MAKING MOLECULES TO TEST THEORIES

A Half-Century of Research on Chemical Reaction Mechanisms

Jerome A. Berson

Some Personal History

I was born to immigrant parents. My father and his brother, then sixteen and eighteen, respectively, had fled Lithuania in 1905 and made their way by ship to Savannah, Georgia, headed for Pensacola, Florida, where their sister had settled some years earlier. My father's Yeshiva-based education was interrupted at about the equivalent of the ninth grade and never again formally resumed, although he strove for all his life to continue his learning as a self-taught scholar. My mother's formal education was even less extensive. She worked as a milliner and later in her short life devoted herself to raising two children.

How to make a living? My father was a proficient student of Hebrew but had no head for business. Neither did his brother-in-law, with whom he tried vainly to establish various entrepreneurial ventures. In search of a profitable occupation, my father traveled around the South, to Mobile, Alabama, and then to Sanford, Florida, and on to Daytona, settling for a while in each town and setting up and soon closing one or another business. As the depression wore on, it seemed that for our family, fortune was always hiding.

I was born in Sanford and we lived in Daytona until I was about ten years old. For a while there my father served as a lay rabbi for a small congregation. Later, years after we had left Daytona, I read some of his sermons, which had been published in the local newspapers. I was stunned by his eloquence. How could my father have written

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Jerome A. Berson was born in Sanford, Florida, in 1924. He attended the public schools of Florida and New York and obtained the degree of B.S. in chemistry (*cum laude*) from City College of the College of the City of New York in 1944. After brief employment as an assistant chemist at Hoffmann La Roche, he served in the U.S. Army Medical Corps during World War II, advancing from private to sergeant. He returned to the study of chemistry in 1946 at Columbia University (M.A. 1947, Ph.D. 1949), where he did his dissertation research with W. von E. Doering. He was a National Research Council Postdoctoral Fellow at Harvard University with R.B. Woodward during the academic year 1949-50. He served on the faculties of the University of Southern California (1950-63) and the University of Wisconsin (1963-69), and at present is Sterling Professor Emeritus of Chemistry at Yale University, where he has taught since 1969. In addition to teaching and research, his activities at Yale have included service as chairman of the Department of Chemistry (1971-74) and director of the Division of Physical Sciences and Engineering (1983-90). The Berson research group has concentrated on the elucidation of reaction mechanisms and the synthesis and characterization of molecules designed to test theoretical concepts. About ninety Ph.D. recipients and seventy postdoctoral associates have contributed to these studies. In recent years, he has written several articles and two books on the history and philosophy of science.

these poetically forceful and fluent passages in English, which was after all a third language for him? I can't help but regret that his singular talent never had a chance to blossom and found no outlet in the harsh mercantile world where he struggled to put bread on the table.

About that time, my mother required surgery for cancer. Her family insisted that she come to New York for the operation and postoperative care. There was not much to detain us in Daytona. So we settled down in the Bronx, where my father was able to get an appointment to a teaching position at one of the synagogues.

From about the age of eleven or so, under influences that still are not clear to me, I had developed a strong interest in chemistry, the science of the metamorphosis of matter itself. The move to New York was a turning point in my development because it put me into a junior high school where my teachers encouraged me to apply to Stuyvesant, the selective public high school that emphasized science.

Eventually I went to City College, got a bachelor's degree in chemistry, worked briefly at Hoffmann-La Roche, the large pharmaceutical company in New Jersey, and then was drafted into the Army. It was 1944 and the Army needed people with enough schooling to be medics. Specifically, I was assigned to be a combat medic.

Later, when the German advance in the Battle of the Bulge seemed to portend an ominous turn in the Allied fortunes, our unit was assigned to an infantry training course, presumably in preparation for a possible combat role.

