

Leslie Iversen, a friend of friends and an inspiring light in neuropharmacology

A. Claudio Cuello^{a,b,1}

Leslie Iversen, a giant of modern neuropharmacology, died peacefully on July 30, 2020, after a lifetime of leading transformational discoveries in the biochemical pharmacology of catecholamines. He was suffering from Parkinson's disease, a pathology that resides fundamentally in a loss of dopamine in brain centers regulating locomotion. For a man who made transformational discoveries on catecholamines, it was an ironic turn of events.

Iversen's major contributions to his field of science, as well as his awards and recognitions, have been amply documented, their magnitude reflected in his election as a Fellow of the Royal Society and an international member of the National Academy of Sciences, as well as being awarded the highest-ranking order of the British Empire Award: Commander of the Order of the British Empire for his services to pharmacology.

Leslie Iversen led a scientific life with a stellar trajectory at Cambridge University, the Medical Research Council (MRC), Merck, Sharp & Dohme Neuroscience Research Centre, and as Visiting Professor of Pharmacology at the University of Oxford. Who was Leslie Iversen? Despite all of these accolades and titles, to friends and close colleagues he was known as "Les." Les was an extraordinarily intelligent individual with a particular talent for identifying which were the important and most significant problems in neuropharmacology and in the neurosciences. He married an equally intelligent person, Susan Kibble (later known as Susan Iversen), whom he met during his undergraduate years at Cambridge. The Les-Sue relationship, besides being a happy marriage, was also a mutually enriching interaction. Sue benefited from Les's discoveries in neuroactive molecules and his wide repertoire of illustrious visiting scientists, while Les benefited from Sue's profound knowledge of experimental psychology.

An excellent reflection of this scientific partnership was the launching, as Editors, of numerous volumes of the *Handbook of Psychopharmacology*, a series that brought for many years the latest developments bridging pharmacology, neurosciences, and experimental psychology. In the same vein, Les and Sue, together with



Leslie Iversen (Right) at the NCPU laboratory with A.C.C. Reprinted from ref. 7. Copyright (2020), with permission from Elsevier.

Les's close friend Floyd Bloom, wrote the highly cited book *Introduction to Neuropsychopharmacology* (1). Les's extensive and transformational scientific discoveries have been recently commendably summarized by friends and coworkers, such as Trevor Robbins (2) and Solomon Snyder, Bevyn Jarrott, Anthony Turner, and Phillip Beart (3).

How did this quintessential British scientist, representing the best of the Oxbridge meritocracy, come about? Behind him there were no generations of academics, nor did he emerge from a traditional family of peerage or hereditary landowners. He came from an unpredictable corner of Exeter. Les was the son of a Danish immigrant family and his father a Branch Manager of the Danish Bacon Company. He completed secondary studies with high marks, which allowed him to obtain a scholarship to join the exclusive Trinity College, Cambridge, where he enrolled in the Natural Sciences program with Botany as his subject of study. In an interview, Les confessed that Botany was his boyhood passion. However, he added: "I decided to change subjects because the teaching was very, very old fashioned, based on systematic classification of

^aDepartment of Pharmacology and Therapeutics, McGill University, Montreal, QC H3G 1Y6, Canada; and ^bVisiting Professor, Pharmacology, Oxford University, Oxford OX1 2JD, United Kingdom

