

***Pathophysiology and  
Clinical Presentations  
Of  
Sickle Cell Disease***

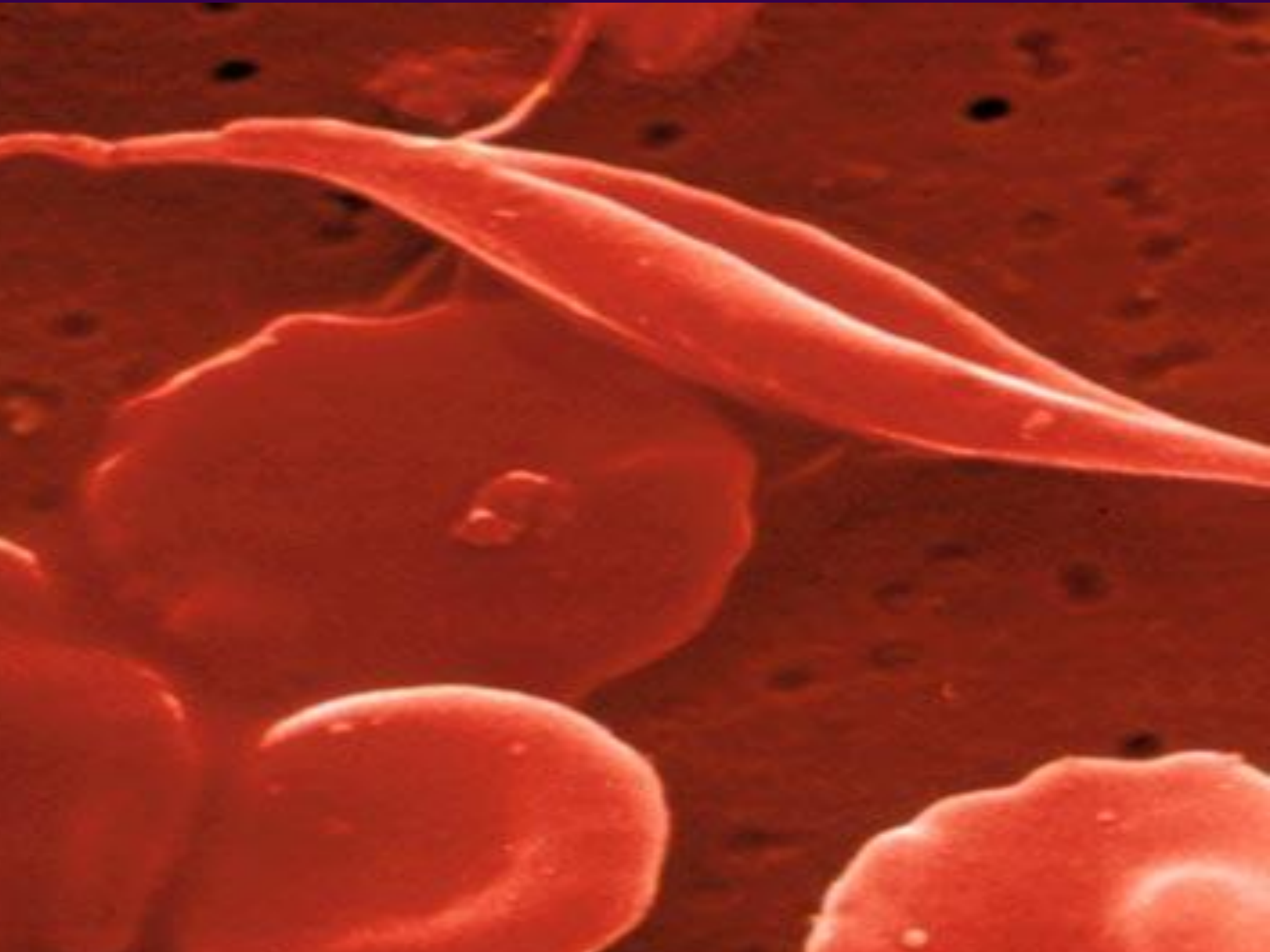
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# Epidemiology of HbS

