Getting small blood cells through small gaps; what could go wrong?

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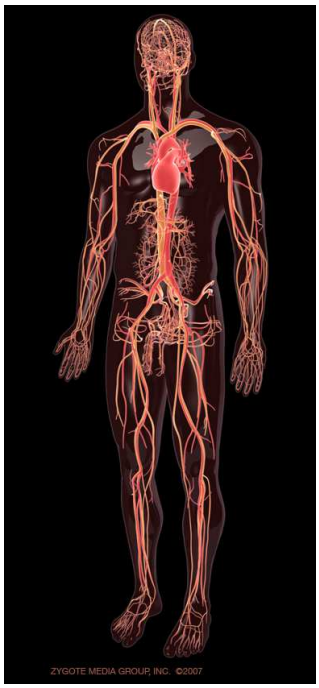
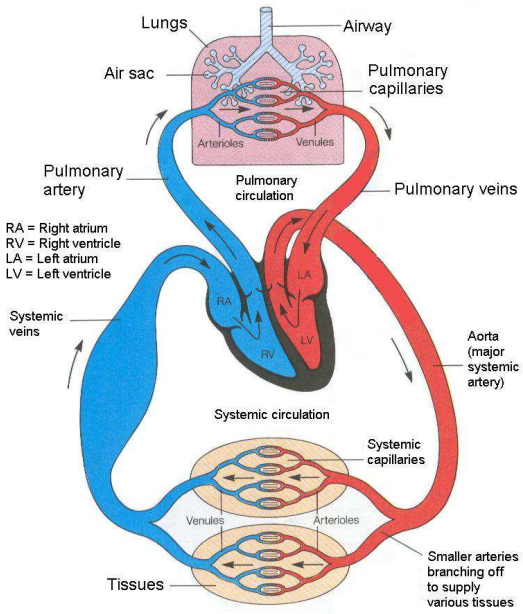
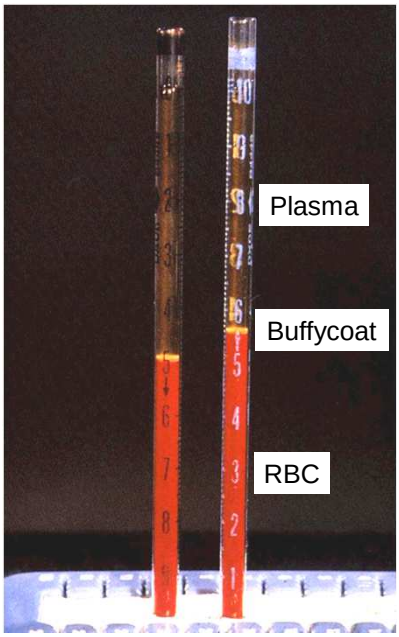
THE UNIVERSITY OF BIRMINGHAM
Centenary 2000



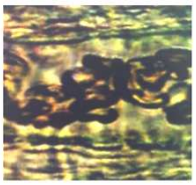
The pumbing (dual circuit)

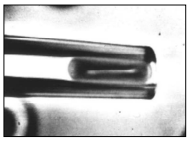


Blood - the 'liquid'

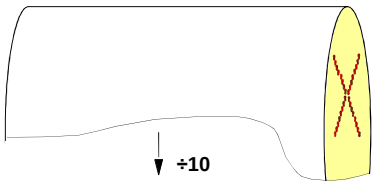


Getting the blood around the circulation: different properties affect flow in different vessels



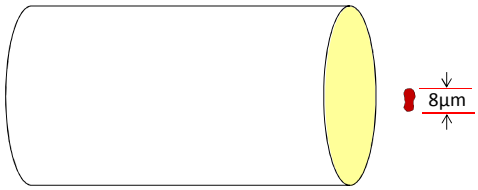


Small artery (~mm)



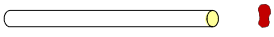
÷10

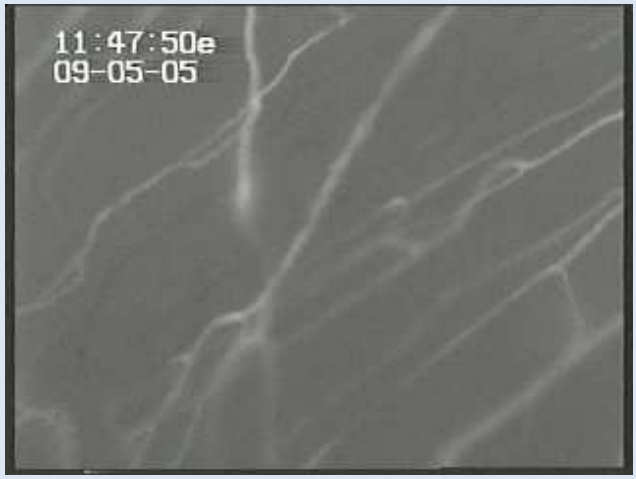
Arteriole (~100µm)



÷10

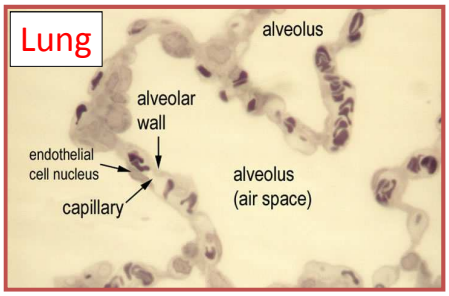
Capillary (<10µm)



