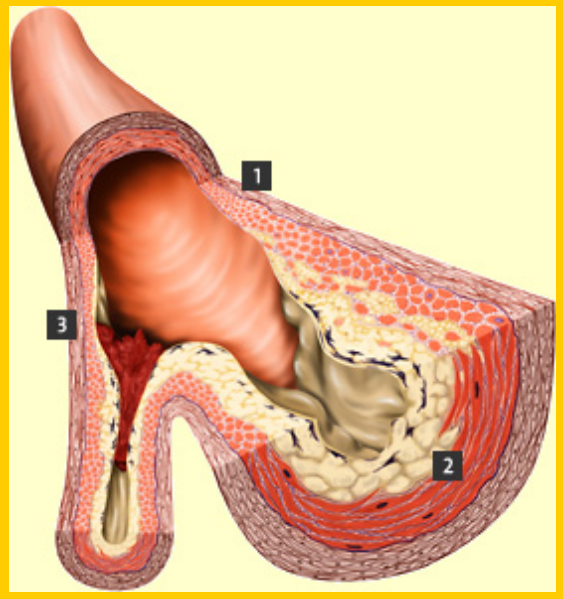

ATHEROSCLEROSIS

Institute of Pathological Physiology

Martin Vokurka
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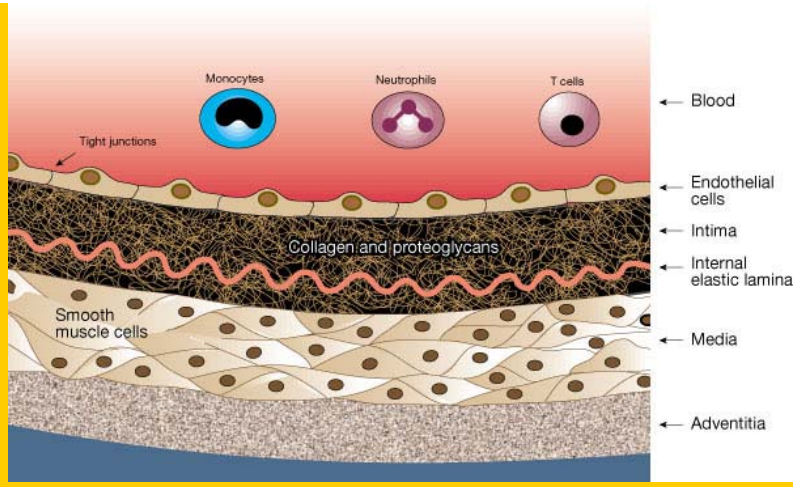
Winter Semester 2010/11

Endothelium



Main functions:

*** regulated permeability**

*** regulation of vasodilatation and vasoconstriction**

*** vessel integrity**

Functional endothelium:

VD: nitric oxide – NO, prostacyclin (PGI_2)

VC: endothelin, angiotensin II

impedes platelets and leukocytes adhesion and aggregation

anticoagulant – trombomoduline

regulation of fibrinolysis: tPA + PAI-1

Endothelial function reflects a **balance between factors such as nitric oxide (NO), which promotes vasodilatation and inhibits inflammation and vascular smooth muscle proliferation, and endothelial-derived contracting factors**, which increase shear stress and promote the development of atherosclerosis.

Current evidence suggests that endothelial status is not determined solely by individual risk factor such as lipids, hypertension, and smoking, but by **an integrated index of all the atherogenic and atheroprotective factors** present in an individual, including known and as yet unknown variables and genetic predisposition.

***Endothelial dysfunction*:**
imbalance between vasoactive and procoagulant/fibrinolytic factors

*** vasoconstriction**
*** inhibition of fibrinolysis**
*** leucocyte adhesion (selectins…)**
*** increased permeability**
*** procoagulant activity**
*** release of cytokins**

Monocytes/macrophages

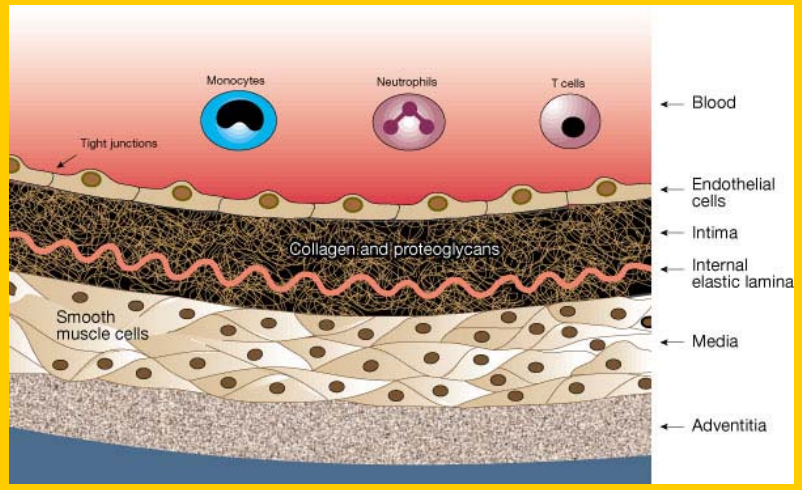
- increased ***attachement*** and ***migration*** to the vessel wall

- production of ***mitogenic*** substances (incl. PDGF), chemotactic factors, oxygen radical species, enzymes etc.

- ***LDL receptors*** (can be downregulated)

- ***scavenger receptors***, mainly for modified LDL (without negative feedback – ***foam cells***, apoptosis, ***inflammation***)

Theese processes play role in atherogenesis itself and also in the development of the atheroma – mainly in its ***stability***



Smooth muscle cells

contraction

upon the stimulation (e.g. PDGF) change to the
secretory phenotype (migration, proliferation,
production of cytokines, collagen, matrix)

