Pathophysiology of Sickle Cell Anemia: Hemoglobin S Polymerization

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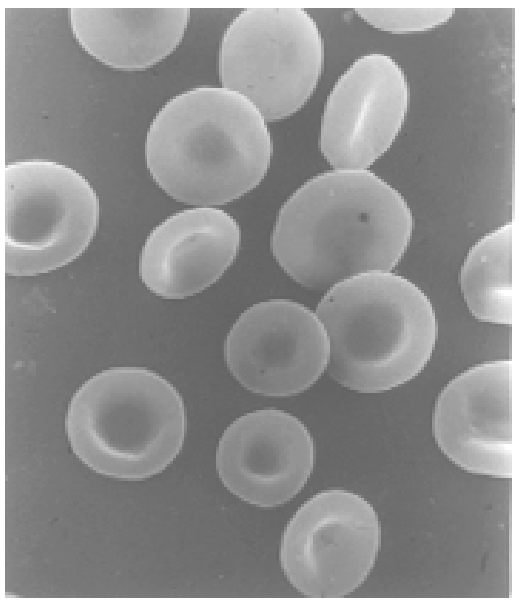
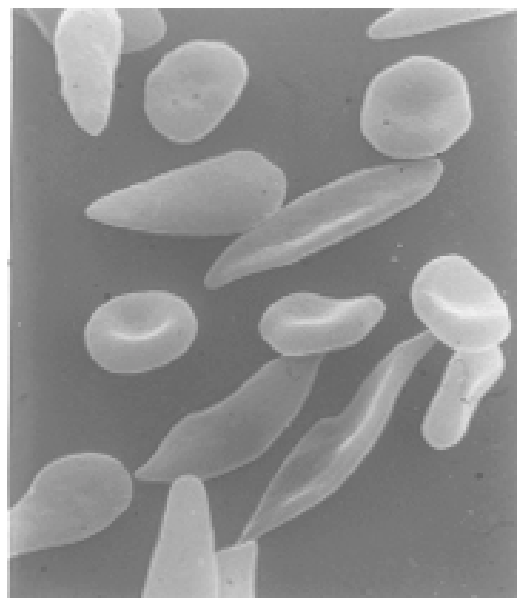
Red Blood Cells from Sickle Cell Anemia

- **Deoxygenation of SS erythrocytes leads to intracellular hemoglobin polymerization, loss of deformability and changes in cell morphology.**

