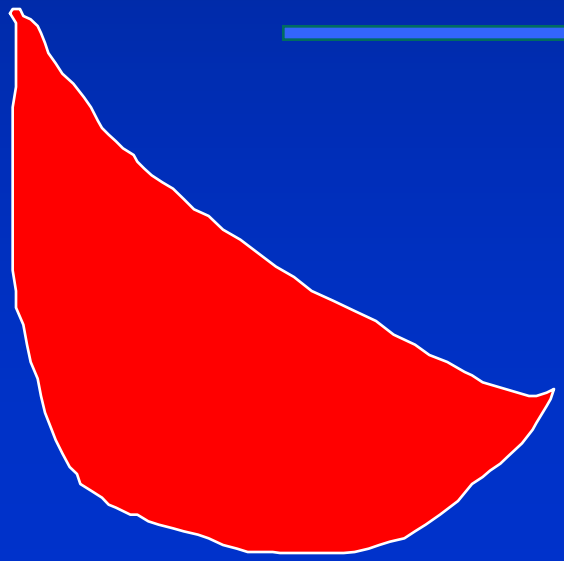
Pathogenesis of sickle cell disease

Professor Irene Roberts

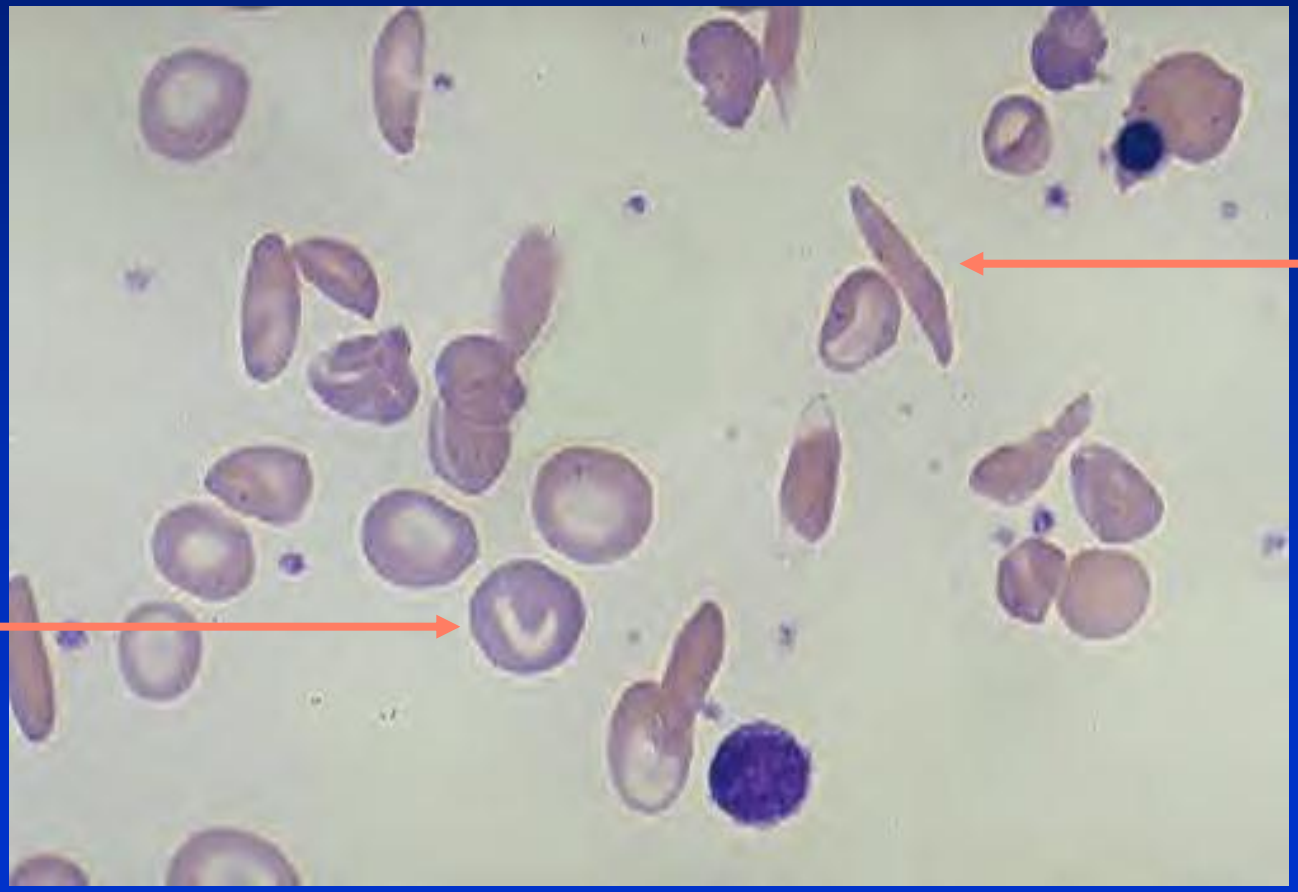


Pathogenesis of sickle cell disease

OBJECTIVES

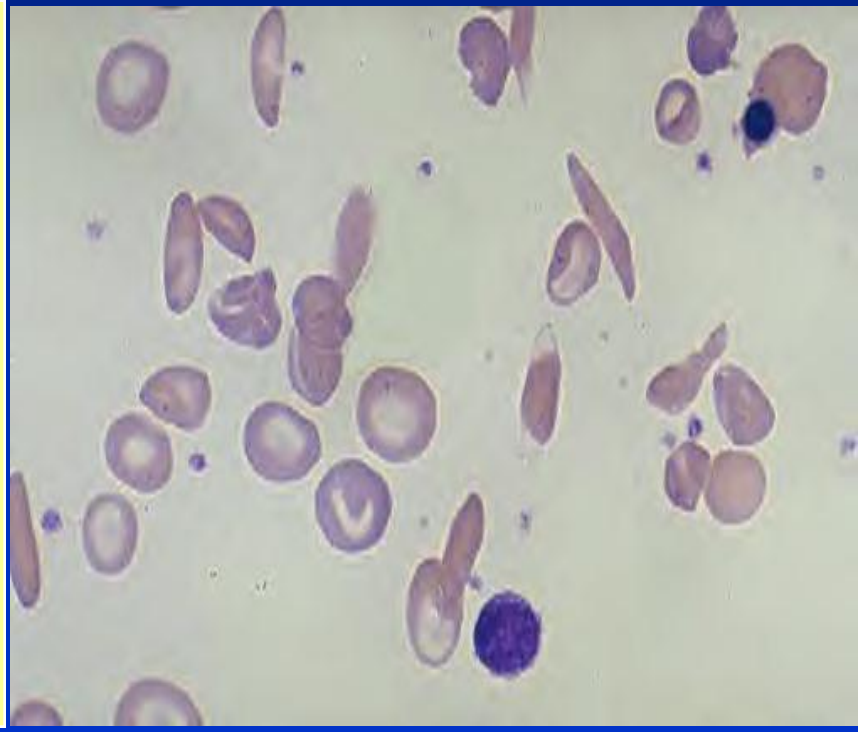
- **Understand the genetics of sickle cell disease**
- **Understand the pathogenesis of vaso-occlusion in sickle cell disease and how this causes the main clinical presentations of the disease**
- **To have some insight into the therapeutic implications of understanding the biology of sickling**

Sickling disorders are caused by inheritance of haemoglobin S



Main types of Sickle Cell Disease

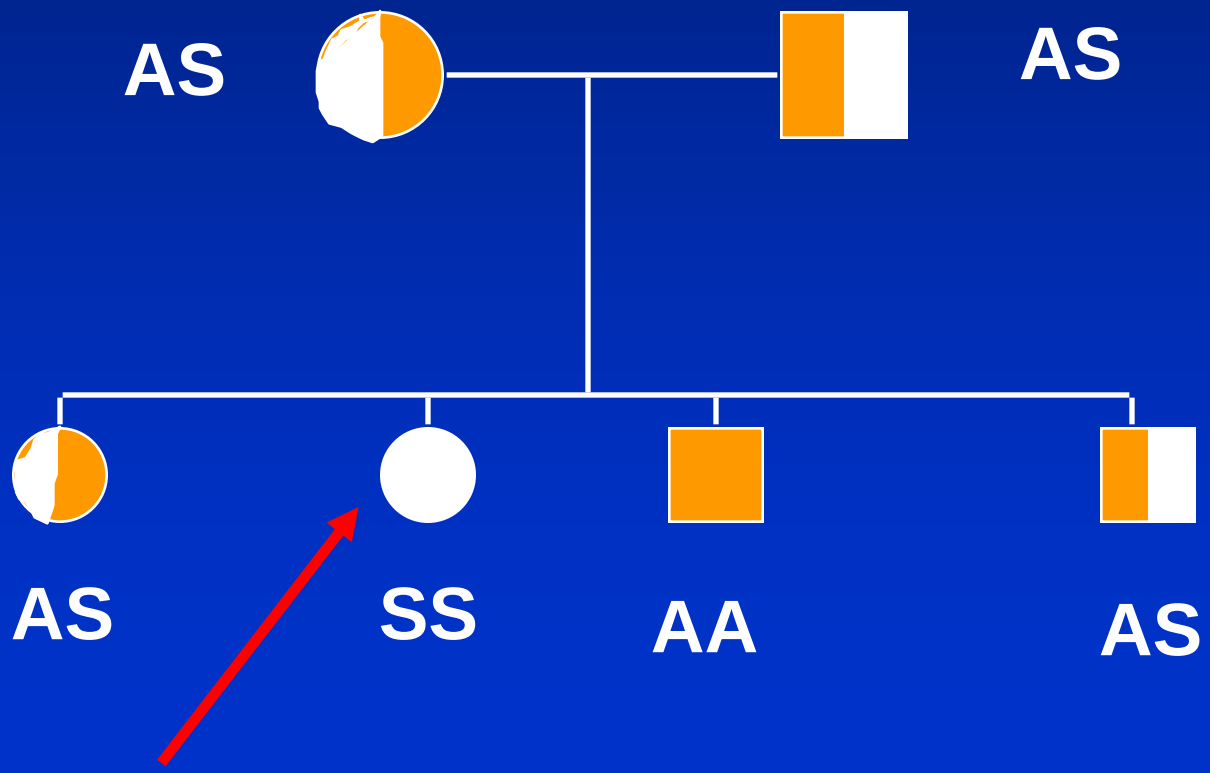
Name	Hb on HPLC
Sickle cell anaemia HbSS	HbS,HbF
SC disease (HbSC)	HbS,HbC,HbF
Sickleβ^0thalassaemia	HbS,HbF
Sickleβ^+thalassaemia	HbS,HbF,HbA



Sickle Cell Disease: sickle cell anaemia

INHERITANCE:

Sickle cell anaemia is also known as HbSS



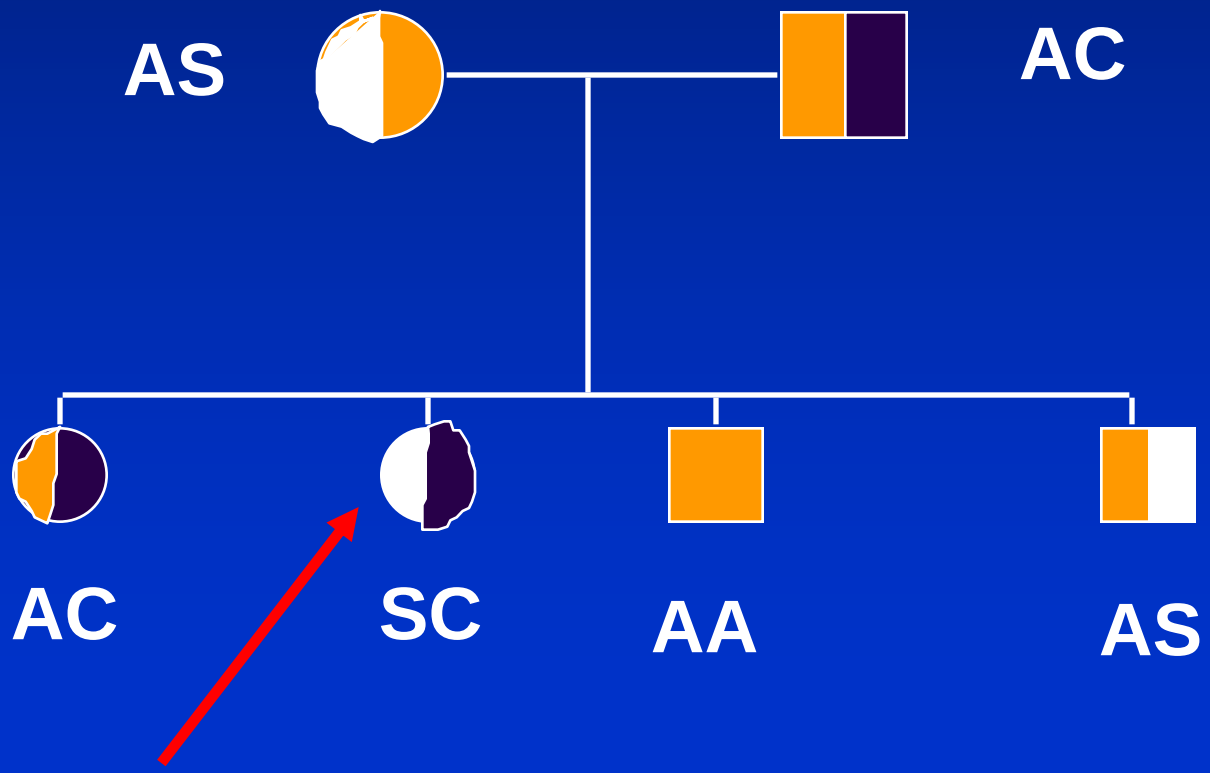
Molecular Basis of Sickle Cell Disease

HbA	HbS
CCT GAG GAG	CCT GTG GAG
Pro Glu Glu	Pro Val Glu
5 6 7	5 6 7
β-globin^{A}	β-globin^{S}

