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Michael Paul Stryker

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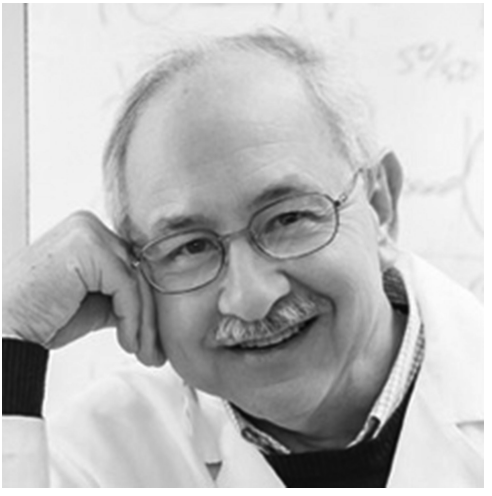

Michael Paul Stryker

Born:

Savannah, Georgia
June 16, 1947

Education:

Deep Springs College, Deep Springs, CA (1964–1966)
University of Michigan, Ann Arbor, MI, BA (1968)
Massachusetts Institute of Technology, Cambridge, MA, PhD (1975)
Harvard Medical School, Boston, MA, Postdoctoral (1975–1978)

Appointments:

Assistant Professor of Physiology, University of California, San Francisco (1978–1983)
Associate Professor of Physiology, UCSF (1983–1987)
Professor of Physiology, UCSF (1987–present)
Visiting Professor of Human Anatomy, University of Oxford, England (1987–1988)
Co-Director, Neuroscience Graduate Program, UCSF (1988–1994)
Chairman, Department of Physiology, UCSF (1994–2005)
Director, Markey Program in Biological Sciences, UCSF (1994–1996)
William Francis Ganong Endowed Chair of Physiology, UCSF (1995–present)

Honors and Awards (Selected):

W. Alden Spencer Award, Columbia University (1990)
Cattedra Galileiana (Galileo Galilei Chair) Scuola Normale Superiore, Italy (1993)
Fellow of the American Association for the Advancement of Science (1999)
Fellow of the American Academy of Arts and Sciences (2002)
Member of the U.S. National Academy of Sciences (2009)
Pepose Vision Sciences Award, Brandeis University (2012)
RPB Stein Innovator Award, Research to Prevent Blindness (2016)
Krieg Cortical Kudos Discoverer Award from the Cajal Club (2018)
Disney Award for Amblyopia Research, Research to Prevent Blindness (2020)

Michael Stryker's laboratory demonstrated the role of spontaneous neural activity as distinguished from visual experience in the prenatal and postnatal development of the central visual system. He and his students created influential and biologically realistic theoretical mathematical models of cortical development. He pioneered the use of the ferret for studies of the central visual system and used this species to delineate the role of neural activity in the development of orientation selectivity and cortical columns. His laboratory pioneered the modern use of the mouse visual system, demonstrating rapid activity-dependent plasticity during a defined critical period and delineating distinct molecular mechanisms responsible for temporally distinct phases of plasticity. In collaboration with the Feldheim group at UCSC, he revealed the interaction between neural activity and molecular signaling mechanisms responsible for the formation of azimuth maps in V1 and superior colliculus and the connections between them. His and the Alvarez-Buylla laboratory discovered that transplantation of embryonic inhibitory neurons into postnatal visual cortex induces a second critical period of juvenile plasticity. His laboratory made the fundamental discovery of the regulation of V1 cortical state by locomotion and delineated much of the neural circuitry responsible.

Michael Paul Stryker

Chance and Choice: Recollections of a Life in Science

Origin and Early Life

My parents could not have been more different from one another, and only in the circumstances of World War II would they ever have met and married. My father was a southern Catholic raised in Memphis, Tennessee, descended from early residents of New Amsterdam via Penn Yan, New York. His grandfather, George Bailey Stryker, had been an inventor and entrepreneur who built a factory that made a particleboard from cotton husks and stalks. The family lost all its money in the Depression to the point where my father and his cousins were sent to work on the farms of distant relatives during the summers so that they would eat well there. My father did manage to go to the University of Mississippi for an accelerated bachelor's degree of science in engineering before enlisting in the Army after Pearl Harbor. The Army sent him to a civil engineering graduate course at Yale and ultimately to a landing ship tank that left Puget Sound with an engine room, but with its superstructure to be constructed en route to islands in the Pacific. The ship carried an all African-American engineering battalion commanded by all southern white officers. They invaded and built air fields on a succession of islands and ended up on Okinawa in preparation for the invasion of Japan.

My mother was the second child of Jewish atheist immigrants from Galicia who had fled the pogroms for New York, ending up in Newark, New Jersey. Her mother was one of nine siblings, eight of whom immigrated to the United States over a 15-year period; the last sibling had to go to Brazil instead after U.S. immigration was closed to east European Jews. My mother's much-older brother was an intellectual, dirt poor but educated at City College and friends with many struggling New York artists, writers, and actors of the 1920s like the Provincetown Players on MacDougal Street in Greenwich Village. He took his young sister there to premiers of Eugene O'Neill plays and hung out afterward with the creators. My mother worked her way through nurse's training and was at New York Hospital at the time of Pearl Harbor. She enlisted in the Army Nurse Corps and was sent to the Pacific, where she took care of injured Merrill's Marauders and the air crews that flew "the hump" from Burma to Chunking. She, too, was sent to Okinawa for the invasion.

With a few hundred nurses on an island with more than 50,000 U.S. soldiers, it seems unlikely that my mother and father should have met,

fallen in love, and become engaged. I can only imagine that each was searching for something different from what was expected of them—a nice Jewish doctor for my mother and a southern belle for my father. As it turned out, they were the only members of that generation of their two large extended families to marry outside their cultures.

My mother returned to her family in Newark a few months after VJ Day. My father's unit took much longer to get home. He had encouraged my mother to visit his family in Memphis, where she felt she was shunned by everyone except the ailing matriarch, my father's great grandmother, who appreciated the nursing care that my mother provided for a couple of weeks. My parents were married in New Jersey about a week after my father returned from the Pacific, and I was born 10 months later. It seemed that the New Jersey family was less hostile to my father than the Memphis family had been to my mother, or perhaps he just had thicker skin. In any case, we never lived near either side of the family all the time I was growing up. It is only in my generation that the cousins have become friends.

My father worked as an engineer and later superintendent for construction companies that built public infrastructure, things like airfields and water and sewage plants. From the time I was born in Savannah, Georgia, until I was six, we moved to eight different cities, mostly in the southeast. My three brothers were born at about three-year intervals after me. From the beginning of my first grade, we moved less frequently, at two-year intervals. The result was a close family, with the ability to make new friends fairly quickly, but with a high degree of self-sufficiency. I was usually happy to read books by myself when there was no one I knew to play with.

We were tremendously lucky to move to a very small town on the side of a wooded mountain across the river from Williamsport, Pennsylvania, when I was six. First- and second grade were in a tiny school with fewer rooms than grades and a beautiful outdoor environment. School was easy for me, and I didn't like to sit still or keep my mouth shut. As a result, I was the only student repeatedly paddled by the first-grade teacher. The mild paddling was humiliating, but the only injury was to my ego, and it helped me become less disruptive between blessed recess periods. My parents learned about the paddling only at the year-end parent-teacher conference when the teacher, who looked like Mrs. Santa Claus, confessed that her ancient ruler, with which she had paddled the chair of the school board 35 years earlier when he was in first grade, had broken on me. My father made a lovely hickory paddle for her the following week. I will always admire the respect that this wonderful teacher showed for me by not complaining about my behavior to my parents and by treating me as a young person able to improve and become more civilized. Her instruction using a phonetic approach to reading was so good that by the end of first grade I could read adult magazines and

books, although I preferred *The Hardy Boy*s and *Tom Swift Jr*., along with *Popular Mechanics*.

