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Personal Reflections on Receiving the Roger Adams Award in Organic Chemistry

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The author reflects on his early experiences as a chemist, and on the subsequent shift in emphasis that his research has undergone from mechanistic and synthetic organic chemistry to natural products chemistry. Finally, the extension of the field of natural products chemistry into the emerging discipline of chemical ecology is noted. This essay concludes with a consideration of the importance of including science in the curricula of all college and university students.

I cannot remember when I first became intrigued with chemistry. But I remember clearly that it was in January 1940, when I had just turned thirteen, that I decided to try to pull together my very spotty knowledge of chemistry. I took James B. Conant's *Organic Chemistry* text along with me on the wonderful trip to Florida that my parents arranged in place of a more traditional birthday party. We made the trip from New York to Miami by train, which meant the excitement of occupying an upper berth in a sleeping car, of ordering exotic foods in the dining car, and the chance to read chemistry for hours without feeling guilty. By the time I got back to New York, it was clear to me that I wanted to be an organic chemist, and probably a teacher, although I had only the slightest idea of what either of these careers actually involved. Although I was equally fascinated by mathematics, I could not figure out how a mathematician earned a living. While the ritual in which a boy becomes a man at the age of thirteen in the Jewish tradition meant very little to me, it happened that my commitment to a life in chemistry coincided exactly with that rite of passage.

It is hard to realize that it is now sixty-five years later. Having been invited to write a Perspective for *The Journal of Organic Chemistry*, I have decided to take advantage of this special opportunity to look back somewhat selectively over those many years and to present a more than usually personal account of them. I will also take the liberty of trying to look forward a bit.

Life in Brooklyn, NY, in the 1930s and early 1940s was incredibly rich in opportunities. A subway ride could take one to Central Park, to the Museum of Natural History, to the Cloisters, or to Carnegie Hall, all for only five cents. One could buy all sorts of intriguing chemicals, and

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FIGURE 1. Stanley Basinsky (a University of Chicago classmate of the author), Michael P. Cava, and Jerrold Meinwald in Venice, Italy during the summer of 1949.

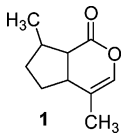
treasures such as retorts and separatory funnels, not only from drug stores, but from local scientific supply houses as well as by mail. My good friend and summer neighbor, Michael Cava, introduced me to the art of making fireworks at an early age, and later on to chemistry experiments we could carry out on weekends in an improvised home laboratory (Figure 1). We made nitrogen triiodide, bromine, chromyl chloride, nitrobenzene, *o*-nitrophenol, methyl orange, malachite green, Congo red, sulfanilamide, and more.... When we were not doing experiments, we were in the great New York Public Library on 42nd Street, hand copying laboratory procedures from the chemical literature. Having gained a bit of chemical sophistication, we would occasionally lecture to one another while a reaction was going on, using a blackboard in the ping-pong room adjacent to our laboratory. We taught ourselves how to identify and characterize unknown organic compounds, based on our reading of the illuminating text by R. Shriner and R. Fuson. All of this experience was great fun. But, of course, it did not give us an appreciation of what it meant to do research.

It was not until years later that this aspect of chemistry became a bit clearer to me as an undergraduate at the University of Chicago, as a result of taking George Wheland's fascinating Advanced Organic Chemistry course, in which the discussions of stereochemistry and of rearrangement mechanisms especially interested me. The chemistry of natural products seemed particularly seductive, and I could hardly believe my good fortune at being admitted to Harvard (where I had not gained admission as an undergraduate), thereby gaining the opportunity to work with my chemical idol, R. B. Woodward. I was particularly lucky to have a laboratory adjacent to Gilbert Stork's office and laboratory, which meant that I could benefit from extensive, informal discussion of all sorts of organic chemistry with Harvard's youngest organic chemistry faculty member whenever we were not otherwise occupied.

