Sickle cell Anemia
A Global Health Problem
**β-Globin gene**
(sixth codon)

T

↓

GAG
(glutamic acid)

→

GTG
(valine)

**Hemoglobin S**

solution

Oxygenated

Deoxygenated

**Hemoglobin S**

polymer

**Hemoglobin S**

cell

**Cell heterogeneity**

**Vaso-occlusion**

Sickled cells
The magnitude of the burden of genetic diseases

- 7 million babies are born each year with either a congenital abnormality or a genetic disease
- Five genetic disorders constitute 25% of these births
  - Thalassemia
  - Sickle cell anemia
  - G6PD
  - Oculocutaneous albinism
  - Cystic Fibrosis
September 15, 1904
- The SS Cearense docked in New York City after an 8 day voyage from Barbados.
- On board was Walter Clement Noel from Grenada who had a painful sore on his ankle that required treatment.
- He then traveled on to Chicago to attend Dental school.

December 1904
- Around Thanksgiving he developed respiratory problems that finally became so severe he sought treatment the day after Christmas.
- Dr. Ernest Irons, an intern performed a history physical and blood work and described pear-shaped and elongated red cells and notified his attending Dr. Herrick.
December 31, 1904
- Ernest Irons did another exam and blood smear and drew a picture of his observations

For two years Irons and Herrick followed Walter Clement Noel through several bouts of illness but never proved the etiology of his illness

After graduating from Dental School Walter Clement Noel returned to Grenada to practice dentistry

1910
- Herrick published the findings in the Archives of Internal Medicine
History of Sickle Cell Disease-Case 2
thanks to Todd Savitt Ph.D

- 1885
  - Ellen Anthony was born in rural Campbell county Va
  - There are very few records but she likely worked as a cook and housemaid

- 1907
  - She developed a severe abdominal crisis and presented to a local physician who sent her to UVA to the charity ward

- September 1909
  - During her 4th admission to UVA that lasted 284 days she was seen by medical student B.E. Washburn from Rutherfordton, NC
  - Washburn’s Attending, Dr. John S. Davis suggested he submit the case to the Virginia Medical Semi Monthly
STUDIES ON A CASE OF SICKLE-CELL ANEMIA*

BY JESSIE BOYD SCRIVER, M.D. AND T. R. WAGNER, M.D.,
Montreal

SICKLE-CELL anemia as a clinical entity is
of comparatively recent recognition, being
first described by Herrick1 in 1910. Since
then there have appeared in the literature nu-
merous reports of clinical histories, pathological
findings, and some laboratory investigations of
this condition. Our reason for reporting this
case is to place on record our observations on the
behavior of the erythrocytes "in situ", and in
this, the first case of sickle-cell anemia to be
reported from our Canadian clinics.

The condition which Herrick described oc-
curred in a negro, 93 years old, who presented
a cardiac enlargement, albuminuria, general
adenopathy, leucopenia, and a secondary anemia
which was not remarkable for the great reduc-
tion in red corpuscles or hemoglobin, but was
strikingly atypical in the large number of
nucleated red corpuscles of the normoblastic
type and in the tendency of the erythrocytes to
assume a slender sickle-like shape. The
shape of the red cells was very irregular and
there was a large number of thin elongated
sickle-shaped and crescentic forms which were
seen both in fresh specimens and in specimens
fixed by heat, alcohol, and ether, and stained
with the Ehrlich triacid stain, as well as with
the control stain. The second case was re-
ported by Washburn2 in 1911, and in 1915
Cook and Mayer3 reported the third case and
considered the condition of familial incidence.
Emler,4 who studied this third case and re-
ported his findings in 1917, presented the
important observation that the number of
sickle-shaped cells increased in sealed wet
blood preparations, and that during periods of
remission, when no sickle cells were found
in the patient's blood, the typical forms
would appear in sealed wet smears on standing.
This characteristic he considered

* From the Department of Medicine, McGill Uni-
versity Clinic, Royal Victoria Hospital, and the Depar-
tment of Pathology, McGill University, Montreal.