HbS is $\alpha_2\beta_2^{Val6}$

Sickle Cell Disease: SC disease

INHERITANCE:



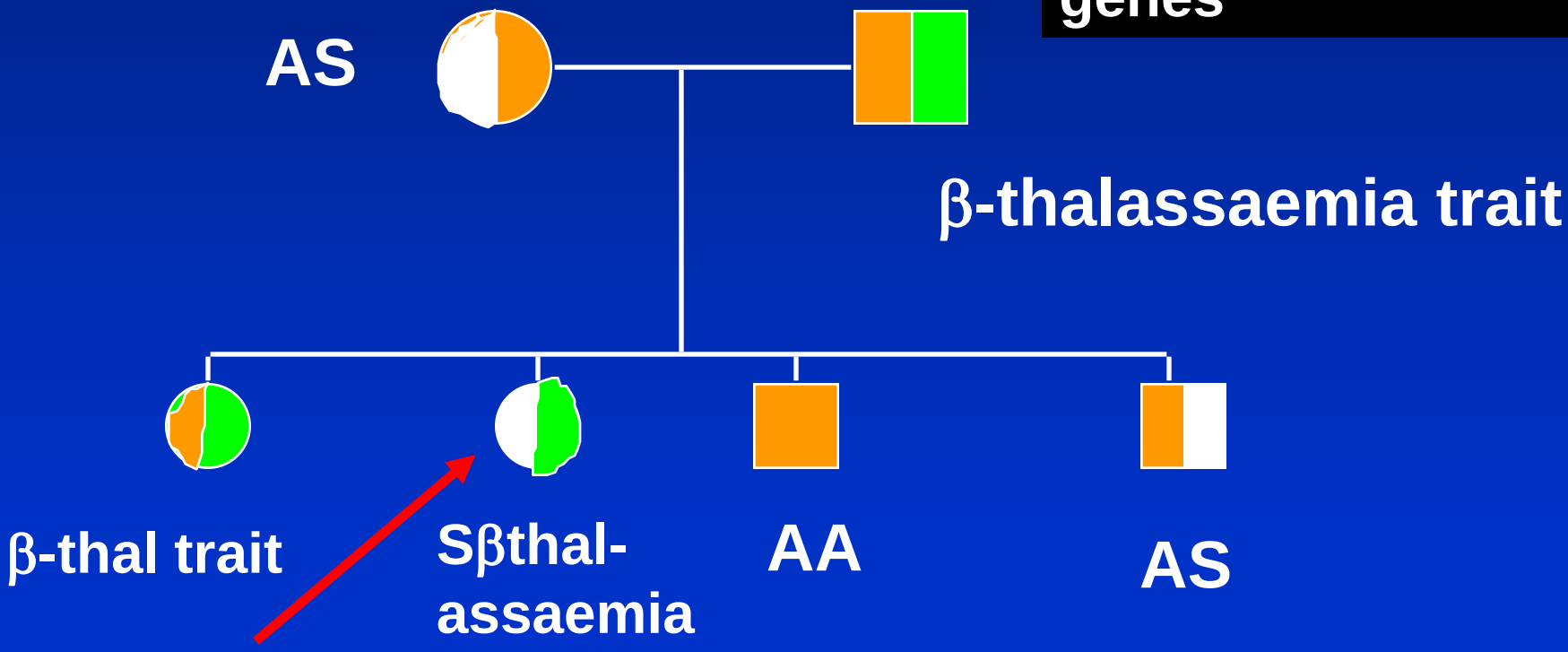
HbC is caused by a β-globin mutation at the same position as HbS:

HbC is $\alpha_2\beta_2^{Val6}$

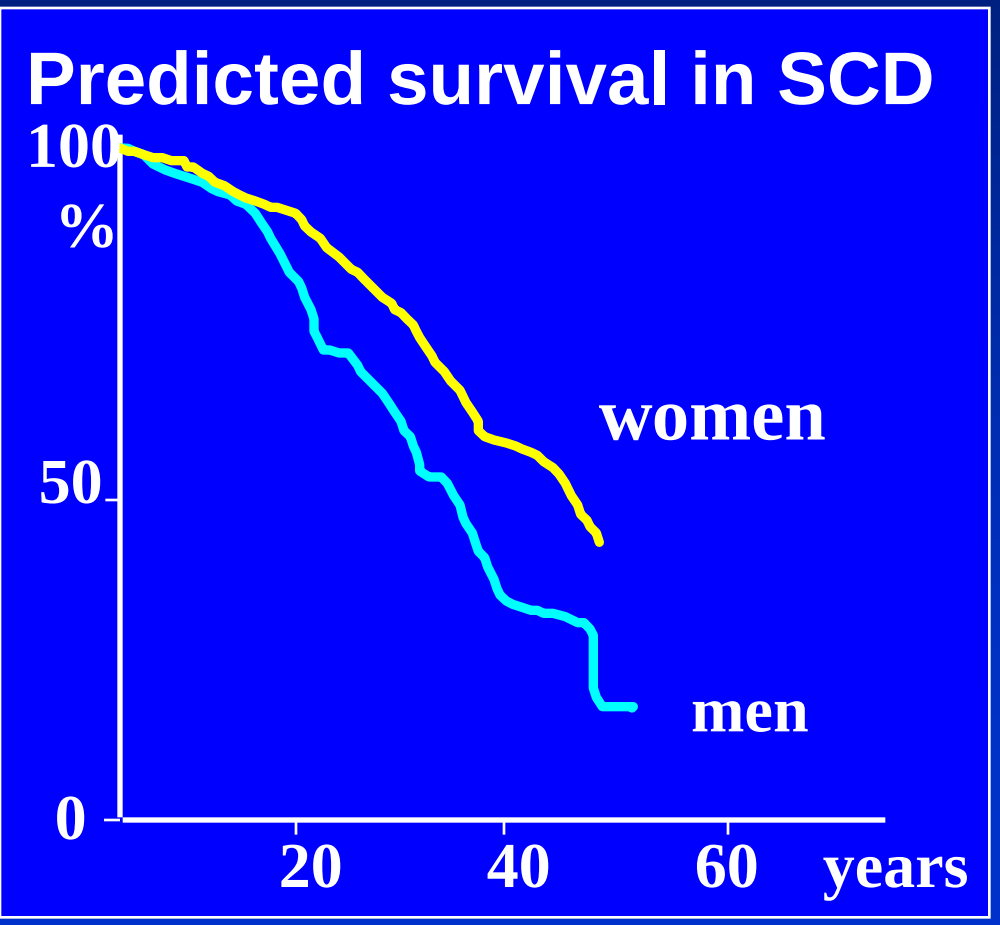
Sickle Cell Disease: S-β-thalassaemia

INHERITANCE:

Co-inheritance of HbS and β-thal trait: patients have no normal β-globin genes



Mortality in sickle cell disease

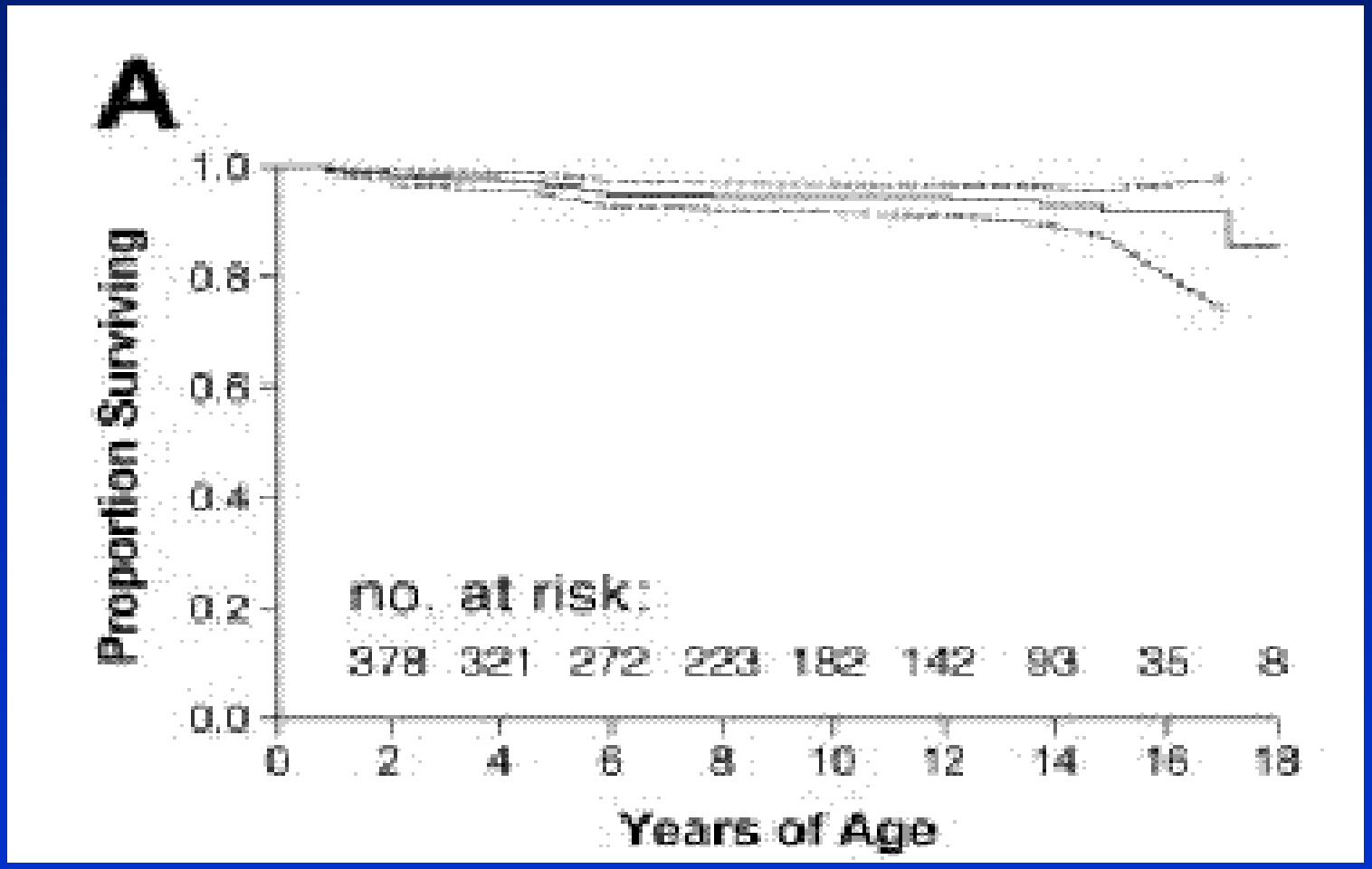


National Institute of Health Cooperative Study of Sickle Cell Disease (SCD)

The median survival for men with HbSS was 42 years and for women was 48 years.