It should not go unmentioned that I had been an active flutist in Stuyvesant High School and as an undergraduate at Chicago and had the opportunity to perform works such as the Leclair flute concerto and J. S. Bach's *Coffee Cantata* with the University's *Collegium Musicum*, under the inspiring direction of Sigmund Levarie (under whom I had also played during a semester at Brooklyn College). In Cambridge I actually began formal flute lessons again, at first under the guidance of James Pappoutsakis (Boston Symphony Orchestra), and finally with the great French flutist, Marcel Moyse. At the time, it was clear to me that I was studying both music and chemistry with two of the world's acknowledged masters!

This is not the time or place to discuss the remarkable chemical education one could gain at Harvard in the late 1940s and early 1950s, but it would be fair to say that essentially the entire body of students and postdoctoral fellows developed, rightly or wrongly, a clear sense of working in the forefront of science. The most exciting experimental results were to be written up as compactly and dramatically as possible and submitted for publication to the *Journal of the American Chemical Society* as Communications to the Editor. Critical reading of the chemical literature and critical listening to seminar presentations played a central role in our training. These habits not only kept us up to date, but on occasion served to uncover new research opportunities.

In January 1952, I was delighted to be able to take up an independent DuPont-funded postdoctoral fellowship ("with the rank of Instructor") at Cornell University. One of the earliest problems on which I worked was the structure of nepetalactone, which S. M. McElvain at the University of Wisconsin had shown to be the active constituent of the essential oil from the mint species *Nepeta cataria* ("catnip"). It was Michael Cava who had suggested the problem to me, and I liked it because it seemed that the Wisconsin group had stopped publishing on the subject and it looked like a realistic problem for a novice. A combination of chemical degradation and the application of the isoprene rule led us to structure **1**, which turned out to be the first recognized example of a methylcyclopentanoid monoterpene ("iridoid"), now known to be a widespread family of natural products.[1]



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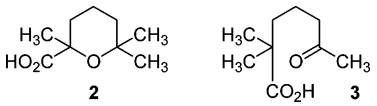
Another problem which I found particularly intriguing was the remarkable acid-catalyzed rearrangement of α-cinenic acid **2** to geronic acid **3**, which I discovered by reading the obituary of Hans Rupe in *Helvetica Chimica Acta*.[2] This transformation had been interpreted as



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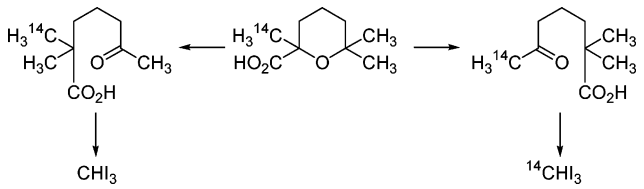
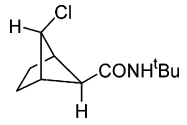
requiring a long-range methyl group migration which, however, had no reasonable mechanistic rationale. What struck me immediately was the fact that this mysterious transformation might not involve a long-range methyl group migration at all: transfer of the *carboxyl group* to the carbon atom bearing the geminal methyl groups would also produce geronic acid! Best of all, simply using

^{14}C to label the methyl group adjacent to the carboxyl in α-cinenic acid, followed by rearrangement, and subsequent haloform degradation of the geronic acid formed, would give cold iodoform if the methyl group migrated or radioactive iodoform if it was the carboxyl that is transferred. A summer visit to the Brookhaven National Laboratory, hosted by Alfred Wolf, gave me the chance to prove that the carboxyl migration hypothesis was the correct one. Shortly thereafter, with a little mechanistic advice from Saul Winstein, we could show that the α-cinenic acid rearrangement could be understood as a series of quite reasonable steps involving the loss and recapture of carbon monoxide, as summarized below.[3]



Rearrangement reactions continued to fascinate me for many years, and aside from establishing the pathways of several alkaloidal examples, we began to study in a systematic way the chemistry of various highly strained ring systems (i.e., bicyclo[2.1.1]hexanes and D-norsteroids) that were readily produced by Wolff rearrangement of the appropriate α-diazoketones.[4] It was during these studies that Arthur Lewis and I discovered that there is appreciable NMR coupling (7 Hz) between protons separated by *four* bonds when they are held in a W-conformation (as in **4**).[5] During these early days at Cornell, Orville Chapman and Paul Gassman worked with me on a variety of rearrangement and small-ring problems before taking off on their own highly productive academic research careers.



