BIOGRAPHICAL MEMOIRS

Jerard Hurwitz

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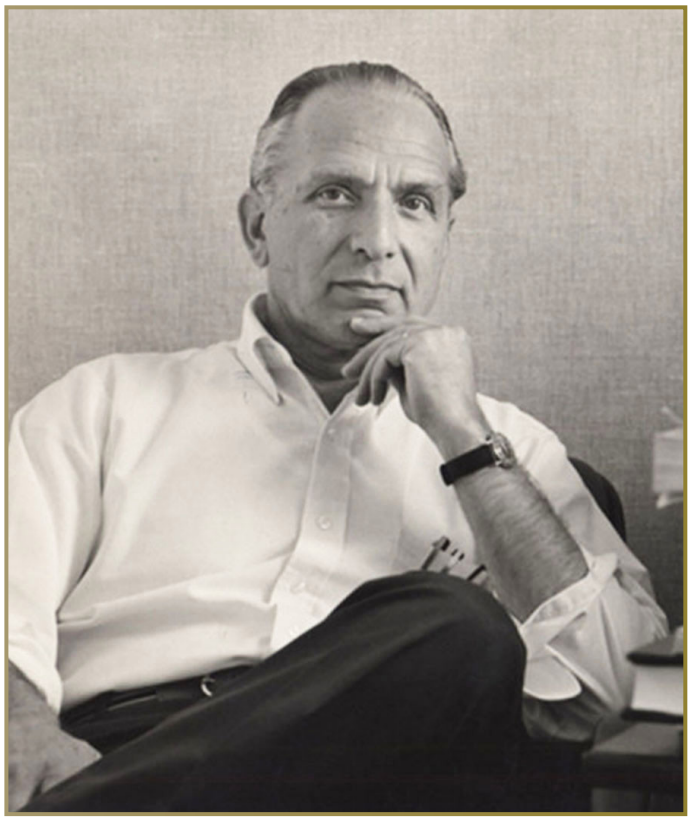
A Biographical Memoir by Stewart Shuman



Jerry Hurwitz was in the vanguard of the generation of twentieth-century biochemists who transitioned from a focus on intermediary metabolism to the challenges posed by the newly elucidated structure of DNA. In a research career spanning seven decades, he contributed profoundly to the field of molecular biology. Jerry's laboratory established the biochemical foundations for the central dogma via the discovery, purification, and characterization of the enzymes that catalyze mRNA synthesis, DNA replication, and nucleic acid modification and repair. Jerry's formative years in science exposed him to the founders of post-war molecular genetics and biochemistry. These experiences gave Jerry a unique perspective on how nucleic acid enzymology would propel the "post-double helix" era of biology.

Early Life

Jerry grew up in the Bronx, New York, the son of Russian Jewish immigrants Hyman and Dora (Garbarsky) Hurwitz. His mother was a seamstress in a sweatshop. His father was a housepainter who was active in union and socialist movements. Jerry reportedly excelled at stickball, a classic New York City street game played with a broomstick and a "spaldeen" rubber ball. He attended DeWitt Clinton High School (an all-male school at the time) on Mosholu Parkway in the Bronx. After a stint at City College of New York, Jerry moved to the University of Indiana (IU) in Bloomington, reuniting there with his elder sister, Zella (who was pursuing graduate studies in psychology), and her husband, Salvador Luria (a future Nobel laureate then on the IU faculty). Jerry graduated from Indiana with a bachelor's degree in chemistry in 1949.

The Making of a (Nucleic Acid) Biochemist

Jerry enrolled as a Ph.D. student at Western Reserve University in the Department of Biochemistry, chaired by Harland Wood, who was renowned for his discovery of CO_2 fixation in heterotrophic organisms (the Wood-Werkman reaction). The department's research efforts centered on intermediary metabolism, and Jerry's first published works while there dealt with the effects of ammonium ions on glycolysis; the enzymatic phosphorylation of pyridoxal (vitamin B6) by yeast pyridoxal kinase; and the substrate repertoire of rabbit liver aldehyde oxidase. The latter two projects entailed enzyme purification and characterization (skills that would dominate Jerry's future opus) and resulted in three solo author papers in the *Journal of Biological Chemistry*. (Today's

graduate students might be surprised to know that this was once quite common in certain scientific circles.) He would eventually publish 145 papers in *JBC* during his career.

Jerry's budding interest in the metabolism of phosphorylated sugars led him to a postdoc with Bernard Horecker at the National Institutes of Health (NIH), during which time he, Arthur Weissbach, Leon Heppel, and Horecker isolated and characterized a series of enzymes involved in pentose phosphate metabolism. It was thus a short leap from Jerry's postdoctoral studies of ribulose-5-phosphate, xylulose-5-phosphate, and ribose-5-triphosphate to his decision to study the enzymology of ribonucleic acid (RNA) synthesis as the focus of his independent research agenda, which he initiated after joining the new Department of Microbiology at Washington University in St. Louis, which had been established by Arthur Kornberg. Early efforts there demonstrated manganese-stimulated incorporation of ^{32}P-CMP into DNA by *E. coli* extracts (eventually appreciated as a reaction catalyzed by DNA polymerase I).

