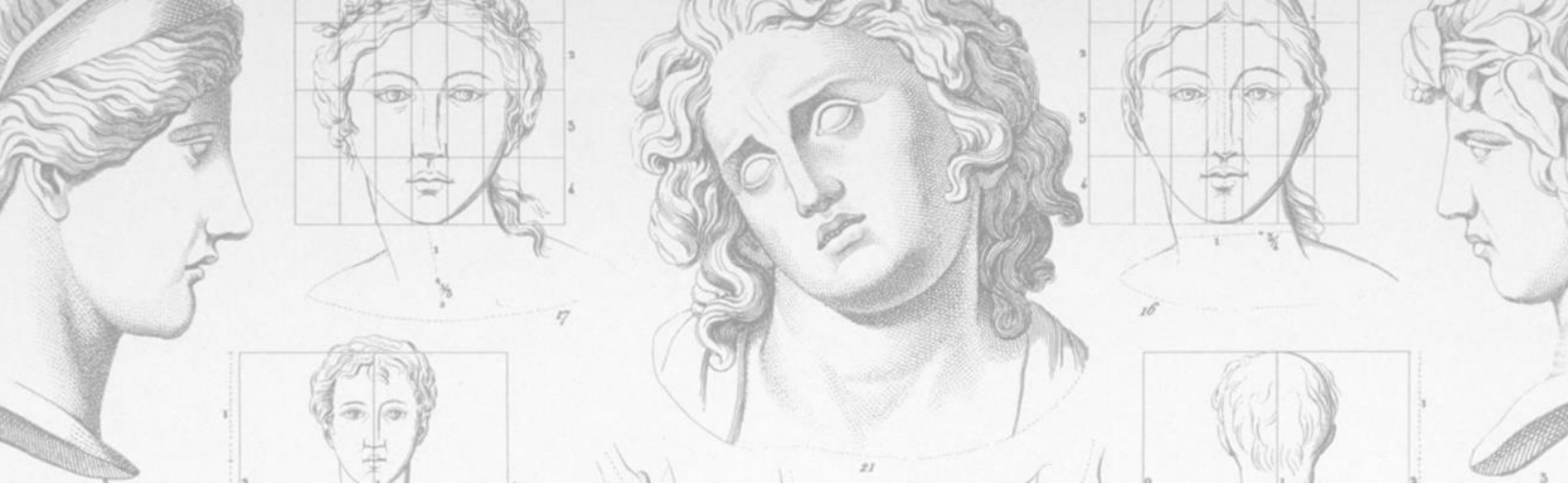

The History of Neuroscience in Autobiography
Volume 10

Edited by Thomas D. Albright and Larry R. Squire
Published by Society for Neuroscience
ISBN: 978-0-916110-10-9

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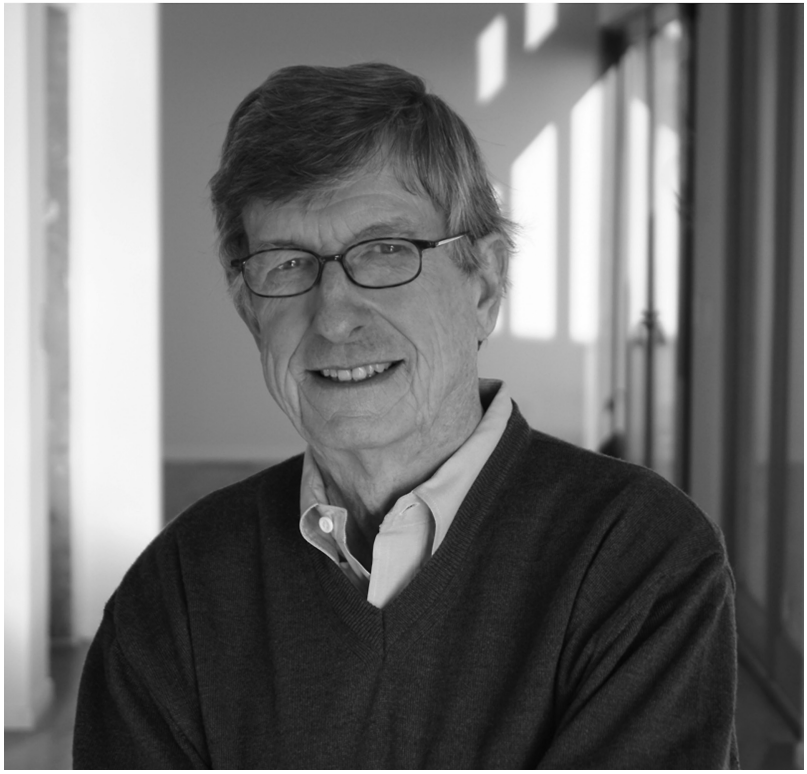
pp. 456–501

https://www.doi.org/10.1523/hon.010011



Roger A. Nicoll

Born:

Camden, New Jersey
January 15, 1941

Education:

Lawrence University, Appleton, Wisconsin, BA (1963)
University of Rochester, School of Medicine, MD (1968)
University of Chicago Hospitals and Clinics, Intern (Medicine) (1969)

Appointments:

Public Health Service, Research Associate (1969–1973)
Research Associate Professor, SUNY at Buffalo (1973–1975)
Assistant Professor, University of California, San Francisco (1975–1976)
Associate Professor, University of California, San Francisco (1977–1980)
Professor, University of California, San Francisco (1980–present)

Honors and Awards (Selected):

Borden Award: Best Research completed during Medical School (1968)
National Institute of Mental Health, Merit Award (1987–1997)
National Academy of Sciences (1994)
National Institute of Mental Health, Merit Award (1997–2007)
Lucie R. Briggs Distinguished Achievement Award, Lawrence University (1998)
Fellow, American Academy of Arts and Sciences (1999)
Morris Herzstein Endowed Chair (1999)
Heinrich-Wieland-Preis (2004)
Perl/UNC Neuroscience Award, with R. C. Malenka (2005)
Gruber Award for distinguished accomplishments in neuroscience, with M. Ito (2006)
National Institute of Mental Health, Merit Award (2007–2017)
24th Annual J. Allyn Taylor International Prize in Medicine, with M. Greenberg (2008)
National Academy of Sciences-Neuroscience Award (2009)
23rd Annual Pasarow Award in Neuroscience, with C. F. Stevens and R. C. Malenka (2011)
Axelrod Prize, awarded by the Society for Neuroscience (2011)
Scolnick Prize, Massachusetts Institute of Technology (2012)
Ralph Gerard Prize, with Richard Tsien (2014)
Grass Lecture, Society for Neuroscience (2014)
Warren Alpert Foundation Prize, with S. H. Snyder and O. Hornykiewicz (2014)

Roger Nicoll is a pioneer in elucidating the mechanisms underlying neuronal communication in the brain. The classical concept that each central neuron integrates an ongoing barrage of transient excitatory and inhibitory postsynaptic currents to produce output spike trains is incomplete, failing to account for the sustained excitability changes that account for such important aspects of brain function as emotion and memory. In electrophysiological experiments of clarity and rigor, Nicoll has revolutionized our understanding of synaptic plasticity in the mammalian central nervous system, revealing a rich repertoire of slow "metabotropic" actions of neurotransmitter. Our current understanding of long-term potentiation (LTP) in the hippocampus is based, to a considerable extent, on Nicoll's contributions. Based on a series of tightly controlled publications, he has demonstrated that LTP is due to the rapid recruitment of glutamate receptors to the synapse. More recently, he has discovered a family of novel auxiliary receptor proteins that are essential for trafficking of glutamate receptors as well as their gating. Based on Nicoll's findings, the molecular underpinnings of memory are beginning to emerge.

Roger A. Nicoll

I am honored to have been asked to write an autobiography for the Society for Neuroscience's *The History of Neuroscience in Autobiography*. This invitation has generated quite a strange feeling for me, because my life has been driven by what comes next. Looking in the rearview mirror has not been part of my character. Once a study has been completed and published, it is history, and I immediately turn to the next challenge in front of me. In addition, writing about myself makes me feel uncomfortable and self-conscious. So I write this as if it will be stored away in some file.

My Parents

I was born in Camden, New Jersey, in 1941. My father was a physicist and worked for RCA, which had its research division in Camden. Shortly thereafter we moved to Princeton, New Jersey, where RCA had built its new research facility. My parents both grew up in Saskatchewan. They had very different upbringings. I know a fair amount about my parents' upbringing because they both wrote about their experiences and passed their accounts on to their children. This has stimulated me to look at my own past. My mother's father was a physician in England, but he had been forced into this profession by his father, also a physician, and had little desire to practice medicine himself. He and my grandmother had a family of eight, living in Surrey, England. Although he saw some patients, he and his wife appeared to rely on a modest inheritance that my grandmother had received. This was not a viable long-term solution. Unlike my grandfather, who was a sedentary bibliophile, my grandmother was restless and had a pioneer spirit. It was largely based on her initiative that the family of 10 set off on a ship in 1906 on a journey that ended up in Earl Grey, on the plains of Saskatchewan, Canada. My mother (nee Neatby) was born in 1907. My grandfather reluctantly continued to see some patients, but, again, not enough to support the family. Thus, my grandmother decided to move the family to a homestead on the prairie and try farming. Farming was even more distasteful than medicine to my grandfather, and this task of running the farm fell on my mother's older teenage brothers. The brothers had help from neighbors, in particular two Swedish brothers who not only helped with the farming but also ended up marrying my mother's sisters.

The family was unlike others on the surrounding homesteads and, except for the Swedish brothers, did not integrate well into the community. My grandparents had come from an educated, conservative, Victorian upbringing and were deeply religious. Reading in the family was valued above all else,

and many of my mother's siblings went on to have distinguished academic careers. Thus, it is not surprising that the Neatby family was seen as eccentric, aloof, and judgmental. One example of this uncomfortable societal relationship occurred after my grandmother voiced concerns about the morals of a neighbor's daughter. When the daughter's parents found out about this, they sued my grandparents and won the case. In 1919, the oldest son took over the farm, and the family moved to Saskatoon, Canada, where my mother finished high school and then went on to the University of Saskatchewan. In time, my mother came to the conclusion that her father suffered from depression and was deeply aware of his shortcomings.

My father's upbringing was demonstrably more "normal." His great-grandparents on both his father's and mother's side came from the United Kingdom and settled near Peterborough, Ontario. My grandfather trained as a pharmacist, and as a young man had moved with my grandmother to Battleford, Saskatchewan. He remained in Battleford, where he worked as a pharmacist for the rest of his life. My father and his siblings grew up in a reasonably well-off environment. The family had one of the first cars in town, a Model T Ford. At an early age, my father became interested in electrical gadgets, such as telegraph, telephones, wet batteries, and radios and how they worked—thus, began his lifetime interest in physics. He went to the University of Saskatchewan, majored in physics, and received a scholarship to attend Cambridge University in England for graduate studies. This was the heyday of the Cavendish laboratories run by Lord Rutherford. I have a group picture of my father and the rest of the members of the Cavendish laboratory. In the picture are nine Nobel laureates, all of whom were still active scientists. At the University of Saskatchewan, my father met my mother who was a classmate. She followed him to England where they were married. Following graduation, he worked for a few years in London at EMI, an electronics and gramophone company. The conditions in Europe in the mid-1930s were rapidly deteriorating, and my parents decided to return to North America. He took a job at RCA, which had its research division in Camden, New Jersey, but soon after we moved to Princeton.

I was the third of four surviving children. The oldest, Patricia, lives in Bloomington, Indiana, and is four years older than I am. Ruth is next in line and has remained in Princeton; she is two years older. Finally, there is Matthew who is five years younger and lives in Minneapolis. Looking back on my childhood, it seems that we lived in cramped quarters. It was an English Tudor–style house with steep slate roofs, located a few blocks from the university stadium. For a family of six, we had three bedrooms and one bathroom, which sounds like a logistical nightmare in the morning; however, I don't remember it causing much of a problem. We shared many outdoor activities while growing up, including two weeks in the summer at our cottage on Lake Newboro on the Rideau Canal, about 30 miles from Kingston, Ottawa. The trip to the cottage was a two-day drive, and we

would camp at various state parks on the way. Our favorite was Whetstone Gulf in New York, which is built in a 400-foot-deep gorge. We befriended the ranger, who remained in charge of the park throughout our upbringing. We would spend much of the time looking for fossils, which were plentiful in the riverbed.

