Dennis W. Choi

Born:

Michigan, 1953

Education:

Harvard College, Cambridge, MA, AB (1974)
Harvard Medical School (Harvard-MIT Health Sciences and Technology Program), MD (1978)
Harvard University, PhD (1978)

Appointments:

Assistant-Associate Professor of Neurology, Stanford University School of Medicine (1983–1991)
Andrew B. and Gretchen P. Jones Professor and Head of Neurology, Washington University Medical School (1991–2001)
Executive Vice President, Neuroscience, Merck Research Labs (2001–2006)
Professor of Pharmacology & Experimental Therapeutics, Boston University (2006–2007)
Professor of Neurology, Pharmacology, and Pediatrics, Emory University (2007–2012)
Director, Brain Science Institute, Korea Institute of Science and Technology (2013–2016)
Professor and Chair of Neurology, SUNY Stony Brook (2012–present)

Honors and Awards (Selected):

Wakeman Award for Neuroscience Research (1992)
Silvio O. Conte Decade of the Brain Award, National Foundation for Brain Research (1994)
Vice-President, American Neurological Association (1996–1997)
Ho-Am Prize in Medical Science, Samsung Foundation (1997)
Christopher Reeve Research Medal (1998)
President, Society for Neuroscience (1999–2000)
Santiago Grisolia Prize (2000)
Member, National Academy of Medicine (2000)
Fellow, American Association for the Advancement of Science (2005)

As a graduate student, Choi discovered the mechanism of action of benzodiazepine drugs, demonstrating potentiation of gamma-aminobutyric acid responses, a key early example of a modulatory rather than agonist or antagonist action at a neurotransmitter receptor. Later as a faculty member at Stanford and Washington University, he initiated systematic studies of insult-induced neuronal death, establishing the utility of primary neuronal cell cultures in identifying underlying mechanisms and contributing to the emergence of therapeutic neuroprotection as a field. Much of his early work focused on excitotoxicity and calcium overload; later his laboratory added study of inappropriate apoptosis and disturbances in the homeostasis of other ions, including zinc and potassium.

Dennis W. Choi

Early Life (1950s–1970s)

I had a happy, albeit in retrospect, odd childhood, notable for a disconnect between expectation and privilege, and entirely too little adult supervision. My parents were immigrants from Korea and China, fortunate in being able to come to America with a small stake that allowed my father to attend a U.S. college. They met while working for U.S. intelligence in postwar Japan as translators, a service that facilitated their immigration.

They both came from highly political families. My paternal grandfather was a young founder of the current Republic of Korea, a member of the Provisional Government in exile that formed in 1919 in Shanghai to resist Japanese colonial rule of Korea. Unfortunately, he was captured and his health broken in a Japanese prison, but he did meet my grandmother ("Florence") in Shanghai. Florence was a fiercely independent woman who learned of the existence of this organization while in high school, and later traveled alone over land to join up—dressing as a man for the hazardous journey and couriering smuggled documents for the resistance. In a formal photograph that I have of Ahn Changho and other Provisional Government officials, including my grandfather, she is one of only two women and she is seated in the front row. My maternal grandfather was a classically educated scholar who served as chief secretary in the Republic of China government under Chiang Kai-shek, prior to Mao Tse-Tung's Communist revolution. Before that, he was a provincial governor (Kweichow), a banker, and a publisher who led the *Ta Kung Pao* newspaper in Tientsin to prominence (it is the oldest active Chinese language newspaper in China today).

I was born in Michigan, and unfortunately for me, my parents made a strategic decision to speak only English at home, rendering me embarrassingly monolingual. My father, fluent in five languages, moved us to a working-class neighborhood in the Boston area while he earned a PhD in mechanical engineering at MIT and joined the faculty at Tufts University. I have early memories of being fascinated by the heavy equipment in his heat transfer laboratory and admiring the precision of his thinking. He also gave me chemistry sets as birthday presents beginning when I was in first grade, launching the Chemistry Phase of my young scientific career.

Initially my experiments consisted of mixing supplied chemicals together in various combinations to see whether anything interesting would happen (of course it never did), but a few years later, I read about the composition of explosives and acquired a mail-order catalog from a professional chemistry supply house. I first ordered a few beakers, and then, in that more innocent

time, had no difficulty ordering kilogram quantities of explosive ingredients, including finely powdered metals. By then my father had departed my life to pursue a career in global industrial consulting, and my mother ignored whatever I was doing up in my bedroom "laboratory." My best friend Dougie, from down the street, however, was thoroughly impressed, and we made an ever-larger series of aluminum foil-wrapped flares which we gleefully set off in backyards and driveways, at one point melting a good-size hole in the asphalt. We had just enough sense to not pack our explosives, so we retained fingers and internal organs for later use. The pinnacle of my Chemistry Phase came in sixth grade, when I saw an ad in the back of my favorite magazine (*Popular Mechanics*) that offered to sell instructions for making a "powerful contact explosive from household supplies" for $2 in cash. Who could resist? The resultant explosive worked but barely crackled. Reasoning that ingredient purity needed to be upgraded, I visited a local compounding pharmacy and negotiated for a bottle of crystals (handed across the counter with a raised eyebrow) in exchange for delivering some packages on my bicycle. The next batches were epic. But our unwise decision to booby-trap a light switch in Dougie's house (in his kid sister's bedroom, just a trace/crackle) sent her into tears and led to us being told by his parents that our chemistry careers were now over.

I was ready to move on anyway, having been given a last science kit from my father that focused on electric circuits. I read up on electronics, and set up a shop in my basement, stocked with parts salvaged from discarded television sets and some amazing military equipment obtained at a local junkyard at scrap metal prices. The Electricity Phase of my career coincided with a major upgrade in my schooling, courtesy of grandmother Florence. While my parents always assumed implicitly that I would become an educated man, being raised by a single mother on an office clerk's salary left the actual path forward to higher education unclear. The span of my world then was limited to the travel radius of my bicycle, and other boys in the neighborhood were aspiring to become auto mechanics, which seemed to me a pretty good line of work. Grandmother Florence had come to live with us, however, bonding with my mother. She was ever doing things: networking with the Boston Korean community, volunteering with the Red Cross, figuring out America. She would tell stories from her large past life, and assure me that I could do anything if I worked at it. When she learned somehow that a private school in Cambridge was looking to diversify its student body, she hopped a bus down and pitched my case. Next thing I knew, I was riding the same bus daily to seventh grade to the Browne & Nichols (B&N) School on a full scholarship.

B&N was good to me, exposing me to a previously unsuspected palette of ideas, horizons, and topics, including Latin and *Moby Dick*. Their charismatic head science teacher, "Doc" Walters, encouraged me with wry humor and a special science prize when I graduated. I developed plans to study

electrical engineering, applying to MIT and two other engineering schools; but I also enjoyed the humanities and had advanced placement in English, so I decided to apply additionally to Harvard and Brown. To my delight, I was accepted by both Ivies. I entered Harvard College before I turned 17, supported by enough scholarship and loans to leave the neighborhood and live in a dorm.

I started on an engineering track, taking math and physics courses and landing my first paid electrical jobs: during the school year, soldering circuit boards for a kind psychology professor, Marshall Haith; and summers, working as a studio technician at the Boston NBC affiliate, WBZ-TV. The latter unusual opportunity came my way again through the mysterious networking of grandmother Florence. I was useful to WBZ because I had obtained a federal first-class commercial radio license through self-study (only passing a written examination was required), and thus, I could be designated the official television transmitter operator when needed. The work was great fun, although I still recall vividly an error I made in the air-switcher room, rewinding an active tape and causing Rex Trailer, a children's show cowboy, to ride his horse fast backward one Saturday morning. Meanwhile, on the side, I satisfied my latent auto mechanic, buying and repairing a series of cheap cars and motorcycles for practical transportation. A hometown buddy, Chet, gifted me with a Yamaha two-cycle motorcycle whose transmission he had blown. I found only one gear unusable, and purchased a replacement from a salvage shop for $10. After patching the gear-case, the Yamaha was my noisy but dependable ride for several years.

I began to have second thoughts about majoring in electrical engineering during my college sophomore year, wondering whether I might rather study something with less definition and more conceptual breadth. A memorable course on Greek drama built around sonorous readings by "the Professor" William Alfred had me thinking sophomore thoughts about the human spirit and mind. Also, my roommate, Dan Weitekamp, had declared a biochemistry major and seemed to have interesting assignments. So I also declared a biochemistry major, choosing it over biology because the former, smaller department offered individual attention to its undergraduates, assigning to each a "tutor" charged with overseeing progress. I figured that having some extra help available might help me catch up.

