# AN ABSTRACT OF THE THESIS OF

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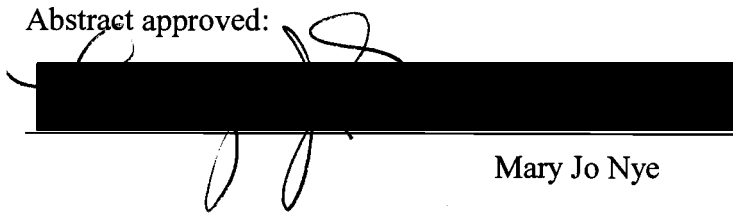

Mary Jo Nye

Linus Pauling incorporated hemoglobin and a disease of the blood, sickle cell anemia, into many of his researches between the mid-1930s and mid-1970s. In the early 1930s Pauling became interested in organic chemistry and named hemoglobin as one of the first biochemical substances that he planned to analyze. In 1935 he published his first paper on hemoglobin, which determined the structure of the four hemes in hemoglobin. Pauling continued to study the structure of hemoglobin until the early 1950s when he proposed that it was an alpha-helix. In 1945 Pauling learned about sickle cell anemia and published an important paper in 1949 with Harvey A. Itano, S. J. Singer, and Ibert C. Wells titled "Sickle Cell Anemia, a Molecular Disease." Pauling investigated hemoglobin into the mid-1970s when he tried to find an orthomolecular therapy for sickle cell anemia. From the mid-1950s to early 1970s, Pauling also used sickle cell anemia to promote negative eugenics, point out the possible mutagenic effects caused by nuclear weapons testing, and propose an evolutionary theory. Additionally, in the final year of his life, Pauling wrote two

forewords for books on sickle cell anemia, which were published in 1994, the year he died. Hemoglobin and sickle cell anemia can be considered a theme within Pauling's work. He often returned to normal and abnormal hemoglobin as his primary substance for examination, and his familiarity with hemoglobin and sickle cell anemia inspired new research.

# It's in the Blood
# The Varieties of Linus Pauling's Work on Hemoglobin and Sickle Cell Anemia

By Melinda Gormley

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I understand that my thesis will become part of the permanent collection at Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

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Melinda Gormley, Author

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*MBG*
*October 11, 2003*

# TABLE OF CONTENTS

# LIST OF FIGURES

# It's in the Blood: The Varieties of Linus Pauling's Work on Hemoglobin and Sickle Cell Anemia

## INTRODUCTION

Linus Pauling's reputation rests on his many and diverse accomplishments that spanned a better part of the twentieth century. His undertakings include his fundamental contributions to chemistry (the nature of the chemical bond and the structure of proteins), his advocacy for world peace, and his promotion of Vitamin C, to name a few. Undisputedly, Pauling was a man who had his hand in many pots.

Some biographers have commented upon the difficulty in finding a common thread in his long and fruitful career. For example, Robert Paradowski stated:

> The Pauling biographer is confronted with an especially difficult task since Pauling made important contributions to such a wide variety of fields, including X-ray crystallography, quantum mechanics, the chemical bond, immunology, and molecular medicine.[1]

On the other hand, Hager noted Pauling's life-long interest in chemical structure. "Molecular structure became a leitmotif for Pauling, a unifying concept that he used successfully to investigate and tie together physics, chemistry, biology, and

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[1] Robert Paradowski, "The Biographical Quest: Some Personal Reflections of a Paling Biographer on the Art and Science of Scientific Biography," The Pauling Symposium: A Discourse on the Art of Biography (Corvallis: Oregon State University Libraries, 1996): 31-57, 49.

medicine."[2] In contrast, Barbara Marinacci noticed that Pauling's different endeavors built upon one another over the years. "There is a remarkable flow from one line of scientific pursuit to another; likewise, his scientific interest and accomplishments led him to consider the relevant needs of and perils to his own species, humankind..."[3] In the thesis that follows, Pauling's disparate scientific career and political statements are viewed through his preoccupation with blood – specifically, his interest in hemoglobin and a disease of human hemoglobin, sickle cell anemia.

Hemoglobin fascinated Linus Pauling:

> Hemoglobin is one of the most interesting chemical substances in the world – to me it is the most interesting of all. (1952)[4]

> You know, hemoglobin is a wonderful substance. I like it. It's a red substance that brings color into the cheeks of girls, and in the course of my hemoglobin investigation I look about a good bit to appreciate it. (1966)[5]

> The hemoglobin molecule, with its striking color and its property of combining reversibly with dioxygen, seemed to me to be especially interesting. (1980)[6]

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[2] Thomas Hager, Force of Nature: The Life of Linus Pauling (New York: Simon & Schuster, 1995): 12.

[3] Linus Pauling, Linus Pauling in his Own Words: Selected Writings, Speeches, and Interviews, ed. Barbara Marinacci (New York: Simon & Schuster, 1995: 13.

[4] Linus Pauling, "The Hemoglobin Molecule in Health and Disease," Proceedings of the American Philosophical Society 96 (5 Oct 1952): 556-65, 556.

[5] Linus Pauling, lecture and introduction, "Science and World Problems," Enzymes in Mental Health, Eds. Gustav J. Martin and Bruno Kisch (Philadelphia, J.B. Lippincott Company, 1966): 13-8, 13.

[6] Linus Pauling, "The Normal Hemoglobins and the Hemoglobinopathies: background," Hemoglobins and Hemoglobinopathies: A Current Review to 1981. Texas Reports on Biology and Medicine 40 (1980-1981): 1-7, 1. In 1972 Pauling wrote an article, translated into Italian, on "Molecular Disease and Orthomolecular Medicine," in which he pinpointed the beginning of his overwhelming interest in hemoglobin. "About forty years ago, after being occupied for ten years on the determination of the structure of organic and simple inorganic molecules, began my

Hemoglobin is a substance inside the red blood cells of human blood. It has two parts: the heme and the globin. The heme contains iron and transports oxygen from the lungs to the tissues as well as takes carbon dioxide from the tissues to the lungs. Globin, a complex macromolecule, is a protein that helps to keep the hemoglobin liquefied. When hemoglobin combines with oxygen and carbon monoxide, it produces oxyhemoglobin and carbonmonoxyhemoglobin respectively.[7]

Pauling began experimenting with hemoglobin in the early 1930s and continued to write about it until his death in 1994. As mentioned above, Pauling found hemoglobin intriguing and he learned all he could about it, chemically, biologically and structurally. The exact structure of hemoglobin was figured out in 1959 by Max Perutz of Cambridge University. However, from the mid-1930s to the mid-1940s Pauling knew as much as anyone about its structure. He had researched and published articles on the subject, and he scoured scientific sources to find out what he could about blood. In 1937, while talking about hemoglobin and magnetism at Oregon Agricultural College (now Oregon State University) in Corvallis, Pauling

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interest in one protein, hemoglobin." (Linus Pauling, "Malattie molecolari e medicina orthomolecolare," Enciopedia della Scienza e della Tecnia Mondadori (Milan, 1972) 258. "Circa quarant'anni fa, dopo essermi occupato per una decina d'anni della determinazione della structura di molecule organiche e inorganiche relativament semplici, cominciai a interessarmi di una proteina, l'emglobin.")

[7] Ronald J. Gillespie, David A. Humphreys, N. Colin Baird, Edward A. Robinson, eds. Chemistry, 2nd ed. (New Jersey: Prentice Hall, 1989): 963; Maxwell M. Wintrobe, ed. Blood, Pure and Eloquent: A Story of Discovery, of People, and of Ideas (New York: McGraw-Hill Book Company, 1980): 733; Ava Helen and Linus Pauling Collection, Speeches 1937, "Hemoglobin and Magnetism," Sigma Xi, Oregon Agricultural College, Corvallis, Oregon, 12 May 1937: 1-5, 2; Pauling, "Hemoglobin Molecule," 556.

discussed the metal present in hemes and the color of the various types of blood in living organisms.[8]

> Hemocyanin, the blood of crabs, snails, abalone, octopi, etc., which is blue when oxygenated and colorless when deoxygenated, is a very complex substance, with a molecular weight which may go as high as five million. Hemocyanin contains copper...
>
> Besides the blue copper blood there exists a green blood (in a worm), called chlorocruorin. This also contains iron, but the pigment is somewhat different from hemoglobin. A manganese blood has been reported for certain shellfish. Most striking of all, however, is the blood of the strange animals called ascidians or sea-squirts...Their blood contains corpuscles of different kinds of colors, blue, green, and red, looking in shape something like raspberries. The metal in this blood is vanadium – though how the animal picked this out of the periodic table I can't explain.[9]

In addition to hemoglobin itself, Pauling was also interested in a disease of the blood, sickle cell anemia. Sickle cell anemia is a deadly, hereditary disease that primarily afflicts people of African descent. The disease got this name because the red blood cells of the sufferers bend into a crescent shape when deoxygenated. (Oxygenated hemoglobin in people with sickle cell anemia is identical to that of healthy individuals.) Pauling learned of sickle cell anemia in 1945 and because of his previous researches on hemoglobin and immunology, he immediately thought he comprehended the sickling process. Years later, he commented upon how quickly the idea had occurred to him: "at once"[10] and in "2 seconds."[11]

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[8] Ava Helen and Linus Pauling Collection, Speeches 1937s.2, "Hemoglobin and Magnetism," Sigma Xi, Oregon Agricultural College, Corvallis, Oregon, 12 May 1937: 1-5.

[9] Pauling, "Hemoglobin and Magnetism," 2-3.

[10] Linus Pauling, "Fifty Years of Progress in Structural Chemistry and Molecular Biology," Daedalus 99 (1970): 988-1014, 1011.

Pauling enlisted Harvey A. Itano, a Ph.D. student in chemistry who had recently received a medical degree, to conduct experiments on sickle cell hemoglobin in order to prove his intuition correct. In 1949, Pauling, Itano and two other colleagues at the California Institute of Technology published an influential paper based on their results, "Sickle Cell Anemia, a Molecular Disease."[12] By describing sickle cell anemia as a molecular disease caused by abnormal hemoglobin, the authors inspired additional research. Within fifteen years of the 1949 paper, researchers had found "scores" of diseases caused by abnormal hemoglobins and a new category of diseases had emerged: hemoglobinopathies.[13] By 1994, forty-five years after Pauling and his co-authors announced their findings, researchers had found over three hundred abnormal hemoglobins.[14]

After 1949, Pauling kept abreast of new developments in the field of hemoglobinopathies and discussed sickle cell anemia when talking about his other concerns and research interests. For example, Pauling used results from work with hemoglobin and sickle cell anemia in discussions on mental deficiency, evolutionary theory, eugenic practices, and nuclear fallout. He guided research in

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[11] Linus Pauling, "The Impact of Molecular Information on Disease," Twentieth Annual Symposium on Blood: Sickle Cell Disease, Wayne State University School of Medicine, Detroit, Michigan, 20 Jan 1972. Pauling Collection, Speeches 1972s.2: 2.
[12] Linus Pauling, Harvey A. Itano, S.J. Singer, Ibert C. Wells, "Sickle Cell Anemia, a Molecular Disease," Science 110 (1949): 543-48.
[13] Linus Pauling, "Molecular Disease and Evolution," Bulletin of the New York Academy of Sciences 40 (1963): 334. My copy is numbered pages 1-9, from http://profiles.nlm.nih.gov. Information is on page 5.
[14] Linus Pauling, foreword, Membrane Abnormalities in Sickle Cell Disease and Other Red Blood Cell Disorders, eds. S. Tsuyoshi Ohnishi and Tomoko Ohnishi (Boca Raton: CRC Press, Inc., 1994): viii-ix, ix.

hemoglobinopathies at Caltech until he resigned in 1963,[15] although Pauling performed very little of his own research on sickle cell anemia after 1949. The interest continued in his direction of researching orthomolecular therapies for sickle cell anemia in the early 1970s.

Pauling coined the term "molecular disease" to describe sickle cell anemia.[16] He often noted the novelty of calling sickle cell anemia a molecular disease and defined the term:

> The expression molecular disease is here used in a special way. All human beings are made up of molecules, and in a sense one might say that all diseases involve these molecules, and perhaps also the molecules that make up bacteria and viruses, and that accordingly all diseases are molecular diseases. The restriction of the expression molecular disease to diseases that are due to abnormal molecules, differing somewhat in structure from related molecules that are present in normal human beings, seems to me a useful one.
>
> Sickle-cell anemia was the first disease to be shown to be a molecular one.[17]

Pauling believed that remedies for molecular diseases could be found once there was an understanding of the molecular structure of normal and abnormal proteins within

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[15] Hager, 551; Linus Pauling, Scientist and Peacemaker, eds. Clifford Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 16-17.

[16] Some scholars have pointed out that Pauling's terminology, although new, was not revolutionary. Feldman and Tauber looked at the history of sickle cell anemia and stated that other investigators had essentially noted in their articles that the disease was at the molecular level, but did not use the term "molecular disease." Simon D. Feldman and Alfred I. Tauber, "Sickle Cell Anemia: Reexamining the First 'Molecular Disease'," Bulletin of the History of Medicine 71.4 (1997): 623-50. Conley mentioned two abnormal hemoglobins (fetal hemoglobin and what eventually was called Hemoglobin M) discussed prior to the Pauling, et al. 1949 paper. C. Lockard Conley, "Sickle Cell Anemia – The First Molecular Disease," Blood, Pure and Eloquent: A Story of Discovery, of People, and of Ideas, ed. Maxwell M. Wintrobe (New York: McGraw-Hill Book Company, 1980): 319-71, 342.

[17] Linus Pauling, "The Molecular Basis of Genetics," American Journal of Psychiatry 113 (1956): 492-95, 492.

the human body. This field of inquiry was to be molecular medicine. In 1962 Pauling noted that two newly emerged disciplines, molecular biology and molecular medicine, would aid in abating molecular diseases. [18]

> I believe that the continued study of the molecular structure of the human body and the nature of molecular disease will provide information that will contribute to the control of disease and will significantly diminish the amount of human suffering. Molecular biology and molecular medicine are new fields of science that can be greatly developed for the benefit of mankind.[19]

About five years later, Pauling coined two terms, orthomolecular medicine and orthomolecular psychiatry, to describe a specific approach to treating molecular diseases and his newest field of interest.[20]

In his later years, Pauling reflected upon the personal and scientific importance of his work on sickle cell anemia and hemoglobin. Nancy Touchette interviewed Pauling and one of his students in 1990, characterizing Pauling as "The First Molecular Biologist." Pauling in one of his more humble statements, said "Well, I thought that was a pretty nice idea that I had in 1945, about molecular diseases." In addition, Touchette wrote that Pauling viewed his work on sickle cell anemia, and the

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[18] Warren Weaver of the Rockefeller Foundation coined the term molecular biology in 1938. As will be discussed in Chapter One, Pauling received funding from Weaver and the Rockefeller Foundation beginning in 1932. For sources about Warren Weaver coining the term molecular biology see Robert Kohler, Partners in Science: Foundations and Naturals Scientists 1900-1945 (Chicago: The University of Chicago Press, 1991): 299; Lily Kay, The Molecular Vision of Life: Caltech, The Rockefeller Foundation, and the Rise of the New Biology (New York: Oxford University Press, 1993): 48-9.

[19] Pauling, "Molecular Disease and Evolution," 8.

[20] Linus Pauling, "Orthomolecular Psychiatry," Science 160 (19 April 1968): 265-71.

coining of it as a molecular disease, as "one of his most creative ideas."[21] Immediately prior to his death, in a foreword to a book on sickle cell anemia, Pauling noted the importance of the sickle cell anemia paper of 1949 to the life sciences. He stated that the sickle cell anemia work and article "contributed to the development of the field of molecular biology."[22] As proof of how much Pauling valued his contribution to medicine, when asked in 1984 about his feelings about resigning from Caltech, Pauling stated, "I'd built up this great research organization in structural chemistry, and I had discovered molecular diseases there at the Institute."[23]

Pauling was not alone in his belief that his work on sickle cell anemia contributed to the field of molecular biology. Francis Crick commented upon Pauling's impact on molecular biology in his book What Mad Pursuit and in a memorial lecture delivered at Oregon State University the year after Pauling died. Crick said that Pauling's contribution to sickle cell anemia, as well as the subsequent work performed at Caltech and elsewhere by other investigators, merged the fields of genetics and protein chemistry. In comparison, prior to the mid-twentieth century most scientists in the two fields worked independently and without the aid of the one

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[21] Nancy Touchette, "The First Molecular Biologist," Journal of NIH Research 2 (July 1990): 59-63, 63. This article is part of the Pauling Collection, Publications 1990p.11.

[22] Pauling, Membrane Abnormalities, ix.

[23] Linus Pauling, Interview, California Institute of Technology Oral History Project, by John L. Greenberg (Palo Alto, California: Archives of the California Institute of Technology, 10 May 1984): 27. From http://resolver.caltech.edu/CaltechOH:OH_Pauling_L

another.[24] Stephen F. Mason wrote in a biographical essay that "By the 1990s, Pauling had come to be regarded as a principal founder of molecular biology, for the range and impact of his contributions to the subjects," including the sickle cell anemia work.[25] Alexander Rich, a former student of Pauling's, viewed Pauling's contribution to medicine through his work on sickle cell anemia as the beginning of molecular biology. Touchette quoted Rich in the following manner:

> Rich counts Pauling as "among the first molecular biologists, if not the first. Why? Because he described the essence of molecular biology in a way that all the rest of us are now following," says Rich. His unearthing of the cause of sickle cell anemia "was the first discovery of a molecular mutation that gives rise to disease. It's very near the beginning of molecular biology as we know it."[26]

There is an abundance of historical literature on each of the three main topics discussed in this thesis – Linus Pauling, hemoglobin, and sickle cell anemia. Most scholars who have written about sickle cell anemia focus on racial issues associated with the disease and discuss Pauling's role in the shifting interpretations of the disease. Keith Wailoo states that Pauling's paper on sickle cell anemia and another paper published in the same year by geneticist James V. Neel marked a turning point in the disease's racial history. Prior to the genetic information presented in these two

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[24] Francis Crick, What Mad Pursuit: A Personal View of Scientific Discovery (New York: Basic Books, Inc., Publishers, 1988): 105-7. Francis Crick, "The Impact of Linus Pauling on Molecular Biology," The Pauling Symposium: A Discourse on the Art of Biography, ed. Ramesh S. Krishnamurthy (Corvallis, Oregon: Oregon State University Press, 1996): 3-18. The Valley Library at Oregon State University has a video recording of the lecture: Crick, Francis, Lecture, "The Impact of Linus Pauling on Molecular Biology," VHS video recording, (Oregon State University, 28 Feb 1995).

[25] Mason, 35.

[26] Touchette, 61.

papers, scientists assumed that sickle cell anemia passed from parent to progeny according to Mendelian laws. In addition, they thought that the disease manifested itself within anyone who inherited the faulty gene; thus sickle cell anemia was considered to be a dominant trait. Pauling and Neel discredited this theory by showing that sickle cell anemia occurs only in people who inherit two recessive genes for the disease. Hence, according to Wailoo, Pauling and Neel helped to break down the racial connotations associated with blood. Specifically, they undermined the concept of "Negro blood" which had previously been used to explain the disease.[27] Thus, Wailoo described Pauling's identification of sickle cell anemia as a molecular disease as "revolutionary."[28] Another scholar who addresses the racial issues associated with sickle cell disease is Melbourne Tapper. Unlike Wailoo, Tapper does not credit Pauling and Neel with breaking down racial stereotypes in discussions of genetics. In contrast, Tapper believes that the new genetic information created a more damaging racial anthropology, substantiated by scientific proof, contributing to racial discrimination based in new eugenic perspectives.[29]

Other scholars have analyzed the history of sickle cell anemia and other abnormal hemoglobins. Among them, C. Lockard Conley wrote an impressively detailed history of sickle cell anemia. He titled his chapter similarly to the Pauling, et al. paper from 1949, "Sickle Cell Anemia – the First Molecular Disease," and stated:

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[27] Keith Wailoo, Drawing Blood: Technology and Disease Identity in Twentieth-Century America (Baltimore: Johns Hopkins University Press, 1997): 134-37.
[28] Wailoo, Drawing Blood, 11.
[29] Melbourne Tapper, In the Blood: Sickle Cell Anemia and the Politics of Race (Philadelphia: University of Pennsylvania Press, 1999): 39-41.

> Identification of the first "molecular disease" led directly to the recognition of hundreds of other abnormalities of hemoglobin synthesis, some of which produce diseases that previously were unknown.[30]

Bruno Strasser in brief essays on Pauling's sickle cell anemia work discusses the importance of the 1949 paper and its impact. He also notes that Pauling's previous research helped him to understand sickle cell anemia at a molecular level, but Strasser does not discuss Pauling's background in hemoglobin research extensively.[31] Simon D. Feldman and Alfred I. Tauber have written on the history of sickle cell anemia and discussed whether Pauling's role has been romanticized. They conclude that his contribution was significant, but that the concept of molecular disease was not entirely novel.[32]

Other scholars have studied aspects of Pauling's work on which I am focusing in this thesis. Gregory Morgan has analyzed Pauling's evolutionary theory of the

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[30] Conley, 359.

[31] Bruno J. Strasser, "Perspectives: Molecular Medicine: 'Sickle Cell Anemia, a Molecular Disease," Science 286 (1999): 1488-1490; Bruno Strasser, "Sickle Cell Anemia and the Origins of Molecular Biology," Linus Pauling: Scientist and Peacemaker, eds. Clifford Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 127-33; Emile Zuckerkandl, Interview in Palo Alto, California, "The Molecular Clock," by Gregory Morgan (11 July 1996).

[32] Feldman and Tauber, 623-650. Feldman and Tauber note that the coining of "molecular disease" is attributed to Pauling, but demonstrate that the work conducted on sickle cell anemia in the first half of the twentieth century was done on a molecular level. They focus on researchers who described the molecular nature of the disease. For example, Feldman and Tauber give an example of three researchers who used the same apparatus and came to similar results five years before Pauling, et al. In 1944 researchers Marie Andersch, Donald Wilson and Maud Menten found a difference between adult and fetal hemoglobin based on electrophoresis experiments. In addition, Andersch, Wilson, and Menten concluded that the protein (i.e. globin) within adult and fetal hemoglobin differ. Andersch, Wilson and Menten are discussed in greater detail in Chapter Two.

molecular clock and interviewed Pauling's primary collaborator on this project, Emile Zuckerkandl.[33] Zuckerkandl himself reminisced about the molecular clock, as well.[34] Pauling's support for negative eugenics (especially his remarks about tattoos) has been mentioned by many historians. For example Lily Kay in a history of Caltech, Diane Paul in a discussion of eugenics, and Keith Wailoo in a history of racial discrimination have all mentioned Pauling's tattoo eugenics, without fully discussing it.[35] No one, that I have found, discusses the fact that Pauling promoted eugenic practices for roughly twenty years (the 1950s to 1970s).

Most historians and biographers have focused their attention on Pauling's theoretical and structural chemistry (the "Nature of the Chemical Bond"), his political activism, or his late career work on Vitamin C. Several biographies have been written about Pauling. Thomas Hager has written a marvelous biography about Pauling, discussing aspects of his life, research and activism.[36] Ted and Ben Goertzel have

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[33] Linus Pauling and Emile Zuckerkandl analyzed the amino acid sequences of the protein portion of hemoglobin in different species and then compared them. Similar amino acid sequences between two different species denoted that the two species are closely related and diverged during evolution more recently than two species with less commonalities in their amino acid sequences. Gregory J. Morgan, "Emile Zuckerkandl, Linus Pauling and the Molecular Clock, 1959-1965," Journal of the History of Biology 31 (1998): 155-178; Gregory J. Morgan, "The Genesis of the Molecular Clock," Linus Pauling: Scientist and Peacemaker, eds. Clifford Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 169-76.

[34] Emile Zuckerkandl, "On the Molecular Evolutionary Clock," Journal of Molecular Evolution 26 (1987): 34-46.

[35] Kay, Molecular Vision, 276; Diane Paul, The Politics of Heredity: Essays on Eugenics, Biomedicine and the Nature-Nurture Debate (New York: State University of New York Press, 1998): 166; Keith Wailoo, Dying in the City of the Blues: Sickle Cell Anemia and the Politics of Race and Health (Chapel Hill: University of North Carolina Press, 2001): 186-87.

[36] For bibliographic information about Hager's biography see footnote 2 above.

focused on certain themes for particular periods in Pauling's life.[37] Anthony Serafini presents an imprecise overview of Pauling's life.[38] Lastly, Robert Paradowski concentrates on Pauling's earlier years and "The Nature of the Chemical Bond," and briefly touches on Pauling's later years.[39] In addition, some compilations have been published. Barbara Marinacci has written brief biographical essays to complement passages taken from numerous publications written by Pauling. Her account comes closest to one of my aims because she sees connections in Pauling's life and research endeavors that developed over time. For example, she says that his work on sickle cell anemia instigated subsequent projects: "The first identification of a molecular disease served as a springboard for much of Pauling's thinking in the years to come."[40] Marinacci and Ramesh Krishnamurthy compiled Pauling's writings on peace and added short passages that link Pauling's messages to the events that instigated them.[41] Thomas Hager and Clifford Mead gathered biographical information written by Pauling, by Pauling's colleagues, and by scholars who have studied Pauling.[42]

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[37] Ted G. Goertzel and Ben Goertzel, Linus Pauling: A Life in Science and Politics (New York: Basic Books, 1995).
[38] Anthony Serafini, Linus Pauling: A Man and His Science (New York: Paragon House, 1989).
[39] Robert Paradowski, "The Making of a Scientist," Linus Pauling: A Man of Intellect and Action (Tokyo: Cosmos Japan International, 1991): 73-103. Robert Paradowski, "The Structural Chemistry of Linus Pauling," University of Wisconsin, diss., 1972 (Ann Arbor: Xerox University Microfilms, 1986).
[40] Pauling, Linus Pauling in his Own Words, 118.
[41] Linus Pauling, Linus Pauling on Peace: A Scientist Speaks Out on Humanism and World Survival, Barbara Marinacci and Ramesh Krishamurthy, eds. (Los Altos, California: Rising Starr Press, 1998).
[42] See footnote 15.

Scientific biography is another body of literature important to my thesis. Although not a comprehensive biography, I discuss sixty years of Pauling's life, from his early thirties to his death at age ninety-four. An aspect of scientific biographies that I have tried to incorporate is balancing the impact of quick, monumental events with the day-to-day toil.[43] For example, Pauling spent ten years working on the structure of hemoglobin and its derivatives before hearing about sickle cell anemia, which he stated he understood immediately. Also, I demonstrate how Pauling's science and politics overlap.[44] When Pauling was introduced to sickle cell anemia he quickly became enamored with the subject and then used his scientific knowledge of the disease not only for scientific research, but also to enforce his political and social statements.

The scientific research Pauling conducted during the 1930s and early 1940s gave him a unique knowledge comprising of structural chemistry, physical chemistry, immunology, and biology as well as an experimental understanding of hemoglobin and its derivatives (oxyhemoglobin and carbonmonoxyhemoglobin). Pauling's unusual scientific background allowed him to contribute significantly to the understanding of why the blood of people suffering from sickle cell anemia distorts into a crescent-shape and his theory of the sickling process of hemoglobin led him to define sickle cell anemia as a molecular disease. This innovative concept of

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[43] Thomas Söderqvist, "Existential Projects and Existential Choice in Science," Telling Lives in Science: Essays on Scientific Biography (Cambridge: Cambridge University Press, 1996): 45-84, 70-74.

[44] Söderqvist, 70-74; James Clifford, "'Hanging Up Looking Glasses at Odd Corners': Ethnobiographical Prospects," Studies in Biography, ed. Daniel Aaron (Cambridge, Massachusetts: Harvard University Press, 1978): 41-56, 45-46.

molecular disease immediately inspired others to analyze the molecular composition of human hemoglobin. A large amount of the subsequent research on abnormal hemoglobin was performed by Pauling's colleagues at Caltech under his direction as Chair of the Chemistry Department. In addition, viewing diseases as molecular ailments inspired new approaches to combating diseases, a field known as molecular medicine.

In the second half of the twentieth century, Pauling's interests diversified and he began exploring numerous areas that drew upon his knowledge of hemoglobin and sickle cell anemia. For example, Pauling integrated his concept of molecular disease with his newest field of interest, mental disorders. From his study of molecular disease and mental deficiency, Pauling learned about numerous genetic diseases – a topic he discussed scientifically, politically, and socially. In time, his research on molecular disease and mental illness provoked him to study nutritional therapies for optimal health, which culminated in his defining orthomolecular medicine and orthomolecular psychiatry and in his establishing the Linus Pauling Institute of Science and Medicine for the research of orthomolecular therapies. Pauling also used hemoglobin for the basis of an evolutionary theory called the Molecular Clock.

Since hemoglobin and sickle cell anemia are my main areas of concentration, I have limited my discussions to matters that include hemoglobin and sickle cell anemia without diverting onto tangents. Where applicable, I have suggested sources that discuss the subjects in fuller detail. The projects that Pauling tackled over his lifetime which did not involve hemoglobin or sickle cell anemia will not be discussed.

Some of these unrelated topics include the three-strand structure of deoxyribonucleic acid (DNA) that Pauling and Corey proposed in December 1952 and published in February 1953, two months before James Watson and Francis Crick's publication.[45] Also, in the early 1960s he formulated "A Molecular Theory of General Anesthesia."[46] In his later years, Pauling published many articles on the structure of inorganic compounds, primarily metals.[47] I aim to investigate an element of continuity in Pauling's work over his lifetime and therefore limit myself to discussing his endeavors that involved hemoglobin and sickle cell anemia.

In the chapters that follow, hemoglobin and sickle cell anemia are investigated as a continuous theme in Pauling's life not only connecting most of his endeavors from the mid-1930s until his death in 1994, but also tracing the path that he took from one discipline to another. Whereas hemoglobin caught Pauling's attention in the mid-1930s and held his interest until his death sixty years later, he heard about sickle cell anemia in 1945 and also discussed the disease until his death. My main focus is on

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[45] Linus Pauling and Robert B. Corey, "A Proposed Structure for the Nucleic Acids," Proceedings of the National Academy of Sciences of the United States of America 39 (1953): 84-97.

[46] Linus Pauling, "A Molecular Theory of General Anesthesia," Science 134 (1961): 15-21.

[47] Some examples include: Linus Pauling and Barclay Kamb, "The Crystal Structure of Lithiophorite," American Mineralogist 67 (1982): 817-21; Linus Pauling, "Evidence from Bond Lengths and Bond Angles fro Enneacovalence for Cobalt, Rhodium, Iridium, Iron, Ruthenium, and Osmium in Compounds with Elements of Medium Electronegativity," Proceedings of the National Academy of Sciences of the United States of America 81 (1984): 1918-921; Linus Pauling, "Apparent Icosahedral Symmetry is due to Directed Multiple Twinning of Cubic Crystals," Nature 317 (1985): 322-24; Linus Pauling, "Factors Determining the Average Atomic Volumes in Intermetallic Compounds," Proceedings of the National Academy of Sciences of the United States of America 84 (1987): 4754-756.

sickle cell hemoglobin, which will be the primary topic discussed in Chapters Two and Three. However, in order to understand Pauling's comprehension of the sickling process, ten or so years of earlier research must be investigated: this is the focus of Chapter One.

# 1

## Before 1945 – Linus Pauling's Scientific Background in Hemoglobin

In 1927 the California Institute of Technology hired Linus Pauling as assistant professor of theoretical chemistry and mathematical physics. Pauling had attended Caltech for his graduate work in chemistry beginning in 1922. Arthur A. Noyes, head of the Research Laboratory of Physical Chemistry at Caltech, took a special interest in Pauling and groomed Pauling to be his successor. Noyes died on 3 June 1936 and after one year of negotiations, Pauling succeeded Noyes as director and chairman of the Caltech chemistry department. Pauling was thirty-six years old.[1]

As an undergraduate and graduate student, Pauling had focused on inorganic chemistry, paying special attention to crystals and eventually learning x-ray crystallography. X-ray crystallography was a new laboratory technique at this time. It allows an investigator to see the three-dimensional shape of the molecule analyzed. Pauling learned x-ray crystallography as an undergraduate at Oregon Agricultural College and immediately put the method into practice. Between 1923 and 1925, while a graduate student, he published seven papers on crystal structures, five of which he included in his thesis to obtain his Ph.D. in Chemistry from Caltech. In the years

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[1] Hager, Force of Nature, 80, 129-31, 210-11. Judith R. Goodstein, Millikan's School: A History of The California Institute of Technology (New York: W.W. Norton & Company, 1991): 178-92.

ahead, Pauling would use x-ray crystallography to determine the atomic structure of organic compounds, especially proteins.[2]

In 1932 Pauling began analyzing not only inorganic, but also organic molecules. How did Pauling gain an interest in organic substances after training and working with inorganic compounds for over ten years? Scholars have raised multiple possibilities explaining why Pauling's interests shifted. In 1932 he applied for a grant from the Rockefeller Foundation with the purpose of primarily examining the structure of inorganic molecules. However, in his grant proposal, Pauling mentioned that his inorganic researches might aid knowledge on organic substances and specifically named "proteins, haemoglobin and other complicated organic substances".[3] It was the possible application of chemistry to living organisms that attracted Warren Weaver of the Rockefeller Foundation.

Weaver was newly hired by the Foundation in 1932, and he would disburse grants in the natural sciences until his retirement in 1959. Weaver had a personal connection to Caltech; his first teaching position was as an assistant professor in Caltech's mathematics department. He had spent less than one year at Caltech, however, before he was drafted into the Army. He later returned to Caltech and taught for another academic year, 1919 to 1920.[4]

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[2] Hager, 86; Goodstein, 181.
[3] Goodstein, 189; Hager, 183.
[4] Hager, 183; Mina Rees, "Warren Weaver," Biographical Memoirs of the New York Academy of Sciences of the United States of America 57 (Washington, D.C.: National Academy Press, 1987): 493-530.

As envisioned by John D. Rockefeller, the Rockefeller Foundation was a philanthropy, which strove to improve living conditions internationally by primarily funding public health and medical education.[5] Their guiding philosophy also encouraged "social control," according to Lily Kay.[6] When the Rockefeller Foundation revamped its organizational structure between 1929 and 1932, the trustees hired Weaver as the man in charge of disbursing the Foundation's money for natural sciences. He spent five years from 1932 to 1937 developing a program that would guide his decisions and appease the Board of Trustees. Initially, Weaver defined his agenda as focusing on "vital processes." By using this term, he wanted to convey that his program concentrated on biological problems, while the funding was available to natural scientists of any discipline. However, the Trustees were wary of the term "vital processes" and eventually Weaver replaced it with "molecular biology."[7]

According to Hager, Pauling's comment about proteins in his grant application of 1932 caught Weaver's attention.[8] Robert Kohler noted that Weaver was not concerned with the substances his researchers investigated, but rather Weaver was interested in Pauling (and others like him) who integrated scientific disciplines. In addition, Weaver did not consciously look for people working with proteins, but eventually realized that proteins were a common research subject among his

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[5] Kohler, 69; Raymond B. Fosdick, The Story of the Rockefeller Foundation (New York: Harper and Brothers, Publishers, 1952): 4.
[6] Kay, Molecular Vision, 22-57.
[7] Kohler, 265-302.
[8] Hager, 183.

grantees.[9] Statements made by Raymond Fosdick, a Trustee of Rockefeller Foundation from 1921 to 1948 and its President during his final twelve years with the organization, concur with Kohler's argument. Fosdick averred that Weaver and the Foundation did not guide people into researching certain substances, but rather they allowed certain disciplines to develop by funding cross-disciplinary projects. Fosdick substantiated his point by noting that inorganic chemistry led Pauling to biochemistry.

