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ARTICLE

Linus Pauling's ''Molecular Diseases'': Between History and Memory

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In 1949, Linus Pauling and his collaborators published a study in the journal *Science* entitled ''Sickle Cell Anemia, a Molecular Disease.'' In this now classic study, they showed that hemoglobin from patients suffering from sickle cell anemia has a different electrical charge than hemoglobin from healthy individuals. This result demonstrated for the first time that an abnormal protein could be causally linked to a disease, and that genes determined the structure of proteins. This report made headline news and had a powerful impact on both the biomedical community and the general public. Fifty years later, this study is discussed in almost every medical and biological textbook and has became a favorite example in editorials to illustrate the progress of biomedical research. This article explores the history of Pauling's sickle cell anemia and its subsequent integration in different collective memories, up to the present day. It also discusses the function of the collective memories of Pauling's discovery for contemporary biomedical research.

KEY WORDS: Linus Pauling; sickle cell anemia; history; collective memory; electrophoresis

INTRODUCTION

In November 1949, America's leading physical chemist, Linus Pauling (1901–1994), and his collaborators at the California Institute of Technology (Caltech) published a study in the journal *Science* entitled ''Sickle Cell Anemia, a Molecular Disease.'' In this study, they showed that the hemoglobin of patients suffering from sickle cell anemia has a different electrical charge than that of healthy individuals. This report made headline news and had a powerful impact on both the biomedical community and the general public. Fifty years later, this study is discussed in almost every textbook on medical genetics, general pathology, hematology, epidemiology, biochemistry, and molecular biology. It has become a favorite example in editorials to illustrate the progress of biomedical research. During 2001, Pauling's classic study on sickle cell disease received almost as many citations as in the years immediately following its publication (Institute of Scientific Information, http:www.isinet.com/).

Pauling's article about sickle cell anemia can thus be used to study what historians refer to as ''collective memory.'' This term designates the shared representations that social groups have of their past. Historians have paid much attention to how collective memories, of the Holocaust for example, shape identities and how they are transmitted though commemorations and oral traditions. Given the widespread importance of collective memory, it is not surprising that it plays a role in science, too [Abir-Am and Elliott, 2000]. There, it usually focuses on past scientific discoveries, great scientists, and renowned institutions. Frequently, narratives about past science are used to illustrate or legitimize existing modes of research organization and specific experimental approaches that are being carried out. Thus, collective memory is as much directed toward the past as toward the present. But not only does it sustain present ways of doing research, sometimes it even brings them into being. For example, the collective memory of penicillin, the wonder drug of the war, has promoted a specific way of thinking about therapy and a specific manner of conducting therapeutic research [Bud, 1998]. Similarly, the collective memory of sickle cell anemia as a molecular disease has sustained a particular kind of therapeutic research, targeting the hemoglobin molecule itself, and eventually the responsible gene, instead of some other step along the chain of events leading to the pathological consequences affecting the patient. According to this view, if sickle cell anemia is a molecular disease, then its therapy must be molecular as well. In this sense, not only does history become transformed into memory, but memory makes history. Collective memory links the past with the future.

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The collective memory of sickle cell anemia as a molecular disease has sustained a particular kind of therapeutic research, targeting the hemoglobin molecule itself, and eventually the responsible gene, instead of some other step along the chain of events leading to the pathological consequences affecting the patient.

This explains why historical writing can become highly controversial, even if the events it refers to occurred over half a century ago—almost an eternity in terms of modern scientific research. Indeed, the work of historians inevitably differs from collective memory. As Pnina Abir-Am has shown in her pioneering studies on commemorations in science [Abir-Am, 1982, 1992; Abir-Am and Elliott, 2000], collective memories can play a crucial role in sustaining experimental designs, research programs, funding channels, and collective identities. Thus, historical writing may conflict with those whose everyday scientific practice is supported by the collective memory of events that are studied by historians [Schechter and Rodgers, 2000; Strasser, 2000].

The aim of this article is twofold: first, to understand why, half a century after its initial publication, Pauling's experimental study is still receiving so much attention, and what role it plays in the collective memory of contemporary biomedical communities; second, to discuss Pauling's discovery in the context of different research traditions of the mid-20th century.

VARIED COLLECTIVE MEMORIES OF PAULING'S MOLECULAR DISEASES

In 1997, Richard Horton, chief editor of the *Lancet*, published an editorial calling for the constitution of a canon of medical literature [Horton, 1997]. He selected a small number of publications that, he believed, deserved to be read by every physician. Pauling's 1949 study on sickle cell anemia was included in this list, somewhere between Hippocratic writings and a recent study in genomics.

The resurfacing of Pauling's study in today's scientific literature is not only the result of its importance in clarifying the nature of sickle cell disease, but also because it exemplifies something more general about medical research and the manner in which it is carried out. Over the past 50 years, Pauling's sickle cell anemia research has been incorporated in very different—and often incompatible—narratives that were constructed by diverse scientific communities. Indeed, Pauling's achievement constitutes what science historian Ludmilla Jordanova [2000] has called ''graspable units, flexible cultural elements, for representing the achievements of science and medicine.'' One can distinguish at least five different stories that have emerged from Pauling's discovery: the funding of clinical research, the value of interdisciplinary research, the importance of clinical research, the importance of laboratory research, and the molecular approach to disease therapy.

