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IRVING MYRON KLOTZ
1916-2005

A Biographical Memoir by
HOWARD K. SCHACHMAN

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IRVING MYRON KLOTZ—distinguished protein chemist, innovative and inspiring teacher, outstanding lecturer on diverse subjects, prolific author, and scholar steeped in history—died on April 27, 2005, at the age of 89. A year after his death his former students, friends, and Northwestern University colleagues held a memorial symposium in his honor. Knowing about his deep-seated interest in intellectual history, some of the presenters organized a poster of his "scientific genealogy" enumerating the direct and indirect influences on his career dating back to the 15th century. His more recent direct scientific forebears were G. N. Lewis and T. F. Young, the latter being his Ph.D. adviser in chemistry at the University of Chicago. Thermodynamics was an abiding focus throughout Irv's creative research career, and the seven additions of his widely acclaimed book, *Chemical Thermodynamics* (1950), along with his book written for researchers in the life sciences, *Ligand-Receptor Energetics: A Guide for the Perplexed* (1997), provide ample evidence of his remarkable success in lucidly conveying complex issues.

Regrettably the poster of his scientific genealogy was incomplete. It omitted an important influence on his view of the world and his approach in attacking and solving intellectual and moral questions. From grade school through high school he spent many hours after school and during vacations attending one of the Chicago Orthodox yeshivas, where he studied Hebrew, the Torah, and most importantly, the Talmud. That training imparted a facility in critical thinking along with the necessity and ability to question settled dogma. This background served him well in his scientific research and teaching in addition to his pursuit of the diverse intellectual projects that interested him throughout his academic career.

EDUCATION, ACADEMIC CAREER, AND FAMILY

After graduation from Marshall High School, a Chicago public school, in 1933, Irv entered the University of Chicago's undergraduate chemistry program. This was followed in 1937 by graduate school, where he was awarded a Ph.D. in chemistry in 1940. He had a broad interest in science, but it is not clear why chemistry was selected as a specialty. Irv enjoyed witnessing the application of chemical principles to a broad range of phenomena. The appeal and fascination of the laws of thermodynamics were overwhelming; especially attractive to him was the recognition that the treatment of energy problems did not require a specific model. For instance, elucidation of the multiple-site binding process (for which he is well known) could in principle be treated with the same equations for many processes at the molecular level or at the macro level. The key to understanding these phenomena was the flow of energy and its direction.

Perhaps the choice of chemistry was also partially motivated by the hope that jobs would be available upon graduation. This was 1940, however, and positions were not plentiful. He had one interview at an oil company where he was informed by a high official that they didn't usually hire Jews, but in his case they would make an exception in view of his academic record and recommendations. Needless to say, he turned down this job offer, much to the distress of his thesis adviser, T. F. Young, who pointed out that such an opportunity might not come again. Because of his poor eyesight, even the army would probably not take him.

Therefore, Irv accepted the only other possible position as a research associate, equivalent to a postdoctoral position, working under Malcolm Dole in the Department of Chemistry at Northwestern University. This war-related research was supported by the National Defense Research Committee and encompassed a number of secret projects, such as developing gases and filters for gas masks. It was during that period that he worked with state-of-the-art spectrometers, an experience that proved indispensable for his future research programs. In 1942 Irv was appointed instructor of chemistry, a position he held for four years prior to moving up the academic ladder. His entire academic career was spent at Northwestern where he was appointed Morrison Professor in 1963, and became Emeritus Professor in 1986, at which time his intellectual pursuits and writing on diverse subjects actually increased.

His survivors include his wife, Mary Sue Hanlon Klotz, whom he married in 1966, and their son, David; his former wife, Themis Askounis Klotz, whom he married in 1947, their son, Edward, and daughter, Audie, and her husband, Paul Fenwick, and grandchild, Emma.

