The vascular endothelium in atherosclerosis

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National Heart and Lung Institute
Imperial College London
Hammersmith Hospital

The vascular endothelium in atherosclerosis

After this lecture you should understand:

- The importance of vascular endothelium for the health of blood vessels
- The importance of vascular endothelium in the development of atherosclerosis
  - Regulation of permeability and leukocyte recruitment
  - The role of blood flow in determining the location of atherosclerotic plaques
  - Endothelial *aging:* cell senescence in atherosclerosis
  - Pro and cons of angiogenesis in atherosclerosis

Structure of Arteries and Veins

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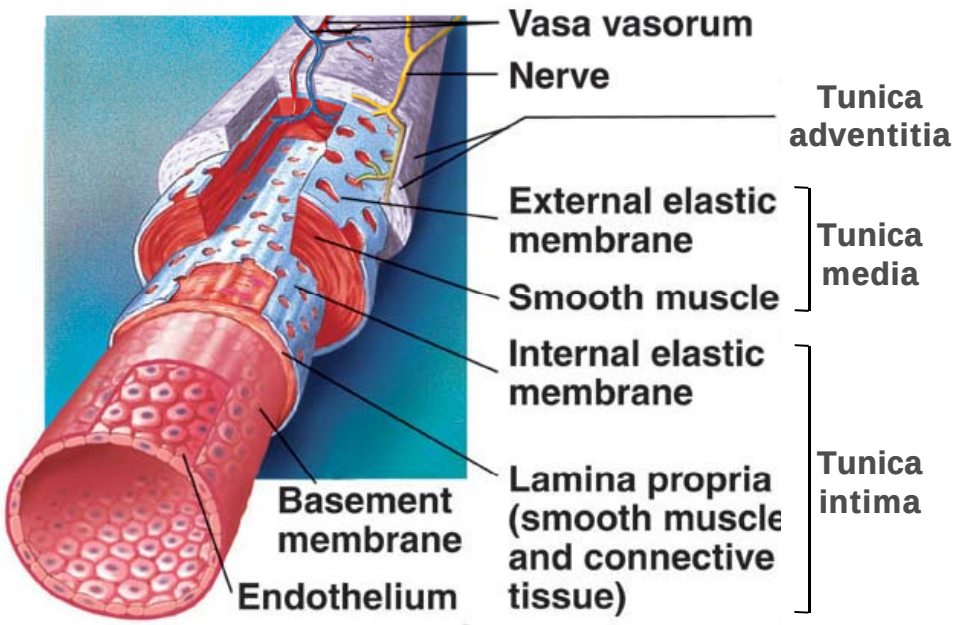


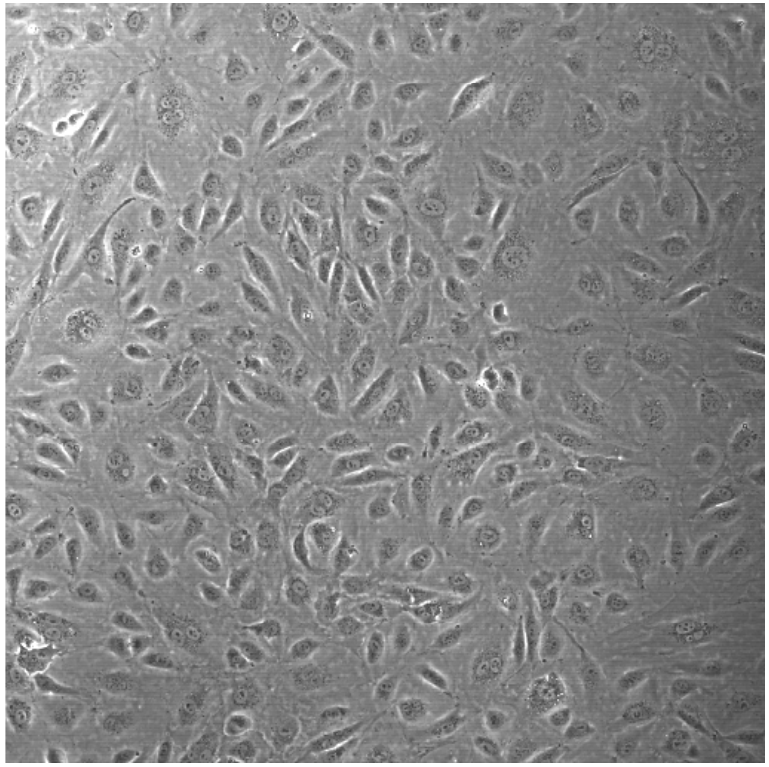
Three layers (except for capillaries and venules):

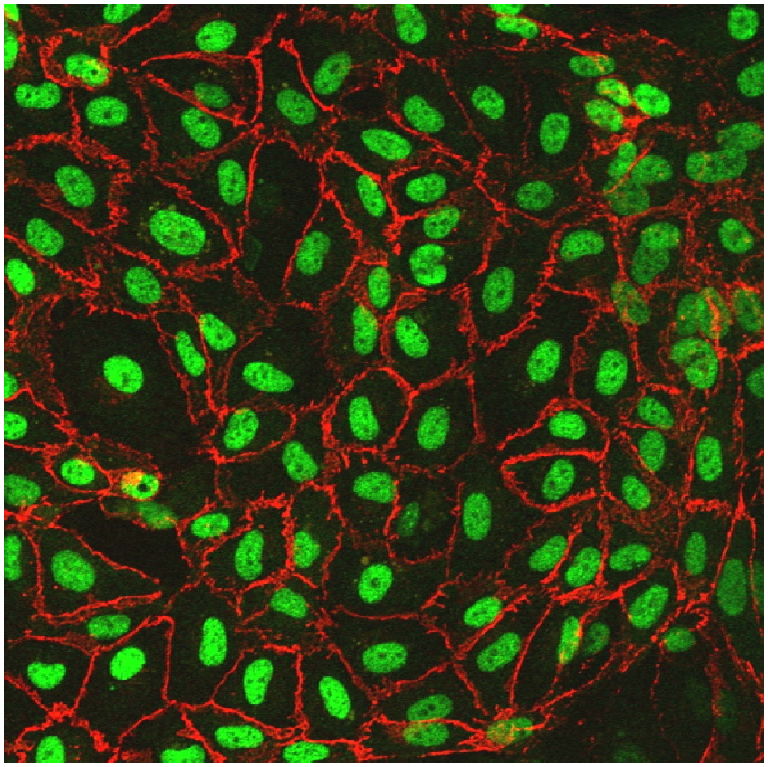
- Tunica intima
  - Endothelium
- Tunica media
  - Smooth muscle cells
- Tunica adventitia
  - vasa vasorum, nerves

Vascular Endothelium

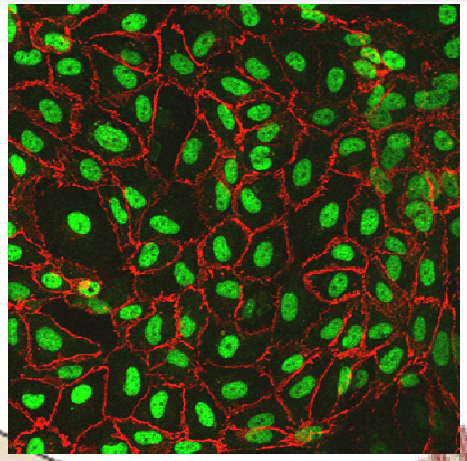
- The Endothelium is the surface separating blood from other tissues
- Very extensive: surface area > 1000 m^2
  weight >100 g
- Acts as a vital barrier separating blood from tissues
- Formed by a monolayer of endothelial cells, one cell deep (*contact inhibition*)
- Endothelial cells are very flat, about 1-2 µm thick and 10-20 µm in diameter
- Not all endothelial cells are the same (*heterogeneity*)
- In vivo, endothelial cells live a long life and have a low proliferation rate (unless new vessels are required: *angiogenesis*)
- Endothelial cell regulate essential functions of blood vessels

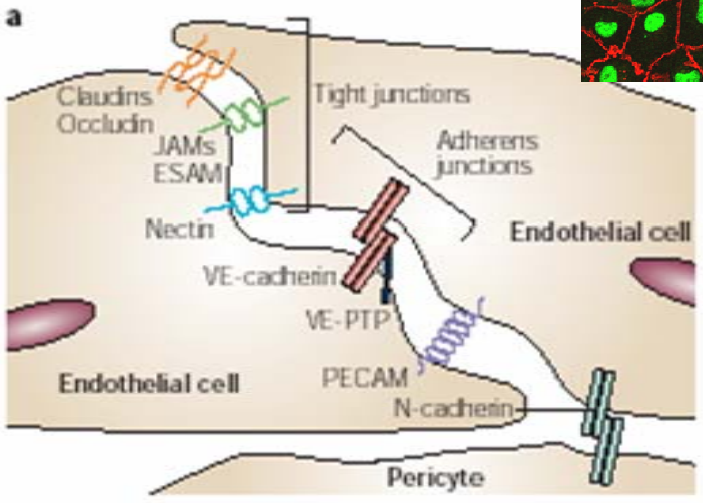
Endothelial cells form a monolayer: contact inhibition