Funding of Clinical Research

The first story to appear, only a year after the publication of Pauling's study, focused on the funding of clinical research. According to its authors, Pauling's breakthrough had been made possible because he was able to use an expensive technical device the Tisselius electrophoresis apparatus (Fig. 1). In 1950, such instruments were only available in well-endowed research institutions such as Caltech, where Pauling was working. Thus, the authors argued, if one wanted to discover more molecular diseases and contribute to medical progress, less prestigious research institutions, and in particular medical institutions, should receive more generous funding to allow the acquisition of such expensive instruments and the training of specialists. As one editorial put it in the *Lancet* in 1950, ''the implications of [Pauling's] work are considerable. [However,] the methods of investigation needed are quite beyond the resources of the purely medical departments'' [Anonymous, 1950].

In 1953, a new method of electrophoresis was introduced. This new technique, in which the proteins migrated across paper, was easier to handle and cheaper than the original Tisselius apparatus. It was almost immediately used to study abnormal hemoglobins [Spaet, 1953]. This new technique made it possible for many more researchers working in medical institutions to join the ''abnormal hemoglobin hunt.'' Even then, however, some clinicians complained that the kind of technologically intensive medical research promoted by Pauling was still far beyond the financial capabilities of laboratories who were working on this topic in ''tropical Africa'' and that the technologies ''should be made available to all'' [Edington and Lehmann, 1956]. As electrophoresis apparatuses became common in laboratories and small medical institutions, Pauling's example lost its weight, and this story sank into oblivion. Today, it is the electron microscope, the cyclotron, and the NMR device that have taken the place of the electrophoresis apparatus to claim for increased funding of medical research.

Need for Interdisciplinary Research

The second story emerged at approximately the same time as the first but has survived longer. As early as 1952, Pauling's study was viewed as a good example of the fertility of interdisciplinary research since it showed that sickle cell anemia was not only a clinical problem but also one that contained a biochemical, genetic, and even anthropological dimension. The authors concluded that multiple disciplines needed to collaborate for the benefit of medical progress, since ''any investigation of one of them almost inevitably involves all the others'' [Anonymous, 1952]. Pauling was taken as a prime example of a researcher crossing disciplinary boundaries, a physical chemist who had

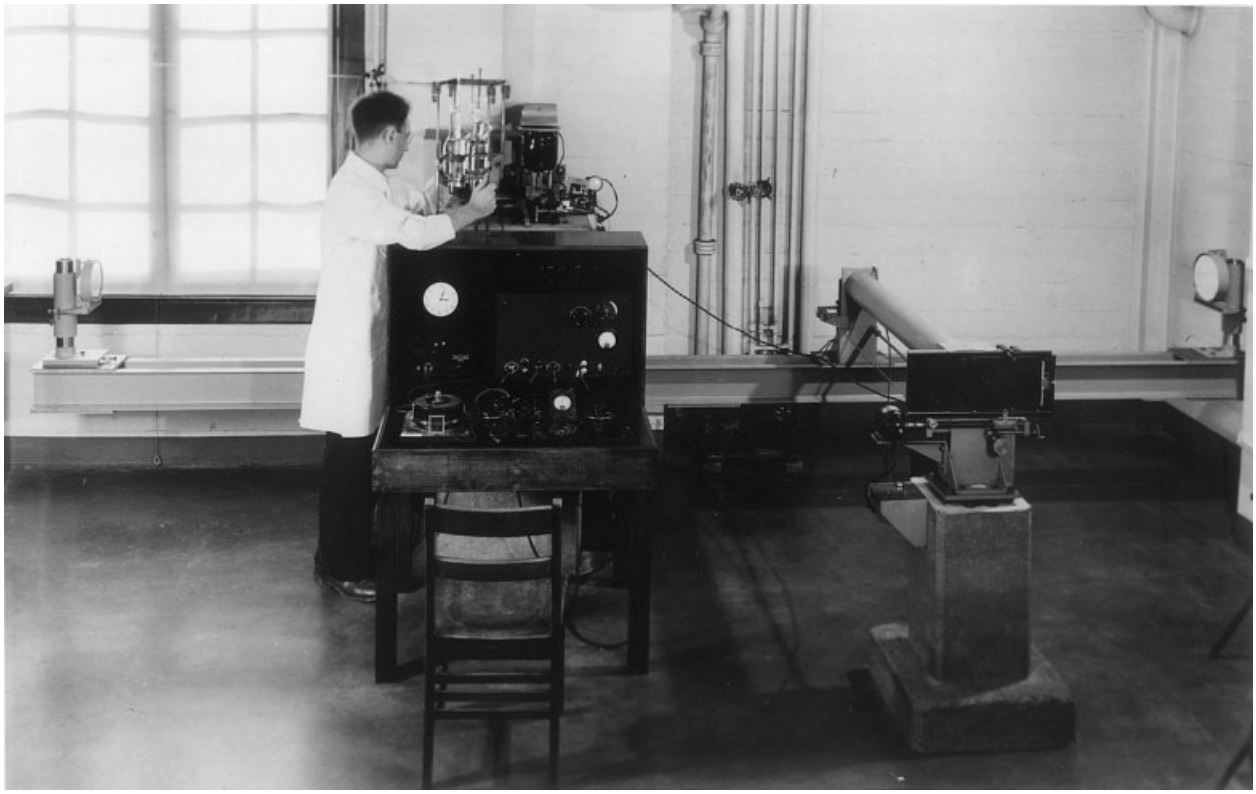

Figure 1. Electrophoresis apparatus at Caltech around 1945. [Courtesy of the Rockefeller Archive Center].