This was an inspired decision. I lucked out in being assigned Barbara Talamo as my tutor, who was then a postdoc at the medical school, and would go on to found and chair the Neuroscience Department at Tufts School of Medicine. With skill and patience, she led me through some remedial readings in a biology textbook, and then had me read, chapter-by-chapter, the book *Nerve, Muscle, and Synapse* by Bernard Katz. That book, illuminated by Barbara's sharp insights, brought it together for me, tying electric circuit behavior to nervous system signal processing. I then successfully sought permission to take two graduate-level seminar courses

in neuroscience at the medical school, one on synaptic physiology, taught by Jack McMahan and Rami Rahamimoff; the other on the visual system, taught by David Hubel and Torsten Wiesel. These were the best courses I have ever taken, and I recall being awed by the faculty and trainees in the Neurobiology Department, the latter including Carla Shatz, David Van Essen, Jim Hudspeth, and Josh Sanes.

I began to plan to attend graduate school in neuroscience. However, I had not gotten far when a singular opportunity came my way. Harvard and MIT, often rivals on opposite sides of Cambridge, Massachusetts, had decided to collaborate on the launch of a medical training program, the Harvard-MIT Program in Health Sciences and Technology (HST). The program combined medical training at Harvard with an expanded exploration of related engineering topics at MIT. Since the program, with 25 MD training slots per year, was just getting going and did not yet have full national visibility, the HST director, Irving London, decided to reach out proactively to selected MIT and Harvard undergraduates to offer them positions. My engineering to biology path, likely coupled with my missionary enthusiasm for neuroscience, brought me to his attention, and I was offered a position contingent on entering directly after my college junior year and completing college concurrently the following year.

I had not seriously considered medicine as a career at that point. There were few Asian students or faculty in U.S. medical schools in those days, and my mother opined that Asian physicians would not be accepted by sizeable segments of the American public. Hopefully, her viewpoint will seem parochial to most today, but America has come a long way to overcome old biases (and still has a way to go). When my parents bought their small Boston-area house, their future neighbors held a meeting to decide whether they could accept the situation. Fortunately, the decision was yes.

Anyway, medicine felt just right to me. I saw it as the engineering side of biology, and admired its humanism. And Dr. London's offer would save me time and expense, allowing me to live as an undergraduate in a college dorm and even take a literature course during my first HST year. So, deal.

Training (1970s–1980s)

HST was grueling, with an unfashionably large number of lecture hours, yet rewarding, with unexpected insights served up regularly by a talented faculty. I recall modeling the human body as an inverse pendulum (very unstable without continuous neuromuscular adjustments) and Farish Jenkins climbing on a table to demonstrate how the arthropod gait differed from the primate gait. Walle Nauta, a founding member of the Society for Neuroscience (SfN), taught us neuroanatomy, regaling us one day about the time he saved a soldier's life in World War II by drilling a hole in the man's skull on a kitchen table and relieving an expanding hematoma.

As the first two years of medical school progressed, I wondered whether I could still gain neuroscientific training. Barbara Talamo encouraged me, and tried to get me a summer position with Steve Kuffler, the head of Harvard's Neurobiology Department, but his lab was not accepting students. She then successfully recommended me to Gerry Fischbach, who had recently come from the National Institutes of Health (NIH) to join the Pharmacology Department. I found Gerry's ideas and approaches inspiring, and decided to interrupt my medical training to study for a PhD with him. Back then, the MD-PhD program was a background administrative entity. One simply finished when one met each degree's separate requirements, often after seven or eight years of study.

My first project leveraged the chick neuronal cell culture system that Gerry and others had pioneered at NIH. I was assigned to study the chemosensitivity of dorsal root ganglion (DRG) cells to gamma-aminobutyric acid (GABA), which by the early 1970s had become recognized as a major vertebrate inhibitory neurotransmitter, specifically implicated in inhibiting sensory afferents into the spinal cord. I would record from DRG neurons with a sharp intracellular pipette, while iontophoresing GABA from a nearby extracellular pipette. The iontophoretic pipette contained 1M GABA, buffered to pH 4, so it would be charged and ejected by positive current pulses. I quickly obtained strong membrane responses and embarked on characterizing these. After several months' work and beginning to plan my thesis, I thought I should do a control experiment, iontophoresing from a pipette filled with 1M buffer at pH 4—but I got the same responses. Big lesson for me: Do control experiments early! This "acid response," seemed curious, but the possibility that local pH transients might play a central nervous system (CNS) signaling function was not yet on radar screens, and I considered it a dead end. (Retrospective lesson: Pay close attention to unexpected lab results.)

I decided to study GABA chemosensitivity instead on cultured spinal cord neurons, a richer system containing excitatory and inhibitory synapses—and no acid responses. Like most electrophysiologists, I loved listening to my preparations, especially late at night when the lab was quiet: the popping and crackling of spontaneous postsynaptic and action potentials as rendered by an audio amplifier. Private conversations among neurons in mysterious code, scaling somehow to form perceptions and thoughts. I would take reams of oscilloscope pictures using a Grass camera with its massive 35 mm film magazine, a photomachine gun.

Progress was initially slow. I found GABA iontophoresis variable, making it difficult to establish reliable baselines that I could challenge with manipulations, and access to equipment was sometimes limiting. I decided therefore to take a break from the lab and work on clinical rotations. I found that I also enjoyed seeing patients and trying to figure out their problems. Meanwhile, perhaps aided by this mental refresh, I came to a couple

of research solutions. First, I found a way to accelerate the lab's planned construction of a third electrophysiology rig, placing a Steelcase office desk on scooter inner tubes for use as an air table, and making a chart recorder out of an ancient electroencephalography (EEG) machine that I found in the department's basement equipment archives. Although this makeshift chart recorder tended to spray ink when excited, it was accurate enough, and I could use it 24/7 because no one else wanted anything to do with it. With ink, EEG paper, and a lot of Kimwipes nearby, it provided an efficient way to track slow voltage responses. No need to spend hours in the darkroom developing film. And, more important, I devised a reliable method for delivering solutions of choice to cultured neurons.

Occasionally, an iontophoretic pipette would plug up and fail to deliver drug. Gerry taught to diagnose this by breaking off the electrode tip so that its contents would leak out. I wondered whether a similar approach could be made to work in a more controlled fashion with a smaller tip, around 3 microns. Nothing came out spontaneously from such a pipette, but it looked like a squirt gun nozzle under the microscope—maybe some air pressure would help? Eric Frank was a postdoc in the lab and a generous scientific mentor to me from day one. When I discussed the situation with him, he went across the quad to the Neurobiology Department and obtained a compressed gas source complete with a mechanical switch. The results were beyond expectation—the "puffer" pipette (Gerry's term) rapidly delivered undiluted pipette contents to a recorded neuron, and then it backfilled slightly when the pressure pulse was terminated, preventing content leakage. It effectively constituted a microperfusion approach, giving Nernst equation fidelity when high potassium buffers were ejected. (Unfortunately, I did not appreciate the commercial potential of the device, or the later emergent Picospritzer apparatus—presumably the result of a parallel thought process and still on the market today—might have had some competition.)

My fellow pharmacology graduate students, including Terry Gibbs, Steve Schuetze, and Chauncey Bowers were bemused by this puffer system (Terry commented that it positioned me to spend my days cheerfully "squirting *** on cells"). One afternoon, Chauncey came by with a vial of chlordiazepoxide and suggested that I squirt it. A bit of reading informed me that this benzodiazepine, the clinically momentous invention of the Hoffman-La Roche medicinal chemist Leo Sternbach, had become the second best-selling drug in the United States (as Librium, surpassed only by its fast-follow cousin, Valium) based on useful anxiolytic actions, but its mechanism of action was still unknown. The lead theory at the time, based on the receptor binding studies of Anne Young and Sol Snyder, was that these drugs were glycine agonists. A few experiments with my puffer system was all that was needed to reveal that chlordiazepoxide did not have a direct effect on membrane voltage or conductance, but when switching back and forth to compare with

GABA, I saw that the response to submaximal GABA (but not glycine) was potentiated right after a chlordiazepoxide pulse.

Another postdoc in the lab, David Farb, joined the project to exclude an inhibitory effect on GABA uptake. Although neuropharmacological drugs at the time were classified as agonists or antagonists, we felt that this potentiation likely reflected action at a modulatory site on or near the GABA receptor and that it might be a more general precedent for drug action. David became another valued lab mentor to me, sharing his expertise in enzyme biochemistry as well as his infectious enthusiasm for life and science. We had an uphill challenge to convince Gerry to let us write up a short report, as he strongly preferred full-length papers, but we eventually convinced him that the finding would not keep and published it in *Nature* in 1977, EEG machine recordings and all. The discovery of the CNS benzodiazepine-binding site was reported in the same year by Squires and Braestrup, as well as by Mohler and Okada. I recall afterward having energetic discussions with David about how much fun it would be to discover a clinically useful drug, overlooking the evident fact that our study had nothing to do with the discovery and development of benzodiazepine drugs.

