When the Tilt-a-Whirl ran over my sister’s foot, Goldie decided it was time to sell the elephants, not that it was completely her decision. Goldie’s father, Martin Lee (the name was changed from Lein during his parents’ emigration from Nordfjord, Norway), was the primary owner of the Howard Amusement Co., a traveling carnival with rides, games of chance, sideshows, chimpanzees, and two elephants. Roger Schramm worked as a roustabout at the company, where he met Goldie Lee, leading to their marriage on January 31, 1935, in Howard, SD. This marriage of my parents was not endorsed by their families, who did not attend the wedding. Roger left the farm of his parents during the sixth grade and had no additional education, supporting himself by working as a carnival roustabout in the summer and by running a trap line and working as a mechanic in the winters. In contrast, Goldie Lee was the class valedictorian of Howard High School at her graduation on May 26, 1927, and the daughter of a college graduate electrical engineer. By 1947, the year I turned 6 and Carol’s foot had been broken, I was the youngest of three children in the Schramm family. Living on the road for half the year under dangerous circumstances was too much for Goldie. The carnival was sold, and Martin took one of his sons and Roger as partners into Lee Electric Plumbing & Heating to provide family stability. The back shop of Lee Electric was a haven of electrical and metal-working tools, a rich environment for learning mechanical skills. Wayne, my older brother, and I were free to drill, plane, turn, weld, torch, melt, and bend any material at hand, and we did, developing a good understanding of how things work.

Chemistry

My interest in chemistry came early through the apparently common male interest of blowing things up. Wayne, my senior by 6 years, together with the Lutheran pastor’s son, had perfected the production of high quality gunpowder using sulfur and saltpeter, then commonly available at the pharmacy, and homemade charcoal (red cedar shingles made the best). Small particle size obtained by long mortar and pestle work was the key. This transformation of simple materials into power fascinated me. I machined a variety of simple guns and cast lead bullets to test on the long-suffering sheds behind our house, one of which housed the family chinchillas. “Schramm’s Chinchilla Ranch, South Dakota’s Largest,” said the sign on the outskirts of Howard, the post-carnival evolution of Roger’s interest in converting animal fur into a livelihood. The chinchilla house was anathema to Goldie because the chinchillas had a sink and running water before similar conveniences were installed in her kitchen. A Gilbert chemistry set as a Christmas present in my preteen years was an attempt to turn my chemical interests in a more benign direction. Glycerol was one of the component chemicals, and with a few judicious additions from the pharmacy and the help of Encyclopedia Britannica, I attempted the synthesis of nitroglycerine in our basement. I carefully loaded a half-ounce bottle with the product, stood well back, and shot it against the chinchilla house with a slingshot. Fortunately for me and the chinchillas, the fuming sulfuric acid I obtained from the pharmacy was apparently not sufficiently anhydrous to yield a high quality product, and thus, the story can continue.
Education

My science curiosity was perhaps unfortunately coupled with traits of introversion, independence, and disregard for authority. Through high school, I was a middle of the class student except in science, where I excelled. I read most of the books in our school library during study hall time and much of both the Americana and Britannica Encyclopedias. Goldie wanted her children to attend college, and like other South Dakota natives, I was entitled to enter the South Dakota State College of Agricultural and Mechanical Arts, our land-grant college where I enrolled as a chemistry major. A hidden blessing of my college education was the need to pay my way. I worked all my spare hours in the chemistry stockroom preparing reagents, unknowns, and standards for the chemistry laboratories. I clearly recall the awe of sitting in the library among the stacks of the Journal of the American Chemical Society for a chemistry literature project. I found true joy in quantitative analysis, my favorite laboratory practice. After taking an elective class in bacteriology in my junior year, Edward C. Berry, Chair of the department, offered me a paid undergraduate research post if I switched majors for my final year. Isolating, resolving, and quantitating the organic acids from fermented silage was one of these research projects.

Unknown to me, Dr. Berry negotiated a graduate fellowship with Robert P. Geyer, his friend in the Department of Nutrition at the Harvard School of Public Health. My first indication was a telephone call from Harvard in July of 1963 asking if I would agree to accept a fellowship for the Master of Science Program in the Department of Nutrition. I agreed, as I had neglected to make other plans. As part of the cooperative graduate program, our curriculum choices included Harvard, Harvard Medical School, and the Massachusetts Institute of Technology (MIT). In my first year, I took a biochemistry course with Konrad E. Bloch and later learned that Chris Walsh was in the same class. Bloch’s course showed that I had much to learn in biochemistry. The next year, 1964, he shared the Nobel Prize in Medicine with Feodor Lynen for their work on cholesterol synthesis. I also took a biochemistry course with Gene Brown and Vernon Ingram (the father of molecular medicine for identification of the single amino acid change responsible for sickle cell hemoglobin) at MIT. These courses fixed my career direction.

