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### The Life Of A Professor

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The Life Of A Professor

I am honored to receive the 2014 Priestley Medal. The award is a tribute to the talented students, both graduate and undergraduate, as well as postdoctoral associates who have trained with me over nearly 50 years. I am proud of these individuals, for their courage in agreeing to venture onto new snowfields to place the first footprints, for their relentless pursuit of the truth, and for their creative ideas and clever experiments that brought insight where previously there was often confusion.

Of equal importance are the many collaborators who have greatly facilitated our ability to make progress in areas beyond our knowledge base. If "professor" stands for "professional student," these individuals have been my teachers. I thank them, the ACS Board of Directors who award this medal, and those who entered and supported my nomination.

While contemplating the message I wish to convey here, I chanced to read in *Nature* an obituary by Alan Bernstein and Janet Rossant describing the biochemist Tony Pawson. In receiving an award in 1998, Pawson spoke of several facets of his life as an academic scientist that mirrored some of the themes that I had already chosen for my Priestley address. Three of them, "the joy of discovery, the privilege of working with talented young people, and the importance of family," together with the opportunity to serve, are told here in the context of my own experiences, which I hope may be a source of inspiration.

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## THE PRIVILEGE OF WORKING WITH YOUNG PEOPLE

### Professor as the professional student

I consider it good fortune to be surrounded by bright young people—students and postdocs—with energy, enthusiasm, and ingenuity. As a professor, or “professional student,” in the environments of Columbia University and Massachusetts Institute of Technology, I learned many things from my graduate students and postdocs. I learned that the amount of time a person spends in the laboratory is not a good measure of what he or she will accomplish. One of my first graduate students, Karen Jennette, commuted 90 minutes each way every day yet managed to get more research done than many of her lab mates.

I learned to recognize and nourish the qualities that make for a good chemistry graduate student, such as commitment and self-reliance. Some of my group members, like captains of sports teams, were noted for their dedication, leadership, positive thinking, unselfish nature, and ability to foster harmony among coworkers. Some, like people raised on farms, were self-reliant, perseverant, and observant.

I learned not to be surprised by the decisions of my group members. My graduate student Wes Sundquist, nearing the end of his fourth and final year, made a pivotal discovery. He placed an NMR tube containing a deep blue solution of a platinum complex in the fridge at the end of the day. When he removed the sample the next day, the solution had turned deep orange. Further studies confirmed unparalleled thermochromic behavior, and he begged me to allow him to stay another year to continue the work. Given his talents, I could hardly say no! Today, Wes is a famous biochemist.

I learned in time that not all Ph.D. chemists pursue a career in chemistry. Law, medicine, elementary and high school teaching, management consulting, and a host of other opportunities are there for chemists with advanced degrees. What matters most is happiness and fulfillment in the job—it should be fun to walk out of the door each morning on the way to “work.” I encourage my students to seek that happiness and to pay little attention to conventional wisdom about a particular occupation. I teach them that the most important decisions in life are made not in the head but the gut.

### Professor as a mentor

How does one help students choose research projects? When graduate students or postdocs begin their research, I ask them to consider the circle of chemistry and to draw a diameter. One semicircle represents small molecules and the other macromolecules. I then ask for a second diameter, perpendicular to the first, defining two more semicircles: making things and measuring things. I then ask, “Which quadrant best defines your interests and talents?” The conversation facilitates further discussion and, ultimately, helps identify the topic that is likely to be a focus of their thesis research.

Academic chemistry is the incubator of innovation, as ideas become reality. Graduate students, unfettered by experience marked with failures, are usually willing to try anything. Yet when I ask first-year graduate students, “What emotion best defines your time thus far in graduate school?” for many, it is fear—fear of falling short of their expectations, of projects that lead to dead ends, of their inability to find their way past experimental obstacles. It reassures them to know that fear is common.

These students are in transition between a course taker/problem-set solver and a pioneer facing an endless frontier of experimental choices. It can be scary not to know where to go next without the benefit of prior knowledge. Deciding when to stop pursuing an objective is one of the most difficult decisions in science. I characterize the transition from undergraduate course taker to graduate student research achiever as “passing through the eye of a needle.” Experiments begin to produce meaningful results, self-confidence is restored, and the road to the Ph.D. is established.

Postdocs bring maturity to the laboratory and skills from their prior training that significantly enrich the environment. Their first group meeting assignment is to present a seminar on their Ph.D. thesis research. It provides a comfort zone for them in their new surroundings while educating other group members about the methodologies they have mastered and how they were taught to think about chemistry.