Anyway, soon after, I was delighted to learn that Gerry and the Pharmacology Department thought my lab work met PhD requirements and that Harvard Medical School likewise considered my completed clinical clerkships sufficient for graduation. The prospect of finishing well ahead of schedule was irresistible. A wiser man would have delayed at least another year, to flesh out the benzodiazepine discovery, establish a presence in the field, and then come back up to speed in clinical skills before internship. But I was in a hurry: I had gotten engaged to my college girlfriend, Yvette Sheline, and could not see how I could marry on my graduate student stipend of $325 a month.

I plunged directly from a thesis defense into marriage and a medical internship at Harvard's Peter Bent Brigham Hospital. (Lesson: not an ideal sequence.) I tried to compensate for my clinical shortcomings by working hard. It was five months before I even looked for the on-call room to catch brief naps during my every third night on call. But eventually the intense training brought me up to speed, and I entered a neurology residency at Harvard's Longwood area hospitals feeling like a doctor. Neurology had become the obvious choice of medical specialty for me. I had ruled out neuropathology (wanted to see patients) and neurosurgery (didn't think I could maintain operative skill while doing research). Psychiatry at the time seemed insufficiently connected with neuroanatomy and neurobiology, but this has changed and I would certainly consider a career in psychiatry today.

My clinical role model was H. Richard Tyler, the chief of neurology at the Brigham, an exceptional neurologist whose physique and analytic style reminded me of Doyle's Sherlock Holmes. I also had an opportunity to learn from other renowned senior clinicians, including Norman Geschwind, Marcel

Mesulam, and Simeon Locke at the Beth Israel Hospital, and an excellent cohort of more junior attending physicians, including Marty Samuels, Mark Hallett, Dennis Selkoe, Mike Moscowitz, Mike Ronthal, and Marc Dichter. Marc was a role model for me—he saw patients, recorded from cultured neurons, and loved his life.

My neurology residency was less demanding than the internship, but I still had more duty hours than would be permitted under current residency training rules, in part because of illness in the resident group. I would sometimes cover neurology for two hospitals simultaneously, running across Longwood Avenue in the middle of the night. I remember a fellow resident taking hospital call while acutely ill, an IV plugged into his arm, rather than impact his colleagues with additional absence. Arnold Kriegstein and Stuart Lipton were neurology residents in the same program, one year ahead, and Paul Rosenberg was a coresident with me. Although all three would go on to have distinguished careers in academic neurology and laboratory neuroscience, the service intensity of the residency program had us preoccupied with clinical issues. I have had great scientific discussions with each, but only later.

Mark Hallett kindly agreed to teach me electromyography during residency; afterward, I completed a fellowship at the Massachusetts General Hospital in EEG and evoked potentials with Keith Chiappa. Subspecializing in the electrical arts of neurology seemed logical, and I also needed to delay job-hunting while Yvette finished her residency in psychiatry at the Beth Israel. During my fellowship, I took stock of my skills and applied for faculty jobs in academic neurology departments. I wanted a clinician-scientist position, but by then, it had been five years since I had done an experiment and I was not the strongest candidate. The alternatives were to take a straight clinical job or to train further in research. The former option was briefly tempting, but I knew I would miss research. Variations on the latter option were moving up when an offer came from Stanford that I thought might work.

Stanford (1983–1991)

The driver for the Stanford offer was my subspecialty training in clinical neurophysiology, as the neurology department needed someone to back up existing EEG and EMG faculty. It was a tenure track job, but only because Stanford had no other track in place at that time in clinical departments. Today, a similar job at Stanford or elsewhere would likely be on a clinician track, and someone taking such a position would have little chance of reestablishing a bench research career.

The department was small, with a modest clinical service and a deep commitment to laboratory research. The chair was David Prince, an eminent neuroscientist who studied epilepsy mechanisms in slice preparations.

The neurology faculty at that time included Steve Waxman, Bruce Ransom, Arnold Kriegstein, Barry Connors, Mike Weinrich, and Steve Peroutka, and the Prince lab attracted outstanding trainees, such as David McCormick, Istvan Mody, John Huguenard, and Scott Thompson. I carried an extra clinical service load compared with other junior faculty, performing the EEG and electromyography (EMG) studies I was hired to do, and serving at one point as acting head of the EEG laboratory. However, David set a fair limit on my clinical responsibilities and encouraged me to attend also to the research that I would need to do to gain tenure. There were only two problems: not enough space, and what to work on.

The department had a single hallway in the basement of Stanford Medical School to support its research, so the only lab space David could assign to me was a small electrophysiology rig room—the proverbial windowless room with a sink. Worse, though, was the problem of my own making, an absence of research momentum after five exclusively clinical years. I thought about returning to studying benzodiazepines, but I had not established a presence in the field and would have to retool. I had bookmarked multiple topics worthy of investigation during residency, but the practicality of starting a laboratory within my limitations had me leaving my intellectual pride at the door and thinking more like the guy with a hammer, looking for nails.

Let's see, neuronal cell cultures (Bruce Ransom had kindly agreed to let me use his culture equipment): electrophysiology. I decided to return to studying the action of central amino acid transmitters, switching to the excitatory side, glutamate, and to a mammalian system, Marc Dichter's murine cortical cell cultures (upon his good advice, given translational goals). The glutamate field was then rapidly expanding, following breakthroughs in receptor pharmacology led by Watkins, Curtis, McLennan, and others, and recognition of its CNS neurotransmitter role. One puzzle caught my eye: the basis for the unusual "negative slope" seen in the current-voltage relationship of the newly delineated N-methyl-D-aspartate (NMDA)-type glutamate receptor. At certain membrane potentials, depolarization paradoxically increased, rather than decreased, cation entry through the NMDA receptor-gated membrane channel, a characteristic that positioned the NMDA receptor to participate in key circuit behaviors. I wrote an R01 grant application to NIH outlining how I would investigate the basis of this phenomenon. The NIH study section was concerned about my hiatus from research, but recommended that I be given a chance: an R01 grant with a two-year duration. Before I could start study, however, the phenomenon was thoroughly explained in beautiful papers published by Nowak and Asher, and Mayer and Westbrook: the voltage-dependent block of the NMDA receptor channel by magnesium ions.

Abruptly project-free yet funded, I began to search for a related new direction that my NIH program officer would find acceptable. Reading further in the glutamate field, I came across John Olney's work describing

glutamate's neurotoxic potential, which he called "excitotoxicity." Although it was clear that glutamate and related analogues could kill neurons, how this occurred was undefined and seemed like a good topic for me. It was possibly relevant to disease, and I thought it was likely related to membrane events and ionic movements. The case for studying excitotoxicity was iced for me when I read a fantastic paper published by Steve Rothman in the *Journal of Neuroscience* in 1984, demonstrating in hippocampal neuronal cell cultures that an early glutamate antagonist, D-glutamylglycine, could block glutamate-induced depolarization, glutamate-induced death, and anoxic neuronal injury.

I set out with my technician to examine the dependence of glutamate toxicity on extracellular ions. Although Steve had added glutamate to the culture medium to achieve long exposure, I worried that such exposure might overemphasize the acute cellular swelling induced by glutamate in an open culture system: neurons exposed to glutamate blew up like balloons and rapidly disintegrated, whereas cell volume expansion in the intact brain was limited by the skull. Going instead with limited, five-minute exposures, I saw that the immediate swelling induced by glutamate could be reversible; potentially more important was a later degeneration occurring hours later. Acute swelling, like glutamate excitation, was dependent on extracellular sodium; the later degeneration, which was rate limiting for neuronal survival after brief glutamate exposure, was dependent on extracellular calcium. The idea that calcium overload might contribute to pathological neuronal cell death fit nicely with observations implicating calcium overload in other forms of toxic cell death involving hepatocytes or skeletal muscle cells.

I submitted my first glutamate paper at the end of 1984 to *Neuroscience Letters*. Around then, my lab space problem vanished. Chronic departmental space requests finally resulted in the school giving the department a block of additional research space; not in the packed medical center itself, but leased in a nearby office building on Welch Road, near the Stanford Shopping Center and adjacent to dentists and real estate companies. The eminent pharmacologist, Avram Goldstein, discoverer of dynorphin, had established a lab there, and was winding down. David Prince assembled the neurology faculty and asked for volunteers to relocate. None of the senior faculty wanted to go, seeing it as a form of exile, so Steve Peroutka and I, the most junior faculty, were ordered to go.