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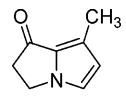
In 1957, our Entomology Department hired Thomas Eisner as an Assistant Professor. We were introduced to one another by a mutual friend, Howard Schneiderman, who had the thought that Tom's research might benefit if Tom could collaborate with a chemist. As it turned out, there was another factor that helped to bring us together. We quickly discovered our mutual interest in classical music. Tom is a gifted pianist who can sight-read just about anything and make it sound as if he knew the piece his entire life. As a consequence, we have been able to enjoy almost five decades of making music together. It soon became clear to me that Tom Eisner had an encyclopedic knowledge of insects: how they lived their lives, defended themselves, courted, found food, etc. Over a single lunch, he might tell me half a dozen stories about insect behavior, most of which involved chemistry in some crucial way. While I had trouble at first keeping these stories straight, I began to understand some of them well enough to see how we could enter into interesting research collaborations. As time went on, the problems Tom described gained in sophistication, and we found that by working together, we were able to gain insights into the roles of organic chemistry in the lives of insects that neither of us would have been able to achieve working alone.

There were several important lessons I learned from this research partnership. One is that molecules do not need to be structurally complex to play a key role in an organism's life. The exploitation of compounds as simple as hydrogen cyanide, or acetic acid and caprylic acid, or *p*-benzoquinone and its alkylated homologues, could take on unexpected interest. In these instances, chemistry might occupy only a small proportion of the final publication. Nevertheless, it was an essential part of the story. On the other hand, we also encountered a wide variety of acetogenins, isoprenoids, and alkaloids whose isolation, characterization, and/or synthesis presented more challenging problems.[6] In these cases, we benefited greatly from the Eisner group's willingness to collect (and dissect if necessary) many individuals of a given species so that we could have enough material to complete a structure proof. In exchange, we would carry out tedious routine analytical tasks such as the quantification of a defensive metabolite in hundreds of individual insect eggs, if Tom felt that the data would reveal something interesting about an insect's chemical defensive strategy.

One of our most far-reaching studies, extending over several decades and continents, has been devoted to elucidating the role of plant alkaloids as defensive chemicals and as the precursors of male courtship pheromones in danaid butterflies and arctiid moths.[7] This work began with Yvonne C. Meinwald's discovery and characterization of danaidone (**5**) from the hairpencils of the Trinidad butterfly, *Lycorea ceres*. It continued with



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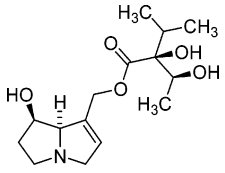
the finding that this heterocyclic ketone is a courtship pheromone in the Florida queen butterfly (*Danaus berenice*). There followed the revelation that **5** is biosynthesized in the African monarch, *Danaus chrysippus,* from the *Heliotropium steudneri* pyrrolizidine alkaloid, lycopsamine **6**. The significance of these findings became



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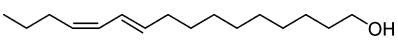
clearer as a result of a deeper study of the chemical relationship between the arctiid moth, *Utetheisa ornatrix,* and its *Crotalaria* food plants. Overall, in the course of this study, we have learned much about the chemistry of plant−insect interactions, about the role of acquired secondary metabolites in insect defense, about the use of sequestered defensive compounds or their metabolites as signaling agents, about the biosynthetic details of the

FIGURE 2. A pair of mating arctiid moths (*Utetheisa ornatrix*). The male transfers to the female a spermatophore containing both sperm and a pyrrolizidine alkaloid. Some of this alkaloid will be incorporated into the female's eggs, providing protection against predators. Some will be retained by the female for her own protection. Photo courtesy of Thomas Eisner.

conversion of a plant alkaloid to an insect pheromone, about maternal and paternal endowment, about the role of chemistry in sexual selection, and about the adaptive value of sexual promiscuity for some female moths (Figure 2).

