BIOGRAPHICAL MEMOIRS

Howard K. Schachman

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A Biographical Memoir by Angela N. H. Creager and Susan R. Wente

Howard Kapnek Schachman's career spanned more than six decades after World War II, reflecting the development of molecular methods in biology and the phenomenal growth of basic research in the biomedical sciences. He was one of the preeminent experts in the technique of ultracentrifugation at a time when macromolecular separation was critical to biochemistry and molecular biology. As a faculty member at the University of California, Berkeley, he was equally involved in political issues of the day, from the Free Speech Movement on campus in the 1960s to congressional debates over scientific misconduct in the 1990s. In his honor, the American Society for Biochemistry and Molecular Biology established the annual Howard K. Schachman Public Service Award in 2001 to recognize outstanding public service in support of biomedical science. He also left his mark on science through mentoring generations of postdoctoral fellows and graduate students, advising more than fifty Ph.D. dissertations.

Early Life and Education

Schachman was born on December 5, 1918, in Philadelphia, the child of Morris and Rose Schachman. As he put it in a recollection for the *Annual Review of Biochemistry*, he was "more interested in social and political issues than in science."[1] He attributed this idealism to the example set by his mother, who was active in progressive Jewish organizations. Schachman wanted to obtain a liberal arts education and then become a rabbi before the realities of the Great Depression and advice from a family friend led him to pursue a more practical path. In 1935, he began his undergraduate studies in chemical engineering at the University of Pennsylvania. He transferred after one year to the Massachusetts Institute of Technology (MIT), graduating with a bachelor of science degree in 1939. His subsequent efforts to find a good job in a chemical company were fruitless, however, because of prevailing antisemitism. His only offers, both unsatisfactory, were from a paint company and a firm making alcohol.

A lecture by physical chemist Max A. Lauffer (1914–2012) on tobacco mosaic virus (TMV), given at Philadelphia's Franklin Institute, inspired Schachman to ask him how to follow in his footsteps. Lauffer told him that a Ph.D. would be essential and that there was an opening for a technician at the Rockefeller Institute for Medical Research (now

Rockefeller University). This opportunity was not in New York, but in the laboratory of chemist Wendell M. Stanley (1904–1971) in the Rockefeller Institute's Department of Plant Pathology in Princeton, New Jersey. Schachman took the job, and his first achievement was devising a modified procedure for preparing purified TMV in a continuous-flow high-speed centrifuge. He also became the go-to technician at Rockefeller who ran sedimentation velocity experiments in the ultracentrifuge for various investigators. This experience led him to develop and publish a new method for calculating sedimentation coefficients, based on an alignment chart and adjusting observational data to standard conditions.[2] It was difficult for him to obtain permission to publish this work as a lowly technician; he succeeded only through the advocacy of Lauffer.[3]

Over this same period, Schachman began coursework during summers towards a Ph.D. in the Department of Physical Chemistry at Harvard Medical School, which boasted particular strength in protein research because of the presence of Edwin J. Cohn (1892–1953).[4] The entry of the United States into World War II ended this aspiration, as a government contract with Stanley's lab required Schachman to work year-round. Instead, he enrolled as a part-time graduate student at Princeton University. As the war continued, it became impossible for him to defer his military service. He applied for a commission in the U.S. Navy Reserve and was appointed as an ensign at the Naval Medical Research Institute in Bethesda. In 1945, he married Ethel Lazarus, who worked for the Emergency Committee of Atomic Scientists based in Princeton and nominally headed by Albert Einstein (whom the couple drove to meetings in their car). They had two children—Marc, an oboist, and David, a lawyer—and, over their nearly seven-decade marriage (Ethel died in 2013), delighted in opening their home for coworkers and guests to share in music, conversation, and friendship.

After his discharge from the Navy, Schachman received one of the very first predoctoral fellowships bestowed by the National Institutes of Health (NIH) and completed his Ph.D. in physical chemistry at Princeton in 1948. His dissertation research, on the physical properties of TMV as determined by centrifugation and viscometry, was conducted in Stanley's laboratory.[5] As Schachman was completing his doctorate, Stanley (who had received the 1946 Nobel Prize in Chemistry) was being recruited by Robert G. Sproul (1891–1975), president of the University of California (UC) system, to head the new Department of Biochemistry at UC Berkeley and establish a Virus Laboratory there.[6] Stanley brought Schachman with him to California in 1948. Schachman started as an instructor and rose through the ranks, but not without some turbulence. During World War II, the university had begun requiring a loyalty oath of all appointees. In March 1949, the UC regents added what was effectively an anti-Communist addendum to the oath.[7] Schachman was one of about 200 non-signers. Thirty-one of these faculty were dismissed over the oath, and others left voluntarily. Eventually, Schachman recognized that not signing at this early career stage would make an academic appointment at any university difficult, and he had a growing family to feed. After some months of having his salary withheld (Stanley loaned him money for rent), he relented and signed. But as he observed in a 1999 symposium on the loyalty oath controversy, "I have always been struck by the Regents' action in 1940 barring Communists at a time when I was much more concerned about Nazis."[8]