In that small town, I and two friends my age worshiped a neighborhood boy four years older who let us help him make soapbox derby racers, take apart and repair gasoline lawnmowers, and make a go-kart. He allowed us to come on all-day hikes and helped us climb cliffs that would have terrified our parents had they known. This small rural town gave us a sense of freedom and self-sufficiency that few children today can experience. It is sad that all of the children we knew who went on to college had to leave that town for jobs elsewhere.

Life for the next few years was quite ordinary, with new schools every other year. The most unusual feature of my upbringing in those years was that my father gave me word problems that taught me mathematics—algebra in third grade, logarithms in fifth, and calculus in sixth grade. He did not pose them as math problems, but as physical ones. One I recall clearly because I struggled with it for some time was calculating how long it would take for an inverted pyramidal sink to drain. I knew that it would drain at a definite time, and my father confirmed that the amount of water flowing down the drain would be proportional to the depth of water in the sink. I calculated the time to drain inch by inch, then quarter inch by quarter inch, but I did not know how to calculate it exactly, or even approximately other than by brute force. Only then did he show me the tricks that everyone learns in first year calculus—equations with derivatives and integrals.

For my seventh-grade year, we moved to a house in Winthrop Harbor, a small town in Lake County, Illinois, that was 200 m from Wisconsin and 300 m from Lake Michigan. After some standardized tests early in the year, the principal of the small junior high school called my parents in and told them that his school could not give me an appropriate education and that he wanted to put me in eighth grade immediately so that I could go to high school more quickly. Combined with my being the only new boy in the school, this change engendered some resentment. I was also the smallest boy in seventh grade, and by far the smallest after I was moved to eighth, so I was beaten up by the other boys quite a few times until I learned to fight well.

Apparently, Lake County had never voted Democratic in a national election since the Republican Party was founded, and our town was ultraconservative and dominated by the American Legion veterans' organization. Even though both of them were war veterans, my parents were excluded and regarded as Communists because they believed in civil rights for Negroes (as African Americans were then called) and were registered Democrats. It was galling to the community when I received the two academic scholarships awarded at eighth-grade graduation—one of which was from the American Legion. The openly expressed racial and religious prejudice that led to my parents' exclusion from the community had the good effect that they were forced to find adult company in the Unitarian fellowship in Racine,

Wisconsin. The Unitarians were then and for many years thereafter one of the few majority white organizations to join in the civil rights struggle led by the black churches in the south.

There were so few people like my parents in Lake County that they became de facto party leaders despite having lived there for only one year, and we were invited to the Democratic Party picnics at Adlai Stevenson's farm. My first year in high school (ninth grade) in Zion, the larger town to whose school Winthrop Harbor students were sent, was also the year of the first televised presidential debates, between Kennedy and Nixon. To foster civics education, the principal of the high school scheduled debates between two students in front of the whole school for the day after each of the four television debates. Many seniors vied to be the surrogate Nixon, but there were no volunteers to take Kennedy's part from the 10th, 11th, or 12th grades, and only one, me, in the 9th grade. So I debated as the liberal candidate against different seniors. This practice of standing up for unpopular views served me well years later in my scientific career.

For me that year was bearable because of two outsider ninth-grade friends, one an Armenian who came to the United States with his family via Persia, Lebanon, and Brazil, and was fluent in all of the languages of his earlier life, and the other a local Robert Redford look-alike farm boy who read too widely to be content with the prejudiced attitudes of the community. Our greatest joy was making rockets that we launched from the Lake Michigan beach. Looking back, it seems only good luck that we did not blow ourselves up. After getting some rockets with single-shot cameras 2,000 ft into the air, our rocket career ended with launch of our 4-ft stainless-steel magnum opus, with a ceramic nozzle. It blew up on the launch pad and started a fire in the woody area above the beach. Hearing the sirens, we ran from our slit trench and fortunately were never caught.

For 10th grade, we moved to Oxon Hill, Maryland, a then mostly rural suburb of Washington, D.C., south of Anacostia near the Naval Research laboratory on the Potomac River, with many military and State Department families who moved as often as we had. As I recall, the 4-H Club was the largest student organization in the high school. However, nearly all the fathers of the students in the science club except mine had doctorates. The school had a few inspiring teachers—an English teacher for me; and, while sometimes oppressive, the school generally did all it could to make life easy for its best students, never penalizing me for missing school to do civil rights activities or regional theater, and sending me to the University of Maryland in the evenings for a graduate-level history seminar.

Civil rights activities, mostly through the Unitarian youth groups, were also important to me during high school. Virginia was a southern state, and its schools were then still mostly segregated, despite the seven years that had passed after the *Brown v. Board of Education* decision. Many of its restaurants refused to serve African Americans, and we high school

students went in nice dresses, sport coats, and ties in mixed-race foursomes, after which we circulated to area churches a boycott list of restaurants that would not seat us. Participating in marches and protests, like the 1963 one on the mall at which Martin Luther King gave his "I Have a Dream" speech and Peter, Paul and Mary sang, made us feel as if we were doing something worthwhile. Later, I regretted that, apparently lacking the courage of my convictions, I had not gone down to Alabama and Georgia with some of my friends to work on voter registration during the summers of 1962 and 1963. I was consumed by guilt for not being in Selma when our Unitarian youth group leader, the Reverend Jim Reeb, was murdered during my first year of college.

Never a sports star, I enjoyed my only experience as the object of cheerleading when our school's team won the championship for two years in a row on what became the longest-running television quiz show in history, *It's Academic*, competing against the Montgomery County and other east-coast schools that were more highly regarded. We won again after my two teammates from the grade above mine left for college at Harvard and Caltech.

A highlight from my high school years was a National Science Foundation (NSF) summer program in mathematics and computers at Virginia Tech in Blacksburg. There I was, for some weeks, given sole charge of the school's IBM 1620 from sometime after midnight to 5 a.m. to write a Simplex Method code that checkpointed itself frequently so that it could restart from where it left off after the computer broke down and was repaired. This was necessary for the program to run to completion because the computer broke down frequently; the IBM repair people seemed always to come within an hour or two after being summoned. This early experience with computers was crucial four years later to my becoming a neuroscientist.

A second high-school highlight was the production of an unauthorized satirical antiwar newspaper that got me and my co-conspirators expelled near the end of the year. The school administration realized they had made a mistake in expelling all of the school's few students who had been admitted to selective colleges, and they let us return to school and graduate.

College Years

In my junior year of high school, after doing well on the PSAT, I received an intriguing brochure from the Telluride Association, one of the two surviving educational projects of L. L. Nunn (Newell, 2015), who built the world's first long-distance AC transmission line and founded the electric power industry in the western United States. The Telluride Association ran summer programs in philosophy, the arts, and politics at Cornell for bright high school students. I was already planning to go to the NSF summer program in mathematics and computers at Virginia Tech, so it was the back page of the brochure that intrigued me—a description of Deep Springs College,

L.L. Nunn's other surviving project, a long-running educational experiment founded in 1917. Deep Springs, located in a high-desert valley on the California–Nevada border, had only 5 professors and 25 students pursuing an educational program in an intentionally isolated community that combined rigorous academics with genuine student self-government and labor to run a cattle ranch. After two or sometimes three years at Deep Springs, students transferred elsewhere for the final two years of their bachelor's degree. After learning about Deep Springs, my plan to go to Yale, where I was offered enough scholarship support to make it possible, seemed too conventional.

Never having been west of the Mississippi, I flew at age 16 to Los Angeles to catch a bus up the Owens Valley to Deep Springs. My father's parting words, as I boarded the airplane, were "Son, if you are going to do something that will worry your mother, don't write home about it." Deep Springs was a fantastic adventure as well as a spectacular education in academics, responsibility, and self-reliance. I arrived thinking that I wanted to be a poet like the one I most admired, Gerard Manley Hopkins. An intensive writing and literature class for the 11 new students with our Rhodes Scholar professor cured me of that ambition but gave me an appreciation for rhetoric and "the grand style" of 18th-century writing. The calculus courses over the two years used the same curriculum as at Caltech and inspired in me the hope that I could be a mathematician as our class size dwindled from 10 to 2 or 3. Economics, philosophy, and music theory courses all had one or two students and did a regular college year's work in one semester. The German course was taught by a former Polish cavalry officer who told us that he was prompted to escape from a prisoner-of-war camp by the German commandant shortly before the other captives were executed only because he could discuss literature and high culture using the subjunctive properly. The professor required us to memorize tens of lines of poetry for each class meeting. I still love reciting German romantic poetry; indeed, doing so mentally was the only way I avoided screaming from claustrophobia during my one cranial MRI 50 years later.

