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IN MEMORIAM

Sheldon Penman: Visionary of cell form and function

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Sheldon Penman made major contributions to the field of RNA synthesis and, more broadly, the nexus between cellular form and gene readout. He will be remembered for his creativity and breadth of expertise, as well as his opposition to what he believed were threatening incursions into science by corporate interests.

Moving from physics (the muon) into molecular and cellular biology—I doubt any such transition was accomplished with such rapid kinetics and immediate impact as was the late Sheldon Penman's. He had an ability to see things in ways different from others, and this enduring ability made him a legend and a warmly admired figure in his newly chosen field.

Penman was born in Philadelphia and was recognized as a prodigy. He did graduate work in physics at Columbia, but while contemplating this field and career, became keen about cell biology. Through a serendipitous connection at Massachusetts Institute of Technology (MIT), he joined the laboratory of the then young but promising RNA scientist James Darnell. Within a year, Penman had assimilated all the relevant lore and had participated significantly in the first demonstration of mRNA in a mammalian cell (Penman et al., 1963). Penman then won a fellowship for physicists entering biology and moved to the Albert Einstein College of Medicine. There he developed a method for isolating the HeLa cell nucleolus. This had been done previously for rat or guinea pig liver by two groups, but he deployed this method to define the RNA synthesis kinetics in each of the nucleolar and nucleoplasmic domains (Penman et al., 1966a, 1966b; Penman, 1966). This work was when I first noticed his name and, like many of my contemporaries and more senior investigators, I thought, *Here is an exciting new person on the RNA landscape.*

Upon taking a faculty position at MIT, Penman's work and engaging persona attracted some of the most stellar students in this rarefied crowd, as well as many talented postdocs. My own letter seeking a postdoc position went unanswered. When I got up the courage to phone him, he said, "I'm sorry, there's a big list. I don't know how to deal with it." There was sincere angst on the phone.

With him so clearly fascinated by RNA biosynthesis, few people at the time sensed what was really on Penman's mind: the idea of cell structure enabling function. Certainly not a new concept, but it was new to him, and he got hyped, which I enjoyed seeing whenever we met. He became absorbed in histology—not a topic most MIT biology professors would. He read all the textbooks and bought large vinyl records that showed all the cell types (this was long before the digital era).

Penman was not the first physicist to get keen about structure beyond their field. Erwin Schrödinger, Max Delbrück, and Francis Crick envisioned biological (i.e., genetic) information as structure. The physicist Richard Feynman at Caltech spent some time working with the young biophysicist Matt Meselson for the same reason (genetic information). But Sheldon's passion was the cell, and how form underlies function.

In 1978, Penman published a paper demonstrating that an extract of HeLa cell nuclei retained sites of nascent RNA (Herman et al., 1978). This study coincided with growing infatuation with EM (more on this to follow). It also was the opening to his forays into nuclear architecture. In 1974, a report had appeared showing that a network of proteinaceous filaments extends throughout the remnant of extracted nuclei (Berezney and Coffey, 1974). This influenced Penman, resulting in the aforementioned paper (Herman et al., 1978), and he then launched a boomlet of studies on this "nuclear matrix," which were seen by some as a key advance but by others as fraught. I was in the latter camp (Pederson, 1998). The issue was that no compelling evidence was marshaled for the existence of a nuclear matrix in the intact, living cell. This is in contrast to the "nucleoskeleton" that underlies or interdigitates the lamina at the nuclear periphery but does not course into and throughout the nuclear interior.

Penman did not limit his vision of cytoarchitecture facilitating gene expression to the nucleus. His increasing awareness of the association of some mRNA with the cytoskeleton led to a parallel track of research in his group, combining EM with related methods. I'll never forget a National Institutes of Health (NIH) site visit I chaired at his lab when a major grant was pending. He opened the morning by vilifying most previous EM of both the nucleus and cytoplasm, claiming it to be a surface image of the section due to limited electron penetration, which is true. I called an early break to remind him that a member of the committee was one of the most statured electron microscopists in the world. (Penman's occasional lack of attention to detail was well known.) He thanked me and backed off