RESEARCH

Although schooled as a physical chemist Irv focused on biological problems in initiating his research career as an independent faculty member. He recognized very early that understanding the biological response to a stimulus from a small molecule required knowledge of the energetic and molecular principles governing interactions between small molecules and macromolecules. In a 1944 paper dealing with antibacterial drugs and their interaction with proteins, he analyzed the mode of action of sulfonamide using data in the literature. He showed that inhibition of bacterial growth could be accounted for quantitatively by assuming that the activity was due to a reversible combination between the basic form of the drug and the neutral form of the protein; moreover, he demonstrated that the law of mass action was applicable. This linkage in research between physical chemistry and biology, established through this analysis of the data of others, persisted throughout his career; and Irv was soon deeply involved in pioneering experimental and theoretical research on protein interactions. He stressed that such interactions were pervasive in all the life sciences encompassing biochemistry, biophysics, pharmacology, immunology, endocrinology, neurobiology, molecular biology, and cell biology. His insightful investigations of these interactions in terms of their strengths and specificities and his efforts to understand the underlying molecular principles soon led him to very fruitful studies of the structure and stability of proteins themselves.

MULTIPLE BINDING SITES ON PROTEINS AND LIGAND-RECEPTOR INTERACTIONS

Using the very simple technique of equilibrium dialysis coupled with spectrophotometry, Irv and his colleagues embarked on a study of the binding of a series of dyes to bovine serum albumin. Their first paper in 1946 demonstrated that a single protein molecule bound many molecules of an organic ion and that both statistical and electrostatic effects must be considered in evaluating the multiple equilibria. Many important papers followed, with a major focus on determining the number of binding sites, the binding affinities, the forces involved in the interactions, and the molecular nature of the binding sites. Free energies, entropies, and enthalpies were determined for the multiple equilibria involved, and various types of amino acid side chains in the proteins implicated in the binding process were identified. Irv's study of the effect of temperature on the binding of methyl orange to serum albumin revealed the apparent paradox of a positive entropy change in the association reactions where superficially there appeared to be a decrease in the number of species. He recognized the analogy to the ionization process of aliphatic organic acids and was among the first to propose correctly that the positive entropy changes in the binding of ions to proteins were attributable to the liberation of water molecules.

This research by Klotz and his colleagues grew into a *tour de force* using equilibrium dialysis to study the binding of small molecules to proteins, and these studies evolved into major investigations of ligand-receptor interactions, formerly the province of pharmacologists and physiologists. His approach was to proceed from the simplest case to the more complex. This was exemplified in the development of treatments based on multiple equilibria to evaluate ligand-receptor complexes. Beginning with his first paper in 1946, Klotz opened the modern era of applying energetics and molecular approaches to these interactions by converting the simple equilibrium-dialysis procedure into a precise and accurate technique for the determination of the values of multiple equilibrium constants for combinations between small molecule ligands and macromolecules. His thermodynamic approaches to evaluating free energies, entropies, and heats of interactions have permeated the field ever since.

Well into his retirement years he continued to refine the analysis of ligand-receptor interactions through different formulations, such as the use of complex numbers. These treatments—described most comprehensively in his 1997 monograph, *Ligand-Receptor Energetics: A Guide for the Perplexed*—

yielded fruitful insight into cooperative and antagonistic interactions. In this volume, which has become a handbook for studies of ligand-binding experiments, Klotz presents the theory and proper way to interpret binding data for these interactions.

