SC Hemoglobinopathy

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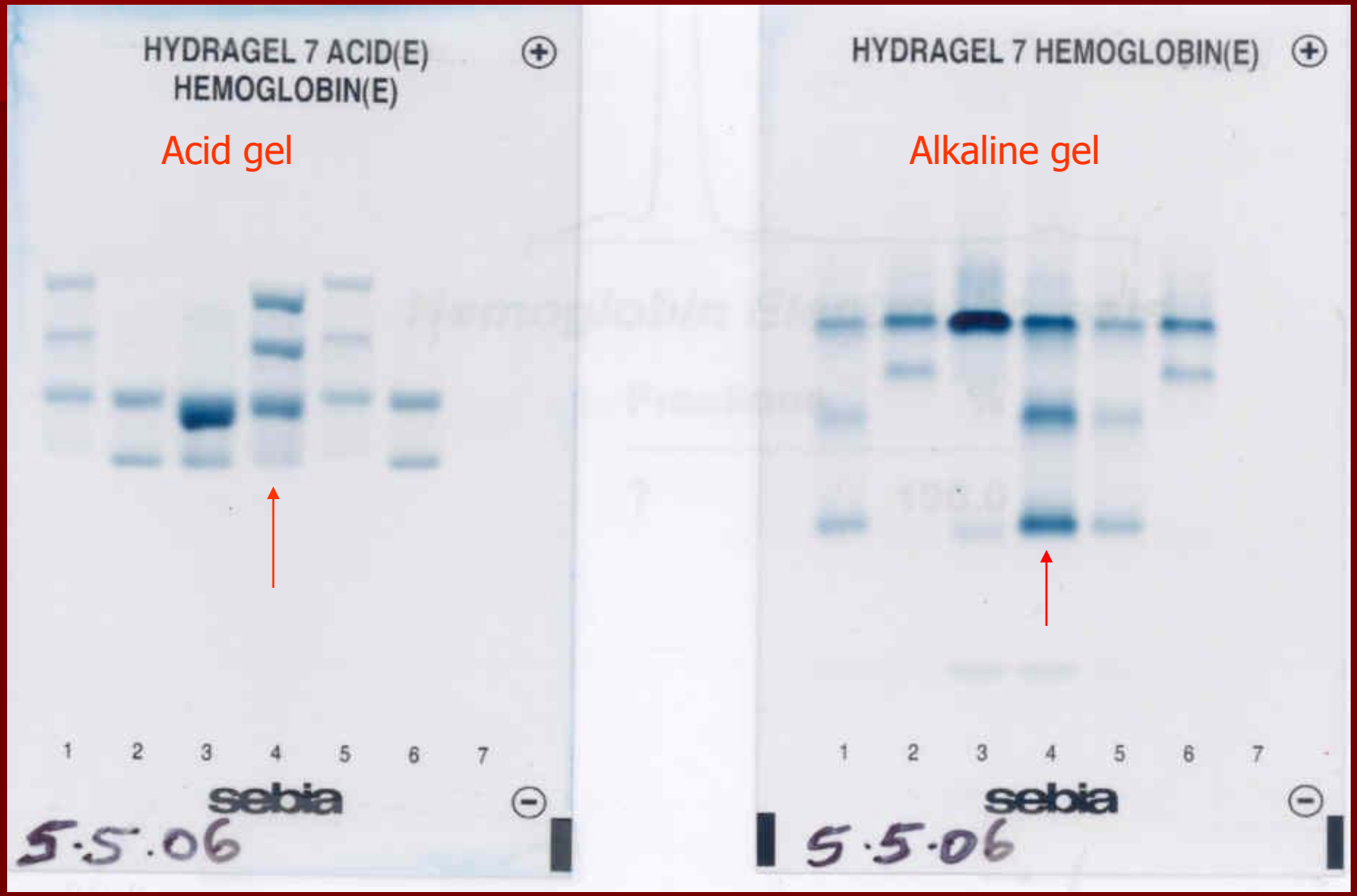
Patient