There are those who view natural products chemistry as the chemical equivalent of "stamp collecting". This is a most unfortunate mischaracterization. Certainly, in its early years, this field did face as a very important objective the task of establishing the structures of the major secondary metabolites found in microbes, plants, and animals. But this was only the beginning. There has always been very good reason, in addition, to place special emphasis on the characterization and synthesis of those naturally occurring compounds with properties that are especially valuable in our own lives, such as artemesinin, the avermectins, β-carotene, civetone, colchicine, indigo, morphine, muscone, progesterone, the pyrethrins, quinine, rapamycin, streptomycin, Taxol, zoapatanol, etc. Stamp collecting indeed!

I would like to emphasize, however, that in addition to these endeavors, there is an entirely new dimension of natural products chemistry that has come to the fore principally in the most recent half century. This has to do with the analysis of the *chemical interactions*, both intraspecific and interspecific, that take place between organisms in nature. While the importance of chemical signaling *within* an organism, via hormones and neurotransmitters, has been well recognized, chemical signaling *between* organisms is a more recent concept. Henri Fabre's surmise early in the 20th century that moths communicate chemically was not reduced to specific molecular understanding until the middle of the 20th century, when Adolph Butenandt characterized bombykol **7** as the female sex attractant produced by *Bombyx mori*.[8]



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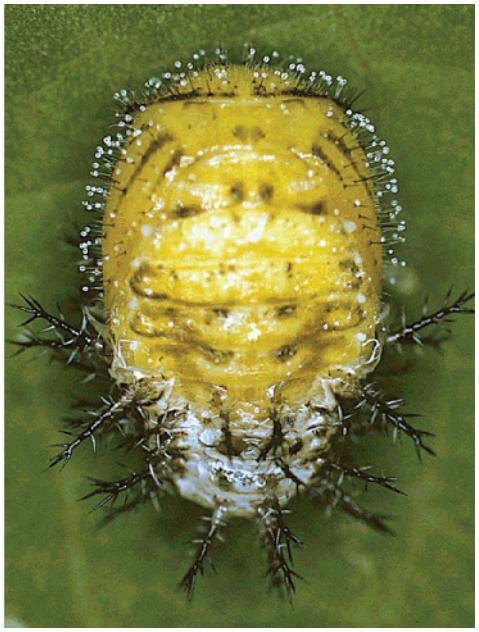


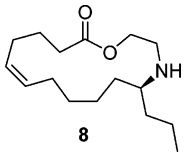
FIGURE 3. Pupa of a coccinellid beetle (*Epilachna varivestis*) showing tiny protective droplets at the end of its glandular hairs. Photo courtesy of Thomas Eisner.

This seminal research can be thought of as the dawn of the modern discipline of chemical ecology. Since all organisms are involved in chemical interactions with other organisms, and since these interactions take place under much less well-controlled conditions than intracellular or intraorganismal signaling, the domain of chemical ecology is almost unimaginably complex and remains largely unexplored. Nevertheless, if one is seeking to understand the interactions between predator and prey, parasite and host, disease vector and target, or to decipher what induces slime molds to aggregate, how animals attract or detect potential mates, how bees find nectar, how plants under attack lure wasps to attack herbivores, and myriads of other chemically mediated natural phenomena, the easiest route is for a chemist to seek out and join forces with a biologist with the appropriate expertise and interests and to initiate chemical ecological research. Looking back on my own career, I can see that this is the path I have followed to a considerable degree. It has led to our learning a wide range of unanticipated, biologically significant chemistry.

