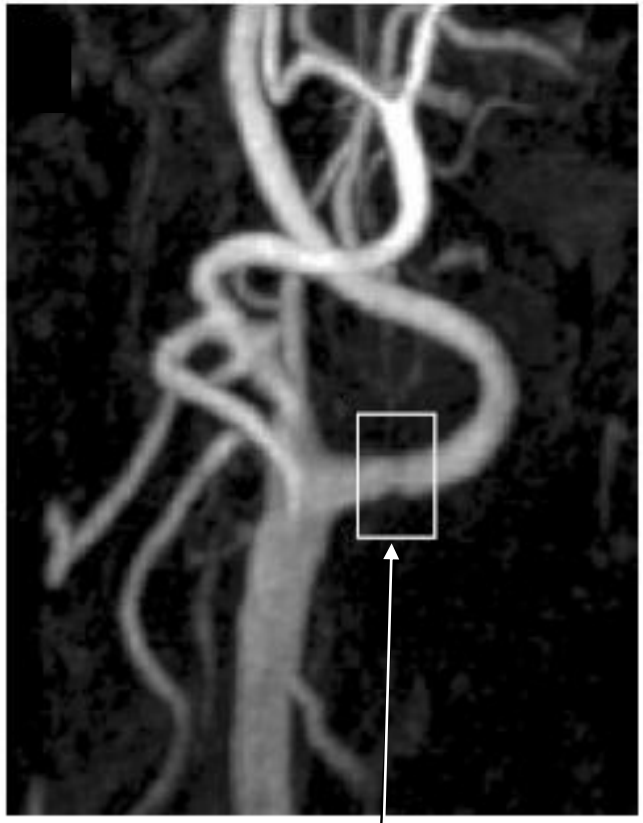
- poorly formed vessels with inadequate pericyte and basement membrane support
- intraplaque haemorrhage linked to acute events – due to physical disruption
- extravasated erythrocytes provides a dual metabolic challenge –lipid from erythrocyte membranes and iron from heme

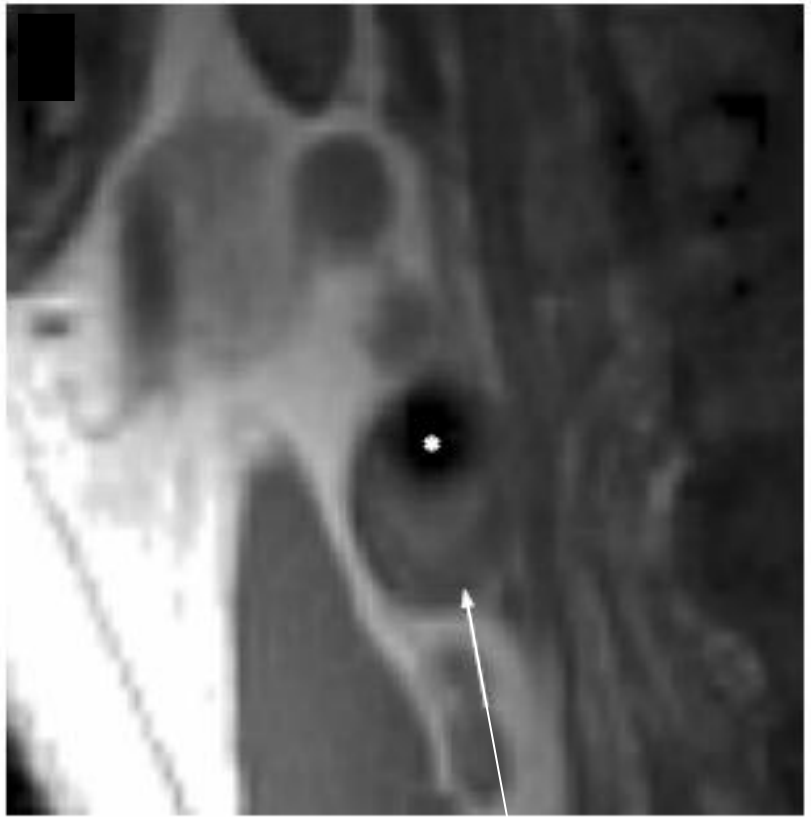
Barger AC et al. N Engl J Med 1984;310:175-177.

