Sickle Cell Disease
It can be *cured*!

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True or False!

Only African Americans get sickle cell disease

False!

Brief History

- Present in Africa for at least 5,000 years
- Many names in many tribal languages
- 1910: Walter Clement Noel – a dental student in Chicago, originally from the island of Grenada
- Cardiologist Dr. James B. Herrick – assigned a resident Dr. Ernest Irons to the case
- Microscopic examination of the blood – “sickle shaped cells”

First Molecular Disease

- November 25, 1949 issue of Science journal
- Described as a ‘Genetic Disease’
- Introduced the concept of a “molecular disease”
- Major impetus to the development of molecular medicine
- Helped establish that genes control the specific structure of protein molecules

Sickle Cell Anemia, a Molecular Disease[1]

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THE 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 lowered, these cells change their forms from the normal biconcave disk to crescent, holly wreath, and other forms. This process is known as sickling. About 8 percent of American Negroes possess this characteristic; usually they exhibit no pathological consequences ascribable to it. These people are said to have sicklemia, 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 anemic individuals, but less than 1 percent of those in the venous circulation of sicklemic individuals, are normally sickled. Experiments *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 the nature of the hemoglobin within the erythrocyte. Sickle cell erythrocytes in which the hemoglobin is combined with oxygen or carbon monoxide have the biconcave disk contour and are indistinguishable in that form from normal erythrocytes. In this condition they are termed promeniscocytes. The hemoglobin appears to be uniformly distributed and randomly oriented within normal cells and promeniscocytes, 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 promeniscocytes undergo sickling. The hemoglobin within the sickled cells appears to aggregate into one or more foci, and the cell membranes collapse. The cells become birefringent (*11*) 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 lysed with water produce discoidal, rather than sickle-shaped, ghosts (*10*).

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

Experimental Methods

The experimental work reported in this paper deals largely with an electrophoretic study of these hemoglobins. In the first phase of the investigation, which concerned the comparison of normal and sickle cell anemia hemoglobins, three types of experiments were performed: 1) with carbonmonoxyhemoglobins; 2) with uncombined ferrohemoglobins in the presence of dithionite ion, to prevent oxidation to methemoglobins; and 3) with carbonmonoxyhemoglobins in the presence of dithionite ion. The experiments of type 3 were performed and compared with those of type 1 in order to ascertain whether the dithionite ion itself causes any specific electrophoretic effect.

Samples of blood were obtained from sickle cell anemic individuals who had not been transfused within three months prior to the time of sampling. Stroma-free concentrated solutions of human adult hemoglobin were prepared by the method used by Drabkin (*3*). These solutions were diluted just before use with the

[1] This research was carried out with the aid of a grant from the United States Public Health Service. The authors are grateful to Professor Ray D. Owen, of the Biology Division of this Institute, for his helpful suggestions. We are indebted to Dr. Edward R. Evans, of Pasadena, Dr. Travis Winsor, of Los Angeles, and Dr. O. E. Burch, of the Tulane University School of Medicine, New Orleans, for their aid in obtaining the blood used in these experiments.