† Received in abridged form before the Ontario
Medical Association, Montreal, June, 1923.
In 1945 Linus Pauling sat in the audience of a lecture by Dr. William Castle about a sickle cell patient.

In that lecture, Dr. Castle noted that the sickling phenomenon was different in arterial blood samples and venous blood samples.

No sickling in arterial blood but sickle forms present in venous blood.
Dr. William E. Castle
Boston City Hospital
Boston
Massachusetts

Dear Bill:

I now have a graduate student [Harvey Itano, M.D.] beginning work on the problem of the relation between the nature of the hemoglobin in sickle cell anemia and the phenomenon of sickling.

He has not found any references in the literature to the work that you were telling me about, which, if I remember correctly, indicated that the dividing line between sickling and non-sickling came at 50 percent oxygenation of the hemoglobin or 50 percent combination with carbon monoxide. Could you tell me whether you and your collaborators have published any of this work, send me reprints if it has been published, and send me a brief statement about the results if it has not been published.

Last summer Dr. Burch told me that he felt sure that the phenomenon was due to a large amount of carbon dioxide. I have read his papers, and it seems to me that all of his results can be explained by assuming that the carbon dioxide treatment removes oxygen.

We are hoping to get some interesting results by studying other compounds of hemoglobin.

With best regards, I am

Sincerely yours,

Linus Pauling
November 25, 1946

Dr. Linus Pauling
Gates and Graf eliminate Laboratories of Chemistry
California Institute of Technology
Pasadena 4, California

Dear Linus:

How nice it is to have a word from you and probably to learn something new as a result of your work on that most interesting condition, sickle cell anemia. With regard to the facts about sickling, it is well established that oxygen and carbon monoxide prevent sickling, and that appears to other gases produce sickling by the removal of one or the other of these. Naturally, there is some effect from carbon dioxide in so far as it alters the saturation curve for oxygen of the hemoglobin by a change in the pH of the system. I would agree with you that Badger’s papers can all be interpreted in terms of removal of oxygen and, indeed, I wrote a critique of one of them for the Year Book of Medicine in which I simply interpolated the abstract of his communication in terms of this explanation.

I think that the literature that would be most useful for you, both for its content and for the references given, is the following:


Our own observations here confirm those of Archer and Weigh. Best sickling begins at about 55 to 60 millimeters oxygen tension. This decrease the sickling by the effect of the viscosity. i.e., the blood flow of blood through a viscometer with appropriate arrangements to maintain the blood at equilibrium with various tensions of oxygen. The viscosity of the blood begins to increase at about 40 millimeters oxygen tension, and rises
Sickle Cell Anemia, a Molecular Disease

Linus Pauling, Harvey A. Itano, S. J. Singer, and Ibert C. Wells
Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California

T HE ERYTHROCYTES of certain individuals possess the capacity to undergo reversible changes in shape in response to changes in the partial pressure of oxygen. When the oxygen pressure is decreased, these cells change their shape from the normal biconcave disk to crescent, bilycrt, and other forms. This process is known as sickling. About 8 percent of American Negroes possess this characteristic; usually they exhibit no pathological consequences attributable to it. These people are said to have sickle-cell, or sickle cell trait. However, about 1 in 40 (4) of these individuals whose cells are capable of sickling suffer from a severe chronic anemia resulting from excessive destruction of their erythrocytes; the term sickle-cell anemia is applied to their condition.

The main observable difference between the erythrocytes of sickle cell trait and sickle cell anemia has been that a considerably greater reduction in the partial pressure of oxygen is required for a major fraction of the trait cells to sickle than for the anemia cells (11). Tests in vivo have demonstrated that between 30 and 60 percent of the erythrocytes in the venous circulation of sickle cell anemia individuals, but less than 1 percent of those in the venous circulation of sickle individuals, are normally sickled. Observations in vitro indicate that under sufficiently low oxygen pressure, however, all the cells of both types assume the sickled form.