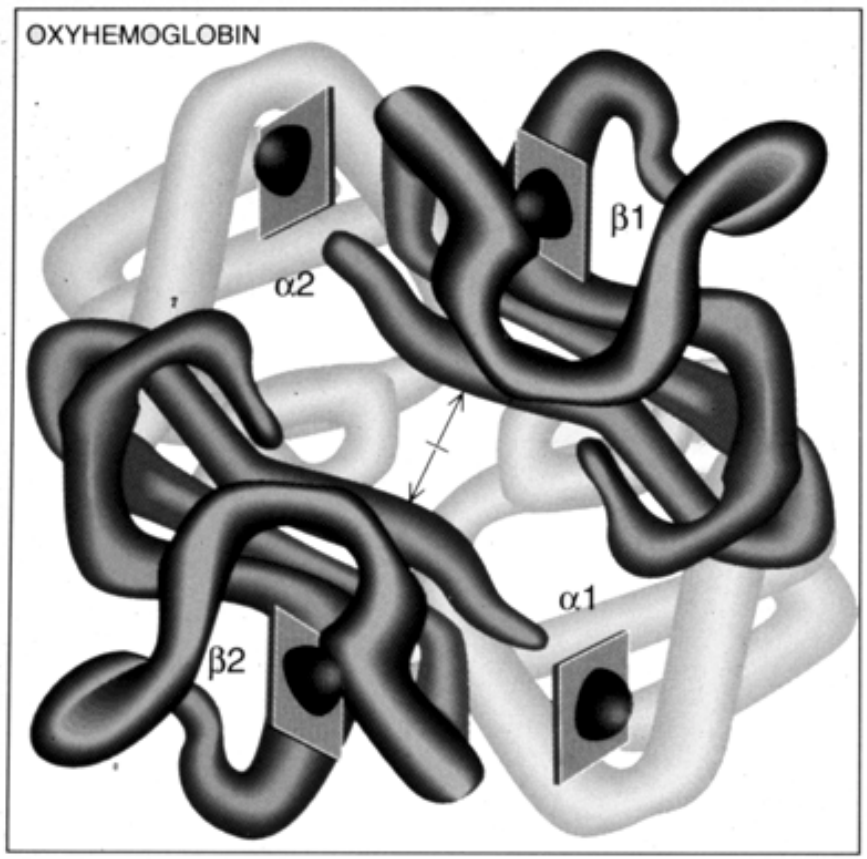
OXY-STATE ⟷ **DEOXY-STATE**



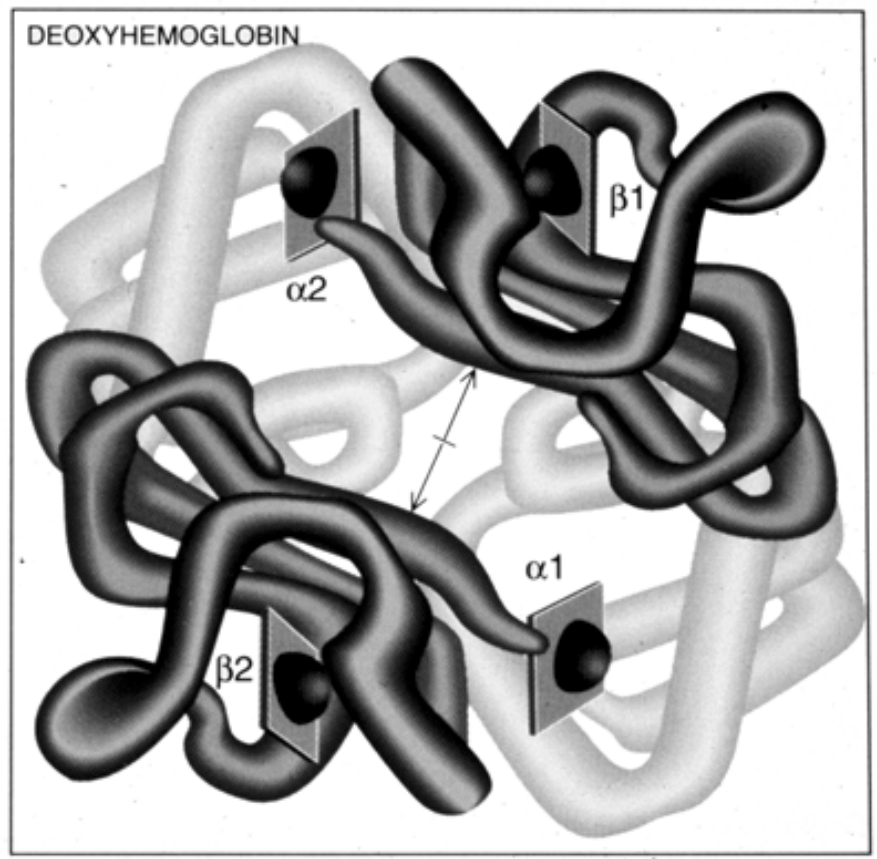


Hemoglobin: The Oxygen Transporter

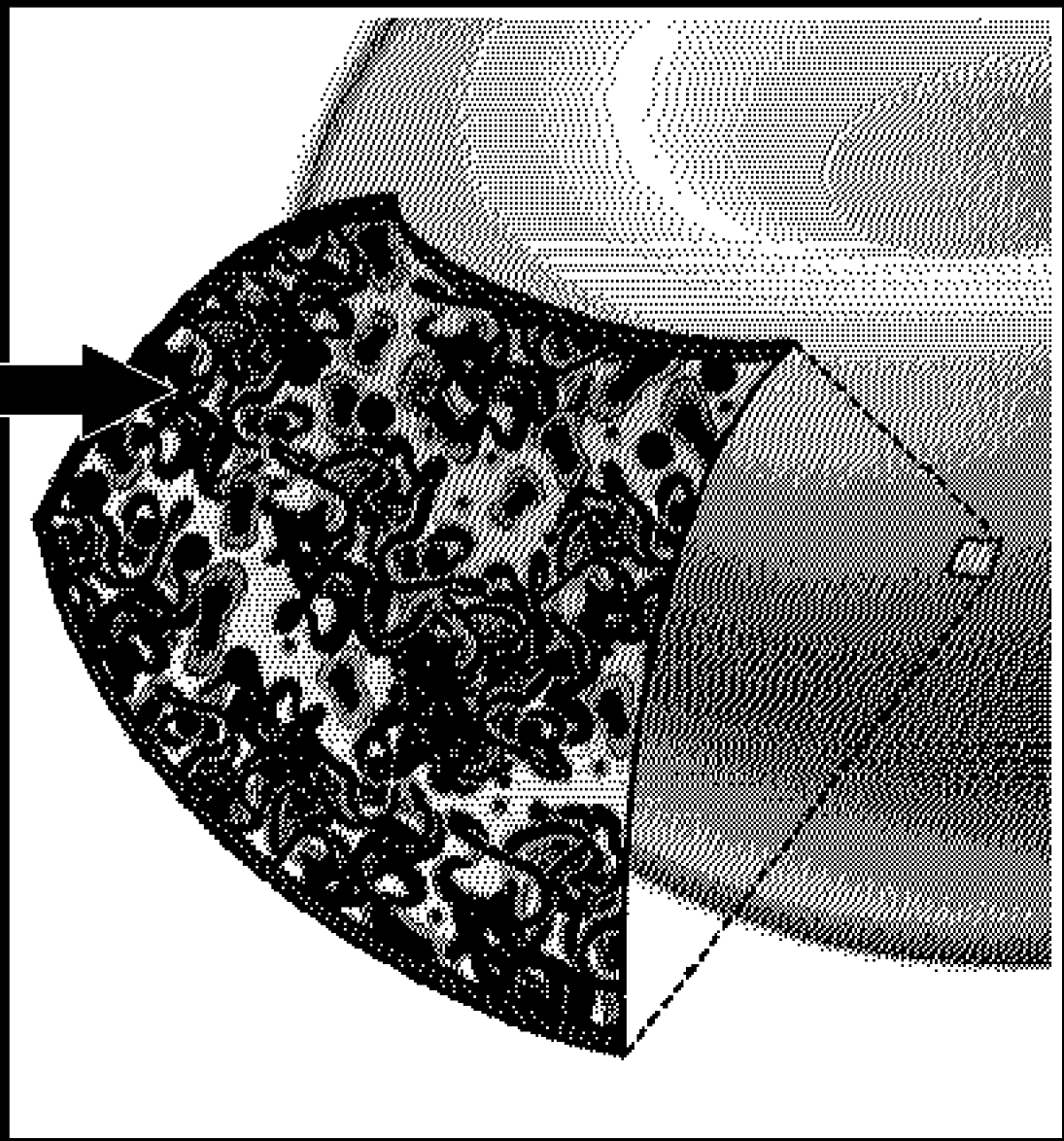
OXYHEMOGLOBIN



DEOXYHEMOGLOBIN

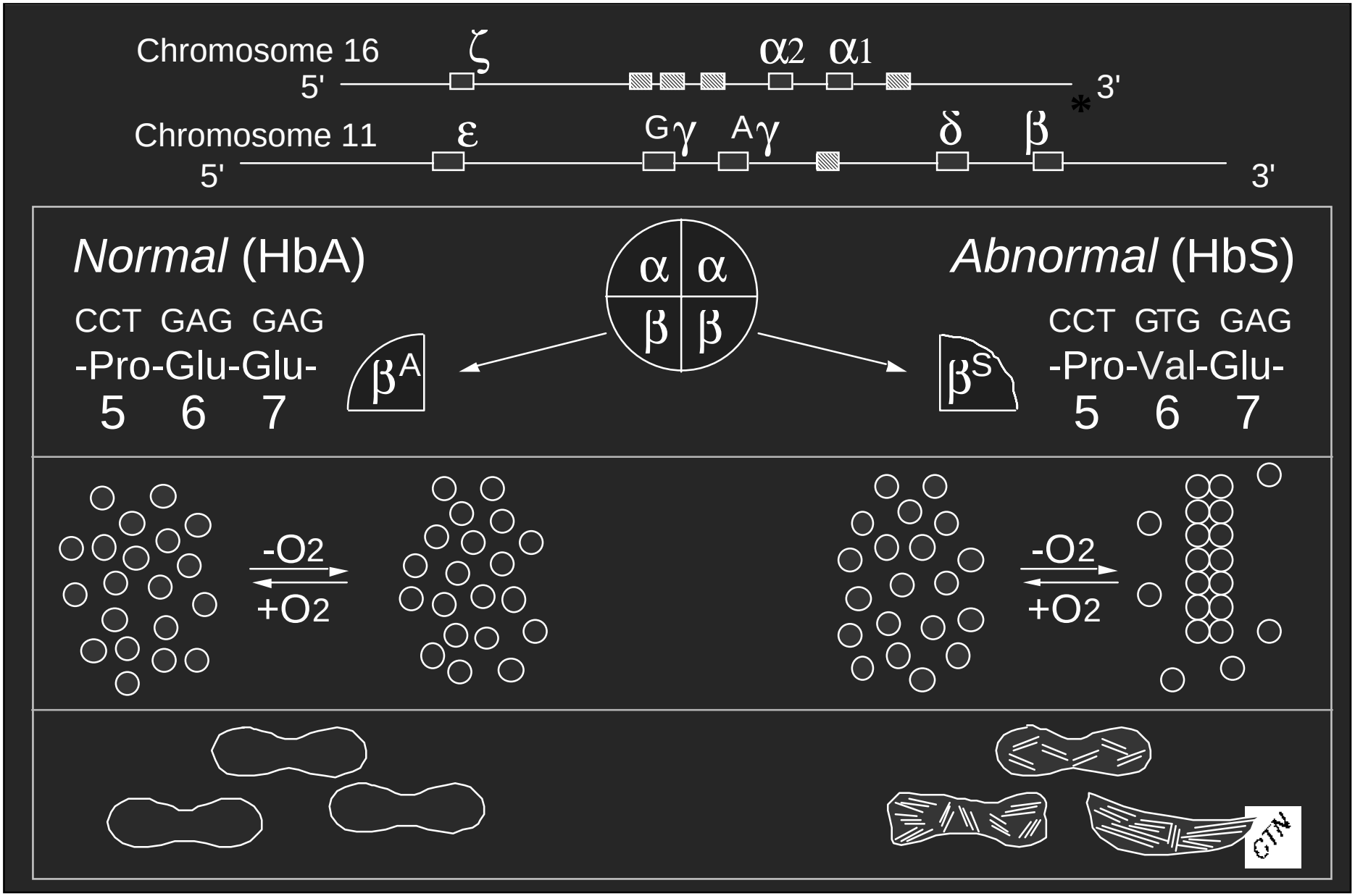


Red Blood Cell



