David Harker

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By Herbert A. Hauptman

THE FOCUS OF DAVE Harker's life, around which all his thoughts and actions revolved, was the science of crystallography, which he dearly loved. To crystallography he gave everything – his time, his energy, his total devotion. So complete was his dedication to this science and so fundamental and many faceted were his contributions that he influenced forever the course of its development. To this day, the Harker section and the Harker construction play essential roles in the determination of the structures of very large molecules. The Harker-Kasper inequalities provided the inspiration for a new branch of X-ray crystallography, the so-called direct methods of phase determination.

PERSONAL HISTORY

Dave was born on October 19, 1906, into a scientific and medical family. He grew up on the side of Mount Tamalpais in Mill Valley near San Francisco within view of the bay end of the Golden Gate Bridge. His father, George Asa Harker, who died when Dave was five years old, was a medical doctor from the University of California at Berkeley. Dave's father introduced the concepts of shape, symmetry, and structure into Dave's life. His earliest memories of his father are of him sitting on the front porch and making plaster molds of his patients' feet, carefully hammering copper into precise forms of arch support.

His mother, Harriette Butler Harker, graduated from Vassar in 1898 and received her M.D. from the University of California at Berkeley. She boasted that she was the first woman in New Brunswick, New Jersey, to go to college, wear trousers, ride a bike, and smoke a cigar. Dave's mother personally took charge of his and his brother's education until the fourth grade. His mother, together with faculty members from Berkeley, taught classes at his high school in exchange for free tuition.

In 1928 Dave graduated with honors in chemistry from the University of California at Berkeley. His undergraduate years had brought him into contact with distinguished faculty that included Joel H. Hildebrand and Wendell M. Latimer.

In 1930 Dave married Katherine De Savich, who, as the daughter of the imperial prosecutor under the tzar, fled Russia in 1917. Katherine later aided Dave in translating scientific books into English. They also spent ten years working on the translation of a Soviet physics journal for crystallography, until her death in 1973. They had two daughters, Tatiana Harker Yates and Liudmilla Harker.

Following the death of his first wife, Dave married Deborah Maxwell in 1974. She died in 1997, six years after Dave's death.

PROFESSIONAL HISTORY

ATMOSPHERIC NITROGEN CORP. (1930-33)

After graduation from Berkeley, Dave continued on as a graduate student, but in 1930 he left to take a job as laboratory technician at the research laboratory of the Atmospheric Nitrogen Corp. in Solvay, N.Y. (near Syracuse). There he weighed samples, made mixtures, and occasionally read scientific journals. In one of these he read a paper on the crystal structure of sodium nitrate and its change as the nitrate groups rotate at elevated temperatures. This beautiful result so impressed him that he resolved to study crystal structures in greater depth at some future time.

CALTECH: THE HARKER SECTION (1933-36)

In 1933 (the depth of the Depression) Dave lost his job. He returned to California with his wife and child, borrowed some money from an old friend of his parents, and entered the graduate school of the California Institute of Technology. There, under the supervision of Linus Pauling, he began to work on the determination of crystal structures using the technique of X-ray diffraction. After some preliminary studies of three or four simple structures, he undertook the solution of his dissertation problem: to determine the structures of the ruby silvers, proustite (Ag_3AsS_3) and pyrargyrite (Ag_3SbS_3), which are isomorphous (i.e., they have the same structure).

Although only six parameters were needed to describe these structures, the methods available at that time (essentially clever trial and error) were totally inadequate. Then, at one of the weekly seminars of Pauling's students, A. L. Patterson's famous 1934 paper on the Patterson function was presented. This function relates the experimentally observable X-ray diffraction intensities with the totality of interatomic vectors in the crystal. Owing to the large number of interatomic vectors, interpreting the Patterson function was, and still is, no easy task. A few nights after the seminar, in Dave's words, he "awoke in the dark, sat up in bed, and yelled, 'It's going to work.'" What he had seen was that the relationships between symmetrically related atoms would produce peaks in the Patterson function on certain planes or along certain lines determined by the known crystallographic symmetries. These "Harker" peaks often lead directly to the atomic position vectors and the crystal structure, particularly in those cases when the Patterson function itself is not readily interpretable. Thus was born the famous Harker section, which effectively made the Patterson function useful. In this way Dave quickly deduced the structures of proustite and pyrargyrite and earned his Ph.D. in 1936. The Harker section has withstood the test of time and even today is indispensable for the determination of macromolecular structures, particularly in those cases where the structure contains a small number of heavy atoms, when Patterson techniques are useful.

