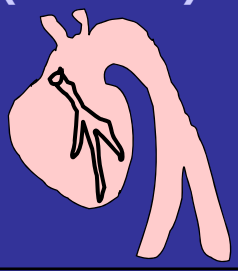
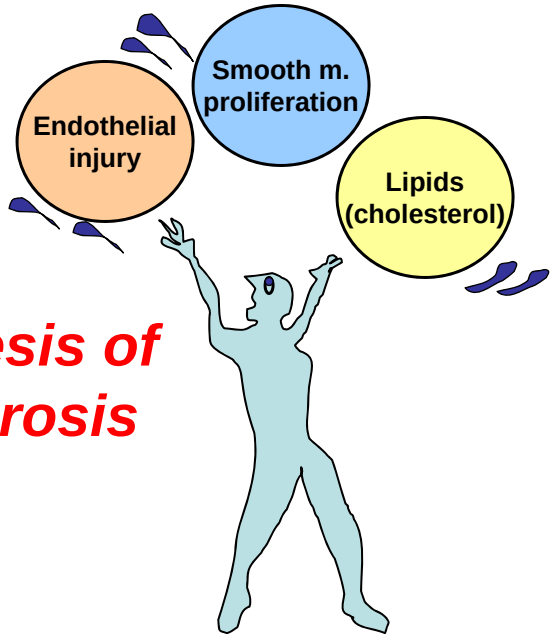
Atherosclerosis

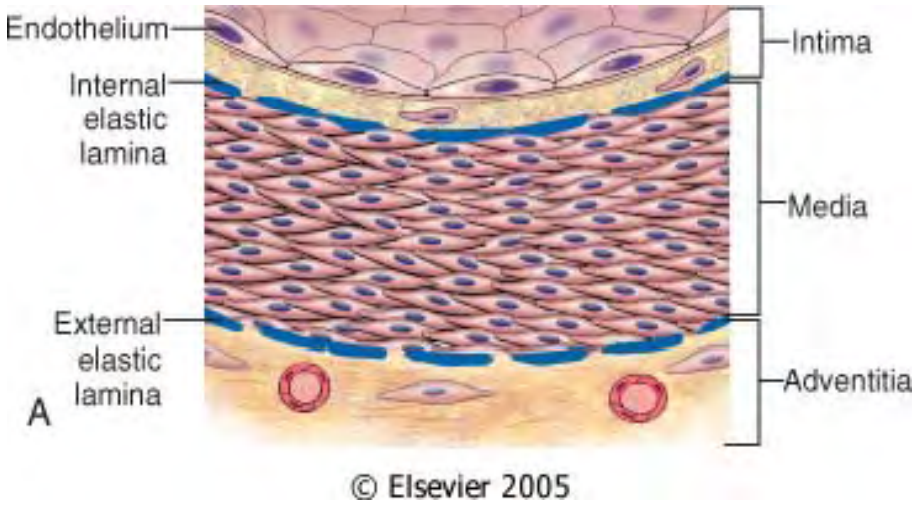
Atherosclerotic Cardiovascular Disease (ASCVD)



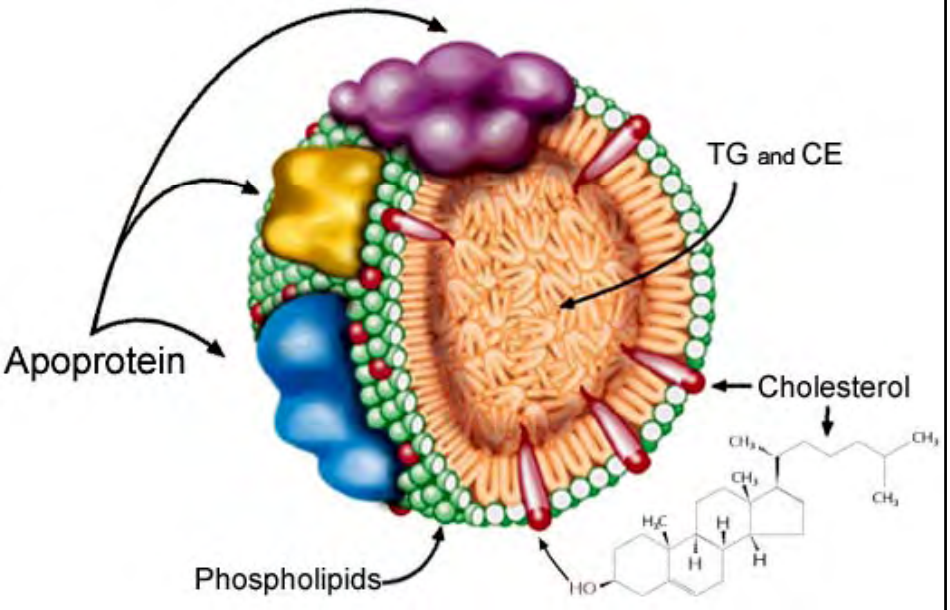


Pathogenesis of atherosclerosis

Normal Artery Structure



Lipoprotein particle



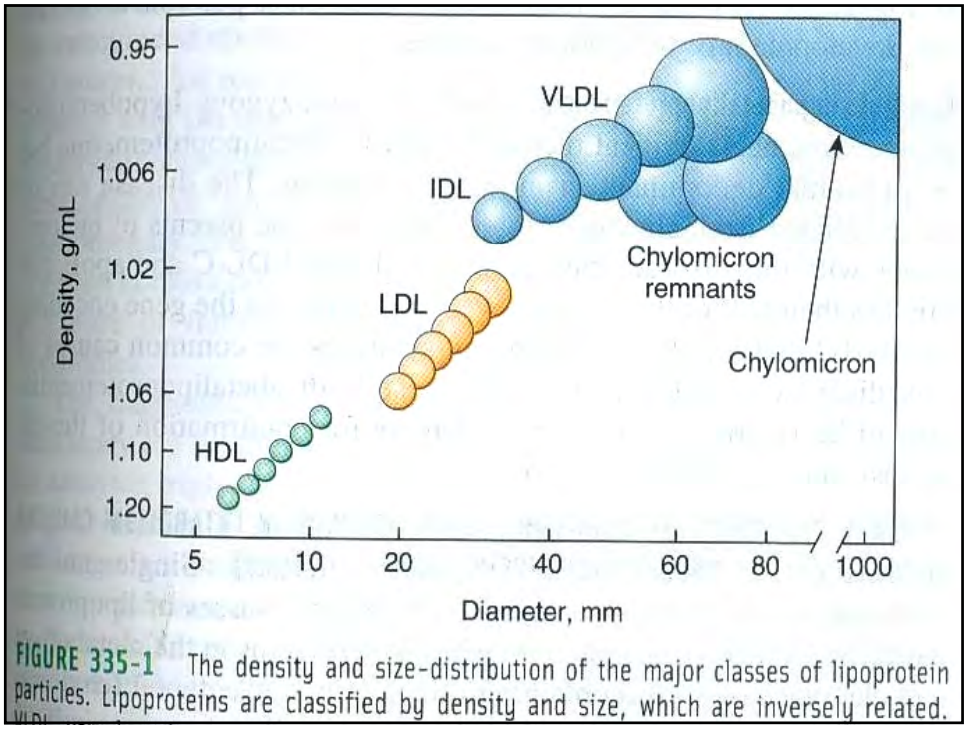
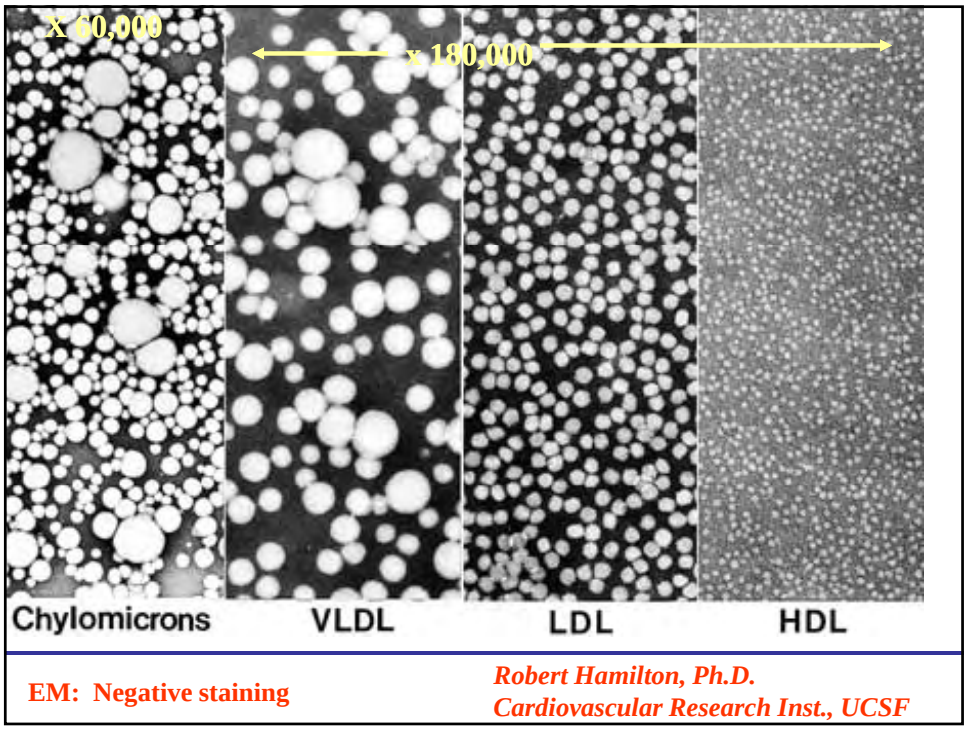
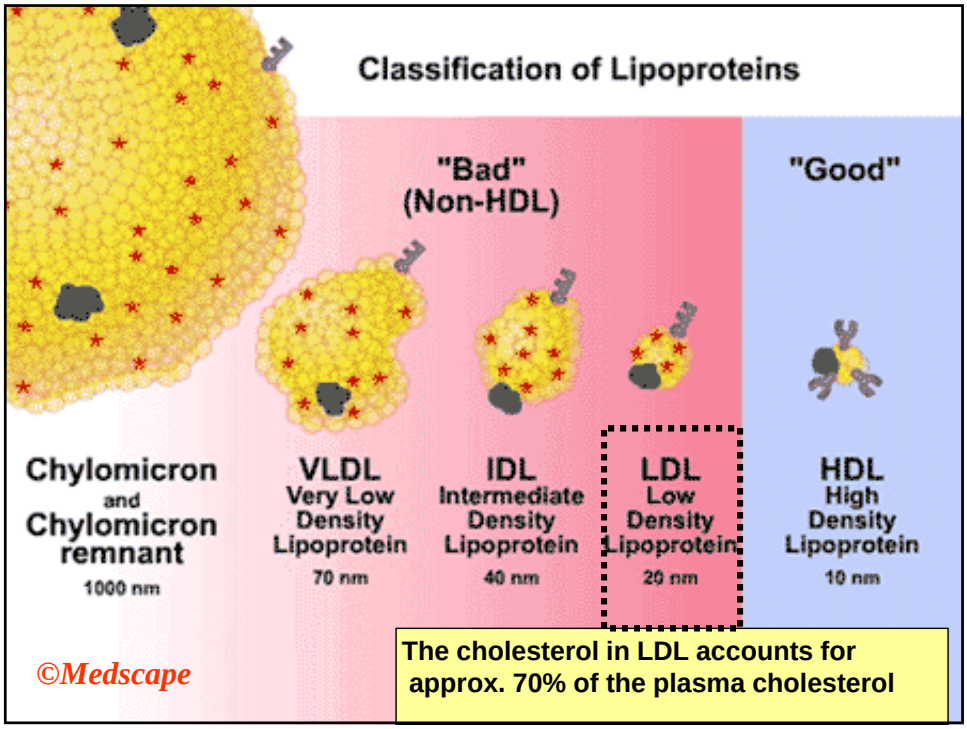


FIGURE 335-1 The density and size-distribution of the major classes of lipoprotein particles. Lipoproteins are classified by density and size, which are inversely related.



