NATIONAL ACADEMY OF SCIENCES

MAHLON HOAGLAND
1921–2009

A Biographical Memoir by
THORU PEDERSON

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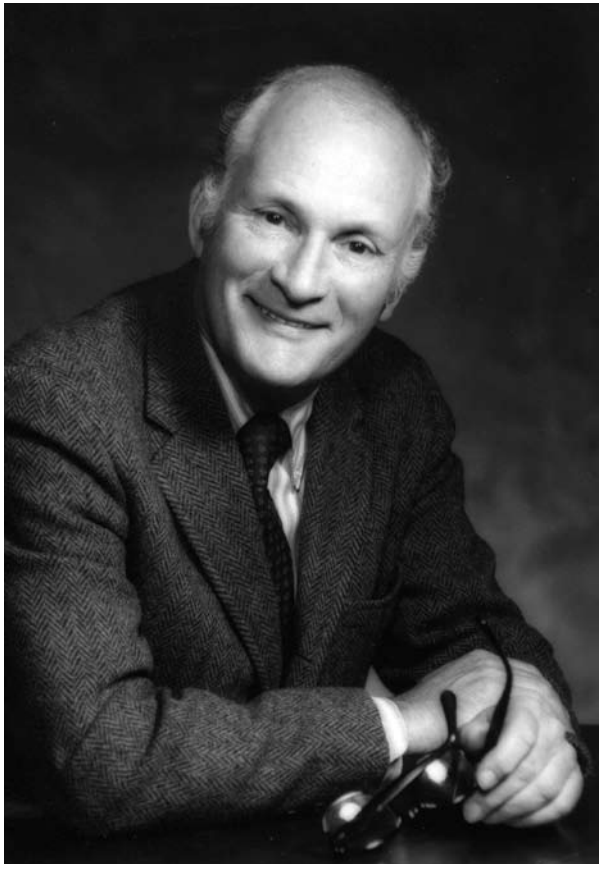
Biographical Memoir



MAHLON HOAGLAND

October 5, 1921–September 18, 2009

BY THORU PEDERSON

MAHLON HOAGLAND ENTERED the guild of biochemistry through an unusual door, promptly made two discoveries that were foundational to the advent of molecular biology, and then complemented his relatively brief research career with inspiring leadership in other domains: mobilizing Congress to support basic biomedical research and becoming an uncommonly articulate educator of the lay public on the process, and joy, of scientific discovery. In his writing for lay audiences he set his bar admiringly at Lewis Thomas and Carl Sagan. Francis Crick once characterized Hoagland as "a gifted amateur" and remarked that the keyword was "gifted." The fact that Mahlon never resented Crick's comment and often repeated it in conversation is an insight into his persona. A constitutional gentleness of outlook, indeed an often-endearing innocence, was one of the hallmarks of this fine man.

Hoagland was born in Boston on October 5, 1921, the first of four children to Hudson and Anna (Plummer) Hoagland. Hudson, only 21 at the time of Mahlon's birth, went on from Harvard University to become a prominent behavioral physiologist. He served as chair of biology of Clark University in Worcester, Massachusetts, from 1933 to 1943 and then as cofounder of the Worcester Foundation

for Experimental Biology. Hudson was also president of the American Academy of Arts and Sciences (1961-1964). In his autobiography (Hoagland, 1990) Mahlon said he and his siblings "were much on our own…in a big, busy, socially-lively household," adding "our parents often acted as though we children were unexpected, but not necessarily unwanted, guests." His mother was a brilliant Bohemian. Once, when Mahlon's brother was asked at school why he had not come wearing boots in bad weather, he replied, "My mother was playing the harp." Mahlon loved that story and, as was evident in all his remembrances, truly adored both his parents and felt their inspiration throughout his life.