Fortunately, I was never called on actually to deploy these new capabilities in combat. The tide turned in the Allies' favor on the Western front, and our unit was returned to approximately its original role as medics. We were shipped to the China-Burma-India theater and spent the rest of the war in Calcutta. Hostilities in Burma had all but ended, so we never had to fire a shot in anger, although the British Royal Navy destroyer escorting our troop ship in the Bay of Bengal did drop a couple of depth charges on a suspected (but unconfirmed) Japanese submarine.

My contribution to the war effort involved no danger remotely comparable to that experienced by the actual combat troops, whose heroism is beyond praise. But Bengal province had its own little hazards—not bullets or bombs but a rich selection of tropical diseases, a few of which I contracted during the time I served as a medical technician in the base hospital.

I was impatient to return to civilian life, especially because a lovely, dark-haired young woman was waiting for me. Bella Zevitovsky and I had met as teenagers, when she was a freshman at New York University and I was a sophomore at City College. By the time I had to leave for the Army, we had become committed to each other and had remained in contact by courtesy of the Army postal service. So time passed very slowly as the war effort gradually wound down after VJ Day in August 1945 and American troops overseas began to return home. Finally, our troop ship landed in New York in early June 1946. By the end of the month, Bella and I were married, and I soon started graduate work in chemistry at Columbia.

Graduate Work

Many of the chemistry graduate students there at the time had backgrounds similar to mine. We had all been branded by the experiences of depression and war, and we were all driven to get on with our lives. That kind of determination became hard to find later in the postwar era.

I think the few post-baccalaureate months I had spent at Hoffmann-La Roche had led me to abandon an early interest in biochemistry and focus on the structure and synthesis of organic compounds, especially naturally occurring substances such as steroids and alkaloids, many of which were known to have profound pharmacological activity. I was fascinated by the intricate connectivity of the bonds holding these structures together and I wanted to learn how to unravel such molecules, and especially how to build them from simpler starting materials.

At the time, Columbia's chemistry faculty included only three people who might have served as a mentor to a student with these interests. One of them was William von Eggers Doering, a thirty-year-old associate professor. Some of you may remember him from his later time at Yale during the years 1952-65. Doering and his postdoctoral mentor at Harvard, Robert Burns Woodward, had made a big splash in 1944 when they announced a total synthesis of the alkaloid quinine. Unfortunately for me, by 1946 Doering's interests had moved off into another avenue of research, the elucidation of the mechanisms of organic reactions. I pestered him to find a natural-product problem for me to work on for my doctoral thesis. After some resistance, he grudgingly suggested a structural problem involving the combination of two molecules of a naturally occurring ethereal oil, isohomogenol. The dimeric compound resulting from that association had been extensively studied in the literature, but there was still some question about its structure and the mechanisms of formation of its derivatives. I was delighted, and by following up on some ideas I had derived from what was known earlier, I found, on paper, the key to the whole problem during the first month I worked on it. From then on, it was simply a matter of nailing down all of my proposals by suitable experiments. The whole job took only eleven months to finish.

Postdoctoral Research

Toward the end of that time, Doering came into my lab and asked, "Have you given any thought to what you are going to do with the rest of your life?" This was a completely unexpected question, and I had to admit that I had no clear idea what I was going to do. I had some vague notions about getting a job in the chemical industry. Doering's response was, "I think you should consider academic work. But first you will need some postdoctoral experience. There is only one person you should go to for that: Bob Woodward at Harvard." Of course, I was aware of Woodward's already towering reputation. Shortly before, he had presented a brilliant lecture at Columbia reporting his critical contribution to solving the structure of the diabolically complex alkaloid strychnine, a problem that had defied the best chemists for decades. Doering

arranged for me to meet Woodward, who turned out to be willing to take me into his group provided I could generate my own funds in the form of a fellowship. I didn't know how to go about this. It was 1949 and very few postdoctoral fellowships were available. One was the National Research Council Fellowship, which was based on a nationwide search. Each department was allowed to support only one candidate. Somehow, undoubtedly with some arm twisting, Doering managed to convince the chemistry faculty at Columbia to support my application. All this took place without my knowledge, so I was stunned to receive notification from the NRC that I had been chosen. I spent a year at Harvard with Woodward working on an alkaloid problem. Woodward's colleagues included several other outstanding researchers in the field, as well as a cadre of bright students, so for a year I was immersed in the discipline I was committed to.