Undergraduate research students, called UROPs at MIT, are a special breed. Because of the many demands placed on their time, they tend to focus intensely when doing their research. One of my former graduate students, Matt Sazinsky, mentored as many as four UROPs at one time, running a minigroup inside the larger group and making remarkable progress in his research program. He is now a faculty member at Pomona College, where this experience has served him well.

### Professor as colleague

Faculty members in chemistry departments are brothers and sisters in education, research, and service. They need to support each other, for it is not easy to make the transitions from student to full professor. Departments that foster collegiality flourish.

At MIT we have had monthly faculty dinners. Preceded by a brief social hour, each of these events was highlighted by a research presentation from one of the faculty, presented as dessert was served. Hearing from the younger faculty was especially valuable, for it often engendered helpful suggestions from senior colleagues and sometimes collaborations.



## Professor as an instructor

Not everyone loves classroom teaching, but I do. Teaching offers the opportunity to bring perspective about the subject to the students, by framing recent advances in the context of existing knowledge.

For the faculty, teaching is a great way to remaster the basics, and it often inspires research ideas. For the students, it can be an amazing experience to have a faculty member take a textbook course and place it in the context of contemporary research.

As an undergraduate at Haverford College, I was a premed English major until Colin MacKay and other faculty, including visitors, exposed me to the beauty of chemistry. I especially love teaching freshmen, where it is both possible and desirable to perform many practical demonstrations to illustrate and enliven the lectures. **The books by Bassam Shkhashiri provide guidance for performing classroom demonstrations in a safe, dynamic, and instructive manner.** Teaching advanced courses has the advantage of smaller class sizes.

As a strong believer in the Socratic method of teaching, I value the opportunity to address questions in real time. A well-planned lecture budgets time for such discussion, where one can sharpen critical skills by encouraging students to question prevailing paradigms. In advising students about courses to take, I tell them that lectures are as much about professors as they are about the specific subject matter. What is said between the lines imparts wisdom beyond that of the printed text.

## THE ROAD TO, AND JOY OF, DISCOVERY

### Choosing a research project— metallointercalators

How does one choose a research project? My preference is to address a specific problem rather than to develop methodology. But exactly what is worth studying? The inspiration can come from many sources.

Senior scientists offer a special opportunity for young faculty starting out. An example is a conversation that I had with the late Bill Phillips of DuPont when I was joining the Columbia University chemistry department as an assistant professor. Phillips recounted a strategy pursued by Michael Beer of Johns Hopkins University to sequence the human genome by attaching heavy atoms to base-specific sites and then reading their positions with an electron microscope.

I envisioned a tactical approach to achieve the requisite specific labeling of the nucleotides. In collaboration with Fritz Eckstein at the University of Göttingen, in Germany, we incorporated sulfur atoms as phosphorothioates into the sugar-phosphate backbone of DNA or RNA to direct the binding of mercury or platinum complexes selectively to these positions. The chemistry worked well, as expected from the “hard-soft acid-base theory.” But despite much effort, it was not possible to read the positions of the heavy-atom beads on the string of DNA nucleotides with sufficient resolution in the scanning transmission electron microscope.

During the course of these studies, however, Karen Jennette, in a proof-of-concept experiment, examined the binding of platinum complexes containing planar fused-ring aromatic heterocyclic ligands to a tRNA molecule having a naturally occurring 4-thioU base. This preliminary work led to an exciting discovery: Seemingly sterically encumbered platinum complexes bound better to the sulfur atom in the tRNA than did less hindered mercury salts.

We proposed that the platinum complexes were intercalating between the stacked base pairs of the double-stranded RNA. Soon thereafter, we proved with newly discovered superhelical DNA that this type of binding, which we termed metallointercalation, was a general phenomenon. Bill Bauer of Stony Brook University, SUNY, was a valued collaborator in this work.

Next, we examined a DNA sample containing the intercalated platinum complex by fiber X-ray diffraction in collaboration with Peter Bond working in Bob Langridge’s lab at Princeton University. Peter had trained with the Nobelist Maurice Wilkins at King’s College London and was an expert in this method. Late on a warm summer evening on the beautiful Princeton campus in 1975, Peter, Karen, and I eagerly awaited the development of X-ray films portraying the diffraction pattern.