The unique self-government of Deep Springs gave me experience in working effectively with very different people. It also gave me an opportunity in taking responsibility, first for the community water supply by repairing its 50-year-old redwood pipeline, and later for the herd of 250 cattle through five months of a winter and spring. Finally, it also gave me practice in leadership, as the labor commissioner responsible for the work assignments of all the other students to meet the needs of the college and ranch.

The only element of my ideal liberal arts education that Deep Springs lacked was women. I managed to see my high-school girlfriend, who studied fruit fly biology at the University of Michigan, by hitchhiking to Ann Arbor, and I looked forward to transferring with her to Yale for our

junior years, which we understood had proposed to become coeducational in the fall of 1966. Yale deferred coeducation, and I certainly did not want to continue at a single-sex institution. My Deep Springs math teacher told me that the mathematician he most admired, the Hungarian Paul Halmos, was on the faculty at Ann Arbor and that I should go there to study with him. Ann Arbor had the additional advantage of having a leading philosophy department, the other subject I was most interested in. So off to Ann Arbor I went, landing in the campus that was a center of anti–Vietnam War activities.

Ann Arbor was huge, the opposite of Deep Springs, and I found myself with five other students in the junior year of the honors math program. I struggled during the first semester, never finishing more than 30% of a test, and I was certain that they were going to kick me out. They didn't, and only midway through the year did I find out that all but one of us were in the same boat and were thought to be doing fairly well. The one student, however, was qualitatively different—he not only finished the exams but also proved additional related theorems. It became clear to me that I could never become a creative mathematician—they seemed to have a different kind of mind, like musical prodigies. I needed to find something else to do, something at which I could hope to excel.

At this point, working on antiwar activities became important for my sanity—helping to organize teach-ins, giving speeches, and doing what I thought was important work for society. By the next year, I was disgusted to see that most of the students were not so much antiwar as they were anti-draft, wanting to preserve their deferments that kept them from joining the mostly poor people sent off to fight and die in that immoral colonial war. The next year, I gave up with the students and worked on Gene McCarthy's anti-war presidential campaign in my spare time. It is hard to convey the joy in our car coming back to Ann Arbor from campaigning in Milwaukee for the Wisconsin primary when we heard on the radio LBJ's speech stating that he would not run for reelection. We never dreamed, of course, that LBJ's decision to bow out would lead to Nixon's election.

Not smart enough to excel at mathematics, I switched my major to philosophy because I thought it was interesting and important. I continued to take what I then thought of as *real* science courses, physics and chemistry, but not biology, catching up on what was not offered at Deep Springs. Staying awake through philosophy lectures, even by philosophers whose written work I admired, proved a challenge, but the questions of meaning, ethics, epistemology, aesthetics, and mind were exciting. I thought that the argument of my philosophy honors thesis was an important one, and I could not see how its conclusion had escaped the leaders of the field: that many philosophical arguments about the distinction between necessary and contingent truth were empty because they depended on contingent facts about the meaning of words. Not surprisingly, the philosophers hated what

I wrote, and I came to believe that real philosophers just wanted to keep arguing, even when a conclusion had become clear.

With three younger brothers for my parents to educate, I wanted to cost them as little as possible, so beginning after Christmas of my junior year I looked for the highest paying job available to undergraduates who could work 20 hours per week. Cleaning rat cages was the winner—it was considerably more lucrative than any other, even counting the necessity for an unpaid shower and a change of clothes afterward. The Brain Research lab, in a falling-down Civil War–era hospital at the edge of campus, was the domain of James Olds, co-discoverer of self-stimulation, the so-called pleasure centers of the brain. His wife, Marianne E. (Nicky) Olds, who had done her doctoral work with the famous Harvard philosopher Willard Van Orman Quine, functioned as the lab manager and was my boss. I enjoyed chatting with her about philosophy and was invited to see what was going on in the lab and to come to the Saturday morning meetings of all personnel, where the criticisms of research presentations could be blistering. In those days, the goal of the lab was to map out the brain regions mediating self-stimulation to locate the neural circuit responsible for reward. Large numbers of rats with stimulating electrodes in different brain sites worked in cages with the stimuli controlled by transistor logic boards wired together with relays; any change in the experiments required rewiring. A Digital Equipment PDP8 computer had just arrived, said to be the first one to have left Massachusetts. I told Nicky that I knew how to program computers and could work with Phil Best, an assistant professor in the group, to make it replace all the hard-wired logic boards used to control and monitor experiments. Thereafter, I no longer had to clean rat cages.

The PDP8 would barely be recognized as a computer now: it had 12-bit words, 4096 memory locations, no operating system, and was programmed in machine language. When you turned it on, you had to set switches on its console to put a program in memory that would read a paper tape with holes punched into it that allowed it to drive a teletype. But it could in principle be made to control and monitor the rat experiments using analog-to-digital and digital-to-analog converters and draw graphs on a pen plotter. I programmed it to, among other things, write letters and numbers on the plotter so that we could annotate experiments, and my first publication (after the newspaper that got me expelled from high school) was this program (in the *Proceedings of the Digital Equipment Users Society*). More important, I became actively involved in the lab and got to know Jim Olds, whom I have regarded ever since as a genius who surely would have won the Nobel Prize had he not died young. I read extensively about brain research, and despite my never having taken a biology course since high school, he and Dr. Best let me carry out an experiment of my own design using cortical spreading depression to probe the laterality of learning a visual task.

The endless arguments of philosophers, based on shaky evidence, came to seem tedious to me, and I thought that we in the Brain Research lab might make real progress toward figuring out how the mind actually worked.

Peace Corps in East Africa

Midway through my senior year, I had to decide what to do next. I felt that I had been in school all my life up to that point and that the easy path was to go to graduate or medical school just because I had been good at that sort of thing. I also felt an obligation to serve the country some way other than by going to war, and I had long been interested in East Africa and Kenya's struggle for independence, having followed the careers of inspiring figures like Jomo Kenyatta and Tom Mboya, a Jack Kennedy–like figure in Kenyan politics. British Prime Minister McMillan had given his "Wind of Change" speech committing Britain to freeing its African colonies, and the former colonies were trying to succeed in the first few years after independence. President Kennedy had created the Peace Corps to help these new countries. I decided that I wanted to go to East Africa as a Peace Corps volunteer.

Like Deep Springs, the Peace Corps was a great adventure. My experience as a land surveyor (taught by my father) and in designing and constructing an extension of the irrigation system at Deep Springs qualified me for a job as an "assistant hydraulics engineer" for the government of Kenya. The others in this job were actual engineering graduates. At that time, there were only four East African graduate engineers in all of Tanzania, Uganda, and Kenya, so that except for a big hydroelectric project done by USAID contractors, most of the water engineering in Kenya was done by about 15 Peace Corps volunteers, a similar number in total of Swedish and Dutch volunteers, and about 20 British contract engineers. In Peace Corps training at a former prisoner-of-war camp in Bismarck, North Dakota, we learned Swahili and the cookbook engineering needed to design water distribution systems before going to Africa. At independence, the government of Kenya had purchased the huge (20,000 acre+) European farms that their owners wanted to sell and divided them up into hundreds of 10–40 acre plots to sell to the former employees of each farm. Once in Kenya, we volunteers met with the new farmers and arranged with them to get loans to distribute water for domestic and dairy use to each plot. With a slide rule and aerial photographs and stereo glasses, along with some finished contour maps, I designed the water systems under kerosene lanterns at night and constructed them during the day with labor contributed by each farm that was to be served. I spoke only Swahili for weeks at a time and became part of the community—we volunteers were very popular because the communities wanted and needed the water systems. Zebras, all kinds of antelope, warthogs, and water buffalo were a continual presence in my yard, along with occasional scarier things, and during several breaks I took trips with

other volunteers to many of the famous sights of that part of the world. Life was genuinely thrilling.

