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Three Decades of Clinical Research in Sickle Cell Disease in the United States

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Outline of Presentation

- Historical perspective
  - 1972 National Sickle Cell Disease Control Act
- The Cooperative Study of Sickle Cell Disease – Significant Studies
- Life expectancy in sickle cell disease (SCD): then and now
- Current multicenter studies
- Difficulties in establishing effectiveness
- Proposed strategies to improve collaboration

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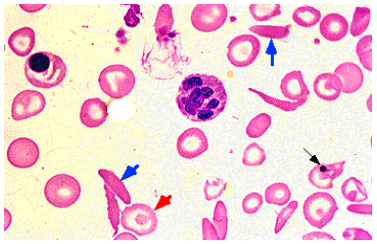
The First Case Described

- Chicago physician, Dr. James Herrick, noted in **1910** that a patient, a dentistry student from the West Indies, had an anemia characterized by unusual red cells that were "sickle shaped"



- Walter Clement Noel completed his training, returned to Grenada and practiced dentistry until he died of pneumonia at the age of 32

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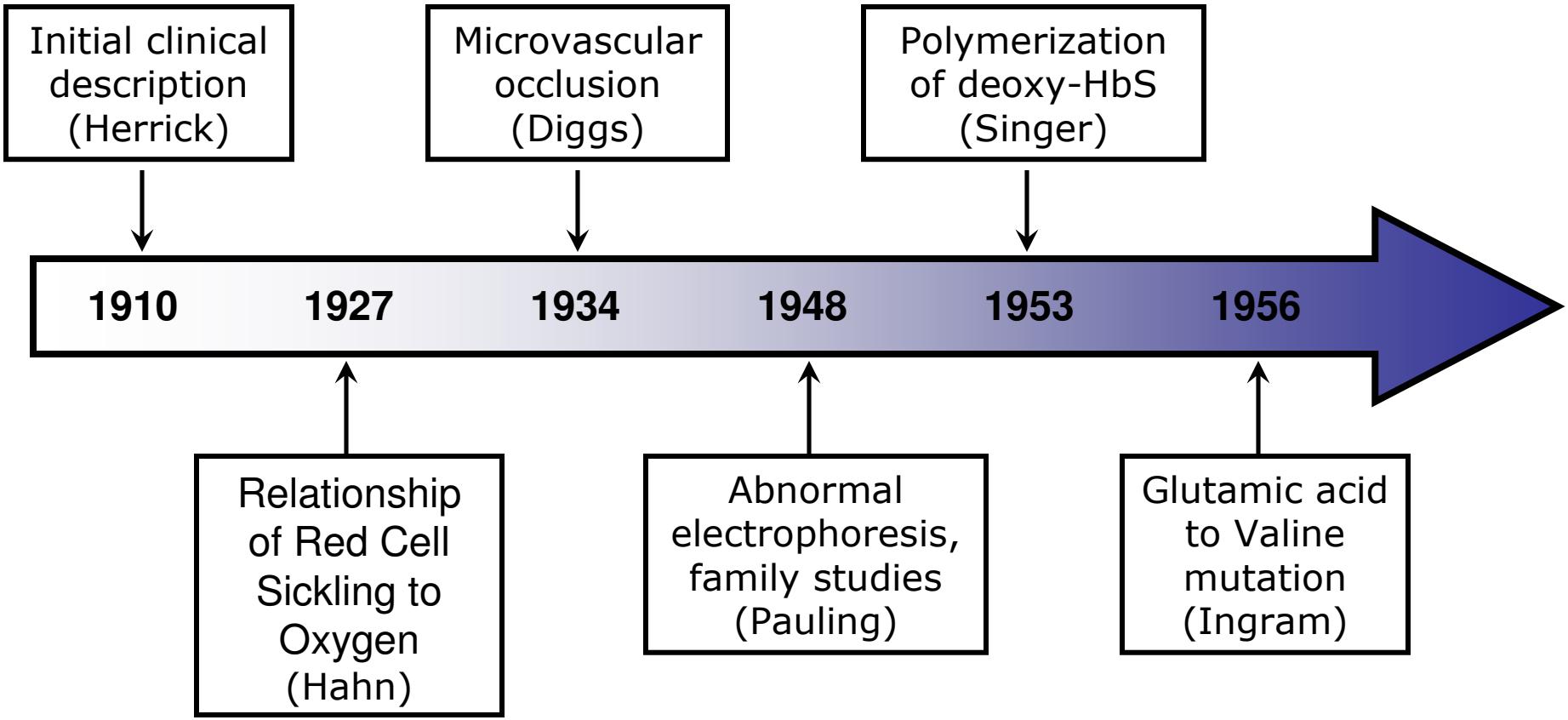
Timeline for Sickle Cell Disease



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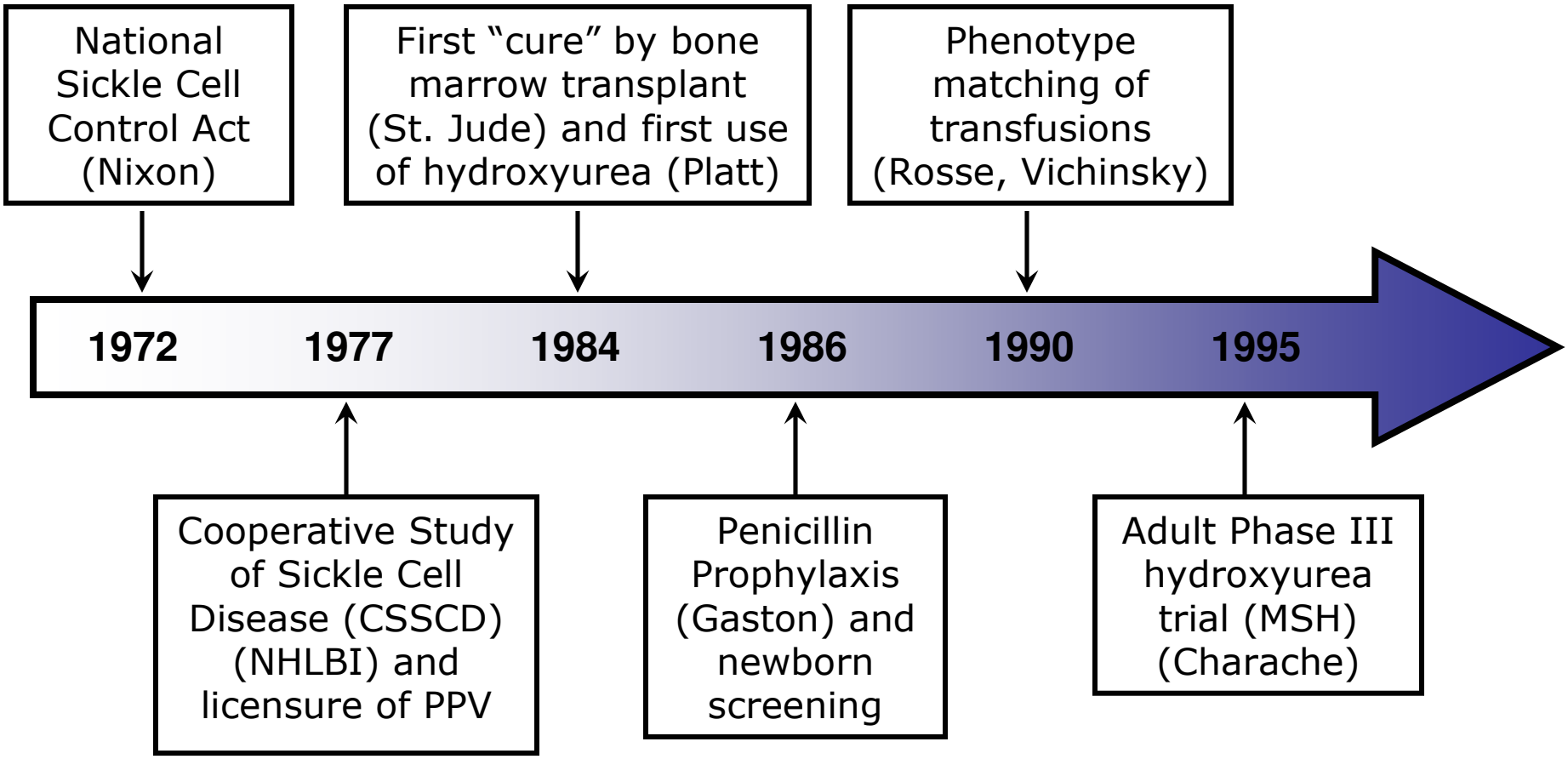
Timeline for Sickle Cell Disease