Natural history of atherosclerosis



Seymour Glagov et al (1987) New Engl J Med 316:1371





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

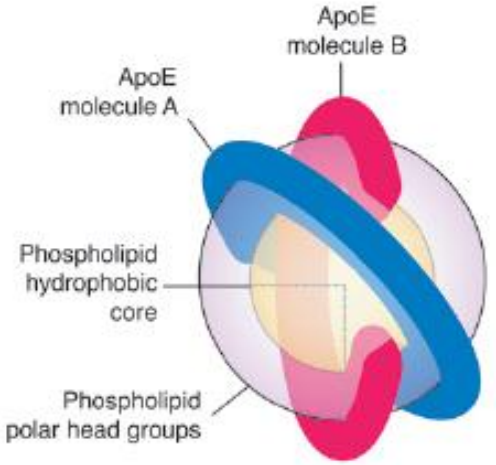
Atherosclerotic plaque occupying ~80% of arterial cross-section

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

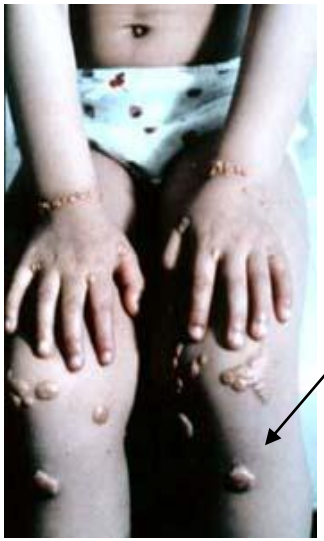
INVESTIGATING MOLECULAR MECHANISMS

Mouse models of atherosclerosis

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

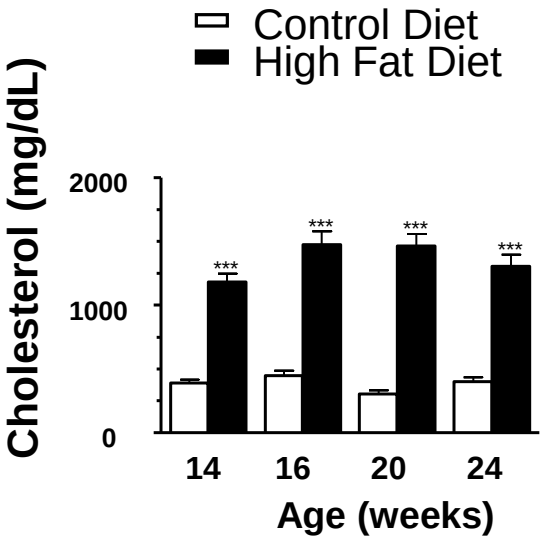


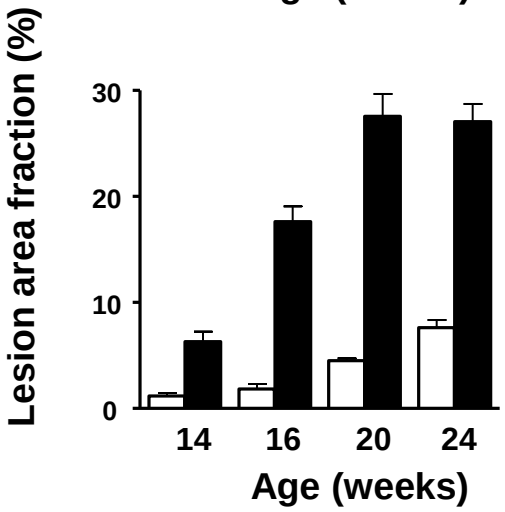
- **LDL receptor -/-**
  - Mutations in familial hypercholesterolaemia