Nevertheless, after a year and some months, I wrote to my brother and asked him to send me the giant book I had seen just before my departure from Ann Arbor: *Neuroscience: A Study Program* (Quarton et al., 1967). I found myself wanting to think about the mind and how it could be studied scientifically rather than continuing to work in development or in the foreign service as some of my fellow volunteers did, some of whom later became U.S. ambassadors. I decided to apply to graduate school. By this time, the Olds lab had moved to Caltech. I was sure that Jim Olds would have me as a student, but I felt that I had learned much of what he would have to teach me, and if I were to go to Caltech I wanted to work with Roger Sperry. I wrote to a friend there to ask if Sperry liked graduate students and heard that he did not. My first choice was then the Institute for Neurological Science at Penn, where the work of Jim Sprague and C. R. Gallistel intrigued me, but I was not accepted there—perhaps not surprising for a philosophy and mathematics major who had never studied any biology. In the giant book, the only neuroscience book that I had, were several fascinating articles from members of the new department at MIT called Psychology and Brain Science. By some miracle, MIT accepted me, probably because they knew that Caltech had done so, and I decided to go there. After this decision, I wrote a long letter to Professor Gallistel outlining the neurophysiological experiment that I thought would answer a question he was pursuing by other means, and two weeks later got a thoughtful reply together with an acceptance at Penn and the offer of a fellowship. But it was too late—I was looking forward to MIT.

Graduate School at MIT

Five days after returning from East Africa, in 1970, I drove my motorcycle from my parents' house near Washington, D.C., up to Cambridge and found the remnants of a commune, "The Old Mole," to live in together with three Quakers who had been active in the antiwar movement. From what I had read in East Africa, Professor Peter Schiller's work on vision in human subjects and alert monkeys seemed most exciting, so I was slated to join his laboratory. He, however, was on vacation with his family on an island in Maine for another couple of weeks. During those weeks, four different senior graduate students came to me one by one to say that I would hear horrible things about Professor Schiller and that, while they were true, I should not change my mind about working with him because it would be worth it. They were correct. Peter taught me how to be the scientist that I am.

It is hard to convey the excitement and the exhaustion of the first year and one half of graduate school. While the five of us in my entering class

had a half-day seminar three times a week that involved massive night time reading, the rest of my time was spent in Peter Schiller's laboratory. Other alert-monkey laboratories spent months training monkeys to fixate a spot of light on a screen before making recordings. During these periods of fixation, the eyes remained in known position, and one could plot visual receptive fields, which are fixed on the retina. Peter had devised a creative strategy that allowed him to study the relationship between eye movements and vision in untrained monkeys—immobilizing one eye by sectioning the nerves that innervate the eye muscles (the fourth and sixth cranial nerves and the ophthalmic portion of the third cranial nerve). The surgery was almost impossibly difficult, and the immobilized eye was then patched so that the animal did not have double vision. Because most eye movements are conjugate, where the two eyes move at the same time and by the same amount, he could study eye movements of the intact eye and then occlude it and remove the patch over the immobilized eye to study visual responses. I got a notion of what the senior graduate students had warned me about when one day Peter did not show up for the difficult monkey surgery, in which I had always assisted, leaving a telephone message that I should do it. I did it, a real challenge. I probably would not have agreed to do so if he had asked me the day before.

For the first few months, Peter would set up a monkey with an electrode in the frontal eye fields, and I would record from neuron after neuron, studying it in relation to eye movements and never finding a visual receptive field. We then went on to study the superior colliculus, where we found visual and eye-movement cells in different layers, and some cells that were active with both visual and motor activity. When we stimulated through the recording electrode, we made the discovery that activating those cells caused an eye movement that brought the eyes to fixate on the location of the visual receptive field. This was a major discovery, and it gave me the enormous satisfaction of seeing two figures I had drawn for our paper (Schiller and Stryker, 1972) appear in the next edition of Mountcastle's *Physiology*, the definitive textbook used in most medical schools.

Our major competitors in this area were Bob Wurtz and Mickey Goldberg at the National Institutes of Health (NIH), who used trained monkeys and studied both the frontal eye fields and superior colliculus. They had found that many of the frontal eye field neurons had visual receptive fields, and I was therefore convinced that we and they must have been recording from different areas. I went down to the NIH, and Bob generously showed me the histology with their electrode tracks, confirming that the brain areas were exactly the same. From this I concluded that the frontal cortex was amazingly plastic, and that the visual receptive fields had been created by the fixation training, a hypothesis that has by now received lots of support from other studies, but one which has never been rigorously confirmed by studying the same neurons before and after training.

Wurtz and Goldberg scooped us on some of our colliculus work, but our rivalry was also one of friendship and mutual respect. When their paper (Wurtz and Goldberg, 1971) was accepted in *Science* before ours was out, they sent us copies of the galley proofs, which we read in the dim light next to our monkey rig. They concluded that these superior colliculus neurons were modulated by *attention*, as indicated by the monkey's looking at the place where the visual receptive field had been, whereas we thought of them as being command motor neurons for moving the eyes, as well as having visual responses. Peter Schiller's joyful comment was "They missed the boat—no, they missed the ocean!" It is interesting that the idea of attention, something we thought at the time to be soft and unscientific, has persisted as its neural substrates have gradually been uncovered, as has the notion of the superior colliculus's containing command motor neurons.

Rivalries like ours with Wurtz and Goldberg are tremendously positive for neuroscience, particularly when the groups are pursing different approaches to the same end. We certainly worked harder knowing that they were onto the same problem, and we clarified our thinking and experiments as ammunition for our conclusion against theirs, yet both groups shared everything they knew when we met. It really was us all working together against the unknown. Peter's and my later experiments on the superior colliculus, including turning on and off its cortical input by cooling, were more fun and satisfying than almost any I have done since (Schiller et al., 1974).

Thesis Project

After my apprenticeship working directly with Peter, he set me free to pursue my own choice of thesis project. I was fascinated by the question of how the brain organizes its precise connections during development, and I had made my own mathematical models of self-organizing systems. While Hubel and Wiesel (1963) had concluded that the organization of the visual cortex was innate, with receptive fields in very young, visually inexperienced cats having basic properties similar to those in mature animals, young colleagues of Horace Barlow at Berkeley, including Jack Pettigrew and Colin Blakemore, presented exciting evidence that visual experience organizes responses (and presumably synaptic connections) in the cortex during early life. The most dramatic reports were Pettigrew's (1974) that neurons required visual experience to become selective for stimulus orientation and Blakemore and Mitchell's (1973) report that all of the neurons in the visual cortex of cats deprived of vision except for parallel stripes inside a cylinder became selective for the orientation of the stripes. I remember the sentiment among most participants at the Rochester vision meeting in 1972—that it was a shame that Hubel and Wiesel had not yet been awarded their Nobel Prize because their error concerning the innate organization of

the visual cortex would detract from their otherwise-monumental discoveries and disqualify them as candidates. This sentiment appears crazy in retrospect, but I shared it. My thesis proposal was to figure out the mechanism of this self-organization by first making it happen on the table in an anesthetized cat.

This work required that I raise cats so that they had absolutely no visual experience and ensure that the neurons studied were a representative sample from the visual cortex that could not have come from a single orientation column. Fortunately, Alan Hein's laboratory at MIT had a room for total dark-rearing of cats, and I optimized electrode penetrations to travel parallel to the layers of the visual cortex, nearly perpendicular to the columns. The greatest challenge for my experiments, however, was to come up with a way to measure the selectivity of cortical responses quantitatively and objectively. Peter also needed to do this for experiments that he planned. At just that time, our department had installed its first PDP11 computer, and it was in a room next to our physiology lab. This was a time long before bit-mapped video monitors were available, and the only way to produce sharp, orientated contours for visual stimulation was with a slide projector. Peter designed a rectangular mechanical aperture that could be rotated 360 degrees and whose four sides could be positioned independently, all using stepper motors. We mounted this in an optic bench, essentially a fancy slide projector, and moved the image of the aperture using galvanometers with mirrors. I wrote the code and wired the electrical interface that allowed the computer to control the optic bench and to record the trigger pulses set off by an action potential in the neuron we were recording. Together, we had created the world's first computer-driven optical display capable of producing randomly interleaved light bars of arbitrary size and orientation. This was precisely what we needed for quantitative results.

