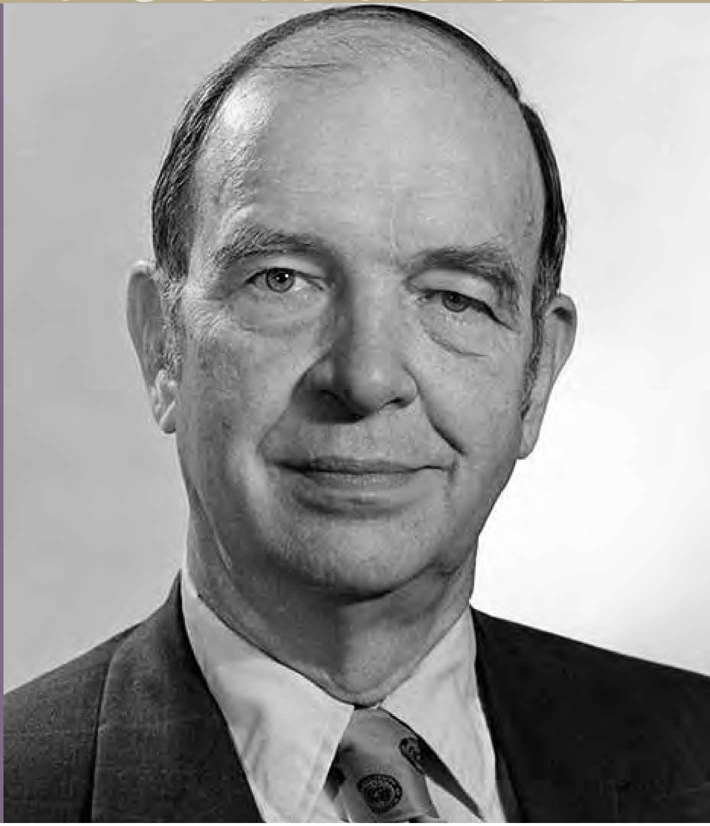
J. Lawrence Oncley

1910–2004

BIOGRAPHICAL *Memoirs*



A Biographical Memoir by
Russell F. Doolittle

NATIONAL ACADEMY OF SCIENCES

J. LAWRENCE **ONCLEY**

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Elected to the NAS, 1947

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By Russell . Doolittle

J. Lawrence Oncley—Larry to most colleagues and JLO to his senior graduate students—was a true pioneer of biophysical chemistry. His contributions were not only reflected in his published papers, but in his broad influence in shaping national policy related to the establishment of biophysics as a discipline of its own, especially during the period 1956–1965.

Born in Illinois but raised mostly in Kansas, Oncley attended Southwestern College in Winfield, Kansas, and graduated in 1928. His introduction to research began as a graduate student at the University of Wisconsin, where his advisor, J. W. Williams,[1] was leading an effort to deduce small molecular structures from dipole moment measurements based on the theoretical descriptions of Peter Debye. In one way or another, "dielectrics" was to remain a fascination for Oncley for the rest of his career.

His PhD was awarded in 1932, after which he received a National Research Council fellowship for postdoctoral work with F. G. Keyes at the Massachussetts Institute of Technology (MIT). While in the Boston area, he visited Edwin J. Cohn's laboratory at Harvard Medical School, where he met another visitor, Jeffries Wyman, who was also keen on the dielectric behavior of solutions and whose recently published precise value for the dielectric constant of water (78.54 at 25 °C) had already caught Oncley's eye. By the standards of the day, both men were apparatus geeks.

Research

In 1932, Oncley returned to the University of Wisconsin for a year to substitute for his former PhD mentor, Williams, who was on sabbatical in Uppsala, Sweden. In 1935, Oncley was back at MIT as an instructor. Cohn had encouraged him to join his own group, but there would have been a delay while fellowship funds were sought. With the

Great Depression at its worst, Oncley accepted MIT's offer of an instructorship, rather than endure the insecurity of waiting for a fellowship.

Undaunted, Cohn managed to arrange for Oncley to pursue experiments at Harvard even while he was employed by MIT, an opportunity that Oncley was glad to accept, at least partly because he found that as an instructor, his MIT laboratory turned out to be his office, a rather restrictive setting in which he still managed to assemble some useful apparatus. But the Cohn lab offered a lot more than space and funds for equipment; it provided an unusually stimulating and exciting environment.

