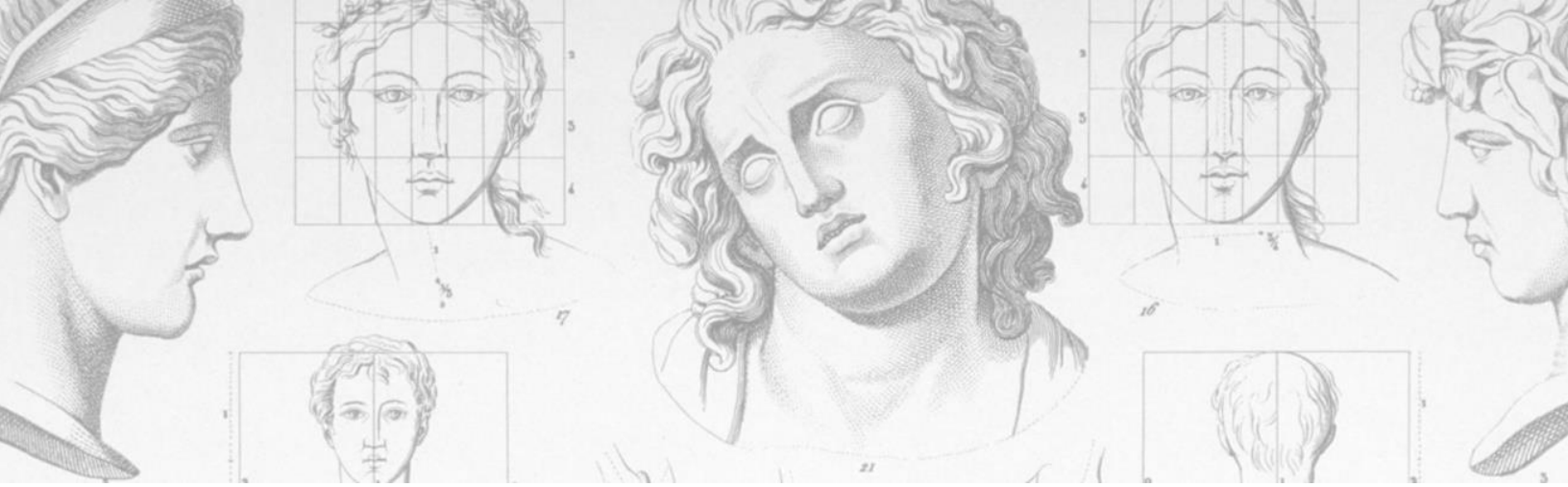

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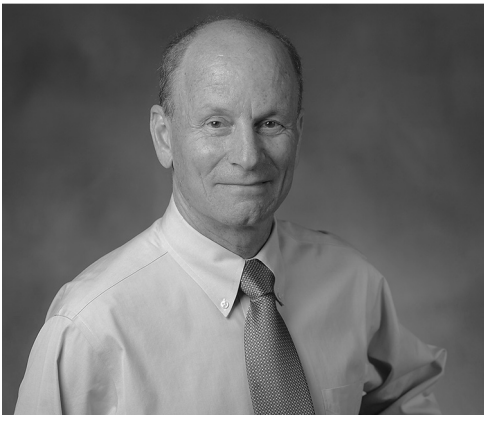

Stephen G. Lisberger

Born:

New York City
October 28, 1949

Education:

Cornell University, Ithaca NY, BA (1971)
University of Washington, Seattle WA, PhD (1976)

Appointments:

Postdoctoral Fellow, University of Munich (1977)
Postdoctoral Fellow, National Institute of Mental Health, NIH (1977–1981)
Assistant Professor of Physiology, University of California San Francisco (1981–1986)
Associate Professor of Physiology, University of California San Francisco (1986–1989)
Professor of Physiology, University of California San Francisco (1989–2011)
Investigator, Howard Hughes Medical Institute (1997–2015)
Professor of Neurobiology, Duke University (2012–present)
George Barth Geller Distinguished Professor, Duke University (2012–present)

Honors and Awards (Selected):

Elected Member, National Academy of Sciences (2022)
Elected Fellow, American Association for the Advancement of Science (2021)
David A. Robinson Lecture, Johns Hopkins University (2014)
Cesar Fernandez Memorial Lecture, University of Chicago (2013)
Bernice Grafstein Prize for Mentoring Women in Neuroscience, Society for Neuroscience (2011)
Elected member, American Academy of Arts and Sciences (2008)
Distinction in Teaching Award, First-Year Medical Students (1998)
McKnight Foundation Development Award (1988–1991)
Young Investigator Award, Society for Neuroscience (1986)
The Academic Senate UCSF, "Distinction in Teaching Award" (1986)
McKnight Foundation Scholar Award (1981–1984)
Alfred P. Sloan Fellow (1981–1983)

Steve Lisberger has been a pioneer in understanding the neural circuit basis for motor control and motor learning using eye movements as a model system in awake, behaving non-human primates. Trained in mathematics and computer science, he turned to neuroscience as a graduate student. Throughout his 50-year career, he has used as tools single-unit electrophysiology, clever target motion paradigms, quantitative analysis of eye movement behavior, and computational modeling. He made important discoveries about how the output from the cerebellar cortex controls movement and about its interaction with the vestibulo-ocular reflex (VOR). His analysis of the neural circuit basis for motor learning in the VOR revealed three parallel VOR pathways with adaptive plasticity present in the vestibular inputs to the cerebellar cortex and to the "cerebellar nucleus" neurons in the vestibular nucleus. The second half of his research career expanded to the analysis of visual guidance of smooth pursuit eye movements. He evaluated how the population response for visual motion is decoded from the extrastriate visual cortex and characterized the neural circuit basis for the decoder as one pathway that estimates the speed and direction of physical target motion and one that evaluates motion reliability and uses it to set the strength of signal transmission from the visual system to the motor system. Most recently, he used motor learning in pursuit eye movements to elucidate the operating principles of a learning neural circuit in the cerebellar cortex.

Stephen G. Lisberger

As I write this, I am completing the first half-century of my career as a neuroscientist. I do not know where the time has gone. It has been great fun even when it wasn't fun. The highlight of my career has been the people I have met and known or even known well. I also am proud of my accomplishments in advancing knowledge. People think of me as an experimental neuroscientist. But I am a computational neuroscientist who does his own experiments and summarizes his model with computer simulations or equations. I enjoy the process of science almost as much as the thrill of discovery. I also enjoy the success of others and I have devoted much energy to scientific leadership and mentoring.

For the first 20 years of my career, I was a neuroscientist almost single-mindedly. But I had a "work/life balance" even before that became something we talked about. I view my life as running along three parallel paths—"science," "family," and "fun"—with the width of each path widening and narrowing dynamically in relation to the competing opportunities and demands of the moment. Of course, "science" and "family" are fun, and it is possible to think about science while pursuing fun activities. Indeed, some of my best ideas in the past 10 years came to me while I was on my bike on the backroads of Chapel Hill. One of my favorite books read during my first trip to Europe in the summer of 1968 was *A Moveable Feast* by Ernest Hemingway—I see science as a moveable feast. This has made it possible for me to enjoy science even during the Covid-19 pandemic. I can do science happily at my kitchen table and over video calls, even if I prefer strongly to do it with people in a group setting.

Growing Up, School, and University

Born in New York City on October 28, 1949, I grew up first in the suburbs in North Stamford, Connecticut, and then as sort of a faculty brat in Ithaca, New York, home of Cornell University. Before too long, I had four younger sisters, and then my father passed away in 1961. I was a solitary child with only a few, but close, friends, and I spent a great deal of my time in my room. I built model rockets that I left my room to fly at an abandoned airstrip next to Cayuga Lake. I became intrigued with transistors and designed (but did not build) a digital computer circuit on a very big sheet of paper. I listened to rock-and-roll in the 1960s on a wonderful old AM radio with tubes that allowed me to receive WLS (Chicago) or WABC (Cousin Brucie in New York) at night. My mother had enough money for us to live comfortably, but I had a pathetic allowance and took a paper route for the *Ithaca Journal* and

mowed lawns for pocket change. I could not be bothered with homework and seldom attended to it until late, frequently turning off my lights until I heard my mother go to her room and then doing homework under the covers with a flashlight.

My first important mentor was Mr. Howitt who taught math in grades seven to nine. It was the start of the "modern math" era, and I took to it right away. He entered me in math contests and took me to various nearby cities on Saturdays to compete. I excelled, and it was one of the only positive influences on my confidence in junior high school. It was a perfect time for me to have a confidence builder, just as I was grappling with my father's untimely death. I remember that my high school calculus teacher, Mrs. Hockett, told me that I could be a theoretical mathematician if I wanted. College math, especially n-dimensional vector spaces and multivariate calculus, disabused me of any such illusions.

My mother arranged for me to enroll at Phillips Andover Academy starting in 10th grade, thinking I needed some male influence given that I was growing up with four sisters and a mother. It was the single most important influence on me academically in my entire life. But I hated it because of the academic and social pressure cooker created by putting a large number of very smart teenage boys together for full-time living and studying. I returned to Ithaca High School after one year plus one week. At Andover, I completed two years of high-school math in one year, allowing me learn computer programming instead of taking precalculus when I returned to Ithaca High School in 11th grade. Here, I found my second critical mentor, Mr. Holman, who invited me to the Cornell Computer lab every Saturday morning while he "operated" Cornell's CDC 1604 computer by running the machine that read punch cards for each job. I rode my bike there every Saturday morning and stayed in the computer room from 8:00 a.m. until noon. I was intrigued by the huge Fortran programs run by the various graduate students, who seemed serious and mysterious to me. Computers and computer programming became major forces in my life before almost anyone knew about them. It was transformational. Andover also taught me how to take notes, how to organize my time, how to deal with the stress of public speaking, and how to recover self-esteem after harsh criticism, all skills that have served me well as a neuroscientist. But the biggest win of the year at Andover was that it allowed me to avoid high-school biology, a huge relief because I was too squeamish to dissect a frog.

As a kid, the family path was poorly developed. The fun path was a challenge for me. I loved sports, but I was small and weak and was challenged to compete with my peers—at least until my senior year of high school when I was number two on the tennis team, an experience that was exhilarating because of the enthusiasm, support, and sense of humor of the coach, Mr. Cowan. The neighborhood kids and I played basketball or whiffle ball or street hockey in the neighborhood almost every day after school,

and we were a "team" even though our families and our aspirations were utterly different. I loved ice hockey, and in those days, the ponds froze in winter and we played outside. I learned to skate when we lived in Stamford, Connecticut, almost as early as I learned to walk. I played intramural hockey in high school but didn't blossom as a hockey player until graduate school. As a child, I went to public skating sessions at Lynah Rink on the Cornell campus, and we rooted passionately for Cornell's hockey team. In a way, I was a college kid on the Cornell campus as soon as I was allowed to ride my bike to campus (seventh grade or so), so I had a very college-oriented youth. I think that is why it has been meaningful for me to return to a full-featured college campus at Duke, where I value both my medical school workplace and the broader academic campus environment.

