Sickle Cell Disease

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

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Disclosures

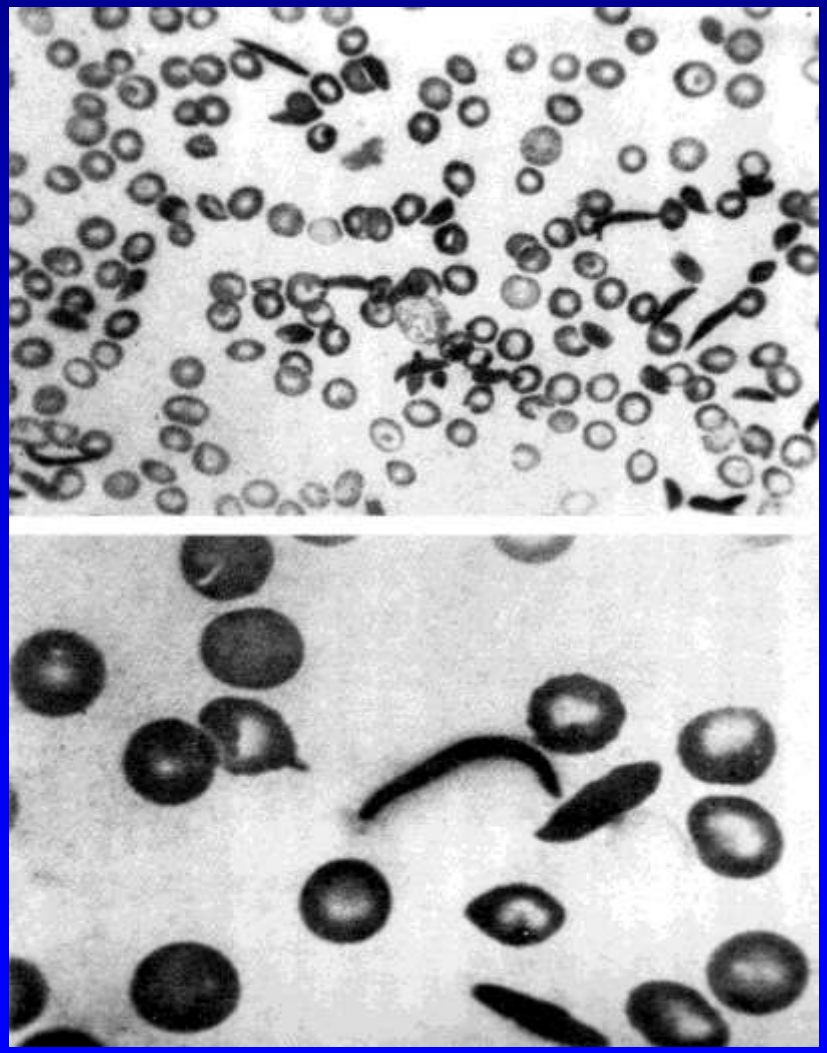
Dr. James Eckman,
Personal/Professional Financial Relationships with Industry

