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Born:

Buenos Aires, Argentina
September 16, 1937

Education:

University of Buenos Aires, M.D. (1961)
University of Buenos Aires, Ph.D. (1962)

Appointments:

Assistant Research Anatomist, UCLA (1964)
Assistant Professor of Pharmacology, University of Buenos Aires (1965)
Professor of Pharmacology, University of Córdoba (1966)
Professor of Pharmacology, Federal University of Rio Grande do Sul, Brazil (1973)
Professor of Physiology, Escola Paulista de Medicina, Sao Paulo (1975)
Professor of Biochemistry, Federal University of Rio Grande do Sul, Brazil (1978)
Professor of Neurology and Chairman of the Memory Center, Pontifical Catholic University of Rio Grande do Sul, Brazil (2004–present)

Honors and Awards (Selected):

Odol Prize for Junior Scientists, National Research Council of Argentina (1965)
Honorary Professor, Universities of Buenos Aires (1991) and Córdoba (2006)
Antonì Esteve Prize, Antonì Esteve Foundation, Barcelona (1992)
Rheinboldt-Hauptmann Prize, University of Sao Paulo (1993)
Basic Medicine Award, Academy of Sciences of the Developing World (1995)
City of Porto Alegre Medal for outstanding services to the community (1996)
Decorations: Great Cross, Order of Scientific Merit, (1996) and Order of Rio Branco (2007), both from the Government of Brazil, and Medal of Merit, State Legislature of Rio Grande do Sul (2009)
John Simon Guggenheim Award (1997)
Açorianos Literary Prize, the City of Porto Alegre (1999)
Memorial Lectures: J.A. Izquierdo (1999), O. Orias (1999), A. Thomson (1999), M.R. Covian (2000), J. Flood (2000), R. Caputto (2000), C.P. Duncan (2001), S.C. Ferguson (2009) and H-J. Matthies (2010)
Lifetime Awards: State Research Foundation, Porto Alegre (2001), International Neuropsychiatric Association (2005), Brazilian Neuroscience Society (2007)
Honorary Citizen of Porto Alegre (2003)
International Neuroscience Symposium for my 70th birthday, Curitiba (2007)
Doctor Honoris Causa, Federal University of Parana, Curitiba (2007), and University of Cordoba (2011).
Foreign Associate, National Academy of Sciences, U.S.A. (2007)
Member, Academy of Sciences of the Developing World (2007)
Creation of the Ivan Izquierdo Research Prize, Clinic Hospital of Porto Alegre (2007)
Conrado Wessel Prize in General Science, Conrado Wessel Foundation (2008)
Premio Ciudad Capital: Ciudad de México (2009)
Premio Almirante Alvaro Alberto (National Science Prize), Brazil (2010)

Ivan Izquierdo and his coworkers demonstrated the main molecular steps of memory consolidation for one-trial avoidance and other tasks in the hippocampus and other brain areas, the separation of short- and long-term memory, and the main mechanisms of extinction and memory persistence. Izquierdo trained over 90 graduate students, and established memory research and set up several centers of excellence in neuroscience in both Brazil and Argentina.

Ivan Izquierdo

I was born in Buenos Aires in 1937. My mother, Margarita Gobic, had come from Croatia in 1913 at the age of 3. My father, Juan Antonio Izquierdo, came from a family who had arrived in 1806 from Barcelona. My parents, my sister Mitzy, and my Croatian grandfather, Agustin, were major influences in my life. Another major influence was the city of Buenos Aires, where in 1937 one-third of the population had been born in Europe and nearly all the rest were descendants of European immigrants. A touch of Indian ancestry was taken for granted among those of us with Spanish roots. So it was a mongrel city, truly cosmopolitan, in which it was impolite to label anybody as a foreigner; Spaniards, Italians, Uruguayans, Bolivians, and Paraguayans were viewed as locals. The most famous tango singer Carlos Gardel had been born in Toulouse; some of the country's best soccer players had played for Italy in the 1934 and 1938 World Cups (and won); American, European, and Mexican pop songs were popular alongside the tangos. My mother sang many of these songs beautifully.

My grammar school taught in Spanish in the morning and in English in the afternoon. It was one of the many bilingual schools in town. In 1950 I entered the Colegio Nacional de Buenos Aires, a high school attached to the University of Buenos Aires and whose teachers included prominent intellectual figures. At that time the country was drifting toward a dictatorship, but the school remained a beacon of democracy. It instilled in me an interest in world culture, science, literature, and above all, political decency.

I keep contact with my sister and with friends from my teenage days. We were born in the last years of general tolerance in a country that was soon to plunge into dictatorships and decades of political turmoil. A Paradise lost.

Borges

In the late 1930s and early 1940s, Argentina was home to many major European artists and intellectuals who came because of political or ethnic persecution at home. Among them, Manuel de Falla, Roger Caillois, Witold Gombrowicz, Jiménez de Asúa, some of my best high school teachers, several friends, and Cajal's disciple Pío del Rio Hortega, who planted the seeds of neuroscience in Buenos Aires with another exile, Christofredo Jakob.

The writer, Jorge Luis Borges, was a towering influence over the ebullient local cultural life of those days. He saw life as "a game with shifting mirrors" and had the strong suspicion that what we call reality may be as

deceiving as Berkeley and Hume had thought it was. I was introduced to Borges's literature by my father and by my high school Spanish teacher Antonio Pagés Larraya. My interest in memory research and, of course, in literature, owes a lot to Borges. He raised or answered some of the most serious questions on memory, like: "When we remember something, do we remember the thing itself or just the last time we remembered it?" He demonstrated that perfect memories are impossible in a short story published in 1944, *Funes the Memorious*: Funes could recall an entire day of his life, but for this he needed another entire day of his life to the last second, which is of course absurd. In other stories Borges postulated games with time and memory, the incorporation of the memory of others, and a world in which memory is believed not to exist.

Borges's notion of a constantly mutant reality (the mirrors that shift) helped me deal with the vertiginously changing world that was beginning about the time I was born. I attended many lectures by Borges at a place called the Free Institute of Superior Studies during my high school years, and I talked with him many times about Robert Louis Stevenson or Joseph Conrad or about Nazism as a monster implanted in the womb of a culture that had given us Goethe, Beethoven, and Heine. Borges's views antedated those of Ingmar Bergman (*The Serpent's Egg*, 1977) by a quarter of a century. I am still haunted by the possibility that similar monsters can be born anywhere, any time. Life painfully taught me that they do.

Medical School and the Apple of Research

I entered the University of Buenos Aires Medical School in 1955. Three months later a military coup toppled the government of General Perón. The new generals in charge promised a rapid return to full democracy, which ended up being neither rapid nor full. In the university the consequences of the coup were immediate and largely beneficial. The university, like most in Argentina in those days, was federal. Several professors who had been ousted by the fallen regime came back, including the most important scientists of Argentina: the 1947 Nobel Prize winner Bernardo Houssay (who discovered the regulation of glucose metabolism by pituitary and other hormones), Luis Leloir (who was to receive a Nobel Prize in 1970 for his landmark work on the role of sugar nucleotides in carbohydrate synthesis), Eduardo Braun Menendez (the discoverer of the renin-angiotensin system and its role in hypertension), and Eduardo De Robertis (who discovered neurotubules and then synaptic vesicles and their contents and had been in exile in nearby Uruguay). These four men would have a large influence in my life. Leloir, perhaps the only genius I have ever known, was a very modest man and taught me the importance of not thinking too much of oneself (*no creérsela*, as they say in Argentina). That is one of the most important things I ever learned.

In Medical School teaching improved overnight: The new professors actually lectured about things that they were *doing,* or that had been discovered by people *they knew*. Braun Menéndez rushed into the classroom one morning and told the students that his friend Vincent du Vigneaud had just won a Nobel Prize for determining the structure of oxytocin.

Many students were attracted by the possibility of working with the famous masters or their disciples. Research had become the apple to bite. So I went to see Professor Houssay in December 1956, right after my Physiology exam, with a research idea of my own. He received me at 6:30 in the morning, we talked briefly, and he told me to come back on January 2. My research career started that day. Houssay was a short, soft-spoken man who gave the right impression of wielding a great authority. He had created a school of Physiology that produced excellent research-oriented professors all over Latin America. My research project proved wrong, but I had bitten the apple for the first time and enjoyed the taste. Houssay believed that young students inclined to science should try different fields before deciding on a definitive one, and he introduced me to Roberto Mancini, an excellent endocrinologist in the Institute of Anatomy chaired by De Robertis in the Medical School. I joined Mancini's lab for the next 2 years (Mancini et al., 1957) and learned a lot from him. He was a kind man with a sharp mind, a great endocrinologist, and a superb scientific writer.

On to Neuroscience

De Robertis and his associates Hersch Gerschenfeld and David D. Sabatini visited the lab often to see their friend Mancini and talked with enthusiasm about their own work. Sabatini taught me a lot about the power of education. His idol and role model was Domingo Faustino Sarmiento, a President who in one term of office (1868–1874) reduced Argentina´s illiteracy rate from 90% to near 0%. This was the foundation of a fantastic development that lasted one century and attracted millions of immigrants.

In 1958, encouraged by Houssay, Mancini, and De Robertis, I decided to move on to neuroscience. The research carried out in the De Robertis lab required many consecutive hours of work, which was beyond my possibilities as a medical student. So he advised me to work with my father, who was his friend. My father had begun a scientific career late in life and did acute experiments on the autonomic system that began and ended on the same day.