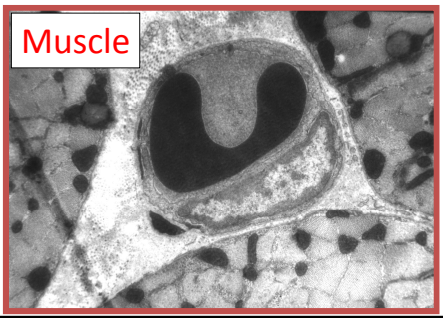


……. getting small cells through small gaps

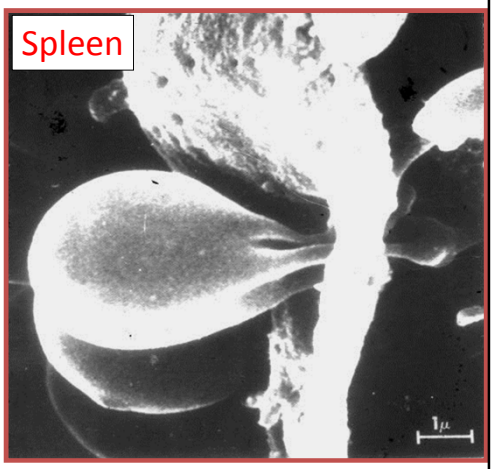
Lung

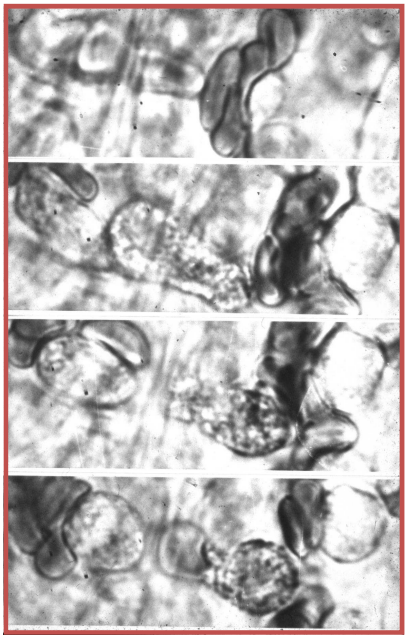


Muscle



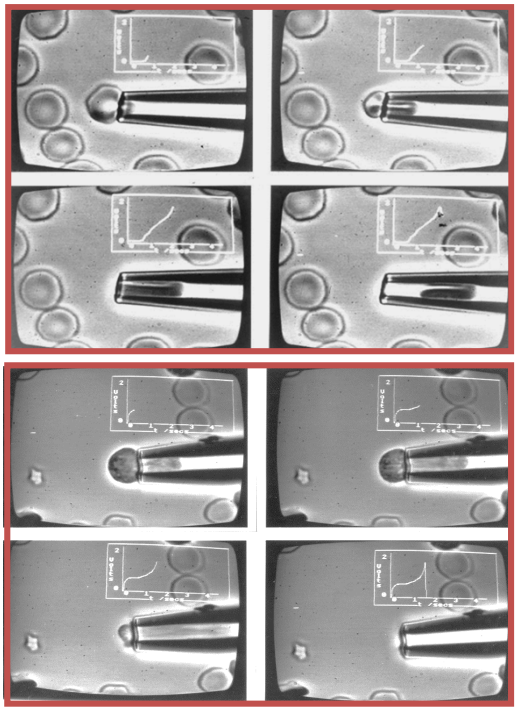
Spleen

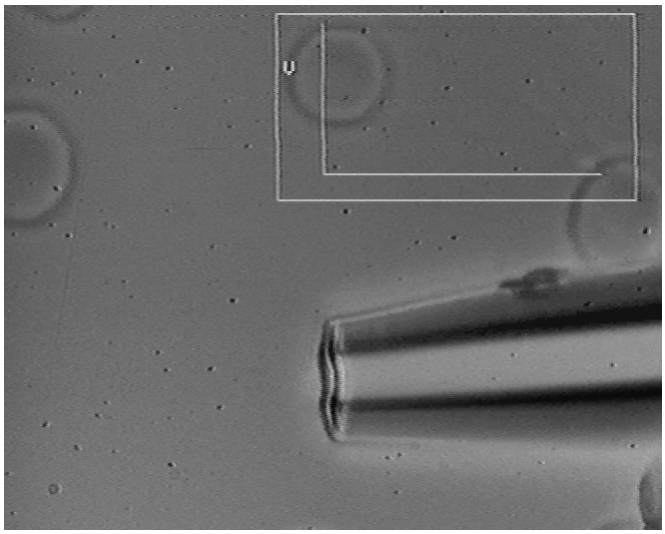




Its not just red blood cells

Ulf Bagge, PhD Thesis, Goteborg 1975

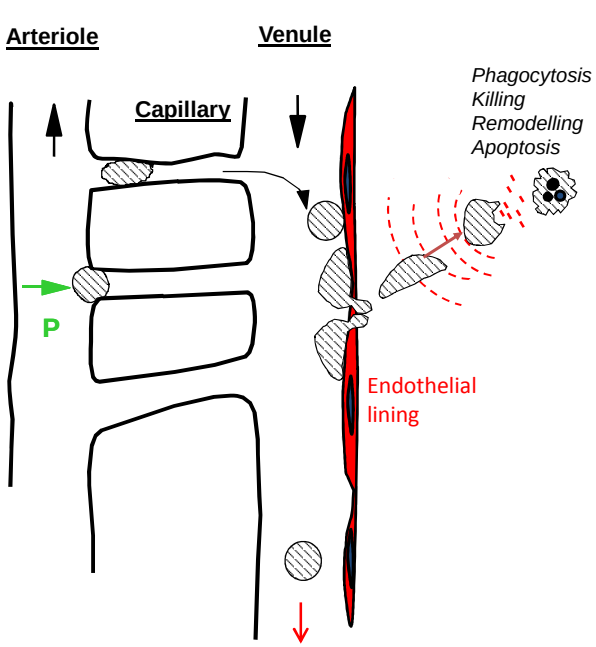


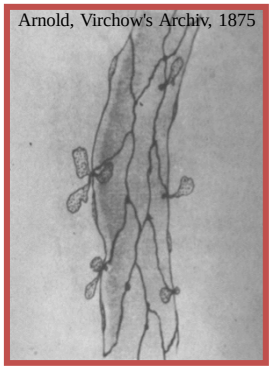


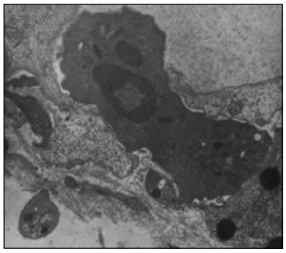
Its not just squeezing through vessels ……

