THE FACULTY OF MEDICINE
Harvard University

Bert Lester Vallee

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 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. 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 there given by a student of the great developmental biologist Hans Spemann. He came to the United States immediately afterwards, the first, and only, fellow of the International Student Service of the League of Nations. He was assigned, as an advisor, to the brilliant mathematician, Richard Courant, who prepped him for entrance to NYU and its medical school. On graduation he interned at Mt. Sinai Hospital in New York City. In that era, many of the Mount Sinai teaching staff were refugees from Germany and Austria bringing with them a strong tradition in clinical diagnosis. This single year of clinical training served Bert well and the prodigious 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 in the blood preservation program of E. J. Cohn and John Edsall, founding fathers of biophysical protein chemistry. He divided his time between HMS and MIT's radioactivity center. While working at the latter, he developed an interest in the biological functions of zinc and other transition elements in white blood cells. 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 the detection and measurement of 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 His method of measurement, using the direct-current arc, now superseded by atomic absorption spectroscopy, was enormously demanding and Bert's meticulous attention to its detail made his laboratory one of the few that could perform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. During this period he met and wed Natalie T. Kugris; 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 Brigham laboratory. This and other international forays played an important role in developing Bert's conviction in the importance of international collaboration.

Bert's initial faculty appointment was through the medical department at Peter Bent Brigham Hospital. Its chief, George Thorn, was keen 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, where he had begun some life-long collaborations, Bert had been impressed with the structure and function of All Souls College and suggested that the nascent institute look to that organization for ideas. The form that ultimately emerged in HHMI was one of supporting independent investigators, not in residence but attached to various other institutions, whose salary and research would be funded, 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 desire to have a basic science laboratory at the Peter Bent Brigham Hospital, was realized when the Rockefeller Foundation decided to back the construction and furnishing of a laboratory for Bert Vallee. The Biophysics Research Laboratory (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 contemporary 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, in 1954, began an incredibly productive period in Bert's scientific research career.

The BRL was organized along continental principles. There was a *geheimrat*, Bert, the laboratory chief; a scientific sub-chief; a laboratory administrator; junior faculty members, and numerous graduate students and post-doctoral fellows. Bert's habit was to make rounds at each investigators 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, all members of the lab convened to hear reports from one or more of the fellows, designated in advance. At these meetings, the conviviality of dinner was replaced by critical evaluation. Woe to any fellow whose report was not crisp and exacting. As trace metal 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 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.

For the next several decades, the laboratory was the seat of a number of seminal discoveries in metallo-biochemistry. The presence of zinc and its role in yeast alcohol dehydrogenase, carboxypeptidase and scores of other enzymes were elaborated. Bert's motto by this time had become "*cogito ergo zinc*". The structure and confirmation of zinc binding sites and the distinction between catalytic, regulatory and structural ones in several enzymes were delineated and generalization of the related coordination chemistry theorized in an entity called the *entatic state*. A unique metal-binding protein, metallothionein, was isolated from horse kidneys and, after much work, its structure defined. Thought, at first, to be a scavenger of toxic elements, it 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 PBBH had spent time in his laboratory. Many of the graduates went on to stellar careers in science or medicine in this country and abroad.

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

On appointment to the Department of Biological Chemistry, Bert was asked to organize a Saturday morning clinic which, 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 them into scientific theater. Cases in 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 2nd year course-of-study for a small group. Using case-based and tutorial instruction (foreseeing 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 the committee on whether HMS should adopt an MD-PhD 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-MD fellowship. Bert believed the additional course-work and discipline of writing a thesis for obtaining a PhD valuable in itself; he felt he had benefitted a good deal from his courses at MIT and was a strong advocate of the combined degree. The committee was divided in sentiment. Bert, discovering that some opponents took long weekends, devised to hold meetings late on Friday when they would be absent. He claims this maneuver allowed to him to obtain an endorsement of the concept and, thus, enabled him to write the MSTP-NIH training grant proposal that was funded to support the program. Bert was its first director. Although, Harvard was a latecomer to this activity it has flourished and is now a leader in attracting students.

In the early 1970s, the first of two chance events occurred that were to markedly 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 Judah who was having difficulty isolating his postulated but elusive tumor-associated angiogenesis factors. The two laboratories combined forces and, with assistance from the NCI, pursued the isolation. However, the project was much more difficult than anticipated as the amounts of material available were miniscule and the lab facilities unable to scale up to the level required. Bert, then a consultant to Monsanto, 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 HMS with the first floor of the Seeley G. Mudd building, three professorships, and twelve years of substantial indirect-cost revenue. (Bert and administrative dean, Henry Meadow, drove a hard bargain.) It 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.

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. The research also was the basis for a ribonuclease inhibitor that was patented, providing School and Laboratory with additional income. As a result, the laboratory was able to expand its research into 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 infarction, was lactate dehydrogenase. When it was found that ethylene glycol was a competitive inhibitor of alcohol dehydrogenase, treatment of the poison's toxicity

was instituted with ethanol. One of us (WECW), as a member of the lab, took the lead in these clinical studies.

Sometime in the late 1970s, the Brigham and Women's Hospital, in the hope of raising money for a new research building, introduced Bert to Edgar Bronfman, CEO of Joseph E. Seagram & Sons and head of the Samuel Bronfman Foundation. Bronfman was intrigued by Bert's interest in alcohol metabolism 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 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. By careful husbanding of expenses by Bert and astute investment management by the Bronfman Foundation and, later, by an independent financial advisor, more than $10M was ultimately made available for the conduct of research.

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 a university in Hong Kong, he continued to be supported by the Endowment. While there, he developed an interest in Chinese herbal medicine. These two interests merged when he found that extracts from the plant Kudzu, long used in the treatment of alcoholism, also inhibited enzymes that metabolize ethanol. He, subsequently, returned to the BRL where he derived from the extract an inhibitor of aldehyde dehydrogenase (2nd step in the breakdown of ethanol) called daidzin. Animal models of alcoholism subsequently 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 his wife looked for means 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 biannual meetings of this group. Since its origin 15 years ago, 25 senior scientists have spent a month's period visiting at host institutions, using the time to meet with colleagues in their fields as well as to establish research collaborations. The biannual meetings have been an

opportunity for the Vallee visiting scholars to hear about each other's work and to develop a convivial fellowship.

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. 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 that will remember him with admiration and affection.

Respectfully submitted,

Earl Davie
Kenneth H. Falchuk
Henry Rosovsky
James F. Riordan
Warren E. C. Wacker
S. James Adelstein, *Chairperson*

1 Visitors to Harvard have included Clarence Ryan (Washington State), Jerold Meinwald (Cornell), Allen Hill (Oxford), Edmund Fischer (University of Washington), Lars Terenius (Karolinska), Klaus Rejewski (Cologne), Gordon Hammes (Duke), Louise Johnson (Oxford), Moshe Yaniv (Pasteur Institute), Chen wen Wu (Taipei), Malcolm Green (Oxford), Hans Jornvall (Karolinska), Alan Fersht (Cambridge), Jesper Haeggstrom (Karolinska), Torsten Wiesel (Rockefeller). Visitors from Harvard have included Lewis Cantley (to Oxford), Peter Howley (to Pasteur & Oxford), Wade Harper (to Oxford), and John Collier (to University of Washington).