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NELSON JORDAN LEONARD
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A Biographical Memoir by
JOHN D. ROBERTS

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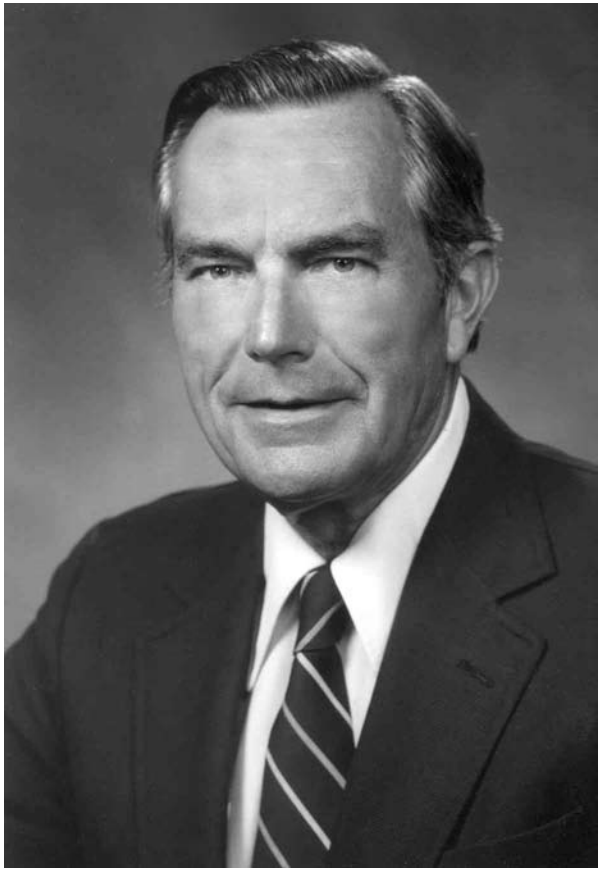
Biographical Memoir



Nelson J. Leonard

NELSON JORDAN LEONARD

September 1, 1916–October 9, 2006

BY JOHN D. ROBERTS

THE PASSING OF NELSON J. LEONARD, at age 90, deprived the chemical world of a consummate scientist who produced highly significant research and possessed qualities that led to wide personal popularity. Nelson was a primary contributor to fundamental knowledge of the chemistry of nitrogen-containing molecules. The sweep of his research covered alkaloids; nitrogen heterocycles; small- and medium-size heterocyclic ring compounds; transannular interactions and reactions; cytokinins natural and synthetic that facilitate cell growth, cell division, and cell differentiation; chemical, spatial, fluorescent, and dimensional probes of enzyme-coenzyme interactions and of nucleic acid structure and function; and fluorescent covalently linked DNA/RNA cross-sections of normal, narrow, and wide dimensions. He is to be ranked as a master in the application of organic synthesis to the solution of important problems in biochemistry and plant physiology.

Nelson Leonard was born on September 1, 1916, in Newark, New Jersey, to Harvey Nelson Leonard and Olga Pauline Jordan. His father's ancestors had come from England in the first half of the 17th century and also from England via Ireland in the beginning of the 19th century. According to genealogical records, a number of these male ancestors

participated in the French and Indian War and the Revolutionary War. They were mainly artisans and farmers, but two were ministers trained at Harvard and Yale, the only college graduates in the family lineage. Nelson's mother's forebears were Huguenots who left France for Germany in the 16th century and sailed to the United States in the mid-19th century. They were also artisans, along with an occasional minister. Both parents' families followed a Puritan work ethic enlivened by music (piano, organ, mandolin, and singing) and an appreciation of nature (hiking, swimming). Olga had partial responsibility for raising her three younger siblings, but she was able to finish high school. Harvey had to leave school at 14 to assist in the support of his parents and two sisters. He eventually became a salesman of men's clothing and developed a large and loyal following of customers who transferred allegiance from store to store in New York City whenever he shifted employers.

Nelson attended public schools in Mount Vernon, New York, and was fortunate to have had several inspirational teachers in high school: Florence E. Brown and Catherine I. Rhodes (mathematics), Malcolm MacGregor (physics), Frank P. Bunker (chemistry), and Alice V. Brower (English). He recalled that Mrs. Brower would appear in class on Monday mornings armed with the book review section of *The New York Times* and would expound on writing and books she felt her students should have on their reading lists. Nelson was active in student politics and, with his beautiful singing voice, also in the school glee club, appearing in operettas and in solo recitals accompanied by Gurney Woodley, a talented pianist and member of Nelson's class.

