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Obituary: Jacques Glowinski (1936-2020)

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Jacques Glowinski, « Glo » as everybody fondly called him in his lab and beyond, one of the last giants of Neuropharmacology, sadly died from the complications of Covid-19, on November 4, 2020. He was one of the early major contributors to Neuropharmacology and a founding father of this discipline in France. Many neuroscientists trained in his lab at the *Collège de France*, established themselves throughout the world (in Europe, United States, Mexico, Canada, Uruguay...) and are still very active in basic and clinical neuroscience research (Glowinski, 2007).

Jacques, « Glo », was someone exceptionally charismatic, deeply human, warm, generous, and faithful in friendship, who knew how to make people around him happy. At barely 30 years old, he established a research group at the *Collège de France* in the small space provided by Pr. Alfred Fessard. This group, which was famously known as the NB group (for *Neuropharmacologie Biochimique*, i.e. Biochemical Neuropharmacology), became a few years later the so called Unit 114 of INSERM (the French Institute for Health and Medical Research), with an internationally acknowledged success over the subsequent four decades. Numerous visitors and colleagues came from France and all over the world to give seminars and for stays of various durations. All of them, including ourselves who had the fortune and privilege to work with Jacques for many years, kept the memory of a warm and friendly laboratory. Typically, the intensely scientific day started with a meeting around tea or coffee, then, for many years, the lunch meal (dishes like at home, what a treat!) was prepared by two lovely ladies, Simone and Suzanne, and tea was served around 5 pm. These friendly moments were an opportunity to meet, to talk about science of course, but also about our lives and the world, all in a warm family-like atmosphere extremely favorable to creativity and profound dedication to research.

One year, after the summer of 1976, when financial support was low, Glo even proposed to his collaborators to make a few weeks break to repaint the lab, which was badly needed. The work was achieved cheerfully by everyone, including David L. Nelson, a young post-doc who had just arrived from Philadelphia the day before, and research was back on the road in a snap in a renovated stimulating environment with the group energized and bonded by Glo's leadership.

As Jacques wrote in his inspiring autobiographic book, written with François Cardinali, « *Le cerveau-architecte* » (Glowinski & Cardinali, 2016), he was born in 1936 to a family of Jewish immigrants from Poland and did not have a privileged preparatory

background for graduate studies. His parents owned a fur shop with a workroom and he was a young child during Nazi occupation but, fortunately, was not captured because he was hidden with part of his family in a farm in the middle of France. After the Liberation, he grew up in a clothing business environment and worked at the end of the week as a salesperson to eke out his existence. Under the influence of his uncle Henri, a pharmacist, resistant fighter and communist, he started to become interested in studies as well as handball that he played at a high (international university) level. Curious, bright, and hard-working, Jacques moved towards studying Pharmacy at the beginning of the sixties, and already showing a keen interest in brain research, he received a parallel training at the Faculty of Pharmacy and Faculty of Sciences at Paris University. On the occasion of an examination at the Faculty of Sciences where he presented his first research work carried out at the Pasteur Institute, on chemical synthesis of tritiated catecholamines, Jacques met Denise Albe-Fessard, professor of Neurophysiology. She proposed that he come and work at the Marey Institute, the top Parisian site for research in this area at the time, which was headed by her husband, Alfred Fessard, holder of the chair of Neurophysiology at the *Collège de France*. Strongly impressed by his energy, vivid intelligence and brightness, the Fessards (known respectfully as “Monsieur and Madame Fessard”) pointed out to Jacques the promising development of a new discipline – Neuropharmacology - at the NIH in Bethesda, under the impetus of Seymour Kety, Irwin Kopin and Julius (“Julie”) Axelrod (who received the Nobel Prize for Physiology or Medicine in 1970). Contact was made, Jacques was seduced and so was Julie, and in the fall of 1963, he, with his wife Isabelle and their very young son, Stéphane, boarded the liner, *France*, heading for a 2-year visit to Bethesda. In Julie Axelrod’s small lab, Jacques teamed up with Leslie Iversen and Solomon Snyder, becoming close friend with both. Together with them, Jacques revealed the full measure of his talents leading to major discoveries on brain catecholamine uptake and catabolism, and on the mechanism of action of antidepressant drugs newly introduced into the clinics. His innovative technique for intracerebroventricular microinjections in the rat allowed important studies of the activity of catecholaminergic systems in diverse brain areas and allowed him to demonstrate the blockade of the uptake of tritiated noradrenaline by the tricyclic antidepressant imipramine and chemically related compounds (Glowinski & Axelrod, 1964). This discovery paved the way for the later development of selective reuptake inhibitors for the treatment of depression. The years with Axelrod provided numerous

discoveries about catecholamines, histamine, and other neurochemicals, and led to the publication of some twenty papers, many of becoming classics in Neuropharmacology. The article by Glowinski and Iversen (1966) on regional differences in catecholamine uptake and turnover, which described a simple way of dissecting the brain for biochemical studies is in fact the most highly cited article ever published in *the Journal of Neurochemistry* (more than 5700 citations !). Indeed, the *Journal of Neurochemistry* was one of his favorite journals, he published 63 papers there, throughout his very productive scientific career (more than 600 original papers; Web of Science).

