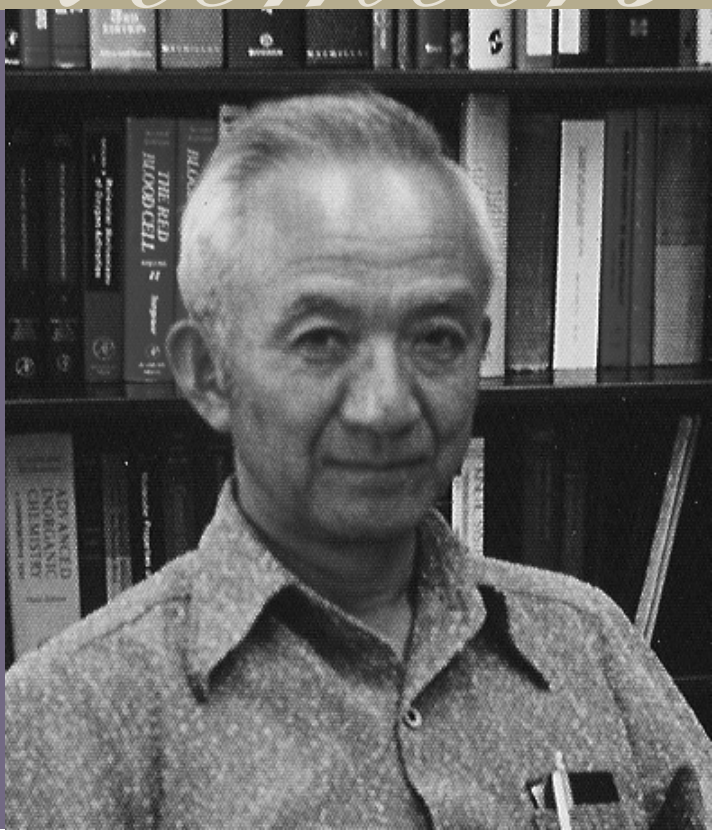
Harvey Itano

1920–2010

BIOGRAPHICAL *Memoirs*



A Biographical Memoir by
Russell F. Doolittle

NATIONAL ACADEMY OF SCIENCES

HARVEY AKIO **ITANO**

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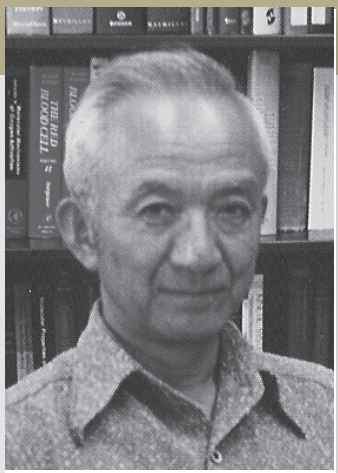


Harvey Itano

By Russell F. Doolittle

Harvey Itano, an undergraduate chemistry major at the University of California at Berkeley, achieved the highest grade-point average of all 4,800 students in his graduating class. At the May 1942 graduation ceremonies, when it came time for the presentation of the Gold Medal for the most outstanding student, University President Robert Gordon Sproul told the assembled throng that Harvey could not be there to accept the medal "because his country called him elsewhere."[1] Indeed, Harvey along with his family and about 110,000 other Japanese Americans living in the American West, was being held under armed guard in an internment camp.

Six weeks later, however, as the result of a determined effort by many people, including President Sproul, Assistant Secretary of War John J. McCloy, and members of the National Japanese American Student Relocation Council (NJASRC), Harvey was released and allowed to begin his studies at the St. Louis University Medical School. He was the first of several thousand Japanese Americans to be released from the interment camps to study at colleges and universities away from the West Coast, which was considered to be a war zone. Much to the annoyance of a commander at the Tule Lake, California, interment camp, Harvey was spirited away on the fourth of July by an NJASRC representative bearing an official release order signed by McCloy. Boarding a train in the middle of the night at Klamath Falls, Oregon, Harvey began the overland journey to St. Louis.[2]

