Aaron Lerner: Perspectives and Lessons Learned from the Melatonin Days

We talk much about translational research, sometimes in rather simple ways, even separating it from basic knowledge. Aaron Lerner created a perfect blend of basic and clinical science during a career that spanned more than 60 years. The discovery of melatonin was but one of his many important discoveries that impacted dermatology and neuroscience, part of his role as the leading contributor to the field of dermatology of the past century.

Becoming a scientist

By the time that Aaron Lerner started on the melatonin project, he had the prepared mind that is so often key to great advances in science. He had, early on, a characteristic zest, curiosity, and capacity for creating scientific knowledge. While he was interested and able in many areas, Lerner’s commitment to science became intense when he started college. He received a BA cum laude in mathematics and chemistry, a medical degree, and a doctorate from the department of physiological and physical chemistry, all within seven years at the University of Minnesota. His research career began when he was a second-year undergraduate with investigations related to dopa, a critical tyrosine derivative involved in pigmentation. Before graduating from medical school, with another student and without an adviser, he was involved in the isolation of a globulin protein that is now recognized as the first isolation of a monoclonal antibody, cryoglobulin.

Through a series of scientific adventures and fortuitous interactions with preceptors and peers during a stint in the Army, Lerner became increasingly interested in issues of pigmentation, such as the processes by which tyrosine was converted to melanin. At Case Western Reserve University, he obtained further superb postdoctoral training in biochemistry, studying processes involved in pigmentation. By the age of 30, he had written a paper with his close colleague, Thomas Fitzpatrick, on melanin pigmentation for a leading publication, *Physiological Reviews;* this paper established them as among the world’s leading experts on the topic.

Pigmentation led to Aaron Lerner’s abiding interest in dermatology and ultimately to a situation at the University of Michigan, where he could obtain residency training and also conduct research. Among many projects during that early phase, one of special import was investigating the pituitary factor that might be involved in the darkening of skin seen in...
patients with Addison's disease. That project was completed in Oregon and included the development of an *in vitro* assay using frog pigment cells. Lerner and his colleagues ultimately discovered what they called melanocyte-stimulating hormone (MSH), a peptide of great importance in dermatology, which is also a part of pituitary stress systems. That peptide—one of the first neuropeptides to be characterized—is a major secretory product of the intermediate lobe of the pituitary and is potentially involved in stress and brain function.

**The melatonin project**

The melatonin project was a natural outgrowth of what had gone before. Lerner came to Yale in 1955 with several of his colleagues. Waiting for their laboratory to be completed, one member of the team, Yoshiyata Takahashi, while doing library research found a neglected paper that was to be very important. The paper, from 1917, demonstrated that pineal extracts from cows could lighten the color of tadpoles. From the work of the Lerner group and that of others it was known that various neuroregulators, such as transmitters, could change the dispersion of melanin granules. Was the factor in the pineal gland a known substance or something new? Lerner and his colleagues already knew how to assay for such materials and agreed to start a project in which Takahashi would perform the bioassays and Lerner would do the extractions.

The project took more than four years (1955–1959), with two phases each of about two years, and involved a small group, but only Lerner was involved from start to finish. He worked every single day. The result was the discovery and characterization of melatonin, a new indole, derived from serotonin, which is remarkable in its effects on pigmentation. The discovery of melatonin reawakened interest in the pineal gland, which had been once thought of as the seat of the soul. We now know that melatonin is important in the integration of information related to light and circadian processes. It impacts the brain, may be important for some reproductive processes, and may be relevant to the understanding and treatment of phase-shift-related disorders, including some forms of depression.

The melatonin team was small but international in origins, with a broad array of backgrounds and interests. Dr. Takahashi was a postdoctoral fellow who had come from Tokyo University to Oregon, where he worked with Lerner, and he came with him to Yale in 1955. In addition to his excellent skills in research work, Dr. Takahashi was deeply absorbed in learning the extant literature on pigment biology and spent much time in the library (a key to the discovery because most people do not go back to read papers from 1917?). An intern with biochemical training, he returned to Japan after two years, having been involved in the early isolation and assay processes. Dr. Takahashi became one of Japan’s leading experts on the liver and served as chair of the Department of Internal Medicine at Gifu University and later the president of a major hospital. He is now deceased.