Platt et al, NEJM 330: 1639, 1994

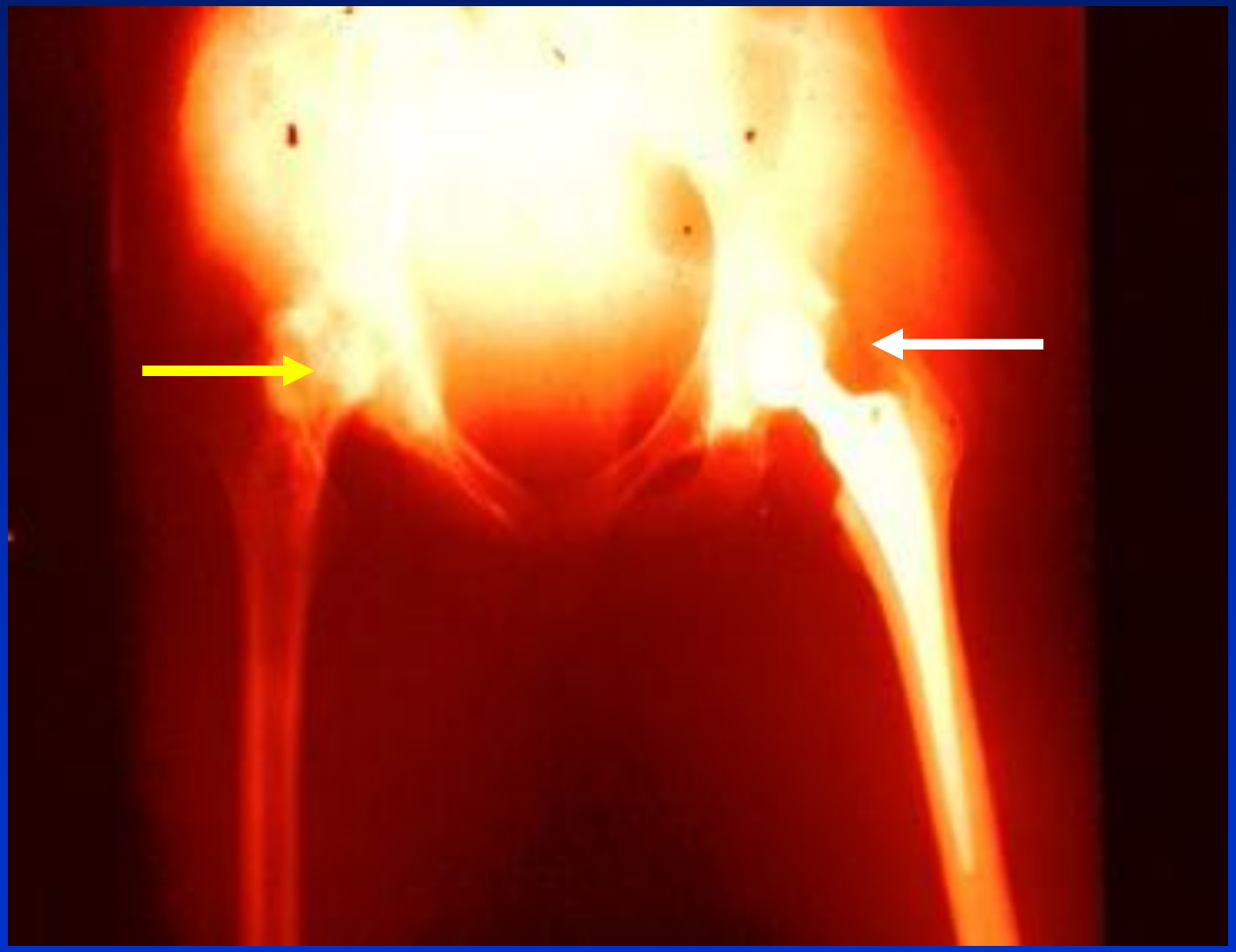
Mortality of children with sickle cell disease



Age	Deaths/ 100 pt yrs
0.2	0.24
2-4	0.43
4-6	1.19
6-8	0.2
8-10	0.0
10-12	0.0
12-14	0.44
14-16	0.88

Quinn et al, 2004

Pathogenesis of sickling

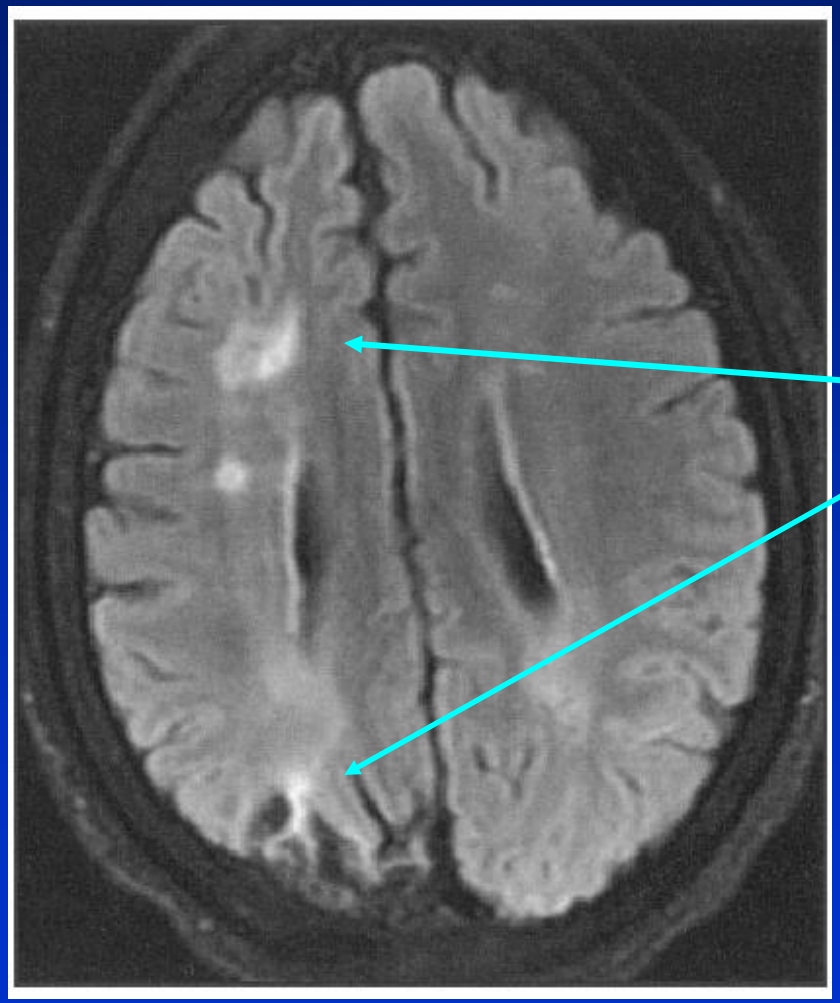


Bilateral osteonecrosis of the hip in an 18 year old woman with sickle cell disease

hip replacement

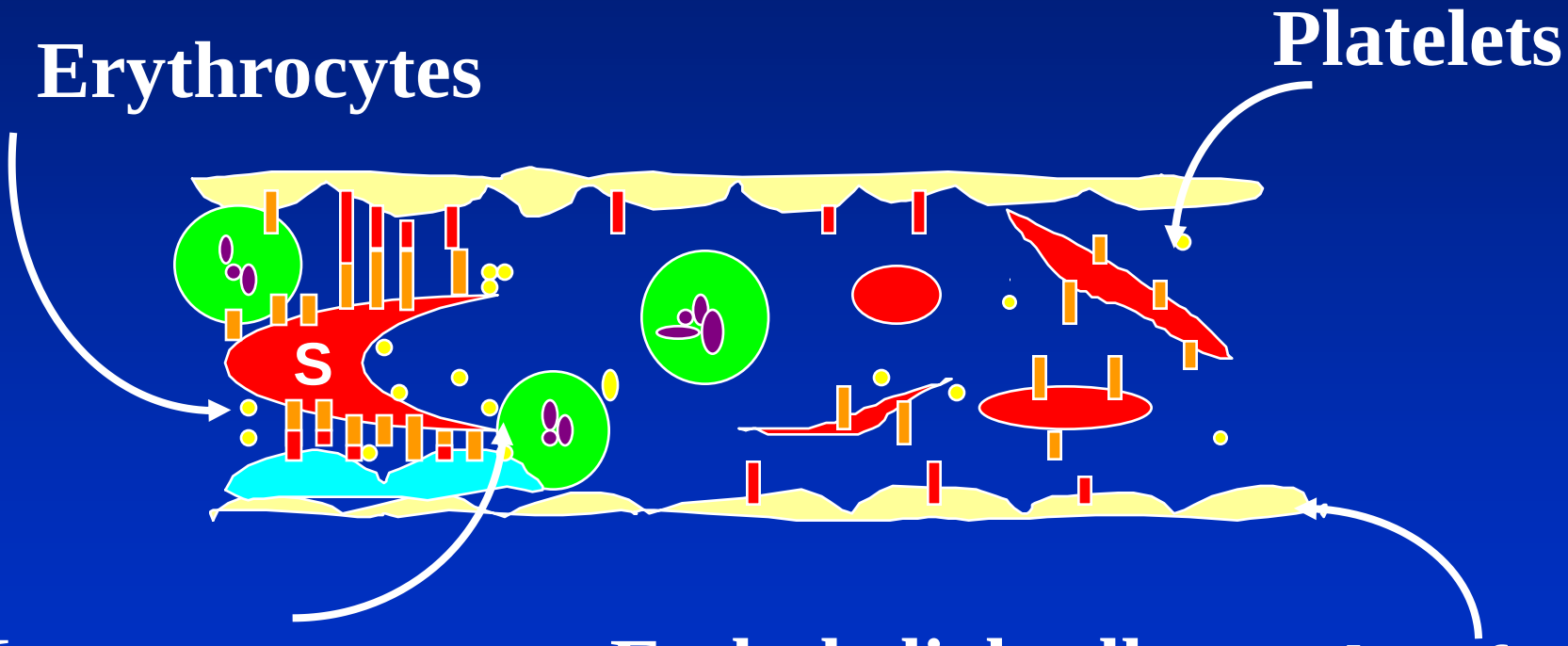
flattening of femoral head

Pathogenesis of Sickling

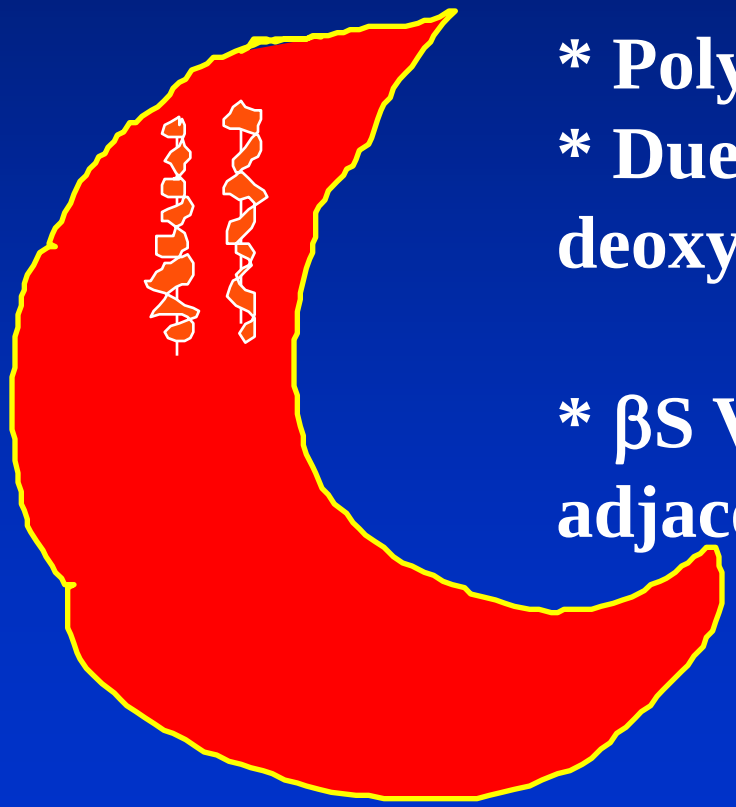


Cerebral infarcts in a 20 year old man with sickle cell disease

Pathogenesis of sickling (vaso-occlusion)



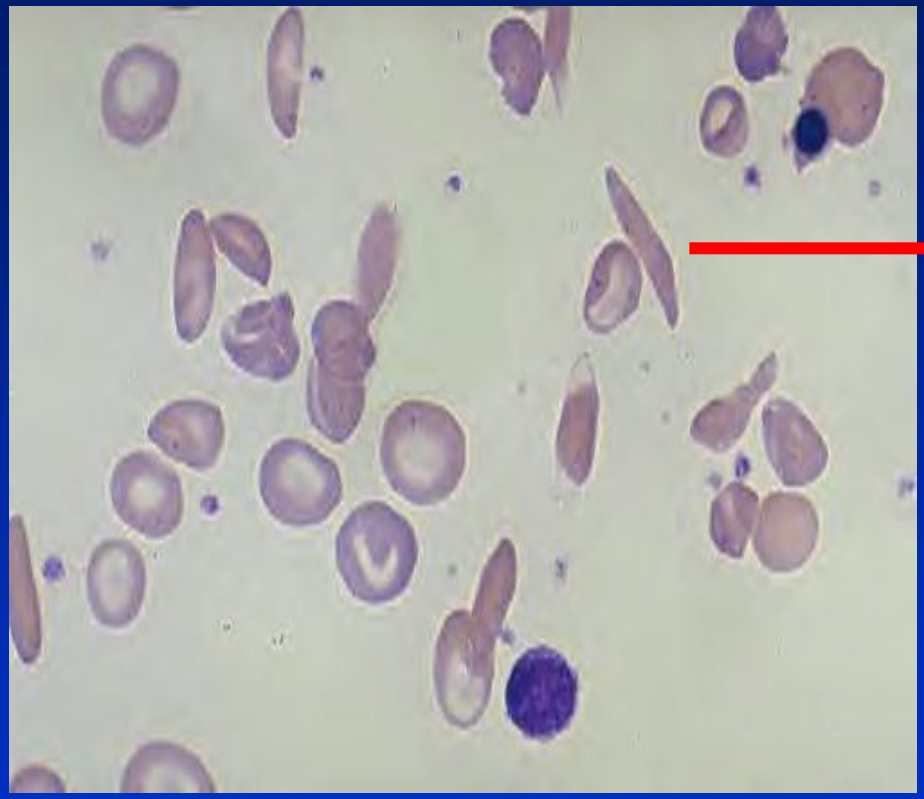
Vascular occlusion in sickle cell disease