As the 2-year master’s program neared its end, I noticed an ad in the Harvard Medical School Library for international research scholars to study biochemistry at the Australian National University in Canberra. The Ph.D. scholarship paid round-trip travel and a living stipend, including travel stipends for family members. By then, Deanna, a fellow undergraduate student from South Dakota, and I had married and had a daughter. We sailed on the P&O Orient ship Himalaya for 18 days from Long Beach to Sydney.

John F. Morrison had recently completed a sabbatical with W. Wallace (Mo) Cleland at the University of Wisconsin and wanted to apply steady-state kinetic theory to an allosteric enzyme (Fig. 1). The first words in my lab notebooks from the Australian National University are “Homogenization of rat livers...” My Ph.D. thesis, “Kinetic Studies of Allosteric Phosphotransferases,” and four publications were the result, with the first appearing in 1968 (1). Allosteric nucleoside diphosphatase had no known function, and the purpose of the project was a pure effort to push steady-state kinetic analysis into a more complex domain. The metabolic function of nucleoside diphosphatase is now thought to be removal of UDP from the endoplasmic reticulum to prevent product inhibition of protein glycosyltransferases (2). Morrison was an excellent enzymologist, an experimental perfectionist, and an expert in kinetic derivations. He also developed a substantial body of work on slow-tight binding inhibitors during the time I spent in his laboratory, a topic that has remained of interest in our continuing research on transition state analogues. Members of my Ph.D. thesis defense committee included Mo Cleland and E. C. Webb of enzymology textbook Dixon and Webb fame.

Morrison’s response to any request for vacation time was “you are paddling your own canoe.” In one of our family adventures, we drove the perimeter of Australia, camping with 3-month-old and 3-year-old daughters over a 6-week period. Only 25% of the roads were paved, and in spots, it was over 300 miles between fuel supplies, an interesting trip and a metaphor for my scientific research career.

Armed with a National Science Foundation-National Research Council postdoctoral fellowship to be taken at any United States federal research laboratory, I spent the
next 2 years at the Life Sciences Division of the NASA Ames Research Center (Mountain View, CA) in the laboratory of Lawrence Hochstein. His lab focused on enzymes from halophilic bacteria isolated from salt pans, and I started an independent project on N-ribosyltransferases with AMP nucleosidase (3), a topic that continued to be my research focus for several years. The Ames Research Center was an interesting environment, with a full NASA-United States Navy airbase. The Navy operated a private pilot flying school for base employees a short walk from the laboratory, and in my spare time, I earned a pilot’s license.

Temple University School of Medicine

I was 29 years old in the summer of 1971 when Gerhard W. E. Plaut offered a faculty position as Assistant Professor of Biochemistry at the Temple University School of Medicine in Philadelphia (Fig. 2). I had shipped a crystalline preparation of the allosteric AMP nucleosidase from NASA and went to work on the characterization of its kinetic, binding, and inhibition properties with my generous startup package of one research technician, $3,000, and all the supplies and equipment I could obtain from other faculty. Research grants from the National Science Foundation were my sole means of support for the formative years of my small laboratory, where all of the work was done by me and one and later two technicians. Collaborations with Gerhard W. E. Plaut, Richard W. Hanson, and Gerald Litwack at Temple and George H. Reed at the University of Philadelphia made Philadelphia a lively scientific environment. Michael C. Scrutton was also a member of our faculty. With his British classical education, Michael was an expert in editing the language in many of my early papers prior to his move to King’s College London. Another colleague, Robert J. Suhadolnik, provided access to nucleoside analogues. My laboratory first became interested in transition state analogues through the finding that the natural product formycin, when phosphorylated to the 5'-phosphate, was a transition state analogue of AMP nucleosidase (4). As the role of the N-ribosyltransferases became implicated in the regulation of cellular adenylate pools and precursors for nucleic acid synthesis, the National Institutes of Health (NIH) began to support the work and has provided almost continuous support for our research for over 30 years.

