BIOGRAPHICAL MEMOIRS

Lubert Stryer

March 2, 1938–April 8, 2024
Elected to the NAS, 1984

A Biographical Memoir by Jeremy Nathans

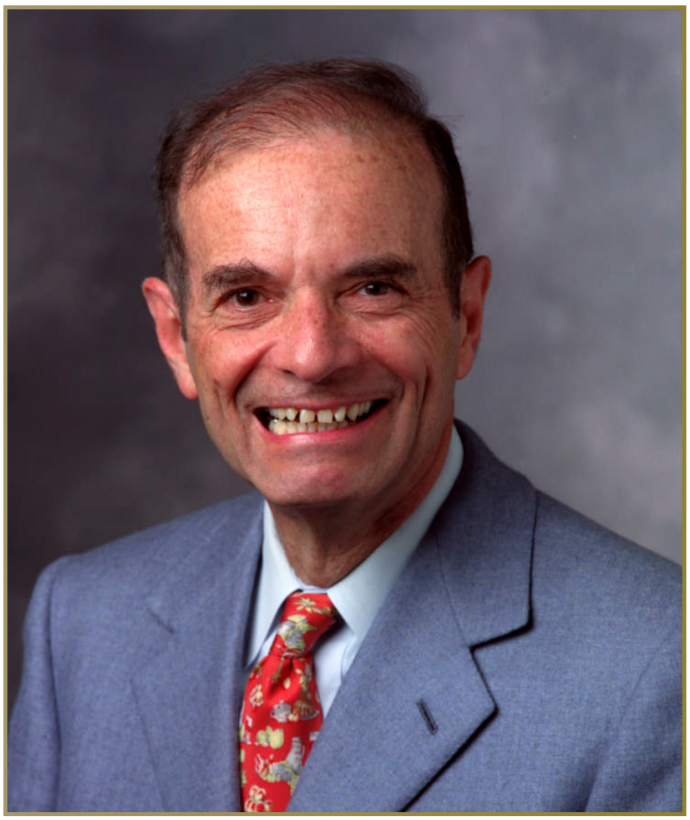

Figure 1 Lubert Stryer.

Lubert Stryer was a man of boundless energy and curiosity whose contributions as a scientist, educator, entrepreneur, photographer, and mentor changed biomedical science and touched the lives of colleagues and students across the globe. His work in the 1970s and early 1980s on the biophysics and biochemistry of vision led to a deep understanding of visual chromophore photochemistry and to his discovery of a G-protein and cGMP phosphodiesterase amplification cascade at the heart of vertebrate phototransduction. He co-founded the biotechnology company Affymax, which pioneered the use of light-directed spatially addressable chemical synthesis, a technology that enabled massively parallel peptide and DNA synthesis and the manufacturing of DNA "chips" for genome-scale hybridization experiments. His now-classic textbook *Biochemistry*,[1] still in print, has inspired millions of students and teachers.

Early Life

Lubert was born in Tianjin, China, in 1938, the child of Jewish parents.[2] Lubert's mother and her family had left Russia in 1915 for Harbin, China, to escape anti-Semitism, and Lubert's father moved from his native Germany to Harbin in the 1930s to escape the Nazi regime. Shortly after Lubert's birth, the Stryer family moved to Shanghai, where Lubert's father ran an export business. One of its main exports was hog hair, which was used in the manufacturing of brushes. Shortly thereafter, world events again upended the life of the Stryer family: the Japanese army overran eastern China, occupying Shanghai from 1941 to 1945. Fortunately, the Stryers were not sent to an internment camp, but instead were allowed to remain in Shanghai's foreign quarter. It was during this time that Lubert had a formative educational experience. He attended a small school run by two Danish women whose approach to education included having the older children teach the younger ones. Lubert thoroughly enjoyed the challenge of explaining concepts to his younger schoolmates, and in later years he credited this experience with instilling in him a love for teaching.

A precocious student from an early age, Lubert skipped two grade levels on his first day at the Shanghai American School when it re-opened in the fall of 1945. Aiming to

enroll in second grade, Lubert was erroneously delivered to a third-grade classroom, where he took a test to assess student preparation. After grading his test, the teacher explained to Lubert that he would not find third grade sufficiently challenging and, therefore, she would arrange for him to transfer to the fourth grade.