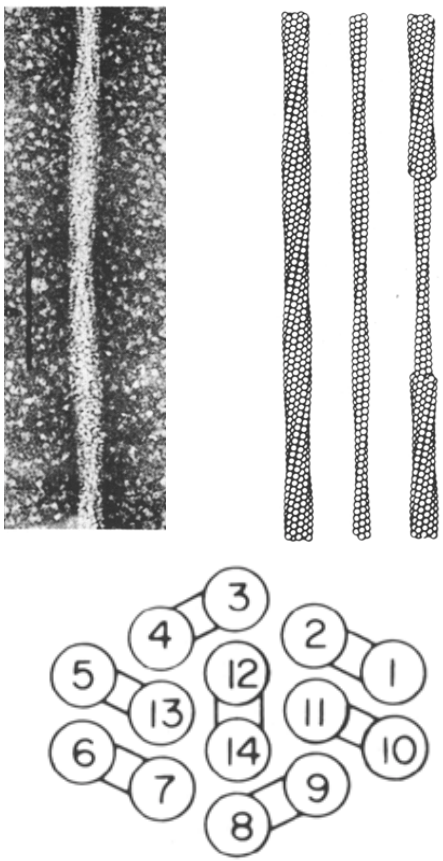
Hemoglobin at 34 g/dl:
-Molecular separation
<1 diameter
-Activity coefficient
~50.

Sickle Cell Mutation



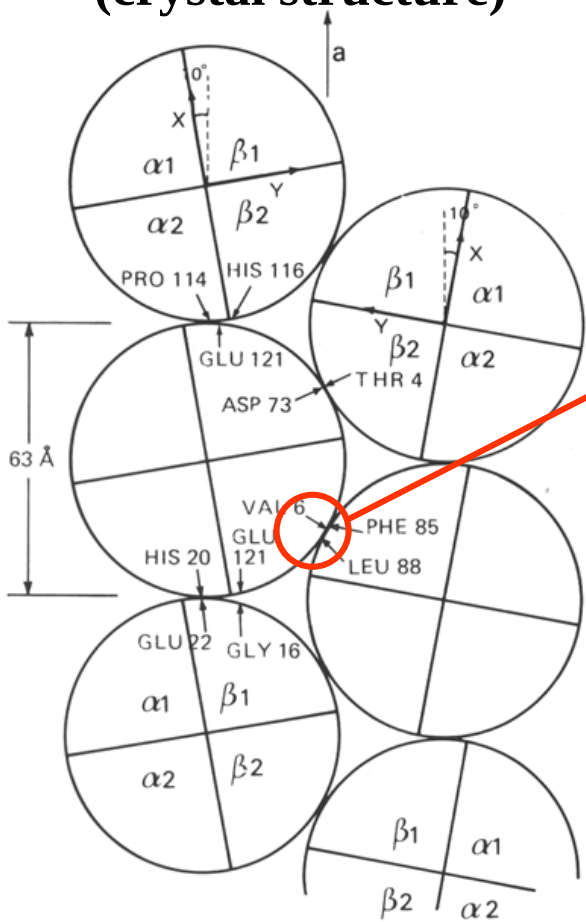
Deoxyhemoglobin S Polymer Structure

A) Deoxyhemoglobin S 14-stranded polymer (electron micrograph)



