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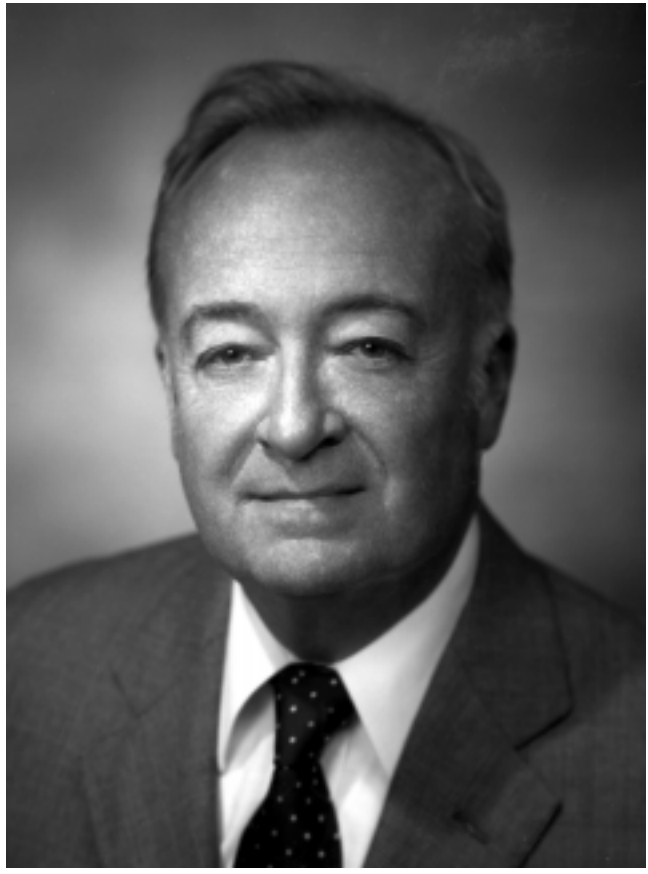

William D. Phillips

WILLIAM D. PHILLIPS

October 10, 1925–December 15, 1993

BY ROBERT G. SHULMAN

WILLIAM DALE PHILLIPS, chemist, nuclear magnetic resonance spectroscopist, and science policy advisor, died at home in St. Louis, Missouri, on December 15, 1993.

Bill Phillips was born October 10, 1925, in Kansas City, Missouri, the first of the two children of Elmer and Mabel Phillips, long-time residents of Kansas City. He graduated from public high school in his hometown at the age of seventeen and entered the U.S. Navy V-12 program in 1943. At the navy's request he studied mechanical engineering at the University of Texas and was commissioned and left active duty in 1946 with the rank of lieutenant (junior grade). Bill returned to finish undergraduate studies at the University of Kansas in 1946 and received a B.A. in chemistry in 1948. For graduate studies he entered the MIT chemistry department. His research was on the vibrational spectra of organic molecules in Richard Lord's laboratory. In this laboratory he learned the nature and basis of spectroscopy, an understanding that enabled him to move freely across different applications of varied spectroscopies. He was in a physical chemistry laboratory that was trying to obtain vibrational and Raman spectra from biological molecules. At that time difficulties arose from the impurities present in

solution of "purified" enzymes. The difficulties of seeing through impurity and macromolecular scattering must have impressed themselves strongly on the young researcher; a few years later when he was in a position to obtain well-characterized spectra from biomolecules, he had a historical perspective on the significance of reliable spectra.

At MIT Bill met Esther Parker, a Wellesley College student, better known to her friends as Cherry, whom he married in 1951. Cherry was a loving partner and assisted Bill in his many adventures.

Upon leaving MIT in 1951 with his Ph.D. in physical chemistry, Phillips accepted a position in the Central Research Department of E. I. du Pont de Nemours and Company, Inc., in Wilmington, Delaware. Bill is widely remembered by the magnetic resonance community for the path-breaking work he did at the du Pont Co. Du Pont was to be his home base for almost 30 years and he rose through the ranks from research chemist to assistant and associate directorships of research and development.