Obviously, Woodward and Doering strongly influenced my scientific values. Beyond that, they generated an atmosphere of intense devotion to scientific work which few of their students could match. Woodward claimed (with a bit of exaggeration) that he usually could be found in his office from eight in the morning until midnight seven days a week, although he did confess that he took Christmas Day off to be with his family. Doering scorned those of his students who allowed family obligations to interfere with the long workdays (and nights) he expected us to devote to science.

Finding an Academic Post and Beginning Independent Research

So you might think it was all clear sailing for me to begin a career teaching and doing research in the field of natural products. But things turned out very differently. First, it was not easy to find an academic job. I had just about given up and applied for a job at the laboratory of Merck and Company, the large pharmaceutical concern in New Jersey. Doering got wind of this and called me up in my lab at Harvard to question my sanity and to give me a stern scolding for even considering such a step. Eventually, after much searching, I received an offer of an assistant professorship at the University of Southern California. I arrived there in 1950 and tried to get a research program going in natural-product structure and synthesis, but it was tough sledding. USC's Chemistry Department had strong competition in the Los Angeles area from both UCLA and Caltech. To use a baseball metaphor, we were a good Triple A team, but prospective students flocked to our neighbors, who were perceived to be major leaguers. Natural-product work, especially synthesis, is a human-power-intensive enterprise. Professors running major synthesis groups routinely supervise fifteen to twenty students and postdocs at a time.

It didn't take long for me to understand all this, and I began to ponder whether there might not be another field of chemistry in which I could make a contribution even with the meager supply of coworkers I could attract. I began to work on reaction mechanisms, probing the detailed pathways by which chemical transformations take place. In making this course correction in my intellectual trajectory, as it were, I needed to find an environment that would expose me to the methods and goals

of the field. Fortunately for me, this subject was being intensely pursued at both of our neighboring institutions. I began to attend the famous Thursday night seminars hosted by Saul Winstein at UCLA, which also included other luminaries such as Don Cram, who was later to win a Nobel Prize, George Hammond, and Jack Roberts. Winstein was a powerful scientific personality, and my interaction with him was pretty close to a decade-long postdoc with one of the most demanding intellects in chemistry. Tragically, he died at the age of fifty-seven.

Studies of Reaction Mechanisms

At first, one or two of my coworkers carried on with our natural-product synthesis program, while a few others worked on mechanistic problems. In the 1950s, the two subfields were not so far apart. Some of the most prominent synthetic chemists also did creative research in mechanisms. For a while I tried to follow this model, but as the fields matured they became more specialized and joint practitioners became rarer. Eventually, I gave up my early ambitions to do synthesis and moved completely into physical organic chemistry.

Students in my group at USC began to study a new phenomenon that we called a "memory effect." Briefly, the work concerned carbonium ions — short-lived, positively charged molecules incorporating a trivalent carbon. We showed that the chemical behavior of these species varied depending on how they were generated. So ostensibly the "same" species behaved differently when made by different methods. This was really unfamiliar territory, because in the history of organic chemistry, one of the standard ways of proving the structure of an organic compound was to synthesize it by some other method and show the *identity* of the materials from the two sources. Our carbonium ions violated this custom by "remembering" their origins. We worked out many examples of this and formulated an overall rationale.

It was during that time, about 1963, that the University of Wisconsin called to ask if I would consider moving to Madison to join their faculty. This was a golden opportunity for me. Wisconsin had been for many years one of the top places in the country for research in organic chemistry. The department could put at my disposal much better facilities than USC could, and there was a steady and plentiful supply of good students. Bella was willing to move, and we left Los Angeles and resettled in Madison in 1963. I felt that I had made it to the big leagues.