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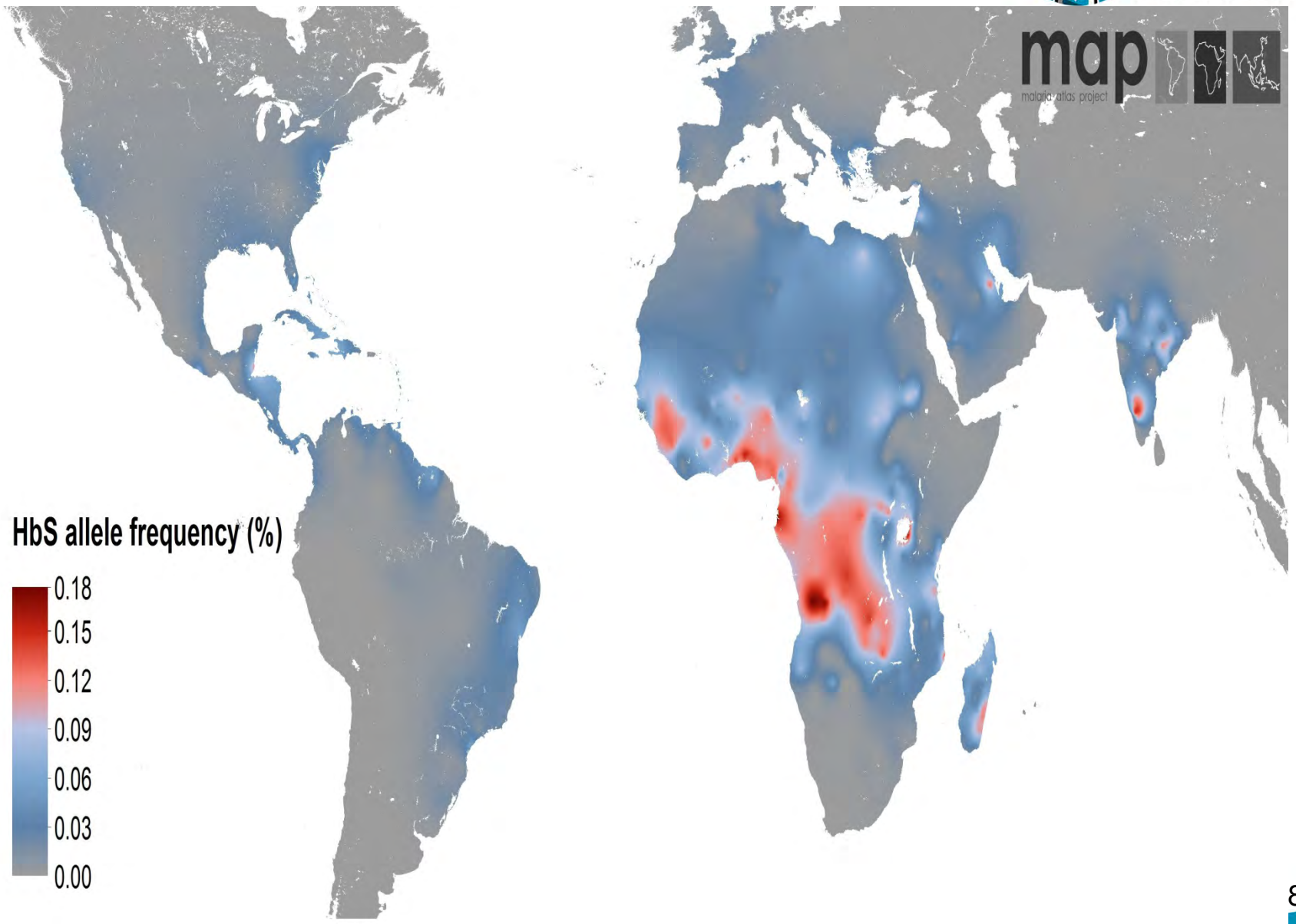
[3] Postdoctoral fellow of the Division of Medical Sciences of the National Research Council.

[4] Contribution No. 1332.

True or False!

A woman with sickle cell disease cannot have a healthy pregnancy

False!


map
malaria atlas project
HbS allele frequency (%)
0.18
0.15
0.12
0.09
0.06
0.03
0.00

How common is it?

- Millions affected around the world
- Common among those whose ancestors came from sub-Saharan Africa
- Spanish-speaking regions in the Western Hemisphere (South and Central America, Caribbean)
- Saudi Arabia, India, Mediterranean countries (Turkey, Greece, and Italy)

How common in the USA?

- Affects approximately 100,000 Americans
- 1 out of 365 Black/African-American births
- 1 out of every 16,300 Hispanic-American births
- 1 in 13 Black/African American babies is born with sickle cell trait

True or False!

People with sickle cell disease cannot get malaria

False!

How costly is it?

- 2005: $11k - $14k per year per child
- 1989-1993 – average of 75,000 hospitalizations due to sickle cell disease in the USA
  - ***COST $475 MILLION***

How deadly is it?

- 1990-1994 – California, Illinois and NY: 1% children with sickle cell disease died as a result of the disease in first 3 years of life
- Mortality rate in < 4 years of age fell by 42% from 1999-2002 (vaccine)
- 1983-86 vs 1999-2202 – mortality decreased by:
  - 68% for ages 0-3 years
  - 39% for ages 4-9 years
  - 24% for ages 10-14 years

True or False!

There is no cure for sickle cell disease