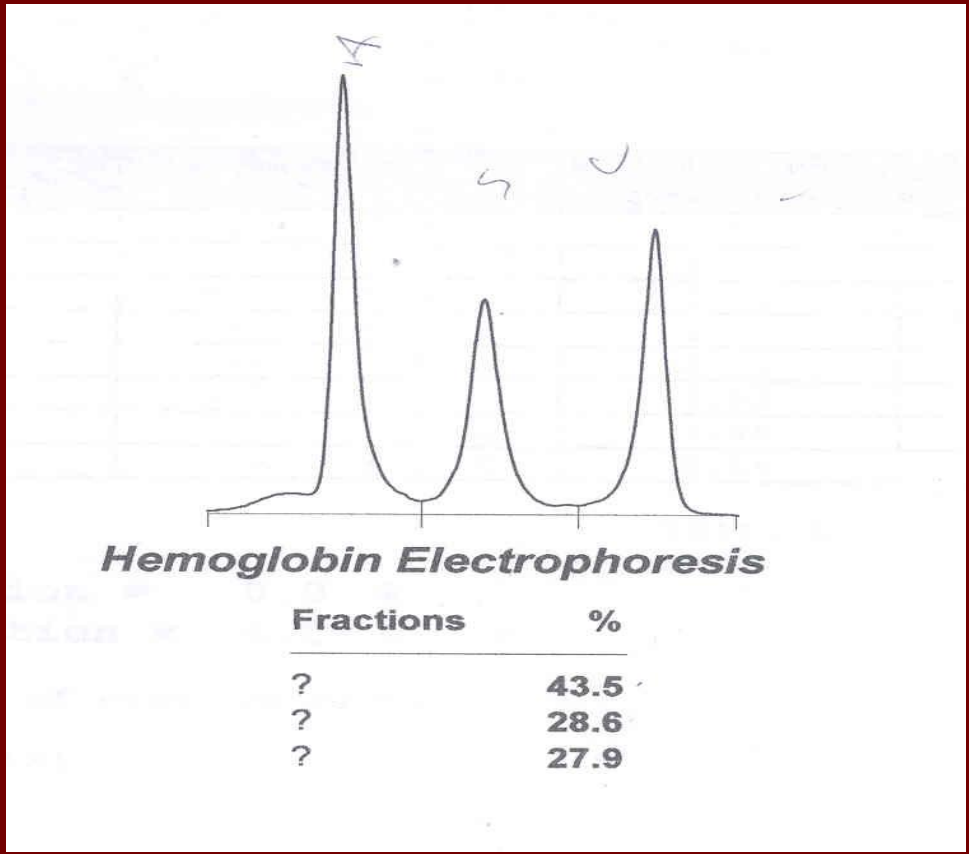
- A 53 y/o AA male with past medical history of sickling crises who was admitted to acute care hospital with pain crisis
- Labs: Hb: 9.8, Hct: 30.4, MCV: 80.7, MCHC: 32.3, RDW: 21.1, WBC: 8.9, Plt: 504, T bili: 1.1