The other critical person present at the start of the project was Teh H. Lee. A graduate student in chemical engineering at the University of Michigan, Lee was one of 30 gifted young people in China selected from 5,000 applicants to obtain graduate training in the United States. He started to work with Lerner while at Michigan and went with him to Oregon and then to Yale. He played a brilliant role in various complex peptide projects, including MSH and ACTH. Lee’s work on the melatonin project involved isolation procedures, and after a period he returned to the highly important work on peptides that was ongoing in the lab at the same time that the melatonin project was in full force. Dr. Lee left the lab in the mid 1960s and continued research on peptides at a veterans’ hospital in Denver, having made extraordinary contributions to dermatology. He has remained in the United States.

In 1957, James Case, a gifted resident in dermatology, came from Oregon. With a degree in chemical engineering and an MS in biochemistry, he was a physician with biochemical experience. Case, who had met Lerner while at Oregon, became a major figure in the isolation and structure studies. Lerner said of him, “He was tremendous worker who could spend night and weekends in the laboratory . . . Jim and I worked together hour after hour on the melatonin project. Even though it often seemed that we never would accomplish the isolation and structural determination of melatonin, we finally succeeded.” Following his work at Yale with its great success, Case went to the University of Washington, where he was very popular (in my recollections, he had a natural grace of movement and spirit). Case was appointed as an assistant professor and as the first head of the section on dermatology at that institution, before his untimely death related to an episode of depression.

Another important new member of the lab was M. Ruth Wright, a physician from England who worked part-time in the lab, which she joined in mid-1956. She was involved in and published work on the development of assays as well as on the localization of melatonin. She was gracious and helpful, and I greatly appreciated her patience in teaching me the bioassay methods—although, out of that and similar other experiences, later in my career I went to great efforts to develop various chemical procedures for neuroregulators. She continued in the lab for a few years, later spent some time in the Department of Pediatrics at Yale, and regrettably passed away at a relatively early age as a result of an auto accident.

Wataru Mori began a postdoctoral fellowship with Lerner in November 1956. He became quite important in the final steps of the melatonin project. Dr. Mori, then and now a man of intelligence, elegance, and effectiveness, graciously responded to my questions about that early phase of the work and his interaction with Dr. Lerner. He expressed deep respect for the fundamental humanity of Lerner, his fairness, and his welcoming attitude and openness to people of other cultures, including those with whom the country then had recently been at war. The following has been slightly modified from Dr. Mori’s written reply:

> **When Dr. Takahashi made up his mind to go back to Japan, he had a talk with Dr. Lerner, who wanted to have some other person from Japan, but this time not biochemical in orientation because [Lerner] had a background of biochemistry and there were other talented biochemists in the laboratory. Therefore, he wanted a morphologist who**
could use a microscope to watch pigment cells. Takahashi wrote this request to his boss in Japan, who recommended me since I was working in the Department of Pathology. . . . I made movies at Yale of the movement of the pigment cells. Very accurate assay was needed. Frogs of the best condition were selected (shipped each day from Wisconsin) and prepared for bioassay. Dr. Lerner was quite busy in clinical work during the day. He went home for dinner and came back to the laboratory. He worked till late and prepared materials for another bioassay for the next day. Our bioassay was performed photometrically, using equipment combining a microscope and a photometer. It was used during the critical points of the isolation work. The assay required “art,” using only the best part of the frog skin, which had to be checked through the microscope. I had to decide. Now I fully understand the meaning of Dr. Lerner’s request: “We need a morphologist now.” James Case was gentle and of very nice character and [during that period] did most of the work in melatonin isolation. He was loved and respected by all of the people around.

Dr. Mori later became chair of the Department of Pathology at the University of Tokyo, the dean of the university’s medical school, and then the president of the university. To Lerner’s great pleasure Mori was the first person from Japan to be elected to the Institute of Medicine of the National Academy of Sciences in the United States. For his multiple extraordinary accomplishments, Dr. Mori has received many honors in Japan, including being chairman of the Health Care Science Institute.