suddenly and successfully entered the field of medical research. As interdisciplinary research was again high on the science policy agenda of the 1980s, as it had been in the 1950s, Pauling's example enjoyed renewed popularity for its illustration of the virtues of this research model [Vogel, 1986].

Importance of Clinical Research

Unlike the second story, which emphasized the benefits of collaboration and interdisciplinary research, the third and the fourth stories both attempted to appropriate Pauling's sickle cell anemia research for a particular field. These two narratives ran in opposite directions, one claiming that the great achievement of Pauling's was based on clinical practice, the other claiming that it was founded in laboratory research.

Up until today, many clinicians have argued that the lesson of Pauling's breakthrough is that clinical practice can lead, sometimes unexpectedly, to fundamental discoveries on "the mystery of biological mechanisms at the molecular level" [Heller, 1969]. Indeed, if Pauling was able to demonstrate the role played by genes in protein synthesis through the example of sickle cell anemia, claimed some clinicians, it was because, in the first place, sickle cell anemia had been recognized as a distinct clinical entity and thoroughly described by generations of physicians. In "this not-so-subtle competition between the master of DNA coding or Michaelis-Menten Kinetics and the clinician who cares for patients," a professor of medicine argued, priority should be given to the clinician, since "we cannot predict the properties of the whole from a knowledge of its isolated parts," sickle cell hemoglobin being a case in point for him [Strauss, 1964].

The proponents of this story often add that one should not forget that the experiments performed by Pauling's group relied on the material resources and skills of the several physicians who provided blood from patients suffering from sickle cell anemia and the sickle cell trait. An editorial published in 1968 in the *New England Journal of Medicine* made this point particularly clear: "Extraordinary clinical investigations have demonstrated important natural phenomena that are only found in man and that could not have been detected with the laboratory methods of contemporary 'basic research.' Now that the basic clinical events have been clearly identified, the ball has been passed back to the laboratory investigators" [Anonymous, 1968]. The role of molecular biologists were of special interest for this particular author: "The era of molecular biology was introduced in medicine when new techniques of electrophoresis were applied to study a clinical phenomenon that had been precisely defined in man: sickle-cell anemia. As other important clinical phenomena become identified by precise investigation of people, are today's molecular biologists equally ready and willing to use their laboratory methods for exploring the world of clinical reality?"

Importance of Laboratory Research

The fourth story challenges the third. However, somewhat surprisingly, it has been told not only by the opposing party, namely, laboratory researchers, but also by clinicians. Linus Pauling was one of the strongest advocates of this narrative (Fig. 2). Under his energetic advertisement in numerous speeches and articles, the sickle cell anemia discovery became emblematic of how basic science could solve medical problems. Clinicians sometimes sided with Pauling. For them, a closer association with laboratory science, especially the kind requiring large physical instrumentation, would bring more prestige to clinical research. It had, for example, already made hematology into a "respectable field," as one clinician put it [Anonymous, 1954].

However, most of those taking up Pauling narrative were laboratory researchers. Beginning in the late 1950s, Pauling's discovery was often highlighted specifically to underline molecular biology's relevance to medicine. This occurred with particular frequency when the promoters of molecular biology were attempting to institutionalize their new disciplines. As the best proof that their discipline could solve medical problems, molecular biologists Max Perutz and Francis Crick in Cambridge, Jacques Monod in Paris, and Edouard Kellenberger in Geneva cited Pauling's sickle cell anemia result in their proposals to build molecular biology institutes [Strasser, 2002]. "From now on," wrote French biochemist Jacques Monod in 1960, "some of the most important problems of pathology fall under the jurisdiction of Molecular Biology...one only has to remember that the demonstration that sickle cell anemia is simultaneously genetic and molecular is a milestone in the development of our discipline" [Monod, 1960].

In the late 1960s, an increasing number of laboratory researchers cited Pauling's 1949 study to make the same point. This happened precisely when, for the first time in postwar America, the continuous increase in the funding for scientific research came to a halt [Wright, 1994]. Biological research was again very much in need of a strong social justification, and Pauling's exam-

Figure 2. Linus Pauling lecturing on sickle cell anemia in Japan in 1954. [Courtesy of the Oregon State University Special Collections, Linus and Eva Pauling Papers].

ple would do precisely that, as Perutz [1976] put it explicitly in *Nature* a few years later, when highlighting the "relevance to medicine" of "fundamental research in molecular biology." For the study of sickle cell anemia research and other diseases, including cancer, Perutz argued that molecular biology had "supplied the basic concepts and techniques." Today, the primary use of Pauling's discovery is this: a legitimization of molecular biology, and more generally of laboratory science, through its relevance to medicine.

