Dilworth W. Woolley

1914–1966

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

DILWORTH WAYNE **WOOLLEY**

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Dilworth Wayne Woolley was an important figure in several of the stages of advancement in biochemistry throughout the 20th century, from the era of vitamin discovery through the beginnings of neurochemistry and research on the structure of receptors. He is best known for his development of antimetabolites as a synthetic, rational approach to pharmacology and for his advocacy of the idea that serotonin had a role in mental illness. He was one of the first to recognize the importance of serotonin in brain function, and his second book elaborated his hypotheses about serotonin's importance in mental activity and mental disorder. His earlier work, in the discovery of vitamins and other important biological molecules, is less well known but was also important.

Wayne Woolley was born in 1914 in the small farming town of Raymond, Alberta, Canada. His parents were immigrants from the United States, part of a migration of members of the Church of Jesus Christ of Latter-Day Saints (LDS or Mormon church) in the late 19th Century. He began publishing early; he said his first publication was at age 17, in a magazine of popular mechanics. He enjoyed working with his hands and even maintained a workshop in his summer home later in life. He attended the University of Alberta, in Edmonton, graduating in 1935.

Although it was the depths of the Great Depression, Wayne managed to proceed directly to graduate school at the University of Wisconsin, thanks to special funds set aside for an early crop of graduate students in what was at that time the Department of Agricultural Chemistry (later named Biochemistry). At Wisconsin he was an unusually intense and dedicated student. He worked on two separate projects and published extensively.

He said that his dissertation committee accepted his 22 manuscripts—either published or submitted—instead of a dissertation, which was decidedly unconventional at the time.

Wayne's main daytime effort focused on metabolism, and especially growth factors in bacteria, including hemolytic streptococci. This work was supervised by W. H. Peterson, whose picture Wayne kept on his desk for the rest of his career. His other project dealt with factors that are necessary for mammalian metabolism, which he conducted under the supervision of Conrad Elvehjem. Wayne's publication rate and devotion to multiple projects demonstrated his exceptional commitment and concentration and his dedication to biochemical research. He was greatly aided in this by his prodigious memory, which enabled him to recall, in detail, every scientific paper he had read.

In 1938 a major paper establishing that nicotinic acid and/or nicotinic acid amide prevented black tongue disease in dogs was published. Authorship of this paper was listed as C. A. Elvehjem, R. J. Madden, F. M. Strong, and D. W. Woolley—in that order. Black tongue in dogs was a model for the severe disease pellagra in humans, and work later showed that these nicotinic acid derivatives (eventually called niacin and sometimes vitamin B3) could cure pellagra-induced psychosis, the major reason for psychiatric hospitalizations in the early 20th Century and the cause of up to 7000 deaths per year.

Pellagra was a common disease in the southern United States, particularly because so many people in the region relied on corn as a dietary staple. Several years later Wayne showed that a factor in corn made pellagra more likely to occur because it bound niacin, making this essential nutrient unavailable for digestion without other treatment. The demonstration that pellagra was a niacin-deficiency disease was possibly the major discovery in the careers of all of the paper's authors, but the order of their names was a bone of contention for Wayne. He felt that he had not been adequately recognized for the work and asserted that while he had produced essentially all of the results reported in the paper, Elvehjem was expert at taking credit. Woolley did not have Elvehjem's picture on his desk.

During his years at the University of Wisconsin, Wayne met, collaborated with, and married Dr. Janet McCarter, a bacteriologist. Janet, in addition to following her own career, played an essential role in his work for the rest of his life.

After receiving his Ph.D. from Wisconsin in 1939, Wayne joined the prestigious Rockefeller Institute for Medical Research, in New York City, which became his professional home until his death in 1966. The institute, later Rockefeller University, is a unique gathering place for elite biochemical and medical researchers, who are free to pursue virtually any avenue of inquiry they wish. Several other biochemists in his cohort of graduate students from Wisconsin also came to the Rockefeller Institute around that time.