Dr. Lerner often expressed his great pleasure that each of these individuals had gotten his start with melatonin!

Memories of a junior and temporary participant in the melatonin team

My own contact with Aaron Lerner came as a medical student at Yale, taking a junior year in research. I wanted to study the neurochemistry of the brain—specifically, to investigate the ways it might be changed by behavior. At the time the Department of Psychiatry at Yale (now a powerhouse in biomedical research) had no pH meter, no labs, and no money. The chair of biochemistry, who believed it would be 100 years before one could usefully study the biochemistry of the brain, declined to lend Psychiatry a pH meter. He had absolute certainty that neurochemistry would not be changed by behavior because, as he stated, “Behavior is like the wind, biochemistry a locomotive, and the wind does not affect the locomotive.” Fortunately, he did tell me that I should talk to the new young head of dermatology about medical research. Wonderful advice! And, for me, life changing.

I met Aaron in 1957–1958, when the melatonin project was in full bloom. He was then in his late 30s. He was a man of medium height, thin, with a natural grace in his movements, a wonderful warm smile of good humor, and kind, never sarcastic, wit. He always wore a white lab coat and had many writing implements, a small flashlight, and, as I remember, sometimes a small slide rule in his pocket. His group had limited lab space, a room smaller than 20 × 20 square feet in the basement, with two or three other smaller rooms of about 10 × 15. The lab was crowded with equipment, neat, and functionally organized in a very efficient manner. Aaron radiated joy in the spirit of inquiry; intense, curious, hypothesis oriented, he had an ability to draw you into the excitement. You could see the dramatic effect of the pineal extracts on tadpoles. He was onto something important. The group was fired up and shared the excitement. Everyone felt that he or she was a vital part of the team. In his memoir of the project, Aaron thanks, by name, the dishwasher as well as each of the others of us in the lab during that period.

Aaron Lerner was as extraordinary a mentor as he was a scientist. The work with him was a key to my approach to science and to my decades of research on neuroregulators, which later included the first demonstration that the wind (behavior) can indeed differentially change the locomotive (neurotransmitters). I was fortunate, being the only medical student in their small, close-knit laboratory. The lab was quiet and intense—not chatty, gossipy, or political, as some are; nevertheless, Aaron often invited me to talk with him in his office or while he was doing lab work. He graciously spent time telling me stories and talking about life and careers in medical research. I cherish having had those special chances to interact with Professor Lerner and only wish I had taken notes! Over five decades he became not only a mentor who had profoundly impacted my work but also a great friend and really a hybrid of friend and family. My respect for him knew no bounds.

Aaron was not afraid of new ideas, new approaches, or new technologies and immersed himself in them. Perhaps growing out of his sound training with excellent people in difficult areas of science, he never seemed fazed by having to consider a new facet. His driving force was the intellectual problem, rather than knowing a specific method and trying to find ways to utilize it. He read widely (all too many scholars don't) and loved books and good libraries. He was intellectual and enjoyed relating ideas to one another; it was part of the secret of his ability to do translational research in such a natural manner. He enjoyed talking with others about what he was reading. In the days before Current Contents, Aaron subscribed to and read Chemical Abstracts—most medical researchers did not sit and read Chemical Abstracts for pleasure and interest: they found it unbelievably dull.

A key aspect of Aaron’s leadership was his ability to bring out the best in each of us. He got the 12.5% out of you that you didn’t know was there; you wanted to get into the lab and get results! Each of us had a role. He knew our strengths and our interests and how to harness them. My project, which worked, was to show that melatonin was released and might be a hormone. (Later, with others, I found that melatonin is made by humans in the pineal gland throughout life, even when it is calcified, and did various pharmacological studies including demonstrating that it affects sleep.) Aaron had persistence, did not take no for an answer, and had the capacity to get everyone involved. He persuaded a major processing company to provide bovine pineal glands for a project that ended up requiring 250,000 glands. I remember a shipment of 100,000 that arrived in a
huge transparent plastic bag. The company had never collected pineal glands before!