> Dr. Pauling...had no direct interest in biology at that time [1933]. He was a physical chemist absorbed in studying the forces which hold molecules together. Despite his apparent remoteness from biology, the grant was voted, primarily because of the fundamental nature of the chemical problem and the brilliant record the young chemist had already made as a researcher. There was also in the background of Weaver's recommendation the thought that these physicochemical studies might eventually bring information concerning the structure of substances important to biology. And this surmise turned out to be correct. For in the course of exploring the electrical forces which bind the inorganic molecules, Pauling was led to test his theories in the more complicated realm of the organic, and this brought him to experiment with hemoglobin, the red pigment of blood. From that, he passed to antibodies, and finally to a study of immunization. Thus, in the course of a few years, he had bridged the gap from purely physical chemistry to the most humanly significant biochemistry.[10]

Thus, Fosdick not only viewed Pauling's switch into organic chemistry as entirely his own decision, but also stated that Pauling chose to study hemoglobin. Years later, Pauling also commented that he developed an interest in hemoglobin on his own accord. When asked if someone at the Rockefeller Institute had led him into studying

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[9] Kohler, 303-06, 330-57.
[10] Fosdick, 159-60.

hemoglobin, Pauling replied "my interest in hemoglobin was not specifically directed by someone at the Rockefeller Institute."[11]

Weaver's comments about Pauling's research in the Rockefeller Foundation's Annual Reports for 1932 and 1933 demonstrate how Weaver was developing boundaries for the Foundation's funding program in the natural sciences. In the summaries, Weaver mentioned that Pauling incorporated chemistry, physics and mathematics to investigate the structure of chemical substances. In 1932 he promoted Pauling by stating that Pauling was converting "chemistry from an empirical to a deductive science." The next year, Weaver summarized Pauling's efforts as a pivotal step towards learning "the structure of chlorophyll, hemoglobin, and other substances of basic biological importance." [12]

Weaver's aims remained pretty stable while he defined his program, but his disciplinary territory did not. The Board of Trustees did not want Weaver's disciplines overlapping with those of Alan Gregg, who funded medical research. In the end, Gregg's program focused on mental sciences like psychiatry, psychology, and neurology because Weaver commandeered medical biology. Weaver's area included biochemistry, biophysics, genetics, radiation biology, general physiology,

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[11] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, Letter from C. Lockard Conley to Pauling dated 25 July 1978, Letter from Pauling to Conley dated 1 August 1978. C. Lockard Conley wrote to Pauling in 1978 requesting information for a chapter he was writing on sickle cell anemia, which was "Sickle Cell Anemia – the First Molecular Disease" in Maxwell Wintrobe's Blood, Pure and Eloquent.

[12] Rockefeller Foundation Annual Report 1932 (New York: Rockefeller Foundation, 1932): 247; Rockefeller Foundation Annual Report 1933 (New York: Rockefeller Foundation, 1933): 209-10.

developmental mechanics, and experimental biology (which included physics and chemistry).[13]

While scholars agree that funding motivated Pauling to some extent, they have offered additional possibilities to explain Pauling's new direction. First, Noyes directed the chemistry department with a focus upon biological matters by striving to bring chemistry and biology together. According to Hager, Noyes tried to reclassify Pauling's appointment in the early 1930s to professor of organic chemistry, but Pauling declined because he wanted to keep his more versatile title, professor of chemistry. Secondly, some say Pauling may have taken the next logical step by moving from the less complex inorganic molecules to more complex organic compounds. For example, Pauling stated that by 1932 he knew enough about the structure of inorganic substances, even the most complicated ones, that he was ready to investigate organic compounds. Thirdly, Caltech's small size allowed the different departments to share information and cultivate cross-disciplinary interests. Lastly and in this vein, Caltech added their biology department in 1929 under the direction of geneticist Thomas Hunt Morgan. Pauling not only attended a weekly lecture on genetics given by Morgan, but also discussed research projects with Morgan and his colleagues.[14]

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[13] Kohler, 233-302; Kay, Molecular Vision, 6-11; William H. Schneider, "The Men Who Followed Flexner: Richard Pearce, Alan Gregg, and the Rockefeller Medical Divisions, 1919-1951," Rockefeller Philanthropy and Modern Biomedicine: International Initiatives from World War I to the Cold War, ed. William H. Schneider (Indiana: Indiana University Press, 2002): 7-50, 38.

[14] Hager, 182; Kay, Molecular Vision, 148; Linus Pauling, "How I Developed an Interest in the Question of the Nature of Life," Linus Pauling: Scientist and

Between 1931 and 1933 Pauling wrote the seven influential papers that gave him the reputation as a founding figure in quantum chemistry. Titled "Nature of the Chemical Bond," he developed rules in these papers explaining how electrons interact and thereby form three-dimensional structures, and he used physics and mathematics to predict empirical chemical structures. In addition, Pauling noted how magnetic data for complex ions revealed which kind of bonds (ionic or covalent) could be formed. [15] Eventually, information from Pauling's "Nature of the Chemical Bond" articles, in conjunction with the work of Walter Heitler, Fritz London and John Slater, became known as the Valence-Bond Theory.[16]

Valence-Bond Theory states that electrons, when forming bonds, share their energy and thus create the most stable structure. Thus, Valence-Bond Theory localized the energy of a molecule within the bonds. An important part of the Valence-Bond Theory was Pauling's concept of resonance, which he explained by primarily discussing organic compounds. Pauling defined resonance in two ways. One, he stated that substances could simultaneously have ionic and covalent bonds. Two, he explained that an element with one single and one double bond gained stability by equalizing the bonds' strengths.[17] Pauling demonstrated his theory of

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Peacemaker (Corvallis, Oregon State University Press, 2001): 134-40; Linus Pauling, "The Discovery of the Alpha Helix," Linus Pauling: Scientist and Peacemaker (Corvallis, Oregon State University Press, 2001): 141-49, 141.

[15] Linus Pauling, "The Nature of the Chemical Bond. Application of Results Obtained from the Quantum Mechanics and from a Theory of Paramagnetic Susceptibility to the Structure of Molecules," Journal of the American Chemical Society 53 (April 1931): 1367-1400.

[16] Goertzel and Goertzel, 66-75; Hager, 146-60.

[17] Hager, 164-66.

resonance through a thorough discussion of the hydrocarbons, which are the basis of organic chemistry.[18]

Upon renewal of his Rockefeller grant in 1934 Pauling learned that the Rockefeller Foundation would fund only work on organic molecules, especially those with biological applications. Thus, Pauling, whose interest was already shifting from inorganic to organic substances, applied for funding to analyze organic compounds.[19] Kay noted that although Pauling requested a three-year contract, the Foundation guaranteed Pauling $10,000 for only one year because the Foundation wanted Pauling to prove his allegiance to their aims. Weaver communicated this to Pauling by emphasizing the importance of working on biological problems and by explaining to

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[18] Linus Pauling and G.W. Wheland, "The Nature of the Chemical Bond. V. The Quantum-Mechanical Calculation of the Resonance Energy of Benzene and Naphthalene and the Hydrocarbon Free Radicals," Journal of Chemical Physics 1 (June 1933): 362-74; Linus Pauling and J. Sherman, "The Nature of the Chemical Bond. VI. The Calculation from Thermochemical Data of the Energy of Resonance of Molecules Among Several Electronic Structures," Journal of Chemical Physics 1 (August 1933): 606-17; Linus Pauling and J. Sherman, "The Nature of the Chemical Bond. VII. The Calculation of Resonance Energy in Conjugated Systems," Journal of Chemical Physics 1 (October 1933): 679-86. The Valence-Bond Theory had competition in the Molecular Orbital Theory. Molecular Orbital Theory proposes that the orbitals extend around the whole molecule, rather than localizing in the bonds. In the 1930s, the Valence-Bond Theory aided research more so than the Molecular Orbital Theory. However, that has changed with the advent of computers because the Molecular Orbital Theory lends itself to computer analysis. Thus, Pauling extended his work in physical and quantum chemistry by applying his fundamental rules to more complex molecules, especially hemoglobin and proteins, in the 1930s. Goertzel and Goertzel, 77-79.

[19] Goodstein, 187-89; Hager, 189; Kay, Molecular Vision, 148-49; Linus Pauling, "Early Days of Molecular Biology in the California Institute of Technology," Annual Review of Biophysics and Biophysical Chemistry 15 (1986): 1-9, 3.

Pauling that he had received the chemistry grant with the understanding that he would investigate biological problems.[20]

Pauling understood Weaver's suggestion and updated Weaver on his growing interest in biological matters. Even though Weaver was convinced of Pauling's commitment by the end of 1935, Pauling continued to express to Weaver his interest in biochemical problems. For example, in February 1938 Pauling told Weaver, "I am getting more interested in biological problems every day, and am anxious to see our new program in effect." This new program was the development of organic chemistry with a focus on biological substances.[21] As late as 1948, while a visiting professor in Oxford, Pauling still felt the need to reiterate his devotion to the Rockefeller agenda.

> I am deeply interested in my new theory of metals, and I want to get the consequences of the new idea worked out before I get back to Pasadena and start in again on biological things. My lectures this term are on intermolecular forces and biological specificity, but I have been devoting my research time to metals.[22]

In 1935, Pauling chose hemoglobin as one of his first organic substances to investigate.[23] Several possibilities have been raised for explaining why Pauling picked hemoglobin as a research subject. First, hemoglobin is easily obtainable.[24] In 1966 during one of his more light-hearted moods, Pauling commented on the accessibility of hemoglobin.

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[20] Kay, Molecular Vision, 148-49.
[21] Pauling Collection, Science 14.031.6, Letters from Pauling to Weaver dated 5 Feb 1938 and 30 March 1938.
[22] Pauling Collection, Science 14.032.6, Letter from Pauling to Weaver dated 27 May 1948.
[23] Goodstein, 188-89.
[24] Hager, 190.

> It is a good substance from the standpoint of a chemist, because of its availability. All you need to do is to catch somebody, introduce a hypodermic needle and draw out a sample of blood. A standard victim of this practice, weighing perhaps 120 pounds (it's easier to catch them small!) contains in the red corpuscles in his blood one and two-tenths pounds of hemoglobin.[25]

Secondly, during the 1930s and 1940s no one knew for sure which substance in the human body controlled heredity, but most scientists believed proteins held the secret to life. Proteins were fragile substances to study, and hemoglobin's accessibility enhanced its allure. Thirdly, hemoglobin can be studied by x-ray crystallography, a technique Pauling had learned while working with inorganic compounds as a graduate student. Lastly, hemoglobin is an extremely large macromolecule; however, it can be broken down and analyzed in sections.[26]

Pauling approached his research on hemoglobin by focusing on a portion of the macromolecule. Thus, he first studied the structural configuration of the heme in hemoglobin, which contains the iron. In comparison, globin is a protein. In 1935 Pauling published his first of many scientific papers on the structure of hemoglobin. He drew upon his profound knowledge of inorganic chemistry and his growing understanding of organic substances, particularly hemoglobin.[27] Pauling devised a

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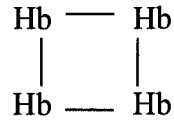
[25] Pauling, "Science and World Problems," 13.

[26] Hager, 189-90; Lily Kay, "Molecular Biology and Pauling's Immunochemistry: A Neglected Dimension," History and Philosophy of the Life Sciences 11 (1989): 211-19.

[27] According to Hager, Pauling voraciously read about hemoglobin (Hager, 190-91), collecting over forty articles dated from 1900 to 1934 on the subject. It is unclear when Pauling amassed the collection; however, he mentioned information gathered from some of these articles in his speech at Oregon State University on "Hemoglobin and Magnetism" in 1937. The articles can be found at: Pauling Collection, Science 6.017.10, Linus Pauling's notes on articles related to hemoglobin and sickle cell

mathematical explanation to a problem that stumped researchers: How do the hemes communicate in order to achieve the successive binding and unbinding of oxygen? It was known that once one oxygen molecule bonded to hemoglobin, then the other three oxygen molecules bind more readily. The same is true for the unbinding of oxygen molecules, after the first oxygen molecule dissociates from the hemoglobin, the rest disconnect more easily. Pauling proposed a structure for the four iron atoms in hemoglobin by using data on oxygen equilibrium curves. He stated that the hemes are arranged in a square, each connected to two of the other hemes and two acid groups.




(Four hemes in a square)

Thus, Pauling structurally connected the hemes to one another, which explained how they communicate thereby allowing the hemes to add or lose oxygen successively. In addition, Pauling calculated the interaction energy required for the molecule to hold the hemes together. According to Hager, this article proved to Weaver that Pauling was dedicated to biological problems and the Rockefeller Foundation's agenda.[28]

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anemia. There are about three articles dated between 1936 and 1940 with the others. All of the articles deal with hemoglobin research, not sickle cell anemia. Based on the articles collected, Pauling seemed chiefly concerned with porphyrins, hemoglobin, hemoglobin derivatives, and substances similar to hemoglobin in other living organisms.

[28] Linus Pauling, "The Oxygen Equilibrium of Hemoglobin and Its Structural Interpretation," Proceedings of the National Academy of Sciences of the United States of America 21 (15 Apr 1935): 186-91. A summary of the above article was published in Science soon thereafter. Linus Pauling, "The Oxygen Equilibrium of

By early 1935 Pauling enthusiastically pursued his hemoglobin research. The Rockefeller Foundation funded projects based on academic years and therefore most of Pauling's grants expired each year at the end of June. On 12 March 1935, Pauling wrote to Robert A. Millikan, Caltech's president, requesting to borrow money from the next year's grant.

> I have now about $250 of the 1934-5 Rockefeller Fund unexpended. I wish to prepare apparatus for our hemoglobin program without delay, and this might make advisable the expenditure of more than this amount before July 1, 1935. Would it be possible for me to use an advance of $250, if necessary, from the 1935-6 fund?[29]

In 1937, Pauling applied for a substantially larger sum of money from the Rockefeller Foundation. Whereas, Pauling's grants had previously amounted to $10,000 per year, he now asked for $35,000 or more annually.[30] In early 1937, Pauling sent an application to Weaver, who reviewed it, revised it, and sent it back to Pauling with suggestions on how to fill out the paperwork. In addition, Weaver stated that there were conditions that Caltech had to agree to accept in order for the Rockefeller Foundation to approve Pauling's application.[31]

On 1 July 1937, after incorporating Weaver's suggestions, Pauling wrote to the Executive Council at Caltech requesting permission to file a grant with the Rockefeller Foundation. He wanted $250,000 over five to seven years. Pauling

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Hemoglobin and Its Structural Interpretation," Science 81 (3 May 1935): 421. Hager, 190-91.

[29] Pauling Collection, Science 14.031 found inside the cash ledger, Letter from Pauling to Weaver dated 12 Mar 1935.

[30] Kay, Molecular Vision, 153; Rockefeller Foundation Annual Report 1934 (New York: Rockefeller Foundation, 1934): 141-42.

[31] Pauling Collection, Science 14.031.5, Letter from Weaver to Pauling dated 19 May 1937.

vaguely stated how the money would be spent "...for the development and support of advanced study and research in organic and structural chemistry, with especial reference to problems of biological importance." He categorized the department's anticipated expenditures into three areas. One, he wanted $10,000 per year for structural chemistry. Two, the department needed $5,000 per annum for permanent equipment. Three, for organic chemistry he wanted the amount of money to increase each year, starting at $20,000 and capping at $35,000.

The Rockefeller Foundation set two contingencies for Caltech to accept in order for Pauling to receive funding. Caltech had to give Pauling $5,000 per year to supplement the money from the Foundation for structural chemistry, and Caltech had to guarantee to spend $50,000 per year on organic and structural chemistry when the Foundation stopped supporting Caltech's chemistry department.[32] The Executive Council agreed to the Foundation's stipulations and on the same day Pauling sent the revised application to Weaver.[33] The Caltech chemistry and biology departments received $300,000 over six years from the Foundation beginning mid-1938.[34]

Over the years Pauling submitted project updates to the Rockefeller Foundation, which helped guarantee the renewal of his grants. In his "Report on Men Carrying on Chemical Research related to Biology at the California Institute of Technology during the year 1938-39," Pauling listed fifteen men who headed up

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[32] Pauling Collection, Science 14.031.2, Letter from Pauling to the Executive Council at Caltech dated 1 July 1937.
[33] Pauling Collection, Science 14.031.2, Letter from Executive Council to Pauling dated 14 Aug 1937; 14.031.5 Letter from Pauling to Weaver dated 14 Aug 1937.
[34] Rockefeller Foundation Annual Report 1937 (New York: Rockefeller Foundation, 1937): 187-89.

areas of research and their assistants. Of those fifteen men only Pauling worked on hemoglobin. In addition, Pauling had seven assistants and only two, Thomas Harrison Davies and Charles D. Russell, aided Pauling on his hemoglobin projects. Both men researched topics that Pauling had written on previously. In the report for the following year, Pauling mentioned that Davies had found that adding heme to globin created a different oxidation equilibrium curve than seen from native hemoglobin. Pauling had discussed the oxidation equilibrium in his first paper on hemoglobin. Russell researched magnetic properties of hemoglobin and published an article with Pauling on their findings.[35]

By 1938, Pauling and Weaver's relationship had changed; the two men wrote to each other requesting advice. Weaver wanted Pauling's opinion about experimental work done by other investigators funded by the Rockefeller Foundation. For example, Weaver asked Pauling for citations to sources on proteins because he wanted to write a non-technical statement discussing why protein research was important. Pauling responded by sending Weaver two summaries of information he had gathered and compiled from his personal files. The first paper was titled "The Molecular Structure of Proteins" and the second, "Hemoglobin and Magnetism."[36] Pauling, on the other hand, wrote to Weaver requesting advice on administrative matters, such as writing grants for the Foundation and rates of pay for investigators funded by the

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[35] Charles D. Russell and Linus Pauling, "The Magnetic Properties of the Compounds Ethylisocyanide-Ferrohemoglobin and Imidazole-Ferrihemoglboin," Proceedings of the National Academy of Sciences of the United States of America 25 (15 Oct 1939): 517-22.

[36] Pauling Collection, Science 14.031.7, Letter from Weaver to Pauling dated 3 Aug 1939. Letter from Pauling to Weaver dated 11 Aug 1939.

Foundation.[37] Thus, Weaver and Pauling had developed a friendship, as well as a working relationship. Overall, Weaver staunchly supported Pauling's work and had the same kind of relationship with Pauling that he had with his other investigators pursuing research in what would be called molecular biology today. However, the friendship between Pauling and Weaver and their respect for one another seemed to be stronger than that which Weaver had with the other researchers.[38]

Within one year of his initial 1935 article on hemoglobin, Pauling in collaboration with Charles D. Coryell, wrote two articles on the magnetic properties and structure of hemoglobin and its derivatives. The second paper dealt with the question of how oxygen and carbon monoxide bind to hemoglobin. In order to answer this question, Pauling devised a new approach for examining hemoglobin – through its magnetic properties. Pauling and Coryell found that oxyhemoglobin and carbonmonoxyhemoglobin have no magnetic moment and therefore all electrons are paired. In comparison, hemoglobin exhibits paramagnetism, meaning that hemoglobin has unpaired electrons. Specifically, Pauling and Coryell stated that each heme has four unpaired electrons. Thus, they determined that the iron in hemoglobin forms ionic (not covalent) bonds with nitrogen and the globin, while oxyhemoglobin and carbonmonoxyhemoglobin form covalent bonds at the same locations. Pauling and Coryell commented upon the drastic structural change that occurs when hemoglobin binds with oxygen or carbon monoxide: "It is interesting and surprising

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[37] Pauling Collection, Science 14.031.6, Letter from Pauling to Weaver dated 5 Feb 1938 and also many of the other letters in this box.
[38] Hager, 192; Kohler, 330-57.

that the hemoglobin molecule undergoes such an extreme structural change on the addition of oxygen or carbon monoxide."[39] Pauling and Coryell could not definitively remark on the significance of their findings, but postulated on the importance. Hence, they stated that the structural change from ionic to covalent bonds most likely explained why hemoglobin bonded more readily with oxygen and carbon monoxide than other substances.

Pauling later reflected upon his work with Coryell and remarked how it enhanced knowledge about the structure of hemoglobin. "These studies of the magnetic properties of hemoglobin and its compounds led to a great increase in understanding of the structure of the hemoglobin molecule in the neighborhood of the heme groups." Pauling also noted that this work led him into two new areas of research. Specifically, it increased his interest in proteins and immunology.[40]

As Pauling stated, the work on magnetic properties piqued his interest in proteins; however, he already was intrigued by them. While visiting the Rockefeller Institute in spring of 1935, Pauling convinced Simon Flexner, the institute's president and a member of the Rockefeller Foundation's board of trustees, to send Alfred Mirsky to Caltech for a couple of years. Mirsky knew a good deal about the denaturation of proteins and had worked on the denaturation of hemoglobin. Pauling

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[39] Hager, 192-4; Linus Pauling and Charles D. Coryell, "The Magnetic Properties and Structure of the Hemochromogens and Related Substances," Proceedings of the National Academy of Sciences of the United States of America 22 (15 Mar 1936): 159-63; Linus Pauling and Charles D. Coryell, "The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin," Proceedings of the National Academy of Sciences of the United States of America 22 (15 Apr 1936): 210-16.

[40] Pauling, "Fifty Years," 1002.

wanted to improve his own understanding of proteins and thought having Mirsky at Caltech would aid his learning process.[41] During the same time that Pauling and Coryell researched the magnetic properties and structure of hemoglobin and it derivatives, Pauling and Mirsky analyzed the structure of native, denatured and coagulated proteins.

In the beginning of the paper, they stated that they were presenting a general theory to explain what happens structurally when a native protein is denatured. In the end, they found that the tertiary structure of native proteins (i.e. the structure produced when a sequence of amino acids folds and binds to itself) depends upon hydrogen bonds, which allow the folded protein to hold its shape. During denaturation the hydrogen bonds break down and the protein loses its tertiary structure. Mirsky and Pauling mentioned several proteins in their article: hemoglobin, egg albumin, enzymes, and myosin to name a few. They also summarized what was known about the denaturation of proteins; their discussion of hemoglobin demonstrates Pauling's increasing knowledge of hemoglobin and its derivatives. In this vein, they mentioned that denaturation of globin from hemoglobin can be reversed if the heme is detached prior to denaturation. They also noted that globin is less stable when detached from the heme and that, depending upon which group is

[41] Hager, 197.

attached to the globin, the stability varies. Thus, carbonmonoxy-hemoglobin is more stable than oxyhemoglobin.[42]

By 1937 Pauling had learned a lot about hemoglobin as is evident from two talks he gave in May and October. He discussed what hemoglobin is, what it does, how large one molecule of it is, and how much hemoglobin is in the human body. He also commented upon his increasing understanding of how hemoglobin transports oxygen and carbon dioxide within the body.

> But it [hemoglobin] does not do this [transport oxygen and carbon dioxide] directly, as I naively supposed until I learned better...Oxyhemoglobin is a stronger acid than hemoglobin itself. On losing oxygen in the tissues, hemoglobin thus makes the blood plasma basic, permitting it to pick up carbon dioxide as bicarbonate ion; then in the lungs on picking up oxygen the hemoglobin makes the plasma acid, thus expelling the carbon dioxide.

Obviously, by this time Pauling had a good command of the chemical differences between hemoglobin and its derivatives, as well as the way they functioned within the human body.[43] Pauling's knowledge about hemoglobin and its derivatives would greatly aid his ability to understand the sickling process undergone by sickle cell hemoglobin, but this was not for another seven years.

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[42] A. E. Mirsky and Linus Pauling, "On the Structure of Native, Denatured, and Coagulated Proteins," Proceedings of the National Academy of Sciences of the United States of America 22 (15 Jul 1936): 439-47.

[43] Pauling Collection, Speeches 1937s.2, "Hemoglobin and Magnetism" delivered at Oregon Agricultural College, Corvallis, Oregon on 12 May 1937; Speeches 1937s.3, "The Significance of Structural Chemistry" delivered on 12 Oct 1937 at Cornell University as part of the George Fisher Baker Lectureship, 1937-38. The same speech was also delivered on 10 March 1938 with a different title "The Structural Chemistry of Blood" in Pomona, California.

As Pauling mentioned, he also gained an interest in immunology around this time. In May 1936 Pauling gave a lecture on the magnetic properties of hemoglobin in Michigan. Karl Landsteiner, who attended the lecture, approached Pauling and requested that they meet and talk about immunology. Landsteiner, also familiar with hemoglobin, worked with it in his discipline of immunology. When he approached Pauling, Landsteiner was one month shy of sixty-eight years old, and he was an established scientist in his field. In 1901, he had determined that different blood types exist in human beings, and he had received the Nobel Prize for this work in 1929. Born in Vienna, Landsteiner had studied internal medicine at Vienna University in the late nineteenth century, followed by two years of training in Switzerland and Germany. He returned to Vienna in 1894 where he remained for over twenty years. In 1918 Landsteiner took a job with the Rockefeller Institute in New York and relocated to the United States. He retired from the Institute in 1939, but remained working there as an emeritus professor until his death in 1943.[44] Upon hearing of Landsteiner's resignation from the Rockefeller Institute, Pauling wrote to Weaver about extending an invitation for Landsteiner to work out of the biology facilities at Caltech. In addition, Pauling requested $50,000 to $75,000 over five years from the Foundation to pay Landsteiner and his assistants. Pauling appealed to Weaver by mentioning that Landsteiner would greatly aid him in one of his current projects, writing a theory of

[44] Paul Speiser and Ferdinand G. Smekal, Karl Landsteiner, trans. Richard Rickett (Wein: Verlag Brüder Hoolinek, 1975).

serological reactions.[45] As mentioned, however, Landsteiner remained in New York and did not relocate to Pasadena.[46]

When Landsteiner approached Pauling in 1936, Pauling doubted his ability to contribute valuable information to Landsteiner's endeavors. However, Landsteiner felt differently and hoped Pauling's knowledge of chemical structures would aid his research. At the time Landsteiner was investigating antibodies, which are proteins that fight infection. In particular, Landsteiner wanted to understand why each foreign protein, or antigen, introduced into a living organism has its own specific antibody. Immediately following their talk Pauling read Landsteiner's recently published book, The Specificity of Serological Reactions. After reading it, Pauling read other books on immunology. When Pauling went to Cornell University in late 1937 for the Baker lectureship he and Landsteiner spent several days discussing immunology.[47] Upon reflection on their meeting, Pauling reminisced that Landsteiner taught him about serology and the available information in the field.[48] Pauling was flattered that Landsteiner took an interest in him and devoted so much time educating him on

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[45] Pauling Collection, Science 14.031.7, Letter from Pauling to Weaver dated 12 Jan 1939

[46] Hager presents two other, earlier attempts by Landsteiner and Pauling to relocate Landsteiner to Caltech. Hager, 238.

[47] According to Peyton Rous, who wrote an obituary for Landsteiner, Pauling and Landsteiner read through the latest edition of The Specificity of Serological Reactions together, while Landsteiner expanded on the information in his book (311). Peyton Rous, "Karl Landsteiner, 1868-1943," Obituary Notices of Fellows of the Royal Society: 1945-1948, vol. V. (London: Morrison and Gibb Ltd., 1949): 295-324.

[48] Pauling, "Fifty Years," 1005; Pauling, "Question of the Nature of Life," 138-39; Hager, 235-38; Linus Pauling, "Analogies between Antibodies and Simpler Chemical Substances," Chemical and Engineering News 24 (25 Apr 1946): 1064-065.

immunology.[49] According to his biographers, Landsteiner gained a newfound passion for his research and was bounding with ideas after talking with Pauling.[50]

Landsteiner's The Specificity of Serological Reactions, first published in 1936, was revised and reprinted in 1945 and 1947. The latter two editions are identical and have an additional chapter at the end written by Pauling, "Molecular Structure and Intermolecular Forces."[51] This book was influential not only for Pauling, but also for Harvey A. Itano, his primary collaborator on the sickle cell anemia work that was undertaken between 1945 and 1949.[52] In Pauling's chapter, as in his article with Mirsky on denaturation, Pauling stressed the importance of intermolecular interactions, which he defined as van der Waals interactions, hydrogen bonds and other weak bonds. He stated that specificity in immunology was most likely due to intermolecular interactions, rather than the breaking and forming of strong bonds. In an effort to thoroughly explain his theory, Pauling laid out the various kinds of bonds that exist in chemical compounds. First, he briefly described the strong bonds which include ionic and covalent bonds, and he discussed the compounds with these types of bonds. Then, he explained in greater detail what he meant by intermolecular interactions and how these weaker bonds applied to immunology. According to Pauling, the surface structure of compounds determines how strongly two compounds bind to one another. In other words, if the two

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[49] Pauling, "Analogies between Antibodies," 1064.
[50] Speiser and Smekal, 116.
[51] Karl Landsteiner, The Specificity of Serological Reactions, revised edition with a chapter by Linus Pauling (1936; Cambridge, Massachusetts: Harvard University Press, 1947).
[52] Conley, 340.

compounds are highly complementary, as Pauling suspected was the case between an antigen and its corresponding antibody, then they can clamp on tightly to one another. Pauling also noted that the large size of proteins, on a molecular scale, required numerous points of the antigen and antibody to come into contact with one another. On the other hand, if the surface configurations were less suitable, the attraction of antigen and antibody for one another, or their ability to stay connected, would diminish. In conclusion, Pauling summarized that the specificity of an antibody to a particular antigen depended upon complementariness in structure. Pauling did not discuss his theory on the formation of antibodies in his chapter.[53]

Before undertaking this chapter for the 1945 edition of Landsteiner's book, Pauling had written a theoretical article in 1940, "A Theory of the Structure and Process of Formation of Antibodies." Pauling suggested that antibodies have the same sequencing in their polypeptide chains, but that the polypeptide chains fold differently.

> I assume, however...that *all antibody molecules contain the same polypeptide chains as normal globulin, and differ from normal globulin only in the configuration of the chain; that is, in the way that the chain is coiled in the molecule.*[54] (Pauling's italics)

According to Dr. Peyton Rous, who wrote Landsteiner's obituary, Landsteiner initially proposed this idea and Pauling expanded it.[55]

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[53] Linus Pauling, "Molecular Structure and Intermolecular Forces," The Specificity of Serological Reactions, ed. Karl Landsteiner (1936; Cambridge, Massachusetts: Harvard University Press, 1947): 275-93.
[54] Linus Pauling, "A Theory of the Structure and Process of Formation of Antibodies," Journal of the American Chemical Society 62 (1940): 2643-657, 2644.
[55] Speiser and Smekal, 116.

In this 1940 article, Pauling presented a theory on the formation of antibodies following up on notions about the behavior of globulin. Globulin, a polypeptide chain that can fold itself into a stable structure, is the substance that becomes the antibody. Antibodies form onto an antigen structure in six steps (see figure 1.1). Step one: an uncoiled globulin surrounds the antigen. Two: both ends of the globulin begin folding around the antigen and the complementary parts of the globulin and antigen attach. The active surface region of the antigen dictates the folding of globulin; thus, numerous configurations are possible. Three: the middle section of the globulin frees itself. Four: one end of the globulin detaches from the antigen. Five: the globulin coils into its stable structure; it is now an antibody. The sixth and final step: the antibody detaches from the antigen.

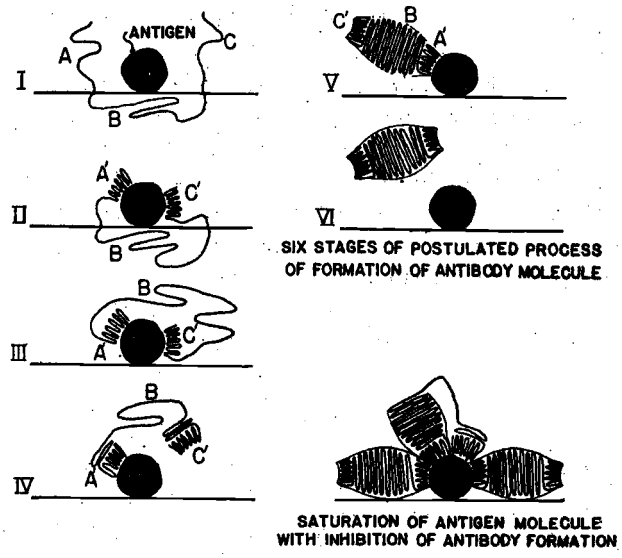


**Figure 1.1**[56]

[56] Pauling, "Theory of Antibodies," 2644-645. Figure 1.1 is from page 2645.

Most immunologists were trained in biology or medicine, not chemistry; however they readily adopted Pauling's theory.[57]

In 1946 Pauling delivered a speech at the first Harrison Howe Memorial Lecture titled, "Analogies between Antibodies and Simpler Chemical Substances." He cohesively explained his thoughts about specificity and complementariness in immunological interactions by comparing the antigen-antibody relationship to crystal formation. Thus, the antibody forms onto the antigen by using it as a template, which explains the complementary structures of antigens and antibodies. Likewise, crystals pack closely together and thereby form a solid mass. If a portion of the crystal is removed, then only a specifically configured molecule can fit into the empty area. As we will see, when Pauling and his colleagues published "Sickle Cell Anemia, a Molecular Disease," they connected the process of sickling to the antigen-antibody reaction. In the 1946 lecture, Pauling explicitly stated that he was concerned with medical issues and would use his knowledge of chemistry to help fight diseases.

> I believe that the thorough investigation of the shapes and sizes of molecules will lead to great advances in fundamental biology and medicine; and because of this belief I am now turning my efforts in this direction…I am convinced that progress in our attack against disease…depends on a better understanding of intermolecular forces and interactions.

Since Pauling had learned about sickle cell anemia in 1945 he may have been thinking about the disease, sickle cell anemia, in particular.[58]

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[57] Hager, 234-41.
[58] Pauling, "Analogies between Antibodies," 1065.

By the time Pauling had written this in 1946, he had gathered a substantial amount of new information with help from two collaborators in immunology, Dan H. Campbell and David Pressman. Pauling's research on immunochemistry coincided with World War II. Pauling aided the war effort by continuing to work on immunology and by branching out into new areas that built upon his previous endeavors.

In January 1940 Caltech borrowed Campbell, a Research Fellow in Immunology, from the University of Chicago where he had been an assistant professor of immunology. One year later Pauling told Weaver that his next step was to retain Campbell and in June, Pauling updated Weaver that Campbell would stay most of 1942.[59] In actuality, Campbell remained at Caltech until his death in 1974.[60] Pressman received his Bachelor of Science degree and Doctorate in Chemistry at Caltech in 1937 and 1940, respectively. He became a Research Fellow in Organic Chemistry at Caltech in 1940 and was promoted to Senior Research Fellow in 1942. He left Caltech in 1946.[61]

Pauling, Campbell and Pressman collaborated on many articles together. In one of the first projects, they substantiated findings made by Landsteiner.[62] Over the

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[59] Pauling Collection, Science 14.031.9 and 14.031.11, Letter from Pauling to Weaver dated 2 Jan 1941 and letter from Pauling to Weaver dated 12 Jun 1941; Hager, 239.
[60] Jacques Cattell Press, ed. American Men of Science: The Physical and Biological Sciences, 11th edition (New York: R.R. Bowkes Company, 1965): 735; The California Institute Archives website, http://archives.caltech.edu/
[61] American Men of Science, 4260.
[62] Linus Pauling, Dan H. Campbell, and David Pressman, "Serological Reactions with Simple Substances Containing Two or More Haptenic Groups," Proceedings of the

next few years they published multiple articles on topics such as complement fixation (a test that determines whether an antigen and antibody are present and reacting with each other) and artificial antibodies. They continued to substantiate findings made by other investigators[63] as well as to present new results of their own. In 1943 they published an article on weak bonds and complementariness in the University of Chicago's Physiological Reviews, which is substantially similar to Pauling's later 1945 chapter in Landsteiner's book.[64]

During the Second World War, the atmosphere changed at Caltech and so did the subjects researched.[65] Pauling, like most of the professors who remained at Caltech, pursued scientific projects that aided the war effort. Two of his endeavors involved hemoglobin. First, he tried to find an artificial substitute for human serum that could be used instead of blood for blood transfusions. Secondly, he wrote a report about a device that determined the amount of carbon monoxide in the air by analyzing blood samples. Pauling pursued these projects in the early 1940s and from his reports and correspondence it is evident that he knew how blood behaved chemically in the human body.

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National Academy of Sciences of the United States of America 27 (15 Feb 1941): 125-28.