In many ways it was fun working with my father, even though we disagreed about almost everything that a father and a 21-year-old son usually disagree about. But we had many good moments, and working together was good for the two of us. We discovered that stimulation of the central end of

the sectioned vagus nerve briefly increases sympathetic tonus (Izquierdo et al., 1959), which 40 years later was shown to influence memory consolidation by Robert Jensen and his group. We also described a stimulant effect of pyrogallol on duodenal motility due to rebound cholinergic activation (Izquierdo and Izquierdo, 1961), which would be the subject of my Ph.D. thesis. In those years the University had a joint M.D./Ph.D. program in order to absorb the large number of students interested in research.

There was to be a Brazilian parenthesis: In late 1958 I met Miguel Covian, an Argentine neurophysiologist from the School of Medicine of Ribeirao Preto, University of Sao Paulo. He gave a very impressive seminar in the Medical School on brain control of the endocrine system. My friends Franco von der Walde, Claudio Suárez, and I asked him if we could spend part of that summer vacation in his lab. He agreed and kindly offered us to sleep in the lab if we wanted. So the three of us spent 2 months that year in Covian's Department of Physiology, living cheap, working hard, and enjoying it a lot. Everybody there was extraordinarily nice to us, including professors Cesar Timo-Iaria, Ricardo Marseillan, Jose Antunes, and Eduardo Krieger, who taught us a lot. I returned the following year for 2 more months. My two trips to Ribeirao Preto reaffirmed my intention to work in neuroscience; and made me fall in love with Brazil, its people, its music, and its joie de vivre.

In Buenos Aires, I saw De Robertis frequently. Through reading and talking with him, I was becoming strongly interested in learning and memory. This was not his field, but he felt a Platonic love for it. In 1959, José "Pepe" Segundo, a top specialist in learning and memory and a friend of De Robertis from his days of exile in Uruguay, visited him in Buenos Aires. Pepe invited me to visit his electrophysiology lab in Montevideo, 1 hour away by plane, where he and his group studied regional brain electroencephalography (EEG) in cats during a variety of conditioned reflexes. I visited Segundo's lab many times and spent the winter vacation of 1960 working with his disciple, César Galeano. Shortly before that, Pepe Segundo had joined the University of California at Los Angeles's (UCLA) Brain Research Institute (BRI).

In 1961 I set up a cheap and simple conditioned reflex lab in the Pharmacology Department of the School of Pharmacy in the University of Buenos Aires, and I worked in it under the advice of Cesar Galeano (Izquierdo and Östman, 1961). In the mornings I attended the excellent Electroencephalography Service of the Military Hospital, where I learned a lot about clinical neuroscience with Abraham Mosovich, a man of great kindness and wisdom, who was the only civilian head of a service in that hospital.

My thesis was approved in early 1962. I applied for, and was awarded, a postdoctoral fellowship from the University of Buenos Aires to work with Pepe Segundo at UCLA. The fellowship began in May 1962.

Go West, Young Man

Before traveling to the United States I made two little trips to nearby Porto Alegre, Brazil, that would change my life. In the first, in January 1962, I met Ivone de Moraes, who was then 19 and as lovely as she is now. In the second trip, in April, on the way to Los Angeles, I asked her to marry me. As will be seen, 1 year later we did marry and I went back to Los Angeles with her. We have just celebrated our 47th wedding anniversary.

Pepe Segundo's lab at UCLA was a happy and active place. Pepe had three research groups in the same lab: one was with Nicolas Buendia, Larry Stensaas, and Curt Bell, who worked on unit recordings from the reticular formation; another was with George Moore and Don Perkel, who did intracellular recordings in *Aplysia* and studied the role of firing patterns in the transmission of messages in the abdominal ganglion.

The third group was with Germán Sierra from Spain, Wanda Wyrwicka from Poland, and me. Wanda was a disciple of Jerzy Konorski, the discoverer of Type II or instrumental conditioning. Wanda, Germán, and I implanted cats with chronic electrodes through which we recorded neocortical and hippocampal EEG and delivered arousing stimuli to the periaqueductal gray. These were used as unconditioned stimuli (USs) and were paired with tones as conditioned stimuli (CSs) during different phases of sleep. We established conditioned arousal during slow-wave and rapid eye movement sleep, first as a classical and then as an instrumental conditioned response, lasting weeks (Izquierdo et al., 1965). But we could not tell whether regions in the brain distant from our recording sites had been "awake" at the time of the CS-US pairings. This problem is intrinsic to all research on learning during sleep and has proven to be insurmountable till this day. It is simply impossible to monitor every cell group and determine whether it is "asleep" or not during sleep, or to know what being asleep means for a small group of brain neurons.

In October 1962 there was the famous Cuban Missiles Crisis that took the world to the brink of a nuclear war. The crisis drew me close to John D. Green, who had been to me just a brilliant neuroscientist till then, and became a good friend from then on. He and I were both foreigners, were very scared, and had no family nearby. So we talked and talked about our fears and hopes, usually over long dinners while the ominous alarm siren sounded in the distance. The Cuban crisis fizzled out before the end of 1962, so I went back to Porto Alegre, married Ivone, and after a few days in Buenos Aires and New York, we settled in Westwood Village where UCLA is. Once back, I finished my work with Pepe Segundo and moved to John Green's lab. John had invited me to work with him upon my return to UCLA.

There was no other period of my life in which I learned more about research than in the 15 months I worked with John Green. His meticulous way of obtaining and analyzing data left a profound impression on me and

changed my own way of working forever. We wanted to study homo- and heterosynaptic facilitation and postsynaptic potentiation in a search for putative bases of learning such as had been proposed by Albert Fessard shortly before; long-term potentiation (LTP) was yet to be discovered. We did intracellular recordings from hippocampal pyramidal cells in vivo. Green had tried hard to get them with Curt von Euler and others and failed, whereas recently both Eric Kandel and Sir John Eccles had succeeded very neatly, using rods of plastic or glass making slight pressure on the alveus in order to keep it from moving with respiration. Green refused to use pressing feet because they changed the polarity and shape of evoked potentials in the CA1 region, so could alter their relationship to unit activity. I was able to confirm those field potential shifts a few years later with Beatriz Vásquez in Córdoba (Izquierdo and Vásquez, 1968). In 1964 the practical result was that Green and I did penetrate a number of cells from cat CA1 without using pressing feet, but they survived too little to be of any use. (Hippocampal slices were also not yet known).

So we moved on to motor neurons in the spinal cord. Two other postdocs joined our team: Maria Candelas Bravo, from Spain, and Emilio Décima, from Argentina. Sir John Eccles himself visited the lab on his way to the 1963 Nobel Prize and gave us plenty of advice as to how to set up the spinal cord preparation. We worked hard for several months till we finally felt we were on the verge of getting good results. But we tried to do too many things with each cell every time we got one; most cells did not survive our successive attempts to record homo- and heterosynaptic facilitation and posttetanic potentiation in sequence.

In February 1964 my son Juan was born in UCLA. John Green enjoyed visiting him at our home. We had long chats with Ivone about life, Mozart, and the Beatles, who had just visited Los Angeles. John, in his Oxonian way, found their music "rather lively."

In March 1964 my fellowship from the University of Buenos Aires was about to end, and the UCLA Department of Anatomy, through the good offices of Pepe Segundo, John Green, John French, and Carmine Clemente hired me as Assistant Research Anatomist. This opened the possibility of staying in UCLA indefinitely since, as they told me, the following step could be a formal appointment as an Assistant Professor. So easy it was to get a job at a major university in the United States in those heady days, when the Americans thought they had a scientific gap to close with the Russians.

Ivone and I pondered what to do next. The School of Pharmacy of the University of Buenos Aires was offering me an Assistant Professor position. However, Argentina was in a state of disarray, having suffered another recent military coup that failed, in the middle of an economic crisis. We felt that the right thing to do (*noblesse oblige*) was to return to that University anyway, in return for the fellowship it had given to me during more than 2 years. So we left UCLA and went back to Argentina in May 1964.

The experiments with John Green on homo- and heterosynaptic interactions were never finished. He died of a heart attack shortly after his marriage a few months later, and Décima, Bravo, and I dispersed. In 1967 I returned to the subject in Córdoba, Argentina, using evoked potentials in the rat hippocampus (Izquierdo and Vásquez, 1968).

The University of Córdoba

Back in Buenos Aires I received my first graduate student, Alicia Merlo. She and I set up a brand-new state-of-the-art, but elementary, electrophysiology lab where we did a nice, detailed study of the projections of the medial forebrain bundle (Izquierdo and Merlo, 1966). We also worked on the effect of peripherally injected catecholamines and cathecol-O-methyl transferase inhibitors on avoidance learning (Merlo and Izquierdo, 1967), which was pioneering at the time.

In 1965 the National Research Council of Argentina gave me my first award: The Odol prize for junior scientists. Bernardo Houssay presided over the ceremony, and the prize was given to me by Eduardo De Robertis.

In January 1966 my second son, Carlos Eduardo, was born in Buenos Aires.

Meanwhile, a new, highly promising scientific center was being established in the second oldest university in the Americas, the National University of Córdoba, founded in 1613 in the center of Argentina. The dean of its School of Chemistry, Ranwel Caputto, a famous neurochemist just arrived from Oklahoma and a disciple of Luis Leloir, invited me to join his School as a Full Professor of Pharmacology. I accepted right away.

In June 1966, Ivone, Juan (2 years), Eduardo (5 months), and I left for Córdoba in a little Renault Dauphine full of luggage. The day we traveled, once more a military coup overthrew a president in Argentina. But now this deposed president was a gentle, old, decent, highly democratic man, and the general who took over soon proved to be just another authoritarian figure. We had no radio in the car, so we learned about the coup only when we stopped at a hotel that night, near Córdoba.