Looking over Bill's contributions to magnetic resonance during this period, one is struck by the breadth, novelty, and depth of his work. No review would do justice to these original, creative applications of nuclear magnetic resonance (NMR) in its infancy, however a few selective observations may help to illustrate his great body of work.

Bill's first publication out of du Pont, a single authored letter to the editor in the *Journal of Chemical Physics* in 1955, described the use of ^{1}H NMR to demonstrate unequivocally the existence of restricted rotation in amides. The lead sentence reads: "Restricted rotation about the C-N bond of amides has been postulated and is an important consideration in theories pertaining to the structure of protein molecules." Clearly in 1955, Bill was thinking about NMR as a tool for probing protein structure, an area that

would become his central focus in later years. But this was 1955, and his spectrometer ran at 40 MHz.

In 1957, again in the *Journal of Chemical Physics*, Bill announced in a letter to the editor: "We have observed anomalous shifts in the proton magnetic resonance spectra of alcohols complexed with paramagnetic ions." He goes on to postulate bond formation between the alcohol ligand and metal ion leading to subsequent delocalization of the unpaired electrons providing a finite density of unpaired electrons at the resonating nucleus. Chemical shifts induced by paramagnetic metal ions would, in time, become a powerful tool for structural elucidation and a major focus of his research.

He observed large shifts of proton resonances in alcohols complexed with Co^{2+} (or Ni^{2+}) and showed from their strong temperature dependence that they arose from anisotropic dipolar interactions between protons and the paramagnetic electrons (1957). He established this mechanism by extending an earlier analysis to these complexes. The anisotropic dipolar interactions, called by MacConnell "pseudo contact," gave large, easily measured shifts that were proportional to $1/r^3$, where r was the distance between the nucleus and the electron spins of the paramagnetic metal ion. Because the other parameters needed to calculate the observed shifts were generally known, the shifts provided an accurate measure of distances between nuclei in aqueous complexes in solution. This method was used many times in small molecular complexes by Bill, his colleagues, and in other laboratories, where it remains a most valuable structural method. However, in those early days before magnetic resonance imaging (MRI), it found its greatest usefulness in paramagnetic metal complexes of biological macromolecules, particularly proteins and nucleic acids. Since the electron g factors were known with respect to the molecular axes, measurements of the

shifted positions of numerous proton resonances in a protein / metal complex could be interpreted to determine proton spatial coordinates. In this case the metal ion itself became the origin of the coordinate system, while the valuable information was the protein structure in solution. The ability to form complexes in solution of organic molecules with paramagnetic ions, with anisotropic electronic dipoles, provided the basis for shift reagents that subsequently became so useful (and profitable) in MRI applications. In later years Bill, in charge of research at Mallinckrodt, had to stand by as competitors earned millions from work that was derived from his pioneering studies. After a decade of development by Phillips and others, this method was the basis of a large-scale dedicated effort to determine the structure of the protein lysozyme.

The same 1957 experiments measured shifts in proton resonances when the alcohols were complexed with Mn^{2+}. As Mn^{2+} is isotropic, the shifts could not be explained by anisotropic dipolar fields so that another explanation was required. This Bill saw was the delocalization of spin density from the metal into molecular orbitals, including orbital wave functions of the hydrogens creating true hyperfine shifts, sometimes called contact interactions. This measured the degree of chemical bonding with the metal and became an important method of describing the degree of covalency, a degree (even though small in accordance with the widely held view that transition metal bonds were ionic) that still measured a significant covalent contribution. In a series of papers in the 1960s, Bill Phillips and coworkers used isotropic contact proton hyperfine interactions to determine the configurations and magnetic properties of paramagnetic bis-nickel(II) chelates of aminotroponeimines. Spin densities from Ni transmitted through N, O, and S atoms connecting conjugated ligands produced

large high- and low-frequency chemical shifts of the protons on the ligands. Synthesis and study of compounds with various ligands allowed the determination of spin densities of a large number of aromatic, cyclic 7-carbon, alkyl, and fluorine substituents. Similar studies were made on nickel(II) salicylaldimines.