Nelson garnered a record number of prizes at graduation, but the year 1933, the trough of the Great Depression, was not a favorable one for high school graduates. With the accession of Hitler to power in January, political storm

clouds were gathering over Europe, and in the United States the banks were closed in March. When the Mount Vernon bank in which Nelson had deposited his hard-earned savings was allowed to reopen, he had only half enough money for a first year of college.

His matriculation at Lehigh University in Bethlehem, Pennsylvania, was made possible by the award of a one-year scholarship, obtained through the efforts of Morton Sultzer, a family friend and alumnus trustee, along with Andrew Buchanan, the admissions officer. Annual renewal of the scholarship, awards of cash prizes, waiting on tables in his fraternity house, WPA work in the chemistry department, and summer jobs provided enough funding for Nelson to squeak by financially. He played varsity soccer and was class president in his junior year. He also took part in theater productions, operettas, and glee club concerts, and he made radio appearances in a double quartet.

An intended chemical engineer through his junior year, Nelson shifted to a B.S. in chemistry at the suggestion of Philip M. Palmer, professor of German and dean of the College of Arts and Sciences, who proposed him for a Rhodes Scholarship to Oxford in his senior year. His most famous professor in the new curriculum was Lawrence P. Gipson, a historian who taught international politics. Nelson was able to do senior research in the private laboratory of Vahan Babasinian and to continue musical performances under the direction of T. Edgar Shields. J. Harry Carpenter, the soccer coach, remained a good friend, even if, according to Nelson, he did not come up to the coach's expectations as a soccer player. While a senior at Lehigh University and in anticipation of his Rhodes Scholarship, Nelson prepared a summary of the scientific papers of Neville Vincent Sidgwick of Lincoln College. He was fascinated by Sidgwick's wonderful book *Organic Chemistry of Nitrogen*, and this interest proved anticipatory of his

own later research on nitrogen compounds. His research director at Oxford was Leslie Sutton, a former student of Sidgwick, who had become a don in Magdalene College. Sutton also directed the research of Norman Davidson, a Rhodes Scholar from the University of Chicago, who later became a distinguished professor at the California Institute of Technology in the field of physical inorganic chemistry and structures and functions of DNA.

Sutton gave lectures on atomic structure and valency. The other distinguished Oxford lecturers who made broad scientific imprints were Robert Robinson (organic chemistry), Cyril Hinshelwood (physical chemistry), and Neville Sidgwick (inorganic chemistry). While at Oxford, Nelson continued his interest in music by participating in the Oxford Bach Choir, the Opera Club, and the Lincoln College Choir, as well as in recitals with organist John Hough and pianist Leigh Gerdin. His sport shifted from soccer to rowing, and he was a strong member of the Lincoln College First Eight.

The beginning of World War II, in September 1939, forced Nelson to return to the United States and terminated his research with Sutton on the determination of valence angles by electric dipole moment measurements mostly of difluoro compounds. Much work on this project is typified by dipole measurements of (4,4'-difluorodiphenyl-)X derivatives where X is a divalent group such as -O-, -S-, -C(=O)-, and $-S^{+}(-O^{-})-$. A much delayed paper on this subject, by Leonard and Sutton, was written at the University of Illinois, Urbana-Champaign, in the summer of 1947 and published in the *Journal of the American Chemical Society* in 1948.

Chemistry was not the only part of Nelson's life that was interrupted by the war. Through family connections, he had met and fallen in love with Louise Cornelie Vermey of the Netherlands. After a year and a half, they became engaged, but they were not to see each other again until after the war

(1945 in the Netherlands), and it was not possible to arrange for her journey to the United States and their marriage until 1947.

Nelson continued his graduate education in chemistry, concluding with a Ph.D. in 1942 at Columbia University, where his study was supported by scholarships, teaching assistantships, and fellowships, along with a position as a Sunday singer at Calvary Episcopal Church. His research consisted of the establishment of the structure and partial synthesis of alstonine, a naturally occurring antimalarial, under the direction of Robert C. Elderfield. Other influential Columbia professors of the time included Harold C. Urey, Joseph Mayer, Louis P. Hammett, and Arthur C. Cope. Fellow graduate students Elkan R. Blout and Josef Fried became lifelong friends. A postdoctoral research assistantship with renowned professor Roger Adams on *Senecio* alkaloids brought Nelson to the University of Illinois. Teaching duties were added in 1943, and these grew to include U.S. Navy and U.S. Army units passing through the university. At about the same time, he joined the team led by professors Charles C. Price III and Harold R. Snyder on antimalarial research directed to synthesis and production of chloroquine in time for its use in the Pacific. At the end of the war, during 1945-1946, Nelson served as a scientific consultant and special investigator in the Field Intelligence Agency, Technical (FIAT) of the U.S. Army and in the U.S. Department of Commerce, European Theater.