During the USC years, as we had moved into physical organic chemistry, our research program had gradually become dedicated to the testing of theory. This was to be a guiding theme of our work throughout the succeeding forty years. Even in the 1950s, when I first began to work in this area, it was clear that the underlying theory of the subject had to be quantum mechanics, because that discipline describes the motion and energy of electrons in the field of nuclei, and because the properties of atoms and molecules, the building blocks of matter, are determined by those energies. Despite that insight, the full application of quantum ideas to mechanistic problems

had to wait until the arrival of powerful computers and programs. Structural and mechanistic questions required the solution of the Schrödinger equation for the case at hand. In 1926 or thereabouts, Paul Dirac had famously remarked that, in principle, with the establishment of wave mechanics, the theoretical basis of most of physics and all of chemistry was now known. He did not neglect to mention, however, that for multielectron systems (a category that includes essentially all of organic chemistry), the exact solutions of the Schrödinger equation are too complex to be stated in closed form. Eighty years later, chemical quantum theorists are still battling over the best approximate computer-aided solutions to use. Nevertheless, the approximate solutions derived from mathematically idealized models do give results for a number of chemical properties that reproduce the experimental values to a high degree of accuracy, at least for simple molecules.

By the 1960s, these computational advances were being diagramed into simple formulas using the standard representations known to all organic chemists. Among the most exciting developments of that period were the Woodward-Hoffmann orbital symmetry rules promulgated by my former mentor Bob Woodward and his colleague Roald Hoffmann, and an essentially equivalent approach formulated by Ken-ichi Fukui called frontier orbital theory. These qualitative theories succeeded in explaining a number of hitherto puzzling experimental observations and, best of all, predicted the outcomes expected of several new experiments that had not yet been tried.

Starting at Wisconsin and continuing at Yale, we began to devise some tests of the new quantum mechanical insights as applied to reactions initiated merely by heating the reactant. In one group of such reactions, the sigmatropic rearrangements, a carbon atom and its attached groups move from one position in the reacting molecule to another. A bond at the origin of migration breaks and reforms at a different site, the terminus of its travel. The conventional prediction was that the *front* face of the carbon atom, the one used to form the original bond, would be the same used to form the new bond. In other words, the migrating carbon should just slide along its pathway and then rebond. However, in 1965, my student George Nelson and I noticed that the Woodward-Hoffmann rules, when properly interpreted, made the startling prediction that the migrating carbon and its attached groups instead should not slide but rather should undergo a somersaulting action that would bring the *back* face of the carbon over to form the new bond with what chemists call "inversion of configuration." During the next couple of years, George completed the experimental test and quite clearly confirmed the orbital symmetry prediction. Not only did the carbon atom turn over, but even the *direction of the somersault* relative to a fixed observation point—clockwise versus counterclockwise—corresponded to prediction.

During the next few years, my laboratory as well as many others continued to test various other predictions of orbital symmetry. The sixties and seventies saw a parade of new phenomena confirming the major features of the new theories, and Hoffmann and Fukui received Nobel Prizes in 1981 for their contributions to this advance. Sadly,

by then Woodward had died. He already had won a Nobel for his work on synthesis, but there is little doubt that had he lived he would have won another and been on the stage in Stockholm again, this time with Hoffmann and Fukui.

In 1967, Yale approached me to join its faculty. I had found working at Wisconsin fruitful and stimulating, and I was then (and still am) grateful to the university for supporting and nurturing my work. Also, our children were strongly opposed to another move. It would be a move that my colleagues at Madison might justifiably have resented as being ungrateful and selfish. We struggled with the moral accounting, but in fact I cannot reduce that process to a strictly logical rationale. Our wish to return to the environs of New York, where Bella and I both had deep roots, contributed a large emotional component. In the end, with some twinges of guilt, we decided to move, and we did so in 1969.