While the quantitative system was under construction, I went ahead with my proposed experiment on my own, recording from a few single neurons that had to be in different orientation columns for many hours and repeatedly mapping their orientation selectivity by hand, as everyone else had always done, between hours-long sessions of exposure to parallel stripes of a single orientation. After many 36- to 48-hour sessions, my results showed a slight change toward the exposed orientation. I wrote up a manuscript on this and took it to Peter for his approval before submitting it for publication. He read it silently, smoking his pipe as I sat in his office, then crumpled it up and threw it in the trash can, saying "Michael, we don't publish sh*t like this from my lab." I left, but in the next few days, he told me all the things that were wrong with my experiment. In retrospect, I am grateful for having been prevented from publishing a bad paper with an incorrect result produced by wishful thinking, despite my strong belief at the time that I was being objective. In any case, it was clear that the quantitative measurements were needed.

I had the great good fortune to be joined in my thesis project by Helen Sherk, a brilliant student from a class a couple of years behind me. Once the quantitative system was working, Helen and I studied very young, visually inexperienced cats and found that the first neuron we recorded was perfectly selective for stimulus orientation, as were nearly all the others. So much for the idea that the organization of the visual cortex required visual experience. Still, our finding of innate selectivity made the Blakemore and Mitchell (1973) report that all neurons became selective for the orientation of stripes to which they were exposed even more exciting, for it indicated a dramatic plasticity. We repeated my earlier experiment using the objective measurement of responses after visual stimulation of anesthetized animals and saw no evidence of plasticity. Only then did we realize that we had to confirm the earlier report before trying to extend it. We replicated the striped cylinders and rearing procedure as closely as possible from the published reports and found no indication that the rearing had any effect when measured objectively. However, Helen realized that when the animals looked up and down, they were exposed to many orientations, so it seemed possible that our attempt at replication was flawed if our cats had looked up and down more than the ones in the original report. Our *Science* paper about this (Stryker and Sherk, 1975) caused great controversy: we seemed to be denying one of the most exciting findings in neuroscience, one that by this time had made it into most psychology textbooks.

The controversy had become transatlantic with the return of Blakemore to the mother ship of neuroscience, the Physiological Laboratory at the University of Cambridge. It was clear that our targeting of penetrations oblique to orientation columns and our objective measurement of responses were appropriate, but we had no way to ensure that something about the visual experience was different in our lab from that in the earlier report. We agreed on a collaboration in which the animals were reared in the Blakemore lab in England with exposure to either horizontal or vertical stripes and sent for recording at MIT, with the results to be presented at the next meeting of the Association for Research in Vision and Ophthalmology (ARVO). All of the visual cortex labs went to ARVO in those days, along with other vision scientists and ophthalmologists engaged in research. Helen and I recorded from the animals blind to their rearing conditions, and when the recordings from all the animals were finished and the data were in the computer and being printed out, we phoned Colin Blakemore to ask how each animal had been reared. He wouldn't tell us. He wanted to know what the results from each animal were first. We ended the conversation feeling totally paranoid. Indeed, the collection of neurons from each animal had a slight bias toward one orientation or another, but it was no more than would be expected from a random sample from a normally reared cat. If, however, the slight biases were consistent with the rearing, the result would be taken as at least a weak confirmation of the Blakemore and Mitchell (1973) report.

We took our dilemma to Professor Emilio Bizzi, whom we regarded as fair and wise and whose own work was sufficiently distant from the visual cortex. Emilio made arrangements for an escrow procedure in which the results of our recordings and the English rearing were held both in Europe and the United States before being compared. As we suspected, the rearing had no effect on the orientation preferences of the visual cortical neurons. Indeed, the random biases were slightly in the opposite direction to the orientation exposed during rearing.

I went ahead with our agreed plan to present the results at ARVO and was surprised to find that our English collaborators were missing. To lighten the considerable tension in the audience, I had used black carpet tape to make a white shirt with vertical stripes on the front like those on many shirts, but with horizontal stripes on the back. I took care to keep my back away from the audience as I started my talk. After going through the rationale and the methods, I first showed the results from the animals exposed to vertical orientations—neurons with a wide range of preferred orientations, but slightly fewer for vertical than for others. I then said that now I would show the results for the animals exposed to horizontal contours and turned around as the next slide came up. The audience exploded in laughter, and I was happy that laughter rather than anger was the result of our clear failure to replicate the famous experiment.

The anger came later, and transatlantic mud was cast widely at my name. How could I make fun of such an issue? Our MIT department supported me and Helen fully, and the shouting eventually died down. We went on to publish our quantitative findings on the development of orientation selectivity without visual experience (Sherk and Stryker, 1976), which was just as Hubel and Wiesel had shown years earlier with hand plotting. We also then collaborated with Helmut Hirsch and Audi Leventhal on experiments in which visual experience was effectively restricted to contours of a single orientation by painting lines on goggles that were worn whenever the animals were not in darkness. There, the results showed a clear effect of the exposure, but it was a selective one (Stryker et al., 1978). Most neurons had become unresponsive or nonselective, and only one-sixth of the neurons were at all selective for orientation, almost all of those for the exposed orientation. In animals exposed to two different orientations, twice as many, about one-third, of the neurons were selective or weakly so, again nearly all of those for one or the other of the exposed orientations. These findings were consistent with the selective preservation of responsiveness in neurons that received stimulation that matched their innate orientation preference. I was disappointed that the entire edifice that my thesis had set out to extend—the beautiful idea that the cortex gets organized by experience—had crumbled. However, I had become notorious, for better or worse, and no one could criticize the technical advances we had made.

Postdoc at Harvard

At that point, I had become skilled at single-cell recording in both alert and anesthetized animals and in histology, and I was well educated in neuropsychology, neuropathology, psycholinguistics, the mathematics and statistics useful for neuroscience, and perception and psychophysics and its history. But I was largely ignorant of modern biology and had only an arcane view of cellular neurophysiology through the lens of Jerry Lettvin's group, in which selective conduction failure at axonal branch points was thought to be as important as transmission at chemical synapses. I considered following Peter Schiller's advice that I should take one of the faculty positions that was offered to me at the completion of my thesis rather than do a postdoc because I could pursue my own research and make short visits elsewhere to learn any new technique I needed. I had not applied for any postdocs when I went to give a lunchtime seminar at the Neurobiology Department at Harvard Medical School. Harvard Neurobiology was a completely closed society in those days and, while everything was shared within the department, no one outside it knew anything about what was going on until a publication appeared or a talk was given at a meeting. In a conversation with David Hubel and Torsten Wiesel later in the afternoon of my seminar, Torsten asked why I didn't come to join their group as a postdoc for a couple of years. Deciding to do that was one of the best decisions I ever made.

The community at Harvard Neurobiology in those days was, in many respects, more like a commune than an academic department. Almost all of the eight or so faculty and all of the 15–20 graduate students and a similar number of postdocs ate lunch together every day, and every day there was a lunch talk, sometimes given by a visitor and more often by one of the participants. At the lunch talks, students and postdocs competed to raise the most devastating criticisms most quickly. It was said that one student's criticisms kept a visitor from getting past his second slide, and when the visitor left the department that afternoon, he vowed never to darken its door again. The intensity was thrilling, and the group felt that it was creating the new neurobiology, combining biochemistry with biophysics, neuroanatomy, pharmacology, and what we now would call cellular and systems neuroscience. Most of postdocs and students cooked dinner there at least half of the nights and were in the lab seven days a week. The department taught a two-year course for its graduate students covering all of the topics just mentioned in successive semesters. A group consisting of most of the postdocs, about 12 of us, took each week's syllabus and reading list from the graduate course as the basis for a weekly two- to three-hour meeting after supper. The postdocs were a terrific group trained in diverse labs, so there was genuine expertise in all of the subjects that we taught to one another. The intellectual ferment was further stoked by "evening meetings" every couple of months, for which the whole department would gather to listen to

all of the members of one lab present its ongoing work to the entire group and receive suggestions and criticisms.