My mother devoted her efforts to raising the four of us. She was very important to me. She realized early on that I had a reading handicap and did everything she could to help me out. Most important, she read to me all the time, which I thoroughly enjoyed. For example, she read *The Adventures of Sherlock Holmes* in its entirety. My father was extremely important to me as a boy as well, although I didn't fully appreciate it at the time. As I was growing up, I spent much of my free time with him, either in the workshop, canoeing, sailboat racing, skate sailing, or skiing—the list goes on and on. In thinking about his influence, there are a number qualities and traits that I most admired and have tried, usually unsuccessfully, to emulate. My father was modest. Despite his impressive education and research achievements, he was one of the most unassuming people I have encountered. There was absolutely no pretense or showiness about him, and with his modesty, came an extraordinary level of integrity. Another remarkable trait of his was his child-like, insatiable curiosity. This is probably the trait I admire most about him, and he maintained it until the very end. I had been worried that when he retired he would be at loose ends because his work meant so much to him. I couldn't have been more wrong. Everything he encountered became a project for him. He would make long lists and spend hours in the Princeton University library researching various topics. Importantly, he would share his findings and his enthusiasm with those around him. He was not merely intellectual, but action-oriented; he would take his ideas to his workshop in the basement. It was an elaborate setup, with drill press, circular saw, band saw, lathe, and glass-blowing equipment. I spent much time with him or on my own there, playing with crystal radios, electric generators, ruby lasers, and many other exciting contraptions. He was a very practical person and both at work and at home he was a hands-on problem solver. He passed on to me the power of the direct approach to answering questions. The idea of having a repairman come to the house never entered his mind. If an appliance broke, he would disassemble it to locate the problem and find a way to fix it. He showed me the power of one's hands in solving problems. My father had difficulty displaying affection, but in retrospect, I can see that he was extremely supportive and nonjudgmental. Although I was doing poorly in school, there was little criticism and instead he encouraged me in those things where I could excel. When I finally found myself and ended up in medical research, he was most supportive. He would keep track of all my papers and, having become an expert at bookbinding in his later years, bound my papers into volumes, until his motor skills prevented him from continuing.

A Couple of Childhood Memories

In high school, I spent the summers doing construction work. The first job was Kendall Park, New Jersey, a massive housing project similar to Levittown. They offered two model houses, priced at ~$16,000 each and the goal was to build ~50 houses that summer. The first day I went to the building site with a couple of my friends, and we were hired. It was hard work in the blazing sun and at the end of the day one friend quit. But two of us stayed on for the entire summer. We were on the framing crew and were paid $1.75/hour. I was told that one of the workers was overheard talking about unions and was immediately fired. Besides framing, there was also an option to do piecework, where you were paid a set amount for each defined project that you completed. We saw a couple of Latinos doing piecework, and they were clearly making more than the hourly wage we were making. So we asked the foreman if we could also do piecework. He agreed. We were excited at the thought of making lots of money. However, by the end of the first day, we learned to appreciate how efficient the Latinos were, because we ended up making less on the piecework scale than on the hourly wage. We sheepishly went back to the foreman and begged to be put back on the hourly wage. He agreed, fortunately. After that first summer, I worked for individual contractors for the next two summers. I enjoyed construction, especially the framing. There was something fulfilling about creating a lasting structure with your own hands. I visited Kandall Park some years ago and the houses were still standing!

Another formative moment was discovering the book *The Silent World* by Jacques Cousteau when it came out in 1953. This was the most amazing book I had ever encountered. Cousteau recounts the history of man's obsession with exploring the oceans, untethered to the world above. He masterfully conveyed this irresistible desire and described his key role in developing the self-contained underwater breathing apparatus (SCUBA), which made this dream a reality. At the time, I was snorkeling off the rock jetties at the New Jersey shore, and it wasn't until much later that I took up SCUBA diving. Cousteau was a hero of mine early on, but I became disenchanted with him. My image of him as an inventor driven by curiosity, was replaced by the image of an egocentric showman who marketed his films in the cloak of science and discovery, when, in fact, they were basically contrived adventure stories, solely for entertainment. However, I do admire him for his early, strong advocacy for the environment and still credit his book for opening up a whole new world and inspiring me with the freedom to explore it.

A Slow Start

By the third grade, both my teachers and my mother realized that I had dyslexia. So during the second and third grade, my mother arranged for me

to have extensive psychological testing and tutoring. However, as anyone with dyslexia well knows, tutoring has no effect. The neuronal wiring in the part of the brain that is responsible for reading is faulty, and, unfortunately, one cannot correct faulty wiring. My only hope was to develop alternative strategies around this handicap, which I finally did, but it took many, many years. My reading is no better now than it was in grade school. Based on reading the English subtitles of foreign language movies, which I rarely go to, I estimate that my reading speed on average is at best a third of what is normal. The one "advantage" to being dyslexic is that it enforces a slow and methodical reading of one word at a time, which firmly imprints the contents of passages into my brain. I am hopeless at spelling. In grade school there were spelling bees. The teacher would select two captains who would stand on either side of the room. They would then alternate selecting their team members from the class. I was invariably the last person chosen. I used to have a paperback dictionary at my side all the time. The only problem is that my spelling was so bad that it was often impossible to find the word. The computer spellcheck program was an improvement because it would at least tell me that the word was misspelled. However, more often than not, the selections of words it offered did not include the word I was looking for. Google has been a lifesaver for me. I use it all the time and it almost invariably, after a couple of tries, finds the word I am searching for.

Dyslexia is a word that is thrown around a lot nowadays, such that its meaning has become rather vague and misleading. For instance, a number of high-profile individuals who are in such professions as law and business claim that they have dyslexia, yet they attended Ivy League schools and are in fields that depend heavily on massive reading tasks. I can only conclude that they must have a different variant of the malady than I do because such accomplishments are absolutely inconceivable to me. There is no way I could come close to performing adequately on the language part of the SAT to be competitive or to complete the test on time. The first time I took an intelligence quotient test, I scored 70 (which at the time was equated with "feeble mindedness"). Fortunately the school psychologist let me take an untimed test and I scored better (118). In those days, having reading problems was more or less equated with being mentally impaired. Thus, for me, it was the stigma associated with dyslexia that was most crippling. I spent much of my energy trying to conceal this defect, and when I failed, the resulting ridicule was unbearable. Thus, I felt terribly vulnerable and had low self-esteem. Above all else, I was frustrated, because deep down inside, I was convinced that my performance didn't accurately reflect my true abilities. It is this frustration, this inability to express myself and be recognized for who I am that became the overriding driving force in my life. It is this handicap that has given me a special empathy for those with similar issues that impair performance, but that do not reflect traits such as intellect, curiosity, and drive, which are equally or more important.

I went to Princeton High School. Princeton was a most unusual place and was dominated by the university. The university was a world-class center for math and physics. My classmates included the offspring of famous physicists, such as Peter Oppenheimer (son of Robert Oppenheimer), David Wigner (son of Eugene Wigner), and Alison Wheeler (daughter of John Wheeler). Not surprisingly, I struggled and did not do well graduating 128 out of a class of 305 with a grade point average (GPA) of 2.13/4.0. It is hard to explain my internal turmoil when surrounded by classmates and friends who were deciding on which Ivy League school to attend, while I was just hoping to go to college anywhere. Eventually, I came across an advertisement in a magazine that saved me. Would-be students submitted their applications to a pool and colleges would look over the application and accept anyone that seemed promising to them. Remarkably, I was suddenly in great demand. It was a great ego boost, even though I had not heard of the majority of these schools. Lawrence College (now Lawrence University) in Appleton, Wisconsin, contacted me, and it looked like a pretty good place. So what did they see in me? Their student body at the time was overwhelmingly from the Chicago area and as an Easterner, I would bring some "diversity" to the school. This notion was quickly confirmed at the social for the first-year students. I bumped into the head of admissions who glanced down at my nametag and said, "Oh, you are the one with the low SAT scores." It was not an encouraging start.

As was entirely predicted by my high school record, the first year in college did not go well. I was placed on academic probation and had one semester to bring my GPA up to a C or I was out. This was a major turning point in my life. My only hope was to focus on science courses and put off course requirements that involved extensive reading. That summer I immersed myself completely in two semesters' worth of biology at Rutgers University and did very well. The credits were acceptable at Lawrence and they brought my GPA up to a C. This was a huge confidence builder. It was the first time I realized that my handicap didn't automatically doom me to mediocrity and that with intense effort, I could take control of my future. From that point forward, I felt that anything was possible. I then focused on science courses and managed to turn things around. In the end, I still had a very mixed record, but my final GPA of 2.5/4.0 represented an improvement over high school. To this day, I owe Lawrence an enormous debt of gratitude for taking a chance with me and sticking with me through those turbulent transitional years. Thus, it was a very special moment for me when I was invited back to receive their Distinguished Alumni Achievement Award in 1998.

In the summer of my third year of college, I worked at the New Jersey Neuropsychiatric Institute, a mental hospital referred to as Skillman. There was a lab run by an internist who practiced medicine in Princeton. There were four or five people in the lab. He would show up about once a week to go over data. The study involved the use of rabbits as a model for arteriosclerosis. A high-cholesterol diet resulted in cholesterol deposits in the arterial

vasculature. My recollection is that the research was to determine whether feeding rabbits a modified rabbit chow had any effect on high-cholesterol-induced plaque formation. I can't remember what was actually changed in the chow; however, I was extremely disappointed with this experience. There was little oversight to the project, and those carrying out the experiments were all technicians. No one ever seemed to ask any questions. Indeed, no one seemed to be at all interested in what they were doing. My recollection is that they would drift in around 10–11 A.M. and then leave around 4 P.M. They also took long lunches. I can remember discussing my disappointment about the research experience with my father. He felt that at my naïve stage, it was rather arrogant for me to be so judgmental. Two years later, I learned that the funding for the project had been terminated, and I felt a sense of validation that I had assessed this situation correctly. In any event, I took a job as an orderly at Princeton Hospital on the evening shift, in addition to the day job, to see what a hospital environment was like. This was a very positive experience. I had time to talk to the attending physicians, who were more than happy to answer my questions. I also got to observe autopsies and learn some anatomy. My hospital experience prompted me to apply to medical school. This is not to say that I was in any way rejecting research, but I concluded that going to medical school would open up the most options for my future.

Medical School

Of course, before you can go to medical school, you have to be accepted into medical school, and with my less-than-stellar college record, my prospects were not bright. Nevertheless, despite a GPA of 2.5/4.0, I got into one: in fact, I got into a fantastic medical school, the University of Rochester School of Medicine. So, how did that happen? The only explanation besides blind luck that I can come up with is that my mother, who was a very eloquent and forceful writer, wrote my essay. The first two years of medical school were heaven to me. The only frustration was that there was no time to "push the pause button" and delve into something I found fascinating.

Given that I ended up turning my back on clinical medicine, one might think that pursuing a PhD degree would have been a more logical path. For me, however, the medical education, at least the first two years, was essential. My tendency from early on had been to find something of interest and then to focus on it relentlessly; I was pretty deep but pretty narrow. The first two years of medical school forced me to step back and take a panoramic view of all of the latest developments in biomedical science. It was invaluable. It confirmed my love for what would eventually become neuroscience (the word had not been coined yet). I had developed an interest in neuroscience in college. Although there were no courses dedicated to the nervous system in college, the profound lesson that evolutionary biology impressed upon me was the supreme importance of the nervous system in coordinating

and determining behavior of organisms as they became more and more complex. I was fascinated by the cephalization of the nervous system, and there was no doubt that the human brain is evolution's crowning achievement. I immediately began considering various approaches by which one might unlock the mysteries of the brain. I thought about neurology, but concluded that it was impossible to carry out rigorous controlled observations. It seemed obvious that, to understand the brain, you had to actually look inside the skull. I turned briefly to neurosurgery as an alternative and attended a number of operations. However, the way neurosurgeons treated the brain, sucking out surprisingly large and irregular chunks of it, made a very negative impression on me. It was hard to imagine how precise data could come out of such coarse procedures.

In the first-year neuroanatomy course, I began to see how one might go about studying the brain at the level that interested me. I was initially attracted to the sheer beauty of the cellular morphology and architecture of the brain, particularly of the cerebellum. Why are the Purkinje cells lined up in a single layer, each with their enormously elaborate dendritic trees? Why does each Purkinje cell receive only a single climbing fiber, which entwines itself around the dendrite, forming hundreds of synapses with it? Because the cells and connections in the cerebellum are unique to the cerebellum, surely answering some of these questions would give us insight into what the cerebellum does. It seems to me that the most tractable approach to understanding the brain would be to focus on the individual building blocks (i.e., the neurons). As the Spanish neuroanatomist Ramon y Cajal so elegantly put it in his autobiography, "The inscrutable mystery of the organization of the brain attracted us irresistibly. We saw that an exact knowledge of the structure of the brain was of supreme interest for the building of a rational psychology. To know the brain, we said, is equivalent to ascertaining the material course of thought and will" (Cajal 1989).

The extraordinary beauty of the cellular architecture that had been so carefully revealed by Cajal, however, tells us very little about what the neurons are actually doing. During my first year, medical students got a demonstration on intracellular recording from frog skeletal muscle. The resting membrane potential, action potentials, and the endplate potential were demonstrated. The idea of being able to record from a single cell was very appealing to me, and I searched around the medical school for someone who was doing intracellular recording and who would take me on during the summer. I came across a professor in the pharmacology department who was using intracellular recording to study the effects of drugs on the heart. I explained that my interest was to use this technique in the CNS. He suggested that I look at the effects of a drug (I can't remember which one) that he had found to have effects on spinal cord reflexes. He proposed that I examine the drug's effects on the excitability of dorsal horn interneurons using intracellular recording. Unfortunately, he had never actually recorded either extracellularly or

intracellularly from nervous tissue; indeed, I don't believe that he had ever done a spinal laminectomy. There was a technician in the lab doing intracellular recording in cardiac tissue. Although he was very helpful, I was largely on my own, and I only had 10 weeks! I borrowed a stereotaxic apparatus from another professor, built my own Faraday cage, and cobbled together a setup with micromanipulators, amplifiers, loudspeaker, stereotactic instrument, oscilloscope, and a Grass kymograph camera.