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

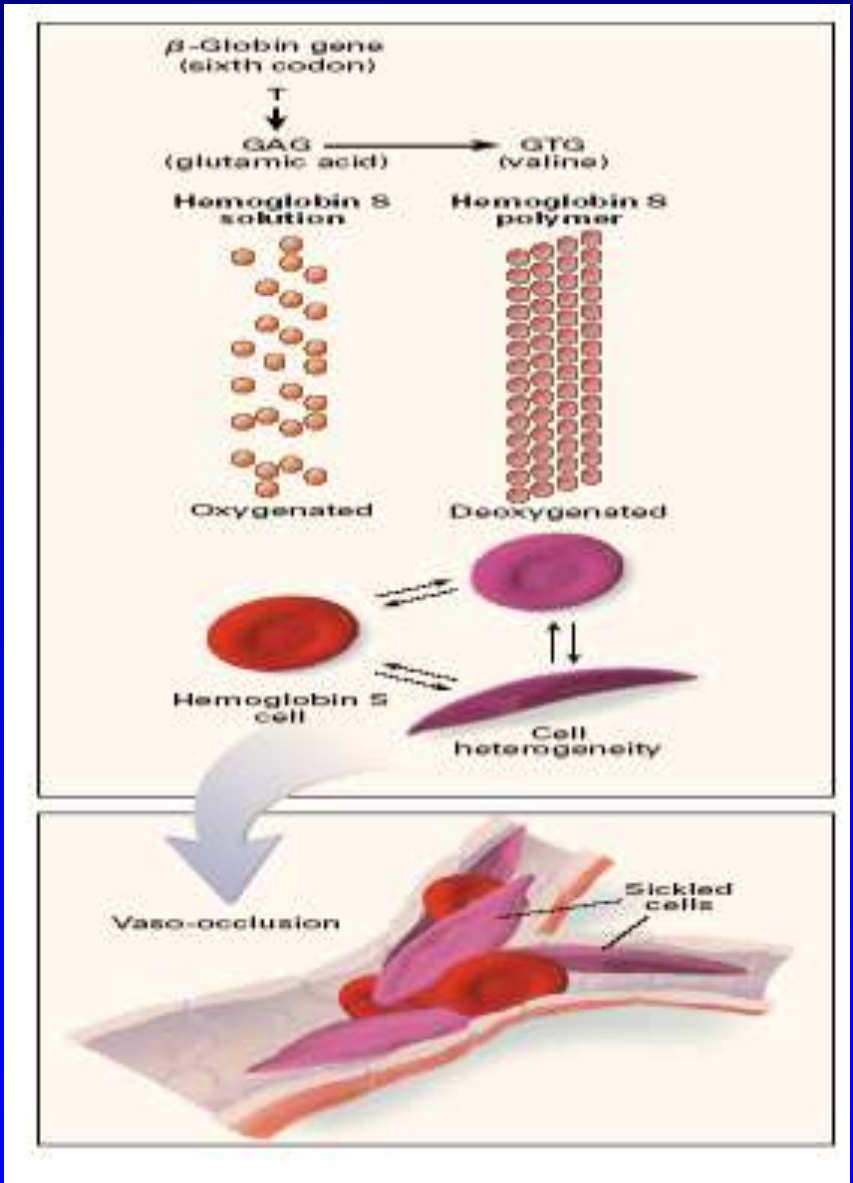
*Consulting, scientific advisory board, industry-sponsored CME, expert witness for company, FDA representative for company, publishing contract, etc.
**Does not include stock in publicly-traded companies in retirement funds and other pooled investment accounts managed by others.

