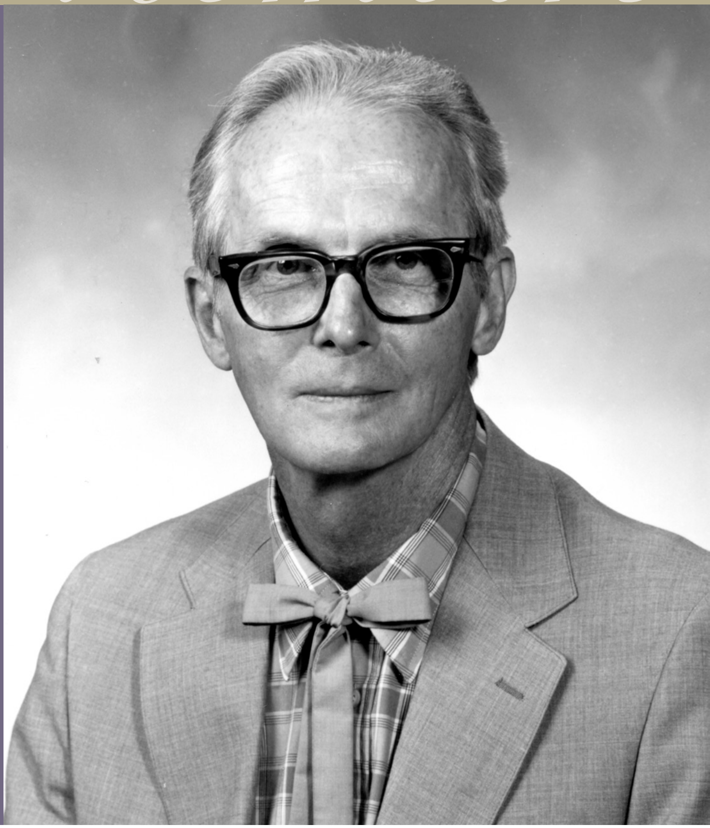
William N. Lipscomb

1919–2011

BIOGRAPHICAL *Memoirs*



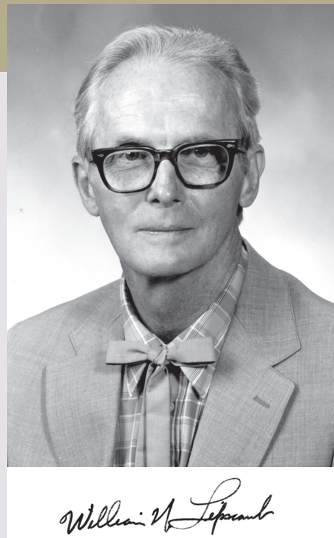
A Biographical Memoir by Douglas C. Rees

NATIONAL ACADEMY OF SCIENCES

WILLIAM NUNN **LIPSCOMB** JR.

December 9, 1919–April 14, 2011

Elected to the NAS, 1961



By Douglas C. Rees

In this era of increasing specialization, William Nunn Lipscomb, Jr. stood out for his remarkable breadth of achievements in science and music, along with a keen sense of humor. A giant of 20th century chemistry, Lipscomb, like his graduate advisor Linus Pauling, developed a deep understanding of chemical bonding and X-ray crystallography to make fundamental contributions in disparate fields ranging from boranes (for which Lipscomb received the 1976 Nobel Prize in Chemistry) to protein structure. His accomplishments in both theoretical and experimental science were extraordinary. Lipscomb was effectively a one person chemistry department as his impact is evident in physical chemistry (structure and bonding), inorganic chemistry (boranes), biochemistry (protein structure), and even organic chemistry, through his work with then graduate student Roald Hoffmann that provided the theoretical underpinnings for the Woodward-Hoffmann rules. In addition to Hoffmann, Lipscomb's academic progeny includes a second former graduate student to win a Nobel Prize, Thomas Steitz, for the X-ray crystal structure determination of the ribosome. Lipscomb was a committed teacher and embodied the principle that research and teaching are inseparable. For over half a century, he inspired his group members and took great pride in their accomplishments as they populated the ranks of chemistry and biochemistry departments throughout the country.

