DAVID SAYRE (1924 – 2012)

When I wrote David to congratulate him on being selected for the IUCr Ewald Prize he replied asking if I knew who was on the selection committee: "Not that I would do anything about it, but I would be very interested to know what might have motivated the selection of the single-particle concept, which to date has produced very little in the way of important science, when crystallography itself is producing such fantastically important science." As I did not know who was on the committee I sent him the text of the announcement of the prize: "The IUCr is pleased to announce that Dr. D. Sayre has been awarded the eighth Ewald Prize for the unique breadth of his contributions to crystallography, which range from seminal contributions to the solving of the phase problem to the complex physics of imaging generic objects by X-ray diffraction and microscopy, and for never losing touch with the physical reality of the processes involved." To which he replied "thanks that helps a little".

To me that exchange represented the quintessential David Sayre and it seemed appropriate to start this appreciation of his life with the article Martin Buerger wrote for *Crystallography in North America* (edited by Dan McLachlan, Jr. and Jenny P. Glusker, ACA, 1983) in which he refers to the fact that in 1950 David was already in touch with the physical reality of the processes involved in our science. Buerger's article also presents the chronology of the formation of the ACA which makes it a fitting addition to our history project in its own right.

Following Buerger's article are three views of David Sayre: a retrospective on his accomplishments by Jenny Glusker and two more personal interactions by Janos Kirz and Ed Lattman.

Judy Flippen-Anderson

It is with great sadness that *RefleXions* reported the death of David Sayre on February 23, 2012. He was truly a visionary scientist. When still a young physics student he realized that it was important to improve our ability to view three-dimensional images of molecules on an atomic scale. During his lifetime he played major roles in several aspects of this goal. This was recognized when he was awarded the Ewald Prize, the highest honor bestowed by the International Union of Crystallography, at the 2008 Congress in Osaka, Japan. With pride in this branch of science he wrote "I have seen a lot of history of our beautiful science. And when I speak of beauty in science, I mean the beauty of science itself, but also mean the beauty of the care that crystallographers devote to it."

David addressed three important scientific problems in his lifetime: (1) how to improve our ability to solve "the phase problem" in crystallography so that good electron-density maps can be obtained from x-ray diffraction data from crystals, (2) how to improve and simplify the communication between crystallographers and computers so that the calculations necessary to obtain electron-density maps will be made easier for the scientist, and (3) how to make it possible, using methods similar to those used currently by crystallographers, to "see" molecules at atomic resolution in non-crystalline (rather than just crystalline) materials.

David and Anne Sayre visit with Kay Onan (center) at the 1984 Fox Chase Symposium called "A Celebration of the Patterson Function".

David, whose father was a scientist, was born in New York City on March 2, 1924. He graduated from Yale University in 1943, aged 19, with a B.S. degree in physics. From there, because of World War II, he took a position as a staff member at MIT in its Radiation Laboratory. His work there on airborne radar involved electronics and circuit design. Once the war was over he joined Raymond Pepinsky's group at Auburn University, Alabama, having, as he wrote, "read one of J. M. Robertson's papers showing phthalocyanine, and I could find no one at Harvard who could teach me how to see molecules." In Alabama he was able to use the "X-ray Analogue Computer" (X-RAC) that had been built by Ray Pepinsky to calculate Fourier syntheses and display contour maps. In this way he could view on the X-RAC screen, for a given crystal data set, the results of computed electron-density maps obtained by introducing several different possible phase sets. For his work there at Alabama University David obtained an M.S. degree. He had married Anne Bowns, a writer, and she took a position at nearby Tuskegee Institute. After a while, however, they decided to move to Oxford University in England where David obtained a D. Phil. degree. It was there that Anne got to know Rosalind Franklin and later wrote about her and the structure of DNA.

For his doctoral thesis, which he obtained in the laboratory of Dorothy Hodgkin, David tackled the crystallographic "phase problem," that is the reclamation of the information on the relative phases of the diffracted beams that is lost during data collection. In the early 1950s many crystallographers addressed this problem and David was among them. His previous studies on electrical circuits at MIT and with X-RAC proved to be very useful in this venture. Historically, attempts to relate the atomicity of a structure to the imposition of conditions on possible values for the relative phases of diffracted beams had already been started by Ott in 1928, Banerjee in 1933, and Avrami in 1938. The further requirement of non-negativity in the resulting Fourier summation was successfully used by Harker, Lucht and Kasper in 1948 in the determination of the crystal structure of decaborane. The unexpected three-dimensional structure that they found revolutionized our understanding of the chemistry of the boron hydrides. It also led to an equation involving the relationships of phases of different structure factors to each other (Harker-Kasper inequalities). Karle and Hauptman in 1950 greatly expanded this with a full set of inequality relationships based on positivity.

