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Biographical Memoir

We are very grateful to Drs Fowler and Welch as well as the National Academy of Sciences for permission to publish this fine biographical memoir.[1]

J. R. Jones
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Alfred P. Wolf

February 23, 1923–December 17, 1998

A Biographical Memoir by Joanna S. Fowler and Michael J. Welch

ALFRED P. WOLF WAS born in Manhattan on February 13, 1923. Al was the son of Margarete and Josef Wolf, who had emigrated from Germany before World War I. Josef Wolf had been a pastry chef on a German cruise ship, and when World War I broke out his ship could not go back to Germany. So he and Margarete, who was a dressmaker, settled in Manhattan raising Al and his older brother John. Al grew up to be the quintessential New Yorker, drinking in the culture and becoming a connoisseur of food and wine, and the arts. His first love was music; in fact, his chosen profession was to be a concert pianist, but as he would later comment, ''I would go to Carnegie Hall and hear Artur Schnabel play the piano, and I quickly realized that I could never be any good.''

What Al did possess was a keen aptitude for science, particularly chemistry. During his long career, he pioneered the development of labeling techniques that used the reactions of hot atoms (i.e., atoms with very high translational energies produced by recoil from nuclear reactions). He used this as a springboard to develop labeling methods to produce organic radiotracers that enriched the field of nuclear medicine and allowed the field of human neuroscience to germinate and to blossom through the use of positron emission tomography, or PET. He is most well known for the role he played in the development of 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG), a radiotracer that stimulated more than two decades of progress in the use of human neuroimaging to study mental illness. ^{18}FDG remains the most sensitive tracer ever developed to image tumors and tumor metastases, and it has provided the means of directly studying the effects of drugs on the human brain.

Al's education at Columbia College was interrupted by World War II, when at eighteen years of age he enlisted in the army and spent some time working on the Manhattan Project in Los Alamos, where he worked on the initiator of the atomic bomb. While at Los Alamos in 1941–1942, he worked on metal *X* and metal *Y*, which he later found out were uranium and plutonium. His group leader at Los Alamos was Richard W. Dodson, who would later become the first chair of the Chemistry Department at Brookhaven National Laboratory, a new national laboratory established in 1947 and dedicated to the peacetime uses of atomic energy. After the war, Al returned to Columbia to finish

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his education. He joined the group of William Doering as a graduate student and worked on the fenchol β-fenchene rearrangement. In an American Chemical Society symposium honoring Al in 1998, Doering described Al's elegant early mechanistic studies by characterizing him as a man having a ''pride of craft,'' and the only one of his graduate students to have his thesis bound in full morocco leather. He set high standards for himself and for others. It was a pattern that he carried through his entire career.

Al Wolf's early studies involved research on the chemical fate of carbon atoms. Initially in collaboration with Carol Redvanly and R. C. (Andy) Anderson, he produced carbon-14 using the Brookhaven research reactor. He rapidly realized that in producing carbon-14, he was studying not only the chemical fate of the carbon atoms but also the radiation chemistry of the target compound. He continued his work using the 20-minute-half-life nuclide carbon-11, which could be produced with much lower radiation doses even though it challenged the chemist in the analysis of the products. Using carbon-11, Al and his colleagues probed unusual reactions of carbon that were not possible to study by other means at that time. When the research required new analytical tools, Al designed and built them, including a flow proportional counter in 1967 and a GLPC instrument designed for short-lived isotopes in 1969. These studies led in a major way to our understanding of these basic systems.

Al's curiosity also drove him to study other systems, and here he made noteworthy contributions to problems in organic chemistry. He developed non-nuclear techniques to study the chemistry of carbon atoms and in the late 1960s he attacked one of the most challenging problems in organic chemistry, that of the synthesis of tetrahedrane. With colleague Philip Shevlin, he made a significant dent in the problem by demonstrating the probable intermediacy of tetrahedrane in the synthesis. Another highlight in Al's career was his study of the selectivity of the reactions of elemental fluorine with aromatic compounds. With his colleague and close friend Fulvio Cacace, he was able to show that aromatic fluorination with elemental fluorine showed the characteristics of electrophilic substitution of low regioselectivity.