I soon began to have doubts about the project and I went to the professor to get help on what to look for when I inserted a microelectrode into the spinal cord. He admitted that he really couldn't help me, but he gave me a copy of *The Physiology of Nerve Cells* by Eccles (1957). Because, as always, reading was a challenge and because I had very little time, I looked up spinal interneurons in the index and was disappointed to find very little on this topic. I put the book aside and forged ahead on my own. However, in no time, it became clear to me that I was in over my head. I had no background whatsoever, not even the neurophysiology section of the physiology course, which was given in the second year. So I reversed directions and started at the beginning of the book to find out what this field of neurophysiology was all about. By the end of the first couple of chapters, I realized that the hunch I had during the demonstration on intracellular recording from muscle was correct. Intracellular recording was unquestionably going to be the way to study the brain. The book documented that with glass microelectrodes it was possible to go deep into the brain and record the private synaptic communications occurring within a single identified neuron. Here was a technique that could bring the beautiful but static cellular architecture of Cajal to life. I spent much of my time during the summer and the next year of medical school devouring the contents of *The Physiology of Nerve Cells* and *The Physiology of Synapses* (1964), which had just been published, along with reading essentially all of Eccles's papers that were listed in the reference sections. I didn't give up completely on the experiments and managed to make a few recordings from motoneurons, which let me examine antidromic action potentials and primary afferent monosynaptic excitatory postsynaptic potentials. Given the conditions, and my rank inexperience, I am amazed that I got anything at all.

I had the pleasure of being taught all of neurophysiology by Bob Doty. He was an early role model of mine and he contributed an autobiography to this series a long time ago. His lectures were unlike the typical medical school lecture. He used no notes, relying entirely on drawing on the backboard. He would focus on presenting the classic papers in neurophysiology. This course was the highlight of my first two years. My fellow medical students were most irritated with this style of lecturing. They just wanted the facts. The second year also introduced me to neuropharmacology. At the time, a great deal was known about the peripheral nervous system (PNS). It was well established that synaptic transmission in the PNS was mediated

by the release of neurotransmitters, in particular acetylcholine (ACh) and norepinephrine (NE), which acted at specific receptors on the postsynaptic cell to control its excitability. On the basis of this fundamental information, a rich and rational pharmacology developed that allowed precise control of normal and abnormal peripheral synaptic function, such as cardiac arrhythmias, hypertension, asthma, and myasthenia gravis. In striking contrast to this sophisticated knowledge of peripheral synapses, virtually nothing was known about synaptic transmission in the CNS—only ACh release onto spinal Renshaw cells had been established. This void, this complete mystery, drew me irresistibly to the brain. Should it not be possible to identify the transmitters and their receptors and with this knowledge construct a rational pharmacology to decipher and treat disorders, such as schizophrenia, depression, Parkinson's disease, or dementia? I was convinced of this and remember presenting to a small-group session in the pharmacology course a recent paper in which Eccles and colleagues (Eccles et al. 1963) carried out a pharmacological study implicating gamma-aminobutyric acid (GABA) as the transmitter for presynaptic inhibition in the spinal cord. The other students were polite, but not nearly as excited as I was about it. I was getting restless.

A Monastic Life

My summer research experience had tantalized me with the unbelievably powerful technique of intracellular recording, but also showed me that the only way to master this technique was to go to a lab that specialized in it. There were not many, so I shot for the top and wrote to Eccles, who was at the Australian National University in Canberra, asking if I could join his lab for a year. He had just won the Nobel Prize and was in great demand. The closest I could get was a brief rejection letter from him. So I looked at other possibilities and, with help from a neurologist at Rochester, I was put in contact with Dr. Gian Salmoraghi at the National Institute of Mental Health (NIMH) at the National Institutes of Health (NIH).

Dr. Salmoraghi was receptive to my request, and I decided to take a year off after the second year of medical school and join his lab at St. Elizabeth's Hospital in Anacostia in Washington, DC. I felt confident in my knowledge of electrophysiology, but less sure of my abilities in the lab. I needed to test myself to see whether I could actually do experiments on my own and discover something, anything. St. Elizabeth's hospital used to be the largest mental hospital in the country, housing 8,000 patients with dozens of buildings on a sprawling campus. I rented a room on the grounds for $20.00/month and led a monastic life focusing 100 percent of my time on research. I ate all my meals at the hospital cafeteria and rarely left the hospital grounds. The only diversion was regularly attending the free concerts by the Juilliard String Quartet, which recently (1962) had been invited to be in residence at the Library of Congress, under the auspices of the Gertrude Clarke

Whittall Foundation. Thanks to the foundation, the Library of Congress has a complete set of Stradivari accompanied by Tourte bows, which are used by the quartet. The Juilliard still plays at the Library of Congress.

The year at St. Elizabeth's was *the* turning point in my life. By its end, I was convinced, rightly or wrongly, that I could hold my own experimentally with anyone in the field. What was so transformative about this experience? Experimental science, especially electrophysiology, provided an exciting level of control. You could essentially have a dialogue with the experimental tissue in real time. You probe the preparation, expecting a certain response. Much to your surprise something else happens. What could that possibly mean? You come up with possible explanations, modify the ongoing experiment, and probe the tissue with another test, and so on. There is nothing more exciting than testing your wits against Nature. You are in the driver's seat, but Nature has the final say. In this process you are led down paths that no one else has ever taken. It is interesting to compare electrophysiology to other disciplines, such as biochemistry and molecular biology, where there isn't this intense immediacy of discovery. I wonder whether I would have been so smitten with research if my first exposure had been in one of these disciplines.

In any case, it was in this mental hospital in Anacostia, that I had finally found my voice. I felt freed from my childhood frustrations and inadequacies. With this new-found freedom, came a sense of empowerment and confidence. It is through carefully crafted and controlled experiments that I communicate. In fact, it's all in my figures. Ideally a figure should be a self-contained narrative, a short story. There should be just enough labeling to guide the reader. The key finding is presented in the first panel, which has to be dramatic and compelling—no statistics required. Hopefully, the reader buys and is intrigued by the initial finding, but immediately comes up with a series of possibility explanations, which then are addressed one by one in the following panels. The goal is that there is no need to read the text, or the figure legends, or, for that matter, to listen to me talk about my work. It's all in my figures. You either believe the figures or you don't. If I have to try to persuade you, I have failed. This is why I have always strived to make figures stand alone, without forcing the reader to dig through the complex figure legends. I try to present data in a way that is intuitive, without extraneous text, to communicate directly via the evidence. I remind the people in my lab when they go back to their computers to make yet another series of changes that, if their story is remembered at all, it will be because of the figures. When a paper is presented in journal club, it is the figures that are discussed.

It is my belief that the underlying drive of a scientist is little different from that of an artist, broadly defined. The motivation is to discover and create something beautiful. Scientists have a constraint, however, in that the product of their creativity has to be "true," that is, reproducible. For most individuals, this act of creation is not enough. In both endeavors, there is a need for validation—that others also find your creation beautiful. Artists and scientists are both needy. Thus, for example, artists go to art

fairs to exhibit their work, with the hope that others will appreciate it (and buy it). They are also subject to the judgment of critics. Scientists publish their findings, a process that can be most painful (particularly when the reviewers do not share the same enthusiasm for your creation as you do). They also seek praise when presenting their findings at meetings.

Even with my newfound self-confidence, presenting my results in public gave me intense anxiety, and for many years, I didn't get a moment's sleep the night before a presentation. Going up onto a stage in front of a crowd was terrifying, bringing out all my worst insecurities and self-doubt. I would write out the introduction and memorize it word for word. I always had the written introduction in front of me, even though I never looked at it—it just served as a security blanket. I would insert the minimal number of words between each slide and focus on the individual traces of electrical recordings on the slides. My goal was to always direct the attention of the audience to the data and away from me (you can imagine the discomfort when I started to write this autobiography).

A Medical Interlude

After my year at NIMH, I returned to medical school. At this time, the Vietnam War was at its peak and all medical graduates were drafted into the military. The only other option was to obtain a medical research position at NIH, which would fulfill one's military requirement; those of us who took this path earned the irreverent moniker "Yellow Beret" (in contrast to the revered Green Berets in the war). It wasn't meant as a compliment. As I was finishing up the year at NIMH, I discussed my future with Dr. Salmoriaghi, specifically asking whether he would take me back into the lab after my internship. Having a position was critical if I was not to be drafted into the regular military. He agreed and assured me that I would not have to put my name into the pool of applicants because of this agreement. He would arrange things so I would be assigned directly to his lab. This looked to be a great bonus for having decided to spend the year at NIH.

As a part of the medical school curriculum, we had a 10-week elective period. By this time, Eccles had moved to Chicago, and I wrote to him again asking to join his lab for this elective period. This time the rejection letter was longer and more positive, but in the end concluded that it really didn't make sense to have me spend such a brief time in his lab. Soon, however, I had a bigger problem. Having completed medical school, I was just finishing up my medical internship at the University of Chicago and was waiting to hear about my assignment to Dr. Salmoriaghi's lab. Other interns were receiving their appointments and I started to panic. I called Dr. Salmoriaghi, and he initially began hemming and hawing. In desperation, I interrupted him and reminded him of his promise, while at the same time imploring him to help me out. He said he would get back to me, and after a short time he did. It seemed that Dr. Salmoriaghi had assumed a higher position and

had recruited Floyd Bloom to take over his lab and needed to discuss the situation with Floyd. Shortly thereafter, Floyd phoned me and said he was delighted to accept me into his lab. I have never felt such relief in my life.

Given the pleasure that I derived from doing experiments, it may not be too surprising that I found clinical medicine to be quite alien. Putting on a white jacket made me feel uncomfortable, especially as a student. I felt like I was pretending to be a doctor. The fact that patients attributed unwarranted wisdom to me, just because I was wearing this jacket, made me feel all the more uneasy. Add to this the fact that as an intern, one has to make very serious decisions and yet has to base them on only limited and imperfect data, made my discomfort all the more acute. I never got entirely over a feeling of inadequacy and responsibility around sick patients. I also couldn't connect to the reward system. In medical school, the intern would ask me to do a ton of scut work and, as a reward, would let me do the next lumbar puncture. The problem was that I didn't really have a burning desire to do a lumbar puncture, but I had to pretend otherwise.

I have grappled my whole adult life trying to understand why my feelings toward the practice of clinical medicine and basic research are so opposed to each other. I have concluded that the two disciplines could not be more fundamentally different. Clinical medicine follows extremely fixed protocols. If you don't follow this protocol and something goes wrong, you will rightly be held accountable. For basic science an immutable protocol is anathema to experimental inquiry. The only constraint in the laboratory is the limit of one's imagination. You are led into uncharted territory by what Nature, the experimental preparation, presents. As a physician, you make an effort to tie together a variety of symptoms into a coherent diagnosis. You consider various possibilities, but can have only limited confidence as to whether they have any validity. A treatment plan is initiated and the symptoms diminish. Was the diagnosis correct? Did the treatment actually work? You will never know for sure. The prospect of following this path was extremely unsatisfying to me.

I am, of course, most thankful that there are individuals who are dedicated to taking care of patients and not distracted by the "academic" details about which I obsess. Indeed, some recent medical problems have reminded me that I literally owe my life to skilled clinicians. Still, even in retrospect, it is clear that the idea of practicing medicine was never an option for me. I had taken and passed the medical boards at the end of my internship. Years later, I was asked whether I would write a prescription for someone. Only then did it dawn on me that I had not paid the nominal fees to get my medical license.

Some of My First Studies

Because my times at St. Elizabeth's Hospital, both during my year off and upon my return after my internship, were so pivotal to my career, I would like to share with you a few of my first studies. At the time, the neurotransmitters of the brain were a complete mystery. There was good evidence that

GABA was a transmitter in invertebrates and was present in high amounts in the brain. Eccles (Eccles et al. 1963) had recently published evidence implicating GABA as the transmitter for presynaptic inhibition. So I looked to see whether GABA might mediate postsynaptic inhibition in the olfactory bulb (Nicoll 1969, 1971). The relay neurons, referred to as mitral cells, form excitatory contacts with the spines of inhibitory granule cells. The granule cells form inhibitory synapses immediately next to the excitatory synapses back onto the mitral cell, an arrangement referred to as reciprocal synapses, the substrate for dendrodentritic inhibition. I used multibarrel microiontophoresis to test the sensitivity of mitral cells to GABA. Similar to its action on other neurons in the brain, GABA inhibited mitral cell activity, and this action was reversibly and selectively blocked by the GABA antagonist picrotoxin (Nicoll 1971). During these experiments, I noticed that application of a glutamate agonist often caused an inhibition, a most puzzling observation. This inhibition was reversed into an excitation by co-applying picrotoxin. These results indicated that in many cases the granule cell spine was more sensitive to the agonist than the mitral cell and activated the reciprocal synapse: Thus, blocking this feedback inhibition with picrotoxin revealed the direct excitatory action on the mitral cell. This result provided strong evidence that the transmitter being released from granule cells is GABA.