The evidence available at the time that our investigation was begun indicated that the process of sickling might be intimately associated with the state and nature of the hemoglobin within the erythrocytes. Sickle cell erythrocytes in which the hemoglobin is combined with oxygen or carbon monoxide have the biconcave disk contour and are indistinguishable in this respect from normal cells. The cells form from normal erythrocytes. In this condition they are termed proerythrocytes. The hemoglobin appears to be uniformly distributed and normally oriented within normal cells and proerythrocytes, and no birefringence is observed. Both types of cells are very flexible. If the oxygen or carbon monoxide is removed, however, transforming the hemoglobin to the uncombined state, the proerythrocytes undergo sickling. The hemoglobin within the sickled cells appears to aggregate into one or more foci, and the cell membrane collapses. The cells become birefringent (27) and quite rigid. The addition of oxygen or carbon monoxide to these cells reverses these phenomena. Thus the physical effects just described depend on the state of combination of the hemoglobin, and only secondarily, if at all, on the cell membrane. This conclusion is supported by the observation that sickled cells when made with water-glycerine-dichloral, rather than sickle-shaped, ghosts (20).

It was decided, therefore, to examine the physical and chemical properties of the hemoglobins of individuals with sicklecell and sickle cell anemia, and to compare them with the hemoglobin of normal individuals in order to determine whether any significant differences might be observed.

EXPERIMENTAL METHODS

The experimental work reported in this paper deals largely with a comprehensive study of these hemoglobins. In the initial phase of the investigation, which concerned the comparison of normal and sickle cell anemia hemoglobins, three types of experiments were performed: 1) with carbonylhaemoglobin; 2) with unabsorbed ferro-haemoglobin in the presence of dichlorethylene, to prevent oxidation to methaemoglobin; and 3) with carbonylhaemoglobin in the presence of dichlorethylene. The experiments of type 3 were performed and compared with those of type 1 in order to ascertain whether the dichlorethylene itself causes any specific electrophoretic effect.

Samples of blood were obtained from sickle cell anemia individuals who had not been transfused within three months prior to the time of sampling. Hematocrit-free concentrated solutions of human adult hemoglobins were prepared by the method used by von Hacke (3). These solutions were diluted just before use with the
The difference between normal and sickle globin genes is recognized.
1954 Allison et al. published in the British Journal of Medicine and article proving the protective effect of Sickle cell trait (AS) against malarial disease explaining the distribution of Sickle cell disease.

However despite this advantage Sickle trait incidence in populations is typically less than 25% due to the severe disadvantage in survival of the homozygous (SS) state.

The distribution of Sickle cell anemia was not completely explained by the protection against Malarial diseases.
If all cases of Sickle cell anemia had the same origin all patients would be cousins and their disease should all be very similar.

This led researchers to look into the origins of Sickle cell anemia to see if there was one place of origin or multiple regions of origin.
There are multiple origins of the Sickle cell Gene.

Data based on associated restriction site polymorphisms that exist with the Sickle Cell Gene.
Global Burden of Sickle Cell Disease

Spread of Sickle Genes

Origins (2000-1000 BC?):
West, Central Africa
India/E. Saudi Arabia

Early migration:
(1000-200 BC)
North Africa,
Mediterranean
Middle East

Later migration:
(1500-1900)
Americas, Europe

Modern migration:
Global

Sickle cell disease, a truly global health problem
Where is Sickle cell Anemia the greatest Healthcare burden?

How many babies are born with SCD?