Molecular Approach to Disease Therapy

Some proponents of the fourth story, however, moved a step further. In 1995, two National Institute of Health (NIH) researchers entitled their editorial in the *New England Journal of Medicine* "Sickle Cell Anemia: Basic Research Reaches the Clinic" [Schechter and Rodgers, 1995]. The two NIH researchers not only claimed that laboratory research, rather than clinical research, made it possible to explain the molecular mechanisms of sickle cell disease, but they also claimed that this approach had "reached the clinic," that we were "at last crossing the threshold to a therapy based on molecular knowledge of the sickle cell" [Schechter and Rodgers, 1995].

This is probably the most disputed aspect in the collective memory of Pauling's sickle cell anemia [Kaushansky, 2000; Nagel, 2001]. It constitutes the core of the fifth and last narrative concerning this discovery. More generally, this story emphasized that Pauling's discovery allowed a "rational approach to chemotherapy" [Klotz et al., 1981] instead of the traditional trial-and-error procedure of screening almost randomly large numbers of potentially effective compounds. Pauling's discovery justified a number of searches for antisickling agents, chosen on the basis of the knowledge of the molecular structure of sickle cell hemoglobin. In the 1990s, the same argument was put forward to support gene therapy, given the fact that, since Pauling's discovery, sickle cell anemia had become one of the diseases where the link between the genetic mutation and its pathological consequences was best understood. A 1998 issue of *Seminars in Hematology*, for example, was titled "From the Genetic Basis to Blood Disorders to Gene Transfer for the Purpose of Gene Therapy" [Luzzatto, 1998]. In 2001, Pauling's work was often rhetorically located as being at the beginning of the road leading to gene therapy, as in a article published in *American Family Physician*, whose introduction starts as follows: "Gene therapy represents the culmination of medical research and its application to human health. Less than 60 years ago, Linus Pauling and others described what was to be the first of many molecular diseases.... The next step, already in progress, is to use the genes themselves as the drugs—replacing or altering the expression of defective or misrelated genes—to treat patients at the molecular level" [Dean and Perkin, 2001].

A HISTORY OF PAULING'S MOLECULAR DISEASES

Now that we have all these different stories in mind, we can turn to the history of Pauling's discovery. The point is not to correct the accounts given by the various collective memories of the discovery [Feldman and Tauber, 1997], because history does not belong to historians, and because collective memory is part of history. The point is, instead, to bring Pauling's discovery into the framework of the science of his time, and to understand the context and the events leading to the discovery that sickle cell anemia is a "molecular disease."

To understand why the American physical chemist Linus Pauling, working at Caltech, an institution devoid of a medical school, got involved with sickle cell anemia research in 1945, we need to go back to his earlier research career. The sickle cell anemia project, far from being a radical turn in Pauling's career, arose from a prior interest in medical research and a fundamentally reductionist ideal. Indeed, his concern with medical research goes back to the 1930s.

By the 1930s, Pauling was already a world-famous physical chemist and had authored the standard textbook, *The Nature of the Chemical Bond* (1930) [Hager, 1995]. At Caltech, where he chaired the division of chemistry, Pauling became involved with two projects related to medicine: the formation of antibodies, and the "structural chemistry of the blood" [Pauling, 1937]. From that time on, he became a fierce advocate, in innumerable speeches and articles, of the relevance of his approach to medicine. In 1937, for example, in his George Fisher Baker Lectureship at Cornell University, Pauling declared: "I am sure that, as a result of the attack from beneath ... in ten or twenty years, the protein problem will have been solved, that we shall be able to say, to mention [the example] of hayfever, how the required protein finds its complementary pattern in the proteins of some people but not of others" [Pauling, 1937]. This quotation is indicative of Pauling's approach to the macromolecular world, an approach he summarized as "accounting for the properties of substances in terms of the shapes of the molecules of which they are composed" [Pauling, 1938].

Pauling's Early Work

Pauling first became interested in hemoglobin in the early 1930s, through his investigations with Charles Coryell on the interaction between oxygen and hemoglobin. He was then supported by the U.S. Public Health Service through a grant for research on the chemistry of the blood. Pauling's first hemoglobin study focused on explaining the sigmoidal curve of oxygen-hemoglobin binding. For Pauling, hemoglobin had a particular place among proteins. In 1938, he wrote, "hemoglobin ... is one of the most interesting chemical substances—perhaps the most interesting of all" [Pauling, 1938]. In addition, hemoglobin had an obvious advantage for Pauling: it was the human protein that was the most readily obtainable in a chemistry laboratory, and it was the easiest to purify. These studies familiarized Pauling with the hemoglobin macromolecule and brought some important biological facts to his attention, one of these being the finding that hemoglobins

of various species have different immunological properties.

