What Is It And Where Did It Come From

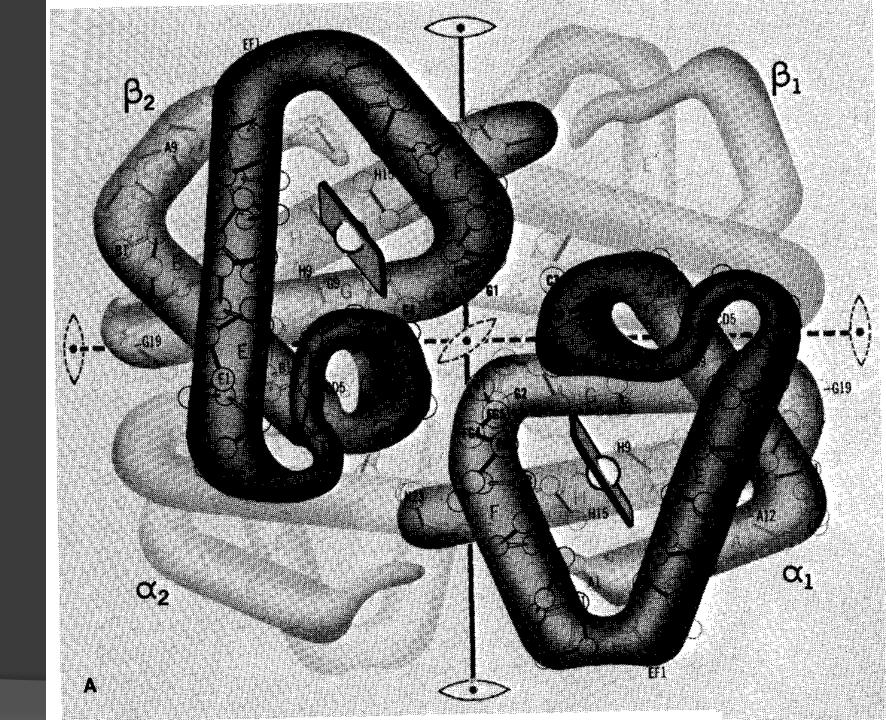
SICKLE CELL DISEASE

What is Sickle Cell Disease?

- Sickle cell disease is a disease of the blood
 - It is due to an abnormal hemoglobin (the red pigment of blood)
- It is inherited (it comes from the parents and is passed to children)
- It causes many problems, including:
 - Pain
 - Disability
 - Loss of organs (strokes, kidney failure, bone damage, etc.
 - Premature death

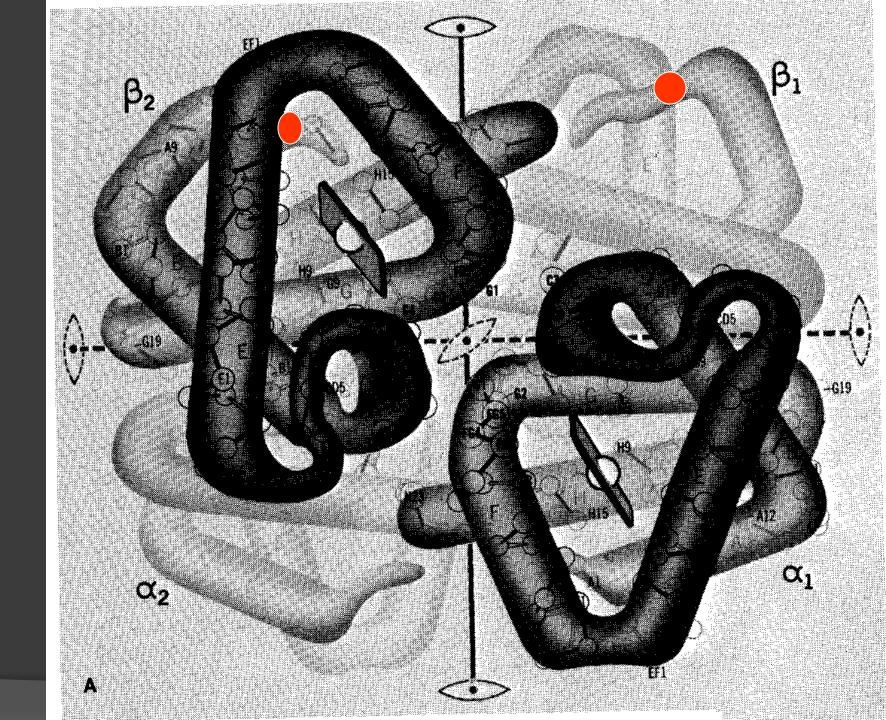
What is Hemoglobin?

- Hemoglobin is the red pigment of blood
- It carries oxygen from the lungs to every part of the body
- It consists of 4 units called chains
- Each chain has about 145 building blocks (amino acids)
- These chains a wound around in a very complicated way



How Is the Hemoglobin of Sickle Cell Disease Different?

