Wm. C. Rose

NATIONAL ACADEMY OF SCIENCES

WILLIAM CUMMING ROSE

1887—1985

A Biographical Memoir by

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NATIONAL ACADEMIES PRESS
WASHINGTON D.C.

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April 4, 1887–September 25, 1985

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WILLIAM CUMMING ROSE, a member of the National Academy of Sciences from 1936, died in Urbana, Illinois, at the age of ninety-eight. Thus ended the career of a dedicated and inspiring teacher and an outstanding pioneer in biochemistry and nutritional science. He rendered the University of Illinois distinguished service until his retirement in 1955. In research he devoted his attention to the intermediary metabolism of amino acids, creatine, uric acid, and chemically related compounds and was renowned for the discovery, isolation, and identification of threonine. The characterization of the last of the amino acids to be found as universal components of proteins led to his determination of the complete essential amino acid requirements of the laboratory rat and culminated in the establishment of the amino acid requirements of humans.

EDUCATION AND EARLY LIFE

William C. Rose was born in Greenville, South Carolina, and spent his childhood in small communities in the Carolinas, where his father, John M. Rose, served as a Presbyterian minister. Money was scarce, particularly since the cleric's small salary was reduced by generous gifts to religious and humanitarian causes, but somehow the necessities were provided and the best possible education was afforded the children in the family. Young Will attended an assortment of local schools until the age of fourteen, when the inadequacy of the education caused his father to remove him from school and tutor him at home. He was well prepared by the time he entered college and had already been introduced to Latin, Greek, and Hebrew and had acquired an interest in chemistry from reading Remsen's *An Introduction to the Study of Chemistry*, a college text his older sister had used. Will wished to attend a large university, but his father thought his son, at age sixteen, was too young and so convinced him to attend Davidson College in North Carolina, a school for which Will developed a lifelong affection.

While in graduate school at Yale University, Rose decided on the branch of chemistry he would pursue. During his initial interview with Russell Chittenden, director of the Sheffield Scientific School, Rose mentioned an interest in food chemistry. This suggestion brought an introduction to Lafayette Mendel, which not only guided Rose's interest and work toward biochemistry but also led to a strong friendship that endured until Mendel's death. In 1911 Rose left Yale for an instructorship in physiological chemistry at the University of Pennsylvania, a department then headed by Alonzo Taylor, which was followed by a short period of advanced study with Professor Franz Knoop at the University of Freiburg. While in Germany, Rose received a cablegram from Galveston asking him to come to the College of Medicine to organize a department of biochemistry. At first Rose was hesitant about the offer because he felt obliged to go back to the University of Pennsylvania, but he was fully reassured by a cable from Taylor containing the terse single sentence, "You darned fool, I recommended you for that job." This message came in response to his own cable in which he had turned down the offer. He then accepted the position of associate professor of biological chemistry at the University of Texas and quickly rose to the rank of professor and head of the department. In 1922 Rose was persuaded to move to the University of Illinois, where he was appointed professor and head of the Division of Physiological Chemistry (the name was later changed to Biochemistry) in the Chemistry Department and found a permanent and very supportive home for his scientific career. He provided dedicated service to that institution for the next thirty-three years.

RESEARCH ACCOMPLISHMENTS

In research Rose displayed a gift for meticulous experimentation and for thoroughness and clarity in preparing his results for publication. His early studies on creatine and its dehydration product, creatinine, carried out with Mendel at Yale and published in 1911, dealt with the role of carbohydrates in the metabolism of these compounds and with the effect of inanition on the creatine content of muscle. In subsequent years Rose and his associates made excellent use of the experimental methods available at the time, chiefly nutritional studies, to explore the metabolic relationship of creatine to creatinine and of both to other nitrogenous substances.

