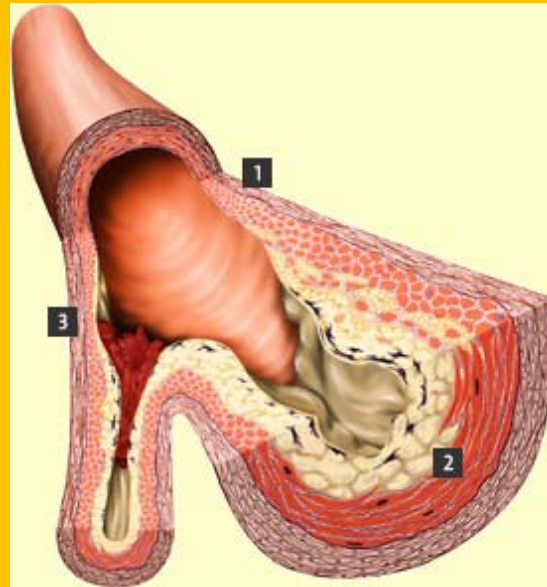




ATHEROSCLEROSIS





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Endothelium

Main functions:

- * regulated permeability**
- * regulation of vasodilatation and vasoconstriction**
- * vessel integrity**

Functional endothelium:

VD: nitric oxide – NO, prostacyclin (PGI₂)

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***)

These 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)

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 ($\geq 140/90$ mm Hg* or on antihypertensive medication)

Low HDL cholesterol (< 40 mg/dL*)

Diabetes mellitus

C-reactive protein (CRP)

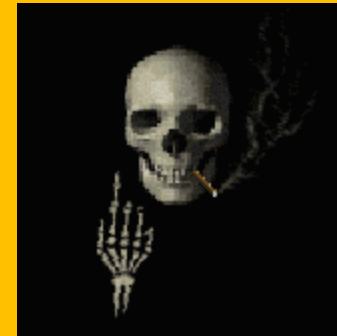
Negative Risk Factor

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.)





***Insulin resistance* – METABOLIC SYNDROME**

***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



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...

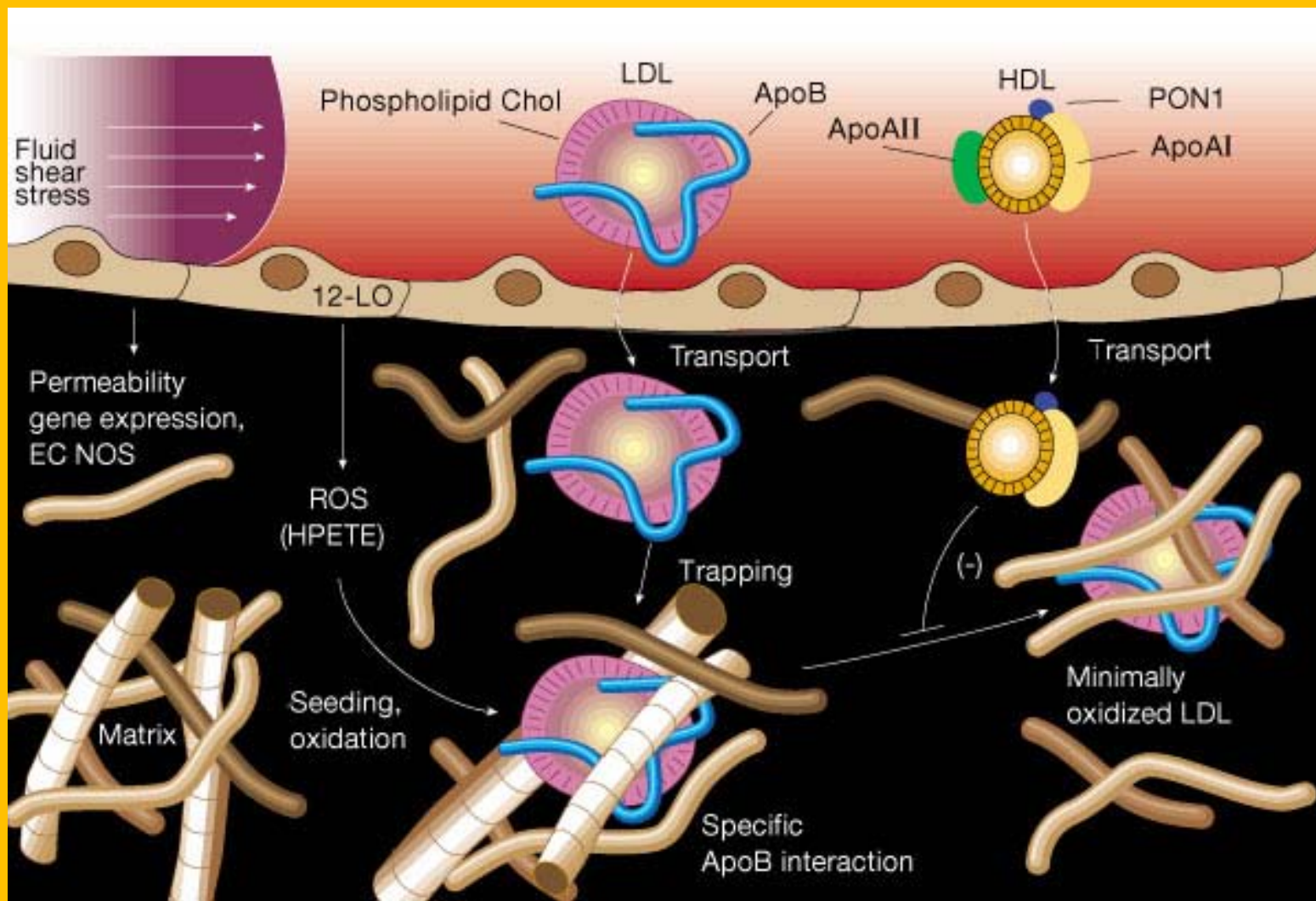
Macromolecules and cell penetration – LDL, monocytes