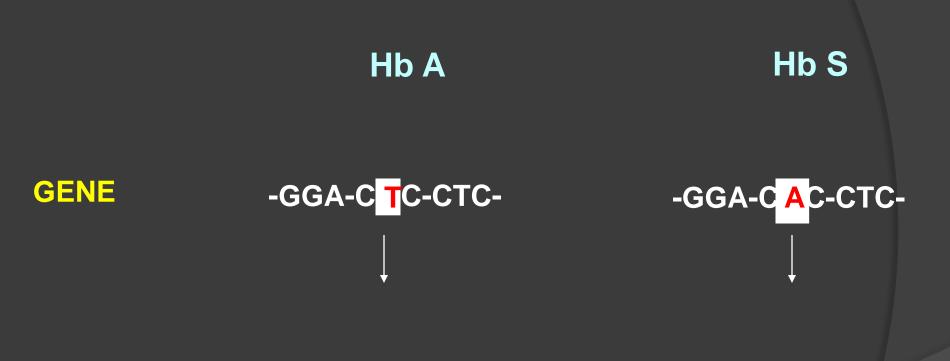
 Two of the building blocks (amino acids) in sickle cell hemoglobin are different from normal



How Is the Hemoglobin of Sickle Cell Disease Different?

- Two of the building blocks (amino acids) in sickle cell hemoglobin are different from normal
- This is due to a change in the gene for hemoglobin
 - One piece out of about 2,000 is changed

Fundamental Defect in Sickle Cell Disease



Hemoglobin Chain





How Is the Hemoglobin of Sickle Cell Disease Different?

- Sickle cell hemoglobin can be detected by examining the blood in the laboratory
 - An individual may have: normal hemoglobin,
 - Both normal and sickle hemoglobin (sickle cell trait), or
 - Only sickle hemoglobin (sickle cell disease)

Identification of Hb S Status by Electrophoresis

B GLOBIN GENES

HEMOGLOBIN
ELECTROPHORESIS
A S

Normal (Hb AA)

----+



Sickle Cell Trait (Hb AS)



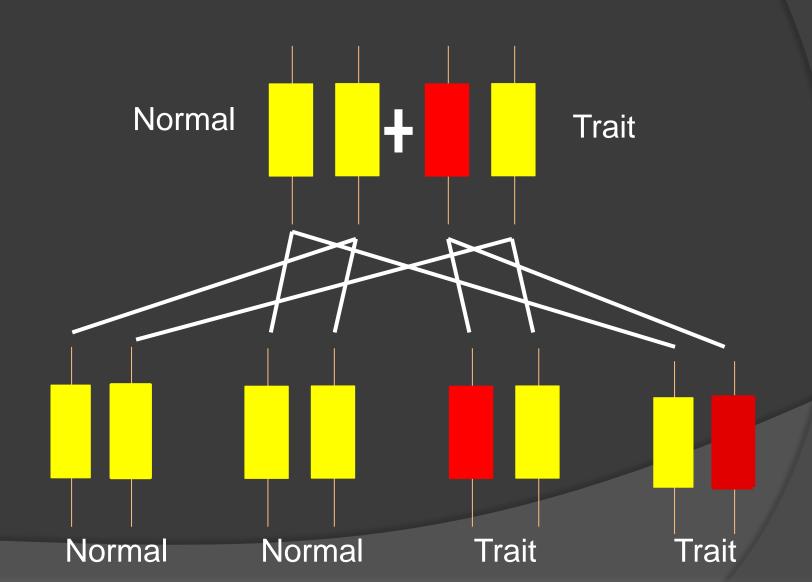
Sickle Cell Disease (HbSS)



How is Sickle Cell Disease Inherited (Passed in the Family)

- Most inherited characteristics are determined by two genes
 - One gene comes from the father
 - One gene comes from the mother
- When one parent has the trait, half of the children are likely to have the trait

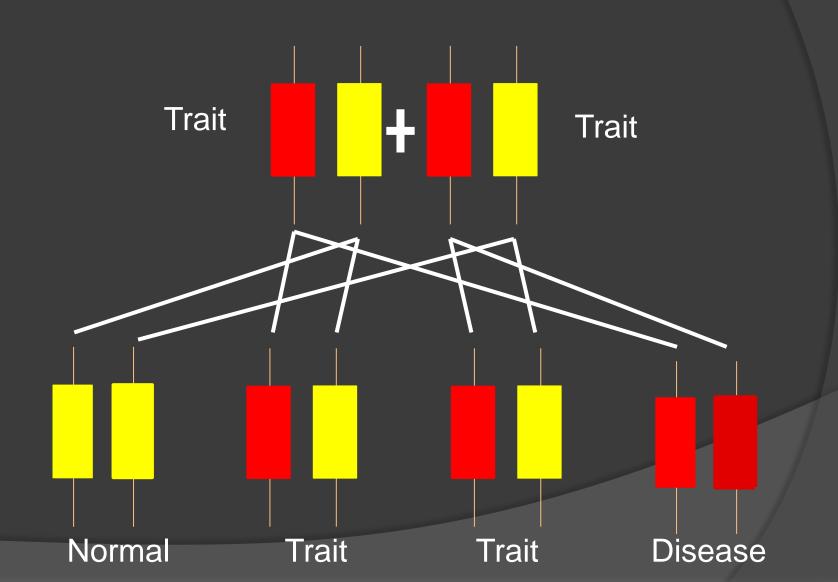
Genetics of Sickle Cell Disease



How is Sickle Cell Disease Inherited (Passed in the Family)