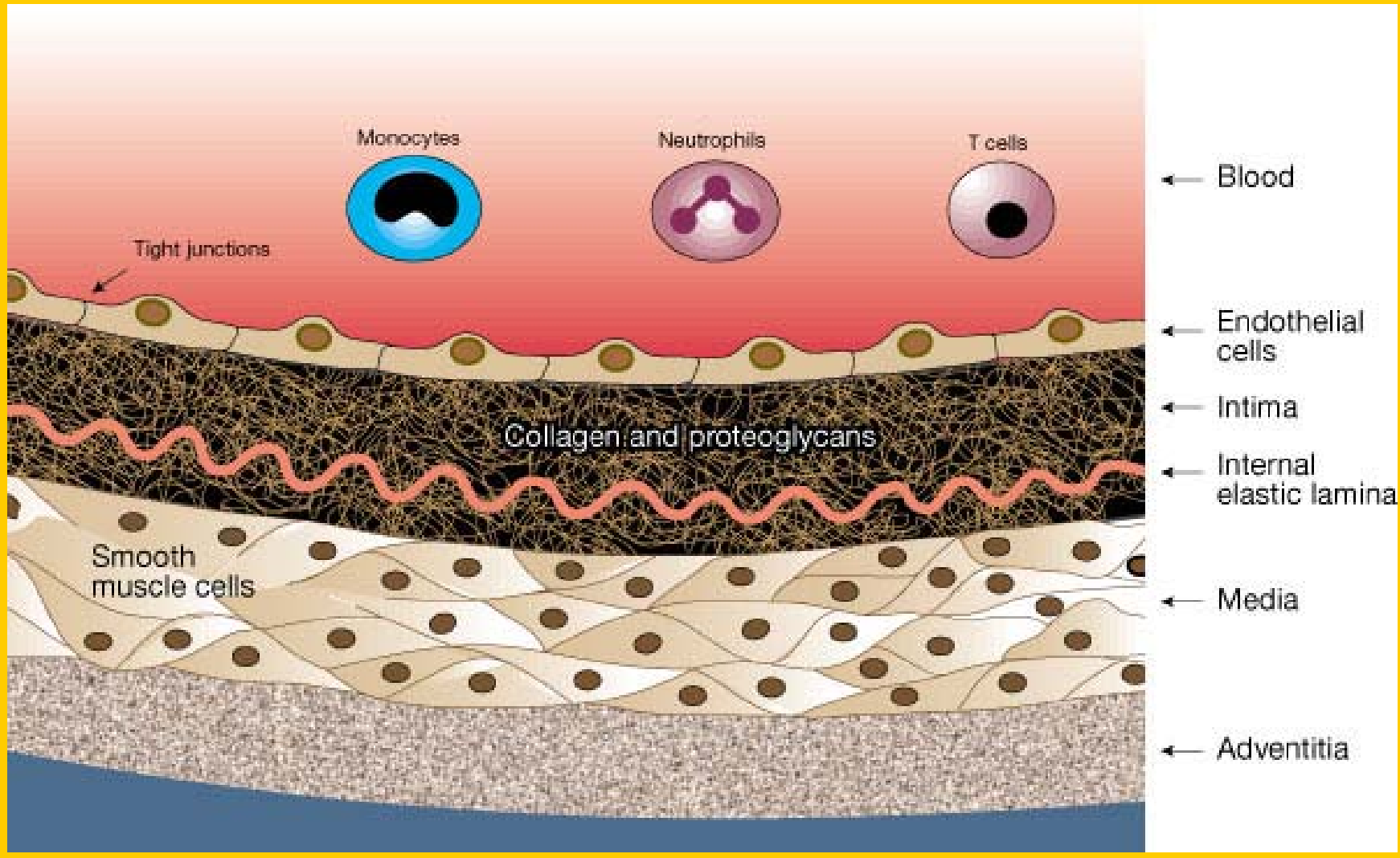

Monocytes
Neutrophils
T cells
Tight junctions
Blood
Endothelial cells
Intima
Collagen and proteoglycans
Internal elastic lamina
Smooth muscle cells
Media
Adventitia

CHART 24-1

Risk Factors in Coronary Heart Disease Other Than Low-Density Lipoproteins

Positive Risk Factors

Age
- Men: ≥45 years
- Women: ≥55 years or premature menopause without estrogen replacement therapy

Family history of premature coronary heart disease (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)

Current cigarette smoking

Hypertension (≥140/90 mm Hg* or on antihypertensive medication)

Low HDL cholesterol (<40 mg/dL*)

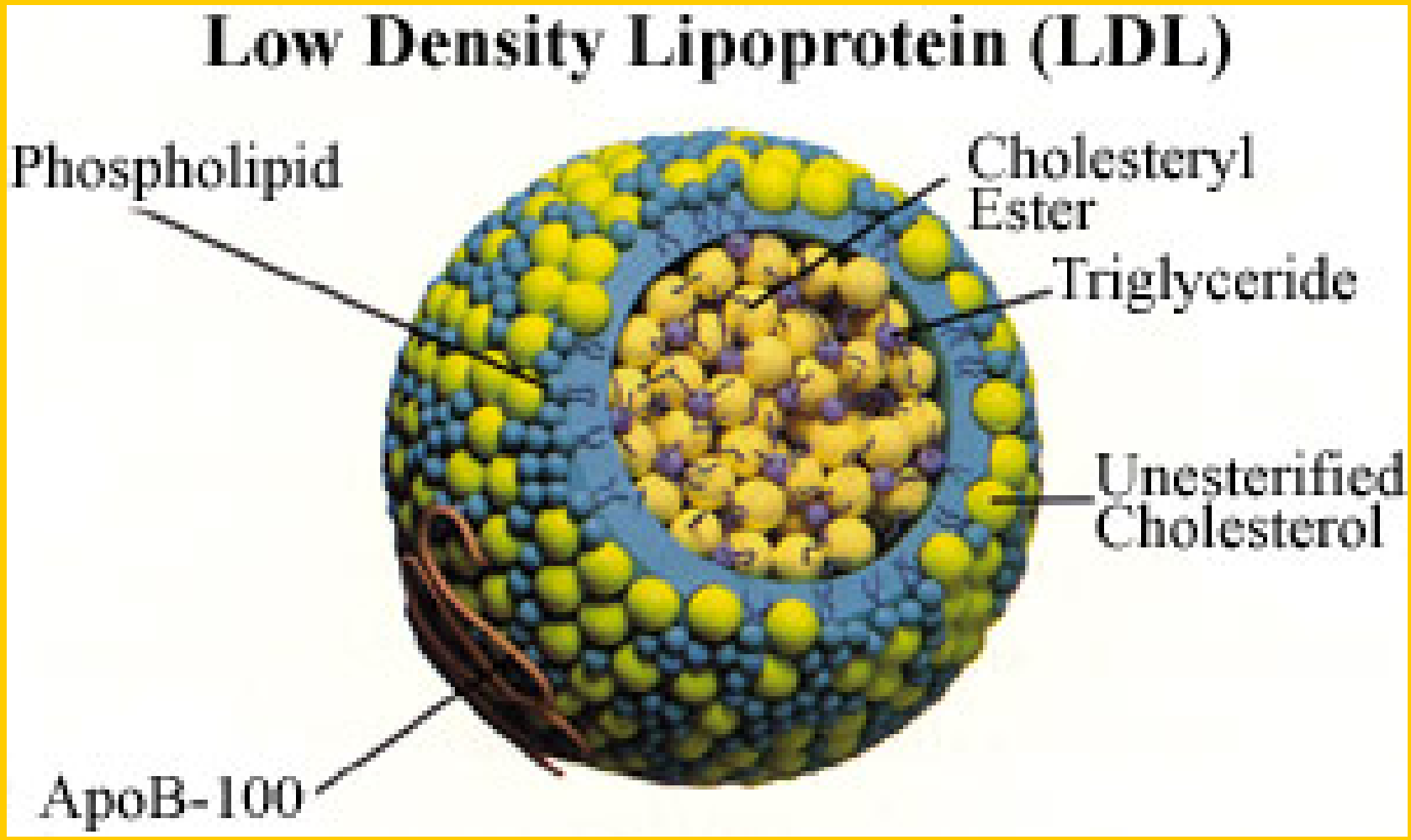
Diabetes mellitus

C-reactive protein (CRP)

Negative Risk Factor

High HDL cholesterol (≥60 mg/dL)

HDL, high-density lipoprotein.
*Confirmed by measurements on several occasions.
(Modified from National Institutes of Health Expert Panel [2001]. *Third Report of the National Cholesterol Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* [Adult Treatment Panel III]. [NIH Publication No. 01-3670]. Bethesda, MD: National Institutes of Health.)


Low Density Lipoprotein (LDL)
Phospholipid
Cholesteryl Ester
Triglyceride
Unesterified Cholesterol
ApoB-100

***Insulin resistence* – METABOLIC SYDROME**

***Nutrition* – saturated fatty acids, cholesterol, high calories intake**

– (poly)unsaturated fatty acids, vegetables…

***Obesity* – android (abdominal) type**

METABOLIC SYNDROME

-waist (visceral obesity): 94/80 cm
-low HDL cholesterol concentration
-increased concentration of triglycerides
-hyperglycemia
- increased BP (>130/85)

DIABETES MELLITUS is crucial
risk factor for cardiovascular disease

Homocysteine is derived from the metabolism of dietary methionine, an ***amino acid*** that is abundant in ***animal protein***.

Requires: adequate levels of ***folate***, ***vitamin B_6***, ***vitamin B_{12}***, and riboflavin.
Evidence is growing that an increased plasma level (>15 µmol/L) is an independent and dose-related risk factor for development of atherosclerosis.
Homocysteine ***inhibits elements of the anticoagulant cascade*** and is associated with ***endothelial damage***.

Supplementation with folic acid, vitamin B_6, and vitamin B_{12} to decrease plasma homocysteine levels can be used, especially in persons with premature cardiovascular disease.

Lipoprotein (a) is similar to LDL in composition and is an independent risk factor for the development of premature CHD in men.

Binds to macrophages through a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques.

Lipoprotein (a) levels should be determined in persons who have premature coronary artery disease or a positive family history.