- ❖ Survival advantage of carriers in malaria-endemic area and subsequent migration
- ❖ HbS has global distribution
- ❖ African haplotypes
  - Senegal, Bantu, Benin and Cameroon
- ❖ Asian haplotype
  - Arab-India
- ❖ HbC and  $\beta$ -Thal also appeared due to malaria selection

# HbS

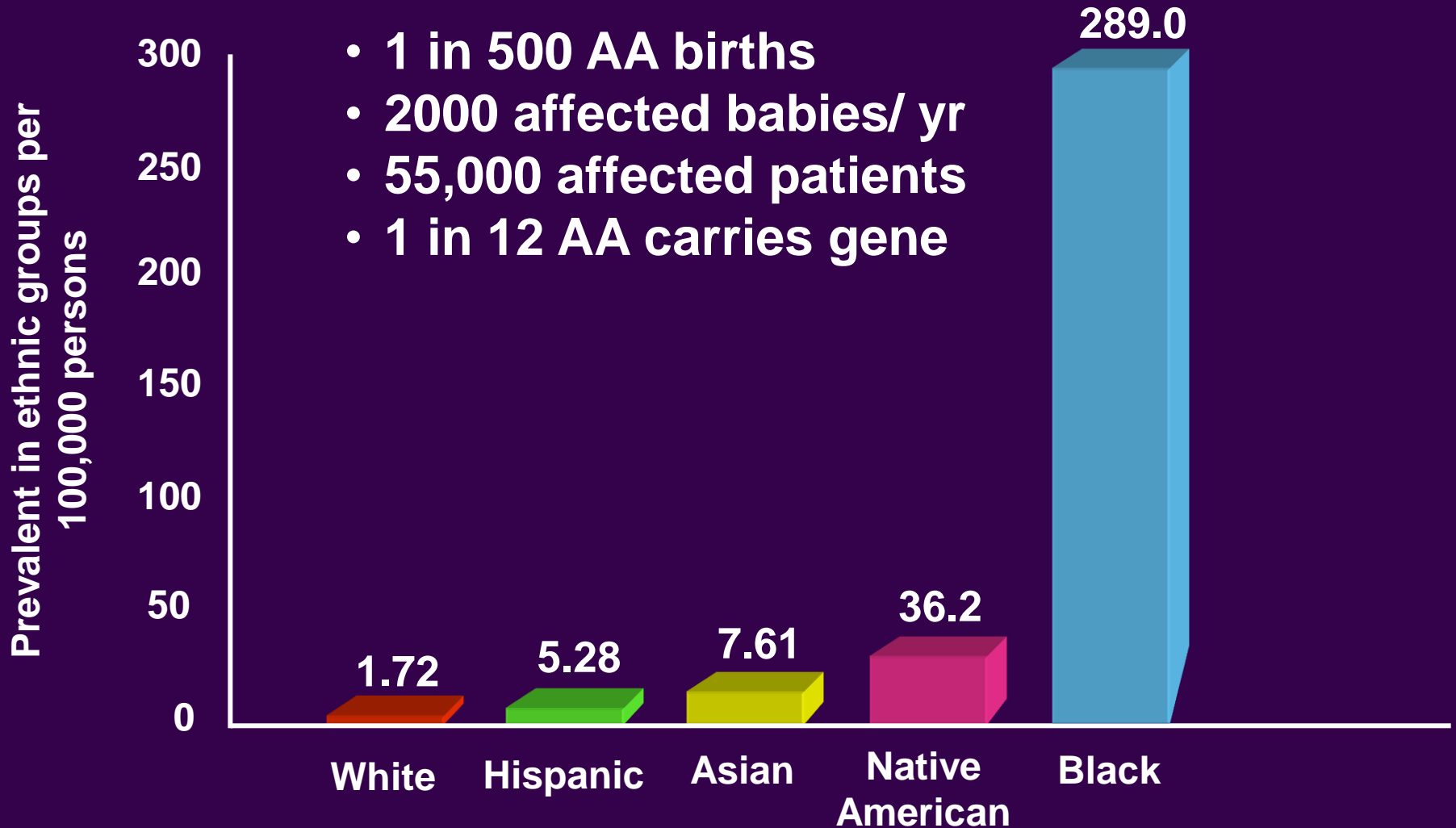
- ❖ **Mutation in  $\beta$ -globin gene –**
  - **6<sup>th</sup> AA in  $\beta$ -globin - GA replaced by valine**
- ❖ **Mutation produces a hydrophobic motif in the deoxygenated HbS tetramer**
- ❖ **Crystallization produces polymer nucleus, which grows & fills the erythrocyte**
  - **Disrupts architecture & flexibility**
  - **Promotes cellular dehydration**