In Córdoba my first job was to discover where could I get someone to sign my appointment as a Professor. The Rector of the University was the personal doctor of the deposed president and was away in Buenos Aires taking care of his illustrious patient. Numbers 2, 3, and 4 in the line of succession were somewhere else too. After a few days of anxiety, number 5 eventually came up and signed my appointment. My second job in Córdoba was to find lab space. For reasons I will never know, my appointment as a Professor of Pharmacology did not imply that there should be any physical space associated with it. The Department of Pharmacology was an imaginary entity straight out from the world of Borges, perhaps an entelechy. Through the generosity of Caputto and the neuroendocrinologist Samuel

Taleisnik I was allowed to use an excellent electrophysiology lab in the latter's private research institute. It had been set up for somebody who had just left the country.

There, with Beatriz Vásquez, Antonia Gladys Nasello and Erna Marichich, we carried out significant work on the regulation of hippocampal electrical activity by extracellular potassium (K^+). We put to test John Green's posthumous hypothesis, sketched out in a 1964 article in *Physiological Reviews*, that hippocampal electrical activity could be self-regulated at different functional levels by $[K^+]_o$ accumulating in the very restricted extracellular space of CA1, particularly in the stratum radiale, where apical dendritic shafts run parallel and close to each other for long distances. We studied this using two approaches, both in vivo: *(1)* to instill onto the surgically exposed hippocampus drugs known to enhance (veratrine) or inhibit (tetraethylammonium) spike-dependent K^+ release (Izquierdo and Izquierdo, 1967); *(2)* to perfuse the alveus under no hydrostatic pressure (I still felt allegiance to John Green´s abhorrence of pressing feet) with isotonic solutions of different K^+ concentrations that would equilibrate with $[K^+]_o$. Green had predicted that at a certain $[K^+]_o$ level there would be a predominance of synaptic enhancement that would underlie both facilitation and posttetanic potentiation, due to a depolarization-induced promotion of Ca^{2+} entry into synaptic terminals; and that above those levels, first the preepileptic phenomenon called "spike complications" (actually envelopes of apical dendritic spikes) and then full-fledged seizures would occur. We succeeded in validating Green's K^+ hypothesis (Izquierdo, 1967; Izquierdo and Vásquez, 1968; Vásquez et al., 1969; Nasello et al., 1969; Izquierdo and Nasello, 1970; Izquierdo et al., 1971). The precise levels of $[K^+]_o$ that enhanced synaptic transmission and those that trigger seizures were determined later by Jan Bures and his group in Prague with K^+ sensitive electrodes, which we had no possibility of getting in Córdoba.

Meanwhile, we had hired Otto A. Orsingher as an Associate Professor in the Department. He came from several years at the Istituto Superiore di Sanità, in Rome, where he had worked with the Nobel Prize winner, Daniele Bovet, and had become a friend of James L. (Jim) McGaugh. I knew Prof. Bovet from my Buenos Aires days; he regularly visited family there and every time he came he also visited me. He was the archetype of a kindly wise man.

Otto and Jim were to become two of my best friends. Otto introduced me to Jim´s recent method to study the effect of drugs on memory consolidation by injecting them right after training, rather than before. Jim understood consolidation as a relatively short-lasting, postacquisitional process through which recently learned information is consolidated into memories (McGaugh, 1966).

In 1969, I met Jim McGaugh in a symposium in Buenos Aires. We got along together very well from the beginning, and our now long-standing

friendship started, fittingly, with a touch of humor. I was translating questions raised by the audience to his presentation, and translating back his responses to the public. At some point, in response to one question, Jim said: "Nothing could be finer." I quipped "Than to be in Carolina"; and right away we sang the third line of that song together and became friends for life. We have a similar attitude toward life, in which humor plays a major role.

Beginning in 1969, Otto, I, and others carried out a number of experiments using posttraining drug injections to study consolidation. We described posttraining memory-enhancing effects of amphetamine, nicotine, and atropine (Evangelista and Izquierdo, 1971, 1972). Otto and I carried out a study of rats inbred for their low performance in a shuttle avoidance task, which we then thought was linked to hippocampal dysfunction but is now known, instead, to result from a high level of anxiety in the animals. We established the memory-depressant (Fulginiti and Orsingher, 1970) and anticonvulsant (Izquierdo and Nasello, 1973) properties of Cannabis compounds.

But life was beginning to become difficult in Córdoba. In 1968 a popular uprising sparked by police brutality lasted several days and the toll was 14 dead, all civilians. The first night of the uprising, soldiers camped in front of our building thought that there were snipers in the terrace, so they shot at our walls during interminable hours. Ivone, our two kids, and I slept in a corridor just because it was two walls away from the street instead of one, and so stray bullets were less likely to hit us. After that, tensions subsided for some time, but urban guerrilla groups began to proliferate all over the country, including Córdoba. Our Department, being in the ground floor, was easy to invade. One week 5 different activist groups occupied the Department, each to be expelled in the evening by the police through the use of force. Our students were scared, all of us were taken hostages for hours, and some of the invaders threatened to kill all the rats and destroy all the equipment, which they said was used to produce results for imperialism. Otto and I had to negotiate each day the release of the hostages, as well as our own safety and that of the animals, first with each invading group and then again with the police. Then, almost every night, bombs resounded all over the city. Córdoba has ceased to be the "bucolic" place Ivone and I had looked for a few years before. However, we loved it so much that we stayed there as long as we could.

In July 1973 right after I had finished talking over the phone with a friend, it rang again and a harsh voice told me that if I insisted to talk with darn Bolsheviks like the person I had been talking with (actually, a moderate center-left biophysicist), they would kill me and my whole family. Ivone and I almost immediately decided to leave Argentina. There were several political murders every day in the country, and both terrorist and paramilitary groups were rampant; so the phone threat could not be taken lightly. The old Paradise had indeed been lost. The option as to where to go was obvious: Ivone´s parents lived in relatively nearby Porto Alegre, and

although Brazil was also under military rule, at least there were no shootings, bombs, or death threats there. Furthermore, Ivone´s father was terminally ill, and we thought it decent to accompany him during the last few months of his life. Our children adored him and he was a great friend of mine. Our idea was to stay in Porto Alegre for a few months and then eventually migrate to the United States.

Porto Alegre and Then São Paulo

So we packed, sold everything we could not pack, and traveled to Porto Alegre. Again, we did not dare to look back because tears would have been too many. My last Ph.D. student in Córdoba had been Mario Tannhauser, from Porto Alegre, who arranged for me a contract in the Federal University of Rio Grande do Sul, starting in August. I was hired as a Professor of Pharmacology. We did not know then that Porto Alegre was to be our home town. Clearly, there were signs of a political opening in Brazil, which according to its rulers, was to be "slow and gradual." But it was an opening after all; quite the opposite of the rapid and violent shutdown that was taking place in Argentina.

It was easy to adapt to southern Brazil: Its lifestyle is very much like that of Argentina. Ivone was born in Porto Alegre and I knew the city well. Brazilians are more optimistic than Argentines, and they are more adept to *laissez passer*, which makes life easier. Now that years have gone by, I find the differences have smoothed out. Perhaps that is the result of the enormous exchange of people between the two countries in the past 30 or 40 years. Actually, cultural and behavioral differences over most of the world have smoothed out.

Initially, the prospects for doing research in Porto Alegre were dim. Except for a few scattered laboratories, the university had almost no tradition of research and a generalized dislike for it. I carved a space at the Physiology Department and did carry out some research work in it, so I could finish some neurochemical work I had initiated in Córdoba (Gattoni and Izquierdo, 1974). I again set up an elementary learning lab, where I studied the effect of several drugs (Izquierdo, 1974a, b) and the effect of maturation (Izquierdo et al., 1975) on pseudoconditioning of rats in a shuttle box.

Ivone´s father died in early 1974. Soon after that, I was invited to take a position at the prestigious Escola Paulista de Medicina, an isolated federal medical school in São Paulo with a long and solid tradition in research. So in January 1975 we moved there. The Dean of the Biosciences School in Porto Alegre, Tuiskon Dick, promised that he would create the conditions for me to return, at the most in 2 or 3 years. He did not accept my resignation and gave me an indefinitely long leave of absence instead, in the hope I would return.

So in January 1975 I took my new position at the Department of Physiology in the Escola Paulista in São Paulo. This was a research-oriented place as I had gotten accustomed to since my days at UCLA, Buenos Aires, and Córdoba. Immediately a few excellent graduate students joined me in my brand-new, but primitively equipped lab: Esper Cavalheiro, Lia Prado de Carvalho, Lineu Calderazzo, and Romeu Schutz. We decided to give continuity to the work on pseudoconditioning and to study its eventual role as a component of shuttle box avoidance conditioning. We reasoned that as there was an identifiable Pavlovian stimulus-pairing component and a separate avoidance contingency component in that form of learning (Rescorla and Solomon, 1967; Izquierdo, 1976), there could well be a pure "drive" or pseudoconditioning factor too, superimposed on the associative components, as suggested by my good friend Wanda Wyrwicka, with whom I exchanged abundant correspondence on this. I had in fact just described neurochemical correlates of pseudoconditioning, so it had a biological substrate of its own.

We trained rats in a shuttle box using acoustic stimuli as CSs and footshocks as USs, and we studied several control training modes: one in which tones and footshocks were interspersed randomly (pseudoconditioning), another in which they were paired on every trial regardless of responses (Pavlovian mode), and another one in which the CS-US interval was varied at random but USs were given only when there had been no shuttling to the last CS (avoidance contingency). We studied the effect of many drugs and several brain lesions on the four behavioral paradigms. Some treatments selectively affected the pseudoconditioning or "drive" component, others affected the Pavlovian component, and others the avoidance component (Izquierdo and Cavalheiro, 1976; Cavalheiro and Izquierdo, 1977; Schutz and Izquierdo, 1979). So we added one more factor, "pure drive" or pseudoconditioning, to the Pavlovian and the avoidance components of shuttle behavior studied by Rescorla.