[63] Linus Pauling, David Pressman, and Dan H. Campbell, "An Experimental Test of the Framework Theory of Antigen-Antibody Precipitation," Science 98 (17 Sep 1943): 263-64.

[64] Linus Pauling, Dan H. Campbell, David Pressman, "The Nature of the Forces between Antigen and Antibody and of the Precipitation Reaction," Physiological Reviews 23 (Jul 1943): 203-19.

[65] Hager, 260.

Pauling tried to find a serum that could substitute for blood and be used for blood transfusions. He worked for the Committee of Medical Research, which had combined with the National Defense Research Committee in 1941 to become the Office of Scientific Research and Development (OSRD).[66] In 1942 Pauling submitted a proposal, "The Chemical Treatment of Protein Solutions in the Attempt to Find a Substitute of Human Serum for Transfusions," which was accepted on 8 May 1942. Two weeks later, Pauling received a letter from Robert Loeb of Columbia University and the National Research Council's Subcommittee on Blood Substitutes stating that he would receive $9,500 for one year of research.[67] With the aid of Campbell, Pauling developed a successful serum substitute that he called oxypolygelatin. Oxypolygelatin was not used, however, because by 1943 there were enough blood donors to make using the serum unnecessary.[68] Even though the government lost interest in oxypolygelatin, Pauling did not. In 1945 he delivered a speech about blood substitutes to the Los Angeles Academy of Medicine, where Pauling stated that he, Campbell, and others had continued to work on the blood substitute and had improved the gelatin.[69] Pauling's scrapbook has newspaper accounts of speeches he delivered as late as 1952, in which he discussed oxypolygelatin.[70]

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[66] Hager, 249.
[67] Pauling Collection, Science 13.011.6, Scientific War Work, 1940-1946.
[68] Hager, 259-60.
[69] Pauling Collection, Speeches 1945s.1: Linus Pauling, "Blood Substitutes," Los Angeles Academy of Medicine, California,16 Feb 1945.
[70] Pauling Collection, Scrapbooks 1951-1960, 6.22: Newspaper Clipping: "He Seeks Plasma Substitute," Vancouver Daily Province, 14 Feb 1952.

As part of his other project Pauling wrote a report describing a spectrophotometric device that would determine the amount of carbon monoxide in the air based upon the concentration of carbon monoxide in a sample of blood. He developed this instrument for airplanes and tanks on the request of the National Defense Research Committee of the Office of Scientific Research and Development (OSRD). His report, filed in July 1943, not only explained the apparatus's functions, but also laid out its positive and negative aspects. Spectrophotometry, the technique used for the apparatus, yielded concentration information through absorption spectra. In his sixty-six page report, Pauling gave very detailed information about hemoglobin and its reactions with other organic compounds. Additionally, he noted that hemoglobin is highly unstable and reconfigures easily. Specifically, hemoglobin quickly undergoes denaturation, oxygenation, reduction, and hydrolysis, as well as readily reacts with atmospheric gases. In the end Pauling found that the device was unsuitable for use because of its bulk, sensitivity and the instability of the reagent, oxyhemoglobin. Overall, the report demonstrates Pauling's grasp of the structural rearrangement of hemoglobin during chemical reactions.[71]

The United States government acknowledged Pauling for his scientific work that aided the war effort. The most prestigious award, which he received in 1948, was the Medal for Merit from President Harry S. Truman. The citation that accompanied the medal recognized Pauling's work on rocket powder foremost. In addition, Truman

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[71] Pauling Collection, Science 13.003.3: Linus Pauling, National Defense Research Committee of the Office of Scientific Research and Development, The Development of a Spectrophotometric Carbon Monoxide Indicating Instrument Using Hemoglobin 1885, 1943.

noted the two projects mentioned above: "He led the way to an oxygen deficiency indicator for submarines and aircraft; and carried out important work on a substitute for human serum." All in all, Truman called Pauling's work "brilliant."[72]

Two other events, independently of his researches in organic chemistry and hemoglobin analysis, probably affected Pauling's future concern with and approach to molecular diseases. One was Caltech's production of insulin for diabetics in its laboratories starting in the early 1920s.[73] The other was personal illness; Pauling was diagnosed in 1941 with Bright's disease, a kidney ailment.[74]

Insulin research began at Caltech about the time that Pauling started his graduate studies in 1922; the next year, Caltech received $10,000 for insulin research.[75] Pauling does not appear to have been directly connected with the insulin work; however, in his later speeches about molecular diseases, Pauling used diabetes as an example of a molecular disease treated by insulin, an "orthomolecular" medical solution.[76] Although it is simply conjecture, Pauling might have learned enough about insulin and diabetes to pique his interest and spur him to follow the research on it. In 1953 the Los Angeles Times paraphrased a statement that Pauling made about

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[72] Pauling Collection, Honors and Awards 1948h.1, Citation for the Medal of Merit from Harry S. Truman to Pauling dated 2 February 1948.
[73] Kay, Molecular Vision, 70-71.
[74] Hager, 252.
[75] Kay, Molecular Vision, 70-71.
[76] Linus Pauling, "Orthomolecular Somatic and Psychiatric Medicine," Zivilisationskrankheiten 12 (1967): 3-5, 3. Zivilisationskrankheiten article can be found at Pauling Collection, 1968p.10; Linus Pauling "Orthomolecular Medicine Defined." Linus Pauling: Scientist and Peacemaker, eds. Cliff Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 177-83, 177-78.

diabetes and insulin, which demonstrates the connections Pauling drew between molecular diseases and genetics, even before there was proof.

> Dr. Pauling is convinced that it may be possible to synthesize insulin, used in treating diabetes. Diabetes may be inherited and the scientist predicts it will be found that this is because of a single flaw in one of the thousands of genes.[77]

In a 1968 discussion on orthomolecular medicine, Pauling said diabetes is a hereditary disease of the recessive gene and that insulin helps to remove glucose from the blood.[78]

Bright's disease, also referred to as Nephritis, manifests itself in people whose kidneys cannot break down large amounts of urea and therefore get overworked. It produces edema (i.e. swelling) of the face and other body parts. In 1941 Pauling was referred to Dr. Thomas Addis of Stanford Hospital for treatment. After performing tests for two weeks, Dr. Addis recommended a nutritional remedy to Pauling. He suggested a strict diet limiting Pauling's intake of proteins, fats, salt, and sugar and increasing his ingestion of vitamins, liver extracts, and water. Protein, in particular, creates large amounts of urea. Pauling adhered to the diet for fifteen years and recovered fully from Bright's disease. After his initial diagnosis, Pauling approached this scientific problem like he would any other – he read extensively about the disease and treatment methods. Pauling found Addis's treatment method was controversial; however, Addis actually attempted to cure Nephritis whereas other physicians did

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[77] Pauling Collection, Scrapbook 1951-1955: 40. Newspaper article, "British Scientist Here Tells of Heredity Study," Los Angeles Times 30 Sep 1953.
[78] Pauling, "Orthomolecular Medicine Defined," 177-78.

not.[79] The similarity between Addis's treatment of Pauling's ailment and Pauling's future support of orthomolecular medicine is striking. In the 1970s Pauling advocated using natural treatment methods for those suffering from sickle cell anemia and he conducted orthomolecular medical research on sickle cell anemia through the Linus Pauling Institute of Science and Medicine.

These twelve years, from roughly 1932 to 1944, shaped Pauling's endeavors for the rest of his life. In the years to come, he continued to focus scientifically on the molecular structure of chemical compounds, especially proteins, including hemoglobin. In addition, he synthesized his scientific knowledge with personal campaigns (e.g. advocating the nuclear test ban and vitamin C). The best, and possibly only, commonality in a majority of Pauling's subsequent activities is molecular disease and molecular medicine, concepts that he developed from researching hemoglobin and learning about sickle cell anemia.

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[79] Hager, 252-56; Goertzel and Goertzel, 107-08; Linus Pauling, Linus Pauling on Peace: A Scientist Speaks Out on Humanism and World Survival, eds. Barbara Marinacci and Ramesh Krishamurthy (Los Altos, California: Rising Starr Press, 1998): 57-58; Mead and Hager, 12.

# 2

# 1945 to 1954 – Sickle Cell Anemia and Abnormal Hemoglobin

Linus Pauling, Harvey A. Itano, S. J. Singer and Ibert C. Wells published "Sickle Cell Anemia, a Molecular Disease" in Science in November 1949. New research pathways opened as a result of the investigations. This chapter analyzes Pauling's work on sickle cell anemia and related problems during the period 1945 to 1954 and provides a cohesive picture of the historical events surrounding this seminal paper.

Pauling first heard of sickle cell anemia in 1945 from Dr. William B. Castle of Boston City Hospital.[1] Castle had an established reputation in medical research by the

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[1] Soraya de Chadarevian questions whether this was the first time that Pauling had heard about sickle cell anemia. She proposed that Pauling possibly learned about it earlier during World War II because the Medical Advisory Committee discussed the problem of sickle cell anemia in black soldiers. See Soraya de Chadarevian, "Following Molecules: Hemoglobin between the Clinic and the Laboratory," Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s, eds. Soraya de Chadarevian and Harmke Kamminga (Sydney: Harwood Academic Press, 1998): 171-201, 174.
Also, Dr. George Burch stated that he had mentioned sickle cell anemia to Pauling in New York in 1941 while he medically treated Pauling, who was suffering from his first major bout of nephritis. Burch later shipped samples of sickle cell anemia hemoglobin to Caltech for research and conducted a clinical trial for Itano and Pauling (as discussed later in this chapter). Pauling replied to Burch that he did not remember the conversation, probably because he was so concerned with his own health. Years later, Pauling responded to a letter he received from a friend, who had read about the 1941 encounter between Pauling and Burch that appeared in an article written after Burch died. Pauling stated, "George Burch attached a plethysmograph [a device that detects circulation] to my big toe, and made some observations at that time. I do not remember his having mentioned sickle-cell anemia to me then, but later he was quite helpful in collaborating with us." (Pauling Collection, B: Individual

1930s, primarily based on his work on pernicious anemia. In the late 1920s, Castle hypothesized that pernicious anemia sufferers are deficient in liver extract. He performed experiments to support his theory and devised a therapy. In a series of papers published in the 1930s and 1940s on pernicious anemia, Castle proved that some people lack the ability to metabolize or absorb nutrients necessary for good health.

Not only pernicious anemia, but also hemolytic anemias, like sickle cell anemia, interested Castle. In the late 1930s, he and another physician, T. Hale Ham, observed that sickle cell hemoglobin acted differently than normal hemoglobin when the oxygen levels were lowered. Thus, deoxygenated sickle cell hemoglobin stayed in solution after centrifugation whereas normal hemoglobin did not. They concluded that the shape and interaction of the sickling cells were responsible for this behavior. Furthermore, in 1940 they noticed that deoxygenated sickle cell hemoglobin had a greater viscosity than normal deoxygenated hemoglobin, normal hemoglobin, or sickle cell hemoglobin. Thus, blood flow in the veins of sickle cell anemia sufferers moved slower than the venous blood of healthy individuals. Additionally, Castle proposed that the decreased blood flow caused the illness.[2]

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Correspondence, George Burch 1940-70, Letter from Burch to Pauling dated 3 February 1970; Letter from Pauling to Burch dated 16 April 1970; Letter from Pauling to Morris J. Nicholson, MD dated 30 July 1986.) Pauling first learned about Burch's statements in a letter from C. Lockard Conley: Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, Letter from Conley to Pauling dated 4 November 1969, Letter from Pauling to Conley dated 17 November 1969.

[2] James H. Jandl, "William B. Castle," Biographical Memoirs of the National Academy of Sciences 67 (1995): 15-40.

In the mid-1940s, Pauling and Castle were on a Medical Advisory Committee which compiled a report for Vannevar Bush, head of the Office of Scientific Research and Development. Bush's influential Science: The Endless Frontier included the committee's outline for post-war funding for medical research. All of the Palmer Committee members, excluding Pauling, were physicians.[3]

During 1945 Castle talked about sickle cell anemia to members of the Palmer Committee. Castle mentioned that the blood of sickle cell patients changes from a normal shape in the arterial blood to a crescent shape in the venous blood. Upon hearing what Castle said, Pauling immediately thought of two important ideas that he and his colleagues would then follow up. First, based upon the information that only deoxygenated blood sickles, he concluded that hemoglobin was involved. In other words, oxygen hinders the blood of sickle cell anemia patients from converting to the crescent shape. Pauling drew upon knowledge he had accumulated in the previous ten years about hemoglobin, oxyhemoglobin, and carbonmonoxyhemoglobin to come to this conclusion.[4] Secondly, he suggested that the structure of sickle cell hemoglobin might differ from that of normal hemoglobin. Thus, deoxygenated sickle cell hemoglobin bonds to itself and deforms into the sickle shape. Pauling later noted that he came to these two conclusions "at once."[5] Years later, Pauling related his structural understanding of sickle cell hemoglobin to his work in immunology by

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[3] Vannevar Bush, Office of Scientific Research and Development, Science: The Endless Frontier (Washington, D.C.: United States Government Printing Office, 1945); Hager, 286.
[4] Pauling, "Fifty Years," 1012; Pauling, foreword, Sickle Cell Disease, xvii.
[5] Pauling, "Fifty Years," 1011.

connecting the concept of complementary structures between antigen and antibody to this new problem:[6]

> According to my own view of immune bodies, complementary structure is responsible for the specificity of combination between antibody and antigen. I now postulated that these hemoglobin molecules combine with one another because of complementariness of structure.[7]

Pauling and Castle told different accounts about the conversation in which Pauling learned from Castle about sickle cell anemia. They disagreed about what information Castle gave Pauling. Pauling stated many times that Castle mentioned that red blood cells, when deoxygenated, get a crescent shape and convert back to normal when oxygen is reintroduced.[8] Castle also remembered telling Pauling about the different shapes of oxygenated and deoxygenated blood, but that he also mentioned that the deoxygenated blood of people with sickle cell anemia demonstrated birefringence in polarized light.[9] Pauling recalled that Castle mentioned birefringence during their second conversation and therefore this information did not aid Pauling's initial understanding of sickling.[10]

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[6] Linus Pauling, "Abnormality of Hemoglobin Molecules in Hereditary Hemolytic Anemias," The Harvey Lectures 1953-4 49 (1955): 216-41, 216-17; Linus Pauling, "Current Opinion: Molecular Disease," Pfizer Spectrum 6 (1 May 1958): 234-35, 234; Pauling, "Fifty Years," 1011.
[7] Pauling, "Current Opinion," 234.
[8] Pauling, "Abnormality of Hemoglobin," 216; Pauling, "Current Opinion," 234; Pauling, "Fifty Years," 1011.
[9] Pauling Collection, C: Correspondence 1963-65, Letter from Castle to Pauling 22 May 1963; Strauss, 621.
[10] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, Letter from Pauling to C. Lockard Conley dated 17 November 1969.

In the end, Pauling and Castle stood by their respective stories,[11] which have been told often. Most scholars tend to reiterate Pauling's statements made during his 1954 Harvey Lecture, "Abnormality of Hemoglobin Molecules in Hereditary Hemolytic Anemias."[12] In comparison, some scholars draw from Castle's statements made in 1964 and quoted in "Of Medicine, Men and Molecules: Wedlock or Divorce?" by Maurice B. Strauss, who was a physician at Boston City Hospital from 1930 to 1946.[13] Two scholars, C. Lockard Conley and Paul Heller, who wrote general histories about sickle cell anemia and molecular biology, respectively, point out the disparity between the two men's recollections.[14] However, most scholars reiterate only one person's memories. For example, biographers usually tell their subject's recollection.[15]

Whatever the details of their discussion, both men agreed the conversation had a profound impact. Pauling retold the story many times after the 1949 paper appeared and he usually mentioned Castle by name.[16] Castle was honored by Pauling's acknowledgement.

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[11] Paul Heller, "Historic Reflections on the Clinical Roots of Molecular Biology," Annals of the New York Academy of Sciences 758 (1995): 83-93, 89.
[12] For sources that quote Pauling's Harvey lecture see: Conley, 338-39; Heller, 89.
[13] For sources that quote Strauss's article see: Conley, 338-39; Jandl, 28; Heller, 89. For information bout Strauss at the Boston City Hospital see: Maxwell Finland and William B. Castle, The Harvard Medical Unit at Boston City Hospital, vol. II (Virginia: The University Press of Virginia, 1983): 132-33.
[14] Heller, 89; Conley, 339.
[15] Hager, 286; Marinacci, 116-17; Strasser, "Origins of Molecular Biology," 128; Jandl, 28; Karnad, 173-74.
[16] For examples of Pauling retelling the story and naming Castle see, Pauling, "Abnormality of Hemoglobin," 216; Pauling, "Current Opinion," 234; Pauling, "Fifty Years," 1011; Linus Pauling, "The Genesis of the Concept of Molecular

> Never has a chance remark of mine turned out so well as my mention to you some years ago during our railroad journey from Denver to Chicago of the phenomenon of birefringence when sickle cells are deoxygenated that had been observed by [Irving J.] Sherman! I have more than once heard of your generosity and circumspection in referring to this conversation when you have spoken on the subject of your magnificent work and that of your associates in sickle cell disease.[17]

Pauling immediately wanted to follow-up on his intuition. Thus, he asked Castle if he could try some experiments, to which Castle agreed.[18] Pauling also spoke with another member of the committee, Dr. Ed Doisy of St. Louis University Medical School. Doisy suggested that Pauling admit his recently graduated medical student, Harvey A. Itano, to the Ph.D. program in chemistry at Caltech.[19] Itano wanted to pursue medical research in the laboratory rather than practice medicine clinically.[20]

Pauling gave Itano the sickle cell anemia project when he arrived at Caltech in September 1946. Prior to his arrival, Itano applied for and received a three-year American Chemical Society Predoctoral Fellowship in Chemistry, which supported

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Disease," Sickle Cell Disease, eds. E.F. Mammen, G.F. Anderson, and M.I. Barnhart, (Stuttgart and New York: F.K. Schattauer Verlag, 1973): 1-6, 1; Pauling, foreword, Membrane Abnormalities, viii; Linus Pauling, foreword, Sickle Cell Disease: Basic Principles and Clinical Practice, eds. Stephen H. Embury, R. P. Hebbel, N. Mohandas, and M. H. Steinberg (New York: Raven Press, 1993): xvii-xix, xvii. For examples of Pauling retelling the story without specifying Castle's name see, Linus Pauling, "Chemistry in Medicine," The Bulletin of the Missouri Academy of Science 1 (1972/1973): 21-26, 21.

[17] Conley, 339; Pauling Collection, C: Correspondence 1921-1957, Letter from Castle to Pauling dated 28 Sep 1955.

[18] George Gray, "Sickle Cell Anemia," Scientific American 185 (1951): 56-59, 56-57; Pauling, "Abnormality of Hemoglobin," 217.

[19] Pauling, "Abnormality of Hemoglobin," 217; Pauling, foreword, Sickle Cell Disease, xviii.

[20] Conley, 340.

him at Caltech from 1946 to 1949.[21] Although Itano finished his Ph.D. in 1950, he stayed at Caltech until 1954, working from 1950 to 1954, as an officer for the Public Health Service of the United States. He then relocated to the National Cancer Institute of the National Institutes of Health in Bethesda, Maryland. During his first four years at Caltech, Itano focused on sickle cell hemoglobin. During his last four years, he continued his research on sickle cell anemia and began looking for and learning about other abnormal hemoglobin. By 1954 Itano found, either by himself or in collaboration with others, three more abnormal hemoglobins. These abnormal hemoglobins that Itano discovered are considered the first four.[22]

At the end of 1945 Pauling was actively seeking for research funding for the biology and chemistry departments at Caltech. In January 1946 he submitted a grant to the Rockefeller Foundation asking for six million dollars over fifteen years for "a joint program of research on the fundamental problems of biology and medicine." The Rockefeller Foundation gave Caltech only $50,000 in 1947 for two reasons. First, Caltech was selecting a new President; Lee A. DuBridge took the position in May 1946, but had yet to prove himself. Secondly, due to the Second World War and the United States government's new interest in funding scientific research, the

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[21] Pauling, "Abnormality of Hemoglobin," 217.
[22] Pauling Collection, I: Individual Correspondence, Harvey A. Itano 1955-1968, "Nomination of Harvey A. Itano for the Theobald Smith Award for 1955 submitted by Linus Pauling."

Rockefeller Foundation's role in sponsoring research was uncertain and the Foundation did not want to enter into long term agreements.[23]

Pauling, aided by DuBridge and George W. Beadle, acquired a continuing grant of $700,000 distributed over seven years from the Rockefeller Foundation in 1948. Beadle, the newly appointed chair of Caltech's biology department, helped Pauling outline the revised program and obtain research funding from other institutes. Beadle, a geneticist, focused on Neurospora and viruses. Like Pauling, Beadle wanted to incorporate chemistry into work in biology, specifically genetics. Beadle had been at Caltech from 1931 to 1936 and then had moved to Harvard University for one year, followed by Stanford University. He agreed to return to Pasadena in late 1945 and before arriving at Caltech in 1946, Beadle had begun working with Pauling to get funding for the joint program. For example, Beadle and Pauling acquired $300,000 over five years from the National Foundation of Infantile Paralysis in January 1947. DuBridge also sought funding from additional groups, such as the American Cancer Society, United States Public Health Service, and many lesser-known foundations. DuBridge had then resubmitted the joint program grant to the Rockefeller Foundation in early 1948 noting that researchers at Caltech had already started what the grant stated they aimed to do. This time, more Rockefeller funding arrived.[24]

Caltech did receive monetary support from groups other than the Rockefeller Foundation, as mentioned above. Beginning in 1946, Caltech received funding from

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[23] Kay, "Molecular Vision," 225-36; George W. Gray, "Beadle and Pauling," Scientific American 180(1949): 16-21, 19.
[24] Kay, "Molecular Vision," 234-39; Rockefeller Foundation Annual Report 1947, 140-43; Rockefeller Foundation Annual Report 1948, 160-62.

the United States Public Health Service for "Investigations of the Chemistry of Blood," with Pauling listed as the primary investigator. From 1946 to 1953 Caltech received $210,026, which is about $30,000 per year. From 1954 to 1957 the Public Health Service gave $8,640 to $12,075 yearly at which point the funding stabilized at $12,075 for the next decade. Additionally, in 1957 Pauling and Corey applied for another grant from the United States Public Health Service for "Molecular Chemistry Applied to Biology and Medicine" and received about $50,000 per year. The research conducted resulted in the publication, "Sickle Cell Anemia, a Molecular Disease," funded by United States Public Health Service.[25] Thus, Pauling continued to seek outside funding for his research progress at Caltech, as was becoming the normal operation of successful research laboratories in the twentieth century.

Shortly after Itano arrived at Caltech in fall 1946, Pauling wrote to Castle requesting reprints of articles on sickle cell anemia written by Castle and his colleagues. Specifically, Pauling wanted information about the "dividing line between sickling and non-sickling." Castle responded that experiments stating that oxygen and carbon monoxide hinder sickling were well-established. Also, he recommended four articles including his article from 1940 on the viscosity of blood.[26]

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[25] Pauling Collection, Science 13.020.6, Public Health Service – National Institutes of Health, Grant information for "Investigations of the Chemistry of Blood," 1946-1965; Pauling Collection, Science 13.020.7, Public Health Service – National Institutes of Health, Grant information for "Molecular Chemistry Applied to Biology and Medicine," 1956-1962.

[26] Pauling Collection, C: Correspondence 1921-1957, Letter from Pauling to Castle dated 6 November 1946 and Castle's response dated 25 November 1946.

Pauling and his collaborators gathered additional articles on sickle cell anemia, which they referred to in their various announcements made in the late 1940s and early 1950s. From these articles they learned what there was to know about the disease. James B. Herrick of Chicago had noticed the sickling phenomena in 1904 and announced his finding in 1910. John Huck had analyzed the blood of many generations of one family and found that many of the family members had cells that sickle. In 1923 Huck claimed that sickle cell anemia was passed from parents to progeny following Mendelian laws, and that it was a dominant trait. At this time the difference between sickle cell anemia and sickle cell trait was not distinguished.[27] In the late 1920s, physicians E. Vernon Hahn and Elizabeth B. Gillespie announced that sickling occurs only when the red blood cells are deoxygenated and that they convert to normal shape when oxygenated. Lemuel Whitley Diggs and J. Bibb showed that the blood of sickle cell patients is fragile and that in extreme conditions the red blood cells can be irreversibly converted into the sickled shape. In 1940 Sherman noted that sickle cell anemia patients have a larger number of crescent-shaped cells in their venous blood and suffer from anemia, whereas those with sickle cell trait have fewer sickling cells and do not suffer from illness. Additionally, Sherman found that sickle cells demonstrate birefringence in polarized light and normal blood cells do not. By

[27] Sickle cell trait and sicklemia describe the condition of people who inherit one normal and one sickle cell anemia gene.

1944 R. C. Murphy, Jr. and S. Shapiro had stated that sickled cells are more rigid than normal red blood cells.[28]

In early 1948 Itano had produced no conclusive experimental results providing information about the difference between sickle cell and normal hemoglobin. However, he had completed some other important investigations. He reproduced experiments that hindered and induced sickling, which acquainted him with the literature and phenomena.[29] He also attempted two unsuccessful experiments that built upon Pauling's previous work with hemoglobin. First, at Pauling's request he analyzed the absorption spectrum of the compounds formed by combining hemoglobin with cyanate and thiocyanate. It was known that a spectrometer gives different values for hemoglobin and its derivatives. However, each compound yielded the same spectrum, and therefore produced no conclusive results. Pauling most likely suggested this procedure because during World War II he had built a spectrophotometer that analyzed the concentration of carbonmonoxyhemoglobin in the air from a sample of human hemoglobin.

Second, Itano examined the magnetic susceptibility of hemoglobin in order to ascertain whether the iron bonds of normal and sickle cell hemoglobin differ. However, a microsusceptometer had to be constructed before conducting this experiment. Ultimately, Itano wanted to ascertain if the kind of bond formed (ionic or covalent) was responsible for the different shapes observed in deoxygenated normal

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[28] Conley, 319-339; Pauling Collection, Science 6.015.1, Transcript of lecture delivered by Ibert C. Wells at the Annual Meeting of the National Academy of Sciences in April 1949, 1-7.
[29] Pauling, "Abnormality of Hemoglobin," 217.

and sickle cell hemoglobin.[30] Pauling had used magnetism in the 1930s to determine whether covalent or ionic bonds formed in hemoglobin and its derivatives. As mentioned, Pauling found that, depending on the substance, a different kind of bond formed in the same location.

Although his attempts failed to yield successful results in detecting a difference between sickle cell and normal hemoglobin, Itano had made headway in other directions. He developed a procedure that quickly indicated whether a blood sample sickled.[31] He later noted in his 1950 dissertation how he came upon this diagnostic test. "The effect on sickling of molecules and ions other than oxygen and carbon monoxide was investigated. This study led to the use of sodium dithionitic for the rapid production of sickling."[32] Itano and Pauling published "A Rapid Diagnostic Test for Sickle Cell Anemia" in January 1949. Additionally, Dan Campbell announced Itano and Pauling's findings the previous February to the United States Public Health Service. Their method used sodium dithionite to cleave oxygen from a blood sample and induce sickling. This procedure was especially effective because it took only fifteen to thirty minutes, rather than hours, to observe sickled cells. As the

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[30] Pauling Collection, I: Individual Correspondence, Harvey A. Itano 1955-1968, Harvey Itano, "Research Report for Admission to Candidacy," April 1948: 1-10.
[31] Pauling Collection, I: Individual Correspondence, Harvey A. Itano 1955-1968, Harvey Itano, "Research Report for Admission to Candidacy," April 1948: 1-10. Based on the Itano's report and dissertation, he found that sodium dithionite reduces oxyhemoglobin and therefore converts erythrocytes into the crescent shape. Itano did not mention Pauling's role in the diagnostic test; however, in his dissertation Itano thanked Pauling for suggesting the sickle cell anemia project and for his guidance throughout the research.
[32] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, "Harvey Akio Itano's Ph.D. Thesis," diss., California Institute of Technology, 1950, 7.

title suggests, Itano and Pauling promoted their procedure as a diagnostic tool for use in clinics.[33]

Others developed similar methods for reducing oxyhemoglobin at this same time. Castle and an associate, Geneva A. Daland, proposed using sodium bisulphate as the reducing agent and their test also produced results in roughly fifteen minutes.[34] Daland and Castle's procedure received more acknowledgment than Itano and Pauling's method.[35] Itano explained why this is the case: the Daland and Castle method is more effective because the sickling inducing agent used by Itano and Pauling, sodium dithionite, reduces quicker, but also decomposes spontaneously. Therefore, it requires more attention and care than sodium bisulfate.[36]

Along with his preliminary results, Itano suggested in a 1948 report that there were eight other options for immediate research, one of which eventually proved successful: "electrophoretic studies on normal and sickle cell hemoglobin." In his synopsis about electrophoresis (which will be described below), Itano briefly mentioned the status of electrophoretic studies on hemoglobin and their utility for his sickle cell research.

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[33] Harvey A. Itano and Linus Pauling, "A Rapid Diagnostic Test for Sickle Cell Anemia," Blood 4.1 (January 1949): 66-68.

[34] Karnad, 172-3; Geneva A. Daland and William B. Castle, "A Simple and Rapid Method for Demonstrating Sickling of the Red Blood Cells: The Use of Reducing Agents," Journal of Laboratory and Clinical Medicine 33 (1948): 1082-88. Daland and Castle submitted their article on 7 July 1948. They mentioned two other reducing agents found by other investigators between when they submitted their article and when the journal published it. They do not mention Itano and Pauling because their paper came out later in January 1949.

[35] Science Citation Index, 1955 to 1964.

[36] Harvey Itano, William Bergren, and Phillip Sturgeon, "The Abnormal Human Hemoglobins," Medicine 35 (1956): 121-59, 124.

> Previous studies on the electrophoretic mobility of human hemoglobin have been mainly of a preliminary nature, and precise electrophoretic data on human hemoglobin are not available. A complete electrophoretic study on normal human hemoglobin would therefore be in itself a useful contribution. In relation to our problem it will yield a basis for comparison with sickle cell hemoglobin.[37]

Itano stated later that he initially tried electrophoresis because the apparatus was available and required small amounts of blood.[38] At the time, Caltech had a problem obtaining adequate samples of sickle cell anemia and trait blood. Pauling finally obtained a regular supply of sickle cell anemia blood in May 1949 from Dr. George Burch of Tulane University, which was used for the experiments discussed in "Sickle Cell Anemia, a Molecular Disease."[39] In addition, the Caltech group received patient blood samples from two physicians in Los Angeles.[40]

Electrophoresis uses electric currents to examine substances that have varying surface charges, and therefore is especially helpful in analyzing proteins. Protein samples in a buffer solution are run through the electrophoresis apparatus, which creates a moving boundary. Moving boundary electrophoresis indicates whether a protein has an overall positive or negative charge on its surface area. The rate of a moving boundary can be manipulated by changing the pH of the substance.[41]

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[37] Itano, "Research Report," 10.
[38] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, Itano's dissertation, 8.
[39] Pauling Collection, B: Individual Correspondence, George Burch 1940-1970, Letters between Pauling and Burch dated from 10 May 1949 to 25 May 1949.
[40] Information about who provided the blood for the experiments see footnote 1 in Pauling, Itano, Singer, and Wells, 543.
[41] Robert A. Alberty, "An Introduction to Electrophoresis Part I: Methods and Calculations," Journal of Chemical Education. 25 (1948): 426-33; George Gray, "Electrophoresis," Scientific American 185 (December 1951): 45-53.

Arne Tiselius of Uppsala, Sweden had developed the moving boundary technique in the 1920s and 1930s. However, the principle behind electrophoresis was developed in the early nineteenth century. Tiselius reported his improvements on the electrophoresis machine in 1937 and further improvements occurred in the next decade or so. For example, in 1939 L. G. Longsworth developed a recording system using peaks and valleys to depict the location of the moving boundary, so that the so-called Longsworth diagrams show the electrophoretic differences between two samples.[42]

Since moving boundary electrophoresis was a relatively new technique in 1948, only about fifty laboratories in the United States had electrophoresis machines.[43] Mass production of the apparatus began around 1950, so that prior to mid-century, laboratories built them. Pauling asked the Rockefeller Foundation in early 1941 for money for immunology research, including construction of an electrophoresis apparatus. Pauling wanted $7,500 to pay for supplies, animals, and equipment:

> [The $7,500] should permit also the construction of a Tiselius apparatus for the electrophoretic separation of antibody fractions by the suggested method of combination with charged haptens, and for other investigations.[44]

Pauling's request was most likely influenced by Landsteiner's infatuation with the device. Landsteiner, Pauling's mentor in immunology, analyzed blood sera with

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[42] Gray, "Electrophoresis," 47-49

[43] About number of electrophoresis machines in USA see Alberty, 45.

