Methionine Catabolism and Cystinuria: the Work of Howard Bishop Lewis

Howard Bishop Lewis (1887–1954) was born on a farm near Southington, Connecticut. He graduated as high school valedictorian when he was 15 years old and then spent the next year working on his parents' farm while waiting to meet the Yale University age requirement for admission. During this time he also taught himself the equivalent of 2 years of high school Greek. He entered Yale University in 1904 and received his B.A. 4 years later. Lewis then spent the next 2 years teaching at Hampton Institute, in Hampton, Virginia, and at the Centenary Collegiate Institute, in Hackettsstown, New Jersey.

Lewis entered the Graduate School of Yale University in 1910, where he worked with Journal of Biological Chemistry (JBC) Classic author Lafayette B. Mendel (1). During graduate school, he spent one summer working at the laboratories of the Connecticut State Hospital in Middletown looking at the nature of the antigen in the Wasserman reaction and his last 2 years at Yale working as Mendel's laboratory assistant.

Following the completion of his doctorate in 1913, Lewis accepted an instructorship in physiological chemistry in the School of Medicine of the University of Pennsylvania. He remained at Pennsylvania until 1915 when he accepted a position at the Urbana campus of the University of Illinois. In 1922 Lewis was called to head the Department of Physiological Chemistry at the University of Michigan, where he remained for the rest of his career. In 1947, the University conferred upon him the John Jacob Abel University Professorship in Biological Chemistry, and he served as director of the College of Pharmacy from 1933 to 1947.

With the collaboration of his students and colleagues, Lewis published an impressive list of scientific articles covering a broad range of topics. Early in his career he became interested in

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the *in vivo* formation of hippuric acid following the administration of benzoic acid. Lewis' interests then shifted to the metabolic behavior of the physiologically important sulfur compounds, particularly the amino acids cystine and methionine. He performed experiments that suggested that cystine is an indispensable dietary component, looked at the oxidation of cystine and its derivatives in the body, and even investigated the cystine content of hair from several species, designing experiments to determine the relationship of sulfur-containing amino acids to the growth and composition of the hair.

As to be expected, Lewis was also interested in cystinuria, the genetic disorder that is characterized by the formation of cystine stones in the kidneys, ureter, and bladder. Lewis and his colleagues performed tests on urine samples from about 11,000 subjects and showed that cystinuria was not as rare a condition as previously thought. The samples were obtained from medical examinations given to students entering the University of Michigan and two neighboring institutions.

Lewis later used several of these cystinuric individuals for further investigations, including the one highlighted in the JBC Classic reprinted here. For this paper, he administered either cystine, cysteine hydrochloride, or *dl*-methionine, combined with a high or low protein diet to a cystinuric subject and measured the amount of extra cystine and sulfur excreted in the subject’s urine. He found that the administration of cystine did not affect cystine excretion, but it did induce a large increase in the sulfur content of the urine. Cysteine hydrochloride and *dl*-methionine, on the other hand, led to increases in the excreted amounts of both cystine and sulfate. Surprisingly, less extra cystine was excreted after methionine was administered to the subject when he consumed a high protein diet. These results led Lewis to conclude that “the utilization of the precursor of the urinary cystine in cystinuria occurs more readily under conditions of a high level of protein metabolism. Such a theory would explain the failure of the cystine sulfur to maintain a constant ratio to the nitrogen or total sulfur of the urine, as the amount of protein catabolized is increased.” Lewis' experiments also confirmed an earlier hypothesis by Erwin Brand (2) who postulated that cysteine is a product of the catabolism of methionine and that the error in cystinuria is a failure of the proper utilization of cysteine and not of cystine. Thus, the extra cystine excreted after the feeding of methionine is derived directly from the degradation of methionine, with cysteine as an intermediary product.

Lewis' scientific curiosity was not limited to cystine and methionine, however, and his later experiments extended to the origin, functions, and metabolic properties of many other amino acids including phenylalanine, histidine, and lysine. In addition to protein metabolism, Lewis studied carbohydrate and branched-chain aliphatic acid metabolism, described new examples of *β*-oxidation, and conducted a series of studies on the hydrolysis of esters of dicarboxylic acids by liver lipase.

Lewis was intimately involved with many organizations and served as secretary (1929–1933), vice president (1933–1935), president (1935–1937), and councilor (1937–1940 and 1941–1942) of the American Society of Biological Chemists (now the American Society for Biochemistry and Molecular Biology). He also served as councilor (1941–1942), vice president (1942–1943), and president (1943–1944) of the American Institute of Nutrition and managed the Placement Service of the Federation of American Societies for Experimental Biology, bringing together many young scientists seeking employment and institutions seeking personnel. At various times in his career, Lewis was a member of the editorial boards of the *Journal of Biological Chemistry*, the *Journal of Nutrition*, *Chemical Reviews*, *Physiological Reviews*, and the *Proceedings of the Society for Experimental Biology and Medicine*. He was elected to the National Academy of Sciences in 1949.1

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REFERENCES


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1 Biographical information on Howard Bishop Lewis was taken from Refs. 3 and 4.