Alkaline and Acidic Hgb Electrophoresis



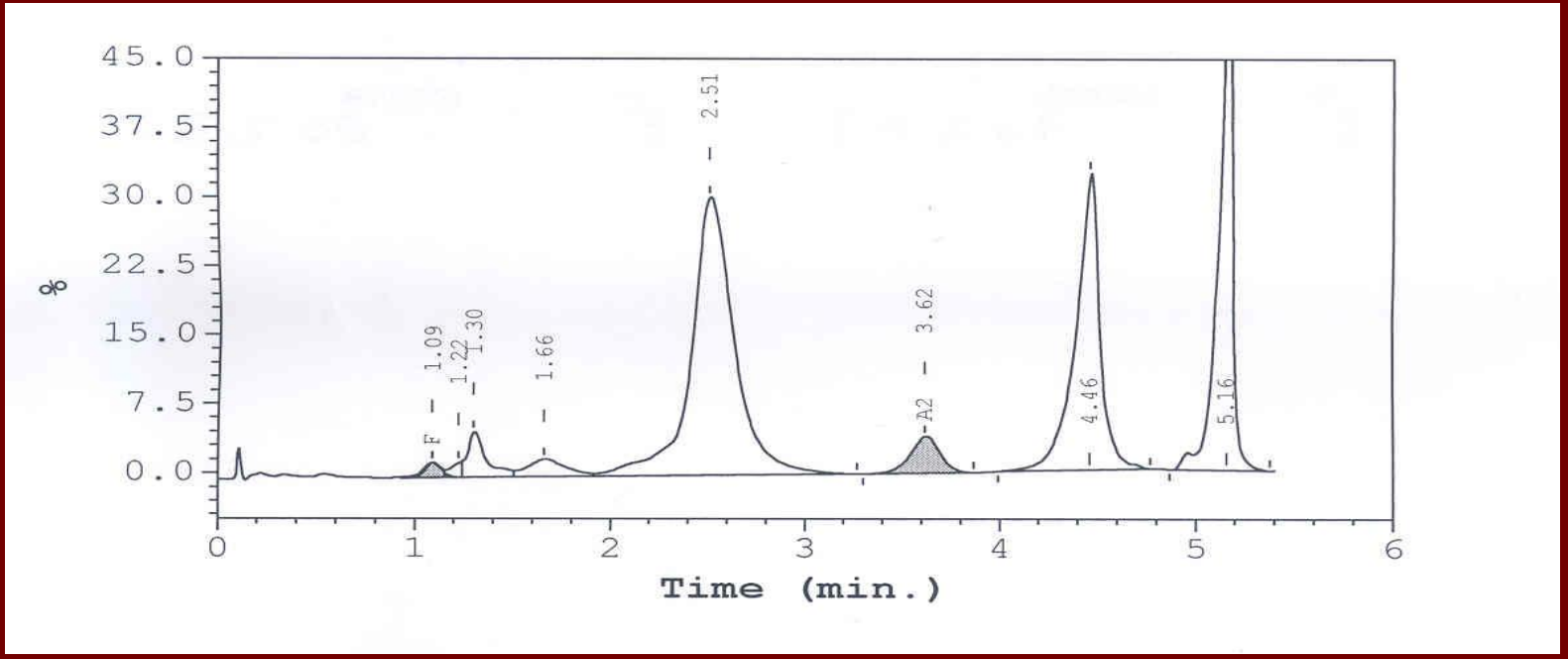
Hemoglobin electrophoresis

- Fractions %
- ? 43.5%
- ? 28.6%
- ? 27..9%



HPLC

Calibrated Area (%)		Area (%)	
F concentration:	0. 9	S-Window	24.1
A2 concentration:	4. 0	C-Window	25.0



Hemoglobin Electrophoresis

Interpretations:

Specimen is from an individual with Hgb SC post-transfusion (Hb S, C, and A components are seen in specimen).

Hemoglobinopathy

- More than 300 hemoglobinopathies have been discovered; 1/3 of these are associated with significant clinical manifestations.
- On average, normal adult Hb contains 95-98% Hb A , 2-3% Hb A2, and 0.8-2% Hb F
- The most prevalent hemoglobinopathy (HbS), is caused by point mutation in hemoglobin beta chain; causing substitution of Val. for Glu. in 6^{th} position of the beta chain.

Hemoglobin S

- ~8% of African Americans are heterozygous for HbS. In Africa where Malaria is endemic the gene frequency is ~30%.
- Deoxygenation of HbS -> polymerization (crystallization/gelatin) -> elongated crescentic or sickle shape; initially reversible with oxygenation, but subsequent sickling -> irreversible despite adequate oxygenation

Hemoglobin S

- In patients with sickle cell trait (genotype AS), HbS is ~ 40% and of HbA ~60% of total Hb. The concentration of HbS falls below threshold necessary to initiate ploymerization; these patients are typically not at risk for crisis
- Sickling disease is associated with one of three distinct genotypes: SS, SC, or sickle-beta-thalassemia; patients with SC and S-beta-thalassemia have milder form of disease than those with SS.