……. its sticking and crawling out

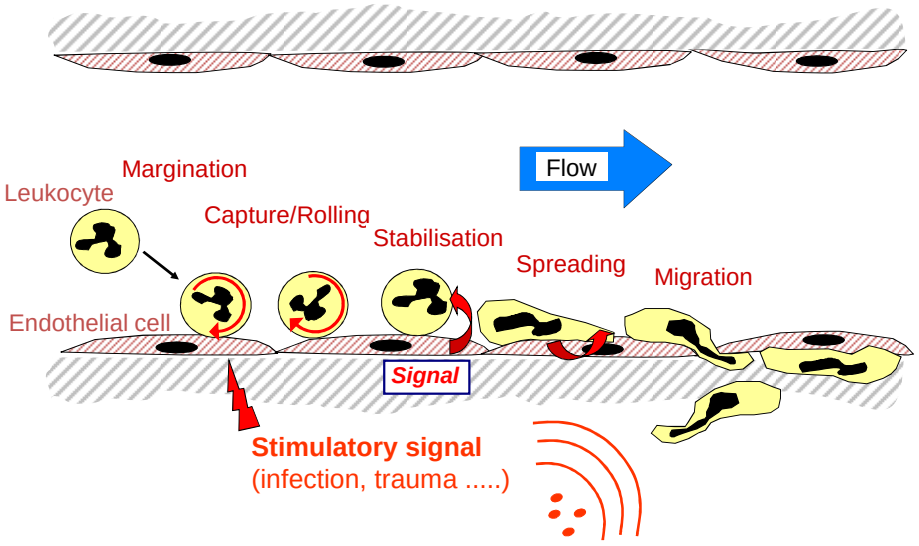
Circulation of neutrophils

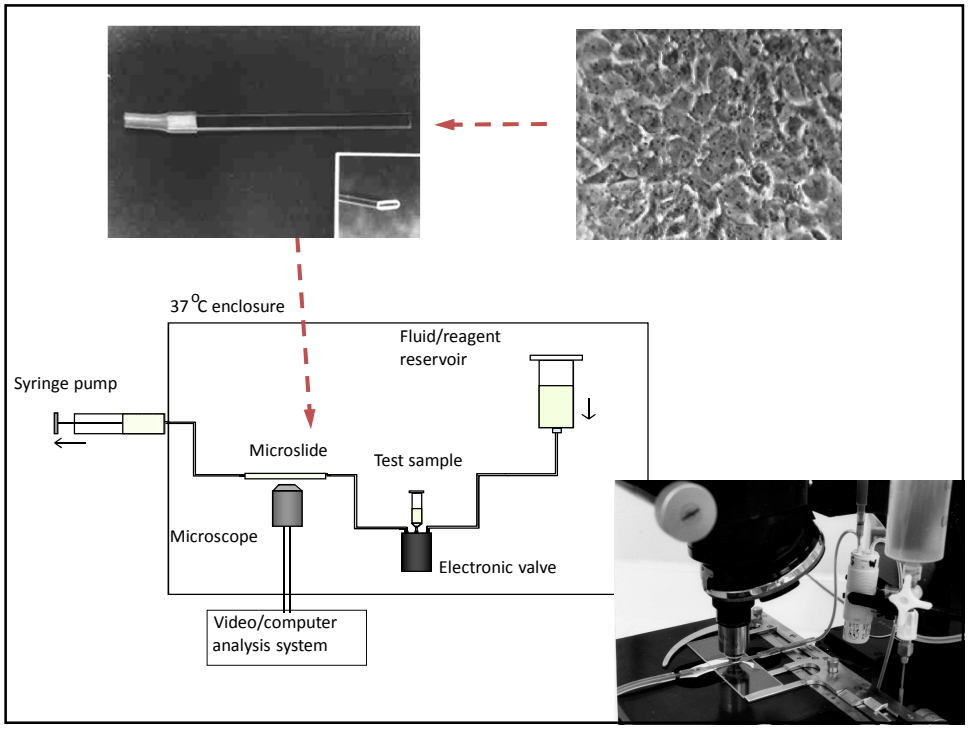




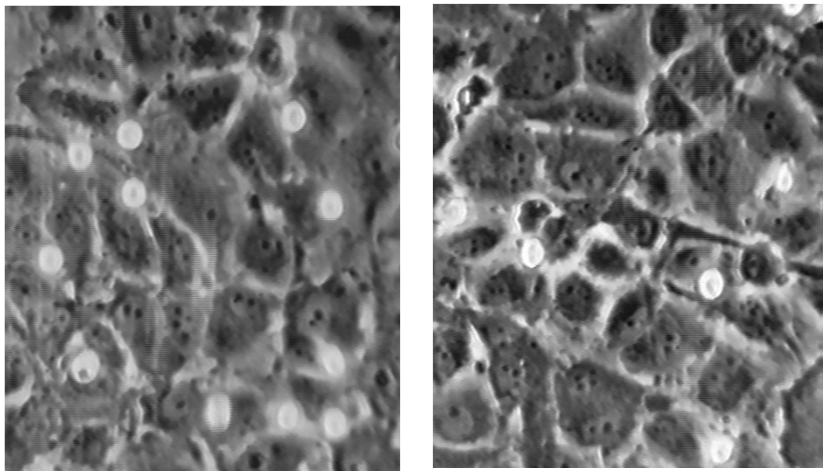


White blood cell recruitment across the vessel wall





Neutrophils rolling or migrating on 'inflammed' endothelium



Low dose

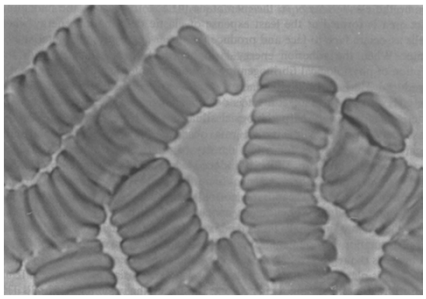
High dose

Tumour necrosis factor

Getting small blood cells through small gaps; what could go wrong?

'Clinical blood cell rheology'

Red blood cells: mechanics



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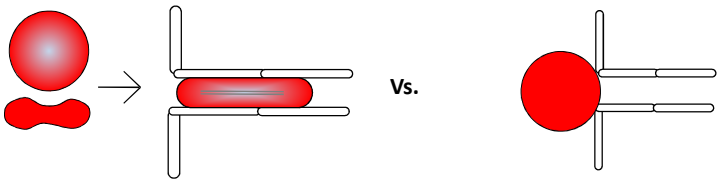
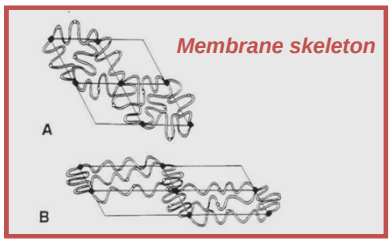
Cellular mechanical factors affecting deformation

CELL GEOMETRY *Surface area:volume* ratio → ability to adapt shape

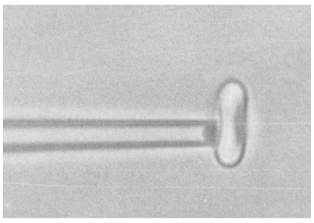


MEMBRANE (rigidity)