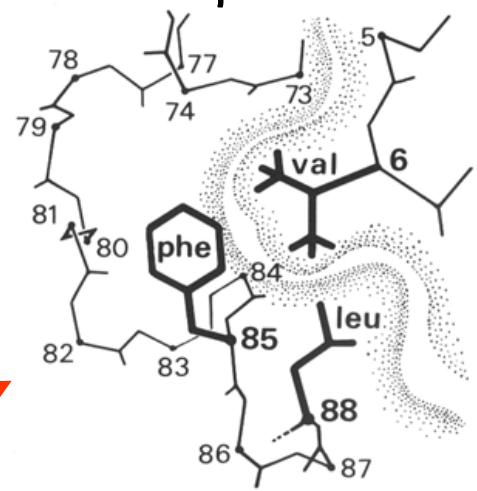
Dykes, Nature 1978; JMB 1979
Crepeau, PNAS 1981

B) Paired strands of deoxyhemoglobin S (crystal structure)

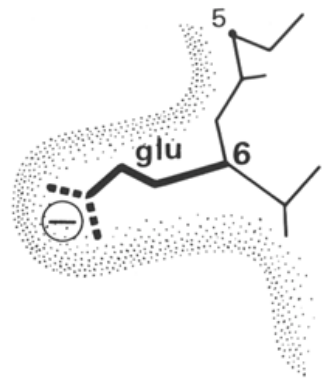


Wishner, JMB 1975

C) Hydrophobic pocket for 6β Val

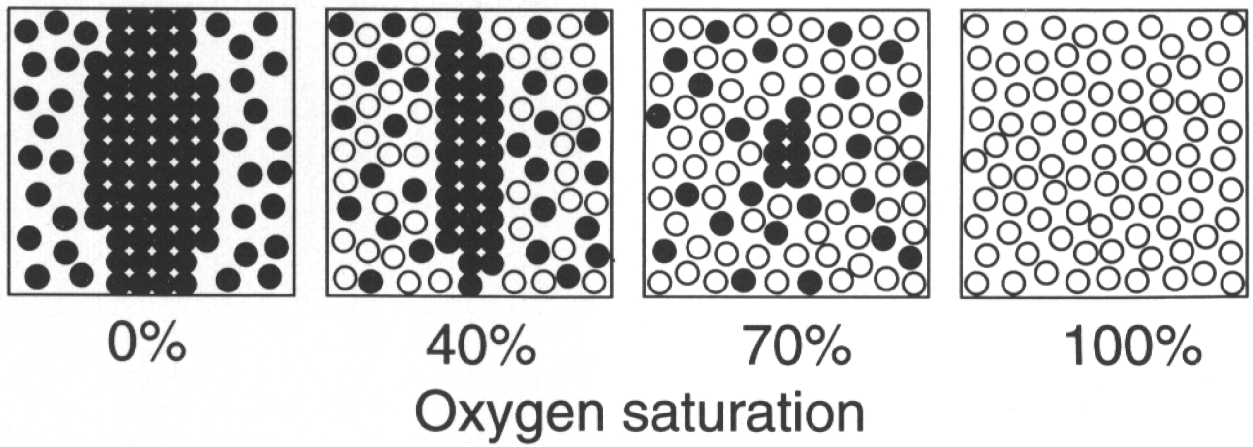


D) Charge and size prevent 6β Glu from binding.



Determinants of Hemoglobin S Polymerization

SS erythrocytes
MCHC ~ 32 g/dl
DeoxyHbS solubility ~16 g/dl

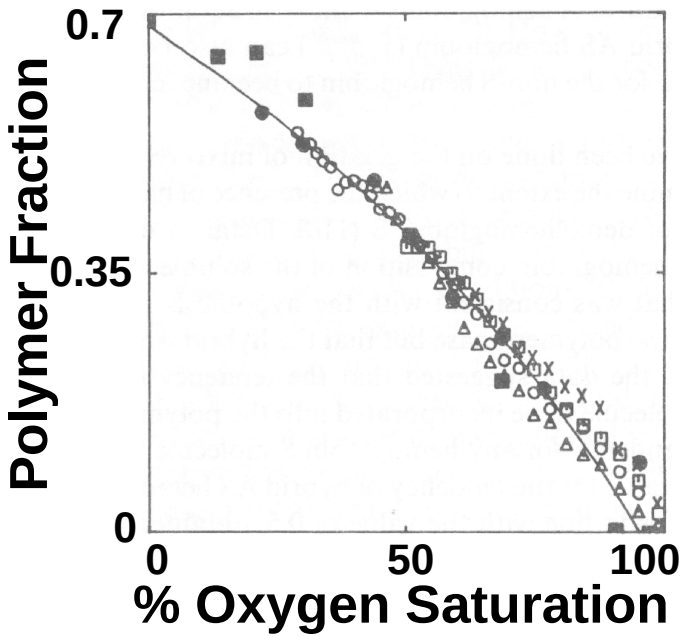


- **Intracellular hemoglobin composition**
- **Intracellular hemoglobin concentration**
- **Oxygen saturation**

