Eugene Patrick Kennedy, 1919–2011

William T. Wickner[1]

Department of Biochemistry, Dartmouth Medical School, Hanover, NH 03755-3844

Eugene Patrick Kennedy died peacefully at his Cambridge home, age 92 years, on September 22, 2011. He was a giant of 20th century biochemistry, and his pioneering studies of lipid biosynthesis and function were a foundation of modern cell biology. He was also a man of immense intellect and genuine modesty, a devoted teacher who inspired his many students and colleagues, and a loving father, grandfather, and friend.

Gene was born September 4, 1919, the fourth of five children of Irish immigrant parents. His early formal education was in the Catholic schools of Chicago, but his real education was from the public library, where he developed an early passion for reading. "While still in grammar school, I happily read my way through a ton of junk," he later wrote (1). After majoring in chemistry at DePaul University, he enrolled as a full-time PhD student in organic chemistry at the University of Chicago while starting full-time work at Armour & Co., joining a wartime effort to fractionate plasma for the battlefield. Assigned to a new facility in Texas for the industrial-scale fractionation of human plasma, he was joined by his college classmate and coeditor of the student newspaper, Adelaide Mjewski (Fig. 1). They wed on October 27, 1943, and had daughters Lisa (1950), Sheila (1957), and Katherine (1960).

With the war's end, Gene returned to Chicago for doctoral studies in Biochemistry, joining the Lehninger laboratory to study fatty acid oxidation in 1947. There, he made the landmark discovery that the tricarboxylic acid cycle, oxidation of fatty acids, and oxidative phosphorylation all occur in mitochondria. After short postdoctoral studies (with Horace Albert Barker at Berkeley studying β-oxidation of fatty acids and with the legendary Fritz Lipmann at the Massachusetts General Hospital studying the activation of acetate by CoA), he returned to Chicago and joined the faculty of Charles Huggins' Ben May Laboratories for Cancer Research at the University of Chicago.

Kennedy's new laboratory focused on the formation of the phosphoanhydride bond between choline and phosphatidic acid to yield lecithin. He found, as did Arthur Kornberg, that cell extracts could catalyze this reaction if given high concentrations of ATP. Because the reaction only occurred with some commercial preparations of ATP but not others, Gene reasoned that a contaminant might be responsible, leading to his seminal discovery (2) that CTP and choline formed CDP-choline, the proximal choline donor to phosphatidic acid. This CDP-linked activation of alchohols or diglyceride is the heart of the biosynthetic Kennedy pathway of phosphoglyceride biosynthesis in mammalian cells (Fig. 2) and the similar pathway in bacteria.

Fig. 1. Gene and Adelaide Kennedy, Cape Cod (photo courtesy of the Kennedy family).

In 1959, he accepted the Hamilton Kuhn Professorship of Biological Chemistry at Harvard Medical School and embarked on the quest to purify membrane proteins. Gene's first love in this endeavor was the lactose permease, dubbed the M (membrane) protein. He devised an elegant double-label method to identify the M protein based on the protection of its unique cysteinyl residue from *N*-ethylmaleimide by bound substrate, thiodigalactoside. It fell to Wilson and others to later isolate the active protein, but a generation of Kennedy laboratory acolytes, purifying more tractable membrane proteins, found that Gene's response to all reports of promising steps was, "I wonder what that would do for the M protein."

By the mid-1960s, Kennedy's laboratory at Harvard had hit full stride, with Phyllis Elfman in the office scrutinizing each expenditure with care, Marilyn Rumley in the near laboratory outside the office doing Gene's experiments and keeping the prized collection of detergents, and a steady flow of graduate students, postdoctoral fellows, and even medical students in the middle and far laboratories. Kennedy taught us all through his simple formulation of questions, an insistence on clear, complete, and simple protocols, looking at the primary data, and maintaining a balanced perspective between the question being addressed and the details of each step. Above all, Gene suffused his laboratory with his devotion to science and his personal kindness to each person. One night, after 24 hours of work purifying phosphatidylserine decarboxylase from the membranes from a 100-lb block of frozen *Escherichia coli*, I picked the lock on Gene's office door and lay down on the couch for a catnap, setting a 2-hour windup alarm clock on the floor near my ear. When I awoke, there was sunlight streaming in the window, the clock had gone off hours before, and Gene

Author contributions: W.T.W. wrote the paper.

The author declares no conflict of interest.