Welch Road was perfect for me, and the presence of a Häagen-Dazs® across the street an additional plus. With ample space and an interesting project, I could tap into the rich flow of talented trainees drawn to Stanford and the beauty of northern California. Mark Goldberg, Evelyn Tecoma, and John Weiss joined my lab during their neurology residency, John eventually enrolling for a PhD and Mark staying on as a full-time fellow afterward. I put a request in with the Stanford neuroscience PhD training program for

students, and matched with Dean Hartley and Jae Young Koh. Bringing Jae to Stanford took extra doing, as he was then in Seoul. The admissions committee was impressed with his perfect test scores and academic record, including a medical degree from Seoul National University, but arranging an interview was problematic. I offered to absorb risks and guarantee him a place in my group, and I met him for the first time in the San Francisco Airport. He looked like a bodybuilder and didn't talk much, but he would bring deep thoughtfulness and creativity to everything he did.

Another early addition to my lab was Hannah Monyer, a Romanian-German physician who had come to Stanford to study EEG. One morning while we were plowing through a stack of EEGs, she asked what I did in the afternoons, and I told her about excitotoxicity. She asked to come by and observe. I recall that others in the group did not think she would be with us very long. She was gifted, multilingual, and worldly, with deep interests in music and literature, but needed instruction on how to use a lab balance. However, she dove into a project to see whether glucose deprivation would trigger excitotoxic neuronal death (it did). By then we had taken a page from the clinical medicine playbook and were assessing late neuronal death by measuring lactate dehydrogenase release from lysed cells, as cardiologists do when assessing heart attacks. Jae showed that this simple approach was nicely linear. However, we were equipment limited and had to measure enzyme activity with a single tube spectrophotometer assay. I came in one morning and saw Hannah sitting on bench stool next to a large pile of tubes, looking a little cross. "In early," I noted. "What do you mean, early," she replied, "I wanted to see some results and I haven't gone home yet." I suspected then that she would make a major mark in research.

Other key members of the Stanford lab later included Laura Dugan, a geriatrician with expertise in free radical biology; Rona Gifford, a Stanford faculty anesthesiologist on research sabbatical; Valeria Bruno, a postdoc from Fernando Nicoletti's lab in Catania, Italy; Ray Swanson, an assistant professor of neurology at the University of California, San Francisco (UCSF), interested in glia; Ray Regan, an emergency medicine physician; and Steve Peters, a postdoc trained in intracellular recording. Money was very short to start. In a silly effort at economy, I hired a Stanford engineering undergraduate, Paul Duffy, to build a commercially available electrophysiology amplifier from scratch, which he did with good cheer. It worked, but was predictably noisier than the commercial device. A $10,000 grant from the Hereditary Disease Foundation, intrigued by suggestions that excitotoxicity might contribute to neuronal loss in Huntington's disease, came just in time. More important in the longer run, the funding was accompanied by an invitation from Allan Tobin to join the foundation's scientific advisory board, giving me a chance to meet and learn from the outstanding scientists associated with the organization, including Robert Horvitz, Ron McKay, John Mazziotta, and Anne Young.

Having implicated calcium in triggering excitotoxic neuronal death, our attention focused on NMDA-type glutamate receptors, which had been shown by then to gate calcium-permeable channels, unlike the monovalent cation channels typically gated by non-NMDA glutamate receptors. As this calcium permeability would predict, NMDA receptors dominated glutamate-induced death, even, as Dean Hartley showed, after termination of glutamate exposure, demonstrating a feed-forward property of excitotoxicity. Non-NMDA, or alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptors, could also trigger excitotoxic death, but typically required more prolonged receptor activation. Mark Goldberg set up a combined oxygen-glucose deprivation (OGD) protocol that triggered cultured neuronal death also prominently mediated by NMDA receptors; this model became widely adopted by the brain ischemia field. Our work fit nicely with key in vivo studies, beginning with the work of Nils Diemer and colleagues showing that extracellular glutamate rapidly accumulated in ischemic brains, and the work of Brian Meldrum and colleagues showing that an NMDA antagonist could reduce brain damage in rats subjected to transient global ischemia.

Evelyn Tecoma and Mark Goldberg also showed that NMDA receptors contributed to the propagation of neuronal death on the edges of a physical scratch in the cultured neuronal cell layer, modeling a traumatic brain insult. We found that both brief intense exposure to glutamate and OGD were pharmacologically well-behaved assays: neuroprotective drugs demonstrated IC_{50}'s and classic competitive or noncompetitive dose-response curves appropriate to their mechanisms of action. Looking downstream, Hannah discovered that free radicals were important mediators of excitotoxic death. We imagined that loss of calcium homeostasis would lead to myriad derangements all sharing responsibility for free radical generation, but there we were wrong; Sol Snyder's lab fingered calcium-activated neuronal nitric oxide synthase as a critical source of excitotoxic free radicals. Later, Laura Dugan developed some spectacular novel antioxidants, based on buckminsterfullerenes, that were neuroprotective in vitro and in vivo.

We had the bandwidth to explore some interesting side topics as well. Jae Koh asked whether vulnerability to excitotoxicity was uniform across the different types of neurons present in cortical cultures, and found a population of cells resistant to NMDA receptor-mediated toxicity, but highly vulnerable to non-NMDA receptor-mediated toxicity. We thought that differential vulnerability to excitotoxicity might help explain the various patterns of selective neuronal death observed in certain neurodegenerative conditions. John Weiss would later pursue the hypothesis that AMPA receptor-mediated excitotoxicity might specifically contribute to selective motor neuron loss in amyotrophic lateral sclerosis. In a search for clinically relevant environmental excitotoxins, John studied the cycad plant amino acid, β-N-methylaminoalanine, which was suspected of triggering an ALS

(amyotrophic lateral sclerosis)–like neurodegenerative disease in Guam, and found that it combined with bicarbonate to form an effective glutamate agonist and excitotoxin.

Another fruitful side project examined the effect of lowered pH on cortical cell death after OGD, as tissue lactic acidosis accompanied brain ischemia in vivo. Consistent with the discovery of Morad and colleagues that pathophysiologically relevant levels of acidity reduced NMDA receptor-mediated currents, Rona Gifford found that such acidity reduced OGD-induced calcium influx and neuronal death. Later we found it could also injure glial cells and potentiate the contribution of AMPA receptors to neuronal death, the latter likely by delaying normalization of intracellular free calcium levels. These experiments highlighted for us both the potential utility of reductionist approaches for dissecting the factors contributing to the pathogenesis of ischemic brain injury, and also their limitations. In vivo, and ultimately, human experiments would be needed to define the weighting of different factors.

Our largest side project, which steadily grew over time, was the study of zinc as a modifier of glutamate action and excitotoxicity, as well as another neurotransmitter toxin in its own right. Noting that zinc was known to be coreleased along with glutamate from many central excitatory synaptic terminals, we thought it had to do something interesting to glutamatergic transmission and found that it could regulate NMDA receptor activation, inhibiting channel opening and blocking channel current. Steve Peters started the project using intracellular recording electrodes, and Chad Christine, a medical student, then extended it to the channel level. We also found that zinc exposure could itself be neurotoxic, a finding that Jae Koh would later pursue at Washington University.

Searching for a suitable practical neuroprotective antagonist for NMDA receptors, we came across a 1985 paper by Church and colleagues reporting that dextrorphan reduced the excitatory effects of N-methyl-aspartate on rat spinal neurons. Given prior safe use of the related morphinan, dextromethorphan, as an over-the-counter cough medicine, we tested both against neuronal death induced by glutamate or OGD, and we found both to be neuroprotective. This finding interested the original inventor of these compounds, Hoffman-La Roche. Roche hired me as a consultant to advise them on entering the field of neuroprotection and began to explore development of dextrorphan as a treatment for stroke. The lead pharmaceutical company in the area at the time was Merck, which had invented the extremely potent NMDA antagonist, MK-801.

This was an exciting time for my lab. We felt that we were doing important work and contributing to ending a then-pervasive nihilism regarding treatments for neurodegenerative diseases, such as stroke or Alzheimer's disease. A growing number of university labs and companies were joining the neuroprotection fight. Appreciation was growing that pathological cell

death was not necessarily an inevitable consequence of insults, such as ischemia, but rather the result of specific molecular cascades potentially subject to therapeutic interdiction. I fantasized that standard neuropharmacology textbooks would someday have a chapter on neuroprotective agents, right up there with chapters on anesthetics or antidepressants.

By 1987, I had run four years off my seven-year Stanford tenure clock, obligating David Prince to sit down with me and notify me that I was not on a trajectory likely to earn tenure. I had only two more years of employment to go, and then a terminal year. He did this kindly and made good suggestions for how I might try to increase my research productivity. The meeting was not as devastating as it might have been, since by then I had some good studies and manuscripts in progress, but it was certainly uncomfortable and humbling. Down the line, I think the experience helped me become a more empathetic faculty mentor in the two academic neurology departments that I would later chair.