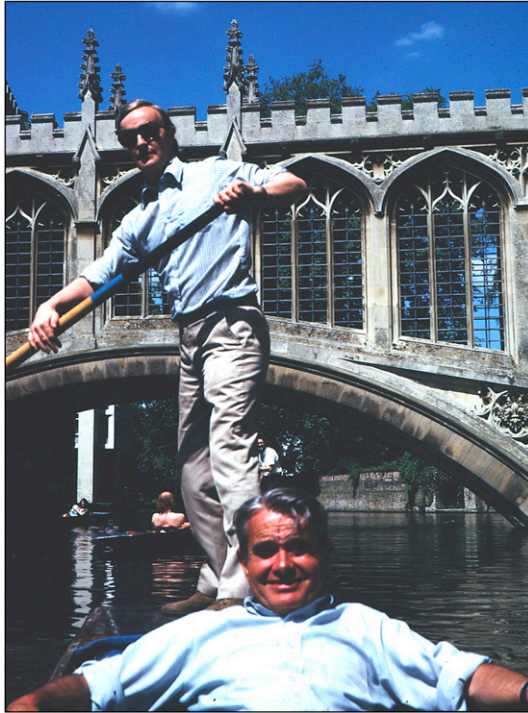
Author contributions: A.C.C. wrote the paper.

The author declares no competing interest.

Published under the [PNAS license](#).

¹Email: claudio.cuello@mcgill.ca.

Published August 5, 2021.



Leslie Iversen punting on the river Cam, with William F. Ganong as a passenger.

plants. They hadn't even heard about biochemistry, which I decided was much more exciting. So, I switched to a three-year degree in biochemistry, which was, and still is, a very strong subject at Cambridge" (4). This commentary speaks volumes of Les's personality. He needed constant intellectual challenges, an aspect reflected in his extraordinary list of fundamental discoveries. However, Les never abandoned his passion for botany, which was later translated into gardening. His beautiful garden at his Hills Road home in Cambridge was a reflection on this lifelong passion for plants. I well remember a long walk with Les discussing science and life, on a not much transited Italian rural path, with intermittent breaks as Les pointed out, with great enthusiasm, the presence of uncommon plants and bushes, identifying them by their Latin names.

Les completed a doctorate in Cambridge under the successive supervision of Gordon Whitby and Arnold Burgen and, following the catecholamine path, with a most successful postdoctoral experience with Julius ("Julie") Axelrod at the peak of his research, leading to his Nobel Prize. Les brought new basic aspects related to catecholamine uptake and release, while establishing a lifelong friendship with Julie and Jacques Glowinski. In his second postdoctoral position at Harvard at the Kravitz laboratory, Les made a seminal contribution, reinforcing the inhibitory role of neuronally released GABA, by then a "young" amino acid neurotransmitter.

Soon after his return to Britain, Les published his best-seller book on *The Uptake and Storage of Noradrenaline in Sympathetic Nerves* (5), a book that I read in my first postdoctoral experience in Argentina

as the "catecholamine bible." It was there and then that I knew that I wanted to meet that scientist. On my return from the Antarctic in 1968, I was invited to a meeting on Antarctic Biology at the Cambridge Scott Polar Research Institute, where I visited Les in his modest laboratory at the Cambridge University Downing site. Les and Cambridge produced a profound impression and my fervent desire of joining his Cambridge laboratory. Upon finishing my second postdoctoral stint at University of California, San Francisco, I went to work with Les for a third postdoctoral position. Upon my arrival by train to Cambridge with my wife Martha and my two little girls, there at the station platform were Les and Sue welcoming us with big smiles.

Les was by then directing the newly created MRC Neurochemical Pharmacology Unit (NCPU). He built a most successful interdisciplinary unit with great young scientists, visiting Fellows, and talented graduate students. On my first day at the laboratory, I told Les what I would like to work on. He said "fine . . . but first I want you to develop a highly sensitive radioenzymatic assay to measure catecholamines." I replied, "Les, I am not a biochemist." Les quietly said, "Anyone who has shown to measure catecholamines with fluorescence assays is for me a biochemist." The proposed technique implied isolating the enzyme catecholamine methyl transferase (COMT) and in my last gesture of resistance, I said, "I might be a biochemist, but I never worked with enzymes." The last verbal punch from Les was, "I will tell you what Julie [Axelrod] told me. With enzymes the only thing you have to do is to keep them cold." That is how the first highly sensitive radioenzymatic assay for catecholamines was born and applied by many until the HPLC era. This exchange also reflected his quiet but firm determination of breaking new barriers and extracting the outmost potential from trainees and collaborators, often well beyond our own personal expectations.