EM: Negative staining

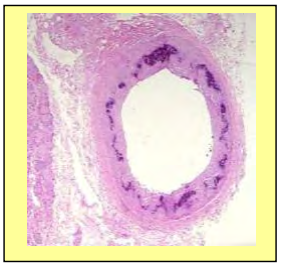
Robert Hamilton, Ph.D.
Cardiovascular Research Inst., UCSF



Arteriosclerosis (Hardening of the arteries)

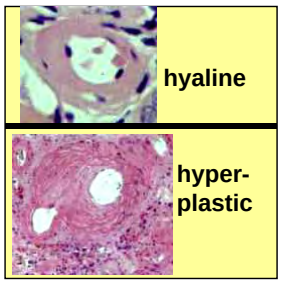
Arterial wall thickening + loss of elasticity

Mönckeberg medial calcific sclerosis



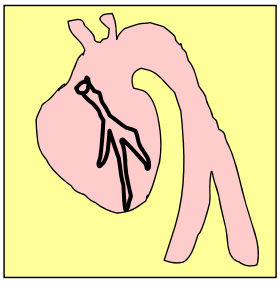
- Age 50
- Radiologic calcif.
- Lumen intact
- Clinically insignif.

Arteriolosclerosis



-small arteries/arterioles
-hyaline type / hyperplastic
-hypertension / diabetes

Atherosclerosis



-aorta & branches + coronary arteries
-ASCVD causes 38% of all deaths in N. America

ATHEROSCLEROSIS: response-to-injury model

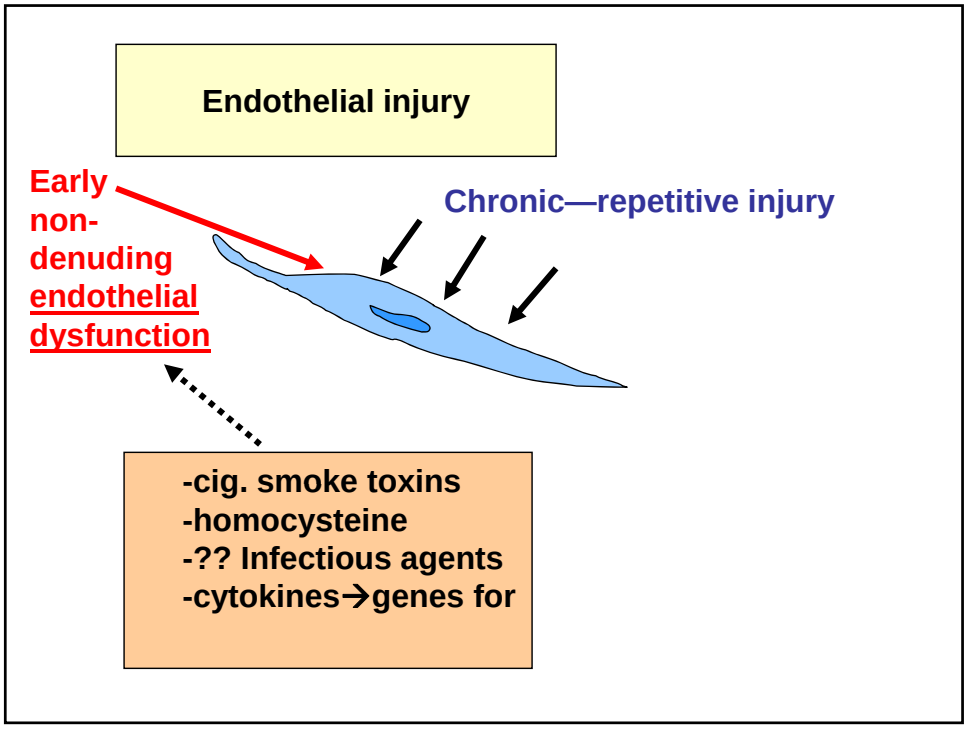
Atherosclerosis is a chronic inflammatory response of the arterial wall to endothelial injury.

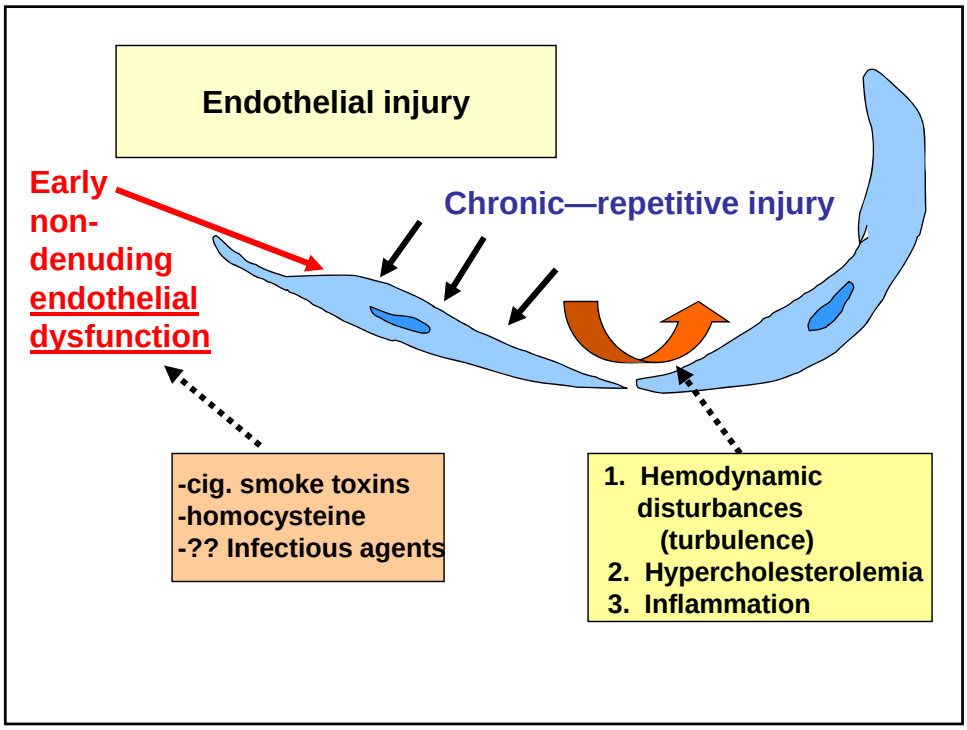
basic tenets

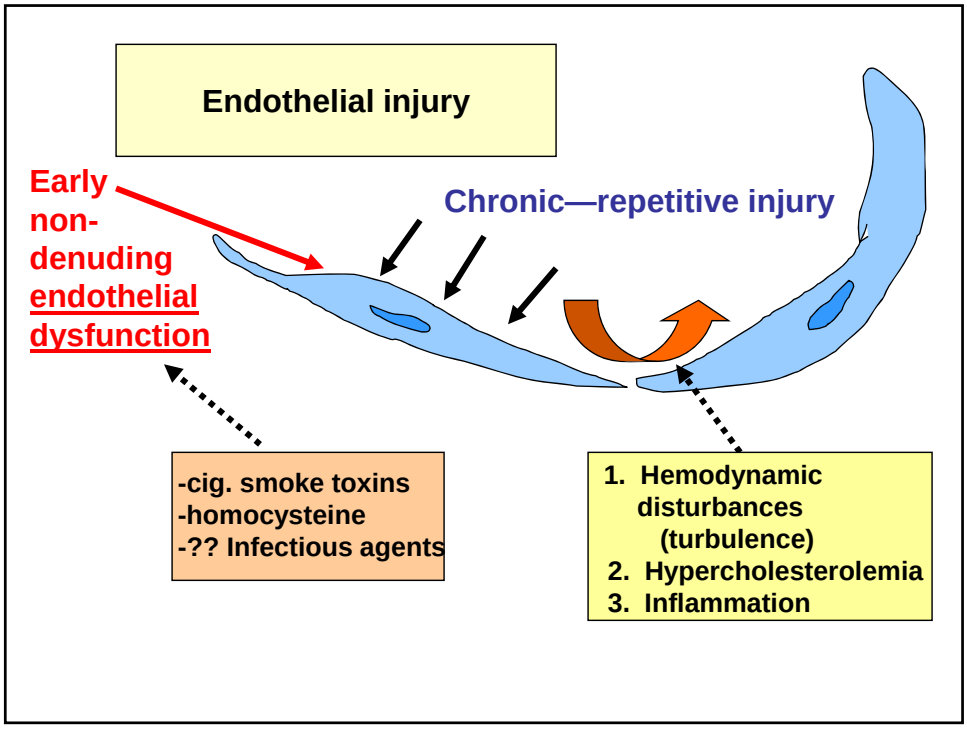
1. Chronic endothelial injury
2. Accumulation of lipoproteins (LDL mainly)
3. Monocyte adhesion to endothelium
4. Platelet adhesion
5. Factors released→SMC recruitment
6. SMC proliferation and ECM production
7. Lipid accumulation: extracellular/mac-SMC