- When one parent has the trait, half of the children are likely to have the trait
- When both parents have the trait
 - One fourth of the children will likely be normal
 - One half will likely have the trait
 - One quarter will likely have the disease

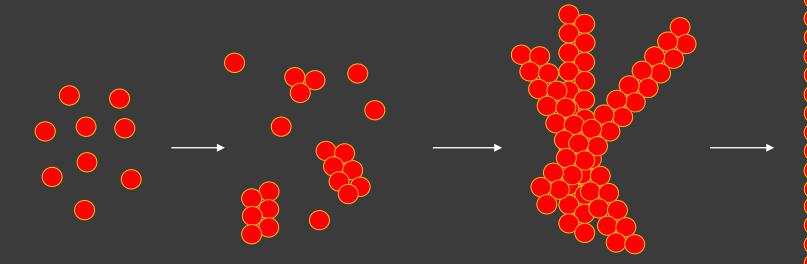
Genetics of Sickle Cell Disease



Why Does the Hemoglobin of Sickle Cell Disease Cause Problems?

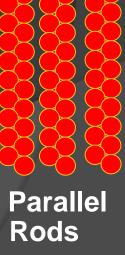
- Two of the building blocks in the hemoglobin are different from normal
- This difference allows the molecules of hemoglobin to stick together in a particular pattern