Hemoglobin S Polymerization in SS Erythrocytes

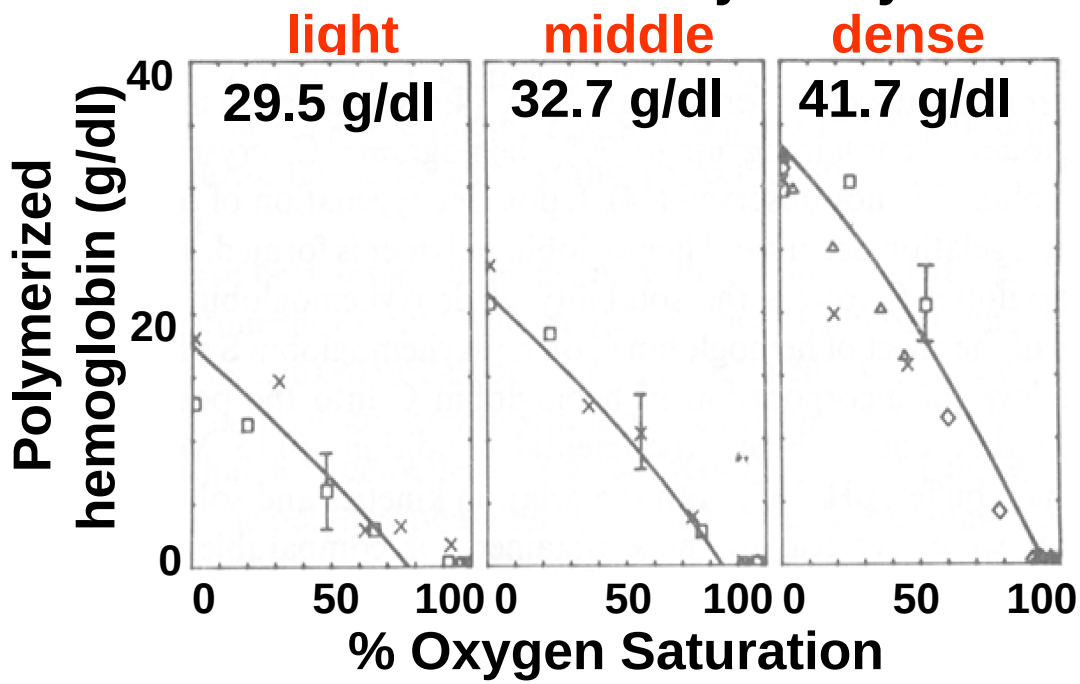
- **Maximal at 0% O_2 sat (oxygen saturation).**
- **Detected at high O_2 sat, particularly in dense cells.**
- **Variable due to heterogeneity in corpuscular hemoglobin concentration.**