PROTEIN STABILITY, STRENGTH OF HYDROGEN BONDS, AND HYDRATION

Like many other physical chemists in the late 1940s, Klotz became intrigued by the recognition that biologically active proteins in aqueous solution existed in specifically folded, compact conformations of remarkable stability. The principal question they addressed was: "What was the main contribution to the stability of a specific structure?" Much of the focus derived from Pauling's proposal that interpeptide (N-H…O=C) hydrogen bonds were major stabilizing factors. But there was concern about the strength of those bonds because the values then being widely used (5 to 8 kcal), though appropriate for the gas phase, solids, or nonpolar solvents, did not seem pertinent for an aqueous environment where water molecules served as a competitor for the peptide bond. Accordingly, in 1960 Klotz and Franzen embarked on a direct experimental approach to determine the intrinsic stability of hydrogen bonds in water and other solvents by using near infrared spectra to study the aggregation of the model compound, N-methylacetamide. From measurements at different temperatures they were able to demonstrate that the enthalpy of hydrogen bond formation in nonaqueous solvents was, as expected, about – 4 kcal/mole, but in water it was virtually zero. These direct experiments with a model compound, along with theoretical treatments of the properties of urea solutions by others, raised concerns about interpeptide hydrogen bonds being the key to protein stability, thereby prompting a search for other factors responsible for their stability.

Again Irv was in the forefront, contributing seminal ideas to account for the stability of proteins based on thermodynamics with an emphasis on the nonpolar side chains of proteins and their interactions with water. Already recognized from his binding studies that the formation of protein-ligand complexes involved favorable entropy changes due to the liberation of water molecules, Irv extended that idea by building on concepts developed by J. D. Bernal and J. A. Butler that in aqueous solutions water molecules can become highly structured around solute nonpolar as well as polar molecules. In considering the diverse properties and behavior of proteins, especially their hydration, he wrote a series of stimulating and insightful reviews drawing attention to the importance of water and to the many known crystalline hydrates of nonpolar molecules that were stable at room temperature. He suggested that similar forms of ordered water might be formed around nonpolar side chains of proteins. This was a topic that generated much interest as physical chemists debated about the forces responsible for the stability of proteins as highly compact structures. Klotz's concept of the apolar bond did not receive the widespread acceptance accorded the proposal by Kauzmann of the hydrophobic bond, but it played a significant role in the debate at that time and led to important investigations by Klotz and others of the distribution of nonpolar side chains between the interior and surface of globular proteins and their accessibility to solvent water molecules. Irv's view that many of the side chains of nonpolar amino acid residues were on the surface and that water would be structured was validated by subsequent X-ray studies.

SPECTROSCOPIC PROBES, BIOINORGANIC CHEMISTRY, AND HEMERYTHRIN

Before X-ray diffraction techniques began to reveal atomic details in proteins, only indirect chemical or physical probes could illuminate the nature of the environment within these macromolecules in the folded form. Klotz, though not trained as an organic chemist, did not hesitate about designing and synthesizing a "tailor-made" compound when it seemed likely to be useful in his studies of the local environment in protein molecules. He was one of the first to take advantage of spectroscopic sensors as probes whose spectra revealed the environment of different domains in protein molecules. His use of azomercurials to modify sulfhydryl groups in proteins permitted interpretation of acid-base ionizations of proteins by circumventing the complications that measurements on unmodified proteins reflect the composite behavior of a large number of identical groups. Through the use of such azomercurials, which subsequently were employed by other researchers, Irv was able to probe the local environment of cysteine residues in proteins.

Early in Klotz's use of equilibrium dialysis to study protein interactions, he investigated the interaction of copper ions with serum albumin, thereby demonstrating the value of noncovalent spectroscopic probes. Their optical spectra when bound to proteins were compared with those in solvents of different polar or nonpolar character. These studies, as early as 1948, generated an interest in bioinorganic chemistry and metalloproteins that persisted throughout Irv's career, leading to extremely rewarding research on nonheme biological oxygen carriers. In vertebrates the oxygen carriers are primarily the nonheme hemocyanins and hemerythrins, the former having copper at the active site, the latter having iron. To Irv the important issue was determining the molecular environment of the oxygen-binding metal in such proteins. Accordingly, starting in the early 1950s, he initiated an extended structural study concentrating on nonheme-iron-containing hemerythrin to compare it with heme-iron-containing hemoglobin. Since the earlier literature was primitive and inconsistent, Klotz started with the most elemental analyses showing that both the iron content and iron-oxygen stoichiometry were substantially different from the previously reported values. Similarly, an extensive investigation of hemerythrin from the crustacean *Limulus* (horseshoe crab) established a molecular weight of 108,000 and that the protein could be dissociated reversibly into monomers of 13,000. This led to studies of the dynamic equilibria and an evaluation of the thermodynamic parameters governing the association-dissociation equilibria. In the 1960s he determined the amino acid composition and primary structure of hemerythrin; with the technology available at that time this was not a trivial achievement.

