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Oxford University, Oxford England, DPhil (Biophysics) (1970)

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Research student in Eaton Peabody Laboratory, Mass. Eye & Ear Infirmary (1966)
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Sir Bernard Katz Award, Biophysical Society (2020)
Ralph W. Gerard Prize, Society for Neuroscience (co-winner with R. A. Nicoll) (2014)
Annual Review Prize, Physiological Society (2014)
Julius Axelrod Prize, Society for Neuroscience (2012)
George Palade Medal (2011)
Harvey Lecture (2009)
MERIT Award, National Institutes of Mental Health (2004)
Elected as Charter Member, Biophysical Society (1999)
Elected to American Academy of Arts and Sciences (1998)
Elected to National Academy of Sciences, 1997
Elected to Academia Sinica (1996)
Walter B. Cannon Memorial Award, American Physiological Society (1996)
Elected Member, National Academy of Medicine (1994)
Magnes Prize, Hebrew University, Jerusalem (1993)
Elected Fellow, American Association for the Advancement of Science (1988)
Javits Investigator, NINDS (1986–1993)
Kenneth S. Cole Medal for Contributions to Membrane Biophysics (1985)
Established Investigator, American Heart Association (1974–1979)
Rhodes Scholar (1966–1969)

Richard Tsien has been a pioneer in the study of ion channels and synaptic transmission. He showed that cyclic AMP regulates a variety of voltage-gated ion channels and thus delineated a cardinal example of neuromodulation. He helped measure cytosolic free calcium and showed how its levels can oscillate even with membrane potential held fixed. His group defined the molecular basis of how calcium channels achieve high selectivity and rapid flux. Tsien and colleagues discovered the N-type channel, the R-type channel, and other exemplars of Ca_V2 calcium channels, and revealed their role in triggering fast neurotransmitter release. Work on Ca^{2+} channels led to studies of synaptic plasticity, long-term potentiation, and the cell biology of synapses, and development of innovative optical approaches. His lab has unraveled mechanisms of homeostatic synaptic plasticity, excitation-transcription coupling, and excitation-alternative splice coupling.

Richard W. Tsien

A Memorable 50-Year-Old Conversation

A rose garden in the Oxford Parks was an unlikely place for a conversation about the radial spread of depolarization in muscle fibers, but there we were more than five decades ago, Professor Alan L. Hodgkin, Nobel laureate, and myself, a 24-year-old graduate student, during a tea break of the Physiological Society. Although his lab was in Cambridge, he knew the garden, having grown up nearby (Hodgkin, 1976). Alan Hodgkin had donated 40 minutes of his precious time to bring me up to speed on his unpublished work with Adrian and Chandler on the cable theory of the spread of excitation in muscle (Adrian et al., 1969), for citation in a book I was co-authoring with my mentors (Jack et al., 1973). Hodgkin had produced an elegant derivation with lots of radial Bessel functions. We touched upon this, but I also pitched questions about what he knew about how signals got from the transverse tubules to the sarcoplasmic reticulum where the calcium was supposed to be. Didn't there have to be some kind of special communication between the two? And were they ever electrically connected? And how did he *know* they weren't electrically connected? And how did the calcium get released to activate the contractile apparatus? And so on and so forth. Alan Hodgkin treated me *very* kindly but squirmed a little bit because I was asking questions for which he didn't have ready answers. Near the end of the conversation, I asked about one of his classic papers with Paul Horowicz, on the voltage-dependence of contraction (Hodgkin and Horowicz, 1960). Hodgkin looked at me, sort of blankly, and said, "You don't happen to have a copy of that paper along, do you?" Being a naive graduate student with little experience, I replied quizzically, "But Professor Hodgkin" (and I was polite enough to address him as "professor"), "you wrote the paper; surely you must know what's in it." He turned to me, and with a slight trace of a smile answered "you know, the reason we write these papers is so that we don't need to keep them in memory."

Because my lab currently works on molecular mechanisms of memory (Cohen et al., 2018), I am fascinated by both everyday and special memories, how they are formed, recapitulated in fragments in dreams, and somehow maintained throughout a lifetime. Recalling Hodgkin's wry remark on that day, my own cheekiness, and the curiosity we shared in questions that would take a half-century to answer (Polster et al., 2015), I reflect on memory, history, scientific enquiry, and the importance of culture. As I write, it's Thanksgiving Day 2019, this manuscript is due in just days, and I'm taking

a train to Washington to see my children and grandkids. My wife Julia and I have just been in a Penn Station deli called Zaro's, started in 1927 by Joseph Zarubchik, a Polish émigré. The book I've been reading is an ambitious account of U.S. history, *These Truths* (Lepore, 2019). Washington is abuzz with talk of President Trump's impeachment, Hong Kong is in turmoil, and the U.S.–China relationship is as complicated as ever. What a time to recall a chat in an Oxford garden a half-century ago.

In a personal history of neuroscience, there's a golden opportunity to transmit lessons learned from one's predecessors. Here are further observations of Alan Hodgkin's particular approach to science I'd like to pass on.

1. *Keep your eyes on the big question that interests you*. Hodgkin's work with Horowicz, leading to the discovery of chloride conductance in skeletal muscle, was found gold, but was intended merely as prelude to the ability to switch the muscle membrane potential rapidly to see how contraction was evoked.
2. *Do your own work first before taking a full scholarly dive into what others have done*. In studying muscle excitability, Hodgkin wanted to learn about the efforts of a competing group at the University of Poitiers only after he'd already formed his own opinion about the common question.
3. *Don't be overly worried if your competition has a better method; focus on what you find with your own*. The Poitiers group had a better way of controlling muscle sodium current, a sucrose gap approach that did away with microelectrodes (Rougier et al., 1968), but Hodgkin and colleagues were unfazed—they knew their strengths (Adrian et al., 1970b).
4. *Treat your adversaries with courtesy but firmness*. Hodgkin's courtesy to Ichiji Tasaki and his challenge to the sodium theory was a case in point (Hodgkin, 1976); in fact, he directed considerable manpower in his group to scotching Tasaki's challenge (Baker et al., 1964; Chandler et al., 1965).
5. *Control the writing of the paper*. Hodgkin's colleagues Richard Adrian, Knox Chandler, Leroy Costantin, and Lee Peachey joked about not being allowed to produce drafts because Alan wanted that job (this isn't so good for mentoring, but it's one way to assert one's authority about the final product).
6. *Fit tasks into suitable time vessels if you can*. According to his cardiac colleague, Silvio Weidmann, Hodgkin wrote down a full theoretical appendix for Weidmann's paper (Weidmann, 1966) on a Cambridge–London train ride. Perhaps he thrived on the pressure.
7. *Adhere to your own standards of conduct*. I asked Hodgkin about Lawrence Bragg's kind introduction to Watson's The Double Helix despite Watson's portrayal of Rosalind Franklin and the questionable

> way she was treated (Watson, 1968), and with pursed lips he replied, "that just shows you what a gent Bragg is."

British physiology was in full flight in the late 1960s, as Hodgkin, Andrew Huxley, and Bernard Katz branched out to study the consequences of the membrane excitability that they had so beautifully clarified (Hodgkin et al., 1952). Clarification of muscle contraction and neurotransmitter release would follow. The setting and the topics all relate in scientific and sociological ways to my own personal tale, involving ion channels, calcium signaling, neuromodulation, synaptic vesicles and excitation-response coupling.

Immigrant Origins

I come from a Chinese immigrant family. I was born in China. I came to the United States when I was two years old. I went to school in the New York City public school system. I spent two years at a private country day school on almost total scholarship. My brothers and I came from a family that was struggling. My father was an engineer, but he could not get security clearance during the Red Scare. I was raised in the crucible of a full-blown New York immigrant experience. We were living in Queens. (quoted in Haseltine, 2019)
My earliest memory is of children walking along a sidewalk on the far side of the road on Halloween. I am not part of their group, nor do I recall the custom of trick-or-treating, but I am buoyed by their happiness. To this day, autumn is my favorite season and my music of choice is autumnal. It's dusk, there's little traffic, and scarce detail about costumes or sounds, but for sure, the kids are walking in line from right to left. Dreams can be like this—definite spatial relationships. When bears fly, there's a clear sense of place, of spatial coordinates, of specific terrain. Perhaps this fits in with theories about how the hippocampus is involved in encoding space and time and pattern, all wrapped up together, and recapitulates them in sleep (Buzsáki, 2011). If my brain is doing this via spike sequences, I will never have primary knowledge; I am simply enjoying the unfolding progression.

I am the eldest of three boys. An early memory with more specific emotional content concerns my middle brother Louis in early 1950—our younger sib, Roger Tsien had yet to come along. I had placed a bicycle with training wheels, a rare special present, near his cot in our crowded apartment in Flushing, New York. Louis fell out of bed, cut his face on the bent metal rod that mounted a training wheel, and had to be rushed to the emergency room for stitches. Although I was supposed to safeguard my younger brother's welfare, I had failed in this responsibility—much worse than being hurt myself. In another family episode, I picked up loose change that had fallen under the couch cushions and stored it in a glass bookcase nearby, without a plan for what to do with the coins. When my furious parents spanked me, I accepted the punishment, but asked if they would report my

wrongdoing to my mother's older brother, Yao-Tze Li (Uncle Y. T. was probably only 40 or so, but was the acknowledged leader of our extended family; he had introduced my parents to each other among other good deeds). In hindsight, this memory shows a tendency toward hoarding and awareness of social hierarchy, topics of neuroscientific interest.

Bayside, Queens, a (Non-) Melting Pot

In the 1950s, our family lived in a working-class neighborhood in Bayside, Queens, in a small brick house at 58-43 204th Street, 10 feet away from our neighbor's house, with a narrow driveway in between. Being packed in together with so many other houses meant that we knew a lot of people in the neighborhood fairly closely. Our next-door neighbors were friendly Italians (the Rovellos) and their bungalow exuded tomato sauce with cheese. I hadn't known what a pizza was and had never had a latke, a Jewish potato pancake, until someone kindly invited me to their house—boy, those latkes were good, straight out of bubbling fat. We were the only Chinese family within a two-mile radius (the Miaos lived in the next town, and were in touch with us). Perhaps in reaction, our parents worked hard to preserve our cultural identity, against the odds. We boys got called all sorts of interesting names, but so did everybody else. I knew all the ethnic insults for Italian, Jews, and Irish, although the Irish were a little bit higher in the totem pole. In this neighborhood, a kid could see the successive waves of U.S. immigration, like layers in sedimentary rock, and realize that you were pretty far down the hierarchy. How to fit in? Knowing about baseball gave a sense of belonging and made it harder for people to look down on you. This happened to be a golden age of baseball in New York, and we all kept track of Willie Mays, Mickey Mantle, and Duke Snyder, the center fielders of the Giants, Yankees, and Dodgers, each a future all-star. I rooted for the Yankees, based in the Bronx, because hardly anyone else in our Queens neighborhood did. Bayside was actually a wonderful place to grow up.

A Quiz Kid of Sorts

Mr. Scher was the homeroom teacher in P.S. (Public School) 162 in a class different than mine. But he would send for me to come into his class. Towering over me, he would squeeze my fat cheeks with his big hand and fire quiz questions at me—capitals of states, little math problems—and chuckle with glee when I managed to squeeze out the answers despite his grip. At the end, I got a gruff, "OK kid, go back to your class." He was mocking me but affectionately showing me off at the same time, and I played my role, I played it straight; it didn't occur to me until much later that he must have had a pretty good idea of what the limits of my knowledge were. This was a powerful reinforcer for gathering bits of information, caching them

away in memory, just because they might come in handy someday. My dad reinforced this by telling me to be observant, only his examples were trivial: how many telephone poles did you count between X and Y?

Fired from First Job

Eighty-seven and a half cents per hour. That was the pay offered to me by the proprietor of a luncheonette, Ben Cantor, working with his wife Rho. I knew that the wage was exactly seven-eighths of a dollar—that was satisfying—and I didn't bargain. Ben apologized that the pay might be better but rationalized it by saying that he was going to teach me many things, including "how to ride in the saddle for a long time" as if he were a master cowboy. That went over my prepubertal head though I could guess that this was something he was proud of. I remember very little about the job itself, only that after a short time Ben fired me because, as he claimed, I was unable to make small talk with the customers. In this regard I can only agree that I was much inferior to Silvio Crespo, a tall, handsome, full-blooded Italian version of a soda jerk; I was short and chubby and wore thick glasses. Beyond being fired from my first job, the most notable part of the story was how I ever got the job in the first place. It was through my mother, Yi-Ying who had sat patiently in Ben's luncheonette to shyly ask him for a job for her son, who needed to know the value of money. Ben told me this story and confided that he was so impressed by my mother's dignity that he couldn't resist the chance to try out her son. Looking back on this and seeing pictures of my mother at the time, no older than my eldest daughter today, I can readily believe that she could make a case through her sincerity and quiet confidence. On some other occasion, with more time before a deadline, I would relish the chance to relay her life history, an amazing story on its own.

Stage Fright and Failure to Improvise

Scientists are trained to improvise and act calm, no matter the circumstance. Bertil Hille once had his slides dropped out of the carousel onto the floor just before a symposium talk organized by Michael Bennett. Bertil calmly put them back into the carousel in random order, correct side up, and proceeded to give his talk anyway. It wasn't always that way for me. I played the clarinet in band and showed Mr. John Cahill, our talented music teacher, the music for "After You've Gone." He got me onstage, began performing his piano accompaniment, and merrily announced without warning that I would now demonstrate the art of improvisation. To be fair, the music had a written out "improvised" part. But with no warning or instruction just to play that part, or even just the main melody, as if improvising, I froze in front of the entire assembly—not a note—while he kept playing enthusiastically. Oddly enough, no one razzed me about this embarrassment.

Boy Scouts, Parenting, and an Early Shot at Public Speaking

Joining the Boy Scouts was one way of belonging. Although my dad was too busy to participate, we had lots of surrogate parents, including the immigrant dad of other Boy Scouts. I remember Bill Vokurka's father, the assistant scoutmaster, using his huge hands to help me with tightly rolling up my sleeping bag. The scoutmaster, Ben Mandel, gave us little sermons about Boy Scout values and we listened intently without an ounce of cynicism. The Boy Scouts chose me for a special public speaking course, held on Saturdays at the New York Public Library, which was reached by taking a bus from Bayside to Flushing, and then by transferring to the IRT subway to Bryant Park. The course drained the stage fright from giving speeches, a lasting benefit. Also, travel to Manhattan awakened an interest in urban architecture. The main library building seemed monumental in size and elegant in design, and it remained a touchstone for our family. I was much more drawn to the public edifices of New York, like the Museum of Natural History, than to Chinatown, which was crowded, dirty, and noisy, and filled with a different kind of Chinese than the Mandarin I knew. Chinatown was in no way a connection with my roots.

Sunday School and Belief in God

My mom was not a Christian, but she wanted to be sure we were equipped for our new life in the United States. When a Lutheran minister came knocking on our door, she allowed him to invite me to attend Sunday School. I did so for two and a half years, enjoying Bible stories, hymns, and a general feeling of being accepted. But I dropped out when it came time to be baptized—if one didn't truly have faith in God, what was the point? Much later I learned that my wife Julia had gone through the same experience in her youth. Because her mother was the star soprano of their Congregationalist Church in Winchester, Massachusetts, a key to their acceptance as Chinese in such a WASP-y New England town, her decision must have taken much more independence than mine.

Sputnik, Science, and Patriotism

Talk about your experiences in that particular neighborhood; did that inform your choice to pursue science? Did you have academic parents, were they encouraging of that?

My parents were comfortable with science, but they didn't push it on us. We three boys were just naturally inclined to it. When the Russians launched *Sputnik* in 1957, Americans felt that they were being outclassed by their adversaries. This prompted me to feel committed to work in science or engineering, encouraged by teachers in what was then junior high school.