# Classification

- ❖ SCD refers to all genotypes with characteristic clinical syndrome
- ❖ SCA - the most common form of SCD, refers to HbSS homozygosity for  $\beta^s$  allele.
- ❖ African origin - SCA accounts for 70% SCD
  - Remainder - HbSC ( $\beta^s$  and  $\beta^c$  alleles)
- ❖ India and Saudi Arabia -  $\beta^s$  is inherited with a  $\beta$ -thal allele (HbS/ $\beta$ ) - accounts for 50%

<b>Year</b>	<b>Discovery</b>	<b>Importance</b>
<b>1910</b>	<b>Sickled RBC in Grenadan dental student</b>	<b>1<sup>st</sup> description of disease linked to abnormal RBC</b>
<b>1924</b>	<b>Hemolysis in SCD</b>	<b>Explanation for Anemia, jaundice and gall stones</b>
<b>1924</b>	<b>Vaso-occlusion</b>	<b>Explanation for ischemic tissue damage</b>
<b>1948</b>	<b>No symptoms in infants noted</b>	<b>Benefits of HbF</b>
<b>1951</b>	<b>Polymerization of deoxygenated HbS</b>	<b>Primary molecular mechanism identified</b>
<b>1980s</b>	<b>Value of penicillin in young children</b>	<b>Reduced mortality, neonatal screening</b>
<b>1984</b>	<b>BMT in SCD + leukemia</b>	<b>Potential cure</b>
<b>1995</b>	<b>Efficacy of hydrea</b>	<b>Only Dz modifying drug</b>
<b>1998</b>	<b>STOP study</b>	<b>Primary stroke prevention</b>

# Sickle Cell Disease in the US





**Complications of SCA**

# Complications of SCA

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- ❖ Pain Crises
- ❖ Hemolytic, megaloblastic, aplastic crises
- ❖ Splenomegaly then autosplenectomy
  - ❖ Acute chest syndrome (ACS)
  - ❖ Cerebrovascular Accidents (CVA)
- ❖ Priapism
- ❖ Bone necrosis
- ❖ Renal complications

# Clinical Phenotypes of SCD

<b>Severe SCD</b>	<b>Distribution</b>
<b>HbS/S</b>	<b>Most common form of SCD</b>
<b>Hbs/<math>\beta^0</math> Thal</b>	<b>Eastern Mediterranean and India</b>
<b>Severe HbS/<math>\beta^+</math> Thal</b>	<b>Eastern Mediterranean and India</b>
<b>HbS/O Arab</b>	<b>North Africa, Middle East, Balkans</b>
<b>HbS/D Punjab</b>	<b>Predominantly Northern India</b>

## Moderate SCD

## Distribution

HbS/C

25-30% SCD of African origin

Mod HbS/ $\beta^+$  Thal

Most cases in eastern Mediterranean

HbA/S Oman

Very rare

## Mild/Very mild

## Distribution

HbS/E

SE Asia

Mild HbS/ $\beta^{++}$  Thal

Most cases in eastern Mediterranean

HbS/HPFH

30% HbF

# Pathophysiology

- ❖ **Disease severity depends on rate & extent of HbS polymerization**
  - **Concentration of HbS**
  - **Extent & duration of deoxygenation**
  - **Co-inheritance of genetic factors that modulate the intracellular HbS or HbF**
    - **$\alpha$ -Thal or HPFH**