They observed that the ingestion of diets high in protein failed to induce the excretion of creatine in normal men and women and concluded that there was no exogenous source of urinary creatine in the absence of creatine in the diet. In addition, no relationship was observed in growing rats between the arginine content of the diet and total creatinine elimination in the urine. Furthermore, in human subjects no evidence could be obtained that exogenous arginine was catabolized to creatine or creatinine. In light of present knowledge, such studies did not reveal the involvement of this amino acid in amidine transfer in creatine biosynthesis, but they are still of fundamental interest. We will have much to say in what follows about the pioneering studies in Rose's laboratory on essential amino acids; suffice it to say here that creatine and creatinine were found to be incapable of replacing dietary histidine for the growth of rats. The knowledge available at that time on the metabolism of creatine and creatinine was ably summarized by Rose in 1933 and 1935 in insightful articles in the *Annual Review of Biochemistry*.

From his own experimental studies and a summary of the literature he published in 1923 in *Physiological Reviews*, Rose concluded that endogenous purines may have their ultimate origin in arginine and histidine but that the extent of their synthesis might be limited to the anabolic needs of the organism. And in studies similar to those referred to above involving creatine and creatinine, he established that neither adenine nor guanine (nor, for that matter, a mixture of all four of these compounds) was capable of replacing dietary histidine for the growth of rats. In addition to his interest in nitrogenous compounds as already summarized, Rose made useful and scholarly contributions to knowledge in several other quite diverse areas, including analytical methods, the nephropathicity of dicarboxylic acids and their derivatives, the occurrence of copper in marine organisms, and digestive enzymes in coelenterates, elasmobranchs, and teleosts. However, after he developed an interest in amino acid metabolism and nutrition at the University of Illinois, Rose devoted himself wholeheartedly to this subject, which soon brought him international recognition.

Many years later, in an article titled "How Did It Happen?", Rose described the events leading up to his first report, in 1924, on an indispensable amino acid. He was aware of the much earlier work of Osborne and Mendel in which zein of corn served as a dietary protein on which rats failed to grow until tryptophan and lysine were incorporated into the ration. That was the first clear-cut evidence that individual amino acids might be required by animals. While at the University of Texas, Rose continued his work on creatine-creatinine metabolism, as already mentioned, and, in order to study arginine as a possible precursor of these compounds, decided to prepare a casein hydrolysate and remove this amino acid as completely as possible. In view of work in another laboratory indicating that arginine and histidine were mutually interchangeable in metabolism, he changed the plan, and after preparing the hydrolysate by enzymatic action, followed by mild acid treatment, he took it to dryness, shipped it to his new scientific home in Illinois, and there removed the arginine and histidine. Rats lost weight on the treated hydrolysate but responded impressively when histidine was included in their food. However, arginine was totally incapable of replacing histidine for growth. Rose rightly considered the difference in response of the animals to the two amino acids to be little short of sensational. Having discovered that histidine is a dietary essential, he decided to investigate the nutritional role of all of the other amino acids as well. Rose realized that work with protein hydrolysates had limitations but used them in place of proteins to show that a variety of closely related synthetic compounds could not be substituted for cystine, histidine (with the exception of imidazolelactic acid), and tryptophan (with the exception of the *N*-acetyl compound, the ethyl ester, and indolelactic and indolepyruvic acids).

Rose then undertook investigations using mixtures of pure amino acids as the source of dietary nitrogen. Following the extremely important observation that diets containing nineteen highly purified amino acids would not support growth, his laboratory made a painstaking effort to identify the missing growth essential in proteins. After several years they finally succeeded in obtaining the unknown compound in pure crystalline form, as described in the 1935 landmark paper by McCoy, Meyer, and Rose. The structure was established as α-amino-ß-hydroxy-*n*-butyric acid, and the purified amino acid was demonstrated to induce maximum growth, thus constituting the first successful attempt to rear animals on a ration containing purified amino acids as the sole source of nitrogen.

In a 1979 symposium on earlier nutritional discoveries, H. E. Carter described how he became a faculty member in biochemistry at Illinois and was given what he considered a wonderful opportunity of participating in the threonine story.[1] He accomplished the chemical synthesis of the four isomers of α-amino-ß-hydroxy-*n*-butyric acid and demonstrated that only one form would support the growth of rats. This isomer, analogous in structure to D-threose and having a steric relationship to that of the other naturally occurring *L*-amino acids, was designated *L*-threonine.