Meanwhile, the discovery of LTP by Tim Bliss in 1973 opened up new possibilities for the biological study of consolidation, and LTP was immediately regarded as a memory model. We had continued to work on the effect of posttraining treatments on memory consolidation. In São Paulo we found that agents that released catecholamines peripherally could strongly affect consolidation (Gozzani and Izquierdo, 1976; Rachid et al., 1977). We were among the first to report brain noradrenaline and dopamine changes in brain regions after aversive training (Schutz et al., 1979).

In addition, our laboratory studied some effects of acute and chronic ethanol on behavior, the EEG, and hippocampal RNA (Prado de Carvalho and Izquierdo, 1977, 1978; Prado de Carvalho et al., 1978). I was to go back to this field several years later, while visiting Jim McGaugh's laboratory, where we found that the amnesic effect of repeated alcohol intoxication could be overcome by muscarinic agonists given systemically (Brioni et al., 1989).

In 1977, Tuiskon Dick, still Dean of the School in which I had worked in Porto Alegre, made good on his promise to create the conditions so that I could eventually return to that city. He gave me a list of equipment and supplies that he could make available for my group and offered to hire some of my current collaborators. Since both my wife and I longed for the less hectic life of Porto Alegre, and now that there seemed to be a possibility to continue my research at a decent level there, we said yes. The return to Porto Alegre was a big challenge: I would have to set up research from scratch in a place where there was virtually none in my field. Dick´s offer had caught me by surprise since I had arranged to spend 6 months with Hymie Anisman in Ottawa. So off to Ottawa we went for part of 1978, and later that year we moved from São Paulo back to Porto Alegre.

Ottawa and Then Porto Alegre

In Carleton University in Ottawa, Hymie and I studied the role of brain catecholamines in different forms of avoidance behavior (Izquierdo et al., 1979), and I also did some research with my old friend César Galeano in Michel Chrétien's lab in the Institute de Récherches Cliniques of Montreal, a great place. We tried to study memory consolidation in mice carrying tumors that secreted pro-opiomelanocortin, the precursor protein to MSH, ACTH, and β-endorphin. We worked a lot and came out with the impression that consolidation and/or retrieval was hampered in those animals, but we had no good controls; regular mice not implanted with tumors were inadequate for that purpose, and so were mice with other kinds of tumors. Michel gave me an ampule of naloxone as a symbolic present and expressed his hopes that it could help me find some physiological role for endogenous opioids on learning and memory back home.

On the way back, Ivone, Juan, Eduardo, and I drove to Florida and spent several days with my good friend Steve Zornetzer in Gainesville. Steve had taught Esper Cavalheiro in São Paulo how to establish status epilepticus in rats by electrical stimulation of the hippocampus, and Esper then converted this into a new procedure to study that phenomenon using peripheral pilocarpine injections instead of electrical stimulation. Esper spent some years in France with Robert Naquet developing his research on epilepsy, and then returned to the Escola Paulista, where he introduced his new line of work, became chief of our old lab, and received world recognition for his discoveries in the field of temporal lobe epilepsy.

In Florida, overlooking an alligator pond, Steve Zornetzer discussed with me his new ideas on endogenous state dependency. He suggested that memories acquired and/or consolidated in a given neurohumoral/hormonal state should be best retrieved when the animal was in a similar state again. This would explain why in a situation of fear we do not readily recall alimentary

behaviors but rather strategies to cope with fear, and why in situations of sexual excitement we recall sex rather than hunger or fear.

The Opioids

The return to the Federal University in Porto Alegre in early 1978 was one clear example of how things can change rapidly in countries with a high metabolic rate like Brazil. I was reallocated to the Department of Biochemistry, where I found some people interested in research. Dick had purchased much of the equipment we needed, and now there was even grant support, mostly from a State Agency. None of this had been there 4 years before.

While my new lab was being set up, I decided to test the posttraining effect of the naloxone given to me by Michel Chrétien on memory consolidation of shuttle avoidance and habituation to a tone. I found a large memory-enhancing effect with the drug in the two tasks, which could be reversed by morphine, which was amnestic on its own. My paper was immediately accepted (Izquierdo, 1979) and appeared more or less simultaneously with one by Jim McGaugh and his group showing the same in an inhibitory avoidance task, and a month after one by Michaela Gallagher describing a similar effect with intra-amygdala infusions. So it appeared that there could be a physiologic amnesic role for endogenous opioids. Among the collaborators of Jim's paper was Beatriz Vásquez, my former graduate student from Córdoba, who was now married to an American and living in California.

I set up a group to study the opioid story in more detail. Maria Angelica Carrasco from Chile, Renato Dias, and the current Rector of that University, Carlos Alexandre Netto, were in that group, among others. Following Gallagher's lead, we placed a bet on the amygdala and found that systemic naloxone increased cAMP levels in that area (Dias et al., 1979); so the amygdala became a putative site of action. Soon afterward, we found that the memory-facilitating effect of naloxone was due to the release of dopaminergic and noradrenergic mechanisms from tonic inhibition by endogenous opioids (Izquierdo and Graudenz, 1980). Right away, we found that at least two endogenous opioids, leu-enkephalin and β-endorphin, caused retrograde amnesia both for avoidance and habituation learning (Izquierdo et al., 1979), so the two were potential candidates for the purported "amnesic" role of opioids (Izquierdo, 1981). We found that different forms of behavioral training caused a sudden reduction of brain β-endorphin levels that lasted 3–6 hr and was interpretable as due to a release of the peptide (Izquierdo et al., 1980). At the same time, other laboratories were beginning to find that the effects of the enkephalins on memory were probably peripheral in origin, so the endorphins became better candidates as brain modulators than the enkephalins, so we concentrated on brain β-endorphin.

My good friend Béla Bohus in David de Wied's lab in the Netherlands had shown that β-endorphin and other endorphins given prior to testing

enhanced retrieval (see references in Izquierdo, 1982). I figured that perhaps Steve Zornetzer's ideas on state dependency could apply to opioid effects. Brain β-endorphin could be acting posttraining in order to induce a state from which memories would become dependent, and naloxone would act by reducing this dependence. We subsequently found that this was the case (Izquierdo, 1980, 1981, 1989, 1991; Izquierdo and Netto, 1985) and so discovered endogenous state dependency for β-endorphin. In the early 1980s we extended the endogenous state dependency hypothesis to the posttraining amnestic effect of ACTH and the catecholamines at high doses (Izquierdo and Dias, 1983; Izquierdo, 1984, 1989).

The release of brain β-endorphin caused by training resulted from the novelty of the training procedure (Netto et al., 1985). Consequently, the presentation of a novel experience (a new environment, a new task, etc.) prior to retention testing enhanced retrieval, presumably by the release of brain β-endorphin, and this effect was counteracted by naloxone. This effect was observed in rodents (Izquierdo and McGaugh, 1985; McGaugh and Izquierdo, 1987) and in humans (Izquierdo and Chaves, 1986).

The opioid peptide story or stories made a big impact and our 1979 naloxone paper immediately became one of the most cited papers in the field of memory modulation. For a long time, naloxone was the most widely studied memory facilitating drug ever, in more tasks and species, including humans, than any other substance (see Izquierdo, 1991a).

Other findings of the 1980s were the effects of posttraining intracerebroventricular histamine on memory consolidation (Almeida and Izquierdo, 1986), which we have revisited recently (Da Silva et al., 2006); the peripheral origin of some of the effects of ACTH and adrenaline on memory (Almeida et al., 1983), and the finding with Larry Cahill and Jorge Brioni that posttraining diazepam, by interfering with the retroactive interference caused by other behaviors, could actually enhance the memory consolidation of avoidance learning (Cahill et al., 1986). This effect was reproduced in humans (Chaves et al., 1990) and may be related to some of the anxiolytic effects of benzodiazepines.

The Beginning of Something New

Toward the end of 1988, in a small Neuroscience symposium near Montevideo I met Jorge Medina, the last disciple of De Robertis, who had died in April that year, and was now in charge of the old master's lab. Medina gave a talk on the presence of endogenous benzodiazepine-like compounds in the brain. He and I had lunch after his talk and we decided to work together on the benzodiazepine story. We became friends from that moment on. Through the years our friendship has grown and grown. In January 1989 I visited his lab for the first time, and we decided to start a collaboration uniting the two labs. We both felt that the opioids had already given us all they could give as

memory modulators, that central and peripheral catecholamines and acetylcholine were already being studied by too many groups, so why not give the putative endogenous benzodiazepines a try. We thought that they might give us a handle into $GABA_A$ receptor–mediated control of memory consolidation, and that this could lead us eventually into the core mechanisms of memory. I had looked at the putative core mechanisms of memory with awe from a distance, as Jim McGaugh had done, over many years. I had felt that the field was not ripe yet for study, since so much of what was published on glutamatergic transmission and LTP had been hypothetical so far, and the eventual role of LTP in memory formation itself seemed difficult to prove. But, Jorge Medina and I now thought, perhaps endogenous benzodiazepine-like molecules could turn out to be a hitherto unsuspected powerful tool for the study of memory formation, entering through the back door of GABAergic transmission.

Jorge and his group and I and my group got together and decided to face the music of endogenous benzodiazepines and dance. At that time, for the first time in years, I had funds; Brazilian support of scientific research had increased a lot since 1973. Over the years, often with sudden oscillations that leave you breathless (and penniless), it continued to improve. One important collateral benefit of the association between Jorge's lab and mine is that often when one of the two had no funds, the other did; so it has been great for survival.