AMERICAN DISCOVERY

Herrick JB Arch Intern Med 6:517-521, 1910



VASO - OCCLUSION



Steinberg MH
Management of Sickle Cell Disease
New J Med 1999;340:1021

CLINICAL CONSEQUENCES OF SICKLE HEMOGLOBIN

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

APPROACH TO TREATMENT

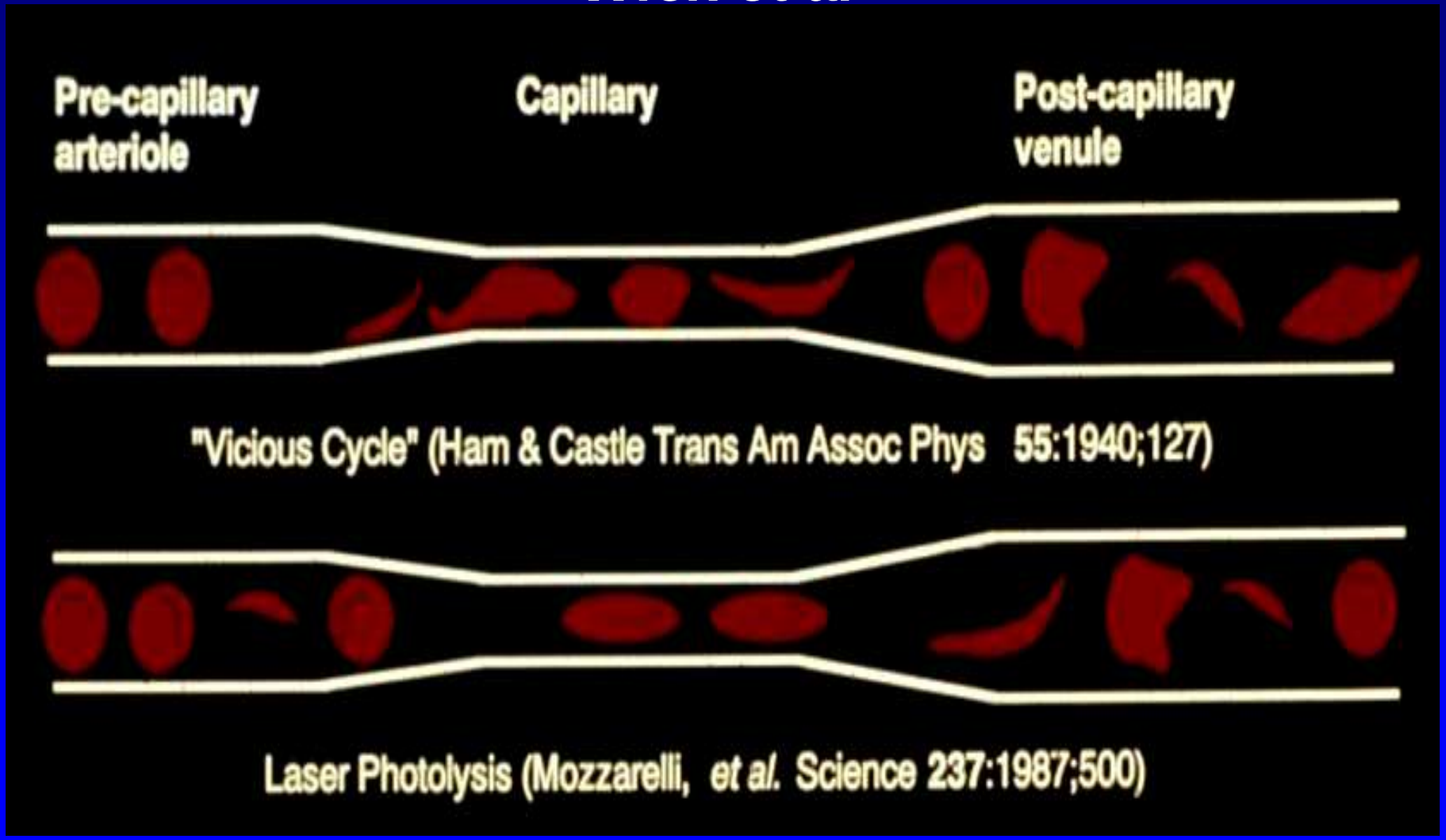
- It is the hemoglobin
  - Decrease sickle hemoglobin concentration
  - Increase fetal hemoglobin