In the months after this official academic warning, my lab's work became more visible and I received invitations to participate in a growing number of scientific symposia. I remember one meeting particularly well—an international meeting dedicated to the neurobiology of CNS excitatory amino acids, held in Manaus, Brazil, in 1988, just before the first glutamate receptor was cloned. The organizers chose Manaus simply because it seemed to be an interesting place that few scientists had previously visited. Travel there was challenging, but the field's momentum ensured strong attendance. I was with a group of American scientists who missed the evening connecting flight out of Rio and had to spend the night slumped in plastic chairs at an open-air bar on the airport tarmac, too much beer mixing with jet fumes and fragments of sleep. We caught a flight the next morning, with me running back to retrieve Mark Bear, still fast asleep in his jet bar chair.

Manaus itself was otherworldly, a place where native Brazilians transitioned from jungle villages into city life, living first in rough, colorful shacks positioned around the city's perimeter, beautiful from a distance but sad up close. Our hotel was old-European elegant, with oddly heavy rugs slightly redolent of humidity and mold. Power was irregular, but the science was exhilarating. Appropriately, Jeffrey Watkins gave the keynote lecture. It was the first opportunity for me to meet some of the field's pioneering senior scientists, whose work I had studied and admired, including Philippe Ascher, Erminio Costa, Carl Cotman, John Davies, Sten Grillner, Uwe Heinemann, David Lodge, Brian Meldrum, and John Olney. Other key scientists present included Graham Collingridge, Michel Cuenod, Gary Lynch, Richard Miller, Michael Rogawski, Robert Schwarcz, Roger Simon, Vivian Teichberg, Tadeusz Wieloch, Anne Young, and Suzanne Zukin. Pharmaceutical company laboratories were represented in force, including by Les Iverson, who was leading the Terlings Park discovery research site for Merck where MK-801 had been invented.

Receptor subtype-selective agonists and antagonists in hand, and molecular cloning of receptors just around the corner, the field had by then moved about a decade past "the dark ages" when a specific transmitter function for glutamate was widely considered unlikely (Watkins and Jane 2006). Yes, glutamate was a cell metabolite, but it also mediated neural signaling and synaptic plasticity throughout the mammalian CNS. The ubiquity and transmitter function of glutamate made its toxicity all the more remarkable. How could evolution permit the development of such a dangerous system, capable of triggering neuronal death in minutes following loss of blood flow, or structural damage? Perhaps a glutamate gun to the head was a small price to pay for a fast and plastic nervous system.

Around the same time, Erminio Costa invited me to join the inaugural faculty of a new international school of neuroscience sponsored by the Fidia Research Foundation and based in Padua, Italy. This appointment was largely honorific, although it began with the privilege of teaching in a week-long seminar course convened in a beautiful and historic monastery in Abano Terme. Lecturing about brain science, and watching monks perform sunlit chores outside while the monastery bells pealed, I felt connected to timeless human endeavors: the tending of bees, the quest for knowledge.

Meanwhile at Stanford, I had maintained steady clinical engagement. I enjoyed teaching and was assigned responsibility for the neurology residency-training program. By the end of 1989, I was granted tenure and promoted to associate professor—and then shortly thereafter, rather abruptly and to my surprise, considered nationally as a candidate to lead neurology departments. I was invited to interview for the neurology chair at Harvard and Beth Israel Hospital where I had trained, vacated by the sudden and sad death of Norman Geschwind. The idea of returning to Boston was appealing, and I was warmly hosted during my interviews by David Potter, who put me up in his Cambridge home in place of the usual hotel. But then another option appeared, after members of a search committee from Washington University visited my laboratory.

The Washington University Neurology Department was large and nationally prominent, drawing patients in from a multistate region and running clinical service volumes that were a multiple of corresponding Stanford department numbers. The dean of the medical school, Bill Peck, was seeking to boost the department's research efforts and was prepared to make a substantial block of laboratory space available to a new neurology chair. I worried about my ability to take on the associated management responsibility, but the opportunity to expand pursuit of neurodegenerative mechanisms both in the laboratory and in clinical trials was for me irresistible. And although some Stanford colleagues opined that they could not imagine trading the Bay Area for the Midwest, I saw adventure there. Beer, bombers, baseball; Gateway to the West,

Mark Twain, the Show-Me state; and with both John Olney and Steve Rothman there, the birthplace of excitotoxicity research. Yvette, who struggled daily for resources as a psychiatrist in the Santa Clara County mental health system, was also offered a full-time academic position at Washington University. We agreed to go, despite a strong counteroffer from Dean David Korn Stanford.

I delayed my departure from Stanford for a year and a half to allow me to complete some ongoing projects. I was also predictably drawn into affairs in St. Louis and ended up with a job and a half to do for quite some time. Lesson: Transition gracefully, but expeditiously.

On the other hand, the extra time working with my Stanford lab was valuable. I attended a superb week-long workshop on the topic of neurodegeneration, a Dahlem Konferenzen sponsored by the German Science Foundation, which was held in Berlin and chaired by Don Price, Hans Thoenen, and Albert Aguayo. The workshop took place during historic change in Berlin, as the Wall had come down only a few months before, and the streets of West Berlin were filled with window-shopping groups of East Berliners, readily recognizable in their faded denim clothes. I found the *Gedachtniskirche*, the Kaiser Wilhelm Memorial Church, especially moving: its blackened, ruined tower a stern reminder of the devastation of war. At the workshop, I benefited from discussions with investigators at the forefront of the development, Alzheimer's disease, neurodegeneration, and growth factor fields. I left with an enhanced appreciation for the importance of programmed cell death in sculpting the nervous system during development, and intrigued by the potential ability of inappropriately triggered apoptosis to contribute to pathological neurodegeneration.

The extended transition period also allowed me to help a neurology resident, Greg Albers, launch his career as a clinical stroke specialist. At the time, given a paucity of proven interventions, vascular neurology was not a recognized subspecialty, and stroke patients were typically managed on general neurology or medicine floors. No special effort was made to get these patients to the hospital quickly, in contrast to patients with heart attacks who were always a top priority for emergency medical service transport. Greg had joined me in some early discussions with Hoffman-La Roche regarding the possibility of developing dextrorphan as a neuroprotective agent for stroke or cardiac arrest. In the process, he became convinced that dedicated stroke centers would soon emerge broadly in U.S. medical centers and be responsible for testing new acute therapies. Following residency, Greg signed on as a clinical fellow with me, in actuality training himself as he explored the frontiers of optimizing stroke care. He went on to join the faculty and cofound the Stanford Stroke Center, the first stroke center in the United States to gain Joint Commission certification as a Comprehensive Stroke Center.

Washington University (1991–2001)

At Washington University, I started faculty recruitment with two Stanford colleagues, Mark Goldberg and Laura Dugan. Later, having completed a medical internship in California, Jae Koh joined the department as a resident trainee. As a framework for expanding departmental research, I designated the department's new laboratory floor the core of a new Center for the Study of Nervous System Injury (CSNSI), dedicated to identifying mechanisms underlying neurodegeneration in acute and chronic disease states, with emphases on convergent pathways and therapeutic countermeasures. This theme was attractively inclusive of a range of faculty research programs, including longitudinal clinical studies led by Leonard Berg and John Morris in the Alzheimer's Disease Research Center, and neuroimmunology studies led by Anne Cross and Michael Racke. Pediatric neurology was historically a division of pediatrics, but I convinced that chair, Harvey Colton, that research synergies would be enhanced by moving the division to neurology. The move had the great consequence of bringing Steve Rothman's and Kel Yamada's laboratories into the CSNSI core. Other faculty recruited early on to join Washington University and the CSNSI were Chung Hsu, an experienced stroke biologist and clinician; David Gutmann, a pioneer in elucidating the molecular pathogenesis of neurofibromatosis; and David Holtzman, a rising star in the Alzheimer's disease field.

Getting my own laboratory restarted took longer than I would have liked, but I had the fortune to recruit a series of outstanding fellows and students, and things gradually picked up. A big boost came when Hoffman-La Roche, increasingly interested in neuroprotection, offered us a major research collaboration. Roche provided unrestricted research support to CSNSI investigators, ultimately about $11 million over 8 years, in exchange for frequent scientific discussions and a right of first refusal for any commercial products stemming from work they supported. I believe we provided Roche with useful guidance, and certainly their support was helpful in advancing our research programs. In a world apart from Stanford equipment-building days, we could afford to buy top-line equipment and all the supplies we needed. Regrettably, such industry seed investments in academic collaborations have become rare in modern times, typically replaced by focused research contracts.