The Cohn laboratory, officially the Laboratory of Physical Chemistry, Harvard Medical School, was already renowned for its research on proteins. It was a unique operation and probably the only one of its kind in the world located at a medical school. Its main operation was headquartered on the fourth floor of Building C1 on the Harvard Medical School quadrangle, and it was there that Oncley began his dielectric measurements on proteins in a closet-size space adjacent to Cohn's spacious office.

These were quite sophisticated experiments that required significant modification of the instruments in vogue at the time. Among the problems to be dealt with was that most proteins were not soluble in the organic solvents (with low dielectric constants) that had been in use with many small molecules. Aqueous solvents had high dielectric constants of their own, and there were also severe polarization effects that had to be corrected. To this end, Oncley assembled a unit with a unique radio frequency bridge circuitry that could deliver a wide range of frequencies for inducing orientation effects in dipolar solutions. During this period he was reunited with Wyman, and he also became friends with George Scatchard at MIT. Both men were genuine experimentalists with whom he could discuss the design and construction of innovative equipment.

Initially, Oncley set out to demonstrate the anomalous frequency dispersion effects predicted by Debye's theory. Eschewing small organic molecules, he chose hemoglobin as a target, the dipole moment of which was predictably huge. With time, his aims shifted to characterizing the electrostatic landscape of proteins in general. He showed that the relaxation behavior of large molecules could be distinguished from that of small ones by a judicious choice of the frequency of charge alternation on the condenser plates, lower frequencies being favored for proteins and higher ones for small molecules.

He went on to study a wide variety of proteins, especially asymmetric ones with electrostatic and hydrodynamic behaviors that could be interpreted in the light of the newly available equations devised by F. Perrin. Up until that time, proteins in solution were mostly modeled as simple spheres. The idea that asymmetric models—prolate or oblate ellipsoids—might be more representative of some macromolecules ("colloids") was just beginning to take hold.

Oncley's work had an immediate effect. Among the proteins he studied were edestin, hemoglobin, gamma globulins (simply called antibodies in those days), and plasma lipoproteins. He did not limit himself to dielectric phenomena; indeed, he broadened his approach to use the full arsenal of physico-chemical techniques being developed in the Cohn lab, including viscosity measurements, flow birefringence, and, as discussed below, sedimentation in the ultracentrifuge.

In 1939, Oncley officially joined the Cohn enterprise with a genuine Harvard appointment, although he was de facto already a member of that team dedicated to determining the size, shape, electrostatics, and hydration of proteins found in blood plasma.

Such characterization demanded pure proteins and, to that end, there was a group effort under way to fractionate human plasma into its individual components. The purification schemes were primarily based on the different solubilities of those proteins under various conditions of temperature, pH, ionic strength, and dielectric constant.

Cohn was a powerful institutional figure who possessed what was apparently direct-line reporting to the president of Harvard, James Conant, who was a chemist. Given this rare privilege, Cohn seemed always able to garner the generous funding that ensured progress would never be hampered by traditional academic bureaucracy.

These were profitable years for Oncley on several counts. Visitors from around the world flocked to the Cohn lab and good postdoctoral talent was always available. Beyond that, Oncley developed strong day-to-day collaborations with luminaries like John Edsall and John Ferry, among others.

The ultracentrifuge

In 1938, Cohn had decided the group needed an ultracentrifuge, which was a major undertaking in those days. Suitable funds were arranged and space for its installation commandeered in the basement of another building on the Harvard Medical School quadrangle (Building E2). Cohn put the newly appointed Oncley in charge of the centrifuge, and for the next 14 years Oncley's office was located in that subterranean site, quite removed from the main lab on the fourth floor of Building C1.

The centrifuge, patterned on one recently installed at the Rockefeller Institute for Medical Research in New York, was probably only the second or third ever built outside of Sweden. It was a custom built, air-driven apparatus, assembled very much under the guidance of an instrument maker, Charles Gordon. Gordon became so fascinated by the machine and the science around it that he remained as Oncley's assistant for the next 23 years, operating and maintaining ultracentrifuges for his entire career.

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The onset of World War II led to enormous advances by the Cohn group in the isolation and largescale production of blood plasma proteins, some of which, like gamma globulin and albumin, had a great bearing on the war effort. The main lab in Building C1 was a unique warren of small lab spaces and cold rooms, many at the sub-zero temperatures used in the cold ethanol approach for the purification of plasma proteins. Additionally, a pilot plant for large-scale plasma fractionation was constructed in Building E2 just above where the ultracentrifuge was built and where Oncley spent most of his time. Often overshadowed by the eminence of Cohn, Oncley played an indispensable role in directing day-to-day activities and devising the various methods of protein preparation.