C-reactive protein (CRP)

CRP is a serum marker for systemic inflammation.
Several prospective studies have indicated that elevated CRP levels are associated with vascular disease.
The pathophysiologic role of CRP in atherosclerosis has not yet been defined.
Measurement of high-sensitivity CRP (hs-CRP) may be a better predictor of cardiovascular risk than lipid measurement alone.

There also has been increased interest in the
possible connection between **infectious agents** (*Chlamydia pneumoniae,* herpesvirus hominis, cytomegalovirus).
The presence of these organisms in atheromatous lesions
has been demonstrated by immunocytochemistry,
but no cause-and-effect relationship has been established.

The organisms may play a role in atherosclerotic development
by initiating and enhancing the inflammatory response.

Pathogenesis

Damage to the endothelium **–** shear stress, smoking, infection ?, hypertension...

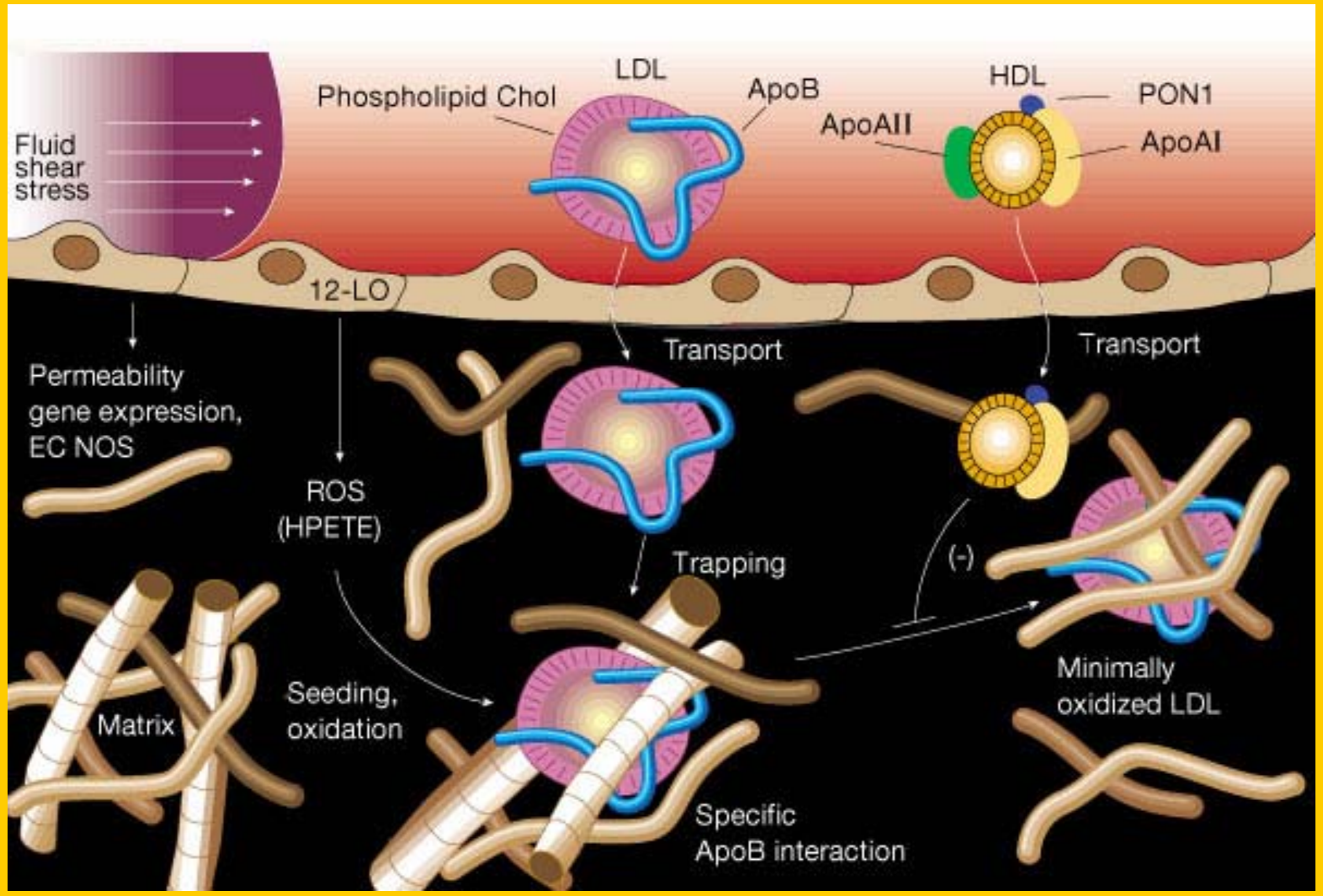
Macromolecules and cell penetration **–** LDL, monocytes

Macromolecules and cell retention **–** LDL, monocytes-macrophages

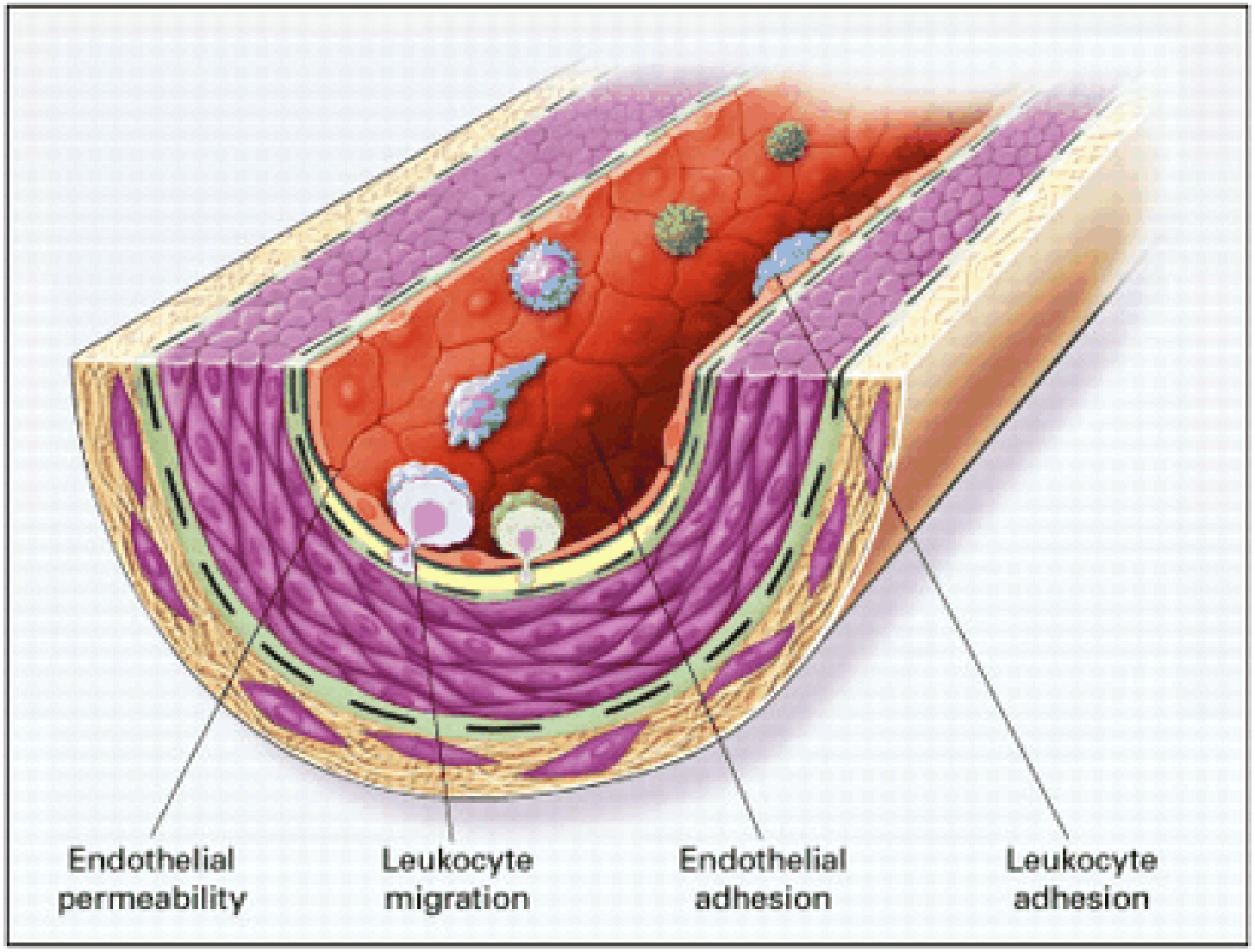
LDL modification: oxidation, glycation, aggregation