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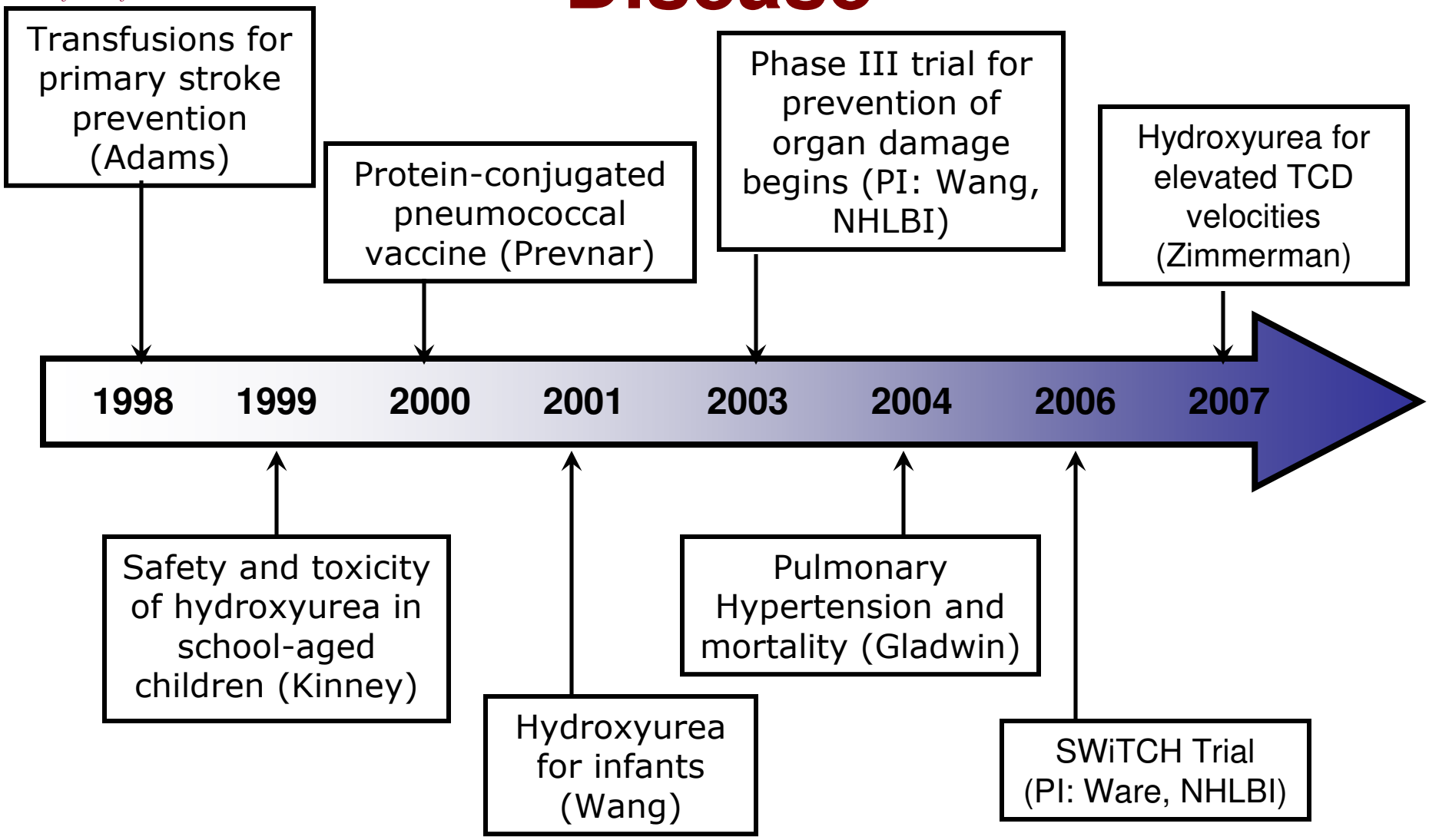
Timeline for Sickle Cell Disease



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National Sickle Cell Disease Control Act - 1972

- Feb 18, 1971 President Nixon made SCD a national priority in his "Special Message to the Congress"
- 1972: National SCD control Act signed into law
- Kick off of the National Sickle Cell Program
- Law mandated scientific research programs should be funded to improve care and quality of life of patients with SCD
  - Establishment of voluntary screening and counseling programs
  - Research in diagnosis, treatment and control of SCD

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National SCD Program

- National Heart, Lung, and Blood Institute (NHLBI) assigned the responsibility of developing and supporting research in SCD

- 1979: creation of the Cooperative Study of Sickle Cell Disease (CSSCD)
  - Rationale: little information on prospective clinical course of SCD
  - Included patients:
    - With mild and severe course
    - From rural and urban areas
    - All genotypes of SCD (SS, SC, Sβ$^+$thal, etc.)
    - > 3000 individuals
  - Improved understanding of risk factors for increased morbidity and early mortality

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Risk Factors for Major Organ Dysfunction or Event Data from CSSCD

Organ/Event	Risk factor	Reference
Painful crisis	↓Hb F, ↑Hct	Platt et al, NEJM 1991
Ischemic stroke	ACS, prior TIA, ↑Hb, ↑BP	Ohene-Frempong, et al, Blood 1998
Loss of splenic function	↓Hb F	Pearson, et al, Pediatrics 1985
AVN	↑pain, ↑Hb, ↓MCV	Miner, et al, NEJM 1991
ACS	↓Hb, ↓Hb F, ↑WBC	Castro, et al, Blood 1994

Modified from Bonds, D. – Blood Reviews 2005

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NHLBI-Sponsored SCD Trials

- PROPS I and II
- Hydroxyurea Phase II trial in adults
- MSH trial
- Pre-operative transfusion trial
- STOP I and II trials
- Phase I/II of hydroxyurea in children (HUG-KIDS)
- ACS
- AVN

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Prophylactic Penicillin Studies (PROPS) I and II

- PROPS I: Initiated in 1983 in 23 sites
- Randomized, double-blinded, placebo controlled trial
- Tested efficacy of oral penicillin (PCN) in the prevention of severe bacterial infection in children with SCA < 3 yrs
- Terminated early (15 months)
- 84% reduction in incidence of infection in the treatment arm