Macromolecules and cell retention – LDL, monocytes-macrophages

LDL modification: oxidation, glycation, aggregation

LDL accumulation in the macrophages – foam cells

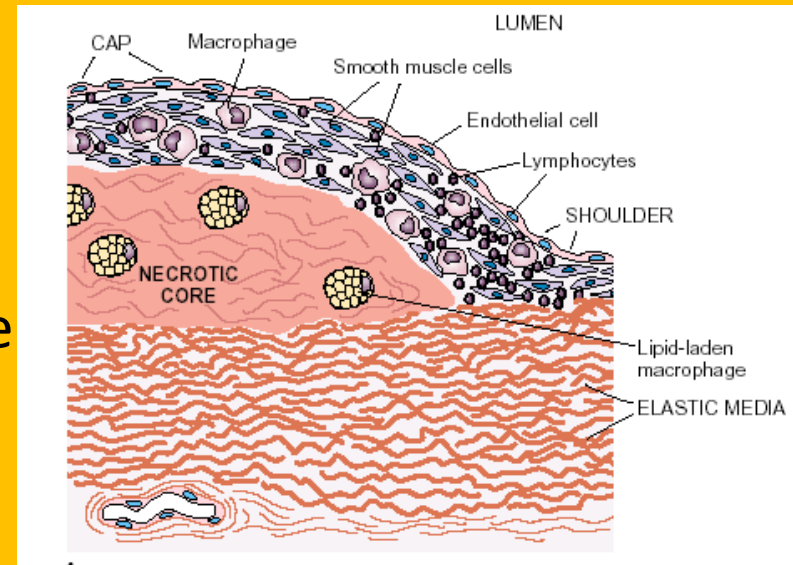
Inflammation – production of reactive oxygen species, cytokines, growth factors, enzymes...



Nature, 2000

Advanced lesion and thrombosis

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



injury to the plaque, intraplaque bleeding...