LDL accumulation in the macrophages **–** foam cells

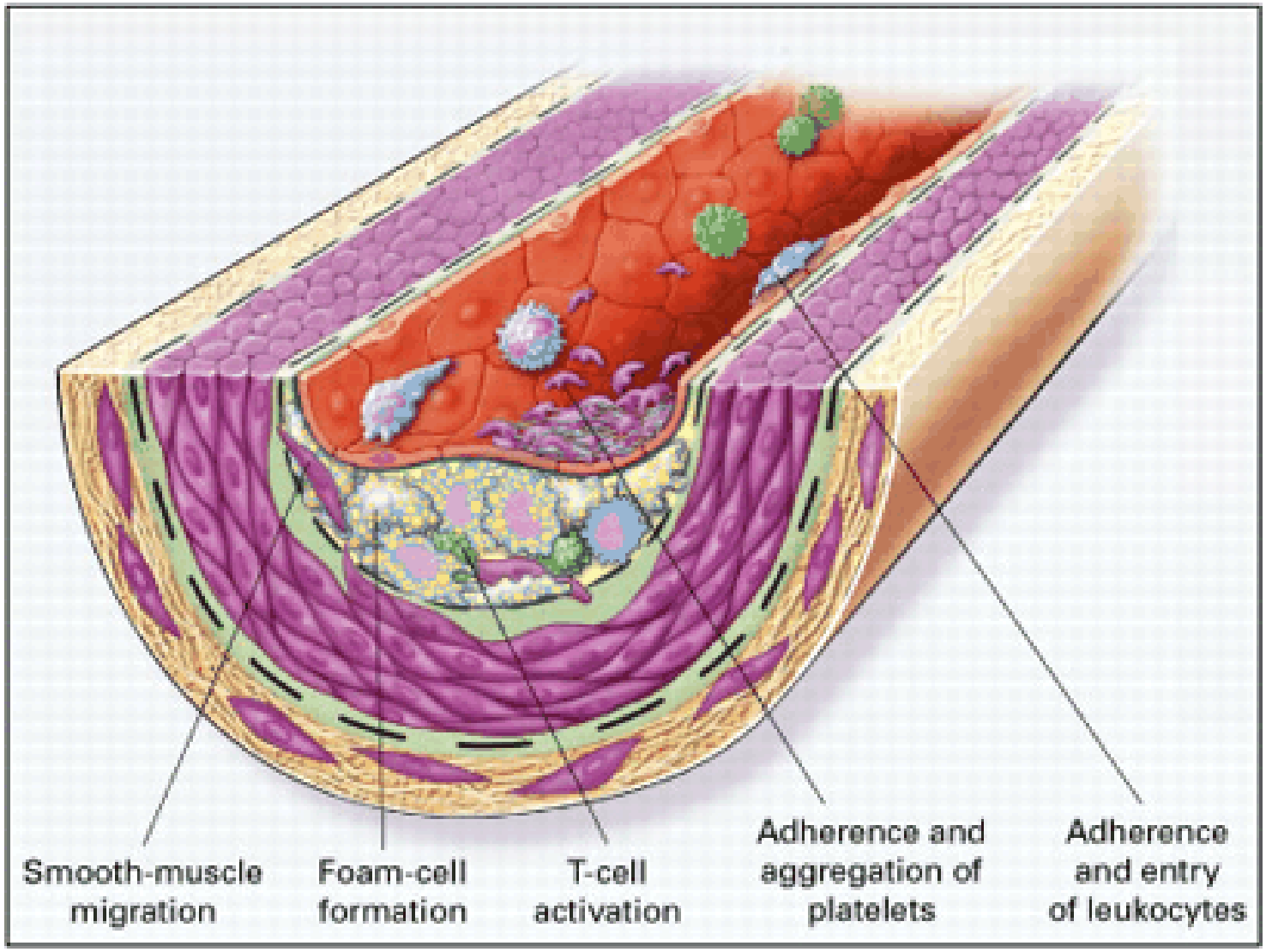
Inflammation **–** production of reactive oxygen species, cytokines, growth factors, enzymes...


Fluid
shear
stress
Phospholipid Chol
LDL
ApoB
HDL
PON1
ApoAII
ApoAI
12-LO
Permeability
gene expression,
EC NOS
ROS
(HPETE)
Transport
Transport
Trapping
(-)
Matrix
Seeding,
oxidation
Minimally
oxidized LDL
Specific
ApoB interaction