[44] Pauling collection, Science 14.031.9, Letter from Pauling to Weaver dated 2 Jan 1941 pages 5-6.

electrophoresis beginning in 1908.[45] When Landsteiner learned of Tiselius's improved apparatus in 1937 he had immediately used the technique as a standard procedure in his researches.[46]

Although Caltech received a substantially smaller amount of money than at first requested ($33,000 paid over three years[47]), they built a Tiselius electrophoresis apparatus nonetheless. Between 1943 and 1946, Stanley M. Swingle, a general chemistry instructor at Caltech, made improvements to the apparatus, and it was this machine that Pauling and his collaborators used in the research reported in their 1949 article.[48] Caltech's researchers must have been impressed by the capabilities of electrophoresis because in 1948 John G. Kirkwood built a new electrophoresis apparatus. According to George W. Gray, a scientific writer associated with the Rockefeller Institute, the new machine worked better than previous ones. Caltech also successfully used this new apparatus to separate proteins in the blood plasma.[49]

In mentioning the current status of electrophoretic hemoglobin research in his Research Report of 1948, Itano noted that it had been shown in 1897 that hemoglobin

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[45] Lily Kay, "Laboratory Technology and Biological Knowledge: The Tiselius Electrophoresis Apparatus, 1930-1945," History and Philosophy of the Life Sciences 10 (1988): 51-72, 58.
[46] Gray, "Electrophoresis," 47.
[47] Kay, Molecular Vision, 175-77.
[48] George G. Wright and Stanley M. Swingle, "The Construction of Tiselius Electrophoresis Cells," Science 97 (18 June 1943): 564; Stanley M. Swingle, "An Electrophoresis Apparatus Using Parabolic Mirrors," Review of Scientific Instruments 18 (February 1947):128-32. Pauling, Itano, Singer, and Wells, 544.
[49] Gray, "Pauling and Beadle," 19.

responds to electric analysis. [50] In 1944, three researchers from the chemistry department at University of Pittsburgh had tried electrophoresis on fetal and adult hemoglobin and successfully detected a difference between the two hemoglobin samples.[51] What Itano did not know was that Theodore Shedlovsky of the Rockefeller Institute tried to use electrophoresis to study the blood of sickle cell anemia patients in the early 1940s, analyzing sickle cell plasma (i.e. the liquid components of blood that transport the red blood cells) between 1940 and 1943. The tests yielded no significant results. Shedlovsky had written a manuscript, but never submitted it for publication, since the Second World War interrupted his experiments in early 1943.[52] When the experiments were brought to Pauling's attention years later, he responded that plasma would not yield the same electrophoresis results as observed when analyzing hemoglobin and its derivatives.[53]

In the summer of 1948, Itano began conducting electrophoresis experiments with help from Seymour Jonathon Singer. They detected a difference between sickle cell and normal adult hemoglobin.[54] Singer, like Itano, was a postdoctoral fellow in Caltech's chemistry department sponsored by the United States Public Health Service

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[50] Pauling Collection, I: Individual Correspondence, Harvey A. Itano. Itano, "Research Report," 10. Kay, "Laboratory Technology," 58.
[51] Feldman and Tauber, 646. Marie A. Andersch, Donald A. Wilson, and Maud L. Menten, "Sedimentation Constants and Electrophoretic Mobilities of Adult and Fetal Carbonylhemoglobin," Journal of Biological Chemistry 153 (1944): 301-05.
[52] Pauling Collection, B: Individual Correspondence, George Burch. Letter from Burch to Pauling dated 3 February 1970, attached are copies of a six letters between Burch and Shedlovsky dated from 14 January 1943 to 23 March 1943 discussing the progress of Shedlovsky's electrophoresis studies with sickle cell anemia plasma.
[53] Pauling Collection, B: Individual Correspondence, George Burch. Letter from Pauling to Burch dated 17 April 1970.
[54] Conley, 340.

when they conducted the electrophoresis experiments.[55] When he arrived at Caltech in 1947, Singer had worked in immunology and therefore knew more about the Tiselius machine and proteins than Itano. In fall 1947, Singer was enlisted to aid Itano with the electrophoresis apparatus, and Singer worked in Caltech's chemistry laboratory as a research assistant until 1951 at which time he went to Yale University to teach.[56]

When Itano and Singer first carried out the electrophoresis experiments, Pauling was in England. He spent from January to September of 1948 at Oxford on an Eastman Professorship and gave over sixty lectures on various topics, including hemoglobin. Hemoglobin was not his only concern during this time, and as has often been highlighted by historians, Pauling sketched out the primary configuration of proteins, later called the alpha-helix in this period. He also spent time developing a theory of metals.[57]

While in England, Pauling kept abreast of developments at Caltech through correspondence. In February, Dan Campbell informed Pauling that Itano's experiments with hemoglobin were producing interesting results and conveyed his confidence in Singer. "Singer is doing a good job and certainly has much more drive than Swingle."[58] Robert Corey, who oversaw the chemistry division in Pauling's absence, corresponded with Pauling primarily about the chemistry department's work

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[55] Pauling, Itano, Singer, Wells, 543.
[56] Hager, 333; Kalte and Nemeh, 773.
[57] Hager, 293; Pauling Collection, Science 14.032.6, Letter from Pauling to Weaver dated 27 May 1948 (see Chapter 1, footnote 22).
[58] Pauling Collection, C: Individual Correspondence, Dan Campbell 1939-1962. Letter from Campbell to Pauling dated 5 Mar 1948.

on proteins. When Pauling asked Corey to recommend a person to conduct about three years of intensive research on proteins, Corey chose Singer.[59] When Corey asked Singer if he was interested, Singer declined because he wanted to finish his current project on immunology.[60] In one letter Pauling relayed to Corey that he went to the Barcroft Memorial Conference on hemoglobin and got many ideas from it. However, he still had three more months before his return.[61]

In 1948, prior to any announcements about the sickle cell anemia studies, Pauling began associating structural chemistry and medical problems in his speeches and publications. Typically, he stressed the importance of studying the structure of organic molecules and used hemoglobin as an example, by focusing upon his own research. He discussed the structure of the hemes and magnetic properties of hemoglobin and also noted what was unknown by stating that although scientists were trying to ascertain the structure of proteins, they had not been successful yet. Then, he concluded by foreshadowing the potentialities of chemistry for medicine. However, Pauling did not use the term "molecular disease" at this time.[62]

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[59] Pauling Collection, C: Individual Correspondence, Robert Corey, Letters between Pauling and Corey dated from 3 February 1948 to 19 June 1948.
[60] Pauling Collection, S: Correspondence 1947-1952. Letter from Singer to Pauling dated 9 April 1948 and C: Individual Correspondence, Robert Corey, Letter from Corey to Pauling dated 13 April 1948.
[61] Pauling Collection, C: Individual Correspondence, Robert Corey, Letter from Pauling to Corey dated 19 June 1948.
[62] Pauling Collection, Publications 1948p.8, Linus Pauling, "The Interpretation of Some Chemical Properties of Hemoglobin in Terms of its Molecular Structure," Stanford Medical Bulletin 6 (February 1948): 215-22; Linus Pauling, "Nature of Forces between Large Molecules of Biological Interest," Nature 161 (8 May 1948): 707-09; Pauling Collection, Publications 1948p.13, Linus Pauling, "Molecular

> We may hope that in the course of time a more thorough understanding of the detailed molecular structure of hemoglobin and other complex substances will be obtained, which will be of aid in the further progress of medicine.[63]

> We may expect that as more precise information about the structure of these molecules is obtained in the future, a more penetrating understanding of biological reactions will develop, and that this understanding will lead to great progress in the fields of biology and medicine.[64]

Evidently, Pauling anticipated the impact of his upcoming publication with Itano, Singer, and Wells. In the years following the publication of their paper, Pauling continually connected studies on chemical structure to medicine and he specifically discussed sickle cell anemia.

In March 1949, Pauling and Itano announced the experimental results from comparing sickle cell anemia and normal hemoglobin with electrophoresis in a journal published by the American Society of Biological Chemists. Their method included a couple of tests analyzing carbonmonoxyhemoglobin and ferrohemoglobin of sickle cell anemia and normal adult hemoglobin. They treated the compounds with buffers and examined the samples at various levels of pH. With the help of Singer, Itano had subjected the samples to electrophoretic analysis by putting them through Caltech's Tiselius apparatus. They found that blood samples from sickle cell anemia patients and normal adults reacted differently in two ways. First, when they graphed the curves of mobility versus pH, the sickle cell hemoglobin curve followed the same

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Architecture and the Processes of Life," lecture, 28 May 1948 (Nottingham, England: Sir Jesse Boot Foundation, 1948): 1-13.

[63] Pauling, "Interpretation," 221.

[64] Pauling, "Nature of Forces," 709.

path as normal hemoglobin, but had a higher isoelectric point (the pH at which the solution will not migrate).

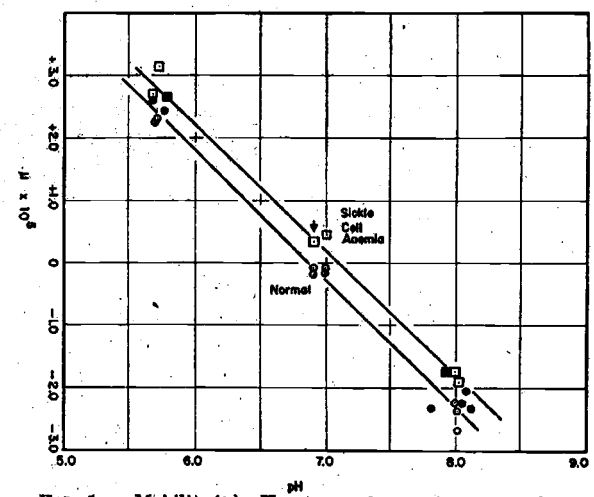


FIG. 1. Mobility(μ)-pH curves for carbonmonoxyhemoglobins in phosphate buffers of 0.1 ionic strength. The black circles and black squares denote the data for experiments performed with buffers containing dithionite ion. The open square designated by the arrow represents an average value of 10 experiments on the hemoglobin of different individuals with sickle cell anemia. The mobilities recorded in this graph are averages of the mobilities in the ascending and descending limbs.

Figure 2.1

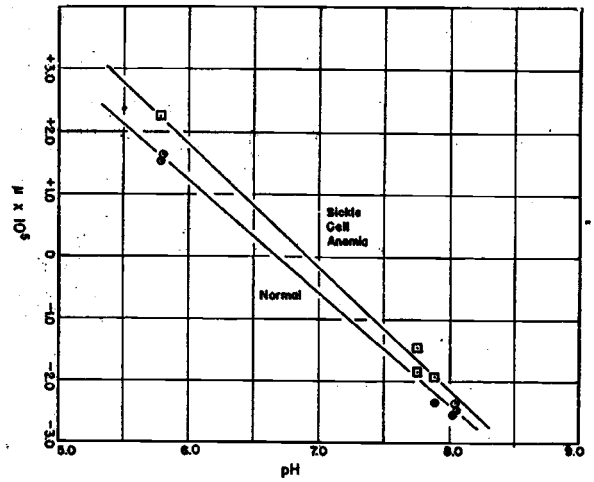


FIG. 2. Mobility(μ)-pH curves for ferrohemoglobins in phosphate buffers of 0.1 ionic strength containing dithionite ion. The mobilities recorded in the graph are averages of the mobilities in the ascending and descending limbs.

Figure 2.2[65]

[65] Figures 2.1 and 2.2 are from Pauling, Itano, Singer and Wells, 544.

Secondly, the two samples of carbonmonoxyhemoglobin at neutral pH acted differently in the electrophoresis machine. "At pH 7.0," they wrote, "sickle cell carbonmonoxyhemoglobin moves as a positive ion while normal carbonmonoxy-hemoglobin moves as a negative ion." Based on these findings, they concluded that the ionizable groups of the two hemoglobins differed. Furthermore, titration studies ascertained that the sickle cell hemoglobin had two to four more positive charges than normal adult hemoglobin.[66] Pauling later stated that Itano, Singer and Wells[67] performed the electrophoresis experiments.[68] In addition to this publication, Itano and Pauling presented the information at two conferences in April 1949. One was the annual meeting of the National Academy of Sciences, where Wells presented the information because Pauling was sick and could not attend.[69]

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[66] Harvey A. Itano and Linus Pauling, "Abstracts in Biochemistry: Difference in Electrophoretic Behavior of Sickle Cell Hemoglobin and Normal Human Hemoglobin," Federation Proceedings 8 (March 1949): 209.

[67] There is some dispute about whether Ibert C. Wells should have been listed as an author on the 1949 Science article. Anthony Serafini quoted Singer as saying, "I have no idea where Bert Wells might be, but his contribution was miniscule: I think it was wrong of Linus to put his name on as he did." In addition, Arthur Robinson, Pauling's partner in establishing the Linus Pauling Institute until they had a falling out in the late 1970s, stated that Pauling added Wells's name for devious reasons. Robinson averred that an article written by four authors was referred to by the first author's name (e.g. Pauling, et al.) whereas an article with three or fewer authors listed all authors in the bibliography. Serafini stated that Pauling wanted the discovery of molecular disease associated with his name; however, Serafini also noted that Pauling's contribution was paramount and he deserved to be the first author (134-36).

[68] Pauling, "Abnormality in Hemoglobin," 217.

[69] Pauling, Itano, Singer, and Wells, 548: "Based on a paper presented at the meeting of the National Academy of Sciences in Washington, D.C., in April, 1949, and at the meeting of the American Society of Biological Chemists in Detroit in April, 1949." Pauling Collection, Science 6.015.1, Copy of lecture given by Wells at the National Academy of Sciences meeting, 6 pages.

In November 1949 the paper "Sickle Cell Anemia, a Molecular Disease" appeared in Science with Pauling, Itano, Singer, and Wells listed as co-authors. They reported similar experimental methods and results to those mentioned above. In addition to comparing hemoglobin from healthy people and those with sickle cell anemia, they reported two other important tests. First, they established that healthy people of Caucasian and African descents have "indistinguishable" hemoglobin. Second, they analyzed blood taken from sickle cell trait patients. From Longsworth scanning diagrams, they found that the mobility of sickle cell trait hemoglobin acted similarly to the mixture they made by combining equal parts of sickle cell anemia and normal hemoglobin. However, the sickle cell trait hemoglobin obtained from individuals had more normal hemoglobin than the manufactured mixture of sickle cell and normal adult hemoglobin.

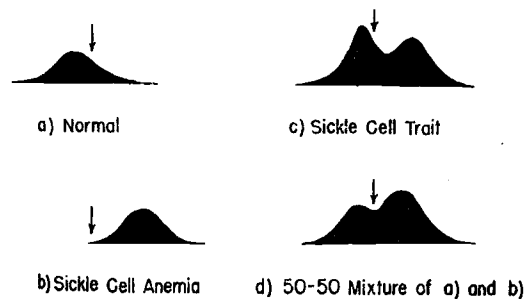


Figure 2.3[70]

[70] Longsworth scanning diagrams of carbonmonoxyhemoglobin. The arrow marks the central point on all diagrams. Note that normal hemoglobin (a) has a rise to the left of the arrow and sickle cell anemia hemoglobin (b) has a rise to the right of the arrow. Figure 2.3 is from Pauling, Itano, Singer and Wells, 545.

They performed additional experiments and ascertained that the ratio of normal to sickle cell hemoglobin in people with sicklemia is about sixty to forty.[71] Wells conducted the experiments that determined this ratio.[72]

At the end of "Sickle Cell Anemia, a Molecular Disease," they discussed three hypotheses based on their experimental results. First, the authors proposed an explanation for the observed differences between normal and sickle cell anemia hemoglobin. As mentioned in Pauling and Itano's previous announcement, the authors postulated that sickle cell anemia hemoglobin has two to four more positive charges than normal hemoglobin. In their attempts to find out more about the difference in charge, they ascertained that the globins are different and the hemes are identical in the two substances.[73] Wells also performed the tests showing that the hemes are identical.[74]

Next, they suggested a theory describing the sickling process. Assuming that the globins differed from one another, sickling happened because a region in the globin of sickle cell anemia hemoglobin had a different surface area (than normal hemoglobin), which complemented another region of the hemoglobin molecule. Thus, they associated the process of sickling with Pauling's theory of complementariness in immunology. In addition, they postulated that the difference in the globin probably occurred near where the iron attached, which explained why the hemoglobin distorted

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[71] Pauling, Itano, Singer, and Wells, 544-46.
[72] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, Itano's dissertation, 24.
[73] Pauling, Itano, Singer and Wells, 543-48.
[74] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, Itano's dissertation, 18; Conley, 340.

into a crescent shape when deoxygenated. In other words, the presence of oxygen attached to the heme obstructed the macromolecule from binding with itself.

> We can picture the mechanism of the sickling process in the following way. It is likely that it is the globins rather than the hemes of the two hemoglobins that are different. Let us propose that there is a surface region on the globin of the sickle cell anemia, hemoglobin molecule which is absent in the normal molecule and which has a configuration complementary to a different region of the surface of the hemoglobin molecule. This situation would be somewhat analogous to that which very probably exists in antigen-antibody reactions. The fact that sickling occurs only when the partial pressures of oxygen and carbon monoxide are low suggests that one of these sites is very near to the iron atom of one or more of the hemes, and that when the iron atom is combined with either one of these gases, the complementariness of the two structures is considerably diminished. Under the appropriate conditions, then, the sickle cell anemia hemoglobin molecules might be capable of interacting with one another at these sties sufficiently to cause at least a partial alignment of the molecules within the cell, resulting in the erythrocyte's becoming birefringent, and the cell membrane's being distorted to accommodate the now relatively rigid structure within its confines. The addition of oxygen or carbon monoxide to the cell might reverse these effects by disrupting some of the weak bonds between the hemoglobin molecules in favor of the bonds formed between gas molecules and iron atoms of the hemes.[75]

About sicklemia hemoglobin cells, they stated that each cell has normal and sickle cell anemia hemoglobin. Thus, sicklemia cells undergo distortion at a lower oxygen pressure than sickle cell anemia cells. Lastly, they noted that their experiments supported the hypothesis that the sickled cells caused illness. Moreover, their experiments proved that abnormal hemoglobin causes the disease.

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[75] Pauling, Itano, Singer and Wells, 546. Pauling quoted this long passage in subsequent articles including: Linus Pauling, "The Hemoglobin Molecule in Health and Disease, Proceedings of the American Philosophical Society 96 (1952): 556-65, 563; Pauling, "Abnormality of Hemoglobin," 222.

In the couple of years after this article appeared, Pauling liked to quote the above passage, and he also expanded his theory about the alignment of sickle cell hemoglobin molecules. Thus, by 1951 Pauling averred that the complementary structure of sickle cell anemia hemoglobin allowed the molecules to attach to one another forming long rods. The rods then bound to other rods, thus creating a liquid crystal. Pauling cited the 1950 work performed by John W. Harris of the Boston City Hospital, who experimentally demonstrated that liquid crystals form.[76]

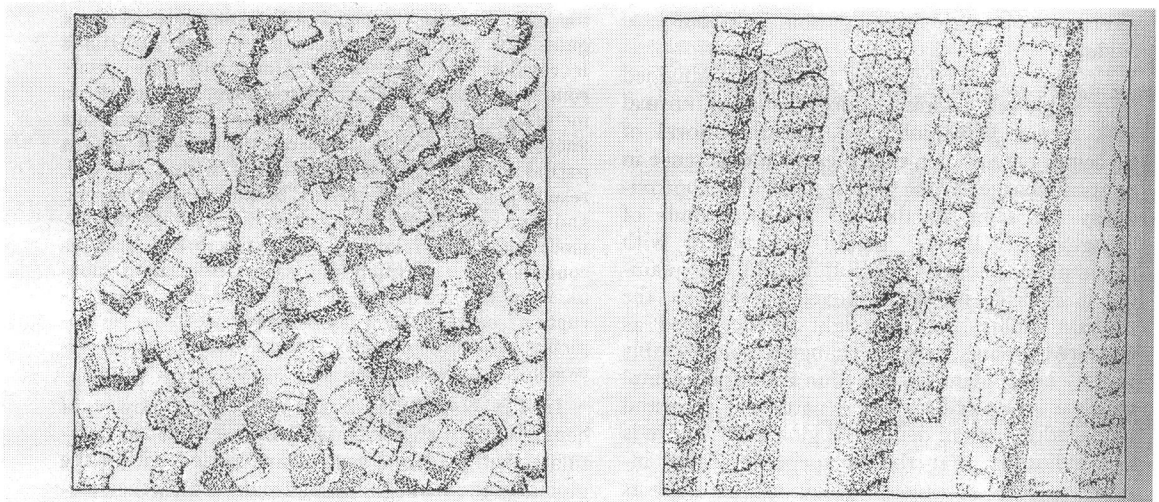

FIG. 5. At the left, molecules of normal hemoglobin or of oxygenated sickle-cell-anemia hemoglobin are shown, with random orientations, and at about the average distance apart characteristic of red-cell contents. At the right long strings of molecules of deoxygenated sickle-cell-anemia hemoglobin are shown, assuming the parallel orientation characteristic of the nematic liquid crystals that presumably form within the red cells in the venous blood of patients with sickle-cell anemia, and twist the red cells into the abnormal shape characteristic of the disease.

Figure 2.4[77]

The final section of the 1949 paper discussed genetics. The authors stated that people suffering from sickle cell anemia were homozygous, whereas people with sicklemia were heterozygous. More specifically, two normal alleles synthesized only normal hemoglobin. Two sickle cell alleles made only sickle cell anemia hemoglobin.

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[76] Pauling, "Hemoglobin Molecule," 556-65; Gray, "Sickle Cell Anemia," 58.
[77] Figure 2.4 is from Pauling, "Hemoglobin Molecule," 564.

Sicklemics with one normal and one sickle cell allele had a ratio of sixty percent normal hemoglobin and forty percent sickling hemoglobin. They also proposed possible explanations for why sicklemics had more normal hemoglobin. Ultimately, the hypotheses stated that most likely normal hemoglobin synthesized more successfully than abnormal hemoglobin; therefore, more normal hemoglobin would be produced. The question was at which point the normal hemoglobin monopolized the process.[78]

In their discussion on genetics, the authors mentioned that James V. Neel of the Heredity Clinic at University of Michigan had published a paper earlier that year and proposed the same genetic conclusion. Neel had stated that sickle cell trait is a heterozygous condition and sickle cell anemia is homozygous and tested his theory by analyzing the blood of parents and their children. He hypothesized that if a child has sickle cell anemia, then both parents will have blood that sickles. On one series of experiments, Neel tested both parents of thirteen children with sickle cell anemia and found that all of the parents had sickling blood, which proved his theory correct. Science published Neel's paper in July 1949, four months before the Pauling, et al. paper.[79] However, Pauling and his collaborators wanted it to be on the record that they reached the same conclusion independently of Neel.[80]

E. A. Beet, a Medical Officer for the Colonial Medical Service, also reached the same genetic conclusion as Pauling, et al. and Neel and published his findings in

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[78] Pauling, Itano, Singer and Wells, 547-48.
[79] James V. Neel, "The Inheritance of Sickle Cell Anemia," Science 110 (15 July 1949): 64-66.
[80] Pauling, Itano, Singer and Wells, 547.

the Annals of Eugenics prior to them, in June 1949. Beet had studied the Bantu tribe of Northern Rhodesia. Primarily, Beet wanted to show that there was a difference between sickle cell anemia and sickle cell trait in an effort to prove that sickle cell anemia occurs less frequently than the trait. Like Neel, Beet tested the blood of family members and drew conclusions based upon the results. He too stated that sicklemia was heterozygous.[81] In his Harvey Lectures during 1953 to 1954, Pauling mentioned Beet's work and reiterated that the Caltech collaborators reached their genetic conclusion prior to the publication of Beet's article.[82]

In the title of their 1949 paper, Pauling and his colleagues called sickle cell anemia a molecular disease because the sickled cells caused the pathology: "...if it [the mechanism for the sickling process] is correct, it supplies a direct link between the existence of 'defective' hemoglobin molecules and the pathological consequences of sickle cell disease."[83] During the years following the paper, Pauling often defined molecular disease and incorporated sickle cell anemia into his discussions, which focused on molecular disease, hemoglobin, nuclear fallout, and evolutionary theories. He considered the coining of a clear definition of molecular disease to be an important, original contribution to understanding the relationship between molecules and disease. Pauling usually included two points in his definition. First, structure influences function, for example an abnormal protein with a different structure from

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[81] E.A. Beet, "The Genetics of Sickle-Cell Trait in a Bantu Tribe," Annals of Eugenics 14 (June 1949): 279-84. This journal changed its name to Annals of Human Genetics in July 1954.
[82] Pauling, "Abnormality of Hemoglobin," 219.
[83] Pauling, Itano, Singer, and Wells, 547. The authors do not cite a prior use of the term molecular disease.

the normal protein causes molecular disease. Secondly, molecular diseases are genetic because the abnormality results from the synthesis of altered proteins as guided by inherited genes. By way of an example, Pauling gave the following general definition of molecular disease in a talk about mental and physical diseases.

> The manufacture of abnormal molecules...is determined by the genetic constitution of the patient; the disease is inherited. A disease of this sort, caused by molecules of abnormal structure present in the patient in place of the molecules of normal structure that are present in normal human beings, is called a molecular disease.[84]

However, Pauling sometimes tailored his definition to the topic at hand, whether that topic was hemoglobin, enzymes, or other proteins. For instance, in a speech at Massachusetts General Hospital on 9 October 1958, Pauling focused his explanation on sickle cell anemia.

> Since there are hundreds of thousands of species of animals, it is probable that there are hundreds of thousands of different kinds of hemoglobin. They differ from one another in their structure, but are similar enough in their properties to justify using the same word, hemoglobin, in speaking of them...in 1949, it was discovered that patients with the disease sickle-cell anemia manufacture a kind of hemoglobin that is different from that manufactured by other human beings. It became clear that it is the manufacture of this abnormal sort of hemoglobin that causes the patients to have the disease sickle-cell anemia, and the disease was described as a molecular disease...the studies of hemoglobin soon led to verification of the idea that sickle-cell anemia is a recessive hereditary disease.[85]

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[84] Linus Pauling, "The Molecular Basis of Genetics," American Journal of Psychiatry 113 (1956): 492-95, 492.

[85] Linus Pauling, "Molecular Structure and Disease," Disease and the Advancement of Basic Science ed. Henry K. Beecher (Cambridge, Massachusetts: Harvard University Press, 1960): 1-7, 2-3.

As a third example, in his 1971 foreword to Molecular Aspects of Sickle Cell Hemoglobin, Pauling noted the originality of the term molecular disease, but also stated that the notion was not novel.

> I think that this may have been the first time that the expression "molecular disease" was used, although of course genetic diseases, inborn errors of metabolism, had been recognized for fifty years, and many scientists would have stated in 1949 that genes were probably molecules, and that genetic disease might be described as molecular diseases.[86]

In addition to defining molecular disease, Pauling liked to quantify information by using statistics to accentuate his point. In this context, Pauling made statements such as the following: Each individual inherits approximately 100,000 molecules of deoxyribonucleic acid; of these 100,000 molecules each parent contributes 50,000.[87] For the most part only people of African descent suffer from sickle cell anemia,[88] and the disease afflicts one in 400 African-Americans.[89] Among African-Americans one in twenty carries sickle cell hemoglobin, and thus roughly ten percent are sickle cell heterozygotes (i.e. sickle cell trait carriers).[90]

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[86] Linus Pauling, foreword, Molecular Aspects of Sickle Cell Hemoglobin: Clinical Applications, ed. Robert M. Nalbandian (Springfield, Illinois: Charles C. Thomas Publisher, 1971): vii-x, vii.

[87] Pauling, "Molecular Disease and Evolution," 1; Linus Pauling, "Molecular Basis of Genetic Defects," Congenital Defects (Philadelphia: J.B. Lippincott, 1963): 15-21, 18.

[88] Linus Pauling, address, Montecito Workshop, Aug 1949, "The Place of Chemistry in the Integration of the Sciences," Main Currents in Modern Thought 7.4 (1950): 108-11, 110.

[89] Linus Pauling, "Structural Chemistry in Relation to Biology and Medicine," Baskerville Chemical Journal 1 (1950): 4-7, 6.

[90] Pauling, "Molecular Structure and Disease," 4. Pauling gave a combination of the above statistics in Linus Pauling, "Our Hope for the Future," Birth Defects, ed. Morris Fishbein (Philadelphia: J.B. Lippincott Company, 1963): 164-70, 169 and

Pauling wasted no time circulating the sickle cell anemia information that he and his co-workers found. In September, about three months before the Science article was published, The Detroit Times conveyed Pauling's sentiments about Caltech's research in an article titled "Discovery of Blood Disease Called Key to Cancer Cure." Reporter Ray Guiles recounted Pauling's optimistic statements and the fact that Pauling and his colleagues detected a molecular disease, which, Guiles reported, was the first to be called such. Pauling, who was delivering a speech at the Detroit Institute for Cancer, had stated that knowledge about molecular diseases might aid cancer research, especially leukemia (a cancer of the blood). Pauling summarized what was known and unknown and how more information on the structural chemistry of diseases might revolutionize medicine.

> We know the abnormal hemoglobin molecule has a positive charge three units greater than in the normal hemoglobin molecule. We still don't know if this means three negative groups are missing, or that there are three extra positive groups. This development, if carried to its logical conclusion, means our structural chemistry and understanding of molecules is getting to the point where it should be of assistance in converting medicine into a real science.[91]

In commenting upon the history of therapeutics, Pauling stated that most antibiotics (like penicillin and streptomycin) were discovered "accidentally," and that researchers did not understand how certain substances fought illnesses. Medical practice had been haphazard in promoting the potential benefits of physical and

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Linus Pauling, "Factors Affecting the Structure of Hemoglobins and Other Proteins," Symposium on Protein Structure, ed. Albert Neuberger (London: Methuen & Co Ltd., 1958): 17-22, 17.

[91] Pauling Collection, Newspaper Clippings 1949n.18, Ray Guiles, "Discovery of Blood Disease Called Key to Cancer Research," The Detroit Times (13 September 1949).

structural chemistry to medicine, according to Pauling. He hoped that the future could be different.[92] Reporter Robert S. McGowan wrote the following after Pauling spoke in February 1950 at University of New Brunswick about "The Place of Chemistry in Medical Research."

> Pauling and Itano now feel that they understand how the defective protein affects the body, and they can predict the properties of a drug which should according to their theories, be a treatment for the disease. They hope to find such a drug, and if it is successful this will be the first time in history that a treatment was logically devised on the basis of fundamental knowledge. [93]

In late 1951 Pauling and Itano enlisted the help of Burch, the physician who supplied Caltech with sickle cell blood samples, to perform clinical trials. Pauling and Itano thought that the sickling process could be obstructed and suggested treating sickle cell anemia patients with carbon monoxide and sodium nitrate therapies.[94] Burch agreed to conduct the clinical trials and immediately submitted a proposal for a Guggenheim Fellowship, which he received.[95] Itano wrote a brief protocol for the clinical trial in early 1952.[96] After many delays, Dr. John C. Paterson started the trials in early 1953 by following the procedures developed by Pauling and Itano. Thus,

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[92] Pauling Collection, Newspaper Clippings 1949n.19, Linus Pauling, "Stellar Role of Physical Chemist Cited," Chicago Journal (19 September 1949); Linus Pauling, "Structural Chemistry," 4-7. Pauling delivered this speech in New York on 7 December 1949.
[93] Robert S. McGowan, "Prospect of Early Advance in Medical Science Given," The Daily Gleaner 8 (February 1950).
[94] Pauling Collection, B: Individual Correspondence, George Burch, Letter from Pauling to Burch dated 5 October 1951.
[95] Pauling Collection, B: Individual Correspondence, George Burch, Two letters from Burch to Pauling dated 9 October 1951 and 6 December 1951.
[96] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, "Notes on a Proposed Therapeutic Program for Sickle Cell Anemia," 21 January 1952.

Paterson administered sodium nitrate intravenously and orally in varying doses. The methods proved unsuccessful because the patients' hemoglobin could not be converted safely without causing toxicity and anoxia. While visiting Tulane, Itano suggested to Paterson that they should try blood transfusions and other treatments since the previous methods did not work. Paterson noted that five of the ten patients who received transfusions had side effects. By 1954 they stopped the trials because satisfactory results were not produced.[97] Itano did not publish the negative findings and a few years later, Dr. Ernest Beutler tried a similar clinical trial using sodium nitrate to treat sickle cell anemia. Beutler, a physician at City of Hope Medical Center in Duarte, California also found that sodium nitrate was too toxic to justify its use.[98]

By April 1950, Caltech researchers had conducted subsequent experiments in an effort to ascertain the difference between sickle cell anemia and normal hemoglobin, which were announced at the annual meeting of the National Academy of Sciences.[99] Wells and Itano tried to determine the ratio of sickle cell anemia and

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[97] Pauling Collection, B: Individual Correspondence, George Burch, Letter from Burch to Pauling dated 5 August 1954 with Paterson's report enclosed. John Paterson, "Report on the work done in a study of the therapeutic management of sickle cell anaemia. The feasibility of rendering cells less susceptible to sickling by converting a proportion of the haemoglobin to methaemoglobin was studied" (no date): 13 pages.
[98] Pauling Collections, I: Individual Correspondence, Harvey A. Itano, Letters from Itano to Pauling dated 18 April 1960 and 1 April 1961. Letter from Itano to Beutler dated 18 April 1960. Itano wrote to Beutler and Pauling because Beutler had read Itano's thesis and the suggestion that sodium nitrate might treat patients with sickle cell anemia; however, Beutler did not acknowledge Itano. Ernest Beutler, "The Effect of In Vivo Modification of Sickle Cell Disease," Clinical Research 8 (1960): 101.
[99] Linus Pauling, Harvey A. Itano, Ibert C. Wells, Walter A. Schroeder, Lois M. Kay, S. J. Singer and R. B. Corey, "Abstracts of Papers Presented at the Annual Meeting of the National Academy of Science: Sickle Cell Anemia Hemoglobin," Science 111 (1950): 459.

normal hemoglobin in sicklemics. Using electrophoresis, they now concluded that the amount of sickle cell hemoglobin in people with sickle cell trait ranged from twenty-four to forty-five percent. (Pauling, Itano, Singer and Wells had estimated in 1949 that sicklemics have forty percent sickle cell anemia hemoglobin.) In addition, they analyzed whether the personal differences depended on any of the following factors: effect of time (i.e. Does an individual's ratio change over time or remain relatively constant?), sex, age, environment, diet, and heredity. Of all the factors they tested, Wells and Itano decided that only heredity might explain the range.[100]

Later, Wells and Itano collaborated with Neel in expanding their prior conclusions by comparing the blood from people with sickle cell trait within a family and between families. They found that the ratio of sickle cell anemia hemoglobin to normal hemoglobin within a family remained relatively stable. However, when they compared the average ratio of one family to another, the values differed significantly. Again, they analyzed whether sex, age, environment or heredity affected the ratio of sickle cell anemia and normal hemoglobin within sicklemics. Based on the variations between families, they ascertained that only heredity made a difference. Furthermore, they proposed that a person's genes might dictate the ratio of sickle cell anemia and normal hemoglobin synthesized within an individual.[101]

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[100] Ibert C. Wells and Harvey Itano, "Ratio of Sickle Cell Anemia Hemoglobin to Normal Hemoglobin in Sicklemics," Journal of Biological Chemistry 188 (January 1951): 65-74.

[101] James V. Neel, Ibert C. Wells and Harvey A. Itano, "Familial Differences in the Proportion of Abnormal Hemoglobin present in Sickle Cell Trait," Journal of Clinical Investigation 30 (October 1951): 1120-124. Neel worked at the University of Michigan while Wells and Itano were at Caltech.

Wells and two other researchers from the Caltech chemistry department, Walter A. Schroeder and Lois M. Kay, examined the amino acid sequences of sickle cell anemia and normal hemoglobin. Schroeder, Kay and Wells could not find a difference between the number of acidic and basic amino acids. However, they stated that certain amino acids might be present in different quantities. Specifically, "hemoglobin from sickle-cell anemics probably contains slightly less leucine and more serine and possibly less valine and more threonine." In addition, they noted that a variation in these amino acids would not affect electrophoretic mobility. Finally, they postulated that the electrophoretic disparity might be due to the folding of the polypeptide chain.[102] Thus, they proposed an explanation for sickle cell anemia similar to Pauling's theory for the folding of antibodies, as discussed in Chapter One.

To reiterate, Pauling had stated in 1940 that antibodies have the same amino acid sequences, but fold in different ways in response to the antigen. However, in a letter to Burch in March 1950, Pauling stated: "This difference [of leucine, serine, valine, and threonine] would not contribute directly to the difference in charge, and I myself do not feel absolutely sure that it exists."[103] In addition, Pauling noted that these amino acid sequence experiments might not be conclusive. "A difference of one

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[102] W.A. Schroeder, Lois M. Kay, and Ibert C. Wells, "Amino Acid Composition of Hemoglobins of Normal Negroes and Sickle-Cell Anemics," Journal of Biological Chemistry 187 (1950): 221-40. For a discussion about the folding proposal for sickle cell anemia, see Strasser, "Sickle Cell Anemia and the Origins of Molecular Biology," 130. Strasser does not discuss the connection to immunology.

[103] Pauling Collection, B: Individual Correspondence, George Burch, Letter from Pauling to Burch dated 10 March 1950.

or two residues of one or another amino acid might be permitted by the analyses, but no difference is required by them."[104]

In January 1950, Pauling wrote an interoffice memorandum to Itano in which he speculated that the possible cause for the observed electrophoretic difference between normal and sickle cell hemoglobin might depend on how the polypeptide folded unto itself. This is the same claim that Schroeder, Kay and Wells made later that year. Pauling stated:

> I think that sickle cell hemoglobin and normal hemoglobin represent two ways of coiling the polypeptide chain characteristic of hemoglobin molecule, and that these two ways are rather stable, being the two stable configurations of the molecule. That is, of course, the globin molecule.

In his memo, Pauling asked Itano to find an article written by Nils Gralén[105] about the two different isoelectric points for denatured and re-natured hemoglobin, by way of comparison to the difference in isoelectric points for sickle cell and normal hemoglobin. Pauling wished to repeat Gralén's experiment and confirm Pauling's theory that polypeptide folding affects the electrophoresis results. Gralén had used electrophoresis on horse hemoglobin and its derivatives and found that the isoelectric points for re-natured hemoglobin samples differ by 0.2 pH from native samples. One had the same isoelectric point as native hemoglobin; the other two were more acidic. (Pauling, et al. found that the isoelectric points of normal and sickle cell anemia carbonmonoxyhemoglobin differed by 0.22 pH.) Pauling proposed that Itano try

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[104] Linus Pauling, "Hemoglobin Molecule," 562.
[105] Nils Gralén, "The Splitting of Haemoglobin by Acids," Biochemical Journal, 33 (1939): 1907-912.

converting sickle cell anemia hemoglobin into normal hemoglobin (and vice versa) by gently heating both samples for several days at a temperature below that which would cause denaturation.[106]

Pauling occasionally incorporated the results of Schroeder, Kay and Wells into his speeches and scientific work in the early 1950s.[107] For example, in 1951 Pauling stated that the "obvious" theory explaining why sickle cell hemoglobin converted into a crescent shape was a difference in amino acid composition; however, the experiment by Schroeder and his colleagues showed no apparent discrepancy in amino acid sequencing. Pauling, then, stated that the experiment by Schroeder, Kay and Wells did not conclusively prove that the amino acid sequences in normal and abnormal hemoglobin were the same or different. In the case that the two hemoglobins have the same amino acid sequences, Pauling noted the folding hypothesis presented by Schroeder, Kay and Wells and proposed that a gene within humans might dictate the way the polypeptide chains fold. The number and amino acid sequencing of end groups was another factor studied in hopes of determining whether the amino acid sequences of normal and sickle cell hemoglobin were the same or different. At this time the number of end groups was thought to be either five or six, and valine had been found on all of them for both normal and sickle cell

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[106] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, Interoffice Memorandum, "Nature of Sickle Cell Hemoglobin," from Pauling to Itano dated 20 January 1950. There is no information on whether Itano actually performed the experiment.