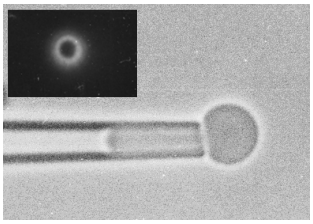


CYTOPLASM *(concentrated haemoglobin solution)*

London, Guys

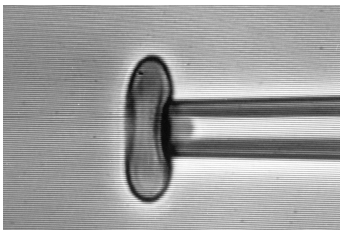


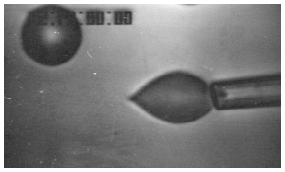
Membrane elastic modulus

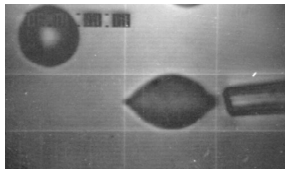


Surface area/volume

Los Angeles

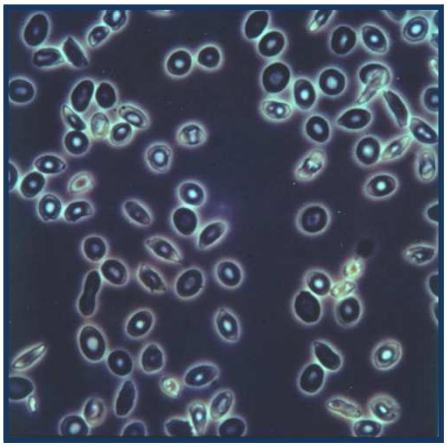




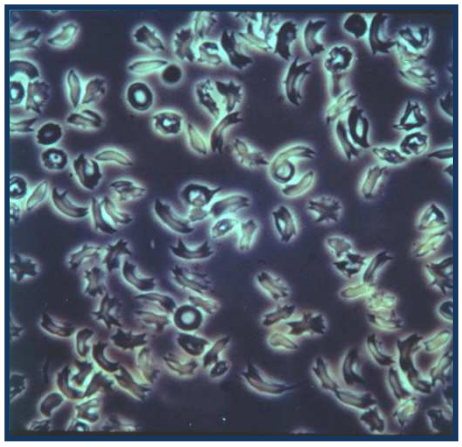


Membrane viscosity

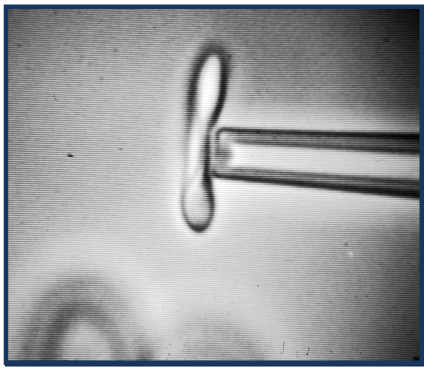
Sickle cell (HbSS) disease



Oxygenated



De-oxygenated

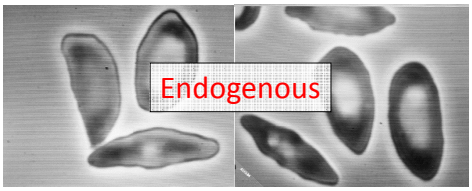


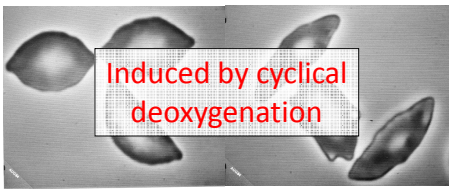
Irreversibly Sickled Cells:

Surface area/volume ↑ x1.25 (Shrunk)

Membrane rigidity ↑ x2

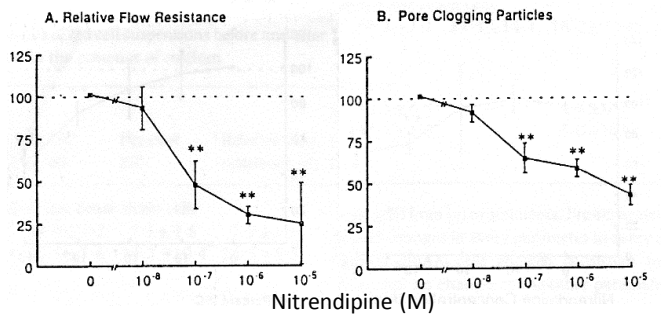
Membrane viscosity ↑ x2.5

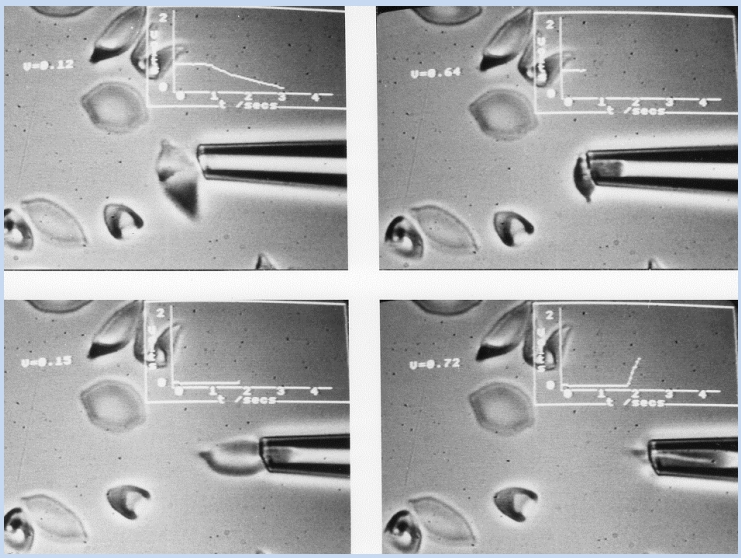


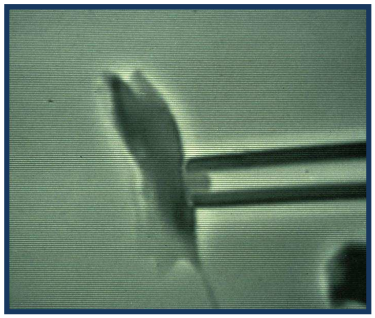


Ca^{++}-dependent K^{+} efflux (Gardos effect)