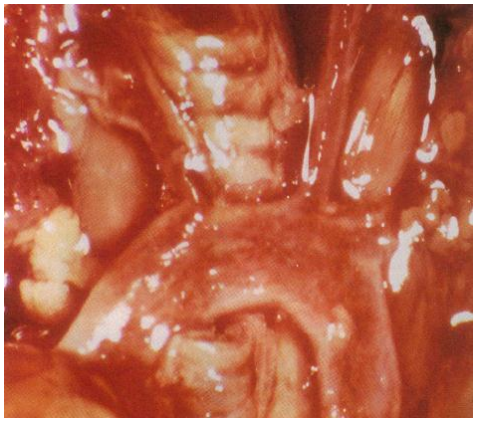


xanthoma

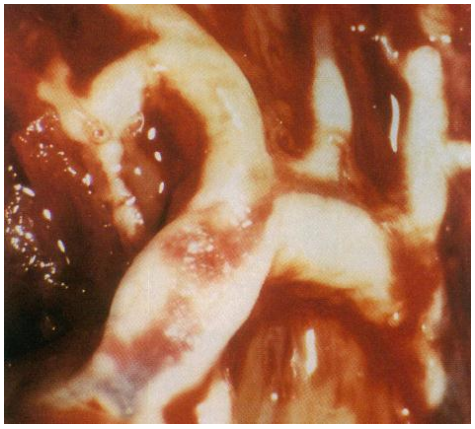
Atherosclerosis in *Ldlr*$^{-/-}$ mice





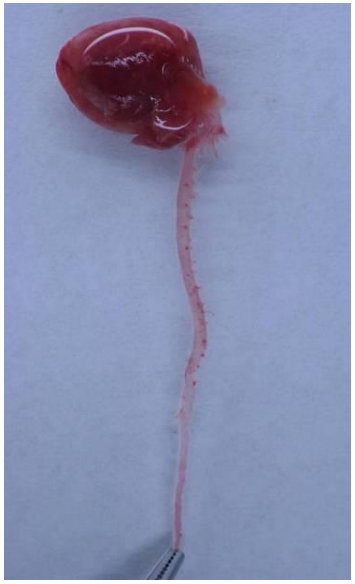


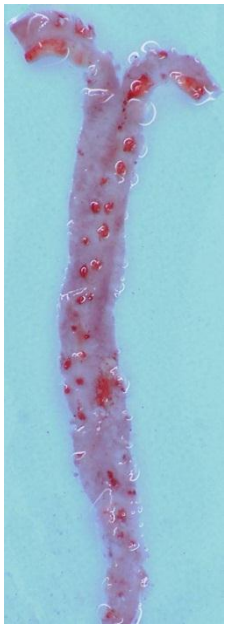
wild-type

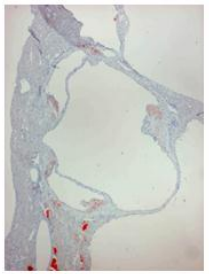
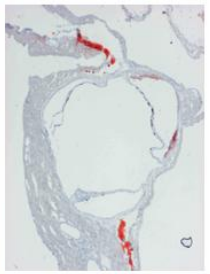
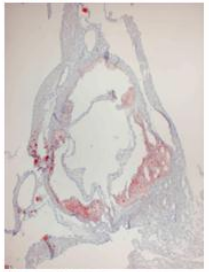
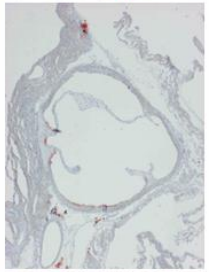
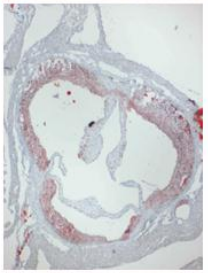
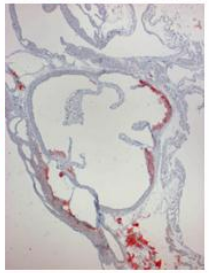
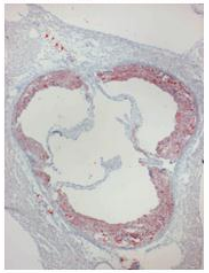
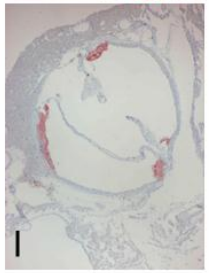


Ldlr-/- high fat 13 mo

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

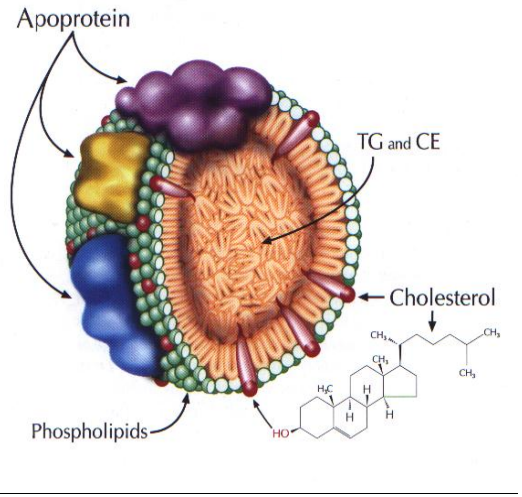
Chemokines & receptors
MCP-1
CCR2
CXCR2
CX3CR1