During these experiments (Nicoll 1972) I noticed that whenever I gave a supplementary injection of the general anesthetic pentobarbital, the mitral cell inhibition was massively prolonged and doses in humans that would just cause drowsiness prolonged inhibition. Halothane, a volatile anesthetic, had the same effect. These effects occurred in the complete absence of any effect on the synaptic excitation of the granule cell spine, so I proposed that anesthetics and sedative hypnotics act selectively on synaptic inhibition and more specifically on prolonging the action of GABA. This remains a widely accepted explanation for the anesthetic–sedative hypnotic effects of barbiturates and other general anesthetics. This work was initiated during my year's leave of absence from medical school and was completed upon my return to the lab now under the leadership of Floyd Bloom. It is important to note that the three papers that I have discussed about GABA are all single-author papers, and I owe Floyd Bloom an enormous debt of gratitude for his graciousness. When I joined him, he said that I clearly already had developed a number of ideas and projects, and I was free to pursue them on my own. Such generosity is rare.

Working with Eccles

As I was finishing up at St. Elizabeth's Hospital, I had to decide on my next step. I had one remaining piece of unfinished business. I wrote to Eccles who was now at SUNY at Buffalo and asked, once again, if I could join his lab. Third time's a charm, and he invited me to join his group. Why this obsession to work with Eccles? I had read virtually every one of his papers

backward and forward, and I wanted to have a context for these discoveries. I also wanted to see how he approached problems and went about doing experiments. It was a crucial stage in my journey. My only regret is that I had not been able to join Eccles in Canberra when I first wrote to him. Eccles was consumed by, and passionate about, science. He maintained a child-like curiosity, just like my father. I can recall him coming down the hall waving a copy of a journal article he had come across that he wanted to share with me. He had an immense ego, and you had to show him the appropriate deference; otherwise, he had little interest in you. We had a wonderful relationship because I wanted to go back and discuss the context of all of his papers. At this stage, I knew their details better than he did, and he loved to regale me with the backstories. When Eccles died I had the honor of writing his obituary for *Science*, reflecting on his contributions to science, which were many (Nicoll 1997). However, I lamented that many of these findings are now taken for granted, and appreciation for his seminal contributions in shaping our understanding of the brain has faded.

He also would bring up philosophical topics because he was writing a book with the philosopher Karl Popper. Eccles had by that time become a "dualist," someone who felt that there must be more to nature than atoms moving in space. I found these discussions excruciatingly painful. His search for something more than materialism left me cold. I remember his returning from a meeting where he debated with the well-known philosopher John Searle from the University of California at Berkeley. It was clear to me that Eccles was way out of his league, but he persisted. Another area of disagreement concerned politics. Eccles was extremely conservative. It was the peak of the Watergate hearings. Eccles was solidly supportive of Nixon and considered the hearings a conspiracy. He also considered John Dean's testimony a series of lies. However, when the Watergate tapes finally appeared and one could listen to the sleazy and profane level of discourse in the Oval Office, Eccles never again brought up politics. He realized from then on that our interaction had to focus entirely on science.

Our initial project was a continuation of a series of experiments that Eccles had pursued for a number of years, which involved studying the flow of information into and out of the cerebellum. In our study, we recorded extracellularly from antidromically identified reticulospinal brain stem neurons (Eccles et al. 1975). Eccles would arrange his schedule so that experiments could be carried out when he was present in the lab. Thus, he was involved in each of the experiments from the surgery to the recordings, which typically lasted late into the night. The speed with which he did a spinal laminectomy was amazing. The experiments involved stimulating a variety of peripheral sensory nerves and constructing histograms of the effects that the stimulation had on the firing of the reticulospinal neurons. These histograms allowed us to make inferences about the effects of the cerebellum in sculpting the firing of these neurons. Many of the responses of the reticulospinal neurons were of long latency, and although the involvement of the cerebellum in shaping

these responses was likely, it was impossible to rule out the possibility that other pathways were importantly involved. Although I learned a great deal about how Eccles went about doing experiments, I found these experiments unsatisfying, and I think he realized that my heart was not in them.

Meanwhile, when Eccles was traveling and not able to carry out experiments, he encouraged me to set up my own experiments in a vacant room. I had been working on the isolated frog spinal cord preparation while I was at NIH. I was interested in using the frog spinal cord to examine the idea that the Cl^- gradient across neurons was not passively distributed, as had been assumed by Eccles and almost everyone else. Previous results by others had found that ammonium (NH_4) ions caused a depolarizing shift in the reversal potential of inhibitory postsynaptic potentials (IPSPs) in spinal motoneurons, suggesting that Cl^- was not passively distributed. To try and get some direct evidence, I examined the effects of NH_4 ions in the isolated frog spinal cord where one could apply drugs in known concentrations. I was able to show that NH_4 ions were very effective in blocking the hyperpolarizing action of both GABA and glycine, consistent with previous in vivo results. Eccles showed a keen interest in what NH_4 might be doing and suggested that we do some experiments in the hippocampus where IPSPs were unusually large. I reminded him of an earlier conversation when he told me that he had cut a deal with Per Andersen, a former postdoc who had introduced the hippocampus to Eccles. The arrangement was that he, Eccles, would not touch the hippocampus if Per did not touch the cerebellum. With a smile, Eccles assured me that the statute of limitations had long since run out on this pact.

For these studies, we would begin each experiment by anesthetizing the cats with nitrous oxide (NO), and when we obtained our first stable records of IPSPs from a hippocampal pyramidal cell, we would inject increasing amounts of barbiturate. This would permit us to directly record the effects of barbiturates on IPSPs. I wanted to follow up on my earlier extracellular recording experiments on the effects of anesthetics on synaptic inhibition in the olfactory bulb (Nicoll 1972). The experiments in the hippocampus went very well, and we clearly established that even very small amounts of barbiturate, equivalent to doses that would just cause drowsiness in people, so that they were clinically relevant, caused a prolongation in the IPSP. Anesthetic doses caused as much as a fivefold increase in duration. I wrote up the first draft of a short paper for *Nature* with these results and listed the authors alphabetically, as I believe Eccles had done without fail throughout his career. Much to my surprise, he put my name first, rather than his own, and made a number of other suggestions (Nicoll et al. 1975). It is hard for me to express how honored I was for this courtesy.

The main purpose of these experiments was to carry out a detailed characterization of the anionic permeability of the channels activated during the IPSP and to determine whether the hyperpolarization was generated solely by the movement of Cl^- (Allen et al. 1977). Using a series of different-sized anions in our recording electrode, we concluded that the anion permeability

of hippocampal IPSPs was the same as that reported previously by Eccles for spinal motoneurons. Much to our surprise, however, NH_4 ions, even in high concentrations, had very little effect on IPSPs. Thus, although most of our results were consistent with a selective increase in Cl^- permeability, it appeared that the mechanism that maintains intracellular Cl^- at a low concentration differed from that at work in motoneurons. One of the first projects that I initiated after setting up my own lab was to examine the effects of NH_4 ions on IPSPs in hippocampal slices where known concentrations of drug could be applied. Although Brad Alger and I (Alger and Nicoll 1983) eventually confirmed the resistance of the IPSPs to NH_4 ions, it is still not clear why NH_4 ions are so much more effective on motoneurons than they are in pyramidal cells.

Perhaps the most important thing I took away from my relationship with Eccles was his championing of Popper's notion of falsification and how it is the fabric of experimental science—it guides every thought and every experiment. There is nothing more rewarding than coming up with an experiment that is so tightly controlled that the result must be accepted, especially if it definitively puts to rest your most cherished idea. It frees you to move on. Psychologically, of course, there is nothing more beautiful than having your pet idea survive the most frontal assault that you can marshal. Your idea survives to live another day! But you must be the harshest critic of your own data, if you want to experience the greatest joy at its success.

A number of years ago I had a discussion with my former postdoctoral fellow, Massimo Scanziani. He mentioned that he had come across a paper that he thought I would be interested in. It was by John R. Platt and entitled "Strong Inference" (Platt 1964). I can't believe that I had not previously come across it. It is my manifesto. I love the "in your face" style of writing. The paper begins: "Scientists these days tend to keep up a polite fiction that all science is equal. . . . This keeps us all cordial." He quotes W. A. H. Rushton: "A theory which cannot be mortally endangered cannot be alive" (p. 349). He elaborates eloquently on Popper: "The difficulty is that disproof is a hard doctrine. If you have a hypothesis and I have another hypothesis, evidently one of them must be eliminated. The scientist seems to have no choice but to be softheaded or disputatious" (p. 350). I have been accused of being disputatious my entire scientific life, and I wear that badge with honor. It is not surprising that I think in black and white, and it is this view that drives the crafting of experiments with the least amount of wiggle room. It is only with great reluctance that I give in to a touch of gray. I am afraid that the long-term potentiation (LTP) field suffers to a degree from soft-headedness. Perhaps this is why I have never felt fully accepted into the LTP club.

I also have acquired the reputation of being competitive, an accusation that I also accept. Both in sports and science I am, indeed, competitive. The rules of the game have to be well accepted by all. Thus, there is a question in the field that everyone agrees is important. The goal is to come up with the most compelling and elegant experiment that will, ideally, convince your

fiercest opponents that your wits outsmarted theirs. Of course, sometimes my competitors outsmart me, and I graciously tip my hat to them. My reaction to reading an excellent paper by an opponent is a mixture of extreme joy and intense envy. The competition is one of the things that I find so exhilarating about science. Most important, you have to play by the rules, just as with tennis, for example. No fudging of data/line calls, and graciously hopping over the net when you are bested.

Confidence in my own abilities and experiments has coexisted with the lingering insecurities and lack of self-esteem from my childhood. Psychiatrists refer to this as reaction formation. Depending on the circumstances, either the confidence or the insecurities hold sway. This has resulted in a lifelong, wild, emotional roller coaster ride. The contradictory emotions have had a profound effect on everything from initiating new projects to taking on a new trainee. These mood swings are also linked to the evolution of a project. As a project takes clear form, my excitement ramps up and reaches exhilaration when the paper is finally accepted. Shortly thereafter, the mood turns to despair, because there is no guarantee that this process of discovery can be repeated. At this point, I would lament "the cupboard is bare."

Launching a Career

My period with Eccles was an essential part of my journey. But I then had to find a job. I applied to around 15 medical schools for a faculty position and received very little response. I was surprised because I had published 16 papers, many appearing in *Science* and *Nature*, where I was either the sole, first author, or last author. I suspect that this was partly because Eccles had never been accepted into the neuroscience establishment in the United States. He was seen as a brash, overbearing Australian and felt as an outsider. He confided in me his regret that the community never embraced him. Thus, amazingly, my association with this Nobel Prize winner may have actually been a detriment in finding a job. Nevertheless, I had applied to two jobs at the University of California, San Francisco (UCSF): one in the physiology department and the other in the pharmacology department. I was invited out for an interview, the only such invitation that I got. Evidently, I did very well, having read all the recent papers of the individuals with whom I interviewed. Yet it wasn't clear where, if anywhere, I'd end up. The two departments could not have been more different. Physiology was a well-respected department with a number of prominent researchers. Pharmacology, on the other hand, was considered to be a backwater, an embarrassment. Physiology took the position that, since pharmacology was initially responsible for inviting me, the offer would come from pharmacology. To me it made no difference. All I wanted was a job where I could do my own research. When the offer from pharmacology came, I leapt at it. As the two years with Eccles were coming to an end, it was a very poignant and bittersweet time. We were both packing our belonging, and I helped him fill piles of mailbags with his collection of volumes of the *Journal of Physiology*, which

went back uninterrupted to the 1920s. While he was retiring to Switzerland, I was moving to California to begin my career. It is amusing to recall that not long after I arrived at UCSF, I encountered a biochemist with whom I had interviewed. He was in disbelief that I had accepted a job in the pharmacology department. How pathetic! But I've had no regrets. Pharmacology was extremely supportive of me and protected my time for research.

I have been fortunate to have had a long and productive career (and, hopefully, it's not over); far too long to cover in detail. In the following few sections, I'll just review a bit of the first work and some recollections of other work. My selections should not be interpreted as meaning that this work is the best or most memorable. Indeed, I wish I had time and space to discuss all of the projects that my students, postdocs, and colleagues were able to accomplish. I am proud of what we did, and I look back on our work and times together with fondness.

The Hippocampal Slice

While I was at NIH, a frustration was developing in the new field of neuroscience. The use of anesthetized animals greatly constrained the types of experiments one could do. Stable recordings were difficult and the use of iontophoresis for pharmacology experiments was extremely limiting; you never knew exactly where the drug was applied or its concentration. During this period, many neuroscientists decided to move to invertebrate model systems, where one could visually identify the large neurons and precisely control solutions bathing the neurons. I was very envious but hesitant to leave the vertebrate CNS. I developed the isolated frog spinal cord, which had first been used in the late 1930s together with sucrose gap recording, which offered many of the advantages of invertebrate models. The primary goal for adopting this preparation would be to understand the mechanism of action of both excitatory (e.g., glutamate) and inhibitory (e.g., GABA) amino acids on primary afferent terminals and motoneurons. This was a compromise between high resolution and physiological relevance, however, and the neuroscience field never really embraced the frog spinal cord preparation.

