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OBITUARY

Alexander George Karczmar (1917–2017)

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Photograph: Alexander George Karczmar ('Niki'), 2017
Courtesy of Marion, Chris, and Greg Karczmar.

The neurochemistry community at large and the Advisory Board of The International Symposia on Cholinergic Mechanisms (ISCM) mourn the loss of Alexander George Karczmar, the elected Honorary President of these international symposia, who passed away peacefully in his Chicago home at the age of 100 on August 17, 2017. For many of us Alex was the essence of cholinergic signaling, and personified its versatile power to send messages between the brain and the peripheral tissues and organs, and to connect between body and soul.

Alex Karczmar (known to many as *Niki*) was born on May 9, 1917, in Warsaw, Poland, where he was raised and educated; first, at the Collegium High School, and subsequently, at the Józef Piłsudski University of Warsaw, where he studied biological and medical sciences and was confronted with antisemitism. In 1939, he emigrated to the United States, where he studied zoology and biophysics at the Graduate School of Columbia University, New York. We referred to the Wikipedia article on Alex to gather information about his early scientific education, and learned that his PhD supervisor was the biophysicist of the quantal nature of vision, Selig Hecht. He also worked on limb regeneration with Oscar Schotte of Amherst College, Massachusetts, and on the latency of neuronal relaxation with Alexander Sandow at the New York University. Alex earned his PhD degree in 1947 and became an Assistant and then Associate Professor of Pharmacology and Therapeutics at the Georgetown University, Washington, DC (1946–1953), where he worked with Theodore Koppanyi, who initiated much of today's forensic science, and introduced him to the cholinergic field. Subsequently, Alex became a fellow at the Sterling Winthrop Research Institute in New York (1953–1956), where he developed his neurochemical skills and contributed to the development of ambenonium (Mytelase), a drug that was used for the treatment of myasthenia gravis, and of the vasodilator amotriphene (Myordil).

These interests and achievements led Alex to join the faculty of the Loyola University of Chicago Medical Center, where he worked for 60 years. For 30 years (1956–1986), he served as Professor and Chairman of the Department of Pharmacology and Experimental Therapeutics, and as the Director of its Institute for Mind, Drugs and Behavior. For the subsequent 30 years (1986–2017), he was an energetic Professor Emeritus of Pharmacology at the Loyola University's Stritch School of Medicine, and a trustee and secretary of the Chicago Association for Research and Education in Science.

Alex initiated his work on the cholinergic system by investigating the mechanism of action of the highly toxic organophosphorus anticholinesterase nerve agents and damage that they cause to organs and tissues. He studied their

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effects on the synapse, as distinct from their direct effect on acetylcholinesterase, their teratogenic impact, the postnatal behavioral outcome following prenatal exposure to them, and the damage that they cause to the blood–brain barrier. These studies contributed to the then novel understanding of the morphogenetic and scavenger roles of the cholinesterases. In the context of this expertise, Alex served as an advisor and consultant to the U.S. military in studying the toxic actions of organophosphates, and contributed significantly to the development of novel therapeutic approaches for protection of both soldiers and civilians from the acute and chronic damage that they cause. The Wikipedia article adds that he also served as a senior research consultant to the Department of Veterans Affairs (VA) (1956–2008) and to the Surgeon General of the United States (1987–2017). He participated in several NIH Study Sections, in the Toxicology Committee of the United States National Academy of Sciences, and served on the editorial boards of *Neuropharmacology*, the *Journal of Pharmacology and Experimental Therapeutics*, the *European Journal of Pharmacology*, *Archives Internationales de Pharmacodynamie et de Thérapie*, among others.

