Martha Vaughan

1926–2018

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

MARTHA **VAUGHAN**

August 4, 1926–September 9, 2018

Elected to the NAS, 1985

By Joel Moss, Edward D. Korn, Christopher Wanjek, and Michael Gottesman

Martha Vaughan, a pioneering biological researcher, conducted some of the earliest investigations into insulin signaling—which helped to define the insulin receptor—and then spent six decades largely focused on G proteins and how they regulate metabolism. These ubiquitous and functionally diverse cell-surface proteins are involved in a multitude of cellular pathways and are the targets for insulin, epinephrine, and a host of other signals. In this way, Vaughan's work influenced numerous domains of biomedical research.

Vaughan earned a bachelor of philosophy degree from the University of Chicago in 1944 and an M.D. from the Yale School of Medicine in 1949. She began her research career as a postdoctoral fellow in Yale's Department of Physiological Chemistry and then interned at New Haven Hospital. In 1951, she joined the Department of Research Medicine at the University of Pennsylvania. The following year she moved to the Laboratory of Cellular Physiology at the National Heart Institute—later the National Heart, Lung, and Blood Institute (NHLBI)—where she served for the remainder of her professional life.

Soft-spoken and unassuming, Martha Vaughan exhibited a demeanor that never masked her prowess as a scientific dynamo, a pioneering female scientist, and an ardent advocate for human rights. Her remarkable research career spanned more than 65 years at the National Institutes of Health, where, in addition to making a string of seminal discoveries, she mentored dozens of post-doctoral scientists who went on to illustrious scientific careers themselves, including Nobel laureate Ferid Murad and numerous NAS members. Indeed, Martha touched, mingled with, or collaborated with some of the greatest biochemistry researchers of the 20th century—all the more remarkable for someone born of modest means in the rural Midwest on the eve of the Great Depression.

Martha was born in Dodgeville, Wisconsin, on August 4, 1926. Her father, who left school at age 11 to help support his family, being the eldest of nine children, was a

self-educated lover of opera and reading. Her mother, before marriage, taught children whose fathers were immigrant workers in the open-pit iron mines of the Mesabi Range in northern Minnesota. Martha's earliest years were spent in Shorewood, Wisconsin, just north of Milwaukee, until the Depression left her father, then working as an accountant, unemployed. Martha's family moved often over the next decade, to wherever work was available. Soon after WWII, the family returned to a more settled existence, back to Shorewood, where Martha started eighth grade, having attended four different schools in four years.

Some of Martha's best-known traits were cemented during these early years. Her father, too, was modest and reserved, a hard-working man of few words. Her mother was a progressive spirit who inspired Martha's concern for human rights. Martha's one element of continuity during a decade-long transiency was her cello playing, a talent she would nurture for many decades as an amateur player of chamber music and co-coordinator of a classical music series at the NIH.

Martha earned her bachelor's degree from the University of Chicago in 1944, part of a cohort of stellar female scientists that included the geneticist Janet Davison Rowley. In 1949, she received her M.D. from the Yale School of Medicine and soon began a career in research as a postdoctoral fellow in Yale's Department of Physiological Chemistry. It was at Yale that Martha revealed a commitment to human rights, joining the Yale chapter of the Association of Internes and Medical Students (AIMS), which concerned itself with progressive issues at that time, such as universal health insurance, racial equality in medical education, vivisection, and the draft.

Also at Yale, Martha formulated what she described as simple "medical school-type questions" about dietary fat in diabetes that, in retrospect, can be appreciated as perceptive and sagacious.[1] Alfred Wilhelmi, then an associate professor and rising star in the field of endocrinology, appreciated Martha's insight and offered her laboratory space in the Department of Physiological Chemistry. Martha's data revealed major derangements of lipid metabolism in diabetes. Metabolic regulation and hormone action quickly became of primary scientific interest to her. While at Yale, she met and was courted by a charismatic metabolism researcher named Jack Orloff. They married in 1951.

Another Yale luminary, John P. Peters, chief of the Metabolic Division of the Department of Medicine from 1922 to 1955, urged Martha to join the laboratory of William C. Stadie at the University of Pennsylvania. (Peters was an advocate for national health

insurance who later would be persecuted for alleged disloyalty to the United States during the McCarthy era—and subsequently exonerated. Peters's loyalty case, which rose all the way to the U.S. Supreme Court, also would have a profound effect on Martha's activism and her support for outspoken, socially minded citizen scientists.)