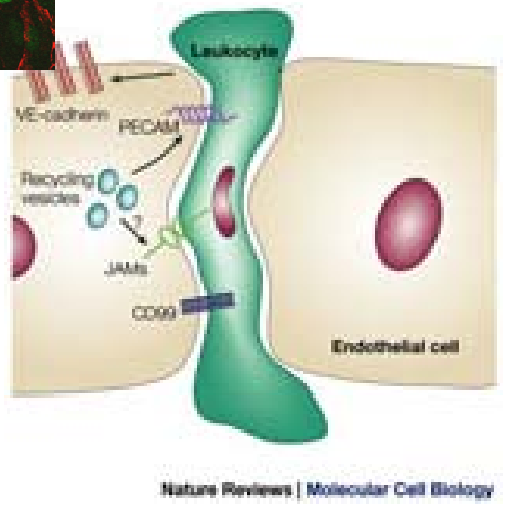




Endothelial junctions

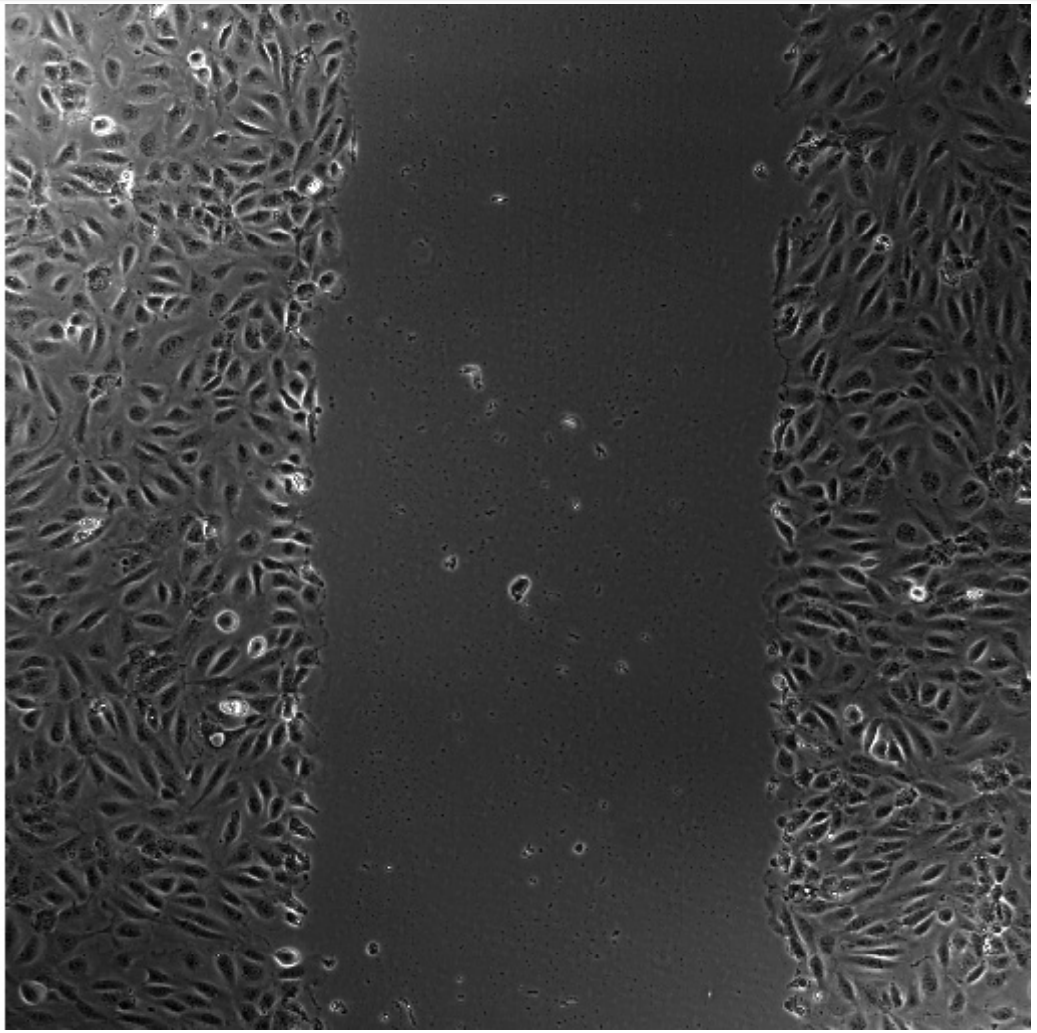






http://www.teaching.anhb.uwa.edu.au/mb140/MoreAbout/Endothel.htm

Endothelial junctions regulate contact inhibition



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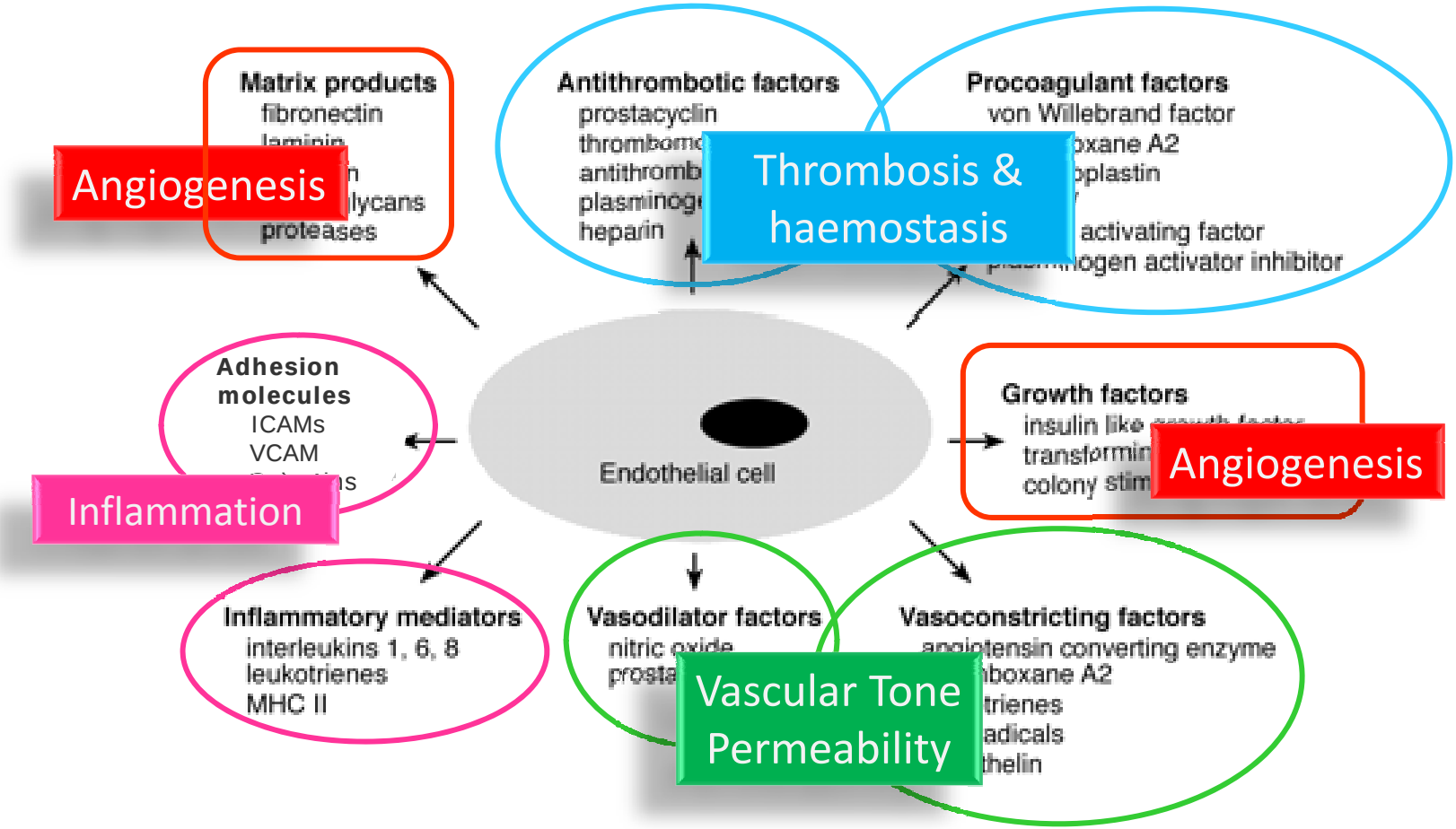
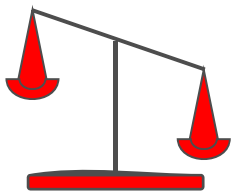
What do endothelial cells do?



Regulation of endothelial homeostasis

Resting endothelium

Anti-inflammatory
Anti-thrombotic
Anti-proliferative



Pro-inflammatory
Pro-thrombotic
Pro-angiogenic

Mechanical stress
Inflammation
High blood pressure
Viruses
OxLDL
Smoking
High glucose

Activated endothelium

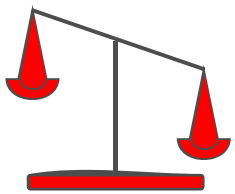
Thrombosis
Permeability
Senescence
Leukocyte recruitment

ATHEROSCLEROSIS

Regulation of endothelial homeostasis

Resting endothelium

Anti-inflammatory
Anti-thrombotic
Anti-proliferative



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Pro-thrombotic
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Mechanical stress
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High blood pressure
Viruses
OxLDL
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High glucose

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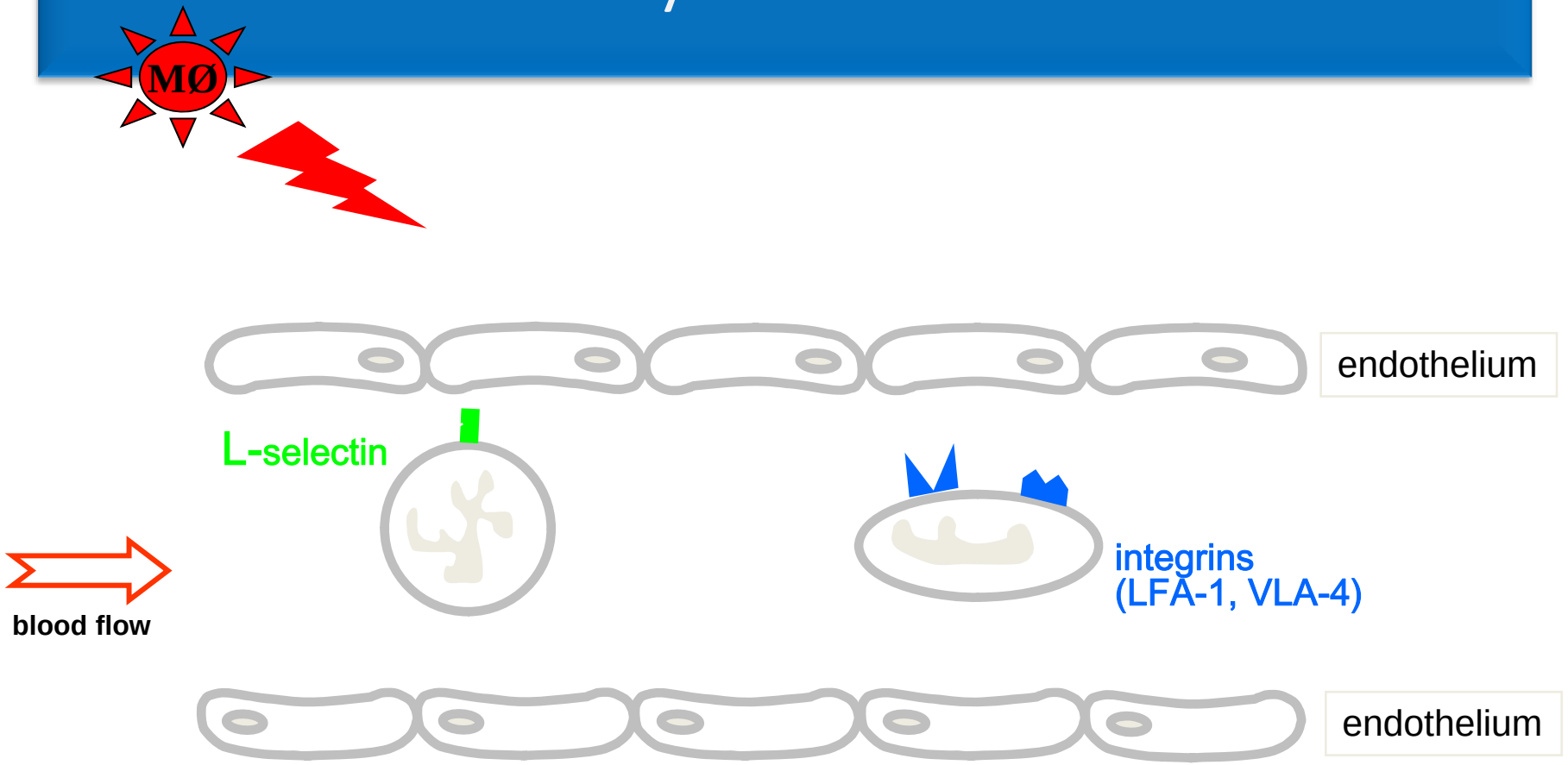
Senescence
Leukocyte recruitment

ATHEROSCLEROSIS

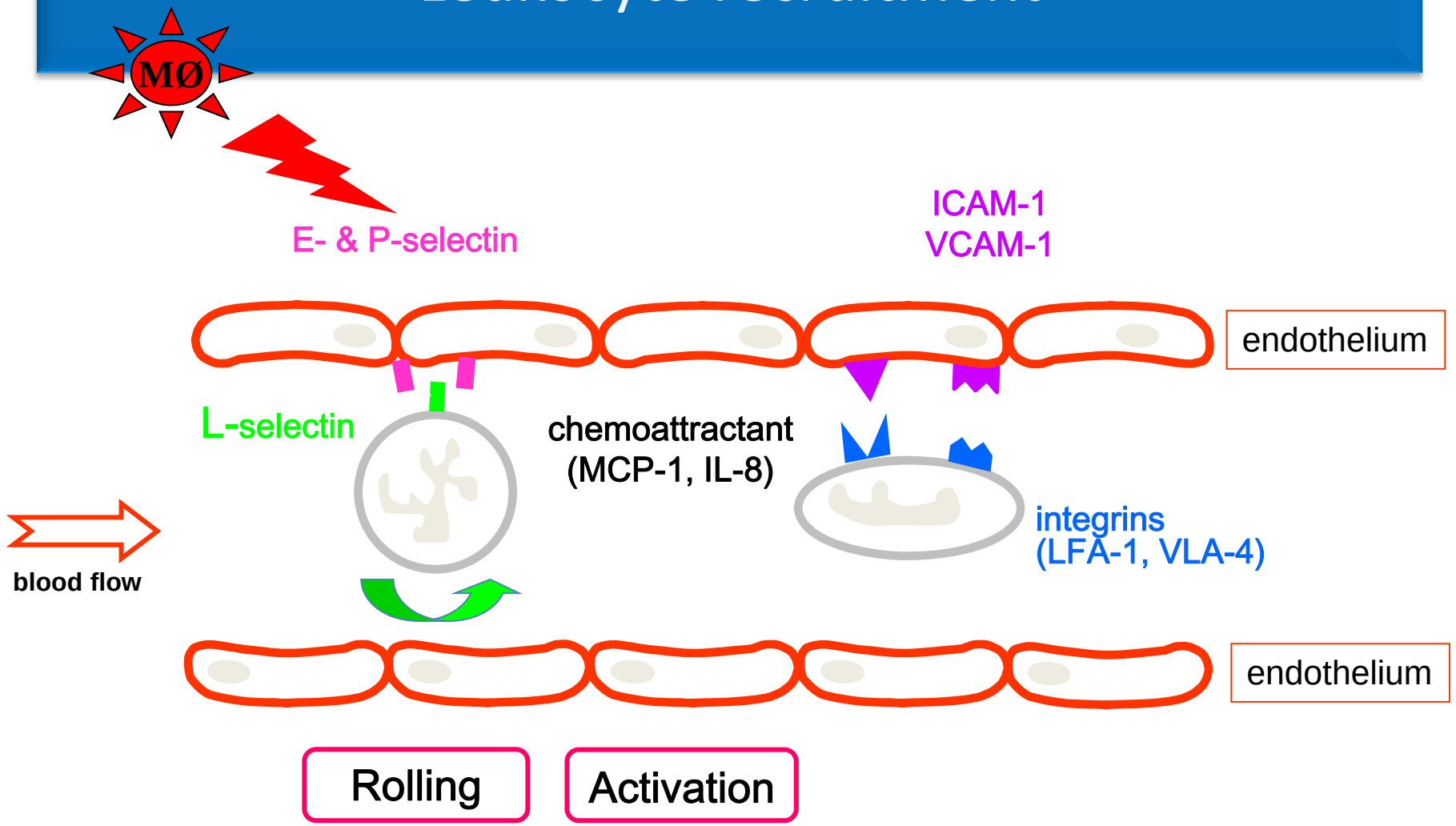
Endothelial dysfunction in atherosclerosis