Formation of "Crystals" of Sickle Hemoglobin



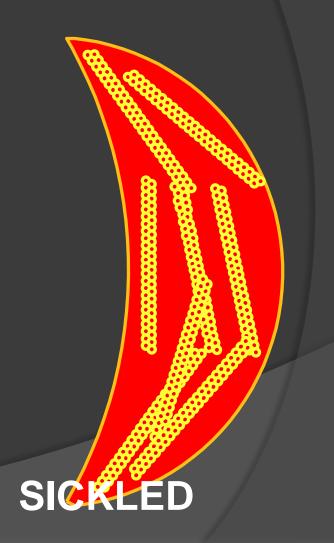
Unpolymerized **Nucleation**

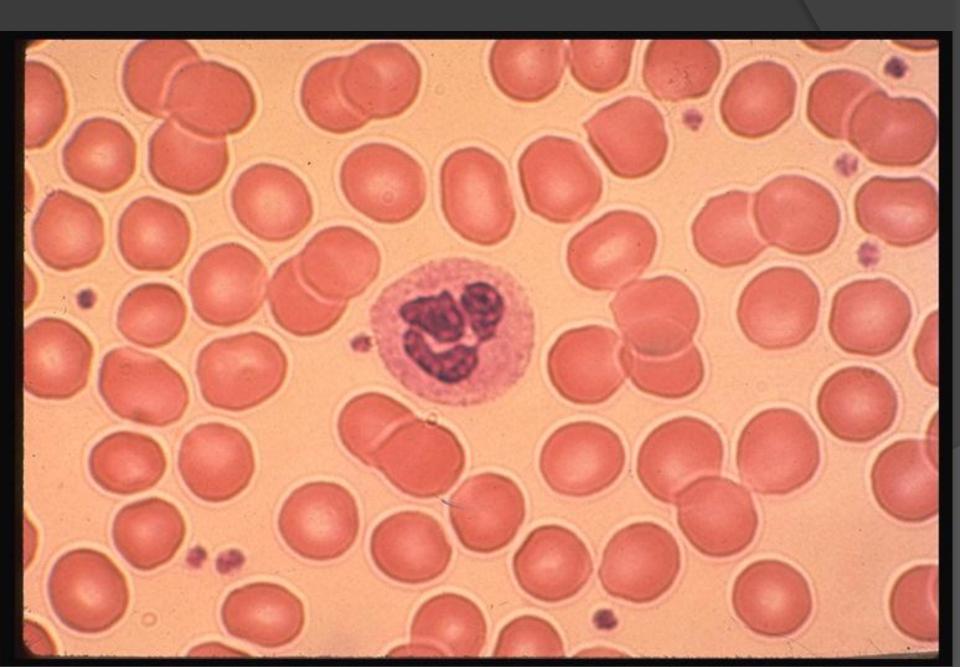
Random Rods

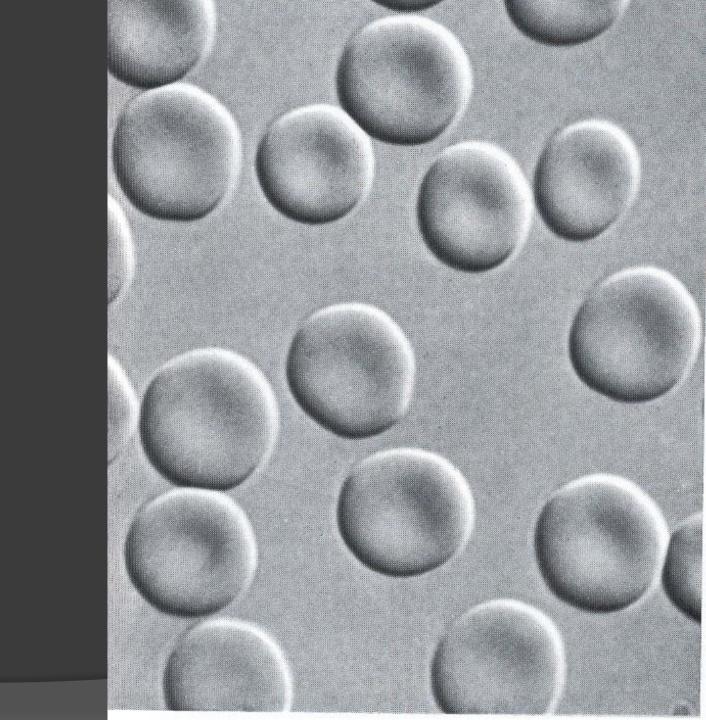


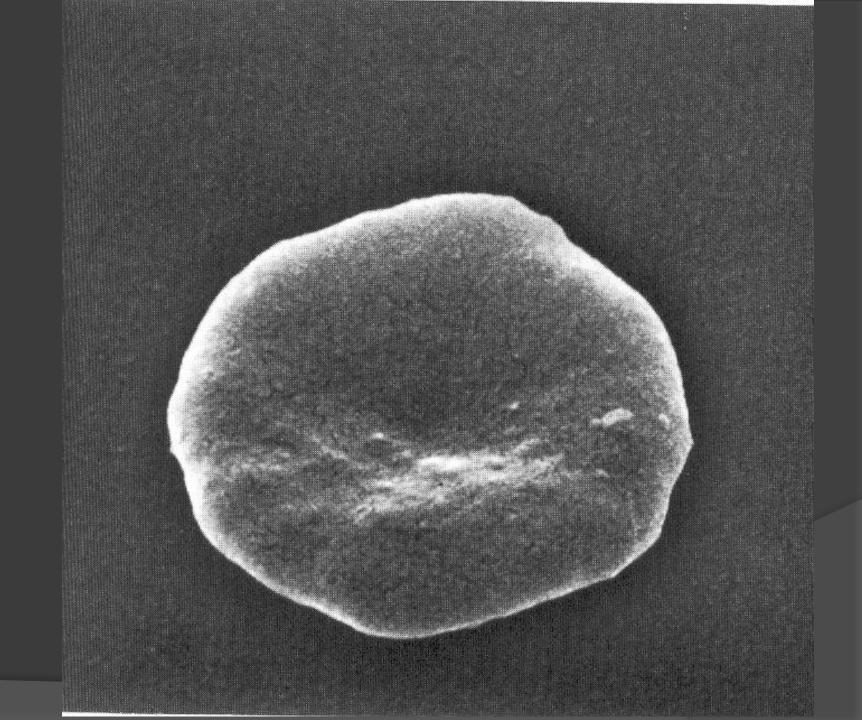
THE SHAPE CHANGE OF SICKLING









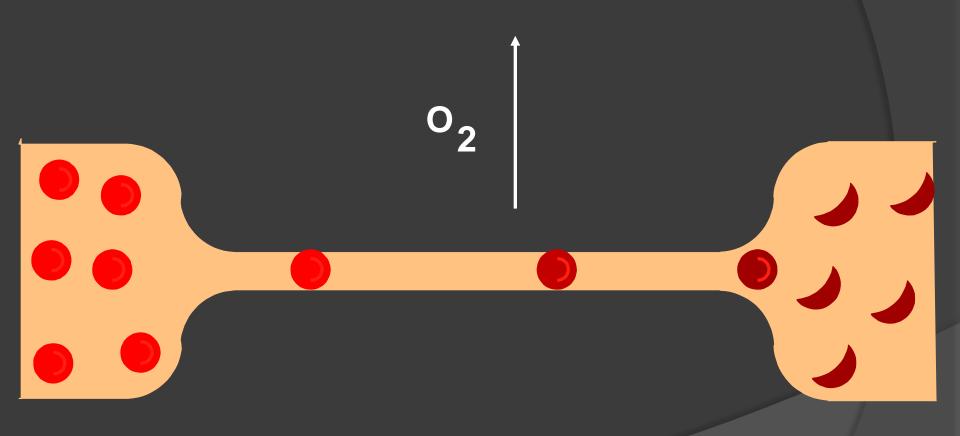