In 1958, Jerry returned to New York to join the Department of Microbiology at the New York University (NYU) School of Medicine, newly chaired by Horecker. At NYU, the search for a DNA template-directed enzyme capable of RNA synthesis proceeded in earnest, propelled by skepticism that NDP-utilizing polynucleotide phosphorylase (discovered in 1955 by Marianne Grunberg-Manago and Severo Ochoa) was the physiological catalyst of RNA biosynthesis. As always in biochemistry, eventual success hinged on deployment of the right assay. In this case, Jerry demonstrated the incorporation of [α^{32}P]UTP (rather than [α^{32}P]CTP or [α^{32}P]ATP, thereby avoiding detection of CCA addition to tRNA or synthesis of poly(A) by poly(A) polymerase) into acid insoluble material by *E. coli* extracts in a reaction that required all four rNTPs and was eliminated by inclusion of RNase or DNase in the reaction mixture. This breakthrough was reported in a brief paper in 1960 entitled "The enzymic incorporation of ribonucleotides into polyribonucleotides and the effect of DNA"—coincidentally in the same issue of *Biochemical and Biophysical Research Communications* as the report by Audrey Stevens of an *E. coli* activity that incorporated labeled ATP into RNA in a reaction requiring all four rNTPs.

Major Research Highlights from the Hurwitz Lab

Jerry's series of landmark papers concerning the "directing role of DNA in RNA synthesis" (1960–66) embraced the discovery of *E. coli* RNA polymerase, the purification of the enzyme,[1] demonstration that rNTPs are the precursors for RNA synthesis and (most importantly) that the RNA produced is a direct copy of the genetic information in the DNA template.[2] He showed that RNA polymerase initiates *de novo* so that the primary transcript retains a 5'-triphosphate end and that chain elongation proceeds in the 5' to 3' direction.[3] Thus, the field of transcription biochemistry was born.

Jerry inaugurated the field of enzymatic methylation of DNA and RNA nucleobases in a series of publications (1963–67) that included: (1) the isolation of multiple AdoMet-dependent methylating enzymes with distinct base-modifying specificities and (2) the demonstration that DNA methylation by bacterial enzymes is species-specific, i.e., DNA from the same species as the enzyme is not methylated in vitro, whereas foreign DNA from a different species is methylated.[4] The latter finding was a harbinger of the eventual discovery of the site-specific restriction/methylation systems that have enabled the precise physical analysis and molecular cloning of DNA.

In the same vein, Jerry discovered or co-discovered many other nucleic acid-modifying enzymes that, in addition to being of crucial importance to DNA and RNA repair, are the workhorses of the modern molecular biology toolkit. These include: (1) polynucleotide kinase,[5] which is used to label the 5' ends of DNA and RNA and was central to the development of chemical methods for DNA sequencing; (2) DNA ligase,[6] the key agent of DNA break repair and the enabler of molecular cloning; and (3) RNA ligase,[7] the first example of an RNA repair enzyme and an invaluable reagent for RNA cloning and transcriptome-wide RNA sequencing.

Beginning in the 1970s, Jerry's lab focused on the mechanisms of DNA replication initiation and replication fork elongation, initially exploiting viruses as tractable model systems and ultimately extending his analysis to the regulation of human DNA replication. His approach was to biochemically fractionate cell-free extracts capable of DNA replication and then reconstitute the steps of DNA replication from purified components (often numbering in the dozens of enzymes and accessory proteins).

The Hurwitz lab, in parallel with the Arthur Kornberg lab, deftly used small bacterial viruses as replicons for in vitro dissection of the bacterial DNA replication machinery and eventual reconstitution of the replication reactions.[8] Key insights were the different strategies exploited by the viruses and the bacteria cell to initiate replication at an origin and then unwind and propagate the bacterial replication fork.

Jerry proceeded to bring the same style of tour-de-force biochemistry to bear on the replication of human DNA viruses (adenovirus and SV40). His efforts, in parallel with those of the Tom Kelly and Bruce Stillman labs, resulted in the identification of multiple novel components of the human replication machinery and the appreciation that a DNA-binding transcription factors can also play a crucial role in DNA replication.[9] Jerry contributed fundamental insights to the role of an SV40 T antigen double-hexamer complex in the recognition and unwinding of the origin of tumor virus

replication.[10] His reconstitutions of a human replication fork from purified components shed light on fork unwinding by helicases, the priming of lagging strand synthesis, the loading of the polymerase sliding clamp, and the division of labor among the three major replicative human DNA polymerases.