At the Rockefeller Institute, Schachman had used two air-driven ultracentrifuges designed and built by Edward Greydon Pickels (1911–2005), a physicist who was working in the New York laboratories of the Rockefeller Foundation's International Health Division. In contrast to the oil-driven analytical ultracentrifuge developed in Stockholm by Theodor "The" (1884–1971) Svedberg, air-driven analytical ultracentrifuges were simpler and easier to operate, though not yet commercially available.[9] Around the end of the war, Schachman was approached by Maurice Hanafin of "Glass Engineering Laboratories" to ask if he would help produce an air-driven ultracentrifuge. Schachman declined, but introduced Hanafin to Pickels and, in 1946, the two of them founded the Specialized Instruments Corporation—better known among scientists as Spinco—to manufacture ultracentrifuges for sale for laboratories.

After arriving at Berkeley, Schachman purchased Spinco's first Model E, an analytical machine. In fact, it was the demand for preparative centrifuges that drove Spinco's success, and Pickels and Hanafin sold Spinco to Beckman Instruments in 1954. Schachman worked closely with Pickels (who stayed on at Beckman) on new methods for ultracentrifugation, developing the synthetic boundary cell in a three-way collaboration with his first graduate student William F. Harrington (1920–1992).[10] In addition, graduate student Ann Ginsburg (1932–2008) and Schachman developed a method for determining molecular weights during the approach to sedimentation equilibrium.[11] It was Schachman's facility with the analytical ultracentrifuge that led to some of his best-known early publications.

He contacted his then-Berkeley colleagues Arthur B. ("Art") Pardee (1921–2019) and Roger Y. Stanier (1916–1982) and offered to subject a lysate of the bacterium *Escherichia coli* to ultracentrifugation to look for cellular particles. They saw two sharp boundaries, one at 30S and one at 50S, which were ribonucleoproteins. Their study was arguably the first observation of what were soon called ribosomes.[12] They also found some smaller RNA molecules that turned out to

Figure 1 Howard Schachman (circa 1955) in front of his Spinco Model E ultracentrifuge in the Virus Laboratory, U.C. Berkeley. *Photograph from Wendell M. Stanley papers, BANC PIC 1988.031, courtesy of the Bancroft Library, UC Berkeley.*

be tRNAs. Stanier then contributed an extract of a photosynthetic prokaryote, anaerobically-grown *Rhodospirillum rubrum*. Again, collaborating with Pardee, they found that colored particles (containing the bacteriochlorophylls and carotenoids required for light harvesting) migrated much more rapidly than the 30S and 50S ribosomes; they dubbed these large particles (about 200S) chromatophores.[13] Schachman said that those two 1952 papers with Pardee and Stanier, the second published in *Nature*, were responsible for his promotion to tenure.[14]

Schachman continued to work on the structure of intact and degraded TMV as well as on pyrophosphatase and rabbit papilloma virus.[15] He also collaborated with Berkeley colleagues on studies of bacteriophage, viral RNA, and DNA, in the latter case using the ultracentrifuge to demonstrate that there were nicks in the double helix.[16] He and nucleic acid chemist Charles A. "Chuck" Dekker (1920–2008), who had joined the faculty in 1951, proposed "an interrupted two-strand model" for DNA, a molecule whose behavior in the ultracentrifuge fascinated Schachman.[17] In effect, this experiment showed the degree of degradation in the calf thymus DNA scientists were using to understand nucleic acid structure (especially in comparison with more intact bacterial or viral DNA). Schachman spent the 1957–58 academic year in the laboratory of biochemist Arthur Kornberg (1918–2007) at Washington University in St. Louis, a choice that reinforced his interest in nucleic acids as well as viruses and enzymes.[18] The very next year (1959) Kornberg was awarded the Nobel Prize in Physiology or Medicine.

