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Obituary

Obituary for John Q. Trojanowski, leading Alzheimer's Disease Researcher

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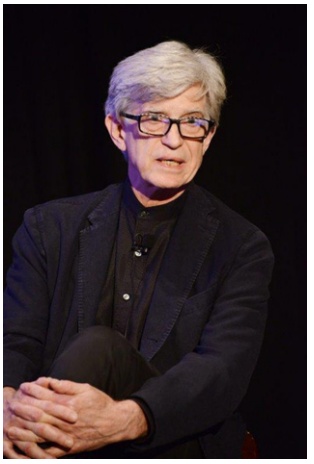

John Q. Trojanowski, PhD

Anyone who has been in the auditorium at a scientific lecture knows this much about the larger-than-life fellow with the wild mop of hair and 6'4" commanding frame. When the talk was over, no matter the speaker or the topic, this guy would be the first to raise his hand, or stand at the mike, with a pertinent question. "Hi, I'm John Trojanowski from the University of Pennsylvania," he would begin. Those in attendance would chuckle or smile for who didn't know John Trojanoswki?

That man, the guy who identified just about every important brain protein at the heart of a broad number of neurodegenerative diseases, the neuropathologist who did just about everything scientific and otherwise with the love of his life at the bench and at home, died on February 8, 2022. He was 75 and had no plans on retiring. In fact, he was still writing grants and papers, and overseeing tens of millions of research dollars to better understand the many pathological proteins that he and Virginia Lee have identified or studied during their 45 years together.

By all accounts, it has been their shared passions for science and each other that has led John Q. Trojanowski and Virginia M.Y. Lee to some of the most significant findings in their field. By the time they arrived at the University of Pennsylvania in the 1980s—they were each given a long and narrow 200 square feet of lab space in the neuropathology department—Dr. Trojanowski told his wife, a biochemist who was also completing an MBA, that they should look for proteins involved in neurodegenerative diseases. He was practical. They both were. And driven. "We can do this," he told her. "And we can be successful at it." He was given the task of opening up a brain bank at Penn, and after doing an autopsy on a person with Alzheimer's decided that they should take this one brain and isolate the stuff in tangles. They went on to identify different isoforms of the tau protein, and the two of them championed the importance of tau as one of the key players in Alzheimer's at a time when the field was obsessed with amyloid. The landmark paper came out in 1991.

"Let's go after Lewy bodies," he said shortly after the tau discovery. Of course, Lewy bodies were part of the pathology of Parkinson's disease and dementia with Lewy bodies, but their biochemical composition was not known. Six years later, the biochemist and neuropathologist, and their colleagues, identified alpha-synuclein as the key player in Lewy bodies in Parkinson's patients. This was also a time in history when scientists and clinicians never considered that Alzheimer's and Parkinson's and other neurodegenerative conditions could actually share pathology. The Lewy body paper was published in 1998.

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Virginia Lee, who decided to park her MBA, knew that they needed to start creating animal models of these diseases. It would be the only route to identifying molecules and testing them on the road to developing treatments. He agreed.

Their next big challenge also arrived from the brain banks. The duo, and their colleagues, noticed that there were brains that seemed to have Alzheimer's or frontotemporal dementia but had no pathological tau in their neurons. The lesions were ubiquitin positive but that was where their knowledge stopped. And it was in 2006 that the couple would add yet another disease protein to the growing list that would change the field. It was known that TAR DNA-binding protein 43 did exactly what its name said it did: bind RNA and DNA for a number of important regulatory functions. But it was never thought to be involved with a disease. The Trojanowski/Lee lab didn't quite believe what they were seeing when they used the TDP-43 antibody to stain the brains of patients who had died of frontotemporal lobar dementia. But there it was. TDP-43 explained about half of the frontotemporal lobar dementia cases that came to autopsy, and tau the other half. But then, they also saw something very strange, and very unexpected. The abnormal conformation of the protein was also in the brains and spinal cords of patients who died of amyotrophic lateral sclerosis. The findings would link very two seemingly-disparate clinical diseases—frontotemporal dementia and amyotrophic lateral sclerosis.

They continued making animal models. The scientists were gathering enough pathological information to begin planting seeds for change. They believe that many people with neurodegenerative diseases have a mix of pathologies when they arrived at the autopsy table. (It would be good to note here that the scientific collaborators did not always agree on things and were well known for their scientific screaming matches that would always end with John Trojanowski acquiescing to Virginia Lee's ideas. And as if nothing caustic had happened, the two of them would walk off, close and harmonious, and head out for a good meal.)

Virginia Lee credits her life partner for steering her into science. At many points in those early days, she wasn't sure what she wanted to do with her life. She is a trained classical pianist who grew up in China and was sent to England for her studies. She would turn to chemistry in college, and then to biochemistry, then to her MBA. John's passion for science paved the way for them to join forces in every aspect of their lives.

And it didn't stop at the basic science of these conditions. Dr. Trojanowski always thought about the patients. By mid-2000 s, they developed a drug discovery program and decided to compete with big pharma because, well, *why not*. They also got some of the first federal grant money to open up an Alzheimer's Disease Research Center, and they began recruiting and training the next generations of neuropathologists and scientists. He was the obvious choice to lead the Biomarker Core for the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI).