In characteristic style Klotz pursued wide-ranging studies of hemerythrin employing all the tools of the physical chemist. These included not only detailed ultraviolet absorption spectroscopy but also Mossbauer and resonance Raman spectroscopy. His aim in this research, which can be best described as a *tour de force* encompassing a 20-year period and involving many collaborators, was to determine how hemerythrin functioned as an effective transport protein. The resulting proposal that binuclear-bridged metals in the form of Me-X-Me were involved as a crucial part of the active site of hemerythrin was confirmed through these extensive studies and subsequently been shown to be applicable to metalloproteins in general.

OTHER FORAYS IN PROTEIN SCIENCE

Throughout his career as both a researcher and teacher, Irv avidly digested the remarkable developments in the understanding of the structure and function of proteins. With an almost insatiable curiosity he looked for areas where he could contribute. Thus, when there was much interest in the process of hydrogen-deuterium exchange for studying the structure and stability of helices, he focused on the factors controlling the rates of exchange and discovered the catalytic effect of imidazole and other general acid-base moieties, thereby establishing the role of the local molecular environment on the dynamics of this exchange.

When efforts to understand sickle cell anemia reached the stage of focusing on HbS, the hemoglobin mutant responsible for the sickling, Irv became interested in the phenomenon. He recognized that the deoxygenated form of the hemoglobin molecule tended to aggregate, leading to the distortion of the red cell, and thought that preventing the conformational change in the mutant molecule upon deoxygenation might eliminate sickling of the cell. Toward that goal and with the hope that the work would lead to use in humans affected by the disease, he devised a set of double-headed aspirin reagents that could crosslink the two beta chains thereby preventing the molecule from changing conformation upon deoxygenation. As has been true with all of Klotz's research this effort has been pursued further with the additional recognition that these reagents might be of clinical value.

TEACHER

Whether it was in freshman chemistry or a graduate course in physical chemistry, Irv had few peers as an instructor. He was recognized both in his own institution and universities throughout the country and abroad as one of the exceptional teachers of chemistry of his generation. To Klotz every lecture was a creative experience with form, beauty, timing, and inspiration. His contributions to education include the training of hundreds of successful biochemists at the undergraduate, graduate, and postdoctoral levels. Many of them have gone on to positions in academic institutions, national laboratories, and other chemical and biochemical enterprises. One of his former students wrote:

As an expositor of science, particularly of chemistry, he had few peers. In his teaching within the university, in his internal and external lectures and seminars and in his training of research students, Klotz consistently devoted himself to excellence—excellence in communication, excellence in the selection of materials for teaching, excellence in the organization and presentation of materials; excellence which results in student and audience understanding of even the most complex subject matter.

For graduate students in chemistry and allied disciplines his contribution to education continues years after his death through his book *Chemical Thermodynamics*. The original version was first published in 1950. In 1972 and in subsequent editions he was joined by one of his first graduate students, Robert M. Rosenberg. The jointly authored seventh edition (2008) was published after his death. This popular textbook has been translated into many other languages, and is known among students as exceptionally clear and logical, the most readable book available in an area that beginners find esoteric and difficult to grasp.

Stimulated by lecturing in the physiology course at the Marine Biological Laboratory in Woods Hole, Massachusetts, Irv decided to write a small volume, *Introduction to Biomolecular Energetics: Including Ligand Receptor Interactions* (1997) for scientists in the life sciences. This very influential book, representing an expanded version of earlier books, has been recognized as the most effective monograph available for learning the fundamental concepts and computations of energy changes in biological transformations. It has had a great influence on students and research workers in biochemistry, molecular biology, and related life sciences.