Thus, the way was paved to classify other amino acids in the essential or nonessential category as judged by the maintenance of normal growth in the rat. Thorough experiments extending over the next two decades led to many important conclusions. Only ten of the twenty-two amino acids known to exist in proteins are indispensable dietary components. These are histidine, isoleucine, leucine, threonine, lysine, methionine, phenylalanine, tryptophan, valine, and arginine. With the exception of arginine, the removal of any one of these from the food of growing rats leads to profound nutritive failure, accompanied by a rapid decline in weight, loss of appetite, and eventual death. However, without arginine the animals continue to gain weight but at a suboptimal rate, thus indicating that this amino acid can be manufactured by the body but only slowly. In a study of the significance of the amino acids in canine nutrition, it was found that those amino acids that are dispensable for the growing rat are also dispensable for the adult dog, as judged by the maintenance of nitrogen equilibrium. Not unexpectedly, arginine is not needed, presumably because the rate of synthesis is adequate in the adult animal. Rose and his associates then determined the quantitative amino acid requirements by establishing the minimum amount needed to support optimal growth in the laboratory rat. In addition, many other interesting findings were made with this species using diets containing purified amino acids. For example, cystine was found to stimulate growth only when methionine was fed in suboptimal amounts and, similarly, the phenylalanine requirement could be partially replaced by tyrosine. In other attempts at substitution by related compounds, argininic acid was shown to be a poor substitute for arginine, and the *D*-isomers of phenylalanine and methionine were found to be active, whereas those of tryptophan and valine were only partly effective. Glycine, glutamate, urea, or ammonium salts were found to serve as a source of nitrogen for synthesis of the nonessential amino acids, and the effect of urea was confirmed with the ^{15}N-labeled compound. In other studies that contributed significantly to knowledge of amino acid metabolism, 5-^{14}C-labeled glutamate was observed to lead to labeled proline and arginine, thus establishing the reversibility of the known reactions in which glutamate is formed from the other two compounds. In addition, the fate of valine was investigated in the phlorhizinized dog, and three of the carbon atoms were found to yield glucose.

The experiments described briefly above provided highly important information about synthetic reactions that animals could and could not accomplish, but the ultimate objective of Rose's investigations was establishment of the amino acid requirements of the human species. In 1942 he took on this research challenge, with healthy male graduate students as the experimental subjects.[2] The diets consisted of corn starch, sucrose, butter fat from which the protein had been removed, corn oil, inorganic salts, the known vitamins, and mixtures of highly purified amino acids. The only variables allowed, other than when changes were purposely made in the amino acids consumed, were distilled water and celluflour, a product that provided bulk but had no nutritive value, nitrogen, or flavor. The only unusual component of this otherwise bland diet was a large brown candy containing a concentrated liver extract as a possible source of unknown vitamins, sweetened with sugar and flavored with peppermint oil, which provided a never-to-be-forgotten taste. Total urinary and fecal nitrogen were determined, and by the criterion of nitrogen equilibrium it was established that the twelve amino acids previously shown to be dispensable for animals were also dispensable for humans. The remaining ten amino acids were then removed from the diet one at a time; a pronounced negative nitrogen balance ensued in the case of isoleucine, leucine, tryptophan, lysine, methionine, phenylalanine, threonine, and valine. In contrast, the removal of arginine had no effect, a finding that was not surprising inasmuch as animals have a limited ability to synthesize this compound, as already stated. The results obtained with histidine, however, were most unexpected, since on a diet lacking this amino acid the subjects all maintained normal nitrogen equilibrium. Thus, only eight amino acids are essential dietary components for the adult human. However, as Rose was careful to point out, certain amino acids not necessary for nitrogen equilibrium under ordinary circumstances might become indispensable during disease or for special needs in detoxification, reproduction, or lactation.