During their years in Japanese-occupied Shanghai, Lubert's father would occasionally show Lubert an American flag and say, "This is going to be your country." In 1948, the Stryer family immigrated to the United States, settling in New York City. Although this move entailed a new direction for Lubert's father—starting over again with a business that imported scissors from Italy—its timing was propitious because the Chinese Communist victory in 1949 would, in any event, have ended his export business.

Like a seedling that has been transplanted to a field with fertile soil and plentiful sunshine, Lubert thrived in the United States. He completed his secondary schooling in the New York City public schools, entered the University of Chicago at age sixteen on a full scholarship, graduated three years later, and at age nineteen began medical training at Harvard University. Lubert's time in Chicago was formative not only intellectually but also personally: while there he met his future wife, fellow University of Chicago student Andrea Stenn. In later years, Andrea would become a renowned author of children's books.

Proteins and Energy Transfer

At Harvard, Lubert had the good fortune to work with Elkan Blout, a physical chemist who was simultaneously directing applied research at the Polaroid Corporation and basic research at Harvard. In Blout's laboratory, Lubert used optical rotary dispersion, a photochemical characteristic of chiral molecules, to show that when non-chiral organic dyes interact with synthetic polypeptides (which are chiral), the dyes acquire optical activity.[3] By the time he graduated from medical school, Lubert was hooked on laboratory research and, in particular, the study of proteins.

At this point, Blout arranged for Lubert to spend a year studying physics, mathematics, and chemistry with Harvard professor and physicist Edward Purcell, the discoverer of nuclear magnetic resonance, and to learn macromolecular X-ray crystallography with Carolyn Cohen at the Children's Cancer Research Foundation and then with John Kendrew at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, United Kingdom. There, Lubert used difference Fourier analysis to visualize the binding of azide, a poison, to the iron atom in myoglobin.[4] In 1963, in the midst of his postdoctoral training, Lubert was recruited by Arthur Kornberg to join the recently created Department of Biochemistry at the Stanford School of Medicine. This move marked the beginning of a sixty-year relationship with Stanford University.

As an undergraduate, Lubert had worked as a waiter in the University of Chicago's Quadrangle Club and had struck up a friendship with emeritus professor James Franck, who in the 1920s had discovered the phenomenon of energy transfer between fluorescent donor and acceptor molecules. In the 1940s, Theodore Förster had advanced the understanding of energy transfer by developing a quantitative theory to predict the effects of fluorophore orientation and distance on the efficiency of energy transfer. The most striking feature of Förster's theory was an inverse sixth-power dependence on inter-molecular distance.

Lubert realized that the steep distance-dependence of energy transfer made it a potentially attractive approach for measuring distances on a molecular scale. To test this idea, Lubert and his student Richard Haugland used Bruce Merrifield's then-new method of solid-phase peptide synthesis to generate a series of oligomers of L-proline, with lengths from one to twelve residues, with a fluorescent donor molecule at one end and a fluorescent acceptor molecule at the other end. L-proline was chosen because it forms an unusual type-II trans-helix with a rise of 3.1 angstroms per residue. The resulting plot of fluorescence resonance energy transfer (FRET) vs. distance beautifully matched the predicted inverse sixth-power dependence.[5] In Lubert's phrase, FRET was a "spectroscopic ruler." FRET has since been used in thousands of studies, its utility enormously increased by the availability of genetically engineered proteins, the development of single-molecule FRET, and the integration of FRET with live-cell imaging.

Vision

Lubert's interest in vision began during his time at Harvard. The pre-eminent vision researchers of the 1950s and 1960s—Ruth Hubbard and George Wald at the Harvard Biological Laboratories and David Hubel and Torsten Wiesel at the Harvard Medical School—were doing groundbreaking work on the photochemistry of vision and the function of the visual cortex, respectively. An additional link was Lubert's medical-school classmate John Dowling, who was conducting research in the Hubbard and Wald laboratory on the biochemistry of vitamin A and its derivatives. In 1966, while surveying the vision field in preparation for a lecture at Stanford Medical School, Lubert decided to shift his research to the biochemistry and biophysics of vision.

One of Lubert's initial forays into the vision field built on his expertise with FRET. The question he posed was: given rhodopsin's native configuration in the disc membrane of retinal rod outer segments, how far is the 11-cis retinal chromophore from the aqueous space on each side of the membrane?