Nature, 2000

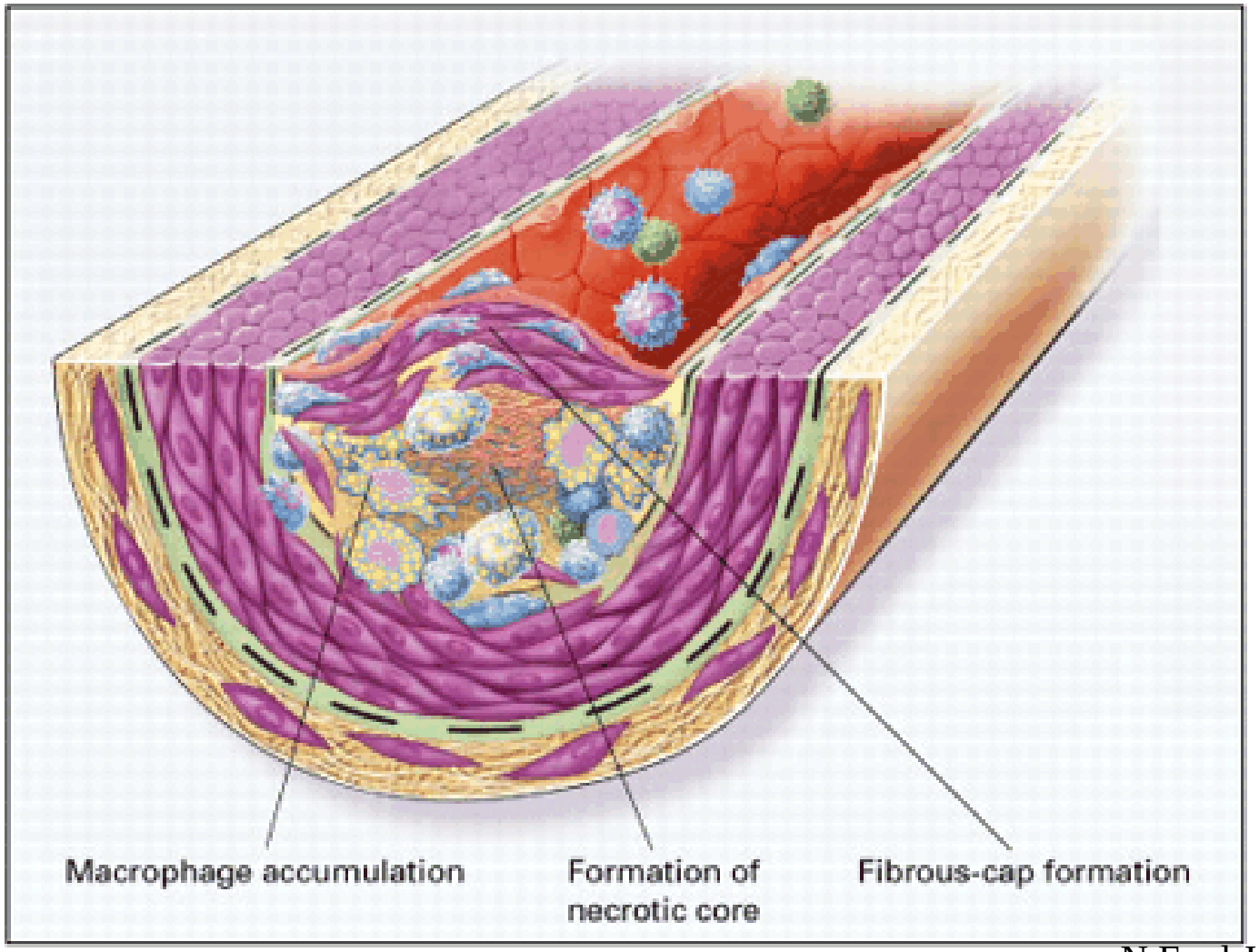


N.Engl.J.Med., 2000



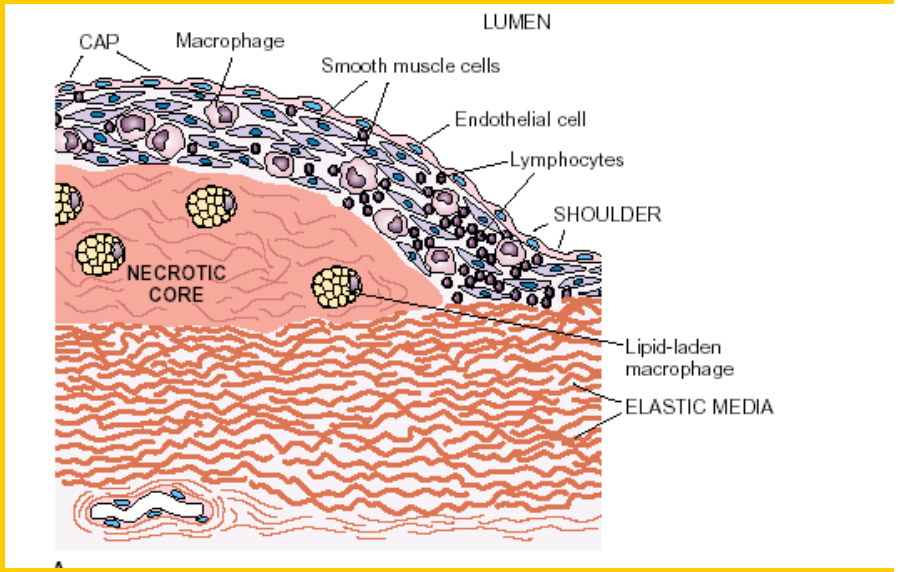
N.Engl.J.Med., 2000

Fibrous changes – fibrous cap



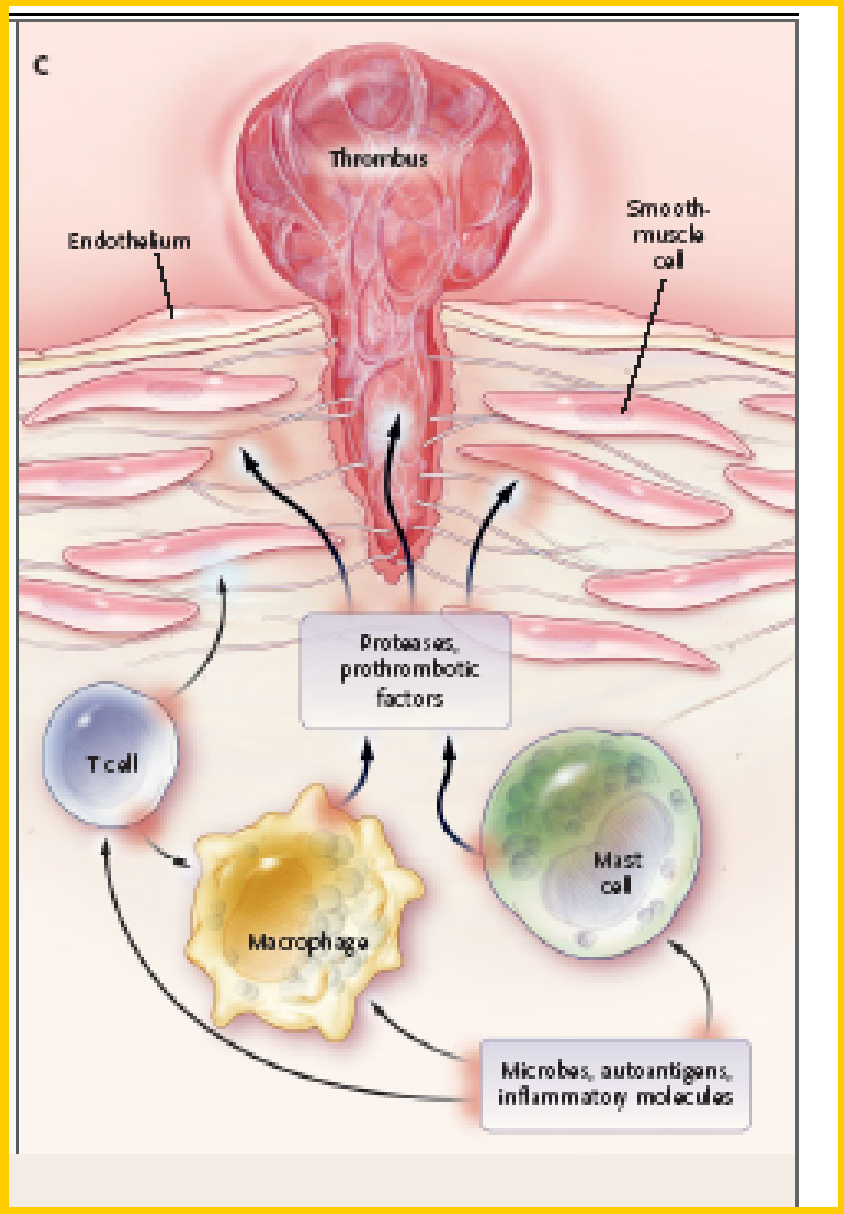
N.Engl.J.Med., 2000

Advanced lesion and thrombosis



plaque stability –
necrotic debris,
inflammatory activitity
neovascularisation + hemorrhage
thinning of the fibrous cap
calcifications
ulcerations

injury to the plaque, intraplaque bleeding...



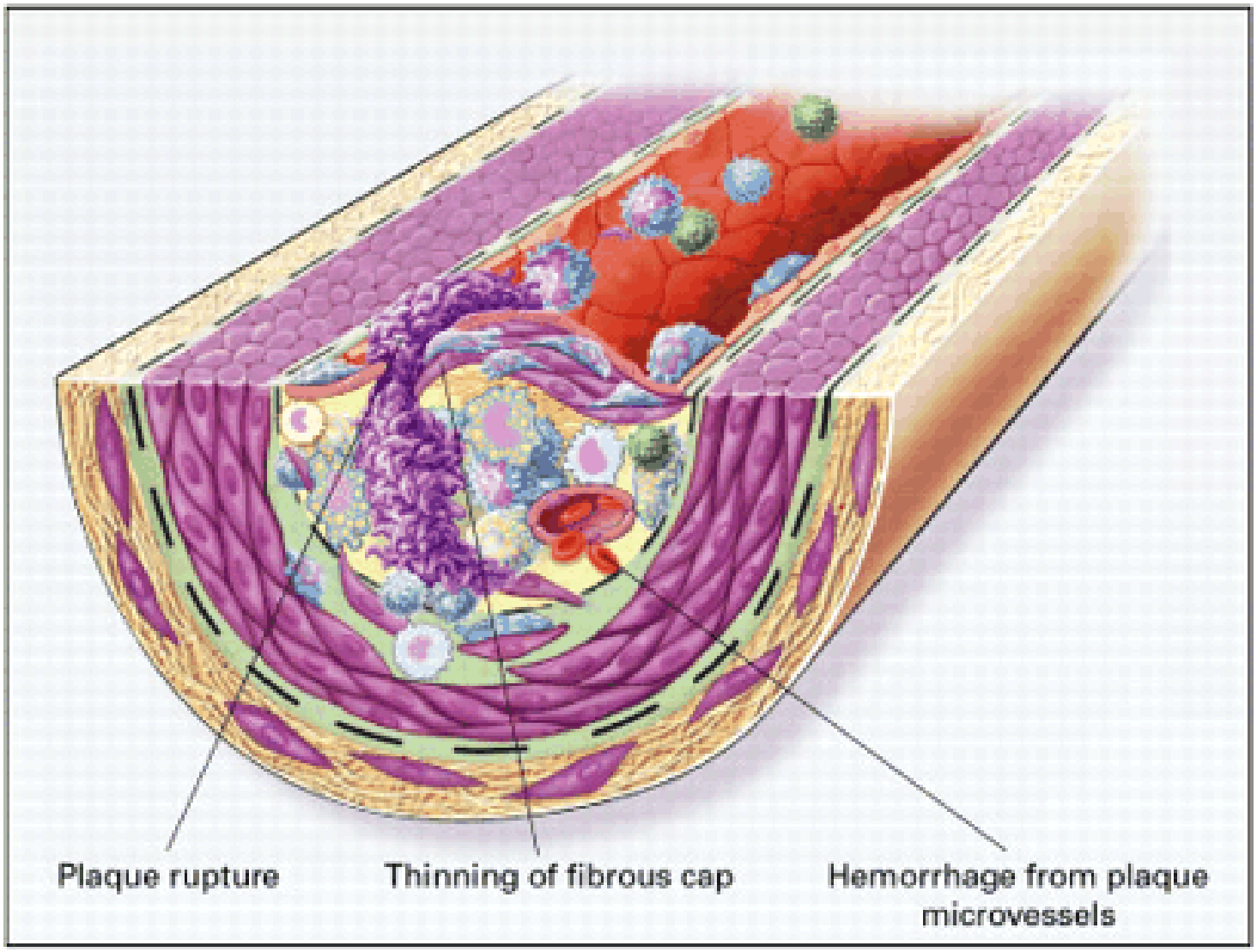
N Engl J Med 2005;352:1685-95.