Early Years: Kentucky, Education, Music and Self-Reliance

Lipscomb was born in Cleveland, OH to Edna and William Lipscomb, but within a year, the family moved to Lexington KY where he grew up with sisters Virginia and Helen. Throughout his life, he was proud of his Kentucky roots, typically sporting a plantation string tie (and undoubtedly the only Nobel laureate with a how-to-tie-a-string-tie YouTube video [ImprobableResearch 2009]). Lipscomb described his childhood as encouraging independence, as his mother taught music with a passion and his father's medical practice took most of his time. Indeed, the qualities of personal responsibility and self-reliance that Lipscomb developed during this period stayed with him throughout his life. (Lipscomb, W. N. 2002) From an early age, he was recognized as scientifically precocious, exceeding the abilities of his teachers; for example, his chemistry teacher gave him free reign to work through textbooks and conduct laboratory research, taking only the course examinations. His mother had given him a chemistry set for Christmas when he was 12 years old, and she later recounted that "he'd make stuff that smells so bad—rotten-egg gas—to chase the girls out. You couldn't go into the house for hours." (Ward 1976) Lipscomb was so experimentally proficient that by the time he was in high school, he had set up an entire lab in his home, large enough that when he graduated and donated his home chemistry lab to his high school, its equipment inventory more than doubled. (Lipscomb, J., 2018)

Music was an important part of family life and Lipscomb took up the clarinet at an early age, while his sister Helen became an accomplished pianist and composer. Helen contracted polio in 1937 at age 17 that had a profound impact on the entire family. Among the other consequences, patients did not want to be in contact with a physician with polio in the family, so Lipscomb's father closed his medical practice and switched to psychiatry with a home office. Lipscomb helped tutor Helen in calculus and other subjects as she was not able to leave home. She eventually taught piano from home, and in one of those coincidences of life, my wife-to-be Becky took piano lessons from her and my mother-in-law-to-be Betty was good friends with Edna Lipscomb. Indeed, I first met Lipscomb when he played clarinet at the memorial service for Helen in Lexington after her passing in 1974.

Although Lipscomb seriously considered a career in music, his college coursework at the University of Kentucky convinced him to pursue science instead. In addition to chemistry and physics, his coursework reflected his strong interest in mathematics. Marjorie Senechal, a Smith College mathematician from Lexington (and a former piano student of Helen Lipscomb's) recounted a conversation in which she asked Lipscomb why he decided to become a chemist instead of a musician. His response (Senechal 2013): "A math class. A math class taught by a German named Fritz John." Fritz John was a German emigre mathematician at the University of Kentucky who was a neighbor of the Lipscomb family and later became a member of the US National Academy of Sciences. Lipscomb was the only student in a summer course taught by John in vector analysis, which introduced him to tensors and matrices and undoubtedly contributed to his subsequent interest in symmetry and group theory. Emblematic of his diverse interests, Lipscomb's first publication was based on a research project inspired by his qualitative organic analysis course (Lipscomb, W. N. and Baker 1942).

Caltech: Structure and bonding

After Lipscomb graduated from the University of Kentucky with a bachelor's degree in chemistry in 1941, he had graduate-school offers from the chemistry program at MIT and from the physics programs at Northwestern and Caltech. Motivated by the higher stipend at Caltech and by what he deduced was a stimulating environment that addressed more current research problems, (Lipscomb, W. N. 2002) in the fall of 1941 Lipscomb entered graduate school at Caltech. He had hitchhiked across the country from Lexington to Pasadena, and his mother later recalled that during this journey he sent his family a postcard tersely stating "Thumb Fun." Lipscomb started out in graduate school studying physics, but he soon came under the spell of Linus Pauling and switched to chemistry after the first semester.

He solved important problems, but instead of falling back on some assembly-line process, he would use whatever method he needed to best solve the problem, including new approaches that he and colleagues devised.

Lipscomb's thesis research focused on molecular structure, using both electron diffraction (Lipscomb, W. N., and Whittaker 1945; Lipscomb, W. N., and Schomaker 1946) and X-ray diffraction. (Hughes and Lipscomb, W. N. 1946) The latter effort, with Edward (Eddie) Hughes was especially significant, as it provided Pauling with a reliable C-N single-bond distance for his analysis of the resonance stabilization of peptide bonds. The Hughes and Lipscomb work was also the first X-ray crystal structure refined by a least-squares method with a statistical treatment of errors, and the second structure solved with any type of least-squares method (the first being Hughes's structure of melamine [Hughes 1941]). This early work exemplified several defining characteristics of Lipscomb's lifetime achievements (Ma 2013)—he solved important problems, but instead of falling back on an assembly-line process, he would use whatever method he needed to best solve the problem, including new approaches that he and colleagues devised.

When later asked how he carried beakers of nitro-glycerin, I heard him reply, “Carefully!”

