BIOGRAPHICAL MEMOIRS

Herbert Tabor

November 28, 1918–August 20, 2020
Elected to the NAS, 1977

A Biographical Memoir by Reed B. Wickner

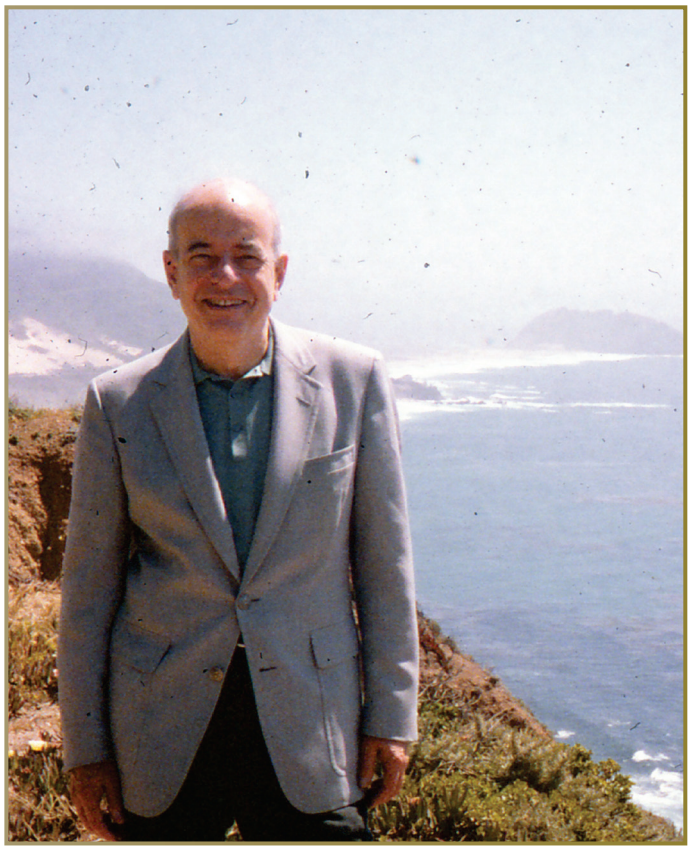

Figure 1 Herb Tabor in 1985 at Big Sur. *Photo courtesy of Richard Tabor.*

Herbert Tabor was best known for his elucidation of the biochemical pathways for polyamines, including characterization of the biosynthetic enzymes, their genes and regulation, and the functions of the polyamines, chiefly using *Escherichia coli* and *Saccharomyces cerevisiae*. His early work in 1943-44 with Sanford Rosenthal, which showed that saline infusions were as effective as plasma in treatment of burns and shock, was very important in World War II and thereafter. He was editor-in-chief of *The Journal of Biological Chemistry* (*JBC*) for nearly forty years, overseeing its dramatic expansion and modernization and leading its conversion from the traditional means of distribution of scientific information to the present web-based system.

Early Life and Education

Herbert Tabor was born on November 28, 1918, in New York City. He was an unusually bright student, and "accelerated" one year in elementary school, one year in junior high, and one year in high school, graduating from Townsend Harris High School in Manhattan in 1933 at the age of fourteen. He entered City College of New York (CCNY) and majored in pre-med studies. One of his classmates was Arthur Kornberg, who was later to become a close lifelong friend. Although acutely aware of the Great Depression, Herb says that he was not severely affected because of his family's modest living style. After two years, Herb transferred to Harvard College, where he majored in biochemistry. Each student in the major was assigned a tutor to guide their thesis work, and Herb's tutor was Robert E. Johnson, under whose instruction Herb did his senior thesis on carotenemia, his first real experience doing research.

Although CCNY had been stimulating, including excellent teachers and a bright student body (with two or three eventual Nobel winners in Herb's class alone), he found Harvard's "intellectual environment—smaller groups, more time for discussion…" helped his development.[1] He graduated *magna cum laude* in 1937 and then attended Harvard Medical School, where his work with A. Baird Hastings on the ionization constant of $MgHPO_4$ was the subject of his first paper, fittingly in the *JBC*.[2] Herb recalled Hastings in

biochemistry and Walter B. Cannon in physiology were particularly skilled teachers who had a strong influence on him.[1] This work indirectly led to his later joining the National Institutes of Health (NIH).