SICKLING IN THE PERIPHERAL CIRCULATION



ARTERIOLE

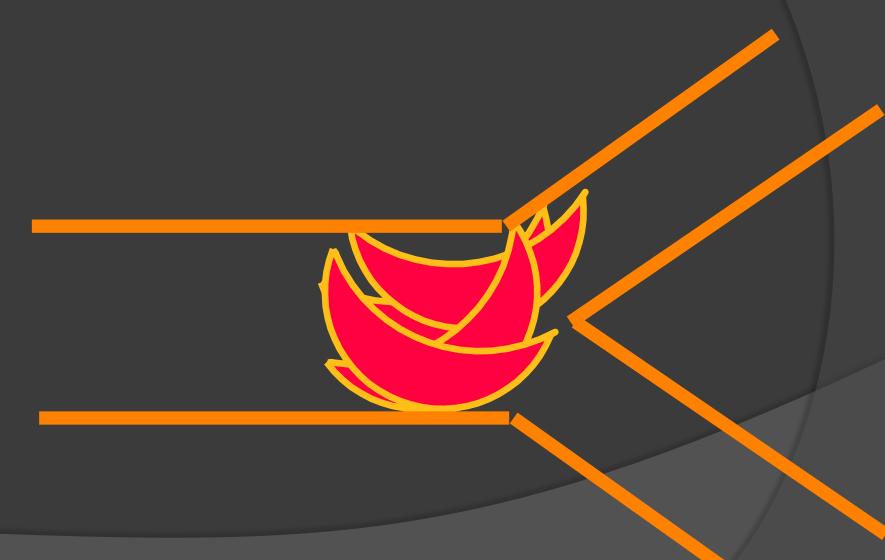
CAPILLARY

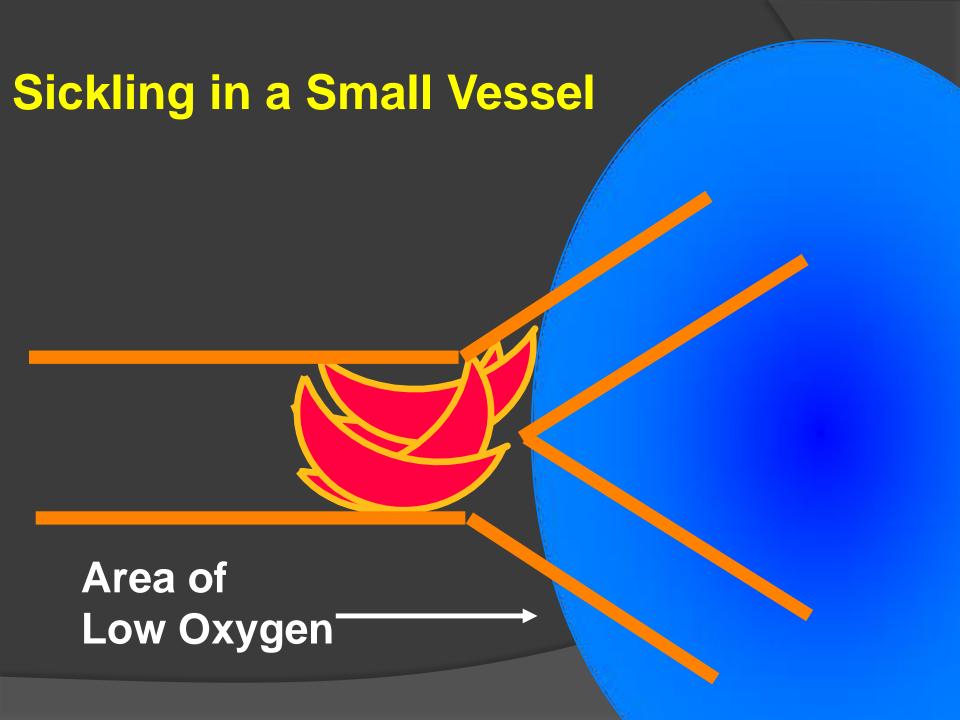
VENULE

Sickling in a Small Vessel



Sickling in a Small Vessel





A Tale of Five Individuals

HOW DID SICKLE CELL DISEASE ARISE?

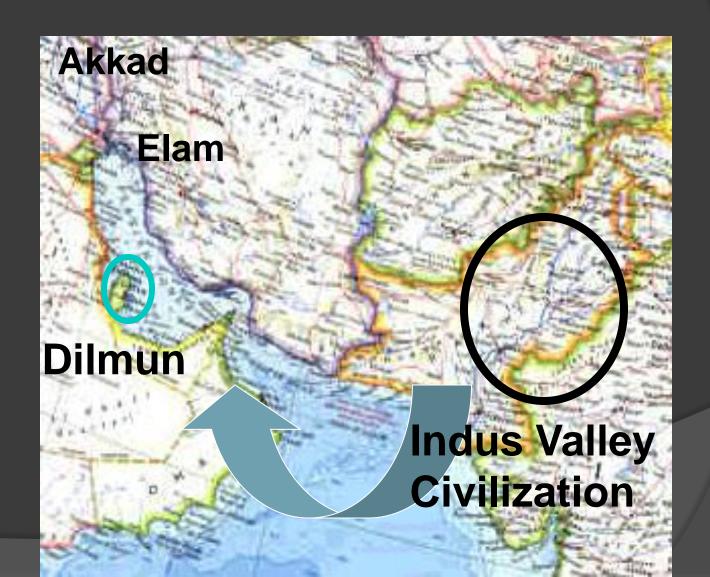
How Did Sickle Cell Arise?