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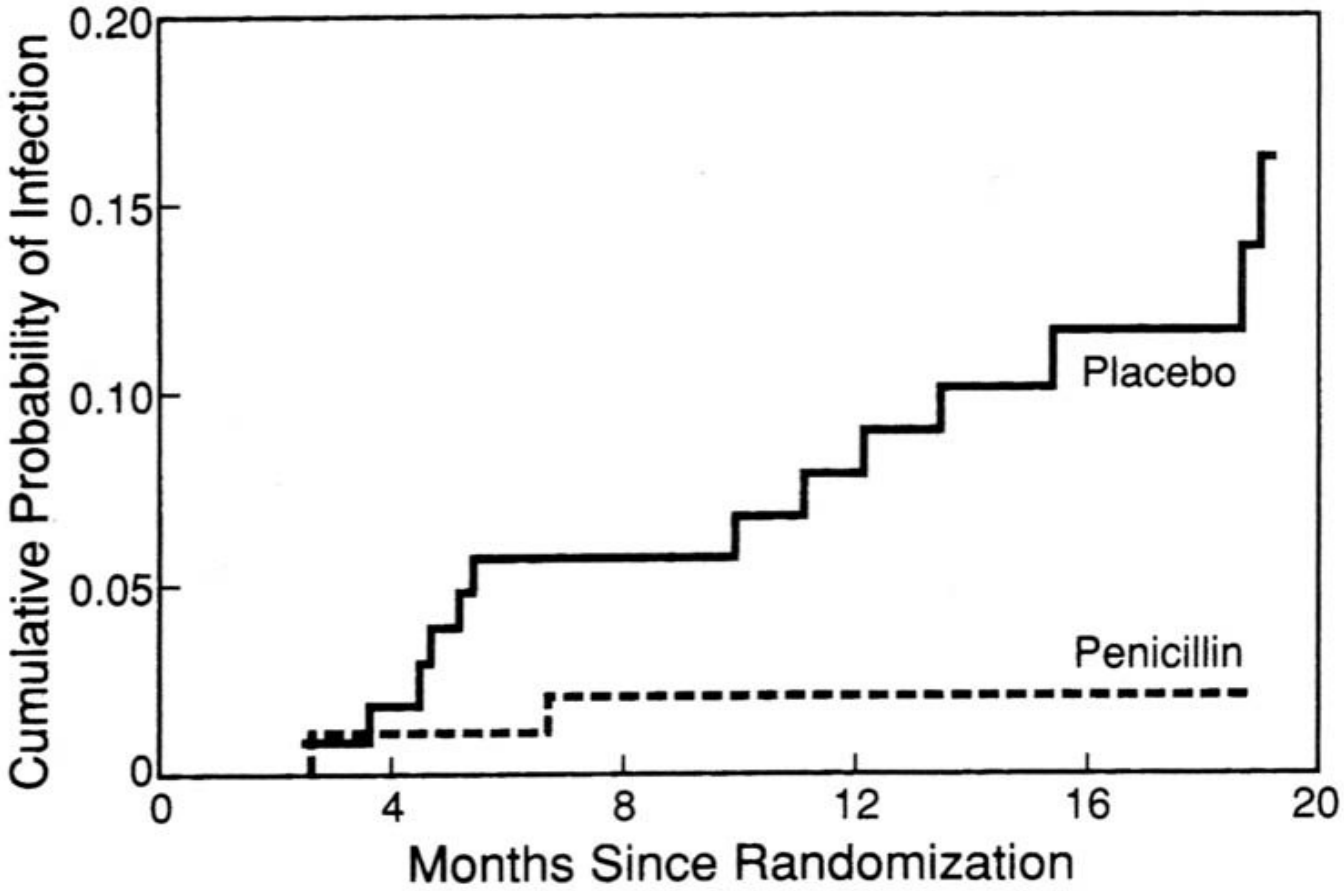
PROPS I study

Prophylaxis with Penicillin Protects Infants with SCA from Pneumococcal Sepsis



Gaston et al. NEJM 314:1593-1599

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Impact on Clinical Care

- Rationale for universal newborn screening for sickle hemoglobinopathies
- **Today all 50 states in the US screen for hemoglobinopathies** (Source: National Newborn Screening Status Report - Updated 08/03/07)

National Newborn Screening and Genetics Resource Center
NNSGRC

- All infants confirmed to have SCD should receive prophylaxis with PCN starting at 6 weeks

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PROPS II Study

- Does PCN reduce incidence of infection by pneumococcus beyond 5 years of age?
- Conclusion:

"Children with sickle cell anemia who have not had a prior severe pneumococcal infection or a splenectomy and are receiving comprehensive care may safely stop prophylactic penicillin therapy at 5 years of age."

- Example of effectiveness trial (required good drug adherence from participants)

Fuletta, et al., J Pediatr 1995; 127:685-90

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Adult Hydroxyurea Phase I/II Trial

- Safety and dosing trial
- Started in 1988
- 7 participating institutions
- 49 adults with Hb SS
- Responsiveness of HbF and toxicity

Table 1. Comparison of Pretreatment Measurements With Measurements at MTD

	Pretreatment Value	Value at MTD	P*
HbF (%)	4 ± 2	15 ± 6	.0001
F reticulocytes (%)	8 ± 5	23 ± 10	.0001
F cells (%)	28 ± 14	73 ± 17	.0001
F/F cell (pg)	5 ± 2	8 ± 2	.0001
Enrichment ratio	4.1 ± 2.6	2.6 ± .8	.0001
Hb (g/dL)	8.5 ± 1.4	9.7 ± 1.8	.0001
Reticulocytes ($\times 10^9$/L)	401 ± 157	243 ± 73	.0001
MCV (fL)	94 ± 8	117 ± 15	.0001
Median CHC (g/dL)	34 ± 3	34 ± 2	.39
Epo (U/L)	202 ± 189	471 ± 673	.03
WBC (cells $\times 10^9$/L)	13.4 ± 3.2	8.4 ± 1.4	.0001
Neutrophil count (cells $\times 10^9$/L)	7.4 ± 2.7	4.6 ± 1.1	.0001
Platelets ($\times 10^9$/L)	447 ± 136	364 ± 73	.0003
Total bilirubin (mg/dL)	3.9 ± 3.4	1.9 ± 1.2	.0001
ALT (IU/L)	36 ± 33	37 ± 29	.78

Values are mean ± standard deviation.
**P* by paired *t*-test.