1. leukocyte recruitment

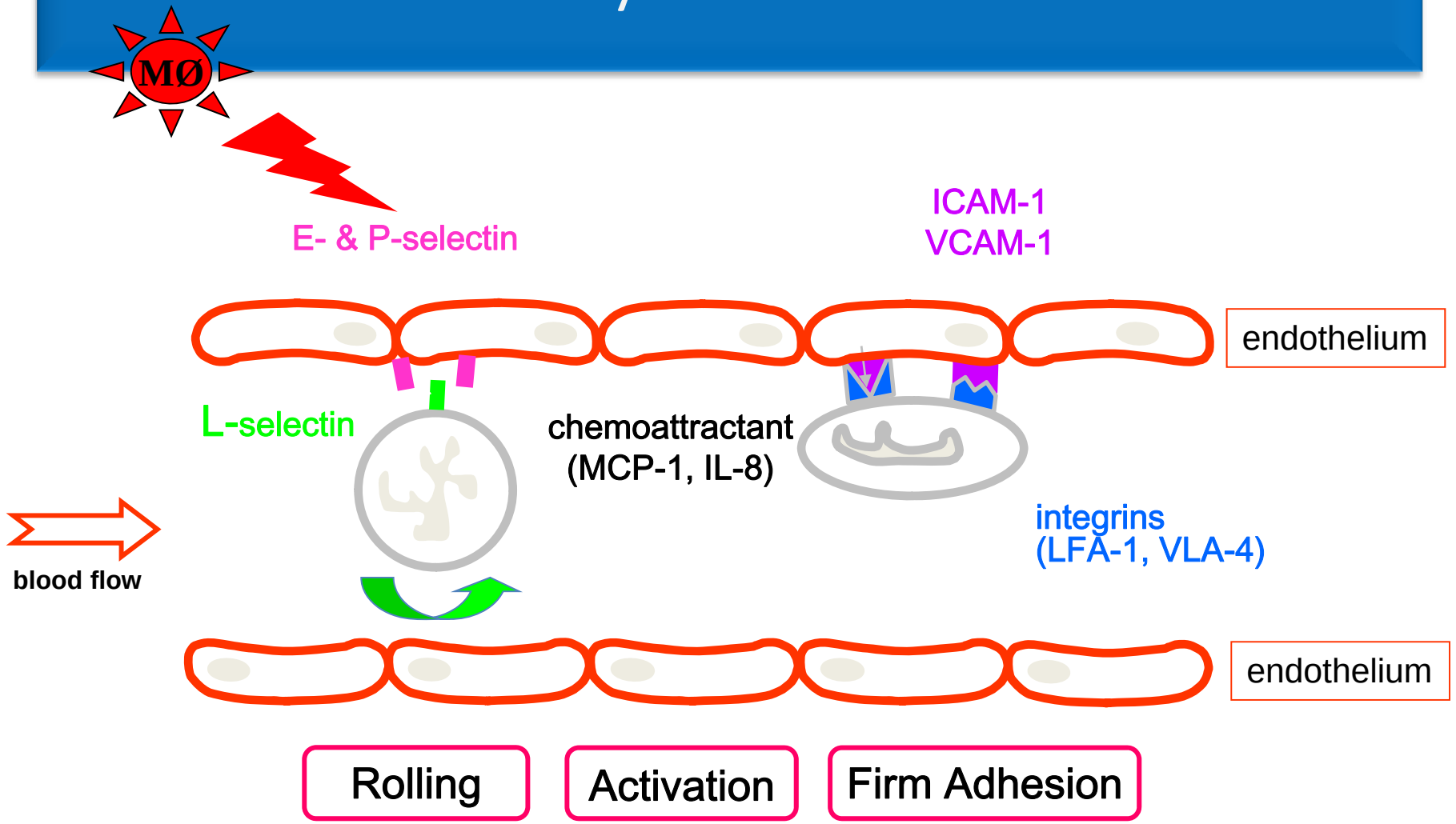
Leukocyte recruitment



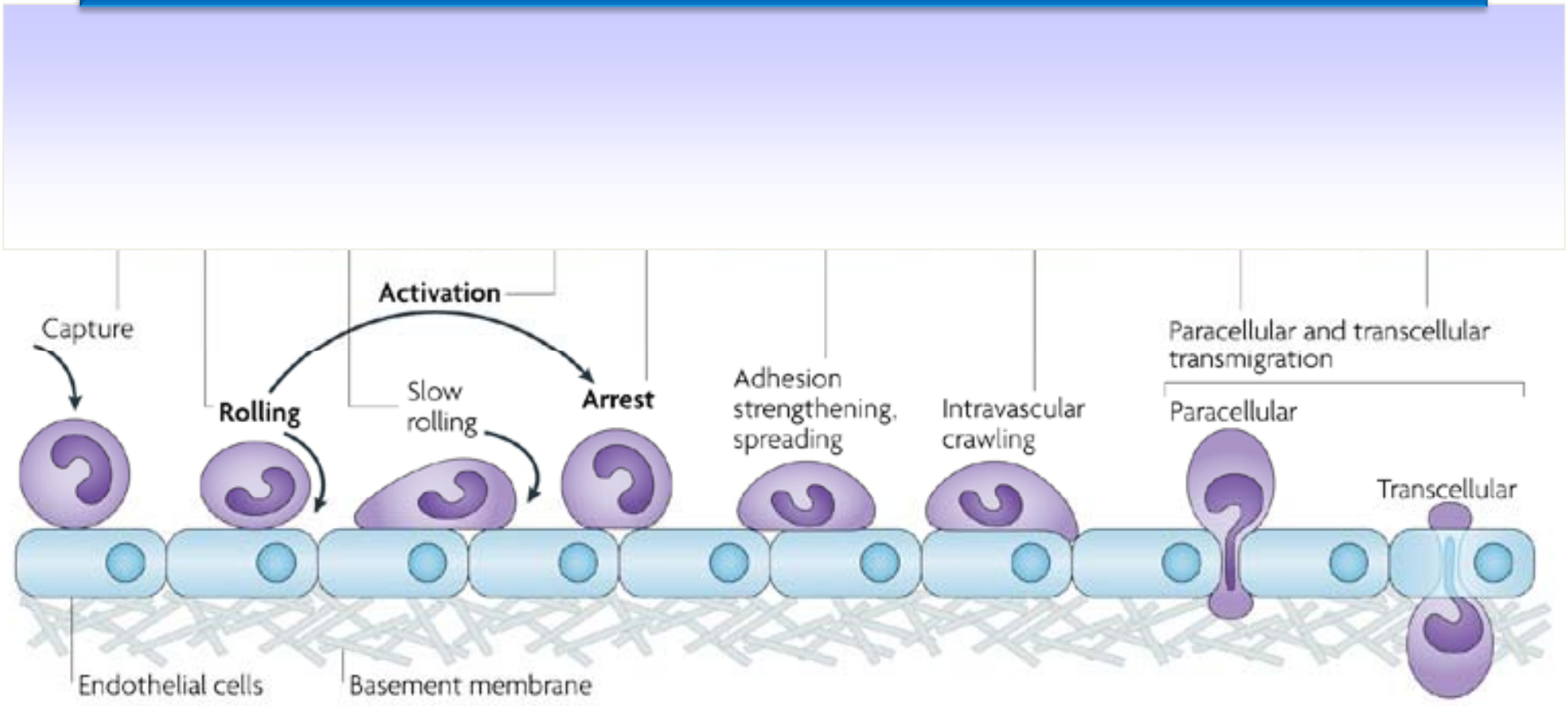
Leukocyte recruitment



Leukocyte recruitment



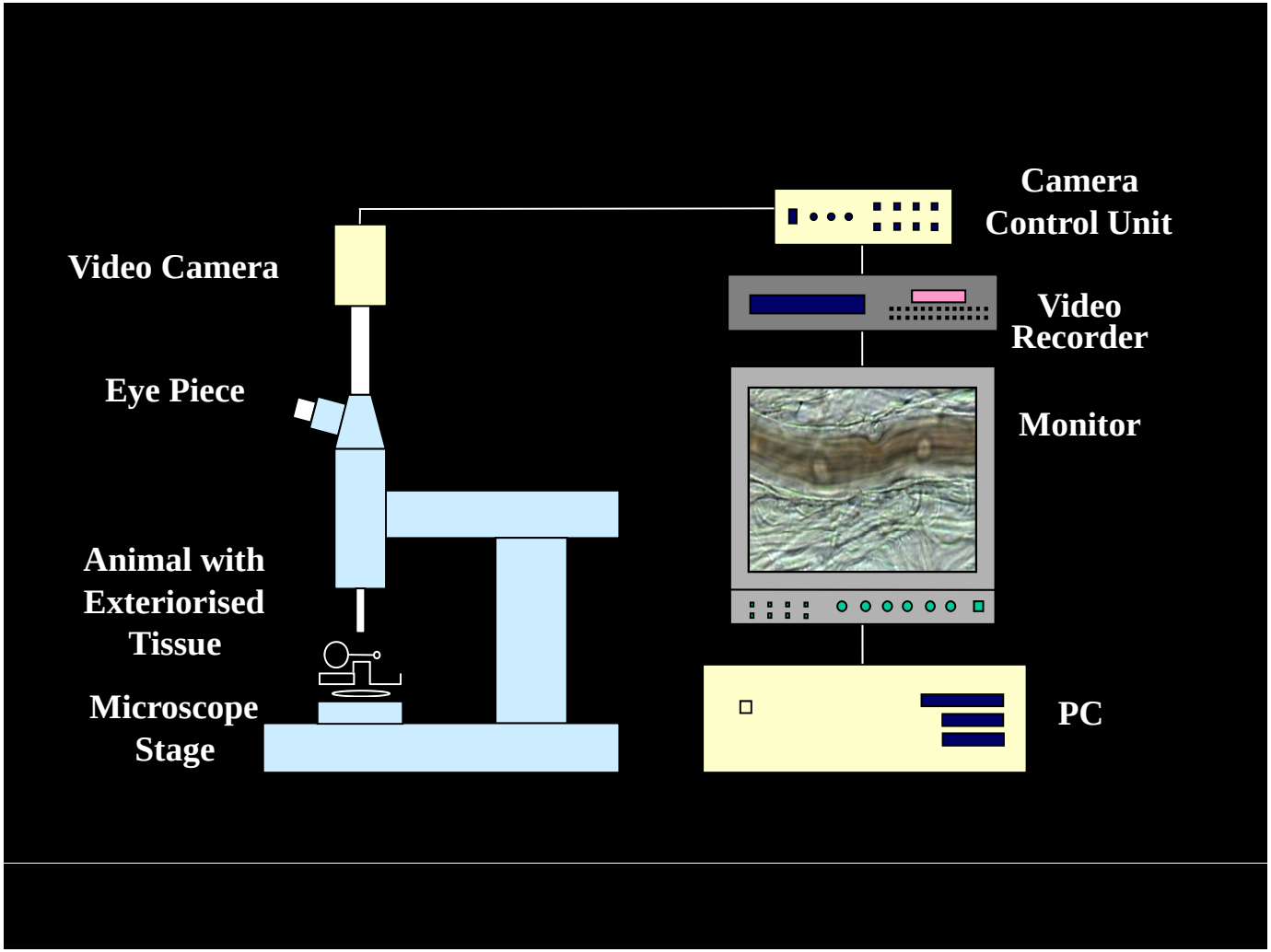
the leukocyte adhesion cascade



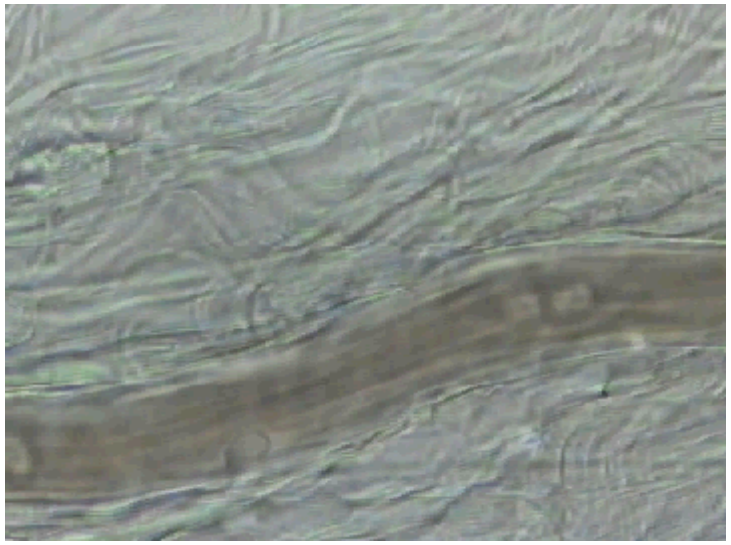
Nature Reviews | Immunology

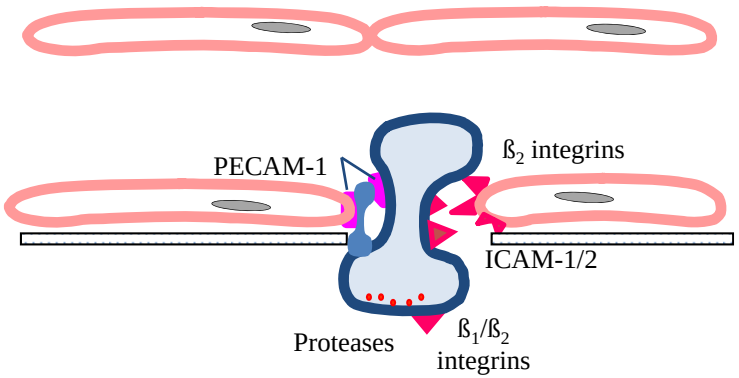
2007 Sep;7(9):678-89.