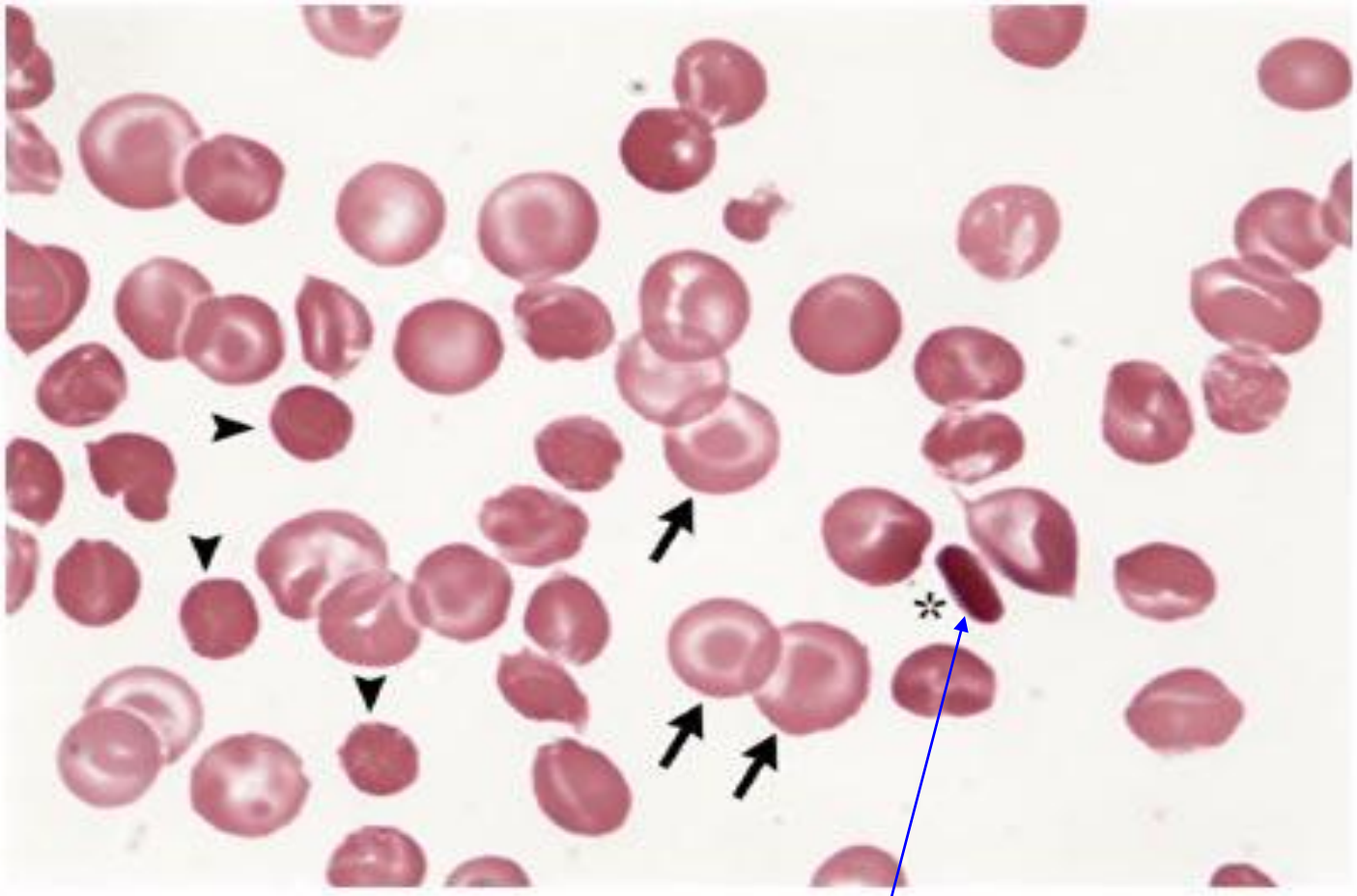
Hemoglobin C

- HbC has mutant beta globin chain where Lysine replaces Glu in codon 6
- Hb C disease, or homozygous state results only in a mild hemolytic anemia
- Highest frequency of HbC is in West Central Africa
- In the USA, most common among African American with carrier rate ~2.3%