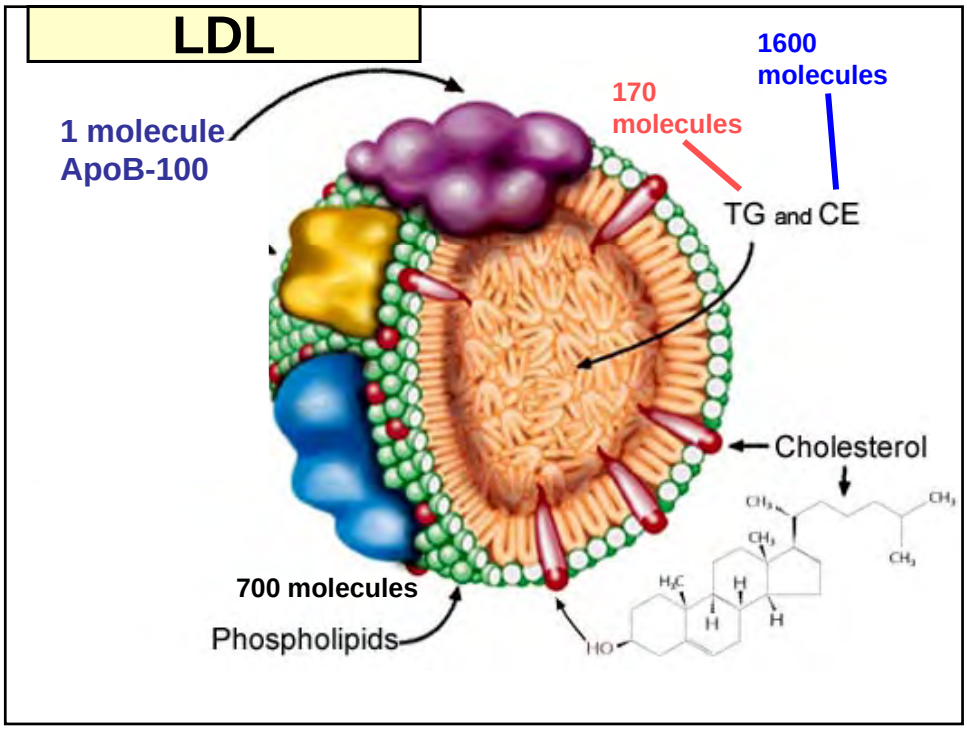
Risk Factors for Atherosclerosis

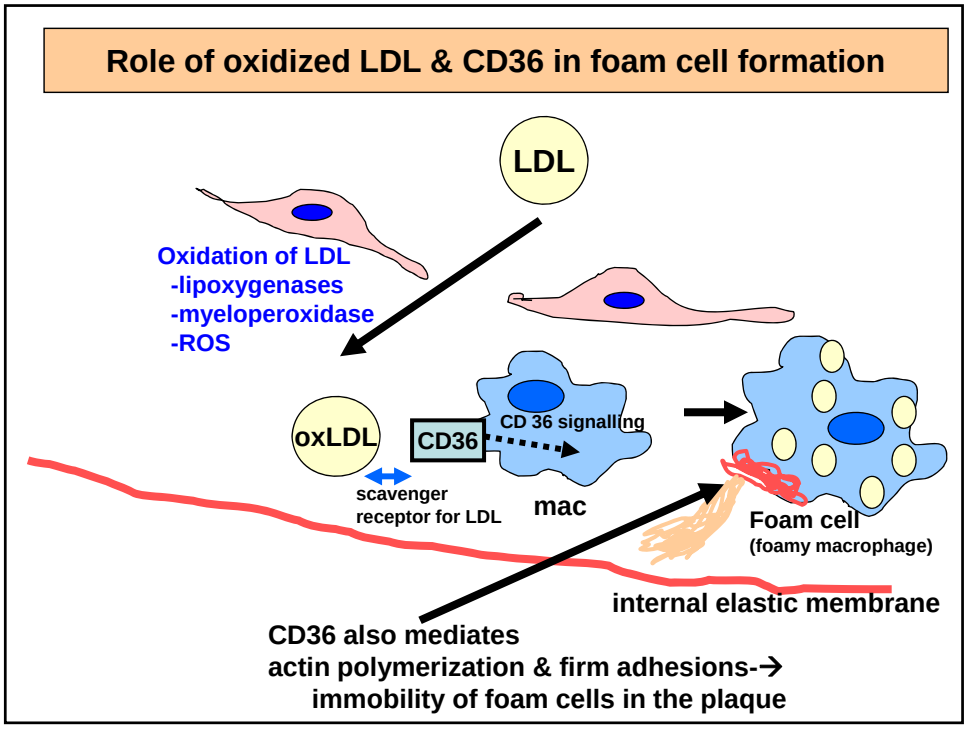
- Hyperlipidemia
- Smoking
- Hypertension
- Turbulence
- Genetics

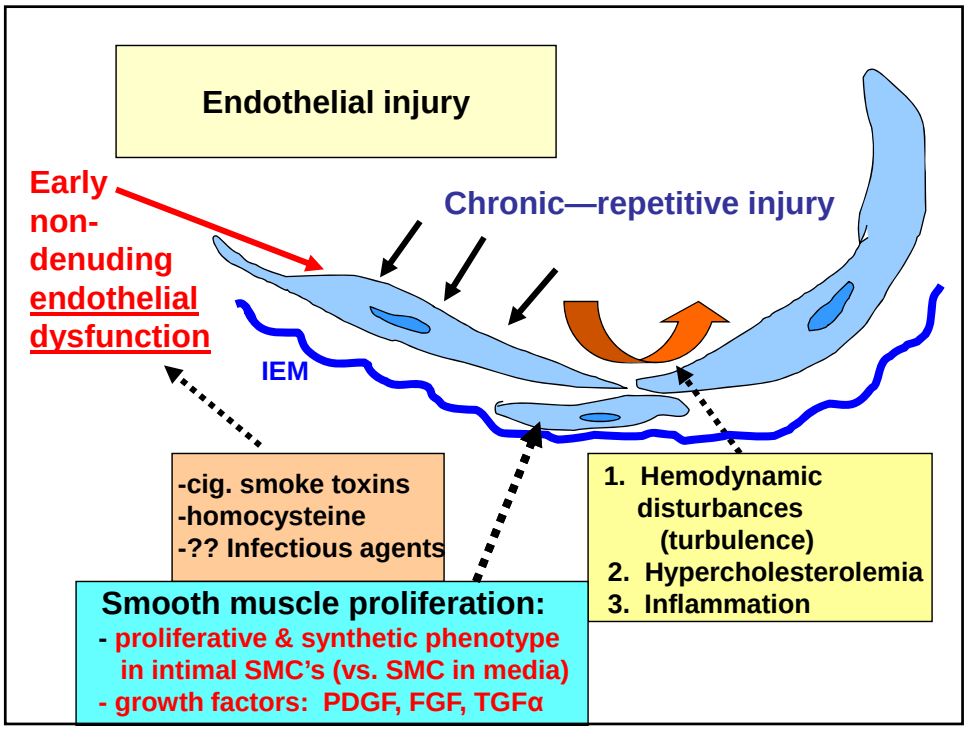

Endothelial injury
Early non-denuding endothelial dysfunction
Chronic—repetitive injury
-cig. smoke toxins
-homocysteine
-?? Infectious agents
-cytokines→genes for


Endothelial injury
Early non-denuding endothelial dysfunction
Chronic—repetitive injury
-cig. smoke toxins
-homocysteine
-?? Infectious agents
1. Hemodynamic disturbances (turbulence)
2. Hypercholesterolemia
3. Inflammation


Endothelial injury
Early non-denuding endothelial dysfunction
Chronic—repetitive injury
-cig. smoke toxins
-homocysteine
-?? Infectious agents
1. Hemodynamic disturbances (turbulence)
2. Hypercholesterolemia
3. Inflammation


LDL
1 molecule ApoB-100
1600 molecules
170 molecules
TG and CE
Cholesterol
700 molecules
Phospholipids


Role of oxidized LDL & CD36 in foam cell formation
LDL
Oxidation of LDL
-lipoxygenases
-myeloperoxidase
-ROS
oxLDL
CD36
CD 36 signalling
scavenger
receptor for LDL
mac
Foam cell
(foamy macrophage)
internal elastic membrane
CD36 also mediates
actin polymerization & firm adhesions-→
immobility of foam cells in the plaque


Endothelial injury
Early
non-
denuding
endothelial
dysfunction
Chronic—repetitive injury
IEM
-cig. smoke toxins
-homocysteine
-?? Infectious agents
1. Hemodynamic
disturbances
(turbulence)
2. Hypercholesterolemia
3. Inflammation
Smooth muscle proliferation:
- proliferative & synthetic phenotype
in intimal SMC's (vs. SMC in media)
- growth factors: PDGF, FGF, TGFα