Charache, et al., Blood. 1992 May 15;79(10):2555-65

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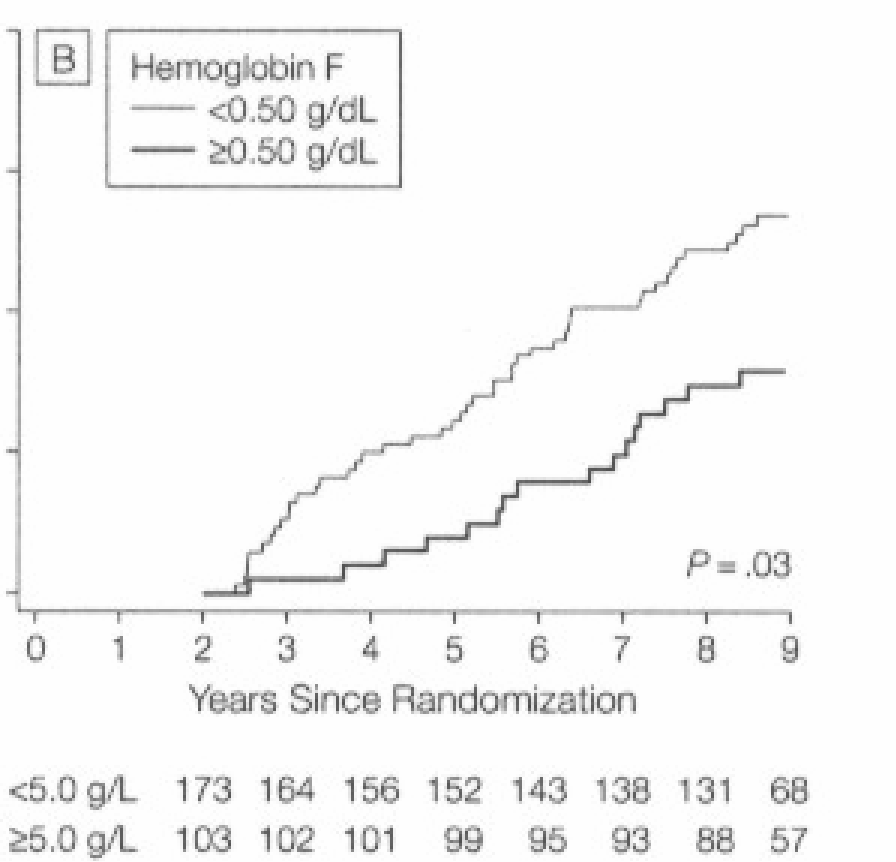
Adult Phase III Multicenter Study of HU in SCA (MSH trial)

- First randomized multicenter trial of HU
- 299 adults with clinical severity
- 21 centers
- Stopped early
- Proof of efficacy of HU in decreasing painful crises by 50%
- Decreased hospitalization for pain, ACS, and number of units of blood transfused
- Clinical implication: approved by the FDA for adults for prevention of painful episodes in 1998

Charache, et al., N Engl J Med. 1995 May 18;332(20):1317-22

Cumulative Mortality Among Adults Treated on MSH Trial Follow up



Steinberg et al, *JAMA.* 2003;289:1645-1651

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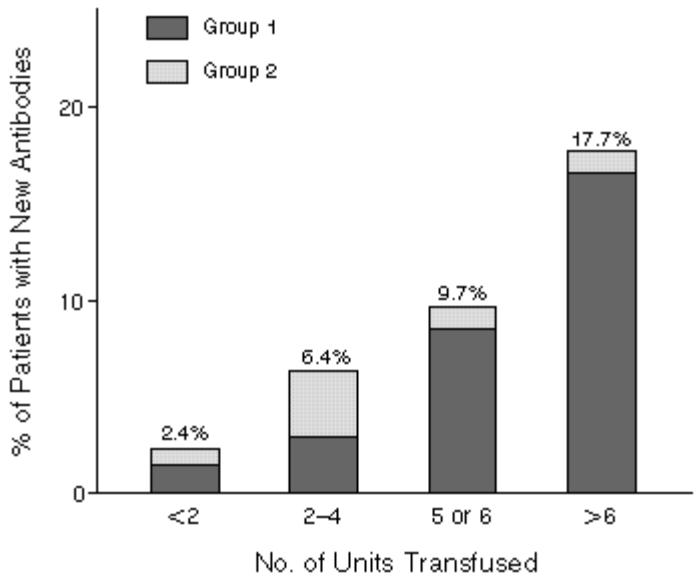
Pre-operative Transfusion Study

- Multi-center randomized study
- 551 patients
- Conservative transfusion regimen (≥ Hb to 10 g/dl) as effective as aggressive regimen (HbS <30%) in preventing perioperative complications
- Clinical implication: less exposure to blood

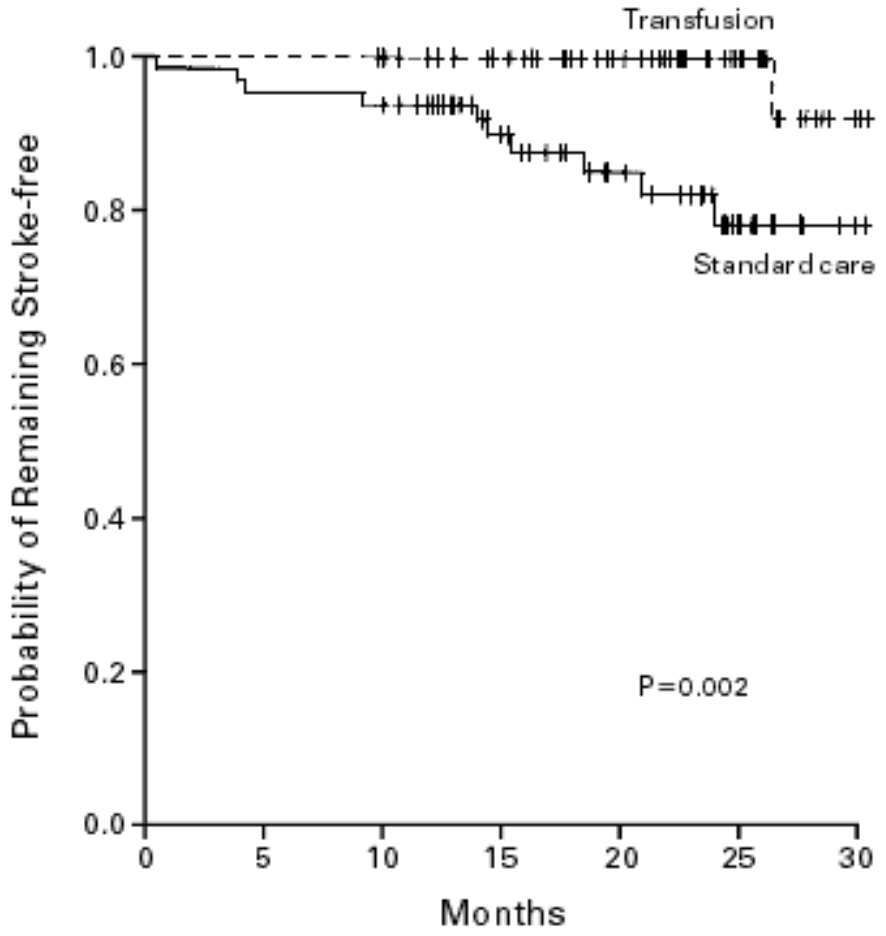


Vichinsky, et al., N Engl J Med 333:206, 1995

Stroke Prevention Trial in SCA (STOP trial)

- 130 children with TCD > 200 cm/sec randomized to receive either transfusion or observation

- Clinical implication: transfusion offered for selected group of patients at high risk for stroke



Adams et al., N Engl J Med 339:5, 1998

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HUG KIDS - Phase I/II of Hydroxyurea in Children

- 84 children between 5 and 15 years
- 52 reached MTD and were treated for 1 yr

Variable	Entry	6 mo	12 mo
No. of patients	84	78	77
Hematology			
Hb (g/dL)	7.8 ± 1.0	8.8 ± 1.0	9.0 ± 1.4
MCV (fL)	85.9 ± 6.6	99.5 ± 9.0	101.3 ± 10.2
MCH (pg)	29.5 ± 2.8	34.1 ± 3.4	34.6 ± 3.6
MCHC (g/dL)	34.3 ± 1.6	34.2 ± 1.1	34.2 ± 1.4
ARC (×10⁹/L)	354 ± 144	204 ± 83	191 ± 100
WBC (×10⁹/L)	13.6 ± 3.9	9.3 ± 3.0	9.2 ± 3.2
ANC (×10⁹/L)	7.0 ± 3.0	4.4 ± 2.1	4.4 ± 2.2
PLT (×10⁹/L)	461 ± 157	371 ± 130	371 ± 153
Serum chemistries			
Total bilirubin (mg/dL)	3.6 ± 2.6	2.9 ± 2.1	2.5 ± 2.0
LDH (IU/L)	1,126 ± 699	921 ± 592	807 ± 520
ALT (IU/L)	27 ± 14	28 ± 20	28 ± 22
Creatinine (mg/dL)	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2
Hb F parameters			
Hb F (%)	7.3 ± 4.9	14.9 ± 6.4	17.8 ± 7.2
	(N = 69)	(N = 70)	(N = 69)
F cells (%)	34.6 ± 17.8	59.2 ± 18.6	66.5 ± 19.6
	(N = 72)	(N = 72)	(N = 68)

Kinney, et al, Blood. 1999 Sep 1;94(5):1550-4.