The first experiments Jorge and I did were quite simple. The systemic administration of flumazenil (an antagonist of the benzodiazepine central-type receptor) or of n-butyl-beta-carboline (an inverse agonist at that receptor) enhanced, and that of the benzodiazepines diazepam or clonazepam depressed, acquisition of one-trial inhibitory avoidance. Flumazenil reversed the effect of the agonists. Flumazenil and the beta-carboline also enhanced retention of habituation to a sound (Izquierdo et al., 1990a,b). The findings suggested an inhibitory modulation of memory formation by endogenous benzodiazepine-like ligands acting on $GABA_A$ receptors in the brain.

Next, we studied the levels of endogenous benzodiazepine immunoreactive substances in the amygdala. Stepping down from the training platform decreased those levels and the ensuing footshock decreased it further. The simplest interpretation was that the immunoreactive substance(s) were released from storage sites by training. Pretraining intra-amygdala flumazenil enhanced memory consolidation (Izquierdo et al., 1990a). This further suggested an inhibitory role of endogenous benzodiazepines in memory formation. We then showed that the $GABA_A$ Cl^- channel blockers, Ro5–4864 and picrotoxin given ip., icv., or into the amygdala caused memory facilitation, and that the specific blocker of the Ro5–4864 (and benzodiazepine) sensitive site of the $GABA_A$ receptor, PK11195, canceled the effect of Ro5–4864 on memory, but not that of picrotoxin (Da Cunha et al., 1991).

Then we reported that both habituation to a novel environment and inhibitory avoidance cause abrupt falls of brain regional levels of benzodiazepine-like molecules and that memory of the two tasks can be enhanced by intracerebral flumazenil microinjection. Stepping down from the platform and receiving a small footshock reduced benzodiazepine-like substance levels substantially in cerebral cortex, amygdala, septum, and especially in hippocampus as compared with untrained rats. The immediate posttraining bilateral intrahippocampal (but not intraseptal or intra-amygdala) injection of flumazenil at very low doses enhanced the retention of habituation; the drug enhanced retention of inhibitory avoidance when given into any of the three structures (Wolfman et al., 1991).

At this point, Medina and I were invited to write a review article on endogenous benzodiazepines and memory for *Trends in Pharmacological Sciences* (Izquierdo and Medina, 1991) and to edit a book on the subject of endogenous benzodiazepines (Izquierdo and Medina, 1993). We had found a new set of down-regulators of consolidation, the putative endogenous benzodiazepines, which could be placed side by side with β-endorphin and other substances as major modulators of memory. But given the difficulty to further characterize them chemically, and the strong possibility that the catecholamines, serotonin, and acetylcholine were much more important modulators, the field sort of fizzled out. There was no possibility of using flumazenil clinically as a memory enhancer in humans because the drug was found to be anxiogenic (Da Cunha et al., 1993). It is clinically used, however, to clear up the cognition deficit seen in liver insufficiency, in which the metabolism of endogenous benzodiazepine-like compounds is impaired (see Izquierdo and Medina, 1993).

We were left with a handle on $GABA_A$ receptors as strong modulators of memory consolidation, which is what we had been looking for. Meanwhile, progress on the various parallel and serial molecular processes triggered by glutamatergic receptors and involved in LTP had become substantial all over the world (see Izquierdo, 1993 for references).

The Real Thing

Jorge Medina and I finally found the courage to attack the core mechanisms of memory formation. Our strategy was very simple: We tested the effect on memory consolidation of bilateral infusions into CA1 in live, behaving animals of all the drugs that were being or had been tested by others on CA1 LTP in slices (see Bliss and Collingridge, 1993). We studied receptor agonists and agonists, drugs that affected the levels of second messengers, and stimulants and inhibitors of a variety of enzymes, mostly protein kinases, given at various posttraining intervals. In addition, we assayed the binding characteristics of the receptors, the levels of the second messengers, and the activity of the enzymes at the same posttraining intervals. The task chosen

was one-trial inhibitory avoidance, then the most widely used in learning studies. It is acquired in a few seconds, so the moment of the initiation of its posttraining consolidation period can be readily determined, uncontaminated by the consolidation of further trials or the retrieval of preceding trials (Izquierdo and Medina, 1997; Izquierdo et al., 2006).

The time seemed finally ripe for the study of memory consolidation in the hippocampus and related brain areas. First, the hippocampus was now generally acknowledged to be the major site of posttraining consolidation (see Squire, 1987; Izquierdo and Medina, 1995, 1997; McGaugh, 2000 for references). Second, there was now a good electrophysiological model to guide our study: LTP, whose underlying mechanisms were beginning to be unraveled (Bliss and Collingridge, 1993). LTP involves long-lasting changes of synaptic strength that, in CA1, rely first on glutamate receptor activation, followed by that of a sequence of protein kinases many of which cross-talk with each other, and then by gene activation and protein synthesis.

We thought that the search for the actual occurrence of LTP during memory consolidation, which seemed to worry most investigators up to the early 1990s (Izquierdo, 1993; Bliss and Collingridge, 1993), was less important than the search for the biochemical steps of memory consolidation itself. In 1991–1992, too little was known about the molecular processes of consolidation and almost nothing about their timing in the posttraining period; but a lot was beginning to be known about LTP. If the sequence of molecular events of consolidation in CA1 turned out to be similar to that of local LTP, then they would be easier to interpret in terms of synaptic changes, regardless of whether actual LTP can or cannot be detected during consolidation. (As will be seen, it can).

As had been the case with LTP (see Bliss and Collingridge, 1993; Izquierdo, 1993; Izquierdo and Medina, 1995 for references), our approach to the study of the biochemical basis of memory formation in the hippocampus and elsewhere was mostly pharmacological, using localized microinfusions of drugs with specific molecular effects (enzyme inhibitors, neurotransmitter agonists or antagonists, etc.). But for us it was also important to measure the activity and/or levels of those substrates at various times after training; that is, we wanted to know not only the nature but also the time course of the changes. Such biochemical measurements are usually not done in LTP studies, chiefly because these are carried out in slices. Since we used whole, behaving animals in order to measure memory directly, we were also able to carry out biochemical determinations in the hippocampus during various phases of memory formation directly (Izquierdo and Medina, 1997; Izquierdo et al., 2006). The importance of establishing the time course of each biochemical step studied was because we needed to compare the pharmacological and biochemical measures not only with each other but also with those known to occur in LTP (Izquierdo et al., 2006). The use of genetically manipulated animals was impractical because in them the changes are

permanent and we were keen on the determination of time courses of reversible changes. Conditional knockouts or virus-transported proteins were not available in those days.

Over 200 students and collaborators were to participate in this work over the next 20 years. Those with whom I published more papers were Martin Cammarota, Lia Bevilaqua, Ramon Bernabeu, Luciana Izquierdo (the wife of my son Juan), Monica Vianna, Claudia Wolfman, Lina Levi de Stein, Daniela Barros, Joao Quevedo, Carlos Alexandre Netto (currently Rector of the Federal University at Porto Alegre), Roger Walz, Marino Bianchin, Jorge Quillfeldt, Diana Jerusalinsky, Marcia Chaves, Claudio Da Cunha, Juliana Bonini, and Janine Rossato. One of them, Claudia Wolfman, who died very young, had attended the same high school I did, but 25 years later; so we shared many memories a quarter of a century out of phase. She was a great friend.

From Neurotransmitters to Early Genes

Our first two papers on the molecular basis of memory consolidation were on the neurotransmitters involved in that process, and they ended up coming out in the same issue of *Behavioral and Neural Biology* (Izquierdo et al., 1992; Jerusalinsky et al., 1992). In the first we showed that immediate posttraining bilateral infusion of the glutamate NMDA receptor antagonist, AP5, into the dorsal CA1 region of the hippocampus, the basolateral amygdala, or the medial septum caused retrograde amnesia for inhibitory avoidance and for habituation learning in rats. The medial septum and basolateral amygdala are two major connections of the hippocampus. Similar effects were obtained with scopolamine, muscimol, and timolol. On the contrary, glutamate, oxotremorine, and noradrenaline caused retrograde memory facilitation. This indicated that glutamate NMDA, cholinergic muscarinic, and β-noradrenergic receptors were necessary for memory consolidation of the two tasks immediately after training in the three structures, and that $GABA_A$ receptors inhibited it. In the second paper we studied the posttraining time course of the amnestic effect of AP5 and of the glutamate AMPA receptor blocker, CNQX, given into CA1, the basolateral amygdala, and the entorhinal cortex. We found that AP5 was amnesic when given into any of the three structures only shortly after training, but CNQX was amnesic when given up to at least 3 hr posttraining in the one-trial avoidance task. The results with the time course of the NMDA and the AMPA receptor blocker were reminiscent of work carried out on CA1 LTP by my good friend Klaus Reymann, from Magdeburg (see Izquierdo, 1993). Subsequently we found a very protracted posttraining time course of ^{3}H-AMPA binding to hippocampal cells (Cammarota et al., 1995), in agreement with data in the literature on other hippocampus-dependent tasks (see references in Izquierdo and Medina, 1995, 1997). The immediate posttraining

role of metabotropic glutamate receptors in consolidation was then ascertained first through the intrahippocampal administration of a nonspecific antagonist (Bianchin et al., 1994) and years later through the use of specific antagonists (Bonini et al., 2003).

Importantly, our findings were compatible with the widespread idea that LTP or a very similar process could underlie memory consolidation, and in addition agreed with those of many others available at that time on a key involvement of muscarinic cholinergic and β-noradrenergic receptors in the modulation of memory formation in the areas studied (see Izquierdo and Medina, 1997; Izquierdo et al., 2004, 2006; Prado et al., 2006 for references).

