Bert L. Vallee

1919–2010

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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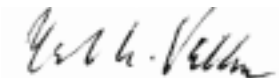
NATIONAL ACADEMY OF SCIENCES

BERT LESTER **VALLEE**

June 1, 1919–May 7, 2010

Elected to the NAS, 1974



By S. James Adelstein and James F. Riordan

Bert Lester Vallee, who died on May 7, 2010, was an iconoclastic figure. He would rail against the bureaucracy of institutions, especially Harvard, but would contribute substantially to their welfare—as a talented trace-metal biochemist, as an innovative medical educator, as a pioneer in academic-industrial relationships, and as a creator of ingenious organizations that promoted biomedical research and collaborative international collegiality.

Bert was born on June 1, 1919, to Josef and Rosa Blumenthal in Hemer, Westphalia, Germany. The family subsequently moved to Luxembourg. He attended the University of Berne, where he received a B.Sc. in 1938 concentrating in zoology—later reminiscing frequently on his course in embryology given by a student of the great developmental biologist Hans Spemann. He came to the United States immediately afterwards as the first, and only, fellow of the International Student Service of the League of Nations. For an advisor, he was assigned the brilliant mathematician Richard Courant, who prepped him for entrance to New York University and its medical school.

On receiving his M.D. degree, Bert interned for a short time at Grady Hospital in Atlanta, where he developed a life-long aversion to both chicken and racism, and for a year at Mt. Sinai Hospital in New York City. In that era, many of the Mount Sinai teaching staff were refugees from Germany and Austria who brought with them a strong tradition in clinical diagnosis. This period of clinical training served Bert well, and the impressive knowledge of internal medicine he derived from it was put to good use in teaching and in advising his friends on medical matters.

During World War II Bert worked at Harvard Medical School in the blood preservation program of E. J. Cohn and John Edsall, founding fathers of biophysicalprotein chemistry.

One of the techniques employed to monitor the viability of red blood cells was to label the cells with radioactive iron. This practice gave Bert the idea that there might be an equivalent means to study leucocyte viability. There was suggestive evidence in the literature that white cells might contain zinc, and Bert looked for a way to measure cellular zinc.

The first problem he encountered was how to isolate leucocytes, and one of his first publications (in the journal *Blood*) described a novel method for doing so (Vallee, et al., 1947). He did some early work using radioactive zinc and later developed a colorimetric chemical assay using dithizone. But he knew that he needed a means that would provide him with greater accuracy and precision. As a consequence he found a way to divide his time between the medical school and MIT's radioactivity center. He realized that zinc analysis was fraught with difficulties, but rather than discourage him it stimulated his interest in the biological functions of zinc and other transition elements in white blood cells.

Bert was determined to overcome the obstacles and find reliable analytical methods. Consequently, after the war, he joined the MIT Spectroscopy Laboratory under the preceptorship of John R. Loofbourow, a biologist, and George Harrison, a physicist, with the purpose of developing sensitive methods for detecting and measuring trace metals. His method of measurement, using the direct-current arc (now superseded by atomic absorption spectroscopy), was enormously demanding, and Bert's meticulous attention to its detail made his laboratory one of the few that could perform reliable analyses. It is during this period that he met and wed Natalie T. Kugris, who became his lifetime companion of 63 years.

Bert's time at MIT was a yeasty one. He not only was working on methods for trace-metal analysis but was also taking courses and broadening his acquaintance with like-minded scientists in this country and abroad. On a visiting fellowship at the Karolinska Institutet in Stockholm, he was able to meet the then-senior biochemist of trace-metal enzymology, Hugo Theorell; some years later Theorell reciprocated by visiting Bert at his laboratory. On the same trip Bert also visited the renowned protein chemist Kaj Linderstrøm-Lang at the Carlsberg Laboratory in Copenhagen. This led to a long-term friendship with Lang's colleague Martin Ottesen, and much later with Ottesen's student Jack Johansen.

These and other international forays played an important role in developing Bert's belief in the importance of international collaboration. One interesting consequence of this was an occasion when he was visited by his colleague Ephraim Katchalski-Katzir, from Israel's Weizmann Institute. It so happened that Katzir had become President of Israel and was

accompanied by a small army of bodyguards who occupied the lab and temporarily halted research.