Protection by Ca++-channel blocker Nitrendipine



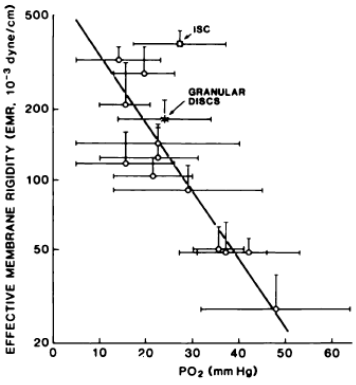


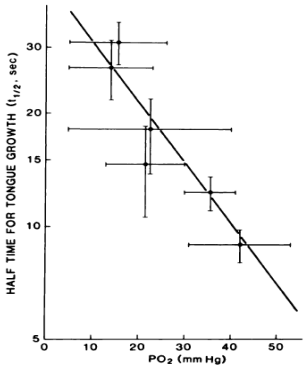


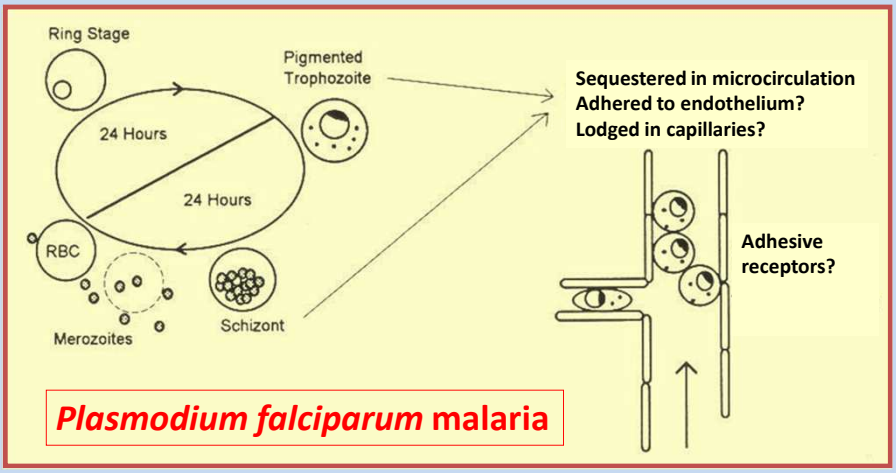
Decreasing oxygen tension
(HbS polymerisation/sickling)

Rigidity ↑ x 5-100

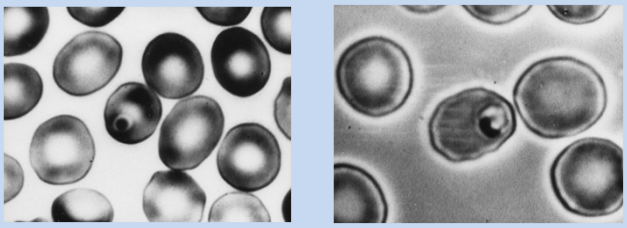
Deformation rate ↓ x 50-200

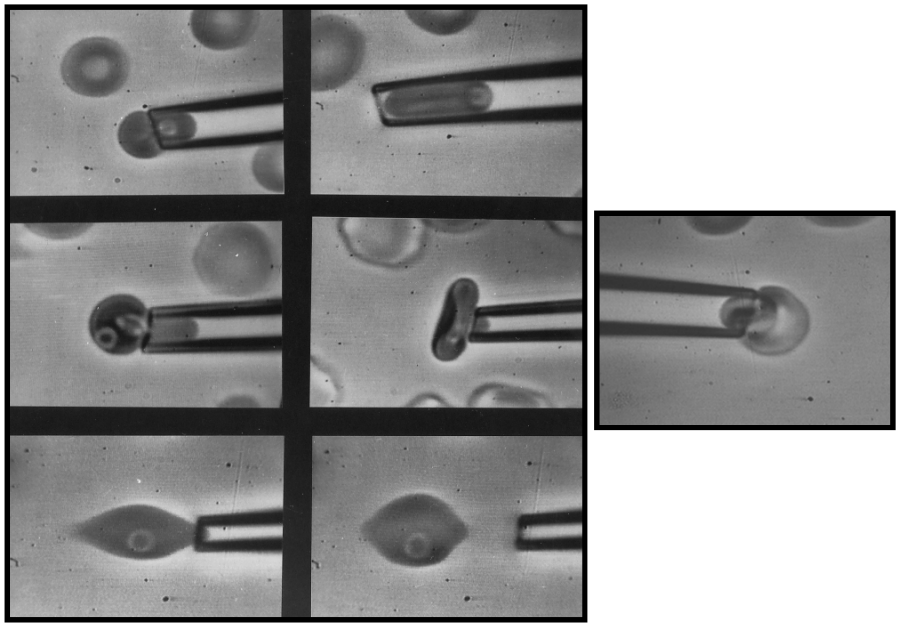




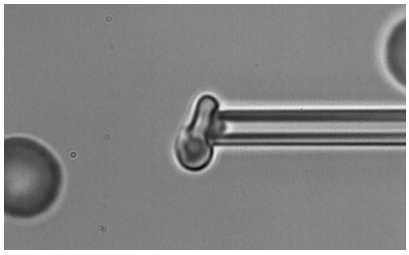


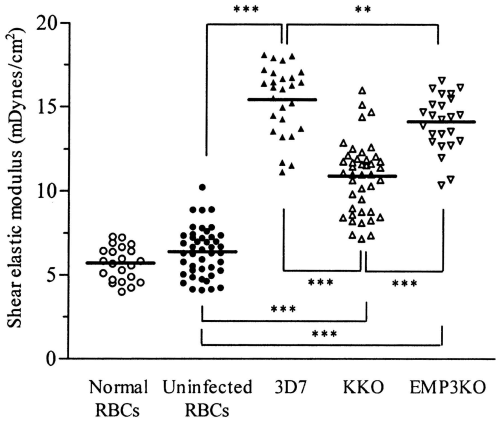
***Plasmodium falciparum* malaria**





Effect of proteins inserted into the red cell membrane revealed by genetic manipulation of the parasite