For example, Mr. Dobbins taught shop, but he talked about what it would be like to get a doctorate in physics at Columbia. I don't remember thinking that going into science and engineering and space competition would put us in the same realm as H. S. Tsien, the famous Chinese rocket scientist who was my dad's first cousin. At that time, we were focused on the Soviet Union as a threat to America. Indeed, as immigrants, we were probably a little over the top with our American patriotism.

You brought up your uncle. Could you speak about what his contributions were? Was that a source of inspiration for you? (Adler, 2015)
My uncle, Tsien Hsue Shen, the Werner von Braun of China, was a student at MIT and later a faculty member at Caltech, actively involved in the early days of the Jet Propulsion Lab; he studied aerodynamics with a famous professor there named Theodore Von Karman, and we assumed, without real evidence, that he was one of Von Karman's best students. The first cousin of my father, H. C. Tsien, Uncle H. S. was both a distant inspiration and source of difficulty for our family during the era of Joseph McCarthy. My uncle had the misfortune to be singled out by the authorities under suspicion of being a communist, which he'd continue to vigorously deny all of his life; much of this is documented in magazine articles and in a book by Iris Chang (Chang, 2008). When H. S. Tsien's mother was ill in China, he had prepared to ship his nonclassified books back to China. This led to his house arrest at his home in Pasadena, which went on for four years. I later visited my uncle in Beijing on two different occasions, part of an interesting relationship with China and Chinese science as mentioned later. For now, I'll continue to chronicle our own family's experience as immigrants whose sincere attempts at blending in to American society were hindered by my uncle's well-known case.

Scarborough School and Social Class

My hopes of helping the exploration of outer space were encouraged by passing a competitive exam for entry into the renowned Bronx High School of Science. This opportunity was dashed by a move to Westchester, out of the NYC school system. My dad chose the town of Elmsford, not weighing heavily its public school system, which was mediocre at time. But my mother, who had missed years of schooling because her parents had given her away to a childless aunt, was dedicated to our education. Spurred by my youngest brother Roger's aversion to public elementary school (he would vomit in protest of being taken to such a boring place despite my mom's best efforts), she found a private school, Scarborough Country Day, that was willing to admit all three of us with minimal tuition, $200 per year per boy. We were not the only scholarship kids, but we were the only non-Caucasians in the

entire school—no African Americans or Latinxs, and only a smattering of Jews and Catholics.

The school had been started by wealthy WASPs in the neighborhood near the Vanderlip estate in Scarborough-on-Hudson, between Tarrytown and Ossining. Here, surrounded by kindness and liberal intentions, I felt particularly acutely the anything-but-equal social ladder of America. Being Chinese, not well-to-do, and short and chubby was to start several steps down. I recall Steven Barry Epstein, a smart and athletic Jewish classmate who came every day to Scarborough from Mount Vernon, New York, who had been delegated to phone me to invite me to a sock hop, as if he were reaching down from the next rung up to lend me a welcoming hand. Other students were also friendly. Attending Scarborough was a valuable experience socially, probably more broadening than Bronx Science would ever have been, because my brothers and I were thrown in with rich and not-so-talented students, mixed with working-class and very talented kids like the Schmidt brothers. Frank and John Schmidt were the best athletes, the best musicians, and the handsomest kids in the school. When after-school athletics finished, they kindly gave me a ride home to Elmsford on their way home to Yonkers, their working-class town. "Charlie Chan the chunky Chinaman," a nickname repeated with affectionate glee, was meant as a sign of belonging; another classmate's calling Steve Epstein a "Wej," behind his back, was nasty. At the time, I readily accepted insults about my origins when they were administered in a direct and friendly way. Accustomed to the teasing, I knew my place in the world.

Mr. J. Fulton Main, the rotund Scarborough vice principal taught science, not as an experimental method or series of concepts but as a collection of facts. Glaciers pushed a *terminal* moraine forward and *lateral* moraines to their side. Repeat. Hypnotic mnemonics, never mind principles; science was fun. Mr. Main had outlasted multiple headmasters but didn't want the pressure of the job. He had a wonderful tenor voice and sang "Comfort Ye My People . . ." from Handel's Messiah every Christmas. At the holiday season, I embraced the uplifting ritual that Christianity provided.

Mrs. Creighton taught not only Latin but also the lives of the Romans. She awakened a lifelong love of language and the roots of words. I remember standing in a school bus and speaking with her (or perhaps it was our French teacher) about the subjunctive mode and its strategic uses.

One of the best teachers, Mr. Stuart Ryder, a wiry, bespectacled young Yale grad, taught social studies. When I pointed out that I had managed to eke out a B+ for a paper on Hegel's philosophy by pulling an all-nighter, he acerbically noted that there was a big difference between a B+ and an A. On one occasion, he kindly took my friend Steve Epstein and me to New Haven to watch a football game at Yale Stadium. Later, Mr. Ryder made it clear that I was not to apply to Yale because that opportunity was to be

saved for Steve. I didn't take that badly because I knew how much it would mean to my friend (he actually studied at Tufts, became an expert attorney, and collected an honorary degree from Columbia at the same graduation as my oldest daughter, Sarah). But it impressed upon me that as a Chinese-American newbie to the school, I was totally outranked.

The most important teacher for my life was Mrs. Helena Jones, the only African-American person in the entire school. Her husband worked on the assembly line at a General Motors factory in nearby Tarrytown. There was no mockery of her race—she wouldn't have tolerated it. Once she scolded me for inattention in her geometry class, saying "you're just loafing." But instead of some kind of punishment or detention, her remedy was to address my boredom by encouraging me to take her courses in both algebra and geometry in the same year, with the expressed purpose of getting me qualified to take senior year calculus. The challenge, and probably the special attention, totally changed my attitude to math and to school. Even though both Mrs. Jones and I would leave Scarborough before my senior year, her intervention allowed me to take senior calculus at another high school, thereby equipping me for an easy ride with college physics thereafter: educational advantage rolling forward. I am forever indebted to Helena Jones for calling me out for laziness and building an early foundation in math.

Livingston, New Jersey, Hospitality and Lack Thereof

Just as I was approaching the rewards of senior year in high school, circumstances intervened again and we moved to New Jersey to be close to my dad's new job at RCA. He had started his own engineering consulting company, but this had failed in the recession of 1958. During the transition period before we moved the whole family to New Jersey, my dad and I drove in his VW bug from Elmsford to East Orange, New Jersey, to meet a kind guidance counselor, Mr. John Mazzone. Mazzone was a colorful Italian American, a great fan of the musical *West Side Story*. He drove us the rest of the way to Livingston High School, chain smoking the entire time. Attending that school had taken some doing because we had trouble buying a house in Livingston—the developer Levin-Sagner had told us that the arrival of Chinese people would bring down housing values in the neighborhood. My brother Roger wrote about this movingly in his Nobel lecture (Tsien, 2010). Our dad protested to the New Jersey governor, Robert Meyner, and so we were grudgingly allowed to buy a house, but on a runt lot where rocks from other properties had been dumped. So we three Chinese-American boys wheel-barrowed rocks around like the Puritan farmers of New England. The high school students showed us no prejudice (there was only one other Chinese student in our class and no other Asians I can remember) and adopted me even in senior year. I played clarinet in the band and mowed lawns to earn money for lessons, took calculus with a gifted math teacher,

and read novels by Thomas Hardy in an excellent English class. One memorable day, I played hooky from school and trekked to Yankee stadium with a baseball player friend named Jeff Allen, who became a beloved clinician and pediatric cancer specialist at New York University (NYU).

A Choice of Colleges

When it came time to apply for colleges, I got an early admission to MIT on the strength of my SAT scores and possibly family connections, and only later received acceptance from Harvard (Yale wasn't even a thought, possibly because of Mr. Ryder's stern command). In contrast to high schoolers today, I didn't apply anywhere else—the early acceptance gave me the chance to be near my academic uncles in the Boston Area and that would have beaten anything else. MIT had offered a $700 scholarship, easily besting Harvard's later offer of $500. Deciding was delayed until the final hour, when this monetary difference, and my mom's persuasive argument that going to MIT would really please my dad, settled the issue. In my 16-year-old's mind, I was on the fence anyway, so why not maximize the total happiness in the world and go along with my dad's wishes? I had consulted with Uncle Y. T. Li, but he had taken a completely neutral position in the MIT–Harvard choice, even though he and his younger brother, Shih-Ying Lee, were both MIT professors. In retrospect, my decision was pragmatic, not rebellious against family tradition for rebellion's sake. MIT proved to be a good option for me, mostly because it gave me valuable opportunities—extracurricular ones—that I would surely have missed at Harvard. Later, my brother Louis would follow me to MIT, while Roger branched out and went to Harvard. Roger had his own perspective on family expectations (Tsien, 2010). I include these early life stories because they convey the combination of frugality, academic confidence, idealism, and practicality that ran through my family. The obstacles we encountered didn't come close to those experienced by other immigrant groups, but they instilled an underdog perspective.

Going to College

Tsien studied electrical engineering at the Massachusetts Institute of Technology, receiving a bachelor degree in electrical engineering in 1965. A master's degree in 1966 was based on spectroscopy of conducting organic polymers at GE research labs in Schenectady.

Joining a fraternity was a big part of the MIT experience, which began for me at 16, in 1961. Occupying a multistory house in Back Bay close to Boston University, Beta Theta Pi was not the Hollywood stereotype fraternity of the film *Animal House*; the hazing and drinking were mild compared with that at more traditional schools. Instead, the Beta House was a community of

male scholar-athletes, who took pride in their seriousness, like NASA astronauts so admired in those days. In each of the years up to my graduation in 1965, the Betas had the highest average grade point, exceeding Dean's list level (4.0/5.0), even better than the women's dormitory; they also won the all-around intramural sports trophy each year. This took hard work, time management, and upperclassmen looking after and indoctrinating the younger students. I was the first Asian American to join, aided by a connection between my immigrant uncles and Professor Charles Draper, an MIT hero, whose son James "Pox" Draper helped my consideration. Sometime later, I was told that another member had wanted to blackball me—selection was based on unanimous vote—but was dissuaded by William Koch, a now surviving member of the conservative Koch brothers. Both Bill and his slightly older twin brother (the late David Koch, who later hosted me in his grand apartment in NYC with his wife Julia) were seniors and kind to me. The Beta House included plenty of conservative Southerners and Midwesterners, far more red than blue, some now lifelong friends. Thus, I had gone from housing discrimination in Livingston to joining an all-white fraternity in little more than a year. In 1961, pre–civil rights movement, my thoughts were not on lofty concepts like racial equality but on making friends and fitting in.

MIT provided great courses, including an introductory class in signal processing by Amar Gopal Bose, the founder of the audio electronics company, one of many charismatic teachers. One of my favorite classes, on history, was taught by Emmet Larkin, an Irish historian who dared his class of engineering geeks to appreciate Thucydides' writings about the Peloponnesian Wars. Larkin was tough, giving almost everyone including me grades no better than B+, my worst grade at MIT, but he also awakened a love of history that lives to this day. Many excellent classes followed, on statistical mechanics, for example, but I particularly savored a multiterm semiconductor course organized by Paul Gray that went all the way from semiconductor physics to the workings of transistors and amplifier circuits. He later became MIT's president, partly on the basis of this innovative teaching. I saw Gray's vertically integrated teaching as a role model for my own attempts at bringing molecular and systems neuroscience closer together, first with Len Kaczmarek and Steve Smith at Yale, and later, in a Stanford course I taught with Steven Baccus, entitled Information and Signaling in the Nervous System.

Having a leg up in math, thanks to Mrs. Jones' guidance in high school, I had time for extracurricular activities. As a coxswain in the freshman crew, I was given the plum opportunity of coxing the big Harvard race, but this ended badly because our boat took on water on a stormy Charles River and sank. I could have bailed with my megaphone but didn't think of it in the panic of the moment. My crew career never recovered, but in sticking it out for three years, I learned a lot about coaching athletes, team effort,

and endurance as I trained in the winter with the oarsmen I coxed for. I loved the coaching part. Midway through MIT, I tried wrestling, partly in response to ridicule about my nonathletic physique from an upperclassman in the Beta house. I managed to reach junior varsity (JV) status in the 123-pound weight class, regularly "pulling weight" by exercising in a rubber suit to sweat down from my natural 130-pound weight, and not doing so badly at wrestling for a nine-minute match. My MIT coaches had encouraged me to try JV athletics at the college level, knowing full well that I had no high school experience in the sport. This was the kind of life experience I gained at MIT that would probably be denied at an athletically more advanced institution such as Harvard. Wrestling, like crew, was a team sport that cemented my love of team efforts and strategy. Although my fraternity brothers admired my determination, and appreciated my organizational skills as scholarship chair, intramural sports chair, and rush chair (head recruiter), I lost the election for president of the Betas to my then-roommate William Roeseler.

Bill Roeseler was older, taller, stronger, and more athletic than I was (a repeated theme, I admit) and just as academically capable and public spirited. As freshmen, Bill and I motorcycled from Boston to New York in freezing weather, heard Jose Feliciano at the Bitter End in Greenwich Village, and climbed Mount Washington in winter together with other Betas. Later, we received two precious honors together—the only MIT juniors of our year to be elected to the Tau Beta Pi engineering society, and as seniors, the Compton Cup for public service, presented by Mrs. Compton, widow of a former MIT president. Bill remains a lifelong friend despite our sharp blue–red political differences. After my house president hopes were dashed, I worked under Bill in the lesser office of pledge trainer, in effect the chief mentor/taskmaster for new freshmen, the next most important leadership role. This was a chance to coach, to pass on values. Two Betas in classes after Bill's and mine were nascent neuroscientists, the late Peter Getting (1967) and Robert Macdonald (1966, more about his critical role in a moment).

Despite the freshman crew debacle, I entered student politics and managed by narrow margins to win election as class treasurer and later senior class president. Class activities were not political—this was before a full-blown antiwar movement—but included organizing events. I put on concerts by the Canadian folk group Ian and Sylvia and saxophonist Stan Getz's group featuring xylophonist Gary Burton, choices ahead of their time in musical taste. The proceeds allowed me to run a concert for our graduating class featuring the famous Dave Brubeck Quartet, charging seniors and their family members $1 each. This "Graduation Eve" gala for families was a first for MIT, and it gave me a chance to play the role of community organizer, behind-the-scenes impresario, and poster artist. The flexibility and personal mentoring that Dean Kenneth Wadleigh offered me in launching Graduation Eve was a special part of MIT—perhaps he saw a future

dean. Once again, I had lucked out in my choice of colleges, even beyond the superb technical education I had gained.

Real-World Experience at General Electric

My dad didn't have a very high opinion of my MIT education—the branch of electrical engineering that I had chosen was much too conceptual, not hands-on like his own mechanical engineering background at Jiaotong University and MIT. I got a chance to do more with my hands in the MIT Cooperative Master's Program, a program with remote sites offering what were in effect research internships with a remote practical supervisor and a nominal head of committee on campus. I opted for GE research labs in Schenectady, New York, up the Hudson from New York City. I had worked for two summers at a power company, Jersey Central Power and Light, to help pay for college, but that involved routine calculations of the impedance of power lines, not research. At GE, I was given projects at the border between materials science and engineering. Students were a rare commodity, so I got lots of good mentoring from Alec Sharbaugh, Oliver Leblanc, and Charles (Chip) Huggins. In the first summer of the GE internship, I measured the critical voltage at which dielectric films broke down. Whenever things didn't work, Alec would say in the most cheerful tone, "Well, that's research!" As with Mr. Main at Scarborough School, it wasn't the information content but the buoyant tone that made it all seem worthwhile.