Major determinants of plaque vulnerability to rupture

(1) the size of the lipid-rich core and the stability and thickness of its fibrous cap

(2) the presence of inflammation with plaque degradation

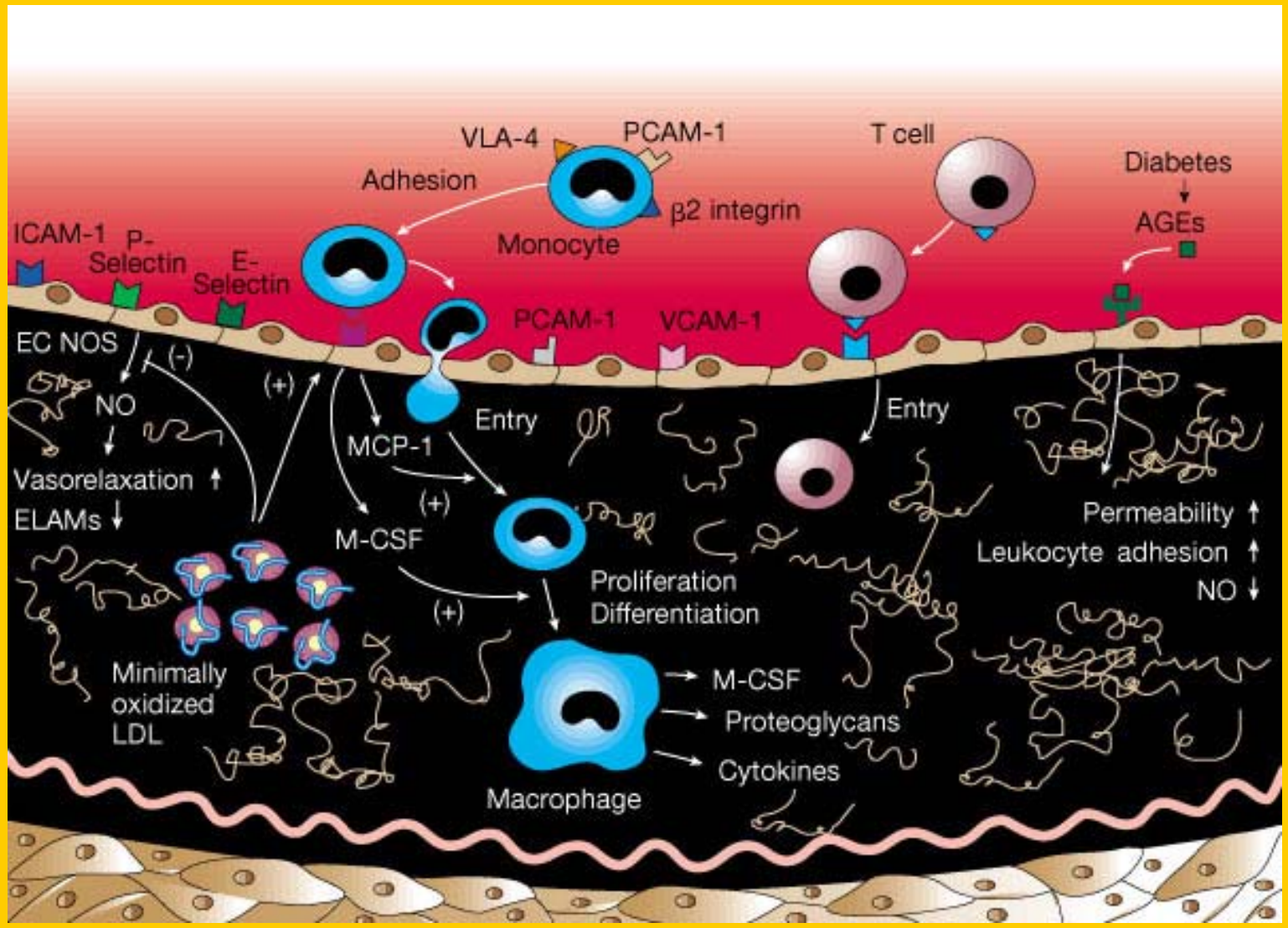
(3) the lack of smooth muscle cells with impaired healing and plaque stabilization