Pathogenic sequence of atherosclerotic lesions

Normal aorta

↓

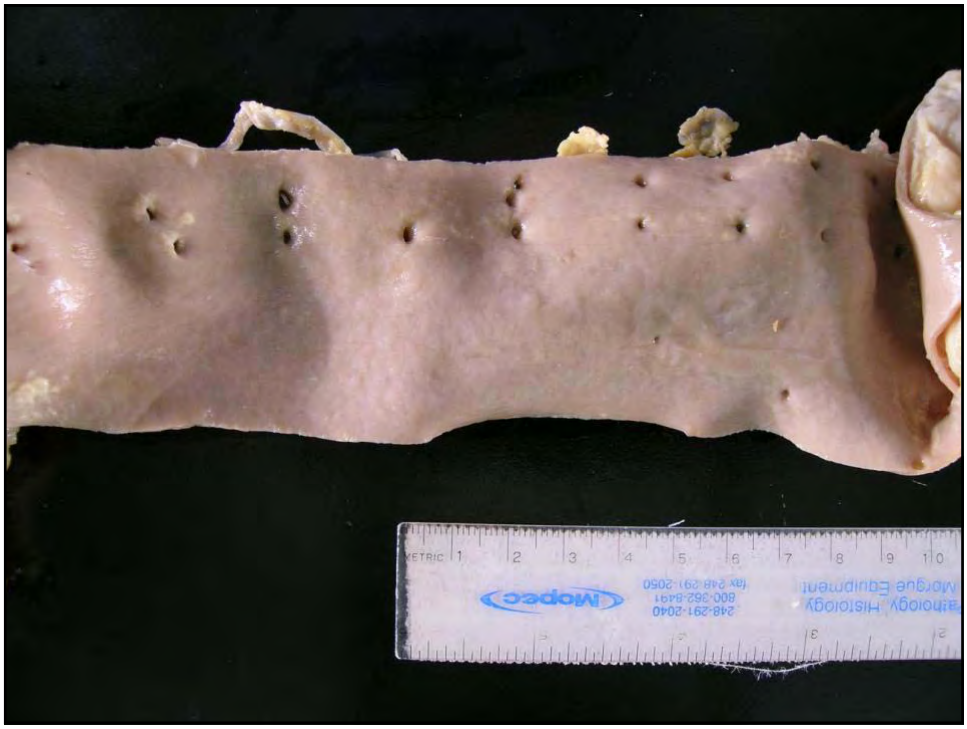
Fatty streak

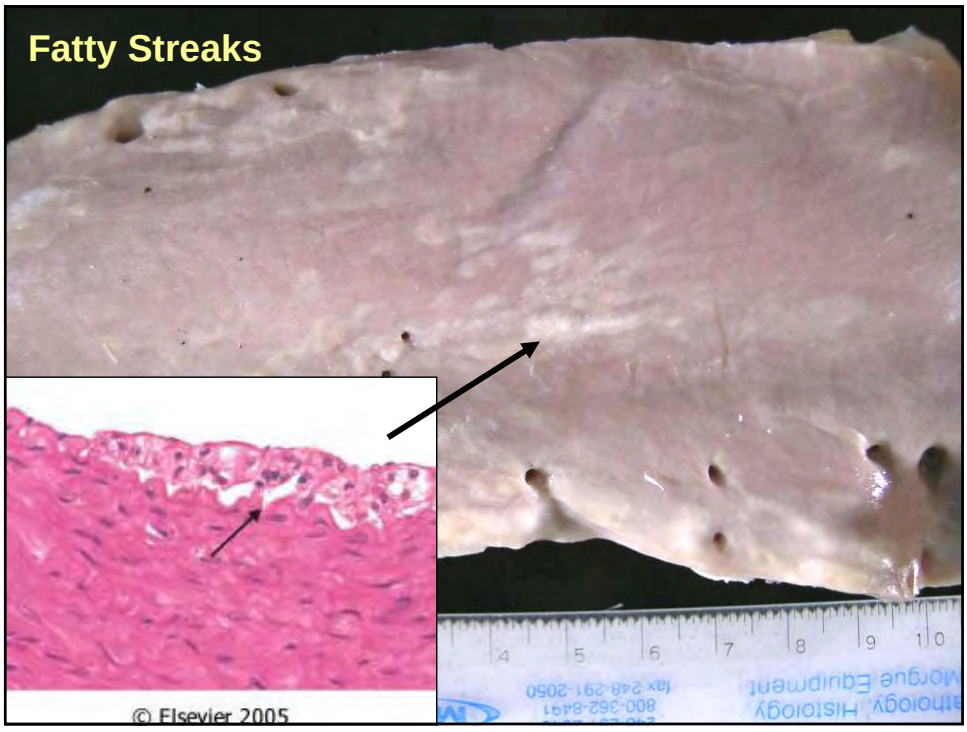
↓

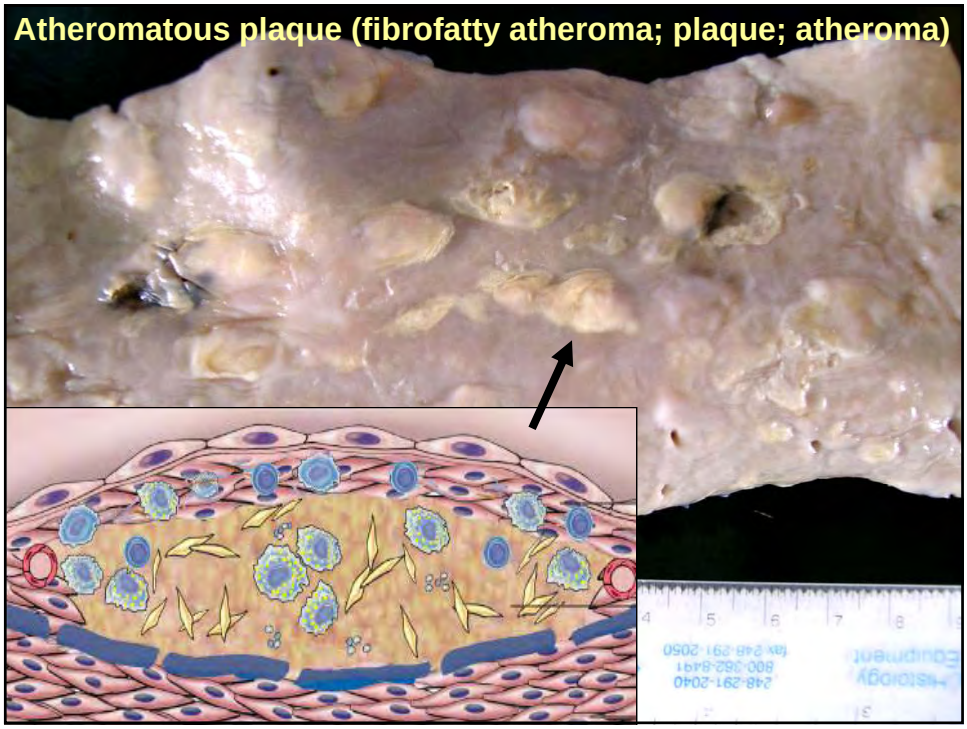
Atheromatous plaque
(fibrofatty plaque)

