HARLAND GOFF WOOD

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HARLAND GOFF WOOD, who was descended from William Goffe (b. 1619), one of the appointed judges responsible for the beheading of King Charles I, was born on September 2, 1907, in the small town of Delavan, Minnesota. His parents, both of whom had only a high school education, taught their four sons and one daughter to work hard and to be self-reliant—the result for the sons: two Ph.D.s, one Ph.D.-M.D., one M.D., and one LL.B; and for the daughter: an honorary LL.D. It is hard to picture Harland Wood as a frail child who spent two years in kindergarten and two years in the first grade. He and his brothers helped on the family’s farm in Mankato, Minnesota, walking the mile home from school at noon to water the stock and then running back after lunch. At Macalester College in Minnesota, he majored in chemistry and there met Mildred Davis, whom he married in 1929. In 1931 he was accepted as a graduate student in bacteriology at Iowa State University at Ames by C. H. Werkman, who was starting to investigate the chemistry of bacterial fermentations. It was there that Harland made his stunning discovery of CO₂ fixation, which up to that time was known to occur only in chemosynthetic and photosynthetic autotrophs. This idea was so controversial
that for some time Professor Werkman doubted the validity of Harland's findings.

From 1935 to 1936 Harland worked as a fellow with W. H. Petersen at the University of Wisconsin, and it was here that he joined Ed Tatum in studying the growth factor requirements for propionibacteria. Harland returned to Werkman's department in 1936 to focus on CO₂ fixation, as will be discussed. Although Harland was tremendously productive at Ames, building a thermal diffusion column for the isolation of ¹³C as well as a mass spectrometer to measure the isotope, Werkman would not initially allow him to work on animals and would not arrange for Harland's future independence at Ames. And so in 1943 he moved to the Department of Physiological Chemistry at the University of Minnesota, and it was there that he used ¹³C-NaHCO₃ labeling of the different carbon atoms of the glucose of rat liver glycogen to study the pathways of glucose synthesis.

In 1946 Harland accepted the position of chairman of the Department of Biochemistry at the School of Medicine of what was then Western Reserve University in Cleveland, Ohio, on the condition, as he told Dean Joseph Wearn, that he be allowed to go deer hunting with his father and four brothers each autumn. He loved duck and deer hunting and even at seventy-nine years of age was seen 35 feet up a tree waiting for a deer. As chairman he brought in an entirely new faculty that was oriented to the use of isotopic tracers to study a variety of metabolic pathways. Under Harland's direction, this young and energetic group, which included future members of the National Academy of Sciences, Merton Utter and Lester Krampitz, created an outstanding national reputation for the department. At the local level, he was also unique. Harland instituted a policy that all honoraria, even for participating in study sections, should go into a student travel fund, since he felt that out-
side activities should have an intrinsic value based on science and not on money—echoes of William Goffe. Departmental seminars were at noon on Saturday and monthly staff meetings were held after that, often until 5:00 p.m., when they were terminated by telephone calls from irate wives. There was a pooling of resources, a sharing of all equipment, and a camaraderie that would be difficult to equal in these times.

Harland Wood spent the last forty-five years of his career at Case Western Reserve University (Western Reserve University merged with Case Institute of Technology in 1968). He retired as chairman in 1965 so that he could have more time for research, and for Harland this meant research at the bench, not just at the desk. He continued “pounding the bench,” as he called it, right up until a few days before his death on September 12, 1991. Lymphoma was diagnosed four years before his death; he died of a fall that resulted in a ruptured spleen. Harland had undergone chemotherapeutic cycles several times, but they never significantly halted his scientific activities. At the time of his death, he held three grants from the National Institutes of Health, had a working group of fifteen associates, and was writing nine manuscripts. At the last meeting of the ASBMB that he attended, he had twelve posters on display and was present to discuss results related to each of them. Between his seventieth birthday and his death, he published ninety-six papers, all in well-respected journals—surely a record for an “elderly” biochemist. He is survived by his wife Mildred and two daughters.

Harland Wood left a long and distinguished record in the life sciences, beginning with his pioneering work with C. H. Werkman at Iowa State College, which demonstrated for the first time that CO₂ is utilized in heterotrophic organisms. In 1935 he demonstrated that the prevailing dogma
that CO$_2$ was utilized only by bacterial autotrophs was incorrect. In a series of studies he determined the products formed from the fermentation of glycerol by propionic acid bacteria in a bicarbonate buffer system and calculated the carbon and oxidation-reduction balances to account for the carbon of the fermented substrate and to ensure that there was a balance of the oxidation-reduction state of substrates and products. Surprisingly, more carbon was found in the products than was supplied by the fermented glycerol. He subsequently discovered that the extra carbon was derived from CO$_2$ in the buffer and that oxidation balanced reduction when the reduction of CO$_2$ was taken into account. He proposed that CO$_2$ and pyruvate combined to form oxaloacetate, which subsequently was reduced to succinate. This pyruvate-CO$_2$ reaction became known as the Wood-Werkman reaction.