SICKLE BIOCHEMISTRY

- Deoxygenation
- Intracellular hemoglobin concentration
- pH
- Temperature

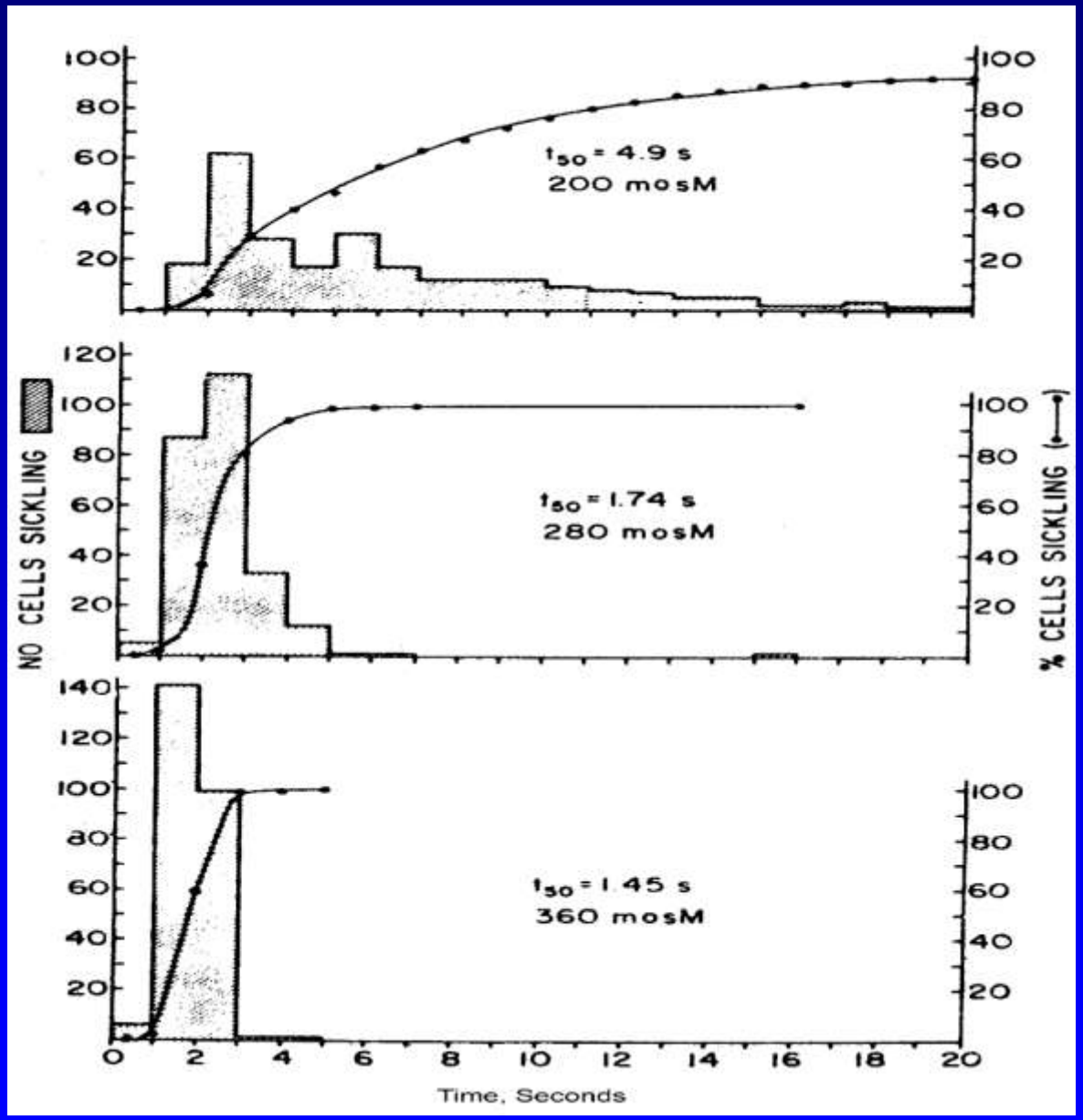
VASO – OCCLUSION

Wick et al



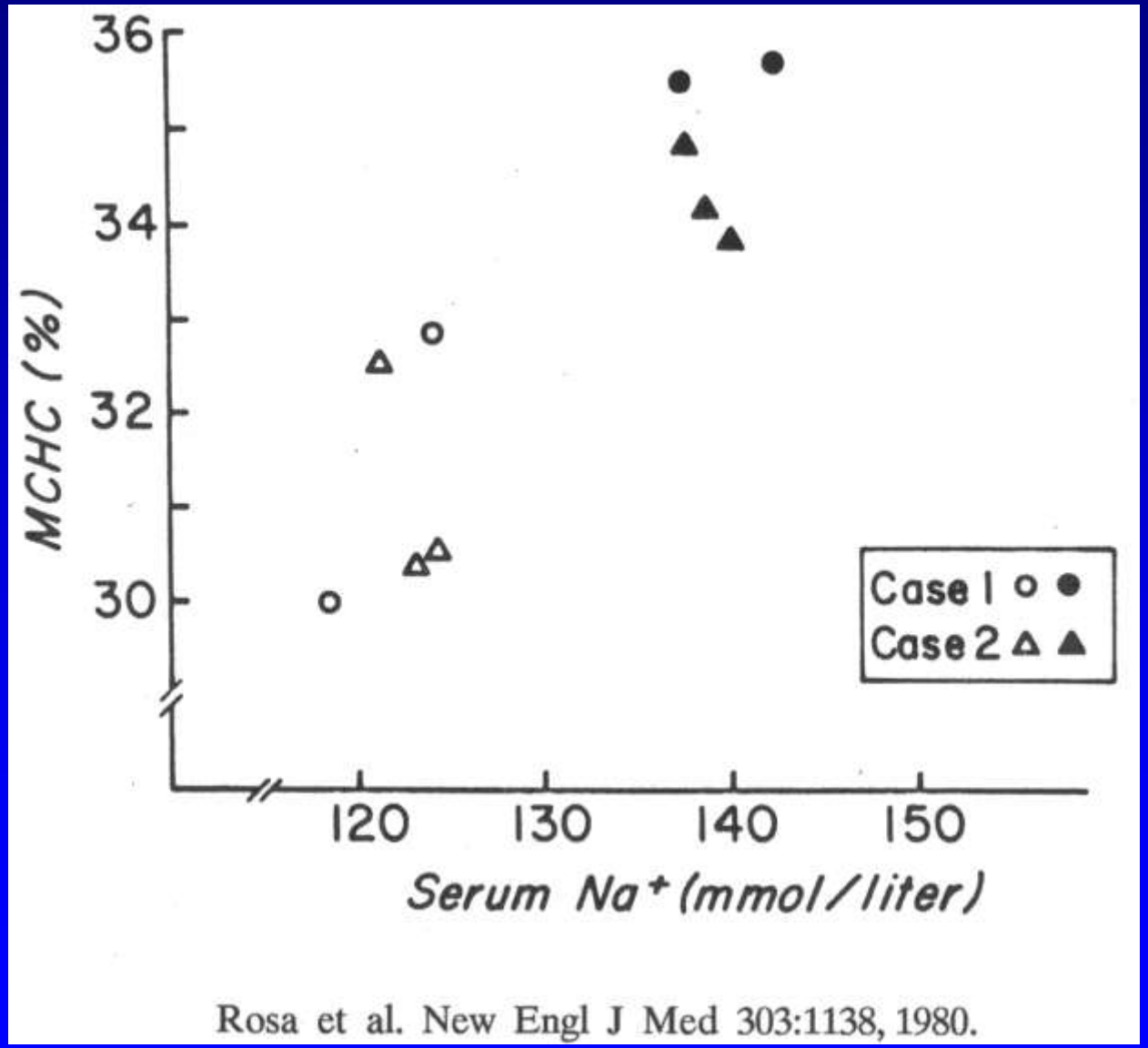
Water

OSMOTIC EFFECTS ON SICKLING



Zarkowsky & Hochmuth J Clin Invest 56:1023, 1975

OSMOTIC EFFECTS ON SICKLING



Rosa et al. New Engl J Med 303:1138, 1980.

OSMOTIC EFFECTS ON SICKLING

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

Case	Conventional Treatment			Induction of Hyponatremia		
	Crises	Duration *	Sodium *	Crises	Duration *	Sodium †
	no.	*days*	*mmol/liter*	*no.*	*days*	*mmol/liter*
1	6	18±6	140±1	2	9±4	136→120
2	7	16±3	143±1	3	4±3	139→125
3	14	7±1	140±2	2	4±0	140→122
Total	27	11.8±2.3		7	5.4±1.4 ‡	