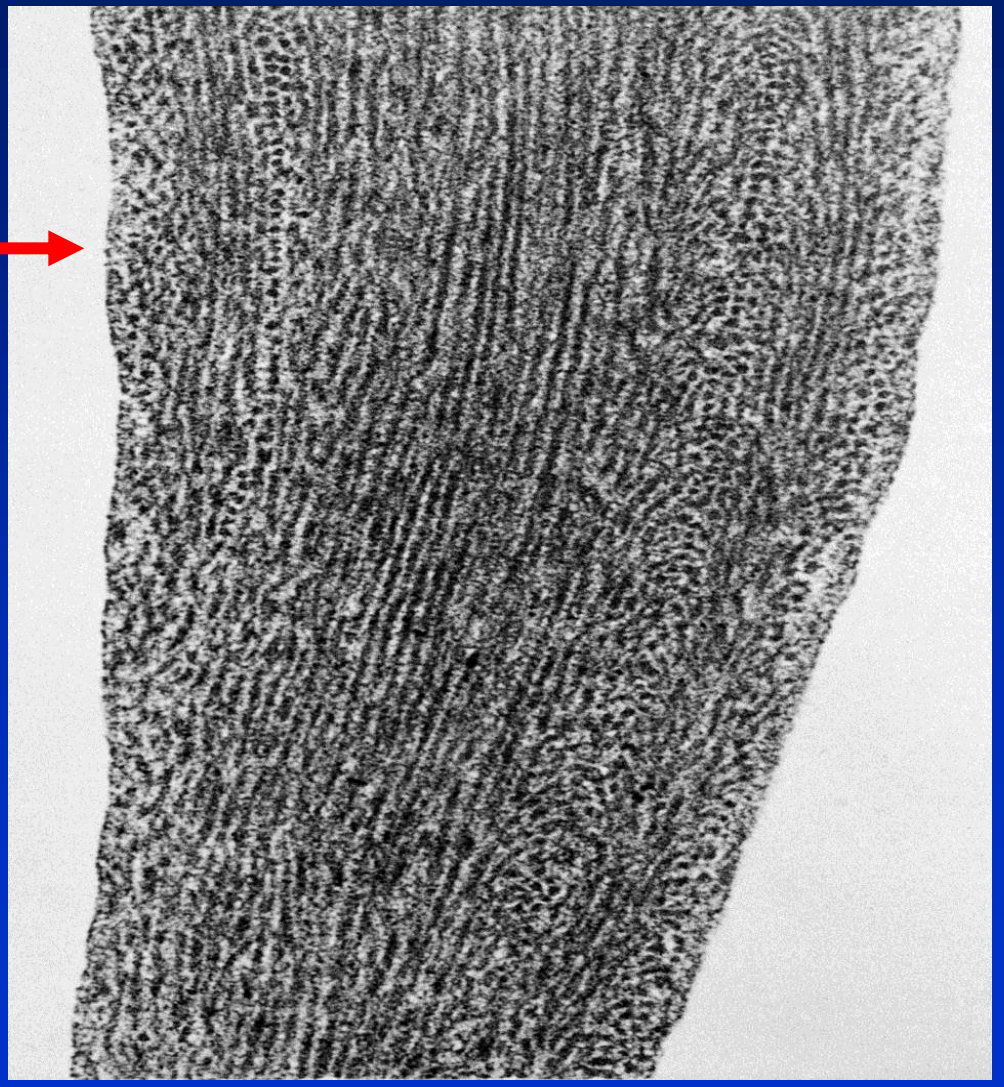
* Polymerization of HbS within cells
* Due to formation of Hb tetramers by deoxy HbS

* βS Val^{6} fits into a hydrophobic pocket on adjacent tetramers (βA Glu^{6} does not)

Pathogenesis of Sickling

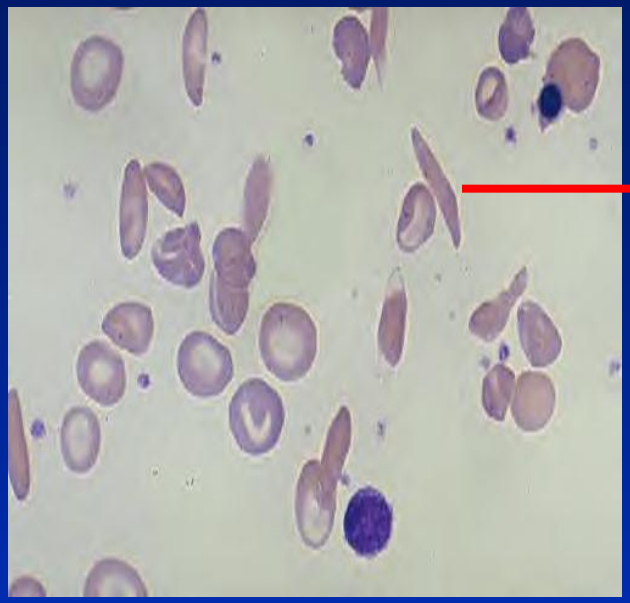


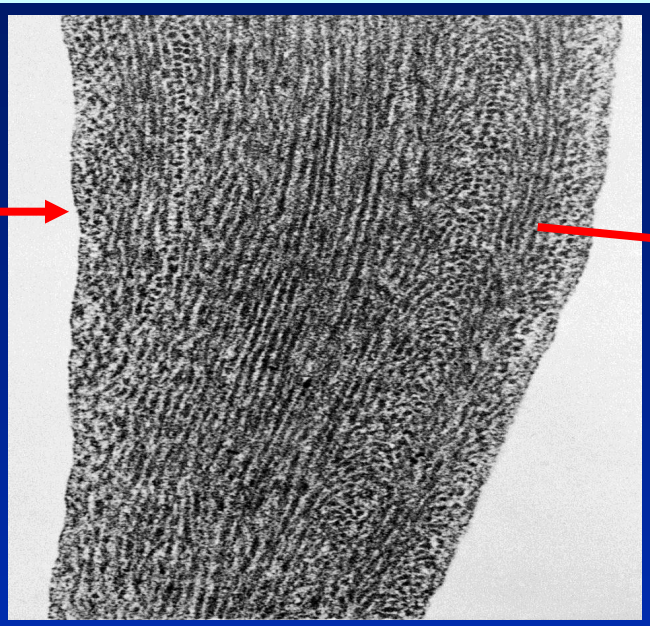
Deoxy HbS: polymerisation of Hb tetramers as βS Val6 fits into hydrophobic pocket on adjacent tetramers

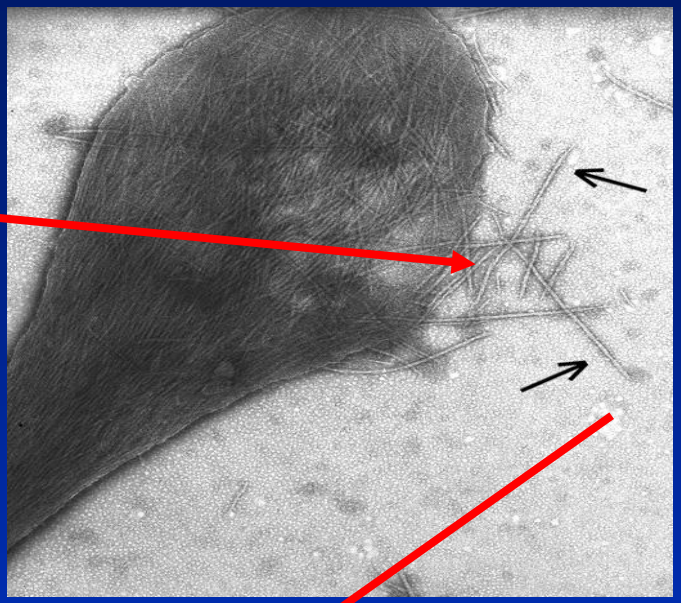


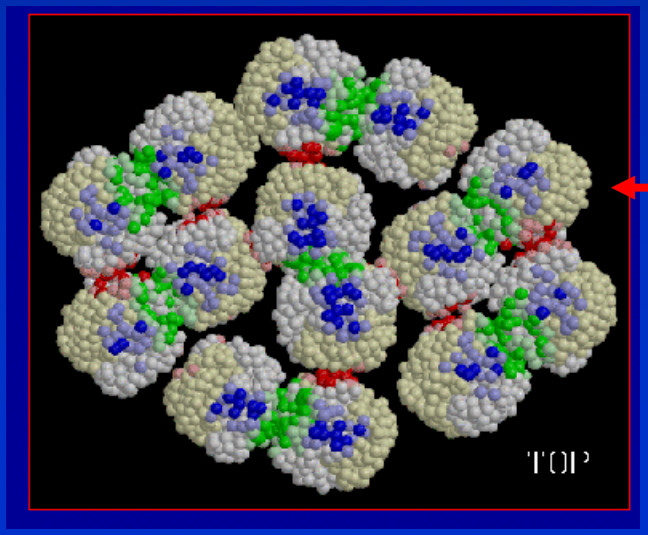
HbS polymers seen by X-ray diffraction

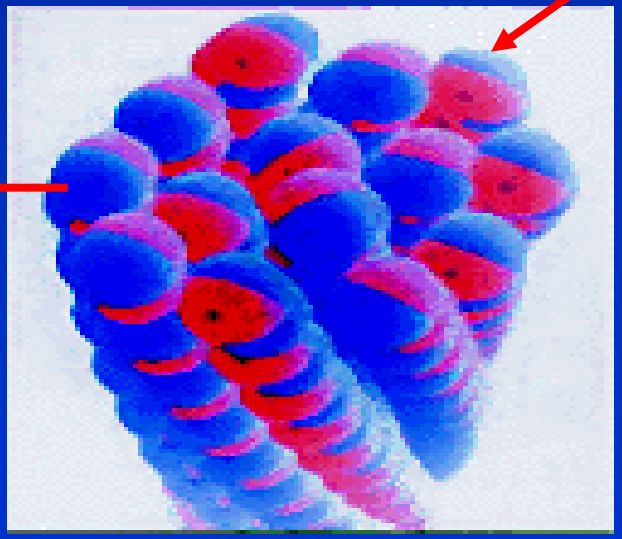
Pathogenesis of Sickling



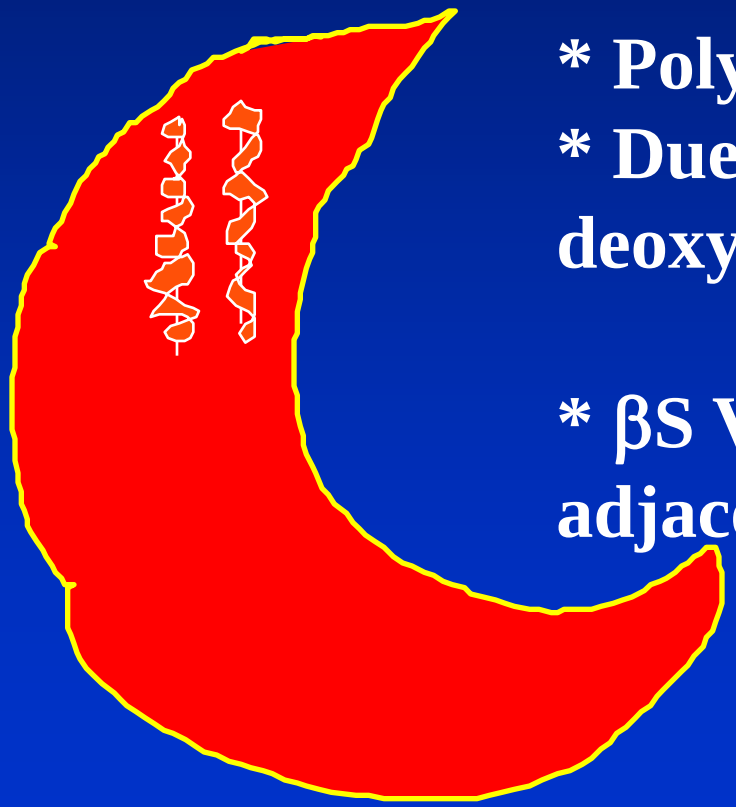








Vascular occlusion in sickle cell disease



* Polymerization of HbS within cells
* Due to formation of Hb tetramers by deoxy HbS

