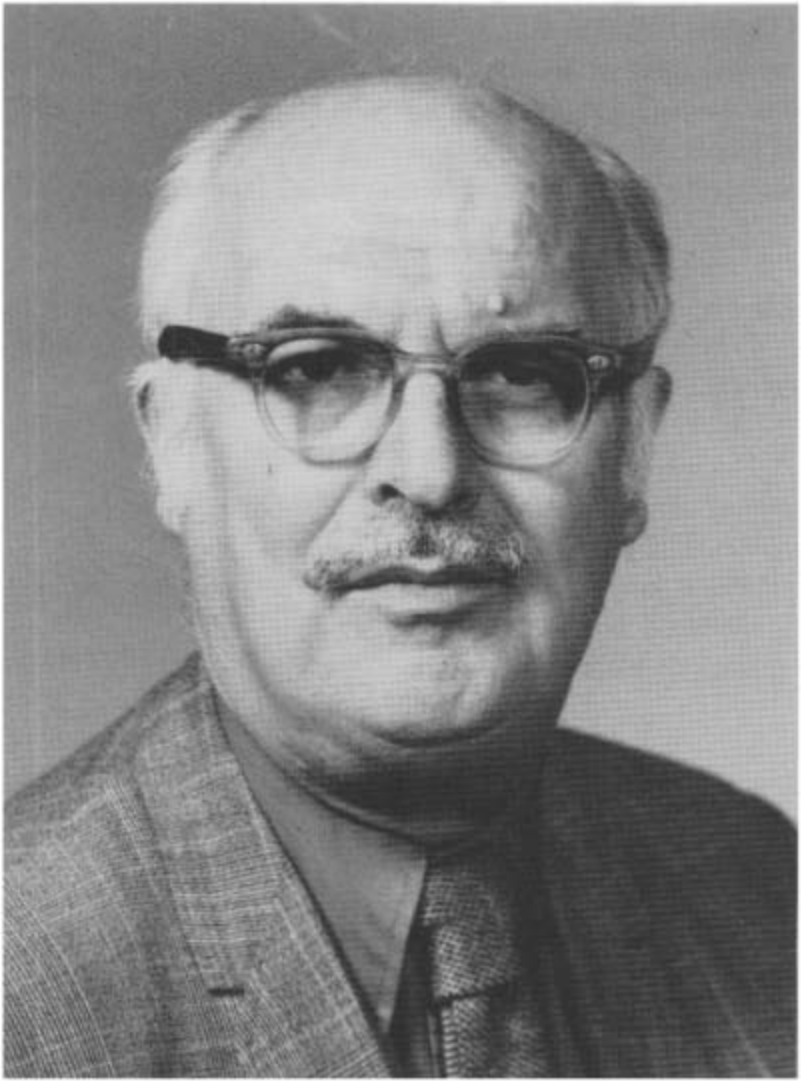
NATIONAL ACADEMY OF SCIENCES

MERTON FRANKLIN UTTER

1917—1980

A Biographical Memoir by
HARLAND G. WOOD AND RICHARD W. HANSON

Biographical Memoir



Merton J. Utter

MERTON FRANKLIN UTTER

March 23, 1917–November 28, 1980

BY HARLAND G. WOOD AND RICHARD W. HANSON

THE MOST SIGNIFICANT CONTRIBUTION to biochemistry made by Merton F. Utter was his demonstration that certain reactions of gluconeogenesis differ from those of glycolysis. For many years it was widely held that the synthesis of glucose (gluconeogenesis) in mammalian liver occurs by reversal of the Embden-Meyerhof pathway by which glucose is converted to pyruvate and lactate (glycolysis). Merton Utter and his coworkers showed that this concept is incorrect. They discovered phosphoenolpyruvate carboxykinase and pyruvate carboxylase, two enzymes that in concert convert pyruvate to phosphoenolpyruvate by a sequence that differs from the glycolytic pathway.