There, superimposed on the famous “cross pattern” of double-stranded Watson-Crick DNA, were 10.2-Å meridional reflections arising from the regular spacing of the heavy platinum atoms stacked according to the “neighbor exclusion” rule (**figure 1a**). This rule dictates that the presence of an intercalator between DNA base pairs excludes the neighboring inter-base-pair

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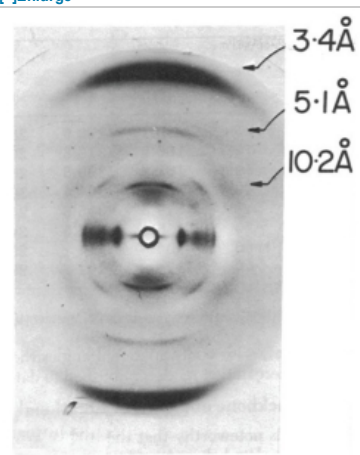


Figure 1a

Credit: *Proc. Natl. Acad. Sci. USA*

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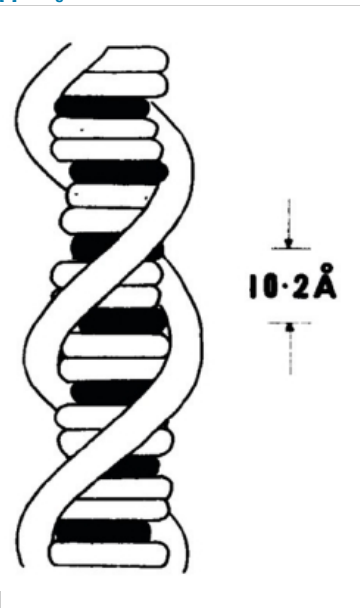


Figure 1b

Credit: *Proc. Natl. Acad. Sci. USA*

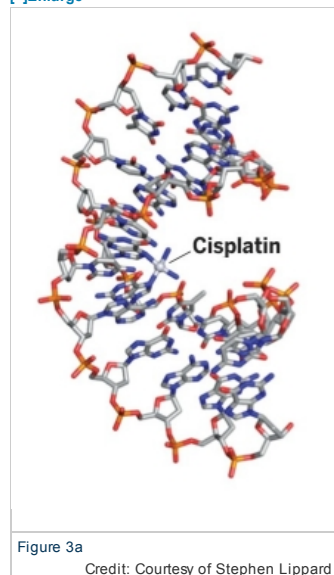
sites on either side. Thus, the Pt–Pt distance would be three times the thickness of an aromatic ring, or about 10.2 Å (**1b**).

It is impossible to exaggerate the joy of this discovery! It had been predicted from indirect methods that intercalators would be subjected to the neighbor exclusion rule in binding to DNA, but no one had visual proof of such. Moreover, it set the course for decades of future research in my group centered on the interactions of transition-metal complexes with DNA.

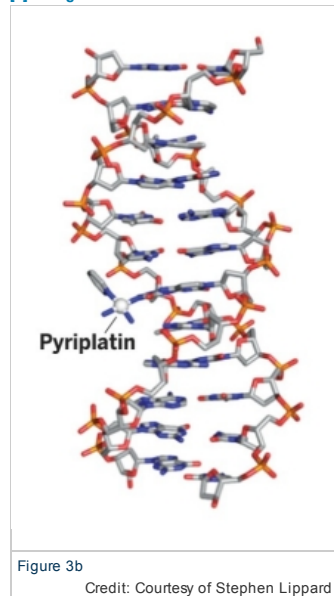
At about the same time, the anticancer activity of cisplatin, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>], was discovered and immediately drew my attention. What more important a project could there be than to understand the mechanism of action of what was to become a leading anticancer drug? Because work by Barnett Rosenberg, who discovered the anticancer properties of cisplatin, and others pointed to DNA as the likely target of the compound, I was eager to apply the research experience gained in studies of metallointercalation to this new project.