Although his father took him to the lab from time to time, Mahlon was more intrigued with Hudson's joy of discovery and creative way of looking at problems than the physiological work itself. Unmotivated in public high school (he was later recognized to be dyslexic), he did better at a private school, and entered Williams College in 1940, transferring to Harvard the following year. In 1943 two milestones occurred in Mahlon's life. He met and married Elizabeth Stratton. And in keeping with the war's urgent need for doctors, he and many other Harvard undergraduates were mobilized and sent across the Charles River to the Medical School. Although not inspired by the curriculum (and thus in league with many first-year medical students), Mahlon was drawn to anatomy and was enthralled by a pediatric surgical text he came across—the classic *Abdominal Surgery of Infancy and Childhood* by William E. Ladd and Robert E. Gross. He soon met two of Harvard Medical School's most gifted surgeon-teachers at the time, Ira Nathanson and Oliver Cope, whose mentorship encouraged him further. Operating on dogs, Mahlon soon realized he had at last found his *métier*, in which a manual dexterity he had earlier experienced in woodcarving and

an appreciation for shape and form (he had been skilled at drawing since a child) all came together.

Having thus set his specialty sights, Mahlon continued through Harvard Medical School expecting to go on to a surgical residency after graduation. But in the fall of 1945 the most defining event in his formative career intervened. He was discovered to have tuberculosis, apparently contracted from a baby he had cared for on the pediatric service before her disease (miliary TB) had been recognized. Because by this time Mahlon had been commissioned as a midshipman in the navy, he was sent to the Chelsea Naval Hospital, where his infection progressed. As his condition worsened he was noticed by an attending, the prominent Boston physician Walter Burrage, who immediately arranged for Mahlon's transfer to the Trudeau Institute in Saranac Lake, New York. Throughout his life Mahlon expressed the view that had he not been found by Burrage, he would have succumbed to TB in that naval ward and what we know of his chart at the time suggests this would have indeed been the culmination.

Mahlon's condition upon admission to Trudeau was indeed serious, as he not only had a lung cavity but the additional diagnosis of intestinal tuberculosis. Nonetheless, over the next year and a half he recovered. During this time, he witnessed the dramatic impact of streptomycin's arrival, and though he did not receive it himself he always felt that this reinforced his latent admiration for medical research. He returned to Harvard Medical School in the fall of 1947, two years after his initial diagnosis, to repeat his interrupted fourth year and graduated the following June. He was due to start an internship at Massachusetts General Hospital but it was canceled when the chief of surgery learned that Mahlon had been (and perhaps still was) tubercular. Mahlon sought and obtained a post at the Peter Bent Brigham Hospital but shortly thereafter a chest film revealed that his tuberculosis

had reactivated. These then were the events that led him to a different career—biochemistry.

Biochemistry itself may not have been Mahlon's primary alternative to surgery at this time. (He had actually not had a particularly deep immersion in it as an undergraduate though he did recall Louis Fieser's organic chemistry course as among his favorites, recalling that the professor had brought the presented molecules to life, appealing to Mahlon's kinesthetic sense.) Rather, he wanted to obtain training in medically relevant research and chose to apply to the Huntington Laboratory at Massachusetts General Hospital (MGH), headed by the physician-toxicologist Joseph C. Aub. As they discussed possible projects Aub told Mahlon about a boy who had been cut by a broken fluorescent light tube and had been seen in the emergency room the previous year and released. He had returned a few months later with granulomas at the sites of his skin lacerations, reminiscent of lung granulomas seen in fluorescent light manufacturing workers who were suspected to have inhaled the phosphor dust. Aub and other toxicologists had begun to finger beryllium, a component of the phosphor, as the causative agent in the formation of these tumors. It had also been discovered that beryllium exposure resulted in bone decalcification, and there was evidence that this involved the metal's impairment of alkaline phosphatase. Working with Robert Grier in Aub's group, Mahlon confirmed beryllium's inhibition of the enzyme, apparently by competing with its essential cofactor magnesium (Grier et al., 1949), and in continuing studies they elucidated the causative action of beryllium in osteogenic sarcoma (Hoagland et al., 1950).

