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A Brief Account of an Adventurous Journey in the Neurosciences

A Tribute to the Contributions of Dr. Kresimir Krnjević

John Phillis
Department of Physiology, Wayne State University, Detroit, Michigan, U.S.A.

Dr. Kresimir Krnjević, the individual honored in this Festscrift publication, was born in Zagreb, the capital of Croatia, in 1927. His father, Juraj Krnjević, was an active member of the Croatian Peasant Party who, after the beginning of King Aleksandar's dictatorship and the formation of the Kingdom of Yugoslavia in 1929, moved his family to Geneva. During the 10 years that the family spent in Switzerland, Dr. Krnjevic became fluent in French. The family returned to Zagreb in 1939, only to leave again in 1941, when the Germans invaded Yugoslavia. As a member of the Yugoslav Government in exile, his father moved to England, but Dr. Krnjevic and his sister were sent for safety to Capetown, South Africa, where he learned the English language. After finishing high school, he moved to Great Britain at the beginning of 1944 and started his tertiary education in the medical school at Edinburgh University, graduating MBChB in 1949. At this point, he made the career decision to undertake PhD. training in the physiology department of the university under the supervision of David Whitteridge Dr. Krnjevic received an Honours BSc. in 1951 and PhD in 1953. His first scientific publication was a proceedings paper in the *Journal of Physiology* (1952, 118 3P-4P), titled "The perfusion of the frog sciatic nerve with electrolyte solutions"[1]. This was followed by two full papers in 1954 on the perineural sheath as a diffusion barrier around peripheral nerves. All of these initial publications were under solo authorship.

Post-doctoral studies took Dr. Krnjević and his wife, Jeanne, to the University of Washington in Seattle (1954-1956), where he continued his studies on Na and K ions in degenerating cat nerves; and where he also recorded age-dependent changes in somatosensory responses in the cortex of kittens. Dr. Krnjević then undertook a second post-doctoral position in the John Curtin School of Medical Research at the Australian National University in Canberra (1956-1958), where he initiated research with R. Miledi on adrenaline and the failure of neuromuscular transmission and other publications on neuromuscular transmission. Both also collaborated with D. R. Curtis on a project to record intracellularly from sacral motoneurons. While in Canberra, he

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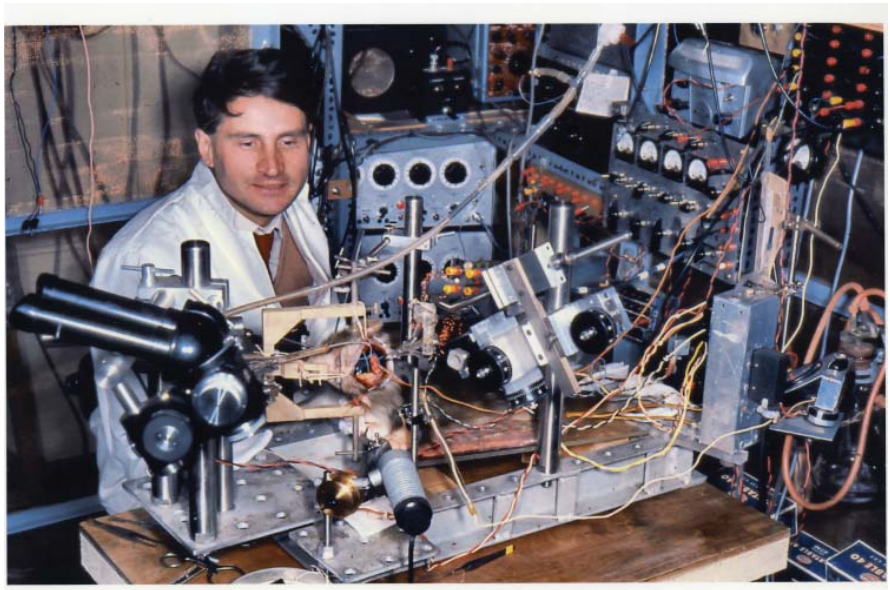

Kresimir Krnjević in his Babraham laboratory recording neuronal activity from a monkey cerebral cortex in 1962.

collaborated with J. C. Eccles (a subsequent Nobel Prize winner) on intracellular recordings from primary afferent fibres and neurons in the spinal cord. In retrospect, it is apparent that his experiences in Canberra set the stage for many of his subsequent explorations of the properties of the central nervous system.

I was fortunate in starting my PhD studies in 1958 at the department of physiology of the John Curtin School of Medical Research following graduation as a veterinarian at the University of Sydney, and was therefore able to become acquainted with Dr. Krnjević during the weekly departmental seminars and the daily gatherings in the faculty tea room.