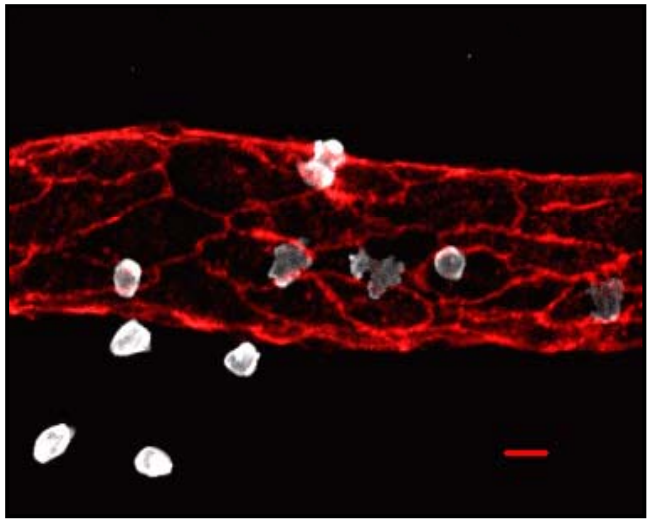
Intra-vital microscopy



Leukocyte rolling and adhesion in post-capillary venules







From Prof. S. Nourshargh , Queen Mary's & Barts, London

venules vs arteries

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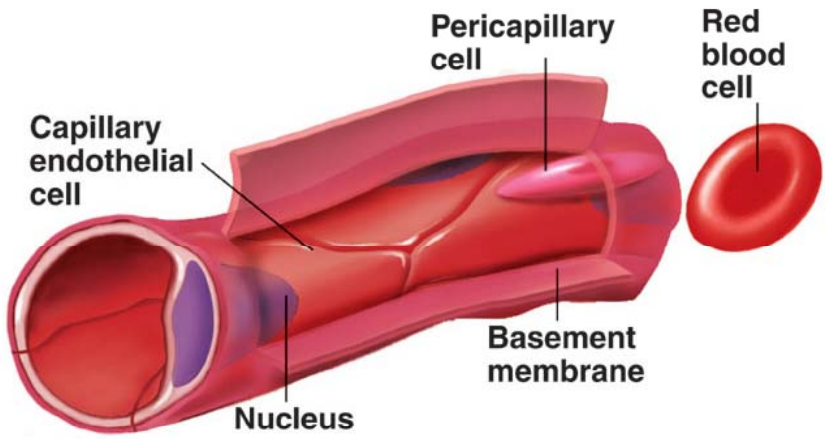

- Capillary: endothelial cells surrounded by basement membrane and pericapillary cells (perycites)
- Post-capillary venule: structure similar to capillaries but more pericytes

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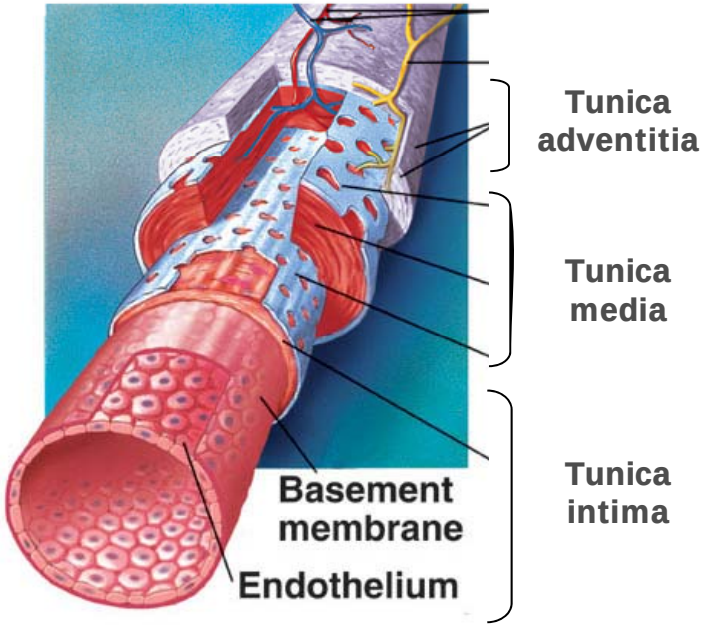
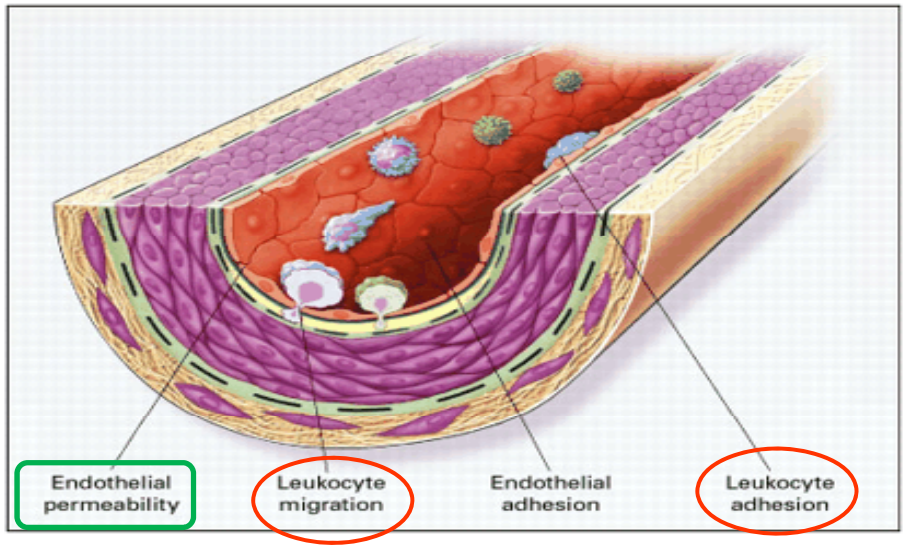


- Artery: three thick layers, rich in cells and extracellular matrix

Leukocyte recruitment in atherosclerosis

- Recruitment of blood leukocytes into tissues takes place normally during inflammation: leukocyte adhere to the endothelium of post-capillary venules and transmigrate into tissues
- In atherosclerosis, leukocytes adhere to activated endothelium of large arteries and get stuck in the subendothelial space
- Newly formed post-capillary venules at the base of developing lesions provide a further portal for leukocyte entry



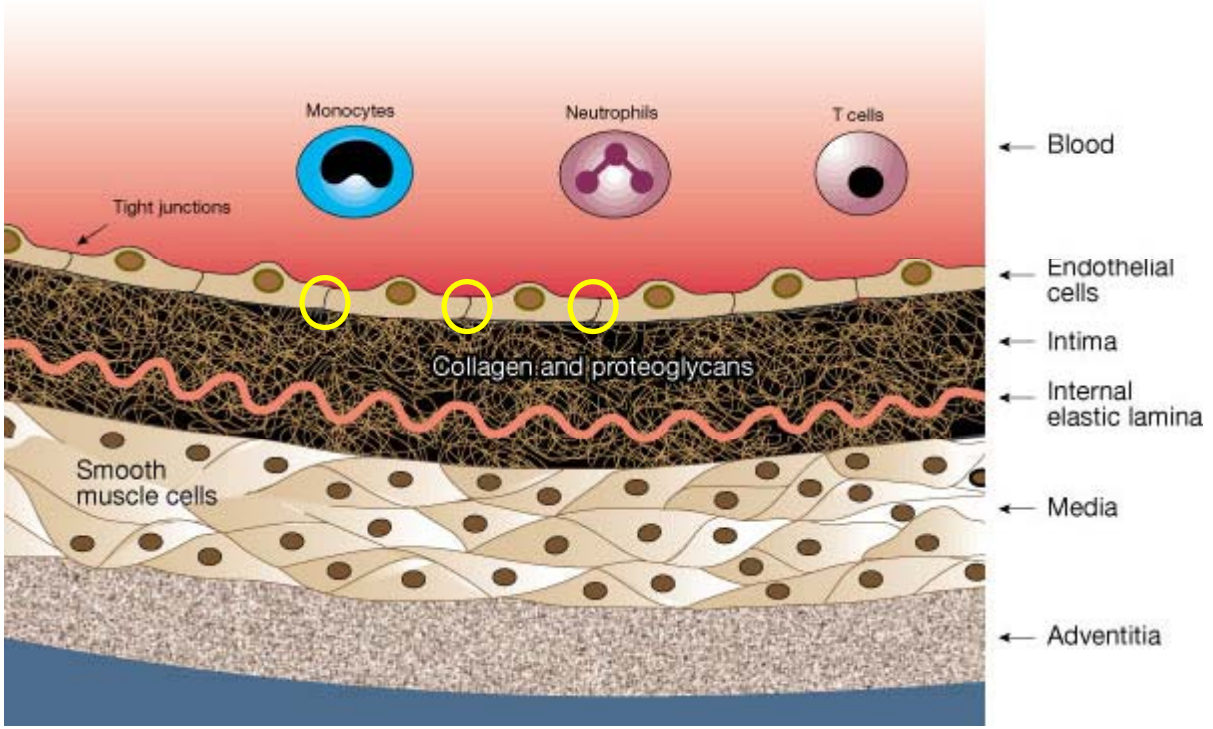
Monocytes migrated into the subendothelial space differentiate into macrophages

Endothelial dysfunction in atherosclerosis

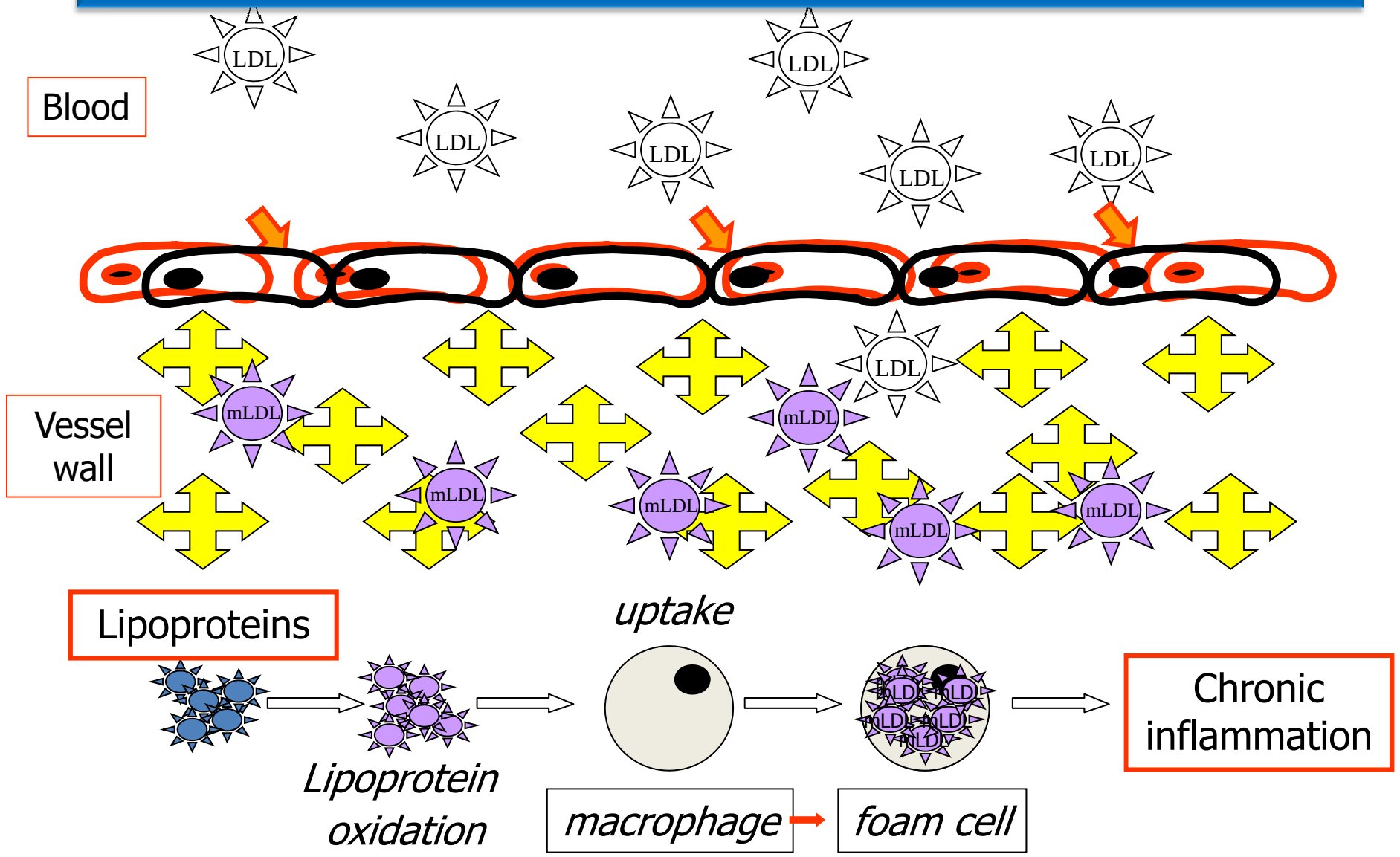
2. permeability

Vascular Permeability

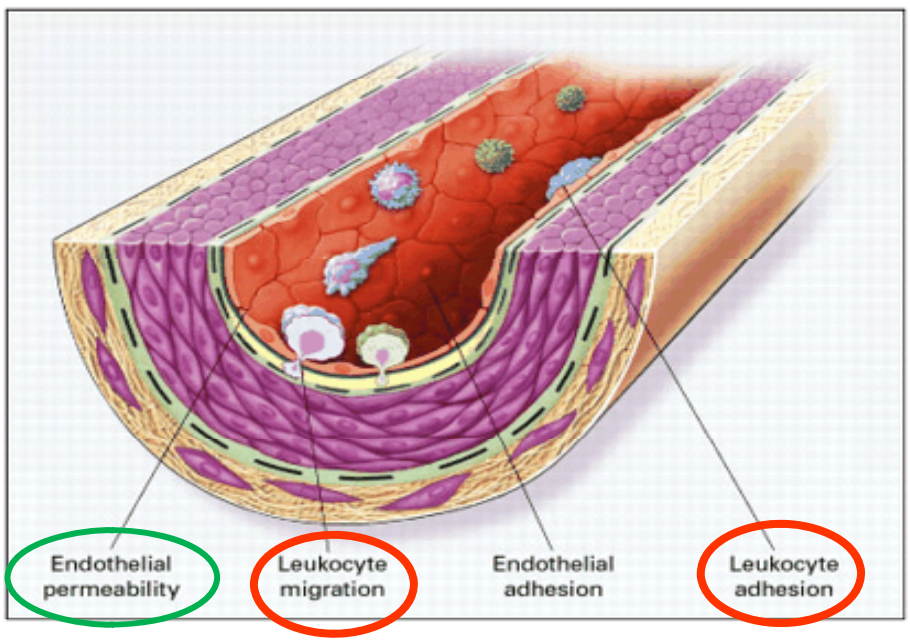
- The endothelium regulates the flux of fluids and molecules from blood to tissues and vice versa
- Increased permeability results in leakage of plasma proteins through the junctions into the subendothelial space