Life at Rockefeller

Throughout his life and career, Wayne was one of the few productive scientists who were severely hampered by an unusually frail body. He suffered from diabetes mellitus as a child—his life was saved by insulin when it became available in 1923, only two years after its isolation and one year after its first use in a human test. He also had rickets as a child, but it was already known that treatment with cod-liver oil was effective, before it was known that ultraviolet radiation was equally effective and well before the chemistry of vitamin D was determined.

While insulin could control Wayne's diabetes, it did not save his eyesight. In his early twenties he began to suffer retinal hemorrhages, due to the diabetes, eventually leaving him completely blind. In 1939, shortly after leaving Wisconsin and starting at Rockefeller, it became clear that his eyesight was failing and that the process was probably irreversible. He decided to take a rare break from work and traveled with his wife, Janet, by train around the United States, to see as much as possible while he still could. He remembered that trip vividly, as he remembered everything else.

He was quite adept at compensating for his blindness and was proud of the fact that many people who knew him only from the talks he gave at meetings did not realize he was blind.

Despite having become blind, Wayne continued to work in the laboratory, closely supervising technicians and the younger investigators working with him. He reserved some tasks for himself and spent surprisingly little time in his office, considering his handicap and his position as head of a department. He was quite adept at compensating for his blindness and was proud of the fact that many people who knew him only from the talks he gave at meetings did not realize he was blind. He was careful to learn where the screens were that showed his slides and where, within each screen, his data were displayed. He was thus able to point accurately to places within each slide when it appeared. And because Janet wasn't much interested in his home workshop and he knew the space so well, he felt no need to install lights in the room.

I remember an event dramatizing his spatial competence that took place one night in 1965. The great power blackout that affected much of the northeastern United States and Ontario occurred on a night when the New York City-wide Enzyme Club was having one of its regular meetings. This was a group of biochemists, including me, from around the city who met monthly at Rockefeller. Because the office where we assembled to head for the dinner was not on the regular power grid but instead used direct current generated in-house, I had not noticed the blackout at first. But when we went into the corridor to go to dinner, a sizable crowd of biochemists were suddenly immobilized by the utter darkness. Wayne took pleasure in calmly guiding us all through the stairs and corridors to the outside.

Wayne's presentations at slide talks demonstrated his very remarkable memory, but only in a small way. Many of us who worked with him had fairly capable memories of our own, but no one had ever encountered a memory like his. In addition to giving talks, doing some work in the laboratory, and dictating frequent scientific articles (averaging about two a month), he dictated two books, complete with references, after he had gone blind. He was able to keep up with the scientific literature with the help of several people in addition to his wife, who took turns reading current articles to him. As far as I could tell, he remembered, in detail, all those he thought significant.

Throughout the 27-year period from about age 25, when he became blind, until his death at age 52, Wayne maintained a highly active personal laboratory and also had a few others under his overall direction. His interests in biochemistry were broad, including a desire to integrate biology from the molecular to the psychological, a quest that possibly began with the demonstration of niacin's ability to clear, quite quickly, the psychosis from the minds of people with pellagra. He was an active and contributing member, within the Federation of American Societies for Experimental Biology, of the American Society for Nutrition, the American Society for Pharmacology and Experimental Therapeutics, and the American Society of Biological Chemists (later, the American Society for Biochemistry and Molecular Biology).

His specific interests always emphasized the synthesis of organic molecules with significant biological activity. A notable early example of this work, done with Jordi Folch-Pi, was the 1942 demonstration that inositol was a component of a brain lipid. At the time of his death, he was working on a hypothesis about the chemical nature of the serotonin receptor, the synthesis of organic molecules with enzymatic activity, and an antimetabolite to vitamin B12 that would attack implanted cancers. His group focused particularly on peptide and protein synthesis, including the synthesis of antimetabolites for biologically active peptides, especially bradykinin (with John Stewart), and an effort toward achieving *in vitro* synthesis of entire enzymes, directly guided by R. Bruce Merrifield. (In 1984 Dr. Merrifield was awarded the Nobel Prize for his synthesis of ribonuclease.)