Merck, Roche, and most other large pharma companies advanced NMDA antagonist drugs for acute stroke neuroprotection, while medical centers and emergency medical services across the country geared up for rapid stroke treatment, minimizing "door-to-needle" delay. This accelerated when the thrombolytic agent, tissue plasminogen activator, was approved by the U.S. Food and Drug Administration for stroke treatment. However, one after another NMDA antagonist program failed. Some failures, as with Roche's dextrorphan program, were due to side effects, but others, as with

the Ciba-Geigy drug CGS19755, appeared to be due to a straight up lack of efficacy.

What went wrong? How could drugs so effective in reducing ischemic infarction in rodent models of stroke fail to show benefit in human stroke? Drawing on perspectives gelled by the Dahlem workshop in Berlin, my lab pursued the hypothesis that ischemic apoptosis was to blame. Intense activation of NMDA receptors triggered a fulminant neuronal death distinct from programmed cell death, and it seemed plausible that such "excitotoxic necrosis" might be exaggerated in experimental rodent models: sharp onset of complete ischemia, lissencephalic brains, and simple vascular territories. In contrast, human stroke is often characterized by a progressive onset, and the gyrencephalic human brain has complex vascular territories and large watershed zones. Threshold insults seemed more likely to allow cells to execute orderly programmed death mechanisms, beyond the reach of NMDA antagonist drugs.

We developed three lines of evidence to support this idea, which remains an unproven but viable hypothesis today. First, Byoung Joo Gwag set up a cell culture model of ischemic apoptosis by blocking excitotoxicity with NMDA plus AMPA antagonists, and then extending the period of oxygen-glucose deprivation until cortical neurons died. This death was apoptotic, associated with cell shrinkage and requiring caspase activity. Lorella Canzoniero and Stefano Sensi showed that the intracellular free calcium levels in these dying cells were lower than normal. Bringing calcium back to normal with a calcium ionophore—or even a glutamate agonist—attenuated neuronal apoptosis; lowering calcium alone could induce apoptosis. We envisioned that the high-level NMDA receptor blockade targeted by industry stroke programs might have beneficially reduced excitotoxic necrosis but swamped this benefit by enhancing ischemic apoptosis.

Second, Cheng Du looked for evidence of ischemic apoptosis in rodent stroke models. At the time, intense ischemic insults were in widespread use; necrosis evolved quickly over hours and final infarction could be accurately assessed the next day. We tried grading the insult down, using shorter periods of transient ischemia, until we found a threshold insult producing little or no infarction one day later. But if we followed instead of sacrificing, we found that infarction gradually progressed over the next days. This "very delayed infarction," a counterpart to the delayed neuronal death known to occur after transient global ischemia, was associated with considerable neuronal apoptosis at the borders of the maturing infarction.

And last, Jae Koh and Sangwon Suh discovered that loss of zinc homeostasis contributed to selective ischemic neuronal apoptosis after transient global ischemia. JinMoo Lee and Greg Zipfel followed that work by identifying a zinc-mediated component in the neuronal apoptosis associated with very delayed infarction after mild transient ischemia. We initially focused on the trans-synaptic movement of presynaptic terminal zinc as the source of

postsynaptic zinc overload, but later elegant work by Elias Aizenmann and colleagues implicated free radical-triggered release of intracellular bound zinc as a more important source.

Our pursuit of ischemic brain injury mechanisms to consideration of apoptosis and zinc overload led us to consider excitotoxic ionic derangements more broadly. Although we had previously focused on calcium and sodium entry through glutamate receptor-gated channels (the latter further enhancing calcium entry), these channels were also highly permeable to potassium: Could potassium efflux from depolarized cells contribute to injury? Shan Ping Yu, a patch clamper recruited from Stony Brook, found that the activation of delayed rectifier-mediated potassium efflux contributed to several forms of neuronal cell apoptosis, and that glutamate receptor-mediated potassium efflux could also play a role. These studies fit with work by Cidlowski and colleagues in monocytes, suggesting that potassium efflux and resultant lowering of intracellular potassium concentrations were key steps enabling programmed cell death pathways, including the activation of caspases.

Other studies in the lab led by Marga Behrens, Uta Strasser, Valerie Heidinger, and Alain Buisson explored the modulatory effects of the metabotropic glutamate receptor system on glutamate receptor function and excitotoxicity. Injury pathways downstream of glutamate receptor or zinc were further delineated by Joy Snider, Christian Sheline, Pat Manzerra, and Shadi Fahrangrazi. Sandy Hewett linked in reactive astrocytes when she found that cytokine-stimulated astrocytes generated nitric oxide that potentiated NMDA receptor-mediated neuronal death. Besides additional work on OGD-induced neuronal death or stroke carried out by Margaret Grabb, Doug Lobner, Deb Babcock, and Arshad Majid, we also were able to extend investigations into spinal cord injury, funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the Christopher Reeve Foundation. I had the privilege of joining an international research consortium organized and supported by the Reeve Foundation: Reggie Edgerton, Rusty Gage, Louis Parada, and Martin Schwab were other members. A Washington University neurology resident and postdoc, John McDonald, represented my lab in this working group, and established a local collaboration with David Gottlieb in neurobiology and Ling Wei in cell biology (Shan Ping Yu's wife) to see whether the transplantation of neutrally differentiated stem cells could improve recovery in vivo after brain or spinal cord injury (it could). John additionally widened the traditional concept of excitotoxicity when in collaboration with Mark Goldberg he demonstrated that oligodendrocytes were highly vulnerable to AMPA toxicity.

When not doing research, I attended to managing neurology department operations. When I assumed responsibility, the department lost a little money each year, despite the benefits of the last vestiges of straight fee-for-service reimbursement—outside of charity work, the department collected much

of what it billed. During my decade tenure as department head, our net collection rate would drop by more than a third; without changes, we would have lost millions of dollars per year on clinical operations. But we expanded services and increased efficiencies, recruiting faculty, opening new subspecialty services and more than quadrupling clinical volume and external research support. By 2001, the department had saved up a sizable endowment and was ranked first in the country in NIH research support (really second, since Harvard's multiple departments were considered separately). This could not have happened without the efforts of a skilled senior administrator, Bob Schaefer, and staff: Laura Waugh, Linda Montague, Micky Wilderspin, Patti Nacci, and Paul Demediuk. Patti's position was new and impactful: helping young faculty write research grant applications. Paul likewise had a new role: A biologist turned information technologist, he set up the departmental computer network well ahead of institutional initiatives, stringing cable himself between rooms. I recall cheering when the department's first IBM Pentium desktop computer ("Rothman's Big Bad Pentium") appeared on the network. Paul's efforts allowed the department to gain a strong internet presence in the early days of the web, with Alan Pestronk's section becoming known in neurology circles as a go-to place for up-to-date information about neuromuscular diseases.

Paul's advanced skills also saved me from an editorial nightmare. Jacques Mallet and I had been approached by Blackwell Scientific to establish a new research journal focusing on the biology of brain diseases. We thought this timely, as papers in this area could sometimes fall between the scope of the clinical and basic neuroscience journals of the time. We launched the *Neurobiology of Disease* in 1994, begging colleagues to send us papers. We got great submissions, but after only a few issues, Blackwell abruptly informed us that they were abandoning the journal, effective immediately. The prospect of letting down the friends who had trusted us to publish their work was unbearable. Fortunately, Paul came up with a creative temporary solution. He scanned the papers and posted them electronically on a dedicated server he set up in the department. Jacques and I assured authors that we would continue to make the papers available on the web indefinitely, if needed. A permanent solution surfaced a few months later, when Graham Lees at Academic Press enthusiastically offered to take on the journal, and arranged for the journal to be indexed in MEDLINE retroactive to the first issue. Today, the journal is absorbed under the Elsevier roof and thriving under new editorship.

Between research, managing the department, and a busy travel schedule, I decided that I could not have my own outpatient practice, but I continued to see inpatients as an attending on the busy main Barnes-Jewish Hospital service each July, welcoming the new residents. I also held regular chief-of-service rounds. This I felt was a true perk of the job—an opportunity to see some of the most interesting or challenging patients of the week. I also

continued to teach when possible. The highlight of my teaching career was an opportunity to direct the Neurobiology of Human Disease course at Cold Spring Harbor, which I did for several years together with Bill Mobley from UCSF. A roomful of energetic, incisive students from diverse backgrounds and multiple countries, long summer days to bounce ideas around with a spectacular series of visiting faculty, the idyllic Banbury Conference Center on Long Island's north shore. What could be better? I still have the t-shirts.

Administration: SfN, Industry, and Academia

I loved my work as a researcher-clinician-teacher, but as department-building and recruitment leveled off, I began to think about taking on another professional adventure. I recalled that when I started, I had asked Dean Peck how long he thought a clinical department head should serve. He had answered without hesitation: 10 years. Long enough to see things through, but not to stagnate.

