Marshall Warren Nirenberg

New York, NY, USA, 10 Apr. 1927 - 15 Jan. 2010

Nomination 24 June 1974

Field Biochemistry

Title Chief of the Laboratory of Biochemical Genetics, Rockville Pike, MD, USA

Commemoration – Marshall Nirenberg was born in New York on 10 April 1927 and died this year, on 15 January 2010. As a child he was diagnosed with rheumatic fever and, because of this, the family moved to Florida. In due course he studied for his undergraduate degree at the University of Florida in Gainesville and did his Ph.D. in biochemistry in 1957, at the University of Michigan in Ann Harbor. He joined the National Institutes of Health shortly after and devoted his research to the relationship between DNA, RNA and proteins, and more specifically, to deciphering the genetic code. I would now like to tell you an anecdote of this period, in which I was directly involved. I was at the NIH at that time, as a professor on sabbatical, and one day Marshall came to my lab and asked me whether by chance I had some poly-L-phenyl-alanine. I answered him that I did not have any, but when he asked me whether I knew in which solvent poly-L-phenylalanine was soluble, I looked up a paper which I had published some years earlier in JACS, on mechanism of polymerization, and found that poly-Lphenylalanine was not soluble, even in such strong solvents as dimethylformamide and dimethylsulfoxide, but was soluble in a saturated solution of hydrogen bromide (HBr) in glacial acetic acid. Such a reagent is used to remove blocking groups such as carbobenzoxy from amino functions, and is used a lot in peptide synthesis. At that moment, for reasons of my research, I was bubbling in my hood HBr through glacial acetic acid. I gave Marshall some of this reagent, and thanks to it, he found that UUU (uridine-uridine-uridine) dictates the formation of Phe, and thus broke the genetic code. I am actually the only person he thanks in the PNAS paper, for which he received the Nobel Prize in Physiology and Medicine in 1968, which he shared with Robert Holley and Gobind Khorana. Now, who in his right mind would use this reagent as a solvent? Some years earlier, I had two test tubes in a jar in my office. One contained polyL-phenylalanine and the other poly-carbobenzoxylysine. My colleague picked what he believed to be blocked polylysine, and after a few minutes he returned and said: 'I cannot understand – it dissolved but did not give the characteristic carbon dioxide bubbles'. I answered: 'Oh gosh, I made a mistake and gave you the wrong test tube', but I also made a note that polyL-phenylalanine dissolves in HBr in glacial acetic acid. If that mistake had not occurred, I could not have helped Marshall in his discovery. A few months later, we were all together at the International Biochemical Congress in Moscow in August 1961. Marshall gave a short talk at one of the many workshops which Francis Crick attended. With the force of his personality, he demanded that Marshall should repeat the talk in the big Hall before thousands of listeners and the rest is history. In 1965 he received the National Medal for Science. In 1974 he was appointed to the Pontifical Academy of Sciences. He was a member of many other learned societies, including the American Philosophical Society, American Academy of Arts and Sciences, National Academy of Sciences USA, and National Institute of Medicine. From 1966 he was Chief of the Laboratory of Biochemical Genetics of the National Heart Institute of NIH, Bethesda. He continued the extension of deciphering the genetic code of all amino acids. At a later stage he entered the field of neurobiology and established many clonal lines of mouse neuroblastoma cells. A neuroblastoma glioma somatic hybrid cell line was generated that expresses abundant opiate receptors, which was used as a model system to explore the mechanism of opiate dependence. These cells were also used as model systems to study many properties of neurons. Marshall Nirenberg was modest, friendly and a lovable character. He died just a few months ago. Blessed be his memory.

Michael Sela

Most important awards, prizes and academies

Awards: Modern Medicine Award (1964); Award from the Department of Health, Education, Welfare, 1963; National Medal for Science (1965); Louisa Gross Horwitz Prize (1968); Nobel Prize in Physiology or Medicine for deciphering the genetic code, shared with Gobind Khorana and Robert Holley (1968). *Academies*: American Society of Biological Chemistry; American Chemical Society; American Neurochemistry Society; Biophysical Society; American Association for the Advancement of Science; European Academy of Sciences and Arts; Society for Developmental Biology; Washington Academy of Sciences; National Academy of Sciences, USA; National Academy of Medicine, USA; American Academy of Arts and Sciences; American Neurological Association; Leopoldina Deutsche Akademie der Naturforscher; European Academy of Sciences and Arts; American Philosophical Society; Pontifical Academy of Sciences.

Summary of scientific research

Since 1966 Professor Nirenberg was Chief of the Laboratory of Biochemical Genetics at the National Heart, Lung, and Blood Institute of the National Institutes of Health in Bethesda, MD. Dr. Nirenberg and his coworkers deciphered the genetic code. First, they determined the base compositions of RNA codons by directing cell free protein synthesis with randomly-ordered synthetic polyribonucleotides; then, they determined the nucleotide sequences of RNA codons by directing the binding of aminoacyl-tRNA ti ribosomes with trinucleotides of known sequence. They also showed that single-stranded RNA, but not double- or triple-stranded RNA, is a template for protein synthesis. Dr. Nirenberg then entered the field of neurobiology and established many clonal lines of mouse neuroblastoma cells. He found that some cell lines synthesized catocholamines, whereas others synthesize acetylcholine. Elevation of cellular cyclic AMP for a number of days shifted the cells from a relatively undifferentiated state to a differentiated state where many neural properties were expressed. Five cell lines were found that form abundant synapses with cultured striated muscle cells. A neuroblastoma-glioma somatic hybrid cell line was generated that expresses abundant opiate receptors, which was used as a model system to explore the mechanism of opiate dependence. Dual regulation of adenylate cyclase by morphine was shown to account for morphine dependence, tolerance, and withdrawal. The neuroblastoma and somatic hybrid cell lines that were established have been used as model systems to study many properties of neurons. Dr. Nirenberg and his colleagues discovered and characterized *Drosophila* and mouse homeobox genes. He has focused on one of the *Drosophila* homeobox genes, vnd-NK-2, which initiates the neural pathway of development in the ventral portion of the neuroectoderm and gives rise to part of the ventral nerve cord. His final studies focused on determining how a pattern of neuroblasts that expressed the vnd-NK-2 gene was formed in the central nervous system.

Main publications

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and Schneider, M.D.), ‘A topographic gradient of molecules in retina can be used to identify neuron position’, *Proc. Natl. Acad. Sci. USA*, 78, pp. 2145-9 (1981); Nirenberg, M.W. (with Wilson, S., Higbashida, H., Rotter, A., Krueger, K., Busis, N., Ray, R., Kenimer, J.G. and Adler, M.), ‘Modulation of Synapse Formation by Cyclic Adenosine Monophosphate’, *Science*, 222, pp. 794-9 (1983); Nirenberg, M.W. (with Kim, Y.), ‘Drosophila NK-homeobox Genes’, *Proc. Natl. Acad. Sci. USA*, 86, pp. 7716-20 (1989); Nirenberg, M.W. (with Mellerick, D.M.), ‘Dorsal-Ventral Patterning Genes Restrict NK-2 Homeobox Gene Expression to the Ventral Half of the Central Nervous System of Drosophila Embryos’, *Developmental Biology*, 171, pp. 306-16 (1995); Nirenberg, M.W. (with Gruschus, J.M., Tsao, D.H.H., Wang, L.-H. and Ferretti, J.A.), ‘The Three-dimensional Structure of the vnd/NK-2 Homeodomain-DNA Complex by NMR Spectroscopy’, *J. Mol. Biol*., 289, pp. 529-45 (1999).