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Impact of the Multicenter Trials

- Enormous efforts to complete studies
- Many challenges
- Collaboration between investigators and NHLBI key to success
- Two leading causes of death in pediatrics prevented today: pneumococcal sepsis and stroke
- Effective means to decrease incidence of pain events with hydroxyurea

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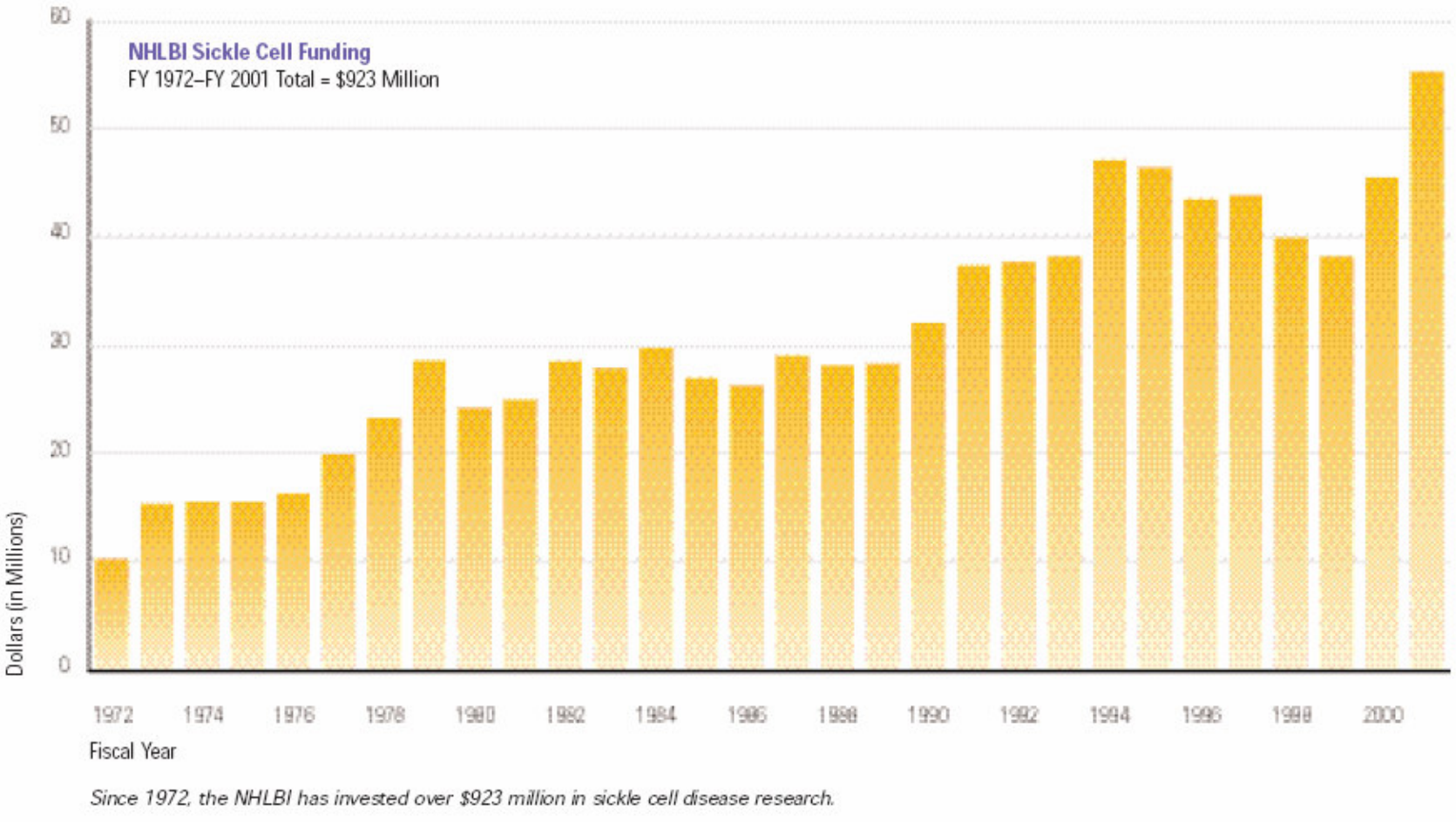
Research Dollars Allocated to SCD Research



Since 1972, the NHLBI has invested over $923 million in sickle cell disease research.

Source: NHLBI

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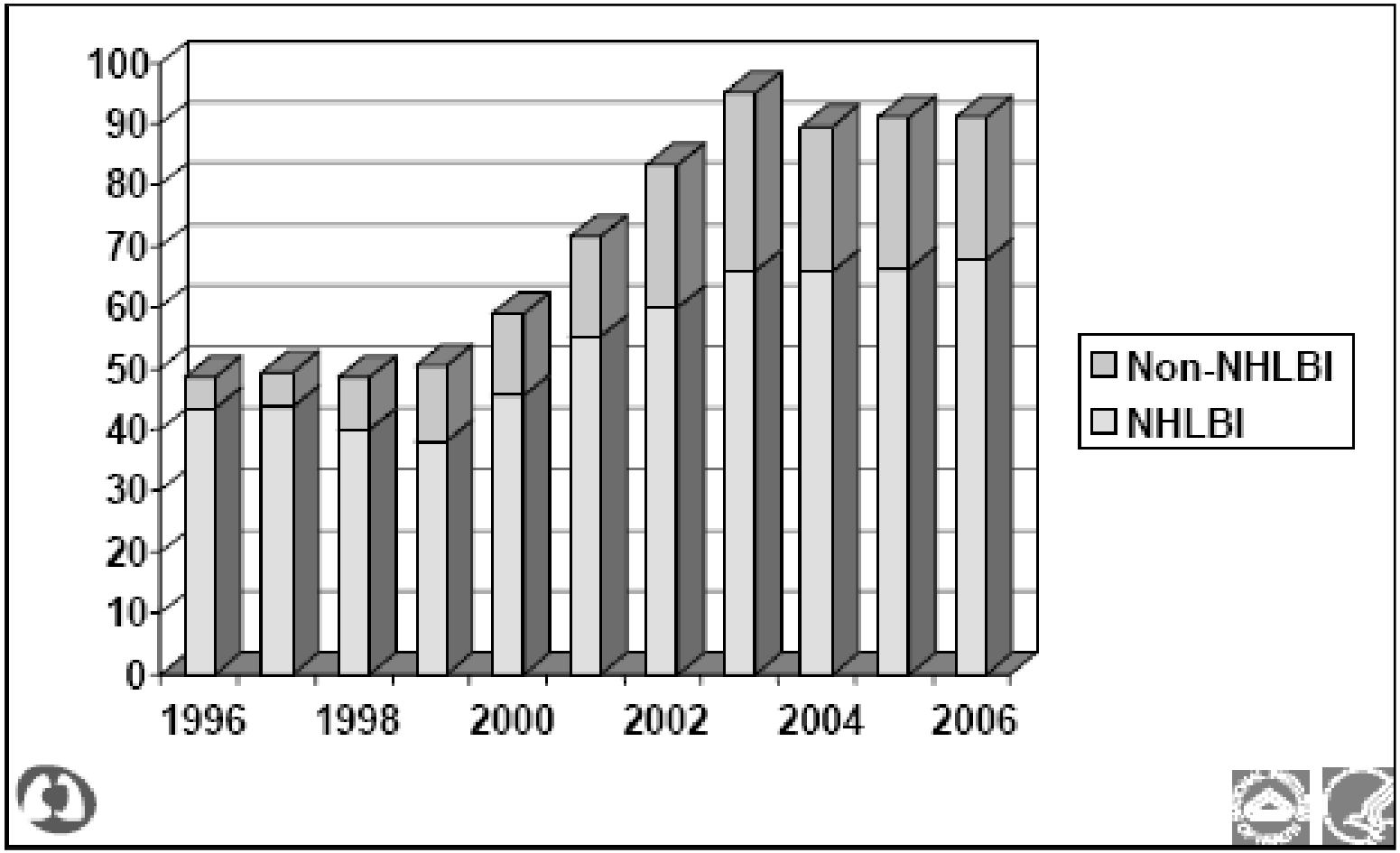
Research Dollars Allocated to SCD Research (recent data)