Kinetic Isotope Effects

Our report of the nanomolar inhibition of AMP nucleosidase by formycin 5'-PO₄ merited an invitation by Richard Wolfenden to speak at an American Society for Biochemistry and Molecular Biology meeting in Atlanta. Mo Cleland was in the audience. Afterward, Mo cornered me and, in his inimitable way, insisted that I had a good system for the application of kinetic isotope effects. Isotope effects were new to enzymology but had an established history in physical organic chemistry and in isotope separation theory. Dexter Northrop, Marion O’Leary, and Mo Cleland had organized a Steenbock Symposium at the University of Wisconsin on isotope effects in enzymology on June 4 and 5, 1976, that summarized the state of the art and predicted that chemistry-based isotope effects could be experimentally revealed in enzymes (5). I attended the Symposium, and it became apparent to me that it was possible to achieve a complete description of an enzymatic transition state by the use of a combination of synthetic isotope chemistry, quantitative analysis, and computational chemistry.

It was not easy, however. I was fortunate to have a superb technician, Hazel (Barner) Leung, previously a technician with Seymour S. Cohn at the University of Pennsylvania and the co-discoverer of thymineless death in bacteria (6). Over a period of several years, we assembled the precursors and enzymes to convert glucose with ³H or ¹⁴C labels in specific positions to ATPs containing specific ³H or ¹⁴C labels (7). By the use of ¹⁵N-labeled adenines, all labels became available for the family of N-ribosyltransferases because ATP is readily converted to other nucleotides and nucleosides. David W. Parkin, a postdoctoral fellow, measured our first complete set of isotope effects, published in the Journal of Biological Chemistry in 1984, a major technical accomplishment (8). Later, we accomplished a similar synthetic strategy for NAD⁺ analogues, making isotope studies feasible for ADP-ribosyltransferases (9).

Chemically correct (intrinsic) kinetic isotope effects report on the bond vibrational structure at the transition state, a complex problem that had not been approached for a reaction as complex as an N-ribosyltransferase. Frank
Mentch, a quantum chemist teaching at the Ogontz Campus of the Pennsylvania State University, was looking for summer work and research during the academic year. Frank had studied quantum chemical models of $\text{H}_3^+$ with James B. Anderson at Penn State for his Ph.D. thesis (e.g. Ref. 10) and was highly qualified to tackle quantum chemical analysis of the kinetic isotope effects for AMP nucleosidase. We were nervous about publishing our first paper showing agreement between extensive experimental kinetic isotope effects and a quantum chemical model of an enzymatic transition state. Richard L. Schowen at the University of Kansas had literally written the book on related theory (11). One Friday in May 1985, I flew our flying club Mooney 201 from Philadelphia to Lawrence, KS, with Frank. We spent the weekend with Dick Schowen and another computational expert, Ian H. Williams from Bath University in the United Kingdom. Both agreed that they could find no obvious faults. After the manuscript was written, William P. (Bill) Jencks at Brandeis University also read it and thought it to be sound. We published this paper in *Biochemistry* in February 1987, the start of our development of enzymatic transition state analysis, a focus that continues today (12).

**Albert Einstein College of Medicine**

Charles Rubin, a friend from the NIH Biochemistry Study Section and a faculty member at the Albert Einstein College of Medicine, asked me to visit Einstein to see if I might be interested in leading the Department of Biochemistry. I visited in the fall of 1986 and was invited back for a second visit in early January 1987. Over the Christmas holiday, I broke my left leg in a skiing accident and was in a cast from my toes to upper thigh. I called Einstein to cancel the visit, but Dominick P. Purpura, the Dean, insisted that I visit despite my fracture. He sent a car from New York with two drivers to carry me if necessary and to make sure I arrived for the scheduled visit. By August of 1987, I had moved to Einstein and agreed to build the department while continuing a research program.

**Transition State Analysis**

With the proof of concept for the application of isotope effects to transition states under our belts, I made the decision to focus on enzymatic transition state analysis even though our first reports received little attention. Several excellent postdoctoral fellows and students were recruited and have been engaged in our specialty of transition state analysis for AMP nucleosidase (13), nucleoside hydrolase (14), AMP deaminase (15), purine nucleoside phosphorylase (PNP) (16), ricin A-chain (17), ADP-ribosylating toxins (18–20), methylthioadenosine $N$-ribosyltransferases (21, 22), and phosphoribosyltransferases (23). One of the original concepts in enzymatic transition state analysis had been to use the transition state information as a blueprint to design transition state analogue inhibitors, an early proposition of Linus Pauling (24) and formalized by Richard Wolfenden (25). In theory, such inhibitors should bind tighter to the enzyme than substrate by the factor of the enzymatic rate enhancement. Rate enhancements of $10^{15}$ are common in enzymology, and such inhibitors could provide unprecedented utility in drug design.