Estimate of Global Frequency of Sickle Cell Gene

# Estimates of number of Cases of Sickle trait and Sickle cell anemia in 2010

## How many people are born with SCD?

<table>
<thead>
<tr>
<th>Region</th>
<th>AS</th>
<th>SS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>5,476,407</td>
<td>312,302</td>
<td>100</td>
</tr>
<tr>
<td>Americas</td>
<td>386,430</td>
<td>12,802</td>
<td>4.6</td>
</tr>
<tr>
<td>Arab-India</td>
<td>1,147,477</td>
<td>46,826</td>
<td>16.9</td>
</tr>
<tr>
<td>Eurasia</td>
<td>256,163</td>
<td>7,493</td>
<td>3.0</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>2,535</td>
<td>21</td>
<td>0.0</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>3,580,207</td>
<td>235,681</td>
<td>75.5</td>
</tr>
</tbody>
</table>

*Piel et al. 2013. Lancet 381:142–51*
Other Hemoglobinopathies such as Hemoglobin C can affect the rate of Sickle disorders.
How many Children are born with C trait or Homozygous Hemoglobin C

<table>
<thead>
<tr>
<th>Region</th>
<th>AC</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>672,117</td>
<td>28,703</td>
</tr>
<tr>
<td>1. Nigeria</td>
<td>148,423</td>
<td>3,099</td>
</tr>
<tr>
<td>2. Burkina Faso</td>
<td>131,454</td>
<td>9,592</td>
</tr>
<tr>
<td>3. Ghana</td>
<td>98,153</td>
<td>4,707</td>
</tr>
<tr>
<td>4. Mali</td>
<td>79,506</td>
<td>4,354</td>
</tr>
</tbody>
</table>

Piel et al. 2013, Scientific Reports | 3 : 1671 | DOI: 10.1038/srep01671
What are the predictions for what will happen to Sickle Cell Anemia in the future?

<table>
<thead>
<tr>
<th>Country</th>
<th>2010</th>
<th>2050</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>305,773</td>
<td>404,190</td>
<td>+32.2</td>
</tr>
<tr>
<td>1. Nigeria</td>
<td>91,011</td>
<td>140,837</td>
<td>+54.7</td>
</tr>
<tr>
<td>2. India</td>
<td>44,425</td>
<td>33,890</td>
<td>-23.7</td>
</tr>
<tr>
<td>3. Congo DR</td>
<td>39,743</td>
<td>44,663</td>
<td>+12.4</td>
</tr>
<tr>
<td>21. USA</td>
<td>2,842</td>
<td>3,379</td>
<td>+18.9</td>
</tr>
<tr>
<td>14. Ghana</td>
<td>5,815</td>
<td>6,855</td>
<td>+17.9</td>
</tr>
</tbody>
</table>

*Piel et al. (2013) PLoS Med 10(7): e1001484. doi:10.1371/journal.pmed.1001484*
So Now, a little more

History
1977 the NIH funded the Cooperative Study of Sickle cell Disease with the following objectives:

- To study the effect of SCD on growth and development from birth through adolescence.
- To study “painful crisis” including the manifestations and therapies being used.
- To determine the nature, duration and outcomes of the major complications of SCD.
- To determine the nature, prevalence, and age related incidence of organ damage due to SCD.
- To determine the economic, educational and vocational levels in patients with SCD.
What are some of the complications which were understood due to this study?

- Early mortality from infections during childhood due to splenic hypofunction
- Painful crisis
- Acute chest syndrome crisis
- Pulmonary arterial hypertension
- Thrombotic stroke and silent strokes in children and adolescents
- Bone infarcts and avascular necrosis
- Kidney and eye changes
- Early mortality before many reach adulthood or during early adulthood.
What have we done here in the United States to improve life for Sickle cell patients?

How have we addressed these Sickle cell complications in the United States?