As an intern at Yale New Haven Hospital in 1942, Herb happened to be the one giving a patient with streptococcal septicemia an injection of penicillin, the first dose in the first major clinical trial of the drug in the United States (it worked!). This trial had been arranged by John F. Fulton, professor of physiology at Yale Medical School, pursuant to whether penicillin should be manufactured in the United States. Twenty-five years later, Herb was describing this episode to Gil Ashwell, by then an old friend at NIH (see below) and already a famous biochemist whose research focused on carbohydrates. Unbeknownst to Herb at the time, that first dose was prepared by Ashwell at Merck, where he was working as a technician before entering medical school. During his internship, Herb also worked with James Hopper in the lab of John Peters on blood volume measurements. In addition to patients with heart, liver, or kidney failure, such measurements are also particularly important in patients with shock or extensive burns, and this may have affected Herb's coming to NIH. After his internship, Herb joined the U.S. Public Health Service and was assigned as the Medical Officer to the Coast Guard cutter USCGC *Duane,* escorting convoys between the United States and Britain or North Africa. The events challenged his limited surgical training (recounted in the article, "It All Started on a Streetcar in Boston"), but he managed without untoward sequalae.[3]

National Institutes of Health

In September 1943, Herb was transferred to the NIH in Bethesda, Maryland. At that time, NIH was newly relocated from downtown Washington, D.C., to six small buildings on land that Helen and Luke Wilson had only recently donated to the government for this purpose. Herb was assigned to work with Sanford Rosenthal, and, as noted in the introduction, they showed that oral saline infusions were an adequate substitute for the usual plasma in the treatment of burns or shock.[4] Because plasma was in short supply during the war years, this was an important advance.

The Seminar

The atmosphere at the early NIH was very collegial, being small and away from D.C. in then-bucolic surroundings. In this informal atmosphere, Herb soon became friends with Arthur Kornberg, Leon Heppel, and Bernard Horecker, each of whom had only recently arrived at NIH. In 1946, they formed a daily lunchtime seminar group, unusual at that time, critically evaluating new papers (mostly in biochemistry) and their own work. Herb recalled,

> "As an indication of the intensity of the seminar group during this period, I mention the following anecdotes. In those days (1949), there were almost no chamber music concerts in Washington except for the Friday evening Budapest String Quartet concerts at the Library of Congress. To obtain tickets (which at that time cost only 25 cents), one had to stand in line at 7:00 AM on the preceding Monday in downtown Washington. To make up for the time lost, the four of us conducted our daily seminar in line while waiting for the box office to open, permitting us to work at the bench through the lunch hour."[5]

This institution (the seminar) grew and continued for many decades with a dazzling array of participants, including Maxine Singer, Gil Ashwell, Jerry Hurwitz, Jesse Rabinowitz, Osamu Hayaishi, Jay Seegmiller, Alan Mehler, Paul Marks, Howard Hiatt, Herman Kalckar, Bruce Ames, Jack Strominger, Hans Klenow, Robert Schimke, Victor Ginsburg, and Chris Raetz, and, in later years, many others. This seminar series was very central to the intellectual life of the early participants and evolved into a joint seminar of Herb's department ("Laboratory" in NIH terms), the Laboratory of Biochemical Pharmacology, and the Laboratory of Biochemistry and Metabolism, led by Gil Ashwell (formerly led by Arthur Kornberg and then Bernard Horecker). Even later, the vigorous give-and-take and careful examination of the paper of the day was very educational for me as a young postdoc in Herb's group. In addition to providing a means to relate major advances, the seminar was what brought the whole department together (or else!), and was a very effective teaching tool, contrasting varied approaches to biological problems, highlighting the advantages and the shortcomings of each approach.

Early Work

From the mid-1940s to the mid-1950s, Herb studied, in collaboration with Arthur Kornberg, the effects of deficiency of folate (or other vitamins) in hemoglobin regeneration.[5] Herb also studied the mechanism of histidine degradation (via formiminoglutamate and folate intermediates) and the use of urinary formiminoglutamate to assess the effectiveness of antifolate drugs used in the treatment of leukemia.[6,7] The polyamines include 1,4 diamino-butane (putrescine), spermidine (putrescine to which an aminopropyl group has been added to one of its amino groups), and spermine (putrescine with both amino groups aminopropylated). These compounds were apparently first identified by Antonie van Leeuwenhoek in seminal fluid and are found in rather large amounts in essentially all living tissue. Sanford Rosenthal found that injected spermine caused renal toxicity, and others had reported that oxidation of polyamines increased

their toxicity to bacteria. It was thought that the injected spermine may be oxidized by a serum enzyme producing the toxic derivative. This was a time when biochemists were purifying enzymes, and Herb recalled being influenced by the other members of the seminar group who were purifying their enzymes of interest. Thus, in what was also one of his first forays into the polyamines, he purified diamine oxidase (histaminase) and showed that it converted putrescine (1,4-aminobutane) to Δ1 -pyrroline.[8]

Marriage

Having first been introduced to her on a "Streetcar in Boston"[3] in 1940, Herb married Celia White (M.D. from Columbia University and the first woman intern in Medicine at the Massachusetts General Hospital) in 1946. She was to become his lifelong collaborator. Their four children (Edward, born 1947; Richard and Marilyn, born 1949; Stanley, born 1954) enriched their busy lives and later developed careers in science and engineering. The Tabors took up residence on the NIH campus in 1949 in one of the modest duplex houses constructed for commissioned officers in the U.S. Public Health Service. Herb and Celia continued to live in these quarters for the rest of their lives, an arrangement that facilitated their frequent return to the lab after supper and on weekends. Although it may seem to the reader that Herb and Celia spent all of their time in the lab, they had a very close family life. In 1952, Celia joined NIH, first working with Rosenthal on the renal toxicity of injected spermine in mice, and later she had an independent position. Herb and Celia then collaborated with a focus on polyamines.