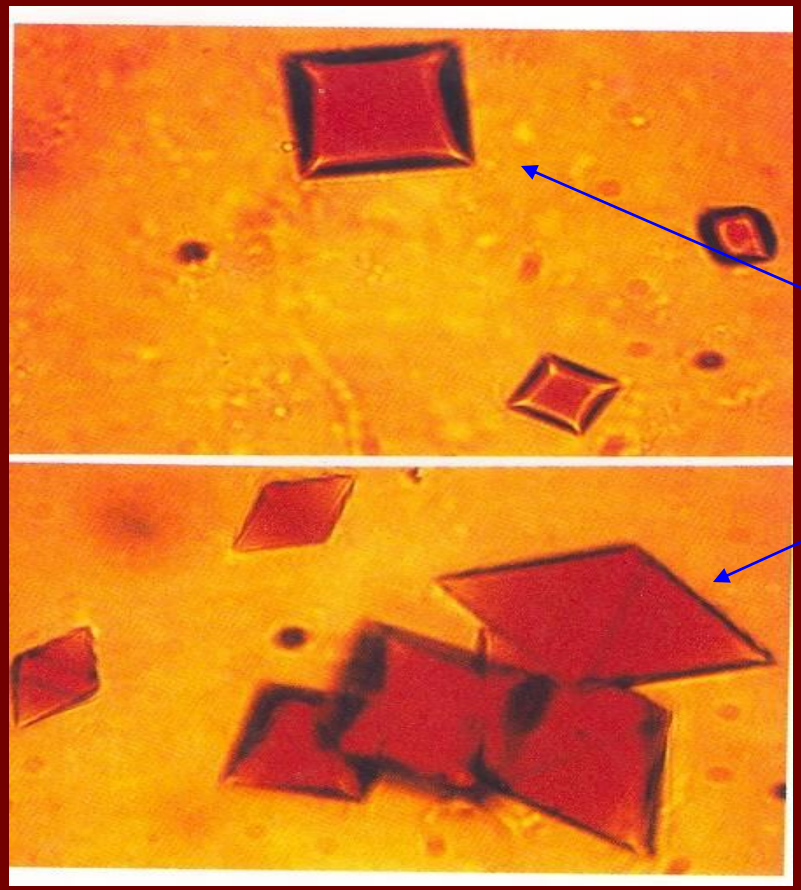
Hemoglobin C

- RBC life span is shortened to ~40 days in HbC (but is ~3x the life span of RBC in sickle cell anemia)
- High MCHC and low intracellular water content (due to inhibition of ion exchange across RBC membrane) are characteristic of HbC containing cells
- Morphology in dried stained blood films: target cells (result of their reduced water content), microspherocytes, and cells with crystalline inclusions (C crystals)

Hemoglobin C



Hemoglobin C



Variants of crystals observed in hemolysates of patients with Hb C:

- Cubic from patient with Hb C-Korle Bu
- Tetragonal crystals observed intracellular in patient with Hb CC, Hb SC

Hemoglobin SC

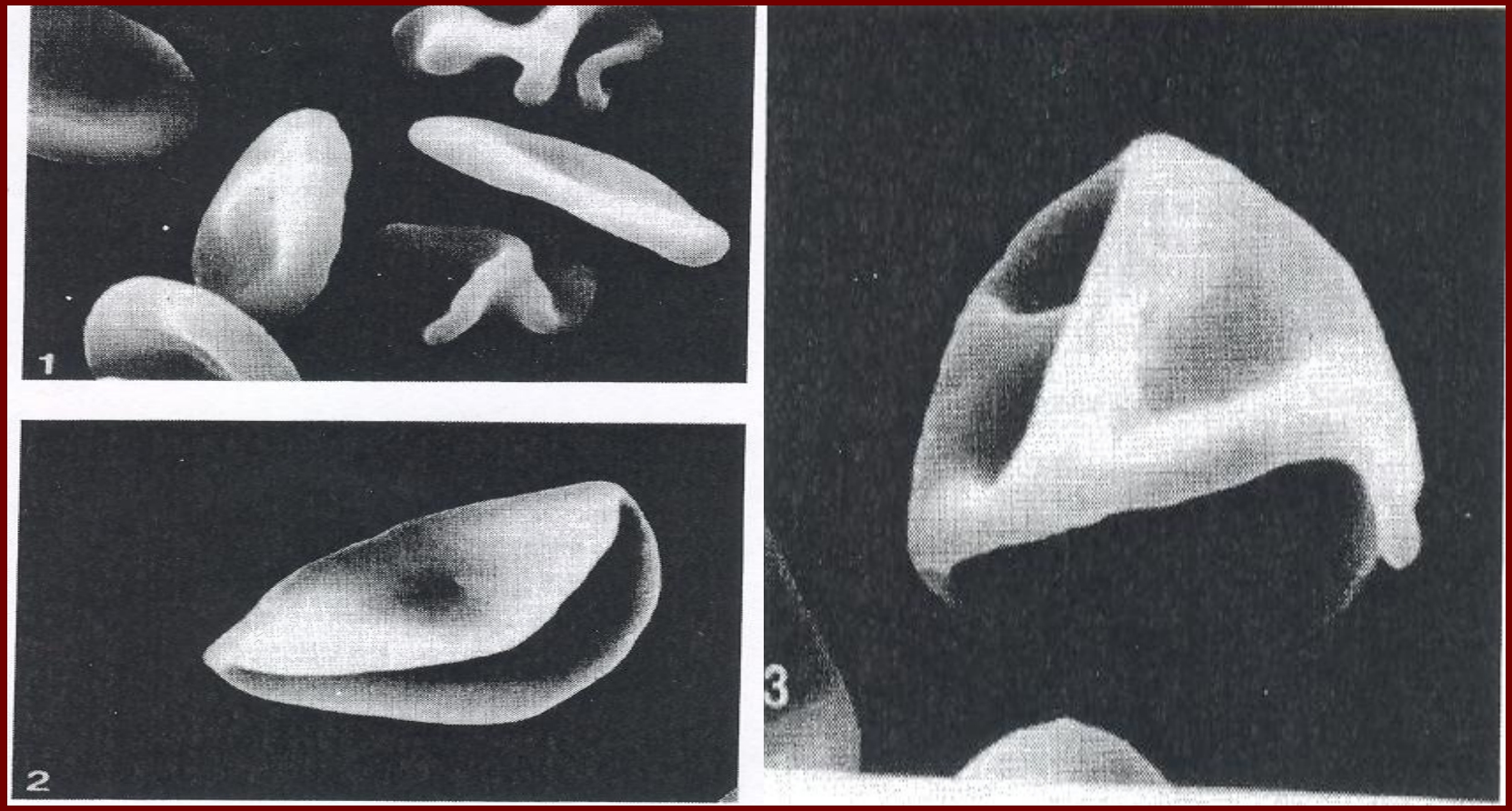
- ~ 1 in 1250 newborns is heterozygote for HbS and HbC
- Erythrocytes in this disorder contain equal amounts of Hb S and C with each component exerting its own pathological effect
- Low intracellular volume caused by HbC effects results in an increase in Hb concentration, hence HbS concentration, increasing likelihood of sickling