The change in the sickle hemoglobin molecule (Hb S) is caused by a mistake in the gene responsible for that chain of hemoglobin

Where Did This Happen?

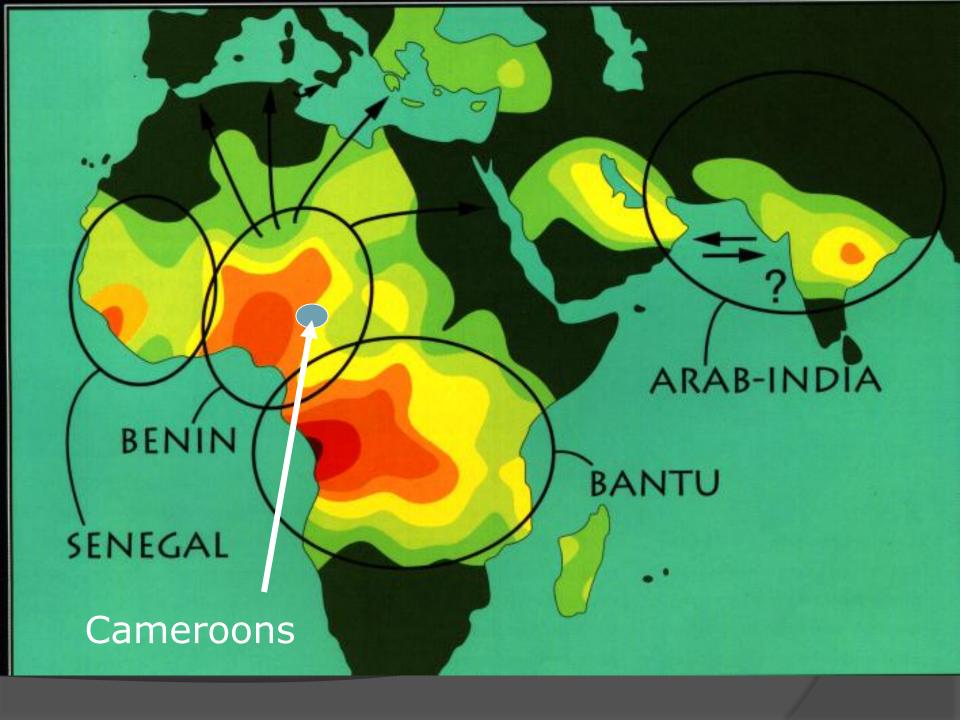
- In India in one individual, ~3,500 years ago
 - It spread to Eastern Arabia
 - Sickle cell persists in the "Hill Tribes" of India
 - Sickle cell disease is more plentiful in one state of India than in the entire United States

The Harappa-Dilmun Axis



Where Did This Happen?

- In India in one individual, ~3,500 years ago
 - It spread to Eastern Arabia
 - Sickle cell persists in the "Hill Tribes" of India
 - The gene is more plentiful in one state of India than in the entire United States
- In Africa in four individuals
 - Near the Congo, ~2,000 years ago
 - Near Nigeria, just a little later
 - In West Africa, sometime later
 - In Cameroons, fairly recently



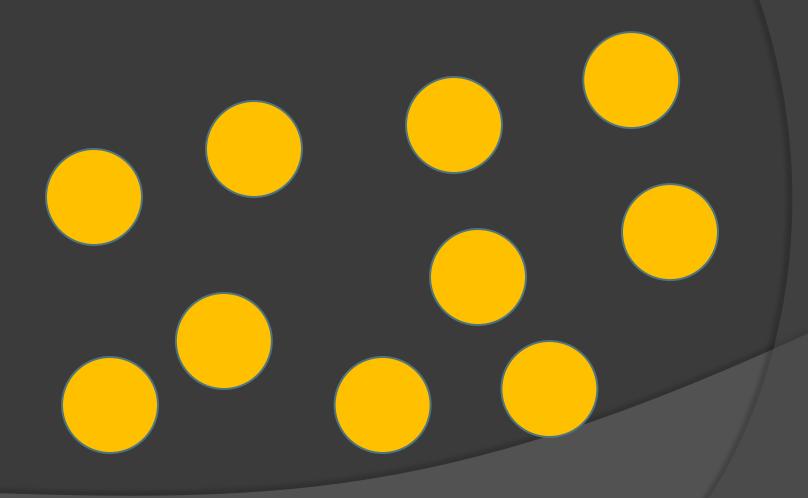
Where Did It Spread?

