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Isabella L. Karle: A Crystallography Pioneer

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The life and work of crystallography pioneer Isabella L. Karle is recounted (1921–2017), as researched from the literature and personal stories of colleagues and family. Her story includes her family background, education at the University of Michigan, research on the Manhattan Project, and 63 productive years at the Naval Research Laboratory. Her life-long partnership and scientific collaboration with husband Jerome Karle, 1985 Nobel Prize winner in Chemistry with Herbert Hauptman, is a big part of her story; however, Isabella has also established herself as a crystallographer *extraordinaire* through her Symbolic Addition Procedure to solve the phase problem, and her unique ability to solve the structures of complex biological molecules, including toxins, antibiotics, and peptides. Her rich family life with three daughters in a lake-front home, do-it-yourself attitude, and passions outside of science round up this portrait of a fascinating and brilliant woman.

Keywords: Isabella Karle, crystallography, biography, X-ray diffraction, phase problem, Nobel prize

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Introduction

When I read Isabella L. Karle's obituary on October 26, 2017, I was immediately intrigued, but equally puzzled. Who is this woman who ''helped [her] husband win [a] Nobel'' (Chang, 2017)? Why have I not heard about this brilliant scientist who combined mathematics and chemistry, as well as experiment and theory, to establish a method for deciphering the three-dimensional structures of biological molecules from X-ray diffraction patterns (Langer, 2017)? While well recognized for her work in the crystallographic community, Isabella Karle's contributions to science were not well known at large.

Born in Detroit, Michigan, in 1921 to immigrants from Poland, Isabella Helen Lugoski did not speak English until she entered first grade. Isabella's mother Elizabeth Graczyk was a self-educated woman who supported her family as a seamstress of automobile upholstery and later by running a restaurant. When she realized how much Isabella loved mathematics, Isabella's mother put her daughter to work, totaling the butcher's weekly bills. Isabella's father Zygmunt A. Lugoski worked for the Detroit Transportation System, painting numbers on city trolley cars and later buses. In elementary school, Isabella's brilliance became quickly evident and she skipped two grades. Isabella's father wanted her to become a lawyer, but Isabella chose to study chemistry. She was inspired to pursue chemistry by reading about the Polish-born Nobel-prize winning physicist Marie Curie who worked on radiation, and motivated by a female high-school chemistry teacher to prepare for university. After a semester at Wayne University (now Wayne State University), Isabella won a 4-year scholarship to the University of Michigan, receiving both bachelor's and master's degrees in physical chemistry by age 20. Her dream of obtaining a doctoral degree faced financial obstacles, since teaching assistantships were offered then only to men. However, upon receiving a Rackham Fellowship from the American Association of University Women, she was able to join the doctoral program.

Isabella met her future husband at a chemistry laboratory bench at the University of Michigan during the 1940–1941 academic year when they were assigned to adjacent seats alphabetically. Jerome Karle, who studied at City College of New York and Harvard, ended up in Michigan only because Harvard had a quota on Jews and was not willing to allow Jerome to continue graduate studies there. Initially, the two did not talk to one another much during their joint course in Michigan, as both were highly competitive, but when Isabella impressed Jerome in how she answered examination questions, he invited her to a concert. They were married in June 1942 after Isabella completed her M.S. degree.

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Both Jerome and Isabella had been working with the Ph.D. advisor Lawrence Brockway since June 1941. While Isabella completed her doctoral work, Jerome started to work on the federally supported Manhattan Project at the University of Chicago in October 1943. Upon completing her Ph.D. in December 1943, Isabella also joined the Manhattan Project on New Year's Day 1944. The project was so secretive that the husband and wife could not reveal to each other what they worked on. Isabella developed efficient techniques to convert impure plutonium oxide to pure plutonium chloride for producing nuclear weapons. Jerome's route focused on converting plutonium oxide to pure plutonium metal.

After a short return to Ann Arbor, where Isabella was appointed as instructor on the chemistry faculty and Jerome worked on a special project for the U.S. Navy, the couple solved their two-body problem by accepting research positions at the main campus of the Naval Research Laboratory (NRL) in Washington, DC. They worked there from 1946 until both retired in July 2009, after 63 years of service each.