During this period, word of Mahlon's laboratory talent had gotten around; one person upon whose ears it fell was another member of the Huntington Laboratory, Paul Zamecnik. Having long been interested in the relationship

between growth control and protein synthesis, Zamecnik, a brilliant rising star, was leading a group trying to dissect these physiological processes into tractable biochemistry. Recognizing Mahlon's potential but also aware of his lack of formal training in protein biochemistry, Zamecnik suggested that Mahlon spend a year at the Carlsberg Laboratory in Copenhagen. (Zamecnik had made a stay at the Carlsberg Laboratory in 1939-1940, but it was cut short by the Nazi invasion of Denmark.)

Mahlon received an American Cancer Society fellowship and arrived in Copenhagen in June 1951 with his wife and three children. Although his research project over the next 15 months did not pan out, he was strongly influenced by the thinking of Herman Kalckar on biochemical energetics. He also recognized, for the second time during his training, that he was situated in a wide-open research institute setting rather than a standard university department. (As he would later note, and we shall here in due course, this realization was key to his attraction to the Worcester Foundation decades later.) Returning to MGH, Mahlon spent a year in a previously arranged postdoc with Fritz Lipmann. This was as synergistic an experience with Carlsberg as could be imagined, as Lipmann's presence had still resonated there (he had spent some of his most catalytic years there, 1932 to 1939), and now Mahlon was working directly with this pioneer of biological chemistry.

Lipmann had presciently suggested that protein synthesis might involve a step in which amino acids are energized in some way. This idea was based on his pioneering work on acetate activation, which had included an assay that involved the formation of a bond between the acetate's carboxyl and an amino group on an acceptor substrate (typically a sulfanilamide). Although Lipmann had considered the analogy between the energetic mechanism of the formation of this

peptide bond and those among amino acids in proteins, he had not directly investigated this nor was the group doing so when Mahlon joined them. It is certain that Mahlon became familiar with the idea at this time but he also did not work on it. Instead, he worked with David Novelli in the group on coenzyme A biosynthesis (Hoagland and Novelli, 1954). Though it had been a superb experience, in his autobiography Mahlon conveyed puzzlement over the Lipmann lab's apparent lack of interest in amino acid activation: "So there I was in the hotbed of biochemical energetics, working under the wing of the man who had made the most prescient guesses about how amino acids are energized for protein synthesis and no one was working on the problem" (Hoagland, 1990). Of course, one might ask why Mahlon didn't just go after it himself and there is no record (yet uncovered) that addresses whether he and Lipmann discussed a plan for Mahlon to do so.

Once in the Zamecnik group, Mahlon investigated amino acid activation in the cell-free protein synthesizing system that was being developed, step by improving step, by Elizabeth Keller, Phillip Siekevitz, and John Littlefield. He employed an assay he had previously encountered in Lipmann's lab, where Werner Maas was using it in studies of bacterial coenzyme A biosynthesis. It was based on the coupling of pyrophosphate with AMP to form ATP, the back reaction catalyzed by enzymes that mediate group transfer reactions of the γ phosphate of ATP onto a substrate (Maas and Novelli, 1953). Within only a few months Mahlon had run all the reactions and controls and had gotten a breakthrough result: in a cell-free system that is synthesizing protein, amino acids undergo an ATP-dependent reaction catalyzed by an activity that generates pyrophosphate (Hoagland, 1955). On the heels of these experiments additional ones soon filled out the picture (Hoagland et al., 1956).

This first major discovery of Mahlon's was immediately recognized as the breakthrough it was, but it was confined to the field of biochemistry. Little if any note was taken of it in the field that had been catalyzed three years earlier—molecular biology. This would soon change, when Mahlon took up a new project in Paul Zamecnik's lab.