Over the years, Alex widened his perspective from a focus on the toxicology of anticholinesterases to encompass multiple aspects of the cholinergic system. In the 1950s, in parallel to Thesleff, he demonstrated the phenomenon of desensitization (receptor inactivation) at the neuromuscular synapse, and described the reciprocal process of sensitization, which is inducible by several drugs such as oxamides and NaF, and which, today, is ascribed to an allosteric receptor change. He also studied the structural nature of central cholinergic receptors and the similarity between peripheral and central muscarinic receptors. In the 1950s and 1960s, together with Kyozo Koketsu, Syogoro Nishi, and Nae Dun, Karczmar discriminated between ganglionic nicotinic, muscarinic, and peptidergic receptors, and described the involvement of second messengers in ganglionic transmission. During the 1960s, he contributed to establishing the pre-eminent role of the central cholinergic system in phenomena such as seizures, electroencephalography (EEG) rhythms, paradoxical sleep, and behavioral changes; in functions such as respiration; in behaviors such as aggression; in perceptions such as nociception, learning, addiction, obsession, and fixation; and in sexual activity. This broad spectrum of studies provided early neurochemical and pharmacological evidence for the interaction between the cholinergic and other neurotransmitter systems. He further demonstrated the impact of cholinergic agonists on schizophrenic behavior, preceding by many years the re-introduction of ketamine as a neurochemical modulator of mood disorders, and proposed that the cholinergic system contributes significantly to alertness, cognitive behavior, and the mammalian 'realistic' appraisal of the environment.

From 1970s onward, Karczmar moved into more psychobiological terrain and explored the 'self' (the 'I') by tracing the concept of the body–mind relation to the earliest history of mankind. He stressed the need to differentiate the 'self' from cognition and perception, and suggested that the current state of neuroscientific knowledge is inadequate to yield an intelligible and parsimonious explanation of the 'I'. Much of his work from then forward was ahead of its time in bridging between neurochemistry and psychobiology by studying the association of 'self' with the cholinergic signaling pathways.

Alex had ties to leading figures in neurochemistry and neuropharmacology around the globe, and was involved in organizing international symposia in places such as Florence, Italy in 1969 with S. A. Barnett and S. Garattini, Chicago in 1978 with Sir John Eccles, and Paris (also in 1978) with Jacques Glowinski, and of course, was intimately involved in all 15 of the ISCM. He was awarded a Guggenheim Fellowship for his studies on paradoxical sleep with Dr. Vicenzo Longo of the Istituto Superiore di Sanita, Rome, and a Senior Fulbright Fellowship for his work on ontogenetic effects of anticholinesterases in primates, together with Dr. William McBride at Foundation 41, Sydney, Australia, of which he subsequently became the acting medical director (1988–1989). He was a charter fellow of the Sherringtonian Society (1969–2017) and a founding member of the American College of Neuropsychopharmacology (1963–2017). His scientific awards include the VA Merit Citation (2002), City of Milano Medal (1969), an honorary professorship at Kurume University, Japan, and visiting professorships at Université Laval, Quebec, the Polish Academy of Sciences, INSERM, Paris, and the University of Pennsylvania.

Altogether, Karczmar published some 400 research papers, reviews, and book chapters, and authored, co-authored, or edited seven books. His textbook, *Exploring the Vertebrate Central Cholinergic Nervous System* (Springer, New York, 2007), reviews the past and the present status of central cholinergic signaling, covering its physiology, pharmacology, and biochemistry, its ontogeny and phylogenesis, and its role in functions, behaviors (including cognition), the 'self', and disease states such as schizophrenia and Alzheimer's disease.

Throughout his career, Alex attributed great value to his role in instigating and maintaining the triennial series of International Symposia on Cholinergic Mechanisms (1970–2016, see https://iscm.sciencesconf.org/). He was a founding member of these global meetings, an active participant in them for over 30 years, and in recognition of his seminal role, was elected Honorary President of the International Advisory Board for these conferences during ISCM XIV, held in Hangzhou, China, in 2012 (see https://iscm.sciencesconf.org/resource/page/id/6).

Alex fondly called his multifarious colleagues in cholinergic research 'cholinergikers' and we feel that he himself was the ultimate 'cholinergiker'. His many friends and

colleagues will remember him affectionately, and will cherish his memory.

Alex is survived by his wife Marion, two sons Chris and Greg, and four grandchildren Alena, Alexandra, Malachi, and Naima.

Acknowledgments and conflict of interest disclosure

The authors declare no conflict of interest.