Lipscomb’s graduate period coincided with World War II, and while he did not serve in the military, he did conduct war-related research as part of a National Defense Research Council program at Caltech, as did other chemistry graduate students at the time. An account of this period may be found in the book *A Bridge Not Attacked: Chemical Warfare Civilian Research During World War II* by Harold Johnston, (Johnston 2003), who was a fellow chemistry graduate student at Caltech. Lipscomb worked on several projects, including how to optimally obscure Los Angeles with smoke so as to prevent aerial attacks, and analysis of nitroglycerin-nitrocellulose propellants; when later asked how he carried beakers of nitroglycerin, I heard him reply, “Carefully!” One consequence of these activities was that two chapters of Lipscomb’s thesis (Lipscomb, W. N. 1946) were classified. An analysis of smoke-particle size based on this work subsequently appeared. (Lipscomb, W. N., Rubin, and Sturdivant 1947)

Although Pauling had a profound influence on Lipscomb’s graduate research, they did not coauthor any papers. Nevertheless, Lipscomb learned from Pauling many important lessons concerning the craft of doing science, particularly how to choose interesting and significant research problems. For example:

> *When I was growing up and learning science and all through my undergraduate days, I thought the worst thing you could possibly do is publish something that is wrong. It turns out that’s not right. Linus taught me that. It is much worse to work on something that is dull. (Lipscomb, W. N. 1991)*

> *It is much better to risk an occasional error in interesting and original research than to be always right in less original or more prosaic studies. (Lipscomb, W. N. 1995)*

> *I also learned how to choose important research areas, how to bring different areas together, how to use the stochastic method, and the importance of extensive background knowledge (‘It’s what you know that counts’) and imagination (‘Have lots of ideas and throw away the bad ones’). (Lipscomb, W. N. 1995)*

It should be noted while Lipscomb would emphasize the priority of interesting and original over risking an occasional error, he did find it distressing to be proved wrong (Lipscomb, W. N. 2002) on the rare occasion that this happened.

After receiving his Ph.D. in 1946, Lipscomb considered a postdoctoral position with Bertram Warren at MIT. Toward that end he prepared a National Research Council (NRC) fellowship proposal on two possible studies: crystal structures of hydrogen-bonded systems displaying residual entropy, and crystal structures of boron hydrides. These proposed efforts were undoubtedly inspired by Pauling's analyses of the residual entropy of water (Pauling 1935) and of bonding in boranes (Pauling 1948); the latter analysis, Lipscomb later noted, he felt was incorrect. Although he was sure that Pauling supported his NRC application, Lipscomb subsequently revealed that Pauling privately told him that he did not think that Lipscomb's proposed research was very interesting. Given the value that Pauling placed on interesting and original research, this reaction could be reasonably interpreted as a criticism. Thus I believe Pauling's response still bothered Lipscomb years later, when he mentioned this critique to me (despite having won the Nobel Prize for this work).

One story from Caltech that was clearly memorable to Lipscomb involved his unassisted triple play on the Caltech Chemistry Department baseball team; his recounting of this event after many years (including that he could have even made a fourth out), exemplified his competitive nature.

There was another story from this period that I never heard from Lipscomb; I only became aware of it shortly before his death, when I unfortunately was unable to discuss it with him. While reading Eddie Hughes's oral history in the Caltech archives (Hughes 1984), I was struck by the concluding paragraph, which involved a discussion of safety issues in the Division of Chemistry and Chemical Engineering. On September 23, 1943, Elizabeth Swingle, the stockroom keeper at the Crellin Laboratory, died after being sprayed with ethylchloroformate when the cap blew off a bottle of that liquid she was carrying. (Pauling 1943a, 1943b; Lipscomb, J. 2011) Hughes reported (Hughes 1984):

> *The first man who got to her was Bill Lipscomb, who was a graduate student then—now a Nobel laureate at Harvard. Why he didn't get it, too, I don't know, because he hauled her off and put her under a shower. He was my first graduate student and I was very proud of him.*

In retrospect, this tragedy may have motivated what seemed an odd quest of Lipscomb's, one day in the late 1970s, when he inexplicably, at least to those who witnessed this event, was obsessed with inspecting the safety equipment in Gibbs Laboratory. This included flooding the lab by testing the safety shower and shortly thereafter emerging triumphantly from the sub-basement having located the respirator. (Honzatko 2018)

Minnesota: Low-temperature crystallography and boranes

In 1946, Lipscomb was appointed assistant professor of physical chemistry at the University of Minnesota. He flourished there, building on the superb foundation in structure and bonding he had acquired as a graduate student, and was soon promoted to associate professor (1950) and professor (1954). For his research program, he targeted crystal structures of boranes and other compounds that in his view posed interesting chemical problems. These projects also required overcoming significant technological challenges, as the crystallography had to be conducted at very low temperatures. Thus the Lipscomb group developed the cutting-edge technology to collect single-crystal X-ray diffraction data at low temperatures, which they did in parallel with independent efforts by Fankuchen (Lipscomb, W. N. 1977). The lab at Minnesota was especially well suited for this type of work: in the winter they would open the windows, letting in the cold dry air to minimize condensation, the bane of low-temperature studies.