After this tour of duty, Nelson became a chemistry faculty member at Illinois. He remained so until his retirement in 1986, after highly successful years in which he was appointed Reynold C. Fuson Professor of Chemistry, professor of biochemistry, and member of the Center for Advanced Study. While the popular concept of a chemistry professor's life is hardly one of intense excitement, one should never overlook

the Archimedean thrill of solving difficult problems, and Nelson deeply enjoyed such thrills of his own and others in the advancement of chemical research. He found a different, but still great, satisfaction in teaching and mentoring interested and skilled research chemists, and he derived intensely personal gratification from their success in leading their fields and acquiring new chemical knowledge.

At the beginning of his career, Nelson adopted as a guiding concept for his research, "organic synthesis with a purpose." To this end, he developed a systematic approach that led to many important results. Early on, with the aid of a catalytic reductive cyclization, he brought about the reductive cyclization of intermediates, which directly afforded *Senecio* and *Lupin* alkaloid components and establishment of their relative stereochemistries. Later came syntheses of selected 1,2-diketones that established the dependence of their spectroscopic properties upon the dihedral angle between the carbonyl groups. Fundamental study of the electrolytic reduction of α-aminoketones provided a new route to medium-ring nitrogen heterocycles. New functionalities were invented based upon transannular reactions across medium rings, which included defining the ring size and the electronic limitations of transannular interactions. He was much admired for his recognition of the iminium groups (the products of enamine protonations) as a fast-acting ionic carbonyl equivalent and for assembly of new families of reactions based upon this functional group. One of his reactions of iminium salts (i.e., with diazomethane) led to aziridinium salts. Nelson and his students thus made available these three-membered ring compounds that had been postulated previously to be mostly unstable intermediates. These aziridinium compounds were investigated systematically, with the attendant benefit of potential synthetic utility based upon their newly discovered ring-expansion reactions.

Nelson's musical career flourished in the Midwest, right along with his academic career in chemistry. Solo appearances as a bass baritone in choral works with the Chicago, Cleveland, and St. Louis symphony orchestras, in Bach festivals, at other universities, and with many different choruses were interspersed with recitals at the University of Illinois, Washington University at St. Louis, and Illinois Wesleyan, Springfield. By 1954 he and Louise (affectionately known as Nell) had four children: Kenneth, Marcia, James, and David. The heavy professional demands of chemistry as well as his commitment to family life made him question his professional singing career. Then in 1955, when he was elected to membership in the National Academy of Sciences, Nelson decided that if his peers had chosen to recognize him as a chemist, he had better do something about it. He realized that there was more scope for originality in full-time devotion to chemistry, and that he could make a more lasting contribution through the literature of science. The family joke claimed differently, namely, that he made the choice of chemistry over music the day that the honorarium from a chemistry lecture equaled what he made singing.

Another decision point for Nelson was reached in 1960, when he was on sabbatical leave aided by a Guggenheim Fellowship, in Basel, Switzerland. He had concluded that organic chemistry was not enough, a dictum that he passed along to his students thereafter, and he devoted much more of his time to reading the current literature of biochemistry rather than organic chemistry. The results of this broadening of his interests soon appeared in research publications emanating from the Illinois laboratory and those of the scientists with whom he collaborated.

With Tozo Fujii he synthesized the cytokinin N^6-isopentenyladenine and with Professor Folke Skoog, plant physiologist at the University of Wisconsin, Madison, he showed that this

compound occurred naturally in the plant pathogen *Corynebacterium fascians* and was a major component responsible for its biological activity. The combined Illinois-Wisconsin search for other natural cell-growth, cell-differentiation factors uncovered eight additional highly active substances from plant, animal, bacterial, and fungal sources. Stereoselective syntheses to produce these compounds, and their structure/activity investigations led to agents more active than the naturally occurring cytokinins. In very low concentrations the cytokinins initiate plant, flower, and tree growth from tissue culture that is basic to horticultural and agricultural development. The Wisconsin collaboration lasted 18 years and resulted in some 50 publications. Recent work by M. D. Siperstein at the University of California, San Francisco, found that isopentenyladenine (iP) is an important link between plant and mammalian systems and, like mevalonate, it stimulates DNA synthesis specifically during the S phase of the mammalian cell cycle.