When isotopic tracers of carbon became available in the late 1930s, Harland was among the first to exploit isotopes in biological studies. He was a true pioneer in developing procedures for the use of these isotopes for metabolic tracer studies. As previously noted, he built a water-cooled thermal diffusion column in a five-story elevator shaft for the separation of $^{13}$C isotopic carbon. Harland was always fond of describing the day that he found the column warped and distorted due to a temporary drop in the water pressure. This drop, he finally discovered, occurred when the home economics class let out and three toilets were flushed simultaneously! To measure $^{13}$C, he also built a mass spectrometer. His innovative work initially provided evidence that citrate was not part of the citric acid cycle because he had assumed that citrate was a symmetrical molecule. In his characteristic manner, he later said in a Lynen Lecture that even though he was wrong it was one of his “most important contributions” to biochemistry. The studies by Wood
and his colleagues in 1945 clearly demonstrated the pathway of CO$_2$ incorporation into specific carbon atoms of glucose derived from hepatic glycogen. Harland graduated briefly from bacteria to cows, where his farm background helped in the injection of $^{14}$C glucose into the artery going to the right udder. Subsequently, by personally milking each side, he determined that lactose was synthesized from free glucose rather than glucose-1-phosphate and that it was glucose that reacted with UDP-galactose to form lactose. In collaboration with Joseph Katz and Bernard R. Landau, Harland also developed methods to estimate the proportion of carbohydrate metabolized in the pentose pathway and glycolysis by studying $^{14}$C distributions in glucose and glycogen. These latter studies were instrumental in establishing the stoichiometry of the pentose pathway.

The overall direction of Harland’s research over sixty years continued to be on CO$_2$ fixation. During the last thirty years of his life, he focused on establishing the reaction mechanism of transcarboxylase (TC) from propionibacteria. This is a key enzyme in the propionic acid cycle, and it transfers a carboxyl group in the conversion of methylmalonyl CoA + pyruvate to propionyl CoA + oxalacetate. The enzyme is also extremely complex, with six identical central subunits, each with two CoA-binding sites, six dimeric outside subunits each of the six with two keto acid sites, and twelve small biotinyl subunits that carry the carboxyl groups between the CoA and keto sites. The kinetics of the reaction did not fit the accepted mechanisms, so Dexter Northrup, then a student with Harland, proposed a new kinetic mechanism for TC that was later verified by Northrup and Wood. Extensive work was done on the separation of the three subunits of TC and on the reconstitution of enzyme activity. Together with a number of associates, Wood studied the quaternary structure of TC by electron microscopy, and this
revealed the “Mickey Mouse” enzyme. Using thin crystals of the enzyme, resolution of the structure at 10 Å was possible by microscopy. The primary amino acid sequence of the biotinyl subunit was determined, and, in collaboration with David Samols, the genes for all three subunits were cloned and sequenced. At the end of his life, Harland was studying the enzymatic properties of a large number of mutants that were generated in the three different subunits and was doing many of the enzyme assays himself. These studies were of great interest because of the complexity of the subunit structure of the enzyme and the ability to examine different aspects of function.

Harland Wood also discovered a novel pathway for carbon monoxide (CO) fixation in acetogens, a group of anaerobic bacteria that synthesize acetate from CO or CO$_2$/H$_2$. This new pathway of autotrophic growth, demonstrated in *Clostridium thermoaceticum* and *Acetobacterium woodii*, differs from all previously described pathways for autotrophic growth, such as the Calvin reductive pentose cycle or the tricarboxylic acid cycle. Much of Harland’s work in the area was done in collaboration with Lars Ljundahl, both at Case Western Reserve University and the University of Georgia. The mechanism of this pathway involves reduction of CO$_2$ to methyltetrahydrofolate and transfer of the methyl group to a corrinoid protein. The methyl group is then transferred to carbon monoxide dehydrogenase (CODH); CO and CoASH/moieties combine with CODH, which catalyzes the formation of acetyl-CoA from the above three groups. Thus, CODH plays a central role in this pathway. Most of the enzymes involved in the various steps of the pathway were purified to homogeneity. The availability of purified enzymes permitted Harland and his collaborators to dissect the pathway and define the role of each enzyme. Detailed studies toward elucidating the mechanism of action of CODH
were initiated. CODH contains six nickel, three zinc, thirty-two iron atoms, forty-two labile sulfides and has three acceptor sites: one for the methyl group transferred from the methyl corrinoid enzyme, a CO site, and a CoASH site. From ESR studies it was shown that the Ni-Fe center is involved in the interaction of the CO group with CODH. Also, the methyl group is bound to a cysteine residue of CODH. The CoASH substrate site has been characterized using fluorescence spectroscopy, circular dichroism, and chemical modification. From these studies it was proposed that both tryptophan(s) and arginine(s) are involved in the binding of CoASH to CODH. Even from this brief review it is clear that Harland Wood, over the sixty years that he was involved in research, “followed the trail of CO₂.”