"They helped create the modern world of neuropathology," said Michael Weiner, MD, a professor of radiology at UCSF. "For many neurologists, dementia was a clinical diagnosis, but pathologists knew it was a disease and they qualified it and defined it and he was one of the leaders in the field."

"Any one of their accomplishments in identifying the pathologies in these diseases would be a capstone to an individual's career," added John Morris, MD, director of the Knight ADRC at Washington University in St. Louis. "John was never limited to a focus in Alzheimer's. He understood the complexity and breadth of these neurodegenerative lesions. What a life they have had."

John Trojanowski was the son of a career Army officer who took his family to live in ten different places, including one in Guam for two years, by the time he left home at 18. He was one of seven children and by far the bookish one in the bunch. (At one point during World War II, they figured out that their fathers may have crossed paths in China. Dr. Lee's father was a pilot serving the Chinese Army during the war, and Dr. Trojanowski's father provided war supplies around Asia.)

The second oldest sibling, John Trojanowski wanted to be a doctor, which went against heading into his father's post-war real estate business in Connecticut. He went off to Kings College in Pennsylvania on a full scholarship and never looked back. He majored in German and studied abroad in Germany and then in Holland. With a liberal arts degree in hand, it was time for him to think about getting the courses he needed in science to apply for medical school. He got into an MD/PhD program at Tufts University School of Medicine. He went to study in Rotterdam for two years during his doctoral degree and worked there for another year. The duo would later construct their time lines to show that they were in Holland and Rotterdam at the same time.

But it wasn't until 1974 when Dr. Lee was a post-doc at Harvard University that the two actually met. His mentor at Tufts, Stan Jacobson, was giving a lecture and Dr. Trojanowski was passing time reading the notice board when Dr. Lee stood nearby, swooning. "I thought he was so handsome," she would later say. She kept seeing him around town—first at a concert he attended with an older man (she thought he might be gay) and then several times with another woman whom she would describe as a bleached blonde with black nail polish. It looked like they had on matching rings, so she assumed then that they were married. It was two years later at a neighbor's house where she had gone to borrow a vacuum that her neighbor and his friends convinced her to go to a local pub with them. They bought her a Coke, and she was standing at the bar when there he was again. That handsome guy, and this time there was no ring on his finger. She made the first move: "Haven't I met you somewhere before?"

They have been together ever since. Dr. Trojanowski was at Massachusetts General Hospital doing a neuropathology residency, and in 1979 Dr. Lee was offered a job at Smith Kline and French, and he followed her to Philadelphia. He got a job at Penn. They got married several years later, and he convinced her to work with him at Penn. And then they had the talk about finding proteins, and the rest, well, was the beginning of a career that made them stand-outs in their fields.

While Dr. Trojanowski was not one to slow down, the last several years were not easy. He slept a lot, and he had several falls, and luckily they were always on the bottom stair inside their house. He would get up and brush himself off. But in mid-December, a day before his birthday, he had another fall and by the time he climbed up the stairs and sat down on their bed he turned to his wife and said: "I think I need to go to the hospital." When they arrived, an MRI would finally put the past few years into sharp focus. There were a number of hematomas along his spine, and he was rushed into surgery. Twice. A series of medical events—a pulmonary embolism and constant infections—made recovery difficult. The spinal cord injuries left most of his body paralyzed. He was on a ventilator and things didn't look good.

In classic Trojanowski/Lee fashion, practical and passionate, they discussed a life well-lived and Virginia Lee organized a Zoom call, where hundreds of colleagues, friends, and family arrived digitally from all corners of the globe to tell John stories. She propped him up on his hospital bed, and she put on his glasses so he could watch the computer screen. It was a larger-than-life hour—raw, reflective, and most of all loving. His doctors thought he had a chance of recovery, but the infections persisted.

"He had such a high level of integrity," said Gerard D. Schellenberg, PhD, head of the Penn Neurodegeneration Genomics Center and principal investigator of the Alzheimer's Disease Genetics Consortium. One of the highlights of his relationship with John Trojanowski, and there were many, he remembers a conference in Uganda where the three of them broke off for two-week trip across the Serengeti in Tanzania. There they were in a jeep staring at a couple of lions chomping on bones when Dr. Schellenberg heard a loud roar—and then a louder roar. "I looked down and John was on the floor of the jeep. Apparently, he decided to stick his head out of the roof and roar at the lions. They looked up at the vehicle and roared ferociously at us. John was so scared he dropped to the ground. They could have been right on top of us in one leap."

Daniel Skovronsky, MD, PhD, was one of the many scientists who trained with them and went on to a distinguished career in drug development. In November, he was in town and stopped by the lab for a visit. While he was Virginia Lee's post doc, John Trojanowski taught him how to cut brains. (He admits, however, he hated autopsies.) They were telling him how proud they are of his work—he is now senior vice president of science and technology at Eli Lilly and Company. At the end of their chat, John Trojanowski said in his gentle manner: "Make sure you tell people you trained with John and Virginia."

By Jamie Talan
jtalan3k@aol.com

Jamie Talan, MPH, is a science writer who has spent her 40-year career writing about the brain. She is an assistant clinical professor of science education at Zucker School of Medicine at Hofstra-Northwell.