During the course of his entire academic career devoted to teaching physical chemistry, Irv also became deeply interested in and committed to interdepartmental courses in science and the humanities. Conscious of the many discussions about two cultures and problems of scientific literacy, he was particularly interested in introducing nonscience students to key concepts and critical thinking in the sciences. For many years and long before it became popular he conducted seminars for students in the humanities, social sciences, and journalism with the general title "Sciences for Non-Scientists." Because of his uncanny ability to present the beauty of chemistry and biochemistry and other branches of science to nonprofessional people, he received innumerable invitations to serve as a guest professor at various universities and lecture on the relationships among science, humanities, and ethics.

HISTORIAN, SOCIOLOGIST, AND PHILOSOPHER

Well aware that undergraduate students of chemistry generally find lectures on the history, sociology, and philosophy of science boring and soporific, he designed a freshman chemistry seminar entitled "Grand Illusions in Science," which dealt with "great discoveries not mentioned in textbooks," such as N-rays, polywater, and spurious cancer cures. Some of the notes from these seminars were incorporated into publications like "Bending Perception to Wish" and formed the basis of dozens of popular lectures that Irv delivered in universities throughout the world. The earliest of these addresses, entitled "The Clouded Crystal Ball," provided an unusual combination of humor and insight into the psychology and sociology of scientists. It was instructive as well as entertaining to nonscientists and scientists alike and was expanded into a volume entitled *Diamond Dealers and Feather Merchants: Tales from the Sciences* (1986). This volume was cited in the National Academy of Sciences publication *On Being a Scientist* as a major contribution in efforts to combat the public outcry in the 1960s against scientists. The collection of essays is indispensable in conveying ethical principles to young aspiring scientists.

Later Klotz delivered a powerful answer to those in government and the press who were attacking science as a highly fraudulent activity through his article "Cooking and Trimming by Scientific Giants" (1992). It traces the history of some of the greatest contributions to science and thereby provides an effective, illuminating description of how science is performed. Concerned that ongoing investigations of misconduct in science in the 1980s had become threatening to the legitimate pursuit of research, Irv also wrote an influential article, "'Misconduct' in Science: Quis Custodiet Ipsos Custodes" (1993), dealing with major examples in the history of science where so-called guardians of scientific integrity were wrong in their attacks on the work of Newton, Galileo, and many others. This paper was followed by a short note in 1998 entitled "A Bill of Responsibilities for Whistleblowers in Science" aimed at reducing the frequency of accusations of misconduct in science that subsequently were judged to be unwarranted.

In lectures to diverse audiences Irv demonstrated a deep interest in the underlying scientific thought processes associated with advances in science and the acceptance or nonacceptance of "odd ball" ideas. The chapter "The Clouded Crystal Ball: Creases of the Mind" presents a discussion of the scientific writings and resulting controversies involving some of the icons of science like Newton, Lord Kelvin, Darwin, and Mendel. At the end of that chapter he raised some basic issues of trust, doubt, and integrity that any scientist should ponder:

> This concludes our non-random walk through the literature of science in search of justifications for administering a few black eyes to scientists of great, or lesser distinction. It is not difficult to be an infallible Monday-morning quarterback. The crucial challenge, however, is to make a correct judgment, ad hoc, not post hoc. We have not been able to discover criteria against which to evaluate each of the many different types of novel ideas arising in

all areas of science. These can have different forms of abstraction, different modes of expression, different goals. From the small assembly of cases that we have examined here, it is hazardous to attempt to extract any guides for early recognition of the ultimate value of a new paradigm. Perhaps no such principles exist.

Klotz then continues with the trenchant remarks:

Practicing scientists in general must operate on the assumption that generally-accepted fundamental views in their field are valid. They cannot pay serious attention to every challenging conceptual or experimental claim, for they would be inundated with diversionary distractions which, in the overwhelming majority of cases, turn out to be totally without merit. On the whole, it does pay to heed the biblical injunction: "Beware of false prophets." Perhaps we can reasonably ask, however, that each of us remember the very perceptive epigram of the greatest and most imaginative of all chemists, Antoine Laurent Lavoisier, who said, "The human mind becomes creased into ways of seeing things."