- Locally at each site of origin
 - The area covered indicates how long the gene has been there
 - By trade routes
- Wherever people from the area migrated or were taken – especially by the African slave trade
 - To Sicily, Greece, and Turkey by the Arab trade in African slaves
 - To the New World by the transatlantic slave trade

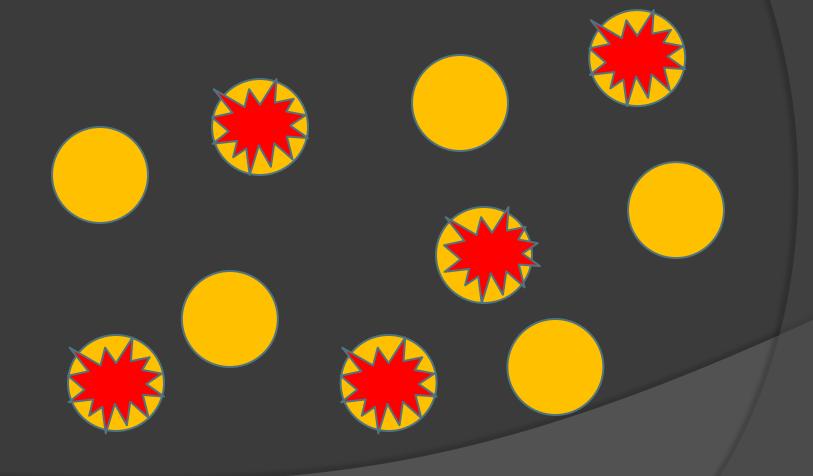
Why Did The Abnormal Gene Become So Common?