[107] Pauling, "Abnormality of Hemoglobin," 221; Pauling, "Nature of Forces," 220.

hemoglobin. Pauling revisited this subject a few years later and published two papers in 1957 with Herbert S. Rhinesmith and Schroeder, which will be discussed below.[108]

Ultimately, Pauling stated that normal and sickle cell hemoglobin have a definite difference in their molecular structure, which causes molecular disease. Even as more evidence supported the folding hypothesis, Pauling did not give up on the possibility that the difference between normal and sickle cell anemia was a difference in amino acid sequences, which triggers different ways of folding. In 1955 Pauling suggested to Makio Murayama that he conduct experiments in order to ascertain whether abnormal hemoglobins are the result of "errors in polypeptide-chain synthesis by the normal gene."[109] Thus:

> Havinga and Itano reported...that there are two ways of folding the polypeptide chains, one characteristic of normal hemoglobin and the other of sickle-cell hemoglobin. It is possible, of course, that even a change in a couple of amino acid residues could effect a change in the way of folding the chains in one part of the molecule.[110]

Egbert Havinga and Itano found that the denatured hemoglobin samples do not completely unfold and are capable of refolding into their native configurations. They suggested that, if Schroeder, Kay and Wells' proposal was correct (that normal adult hemoglobin and sickle cell hemoglobin have identical polypeptide chains, which fold

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[108] Pauling, "Hemoglobin Molecule," 562-63.
[109] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, "Proposed Research on Human Hemoglobin," Inter-office Memorandum from Pauling to Makio Murayama dated 18 August 1955.
[110] Pauling, "Factors Affecting Structure," 18. (1958)

differently), then the partial unfolding as observed by Havinga and Itano explains how hemoglobin refolds into its native structure.[111]

Pauling remained dissatisfied with the polypeptide folding hypothesis noting in August 1957 that his work with Max Delbrück in 1940 had proposed a two-step replication process, which used a template to produce a complementary molecule. Pauling noted that recent genetic work on nucleic acids by James Watson and Francis Crick showed that amino acid sequencing dictated folding. He referred to this as the template theory, which he thought correct, although unproven. M. L. Anson and Mirsky had shown, too, that a denatured polypeptide chain refolded into its native configuration, with the amino acid sequence dictating how the polypeptide chain folded.[112]

In the same week that Pauling was presenting this August 1957 talk, Nature published an article by Vernon M. Ingram, a protein chemist at the Cavendish Laboratory in Cambridge. Ingram conclusively showed that normal and sickle cell hemoglobin differ by one amino acid.[113] In October 1956, Ingram had developed fingerprinting, a technique that maps on paper the various amino acids in a protein

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[111] E. Havinga and Harvey A. Itano. "Electrophoretic Studies of Globins Prepared from Normal Adult and Sickle Cell Hemoglobins," Proceedings of the National Academy of Sciences of the United States of America 39 (1953): 65-67.

[112] Linus Pauling, "The Nature of the Forces Operating in the Process of the Duplication of Molecules in Living Organisms," The Origin of Life on Earth, eds. F. Clark and R.L.M. Synge (New York: Pergamon Press, 1959): 215-23 219-20.

[113] Vernon Ingram, "Gene Mutations in Human Haemoglobin: The Chemical Difference between Normal and Sickle Cell Haemobglobins," Nature 180 (18 August 1957): 326-8. For information about Ingram and his interest in sickle cell anemia see: Daniel J. Kevles, In the Name of Eugenics: Genetics and the Uses of Human Heredity (New York: Alfred A. Knopf, 1985): 235-37.

sample, and he had published an explanation of the method and results from the comparison of sickle cell and normal hemoglobin. Fingerprinting, a two-step process, utilizes paper electrophoresis and paper chromatography. It produces splotches on paper at various locations; each mark corresponds to a peptide (two or more linked amino acids). By comparing the fingerprints of sickle cell and normal hemoglobin, Ingram found that one spot differed between the two fingerprints and concluded that normal and sickle cell hemoglobin have a small difference in their amino acid sequences.[114]

Less than one year later, Ingram followed up his initial paper on fingerprinting with the article that explained the exact difference between normal and sickle cell hemoglobin. Accordingly, he stated that normal hemoglobin has a glutamic acid in the fourth peptide chain whereas sickle cell hemoglobin has a valine at the same location.[115] Ingram also acknowledged the importance of Pauling and his colleagues' 1949 paper in Science.

> We owe to Pauling and his collaborators the realization that sickle cell anaemia is an example of an inherited 'molecular disease' and that it is due to an alteration in the structure of a large protein molecule, an alteration leading to a protein which is by all criteria still a haemoglobin. It is now clear that, per half-molecule of haemoglobin, this change consists in a replacement of only one of nearly 300 amino-acids, namely, glutamic acid, by another valine-a very small change indeed.[116]

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[114] Vernon Ingram, "A Specific Chemical Difference between the Globins of Normal Human and Sickle-Cell Anaemia Haemoglobin," Nature 178 (13 October 1956): 792-94.
[115] Ingram, "Gene Mutations," 326-28.
[116] Ingram, "Gene Mutations," 327.

Pauling immediately incorporated Ingram's results into his speeches to convey the view that only a small genetic change causes molecular diseases. For example, Pauling pointed out the minuteness of the difference through statements such as, "As to the degree of abnormality in sickle cell hemoglobin, it is astonishing how small it is,"[117] and

> ...the amount of abnormality of the mutated gene is small, in a molecular sense. For example, we may say that the gene defect that is responsible for sickle cell anemia amounts to an abnormality of less than 1 per cent of the DNA molecule.[118]

In 1958 and afterwards, Pauling stated that only two amino acid residues in 600 differ. The reason for using different quantities than Ingram's one in 300 was that the replacement of glutamic acid in normal hemoglobin with valine in sickle cell hemoglobin occurs in two of the four polypeptide chains in human hemoglobin. When stating that there were two amino acid differences in 600, Pauling also mentioned work completed at Caltech by himself and two colleagues.[119] In 1957 Pauling, Rhinesmith and Schroeder announced that normal adult hemoglobin has four polypeptide chains of two different types, which they called alpha and beta. Rhinesmith was a research associate at Caltech from 1955 to 1957.[120]

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[117] Pauling, "Current Opinion," 235.
[118] Pauling, "Our Hope," 167.
[119] Pauling, "Molecular Structure in Relation to Biology and Medicine," 6-7; Pauling, "Molecular Structure and Disease," 4.
[120] Herbert S. Rhinesmith, W.A. Schroeder, and Linus Pauling, "A Quantitative Study of the Hydrolysis of Human Dinitorphenyl (DNP) globin: The Number and Kind of Polypeptide Chains in Normal Adult Human Hemoglobin," Journal of the American Chemical Society 79 (1957): 4682-686.

After 1957, when Ingram announced that one amino acid differs in normal and sickle cell hemoglobins and Rhinesmith, Schroeder, and Pauling determined that hemoglobin has two types of polypeptide chains, many researchers tried to ascertain where the amino acid substitution occurred on the polypeptide chain. In 1958 Itano and Singer were unable to state the exact location of the replacement, but narrowed down the possibilities. For example, they concluded that the replacement had to occur within five Angstroms from the dyad axis (where the hemes are bound together) in order to be on the surface of the molecule and support the explanation of how sickle cell hemoglobin contorts into a crescent shape as described by Pauling, et al in "Sickle Cell Anemia, a Molecular Disease." In addition, they stated that if only one amino acid replacement occurs, then only one of the two types of polypeptide chains (either the alpha or the beta) differs between normal and sickle cell hemoglobin.[121]

In 1959 two experiments showed that the replacement of glutamic acid with valine occurs on the beta-chains.[122] Jerome R. Vinograd, W.D. Hutchinson, and Schroeder of Caltech showed that the beta-chains of sickle cell and normal hemoglobin differ, whereas their alpha-chains are identical.[123] Ingram also

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[121] Harvey A. Itano and S. J. Singer, "On Dissociation and Recombination of Human Adult Hemoglobins A, S, and C," Proceedings of the National Academy of Sciences of the United States of America 44 (1958): 522-29.
[122] Pauling, "Molecular Structure and Disease," 4.
[123] Linus Pauling, "Molecular Structure in Relation to Biology and Medicine," Ciba Foundation Tenth Anniversary Symposium on Significant Trends in Medical Research, eds. G.E.W. Wolstenholme, Cecilia M. O'Connor, Maeve O'Connor (Boston, Massachusetts: Little, Brown, and Company, 1959): 3-10, 7.

demonstrated that the difference occurs in the beta-chains and, in addition, stated that the substitution occurs at the sixth position from the N-terminus.[124]

Itano and Singer continued to research abnormal hemoglobins. From the mid-1950s to the early 1960s, they focused on genetic aspects, especially the synthesis of polypeptide chains in normal and abnormal hemoglobin. At this time, researchers pinpointed how the amino acid sequences of other hemoglobins differ. For example, J.A. Hunt and Ingram discovered that the amino acid sequence of Hemoglobin C differs from sickle cell hemoglobin and normal hemoglobin at the same site on the beta-chain; thus, Hemoglobin C has lysine in the same location that sickle cell hemoglobin has valine and normal hemoglobin has glutamic acid.[125] Soon thereafter, Murayama and Ingram found that Hemoglobin I differs from normal hemoglobin on the alpha-chain.[126] Itano tried to understand how genes control the synthesis of the amino acid sequences in hemoglobin. In the mid-1950s, he stated that an individual can synthesize blood of one or two types only because an individual has a pair of genes controlling the synthesis of hemoglobin.[127] After information about the alpha

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[124] Pauling, "Molecular Structure in Relation to Biology and Medicine," 7; Pauling, "Molecular Disease and Evolution," 6; Pauling, "Molecular Basis of Genetic Defects," 17.

[125] J.A. Hunt and V.M. Ingram, "Allelomorphism and the Chemical Differences of the Human Haemoglobins A, S and C," Nature 181 (1958): 1062-063.

[126] J.A. Hunt and V.M. Ingram, "The Genetical Control of Protein Structure: The Abnormal Human Haemoglobins," Ciba Foundation Symposium on Biochemistry of Human Genetics, eds. G.E.W. Wolstenholme and Cecilia M. O'Connor (Boston: Little, Brown and Company, 1959): 114-27, 119.

[127] Harvey A. Itano, "Specificity in the Interaction of Sickle Cell Hemoglobin Molecules," Molecular Structure and Biological Specificity, eds. Linus Pauling and Harvey A. Itano. (Washington D.C.: American Institute of Biological Sciences, 1957): 166-73.

and beta chains became known, Itano researched the two hemoglobin chains individually. Thus, Singer and Itano conducted experiments using normal and sickle cell hemoglobin, which showed that upon dissociation two non-identical molecules are formed; in other words the alpha and beta chains remain connected to their identical partners (alpha to alpha and beta to beta). Also, they found that each chain had one heme attached to it. In the end, they proposed that the synthesis of alpha and beta chains was controlled by different genetic loci; however, they noted there were difficulties with this proposal.[128] In 1959 and 1960, Itano and Elizabeth Robinson substantiated the claim made by Itano and Singer that the synthesis of the alpha and beta-chains are dictated by different loci. In addition, they postulated that the identical chains (e.g. the two beta-chains of sickle cell anemia hemoglobin) are synthesized by different genetic sites. Thus, Itano and Robinson proposed that it was possible for a person to have four different types of hemoglobin, one for each chain.[129] In addition to experimental papers, Itano also wrote articles summarizing the status of research on abnormal hemoglobin.[130] For example, Pauling and Itano edited a symposium volume together in 1955 on Molecular Structure and Biological Specificity. Itano

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[128] S. J. Singer and Harvey A. Itano, "On the Asymmetrical Dissociation of Human Hemoglobin," Proceedings of the National Academy of Sciences of the United States of America 45 (1959): 174-84.

[129] Harvey A. Itano and Elizabeth A. Robinson, "Formation of Normal and Doubly Abnormal Haemoglobins by Recombination of Haemoglobin I with S and C," Nature 183 (1959): 1799-800. Harvey A. Itano and Elizabeth A. Robinson, "Genetic Control of the α- and β-Chains of Hemoglobin," Proceedings of the National Academy of Sciences of the United States of America 11 (1960): 1492-501.

[130] Harvey A. Itano, "Human Hemoglobin," Science 117 (1953): 89-94; Itano, Bergren and Sturgeon, "Abnormal Human Hemoglobins, 121-59; Harvey A. Itano, "Clinical States Associated with Alterations of the Hemoglobin Molecule," Archives of Internal Medicine 96 (1955): 287-97.

contributed the article "Specificity in the Interaction of Sickle Cell Hemoglobin Molecules" in which he compared the electrophoretic behavior and solubility of multiple hemoglobins as well as the rate of synthesis of the hemoglobins present in hybrid diseases. In other words, people with sickle cell trait have more normal hemoglobin than sickle cell anemia hemoglobin and do not suffer from anemia.[131]

At the end of the 1949 paper Pauling, et al. had stated that they planned to analyze the blood of individuals with other hereditary hemolytic anemias.[132] Itano successfully found three other abnormal hemoglobins within the next five years, and, as mentioned above, these were considered the first four found. In 1950, Itano and Neel reported the second abnormal hemoglobin based on Longsworth scanning diagrams from electrophoresis analysis. They compared the diagrams of the new hemoglobin to sickle cell anemia and normal hemoglobin and found that they differed. They surmised that the new abnormal hemoglobin was passed on genetically as a dominant trait, rather then recessive (as is the case for sickle cell anemia).[133] This second abnormal hemoglobin is now referred to as hemoglobin C.

Itano alone discovered the third abnormal hemoglobin, hemoglobin D. He conducted electrophoretic analysis on the carbonmonoxyhemoglobin derivative and studied the solubility of the samples. The blood sample that Itano used was a mixture of sickle cell anemia hemoglobin and the new abnormal hemoglobin. His sample

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[131] Linus Pauling and Harvey A. Itano, eds., Molecular Structure and Biological Specificity (Washington D.C.: American Institute of Biological Sciences, 1957).
[132] Pauling, Itano, Singer and Wells, 548.
[133] Harvey A. Itano, and James V. Neel, "A New Inherited Abnormality of Human Hemoglobin," Proceedings of the National Academy of Sciences of the United States of America 36 (1950): 613-17.

reacted identically to sickle cell anemia hemoglobin in the electrophoresis apparatus. However, the solubility of his sample resembled that of normal hemoglobin, which differs greatly from the solubility of sickle cell anemia hemoglobin. In this article Itano also proposed a systematic nomenclature for abnormal hemoglobins. He suggested that normal hemoglobin be called hemoglobin A and sickle cell hemoglobin be referred to as B, and that newly found hemoglobin be named by the next alphabetical letter. For the most part his system was instituted; however, sickle cell hemoglobin is called hemoglobin S (not B).[134]

Itano, William Bergren and Phillip Sturgeon found the fourth abnormal hemoglobin, designated hemoglobin E. Bergren and Sturgeon worked at the University of Southern California's School of Medicine. Electrophoresis experiments determined that hemoglobin E differed from the other known abnormal hemoglobins.[135] All of the abnormal hemoglobins that Itano found were observed in people who also had sickle cell hemoglobin. After finding these additional abnormal hemoglobins, it was realized that what had been considered atypical cases of sickle

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[134] Harvey A. Itano, "A Third Abnormal Hemoglobin Associated with Hereditary Hemolytic Anemia," Proceedings of the National Academy of Sciences 37 (1951): 775-84; Anthony C. Allison wrote the article which established the initials used for referring to each hemoglobin. Anthony C. Allison, "Notation for Hemoglobin Types and Genes Controlling Their Synthesis," Science 122 (1955): 640-41. Researches noticed the need for a systematic nomenclature. Itano, Neel, and other participants discussed the problem during a symposium in 1953 and published their conclusions in Science: Amoz I. Chernoff, Ben Fisher, John W. Harris, Harvey A. Itano, Eugene Kaplan, Karl Singer, James V. Neel, "A System of Nomenclature for the Varieties of Human Hemoglobin," Science 118 (1953): 116-17.

[135] Harvey Itano, William Bergren, and Phillip Sturgeon, "Identification of a Fourth Abnormal Human Hemoglobin," Journal of the American Chemical Society 76 (1954): 2278.

cell disease were actually hybrid pathologies, like sickle-cell hemoglobin C disease.[136] However this was not the last abnormal hemoglobin that Itano helped find. In 1956 Itano and three colleagues announced the finding of a new abnormal hemoglobin, Hemoglobin J.[137]

Eventually, Paul Heller pointed out that in 1948 two German investigators, M. Hoerlein and G. Weber, had found abnormal hemoglobin and had determined that the globin differed from that in normal hemoglobin. In 1955, Karl Singer (not S. J. Singer) brought attention to Hoerlein and Weber's work and proposed naming it hemoglobin M. Heller, a physician who had conducted research on hemoglobin M prior to writing his editorial, briefly compared the conclusions drawn by Hoerlein and Weber to those of Pauling, Itano, Singer and Wells.

> Hoerlein and Weber correctly concluded that they were dealing "with a variant of the globin component of the hemoglobin molecule." This discovery preceded by almost 2 years the classical paper describing the abnormal electrophoretic mobility of hemoglobin S, which is generally credited with having introduced the era of molecular pathology.[138]

The work that Itano accomplished while at Caltech was impressive. In 1955 Pauling nominated Itano for the Theobald Smith Award, which was given by the American Association for the Advancement of Science to an American investigator thirty-five years or younger. The Theobald Smith Award was awarded to those who "demonstrated research in the field of the medical sciences, taking into consideration

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[136] Itano, Bergren, and Sturgeon, "Abnormal Human Hemoglobins," 123.
[137] Oscar A. Thorup, Harvey A. Itano, Munsey Wheby, and Byrd S. Leavell, "Hemoglobin J," Science 123 (1956): 889-90.
[138] Paul Heller, "Hemoglobin M – An Early Chapter in The Saga Of Molecular Pathology," Annals of Internal Medicine 70 (1969): 1038-041.

independence of thought and originality." The recipient was presented with $1000 and a bronze medal.[139] In his nomination, Pauling described Itano's sickle cell anemia research and subsequent work on other abnormal hemoglobin. Additionally, Pauling acknowledged Itano's original contributions to hematology by stating that Itano instigated further research on abnormal hemoglobin and their hemoglobinopathies, of which about twelve had been discovered. Itano did not receive this award; however, his contributions were immediately recognized in other ways. He had received the 1954 Eli Lilly and Company Award in Biological Chemistry and he was invited to give the George Minot lecture in 1955.[140]

Pauling and Itano corresponded throughout the following years after Itano left for Bethesda, Maryland. They discussed the status of hemoglobin research and exchanged Christmas cards.[141] Itano spent from 1954 to 1970 working in various positions for the National Institutes of Health, particularly as a surgeon for the National Cancer Institute and as a senior surgeon and medical director for the National Institute of Arthritis and Metabolic Disorders. In 1970 Itano went to the

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[139] "Grants, Fellowships, and Awards," Science 122 (1955): 70. Announcement describing the award also found with Pauling's nomination of Itano: Pauling Collection, I: Individual Correspondence, Harvey A. Itano, 1955-1961, "Nomination of Itano for the Theobald Smith Award for 1955."

[140] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, 1955-1961, "Nomination of Itano for the Theobald Smith Award for 1955," and letter from Allan D. Bass, MD and Secretary of the Medical Sciences Section of the American Association for the Advancement of Science to Pauling dated 18 November 1955. Itano's Minot Lecture gave an overview about the known abnormal hemoglobins: Itano, "Clinical States," 287-97.

[141] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, Assorted correspondence and the Itano family Christmas cards.

University of California at San Diego, where he retired in 1988 and became an emeritus professor of the Department of Pathology.[142]

During the early 1950s Pauling continued to work on the fundamental structure of proteins. In April 1951 he published with Corey and Herman R. Branson an analysis of the structure of two helixes in proteins, one with 3.7 residues per turn and the other with 5.1 residues per turn. Later, the 3.7 and 5.1 residue helixes were named the alpha-helix and gamma-helix, respectively.[143] In another article Pauling and Corey discussed the structure of hemoglobin and concluded that hemoglobin was an alpha-helix. This work on protein structure has been well detailed in the literature of the history of science.[144]

Pauling also returned to studying the structure of the heme portion of hemoglobin with the help of Robert C. C. St. George, a postdoctoral fellow. In late 1951 they analyzed the possibility that steric hindrance explained the structural configuration of the heme to heme interaction. Pauling believed that a better

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[142] Kalte and Nemeh, 2003, 946.

[143] Linus Pauling, Robert B. Corey, and H. R. Branson, "The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain," Proceedings of the National Academy of Sciences of the United States of America 37 (1951): 205-11.

[144] Linus Pauling and Robert B. Corey, "The Polypeptide-Chain Configuration in Hemoglobin and other Globular Proteins," Proceedings of the National Academy of Sciences of the United States of America 37 (1951): 282-85. For an overview of the several protein structures proposed by Pauling and Corey see: Robert Corey and Linus Pauling, "The Structure of Proteins," Frontiers in Science: A Survey, ed. Edward Hutchings, Jr. (New York: Basic Books, 1958): 28-36. For more information about Pauling's contributions to the structure of proteins see: Kay, Molecular Vision, 263-64; Hager, 368-79; Judson, 63-69; Linus Pauling, "The Discovery of the Alpha-Helix," Linus Pauling: Scientist and Peacemaker, eds. Clifford Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 141-49.

understanding of the heme was necessary. He had previously mentioned this need in a lecture delivered while he was in England in 1948. Ultimately, Pauling wished to ascertain whether the hemes were on the surface or interior of the hemoglobin molecule. He proposed in 1948 that the hemes were embedded within the hemoglobin molecule and that the oxygen and carbon monoxide molecules pushed the molecule apart to make oxyhemoglobin and carbonmonoxy-hemoglobin. Additionally, when the ligands reshaped the hemoglobin molecule, the other oxygen or carbonmonoxide molecules attached more easily. St. George and Pauling experimentally substantiated Pauling's theory using spectrophotometry. In their experiments they attached several alkyl isocyanides to various hemoglobins in an effort to observe the bond between iron and its ligand as well as the effects of differently sized and shaped ligands attached to the heme. Sickle cell anemia hemoglobin was one of the hemoglobin samples analyzed. According to St. George and Pauling, steric hindrance of the heme supported the sickling hypothesis proposed by Pauling, Itano, Singer, and Wells in "Sickle Cell Anemia, a Molecular Disease."

> Our postulate provides an obvious explanation of the action of oxygen in preventing the sickling of sickle-cell-anemia erythrocytes. We have visualized the sickling process as one in which complementary sites on adjacent hemoglobin molecules combine. It was suggested that erythrocytes containing oxyhemoglobin or carbonmonoxyhemoglobin do not sickle because of steric hindrance of the attached oxygen or carbon monoxide molecule. This steric hindrance effect might be the distortion of the complementary sites through forcing apart of layers of protein, as is suggested by the isocyanide experiments.[145]

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[145] Robert C.C. St. George and Linus Pauling, "The Combining Power of Hemoglobin for Alkyl Isocyanides, and the Nature of the Heme-Heme Interactions of Hemoglobin," Science 114 (1951): 629-34. The quote is from page 633. Pauling's

In addition to his laboratory work, Pauling gave speeches about hemoglobin and sickle cell anemia during the late 1940s and early 1950s, a practice he would continue throughout his lifetime. He typically summarized the history of hemoglobinopathies, paying special attention to work done at Caltech. Thus, Pauling noted that sickle cell anemia was the first molecular disease and instigated future research conducted by Itano and others. He also conveyed his confidence for the future based on scientific progress.[146]

Other endeavors also occupied Pauling's time and concern from 1945 to 1954, but these activities are not the focus here. In 1949 Pauling was President of the American Chemical Society. Pauling faced numerous burdens from 1950 to 1954 resulting from political sentiments in America, resulting in his losing funding from the Office of Naval Research and the Eli Lilly Corporation as well as an internal audit at Caltech, which eventually found him innocent of Communist activities.[147] The State Department denied passports to Pauling, reinstating his regular passport in 1954 so that he could travel to Stockholm to receive the Nobel Prize in Chemistry, which

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discussed the importance of this paper in other articles: Pauling, "The Discovery of the Alpha Helix," 142.

[146] Linus Pauling, "The Place of Chemistry in the Integration of the Sciences," Main Currents in Modern Thought 7 (1950): 108-11; Pauling, "Structural Chemistry," 4-7; Linus Pauling, "The Hemoglobin Molecule in Health and Disease," Proceedings of the American Philosophical Society 96 (1952): 556-65; Linus Pauling, "The Significance of Molecular Structure to Biology," Leroy Egerton Westman Memorial Lecture, Chemistry in Canada (July 1954): 36-37; Pauling, "Abnormality of Hemoglobin," 216-41; Linus Pauling, "Abnormal Hemoglobins and the Molecular Structure of the Human Body," California Institute of Technology Archives, Audiocassette of a lecture given at Caltech, 1955 or 1956.

[147] Hager, 338-82; Funding and Caltech internal review information on 356-57.

he won for his work on the chemical bond.[148] From 1945 to 1954, Pauling spent a great deal of time learning and speaking about nuclear weapons and peace so that after about 1956 he split his time evenly between scientific and peace work.[149]

By 1956 most of his original work on the structure and function of hemoglobin had been completed, although he would continue to study possible mechanisms for inhibiting sickling of blood cells. He had conducted many scientific experiments from 1935 to 1945 using hemoglobin and its derivatives (oxyhemoglobin and carbonmonoxyhemoglobin), which established his thorough knowledge of these substances. Pauling's familiarity with hemoglobin allowed him in 1945 to understand the sickling process of sickle cell diseases. After four years of experimental work on sickle cell hemoglobin in a Caltech laboratory, Pauling and his colleagues proposed in 1949 that sickle cell anemia is a molecular disease, a novel concept that instigated new areas of research on abnormal hemoglobin and hemoglobinopathies at Caltech and elsewhere. As seen from the above discussion of subsequent research undertaken by the four authors of the 1949 Science paper, Itano, Singer and Wells continued on the same vein by analyzing abnormal hemoglobin and its synthesis; whereas Pauling returned to structural chemistry, particularly the structures of proteins. Chapter Three will discuss the variety of ways that Pauling used his knowledge of normal and abnormal hemoglobin during the next twenty years of his life (from the mid-1950s to

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[148] Goertzel and Goertzel, Linus Pauling : A Life in Science and Politics, 112-32; Hager, 400-55.

[149] Linus Pauling, "An Episode that Changed My Life," Linus Pauling: Scientist and Peacemaker, eds. Clifford Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 192-94, 194; Hager, 461-64; Goertzel and Goertzel, Linus Pauling : A Life in Science and Politics, 114.

mid-1970s) and that he continued to address the subject intermittently until his death in 1994.

# 3

# 1954 to 1994 – Molecular Implications: Eugenics, Genetics, and Medicine

The decade from 1945 to 1954 was a pivotal time for Pauling and shaped a number of projects he embarked on over the next forty years. One of the lasting changes in Pauling's scientific life started in 1953 when he developed an interest in mental illnesses, and began applying his concept of molecular disease to mental deficiencies.[1] As Pauling combined his knowledge of sickle cell anemia with his growing understanding of other genetic diseases that cause physical and mental disabilities, he started two new endeavors. First, from the mid-1950s to early 1970s, Pauling promoted positive eugenics, a socially and politically controversial subject, by advocating genetic counseling for those who were afflicted by or were carriers of genetic diseases. Second, he started an institute in 1973 in which the researchers examined the therapeutic effects of high doses of vitamins and other nutrients normally found within the human body and conducted studies on people suffering for various illnesses, including sickle cell anemia. Pauling coined the term "orthomolecular" to describe these types of therapies.

Another major area that occupied Pauling's time after the mid-1950s was his peace work. Hager commented that Pauling's career path shifted around 1954 after he was awarded the Nobel Prize in Chemistry, an accolade that gave Pauling new prestige and more financial independence. According to Hager, Pauling changed his

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[1] Marinacci, Pauling in His Own Words, 216-17.

primary concern from structural chemistry to peace.[2] Yet, in campaigning for an end to nuclear weapons testing and the possibility of nuclear war, he stressed molecular diseases caused by fallout and passed to future generations as mutagenic effects. He also developed original ideas on the "molecular evolutionary clock" using analysis of the hemoglobin of humans and other species. In 1994 (the year he died) two books on sickle cell anemia contained forewords by Pauling. Thus, hemoglobin and sickle cell anemia remained interests of Pauling's for the rest of his life.

**Mental Deficiencies and Molecular Diseases**

On 7 July 1955 Pauling met with three men about a collaborative research project on mental illnesses, which would be conducted largely at Caltech. Pauling was somewhat familiar with mental disorders; since 1938 he helped to allocate monies from Caltech's Hixon Fund, which supported research on human behavior.[3] Two of the men, George Tarjan of Pacific State Hospital and Stanley Wright of UCLA Medical School, worked with mentally disabled people and were willing to aid research at Caltech. Richard Morgan was a member of the California Office of the Department of Mental Hygiene. The men discussed possible areas of research and decided that Pauling should submit a grant proposal to the Ford Foundation.[4]

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[2] Hager, 461-62.
[3] Kay, Molecular Vision, 98. Some of the projects supported by the Hixon Fund included electroshock therapy and clinical analysis of mental disorders.
[4] Pauling Collection, Science 14.077.2, Correspondence with Ford Foundation, 1955, "Basic Biochemical Research Related to the Problem of Mental Deficiency," meeting notes dated 7 July 1955: 1-15, 1-4.

The Ford Foundation's mission was "to receive and administer funds for scientific, educational, and charitable purposes, all for the public welfare." Pauling had worked with the Ford Foundation previously, in early 1949. The Ford Foundation wanted to incorporate chemistry and human welfare into its programs and asked Pauling for his advice. Pauling wrote to thirty renowned chemists in the United States requesting feedback. In addition, he hosted a dinner meeting in New York on 11 February 1949, which some of these chemists attended, to discuss the issue. Pauling compiled the information he received from the other chemists and submitted it to the Ford Foundation. According to Pauling, two main concerns among the chemists were peace and hunger. Most of the chemists present at the dinner discussion proposed that the Ford Foundation should support biological chemistry and "research in borderline fields between chemistry and other branches of knowledge." The following year, the Ford Foundation published a report outlining its aims and its hope that science would aid in world peace, economic equality (stopping hunger), and human conduct.[5]

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[5] Pauling Collection, Science 14.034.1, "Report of the Trustees of the Ford Foundation," dated 27 September 1950. The quotation about the Ford Foundation's aim is from page 7; Many letters from Pauling to chemists dated January and February 1949; Linus Pauling, "Suggestions of Chemists about Program and Operation of the Ford Foundation," dated 7 March 1949, 1-4. The quotation about what kind of chemistry should be supported is from page 2. Francis X. Sutton noted the importance of the Report to the future undertakings of the Ford Foundation, "the document became a kind of sacred text, scrutinized for many years by those charged with planning or justifying the Foundation's programs." For information on the early years of the Ford Foundation and about the Foundation's Report and its impact see: Francis X. Sutton, "The Ford Foundation: The Early Years," Daedalus 116 (1987): 41-91, 47-53.

The notes from Pauling's 1955 meeting with Tarjan, Wright, and Morgan summarized why Pauling decided to pursue this new venture and what kind of research he proposed to do.

> Dr. Pauling explained the reasons behind his developing interest in the field of mental deficiency. His research in hematology has now developed this area to the point where other researchers have taken over and will carry on. He has been considering the possibility of a biochemical approach in cancer research, but this area is already well supported in basic research in cancer. However, apparently little or nothing has been done in basic biochemical research in the area of mental deficiency. Dr. Pauling is interested in such research primarily as an avenue toward better understanding of biochemical processes in general, and made clear to the group his lack of research interest in the clinical and therapeutic applications of whatever findings might come out of the basic research.[6]

As was the case for his work on the nature of the chemical bond and protein structure, Pauling wanted to establish fundamental principles within this field. Cancer research intrigued Pauling at this time, but he would not pursue this path until after the late 1960s when he promoted the therapeutic advantages of vitamins, especially Vitamin C.

As a result of the meeting, Pauling submitted a grant to the Ford Foundation, "A Proposed Program of Research on Biochemical and Structural Chemical Factors in Relation to Mental Disease, especially Mental Deficiency," requesting $115,000 annually for seven years. Pauling envisioned that the work on mental deficiencies would align with Caltech's joint program in biology and chemistry, which targeted medical problems.

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[6] Pauling Collection, Science 11.077.2, "Basic Biochemical Research," meeting notes dated 7 July 1955: 2.

> It is proposed that a program of fundamental study of mental deficiency, especially in relation to molecular abnormalities such as have been shown to be responsible for sickle-cell anemia and other hereditary hemolytic anemias, be made part of this [Caltech's joint] program.[7]

Thus, Pauling wanted to incorporate mental deficiency into his concept of molecular disease. In his twenty-eight page grant proposal, Pauling explained sickle cell anemia and other molecular diseases caused by abnormal hemoglobin in detail. Then, he connected the research on molecular diseases to the work he proposed to conduct on mental illnesses. Additionally, he defined molecular disease.

> It seems not unlikely that most cases of mental deficiency can be attributed to molecular disease...The expression molecular disease as first applied to sickle-cell anemia implies, however, that the disease results from the manufacture by the patient of abnormal molecules in place of the normal ones that are manufactured, and perhaps a disease should not be described as a molecular disease until the abnormal molecules have been identified...It is likely that phenylketonuria, which is responsible for about one half to one percent of the institutionalized cases of mental deficiency, can be shown to be a molecular disease...[8]

Pauling's grant proposal also outlined some of the experiments his investigators would try. For example, Pauling mentioned that Caltech would investigate the amino acid sequences of the polypeptide chains of various proteins and how the body synthesizes proteins. Also, Pauling noted that Caltech would do

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[7] Pauling Collection, Science 11.077.2, "A Proposed Program of Research on Biochemical and Structural Chemical Factors in Relation to Mental Disease, especially Mental Deficiency," 21 July 1955: 1-2, 1.

[8] Pauling Collection, Science 11.077.17, "A Proposal to the Ford Foundation on Biochemical and Structural Chemical Factors in Relation to Mental Disease, especially Mental Deficiency," 1 August 1955, 28 pages plus photographs and floor plans of Caltech's Norman W. Church, Crellin, and Kerckhoff laboratories: 3.

research on enzymes.[9] Pauling's proposal to the Ford Foundation mentioned two hereditary diseases causing mental illness: phenylketonuria[10] and mongolism.[11] These two diseases were also mentioned during the July meeting Pauling had attended earlier that year. At the meeting Tarjan encouraged Pauling to focus on phenylketonuria and mongolism because his hospital had patients suffering from these diseases (fourteen and 400, respectively).[12] Based on Pauling's comments during this meeting, his knowledge of specific mental diseases seemed relatively limited and afterwards he followed up on Tarjan's suggestion by seeking information about phenylketonuria and mongolism.[13] Caltech's Committee of Contracts approved Pauling's grant and forwarded it to the Ford Foundation, which awarded Caltech $90,000 per year for five years in April 1956.[14]

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[9] Pauling Collection, Science 11.077.2, "A Proposed Program," 1; Science 11.077.17, "A Proposal to the Ford Foundation," 5-9.