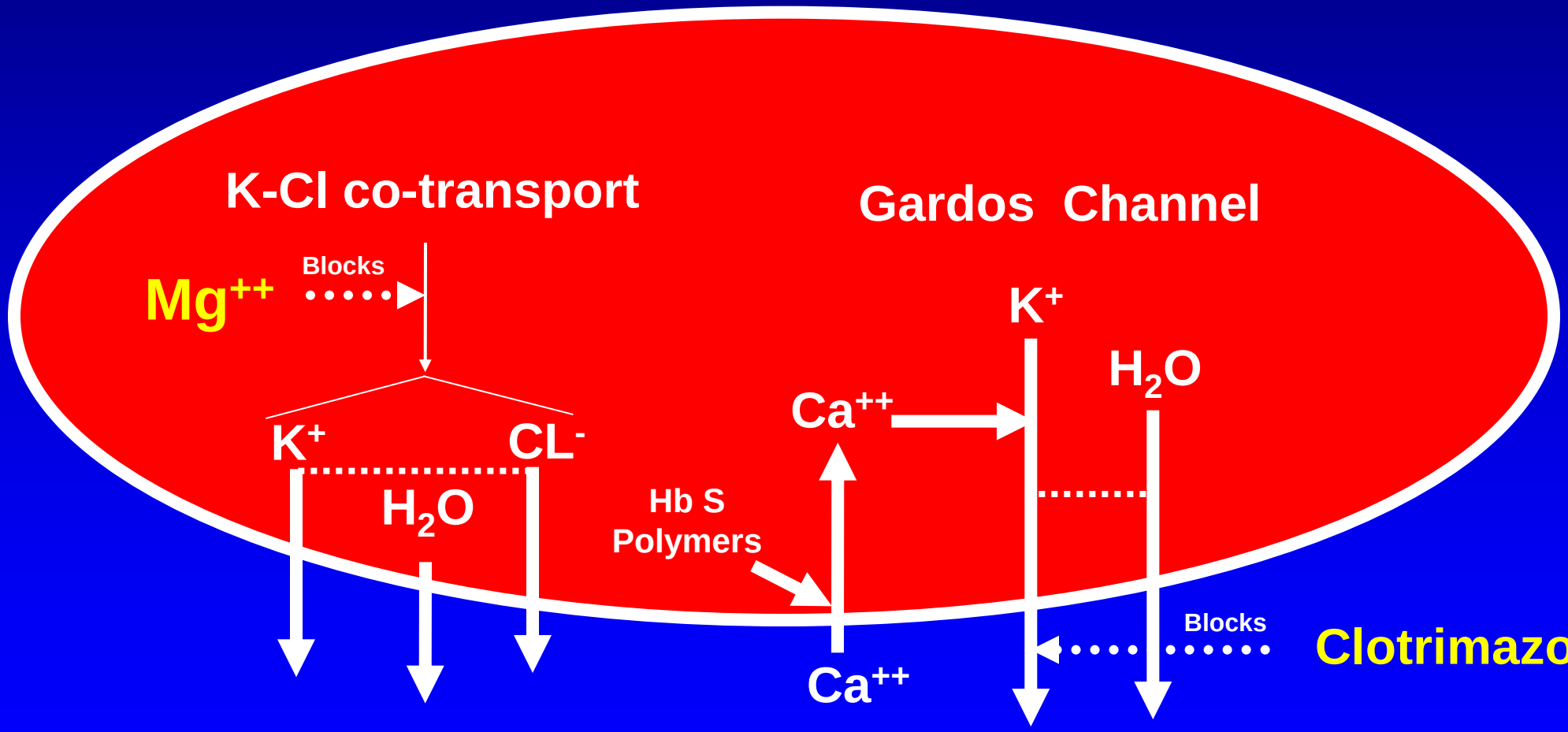
*Values are reported as the mean ±S.E.

†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.

Rosa et al. New Engl J Med 303:1138, 1980.