Later, Leblanc and Huggins guided my experiments using electron paramagnetic resonance (EPR) to study the properties of organic polymers made by a chemist named John Lupinski. Huggins was smart and ambitious, and he nattily dressed in crisp white business shirts and chain smoked (smoking was allowed in the workplace back then—think Mad Men). Leblanc was quietly intelligent and more casual (plaid shirts), and like Huggins, he spoke with a North Carolina drawl. Together, they directed my study, cheered the experiments, and put together a first-authored paper for us in the *Journal of Chemical Physics* (Chip had wistfully talked about *Nature*, but Ollie talked him out of it). They were closet professors, working in a setting that rivaled Bell Labs, without the pressure of academia, going home when they wanted. For my part, I loved listening to their stories, working at the EPR machine, improving my tennis, and having the time to take up folk guitar. Schenectady was close enough to Massachusetts to allow me to drive a blond, folk-singing secretary to Woods Hole for a long day's date, riding in the VW bug passed on from my dad. I roomed with another MIT student, Joe Waters from Mississippi, who loved country music and finger-picking "Wildwood Flower." Unlike Julia, my beloved partner of five decades, who abhors anything with a twang, I came to love it.

In our guitar playing, Joe and I met another young scientist who seemed mortal enough—not an athlete at all, a confident nerd—despite his status

as a former Rhodes scholar. This helped dispel my notion that all Rhodes scholars were stars in sports like Pete Dawkins (or later, Bill Bradley) and so I decided to apply myself. GE was critical in emboldening this by providing research experience, warm mentorship and a chance to grow socially. After applying from New Jersey, having really lived there for only one year, I emerged from that state, proceeded to the Middle Atlantic regional interviews at Johns Hopkins in Baltimore, where I wound up competing with Henry Lester, now an honored fellow neuroscientist, who had been at Harvard like so many other contestants. Four out of twelve were selected for the scholarship. I would be the only Asian in the group of 32 scholars, but one of the other Mid-Atlantic winners, representing New York state, was Richard Joseph, of Afro-Caribbean descent, now a distinguished political scientist, teaching at Northwestern. In all of my education up until then, Richard was the first black person that I can remember encountering, not counting Helena Jones at Scarborough School. My family had been a dot of Chinese in a sea of white.

After my good fortune in being awarded the Rhodes Scholarship (and the alternative Marshall Scholarship, which I was counseled to decline), I had to decide on what to do next. The Rhodes offered a graduate education in any subject that I might choose, regardless of what I had proposed in the application. Robert Macdonald, whom I've already mentioned as a fraternity brother and friend of mine, had fallen in love with a new field called neuroscience and with born-again fervor saw an opportunity to win another convert. I was resistant, but he simply wouldn't take "no" for an answer. I had convinced the Rhodes committee that I would gain an Oxford training in solid-state physics, in preparation for a career as a scientist-statesman, perhaps a Presidential Science Advisor or a cabinet member like Steven Chu of today. But Macdonald persisted and eventually beat down my resistance, insisting that at the very least I should seek advice from a famous auditory physiologist named Nelson Kiang. I went to see Kiang, a charismatic and intense researcher, at the Eaton Peabody Lab of Auditory Physiology at Massachusetts Eye and Ear (part of Mass General) that he headed. There, Kiang gave me two pithy pieces of advice: first, learn about evolution; two, seek out Stephen Kuffler. I followed these pieces of advice, and came under Kuffler's spell (more below). I happily accepted Kiang's invitation to spend my remaining moonlighting time before Oxford at the Eaton Peabody laboratory.

During spring and summer semesters in 1966, back at MIT after my GE experience I had time to learn some biology. Unfortunately, lacking prerequisites, I was not allowed to take Joel Brown's experimental course in neuroscience. The best that I could muster was a lab course in microbiology taught by Salvador Luria. There I learned to pipette, using old-school mouth suction to take up solutions, some containing nasty bacteria such as *Salmonella*. My lab partner, Joseph Malpeli, later a visual neurophysiologist,

was infinitely patient and managed during our breaks from pipetting to teach me about the 20 amino acids and why they were interesting. Some evenings were spent working with two young faculty, William Peake and Thomas Weiss. We set out to try to put a microelectrode into a cochlear hair cell, not in a convenient model animal but in the cochlea of a cat, a quixotic project that has never been done to the best of my knowledge—people work with much more reduced preparations. The goal made sense in the abstract because Kiang's classic recordings from the auditory nerve had been made in the cat, following in the footsteps of Kuffler's work in the visual system. I fondly remember evenings in the lab with both of them, Weiss made the microelectrodes in a nearby lab, and Peake and I tried to get ready to make recordings. They were both kind and supportive and seemed to enjoy the opportunity to stay out late to guide a naïve student. I also pulled an all-nighter with a master's student, Michael Wiederholt, who was doing recordings from a cat's auditory nerve bundle, my first glimpse of *in vivo* electrophysiology. Enduring my questions was probably exhausting, although he didn't outwardly complain. I watched Kiang preparing his book on cochlear nerve recordings, laboring obsessively over the massive figures, and was admonished that the traces were as important as the writing. As we approached summer, Kiang gave me a pep talk about being more engaged with the project, but I was distracted while taking German at Harvard Summer School (my only C+, I forgot to study the subjunctive forms of German verbs) and, liberated from the overachiever's weekly grind at MIT, dating a sweet girl (a judge's daughter and good person—enjoying, for example, a picnic at the Boston Pops Concert on the Charles River on Bastille Day). I was also preoccupied about what would happen in Oxford.

Your research has mainly focused on various aspects of neuroscience recently. But, as I understand it, you actually started out in cardiac physiology. Can you tell me a little bit about how you got started in cardiac physiology and how you came to change? (Adler, 2015)

My master's degree in electrical engineering had led to the chance to go to Oxford for a two- or three-year study program with tuition and living expenses paid, an amazing opportunity. But what to do? The two choices presented from Oxford were working on excitable tissues with Denis Noble, who at the time was really just an assistant professor, or on oscillatory contractions of insect flight muscle, with J. W. S. Pringle, a senior scientist and member of the Royal Society. I went to hear Professor Pringle speak but lacked the right background to appreciate his work using x-ray crystallography to get at structural dynamics of muscle cross-bridges at various stages of the contractile cycle. When Pringle, a tall distinguished man with a dry quiet voice (think Dicky Merton in *Downtown Abbey*), showed diagrams of x-ray intensities in Fourier space, one after another in a dark

room, I kept falling asleep. I decided then and there that I was not cut out to work on insect flight muscle, but would take my chances in approaching the young Denis Noble, who had written just one paper on his own, not even an experimental paper but a 66-page review article about the Hodgkin–Huxley equations, describing the dynamics of excitable membranes (Noble, 1966). I wrote to Noble, and, after a long delay, finally got a letter accepting me as a potential graduate student, no conversation, sight unseen. I learned later that the Warden of Rhodes House, Sir Edgar Williams, knew Noble through their joint affiliation with Balliol College and had helped with the arrangements.

Sailing to England

Just as correspondence involved letters, not email, travel to Oxford took place by steamship, not airplane. Thus, I had five whole days to mingle with other members of our class in the relatively luxurious setting of an ocean liner, the *Queen Elizabeth*. The crossing was rough, and one of our now-renowned classmates, the film director Terence Malick, spent much of the passage seasick in the bar, passing the time by eating peanuts. I met Terry because I had decided to fill the time productively by systematically and earnestly interviewing my classmates to jot down something about their backgrounds. In this way, I met David Kendall, now famous for his high-profile cases as a Washington attorney, some involving the Clintons, and learned that he had been shot at during his voter registration activities in Mississippi. Where did I get the nerve, an MIT electrical engineer, to compile profiles of our band of roughly 30 (out of 32) U.S. Rhodes scholars? I don't remember feeling any embarrassment back then, just exuberance about the life journey we were all embarking on; I was merely using the time efficiently, gathering data. What else was there to do?

By this time, it was clear that I had somehow opted for roads less traveled: MIT, not Harvard; science, not liberal arts; and rather than Balliol, the academic epicenter of Oxford, Wadham College, a smaller and less famous college nearby, strategically situated partway along a well-worn path between most of the colleges (residences for both students and dons) and the Oxford University Science area. This realization could have dawned even earlier, in Cambridge, Massachusetts, had I attended a meeting for a dozen soon-to-be Rhodes scholars, where I would have been the lone MIT person, all the rest from Harvard. Many of these people later turned out to be friends. Meanwhile, Wadham had a famous and friendly warden (their name for the head of college, not the person at the gate to the college, as I learned the hard way). Sir Maurice Bowra was a renowned classicist, born in China, famous for his independence and quips. Vociferously anti-Nazi, Bowra met Adolph Hitler way early in his rise to power and replied to Hitler's "Heil Hitler" with an instant "Heil Bowra."

Bowra's authentic and eccentric charisma imbued Wadham College with good cheer. There was a nice mix of Rhodes scholars from Canada, Australia, and the United States, including a distinguished Canadian biochemist-in-training, John Bergeron. I enjoyed vacation travel to Ireland with these men, grouped not by our fields but by our status as ex-colonials amidst a landscape of British undergraduates. The locals seemed to read me as American, not Chinese or Chinese American, because of accent, body language, and Yankee brashness. Rhodes scholars were assumed to be competent, older, and replete with odd tribal customs of their own. In 1966–1967, early in the Vietnam War, our antiwar activities included the penning of a letter to President Johnson questioning the wisdom of war that appeared in the *New York Times*. Mild stuff compared with what was to follow. I was told that my engineering background marked me as too conservative to sign, but I scurried around Oxford in the predawn hours, doing my bit to gather signatures—in the end, 50 Rhodes scholars signed, 20 out of 32 of our 1966 class. A predawn image of awakening Curt Hessler in his underwear sticks with me. Friends like Stewart Early and Wesley Clark stood out as being in honorable opposition to the letter. We all saw this as an honest difference of opinion to be respected, not as polarizing as politics today. My father, by this time a naturalized American, staunchly conservative, was intensely displeased with my signing the letter even though it merely questioned the wisdom of the conflict in a respectful tone.

As a Rhodes Scholar and junior fellow at University College Oxford, Tsien graduated with an Oxford DPhil in Biophysics in 1970, working under the superb mentorship of Denis Noble (a cardiac electrophysiologist) and Julian Jack (a cellular neurophysiologist). His doctoral thesis with Noble described outward currents that support the cardiac action potential repolarization and repetitive firing; Tsien also worked with Jack and Noble on a book, Electric Current Flow in Excitable Cells. (Adler, 2015)

I had never met Noble, and without today's Google Images, had no idea of what he even looked like. I went to the Oxford lab every day for about a week (no security, one simply walked in), only to be told by Keir Pearson (a Rhodes scholar from Tasmania, now known for his work on motor control) that, no, Denis wasn't in today. Finally, one day I met him—a slim man with reddish brown hair, pageboy cut, wearing a slightly rumpled yellow tie and proffering a limp handshake to meet my ex-wrestler's bone crunch. Not much to say except a shy welcome, see you tomorrow. Soon it became clear that although I had intended to work on the brain, Denis Noble was not doing any experiments on neurons or nervous tissue; he was actually studying the electrical basis of the heartbeat. So, I had to choose then and there between working on the brain or joining with Noble in trying to unravel the underpinnings of the cardiac action potential. And, since I knew no biology, *everything* seemed interesting. This began what proved to be a nearly two-decade detour toward my eventual career as a neuroscientist.

Denis Noble is now a fellow of the Royal Society, recipient of the Order of the British Empire and multiple honorary degrees, and former president of the International Union of Physiological Sciences (IUPS). It's been more than a half-century since he drove an old car to the 1963 IUPS meeting in Leiden and showed traces of a computed cardiac action potential based on an extension of Hodgkin and Huxley's equations for squid axon (Noble, 1962). An authentic wunderkind, Noble's formal advisor was Otto Hutter, celebrated for his work with Wolfgang Trautwein in Steven Kuffler's lab, recording effects of sympathetic and parasympathetic stimulation on cardiac pacemaker potentials (Hutter and Trautwein, 1956). But Denis's computations were done on his own (Noble, 1962), with only advice from senior faculty at University College London (UCL). Today, the framework for such computations can be downloaded from the internet by high school students, but in those days, simulation of membrane excitability required sophistication and a struggle to get computer time, and seeing authentic-looking cardiac action potentials was a big deal.

Denis's donnish outward appearance and eloquent British orations were deceiving; although he had learned to fit in, his roots were humble, east end of London, not really Oxford at all but in some ways the epitome of Oxford. Time in France as a child had given him an affinity for French culture—cooking, literature, and the spoken word. Apart from his brilliance, both in math and in discourse, what set Denis apart was his love of philosophy, and perhaps secondarily, his yen for argumentation on behalf of a cause. Think of a linguistically precise Oxford philosopher rolled up with Joan of Arc, dressed in armor and ready for a righteous battle. All of these traits come together in his advocacy for the culture of Occitania. Activists can derive inspiration from Noble's current writings in *The Music of Life* (Noble, 2006), which champions a physiological view of biological systems rather than a narrower "selfish gene" approach (Dawkins, 1989). Denis has fought for public support of science and, in so doing, spearheaded a still-famous academic coup at Oxford that denied Margaret Thatcher an honorary degree because of her draconian policies toward science funding. Denis Noble would be a fitting subject for a full-blown biography or novel.

Denis made no attempt at inculcating me with his personal characteristics, although we spent a lot of time together during our three years together in Oxford while I was his doctoral student. I was treated as a privileged acolyte, friendly colleague, and thirsty sponge for information. Given differences in our roots, and my lack of real biology background, how did I get so much of Denis's attention? It started with Oxford-style tutorials, weekly one-on-one meetings, going over his approach to membrane excitability. No attempt at breadth—that was for me to get on my own. Denis left Keir Pearson and Dick Stein mostly alone to work on the nervous system—he was (and then we were) going to focus on cardiac action potentials.

He showed me how to collect hearts at the local slaughterhouse and to obtain two-electrode voltage clamp currents from bundles of heart muscle cells called Purkinje fibers. But then he hardly appeared in the lab for experiments, for life as an Oxford don was busy, and I seemed to relish experiments. I once asked him where the sheep heart's natural pacemaker (sinoatrial node) was—he wasn't sure. Denis left me to make my own mistakes, without much experimental guidance or interference.

Happily, I passionately loved doing experiments and, as his sole source of data, was given tremendous access to analyze and discuss the results with him. We would walk together to the covered market to buy food, chatting as we went along, talking about philosophy as much as science, walking back to his place where I would serve as sous-chef for his evening cooking. This often culminated in his bringing a tray of delicious Indian curry up to the bedroom of his wife Susan, a physiologist in her own right, who coped with depression by reading classic British novels. Often, Denis and I then ate together, continuing our discussions. Sometimes the Indian cooking extended to a dinner party, with Denis providing a variety of dishes and his colleague and friend Julian Jack bringing over a Pavlova, a dessert concoction made of egg white crust replete with cream and passion fruit. I introduced Denis to guitar playing, which he took up much more seriously than I later on. Our social life extended to a vacation together in 1968, on Lake Windermere in England's Lake district, a two-car party with Denis, Susan, and their daughter Penny, my then-girlfriend Jane and myself, and Julian Jack and Steven Redman. Each scientific pair was working on a manuscript, pivotal work that would appear in the *Journal of Physiology*, our top-tier venue for longer publications (Jack and Redman, 1971a, 1971b; Noble and Tsien, 1969a, 1969b). Some time later, my future wife Julia and I would join Susan and Denis to attend an Oxford ball—an all-night party with dancing and champagne. Susan entertained us with risqué stories of their courtship, providing salty humor to counterbalance Denis's shy formality. I mention all this to convey how personal interactions intertwined with scientific advances, a kind of life experience that is much harder to imagine today. When I began work in his lab, I was 21 and Denis was 29.