There is a good reason why the extension of natural products chemistry into the domain of chemical ecology is taking place now. In part, it is because chemists have only relatively recently begun to appreciate the dynamic aspects of natural products chemistry, to recognize the importance of considering adaptive value, and of thinking along evolutionary lines. It is also because enormous advances in analytical techniques in recent decades have made problems that could not have been studied fruitfully in the past experimentally accessible. Both analytical and preparative chromatography have revolutionized the art of separation. In addition, single crystal X-ray crystallography, mass spectrometry, and NMR spectroscopy have completely changed the way molecular structures are determined. Much of the laboratory work that

my research group does now involves procedures that did not exist at all during my days as a graduate student. In our own laboratory, a novel approach to the analysis of naturally occurring mixtures that Frank Schroeder had initiated as a graduate student in Hamburg and has continued to develop at Cornell has been especially productive. A brief account of three examples of this methodology should serve to demonstrate its potential significance.

A dozen years ago, we described a small family of defensive alkaloids, the azamacrolides, produced by glandular hairs which cover the pupa of a coccinellid (ladybird) beetle, *Epilachna varivestis* (Figure 3). The most prominent member of the group is epilachnene **8**, characterizedby Athula Attygalle and Kevin McCormick.[9]



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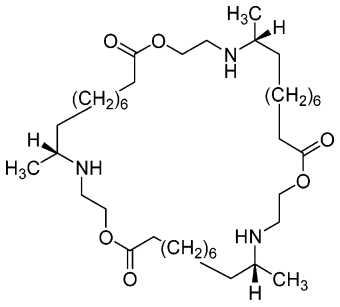
These are macrocylic lactones, derived biosynthetically from a fatty acid and serine.[10] We proceeded to search for related alkaloids from the pupa of the congeneric squash beetle, *Epilachna borealis*, using our standard GC−MS analytical approach. Surprisingly, no alkaloids were detected by this method. It turned out that the secretion is nevertheless laden with higher molecular weight "polyazamacrolides", which were discovered initially *only* by turning to the *direct NMR analysis of the crude secretion*. Subsequent detailed analysis revealed that the *E. borealis* pupa is protected by a combinatorial library of oligomeric lactones (for example, **9**) built entirely from three homologous hydroxyethylamino fatty acids.[11] These compounds (including 42-, 56-, 70-, and 84-



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membered ring examples which we synthesized)[12] proved repellent to ants. We are now exploring the biological activities of the polyazamacrolides, which appear to be the largest ring alkaloids to have been found in nature, in more detail. Preliminary results suggest that they target specific neurotransmitter receptors.

In more recent research, this time on the small molecules of spider venoms, we have again found that the direct NMR analysis of material from a biological source has enabled us to characterize a new family of natural products: sulfate esters of nucleosides and of glycosylated nucleosides, for example, **10** and **11** (Figure 4).[13] It will be exciting to explore the biological activities of these previously undetected venom components.

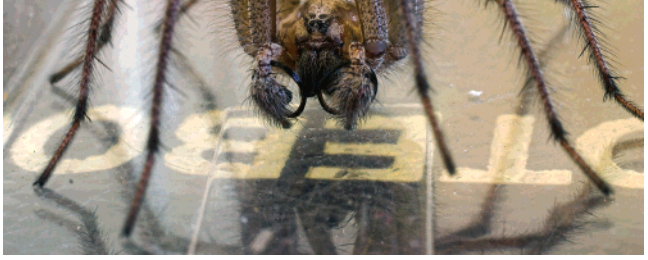
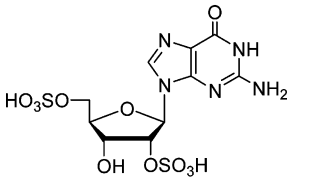


FIGURE 4. Funnel web spiders, such as *Agelenopsis aperta* shown here, typically produce venoms containing sulfated nucleosides. Photo courtesy of Dr. Frank C. Schroeder.