# Clinical Manifestations

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- ❖ **Driven by two major pathophysiological processes**
  - **Hemolysis**
  - **Vaso-occlusion**

# Complications of SCD

<b>Hemolysis – Endothelial Dysfunction</b>	<b>Vaso-occlusion Viscosity</b>
Higher hemolysis rate	Lower Hemolysis rate
Higher Plasma Hb and arginase and low NO	Higher Hb and high plasma arginine
CVA, PH, Leg ulcers Priapism	ACS, Pain crisis, Osteonecrosis

# Abnormal Solubility

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- ❖ Deoxy HbS polymerizes when  $> \sim 16\text{g/dL}$
- ❖ Extremely sensitive to RBC hydration
- ❖ Sickling stimulates deformation-dependent cation-water leak
  - Persistent cell dehydration
  - Increased cytoplasmic viscosity
  - Directly causes poor cell deformability

# Vaso-occlusion

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- ❖ **HbS polymerization often triggered by inflammation**
- ❖ **Acute vaso-occlusion - entrapment of deformed and rigid RBCs & WBCs in microcirculation (postcapillary venules)**
  - **Tissue ischemia**
  - **Followed by restoration of blood flow which further promotes tissue injury**

# Vaso-occlusion

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- ❖ **Reperfusion causes oxidant stress:**
  - **Activation of vascular oxidases**
  - **Inflammation with cytokine release**
  - **Increased expression of ECAM**
  - **Leucocytosis**
- ❖ **Bone marrow infarction leads to fat embolization - contributes to vascular occlusion in the lungs - ACS**

