Sickle Cell Disease
Why Is A Simple Genetic Disorder So Hard To Treat And How Are We Doing?

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Winship Cancer Institute
Emory University School of Medicine
Director, Georgia Comprehensive Sickle Cell Center
Dr. James Eckman,
Personal/Professional Financial Relationships with Industry

<table>
<thead>
<tr>
<th>External Industry Relationships *</th>
<th>Company Name(s)</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers**</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Consulting, scientific advisory board, industry-sponsored CME, expert witness for company, FDA representative for company, publishing contract, etc.

**Does not include stock in publicly-traded companies in retirement funds and other pooled investment accounts managed by others.
AMERICAN DISCOVERY
Herrick JB Arch Intern Med 6:517-521, 1910
VASO - OCCLUSION

Steinberg MH
Management of Sickle Cell Disease
CLINICAL CONSEQUENCES OF SICKLE HEMOGLOBIN

- Hemolytic anemia
- Increased severity of infection
- Tissue infarction with organ failure
- Episodes of pain
APPROACH TO TREATMENT

• It is the hemoglobin
  – Decrease sickle hemoglobin concentration
  – Increase fetal hemoglobin
SICKLE BIOCHEMISTRY

- Deoxygenation
- Intracellular hemoglobin concentration
- pH
- Temperature
VASO – OCCLUSION

Wick et al

Pre-capillary arteriole  Capillary  Post-capillary venule

"Vicious Cycle" (Ham & Castle Trans Am Assoc Phys 55:1940;127)

Water
OSMOTIC EFFECTS ON SICKLING

Zarkowsky & Hochmuth J Clin Invest 56:1023, 1975
OSMOTIC EFFECTS ON SICKLING

![Graph showing MCHC (percentage) vs. Serum Na⁺ (mmol/liter) for Case 1 and Case 2.](image)

## OSMOTIC EFFECTS ON SICKLING

### Table 3. Effect of Acute Induction of Hyponatremia on the Duration of Sickle-Cell Crisis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Conventional Treatment</th>
<th>Induction of Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRISES</td>
<td>DURATION *</td>
</tr>
<tr>
<td></td>
<td>no.</td>
<td>days</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>18±6</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>16±3</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>7±1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>11.8±2.3</td>
</tr>
</tbody>
</table>

*Values are reported as the mean ±S.E.
†Figures before and after the arrow denote sodium concentrations before and after hyponatremia was induced.
‡P<0.01 by Student’s t-test for group mean.

Hb F INHIBITS SICKLING

- No sickling early in life (Watson 1948)
- Hb F directly interferes with Hb S polymerization (Singer & Singer 1952)
- Mild sickle cell in Saudi Arabians and HPFH (Perrine et al 1978, Others)
- Crisis rates vary inversely with Hb F levels
- Survival advantage with increased Hb F (CSSCD, Platt et al 1991)
• 5 - Azacytidine increases F cell production in anemic Baboons (DeSimone et al 1982)

• Hydroxyurea increases Hb F in SS patients (Charache et al 1992)
  – Used by hematologists for many years
  – Long history with relative safety
HYDROXYUREA
HYDROXYUREA INCREASES Hb F

Charache et al Blood 79:2555, 1992
## MULTICENTER HYDROXYUREA TRIAL

<table>
<thead>
<tr>
<th>Group</th>
<th>Hydroxyurea</th>
<th>Placebo</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Episodes</td>
<td>2.5 / year</td>
<td>4.5 / year</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Pain Admits</td>
<td>1.0 / year</td>
<td>2.4 / year</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Acute Chest</td>
<td>25 episodes</td>
<td>51 episodes</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Transfused</td>
<td>48</td>
<td>73</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Total Units</td>
<td>336</td>
<td>586</td>
<td>p = 0.004</td>
</tr>
</tbody>
</table>

*Van der Waerden’s test.

# Hydroxyurea Improves Survival

Adults: 131 treated with Hydroxyurea and 199 usual care for up to 17 years (median 8 verses 5 years)

## 10 Year Predicted Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Hydroxyurea</th>
<th>No Hydroxyurea</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>86 %</td>
<td>65 %</td>
<td></td>
</tr>
<tr>
<td><strong>Hb SS</strong></td>
<td>100 %</td>
<td>10 %</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Hb S $\beta^0$</strong></td>
<td>87 %</td>
<td>54 %</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Hb S $\beta^+$</strong></td>
<td>82 %</td>
<td>66 %</td>
<td>0.369</td>
</tr>
</tbody>
</table>

Voskaridou E et al.  Blood 2010; 115: 2354-2363
Patients receiving hydroxyurea (N=131)

Patients not receiving hydroxyurea (N=199)

p=0.001

% Survival probability

Survival (Years)
Erythropoietin (EPO)

- EPO has been investigated since 1906.
- In 1989, the U.S. Food and Drug Administration approved the hormone, called Epogen, which remains in use today.
- Widely used in patients with ESRD for Anemia.
EPO in Sickle Cell Disease

- EPO release increases exponentially with decrease of hematocrit in patients.
- Therefore often elevated in chronic anemic states
- In SCD patients EPO levels increases at a lower hemoglobin concentration and are of a lower magnitude.
- Marrow response also appears to be blunted.
EPO in Sickle Cell Disease

• Often can be used as an alternative to transfusion
  – Alloimmunized patients
  – Those refusing on religious beliefs
• Useful in patients with sickle cell disease and renal failure.
• Also tried to improve the response to hydroxyurea.
EPO with or without Hydroxyurea

- Erythropoietin, whether alone or in combination with hydroxyurea, offers no measurable benefit.
- No significant effect on the percentage of hemoglobin F—containing reticulocytes (F reticulocytes) or red cells (F cells).
EPO with Hydroxyurea

• Rodgers et al. NEJM 1993; 328:73-80
• There was a 28 percent increase in the number of reticulocytes containing fetal hemoglobin and a 48 percent increase in the percentage of fetal hemoglobin, as compared with the maximal values obtained with hydroxyurea alone.
• In SCD patients median dose >200 U/Kg/dose is higher than that in ESRD.
We have seen cures.

Marrow transplant leaves 2 Ga. boys free of sickle cell

By Anne Rochell
STAFF WRITER

Normally, doctors won’t say they’ve cured an incurable disease such as sickle cell anemia, but they’re coming close to saying it about two Atlanta-area children.

The boys, ages 5 and 12, recently received bone marrow transplants and have been declared disease-free, say doctors at Emory University School of Medicine.

“The prospects are superb that they are cured,” said Dr. John Wingard, director of Emory’s bone marrow transplant program.

The children are the first patients in Georgia, and among fewer than 30 worldwide, to undergo a bone marrow transplant to treat sickle cell anemia, said Dr. James Eckman, director of Emory’s sickle cell center at Grady Memorial Hospital.

Seventy percent to 80 percent of the patients who have undergone transplants have been cured.

One of the two Atlanta children, Seye Arise of Tucker, now goes to school, plays ball and giggles uncontrollably like any other 5-year-old.

But he can remember how it was before his operation at Egleston Children’s Hospital at Emory last November, when he received bone marrow from his older brother.

“Everything hurted,” he said.

The second patient, 12-year-old Roger Johnson of Jonesboro, received marrow from his older sister in April and will return to school in October, an Egleston spokeswoman said.

Please see CURE, A12.