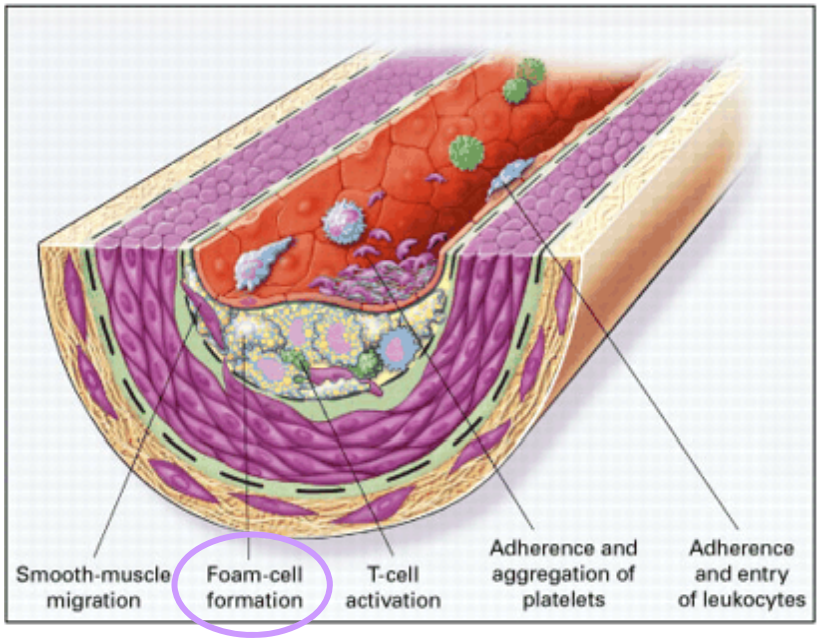
Lipoprotein trapping and oxidative modification



Pathogenesis of Atherosclerosis: Inflammation Model



1. Endothelial Dysfunction in Atherosclerosis



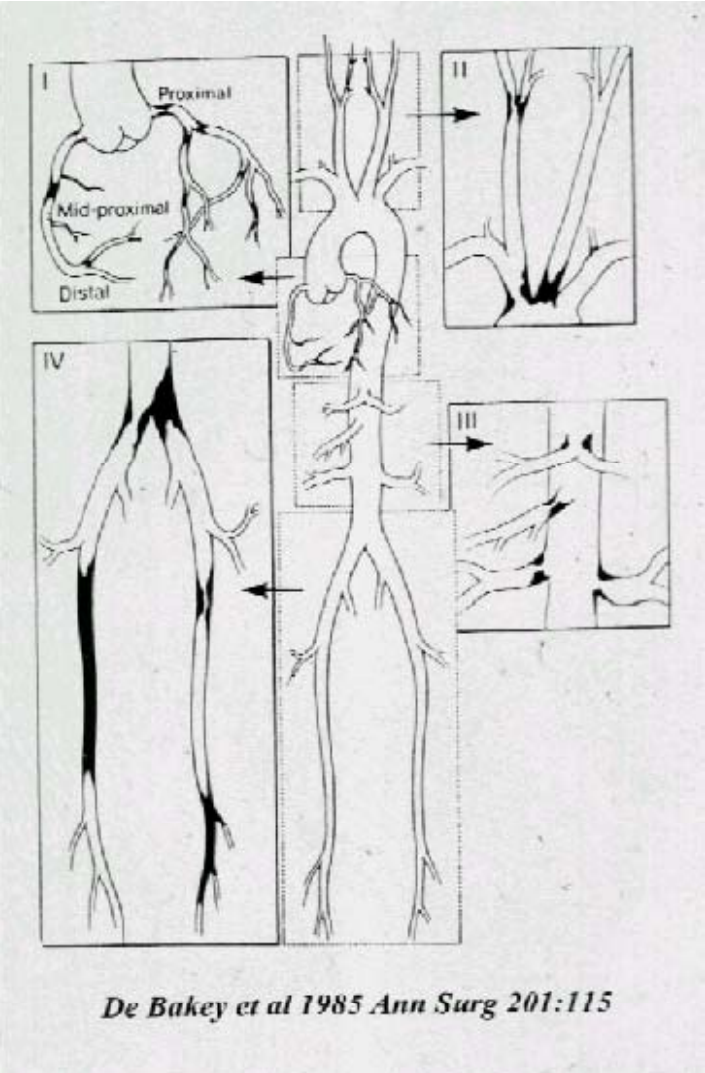
2. Fatty-Streak Formation in Atherosclerosis

from Ross, R. Nature. 1993;362:801

Endothelial dysfunction in atherosclerosis

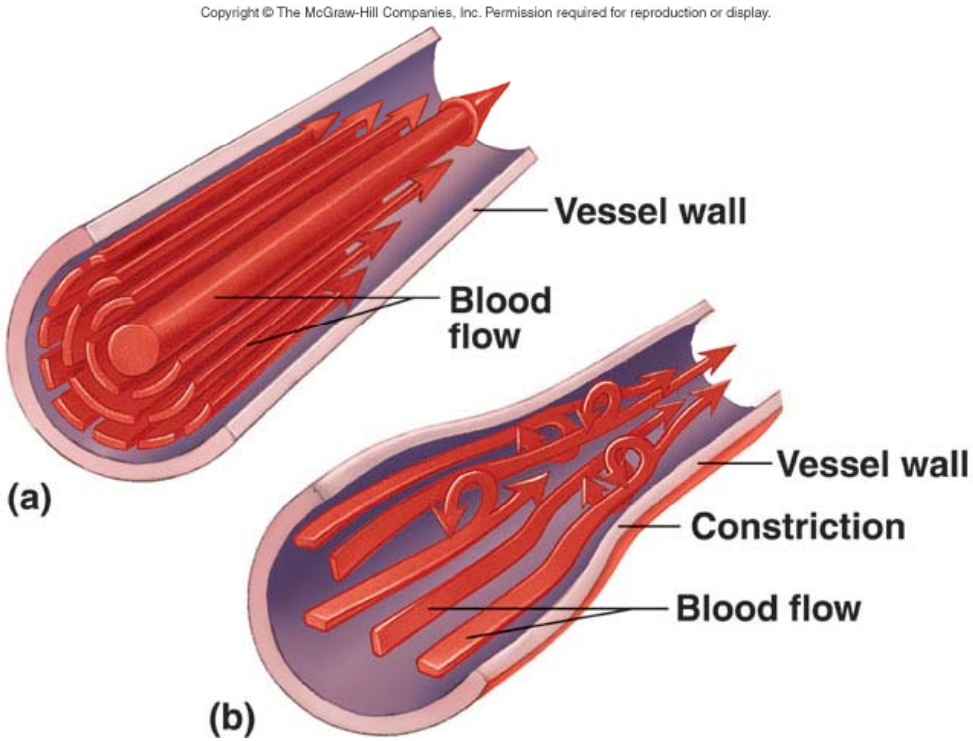
3. blood flow

Why does atherosclerosis occur at branch points ?



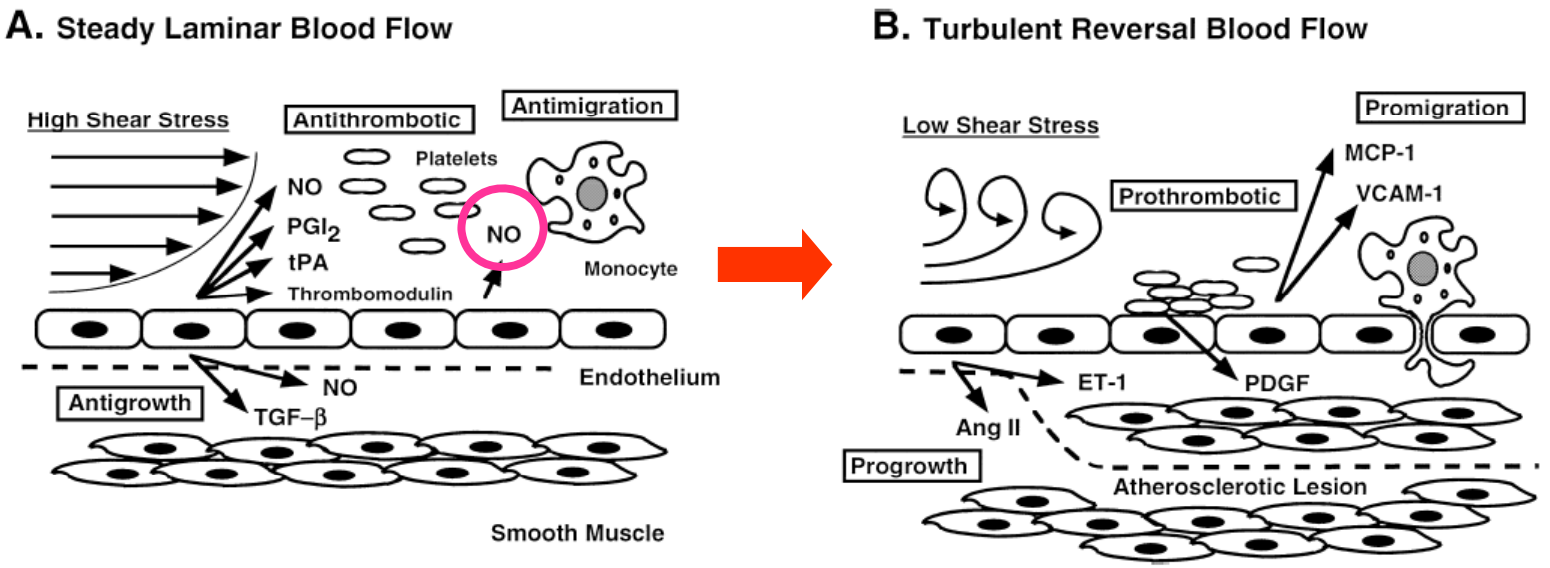
De Bakey et al 1985 Ann Surg 201:115

Laminar and Disturbed Flow



- Laminar flow
  - Streamlined
  - Outermost layer moving slowest and center moving fastest
- Disturbed flow
  - Interrupted
  - Rate of flow exceeds critical velocity
  - Fluid passes a constriction, sharp turn, rough surface

Endothelium and Blood Flow



Laminar blood flow promotes:

- Nitric oxide production
- factors that inhibit coagulation, leukocyte adhesion, SMC proliferation
- endothelial survival

Disturbed blood flow promotes:

- coagulation, leukocyte adhesion, SMC proliferation
- endothelial apoptosis

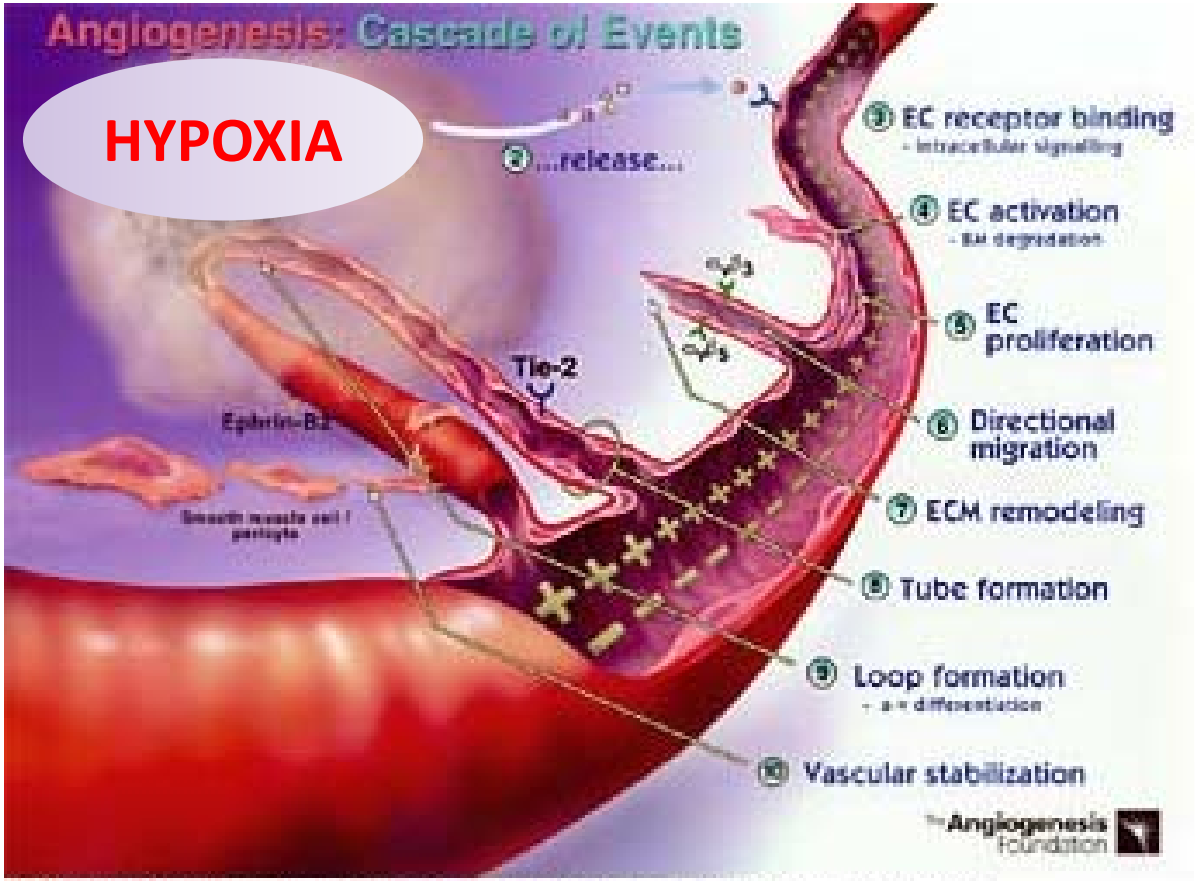
From J. Pharmacol Sci 91:172;2003

Endothelial dysfunction in atherosclerosis

4. angiogenesis

ANGIOGENESIS

Formation of new blood vessels by sprouting from pre-existing vessels



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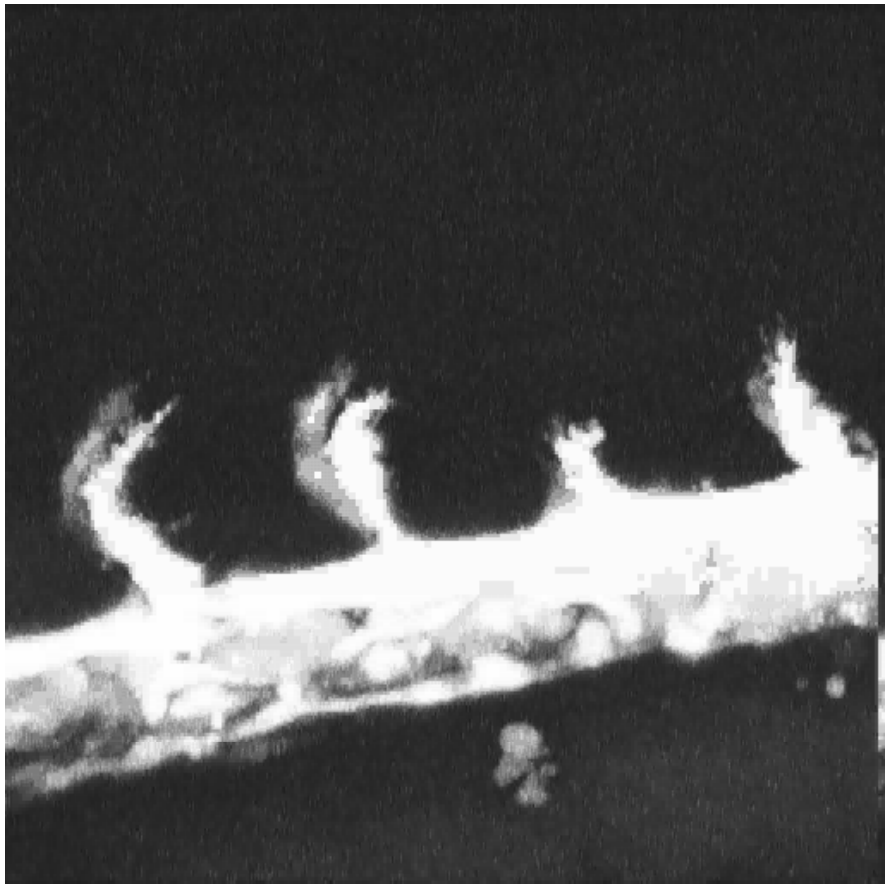
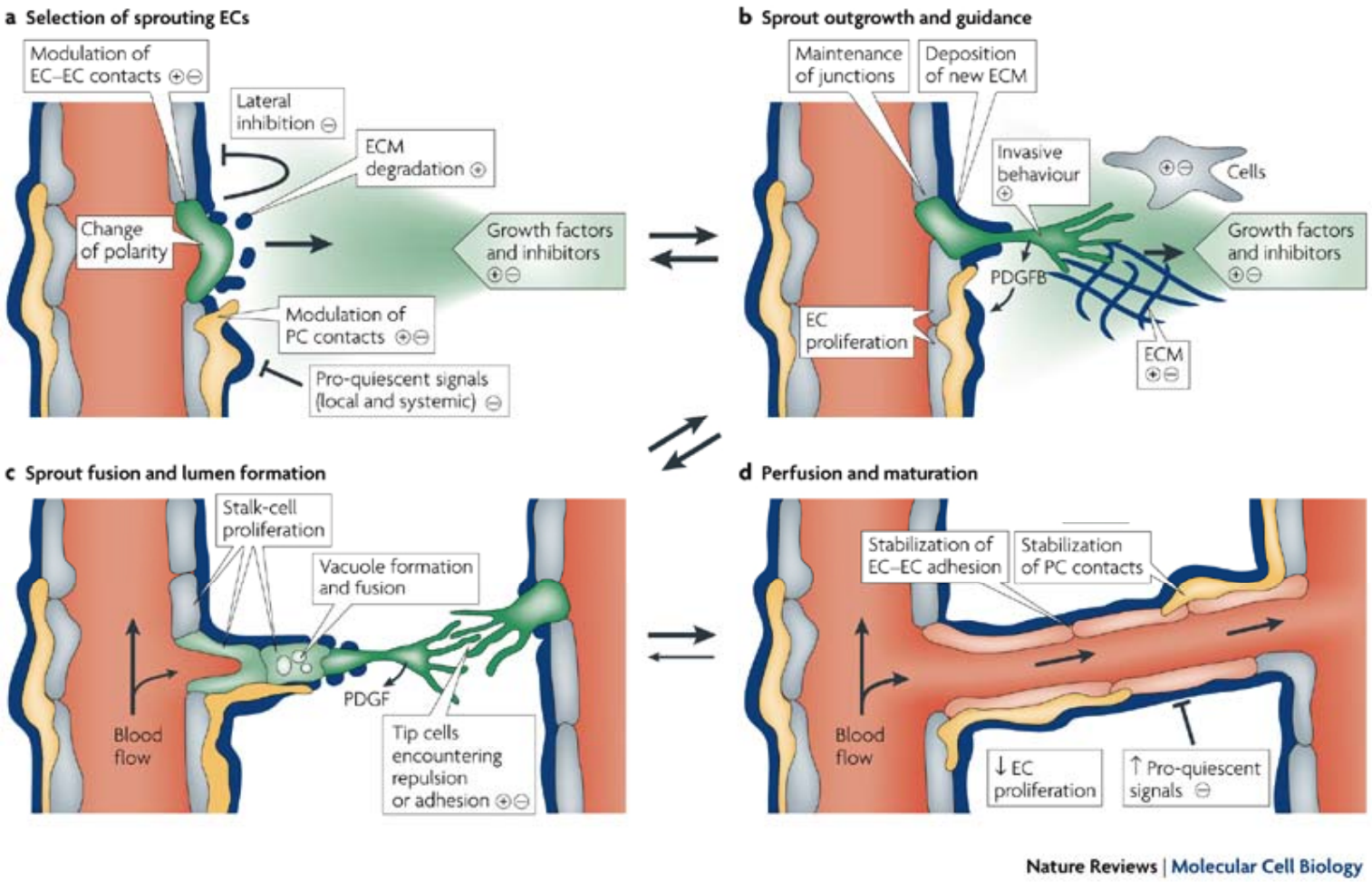
Angiogenesis live



Video from Brant Weinstein, NIH

http://www.youtube.com/watch?v=7YgwJeVEgvU&feature=related

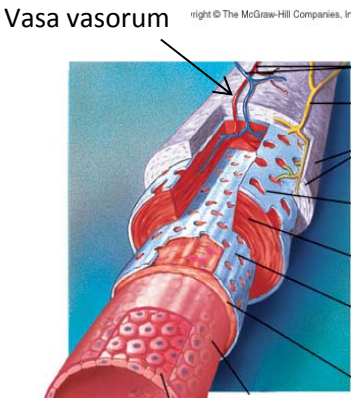
Angiogenesis

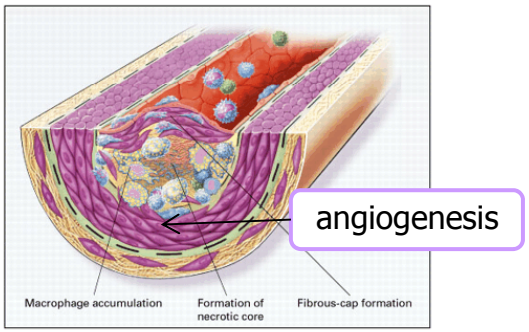


Adams & Alitalo, Nat Rev Mol Cell Biol. 2007 Jun;8(6):464-78

Angiogenesis and cardiovascular disease

Angiogenesis promotes plaque growth

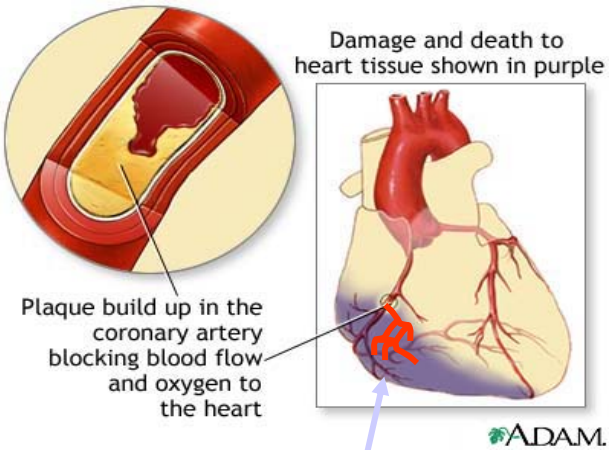




The Janus paradox

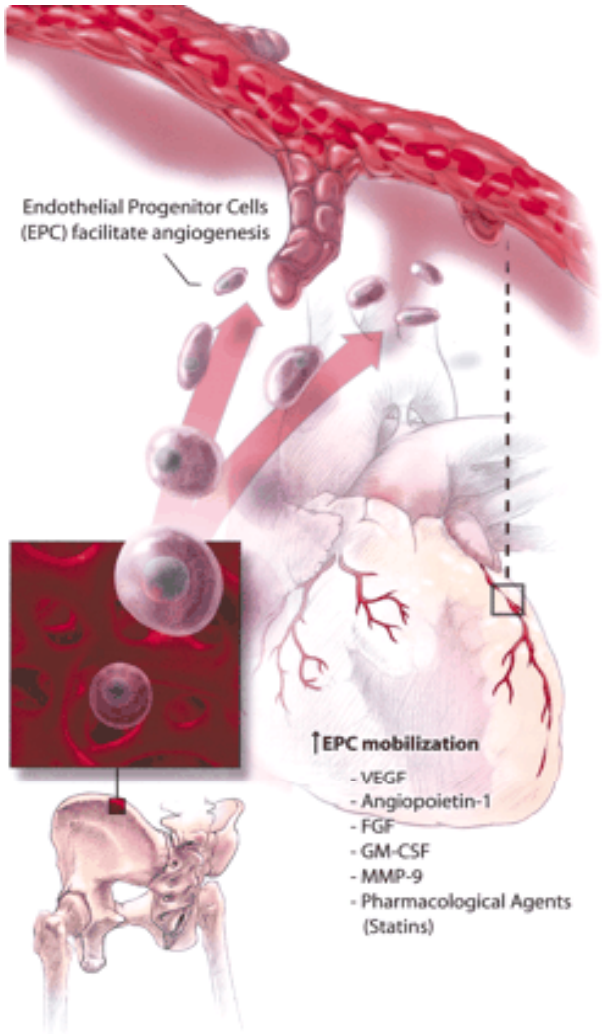
Janus:
roman God of gates, doors, beginnings (January)
Looking on opposite directions, two-faced

Therapeutic angiogenesis prevents damage post-ischemia



Deliver growth factors/stem cells to the ischemic heart region to induce new vessel growth

Endothelial Progenitor Cells, Angiogenesis and Vascular Homeostasis



Szmitko et al, Circulation. 2003;107:3093

- Endothelial Progenitor Cells (EPC): circulating bone marrow (BM)-derived CD34+ stem cells, of haematopoietic lineage, which can differentiate into mature endothelial cells
- EPC mobilisation from the BM may be triggered by ischemia, pro-angiogenic growth factors, statins
- Circulating EPC migrate and home to sites of ischemia and contribute to re-endothelialization and angiogenesis
- Two (or more) types of bone-marrow progenitors:
  - PAC: Pro-Angiogenic Cells
  - Endothelial progenitors
- *But: identity of EPC and their real role in angiogenesis is controversial*