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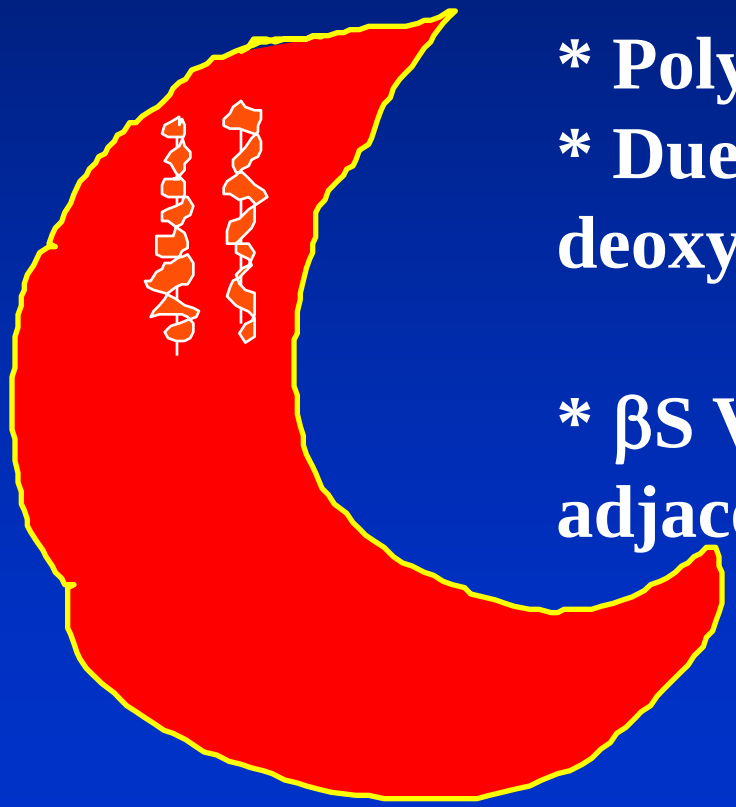
Prevention of polymerization prevents vascular occlusion in sickle cell disease

Vascular occlusion in sickle cell disease



* Polymerization of HbS within cells
* Due to formation of Hb tetramers by deoxy HbS

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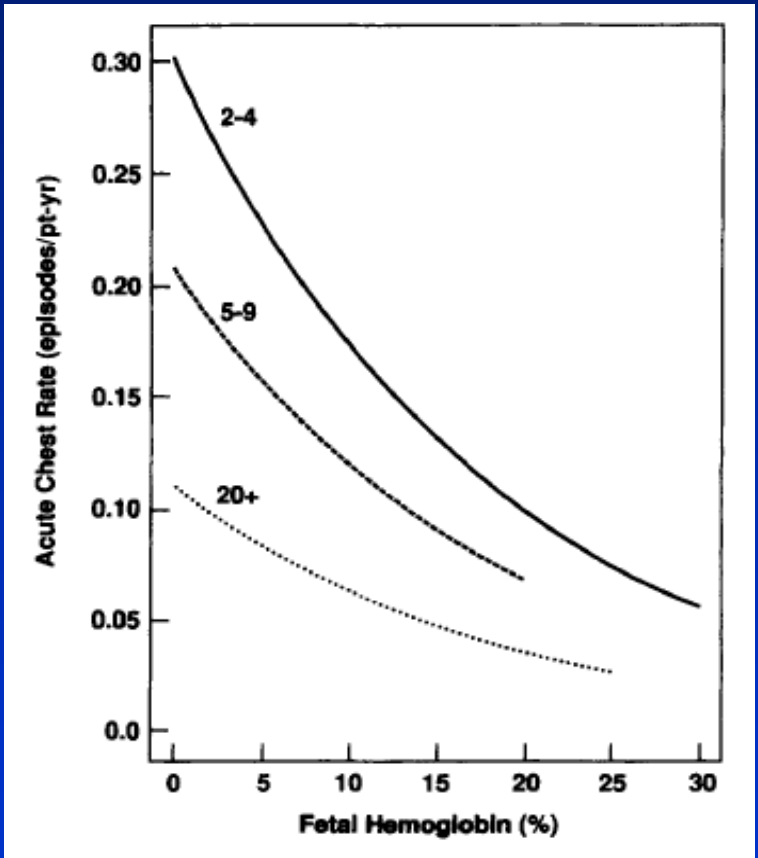
HbF
increases the solubility of HbS

Role of HbF in ameliorating sickle cell disease

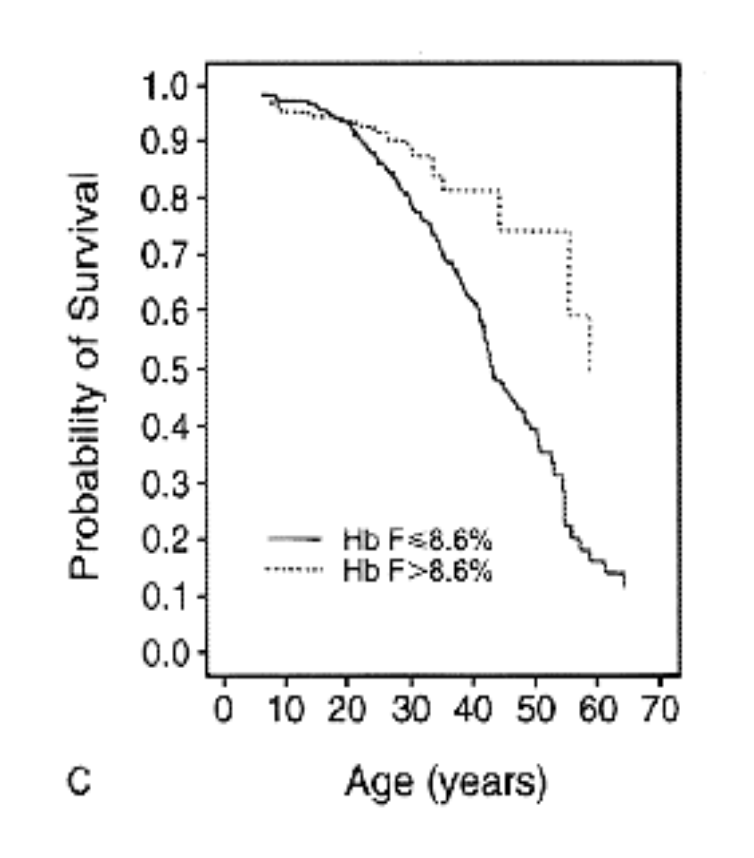
- Natural history
  - infants
  - mild disease in Saudi Arabia, India and HPFH
  - HbF predicts SCD severity
- Effects of HbF *in vitro*, eg HbS polymerization
- Effects of HbF modulation *in vivo*

HbF predicts clinical severity in SCD:

Co-operative Study of Sickle Cell disease (CSSD)



Acute Chest Syndrome
Castro et al, Blood 1994

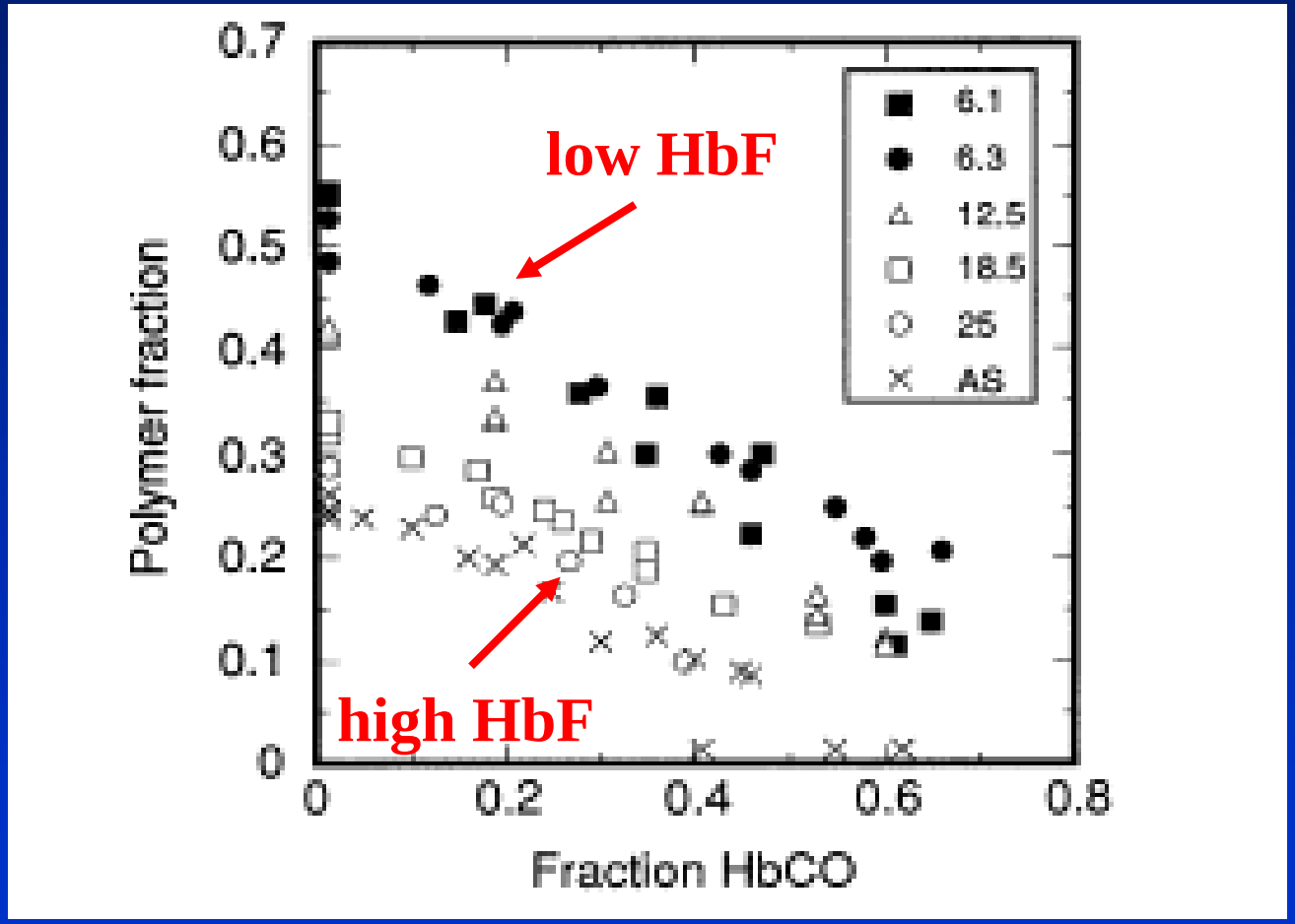


Overall survival
Platt et al, NEJM, 1994

Role of HbF in ameliorating sickle cell disease

- Natural history
  - infants
  - mild disease in Saudi Arabia, India and HPFH
  - HbF predicts SCD severity
- Effects of HbF *in vitro*, eg HbS polymerization
- Effects of HbF modulation *in vivo*