Following his experiences in Canberra, Dr. Krnjević accepted a position as Scientific Officer at the Agricultural Research Council Institute of Animal Physiology in Babraham, Cambridge, U.K., under the recently appointed director (J. H. Gaddum). The institute had attracted a stellar cast of neuroscientists, including C. O. Hebb, V. P. Whittaker, M. Vogt, R. D. Keynes, D. F. Sharman, J. F. Mitchell R. Laverty, A. Silver, A. D. Bangham, and R. M. Dawson, making it one of the premier sites for neurophysiological/neuropharmacological/neurochemical studies in the U.K. Once installed, Dr. Krnjević rapidly amassed the equipment necessary to replicate that which he had been using in Canberra to study neurons in the central nervous system. He was assisted in this by the mechanical engineering facilities at Cambridge University.

As I was finishing my PhD. program under D.R. Curtis, Eccles announced that on a recent trip to the U.K. he had arranged, with Sir Henry Dale, for me to receive a Wellcome Research Fellowship for postdoctoral studies at the ARC Institute of Animal Physiology for 1961-1962. Working with Dr. Krnjević, we initiated original studies on the neuropharmacology of cat (and some monkey and rabbit) cerebral cortical neurons. For me personally, this was an exceptionally productive and exciting period of my life. Using 5-barrelled micropipettes, we were able to demonstrate a slow excitant muscarinic action of acetylcholine on cerebral cortical neurons, including corticospinal projection neurons (Betz cells). After testing glutamate

and GABA on cortical neurons we suggested that these agents were ideally suited to be excitatory and inhibitory transmitters, respectively, in the cerebral cortex. The subsequent development of blockers for these amino acids confirmed this proposal.

In 1964, Dr. Krnjević accepted an invitation to be a Visiting Professor in the department of physiology at McGill University in Montreal. Given his ability to converse freely in both English and French, Dr. Krnjević found Montreal to be an attractive location, and he accepted a position as director of the anesthesia research dDepartment at McGill, holding this position from 1965 to 1999. He also served as chair of the department of physiology at McGill from 1978 to 1987. In 1978, he was honored by an appointment to a named professorship as the Joseph Morley Drake Professor of Physiology. Dr. Krnjević formally retired in 1999 but remains active as the Joseph Morley Drake Emeritus Professor of Physiology.

Dr. Krnjević's many scientific achievements have been recognized by his being the recipient of numerous national and international awards, including: Fellow of the Royal Society of Canada, 1975- ; Gairdner International Award, 1984; Officer, Order of Canada, 1987; Member, Croatian Academy of Arts and Sciences, 1992; Wilder Penfield Prize, Govt. of Quebec, 1997; and Spiridion Brusina Prize, Croatian Natural Science Assoc. 2001. He also served as the chief editor of the *Canadian Journal of Physiology and Pharmacology* (1972-1978) and as an associate editor of several other journals. Three of his papers have been rated as Citation Classics by Current Contents, which also named him as one of "The 1,000 most-cited contemporary authors" in 1982. The manuscript, titled 'Iontophoretic studies of neurones in the mammalian cerebral cortex, (1963) by Krnjević and Phillis was identified as an "Original Classic Paper" by the *Journal of Physiology* (2005, 569, 1-2).

Over the course of his scientific life, Dr. Krnjević has published some 237 research papers and reviews, and co-edited four books. He has trained 54 graduate students/post-doctoral fellows both in North America and Europe, a high proportion of whom have gone on to successful, independent research careers. The contents of this Festschrift illustrate just how effectively he has been able to transmit his enthusiasm for, and insights into, scientific investigation to these individuals.

During the past 50 years, Dr. Krnjević's research activities have been largely focused on in situ or in vitro studies on the cerebral cortex, hippocampus, cuneate nucleus, and spinal cord, with the emphasis placed on the actions of putative neurotransmitters and the changes in neuronal membrane permeability's to ions such as sodium, potassium, and calcium. A particularly interesting report was the publication by K. Krnjević, R. Pumain, and L. Renaud,[3] which attributed the excitant actions of acetylcholine via muscarinic receptors on cerebral cortical neurons to a reduction in the resting membrane K^+ conductance, also reducing the delayed K^+ currents associated with the action potential.

The original findings revealed in subsequent studies by Dr. Krnjević and his colleagues are too numerous to describe in this brief introduction to the Festschrift, but many of the subsequent reports will refer to earlier publications from the laboratory.

With the Festschrift in mind, I contacted Dr. Krnjević recently to enquire if he had ever defined his scientific pursuits over the years as occurring in overlapping phases. How did one set of projects lead to the next? I found his reply to be most interesting and take the liberty of citing it here:

"I've never tried to analyze the progress of my 'scientific pursuits'. If there is a pattern, it's in a progressive move from the utmost periphery (frog sciatic nerve, crayfish stretch

receptor, NM junction) up to the spinal cord (in Canberra) then to the cortex (at Babraham) on the one hand; and at the same time and overlapping, from basic cellular/synaptic mechanisms towards cognitive function, consciousness, anesthesia, and most recently even behavioral correlates.[4] In a sense, that's what I had in mind all along. When I saw Phillip Eggleton (in Edinburgh) about graduate work, he asked me what aims I had. Having recently taken a course in psychology, I said that I'd like to work towards bringing psychology and physiology closer. It's curious that only now, nearly 60 years later, can I see myself moving somewhat along that arduous path."

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