### Platinum anticancer drugs

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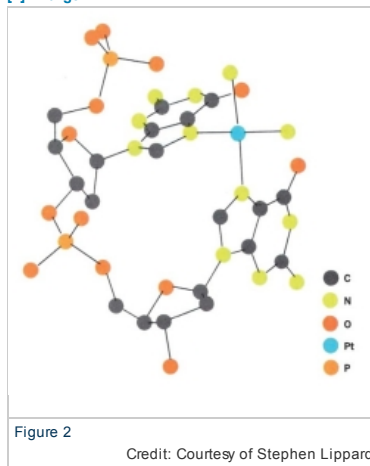


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to investigate the roles of inorganic species, specifically Zn<sup>2+</sup> and nitric oxide, at the interface of inorganic chemistry and neuroscience led to constructs that can serve as signaling agents for neurotransmitters. Included are sensors for mobile zinc (Shawn Burdette, Liz Nolan, Chris Chang), nitric oxide (Mi Hee

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Our investigations of platinum anticancer agents produced many rewarding discoveries and much satisfaction to my research group members involved in the pursuit. Some of the high points include the following: structural characterization of a crystalline “platinum blue” by Jackie Barton (**see cover**); elucidation of the major adduct, an intrastrand d(pGpG) cross-link, formed by cisplatin on single-stranded DNA by Suzanne Sherman (**figure 2**) and double-stranded DNA by Tricia Takahara (**3a**); discovery by Sue Bruhn, Pieter Pil, and Jeff Toney, as well as Brian Donahue in collaborator John Essigmann’s lab at MIT, that high-mobility-group proteins bind to the platinated DNA cross-link; and determination of the X-ray structure of one such protein/platinated DNA adduct by Uta-Maria Ohndorf (**4**).

We also deduced many aspects of the molecular mechanism of cisplatin, which ultimately led to the realization that monofunctional platinum complexes, which form only one bond to the DNA bases, could also display potent anticancer activity. Unlike the intrastrand cross-links formed by cisplatin, adducts formed by monofunctional complexes do not bend DNA, which retains the canonical Watson-Crick structure upon platination (work by Ryan Todd, **3b**).

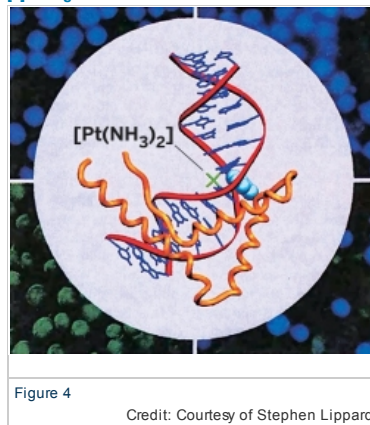
Monofunctional complexes provide an untapped source of novel anticancer drug candidates, and they are not restricted to platinum. They provide the potential for new metal-based cancer treatments.

### Reductive coupling, nonheme iron proteins and models, and metalloneurochemistry

Platinum chemistry represents only one facet of our research program. Many other projects produced joyful discoveries that are briefly recounted here. Included are reductive coupling of adjacent isonitrile or carbonyl ligands in second- and third-row early-transition-metal complexes to form C–C bonds (work by Chiu Lam), the most interesting of which to me was a coordinated dihydroxyacetylene generated from carbon monoxide (Ray Vrtis, **figure 5**); the first model of a carboxylate-bridged diiron protein active site, that of hemerythrin (Bill Armstrong, **6**); determination of the structure of the hydroxylase component of soluble methane monooxygenase (Amy Rosenzweig, **7**); and a “molecular ferric wheel” produced in pursuit of a model of the ferritin core structure (Kingsley Taft, **8**) that defined “wheels” as a branch of self-assembled polymetallic chemistry.

Work to obtain fluorescent probes

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Lim), nitroxy (Joel Rosenthal), as well as the pathological metal ion mercury (Liz Nolan).

Studies in collaboration with Jim McNamara at Duke University used a very rapid zinc chelator, ZX1 (Xiao-an Zhang), which enabled us to prove a role for mobile zinc at the mossy-fiber/CA3 synapse in the brain's hippocampus that is critical to control of the efficiency of communication between these nerve cells. We use the term metalloneurochemistry to describe this line of investigation.

### Grand challenges in fundamental chemistry

In many of the foregoing examples, the motivation was either to understand metal-based chemistry that underlies important functions in bioinorganic chemistry or to apply coordination chemistry to probe biological signaling and to diagnose or treat disease. But there are many unmet challenges in fundamental chemistry for consideration in choosing research projects. More than a decade ago, I wrote a list of these "grand challenges" ([C&EN, Aug. 7, 2000, page 64](#)) and have discussed them with physicists, biologists, and other scientists as examples of important goals in pure chemistry. Significant progress has been made in addressing these challenges. Some of my favorites are the following: to create self-replicating molecules and self-correcting chemical reactions, to devise reagents and pathways for activating chemical bonds viewed to be inert, to modify chemically a portion of a molecule having many functional groups without protection/deprotection steps, and to refine and utilize the chemistry of polyatomic radicals.