Education was a tradition in Harvey's family. His father, Masao Itano, emigrated to the United States in 1906 at the age of 17 because he had heard that in America one could work one's way through college. He did so, graduating from UC Berkeley in 1917. Harvey grew up in Sacramento, the oldest of four children of Masao and Sumako Itano. His siblings were Dean Tsuyoshi, Edith Kazue, and Masashi. On February 16, 1942, after the attack on Pearl Harbor and before the general roundup of Japanese Americans living in the West Coast region, Masao was arrested by the F.B.I. as a potentially

dangerous enemy alien. The day after his arrest, as he was being transferred from the Sacramento jail, he saw Sumako waiting in the crowd and shouted to her, "Tell Harvey to continue to study," and she yelled back, "I already did."[3] It was more than a year until the government decided that Masao was not dangerous and allowed him to join his family at Tule Lake.

Harvey Itano in an interment camp for Japanese Americans, May 1942. Photo by Dorothea Lange for the Department of Interior, War Relocation Authority. U. S. National Archives and Records Administration, record #537777.

Harvey attempted to join the Army through the Specialized Training Program, like others in his medical school class. This would have allowed him to complete his medical training and then serve in the Army. His application was denied because he, like other Japanese Americans of draft age, was classified 4-C, a category used for aliens and dual nationals—even though he was neither. Later, after Japanese American men were reclassified 1-A, he was again denied entry into the program. Even an appeal to Assistant Secretary of War McCloy proved fruitless.[4,5] At the time, medical schools were operating under an accelerated year-round schedule, and as a result, Harvey received his M.D. in 1945, just before the end of the war. He undertook an internship at the City of Detroit Receiving Hospital, but by this time he was convinced he wanted to do biomedical research.

At the suggestion[6] of E. A. Doisy, the eminent St. Louis researcher who had received the Nobel Prize in 1943 for his work on vitamin K, Harvey wrote to Linus Pauling to see if he could attend the California Institute of Technology as a graduate student to work toward a Ph.D. Pauling responded promptly and favorably,[7] and in the fall of 1946 Harvey arrived in Pasadena for what was to be an almost 8-year stay at Caltech.

Sickle-Cell Hemoglobin

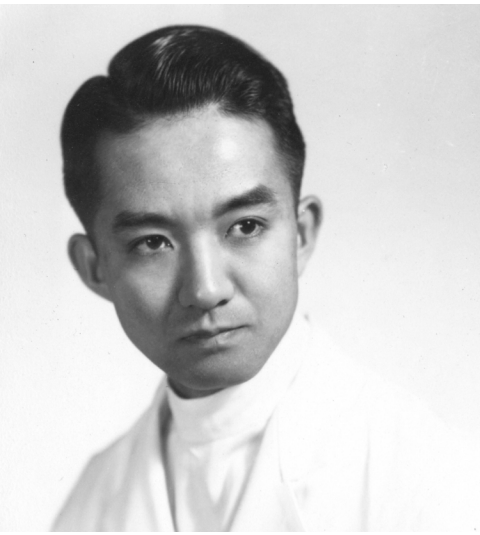
Harvey Itano is best known for his role in the discovery of the hemoglobin difference in sickle-cell anemia,[8] so it is worthwhile to consider here some of the background to that breakthrough finding. The seed of the project was planted some time in 1945 when William Castle, a professor of medicine at Harvard Medical School and an expert on sickle-cell disease, found himself in a long conversation with Linus Pauling on a train ride between Denver and Chicago.[9] During that conversation Castle mentioned that when [red blood] cells were deoxygenated and assumed the resulting characteristic sickle shape, they became birefringent—doubly refractive of light—and "that might be the kind of thing in which he (Pauling) would be interested."[9] Doubtless the mention of birefringence reminded Pauling of his own experiments of a decade earlier when he and a colleague had shown that a deoxygenated hemoglobin molecule was paramagnetic, but when oxygenated it was not (that is, it was *dia*magnetic*)*.[10] Paramagnetism, molecular alignment, and birefringence are fellow travelers.