Sparing effect of HbF on HbS polymerization



HbF 6%

HbF 12.5%

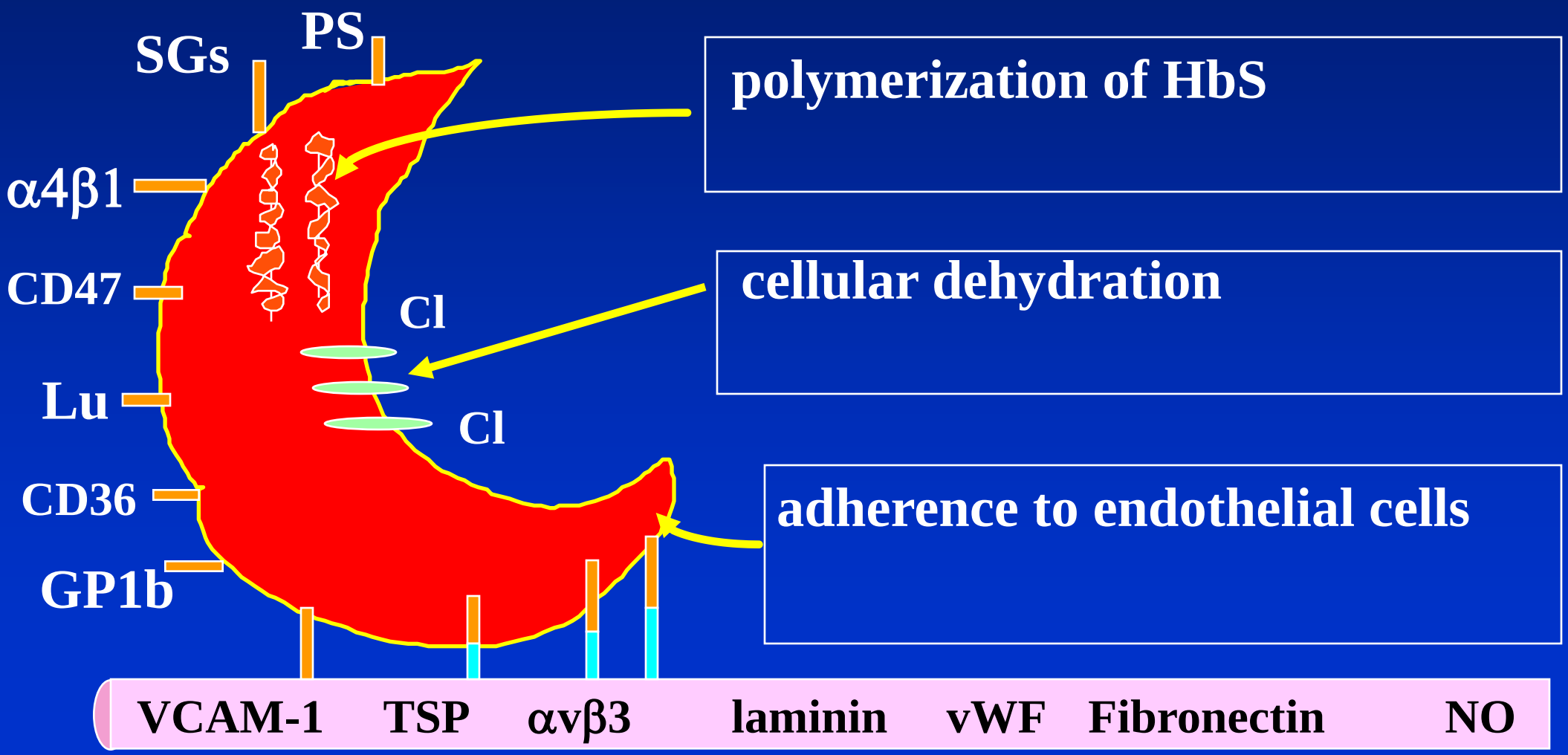
HbF 18.5%

HbF 25%

x Hb AS
(low HbS)

Poillon et al, PNAS 90: 5039-43, 1993

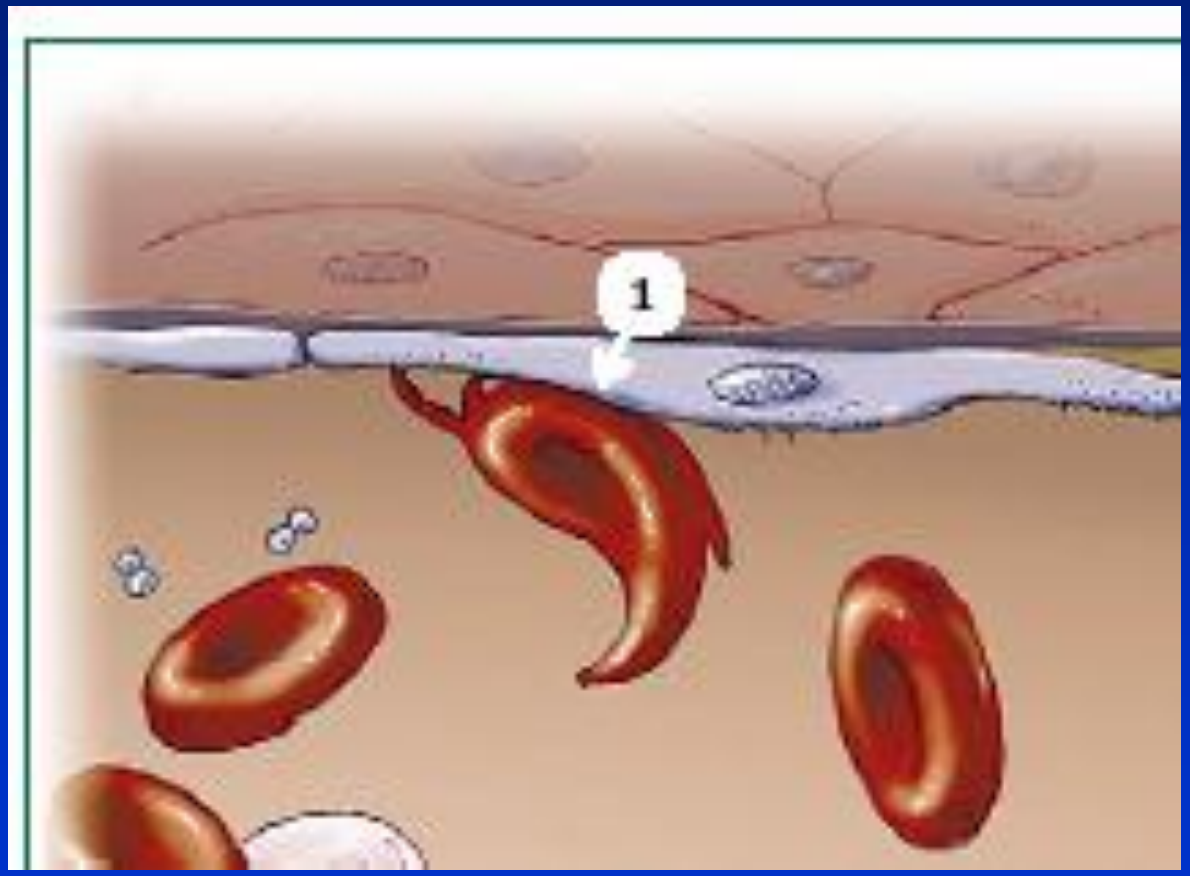
Vascular occlusion in sickle cell disease



Adhesion pathways mediating sickle cell adhesion

Red cells	Endothelial / extracellular matrix
$\alpha 4\beta 1$ integrin	VCAM-1, fibronectin
Sulphated glycans	vWF, thrombospondin (TSP), $\alpha v\beta 3$
CD47 (IAP)	vWF, TSP, $\alpha v\beta 3$ integrin
CD36 (platelet GpIV)	vWF, TSP, $\alpha v\beta 3$
PhosphatidylSerine	vWF, TSP, $\alpha v\beta 3$
Glycoprotein 1b	vWF (von Willebrand factor)
Lutheran blood group	laminin

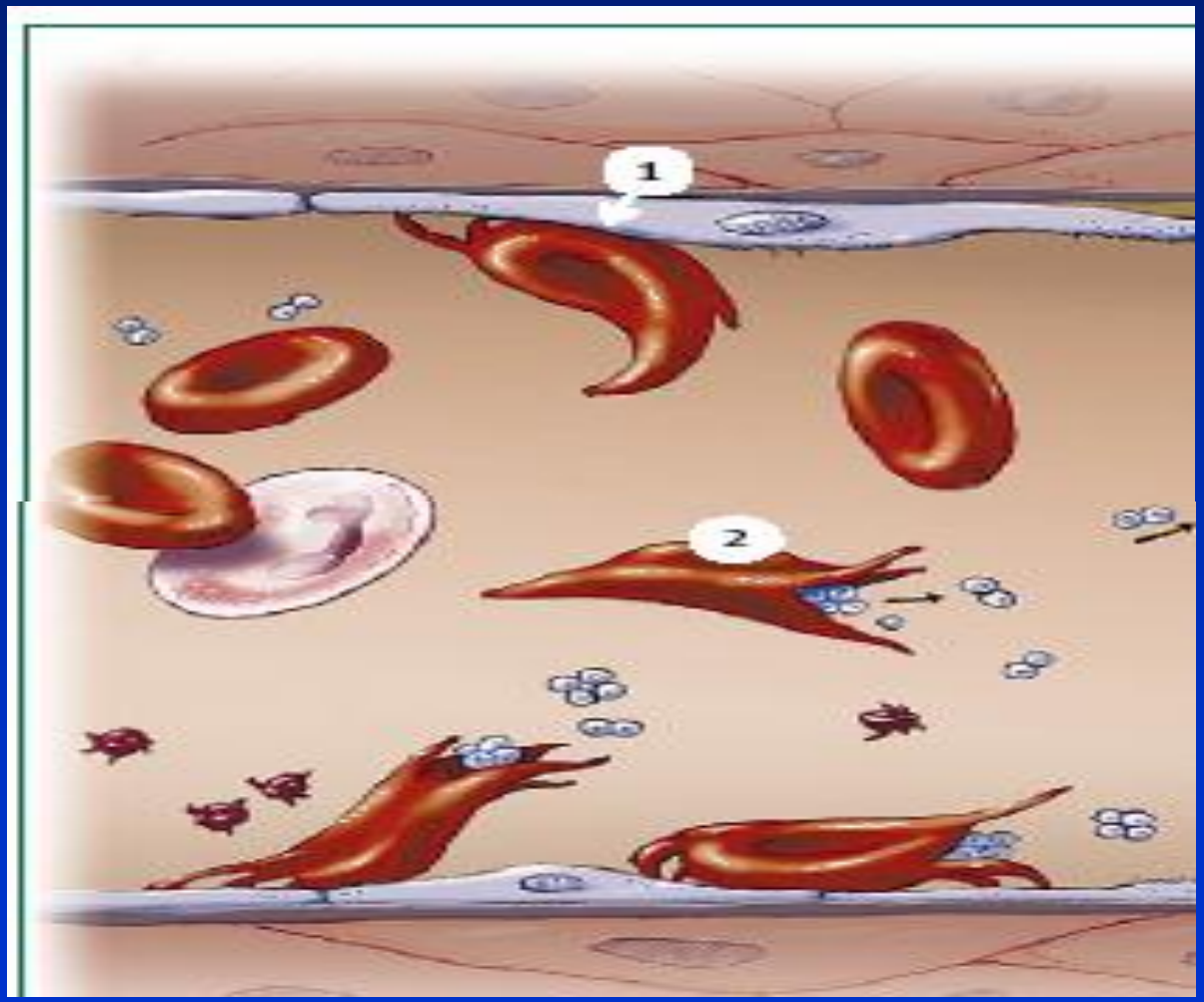
Pathogenesis of Sickling



The development of vaso-occlusion

STEP 1
Red cell adhesion to the endothelium and extracellular matrix proteins

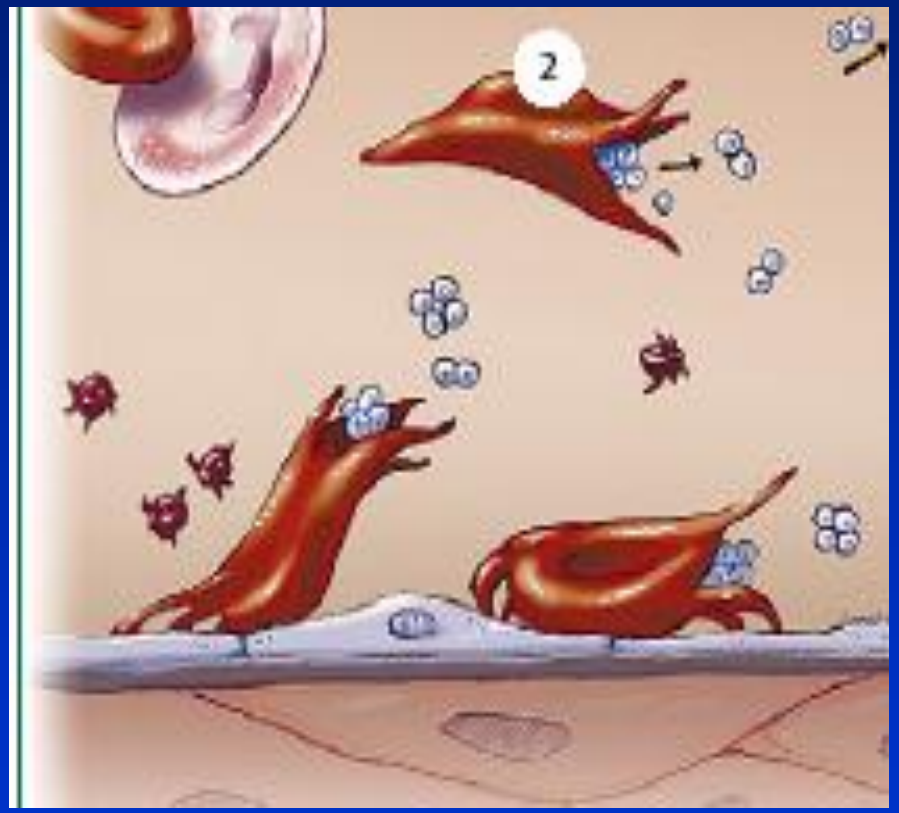
Pathogenesis of Sickling



The development of vaso-occlusion

STEP 2
The role of haemolysis: intra-vascular haemolysis reduces nitric oxide (NO) bioreactivity