Polyamines

Herb and Celia together devoted the bulk of their careers to the study of the polyamines putrescine, spermidine, and spermine. At the onset, nothing was known of their biosynthesis or function. The Tabors described their biosynthetic pathways in bacteria and yeast, the enzymes and their regulation, and the functions of polyamines. Putrescine is made mainly from ornithine by decarboxylation[9] by an enzyme regulated by feedback degradation. Spermidine and spermine are made by transfer to putrescine of aminopropyl groups from decarboxylated adenosylmethionine.[10] The adenosylmethionine decarboxylase has an unusual pyruvoyl prosthetic group.[11] The Tabors discovered that polyamines are acetylated at low temperature and glutathionylated in stationary phase.[12,13] The Tabors isolated mutants in the biosynthetic enzymes in *E. coli* (with Ed Hafner) and *S. cerevisiae* (with Murray Cohen, Anil Tyagi, Qiao-Wen Xie, Keiko Kashiwagi, and Nobuko Hamasaki-Katagiri) and constructed polyamine-free strains of each whose growth proved to be suboptimal (*E. coli*) or arrested (yeast) without added amines, demonstrating the critical importance of these compounds.[14] These strains became important tools for many in the polyamine field. The Tabors showed that translation, as measured by nonsense codon read-through or ribosomal frameshift efficiency, was critically affected by polyamine deficiency.[15,16] Moreover, the slow growth of *E. coli* mutants became no growth if cells also had an *rpsL* (ribosomal protein S12) mutation producing streptomycin-resistance.[17] In addition, the spermidine-derived hypusine modification of the translation factor eIF5A is the most growth-limiting function of spermidine in yeast.[18] Polyamine-deficient yeast mutants were oxygen-sensitive and polyamine-deficient *E. coli* were sensitive to the oxygen-generating compound paraquat, showing that polyamines have an important role in protection from oxidation.[19,20] Following the Tabors' early discovery of glutathionylspermidine in *E. coli,*[13] trypanosomes were found by others to have a diglutathionylspermidine that was important in protecting them from oxidation, leading to the use of the ornithine decarboxylase inhibitor difluoromethylornithine as an effective treatment for some cases of trypanosomiasis. With Manas Chattopadhyay, Herb showed that polyamines are critical for the glutamate-dependent acid resistance of *E. coli,* mediated by the alternative σ factor (rpoS), the transcription factor GadE, and the two glutamate decarboxylases.[21] Their 2015 paper reporting these results in the *JBC* was published seventy-two years after Herb's first *JBC* paper.

The Journal of Biological Chemistry

Herb became a member of the Editorial Board of the *JBC* in 1961, an Associate Editor in 1968, and the Editor-in-Chief in 1971, a post he would hold for thirty-nine years. Herb oversaw the more than tenfold expansion in the size of the journal, along with a broadening of its scope from strictly biochemistry to include genetics, cell biology, and other related areas. Under Herb's leadership, the *JBC* advanced the technology of journal publishing, with production of the first digital (CD) version in 1992, and in 1995 became the first scientific journal to publish an online version.[22] As Editor-in-Chief, Herb handled many problem papers, such as complaints about the quality of the reviews, authorship issues, and referencing problems, as well as assigning papers to Associate Editors. I learned from Herb that, "There are only two kinds of scientists: those who don't refer to you, and those who don't refer to you enough." Herb had great respect for the authors. Complaints about a rejection were usually answered with the offer of re-review by another expert in the area. Efforts were made to speed all reviews.

On August 20, 2020, at the age of 101, Herb Tabor died peacefully at his home on the National Institutes of Health campus in Bethesda, Maryland. Herb was a modest,

soft-spoken man, totally devoted to science, did laboratory work himself throughout his whole career, and worked very hard until the end. He never had a large group, and gave some of his postdoctoral fellows a great deal of independence. For example, Chris Raetz began his work on mutants in enzymes of membrane lipid metabolism as a postdoc with Herb.[23] Herb had a "critical," to use his word, attitude toward research (including his own), meaning that careful examination of the evidence was always appropriate, and whether the conclusions were justified by the data was not a given. When confronted with an overexcited speaker showing that component A and component B formed a complex, Herb was more than once heard to declare that "the cell is a complex." Although many studies reported the binding of the polyamines to negatively charged components in vitro or in cell extracts, Herb was unconvinced that this represented their true location in vivo because, of course, "opposite charges attract." Herb was a truly fine person, very serious, but not without a sense of humor. His exposition on some subject might end with, "I've told you all I know, maybe more." Herb Tabor is already missed, but the lessons he taught us live on.

Acknowledgements

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More detailed information may be obtained in references 1, 2, 25–28 below.

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