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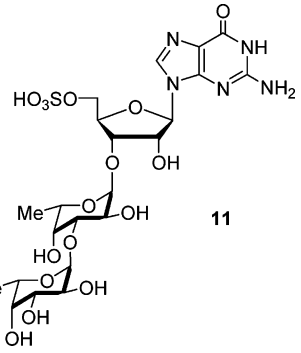

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The great virtue of NMR analysis as the first stage of examining even crude extracts of natural products is its nondiscriminatory character: however volatile or involatile, polar or nonpolar, stable or unstable, easy or difficult the ionization of a compound may be, its presence in a native extract will be noted by virtue of its NMR spectrum, and its loss, or the creation of artifacts during subsequent fractionation procedures, can be observed by spectroscopic examination of purified fractions. If one is searching for compounds about which essentially no structural information is yet known, this nondiscriminatory technique is particularly useful.

The chief shortcoming of depending on NMR spectroscopy as the preferred initial analytical technique in natural products research is its low sensitivity compared to mass spectrometry. However, using newly developed capillary NMR probe technology, the amount of sample required in order to obtain useful structural data from an unknown constituent can be in the 20 μg range, as we have found in our most recent study of the defensive steroids in the hemolymph of a relatively rare, diurnal firefly, *Lucidota atra*. In this case, we have been able to assign structures to thirteen new steroids in the extract obtained from only a few dozen individuals.[14]

What might one anticipate to be the future of natural products chemistry and chemical ecology in this post-genomic, post-9/11 age? Is there anything left to discover?

The answer to this question is certainly a resounding "yes". To begin with a small example, there are roughly 40,000 described species of spider, all capable of paralyzing their prey, but less than 1% of their venoms have been subjected to careful analysis. Surely there are great opportunities here for the discovery of novel neuropharmacological agents. There are about a million described insect species, and a conservative estimate of three million species of insect on earth all together. We can estimate, then, that 99.9% remain as potential targets for chemical study. Among soil bacteria, something like 99% are presently unculturable. Nevertheless, these organisms are known to be genetically extremely diverse, and it appears highly likely that a knowledge of their secondary metabolites would be not only chemically fascinating but also of great value to medicine and agriculture. It is certain that the study of extremophiles will greatly broaden our understanding of what kinds of chemistry can support life. We can conclude that most of nature remains to be explored at the molecular level. It is important to note, in this context, that there is some urgency connected with this endeavor. With the rapid loss of the earth's rain forests, as well as various other factors resulting in the extinction of significant numbers of species, much of the potentially valuable chemical diversity to be found in our earth's biodiversity is in danger of being lost before it can be studied!

It is a remarkable fact that the techniques available for chemical exploration are constantly improving. Considering structure determination alone, we can accomplish today with micrograms of an unknown, natural, small molecule what would have required milligrams in 1950, and grams in 1900. Likely we will need no more than nanograms in 2050, and perhaps picograms by 2100. (Our colleagues in physical chemistry, after all, are already publishing papers dealing with single molecules!) Although harder to quantify, advances in synthetic methodology will certainly continue to make target compounds ever easier to produce. Enzymes will undoubtedly play a much larger role in organic synthesis than they do at present.

On the macromolecular front, progress appears to be equally dramatic. Since small molecules exert their effects largely by their interactions with one or more protein molecules, parallel advances in proteomics and genomics can be depended on to give us long sought-for insights into the mechanisms of bioactivity.