After Cambridge I returned to Argentina to find a country in disarray with extreme political violence. My life was at risk, and we decided to emigrate. Among offers from the United States and the United Kingdom arrived an elegantly handwritten letter from Les inviting me to join NCPU as a member of the MRC Scientific Staff, a letter that changed my life and that of my family. Les directed the NCPU from 1971 to 1982. The unit operated initially within the Department of Pharmacology, later becoming its Neurobiology Division at the time of Les's departure, when he took on Directorship of the Merck, Sharp & Dohme Neuroscience Research Centre.

For many of us, "the Iversen's children," the years at the NCPU signified the best scientific output of his career, with numerous firsts on the biochemical pharmacology of catecholamines, uptake and release of neurotransmitters from minute, microscopically dissected, identified central nervous system areas, the discovery of "dendritic" release of dopamine, the identification of novel peptides in the spinal cord and brain, their stimulus-dependent release, the evidence that the enkephalins blocked the release of substance P from nociceptive sensory terminals, and fundamental

aspects of GABA pharmacology, including its occurrence in neurons and glia. This broad biochemical pharmacology menu also included some of the first translations of such findings to the human brain in health and in neurodegenerative conditions, work that established seminal contributions to “The chemistry of the brain,” as Les entitled his 1979 article in *Scientific American* (6), a brain chemistry outlook that resulted from his research experience and his discussions about the boundaries of neuropharmacology and the neurosciences with many—notably Floyd Bloom, Solomon Snyder, and Masanori Otsuka—as well as with the large list of NCPU trainees (the Iversen’s children).

There were no barriers at the NCPU between Les, the staff members, visiting scientists, and the graduate students. The T-shirt laboratory logo was a portrait of Winnie the Pooh holding a brain with the words “A brain with little bear.” Often, research projects were discussed sitting on the lawn outside NCPU, at

receptions at Les and Sue’s home, or having the communal beer closing the research week on a Friday afternoon.

The last time I met Les was on March 29, 2018, at the idyllic Corbett’s Cottage in Wiltshire, United Kingdom, which Les and Sue shared with their daughter Amy and family. We had a long conversation, exchanging the latest information about all the main characters of the old NCPU. He asked me what I was up to. I told him that I was coming from giving an opening talk in memory of Rita Levi Montalcini at an Alzheimer’s meeting in Torino and I mentioned that I presented a video of the NGF metabolic pathway, a metabolic pathway that he previously defined as “a nice detective story.” He asked me to show him the video. I brought my laptop and on ending the presentation Les asked, “Claudio, can I have a copy?” It was a much-appreciated compliment and our farewell encounter.

- 1 L. Iversen, S. Iversen, F. E. Bloom, R. H. Roth, *Introduction to Neuropsychopharmacology* (Oxford University Press, 2009).
- 2 T. W. Robbins, L. Leslie, Iversen, Ph.D., (1937–2020). *Neuropsychopharmacology* **45**, 2132 (2020).
- 3 S. Snyder, B. Jarrott, A. Turner, P. Beart, Leslie Iversen (1937–2020). *J. Neurochem.* **155**, 345–347 (2020).
- 4 T. A. Ban, In Celebration of Leslie Lars Iversen (1937–2020), International Network for the History of Neuropharmacology (January 7, 2021), <https://inhn.org/biographies/in-celebration-of-leslie-lars-iversen-1937-2020-by-thomas-a-ban.html>.
- 5 L. Iversen, *The Uptake and Storage of Noradrenaline in Sympathetic Nerves* (Cambridge University Press, 1967).
- 6 L. Iversen, The chemistry of the brain. *Sci. Am.* **241**, 134–149 (1979).
- 7 A. C. Cuello, “Augusto Claudio Guillermo Cuello” in *The History of Neuroscience in Autobiography*, L. R. Squire, Ed. (Academic Press, NY, 2001), vol. 3, pp. 169–213.