Bert's first faculty appointment, was to the medical department at Peter Bent Brigham Hospital (now the Brigham and Women's Hospital) at Harvard. Its chief of medicine, George Thorn, was eager to have a basic research program to complement the clinical ones. In addition, Thorn was a principal advisor to the group helping Howard Hughes establish his biomedical research institute and suggested that Bert be asked to provide advice. On a visit to Oxford University, where he had begun some additional life-long collaborations, Bert had been impressed with the structure and function of All Souls College, and now he suggested that the nascent institute look to that organization for ideas. The form that ultimately emerged at the Howard Hughes Medical Institute (HHMI) was one of supporting independent investigators, not in residence but attached to various other institutions. Their salaries and research would be funded by the HHMI, thus freeing them of the chore of writing multiple grant proposals and of carrying a heavy teaching load. Bert believed that some of the structure that ultimately was put in place derived from his recommendations.

George Thorn's wish for a basic science laboratory at Peter Bent Brigham was realized in 1954, when the Rockefeller Foundation decided to back the construction and furnishing of a laboratory for Bert Vallee. It was initially called the Trace Metal Laboratory, and a sign to that effect was dutifully placed on the laboratory door. The story goes that within days ambitious clinicians were lining up in the hallway, specimens in hand, seeking analyses that would bring them fame and fortune. It so happened that the Biophysical Society was holding a meeting in Boston at that very time, and this coincidence inspired Bert to rename his laboratory the Biophysics Research Laboratory (BRL). The original sign disappeared, and, as no one knew what biophysics meant, peace and quiet prevailed.

The BRL was located in the bowels of the hospital, under an open general male ward. On entering from a somewhat grimy basement, one found a shiny biochemical and biophysical research space equipped with the latest in instrumentation; its centerpiece was a large Jarrell-Ash emission spectroscope built to Bert's design. (Bert once admitted that when he first entered the finished lab he said to himself "What if zinc has nothing to do with anything?") Thus began an incredibly productive period in Bert's scientific research career, funded largely by a program-project grant from the NIH that lasted for 20 years.

The BRL was organized along continental principles. There was a geheimrat (roughly, highest advising official), Bert, the laboratory chief; a scientific sub-chief, Fred Hoch; a laboratory administrator; junior faculty members, graduate students, and numerous post-doctoral fellows. Bert's habit was to make rounds at each investigator's work station, pipe in mouth, prepared to enjoy any new joke to be offered as well as scientific findings. Each Thursday evening, often after a convivial dinner in the hospital cafeteria, all members of the lab convened to hear reports from one or more of the fellows, who had been designated in advance.

At these meetings the conviviality of the dinner was replaced by critical evaluation. Woe to any fellow whose report was not crisp and exacting. As tracemetal analysis requires meticulous attention to purity and exactness in measurement, mastering the art is not for the less careful. Consequently, every fellow had to demonstrate proficiency in reproducing a standard dithizone method for determining zinc before undertaking a new research problem. Errors in accuracy, repeatability, reproducibility, and precision were all fair game for censure. While Bert was quick to criticize failures in analysis, he would equally enthuse about new findings and innovative proposals.

Bert's experience in trace-metal analysis ingrained in him an obsession for attention to detail. This became painfully obvious at these Thursday evening meetings when it was time for an American Chemical Society, American Society for Biological Chemistry, or other meeting. It took several weeks of oral presentations of abstracts, with multiple revisions, however trivial, before they could be submitted to a meeting. This phase would be followed by endless drafts of the talks themselves, along with countless revisions of the slides. Bert had a great enthusiasm for colored slides (years before Power Point) and in the end everyone had to admit that the final products were, indeed, exceptional.

Over the next several decades the laboratory was the seat of a number of seminal discoveries in metallobiochemistry. Perhaps the first was the finding of zinc in bovine pancreatic carboxypeptidase (CPD). There had been a report in the literature that CPD was probably a magnesium-dependent enzyme. Bert had been invited to give a seminar in the Biochemistry Department at the University of Washington and while there he told Hans Neurath that he was skeptical of this possibility. Neurath, an expert on pancreatic proteases, including CPD, offered to provide Bert with some of the enzyme for trace-metal analysis.

Bert found zinc, and CPD became the first zinc enzyme discovered in the United States and only the second, after carbonic anhydrase, known in the world (Vallee and Neurath,

1954). Within a year he further reported that alcohol dehydrogenase from yeast was also a zinc enzyme. After that the BRL elaborated scores of other zinc enzymes. Bert's motto soon became "cogito ergo zinc." Later, he and his researchers delineated the structure and confirmation of zinc binding sites and the distinction between catalytic, regulatory, and structural ones in several enzymes and theorized the generalization of the related coordination chemistry in an entity called the entatic state (Vallee and Williams, 1968).