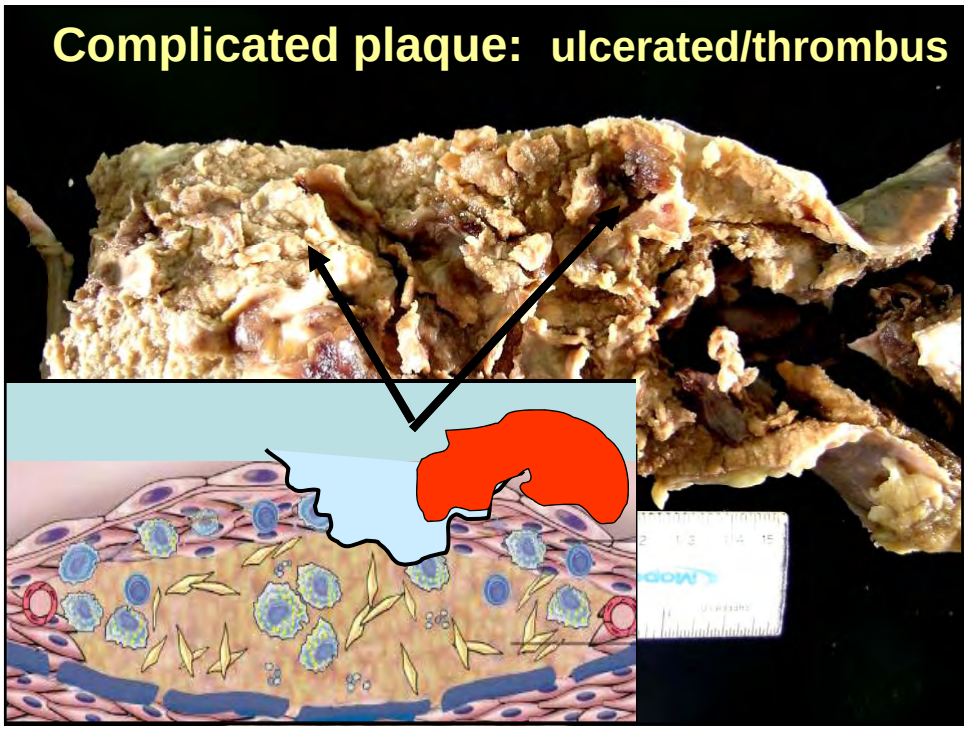
↓

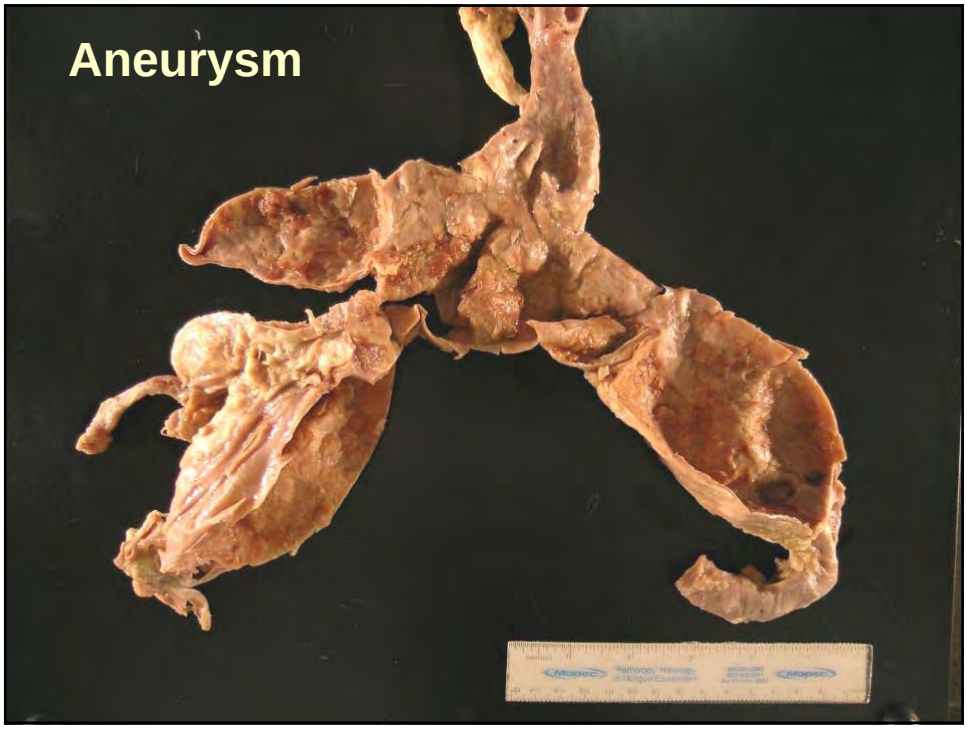
Complicated plaque

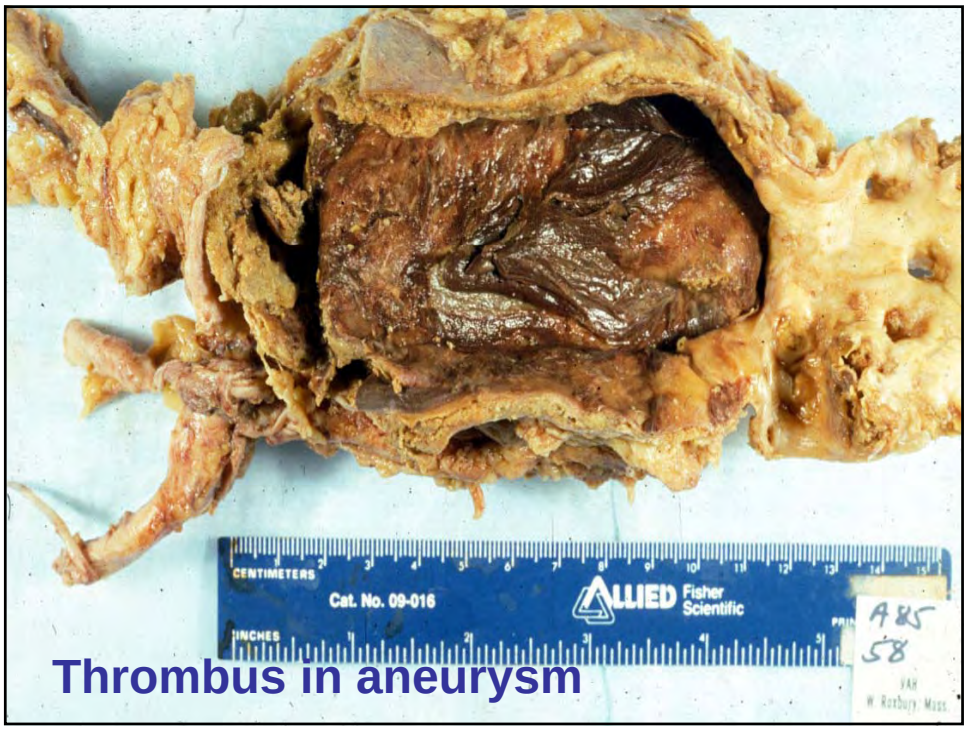



Fatty Streaks
© Elsevier 2005

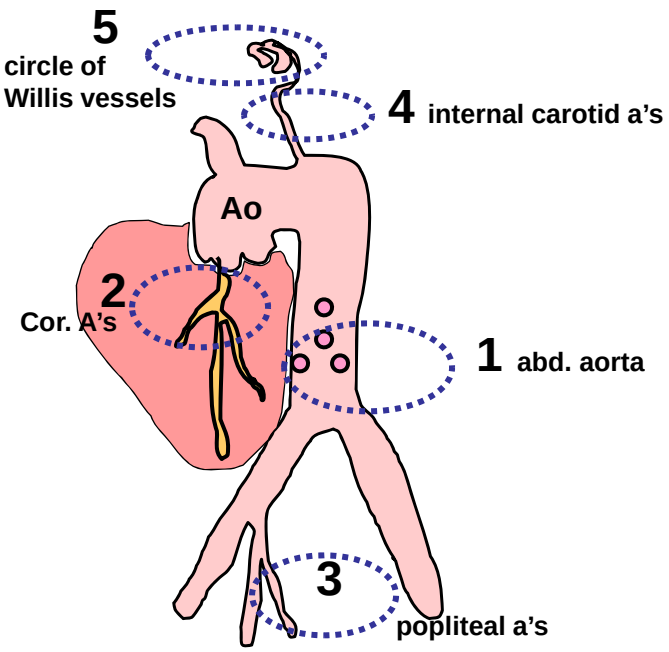

Atheromatous plaque (fibrofatty atheroma; plaque; atheroma)


Complicated plaque: ulcerated/thrombus

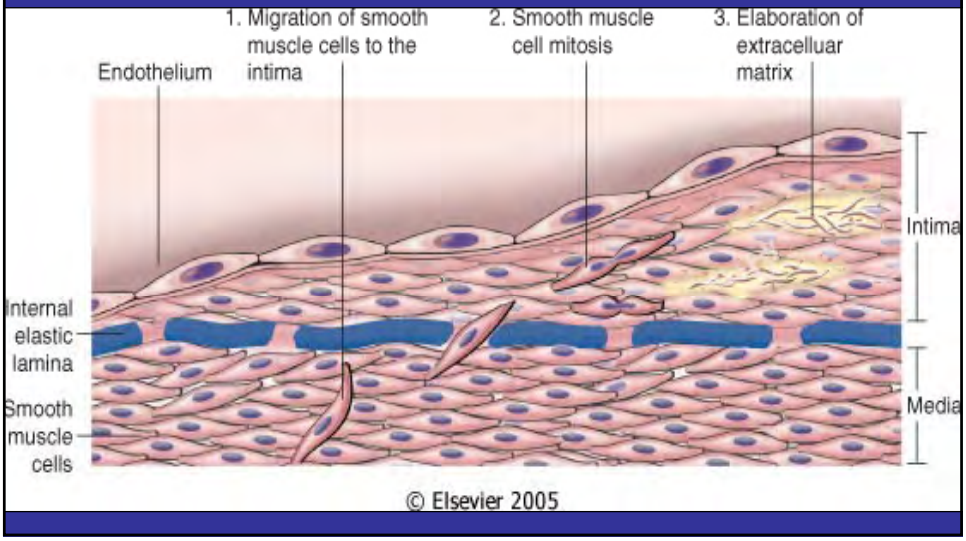

Aneurysm


CENTIMETERS
Cat. No. 09-016
ALLIED Fisher Scientific
INCHES
A85
58
Thrombus in aneurysm

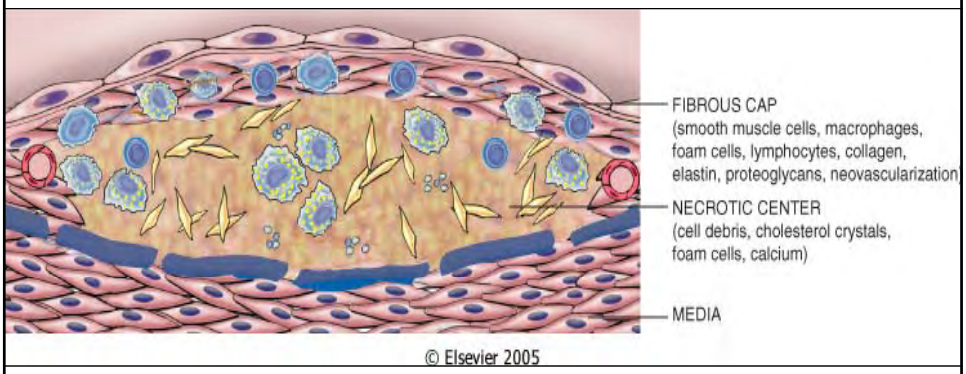
ATHEROSCLEROSIS: Vessel involvement: desc. order

