Oliver Howe Lowry – the 'incorrigible addict' of micro-analytical methods

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Oliver H. Lowry was a researcher with avant-garde passion for development of micro-analytical methods that later became his raison d'être. This article attempts to bring out the life sketch of Lowry, the genius credited with, amongst other laurels, a research paper on protein estimation that has been the most cited in the publishing history. This note highlights the challenges and success stories, the personal and academic journey of Lowry in various institutions of repute, unparalleled contribution to the domain of biochemistry and nuances of his personality.

Protein estimation is a regular feature in the laboratories worldwide. Amongst others, executing the protocol developed by O. H. Lowry (in its original form or with various modifications) is almost an everyday affair. Browsing the internet unmasks a fascinating revelation: the research paper on protein estimation, authored by Lowry *et al.*[1] has been the most cited in the publishing history[2]; the number stands at 210,537 as of 9 September 2019 (courtesy: Google Scholar). Passion for and contribution to the domain of micro-analytical methods have made Lowry a common and inseparable name in various laboratories all over the world. This note describes the incredible journey of this genius.

As the youngest of five children, Lowry was born in Chicago on 18 July 1910 to a religious family with lineage, intricately associated with the American Revolution[3]. His mother had a strong reverence to education. His father was a teacher, principal and also shouldered the responsibility of superintendent in the Chicago public school system. It is of pertinence to note that his father instead of answering the 'why' questions put forth by the young Lowry, encouraged his son to find the solutions himself – a strategy that had fueled his inquisitive mind even more in the later days. Lowry[3] mentions that he had a feeling of inferiority due to the accomplishments of his siblings in various fields. However, a perfect score of 100 in a high-school intelligence test (obviously not considered as a sign of academic brilliance by him, reflecting his humility) ushered in him a sense of determination to scale heights of achievement in the future. He skipped school a couple of times and worked for a considerable period as a seaman on a cargo-boat to the Philippines and Korea, and also worked on his uncle's ranch in Nebraska in his teens.

The unmasking of facts, features and phenomena in the domain of biochemistry was still in its burgeoning stage in 1930s and as such anything novel in this field was expected to spark tremendous interest across the scientific fraternity. Driven by this, an enthusiastic friend convinced Lowry to switch from chemical engineering to biochemistry. With a Bachelor's degree in chemistry in 1932 from Northwestern University, Lowry enrolled at the University of Chicago as a graduate student in physiological chemistry. Frederick Koch (who was striving to isolate testosterone from urine at that time) was his thesis advisor. Starting with the development of a method (though never published) for measuring ketone bodies in 1 ml of blood, micro-analytical methods became his raison d'être. During his second year, the Dean asked Lowry if he was interested to enroll in the university's M D–Ph D programme. Previous exposure to a number of pre-clinical courses enabled Lowry to compress four academic years into three calendar years. In 1937, he received both a doctorate in physiological chemistry and a medical degree. It is of pertinence to note that Lowry never practised medicine; however, his educational background surely helped him to widen his perception about biological systems.

Lowry served at Harvard University as an instructor from 1937 to 1942. Here, he started working on one of Baird Hasting's prime interests: electrolyte metabolism. Lowry successfully pioneered protocols to measure electrolytes in milligram-size tissue samples. Justifying the micro-techniques on the reasoning that 'cells, just a little ways apart are often very different', Lowry, in collaboration with a number of eminent scholars of the time, successfully studied electrolyte changes in the myocardium, heart, skeletal muscle, liver, brain and kidney, attributed to conditions like ischaemia, hypoxia and ageing. Micro-methods were also developed for measuring collagen and elastin. Lowry received a much-coveted fellowship from the Commonwealth Fund to work with Kai Linderstrøm-Lang at the Carlsberg laboratory in Copenhagen, Denmark during World War II. He remained a life-time aficionado of Lang (a multifaceted personality) for the latter's success in inventing and devising a whole scheme of quantitative histochemistry, complemented by a gamut of befitting devices.

From 1942 to 1947, Lowry worked at the Public Health Research Institute (PHRI) of the city of New York, where he developed micro-methods to screen vitamin deficiencies in children using pin-pricks of blood. With a desire to do a little as a researcher during the war days, Lowry worked in close collaboration with Otto Bessy (Department of Biological Chemistry, University of Illinois, College of Medicine, Chicago) and later Helen Burch (Department of Chemistry, Columbia University, New York) in a number of pertinent nutritional studies. Residents from Munich, various personnel from the Royal Canadian Air Force as well as volunteers from the staff at PHRI participated actively in these studies. The alkaline phosphatase method as well as colorimetric procedure for quantification of inorganic phosphate (under conditions not harsh enough to solubilize the unstable organic phosphates) saw their genesis at PHRI. This was also the period wherein Lowry initiated the revolutionary, simple, yet sensitive method for measuring the amount of protein in