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

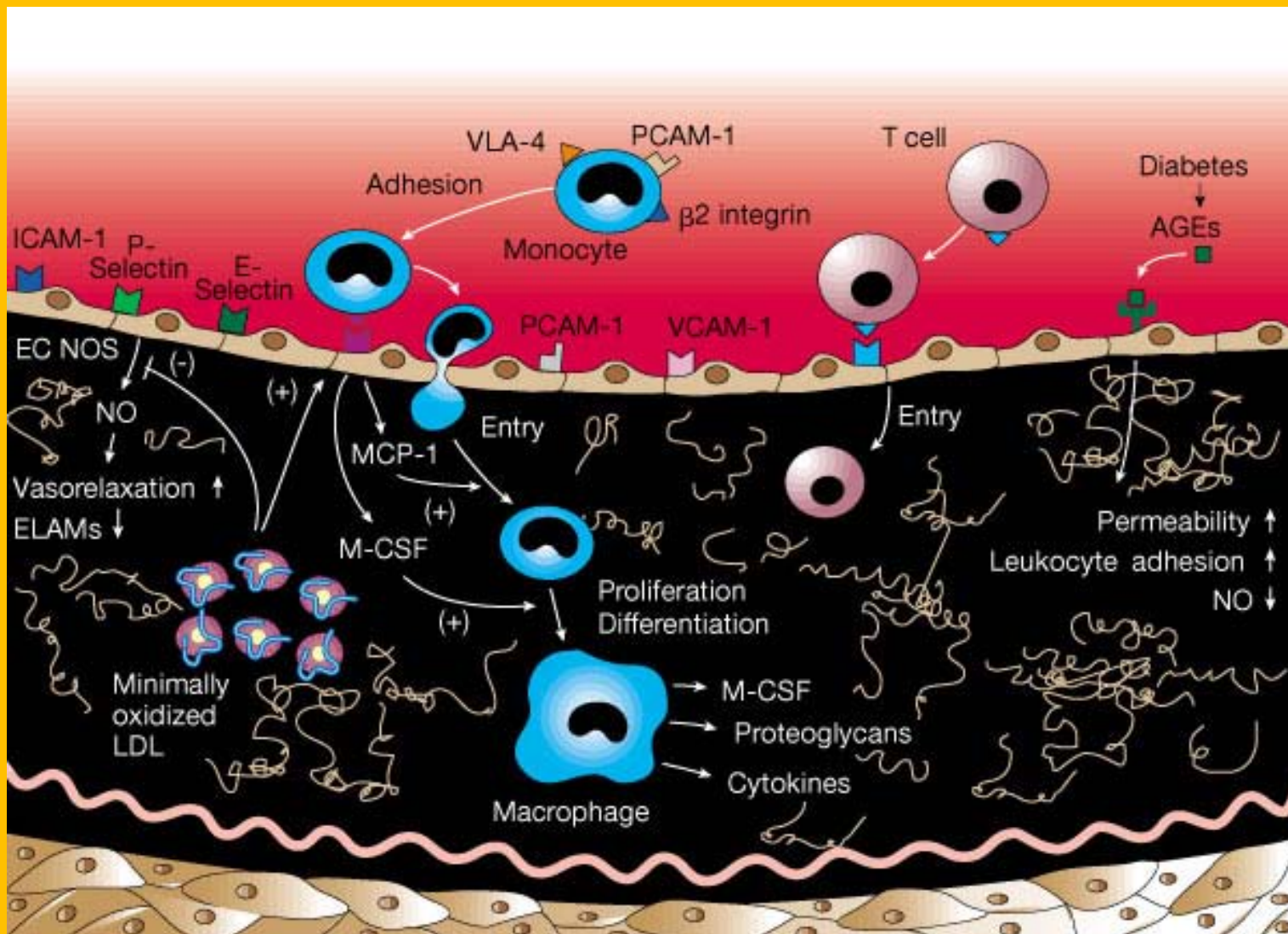
(3) the lack of smooth muscle cells with impaired healing and plaque stabilization