Harland Wood was also a pioneer in studying the role of pyrophosphate and polyphosphate as energy sources. It has long been accepted that the energy contained in the anhydride bond of pyrophosphate is not utilized efficiently by cells. However, Harland, together with Nelson Phillips, showed this not to be true by the isolation and characterization of bacterial enzymes that utilize pyrophosphate in reaction with oxaloacetate, with phosphoenolpyruvate, and with fructose-6-phosphate. Inorganic polyphosphates have been considered by others as primitive sources of energy. Harland extensively studied the enzymatic synthesis of polyphosphate from ATP and showed that a bacterial glucokinase utilizes polyphosphate much more effectively than ATP in the reaction with glucose. Two separate sites exist on the enzyme for these two sources of high-energy phosphate. This enzyme may represent an intermediate stage of evolution from a polyphosphate-dependent metabolism to an ATP-dependent metabolism.

Harland Wood’s outstanding career was marked by many innovations. However, what most characterized Harland was
his scientific style. He was remarkable for several reasons. First, one could always feel the sense of excitement and drive that he brought to the experimental aspect of science. The focus of the excitement was always on discovery. Second, he continually developed and applied the latest technology to his experimental problem. There were many jumps from fermentation balances all the way to gene sequencing. Finally, he was able to collaborate with others very productively, particularly those with expertise in specific areas where the scientific results could not have been achieved by either group alone. The flavor of the man and his approach to science are best captured by Harland himself in his autobiography in the *Annual Review of Biochemistry* in 1985.

Harland Wood’s outstanding career was marked by many innovations in other areas. As chairman of the biochemistry department at Western Reserve University, he led the curriculum reform that resulted in an integrated organ-system-based method for teaching the first two years of medical school; this curriculum has had a great impact on medical education nationally. He swayed the faculty to vote for the new curriculum with the challenge, “How do you guys know it’s not going to work unless you run the experiment?” He served as chairman of the biochemistry department for twenty years, as dean of sciences at Case Western Reserve University from 1967 to 1969, and finally as university professor and university professor emeritus from 1970 to 1991.

Harland Wood was president of the American Society of Biological Chemistry from 1959 to 1960. First as secretary-general and then as president of the International Union of Biochemistry in 1982-83, he did a great deal for that organization’s revitalization. He served on many study sections, and his strong support for younger biochemists during his tenure on one of those study sections became known
as “The Wood Factor.” He was a member of many advisory boards and served as an editorial board member of a number of important journals. As a young member of the Editorial Board of the *Journal of Biological Chemistry*, he was instrumental in eliminating self-perpetuating appointments when he resigned after five years and argued, “Listen, if all you guys died tomorrow, a good board could be picked the next day to replace you.” He received a number of prestigious awards, including the Eli Lilly Award, the Carl Neuberg Medal, the Lynen Lecture Medal, the Waksman Award, the Rosenstiel Award, the Michaelson-Morly Award, and the National Medal of Science. He held honorary degrees from Macalester College, Northwestern University, the University of Cincinnati, and Case Western Reserve University. He was a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the Biochemical Society of Japan and served on the President’s Science Advisory Committee under Presidents Johnson and Nixon.

In a 1985 *Annual Review of Biochemistry* article, Harland Wood wrote that “scientists are the fortunate few who earn a livelihood by pursuit of a hobby. This hobby sometimes consumes their every thought, but usually it provides a deeply satisfying life.” He continued, “Many highly successful scientists desert the laboratory bench early in their careers and thereafter direct the research of their co-workers. My goal has been to remain personally active in the laboratory as long as I am involved in science.” And so he did.

Over the sixty years that Harland Wood spent in science, he made countless friends in many countries who revered him not just for his accomplishments but for his intellectual honesty. Here was a man without pretensions, whose opinions and decisions were always based on principles and not on personal factors, a man whose mind was open to new ideas and concepts, a man who by his example and
encouragement got the best out of his associates, and a man who, once he made up his mind, would drive straight toward his goal. In him one felt the warmth, strength, and integrity that made him unique and irreplaceable.
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