To answer this question, Lubert and student David Thomas measured the efficiency of energy transfer from a Terbium (Tb^{+3}) donor to rhodopsin's 11-cis retinal chromophore, the acceptor.[6] This experiment showed that with the donor present on only the inside or only the outside of oriented disc membranes, the energy transfer efficiencies were nearly the same, implying that 11-cis retinal resides close to the center of rhodopsin's transmembrane region, a conclusion that was confirmed years later by the X-ray crystal structure of rhodopsin.

In the 1960s and 1970s, the central mystery in photoreceptor physiology was the mechanism by which a photochemical change in rhodopsin was communicated to the cell's plasma membrane to generate a change in electrical potential. It was known both from Selig Hecht's classic psychophysical experiments in the 1940s and from Denis Baylor's and King-wai Yau's suction electrode recordings from single rod outer segments in the 1970s (performed at Stanford in a laboratory just one floor above Lubert's laboratory) that rod photoreceptors could reliably respond to the absorption of a single photon—the ultimate physical limit of detection. Clues from several investigators pointed to important roles for GTP and for cGMP hydrolysis in signal transduction, but how these pieces fit into the puzzle was unclear.

With postdoctoral fellows Bernard Fung and James B. Hurley, Lubert showed (1) that photo-activated rhodopsin catalyzes the release of GDP and the uptake of GTP by a protein that they named Transducin, (2) that Transducin in the dark is present as a hetero-trimeric complex of alpha, beta, and gamma subunits, (3) that GDP and GTP each bind to the alpha subunit, most likely at the same site, (4) that GTP binding leads to the dissociation of alpha from beta+gamma subunits, (5) that the alpha subunit can stoichiometrically activate an abundant photoreceptor-specific cGMP phosphodiesterase by displacing a small inhibitory subunit, and (6) that the alpha subunit has an intrinsic GTPase activity that releases GTP's terminal phosphate, thereby returning the Transducin complex to the inactive GDP-bound alpha+beta+gamma complex.[7,8] These discoveries revealed a remarkable evolutionary conservation between the signal transduction pathway in a sensory system and the then-emerging picture of adrenergic signaling from receptor to adenylate cyclase via a G-protein. In the years since these first experiments, it has become clear that nature uses G-protein signaling for a wide array of physiologic processes, including rod and cone vision, olfaction, taste, acid secretion in the stomach, calcium sensing, and neurotransmission via metabotropic receptors.

Affymax and Affymetrix

In 1989, Alejandro Zaffaroni, a legendary biotech entrepreneur, recruited Lubert to the position of founding scientific director of Affymax, a nascent company that would have as its goal the development of combinatorial chemistry and related technologies. In a prescient move, Lubert then recruited Stephen Fodor, an expert in photochemistry, to spearhead a new approach to combinatorial chemical synthesis. The Affymax team envisioned a wedding between two technologies: solid-phase synthesis of linear polymers, as pioneered for peptides by Merrifield, and photolithographic production of integrated circuits, the technology that gave Silicon Valley its name. More specifically, the plan involved chemical synthesis on a two-dimensional glass surface, with each of thousands of different polymer sequences being synthesized in micron-scale square territories that tiled the surface in a checkerboard pattern. Within each territory, polymers of one particular sequence would be synthesized by step-wise addition of monomer building blocks. At each cycle of monomer addition and for each territory, the decision whether or not to add a monomer would be determined by whether that territory was irradiated, a step that served to release a photolabile protecting group from the end of the polymer. Sequential irradiation through a series of micro-manufactured masks would determine, square-by-square, the pattern of reactivity for each cycle of monomer addition.

Within two years, the Affymax team had reduced the concept of light-directed spatially addressable parallel chemical synthesis to practice, and in an early demonstration, they synthesized a checkerboard with 1,024 territories displaying peptides with differential binding to a monoclonal antibody tagged with a fluorophore.[9] The Affymax team also demonstrated this strategy with DNA synthesis, and a second company, Affymetrix, was founded to develop and manufacture DNA "chips" that could be used to interrogate complex mixtures of cDNA or genomic DNA by hybridization. Synergizing with newly available sequences of eukaryotic genomes and cDNA clones in the early 2000s, the Affymetrix DNA chips ushered in the era of whole-genome transcriptome analysis.

