

VIRULENCE PROFILES

Virulence profile: Laura Manuelidis

Laura Manuelidis

Section of Neuropathology (Surgery), Yale Medical School, New Haven, CT, USA

Tell us about your early days and career wishes as a child

I grew up in Brooklyn during WWII and freely roamed the streets, spoke to a vast assortment of people, and slipped into the movies underage where they were playing concentration camps, the atom bomb and Superman. I alternately dreamed of becoming a classical dancer and a champion for the oppressed. The fabric of our abode was filled with diverse people, literature and architecture. The latter meant endless walks around construction sites before finally getting to swim at Coney Island. Little did I know that architecture would provide the cement and steel for my later appreciation of biologic structures from different perspectives.

When did you first develop an interest in science and who influenced you?

My interest in science did not exist until I went to Jamaica High School with 5,000 other students of various talents. George Vecsey wrote about the fabulous athletes there, and as part of the swim team, I helped teach students who had never been to a beach or pool. At the same time, I nearly flunked biology because I couldn't understand the difference between plants and animals, and worse, I was riveted by the incessant warfare of euglena eating the paramecia, rather than the names of various vacuoles going down and out.

A big boned Swedish teacher named Mrs. Blenderman, handsome as a cedar in winter, decided I must be redeemable because my brother and mother were intelligent. That was true optimism in the face of contrary evidence. She persisted, and took me under the branches of biology during lunchtime to imbibe sagas of scientific experiments. In one most memorable, a fly was injected with blood from a schizophrenic, and the fly then fed to a spider. Afterwards the spider was unable to weave an organized web. She asked me, "How do you think they got the spider to eat a dead

fly?" After a pause, she said, "By using a tuning fork at the same pitch as a buzzing lively fly." That first stimulated my curiosity about the brain and its disorganization by chemicals. The subtler lesson of that story, especially facing the apparently insoluble, is that one must be cunning to get nature to reveal her secrets. I also had the good fortune of taking a History of Science course that sped from Cheops to Ptolemy to Copernicus and on to Einstein waving at us from his passing train. The course juxtaposed closed systems of belief with the wonder of uncharted discoveries, something that was to influence my later assessment of "prions."

Tell us about your education and experiences at university

At Sarah Lawrence College (SLC), as a neophyte writer, I chose Muriel Rukeyser as my don. Her fierce integrity and generosity were joined to her extraordinary encompassing intellect. As literature she gave us the original works of Harvey with his elegant discourse on the circulation of blood, Hooke's *Micrographia* in graphics and words displaying the new microscopic world, and Darwin's floridly beautiful Victorian passages on the wind-swept trees of the Galapagos. So I became prepared for the inseparable beauty of art and science. Muriel wrote a book on J. Willard Gibbs in his thermodynamics (think Whitman) and the *Amistad* that propelled me to Yale. Other background experiences leading to medicine included a transfer program to Spellman where lynchings were still ongoing and restaurants segregated, where summers at Harvard took me to morning classes of chemistry and physics, afternoons to the locked men's and women's violent wards, and evenings looking at some friends taking LSD from my corner studying. It was the time of Timothy Leary in the square, Martin Luther King was building a coalition, and the Vietnam War was about to come to town.

CONTACT Laura Manuelidis ✉ laura.manuelidis@yale.edu 📍 Section of Neuropathology (Surgery), Yale Medical School, 333 Cedar Street, Room FMB, New Haven, CT 06510, USA.

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This amalgamation of events led to questions about the brain and the process of thinking, a subject I might learn most about in medical school. Since I couldn't hold a job as a speedy non-conversational waitress, couldn't type, and wanted to become independent, I applied to a few medical schools where they seemed to be most interested in my late night accommodations and plans to marry. Thomas Forbes, the gentle dean of students who taught history of medicine and anatomy, engaged me in real conversation and thought I might do well in the Yale "system," an exploratory and innovative program, deeply committed to the independence of its students. Though it was a jolt to be confronted by a strange male society of competition and pecking order, with little space for literature and the arts, my classmates were most forgiving to me, and I developed enormous respect and admiration for their compassion and decency. We became a committed and coherent team communicating in the same secret language and acronyms of medicine. A great and profound education I fortunately stumbled into, filled with physical knowledge of the body that supersedes politics and vanity.

Who were your mentors?

It was initially difficult to find others in the med school equally obsessed with the classical dualism between matter and spirit (thought). I was assigned to the group led by the neurophysiologist Jack Flynn who had left the priesthood to study the neurologic basis of aggression. I fell in love with his encyclopedic knowledge and worked in his lab for 4 years doing my thesis on the convergence of pain pathways and hearing. He introduced me to the original writings of Cajal and Sherrington. On the side we discussed Aristotle's *de Anima*, and I became part of his family. His lab was not for everybody as he let you flounder around until you found your own question and its logical experiments.