Non-Kekulé Molecules

At Yale, along with our continuing program on thermal reactions, we began a new line of research which continued right through the next three decades. Again this work was stimulated by our interest in the interaction of theoretical prediction and experimental test. We began to study the so-called non-Kekulé molecules. An explanation of what this really was about would get too technical, but suffice it to say that these strange species are fundamentally different from other molecules. Non-Kekulé molecules exist despite their violation of the most basic tenet of organic chemistry, namely Kekulé's rules of valence. So these are molecules in which there are enough atoms but not enough bonds to constitute a full-valence Kekulé structure. One (or more) of the bonds is stretched so far that interaction between one (or more) pairs of atoms can be said to be broken. As you might expect, these substances, existing at the very edge of covalency, have only a fleeting existence under ordinary laboratory conditions. The trick is to design special circumstances that permit them to be observed. Those years were exciting and full of surprises as we learned how to generate them and examine their properties.

Teaching and Learning

When I was searching for an academic job in 1949-50, I tried to get some advice about teaching from my mentor, Woodward. He was a bit impatient about this—understandably so—because he rarely, if ever, taught any formal courses. I remember looking up his teaching assignment in the Harvard catalogue when I got to Cambridge, thinking that perhaps I could sit in on some of his lectures. I noted that classes for other professors were often listed as "Professor X, Tuesdays, Thursdays, and, at the pleasure of the instructor, Saturdays." In Woodward's case, however, there was a subtle inversion of word order. The listing showed "Professor Woodward, at the pleasure of the instructor Tuesdays, Thursdays, and Saturdays." He advised me, in all seriousness, that when (and if) I was called for an interview for an academic job, I should make clear that I intended to satisfy any teaching obligation by supervising the research of graduate students and postdocs.

Fortunately, I did not follow that suggestion to modify the standard academic job description. I taught graduate or undergraduate formal classes every semester. Some of those undergraduate courses had up to three hundred students registered, and even with teaching assistants to lead the small study sections and help grade the exam papers, it was work. But along with that came the opportunity to interact with bright students. They kept me on my toes and would not accept sloppy or off-the-cuff answers to their questions. Occasionally, one of their questions even stimulated a line of thought that led to something fruitful in my research.

My relationship as a mentor to usually twelve to fifteen graduate students and postdocs, as well as an occasional undergraduate, was a central academic and personal experience. By coming into the field much later than I did, those young people had the advantage of being on the forward edge of new ideas and developments. Our group seminars were the mechanism by which that knowledge was passed around to all the group members, especially to me. I still miss that interaction, years after I retired.

I kept my teaching and research going until 1994, when the last of the graduate students left. I continued research for a few years with a small team of postdocs and closed down my lab in 1997-98.

Excursions into History and Philosophy

In later years, the guiding theme of the interaction of theory and experiment led me into the fields of history and philosophy of science. I was fascinated by the origins of theories. What were the questions Kekulé, Emil Fischer, Baeyer, and the other early giants of organic chemistry were trying to answer when the need for a new theory became evident to them? What experiments were crucial in supporting or refuting the new theories? How did these advances gradually work their way into the consciousness of the chemical community?

Professional historians of science probably get a certain amount of amusement out of the attempts of ex-scientists to do research in history. Nevertheless, after my retirement, and with no formal preparation, I started doing it. In a review of my first book, the reviewer, himself a part-time historian of science, told the following story:

> Two men met at an academic cocktail party and introduced themselves to each other. Mr. A asked Mr. B, "And what is your field?"
>
> B replied, "Oh, I'm a cardiovascular surgeon, but when I retire in a few years, I intend to do some research and writing in the history of science. And what is *your* field?"
>
> A said, "Oh, that's very interesting! Actually, I'm a historian of science, but when I retire in a few years, I intend to do some cardiovascular surgery."

During retirement, I have written two books and a number of articles and lectures on the history and philosophy of science. I hope to continue this kind of unlicensed activity.