I stayed in Ithaca for college at Cornell University. I lived in the dorms my first year, a fraternity my second and third years, and a house by Cayuga Lake as a senior. I planned to major in physics, but that plan was dashed in the first semester of my sophomore year when I could not get up for the required course for majors at 8:00 a.m. on Tuesday, Thursday, and Saturday. I note that my daughter Emika proved much tougher than I and completed a physics major at Cornell in 2016, just 45 years behind me. I changed to economics which I enjoyed but found to be "too soft." During the economics phase, I had the amazing experience of taking a seminar in the "Economics of Regulation" from Alfred E. Kahn who went on to deregulate the airlines as head of the Civil Aeronautics Board. Turnabout is fair play—in the course, he was a strident regulator. I ended up as a math major, mainly because Cornell did not have a computer science major in those days. One of the great features of Cornell was that star faculty taught undergraduate courses. I audited the Introduction to Biology Course taught by Bill Keeton (he wrote the book), I took Shakespeare from Arthur Mizener, one of the preeminent Shakespeare scholars of his era, and "Mill, Marx, and Nietzsche" from Werner Danhauser, again the preeminent Nietzsche scholar of the time.

After my sophomore year, two important accidents occurred. First, my year of computer programming in 11th grade gave me the background to receive the top grade in a large graduate-level computer science course as a freshman. The professor, Dick Conway, called me afterward and offered me a job in what I think of as the first dot-com, *Compuvisor*. I worked with him, Howard Morgan, and Bill Maxwell to develop a programming language called ASAP, which was the predecessor to VisiCalc, Lotus 123, and Excel. I almost became a computer professional—there is no telling where I would be today but for the second accident. At the start of the summer when I was a rising junior, Amy Pruitt (my then-girlfriend's roommate) gave me a book called *Neurophysiology, a Primer* by Charles F. (Chuck) Stevens. I read it and my reaction was: "OMG, I had no idea you could study how the brain works, that's what I want to do." I continued to work for *Compuvisor*, but

I immediately started taking neurobiology courses. At Cornell, that was mainly psychology, for example, with the greats J. J. and Eleanor Gibson, or a graduate course in animal behavior with Tom Eisner, Steve Emlen, Jeff Camhi, and Bill Keeton. I applied to graduate school in neuroscience and matriculated to the Department of Physiology and Biophysics (PBio) at the University of Washington (UW, pronounced Udub) in Seattle. My Uncle Dick, a banker, was correct when he told me that "Seattle is depressed," but it was a fantastic place to live and study, and I enjoyed a terrific environment at UW. I owe a great debt to the faculty leaders of PBio, Harry "Pat" Patton, Bertil Hille, Thelma (Temy) Kennedy, Wayne Crill, and Orville Smith, for the environment they created and the way they supported their students.

Initiation to Science

The second person I met after I arrived at UW was Chuck Stevens. He and I both worked at the lab almost every evening and his lab was right next to the bullpen for first-year graduate students. We talked frequently and started a friendship that has lasted many years. Like me, Chuck was a theorist who did his own experiments and summarized them with equations. We had a great deal in common. When I told him years later that his book had turned me from computers to neuroscience, his flattering response was "that alone makes it worthwhile to have written the book."

It is frightening how little I knew about science and neuroscience when I started graduate school. I had never read a scientific paper, never been trained to think in terms of experimental questions and answers, and never learned much of anything about neurons or brains. All I knew was how to program computers and a little bit of abstract mathematics. In the fall quarter of my first year, we had a course taught by Chuck Stevens. It was at the same time the most frightening episode of my entire education and the beginning of me as a scientist. Chuck would come into class at 9:00 a.m., put his thermos of coffee on the table at the front of the room, pour himself a cup, and say "give me a few minutes." He was deciding the structure of the next 50 minutes of class and what he was going to say. Once the caffeine started to work, he would draw his lecture about cell membranes and the proteins within them (e.g., Na-K pumps) on the blackboard. Now and then he would stop and say, "Steve, what experiment would you do to test this." Fortunately, Stephen J. Smith, now of the Allen Institute, sat behind me in class and would always pick me up by giving a cogent answer. I simply was not ready to think in terms of experiments about the cell biology of neurons—or about much else, for that matter.

I stopped looking at Twitter some time ago because I grew tired of hearing the narrative that "graduate school sucks." Maybe I had a charmed five years in graduate school, but I think we need to figure out how everyone can have the same charmed graduate career. For me, a major contributor to

my happiness in graduate school was the first person I met at UW, Albert Fuchs, who was assigned to me as my first-year adviser and became my thesis adviser. I found the eye movement system that Albert investigated appealing in its combination of simplicity, accessibility of the essential neural circuits, and natural amenability to quantitative analysis and the thought processes of an engineer. Albert told me, "We already know how the final motor machinery in the brainstem works and what the sensory inputs look like in the visual cortex—all we need to do is figure out what happens across the 2 or 3 synapses that connect them." We are still working on that!

I started graduate school in 1971 when the theory of cerebellar learning had just achieved prominence. During the previous 10 years, experiments by Masao Ito, Sir John Eccles, and others had brilliantly elaborated the circuitry of the cerebellum and the signs of the synapses within the canonical circuit. Seminal papers by David Marr (1969) and James Albus (1971) posited that inputs on the climbing fiber caused changes in the strength of synapses from parallel fibers to Purkinje cells. Ito (1972) gave functional context to the theory. In addition, the collaboration of Bob Baker, Wolfgang Precht, and Rodolfo Llinas (1972) had just discovered that Purkinje cells in a part of the cerebellar cortex called the "flocculus" inhibit neurons in the vestibular nucleus and that the vestibular nucleus neurons are interneurons in the three-neuron vestibulo-ocular reflex (VOR) arc. The VOR uses inputs from the vestibular apparatus that signal head turns to drive an eye movement that compensates for head turns. It keeps the eyes stable in space as we move about. Errors in keeping the eye stable in space cause "retinal slip," the motion of the visual scene across the retina.

Ito (1972) postulated, and Kyoji Maekawa and Jerry Simpson (1972) demonstrated, that the climbing fiber input to the flocculus responds to visual inputs. Over the mossy fiber-parallel fiber pathway, the flocculus receives vestibular inputs as a side loop of the brainstem VOR pathways. Ito's theory was simple: if the VOR makes an error, the visual scene slips across the retina. Climbing fibers in the flocculus signal the error. Plasticity modifies the strength of the vestibular parallel fiber inputs. Changes in simple-spike firing of Purkinje cells correct the VOR through their direct projection to the brainstem VOR pathway.

For me, this all came together at a small meeting at the Good Samaritan Research Institute in Portland, Oregon, in the spring of 1972. The flocculus was the anatomical substrate for taking advantage of the accessibility of eye movements to study cerebellar learning. I was intrigued.

Joe Kimm and Albert Fuchs had been recording single axons in the vestibular nerve of monkeys, and Albert told me that they had recorded lots of fiber activity related to eye movements in the structure that lies just above the vestibular nerve. I put two and two together and realized that they were recording mossy fiber inputs to the flocculus. I petitioned Albert to allow me to try to find Purkinje cells in the flocculus. The first

20 electrode penetrations were frustrating. It was easy to find the part of the cerebellum with mossy fibers related to eye movements. But when I isolated Purkinje cells, identified by the characteristic infrequent popping of the climbing fiber, their simple-spike activity (caused by mossy fiber inputs) was unmodulated during the VOR.

Then, ah ha! Serendipity struck! I found a Purkinje cell that showed strong modulation of simple-spike firing rate. Why? During experiments, the monkey faced an eight-inch radius dome that had seven push-buttons with LEDs in them spaced along the equator of the dome. The monkey's job was to push the lighted button in exchange for applesauce, something he did only after looking at the button. That allowed us to calibrate the electro-oculogram electrodes that we used to monitor eye position and to get the monkey to look where we wanted him to. The dome was attached to the monkey's chair and moved exactly with him when we turned the chair to evoke a VOR. I had been recording from Purkinje cells while rotating the monkey back and forth in the dark to study them during the VOR, but on this day, I accidentally left the room lights on. Instead of making a VOR in the dark, the monkey was preventing his VOR by tracking the button in front of him as it moved exactly with him. I quickly corrected this "error" by placing the monkey in the dark and the modulation of Purkinje cell firing went away. This was the rule, not the exception. Purkinje cell simple-spike firing is modulated strongly when the animal cancels his VOR by tracking a target that moves exactly with him. Firing is weakly or not-at-all modulated during the VOR in the dark. I published this finding in my first paper (Lisberger and Fuchs, 1974) as a short communication in *Brain Research*, a prestigious venue in those days.

In parallel, my future postdoc mentor Fred Miles and I went on to discover that Purkinje cell simple-spike firing is also modulated strongly when the monkey tracks a smoothly moving target with his head stationary (Miles and Fuller, 1975; Lisberger and Fuchs, 1978a). We both realized that the responses during cancellation of the VOR arise in the vestibular system and are related to head velocity; the responses during tracking with the head stationary are a corollary discharge of the signal related to eye velocity going to motoneurons. The head and eye velocity inputs cancel during the VOR because eye and head velocity are equal and opposite. David A. Robinson recognized that Purkinje cell output is related to eye velocity relative to the stationary world (also known as "gaze velocity") and named these horizontal gaze velocity Purkinje cells (HGVPs). Fred Miles pointed out to me that Purkinje cells form an internal model of what happens in the orbit where head and eye velocity sum to create the desired eye velocity relative to the world. Knowing that the Purkinje cells were two synapses from the motoneurons, it was easy to develop a story of the functional roles for each aspect of their discharge. During the VOR in the dark, the brainstem has it all figured out, and the cerebellum leaves well-enough

alone. If the VOR isn't appropriate for the motion of the target, then the cerebellum engages.

In my data, the climbing fiber responses occurred out of phase with simple-spike firing during tracking of a moving target, with or without head rotation. Fred Miles did not observe modulation of climbing fiber responses, probably because he used a much lower set of eye and head speeds than I did. I submitted a paper on the modulation of climbing fiber activity, but it was rejected by *Experimental Brain Research*, and the reviews were so outrageous that Albert and I decided not to try to fix it. My first PhD student, Leeland Stone, revisited the climbing fiber responses as part of his PhD thesis (Stone and Lisberger, 1990). Climbing fiber firing still occurred out of phase with simple-spike firing. Lee went a step farther and used an elegant analysis to provide evidence that the climbing fibers were being driven by retinal slip. He computed averages of retinal slip aligned on the (rare) occurrence of climbing fiber responses and demonstrated that a brief retinal slip of a few degrees per second (deg/s) preceded climbing fiber responses by 100 ms, a typical visual delay. He found no evidence that climbing fibers caused any eye movement.