These findings were parallel to NMR experiments I was doing at Bell Telephone Laboratories on the ^{19}F resonances in transition element fluorides and very directly related to ESR experiments of the hyperfine interactions with protons of organic free radicals done in many laboratories but most significantly by Harden MacConnell. Although there was no occasion when the three of us were together at a meeting (the similarity of the mechanisms were obscured by the differences of techniques [solution NMR, solid state NMR, and ESR]), still in Bill's mind and mine (we acknowledged afterwards) we were watching closely each other's results and, at least in my case, watching with admiration. These earlier studies of paramagnetic complexes were the basis of Bill's future studies of shifted resonances in the paramagnetic proteins such as cytochrome C and plant and bacterial ferrodoxins.

In the early 1960s Phillips realized that modern physical methods had great potential for biological research. He took a leave of absence to go to MIT for postdoctoral work in biochemistry for the academic year 1962-63. This was a significant break from his early emphasis on fundamental electronic and structural properties of inorganic, organic, and organometallic compounds (he had published approximately 30 papers, mostly NMR and ESR, on the earlier work). Collaborators who made significant contributions included J. J. Drysdale, C. E. Looney, E. L. Muetterties, H. C. Miller, J. Foster, D. B. Chestnut, R. E. Benson, D. R. Eaton, D. R. Josey, and R. E. Merrifield. The move into biological mol-

ecules had been clearly his intention even as early as his first NMR experiment, but the direction was consolidated by NMR studies on nucleic acids finished after a year at MIT.

With the highest-frequency high-resolution NMR spectrometers and the newly available computer of average transients (CAT), Bill Phillips with his long time collaborator C. C. McDonald and his biological collaborator, former physicist Sheldon Penman, started his explorations of the NMR spectra of biological molecules. The CAT gave the sensitivity needed for studying the dilute solutions obtainable for macromolecules. In this he profited from the development of CAT by Oleg Jardetzky and by L. C. Allen and L. F. Johnson, and he expressed appreciation of their advances, which made his work possible. Also he generously acknowledged the pioneering work by Jardetzky, who had been studying proteins and their constituent amino acids for several years and who had recently reported studies of nucleic acids similar to those of the Phillips group.

The 1964 *Science* article entitled "Nucleic Acids: A Nuclear Magnetic Resonance Study" showed how NMR can serve as the method of choice for studying the structure and dynamics of nucleic acids in solution. Starting with solutions of the single base polynucleotides (i.e., poly A), they showed the resonances observed at room temperature shifted to lower fields as the temperature was increased to 60°C but did not shift further at still higher temperatures. They interpreted this to result from the conversion of an ordered configuration to a random coil, with the shifts at lower field coming from ring currents of the neighboring stacked bases. Other experiments, taking advantage of their interpretation that the shift reflected structural order, were made of different compositions of poly A and poly U. The results showed that "at 25°C poly (A+U) is formed when the mole

fraction of U is less than 0.50 and that poly (A+2U) is formed when the mole fraction of U is greater than 0.66."

In addition to the structural information they obtained kinetic information about the changes with temperature or the "melting." Raising the temperature of the poly A-poly U complex through the melting transition brought out sharp resonances of poly A and poly U, which appeared suddenly without any gradual sharpening, indicating that the melting was an all-or-nothing process without significant rapid exchange between melted and ordered forms. This kind of information, particularly easy to obtain from NMR melting experiments dominates folding or melting data to this day.

In subsequent experiments, Bill and his colleagues extended melting studies to several small proteins, concentrating on ribonuclease and lysozyme. Their subsequent studies were the fulfillment of the promise in his 60-MHz studies of nucleic acids in which narrow lines were observed after destroying the ordered 3-dimensional structure.