Having established the requisite low-temperature techniques, Lipscomb's group determined the structures of a series of boranes. (Lipscomb, W. N. 1954, 1963) Numerous challenges had to be surmounted to solve these structures. The compounds are unstable, and they could explode if a vacuum line cracked. The crystals were grown in the X-ray setup, so by necessity the data were collected from a randomly oriented crystal, often of uncertain stoichiometry. Because the structures were unknown and the constituent atoms (B and H) among the weakest at scattering X-rays, the structure determination was nontrivial. But within eight years after arriving at Minnesota, these efforts culminated in the 1954 paper "The Valence Structures of the Boron Hydrides" which Lipscomb coauthored with W. H. Eberhardt and B. Crawford, Jr., to describe the generality of three center bonds in the boranes (Eberhardt, Crawford, and Lipscomb, W. N. 1954).

This paper opened a new era in the understanding of the chemical bond, and it was at the heart of Lipscomb's Nobel Prize citation. While significantly advancing the field, it was clear to the authors that not everything they proposed was definitively established, however. They wrote:

> *We have even ventured a few predictions, knowing that if we must join the ranks of boron hydride predictors later proved wrong, we shall be in the best of company.*

As well as any of Lipscomb's publications, this paper exemplifies the philosophy he learned from Pauling "it is much better to risk an occasional error in interesting and original research, than to be always right in less original and more prosaic studies."

While at Minnesota, Lipscomb's group made a number of innovative crystallographic advances. These contributions included modeling the effect of disorder on the diffraction pattern (King and Lipscomb 1950), the possibility of using multiple reflections to acquire phase information (Lipscomb, W. N. 1949), and early applications of computers in crystallography for the refinement of anisotropic temperature factors and the preparation of electron-density maps with different colors (Rossmann, et al. 1959). Lipscomb appreciated the power of computers in crystallography and chemistry, but because the computer programs he used were generally written in his group to solve the problems at hand and not for general distribution to the broader community, these computational advances were not perhaps as well appreciated as his scientific advances.

It was in Minnesota that the sobriquet "the Colonel" was conferred upon Lipscomb by his first graduate student, Murray King, as a reflection of Lipscomb's Kentucky origins. When addressing him in person, however, the group still called him Professor Lipscomb; they used "the Colonel" only in conversation amongst themselves (Dickerson 2018). Nevertheless, the appellation ultimately stuck, and many of us undoubtedly had the experience of first addressing Professor Lipscomb only to get the unexpected response, "Call me the Colonel." In 1973, Lipscomb officially received the honorific title of Kentucky Colonel from Wendell Ford, then governor of Kentucky.

Harvard: Computation, protein structure, and the Nobel Prize

In 1959, Harvard University lured the Colonel with an appointment as professor of chemistry, to the great disappointment of his Minnesota colleagues. He was subsequently (in 1971) named the Abbott and James Lawrence Professor of Chemistry, an appointment he held until he retired in 1990.

Lipscomb's move to Harvard was accompanied by the pursuit of significantly more complex problems in the areas of bonding and structure, aided by the greater computing power that was becoming available. Within a few years after arriving at Harvard, he had major efforts underway in two areas: the development of the extended Hückel method for molecular orbital calculations; and the crystal structure determination of the digestive enzyme carboxypeptidase A. Meanwhile, Lipscomb continued his studies of borane structures and low-temperature crystallography, including the extension of the latter to temperatures between that of liquid helium and liquid nitrogen. (Streib and Lipscomb, W. N. 1962) These efforts resulted in the structure determinations of diborane, (Smith and Lipscomb, W. N. 1965) as well as of N_2, O_2, and F_2. Roald Hoffmann, the Colonel's first Harvard graduate student, (Hoffmann 2013) recalled the unforgettable environment provided by the closely packed desks on the top floor of the Gibbs Laboratory that promoted extensive interactions between experimentalists and theorists. This was certainly my experience some 15 years later, when my interactions in that same room with Dennis Marynick, a computational postdoctoral fellow, were a highlight of my time as a graduate student.