Seminars in neurophysiology were closed to me as a woman student. Jack suggested I pursue an internship to have broader professional opportunities. That was not difficult since I was also taken with pathology, the evolution of disease, the ultimate history of an individual, slice by slice of sequential time. Pathology emphasized broad principles of medicine and combined teaching and scientific discovery. Moreover, the Pathology department at Yale in the 1960s was full of outspoken renegades who loved to poke the established order with its parade of pomposity. Foremost was the chairman Harry SN Greene, one of the great lecturers at Yale, who had a shrunken head on his office wall that he assured you was Dean Winternitz. He thought women were smarter than men, and actively tried to recruit African Americans into

the department. He offered me an internship and residency position, and said I could even work on the nervous system. He also introduced me to Peyton Rous whose work on the slow action of chemical carcinogens, and retroviral induction of sarcomas, remain classics. Thus I first became cognizant of the role of viruses and environmental factors in progressive late-onset diseases. Strange reports about kuru, a dementia in New Guinea, also entered my world as I worked in East Pakistan (Bangladesh), and met epidemiologists and other visitors looking for its cause, possibly a toxin from mustard seeds or an inherited disease. Little did I suspect that these infectious pathogens would become an intense part of my professional life, and my personal life, shared with my husband Elias E. Manuelidis, my Apollonian better half. He deserves more than a paragraph of his own.

Lewis Thomas, a man of grace and unstoppable curiosity, became chairman of Pathology and for a short stint Dean, escaping as often as he could to do experiments on mycoplasma infections. He took a small office with the first picture of earth from the 1968 Apollo mission. That encouraged my initial forays into conversations with him. He thought my idea of looking for gene amplification in brain tumors was terrific, and immediately brought up other obscure biological examples where amplification probably operated. We both bonded over the Quartet Italiano playing Beethoven's Opus 133 and whale songs. He also appreciated intelligent women, including his wife and daughters, made me an assistant professor, and was a continual source of encouragement in the face of later academic adversities and empty fashions.

What do you like most about your work as a physician/scientist?

That one is always learning. I also need the physical activity and challenges of working in the lab, and the interaction with students and others in the university and hospital.

What was your most significant scientific accomplishment?

That's like asking which one of your children do you love most. So far, several contributions have withstood the test of time. These discoveries are really serendipities in two seemingly disparate fields that now are coming together again for me: repeated DNAs and chromosome organization in the nucleus, and the story of Transmissible Encephalopathies. Both are unfinished.

In 1970 the NIH agreed to support my innovative (their term) approach to DNA-chromosomal changes in glioblastomas. I doubt I, or someone like me, would receive such

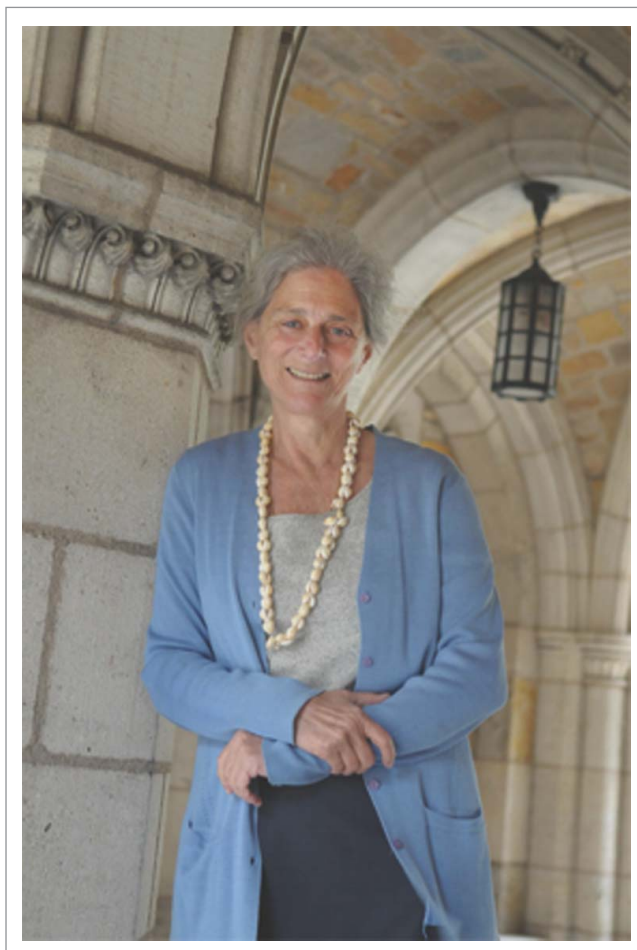


Figure 1. About Laura Manuelidis. Laura Manuelidis received her medical education and training at Yale and stayed on as a faculty member, ultimately becoming Head of Neuropathology section responsible for teaching, diagnosis and research. Her publications include >100 non-redundant scientific articles, two books of poetry, and occasional eclectic essays. Additional details for her lab and related links at <http://medicine.yale.edu/lab/manuelidis/index.aspx>.