These investigations continued into the early 1950s, resulting in sixteen papers in *The Journal of Biological Chemistry*, which C. Glen King, trustee of the Nutrition Foundation, described as a series that stands as a classic in the history of nutrition and for the benefit of humans. Importantly, the studies established the quantitative as well as the qualitative amino acid needs. Levels ranging from as low as 0.25 grams per day of tryptophan to as high as 1.1 grams per day of several other amino acids were proposed as minimal levels, with twice as much providing what was considered to be a safe margin.

In further investigations with Illinois graduate students as subjects, who were grateful in those days for the free rations, the dollar a day they were paid, and the prospect of seeing their initials in print in Rose's widely read publications, Rose made many other significant findings. A higher caloric intake is needed to maintain nitrogen equilibrium on diets containing mixtures of purified amino acids as compared to casein, for reasons that are not yet well understood. Cystine spares part of the methionine requirement, which is of significance in those parts of the world in which the latter appears to be the limiting amino acid in native diets. Similarly, tyrosine spares part of the phenylalanine requirement. In studies involving the *D* isomers of the essential amino acids, only that of methionine was found to be well utilized by the human organism. Of related interest, acetyl-*L*-tryptophan is effective but not the acetyl-*D* form, a matter of metabolic and also practical importance in view of reports by others in the literature that the acetyl-*DL* preparation might be fully utilized and thus be less costly as a dietary supplement than racemic unsubstituted tryptophan.

Another report by other investigators that could not be confirmed in the Rose laboratory, much to his relief and that of his subjects, was the claim that arginine deficiency adversely affects spermatogenesis. Thus, the only changes observed in these relatively short term studies when an essential amino acid was removed from the diet were negative nitrogen balance, a loss of appetite, and a sense of fatigue.

The above account, though necessarily brief, may give the reader an idea of how an unexpected finding made in a study on the possible relationship of amino acids to creatine synthesis eventually led to discovery of the last of the amino acids occurring in proteins and to establishment of the qualitative and quantitative amino acid requirements of animals and of the human species. Indeed, no other scientist has had a comparable record in identifying and establishing the quantitative requirements for so many essential nutrients.

Rose's findings have had many useful applications in addition to their contribution to basic knowledge. For example, they made it possible to predict the nutritional quality of a protein for human diets from the amino acid composition, rather than from animal tests, and to devise highly effective mixtures of amino acids for the intravenous feeding of surgical and pediatric patients. In 1942, partly in response to wartime nutritional problems and to the change in emphasis from acute to chronic dietary deficiencies, two important institutions were created—the Nutrition Foundation and the Food and Nutrition Board of the National Research Council. Rose played a significant role in the development and ongoing activities of both of these nongovernmental organizations, serving as a member of the Scientific Advisory Board of the former from 1943 to 1956 and as a member of the latter from 1940 to 1947. With the Food and Nutrition Board, he was instrumental in advising governmental agencies on the implications of meat rationing and on minimum desirable daily allowances, as well as on the dietary usefulness of vegetable proteins. As chairman of its Committee on Protein Foods, Rose dealt with problems of supply and nutritional quality of protein foods. The results were issued in two comprehensive publications, titled *The Evaluation of Protein Nutrition with Emphasis on Amino Acid Proportionalities* and *The Evaluation of Protein Nutrition.*

PERSONAL TRAITS

Despite his many professional duties and dedication to his research and his students, Rose found time for other interests. In 1913, upon his return from Freiburg, he married Zula Franklin Hedrick, a North Carolinian. She was at his side for many happy years, and the "two Roses" exerted a wonderfully positive influence on all who knew them. They had no children of their own but instead a large "family" in which they took a personal interest—the ninety graduate students who studied under Will Rose, of whom fifty-six received the Ph.D. degree. In later years he often commented on his extraordinarily happy family life until Zula's death in 1965, his exciting professional life, and the thrill of watching his students grow into professional stature.