At almost the same time, having met the immunologist Karl Landsteiner in 1936, Pauling became involved with immunological research [Kay, 1989]. During the following years, he developed an "instructive" theory of antibody formation, published in 1940, which stated that immunological specificity, that is, the structure of the antibody, is acquired in the presence of the antigen only by a process of "molding," and that it should be explained in terms of the complementarity between the structure of the antigen and the structure of the antibody [Pauling, 1940]. Thus, for Pauling, specificity lay in the complementarity of two shapes, whatever their chemical structure or composition. An extract of a 1946 speech conveniently summarizes his approach: "the specificity of the physiological activity of substances is determined by the size and shape of molecules, rather than primarily by their chemical properties, and ... the size and shape find expression by determining the extent to which certain surface regions of two molecules (at least one of which is usually a protein) can be brought into juxtaposition—that is, the extent to which these regions of the two molecules are complementary in structure" [Pauling, 1946].

Pauling thought that the principle of "complementariness," as he called it, could explain not only antibody-antigen interaction, but also gene replication, enzyme-substrate interaction, and crystallization [Strasser, 2001]. He suggested that diseases should be explained in the same way, by complementary structures or by mismatches between structures [Pauling, 1937]. During the following years, Pauling insisted on how much he hoped this principle would become explanatory for biological and pathological processes, without, however, having at hand any other example than the formation and specificity of antibodies.

Pauling's Interest in Hemoglobin and Sickle Cell Anemia

With these lines of Pauling's research in mind, hemoglobin structure and antibody formation, we must now turn to the event that was the most important in involving Pauling with sickle cell anemia research—World War II. Indeed, as the United States entered the war in December 1941, Federal authorities decided that science would be mobilized, too. A newly created agency, the Office of Scientific Research and Development (OSRD), presided over by Vannevar Bush, an electrical engineering professor from MIT, organized the scientific mobilization along well-defined objectives. Linus Pauling was assigned, among other projects, the task of developing blood substitutes for the battlefield and an oxygen meter for use in submarines. He was, of course, not alone working on these projects. He was called on to collaborate within an interdisciplinary team of researchers, including several clinicians. This was Pauling's first research experience in close collaboration with medical researchers.

As the war was drawing to a close, President Roosevelt asked Vannevar Bush to draft a report on how to support scientific research in times of peace. Linus Pauling was appointed to the Medical Advisory Committee that assisted Vannevar Bush with the preparation of his famous report, "Science: The Endless Frontier" [Bush, 1945]. Pauling's attention was drawn to sickle cell anemia in 1945 by William B. Castle, a clinician from Harvard (not to be confused with the Harvard geneticist William E. Castle), who served on the same committee and had worked for many years on sickle cell anemia.

Sickle-shaped blood cells had first been recognized by physician James Herrick in 1910 in a patient suffering from severe anemia [Herrick, 1910]. In the years that followed, many clinical and laboratory findings enriched this picture and showed, most importantly, that there was an asymptomatic form of the disease, the "sickle cell trait" [Hahn and Gillepsie, 1927; Feldman and Tauber, 1997; Sargent, 2001]. The disease was soon found to be hereditary and transmitted as a single factor according to the Mendelian law, even though the precise genetic basis remained unclear [Huck, 1923]. In the United States, the disease was predominantly found among people of African descent, affecting about 0.5% of that population. Back in 1945, many physicians, in fact, thought it was exclusively confined to that population, a belief that corresponded to the prevailing ideas about the specificity of "Negro blood" [Wailoo, 1997].

Pauling was intellectually well prepared when Castle told him about sickle cell anemia, especially when he mentioned that only deoxygenated blood of sickle cell anemia patients had sickle-shaped red cells under the microscope. The oxygen-dependent sickling suggested that hemoglobin was probably involved in the sickling process, causing the cells to acquire their distorted shape. This idea was not a new one, since it had been put forward by Hahn and Gillepsie [1927] as early as 1927. Castle also revealed to Pauling that blood cells of sickle cell anemia patients became birefringent in polarized light, indicating some kind of molecular alignment. Pauling immediately guessed that for these patients "perhaps the Hb [hemoglobin] molecule changes shape" [Pauling, 1945], following the same line of reasoning he had followed to understand antibody formation, and decided to investigate this question further.

For years, Pauling had been searching assiduously for the kind of medical problem that would permit him to demonstrate the power of his physical chemistry approach to biology and medicine. In 1944, thinking about postwar research, Pauling wrote, "I think that part of our postwar program of intensive research might deal with hemoglobin" [Pauling, 1944]. Like many other scientists, he was also eager to convert wartime research funds into peacetime support for science, along the lines of Bush's "Endless Frontier," which emphasized that basic research was indispensable to meet the postwar needs of the American public. Bush's favorite example was precisely the "War Against Disease" [Bush, 1945]. Thus, for Pauling, the sickle cell anemia project represented a timely convergence of political, financial, and intellectual interests.

Molecular Basis of Sickle Cell Anemia

Pauling assigned the sickle cell anemia project as a PhD thesis topic to Harvey A. Itano, a young medical researcher who had earned an MD from St. Louis University the previous year [Conley, 1980]. In 1947, Pauling hired another postdoctoral fellow, the physical chemist John Singer, to work on the project. The group first tried ultracentrifugation and free diffusion measurements without being able to show any difference between normal and sickle cell anemia hemoglobin. In other experiments, they investigated the properties of heme and again did not find any difference. Itano tried several other different physical and chemical methods to distinguish the hemoglobins, but to no avail.