I vividly remember a particular experiment, #78-1, that yielded the bulk of the data for the story written up at Lake Windermere. Over the course of a singularly long (4 hour) recording from cardiac bundles, I obtained a complete dissection of two components of outward current, at various times known as I_{x1} and I_{x2}, $I_{Kr(rapid)}$ and $I_{Ks(slow)}$ or hERG and K_{VLQT1} (we got most of the basic properties right but lost the naming battle and most of the credit). I had a date with Jane, who was an anthropology doctoral student, and I had to stand her up to finish the experiment (no cell phones), but she understood its importance and accepted my apology. Now that we knew how I_{Kr} and I_{Ks} could be separated, I handed Denis the multiple rolls of heat-sensitive chart recorder paper, challenging him to do the analysis, a task with lots of

plotting on semilog graph paper that I knew he would enjoy. An equally thrilling set of data, on epinephrine's effect on cardiac pacemaker current, had come off the chart recorder about a year earlier. Both of these findings were somewhat heretical: our emerging picture of multiple types of potassium channels was different than Noble's own model and clashed with preconceptions based on the simpler workings of the squid axon. Nowadays, folks accept without question that heart cells display a rich diversity of outward currents (Chiamvimonvat et al., 2017; Nerbonne and Kass, 2005), but this seemed implausible at the time. The finding of a neurotransmitter modifying a voltage-gated channel by shifting its voltage dependence (Hauswirth et al., 1968) was also quite novel compared with acetylcholine quickly activating a ligand-gated conductance (studied by those whom Kuffler termed "millisecond men"). Denis and I believed in our data and weren't fazed by coming up with oddball findings. The experiments on K currents supporting the cardiac plateau and neuromodulation of pacemaker current would form the basis of later work in my own lab.

Steve Bergman (a.k.a. Samuel Shem)

I simplified the reality in saying that Noble had only me to look after. Perhaps the most fascinating part of the story was his other doctoral candidate, from the same boatload of U.S. Rhodes scholars, Steven J. Bergman. Little did any of us know that under the pseudonym Samuel Shem, Steve would later publish the famous *House of God*, a classic novel about medical training that has sold more than two million copies and was put on a par by John Updike with Joseph Heller's *Catch-22*. Chunks of hospital slang that he invented are now used in practice. Steve and I became acquainted on the *Queen Elizabeth*, when I learned that he had played basketball at Harvard and was headed to Balliol under the supervision of the self-same Denis Noble. Moreover, Steve had worked on the brain, specifically, on the role of calcium in memories. In Dan Pollen's lab at Harvard, Steve had used his fine motor skills to cannulate blood vessels in the brain to manipulate the calcium in blood, looking for a change in the encoding of memories. Retrospectively, one could argue about whether the experiment would work in practice, because intracellular calcium is so tightly regulated, but there's no doubt of its prescience. Once at Oxford, Steve read Samuel Beckett and wanted to write plays, not do experiments, although he was canny enough to follow in Keir Pearson's footsteps and complete his doctorate on a physiological aspect of a simple form of memory, conditioning of the leg-lifting behavior of a cockroach. Just as Noble was incredibly kind to me, he also forever shaped Steve's life by simply allowing him to do his own thing, guilt-free.

Coincidentally, I eventually worked on the role of calcium in memory, and Steve went on to become a psychiatrist and famous author and deliverer of inspiring graduation speeches. Steve/Shem's cynical, irreverent, sexy,

but ultimately hopeful novel *House of God* helps many medical students get through their training (I even had the pleasure of prescribing *House of God* to one of my own students in his darkest days of working in Bellevue Hospital). To complete the ironic arc, Steve Bergman is currently a clinical professor in medicine and psychiatry at NYU, which recently celebrated the 30th anniversary of *House of God*, featuring the real-life counterparts of his intern characters. With his partner Janet Surrey, Steve wrote a prize-winning play about the founders of Alcoholics Anonymous, Bill W. and Doctor Bob, that galvanizes community groups fighting alcoholism. Steve has just come out with a sequel to *House of God*, entitled *Man's 4th Best Hospital*. No longer denounced by the medical establishment, a chapter from *Man's 4th Best Hospital* was published verbatim in *Journal of the American Medical Association*. The novel contains a female character, Rosie Tsien, modeled after me, and a fictional discovery based on our shared interest in calcium and memory and my current work. Novelists struggle even harder than researchers to get published and read, but they have special powers. I love Steve's fictionalized stories about raising his adopted Chinese daughter, called Spring in the novel, which resonate with my personal experience; I am thrilled that Spring and Rosie get to interact. But foremost in my mind, beyond my surprising inclusion in someone else's fiction, is something that Bergman has long since forgotten: his kindness to me after my first biological seminar, on using Eyring's rate theory ideas to think about the energetics of channel opening and closing (Tsien and Noble, 1969). This was a full-blown departmental seminar by a mere doctoral candidate, another occasion in which Denis Noble blithely allowed me a risky opportunity, a chance to fail in presenting my upstart ideas. What I remember about the talk were the rookie mistakes I made in fielding the questions and how afterward Steve, in full future-psychiatrist mode, reminded me of the upside. It is part of Denis Noble's legacy that he shaped Steve's and my careers so profoundly, without appearing to think hard about it. Because my memory of that seminar, and Denis's and Steve's roles, has been retrieved, considered, regretted, and put away again for five decades, it may be in my top 10 to hang on to when Alzheimer's sets in.

Julian Jack as a Special Mentor

Julian Jack was my other scientific parent-slash-older brother during these formative years. A New Zealand Rhodes scholar, Julian was a fellow of University College Oxford and had a lab in the Physiology Department, working on spinal cord neurophysiology. Neurotree traces Julian's lineage back through Archie McIntyre to Sir John Eccles; thus, through Julian, I am in Eccles' line and a distant cousin of Roger Nicoll, who is proud to have worked directly with Eccles. As junior faculty, Julian and Denis respected each other and were both known for their youthful brilliance in

a conservative Department of Physiology, headed by G. L. Brown and later David Whitteridge. In the late 1960s, long before they ascended to central positions in Britain as fellows of the Royal Society and leaders of the Save British Science movement (Noble) and of the Wellcome Trust (Jack), Denis and Julian could still regard themselves as outsiders.

This was only partly true in Denis's case, because he was well known and respected by the British establishment through his UCL and Hodgkin–Huxley connections. As a New Zealander, Julian was one step further removed, and by nature, took a critical view of orthodoxy. His tutorials with me were about vision and presented a balanced picture of what Hubel and Wiesel had and had not done. Although I was ostensibly a researcher in cardiac physiology, Julian took the time to expose me to systems neuroscience and its underlying connections to cellular biophysics. With his New Zealand education, medical degree, and Scottish genes, Julian could be disapproving of people taking shortcuts in life. He once made me back up a glib but correct statement with a full-on blackboard derivation invoking the superposition principle. He frowned upon Steve Bergman's hiring another person, an MIT grad, to do computer programming for his thesis. Julian was tough on people whose work appeared superficial—sometimes he may have thought that about some of my research with Denis. Like a stern brother, he didn't use much overt praise—"able" was the best rating that he ever gave me directly—but like Mrs. Helena Jones, he knew that this form of tough love was both effective and appreciated. Thanks to Julian Jack's encouragement and recommendation, I was elected a junior fellow two years before finishing my doctoral work, enabling me to dine and interact with the faculty in his college, University College Oxford (Univ). Not only did I have a chance to chat with distinguished scholars like John Albery, H. L. A. Hart, and George Cawkwell, but also I caught up with some of the worldly knowledge and scholarly breadth that I had missed by going to MIT rather than Harvard.

University College housed many social groups humming along intensely without much interaction. While dining with the dons, I also hung out with expat Americans in the same college. For example, the Rhodes scholar class of 1968 stands out in my mind because they were more galvanized with anti-war fervor than those that came before them. Each class that came along was more and more militant. University College was home to Bill Clinton, Robert Reich, and John Isaacson. I remember meeting them at a mixer in Univ, upon my transfer from Wadham and their arrival to Oxford. Bill Clinton wore a war surplus jacket and was a friendly, confident, an attentive listener. I was dismayed when Bob Reich disparaged my Rhodes career path as that of a "technocrat," not realizing that his picking an argument with me was a surefire way of starting up a conversation, a form of intellectual engagement. Clinton, Reich, and I would wind up at Yale at the same time, and Reich and I would live in the same house for two years. In the fall of

1968, the Vietnam War was on everyone's minds. No one knew what anyone was going to do.

All of these vivid Oxford experiences in University College would not have transpired without Julian Jack's intervention. Julian's Wikipedia entry cites his celebrated doctoral students, Michael Hausser and Dimitri Kullmann (who, like Jack, are both members of the Royal Society), but has no mention of his lifelong partnership with Steven J. Redman, an electrical engineer turned electrophysiologist who spent years with Jack in Oxford (Jack et al., 1971; Jack and Redman, 1971a, 1971b). This was a match made in heaven, a pleasure to watch. Steve Redman was like another older brother to me, both kind and stern all at once. It gives me great joy to have spent time studying synaptic transmission and dendritic properties, a field that they helped pioneer along with Wilfrid Rall (Rall et al., 1992).

Jack and Noble Provide Perspective on the British Physiological Establishment

As young faculty, Denis Noble and Julian Jack organized an unconventional seminar series that met on Saturday mornings and gathered Britain's best and brightest. Oxford was central enough to access from other centers of physiology and biophysics. We heard talks by Horace Barlow, Colin Blakemore, William Rushton, Fergus Campbell, Ainsley Iggo, Jack Diamond, Richard Adrian, Richard Keynes, and Roger Thomas, to name a few, without concern about any conceptual separation of biophysics, physiology, and neuroscience. As a student of both Noble and Jack, with a natural inclination to ask questions encouraged at MIT, I had many chances to interact with the British scientific establishment. The Saturday seminars and regular meetings of the Physiological Society gave me opportunities for one-to-one interactions with Alan Hodgkin, Andrew Huxley, and Bernard Katz and thus a personal bridge to British physiology at its best. I can illustrate this with interactions with Peter Baker, the scientist who took squid giant axons, extruded the axoplasm from them like toothpaste and showed reconstitution of excitability upon refilling with artificial solution (Baker et al., 1961). We met in Aberdeen Scotland at a Physiological Society meeting, my first presentation of an abstract. Baker was working with Hodgkin and Mordecai Blaustein on the sodium pump. Parched for biophysically minded colleagues at the small, remote meeting, he drew the figures of their nascent paper on index cards—lots of saturating functions showing how flux varied with ion concentration. This interaction led to a memorable day when he kindly came from Cambridge to Oxford to pick me up before continuing down to Plymouth in England's southwest corner, an all-day drive. I don't remember what we chatted about along the way, but I appreciated that I was receiving special treatment from a member of the Cambridge establishment. Baker had so much pent-up desire to experiment that he began dissecting an axon

almost immediately upon arrival at the Marine Station. Even more myopic than me, Baker's nose was practically pushed up against the specimen. That evening, I was to meet someone who became a lifelong friend, Larry Cohen.

It was Andrew Huxley, not Alan Hodgkin, who had been Noble's role model at UCL. He was the most feared of the British physiological elite. Forewarned by Denis about his long silences, I found him to be much more approachable than reputed. He actually liked being asked direct questions, especially if they were intellectually challenging. He clearly appreciated the attention conferred by his Nobel Prize, but felt that his scientific big brother Hodgkin had overshadowed him in the field of excitability, and he made no bones about wanting to win a prize on his own. I once asked Huxley a question about the position-dependence of cross-bridge attachment, drawing a natural analogy to the voltage-dependence of channel opening in excitable membranes. Decades later, his colleague Robert Simmons reminded me of this question, and let me know how much it annoyed him, perhaps thinking protectively that Huxley would find it awkward. I also remembered the question, but recollect that Huxley answered it with delight, as if someone out there were curious about a recurrent theme in his scientific life.

As a German refugee, Bernard Katz was one of a highly distinguished group of European scientists who had found their way to the United Kingdom and had seemingly been well taken care of. I have written elsewhere about Katz's seminal discoveries and the tortuous history of calcium channel discovery (Tsien and Barrett, 2004). Around 1990, I met Katz in his office in UCL after my lab had started work on calcium channels, neurotransmission and long-term potentiation (LTP). I remember him as very curious, thoughtful, precise, and modest. Here, I'll simply mention that his compact primer on cellular physiology, the renowned *Nerve, Muscle and Synapse* (Katz, 1967), was a big early influence, and a paperback copy was my early gift to my future wife Julia Shiang when she came to Oxford to study biochemistry for a junior year abroad. Julia means the world to me—I have many stories about our 51 years together that I'll save for a family document in which space is not limiting. For now, suffice it to say that giving Katz's book to Julia was the highest token of courtship. I would like to acknowledge Katz and his friendly competitor and admirer, Chuck Stevens, for motivation to work on mechanisms of transmitter release, vesicle fusion, and postsynaptic responses.

Most neuroscientists tend to focus on the most famous contribution of individual researchers, sometimes forgetting other contributions cast in the shade of the biggest discovery. In the late 1960s, in the wake of Hodgkin and Huxley's 1963 trip to Stockholm, and before Katz's 1970 prize, each of the three had turned their attention to downstream consequences of excitability, what would now be called excitation-response coupling. Hodgkin worked on muscle activation, including the surface action potential and radial spread of depolarization (Adrian et al., 1969, 1970a, 1970b), as mentioned earlier.

Huxley made significant contributions to understanding muscle activation (Huxley and Taylor, 1958) but then went on to muscle contraction itself (Huxley and Simmons, 1971). Katz had already switched to synaptic transmission as studied at the neuromuscular junction and later, the squid giant synapse (Katz and Miledi, 1971). Looking back on this, there may have been some attempt to give Bernard Katz a shot at his own place in the sun. Rodolfo Llinás once told me that Eccles asked him to wait a season before starting experiments that would compete with Katz and Miledi's work on the squid giant synapse (although famously fierce and independent, Llinás graciously complied).

An Early Opportunity to Teach Physiology

During my fourth and last year in Oxford, Denis Noble took a sabbatical in Edmonton, Alberta, where Keir Pearson and Dick Stein had gone as faculty members. This gave me the opportunity of taking over Noble's teaching, even though I hadn't yet completed my doctorate. I gave his cardiac lectures and took over some of his tutorials, another opportunity for which I owe Denis. The tutorial system put me in one-on-one contact with students who were bright but not necessarily very motivated, so I could in some cases play the role of my high school math teacher Helena Jones. Happily, all three students that I tutored got a "first," the top grade. When it came time to present my dissertation, I received permission to bind four of our papers together with an introduction. Defending the thesis took place after lunch with my examiners, Humphrey Rang and Richard Adrian, arranged by my substitute doctoral advisor, a feistily charming Scottish don named Jean Bannister in her home base, Somerville College. At lunch, Julian Jack plied the examiners and me with multiple bottles of wine to get everyone loose. The exam, in a hot closet-size space, was much less memorable, but I recall Richard Adrian pointing out in good humor that it wasn't clear who was examining whom. As Alan Hodgkin's colleague, his cheerfulness was an extension of Hodgkin's earlier kindness, supplemented by Adrian's natural flair for mentoring.