Having demonstrated that an enzyme contained zinc, Bert wanted to know what the zinc was doing there. In the case of CPD he found that if he removed the zinc the enzyme became inactive.

Bert was not so enamored with zinc that he lost interest in other trace elements. Indeed, he was more than cognizant that other metals, such as copper and iron, were known to play a role in biology. He attributed the general awareness of these metals to the fact that they had a visible color in solution whereas zinc was colorless. Another metal that captured his attention was cadmium. While it was not known to be biologically essential, its place on the periodic table—just below zinc—made him suspicious. His hunch paid off. In 1957 he and Marvin Margoshes reported on a unique metalbinding protein, metallothionein (Margoshes and Vallee, 1957), which they isolated from horse kidneys and whose structure, after much work, they defined. Thought at first to be a scavenger of toxic elements, metallothionein is now known to have an important role in metal homeostasis and redox activity.

These advances were the result not only of Bert's exceptional intuition and embrace of the latest technology but also his capacity to attract young scientists and clinicians of outstanding ability. Over one period, almost all of the recent medical chief residents at the Peter Bent Brigham Hospital had spent time in his laboratory. Many of the graduates went on to stellar careers in science or medicine in this country and abroad.

Having demonstrated that an enzyme contained zinc, Bert wanted to know what the zinc was doing there. In the case of CPD he found that if he removed the zinc the enzyme became inactive. This was not an easy task to accomplish, owing to the ubiquitous nature of zinc contamination; it required extraordinary precautions to achieve zinc (and other metals)–free conditions. Bert found that he could restore activity to CPD not only with zinc but with other divalent metals as well. One was cobalt, which has a visible absorption spectrum and is paramagnetic. It lends itself to an array of spectroscopic tech-

niques including EPR, EXAFS, CD, and MCD. Bert and his colleagues exploited all of these technologies over the years and firmly validated the lab's expertise in biophysics.

Bert recognized that the protein component of a metalloenzyme was more than just a metal carrier. In the days before mutagenesis there were limited means to study enzyme active sites, so Bert and his co-workers used conventional chemical modifications and invented new ones to show that there was a critical tyrosine residue and a glutamic acid residue involved in CPD catalysis. One outcome of this work was the demonstration that the structures of CPD in the crystal and solution states were different (Johansen and Vallee, 1975). This finding was somewhat disconcerting to crystallographers who believed that crystal structures were sacrosanct.

With alcohol dehydrogenase, Bert used many of the same metal-focused approaches to look at its mechanism of action. With the aid of a novel double-ternary complex affinity chromatography technique he was able to isolate the enzyme from human liver and discovered that it was a mixture of multiple isozymes. This led him to examine isozyme patterns in different individuals with the objective of finding clues to alcohol metabolism.

Bert wanted to extend his investigations into the role of zinc in biology to include intact cells. He judiciously chose to study the unicellular organism Euglena gracilis. It could survive but not proliferate in a zinc-deficient medium. These studies were very fruitful and led to the identification of zinc as a component of nucleotide polymerases and of proteins that regulate gene expression (Falchuk, et al., 1975).

Several years after the inauguration of the Biophysics Research Laboratory, Bert was promoted to associate professor of medicine, then a permanent appointment at Harvard Medical School. He had also assumed the position of directing the Brigham Clinical Chemistry Laboratories and was appointed Physician, a senior post at Peter Brent Bigham. His new position as a physician-scientist whose primary activity was research rather than the care of patients, was, for some, controversial. The matter was happily resolved on Eugene Kennedy's arrival as chairman of Biological Chemistry; he arranged for Bert to assume a tenured spot in that department. Shortly thereafter, Dean George Packer Berry called Bert to the Paul C. Cabot chair in recognition of his contributions to the medical school. Bert, who had been unsure of his relationship with Berry—as he subsequently was with other academic administrators—when told about this appointment, claims to have replied "Dean Berry, I am speechless"—to which Berry retorted, "the ultimate triumph of my career."

On his appointment to the Department of Biological Chemistry, Bert was asked to organize a Saturday morning clinic that, running in parallel with the first-year course in biochemistry, would present examples of biochemical abnormalities in disease. He accepted this assignment with great enthusiasm and, being a natural showman, turned the clinics into scientific theater. Cases of gout, porphyria, and other chemical disorders were presented, often with exotic graphics that were the stock-in-trade of his lectures. A number of former students remember these presentations with delight.

