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Editorial

John W. Daly (1933−2008)

John William Daly was born in Portland, OR, on June 8, 1933. He obtained his B.S. from Oregon State College in 1954, and his M.A. the following year with Bert Christensen on the synthesis of purine and pteridine alkaloids. His Ph.D. work was done at Stanford University with Richard Eastman, studying the terpenes of peppermint oil. Upon its completion John accepted an NIH postdoctoral position with Bernhard Witkop in the Laboratory of Chemistry at the National Institute of Arthritis and Metabolic Diseases (NIAMD). John was soon appointed to the permanent staff and became the founding Chief of the NIAMD-derived Laboratory of Bioorganic Chemistry in 1981. He served as LBC Chief (now in NIDDK) until stepping down in 1997 and becoming NIH Scientist Emeritus in 2003. A testament to John's tireless enthusiasm for solving those scientific problems that still captivated him, he "retired" in 2003 so as to focus more intently on doing research, publishing 45 papers between 2003 and his passing on March 5, 2008. His works continue, with 14 scientific papers published posthumously and more in preparation. In all, John authored or coauthored over 700 papers in chemistry, ecology, and pharmacology, including 22 in the *Journal of Natural Products*, one a comprehensive review describing over 800 amphibian alkaloids.[1a] John was also active in the ASP, serving on numerous committees and on the editorial board for the *Journal of Natural Products*.

The nature of science is collaborative, and John had many collaborators, more names than would fit in this space. These led to some of his most impactful discoveries. The unique environment at NIH served John well, with many experts a short walk from his office. While a postdoctoral fellow, John worked with pharmacologist Julius Axelrod on catecholamines, determining the mechanism of methylation with *S*-adenosylmethionine. Collaboration with Sidney Udenfriend, Don Jerina, and Gordon Guroff led to the discovery of the "NIH-shift", a rearrangement in aromatic hydroxylation via an arene oxide.[2] This process is a major pathway in carcinogenesis caused by polycyclic aromatics. Work with Solomon Snyder led to the discovery that caffeine inhibited adenosine receptors and opened up the area of purinergic receptors along with collaborator Kenneth Jacobson.[3]

John was considered a world expert on the pharmacology of caffeine and xanthines. John and Kenneth Seamon determined the mechanism of action of the *Coleus* diterpene forskolin as activating adenylate cyclase, leading to further collaboration with Philip Skolnick and Joachim Schultz on cyclic-AMP as a second messenger.[4] Fabian Gusovsky, Cyrus (Bob) Creveling, Kenneth Kirk,

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Edson Albuquerque, and many others worked with John on a variety of pharmacological questions, many involving natural products such as the alkaloid reserpine[5] and the polyether maitotoxin.[6]

John was both a chemist and a pharmacologist. His fascination with the chemistry and biology of bioactive natural products took him in many directions. Perhaps his most well-known natural products work began when he was sent to obtain additional extracts of skins of the frog *Phyllobates aurotaenia* that the Chocó tribe in Colombia used to poison blow darts. The active principle, an alkaloid later named batrachotoxin, had been isolated, purified, and characterized in 1963 by Witkop postdoc Fritz Märki, working with field biologist Martè Latham.[7a] The structure was determined in 1968 with chemist Takashi Tokuyama and crystallographer Isabella Karle.[7b] Subsequent collaboration with herpetologist Charles Myers led to novel alkaloids from many dendrobatid species. The frog alkaloid program blossomed over four decades, producing hundreds of papers on the chemistry and biology of alkaloids from poison frogs. Over 800 compounds have been described in 20 structural classes from four worldwide anuran families.[1a] Together with several key collaborators, John demonstrated that most are sequestered from their arthropod diet, although a few are biosynthesized or modified by the frogs.[8]

It is also remarkable to note that many of these findings were revealed from experiments that were more often than not taking place in the terraria in John's office, where he maintained many amphibians over the years, performing various feeding and alkaloid retention studies. Indeed, it was a pleasure to go into John's office for a discussion and hear the trills of various species he had under study. The diverse structures and biological activities of the alkaloids from these frogs have attracted the interest of pharmacologists, ecologists, and synthetic/medicinal chemists. This work was done largely in collaboration with chemists Thomas Spande and Martin Garraffo and biologist William Padgett, who made up the core of John's laboratory, along with many students, technicians, and postdoctoral fellows. John was dedicated to mentoring and gave candid and earnest advice. He cared both about what his people worked on and how they developed as scientists. He even went so far as to pay from his own pocket for a former postdoctoral fellow to attend a meeting at which John received the Schwarting Award from ASP, because the fellow had been a coauthor on the paper and he wanted to help his career. John was easy to talk to and was eager to share his knowledge and insights. As Martin Garraffo put it, "You could milk the guy (for information) and he would love to be milked." John admired Julius Axelrod and particularly his precept of performing simple experiments that gave useful results, a guide that he applied to his own work. John was also committed to a leadership role as Chief of the Laboratory of Bioorganic Chemistry, showing strong support for incoming investigators and facilitating research for all LBC members. John believed in the importance of serendipity in science. Today's emphasis on applied, hypothesis-driven research sometimes regards curiosity-driven natural products work as mere "fishing". However, John believed that this is precisely how new compounds and new activities are found, often with properties that change prevailing biological paradigms. John's work with Spande, Garraffo, Barbara Badio, and Michael Edwards on epibatidine is a case in point.[9] Epibatidine was identified by its production of a Straub-tail response in mice, a classical test for opiates. However, the response was blocked by the nicotinic antagonist mecamylamine and not the opiate antagonist naloxone. Its potent analgesic properties reinvigorated nicotinic-receptor pharmacology. Epibatidine and histrionicotoxin provided pharmacologic tools for the characterization of nicotinic receptors,[9b] while batrachotoxin and the pumiliotoxins are important probes for sodium channels.[7c] Labeled versions of these alkaloids are used for visualization and quantification of their biological receptors in cells and tissues. These compounds and others continue to be enabling tools for pharmacology and drug development, and more are likely to follow from John's great body of work.

John was a fisherman, literally and figuratively. He particularly enjoyed billfishing, having caught many species over the years. He had planned to fish for striped marlin in Hawaii during the 50th anniversary meeting of the ASP, which he of course did not make. John and Rick Fitch were politely ejected from the golf course at the 2004 International Congress on Natural Products Research in Phoenix for fishing the water hazard. John made arrangements to fish at nearly any speaking engagement he accepted. When on collecting trips in Central and South America, John often fished during what little free time was available, sometimes catching peacock bass or dorado. On his door was a note that said "Walk softly and carry a big fish". Whether pursuing billfish or new discoveries, he demonstrated amply that if one knows where and how to fish, it can be a very productive enterprise.

John's contributions to natural products chemistry and pharmacology have been recognized with numerous awards, including Research Achievement (1997) and Arthur E. Schwarting (2003) Awards from the ASP, the Ernest Guenther Award in Natural Products Chemistry from the ACS in 2003,[1b] and the Karl Wilhelm Scheele Award from the Swedish Academy of Pharmaceutical Sciences in 1999. John was also elected as a member of the National Academy of Sciences in 1997.

John is survived by two daughters, Kathryn Daly and Shannon Ostrander, his sister Hildred Powers, and his life partner, Kathleen McKnight.

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