JOHNS HOPKINS YEARS: THE DONNAY-HARKER LAW (1936-41)

Having become a physical chemist in 1936, Dave took an academic job in chemistry at the Johns Hopkins University, where he taught freshman chemistry, graduate courses in crystal structure, crystal chemistry, and quantum mechanics. He also inherited some X-ray diffraction equipment left over by his predecessor M. L. Huggins.

Since in those days research money was in very short supply, he and his students made their own equipment from secondhand materials. In this way they set up a continuously pumped X-ray tube and with its aid worked on several crystal structure problems. Of these, the structures of acetamide and hydrazinium difluoride were published.

During Dave's tenure at Johns Hopkins, Dorothy Wrinch came to visit the university for about a year. She and Irving Langmuir, who visited Johns Hopkins occasionally, engaged in extended discussions concerning her theories of protein structures. Dave was drawn into their conversations and soon became interested in the problem of protein structure determination. In addition, during this period, W. T. Ashbury of Leeds gave a colloquium on the structures of fibrous proteins. Dave, in his words, "became infected with the protein structure virus, but for many years it lay dormant."

During those years, Dave met Professor J. D. H. Donnay of Johns Hopkins and George Tunnell of the Geophysical Laboratory in Washington, D.C. From these prominent mineralogists Dave learned classical crystallography, some mineralogy, and the significance and measurement of crystal faces. It was Donnay's goal to correlate the internal structure and external face development of crystals. The earlier attempt to do this by Bravais resulted only in a rather poor approximation. Donnay and Harker discovered that the order of decreasing prominence of the faces of a crystal was the same as the order of decreasing interplanar lattice spacings, including the halvings, thirdings, and quarterings due to the space group symmetries. This correlation, while still not perfect, was an improvement over Bravais's earlier attempt. It is known in mineralogical circles as the Donnay-Harker law.

GENERAL ELECTRIC: THE HARKER-KASPER INEQUALITIES (1941-50)

In 1941 Dave received an offer from W. D. Coolidge to work in the famous research laboratory of the General Electric Company and after some hesitation he accepted it. He became a member of the metallurgy division at General Electric and proceeded to learn properties of metals using X-ray diffraction and other crystallographic methods. Owing to the liberal policy of the General Electric research laboratory in those days, Dave was not compelled to work exclusively on metals, although he did publish several papers on solid state reactions characteristic of them, including a paper on grain shape and grain growth, another on order-disorder reaction, and several others.

Although Dave is known primarily for his contributions to X-ray crystallography, his metallurgical papers had a considerable impact on the physical metallurgical community. One of these, in particular, was primarily concerned with the microstructural

subtleties associated with the ordering reaction in the alloy AuCu in which there is a change in unit cell from cubic to tetragonal. His theoretical analysis of the complex microstructures, which are to be expected as a means for the material to avoid long-range internal stresses, was far ahead of its time and had considerable influence on the research concerned with ordering reactions in alloys.

During his years at General Electric, Dave also developed an X-ray method for finding the orientation of quartz fragments, so that oscillator plates could be cut from them. In addition, he did several pieces of crystallographic work for other divisions of the laboratory. He also started work on the design of X-ray diffraction equipment with which the diffracted intensity would be measured with a Geiger-Müller or other particle counter.