Not long after, in his 1946 letter to Harvey accepting him as a graduate student, Pauling wrote that he was "very much interested in having a study carried out of the relation of the sickling of red cells in sicklecell anemia to the chemical nature of hemoglobin in the cells, and perhaps this would be a suitable problem."[7]

In fact, as soon as Harvey arrived in Pasadena, he began preliminary work on blood from people suffering from sickle-cell anemia. It was not until more than a year later that they subjected the hemoglobin of such afflicted people to serious analysis, by which time two postdoctoral students, S. Jonathan Singer and Ibert C. Wells, had joined the group. Given his past experiments on the magnetic properties of hemoglobin, Pauling had suggested that magnetic susceptibility might be the experimental course for showing a difference between the hemoglobin molecules in normal blood and in the blood of sickle-cell victims. As it happened, Pauling was scheduled for a sabbatical in Oxford, England, and he left the group with that thought.

While he was away, however, Harvey and Jon Singer decided instead to construct an electrophoresis— the movement of particles through fluid in an electric field—of the moving-boundary sort introduced by the Swedish chemist and Nobel Laureate Arne Tiselius. In the summer of 1948 they first saw signs of a difference in the electrophoretic mobility of normal and abnormal hemoglobins. Concurrently, Ibert Wells was busy showing that there was no difference in the heme portions of the two kinds of hemoglobin.

The electrophoresis results were clear and dramatic: sickle-cell hemoglobin molecules migrated differently from normal hemoglobin in an electric field. Clearly there was a difference in the number of ionizable groups, the sickle-cell hemoglobin having an extra net positive charge. Not only that, the hemoglobin of heterozygous individuals—that is, those who had the sickle-cell trait—was a mixture of two forms. For the first time the structure of an abnormal human protein had been shown to be the result of a genetic mutation. Pauling may have been confident that the sickling of red blood cells was due to altered hemoglobin, but it remained for his students to savor the moment of discovery. The first reports of this work were presented in April 1949 by Harvey at a Federation Meeting (American Society of Biological Chemists) in Detroit,[11] as well as by Pauling at the April 1949 meeting of the National Academy of Sciences. The full article appeared in *Science* in November 1949.[8]



Harvey Itano as a recently graduated M.D.

The same year he achieved this success, Harvey married Rose Sakemi, whom he had met while they were both students at Berkeley. Thanks to the NJASRC, in time Rose had been released from the Poston, Arizona, internment camp and completed her B.S. degree at Milwaukee-Downer College in 1944. Over time they had three sons: Wayne, Glenn, and David.

Significance of an Abnormal Hemoglobin

The electrophoresis experiments on sickle-cell hemoglobin were much more than a simple demonstration that this was the first disease to be traced to changes in molecules. In addition to the obvious clinical significance, there were genetic and protein structure implications. Beyond that, the findings offered an explanation of the molecular basis of red-blood-cell sickling.

Consider the following, relatively wordy but prescient, explanation given in the 1949 *Science* article:

> *Let us propose that there is a surface region on the globin of the sickle cell anemia hemoglobin which is absent in the normal molecule and which has a configuration complementary to a different region of the surface of the hemoglobin molecule. Under the appropriate conditions, then, the sickle cell anemia...molecules might be capable of interacting with one another...to cause at least a partial alignment...resulting in the erythrocyte's becoming birefringent, and the cell membrane's being distorted to accommodate the now relatively rigid structures within its confines.*[8]

The prediction that an altered surface patch of the sickle-cell hemoglobin must be complementary with another part of the protein, with their association giving rise to polymerization was so accurate as to border on the clairvoyant. The findings were also completely in accord with what was just becoming known about the genetics of sickle-cell disease and were especially consistent with the realization that people with sickle-cell trait (sometimes called "sicklemia") were heterozygous for an allele and had two forms of hemoglobin—one normal and one just like the form found in those homozygotes with the full-blown disease.