Richard Adrian as a Beneficial Influence on Two Brothers

Later, Adrian would become Roger Tsien's supervisor at Churchill College Cambridge (Tsien, 2010). Roger managed to steer safely clear of me (and Louis Tsien, our middle brother)—Harvard, not MIT; Marshall, not Rhodes; Cambridge, not Oxford. But his own doctoral trajectory would put him into the orbit of the very same Cambridge scientists that I had known: Adrian, Hodgkin, and Richard Keynes, who took him on at Cambridge, seemingly without hesitation. Determined to make his chemical prowess pay off physiologically, Roger worked at first on synthesizing pharmacologically active derivatives of tetrodotoxin (Tsien et al., 1975). Later, joining forces with Timothy J. Rink on nonexcitable cells proved to be one of Roger's break-

through career moves (Rink et al., 2016; Tsien, 2010). Just as Roger's journey connected classic British neurophysiology with modern fluorescent indicators (Zhang et al., 2002), my own career has linked the same small band of scientists to modern optogenetics, through my former graduate students Karl Deisseroth and Edward Boyden, and a former course student, Feng Zhang (Boyden et al., 2005; Zhang et al., 2006).

Joining the Yale Faculty

I went straight from Oxford to an assistant professorship at Yale in 1970, in the middle of the Vietnam War. Skipping the postdoc stage was not the most conservative strategy, but I did it partly to avoid the military draft. As a 25-year-old, I was approaching the end of my educational deferment (age 26). My new physiology chair, a renowned kidney physiologist named Gerhard Giebisch, had offered the job to Harald Reuter, but Harald had an offer in Europe, turned down the Yale position, and graciously recommended me for the job. I first met Reuter at a memorable Gordon Conference, where I presented our work on cardiac repolarization (more about Reuter later). Here is direct quote from a letter I wrote to my parents at the time (March 23, 1969):

> A flurry of scientific visitors arrived. A man named Reuter, who I'd met in N.H., and a Japanese called Tomita—both very capable and pleasant. Denis, Otto and I entertained them for two days of very hectic conversation, and a Chinese meal. Then, two days of Physiological Society meeting in London, and more talks. . . . Reuter, in fact, was almost to [the] point of accepting the job at Yale this summer, but changed his mind when offered a professorship in Bern, Switzerland. The environment at Yale was better, he thought, but he was concerned that his children should become utterly Americanized—there were already signs of this after a year at the Mayo Clinic. And so, he wrote to the head of the department at Yale and suggested that they ask me! It's nice to have scientific friends, especially when they are as honest and straightforward as this man is. We are also in [the] peculiar position of being able to appreciate each other's work.

Knowing that during my post–Gordon Conference tour I had looked at good places, including Penn and UCLA, Giebisch sent me a telegram offering me the job at Yale, sight unseen, urging me to fly over to visit to seal the deal. Lest this seem a precipitous gamble on their part, the slot was for the time-sensitive replacement of a retiring professor and the startup package was $15,000. Upon visiting, I instinctively trusted Gerhard Giebisch and I had already met and liked Knox Chandler, one of Hodgkin's colleagues at Cambridge, and Larry Cohen, who had put me up at Plymouth Marine Station after my long drive with Peter Baker. Thus, I accepted Gerhard's

offer on the spot, without any negotiating or even seeing the lab space. This seems incredibly naïve in retrospect, but like other quick decisions in my life, it happened to turn out well, after a few scary bumps. I would remain on the faculty at Yale for 18 years. During that time, I made a transition from cardiac electrophysiology to working on neurons and studying neuronal ion channels. This wasn't nearly as drastic as it sounds because channel modulation and calcium signaling remained universal themes throughout.

Because I am leveraging my limited personal experience to sketch out the scientific scene in 1970, let me spell out how close-knit these admittedly privileged institutions were. Chandler had worked directly with Hodgkin (Adrian et al., 1969); Cohen under Richard Keynes (Cohen et al., 1968); A. R. (Bob) Martin at Yale had been a postdoc in Bernard Katz's lab in University College (Boyd and Martin, 1956); and Gerhard Giebisch had performed early voltage clamp recordings of putative calcium currents in Bern with Silvio Weidmann (Giebisch and Weidmann, 1971), Hodgkin's main cardiac disciple, a pioneer in his own right, and a caring scientific uncle to me. Giebisch's predecessor at Yale, Carlton C. Hunt, had published classic papers with Kuffler (Kuffler and Hunt, 1952). Denis Noble was a disciple of Huxley, and so forth. Neurotree depicts scientific lineages, but historians of science might well consider departmental groupings like those in Cambridge, Oxford, Bern, and Yale, and biological kinship as well. Richard Adrian studied with Hodgkin, but his biological father, Nobel laureate E. D. Adrian, who had shown that biological systems can encode natural stimuli in trains of impulses, was Hodgkin's mentor. Richard Keynes's middle name, Darwin, acknowledges his great-grandfather Charles. British physiology in the late 1960s was a veritable scientific greenhouse, producing seedlings not only for England but also for export to the United States and Germany.

Ferment at Yale in Early 1970s

Although I abandoned any thought of a career juggling science and politics, life as a junior faculty member Yale had its real-world, political aspects. My acquaintance with H. L. A. Hart morphed into encounters with Guido Calabresi, a legal scholar at Yale on a Rhodes selection committee. As a precocious faculty member, I naturally gravitated to peers who were students in professional schools. Whereas I had already decided what I wanted to do—to study neuromodulation and signaling—they weren't so sure about their goals. Steven Bergman and our mutual friend William Clark went to medical school at Harvard and later lived the uncertain life of the *House of God*. Our legally or politically minded Oxford acquaintances mostly wound up at Yale (or Harvard) law school, or so it seemed. Several people I saw most often, David Kendall, Bill Clinton, and Curt Hessler, were all Yale law students. I lived in a house with Robert Reich and another charismatic law student named Nancy Bekavec, who later became head of Scripps College.

Our other housemate, Maura Smolover, designed beautiful sets in the drama school, and we made dinners together in a house in downtown New Haven in one of several sketchy neighborhoods where I lived, later with Julia. Although I could have retreated to a purely monkish existence in the lab, I was stimulated and distracted by the tumultuous atmosphere in New Haven, a community imbued with antiwar sentiment and featuring already emerging stars like Hillary Clinton, Meryl Streep, and Christopher Walken. At a personal level, Yale was a continuation of Oxford except that I now had a real job and had to prove that I could do research on my own.

Not Good at Starting a Lab

Then reality set in. I felt very welcomed by the Yale Physiology Department, but the available space was a large room in the basement that lacked windows: no natural light whatsoever. We painted the walls blue. Lacking postdoc experience or any serious mental preparation, I was pretty bad at beginning my own lab. To begin with, I wasn't so good at the biology, having missed out on medical school and a real graduate school; I made many rookie mistakes. It took many trips to a slaughterhouse miles outside of New Haven before I got healthy Purkinje fiber recordings. A new doctoral student, Wayne Giles, barely two years younger than me, had worked with Susan Noble in Oxford for a master's degree and had a much better idea of how to get the lab going. Unfortunately, Wayne felt isolated in New Haven (which he perceived as too much like New York City!) and missed his Canadian sweetheart. He went home during one winter break without letting me know he was leaving the lab. This was devastating to me. Wayne came back later from Canada to defend his thesis and went on to become a distinguished endowed professor and dean in Canada.

What saved me then was that I was good at recognizing talent, teaching what I did know, and picking juicy basic problems that had some degree of clinical significance. I took on Robert S. (Rocky) Kass as a postdoc and W. Jonathan Lederer as an MD-PhD student, both only a year younger than me. We and our spouses got along well socially. Rocky and Jon later went on to positions of scientific prominence and leadership at Columbia and University of Maryland, building in innovative ways on the basis of their early interests in our group at Yale. It was a good thing for all of us that they seemed unconcerned about the career risk of joining such a young lab.

Adler: You actually stayed in cardiac physiology for quite a while.
RWT: The problems that we were working on were so fascinating that I couldn't resist the idea of staying there. (Adler, 2015)

It made sense to study ion channel modulation in heart cells. Personal experience tells us that the rhythm and strength of our heartbeat come under

powerful control by our brain. My work with Noble in Oxford had vividly demonstrated that adrenaline, a cardiac accelerator, modified the voltage-dependence of a voltage-gated channel by shifting the midpoint of its activation curve toward more depolarized potentials (Hauswirth et al., 1968). Harald Reuter had shown that inward plateau currents, putatively carried by calcium ions, were augmented by adrenaline (Reuter, 1967). I was keen to delve more deeply into the mechanisms of these observations in my own lab at Yale. Did adrenaline (also known as epinephrine) modify the electrical field felt by the voltage sensor of the pacemaker current (Tsien, 1974b) or did the neuromodulator act through a second messenger system involving a newly discovered intracellular messenger, cyclic AMP? I tried to answer these questions with experiments in Purkinje fibers, my only solo experimental papers (Tsien, 1973, 1974a, 1974b). Phosphodiesterase inhibitors that lacked net charge evoked the same voltage shift and occluded the effect of adrenaline, arguing against an electrostatic mechanism and in favor of a scenario involving cAMP (Tsien, 1974b).

I had stimulating conversations with Paul Greengard, who assigned his technician Michael Schorderet the task of assaying cAMP in Purkinje fibers. Though the assays were never successful, Paul passed on a career-long fascination with the power of phosphorylation. Together, we published a paper in *Nature New Biology* on the role of cAMP in adrenergic modulation (Tsien et al., 1972). Not entirely trustful of experiments using butyryl derivatives of cAMP, my further contribution was to test directly the impact of cAMP elevation, by introducing it via iontophoresis from an intracellular microelectrode (Tsien, 1973). Later, I teamed up with Robert Weingart in Bern to show that radiolabeled cAMP readily diffused from cell to cell within bundles of cardiac muscle cells, thus acting as an intercellular messenger (Tsien and Weingart, 1974, 1976). We observed an increase in the strength of contractions as well. Our experiments on cAMP prompted Harald Reuter to show that dibutyryl cAMP augmented putative calcium currents. He generously offered us co-authorship of his 1974 paper (Reuter, 1974), but we declined, having not contributed directly to the experiments, only to their framing. Looking back on this early era, I am pleased to see my choice of an intriguing problem and implementation of direct approaches but cognizant of how uptight I was about questions of authorship. But this reflected the purist spirit of the British labs I most admired.

Controversy about Calcium Currents

Among neuroscientists, my lab is strongly associated with calcium channels, but at the time of arriving at Yale, this was not a major focus. Toward the end of my job seminar at Yale, which described how cardiac action potentials repolarize (the area broken open by experiment #78-1, written up in the Lake District vacation with Noble), Gerhard Giebisch gently pointed out

that my talk had focused exclusively on the roles of potassium currents, with nary a mention of calcium currents that he had worked on with Silvio Weidmann (Giebisch and Weidmann, 1971).

At the time, the very existence of calcium currents was controversial. Ted Johnson and Mel Lieberman were excoriating researchers using existing methods to attempt to distinguish fast sodium currents from kinetically slower currents assigned to calcium influx (Johnson and Lieberman, 1971). Reminding us that the squid axon managed perfectly well to spike with only sodium and potassium channels, Johnson and Lieberman argued that calcium currents were artifacts of poor voltage control. Harald Reuter came under particularly heavy fire, stirring my sense of loyalty to Reuter and Noble-like zest for debate. Through the late 1970s, my group worked earnestly on various multicellular preparations to improve the ability to isolate sodium and calcium currents. We adapted the three-microelectrode method of Adrian, Chandler, and Hodgkin to measure axial voltage drops as measures of inward membrane current (Kass et al., 1979). Sensitized to the problems inherent to heart cell bundles with narrow extracellular spaces, we developed rabbit Purkinje fibers as a system for studying fast sodium currents (Colatsky and Tsien, 1979). Using this preparation, a study on the mechanisms of a local anesthetic block of sodium channels by Bruce Bean and Charles Cohen (Bean et al., 1983) has been heavily cited and helped launch two outstanding careers in academia and industry.

The criticisms fired off by Johnson and Lieberman were neither diplomatic nor completely wrong. Indeed, problems of ion accumulation and depletion blemished some of the work Noble and I had done in Oxford (Noble and Tsien, 1968), to my later chagrin. In contrast, despite relatively primitive methods, the studies at Oxford and Yale were successful enough to identify many of the cardiac ionic current components that are featured in textbooks today, even though our original observations are often not cited (Hauswirth et al., 1969; Noble and Tsien, 1969a, 1969b; Siegelbaum and Tsien, 1980). I gleaned valuable life lessons: don't expect to get credit for work unless it is more than 90% correct, pick a simple memorable terminology, and be grateful for a little bit of luck. Slack we were not cut for cardiac currents came back with dividends for neuronal channels once our lab became better known.

Advent of Single-Cell and Cell-Attached Patch Clamp Methods

Much of the painstaking work with microelectrodes was swept away by the advent of dissociated cells, single-cell methods, and single-channel recordings. Suction pipette methods of Kostyuk's group were quickly followed and overshadowed by Erwin Neher and Bert Sakmann's Nobel Prize–winning patch clamp method (Hamill et al., 1981). I remember walking along Frontage Road behind Yale Medical School when Erwin told me of

his findings on single acetylcholine receptor channel recordings with Joe Henry Steinbach in Chuck Stevens's lab (Neher and Steinbach, 1978). Even before the gigaseal–patch clamp revolution, Kai Lee brought to us methods for dissociating heart cells and recording from them with suction pipette from A. M. "Buzz" Brown's lab at Galveston. We used these recordings to show that calcium channels can support outward currents, thus defining their extreme selectivity for calcium over monovalent ions (Lee and Tsien, 1982). We also showed that all of Albrecht Fleckenstein's "calcium antagonists" acted in a use-dependent manner (Lee and Tsien, 1983), not unlike local anesthetics acting on sodium channels. Soon thereafter, Harald Reuter invited me to come to Bern to work with him, Chuck Stevens, and Gary Yellen in trying to record calcium channels in tissue-cultured cells.

I am quite nostalgic about these experiments with Harald, Chuck, and Gary, both for the thrill of seeing single L-type channels opening and closing and for the human interactions. We worked as a team—some days, Chuck would make and fill pipettes with isotonic $BaCl_2$ and gingerly hand them off to whichever of us was at the rig. One day, while Chuck and Harald were away, Gary Yellen and I had our best experiment on channel inactivation, good enough to dominate a whole figure of our later *Nature* paper (Reuter et al., 1982), and we followed it up by celebrating his 21st birthday with my wife Julia. Chuck, his wife Jane, and daughter Megan invited us all over for Thanksgiving, making considerable effort to get traditional fixings even in Switzerland, and Chuck entertained our one-and-a-half-year-old daughter Sarah by jingling and exchanging his car keys. A father of three daughters, Chuck never seemed to tire of handing off the keys, nor did Sarah.

Calcium Channel Selectivity and Permeation

Peter Hess capitalized on the advent of gigaseals and our experience with Ca2+ electrodes by putting the Ca2+ sensitive resin in a patch pipette and accessing intracellular Ca2+ levels. I thought this would be a natural project for Peter to follow up, given his background in intracellular Ca2+ regulation, but he got very angry at me and fiercely expressed his desire to be at the heart of the action on single-channel studies. We informed Erwin Neher of Peter's promising lead on intracellular ion measurements but never followed it up; Peter got his wish and the rest is history (Hess et al., 1984; Hess and Tsien, 1984; Nilius et al., 1985).