Shortly after I got to UCSF, a very bright graduate student, Craig Jahr, asked if he could join my lab, and, after overcoming some internal anxiety about taking on this major responsibility, I agreed, and Craig became my first student. It was a great decision, and Craig was soon making excellent progress in working up an in vitro preparation of the turtle olfactory bulb. The turtle bulb was closer, but still not quite the warm-blooded brain preparation, that neuroscience was after.

Some years earlier, two papers appeared from Per Andersen's lab in Oslo. The first by Skrede and Westgaard (1971) showed that one could make transverse slices of the guinea pig hippocampal formation, maintain them in vitro for hours, and record field potentials from them. The second paper by Schwartzkroin (1975) showed that one could stably record intracellularly

from pyramidal cells in the slices and replicate all of the findings that previously had been made with intracellular recording from anesthetized animals by Kandel and Spencer (Kandel et al. 1961). With this slice preparation, one could now do experiments as elegant as those being carried out in invertebrate models and yet could be recording from the real thing—mammalian cortical tissue! Upon my arrival at UCSF, my number one goal was to set up the hippocampal slice preparation, but by the mid-1970s, there were still only a handful of laboratories in the world that had the slice preparation working, and I had no direct access to any of them. Fortunately, Brad Alger had written to me about working in my lab. He was completing his PhD in Tim Tyler's lab at Harvard using field potentials in the hippocampal slice. He wanted to learn how to do intracellular recording and wondered whether I might be interested in getting the slice preparation. I was, and it was off to the races. Given that we knew virtually nothing about the neurotransmitters in the brain, there was a ton of low-hanging fruit. I consciously decided not to study excitatory synaptic transmission and glutamate. First, a great deal of work had been done characterizing the excitatory action of ACh at the neuromuscular junction, and it seemed to me that, although the receptors–transmitters might be different in the brain, the ionic mechanism would be similar. Second, the pharmacology of excitatory amino acids was in its infancy, and there was no solid evidence that glutamate was, in fact, a transmitter in the brain. I was more interested in GABA, which had been shown to be a transmitter at the crustacean neuromuscular junction and was present in very high amounts in the brain.

GABA and Synaptic Transmission

As discussed earlier, my initial interests were in understanding the role of GABA in inhibitory synaptic transmission. This involved identifying somatic and dendritic inhibitory pathways in the hippocampus (Alger and Nicoll 1982) and the role of GABA in dendrodendritic inhibition in the olfactory bulb (Jahr and Nicoll 1982). Remarkably, in one of our first efforts, we found that the opioid peptide encephalin selectively reduced synaptic inhibition in the spinal cord, olfactory bulb, and hippocampus (Nicoll et al. 1980), a previously unsuspected unity, which also demonstrated the power of the in vitro approach. During these studies, we noted that the action of GABA antagonists was complex. Although the antagonists clearly reduced the IPSP, there was a slower component that actually increased in size (Newberry and Nicoll 1984a). Furthermore, this component was not mediated by an increase in chloride conductance. Detailed studies indicated that it was mediated by an increase in potassium conductance (Newberry and Nicoll 1985). What was responsible for this slow IPSP? The fact that it actually increased in the presence of GABA antagonists, which greatly enhance the excitability of interneurons, suggested that it might be mediated by the interneurons. This notion was further supported by the finding that enkephalins, which

selectively silence interneurons, also reduced the slow IPSP (Newberry and Nicoll 1984a). During this period, Norman Bowery published a series of truly elegant papers showing that GABA had a presynaptic inhibitory effect that was not blocked by GABA antagonists and that baclofen was an agonist at this receptor. He termed this new receptor the $GABA_B$ receptor and termed the classical receptor the $GABA_A$ receptor. Remarkably, we found that baclofen activated a potassium conductance in pyramidal cells (Newberry and Nicoll 1984b, 1985) and that this effect was mediated via G-proteins (Andrade et al. 1986). Finally, the moment that a $GABA_B$ receptor antagonist became available, we showed that this antagonist selectively blocked the slow IPSP (Dutar and Nicoll 1988). $GABA_A$ and $GABA_B$ receptor signaling provides a fascinating example of how profoundly different the signaling properties of two receptors, activated by the same transmitter, can be. $GABA_A$ receptors are primarily synaptic, low affinity, and fast, and they convey highly reliable point-to-point signaling. In striking contrast, $GABA_B$ receptors are extrasynaptic, high affinity, and slow, and they require high-frequency synaptic activation or the activation of multiple neighboring synapses, thus allowing for spillover and for "pooling" of GABA. This "diffuse" action of GABA on $GABA_B$ receptors is strongly controlled by GABA uptake (Isaacson et al. 1993).

Neuromodulation

I was also fascinated by such "peripheral" transmitters as NE, ACh, serotonin, and dopamine. Although present in the brain, how they exerted their actions there was a complete mystery. The advantage to examining these transmitters was that they each had a very rich pharmacology of agonists and antagonists. With Dan Madison, my second graduate student, I decided to look at the action of NE in the hippocampus. The application of NE caused a highly variable and modest hyperpolarization of pyramidal cells—rather underwhelming. We wondered whether it affected excitatory synaptic transmission and decided to mimic excitatory synaptic actions by iontophoresing glutamate onto the cells. Much to our amazement, pulses of glutamate, that only elicited a couple of spikes normally, evoked a train of high-frequency spikes in the presence of NE (Madison and Nicoll 1982). We showed that this profound effect was due to NE blocking a calcium-activated potassium current (I_{AHP}), which normally provides a break to repetitive action potential firing. Interestingly, we found that the response to a barely suprathreshold ramp depolarization was blocked by the direct NE-induced hyperpolarization, while at the same time, the response to a step depolarization was greatly enhanced (Madison and Nicoll 1986). We concluded that NE greatly enhances the signal-to-noise ratio, suppressing weak signals and enhancing strong signals. We attempted to duplicate this action of NE by stimulating NE containing fibers in the slice. Indeed, stimulating the slice resulted in a blockade of I_{AHP}. Disappointingly, NE antagonists failed to block this effect, but we later found that ACh muscarinic receptor antagonists did block it

(Cole and Nicoll 1983). ACh has the same effect as NE on I_{AHP}, but it uses a different second messenger pathway. The elucidation of the actions of NE, ACh, serotonin, and dopamine kept me busy for a good decade. These studies revealed that different neurotransmitter receptors that use either the same or different coupling mechanisms converge onto the same ion channel. Conversely, virtually all neurotransmitters act on more than one distinct receptor subtype, coupled to different ion channels in the same cell. Thus, the existence of both convergence and divergence in neurotransmitter action results in a remarkable diversity in neuronal signaling (Nicoll 1988).

LTP

Despite the continued allure of GABA and the other neurotransmitters, my attention was increasingly being drawn to an area in neuroscience that I had steadfastly ignored. Based primarily of the work of Jeff Watkins, the pharmacology of excitatory amino acids was blossoming. It was also abundantly clear that excitatory synaptic transmission was not, as I had erroneously concluded from the motoneuron excitatory drive of muscle, simply a stereotypic way of depolarizing the cell. Instead, multiple glutamate receptor subtypes provided a remarkable richness in neuronal communication. Most important was the discovery of LTP (Lomo 1966; Bliss and Lomo 1973). This was certainly the most extraordinary synaptic behavior that I have encountered in my career. And the fact that it had all the hallmarks expected for the cellular basis for learning and memory did not escape my attention or that of others. Nevertheless, it is interesting to note that it took approximately 10–15 years after the discovery of LTP before a mechanistic understanding of the phenomenon began to emerge. The reason for the long delay after the discovery is threefold. First, initially, the pharmacology was extremely poor and it wasn't even clear that glutamate was the transmitter at these excitatory synapses. Second, one was greatly constrained in the types of experiments that could be done in vivo. Third, LTP was irreversible; once the effect occurred, that was it; it seemed that the only way to study it would be to do group studies, comparing a set of control slices to experimental ones, and analyze the results statistically. This approach was anathema to me, especially because of the large variability in the magnitude and even the occurrence of LTP; I wanted to be able to tackle problems more directly. The irony is that Brad Alger was one of the first to demonstrate long-term potentiation in the slice and is credited with the first use of the acronym LTP (Alger and Teyler 1976). We had many discussions about LTP, but in the absence of any knowledge about the pharmacology of excitatory synapses, we were unable to come up with any interesting experiments. Perhaps LTP is the field that I am most associated with. I recently reviewed the history of LTP describing all of its twists and turns, and my participation in many of them (Nicoll 2017).

Here I will highlight a few of events that had the biggest impact on me. When I entered the field, it was established that LTP initiation required

the activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors. However, there was much debate on how LTP was expressed: What actually changed at the synapse? Was the increase in synaptic strength due to a postsynaptic modification or, alternatively, to an increase in the release of glutamate? The latter mechanism would necessitate a retrograde factor, because it was established that postsynaptic NMDA receptor activation was required. We published a paper with the provocative title "A Persistent Postsynaptic Modification Mediates Long-Term Potentiation in the Hippocampus" (Kauer et al. 1988) in which we showed that LTP is expressed primarily as an increase in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptor responses compared with NMDA receptor responses. We argued, and showed experimentally, that increasing synaptic glutamate release by posttetanic potentiation caused an identical increase in both components. These findings pointed to a selective postsynaptic modification of AMPA receptor transmission during LTP. Gary Lynch published a paper in the same year with similar results and conclusions (Muller et al. 1988). Although there was some debate as to whether there was any change at all in the NMDA component, all subsequent studies have confirmed that LTP is primarily expressed on the AMPA receptor component. It seemed to me that these experiments had very little wriggle room for a presynaptic expression mechanism.

Nevertheless, within little over a year after publishing the paper with Kauer and colleagues, two other papers appeared in *Nature*, one by Dick Tsien, entitled "Presynaptic Mechanism for Long-Term Potentiation in the Hippocampus" (Malinow and Tsien 1990) and one by Chuck Stevens entitled "Presynaptic Enhancement Shown by Whole-Cell Recordings of Long-Term Potentiation in Hippocampal Slices" (Bekkers and Stevens 1990). Both papers examined the probabilistic trial-to-trial fluctuation in transmitter release, including examination of the "failure" rate, before and after LTP. They elegantly showed that both the fluctuation and the failure rate decreased following LTP. Based on the classical studies of Del Castillo and Katz at the neuromuscular junction (NMJ), these results seemed to definitively establish a presynaptic modification, the opposite conclusion from mine. These papers were devastating. How had I screwed up? It seemed as if I had a 50:50 chance and blew it. The evidence in these experiments was compelling and was immediately embraced by the neuroscience community. By far the lowest point in my scientific career was a Cold Spring Harbor meeting that took place from May 31 to June 6, 1990. Although their papers had not yet appeared in *Nature*, everyone was aware of their findings, so there was a lot of buzz. I had decided to talk about something unrelated to LTP—to get as far away from LTP as possible. Much to my chagrin, I discovered at the beginning of the meeting that Dick, Chuck, and I were included in one session. It was clear that I had to say something about LTP. I had brought no slides on LTP, so I went to the library and made a few overheads of figures from my papers in an attempt to explain how I had reached my conclusions. I followed their two talks. Their talks were universally

acclaimed as the highlight of the meeting. After my talk, I literally picked up my bags, left the auditorium, went to the train station, and took the train to Princeton to recover with my parents.

There is more to this story. Dick and Chuck were the rising stars in neuroscience. Dick had attended MIT, majoring in electrical engineering and went to Oxford as a Rhodes Scholar, where he carried out quantitative biophysical studies on cardiac pacemaking currents. He had recently completed a series of truly elegant studies defining the subclasses of calcium channels. Chuck graduated from Harvard, obtained an MD from Yale and then a PhD from the Rockefeller University. Among a number of landmark studies, he had applied voltage clamp analysis of ACh-induced fluctuations at the neuromuscular junction to infer the conductance of single Ach receptors and their kinetic properties. They were both highly respected for their quantitative rigor. I found them both overwhelmingly intimidating. They brought to the surface all my childhood feelings of inadequacy. At the time, they were both at Yale University. Much to my horror, Chuck became interested in the hippocampus and recruited my first graduate student Craig Jahr to join his lab. This horror was compounded when Dick soon after recruited my second graduate student Dan Madison to do postdoctoral work in his lab. I was certain that it was only matter of time before I was exposed as a lightweight. I was a nervous wreck. When the two *Nature* papers appeared, my worst nightmare had come true.

My first reaction was to admit defeat and move as far away from LTP, Dick, and Chuck as possible. On reflection, however, I really had no choice other than to find out where I had gone wrong; not to do so would have been an admission that somehow my papers were simply wrong. LTP became an obsession—I could not get it out of my mind. There must be an answer to this conundrum—both positions could not be true. So the very first experiments were to see whether we could repeat the basic results presented in the two *Nature* papers. These results were quickly repeated (Kullmann and Nicoll 1992; Manabe et al. 1993); thus, the findings were unimpeachable. The bottom line is that both sets of data, that is, the preferential enhancement of the AMPA component during LTP and the decrease in failures, are correct. This immediately elevates the discussion to a higher plane because, all too often, the argument degenerates into a failure to replicate. However, one must face the fact that one of the conclusions must be wrong. Which one and why? During this period, my close colleague David Julius had, in my absence, modified my screen saver to repeatedly flash, "It's presynaptic!"