When asked what accounted for his longevity, Rose simply commented that he had been interested in everything all his life. He particularly enjoyed birdwatching, amateur photography, travels by automobile, and the history of science. He and his wife made numerous tours of the country by car, and until he was ninety-five he drove annually to Davidson, North Carolina, where he spoke to chemistry classes on the campus. Because of his extreme caution as a driver, it was a source of some amusement to his friends at Davidson College that at age ninety-three Rose got a speeding ticket during the drive down from Illinois. On another such visit he had to have a heart pacemaker installed, after which he got in his car and drove himself home to Illinois. Rose was the class historian at his undergraduate college, and he took a strong interest in the origins of Davidson College as well as of all the other institutions he was associated with over the years and of science in this country in general. After painstaking verification of the historical facts, he wrote fascinating and insightful accounts of the early days of American biochemistry. In "John R. Young, First American Biochemist," an introductory essay to a monograph by Young, originally published in 1803 and titled *An Experimental Inquiry into the Principles of Nutrition and the Digestive Process*,[3] Rose described a remarkable thesis submitted to the University of Pennsylvania for the degree of doctor of medicine. Considerable space is devoted to the careers of Young's teachers, including the famous Benjamin Rush, and how the youthful author "takes issue with the most revered authorities of his era—Spallanzini, Cullen, and Rush—and then proceeds to prove that each was guilty of erroneous conclusions." In "Recollections of Personalities Involved in the Early History of American Biochemistry,"[4] Rose describes his association with scientists responsible for the early development of this field and provides warm insight into their contributions and personal characteristics. The final paragraph of that article is quoted here because of the remarkable insight it provides:

> Because of the early start of the Yale laboratories, and the superior genius of Samuel W. Johnson, Russell H. Chittenden, and Lafayette B. Mendel, it is not surprising that such a large proportion of the biochemists produced in this country until approximately 1915 had their training at Yale. This would have occurred wherever Johnson, Chittenden, and Mendel happened to be located—at Harvard, Chicago, here, or anywhere. Intellects of their caliber would have found a way to do what they did regardless of the place in which fate cast their lot. In the development of a university, as in the life

and growth of an individual, progress and ultimate attainment depend so largely upon the vision, enthusiasm, and determination of the individual participants. Perhaps, this is a truth that each one needs to remember as he carves his future out of the events and experiences of the present.

For many years Rose taught the two core biochemistry courses at Illinois and exhibited a rare talent at imparting enthusiasm about biochemistry to the undergraduate and graduate students who attended his meticulously prepared lectures. The subject came alive with his engrossing stories about the early history of the field and the personalities involved. No mention of his remarkable ability as a teacher would be complete without reference to the weekly graduate student seminars and teas at which he presided, imparting scientific knowledge and on some occasions entertaining his audience as an incomparable raconteur.

His students were somewhat in awe of the professor, perhaps wondering whether they could meet his exacting standards or could hope to emulate the seeming ease with which he succeeded in all of his professional endeavors. They learned in time that behind his somewhat reserved and formal manner was a genuine warmth and an understanding that young scientists develop their full potential only by profiting from their mistakes. His faculty colleagues also admired his many talents and sterling personal characteristics. Herbert E. Carter, who became the second member of the faculty of the Biochemistry Division in 1932, has commented that he became interested in biochemistry upon hearing Rose's lectures and states, "I recall with deep gratitude that following my graduate work in organic chemistry Dr. Rose invited me to join the Biochemistry Division. His only request of me was that I undertake the chemical synthesis of the newly discovered threonine, a project which was very fruitful in leading to my own areas of research. He enriched my life as mentor, colleague, and friend for fifty years." Carl S. Vestling, who became the third faculty member of the division, made the following remarks when he served in 1981 as moderator of "Conversations with William C. Rose," a tape-recorded group discussion:

> Absolutely uncompromising in all matters involving integrity and sincerity, he has personified many of those qualities of loyalty, unselfishness, and friendliness which mark the unusual individual. He has shown a unique blend of decisiveness and unpretentiousness in his relationships to his associates.