There is much more to the graduate school story, but the executive summary is that I received my PhD in 1976 and published the two papers that are still my most cited nonreview papers (Lisberger and Fuchs, 1978a, 1978b). I am deeply indebted to a few people who made a huge difference in my graduate career. Albert Fuchs was an awesome mentor who walked the line between guidance and independence perfectly. Mike King and Craig Evinger were close friends and coconspirators and together we developed a great lab group. I was inspired by Erich Luschei, who taught me how to program the Digibits and all about quantitative control of behavior. It was a work-hard-play-hard paradigm that I think originated for me at Cornell, itself a work-hard-play-hard school. We had a great time outside of the lab, and there were many times when the "have fun" path was wide and the science path very narrow. I took the *Mountaineers'* climbing course and we scaled multiple peaks and hiked many gorgeous trails in Washington State. Most memorable was climbing Mt. St. Helens before it blew up and taking several backpacking trips into the Enchantment Lakes. I played on the UW hockey club, one year centering for Craig Beveridge who had a tryout with the Vancouver Canucks and Jim Wellington who started for the University of Vermont in Division III. Every good pass turned into an assist. We practiced a couple of times a week and played in the Northwest Amateur Hockey League. It was the pinnacle of my ice hockey career. I started exercising regularly in February of 1972 and became an avid runner. Sad that my joints no longer allow me to run, but this was my main form of exercise for 30 years. Graduate school was a time when I blossomed personally and intellectually. I strive to create the same positive experience for all PhD students.

In Search of the Modifiable Synapse or "The Fastest Boys at the NIH"

Postdoc is said to be the best time of a scientist's career. For me it was really good, but maybe not better than my graduate school experience. Again, I was blessed with a fabulous mentor in Fred Miles. Fred had taken on the very large task of chasing the modifiable synapse (pronounced s-eye-napse, please, in Fred's English) for motor learning in the VOR. Before I arrived in 1977, he had pretty much found Ito's hypothesis for VOR learning to be wanting (Miles et al., 1980a), and he had documented that VOR learning had zero effect on the responses of fibers in the vestibular nerve (Miles et al., 1980b).

Fred and I had a pretty simplistic view of how to find the site of the modifiable synapse in those days, and we set out to do a simple experiment. If the site of learning wasn't in the cerebellar cortex or the vestibular nerve, then we reasoned it must be in the brainstem. So, my first project as a postdoc was to record as many neurons in the vestibular nuclei as I could, both before and after motor learning in the VOR. Long, tedious recording sessions led to a negative result (Lisberger and Miles, 1980). We found no evidence that changes in the size of the VOR had any effect on the responses of neurons that were related principally to head turns and not to eye movements. One of the reviewers of the paper reported that "the authors have taken a seemingly rich and interesting subject and converted it into a boring and vacuous effort." Ouch. And, 10 years later I discovered that we threw out the baby with the bathwater: we encountered but had not recorded from the right neurons—namely, the neurons that did respond in relation to eye movements. Ed Keller and Wolfgang Precht (1979) had recorded from them and discovered that the key neurons disappeared from the sample when learning had rendered the amplitude of the VOR really small, but they didn't do the right experiments to identify them either.

I learned a ton from Fred about how to do science, how to think about science, and how to write about science. He introduced me to "plasticity." We invented a strategy for learning about how brain circuits work through strategic and quantitative analysis of behavior. By recording the effect of VOR learning on an arcane visual-motor reflex called the "optokinetic response," we predicted which neural circuits would or would not contain sites of learning (Lisberger et al., 1981). We developed the concept that the VOR could "learn by doing," and the theory that signals related to motor activity were sufficient to cause learning. We theorized in a paper in *Annual Review of Neuroscience* (Miles and Lisberger, 1981) that the output from the flocculus was exactly the "doing" signal that was needed to guide learning in the vestibular nucleus. We tested the hypothesis in futility by coordinating electrical stimulation in the bilateral flocculi with vestibular rotation in the dark. Our stimulation probably was too crude and unnatu-

ral, but 32 years later, Jennifer Raymond's lab validated the theory with an elegant application of optogenetics in mice (Nguyen-Vu et al., 2013). Fred and I also invented the idea that we should use a transient vestibular stimulus rather than sinusoidal rotation so that we could study the latency and temporal evolution of behavioral and neural responses rather than merely the steady-state. We did not do much with it because, well, our vestibular stimulator was wholly unsuited to the task. I leveraged the transient stimulus to huge advantage later. But it is important to know who invented the approach. I just used it. Fred was burned out on the VOR and on single-unit recordings in monkeys, and I took the project away to make it my own.

My experience at NIH was terrific. It was a work-hard-play-hard environment, just like graduate school and college. I had very good colleagues in Ed Evarts's Laboratory of Neurophysiology, and we had a great community of neuroscience postdocs across the NIH campus. We had fun together, too. The RIFs (named after an impending reduction-in-force at NIH) developed into the best men's softball team at the NIH and won the intramural championship. Our running relay team—myself, Von Jennings, Jerome Sanes, Miles Herkenham, and Ed Evarts—finished second in the first annual "Director's Cup," a five by half-mile relay on the NIH campus. I still think of us as the "fastest boys at the NIH" because the team that won was from the Food and Drug Administration, technically not the NIH. During my four years at NIH, I had a close relationship, including daily lunch, with Bob Wurtz's lab on the floor below us. While I was at NIH, Bob was given his own lab, the Laboratory of Sensorimotor Research, and I guess I might have stayed on there. But I wanted to return to my roots as an academic following the engram that developed during my critical period when I grew up with the benefits of Cornell's campus.

San Francisco and the Rise of UCSF

I accepted a faculty position at the University of California, San Francisco (UCSF) in 1981 in the Department of Physiology and Division of Neurobiology. It was special for me to return to my father's 1916 birthplace and to be in the same city as my paternal grandmother, who was 96 years old when I arrived at UCSF.

My bosses at UCSF were Fran Ganong and Zach Hall. The initial renovation of my lab provided me with an office for myself, an office for a couple of lab members, a closet for training monkeys, and a single combination of a rig-room and behavior room for monkey experiments. Monkeys lived nearby. We wheeled them through a public corridor in covered primate chairs. Between 1981 and 1994, I published 24 papers that were completed in that 600-square-foot space, including my major series of papers that elucidated the neural circuit basis for learning in the VOR. When UCSF was

on the Parnassus Campus, no one had a lot of space and we had a highly collaborative, interactive community. A lesson for the future?

UCSF had a great and growing neuroscience community. I received fantastic support and mentoring from Zach Hall, Michael Stryker, and Allan Basbaum. The community was small at the outset but grew quickly, especially in the 1990s when we created the W.M. Keck Foundation Center for Integrative Neuroscience to pull our systems neuroscientists into a single space. Key hires included Allison Doupe, Ken Miller, and many others into the systems neuroscience community and Marc Tessier Lavigne and Cori Bargmann in the Department of Anatomy. The Keck Center's renovated space opened in 1994 and shortly thereafter we became one of the first five Sloan Centers for Theoretical Neurobiology. At the same time as UCSF was becoming the national leader in all things molecular and cellular, including neuroscience, the Keck Center and Sloan Center put us on the map in questions of how the brain works when it is working. By 2000, UCSF was among the best neuroscience groups in the country. Lots of places had great faculty and great students. But UCSF also had great community. This was Zach Hall's vision and accomplishment. I try to emulate him in my current position as chair of neurobiology at Duke.

In USCF's systems neuroscience, I saw a huge pivot in the 1990s. The principal investigators (PIs) in the Keck Center were quantitative, but our science was not leveraging neural theory or neural computation. With the funds from the Sloan Center, we began to hire postdocs who had just gotten their degrees in a quantitative science, mostly physics. Many of them succeeded in our environment, remarkably without being remade to be like "us." More important, I saw a qualitative change in how each lab approached its research, and I think it elevated our science hugely. Bill Bialek was a regular visitor and spent six months in residence as part of the Sloan Center. His presence made a big difference to our Sloan postdocs, the faculty, and me. He and I struck up an amazing collaboration, I learned a huge amount from him, and he changed how my lab approached science.

My personal life also pivoted in the 1990s. Bill Newsome introduced me to a postdoc in his lab, Chieko Murasugi. We married in 1992, and our children Emika and Theodore were born in 1994 and 1997. Chieko was a neuroscientist who worked on eye movements, having received her PhD with Ian Howard at York University in Canada. She dropped science like a hot potato shortly after we married in favor of art, her real love, and became an abstract painter. The 1990s were intense with all the scientific developments and the family. We purchased our first dream house seven blocks from UCSF, which allowed me to walk to work and prevented a long commute so that I could be home for breakfast and dinner. In due course, we raised the roof and built a third floor onto the house to create a gorgeous studio for Chieko and an office for me. The studio became a bedroom for Emika when she started

high school on the premise that it would give her a place to spread her wings a bit at home and keep her off the streets. As far as I know, it worked.

After Emika was born in 1994, the 1990s and the first decade of the 21st century were crazy with a constant balancing of work and life. Somehow, we survived. The kids had tons of activities. Both became stellar musicians (long story), great friends to me, and people very different from each other. We had many memorable family vacations, mostly based on miles accumulated from my work travels. My favorite anecdote from the whole time was from an exchange I had with one of Theodore's little league coaches. On a Sunday morning, I dropped him at the field on Treasure Island in the middle of San Francisco Bay an hour before the first pitch and told the coach, "I'll be back in time for the game, I am going back to the City to do some work in a café." I returned at game time and the coach asked me, "Did you finish your work?" Of course, in science we never finish our work, nor was it ever in my mind that I would "finish my work." I laughed to myself. I still wonder if I ever will "finish my work" and how I will know that I have finished.

Cracking the VOR Circuit and Learning in Monkeys

The pinnacle of my contribution to neuroscience was my series of 1994 papers on the neural circuit basis for motor learning in the VOR, published back-to-back-to-back-to-back in the *Journal of Neurophysiology* with me as the first author of all four papers (Lisberger, 1994; Lisberger et al., 1994a, 1994b, 1994c). I set out to find the neural circuit basis for VOR learning when I moved to UCSF and started my own lab. It was very much my work, of course with some help from trainees and staff, but I was the intellectual force behind it. Those papers have stood the test of time, although there have been additions, subtractions, and adjustments to the story.

I concluded that there are two sites of learning in the circuit for the VOR. One site is in the vestibular nucleus at the synapses of vestibular inputs onto neurons that I called floccular target neurons (FTNs) because they are inhibited at monosynaptic latencies after single-shock stimulation in the flocculus. The other site is in the vestibular inputs to Purkinje cells in the cerebellar cortex, presumably at the parallel fiber to Purkinje cell synapse. Both sites are needed to allow a circuit model of the VOR to reproduce neural firing patterns and eye speeds during the VOR before and after VOR learning. But there is nuance to my conclusion, nuance that has been swept under the rug, misunderstood, or ignored. Direct measurements of the vestibular sensitivity of Purkinje cells show that learning in the cerebellar cortex is in the "wrong" direction—that is, the direction opposite to that needed in Ito's theory to cause VOR learning. My data agreed with Fred Miles's earlier data (Miles et al., 1980b). My computational models suggest that the learning in the cerebellar cortex rebalances the brainstem and cere-

bellar pathways and allows the system to remain stable at its new settings, instead of causing learning.