It was during Dave's tenure at General Electric that he and his collaborator John S. Kasper produced their paper on the inequalities among the crystal structure factors, the famous Harker-Kasper inequalities. Because these inequalities constitute the first contribution to the direct methods of phase determination, which now (1997) has a fifty-year history and which continues to be a subject of intense interest, activity, and importance, it is appropriate to describe in some detail the circumstances surrounding their discovery. We are fortunate to have first-hand accounts by the authors. First, Dave's account:

> One problem in particular fascinated us – the determination of the crystal structure of decaborane, $B_{10}H_{14}$. This turned out to be surprisingly difficult. It was borne in upon Dr. John S. Kasper and me that a structure which could not easily be guessed at approximately from known stereochemical principles, could not be solved by the traditional trial and error methods. Some twenty structures for the $B_{10}H_{14}$ molecule had been published, but none could be made to fit the X-ray diffraction data from the crystals.

One day John Kasper was sitting at his desk staring gloomily at a lot of algebra he had been writing down. I looked over his shoulder and said something like, "What on earth is that?" and he replied "Schwartz's Inequality for a structure factor, but it doesn't seem to help." He then kept on writing, while I looked on. I said, "Oh, well, let's expand those squares of cosines into functions of double angles." So we did. Then it hit us both, I think, at the same time. "Say! We can get the signs of some structure factors from this!" Then we went madly to work, and in a couple of weeks we had enough algebraic apparatus assembled "unitary" structure factors, sum and difference inequalities, etc. – to be useful. Kasper applied this schema to the decaborane data and came out with a preliminary model which explained the diffracted intensities from one zone, and, after another couple of months, the complete structure emerged. Thus was born the subject of "sign determination" from intensities. This was in 1947.

At my request John Kasper sent me his account, with a postscript by his wife Charlys:

> Here is my version of the origin of the sign-determining inequalities. First, I would like to give you some background information that may be of interest to you.

At the 1946 meeting of ASXRED (American Society for X-ray and Electron Diffraction) at Lake George, N.Y., a method of attacking the phase problem was presented by A. Booth, namely, the method of steepest descent. While this did not turn out to be a viable method, considerable discussion of the phase problem ensued. Nothing useful resulted, however, and there was a consensus that nothing could be done about obtaining phases and that it was a waste of time to think about it. Among the minority were Dave Harker, Buerger, and Fankuchen, although no convincing evidence could be given to justify the optimistic viewpoint. For Dave and myself the phase problem was on our minds although we were quite busy with other problems at G. E.

I became intrigued with the fact that the straightforward squaring of a real structure factor, F_{hkl} (with cosine terms) contained, in part, the sum of modified cosine squared terms. These latter could be rewritten, by virtue of the relation $2\cos^2 A = 1 + \cos 2A$ as components of $F_{2h,2k,2l}$. A relation then exists between F^2hkl and $F_{2h,2k,2l}$, but also with the summation of cross terms. I did not know what to do with the cross terms and so I put the thing aside. Some days later (in 1947) it occurred to me that Schwartz's inequality would deal only with the desirable summation of cosine^2 terms. Accordingly, one morning at work I wrote down the relationship between F^2_{hkl} and $F_{2h,2k,2l}$ resulting from the application of Schwartz's inequality. No sooner had I written this down, when Dave walked in the office and looked over my shoulder. "What is that?" Dave asked. "That is the result of applying Schwartz's inequality to a structure factor," I replied. After satisfying himself that what I had written was alright, Dave became quite excited and remarked: "You can determine signs with that." "That's right," I replied.

I was unhappy, however, that the treatment so far was only for the case of one kind of atom. Dave said that could be fixed, and in short order he proposed using the unitary atomic structure factor, . This enabled treatment of more general situations.

For the next few weeks Dave was immersed in the applications to various symmetries and space groups, and other ramifications, such as sum and difference formulas. He also produced an elegant write up of the work. I concentrated on its application to the Decaborane problem which was uppermost in our minds.

I realize that my version is not exactly the same as one that Dave has given, but I stand by it. We were in communication in 1989, with the goal of achieving a version that was mutually agreeable, I regret deeply that Dave's illness prevented the

completion of that project.