In the Hubel and Wiesel group, one of the big ideas, new at that time, was the combination of anatomy and physiology, exemplified by their demonstration with LeVay that projections from eye-specific layers of the lateral geniculate nucleus to the visual cortex matched its ocular dominance columns. We all collaborated with many of our colleagues on many different related projects. I was fortunate to work with Simon LeVay and Carla Shatz on anatomy-physiology projects involving ocular dominance plasticity, which prepared me for much of my later career (Shatz and Stryker, 1978; LeVay et al., 1978).

I was also lucky enough also to work closely with Hubel and Wiesel on a goal they had long sought—that is, determining the overall arrangement of cortical orientation columns. Louis Sokoloff at the NIH had pioneered the use of radiolabeled 2-deoxyglucose (2DG), a sugar that is incompletely metabolized by neurons and that accumulates in them at a rate proportional to metabolic activity. By closing one of the animal's eyes and showing visual stimuli to the other after injecting 2DG, he had used it to reveal presumptive eye-specific layers in the lateral geniculate nucleus (LGN) and cortical ocular dominance columns. I was to visit Sokoloff to learn the technique, and Hubel and Wiesel and I would then use it to demonstrate orientation columns and make microelectrode recordings to verify what the labeling actually showed. Louis Sokoloff was a delight, taking great joy in taking me through the differential equations that modeled 2DG labeling on his new HP calculator.

When I returned to Boston, having mastered the technique, difficulties arose as we scheduled our first experiment. The neurophysiology tradition observed by Hubel and Wiesel, as well as by my doctoral program mentor Peter Schiller, was that no one put his name on a paper unless he or she had done a significant part of the experiment with his or her own hands. For example, Schiller's name was not on any of my thesis papers. In later life, I tried to continue this tradition in my own lab, but eventually I was forced by grant reviewers to adopt the practice from biochemistry that was common in medical schools, in which the lab head's name goes on everything even if his contributions are only financial support and criticism of the manuscript. The demonstration of the tangential organization of orientation columns was important to Hubel and Wiesel as a sort of capstone to their initial discovery of them, and they definitely wanted their names on the paper. But for them, this meant that they actually had to do the experiments with me. Torsten was the department chair, and frequently off to administrative meetings, and David traveled the world giving honorary lectures. The first experiment that would have all three of us in the lab for the entire day was six weeks hence. The next one after that was a month or two later, with similar intervals for subsequent experiments. After

I had made and processed the tissue sections, I had to give them to David to reconstruct them in relation to our microelectrode penetrations. As a consequence, the work went much slower than it would have if I had been free to do these experiments myself, and with many fewer cases, but the Hubel, Wiesel, and Stryker (1977, 1978) papers really did have equal contributions from the three authors.

Teaching a Cold Spring Harbor summer course on techniques for studying the vertebrate central nervous system for two years with Carla Shatz and Peter Kirkwood was another formative experience. Getting to know this laboratory's stellar group of molecular biologists and geneticists and discussing their work as we ate with them in the dining hall every day taught me an enormous amount about a wide spectrum of biology. Our course combined lectures by us and distinguished visitors with grueling laboratory experiments. During the first year, Francis Crick, who was just beginning to turn to neuroscience, sat in on many of the lectures, and we got to know him well.

One of the greatest influences on my later career was a three-month period in 1977 after Bill Harris arrived following his Caltech doctorate in Seymour Benzer's fruit fly neurogenetics lab. Bill shared an office and lab with me. We spent many hours a day together trying to figure out what was the most important question in neuroscience that it might be possible to address. We actually hid out from Hubel and Wiesel, who seemed to us to become increasingly disappointed that we had no new experimental results and seemed to be worried that they had made a mistake in inviting us to join their group. Bill and I converged on a common question: what is the role of patterns of neural activity in guiding the development of precise connections in the brain? The next stages of both of our careers pursued this question with divergent approaches. Bill took advantage of genetics, and I took advantage of electrodes and pharmacology.

University of California, San Francisco

By my third postdoctoral year, I ached to have my own show, out from under the gaze of my Boston mentors. None of them thought that the research that I wanted to do, if I were to start my own lab at Harvard or MIT, was particularly interesting compared with what they thought I ought to do. My Harvard friends Zach Hall and fellow postdoc Louis Reichardt had gone to University of California, San Francisco (UCSF) in the previous two years, and while people in Boston found that incomprehensible, UCSF was beginning to become known for basic science, at least in molecular biology. In addition, it had the advantage of being 3,000 miles away from Boston. I was thrilled when they offered me a faculty position.

Arriving there, I found a social atmosphere that could not have been more different from Boston. People enjoyed life and did not feel that they had to be in the lab seven days a week when there was nothing that actually

needed to be done on a Sunday. The faculty was egalitarian, with the labs of the assistant professors the same size as those of the senior faculty, and the important matters were discussed among the entire faculty. Intellectually, it was completely open and mutually supportive, with the basic scientists from all fields talking with one another about their best ideas, sharing reagents and equipment, and frequently collaborating. In and out of the laboratory San Francisco's social atmosphere was liberating, in contrast to a much more class-bound society in Boston. One of the machinists in the department shop doubled his income by buying and selling modern art, and the telephone installer in the flat we rented invited us to his poetry reading on a weekend. Survival Research Laboratories made giant fire-breathing monsters that fought with one another on vacant lots, at least until the fire department arrived, and performances combining new theater, dance, poetry, music, and computer animation went on in the evenings. And I was the local expert on the visual cortex, free to do the experiments I wanted with no overlay of disapproval.

The neurobiology group was small, with most of its members from a single age-cohort: Zach Hall, Roger Nicoll, Mike Merzenich, Howard Fields, Mike Dennis, John Heuser, and Louis Reichardt were the younger members with appointments in the Physiology Department. Zach led the formation of an interdepartmental graduate program in neuroscience, which became our intellectual home. As a minor figure in the field, still in the shadow of its giants, I did not draw spectacular postdoctoral candidates for the first 12 years, and I recall advising one who did apply that he could do better—he should talk with Torsten Wiesel or David Hubel. But our neuroscience program drew amazing doctoral students, many of whom were drawn to my lab.

The Role of Neural Activity in the Formation and Plasticity of Ocular Dominance Columns

My main goal was the one set in the discussions with Bill Harris: to determine whether and, if so, how neural activity guided the development of connections. The half-millimeter size of the ocular dominance columns in the visual cortex of adult cats let us address this question anatomically as well as physiologically. My thinking was that events that actually take place at the scale of synapses, too small to be viewed except by electron microscopy, worked together to create these macroscopic structures. Our earlier work with LeVay had suggested that the projection from the retina to the LGN and on to the primary visual cortex was topographic, but that the inputs from the two eyes initially overlapped completely in the binocular zone (LeVay et al., 1978). In the hippocampus, the phenomenon of long-term potentiation (LTP) provided a mechanism for reinforcing connections that were simultaneously active. The development of ocular dominance columns

in the input layer of the visual cortex could be explained if correlated activity drove the rearrangement of connections, and activity within each eye was better correlated than activity between the two eyes. I set out to test this idea in two ways: experimentally, by blocking activity in the two retinae pharmacologically during the time when eye-specific segregation was taking place in the cortex, and theoretically, after Ken Miller joined the lab following his training in theoretical physics. Both of these experiments took longer than was allowed before consideration of my promotion to tenure. But luckily, I also had taken on a few smaller projects that bore fruit more quickly, including a little *Nature* paper (Schoppman and Stryker, 1981), which gave my department the cover it needed to keep me around.