Sayre's approach, which he called "atomicity-based direct phasing," was to introduce a "squaring-equation method" for use in phase determination. David worked with the general idea that atoms are small and discrete points (relative to the spaces between them) and can act as constraints on the relative phases (relative to the choice of origin) of the diffracted beams. If the electron density within a crystal consisting of equal atoms is squared, the resulting "squared" density is similar to the original density but the peaks have sharper shapes. A general result of Fourier theory is that the "squaring" of any function is equivalent to self-convoluting it. David wrote out the equation for the self-convolution of an array of structure factors and concluded that, for an equal-atom structure, the phase of $F(h)$ is related to that of the product $\Sigma F(k)F(h - k)$. (See equations1.1, 1.2, and 1.3 given in *Acta Crystallographica* **5**, 60-65, 1952. See also his article in ACA *RefleXions*, Winter 2010). This was "Sayre's equation," exact for an equal-atom structure, and a most important advance in our understanding of direct methods. David then applied his conclusion successfully to the determination of the crystal structure of hydroxyproline. In this publication, he wrote to me with respect to structure determination methods, "I gave the basic 3-step process -- examination of triplets to find initial phase sets, use of a convolutional relationship to expand the phase sets, and use of a figure of merit to make a selection -- which remained in use without essential change until fairly late in the 1980s."

$$F_H = \theta_H \sum_K F_K F_{H-K}$$

David then applied his newly found method to the determination of other crystal structures. Back in the United States David went, as a Research Associate, to the University of Pennsylvania in Philadelphia, where he worked with Peter Friedlander on the crystal structure of the carcinogenic molecule 7,12-dimethylbenz[*a*] anthracene. Together they found that this polycyclic aromatic molecule is not planar because of steric overcrowding, a feature that may enhance its interactions with certain biological molecules, such as DNA. At that time, however, a three-dimensional crystal structure determination required extensive and expensive computational assistance in view of the complexity of the equations to be solved. With a welcome offer of some free time on an IBM 701 computer in New York, David wrote a program that impressed Jim Backus of IBM so much that he "borrowed" him for the FORTRAN project in 1955; David stayed there at IBM, mostly at the T. J. Watson Research Center in Yorktown Heights, New York, until he retired in 1990.

At IBM David was the assistant project manager of the group that developed that programming language, Fortran. The aim of the team was to design a device that would translate a language that people readily understood into the binary language of a computer, and vice versa. The programming language that they developed made it easy for scientists and engineers to do their own programming and relieved them of the necessity of assigning experts to do it. Therefore it simplified communication between crystallographers and computers, and crystallographers used it as soon as it was available. David worked on important portions of this project with Dick Goldberg, and details can be found in an article published in ACA *RefleXions* in the summer of 2007. He also wrote the Fortran program manual that, as Backus wrote, "stood for some time as a unique example of a manual for a programming language..." and received much praise for producing an easily understandable book.

The ability to "see" molecules, whether in a crystal or not, continued, however, to intrigue David, and he returned to this problem. He was concerned about the "future of large-biomolecule crystallography," noting that these molecules are fragile in the x-ray beam and do not crystallize readily, if at all. Initially he worked on a possible supermicroscope but the required nature of the lens material, suitable for x-rays, provided a problem. Microscopes based on Fresnel zone plates had produced images, and David worked on these for a while, but then, in 1980, introduced the concept of "lensless imaging." His important contribution was the realization that actual crystallinity is not essential. If the object is non-crystalline (non-periodic), then the intensity pattern is continuous (unlike the pattern, intercepted as spots, from crystals). This continuous diffraction pattern, although weaker in intensity, can be sampled finely enough so that lost phase information can be found by iterative computational methods. The lack of the need for crystallinity makes it possible to image structures, such as that of a single biological cell, which are beyond the present capabiliity of x-ray crystallography. The availability of intense synchrotron sources of x-rays has aided this new method of *X-ray diffraction microscopy.* In the 1980's David and co-workers recorded diffraction patterns from several non-crystalline samples. In the 1990's, they were able to apply an iterative algorithm together with oversampling of the diffraction pattern (measuring more diffraction data than a crystal would provide) to find the relative phases for a diffraction pattern. The final breakthrough came when they succeeded in reconstructing a three-dimensional structure from an experimentally recorded diffraction pattern. This achievement opened up the field of *X-ray diffraction microscopy.* David described this work, done in collaboration with many others including Janos Kirz, John Miao, Henry Chapman, David Shapiro and Chris Jacobsen, when he received the Ewald Prize in Japan. He gave his award lecture to a spellbound audience, describing the opportunities that arise "when one can drop the assumption that the specimen in the diffraction experiment must be a crystal."