The Hurwitz Style of Science

Jerry was passionate about science and especially dedicated to the tactile aspects of benchwork. He worked six days a week, and woe betide any lab members who didn't. Jerry spent a sabbatical year in Paris at the Pasteur Institute in 1968 and was reportedly incredulous that his French colleagues would take two hours off for lunch instead of doing things in the lab. He never stopped doing his own experiments, and he was forever in search of some new activity that those who trained with him in the late 1970s affectionately named "imaginase." He walked around with an ice bucket under each arm until the day in March 2018 that he closed his lab door and (with fervent reluctance) became an emeritus professor.

Jerry's unique style as a rigorous mentor made a lasting imprint on the scores of graduate student and postdoc alumni of the Hurwitz lab. He had high expectations and didn't mince words when he felt they were not being met. The stories of Jerry's lab meetings are the stuff of legend. Yet, he did not stand on formality, and the quickest way to gain his lasting respect was to rebut with force and conviction (along with the data) whatever criticisms were being heaped. That so many of Jerry's trainees became illustrious scientists in their own right is his enduring legacy.

Jerry was a charming raconteur whose anecdotes regarding twentieth-century biochemistry and its personalities instilled the sense in a young scientist of belonging to a vibrant intellectual continuum greater than any individual or niche field. His deep connections to the tradition of intermediary metabolism and nucleotide sugar biochemistry, under the tutelage of Wood and Horecker, as well as his storytelling skills, can be appreciated by reading his Reflections piece in *JBC* on the discovery of RNA polymerase.[11]

Jerry's perspective was profoundly influenced by his personal and intellectual connections to the Phage Group centered around Salva Luria and Max Delbruck (a signed photograph of whom was on prominent display in Jerry's office). He took the phage course at Cold Spring Harbor Laboratory in 1951 and, though he never closed the cultural divide between the biochemists and the molecular geneticists, he made lots of hay purifying novel enzymes from phage-infected bacteria and relied heavily on the availability of *E. coli dna*$^-$ mutant strains to implement biochemical complementation assays for the purification of genetically defined bacterial DNA replication factors.

Notwithstanding his intensity as a scientist and pride in his lab's work, Jerry was never one to sit on past laurels. Indeed, he conducted his professional life with a healthy humility that acknowledged the role of good fortune in success (but also the possibility of being wrong every now and then). His closing remarks in his Reflections say it perfectly: "The discovery of DNA-dependent RNA polymerase, simultaneously made by Sam Weiss, Audrey Stevens, and my own laboratory, was an exciting and stimulating period. It convinced me that I could do important work even if it required fierce competition. However, it also made me realize that if we had not made these discoveries, others would have soon after."

The Hurwitz Legacy

Jerry left a deep footprint in the scientific landscape of New York City, where he grew up and where he returned to build his independent academic career: at the NYU School of Medicine (1958–63), the Albert Einstein College of Medicine (1963–84), and Memorial Sloan Kettering Cancer Center (1984–2018). He was a major factor in the dynamic and highly interactive research scene at Einstein, a new school when it opened in 1955. Einstein provided a safe haven for many distinguished faculty scientists who had been persecuted during the during the McCarthy era, a fact that resonated with Jerry's left-leaning politics (a legacy of his union-organizer father and exemplified by his decision to leave NIH rather than take a loyalty oath). Recruited to Sloan Kettering by his close friend and colleague Paul Marks (its president from 1980–99), Jerry helped steer a transformative enrichment of the science at Sloan Kettering.

Jerry was the recipient of many honors, including the Eli Lilly Award in Biological Chemistry, an American Cancer Society Research Professorship, and election to the American Academy of Arts and Sciences and the National Academy of Sciences.

Jerry was the proud father of two daughters, Deena and Jodie, with his first wife, Muriel Gould Hurwitz (m. 1950). In the 1960s and 1970s, Jerry would spend one month every summer vacationing with his family at their house in Woods Hole, where he would hone his tennis game and enjoy the friendship of the many academics (including Zella and Salva) who summered there. All this relaxation did not quench Jerry's thirst for the latest progress at every lab bench back at Einstein. Lab members would take turns at the lab wall phone (remember those?) to be interrogated by Jerry.

In 1981, Jerry married Ora Rosen, then chair of Molecular Pharmacology at Einstein, and they moved together to Sloan Kettering in 1984. There, Ora's lab achieved a breakthrough in cell biology by cloning the gene for the human insulin receptor. She passed away in 1990 from breast cancer. He is survived by his third wife, Mary Soyer.

Acknowledgments

Deena Hurwitz is a human rights lawyer (continuing the family legacy of progressive activism). Jodie Hurwitz obtained her medical degree at Einstein and specializes in cardiac electrophysiology. I am grateful to them for sharing memories of their father.

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