The experimental test of blocking the formation of ocular dominance columns by repeated infusion of tetrodotoxin (TTX) into the two eyes was a success at a coarse level, indicating that retinal activity was required. However, it was so difficult technically that it seemed too uncertain of success for a graduate student project, and further work on this project was carried out by me with a technician and later a talented mature research scientist. The publication of this work (Stryker and Harris, 1986) was delayed by several years for no good reason. It was complete by late 1983 but did not appear until 1986. Students now would never believe how slow and laborious it was to make perfect photographic prints in many copies and assemble them into montages for shipment to a journal, which would mail them out to reviewers. When things were lost in the mail, publication was delayed by an extra half year or more. After acceptance, a paper might not actually be published for an additional year.

I regard this paper as part of my most important contribution to neuroscience. Showing that activity was necessary for the formation of a pattern of orderly connections in the visual system that takes place prenatally in monkeys and humans established the principle that neural activity can play a role in development that is distinct from experience. Neuroscience had regarded the nature-versus-nurture or innate-versus-experiential question as being the same question as chemical specificity versus activity dependence. My experiments had provided evidence that retinal activity played a role in something that was clearly innate in other species, because visual experience is absent *in utero*. Later work provided numerous examples of experience affecting chemical signals for development. It seems obvious now that finding the mechanism—activity versus chemical specificity—does not answer the nature/nurture question, but it was not so at the time.

Preventing the formation of ocular dominance columns by retinal activity blockade did not show, however, what happened to the cortical arbor of individual LGN-cell axons. The next steps were very difficult and laborious experiments in which early retinal activity blockade using TTX (or control infusions that did not block activity) were combined with injections of tracers into the LGN that let us reconstruct entire axonal

arbors that grew with or without retinal activity blockade (Antonini and Stryker, 1993a). Indeed the arbors were patchy, corresponding to ocular dominance columns when there was normal retinal activity, and continuous when activity was blocked. We used the same approach to examine what happened to these geniculocortical inputs when occluding the vision of one eye during the critical period caused its ocular dominance columns to shrink, and we found that arbors serving the deprived eye lost half of their extent and at least half of their synaptic boutons in less than a week (Antonini and Stryker, 1993b).

The activity blockade experiments also did not establish that it was the pattern of activity rather than its amount that mattered. To address that question, I tried an even more difficult experiment—blocking all naturally occurring retinal activity with TTX and introducing controlled patterns of activity by stimulating the two optic nerves alternately through separate electrodes or by stimulating them simultaneously through an optic tract electrode. The assays of the effect of the different patterns of activity were both physiological and anatomical: microelectrode recording of ocular dominance along penetrations that would cut across many ocular dominance columns, if they were present, and transneuronal tracing of the anatomical projection from one eye through the LGN to the cortex. The results of the physiological assay were clear. Alternate stimulation allowed ocular dominance columns to form and enabled cells dominated by one eye to be clustered together, alternating with clusters dominated by the other. Simultaneous stimulation, in contrast, left nearly all of the cells responsive to both eyes, with no evidence of clustering according to eye dominance, which was exactly the same as if there were no activity at all. The anatomical tracing experiments were mostly marred by various artifacts, and only a few provided interpretable results, all of which were consistent with the physiology.

I presented the preliminary results of these experiments at various meetings, with the reports appearing in books (Stryker, 1986, 1989), but I refrained from submitting a paper that I regarded at the time as a *magnum opus* in the hope that I could improve the anatomical tracing. Eventually I gave up, and I have regretted ever since that I did not publish a real paper on this work that had consumed so much of my effort over the years. The advice I give to young colleagues and have mostly followed myself since that time is that it is self-destructive to let the perfect be the enemy of the good. If you have sound, important findings and can't do the ideal experiment to confirm or extend them after a year or two, then publish what you have and move on. Perhaps it won't be a cover story in *Science*, but you owe it to the field and to the institutions that supported the work to put it into the literature where it will be seen, and maybe someone cleverer than you will take the next step.

The theoretical work on ocular dominance column development was made possible by Ken Miller's joining the lab for his doctoral research. I had played for some years with crude computer simulations of activity-dependent development, and several simulations had appeared in the literature. The trouble with all of the computer simulations was that they were no more enlightening about mechanism than watching biological development itself, and they had so many parameters that simulations could never explore all of the relevant parameter space. The problem that Ken took on was to determine what factor—the size of the afferent arbors, the degree of correlated activity, the properties of the synaptic plasticity rule, or the spread of excitation and inhibition in the cortex—is responsible for determining the spacing of ocular dominance columns. I insisted on a model in which all the parameters and the outcomes could at least in principle be measured in feasible experiments so that our model would have a genuine, quantitative connection with biological reality. Ken had acquired an appreciation of what kinds of features could reliably be measured because I had him carry out a neurophysiology experiment as part of his doctoral training (Miller et al., 1989). We hoped to solve the problem of ocular dominance column development analytically, so that we could appreciate the role of each factor through its contribution to an equation.

To work on this problem, we used the San Diego Supercomputer Center to run simulations, but Ken persisted in trying to derive an analytic solution to the most important limiting cases. My education in mathematics was finally useful in allowing me to understand the progress that Ken was making. We talked with several mathematicians, including ones who worked on computational fluids, which can form periodic patterns, but the crucial help at several points came from the late Joseph B. Keller, a wonderful, modest mathematician at Stanford whose stature in the field I did not appreciate until, during the time he was helping us, I saw his picture in the newspaper getting the National Medal of Science. The Miller, Keller, and Stryker (1989) *Science* article was the first model of such a complex phenomenon in brain development in which the roles of each factor could be understood in the form of equations. The understanding resulting from this model guided much of my work for the next decade.

Michael Merzenich and Adult Cortical Plasticity

My laboratory was located adjacent to that of Michael Merzenich, whose main activity at the time I arrived at UCSF was doing the basic science for the cochlear electrical stimulation prosthesis for profoundly deaf people. The inability of the cochlear prosthesis to reproduce the normal pattern of activity in the eighth nerve, in combination with its remarkable success at restoring high levels of speech perception in patients, convinced Mike that the brain of normal adult humans was remarkably plastic. Mike had been

Vernon Mountcastle's graduate student working on somatosensory physiology for his doctorate. Not long after I arrived at UCSF, Mike returned to somatic sensation during a sabbatical at Vanderbilt with his old friend from postdoctoral years, John Kaas. Their work with students revealed dramatic plasticity of the topographic maps in somatosensory cortex following partial peripheral deafferentation. I was very skeptical about large-scale plasticity in primary cortical areas of the adult brain. After Mike returned from sabbatical, he and I worked together every Monday on somatosensory cortical plasticity, which we studied with high-resolution microelectrode mapping, making about 300 microelectrode penetrations over 12 hours in each session, before and at intervals of weeks after peripheral or cortical lesions (Merzenich et al., 1984; Stryker et al., 1987). The adult plasticity was clearly genuine.

For several years, until my own lab's work on the visual cortex kept me from taking Mondays off, this collaboration was as stimulating as it was arduous and was a forum for a continuing argument between us that we sought to resolve by planning experiments. I poo-pooed the modest plasticity he and I had found in the adult brain in contrast to the dramatic effects of manipulations early in development. Mike countered that adult plasticity could be much greater than we had found to date, and that in any case, our research had to be directed toward changes that could be induced after early development if our work was to do any good uncovering potential therapies for human patients. I thought that the next step in this research should be to understand the anatomical basis of the reorganization of cortical maps that we found. Mike, in contrast, thought that it was most important to discover factors that promoted the induction of this plasticity, by doing experiments using behavior to manipulate neural activity and attention and using pharmacology to manipulate neuromodulators. As it has turned out, Mike's approach has been fruitful and has led to useful therapies. But we still don't know the anatomical or neural circuit basis of most of the phenomena of adult cortical plasticity, and we ultimately will need to do so. Perhaps ironically, much of the current work in my laboratory is focused on mechanisms of adult plasticity in the visual cortex.

This long-lasting debate with one of my closest friends and most respected colleagues has been a highlight of my intellectual life. We differ in background, approach, and style but agree on what constitutes a good experiment and the value of trying to carry it out.