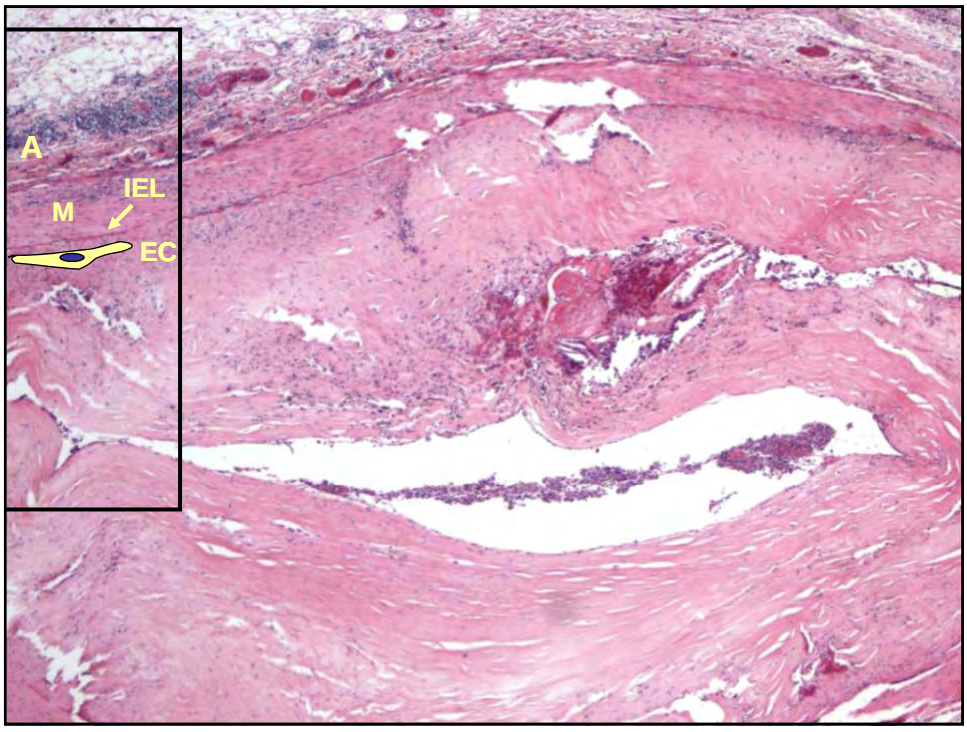


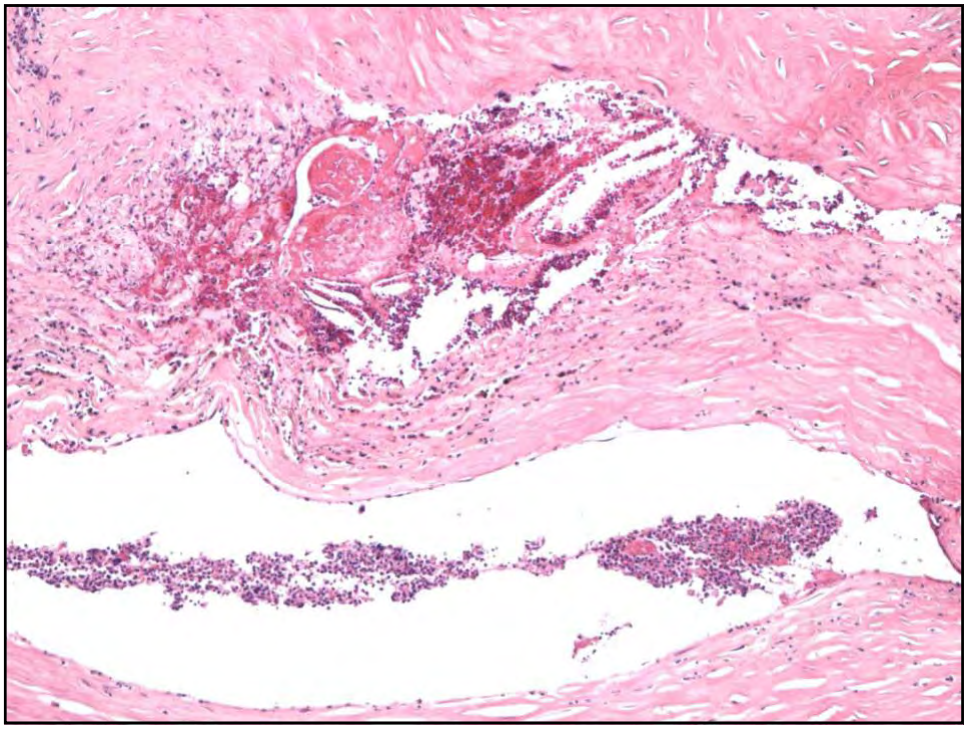
Development of the smooth muscle cap

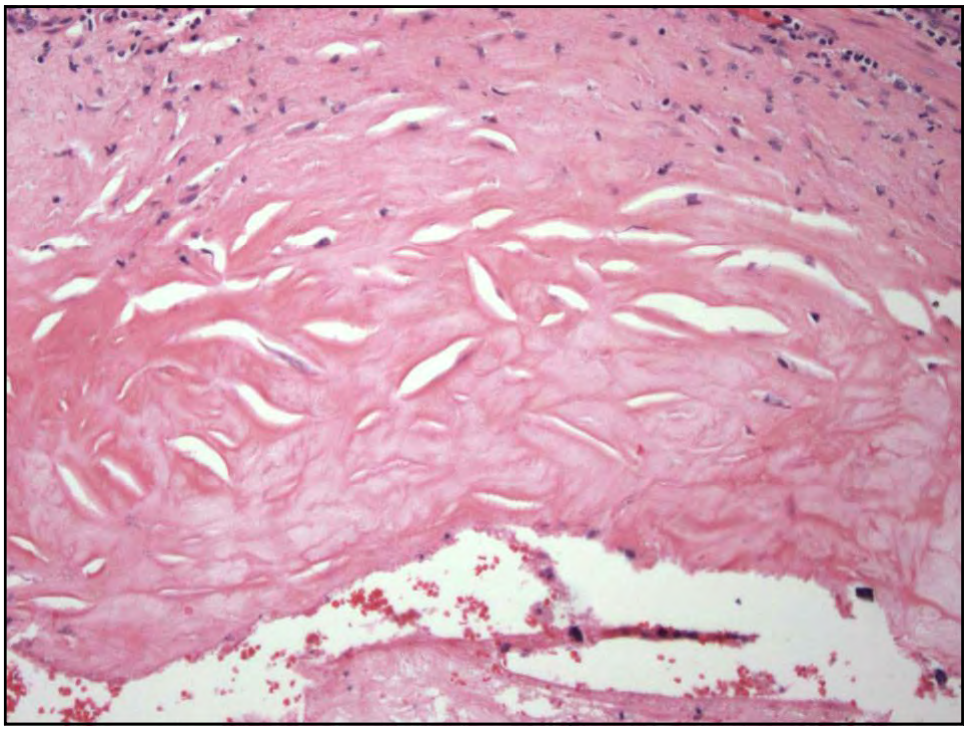


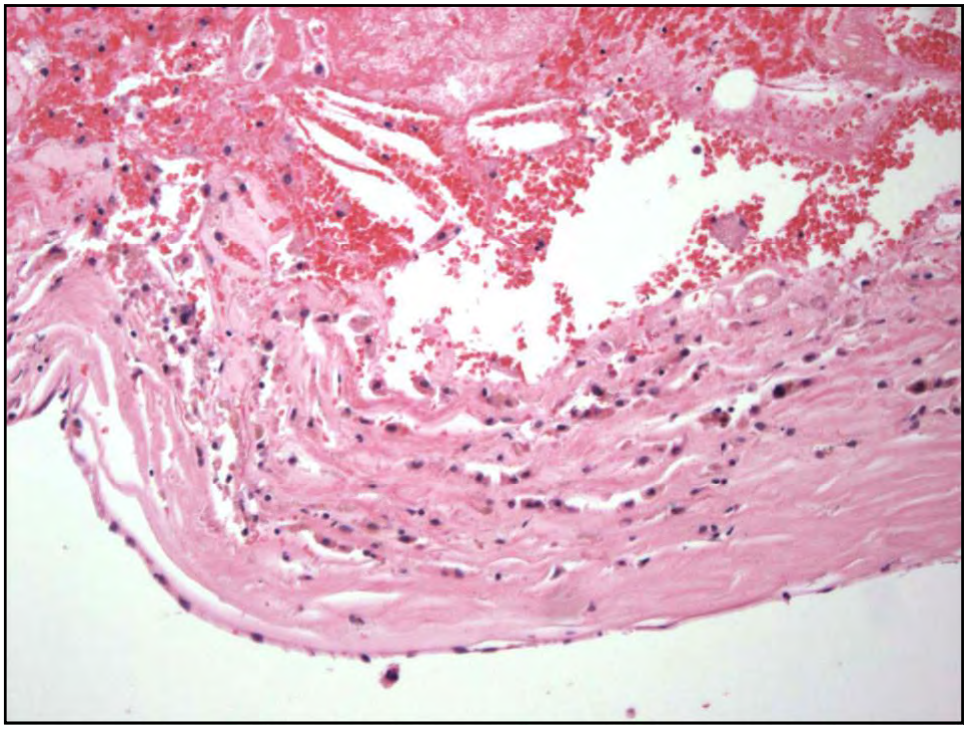
Atherosclerostic Plaque Structure

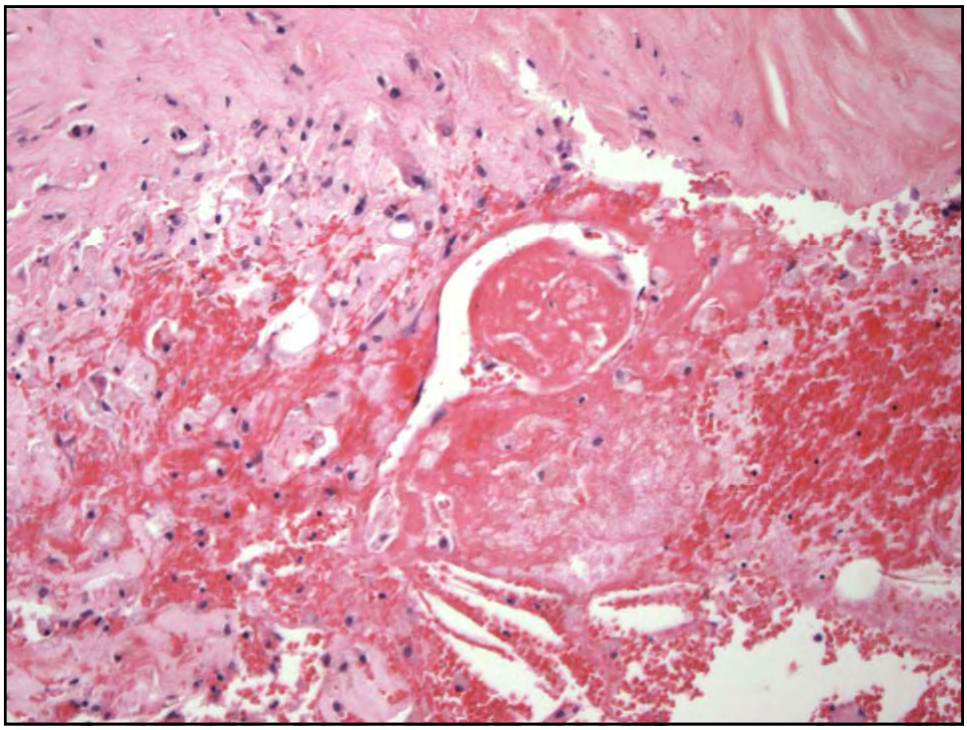


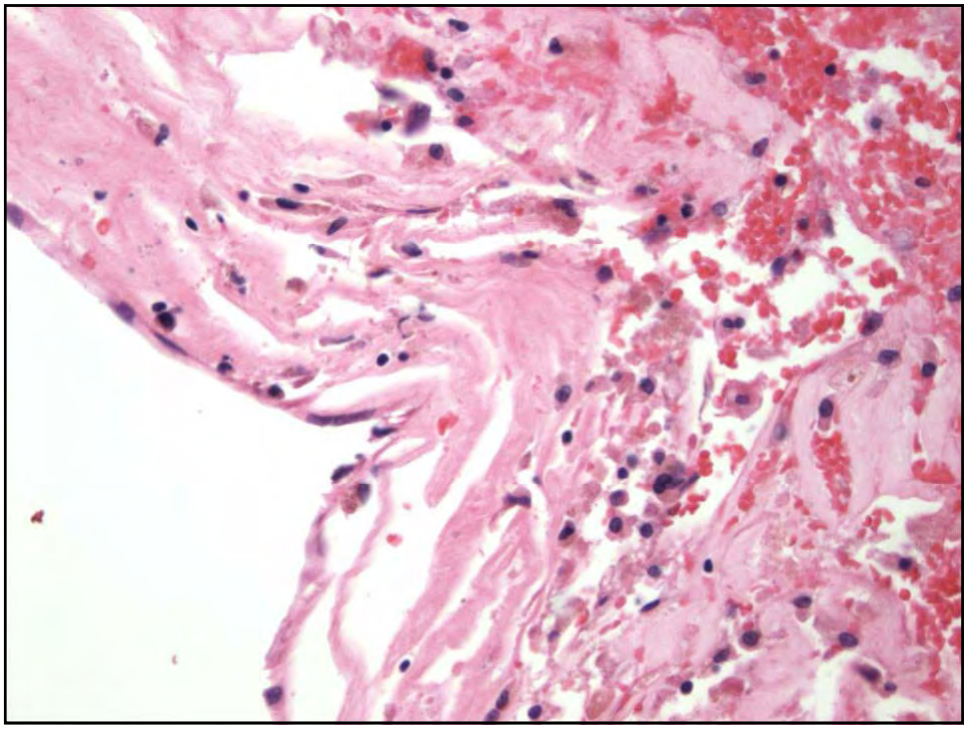