He then turned to electrophoresis—at that time a new technique designed to separate molecules according to their electrical charge—which had already been used to analyze other blood proteins. Caltech was one of the few institutes in the world to own an electrophoresis apparatus, an instrument that had just become commercially available [Kay, 1988]. In the spring of 1948, Pauling left for England to spend several months lecturing at various locations. When he returned, Itano had finally found a slight difference in the electrophoretic mobility of normal and sickle cell hemoglobin, indicating that they carried a different electrical charge (Fig. 3). The authors then argued that, in a mechanism "somewhat analogous" to the antigen-antibody reactions, "there is a surface region on the globin of the sickle cell anemia hemoglobin molecule [which] has a configuration complementary to a different region of the surface of the hemoglobin molecule," causing a partial alignment of the molecule within the cell and the characteristic sickle-shaped distortion of the cell membrane [Pauling et al., 1949].

The originality of Pauling's work was that it suggested a causal link—not a mere correlation—between the existence of "defective" hemoglobin molecules and the pathological consequences of sickle cell disease, raising the possibility that all diseases might eventually be explained in a similar way.

The results were first published in March 1949 and then presented at two conferences, in April 1949 at the meeting of the National Academy of Sciences in Washington, DC, and at the meeting of the American Society of Biological Chemists in Detroit [Itano and Pauling, 1949]. The full study was published some months later in *Science*, bearing the now famous title "Sickle Cell Anemia, a Molecular Disease" [Pauling et al., 1949].

Not only was Pauling's group able to demonstrate that patients with sickle cell anemia have a different type of hemoglobin than healthy individuals, but also that blood taken from patients affected with the sickle cell trait, an asymptomatic form of the disease, contained a mixture of normal and defective hemoglobin in approximately equal amounts. They concluded that the sickle cell trait reflected a heterozygous condition, while sickle cell anemia reflected a homozygous one. Apparently, they reached this conclusion independently of James Neel, who had arrived at the same result by genetic analysis and had published it a few months earlier [Beet, 1949; Neel, 1949]. Finally, Pauling et al. noted that "the hemoglobins of white and Negro individuals were found to be indistinguishable."

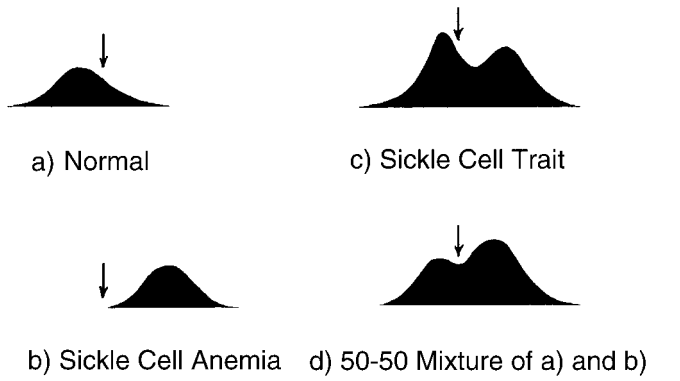

Figure 3. The 1949 electrophoresis result of Pauling et al. Reprinted with permission from Pauling et al. 1949. Science 110:543–548. Copyright 1949, American Association for the Advancement of Science.

Significance of Pauling's Study

What, then, was new about Pauling's study? By the time it appeared, it was well established that adult and fetal human hemoglobin differed in electrophoretic mobility. Thus, sickle cell hemoglobin was not the first hemoglobin variant to be described. What Pauling's sickle cell anemia work demonstrated was that genes could qualitatively alter the structure of proteins, and that mutations could therefore result in structurally different proteins. In the 1940s, Beadle and Tatum had developed the "one gene–one enzyme" hypothesis, but it was not yet clear whether genes controlled anything beyond the absence or presence of a particular enzyme. This explains why Pauling's result was so important for researchers interested in understanding biological processes at the molecular level. In particular, molecular biologists took Pauling's result as a landmark in the development of their discipline.

There was, however, a second dimension to Pauling's study, which was equally important. At the time it was published, several diseases had already been correlated with altered electrophoretic patterns of blood proteins. In

1948, a nearly 100-page article reviewed the role of the plasma proteins in disease, explaining that ''investigations have revealed quantitative changes in the concentration and fractional distribution of the various proteins in many disorders, and in some diseases also qualitative changes, reflecting modification of protein normally found or the appearance of abnormal protein not normally present'' [Gutman, 1948]. The originality of Pauling's work was that it suggested a causal link—not a mere correlation—between the existence of ''defective'' hemoglobin molecules and the pathological consequences of sickle cell disease, raising the possibility that all diseases might eventually be explained in a similar way. This second aspect became the core of most of the stories I have outlined above.