With the end of the war, large quantities of pure proteins, no longer needed for military purposes, were available for study. The pilot plant fractionation procedures were such that a single run yielded as much as a kilogram of pure albumin.

By this time, Oncley had developed a special interest in the interactions of lipids with proteins, including the binding of fatty acids by what was then called "serum albumin" (today plasma albumin). Together with his students, he showed that the large dipole moment of albumin was due almost entirely to the multiple molecules of fatty acid that were bound to it. Stripping away that fatty acid artfully, so as not to denature the albumin itself, was difficult. In the preparations that were ultimately used, these acids were removed by exposing the albumin complex in solution to a rat epididymal fat pad, an entity with an exquisitely high affinity for fatty acids and one that could out-compete the albumin.

In later studies, Oncley's work led to the purification and characterization of plasma lipoproteins associated with cholesterol. These purification procedures began with the well-known Cohn fractions III-0 and IV-1, but they went on to use, for the first time, preparative ultracentrifugation to float off the lipoproteins in a "medium of sufficiently high density to cause the β-lipoprotein to rise slowly toward the surface." This led to the now common distinction between low-density (LDL) and high-density (HDL) lipoproteins.

In 1942, Oncley won the American Chemical Society Award in Pure Chemistry, and in 1947, at the very young age of 37, he was elected to the National Academy of Sciences.

Biophysics as a new discipline

During the late 1950's, Oncley became heavily involved in a mammoth national enterprise, partly in response to the October 1957 launch of a space satellite by the Soviet Union. Sputnik was to many a signal that the United States had lost its international edge not only in space, but in science overall.

One of the immediate reactions was the arranging of a four-week conference in the summer of 1958 on the subject of biophysics. The conference was sponsored by the Biophysics and Biophysical Chemistry Study Section of the National Institutes of Health and was officially called "A Study Program in Biophysical Science." It was held in Boulder, Colorado, and Oncley was the principal organizer.

Many of the country's leading biomedical scientists participated in the conference. The proceedings were published in the January and April 1959 issues of *Reviews of Modern Physics* and then reprinted as a book that same year by John Wiley & Sons,[2] for which Oncley was the chief editor among a team of five that included F. O. Schmitt, R. C. Williams, M. D. Rosenberg, and R. H. Bolt.

The book's sixty-one chapters covered the gamut of biochemical and biophysical approaches to macromolecules—proteins, nucleic acids and carbohydrates—and it included several strong chapters on nerve and muscle physiology, as well as electron microscopy. The fifty authors (several of whom wrote more than one chapter) were a veritable who's who of American premium biochemists and biophysical scientists (the group included a few who were not Americans); five of the authors would subsequently receive the Nobel Prize (Calvin, Hartline, Katz, Kendrew, and Kornberg). At a subsidized price of $6.50, the book was a wonderful bargain, affordable even for graduate students.

It was in the wake of that enterprise that a clamor arose for a journal devoted exclusively to biophysics. A committee, including Oncley, was set up and recommendations made for such an endeavor. The launching of the *Biophysical Journal* and all the complications that went with it was described in a reflection Oncley wrote in 1990.[3]

Oncley was the second editor of the journal, serving in the period from 1964 to 1966. The occasion also heralded the start of a biophysics program at Harvard, an enterprise for which Oncley was very influential after getting Arthur K. Solomon to be the program's first leader.

Another chapter

Cohn died on October 1, 1953, and the October 9, 1953, issue of the Harvard Crimson student newspaper carried the story, "Oncley Seen as Cohn's Successor for Blood Protein Experiments." The article quoted an un-named official at Harvard Medical School who said "that Cohn had held Oncley in the highest regard and had been grooming him to take charge of Cohn's experiments." The article noted, however, that Oncley would not necessarily be appointed at the same elevated rank that Cohn held. Cohn had held a rare and exalted position, and with it a good deal of power and influence.

Oncley received a letter from Michigan. Presuming it to be a thank-you note, he stuffed it in his pocket for later reading. It was a month or two later that his wife, preparing to have the suit cleaned, found the unopened letter.

As it happened, not everyone at Harvard Medical School was enamored with the distinction of being the only medical school in the world with a Department of Physical Chemistry, especially with its members, eminent as they might be, not having to teach medical students. A move was initiated to absorb the "Cohn group" into the Department of Biological Chemistry, which was headquartered in the neighboring wing in Building C2 and headed by A. Baird Hastings.