At this time there were many studies, many of them my own, that implicated a postsynaptic mechanism for the expression of LTP, reviewed in (Nicoll 2003)—the only generally accepted evidence for a presynaptic change involved the change in "failure rate," the frequency that a stimulus did not evoke a synaptic response. Therefore, I designed a number of experiments as alternative approaches to directly interrogate the release of glutamate during LTP (Manabe et al. 1993; Manabe and Nicoll 1994; Luscher et al. 1998). Despite

the high sensitivity of these assays, we came up empty-handed; we could find no direct evidence that glutamate release was actually facilitated. The most definitive series of experiments for me was entitled "Long-Term Potentiation: Evidence Against an Increase in Transmitter Release Probability in the CA1 region of the Hippocampus" (Manabe and Nicoll 1994), which involved the drug MK-801, a use-dependent irreversible NMDA receptor antagonist. When glutamate is released, it opens NMDA receptors, and MK-801 immediately enters and irreversibly blocks the pore of these activated receptors. Repeated activation of the synapses results in a gradual decrease in the size of the NMDA receptor current and, most important, the rate of this decrease is dependent on the amount of glutamate that is released per stimulus. If LTP was expressed by an increase in the release of glutamate, we should see an increase in the rate at which MK-801 enters and blocks the channels at synapses that had undergone LTP compared with unpotentiated synapses. Yet, despite the exquisite sensitivity of this assay, we could detect no change in the amount of glutamate released during LTP. We summarized our findings as follows: "How can the present results be reconciled with studies using quantal analysis? The decrease in failures is usually interpreted as an increase in P_r (probability of release). Alternatively, the decrease in failures could reflect the appearance of patches of functional AMPA receptors on the postsynaptic cell." Within a year, we (I was now collaborating with Rob Malenka) were able to provide experimental evidence for the presence of "silent synapses" that were converted to active synapses during LTP (Isaac et al. 1995). Remarkably, a substantial number of hippocampal synapses are normally silent, in the sense that there are no functional AMPA receptors, although they do contain a normal complement of NMDA receptors, whose electrical activation cannot be detected at resting membrane potentials. Thus, from an electrical point of view, such a synapse is "silent." LTP rapidly unsilences these synapses with the all-or-none insertion of a population of AMPA receptors. Identical findings were reported by Malinow and colleagues (Liao et al. 1995) as well as by many other subsequent studies. With this new insight into the basic physiology of hippocampal synapses, we were able to provide a postsynaptic explanation for the decrease in failures of synaptic transmission, which had been the only apparently direct evidence for a presynaptic change. These findings quickly swayed public opinion back to the postsynaptic side of the synapse. Since the publication of these findings, virtually all the work on NMDA receptor-dependent LTP has focused on the nature of the postsynaptic modification. Thus, although the pathway to this conclusion seemed torturous and was bewildering, the answer as to the site of LTP expression turned out to be quite simple. The data on both sides of the argument were correct. It was the interpretation of the data that had to be modified, which had to await new insight into basic properties of hippocampal excitatory synapses. This is a saga of science at its best.

With the evidence that the increase in the number of functional AMPA receptors is the dominant mechanism in LTP, attention has shifted to the

underlying mechanisms that control synaptic AMPA receptor trafficking. I remain disputatious. AMPA receptors in CA1 pyramidal cells are composed of heterotetramers of the subunits GluA1-3. It has long been held that both basal synaptic transmission and LTP are dependent on the subunit composition of the AMPA receptor (Malinow and Malenka 2002; Huganir and Nicoll 2013). Specifically GluA1-containing receptors are excluded from the synapse and require LTP for their insertion (Hayashi et al. 2000; Shi et al. 2001). We took a genetic approach to address this issue by systematically deleting these subunits in conditional knockout (KO) mice, either individually or together (Lu et al. 2009). With this approach, we could delete all endogenous AMPA receptors by generating mice in which GluA1-3 were floxed and then by replacing the endogenous receptors with genetically modified subunits (Granger et al. 2013). Much to our surprise, we found that homomeric GluA1 receptors trafficked to the synapse constitutively. Furthermore, we could find no subunit specificity to either basal or activity-dependent AMPA receptor trafficking. In fact, expression of a kainate receptor, which has limited homology with AMPA receptors and is not normally expressed at these synapses, showed normal LTP. Thus, in contrast to prevailing opinion, LTP appears to be quite promiscuous. So once again we are confronted with two seemingly incompatible observations. The only difference between our experiments and the previous ones was that the previous experiments used subunits in which GFP was inserted in the extracellular amino terminal domain (ATD), whereas we used untagged receptors. Remarkably, the presence of GFP on GluA1, but not GluA2, prevents basal trafficking, but LTP overcomes this inhibitory effect of GFP (Diaz-Alonso et al. 2017). Thus, once again, we could repeat all of the previous findings and provide an explanation for the differences.

There are many outstanding and intriguing questions in this field. What is the glue at the postsynaptic density (PSD) that captures and holds AMPA or kainate receptors at the synapse? Presumably, these receptors have something in common that is recognized by proteins in the PSD. Perhaps the most important unresolved issue in the field of LTP is the mechanism underlying its persistence, that is, the memory. It is this property that makes LTP such an attractive model for a cellular substrate for memory. Calcium-calmodulin kinase II (CaMKII) has received the most attention, but there remain many seemingly conflicting observations. Stay tuned!

Endocannabinoids

During the 1990s, I became intrigued with a curious discovery that Brad Alger had made in the hippocampus, which he termed depolarization-induced suppression of inhibition (DSI; Pitler and Alger 1992). Since leaving my lab, Brad had continued to work on GABA-mediated synaptic inhibition. On the basis of a series of meticulous experiments, he had clearly established that DSI was induced by depolarization of the postsynaptic cell but was expressed

as an inhibition of GABA release. This was extremely interesting because it was the first compelling example of retrograde transmission, in which a signal was released from the postsynaptic cell and traveled backward to act on the presynaptic terminal. A great deal of discussion and many claims were embedded in the literature about retrograde factors and LTP. This reached a fever pitch with LTP and NO. In my lab, we could find no support for any involvement of NO in LTP, and I was quite sour about the concept of retrograde transmission in general. However, with DSI we had a very simple phenomenon, which unequivocally involved retrograde transmission.

I found DSI irresistible, and Rachel Wilson, a student in my lab, decided to examine this robust phenomenon in detail (Wilson and Nicoll 2001). Rachel first carried out a series of experiments characterizing some of the intriguing properties of DSI. By recording from pairs of nearby pyramidal cells, she found that the spread of DSI was spatially restricted to about 20 μm from the originating cell. She also found that uncaging Ca^{+2} induced DSI, but that the action of Ca^{+2} did not involve a classic SNARE-based exocytotic process. Around this time I visited the University of Washington, and I met with my former student Jeff Isaacson, who was then a postdoc in Bertil Hille's lab. He was studying dendrodendritic inhibition in the olfactory bulb and had demonstrated that glutamate could spill over from excitatory synapses in the olfactory bulb. I had a chat with him, and out of the blue, he asked me what I thought of DSI. This caught me totally by surprise, because DSI was at that time rather obscure. He was about to start talking about it, and I immediately stopped him, telling him that I was actually working on DSI and felt uncomfortable exchanging information at that point. I left that meeting wondering why Jeff was thinking about DSI at all, but decided that it was due to his interest in glutamate spillover. One of the ideas in the DSI field was that glutamate was released from the pyramidal cell and acted on presynaptic metabotropic glutamate receptors on inhibitory terminals, and I satisfied myself that this was the connection that Jeff was making. Rachel and I continued our studies on DSI, and Rachel nailed down a number of key steps. She also tried several possible candidate chemical messengers that might mediate DSI, as the holy grail of this project was the identification of the retrograde factor. At about this time, Jeff passed through the Bay Area on his motorcycle and arrived at my door unannounced. We started chatting about all sorts of things, and then he brought up our previous discussion about DSI. He told me his interest in DSI had been sparked by some immunohistochemical results that Ken Mackie had presented in one of Hille's lab meetings. Ken had an antibody for the CB1 cannabinoid receptor, the main brain receptor for the active constituents of marijuana, and showed heavy labeling of the terminals surrounding the cell body of pyramidal cells. This piece of evidence had suggested to Jeff that an endocannabinoid might be involved in mediating DSI. I am embarrassed to confess that my knowledge of endocannabinoids was very limited. It is my recollection that Jeff

had tried some direct experiments to test this idea, but without obtaining a definitive answer. Nevertheless, based on Jeff's input, we ordered the CB1 antagonist AM251 and the CB1 agonist WIN55212-2. The antagonist completely blocked DSI. Furthermore, the CB1 agonist mimicked and occluded DSI. My goal for this project had simply been to identify the retrograde messenger, even if it turned out to be a boring molecule. However, the fact that the molecule had such unusual signaling properties, unlike any previously characterized neuronal signaling molecule, and that it helped to explain the cellular actions of marijuana in the brain was beyond belief.

The SfN meeting was fast approaching and Rachel had submitted an abstract describing her work on DSI, before the linkage to endocannabinoids had been made. We had submitted a full-length paper to *Science* describing the endocannabinoid story, but we had nothing in print that would establish our claim to priority for the discovery. Nevertheless, we decided to totally spill our guts and announce the story, even though the paper had not been accepted for publication. However, I felt that of all the papers I have published this one would be a slam-dunk. As Rachel was presenting her poster at the meeting, the word spread and she was soon inundated with attention; everyone there, it seemed, wanted to know the details. Shortly after the meeting, we received the decision from *Science.* The paper was rejected! We got the most maddening and disingenuous reviews I have received in my career: Reviewer 1: "This is a nice study that provides new information on the mechanisms underlying DSI . . . *While* the results are compatible with this proposal, I cannot agree with the authors when they imply that their evidence is conclusive." Reviewer 2: "The manuscript presents an intriguing premise. . . . *However*, it is unclear whether alternative explanations for the results can be entirely eliminated." Reviewer 3: "The major merit of the paper is that the authors provide experimental data indicating that cannabinoids are the most likely agent responsible for the induction of DSI. . . . *Nevertheless*, the significance of these results for the function of the nervous system remains unclear. . . . Thus, while the paper contains useful results, I doubt that it is warranted to have it published in *Science*."

We strongly suspected that our paper had been reviewed by people in the endocannabinoid field, who simply couldn't accept the idea of total strangers stepping on their turf. Worst of all, we had let the cat out of the bag, informally publicizing our findings, and yet had no insurance that our priority would be properly acknowledged. We'd have to resubmit to another journal, but the delay meant that the paper would not appear in the year 2000. We immediately reformatted it for *Nature* and waited for what seemed like forever to hear back from them. It was now early 2001, and Dan Madison, now at Stanford, asked me about the status of our paper. He had been asked to write a commentary for two papers, one by Kreitzer and Regehr (2001) and the other by Ohno-Shosaku and colleagues (2001), to be published in *Neuron* on endocannabinoids and retrograde transmission at synapses in the

cerebellum and the hippocampus, respectively. He was wondering whether we had anything in press that he could cite. We were about to be scooped. The reviews from *Nature* arrived and two of the reviews were very positive, but the third reviewer said that Alger had published evidence that glutamate was the retrograde factor and so who was she or he to believe? By this time, Brad had repeated the CB1 antagonist experiments and had backed away from glutamate, so I asked him if he would be willing to send me a letter summarizing his own position on DSI. He graciously provided a letter, which I forwarded to *Nature*. Finally, our paper found a home (Wilson and Nicoll 2001). What a harrowing experience. In an interesting footnote, all three papers, ours, Regehr's and Kano's, plus a theoretical paper by Elphick and Egertová (2001) proposing that endocannabinoids might be retrograde messengers, all appeared in print on the very same day, March 29, 2001, in three different journals. Although we may have missed a 2000 publication date, everyone got a piece of the pie, while broadly confirming and complementing each other's findings (Wilson and Nicoll 2002).

TARPs

At around this time, Lu Chen from Richard Thompson's lab inquired about joining my lab as a postdoctoral fellow. She showed me her data from the *waggler*/*stargazer* mutant mouse in which a putative neuronal calcium channel subunit was mutated (Chen et al. 1999). *Stargazer* was discovered as a spontaneous mutation resulting in a bizarre set of behavioral abnormalities characterized by distinctive head-tossing, an ataxic gait, and spike-and-wave seizures characteristic of absence epilepsy (Noebels et al. 1990). Some of the behavioral abnormalities were similar to those of other mutant mice, *tottering* and *lethargic*, harboring defects in genes encoding calcium channels, suggesting that the mutated protein in *stargazer* might be a calcium channel subunit. Indeed, the mutated gene was *Cacng2* with structural similarity to the gamma auxiliary subunit of the skeletal muscle voltage-gated calcium channel (Letts et al. 1998). Although *Cacng2* showed structural similarity to *Cacng1* of skeletal muscle, the effects on calcium channel function are variable and modest.