RECOGNITION AND AWARDS

Rose's research achievements and reputation as a stimulating and inspiring teacher brought him wide recognition and many honors. These included numerous invitations to lecture and serve as a consultant on biochemical aspects of nutrition. In addition to his work on behalf of the Nutrition Foundation and the National Research Council, as already described, he served on the Council on Pharmacy and Chemistry of the American Medical Association, the Advisory Board of the Wistar Institute, and the National Advisory Health Council of the U.S. Public Health Service. He received honorary doctor of science degrees from Davidson College, Yale University, the University of Chicago, and the University of Illinois and was elected to membership in the National Academy of Sciences. As an indication of his leadership qualities and the respect of his colleagues nationally, he was elected to serve as president of the American Society of Biological Chemists from 1939 to 1941 and president of the American Institute of Nutrition from 1945 to 1946. Other major honors included the Osborne and Mendel Award of the Institute of Nutrition, of which he was the first recipient (1949); the Willard Gibbs Medal of the American Chemical Society (1952); the Charles F. Spencer Medal of the American Chemical Society (1957);

the Twentieth Anniversary Award of the Nutrition Foundation (1961); and the National Medal of Science for 1966, conferred by the President at the White House.

On the occasion of his ninetieth birthday, Rose's former students, colleagues, and friends assembled in Urbana to join him in the celebration. He was much surprised when presented with a handsome bronze plaque announcing the establishment of the William C. Rose Lectureship in Biochemistry and Nutrition "on the occasion of his 90th birthday and presented with love, admiration and gratitude by his family of former students and colleagues." The plaque showed, in addition to his likeness and a sketch of the Noyes Laboratory, the structures of the essential amino acids and the stereochemistry and crystal structure of threonine, with a quotation and chart from his classical 1935 paper published in *The Journal of Biological Chemistry*:

> The data demonstrate conclusively that the crystalline compound is the new essential we have been endeavoring to isolate for several years. Furthermore, the experiments shown in Chart 1 represent the first successful efforts to induce growth in animals upon diets carrying synthetic mixtures of highly purified amino acids in place of proteins.

It may be noted that this prestigious national award, now administered by the American Society for Biochemistry and Molecular Biology, has been presented annually since 1978, and the awardees have all received a duplicate of the same plaque. The lectures of the recipients were originally given in Urbana to allow Rose to attend but are now presented at the society's national meetings. William J. Haines, a former student, made the following closing remarks at the celebration:

> Dr. Rose enhanced the quality of life for his students—by encouraging and supporting those things which enriched the mind and spirit. Good character was the essential raw material—good taste was the product. His per-

sonal dedication to the highest quality of performance was projected in his wise counsel. For all this, he demanded nothing in return, except excellence in performance (and behavior) of his academic children and their children, the latter whom he considers to be his academic grandchildren.

No scientist could ask for a finer memorial than having made major discoveries that contributed to the welfare of the human race and having received the respect, admiration, and gratitude of a family of former students and colleagues.

THE AUTHORS ARE GRATEFUL to Leland M. Park for material from the Davidson College Library Archives, Davidson, North Carolina, that deals with Rose's early days there and his longstanding relationship with the college; to Ellen Handler and Robert T. Chapel for useful information from the University of Illinois Archives; and to the National Academy of Sciences for a brief tribute written by Caroline K. McEuen after Rose's death.

NOTES

1. H. E. Carter. Identification and synthesis of threonine. *Fed. Proc.* 38(1979):2684-86.
2. Fifty years later the first two human subjects recalled the early experiments. J. E. Johnson and W. J. Haines. Role of amino acids in human nutrition. *FASEB Journal* 6(1992):2361-62.
3. Published in 1959 by the University of Illinois Press, Urbana.
4. *Journal of Chemical Education* 46(1969):759-63.

SELECTED BIBLIOGRAPHY

1926

With G. J. Cox. Further experiments on the alleged interchangeability of arginine and histidine in metabolism. *J. Biol. Chem.* 68:217-23.