One of my lab's mantras is that "the truth is complicated." My science doesn't simplify a story just to make it accessible or palatable. For example, the previous paragraph summarizes the VOR story in 200 words, but the four papers in 1994 occupied nearly 90 pages of the *Journal of Neurophysiology*, with a total of 63 figures and 178 panels. My full contribution to the neural circuit basis for VOR learning appears in about 22 original papers. Even an essay of the scope of this one cannot capture all the important detail. My strength and weakness as a scientist are the same: I value that detail. So, my strategy in this essay is to outline the key insights that drove the research, rather than trying to explain all the details.

The first insight that drove my research on VOR learning was the need to identify the neurons that received monosynaptic inhibition from the flocculus. Fred Miles and I had successfully implanted Peter Rhodes's bipolar concentric stimulating electrodes in the flocculus, so I decided to do this again and now record from the brainstem and search for neurons that were inhibited by single shocks. We lowered the stimulating electrode toward the correct stereotaxic coordinates with the monkey in his chair and awake and cemented the electrode in a location where stimulation evoked ipsiversive smooth eye movements. Single-shock stimulation caused monosynaptic inhibition of a distinctive group of neurons that we called FTNs. Their responses during the VOR underwent profound changes in association with learning, changes that far exaggerated the changes in the VOR itself.

The second insight was that the tradition in the field of using sinusoidal oscillation of the monkey as a vestibular stimulus was depriving us of critical information about timing. So, we improved the strategy that Fred Miles and I had tried to deploy of using a transient pulse of head motion as a stimulus. Our stimulus never was perfect, but this strategy quickly revealed that the earliest part of the VOR response, the first 5 ms, was unmodified by learning while the modified part of the response happened later (Lisberger, 1984). For our stimulus, VOR latency was 14 ms and the latency of the modified pathways was 19 ms. We concluded that parallel brainstem pathways were unmodified vs. modified. Our recordings (Lisberger et al., 1994b) later established that the unmodified pathways use a brainstem interneuron that responds with very short latencies called the PVP by David A. Robinson for position-vestibular-pause. The modified pathways use the FTNs as the brainstem interneuron. FTNs respond during the VOR with latencies that are compatible with the modified component of the eye movement response. The flocculus inhibited only the modified pathway—or perhaps more accurately, the FTNs were subject to learning and became different from the PVPs because they received inputs from floccular Purkinje cells.

The third insight came from a wonderful collaboration with Terry Sejnowski. In the late 1980s and early 1990s, Terry had invented "NETtalk," an artificial neural network that learned iteratively to pronounce written English text by matching its own output to phonetic transcriptions. He was a guru, perhaps "the" guru, of three-layered neural networks that learned by back propagation (backprop). Backprop was a mathematically derived learning rule that used the chain rule (I remembered this from my math major) to propagate errors in network output backwards to the weights between model units. It changed the weights in a direction that would reduce error the next time. It was like having a screwdriver that could turn each weight in the network up and down a little bit and retain the direction of change that reduced output error. I had great visits to the Salk during our collaboration. I would fly down in the early evening, and Terry and I would have an animated dinner; frequently I stayed at his house. We would think and talk the next day, I would attend tea at 3:00 p.m. with Terry's lab, including Francis Crick and Patricia Churchland, and then rush to the airport for the short flight back to San Francisco. When I read anything written by Terry, Francis, or Pat, I can hear them each saying it in their own distinctive way. Pat went on to join my scientific family as both of her children received their PhDs from my lab.

Terry and I started from Barak Perlmutter's elaboration of backprop into recurrent networks. We implemented it to work on signals that varied as a function of time on a scale of milliseconds and used it to explore how a network with the architecture of the VOR circuit would compute. We were interested in whether the sites of learning could be anywhere in the network, or if the circuit architecture or the behavioral tasks it had to solve would constrain the sites of learning. The sites of learning were narrowly constrained if we forced the network to learn a modified VOR under conditions in which it had to both generate a VOR and track moving targets with the head still or turning. Learning had to occur in parallel in the vestibular inputs to the model network's FTNs and floccular Purkinje cells and the learning on Purkinje cells had to involve changes in time constants as well as the amplitudes of neural signals. Terry's brilliance at assembling a story led to a short paper (Lisberger and Sejnowski, 1992a), but our most important discoveries were relegated to a technical report from UCSD (Lisberger and Sejnowski, 1992b). The latter guided a generative learning neural circuit model that I published in the fourth of my papers in 1994.

I have learned over the years that my greatest ability is to conceive and navigate a *process* that solves big problems. My contributions to understanding learning in the VOR relied very heavily on my management of process. The key inventions—electrical stimulation of the flocculus, transient vestibular stimuli, and the backprop model—all were the results of two minds working together, mine with either Fred's or Terry's. Throughout

my career, major developments in my own research started through collaborations with amazing senior scientists and were brought to fruition by my persistence and management of the research process.

By 2021, much has been added to the VOR learning story. In monkeys, Jennifer Raymond and I verified that the learning mechanisms in the VOR "know" about the 100 ms difference between the latency of the vestibular signals subject to learning and the latency of the visual signals that instruct learning (Raymond and Lisberger, 1998). Jennifer's lab demonstrated that long-term depression of parallel fiber to Purkinje cell synapses in the mouse flocculus is tuned for this time difference, placing the burden of temporal-credit-assignment on the cellular mechanisms of plasticity (Suvrathan et al., 2106). Multiple labs have developed VOR learning preparations in mice and the story has become more granular. For example, different neural sites and mechanisms are responsible for learning that increases vs. decreases the size of the VOR. Jason Christie and Sascha du Lac have made important contributions. Chris deZeeuw provided a wealth of evidence for many details of cerebellar learning. Chris and I became especially good friends recently, and I learned much from him as coauthors with Jennifer Raymond of a recent *Perspective* in *Nature Neuroscience* (de Zeeuw et al., 2021). The three of us truly contributed equally to the paper, and I am the middle and corresponding author.

One tragic omission from the thinking about VOR learning in mice is the failure to include the eye movement input to the flocculus in interpreting any of the data. I hope that will change. Other niggling issues remain. First, my recordings (and Fred Miles's) were made after weeks of continuous exposure to conditions that cause VOR learning. The learning demands on the cerebellar cortex could be completely different after 10 minutes vs. weeks of learning. The Ito theory might be correct for the first 10 minutes of learning—just not after 10 days. Second, the terminology "flocculus" has proved to be tricky. In the monkey, the strictest use of terminology notes that the flocculus is continuous with the ventral paraflocculus. Most of the knowledge from monkeys comes from recordings in the ventral paraflocculus, which is very small in other species. With the help of neurosurgeon Luc Jasmin, we demonstrated that lesions of the more caudal flocculus had small effects on either pursuit eye movements or VOR learning. Lesions that extended more anteriorly to include more ventral paraflocculus had much larger effects on both (Rambold et al., 2002). We think that the evolution of pursuit eye movements expanded the ventral paraflocculus to join the flocculus in controlling eye movement. We use the terminology "floccular complex" to encompass both.

Sadly, few if any labs are studying motor learning in the VOR in monkeys now. I think there is still much to do in monkeys, even using conventional techniques, and eventually by deploying modern molecular approaches as well. The story deserves to be completed, including taking advantage of the

approaches that are possible in both mice and monkeys to constrain the final models.

Visual Control of Movement

When I started my independent career at UCSF, I knew that the VOR learning project was risky and difficult. I would need some low-hanging fruit for my trainees and for papers for my tenure dossier. I already had published my first paper on smooth pursuit eye movements (Lisberger et al., 1981), so I chose the neural basis for pursuit as a parallel project that seemed likely to yield more papers sooner. My first NIH grant was entirely on pursuit, although it included identifying FTNs by electrical stimulation in the flocculus. It was funded for three years starting on the day I arrived at UCSF.

Again, I start with a succinct summary of what I learned about how a moving target leads to accurate smooth eye movements. The middle temporal visual area of the extrastriate cortex (MT) represents the image motion (defined as target motion across the potentially moving retina) that drives pursuit. Sensory signals proceed from MT to the pontine nuclei in a pathway that estimates the speed and direction of image motion by finding the preferred speed and direction of the most active MT neurons. Sensory signals from MT also pass through the parietal cortex to the smooth eye movement region of the frontal eye fields (FEF_{SEM}). FEF_{SEM} implements a reliability-weighted combination of sensory data and priors based on past experience. FEF_{SEM} sets how much credence should be given to the estimates of physical image motion by adjusting the strength or "gain" of visual-motion transmission. The gain mechanism prevents visual sensory signals from having unfettered access to the motor system. Signals from FEF_{SEM} and MT converge in the pons and pass to the floccular complex of the cerebellum and the oculomotor vermis. There, pontine inputs integrate with positive feedback of an eye velocity corollary discharge and create Purkinje cell simple-spike output that inhibits last-order interneurons in the vestibular nucleus and drives motor output.

Several key insights were critical. The first insight occurred in a collaboration with Bill Newsome and Bob Wurtz while I was at the NIH. In 1978 or 1979, a big NIH-wide systems neuroscience journal club discussed a paper on MT neurons. Bill, Bob, and I thought that MT might provide the visual input for pursuit, and we decided to ask how lesions of MT affected pursuit. We knew that MT was organized retinotopically, so we would have to study pursuit by placing the moving target in the lesioned part of the visual field. We appropriated the "step-ramp" target motion invented by Rashbass (1961). The monkey fixated at straight-ahead, and we controlled retinal location by stepping the target to a specific retinal location as it started to move. We measured the first 100 ms of the eye movement response before any eye movements could change the retinal location, speed, or direction

of the stimulus. The initiation of tracking in the "open-loop interval" was a response to a visual stimulus that we controlled with the step and the ramp. This step-ramp target motion moved us away from analysis of steady-state behavior for sinusoidal target motions and into a new era in studying smooth eye movements. Bob, Bill, and I discovered that surgical lesions of MT create a visual scotoma for the initiation of pursuit without any effect on the ability to generate the motor behavior for visual field locations outside of the scotoma. We had some concerns about the surgical lesions, and so we decided to publish only some fundamental discoveries about visual control of pursuit from the prelesion data. Sadly, an anonymous (sort of) reviewer prevented us from publishing the paper. Later, Bob and Bill replicated the lesions results with ibotenic acid lesions of MT and came up with better-controlled data (Newsome et al., 1985). My first independent publication was a cleaner version of the fundamental discoveries about normal pursuit that I think of as kicking off the modern analysis of smooth pursuit eye movements (Lisberger and Westbrook, 1985). It was great to collaborate with Bill, who also became a terrific friend. He brought tons of energy and optimism to the table, not to mention considerable scientific insight. I only regret that we have not copublished except as the 7th and 20th authors on a paper by Mark Churchland that used data from both of our labs with no extra effort from either of us (Churchland et al., 2010).