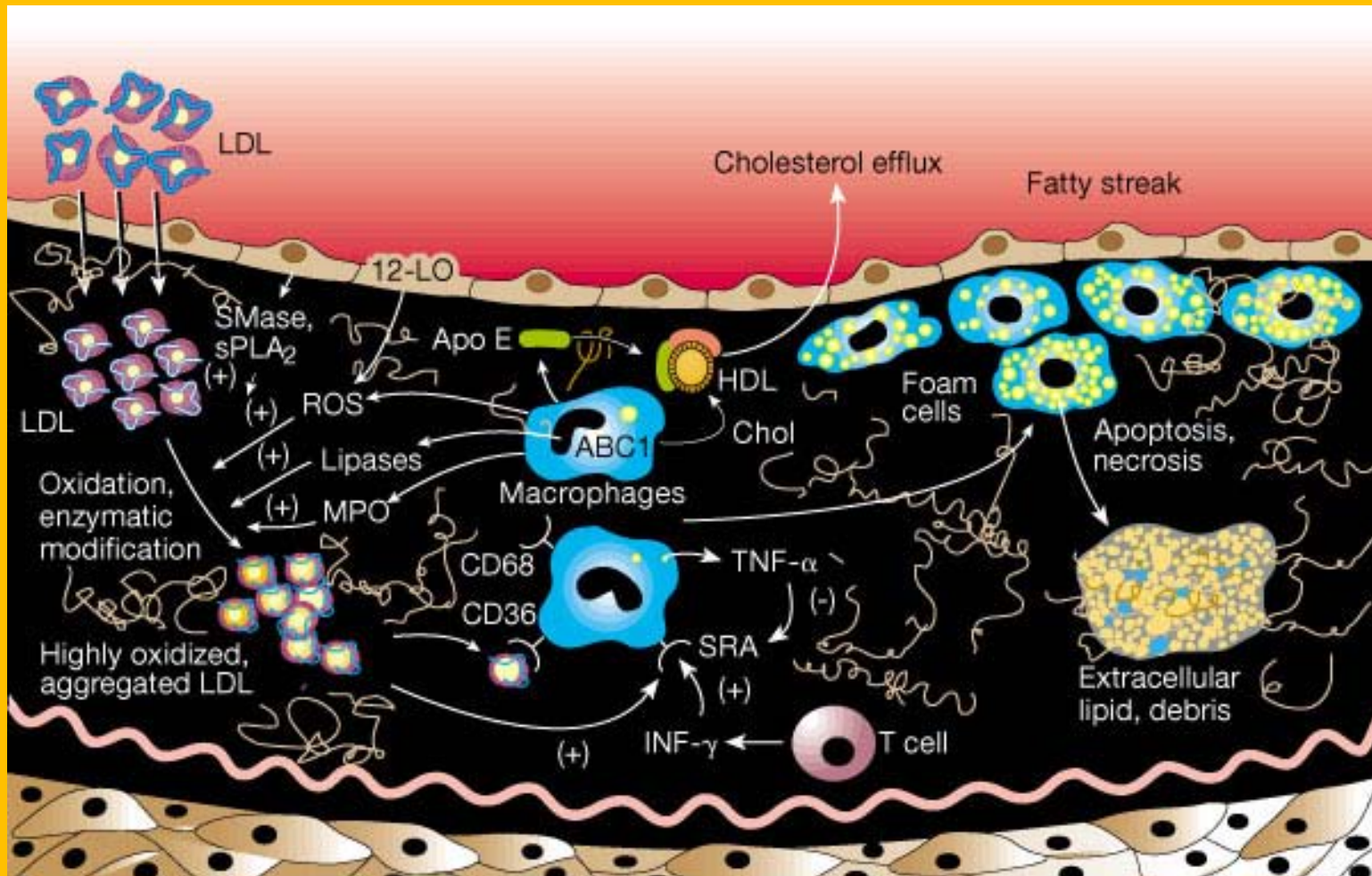
Sequelae:

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

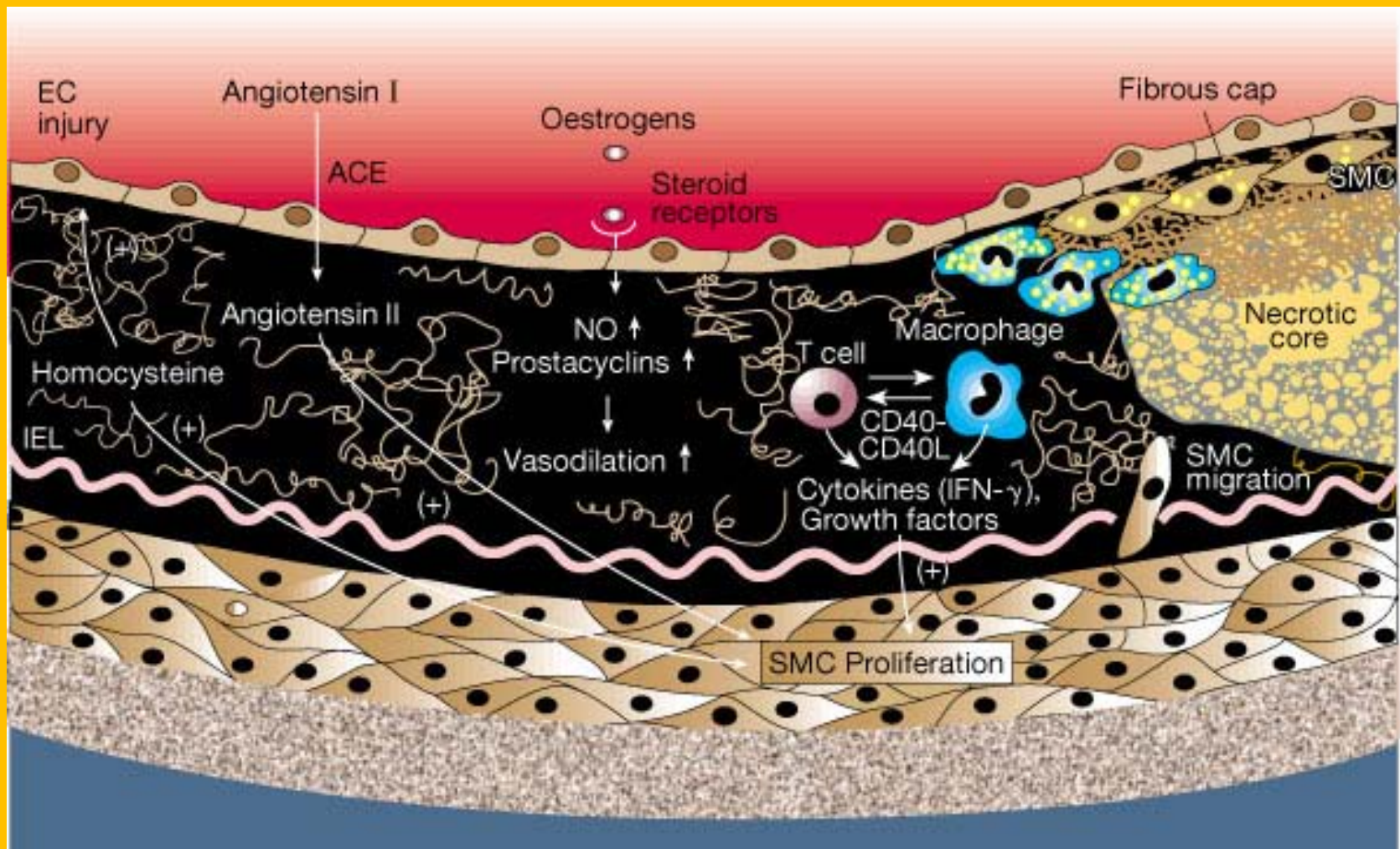




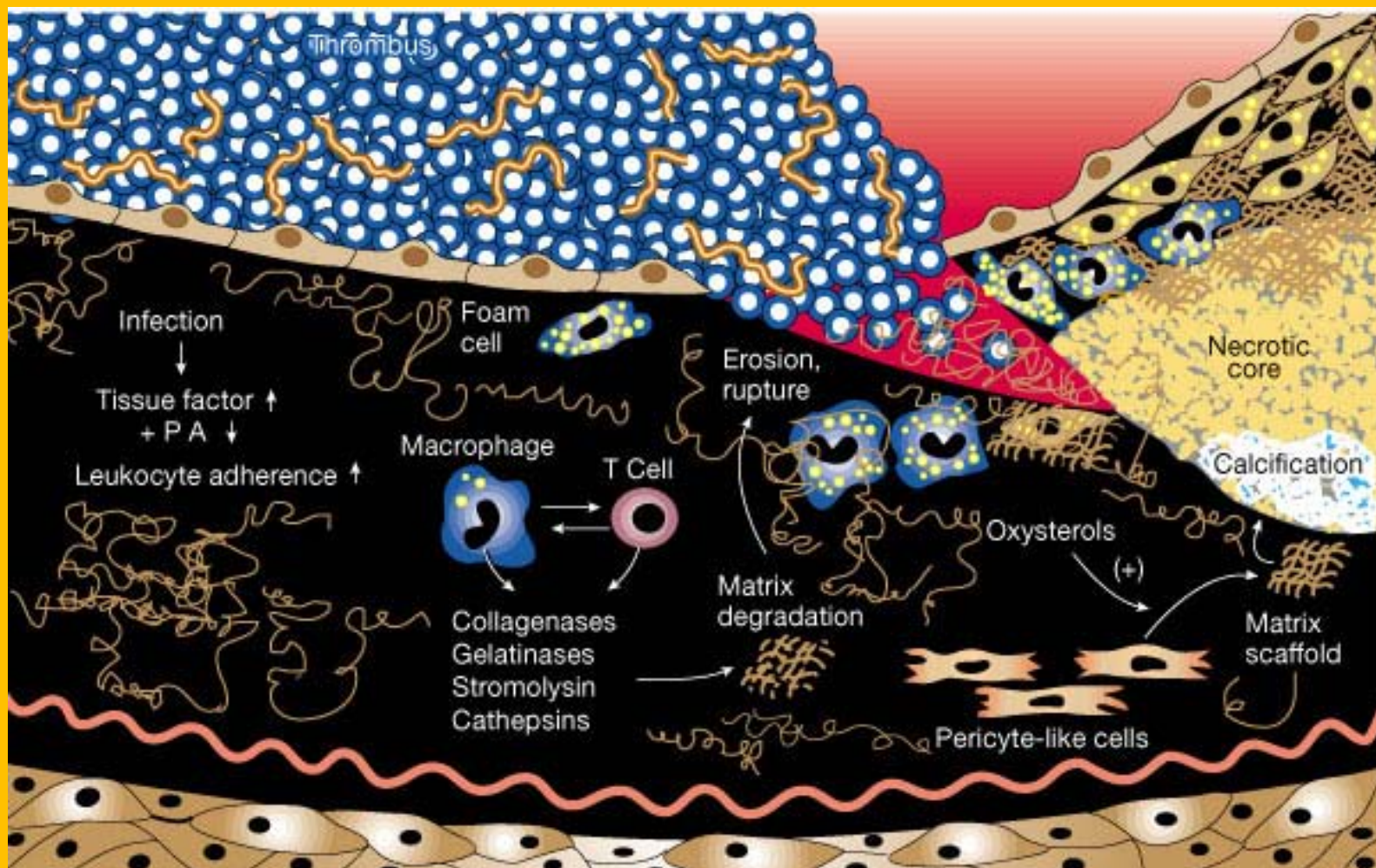
Nature, 2000



Nature, 2000



Nature, 2000



Nature, 2000

Clinical consequences

- **heart**: coronary heart disease
- **brain**: cerebrovascular diseases (ischemia-infarction, intracerebral bleeding), vascular dementia
- **kidneys**: impairment 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