Everyone who met Peter Hess would attest that he was a brilliant and strong-minded scientist. After attaining the rank of full professor at Harvard, he died of glioblastoma in his early 40s. As a postdoc in our lab, he tackled the question of how calcium channels can be extremely selective for calcium ions, yet support a rapid rate of ion transfer. Other groups, having observed a saturating relationship between external Ca2+ concentration and channel flux with half-maximal flux in the ~10 mM range, conceptualized

permeation in terms of divalent cation interactions with a low affinity binding site (Hagiwara and Byerly, 1981; Kostyuk, 1981). Millimolar Ca2+ also reduced the flux of Ba^{2+} or Sr^{2+} ions (Vereecke and Carmeliet, 1971). We found, however, that merely micromolar Ca2+ sufficed to half-block the current supported by Na+ or Li+ ions, fitting with the channel's high selectivity. Hess and I reconciled these observations by constructing a model of the pore, whereby ions move single file, like gramicidin or K+ channels (shades of Hodgkin and Keynes). We proposed that occupancy of a high-affinity site by a single Ca2+ suffices to prevent Na+ flux, while raising Ca2+ to millimolar levels drives pore occupancy by two Ca2+ ions and high rates of Ca2+ influx (Hess and Tsien, 1984). McCleskey and Almers independently proposed a similar model (Almers and McCleskey, 1984). Their group had additional evidence that the pore was wide enough to accommodate tetramethylammonium and could exclude sieving as a mechanism of Ca2+ selectivity.

Fast forward a decade to the mid-1990s, when L-type channels had been cloned and sequenced. Jian Yang, Patrick Ellinor, Ji-Fang Zhang, and William Sather were all keenly interested in the molecular basis of Ca2+ channel selectivity and permeation, a lot of horsepower for one problem. Now we could show directly, using Ca2+ channels cloned by Numa's group, that a high-affinity site for Ca2+ binding depended on four conserved glutamate residues in homologous positions in each of the four repeats of the pore-forming $Ca_V1.2$ subunit (Ellinor et al., 1995; Yang et al., 1993). This led to a revised model in which (1) the ion permeation pathway is much wider than the diameter of Ca2+ or Na+ (both 2 Å); (2) that acidic side chains, be they glutamates or aspartates, protrude into the pore and provide a flexible complex to closely coordinate one or more Ca2+ ions when these are present; (3) selectivity arises because monovalent ions like Na+, Li, or K+ cannot leapfrog ever-present Ca2+ ion(s); and (4) rapid throughput of ions is possible because a newly incoming Ca2+ can loosen the affinity for an already present Ca2+ further along the permeation pathway (Ellinor et al., 1995; Yang et al., 1993). Others have made compelling arguments to add to an emerging consensus (Armstrong and Neyton, 1991; Dang and McCleskey, 1998; Kuo and Hess, 1993; Sather and McCleskey, 2003; Yue and Marban, 1990).

Today, a full 36 years after the 1984 proposals from Yale and UW, a trio of three-dimensional (3D) structures are now available for voltage-gated calcium channels, two for an L-type channel ($Ca_V1.1$ from skeletal muscle, characterized with 0.5 mM and 10 mM external Ca2+), and a T-type channel (a cloned $Ca_V1.3$ subunit). These cryo-EM structures all come from the amazing work of Nieng Yan and colleagues (Wu et al., 2016; Wu et al., 2015; Zhao et al., 2019). The 3D structures indicate that our ideas were basically right: the pore contains at least one Ca2+ ion even at 0.5 mM external Ca2+ and two closely spaced Ca2+ ions at 10 mM Ca, consistent with both

a high-affinity site and the possibility of multiple divalent cation occupancy. The overall permeation path shows no hint of an additional divalent cation binding site distant from the EEEE locus. The pore is relatively wide, although not quite as wide as predicted from organic cation permeation. The pore size of $Ca_V3.1$ (EEDD) is actually smaller than that of $Ca_V1.1$ (EEEE), as we predicted based on organic cation permeation (Cataldi et al., 2002). Despite the large pore size, the Ca2+ ion(s) are largely if not entirely dehydrated. Glutamate side chains protrude into the pore lumen and help make up the high-affinity site (though these side chains were not well resolved in the first structures), thus providing the carboxylate groups to coordinate the Ca2+ ions. The four repeats show clear asymmetry, I-III being different than and dominant over II-IV (Chen et al., 1996; Chen and Tsien, 1997; Ellinor et al., 1995; Yang et al., 1993). Carbonyl oxygens from the amino acid one position past the key glutamates also contribute to Ca2+ coordination, as Sather's group has reported (Williamson and Sather, 1999). Like my group, other labs contributing to this field (Armstrong and Neyton, 1991; Dang and McCleskey, 1998; Kuo and Hess, 1993; Sather and McCleskey, 2003; Williamson and Sather, 1999; Yue and Marban, 1990) can all take heart from substantial vindication of their contributions to understanding what makes a calcium channel a calcium channel.

Modes of Channel Gating as a Basis for Modulation by Drugs and Neurotransmitters

Our lab has long been interested in state-dependent interactions between channels and modulatory agents, such as transmitters, hormones, agonists, and antagonists. A general theme not unique to calcium channels is that these agents preferentially interact with particular states of the channel and therefore act in time- and voltage-dependent manner. This is certainly true of antiarrhythmic agents, such as lidocaine for sodium channels and "calcium antagonists" for calcium channels.

Calcium channels not only undergo rapid switching between closed and open states of the channel but also display higher-order transitions between different patterns of gating, something we termed modes of gating (Hess et al., 1984). We observed striking examples of this in unitary patch clamp recordings, whereby a single channel suddenly changes its open probability from hardly open at all (low P_o) to strongly open (high P_o). A variant on nifedipine known as Bay K 8644 greatly increased the chances of the high P_o mode and thus increased calcium influx. This was both a conceptual advance in illuminating an elegant way of modulating calcium influx—channel phosphorylation by protein kinase (PKA) or Ca(2+)-calmodulin stimulated protein kinase II (CaMKII) did much the same thing. Modal gating was also a methodological gift because long channel openings in the high P_o mode also opened the way for scrutiny of detailed properties of

the open state, including the flux rate of permeant ions like Ca^{2+} and Ba^{2+} the moment-to-moment blockade by impermeant ions like cadmium (Cd^{2+}). I vividly remember arriving at a meeting, fresh from airport with luggage in tow and hearing Casey van Breemen talk about the Bay K drug, filled with excitement in anticipating what a boon it would be. Nowadays, we know that Bay K 8644 has a binding niche in the Ca_V1 channel, which is partially overlapping but distinct from blocking agents, but no one has yet determined the precise molecular basis of modal switching. One would think that, in the period of time between 1984 and today—some 30 years—that someone would have clarified this at the molecular level. But no one has. What we do know is that G protein subunits and protein phosphorylation are powerful regulators.

Transitioning from Heart to Brain via Calcium Channel Types

Did you always have in the back of your mind that you'd get to neuroscience, having fallen in love with it on the basis of your friend [Robert Macdonald]'s lobbying? Or did you just happen to find a problem you were interested in and make the shift? (Adler, 2015)

I stayed interested in the brain, and in learning and memory, throughout my career. For example, just before my doctoral submission, I wrote an essay about the importance of understanding vision and the role of molecular biology in deciphering it. Entitled "Biological Variations on Themes by Descartes," and published as part of a multi-authored tribute to Maurice Bowra, the pop piece was inspired by Descartes' diagram featured in a fascinating lecture by Colin Blakemore. The essay had both merit and flaws, but it provides an early pointer to my long-term interest in neuroscience. Although my Yale lab's work on the cell biology of excitable cells bore general relevance to brain cells, our experimental efforts on neurons would be delayed for some 15 years.

Elucidating Calcium Channel Diversity

The advent of patch clamp recordings swept away concerns about the authenticity of Ca2+ channels and lowered energy barriers for switching cell types. Martha Nowycky, who had worked on adrenergic modulation of L-type channels with Bruce Bean (Bean et al., 1984), began patch-clamping dorsal root ganglion neurons with Aaron Fox. Martha came from the Neuroanatomy Department at Yale and had a broader neurobiological perspective than the rest of us. Before joining my lab to work on vertebrate cells, Aaron Fox had been mentored by Sally Krasne and Susumu Hagiwara and had studied calcium channels in invertebrate eggs. Ed McCleskey, already mentioned, had worked on the biophysics of calcium channels in skeletal muscle with Wolfhard Almers. We started off expecting that these

sensory neurons wouldn't be that much different than the heart cells we were studying in another corner of the lab. Our guinea pig heart cells displayed unitary currents of T- and L-type channels (Nilius et al., 1985), much as expected from Bean's own whole-cell recordings (Bean, 1985) and earlier reports from other cell types from Hagiwara, Lux, Carbone, and Armstrong (Armstrong and Matteson, 1985; Carbone and Lux, 1984; Hagiwara et al., 1975; Matteson and Armstrong, 1986). The voltage dependence of T-type channels had been anticipated by Llinás (Llinás and Yarom, 1981) and made them easy to pick out. But Martha noticed patterns of channel opening that couldn't be reconciled with just two distinguishable types of calcium channels. The hardest part was to separate what would later prove to be L-type (Ca_v1) and N-type (Ca_v2) channels. Fortunately, pharmacology helped us (Nowycky et al., 1985a). We already knew of the aforementioned 1,4-dihydropyridine derivative, Bay K 8644, that dramatically increased the openness of L-type channels in the heart (Hess et al., 1984). Bay K 8644 acted selectively on the L-type channels in neurons, sparing the maverick N-type openings. Our designation "N-type" stood for *neuron*-specific and *neither* of the other two types, that is, T-type or L-type channels (Nowycky et al., 1985b). What made this discovery interesting is the fact that we found a type of calcium channel that seemed to be neuron specific (Tsien et al., 1987), raising the possibility that it might play some kind of special role.

Marine Conesnails and Neurotransmitter Release

Then, almost like a *deus ex machina*, a newly discovered form of toxin, omega-conotoxin GVIA, came on the scene thanks to pioneering work of Baldomero ("Toto") Olivera and Doju Yoshikami. Back then, the toxin wasn't known as "GVIA" but simply as omega-conotoxin. Toto and Doj joined us in collaboration led by Ed McCleskey, Aaron Fox, and Dan Feldman, showing that the toxin blocked the N-type channel (McCleskey et al., 1987). In so doing, GVIA blocked transmitter release from sympathetic neurons, which we showed in further collaboration with Richard Miller's group (Hirning et al., 1988). Our lab was fortunate in many respects, particularly in having a small but excellent group of scientists, all willing to follow the gradient of the most interesting biology. Our collaborations with other labs were quickly set up, neatly combined everyone's expertise, and led to brief papers with a straightforward conclusion. As a result, between 1985 and 1989, we not only were able to describe a new type of calcium channel but also to show its role in transmitter release. And just as the discovery of N-type channels led to our interest in synaptic transmission, synaptic transmission led us to synaptic plasticity and an interest in learning and memory. So, within the space of five years, we had gone from being a cardiac electrophysiology lab to a lab that was working on LTP.

Robert Malinow, Daniel Madison, and I began studying LTP while we were still at Yale, and carried on full force after changing institutions together in 1988 (Malinow et al., 1988; Malinow et al., 1989). Our interest was in the involvement of protein kinases in the synaptic strengthening, and for one paper, we teamed up with Howard Schulman. Our work anticipated future studies of how calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) each contribute to induction and maintenance of LTP. Synaptic plasticity is an ongoing area of activity in our lab that I will review elsewhere.

Another memorable set of Yale-based interactions took place in 1987, at a membrane course at the Institute of Physiology in Shanghai, headed by the famous Chinese neuroscientist T. P. Feng (Tsien, 2007). Feng had made fundamental contributions to understanding activation in muscle and nerve and was a fascinating link between A. V. Hill's lab in the United Kingdom and China. My scientific grandfather Otto Hutter was the convener of the course, and Peter Hess, Diane Lipscombe, Bernd Nilius, Fred Sigworth, Li-Yen Mae Huang, Victor Pantani, and I were the instructors. To help establish single-cell and single-channel recording methods in China, we brought the patch clamp amplifiers and computers for data acquisition with us, and then donated the computers. As someone born in China, it was satisfying to have contributed to the upswing of biophysics and neuroscience in the home of my ancestors (Tsien, 2007).

Amazing Mentors at Yale

Rick Aldrich and David Clapham have given informal interviews about the atmosphere at Yale and the membrane biophysics that was done there. For example, Fred Sigworth pioneered both early analysis of electrical single-channel recordings and modern-day structural analysis of single-channel particles visualized by cryo-electron microscopy (cryo-EM). For my part, I would like to express my appreciation for four exceptional neuroscientists who I looked up to and learned from.

Knox Chandler, one of the brightest scientists I have ever met, was as quick with a biting quip as he was thorough and slow in writing up papers. His amazingly careful papers with Meves actually began as a rebuttal of Ichiji Tasaki, at Alan Hodgkin's request. I greatly admired Chandler's experiments with Martin Schneider on membrane charge movements as a key step in E-C coupling (Schneider and Chandler, 1973), a partial answer to my rose garden queries of Hodgkin. Knox's personality dominated seminars and long lunches within the Physiology Department. He and his wife Caroline were generous in providing friendship, hospitality, and sage advice to me, Rocky Kass, William Gilly, and others.

Chuck Stevens was recruited from the University of Washington, Seattle, soon after I arrived at Yale. Later, he headed up a Section of Molecular

Neurobiology, where he assembled a dazzling cast of scientists, including several future National Academy Members. Chuck is a highly accomplished mentor and talent-spotter, but like Knox Chandler, Bertil Hille, Clay Armstrong, George Eisenman, and other brilliant exemplars of their generation, Chuck had an aversion to full-blown administration. This gave me pause when I had such choices to make about starting new academic entities at Stanford and NYU.

Larry Cohen was an early prototype of a tool-builder, much more fashionable now than when he began his pioneering work on voltage-sensitive dyes. He gave us an underappreciated glimpse of the ensemble recordings that pervade modern systems neuroscience, and stood up against overly simplistic views. While we were mutually supportive friends, Larry Cohen often teased me about my ethnic origins with politically incorrect, albeit affectionately delivered epithets, evocatively recounted in a whole chapter about Larry (Nicholls, 2015).

J. Murdoch Ritchie was the chair of the Pharmacology Department, a sister department to the Physiology Department that saw Gerhard Giebisch and Joseph Hoffman as chair. Murdoch had worked with R. D. Keynes and appreciated the importance of getting at the molecular underpinnings of excitability. He provided a role model of someone who was very good at experiments but willing to do administration for the benefit of others. He gave me great advice about an authorship conflict and told me not to let my review articles be boringly middle of the road.

Why It Wasn't So Hard to Leave Yale

Robert Berliner, dean of Yale Medical School and a member of the Physiology Department, always appeared dressed in a tweed jacket that smelled of the pipe he smoked. He once told me casually that the chairmanship of the Department of Physiology was preordained to go to Walter Boron as an extension of the Yale kidney dynasty. Berliner had worked on the kidney and Gerhard Giebisch (my first chair) and Emile Boulpaep (the current chair) were renal physiologists, so Walter was a logical choice. At the time, I wouldn't have been eager to serve as chair of such a top-heavy department, and I respected Walter Boron, his diligence, fairness, and contributions to science. Nonetheless, Berliner's dismissal of anyone but Walter, simply on grounds of field, took me aback. Likewise, George Palade, whose name graces a prize I later won, seemed surprised and instantly dismissive of my inquiring about the future prospects of an endowed chair. The lesson was that a scientist's stock in their home institution often lags behind their market value elsewhere (creating perennial challenges for institutional leadership, something I now feel acutely).

Back then, some leading competitors of Yale seemed to hold a much higher opinion of our work. For example, Daniel Tosteson at Harvard and

Daniel Nathans at Johns Hopkins were highly respected leaders who tried with their own special charisma to recruit me to Boston and Baltimore, respectively. Julia, the alpha dog of our family, was open to Harvard but adamantly against Baltimore (its downtown had the same problems as New Haven, and she was opposed to living in the suburbs). For once, the "spousal excuse" was true, as I quickly informed Dan Nathans; within weeks, they approached my brother Roger Tsien, but he also eventually said no. In the end, I passed up three excellent opportunities to take up positions that came bundled with an investigatorship with the Howard Hughes Medical Institute (HHMI), including one linked with a retention offer at Yale. The then-dean Leon Rosenberg worked hard to keep both Chuck Stevens and me from exiting Yale, but in the end, we both left. For me, the allure of starting a new department at Stanford was too much, regardless of passing up an HHMI appointment, which was then prohibited for scientists serving as a departmental chair. I wound up interacting closely with Max Cowan, the head of HHMI, on Stanford's HHMI appointments and have since served on many HHMI bodies, including the Scientific Review Board, the Medical Advisory Board, and Janelia Farm Advisory Board.