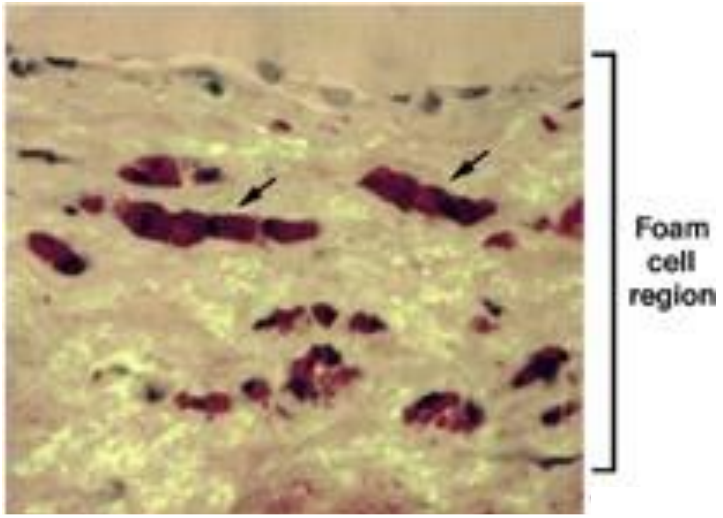
Cytokines
IL-1
TNFa
IL-4
IL-6
IL-12
IL-18
IFNg

Decelerators

IL1RA
TGFb
IL-10

Foam cells

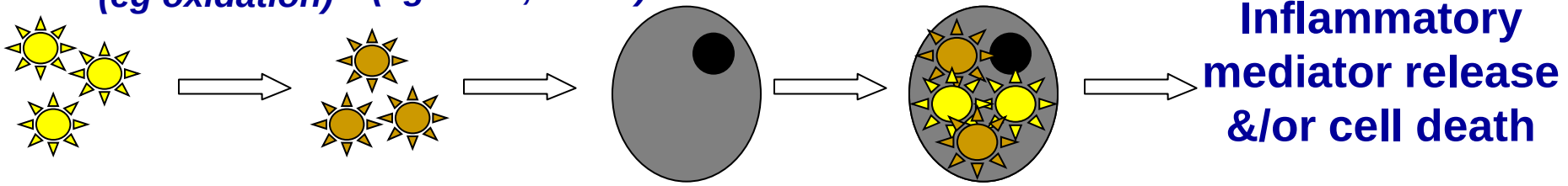




from Dr Howard K

lipoprotein modification (eg oxidation)

via scavenger receptors (eg SR-A, CD36)