Examination of the *stargazer* mouse by Masanobu Kano (Hashimoto et al. 1999) and Chen and colleagues (1999) revealed the most extraordinarily selective synaptic defect imaginable. Mossy fibers are the primary excitatory input to the cerebellum. They synapse on granule cells, which then form excitatory synapses on Purkinje cells via parallel fibers. In wild-type animals, the mossy fiber to granule cell synapse is a classical excitatory synapse activating both AMPA and NMDA receptors; however, in this mutant mouse, the AMPA component was entirely missing, but the NMDA component was normal: a genetic mutation that creates "silent synapses!" What an unbelievable gift of Nature. Remarkably, within the space of a

year or so, Masanobu Kano and I both had stumbled onto endocannabinoids as retrograde messengers and the use of the *stargazer* mouse in elucidating AMPA receptor trafficking. Thus began a wonderful collaboration with David Bredt and the emergence of the role of transmembrane AMPA receptor regulatory proteins (TARPs) as auxiliary AMPA receptor proteins. Surprisingly, the studies on PSD-95 (El-Husseini et al. 2000; Schnell et al. 2002) and membrane-associated guanylate kinases (MAGUKs), which began in David's lab, dovetailed perfectly with the study of TARPs, because it turned out that the MAGUKs' role in trafficking AMPA receptors is mediated through its binding to TARPs (Nicoll et al. 2006).

Collaborations

I developed scientifically as a loner. All I needed was some space and equipment to do experiments. I asked nothing from those around me, nor did I expect anything from them. Whether I survived or failed was entirely up to me. In my opinion that's the way it should be. It is the control of one's own destiny that I found so empowering about science. Although I eventually became comfortable sharing my science with postdocs and graduate students in my lab, I did not collaborate with other colleagues for 13 years. I felt extremely uncomfortable at the possibility of losing any control over my science and the potential political conflicts over who did what. This issue of freedom has been a recurring theme throughout my career and all aspects of my life. Whenever I discuss science with a colleague, I am most sensitive to the colleague bringing something up that I am either working on or interested in working on. If this happens, as it did with Jeff Isaacson, I immediately interrupt the conversation and confess that the topic is too close to my own interests. What I most want to guard against is the possibility that a colleague could look back and feel that I had ripped him or her off. I was obsessed with being independent.

This all changed with Rob Malenka. He had spent a number of highly successful years as a postdoc in my lab. He then joined the psychiatry department at UCSF, which was awkward for me and, once again, brought up the issue of freedom and independence. Given my own obsession with controlling the science around me, the only arrangement that I felt I could live with was a complete separation; we would have no meaningful intellectual interactions at all. Needless to say, this was most uncomfortable for both of us. For instance, one of his students approached me to be on their thesis committee. I explained how this put me in a difficult position: If this project overlapped with what I was doing, then I would either have to give it up, which I was most reluctant to do, or enter into competition, which was also unacceptable.

Rob had established his own independence, producing a series of elegant papers on the mechanisms underlying long-term depression, a field in which I had never worked. Nevertheless, the tension between us was

unhealthy. Rob was weighing an attractive offer from Stanford which would have completely severed our relationship, which had remained one of great mutual respect, and we finally sat down to confront the situation. We decided to essentially join our labs together. For someone who had avoided collaborations for so many years, this seemed totally out of character; however, the merger went well. There was twice as much data to chew on and twice as many people to work with. Also, and quite surprisingly, I found that this arrangement allowed me to finally relax. What I had worried most about with collaborations never occurred. Not once did we have a disagreement about authorship or credit. On projects that originated from Rob's lab, he was senior author, and visa-versa. Rob was always very upfront in his interactions, and I was never caught by surprise. It was an extremely productive period; we collaborated on a total of 50 papers. My collaboration with Rob was pivotal to my science. We had just published our paper on silent synapses (Isaac et al. 1995), providing a compelling postsynaptic explanation for the changes in failure rate during LTP. Public opinion dramatically turned to a postsynaptic expression mechanism. Suddenly, LTP was now a receptor trafficking problem. However, neither Rob nor I had any knowledge about cell biology or molecular biology. So Rob initiated a collaboration with Mark Von Zastrow on the activity-dependent trafficking of tagged AMPA receptors. This collaboration drove the point home that to remain a competitive researcher in the field of LTP, it was essential to collaborate. Rob was again offered a very attractive package from Stanford and this time he could not refuse and decided to move. Since Rob had initiated the collaboration with Mark, future collaboration with me alone was not an option. I was in a state of panic.

It was during this period of crisis that I began talking with David Bredt. Eric Schnell, a student who transferred to my lab after Rob moved to Stanford, had done a rotation in the Bredt lab. He worked with Alaa El-Din El-Husseini, a postdoc in David's lab and tagged PSD-95 with GFP. Alaa had found that expression of PSD-95 enhanced postsynaptic clustering of glutamate receptors and thus it was of interest to examine the physiological consequences (El-Husseini et al. 2000). This resulted in a long and exciting collaboration with David Bredt and members of his lab, focused largely on the role of TARPs and MAGUKs in AMPA receptor trafficking and function. After many highly productive years, David decided to try his hand at developing pharmaceuticals at Ely Lilly Co. Yet another marriage ending in divorce!

Also, around this time it was my good fortune that Katherine Roche at NIH expressed interest in the possibility of setting up some collaborations. Her focus on the role of protein phosphorylation nicely complemented my approach based on functional assays. Our studies on neuroligins are a great example of the interplay between these strengths (Shipman et al. 2011; Bemben et al. 2014). The study that stands out as one of the

most complicated mysteries that I have ever encountered was the understanding of how the auxiliary AMPA receptor protein cornichon (CNIH) controls AMPA receptor trafficking and gating (Shi et al. 2010; Herring et al. 2013). Solving the mystery took us on a torturous, winding path that had many blind alleys. This study ended up with our generating CNIH2 and CNIH3 conditional KO mice, and the use of GluA1 KO mice, GluA2 KO mice, γ-2 KO mice, and γ-8 KO mice. Despite its enormous complexity, this turned out to be one of my more satisfying stories because, although so many pieces initially didn't make sense, the role of CNIH appears to be rather simple: It is necessary for the selective forward transport of GluA1 out of the endoplasmic reticulum and is entirely consistent with its trafficking role in yeast and flies. Ironically, while this study is one of the ones that I am most proud of, it has basically fallen on deaf ears; the community at large has been slow to embrace it. Why some results are immediately accepted while others languish without attention is a puzzle that I have never solved.

Balance to a Life in Science

Family

While I was working at St. Elizabeth's Hospital, I passed a woman in the hall carrying a couple of beakers. She was a new face, a postdoctoral fellow in a neighboring lab, so I started chatting with her. Diana had just arrived from London, and we hit it off very quickly. In three months, we were married. I owe an enormous amount to Diana, who had the onerous task of educating me and exposing me to everything outside of science. I was as opposite to "well rounded" as anyone could be. Somehow, I convinced her to relocate to Buffalo, a striking contrast to Washington, DC, and London. She completed medical school there, and we then moved to San Francisco. Diana has been at UCSF and the VA Medical Center for her entire career, where she has led as chief of staff for more than two decades. Unfortunately, after 18 years, our marriage ended in divorce. I take much of the responsibility for this, being consumed with my own scientific world while failing to provide the emotional bonding required of a relationship. I regret not having found the balance in life that would have made for a more successful marriage.

Despite these shortcomings of the past, Diana and I maintain a positive relationship sharing someone who is amazing, our son David. I was 40 years old and a full professor when he was born, so my career was fully established, and I was able to devote time to him. He was a gifted student, which was most exciting for me, given my own childhood academic problems. I was and am extremely proud of him, and like most parents, I enjoy vicariously his many successes. Much of the time I spent with him involved

outdoor activities. Skiing was the most important sport that I introduced David to when he was just four years of age. We would regularly spend long weekends at Lake Tahoe during the winter. We skied at virtually all of the resorts in the area but settled on Squaw Valley both because of the variety and the challenge of the slopes. During the summer, we did a lot of hiking and some camping. As mentioned earlier, we had a family cottage in Canada, and when David was young, we would spend time there in the summers. So many activities to keep us busy—canoeing, swimming, water skiing, fishing, and hiking!

When Diana and I got divorced, we both agreed that David was the most important part of our lives, and we shared equally in bringing him up. We protected him from any issues that the two of us might have had. He went to the East Coast to university and worked in hedge funds for a number of years in New York City and Boston. Much to our delight, he moved back to the Bay Area and is married to a wonderful woman, Patricia, with whom he has two fantastic sons, Andrew, who is five, and Edward, who is three. Now that David and his family are back in the Bay Area, Diana and I spend time together sharing in the joy of having grandchildren.

More than 20 years ago, I met a very engaging woman on the public tennis courts. JoAnn Blomgren and I have been very close ever since. Aside from tennis, which we play virtually every weekend of the year, we have many things in common and enjoy being together. It never ceases to amaze me as to how she can put up with all of my idiosyncrasies. She is a very forgiving person and has brought me much pleasure and comfort.

Sports

Sports have played a central role throughout my life. I played the usual sports—soccer, basketball, and baseball in grade school—but was only average in these team sports. I preferred solo sports.

Pole vaulting: During my first year of high school, the math teacher, who was the football coach and the track coach, suggested that I should try pole vaulting. I had never met this teacher, although my older sister was a favorite student of his, and I hadn't a clue as to what pole vaulting was all about. I decided to give it a try. Pole vaulting is not easy. To be perfectly honest, my goal during the first year was to clear a height that was higher when using a pole than when not. One of the more humiliating moments during that first year was when the baseball practice on the neighboring field had finished and one of the baseball players was walking by and asked if he could try out my pole. He picked up the pole, and holding it improperly, ran down the runway and cleared a height that was beyond what I was capable of doing at the time. Afterward he picked up his baseball mitt, said thanks, and ran off. So why did I keep pole vaulting through high school and college? My

father was not very encouraging and felt that I should pick up a sport that I could enjoy for the rest of my life. Yet I persevered. It appealed to me in the way that many things did: The only explanation I can come up with is that the goal is very simple, and you can track your progress precisely. As the Russian Sergey Bybka, arguably the greatest pole vaulter of all time, said, "I love the pole vault because it is a professor's sport. One must not only run and jump, but one must think. . . . I love it because the results are immediate and the strongest is the winner." The other benefit, perhaps not as lofty, is that it was not a popular sport. This, I suspect, was the reason that the coach approached me about pole vaulting in the first place. Anyway, depending on the track meet, there were either three or five ribbons and medals awarded, and quite often, there would be fewer contestants than there were medals. So all I had to do was clear the first height to be assured a medal of some kind. The first height was decided by the contestants and had to begin with the lowest height requested. The others could pass the low heights if they felt it was beneath them. I never took a bye and always made my first height. Now it should be clear as to why I had a drawer full of medals. Interestingly, Eccles had also been a pole vaulter in college. He never confessed to his highest height, and you may have noticed that this piece of information is missing from my summary as well.

Skiing: Skiing was my real passion. I started skiing when I was about four years old. My father had obtained old skiing equipment at a rummage sale. It was rudimentary, but it allowed us to go out in the fields behind the house and do primarily cross-country skiing. There were, however, a few gentle slopes, which gave me a taste of the thrill of downhill. When I was around 7 to 10 years old, there were a few special occasions when I got to go to a hill called Peapack about 30 miles north of Princeton. This was normally a pasture, but the farmer had installed a rope tow that was powered by an old truck engine. They had night skiing with floodlights. When it snowed hard, we would have to put snow chains on our car tires to get to Peapack. All I can remember was that this hill was unbelievably daunting—it seemed so steep. Years later when we would drive by this hill, it was hard to imagine how I could have felt the way I did. It was certainly not above the grade of novice. At some point, the farmer stopped setting up the rope tow. Eventually, many years later, other places like Great Gorge in northern New Jersey and Camelback in Pennsylvania came into being. When I was a bit older, the family would go on skiing vacations to New England. We would stay in Albany with friends of my parents and ski at local places. This included Bousquet Ski Area, which is still going strong, but other areas didn't fare so well. For instance, Dutch Hill was a favorite place in southern Vermont. It closed in 1985, and many years later, there was an article in the sports section of the *New York Times* on the demise of New England's small ski resorts. There was a picture of the old rusted chair lift still standing at Dutch Hill—very sad. During high school, I

never missed a winter without a trip to New England, and I have been to the vast majority of the New England ski resorts since.

One of the activities at the top of the list for my son David was skiing. Lessons started when he was four. At first, I would put him into a ski school in the morning and then ski with him in the afternoon. However, this didn't last long. He gave me an ultimatum. Either we skied together, or he wasn't interested. David eventually developed into a fantastic skier, far better than I am. We'd spend all our time on Double Black Diamond slopes with huge moguls. I would always push myself to the limit and although falling more often than most skiers, I rarely got injured. I loved the challenge. My other favorite type of skiing was powder on wide-open slopes or glades. There are few moments in life that can beat a day of skiing in deep, fluffy powder and the feeling of floating and freedom that you get. Unfortunately, of all the sports I enjoy, skiing is the one that is most affected by aging. I just no longer have the reflexes or strength to link the moguls together and thus fear has, appropriately, crept in and taken the fun out of it.