This discovery opened new vistas in the study of metabolism, and over the past decade it has become evident that the two enzymes discovered by Utter and coworkers are also important in the regulation of both carbohydrate and lipid metabolism. Utter, together with Dr. Bruce Keech, demonstrated that acetyl-CoA regulates the activity of pyruvate carboxylase, thus providing one of the first examples of allosteric control of an enzyme. Furthermore, the rate-limiting step in gluconeogenesis is catalyzed by phosphoenolpyruvate carboxykinase, whose levels in mammalian liver and kidney are regulated by insulin, glucagon, epinephrine, and gluco-

corticoids. This enzyme has been extensively studied as a model for the action of these hormones on gene expression in mammalian tissues. Prior to his death, Utter's studies had increasingly centered on the interface between disease processes and basic biochemistry. His laboratory was considered one of the leading centers studying inborn errors in the metabolism of pyruvate, and his collaboration was constantly sought by clinical investigators anxious to verify the absence of specific enzymes in patients suffering from various diseases. The scope of his science was broad. He stood for precise and excellent experiments, and his advice was sought on a wide variety of subjects. His was a keen intellect, but he was always modest and friendly, and was possessed of a sharp wit. Merton Utter's interests extended to all aspects of life: science, sports, politics, literature, and the arts.

UTTER'S BACKGROUND

Merton Franklin Utter was born at Westboro, Missouri, on March 23, 1917. His parents were Merton Franklin Utter, Sr., and Gertrude R. McMichael Utter. His father and grandparents, Mr. and Mrs. L. P. Utter, had moved to Missouri from Trempealeau, Wisconsin. His maternal grandparents were Mr. and Mrs. A. R. McMichael of Coin, Iowa. Most of his ancestors came to New England and New York from the British Isles in the seventeenth and early eighteenth centuries. When he was a few months old, Merton's parents moved to New Market, Iowa, where his father was a banker, and his early school years were spent there. His mother gave piano lessons and played piano and organ for churches most of her life. It was from her that Merton acquired a deep and lifelong love of music.

In 1930, when Merton was in the eighth grade, the family moved to Coin, Iowa. He graduated from the high school there in 1934 and entered Simpson College at Indianola,

Iowa. The death of his father in an auto accident in the summer of 1935 interrupted his college studies briefly, but he graduated from Simpson in 1938, supporting himself through scholarship aid and by managing the campus bookstore. He was a fine athlete and excelled in track and basketball. At Simpson he distinguished himself in the field of chemistry, and on the advice of his professor he enrolled in graduate school at Iowa State University at Ames. In 1942, with the aid of fellowships, he was able to complete the work for his Ph.D. degree, which he received in microbiology in the laboratory of Dr. C. H. Werkman. In that year he was appointed an instructor in bacteriology.

On September 2, 1939, while at Ames, he married Marjorie Manifold, whom he had known since high school. Members of her family were also longtime residents of Coin and vicinity (Page County). In 1944 the Utters moved to Minneapolis, where he was assistant professor of physiological chemistry at the University of Minnesota, and in 1946 they moved to Cleveland, Ohio, where he was appointed associate professor of biochemistry at Western Reserve University School of Medicine. A son, Douglas Max Utter, was born on December 8, 1950. In 1956 Merton Utter was promoted to professor, and in 1965 he became chairman of the Biochemistry Department and continued in that position until 1976. Thereafter he devoted his full time to research and teaching in the Department of Biochemistry.

He and his family spent three years abroad on leave of absence from Case Western Reserve University. In 1953, he traveled with his family to Adelaide, Australia, where he was a Fulbright Fellow at the University of South Australia. In 1960 he served as visiting professor at Oxford University in England and in 1968 at the University of Leicester. Recently, Sir Hans Kornberg reflected on the year spent by the Utter family in Leicester.

It seemed appropriate that 7 years later they, Marge, Mert and Doug, should come back to Leicester. They lived around the corner from us and every morning either Mert would come and ring my doorbell and I would hastily wipe the last vestiges of breakfast toast off my face and then walk with him across the park; or I would call for him on wet days in a monstrous car, a 12 seater. When you walk with someone for a whole year you get to know him pretty well. Mert had a tremendous interest in the comparative side of biological phenomena. We used to talk about this sort of thing trying to discover the reason why, for example, you have a perfectly good enzyme, pyruvate carboxylase, which a perfectly good bacteria like *E. coli* should resolutely refuse to use, and instead it used PEP carboxylase but used the same mechanism of control. And we would play games like *what if,* and *supposing that.* This to me brought out the one feature of my association with Mert which I remember distinctly with the strongest affection. He was a tremendous person to be with because he would toss ideas around and he, like me, had this fatal fascination for playing on words. We would usually end our walks giggling helplessly as we went into the department where they must have thought us ready for certification as lunatics.