Many in our field view chemistry as the "central science." I am not one who favors this description, for it could be interpreted to mean that we are a service discipline—one that touches on many surrounding areas (biology, chemical engineering, solid-state physics, materials science, neuroscience, medicine) without recognition that we have a plethora of important grand challenges. My list of goals is neither complete nor even necessarily a good one. I encourage others to improve and expand it.

Synthesis is the heart of chemistry. It is the singular pursuit in our science that is unlikely to be seriously addressed by colleagues in neighboring disciplines, who often co-opt our ideas and language (witness: synthetic biology) with little likelihood of supplanting what we chemists recognize as synthesis.

Theoretical, physical, analytical, and other chemists for whom synthesis may not be a prime objective nonetheless serve the art and science of making things by providing insights into the nature of bond-making and bond-breaking reactions, steps that ultimately underlie all chemical synthesis. Circling back to my own research, the synthesis of new molecules and the physical understanding of biochemical transformations that generate essential biomolecules are intimately involved in many of the projects that my lab has undertaken.

## THE OPPORTUNITY TO SERVE

The Priestley Medal specifically recognizes "distinguished services to chemistry," which thus far have been exemplified by some of my research contributions and by the education and mentoring of students. But there are many other opportunities to serve that can enrich one's professional life.

I am grateful for the invitations to serve the inorganic chemistry community as editor of *Progress in Inorganic Chemistry* and the bioinorganic chemistry community as associate editor of *Inorganic Chemistry* and then the *Journal of the American Chemical Society*. I thank Bruce Armbruster and University Science Books for encouraging me, in collaboration with Jeremy Berg, to write our textbook, "Principles of Bioinorganic Chemistry."

The opportunity to serve on two National Institutes of Health study sections allowed me to give back to the community that enriched my professional life by supporting my research activities. This service had an unexpected benefit in sharpening my skills in writing grant applications. It reinforced my conviction that a major strength of science in the U.S. is the need to pass critical peer review in order to continue one's research. Seniority is no guarantee of continued funding.

A rather unusual opportunity to serve came in 1991 when I was invited to become Housemaster of MacGregor House at MIT, a coeducational

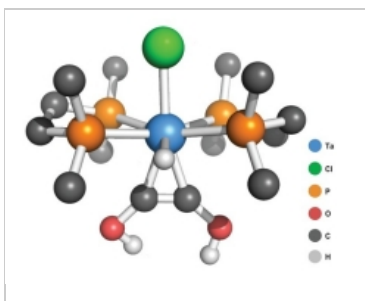


Figure 5

Credit: Courtesy of Stephen Lippard

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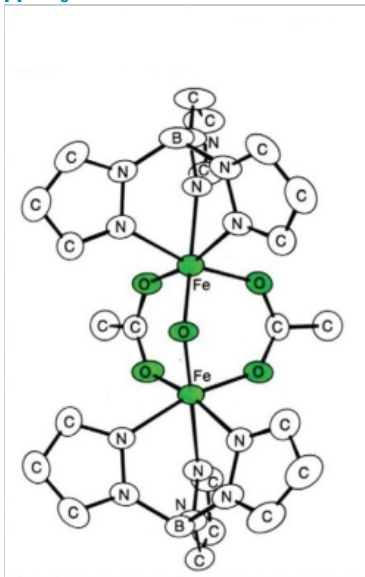


Figure 6

Credit: Courtesy of Stephen Lippard

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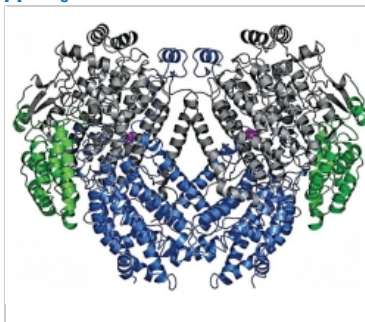


Figure 7

Credit: Courtesy of Stephen Lippard

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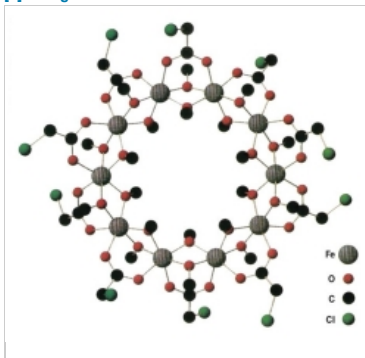


Figure 8

Credit: Courtesy of Stephen Lippard

undergraduate dormitory housing approximately 350 students. During the first year, I volunteered to teach a yearlong course on baroque musical instruments and performance, which met from 9 PM to midnight on Mondays and was restricted to MacGregor residents.