Harvey earned his Ph.D. in chemistry and physics at Caltech in 1950. His dissertation was titled "Contributions to the Study of Sickle Cell Hemoglobin." Now that it had been shown that sickle-cell hemoglobin had an electrophoretically distinguishable feature, it was apparent that there must be more genetic variants, both in the general population and especially among persons with hemolytic anemias. To pursue the point, Harvey teamed up with the eminent University of Michigan geneticist James V. Neel, who had a long-standing interest in the genetics of sickle cell disease and thalassemia (also known as Cooley's Anemia), a clinical condition in which the amounts of circulating adult hemoglobin are greatly diminished. In 1951 they reported the discovery of what came to be designated hemoglobin C, the first of a long series of mutant forms. In this case the change in electrophoretic mobility was in the opposite direction to what was observed for sickle-cell hemoglobin, there being an additional net negative charge instead of positive. This abnormal hemoglobin did not cause sickling, but the afflicted persons were definitely anemic.[12] After that came hemoglobin D, and then E. By 1956 ten different abnormal hemoglobins had been reported, and in more than half of the reports Harvey

was either the author or co-author. In several of these studies he was helped by doctors at Los Angeles Hospital who were following various cases of anemia.

Several of the early abnormal hemoglobins were identified because they happened to occur in persons who also had thalassemia. The low hemoglobin content seen in thalassemia could be due either to increased destruction (short half-life) or to decreased synthesis. Today we know there are a variety of mutations that can lead to interruptions of synthesis, including deletions, frame shifts, and so forth, but at the time it was not at all obvious that a mutation within a gene itself could influence the rate or degree of synthesis.

With regard to the abnormal hemoglobins, at first it was a surprise that the ratios of the component hemoglobins in heterozygotes were not exactly the same as when compared with in vitro 1:1 mixtures of normal and sickle-cell hemoglobins,[13] and it was Harvey who surmised that something was awry with the protein biosynthesis machinery.[14] At the time, however, not enough was known about how proteins were made to identify what was wrong. Nonetheless, the protein synthesis problem was constantly on Harvey's mind, and he wrote a number of papers about the genetic control of hemoglobin synthesis. It was known that in some persons with abnormal hemoglobins, the synthesis of foetal hemoglobin persisted long after birth. If the basis for this phenomenon could be established, there would be hope for curing anemias in general.

Progress on Hemoglobin Abnormalities

The exact nature of amino acid replacement in sickle-cell hemoglobin was determined by Vernon Ingram in Cambridge, England, in 1957.[15] The replacement of a glutamic acid residue by a valine was in exact concordance with the electrophoretic change Harvey had determined by Tiselius electrophoresis in 1949. Coincident with Ingram's 1957 report in Nature, Harvey published a long analytical review in Advances in Protein Chemistry.[16] The review covered just about every event that had occurred in hemoglobin biology since the 1949 break-through, included descriptions of the ten or more abnormal hemoglobins that had been characterized by then. The review was ahead of the game, also, when it came to commenting on the evolution of the genes for the various hemoglobin subunits. Showing great insight, Harvey clearly stated that the different globins were likely the result of past gene duplications in some distant ancestor. It must be appreciated that at the time the "one gene, one enzyme" dictum had not yet morphed into the "one gene, one polypeptide" stage, and the notion that hemoglobin was in fact the result of

two different genes encoding two different polypeptide chains was only gradually (but broadly) dawning.

In fact, for half a century, at least since the early work of Swedish chemist and Nobel Laureate Theodor Svedberg, it was suspected that hemoglobin was composed of four subunits. The protein contains four iron atoms and four hemes and has a molecular weight four times that of myoglobin. The question was, were all four subunits identical? By the 1950s the preferred method for answering the question was end group analysis, and in human adult hemoglobin only amino-terminal valine was found, at about four residues per mole. In his thorough review of all the data, Harvey noted that in sheep and cattle, however, there were two kinds of end group (valine and methionine), and concluded that there had to be two each of two kinds of polypeptide in human adult hemoglobins. He went on to discuss how gene duplications could account for all the various hemoglobin chains, including myoglobin and foetal hemoglobin. These were thoughts well ahead of their time.