Research was a joy to Aaron, which he transmitted to those who worked with him. He liked to do research with his own two hands. Fortunately he enjoyed lab work, because there were no funds for technicians in the lab. He could do everything, including the scut that many lab directors would never think of doing themselves. I have a vivid memory of Aaron operating a large Craig countercurrent instrument separating fractions for biological assay. He also enjoyed inventing, exemplified by his development of the Lerner Lab Jack for placing equipment at exactly the right height. Aaron was good with his hands and said that as a youngster he enjoyed repairing things and watching tradespeople, for whom he had great respect. He always liked mechanical things that worked well and, known for his ability to repair anything, had a very impressive and complete workshop at home. When young he had worked on cars, but he drove rather nondescript vehicles as a faculty member—for his 65th birthday his sons gave him a new Corvette!

What made Lerner so effective?

Aside from his skills as a scientist and in motivating people and running the lab, Aaron had guts and he wasn't afraid of a fight. The first presentation at Yale of the structure of melatonin was to the department of biochemistry. After Aaron's talk, the chair stated in the strongest possible terms that the proposed structure of melatonin had to be wrong—if both active groups of the parent molecule, serotonin, were blocked, the structure that Aaron had proposed could not be correct. Aaron, always soft-spoken, graciously but forcefully stood his ground. It was a dramatic moment, but as a medical student working with him I was terrified. Aaron was right.

There are also many things I remember about Aaron's style of administration. A well-organized and tireless worker, he came in after a swim early each morning, usually before anyone else, knowing exactly what needed to be done that day. He knew how he was going to balance the lab work with his clinical and administrative tasks. In five decades, I have never known anyone at any institution who could handle those different domains so cleanly and effectively.

Among his administrative tricks was a unique filing system: piles of files and papers, high but neat. He knew where everything was within a given pile. I often saw that in his hands (but unfortunately not in mine today) it was a fast way to retrieve things. He had spunk and did not take no for an answer in an administrative knockabout. Who else on the Yale faculty 50 years ago, having to be in two cities at the same time, would have chartered a small private plane and then bemusedly explained to Yale administrators why it was necessary—and won? Indeed, Aaron was very careful with budgets and with expenses, and he was scrupulously honest. He called things as he saw them and always pushed Yale to expand still further its great research enterprise and needed facilities, as well as its need to improve such things as pensions for its nonfaculty employees.

As an administrator, Aaron radiated a love of his department. He thought about how to make it better and how to help the people in it; he enjoyed and developed people regardless of their interests—whether they were slated to go into dermatology or psychiatry or become university administrators. He was especially kind about my interest in psychiatry—he pointed out that one could do the same research on neurotransmitters in dermatology and have immediate access to the tissue. He enjoyed people regardless of their role, rank, or background and treated everyone with enormous warmth and respect, and they recognized his genuine interest in them as well as in their work.

Aaron took the clinical world seriously and esteemed the people in it. He was a spectacular clinician at Yale, where clinical excellence was a prized value. With his wonderful intelligence and memory for detail, Aaron had an ability to quickly evaluate clinical problems of great complexity. He was known for being able to see a large number of patients in any given clinic session but with such interpersonal warmth and directness that the patients did not feel rushed and loved him. He took residents seriously. Three in particular stand out in my memory because while young they functioned as faculty and clinical leaders, were involved in exciting research in various areas, and were completely trusted by Aaron: Marie-Louise Johnson, MD, PhD, who in addition to being a well-regarded dermatologist went on to make substantive contributions to the study of the atomic bomb survivors and is now a member of the Institute of Medicine; Joseph McGuire, MD, who had an outstanding clinical and research career at Yale and Stanford; and Irwin Braverman, MD, who has had a distinguished academic and clinical career at Yale.