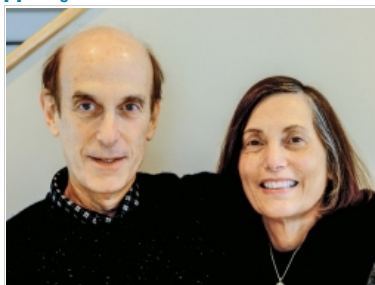
I play the harpsichord and enjoy baroque music, so sharing this pleasure with the undergraduates was of interest. Moreover, it provided an opportunity to enrich the lives of young people in a manner similar to what I had enjoyed as an undergraduate at Haverford. The course, which required approval from the music department, was given pass/fail and could not be counted toward the major.

Little did I know what I was taking on! Not being trained in music education, running this course was one of the harder things that I have ever done. The learning curve required to prepare and teach the material was steep. But with help from faculty at the nearby Longy School of Music, who came and demonstrated their baroque instruments to the students, and thanks to the talents of those enrolled, we made it work. We gave two public concerts, which were well attended and quite enjoyable.

One of the students in my course, a pianist and composer with enormous talent named José Elizondo, was quite taken with the harpsichord that I had raised funds to rent for the academic year. It was housed in the MacGregor House music room, where the course met. In addition to science and engineering, José loved and wanted a career in music. But his father, who expected José to join the family's potato farming business, was initially reluctant to support even what he saw as his son's more practical electrical engineering degree. Music was out of the question as a career option.

But with much effort and dedication, and thanks to opportunities MIT provided, including my seminar, José pursued both degrees. When the San Jose Symphony Orchestra premiered his first symphonic suite, he received a standing ovation by a crowd of 25,000. At age 24, he was the youngest composer to have his work performed by that orchestra. Of great satisfaction to me was his informing me that his father attended that premiere and finally became reconciled with his choice of music as a career.

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**Steve and Judy Lippard**

Credit: Courtesy of Stephen Lippard

## THE IMPORTANCE OF FAMILY IN THE LIFE OF A PROFESSOR

It is not easy having an academic scientist as a life partner. I have accordingly counseled my group members to choose wisely. That person must understand the dedication required for success and fulfillment. Chemistry experiments set up on Friday afternoon may often not wait until Monday morning to be worked up and extended. Some experiments require attention late into the evening or even a return to the laboratory long after normal business hours.

Unlike many professions, experimental chemistry cannot be done from the comfort of one's home via

the Internet. I have witnessed a number of relationships, including marriages, dissolve because the partner of a chemist did not understand what is required to support them in their choice of career.

My personal situation has been extraordinary, as many can attest who had the good fortune to know my late wife, Judy. We met at an MIT mixer (my first and only one) in September of 1963, when she was an undergraduate at Simmons College and I was a graduate student at the Institute. We were engaged in December and married the following August. She was 21, and I, 23. Although her talents for painting, sculpture, and other forms of art were substantial, she chose instead to devote herself to our children and to our family, supporting me in my career. Many if not all who know me well credit Judy for my success as a scientist. It is true. She was then and to the end my greatest fan.

Only much later, when I became associate editor of *Inorganic Chemistry* and then the *Journal of the American Chemical Society*, did Judy begin a career, as a journal editorial assistant. This was a post that she finally relinquished when we had to abandon our work on *JACS* in August of last year. Judy worked from her bed in Massachusetts General Hospital until her cancer became too much for us to continue.

Judy was very brave and wise as she faced her death, counseling family members to make their days count and to help, respect, and love each other going forward. Her major regret was not being able to see our beautiful twin granddaughters, now four years of age, graduate high school.

I took her nearly everywhere I traveled, and the communities of inorganic and bioinorganic chemists were counted among her good friends. The outpouring of letters and e-mails that came to me after her death on Sept. 9 of last year is extraordinary. I conclude my remarks by honoring Judy. The love that we had

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**DOUBLE JOY**

Lippard's twin granddaughters, Lucy (top) and Annie.

Credit: Courtesy of Stephen Lippard

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for each other endures in my heart and mind. I dedicate this Priestley lecture to her memory.

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**Trailblazer And Mentor  
The Life Of A Professor**

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Credit: Courtesy of Stephen Lippard

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