From what you say I wonder if you have the autobiography which was written in 1961, and which Dave sent to me in 1989. It is very interesting reading to anyone who knew Dave. I have little to add to it. I would mention what a good and influential teacher he was. I first knew Dave as a teacher of freshman chemistry at Johns Hopkins. He revolutionized the course with emphasis on basic principles. His approach was adopted by students who subsequently taught chemistry. He only mentions his work in metallurgy, but his contributions were fundamental in the areas of grain growth and recrystallization and in order-disorder phenomena. I would like to add that the single crystal orienter he developed was the first such device for use with a counter.

I hope this is useful to you. I am not able to do many things because I now am legally blind. That is why I am unable to attend the tribute to Dave.

I would appreciate a copy of the Biography when it is done.

Sincerely,

John S. Kasper

JSK:clk

P.S. I am typing this for John. I was working closely with both John and Dave on the decaborane problem at the time and clearly recall the sequence of events as John has described. I was also working in the office while John was busy working with the relationship of Schwartz's inequality and the structure factors to possibly help determine signs when Dave arrived in the office and became very excited at the possibilities of its use. It was an event one doesn't forget.

Charlys Lucht Kasper

It is appropriate to point out here the mathematical basis of the Harker-Kasper inequalities since this is not mentioned explicitly in their paper. This is simply the non-negativity property of the electron density function, a fact implicitly assumed in their analysis.

After a good deal of prodding on Dave's part, the X-ray department of General Electric was finally persuaded to build its first counter diffractometer for powder patterns, although not before the North American Philips Co. had already put a similar device on the market. Next, Dave set about adapting it to single crystal work. By 1949 he had built several models and had used them successfully, mostly on metallurgical problems.

During his time at General Electric, Dave served as president of the Society for X-ray and Electron Diffraction (1946). He also headed the American delegation to the London conference where the formation of the International Union of Crystallography was proposed and later was established, along with its adhering body in the United States, the U.S. National Committee for Crystallography.

BROOKLYN POLY YEARS: THE HARKER CONSTRUCTION AND RIBONUCLEASE (1950-59)

The next phase in Dave's career was triggered in the fall of 1949 by Irving Langmuir, who asked him what he would do with a million dollars. To this seemingly rhetorical question Dave's offhand response was that he would take ten years off and determine the structure of a protein. To Dave's great surprise, within two weeks Langmuir came to his office and announced that he could raise the money. Dave suddenly realized that determining the structure of a protein was what he had wanted to do for some time. After months of interminable negotiations, the decision finally was made to establish the Protein Structure Project at the Polytechnic Institute of Brooklyn in July 1950. There Dave and his team built a good single-crystal X-ray diffractometer with counter detection of the diffracted beams. The central device in this unit was a sort of theodolite arrangement for orienting the crystal in any possible way. They called this device a "Eulerian cradle," because the angular motions it could give the crystal were Euler's angles. This instrument was eminently successful, and led to the commercial goniostat, which soon became increasingly popular. Much of the success of this instrument was due to its careful design, for which Thomas C. Furnas, Jr., was primarily responsible.

They chose ribonuclease as the protein on which to work, because it could be had relatively pure at a reasonable price, could be readily crystallized, and it had a quite small molecular weight. Murray King crystallized this substance in fourteen different modifications eventually. He also invented the method of attaching heavy atoms to specific sites in the protein crystals by "dyeing" the crystals with specially synthesized dyes, the molecules of which contained heavy atoms. Dave worked out the scheme of phase determination for protein structure factors, which involved using the intensities from three isomorphous crystalsone undyed, the other two dyed with heavy atoms in different arrangements, a scheme used by macromolecular crystallographers to this day. It turned out that Professor Bijvoet of Utrecht had found the same principle a few years earlier, but he had not emphasized it in his papers. This scheme, since called the method of multiple isomorphous replacement, led to the first successful structure determinations of crystalline proteinsthose of myoglobin by Sir John C. Kendrew and of hemoglobin by Max F. Perutz, both of Cambridge University. For this work they received the Nobel Prize in chemistry for 1962.