The Harvard graduate students Hoffmann, Lawrence Lohr, and Richard Stevens had participated in the development of the extended Hückel method, which paved the way for bonding calculations of increasingly large molecular systems. Hoffmann recalled (Hoffmann 2018) that Lipscomb's theoretical excursions into extended Hückel and early *ab initio* calculations (such as his work with Russell Pitzer calculating the barrier to internal rotation of ethane [Pitzer and Lipscomb 1963]) did not meet with an enthusiastic response from some members of Harvard's chemistry department, who thought they hired a crystallographer. In any case, Lipscomb utilized these methods with great success both for small and large molecules, including in the analysis of reaction pathways (Halgren and Lipscomb, W. N. 1977) and enzyme mechanisms, (Scheiner and Lipscomb, W. N. 1977) and in Lipscomb's pioneering work on the nonempirical quantum-mechanical calculation of chemical shifts. (Lipscomb, W. N. 1966)

Over time, the protein crystallography effort became the dominant (although by no means the exclusive) effort of the group. Lipscomb had been contemplating working on larger structures while at Minnesota, and apparently at the suggestion of Bert Vallee (Hartsuck, et al. 1965) his group started working on the structure of the zinc-containing protease carboxypeptidase A (CPA), using material initially provided by Hans Neurath. At the time the CPA project was initiated, only the structure of myoglobin had been solved to high resolution. With a superb group of postdoctoral fellows and graduate students, including Martha Ludwig, Hilary Muirhead, Flo Quiocho, Jean Hartsuck, Tom Steitz, George Reeke, J. C. Coppola, and Paul Bethge, the CPA structure was solved in 1967. (Lipscomb, W. N., et al. 1967) This was the first metalloenzyme of known structure, and it was tied with three other proteins for being the third protein structure determined (after myoglobin and lysozyme). The Lipscomb group studied complexes of CPA with various ligands and inhibitors over the next several decades, with the result that this work elucidated the binding sites for substrates and supported detailed mechanistic proposals for hydrolysis of the peptide bond.

Before Steitz left the group, he started working on a second enzyme, the allosteric enzyme aspartate carbamoyltransferase, then known as aspartate transcarbamylase, or ATCase (Steitz, Wiley, and Lipscomb, W. N. 1967) (for consistency with the usage in the group, ATCase will be used in this memoir). This enzyme served as the focus for much of the crystallographic activity in the Colonel's group for the next 20+ years. Don Wiley, Brian Edwards, David Evans, and Stephen Warren subsequently spearheaded the ATCase project, producing a low-resolution structure by the early 1970s that cracked the door on the structural basis of the allosteric regulation. (Wiley, et al. 1971) Advancing to high resolution was a long and challenging experience, however, that ultimately bore fruit in 1982 through the efforts of James Crawford, Hugo Monaco, and Richard Honzatko. (Honzatko, et al. 1982) As with CPA, complexes of ATCase with substrates and inhibitors defined, over the next several decades, the allosteric mechanism of this paradigmatic system.

Early in the morning of October 18, 1976, Paul Kuttner and I were in the student room next to Lipscomb's office when another student received a phone call. Paul and I overheard parts of the conversation, and it was clear it concerned the Nobel Prize. This was, of course, pre-Google days, so Paul immediately called the *Boston Globe* to find out who had won it. When told Professor Lipscomb of Harvard University, we looked at each other in amazement. Equally amazing was the Colonel's presence in the office at that time (in hindsight, of course, this was not an accident). We ran to the office to tell him, "Congratulations, you've won the Nobel Prize." He responded, "Are you sure?" Fortunately, the information was correct, and the aftermath of the announcement was a very exciting time to be in the group.

In retrospect, the decade following the Nobel Prize was one of transition for Lipscomb and his group. The receipt of the Nobel Prize provided him with the validation of his scientific accomplishments and while he was still certainly ambitious, I believed he had achieved what he wanted in terms of stature. As an example, once when I was stuck on a problem, he told me that he was only interested in the answer, and wasn't trying to win a second Nobel Prize – this was not intended as a joke but as a serious statement of his motivation for solving the problem. It was during this time that the high resolution ATCase structure was finally solved; moving beyond the low resolution structure obtained in the early 1970s had been a frustrating process for all parties—students, postdocs and advisor—but with the high resolution structure, the allosteric mechanism could be described in molecular detail. Beyond these professional developments, while Lipscomb was quite private in his personal life, it was clear that Jean Evans was a wonderful partner for him and their marriage during this period was an important life event.