Soon afterward, we found that blockade of the posttraining hippocampal synthesis of the so-called retrograde messengers linked to cGMP-dependent kinase (Bernabeu et al., 1997b), CO (Fin et al., 1994; Bernabeu et al., 1995), and NO (Fin et al., 1995), and blockade of the platelet-activating factor (Izquierdo et al., 1995) disrupted memory consolidation. This suggested a role of the three messengers in memory consolidation in hippocampus (Medina and Izquierdo, 1995). This was to be expected from the fact that all of them enhance glutamate release (see Medina and Izquierdo, 1995; Bernabeu et al., 1997a). We have recently extended this role of NO to the basolateral amygdala (Zinn et al., 2009). The NO mechanism in amygdala is linked by a β-noradrenergic mechanism to the expression of the multifaceted brain-derived neurotrophic factor (BDNF) and is involved in consolidation of object recognition memory (Furini et al., 2009).

Following the steps of my good friend Aryeh Routtenberg, we investigated the role of hippocampal protein kinase C in memory consolidation of the one-trial step-down avoidance task. The postinduction administration of inhibitors of this enzyme family hinders the establishment of long-lasting LTP (see references in Izquierdo, 1993). In accordance with this, we observed that the infusion of inhibitors of this enzyme into CA1 caused retrograde amnesia; the effect was maximum 30 min posttraining and then declined over the next 2 hr (Jerusalinsky et al., 1993). Activity of the enzyme, and phosphorylation of its substrate, the presynaptic protein GAP-43, followed a similar time course, with a peak 30 min posttraining and then a decline (Bernabeu et al., 1995). The main PKC isoform involved was later identified as being PKCβ1 (Paratcha et al., 2000). More recently we described a role for PKC in memory consolidation also in amygdala and parietal cortex (Bonini et al., 2005).

Then we studied the involvement of hippocampal calcium calmodulin kinase II (CaMKII) in memory consolidation. The enzyme had been found to play a crucial role in the early phase of CA1 LTP in part mediated by phosphorylation of the AMPA-sensitive GluR1 (Bliss and Collingridge, 1993). Infusion of the CaMKII inhibitor KN62 into CA1 or the basolateral amygdala in the first couple of hours after inhibitory avoidance training caused retrograde amnesia; the effect was lower if infusions were delayed 1 or 2 hr

(Wolfman et al., 1994). Time- and training-dependent increases in CaMKII activity correlated with GluR1 phosphorylation were reported at about the same time for LTP and for one-trial avoidance (see Cammarota et al., 1998).

Next, we turned to the cAMP-dependent protein kinase (PKA) in hippocampus. This enzyme had been shown by Kandel and his coworkers to be important for the phosphorylation of the constitutive transcription factor CREB, a step crucial for the establishment, 2–4 hr after induction, of LTP (see Izquierdo and Medina, 1995, 1997). Phosphorylated CREB is a molecular marker of consolidation processing and novelty detection (Viola et al., 2000; Izquierdo et al., 2001). We found a peak of hippocampal PKA activity immediately after one-trial avoidance training, followed by a second peak 2–6 hr later. Both peaks correlate with increases in cAMP levels (Bernabeu et al., 1996), with the requirement of hippocampal D1 receptor activation, and with peaks of pCREB levels (Bernabeu et al., 1997a). The existence of the two peaks agreed with previous findings by Hansjürgen Matthies and his collaborators in the 1960s, and with our own later finding, of two simultaneous peaks of gene expression (Igaz et al., 2002) and both anisomycin- (Quevedo et al., 1999) and rapamycin- sensitive protein synthesis (Slipczuk et al., 2009).

Then we studied the participation of the hippocampal extracellularly regulated kinase (ERK) system in consolidation. As had been the case with PKA, the involvement of the ERK system in the establishment of LTP had also been established before—in this case by David Sweatt and his group in Texas. Inhibitors of the enzyme that converts ERK1 into ERK2 infused at different times after training in CA1 caused retrograde amnesia for the avoidance task (Walz et al., 1999, 2000; Alonso et al., 2002b). Cammarota et al. (2000) showed that the posttraining increases of CaMKII, PKC, PKA, and ERK2 triggered by one-trial avoidance learning required the previous activation of NMDA receptors in CA1 at the time of training. The ERK activity increase that follows behavioral training in the hippocampus is related to the aversive component of the tasks (Alonso et al., 2002a, b).

We demonstrated a role in consolidation for a variety of other kinases as well, at different times after training: phosphoinositide 3-kinase (Barros et al., 2001), the N-terminal Jun kinase (Bevilaqua et al., 2003a); Src-kinase (Bevilaqua et al., 2003b), and the p38 kinase (Rossato et al., 2006). In all cases their role and its time course were similar to those reported for LTP (see the last three mentioned papers for references).

We also showed that, again much like in LTP, nerve growth factor (NGF) and particularly BDNF are important for memory consolidation, the former in the hippocampus (Walz et al., 2000) and the latter both in the hippocampus (Alonso et al., 2002) and the parietal cortex (Alonso et al., 2005); in the former for both short- and long-term memory and in the latter only for long-term memory consolidation.

We found that the early genes Fos, Jun, Src, Elk, Fra-1, and zif268 are all produced in the hippocampus after training in the one-trial avoidance task (Cammarota et al., 2000; Paratcha et al., 2000). The findings fitted with those of others in other tasks (see Izquierdo and Cammarota, 2004).

Meanwhile, a Major Change

In May 2003 I reached my 25 years of service at the Federal University and retired. Fortunately I received an offer from the Pontifical Catholic University of Rio Grande do Sul (PUCRS). It was the kind of offer one cannot refuse: They wanted me to install a brand new Memory Center, so they offered to build a new set of laboratories and asked me to bring my current collaborators to work with me. So I accepted, and through the good offices of the Catholic University the transition was very smooth and we were all able to keep on working more or less as usual while the complex process of moving went on. A bit like the last part of Haydn's "Farewell" symphony in which the musicians leave one by one but the music goes on. Here we did leave, but we were moving to another orchestra just a few blocks away. The smoothness of the move was guaranteed by the efforts of Lia Bevilaqua and our invaluable technician and factotum, Daniela Montenegro Cardoso (wife of my son Eduardo). The students (Janine Rossato, Juliana Bonini, Julia Clarke, Ramon Lima, Weber Da Silva, Cristiano Köhler) and our two postdocs (Martin Cammarota, Lia Bevilaqua) came along.

The Memory Center of PUCRS was officially inaugurated in 2004. By early 2005 the transition had been completed, and all our research activity has been since then carried out at the Memory Center of the Pontifical Catholic University. I was appointed Full Professor of Neurology at the Catholic University Medical School and head of the new Center. Martin Cammarota was shortly afterward appointed Associate Professor and vice-director of the new unit. More recently Lia Bevilaqua and Janine Rossato were also appointed Associate Professors, and we were given funds for four postdoctoral fellows in the new lab.

On with the Show

During this transition, with my good friends Ricardo Brentani and Vilma Martins, from the Ludwig Institute of São Paulo, we showed that posttraining activation of PKA and the ERK pathway requires binding of the physiological prion protein to laminin (Coitinho et al., 2006) and to the stress inducible factor I (Coitinho et al., 2007), which may be among the hitherto unknown physiological roles of the physiological prion protein (Linden et al., 2008). The knockout of this protein in mice or the action of an antibody against it in rats results in memory impairments visible only after the age of 8–9 months (Coitinho et al., 2003).

With my friends Marco and Vania Prado, now in the Robarts Research Institute of the University of Western Ontario, we examined the deficits of learning and memory in mice unable to express the vesicular acetylcholine transporter (Prado et al., 2006).

In the new lab we investigated the effect of a number of drugs that influence CaMKII, ERK, and PKA activity when given at various times post-training on retention of the one-trial task (Rossato et al., 2004; Bonini et al., 2005; Bevilaqua et al., 2005). We found that although the effects are qualitatively similar across brain structures (basolateral amygdala, entorhinal cortex, parietal cortex), their time course is different in each one of them. So these other brain structures probably also participate in consolidation using the various signaling pathways studied, but in sequences different from those of CA1 LTP (Izquierdo et al., 2006).

We found that synchronously with the two peaks of transcription-dependent, anisomycin-sensitive protein synthesis in CA1, two parallel peaks of mTOR-mediated translation are also required in the hippocampus for memory consolidation of both the one-trial avoidance task (Bekinschtein et al., 2007) and an object recognition task (Myskiw et al., 2008). The m-TOR-mediated translation occurs mostly at dendrites making use of preexisting mRNAs, is regulated by BDNF and mediates the synthesis of GluR1, essential for memory formation (Slipczuk et al., 2009).

Thus, step by step, over 15 or so years we have shown that memory consolidation of one-trial avoidance and other tasks uses the CA1 region of the hippocampus and involves the same steps that have been described for local LTP in the same sequence and with the same time course (Izquierdo and Medina, 1997; Izquierdo et al., 2006). In addition, we showed that other brain regions are also involved, among them the basolateral amygdala, the medial septum (Izquierdo et al., 1992), the entorhinal cortex (Izquierdo et al., 1995, 1997; Ardenghi et al., 1997), and the anterodorsal and medial prefrontal cortex (Izquierdo et al., 2007). Several of the molecular changes that occur in CA1 and are also seen in the basolateral amygdala depend on the previous activation of NMDA receptors in the former and on that of noradrenergic β-receptors in the latter (Cammarota et al., 2008). In CA1 but not in the other regions the mechanisms of consolidation are similar to those of CA1 LTP (Izquierdo et al., 2006), and indeed LTP of the CA3-CA1 Schaeffer collaterals pathway was described that same year during the consolidation of one-trial inhibitory avoidance by Whitlock et al. (2006) and in trace eyeblink conditioning by Gruart et al. (2006). Furthermore, LTP of the CA3-CA1 synapse carried out prior to training occludes acquisition of the eyeblink task and others. These findings were extended recently to a nonaversive task, object recognition, whose consolidation also requires the CA1 region (Clarke et al., 2010). This last finding points to a general role of the molecular chain of events of LTP in the processing of memory consolidation in CA1 and was obtained in collaboration with José María Delgado-García's group in Seville.

