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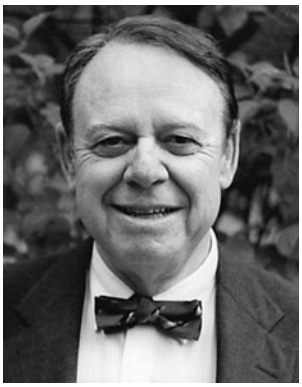
OBITUARY

Bert L. Vallee, "Mr. Zinc" (1919–2010)



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Bert Vallee was born in Germany in 1919 but was educated in Switzerland. He came to New York in 1938, aged 19, and wished to enroll as a student of science and medicine at New York University. When he was told that he had to choose between the two he chose medicine. However, he studied science extramurally and took a Bachelor of Science at Bern University, Switzerland in 1942. He completed his MD at New York University in 1943 but never followed this up with clinical work. He moved to Boston, joining Cohn and Edsall in a joint Harvard/MIT group that was studying blood preservation. There he picked up an interest in both protein chemistry and in analysis, mainly of blood Na, K, and Ca. The analytical section was headed by Prof. Loofborough about whom Vallee later on always spoke with great regard.

Two analytical techniques were used and improved by Vallee both in this period and subsequently: mass spectrometry and flame spectroscopy. Vallee's first analytical paper of note was a comparison of red oxygen-carrier cells and the metabolically active white blood cells, which gave him inspiration for much of his subsequent work. He observed that the white cells contained a large amount of zinc in contrast with the less active red cells that contained heme iron but little zinc. He realised that zinc must have very important functions in active metabolising cells and was potentially of as great interest in human health as iron. Subsequently he was at first supported at a somewhat low level by the Harvard Medical School but was able to build a laboratory in a large cellar of the Peter Bent Brigham Hospital, which he duly equipped for analytical studies of mostly zinc in proteins. He was fortunate to make a connection with Hans Neurath, a protein chemist studying carboxypeptidase, which was thought to contain magnesium, but in 1954 Vallee showed it to be a zinc metallo-enzyme. The work illustrates his great ability and care in such analyses for it demanded very clear, high standards of accuracy and reproducibility. It opened the whole important field of zinc in nutrition. He became the Paul C. Cabot Professor at Harvard.

In 1954–1955, in an exchange of letters with me, we discovered our overlapping interests. Vallee was a medical metalloprotein biochemist and analyst while I was a biological inorganic chemist. He invited me to join him for the summer of 1956 and again in 1966–1967 working on the two zinc enzymes he had by then discovered, carboxypeptidase and alcohol dehydrogenase. In six papers from 1955 to 1968 we showed how to use metal substitutions in the study of enzymes, importantly cobalt for zinc (but many others too), and the nature of inhibitors of the zinc enzymes. For Vallee the latter was seen as a way to find potential medically valuable drugs that bound zinc. In

1968 we proposed the entatic state nature of metalloenzyme sites. In 1967 Vallee discovered the cadmium metallothionein and more recently has pursued the value of it as a zinc protein in homeostasis. He saw the medical significance of his work and that it had clear implications for the food and drink industry. In this he was clearly a leader of a major field. Carboxypeptidase is a digestive enzyme and alcohol dehydrogenase has obvious connections to the interests of the alcohol drinks industry. It is now known that zinc proteins are close to 10 percent of the human proteome. As a consequence, his work not only enjoyed academic support and acclaim but was very greatly aided by industry, which he advised. From 1960 Vallee began to widen his studies of zinc enzymes to detailed evaluation of organic reagents for uncovering the amino acids involved in enzyme activity, to the kinetics of the enzymes, and to the functions of metallothioneins, which studies he continued for the rest of his life. He did work on a further zinc enzyme, a ribonuclease, and frequently reviewed the field of zinc biochemistry, but I believe that by moving away from analysis he missed discovering two important aspects of zinc biochemistry that would have added considerable lustre to his reputation as Mr. Zinc. They are the zinc fingers and the biochemistry of zinc in the brain. In fact, he turned with success to an additional different study. With Judith Folkman he searched for the activity factor of angiogenesis in cancer growth and uncovered the nature of an enzyme, angiogenin. It proved to be a phosphatase, an enzyme that does not require metal ions. Despite these changes of interest, he remained a strong advocate of the value of studies of zinc biochemistry on which he frequently lectured.

During his career he was awarded many prizes, medals, and honorary degrees. He was a member of the National Academy of Sciences. Several of his research pupils are now well-known figures in metallo-biochemistry. I remain extremely grateful to him for allowing me to study in the Harvard Medical School. From its courses that I attended and from him I learned much of medical biochemistry. He will be remembered by all who knew him as a man of intelligence and humour, with a strong desire to remain independent in an effort to solve medical problems linked, at first, to zinc. Before he died, he and his devoted wife set up a foundation for funding professional science exchanges, the Vallee Foundation.

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