Pathophysiology of Sickling

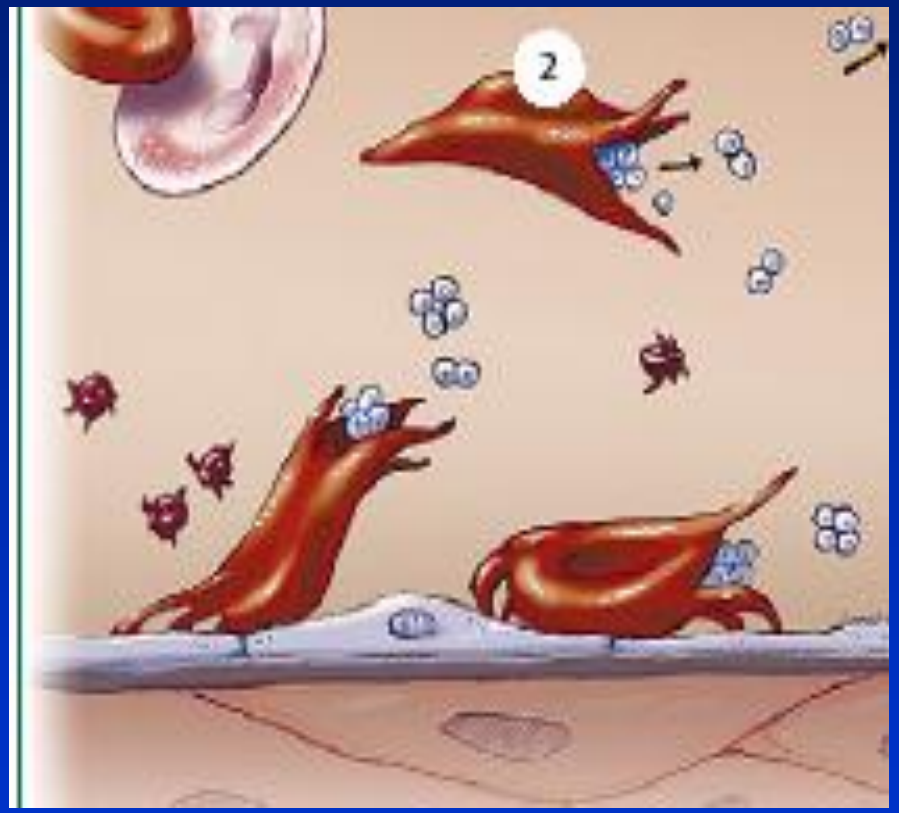


Depletion of NO

Intravascular haemolysis releases from the red cell into the plasma:

- **FREE HAEMOGLOBIN**
- **ARGINASE**
- **LDH**

Pathophysiology of Sickling



Depletion of NO

Intravascular haemolysis releases from the red cell into the plasma:

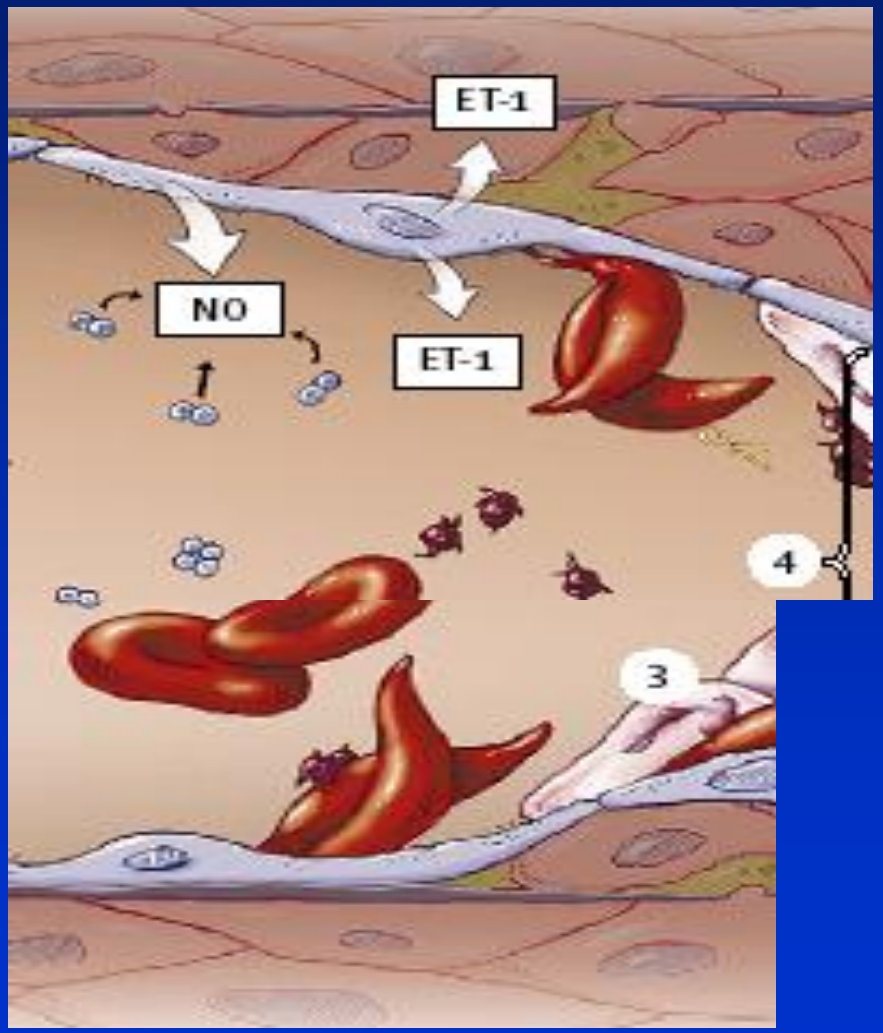
- **FREE HAEMOGLOBIN inactivates NO**
- **ARGINASE depletes arginine for NO production**
- **LDH- marker of haemolysis**

Pathogenesis of Sickling

Nitric oxide

- chronic activation of NO
- increased metabolic demand for NO during VOC
- lower NO levels in patients during VOC
- sickle WBC release increased superoxide-> scavenge NO
- decreased endothelial NO synthase

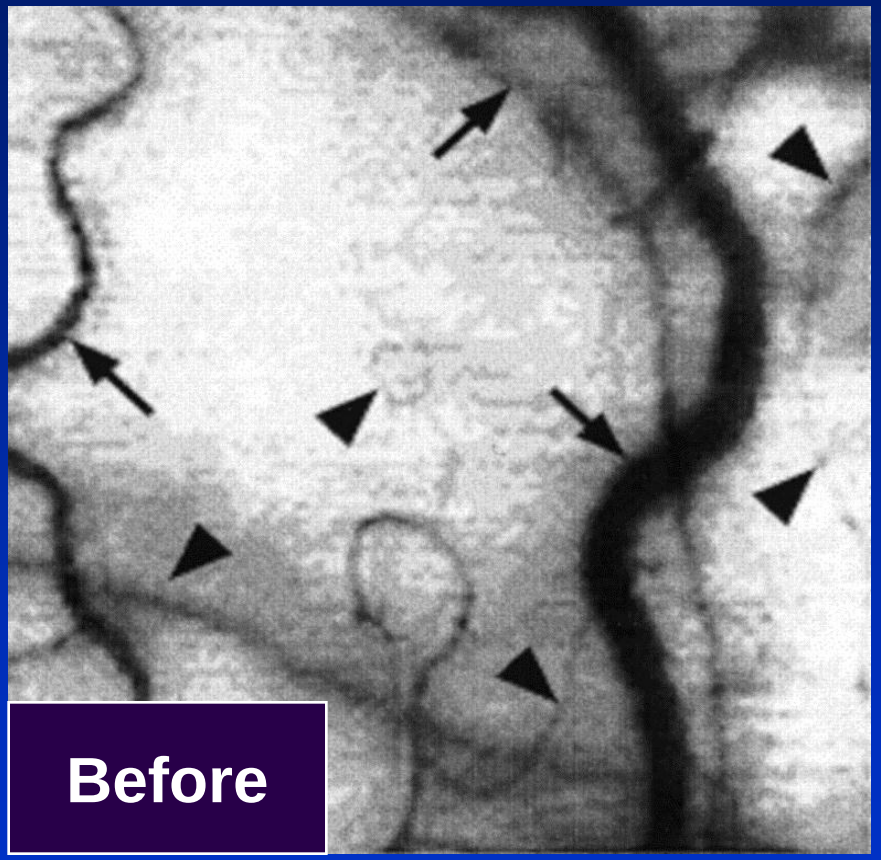
Pathogenesis of Sickling

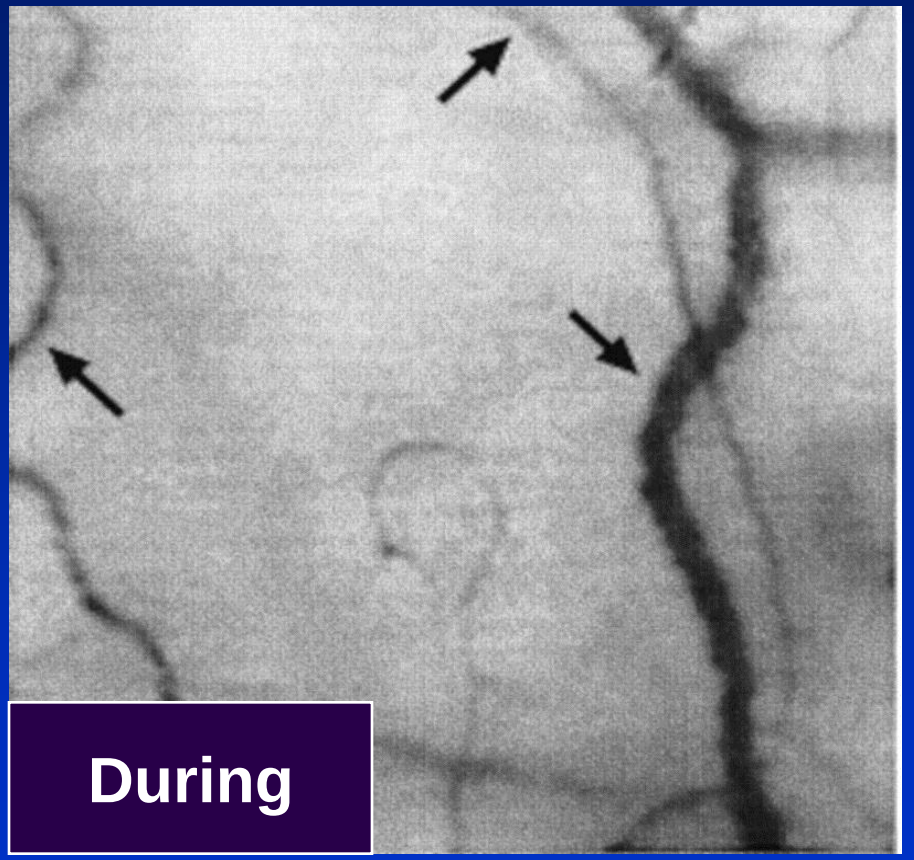


The development of vaso-occlusion

STEPS 3 AND 4
Proinflammatory state mediated by red cell adhesion and haemolysis leads to leucocyte adhesion (selectins), platelet activation, release of endothelin-1 (ET-1) and scavenging of NO by haemoglobin dimers

Microvascular changes during sickle crisis





Cheung, *et al*. Blood 2002

Sickle Cell Disease

VASO-OCCLUSIVE CRISES: clinical features I

- Usually present with pain
- Often accompanied by fever
- Bone pain is the most common
- Other sites include lung, liver, spleen and gut
- Distribution of pain depends on age

Sickle Cell Disease

VASO-OCCLUSIVE CRISES: clinical features II

INFANTS	**Dactylitis** **Splenic sequestration**
CHILDREN	**Long bones** **Acute chest syndrome**
CHILDREN & ADULTS	**Abdominal pain** **Back pain**