# Vaso-occlusion & polymerization

Vaso-occlusion: increased H

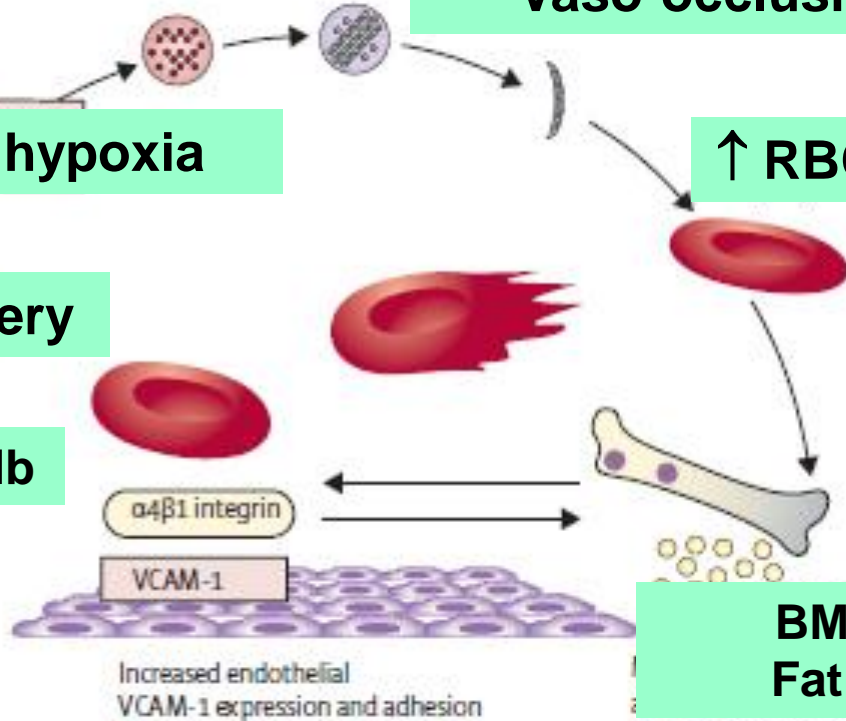
Regional hypoxia

↑ RBC rigidity

↓ O<sub>2</sub> delivery

Denatured Hb

Blood Shunting from V to A



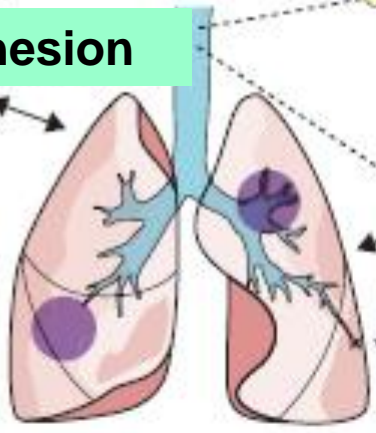
BM infarction  
Fat Embolism

*~Rees et al  
The Lancet 2010*

↑RBC adhesion

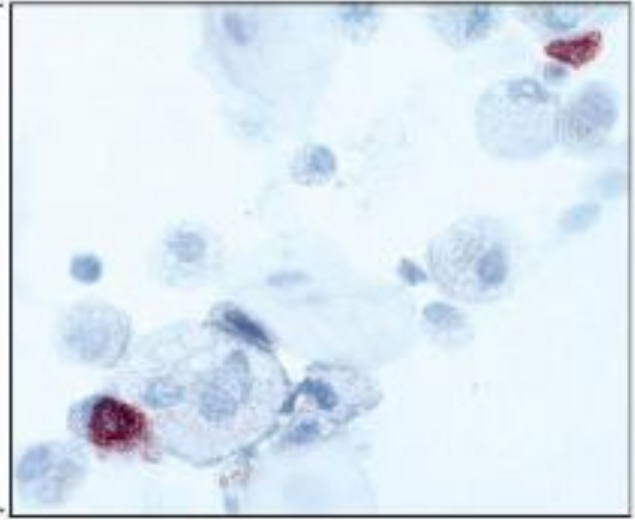
Inflam+  
PL A2

Hypoventilation  
Atelectasis



ACS

Infection



# Hemolysis in SCA

- ❖ **HbS polymerization contributes to hemolysis - inter-individual heterogeneity**
  - One-third intra-vascular
  - Two-thirds extra-vascular
- ❖ **All four fundamental destructive mechanisms:**
  - Red cell trapping
  - Red cell breakage
  - Osmotic lysis
  - Erythrophagocytosis

# Other Effects of Sickling-Induced Membrane Deformation

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- ❖ Reoxygenation leads to vesiculation due to uncoupling of the lipid bilayer
  - PS positive MP
- ❖ Likely cause of the abnormal membrane complement deposition (and activation)
  - ? lysis of irreversibly sickled cells

# Membrane Defects

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- ❖ Hemichromes cause clustering of Band 3 with binding of naturally-occurring autologous anti-Band 3 IgG
- ❖ Sickle RBCs carry abnormal amounts of IgG (but not enough for DAT+) and complement
- ❖ Opsonization enhances erythrophagocytosis of RBC