By Darwinian (natural) selection

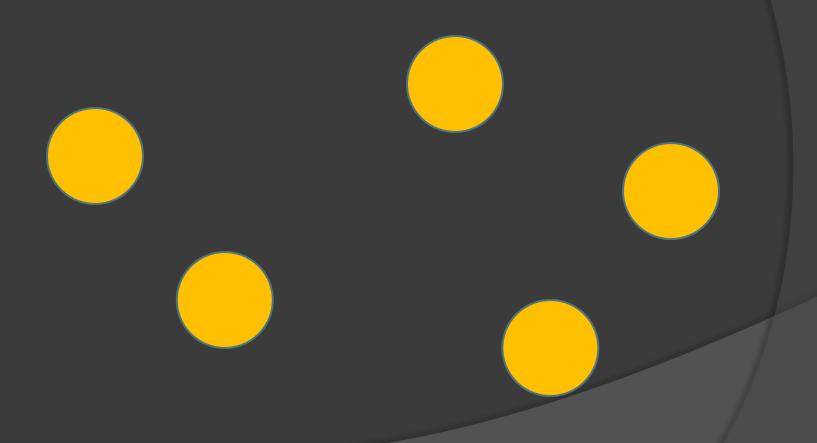
Population Before Disease Strikes



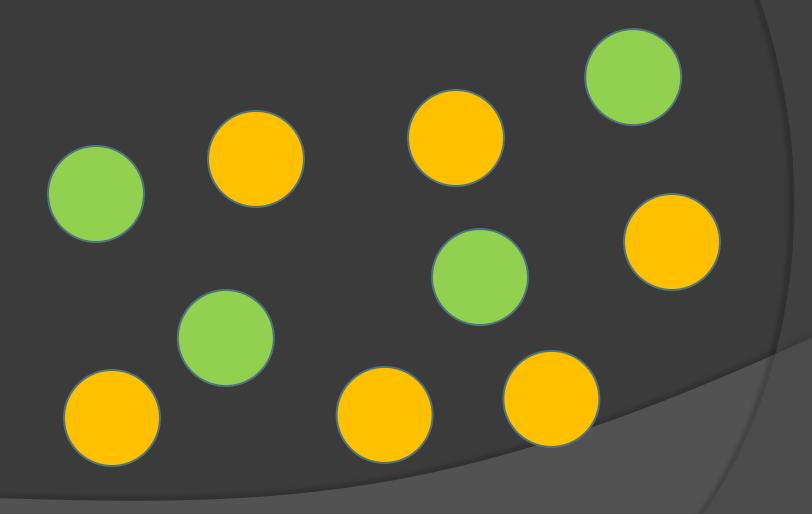
Disease Strikes



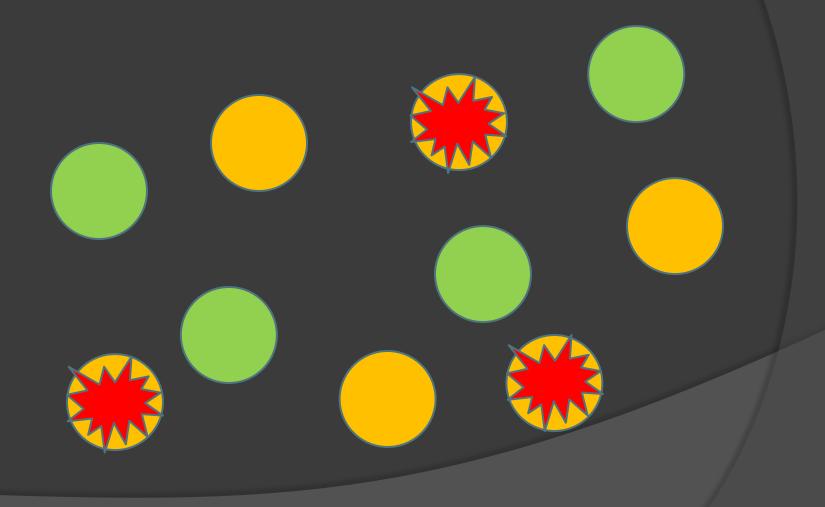
Population After Disease Strikes



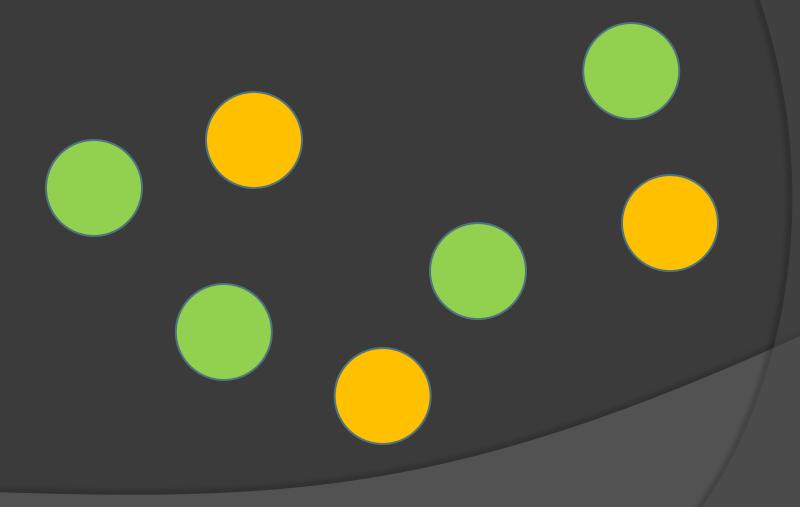
Some People (in Green) Are Resistant to the Disease



Some People (in Green) Are Resistant to the Disease When It Hits



The Percentage of Resistent People Is Increased



What Is Malaria?

- Human malaria started many, many years ago, probably from birds
- Organism develops within red blood cells
- Transmitted by tropical mosquitos

Malaria

- Became a public health problem after settled life began in tropics
 - People lived close enough together that the mosquitoes could spread the organism
- Malaria occurs throughout the tropics
 - 1-2 million people affected each year
 - 216 million cases in 2101
 - >300,000 deaths in 2010

Sickle Cell Disease and Malaria

- Sickle cell <u>trait</u> protects against malaria
 - The reason is not known
 - Based on population studies
- Malaria is fatal in sickle cell disease
- This is called "trait advantage"
 - One dose of the gene is helpful
 - Two doses of the gene are harmful
- Why everybody in Africa does not have sickle cell trait:
 - If everybody had the trait, too many people would have the disease

Other Changes In Red Cells That Confer Protection Against Malaria

- Hemoglobin C
 - Started in one person in Burkina Faso about 1000 years ago
- Hemoglobin E
 - Started in people in Southeast Asia
- Thalassemia
 - Many kinds, mostly with "trait advantage"
 - One kind (α thalassemia) has so little downside in people with two doses of the gene as to become universal in the population
- G6PD deficiency

Other Changes In Red Cells That Confer Protection Against Malaria

- Absence of Duffy blood group
 - Almost all Africans lack this factor; all other people have it
 - One person started the gene many, many years ago
- Two doses of the gene have no downside
- The absence of the factor means that one type of malaria (called "vivax malaria") cannot invade the red cell
 - Vivax malaria does not now exist in Africa

What Has Been The Effect of These Protections or Their Lack on History

- People lacking them could not live in tropical, malarious Africa
- Natives of the tropical parts of the New World were decimated when malaria was introduced
 - Descendants of African slaves, who were resistant, replaced them
- Local patterns of living in the southern States were altered
 - "Upcountry" homes in South Carolina

FONDEE LE 8 DECEMBRE 1856 SOEURS NOTRE-DAME DES Nom et Prénom date de détés age. lieu de sépulture. Sr Julie (J. Réjol) 1893 25ans Cime -Sr Dydime (M. Brehier) 1897 35 ans tière Sr Nicandre(J.Lemaître) 1901 28 ans français sr Philéas(N. Ogé.) | 1901 27ans de sr Maur (L.Berrvyer) 1906 29ans Quidah. sr Arsène (A. Bonnet) 1918 36ans sr Perpetue (J.Gviho) 1925 sr Marie (P. Germaine) 1936 27ans Sr Honorius (C. Arpin) 1947 cf.doc. Eglise. de l'Immaculée-Con. ception 8 Décembre 1989 `28 P''.

What Has Been The Effect of These Protections or Their Lack on History

- People lacking them could not live in tropical, malarious Africa
- Natives of the tropical parts of the New World were decimated when malaria was introduced
 - Descendants of African slaves, who were resistant, replaced them
- Local patterns of living in the southern States were altered
 - "Upcountry" homes in South Carolina

What Has Been The Effect of These Protections or Their Lack on History

- People lacking them could not live in tropical, malarious Africa
- Natives of the tropical parts of the New World were decimated when malaria was introduced
 - Descendants of African slaves, who were resistant, replaced them
- Local patterns of living in the southern States were altered
 - "Upcountry" homes in South Carolina

Summary

- Sickle cell arose as a protection against malaria
- It started from no more than 5 individuals
- It increased in the population by natural selection of individuals with the trait
- Thus, it is one of several "improvements" that allowed people to live where malaria is common