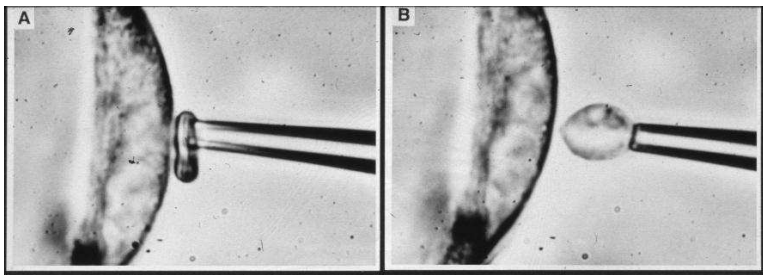




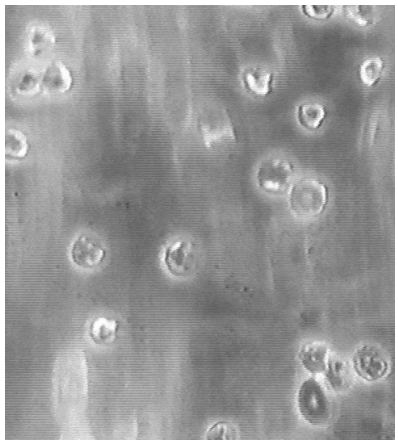
Glenister F K et al. Blood 2002;99:1060-1063

Getting small blood cells through small gaps; what could go wrong?

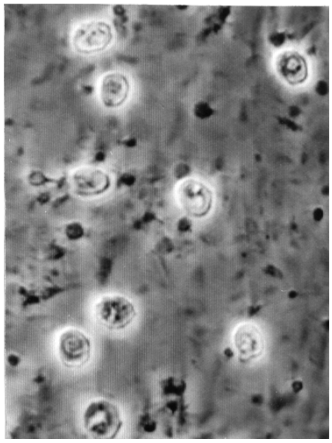
Red blood cells: adhesion



Parasitised red cells can mimic ability of white cells to roll and stop on endothelium



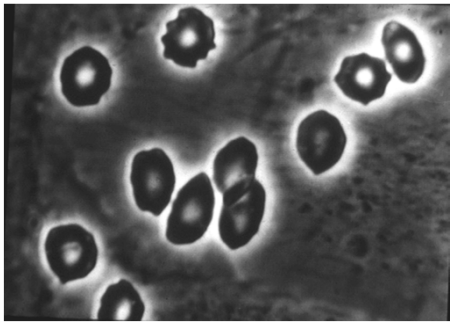
Endothelial cells

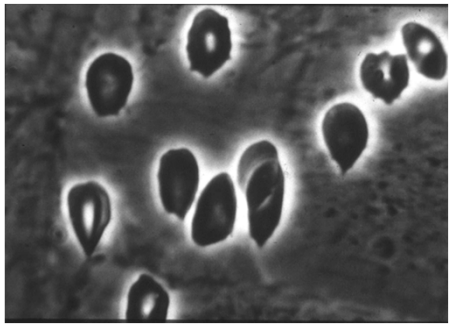


Platelets

Sequestration in blood capillaries key to pathogenesis?

Sickle cells can also adhere to endothelium from flow





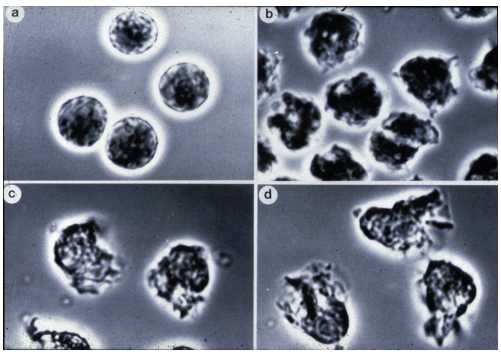
Adhesion may delay sickle cells in microvessels

Along with dehydration this allows sickling

Outcome – log-jam of rigid cells causing occlusion

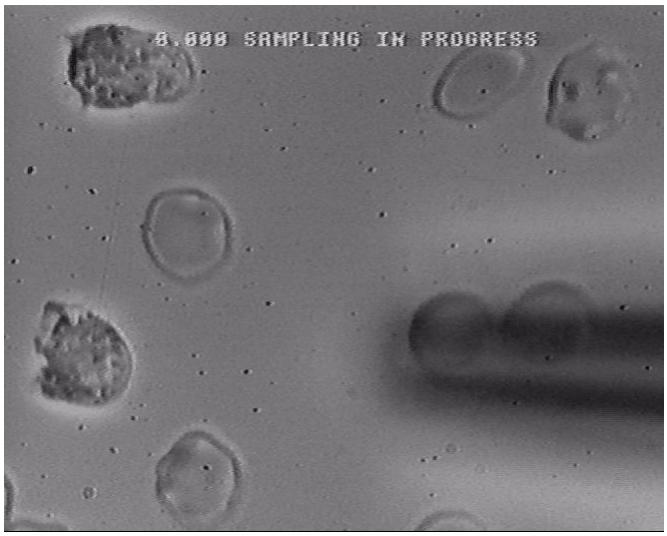
Getting small blood cells through small gaps; what could go wrong?

White blood cells: mechanics

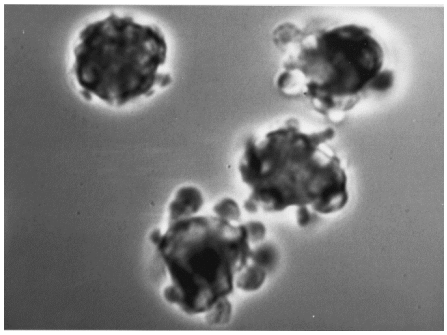


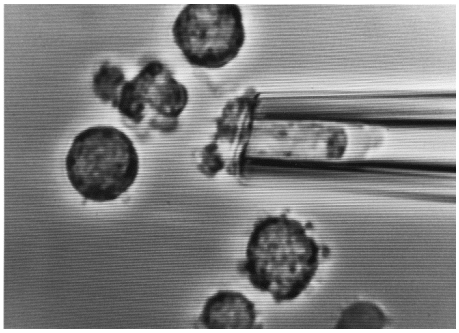
Slide 30/45

'Activated' neutrophils

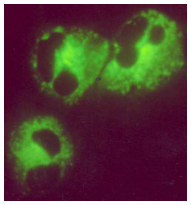


Effect of exposure to cigarette smoke

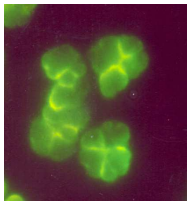




Small vessel inflammation (vasculitis) associated with anti-neutrophil cytoplasm antibodies (ANCA)