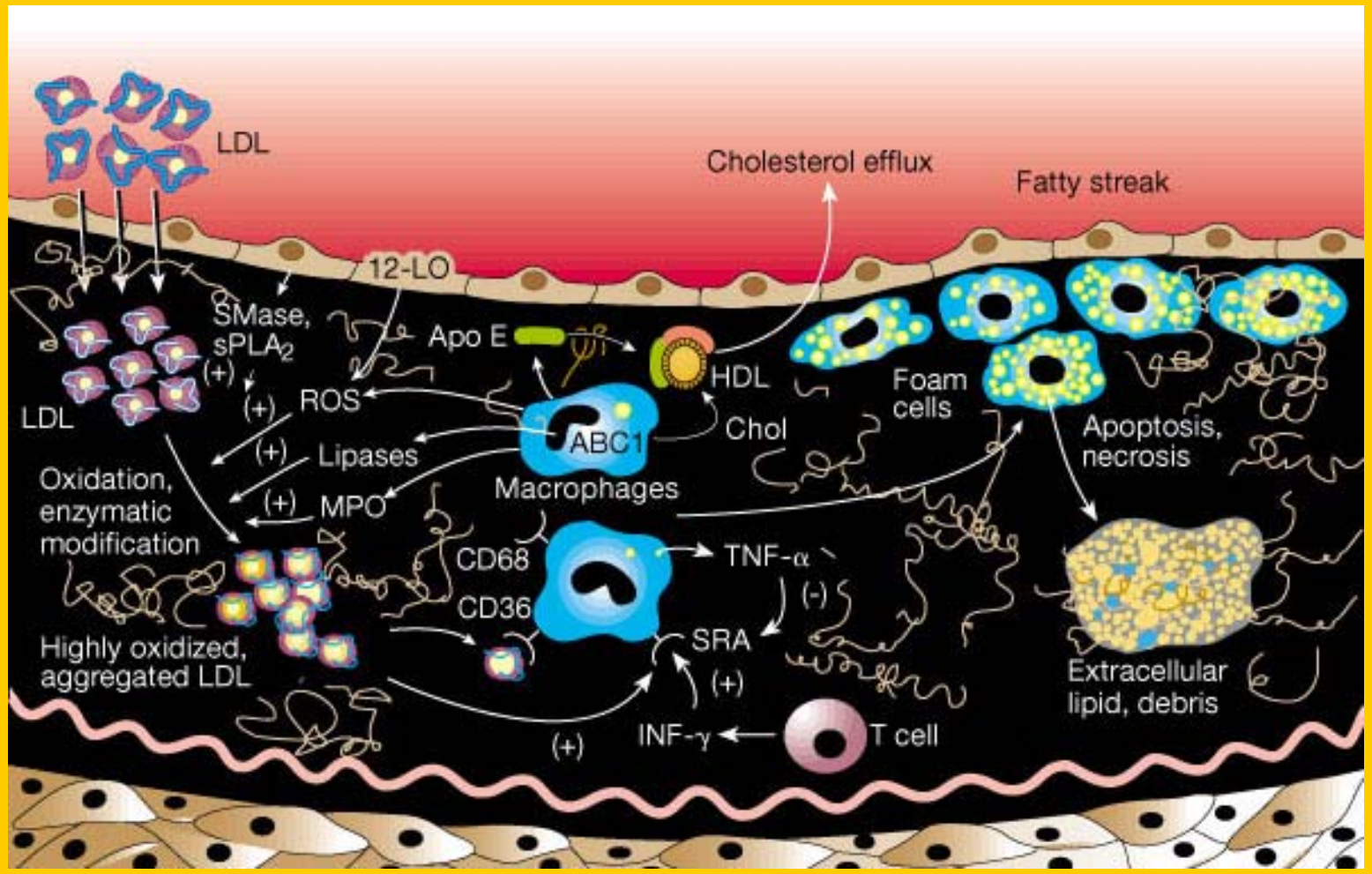
N.Engl.J.Med., 2000

Sequelae:

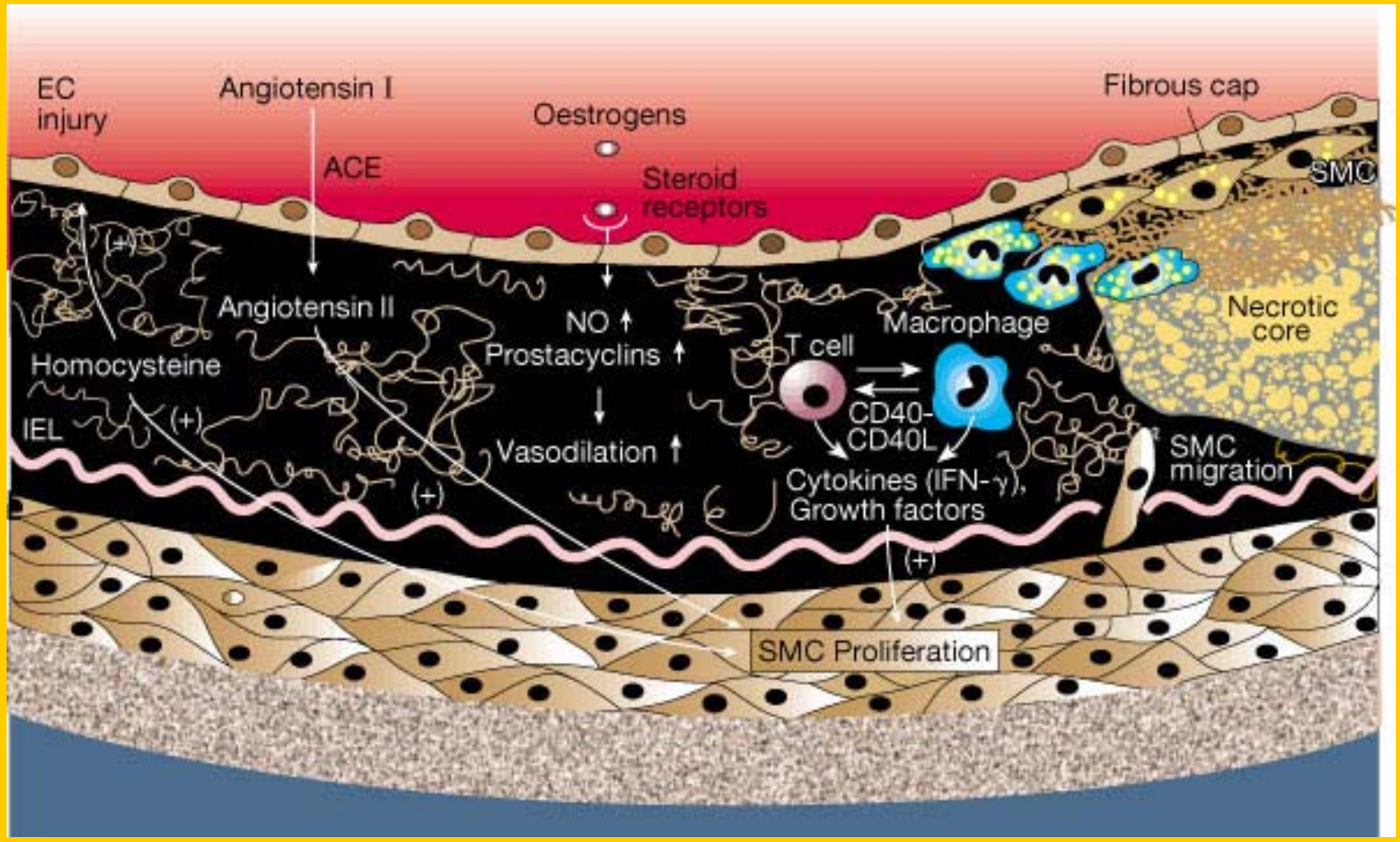
- ***stenosis*** – hemodynamic changes - ischemia
- ***complete occlusion*** – rupture + thrombosis = necrosis
- ***aneurysm*** – weaking of the vessel wall


VLA-4
PCAM-1
T cell
Diabetes
Adhesion
β2 integrin
Monocyte
AGEs
ICAM-1
P-Selectin
E-Selectin
PCAM-1
VCAM-1
EC NOS
(-)
(+)
NO
Entry
Entry
MCP-1
Vasorelaxation
ELAMs
(+)
Permeability
Leukocyte adhesion
NO
M-CSF
Proliferation
Differentiation
(+)
Minimally
oxidized
LDL
M-CSF
Proteoglycans
Cytokines
Macrophage