Unfractionated SS erythrocytes



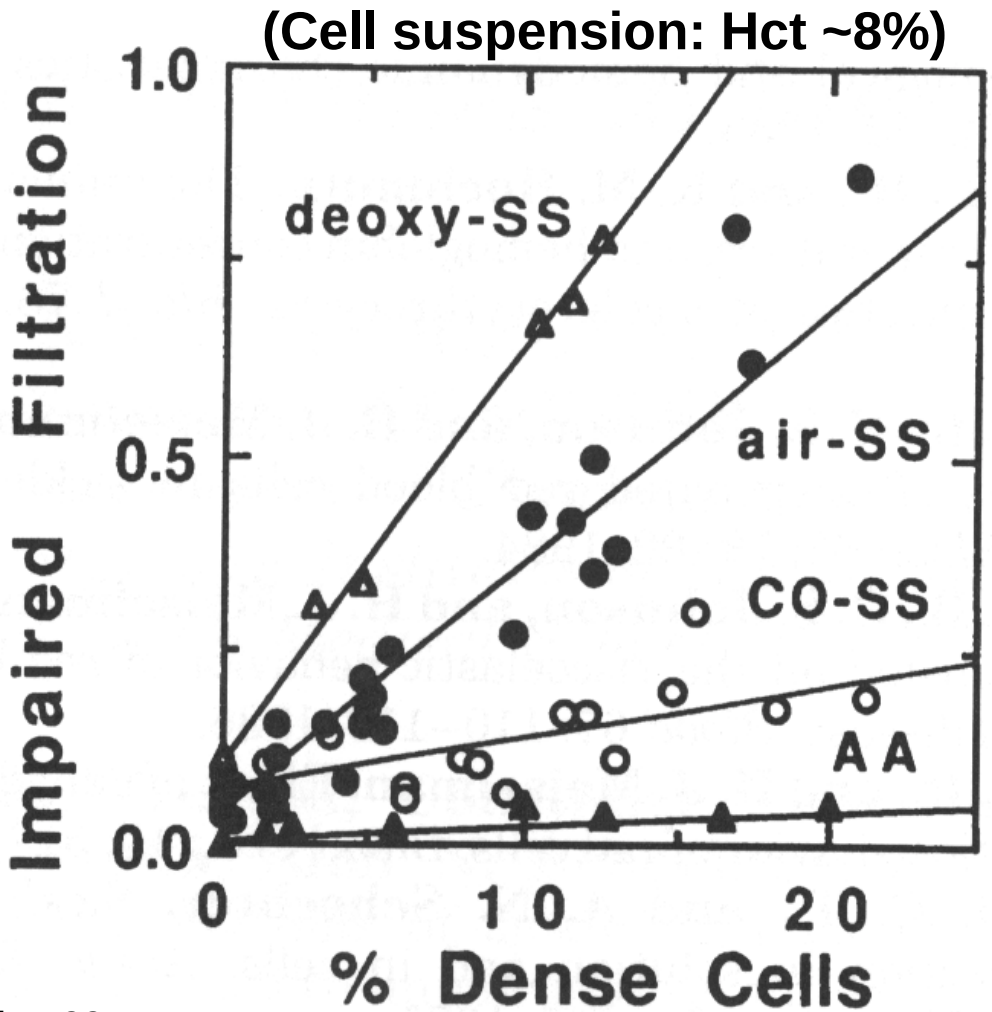
Noguchi, PNAS 1980

Fractionated SS erythrocytes



Noguchi, JCI 1983

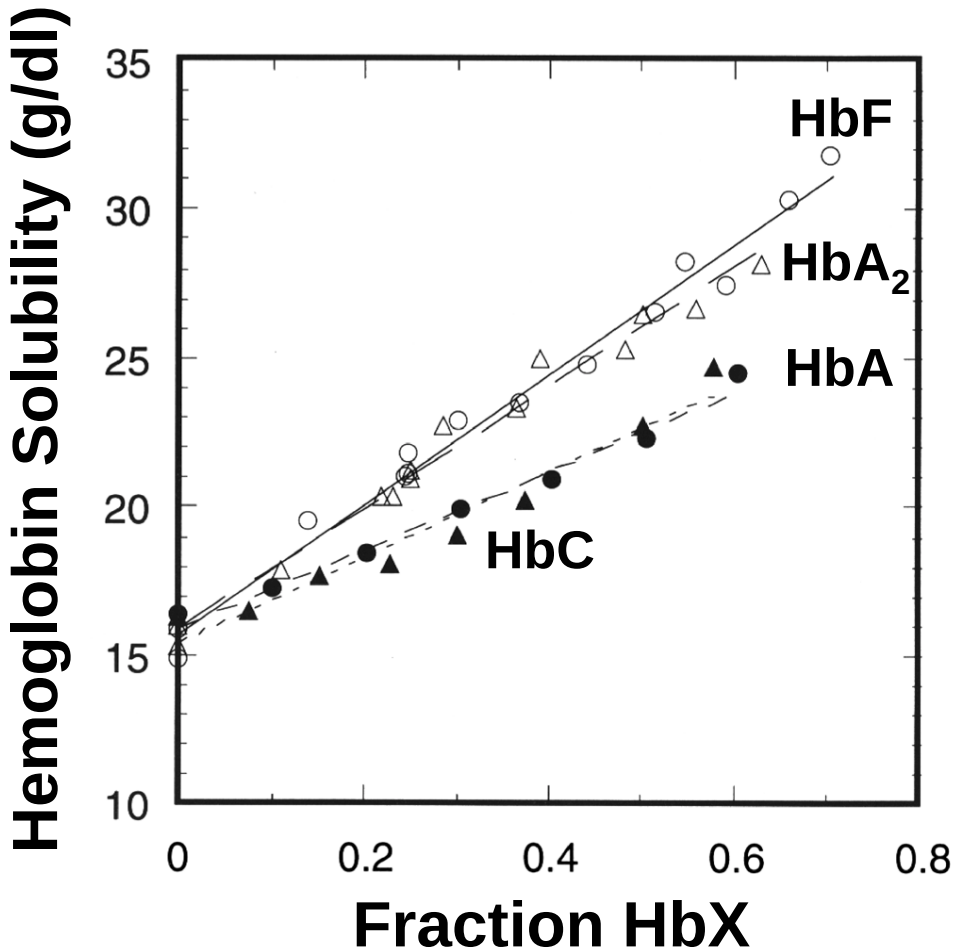
SS Dense Cells Impair Filtration Even at High Oxygen Saturation



Hiruma, Noguchi et al., 1995

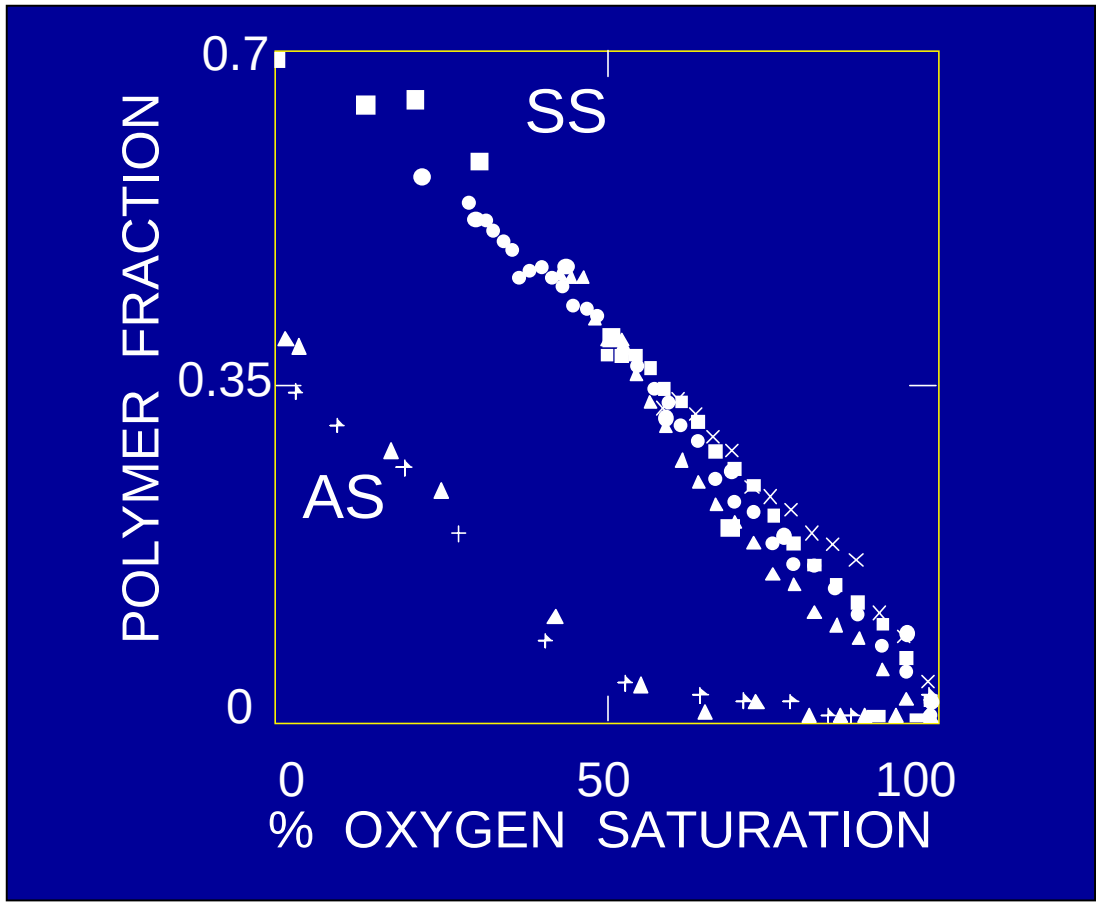
Mixtures of HbS with Other Hemoglobins Increase Deoxyhemoglobin Solubility

