

A tribute to Professor Ivan Izquierdo

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Professor Ivan Antonio Izquierdo, the great Argentinean and Brazilian neuroscientist, left us early in February due to complications of pneumonia, not related to COVID-19. Enjoying a prolific academic career, he discovered how memory is processed and influenced many generations of Brazilian scientists. This brief account of his extraordinary scientific legacy is a tribute to this remarkable thinker and human being.

Izquierdo was born in Buenos Aires, in 1937, and took his MD and PhD at the University of Buenos Aires. After a post doctoral period he moved to the University of Cordoba, with his wife Ivone and two kids, Juan and Eduardo, and started to work on the neurobiology of memory. However, in 1973 the family decided to come to Brazil because of perils of popular uprisings and political prosecutions in curse by the Argentinean military government. Following a brief period in São Paulo, Izquierdo settled in Porto Alegre to work at the Biochemistry Department of the Universidade Federal do Rio Grande do Sul, where he created and run the Center of Memory for almost 25 years. After retiring, he created the Memory Center at the *Pontifícia Universidade Católica – RS*, now part of the Brain Institute of Rio Grande do Sul, where he worked until 2020.

Izquierdo's main contributions were in the fields of pharmacology and molecular basis of memory function. He was the first to demonstrate that the brain beta-endorphin system participates in memory regulation and to show its activation by detection of novelty in the learning environment. The benefits of novelty exposure in facilitating retrieval were shown in rodents and in humans, both in healthy volunteers and in the elderly¹. Along with studies on ACTH and adrenaline, his findings also corroborated with the state dependency theory of memory retrieval². Later his group went on to study the endogenous benzodiazepines participation in memory consolidation, both its pharmacology and the location and activity of specific receptors in the brain³.

One of his major challenges was the approach to the core mechanisms of memory formation. By exploring the pharmacology, second messengers and enzyme activities in the CA1 subfield of the hippocampus and on other brain areas, he showed a great correlation with the molecular mechanisms known to be involved in Long Term Potentiation, LTP⁴. Remember that LTP is taken as a paradigm of learning-induced neuroplasticity in which long-lasting molecular and morphologic changes modify the synaptic strength. Although it is not yet possible to demonstrate LTP in human memory formation, such molecular construct offers an acceptable scientific roadmap to understand, and to challenge, memory mechanisms as a conserved strategy along neural evolution.

The dissection of the brain structures and the distinct mechanisms of the most studied forms, long-term and short-term, of memory led to the study of a particularly interesting phenomenon: the extinction learning. Briefly, the association of a set of stimuli (CS) with a reinforcement (US) leads to a conditioned response (CR). However, the CR can be inhibited when the CS is presented in the absence of the US, that is, the subject learns to inhibit the CR. Unravelling the mechanism of this Pavlovian type of learning/memory can be of interest for clinicians working with stress-related disorders. For instance, extinction is used as a technique of "exposure therapy" for the treatment of post-traumatic stress disorder and other forms of fear-related memory disturbances⁵.



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There are many other important scientific contributions of Izquierdo that are worth knowing; a good account of these can be found in his scientific autobiography³. He published more than 600 papers that received around 25 thousand citations (H index of 80!). Izquierdo was the most cited Brazilian, and Latin-American, scientist during many years and received national and international prizes. His scientific endeavor had a formidable impact in the development of Brazilian neuroscience. He supervised almost one hundred graduate students, now mostly dedicated to science in universities and research institutions, and a lot many undergraduates in the Science Initiation Program. Brilliant researcher and charismatic team leader, Izquierdo was called *Master* by his students and colleagues. A man who taught by his example, that was respected because of what he did and think. Certainly one of the most influential scientists in Brazilian academy and admired by the lay public. Passionate about literature and music, Izquierdo was a great admirer of his fellow countryman Jorge Luiz Borges, and wrote essays, short stories and novels regularly since 1991. In his book "Art of Forgetting", inspired in a Borges character and in knowledge about memory modulation, he discusses why

and how we forget, and the importance of that for thinking and surviving.

Master Izquierdo departed peacefully and surrounded by his beloved family after accomplishing a most beautiful mission. His unique scientific and personal legacies remain and survive in all those who were fortunate to have their hearts and brains touched by his life, works, words and unforgettable memories.

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