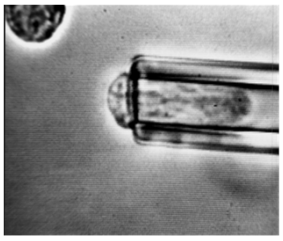


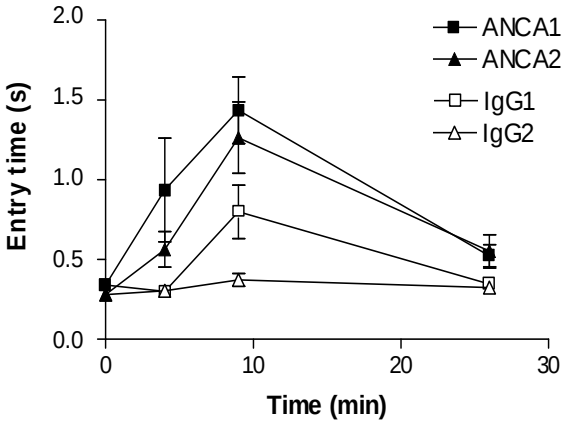
Cytoplasmic (c-) ANCA:
- Coarse granular staining
- Specificity for proteinase 3 (PR3)
- Most commonly associated with Wegener's granulomatosis



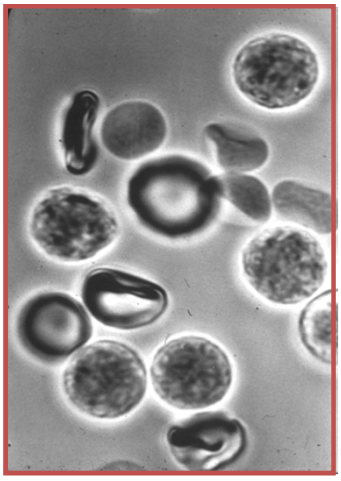
Perinuclear (p-) ANCA:
- Staining restricted to sites around the nucleus
- Specificity for myeloperoxidase (MPO)
- Most commonly associated with microscopic polyarteritis

ANCA derived from plasma of patients with vasculitis causes rigidification of neutrophils

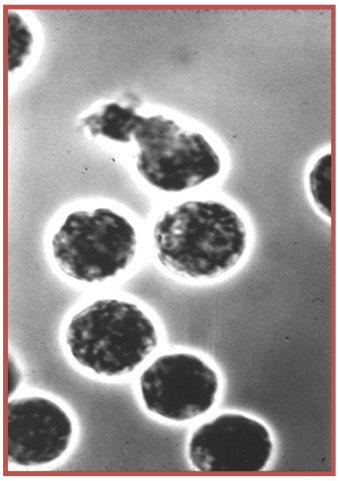




Effect of surgical interruption of blood flow (ischaemia and reperfusion)

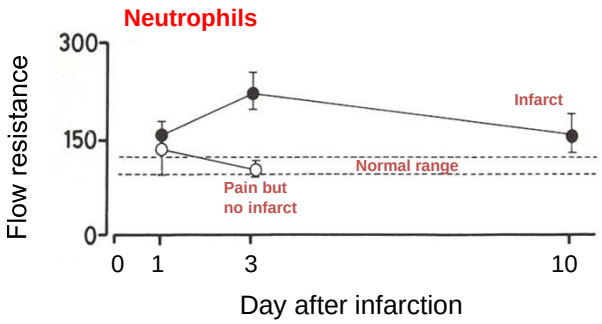


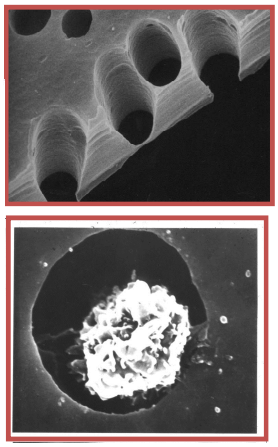
Healthy control



After repair of aortic aneurysm

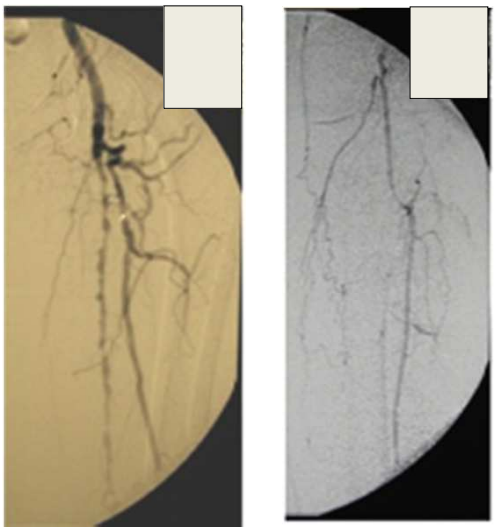
Flow resistance of neutrophils after acute myocardial infarction





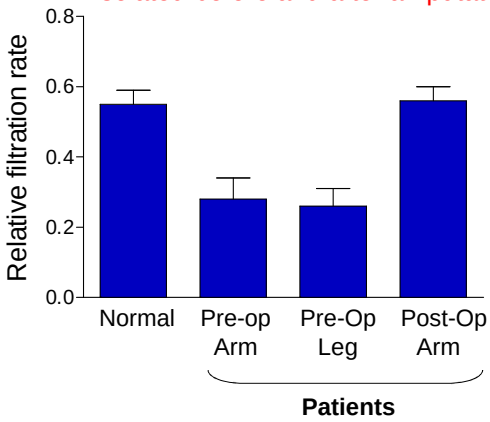
Peripheral vascular disease - chronic ischaemia of the leg

X-ray - Angiograms



Critical leg ischaemia: Flow resistance of neutrophils

Filtration rate of neutrophils:
isolated before and after amputation

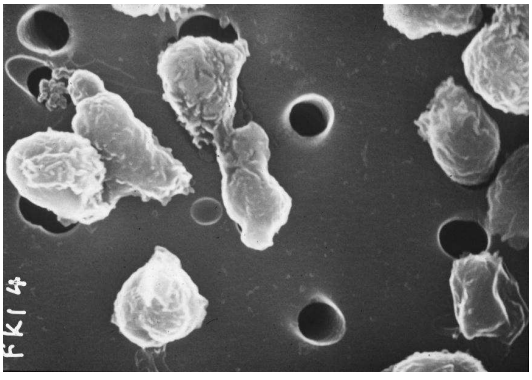


Activation of neutrophils may cause problems systemically as well as in affected ischaemic tissue

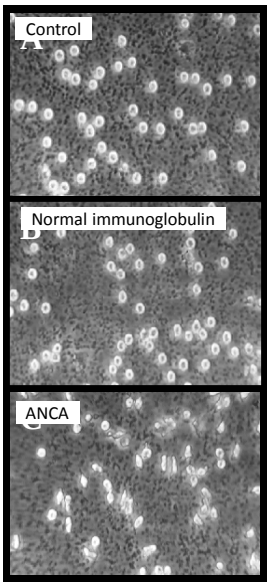
Getting small blood cells through small gaps; what could go wrong?