Teaching and Mentoring

Throughout his career, Lubert's approach to science was characterized by energy, curiosity, and deep insight. He brought a distinctive clarity to the questions he was addressing, and he enjoyed the rigor of quantitative thinking and mathematical modeling. Lubert was an early convert to computer programming, and he had a computer in his office many years before most of his colleagues. Not surprisingly, Lubert's enthusiasm and lucid thinking made him a superb teacher, whether in one-on-one discussions or in a lecture hall. In the 1980s, Lubert gave a course on ion channels simply because he thought that this topic was exciting and important. For many attendees, Lubert's lectures served as the gold standard

for clear and inspiring exposition. After hearing Lubert and his colleague Denis Baylor deliver a pair of lectures on light detection by vertebrate photoreceptors, the author of this essay switched his Ph.D. thesis topic to vision research.

Lubert's widest reach as a teacher came from his textbook, *Biochemistry*. Lubert began writing this book at a time when biochemistry courses largely focused on intermediary metabolism. Lubert's fresh perspective was shaped by his appreciation for the importance of macromolecular structure and the flow of information in biological systems. The final section of the book, titled "Molecular Physiology," posed a series of questions beyond the scope of traditional biochemistry and challenged the reader to think broadly about biological processes in terms of their molecular foundations. With crisp prose, an emphasis on molecular structure, vivid four-color illustrations, and eventual translation into more than ten languages, *Biochemistry* has inspired millions of students and teachers. After solo authoring the first four editions (1975, 1981, 1988, and 1995), Lubert recruited Jeremy Berg and John Tymoczko to join him as co-authors. Starting with the fifth edition (2002), the Berg-Tymoczko team assumed responsibility for moving *Biochemistry* into the twenty-first century with expanded topics, clear writing, and many new and striking illustrations.

Lubert moved to Yale University in 1969 and then returned to Stanford in 1976 to establish and direct the Department of Structural Biology, the first of its kind in the nation. The department was located in a beautiful new research building (the Sherman Fairchild Building), and Lubert recruited an extraordinary group of young faculty members, including Roger Kornberg, James Spudich, and Nigel Unwin. In later years, as Lubert's interests shifted increasingly to neuroscience, he joined the Department of Neurobiology, and he devoted himself to nurturing Stanford's neuroscience community. Liqun Luo, a professor of biology at Stanford, wrote in the introduction to his textbook *Principles of Neurobiology,* "This book would not have been possible without the help of Lubert Stryer, my mentor, colleague, and dear friend. From inception to completion, Lubert has provided invaluable support and advice. He has read every single chapter (often more than once) and has always provided a balanced dose of encouragement and criticism, from strategic planning to word choice."

Lubert's wisdom and generosity were especially helpful to young scientists. The following story illustrates his approach. In the late 1990s, Lubert and the author of this essay were on a grant review committee for a private foundation. In the final rankings, there was a grant application from an assistant professor that fell just short of the cut-off, as determined by the available funds for that year. There was a general consensus around the table that receiving this grant would provide a big boost for the applicant, but there did not seem to be any way of making that happen. Then, Lubert simply said that he would pay for it from his royalty account. And that was it. No fanfare. Just an immediate reaction to do what was best for someone else.

Retirement Years

After closing his research laboratory, Lubert and Andrea made a series of expeditions across the globe, including to sub-Saharan Africa, western China and central Asia, India, Madagascar, and Antarctica, both to see the world and to photograph what they saw. The resulting photographic collections[10] serve as an enduring homage to the beauty of the natural world and to the people who Andrea and Lubert met on their travels.

Conclusion

Lubert's scientific, educational, and biotechnology contributions were widely recognized. His honors included the American Chemical Society Award in Biological Chemistry (now the Eli Lilly Award, 1970), election to the National Academy of Sciences (1984), the Newcomb Cleveland Prize from the American Association for the Advancement of Science (1992), and the National Medal of Science (2006). Undistracted by his fame, Lubert's focus was on his family, his colleagues, his students, and the joy of sharing science, music, and art. In a 2012 autobiographical essay, Lubert summed up his feelings of gratitude about his career and his life: "I am grateful to this country for opening its doors to me as an immigrant child in 1948 and providing limitless opportunities in the decades that followed, and, above all, I am grateful to my wife Andrea for her devoted support, wise counsel, and love over more than 50 years."[10]

Acknowledgments

The author is grateful to Catherine Dulac, Peter Kim, Liqun Luo, and James Spudich for helpful comments on the manuscript.