David has been an interactive and friendly member of ACA, receiving the Fankuchen Award in 1989, and serving several times on the US National Committee for Crystallography. He was President of ACA in 1983. His scientific studies have improved the quality of work each crystallographer can do. David was a great friend and co-edited a book with me and Guy Dodson on Dorothy Hodgkin, the mentor of the three of us. He and Anne were always a treat for Don and me to interact with at meetings. I was particularly touched when he asked me to introduce him when he received the Ewald Award. Therefore I have concentrated here on his science, as I know he would have wished. He will be greatly missed.

Jenny P. Glusker

It was a remarkable coincidence: For 1972-73 I had a Sloan Fellowship that allowed me to take a year off from teaching at Stony Brook University. I decided to use it to learn about biophysics and structural biology. Dorothy Hodgkin kindly offered to host me for the year, and mentioned that she would have one more American visitor.

The other visitor turned out to be David Sayre. He was on leave from IBM. As we met, we were both surprised to learn that our homes were barely four miles apart on Long Island.

My career up to that point was in particle physics. I had never heard of the Sayre equations, of direct methods, or even of David's central role in the genesis of FORTRAN.

Shortly after our arrival in Oxford David gave a seminar on Fresnel zone plates. He pointed out that they could be used to focus x-rays, and that IBM's microfabrication technology could be used to fabricate them with the desired characteristics. This seminar changed my life, and was the beginning of our collaboration that lasted well over 30 years.

David was a most generous collaborator. His visionary ideas guided our work throughout. Once back on Long Island I tagged along on occasion as David went on his daily commute to IBM at Yorktown Heights. David told everyone that the drive through the Bronx took "only" two hours each way, and of course he knew all the shortcuts. Nevertheless, we made it in two hours only once in my experience. But David and his wife Anne had this exquisite house at the Head of the Harbor, and moving closer to IBM was out of the question.

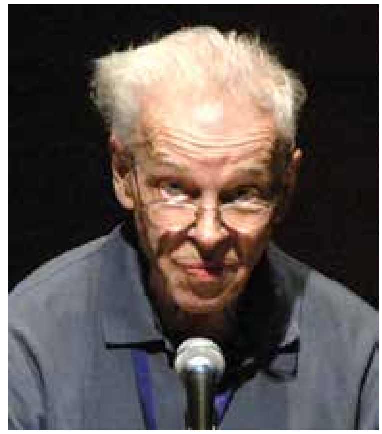
The long commute had advantages for me. In time, David spent more time visiting nearby Stony Brook University, rather than driving to IBM. He was warmly welcomed by faculty and students alike. He became adjunct professor, gave some highly appreciated lectures, and supervised several PhD students. This trend accelerated after his retirement from IBM in 1990. He also participated in our experimental work at the National Synchrotron Radiation Lab in nearby Brookhaven National Laboratory.

When Anne developed a debilitating illness, and David was stricken with Parkinson's disease, the Sayres moved to a retirement community in New Jersey. Subsequently I moved to Berkeley, but our collaboration continued. Our next to last joint paper was published in PNAS in 2005. It was based largely on the PhD thesis of David Shapiro. The young David assisted the old David when the latter delivered his address accepting the Ewald prize in Osaka in 2008.

I last visited David Sayre the day before Thanksgiving of last year. He looked old and frail at the age of 87. He did not make it to 88. He was a wonderful friend and mentor, and I miss him greatly.