At about the same time as it was realized that normal adult hemoglobin had two pairs of polypeptide chains (not yet called α and β chains), researchers learned that the adult hemoglobin molecule could be dissociated into subunits at acid pH, and that the protein re-associated when neutralized.[17] Harvey and Jon Singer reasoned that if this simple exercise was performed on mixtures of normal and abnormal hemoglobins, they ought to be able to generate hybrid forms, and in fact they did.[18] Pursuing the matter further, Harvey showed that hybrid proteins generated from appropriately chosen mixtures of two different abnormal hemoglobins include a fraction of molecules that were completely normal.[19] These were cases where the mutant forms were on different chains. For example, in hemoglobin C the mutation was on the β chain, whereas in hemoglobin I it was on the α chain. Each had one normal chain, and in the re-assortment of recombination, a fraction of molecules was formed that were perfectly normal.

A final word about the 1949 breakthrough.

In retrospect, the choice of Tiselius electrophoresis was critical to the huge success of the project. It was a perfect method for characterizing the wide variety of different hemoglobin abnormalities that depended on amino acid replacements involving net charge. That the method was quantitative for the amounts of different hemoglobin was also key, especially for heterozygous situations in which the relative amounts of normal and abnormal proteins could be measured. By contrast, measurements of magnetic susceptibility would have led to a dead end. In fact, many years later such an experiment was

conducted on sickle-cell hemoglobin,[20] and I think it is fair to say that nothing much was learned beyond what was already known before the 1949 experiments.

Some Clinical Aspects

Before 1949, laboratory tests to determine whether a person had sickle-cell disease were based strictly on red-cell morphology. Each test took 12 or more hours of observation to find if the cells would change shape on a microscopic slide under a cover slip while the blood slowly became deoxygenated. During the run-up to the big electrophoresis experiment Harvey, having learned that more than 10 percent of the black population in the United States was genetically at risk for sickle-cell disease, and realizing that a simpler test would be of great benefit in making diagnoses, had been looking for ways to shorten the assay time. In 1949 he and Pauling reported a simple assay whereby sodium dithionite was used to scavenge the oxygen, thereby greatly speeding up the sickling process to the point where the test could be done in less than a minute.[21]

Only the blood of people known to have sicklecell disease was described in that initial report, although Harvey and Pauling noted that the test should also work for persons with the trait—that is, carriers. Subsequently, Harvey began a series of more definitive tests that depended directly on the solubilities of normal and abnormal hemoglobin in strongly buffered phosphate- dithionite solutions with defined ionic strengths. These tests showed that the mixture of the normal and abnormal hemoglobins that occurs in carriers could easily be recognized.[22]

Years later, in the late 1960s, Ortho Diagnostics began manufacturing what they called the "Sickledex" test for hemoglobin S, without divulging the principle of the assay. The test was very soon in widespread use. For reasons I haven't been able to unearth, in 1970 a U.S. Army Medical Research panel was constituted to look into the Sickledex test and determine its basis, as well as to see if it could be modified for use with large populations.[23] Pointedly, the main finding of the report was "the Sickledex test is a version of the Itano solubility test which is predicated on the unique and extraordinary insolubility of deoxygenated hemoglobin S in phosphate buffer systems."[23]

Changing Locations

In 1954 the Itanos moved to Bethesda, Maryland, where Harvey set up a laboratory at the NIH in the National Institute of Arthritis and Metabolic Diseases (NIAMD). In fact, Harvey had joined the U.S. Public Health Service (USPHS) as a commissioned officer in May 1950 and essentially had been "on loan" to Caltech for four years, "assigned by

the National Cancer Institute." Eventually he became chief of the Section on Chemical Genetics, Laboratory of Molecular Biology, at the NIAMD.