- **HbA or HbC increases deoxyHb solubility in mixtures with HbS.**
- **HbF or HbA_2 have an even greater "sparing" effect.**



Poillon, Kim, Rodgers, Noguchi, Schecter, PNAS 1993

Hemoglobin Polymerization in AS and SS Erythrocytes

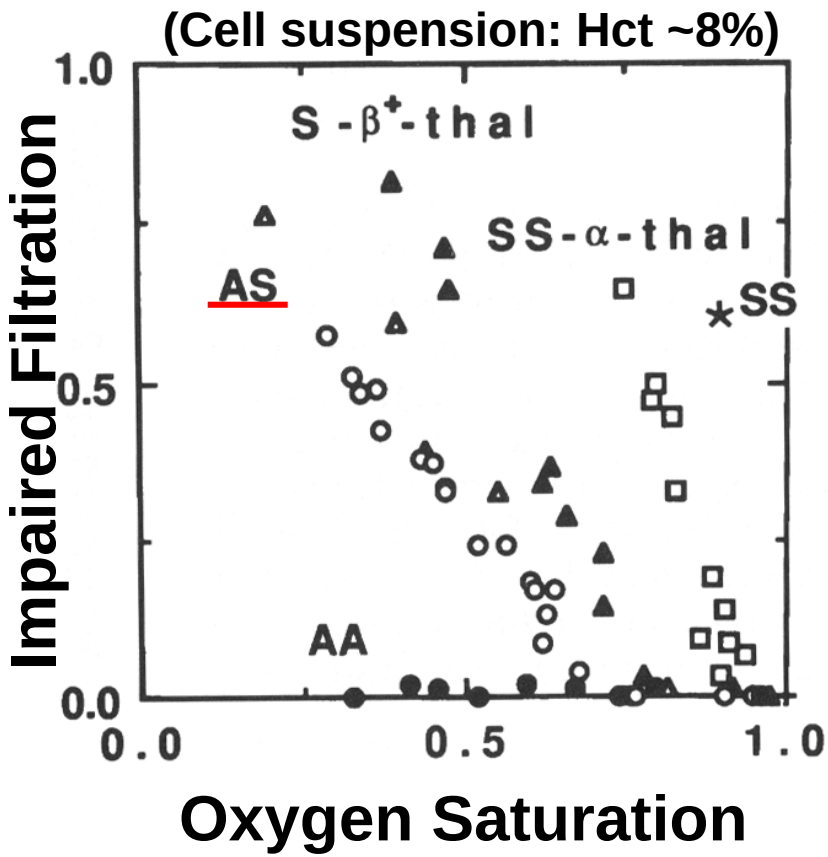


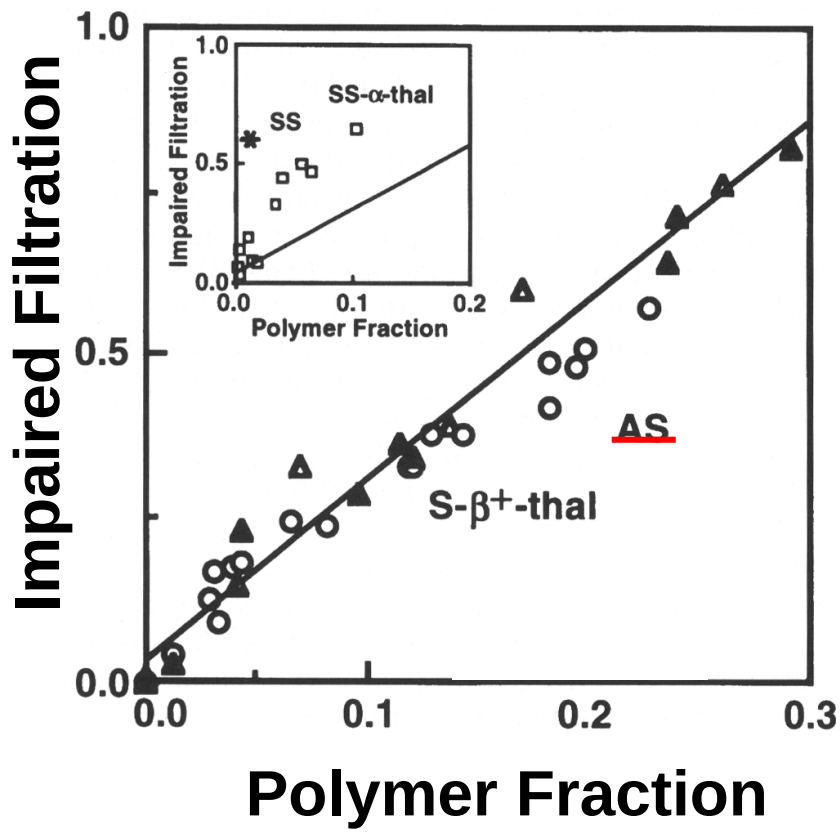
Polymerization tendency of AS hemoglobin ($\alpha_2\beta^A\beta^S$) hybrid: 0.5 times hemoglobin S ($\alpha_2\beta^S{}_2$)

Noguchi, PNAS 1980; Biophys J 1984

Impaired Filtration and Polymer Fraction

- **Filtration is impaired in AS erythrocytes, but at markedly lower O2 sat compared with other sickle due to lower polymerization tendency.**