Irv's questioning mind and skepticism about reports from those he considered revisionist historians, journalists, and dramatists coupled with his intense focus on accuracy led him to a detailed study of the efforts by German scientists to develop the atomic bomb during World War II. This included reading original documents in German and listening to the transcripts of the surreptitiously recorded private conversations of the 10 leading imprisoned German atomic scientists at Farm Hall, England. The resulting publication, "Captives of Their Fantasies: The German Atomic Bomb Scientists" (1997), along with several lectures on the topic constituted a clear rebuttal to the view expressed by Heisenberg "that moral scruples had restrained him and his colleagues from trying to produce an atom bomb for Hitler." To Irv Klotz this story is another example of one of his major themes dealing with the ethics and sociology of scientists bending perception to wish.

Intensely concerned with education at all levels, Irv wrote a series of insightful articles such as "Multicultural

Perspectives in Science Education: One Prescription for Failure"; "Science Literacy: What Do We Mean by It, and What Do We Want?"; and "Postmodernist Rhetoric Does Not Change Fundamental Scientific Facts." In the midst of the debate over intelligent design he sent a tongue-in-cheek letter to a Chicago newspaper entitled "Why We Should Teach Creationism in School" and was particularly amused by the complimentary response it elicited from an individual who was contemptuous of the concept of evolution. There were few areas in the history, sociology, and philosophy of science that didn't attract his attention and lead to incisive commentaries on very diverse subjects.

HONORS

In the course of his career Irv received many honors starting with the Eli Lilly Award of the American Chemical Society in 1949. He was elected to the American Academy of Arts and Sciences in 1968, the National Academy of Sciences in 1970, and the Royal Society of Medicine in 1971. He received the Professional Achievement Award of the University of Chicago Alumni Association in 1987 and the William C. Rose Award of the American Society for Biochemistry and Molecular Biology in 1993. Starting in 1963 when Klotz was the Reilly Lecturer at Notre Dame University, he was a distinguished lecturer at many institutions throughout the country, including Ohio State University and University of Buffalo in 1967, Baylor University in 1970, Florida State University in 1977, Oberlin College in 1981, University of Iowa in 1985, and Mayo Graduate School in 1994.

A CLOSING TRIBUTE

One can locate numerous tributes and can admire the lengthy list of contributions and awards he received during his career. However, the tributes he might appreciate most would not involve listing his accomplishments or awards. Rather, he would be most gratified to learn that a thought process or methodology we learned from him or his work was then used to advance the scientific state of the art in another scientific discipline, chemistry or otherwise. At the memorial symposium the year after he died one of his former students said, when faced with a technical challenge, he would often ask himself, "How would Irv Klotz have solved this problem?" That simple questioning really is a tribute that he would have admired.

In closing, I would like to add a comment from my former student, Sue Hanlon, who then became a postdoctoral fellow with Irv Klotz and later his wife. She wrote,

> Upon driving one day I chanced to hear an aria from Turandot played on the car radio, I suddenly wondered if Puccini, or indeed any of the great composers of the past realized how much pleasure their music would bring many years after their death. And, suddenly, the same thought came to me about the enlightenment that the works of scientists in many fields had brought to the understanding of natural processes. In many instances, one is not even aware of using major concepts elaborated by Newton and others. There is, however, a crucial requirement for the current enjoyment of great works of music, the arts and science. The present appreciation and understanding of the past requires people who are able to perform and interpret and expound on past achievements, as well as make their own contributions. In our own careers, someone had to teach us how to do science. Irving Klotz was such a person who contributed not only directly by his own research but also as a teacher and educator, par excellence.

IRVING KLOTZ'S FAMILY MEMBERS were enormously helpful to me in writing this memoir by furnishing ideas, documents, and criticisms. I thank them for their invaluable contributions.

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