funding today. It was a high-risk project. After many failed attempts to find tumor-specific DNA bands by analytical CsCl centrifugation (and inexcusable late dinners for my family), a graduate student showed me the first reports that used restriction enzymes to cut Φ X174 plasmid DNA. I immediately realized this was the way to systematically define segments of the mammalian genome. Despite doubts that any DNA more complex than Φ X would show anything interpretable, several colleagues let me help purify a few restriction enzymes in exchange for a small sample. I used these enzymes to digest human DNA from tumors and normal placenta. When I saw my gels with the first bands of complex mammalian DNA spread out before me in the 1970s, it was like Cortez staring out at the Pacific. There were the centromeric α satellites that I sequenced in 1976, and long interspersed human DNAs, or LINES in 1982. The Stanford database contained only 50 sequences, and none

matched. LINE homologies with ancient retroviruses, uncovered later, led to the recognition of the long symbiotic integration of environmental viruses with mammalian genomes.

My NIH cancer grant support for 25 years also allowed me to investigate higher levels of repeated DNA motifs in chromosomal organization. High-resolution non-isotopic labeling was developed here with David Ward, and subsequently has also been used for many diagnostic and fundamental contributions of others. I was most intrigued by the unmapped structure of the nucleus, and realized from initial studies of centromere positioning that DNA was far more organized in the nucleus than suspected. It was more cohesive than the spaghetti-like models of chromatin or thin section ultrastructural images. By developing computer three-dimensional approaches to reconstruct specific DNA domains by confocal and electron microscopy we showed that different neuronal and glial cell types have distinct arrangements of whole chromosomes in their nuclei. These clearly subserve global functional differences. Some chromosomes move during development and differentiation, and also in response to functional states, as in epilepsy. While many others concentrated on the small linear motifs of newly discovered specific genes, the importance of much larger chromosomal domains, partially organized by non-coding repeated DNAs, has recently reemerged.

During this same time I began to work on CJD, a transmissible encephalopathy (TSE), because my husband succeeded in serially transmitting the infection to guinea pigs, a more useful experimental model than existing primate models. We were able to transmit CJD cases to various rodents using different routes of inoculation, including the eye. CJD was clearly caused by a different agent strain than sheep scrapie strains. Novel findings with some biologic import included the demonstration that myeloid cells of the blood carried the infectious agent, that the agent was not transmitted to offspring from infected mothers, i.e., not genetic, and that host microglial responses preceded amyloid plaque formation. More recently, we developed monotypic tissue cultures infected by many different stable TSE strains and these agents all rapidly replicate, in contrast to their long suppression and latency in animals. We are not partisans of prions, a protein infectious agent without nucleic acid, because the reproducible evidence strongly implicates a virus with strain-determining nucleic acid. Most notably, we showed brain particles without detectable prion protein are highly infectious. Moreover, infectivity is destroyed by nuclease treatments that have no effect on prion protein. Thus TSE agents, as viruses, require genetic material to produce infection.

We think that environmental nucleic acid sequences from the microbiome, such as the circular SPHINX

DNAs uncovered in our laboratory, may ultimately define the virulence of different TSE strains. They may also have a role in other neurodegenerative diseases and in neoplastic transformation. Thus one returns to the paradigm of retroviruses that can become pathogenic, or quiescently exist as avirulent symbiotic elements. A vast new territory to explore.

What advice would you have to junior people entering the field?

What is the question you most want to answer? Go there. Look in the corners that others are ignoring. Do the

experiments yourself, and doubt your own results until they are unassailable. That builds true confidence. Persist, but know when to try another route. Use your best talents. If your results take you to something you didn't expect, follow it. Enjoy the challenges and don't be afraid to change: Truth is a restlessly moving object of desire. If you are just starting out, find a person to work with who has time for you and your continuing education, who is authentic intellectually and scrupulously honest. Take time off to watch the tide coming in and going out and coming in again. Or listen to Bach and Bessie Smith. And, as Harry Greene used to say: "Don't let the bastards get you down."