[1]E-mail: Bill.Wickner@Dartmouth.edu.

www.pnas.org/cgi/doi/10.1073/pnas.1117398108

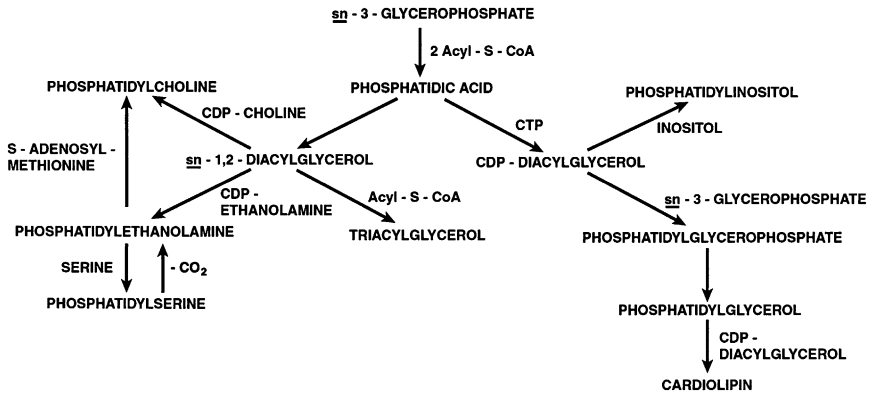

Fig. 2. The Kennedy pathway of lipid biosynthesis in mammalian cells.

Lessons I Learned from Eugene Kennedy

Discovery of novel composition and function takes priority.
Development of in vitro assays in crude systems is crucial.
A clever experiment is worth more than a piece of equipment.
Curiosity driven research generates the best science.
It helps to sprinkle ideas around the lab in an informal way.
Every person has their own project and can talk about it.
Scientific criticism is not personal; everything is on the table.
People move on to their next position in a timely manner.

Fig. 3. From Chris Raetz as presented at the Kennedy 90th birthday Festschrift.

was towering over me, smiling broadly. "How's the prep going?" he asked, as I staggered off the couch, stammered an apology, and fled. He never asked how I got into his office.

One measure of the devotion of Gene's alumni is that three Festschrifts were organized to honor his 65th, 70th, and 90th birthdays. The first Festschrift, at Woods Hole, included Gene's own advisors, Al Lehninger and Fritz Lipmann. Lehninger was still productive and gave a masterful presentation, but it was the elderly Lipmann who stole the show. Short and frail, his talk was not sentimental but immediately focused on his recent studies of protein sulfation. He concluded that he was getting on in years and now worked alone, and he thanked Woods Hole for laboratory space and the National Science Foundation for support. Just imagine—Lehninger, Lipmann, and Kennedy all together—we were in the presence of the Gods of Biochemistry, and we knew it. The second Festschrift was at Princeton, and Gene spoke to us of remaining true to the science and the people in our laboratories, while steering our ships to avoid the Scylla and Charybdis of seeking honors or administrative positions.

Gene quietly closed his laboratory in 1993, with Marilyn still there to help him on the last day. After Adelaide passed away in 1999, Gene focused entirely on family, teaching chess to each grandchild and inspiring their interest in math and science; however, the alumni would not let go. The third Festschrift, in honor of Gene's 90th birthday, was held in Boston 2 years ago. Speakers, reflecting now on their own careers and lives and the lives of laboratory mates of their era, recounted the early years in Chicago as students (Talalay), the Kennedy Chicago laboratory in the 1950s (Paulus), and Boston in the 1960s (Chang) and beyond (Geiger, Raetz, and Snider). Chris Raetz, perhaps Gene's favorite student and then in his own battle with illness (3), traced the fate of each project from the Kennedy laboratory of the early 1970s and each laboratory mate, concluding with the inimitable lessons learned from Gene for a life in science (Fig. 3).

These timeless lessons are as great a legacy as Gene's own remarkable discoveries. He was an unabashed advocate for small, low-technology, question-driven science. Gene focused on only a few young students and fellows at a time, encouraging their initiative and direction but always eager to sit down together to go over the data and plan more experiments. The warmth that he lavished on his family spilled over to his laboratory family, with memorable summer parties in Woods Hole. He has been a unique role model to his students and fellows as well as his peers.

Kennedy was elected to the National Academy of Science and the American Academy of Arts and Sciences and was the recipient of the University of Chicago Distinguished Service Award (1966), The Gairdner Foundation International Award (1976), The Heinrich Wieland Prize (1986), and The Rose Award from the American Society for Biochemistry and Molecular Biology (1992). His science is for the ages, and his warmth, humor, and kindness live on in his many students and his family. He is survived by his three daughters and their families: Sheila Kennedy, professor of architecture at Massachusetts Institute of Technology, and her husband Frano Violich, both of their architecture firm KVA; Lisa Kennedy Helprin, a lawyer, and her husband Mark Helprin, a writer; and Katherine (Kit) Kennedy, an environmental lawyer, and her husband Matthew Diller, Dean of the Cardozo School of Law; as well as six grandchildren, Olivia Hodes, Alexandra Helprin, Ava and Francesca Violich, and Michael and Peter Diller.

1. Kennedy EP (1992) Sailing to Byzantium. *Annu Rev Biochem* 61:1–28.
2. Kennedy EP (1989) Discovery of the pathways for the biosynthesis of phosphatidylcholine. *Phosphatidylcholine Metabolism*, ed Vance D (CRC, Boca Raton, FL), pp 1–8.
3. Wickner WT, Stubbe J, Hirschberg CB, Garrett T, Dowhan W (2011) Chris Raetz, scientist and enduring friend. *Proc Natl Acad Sci USA* 108:17255–17256.