PREVENTION OF RBC DEHYDRATION



Bunn New Engl J Med 337:762, 1997

Hb F INHIBITS SICKLING

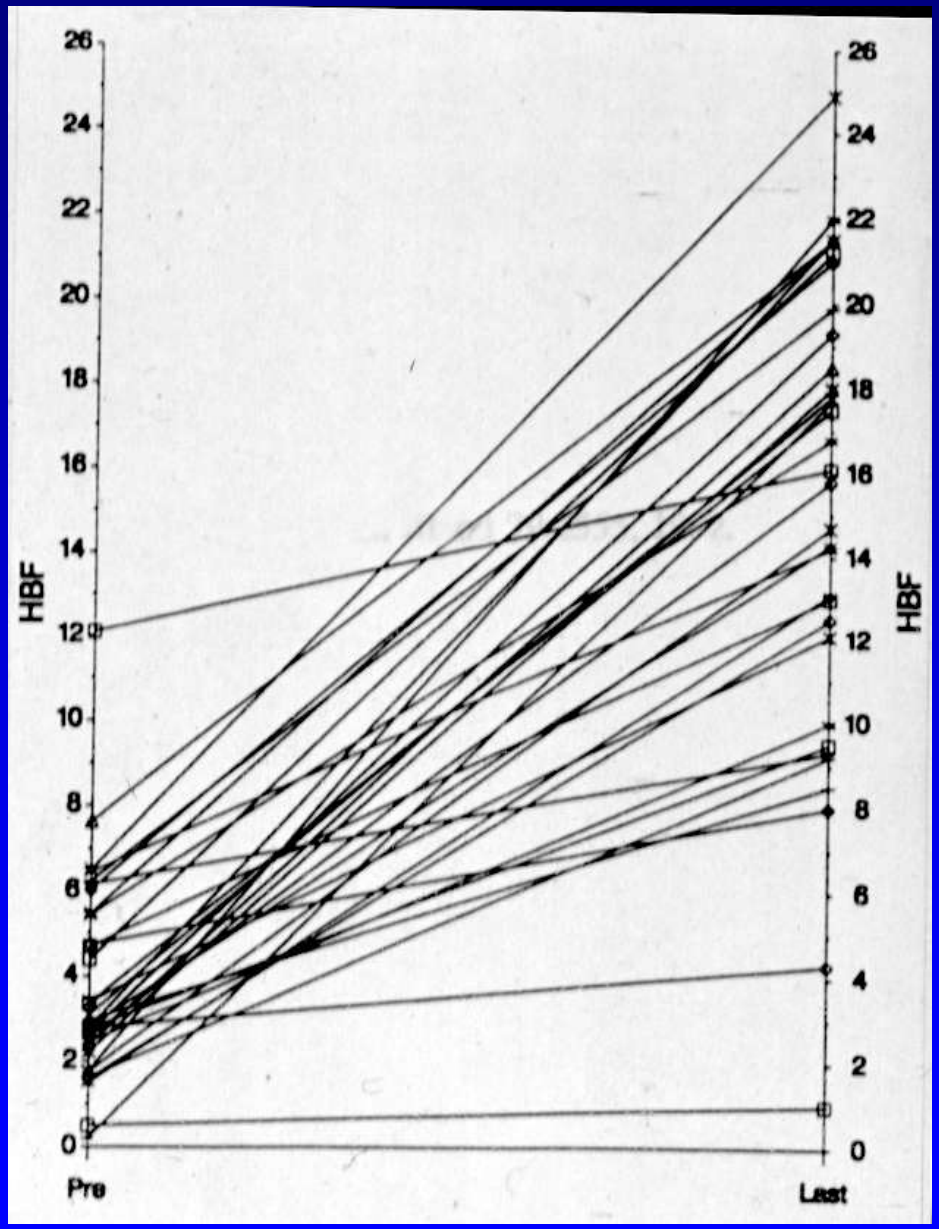
- No sickling early in life (Watson 1948)
- Hb F directly interferes with Hb S polymerzation (Singer & Singer 1952)
- Mild sickle cell in Saudi Arabians and HPFH (Perrine et al 1978, Others)
- Crisis rates vary inversely with Hb F levels
- Survival advantage with increased Hb F (CSSCD, Platt et al 1991)

INDUCING Hb F SYNTHESIS

- 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

Group	Hydroxyurea	Placebo	p value*
Pain Episodes	2.5 / year	4.5 / year	p < 0.001
Pain Admits	1.0 / year	2.4 / year	p < 0.001
Acute Chest	25 episodes	51 episodes	p < 0.001
Transfused	48	73	p < 0.001
Total Units	336	586	p = 0.004

*Van der Waerden's test.

Charache et al. N Engl J Med 322:1317, 1995.