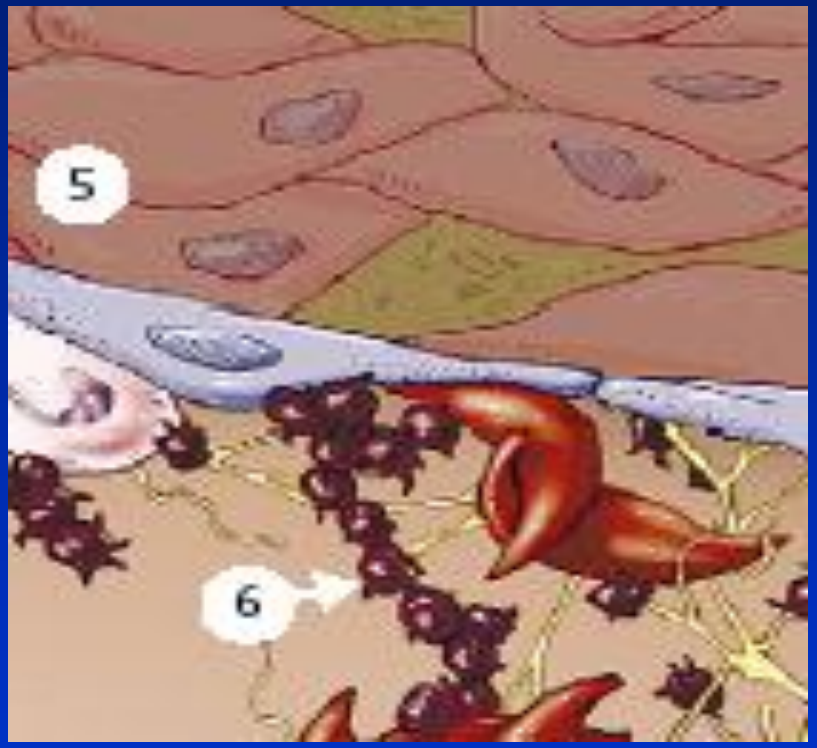
Sickle Cell Disease

VASO-OCCLUSIVE CRISES III:

Crises may be precipitated by:

- dehydration
- infection
- exercise
- cold
- emotional stress

Pathogenesis of Sickling

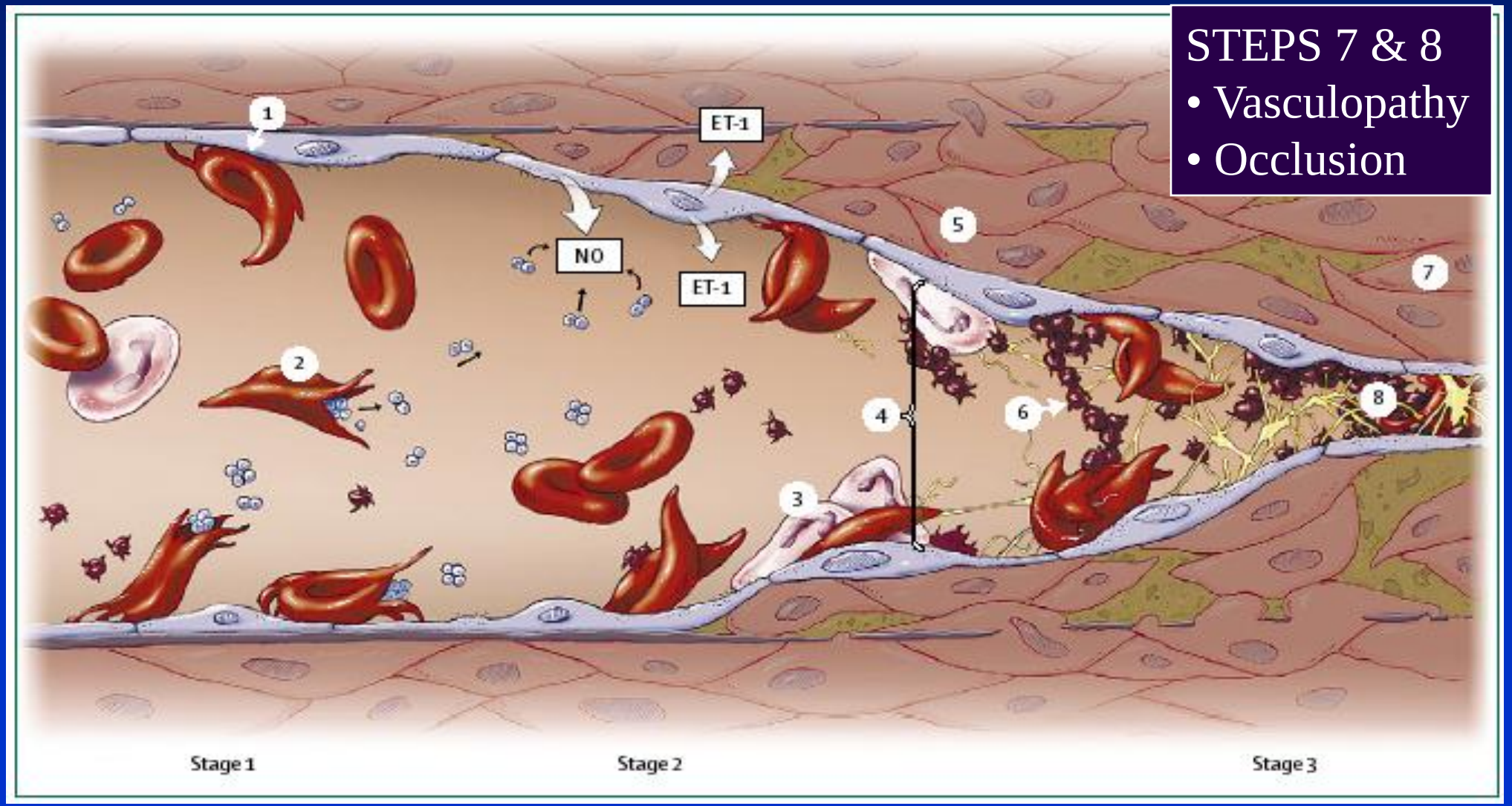


Chronic vascular damage in sickle cell disease

STEPS 5 AND 6

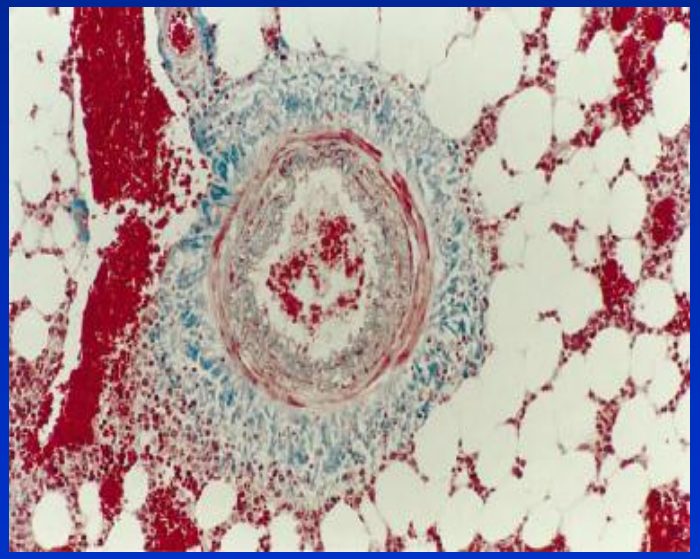
Proliferation of smooth muscle cells and fibroblasts in the intimal layer; platelet aggregation and progression of luminal narrowing

Pathogenesis of Sickling



Sickle Cell Disease

CHRONIC ORGAN DAMAGE



CNS: stroke, occult damage

Kidneys: papillary necrosis, renal failure

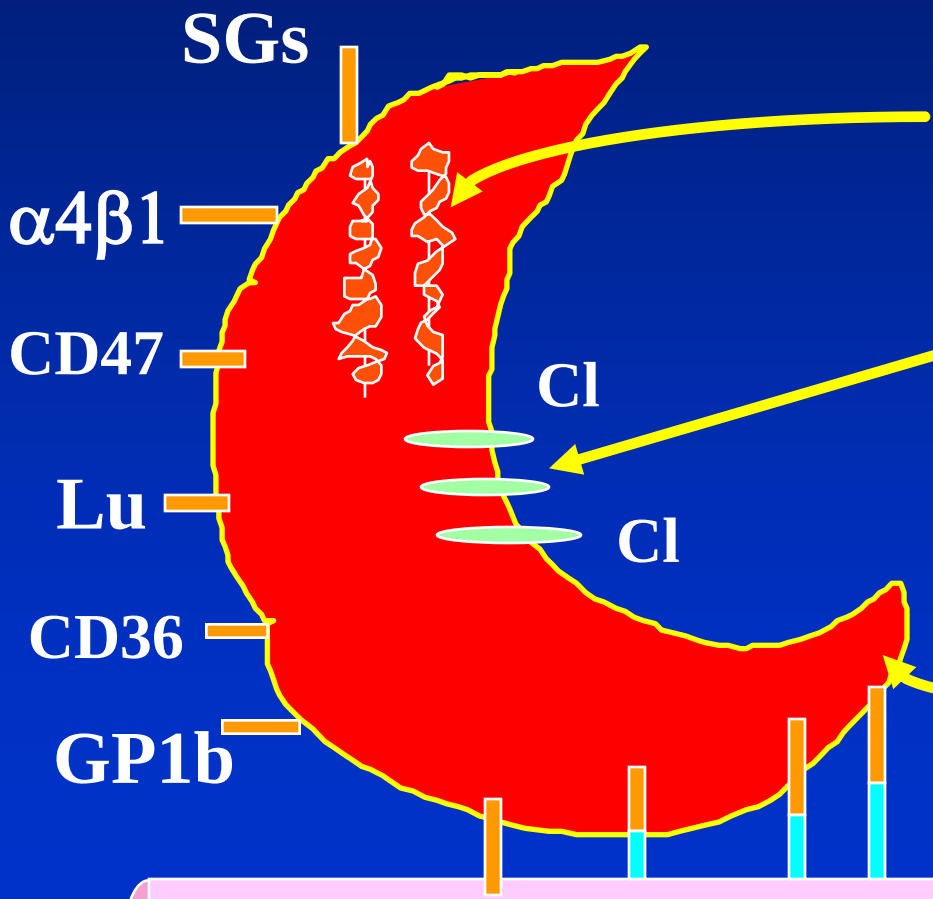
Eyes: retinopathy

Bones/joints: osteonecrosis

Lungs: chronic lung disease

Multi-organ failure: sudden death

Preventing vascular occlusion in sickle cell disease:



polymerization of HbS
↑ HbF within cells

cellular dehydration
Mg, chloride conductance blockers

adherence to endothelial cells
modify RBC-endothelial interactions

VCAM-1 TSP αvβ3 laminin vWF Fibronectin NO

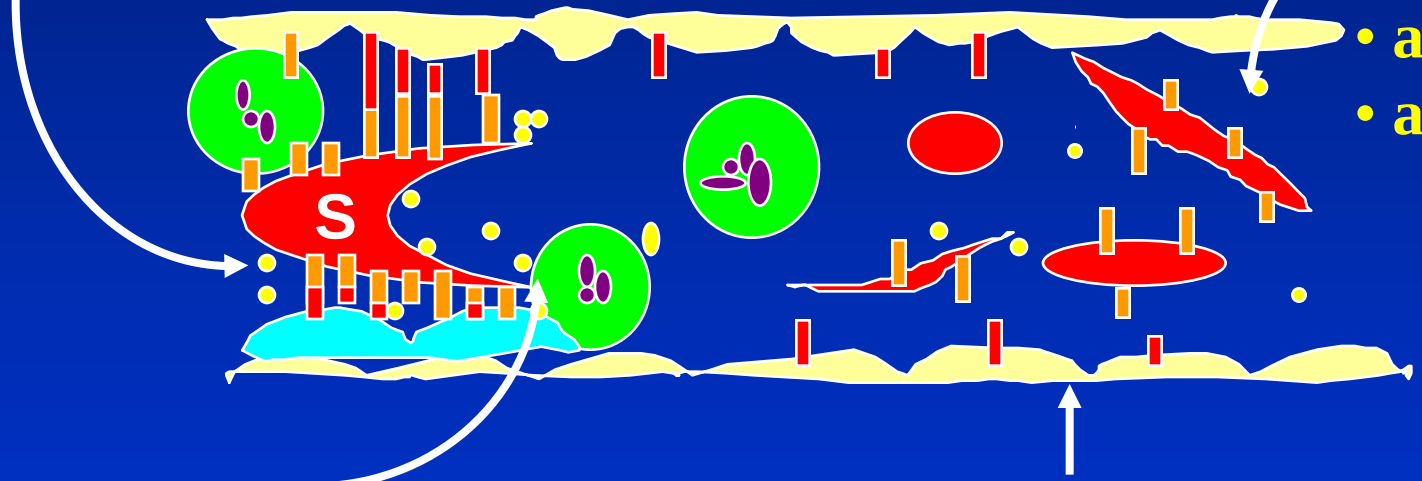
Vaso-occlusion in sickle cell disease-therapeutic approaches

Erythrocytes

- modulating HbF
- Mg/Cl conductance blockers

Platelets/ Coagulation

- anti-platelet drugs
- anticoagulants



Leucocytes

- hydroxyurea
- anti-inflammatory drugs

Endothelial cells

- NO
- arginine
- statins

heparin
sildenafil
ET-1 antagonists