Source: NHLBI

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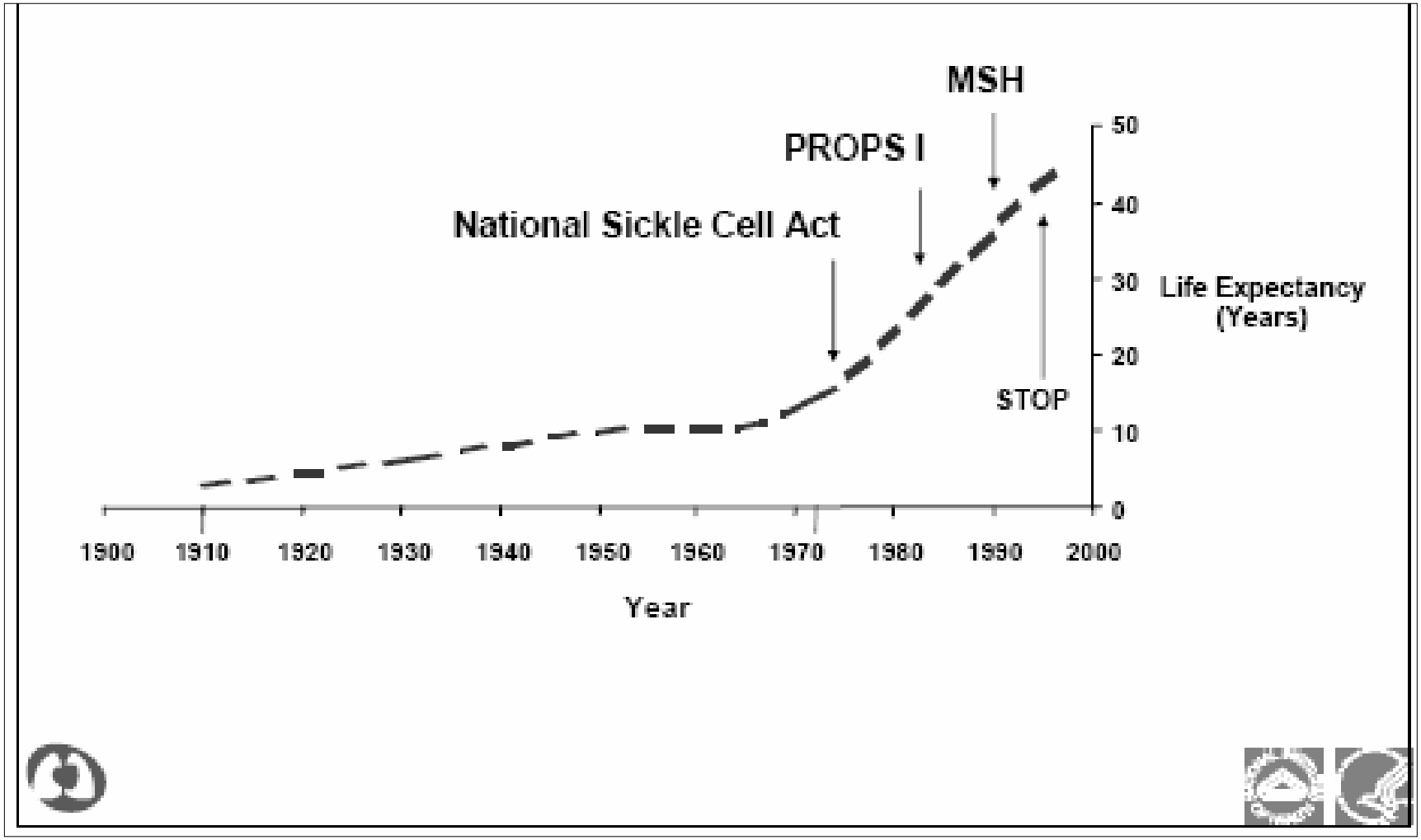
Survival in SCD



Source: NHLBI

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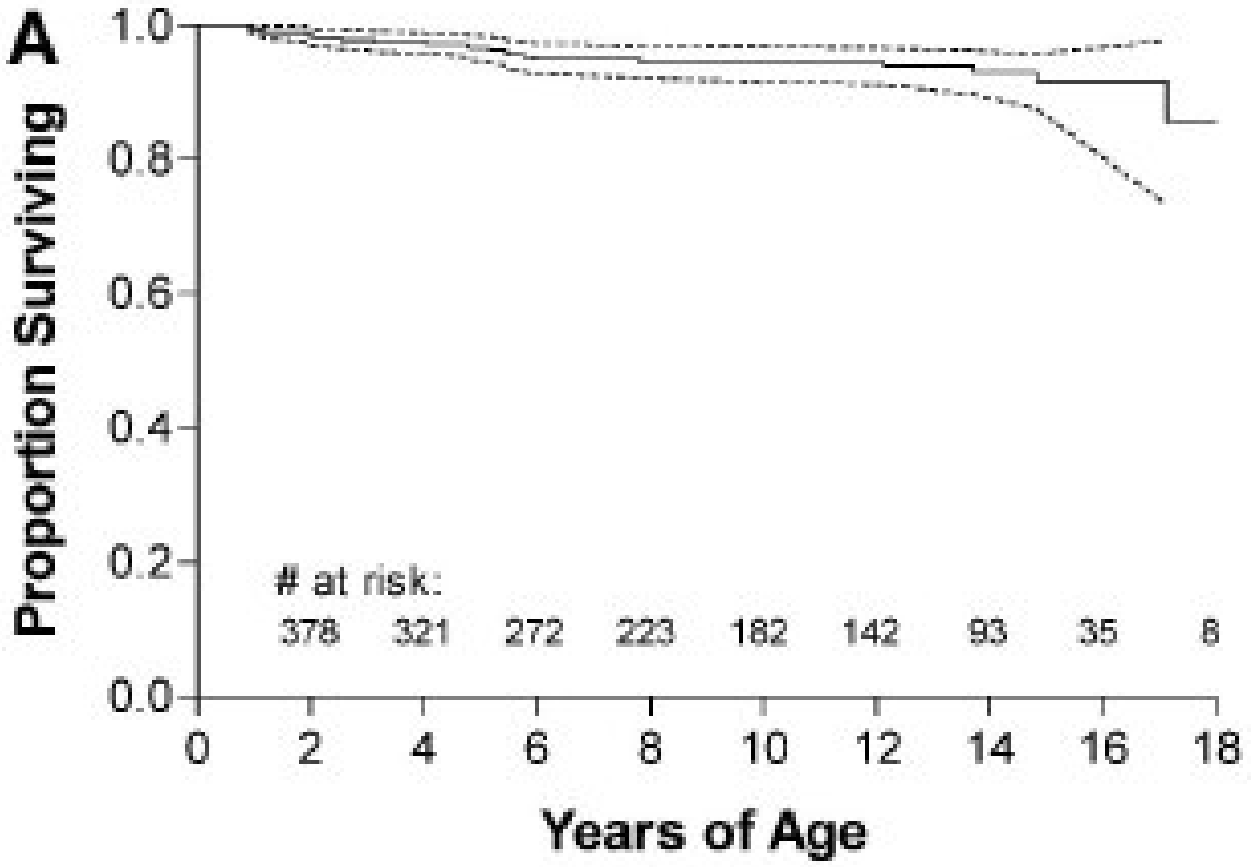
Survival in SCD
Recent Data (Dallas Cohort)