Janos Kirz

My remembrance: I first met David Sayre intellectually long before I met him in person. In the early 1960s, when I was in graduate school, I thought that I had found a new way to put x-ray data onto an absolute scale. When I excitedly presented this result to my boss, Warner Love, he gently informed me that the idea had been put forward by David Sayre at least a decade before. To be honest, at that moment I was only dimly aware of who David was. Warner, who had worked for several years with David at the Johnson Foundation in Philadelphia, introduced me to David's work. I then went eagerly to the literature and read, I believe, everything he had published in crystallography up to that time. I was enormously impressed with the clarity of his thinking and with the depth of his insights.



Some years later I finally got to know David through casual encounters at a number of crystallography meetings. Our paths did not start to cross seriously until the early 1980s, a time at which I was contemplating shifting the focus of my research into the nascent area of x-ray microscopy. I discussed with David and Janos Kirz the possibility of doing a sabbatical with them at Brookhaven. But prudence (and my departmental chair) intervened and I stayed put at Johns Hopkins. However, my reading in x-ray microscopy, and my obvious interest in the field, prompted David and Janos to invite me to be a member of the advisory committee for their x-ray microscopy facility at the Brookhaven National Laboratory. I served for 3 or 4 years in the middle 1980s; my CV is curiously silent on the exact dates. Through meetings of the board and other conversations I saw close-up the development of several different tracks for x–ray microscopy in which David was involved. There was the work on scanning electron microscopy, made possible by Fresnel zone plates fabricated at IBM. Most exciting to me, however, was the idea of what David called diffraction microscopy, in which a single object, such as a cell, would be illuminated by an x-ray beam, and the continuous diffraction pattern produced by the object would be measured. The belief that such a diffraction pattern could be phased harkened back to a famous paper by David in 1952, entitled "Some Implications of a Theorem Due to Shannon." In this work he showed that for a centrosymmetric crystal one could phase the diffraction pattern if it were sampled at reciprocal lattice points with half-integral as well as integral indices. Both the ideas behind diffraction microscopy and the extremely elegant work needed to create a viable experimental apparatus impressed me greatly. For example, there was the seemingly trivial idea of eliminating scattering from the beamstop by drilling a tiny hole in the detector and putting the beamstop behind it. My advisory committee service ended when Janos Kirz moved on to Berkeley, and David continued his collaboration with him long distance. I kept track of what was going on through the literature and by occasional chats with David. Many of the plans for diffraction studies of single molecules being developed for the Linac Coherent Light Source at Stanford echo the ideas that David put forth a generation ago.

My last interactions with David came about when he hesitantly asked me if I would be willing to serve as the executor of his living will. I viewed this as a great honor and vote of confidence, and of course I said yes. Partly as a result of this agreement, I visited David every 6 months or so in his home in New Jersey to see how he was doing and to make sure that the terms of his living will were what he still wanted. Executor's duties took up only a tiny fraction of the time, and we had wonderful conversations about his work. That stewardship came to an end when I moved to Buffalo, a location too far from New Jersey for me to carry out the duties of executor as promptly as they might be needed.

David is genuinely one of the great intellectual figures in modern crystallography and diffraction, and epitomizes the phrase "a gentleman and scholar." It was a great privilege to know him. I will treasure our friendship forever.

Eaton Lattman

ACA Los Angeles (2001) session on New Computational and Experimental Approaches. From Left to right: Zbigniew Dauter, Janos Hajdu, Tom Terwilliger, David Sayre, Qun Shen, Mike Soltis and Jack Johnson.

In their description of the session Tom Terwilliger and Mike Soltis reported that "David Sayre talked about the oversampling method for phasing and its potential applications to imaging objects sized in the 10 to 3000 nm range. The general idea is to measure the continuous diffraction pattern from a finite object with an approximately known envelope, and use the resulting overdeterimination of the phase information to reconstruct the image. Data collection is accomplished using a fairly conventional diffraction experiment but with considerably larger exposures. Sayre's group has been able to observe 18 nm resolution data from a 3000 nm dried yeast cell at room temperatures. They will soon attempt to collect higher resolution data from a frozen hydrated cell at liquid nitrogen temperature. For studies of small assemblies (proteins and viruses for example), the plan would be to utilize the suggestion of Janos Hajdu based on the intense radiation from a free electron laser x-ray source.".