So we have identified the main molecular events underlying memory consolidation in CA1 in live, behaving animals and found them to be very similar to those of LTP in hippocampal slices. This, of course, can be taken to endorse the numerous postulations of LTP as a (if not *the*) substrate of memory, particularly hippocampal LTP (see Bliss and Collingridge, 1993; Izquierdo and Medina, 1995; Whitlock et al., 2006 for references). However, we still do not know if the similarities between the biochemistry of LTP and memory consolidation in CA1 simply reflect the fact that both processes require a similar molecular chain of events leading to synaptic strengthening, or indicate instead a role of actual LTP in memory formation. The occurrence of LTP at the CA3-CA1 synapse seen during consolidation could be a side effect of the molecular changes, rather than a causally related phenomenon. Obviously other brain areas that consolidate memories use different processes and/or different forms of LTP for this, inasmuch as their posttraining biochemistry is different from that of CA1 (i.e., entorhinal, parietal, and cingulate cortex, etc.; Izquierdo et al., 2006).

Short- and Long-Term Memory

Memory can be measured in the first few minutes or hours after acquisition, or many days or even years later. Is it the same memory trace at the early and the late measuring periods? In other words, are short- and long-term memory (STM, LTM) parts of a single process, or is each of them a different form of memory? William James raised this fundamental question in his famous book *Principles of Psychology* (1890), in which he actually termed them primary and secondary memory. STM has long been known to decline fast and to be labile; LTM supposedly contains less information but is much more stable (although this view has been highly contested in the past 10 or 20 years).

Many people grew accustomed to thinking that memories begin as short term and are then transformed by new proteins or something else into long-term memories. But if this were so, a suppression of STM should necessarily prevent LTM from taking place. This is not the case in clinical observations. Indeed, a failure of short-term memory with preserved long-term memory is typical of delirium, and it has been reported in patients with neocortical lesions (Warrington and Shallice, 1969).

We studied the dichotomy between STM and LTM in detail in a series of articles that began with a note in *Nature* in 1998. To make a very long story short, over the years we reported that 11 different drug treatments given into either hippocampus or entorhinal cortex selectively block the short-term memory of one-trial inhibitory avoidance measured 1.5 or 3 hr after training without affecting the LTM for the same task in the same animals, and another 15 treatments affect both memory types differently (i.e., they

enhance STM and depress LTM, or do not affect one of the two but strongly affect the other; Izquierdo et al., 1998, 1999, 2000, 2001; Vianna et al., 1999). Besides, we were able to extricate in relative detail the separate involvement of discrete signaling systems, such as the PKA (Vianna et al., 1999) and the ERK pathways in the hippocampus in both STM and LTM (Igaz et al., 2006). Depending on the time at which inhibitors or stimulants of the enzymes are infused, they can separately affect one or the other memory type by actions on different substrates (Vianna et al., 1999; Izquierdo et al., 2000, 2001).

We have thus shown that the STM that lasts up to 3 hr and the LTM that lasts days or weeks involve two distinct, parallel but essentially separate processes. There are several types of STM, however; one of them lasts a few seconds or minutes and is used as working memory (see Izquierdo et al., 2001, 2007), and others last several hours and are often called intermediate memories. A comparative analysis of these other STM types is desirable, but the limits between them are tenuous and that analysis is difficult (Izquierdo et al., 2007).

Does the Long-Term Trace Travel?

In most accounts of memory, declarative memories are supposed to depend on the hippocampus for a limited period of time, after which the neocortex can support memory on its own (Squire, 1987).

In a study that became instantly popular because it superficially appeared to fit with that notion, we found that the AP5- and muscimol-sensitive mechanisms thought to be responsible for the onset of memory consolidation of inhibitory avoidance enter into play in hippocampus and amygdala right after training, 30–60 min after training in the entorhinal cortex, and 60–180 min after training in the posterior parietal cortex (Izquierdo et al., 1997). More recent research suggests that different molecular systems involved in consolidation enter into play at different times in the first 3–6 hr that follow one-trial avoidance training in different brain areas (Bonini et al., 2003; Izquierdo et al., 2006). Retrieval of this task can be blocked by CNQX given into any of the four structures 1 day after training, or into entorhinal or parietal cortex but not hippocampus or amygdala 1 month later, or into the parietal cortex but not in the other three regions 2 months later (Izquierdo et al., 1997).

Perhaps memory traces do not "travel," but are recorded in rapid sequence or simultaneously in multiple sites, possibly using different biochemical processes in each; and then some of the sites lose importance over time, because of disuse, aging, or other factors. The different persistence of the traces in different sites may account for what many regard as its "traveling" from one site to another over time.

Extinction Learning

In recent years, attention was drawn to consequences of retrieval upon memory (see Vianna et al., 2001; Cammarota et al., 2005). It had been known since Pavlov (1927) that repetition of conditioned stimuli without reinforcement leads to extinction, which is a learned inhibition of retrieval. If animals or humans, after having been trained to associate a given set of stimuli (CS) with another set of stimuli (US), are presented repeatedly with the CS alone, omitting the US, they learn to associate the CS with the lack of US. The new association (CS–no US) replaces the former CS–US association, and subjects learn to inhibit performance of the original conditioned response.

Knowledge of the mechanisms of extinction is important both for physiology and for clinical practice. Extinction is widely used, often under the name of "exposure therapy" for the treatment of the posttraumatic stress disorder and other forms of fear-related memory disturbances (Izquierdo et al., 2008); patients are reexposed to aspects of a traumatic experience but without the fear or the consequences originally associated with it. So in 2001 we began to study the possible role of the hippocampus, basolateral amygdala, and entorhinal cortex in extinction of the one-trial avoidance task, and the participation therein of signaling pathways, gene expression, and protein synthesis.

We clearly established that the initiation of extinction stems directly from retrieval, indeed from some of the molecular substrates of retrieval: It is blocked by a single hippocampal infusion of an NMDA receptor antagonist; or of inhibitors of PKA, CaMKII, and ERK; or of inhibitors of gene expression or protein synthesis given right before or after the first of several retrieval sessions (Vianna et al., 2001, 2003; Szapiro et al., 2003; Cammarota et al., 2004, 2005). Hippocampal PKA and ERK participate in the retrieval process (see Izquierdo et al., 2006). They are, of course, also necessary for the original consolidation (see earlier). Importantly, all these systems are required for extinction at the time of retrieval, but not minutes or hours later; therefore, they do not operate in sequence in extinction as they do in consolidation, but rather more or less simultaneously. Several of the same molecular processes (NMDA receptors, protein synthesis, PKA, and CaMKII) also play a key role in extinction in the basolateral amygdala (Vianna et al., 2004) and in the entorhinal cortex (Bevilaqua et al., 2006).

So we added several brain structures to the map of brain regions that control extinction and showed some of the molecular events involved in each. In all likelihood, extinction depends on the operation of different areas for different types of memory, and these act in concert in order to acquire the inhibition of the original learned response (see Izquierdo et al., 2008). Importantly, we established that extinction effectively is initiated by retrieval of the memory-to-be-extinguished, and it uses molecular processes

involved in retrieval itself (Vianna et al., 2001, 2003; Szapiro et al., 2003; Cammarota et al., 2004, 2005; Bevilaqua et al., 2006). In some particular tasks other brain regions may play a role in extinction, such as for example the insular cortex in conditioned taste aversion, a task that depends highly on that area (see references in Izquierdo et al., 2007; Quirk and Mueller, 2008).

Importantly, we also observed that, in the rat, an increase in the time of exposure to the lack of a footshock in an inhibitory avoidance extinction setting (i.e., the "no-US" component of the task) enhances extinction to the point of uninstalling a fear-motivated memory (Cammarota et al., 2003). This is of course directly applicable to exposure therapy.

Besides extinction, we also studied the more recently described process of reconsolidation that also originates from unreinforced retrieval, particularly if this is carried out shortly after the original training (Bevilaqua et al., 2010). After some difficulty in obtaining it in inhibitory avoidance (Izquierdo and Cammarota, 2004; Cammarota et al., 2004), we succeeded in detecting reconsolidation in tasks in which it had not been described before (object recognition, spatial learning), and its dependence on hippocampal protein synthesis (Rossato et al., 2006, 2007). The conditions under which extinction predominates over reconsolidation or vice versa are not yet known; except that the latter is not seen in test sessions carried out more than 2–5 days after the last training session.

Memory Persistence

Some LTMs may last just a day or two, and others may persist for many weeks or for a lifetime. In some cases the long persistence is accounted for by the degree of emotional arousal at the time of consolidation (McGaugh, 2000); that is, we all remember where we were and whom we were with when the 9/11 attacks occurred or when John Kennedy was shot. But in many cases persistence might have other causes: Many of us remember Ohm's Law or the Pythagoras theorem from high school regardless of their low emotional content.

In one of my periodical visits to Jorge Medina's lab, in 2006, we discussed the possibility that there could be some mechanism hours or days after memory consolidation that would ensure the persistence of some memories for a long time, independently of retrieval. So we talked it over with our common friend Martin Cammarota, who had obtained his Ph.D. with Jorge and has been in my lab since 2002. Subsequently we carried out a series of experiments in both labs in order to investigate putative mechanisms of persistence.

