

Obituary

Philippe Ascher (1936–2022)

With the passing away of Philippe Ascher, a giant of neuroscience and an unanimously respected guide of the French neuroscience community has disappeared.

Philippe Ascher was born in a Jewish family originating in Hungary and in France. Philippe Ascher's father, a left-leaning medical doctor, took pride in the fact that his first child was born on the year (1936) when the socialist Léon Blum led the Popular Front coalition to electoral victory. But he did not have a blind faith in his country's future. Shortly before the outburst of war, he relocated his practice and his family from Metz, in northeastern France, to the Lot region in the southwest. This prescient decision certainly contributed to safeguarding the family during the war.

Philippe Ascher was tempted by medical studies but eventually opted for scientific research. Trained at the Ecole Normale Supérieure (ENS) in Paris, he started his scientific career doing electrophysiological recordings in cats. He soon shifted to intracellular recordings in the simpler nervous system of the marine mollusk *Aplysia*, with the aim of deciphering basic cellular mechanisms underlying complex neuronal functions. Alongside the parallel studies by Eric Kandel, Philippe Ascher's work in the 1970s and 1980s (together with his wife, JacSue Kehoe) established some of the current notions on the action of neurotransmitters in this system.

In 1970, in a rather unexpected consequence of the 1968 upheaval of the French universities, Philippe Ascher was given the opportunity to create a neurobiology laboratory at the ENS. This laboratory functioned as a collective enterprise involving Ascher's wife, JacSue Kehoe, Hersch ("Coco") Gerschenfeld, and a few young colleagues. The rigor, originality, and cooperation in this laboratory, combined with Philippe Ascher's benevolence, humor, and profound lack of interest in frantic speed and competition, created an environment that distinguished it from many other laboratories. This laboratory quickly attracted world-

wide recognition, and it served as a cradle for many young neuroscientists from all origins.

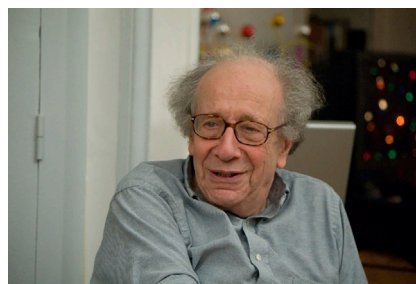
In the early 1980s at the ENS laboratory, Philippe Ascher shifted back to mammalian synapses. Based on his previous work in *Aplysia*, he demonstrated that several blockers of acetylcholine-sensitive channels of the autonomous nervous system act by plugging the open channel; furthermore, he showed that when the blocker was electrically charged, the block was influenced by the membrane potential—and the more so if the blocker was doubly charged. These studies had a profound impact on our understanding of the mode of action of pharmacologically important drugs, and they also paved the way to the first great "hit" of Philippe Ascher's career, the discovery of the block of NMDA receptors (NMDARs) by extracellular Mg^{2+} ions.¹ By showing that NMDARs were specifically sensitive to blockage by Mg^{2+} ions at negative, but not positive, membrane potential, the work of the Ascher group (together with the parallel work of the Mayer and Westbrook laboratory in the United States) set entirely new standards for studies of mammalian synaptic transmission. Their discovery pinpointed the entrance of the channel associated with the NMDAR as a crucial locus of interaction between presynaptic and postsynaptic activity.

A hallmark of Hebbian synaptic plasticity is that a synaptic change requires simultaneous activation of both pre- and postsynaptic neurons. While Hebbian synaptic plasticity had been proposed in

the 1940s, the underlying mechanism had long remained a mystery. The discovery of the block of NMDAR channels by Mg^{2+} provided an elegant solution to this conundrum. Activation of postsynaptic NMDARs requires not only the activation of the presynaptic neuron, resulting in the release of glutamate, but also the activation of the postsynaptic neuron, resulting in membrane depolarization and relief of Mg^{2+} block. This mechanism is now recognized as the reason why NMDAR-dependent long-term synaptic potentiation (LTP), the most thoroughly studied form of long-term synaptic plasticity, obeys Hebb's principle.