Throughout his career, Al continued to build a strong research group at Brookhaven, and many came from around the world to work with him. This led to what came to be known affectionately as the

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"Wolf Pack," which consisted of Al, a core group of Brookhaven scientists, including David Christman, and an ever-changing group of postdoctoral fellows and students who were stimulated by Al's continual challenges to go beyond observation to understand the phenomena at the fundamental level.

Al carried this challenge more and more into the area of biology and medicine, and by the mid-1960s his fundamental studies had laid the groundwork for the synthesis of simple molecules labeled with the short-lived positron emitters in pure form and high specific activity for tracer applications in medicine using a PET. The chemistry of two of these isotopes, carbon-11 and fluorine-18, became a focus because they lent themselves to incorporation into organic compounds. However, their chemistry was dominated by their short half-lives: carbon-11 has a 20.4-minute half-life and fluorine-18 has a 110-minute half-life. Al and his group precisely measured the excitation functions of many nuclear reactions and produced important medical isotopes, including C-11 and F-18. These measurements on C-11 and F-18, in particular, are standards around the world. In parallel with these measurements Al and his group (including David Christman and Ronald Finn) made a major breakthrough in the development of nitrogen gas targets producing C-11-labeled precursors. The bombardment of nitrogen gas with protons produces carbon-11 and an alpha particle ($^{14}N(p, \alpha)^{11}C$). If nitrogen with a trace of oxygen is bombarded with protons of sufficient energy, C-11 is produced in the chemical form of carbon dioxide. If hydrogen is present during the bombardment, methane is produced. This can rapidly be converted to carbon-11-labeled cyanide in the presence of ammonia and Pt at 1000°C. Al made similar contributions to the development of F-18-labeled precursors and with Richard Lambrecht developed a neon gas target for the production of F-18-labeled elemental fluorine, which was first presented in 1973. Here a target of neon gas is bombarded with deuterons producing F-18 and an alpha particle. When a small amount of fluorine gas is present, F-18-labeled elemental fluorine is produced. Later when F-18 in the form of hydrogen fluoride was needed for the synthesis of high specific activity tracers for neuroreceptor studies, he and Tom Ruth measured the $^{18}O(p,n)^{18}F$ excitation function and with Bruce Wieland developed a small-volume enriched water ($H_2{}^{18}O$) target. Early on, Al became an expert on cyclotrons and generously provided advice to dozens of institutions worldwide that were starting PET programs.

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Interestingly, the basic studies of fluorine-18 not only led to the labeling of biological compounds but also to new knowledge in the area of atmospheric chemistry. Al's long-time friend F. Sherwood Rowland, originally a halogen-hot-atom chemist, used his background in this area to understand the decomposition of ozone by species formed from freon.

Although producing isotopes like carbon-11 and fluorine-18 is a challenge, creating organic compounds from simple labeled compounds like cyanide, carbon dioxide, fluoride, and fluorine gas was an equal problem. To prepare an organic compound labeled with carbon-11 one has about 45 minutes; otherwise all is lost to radioactive decay. Success hinges on the availability of large quantities of synthetically useful labeled precursor molecules. Al's studies gave the organic chemist carbon-11-labeled carbon dioxide and cyanide and fluorine-18-labeled fluoride ion and elemental fluorine from which to synthesize complex radiotracers; this knowledge formed the basis of a new interest in developing positron-emitter-labeled radiotracers so that the tracer method could be applied to visualize biochemical transformations in living systems, including the human body.

Positron decay is at the heart of PET. When a positron emitter decays, it results in the production of two high-energy (511 KeV) annihilation photons emitted at approximately 180 degrees. These are energetic enough to penetrate the body barrier, and they can be imaged using coincident detection. Prototype PET scanners were developed in the early 1960s. By the early 1970s, radiotracer chemistry and PET instrumentation were growing hand in hand with new discoveries in one area, stimulating growth in the other. Al realized that advances in chemistry would be a major driving force in the field, and this drove him to solidify radiotracer chemistry in its own right. He along with several other leading chemists from around the world (Monte Blau, Yves Cohen, Dominique Comar, W. Maier-Borst, Aldo E. A. Mitta, Tadashi Nozaki, Gerhard Stöcklin, Michael J. Welch, and David Silvester) established the International Symposium for Radiopharmaceutical Chemistry for chemists to come together and grapple with the unusual problems of working with very short-lived isotopes at a sub-micromolar reaction scale. The first symposium was held at Brookhaven in 1976; the meeting held every 2 years since, has grown in size and breadth, with an increasing emphasis on understanding and probing the interactions between chemical compounds and living systems, while focusing on the central science, chemistry.