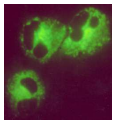
White blood cells: adhesion and migration

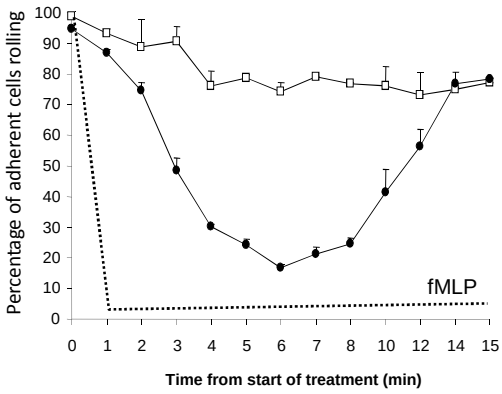
(at the wrong time/wrong place)



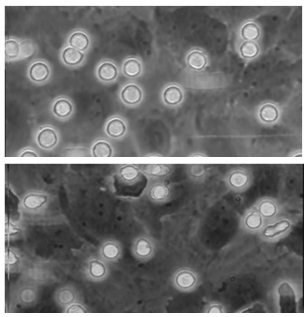
ANCA causes rolling neutrophils to become to stationary adherent

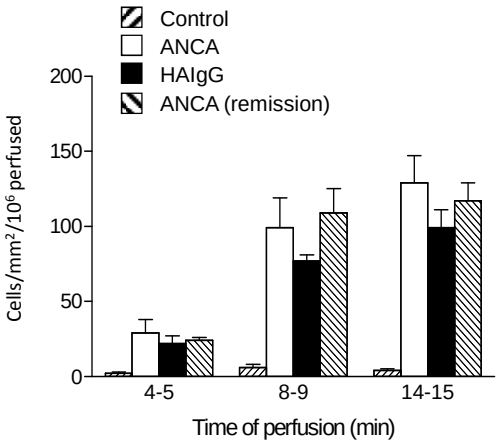






ANCA also promotes migration across endothelium



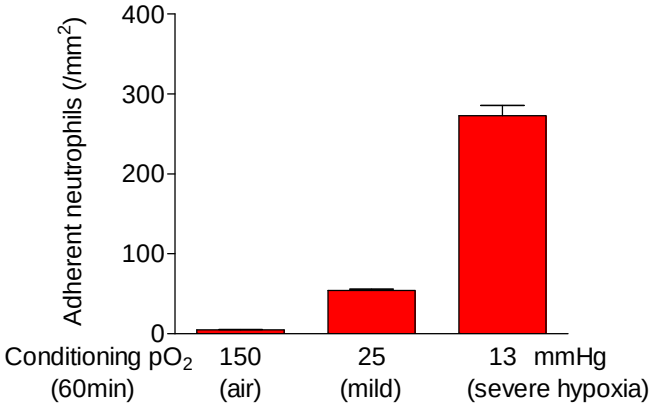


ANCA contribution to pathology of vasculitis?

Combined with ..... ?

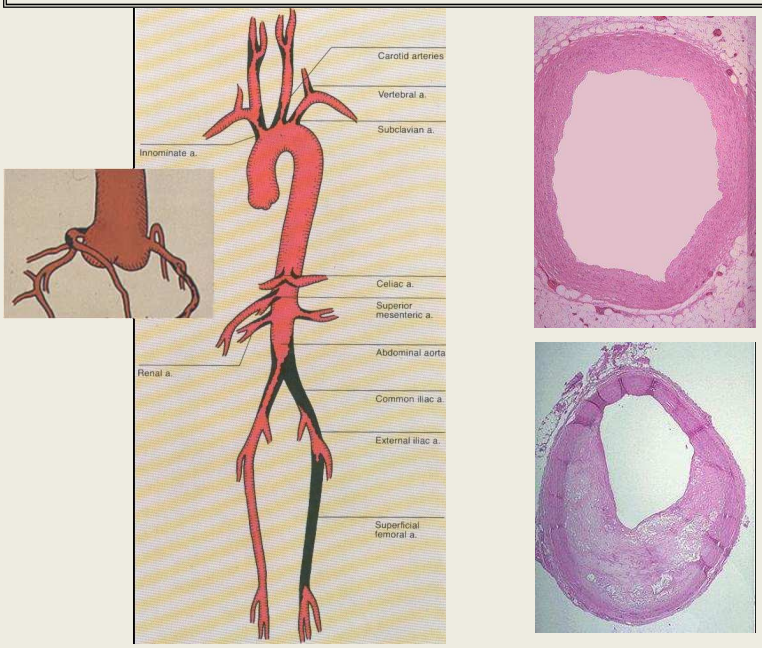
Exposure of endothelial cells to hypoxia and re-oxygenation

→ adhesion of flowing neutrophils on <u>return</u> of oxygen



Hypoxia/reoxygenation <u>one</u> driver of neutrophil infliltration

Atherosclerosis - vicious cycle of leukocyte activation?



Clinical blood cell rheology – therapeutic lessons?

Sickle cell disease

Shrinking as a key factor in flow impairment (deformability, polymerisation, adhesion)

Malaria

Inhibit sequestration to attack the parasite life-cycle

Leukocytes and vascular disease *:*

Don't let them get too excited

Quieten them down

Stop them sticking

Guy's Hospital Medical School

University of Southern California, Medical School

St. George's Hospital Medical School

University of Birmingham Medical School

British Heart Foundation

Arthritis Research Campaign

The Leverhulme Trust

MRC Medical Research Council

EPSRC Engineering and Physical Sciences Research Council

bbsrc biotechnology and biological sciences research council