

ACTIVITY 1: Handout

From Sarjeant, Graham R., *Sickle Cell Disease* Oxford: Oxford University Press, 1985

THE CASE OF SICKLE CELL ANEMIA

Sickle Cell Anemia is a serious disease that is now understood at the molecular level. There is real hope for a cure, or at least much better medication. What happens when you have it, how did scientists discover it, and what causes it?

A Patient's View

In Sickle Cell Anemia...

"The child becomes pale, tires easily, eats poorly and may complain of pain in the arms, legs, back and abdomen...When these symptoms become severe, this is known as a sickle-cell crisis. For variable periods...even chronically anemic patients may go along without any complaints. Then with an attack of tonsillitis or common cold or sometimes for no apparent reason, they become acutely ill for a week or two. The first sign of crisis is usually loss of appetite followed by paleness and weakness. Pain in the abdomen, legs and arms may be severe and there may be some swelling in the joints."

- M.I. Johnson, *The World and the sickle-cell gene: a study in health education*, New York: Trado-Medic Books, 1985, p. 54.

As the children grow up, their hands and feet may swell, their spleen can get blocked by blood cells and therefore swell, bones can be destroyed, and, beyond these and many other symptoms, there is the risk of sudden death.

There are now known to be a cluster of sickle cell diseases, but we will focus here on the classic Sickle Cell Anemia.

The Detectives find that the hemoglobin is different

In 1910 a 20 year old student from the East Indies who was attending a professional school in Chicago came to a doctor. He was in great pain. When his doctor, James Herrick, looked under the microscope at his patient's blood, he saw bizarre blood erythrocytes (red blood cells) that were "sickle shaped," fragile and sticky (See the picture above.) His description of this sight was the first report of Sickle Cell disease in western literature. Many Africans had, of course, noticed the disease pattern already, as it appears to have developed in Africa and survived as a defense from malaria.

In 1927, Hahn and Gillespie showed that sickling of the red cells was related to the delivery of less oxygen. What could be the problem?

Between 1945 and 1949 Janet Watson, a hematologist in Brooklyn, noticed that the sickling of cells began only after fetal hemoglobin in the young infant was replaced by the slightly altered variety, adult hemoglobin. This natural process, a transition occurring in each one of us, was her clue that the real culprit was adult hemoglobin.

In 1945, while riding together on a night train between Denver and Chicago, a fellow scientist introduced Linus Pauling to the problem of Sickle Cell. Four years later, in 1949, Linus Pauling and colleagues used the then-new technique of protein electrophoresis to confirm Janet Watson's inference. The protein hemoglobin molecule of patients with Sickle Cell disease was really different from the hemoglobin of healthy people. Sickle Cell became the first identified protein disease!

Later researchers found that the injured hemoglobin made "tactoids," or liquid crystals of protein hemoglobin, which were less soluble and stickier than tactoids of normal hemoglobin. Why did this change in hemoglobin bring Sickle Cell patients such pain and suffering?

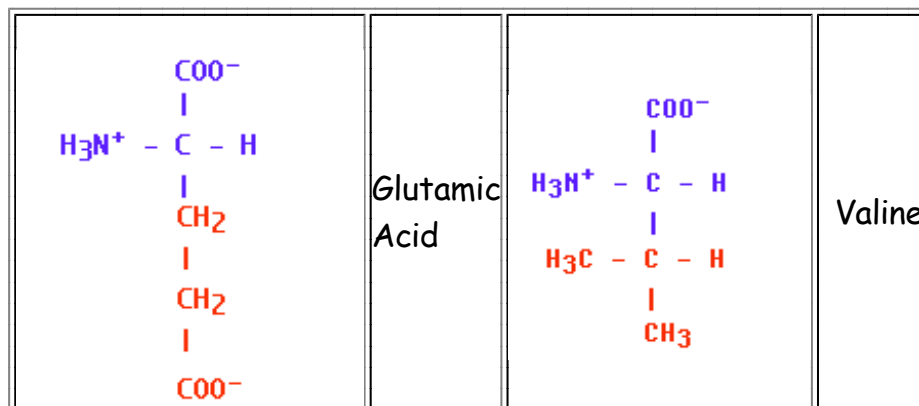


Amino Acid Substitution in Sickled Hemoglobin

In 1956, scientist Vernon Ingram, the pioneer hemoglobin researcher, mapped out the amino acid sequence of sickle cell hemoglobin, and showed that there was one amino acid difference between normal and diseased hemoglobin -- the glutamic acid amino acid at position 6 on the globin chain had been replaced by a valine amino acid. What difference could such a small change make in a molecule as large as hemoglobin, made of hundreds of amino acids?

Summary Questions:

1. How could a difference in amino acids result in a disease?
2. Look at the molecular structure of glutamic acid and valine. Can you find any differences in their formulas?



3. What are the properties of the original amino acid? of the substituted amino acid? (Check the [Chart of Amino Acids](#))

Develop a hypothesis about how these properties might affect the shape of the protein hemoglobin.

Have extra time? See a longer report at the Harvard Sickle Cell site:
http://sickle.bwh.harvard.edu/scd_background.html