A major administrative challenge had already come my way, unexpectedly, from SfN. I had been active in the Society, chairing the Program Committee and serving as a councilor. In 1998, I began concurrent service as treasurer and president-elect, joining an Executive Committee with President Ted Jones and Past-President Lorne Mendell. In this unusual dual role, I could see that the Society had some key organizational weaknesses. It was dependent on a successful annual meeting to cover each year's expenses and hence vulnerable if circumstances (e.g., weather) impaired a single meeting's attendance. Under Ted's steadfast leadership, the Executive Committee took a deep breath and began the difficult and initially controversial process of revamping Society processes and administration. During my year as president, an ad hoc advisory committee, consisting of Ray Dingledine, Gerry Fischbach, and Bernice Grafstein, provided additional counsel, and the next two Society presidents, Don Price and Rusty Gage, did the heavy lifting to put new processes in place. Rusty ultimately led the recruitment of Marty Saggese as executive director. I consider the present SfN to be an exemplar of a modern academic society, extensively and effectively engaged in support of neuroscience and landlord of its own headquarters building in Washington, DC.

In formulating academic initiatives for the SfN, I drew upon perspectives gained during service as chair of the U.S. National Committee to the International Brain Research Organization and worked to enhance partnerships with neuroscience societies outside North America, as well as with the Dana Alliance for Brain Research. As one of a small number of clinicians to serve as SfN president, I actively supported the SfN's growing interest in disease biology and societal impact. I used the traditional privilege of organizing a Presidential Symposium for the purpose, unusual at the time, of bringing in a lay speaker who I thought had something important to say

to neuroscientists. Christopher Reeve described his experiences with spinal cord injury and public advocacy in an evening lecture, riveting a packed lecture hall with articulate whispers, punctuated by respirator breaths. Later, he toured a poster session and seemed heartened and impressed. I also convinced Merck to provide no-strings support for the Presidential Symposium for a decade, setting a precedent for the more vigorous external fundraising that continues today. More longitudinally, I have been pleased to have served for many years on the committee for the SfN's Neurobiology of Disease Workshop, part of the annual meeting—a wonderful tradition founded by the distinguished invertebrate neurobiologist, Ed Kravitz.

Two extraordinary job offers came in at about the same time in 2001. First, after a national search, NIH Director Ruth Kirstein offered me the directorship of NINDS. I was honored and tempted—to this day, it remains for me the "road not taken" that I still reflect upon. I had gotten to know NINDS well, having served on Study Section and Council, as well as an ad hoc advisor to two NINDS directors. But then another offer took shape: a chance to lead neuroscience drug discovery and clinical development at Merck Research Laboratories.

Merck had a reputation for being a science-driven company that discovered its own drugs. Furthermore, it had plans to expand an already large commitment to neuroscience drug development, building a new discovery site in Boston. I worried about leaving academia and knew that I would miss having my own lab, as well as clinical neurology and teaching. I had recently gained competitive renewal of my two NIH program project grants and R01, funding CSNSI research teams studying mechanisms of stroke and spinal cord injury. But I thought that the Merck position represented a rare opportunity to contribute directly to the development of needed drugs, going beyond what I was then doing as an academic collaborator or advisor to several companies. Also, on a personal and sad note, my marriage to Yvette had become strained. Divorce is not a good reason to change jobs and move, but it would be inaccurate to say that it did not factor in. After debating only briefly, I took the plunge, moving from St. Louis to outside Philadelphia where the company's research and development (R&D) was headquartered.

Working for Merck was quite a change from academia. I enjoyed the multidisciplinary team environment, as well as learning industry methods for discovering and developing new drugs. But I also experienced what a lengthy and challenging process this could be. The only neuroscience drug to make it out the door during my five-year employment was Emend, a small molecule neurokinin receptor antagonist for the treatment of chemotherapy-induced nausea and vomiting. A first-in-class drug candidate, it had been created under Les Iversen's leadership at Terlings Park, and hopes were high that it would open a new dimension in treatments for depression. Unfortunately, the molecule did not show efficacy in large Phase III

depression trials. The project team managed to pivot admirably and salvage the program, leveraging dosage information gleaned from human brain PET receptor occupancy studies and observations of anti-emetic effects in ferrets. Emesis clinical trials were quickly successful. Although Emend's market size was modest by pharma standards, it represented a useful addition to available therapies, and the company received warm letters from grateful cancer patients.

I looked forward to seeing other interesting pipeline drugs also advance. However, one day in late 2004 as I was convening an external expert workshop on Alzheimer's disease targets, the company's wires lit up with news that cardiovascular risks of its blockbuster drug, Vioxx, had been confirmed in a major study. Over the next days, Merck pulled Vioxx from the market; as Merck's stock price tumbled, it embarked on budget reduction, including a sharp downsizing of neuroscience research. I argued that the cost savings of this downsizing were too little to justify its negative impact on future pipelines, but the prevailing view was that neuroscience drug R&D produced a lower return on investment than R&D in some other areas, because of lower success probabilities and longer development times. Research sites in San Diego and Terlings Park were shuttered and not much later I was personally downsized. It meant a lot to me that remaining neuroscience leadership arranged an unofficial dinner to see me off.

During my post-Merck job search, I held a research professorship in the Department of Pharmacology at Boston University, thanks to David Farb, my friend from benzodiazepine days and the department's chair; as well as a visiting professorship at Oxford, thanks to the medical school dean, Alastair Buchan. I did seriously consider another industry position. After being approached by a search firm, I interviewed for a job as head of R&D for a large biotechnology company. I had completed a required, day-long executive psychological profiling (finding: mostly not crazy) and was negotiating compensation and a relocation package when I read the news that the company had just been acquired by a larger company. I never heard another word about the job (other than a single "hang on" that morning from the search firm) and realized that the recruitment process was no more than cover for the ongoing acquisition.

I subsequently focused my attention on academic jobs, declining an offer to lead neuroscience drug discovery from another pharma, and was delighted when Mike Johns, the head of health sciences at Emory University, suggested that I come there to direct a newly established university-wide neurosciences initiative/institute. Emory had gained a windfall when it licensed the faculty-invented antiretroviral drug, Emtriva, to Gilead for a cash payment of $525 million, enabling it to launch several exciting new initiatives, including in neurosciences. Getting the initiative going was enormous fun, made easy by Emory's collaborative culture and accomplished faculty. I reported to Mike (and later his successor, Fred Sanfilippo) as well as the provost, Earl

Lewis, and had the pleasure of working with many members of the neuroscience community there, including Allan Levey, Ray Dingledine, Charlie Nemeroff, Mahlon DeLong, Helen Mayberg, Tim Olsen, Carolyn Meltzer, Stuart Zola, Greg Berns, Elaine Walker, Don Stein, Paul Wolpe, and Paul Lennard. The initiative emphasized interdisciplinary explorations, including at the emerging interfaces between neuroscience and the humanities or social sciences. Given my medically oriented background, these explorations were particularly fascinating to me. I served as a facilitator at large, with funds to support pilot studies and aid recruitments. To push my own academic comfort zone, I elected to teach a seminar course on artificial intelligence to undergraduates.

However, as the initiative coordinating committee was laying the groundwork for expanding research space and fundraising, the Great Recession of 2007 hit. Emory, well endowed and dependent on endowment income for operating expenses, was highly affected and had to put luxury initiatives, such as the neurosciences initiative, on slow track. To utilize my freed-up effort, Fred Sanfilippo appointed me Vice President for Academic Health Affairs at the health sciences center, responsible for overseeing the academic elements of inter-school centers, such as the Cancer Center, or a contemplated new Vascular Disease Center. This was an excellent job in academic administration, but too removed from neuroscience to be completely fulfilling for me.

I decided then to take an academic leave of absence for two years, generously permitted by Emory, to work for the Simons Foundation in New York City, focusing on their Autism Research Initiative (SFARI). This gave me an opportunity to work on the pleasant, supply-side of the grant business, working with excellent scientific colleagues to identify and support the best studies. I developed admiration for Jim and Marilyn Simons and an appreciation for the major and unique contributions their foundation is making to society in mathematics and biology. Contrary to expectation, speaking as a former Boston-area townie constitutively suspicious of New York City, I ended up liking the city a lot. More important, I met Melanie, an obligate area resident and knew quickly that I had to remain in New York.

Back to Basics: Stony Brook Neurology and Korea Institute of Science and Technology

During my search for a New York position, the new medical school dean at SUNY Stony Brook, Ken Kaushansky, asked Bud Rowland, the former chair of neurology at Columbia University, and me to come in as consultants to evaluate the neurology department at Stony Brook. The previous chair of that department, James Davis, had been tragically killed in a private plane crash, and the department had been under acting leadership for years. Bud and I made the easy recommendation that the institution

invest in recruiting a chair and rebuilding the department. Ken offered me the position, and I gladly accepted.

