Thressa C. Stadtman

1920–2016

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

THRESSA CAMPBELL **STADTMAN**

February 12, 1920–December 11, 2016

Elected to the NAS, 1981

Terry Stadtman

By Vadim N. Gladyshev, P. Boon Chock, and Rodney L. Levine

Thressa C. Stadtman was a trailblazer in research on anaerobic electron transport, vitamin B_{12} metabolism, and selenium biochemistry. For her doctoral thesis work, she investigated the mechanisms of methane fermentation mediated by extracts from two anaerobic microorganisms, *Clostridium sticklandii* and *Methanococcus vannielii*, which she isolated from mud that she scooped up from the San Francisco Bay (1, 2). These two microorganisms defined her entire career, as she used them to identify new B_{12} coenzyme-dependent enzymes that catalyzed intermediate steps in the anaerobic conversion of lysine to fatty acids and ammonia, and later to identify selenium-dependent enzymes and seleno-tRNAs, during her studies at the National Institutes of Health.

Stadtman received a B.S. in bacteriology in 1940 and an M.S. in 1942, both from Cornell University. She earned her Ph.D. from the University of California, Berkeley, under the guidance of Horace Barker, who discovered the active form of B_{12}. After graduating in 1949, she did a postdoctoral stint at Harvard. In 1950 she moved to NIH's National Heart Institute, where she continued her research until her retirement in 2009.

Thressa "Terry" Campbell was born in 1920 in Sterling, New York, and was reared on a large farm. She excelled in high school and was valedictorian of her class. She studied biochemistry and earned a B.S. (1940) and M.S. (1942) from Cornell University, then went on to attain a Ph.D. in 1949 from the University of California-Berkeley under the mentorship of noted biochemist Horace Barker. While working in Barker's lab, she met his technician and graduate student, Earl Stadtman. Terry and Earl were married in 1943.

After they both received their doctorates in 1949, they moved to Boston, where she did postdoctoral training with a future Nobel laureate, Christian Anfinsen, at Harvard

Terry Stadtman in high school.

Medical School, while Earl worked at the Massachusetts General Hospital with Fritz Lipmann, also a future Nobel laureate. When Anfinsen was offered a position as chief of the Laboratory of Cellular Physiology and Metabolism at the NIH in the newly formed National Heart Institute, he invited Terry to move with him to continue her work on bacterial cholesterol oxidase. At that time, NIH was one of the few institutions that would hire a married couple as independent investigators. Earl was able to tag along as the accompanying spouse because Anfinsen also offered him a position. They moved to NIH in 1950.

Terry's initial scientific goal at NIH was to elucidate principles of biochemistry by studying the metabolism of anaerobic bacteria, organisms that seemed capable of almost any imaginable chemical reaction. While chemists had to use harsh solvents and high temperatures to make many reactions happen, these microbes easily achieved the same reactions with extraordinarily high yields at ambient temperatures in aqueous solutions! Using extracts from *M. vannielii* and *C. sticklandii*, Terry studied mechanisms of amino acid fermentation and methane production from carbon dioxide. Her research gave many insights into anaerobic electron transport and vitamin B_{12} metabolism (3, 4). In the course of these studies, Terry and her colleagues discovered four of the vitamin B_{12}-dependent enzyme systems. She also established that the free form of B_{12} can function as a methyl-group carrier and that its deoxyadenosyl-coenzyme forms serve as hydrogen carriers.

Terry and Earl graduation. 1949.

Terry pipetting. Even after becoming a senior investigator, she always had a project on her own and carried out experiments herself.

Her findings provided the basis of our understanding of methane biosynthesis. In recognition of her contributions, a new methane-producing organism was named *Methanosphaera stadtmaniae* in her honor (5).

Terry's pioneering work on selenium biochemistry began with her 1973 publication reporting that a low-molecular -weight subunit of the *Clostridial* glycine reductase is a selenium-containing protein (6). In 1976 Terry and her colleagues became the first to demonstrate that selenium was present in this protein (Selenoprotein A) in the form of selenocysteine (7). This finding is viewed by many as her most important discovery. It defined the selenoprotein field, as selenocysteine is the only known chemical form of selenium used by humans and other eukaryotes. Terry went on to establish that selenocysteine is an essential constituent of several other enzymes (8, 9).

In prokaryotes, in addition to its use as a part of selenocysteine residue, selenium is present in the form of a cofactor. With one of us (VNG), Terry discovered that it is coordinated with molybdenum in the active site of nicotinic acid hydroxylase from *C. barkeri* (10). We also showed that selenium (in the form of selenocysteine) is coordinated with molybdenum in formate dehydrogenase H from *Escherichia coli* (11). Working with Peter Sun of the National Institute of Allergy and Infectious Diseases, we solved the crystal structure of this protein, revealing mechanistic details about the protein, which contains, in addition to selenocysteine, molybdenum, molybdopterin cofactor, and an iron-sulfur cluster (12).