Tennis: One thing that I regret is not taking up tennis when I was young. My father played doubles every once in a while, but he did not really encourage us to play tennis, unlike other sports. It wasn't until I moved to Marin County, California, that I became obsessed with the sport. I took lessons and joined a tennis club and U.S. Tennis Association teams. I had a very unorthodox style of play. For starters, my groundstrokes were not all that reliable. Thus, I developed a very aggressive style of play that involved serve and volley and rushing the net when receiving serve. At the level that I was playing, this usually caught my opponent off guard. The trick was to get the match over with before he could adjust. As a result, I could often beat players who were considerably more skillful than I. It would drive them crazy. Unfortunately, if they did catch onto my game, the result was most embarrassing. I would look like a fool, rushing the net and repeatedly being passed. Nowadays, all I play is doubles, which lends itself to my style of tennis, since controlling the net is critical.

Sailing: When growing up I did a lot of sailing with my father. He bought a used "Penguin" international class of dingy (11 foot). It used to be the third largest international class of boat. What made it popular was that you could buy a kit with all the plywood pieces cut and assemble it on your own. As a watercraft, it did not have many other attributes and it has been replaced by far better designed boats. However, the local sailing club had about 15 or so owners of Penguins and summer races were held every Sunday. When there was wind, the races could be very exciting, but when there was no wind, it was really boring. Crewing could also be boring. Thus, I negotiated with my father that we would alternate being skipper. There was one incident that I vividly remember. There was a big international regatta on the Barnegat

Bay, by the ocean, with about 70 Penguins—so some of the top-ranked sailors in the world were there. One of the participants was Britton Chance, a famous biochemist from the University of Pennsylvania, who had won a gold medal in sailing at the 1952 Summer Olympics. He had named his boat the "Snark" and everybody knew it. In one of the races we were, not surprisingly, in the middle of the pack, when a boat approached on starboard. My father was sailing and we were on port, and he felt that he had enough time to get past the approaching boat. However, this forced the approaching boat to make a minor adjustment and the sailor on it unloaded a long barrage of obscenities at us. It was Britton Chance in the Snark. I am sure he felt frustrated having to share the middle of the pack with us and we had probably cost him a few seconds. My father and I both felt very small. Interestingly, his son Britton Chance Jr. became a renowned Naval architect who played a critical role in the design of a number of America's Cup vessels.

In the winters, my father would skate-sail and bring me along. The sail consisted of two long large aluminum poles assembled in the form of a cross upon which the sail was rigged. My father made all of his hardware and sails from scratch. One of his sails was made with Army Surplus fluorescent pink signaling panels. This seemed so out of character; I guess there must have been a bit of the showboat in him. The sail would be positioned to windward, and the boom rested on your shoulder and leaned into the wind. Depending on the wind, one could reach outrageous speeds of about 50 mph. Unlike a sail boat, one could not control the force of the wind on the skate-sail, so if you got going so fast that you were on the verge of wiping out, the only recourse was to turn into the wind and hold the sail over your head. One could make very elegant jibes, turning down wind, because you were going much faster than the wind speed. There were three downsides to skate-sailing. First, speeding across the ice in freezing wind was really uncomfortable and, second, the pressure on your ankles, which took all of the force, was painful. For me, the pain would limit how long a reach I could endure. Finally, the skate-sailing season was unpredictable and short; it began when the ice on the lake was thick enough to skate, and ended with the first snowfall. We would regularly go to the lake and with an axe make a hole and measure the thickness. Maybe unsurprisingly, skate-sailing never really caught on as a sport and most of the images of it on the web date back to the first half of the last century.

During one of the summers early in high school, a friend of my father's loaned us a Sailfish "boat" for the summer. It was a board-boat style and you sat on the surface. The Sailfish was a forerunner of the Sunfish, which ended up being far more popular. The Sunfish was larger and had a well on the deck for placing your feet. The wonderful thing about the Sailfish is that you were right on the water, and with a brisk wind, it would plane across the top of the water, which would really get your juices flowing. It was not all that stable, especially when pushing the limits, and so it would

often capsize, although it could be quickly righted by standing on the centerboard. On one of my outings, a photographer for the local newspaper the *Princeton Packet* took a series of photographs of me, which appeared in one of the summer editions, evidently a very slow time for news. To me, the Sailfish was the best experience one could have sailing—you were extremely close to the water, it was fast, you could plane (albeit infrequently), and if you went too close to the edge, you capsized—no big deal.

So fast-forward a few decades. As I would drive across the Golden Gate Bridge in the summers on my way home from work at UCSF, I would glance at the Bay and see these long streaks of white water. On closer inspection, it appeared that at the front of the streak was a human being; a windsurfer. Unbelievable! Here was a guy on a small board going faster than I was in my car. This was clearly a Sailfish on steroids. I identified the launching site, Crissy Field, and on the weekend went to see what was happening, and I was introduced to a totally different world. The language, not very intellectual, was devoted to the complexity of the gear, an obsession with every little minuscule detail of the wind, weather, tides, and how to decide on the sail size—it was all brand new. Observing the sailors (windsurfers call themselves "sailors") approach the beach at high speed and then smoothly glide through a jibe was utterly mesmerizing. It was irresistible. I bought all the necessary gear, heavy wet suit, board, mast, boom, harness, and sails and headed out to Larkspur Landing, immediately next to San Quentin Prison. This is not far from my home and was the safest place in the Bay to learn how to windsurf. I would cross the channel to the other side where the water, depending on the tide, was between three and seven feet deep. It is here that I actually learned to windsurf. At first, it was extremely difficult for me, and the first season brought me little pleasure. What kept me going were the small incremental accomplishments and watching other sailors executing flawless planing jibes right in front of me. Since they could do it, I had to be able to! I slowly improved and graduated from a large board to a short board that barely floats when standing still.

Windsurfing is not just ripping across the water at 40 mph. You have to be able to turn around. This is not trivial on a board that barely floats. Jibing is what makes windsurfing such an exciting sport and it is how you judge the competence of a windsurfer. When done properly, the jibe is a thing of beauty. It is one continuous seamless series of steps in which you remain on a plane throughout and then off you go lickety-split in the opposite direction. It is very much like pole-vaulting where, in rapid succession, one step follows another, and they all have to be linked seamlessly together. I had a DVD on learning to jibe, and I would religiously watch it before going out. Then, after an afternoon session of failed or imperfect jibes, I would watch the DVD again in the evening. After watching it for hundreds of times, it finally gave out. The important point is that every once in a while, I completed

what I thought was a perfect jibe and it is intoxicating—intermittent reward is a powerful reinforcer of behavior. This is what kept me going.

After a couple of seasons of sailing at Larkspur Landing, I was confident enough to sail at Crissy Field. I must confess that for a number of seasons, I felt a mixture of exhilaration and intense fear and anxiety. There was incessant boat traffic and huge container ships that cast enormous wind shadows as they approached—not good for staying upright on your board—and then there were ferries and fishing boats, which traveled at high speed and didn't seem to care about what was in front of them, including windsurfers.

For many years, I sailed completely on my own. Although I would chat with some of the guys, I never teamed up with anyone. I was aware that Bob Stroud, a protein crystallographer and a colleague in the UCSF Biochemistry Department, was an avid windsurfer and was more advanced than I. I initially kept clear of him because I didn't have the confidence to keep up. I finally got the courage to approach him, and we started to sail together. This was transformative for me. My confidence and skills increased enormously. Carrying a marine radio added tremendously to my comfort. The worst thing that could happen was suffering the humiliation of being rescued by the Coast Guard. This happened to me once when I broke my boom in the middle of the Golden Gate. For many years, a small group of us were sailing buddies. The group consisted of Bob Stroud; Jeff Blaney, director of computational chemistry and cheminformatics at Genentech; Jeff's wife Leslie (the best sailor of the bunch); and Bill McCurdy, a physical chemist at the University of California, Davis. We would check in with each other in the early afternoon to decide on the best sailing site and then meet up a bit later. A particularly popular site is Crissy Field, where after launching, one sails up to the Golden Gate. Perhaps the most challenging site is off Treasure Island in the middle of the Bay. One launches directly into the full force of the wind. It was "off limits" for many years with four signs posted next to each other: "Sailboarding Prohibited," "Warning Sudden Drop Off," "Warning Strong Currents," and "Warning Slippery Rocks." Below each of these warnings was "Drowning Hazard." Because it is such an ideal site, windsurfers ignore these prohibitions. After an afternoon of sailing, we would often end up having dinner together. For 25 years, weekends in the summer were occupied with tennis in the morning and windsurfing in the afternoon. On Mondays, I would be exhausted, and my body sore all over.

In the winter, when the wind shut down in the Bay, I took trips to windsurfing destinations, such as Baja, Mexico; Maui, Dominican Republic; and Ariel, Costa Rica. I eventually gave up traveling to far away places because one was entirely dependent on the weather and often ended up having a number of calm days with nothing to do. Also sailing from morning to evening is extremely exhausting.

What is it that makes windsurfing so exhilarating? It is for me the Platonic ideal form of sailing. You are as close to the water as you could

possibly be—sometimes actually in it. This gives you an intense feeling of speed. With a short board, you are intimately interacting with the ever-changing surface, planning how to approach the water pattern in front of you. In addition, the wind is constantly changing. At every instant, you have to integrate the information from waves, chops, and swells, with the ever-changing wind speed. The output of this integration is transmitted to your feet, which guides the direction of the board, and to your arms, which controls the position of the sail. When a gust hits, you have to let the sail out to bleed the wind. This is the only time when I am conscious and yet my brain is completely freed of everything except for the moment before me. It is highly therapeutic. It clears out the cobwebs from my brain.

Reading, Music, and Art

The vast majority of my reading is devoted to scientific manuscripts. I do not read novels. The work that goes into reading a novel far exceeds any pleasure. The little nonscientific reading in which I engage is driven by the desire to learn something. Examples of books that I thoroughly enjoyed include *Steve Jobs* by Walter Isaacson, *Fermat's Enigma: The Epic Quest to Solve the World's Greatest Mathematical Problem* by Simon Singh, and *The Making of the Atomic Bomb* by Richard Rhodes.

Although I never learned to play a musical instrument, I fell in love with classical music early in college. I always had the classical music radio station on while I studied. This continued through medical school and during experiments. I also regularly have it on while driving the car. I like all kinds of classical music, but am particularly fond of chamber music and especially string quartets.

I have recently become smitten with modern glass blowing, thanks to a considerable degree to Mark Mayer. I have acquired a number of wonderful pieces by such artists as Tobias Mohl, Nancy Callan, J. P. Canlis, and Lino Tagliapietra that adorn my house. Lino is in a class of his own with unsurpassed technical and artistic skills. The DVD entitled *The Time of Lino* is inspirational. He is still going strong at age 83.

Mentorship and Legacy

My early obsession with going it alone immediately presented a problem as I set up my lab. It is expected that a new faculty member establish a research program and hire postdoctoral fellows and graduate students. The responsibility of having others depend on me made me feel uneasy. I did not feel at all confident that I had enough ideas to go around. It was the relentless badgering of a first-year graduate student, Craig Jahr, that finally made me cave in, and so began my doing science with others. I can't think of anything more enjoyable about science than going over raw data with a

student or postdoc and sharing in the excitement and the frustration associated with trying to understand what it all means. Ideas are thrown back and forth, forth and back; most of them go nowhere. But a few good ones pop up. The key is that the two of us are equals; there can be no hierarchy in the discussions. It is irrelevant as to who came up with the idea. What is important is to get as many ideas on the table as possible, because without this brainstorming, the clincher experiments will certainly never come up. I have to confess that, originally, part of the allure of science was the idea of discovering something great that would give me a degree of immortality. As I matured as a scientist, it became clear that the half-life of most discoveries, including my own, is rather short. Instead, one of the most exciting aspects of science is the realization that it is students and postdocs who will carry on long after your name dissociates from the discoveries. So, I finish with a list of the students and postdoctoral fellows who I have had the pleasure and privilege of working with. I thank you all for joining me in such an amazing journey. This autobiography is dedicated to you.

Craig Jahr
Bradley Alger
Martin Wojtowicz
Daniel Madison
Alison Cole
Nigel Newberry
Rodrigo Andrade
Robert Malenka
Barrie Lancaster
Patrick Dutar
Julie Kauer
Pankaj Sah
David Perkel
Robert Zalutsky
Jose Solis
Pius Renner
Jeffrey Isaacson
Dmitri Kullmann
Toshiya Manabe
Marc Weisskopf
David Wylie
Oliver Manzoni
Pablo Castillo
Massimo Scanziani
Paul Salin
Pierre-Marie Lledo
Gang Tong
Stephane Oliet
Steve Gomperts
Albert Hsia
Carl Peterson
Kaspar Vogt
Christian Luscher
Matthew Frerking
Qiang Zhou
Jack Mellor
Min Yi-Xiao
Rachel Wilson
Eric Schnell
Lu Chen
Dietmar Shmidt
Kimberly Moore
Kaiwen Kam
Nathalie Rouach
Valentine Stein
Karen Menuz
Hillel Adesnik
Guillermo Munoz
Aaron Milstein
Wei Zhou
Sandip Panicker
Anastassios Tzingounis
Seth Shipman
Kate Lovero

Jonathan Levy
Adam Granger
Wei Lu
Yun Shi
Carleton Goold
Alexander Jackson
John Gray
Sabine Blankenship
Mackinzie Howard
Bruce Herring
Nengyin Sheng
Argentina Lario
Yujiao Sun
Salvatore Incontro
Meryl Horn
Quynh Anh Nguyen
Samantha Esselmann
Wucheng Tao
Javier Diaz-Alonso
Michael Bemben

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