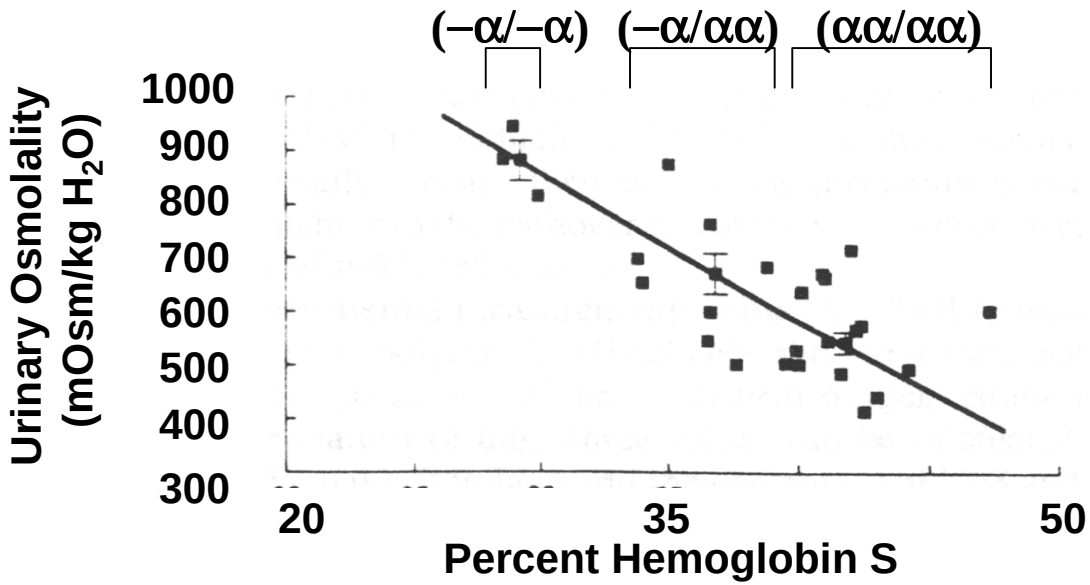




Hiruma, Noguchi et al., 1995

Defective Urine Concentrating Ability in Sickle Cell Trait

- **High osmolality and low O_2 sat of the renal medulla are conditions that favor polymerization.**
- **Hemoglobin polymerization correlates inversely with urine concentrating ability.**
- **α-Thalassemia reduces %HbS, and polymerization potential.**

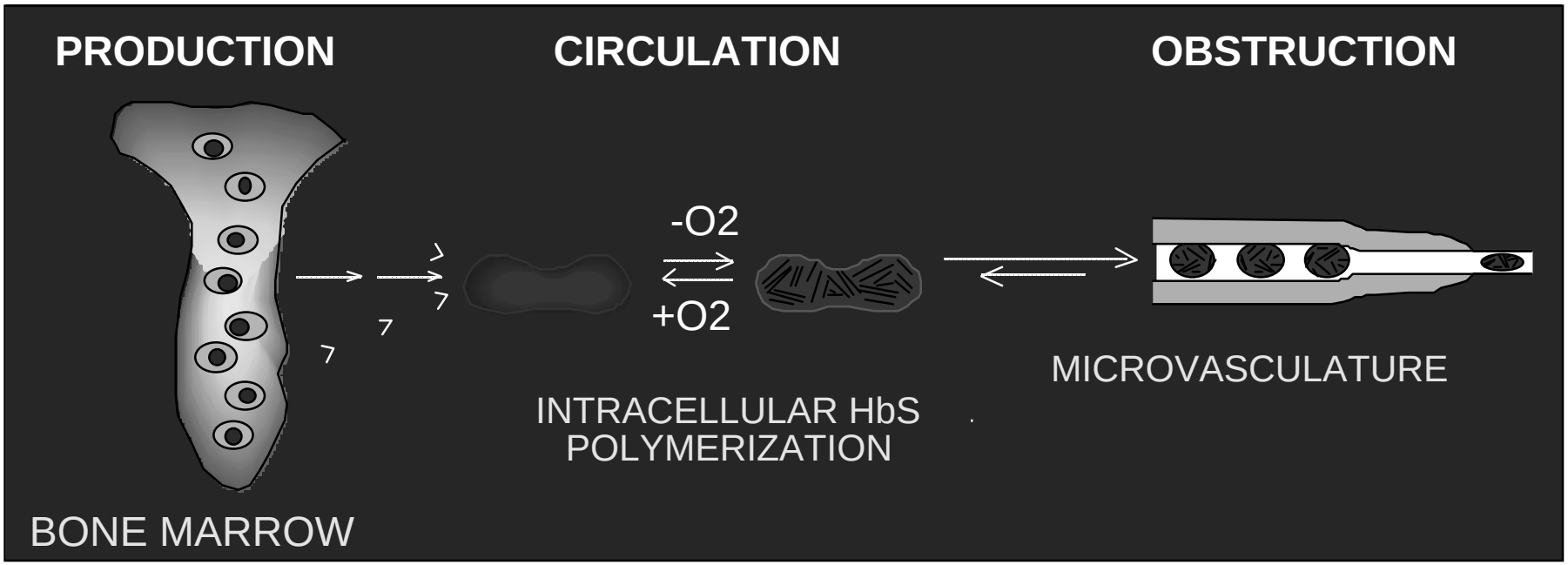


Gupta, Kirchner, Nicholson, Adams, Schechter, Noguchi, Steinberg, JCI 1991

Hemoglobin Polymerization in Sickle Trait Erythrocytes

- **Although disease manifestation is not generally associated with sickle trait individuals, AS erythrocytes can undergo hemoglobin polymerization at extreme deoxygenation or dehydration.**
- **As in SS cells, determinants of polymerization potential in AS cells are intracellular hemoglobin composition that is modified as a function of α-globin genotype, intracellular hemoglobin concentration and oxygen saturation.**
- **In the kidney, the hyperosmolality and low oxygen tension of the renal medulla results in a urine concentrating defect associated with HbS polymerization determined by % HbS.**

Therapeutic Approaches for Sickle Cell Disease



- **Strategies to reduce hemoglobin S polymerization**
  - **Increase hemoglobin F**
    - **Hydroxyurea, butyrate, erythropoietin**
  - **Prevent sickle cell dehydration**
    - **Clotrimazole, Mg^{+2} pidolate**