Starting a Department from Scratch at Stanford

In 1988, I accepted a position at Stanford University to create a new entity, the Department of Molecular and Cellular Physiology (MCP). Stanford medical school's department of physiology had one remaining faculty member, a reproductive physiologist near retirement. The head of the search committee, James Spudich, a pioneer in the field of cell motility, asked me for informal input, and I gave them so much advice that they simply offered me the position. At 43, I had no real administrative experience but relished the challenge of starting a new department from the ground up.

In hindsight, our new department was probably a bit of an afterthought. Under the leadership of Nobel laureate Paul Berg, the launching of the Beckman Center was well underway, composed of Stanford's famous Department of Biochemistry on the fourth floor, a new Department of Developmental Biology, a spinoff of biochemistry, headed by Lucille Shapiro on the third floor, and an HHMI unit featuring investigators like Mark Davis and Gerald Crabtree on the second floor. Adding MCP on the ground floor allowed Stanford to fulfill teaching obligations and to link physiology and medicine, developmental biology, and molecular biology. Although "physiology" implied old-school organ studies, inserting "molecular and cellular" as a prefix seemed to capture something fresh. Thus, Stanford was ready to gamble the grand sum of $3 million to bankroll the new department. Fortunately, the New York–based Mathers Charitable Foundation provided start-up funds, beginning a close relationship that continues to this day. Max Cowan of HHMI had agreed to support two faculty members directly,

and another HHMI position would become available through collaboration with the Stanford's Department of Medicine. Spudich and Eric Shooter, then chair of the Department of Neurobiology would join with Libby Kirk-Fulton, an administrative power in biochemistry, to save the naive chairperson from too many novice mistakes.

One of Kirk-Fulton's first moves was to steer me sternly to hire an experienced business manager, Shayne Frankel, who came over from Stanford's Medical Microbiology Department. Shayne enjoyed the challenge of starting a new department in a brand-new building with an inexperienced chair. MCP was clearly the youngest sib, the runt of the litter, with none of the tradition of Shooter's Department of Neurobiology, an heir to both the excellence and somewhat insular outlook of Kuffler's famous department at Harvard. But our department benefited from the backing of then-Dean David Korn, a gruff and outwardly cynical mover and shaker, who always gave me the feeling that he had our backs as academic underdogs.

What no one really expected was that the growth of my personal interest in neuroscience, fresh resources, and influx of energetic young people would combine to make MCP a hotbed of molecular neuroscience and cell biology. Our able colleagues in the Neurobiology Department may not have been prepared for an MCP Department with so many neuroscientists in it. But that's what Daniel Madison, Thomas Schwarz, Stephen Smith, and Richard Lewis were. HHMI investigatorships supported Richard Aldrich and Richard Scheller, both already at Stanford, in adding their strengths to the nascent group. The current chairperson, Miriam Goodman, came to Stanford from Columbia University, and studies touch sensation all the way from sensory ion channels to brain signals. Neuroscience thrived in a healthy mix with studies of the physiology and cell biology of nonexcitable cells. For example, Brian Kobilka took up a junior HHMI position under the aegis of Stanford's Department of Medicine to work on adrenergic receptor signaling. James Nelson, a cell biologist and leader in studies of how epithelial polarization develops and is maintained, came from a cancer institute near Philadelphia. Richard Lewis clarified mechanisms for calcium entry and gene activation in immune cells, building on his previous work studying cochlear hair cells. Like Rick Aldrich and Miriam Goodman, all three of these scientists later served as rotating chair of MCP, combining their excellent science with institutional service. Later, we would be joined by Merritt Maduke, a channel biophysicist, and William Weis, Axel Brunger, and Christopher Garcia, all remarkable structural/cell biologists. Although MCP had neuroscience as one of its foci, everyone felt open to explorations of non-neuro areas. Perhaps I am forgetting, but there weren't the kind of territorial conflicts over areas of recruitment that I had seen at Yale.

Over the years, we developed a warm sense of family and accomplished remarkable things while mentoring outstanding trainees (Karl Deisseroth,

Edward Boyden, Richard Mooney, Erin Schuman, and Timothy Ryan come to mind as representative examples). Investigators and their lab members interacted in the halls, in seminars, and at annual retreats at or near Asilomar. There was room for silly congeniality. Our lab won two Asilomar Halloween contests for best costume, one a headdress for disco partying made of discarded computer parts such as floppy disks (remember them?), another a Snow White costume that Rachel Groth coaxed me to wear while the lab came as the Seven Dwarfs (thankfully, no photographic evidence survives). Amidst the jollity, we had scientific sessions as high in quality as any symposium at the Society for Neuroscience (SfN) or the American Society of Cell Biology (ASCB).

Return on Investment

I look back with satisfaction on accolades MCP garnered after I left in 2011. Currently, three of the faculty members in this little department are Nobel Laureates. Brian Kobilka was awarded the 2012 Nobel Prize in Chemistry for determining the first structure of a G protein coupled receptor, something he had wanted to do ever since his recruitment from a Duke postdoc with co-winner Robert Lefkowitz in 1989. Thomas Südhof, honored in Stockholm for his work on synaptotagmin and calcium-triggered secretion, has spoken eloquently about how "Science happens in the interaction between people. . . . It's not an activity carried out by an isolated individual." Steven Chu brought unusual perspective as both a Nobel Prize–winning physicist and a former energy secretary and has now turned to biological problems. With these and other awards (e.g., a Lasker for Richard Scheller), MCP gave Stanford a pretty good return on its $3 million investment. Our faculty learned many lessons at Stanford: how to foster interactions, and how to help people do things they can take pride in and get credit for. I greatly appreciate the confidence that Stanford showed in allowing us to build a department from the ground up. Equally important were the individuals who supported the department, particularly Shayne Frankel, Elizabeth Lasensky, Cathy Booth, David Profitt, Elisabeth Einaudi, and other folks who led or served on our excellent staff.

Studies of Calcium Channel Diversity, Function, and Neuromodulation

By the early 1990s, our appreciation of distinctions among multiple calcium channel types had been extended by molecular cloning, thanks to Shosaku Numa at Kyoto and Terry Snutch with Norm Davidson and Henry Lester at Caltech and later at the University of British Columbia. The channel subfamily exemplified by N-type channels, now known as Ca_V2 channels, consisted of three different pore-forming subunits, encoded by three distinct

genes. A thorough and up-to-date summary can be found in a supplemental figure of a recent *Nature* paper on the 3D structure of a T-type channel (Zhao et al., 2019). We failed to isolate the N-type channel cDNA, an honor earned by Terry Snutch's group (Dubel et al., 1992); however, we succeeded with Bill Horne and Tom Schwarz in cloning the first exemplar of $Ca_V2.3$ channels (Ellinor et al., 1993). We also collaborated with Shosaku Numa's lab in studying the channels encoded by $Ca_V2.1$ (Sather et al., 1993). Just as collaboration with Olivera and Yoshikami broke new ground in pharmacological dissection of N-type Ca2+ channels ($Ca_V2.2$ in modern terminology) (McCleskey et al., 1987), partnership with Michael Adams at the University of California, Riverside, established that what we called P- and Q-type channels (both $Ca_V2.1$ gene products) were very differently inhibited by ω-AgaToxin IVA (Jun et al., 1999; Sather et al., 1993). Likewise, in a collaboration with George Miljanich and colleagues at Neurex, we showed that a peptide venom SNX-482 was a potent inhibitor of R-type ($Ca_V2.3$) channels (Newcomb et al., 1998). Thus, following the collaboration with Olivera and Yoshikami, specific toxin blockers for individual subtypes of the maverick family of calcium channels became available within little more than a decade.

Like Tomiyuki Takahashi (Takahashi and Momiyama, 1993) and Kathleen Dunlap (Luebke et al., 1993), our lab was also interested in studying the roles of the Ca_V2 channels in synaptic transmission. David Wheeler and Andy Randall showed that N-, P/Q-, and R-type channels all contribute to synaptic transmission at archetypical brain synapses (Wheeler et al., 1994) and cooperate even at the level of individual synapses (Wheeler et al., 1996). Today, the standard procedure for dissecting Ca2+ channels that support transmitter release is to use ω-conotoxin GVIA (N-type), ω-AgaToxin IVA (P/Q-type), and SNX-482 (R-type), each an agent we helped put on the map.

Interest in LTP

The early 1990s saw intense interest in LTP as a putative basis for learning and memory. Roger Nicoll has given an evocative account of the development of ideas in this era (Nicoll, 2017). Here I will stick to dry facts and be brief, saving a more detailed and data-oriented treatment for another occasion. Robert Malinow and I performed quantal analysis (Malinow and Tsien, 1990) that was subsequently replicated by other groups (Larkman et al., 1992; Stricker et al., 1996). Because we saw consistent changes in quantal amplitude, we never interpreted the results as purely presynaptic. However, one hint of genuine presynaptic involvement was potentiation of NMDAR-mediated transmission (Malgaroli et al., 1992; Tsien and Malinow, 1990), a finding also reported by others (Bashir et al., 1991). Aware of the interpretational ambiguity of quantal analysis, we

sought more direct ways of establishing a bona fide presynaptic change, switching to hippocampal cultures, and found compelling evidence for presynaptic modifications following NMDAR-mediated LTP (Malgaroli et al., 1995; Malgaroli and Tsien, 1992). This work was also later replicated and extended to show roles of PKA, nitric oxide, and cyclic GMP-dependent protein kinase (Antonov et al., 2003; Arancio et al., 1995; Wang et al., 2005). Recent work with Nicolas Chenouard traces the underlying mechanism to a redistribution of presynaptic resources through actin-dependent transport of synaptic vesicles along the axon.

Advancing Cell Biological Approaches to Neurotransmission

Debate about the locus of expression of LTP had one additional benefit: focusing attention on the cell biology of presynaptic terminals. The activity-dependent uptake of a vesicle-staining dye, FM1-43 (Betz et al., 1992; Betz et al., 1996) facilitated studies of hippocampal synapses (Murthy et al., 1997; Ryan et al., 1993). We studied quantal events at visually identified single synapses and showed that AMPA receptors were far from saturated (Liu and Tsien, 1995), in agreement with work from the Stevens lab (McAllister and Stevens, 2000). Later, we used brightly fluorescent quantum dots to track the functional status and location of single synaptic vesicles (Park et al., 2012; Zhang et al., 2007; Zhang et al., 2009). Debate about the fate of once-fused vesicles and an intriguing mechanism known as kiss-and-run goes on (Alabi and Tsien, 2013), and warrants further review of fresh data, including direct visualization of kiss-and-run events in non-neuronal systems (Eyring and Tsien, 2018; Shin et al., 2018).

Activity-Dependent Gene Expression

In the mid-1990s, two remarkable researchers in our lab, Karl Deisseroth and Haruhiko Bito, instigated studies of how neuronal activity controls transcription, later joined by other excellent members of our lab, such as Paul Mermelstein. Excitation-transcription coupling remains a topic of interest in our lab, and the great work of trainees like Damian Wheeler, Rachel Groth, Huan Ma, Samuel Cohen, Boxing Li, and Michael Tadross deserves reviews of its own. My colleagues and I have never discussed it, but I hope that they will take pleasure in the historical resonance between my rose garden talk with Alan Hodgkin about E-C coupling, and our later work together on E-T coupling and excitation-alternative splice (E-AS) coupling. It is exciting to have identified a novel mechanism for signal transmission, involving translocation of CaM complexed with γCaMKII (Ma et al., 2014) and to have shown a critical role of such translocation for behavioral memory (Cohen et al., 2018).

Willingness to Leave Stanford

To this day, I sometimes meet people like Dutch systems neuroscientist, a fan of Bill Newsome, who was incredulous that anyone would voluntarily move away from Stanford. Indeed, Stanford's high-quality faculty are remarkable as are its facilities and campus complete with horse farm, botanical garden, golf course, and shopping center. This campus harbored an architecturally distinctive house where Julia and I raised our three children. Sarah, Greg, and Alexa each took a eucalyptus-lined path to an excellent public elementary school that Bill Newsome's sons also attended and contributed to life in a high school with features of Scarborough, Livingston High, and Bronx Science rolled up into one. It was bucolically beautiful, safe, and a terrific place to raise a family. But after more than two decades at Stanford, in many ways a company town, Julia was keen to move to San Francisco. Grateful for our Stanford experience, we were also open-minded about leaving it behind.

Berkeley as an Intriguing Opportunity

I was given attractive offers at both University of California, Berkeley, and NYU to spearhead the building up of neuroscience. The recruitment at Berkeley was led by Muming Poo and Robert Tjian, two highly respected scientists with well-known leadership talents, and driven by John Ngai. As a public university with a tradition of excellence, Berkeley tapped into my altruistic side and offered my family a chance to continue its California lifestyle. I very much liked the people and spirit at Berkeley but then practicalities set in. The then-chancellor spent much of our interview dreading his very next appointment—to announce the elimination of Berkeley's baseball team. Further highlighting Berkeley's resource shortage, the then-dean offered about $13 million to strengthen neuroscience but stipulated payback of almost all of this money before any new philanthropy could be routed to Berkeley neuroscience.

NYU Offers the Chance to Join a Medical Center on the Rise

In 2011, Julia and I moved from Stanford to NYU, where I head up a new Neuroscience Institute at the NYU Langone (now NYU Grossman) School of Medicine. I also lead a distinguished department of neuroscience and physiology, formerly chaired by Rodolfo Llinás, and mentor a group of amazing faculty, both within the Institute and department and outside it. The Neuroscience Institute was launched with a $100 million gift from Fiona and Stanley Druckenmiller, two generous and farseeing philanthropists, close friends of Kenneth Langone and admirers of Robert Grossman, who have led NYU's upswing in recent years. Although the Druckenmillers aimed to support fundamental research in neuroscience, with no strings

attached, our Institute has built on their unspoken intentions and endeavored to make connections with research-oriented clinicians. For example, Gyuri Buzsáki (my most senior recruit) and I both enjoy our close collaborations with Orrin Devinsky, head of the Epilepsy Center. We work together on a U19 project with Robert Froemke and Dayu Lin, exemplars of the excellent faculty at NYU in studying oxytocin, currently in clinical trials to test its possible therapeutic benefit. We received generous funding from Paolo Fresco to work on Parkinson's. Our core faculty are often cross-appointed in clinical departments and regularly help with recruitment, retention, and mentoring.

Community and Education

I have spoken about NYU elsewhere (Haseltine, 2019) and regard it as a demanding yet fulfilling adventure worth an essay on its own. Briefly, my colleagues and I are hopeful of achieving two major goals. First, to bring molecular and cellular neuroscience and systems neuroscience closer together. Second, to strike the right balance between exclusivity and inclusion. Some leaders invoke an elitist spirit to create a tight-knit community: Kuffler's Neurobiology Department was a prime example (McMahan and Katz, 1990). In building the NYU Neuroscience Institute, my co-founder Gord Fishell and I strove for excellence but had a far more inclusive community in mind. Our seminar series, weekly progress reports and annual retreat are all open to the wider community of neuroscientists at NYU, including med school researchers not housed in our new science building as well as members of the Center for Neural Science (CNS) started by Tony Movshon at NYU's main campus at Washington Square, two miles downtown. We join with our CNS colleagues to co-administer a graduate program that draws excellent students.