Bert had also thought quite a bit about how best to combine science with medicine in the instruction of medical students. He was given permission, with their consent, to oversee the second-year course of study for a small group. Using case-based and tutorial instruction (foreshadowing a curricular change introduced in the 1980s), he led the group through a combination of patho-physiology and physical diagnosis. The course was a great success and was repeated at least once. In addition, Bert fashioned a course in human biology and medicine for hospital-based scientists. This, too, was a success, as the students performed well on examination by others on the clinical faculty.

In addition to these courses, Bert chaired a committee formed to decide whether Harvard Medical School should adopt an M.D.-Ph.D. program. The faculty was of mixed opinion on this matter, some claiming that one doctorate was sufficient and that research training in the biomedical specialties could better be obtained in a post-M.D. fellowship. Bert believed the additional coursework and the discipline of writing a thesis for obtaining a Ph.D. were valuable in themselves. He felt he had benefited a good deal from his courses at MIT and was a strong advocate of the combined degree. The committee, like the medical faculty, was divided. Bert, having learned that some opponents took long weekends, devised to hold meetings late on Friday, when they would be absent. He later claimed that this maneuver allowed to him to obtain an endorsement of the concept and, thus, enabled him to write the Medical Science Training Program-NIH training grant proposal that was funded to support the endeavor, with Bert as its first director. Although Harvard's med school was a latecomer to this kind of curriculum, it has flourished, and the school is now a leader in attracting students.

In the early 1970s the first of two chance events occurred that were markedly to alter the nature and support of the laboratory's research activities. Since its inception, the BRL had an advisory board, one of whose members was Arthur Kornberg. On a visit to Judah Folkman, he afterwards came to see Bert. Kornberg was aware of the BRL's expertise in protein chemistry and suggested that this could be of great benefit to Folkman, who

was having difficulty isolating his postulated but elusive tumor-associated angiogenesis factors. The two laboratories joined forces and, with assistance from the National Cancer Institute, pursued the isolation. The project, however, was much more difficult than anticipated, as the amounts of material available were miniscule and the lab facilities thus could not scale up to the level required.

Bert, then a consultant to the Monsanto Company, was aware of the company's fledgling interest in biotechnology. He offered them the opportunity to gain valuable experience in this newly emerging field by becoming partners in the angiogenesis effort. Thus, in 1974, Harvard and Monsanto embarked on a radical departure from conventional academic research by entering into a joint venture catalyzed by Bert and Monsanto Vice-President Monte Throdahl. This was an academic-industrial enterprise on a large scale, perhaps the first of its kind in terms of funding and duration. It provided Monsanto with a "window on biology" and facilitated their conversion from a producer of bulk chemicals to a leader in agricultural bioengineering. In exchange, the company provided the Harvard Medical School with the first floor of the Seeley G. Mudd Building, three professorships, $2 million in annual direct support, and 12 years of substantial indirect-cost revenue. (Bert and the administrative dean, Henry Meadow, drove a hard bargain.)

The operation was overseen by an external review committee and was the basis of new institutional policies concerning intellectual property. It was also the source of much contentious discussion in academic circles as to the role of industrial affiliation in universities. One particularly satisfying aspect of the project, as far as Bert was concerned, was its overarching theme of organogenesis and the nostalgia that rekindled for his days in Berne studying embryology. Also, 1974 was an auspicious year in that it saw Bert elected to membership in the National Academy of Sciences.

From the large pots of medium that Monsanto had used to culture cancer cells, the BRL ultimately extracted and identified angiogenin, a ribonuclease-like molecule that is one of a number of angiogenic factors (Fett, et al., 1985). The research also led to the purification of a ribonuclease inhibitor that was patented, providing the med school and the lab with additional income. As a result, the laboratory was able to expand its research in other directions.

Because Bert, as well as many of his associates, had a background in medicine, the BRL always had an interest in bringing its fundamental findings into clinical utility—what today might be called translational research. On the basis of the lab's discoveries, one of the first enzymes, whose blood level was employed in the diagnosis of myocardial

Bert Vallee in the MIT spectroscopy laboratory circa 1949.

infarction, was lactate dehydrogenase. Separately, when it was found that ethylene glycol was a competitive inhibitor of alcohol dehydrogenase, treatment of the poison's toxicity in patients was instituted with ethanol.