A few years earlier, doing his own experiments (as he did at the bench far into his long career), Zamecnik wondered if the cell-free protein synthesis system his lab was perfecting might be synthesizing RNA. (This was well before the discovery of a role in protein synthesis for any kind of RNA, notwithstanding the presence of RNA in the particulate fraction of the systems i.e., microsomes). So one morning Zamecnik added C^{14}-CTP to the system. But as a control, he also added a C^{14}-labeled amino acid to another tube and found that it got incorporated. Zamecnik put this finding on the shelf but reminded Mahlon of it. Now armed with all the necessary techniques, Mahlon demonstrated that amino acids, once activated, become joined to RNA present in the 100,000 x g supernatant fraction (Hoagland et al., 1958). In a few months of experiments mightily enabled by the good fortune of Mahlon's training, he and Zamecnik had discovered a missing link in gene expression. As biochemists they called it "soluble RNA." The name didn't last long. They had discovered something much portentous, something Francis Crick had said "had to exist" (in whatever form). They had discovered transfer RNA. They had also presciently noted that once bound to this soluble RNA, the amino acid passed directly into nascent protein without being released. This was of course the first intimation of how the aminoacyl-tRNA synthetases operate.

In the winter of 1956-1957 the biochemistry and molecular biology schools began to realize that they could no longer avoid each other, either as epistemology or in person. Crick

visited Hoagland and Zamecnik in the spring of 1957, elated that their findings had confirmed his prediction. Zamecnik was not taken with Crick (something that historians will have to try and decipher) but Mahlon was. Crick invited Mahlon to come and work with him to see if they could make more progress on how the generic amino acid-tRNA linkage Mahlon had discovered might be refined into a study of individual amino acid translation, the coding problem on which Crick and his colleagues Sydney Brenner and George Gamow were light years ahead of others. Mahlon accepted the offer and set up a lab at the Molteno Institute. As Mahlon recounted in his autobiography, the project did not go well. A sketch Mahlon made at the time shows Crick trying to catch a rat under the lab bench, the fleeing rodent as elusive as the project's goal turned out to be. Perhaps this experience gave Mahlon some perspective on Crick, tagging him a "gifted amateur." They remained good friends for many years and at a symposium in San Diego in the 1990s I had the occasion at a lunch to observe how fond they were of each other. Mahlon attracted the very best minds, in part because he was so nonthreatening. The admiration in which the likes of Crick, James Watson, Gobind Khorana, and Alex Rich held him says a great deal.

In 1960 Mahlon took his first faculty position, in the Department of Bacteriology and Immunology at Harvard Medical School chaired by Bernard Davis. Teaching in Davis's department proved challenging and Mahlon would later often recount, without a trace of embarrassment, how Davis would attend his lectures and then summon him to his office for postmortems. In his lab Mahlon began to ponder whether his discoveries could have a "second act." He reasoned that differences in protein synthesis rate might find their explanation in an experimental dissection of a system in which such a shift occurs. At this point he remembered

the work of a gifted scientist in the Huntington Laboratory, a pioneer in her own right, Nancy Bucher. She had been intrigued with the phenomenon of liver regeneration and had done a remarkable experiment showing that a rat whose circulation had been joined to one that had undergone a partial hepatectomy underwent a regenerative response, a breakthrough in the growth control field, as it demonstrated that the growth factor was in the bloodstream. In a series of studies Mahlon and his lab productively pursued this idea, aided in particular by a Harvard medical student, Sam Wilson (who went on to a distinguished and continuing research career at the National Institutes of Health in the field of DNA repair). Mahlon's work at this time was centered on what later became known as translational control, though the term was not yet in wide use.

In 1967 Mahlon was offered and accepted the chair of biochemistry at Dartmouth Medical School. He had remarried in 1961, to Olley Jones Robbins, and for reasons more personal than scientific had grown disenchanted with the Harvard Medical School landscape. At Dartmouth he attempted a bold curriculum revision for the Biochemistry Department, involving the new discoveries about gene expression and molecular biology. His efforts were rebuffed by what he perceived to be a conservative administration. These travails were frustrating and took time away from his research.