Although some of our researches ultimately had practical and even commercial applications, we never started out with that objective, so I am grateful to the government granting agencies that nevertheless supported us for many years. That farsighted vision of how basic research can produce useful results was something that carried over from the Vannevar Bush era, immediately after World War II.

Frankly, I must confess that when I started teaching almost sixty years ago, I had stars in my eyes. I expected that the university always would remain a place where trained minds could confront the riddles of nature and strive to solve them. I also expected that that effort would continue to be valued, not only by the university itself but also by the greater society. And for a while, those hopes were more or less fulfilled. The government granting agencies seemed to accept, within rather generous limits, the wisdom of letting the internal dynamic of a scientific field determine what the important problems were.

It is true, of course, that we in chemistry were supported not only by the National Science Foundation and the National Institutes of Health, but also by armed forces agencies, each with a defined programmatic agenda. However, the Office of Naval Research, the Atomic Energy Commission, the Air Force, the Army Ordnance Corps, and others were surprisingly lenient in their interpretation of what research was relevant to their missions. Many chemists engaged in basic chemical investigation under their aegis, and very little explicit justification was expected. The agencies still seemed to accept the argument of Bush's "Science, the Endless Frontier" that the most innovative advances would emerge from a broad sweep of unfettered investigation.

Our little slice of paradise was too good to last. Time does not permit an analysis of why free enquiry came under ever-growing suspicion and hostility in Congress and official Washington, but by the early 1970s, restrictions on the course of research were becoming evident. In response to pressure from Congress, mission agencies imposed more stringent regulations on the relevance of proposed research. The result was to channel research into areas deemed likely to bring tangible benefits.

Now, in my view, citizens have every right to be interested in what scientists are doing with public funds, but what was, and still is, being overlooked was the unpredictable element of research. No one is smart enough to predict accurately the eventual applicability of a discovery.

Universities began to feel the pinch as grants for free scientific inquiry began to be cut. The government funds thus liberated began to flow into more applied areas. A couple of recessions and a lot of political wrangling did not help, and the message became clear that something had to be done to sustain the academic research enterprise.

Academic administrations addressed these problems in several ways. For one, they began to expand their ties to industry. In my field of chemistry and in other allied fields such as biochemistry, biology, and the medical sciences, these pressures generated a new kind of hybrid, an arrangement in which university and industrial

laboratories worked hand in glove to solve problems of interest to the profit sector. Like many other research universities, Yale sensed the opportunity to bolster its research support from this source.

In the areas of research with which I am most familiar, the main industrial support comes from the pharmaceutical industry. Although, unfortunately, the details of such arrangements usually are not made public, the Yale *Principal Investigator's Handbook*, available on-line, outlines certain guidelines for such collaborations. Taken one by one, the terms may not seem onerous. For example, one of the stipulations is that the academic institution has the right to publish any information resulting from the research, but only subject to a three-month grace period, during which the company has the right to delay publication. At Berkeley, I have learned, the period may be up to six months. This is granted, it is said, to permit the company to inspect the proposed paper(s) for so-called proprietary information, which apparently the company has the right to delete.

Three to six months may not seem like such a long time to grant the company to protect its interests. I would guess that most of my colleagues who have such arrangements do not see what all the fuss is about. Is this not, the argument goes, a small price to pay for the generous support the company gives to our research? I don't know the exact numbers, but Yale probably generates some tens of millions of dollars every year from these relationships.

I must say that they make me profoundly uncomfortable. Among a number of other authors, Derek Bok, a recent president of Harvard, has collected in his book *Universities in the Marketplace* several examples in which egregious transgressions of academic freedom have come out of such collaborative deals. A notorious case occurred not long ago at the University of California at San Francisco Medical School.