After completing an 18-month medical internship at New Haven Hospital in 1951, Martha joined the Department of Research Medicine at the University of Pennsylvania in Philadelphia. There, Stadie and Neils Haugaard, a Danish researcher in his lab, had indirect evidence of insulin binding to rat diaphragm muscle and wanted to study this binding directly. Martha did so using ^{131}I- and ^{35}S-labeled insulin.[2] The trio quickly realized, however, how challenging it was to adequately characterize labeled insulins when the structure of native insulin was itself unknown.

Martha would need to learn more about protein structure and metabolism, and she turned to none other than Christian Anfinsen. Anfinsen had a lab at the NIH, in what was then called the National Heart Institute (NHI), created in 1948. Martha had a connection there through her husband, who had joined the NHI Laboratory of Kidney and Electrolyte Metabolism in 1950. With his help, Martha by 1952 found her way to Anfinsen and the NHI Laboratory of Cellular Physiology. Martha worked closely with with Anfinsen, who would become known for his study of the essential building blocks for making proteins and their 3-dimensional folding, which earned him a Nobel Prize in 1972. Specifically, Martha collaborated with Anfinsen and Daniel Steinberg, also newly arrived at the NHI, on studies of amino acid analogs related to the specificity of protein synthesis.[3] Later, she and Steinberg became the first to characterize hormone-sensitive lipase in adipose tissue and its key role in controlling rates of free fatty acid mobilization.[4] Upon becoming an independent investigator in 1954, Martha joined the U.S. Public Health Service (PHS), a uniformed-service division within the Department of Health and Human Services. The PHS enabled Martha to continue her full-time basic research at the NIH while offering her the opportunity to provide humanitarian aid and public health service during times of crises. Martha advanced in rank during her 35-year service from senior assistant surgeon to medical director.

Also during these heydays of the 1950s at the NIH, Martha was well embedded in what was later recognized as the dynasty of NIH Building 3. She worked as an equal among an elite core of researchers, a mind-boggling collection of scientific talent that included the aforementioned Anfinsen as well as Julius Axelrod, Robert Berliner, Robert Bowman, Nina Braunwald, Bernard Brodie, Donald Fredrickson, Leon Heppel, Edward Korn,

Arthur Kornberg, James Shannon, Thressa and Earl Stadtman, and James Wyngaarden. Of the 82 doctoral-level scientists in Building 3 in this period, 27 became members of the National Academy of Sciences and three—Anfinsen, Axelrod, and Kornberg—became Nobel laureates. Martha later recalled Building 3 as also being home to lab animals that included cats, dogs, cows, pigs, sheep, and chickens. It was not uncommon for Martha to ride the elevator with four-footed and winged colleagues. (The ventilation system, unfortunately, was not so accommodating. "When anybody used the vent hood downstairs to carry away noxious fumes, they would let us know," Martha said.[5] The warning alerted her to turn off the air conditioner, which would have sucked the fumes into her lab.)

It's worth noting here that Martha and Jack were one of the great "power couples" at the NIH, along with Terry and Earl Stadtman, Nina and Eugene Braunwald, Herb and Celia Tabor, Ruth Kirschstein and Alan Rabson, and a few others. While it is common to see married couples in the same workplace today, anti-nepotism rules before the 1960s made it difficult for scientific couples to perform research in the same institution or university. Martha's success as a scientist demonstrated that welcoming scientific couples made for good science, and that message spread nationwide.

Martha also quietly, unintentionally, but nevertheless substantially, inspired a generation of young female scientists who would strive for leadership positions. She was a great female scientist at a time when too few women were choosing, or were able to choose, careers in science. She was among the first female lab chiefs at the NIH. She rose to the rank of head of the Section on Metabolism in the Molecular Disease Branch of the National Heart and Lung Institute (NHLBI) in 1968; then chief of the Institute's Laboratory of Cellular Metabolism in 1974; then deputy chief of the Institute's Pulmonary-Critical Care Medicine Branch in 1994. During the 1950s she gave birth to three boys, who would later recall their mother squeezing the most out of the 24-hour day, reading journal articles during her boys' school pickup, music lessons, or choir practice at Washington's National Cathedral, and relaxing very late at night with a non-scientific book and a glass of scotch.