Hemoglobin SC

- Incubation of Hb SC with 3% NaCl induces formation of crystals, which are observed in Wright's and vital-dye stained smear.

- Other features are "target cells" and "folded" RBC; "folded RBC" are strikingly apparent under electron microscopy (single fold / pita-bread type, or highly folded types)

Hemoglobin SC
EM of RBC



HbF level in HbSC

- HbF level in HbSC is lower than in sickle cell anemia, probably because of less hemolysis and bone marrow expansion in HbSC, or possibly because of lack of critical genetic element that is present in sickle cell anemia that is necessary for increased transcription of gamma globulin gene

Hemoglobin SC

- HbC crystals are more likely to form in cells with low HbF content.
- HbF inhibition of HbC crystallization might contribute to the potentially beneficial effects of hydroxyurea in HbSC disease (increase in HbF in response to treatment).

Clinical Features of HbSC disease

- All complications that occur in sickle cell anemia patients have been also reported in patients with HbSC, but most appear less frequently and/or at a later time in HbSC disease compared to sickle cell anemia.

Clinical Features of HbSC

Compared to sickle cell anemia, in HbSC disease:

- Hemolysis less intense and anemia milder, and less frequent complications such as cholelithiasis and aplastic episodes
- Acute chest syndrome occurs less frequently with much less likelihood of progression to chronic lung disease
- Splenic function is often preserved leading to reduced incidence of infection with encapsulated bacteria, but the risk of splenic sequestration crisis in adulthood exists

Clinical Features of HbSC

- Vasoocclusive disease occurs with a milder clinical course, and painful episodes occur at half frequency
- Osteonecrosis of bone is only slightly lower than in sickle cell anemia
- Proliferative sickle retinopathy is much more prevalent, it can occur in 1/3 of HbSC disease patients vs. only ~3% of patients with sickle cell anemia

Experimental Therapy

Restoration of normal cellular cation content and density by drugs that interfere with cell membrane's ions transport:

1- Clotrimazole, an antifungal agent reduced cellular dehydration in vitro in a transgenic animal.
2- Magnesium salts can cause cell rehydration through its action on ion transport.
3- Hydroxyurea can also cause reduction in cell density of HbSC erythrocytes that may be independent of any change in HbF.

References

- http://content.nejm.org/cgi/content-nw/full/350/26/e24/F1
- Emedicine. "*Hemoglobin C Disease*" Author: Carter, Suzanne
- Steinberg, Martin, Forest, Bernard, Higgs, Ronald: Disorders of Hemoglobin