Coda

I am sending off this piece on January 5, 2020, which happens to be the birthday of Julia Shiang, who remains the light of my existence, full of surprises, the joy of life, and more than a few strong opinions. The year 2020 will be the 50th anniversary of my halting attempts to start up my own lab with help from wonderfully supportive senior faculty, wise chairperson, and risk-tolerant trainees. Stories about my Chinese immigrant background, schooling, friends, and outstanding early mentors help explain the curiosity that has driven my lab and the mix of idealism and pragmatism that has fueled my department-building. Each of my institutional transitions, spaced about 20 years apart, enabled a new tack: filling a vacated position at Yale replaced organ physiology with cell biology and signaling and enabled a transition to neuroscience; reviving a moribund department

of physiology at Stanford advanced molecular neuroscience and cell biology; starting an institute at NYU now fosters closer ties between cellular and systems neuroscience. It has been my privilege to study how membrane excitation triggers diverse cellular responses such as contraction, secretion, transcription, and now alternative splicing, as presaged by the Oxford rose garden conversation so long ago. Calcium channels held our attention as both biophysical marvels and elegant signal transducers, performing more vital functions than a Swiss army knife. I am lucky to be a memory-laden link between the excitability studies of my scientific forbears and the optogenetics of some renowned scientific descendants. I thank the colleagues, trainees, and friends—many who I didn't have space to mention individually but are listed in the attached table—who worked so hard and so well to make this journey meaningful for my scientific family.

Trainee Name (where training occurred)	**Postdoc/Grad Student**	**Training Period**	**Current Position, Institution**
Wayne Giles (Yale)	Graduate student	1970–1974	Professor Emeritus, Department of Physiology and Pharmacology, Faculty of Kinesiology, University of Calgary, Canada
W. Jonathan Lederer (Yale)	MD-PhD student	1971–1975	Professor of Physiology, Director Center for Biomedical Engineering, University of Maryland School of Medicine
Robert Kass (Yale)	Postdoc	1971–1976	Professor of Pharmacology, Chairman Department of Pharmacology, Columbia University
Steven Siegelbaum (Yale)	Graduate student	1975–1978	Gerald D. Fischbach Professor of Neuroscience and Pharmacology, Chair Department of Neuroscience, Columbia University Zuckerman Institute
Robert Weingart (Yale)	Postdoc	1975–1977	Emeritus Professor, Department of Physiology, University of Bern
Thomas Colatsky (Yale)	Postdoc	1977–1979	Director, Division of Drug Safety Research at FDA
Eduardo Marban (Yale)	MD-PhD student	1976–1980	Mark Siegel Family Foundation Distinguished Professor, Executive Director, Cedars Sinai Hospital, UCLA
Lee, Kai S. (Yale)	Postdoc	1981–1982	Cardiovascular Diseases Research Unit, Upjohn Company, Kalamazoo Michigan
Charles J. Cohen (Yale)	Postdoc	1979–1982	Vice President-Biological Sciences, Xenon Pharmaceuticals

Trainee Name (where training occurred)	Postdoc/Grad Student	Training Period	Current Position, Institution
Bruce Bean (Yale)	Postdoc	1979–1983	Professor of Neurobiology, Harvard Medical School
Jeffry Lansman (Yale)	Postdoc	1983–1985	Professor Emeritus of Cellular & Molecular Pharmacology, UCSF School of Medicine
Martha Nowycky (Yale)	Postdoc	1982–1985	Professor of Pharmacology, Physiology, and Neuroscience, New Jersey Medical School at Rutgers
Edwin McCleskey (Yale)	Postdoc	1985–1987	Science Officer at Chan Zuckerberg Initiative
Bernd Nilius (Stanford)	Visiting scientist	1985	Department of Cellular and Molecular Medicine, VIB Center for Brain and Disease Research, Leuven, Belgium
Peter Hess (Yale)	Postdoc	1983–1987	Deceased, Former Professor of Cellular and Molecular Physiology at Harvard Medical School
Aaron Fox (Yale)	Postdoc	1984–1987	Professor at University of Chicago
Christopher Benham (Yale)	Postdoc	1986–1988	Head of Department of Clinical and Pharmaceutical Services, University of Hertfordshire, Hatfield, Hertfordshire
Sam Kongsamut (Yale)	Postdoc	1987–1991	Co-Founder, Vice-President Research and Development at BryoLogyx
Daniel Madison (Yale)	Postdoc	1986–1988	Associate Professor, Department of Molecular and Cellular Physiology, Stanford University
Robert Rosenberg (Yale)	Postdoc	1985–1988	Professor of Biology at Earlham College
Keith Bley (Yale)	Graduate student	1985–1988	Chief Development Officer, BioIntervene Inc
Jeffry Isaacson (Yale)	Technician/mentee	1986–1988	Professor, Department of Neurosciences, UCSD
Diane Lipscombe (Yale, Stanford)	Postdoc	1986–1990	Professor of Neuroscience, Carney Institute for Brain Science at Brown University
Roberto Malinow (Yale, Stanford)	Postdoc	1986–1990	Professor Department of Neurosciences, Center for Neural Circuits and Behavior, UCSD
Hollis Cline (Yale, Stanford)	Postdoc	1989–1990	Hahn Professor and Chair, Department of Neuroscience, Scripps Institute
Antonio Malgaroli (Stanford)	Postdoc	1989–1993	Professor of Physiology at Università Vita-Salute San Raffaele, Milan, Italy

Trainee Name (where training occurred)	Postdoc/Grad Student	Training Period	Current Position, Institution
Julie Kauer (Stanford)	Postdoc	1989–1991	Professor of Psychiatry and Behavioral Sciences, Stanford University
Anne Delcour (Stanford)	Postdoc	1990–1992	Professor of Biology and Biochemistry and Associate Dean for Graduate Studies, University of Houston
David Friel (Stanford)	Postdoc	1988–1994	Associate Professor, Department of Neurosciences, Case Western Reserve University
Felix Schweizer (Stanford)	Postdoc	1990–1994	Professor of Neurobiology, Brain Research Institute, UCLA
William Horne	Postdoc	1989–1994	Chair, Department of Small Animal Clinical Sciences and Professor of Anesthesiology, Michigan State University College of Veterinary Medicine
Patrick Ellinor (Stanford)	Graduate student	1990–1996	Director of Cardiac Arrhythmia Service at Massachusetts General Hospital, Professor of Medicine at Harvard Medical School
Jian Yang	Postdoc	1990–1993	Professor, Department of Biological Sciences, Columbia
William Sather	Postdoc	1991–1995	Associate Professor, Department of Pharmacology, University of Colorado Denver
Ji-Fang Zhang (Stanford)	Postdoc	1991–1996	Associate Professor, Farber Institute for Neuroscience, Thomas Jefferson University
Andrew Randall	Postdoc	1991–1994	Professor in Applied Neurophysiology, University of Exeter
Tsutomu Tanabe	Visiting scientist	1991–1995	Professor, Cognitive Medicine, Pharmacology and Neurobiology, Tokyo Medical and Dental University
Karl Deisseroth (Stanford)	MD-PhD student	1992–1998	Professor of Bioengineering, Psychiatry & Behavioral Sciences, Stanford University
Jeremy Bergsman (Stanford)	Graduate student	1992–2000	Practice Vice President at Gartner, San Francisco
Anatole Menon-Johansson (Stanford)	Postdoc	1993–1995	NHS Foundation Trust, Sloan and Legatum Fellow at MIT
Guosong Liu (Stanford)	Postdoc	1993–1996	Professor, School of Life Sciences and School of Medicine, Tsinghua University

Trainee Name (where training occurred)	Postdoc/Grad Student	Training Period	Current Position, Institution
Haruhiko Bito (Stanford)	Postdoc	1993–1997	Professor of Neurochemistry, University of Tokyo
David Wheeler (Stanford)	MD-PhD student	1993–1998	Medical Practice, Neurology, Epilepsy, and Clinical Neurophysiology, Wyoming Medical Center
Ilya Bezprozvanny (Stanford)	Postdoc	1994–1996	Carl J. and Hortense M. Thomsen Chair in Alzheimer's Disease Research and Professor, Department of Physiology, UT Southwestern Medical Center
Jonathan Stocker (Stanford)	Postdoc	1995–1996	Executive Director, Clinical Development at Tetherex
Min Zhuo (Stanford)	Postdoc	1995–1996	Michael Smith Chair in Neuroscience and Mental Health and Professor, Department of Physiology, University of Toronto, Canada
Xiao Hua Cheryl Chen (Stanford)	Postdoc	1995–1997	Vice President, LiLaw Incorporated
Jurgen Klingauf (Stanford)	Guest researcher	1995–1998	Professor, Center for Soft Nanoscience, WWU Munster
Ege Kavalali (Stanford)	Postdoc	1995–1998	William Stokes Chair In Experimental Therapeutics and Acting Chair, Department of Pharmacology, Vanderbilt School of Medicine
Vadim Degtyar (Stanford)	Postdoc	1996–1998	Associate Editor, Frontiers in Medical Technology (Regulatory Affairs), Academic Editor, PLoS ONE
Naibo Yang (Stanford)	Postdoc	1996–1998	Director, Immunogenetics, Complete Genomics
Paul Mermelstein (Stanford)	Postdoc	1996–2000	Professor, Department of Neuroscience, University of Minnesota
Stephen M. Smith (Stanford)	Postdoc	1996–2000	Professor of Medicine, Physiology and Pharmacology, Oregon Health and Science University
Yoon Namkoong (Stanford)	Guest researcher	1997–1998	Research Associate, McGill University
Sukwoo Choi (Stanford)	Postdoc	1997–2000	Professor, Department of Biological Sciences, Seoul National University
Gong Chen (Stanford)	Postdoc	1997–2001	Verne M. Willaman Chair and Professor, Life Sciences, Penn State University

Trainee Name (where training occurred)	Postdoc/Grad Student	Training Period	Current Position, Institution
Erika Piedras-Renteria (Stanford)	Postdoc	1997–2001	Associate Professor, Department of Cell and Molecular Physiology, Loyola University Chicago
Geoffrey Pitt (Stanford)	Postdoc	1997–2001	Adjunct Professor in the Department of Medicine, Duke University School of Medicine
Gangyi Wu (Stanford)	Postdoc	1997–2001	Research Associate Professor, Charles H. Smith Life Sciences Laboratory, Penn State University
Jason Pyle (Stanford)	MD-PhD student	1997–2004	Chief Executive Officer, BaseHealth; Venture Partner, Radicle Growth
Lindsey Glickfeld	Undergraduate	1998–2002	Assistant Professor, Department of Neurobiology, Duke Universtiy
Mauro Cataldi (Stanford)	Postdoc	1998–2000	Department of Neuroscience, University of Naples Federico II, Italy
Alex Aravanis (Stanford)	MD-PhD student (E.E.)	1999–2005	Co-Founder and Chief Scientific Officer, Head of R&D, GRAIL
Tara Thiagarajan (Stanford)	Graduate student	1999–2005	Chairman and Managing Director, Madura Microfinance
Edward Boyden (Stanford)	Graduate student	1999–2006	Y. Eva Tan Professor in Neurotechnology, Professor of Biological Engineering and Brain and Cognitive Sciences, MIT Media Lab and McGovern Institute
Jimok Kim (Stanford)	Postdoc	2004–2006	Scientific Review Oficer, National Institute of Dental and Craniofacial Research
Henry Lam (Stanford)	Graduate student	2004–2006	Director, Deutsche Bank Prime Brokerage Sales & Consulting, Hong Kong
Xue Han (Stanford)	Postdoc	2005–2006	Associate Professor, Bioengineering, Boston University
Mia Lindskog (Stanford)	Postdoc	2002–2006	Assistant Professor, Department of Neuroscience, Karolinska Institutet, Sweden
Yu-Qing Cao (Stanford)	Postdoc	2000–2006	Associate Professor of Anesthesiology, Hope Center for Neurological Disorders, Washington University, St. Louis, MO
Curtis Barrett (Stanford)	Postdoc	2001–2007	English Editing Solutions, Bunnik, Utrecht Province, Netherlands
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Trainee Name (where training occurred)	Postdoc/Grad Student	Training Period	Current Position, Institution
Damian Wheeler (Stanford)	Postdoc	2002–2008	Co-Founder and CEO at Translucence Biosystems
Y. Joyce Liao	Neurology fellow	2003–2006	Associate Professor of Opthalmology and of Neurology, Stanford Medical Center
N Charles Harata (Stanford)	Postdoc	2003–2009	Associate Professor of Molecular Physiology and Biophysics, University of Iowa
Qi Zhang (Stanford)	Postdoc	2004–2012	Research Assistant Professor, Biomedical Science, College of Medicine, Florida Atlantic University
Damon Poburko (Stanford)	Postdoc	2008–2011	Associate Professor, Biomedical Physiology and Kinesiology, Simon Fraser University
Scott Owen (Stanford)	Graduate student	2005–2012	Assistant Professor, Department of Neurosurgery, Stanford University
Rachel Groth (Stanford)	Postdoc	2006–2012	Associate Director, Biogen, Cambridge, MA
Yulong Li (Stanford)	Postdoc	2006–2012	Principal Investigator, School of Life Sciences, Peking University
Hyokeun Park (Stanford)	Postdoc	2007–2012	Assistant Professor, Department of Physics, Hong Kong University of Science and Technology
Patrick Bader (Stanford, NYULH)	Postdoc	2008–2013	Psychiatrist, Bern, Switzerland
Ananya Mitra (Stanford)	Postdoc	2008–2012	Associate Director at Alector, San Francisco
Li Li (Stanford)	Graduate student	2008–2012	Assistant Professor, Anesthesiology, Seattle Children's Hospital
Michael Tadross (Stanford)	Postdoc	2009–2012	Assistant Professor of Biomedical Engineering, Duke University
Abdul Rasheed Alabi (Stanford, NYULH)	MD-PhD student	2009–2014	Research Fellow in Medicine, Massachusetts General Hospital
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Nicolas Chenouard (NYULH)	Postdoc	2012–2017	Postdoctoral Researcher, University de Bordeaux
Boxing Li (NYULH)	Postdoc	2012–2017	Investigator, Sun Yat-Sen University
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Trainee Name (where training occurred)	Postdoc/Grad Student	Training Period	Current Position, Institution
Samuel Cohen (NYULH)	MD-PhD student	2012–2018	Resident, Stanford University
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Caitlin Mullins (NYULH)	Graduate student	2013–2019	Boston Consulting
Katie Eyring (NYULH)	Graduate student	2014–2019	Postdoctoral Fellow, UCLA, K00 Awardee
Nataniel Mandelberg (NYULH)	MD-PhD student	2015–2019 (MD/PhD)	Medical Student, NYU
Simón(e) Sun (NYULH)	Graduate student	2015–present	Graduate student, NYU
Simon Chamberland (NYULH)	Postdoc	2017–present	Postdoc, NYU
Xiaohan Wang (NYULH)	Postdoc	2018–present	Postdoc, NYU
Jingjing Liu (NYULH)	Postdoc	2019–present	Postdoc, NYU
Raquel Moya (ISG, NYULH)	Graduate student	2019–present	Graduate student, NYU
Erica Nebet (NYULH)	Undergraduate	2017–present	Undergraduate, NYU
Monica Hanani (NYULH)	Undergraduate	2019–present	Research Technician, NYU

Coda on Coda

I'm very grateful to Thomas Albright for his superb editing, and both Tom and Larry Squire for this opportunity. As I submit a near-final version, it's mid-April, partway through the 2020 spring of COVID-19. We face enormous medical, economic, and political challenges; NYC is an epicenter of the outbreak and China is a target of criticism, pertinent to this story. Perhaps recalling past decades will hearten us and remind us of useful roles we can carry out as part of society at large.

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