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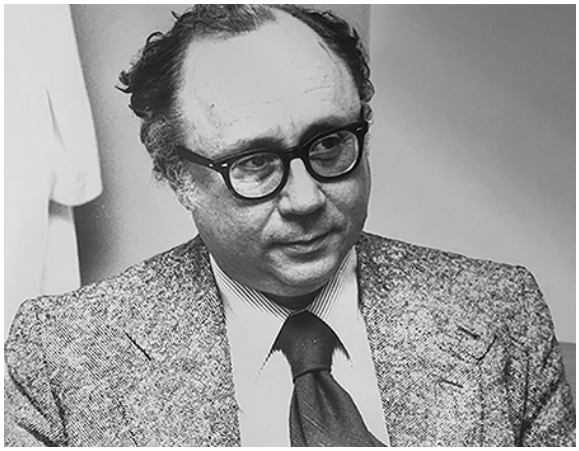

Sheldon Penman, 1930–2021. Image courtesy of Joshua Penman.

his tirade about "conventional EM." Later that day, when things were still not going particularly well, a postdoc presented findings in which cells were extracted with Triton and then overlain with micrococcal nuclease-treated rabbit reticulocyte lysate and S^{35}-methionine, recording the translation of mRNAs that had remained attached to this cytoskeleton preparation. Penman's pending grant had been DOA as of noon, but at 2 p.m. was on its way to a top score. Subsequently, his group made further advances in our understanding of how cell shape and motility influence gene expression by the regulation of translation of certain mRNAs by virtue of their cytoskeletal association.

Penman was a caring mentor, but this also included pushing his students and postdocs to promptly write up their papers and get them submitted, knowing that these kinetics could help them. More than one of them have recalled this, with appreciation understood later as they were succeeding on their own.

I close on a few personal memories. Penman was a perfectionist. One time after a lovely dinner he prepared, he wrote me to say that he had committed a terrible error, serving a dry red wine with a slightly vinegary Southeast Asian soup. My wife and I hadn't noticed because we lacked then (and now) his culinary sophistication.

Penman had a wonderful sense of humor and a booming laugh that carried across the room. He also enjoyed foiling technology. For example, he showed colleagues how to open an ultracentrifuge while the rotor was still spinning (overriding a door lock switch in the back) and then slow it with one's hands until 500 rpm or so, allowing it to softly come to rest. Not much time was saved in the grand scheme of things, but that was so him. In another example that reflected his physics insights, he became exercised about cell homogenizers made of glass. He saw people using them as "grinders" and also decided that even the "tight-fitting" ones were too loose. During his seminal nucleolar isolation work at Albert Einstein College of Medicine, he had the machine shop make stainless steel homogenizers with a 0.002-inch clearance. As he once explained me: "Thoru, the principle is the force generated on the cells as they encounter the hydrostatic pressure and rheology as they pass through that narrow channel, with the swollen cells' diameters unable to resist."

Penman was politically active. He went to Vietnam during the war to observe the Cambodian "killing fields" from the air and later ranted about this horror. In other corridors he was conservative, including in academia. He vigorously opposed the creation of the Whitehead Institute at MIT, believing that this was selling out to money and possible undue control. In this specific case he was proven wrong, but his vanguard position was valid as to the general issue.

In the 1990s, Penman went through a phase where he attacked gene-cloning molecular biologists, saying things like, "Emergent properties of an organism can never be found in the linear DNA sequence." I admired him for saying this (and almost agreed) but retorted, "Sheldon, you know you will change your position." Sure enough, the next NIH grant of his I got to review had the cDNA sequence of a nuclear protein mRNA as preliminary data. As to his vision of a nuclear matrix, he may have been wrong as to its existence, but he clearly saw that gene expression might be linked to nuclear architecture. We now know that the determination of differential gene expression resides to a considerable degree in the 3D folded genome itself. We should always applaud those who, like Penman, had the right concept, and not dwell on whether or not they got the details.

Penman published over 300 papers, including many in his later years focusing on new ideas for cancer imaging and treatment, his unbounded creativity not the least in decline. Earlier, a seminal achievement was the founding in 1974 of the journal *Cell* with his MIT colleague Howard Green. Penman was a member of the U.S. National Academy of Sciences and the American Academy of Arts and Sciences. He shared the 1998 E.B. Wilson Medal of the American Society for Cell Biology with James Darnell, so deserved for them both and so fitting for them to share given their extraordinary productive/breakthrough early times, which I think of as "heterogeneous catalysis," using the chemistry reaction metaphor.

Sheldon Penman was a unique force in molecular cell biology. He is to be remembered for his penetrating intelligence and foundational work, and his stance of always challenging orthodoxy. I and so many others of his admirers will never forget him.

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