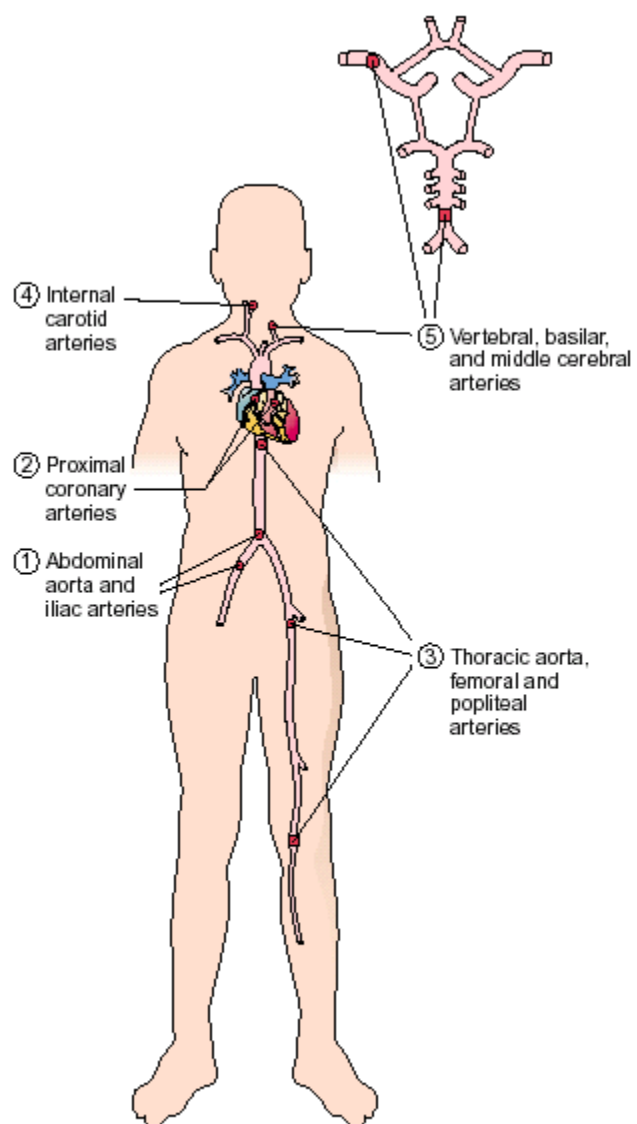


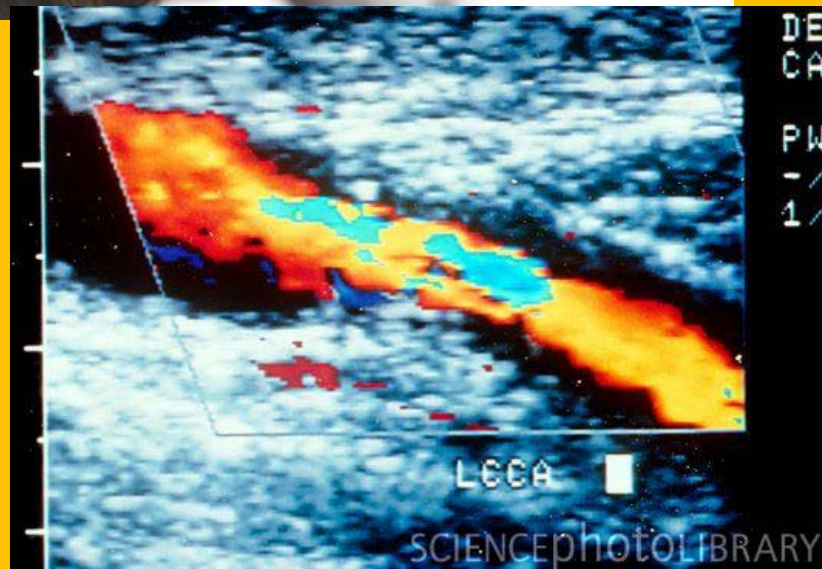
FIGURE 24-5 Sites of severe atherosclerosis in order of frequency. (Rubin E., Farber J. L. [1999]. *Pathology* [3rd ed., p. 508]. Philadelphia: Lippincott-Raven)

Diagnosis

- ultrasound



Caption: Atherosclerosis & clot formation. Coloured doppler ultrasound scan showing atherosclerosis (narrowing) of the carotid artery in the neck. This artery (red/yellow) is the main vessel supplying blood to the brain. Its normal width is seen at the upper left of the scan. At the centre of the scan, blood flow is restricted because the artery has been narrowed by the build up of fatty deposits, known as atherosclerosis. There are multiple signs of clot formation (blue) at the area where blood flow is most turbulent at the narrowed part of the artery. Surgery may be needed to widen the artery and remove the clots