Sometime in the late 1970s the renamed Brigham and Women's Hospital, in the hope of raising money for a new research building, arranged for Bert to be introduced to Edgar Bronfman, CEO of the Seagram distilling company and head of the Samuel Bronfman Foundation. Bronfman had often wondered why many people are able to drink alcohol responsibly while others abuse it. Consequently, he was intrigued by Bert's interest in alcohol metabolism and his work with human isozymes, but he was not in the least interested in funding a building. Charles Giel, Bronfman's personal physician, was present at the first Vallee-Bronfman meeting and suggested afterwards that an alternative would be for Bronfman to support scientific research rather than construction. In time, Bronfman agreed.

Legal technicalities required that the corpus of the $5.8M gift remain invested in the Bronfman Foundation, which would then contribute, according to expenditure, to a 501(C)(3) entity other than Harvard University for the uses of Bert's laboratory. To circumvent this complication, Roger Moore (then counsel to the university) proposed that a tax-exempt endowment be set up for the benefit of the President and Fellows of Harvard College that would disburse the funds. Known as the Endowment for Research in Human Biology, it was governed by a board of directors that included the incorporator, Bert, as well as representatives from Harvard and the Bronfman Foundation.

An advisory committee was also formed to review and evaluate the progress of the work; chaired by Bert, its members included three independent scientists. With careful husbanding of expenses by Bert and astute investment management by the Bronfman Foundation and, later, by an independent financial advisor, more than $10 million was ultimately made available for research. It was at this time that the lab name was changed

from the Biophysics Research Laboratory to the Center for Biochemical and Biophysical Sciences and Medicine (CBBSM). Some years later Bert's title was also changed, to the Edgar M. Bronfman Senior Distinguished Professor.

The pursuit of a treatment for alcoholism was aided by another seemingly chance event. Wing-Ming Keung had been a post-doctoral fellow under Bert in 1980-81, studying metalloenzymes. When he left to join the faculty at the Chinese University of Hong Kong, he continued to receive support from the Endowment. While there he developed an interest in Chinese herbal medicine, specifically as it relates to treating alcohol abuse. He interviewed many herbalists and discovered that a common ingredient used for this purpose was an extract from the root of the plant Kudzu. He found that such extracts also inhibited enzymes that metabolize ethanol. Subsequently, he returned to the CBBSM, where he derived from the extract an inhibitor of aldehyde dehydrogenase (second step in the breakdown of ethanol) called daidzin (Keung and Vallee, 1993). Animal models of alcoholism then showed that administration of the compound turned rats and hamsters away from preferring alcohol to water. Pursuit of this compound and other derivatives for human use, under license, was taken up by a sequence of biotech companies. It is currently being investigated by Gilead Sciences.

Bert and Natalie Vallee had no children and lived relatively frugally. Their sole indulgence was horseback riding in Arizona and Montana. The rest of their disposable income, derived from Bert's salary and consultancies with chemical and petroleum companies (for whom trace metals are of importance), was invested under the guidance of a wise counselor. Thus, with a substantial nest-egg, he and Natalie looked for ways to perpetuate their interests. They decided to create a foundation promoting dialogue between active and prominent biomedical scientists around the world, first by sponsoring visiting professorships among institutions in which Bert had developed close collaborations and second by organizing biennial meetings of this group.

Since its origin 17 years ago, 30 senior scientists have spent a month visiting at host institutions, using the time to meet with colleagues in their fields as well as to establish research collaborations. The biennial meetings have been an opportunity for the Vallee Visiting Professors to hear about each other's work and to develop a convivial fellowship. Most recently the foundation endowed the B. L. and N. K. Vallee Award in Biomedical Science, presented annually by the American Society for Biochemistry and Molecular Biology.

Bert Vallee had an overwhelming persona. This strength of character kept him active despite repeated bouts of Guillain-Barré paralysis that rendered him physically handicapped. His single-minded concentration on achieving his goals, coupled with a sharp intelligence, allowed him to accomplish much. He cherished his friendships, professional and secular, but could heap opprobrium on those he felt stood against him and what he was trying to accomplish. Bert relished bringing his friends together and entertaining them at home, at his clubs, in Alsace, in a Tuscan conference village, and in meetings of the Vallee Visiting Professors under the aegis of his and Natalie's foundation. And it is particularly this group of familiars who will remember him with admiration band affection.

ACKNOWLEDGEMENTS

Portions of this memoir appeared previously in *Bert Lester Vallee: Memorial Minute*—Harvard Medical School and appear with the permission of Harvard University. Photographs in the memoir are courtesy of the authors and the B. L. and N. K. Vallee Foundation.

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