The same year Mahlon moved to Dartmouth, 1967, something else happened that proved to be momentous. At the Worcester Foundation for Experimental Biology, its cofounder Gregory Pincus had died, at only 63. Pincus had been the science side of Hudson Hoagland's entrepreneurial panache and the two of them had made the Worcester Foundation into a Mecca of steroid hormone research and reproductive biology in the 1950s and 1960s, including work that led to

the oral contraceptive and human in vitro fertilization. When Pincus died, Hudson Hoagland was 67. Although youthful by today's standards, he and the trustees felt it was time for new blood. So the chair of the Board of Trustees, the Boston oncologist Sidney Farber, visited Mahlon at Dartmouth and asked him to succeed his father as president of the Worcester Foundation. He declined. Over the next two years Mahlon became more disenchanted with Dartmouth, considering its perceived conservatism to be unrelenting. A second call from the Worcester Foundation came in 1970, and this time he accepted.

In making this decision Mahlon had some key background information about what was happening on the national landscape. Sidney Farber and the philanthropist Mary Lasker had been working furiously in Washington to bolster congressional funding for cancer research. Both Farber and Lasker were on the Board of Trustees of the Worcester Foundation at the time. This temporal conjunction of the opportunity at the Worcester Foundation for a redirection toward Mahlon's own research interests in growth control at the level of gene expression, fueled by increased NIH funding and his growing dissatisfaction with life at Dartmouth, are what led Mahlon to reconsider. He accepted the post in 1970, having been alerted by Farber and Lasker that President Nixon would be signing the National War on Cancer Act soon, which he did. (In a televised interview years after his resignation Barbara Walters asked Nixon what he considered his greatest legacy. Most viewers thought he would say opening the door to China. To the surprise of many he said instead that it was signing the National Cancer Act of 1971, which created a bright-line congressional funding mechanism to an NIH cancer unit that had been formed, without much fanfare, 33 years earlier.)

At the Worcester Foundation Mahlon created a new focus for the institution his father had started, enabled in part by a Specialized Cancer Center grant from the National Cancer Institute in 1971 (ironically predating even the Comprehensive Cancer Center grant from NCI to Farber's own institution). The NCI site visit for Mahlon's pending application started off as a potential disaster when a key figure about to be recruited called in the middle of the previous night to say he had changed his mind. Mahlon sadly reported this as the site visit opened and then watched, with astonishment but joy, as the committee rallied to his sense of vision and subsequently rated his proposal a top score, believing that notwithstanding an inaugural member's bailout, he would attract good talent.

At the Worcester Foundation Mahlon saw the elements of the research institute environment he had encountered and admired both at MGH's Huntington Laboratory and in Copenhagen at the Carlsberg Laboratory. In all of his addresses to the Worcester Foundation's trustees and donors in later years he emphasized how such an open setting was conducive to progress.

By the time Mahlon took over the Worcester Foundation he knew that his ideas for exploiting his discoveries from the 1950s to solve the mechanisms of translational control of growth in regenerating liver were long out of reach, both due to his diminished interest and the mounting advances of other investigators. In a profound turnaround, by 1973 he had decided to devote himself to two other callings. Both sprang from a long pondered realization that he loved discussing science with lay audiences. He started on this new venture by writing columns for the Worcester newspaper. These were so enthusiastically received, as were his talks to lay groups, that he decided to try writing for a broader audience. His first book, *The Roots of Life: A Laymen's Guide to Genes, Evolu-*

tion and the Ways of Cells (Hoagland, 1978), was acclaimed by many as something in this form not seen since Loren Eisley, Carl Sagan, or Lewis Thomas

At this time Mahlon also turned his attention to the funding of biomedical research, particularly championing basic research. In these years the adjective "unfettered" entered his vocabulary as if it were being whispered by an admiring muse behind the curtain, smiling and leading him on. Aware that some of the biomedical research societies had worked in this vineyard (the American Society for Microbiology most ably up to that time), Mahlon had the idea to engage key leaders as actual lobbyists, not in the pejorative sense but as the nobility of the profession. Assisted by a knowledgeable Washington adviser, Bradie Metheny, Mahlon organized a group that after a few short-lived naming trial balloons, became the Delegation for Basic Biomedical Research. The initial group included Maxwell Cowan, Donald Frederickson, Seymour Kety, Arthur Kornberg, Francis Moore, George Palade, Lewis Thomas, and James Watson. When Mahlon got their and other acceptances, all in short order, he expressed some surprise that they had all stepped up, thinking that his name had disappeared from their memory of his science decades earlier. As I and others told him at the time, they hadn't accepted because he discovered amino acid activation and transfer RNA. They had accepted because by this stage of his career Mahlon's passion for the cause and his uncommonly articulate ability to convey this had become well known to them.