A SUMMARY OF HIS RESEARCH

Early Research. Utter's first scientific paper was published in the *Iowa State College Journal of Science* (1940) and was entitled "The Preparation of an Active Juice from Bacteria." Utter was always modest and unpretentious. A title such as, "A Unique and New Procedure for Preparation of Active Enzymes from Bacteria" would have been more to the point and sounded more sophisticated, but that was not his style. The solubilization of bacterial enzymes was a significant accomplishment. At that time, soluble enzyme systems capable of fermenting carbohydrates had not been demonstrated in bacteria, and consideration of their intermediary metabolism was in large part based on what was known from studies of enzymes from yeast and animal tissue.

Those were the "horse and buggy" days of biochemistry. The citric acid cycle had just been described by Krebs, and

many details of the Embden-Meyerhof pathway were not completely understood. There were no commercial sources of enzymes or of coenzymes such as adenosinetriphosphate (ATP) and nicotinamide diphosphate and triphosphate (NAD and NADP). It was a time of "do-it-yourself or go without." To solubilize enzymes, bacteria were mixed with ground glass and the mixture was forced between the interface of two tightly interfitting cones. For this purpose, a glass tube was sealed to the neck of one Erlenmeyer flask and the bottom of the flask was cut off. A second Erlenmeyer flask was sealed off at the neck so that it fit inside the open end of the first Erlenmeyer flask. The inner flask was attached to a motor to cause it to rotate within the outer flask. A mixture of the bacteria, together with ground glass, was placed in the tube of the outer flask, and the mixture was forced, using considerable effort, from the tube between the rotating cones using a plunger. These were the depression years, so if a beaker was broken, it was saved and the glass was put in a ball mill to replenish the ground glass. This procedure for the preparation of bacterial enzymes was used for many years by researchers in C. H. Werkman's department.

At about the same time, a mass spectrometer for measurement of ^{13}C was being constructed by the group in the laboratory, as well as a thermal diffusion column five stories high for concentration of this stable isotope. It was the ingenuity and hard work of graduate students such as Merton Utter that made the laboratory of C. H. Werkman, which was situated in the middle of the farm belt of Iowa, a leading center for study of microbial metabolism.

This is the environment in which Merton Utter started his research. He had a nine-month fellowship that paid $50 monthly. His wife Marjorie worked as a secretary with Dr. Theodore Schultz in the Department of Economics at Iowa State College, now Iowa State University. Interestingly, Dr.

Schultz, who by then had moved to Chicago, was a winner of the Nobel Prize in Economics in 1979.

Merton Utter's research was truly pioneering. In 1941 a paper was published in the *Journal of Bacteriology* entitled "The Occurrence of the Aldolase and Isomerase Equilibria in Bacterial Metabolism." Aldolase and isomerase are two important enzymes of carbohydrate metabolism. There were two more papers published in the *Journal of Biological Chemistry* in 1942: "Effect of Metal Ions on the Reactions of Phosphopyruvate by *Escherichia coli*" and "The Dissimilation of Phosphoglyceric Acid by *Escherichia coli*." Phosphoglyceric acid had been shown at that time to be a key compound in the metabolism of carbohydrate by yeast and mammalian tissues. In 1943 Utter published "The Role of Phosphate in the Anaerobic Dissimilation of Pyruvic Acid" and in 1944 the "Formation and Reactions of Acetylphosphate in *Escherichia coli*" and "Reversibility of the Phosphoroclastic Split of Pyruvate." (At that time, Fritz Lipmann had just discovered the role of acetylphosphate in metabolism.) Anyone who is familiar with the history of biochemistry recognizes from the titles that Merton Utter's early work was at the forefront of biochemistry, just as it has been at the forefront of carbohydrate metabolism to this day. Methods of isolation of enzymes and study of their properties were in their infancy. Utter's studies helped to show that bacteria share similar metabolic pathways with mammals and that all forms of life exist in large part by the same biochemical processes. Soon bacteria were to become the major subject for study of intermediary metabolism and molecular biology.

Studies on Fixation of CO_2. The fixation of CO_2 by heterotrophic organisms was discovered by H. G. Wood and C. H. Werkman in 1936. Later they proposed that the fixation occurred as follows:

$$*CO_2 + CH_3\,CO\,COOH \longrightarrow HOO*C\,CH_2\,CO\,COOH$$

This reaction became known as the Wood and Werkman reaction. It was not until 1948, however, that S. Ochoa, A. H. Mehler, and A. Kornberg purified an enzyme that fixed CO_2 to form a dicarboxylic acid. Subsequently, the enzyme was named the malic enzyme and shown to catalyze the following reaction:

$$CO_2 + \text{pyruvate} + NADPH \overset{\text{malic enzyme}}{\rightleftharpoons} \text{malate} + NADP$$