# Role of Free Hb

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- ❖ **Important disease mechanism IVH**
- ❖ **Free plasma Hb generates reactive oxygen species**
  - Hydroxyl
  - Superoxide radical
- ❖ **A potent scavenger of nitric oxide**

# Nitric Oxide

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- ❖ **NO produced by the endothelium**
  - **Basal vasodilator**
  - **Inhibits platelets and coagulation**
  - **Regulates adhesion molecules - VCAM, ICAM & the selectins**

# Plasma Arginase

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- ❖ **IVH releases enzymatically active arginase**
- ❖ **Which can deplete blood arginine**
  - **Arginine substrate for NO**
- ❖ **Impaired eNOS function**
- ❖ **Impaired NO bioavailability**

# Vasculopathy

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- ❖ **As at risk patients age, vasculopathy develops characterized by**
  - **Pulmonary hypertension**
  - **Systemic hypertension**
  - **Endothelial dysfunction**
  - **Proliferative changes in the intima & smooth muscle of blood vessels**

# CVA - Vasculopathy

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- ❖ **10% SCA develop CVA by the age 20**
- ❖ **Vasculopathy seen in MCA and ICA**
- ❖ **Detected as early as 2-3 yrs of age by increased TCD blood flow**
- ❖ **With blood transfusion therapy – it is reversible – STOP study**