solution. He determined that the Folin phenol reagent (phosphomolybdicphosphotungstic acid) would bind readily to copper-treated protein. The reduction of the bound reagent resulted in a colour change from yellow to blue, which could be used to determine protein concentration[1]. He performed a thorough study of the procedure, documented its pros and cons along with the results it gave with a myriad of proteins and tissues in comparison with other methods. The method, albeit challenged by intrinsic limitations[4], was simple, sensitive and reproducible. With Earl Sutherland's prompting, Lowry finally submitted his paper to the *Journal of Biological Chemistry*, however, it was returned for major scissoring. Lowry's paper was eventually accepted in a trimmed form. This marshalled in a new era of protein biochemistry.

Lowry chaired the Department of Pharmacology at Washington University in St Louis and was Dean of the School of Medicine from 1955 to 1958. He sought support from the Committee on Growth of the American Cancer Society for revelation on the 'quantitative histochemistry of the nervous system'. During this period, he pioneered the methods for freeze–drying tissue sections that permitted retention of metabolically labile substances at levels that were the *in vivo* at the moment of freezing. The invention of a microbalance that could measure less than one-millionth of a gram is credited to this genius. Besides unmasking the logistics of the glycolytic pathway in the brain, enzyme-assays based on fluorescence of NADH and NADPH, and enzymatic cycling technique (in which enzyme systems are used to measure the pyridine nucleotides generated by specific enzyme reactions) developed by Lowry had a colossal impact in biology and medicine. Remarkably, Lowry referred to the enzyme phosphofructokinase (PFK), allosterically regulated by various positive and negative effectors, as 'the most complicated enzyme alive'. At this juncture, it is of relevance to note that the quantitative histochemistry techniques and microchemical methodology had inspired a number of pertinent biological studies to be undertaken. As an exemplary anecdote, 45 years ago, Elizabeth Barbehenn, then a graduate student and Raymond Wales, a visitor from Monash University in Australia, tried to unveil the growth supportive role of pyruvate or lactate vis-à-vis non-supportive role of glucose as sole carbon source while culturing fertilized mouse ova, prior to the eight-cell stage[3]. Based on about 1000 ova from 50 mice, analysis of the flux of metabolites (glucose-6-phosphate, fructose-6-phosphate, fructose-l,6-bisphosphate, citrate and malate) and regulation of the key enzymes (PFK and hexokinase) revealed a fundamental aspect: glucose needs to be used up to pile up glycogen as a reserve for implantation, while energy requisite could be met by pyruvate. The study was later extended to human ova, for which data were obtained for 17 enzymes of eight metabolic pathways. Furthermore, about three decades ago, Lowry and his team reported that 2-deoxyglucose and 2-deoxyglucose-6-phosphate could be separately quantified enzymatically with $NADP^+$ as cofactor. Lowry in his various research publications had emphasized upon the application of biocatalysts, their metabolites and cofactors as well as enzymatic amplifier protocols, owing to the convenience, sensitivity and specificity of the biocatalysts.

Lowry has been capped with a number of laurels and titles, including the John Scott Award in 1963 from the Board of City Trusts of Philadelphia and, the Borden Award of the Association of American Medical Colleges in 1966. He was elected to the American Academy of Arts and Sciences in 1957, the National Academy of Sciences in 1964, and Royal Danish Academy of Sciences in 1968. In 1970, *Nature* christened him among the world's 50 most eminent scientists. In 1988, he was awarded the Medal of the 30th Anniversary of the Cosmic Era, USSR, for ground-breaking work on long-term effects of weightlessness on muscles. Washington University established the Oliver H. Lowry Prize Lectureship in 1978.

The Google Scholar webpage link of Lowry, highlights his valuable scientific contributions (https://scholar.google.com/citations?hl=en&user=YCS0XAcAAAAJ&view_op=list_works&sortby=pubdate). The distinguished Professor Emeritus suffered from Alzheimer's disease and breathed his last on 29 June 1996 in St Louis at the age of 85 years. The biographical information as mirrored in the *Annual Review of Biochemistry*[3] echoes the ways how a genius creates his own non-conventional avenues to walk on and then leaves his footprints for eons.

1. Lowry, O. H., Rosebrough, N. J., Farr, A. L. and Randall, R. J., *J. Biol. Chem.*, 1951, **193**, 265–275.
2. Kresge, N., Simoni, R. D. and Hill, R. L., *J. Biol. Chem. Classics*, 2005, **280**, e25–e28.
3. Lowry, O. H., *Annu. Rev. Biochem.*, 1990, **59**, 1–27.
4. Valmikinathan, K. and Shanmugasundaram, E. R. B., *Curr. Sci.*, 1962, **31**, 460–461.

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