Nelson's laboratory provided important fundamental findings on the reaction of diethyl pyrocarbonate (DEP) with adenosine and adenosine-containing nucleotides and dinucleoside phosphates, culminating in 1973 with the showing that DEP, as a chemical probe, can serve for detecting adenosine or deoxyadenosine modification at exposed sites in RNA or DNA or of capability for initiating sequential analysis at a modified A. This idea has been amply validated in other laboratories for (1) detection of higher-order RNA structures; (2) chemical probing for tRNA-ribosome complexes; (3) detection of cruciform DNA structures; (4) location of the sites of B- to Z-DNA transitions; and (5) footprinting of the binding of antibiotics and intercalators to DNA.

Concomitant with research on triacanthine (3-isopentenyladenine) and related cytokinins, work on spatial probes of enzyme-coenzyme interactions was begun with the synthesis

of 3-isoadenosine and its phosphates. Leonard and Laursen, with the collaboration of other laboratories, showed that the range of similar biological activities for the 3-isoadenylates with the adenylates (9-substituted on purine), while initially surprising, turned out to be readily understandable in spatial terms. Thus, the superposition of the purine ring of a 3-isoadenosine derivative over that of adenosine illustrates the close spatial relationship that exists between the two, especially as regards the proximate location of the individual nitrogens in each. A definitive study at Illinois (1996) confirmed the hydrogen-bonding pattern that had been postulated 30 years earlier and helped in the understanding of the parameters limiting early nucleic acid development in nature. Nelson deduced that nature might have discarded the N3 (vs. N9) attachment site for purines because of chemical instability but not of structural incompatibility.

Nelson's derivatization of nucleosides, nucleotides, and coenzymes by fluorescent probes placed him among the most often quoted scientists. He was successful in providing reagents for 4-thiouridine, cytidine, adenosine, and guanosine. Incorporation of fluorescence into the related coenzymes facilitated understanding of the modes of binding of coenzymes or cofactors to enzymes. The greatest success came from the chloroacetaldehyde modification of adenosine triphosphate (ATP) to produce I,N^6-ethenoadenosine 5'-triphosphate, or ∈ATP, a fluorescent ATP of high quantum yield, long lifetime, and selective activity with various enzymes (with the collaboration of J. R. Barrio, J. A. Secrist III, and G. Weber). H. Bartsch of the International Agency for Research on Cancer, Lyon, France, noted in 1984 that the real renaissance of cyclic nucleic acid-base adducts began in 1972, with Nelson's work. Many other applications were found, including coenzyme-enzyme interactions, coenzyme binding to proteins, DNA and RNA structural diagnosis (e.g.,

cruciforms, Z-DNA), and activation of carcinogens (e.g., vinyl chloride).

Nelson also pioneered the construction and application of totally synthetic fluorescent dimensional probes to provide details as to both size and locus of enzyme-coenzyme binding sites. This idea involved testing of the dimensional restrictions of enzyme-active sites by using synthesis to stretch the cofactor by known magnitudes. Such compounds had not been made previously, nor such a concept expressed, except in terms of general bulk requirements. A specially effective application was in the assessment of the space available for the adenine portion of ATP through fluorescence studies of the action of *linear*-benzo-ATP with crucial enzymes and transport proteins (in collaboration with D. I. C. Scopes, P. VanDerLijn, and J. R. Barrio).

In 1973, at the beginning of Nelson's fifth year in the Center for Advanced Study, the University of Illinois appointed him to the double position of professor of chemistry and biochemistry. His final forays into the synthesis of nitrogen hetereocycles included the synthesis, chemical behavior, and valence-orbital structure of tri-*s*-triazine and 1,2,4,6-tetraazapentalene. The first of these is a fundamental N-aromatic ring system consisting of a coplanar arrangement of three fused *s*-triazine rings, with a 12π-electron periphery. This long sought nucleus, first conceived in correct formulation by Pauling and Sturdivant in 1937, finally became available with the aid of R. Hosmane, and M. A. Rossman in a remarkably abbreviated synthesis. The azapentalene heterocycle was prepared to provide a basis to covalently link RNA/DNA cross-sections with molecular architecture similar to the hydrogen-bonded base pairs in a double helix.

