OBITUARY

Marshall Nirenberg (1927–2010)

A humble, gentle and visionary giant of molecular biology.

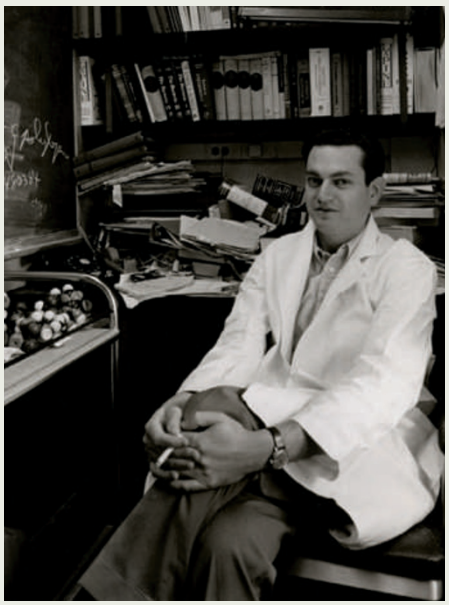
Marshall Warren Nirenberg was only 34 years old when, in August 1961, he reported his studies on the genetic code at the International Congress of Biochemistry in Moscow. For this and subsequent work he was awarded the 1968 Nobel Prize in Physiology or Medicine, together with Gobind Khorana and Robert Holley, "for their interpretation of the genetic code and its function in protein synthesis." He was the National Institutes of Health's first Nobel laureate, and achieved these discoveries by a series of brilliant biochemical approaches — thereby disproving Ed Tatem's 1958 prediction that it would take a lifetime to break the code.

His fascination with biology began early in his life. Following a family move in his youth from New York City to a Florida dairy farm, he became an expert naturalist — studying birds, catching and releasing snakes, and collecting spiders. One previously unrecognized spider species from his collection was named "Marshall" by the American Museum of Natural History in New York City. His fascination with nature endured for a lifetime.

Nirenberg graduated in 1948 from the University of Florida in Gainesville, and obtained a PhD in carbohydrate biochemistry from the University of Michigan in Ann Arbor. He first came to the National Institutes of Health in 1957, joining the laboratory of Gordon Tomkins there three years later. Although Nirenberg's bold plan to decipher the genetic code was considered "suicidal" by one senior scientist, Tomkins was a supporter of the endeavour. On reflection, Nirenberg himself commented that the "goal was worth the risk".

Indeed it was. His research answered the central question of how the hereditary information stored in DNA is translated into cellular proteins. He developed a succession of *in vitro* biochemical assays that led to the determination of the nucleic-acid content of the cell, the finding that trinucleotide sequences (codons) define a protein's amino-acid sequence, and the discovery of 'punctuation signals' — codons that mark the beginning and end of a peptide — and of the universality of the genetic code. Each approach was simple in execution but elegant in concept.

The first assay Nirenberg developed was a bacterium-based *in vitro* protein-synthesis method. Together with Heinrich Matthaei, he made the crucial discovery that RNA, rather than DNA, programmed the synthesis of proteins. This finding led to a bold shift to studying synthetic RNA polymers — composed of single, or random mixtures of,



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uracil, cytosine, adenine and guanine bases — as the 'messenger' RNA intermediate. And an outcome of this extraordinarily successful approach was the observation that polyuracil directed the synthesis of only polyphenylalanine.

On hearing of this breakthrough — DNA to mRNA to protein — described by Nirenberg in a small session of the 1961 Moscow congress, Francis Crick asked him to repeat his presentation to the entire congress in a special session. Nobel-prizewinning biologist Harold Varmus, at the time an aspiring student of English who was travelling in Moscow, remembers the presentation as being instrumental in changing the direction of his career from literature to science. At a more general level, the public announcement of this simple *in vitro* assay for protein synthesis triggered the race to match the base content of the genetic code to each of the 20 amino acids that constitute proteins.

Two technologies were, however, required to prove that the code was triplet and to determine the sequence order: an *in vitro* assay for molecules that interact with ribosomes (cellular factories for protein synthesis); and a method for generating synthetic codons to artificially recreate the process of translation. Nirenberg and Philip Leder developed a simple translation assay in which they used radioactively labelled aminoacyl transfer RNA, partially purified ribosomes and RNA codons to detect the stable translation complex. This elegant assay nonetheless required synthesis of all 64 possible codon triplets from the four bases to determine exactly which codons translate into each of the 20 amino acids. Nirenberg's laboratory synthesized the codons biochemically using an enzyme-based approach, and showed that an adenine triplet — but not a doublet — made only the tRNA for lysine and bound to the ribosome.

The translation assay was also a key analytical tool for subsequent achievements by other researchers in the field (including myself); these included the chemical, rather than enzyme-based, synthesis of codons by Gobind Khorana, which led to the rapid assignment of codons by both his and Nirenberg's laboratories, the finding that a single tRNA molecule could recognize more than one codon (the wobble concept), and the demonstration that the genetic code is universal across species — the topic of Nirenberg's address at a Vatican-sponsored meeting in 2008. Moreover, deciphering the genetic code made possible the spectacular era of DNA sequencing, recombinant DNA technology and genome projects that followed.

After his seminal work in molecular biology, Nirenberg redirected his research to neuroscience, investigating, among other questions, the cellular and biochemical basis of opiate addiction, and developing cellular models for the formation of the synaptic junctions between neurons. Throughout his career, Nirenberg put great emphasis on nurturing young scientists, and many of the researchers he trained are award-winning leaders in their own fields. One example is the American Chemical Society's recognition a few months back of his 'code team', nominated by Nirenberg himself.

Nirenberg's character created the environment I remember while working as a research associate in his lab. He combined an engaging, but retiring, personality with scientific focus. His laboratory, although small (112 square metres), fostered collaborative and successful ideas. His unusual circadian rhythm meant late-night planning of experiments, and excitement in the laboratory about implementing them the following afternoon. He strove to develop several approaches to a single question, while always seeking simplicity and accuracy. Our papers, for example, seldom had fewer than ten drafts in the pursuit of precision and clarity.

Nirenberg died from cancer on 15 January. For 41 years, Nirenberg's partner in life and science was, until her death, his first wife Perola Zaltzman. His second wife, Myrna Weissman, also shared his love of science, and her extensive family brought youth and excitement to Nirenberg's final years.

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