These results were inspired by Bill's stay in the biology department at MIT for a sabbatical. There he interacted with Alex Rich and Sheldon Penman, like himself trained in physics and chemistry, who had already successfully switched to biological studies. Upon his return to DuPont, Bill pursued the goal of obtaining a higher field NMR spectrometer than those previously available. The new model would use a superconducting magnet. The first commercially available high-resolution NMR spectrometer was made by Varian Associates and was installed in the DuPont Central Research Laboratory in 1966. This spectrometer in Bill Phillips's hands was a turning point in the study of biological macromoles. Although sharp lines had been seen previously in melted nucleic acids, as discussed above, and although Oleg Jardetzky and his colleagues had been studying histidine protons and titrating them, the 220-MHz spectra

that Bill introduced to the world at the second meeting of the International Society of Magnetic Resonance in Biological Systems in Stockholm in 1966 created a revolution in our thinking.

This society, which meets every two years, was formed by a group of attendees at a Gordon Conference on Magnetic Resonance in the summer of 1962. The organizing committee consisted of Bill Phillips, Oleg Jardetzky, Mildred Cohn, Josef ("Terry") Eisinger, and me. The first meeting was held in 1964 at the old stately headquarters of the American Academy of Arts and Sciences, which was to elect Bill to membership some years later. The society has continued to the present, holding meetings every two years around the world. Each meeting is organized by a different group of three or four scientists who volunteer to raise the money and do all the work. Bill was one of the organizers of two of the meetings held in the United States, the first being his participation in the 1968 meeting held in Fairly House, Virginia. The history of these meetings, held in an unselfish scientific spirit almost always in inexpensive out-of-season schools and universities, captured the spirit of innovative, commemorative science that Bill epitomized, which was unique to those times.

Into this small world Bill Phillips gave a revolutionary talk at the Stockholm meeting in 1966. He showed the 220-MHz NMR spectra of several proteins, lysozyme, ribonuclease, cytochrome C, and Fe-S proteins as well as of nucleic acids. In previous high-resolution NMR studies of proteins at 100 MHz, Bill and others, particularly Oleg Jardetzky, had shown some well-resolved lines that were separated by interaction with their unique environment from the broad hump containing the hundreds of unresolved lines. Although the separated resonances of histidine protons usually gave reasonably narrow lines, it seemed as if the large majority

of the proton resonances were too broad to ever be resolved. In one spectacular spectrum after another Bill Phillips's presentation blew away this pessimism and opened a broad, unlimited future of high-resolution NMR studies of macromolecules.

Inasmuch as imitation is the sincerest form of flattery, I can report that I rushed home to Bell Telephone Laboratories to report Bill's results, a story so convincing that Bell Labs authorized us within 10 days to order the second 220-MHz spectrometer. Bill Phillips's 220-MHz spectra were one of the eye openers of my scientific life. He had the vision to convince DuPont to purchase the first of its kind, based upon his earlier studies of nucleic acids and proteins at lower magnetic fields.

During the next several years, the NMR studies by Bill with his long-time collaborator Cam MacDonald dominated the field. Particularly his studies of the paramagnetically shifted resonances in ferrodoxins and cytochrome C set new standards of resolution and elegance. These were supported by two particularly gifted postdocs, Jerry Glickson and Martin Poe.

Retiring as assistant director of research and development in 1978, Phillips returned to his native Missouri and assumed the positions of chair and Charles Allen Thomas professor of chemistry at Washington University, where he led the chemistry department to national prominence. Bill's six-year stint at Washington University led to the rebirth and growth of the Department of Chemistry. He was, however, clearly uncomfortable with the politics and limited resources of the academic environment. In 1984 he returned to the private sector as senior vice-president of research and development at Mallinckrodt, Inc., in St. Louis.