Following this discovery, Ochoa and collaborators suggested that this enzyme catalyzed the primary reaction in the fixation of CO_2 and that oxalacetate is formed by coupling the following two reactions:

$$CO_2 + \text{pyruvate} + NADPH \overset{\text{malic enzyme}}{\rightleftharpoons} \text{malate} + NADP$$

$$\text{Malate} + NAD \overset{\text{malic dehydrogenase}}{\rightleftharpoons} \text{oxalacetate} + NADH$$

$$\text{Sum: } CO_2 + \text{pyruvate} + NADPH + NAD \longrightarrow \text{oxalacetate} + NADP + NADH$$

Ephraim Racker summarized the status of work in this field at a meeting on CO_2 fixation in 1950, when he proposed a toast to the "wouldn't work reaction."

Although the enzymatic basis for the Wood and Werkman reaction continued to be elusive, Utter and K. Kurahashi showed that chicken liver forms oxalacetate without the involvement of malic enzyme. They isolated a new enzyme, P-enolpyruvate carboxykinase, which catalyzes the formation of oxalacetate with fixation of CO_2, using guanosine di- and triphosphate (GDP and GTP) as high-energy intermediates:

$$\text{P-enolpyruvate} + CO_2 + \text{GDP} \overset{\text{P-enolpyruvate carboxykinase}}{\rightleftharpoons} \text{oxalacetate} + \text{GTP}$$

Utter's Discovery of the Mechanism of Conversion of Pyruvate to P-enolpyruvate. It was the finding of P-enolpyruvate carboxykinase that launched Utter into the studies of gluconeogenesis. He was aware that because of the high, negative free-energy change it was unlikely that P-enolpyruvate was formed from pyruvate by a simple reversal of the pyruvate kinase reaction.

$$\text{P-enolpyruvate} + \text{ADP} \overset{\text{pyruvate kinase}}{\longrightarrow} \text{pyruvate} + \text{ATP}$$
$$(\Delta G^{0\prime} = -7 \text{ kcal/mole})$$

As a possible solution, both H. A. Krebs and Utter (1954) independently proposed that pyruvate might be converted to P-enolpyruvate by the combined action of the malic enzyme and P-enolpyruvate carboxykinase by the following sequence:

$$\text{Pyruvate} + CO_2 + \text{NADPH} \overset{\text{malic enzyme}}{\rightleftharpoons} \text{malate} + \text{NADP}$$

$$\text{Malate} + \text{NAD} \overset{\text{malic dehydrogenase}}{\rightleftharpoons} \text{oxalacetate} + \text{NADH}$$

$$\text{Oxalacetate} + \text{GTP} \overset{\text{P-enolpyruvate carboxykinase}}{\rightleftharpoons} \text{P-enolpyruvate} + \text{GDP} + CO_2$$

Sum: Pyruvate + GTP + NADPH + NAD $\longrightarrow$
P-enolpyruvate + GDP + NADP + NADH

The thermodynamics of this sequence are not particularly favorable, but by coupling the oxidation of NADH to other reactions it was considered possible to maintain a high ratio of NADPH/NAD, thereby favoring the synthesis of the P-enolpyruvate.

It was an investigation of the above reaction sequence that led to the discovery of the major anaplerotic enzyme, pyruvate carboxykinase. Utter and coworkers then found that mitochondria from chicken liver contained only trace amounts of either pyruvic kinase or malic enzyme, but they could still form significant amounts of P-enolpyruvate from pyruvate. These experiments provided the first clear evidence that neither of these enzymes was required for the net synthesis of P-enolpyruvate. Since Utter knew that P-enolpyruvate could be formed from oxalacetate, it was natural to look for an enzyme that could form oxalacetate from pyruvate. In 1963 Utter and D. B. Keech found such an enzyme in the mitochondria of chicken liver (later named pyruvate carboxylase), which catalyzed the direct carboxylation of pyruvate. Utter had thus found the enzymatic basis of the "*wouldn't work reaction,*" twenty-five years after it had been postulated as a possible mechanism for the formation of dicarboxylic acids by CO_2 fixation. Pyruvate carboxylase, when coupled with P-enolpyruvate carboxykinase, catalyzed the formation of P-enolpyruvate as illustrated below.