At the NRL during the 1940s, Isabella and Jerome developed an experimental apparatus for electron diffraction for characterizing the structures of gaseous molecules. Their electron diffraction work provided invaluable insights into key principles that led them later to their successful treatment of the phase problem in X-ray crystallography. During the mid 1950s, Isabella also set up the NRL X-ray crystallography facility, with the goal of helping prove that the Karle and Hauptman solution to the phase problem was valid (see below). She was further motivated by characterizing the structures of biological molecules by X-ray crystallography. During these two decades, the Karles brought to the world three daughters: Louise (1946–), Jean (1950–), and Madeleine (1955–).

To appreciate the Karles' contributions to crystallography, it is helpful to understand the scientific background of this technique (Sanz-Aparicio, 2015). The discovery of radiation by X-rays by Wilhelm C. Röntgen in 1895 opened many avenues of research in medicine and science, from observing bones to deciphering the complex three-dimensional shapes of biological molecules of life like DNA and proteins. Shape is key to understanding how biological macromolecules work and how to develop tailored drugs that fit snuggly within these molecules and inhibit their motions and functions. This structural fit is central to modern drug discovery, from fighting the common cold to Covid-19 antiviral therapy. While Rosalind Franklin's famous 1952 X-ray image (known as Photograph 51) allowed the general inference of the double-helical structure of the DNA molecule, detailed deciphering of its structure could not be constructed from the X-ray diffraction patterns alone. At that time, the best that could be done, an innovation in its own right, was Crick and Watson's deduced wire models from the diffraction clues, suggesting an overall arrangement for the DNA molecule consistent with all the chemical and biochemical data available at the time.

In the 1950s, information about crystal systems was highly limited. While atoms in the molecule can arrange in patterns, like a helix, they can also be more random. The X-ray patterns are a measure of the different X-ray intensities (amplitudes) and periodicities (phases) encoded in the light waves, which in turn reflect the positions of the atoms (nuclei and electrons) in the crystal. To determine exact molecular structures, crystallographers analyze the patterns to deduce coordinates or locations of each atom in the system. In mathematical terms, these patterns reflect both the intensity and the phases of the diffracting light beam. A direct mathematical relationship exists between all these intensities and phases and the electron density, or molecular structure; specifically, using Fourier transforms, a periodic mathematical function, a transformation from the X-ray patterns to the molecular structure, and vice versa, can be achieved. The trouble is that only the amplitudes of X-ray waves can be measured directly in diffraction experiments; the phase information is lost in the detection. This is the well-known ''phase problem'' (Hendrickson, 1985).

When the Karles started to work at NRL, no general method for solving the phase problem, or retrieval of phase information from X-ray diffraction patterns, and hence molecular structure, was known. An earlier systematic approach to deduce three-dimensional molecular structures from crystallography by A. L. Patterson involved locating heavier atoms in the system, followed by successive approximations to locate the other atoms. The Patterson method, however, breaks down when many atoms exist of nearly the same molecular weight.

With the insights gained from the electron diffraction apparatus that Isabella and Jerome set up at NRL for gaseous molecules, Jerome and NRL colleague Herbert Hauptman formulated a set of equations that could in theory solve the phase problem in crystals. Their insight relied on the fact that an initially overdetermined set of equations (more equations than unknowns) could be solved by incorporating special relationships among the variables and the constraint of nonnegativity for the effective electron density.

Their theory of ''direct methods'' (Karle and Hauptman, 1950) for phase determination for high-resolution diffracting crystals, however, was difficult to apply in practice. It was Isabella's ''Symbolic Addition Procedure'' (Karle and Karle, 1963, 1964, 1966a, 1966b) that filled this critical gap by devising a clear and general procedure to apply the theory at large. Her key insight was that although not all the phases could be retrieved, only a few (no more than 5) are sufficient to evaluate the other values from known mathematical dependencies. She further showed that these unknown variables could be determined by numerical computations.

Wayne Hendrickson, a renowned crystallographer from Columbia University who was part of the Karles' research group at NRL during the 1970s and early 1980s, recalled Isabella's work style: ''Isabella worked mostly at a large table in the conference room where she spread out four-foot-wide sheets of paper onto which she drew the projections of her molecules as they emerged from the calculations, which were done on computers at a central site, and used wire models to obtain three-dimensionality. At lunch time, she would roll these sheets to clear space for the group to gather, often for lively political discussions.''

Daughters Jean and Louise recall how their mother's work did not cease at the laboratory. Their mother brought home the same sheets of vellum, spread them out on the dining room table, and anchored them with brass candlesticks. The eldest daughter Louise helped her mother by reading off the electron density values from computer output, while her mother plotted them. As Louise grew older, she was allowed to draw the contours representing electron density distributions.