In following years, Philippe Ascher's group pursued groundbreaking studies on the NMDA receptor. Importantly, the group pointed out that NMDAR channels are highly permeant for Ca^{2+} ions. This finding threw light on the role of NMDAR channels in excitotoxicity, and it paved the way to subsequent studies on the key role of the postsynaptic surge in Ca^{2+} in inducing LTP. But, the second jewel of this period is the discovery of the dual agonist action of glutamate and glycine in NMDARs.² The finding that glycine is a mandatory co-agonist of NMDARs came as a surprise, since glycine was previously thought to be inhibitory and it was not expected to act at glutamatergic synapses. It opened new avenues in the study of the regulation of NMDARs and their therapeutic potential that are still actively pursued in the present. The Nowak et al. paper and the Johnson and Ascher paper both appear among the three most-referenced neuroscience papers in recent decades.³

Philippe Ascher stayed at ENS until he resigned from all administrative duties in 2001. As an emeritus professor, he then moved to the nearby Parisian School of Medicine at Saints Pères. In this new environment, he moved away from biophysical studies of ion channels to return to the study of synaptic function. He dedicated himself to experimental work in collaboration with more junior scientists. Together with ENS colleague Mariano Casado and others, he unveiled the role of



Philippe Ascher



Philippe Ascher and his wife JacSue Kehoe at the Laboratoire de Neurobiologie of the ENS in the '90s

presynaptic NMDARs in cerebellar long-term depression (LTD). More recently, in collaboration with Boris Lamotte d'Incamps, he studied the properties of synapses made by axon collaterals of spinal cord motoneurons onto Renshaw cells. These are mixed cholinergic/glutamatergic synapses, thus combining the lifelong interests of Philippe Ascher for cholinergic and glutamatergic receptors.

Apart from his personal scientific work, Philippe Ascher exerted an immense influence as a professor and mentor of young scientists as well as a renovator of the French scientific system. During the 1970s and 1980s, JacSue Kehoe and Philippe Ascher spent their summer months teaching a hands-on introductory course of neurobiology at Cold Spring Harbor. This course served as a bootstrap to a number of prominent neuroscientists in the United States. At ENS, Philippe Ascher stubbornly fought, and eventually abolished, an archaic research-teaching system that had reigned unchallenged for

many decades. He replaced this antiquated system with a modern biology department open to promising young scientists, and he acted as director of this department for years. He also contributed to renovating and modernizing the teaching at ENS, where he exerted a profound influence on generation after generation of students. He was also the organizer of an association called "Qualité de la Science" that lobbied for many years to improve the conditions of development and funding of scientific research in France. In recent years, he developed two systems of MD-PhD careers for French medical students, where there was nothing of the kind before, and he lobbied successfully to raise the money necessary to run these programs. As an emeritus professor at Saints Pères, he would occasionally interrupt his daily experiments to run crash neuroscience courses for the benefit of elated MD students.

Philippe Ascher's personal style was made of simplicity, generosity, and openness. He was passionate about his research and intensely curious about all aspects of science, but also easygoing and full of joie de vivre. He had an uncanny ability to establish an easy communication with students and young scientists, to listen to their questions, and to provide suggestions that sometimes proved as prescient as his father's decision to move to the Lot region. His view of scientific research was not favoring large organizations or heavy technical investments, but rather very small teams and small budgets. As indicated by the name of the "Qualité de la Science" association, he valued quality much more than quantity in science. He was also a firm

believer in the necessity of direct control of any research that came out of his group. He personally performed experiments up to the week preceding his death. He brilliantly showed with his studies on NMDARs that even a team of two people with modest equipment but sharp minds could make landmark discoveries.

Philippe Ascher was an accomplished scholar and humanist. His example will serve as an inspiration for many remaining friends and colleagues.

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