The delegation had great success and led to other such efforts. At this time Mahlon wrote a second book, *Discovery: The Search for DNA's Secrets*, in which he again luminously conveyed the process and joy of scientific discovery (Hoagland, 1981). He retired from the Worcester Foundation in 1985 and moved to Thetford, Vermont. Ironically, even though his

brief time at Dartmouth had been institutionally unhappy, he had made many lifelong friends there, and had always felt drawn to its graceful hills. He was very active for the next 20 years. He renewed his passion for wood sculpture that had first surfaced in his youth, clearly preordaining his early surgical skill and aspiration. He also undertook a mammoth book with the artist Bert Dodson, *The Way Life Works* (1995). It remains *sui generis* and subsequent editions have been translated into several languages worldwide. This remarkable book, in which every dimension of biochemistry and molecular biology is presented in acutely engaging portrayals, never exceeded in publishing, is one of the most fitting tributes to Mahlon's skills: a great eye and an uncommon desire and talent to teach. Subsequently, in collaboration with his elder daughter, the book was transformed into a well-received high-school text (Hoagland et al., 2001).

Mahlon Hoagland received the 1976 Benjamin Franklin Medal from the Franklin Institute and the 1982 Book Award of the American Medical Writers Association. He was elected to the National Academy of Sciences in 1984.

Late into his eighties Mahlon remained keenly interested in molecular biology and initiated innovative tools for teaching molecular biology in high schools. He remained tuned to ongoing RNA science and was excited by the discoveries of RNA interference and microRNAs, living to see the dramatic progression of these fields up to just before his death. Upon his retirement in 1985, a lectureship in his honor was established by the Worcester Foundation and he came to hear Bernard Davis, James Watson, David Baltimore, and Gobind Khorana. (Philip Leder's Mahlon Hoagland Lecture was aborted when a man delivering some potted plants for the auditorium left a bomb threat that morning. The bomber's layman reading of the posted lecture title, on the role of the c-*myc* gene in mouse breast cancer, led him to

believe that the Worcester Foundation was promoting animal abuse. The building was cleared, the eponymous Shrewsbury fire chief Raymond LaFlamme and his inspectors declared it safe, but by then Mahlon, Leder, and others were having a delightful luncheon elsewhere, perhaps almost as stimulating as the lecture might have been.) In subsequent years Mahlon Hoagland lecturers of a younger breed appeared (Mark Ptashne, Elizabeth Blackburn, and Harry Noller).

Up until just months before his death Mahlon remained very active. He was a beloved member of the local community in Thetford, Vermont, who saw him more as an engaging raconteur at the local coffee shop than a famous man of science, the latter a representation he never sought. In these years he also was the primary caretaker of his beloved wife Olley. After her death, Mahlon began to confront his own mortality, faced with an aortic stenosis and progressing kidney failure. Ironically, even though he once wanted to be a surgeon, Mahlon held a lifelong skepticism about the medical profession. After consulting all the top specialists at Dartmouth, including one of his former Harvard medical students, he elected not to undergo treatment. At home and in full cognitive range, with his children near him, he stopped eating and took only water in his final days and died peacefully on September 18, 2009, 10 days before what would have been his 88th birthday.

Mahlon Hoagland was a biochemist of brief but enduring accomplishment, who went on to serve the profession in ways that rivaled his laboratory discoveries. He was a pioneer of the axis of biochemistry that gave birth to molecular biology, and then walked with eloquence into other hallways as a gifted spokesperson for our profession and our love of it. In both domains he has left us a cherished legacy.

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