Martha noted being "enormously indebted" to Christian Anfinsen, with whom she would maintain a lifelong friendship. But by the close of the 1950s, she would move away from protein function and toward adipose tissue metabolism and the hormonal control of lipolysis, the first step in the direction of cyclic nucleotides that would define her research career.[6] Around 1958 Robert Gordon, also in Anfinsen's lab, had shown

Martha "at home" in her lab.
(Photo Hank Grasso, NIH.)

that epinephrine increased the release of free fatty acids from adipose tissue.[7] Martha soon found that glucagon did so, too. She had been investigating the action of oral hypoglycemic agents such as tolbutamide, focusing on their inhibition of epinephrine-induced glycogenolysis in liver.[8] With prostaglandins provided by Sune Bergström, another future Nobel Prize winner, Martha's research group demonstrated the antilipolytic action of prostaglandin El and inferred that it also might act through cyclic adenosine-3,5-monophosphate (cAMP).[9]

Martha continued this line of research on adipose tissue metabolism with an emphasis on lipolysis and the hormone-sensitive lipase until 1968. Then, with a postdoc in her lab named Ferid Murad and a new NIH recruit named Vince Manganiello, Martha turned her attention to the control of cAMP content in fat cells and its relationship to lipolysis. In the ensuing years, with many collaborators, she investigated cAMP in polymorphonuclear leukocytes as related to phagocytosis and glycogen metabolism and found several agents that increase cGMP in leukocytes and also enhance their chemotactic responsiveness. In the ensuing years, with many collaborators, she investigated cAMP in polymorphonuclear leukocytes as related to phagocytosis and glycogen metabolism and found several agents that increase cGMP in leukocytes and also enhance their chemotactic responsiveness. In the ensuing years, with many collaborators, she investigated cAMP in polymorphonuclear leukocytes as related to phagocytosis and glycogen metabolism and found several agents that increase cGMP in leukocytes and also enhance their chemotactic responsiveness. In the ensuing years, with many collaborators, she investigated cAMP in polymorphonuclear leukocytes as related to phagocytosis and glycogen metabolism and found several agents that increase cGMP in leukocytes and also enhance their chemotactic responsiveness.e such agent, ascorbic acid, turned out to be of particular clinical interest to Martha. With John Stoner and Manganiello, she found that bradykinin might act through cGMP, foreshadowing Murad's Nobel-winning work.[10] These early 1970s experiments also yielded indirect evidence that agents such as

bradykinin, which caused accumulation of cGMP, increased prostaglandin synthesis in the lung and are involved in the critical physiological contraction of the umbilical artery at birth.[11]

By the end of the 1970s, much of Martha's work was related to choleragen, or cholera toxin, launching what would become a decades-long collaboration with Joel Moss, a physician scientist who was then a research associate and pulmonary fellow at NHLBI. Together they discovered that cholera toxin exerted its effects on mammalian cells by adenosine diphosphate (ADP) ribosylation, the transfer of an ADP-ribose group from nicotinamide adenine dinucleotide (NAD) to an acceptor molecule.[12] They later discovered that mammalian cells contain endogenous enzymes with activities that mimic the ADP-ribosyltransferase activity of cholera toxin. Martha was way ahead of the curve on her cholera research, using adipose tissue instead of intestinal tissue. The editors of *Nature* were not at all convinced by her unconventional approach but eventually acquiesced and published what is now considered a landmark paper in 1970![13]

Martha's subsequent work over the 1980s and 1990s would focus on ADP-ribosylation factors, a family of low-molecular-weight guanine-nucleotide-binding proteins that activate cholera toxin and modulate intracellular vesicular transport, and also BIG1 and BIG2, which are two guanine-nucleotide-exchange proteins.[14] She and her colleagues demonstrated that BIG1 and BIG2 function as A-kinase anchoring proteins (AKAPs), suggesting a mechanism for BIG1 and BIG2 to serve as a node for "cross-talk" between cAMP-signaling pathways and guanine-nucleotide-binding-protein signaling pathways, including vesicular transport. Her research on cholera toxin and ADP-ribosylation came to define the field, ultimately leading to her election to the National Academy of Sciences in 1985, the citation for which reads: "Vaughan's pioneering studies on adipose tissue metabolism, her elucidation of the mechanism of action of cholera toxin on the adenylate cyclase system, and her brilliant work on the phosphodieseterases have had a major influence of current concepts of metabolic regulation."[15]