**Transition State Analogue Design**

Benjamin A. Horenstein received his Ph.D. degree with Koji Nakashima at Columbia University and had planned for a postdoctoral position with Peter G. Schultz in California. At the last minute, Ben needed to stay in New York for personal reasons and came to my lab, bringing his own support in an American Cancer Society fellowship. Ben was an expert in experimental, computational, and molecular model chemistry. From his transition state structure for nucleoside hydrolase, he modeled molecular electrostatic potential maps to serve as inhibitor design blueprints (26). Several of these were synthesized and proved to be powerful inhibitors (27). These findings took us in the new direction of inhibitor synthesis. However, synthetic organic chemistry was not a primary strength in the Schramm laboratory, and almost by accident, we formed one of sciences’ most productive collaborations with a synthetic chemistry group in New Zealand.

**Carbohydrate Chemistry and Industrial Research Ltd.**

Paul Atkinson, a New Zealander, was a fellow faculty member at Einstein and a supporter of our plans to strengthen spectroscopy. I needed his help to argue with Harry Eagle, the father of Eagle’s medium and the Facilities Dean, for instrument purchases. Paul soon decided to return to New Zealand to school his growing children and to head one of the research sections at Industrial Research Ltd. (Lower Hutt, New Zealand), a federal-private partnership to drive science technology. In his discussions with other research groups at Industrial, Paul met Richard H. Furneaux and Peter C. Tyler, leaders in the Carbohydrate Chemistry Group. Paul suggested that Richard and Peter might want to visit me on their upcoming trip to New York. After discussing transition states in my office, we had drinks and dinner in Manhattan. Over drinks, I drew the structure of a molecule I thought would be a good transition state analogue for the $N$-ribosyltransferases on a bar napkin. This was 1994, and by 1997, this molecule and several close relatives had been synthesized.
From Theory to Therapy

The first of the “bar napkin” inhibitors was designed to match an early, dissociative $N$-ribosidic bond loss transition state structure, typified by bovine PNP. Peter synthesized this difficult (four stereochemical centers) molecule, which we named Immucillin-H. It is a 23 pm inhibitor of bovine PNP, binding almost 1 million times tighter than the normal substrates (Fig. 3) (28). It is also a 56 pm inhibitor of human PNP.

As the human genetic deficiency of PNP causes the onset of T-cell immune deficiency, it was proposed that inhibitors of the enzyme might be beneficial in cases of T-cell cancers and T-cell autoimmune disorders. This molecule is currently in advanced clinical trials for cutaneous T-cell leukemia, one of the more common forms of T-cell cancer (29).
In the meantime, we found that the transition state structure of human PNP differed from that of bovine PNP, and a second generation inhibitor, 4’-deaza-1’-aza-2’-deoxy-1’,9-methylene (DADMe)-Immucillin-H, was synthesized specifically for human PNP by Gary B. Evans at Industrial Research Ltd. (Fig. 4). This molecule has only two stereochemical centers and is a 9 pM inhibitor of human PNP, binding over 4 million times tighter than substrates (30). It has cleared a Phase IIa clinical trial for autoimmune disorders. Yet another member of this family is undergoing antimalarial trials in primates.

Similar approaches have produced picomolar and femtomolar inhibitors for enzymes involved in mammalian cancers (31) and in bacterial quorum sensing (32). The best of these bind to bacterial enzymes nearly 100 million times tighter than normal substrates. It is rare that the molecules resulting from academic research have properties suitable for clinical development. The success rate of this program demonstrates the power of transition state theory when coupled to robust synthetic chemistry skills.

New Directions

Transition state theory linked to the isotope effect approach gives a useful but static picture of reactants at the instant of barrier crossing. Protein dynamic motion is likely responsible at the detailed atomic level. With colleagues Robert Callender and Steven D. Schwartz at Einstein and R. Brian Dyer at Emory University, we are probing protein motions over broad time scales linked to catalysis (Fig. 5). By a combination of computational (33) and experimental (34) approaches, evidence is accumulating that transition state barrier crossing is linked to very fast femtosecond motions of protein atomic vibrations. Of course, the well known slower conformational changes that close the catalytic site after substrate binding and the slow opening of the catalytic site to release products are also essential. However, the timing of transition state formation appears closely linked to the very fastest motions of proteins, those on the time scale of single bond vibrations. These insights have provided a wonderful framework for the integration of transition state structures and x-ray crystal structures of complexes with tightly bound transition state analogues into a complete picture of protein action from binding substrates, transition state formation, and product release. After a few billion years of evolution, Mother Nature has created truly remarkable catalytic machines. We have learned many but certainly not all of the enzymatic secrets in less than a century.