Quinn et al., Blood, 1 June 2004, Vol. 103, No. 11, pp. 4023-4027

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Current Interventional Multicenter Trials NHLBI-funded

- **BABY HUG**: phase III randomized double-blinded placebo-controlled trial for children from 9 to 18 months with SCA. Aim: Investigate HU effectiveness in preventing organ damage (spleen and kidney)

- **SWiTCH**: phase III randomized trial for children from 5 to 18 yrs with SCA. Aim: Compare HU plus phlebotomy vs. transfusion and oral iron chelator for prevention of secondary stroke and iron overload

- **WALK-PHASST**: phase III randomized double-blinded placebo controlled trial for patients ≥ 12 yrs. Aim: determine the effects of 16 weeks of sildenafil on pulmonary hypertension

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Current Interventional Multicenter Trials NHLBI-funded

- **ASSERT**: randomized double-blinded trial of ICA-17043 with or without Hydroxyurea Therapy for patients 17 to 66 yrs

- **Nitric Oxide Inhalation:** safety and efficacy of nitric oxide for inhalation in the treatment of vaso-occlusive pain crisis. Patients with SCA ≥ 10 yrs

- **ASSET:** long-term safety, tolerability and efficacy of bosentan in patients with pulmonary hypertension. Patients ≥ 16 yrs

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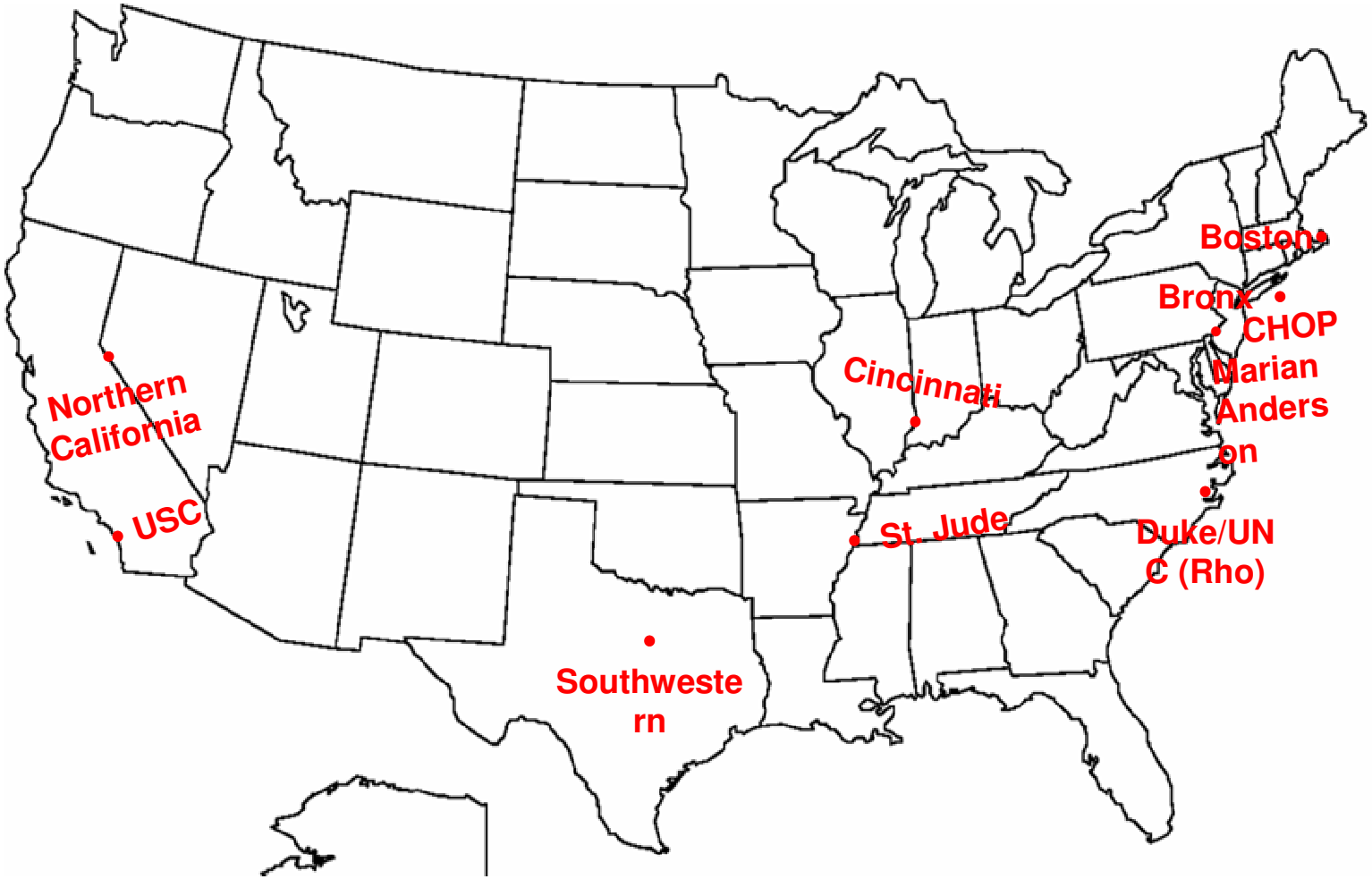
Current Multicenter Trials
10 Comprehensive SC Centers



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Current Multicenter Trials Comprehensive SC Centers

- **ARGININE Trial**: Phase II study to assess the physiological effects (both deleterious and beneficial) of the administration of oral arginine, a precursor of NO, in patients with SCD

- **Dexamethasone for ACS:** Phase III randomized study to determine whether administration of dexamethasone decreases the duration of hospitalization and symptoms of ACS

- **CHAMPS:** Phase II randomized double-blinded study to compare the effectiveness of hydroxyurea and magnesium pidolate (alone or in combination) in reducing the density of Hb SC erythrocytes

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Current Multicenter Trials Comprehensive SC Centers

- **Neuropsychological Dysfunction:** evolution of neurocognitive dysfunction in neurologically asymptomatic adult patients with SCD and assessment of the effect of transfusion on subjects with decreased neurocognitive function

- **C-DATA:** epidemiological collection of clinical and diagnostic data on sickle cell patients from all participating Centers

