Norton Zinder

Photo courtesy of The Rockefeller University

In Memoriam Norton Zinder (1929–2012) Geneticist

Zinder, a superb geneticist (who also embraced biochemistry), died on February 3, 2012, following a long illness. He was 83. Zinder came of age at the dawn of microbial genetics. A prodigy with an eidetic memory, he was only 15 when he graduated from the Bronx High School of Science, where he built his first incubator for growing bacteria (a 60-W light bulb in a box with a thermostat). After earning his undergraduate degree at Columbia University only 3 years later, he migrated to the University of Wisconsin in Madison; his sweetheart and bride, Marilyn, soon joined him. As a graduate student with Joshua Lederberg (another Bronx-born wunderkind a few years his senior), he commenced to extend Lederberg's studies of bacterial conjugation. While trying to understand why his *Salmonella* were not behaving properly, Norton discovered transduction, the process by which viruses carry DNA from one organism to another. Norton always was sure that animal viruses do the same with their eukaryotic host. That is now well established. The *Perspectives* article that Norton wrote for GENETICS (*Genetics* 1992 132: 291–294) marking the 40th anniversary of the discovery of transduction provides a captivating description of how the combination of chance, insight, and careful experimentation led to that discovery and his deduction that the process is mediated by phage. Norton also participated in the discovery of penicillin selection and co-authored a landmark paper with Lederberg, "Concentration of biochemical mutants of bacteria with penicillin" (*J Am Chem Soc.* 1948 70: 4267). Years later he delighted in showing visitors a filter paper that he had retrieved from an old lab notebook that he used to replicate some of those mutants.

After joining the faculty of The Rockefeller University in 1952, Zinder and Tim Loeb, his first student, isolated bacteriophages that could grow only on strains carrying the F (fertility) factor responsible for bacterial sex. Thus was the first phage with an RNA genome (f2) identified. Access to large quantities of a homogeneous RNA opened the door

to many fundamental questions, which Norton and his students attacked with vigor. Always there were mutants—and, once they knew that the genome was the message, biochemistry—that revealed the nature of nonsense suppressors and how protein synthesis initiates and terminates. In the late 1960s, a NOVA television program, "Stop or Go," explained some of these discoveries. Norton and his lab members reenacted their search for conditional-lethal f2 mutants, their elation at finding them, and the experiments that led them to suppressor tRNAs, the n-formyl methionine that initiates protein synthesis, and translation stop codons.

The availability of pure f2 RNA also led to the identification of RNase III by a frustrated student, the late Hugh Robertson, who was trying to synthesize active f2 replicase *in vitro*. Expecting to find an increase in double-stranded RNA upon replicase action, Robertson instead kept seeing a decrease. Norton insisted that something in the protein synthesis extracts must be digesting naturally double-stranded regions of f2 RNA, which led to the discovery of the first enzyme specific for double-stranded RNA. Many years later its eukaryotic relative was found: Dicer, the enzyme involved in the generation of siRNA.

Along with f2, Zinder and Loeb discovered filamentous phage f1, containing a single-stranded DNA genome. In addition to providing easy access to single-stranded DNA for sequencing, f1 made possible his development of phagemids (plasmid-filamentous phage hybrids), which led to remarkable biotechnology achievements such as phage display and, more recently, the nano-battery. Having determined (via mutants, of course) that two sites on double-stranded f1 replicative form DNA made it susceptible to the "B" restriction system described by Werner Arber and colleagues (Arber and Linn 1969), Zinder was eager to explore host restriction and modification at a biochemical level. A puzzling observation was that the *EcoB* enzyme did not produce a clear pattern of recognizable fragments, even though Hamilton Smith at Johns Hopkins was obtaining clean DNA fragments using a restriction enzyme from *Haemophilus*.

This mystery was solved when it was found that *EcoB* requires ATP but the *Haemophilus* enzyme does not, and that the ATPase activity of *EcoB* is dependent on the length of DNA presented to it. It may have been in this context that Norton ruefully admitted the power of a “trivial” biochemical experiment to overthrow the most elegant genetic deduction. After some head scratching, the conclusion became clear: the genetically defined sites on ϕ 1 DNA are entry sites for the nuclease, which uses ATP to travel along the DNA and eventually cut it. That made these type I restriction enzymes interesting, but not very useful; the utility of type II restriction enzymes, such as the original from *Haemophilus*, is difficult to overestimate.

Norton retained the youthful informality of a wunderkind even as he matured. He could often be found perched cross-legged on the horizontal freezer in the open “big lab” that he designed, talking with students (whom he referred to as “Zinder Kinder”), scrutinizing their plates. Former post-doc (now a Duke University emeritus professor) Robert E. Webster remembers that Norton “was always motivating you by being around and getting you thinking about the big picture. With Norton, it was not hard to always see the forest and not just the trees.” His lively intelligence did not allow for linear conversation: his ideas bounced and ricocheted in many directions. An ability to follow his intellectual leaps and discontinuities may have been what selected for the outstandingly able students whom he trained. One of them, current Rockefeller University professor Jeffrey Ravetch, eulogized

Norton: “He expected greatness; he demanded independence, creativity, and critical thinking.”

Zinder’s restless intelligence led him to wider stages on which he could be outspoken and brutally frank. When he became aware that the tumors of cancer patients treated with an initially effective drug eventually became resistant to that drug, necessitating a second drug to which the tumor became resistant, he crossed the street to the Sloan-Kettering Institute for Cancer Research to explain mutation frequencies to the doctors and why treating with multiple drugs simultaneously should prevent the appearance of “escape” mutants. In science policy, he argued for proceeding slowly with recombinant DNA experiments until potential pitfalls could be discerned; he chaired a U.S. Army committee and guided generals to low-risk methods for disposal of aging chemical weapons. And he joined Jim Watson, his great friend (and one-time competitor), in supporting the National Institutes of Health human genome project at a time when many scientists opposed it as an expensive sink for research resources.

Zinder is survived by two sons, Stephen, a professor of microbiology at Cornell University, and Michael, a lawyer in New York; his daughters-in-law Chris and Charlotte; and five grandsons. His wife, Marilyn, died in 2004.

Literature Cited

Arber, W., and Linn, S., 1969 DNA modification and restriction. *Annu. Rev. Biochem.* 38: 467–500.

Marjorie Russel and Peter Model