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Isabella's 1966 article (Karle and Karle, 1966a) contains several pages of computer calculations that demonstrate how to recreate all the structure factors, functions of the scattering pattern from all the atoms in the crystal system. Isabella proved the success of her technique on an unusual cyclic oligopeptide with two layers of molecules of different packing arrangements (Karle and Karle, 1963). She then followed her success on other more complicated non-centrosymmetric structures, including that of an amino acid (Karle and Karle, 1964) and an alkaloid (Karle and Karle, 1966a), a type of nitrogenous organic compound extracted from plants (e.g., caffeine, nicotine, morphine). Thus, Isabella's pioneering contribution not only demonstrated the validity and generality of the theory but also prescribed the practical steps for its application on modern computers with accuracy and efficiency.

Isabella was the first to publish the structures of many important molecules like peptides, steroids, toxins, and antibiotics, paving the way for modern crystallography, an invaluable tool in modern biochemistry, biophysics, and drug discovery. With her successful practical approach to solving crystal structures, coupled with insight and intuition, Isabella's work independent of Jerome established her as a crystallographer *extraordinaire*. She illustrated the technique's utility in industry and medicine by determining structures of pesticides and poisons. In one application, her team's resolution of the structure of a natural but exotic substance that acts as a natural pesticide led to the development of a synthetic analog as an efficient pest repellent. Her studies of frog venom allowed her collaborators to develop an inexpensive toxin that could be used in medicine to block nerve impulses. Her structure of the cyclic decapeptide antamanide from a fungus is a potential antitoxin for poisons found in death cap mushrooms as well as possible treatment for edema. Her antibiotic valinomycin has been made into a commercial product.

As her successes became known, Isabella brought young women into her laboratory and taught them crystallography. She also taught summer workshops to educate young crystallographers from around the world in her Symbolic Addition Method. She focused on molecules with complex stereochemistry and pushed the envelope to handle larger and larger structures. As Isabella's fame for solving the structures of many difficult structures spread throughout the community, collaborators across the world started to send her samples of their crystals in glass vials. These include her famous frog toxins (batrachotoxin, histrionicotoxin, and pumiliotoxin), mushroom toxins, and various polypeptides as mentioned above. Daughter Jean recalls how her mother salvaged samples that were damaged during shipment by trying to separate crystals from shards of broken glass vial pieces using a microscope. Isabella's models of frog toxins are exhibited (un-named) at the American Museum of Natural History in NYC, in the amphibian section.

When Jerome Karle and Herbert Hauptman were awarded the Nobel Prize in Chemistry in 1985 for their development of direct methods for structure determination by crystallography (Hendrickson, 1985; Schechter, 1985), the Nobel Committee completely ignored Isabella's crucial role in solving the problem in practice. Many in the crystallographic community questioned the choice, most notably Jerome Karle. Fortunately, Isabella was honored by numerous national and international awards, such as President of the American Crystallographic Association (ACA) in 1976, Honorary doctorate from Wayne State University (1979), Garvan Medal of the American Chemical Society (1976), Gregori Aminoff Prize from the Royal Swedish Academy of Sciences (1988), the Navy Distinguished Civilian Service Award (1993), Bower Award and Prize for Achievement in Science by the Franklin Institute (1993), and the National Medal of Science from President Clinton in 1995. She was an elected member of the National Academy of Science and of the American Philosophical Society. Besides her seminal mathematical method development, she is recognized as an expert in the study of cyclic polypeptides like the antibiotic valinomycin, the antitoxin antamanide, and the natural analgesic of the brain, enkephalin.

Isabella died at 95 from a brain tumor, while Jerome died at 94 from liver cancer. They were both exposed to radiation during their work on the Manhattan project.

The couple's three daughters are all scientists (two chemists and one geologist). They describe a happy family life in a house that Isabella designed on a lakeside lot in northern Virginia, where the parents had summer parties in the backyard, playing badminton and swimming with their guests. Many guests included crystallographers from NRL, the Geological Survey, the Bureau of Standards (now NIST), and the Smithsonian Natural History Museum.

Isabella's do-it-yourself mentality and frugality—rooted in her family background and coming of age during the Depression—were not only practiced at home but also passed onto the children. Besides designing her own house, Isabella sewed large curtains for all five bedrooms and the huge living room in their home (see family photo in Fig. 1), as well as many of her own clothes, especially dresses. The sewing talent was passed on for at least three generations. The youngest daughter Madeleine sewed her own wedding dress, a long traditional white-satin gown. Isabella and Jerome also constructed flagstone walkways around the house and laid tiles along the patterns they designed.