$$\text{Pyruvate} + CO_2 + \text{ATP} \xrightarrow{\text{pyruvate carboxylase}} \text{oxalacetate} + \text{ADP} + P_i$$

$$\text{Oxalacetate} + \text{GTP} \underset{\text{carboxykinase}}{\overset{\text{P-enolpyruvate}}{\rightleftharpoons}} \text{P-enolpyruvate} + CO_2 + \text{GDP}$$

$$\text{Sum: Pyruvate} + \text{ATP} + \text{GTP} \longrightarrow \text{P-enolpyruvate} + \text{ADP} + \text{GDP} + P_i$$

This sequence is energetically favorable because it combines cleavage of two high-energy phosphates from ATP and GTP to drive the overall synthesis of P-enolpyruvate. A beautiful summary of this research was published in a 1963 article by

Utter in the *Iowa State College Journal of Science,* which contained a compilation of papers by C. H. Werkman's students. Today this pathway of P-enolpyruvate formation from pyruvate is widely held as the key, pacesetting step in gluconeogenesis. The degree of the regulation of the two enzymes in this sequence, pyruvate carboxylase and P-enolpyruvate carboxykinase, now serves as a model for control of metabolic pathways and remains a major legacy of Merton Utter's scientific work.

Structure of Biotin Enzymes. One portion of Utter's research that had a large effect was his 1966 study, in collaboration with R. C. Valentine, N. C. Wrigley, M. C. Scrutton, and J. J. Irias, using electron microscopy to determine the structure of pyruvate carboxylase from chicken liver. This was one of the earliest applications of electron microscopy for investigation of the quaternary structure of enzymes. Negative staining techniques showed square-planar tetramers with vivid clarity. It was these studies that convinced one of us (H. G. W.) to undertake similar studies with another biotin enzyme, transcarboxylase, and no doubt induced others to adopt the procedure.

That pyruvate carboxylase was being visualized seemed compelling. Pyruvate carboxylase was known to contain four biotins, which was in accord with the observed tetrameric structure. Also, estimates from the dimensions of the profiles of the four subunits were in accord with the observed molecular weight of the enzyme. These square tetramers were observed in pyruvate carboxylase preparations from the livers of a variety of animals, including the chicken, turkey, beef cattle, and calf. In addition, Gottschalk and coworkers (*European Journal of Biochemistry,* 64 [1976]:411–21) at the University of Göttingen, Federal Republic of Germany, reported that pyruvate carboxylase of rat liver had a square tetramer shape. Finally and most convincingly, pyruvate carboxylase

was known to be cold sensitive. The enzyme dissociates to its subunits in the cold, with loss of enzymatic activity; upon rewarming, the subunits reassociate with accompanying return of activity. The square planar tetramer dissociated to subunits in the cold, which were observed in the electron microscope; on rewarming, they reassociated to the square tetramer.

To Utter's amazement and chagrin, thirteen years later he and his coworkers found that the square-shaped tetramers were not pyruvate carboxylase. It was a minor, highly visible impurity present in purified pyruvate carboxylase. The pyruvate carboxylase dissociated during preparation of the grids to faintly visible material, leaving the minor contaminant highly visible. Independently and at the same time, N. H. Goss, P. Y. Dyer, D. B. Keech, and J. C. Wallace at the University of Adelaide in Australia found that the square tetramer is not pyruvate carboxylase. Utter and his former collaborator, D. B. Keech, by mutual agreement, published their new results on the correct structure of pyruvate carboxylase in the same issue of the *Journal of Biological Chemistry.*

The identity and function of the square tetramer remains a mystery. A better design of a protein could not be constructed by the Devil himself to mislead a brilliant scientist. Although there is not complete agreement, the overall configuration of pyruvate carboxylase from chicken, sheep, and rat appears to be a tetrahedron-like structure consisting of two pairs of subunits in different planes orthogonal to each other, with the opposing pairs of subunits interacting on their convex surfaces (F. Mayer, J. C. Wallace, and D. B. Keech, *European Journal of Biochemistry,* 112 [1980]:265–72).

Inborn Errors in the Enzymes of Pyruvate Metabolism. Later in his career, Merton Utter turned his attention to the causes of lactic acidosis in children. Many of the diseases in this ill-defined category of childhood disorders are thought to in-

volve inborn errors of enzymes in pyruvate metabolism. During the last decade of his life, Utter and his coworkers began a systematic study of these enzymes in human populations. He developed sensitive enzymatic assays for pyruvate dehydrogenase, pyruvate carboxylase, P-enolpyruvate carboxykinase, and pyruvate kinase using easily obtained tissues, such as cultured skin fibroblasts, reticulocytes, or lymphocytes. He was able to demonstrate, for example, that contrary to the prevailing opinion, Leigh's disease did not involve a deficiency in pyruvate carboxylase. His skill as an enzymologist was a major factor in the development of a standard assay for pyruvate dehydrogenase in human tissues that accurately and reproducibly measured the true basal rate of activity of this enzyme. His laboratory had, at the time of his death, become a reference point for many clinicians interested in collaboration in determining the absences of a specific enzyme in pyruvate metabolism in patients.