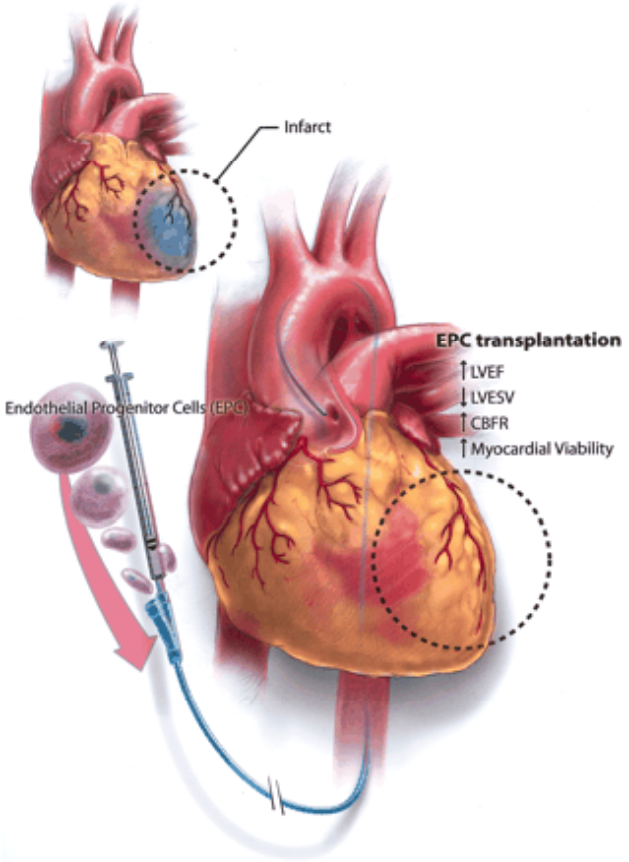
Bone marrow-derived progenitors for therapeutic angiogenesis in CV disease

- Injection of autologous EPC or other progenitors at sites of ischemia in patients with ischemic heart disease/MI : improvement in heart function *(Circulation 2002;106:3009)*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2006 VOL. 355 NO. 12

Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction



<u>Update at 2012:</u>

- Thirty-three randomised clinical trials (1765 participants)
- high degree of heterogeneity
- moderate improvement in global heart function is significant and sustained long-term

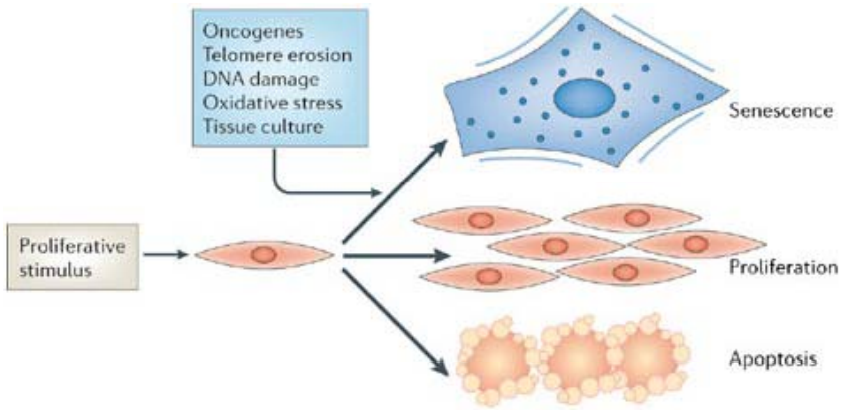
Rev in : Clifford DM et al. Stem cell treatment for acute myocardial infarction. Cochrane Database Syst Rev 2012; 2

Endothelial dysfunction in atherosclerosis

5. senescence

Cellular senescence

- Replicative senescence: the limited proliferative capacity of human cells in culture
- Senescence as response to stress and damage : locks cells in a permanent form of growth arrest
- Linked to progressive shortening and dysfunction of telomeres (ends of chromosomes)
- Senescent cells have distinctive morphology and acquire specific markers, e.g. β-gal



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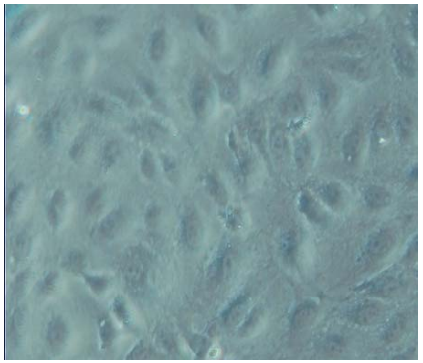
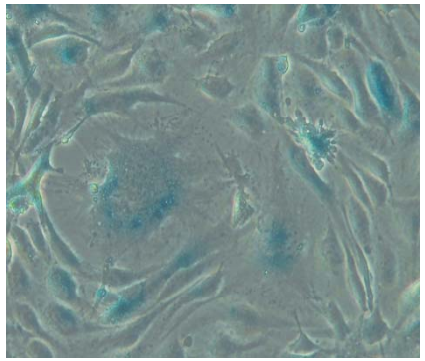
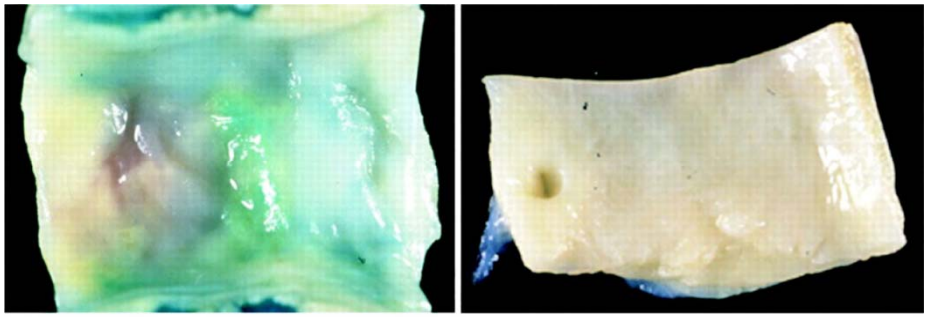




Atherosclerosis and endothelial senescence

SA {beta}-gal-positive vascular cells in human atheroma



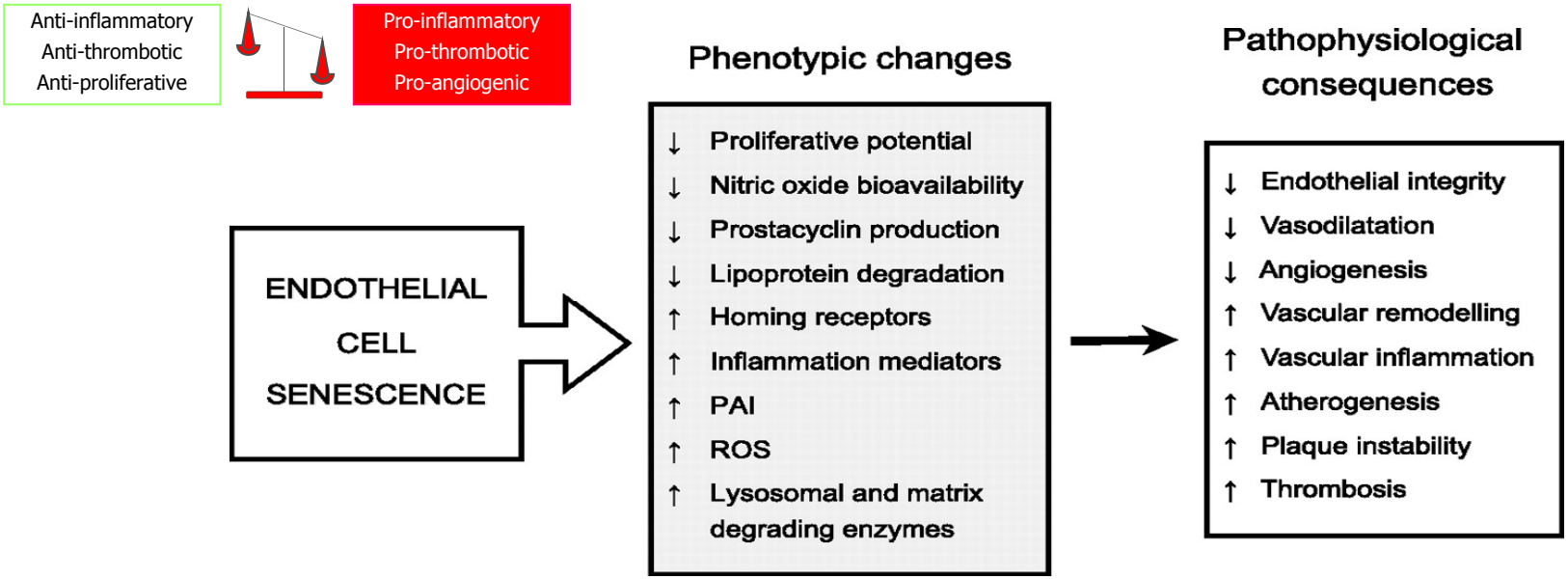
CA **IMA**

- Atherosclerotic lesions: vascular cells with morphological features of senescence *(Burrig KF et al, Arterioscler Thromb 1991)*

- Senescent-associated β-gal activity in human coronary arteries *(Minamino T et al, Circulation Research 2007)*

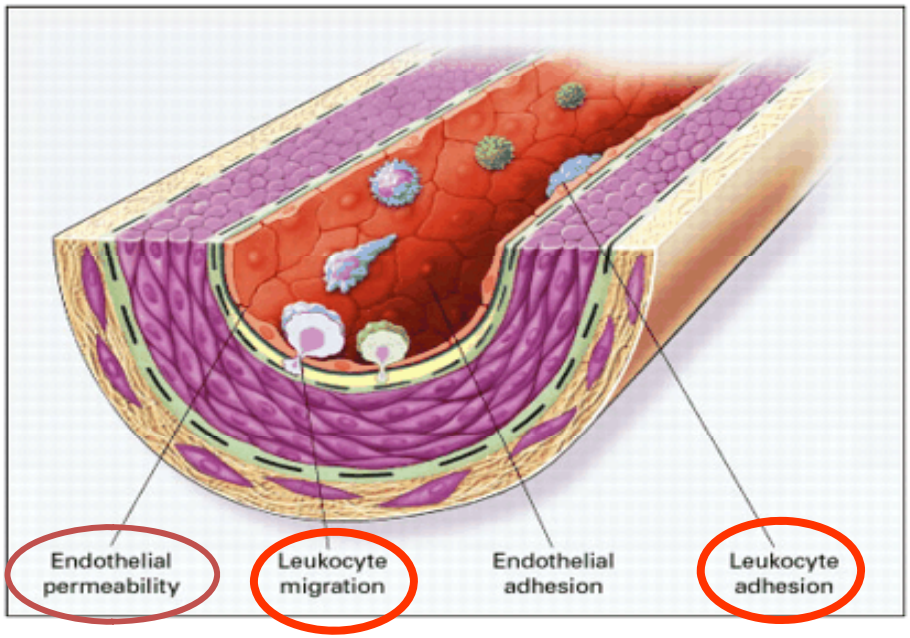
Endothelial senescence: consequences for vascular function

- Endothelial cell senescence can be induced by CV risk factors, such as oxidative stress, that promote increased cell replication to replace dead or damaged cells
- These changes result in a pro-inflammatory, pro-atherosclerotic and prothrombotic phenotype



Erusalimsky, J Appl Physiol 106: 326-332 2009

Pathogenesis of Atherosclerosis: Inflammation Model



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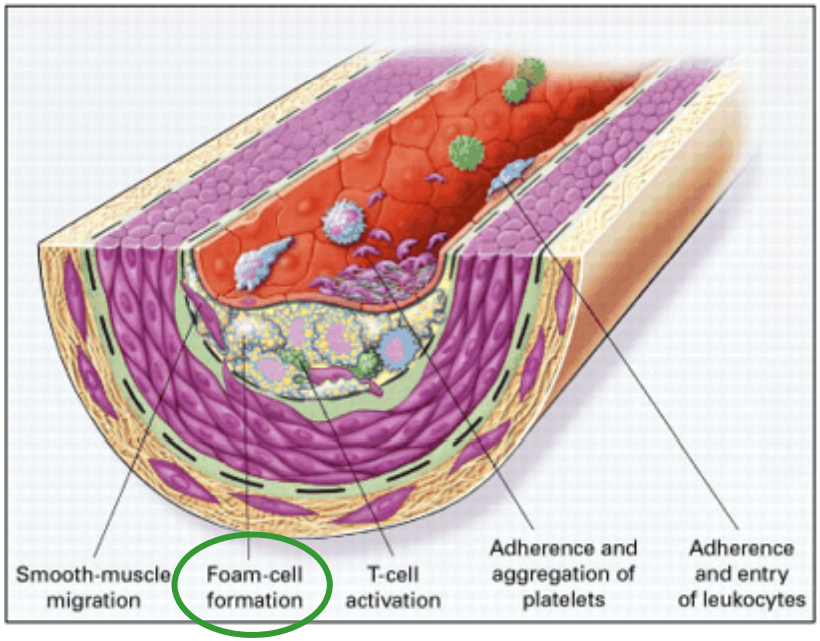

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from Ross, R. Nature. 1993;362:801