In the laboratory that Nelson maintained at the University of Illinois after his retirement in 1986, his postdoctoral associate, Balkrishan Bhat, used the covalently linked DNA

cross-section as a template to provide stabilization of an adjacent (terminal) dA·dT base pair and to indicate the prospect of self-assembly when dA and dT are attached on opposite sides of the template. All told, Nelson published 438 papers, and his roster of coworkers included 120 Ph.D. students and 90 postdoctorates. Although Nelson averred he was impractical ("synthesis with a purpose"?), he also was granted eight patents over the course of his career.

To honor Nelson's many years at the University of Illinois, Nell established, in 1986, the Nelson J. Leonard Distinguished Lecture fund, with additional contributions from Eli Lily and Company, the Monsanto Company, Organic Syntheses Inc., and Nelson's friends, colleagues, and students. Each year the fund brings a chemist of international renown to the campus, most recently Roger Y. Tsien, University of California, San Diego, and winner of the 2008 Nobel Prize in Chemistry.

In 1987 Nell died of cancer, and before long, Nelson, too, was also diagnosed with cancer, necessitating a very serious surgery called a pancreatoduodenectomy, also known as the Whipple procedure. After recovering, he became a Fogarty scholar-in-residence at the National Institutes of Health (1989-1990) in association with Arnold Brossi. This was followed by appointment as Distinguished Visiting Professor at the University of California, San Diego, under the auspices of D. R. Kearns and M. Goodman. In 1991 he became a Sherman Fairchild Distinguished Scholar in the Division of Chemistry and Chemical Engineering at the California Institute of Technology, and in 1992 to everyone's delight he accepted an appointment as a faculty associate that lasted until his death in 2006.

Nelson was a wonderful resource for our younger faculty, unstinting in his advice for and encouragement of their early careers. He was also a very highly valued member of the institute's undergraduate admissions committee. With several

thousand applications and a policy of no admission without scrutiny and approval by at least one faculty member, there were many folders to read, and Nelson was the champion reader for many years in a row. He really enjoyed the contact with students that he gained through their applications, and he was strong in his support of those whose grades or test scores were not optimal, but who—in his opinion—were likely to be standouts at Caltech. It is interesting to note that none of his children followed him into the sciences, but he did not find this a disappointment. He had discovered his own passion, and he expected them to find theirs, too. He was supportive of and enthusiastic about their career choices.

I first met Nelson in 1945, but we did not have a close relationship until I was selected for the Board of Editors of *Organic Syntheses* in 1955. This initial relationship was strengthened by our joint service for several years on the Chemistry Advisory Committee of the National Science Foundation and not long after that with our elections to the National Academy of Sciences. At the Academy we had the exciting experience of being present when, shortly after his election to the Presidency, John F. Kennedy came to the annual Academy meeting and spoke eloquently to the assembled members about his attitude toward science (as far as I know, a first such occasion for the Academy and an incumbent president).

When Nelson and Nell built an elegant vacation home in Snowmass, Colorado, my wife, Edith, and I were frequent guests for a series of scientific meetings they developed. These gatherings featured daily skiing, delicious dinners, and argumentative evening chemistry lectures with other skiers who also possessed impeccable chemical credentials in the physical, inorganic, theoretical, biochemical, or organic disciplines. Our relationship was further broadened scientifically by ^{15}N NMR studies carried on at Caltech, mostly

of Nelson's samples of nucleotides, which resulted in four joint publications.

During the course of Nelson's career, he served as a consultant for Phillips Petroleum Company, Monsanto Chemical Company, and Eli Lilly and Company, in that order. He lectured widely nationally and internationally. He was 38 when, in 1955, he was elected to membership in the National Academy of Sciences. He was also chosen a fellow of the American Academy of Arts and Sciences Midwest Center and was elected in 1996 as a member of the American Philosophical Society. The American Chemical Society Award honored his achievements for creative work in synthetic organic chemistry in 1963, and he received the Medal of the Synthetic Organic Chemical Manufacturers Association in 1970.

The latter, Nelson regarded as especially significant because in his award address, he imparted the elements of his thinking on the subjects of "negative" yield(s) of unwanted byproducts and "desyntheses" or "reverse" syntheses, involving intentional degradation of human-made materials. He addressed the need to train students about disposal problems and to challenge industrial researchers to take the long view and learn how to degrade products they intended to make on a large scale once the products served their purpose and were discarded. Nelson ended his talk saying, "We would like to be certain that while we continue to augment nature in many favorable ways, we do not foul it or disrupt its life-giving cycle" (*Chemical and Engineering News*, January 22, 1970). Nelson had not anticipated the enthusiastic accord that he would receive from the attendees and subsequent letters he received from C&EN readers. A very significant result of his message came in the next year, when the Synthetic Organic Chemical Manufacturers Association

Medal was given for environmental chemistry instead of for synthetic chemistry.