ROSWELL PARK CANCER INSTITUTE: THE STRUCTURE OF RIBONUCLEASE (1959-76)

From 1950 to 1959 Dave and his team worked at the Brooklyn Polytechnic Institute on the crystal structure problem presented by the protein ribonuclease. In 1959 Dave moved the whole project to the Roswell Park Cancer Institute (then known as the Roswell Park Memorial Institute), where he accepted the position of head of the biophysics department. Due to the efforts of visiting crystallographers, a number of critical problems were solved during the Roswell Park years. M. V. King solved the problem of dyeing the protein molecules in crystals and he prepared ribonuclease in fourteen different crystal forms. F. H. C. Crick discovered the strong temperature dependence of the diffracted X rays from the protein crystals mounted in sealed capillaries and showed how to control it. V. Luzzati showed how the intensity statistics were related to the structure of the protein crystals and why the standard statistical methods could not be applied in these cases. A. Tulinsky worked out the exact structure of beryllium basic acetate and made it into a useful intensity standard. G. Kartha developed new ways of using the diffraction data from non-centrosymmetric crystals. A. de Vries showed how anomalous dispersion effects could help in determining the structures of crystalline proteins. J. Bello discovered new ways of labeling ribonuclease crystals with heavy atoms. T. C. Furnas, Jr., built their counter diffractometer, aided by that artist in instrument construction W. G. Weber.

The stage was set to begin to collect X-ray crystallographic data from which the structure of ribonuclease could be determined. This goal was finally reached in 1967 with the determination of the crystal and molecular structure of ribonuclease, the first protein structure to be determined in the United States.

In the years following the determination of the structure of ribonuclease, Dave was honored locally by three major awards. In 1967 he received the Sigma Xi Award for meritorious service to science from the State University of New York at Buffalo. The *Buffalo Evening News* awarded Dave its Outstanding Citizen Award in 1968, and the western New York section of the American Chemical Society awarded him the Schoellkopf Prize in 1969.

THE FINAL YEARS: HAUPTMAN-WOODWARD MEDICAL RESEARCH INSTITUTE (1977-91)

In 1976 Dave retired from the Roswell Park Cancer Institute, but he continued his crystallographic studies as a research scientist emeritus at the Hauptman-Woodward Institute (then known as the Medical Foundation of Buffalo). He became interested in the more mathematical aspects of crystallography, in particular the theory of colored space groups and a description of several classes of infinite polyhedra.

During the next fifteen years, Dave was honored with several appointments and awards. The year 1977 marked Dave's election to the National Academy of Sciences and the American Academy of Arts and Sciences. Two years later, in 1979, he was nominated for a Nobel Prize. In 1980 the American Crystallographic Association honored him with the prestigious Fankuchen Award in recognition of his services to crystallography, in particular his research accomplishments and his role as a teacher of crystallography. In 1981 the State University of New York at Buffalo awarded Dave an honorary degree of doctor of science in recognition of his long and outstanding career in science, the first such award by this university. In 1984 Dave received the Gregory Aminoff Medal in Gold from the Royal Swedish Academy of Sciences in recognition of his fundamental contributions to the development of methods in X-ray crystallography and for his determination of the molecular structures of biologically important substances. On Dave's eighty-second birthday, in 1988, the David Harker Endowment Fund was established by an anonymous donor at the Hauptman-Woodward Institute in Buffalo. The fund is intended to support research and lectures in crystallography. In 1989 Dave prepared a paper announcing his discovery of four new types of polyhedra, which he named the "tortuously corrugated two dimensionally infinite polyhedra." This paper was published shortly before his death in the January 1991 issue of *Proceedings of the National Academy of Sciences*.

In conclusion, Dave was a warm and friendly man, courteous and unpretentious, concerned to be helpful, particularly to younger colleagues; and his teaching was unsurpassed. He was reserved, almost shy, an old-fashioned gentleman with old-fashioned values. He was one of the greatest crystallographers of this century, but he was never patronizing to others, young or old. He was kind and gentle and, at the same time, a man of uncompromising honesty and integrity. He was a tireless seeker of the truth, wherever he could find it, and in this quest he succeeded as few others have. On February 27, 1991, Dave died of complications due to heart disease and pneumonia.

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