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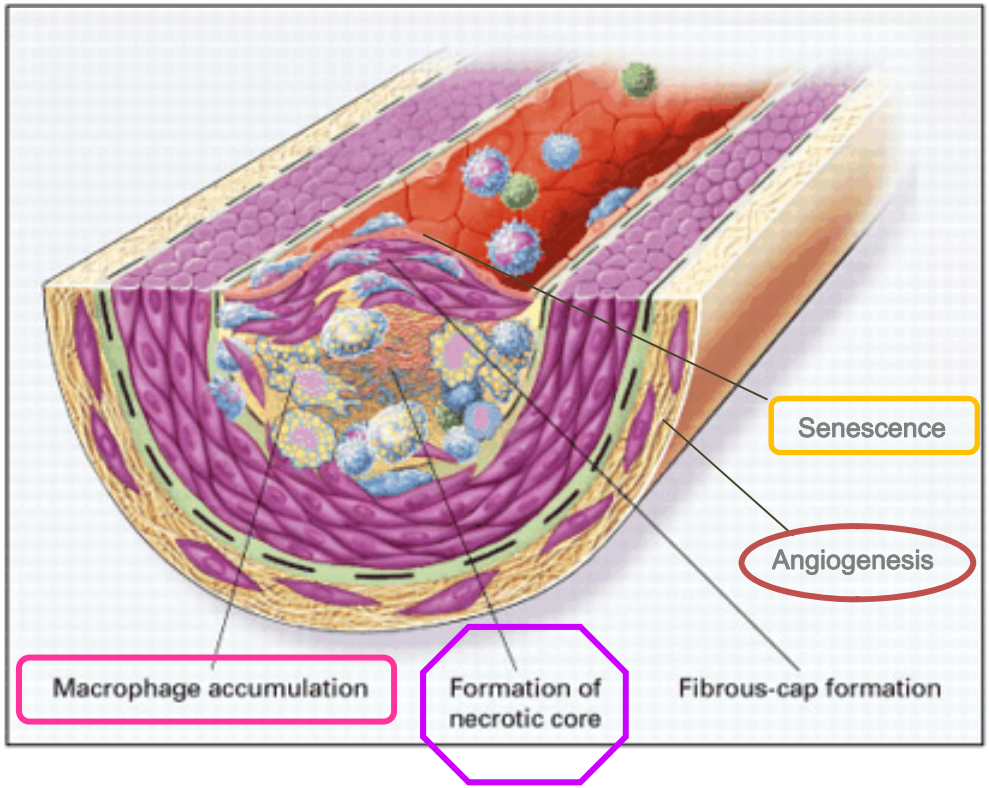
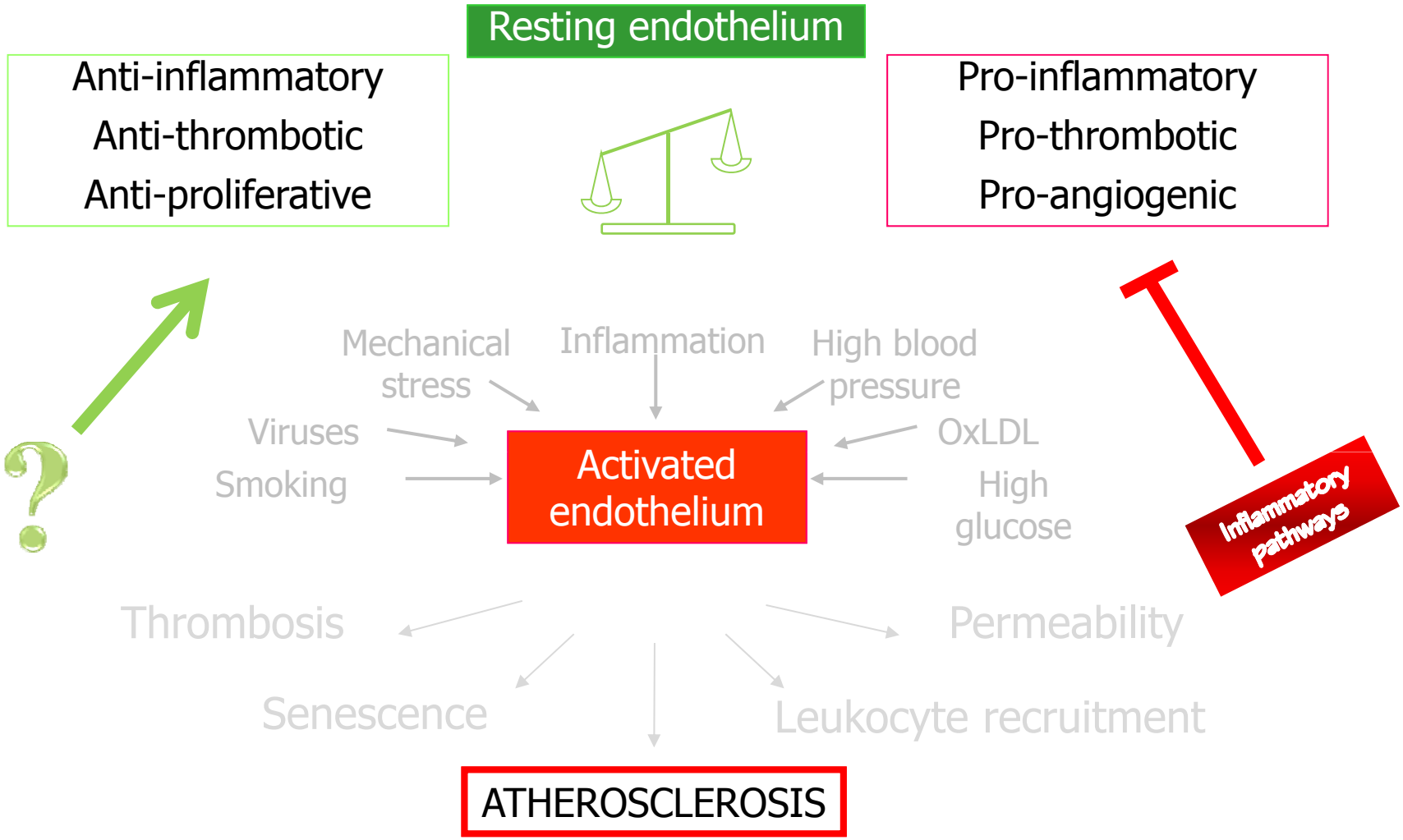


3. Formation of an Advanced, Complicated Lesion of Atherosclerosis

from Ross, R. Nature. 1993;362:801

How to protect the endothelium and prevent atherosclerosis?



The French Paradox

Male death rates for CAD - 1990

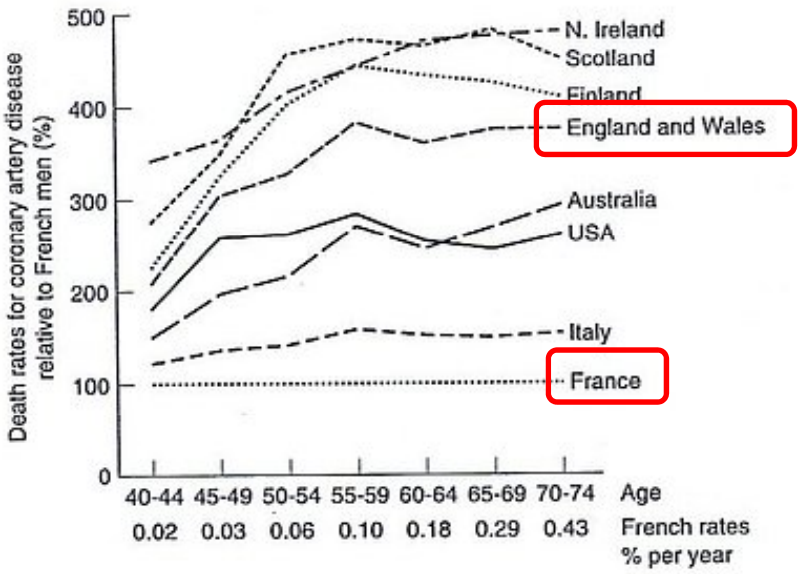


FIGURE 22.1 French paradox: red wine and CAD. Age-specific male death rates in 1990 for CAD, in comparison to France (100%). The French death rates due to CAD (% per year) are given by age group. In 1990 the death rate at all ages was the lowest in France.

(Balkau et al, Ann Epidemiol 1997)

"..... Taken together with the fact that the French consume a far larger amount of red wine than people from other countries, these data support the beneficial effect of red wine in the prevention of atherosclerosis and its complication" (Balkau et al, Ann Epidemiol 1997)

Does diet or alcohol explain the French paradox? Lancet. 1994 ;344:1719-23

The cardiovascular benefits of red wine and Resveratrol

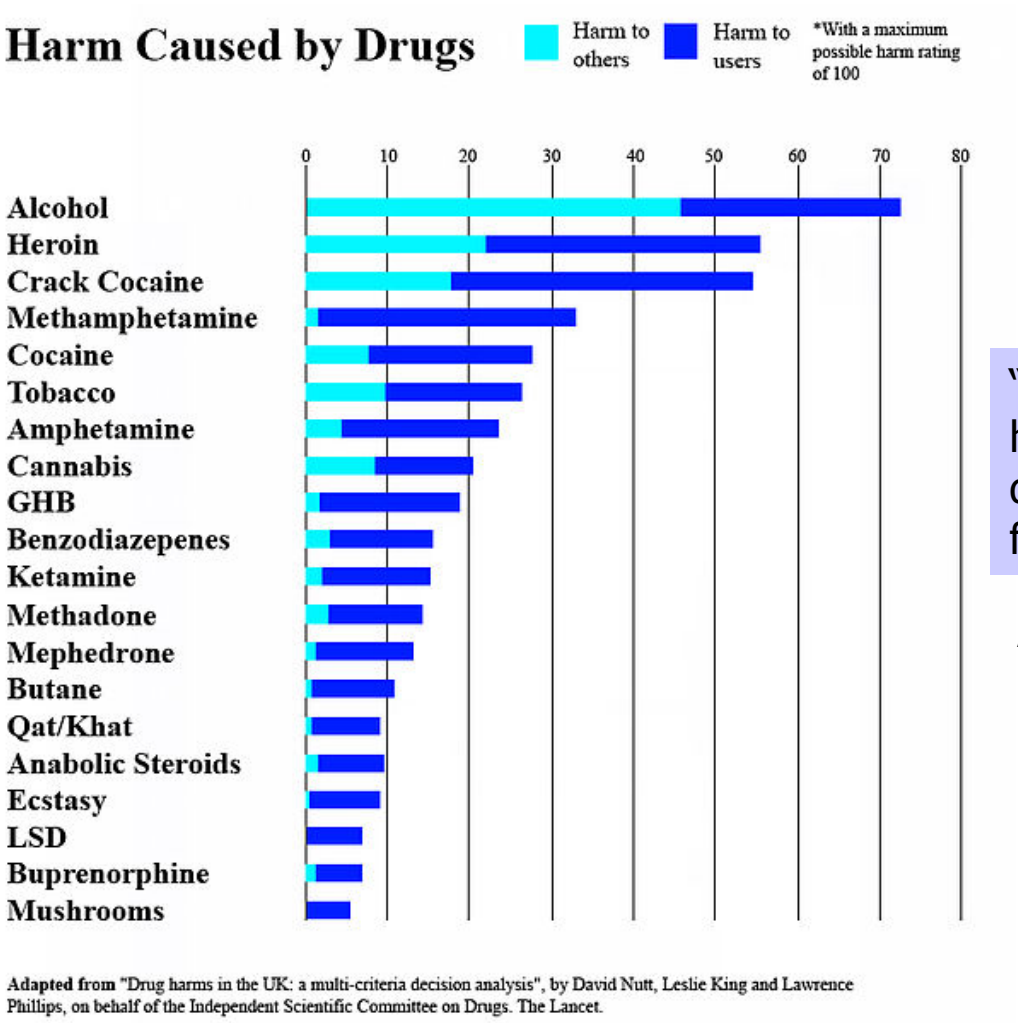
In vitro and Animal models

- Resveratrol promotes endothelail protective pathways (eNOS) (Wallerath Circ 2002)
- Resveratrol acts as an anti-aging compound and reduces vascular cell senescence (Tang, J Nutr Biochem. 2012)

Humans

- Red Wine prevents pro-inflammatory changes induced by a high fat meal in leukocytes (Blanco-Colio, Circulation, 2000)
- Red Wine Consumption Increases Circulating Endothelial Progenitor Cells and Improves Endothelial Function in Obese Type II Diabetics (Seck, Circulation 2007)
- Resveratrol, like other toxins, has an hormetic (i.e. dose-response) action:
  - beneficial effects at **lower** doses
  - cytotoxic effects at **higher** doses

The problem with alcohol.....



Adapted from "Drug harms in the UK: a multi-criteria decision analysis", by David Nutt, Leslie King and Lawrence Phillips, on behalf of the Independent Scientific Committee on Drugs. The Lancet.

"...alcohol ... is by far the most harmful; not only is it the most damaging to societies, it is also the fourth most dangerous for the user."

David Nutt, Lancet November 2011

The vascular endothelium in atherosclerosis

After this lecture you should understand:

- The importance of vascular endothelium for the health of blood vessels
- The importance of vascular endothelium in the development of atherosclerosis
  - Regulation of permeability and leukocyte recruitment
  - Endothelial *aging:* cell senescence in atherosclerosis
  - Pro and cons of angiogenesis in atherosclerosis