By nature, Harvey was not one for directing a large group enterprise. He enjoyed hands-on research and for the most part kept his operation limited to a single research assistant and a few postdoctoral fellows. He enjoyed seeing the results of his own thinking first hand. During his NIH years he published many of his papers alone or with his research assistant, Elizabeth Robinson.

Harvey Itano in his UCSD Laboratory.

He continued to work on a variety of hemoglobin problems, including tracking down more abnormalities. Protein sequencing was big in the 1960s, and Harvey made some noteworthy contributions on the technical side. In particular, he and a colleague developed a very sensitive fluorescent stain for arginine-containing peptides.[24] Much to the delight of sequencers like me, it was simple and always worked.

In 1970 Harvey, along with a number of other well-known NIH researchers, was wooed away from the NIH by the newly opened School of Medicine at the University of California, San Diego. At the time, native Californians were easy targets for such recruitments. It was also timely for him, partly because he qualified as a USPHS retiree with 20 years of service (including those four years of Caltech service). Not only that, but as a USPHS retiree with a rank equivalent to that of a navy captain, he could play golf free at the various military golf courses around San Diego, as well as use local post exchanges. This tickled him, as did the salutes he received from the sentries because the sticker on his car identified him as a high-ranking officer. More seriously, he was able to renew friendships with old colleagues from his Caltech days, including S. J. Singer. There were also research attractions, including a budding collaboration with Teddy Traylor, a renowned porphyrin chemist.

In 1954 Harvey received the prestigious Eli Lilly Award in Biological Chemistry from the American Chemical Society for his discovery of the hemoglobin abnormality in the red blood cells of persons with sicklecell anemia, and in 1972 he received the Martin Luther King Achievement Award for that discovery and the many follow-up contributions he made that had bearing on sickle-cell disease, its testing, and its genetics. In 1979 he was elected to the National Academy of Sciences, the first Japanese American so honored. In 1987 he was awarded an honorary Doctor of Science degree by St. Louis University, and in 1998 he was elected to the American Academy of Arts and Sciences.

Family and Friends

As a youth, Harvey had been an Eagle Scout, and camping in California had always appealed to him. He was an avid fisherman and backpacker. He wasn't a solitary person in the social sense, but rather a quiet and modest man who enjoyed the peace and grandeur of nature.

In his later years he became fascinated by his Japanese heritage. Accompanied by his family, he had spent a sabbatical year as a visiting professor at Osaka University in 1961-62, at which time he began to think seriously about his ancestral roots. In 1997 Harvey and his siblings erected a stone monument on the centuries-old family homestead in Fukutani, Japan with an inscription describing the history of the Itano family from the late 1500s up to the emigration of Masao to America.

In 1985, on Harvey's 65th birthday, his colleagues threw him a retirement party at UC San Diego. Linus Pauling kicked off the celebration with a lecture on orthomolecular medicine that he began by describing Harvey's pioneering work in determining the nature of hemoglobin S. That weekend, there was also a gala dinner attended by friends from all over the country, during which many anecdotes were told and accolades bestowed. On the recommendation of his wife, his friends and colleagues presented him with something that Rose said Harvey had always coveted but had been too frugal to buy: a complete set of the *Encyclopedia Britannica*. The gift not only epitomized Harvey's scholarly personality but also demonstrated the genuine affection that everyone had for him.

ACKNOWLEDGEMENTS

I was aided in the preparation of this biography by extensive information provided by Dr. Wayne Itano. All letters and the memoir of Masao Itano are in the H. A. Itano Collection, Mandeville Special Collections Library, University of California at San Diego. Some other detailed references also appear in the article by C. Lockard Conley.[9] cited below. I hope my own remarks have not been overly colored by my 45-year personal friendship with Harvey, whom I admired beyond description.

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