Hydroxyurea Improves Survival

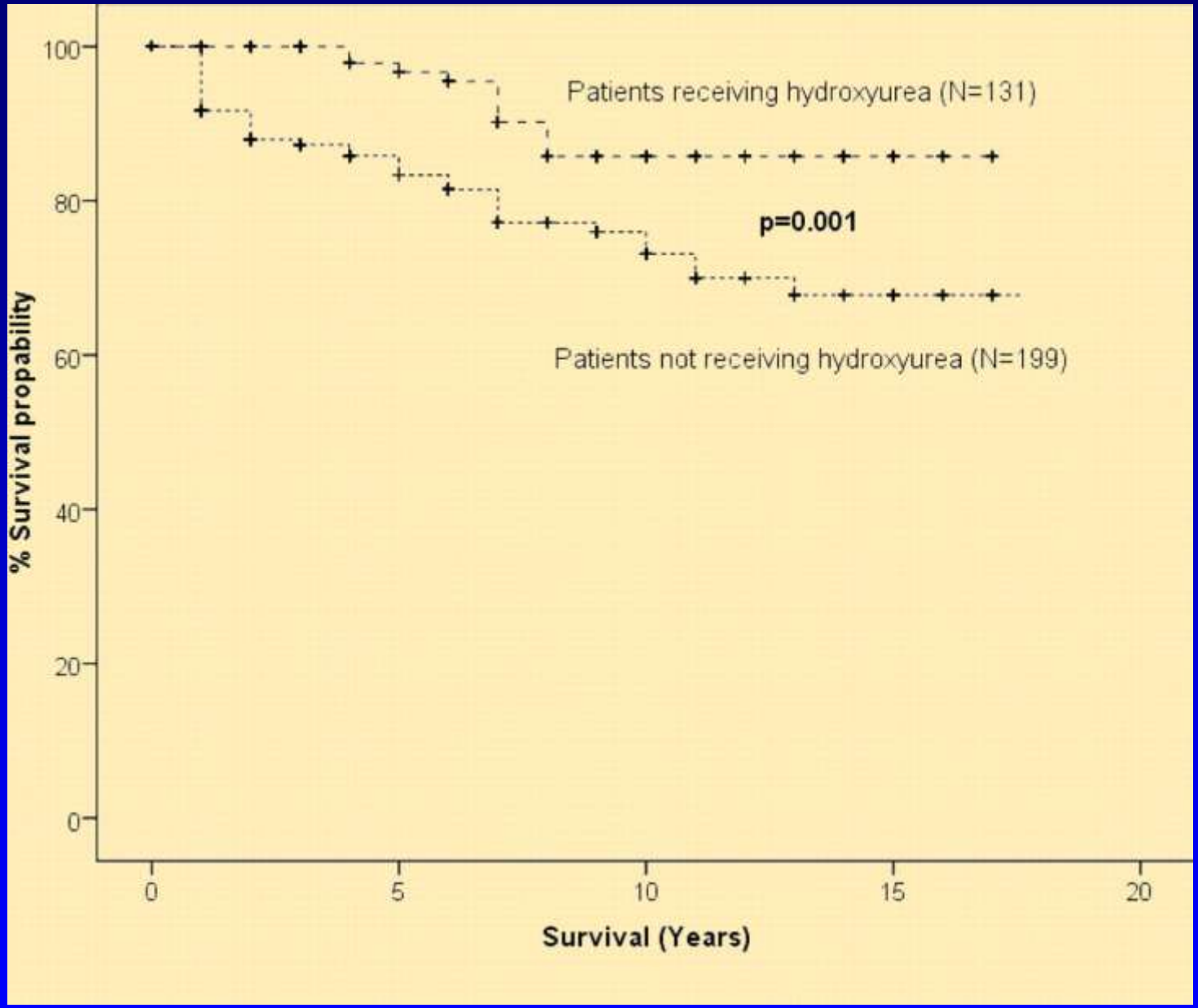
Adults: 131 treated with Hydroxyurea and 199 usual care for up to 17 years (median 8 verses 5 years)

10 Year Predicted Survival

Group	Hydroxyurea	No Hydroxyurea	P value
Overall	86 %	65 %	
Hb SS	100 %	10 %	< 0.001
Hb S β^o	87 %	54 %	<0.001
Hb S β^+	82 %	66 %	0.369

Voskaridou E et al. Blood 2010; 115: 2354-2363

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Eckman J R Blood 2010;115:2331-2332

Erythropoetin (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 Hydoxyurea

- Goldberg et al NEJM 1990; 323:366-372
- 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 Hydoxyurea

- 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** ▶

DAVID TULIS / Staff

Seye Arise is back in class at Nesbitt Elementary School in Tucker after a bone marrow transplant tamed his sickle cell anemia.