[10] Also referred to as phenylpyruvic oligophrenia or PKU.

[11] Today, mongolism is commonly referred to as Down's Syndrome.

[12] Pauling Collection, Science 11.077.2, "A Proposed Program," 1-2; Science 11.077.2, "Basic Biochemical Research," meeting notes dated 7 July 1955: 1-15, 4-15.

[13] Pauling wrote to JBS Haldane on 18 July 1955 asking him for information about mental deficiency, especially phenylketonuria and mongolism. Haldane replied that mental deficiency was not his field and that he went to his colleague, Lionel S. Penrose, who worked on phenylketonuria for information. Additionally Haldane said of mongolism, "I think you would be as likely to find biochemical abnormality in the mother of a "mongol" about the second or third month of pregnancy, as in the child. The trouble is that one does not know what mothers are going to bear children of this type." This is the only reference I have seen to Pauling following up on mongolism as a potential research topic. Pauling Collection, Individual Correspondence, JBS Haldane, 1955-1960, letter from Pauling to Haldane dated 18 July 1955, letter from Haldane to Pauling dated 9 August 1955.

[14] Pauling Collection, Science 11.077.3, Caltech's approval of Pauling's Ford Foundation grant, dated 28 July 1955; Letter from Bernard Berelson, Director of the

Time announced Pauling's new venture supported by the Ford Foundation in the 10 September 1956 issue. The brief summary discussed sickle cell anemia as the inspiration for Pauling's new research pathway. In addition, it mentioned Pauling's hope that mental diseases could be explained by molecular abnormality and mentioned phenylketonuria as an example.[15] People wrote to Pauling commenting upon his interest in mental diseases. For example, Eugene J. Hochman of Toledo, Ohio told Pauling:

> You are a prince of a new nobility and, by your announcement alone, you have already gifted the hopeless with the supreme gift of hope. If your efforts should culminate in fruitful achievement, you will have liberated the most oppressed minority of mankind...for the human tragedy is not to be born and to die, but to be born and not to grow.[16]

Pauling responded to Hochman by stating that Hochman's note gave him "the most happiness" of the many letters he had received for the past two months.[17]

In subsequent years, Pauling regularly connected molecular disease and mental deficiency and he usually demonstrated the link by discussing sickle cell anemia and phenylketonuria. Phenylketonuria is a disease in which babies develop physical and mental disabilities after birth. In 1934, Asbjörn Fölling of the University of Oslo discovered the disease and provided evidence that it caused mental retardation. Thus, Fölling called it imbecilitas phenylpyruvica. In addition, Fölling

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Behavioral Sciences Program, Ford Foundation, to Pauling dated 18 April 1956 informed Pauling of how much the Ford Foundation awarded his grant proposal.

[15] "Genes and Mental Defectives," Time 68 (10 September 1956): 102.

[16] Pauling Collection, Science 11.077.14, Letter from Eugene J. Hochman to Pauling dated 9 September 1956.

[17] Pauling Collection, Science 11.077.14, Letter from Pauling to Hochman dated 29 October 1956.

showed that those suffering from the disease could not break down phenylpyruvic acid. He also noted its repetitive occurrence within families.[18] The name commonly used today, phenylketonuria, was established one year later by Lionel S. Penrose of the Royal Eastern Counties Institution of Colchester. Additionally, Penrose stated that phenylketonuria manifests itself in persons who are homozygous recessive for this genetic abnormality.[19] (Likewise, sickle cell anemia affects those who are homozygous recessive for sickle cell hemoglobin.) George A. Jervis substantiated Penrose's hereditary claim in 1937. About fifteen years later, Jervis also established that those suffering from phenylketonuria do not produce the enzyme, phenylalanine hydroxylase, which converts the amino acid phenylalanine into tyrosine.[20] Others produced similar results as Jervis around the same time, the early to mid-1950s.[21]

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[18] Asbjörn Fölling, "Phenylpyruvic Acid as a Metabolic Anomaly in Connection with Imbecility," Nord. Med. Tidskr. 8 (1954): 1054-59; Asbjörn Fölling, "Phenylpyruvic Acid as a Metabolic Anomaly in Connection with Imbecility," Zeitschrift fur Physiologische Chemie 227 (1934): 169-76. For a history of Fölling's role see: Siegried A. Centerwall and Willard R. Centerwall, "The Discovery of Phenylketonuria," Phenylketonuria, ed. Frank L. Lyman (Springfield, Illinois: Charles C. Thomas, Publisher, 1963): 3-10 or Siegried A. Centerwall and Willard R. Centerwall, "The Discovery of Phenylketonuria: The Story of a Young Couple, Two Retarded Children, and a Scientist," Pediatrics 105 (2000): 89-103.

[19] L.S. Penrose, "Inheritance of Phenylpyruvic Amentia (Phenylketonuria)," Lancet 2 (1935): 192-94.

[20] G.A. Jervis "Phenylpyruvic Oligophrenia: Introductory Study of 50 Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid," Archives of Neurology and Psychiatry, 8 (1937): 944-63; G.A. Jervis, "Phenylpyruvic Oligophrenia Deficiency of Phenylalanine-Oxidising System," Proceedings of the Society for Experimental Biology and Medicine 82 (1953): 514-15.

[21] S. Udenfriend and S.P. Bessman, "The Hydroxylation of Phenylalanine and Antipyrene in Phenylpyruvic Oligophrenia," Journal of Biological Chemistry 203 (1953): 961-66; S. Kaufman, "The Enzymic Conversion of Phenylalanine to Tyrosine," Biochemica et Biophysica Acta 23 (1957): 445-46. For sources on the general history of phenylketonuria see: Willard R. Centerwall and Siegried A.

Articles about the treatment of phenylketonuria started appearing in the early to mid-1950s; however, the proposed treatment methods were not widely used until the 1960s. In 1956, F.A. Horner and C.W. Streamer published proof that a phenylalanine restricted diet curbed the mental manifestations caused by phenylketonuria.[22] Their clinical trial built upon information published previously by Horst Bickel, John Gerrard, and Evelyn M. Hickmans of the Children's Hospital of Birmingham, who showed that the behavior of phenylketonuric children improved when they were on a low phenylalanine diet.[23] By 1961 many articles were published about the link between diet and disposition of those suffering from phenylketonuria. Thus, the connection between nutritional intake and the mental effects of phenylketonuria were firmly established by this time.[24]

In the early 1960s, improved diagnostic tests were developed and treatment information was circulated. The best of the new detection methods analyzed blood samples and ascertained prior to releasing the baby from the hospital whether the newborn suffered from phenylketonuria. In response, hospitals started screening

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Centerwall, U.S. Department of Health, Education, and Welfare, Phenylketonuria: An Inherited Metabolic Disorder Associated with Mental Retardation (Washington D.C.: U.S. Government Printing Office, 1972): 1-5.

[22] F.A. Horner and C.W. Streamer, "Effect of Phenylalanine-Restricted Diet on Patients with Phenylketonuria: Clinical Observations in Three Cases," Journal of the American Medical Association 161 (1956): 1628-630.

[23] H. Bickel, J. Gerrard, and E.M. Hickmans, "Influence of Phenylalanine Intake on Phenylketonuria," Lancet 2 (1953): 812-13; H. Bickel, J. Gerrard, E.M. Hickmans, "The Influence of Phenylalanine Intake on the Chemistry and Behavior of a Phenylketonuric Child," Acta Pediatrica 43 (1954): 64-77.

[24] Centerwall and Centerwall, "The Discovery of Phenylketonuria," 97-98; Gladys M. Krueger, U.S. Department of Health, Education, and Welfare, Phenylketonuria: A Selected Bibliography (Washington D.C.: U.S. Government Printing Office, 1963); Paul, Politics of Heredity, 140.

newborns for the disease. Massachusetts in 1962 was the first state to require screening for phenylketonuria. By 1965, thirty-two states routinely screened newborns for the disease.[25] In addition to screening, the U.S. government published educational booklets for parents of phenylketonurics. Recipes for low phenylalanine diets were also made available.[26] By 1963, five dietary supplements, low in phenylalanine and high in other amino acids, were commercially available for phenylketonurics.[27]

Starting in the fall of 1955, Pauling began discussing phenylketonuria in his speeches about molecular disease and drew parallels between phenylketonuria and sickle cell anemia. For example, Pauling spoke about enzymes at the Henry Ford Hospital in Detroit and mentioned that phenylketonuria is caused by an inborn error resulting in the sufferer's inability to manufacture the enzyme that converts phenylalanine to tyrosine. He also noted that the chemical structures of enzymes were unknown at this time. Ultimately, Pauling encouraged more work in the structural chemistry of enzymes and foresaw a day when artificial enzymes would be used to

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[25] Paul, 140-41, 173-86; Diane B. Paul and Paul J. Edelson, "The Struggle over Metabolic Screening," Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s (Sydney, Australia: Harwood Academic Press, 1998): 203-20, 204-06. Today all fifty states and Washington D.C. test newborns for phenylketonuria: Centerwall and Centerwall, "The Discovery of Phenylketonuria," 98.

[26] For a bibliography by subject (Dietary Management and Treatment, Diets and Recipes) see Krueger.

[27] H. Bickel and W. Grüter, "Management of Phenylketonuria," Phenylketonuria, ed. Frank L. Lyman (Springfield: Charles C. Thomas, Publisher, 1963): 136-72, 137.

treat enzymatic diseases.[28] In a speech to the American Psychiatric Association, Pauling again connected sickle cell anemia and phenylkentonuria; this time he stated that sickle cell anemia could be used as a template for understanding mental illnesses.

> The discovery of the abnormal hemoglobins has provided us with a far deeper understanding of the hereditary hemolytic anemias than existed before. In the same way, much may be done in increasing our understanding of phenylpyruvic oligophrenia.[29]

In addition, Pauling stated that most mental illnesses were molecular diseases that resulted from abnormal concentrations of molecules within the body.[30] By the mid-1950s, Pauling had associated himself with a new field, mental illness, and had unequivocally connected mental deficiency to his concept of molecular disease.

**Pauling Promotes Genetic Counseling**

In his speech to the American Psychiatric Association Pauling touched on a subject that he would promote for the next fifteen years – genetic counseling for carriers of molecular diseases.[31] Pauling explained the possible genetic make-up of an

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[28] Linus Pauling, "The Future of Enzyme Research," Enzymes: Units of Biological Structure and Functions, ed. Oliver H. Gaeblers (New York: Academic Press, 1956): 177-82, 180-82.
[29] Linus Pauling, "The Molecular Basis of Genetics," American Journal of Psychiatry 113 (1956): 492-95, 494.
[30] Pauling, "Molecular Basis of Genetics," 492.
[31] It should be noted that Pauling used the term 'negative eugenics' in the late 1960s, but not before then. Pauling's statements about genetic counseling reflect the typical comments made by those promoting eugenics, although Pauling's role was not discussed by the following authors. Paul, 133-56; Daniel J. Kevles, In the Name of Eugenics: Genetics and the Uses of Human Heredity (New York: Alfred A. Knopf, 1985): 253-64.

offspring between two heterozygotes in order to convey the chances that a couple would have an unhealthy child.

> When two of the heterozygotes, the carriers of the sickle-cell-anemia gene, marry, one-quarter of their children may be expected to have the disease sickle-cell-anemia, one-quarter to be normal, and one-half to be carriers like the parents.[32]

Pauling did not discuss problematic marriages when he mentioned sickle cell anemia; he only did so with phenylketonuria. He proposed that possible carriers should undergo genetic tests and if found to be heterozygous for the disease then that person should avoid marrying another carrier.[33] However, at this time no test existed that could determine whether a person was a carrier of phenylketonuria. Pauling had previously remarked on the need to develop a method for pinpointing carriers: "...we might inject phenylalanine into the blood stream and carefully measure its rate of conversion, as a means (in fact, the only means) of identifying phenylketonuria carriers."[34]

Historians link genetic counseling of the 1950s and 1960s to eugenics because genetic counselors usually gave biased advice. Thus according to Frederick Osborn, who in 1968 wrote a book about "what eugenics was, is, and ought to be," clinics

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[32] Pauling, "Molecular Basis of Genetics," 493.
[33] Pauling, "Molecular Basis of Genetics," 494.
[34] Pauling Collection, Science 11.077.2, "Basic Biochemical Research," meeting notes dated 7 July 1955, 14. Paul and Edelson noted a major difference between screening for sickle cell diseases and phenylketonuria. Sickle cell diseases can be identified in anemics and carriers by analyzing blood samples. Thus, couples can be advised against procreating infected children. In comparison, phenylketonuria can only be detected within those who have the disease, and not people who carry the disease. Thus, the only way to advise parents against having a child with phenylketonuria is if the parents have already had one child with the disease (265).

reported that counselors usually influenced people "in a eugenic direction."[35] Genetic counseling differed from the prior eugenics movement in two ways. One: counseling focused on the individuals, whereas eugenics of the early twentieth century had promoted practices that benefited society as a whole. Two: genetic counseling typically targeted genetic diseases rather than people of a certain class or race.[36] The popularity of genetic counseling rose after 1960 in response to new information gathered in the 1950s and early 1960s about abnormal hemoglobins and phenylketonuria (as discussed above).[37]

Pauling invoked the same arguments as used by other scientists who promoted counseling at this time; thus in 1958, Pauling suggested genetic counseling for prospective parents as a way to stop the spread of molecular diseases and minimize human suffering.[38] He did not mention specific regulations that should be enforced, but felt that prospective parents should be tested for molecular diseases and then decide whether or not to have children based upon the results of their tests.

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[35] Frederick Osborn, The Future of Human Heredity: An Introduction to Eugenics in Modern Society (New York: Weybright and Talley, 1968): 91.

[36] Paul, 133-42; Kevles, 251-55. Paul states that the word 'eugenics' did not garner negative responses until the 1970s when people began associating eugenics with compulsory action. Thus, during the 1950s and 1960s, especially after Watson and Crick figured out the structure of deoxyribonucleic acid in 1953, geneticists used the term 'eugenics' without backlash and with new aims. Kevles seems less convinced that the term 'eugenics' was acceptable in the 1950s and 1960s; however, he too notes that it was used until the early 1970s. Osborn state that the word 'eugenics' was not associated with genetic counseling (Osborn, 91).

[37] Kevles, 254-55.

[38] In addition to Pauling, Osborn also noted the need to decrease "human suffering." Thus, Osborn promoted eugenic tactics for mental and physical diseases because "The immediate problem is the relief of human suffering" (96).

> Surely we can find some way in which this result, the purification of the pool of human germ plasma, can be achieved without great human suffering. As more and more tests for heterozygosity are developed, predictions can be made with greater and greater reliability about the probability of birth of defective children, and advice can be given to prospective spouses or parents about the desirability of their contributing to the welfare of the human race as a whole by preventing the transmissions of seriously defective genes to the next generation.[39]

Thus, Pauling advocated acknowledgment and action by carriers of genetic defects. At this time he was ambiguous about specific eugenic protocols that should be invoked to stop the spread of molecular disease in the world; however, he mentioned that one method of prevention was encouraging the universal introduction of birth control.[40]

What was Pauling talking about when he referred to "the pool of human germ plasma?" Pauling did a thought experiment in which he accumulated the genetic material from all of the human beings on Earth into one mass, which he called "the pool of human germ plasma."

> There are in the world today about 2,700,000,000 people – nearly three billion people. They are the human race. These nearly three billion people are what they are because of the genes, 100,000 each, that they inherited from their parents. If all of these genes, 100,000 each for nearly three billion people, were to be collected together, they would form a little sphere abut 1/25 of an inch in diameter. This is the pool of human germ plasma that has determined the nature of the human race as it is today.[41]

Pauling believed that "the pool of human germ plasma, which determines the nature of the human race, is deteriorating." Thus, he expressed the hope that knowledge

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[39] Pauling, "Molecular Structure and Disease," 7.
[40] Pauling, "Molecular Structure and Disease," 1-7.
[41] Linus Pauling, No More War! (Westport, Connecticut: Greenwood Press, Publishers, 1975): 50.

about molecular diseases would decrease the amount of human suffering in the world.[42] Pauling not only talked about human germ plasma in reference to molecular diseases, but also mutations caused by fallout from nuclear weapons' testing.

**Pauling Relates Sickle Cell Anemia to the Mutagenic Effects caused by Nuclear Fallout**

Between 1958 and 1963 Pauling occasionally mentioned molecular disease when talking about the repercussions caused by nuclear fallout and typically drew one connection between the two topics – genetic mutations and their resultant birth defects.[43] Pauling substantiated his call for world peace by elaborating on radiation's mutagenic effects. Pauling urged a ban on nuclear weapons testing and mentioned the potential health hazards and human suffering caused by the tests to support his statements. In 1958, in a speech on "Molecular Structure and Disease," Pauling discussed abnormal hemoglobins extensively and at the end commented briefly upon mutations caused by nuclear radiation. Just as in his promotion of genetic counseling, Pauling stressed the importance of what he called "purifying" the human germ

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[42] Linus Pauling, "Molecular Disease," American Journal of Orthopsychiatry 29 (1959): 684-87.

[43] Like Pauling, others also connected radiation and disease. Thus, Osborn stated in 1968: "The improvement of the environment is as important as the improvements of the hereditary base, for the two are closely related in the evolutionary process" (103). Osborn mentioned that radiation increased mutations. Neel noted in 1973 that not enough was known about the effects of radiations (X-ray or nuclear) on human beings and that once more was known a decision about exposure to radiation would have to take into account the benefits and detriments from the exposure. James V. Neel, "Social and Scientific Priorities in the Use of Genetic Knowledge," Ethical Issues in Human Genetics: Genetic Counseling and the Use of Genetic Knowledge (New York: Plenum Press, 1973): 353-68, 358.

plasma. He had two main concerns. First, he stated that medical progress had increased the number of people with molecular diseases who lived "essentially normal lives." More specifically, medical advances allowed those with genes for molecular defects to procreate. In other words, those with defective genes, who in previous generations would not have had children and would not have perpetuated the mutation, were now capable of procreating and continuing the defects.[44] Secondly, Pauling mentioned that technology, such as X-rays and nuclear weapons, increased exposure of the human gonads to radioactivity and correspondingly increased the number of defects by introducing new mutations.[45] Later, Pauling differentiated between necessary and unnecessary exposure to radiation. Thus, he stated that some kinds of radiations were unavoidable, such as X-rays, while others could be avoided, specifically exposure to radioactive fallout caused by nuclear weapons.[46]

To clarify his point about molecular diseases, Pauling discussed sickle cell anemia. By this time, Pauling could draw upon the experimental work completed by Ingram in 1956 and 1957 in which Ingram had ascertained the difference between

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[44] This is a general argument that goes back to Charles Darwin, Herbert Spencer, and Francis Galton.

[45] Pauling, "Molecular Structure and Disease," 6-7. Pauling also discussed birth defects caused by fallout from nuclear weapons testing during this time. For example, in an article on Carbon-14 he presented other people's calculations and his own estimates of defects caused by fallout's by-products, specifically concentrating on Carbon-14. Similar to his articles mentioning fallout and molecular diseases, like sickle cell anemia, Pauling mentioned gonad exposure in this article. For Pauling's discussions about the detriments of gonadal exposure to radiations see: Pauling, No More War! 56-67; Linus Pauling, "Genetic and Somatic Effects of Carbon-14," Science 128 (14 Nov 1958): 1183-186.

[46] Pauling, "Molecular Disease," 686; Pauling reiterated this statement four years later in his chapter in the book Birth Defects: Pauling, "Our Hope," 170.

sickle cell hemoglobin and normal hemoglobin. Hence, Ingram had found that of the 300 amino acid residues in hemoglobin, only one differs; whereas normal hemoglobin has a glutamic acid at one of its loci, sickle cell hemoglobin has valine at the same locus.[47] According to Pauling, Ingram's work gave credence to the idea that a gene mutation altered the amino acid sequence of hemoglobin, which in turn changed its structure and caused sickle cell anemia.

> In all of the abnormal human hemoglobins that have been studied, only one amino acid residue is different from that in normal adult human hemoglobin – only one out of 141 if the abnormality is in the alpha chain, one out of 146 if the abnormality in the beta chain. This is the result of a gene mutation. Cosmic ray, high energy radiation from natural radioactivity, or some other mutagenic agent has attacked the gene that controls the synthesis of the polypeptide chain in such a way as to change its nature, to replace one of the nitrogen bases by another. As a result, a single amino acid residue is different in the chain from that in the molecules manufactured by normal human beings. Very often this difference of just one amino acid residue in the chain leads to a disease.[48]

Although the historical circumstances behind the gene mutation from normal to sickle cell hemoglobin could not be determined, Pauling used the example of sickle cell anemia to show how the replacement of one amino acid produced molecular disease in humans. Thus, the example of sickle cell anemia demonstrated the potential threat of nuclear fallout. In other words, if the replacement of one amino acid in hundreds could cause the deadly disease, sickle cell anemia, then the potential hazard from

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[47] Ingram, "A Specific Chemical Difference," 792-94; Ingram, "Gene Mutations," 326-28.
[48] Pauling, "Science and World Problems," 14-15.

gene mutations caused by nuclear fallout could cause comparable suffering or worse.[49]

It should be noted that Pauling occasionally discussed molecular diseases caused by fallout without specifically mentioning sickle cell anemia. In one such case, Pauling mentioned molecular diseases, mutations caused by exposure to radiation, the need for tests that diagnose carriers of molecular diseases, and the need to limit reproduction among potential carriers. He argued many similar points to those addressed through his discussions of sickle cell anemia and phenylketonuria. However, he wrote about hemophilia, which is a hereditary disease of the blood; the blood of the sufferer does not coagulate and therefore bleeding can not be stopped easily.[50] Likewise, Pauling discussed hemophilia, but not sickle cell anemia, in his book No More War! Pauling noted that nuclear fallout causes mainly adverse birth defects and that radioactivity increases the number of bad genes. He specifically mentioned two mental diseases caused by bad genes, phenylketonuria and schizophrenia.[51]

**Pauling Espouses the Link between Malaria and Sickle Cell Anemia**

Pauling's concern about the spread of sickle cell hemoglobin arose from its high frequency in the human population. Pauling stated that the mutation perpetuated because it protected individuals from contracting malaria. Pauling drew on work

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[49] Pauling, "Molecular Disease," 684-87.
[50] Linus Pauling, introduction, Molecular Genetics and Human Disease, ed. Lytt I. Gardner (Springfield, Illinois: Charles C. Thomas Publisher, 1961): ix-xi.
[51] Pauling, No More War!, 67-72.

performed by three investigators who established the connection between sickle cell anemia and malaria. P. Brain first stated that sickled hemoglobin might protect against malaria in 1952. Hermann Lehmann in 1953 substantiated Brain's claim. The following year, Anthony C. Allison of Oxford University conducted an experiment in Kenya on fifteen Africans that demonstrated the link. Pauling pointed out the possibility that sickle cell hemoglobin might not nourish the mosquito, thereby explaining why those with sickled cells are protected. [52] In one article, Pauling restated Allison's theory that the mosquito, *Plasmodium falciparum*, which lives part of its life in the red blood cells, dies because it is crushed when the hemoglobin sickles. Pauling's theory described the sickling process and Allison's statements demonstrated how sickle cell trait protected against malaria. "Accordingly, we have a molecular mechanism not only for the disease sickle-cell anemia, but also for the protection that the heterozygous condition provides against malarial infection."[53]

In general, Pauling noted that while some molecular mutations are detrimental, sickle cell trait protected against malaria and benefited these individuals. He described three genetic possibilities and translated what each meant for the individual's health as well as explained the genetic make-up of a population procreating in a region with high incidences of malaria. First, people with normal hemoglobin are homozygous dominant and do not exhibit crescent shaped

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[52] Pauling, "Abnormality of Hemoglobin," 234-35; Pauling, "Significance of Molecular Structure to Biology," 37; Pauling, "Molecular Basis of Genetics," 493; Itano and Pauling, "Abnormal Hemoglobin," 519-20; Pauling, "Molecular Disease and Evolution," 4. Only Allison was mentioned in Pauling, "Nature of Forces," 222; Pauling, "Molecular Structure and Disease," 5.

[53] Pauling, "Molecular Basis of Genetics," 493.

hemoglobin; therefore, they do not have sickle cell trait or sickle cell anemia and additionally are not protected against malaria. Most likely, the majority of these people would die from malaria and therefore stop procreating. Secondly, those born homozygous recessive for sickle cell hemoglobin suffer from sickle cell anemia and typically die young, usually without procreating. Thirdly, those with heterozygous hemoglobin have sickle cell trait and withstand infection from the malaria parasite. These people benefit most in an area with high mortality rates from malaria because they do not contract either disease full-blown.[54] Pauling calculated that in every generation fighting malaria, 1.5 heterozygotes would be born to every one person with normal hemoglobin. Thus, under these conditions the number of people born with sickle cell trait increases rapidly.[55]

In areas where malaria is not endemic, Pauling confidently averred that the sickle cell mutation was being removed from the human germ plasma. However, Pauling thought that the natural rate of removal happened too slowly in comparison to the introduction of new mutations. Thus, he promoted eugenic practices as a way to decrease the number of mutations that passed to future generations.[56]

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[54] Pauling, "Abnormality of Hemoglobin," 235; Pauling, "Molecular Basis of Genetics," 493; Pauling, "Molecular Structure," 5; Pauling, "Nature of Forces," 222-23; Pauling, "Our Hope," 168; Emile Zuckerkandl and Linus Pauling, "Molecular Disease, Evolution, and Genic Heterogeneity," Horizons in Biochemistry, eds. Michael Kasha and Bernard Pullman (New York: Academic Press, 1962): 189-225, 193-94.

[55] Pauling, "Nature of Forces," 223.

[56] Pauling, "Molecular Structure and Disease," 1-7.

**Pauling's Negative Eugenics Program**

Beginning in 1962, about four years after Pauling's initial statements on genetic counseling, he promoted his first eugenics agenda. It was straightforward and got attention. His ultimate goal was to decrease human suffering by eliminating the factors that caused it; to this end, Pauling stated that molecular diseases, like sickle cell anemia, warranted legal intervention. He suggested two criteria. First, a law should require testing for sickle cell hemoglobin in African-Americans. Secondly, in an effort to eliminate sickle cell hemoglobin from the human population, marriage and procreation restrictions should be invoked. Accordingly, if one heterozygote and one homozygous dominant (i.e. a person with normal hemoglobin) marry, then there should be a limit on how many children they can have. If two heterozygotes marry then they should not be allowed to have children. In addition, if two heterozygotes marry, then there is a twenty-five percent chance that they will have a baby with sickle cell anemia. Coupling chance with concern for human suffering, Pauling advocated intervention from authorities.[57] "This percentage is much too high to let private enterprise in love combined with ignorance take care of the matter."[58]

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[57] Zuckerkandl and Pauling, "Molecular Disease, Evolution," 220-22. Although this information comes from an article written by Zuckerkandl and Pauling, Zuckerkandl stated that he conceptualized and wrote most of the article except for the last section, "Fighting Molecular Disease" (220-22), which was Pauling's idea: Emile Zuckerkandl, interview, in "The Molecular Clock," by Gregory Morgan (Palo Alto, California, 11 July 1996): 1-30, 9.

[58] Zuckerkandl and Pauling, "Molecular Disease, Evolution," 222. Pauling reiterated this statement a couple of times. Once, he mentioned that he was quoting Zuckerkandl: Pauling, "Our Hope," 169. Another time, Pauling paraphrased the statement without mention of Zuckerkandl. He said, "I believe that the chance of twenty-five percent is too great to permit the prospective parents to be left in

Pauling repeatedly promoted the need for blood tests and procreation restrictions in his subsequent speeches. Thus, Pauling delivered a speech at the First Inter-American Conference on Congenital Defects and again discussed sickle cell anemia and the genetic chances that a child will be born with sickle cell anemia from heterozygous parents. In addition to outlining the laws that he thought should be put into effect for carriers of sickle cell anemia, Pauling stated that similar rules should be invoked for carriers of phenylketonuria.[59] Eventually, Pauling added other hereditary molecular diseases to his list: "For fibrocystic disease, as for sickle cell anemia, phenylketonuria, and many other diseases..."[60]

Pauling's statements at the Conference on Congenital Defects received commentary from the monthly publication Pediatric Herald in an article titled "Eugenic Approach to Prevention of Congenital Anomalies Urged." The author stated that Pauling was "the strongest advocate of a eugenic approach to prevention of congenital anomalies at the conference." In addition to summarizing Pauling's speech, the author also quoted Pauling on a doctor's potential role in curbing the spread of molecular diseases.

> It would seem to me perfectly logical and proper for physicians to routinely seek such carriers, particularly through premarital testing in high-risk populations such as the Negro people. If, in this screening,

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ignorance about it.": Linus Pauling, "Academic Address," Biological Treatment of Mental Illness, ed. Max Rinkel, MD (New York: L. C. Page and Company, 1966): 30-37, 36.

[59] Pauling, "Molecular Basis of Genetic Defects," 21.

[60] Quote from: Pauling, "Our Hope," 169. Similar statements made in: Pauling Collection, Speeches 1963s.12, Linus Pauling, "The Molecular Basis of Sickle-Cell Anemia and Other Diseases," Scientific Assembly of the National Medical Association Convention, Los Angeles, 13 August 1963.

> the doctor finds that a marriage between two carriers is contemplated, it is his duty to explain the danger and to counsel against the union.[61]

Time also printed a small synopsis of Pauling's speech in an article titled "Inheriting Bad Health." According to the anonymous author, Pauling stated that blood tests should be required: "We should begin now by requiring by law that the simple blood test to detect carriers of sickle-cell anemia be performed before a marriage license is issued." Pauling added that the same should be true of other anemias afflicting people, like thalassemia.[62] In addition, Pauling stated that ultimately the decision on whether or not to have children lies with the prospective parents.[63]

As mentioned, Pauling usually connected his discussions on molecular diseases and nuclear fallout by stating that both caused genetic mutations; however, in 1968 Pauling drew parallels between sickle cell anemia and fallout by noting that both necessitated laws. The article was published in an issue of the UCLA Law Review that focused on the potential legal repercussions of recent biomedical advances: "Designed to shed light on present and future biomedical advances, the symposium has as its underlying theme the idea that law must anticipate and prepare for the scientific advances of tomorrow if it is to remain vital."[64] Other topics

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[61] "Eugenic Approach to Prevention of Congenital Anomalies Urged," Pediatric Herald March 1962, 3(2): 1, 7.
[62] Thalassemia, also called Cooley's Anemia, is similar to sickle cell anemia, however it inflicts Greeks and Italians. (Wailoo, Dying in the City, 194).
[63] "Inheriting Bad Health," Time 2 February 1962: 37.
[64] "For the record," UCLA Law Review 15 (1968): vii-viii, vii.

discussed included artificial kidney machines, organ transplants, and cyronic suspension (the preservation of human bodies by freezing them).

Pauling first noted the need for laws against nuclear weapons testing; however, he only briefly discussed nuclear laws and stated that he planned to focus the article on the laws needed for sickle cell anemia and other molecular diseases. In order to establish that there was too much suffering caused by molecular diseases, Pauling presented statistics about sickle cell anemia and sickle cell trait in the United States. Accordingly, he estimated that about two million people in America were sickle cell heterozygotes, and of those about 100,000 were married to one another. Considering that the probability of two heterozygotes having a child with sickle cell anemia is twenty-five percent, Pauling stated that about 1,200 babies were being born with sickle cell anemia per year and "doomed to a life of suffering and an early death."[65]

Pauling proposed a method for reducing the amount of sickle cell hemoglobin in the world, thereby reducing the amount of suffering. His proposal drew upon his previous propositions and reiterated his promotion of legislation: Pauling stated the need for implementing a law requiring a diagnostic test that would ascertain whether a person had hemoglobin that sickled. Pauling declared that a law should also require the dissemination of information to those who tested positive for sickling hemoglobin. Drawing upon his previous statements, Pauling mentioned that the

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[65] Linus Pauling, "Reflections on the New Biology: Foreword," UCLA Law Review 15.2 (1968): 267-72, 269.

literature given to carriers should suggest a maximum number of progeny allowed by carriers.[66]

Pauling also advocated two new tactics to reduce suffering from sickle cell hemoglobin. Firstly, Pauling stated that carriers should have an obvious mark denoting their disease, which would allow carriers to identify and avoid others with the same affliction. His proposal was a tattoo on the forehead.

> I have suggested that there should be tattooed on the forehead of every young person a symbol showing possession of the sickle-cell gene or whatever other similar gene, such as the gene for phenylketonuria, that he has been found to possess in single dose. If this were done, two young people carrying the same seriously defective gene in a single dose would recognize the situation at first sight, and would refrain from falling in love with one another. It is my opinion that legislation along this line, compulsory testing for defective genes before marriage, and some form of public or semi-public display of the possession, should be adopted. [67]

Additionally, Pauling advocated that two heterozygous parents should consider abortion as a preventative method and stated that he came to this decision after deliberating over the amount of suffering caused by abortions in comparison to the suffering of a defective child.[68] In conclusion to his statements about legislation for sickle cell anemia, Pauling noted that his proposals advocated negative eugenics, which he felt was a less complicated matter than positive eugenics (i.e. promoting

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[66] Pauling, "Reflections," 271.
[67] Pauling, "Reflections on the New Biology," 269. This is the earliest reference that I have found to Pauling's promotion of tattoos, even though he states that he has mentioned them previously.
[68] In 1973, five years after Pauling made this statement, abortion was legalized in the United States (Paul, 143).

legislation to create superior human beings and sterilize, castrate, or kill inferior human beings).[69]

Many historians have commented on Pauling's tattoo eugenics. Diane B. Paul stated that "Pauling wrote at a time when it was still acceptable to urge social responsibility in reproduction."[70] Lily Kay compared Pauling's tattoo proposal to the yellow star that Nazi Germany law forced Jewish people to wear during World War II.[71] Although Pauling did not propose sterilization or genocide – two practices used by the Nazis – Pauling did help gather support for controlling procreation and publicly labeling carriers. In addition to the parallel between Pauling promoting tattoos and the Nazis requiring yellow stars, in the early 1970s some opponents of genetic counseling referred to it as "black genocide."[72]

Pauling's suggested tactics were highly controversial. Psychiatrist Roderic Gorney, who also spoke at the UCLA symposium, outlined three methods for dealing with the new biology. One method was negative eugenics, which he noted "is already under way." Ultimately, Gorney was concerned that new scientific and medical advances allowed people to dictate evolution. Thus, he stated that the genes for genetic diseases were plentiful in people, but that natural selection had kept the diseases from becoming a problem in society. However, he noted that new technologies, like medicines to fight infections, allowed people to stay alive longer causing an "unnatural selection." In other words, people with weaker constitutions

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[69] Pauling, "Reflections," 267-72.
[70] Paul, 166.
[71] Kay, Molecular Vision, 276.
[72] Wailoo, Dying in the City, 186-87.

who in the past would have died without procreating were living normal lives and having babies. Pauling also made this claim in the late 1950s to mid-1960s, as mentioned above. According to Gorney, negative eugenics was problematic because parents could possibly have a healthy child; however, that child might carry the defect and could pass it on to his/her own children.[73]

In October 1968, Pauling gave a speech at Mount Sinai School of Medicine in New York and he again advocated marriage restrictions, tattoo eugenics, and limitations on the number of children allowed by sickle cell carriers. Pauling reiterated statements made earlier that day by Sir Peter Medawar, recipient of the 1960 Nobel Prize in Physiology and Medicine. Specifically, Pauling substantiated Medawar's comments about the progression of medical progress and the deterioration of the human germ plasma.[74] Medawar, like Pauling, thought that negative eugenics should be invoked, but stated that positive eugenics should not be used.