In an arrangement with a well-known British drug firm, an assistant professor at UCSF carried out a statistical comparison of the efficacy of the company's leading drug and that of a generic version of the drug. The drug firm's version typically sold at a price about four times that of the generic. The agreement, certified by the medical school's administration, contained the stipulation that final permission to publish the results rested with the company. The assistant professor was concerned about this and consulted her dean's office, which assured her that this was just boiler-plate formality and would never be enforced.

After some time, the researcher wrote up her results for publication. Her research showed *no difference* between the efficacy of the full-price drug and the generic. She sent a copy to a prestigious journal, where it was accepted after extensive peer review by no less than five referees. She also sent a copy to the company, which immediately demanded that she retract the paper, not because it contained proprietary information, but because alleged methodological flaws in her research protocol made her findings suspect. Accompanying this was an explicit threat that if she did not retract the paper, both she personally and the University of California would face a lawsuit.

UCSF refused to back her up and essentially cast her on her own devices, that is, to capitulate or deal with the legal consequences. It seems clear that the motivation for the company's action was not *proprietary* concerns but rather a desire to suppress scientific findings unfavorable to its commercial interests.

This is just one of many examples that have come to light. Let me emphasize that I don't think academic-industry conflicts are *always* the result of evil managers manipulating people and scientific research. Nor can I provide an example at Yale of tolerating such an arrangement.

What worries me goes beyond that. The problem is this: The goals of the pharmaceutical industry and of industry generally are very different from those of the academic scientist. Industrial firms are responsible to their stockholders. What I might consider shady practice, such as Merck's concealment of what they knew about the dangers of their blockbuster drug Vioxx, apparently is not illegal. Conversations I have had with individuals associated with the pharmaceutical industry made me aware of the fact that this kind of action is one that any pharmaceutical firm might be likely to take. Until it was exposed, it protected the profits flowing in from the worldwide sale of the drug. I think that if a company has a commitment from a faculty member agreeing to a three- to six-month option to retard publication, the company will have a strong motivation to use all of that delay, especially if the research has turned up something disadvantageous. Six months of income from a billion-dollar-a-year drug is a considerable sum. It is claimed that such an instance is rare. I know of no way to verify that, but in any case, why should we leave ourselves vulnerable to it at all?

To my mind, there is a basic incompatibility between the goal of industry, which has been and still is profit, and academia, which has been, and I *hope* still is, knowledge and science. By the kinds of deals now common and being urged upon us by university administrations, we run the risk of blurring the difference.

There is another subtle corruption that can creep into academia as a result of such relationships. Once these practices become entrenched, there is a strong pressure to reconfigure disciplinary units in the university so that they come into alignment with the goals of the collaborative arrangements. This can have and has had the effect of skewing the intellectual structure of a department by making new appointments that facilitate active participation in joint industry-academic activity. Soon the value systems by which academic excellence and achievement traditionally have been measured are invaded by a new set of considerations. How likely is the research proposed by this faculty candidate to attract collaboration from the pharmaceutical industry? Has this candidate the savvy needed to set up his or her own company? Or better, a suite of companies? Of course, I am quite aware that skeptics will ascribe my concern over this aspect of the problem to the longings of a dinosaurian emeritus for the good old days when *his* kind of science was all the rage.

It is undeniable that problems of interest to industry can offer academic scientists fertile fields worthy of their efforts. But it is my impression that in actual collabora-

tions with industry, the arrangement usually involves some quid pro quo. It is naïve to regard corporate grants to academic collaborators as philanthropic.

My idea of a university was a place where independent and unbiased analyses would be generated on matters of concern not only to the academic community but also to the citizenry. I admit that I am now too old to believe that the new style can be entertained in the long run without sacrifice of some values crucial to the true aims of the university as I imagined them to be sixty years and more ago.

What can be done now? Effecting fundamental change in this area may be a quixotic goal, but if it is ever to come, we need to decide whether the issues raised here are of general concern to the faculty. If they are not, the game is over, and perhaps no further discussion is needed. If they are, then we need to examine how well we and other universities are doing in maintaining or restoring the properly distinct roles of academia and the corporate world.