The 1949 study gave Pauling a new notoriety in the field of medical research, and it appeared to validate ''that life is basically an affair of molecules'' [Gray, 1951]. Under Pauling's energetic advertisement, the discovery became emblematic of how basic science could solve medical problems. In 1956, for example, he asserted: ''I believe that chemistry can be applied effectively to medical problems, and that through this application we may look forward to significant progress in the field of medicine, as it is transformed from its present empirical form into the science of molecular medicine'' [Pauling, 1956a]. The same year, he endorsed the view that ''man is simply a collection of molecules'' and ''can be understood in terms of molecules'' [Pauling, 1956b].

He endorsed the view that ''man is simply a collection of molecules'' and ''can be understood in terms of molecules.''

Disappointments and Success

Immediately after publishing the 1949 study, Pauling tried to establish a medical research institute at Caltech devoted to molecular medicine. Public and private funding agencies remained skeptical of Pauling's approach, however, and he was unable to attract the necessary funds [Kay, 1993]. Yet, based on their knowledge of the molecular nature of sickle cell anemia, Pauling and Itano proposed several treatments (carbon monoxide or sodium nitrite) to prevent the sickling of red cells, which were tried out by a physician working in New Orleans. After 2 years of clinical trials, the results proved disappointing and were never published [Pauling, 1954a]. Unfortunately, this would not be the last of such failures. Even today, our extremely detailed understanding of the molecular etiology of sickle cell anemia has led to new diagnostic possibilities but has contributed only modestly to improvements in therapy.

In the 1950s, Itano and others moved on to generalize their approach to other blood pathologies. By 1957, more than 10 different types of hemoglobin had been described using electrophoresis [Anonymous, 1957]. For Pauling, however, the main challenge was to pinpoint the origin of the electrophoretic difference—either a difference in the amino acid composition or in the folding of the normal and pathological hemoglobin [Strasser, 2001]. With Walter A. Schroeder, he performed chromatographic analyses of normal and sickle cell anemia hemoglobin in 1950 but was unable to find a difference in amino acid content that could explain the electrophoresis result, a conclusion soon confirmed by others [Schroeder et al., 1950]. For Pauling [1954b], this question was important not only because it would ''throw light on the mechanisms of production of the disease,'' but also because it could ''provide information suggesting possible clinical treatment.''

In addition to the inherent technical difficulties, these studies were rendered more difficult by the fact that they required large amounts of blood. Since sickle cell anemia was mainly found among the African American population, a population not well represented in California in the 1940s, it was hard to conduct sickle cell anemia studies on the West Coast. For the small amounts of blood needed for the initial electrophoretic studies, Pauling managed to get his supply from patients of two Los Angeles hospitals [Itano, 1950]. However, when he moved on to amino acid determination, supply became a difficult issue. Pauling therefore engaged in a collaboration with a professor of medicine in New Orleans, who, in the South, had access to a larger number of patients of African descent.

After Pauling's initial study, many other researchers around the world engaged in the study of sickle cell anemia hemoglobin. The British crystallographer Max Perutz, for example, used X-ray diffraction to try to understand the structural basis of the electrophoretic difference [de Chadarevian, 1998], but had to conclude that his ''crystallographic results provide no clue'' to this question [Perutz et al., 1951].

Then, in 1957, groundbreaking news arrived from England. Vernon Ingram, working at the Medical Research Council molecular biology research unit in Cambridge, had succeeded in identifying a single amino acid difference between normal and sickle cell hemoglobin that explained the different electrophoretic mobility of the two proteins. His success was the result of a new method he had devised. He first digested enzymatically the hemoglobin and then combined paper chromatography with electrophoresis for the separation of the small peptides. He called his method ''fingerprinting'' [Ingram, 1956, 1957].

The importance of this result went far beyond the etiology of a particular disease. Indeed, for the first time it was demonstrated that an alteration in a Mendelian gene caused an alteration in the amino acid sequence of the corresponding polypeptide chain. Ingram had brought the understanding of gene function one step further. Not since the proposal of a double-helical structure for DNA in 1953 had the research interests of geneticists, biochemists, and structural biologists merged so closely. Just how it was that DNA sequences determined the amino acid sequences of

proteins (the coding problem) became a pressing challenge that molecular biologists and biochemists sought to address. By 1966, the genetic code had been deciphered, and it was finally clear how the information in DNA was translated into protein.

Indeed, for the first time it was demonstrated that an alteration in a Mendelian gene caused an alteration in the amino acid sequence of the corresponding polypeptide chain.

Political Activist and Humanitarian

The sickle cell anemia project represented a turning point in Pauling's career. After he received the Nobel Prize in Chemistry in 1954, Pauling became increasingly involved in political activities and shifted his remaining research toward medical problems such as the molecular basis of mental illness and his controversial vitamin C crusade. His medical research resonated with his peace activism, when, for example, he proposed that nuclear bomb testing was the source of an increased mutation rate, causing innumerable molecular diseases. Pauling received the Nobel Peace Prize in 1962 for his fight against atmospheric nuclear testing and his championship of international peace.