# Pulmonary Hypertension

- ❖ Increasingly recognized complication of SCD in teenagers and adults
- ❖ Echocardiography – measure tricuspid regurgitation jet velocity
  - Normal = 32 mm of Hg
  - Mild PH = >35 mm of Hg
  - Mod-severe PH = >45 mm of Hg

# Hemolysis and Pulmonary Hypertension

- ❖ PH results from vasculopathy
- ❖ A clinical subphenotype of “hyperhemolytic” patients - “hyperhemolysis paradigm” (HHP)
  - They have low H/H
  - High % retic count
  - High LDH

# Biomarkers of Hemolysis (RBC Lifespan)

- ❖ RBC average life span 15-17 days with enormous variability (6 - 35 days)
- ❖ **Uncorrected retic count (retic%) is dependent upon marrow generative capacity - hence the most robust correlate with lifespan**
- ❖ Paradoxically, the corrected retic count (absolute retic count) is less useful

# Biomarkers of Hemolysis (RBC Lifespan) - 2

- ❖ H/H weak correlate of hemolysis rate
- ❖ Indirect bili, LDH and AST, plasma Hb/heme and arginase are only quaternary hemolysis biomarkers
- ❖ Haptoglobin and hemopexin also not very helpful

# Ineffective Erythropoiesis

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- ❖ **Small or even trivial contribution to anemia**
- ❖ **Recently examination of BM - damaged erythroid precursors as soon as hemoglobinization begins**
- ❖ **Derives from the instability of HbS with its consequent oxidant toxicity**

# Hypercoagulable State



Differences Between a Believer and Non-Believer

# Hypercoagulable State

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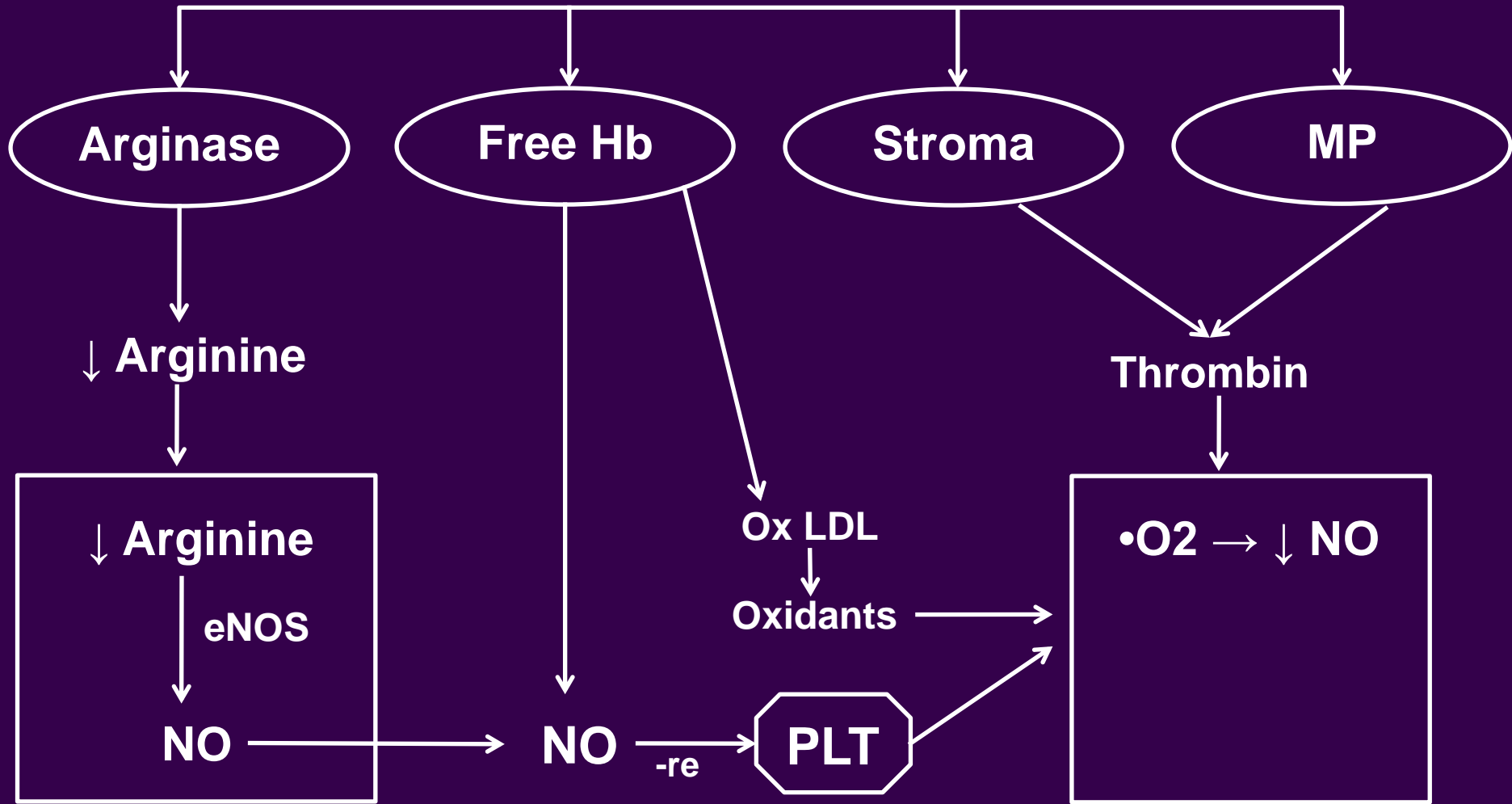
- ❖ **Chronic depletion of NO contributes to the hypercoagulable state**
- ❖ **Good correlation between the rate of hemolysis and activation of**
  - **Platelets**
  - **Coagulation**
- ❖ **Numbers of MP increased further by the functional asplenia**