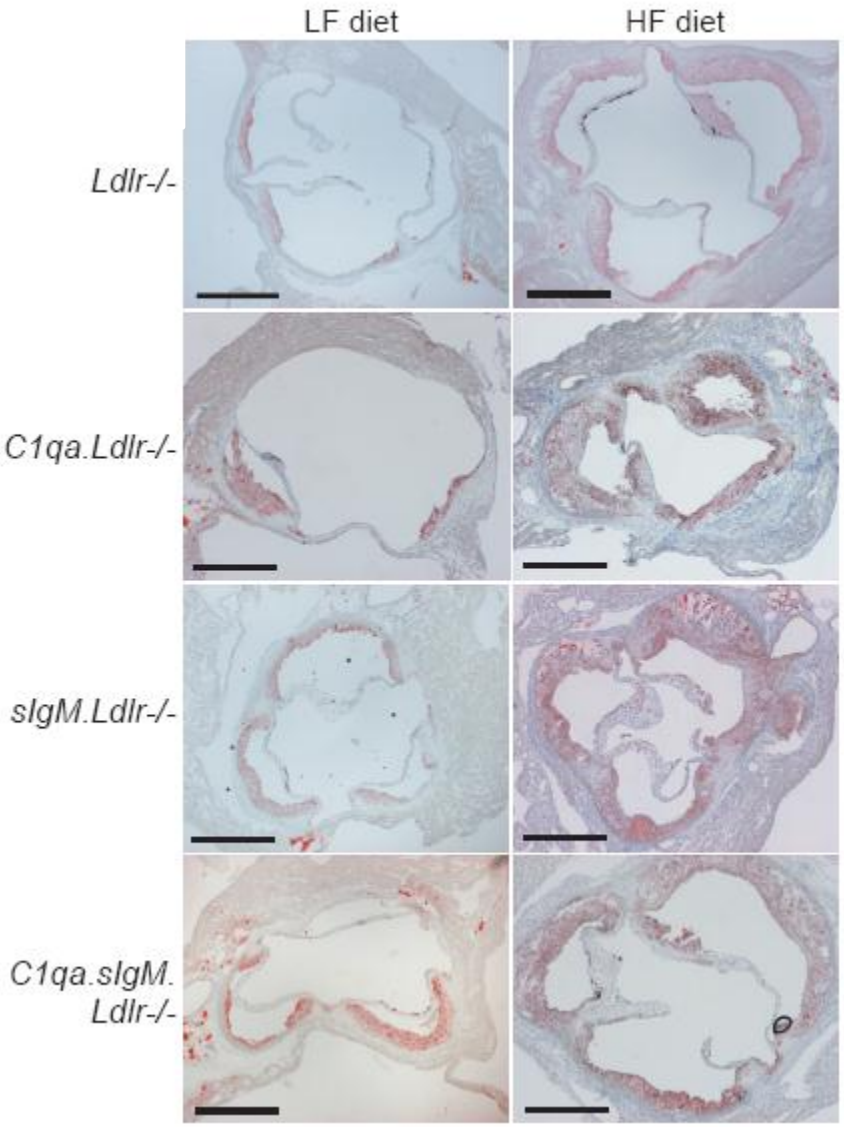


Macrophage

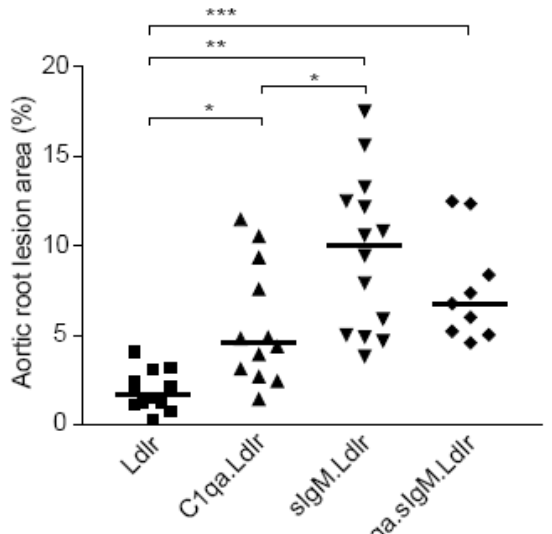
"foam cells"

Inflammatory mediator release &/or cell death

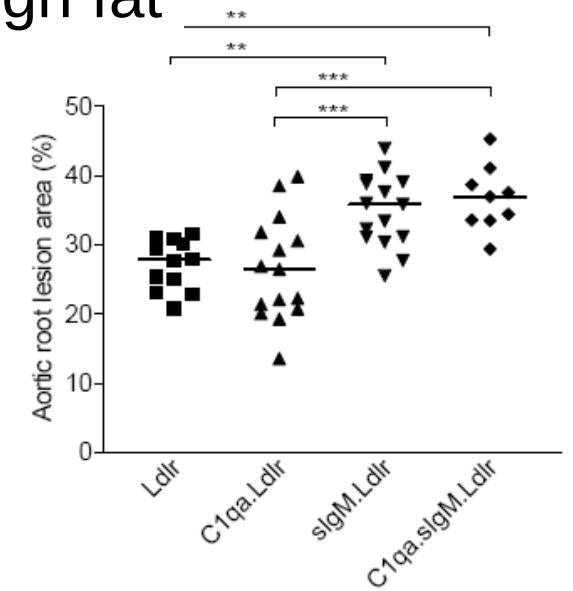
IgM and complement C1q deficiencies accelerate atherosclerosis



Low fat

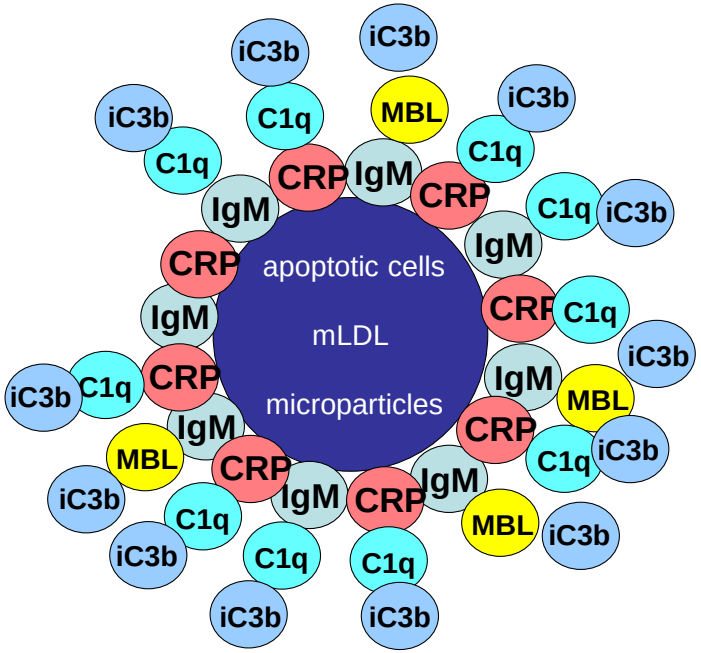


High fat



Lewis et al 2009 Circulation 120:417

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



Homeostatic clearance

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