The second insight came from analysis of an arcane feature of pursuit. Once a monkey initiates pursuit, eye velocity oscillates around target velocity at a frequency as high as 6 Hz. We were pretty sure that the oscillations were a symptom of a high-gain, closed-loop feedback control system, but why can the same subject not track sinusoidal target oscillation at 6 Hz? We discovered that the explanation is what we now call "gain control." Visual motion has very weak access to the motor system when the subject is fixating a stationary target and much stronger access when the monkey is tracking a moving target (Goldreich et al., 1992; Schwartz and Lisberger, 1994). Then, Masaki Tanaka took a page from the book of Newsome. Bill's lab found that stimulation in area MT could change what a monkey told you he had seen (Salzman et al., 1990). Masaki found that stimulation in FEF_{SEM} could change what the pursuit system said it had seen and make it respond much more strongly to a given target motion (Tanaka and Lisberger, 2001). We concluded that the output from FEF_{SEM} doesn't drive eye motion, but rather modulates how strongly sensory inputs drive eye motion. This is still true 20 years later and is a major feature of how we understand the neural control of pursuit.

The third insight was courtesy of my terrific friend and long-time collaborator Tony Movshon. I participated in the Cold Spring Harbor Course on Vision in 1988, and on the way back to New York City in his car, Tony explained to me that Rich Krauzlis's and my ideas about representations of both image acceleration and image velocity in MT (Krauzlis and Lisberger,

1989) had to be wrong and could be disproved in a few simple recording experiments. We agreed to collaborate. I spent many months at NYU for the next 10 years, we recorded from MT of anesthetized monkeys, and I decoded image acceleration but not image deceleration from MT. Sadly, Tony was correct. Our behavioral experiments and models of pursuit required image deceleration to keep eye speed from overshooting the target during pursuit initiation, a problem I still haven't solved. But my time with Tony was a scientific awakening. Tony thinks deeply about perception, motor behavior, theories of sensory processing, sensory neural responses, and much more. He pushed me intellectually. Our experimental designs went way beyond anything I had ever imagined. Tony had me program motion energy models. Tony also happens to be more knowledgeable about classical music, and almost everything else, than anyone I know. We share huge enthusiasm for air travel and its idiosyncrasies, although Tony's travels make me look like a homebody, even during my 15 consecutive years of flying more than 100,000 miles each year on American Airlines. We remain best of personal and scientific friends.

The fourth insight resulted from a collaboration with Bill Bialek that grew out of UCSF's Sloan Center for Theoretical Neurobiology. During one of his visits to our Center, Bill came to my office door and asked: "This system you study, pursuit eye movements—how variable is it?"

I responded: "It is fairly reliable but still pretty variable."

To which Bill replied: "I think we could learn something if we could put a number on that."

The next day, I collected hundreds of eye movement responses to the same seven target motions. Bill took the data home and a year later he came back, said he understand the variation, and backed that up with an equation he wrote on my whiteboard. The equation said that more than 90 percent of the trial-by-trial variation in the initiation of pursuit could be understood as small errors in estimating the direction, speed, and time of target motion. Leslie Osborne picked this up, collected much more data, and concluded that sensory noise was the primary cause of motor variation (Osborne et al., 2005). We no longer think her conclusion is correct, but the data stand, and Leslie's conclusion was half-wrong for innocent reasons.

A chance conversation, a single experiment, and astute analysis by Bill Bialek transformed my research program and put variation on my map as a part of the neural code that mattered and as a tool for analyzing systems. It marked the end of averaging the responses to 16 repetitions of the same stimulus and declaring victory. Suddenly there was a good reason to repeat the same stimulus 100, 200, or even 500 times and analyze trial-by-trial statistics. Javier Medina discovered impressive trial-by-trial correlations between the responses of individual Purkinje cells and eye speed at the initiation of pursuit (Medina and Lisberger, 2007). Sonja Hohl recorded shocking trial-by-trial correlations between the responses of individual neurons in MT and

eye speed at the initiation of pursuit (Hohl et al., 2013). Before she did her experiments, Sonja described them at the Cold Spring Harbor Course on Vision. She reported to me that Tony Movshon and Eero Simoncelli told her the experiments "wouldn't work." Tony had once told me that our ideas about the sensory origin of motor variation had to be wrong because "there are so many neurons in MT that the sensory noise will average out." True, if the neural responses vary independently. But we understand "neuron-behavior" correlations as unavoidable consequences of the "noise correlations" between neurons with similar sensory or motor preferences in a given part of the brain (Huang and Lisberger, 2009).

Seth Egger rediscovered recently (Egger and Lisberger, 2022) something that David Schoppik and Kathy Nagel had started to explore (Schoppik et al., 2008), namely that neuron-behavior correlations provide powerful constraints on models of the pursuit system. Seth also demonstrated that part of the trial-by-trial variation in pursuit comes from noise in the gain of visual-motor transmission, while part comes from correlated sensory noise as Leslie Osborne had concluded. As is always the case in science, we weren't alone in analyzing neural and motor variation. It had started with Harris and Wolpert's (1998) report of signal-dependent "motor" noise but proceeded in parallel in many labs. It is unknowable and immaterial who was first—we participated in an "age of variation" in systems neuroscience and it opened our eyes. And it was a big focus of the Keck Center at UCSF, led to our NIMH Conte Center entitled "Variation as a Neural Code," and infiltrated the thinking and research of many of us.

I remain steadfastly loyal to pursuit eye movements as a model system. We can quantify the sensory input and motor output and, if we measure the eye movements, we know how neurons in the motor system are firing. It gives us profound interpretational power and my aspiration is to take advantage of that. My goal is to develop a circuit model of pursuit that (1) has the architecture of the pursuit circuit; (2) operates on a millisecond timescale throughout a two-second initiation and steady-state of pursuit; (3) has model neurons with mean, variance, and neuron-behavior correlations that mimic those recorded at different nodes of the pursuit circuit; (4) reproduces behavioral and neural responses to many target forms, including those with degraded motion reliability; and (5) operates autonomously based on the feedback structure of a closed-loop system that eliminates its sensory input within 200 ms but still produces persistent motor output. Maybe then I will have "finished" my work.

Cerebellar Learning, Redux

I thought I had declared victory over cerebellar learning in the 1990s, but Javier Medina had other ideas. He came to work with me as a postdoc in 2001 and reshaped our nascent efforts in studying motor learning in smooth

pursuit eye movements. In collaboration with Megan Carey, he developed a paradigm for eliciting reliable motor learning in the direction of pursuit eye movements (Medina et al., 2005). Learning trials started with target motion in a fixed "pursuit" direction and then, 250 ms later, a component in an orthogonal, "learning" direction. Learning is expressed in pursuit as an eye movement that takes the eye in the learning direction at a time that anticipates the instruction. Further, direction learning in pursuit has the same time selectivity as Mike Mauk had found in classical conditioning of the eyelid response (Perrett et al., 1993). By comparison with learning in the VOR, pursuit learning occurs quickly. It was possible to record from floccular Purkinje cells during baseline pursuit before learning and then throughout the substantial learning caused by a block of 100 repetitions of the same learning trial. Javier demonstrated that instructive changes in target direction caused climbing fiber spikes on about 40 percent of trials and that 100 learning trials caused a well-timed suppression of simple-spike activity of about 20 spikes/s. Correlative for sure, but the direction, reliability, and timing of the responses were nicely in line with the Ito hypothesis of cerebellar learning in the eye movement motor system and, remarkably, involved the same Purkinje cells that participate in VOR learning (Medina and Lisberger, 2008).

Our research on pursuit learning led David Herzfeld to a statement of four principles of operation of a learning neural circuit (Herzfeld et al., 2020).

- Principle 1: The earliest learning, even after a single instruction, is fast and easily forgotten and occurs at the parallel fiber to Purkinje cell synapse in the cerebellar cortex, driven by inputs on climbing fibers.
- Principle 2: Early learning in the cerebellar cortex transfers to later, slower learning in the cerebellar nucleus, instructed by the learned simple-spike responses in Purkinje cells.
- Principle 3: Neural inputs to each site of learning need to signal the context at the time of the instruction to be subjected to learning. For pursuit learning, those inputs have different functional relationships to eye movements in the cerebellar cortex vs. the cerebellar nucleus.
- Principle 4: Feedback from Purkinje cells through the cerebellar nucleus to the inferior olive modulates the transmission of errors via the climbing fibers and limits the amount of learning that is possible in the cerebellar cortex. Learning must be transferred out of the cerebellar cortex to consolidate and persist, leaving the cerebellar cortex in a nimble learning state most of the time.

A single critical insight jump-started and drove our discoveries about pursuit learning. Javier came to me about noon one day as we were preparing a paper on neural learning in floccular Purkinje cells and said: "Steve,

there is a problem." Pushed to elaborate, he explained that most of the neural and behavioral learning occurred over the first 30 learning trials, when there were at most 12 climbing fiber responses to the instruction. He went on to predict that "there is no way 12 climbing fiber responses could cause a 20 spike/s depression of simple-spike firing. The cerebellar learning theory must be wrong."

I don't know how I had this idea. I said to Javier: "This isn't a problem, it is an opportunity. If 12 climbing fiber inputs are causing a 20 spike/s depression, then each climbing fiber should cause a 2 spike/s depression and you should be able to measure that." I suggested that he break the sequence of trials into pairs, separate the pairs according to whether or not the first trial included a climbing fiber response to the instruction, and ask whether the simple-spike firing showed a small depression on the second trial if (and only if) there was a climbing fiber response on the first trial. Javier came back late that afternoon and said: "You are completely crazy, but I will do the analysis." It worked. A single climbing fiber input is linked tightly to a well-timed depression of simple-spike firing on the next trial. I remained a little concerned that our discovery was "too good to be true" and I predicted correctly that the reviewers of the paper would tell us to do it again. Fortunately, one reviewer also suggested a way to "do it again" with the data we already had and didn't require us to redo the experiments on more monkeys. Still, it was a great relief when Jennifer Raymond's lab found the same single-trial effects in data recorded during motor learning in the VOR (Kimpo et al., 2014), and David Herzfeld found related effects in data recorded by Robi Soetedjo and Yoshiko Kojima in the oculomotor vermis during saccadic adaptation (Herzfeld et al., 2018). If I had to name my lab's single most important discovery, this would be it.

Javier's discovery of single-trial plasticity of simple-spike responses was based on a tiny database. The next step was to develop a paradigm that would allow us to investigate single-trial learning and plasticity in depth. Yan Yang invented the "random direction paradigm," in which the instruction was randomized between two directions along a learning axis so that there was no long-term learning (Yang and Lisberger, 2010). Now, we could present 400 instructions while recording from a single Purkinje cell, meaning that we might get as many as 80 climbing fiber responses for each recording. Yan obtained beautiful data. She verified single-trial plasticity of simple-spike responses linked to climbing fiber inputs. She solidified that single-trial learning in eye movements was larger if there had been a climbing fiber response on the previous trial in the Purkinje cell under study (Yang and Lisberger, 2013). She added that single-trial learning in eye movements and plasticity in cerebellar output both scaled with the duration of the calcium-related events caused by climbing fiber spikes (Yang and Lisberger, 2014). Not only did this make me feel more confident of climbing-fiber driven single trial plasticity and learning, but it also implied that on

any given trial, climbing fiber events occurred either on most Purkinje cells or on a few.