PERSONAL ASPECTS IN MERTON UTTER'S LIFE

Merton Utter was a man of great personal charm and dignity. His life was dedicated to scholarship and the ideals of university education. He loved books and all his life read widely, particularly in history, biography, and politics. He was a quiet and unassuming gentleman whose advice was often sought by his colleagues and students. He was a man of unfailing charity who did not speak ill of others and whose personal qualities will be long remembered by all who knew him. Paul Berg, a student in the Department of Biochemistry at Western Reserve University in the 1950s, commented recently:

> One of the things about Mert which I will always remember is that while we learned that science was exciting and pertinent and that it required a kind of commitment, day and night preoccupation, Mert made science fun. In chatting with us, he would see the less intense side of things

as well as the importance of what we were trying to talk about. He would chat about music, art, baseball. He made being in the lab a great joy. It was always a pleasure for me to come into the lab, morning, noon and night and find Mert there.

Merton Utter served with distinction as an associate editor of the *Journal of Biological Chemistry* and helped to guide the editorial policies of the journal during the period of its most rapid expansion. He was a member of numerous study sections and national committees, and his quiet and judicious manner made him a valued member of numerous national panels concerned with research policy.

Merton Utter spent virtually his complete university career as a member of the Department of Biochemistry at Case Western Reserve University School of Medicine. He trained numerous biochemists and medical students during his career as a research scientist and teacher. His knowledge of biochemistry was encyclopedic, and he was a superb teacher. His sudden death at the age of sixty-three was a serious blow to those who knew and loved him. A symposium was held at Case Western Reserve University School of Medicine in May of 1982 to honor the memory of Merton Utter. The sentiments of all who attended were expressed in a letter written at the time of his death by Dr. Albert S. Mildvan:

It was with shock, and with the deepest of sadness that I read your letter today, telling of our loss of Mert Utter. His life's work can only be described as monumental. I am grateful to have had the privilege of collaborating with this great scientist and person.

In thinking of Mert, I recall the pleasure of hearing his witty lectures on his research. With profound modesty he would make his great discoveries sound like the result of a series of unexpected accidents. This didactic technique greatly encouraged and inspired the next generation of scientists, indeed all of us, who try to emulate this high example.

HONORS AND DISTINCTIONS

DEGREES

B.A., Simpson College, 1939
Ph.D., Iowa State University, 1942

PROFESSIONAL APPOINTMENTS

Instructor in Bacteriology and Research, Associate in the Agricultural Experiment Station, Iowa State University, 1942–1944
Assistant Professor in Physiological Chemistry, University of Minnesota, 1944–1946
Associate Professor of Biochemistry, Western Reserve University, 1946–1956
Professor of Biochemistry, Case Western Reserve University, 1956–1980
Director, Department of Biochemistry, Case Western Reserve University, 1965–1976

PROFESSIONAL ACTIVITIES

Metabolic Biology Panel, National Science Foundation
Biochemistry Study Section, National Institutes of Health
Program Project Committee, AMDD Institute, National Institutes of Health
Associate Editor, *Journal of Biological Chemistry*
Editorial Board, *Journal of Biological Chemistry*
Editorial Advisory Board, *Biochemistry*
Editorial Board, *Trends in the Biochemical Sciences*
Biochemistry Panel, National Board of Medical Examiners
U.S. Representative, International Union of Biochemistry

HONORS

Fulbright Senior Research Fellow (Australia), 1953–1954
Paul Lewis Award in Enzyme Chemistry, 1956
National Science Foundation Senior Research Fellow (Oxford), 1960–1961
National Science Foundation Senior Research Fellow (Leicester), 1968–1969
National Academy of Sciences, 1973
American Academy of Arts and Sciences, 1972

PROFESSIONAL SOCIETIES

American Society of Biological Chemists
American Association for the Advancement of Science
American Chemical Society
American Society of Microbiologists
Biochemical Society (England)
New York Academy of Sciences
Society of Experimental Biology and Medicine

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