- Diagnosis unknown – Universal New Born Screening, genetic counseling
- Early mortality – Penicillin prophylaxis for children
- Acute pain crisis/Acute Chest syndrome – Hydroxyurea
- Strokes and silent strokes – transcranial dopplers, RBC exchange, hydrea
- Cure for sickle cell anemia – Stem Cell Transplantation
How big is the Healthcare gap between Sickle cell patients in the US and in Africa?
Just a reminder of the burden of Sickle cell disease

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>SICKLE CELL BIRTHS/YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria</td>
<td>91,011</td>
</tr>
<tr>
<td>Tanzania</td>
<td>11,877</td>
</tr>
<tr>
<td>Uganda</td>
<td>10,877</td>
</tr>
<tr>
<td>Angola</td>
<td>9,017</td>
</tr>
<tr>
<td>Cameroon</td>
<td>7,172</td>
</tr>
<tr>
<td>Zambia</td>
<td>6,039</td>
</tr>
<tr>
<td>Ghana</td>
<td>5,815</td>
</tr>
<tr>
<td>Guinea</td>
<td>5,402</td>
</tr>
<tr>
<td>Niger</td>
<td>5,310</td>
</tr>
<tr>
<td>Sub-Saharan Africa Total</td>
<td>242,187</td>
</tr>
<tr>
<td>Worldwide Total</td>
<td>305,773</td>
</tr>
</tbody>
</table>
Sickle Cell Disease in Africa
A Neglected Cause of Early Childhood Mortality

Scott D. Grosse, PhD, Isaac Odame, MB, ChB, MRCP, Hani K. Atrash, MD, MPH,
Djesika D. Amendah, PhD, Frédéric B. Piel, PhD, Thomas N. Williams, PhD

.....although current data are inadequate to support definitive statements, they are
consistent with an early-life mortality of 50%–90% among children born in Africa with SS
disease.”
Sickle-cell anaemia

Report by the Secretariat

...sickle-cell anemia contributes the equivalent of 5% of under 5 deaths on the African continent, more than 9% of such deaths in West Africa, and up to 16% of under-5 deaths in individual West African countries.
How various levels of Public Health infrastructure can impact Sickle cell mortality

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Low/Middle-Income Countries (GNI = ≤ US$12,275)</th>
<th>High-Income Countries (GNI &gt; US$12,275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>Poor access to public health infrastructures</td>
<td>Good access to public health infrastructures</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>Good access to public health infrastructures</td>
<td>Specific interventions for children with SCA (e.g., diagnosis, treatment)</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>Specific interventions for children with SCA (e.g., diagnosis, treatment)</td>
<td>Universal screening programme (optimum)</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>Universal screening programme</td>
<td>Universal screening programme (optimum)</td>
</tr>
</tbody>
</table>

Source: doi:10.1371/journal.pmed.1001404.t002
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Access in Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Newborn screening; penicillin prophylaxis;</td>
<td>Affordable / increasing availability</td>
</tr>
<tr>
<td>anti-pneumococcal vaccination</td>
<td></td>
</tr>
<tr>
<td>2. Comprehensive care coordination</td>
<td>Limited / Affordable</td>
</tr>
<tr>
<td>3. Better pain management</td>
<td>Affordable / very limited availability</td>
</tr>
<tr>
<td>4. Family-patient education</td>
<td>Possible / affordable</td>
</tr>
<tr>
<td>5. Hydroxyurea</td>
<td>Affordable / increasing availability</td>
</tr>
<tr>
<td>6. Chronic RBC transfusion</td>
<td>Affordable / increasing availability</td>
</tr>
<tr>
<td>7. Hematopoietic stem cell transplantation</td>
<td>Very limited availability</td>
</tr>
</tbody>
</table>
# Newborns with SCD Increasing Globally

## 2010-2050 Estimated Newborns with SCD-SS

### Impact of Public Health Interventions:

1. Implementation in 2015 of
   - prenatal diagnosis,
   - penicillin prophylaxis, and
   - “vaccination” for children with SCD-SS,
   can reduce mortality among children under-5 with SCD-SS,
   prolong the lives of 5,302,900 SCD-SS newborns with by 2050.

2. Large-scale universal screening
   could save the lives of up to 9,806,000 newborns with SCD-SS globally, 85% of whom will be born in sub-Saharan Africa

*Piel et al. (2013) PLoS Med 10(7): e1001484. doi:10.1371/journal.pmed.1001484*
Thank you for your attention