Collaborating with August Böck of Munich, Dolph Hatfield of the National Cancer Institute, and others, Terry established that selenocysteine is inserted co-translationally

and that the UGA codon in the formate dehydrogenase gene corresponds to selenocysteine (13, 14). Together with findings from other investigators, her research established selenocysteine as the 21st amino acid, sharing its codon with the termination process (8).

Terry also contributed significantly to selenium biochemistry in eukaryotes. With Takashi Tamura, she found that human thioredoxin reductase is a selenoprotein (15). With VNG, she discovered that selenocysteine in this protein is located in a conserved C-terminal penultimate position and is encoded by a UGA codon, previously thought to be a stop codon in this gene (16). This also revealed a novel active site located on the flexible arm that delivers reducing equivalents from FAD in the N-terminal portions of the protein to thioredoxin, the natural substrate of thioredoxin reductase.

In 1984 Terry and colleagues showed that the selenium-containing nucleoside in several bacterial seleno-tRNAs was 5-[(methylamino)methyl]-2-selenouridine (17, 18, 19). With Matt Wolfe, they then discovered the enzyme, selenouridine synthase, that catalyzes this modification (20).

Terry also discovered that SelD from *E. coli* is a selenophosphate synthetase (19). Collaborating with Robert Balaban at the National Heart, Lung, and Blood Institute (NHLBI), she established that selenophosphate is the immediate selenium donor for the biosynthesis of selenium-containing biomacromolecules, selenocysteine in proteins, and 5-methylaminomethyl-2-selenouridine in seleno-tRNAs. A series of publications from 1996 until her retirement elucidated the mechanism by which selenophosphate synthetase catalyzes the synthesis of selenophosphate.

Selenium is now known to be an essential trace element, with 25 genes coding for selenocysteine-containing proteins in the human genome. There are multiple laboratories across the world that study these proteins, many of which are oxidoreductases, and other aspects of selenium biology. In selenoproteins, selenocysteine is the key functional group that is directly involved in catalysis. It's not surprising that, due to her discovery of selenocysteine in proteins, Terry became known as the "mother of selenium biochemistry."

Terry was elected to the National Academy of Sciences in 1981 and the American Academy of Arts and Sciences in 1982. Among her honors, she received the William C. Rose Award of the American Society for Biochemistry and Molecular Biology (ASBMB) in 1986, the Klaus Schwarz Medal from the International Association of Bioinorganic Scientists in 1988, and the inaugural L'Oreal Lifetime Achievement Award for Women in Science from L'Oreal–UNESCO in 2000. A 2016 book on *Selenium in Biology and*

The L'Oreal Award that Terry received in 2000.

Human Health was dedicated to Terry and August Böck. In 2017, at a meeting commemorating 200 years since the discovery of selenium by Berzelius, the keynote was named the Thressa Stadtman lecture, in honor of her contributions to the field. That same year, a symposium jointly honoring Berzelius and Terry was held at the meeting of the Society for Free Radical Biology and Medicine. The ASBMB presents the Earl and Thressa Stadtman Distinguished Scientist Award every other year to an established scientist for his or her outstanding achievement in basic research. The award alternates with the Earl and Thressa Stadtman Young Scholar Award, which goes to a scientist with 10 years or less experience as an independent investigator. The awards were established by friends and colleagues of the Stadtmans to honor their legacies as scientists and mentors.

Terry and Earl created a superb mentoring environment at the NIH in which many outstanding scientists were trained. The Stadtmans' rigor in scientific inquiry and their superbly successful mentoring is affectionately known as "the Stadtman Way" (see https://history.nih.gov/exhibits/stadtman). Their Journal Club, initially feared by newly arrived trainees and then enthusiastically embraced, was the furnace where scientific rigor was forged. No detail or question was too trivial to be brushed aside. The Stadtman Way also included Terry and Earl's generous sharing of publication credits with more junior scientists. Camaraderie, lively and friendly discussions, and lab parties led to lifelong friendships among those lucky enough to be shown the Stadtman Way.

Terry and Earl at the Lab Party on the occasion of their 60th wedding Anniversary.

Terry and Earl at opening of the NIH Exhibit "The Stadtman Way: a tale of two biochemists at NIH."