Our first findings in this new line came out in late 2007 (Bekinschtein et al., 2007a) and early 2008 (Bekinschtein et al., 2008b). We found that anisomycin given bilaterally into the CA1 region of the rat hippocampus 12,

but not 9 or 24 hr, after one-trial inhibitory avoidance training greatly impaired memory of the task measured 7 but not 2 days later. The same effect was obtained using an antibody against BDNF instead of anisomycin. Thus, intact protein synthesis, possibly that of BDNF, is needed in CA1 12 hr after training in order for memory to persist beyond 2 days and for at least 1 week (Bekinschtein et al., 2007b). This is 6 hr after posttraining consolidation is officially complete (McGaugh, 2000; Izquierdo et al., 2006).

The administration of human recombinant BDNF into CA1 12 but not 9 or 24 hr after training stimulated memory persistence beyond 2 days and overcame the deleterious effect of anisomycin or the antibody on memory persistence. In addition, we observed an increase of BDNF immunoreactivity in CA1 12 but not 9 or 24 hr posttraining that could be prevented by a BDNF-related antisense oligonucleotide but not by a missense oligonucleotide. The effects of BDNF on persistence depended on the phosphorylation of ERK1 and correlated with the enhanced expression of c-Fos and zif-268 24 hr after training. Inhibition of the synthesis of BDNF 12 hr after training by an antisense oligonucleotide impairs memory persistence beyond 2 days (Bekinschtein et al., 2008). These results added to several others on the effects of BDNF on memory obtained in our laboratories (see Alonso et al., 2005; Bekinschtein et al., 2008a) and pointed to a role of this substance in memory persistence as a major effect.

What triggers the release of BDNF that occurs in CA1 12 hr after training that enhances memory persistence beyond 2 days? Some observations in humans suggested that it could be a dopaminergic mechanism acting about12 hr after learning. After the age of 40 years, normal subjects remember correctly the name and the two main actors of a movie seen incidentally on TV 2 days before, but not those of a movie seen 7 days before; this forgetting was overcome by a low dose of the dopaminergic drug, methylphenidate (Izquierdo et al., 2008).

So we investigated the possible role of activation of the ventral tegmental area (VTA), a dopaminergic nucleus that innervates the CA1 and other areas of the brain (see references in Izquierdo et al., 2008 and Rossato et al., 2009). Infusion of the D1 dopamine receptor antagonist SCH23390 into CA1 12 hr, but not immediately or 9 hr, after one-trial avoidance made rats amnestic for this task 7 or 14, but not 2 days, after training with a 0.8 mA footshock. The effect was counteracted by intrahippocampal BDNF. In animals trained with a 0.4 mA footshock the memory did not last more than 2 days in controls but lasted 7 or 14 days in those treated with intrahippocampal infusions of the D1 agonist, SKF38393. In animals trained with a 0.8 mA footshock there was, and in those trained with 0.4 mA footshock there was not, an increase of hippocampal BDNF levels; the former was enhanced by SKF38390 and depressed by SCH23390. Stimulation of the VTA with NMDA 0 or 12 hr posttraining caused similar effects to those of BDNF or SKF38393 given into CA1. Inhibition of glutamate receptors with

AP5 given into the VTA immediately or 12 hr posttraining had similar effects to those of intrahippocampal SCH23390 or anti-BDNF administration. Thus, the persistence of long-term memory depends on activation of VTA-hippocampal dopaminergic connections and can be specifically modulated by manipulating this system at definite time points (Rossato et al., 2009). The VTA probably detects saliency of the data to be memorized (see Izquierdo et al., 2008; Rossato et al., 2009).

An additional, possibly related mechanism that regulates memory persistence occurs at 24 hr after training in the hippocampus: It involves the synthesis of various postsynaptic proteins in hippocampus (Bekinschtein et al., 2010) triggered by a late wave of c-Fos 12 hr posttraining (Katche et al., 2010). Data suggest this late event is linked to the dopamine regulated BDNF mechanism discussed earlier.

The VTA, BDNF, and c-Fos-dependent mechanisms of persistence are independent of sleep: They have been observed in animals trained in the morning or in the evening; that is, at the beginning or the end of the rat's sleep cycle (Bekinschtein et al., 2007b, 2008b, 2010; Rossato et al., 2009; Katche et al., 2010).

The findings noted in this section explain why some consolidated memories persist longer than others that had been similarly acquired and presumably consolidated. They point to the existence of one or more late postconsolidation mechanisms regulating memory persistence (Medina et al., 2008). These mechanisms can legitimately be viewed as the links between the initial consolidation process as defined by McGaugh (1966, 2000), which is now often called cellular consolidation, and the process that maintains long-term memory over weeks, months, or years, which is sometimes called systems consolidation (see Katche et al., 2010 for references). Cellular consolidation takes place in the hippocampus for many memories (see Clarke et al., 2010) and lasts a few hours (Izquierdo et al., 2006). Systems consolidation is believed to take place in the neocortex and to last weeks, months, or years (see Squire, 1987; Izquierdo et al., 1997). It is convenient for the duration of memory that the processing of the original memory trace persists long enough in the hippocampus so as to permit the initial steps of systems consolidation in the neocortex (Medina et al., 2008; Katche et al., 2010).

In addition, the findings commented in this section throw some light into the well-known fact that after 40 years of age—not necessarily in old age—we remember not-so-important things for a shorter time than we do when young. This may be a boon for a useful cognitive life. Perhaps to forget where we parked our car last Friday helps to remember where we parked it today. Perhaps to forget about last week's TV movie may help us concentrate on the results of the experiment we did last week or the business we have to do tomorrow. There must be a reason why world leaders are usually not chosen among those below 40 in fields involving some sort of intellectual

endeavor, from science to business and politics. Maybe it is useful to forget the not-so-important memories of a few days ago and concentrate on what really matters, including "the big picture." Borges said so much in *Funes the Memorious*: "One needs to forget in order to make generalizations, in order to think."

It seems that memory persistence is a postconsolidational phase that involves several distinct events in the hippocampus 12 hr after acquisition, dopaminergic activation by fibers coming from the VTA and hippocampal BDNF expression and ERK-mediated mechanisms, and c-Fos production; 24 hr posttraining, there is a new round of learning-related Fos-triggered protein synthesis. It also seems clear that the phase of memory that determines persistence is very important and that without it consolidation (or eventually reconsolidation) would be of little consequence in the long term. The obliteration of the persistence phase by dopamine blockers, or by an antibody against BDNF given into CA1 (Bekinschtein et al., 2008; Rossato et al., 2009), or of an antisense oligonucleotide that blocks c-Fos expression (Katche et al., 2010), 12 hr posttraining, effectively cancels the memory that had been acquired and consolidated. It becomes as if it had never existed.

Looking Back

While my work went on, Ivone's life and mine were changing slowly, but at a faster pace than we were conscious of. The two boys grew, became adults, got married, and had their own children, who are now our dear grandchildren, Francisco, Felipe, Maria Eduarda, and Mauricio. Their mothers are like two daughters for us.

We visited many lands and made many friends. Actually, one of the assets of being a scientist is, in my opinion, the large number of good friends one can make along the way.

My life has been intense and complex, and it involves many ties with many people. So, perhaps like everybody else, I became a complex embroidery of thoughts, reasonings, beliefs, and feelings that have their origin outside of me. I owe a lot to many of the persons mentioned in this text. The avatars of Argentine, Brazilian, and world politics no doubt had a big influence too, even though I stayed clear of them as much as I could.

I was invited to many meetings all over the world and received over 50 major national or international prizes and distinctions. In 2007 I was elected as a foreign associate of the National Academy of Sciences, which I view as one of the highest distinctions I ever received, together with my appointments as Doctor Honoris Causa of the University of Paraná and Honorary Professor of the Universities of Buenos Aires and Córdoba.

I participated a lot as advisor to the two major financing agencies of Brazil, the Financiadora de Projetos and the National Research Council,

and to the large cohort of scientists who articulated the current very extensive program of fellowships for graduate studies of Brazil. This program turned Brazilian science from the almost secret practice of a few into an endeavor of thousands. Once we get rid of the last remnants of amateurism and bureaucratism, Brazilian science and in particular neuroscience will grow fast. I am also advisor to scientific agencies of 20 countries of the Americas, Europe, and Asia. I am very proud of being one of the initiators and managers of the Brazil-Argentina agreements on Science & Technology, which has now become a large structure. I was assigned to this job because of the success of my long collaboration with Jorge Medina's lab, the longest-lasting and most productive joint scientific project between the two countries ever (Izquierdo, 2008).

So I was an Argentine neuroscientist during the first half of my life and a Brazilian neuroscientist during the second half. Legally, I have the two nationalities, which makes me glad for having been able to install memory research and good neuroscience centers in the two countries and thus contribute to their scientific development.

There Are More Things

This autobiography would be incomplete if I did not mention the key role that literature and music have played in my life. I have always been an avid reader and enjoy the sound and often the fury of words. I have written literature sporadically since 1950 and regularly since 1991. I published two books on memory for the lay public, as well as several books of essays and short stories in Spanish and in Portuguese. Writing began as a hobby; now it is a need.

Music has always been important for me. Beethoven, Mozart, Ellington, and Reinhardt play a major role in my life. Going to the opera, to concerts, or to the Spanish *zarzuelas* with our parents was a big thing for my sister and me during childhood. Now, Ivone and I sing pop songs regularly in a club in our neighborhood—she much better than I. We both had some formal training in music: I studied classic guitar between the ages of 7 and 18, and she studied the piano and practiced singing. After I entered medical school I never found the daily hours of training I would have needed to play the guitar reasonably well, and I felt frustrated. But now my grandson Felipe plays much better than I ever did. Every now and then he stays at our home over the weekend and Ivone and I wake up softly in the middle of the night with some beautiful music by Bach, Sor, or Tárrega coming from the living room. That is as close to heaven one can get while still alive. That, and talking about life with my loved ones, including some I used to play with on the floor (alas!) so few years ago.

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