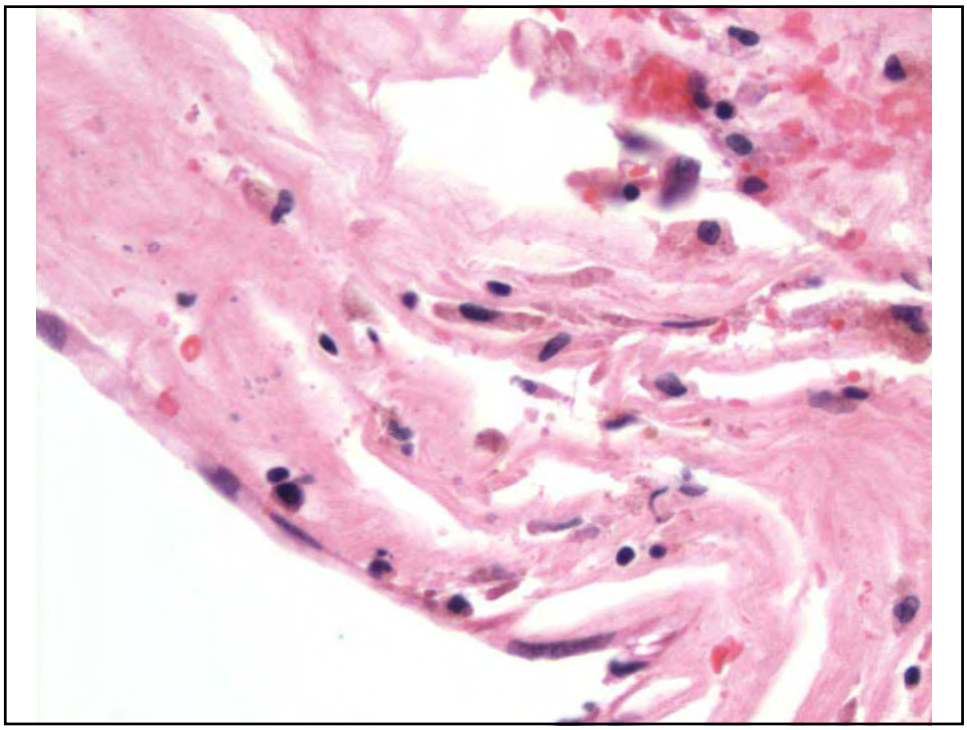


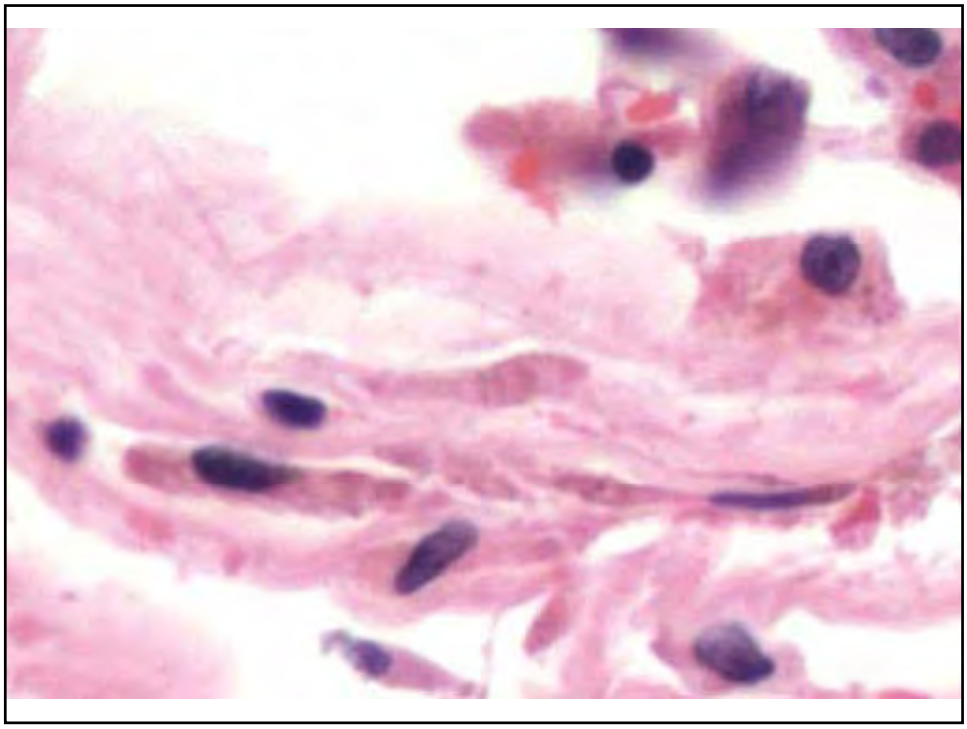


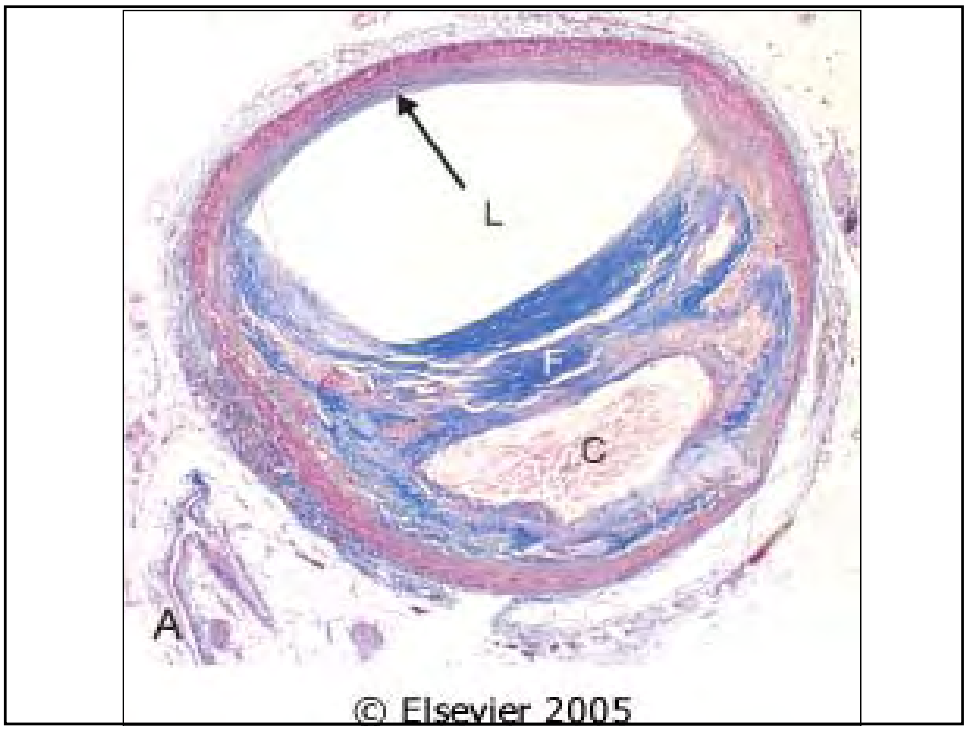











L
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C
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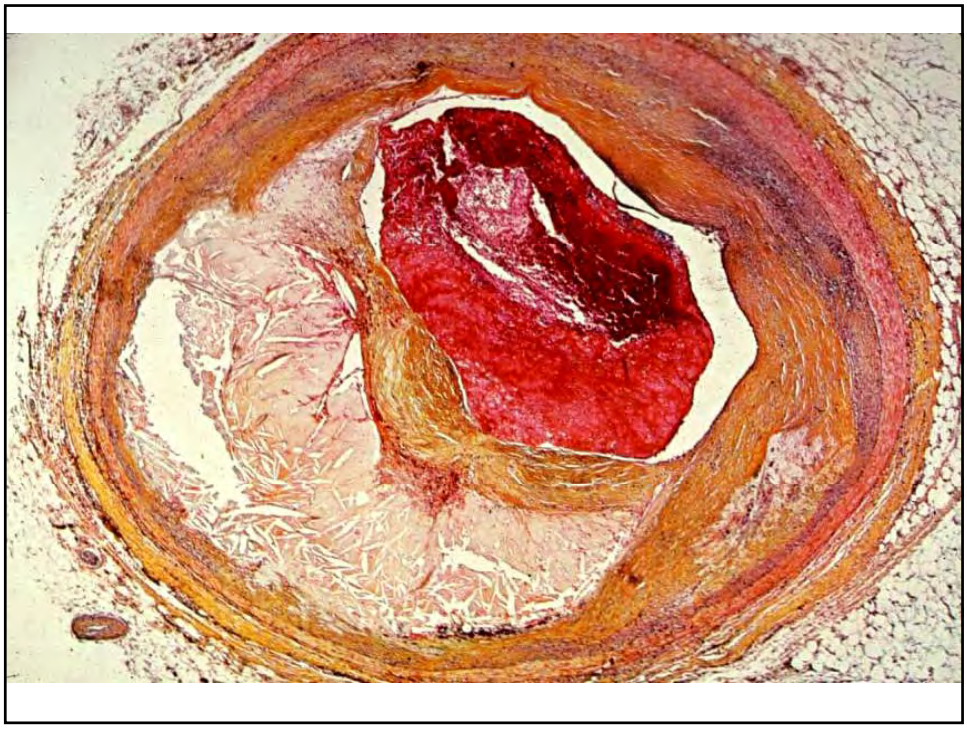
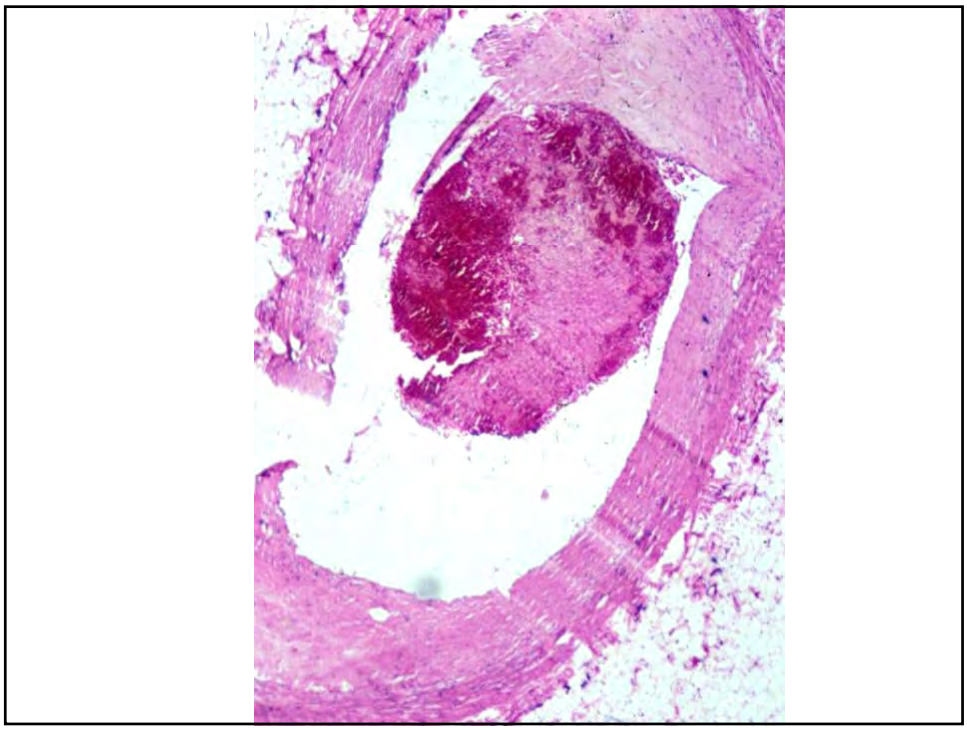