In addition to his efforts to discover molecules that are important in nutrition, Wayne's two major thrusts over his years at Rockefeller were on antimetabolites and serotonin, and the two overlapped. He worked for years trying to synthesize antimetabolites—drugs designed to interfere with the normal binding of molecules to their receptors or enzymes, allowing a rationally directed and measured degree of therapy by their use. The first part of this work was summarized in his first book, *A Study of Antimetabolites*, published in 1952.

His second major effort, on the role of serotonin in mental disorders, partially grew out of this work. Based on the hypothesis that lysergic acid diethylamide (LSD) was an antimetabolite of serotonin, Wayne and Elliott Shaw synthesized compounds that were designed to be a series of structural intermediates between the serotonin molecule itself and LSD. They demonstrated that these molecules were antimetabolites of serotonin and had behavioral effects in experimental animals.

From this work and the work of others, Wayne and Elliott proposed their serotonin hypotheses of psychosis, first published in 1954. These hypotheses were reviewed and described in detail in Wayne's second book, *The Biochemical Bases of Psychoses*, published in 1962. One particular hypothesis, which seems prescient in hindsight, was that disorders of serotonin function or metabolism were the basis of bipolar psychosis "in extroverts." Current relief of depression with selective serotonin reuptake inhibitors does seem to fit with this hypothesis.

Another aspect of Wayne's work, not often mentioned, is the role of serotonin in learning and memory. He was among the first to propose that disorders of serotonin function were disruptive to learning. Again, subsequent work by many others has shown that serotonin, as well as other neurotransmitters, plays a significant role in the learning process.

Wayne died in 1966 while on a trip to a pharmacological conference in Brazil. He had a long-standing interest in archeology and took a side trip to Cuzco, Peru, the capital of the early Inca empire, on his way to Brazil. Cuzco lies at an elevation of 11,200 feet in the Andes Mountains, and he traveled there in the full knowledge that it was dangerous for him to do so. He had suffered a stroke the previous winter serious enough for him to be hospitalized. Because of his diabetes and the length of time he had had it, he likely had heart disease as well. At Cuzco, he suffered a myocardial infarction and died.

In his too-short career, Wayne had been a remarkably productive scientist and a constant source of novel scientific ideas. His accomplishments were honored with the Mead Johnson Award in 1945, the American Pharmaceutical Manufacturers Association Award in 1948, and the American Chemical Society's Eli Lilly Award in 1940 and again in 1948. He received an honorary M.D. degree from the University of Amsterdam and an honorary Ph.D. from the University of Alberta. He was elected to membership in the National Academy of Sciences in 1952 and was nominated at least once for a Nobel Prize, for the discovery of pantothenic acid as an anti-dermatitis factor in mice. (Roger J. Williams separately made the same discovery at about the same time, published his results in the same issue of *Science*, and was also nominated for a Nobel Prize in the same year.)

Personal postscript

Having had the privilege of working with both Wayne and Elliott Shaw, I should point out that Elliott, after leaving Wayne's laboratory at Rockefeller, went on to develop the highly useful affinity labeling technique for identifying amino acids at the active sites of enzymes. By designing molecules that would bind to the active site in a manner similar to a substrate, but then bind covalently, he was able to make important contributions to understanding the mechanisms of enzymes, especially in the serine protease families. This work was a logical and important extension of the antimetabolite studies that began with Wayne Woolley.

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Most of this biographical memoir has come from personal observation. I had the privilege of working directly with D. Wayne Woolley for the last three years of his life, during which we spent a great deal of time together. I was also fortunate to meet many of his previous collaborators. I am also indebted to the biography by Thomas Jukes, published in *The Journal of Nutrition* in 1974.

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Wayne Woolley published 232 journal and symposium book articles in 32 years, beginning in 1935. More than 80 percent of these have him as either the sole author or the senior author. I have selected a few of those publications that have had the most lasting impact.

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