Diagnosis

- ultrasound

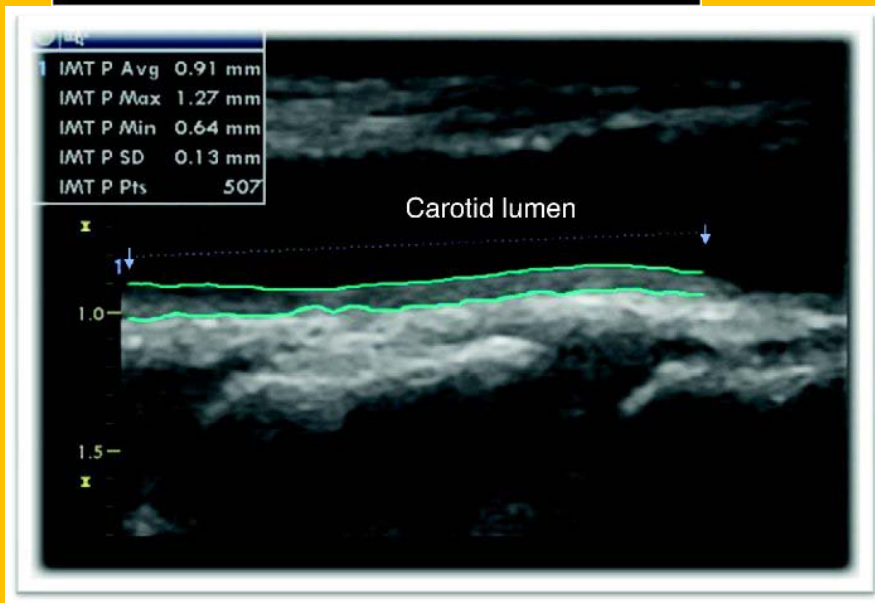
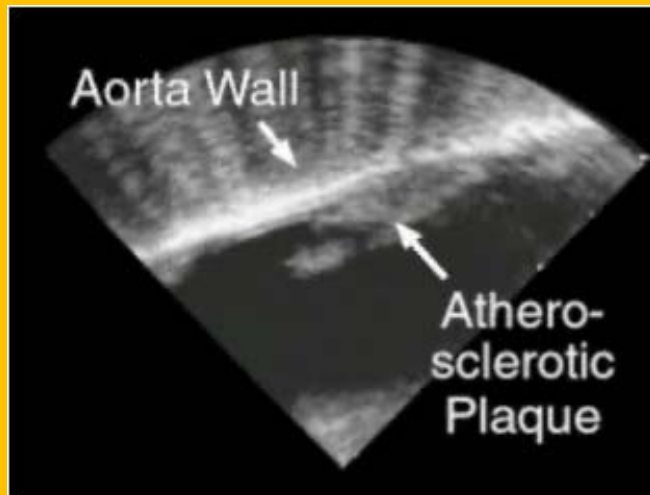
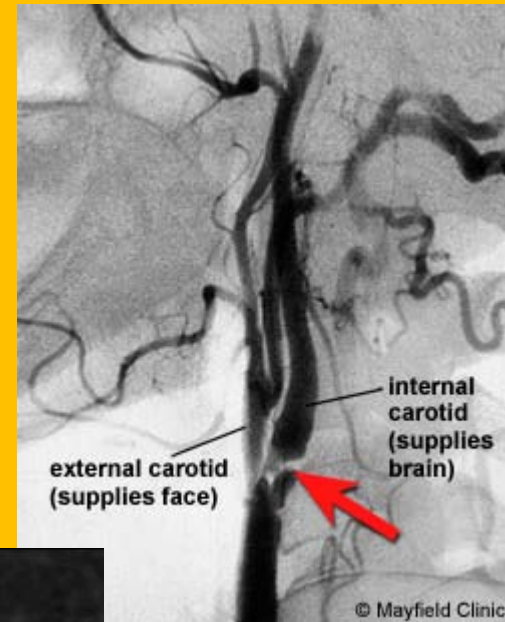


Figure 1. Carotid ultrasound showing a pathological increase in the mean (0.91 mm) and the maximum (1.27 mm) carotid intima-media thickness by means of automated border detection. IMT, intima-media thickness.

Diagnosis

- angiography





The End