The book by Aaron and his first wife, Marguerite, Dermatologic Medications, grew out of their joint love for the clinical and educational world. It also reflected their style: effective, important, and concise. Once, Aaron had an hour to give a lecture to the medical students; he completed a superb presentation in 20 minutes and stopped. This was the only time that happened in my 5 years at Yale. He had that same efficiency about time in other presentations, such as site visits on grants. Aaron's widow, Mildred Lerner, has graciously given me a copy of a 1985 memo in which he instructed the members of a team preparing for a visit from the National Institutes of Health on the necessity of sticking to the brief time allowed for each talk and the importance of absolute readability for their slides—"Don't say 'please excuse this slide'"—completely typical of his approach, which was to create optimal efficiency while treating the visitor or the student with respect.

Through his administration, research, teaching, and clinical work, Aaron Lerner demonstrated the power of quiet charisma. He was a man of absolute grace, who enjoyed everyone but handled everything quietly. Almost self-effacing, he never tried to draw attention to himself; he did not brag, he did not shout. Yet everyone who worked with him knew instinctively not only that Aaron was a person of great intelligence and capacity but also that they could trust him completely. And they knew that he wanted to help them.

Aaron's mentorship included interactions about life as well as about science, and I was fortunate to receive those lessons
through the decades. One lesson was the value of a practical perspective. At one point, I needed fresh bovine pineal glands for an enzyme assay. Aaron sent me to a small kosher slaughterhouse in a neighboring town. One of the members of the family who owned the place welcomed me graciously. He provided the head of a just-sacrificed animal, a large axe, and a high solid pedestal. I gave it my best. The head slid off the pedestal. Without a word, he took back the axe with one hand, picked up the head with the other, and with one powerful, well-aimed swing, split the head, revealing the pineal gland. Then he told me that two decades earlier (during the depression and before World War II) he had done very well in college but had not been accepted into medical school (in those days the admitted class in many schools was limited to 3% to 5% persons of Jewish background) and instead joined the family business. My new friend at the slaughterhouse warmly wished me well. Aaron and I discussed the experience, as we also talked at various times about positive and negative aspects of redevelopment of New Haven, the opening of opportunity, and civil rights. He had a strong moral sense; although nonpartisan in our discussions, he expressed strong beliefs in pragmatic politics to achieve good aims, and a commitment to justice—or the elimination of injustice wherever we could.

I want to mention personal aspects of our relationship for which I am deeply thankful. Aaron and Marguerite were critical role models; my late wife, Patricia, and I were newly married when we met Aaron and Marguerite. Marguerite was a gifted clinical dermatologist and also an author of children’s books. They were the first couple we knew in which both were successful academics. They had four sons, of whom they were very proud. They lived simply and unpretentiously. We were Californians and they lived in a California-style house they had designed themselves. Aaron was a great biochemist, but he could also do a splendid barbeque. We could sense in the way they interacted with each other that they were very happy together. They were our models as we developed our lives, in which Pat became a faculty member in sociology at Stanford and a pioneer in the study of the relationship between social behavior and physiology.

Aaron was always a teacher. Our son, Isaac, now executive director of the Austin Technology Incubator, remembers that when he was a youngster, Aaron visited Palo Alto and gave him a slide rule (Aaron loved slide rules!) and spent an hour teaching him how to use it. He always asked after Isaac.

Aaron was a role model to me through his handling of Marguerite’s illness; his thoughtful caring attention was palpable. It was important as I dealt with the brain tumor that Pat had for half the 36 years we were married. Aaron and Millie, his widow, were together for about 2 decades. Millie had a high position in nursing at Yale. Aaron and Millie as a couple were again very important role models; their loving and moving interaction gave a profound sense that one can unexpectedly enter a new relationship and the miracle of having had two great loves. I have experienced that through my marriage to Rosemary Stevens.

I went to New Haven last year to see Aaron. Although ill, he was his indomitable self—with his wit and quick understanding, his usual quiet shy smile, his dignity and selflessness, and, as always, his intrinsic creativity and infectious pleasure in ideas. Aaron Lerner truly was the ideal mentor who became a cross between a profound friend and a much-loved family member. With his capacity to enjoy the multiple forms of success of the people who had worked with him, he expressed his pride in the continued excellence of the department and lasting love of his chosen field.

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