> Positive eugenics may be said to have had the ambition of raising a superior kind of human being…'Negative eugenics', by contrast, has the altogether lesser and more realistic ambition of diminishing and as far as possible correcting, the distress caused by deleterious genes and genetic conjunctions.[75]

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[73] Roderic Gorney, "The New Biology and the Future of Man," UCLA Law Review 15 (1968): 273-356. Gorney's article came from a book he recently published: Robert Gorney, The Human Agenda (New York: Simon and Schuster, 1968): 209-21.
[74] Linus Pauling, "Medicine in a Rational Society," Journal of the Mount Sinai Hospital of New York 36 (1969): 194-99.
[75] P.B. Medawar and J.S. Medawar, "Eugenics," The Life Science: Current Ideas in Biology (New York: Harper and Row, Publishers, 1977): 56-65, 60. Peter Medawar made similar statements in an early article. Peter Medawar, "The Genetic Improvement of Man," The Hope of Progress (London: Methuen and Company, Ltd., 1972): 69-76, 76.

Medawar used many of the same arguments as Pauling and in very similar ways. Thus, he mentioned the benefit of having sickle cell hemoglobin in malarial areas and discussed the possible genetic outcomes of a baby from parents who are carriers of the same disease.

> When two victims of sickle cell trait bear children, then according to Mendelian rules approximately one quarter will be normal, half will be carriers like their parents and one quarter will be the homozygous victims of sickle cell anaemia, which is almost invariable fatal.[76]

Medawar also promoted counseling against marriages and procreation between heterozygotes.

> Most overt cases of the [recessive] disease could be eliminated in one generation if, having been identified, the carriers of the *same* harmful recessive gene were to be discouraged from marrying *each other* or at least from having children by each other... What is being proposed here is that carriers of the *same* harmful recessive gene, when they can be identified, should either be discouraged from childbearing or warned of the consequences of doing so – to wit that approximately one quarter of their children will be afflicted by the malady of which the gene is a determinant.[77]

Pauling and Medawar's speeches at Mount Sinai received press from Barbara Yuncker, a renowned scientific writer for the New York Post.[78] In her article titled "Bad Genes and Marriage," she quoted Pauling on his promotion of tattoos denoting genetic disease. Pauling acknowledged that a less obvious demarcation might be more plausible.

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[76] Medawar and Medawar, 60.
[77] Medawar and Medawar, 63-64. Authors' italics.
[78] Information about Barbara Yuncker is from a biographical sketch found on the DePauw University website: http://www.depauw.edu/library/archives/inventories/YUNCKER1.htm. Found on 5 September 2003.

> I agree we should keep these carriers from marrying one another. I have advised, not entirely joking, that individuals should have tattooed on their foreheads symbols for the defective genes they carry...Because of certain objections which might be raised, a ribald friend suggests it would be better to tattoo symbols in Braille on their abdomens.[79]

Like Pauling, Medawar also advised against marriages between carriers of hemolytic anemias and phenylketonuria because of the potential birth defects. Medawar substantiated his opinion differently than Pauling: he stated that parents have not been given the right to bear invalids.

> It is humbug to say that such a policy violates an elementary right of human beings. No one has conferred upon human beings the right knowingly to bring maimed or biochemically crippled children into the world.[80]

In the early 1970s, Pauling continued to promote eugenic practices for curbing molecular diseases. Hence, in 1971 he stated that he wanted to eliminate sickle cell disease from the human germ plasma, but did not mention what methods should be invoked.[81] However, about one year later, an audience member accused Pauling of being a racist after he gave a lecture titled "Abnormal Hemoglobin Molecules in Relation to Disease" at Michigan State University on 21 April 1972.[82] Dr. Robert Nalbandian, a pathologist and physical chemist who studied sickle cell anemia, wrote to Pauling two weeks later about the incident.

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[79] Barbara Yuncker, "Bad Genes and Marriage," New York Post 12 October 1968: 12.
[80] Yuncker, 12.
[81] Pauling, Molecular Aspects, ix-x.
[82] Unfortunately, there are no notes from the Renaud Lectures Pauling delivered at Michigan State University from 19-21 April 1972. Pauling Collection, Speeches 1972.

> I was stunned to hear in the question and answer period you, of all human beings, accused of racism because you, like myself, urge mass screening and vigorous genetic counseling against having children in heterozygote S matings. The only hope of Black Americans and others of the elimination of this dreadful disease as soon as possible is by such methods. How pathetically confused and misguided zealots can be!! [83]

The audience's reactions to Pauling's statements demonstrate the change in views developing at this time as a result of the Civil Rights Movement. In the early 1970s eugenic statements about sickle cell diseases, like those made by Pauling, came under attack by civil rights activists, who were wary of compulsory screening for the disease. By early 1972 not only was sickle cell anemia a major focus of the United States government because of the National Sickle Cell Anemia Control Act of 1972, but also discussions flared about the inferiority stigma associated to African-Americans because they were the primary carriers of sickle cell hemoglobin.[84] Pauling, who openly supported controversial opinions throughout his lifetime (by refusing to comply with anti-communism demands, promoting the test ban treaty, and advocating the benefits of vitamin C), took an unusual course in the case of sickle cell diseases. After twenty years of supporting negative eugenics, he became silent about eugenic issues around 1972 at the height of the controversy. The difference between Pauling's other crusades and sickle cell anemia is that Pauling took a liberal stance against communism, nuclear weapons testing, and conventional medical practices;

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[83] Linus Pauling Archives at Oregon State University, Nalbandian correspondence found in the book he edited. Molecular Aspects of Sickle Cell Hemoglobin: Clinical Applications, ed. Robert M. Nalbandian (Springfield, Illinois: Charles C. Thomas Publisher, 1971).

[84] Wailoo, Dying in the City, 187.

but with sickle cell anemia he expressed more conservative opinions and did not side with the underdog, African-Americans.

By 1970 the demand for voluntary sickle cell screening programs increased. Some of those requesting voluntary widespread screening were African-Americans. For example, the Black Athletes Foundation led by Willie Sturgell of the Pittsburgh Pirates and World Heavyweight Champion Muhammed Ali circulated information about the disease's symptoms and suggested to African-Americans that they get tested for sickle cell trait.[85] In addition, President Nixon supported the National Sickle Cell Anemia Control Act, which Congress passed in 1972.[86] The Control Act aimed at screening, educating, and counseling carriers of sickle cell trait as well as setting up a research institute to study the cause and treatment of sickle cell diseases.[87] Proponents of the act, like Walter E. Fauntroy a Representative from Washington D.C., promoted genetic counseling similarly to Pauling.

> Those who are found to carry an abnormal hemoglobin gene could be counseled to be sure that their mates were tested. Only in this way can heterozygote pairs be detected, and only in this way can informed decisions be made about childbearing among "at risk" parents. This is not to suggest that a couple will decide to have no children; it is to suggest that whatever they do will be done on the basis of an informed and intelligent decision. [88]

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[85] House of Representatives, Hearing before the Subcommittee on Public Health and Environment of the House Committee on Interstate and Foreign Commerce, Research, Treatment and Prevention of Sickle Cell Anemia (Washington: United States Government Printing Office, 1972): 45-48.

[86] Kevles, 255-58, 278. In the same year after the passage of the Sickle Cell Anemia Act, the National Cooley's Anemia (also known as thalessemia) Control Act passed. In 1976 the National Genetic Diseases Act was enacted, which enveloped the other two acts and also included other genetic diseases.

[87] House of Representatives, 4.

[88] House of Representatives, 32.

Although the act specified that the program was voluntary, discussions between the Representatives and physicians demonstrate that many people felt that screening for sickle cell trait should be routine. James R. Kimmey, Executive Director of the American Public Health Association, suggested that hospitals screen for sickle cell trait whenever they took blood samples from African-Americans. Others thought that sickle cell trait screening should be added to the blood tests done for marriage licenses, as Pauling had suggested ten years earlier.[89]

Government officials and physicians were not the only people discussing whether screening should be voluntary or routine for sickle cell hemoglobin carriers.[90] Nalbandian bolstered compulsory mass screenings and genetic counseling for sickle cell anemia.

> The testing techniques for hbS [sickle cell hemoglobin] coupled with vigorous, advocative [sic] genetic counseling, can eliminate sickle cell disease from the U.S. in 1 or 2 generations. Unfortunately this potential gain in the general health level of Black Americans will NOT be realized at present because of the overriding influence of prevailing secondary societal, political, and personal considerations...Current attitudes in the U.S. on mass screening and passive genetic counseling simply operate to perpetuate the scourge of sickle cell disease into future generations.[91]

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[89] House of Representatives, 71, 99. In 1972 forty-five states required blood tests prior to issuing a marriage license. Pauling mentioned marriage licenses in 1962; he was quoted in "Inheriting Bad Health," Time 2 February 1962: 37.

[90] Kevles, 277.

[91] Pauling Collection, Science 6.016.2, Robert M. Nalbandian, Col. Frank R. Camp, Jr., and Raymond L. Henry, "The Case for Mass Screening of Sickle Cell Hemoglobin," Abstract presented at the First National Symposium on Sickle Cell Disease, no date. According to a synopsis on John Hercules of the National Heart and Lung Institute, he organized the First National Symposium on Sickle Cell Disease held in June 1974. From http://www.rhofed.com/sickle/pdfs/hercules.pdf

In 1974, Neel worried about the possibility of compulsory measures for people with genetic diseases because he felt that screening, genetic counseling, and treatment should be voluntary.[92] Doris Y. Wilkinson, a medical sociologist, fought against mandates for preventing the spread of sickle cell anemia because she felt they were racially discriminatory. Wilkinson pointed out that the services provided by the 1972 Sickle Cell Anemia Control Act were designated as voluntary and lamented that some aspects had become compulsory in the two years since the Act had passed.

> Recently sickle cell has spiraled explosively into the political arena and stringent health legislation has become a special form of medical politics. As marriage counseling law, mandatory testing, legislation, and a vast array of "beneficent" proposals have erupted almost simultaneously from coast to coast, sickle cell appears to out rank politically other diseases. In some areas, mandatory testing of infants has been proposed or enacted, and since compulsory – against the wishes of their parents.[93]

Ultimately, Wilkinson asked her reader whether mandatory laws for the control of sickle cell anemia were to benefit African-Americans or Caucasians. Historian Keith Wailoo has noted the controversy surrounding the 1972 Control Act, especially because the Act helped to pinpoint carriers. Many who supported the Control Act argued that electrophoresis should be used to designate carriers of sickle cell hemoglobin. Wailoo states that electrophoresis changed the way people viewed sickle cell diseases in the second half of the twentieth century, and as a result after the late 1960s, genetic counselors and social policymakers targeted carriers of sickle cell hemoglobin. Some African-Americans viewed genetic counseling as a tactic to

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[92] James V. Neel, "On Emphases in Human Genetics," Genetics 78 (1974): 35-40, 38.
[93] Doris Y. Wilkinson, "For Whose Benefit? Politics and Sickle Cell, The Black Scholar 5 (1974): 26-31, 27.

control the population and an effort to impinge on their rights to make their own decisions.[94]

Pauling's eugenic statements were most likely cultivated by two foundations from which he received generous grants: the Rockefeller Foundation and the Ford Foundation. From the 1920s to 1950s, the guiding philosophy of the Rockefeller Foundation was the "Science of Man," which connected the Foundation's programs in medical, natural and social sciences and encouraged "social control." According to Kay, the philosophy successfully filtered down to those associated with the Foundation. Thus, Weaver, who supported the "Science of Man" within the natural sciences program, most likely influenced Pauling's promotion of eugenics. Like the Rockefeller Foundation, the Ford Foundation tried to make political and social statements by bolstering behavioral sciences with applied sciences.[95]

**The Molecular Evolutionary Clock**

During his final years at Caltech, the early 1960s, Pauling started a new line of inquiry with the aid of Emile Zuckerkandl. They proposed an evolutionary theory called the molecular clock, in which they analyzed the hemoglobin of different species. Specifically, they compared the amino acid sequences of hemoglobins and speculated how many million of years ago two species deviated from a common progenitor. In addition to hemoglobin from healthy human adults, they also examined

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[94] Wailoo, Drawing Blood, 180-87; Wailoo, Dying in the City, 185.
[95] Kay, Molecular Vision, 48-50, 98, 274-75. The Ford Foundation was incorporated on 15 January 1936. See: Pauling Collection, Science 14.034.1, "Report of the Trustees of the Ford Foundation," 27 September 1950, 3.

abnormal human hemoglobin. Pauling and Zuckerkandl proposed that other proteins could be analyzed, although they performed their experiments on hemoglobin and related proteins; for example, they examined cytochrome c, which contains iron and aids respiration through intracellular oxidation.

> I believe that it will be possible, through the detailed determination of amino-acid sequences of hemoglobin and other molecules, to obtain much information about the course of the evolutionary process, and to illuminate the question of the origin of species.[96]

Scientists accepted Pauling and Zuckerkandl's proposal slowly because of the constant rate of evolution that they proposed; however, prominent men of science have noted its impact, and investigators have expanded upon Pauling and Zuckerkandl's original research.[97]

Pauling developed his interest in the link between hemoglobin and evolution through his earlier work. Landsteiner, Pauling's mentor in immunology, thought serology could improve knowledge of evolution. Thus, in the second chapter of his book The Specificity of Serological Reactions, Landsteiner stated, "...it would be possible to outline broadly the genealogical tree of animals on the basis of serum

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[96] Pauling, "Molecular Disease and Evolution," 8.

[97] For a discussion of later research by other investigators on the molecular clock see: Emile Zuckerkandl, "On the Molecular Evolutionary Clock," Journal of Molecular Evolution 26 (1987): 34-46, 39-44. For information about the impact and doubts of the molecular clock see: Gregory Morgan, "Emile Zuckerkandl, Linus Pauling, and the Molecular Clock, 1959-65," Journal of the History of Biology 31 (1998): 155-78, 174-78; Gregory Morgan, "The Genesis of the Molecular Clock," Linus Pauling: Scientist and Peacemaker, eds. Cliff Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 169-76, 174-76.

reactions alone if the data were extensive enough."[98] Additionally, Landsteiner mentioned hemoglobin in particular:

> ...species specificity is not restricted to serum proteins. Thus, precipitins can be prepared which distinguish the hemoglobins and hemocyanins of various kinds of animals. One can safely assert that the differences depend upon the globin, the prosthetic group [i.e. the heme] probably being the same in all hemoglobins...[99]

As discussed in Chapter One, Pauling was familiar with Landsteiner's book and wrote a chapter for the 1945 edition.

Ultimately, Landsteiner believed that successful chemical reactions between the bodily fluids of two different species would demonstrate common lineage. Landsteiner and C. Phillip Miller, Jr. mixed the immune sera and red blood cells of two different species; their experiments examined man and primates. They used titration and absorption experiments to observe agglutination of the mixture and found that antisera (a serum with antibodies) from man was absorbed more readily by the red blood cells of higher primates than that of man and the lower primates.

> The difference between the bloods of the lower monkeys on the one hand and of man and the anthropoids on the other is considerably greater than that between the two latter, as is seen from the titers of the immune sera and the results of the absorption experiments."[100]

Landsteiner and Miller used all four types of human bloods (A, B, AB, and O) for their experiments because they wanted to see if the various blood groups yielded different results. Landsteiner had received the 1929 Nobel Prize for the discovery of

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[98] Landsteiner, 14.
[99] Landsteiner, 20.
[100] Karl Landsteiner and C. Phillip Miller, Jr., "Serological Studies on the Blood of Primates. I. The Differentiation of Human and Anthropoid Bloods," Journal of Experimental Medicine 42 (1925): 841-52, quotation from page 851.

blood groups. Landsteiner and Miller also analyzed the blood of anthropoid apes and found that apes have four blood groups analogous to the four human blood groups. Blood groups had already been compared for frequency of blood type among and between the human races. Landsteiner and Miller stated that this new information relating the blood of humans and the higher primates substantiated the theory that blood groups existed prior to the evolution of man from ape.[101] The technique of Landsteiner and Miller's experiments differed from Pauling and Zuckerkandl's approach; however, their concepts and conclusions were similar.

Pauling suggested their project to Zuckerkandl when he arrived at Caltech in 1959 as a postdoctoral fellow. Zuckerkandl originally worked with Richard T. Jones, a graduate student at Caltech, who taught Zuckerkandl fingerprinting – the technique Zuckerkandl used to compare the amino acid sequences of various hemoglobins.[102] As mentioned in Chapter Two, fingerprinting is a dual process of paper electrophoresis and paper chromatography, which produces a migration pattern that differentiates between the various amino acids of polypeptide chains. After producing patterns for many species, Pauling and Zuckerkandl compared the fingerprints and concluded which species were closely or distantly related. Thus, they argued that the hemoglobin genes of humans and primates had stabilized before the two organisms diverged evolutionarily. More specifically, they found that there was a closer

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[101] Karl Landsteiner and C. Phillip Miller, Jr., "Serological Studies on the Blood of the Primates. II. The Blood Groups in Anthropoid Apes," Journal of Experimental Medicine 42 (1925): 853-62.

[102] Morgan, "Zuckerkandl," 162; Zuckerkandl, "On the Molecular Evolutionary Clock," 34.

relationship between the hemoglobin of humans and apes than humans and orangutans. In addition, they stated that human hemoglobin was more similar to pig and cattle than to fish, which substantiated the theory that fish and land animals separated long ago and proceeded to follow different evolutionary paths.[103]

Zuckerkandl, Jones, and Pauling briefly mentioned abnormal hemoglobins in their paper. They proposed that normal adult hemoglobin is more stable than its mutated forms and therefore might revert to its more stable form, a process called back-mutation. Also, the instability of abnormal human hemoglobin explained why various abnormal hemoglobins had different amino acid mutations at the same alleles.[104]

Zuckerkandl and Pauling wrote several articles on hemoglobin and evolution between 1960 and 1965, one of which focused on molecular disease.[105] In this article, they expanded the evolutionary theory and included a timeframe; thus, they proposed that one amino acid substitution occurs for every eleven to eighteen million years.

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[103] Pauling Collection, Science 6.015.9, Press release dated 16 September 1960;Emile Zuckerkandl, Richard T. Jones and Linus Pauling, "A Comparison of Animal Hemoglobins by Tryptic Peptide Pattern Analysis," Proceedings of the National Academy of Science of the United States of America 46 (15 October 1960): 1349-360.

[104] Zuckerkandl, Jones and Pauling, 1349-360.

[105] Some of the briefer articles on the molecular clock written by Zuckerkandl and Pauling that are not discussed extensively include: Linus Pauling, and Emile Zuckerkandl, "Chemical Paleogenetics: Molecular 'Restoration Studies' of Extinct Forms of Life," Acta Chemica Scandinavica 17 (1963): 9-16; Emile Zuckerkandl and Linus Pauling, "Molecules as Documents of Evolutionary History," Journal of Theoretical Biology 8 (1965): 357-66.

They did not name their theory in this article.[106] The extensive discussion of molecular diseases drew upon Pauling's knowledge of sickle cell anemia. Thus, they wrote about the protective value that sickle cell hemoglobin has in fighting malaria, and they presented eugenic methods for combating the spread of molecular diseases using sickle cell hemoglobin as the main example.

In the introduction of their paper, Zuckerkandl and Pauling linked evolution and molecular diseases by stating that evolution could be considered a molecular disease. For example, they proposed that "...to evolve must most often have amounted to suffering from a disease. And these diseases were of course molecular." Also they stated:

> The study of molecular diseases leads back to the study of mutations, most of which are known to be detrimental. All loss mutations in a broad sense of the word – involving either the total loss of a protein or the loss of protein function through a structural alteration of the protein – are molecular diseases...More highly evolved organisms have lost powers of synthesis that more primitive organisms possess. It thus appears possible that there would be no evolution without molecular disease. A maintenance of molecular health, although in the interest of the individual, is opposed to evolution. However, only a small fraction of the molecular diseases that occur are used by and turned into evolution.

As a specific example, Zuckerkandl and Pauling noted that higher organisms do not synthesize vitamins internally like lower organisms do, but instead ingest necessary nutrients through diet. (In the late 1960s and afterwards, Pauling often mentioned that humans and primates cannot manufacture vitamin C, whereas lower organisms like pig and cattle can. He used this argument to promote orthomolecular medicine,

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[106] Morgan, "Genesis," 173; Zuckerkandl and Pauling, "Molecular Disease, Evolution," 201.

specifically the ingestion of high doses of vitamin C by human beings for optimum health.[107]) In this article, Zuckerkandl and Pauling confined their discussion of molecular disease to heredity factors that can change the amino acid sequence of a polypeptide chain, which then affects the structural configuration of the molecule and causes illness.[108]

Zuckerkandl and Pauling produced another lengthy paper, which focused on "Evolutionary Divergence and Convergence in Proteins." They proposed that when an amino acid is replaced by another amino acid, the change is conservative or radical: a conservative change occurs frequently, whereas a radical change happens rarely. According to Zuckerkandl and Pauling, only three abnormal hemoglobins of the twenty-two analyzed undergo a radical change, of which sickle cell anemia hemoglobin is one. Thus, the replacement of glutamic acid in normal adult hemoglobin with valine in sickle cell anemia hemoglobin is a radical change.[109] Zuckerkandl and Pauling also re-evaluated some of the articles that came out of Caltech in the early 1950s, which followed the sickle cell anemia paper. Thus, they substantiated the claim made by Neel, Wells and Itano in 1951, which stated that genes control the ratio of normal and abnormal hemoglobin in heterozygotes. They also expanded the theory by stating that inter and intra-genic multiplication occur.

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[107] Linus Pauling, How to Live Longer and Feel Better (New York: W. H. Freeman and Company, 1986): 79-80; Linus Pauling, "Orthomolecular Psychiatry," Science 160 (19 April 1968): 265-71, 265.

[108] Zuckerkandl and Pauling, "Molecular Disease, Evolution," 189-94.The quotations are from 190 and 191 respectively.

[109] Emile Zuckerkandl and Linus Pauling, "Evolutionary Divergence and Convergence in Proteins," Evolving Genes and Proteins: A Symposium, eds. Vernon Bryson and Henry J. Vogel (New York Academic Press, 1965): 97-166, 128-34.

Additionally, Zuckerkandl and Pauling proposed an evolutionary relationship associating the types of chains (alpha, beta, etc.) in organisms. As mentioned above, Rhinesmith, Schroeder and Pauling discovered the alpha and beta-chains in adult human hemoglobin in 1957.[110]

When discussing molecular diseases, Pauling occasionally mentioned the molecular clock. For example, in a speech delivered in 1968 Pauling mentioned the relationship between horse, ape, normal human adult, and sickle cell hemoglobin by discussing Zuckerkandl's experimental work.

> He [Zuckerkandl] found that in the beta chain of the human and the beta chain of the horse, for example, 20 of the 146 amino acids are different; but with human and gorilla, only one is different. It is the same amount of difference, just one amino acid residue, as between ordinary humans and sickle cell anemia patients, who manufacture sickle-cell-anemia hemoglobin.[111]

Pauling also proposed that the amino acid replacement, which causes sickle cell anemia, is an intermediary step in evolution. Thus, he stated that the replacement of glutamic acid in normal adult hemoglobin with valine in sickle cell hemoglobin aided people from contracting malaria. Pauling thought that eventually the valine in sickle cell hemoglobin would be replaced by a different amino acid, one which would protect people who were homozygous recessive from malaria and would not cause the deadly disease, sickle cell anemia. He stated that Hemoglobin C (which has a lysine at the same locus) was most likely the next evolutionary step to fitter human

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[110] Zuckerkandl and Pauling, "Evolutionary Divergence," 152-59.
[111] Linus Pauling, "Medicine in a Rational Society," Journal of the Mount Sinai Hospital of New York 36 (1969): 194-99, quote from 196.

beings.[112] Four years later more information about genetic synthesis became known, and Pauling noted the fallacy in his theory that sickle cell hemoglobin is an intermediary stage in the evolutionary process between normal adult hemoglobin and Hemoglobin C. Hence, he stated that sickle cell hemoglobin and Hemoglobin C both developed from normal adult hemoglobin because the substitution of valine in sickle cell hemoglobin with lysine in Hemoglobin C would require three mutational steps; whereas the replacement of glutamic acid with valine or lysine requires only one step.[113]

**Orthomolecular Therapy**

At the same time that Pauling and Zuckerkandl were conducting research on the molecular clock theory, Pauling resigned from Caltech and tried to find a new workplace. Over the years that Pauling worked at Caltech, he had problems with some of the conservative people associated with the Institute, who disliked his liberal politics. In response to Pauling's alleged association with communism, Caltech administrators stopped giving him pay raises, and in 1958 Pauling reluctantly agreed to resign as Chairman of the Chemistry Department. In 1963 administrators needed more work stations in the chemistry laboratories, and the new Chairman of the Chemistry Division informed Pauling that some of his laboratory space being used for research on mental diseases was needed for research in other areas. In addition to his liberal politics, Pauling had been diligently pursuing peace work in the political arena

[112] Pauling, "Molecular Disease and Evolution," 5.
[113] Zuckerkandl and Pauling, "Molecules as Documents," 362-63.

since the late 1940s, and in 1963 he was awarded the 1962 Nobel Peace Prize. Winning the prize and its monetary award spurred Pauling to resign from Caltech.[114]

For the next ten years Pauling worked at a few locations and then in 1973 decided to start his own institute, eventually named the Linus Pauling Institute of Science and Medicine, with the help of Arthur Robinson. Robinson had been an undergraduate at Caltech in the early 1960s; he went to University of California at San Diego (UCSD) for his graduate degree and then stayed to teach. While Robinson was at UCSD, Pauling also taught there and influenced Robinson to pursue orthomolecular medicine. When Pauling left San Diego for Stanford University, Robinson followed. Robinson oversaw the daily administration of the Institute for its first five years. In 1978 Pauling asked Robinson to resign from his position as president of the Linus Pauling Institute.[115]

The Linus Pauling Institute focuses its research on orthomolecular medicine and orthomolecular psychiatry, disciplines that Pauling defined in 1968. Pauling described orthomolecular therapies as using large doses of substances normally present in the body (e.g. vitamins), instead of introducing man-made substances (e.g. antibiotics). Orthomolecular medicine uses natural treatments for diseases, such as the treatment of diabetes with insulin. Orthomolecular psychiatry treats diseases causing

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[114] Goertzel and Goertzel, Linus Pauling: A Life in Science and Politics, 136, 150, 193-94; Hager, 493, 545-53.

[115] Hager, 586-93, 603-04; Goertzel and Goertzel, Linus Pauling: A Life in Science and Politics, 224-37. According to the Goertzels' biography of Pauling, it is unclear the exact reason why Pauling asked for Robinson's resignation. A lawsuit between Robinson and the Institute ensued and the rift between Pauling and Robinson was never resolved.

mental retardation, for example, prescribing a low phenylalanine diet for phenylketonurics.[116] Pauling claimed that his interest in this field arose from his learning about experiments performed by Abram Hoffer and Humphry Osmond using high doses of niacin to combat mental illnesses. In 1965 Pauling had read Hoffer's book, Niacin Therapy for Psychiatry, which described "megavitamin therapy." Pauling's interest grew early the next year when biochemist Irwin Stone informed Pauling that he would live longer if he took large doses of vitamin C.[117] As pointed out by Barbara Marinacci, Pauling "surprised, even shocked" scientists when he started promoting vitamins; however, Marinacci noted that Pauling followed a logical path from molecular medicine to orthomolecular therapies.[118] Indeed, Pauling himself eventually mentioned the link between his concept of orthomolecular therapies and the treatment administered for his nephritis by Dr. Thomas Addis beginning in the early 1940s. As mentioned in Chapter One, Addis put Pauling on a special diet and in time Pauling overcame the illness.

> I now realize that Addis's regimen was completely orthomolecular. I received no drugs. My treatment involved only the regulation of the intake of substances normally present in the human body: increased intake of water, vitamins, and minerals and decreased intake of protein and, for a time, salt, combined with some rest in bed.[119]

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[116] Pauling, "Orthomolecular Psychiatry," 265-71. In this article Pauling mainly discusses orthomolecular psychiatry, as the title suggests. Linus Pauling, Vitamin C and the Common Cold (San Francisco: W. H. Freeman and Company, 1970): 65-71.
[117] Hager 564-65. Stone was addressing a comment Pauling had made in a speech. Pauling stated that he hoped to live another fifteen to twenty years. Also see: Pauling, Vitamin C and the Common Cold, 4-5.
[118] Marinacci, 209.
[119] Kevin V. Lemley and Linus Pauling, "Thomas Addis," Biographical Memoirs of the National Academy of Sciences of the United States of America 63 (Washington D.C.: National Academy Press, 1994): 3-46.

In 1985 Zuckerkandl outlined the Institute's aim by discussing the connection between molecular disease and orthomolecular medicine. He worked at the Linus Pauling Institute and became its president and director in 1980, a post he left in 1991.[120] Citing the scientific and medical significance of the sickle cell anemia article by Pauling, Itano, Singer, and Wells, Zuckerkandl noted that whereas some mutations in deoxyribonucleic acid (DNA) do not cause debilitating molecular diseases, others do. About the non-harmful diseases, Zuckerkandl stated that people are not affected because they combat them with proper nutrition and vitamins. Of the molecular diseases causing illnesses, there are two types resulting from high or low levels of nutrients. He pointed out that it is easier to treat a nutrient deficiency (rather than an overabundance) and mentioned that orthomolecular medicine strives to develop optimal health by manipulating elements already present in the human body. Ideally, the Institute aimed to use "protein profiling" to establish an individual's nutritional requirements for optimal health. "Protein profiling" examined a person's protein and enzyme levels and then tailored nutritional advice to that individual. In 1985 Zuckerkandl noted that the Linus Pauling Institute was best suited to carry out this research, funds permitting.[121]

Starting in the late 1960s, Pauling had rigorously promoted vitamin C as a method to deter the common cold and cure cancer. Many medical professionals

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[120] "Dr. Emile Zuckerkandl Elected President and Director," The Linus Pauling Institute of Science and Medicine Newsletter, 1.8 (1980): 1-3, 1.

[121] Emile Zuckerkandl, "From Molecular Disease to Orthomolecular Treatment: The Case of Suboptimal Health," The Linus Pauling Institute of Science and Medicine Newsletter 2.7 (1985): 1-2, 7.

undermined Pauling's claims and discredited his authority in medicine. These physicians noted that Pauling's well-established reputation was in chemistry and peace (as his Nobel Prizes proved), but not nutrition. They pointed out that Pauling did not conduct his own experiments, but rather re-evaluated the literature on vitamin C published in medical journals over numerous years. Additionally, he based his statements that vitamin C improves health by coming to different conclusions than the authors of the papers he had read. Pauling's adversaries found his approach problematic, especially because the original investigators had stated that no definite conclusions could be made.[122] In a 1990 interview, Pauling relayed his dismay that medical professionals discredited his statements and mentioned the irony that the journal editors valued his research on sickle cell anemia, but not on vitamin C and other nutrients.

> Modern Medicine published an attack on me for a whole lot of things. I wrote to the man, the editor of Modern Medicine and said, "You remember that Modern Medicine gave me the Modern Medicine Award four or five years ago for my work on sickle cell anemia? And here you are attacking me."...I had been astonished by the medical

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[122] Rima D. Apple, "'Superior Knowledge': Pharmacists, Grocers, Physicians, and Linus Pauling," Vitamania: Vitamins in American Culture (New Jersey: Rutgers University Press, 1996): 54-84, 75-84. For a detailed account of the vitamin C debate with Pauling as a key player see: Evelleen Richards, Vitamin C and Cancer: Medicine or Politics? (London: Macmillan Professional and Academic, Ltd., 1991). The skepticism among medical professionals about Pauling's promotion of vitamin C is well documented see: Goertzel and Goertzel, Linus Pauling: A Life in Science and Politics, 201-08; Hager, 573-97; Pauling, Vitamin C, the Common Cold, and the Flu (San Francisco: W. H. Freeman and Company, 1976): 121-38; Pauling, How to Live Longer, 300-16; Steve Austin and Cathy Hitchcock, "The Linus Pauling-Mayo Clinic Controversy Involving Vitamin C and Cancer Tests," The Consumer's Medical Journal, 71 (1994): 10, 2 pages.

> profession, the response of the medical profession to orthomolecular ideas.[123]

Prior to starting the Linus Pauling Institute, Pauling worked at Stanford University where he met Dr. Paul Wolf, director of the clinical laboratory at Stanford's medical center from 1968 to 1974.[124] In 1971 Pauling and Wolf discussed starting clinical trials on sickle cell anemia sufferers by way of orthomolecular methods using vitamin C, urea, and nicotinic acid (also called niacin). Pauling had heard promising things about nicotinic acid from Hoffer; thus, he was confident that "n. [nicotinic] acid would be much more effective than either ascorbic acid [vitamin C] or urea."[125] About one year later, Wolf responded that nicotinic acid did not block or reverse sickling and that research on niacin no longer interested him. He suggested to Pauling that they submit a funding proposal to the National Heart and Lung Institute for research on the treatment of sickle cell anemia with vitamin C.[126]

As a result of the 1972 National Sickle Cell Anemia Act, the United States government allocated large amounts of money to sickle cell anemia research. The one million dollars set aside in 1971 increased to five million for 1972. By February 1972 the five million for that year was increased to ten million dollars, and President Nixon

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[123] Linus Pauling, "Interview with Dr. Linus Pauling," by Wayne Reynolds, Big Sur, California, 11 November 1990, Linus Pauling: Scientist and Peacemaker, eds. Cliff Mead and Thomas Hager (Corvallis: Oregon State University Press, 2001): 31-55, 53. Also, Pauling mentioned the comments made in Modern Medicine in two of his books: Pauling, Vitamin C the Common Cold and the Flu, 136-37; Pauling, How to Live Longer and Feel Better, 311-12.

[124] Pauling had started working at Stanford in the fall of 1969 (Hager, 571).

[125] Pauling Collection, W: Correspondence, 1971-1973, Letter from Pauling to Paul Wolf dated 13 January 1971.

[126] Pauling Collection, W: Correspondence, 1971-1973, Letter from Wolf to Pauling dated 7 December 1971.

suggested that fifteen million dollars be made available for 1973. The Act stipulated that the National Heart and Lung Institute, which operates under the National Institutes of Health, would decide how to allocate the money.[127]

Pauling and Wolf drafted a proposal for trials to search for an anti-sickling agent through dietary control. They believed that there was a relationship between metabolism and diet, which could aid prevention and treatment of sickle cell anemia. They proposed to analyze the urine of sickle cell patients using a test developed by Robinson and his colleague, Dr. Roy Teranishi. They hoped that the urine test might "throw light on the mechanism of sickling and the reasons for the occurrence of crises of the disease." As a selling point, the proposal marketed Pauling's earlier sickle cell anemia research.

> It is worthy of note that the project director [Linus Pauling] for this research performed pioneering work in the molecular understanding of this disease and has continued to play an influential role in continued research to date.

According to the proposal, Pauling and Wolf were aware that the National Institutes of Health had more money to allocate to sickle cell disease research. [128]

In June 1972, Pauling, Wolf, Robinson and three other men met with Dr. Foster of the National Institutes of Health and Dr. John Hercules of the National Heart and Lung Institute to negotiate the sickle cell anemia contract and eventually

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[127] House of Representatives, 1, 29. Information about the amount of money set aside each year: 78-79.

[128] Pauling Collections, Science 6.016.2, "The Involvement of Humoral, Metabolic, and Molecular Factors in Sickle Cell Crisis," no date, Abstract, 1-2. The proposal did not have a date, but noted that they wanted the funding to start in summer of 1972.

received $92,000.[129] Prior to the meeting, Dr. Israel Rabinowitz of the Stanford University Clinical Laboratory, one of the men present at the meeting, suggested to Pauling that they team up with the Mid-Peninsula Sickle Cell Anemia Foundation, which needed $10,000 to $15,000 to operate a screening and counseling program. If Pauling could get the money from the National Institutes of Health, then the Mid-Peninsula Foundation would give Pauling and his collaborators the electrophoresis data. Pauling agreed to negotiate for the funds; however they did not allocate any money to the Mid-Peninsula Foundation.[130]

Pauling and Wolf devised another clinical trial in the summer of 1972 using vitamins C and E for sickle cell patients. The concept for the trial arose from Pauling's desire to prove the efficacy of vitamin C. As mentioned, many medical doctors undermined Pauling's concept of orthomolecular medicine; in response Pauling regularly asked for more information about medical trials that failed to show the benefits of orthomolecular therapies, especially vitamin C.[131] Thus when Pauling read a short statement written by Dr. Mervyn L. Goldstein of New York, which said

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[129] Pauling Collection, Science 6.017.8, Linus Pauling office memorandum dated 19 June 1972 regarding 16 June 1972 meeting with Dr. Foster, NIH. For information stating that they received the grant see: Pauling Collection, N: Individual Correspondence, Robert Nalbandian, Letter from Nalbandian to Pauling dated 12 October 1972.