Since Yan's key papers in 2013–2014, the lab continues to explore cerebellar learning in pursuit eye movements. We learned that pursuit learning evolves over multiple timescales (Hall et al., 2018). We think that different time courses arise at different learning sites. We obtained preliminary evidence that consolidation over longer learning blocks causes learning to be transferred out of the cerebellar cortex, presumably to the cerebellar nucleus. We have started to employ approaches with multicontact probes to assess neural correlates of plasticity other than at the parallel-fiber to Purkinje cell synapse. My goal, in collaboration with Court Hull, Javier Medina, and Nicolas Brunel, is to construct a biologically motivated circuit model of the cerebellum that includes all neuron types, transforms the known mossy-fiber inputs into the known Purkinje cell output, and learns autonomously in a way that mimics biology, complete with realistic first- and second-order statistics of neural responses. Then I wish to fit that model into the larger model of the pursuit circuit outlined in the previous section.

The Cerebellum: Back to the Future

My CV lists 152 "original" publications. Only about 33 of these are on the cerebellum. The small number belies how central the cerebellum has been in my career. It is my favorite brain structure. In my earliest days as a student, I was influenced profoundly by the papers, the passion, and the personal attention I received from greats like Masao Ito, Rodolfo Llinas, Bob Baker, and even Sir John Eccles. I had the enormous honor of knowing these individuals personally, and others who influenced the cerebellar field profoundly such as Jerry Simpson, Tom Thach, Peter Strick (senior to me but still active), David A. Robinson, Geoffrey Melvill Jones, and of course my graduate and postdoctoral mentors, Albert Fuchs and Fred Miles.

I have watched the field of cerebellar research go through multiple evolutions. In 1972, cerebellar learning was one of the most exciting concepts of neuroscience and *The Cerebellum as a Neuronal Machine* had been published only recently (Eccles et al., 1967). But then, it got complicated and, perhaps more important, we did not have any access to methods to establish causation. We knew that the parallel-fiber to Purkinje cell synapse was subject to long-term depression caused by climbing fiber inputs (Ito and Kano, 1982), but does that happen in real life? Neuroscience was correlative then, and we needed to establish causation. In the meantime, other aspects of neuroscience moved to the forefront: modern anatomical methods, neural networks, gene-targeting knock-outs, functional imaging, brain machine interfaces, and the neurophysiology of "cognition," to name a few. Cerebellum was reduced to a smallish field that risked imploding through

self-criticism. We did not know it, but we were waiting for technology to loop back to us in the 21st century and enable answers to the kinds of questions we had in the 1980s.

Thanks to the efforts of a handful of cerebellar neuroscientists younger than I, the field is back on its feet and is flourishing. The Gordon Research Conference on the Cerebellum started in 2011, was an immediate success, and has grown better and better over the years. Kamran Khodakhah invited me to present the inaugural Keynote Lecture in 2011, bestowing on me one of the greatest honors of my career. Roy Sillito started the Cerebellum Social at the Annual Meeting of the Society for Neuroscience (SfN) and it was an immediate hit. Attendance was great and people wanted to be there rather than at the companion socials. We had several informal meetings of cerebellar neuroscientists to talk about how we could support the growth and success of our field while maintaining scientific standards. Those meetings created a unity of purpose. Now, modern molecular approaches are integrated into cerebellar research and there are many labs run by young cerebellar scientists. I am proud that one of my trainees, Megan Carey, has assumed complementary leadership roles in nurturing and expanding cerebellar neuroscience. The terrific Grass Lecture of another trainee, Jennifer Raymond, shone a spotlight on our field at the 2019 Annual Meeting of the SfN. The future looks bright for cerebellar research.

Eye Movements as a Window on the Brain

I chose to research eye movements because I believe that we can use eye movements as a model system to understand general properties of how the brain works. Eye movements afford many advantages. We know the sensory stimuli that drive eye movements—head turns (VOR), eccentric target positions (saccades), and target motion (pursuit)—and we can deliver those stimuli precisely and accurately. We can measure eye movements quantitatively with magnetic search coils and increasingly with video technology. I refined our surgical procedures for implanting eye coils to the point at which coils seldom need to be replaced (thanks to Howard Egger of NYU for showing me the surgery and Creig Hoyt of UCSF for teaching me how to suture halfway through the sclera). The final motor machinery for eye movements is in the brainstem (rather than the spinal cord) where it is accessible to microelectrodes in behaving monkeys. If we know the kinematics of eye movement, we can use known equations to describe the time-varying firing rates of the extraocular motoneurons and of many brainstem and cerebellar neurons. The depth of knowledge about the connections and activity in the final motor machinery for eye movements affords interpretational power for recordings of neural activity elsewhere in the brain. The field, including my lab, has realized that potential to some degree. We have illuminated general principles of brain function in sensory decoding, cerebellar learning,

Bayesian-like sensory-motor behavior, and mechanisms that create persistent activity.

In sensory decoding, we sat on the shoulders of two seminal contributions (Groh, 2001; Salinas and Abbott, 1994). In Jennifer Groh's framework, the population response in area MT is a "place code" in the sense that the speed and direction of target motion is represented by which neurons are most active. In contrast, the signals that drive smooth eye movement are a "rate code." In the cerebellum, firing rate encodes eye velocity and direction is represented roughly along the horizontal and vertical axes. We deployed vector averaging calculations to show how to transform the sensory code into motor commands. We made it work, while also realizing the importance of the amplitude of neural responses, as pointed out by Krekelberg et al. (2006). Recently, however, we had an epiphany. The sensory-motor decoder for pursuit eye movements isn't an equation. It is a set of parallel neural circuits that implement the strategies proposed by theorists but in very brain-like ways. We now think of the sensory-motor decoder as a question of how the brain implements equations. Our extensive data on the first- and second-order statistics of neural responses in multiple nodes of the pursuit system provide constraints on a circuit model of decoding. Similar logic should work for other sensory-motor systems, and I look forward to seeing it applied to decode the output of the dynamical system framework (Shenoy et al., 2013).

The entire cerebellum has the same architecture, so I used to think that all parts worked and learned according to what we knew about the floccular complex and eye movements. I think research on eye movements, including ours, has revealed principles that generalize. But the task for the rest of the cerebellum is more complicated than it is for its eye movement regions. An important concept for control of limb movements has been that the cerebellum learns "internal models." I think of the processing in the floccular complex in terms of an internal model. Purkinje cells sum signals related to eye velocity with respect to the head and head velocity with respect to the world. This coordinate transformation—from eye to head coordinates—computes an internal model of the orbit and represents eye velocity with respect to the world (also known as gaze velocity). This internal model seems almost trivial compared with those needed for arm movement, and I wonder whether the concept generalizes. My belief about generalization of our findings on cerebellar learning is undermined further by recent discoveries of climbing fiber signals that seem more appropriate for reinforcement learning than for traditional cerebellar error-correcting learning (Heffley and Hull, 2019). Even in classical conditioning of the eyelid response, climbing fiber responses shift back to the conditioned stimulus instead of the unconditioned stimulus after full conditioning (Ohmae and Medina, 2015). Perhaps these complications will prove to be layers on top of the simple principles enunciated in research on eye movements. Perhaps the floccular

complex, where climbing fiber responses signal movement errors and also are modulated by reward size (Larry et al., 2019), will provide insight.

"Bayesian inference" is shorthand for a computation that the brain performs routinely, namely a reliability-weighted combination of current sensory data with adaptable priors (or expectations) based on context and past experience. We demonstrated that pursuit obeys Bayesian inference in the sense that it is based on the relative reliabilities of context and sensory data (Yang et al., 2013; Darlington et al., 2017). We controlled context by providing a blend of target motions in blocks that were mainly slow (2 deg/s) or mainly fast (20 deg/s) but always included a few probe trials at the fixed speed of 10 deg/s. We controlled motion reliability by adjusting the contrast of the moving target. When tested with a given probe target speed, the strength of the initiation of pursuit is biased toward the speed of most of the target motions in the block. The bias is greater when the contrast, that is the motion reliability, of the sensory stimulus is lower. Our data implied that the prior would be implemented by control of the strength of visual-motor transmission, linking to our demonstration of control of visual-motor gain as a key component of the pursuit circuit. Tim Darlington used this paradigm to demonstrate the neural computations that implement Bayesian inference for pursuit in FEF_{SEM} (Darlington et al., 2018). He discovered a ramp of preparatory firing during fixation even before the target started to move. The amplitude of the ramp depended on whether most of the target motions in a block were slow or fast. Thus, the preparatory activity represented the prior. The activity in FEF_{SEM} during pursuit initiation encodes the maximum *a posteriori* estimate of target speed that appears to be computed by combining visual motion inputs with the prior represented in the preparatory activity. A recurrent local circuit model with balanced excitatory and inhibitory model neurons reproduced all the features of the representation in FEF_{SEM}, and even adapted autonomously as did the monkey's pursuit behavior when presented with mostly fast vs. mostly slow target motions. FEF_{SEM} may be an example of how Bayesian behavior can be implemented with neural circuits and may be a potential template for other systems in which behavior results from a reliability-weighted combination of sensory data and priors based on past experience.

An autobiographical essay by Steve Lisberger would not be complete without some self-criticism. When I started my career in 1971, we viewed eye movements as a "window on the brain" that would reveal general properties of brain circuits. Sometime between then and now, that vision went off the rails. I think some of us still have that vision. Also, eye movements have proven invaluable to probe decisions, attention, learning, and other higher brain functions. But I think the field lost its way. Instead of my vision of using eye movements to discover general brain properties, most of the field descended into discussion and analysis of intricacies using jargon that left most neuroscientists out of the discussion. Research on the control of

eye movements turned inward and became increasingly arcane and inaccessible to the rest of the field. I wonder whether I could have exerted leadership that would have prevented this inward turn. For sure, I aligned myself with good friends who had a much broader view of systems neuroscience—people like Tony Movshon, Bill Newsome, Michael Stryker, Carla Shatz, Terry Sejnowski, Bill Bialek, and Dora Angelaki, to name a few. I think the eye movement field saw me as a "social climber" rather than as a leader, and I didn't do much to change that view and explain to them what I saw as the rightful destiny of eye movement research. I regret that eye movements have failed—not entirely but to some degree—to lead neuroscience by revealing general principles of how the brain works. I hold myself partly responsible.

Howard Hughes Medical Institute

It was a huge luxury to be an investigator of the Howard Hughes Medical Institute (HHMI) from 1997 until 2015. That said, I always believed that at least 3,200 scientists were as qualified to be HHMI investigators as the 320 of us who were lucky enough to be selected. I celebrated two renewals before my nonrenewal cast me into one of the most distinguished clubs in the field, the club of *former* HHMI investigators. I was worried about getting back into the NIH system and it was a struggle to do so—my main grant from the National Eye Institute went unfunded as an A0 and an A1 and then again as a new A0 before being funded as a second A1.