Two of us (PBC and RLL) were long-term colleagues in the Laboratory of Biochemistry. VNG did a postdoctoral training stint with Terry in the 1990s, when she was already in her 70s. She dressed elegantly, with high-heeled shoes, and drove a Mustang—rather fast, too. Even into her 80s she worked at the bench, carrying out experiments with her own hands. She could be temperamental and strict, but never indifferent. To VNG, the training in the Laboratory of Biochemistry was when he discovered the beauty of science. The Nobel Laureate Michael Brown at the University of Texas Southwestern Medical Center, who also did a postdoctorate at NIH, says,

> *What I remember most about Terry was her enthusiasm for science.... Terry was outgoing and always eager to discuss data, whether they were her own or that of others. Her interest in biology was as pure as that of anyone I ever knew. Terry loved scientific beauty without any concern for its utility. She was a scientist's scientist.*

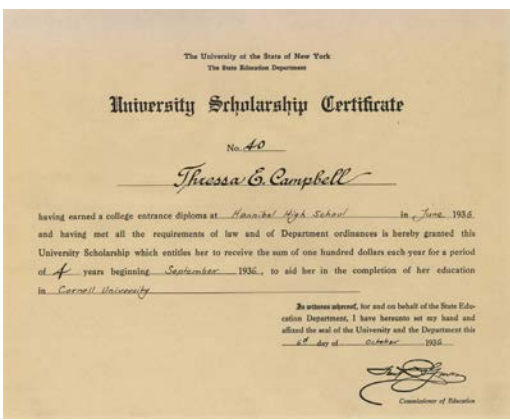
Terry, with the whole-hearted support of Earl, championed and supported women in science. She had been able to attend Cornell only because of scholarship support and

Terry at the banquet of the symposium in honor of her and Earl's 80th birthdays - Philadelphia, March 2000. (photo by Bob Hohman.)

working as a waitress for four hours a day. This is why she generously endowed the Stadtman Scholarship Fund for female undergraduates and the Stadtman Fellowship Fund for female graduate students at Cornell to provide support for women who are majoring in the sciences. Being optimistic about the future for women in science, she specified that when women no longer face roadblocks to careers in science, Cornell may redirect the Stadtman funds to support other groups who still face impediments in becoming scientists.

Terry retired from the NIH in 2009, 59 years after her arrival. For most of that time, she was chief of the Section on Intermediary Metabolism in the Laboratory of Biochemistry, NHLBI, where Earl was the lab chief. In her recollections of this experience in 2002, she wrote:

I have had a very lucky and satisfying scientific career, and I am especially grateful to all of my talented and hard-working postdoctoral associates and assistants without whom this would never have happened. I am indebted to NIH for the generous support given to me for 50 years to conduct basic research in the areas of my interest. I continue to derive a great deal of pleasure and satisfaction from working in the laboratory myself, and I hope to be able to continue for some time. All of these years I have benefitted enormously from the discussions of science with my husband when we shared each other's problems over a bottle of wine at dinner (9).



The University of the State of New York
The State Education Department

University Scholarship Certificate

No. 40

Thressa E. Campbell

having earned a college entrance diploma at Hannibal High School in June 1936 and having met all the requirements of law and of Department ordinances is hereby granted this University Scholarship which entitles her to receive the sum of one hundred dollars each year for a period of 4 years beginning September 1936, to aid her in the completion of her education in Cornell University

In witness whereof, for and on behalf of the State Education Department, I have hereunto set my hand and affixed the seal of the University and the Department this 28 day of October 1936

Commissioner of Education

University Scholarship Certificate that Terry received upon completing high school. She used this award to attend Cornell. 1936.

Terry in her Beaune Vineyard. 1995.

Earl and Terry lived in a house on six acres adjacent to Rock Creek Regional Park in Montgomery County, Maryland, just north of Washington, D.C.. Rock Creek Park was one of the places where President Abraham Lincoln sometimes took carriage rides to try to unwind a bit during the Civil War. After Earl's death in 2008, Terry deeded their property to expand the park. In accepting the gift, the park commissioners gave that section of the park the legal name the Stadtman Preserve. It features a mature forest, steep slopes, floodplain, wetlands, a stream, and nearly a thousand azaleas and rhododendrons planted by Earl.

Terry also tried her hand at applied biochemistry. In the early 1990s she purchased a first-growth vineyard in the Burgundy region of France known by the name "Les Chouacheux." She, Earl, and a microbiologist friend from Berkeley, Terry Leighton, then launched a classic Stadtman experiment aimed at answering the question, "If we make a pinot noir wine with Burgundy grapes but with Napa Valley yeast and fermentation techniques, will it taste like a French Burgundy or a California Pinot Noir?" Their answer to the question turned out to be, "We're not sure, but it's a really good wine!" Although the results of this experiment were never published, we can personally attest to the outcome: They were really good wines. Terry outlived Earl by eight years, passing away on December 11, 2016, at the age of 96.

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