- **Epidemiology of Priapism:** large-scale survey to evaluate prevalence, demographics, and clinical characteristics of priapism among the CSCC population

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Current Multicenter Trials Clinical Research Network

- New mechanism for NIH-funding
- Focus on phase III trials
- Funding started in 2005 for 8 centers

- **PROACTIVE** Study: simple transfusion to prevent ACS in pts at high risk (admitted for pain, fever, and elevated PLA_2 level). Age >2yr

- **Losartan** for prevention of progressive nephropathy in pts with micro and macroalbuminuria. Randomized 3-4 yr trial or losartan vs placebo. Age >12 yr

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Current Multicenter Trials National

Institute of Neurological Disorders and Stroke (NINDS)-funded

- **SITT**: randomized trial for patients 5 to 14 yrs. Effectiveness of blood transfusion therapy for prevention of silent cerebral infarct

- **Aspirin Prophylaxis:** Open label trial for patients 2 to 7.9 yrs. Evaluation of safety and tolerability of daily low-dose aspirin (2.5 - 5.1 mg/kg daily for 12 months)

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New Drugs and Old Drugs with New Indications

- Arginine
- Glutamine
- Sildenafil
- Simvastatin (effect on vasoreactivity, endothelium adhesion, inflammation)
- Inhaled Nitric Oxide
- Dexamethasone
- Niacin
- 6R-BH4 (effect on endothelial function)
- L-citrulline
- Decitabine
- Anti-depressants for migraine frequency and severity
- Overnight CPAP (effect on processing speed)

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Drug Combinations

- HU/Magnesium pidolate: St. Jude Hospital
- HU/Clotrimazole: UNC, Children's Hospital Boston
- HU/Epo: Howard University, NIH
- HU/ICA-17043: multiple sites (Icagen)
- Mg/dipyridamole: Children's Hospital Cincinnati

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Challenges of Establishing Effectiveness

- So, if important studies showed efficacy, why isn't everybody using them?

- Facts:
  - TCD not widely used for stroke screening
  - HU not widely used for pain prevention

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Challenges of Establishing Effectiveness

Why reluctance in using hydroxyurea?

- Patient concerns about a drug used primarily to treat cancer
- Physician concerns about potential long-term mutagenic and teratogenic effects
- Lack of familiarity with chemotherapeutic agent
- Resistance among patients to use an experimental agent

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Challenges of Establishing Effectiveness

- Why reluctance to offer primary stroke prevention?
  - TCD not widely available
  - Good trained examiners hard to find
  - Reluctance of patients to blood transfusions
  - Perception of patients that risk of stroke (~10% per year) not high enough to warrant potential benefits of transfusion
  - Resistance of physicians to place their patients on an indefinite blood transfusion regimen (treating many to help few)

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Challenges of Establishing Effectiveness

"Important therapeutic advances are bound to have very limited impact on the natural history of any human disease unless they are widely accepted by patients they are intended to help" (Frenette and Atweh, JCI, vol 117 number 4, 2007)

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Challenges to Performing Research

- SCD is heterogeneous, therefore, hard to establish priorities and set goals for research
- Difficult to predict which patients will develop problems before organ damage
- Only subset of patients has access to modern care and research
- US medical care is fragmented
- SCD affects population largely disadvantaged by socioeconomic factors (disparities of health unrelated to SCD)

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The Funding Gap

- Since 1972, total number of grants increased by a factor of 10
- NIH is the main (not the only one) source of funding for SCD
- In 2004:

	SCD	Cystic Fibrosis
NIH funding (millions of dollars)	$90	$128
Other funding (millions of dollars)	$0.4	$152.2
Total	$90.4	$280.2
# patients in the US	80K	30K
$/patients	$1130	$9340

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Why is SCD Funding So Limited?

- Not enough public awareness?
- Negative stigma with SCD?
- Do we need a celebrity like the Muscular Dystrophy Association?

Jerry Lewis

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The Clinical Care Gap

- Only minority of SCD patients receive care in the comprehensive Sickle Cell Centers
- Clinical care for SCD patients not uniformly distributed
- Differences in rural versus urban areas
- Differences in privately versus publicly insured patients
  - Less rates of PCN use among publicly insured children in Tennessee and Washington (Sox et al, JAMA. 2003 Aug 27;290(8):1057-61)

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The Clinical Care Gap

- Diffusion of medical knowledge is slow and uneven

- Does race matter? (SCD mostly AA in the US)

"Conscious and unconscious racial bias adversely affects the availability of resources not only for research and the delivery of care, but also for the improvement of that care" (Telfair, et al, J Health Care Poor Underserved. 1998 May;9(2):184-95)

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Research and Excellent Clinical Care Cannot Be Apart

- Provision of medical home (multidisciplinary care)
- Integration of primary and specialty care
- Patient and family education of SCD
- Genetic counseling
- Prevention of infection (PCN use, fever as an emergency)
- Screening for stroke risk
- Regular eye exams
- Neurocognitive testing and academic support
- Judicious use of blood transfusion (minor Ag matching)
- Treatment of renal, pulmonary, cardiac complications

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New Efforts of Collaboration

Establishment of a Sickle Cell Disease Collaborative Research Group organized with the support of the American Society of Hematology (ASH) – May 2007

American Society of Pediatric Hematology and Oncology (ASPHO) – June 2007

aspho The American Society of Pediatric Hematology/Oncology

AMERICAN SOCIETY OF HEMATOLOGY

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ASH Research Agenda

- **Execute large scale trials of hydroxyurea and chronic transfusion, including careful study of effectiveness as well as efficacy**
- **Better characterize clinically relevant endpoints, including mortality, event rates, hematologic measures, and HRQOL**
- **Understand sickle cell pain, collaborating with pain experts in other disciplines**
- **Design small molecules that inhibit sickling**
- **Expand stem cell transplantation opportunities**
- **Collaborate far more with the international SCD community**

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ASH Research Agenda

The Vision: What Elements are Necessary for The Group's Success?

- **Collaborative spirit among investigators and institutions**
- **Training of more clinical and translational investigators**
- **Increased funding from NIH starting with RFA's for pilot projects**
- **Involvement of HRSA, CDC, CMS in supporting the research agenda**
- **Active engagement of relevant advocacy groups, community organizations, and professional societies**
- **Recognizing and overcoming barriers to success**

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ASPHO Summit: Opportunities Identified

1. **Access to care**: addressing medical, geographic, and financial barriers
2. **Health care delivery:** create more (±150) "Centers of Excellence"
3. **Defining best practices:** guidelines for standards of care
4. **Population-based clinical research:** All centers of excellence would participate
5. **Population-based surveillance systems to measure outcomes**
6. **Improving transfusion medicine services:** donor recruitment, minor antigen matching, and pheresis
7. **Developing a single, unified voice:** constituencies involved in SCD, with one goal: everyone moving forward in one direction
8. **Optimizing fundraising**

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ASPHO Summit

- White Paper to be developed summarizing the deliberations, including the major opportunities and proposing task forces to implement specific action

- Draft of the White Paper to be presented at the combined SCDAA/Sickle Cell Disease Investigators meeting in Washington D.C. in September 2007

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The Bottom Line

- Research is necessary but not sufficient to improve the lives of those affected by SCD

- Quality of care and access to care are issues of public policy and societal values

- Basic science and clinical investigators care about the quality of and access to care for patients

- All constituent groups must collaborate to achieve success, since no single group can address all the relevant problems alone

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"Teamwork is essential. It allows you to blame someone else."

Finagle's Eighth Rule

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Agradecimentos

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OBRIGADA!