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Classics

A PAPER IN A SERIES REPRINTED TO CELEBRATE THE CENTENARY OF THE JBC IN 2005

JBC Centennial
1905–2005
100 Years of Biochemistry and Molecular Biology

The Most Highly Cited Paper in Publishing History: Protein Determination by Oliver H. Lowry

Protein Measurement with the Folin Phenol Reagent
(Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951) *J. Biol. Chem.* 193, 265–275)

On Tyrosine and Tryptophane Determinations in Proteins
(Folin, O., and Ciocalteu, V. (1927) *J. Biol. Chem.* 73, 627–650)

Oliver Howe Lowry (1910–1996) was born in Chicago, the youngest of five children. He enrolled at Northwestern University in chemical engineering, hoping to combine chemistry and engineering to emulate his two oldest brothers. However, he switched his major to biochemistry two years later, after spending the summer with an enthusiastic pre-med friend who convinced him that "so little was known about biochemistry that anything (he) found out would be new" (1).[1]

Lowry received a bachelor's degree in chemistry in 1932 from Northwestern University and entered the University of Chicago as a graduate student in physiological chemistry. With Frederick Koch as his thesis advisor, Lowry started what would be a lifelong study of micro methods when he developed a method for measuring ketone bodies in one milliliter of blood. During his second year, the Dean asked Lowry if he would like to enroll in the University's M.D.-Ph.D program. The University of Chicago was one of the few schools that offered an M.D.-Ph.D. program at that time. Because he had already taken many of the preclinical courses, Lowry was able to squeeze four academic years into three calendar years, and in 1937, he graduated with both a doctorate in physiological chemistry and a medical degree. Although he never practiced medicine, he said his medical degree "added to my enjoyment of biomedical research, broadened my perspective about living systems, and (was) good for my ego" (1).

While at the University of Chicago, Lowry met A. Baird Hastings, author of a previous *Journal of Biological Chemistry* (JBC) Classic (2). Hastings agreed to let Lowry work in his laboratory at Harvard University, and after graduating from Chicago, Lowry started working on one of Hastings' basic interests: electrolyte metabolism. Lowry was able to develop micro methods to measure electrolytes in milligram-size tissue samples, and the methods allowed them to study electrolyte changes in the myocardium, heart, skeletal muscle, liver, brain, and kidney. He also developed micro methods for measuring collagen and elastin.

Hastings also arranged for a fellowship from the Commonwealth Fund that allowed Lowry to work with Kai Linderstrøm-Lang at the Carlsberg laboratory in Copenhagen. Lowry was greatly influenced by Linderstrøm-Lang, calling him "the most talented human being I have ever known" (1). Linderstrøm-Lang shared Lowry's interest in microanalytical methods and had invented and developed a whole scheme of quantitative histochemistry together with the appropriate devices. During their time together, Lowry's interest in micro methods increased to the point where he declared, "If I was attracted to micro methods before I went to Copenhagen, I was an incorrigible addict by the time I left" (1).

Between 1942 and 1947, Lowry worked at the Public Health Research Institute in New York City, where he developed micro methods that could screen for vitamin deficiencies in children using very small amounts of blood. It was during this period that he also worked out a simple

[1] All biographical information on Oliver H. Lowry was taken from Ref. 1.