Since joining Stony Brook in 2012, I have worked on expanding both the faculty and the residency. Stony Brook operates the only academic medical center on the eastern two-thirds of Long Island, so the department's priority is working with network partners to provide appropriate clinical services to the 1.5 million people resident there. To support the department's predominantly clinical research programs, I have initiated several pilot therapeutic clinical trials in the areas of stroke and autism, using repurposed drugs already approved for use in humans. I continue to serve as a scientific advisor to several companies and will start work again shortly with the Christopher & Dana Reeve Foundation as an advisor.

Besides working at Stony Brook, I recently completed a term as Director of an overseas neuroscience research institute, the Brain Science Institute (BSI) in Seoul, which accordingly supported part of my Stony Brook salary. The BSI is part of the Korea Institute of Science and Technology (KIST), a government-supported research organization predominantly working in engineering and computer sciences. Appointed by KIST President Kil-Choo Moon, I found working at KIST both scientifically and personally meaningful. I especially enjoyed overseeing projects combining biology and engineering, such as one led by Tae Song Kim, YoungSoo Kim, and Kyo Seon Hwang that combined drug administration with a novel microelectromechanical sensor to detect beta amyloid species at femtomolar concentrations. The BSI licensed this technology out to a biotechnology company seeking to develop a blood diagnostic test for Alzheimer's disease. Being a largely remote director was possible because I had an on-site partner, Dong Jin Kim, an accomplished medicinal chemist and capable leader who concurrently served as Acting Director. At the end of 2016, Dong Jin and I turned leadership responsibilities over to a new BSI Director, Uhtaek Oh. I have agreed to continue working with the KIST BSI and Uhtaek as chair of their external scientific advisory board.

A personal highlight of my time as BSI director occurred in 2016, when KIST celebrated its fiftieth anniversary. KIST was established with resources—even basic building materials were needed—gifted by U.S. President Lyndon B. Johnson, in gratitude for South Korea's wartime aid in Vietnam. Its subsequent value to the country's extraordinary industrial and economic growth reflects well on the wisdom of Korean President Park Chung Hee's original, and apparently unexpected, ask. As part of its commitment, the United States sent over an advisory team contracted from Battelle Memorial Institute, and it turned out that my father Harry was the Battelle engineer selected to lead the U.S. team and help develop initial strategic plans. Harry joined me at KIST for the fiftieth anniversary celebration, and KIST President Byung Gwon Lee presented him with a special award on stage. I had not spent much time since childhood with my father,

so this event provided us with a rare opportunity for reflection, bringing us closer.

When in Korea, I also advised a Suwon-based biotechnology company founded by my former postdoc, Byoung Joo Gwag. This company, GNT Pharma, is bringing a version 2.0 NMDA antagonist drug, Neu2000, forward for acute stroke neuroprotection, and has begun initial multicenter efficacy trials in Korea and China. Their candidate drug differs from first-generation candidates in being a weak, fast antagonist with selectivity for the N-methyl-D-aspartate receptor subtype 2B (NR2B), hopefully able to blunt acute excitotoxicity without going too far and facilitating calcium starvation and apoptosis. Their drug additionally incorporates a second mechanism, free radical scavenging, aimed at ameliorating downstream injury pathways and reperfusion injury.

Another promising next-generation NMDA antagonist drug candidate in current development is NA-1, invented by Michael Tymianski at the University of Toronto. NA-1 acts to decouple NMDA receptor activation from free radical generation by inhibiting interactions with postsynaptic density protein 95. It reduced strokes in patients undergoing endovascular repair of cerebral aneurysms and is being tested in a large multicenter stroke trial in Canada.

Closing Thoughts on the Neuroscience Phase of My Life

Although teaching has not been the primary focus of my career, it has been steadily important to me for personal fulfillment and contribution. I am proud of the 50-plus PhD students and postdoctoral fellows that I trained in my lab (the net teaching vector being admittedly reversed in some cases). About half hold senior faculty positions at various universities around the world, many as department heads, division chiefs, or center directors. Other former fellows work as scientists or program officers in industry, research institutes, or foundations. I am also proud of my three grown sons, and perhaps especially so of my oldest son Eric. Since right after his freshman year in college, Eric has struggled with severe bipolar disease and has been hospitalized numerous times for psychotic breaks. Yet, he has managed between hospitalizations to complete college and gain a master's degree in social work, setting a goal of helping individuals with mental health disorders like himself. My middle son, Alex, is in neurology residency and I hope the Neuroscience Phase of his life turns out to be as good as mine has been. He is off to a strong start and has a brilliant baby daughter. When my youngest son, Jason, was a child, he told me that he thought I worked too hard and would do something completely different, which he has. After enlisting in the U.S. Army and serving as a lieutenant in Iraq, he now works in the financial sector.

I would dearly like to see stronger translation of neuroscience to ameliorate disease impact. I am concerned that the assessment of neuroscience R&D as financially uncompetitive has become a broad pharma trend, as multiple companies have reduced or exited neuroscience over the past several years. These reductions affect the entirety of the neuroscience research ecosystem, including small companies and academia, and lower the probability of needed new drugs emerging sooner rather than later. Ultimately, advances in understanding disease and better drug development processes will prevail, but there are many calls on available budgets and lives are at stake now.

One practical, relatively budget-neutral remedial step that could be taken now is to modify market protection for new drugs. Current U.S. policy, based on patent law, accords the same market protection to a "me-too" drug adding little to current therapies, as it would to a breakthrough drug capable of stopping or reversing Alzheimer's disease, or limiting stroke damage. In fact, the former would likely have longer market protection, as its clinical testing would likely be faster and burn less time on its chemical entity patent clock. Assigning additional market protection to selected therapies needed by society, but not favored by an industry risk or reward calculus, would encourage private investment in developing these drugs.

Another policy change that might encourage industry to reinvest in neuroscience R&D would be the creation of additional flexibility in regulatory approval mechanisms. The safety, efficacy, and medical impact profile of each therapy is graded and different, yet our current regulatory system offers essentially only a single, all-or-none approval threshold. An "adaptive approval" mechanism (Eichler et al 2012), providing intermediate levels of approval and marketing rights for safe, breakthrough drugs showing promise in late development would allow industry sponsors to gain some limited early income to help defray the costs of final large trials, thereby reducing risk.

Recently, the American Brain Coalition (ABC) has launched a task force to explore these issues and find ways to increase private investment in neuroscience R&D. The ABC is a nonprofit public advocacy organization, with academic society, disease foundation, and industry members, that seeks to understand brain functions and reduce the burden of brain diseases. I have joined this task force, and hope that it can help bring about changes to serve society's interests.

On a scientific note, I think that the translation of neuroscience discoveries to therapeutics could be enhanced by a couple of paradigm shifts, and I hope to model these in a small way in my own clinical research at Stony Brook. First, more screening of candidate approaches in pilot clinical trials is needed. A plethora of possible therapeutic approaches have been identified by now in myriad laboratories around the world, but animal disease models, which are great tools to dissect disease mechanisms, have

recurrently disappointed as predictors of clinical efficacy. Even if industry neuroscience R&D had not been reduced, the conventional pharma approach of exquisitely selecting a few candidate therapies for thorough sequential clinical testing could not do justice to the large pool of ideas now accumulating in the neuroscience community. Utilizing the bandwidth of academic medical centers, disease foundations, and biotechnology companies to conduct an expanded number of pilot trials would increase society's ability to sift through this stack and identify the most promising approaches for further testing in full-scale trials.

Second, more approaches concurrently targeting multiple disease mechanisms, either with agents designed for this purpose or with drug combinations, are essential. Efforts to treat nervous system diseases to date have overwhelmingly targeted single mechanisms, and as selectively as possible. Although this approach is intellectually satisfying and easier to advance in drug development than combination treatments, the recognition of a growing number of parallel pathogenic mechanisms in the brain injury field is also occurring in other areas. This is not surprising. Many effective therapies for infectious diseases or cancer would fail in monotherapy trials.

Looking back, the Neuroscience Phase of my life has been terrific. It has allowed me to ponder, to contribute, to teach, to meet extraordinary people, and to learn continuously: the proverbial firehose. I have changed duties and venues more than some, but I would not trade the attendant adventures and learnings for a monotonic career. When I consider my first branch point, and the possibility that my career expertise at this moment might have been restricted to effecting quick spark plug changes, I feel deeply grateful for the opportunities that have come my way and to the people who have generously supported me, beginning with grandmother Florence and my parents. Blind good luck also obviously helped me out a lot.

I do not envision ever completely leaving neuroscience, but I am now looking forward to opening a new phase.

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