With the increasing attention to DNA, biochemists wanted to identify various macromolecules in the ultracentrifuge, not only assess their overall size and shape. Schachman helped to develop new scanning systems, particularly an approach based on absorption optics, which could differentiate nucleic acids and proteins.[19] In part because this system provided a less mathematically demanding way (than using changes in the equilibrium across boundaries) of using sedimentation velocity experiments to look at molecular interactions, this was a major advance in ultracentrifugation. In a particularly elegant demonstration of this, Izchak Z. Steinberg and Schachman showed that one could detect the binding of methyl orange to bovine serum albumin by following each molecule at a specific wavelength.[20] The availability of absorption optics drove the popularity of the analytical ultracentrifuge among biochemists.

The Berkeley collaboration that most affected Schachman's research was with his junior colleague John C. Gerhart.[21] Schachman was working already on the quaternary structure of proteins, showing that the ultracentrifuge was exceptionally well-suited for studying subunit dissociation and reassembly.[22] Gerhart had come to Berkeley in 1958 as a graduate student mentored by Art Pardee, who was working on the biosynthesis of pyrimidines. Pardee and Richard A. Yates (1930–2024) had discovered feedback inhibition through their observation that the activity of *E. coli*'s aspartate transcarbamoylase (ATCase)—which catalyzes the condensation of L-aspartate and carbamoyl phosphate to form N-carbamoyl-L-aspartate and inorganic phosphate—was controlled by cytidine, a nucleotide end-product of the pyrimidine pathway.[23] Strikingly, Gerhart found that the kinetics of the purified enzyme were sigmoidally dependent on the substrate aspartate.[24] He demonstrated that the feedback inhibitor was CTP and appeared to compete with the substrate aspartate, despite their marked structural dissimilarity. In addition, ATP also competed with CTP, but with ATP enhancing enzyme activity. CTP's inhibition could be eliminated by treatment with heat or mercurials, which also resulted in Michaelis-Menten kinetics. Gerhart suggested that the inhibitor site was different from the active site and that feedback inhibition might involve subunit interactions, as exemplified by hemoglobin's cooperative binding of oxygen.[25]

After Gerhart was hired as an assistant professor at Berkeley in the then-newly established (1964) Department of Molecular Biology (subsumed into the current Department of

Molecular and Cell Biology in 1989), he began collaborating with Schachman to examine the structure of ATCase in the analytical ultracentrifuge. Gerhart and Schachman found that upon treatment with mercurials, the single protein (11.7S) separated into two components (2.8S and 5.8S). The catalytic and regulatory binding sites were located on different subunits, which could be reconstituted into the intact enzyme through removal of the mercurial compound.[26]

ATCase, a heterododecamer composed of two catalytic trimers held together by three regulatory dimers, occupied Schachman for the rest of his career. Moreover, it became an excellent model system for studying allosteric regulation. In 1961, Jacques L. Monod (1910–1976) and François Jacob (1920–2013) drew attention to the fact that regulatory molecules, whether they controlled the activity of enzymes or genes, could be chemically distinct from substrates: for expression of β-galactosidase, inducers and substrates need not be identical; and, for proteins, effectors dissimilar to the substrates could modulate enzyme activity. They christened such protein effectors "allosteric."[27] They further developed the idea of allostery in a paper with Jean-Pierre Changeux (then a graduate student of Monod studying feedback inhibition in threonine deaminase) to encompass feedback inhibition, cooperative binding, and other examples of effector-modulated protein activity.[28] There they cited the instructive view of enzyme regulation posited by biochemist Daniel E. Koshland Jr. (1920–2007), in which binding of small-molecule effectors induces a conformational change in the protein.[29] In 1965, Monod, physical chemist Jeffries Wyman (1901–1995), and Changeux introduced an alternative concerted model for allosteric regulation. The MWC model proposed that there are only two enzyme states, an R ("relaxed") state of high activity and a T ("tense") state of decreased activity. The model attributed changes in enzyme activity to the number of enzyme molecules in the population that had undergone the "allosteric transition" from one state to another, a thermodynamic shift stabilized by the binding of effectors. They also distinguished "homotropic" effectors, namely substrates, from "heterotropic" ones, non-substrate ligands.[30]

ATCase provided an excellent test system for the MWC model, according to which the binding of ATP or substrates shifted the allosteric equilibrium by stabilizing the R state, whereas CTP shifted the allosteric equilibrium by stabilizing the T state. Monod visited Berkeley while working on the 1965 paper and was thrilled with the findings of Gerhart and Schachman. Indeed, Monod had been following Pardee's and then Gerhart's work on ATCase from the late 1950s. Schachman said Monod thought it was obvious that having two different types of subunits was the perfect way to achieve allosteric control—although, as it turns out, the arrangement exhibited by ATCase is more the exception than the rule.[31] Changeux came to collaborate with Gerhart and Schachman in 1966, the same year that Koshland and his postdocs George Némethy (1935–1994) and David L. Filmer (1932–2021) published their "induced fit" model for allosteric control.[32] In contrast with induced fit, the MWC model predicted preservation of symmetry, so that all of the subunits in a given molecule of ATCase would be expected to be in the same state, T or R, and never an intermediate mixture of R and T subunits in the same molecule.