On the basis of Martha's half-century-long research career, and on the occasion of her approaching 75th birthday, the NHLBI held a two-day symposium in her honor in 2001—an event that would draw no fewer than three Nobel laureates as speakers, including Ferid Murad and Martha's friends and collaborators Alfred Gilman and Joseph Goldstein. It was a great time and nice tribute to someone many assumed to be in the winter of her research career. Little did her colleagues imagine that she still would have more than another decade ahead of solid research findings, such as how the G protein

activators BIG1 and BIG2, discovered in her lab, regulate cell migration in wound healing.[16] She also investigated the control of intracellular vesicular trafficking by ADP ribosylation factors (ARFs), a family of low-molecular-weight G proteins, and their regulatory partners.[17]

Martha authored or co-authored more than 365 papers and book chapters and was a generous citizen-scientist, serving in editorial positions with several research journals, including more than 20 years with the *Journal of Biological Chemistry*. At the NIH, from 1979 to 2007, she was a board member and, for two of those years, president of the Foundation for Advanced Education in the Sciences, an NIH-associated private organization that sponsors academic courses, job-related training, cultural events, and other services for NIH staff.

Upon her election to the NAS Martha became a correspondent of the Academy's Committee on Human Rights and then served on the committee from 1992 to 1998. During this time, she supported individual scientists subjected to human rights abuses as a result of their professional activities or for having peacefully spoken out about injustice within their societies. This is best reflected in her advocacy for people disappeared and presumed dead in Guatemala. The Guatemala efforts, spurred in part by the horrendous stabbing death of anthropologist Myrna Elizabeth Mack Chang by a military death squad, represented a new kind of undertaking for the committee: dealing not with prisoners of conscience, often tortured and lingering in jails, but rather with victims who have been murdered.[18] Martha was instrumental in helping the NAS committee in this new direction and ultimately obtaining posthumous justice for Myrna Mack and many other victims. Quiet, firm, persistent, and detail-oriented, Martha worked in harmony with the committee's non-confrontational, behind-the-scenes advocacy. She supported the committee for more than 32 years.

Martha retired from the NIH in 2012 and was named NIH Scientist Emerita, a position that allowed her to continue her scientific pursuits and her mentoring, which she cherished above all. Many of the stories of Martha Vaughan and Jack Orloff center on the cigar-chomping, insult-flinging, larger-than-life character Jack, who died in 1988. As the saying goes, opposites attract. Jack adored Martha, and many of us saw her as the yin to Jack's yang. But Martha was a spirited individual, herself. Three anecdotes uniquely speak to Martha's personality. One, recounted by many of her postdocs, concerns the red ink that was actually red pencil. Martha was a thorough and aggressive editor who filled

her postdocs' manuscripts with insightful commentary in red. But the red was in pencil, oddly enough, and not ink, perhaps a metaphor for Martha's pursuit of clarity without shouting — "Speak softly and carry no stick," as her NHLBI colleague Rodney Levine said at Martha's memorial symposium in 2019.

There are several stories of Martha as a survivor: socially (a female in a male-dominated field), physically (breast cancer in the late 1950s), and emotionally (death of her middle child, David, in 2015). Among her more cataclysmic trials was a traumatic brain injury from a fall in the 1990s that left her in a coma for several days. She was nearly 70 years old; and although tough, she wasn't of a particularly robust physical nature. She was recently widowed, as well. Doctors were convinced she'd never regain her cognitive abilities. Friends and colleagues at the NIH also were unsure. Long-time NHLBI collaborator Ed Korn went to visit her in the hospital and found her casually reading a newspaper…upside-down. She was faking it, you see, pretending she could read and not wanting anyone to worry about her condition. We can relay this now as a funny anecdote that captures Martha's spirit, although it was worrisome then, for sure.

A few years after this, a terrific derecho windstorm blew over a massive tree, which smashed Martha's house and car. This was on a Friday. On Saturday, she bought a new car and found an apartment to rent; on Monday, she was back at work with hardly a word to say about the "tough" weekend. She never did return to that house. Eyes focused forward.

Like many great scientists who spend their entire career at the NIH, Martha possessed a quiet humility that concealed her immense contributions to the field of biochemistry. She made lasting contributions toward understanding fundamental signal transduction mechanisms. Modest, unpretentious, dignified, and confident, she was omnipresent in the corridors of the NIH and a guiding voice in the larger biochemistry field for more than 65 years, a truly remarkable person that no one who had the honor to know her will forget. She breathed her last on September 8, 2018.

ACKNOWLEDGMENTS

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