The Nobel Prize did not, of course, mark the end of the Colonel's scientific career, but he continued for another 35 years pursuing the themes of bonding and structure. His research continued to embrace such diverse areas as molecular orbital theory (Marynick and Lipscomb, 1982), small molecule structures (Shoham, et al. 1984), and studies on the structure and mechanism of CPA and ATCase. New projects were also launched, most notably in the protein structure arena with fructose-1,6-bisphosphatase, (Ke, et al. 1989) leucine aminopeptidase, (Burley, et al. 1990) HaeIII methyltransferase/DNA, (Reinisch, et al. 1995), human interferon beta, (Karpusas, et al. 1997) and chorismate mutase. (Chook, Ke, and Lipscomb 1993). His final publication, finished before his death on April 14, 2011, detailed the latest efforts on the structure and mechanism of ATCase that he had pursued for the previous four decades. (W. N. Lipscomb and Kantrowitz 2012)

Personal reflections

Lipscomb embodied the principles identified by Faraday as the secret to success in science: work, finish, publish. (Gladstone 1874) While he did assume administrative responsibilities (including as president of the American Crystallographic Association in 1955 and chair of the Harvard Department of Chemistry from 1962 to 1965), he successfully avoided what William Lawrence Bragg termed the fatal enemy of science—the full engagement book (Bragg 1968)—and kept a laser-like focus on his research. Lipscomb also used sabbaticals to advance his science for example, his Guggenheim Fellowship stay at Oxford in 1954–1955 catalyzed his interest in the crystallography of larger structures, having been inspired by Dorothy Hodgkin's work on vitamin B_{12}. He continued to follow Pauling's model of having lots of ideas and throwing away the bad ones; as captured by Eric Gouaux in the Memorial Service for Lipscomb at Harvard, (Gouaux 2011) it was important for the Colonel to make his mistakes as quickly as possible so as to discover the most productive route to solving a problem. Further, the goal wasn't just to do the work; publication was essential. Lipscomb once said to me, "What's the point of doing this if you aren't going to publish?" The net result was that Lipscomb published 667 papers over his scientific career. This number would have been even higher had he not allowed students to sometimes publish work without him as a coauthor—perhaps another consequence of Pauling's influence on Lipscomb.

Lipscomb was fearless, and would frequently change projects and take on new challenges. Like Pauling, the Colonel made contributions in many areas, including a number of studies in which he planted the first flag in a new field but was working on too many other projects to follow up fully. As an example near and dear to my heart, the Colonel's structure of Roussin's black salt with a [4Fe:3S] core captured the essence of iron sulfur clusters a decade before their existence in proteins was recognized. (Johansson and Lipscomb 1958) Whether exploring mechanism, bonding, or dynamics, the foundation of Lipscomb's research was structure. The power of structure in chemistry and biology was impressed upon me by the realization that the same equipment (more or less) used to study boranes could be used to study protein structures.

As an advisor, the Colonel had a remarkable ability to inspire students to take ownership of projects, a trait perhaps acquired from his psychiatrist father. (Burley 2013) He didn't micromanage our work, and we never felt that we were technicians cranking out one small piece of some puzzle of his. Rather, the research project was our problem, and it was our responsibility to figure out how to solve it. I vividly remember the experience when, as a new graduate student, I reported to Lipscomb that the X-ray generator didn't work. When I left his office, I clearly understood that fixing the X-ray generator was my responsibility, although he never said so explicitly. To a degree I find even more remarkable with hindsight, Lipscomb was frequently available to discuss problems, projects, and results. He didn't seem to travel much for conferences or seminars, at least during the time I was in his group (Tom Steitz reported a similar observation about his time with the Colonel as a graduate student [Steitz 2013]). Lipscomb would wander through our offices several times a day, often whistling as he approached. We learned to use this sound as an early warning system to either quickly prepare for a discussion or to escape through one of the side doors if we weren't yet ready to provide an update.

Through the lens of time, I am now even more impressed with the trust that Lipscomb had in our results. When I was in his group, we never went over any original data or looked at electron density maps together, never had any group meetings, etc., but he knew how to ask the right questions to make sure things were on track.

The Colonel's ability to nurture and support his charges to find what worked and what didn't was an invaluable lesson. As just one illustration, Dennis Marynick recounted (Marynick, 2018) his ultimately successful experience working around a programming error on a crystal-structure refinement problem that took several weeks to solve:

> *When I told (Lipscomb about) this, I expected him to be mildly annoyed, but he literally gushed over how insightful I was for picking out such a subtlety, considering it was my first (and last) crystal structure.*

Working through our research problems could have the flavor of test pilots' experiences as described by Tom Wolfe in *The Right Stuff*. The plane (i.e., project) is hurtling toward Earth and the pilot (i.e., student) is working furiously to avoid crashing (Wolfe 1979):

> *I've tried A! I've tried B! I've tried C! I've tried D! Tell me what else I can do!*

The Colonel would be on the ground, guiding us to a landing—perhaps rather rough, but at least we'd be able to walk away when the dust settled.

Although the Colonel was a wonderful advisor for me and many other group members, there was a sink-or-swim aspect to the group, and not everyone flourished in this environment. Lipscomb was supportive and generally patient with our transgressions, but there was a line you didn't want to cross and have him become really upset with you for something you did. In extreme cases, this evolved into a sense of betrayal; grudges could be long-lasting and he was known to not be shy in expressing these views. This aspect of Lipscomb's personality contributed to what could be described as being geared up to fight (Yonath 2013), but at least in retrospect to me, these qualities made him more human through the juxtaposition of creativity, ambition, and passion.