With so many things to do, and ever-improving means by which to do them, we can expect to see renewed interest in the chemistry of natural products in the coming decades. From the viewpoint of pure science, to understand the biotic world, we need to understand the chemical interactions that provide it with its silent, invisible, but nevertheless essential, channels of chemical communication. And in the "better things for better living" category, natural products or compounds based on the structures of natural products will continue to contribute in a major way to medical practice. These opportunities are bound to attract the young and curious to natural products-related research. Certainly, it would be very helpful if organic chemists had a charismatic spokesman in the league of Richard Feynman, Carl Sagan, or Edward O. Wilson who could communicate the excitement and promise of our field to the public. (Perhaps the reason we do not is that chemists have cultivated the art of thinking on a small, molecular scale and do not often paint the bigger picture. Most of us have yet to find the vocabulary with which to inspire and instruct a general audience.)

There are, of course, difficulties to be overcome. We are all aware that research in natural products chemistry, and in organic chemistry generally, has become very much dependent on expensive instrumentation (largely as a consequence of all the wonderful analytical advances discussed earlier). It is likely that future support of the entire field of chemistry will require an improved perception of its utility to society. Right now, according to a recent discussion in *The New York Times*, Army officials are proposing, and Congress is considering, a $145 billion program in support of "Future Combat Systems", not including an additional $25 billion for an accompanying communications network.[15] Clearly our political leaders are able to think on a grand scale. We need to do whatever we can to educate our population to a point where a challenge such as that presented by the widespread bacterial resistance to currently available antibiotics is recognized and accepted with the enthusiasm and determination that our representatives now demonstrate for many less constructive endeavors.

Toward this end, it is important for our society as a whole that our students in liberal arts curricula, and especially nonscience majors throughout our colleges and universities, be exposed to science courses that give them a clear picture of what we know and what we do not know about our universe. They also need exposure to how scientists approach problems, test hypotheses, and assess risks and potential benefits. I have had a chance to incorporate some of these ideas into my own teaching.[16] "*The Language of Chemistry*" is a course I designed and have taught at Cornell for many years, and I believe it takes an interesting step in the right direction. This course is aimed at nonscience majors; it has no prerequisite, and through a consideration of a half-dozen or so carefully selected case studies, it gives students a fair idea of how chemists study and solve intriguing problems at the interface between chemistry and biology. In my judgment, we need to offer more chemistry courses of this type, since typical introductory chemistry courses are hardly geared toward creating enthusiasm for and understanding of what chemists do and why they are doing it.

In closing this rather rambling essay, I must acknowledge that I have enjoyed the enormous privilege of being able to pursue both research and teaching in chemistry far beyond my expectations of sixty-five years ago. These endeavors have also provided unimagined opportunities for travel and for scientific collaboration, not only in the USA, but also in Europe, Africa, Central and South America, China, and Japan. There have even been occasions, such as the celebration of the 70th anniversary of *La Maison de la Chimie* in Paris last summer, at the kind invitation of its President, Pierre Potier, when I could combine a musical offering (in that case with my good friend Eiichi Nakamura and our wives, Yoko and Charlotte) with a scientific undertaking. Occasions of this sort have always been deeply enjoyable. I hope that my

teachers, were they aware of what I have been up to during these many years, would not have considered their efforts on my behalf to have been entirely in vain.

Acknowledgment. I am indebted to Dr. Frank C. Schroeder not only for his contributions to our research program in recent years, but also for his help in preparing this manuscript and the cover graphic. The preparation of this manuscript also depended critically on the skills of Rita Pirsic. I am particularly grateful to all of my postdoctorals, graduate students, and undergraduates for their enthusiastic and productive collaboration. Our research has been generously supported by a number of agencies; the NIH's Institute of General Medical Sciences has played a central role in our work. Other support from NIH's Institute of Allergy and Infectious Diseases, the National Science Foundation, and the Research Corporation is also gratefully acknowledged. Occasional grants from the Schering Plough Research Institute, Merck, and Glaxo have been important to us. Finally, the development of "*The Language of Chemistry*" was made possible by invaluable support from the Mellon Foundation, the Henry and Camille Dreyfus Foundation, and the National Science Foundation.

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