# Hypercoagulable State

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- ❖ Both MP and RBC that are PS-positive hence promote generation of thrombin
- ❖ PS activates TF and supports prothrombinase complex
  - Increased thrombin generation
- ❖ Expression of various adhesion molecules on endothelium promotes thrombus formation

# Products of I.V.H. in Plasma



**Relax Smooth Muscle**

# Genetic Modifier

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- ❖ **Two best established genetic modifiers are**
  - **Co-inheritance of  $\alpha$ -thalassemia**
  - **Fetal hemoglobin concentration**

# $\alpha$ -Thalassemia

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- ❖ Reduced concentration of HbS in each RBC decreased tendency of HbS to
  - polymerize and hemolyze
- ❖ Reduced occurrence of stroke, gall stones, leg ulcers, priapism
- ❖ However, pain frequency is increased possibly due to increased Hct and viscosity

# HbF

- ❖ **Instability of HbS inhibited by HbF**
- ❖ **HbF correlates robustly and linearly with red cell lifespan**
  - ~2 weeks for non-F cell
  - 6-8 weeks for F-cells
- ❖ **PH patients with “hyperhemolysis”**
  - lower average HbF values

# Hydroxyurea

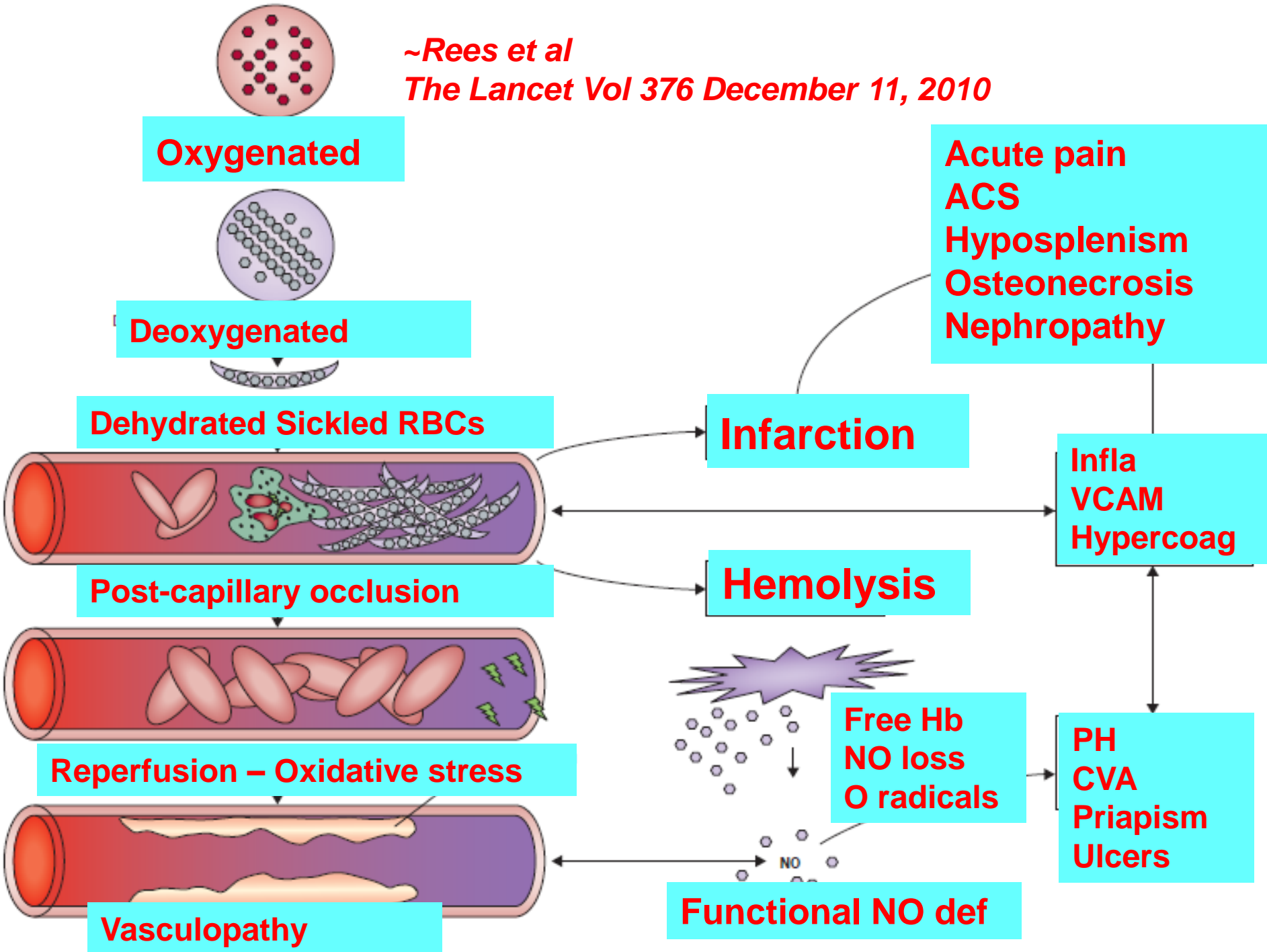
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- ❖ **Cytotoxic drugs increase HbF conc**
- ❖ **Hydroxyurea selected because of its oral efficacy and low toxic effects**
- ❖ **RCT- hydroxyurea decreased**
  - **Frequency of painful episodes**
  - **Acute chest syndrome,**
  - **Need for blood transfusion**
  - **Admission to hospital**

**Thus pathophysiology of SCA is so COMPLEX that....**



*~Rees et al  
The Lancet Vol 376 December 11, 2010*



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“Wake up! You’re the next interesting speaker!”

# Summary

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- ❖ Pathophysiology is very complex
- ❖ Hemolysis and vaso-occlusion appear to have different clinical phenotypes
- ❖ Hemolysis causes chronic vasculopathy responsible for CVA, PH, leg ulcers and priapism
- ❖ Veno-occlusion causes ACS, pain crisis, hyposplenism, nephropathy and osteonecrosis