Schachman turned to the ultracentrifuge to register conformational changes associated with the allosteric transitions in ATCase. To this end, he and his coworkers drew on Rayleigh interference optics, having devised a way to record two different sedimentation velocity patterns simultaneously in the same ultracentrifuge run: one a protein sample alone, the other the same protein with a ligand (substrate or effector). Even a relatively modest conformational change could be detected using interference optics to measure directly the difference in sedimentation rate between the two samples. Pickels (still at Beckman) designed a commercial Rayleigh interferometer, facilitating the spread of this method among protein biochemists.[33] For ATCase, comparing the unliganded holoenzyme to that bound to carbamoyl phosphate and the aspartate analog succinate showed a remarkable 3.5 percent *decrease* in sedimentation coefficient versus the increase expected simply from the added mass of the bound ligands.[34] The work of Schachman and his collaborators, in the late 1960s and beyond, showed that ATCase fit the MWC model beautifully.[35] Schachman adhered to this concerted model for the structural transitions in ATCase for the duration of his career.[36]

Schachman went on to examine in greater detail the structural organization of ATCase and its mechanism for subunit assembly, which he regarded as keys to understanding the enzyme's functional properties. With a number of graduate students and postdoctoral fellows, as well as his long-time research assistant Ying R. Yang, the heterododecamer was taken apart, its pieces modified, and then put back together for further studies. Mixing catalytic oligomers that were exposed to limited chemical modification (succinylated) with unmodified catalytic oligomers, and reversibly denaturing the mixture with urea, resulted in a four-member set of oligomers with different electrophoretic mobilities due to the different numbers of succinylated catalytic subunits.[37] The four-member set was only possible if the catalytic subunits first assembled into a trimer. Knowing the regulatory subunits were dimers (based on their cross-linking analysis), Schachman's group posited a theoretical scheme of all possible intermediate assembly reactions, ten in total; the lab's in vitro studies identified key steps with few stable intermediates, one

in particular being with two catalytic trimers and two regulatory dimers.[38] These studies supported a structural organization for the holoenzyme that helped put to rest competing models.

With the molecular biology revolution of the late 1970s and 1980s, Schachman and his lab members eagerly pivoted to apply genetic approaches to their protein chemistry. Indeed, Schachman himself went to the bench to finish critical experiments defining interallelic complementation in the operon of the contiguous *E. coli pyrB* and *pyrI* genes encoding the catalytic and regulatory polypeptides, respectively.[39] Defining the critical active site residues came from a combination of in vitro chemical modification, in vivo genetic screens, and finally site-directed mutagenesis.[40] Schachman was especially intrigued with the question "why trimers?" Again, combining modified pieces offered key insights. Schachman and coworkers assembled catalytic trimers with different active site residues changed by site-directed mutagenesis of the *pyrB* gene.[41] Mixing two different loss-of-function catalytic mutants with each other resulted in the isolation of specific trimer hybrids with one-third the catalytic activity, even though all three subunits harbored an inactive mutant. Furthermore, mixing wild type with a double mutant loss-of-function yielded a hybrid trimer with only one-third the catalytic activity, even though it had two wild type subunits and only one inactive (though double mutant) subunit. This positive and negative complementation was only possible if the catalytic active site resided at the interface between two subunits, a result that provided an in vitro explanation for the genetic mechanisms of dominant negatives.[42] This finding also satisfied Schachman's fascination with trimer assembly being a critical aspect of *E. coli* ATCase structure and function.

Schachman and his coworkers developed a number of experimental ways to manipulate ATCase, generating mutant holoenzymes in the fully inactive T-state, or with precisely limited numbers of active catalytic sites, or with regulatory chains altered such that the unliganded mutant holoenzyme's T-state/R-state equilibrium shifted. These modified forms of the enzyme, along with the advent of a tight-binding bisubstrate analog N-(phosphonacetyl)-L-aspartate (dubbed PALA), facilitated further testing of the global conformational change hypothesis.[43] During sedimentation velocity experiments, boundary spreading measurements of mixtures of wild type holoenzyme bound to PALA (a fully R-state population) and inactive T-state holoenzyme revealed no intermediate states in the homotropic effector (substrate)-induced allosteric transition.[44] Independent tests for the action of the heterotropic effectors with the altered regulatory chain form of ATCase (with its T-state destabilized relative to the R-state) showed the regulation of activity was the result of preferential binding to different states: the inhibitor CTP to the T-state, and the activator ATP to the R-state.[45] This conclusion was later validated with wild type holoenzyme in a series of NMR studies with Toronto-based collaborator Lewis E. Kay.[46] In sum, Schachman and his group showed the ATCase allosteric mechanism was fully explained by the MWC model.