Although Oncley, who had only recently been promoted to full professor several years after his election to the National Academy of Sciences, assumed Cohn's scientific duties ably and was now comfortably situated in Cohn's large old office, the center of power was shifting.

Ominously, John Edsall moved across the river to the Biology Department on the main campus and in 1958 became the editor-in-chief of the *Journal of Biological Chemistry.* And in 1960, Douglas Surgenor, the only other faculty member remaining from the Cohn dynasty, left Harvard to become chair of the Biological Chemistry Department at the University of Buffalo. The fourth floor of Building C was gradually losing its luster as a world-wide force.

Early in 1961, Oncley was asked to lead a visiting committee to look into the start of a biophysics program for the University of Michigan in Ann Arbor. After its visit to Ann Arbor, the committee enthusiastically recommended that such a program be undertaken, and as soon as possible.

Not long after the committee's report was submitted, Oncley received a letter from Michigan. Presuming it to be a thank-you note, he stuffed it in his pocket for later reading. It was a month or two later that his wife, preparing to have the suit cleaned, found the unopened letter.

The envelope contained more than a thank-you note; Michigan wanted Oncley himself to come and set up the new biophysics center that the committee had so warmly endorsed. Slightly embarrassed by the delay in responding, Oncley graciously, if somewhat sheepishly, agreed to think about it. In the end, he decided it was a timely offer, and with that he set about moving his research group and his family to Ann Arbor.

It was a good move on his part and a great one for Michigan. The university's new Biophysics Research Division was a huge success. Twenty years later, in 1982, not long after Oncley's formal retirement, the J. Lawrence Oncley Lecture was established in honor of his role in establishing the discipline of biophysics.

The University of Michigan was a setting in which Oncley felt very comfortable. He was at heart a genuine mid-westerner. Other members of the Cohn group had made the transition to the heartland successfully: his good friend John Ferry had gone to the University of Wisconsin at Madison, and his former student Frank Gurd to the University of Indiana. The hub of protein science was no longer restricted to Cambridge, Massachusetts.

A personal remembrance

I was one of Oncley's graduate students during that transitional period of 1960–1962. (I had started my research with Douglas Surgenor, who, as noted above, left Harvard after Cohn's death.) What I remember most fondly was Oncley's big, sunny, fourth-floor office (formerly Cohn's) with its wellworn oriental rug. There was a huge table with papers piled high. He had another big table in a study at home that was piled equally high with more papers.

I can still see Oncley with his rumpled, vested suit, the gnurled brow, a match hovering above his stubbornly unlighted pipe. And, in those mostly pre-computer days, he was forever performing paper-and-pencil calculations during every spare moment in order to process raw data from various experiments.

He was an especially good listener, always responding with a cheerful remark. His sense of humor was wry. Physically large and lanky, he was an inherently gentle person, even-tempered to a fault. He was liked and respected by all around him.

Oncley worked hard in setting up the new program at Michigan, and it took a toll on some of the things he loved, including his dielectric studies on “serum albumin” (he never could bring himself to calling it “plasma albumin,” nomenclature purists aside), although he did manage to keep some experiments going with his former graduate student, Walter Scheider, who moved with him from Harvard to Michigan.[4]

In his later years, after he had formally retired from the faculty, I heard from others that Oncley became an avid fan of University of Michigan basketball. I was aided in the preparation of this biography by information provided in an obituary prepared by J. E. Penner-Hahn and R. L. Kuczkowski as a part of the Faculty History Project at the University of Michigan. Some background about the Cohn laboratory was taken from the 2002 book *Edwin J. Cohn and the Development of Protein Chemistry* by D. M. Surgenor. Many other facts were taken from reflections written by Oncley himself, including one on the origins of the *Biophysical Journal*[4] and, very particularly, another that appeared in *Biophysical Chemistry* in 2003.[5] The story of the unopened letter from the University of Michigan in 1961 is a first-hand account.

NOTES

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2. J. L. Oncley, F. O. Schmitt, R. C. Williams, M. D. Rosenberg, and R. H. Bolt, eds. (1959). Biophysical Science. A Study Program. Published in *The Reviews of Modern Physics*, January and April 1959. New York: John Wiley & Sons, Inc.
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5. J. L. Oncley (2003). Dielectric behavior and atomic structure of serum albumin. *Biophys. Chem.* 100:151-58.

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