Highly respected internationally as a scientist of the first tier, Phillips was also deeply involved in science policy is-

sues. He was science advisor to governors Bond and Ashcroft of Missouri and president of the Missouri Advanced Technology Institute prior to accepting a role on the Bush administration's Science Advisory Board. Moving to Washington, D.C., he chaired the National Critical Technologies Panel, whose first biennial report, presented to President Bush in 1991, became a blueprint for government action. In clear, lucid, direct prose the report convincingly advocated enhancing and securing for the United States those technologies they identified as critical to national security and economic competitiveness.

His skill as a science and technology advisor was widely recognized, and he served on the advisory committees of numerous academic and governmental programs, as well as on the editorial boards of many prestigious scientific journals. Phillips was particularly active in the science and technology of the St. Louis region, serving on the boards of directors of Mallinckrodt, Inc., Sigma-Aldrich, Inc., the Missouri Corporation for Science and Technology, the St. Louis Science Center, the St. Louis Technology Center, as well as Celgene Corporation of Warren, New Jersey. He was actively pursuing many of these interests at the time of his death.

Friends remember Bill Phillips for his great honesty and integrity and for the encouragement and support he gave young scientists. Phillips was renowned for his far-reaching, global assessments of issues and policies both in and outside the technology arena. There is no secret summary of an individual's life; there are always in any simplified representation loose ends and inconsistencies that multiply with familiarity. But in Bill's life, as known to his professional colleagues and friends, there were two well-characterized directions that he followed, often simultaneously. The first was his thrill in scientific innovation. He loved the first

appearance of a discovery, the observation and explanation of a novel scientific result. He sought new directions such as his NMR results and always reached out beyond what was known to be possible. His novel early discoveries were of shifted resonance in paramagnetic samples, of shifted and well-resolved resonances in biomolecules, and of their dependence on the solution conformation. He was truly delighted by these insights and he unrolled sheets of spectra for visitors like a dedicated oenophile escorting a visitor through his cave or a creative jeweler displaying his rings and necklaces. With his broad happy smile, his cigar, and his sense that these data were a good thing in life, he communicated warmth and pleasure. Beautiful data were not the results of a dedicated attack with modern weapons in the scientific war on nature's heavily guarded secrets. They were the lovely stones picked up on a walk (although too strenuous a walk for many) exploring a new part of the world.

A similar gentle acceptance permeated Bill's other main professional direction. Despite his enduring love of science, because the description above is truly that of love and interest, Bill was continually drawn into a more worldly administrative direction. He went somewhat up the administrative ladder at DuPont, took upon himself the job of synthesizing plant food fit for humans, came back to his beloved Missouri to rebuild the Chemistry Department at Washington University where he served many administrative responsibilities, went to Mallinckrodt as senior vice-president for science and technology and finally went to Washington to serve as associate director of the Office of Science and Technology Policy.

At different times in his life we met and we would talk about new science and the hope of the field we shared. Often Bill would have to express his regrets of not having

been able to commit himself more completely to research. But the demands for his attention to the more administrative responsibilities needed the same somewhat delicately poised curiosity and intellectual ease as scientific research. In no case was it a harsh world, nor a strongly challenging environment, but both to science and to administration Bill Phillips brought a similar sense. They were part of a fine enterprise; they reached out to worthwhile goals; and he could do his share. He never valued his share highly enough. Bill was modest and kind so that the extremes of building a large scientific group to hammer out a field and a career or to fight his way up administratively were not in his lexicon. Bill was pleased that he was able to contribute to what he considered worthy activities, and we who loved him were always thrilled to share with him. These two professional directions brought out similar fine human qualities in him.

Phillips is survived by his wife of 43 years, Esther ("Cherry") Parker, their two children, Katherine Daniels of St. Louis and Edward D. Phillips of Virginia Beach, Virginia, and two grandchildren. His ashes are buried in Kansas City, Missouri.

I WOULD LIKE TO THANK J. J. H. Ackerman and J. Glickson for their helpful suggestions.

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