The possible medical relevance of Pauling's laboratory research served as a legitimization of his research vis á vis private foundations and the general public for his entire research career after the sickle cell anemia discovery. However, one should see this medical rhetoric not merely as a way of securing funding in postwar America and assuring public support, but also as a profound commitment on the part of Pauling toward diminishing suffering. His vitamin C crusade and his antinuclear testing campaign, as well as his support and involvement in therapeutic programs and trials until the end of his life, bear testimony to his constant belief that science can contribute to the wellbeing of humanity. Furthermore, in his private life, Pauling had known already back in 1941 that he suffered from a rare kidney disease [Hager, 1995]. The strict diet he had to follow for the rest of his life was a daily reminder of his incurable disease. He often reflected on the causes, molecular of course in his mind, of his own illness [Pauling, 1941]. However, as shown by science historian Diane Paul [1995], Pauling's eagerness to eliminate human suffering, especially when due to molecular diseases, also led him to radical positions in the late 1960s. ''Should we not,'' asked Pauling in 1968, ''with the information now at hand, eliminate this source of suffering from the world? If all pairs of sickle-cell-anemia heterozygotes were to refrain from having children, there would be no infants born with this disease. This suffering would be eliminated.'' Pauling went even a step further, suggesting ''that there should be tattooed on the forehead of every young person a symbol showing possession of the sickle-cell-anemia gene or whatever other similar gene.'' Pauling added, ''It is my opinion that legislation along this line, compulsory testing for defective gene before marriage, and some form of public and semi-public display of this possession, should be adopted'' [Pauling, 1968].

The sickle cell anemia project represented a turning point in Pauling's career.

CONCLUSION

By presenting, side by side, the history of Pauling's sickle cell anemia research and its appropriation in collective memories, this article has explored the possible connections between history and memory. The history of Pauling's research is obviously much more complex than the stories that have made him into a modern-day Claude Bernard or Louis Pasteur [Sinding, 2000], illustrating a specific set of relationships between laboratory science, biomedical knowledge, and therapeutic applications. Indeed, the intricate history of Pauling's sickle cell work does not easily lend itself to partisan appropriations. As this article has highlighted, Pauling's involvement with sickle cell anemia, far from constituting a break in his research enterprise, was a direct consequence of his earlier interest in medical problems, going back to the 1930s. His success depended not only on his technical virtuosity and the power of the new physical instrumentation, but also on the combined resources and knowledge from the clinic [Feldman and Tauber, 1997; de Chadarevian, 1998]. More than anything else, perhaps, Pauling's research project exemplifies the growing number of alliances, in the postwar years, between laboratory researchers from different disciplines and clinicians, centered around particular molecules [de Chadarevian and Kamminga, 1998].

The reason it was possible for so many different research communities to appropriate Pauling's discovery in their own collective memory is precisely because it resulted from many different research traditions, predominantly human genetics, hematology, and protein chemistry. Pauling's molecular diseases could thus become a ''boundary object,'' that is, a scientific object ''which inhabits several intersecting social worlds,'' and which is appropriated differently by various social groups, and yet remains sufficiently robust to allow translating between these different viewpoints [Star and Griesemer, 1989].

In the same way, the DNA double helix became such an object for different social groups, again because it came about through a convergence of approaches in microbiology, crystallography, and biochemistry. In particular, the double helix did much to bring together the communities of crystallographers and phage researchers and made possible the renegotiation of their professional roles during the 1950s around a new identity, ''molecular biology,'' as they called it. This new social grouping was possible not so much because the double helix

explained genetics at the molecular level, but because it was a discovery to which different communities believed they had contributed.

Molecular diseases have played a similar role for the field of medical genetics by cementing distinct and sometimes divergent approaches, such as family pedigree tree methodology, clinical expertise, and laboratory science. Molecular diseases have also constituted effective ''cultural bridges'' [Jordanova, 2000] between professionals and their publics. Pauling, being perhaps not enough of a physician, has been replaced in various narratives on the progress of medicine by another historical figure, that of physician Sir Archibald Garrod, best known for his ''inborn errors of metabolism'' [Bearn, 1960]. Garrod epitomizes in a similar way the convergence of clinical and laboratory research around inherited diseases.

The collective memory of Pauling's discovery is as diverse as it is extensive. It has changed over time and acquired new meanings, as research practices and social configurations in biomedicine have evolved. The collective memories are thus as much a reflection of Pauling's achievement as the historical context in which it is remembered, and the professional identities of those who remember it [Abir-Am and Elliott, 2000]. However, by adopting Pauling as a hero of modern medical research, and his sickle cell hemoglobin discovery as a landmark in the progress of medicine, collective memories have simultaneously taken on board a specific ideal of medical research. This ideal, as fresh today as it was in Pauling's mind in the 1930s, is expressed by the belief that therapeutic intervention must be at the same level as the etiological description of a disease. The postwar success of antibiotics did much to popularize this ideal in and outside medical communities. Now that inherited diseases are thought of as molecular diseases traced all the way down to a faulty gene, it can seem natural that gene therapy is the only therapeutic solution and represents, as an editorial in the *American Family Physician* has put it, ''the culmination of medical research and its application to human health'' [Dean and Perkin, 2001]. However, as science historian Hans-Jörg Rheinberger [1995] has warned us, is this not ''grounded on another shared misunderstanding: healthy genes, not cure, for the whole population''?

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