The Colonel's ability to distill a problem to the core essence made him an effective scientist and teacher. His underlying philosophy was that teaching and research are one and the same: "When I do research, I get materials for my lectures, and when I teach I get ideas for my research." (Eaton 2002) Lipscomb's lectures (and lecture notes) on crystallography, chemical bonding, and group theory were models of clarity. He was at home teaching both general chemistry and more advanced courses—in protein structure, theoretical chemistry, and X-ray crystallography. Over his career, Lipscomb taught 13 different chemistry courses, and he confided to his son that when he needed to learn an area of chemistry in greater depth, the first thing he would do is sign up to teach a course in it. (Lipscomb, J. 2018) Clarity of expression and presentation were also evident in his published papers, and for many of us, writing such papers was a real learning experience. We prepared the initial drafts, which Lipscomb would then return to us covered in red (in those pre-word-processing days) as he worked with us to help us rewrite the paper. It should be noted that the impact of Lipscomb's teaching went well beyond his "official" students and postdocs; Nobel laureate Ada Yonath describes first interacting with Lipscomb through attending his protein structure course as a postdoc at MIT. While she never worked with him directly, she "felt extremely lucky to have the opportunity of benefiting from his guidance" in the years following that course (Yonath 2013) which Lipscomb clearly enjoyed as well. Indeed, Yonath is often included as one of three Lipscomb progeny to win the Nobel Prize (Memorial Minute of the Harvard Faculty of Arts and Sciences 2013).

Lipscomb was a contradiction in many ways—he achieved the highest recognition in science, yet he struck me as a loner and even a rebel. For example, he was vigorously opposed to smoking years before this position became public policy (and a stance in stark contrast to his colleague R. B. Woodward; Lipscomb's father was also a heavy smoker), and who else on the Harvard faculty would wear a string tie? The traits of independence, personal responsibility, and self-reliance that he learned as a child remained throughout his life, were reflected in a modest lifestyle and disciplined work ethic. Lipscomb's down-to-earth nature was well captured in an account by James Howard, a sabbatical visitor during 1980–1981 from the University of Minnesota (and, as a direct result of this sabbatical, my subsequent postdoctoral advisor and long-time collaborator). The Colonel once stayed at the Howard's home while visiting Minneapolis; Jim recalled how Lipscomb described his custom of "traveling light (e.g., two shirts for a week) as he ironed his shirt, standing in his sleepwear, in our laundry room!" (Howard 2018) It is hard to imagine many other luminaries at the top of their profession so engaged.

Although Lipscomb was extraordinarily serious about science, he also had a healthy irreverence about the practice of science that was reflected in his humor. I provide several examples here and refer the interested reader to a more extensive discussion in Lipscomb, J. (2013)

Lipscomb enjoyed pranks. As one example, he once told me that as a graduate student at Caltech, he replaced the unexposed X-ray film used to determine crystal orientation with exposed films already used for this purpose. Needless to say, the unsuspecting student who was trying to orient their crystal with these films was completely perplexed why the orientation kept changing in inexplicable ways. Ultimately, the prank was revealed when a film was "developed" that had reflection indices already assigned.

In his lectures on protein structure at Harvard in pre-computer graphics days, Lipscomb would bring in a physical model constructed of an alpha helix, telling us that one needed to be sure to build two helical turns, since "one good turn deserves another."

Lipscomb's humor in scientific publications is still striking to me since it conflicts with the dry style that exemplifies this literature. Among my favorites are the reference to "What I tell you three times is true" from Lewis Carroll's "The Hunting of the Snark" concerning the challenges in elucidating various borane structures (Lipscomb, W. N. 1959) and the reference to Sherlock Holmes about the approach used to solve the boron arrangement in a B_9 borane (Dickerson, et al. 1956) "…when all other contingencies fail, whatever remains, however, improbable, must be the truth." Dennis Marynick recounts (Marynick, 2018) that Lipscomb added the last sentence to their paper on the crystal structure of beryllium borohydride "Concerning the probable gas phase structure, we wish to suggest a close relationship to the appropriate fragment of this solid-state structure, but we dare not do so!" (Marynick and Lipscomb 1972)

From 1993 to 2010, Lipscomb participated in nearly all the Ig Nobel Prize ceremonies, as detailed in a special issue of the Annals of Improbable Research (Abrahams 2011). He served as the prize in the first "*Win-a-Date-with-a-Nobel-Laureate*" contest in 1993, sang in operas including "*The Jargon Opera*" and "*The Count of Infinity*", and danced in the premier (and only performance) of the ballet "*The Interpretive Dance of the Electrons,*" in addition to presenting the Prizes to the recipients. Improbably, he was the most frequently pictured person on the cover of the *Annals of Improbable Research*.