References

1 Stryer, L. 1975. *Biochemistry.* New York: W.H. Freeman and Company.

2 Lubert Stryer, interview by David J. Caruso at Stanford University, December 3–4, 2008, Oral History Transcript # 0631, Philadelphia: Science History Institute.

3 Stryer, L., and E. R. Blout. 1961. Optical rotatory dispersion of dyes bound to macromolecules. Cationic dyes: Polyglutamic acid complexes. *J. Amer. Chem. Soc.* 83:1411–1418.

4 Stryer, L., J. C. Kendrew, and H. C. Watson. 1964. The mode of attachment of the azide ion to sperm whale metmyoglobin. *J. Mol. Biol.* 8:96–104.

5 Stryer, L., and R. P. Haugland. 1967. Energy transfer: A spectroscopic ruler. *Proc. Natl. Acad. Sci. U.S.A.* 58:719–725.

6 Thomas, D. D., and L. Stryer. 1982. The transverse location of the retinal chromophore of rhodopsin in rod outer segment disc membranes. *J. Mol. Biol.* 154:145–157.

7 Fung, B. K.-K., and L. Stryer. 1980. Photolyzed rhodopsin catalyzes the exchange of GTP for GDP in retinal rod outer segment membranes. *Proc. Natl. Acad. Sci. U.S.A.* 77:2500–2504.

8 Fung, B. K.-K., J. B. Hurley, and L. Stryer. 1981. Flow of information in the light-triggered cyclic nucleotide cascade of vision. *Proc. Natl. Acad. Sci. U.S.A.* 78:152–156.

9 Fodor, S. P. A., et al. 1991. Light-directed, spatially addressable parallel chemical synthesis. *Science* 251:767–773.

10 Stryer's photographs are available at https://Stryerphoto.com.

11 Stryer L. 2012. Exploring light and life. *J. Biol. Chem.* 287:15164–15173.

Selected Bibliography

1961 With E. R. Blout. Optical rotatory dispersion of dyes bound to macromolecules. Cationic dyes: polyglutamic acid complexes. *J. Amer. Chem. Soc.* 83:1411–1418.

1967 With R. P. Haugland. Energy transfer: A spectroscopic ruler. *Proc. Natl. Acad. Sci. U.S.A.* 58:719–725.

1970 With J. Yguerabide and H. F. Epstein. Segmental flexibility in an antibody molecule. *J. Mol. Biol.* 51:573–590.

1976 With R. Mathies. Retinal has a highly dipolar vertically excited singlet state: Implications for vision. *Proc. Natl. Acad. Sci. U.S.A.* 73:1169–2173.

1980 With B. K.-K. Fung. Photolyzed rhodopsin catalyzes the exchange of GTP for GDP in retinal rod outer segment membranes. *Proc. Natl. Acad. Sci. U.S.A.* 77:2500–2504.

1981 With B. K. Fung and J. B. Hurley. Flow of information in the light-triggered cyclic nucleotide cascade of vision. *Proc. Natl. Acad. Sci. U.S.A.* 78:152–156.

With G. Hayward, W. Carlsen, and A. Siegman. The retinal chromophore of rhodopsin photoisomerizes within picoseconds. *Science* 211:942–944.

1982 With D. D. Thomas. The transverse location of the retinal chromophore of rhodopsin in rod outer segment disc membranes. *J. Mol. Biol.* 154:145–157.

With V. T. Oi and A. N. Glazer. Fluorescent phycobiliprotein conjugates for analyses of cells and molecules. *J. Cell Biol.* 93:981–986.

1988 With K.-W. Koch. Highly cooperative feedback control of retinal rod guanylate cyclase by calcium ion. *Nature* 334:64–66.

1991 With S. P. A. Fodor et al. Light-directed, spatially addressable parallel chemical synthesis. *Science* 251:767–773.

1992 With S. Zozulya. Calcium-myristoyl protein switch. *Proc. Natl. Acad. Sci. USA* 89:11569–11573.