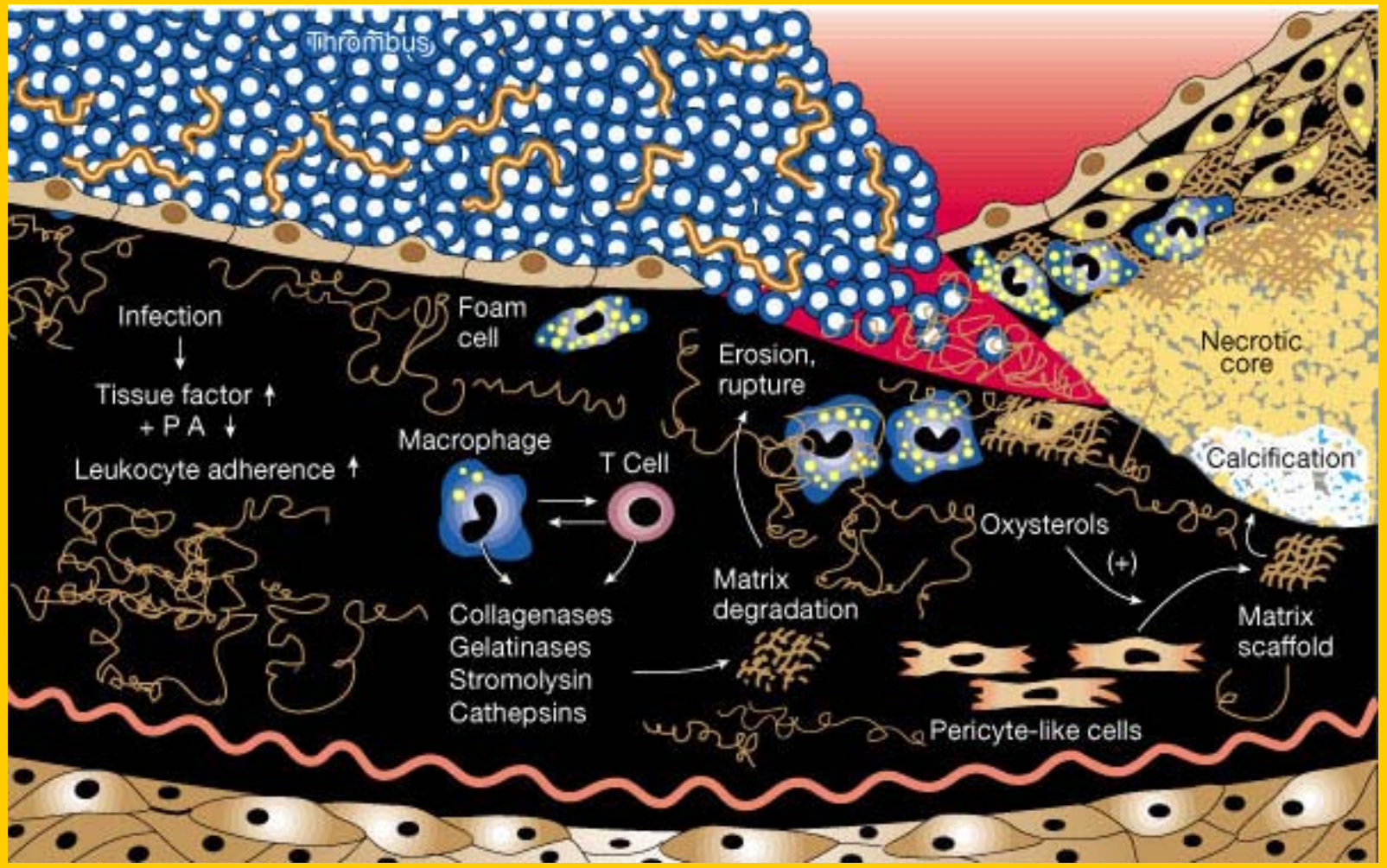
Nature, 2000


LDL
Cholesterol efflux
Fatty streak
12-LO
SMase,
sPLA2
(+)
Apo E
HDL
LDL
(+)
ROS
Foam
cells
ABC1
Chol
(+)
Lipases
Apoptosis,
necrosis
Oxidation,
enzymatic
modification
(+)
MPO
Macrophages
CD68
TNF-α
(-)
CD36
SRA
Highly oxidized,
aggregated LDL
(+)
Extracellular
lipid, debris
INF-γ
T cell
(+)

Nature, 2000


EC injury
Angiotensin I
ACE
Oestrogens
Steroid receptors
Fibrous cap
SMC
Angiotensin II
NO
Prostacyclins
Vasodilation
Homocysteine
IEL
T cell
Macrophage
CD40-CD40L
Cytokines (IFN-γ), Growth factors
Necrotic core
SMC migration
SMC Proliferation
(+)

Nature, 2000


Thrombus
Infection
Tissue factor ↑
+ PA ↓
Leukocyte adherence ↑
Foam cell
Macrophage
T Cell
Collagenases
Gelatinases
Stromolysin
Cathepsins
Erosion, rupture
Matrix degradation
Necrotic core
Calcification
Oxysterols
(+)
Matrix scaffold
Pericyte-like cells

Nature, 2000

Clinical consequences

- **heart**: coronary heart disease
- **brain**: cerebrovascular diseases (ischemia-infarction, intracerebral bleeding), vascular dementia
- **kidneys**: impairement of renal functions, renovascular hypertension
- **lower extremities**: ischemic disease
- **aorta**: hypertension, aneurysma
- **a. carotis interna, a. vertebralis**: brain circulation disturbances, embolisation
- arteries of **pelvis**: erectile dysfunction etc.
- arteries of the **abdomen**: angina abdominalis

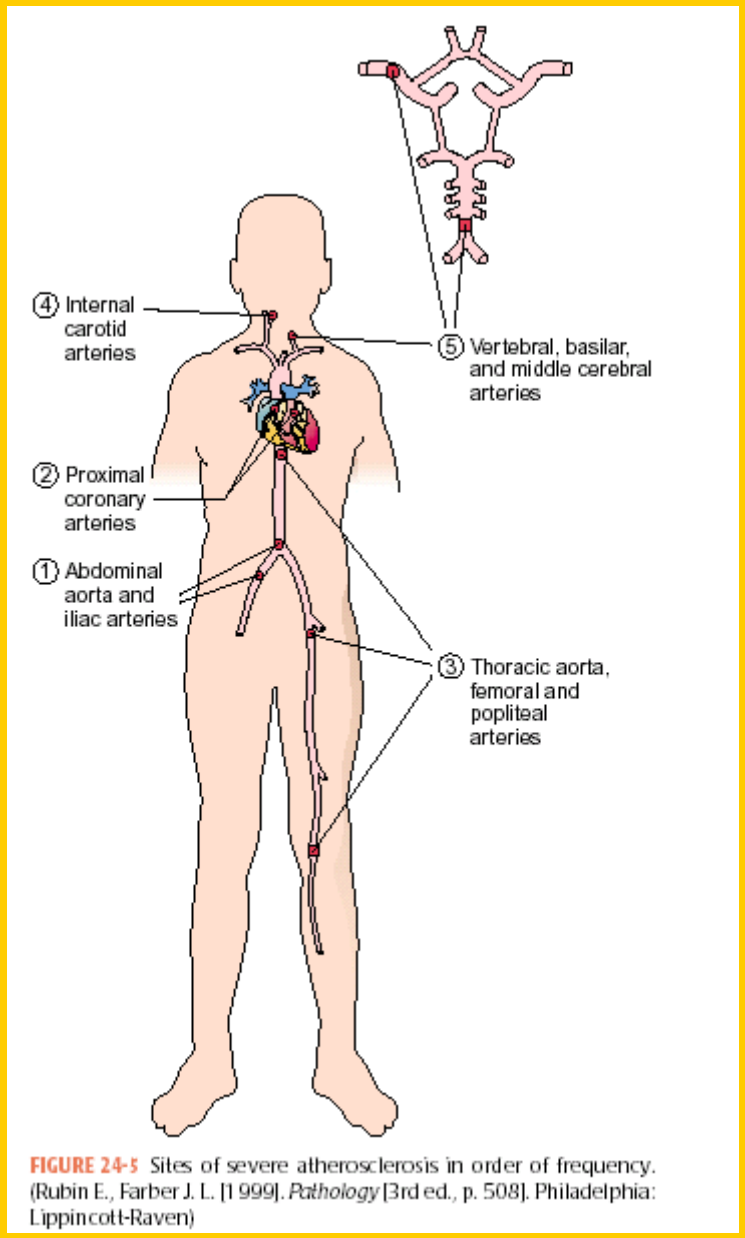
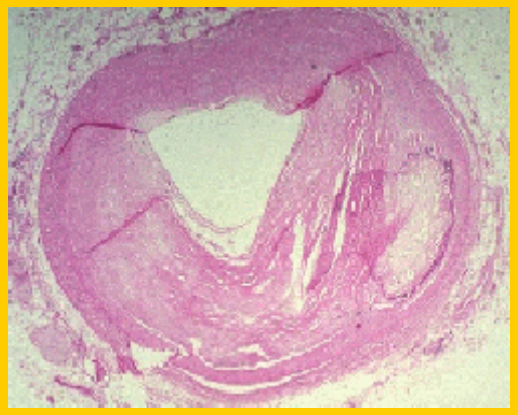


FIGURE 24-5 Sites of severe atherosclerosis in order of frequency. (Rubin E., Farber J. L. [1999]. *Pathology* [3rd ed., p. 508]. Philadelphia: Lippincott-Raven)



The End