Danna and Nathans: Restriction enzymes and the boon to modern molecular biology

In 1971, a paper published in PNAS (1) helped jump-start the era of modern molecular biology and biotechnology, eventually giving rise to many of the genetic advances that seem so commonplace today. The article, written by Academy member Daniel Nathans and his then graduate student, Kathleen Danna, exposed the marvelous utility of restriction enzymes. In the accompanying Perspective highlighting this classic work of scientific literature, Rich Roberts provides a historical account of the scientific discoveries leading up to the PNAS paper and the unparalleled scientific advances made after its publication.

Leaving Medicine for Research

The road to the discovery of restriction enzymes began in 1945, when Nathans enrolled in an undergraduate chemistry program at the University of Delaware (Newark). Lingering in Wilmington, DE, the same town where he was born and raised, Nathans initially lived at home and commuted to class by hitchhiking. He was the last of eight children born to Russian Jewish immigrant parents, who encouraged his natural interest in science. Nathans claimed that his father saw him as "the last chance to have a doctor in the family" (2).

"Becoming a physician also seemed more attractive to me than any other alternative I knew about," Nathans noted (3), so he applied to medical school and received a scholarship at Washington University (St. Louis). However, an intense summer session of research convinced Nathans that his future lay in research and teaching rather than in medical practice. After he received his medical degree in 1954, an internship at Columbia-Presbyterian Medical Center in New York, followed by 2 years as a clinical associate at the National Institutes of Health (Bethesda), confirmed Nathans' desire to focus on research.

Much to the surprise and dismay of his father, Nathans left medicine and began his basic research career at The Rockefeller University (New York) in 1959. However, tired of sitting through endless lectures, Nathans abandoned his Ph.D. program at Rockefeller and started laboratory research on bacterial proteins and viral RNA. Although he never obtained a Ph.D., the work gave him confidence and experience with biochemistry, leading to a faculty position in the microbiology department at The Johns Hopkins University School of Medicine (Baltimore) in 1962. In Nathans' own words, he became "a one-man 'Division of Genetics' " (3), which gradually morphed into a sizable group, including graduate student Kathleen Danna, fellow professor Hamilton O. Smith, and Smith's postdoctoral student Thomas Kelly. This combination of talents would prove highly fruitful in the years to come, as Roberts asserts in his Perspective.

A Colossal Understatement

After some departmental shuffling, Nathans was asked to teach medical students about animal viruses. The topic intrigued him, so he switched tracks in his research to study a relatively simple tumor virus, simian virus 40 (SV40). To learn how to grow and handle SV40, Nathans went on sabbatical to The Weizmann Institute of Science in Rehovot, Israel, in 1969. Roberts chronicles the developments that Smith made during Nathan's absence, noting that Smith corresponded with Nathans to keep him abreast of the research on endonucleases. In what proved to be a colossal understatement, Nathans wrote in a personal letter to Smith that the finding "could be useful for many things." Nathans' research team would begin a few preliminary experiments, he noted in the letter, "if everybody is interested to see if it looks promising."

Upon his return to Johns Hopkins, Nathans began studying the effect of Smith's enzyme on SV40. Danna soon joined the project, and the work became the subject of her dissertation. Nathans sensed Danna was ready for a change—an earlier dissertation project had ended in chaos, with pulverized rat liver spilled across Danna's laboratory bench. Although Nathans was a rather serious and formal person compared with others in the laboratory, the two worked well together.

"He was always available, but he didn't breathe down your neck all the time," said Danna, currently an associate professor at the University of Colorado (Boulder). "You would try hard to solve a problem and then go to him if you needed help."

A Clear Vision

Smith and his postdoctoral student Kelly made rapid progress with their independent study of the *Hemophilus influenzae* restriction enzyme, concluding in 1970 that the enzyme cleaved DNA only at sites with a specific arrangement of base pairs. However, after publishing their findings (4), the scientists abandoned the subject of restriction enzymes and went on to other research.

"I did my nice piece of biochemistry and, for some reason, I wasn't interested in the actual application of the enzyme," said Smith, an Academy member and currently the scientific director at the Institute for Biological Energy Alternatives (Rockville, MD). "I just more or less published my work and put it on the shelf."

However, Nathans and Danna continued work on the enzyme, with a different spin than that of Smith and Kelly. "If you look back on it, it seems like such a simple notion. But the fact is, I think Dan saw the utility of this much more clearly than even those of us who were very close to the work," said Kelly, an Academy member and currently the director of Sloan–Kettering Institute (New York). "Clearly, he must have had a vision at the very beginning of this that just the simple idea of being able to separate the fragments of viral DNA into specific pieces would have enormous applications," said Kelly.

A Lasting Legacy

Throughout his life, Nathans continued to play an integral part in molecular biology and genetics research. After an extremely fruitful career at Johns Hopkins, spanning years as the department chair and including a period as university president as well as numerous accolades, Nathans succumbed to leukemia in 1999. However, as Roberts outlines in the Perspective, the legacy of Nathans' 1971 PNAS paper is readily visible in almost all areas of modern biotechnology.

Christen Brownlee,
Freelance Science Writer

1. Danna, K. & Nathans, D. (1971) *Proc. Natl. Acad. Sci. USA* **68**, 2913–2917.
2. DiMaio, D. (2001) in *Biographical Memoirs*, ed. Berry, R. S. (Natl. Acad. Press, Washington, DC), Vol. 79, pp. 262–279.
3. Odelberg, W., ed. (1979) *Les Prix Nobel. The Nobel Prizes 1978* (Nobel Foundation, Stockholm).
4. Kelly, T. J. & Smith, H. O. (1970) *J. Mol. Biol.* **51**, 393–409.