In 1997, HHMI made a big step into systems neuroscience by adding Bill Newsome, John Maunsell, Tom Albright, and myself as investigators. The Science Meetings we were required to attend every year were a real highpoint, especially as the cadre of systems neuroscientist expanded and lots of molecular and cellular neurobiologists started to study brain circuits. We were in a Science Meeting at HHMI Headquarters in Chevy Chase, Maryland, on September 11, 2001, when the Twin Towers were brought down. It was dramatic and unsettling. I remember our collective shock and concern for our New York colleagues' friends and family. I remember the stunning silence in the skies as we sat outside on the evening of September 11. I remember our feeble attempt at conducting an impromptu scientific meeting that same evening. I was supposed to be the next speaker when Tom Cech interrupted to tell us there had been a terrorist attack in New York and the formal meeting would be suspended. The talk I gave that evening was terrible—it would not have been a good thing if I had given the same talk at the real Science Meeting.

HHMI came at a tipping point in my career. I had published my papers on motor learning in the VOR in 1994 and the lab was small. Before 1997, I had been an independent investigator for 16 years and only 3 PhD students had joined the lab. It was a transition point for postdocs: everyone who was

in the lab in 1997 was gone by 1998. Before HHMI, I had done much (but not all) of my own research. In my first 10 years as an HHMI investigator, 11 postdocs and 9 PhD students joined the lab. They brought new energy and new ideas and my research thrived. The lab was bigger than ever, reaching 12 scientists plus me at one point. It was stimulating and productive. My trainees changed my research program dramatically during that time. I do not know whether that would have happened if I had not been an HHMI investigator. Fortunately, we cannot "rerun the tape" (attribution to Stephen Jay Gould), and I do not care to know.

Leadership

During the Covid-19 pandemic when we mostly worked from home and kept our distance from each other, my view was that we were doing research but not doing science. Our trainees were coming to the lab to do their experiments, but there was no interaction, no chance insights over discussions at the coffee machine. We were doing what we had promised our granting agencies, but we were not delivering added value. Leadership is about creating a culture in which research turns into science. Of course, it also is about creating a culture of excellence, professionalism, inclusiveness, integrity, and support for everyone, and I have strived to succeed at the whole package.

I guess people saw me as a leader. Or maybe they merely realized that I am not good at saying "no." In 1990, my colleagues asked me to be the director of the W. M. Keck Foundation Center for Integrative Neuroscience, founded with a generous gift from the Keck Foundation to bring our systems neuroscientists together by remodeling 10,000 square feet of space on the eighth floor of the Health Sciences East (HSE) tower. In the Keck Center, we had the crazy idea that labs didn't have to be silos. We divided the 105-by 105-square-foot space diagonally into a triangle for dry labs and a triangle for animal labs, the latter connected to the vivarium by a back door. We created six or seven bullpens for our lab members and required that each bullpen have major representation from at least two labs. We clustered the rooms where each lab did their wet research but didn't partition the labs. It worked. People talked to each other, collaborations sprang up between labs, and it was a vital, active, fun place to do science.

The Keck Center had a big impact on neuroscience at UCSF and its creation was temporally correlated with UCSF's final rise to the top of the field. The concepts behind the Keck Center weren't new to UCSF. It was simply UCSF's concepts instantiated in a group that was interested in how the brain worked while it was working. But the Keck Center was an example of how establishment of an appropriate physical structure can have a huge impact on science. We hired brilliant assistant professors who embraced the idea that great colleagues and collaboration were more important than

space and money—Allison Doupe, Ken Miller, Philip (Flip) Sabes, Loren Frank, and Michael Brainard in the early days and others later. We developed the Sloan Center for Theoretical Neurobiology and recruited quantitative postdocs who changed how we did our science.

I don't take credit for most of what we did—in many ways, I was the person who developed and managed the process to implement the brilliant ideas of my colleagues. The original Keck Center included myself, Mike Merzenich, Christoph Schreiner, Roger Nicoll, Howard Fields, Allan Basbaum, Michael Stryker, Allison Doupe, and Ken Miller. Zach Hall, one of my main leadership mentors, was very much the "man behind the curtain." His advice, support, and efforts made a huge difference. I learned a ton from him. Between the founding grant from the Keck Foundation, generous funding from the Sloan Foundation, some philanthropy, 10-years of Program Project support from National Institute of Neurological Disorders and Stroke (NINDS), and 5-years of a Conte Center from the National Institutes of Mental Health, we had terrific financial support. But we were more than well-funded. We had a community that made a difference, and we used our funding to move science and the culture of science forward qualitatively.

It was difficult for people to imagine why I would leave UCSF and San Francisco. Indeed, up to the day I announced my decision, I do not think any of my colleagues believed that I would leave. Yet many of us moved to other positions. The place thrived even as people who seemed like senior leaders and glue departed, validating the notion that it is something in the overall culture that makes UCSF special. For me, however, there also was a glass ceiling. I had leadership aspirations, and they never were going to be realized at UCSF. I had concerns about how strongly the Department of Physiology was going to support neuroscience, especially systems neuroscience. And personally, San Francisco had gone from an easy wonderful place to live in 1981 to an expensive and crowded place to live that presented many challenges for everyday life. For complicated and personal reasons, the last five years at UCSF were not very happy years for me in my job. So, I was ripe to be plucked. We were in Eilat, Israel, for the night before crossing the border to Jordan to visit the amazing archeological site at Petra when Nicole Calakos Emailed me to ask if I would throw my hat in the ring to become chair of neurobiology at Duke. We discussed it as a family over dinner at a Brazilian steakhouse, the family was unanimously on board, and, 11 months later, Dean Nancy Andrews offered me the job.

UCSF and the Keck Center had something special that I tried to create anew at Duke. I accepted the job in June 2011 and started in early September 2011. For nine months, I commuted between San Francisco and Durham, making two to three weeklong trips to Durham each month. I had an apartment near the Duke campus and, after a while, a car that I barely needed. I devoted 100 percent time and effort to getting things rolling at Duke. I started with a sense of urgency because I saw that it was necessary. Duke

Neurobiology had enjoyed glory days in the 1990s and at the start of the 2000s under the stewardship of Dale Purves, but because of forces outside of his control, Jim McNamara had faced huge obstacles as Dale's successor. By the time I got there, the carriage was sitting by the side of a bumpy road with the wheels totally off. Larry Katz had passed away (a tipping point), many senior members of the group had left, and morale was low. Of the faculty in the Department of Neurobiology at the time I was recruited, only five remain today. Twelve, including me, are new.

My main leadership goals at Duke were to establish a culture of "us" rather than "me" and to hire great faculty who would embrace that culture. I saw myself as using leadership to change how science is done, not simply to make the department financially successful. I recognized during my recruitment that many young faculty across the campus were going to be star neuroscientists. I saw my role as getting them all to the table. Yes, I was given generous resources (do I detect a theme here: HHMI, Keck/Sloan, now Duke?), and my goal was to use those resources to change how science is done at Duke Neurobiology. I am pleased with how it has turned out. Duke Neurobiology now includes about 50 faculty across 17 departments in the Schools of Medicine, Engineering, and Arts and Sciences. But more important, we have an inclusive culture in which the faculty collaborate and interact. Also, remembering the impact the Sloan Center for Theoretical Neurobiology had at UCSF, I have been intentional about bringing theory and computation into the community. Again, I see a qualitative change in the way that many purely experimental labs are doing their science.

I never shied away from a leadership role. Spurred on by a postdoc colleague from the NIH days, David Friedman, I helped start an ad hoc Committee on Scientific Literacy for the SfN. Our committee played a big role in starting the SfN's initiatives in this area by organizing a symposium at the annual meeting of a high school science teachers society. I do not recall the details, but I think our ad hoc committee gradually evolved into the current standing Public Education and Communication Committee. I was elected treasurer of the SfN in 2012 and as treasurer I chaired the Finance Committee and served on the Audit Committee, the Investment Committee, and Council. I agreed to run for president of SfN once and lost to Rick Huganir. I had a vision for what I would have done if elected, but in the end, I merely was immunized against running again. I served as the chair of the Sensory-Motor Integration (SMI) study section and I have cochaired numerous study sections for the BRAIN Initiative. As a study section chair, I try to make a contribution to neuroscience by making sure that the review process is fair and unbiased, and that the applicants receive narrative feedback that matches their numerical scores so that they have actionable criticisms.

I was a high-level editor for two journals. For the *Journal of Neuroscience*, I served as section editor and senior editor for 10 years. I led the initiative

to take the manuscript handling and editorial processing online for the journal and was very closely involved in the design of the manuscript handling system we adopted. Given how we take this and much more for granted now, it is shocking to recall that I had to work against very considerable resistance. Once he was persuaded of its virtues, Marty Saggese, then the new executive director of the SfN, became a major ally in this effort and a very good colleague and friend for years since then. I took one year off from being an editor after my term ended at the *Journal of Neuroscience* and then became the associate editor for the International Brain Research Organization's (IBRO's) flagship journal *Neuroscience*, working under Ole Petter Ottersen for four years. Finally, I was the chief editor of *Neuroscience* for six years. Editorial service to *Neuroscience* is an important community service because the profits from *Neuroscience* provided IBRO's entire revenue stream in those days.

Mentoring

My contribution to science has been multiplied by a commitment to mentoring. In my own laboratory, I have mentored 15 PhD students and 29 postdocs. Of these, 32 remained active in scientific research (including 5 who are still in my lab) and most of the others have high-level positions in the for-profit or not-for-profit worlds. Many have gone on to have distinguished careers. Of my 44 mentees, 16 were women, and I received the Bernice Grafstein Prize from the SfN in 2011 to recognize my successes in mentoring women.

I devoted considerable effort to mentoring of junior faculty. At UCSF, I was a primary mentor for Allison Doupe (my late, great friend and coconspirator), Ken Miller, Michael Brainard, Philip (Flip) Sabes, Loren Frank, Eddie Chang, Vikas Sohal, and others. Three of them have gone on to become HHMI investigators and Eddie won the Blavatnik Prize for Young Scientists. Of course, the success of these scientists is a testimony to their brilliance, but I like to think that my guidance helped to channel that brilliance. At Duke, I have mentored Rebecca Yang, Anne West, Lindsey Glickfeld, Kevin Franks, Court Hull, Jeremy Kay, Greg Field, Eva Naumann, Anita Disney, Kafui Dzirasa, John Pearson, Nicole Calakos, Mike Tadross, Tim Dunn, Greg Cogan, Jeff Beck, Cagla Eroglu, and others. Many of these faculty are not in my department and are not among my direct reports, but I am a mentor-at-large and I offer free advice to anyone.

One of my major mentoring successes has been guidance in scientific thinking for Duke Neurobiology graduate students. I run the Neurobiology Study Section in a course called "Grant Writing," but I view the course as training in how to think about their own project in depth (for the first time for most of them) with a draft of a National Research Service Award (NRSA) application as a by-product. The study section has been enormously

successful and rewarding for me. I now have had the chance to guide each of the students in Duke Neurobiology in their science and their approach to science early in their career. They appreciate my style (tough love) and the excellent and honest guidance I give them, and so I serve on many PhD thesis committees and I provide informal mentoring for many of them. My office door is open and they seem to be comfortable coming to talk to me.