1929

With C. P. Berg. Tryptophane and growth. I. Growth upon a tryptophane-deficient basal diet supplemented at varying intervals by the separate feeding of tryptophane. *J. Biol. Chem.* 82:479-84.

1931

Feeding experiments with mixtures of highly purified amino acids. I. The inadequacy of diets containing nineteen amino acids. *J. Biol. Chem.* 94:155-65.

With W. Windus and F. L. Catherwood. Feeding experiments with mixtures of highly purified amino acids. III. The supplementing effect of casein fractions. *J. Biol. Chem.* 94:173-84.

1934

With C. T. Caldwell. Feeding experiments with mixtures of highly purified amino acids. V. Additional properties of the unknown growth essential present in proteins. *J. Biol. Chem.* 107:57-73.

1935

The metabolism of creatine and creatinine. *Annu. Rev. Biochem.* 4:243-62.

With M. C. Womack. Feeding experiments with mixtures of highly purified amino acids. VII. The dual nature of the "unknown growth essential." *J. Biol. Chem.* 112:275-82.

With R. H. McCoy and C. E. Meyer. Feeding experiments with mixtures of highly purified amino acids. VIII. Isolation and identification of a new essential amino acid. *J. Biol. Chem.* 112:283-302.

1936

With C. E. Meyer. The spatial configuration of α-amino-ß-hydroxy-*n*-butyric acid. *J. Biol. Chem.* 115:721-29.

1939

With E. E. Rice. The significance of amino acids in canine nutrition. *Science* 90:186-87.

1942

With W. J. Haines and J. E. Johnson. The role of the amino acids in human nutrition. *J. Biol. Chem.* 146:683-84.

1946

With M. Womack. The partial replacement of dietary phenylalanine by tyrosine for purposes of growth. *J. Biol. Chem.* 166:429-34.

1948

With M. J. Oesterling and M. Womack. Comparative growth on diets containing ten and nineteen amino acids, with further observations upon the role of glutamic and aspartic acids. *J. Biol. Chem.* 176:753-62.

1949

Amino acid requirements of man. *Fed. Proc.* 8:546-52.

With L. C. Smith, M. Womack, and M. Shane. The utilization of the nitrogen of ammonium salts, urea, and certain other compounds in the synthesis of non-essential amino acids *in vivo*. *J. Biol. Chem.* 181:307-16.

1954

With G. F. Lambert and M. J. Coon. The amino acid requirements of man. VII. General procedures; the tryptophan requirement. *J. Biol. Chem.* 211:815-27.

1955

With B. E. Leach, M. J. Coon, and G. F. Lambert. The amino acid requirements of man. IX. The phenylalanine requirement. *J. Biol. Chem.* 213:913-22.

With M. J. Coon, H. B. Lockhart, and G. F. Lambert. The amino acid requirements of man. XI. The threonine and methionine requirements. *J. Biol. Chem.* 215:101-10.

With R. L. Wixom. The amino acid requirements of man. XIII. The sparing effect of cystine on the methionine requirement. *J. Biol. Chem.* 216:763-73.

With R. L. Wixom. The amino acid requirements of man. XIV. The sparing effect of tyrosine on the phenylalanine requirement. *J. Biol. Chem.* 217:95-101.

With R. L. Wixom, H. B. Lockhart, and G. F. Lambert. The amino acid requirements of man. XV. The valine requirement; summary and final observations. *J. Biol. Chem.* 217:987-95.

With R. L. Wixom. The amino acid requirements of man. XVI. The role of the nitrogen intake. *J. Biol. Chem.* 217:997-1004.

1956

With E. E. Dekker. Urea as a source of nitrogen for the biosynthesis of amino acids. *J. Biol. Chem.* 223:107-21.

1968

The sequence of events leading to the establishment of the amino acid needs of man. *Am. J. Publ. Health* 58:2020-27.

1979

How did it happen? *Ann. N.Y. Acad. Sci.* 325:229-34.