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IN MEMORIAM

Edward F. Domino, Ph.D. (1924–2021)

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Edward F. Domino, Ph.D., the pioneering neuropharmacologist and a coiner of the term "dissociative anesthesia" died on November 3, 2021 at the age of 96. At the time of his death, Ed was Professor Emeritus of Pharmacology at the University of Michigan, where he spent nearly all of his career.

Ed's early training in both electrical engineering and pharmacology set the stage for his later career studying the electrophysiologic effects of drugs [1]. Ed was born in Chicago in 1924. He served as an electronics technician in the Navy in World War II. Afterward, he graduated from the University of Illinois with bachelor degrees in electrical engineering and "premedicine." He remained at the University of Illinois for his M.D. and M.S. (pharmacology) degrees. With his background in electrical engineering, he initially landed him a part-time faculty position at the University of Illinois assembling an EEG machine.

Ed and his collaborators pioneered the study of phencyclidine and ketamine [2]. In 1953, Ed obtained a position in the Department of Pharmacology at the University of Michigan. His Department Chair, Dr. Maurice Seevers, encouraged him to study in animal models the Parke Davis drug, phencyclidine, promising him a grant that would support the initiation of his research career. Building on Ed's studies, his collaborators Dr. Elliot Luby, Jacques Gottlieb, and colleagues at the Lafayette Clinic of Wayne State University conducted the first study of phencyclidine in psychiatry, published in 1959 [3]. That study was the first to describe similarity between phencyclidine effects in healthy individuals and schizophrenia. This line of research was impeded by limitations in neuroscience of that era. A binding site for phencyclidine was not identified until 1979 and its primary mechanism of action was identified in the 1980s as uncompetitive antagonism of the NMDA subtype of glutamate receptor.

For many, Ed's pivotal characterization of the behavioral and neural effects of the phencyclidine derivative, ketamine, stands as the key accomplishment of his career. Ketamine was shorter-acting and less potent than phencyclidine. Ketamine's ease of use, safety, tolerability, and antinociceptive effects have made it among the most successful human and veterinary anesthetic agents, globally. Ed and his collaborators administered the first dose of ketamine to a human on August 3, 1964 [4]. Sensory distortions were a distinctive feature of subanesthetic doses of ketamine as described by Ed and his colleague, Dr. Guenter Corssen [5], "subjects…felt that they were in outer space or had no arms or legs" (p.36) even though their sensory reflexes were intact. They explained this paradox on the basis of their electrophysiologic studies, that suggested that ketamine produced a sort of "sensory deprivation" state, i.e., sensory input would be received by "cortical receiving areas but fail to be perceived in some of the association areas because these are depressed." This led them to suggest that "the state induced by CI-581 (ketamine) be called, 'dissociative anesthesia.'" (p.37). They also used the term "dissociation" to describe the alterations in perception produced by ketamine and "dissociative anesthetics" became a widely used descriptor for NMDA glutamate receptor antagonist anesthetics.

Ed's seemingly limitless passion for scientific innovation led him to make contributions to many areas of science throughout his long career. As one would expect, he pursued a deep understanding of the neuropsychopharmacology of ketamine. In the 1960s, he and his collaborators also studied the psychedelics. Later, he explored cannabis and nicotine effects on brain function. His work spanned research conducted in rodents, non-human primates, healthy humans, and patient populations. He collaborated with scientists around the world, who were drawn to his creativity and magnetic enthusiasm; traits that were characteristic of him throughout his career. In collaboration with these scientists, he became engaged in research utilizing approaches and technologies that emerged relatively late in his career including molecular genetics, positron emission tomography and functional magnetic resonance imaging. Although he retired in 2000, he remained quite active thereafter.

The importance of Ed's contributions to neuroscience and psychiatry became clearer as subsequent generations of scientists revisited the work that Ed, Elliot Luby, and others began in the 1950s. An influential paper by Drs. Daniel Javitt and Stephen Zukin drew attention to the potential relevance of NMDA glutamate receptor signaling to schizophrenia [6]. With assistance

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from Ed and Elliot Luby, my collaborators and I were able to obtain permission to study the cognitive and behavioral effects of ketamine in healthy subjects [7], re-launching the effort to understand the mechanistic basis for the schizophrenia-like effects of ketamine and to use the resulting insights to better understand the systems neuroscience of schizophrenia and to develop novel therapeutics for this disorder.

The discovery of the rapid antidepressant effects of ketamine in depressed patients [8] was very exciting to Ed and it builds on his early studies (to hear him lecture on this topic, see: https://www.med.umich.edu/mva/library.html). In Ed's writings, ketamine was a powerful psychopharmacologic tool that carried medical risks, particularly the risk for addiction. However, he was confident that one could "tame the ketamine tiger" to take advantage of its therapeutic potential [4].

Ed was beloved by those who worked closely with him. The University of Michigan created the Edward F. Domino Lecture in Consciousness Science in 2016, the Edward F. Domino Research Professorship in 2017, and the Edward F. Domino Research Center in 2018 (https://medicine.umich.edu/dept/domino-research-center/message-director).

He is predeceased by his wife, Antoinette (Toni) and his son Lawrence. He is survived by his sister, Pat (Tony) Torres; sister-in-law, Lucy Domino; and his children, Karen (Gene) Domino, Debra (Craig) Pulley, Kenneth (Zarina) Domino, and Steven (Karen) Domino. He also had ten grandchildren and four great grandchildren. He is also survived by Kathleen Baines, his partner for 13 years, who joined him frequently at ACNP, SOBP, and CINP meetings. He was accepted into ACNP membership in 1961 and was a Fellow Emeritus.

I am greatly saddened by Ed's passing, but every time I think of him, I smile. I never saw him less than completely in the thrall of a new idea or project. One of his greatest pleasures was to introduce and then revel in the success of his trainees and junior colleagues. Ed was very helpful when I approached him the late 1980's to get advice about testing ketamine. Since that time, he has been a valued advisor and supporter. In 2016, I was greatly honored to deliver the inaugural Edward F. Domino Lecture in Consciousness Studies, within the University of Michigan Center for Consciousness Science. It was wonderful opportunity to thank him for his contributions to our field and to celebrate his life and career with him, his family, colleagues, and trainees.

Donations in Ed's memory may be made to support the Edward F. Domino Research Center at the University of Michigan (victors.us/edwarddomino).

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Consultant Note: – The Individual Consultant Agreements listed below are less than $5,000 per year

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NON Federal Research Support

AstraZeneca Pharmaceuticals provides the drug, Saracatinib, for research related to NIAAA grant "Center for Translational Neuroscience of Alcoholism [P50AA012870, years 16–20]

Novartis provides the drug, Mavoglurant, for research related to NIAAA grant "Center for Translational Neuroscience of Alcoholism [P50AA012870, years 21–25].

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ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41386-022-01280-x.

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