Music was a central interest for Lipscomb throughout his life. During the period I was in his group, this interest was most apparent in his annual summer attendance at a music camp in Vermont, but for earlier generations of group members, it was an important part of group activities. Richard Dickerson (2011) recalls:

> *When I was a grad student with him at the University of Minnesota, 1953–1957, it was a characteristic feature of laboratory parties at his house that, sometime during the evening, he and some of the other guests would break out instruments and begin playing chamber music. Many of these 'other guests' at his parties were from the U. of Minnesota School of Music or the Minneapolis Symphony. The Symphony's home base was the auditorium of the U. Minn. campus, and Lipscomb was friends with many of its members. And oddly enough, when these guests*

sat down to play, they usually discovered that they were short by one clarinet, so the Colonel would selflessly volunteer his services!

After moving to Harvard, Lipscomb not only played a key matchmaking role in bringing Joan Argetsinger and Tom Steitz together, but also played in a chamber group for their wedding, which was held in Minneapolis.

Lipscomb never rested on his laurels and was always looking to the future. I was fortunate to have spent much of my graduate school career in the 5th floor lab in the Gordon McKay Laboratory. Assorted legacies from many of my predecessors were strewn about the lab, and I was able to read notebooks and manuscripts detailing various crystallographic projects. I was especially impressed with the small molecule work that was done, since it seemed that some clever observation (such as systematic trends in the intensities of various classes of reflections) or a novel Patterson method were used to solve each structure. On one occasion, I remember asking the Colonel what he felt was the hardest structure to have been solved in his lab. I expected to hear a heroic account about a borane, or some other small molecule where the structure was only solved by some amazing insight, analytical prowess, or experimental wizardry. Accordingly, I was surprised and at first somewhat disappointed to hear the answer: "Aspartate transcarbamylase, since we haven't finished it yet." (This was around 1978.) I later appreciated that this attitude is essential in science; once a project is completed, it is in the past, while the new challenges and the best work are in the present and the future.

But inevitably, the relentless advance of time inexorably leads to a point when future prospects becoming more constrained. Lipscomb was not happy about reaching the age of mandatory retirement in 1990; he considered voluntary retirement as "giving up" and even mandatory retirement was distressing. Maintaining a laboratory was critical for him, but with time, it became more difficult to renew his federal grant support which was a devastating development. I once called the Colonel during that period and found him quite upset, as he was trying to deal with the loss of his NIH grant. He was especially angry that the reviews included critiques of the cryocrystallography and refinement methods that he had done much to pioneer in his small molecule studies. I was puzzled by his insistence on keeping a laboratory going with an eclectic collection of projects that seemingly lacked the big-picture focus of boranes or carboxypeptidase. But I ultimately realized that the Colonel was a scientist, and as a scientist he had to have a laboratory, whether as a boy growing up in Lexington, Kentucky, or as Nobel Prize-winning scientist at Harvard in the twilight of an illustrious career.

Lipscomb is survived by his son James, daughters Dorothy and Jenna, and wife Jean. He was predeceased by his first wife, Mary Adele Sargent Lipscomb.

Finale

At regular intervals, former group members would get together for a birthday symposium honoring Lipscomb. The presentations would range widely, from bonding theory and computational chemistry to inorganic chemistry to protein structure—an incredible breadth that reflected Lipscomb's scientific interests. As Tom Steitz once summarized, "The only person who understood every talk was the Colonel." Lipscomb exemplified the best traditions of academic research, and his scientific legacy continues to inspire us. Thank you, Colonel.

Author's note

I had the great fortune of working with the Colonel, from 1976 to 1981 at Harvard, as a biophysics graduate student and briefly as a postdoctoral fellow. I joined his group shortly before he received the Nobel Prize. At that time, Lipscomb's pioneering contributions to borane chemistry and protein crystallography had already been made, so I did not have an eyewitness view of those epic developments. But I certainly witnessed his creativity, drive, and competitiveness.

In preparing this memoir, I made extensive use of Lipscomb's autobiographical sketch (Lipscomb, W. N. 2002) and the biographical notes of his son James Lipscomb; (Lipscomb, J. 2013) material without an explicit reference comes from these sources. I have also drawn on a discussion of the scope of Lipscomb's research by Gareth Eaton (Eaton 2002) and on the remembrances of former group members assembled by Jianpeng Ma. (Ma 2013)

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