Perhaps my greatest success as a mentor was to help Richard O'Brien, chair of neurology at Duke, with the development of a successful application for an Alzheimer's disease Research Center (ADRC). Once again, my role was process. I didn't know much about Alzheimer's disease then, but I learned from Rich and I channeled his brilliance on how an ADRC should look at Duke into a process that ultimately identified (1) ideal leadership in Heather Whitson; (2) a fantastic and forward-looking set of cores; (3) a collaboration with our neighbor nine miles south in Chapel Hill, the University of North Carolina; and (4) a first-time application that was funded in 2021. My guidance and mentoring were necessary (but not sufficient) for this success. Credit goes to Rich's brilliance about Alzheimer's disease and to Heather's awesome organizational skills.

Animal Rights

The most difficult part of my career was 28 years of harassment by so-called animal rights groups. Fred Miles once told me that he would have quit science if subjected to the pressures I had experienced. I agree with him that it was incredibly tough. It wasn't just the episodic harassment, horrible publicity, demonstrations in front of UCSF, and fear for the safety of myself and my family. It was also the knowledge that even when it was quiet, the other shoe could drop without a moment's notice. I am and always have been resilient. Perhaps I was prepared for dealing with this kind of situation by the uncertainty I faced as a child as to when my stressed mother, as a widow at age 36 with 5 kids under 12, would explode in my face. I persevered.

It all started in about April 1983 when a well-known TV personality declared on Animal Rights Day in Davis, California, that my two monkeys, Beau and Captain, were being deprived of food and water for "some stupid experiment." The story broke all over the news media. UCSF's Institutional Animal Care and Use Committee (IACUC) summoned me to their meeting the next day. On the basis of what they had read in the news media, the IACUC was prepared to suspend my protocol. But Mary Dallman, a senior neuroendocrinologist in my department and an animal user pointed out that I had done nothing wrong. It wasn't my fault that an animal activist had broken into UCSF's animal facility, awakened my monkeys in the middle of the night, and taken photographs of groggy monkeys in unflattering light. At that moment, I joined a select club of neuroscientists who would experience animal activism, in some cases much more severely that I would.

We learned a lot from that first episode. Zach Hall's brilliant intuitions, personal counsel, and undying support made a big difference. We learned about the modus operandi of the animal activists, we learned that Richard Nixon's policy of stonewalling was a good one, we learned that I as the accused should never represent myself, and we learned that time almost always would heal all wounds. My good friend Rick Van Sluyters was a target across the bay at UC Berkeley and we coordinated and consoled each other with humor not fit for repeating.

I once sat next to an airline pilot on a cross-country flight and I asked him what it was like to fly a commercial airliner. His response: "hours and hours of utter boredom punctuated by moments of abject terror." My next 25 years after 1983 were similar. Plenty of time to do my science, punctuated by moments of frightening terrorist actions against me by the animal activist groups. Over the years, there were two public hearings on my research at the meetings of the San Francisco Board of Supervisors. Louis Reichardt led a large group of neuroscientists to pack the room for the first meeting and successfully overwhelmed a poorly prepared presentation by the animal activists. For the second meeting, my lab was bigger and more militant, and Megan Carey agreed to testify. When she answered that she had never seen any of the atrocities that were alleged, they asked her whether she had ever been to my "secret lab"! Megan still asks to see my secret lab. On a third occasion, around 2003, the Board of Supervisors was asked again to investigate. Gavin Newsom, now governor of California but then the chair of the Board of Supervisors (I think) threw out the first pitch at "opening day" for the San Francisco Little League. While my six-year-old son Theodore was getting a hot dog with the rest of his team, I approached the pitcher's mound and introduced myself to Gavin as "the guy at UCSF with the monkeys." I was all prepared with an elevator speech, but Gavin just said: "Oh, yes, we know about that. You have nothing to worry about."

I found it unsettling when the animal activists glued the locks on the front door at our home and then crowed about it in their blogs and on their websites. It was frightening that they knew who we were and where we were. As soon as the locksmith left the house, I walked the seven blocks to UCSF and straight to the office of the executive vice chancellor of UCSF, Eugene Washington. I burst through his assistant's office saying that I did not care what Gene is doing, I needed to talk to him. Gene immediately authorized 24-hour protection at the house and a security appraisal. The security professionals made quite a few recommendations, and UCSF had them done. Gene's responsiveness made a big difference to me and the family. At that time, I also made appointments to visit the head of school at both children's schools to educate them about the animal activist movement and how it was affecting us and to tell them what sorts of (very low probability) events they should be alert to. Those were not easy meetings.

Along with the negative publicity and overt attacks from outside, I also experienced challenges from legitimate regulators, namely the UCSF veterinarians and the USDA inspector. Whenever the USDA inspector visited, he went straight to my protocol looking for something marginal or wrong. We were diligent about animal care and animal welfare, thanks very much to my staff, Karen MacLeod, Elizabeth Montgomery, and Stefanie Tokiyama. He didn't find much and I didn't get into more trouble, but there always was the concern. My problems with our USDA inspector ended at an Annual Meeting of the *Society for Neuroscience*. I spoke on the *Animal Panel* about my experiences and about all the refinements we had made in my research on monkeys, including our decision to place the monkeys in sanctuaries when we were finished using them for research, rather than euthanizing them. Our USDA inspector was at that talk. He came up to me afterwards, introduced himself, and thanked me for my informative presentation. That was the end of my issues with him. I think it has been constructive to speak openly about what I experienced with animal activism and it is cathartic. I do not condone the activists' methods, but I also think we have come a long way since 1983 in ensuring the welfare of experimental animals in our labs.

Then and Now

Things have changed. In the 1970s, eye movements were the hottest model system on the planet and everyone wanted to record the electrical activity of single neurons in the brains of behaving monkeys. Now, eye movements have become a niche system. Monkey research is a tiny corner of neuroscience and is not expanding. New techniques have exploded serially into the field, taken over much of neuroscience research, and then retracted into their rightful place in the neuroscientist's tool kit. In the 1970s, it was single-unit recording in awake behaving monkeys. In the 1980s, it was tract tracing with horseradish peroxidase. In the 1990s, it was computational modeling and parallel distributed processing. In the 2000s, it was gene targeting knockouts and fMRI. In the 2010s, it was optogenetics and other molecular approaches. What is next?

At my first SfN meeting in San Diego in 1973, there probably were fewer than 2,000 attendees and it was very personal. I remember meeting Steve Kuffler in the hotel pool. Now, there are 30,000 attendees, and it can feel quite impersonal and difficult to connect. When I started my first faculty job in 1981, I activated my first R01 on the day I arrived. That was the rule; not the exception. Now, we counsel new faculty to wait a couple of years to apply for their first R01 and to live off their startup funds. It never occurred to me that my first grant would not be funded. Now I and everyone else worries about whether their first, next, or last grant will be funded. In the 1970s, a paper in the *Journal of Neurophysiology* was the pinnacle of one's career. Many of my most important papers were published in *JNP*.

Of the 152 papers on my CV, 22 appeared in what we think of as prestige journals and 101 in either the *Journal of Neurophysiology* or the *Journal of Neuroscience*. Now we value a paper by where it is published as much as by what it contributed. I don't like this change, but I understand that my trainees perceive a need for high-profile publications.

I understand that there always will be "then and now" and that those of us who were around for "then" will lament the changes that created "now." Still, science used to be smaller, personal, and supportive. Now it has become too big, quite impersonal, and cutthroat. I would like to see us return to the good old days to some degree. Science needs to be about advancing knowledge and improving our world, not about self-promotion. To go back to "then," the incentives will need to change.

People

Near the end of her life, my mother once said to me: "I have had a great life, except for the deaths of close family members." In her case, that included two husbands, one long-term boyfriend, a daughter, a sister, a brother-in-law, both parents, and both parents-in-law. I feel the same way about my career as a neuroscientist. I have had a charmed career, except for the deaths of close colleagues. Roy Steinberg was a fantastic scientist and a regular Saturday morning coffee companion at the Tassajara bakery in Cole Valley, San Francisco. Carol Basbaum was not a neuroscientist, but Allan Basbaum was a close colleague, friend, and adviser, and I admire how both of them dealt with her life and death. Allison Doupe was a treasured friend and colleague, and a coconspirator in the design and construction of the Sandler Neuroscience Building (originally "19A") at Mission Bay. I remember sitting on a bench outside the New Orleans Convention Center when I was recruiting Allison to UCSF, hearing her vision for how birdsong would conquer the world of neuroscience. She had it right, and she turned a lot of her vision into reality. I miss her terribly.

Science is full of great people and I have had the honor of knowing and working with some of them. The correlation between greatness as a person and stardom as a scientist is zero (or maybe negative). Some people are brilliant in life, some are brilliant in science, and a few are brilliant in both. I cannot even begin to mention the scientists (and nonscientists) who have been role models for me in some aspect of my life.

Chieko, Emika, and Theodore (also called Theo) have been great supporters and advisers. Chieko received a PhD from York University in experimental psychology with Ian Howard, so she understands the pressures and challenges of a life in science. She was always incredibly supportive of my need to work in all unscheduled moments and of the critical importance of travel for science. I've been equally supportive of her art career. I used travel to work intensely and I used travel to write, freeing up time to be with

the family on weekends and evenings. I recall sending her an email one day in a February or March that said, "My grant got funded, let's celebrate!"

She responded, "You wrote a grant?"

And I replied: "Yes, on airplanes last summer."

Emika once said to me: "Dad, I want to do neuroscience, like you do, but I need goals that are months away, not 50 years away." She gets science and as someone who goes all in on everything she does, she understands why I had to do the same thing. But she also appreciated that I would get up at 4:00 a.m. on Saturday to take her to a crew regatta and then would freeze by the water for the 30 seconds when I could see her boat come in. Theodore is like me in that he only does stuff that is relevant to him. He is the athlete I always wanted to be, and we have enjoyed many afternoons together at the ballpark—watching the Giants at AT&T Park or just working on his fastball at Grattan playground. Theodore is acutely aware of what is going on around him, much like his dad. He also knows as much about the past 50 years of music as anyone I know and always amazes me with the breadth of his knowledge about many things. We've had many special vacations as a family—most of them enabled by the miles I accumulated in my travels. And we have been healthy. I've been lucky.

Finally, just like everyone else in neuroscience, my science has been done by my students and postdocs. I succeeded because I sat on their shoulders. I was not able to mention all of them in the narrative, so I list them here without commentary in approximate chronological order. Almost all of them are stars in their chosen walks of life, and I am proud of them as my scientific children.

Students: Leland Stone, Edward Morris, Richard Krauzlis, Maninder Kahlon, Nicholas Priebe, Mark Churchland, Justin Gardner, Anne Churchland, Megan Carey, David Schoppik, Sonja Hohl, John O'Leary, Jennifer Li, Ramanujan Raghavan, Timothy Darlington, Stuart Behling.

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