[130] Pauling Collection, R: Correspondence, 1970-1974, Letter from Israel Rabinowitz to Pauling dated 13 June 1972. Pauling Collection, Science 6.017.8, Linus Pauling office memorandum dated 19 June 1972 regarding 16 June 1972 meeting with Dr. Foster, NIH.

[131] The vitamin C controversy is well documented see: Hager, 573-97; Richards, Vitamin C and Cancer; 75-170; Pauling, Vitamin C, the Common Cold, and the Flu, 121-38; Steve Austin and Cathy Hitchcock, "The Linus Pauling-Mayo Clinic Controversy Involving Vitamin C and Cancer Tests," The Consumer's Medical Journal, 71 (1994): 10.

that vitamin C exacerbated the symptoms of a patient suffering from sickle cell-thalassemia disease, Pauling wrote to Goldstein requesting information about his patient. Specifically, Pauling wanted to know the amounts of vitamin C she had taken during sickness and health, the dates of her sicknesses, and statements about the nature of the bouts of sickness.[132] Pauling also wrote to Wolf about the matter, enclosing the article and telling Wolf that he wanted to research the effects of high doses of vitamin C on sickle cell patients. A couple of months later Pauling wrote a letter to Wolf summarizing the trial they discussed conducting. They had decided upon a strict dietary plan, which included eliminating sucrose, and adding four grams of vitamin C per day, 800 milligrams of vitamin E per day and some other nutritional substances.[133]

In the early 1970s, Pauling solicited organizations other than the National Institutes of Health for funding for sickle cell research. In October 1971 Pauling asked Nalbandian for contact information for the International Sickle Cell Anemia Foundation because Pauling hoped "to used the highly developed methods of analysis of urine that are new operating at our laboratory in a study of sickle-cell anemia, and especially of the effect of the increased blood urea concentrations on biochemical

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[132] Mervyn L. Goldstein, "High Dose Ascorbic Acid Therapy," Journal of the American Medical Association 216 (1971): 332; Pauling Collection, G: Correspondence 1970-1976, Mervyn L. Goldstein, Letter from Pauling to Goldstein dated 6 June 1972. There is no reply from Goldstein.

[133] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, Two letters from Pauling to Wolf dated 12 June 1972 and 25 August 1972.

reactions taking place in the human body."[134] In November 1975 Pauling wrote to Edward Broome of San Francisco's Sickle Cell Anemia Research and Education, Inc. (SCARE) and mentioned that he wanted to conduct research on patients using nutritional therapies by means of orthomolecular medicine. Robinson wrote a more specific letter to Broome outlining the plans for the medical trial and the funding the Institute required. The Institute had formulated a nutritional supplement with "amino acids, salt, and a bulk source of calories," which they planned to start using on patients suffering from various diseases. Robinson noted that they wanted fifty sickle cell anemia patients supplied from Broome's organization and about $10,000 to pay for the supplement and researchers. Broome replied that the Sickle Cell Anemia Research and Education, Inc. would not fund the research due to cutbacks. "Until the Congress reaffirms the National Sickle Cell Anemia Control Act now pending before it, the federal priority reduction in this field will reverberate throughout the world."[135]

Pauling corresponded with physicians conducting trials on sickle cell anemia. For example, Robert G. Houston of the Foundation for Mind Research in New York sent Pauling a paper he had written, which analyzed the effects of vitamin $B_{17}$ (also called nitrilosides) on sickle cell patients. Houston had read Pauling's foreword in Molecular Aspects of Sickle Cell Hemoglobin in which Pauling discussed several

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[134] Pauling Collection, N: Individual Correspondence, Robert Nalbandian Letter from Pauling to Nalbandian dated 11October 1971.

[135] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, Letter from Pauling to Broome dated 30 November 1975, Letter from Robinson to Broome dated 16 December 1975, Letter from Broome to Pauling dated 26 March 1976. In spring of 1976 Congress passed the National Genetic Disease Act, which replaced the National Sickle Cell Anemia Act (Kevles, 256).

possible orthomolecular therapies for sickle cell anemia, including vitamin C and niacin.[136] Pauling and Houston corresponded for the next two years about Houston's work.[137]

Pauling also corresponded with Nalbandian of Blodgett Memorial Hospital in Michigan. Nalbandian studied under Murayama, a student of Pauling's at Caltech for two years starting in 1954, and together Nalbandian and Murayama conducted clinical trials on sickle cell anemia patients using urea.[138] Urea looked promising in the early 1970s as a desickling agent or an inhibitor of sickling. Nalbandian and Murayama developed their urea treatment from Pauling and Mirsky's 1936 paper on denaturation and Murayama's 1966 paper on the molecular basis of the sickling process. Urea breaks hydrophobic bonds, which are formed when the red blood cells distort into a crescent shape. Also, urea in a sugar solution successfully converts sickled cells to the normal discus-shaped, however too much urea causes dehydration and the red blood cells to lose hemoglobin (i.e. hemolysis).[139] By 1974 most clinicians gave up on urea because they could not successfully reproduce

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[136] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, Letter from Houston to Pauling dated 29 March 1973; Pauling, Molecular Aspects of Sickle Cell Hemoglobin, ix.

[137] Other correspondence between Pauling and Houston can be found in Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia; Pauling Collection, Science 6.016.2, Letter from Houston to Pauling dated 18 June 1974.

[138] "Sickle Cell Anemia: Advances Continue amidst Medical, Political Controversies," Medical World News 11 (3 December 1971): 36, 7 pages, 41.

[139] Makio Murayama and Robert Nalbandian, Sickle Cell Hemoglobin: Molecule to Man (Boston: Little, Brown and Company, 1973): 130-87. In Chapter Three Murayama discusses his molecular theory of the sickling process. The original paper is: Makio Murayama, "Molecular Mechanism of Red Cell 'Sickling'," Science 153 (1966): 145-49.

Nalbandian's clinical trials.[140] Pauling also became wary of urea as a treatment method for sickle cell anemia and one year after writing a foreword for Nalbandian he declined writing another foreword to Nalbandian and Murayama's upcoming book, which had two chapters on using urea for treating sickle cell anemia crises.[141] In December 1971 Nalbandian wrote to Pauling that a television documentary was going to be filmed about sickle cell anemia and requested an interview from Pauling. Pauling agreed and suggested that Itano also be contacted, to which Nalbandian complied. Produced by the ABC affiliate station in Grand Rapids, the 1971 documentary, "Sickle Cell Anemia: Paradox of Neglect," won an Emmy. Nalbandian commended Pauling for his contribution by stating, "We all believe that without your participation we never would have won it."[142] Nalbandian continuously praised Pauling for the extensive work he had contributed to the understanding of sickle cell anemia as seen when he asked Pauling to write the foreword to the book he edited, Molecular Aspects of Sickle Cell Hemoglobin.

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[140] Pauling Collection, Science 6.017.8, Correspondence re: Hemoglobin and Sickle Cell Anemia, "Sickle Cell Cure Falters in Tests," San Francisco Chronicle 4 March 1974. Wailoo, Dying in the City, 191.

[141] Pauling Collection, Nalbandian Correspondence, Letter from Nalbandian to Pauling dated 2 May 1973. Pauling wrote the foreword for Molecular Aspects of Sickle Cell Hemoglobin: Clinical Applications, ed. Robert M. Nalbandian (Springfield, Illinois: Charles C. Thomas Publisher, 1971). The book that Pauling declined writing the foreword for was Makio Murayama and Robert Nalbandian, Sickle Cell Hemoglobin: Molecule to Man (Boston: Little, Brown and Company, 1973).

[142] Pauling Library, Robert M. Nalbandian, ed., Molecular Aspects of Sickle Cell Hemoglobin: Clinical Applications (Springfield, Illinois: Charles C. Thomas Publisher, 1971), Letter from Nalbandian to Pauling dated 1 May 1972. The letter was in the book.

> It must be most gratifying, even to a man of your numerous distinctions, to see how one of your powerful ideas in 1949 has burgeoned so productively in so many diverse fields of science. The research work we have done on sickle cell anemia is a direct consequence of your epochal 1949 paper in Science.[143]

After the early 1970s, the amount of research that Pauling conducted on sickle cell anemia and hemoglobin diminished significantly, yet he continued to read about the subjects, as will be seen in the next subsection. Stephen Lawson, who has worked at the Linus Pauling Institute since the late 1970s, noted that the Institute had little money to work with and most of it came from private donations. With the limited funds, the Institute pursued research on the therapeutic benefits of vitamins for fighting cancer, a topic that excited Pauling greatly. Also, private money contributed to the Institute was spent as the donors requested. Most likely, Pauling's work on hemoglobin and sickle cell anemia reduced out of necessity because of his increased interest in cancer and orthomolecular therapies and because funding did not allow Pauling to have side projects outside of the Institute's scope. Possibly it was too expensive to invest in the machinery needed to produce important hemoglobin research, especially when the Institute could analyze urine instead. Additionally, few of Pauling's co-workers at the Institute had worked with hemoglobin.[144] Pauling contributed scientific ideas even when he lacked funds, a laboratory, and students by writing theoretical articles.

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[143] Pauling Collection, N: Individual Correspondence, Robert Nalbandian, Letter from Nalbandian to Pauling dated 29 December 1971.

[144] Personal conversation with Stephen Lawson of the Linus Pauling Institute of Science and Medicine on 7 October 2003. One person at the Institute that had worked with hemoglobin was Emile Zuckerkandl, but his focus shifted to other projects while at the Institute.

**Pauling Disputes Citations and Follows-Up on his Prior Hemoglobin Publications**

Reputation is important is science. It gets the investigator money for research, a good position at a good institution, and much more. There are many factors that establish and preserve one's reputation including priority and recognition. Priority goes to the person who publishes first and ideally, the scientist is attributed with the discovery ever after. Therefore, proper recognition through citations is a key factor in establishing a scientist's reputation. Even though Pauling's name was well-established in science by the 1960s, he still valued his good reputation and the continued recognition of his prior work, just as he had worked to establish his priority and originality in earlier years.

Throughout his lifetime, Pauling read articles that related to his earlier work on hemoglobin. In a couple of cases, he published statements critiquing recent work. In 1961 Itano and Pauling published in Nature a letter to the editor disputing some of Vernon Ingram's publications on hemoglobin in the same journal, because he had not properly recognized the research of others in his citations. Also, in 1964 and 1977 Pauling revisited his work on the iron-oxygen bond in hemoglobin and its derivatives.

On 1 April 1961 Itano wrote Pauling for advice on what to do about Ingram's disregard for acknowledging others' work in his citations. Itano conveyed his concern to Pauling that Ingram used ideas without proper recognition by saying that it was "a matter that I feel is of serious concern to all of us who have worked for many years on the abnormal hemoglobins." Enclosed with his letter, Itano inserted four pages of

excerpts taken from four articles: Pauling's Harvey Lecture (1953),[145] a paper by Itano (1957),[146] a paper by Ingram and Stretton (1959),[147] and a paper by Ingram (1961).[148]

Itano described his concern by comparing what he and Pauling had said, which Ingram and A.O.W. Stretton had failed to cite. Itano stated that in Pauling's Harvey Lecture he mentioned that thalassemia is like the other abnormal hemoglobins because their alleles are located on the same loci and that the globin restricts the heme from the molecule. According to Itano, Ingram and Stretton stated in their introduction that others had previously put forth this idea; however, the authors had neglected to cite the original works. In addition, Itano found their use of his exact words without citation most problematic.

Itano wanted Pauling's opinion on what to do and stated that he had not written Ingram, but thought that he should write directly to Nature.[149] Pauling substantiated Itano's concern by saying, "I too have been disturbed...and his last paper in Nature seemed to me to be worse than the earlier ones." Pauling noted that Ingram also failed to cite the 1949 Science paper. He suggested that either Itano alone

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[145] Linus Pauling, "Abnormality of Hemoglobin Molecules in Hereditary Hemolytic Anemias," The Harvey Lectures 1953-4 49 (1955): 216-41.
[146] Harvey A. Itano, "The Human Hemoglobins: Their Properties and Genetic Control," Advances in Protein Chemistry 12 (1957): 215-68.
[147] Vernon Ingram and AOW Stretton, "Genetic Basis of the Thalassaemia Diseases," Nature 184 (19 December 1959): 1903-909.
[148] Vernon Ingram, "Gene Evolution and the Haemolgobins," Nature 189 (4 March 1961): 704-08.
[149] Oregon State University Archives, Itano correspondence, letter from Itano to Pauling dated 1 April 1961.

or the two of them together should write a letter to Nature.[150] They did the latter; Itano drafted the letter and Pauling reviewed it before submission.[151]

Nature published Itano and Pauling's letter in the 22 July 1961 issue. In the letter, Itano and Pauling stated that four papers published in Nature between 1959 and 1961, written by either Ingram alone or with Ingram as one of the authors, were "remarkable for the extent to which the custom of giving pertinent references to the ideas and findings of others has been ignored." Itano and Pauling cited not only their own work, but also other investigators that Ingram had disregarded. Ingram never replied. [152]

Itano left for Osaka during that summer and wrote to Pauling in August requesting an update on the issue. Itano also noted that Ingram and Stretton published another paper in Nature (17 June 1961) that failed to cite his 1957 paper and the work completed by Schroeder and his collaborators. There is nothing further from Pauling to Itano on the matter. Yet, in December of that year Itano wrote to Pauling from Japan asking for copies of the letter to Nature because he had received "numerous requests...for reprints of our joint communication on thalassemia and the normal

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[150] OSU Archives, Itano correspondence, letter from Pauling to Itano dated 11 April 1961.
[151] OSU Archives, Itano correspondence, letter from Pauling to Itano dated 11 April 1961 and letter from Itano to Pauling dated 14 April 1961.
[152] Harvey A. Itano and Linus Pauling, "Thalassaemia and the Abnormal Human Haemoglobins," Nature 191 (22 July 1961): 398-99.

hemoglobins in Nature." Pauling's secretary sent Itano two hundred copies of the article per his request.[153]

Pauling not only kept abreast of information on abnormal hemoglobin, but also on the structure of hemoglobin and its derivatives. In 1964 Pauling critiqued Joseph J. Weiss's article in Nature. Weiss had examined the bond between iron and oxygen in his article. Pauling disagreed with Weiss who said that oxyhemoglobin contained ferric iron with a positive charge of three.[154] Pauling still believed oxyhemoglobin had ferrous iron, and a positive charge of two and he mentioned the rule that stated that oxyhemoglobin had to have an even oxidation number. He also still supported his earlier conclusion, made with Coryell in 1936, that oxyhemoglobin was diamagnetic. Lastly, Pauling believed that more could be said about the iron-oxygen bond in 1964 than was possible when he discussed it in 1948 and 1949 because of the improved knowledge of the chemical bond and the structure of oxyhemoglobin developed during those fifteen years. Then, Pauling presented his new ideas. Weiss replied stating that the structure could still be diamagnetic and that perhaps the conventional definitions needed revising if they disagreed with the observed phenomena.[155]

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[153] Pauling Collection, I: Individual Correspondence, Harvey A. Itano, Letter from Itano to Pauling dated 23 August 1961, Letter from Itano to Pauling dated 8 December 1961, Letter from Pauling's secretary Linda Hopkins to Itano dated 12 December 1961.

[154] Joseph J. Weiss, "Nature of the Iron-Oxygen Bond in Oxyhaemoglobin," Nature 202 (1964): 83-84.

[155] Linus Pauling, "Nature of the Iron-Oxygen Bond in Oxyhaemoglobin," Nature 203 (1964): 182-83.

As a final example of his later continued interest in hemoglobin, in 1977 Pauling returned to the problem of the iron-oxygen bond by critiquing a laboratory technique recently developed that analyzed the electronic structure of hemoglobin and its derivatives. Pauling found the new technique inconclusive because the new method changed the blood so that it inaccurately represented the oxyhemoglobin in living organisms.[156]

From the 1930s when he initially developed an interest in hemoglobin until the later years of his life, Pauling continually read new information about hemoglobin and sickle cell anemia, especially that which built upon his publications. Based on his active participation in these issues, Pauling obviously valued the research that he had conducted involving normal and abnormal hemoglobin and he wanted to keep a good scientific reputation in this area. There may have been other reasons why Pauling felt compelled to address these issues. In 1964 Pauling worked at the Center for the Study of Democratic Institutions in Santa Barbara and did not have a laboratory for conducting research and (as mentioned above) in 1977 the Linus Pauling Institute had little money for research.[157] However, he could contribute to his previous researches on hemoglobin by revisiting his earlier projects.

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[156] Linus Pauling, "Magnetic Properties and Structures of Oxyhemoglobin," Proceedings of the National Academy of Sciences of USA 74 (1972): 2612-613.
[157] For information about Center for the Study of Democratic Institutions see: Hager, 555-56. For information about funding at the Linus Pauling Institute see: Hager, 600-02.

**Awards and Recognition for Pauling's Contributions to Understanding Sickle Cell Anemia**

The significance of Pauling's work on sickle cell anemia has been acknowledged in citations, honors, awards, and commemorations. Zelek S. Herman, Pauling's personal assistant in the 1980s at the Linus Pauling Institute, put together a list from the Science Citation Index of Pauling's twenty-five most cited publications between 1955 and 1983. "Sickle Cell Anemia: A Molecular Disease" was third on the list with 617 citations. Pauling's most cited publication, The Nature of the Chemical Bond, and the Structure of Molecules and Crystals, had three editions (1939, 1940, and 1960) and over 16,000 citations. The second most cited work with 841 citations was also a textbook, Introduction to Quantum Mechanics, with Applications to Chemistry (1935), which Pauling wrote with E. Bright Wilson, Jr.[158] Following after "Sickle Cell Anemia: A Molecular Disease," with 525 citations, was Pauling's article with Corey and Branson on "The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain."

Pauling also received other honors and awards for his sickle cell anemia work. The American Association of Clinical Chemists made Pauling an honorary member in 1957 for his work on the nature of the chemical bond, in structural chemistry, and for "[His] theories and execution of brilliant experiments contributed to the understanding of proteins, immunological reactions and developing the concept of

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[158] Zelek S. Herman, "The Twenty-Five Most Cited Publications of Linus Pauling," Roots of Molecular Medicine: A Tribute to Linus Pauling, ed. Richard P. Huemer (New York: W.H. Freeman, 1986) 254-59.

'molecular disease.'"[159] In 1963 Modern Medicine, a publication of the American Medical Association, gave Pauling an Award for Distinguished Achievement "for his interdisciplinary achievement showing relationships between fundamental genetic mechanisms and the molecular structure of proteins." Although the award itself does not specifically mention sickle cell anemia, the magazine article focused on Pauling's coinage of 'molecular disease' and his work on sickle cell anemia. Modern Medicine requested nominations from "deans of medical schools, leaders of medical organizations, and members of the Modern Medicine editorial board."[160] In 1972 Pauling also received the Dr. Martin Luther King, Jr. Medical Achievement Award for his "outstanding contribution in research for sickle cell anemia." Itano accepted the award for Pauling who could not attend the event.[161] In 1963 "Sickle Cell Anemia, a Molecular Disease" was reprinted in a book containing the most important scientific publications on human genetics; the articles chosen also demonstrated the progression of the genetics. In a section titled "The Hemoglobinopathies" the Pauling, et al paper was introduced in the following manner:

> The demonstration that sickle cell hemoglobin differs in electrophoretic mobility from normal hemoglobin led to the entitled inference: "Sickle cell anemia, a molecular disease." This

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[159] Pauling Collection, Honors and Awards 1957h.1, American Association of Clinical Chemists, 5 March 1957.

[160] Pauling Collection, Honors and Awards 1963h.1, Modern Medicine Award for Distinguished Achievement, 1 January 1963. Modern Medicine 7 January 1963: 73-74, 93-95.

[161] Pauling Collections, Honors and Awards 1972h.7, Dr. Martin Luther King, Jr. Medical Achievement Award. President Richard Nixon also received an award "for sponsoring governmental funding for research of sickle cell anemia," according to journalist Tyree Johnson. Tyree Johnson, "Guest List to Spice Sickle Fete," Philadelphia Daily News 11 May 1972: 19.

> astonishingly simple concept is of fundamental importance to medicine for the ultimate understanding of the origins of sickness, and to biology for the insight into what genes do. In the author's words, "This investigation...reveals a clear case of a change produced in a protein by an allelic change in a single gene involved in synthesis.[162]

In 1999, in tribute of the fifty-year anniversary of the article by Pauling, Itano, Singer and Wells, some people wrote about the article and its impact over the years.[163]

Some people believe that Pauling's sickle cell anemia work should have been mentioned in his 1954 Nobel Prize in Chemistry or that he should have been awarded a Nobel Prize in Medicine and Physiology. When given Modern Medicine's Award for Distinguished Achievement, it was said that: "Although a landmark in biochemical genetics, Dr. Linus Pauling's discovery that sickle cell anemia is a molecular disease was not even mentioned in his Nobel Prize citation in 1954."[164] Hager noted that Pauling had heard that he was considered for the Nobel Prize for his sickle cell anemia work.[165] Ted, Mildred, and Victor Goertzel stated that Pauling's

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[162] Linus Pauling, Harvey A. Itano, S. J. Singer, Ibert C. Wells, "Sickle Cell Anemia, a Molecular Disease," Papers on Human Genetics, ed. Samuel H. Boyer IV (New Jersey: Prentice-Hall, Inc., 1963): 115-25. The quotation is from 115. The book's aim was noted in the introduction (ix). Other articles that appeared in the same section as the Pauling, et al article were Neel's "The Inheritance of Sickle Cell Anemia" and Ingram's "Gene Mutations in Human Haemoglobin: The Chemical Difference Between Normal and Sickle Cell Haemoglobin."

[163] Asher Dubb, "Fifty Years Ago: The Birth of Molecular Medicine," Adler Museum Bulletin, 25 (1999): 1 page; Tracy Smith, "The First Molecular Explanation of Disease," Nature of Structural Biology 6 (1999): 307; Bruno J. Strasser, "Perspectives: Molecular Medicine: 'Sickle Cell Anemia, a Molecular Disease," Science 286 (1999): 1488-490.

[164] Pauling Collection, Honors and Awards 1963h.1, Modern Medicine Award for Distinguished Achievement, 1 January 1963. Modern Medicine 7 January 1963: 93.

[165] Hager, 467. Pauling was nominated for Nobel Prizes in Chemistry before he received the award in 1954. For example, in 1945 John Kirkwood and Robert Livingston independently nominated Pauling for his work in immunology. Others

sickle cell anemia work warranted a Nobel Prize in medicine, but noted that Pauling had already won two unshared Nobel Prizes.[166] During a banquet at Caltech for Pauling's eighty-fifth birthday the speakers described Pauling as "the greatest chemist of the twentieth century" and "the true father of molecular biology." Additionally, some stated that Pauling should have received a third Nobel Prize acknowledging his contribution to understanding sickle cell anemia.[167]

**Conclusion**

In the forty-five years after Pauling and his colleagues published "Sickle Cell Anemia, a Molecular Disease," Pauling continually drew upon his knowledge of normal and abnormal hemoglobin. Although sickle cell anemia was peripheral to most of Pauling's work after 1949, he integrated sickle cell hemoglobin into many of his subsequent projects whether scientific, social, or political. Pauling used hemoglobin in scientific research as seen with his work on the Molecular Evolutionary Clock and orthomolecular therapies for sickle cell diseases. He also discussed social and political aspects of sickle cell anemia as seen by his promotion of genetic counseling and his analogy between the mutagenic effects of nuclear fallout and abnormal hemoglobin. In addition, Pauling employed hemoglobin to

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noted his work on the theory of valence and resonance, proteins and biologically important molecules, x-ray crystallography, and quantum mechanics. Information about the 1954 and later Nobel Prizes is not available. Thanks to Mary Jo Nye for giving me this information.

[166] Ted G. Goertzel, Mildred George Goertzel, and Victor Goertzel, "Linus Pauling: The Scientist and Crusader," Antioch Review 38 (1980): 371-82.

[167] Hager, 620.

different extents in his various projects. For example, he analyzed hemoglobin as the primary substance for his experiments of the Molecular Evolutionary Clock, whereas he used hemoglobin as one of many examples to demonstrate that the alpha-helix is a fundamental structure of proteins.

All in all, Linus Pauling's hemoglobin and sickle cell anemia work spanned the majority of his scientific career, from 1935 when he analyzed the bond between the four hemes of hemoglobin, to 1994 when he wrote two forewords for books about sickle cell anemia. In the end, the role of hemoglobin and sickle cell anemia in Pauling's various endeavors demonstrates versatility in his use of normal and abnormal hemoglobin, continuity within his research and crusades over his lifetime, and linkages between his seemingly unrelated accomplishments.

# CONCLUSION

Linus Pauling used hemoglobin and sickle cell anemia as a continuous theme in his research and publications during his lifetime. In the early 1930s, Pauling shifted his primary interest from inorganic to organic chemistry and one of the first biochemical substances that Pauling listed for experimentation was hemoglobin.[1] Pauling's first paper on hemoglobin analyzed the structure of each heme in relation to the other three hemes; he used a mathematical proof to show that the hemes were arranged in a square, each attached to two others. In the mid-1930s to mid-1940s Pauling experimented with hemoglobin and its derivatives by looking at its magnetic properties with Charles D. Coryell. At this time, Pauling also learned about immunology from Karl Landsteiner and contributed to this field as well. In 1945, when William B. Castle spoke about sickle cell anemia to the Palmer Committee, Pauling's earlier work enabled him to understand that hemoglobin was involved in the sickling process and he likened his interpretation of the biochemistry of the disease to his theory of the antigen-antibody reaction. In the early 1950s, Pauling and Robert B. Corey proposed that hemoglobin was an alpha-helix, one of Pauling's fundamental structures for proteins. Also starting in the mid-1950s, Pauling diversified his interests, yet drew on his knowledge about hemoglobin and sickle cell anemia when he developed treatment methods for mental and physical molecular diseases, advocated social practices (i.e. genetic counseling and negative eugenics)

[1] The other substances were categories: proteins and other complex organic substances. See Chapter One.

for carriers of molecular diseases, and compared the bloods of species to propose the Molecular Evolutionary Clock theory. By no means is hemoglobin the only substance that interested Pauling and not all of his endeavors involved hemoglobin; yet, a number of Pauling's seemingly unrelated endeavors have hemoglobin and sickle cell anemia as a commonality. Thus, hemoglobin and sickle cell anemia constitute a unifying theme among Pauling's many and diverse interests during his lifetime.

Gerald Holton discusses themata in his 1973 book, Thematic Origins of Scientific Thought: Kepler to Einstein. He stated that the "nascent moment," the time leading up to a discovery when a scientist puts together his ideas, is as important as the confirming proof that an idea works, but that the "nascent moment" is often overlooked. In alignment with Holton's "nascent moment," I have analyzed in Chapter One the experimental and theoretical background that enabled Pauling to understand the structural conversion of hemoglobin in sickle cell anemia. In this case, Pauling's scientific background from experimenting with hemoglobin and theorizing in immunology enabled him to make an "intuitive leap" and contribute fundamentally to pathology, hematology, and medicine. Pauling's insight inspired additional work on abnormal hemoglobins and their pathologies, as discussed in Chapter Two, in the work of Harvey A. Itano, S. J. Seymour, and Ibert C. Wells. [2]

Holton defines themata as a third dimension in addition to the analytical and empirical dimensions of scientific creativity. Themata are "fundamental

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[2] Gerald Holton, Thematic Origins of Scientific Thought: Kepler to Einstein (Cambridge, Harvard University Press, 1973): The "nascent moment" is discussed on pages 17-29. See page 18 for information on the "intuitive leap."

preconceptions of a stable and widely diffused kind that are not resolvable into or derivable from observation and analytical ratiocination. They are often found in the initial and continuing motivation of a scientist's actual work, and also in the end product to which his work reaches out."[3] In some cases, thematic concepts are driven by a scientist's preconceptions. For Pauling, hemoglobin and sickle cell anemia were thematic concepts motivated by his approach to problems in structural chemistry and his concern for human suffering. More specifically, Pauling solved problems in structural chemistry by looking for simple structures consistent with the available experimental data. Furthermore, he tried to ascertain the fundamental structures for a category of chemical compounds, for example the alpha-helix for proteins. Pauling has often been quoted as saying that he approached scientific problems by asking, "What is the most simple and general picture of the world that we can formulate that is not ruled out by these experiments?"[4] Pauling applied his rule to normal hemoglobin many times by analyzing the structure of the heme and the globin individually and in relation to each other, as well as theorizing about the structure of sickle cell hemoglobin. In addition, his concern for human suffering was a thematic component to his interest in sickle cell anemia as demonstrated when he tried to find a treatment for the disease in the early 1950s with Itano and George Burch and in the early 1970s with Paul Wolf and others. Pauling also attempted to diminish human suffering by promoting negative eugenics from the mid-1950s to early 1970s.

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[3] Holton, 24.

[4] Marinacci, 100; Hager, 239-40. Hager's quotation reads, "What is the most simple, general, and intellectually satisfying picture of the world that encompasses these observations and is not incompatible with them?"

Pauling promoted a negative eugenics program that grew more rigorous over time. At first, Pauling advocated genetic counseling, a position that aligned with that of others who were concerned about the spread of molecular diseases. Although controversial, Pauling's statements did not initially receive the degree of criticism that soon would occur. During the late 1960s and early 1970s, people supporting the United States civil rights movement sought equality for African-Americans. As the civil rights movement intensified, Pauling increased his eugenic measures by proposing the enactment of laws to curb the spread of molecular diseases. Some viewed Pauling's restrictions for carriers of sickle cell anemia as racially prejudiced and he soon stopped discussing eugenics.

"Sickle Cell Anemia, a Molecular Disease" by Pauling, Itano, Singer, and Wells not only was a revolutionary paper in making popular the general concept of molecular disease, but also in inspiring subsequent research in hematology. Scientists from various fields including biochemistry, genetics, hematology, and clinical medicine, contributed to the pursuit of finding, understanding and treating abnormal hemoglobins. Considering that molecular biology is a discipline comprised of multiple fields including biology, chemistry, medicine, and genetics, it is not surprising that many of Pauling's contemporaries view his work on sickle cell anemia as pivotal to establishing molecular biology.

My study of Pauling's work on hemoglobin and sickle cell anemia adds new insights and depth to previous historical investigations on Pauling's research and influence in chemistry, molecular biology, and medicine. From my work some

general conclusions can be stated about Pauling's tactics for conducting laboratory research, gaining funding, and establishing his priority and originality.

Foremost, my thesis shows that Pauling did not accomplish his work alone, but in fact, he directed research and had the help of numerous collaborators over the years. Pauling had the idea and coined the term molecular disease. He knew that hemoglobin controlled sickling, an insight that guided the analysis conducted in the laboratory. Yet Pauling usually did not carry out the laboratory work himself, and he indeed suggested unsuccessful experimental techniques in this case, namely absorption and magnetic investigations. While Pauling was in England in 1948, Itano suggested trying electrophoresis and, with the help of Singer and Wells, conducted experiments that proved Pauling's intuition correct. Additionally, Pauling surrounded himself with people who helped him achieve his goals. In 1935 he wanted to learn more about protein denaturation and brought Alfred Mirsky of the Rockefeller Institute to Caltech for a couple of years. When Karl Landsteiner retired from the Rockefeller Institute in 1939, Pauling tried unsuccessfully to get him a position in Caltech's biology department. Similarly, Pauling enlisted Arthur Robinson's help to start the Linus Pauling Institute in the early 1970s.

Pauling's skill at writing scientific research grants helped him to gain sizeable funds from outside organizations. His success as a chemist at Caltech depended largely on the Rockefeller Foundation's investment in Caltech and in Pauling himself, which allowed for sufficiently more laboratory space, equipment, and researchers. Additionally, Pauling's vision for the future of Caltech and his fundraising efforts

contributed to building Caltech into a premier scientific research institute. The Ford Foundation's grants also helped Pauling to enter a new discipline, the study of mental deficiencies.

Like most scientists, Pauling valued the originality of his work and concerned himself with establishing priority for many of his hemoglobin projects. For example, Pauling was concerned with priority in 1949 and explicitly stated that he and his collaborators determined, independently of James V. Neel or E. A. Beet, that sickle cell anemia is a hereditary disease caused by two recessive genes. In the 1970s, Pauling wrote to scholarly journals defending his earlier work on the structure of hemoglobin.

Scientists and historians have recognized Pauling's role as originator of the concept of molecular diseases. He received acknowledgement for his novel idea through honors and awards (see Chapter Three) and by recognition for his contribution to molecular biology (see the Introduction). In addition, some scientific books with contributions from his collaborators and colleagues claim that Pauling coined the term molecular disease, which led to the field of molecular medicine. Two examples are to be found in The Roots of Molecular Medicine: a Tribute to Linus Pauling (1986) and Molecules in Natural Science and Medicine: an Encomium for Linus Pauling (1991).[5]

[5] Richard P. Huemer, ed., The Roots of Molecular Medicine: A Tribute to Linus Pauling (New York: W.H. Freeman, 1986); Zvonimir B. Maksić and Mirjana Eckert-Maksić, eds., Molecules in Natural Science and Medicine: An Encomium for Linus Pauling (New York: Ellis Horwood, 1991).

Indeed, the concept of molecular disease prompted the development of molecular medicine, which has grown significantly in recent years. The number of journals and institutions specializing in the subject demonstrates this. The earliest journals with this focus started in the mid-1970s: the Journal of Molecular Medicine (1975) in Germany and Molecular Aspects of Medicine (1976) published from England and the United States. More recent journals include Molecular Genetic Medicine (1991), Molecular Medicine (1994), Biochemical and Molecular Medicine (1995), and Molecular Medicine Today (1995). Additionally, many universities have molecular medicine institutions associated with them, such as the Weatherall Institute of Molecular Medicine at the University of Oxford and the La Jolla Institute of Molecular Medicine at University of California, San Diego.[6] Many of these journals and institutions aim to unify experimental biology and clinical medicine.

Pauling hoped that biochemical sciences would aid medical discoveries and treatment of diseases. In 1959 he looked forward to the determination of the first protein structure and the complete structure of a molecule of deoxyribonucleic acid (DNA). He anticipated that this information would improve knowledge about enzyme activity, gene duplication, and protein synthesis and he conjectured about the impact this information would have on medicine:

> We shall then have a detailed understanding of...the ways in which abnormal molecules give rise to the manifestations of the diseases that they cause, the ways in which drugs and other physiologically active substances achieve their effects. When this time comes, medicine will have made a significant

[6] Both institutes started in 1989. The Weatherall Institute of Molecular Medicine was called the Institute of Molecular Medicine until renamed in 2000.

> start in its transformation from macroscopic and cellular medicine to molecular medicine.[7]

Indeed, Pauling thought that current research on deoxyribonucleic acid was revealing "the fundamental code of life" and that:

> We must keep in mind even the distant possibility that the abnormal DNA molecule of a genetically defective child might be replaced by its normal counterpart or by a surrogate DNA molecule to prevent the manifestations of the congenital defect.
>
> Other possibilities, perhaps not so far in the future, are the introduction of normal cells to replace some of the defective cells, and the manufacture and the use of artificial enzymes to replace the enzymes that are lacking because of the gene defect.[8]

Pauling's optimism was not far off the mark.

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[7] Pauling, "Molecular Structure in Relation to Biology and Medicine," 9-10.

[8] Pauling, "Our Hope," 166. Pauling made comparable statements in 1964: Pauling, "Possibilities for Further Progress," 7. As early as 1956, he had mentioned the possibility of using artificial enzymes: Pauling, "Future of Enzyme Research," 180-81.

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