Colleagues

Exceptional people in my lab, including technicians, Ph.D. students, postdoctoral fellows, and excellent collaborators, have taught me more than I have taught them. In addition to the names I have mentioned, others are cited in the references and deserve credit for making enzymatic transition state applications a reality. Many graduates of the lab now have successful careers in science. I know that they have shared the inspiration of a novel discovery, the first look at a transition state, the almost unbelievable dilutions needed with picomolar inhibitors, a steady-state rate slowing rapidly as the slow-onset period of a transition state inhibitor kicks in, the first crystal in a drop, being able to repeat small kinetic isotope effect measurements accurately time and time again, the right mass after a complex synthesis, or even a fat band of a novel protein on an SDS gel. Science is never easy and is always demanding: one more, another, and another control and then repeat, repeat to make sure it is right. But after the results provide you alone the first peek into the future, you know it is worth the effort.

Building a Department

Although transition state analysis and related catalytic mechanisms of enzyme action have been my consuming research passion, my primary responsibility to the Albert Einstein College of Medicine was to build a strong Department of Biochemistry. The history of this department
began with Abraham White, the first Chair of the department, coauthor of an early biochemistry textbook milestone (*Principles of Biochemistry*, by A. White, P. Handler, and E. L. Smith), and one of the original academic founders of the Albert Einstein College of Medicine in 1955 (35). My goal was to develop the department to be the home of strengths and expertise in biochemical mechanisms and structure. In addition to these strengths, the department could then serve as a link between molecular science and the very strong programs in biology, genetics, and neuroscience already at Einstein. The Dean agreed to support development of new programs in crystallography, NMR, and mass spectrometry facilities, cores essential for molecular based research. This approach, together with related faculty members who use these facilities, has been a success and has provided an active collaborative spirit in the College of Medicine. Our own research has benefited, with excellent collaborators in crystallography, NMR, and mass spectrometry. The department is now a healthy mix of junior and senior faculty members, with a focus on understanding fundamental mechanisms of biochemical function with some link to human health and disease (Fig. 6).

**Science History**

Students of history realize that in the time line of human development, there has been no time as kind to intellectual pursuits as in recent civilization. The affluence of our culture has freed most of our time for intellectual pursuits if we choose. The meritocracy system of supporting research requires persistence together with inspired work both at the lab bench and on paper. By rewarding novelty, there have been remarkable successes in the development of knowledge. Our generation of researchers has been the fortunate recipient of sufficient resources to permit the discovery of new methods, almost faster than we can use them, surprising new fundamentals of biology, and promising agents to improve human health.

**Global Future**

But our affluence is not benign. Our reckless exploitation and consumption of fossil fuels in just 100 years have provided an unprecedented quantity of cheap energy at the risk of making the future earth unsuitable for habitation. My concerns extend beyond greenhouse gas problems. Access to cheap energy permits most of the world to surf a wave of excess. We live as though these resources are limitless, but they are not. Excess energy consumption and crop genetic advances drive huge world food production, permitting unsustainable population growth that demands more energy, an autocatalytic cycle. After the oil is gone in the next few decades, we have coal for hundreds of years, so why worry? We need to break from short term thinking and do our best to provide humanity with a supply of the finite, valuable fossil fuel resources for thousands of years into the future. To give generations thousands of years from now a chance to live in an industrial society, it would be prudent to leave fossil fuels in the earth as feedstocks for essential uses we may be unable to imagine today. Replacement of energy needs by nuclear and other CO$_2$-free technologies is feasible now and is essential before we deplete fossil fuels, not after. Equally essential is controlled population growth to limit the earth’s agricultural burden and the autocatalytic energy consumption cycle.

*Address correspondence to: vern@aecom.yu.edu.*

**REFERENCES**

1. Schramm, V. L., and Morrison, J. F. (1968) *Biochemistry* 7, 3642–3652
2. Fleischer, B. (1983) *J. Histochem. Cytochem.* 31, 1033–1040
3. Schramm, V. L., and Hochstein, L. I. (1972) *Biochemistry* 11, 2777–2783
4. DeWolf, W. E., Jr., Fullin, F. A., and Schramm, V. L. (1979) *J. Biol. Chem.* 254,