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Al had a passion for knowledge. He believed in the power of the tracer method and he developed the tools to apply it in the human body. At the same time he set the standards for PET research throughout the world. Nowhere is his vision and leadership more powerfully illustrated than in his role in the development of ^{18}FDG in 1976. This was a remarkable collaboration between Al and his group and David Kuhl, Martin Reivich, and Louis Sokoloff. It began in 1973 to develop a method for measuring brain glucose metabolism in the living human. Al successfully led the effort to synthesize 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG). He coined the term "metabolic trapping" as a principle of radiotracer design to describe the trapping of ^{18}FDG-6-phosphate in cells as a marker of glucose metabolism in a paper published in 1978 (*Journal of Nuclear Medicine* 19:1154–1161). The first synthesis of ^{18}FDG was carried out at Brookhaven in 1976 by Tatsuo Ido. It took one half-life (110 minutes), and the product was flown by private plane to the University of Pennsylvania, where the first brain and body images were made on the Mark II scanner developed by David Kuhl. This was the very first time that brain glucose metabolism was mapped in the living human. This is well recognized to have been a watershed in the current worldwide growth of PET for basic and clinical research and diagnosis. Al went on to push the use of ^{18}FDG and other radiotracers in neurology and in psychiatry (with New York University colleagues Jonathan Brodie, Tibor Farkas, and Mony DeLeon). The fruits of his efforts abound, including an internationally recognized research program in imaging in substance abuse research at Brookhaven.

Al derived great satisfaction from teaching, and for 30 years (1953–1983) he taught organic chemistry at night at the Columbia University School of General Studies. Though this involved a long trek from Brookhaven, which is about 60 miles east of New York City, the environment and energy of the city and his strong rapport with students were powerful reinforcers. Though he bemoaned the fact that a majority of the students were pre-med candidates, when bright students were challenged to pursue chemistry, Al happily declared victory. He also enjoyed his group at Brookhaven, holding wine tastings, walking tours of New York City, and ski trips to Vermont. He was an extraordinary travel guide, and it was not unusual for members of the Chemistry Department to seek his travel advice and to use his extensive collection of maps of cities throughout the world.

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Al's favorite city was Rome, and he had a passion for all things Italian. In 1969, when he began consulting for the National Research Council of Italy, he learned Italian and on more than one occasion prepared pasta and espresso for the group in the chemistry laboratory at Brookhaven. Though Al loved cities, he also appreciated the wilderness, including hiking, rock climbing in California, and camping in the Adirondacks. He never compromised on food, however, and carried fresh eggs packed in a special padded egg case on his mountain treks. No matter where he was in the world, Al could be counted on to seek out the finest restaurants, museums, music, ballet, or architecture.

Not surprisingly, Al Wolf received many honors during his long career at Brookhaven. He was a member of the National Academy of Sciences (elected in 1988). He received the Nuclear Chemistry Award of the American Chemical Society (1971), the Society of Nuclear Medicine Paul Aebersold Award (1981), the Hevesy Nuclear Medicine Pioneer Award (1991), and the Melvin Calvin Award of the International Isotope Society (1997), to name a few. He chaired the Chemistry Department at Brookhaven from 1983 to 1987. During his long career, he published over 325 papers on basic and applied research in chemistry and nuclear medicine.

Al was not only a strong scientific leader and a mentor to many; he was also our friend. Those of us who knew him well also appreciated his passion, his drive, and his willingness to stand up and fight for what he believed. We could not imagine a stronger or a more articulate ally. Though he left us with much new knowledge, more importantly, he left us with the tools to grow more knowledge. He stimulated and inspired the dozens of scientists around the world who worked with him over the years. Indeed most of the world's cyclotron-PET centers have one or more individuals who, to their great advantage, spent part of their careers at Brookhaven working with Al Wolf.

Al died on December 17, 1998, after a long illness. His wife, Elizabeth (Helga), died in April 1998. He is survived by his son, Roger, an architect living in Santa Monica, California, and two granddaughters, Allison and Madeline. He is sorely missed by his friends throughout the world.

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