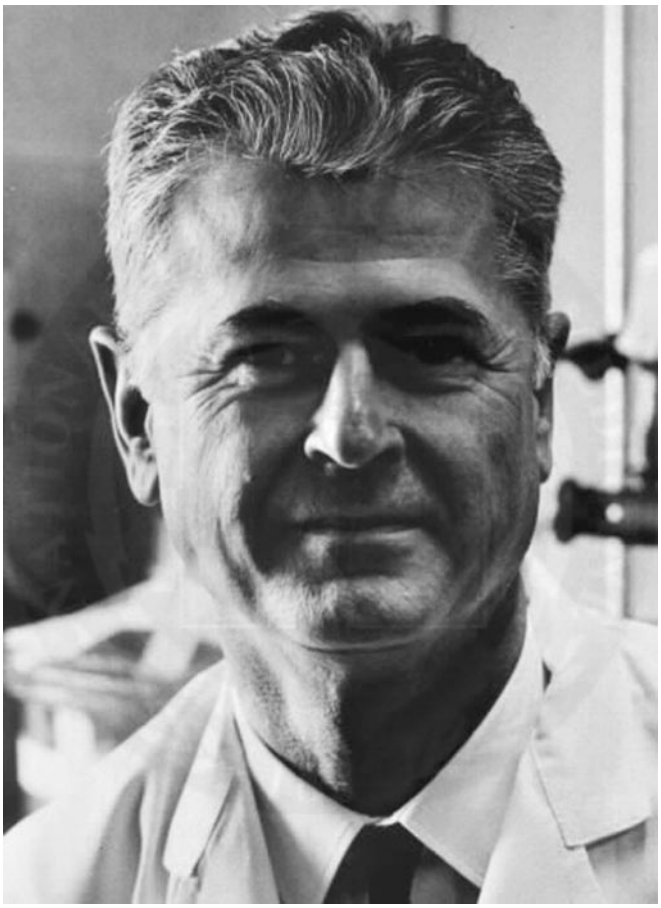

Photo courtesy of the National Library of Medicine.

yet sensitive method for measuring the amount of protein in solutions. This paper, which is featured here as a JBC Classic, is the most highly cited paper in science. As of January 2004, it was cited 275,669 times.

Lowry's method was based on the "Phenol Reagent" developed by Otto Knut Olof Folin (who was featured in a previous JBC Classic (3)) and Vintila Ciocalteu for use in protein determinations. The Folin-Ciocalteu paper is also reprinted here as a JBC Classic. Lowry determined that the Folin phenol reagent (phosphomolybdic-phosphotungstic acid) would bind readily to copper-treated protein. Over time, the bound reagent was reduced, resulting in a color change from yellow to blue, which could then be used to determine protein concentration.

Despite the great practical applications of Lowry's method, he did not publish the details immediately. Instead, he passed them on to whoever wanted them. One of the recipients of the method was Earl Sutherland, who complained of being tired of referring to "an unpublished method of Lowry." With Sutherland's prompting, Lowry finally performed a thorough study of the procedure: its limitations and virtues and the results it gave with different proteins and tissues in comparison with other methods. Lowry's first submission to the JBC was returned for drastic shortening, but the paper was eventually accepted in an abbreviated form.

In 1947, Lowry was invited to become Head of the Department of Pharmacology at Washington University in St. Louis. He recalled, "This was quite a gamble on the part of the university. I had never had a real course in pharmacology, nor had I done any research that was even marginally pharmacological. Moreover, my two predecessors, Carl Cori and Herbert Gasser, were both Nobel Laureates, and there was no sign that I would get to Sweden except as a tourist" (1). Despite these initial doubts, things worked out for Lowry and he chaired the Department of Pharmacology for the next 29 years and was Dean of the School of Medicine from 1955 to 1958.

At Washington University, Lowry's passion for measuring minute quantities of biological substances led him to quantitative histochemistry. He eventually pioneered methods for freeze-drying tissue sections from which he was able to dissect out small portions for weighing and analysis. Since there was no balance sensitive enough for his experiments, he invented a

microbalance that could measure less than one-millionth of a gram. Lowry also designed a very sensitive method to measure a wide variety of metabolites and enzymes based on the fluorescence of NADH and NADPH and an amplification technique called enzymatic cycling in which enzyme systems are used to amplify the pyridine nucleotides generated by specific enzyme reactions.

Lowry received many honors in recognition of his scientific achievements, including the John Scott Award (1963) from the Board of City Trusts of Philadelphia and the Borden Award of the Association of American Medical Colleges (1966). He was elected to the American Academy of Arts and Sciences in 1957, the National Academy of Sciences in 1964, and the Royal Danish Academy of Sciences in 1968.

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