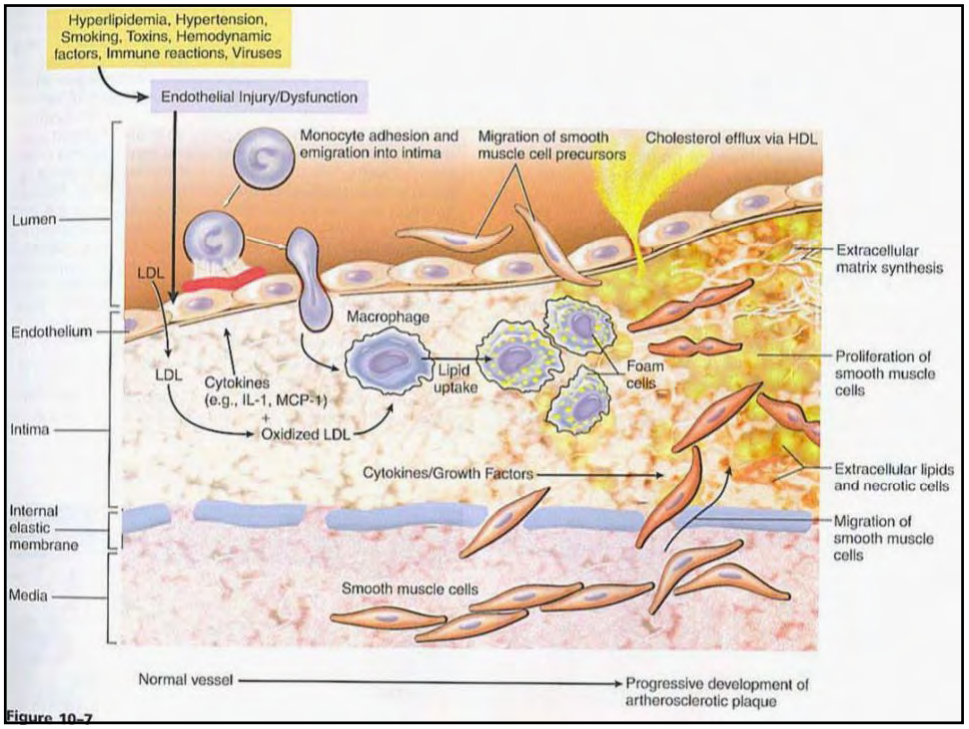
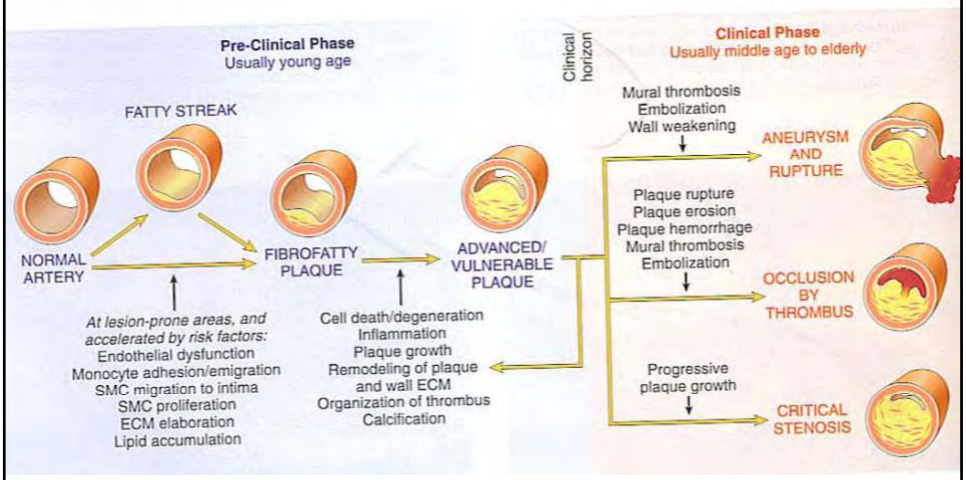


Figure 10-7

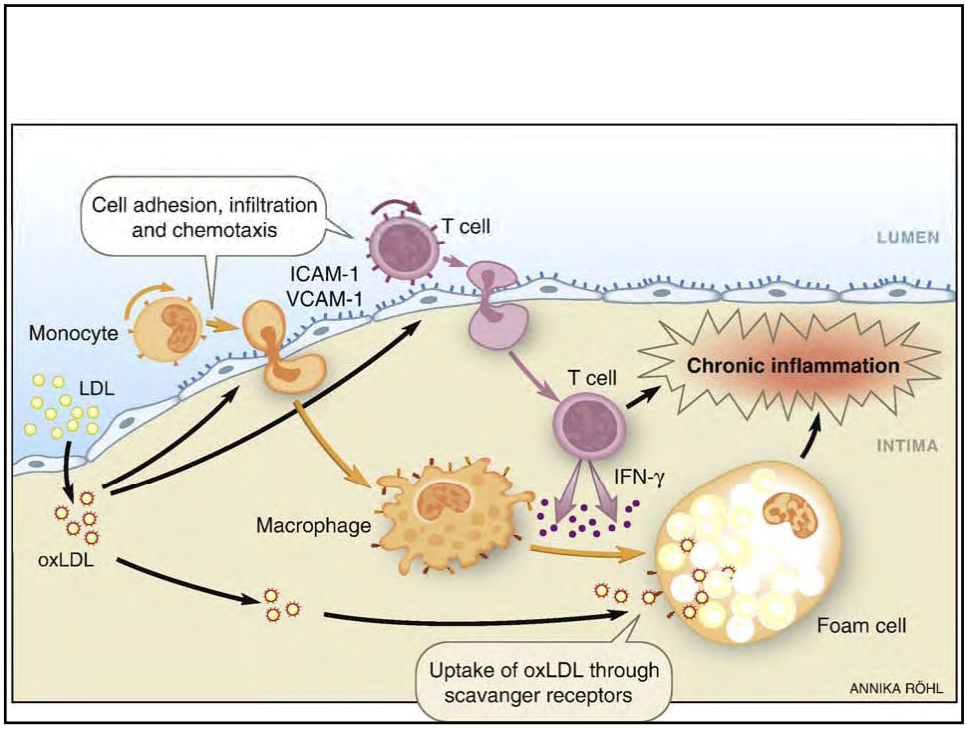


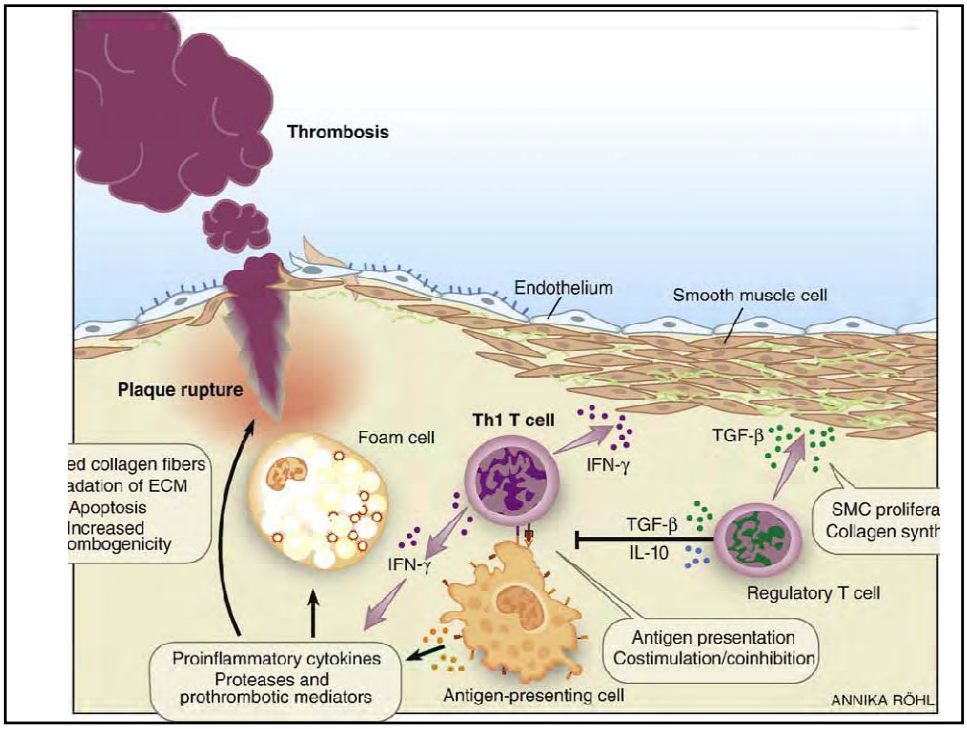
Natural history of atherosclerosis

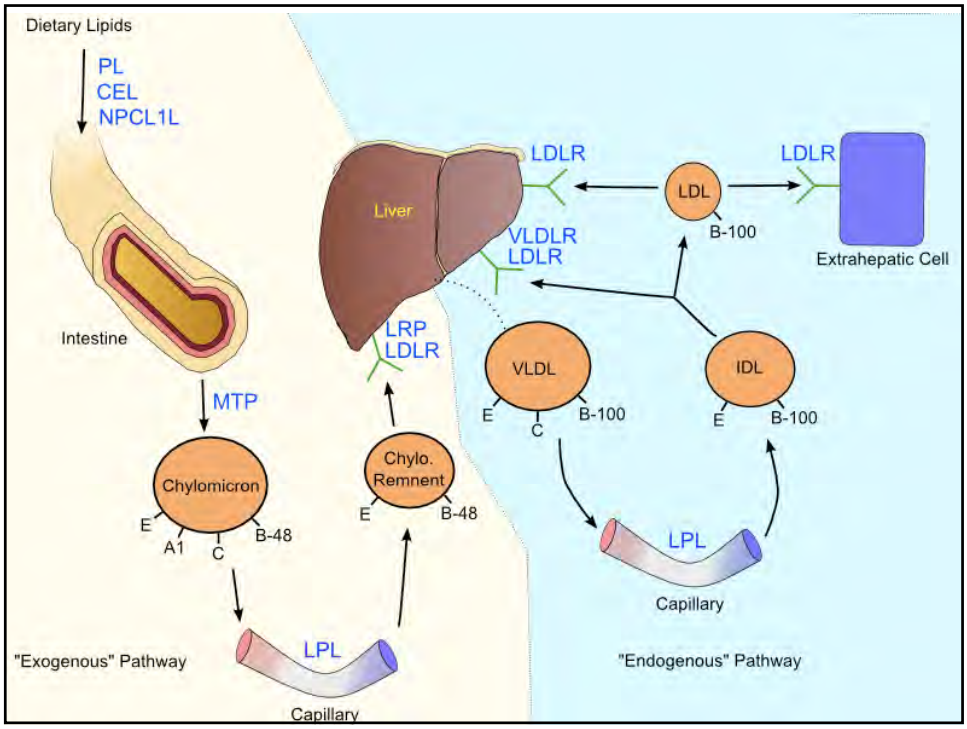
Robbins 8/e

Atherosclerosis (AS): Summary

1. AS is an intima-based lesion with a fibrous cap and atheromatous (gruel-like) core
2. Constituents: SMC's, ECM, inflamm., lipid, necrotic debris
3. Endothelial injury + inflammation drive AS: risk factors influence EC dysfunction, SMC recruitment and activation
4. AS plaque complications: *rupture—thrombosis—hemorrhage—embolization*
5. Rx: risk factor recognition + reduction


Cell adhesion, infiltration and chemotaxis
T cell
LUMEN
ICAM-1
VCAM-1
Monocyte
LDL
T cell
Chronic inflammation
INTIMA
IFN-γ
Macrophage
oxLDL
Foam cell
Uptake of oxLDL through scavanger receptors
ANNIKA RÖHL


Thrombosis
Endothelium
Smooth muscle cell
Plaque rupture
Th1 T cell
Foam cell
IFN-γ
TGF-β
ed collagen fibers
adation of ECM
Apoptosis
Increased
ombogenicity
TGF-β
IL-10
SMC prolifera
Collagen synth
IFN-γ
Regulatory T cell
Antigen presentation
Costimulation/coinhibition
Proinflammatory cytokines
Proteases and
prothrombotic mediators
Antigen-presenting cell
ANNIKA RÖHL


Dietary Lipids
PL
CEL
NPCL1L
Intestine
MTP
Chylomicron
E
A1
C
B-48
LPL
Capillary
"Exogenous" Pathway
Liver
LDLR
LDL
B-100
LDLR
Extrahepatic Cell
VLDLR
LDLR
LRP
LDLR
Chylo.
Remnent
E
B-48
VLDL
E
C
B-100
IDL
E
B-100
LPL
Capillary
"Endogenous" Pathway