When Jacques returned to France in late 1965, he rapidly obtained a researcher position at INSERM, and Pr Fessard provided him with some space in his department. At that time, the discipline of Neuropharmacology was a vision to be built into reality in France, and Jacques took on the task, leading to the success and national and international glory that we know. He attracted several young students from the Faculty of Sciences including Anne-Marie Thierry, Marie-Jo Besson, France Javoy, Francis Héry, as well as talented individuals from technical schools, André Chéramy and Gérard Blanc. Very soon he was also joined by clinicians who spent internships in his lab and by scientists from the pharmaceutical industry. Seymour Kety and Louis Sokoloff, who had become his friends when he was at the NIH, spent sabbaticals with him and helped to launch his lab further. The exceptional creativity of Jacques saw its pinnacle with the development of innovative approaches to measure neurotransmitter release *in vivo*, in the rat, cat and monkey, and *in vitro* (from brain slices and later cells in culture). The study of neurotransmitter synthesis and fine regulatory mechanisms in discrete brain areas *in vivo* allowed the demonstration of the preferential role of newly synthesized monoamines in neuromodulation (Besson et al., 1969, Javoy & Glowinski, 1971). At a more conceptual level, he developed the idea of three integrated brain systems, with executive (sensori-motor and cognitive), modulatory (monoamines, neuropeptides), and metabolic (glial cells) contributions, for his fully attended lectures at the *Collège de France*. Throughout these years, Jacques' laboratory, or "Glo's lab", welcomed many scientists in an enlarged convenient environment, with a multidisciplinary approach boasting a wide array of cutting edge technologies, including molecular and cellular neurophysiology, immunocytochemistry, cell culture, molecular pharmacology, and the thorough study of rat behavior. These extensive

neuropharmacological approaches were applied not only to monoamines, but also to other neurotransmitters such as acetylcholine, neuropeptides (particularly substance P and enkephalins), glutamate and GABA. Over the years, major discoveries included (i) the identification of the mesocortical dopaminergic pathway, the characterization of its role in cognitive functions (Thierry et al., 1973) and in the mechanisms of action of antipsychotics, (ii) the demonstration of dendritic release of dopamine in the substantia nigra and its importance in the regulation of nigrostriatal neurons by autoreceptors (Nieoullon et al., 1977; Chéramy et al., 1981), (iii) the key role of interactions between neurons and astrocytes for neuronal differentiation (Denis-Donini et al., 1984), (iv) the role of gap junctions and connexins in astrocyte networks (Giaume et al., 1991), (v) the identification and characterization of multiple receptors for serotonin (Gozlan et al., 1983), substance P (Beaujouan et al., 2000), without forgetting (vi) the analysis of the regulatory mechanisms of these various neurotransmission systems in validated animal models of brain diseases (Agid et al., 1973).

In recognition of the major contributions of Jacques and his laboratory to Neuropharmacology, he was elected Professor at the *Collège de France* (chair of Neuropharmacology, 1982-2006) and member of the French Academy of Sciences (1992). He participated in the executive board of INSERM (1979-1992) and received prestigious awards (Richard Lounsbery prize, 1986 ; *Grand prix de la Fondation pour la Recherche Médicale* 2002 ; Inserm Honour prize, 2005 ; *Life Achievement Award* of the European College of Neuropsychopharmacology, 2008, to name only a few). He was appointed President of the French Society for Neuroscience (1995-1999) and he participated in the launching of the European Neuroscience Association (later to become FENS).

A man of conviction and dialogue, Jacques Glowinski worked throughout his career to establish efficient links between academic research, medicine, and the pharmaceutical industry. Many physicians, several who later became clinical department heads, were trained in his lab and were inspired by his humanistic concepts to revisit their approaches in neurology and psychiatry. As soon as he started his lab at the *Collège de France*, Jacques established close links with the pharmaceutical company Rhône-Poulenc (which later became Sanofi due to a merger/acquisition process). By hosting Rhône-Poulenc scientists in his Unit, he contributed to the development of the company's neuroscience research labs and

participated in strategies targeted towards neuro-psychiatric diseases. In this respect, he was a visionary in France, promoting private-public interactions that were very rare at the time and required the courage to resist criticisms from the academic world. Ironically, many of his early critics later followed his example. His open mindedness and humanistic vision led him to help his friend Bernard Esambert launch the *Fédération pour la Recherche sur le Cerveau*, that united several patient and family associations with private foundations to support Neuroscience research in France.

After his US experience, Jacques Glowinski's whole career was spent at the *Collège de France*, where he was elected to the key position of "Administrateur" (Director, 2000-2006). As early as 1991, Jacques Glowinski was involved in the « Grand Projects » operation to renovate the *Collège de France*, for which André Miquel, Director at that time, entrusted him to lead. He was then able to undertake and successfully attain what had been his dream since his arrival at the place, to renovate and reorganize this prestigious institution whose buildings were in poor shape. The aim was to restore it to good conditions to host cutting edge research and to provide high level education open to a large audience, at the center of an intellectual life in sciences and humanities in France. It should be noted that the *Collège de France* is a unique institution, created in 1530 by King François the 1st, to contrast with what was then perceived as a dogmatic Sorbonne. Its mission is and has always been to provide education that is open to all, without restrictive requirements and without the authority or obligation to deliver academic or professional degrees. For his successful undertaking, Jacques was acknowledged by the highest French official honors. In the process of leading these renovations, Jacques unraveled other facets of his personality, specifically his remarkable drawing skills and his steadfast passion for architecture, which led him to be called upon after 2006, when he was Professor Emeritus, to play a key role in the reorganization of the vast Paris-Saclay University campus for research and innovation. His many contributions at multiple levels now constitute an immense legacy, with a long-lasting impact on Neuroscience in France and beyond, on advocacy and organization of research.

Jacques, our dear « Glo », was not only a world leading neuroscientist but also a visionary and caring man with an entrepreneurial spirit and a great personal warmth. This unique combination profoundly influenced those who met him, making him unforgettable. He will be deeply missed. May he rest in peace.



Jacques Glowinski in the courtyard of the Collège de France during "his" renovation works

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