Across Schachman's long career, his scientific prowess was fueled by joining classic questions about structure-function relationships with versatile model systems and cutting-edge technology. As he developed a variety of new methods extending the utility of ultracentrifugation, he was passionate about helping others learn these approaches. He was also not limited by this expertise. One of his final experimental forays involved creating genetic constructs encoding circularly permutated polypeptide chains of the ATCase catalytic subunit, to see if this monomer form could function (it could).[47] The most pressing matter was to use whatever approach was best for answering the question, including the full suite of biophysical methods as well as tools from genetics and molecular biology.

A consistent theme during Schachman's ATCase work was his vigorous questioning of protein crystals as models for protein function in solution. He did venture to investigate some questions with x-ray crystallography, most notably through collaborating with his Berkeley colleague Thomas C. Alber (1954–2014).[48] Schachman's rigor for data standards was at the highest level, as was his expectation for data transparency and sharing. He led the effort requiring x-ray crystallographers to deposit coordinates with a registry (the Protein Data Bank) when they published their results to remain eligible for federal funding. This took political acumen and connections, as well as finding the right partner with the National Institutes of Health. It also set the stage for the data-sharing standards we have today.

Schachman was a splendid teacher; generations of graduate students at Berkeley relished his Biochemistry 206 "Physical Chemistry of Proteins" course. He also taught in the summer physiology course at the Marine Biological Laboratory in Woods Hole, Massachusetts. There he displayed the quick wit and humor remembered by everyone who heard him. As long-time course instructor Thoru Pederson recalled, Schachman opened his lecture in 1981 with the declaration "I have become a molecular biologist." Pederson continued, "he then proceeded to explain that his group had synthesized a cDNA for the ATCase mRNA and had just begun sequencing it. He continued, 'And here's what we have so far,' at which point he put up a slide with the huge letters AUG."[49] He was especially famous for his carefully crafted joke slides, such as the graph of a slow rise and steep decline representing the "originality of grant request" (x-axis) versus the "probability of grant request being funded" (y-axis).[50]

Figure 2 Schachman's great granddaughter Ainsley Schachman and her father Matt Schachman (Howard's grandson) watch him load a sample into a modern Beckman analytical ultracentrifuge, Stanley Hall, UC Berkeley, September 3, 2015. *Photograph courtesy of Howard's son David Schachman.*

For members of the Schachman lab in our generation (the 1980s), the highlight of each day happened at 3 p.m. over coffee. Schachman regaled lab members with stories of past struggles—including how he opposed university policies that suppressed free speech and advocated for students detained for protesting the Vietnam War—as well as what were then current battles. In 1988, he became president of the Federation of American Societies for Experimental Biology at a time when Washington, D.C., was roiled by claims of fraud by taxpayer-supported scientists. The U.S. Congress had already passed legislation in 1985 requiring institutions receiving NIH funds to create an administrative system to review reports of such scientific misconduct. Allegations against MIT scientist Thereza Imanishi-Kari, based on data published in a 1986 paper with David Baltimore in *Cell*, intensified public concern about widespread malfeasance by biomedical scientists.[51] Testifying before Congress, Schachman emphasized the difference between fraud and sloppiness. Unless carefully defined, he noted, "scientific misconduct" might not recognize that error was not the same as dishonesty.[52] As he put it in *Science*, "we must distinguish between the crooks and the jerks."[53] Moreover, he worried that concerns about fraud were obscuring the "importance of intellectual freedom and trust in a creative process that has been remarkably successful."[54] Owing in part to his efforts, actionable misconduct is confined to intentional data falsification, fabrication, and manipulation and to plagiarism committed during the planning, implementation, or reporting of research results. Long after retiring, Schachman regularly taught the "Responsible Conduct of Research" course at Berkeley. He also served as ombudsman for the NIH when Harold E. Varmus was its director (1993–99), traveling to universities all over the country to listen to the concerns of fellow researchers who relied on public funding.

Taken together, Schachman's advocacy for academic freedom and ethical leadership were as significant as his outstanding research, teaching, and mentoring. Alongside rigorous protein biophysics, he taught us that the "ivory tower" was a myth and that academic scientists, rather than cloistering themselves, should address the social conditions and consequences of research—without ever losing their sense of humor.

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