Isabella enjoyed cooking and baking on weekends, especially chocolate desserts, which Jerome loved. Isabella took pleasure in gardening and swimming, solving the daily newspaper crossword puzzles, and assembling jigsaw puzzles. She also loved picnics. The family often ice skated together in the late evenings of winter, in an outdoor rink near the Pentagon open till midnight.

Their daughters enjoyed many domestic and foreign trips with their parents during their formative years. They visited their grandparents in Detroit and Coney Island, and joined their parents at crystallography meetings in the United States and abroad. Louise recalls attending such a meeting when she was five in Tamiment, a Pocono Mountains resort. While her parents worked, she explored the premises. As the other daughters grew older, they came along too, and the eldest traveling was responsible for them, as well as for other scientists' children.

Science meetings often preceded family vacations. Jean recalls an ACA meeting in Bozeman, Montana, after which the family visited Yellowstone National Park. After an ACA meeting in Boulder, they toured Colorado. During the 1960s and 1970s, the family attended meetings in Europe with all or some of their daughters, traveling by ship. Isabella wrote at least one article on each such Atlantic crossing. While

FIG. 1. Family photograph at the recreation room of the Karles' lakefront home, with Isabella's curtains in the background. From *left* to *right*: Madeleine, Jean, Isabella, Louise, and Jerome seated at the piano. Karle family photo, used by permission.

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their parents worked, the girls explored foreign tourist sites, zoos, and museums, often becoming proficient in public transport at those cities. After such crystallographic meetings in Europe, the family traveled by car in a purchased VW Beetle that held them and all their luggage. The car was shipped to the United States by the end of the trip. The daughters still enjoy traveling by sea to this day, including cruising.

The daughters were undoubtedly thoroughly influenced by their parents' devotion to their work and their close collaboration during their 70-plus years of marriage. ''The two of them seemed inseparable,'' recalls Hendrickson. ''They drove back and forth together daily between the lab and their home in Virginia; although working in separate spaces, there were frequent stops at Isabella's table by Jerome from his office down the hall; and mainly they went together to the same science meetings, especially ACA meetings but also the monthly Washington Crystal Colloquium meetings and dinners.''

Whatever the outcome of one big prize, the Karles appeared to have a long happy life that produced great science and three successful and brilliant daughters, a much more important reward.

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Author's Background

T.S. is Professor of Chemistry, Mathematics, and Computer Science at New York University. Her research focuses on computational biophysics, specifically chromosome folding and gene regulation. She has published more than 250 research articles and is the author of an interdisciplinary textbook on molecular modeling (Springer-Verlag, Second Edition, 2010).

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References

Chang, K. (2017). *Isabella L. Karle Dies at 95; Findings on Molecules Helped Husband Win Nobel*. (The New York Times, New York, NY).

Hendrickson, W.A. (1985). The 1985 nobel prize in chemistry. Science **231,** 362–364.

Karle, I.L., and Karle, J. (1963). An application of a new phase determination procedure to the structure of cyclo(hexaglycyl) hemihydrate. Acta Cryst **16,** 969–975.

Karle, I.L., and Karle, J. (1964). An application of the symbolic addition method to the structure of L-arginine dihydrate. Acta Cryst **17,** 835–841.

Karle, I.L., and Karle, J. (1966a). An application of the symbolic addition procedure to space group P2, and the structure of the alkaloid panamine, $C_{20}H_{33}N_3$. Acta Cryst **21,** 860–868.

Karle, J., and Hauptman, H. (1950). The phases and magnitudes of structure factors. Acta Cryst **3,** 181–187.

Karle, J., and Karle, I.L. (1966b.) The symbolic addition procedure for phase determination for centrosymmetric and noncentrosymmetric crystals. Acta Cryst **21,** 849–859.

Langer, E. (2017). *Isabella Karle: Chemist Who Revealed Molecular Structures and Helped Husband Win Nobel Prize*. (The Washington Post, Washington, DC).

Sanz-Aparicio, J. (2015). The legacy of women to crystallography. Arbor **191**, a216.

Schechter, B. (1985). Nobel prize in chemistry to Hauptman and Karle. Phys Today **38,** 20–21.

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