Nelson was particularly grateful for the Roger Adams Award in Organic Chemistry by the American Chemical Society in 1981, while his children were more impressed by awards for excellence in teaching in the University of Illinois School of Chemical Sciences in 1980 and 1984. Other lectureships and awards continued after his retirement, including the 1991 George W. Wheland Award of the University of Chicago, the initial Creativity Award of the University of Oregon in 1994, and the Arthur C. Cope Scholar Award of the American Chemical Society in 1995.

Nelson received the first Paul G. Gassman Distinguished Service Award of the Division of Organic Chemistry of the American Chemical Society in 1994, in recognition *inter alia* for his years of editorial work for the *Journal of Organic Chemistry, Organic Syntheses, Journal of the American Chemical Society, Biochemistry, Chemistry International,* and *Pure and Applied Chemistry*, as well as his service on committees of the National Science Foundation, National Research Council, Alfred P. Sloan Foundation, National Institutes of Health, John Simon Guggenheim Memorial Foundation, and Searle Scholars Program in the Chicago Community Trust. He was active in the divisions of Organic Chemistry of the American Chemical Society and the International Union of Pure and Applied Chemistry. His earned degrees included a B.S. in 1937 from Lehigh University, a B.Sc. in 1940 and D.Sc. in 1983 from the University of Oxford, and a Ph.D. from Columbia University in 1942. His honorary degrees included Sc.D., 1963, Lehigh University; Doctor Hon. Causa, 1980, Adam Mickiewicz University, Poznań, Poland; and D.Sc. (Hon.), 1988, University of Illinois, Urbana-Champaign. He was elected a foreign member of the Polish Academy of Sciences in 1977

and an honorary member of the Pharmaceutical Society of Japan in 1989.

Over a period of five decades, Nelson's research showed him to be a leader rather than a follower, a successful explorer in areas other than organic chemistry but with the advantage of a firm base in synthetic and structural organic chemistry. He was also a major force in bioorganic chemistry and a most energetic supporter of younger colleagues.

When Nelson moved to Caltech, he instantly became one of Pasadena's most eligible and handsome unmarried males. My wife, Edith, and I decided that he would be a good match for our longtime friend Margaret Taylor Phelps. Our plan was to introduce Nelson and Peggy and have them enjoy each other's company at my 75th birthday dinner. To our surprise, this plot failed dismally. What did work was to take advantage of the fact that both had vacation homes in the Aspen, Colorado, area and both were excellent skiers, and to urge them to ski together. Before very long—on November 14, 1992, to be exact—they were married in the presence of all of their family members. The marriage was a great success, and several times afterward I was asked by other women friends the question, without possibility of an affirmative answer, "Can't you find me a Nelson, too?"

Nelson was a fast and fearless skier into his 80s, but he finally had to give up the sport because of injuries. Besides skiing, he and Peggy greatly enjoyed travel and classical music. He served on the board of directors of the Pasadena Symphony, and in 2001 when he turned 85, she established an endowment—the piano chair for the orchestra—in his honor. The two of them stayed in close touch with family, friends, and chemistry colleagues and spent much of each summer enjoying the Great Lakes in Canada and Michigan. At the same time, Peggy introduced Nelson to the world of contemporary art, with considerable travel centered on art

and architecture. One of their more exotic trips was to join a group circumnavigating the world in a series of chartered jets. Nelson particularly enjoyed crossing twice over Mount Everest, while sitting in the copilot's seat.

A few months before his 90th birthday, Nelson was diagnosed with multiple metastatic cancers. Family members took turns traveling to be with him, and he passed away quietly and peacefully at home on October 9, 2006. Over the last few years of his life he wrote a personal history, called *More Than a Memoir,* that described what he felt were the essentials of his life and career and related his philosophy. The book was printed privately and given to family members, friends, and colleagues and sent to selected academic institutions and libraries for their reference collections. Much of this memoir and of the selected bibliography was drawn from Nelson's book, which is still available from Xlibris and on the Caltech Library's website.

Even after his death, Nelson's appreciation for the sciences lives on. The Huntington Library in San Marino, California, has a permanent exhibit called "Beautiful Science: Ideas that Changed the World." The gallery guide is produced in memory of Nelson Leonard, "a chemist who understood the beauty of science."

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