Ferrets

Many of the events I wished to study, such as the emergence of visual cortical orientation selectivity, began soon after birth in the cat, and neonatal kittens were fragile experimental subjects. Ferrets, which the Guillery laboratory had studied anatomically and found to have a typical carnivore

LGN and visual cortex, resembled long, skinny cats. The exciting thing about the ferret was that its brain appeared to develop at the same pace as the cat's, but it was born two weeks earlier with its visual system like that of a two-weeks prenatal cat. My initial hope was to study events like the origin of orientation selectivity that were neonatal in the cat in a hardy two-week-old ferret. I also hoped to study other events that were prenatal in the cat, such as the role of neural activity in the segregation of inputs from the two eyes into different layers of the LGN. While no one had ever recorded from the visual system of the ferret, I was confident that in a couple of years, we could repeat in the ferret every important experiment that had been done on the organization and development of cat's visual system.

My first graduate student, Kathleen Zahs, took on the task of characterizing the visual system of the ferret so that we could begin to use it for studies of development and plasticity (Zahs and Stryker, 1985). We first studied the LGN and found the properties of the neurons very similar to those in the cat, as we had hoped, but with a clearer distinction between the brisk (X- and Y-like) and sluggish (W-like) responses. Guillery had pointed out a pair of sublaminae ("leaflets") in each of the main layers of the LGN. For no good reason, I was certain that these sublaminae would correspond to a division between X-like linear inputs and Y-like nonlinear inputs from the retina. We made recordings from a number of ferrets to study the linearity of their responses and failed to see the difference between the leaflets. For months, through many experiments, we missed the obvious function of this subdivision, despite its being clear without exception in our data and despite hearing from McConnell and LeVay (as we were doing our experiments) that in the mink, a closely related carnivore, the leaflets reflected a segregation of on-center and off-center retinal inputs (Stryker and Zahs, 1983). This episode has stood out in my mind ever since as a warning about the potential danger of hypothesis-driven research and the need to look at all features of the data as they come in. If the hypotheses are too narrow, it is possible to miss the obvious.

After we knew the basic organization of the ferret visual system from Kathy's work, another wonderful student, Barbara Chapman, joined me and Kathy in an attempt to use physiology to confirm or refute the anatomical hypothesis of Hubel and Wiesel on the origin of orientation selectivity in visual cortex. Was it the result of convergence of input onto simple cortical cells from geniculate cells whose receptive fields lay along a line in the visual field? We measured the preferred orientation of one cortical column and then silenced the cortical cells pharmacologically so that we could record the tiny spikes produced by the cortical arbors of geniculate cells. In most cases, the receptive fields of these arbors were precisely aligned with the preferred orientation of the cortical cells (Chapman et al., 1991), providing strong confirmation of Hubel and Wiesel's hypothesis. Ed Ruthazer, another wonderful student, showed that the formation of patchy

clustered corticocortical connections first emerged just before orientation selectivity began to develop and became prominent at the same time as mature selectivity was beginning. Neural activity was absolutely necessary for this development (Ruthazer and Stryker, 1996). The results indicated that the anatomical specificity of long-range horizontal connections in the visual cortex results from an activity-dependent process that initially can use spontaneous activity in the cortical and thalamic networks to establish crude periodic connections and that later uses visual cues to refine these connections.

Barbara Chapman then investigated the role of neural activity in the development of orientation selectivity, half of my original reason for adopting the ferret. She found that neural activity in the visual cortex was absolutely necessary for orientation selectivity to develop at all beyond its infantile state, which we believed might result from random connectivity (Chapman and Stryker, 1993). Visual experience was also necessary for fully normal development, but orientation selectivity developed to some extent even in animals in which vision was compromised by eyelid suture. Her findings raised the question of whether the primitive orientation selectivity we saw initially was the seed for normal development, or whether the adult orientation selectivity developed independently of its initial activity-independent state. Pursuing this question gave rise to another delightful collaboration with Tobias Bonhoeffer. Partly in San Francisco and then at the Max Planck Institutes in Frankfurt and Munich-Martinsreid, the three of us worked together to use intrinsic signal optical imaging to look at the pattern of orientation columns in ferret visual cortex as it first emerged and then matured, tracking development in individual ferrets (Chapman et al., 1996). Surprisingly, the pattern of orientation columns was stable after even the first initial hints of its appearance, at an age when Barbara's earlier microelectrode recordings had shown only slight selectivity. This finding was consistent with Ruthazer's anatomical experiments in suggesting that intracortical connections played a stabilizing role. Barbara stayed in Germany to finish our joint experiments after I had to return to San Francisco to teach, and she and Tobias completed additional experiments for another interesting paper. The friendships made working together night and day are lifelong.

Another motive for turning to ferrets was to determine whether neural activity was responsible for the segregation of eye-specific layers in the LGN. The layers formed very early in development, and I tried for many months to create the technology to carry out this experiment in baby ferrets. Taking the next step toward solving this problem reactivated an old collaboration with Carla Shatz, who had been a friend since Boston days and who had moved to Stanford at the time I went to UCSF. Carla had become expert at prenatal surgery for her studies of retinogeniculate innervation. We worked together to equip fetal cats with what looked like a scuba

tank but was really an osmotic minipump that delivered TTX to the LGN to block activity during the two weeks encompassing retinal innervation and layer formation. Tracing retinal inputs after this treatment revealed no indication of the eye-specific layers that would normally be present, but retinotopy appeared to be preserved (Shatz and Stryker, 1988). Our result was interpretable only if there actually had been spontaneous activity in the developing visual system for the TTX to block, but we had no evidence that there was any. We reported our finding in the same issue of *Science* in which Lucia Galli and Lamberto Maffei revealed that there was clear periodic activity in centrally projecting retinal ganglion cells in fetal rats at a comparable stage of development (Galli and Maffei, 1988). The two papers together provided strong support for a role for spontaneous retinal activity in organizing central connections.

The final chapter in the story of the formation of eye-specific layers in the LGN was not written until much later. Torrealba and co-workers had shown earlier that there were multiple topographic maps in the optic tract that appeared to reflect the temporal order in which different retinal ganglion cells grew. It appeared possible that the earliest inputs, from the contralateral eye, reached the innermost border of the LGN first and remained there, forming an eye-specific layer, with the later-arriving inputs forming additional layers. Much later, in her independent lab, Barbara and co-workers showed that transiently blocking retinal activity until inputs from both eyes had reached the LGN removed the advantage of the early arriving inputs. When activity was then restored, the laminae formed in a process requiring activity, but their arrangement was random (Huberman et al., 2002).

Institutional Engagement at UCSF

From the time of my arrival at UCSF, I was happy to contribute to the institution and did so in many ways. I was active in graduate program teaching and did not shirk search committees or other somewhat-optional features of academic life. When Zach Hall became physiology chair, I became co-director of the neuroscience program together with Louis Reichardt, as well as vice chair of the department. While I was generally very happy at UCSF, I found it hard in 1993 to resist the temptation to leave UCSF for additional desperately needed lab space and the ability to move to an even more desperately needed bigger house, as my family had grown. A commitment from the chancellor that my needs would be met in San Francisco allowed me to remain, and part of the reason I was happy to remain was that I had the perfect department chair, giving me all the influence I wanted over our affairs with almost none of the work. I was blindsided a few months later when Zach moved to the NIH to become director of National Institute of Neurological Disorders and Stroke. The dean called me into his office and

told me "Michael, you have to step up to the plate." I was happy to chair the department for the next 10 years, and it ended up being 12 years before I was allowed finally to return full time to my lab. I took enormous pleasure and pride in recruiting terrific young scientists to UCSF and in helping them become successful.

Other activities outside the lab were also exciting. Essentially without informing the central administration, a group of faculty involved in graduate education, led by J. Michael Bishop, created the UCSF Program in Biological Sciences (PIBS), which encompassed graduate programs over a wide range of biology from biophysics through molecular biology and genetics to cell and developmental biology and neuroscience. PIBS changed the course of graduate education by moving it out of the departments and putting stipend support in the hands of the students, who became free to work with any of the PIBS faculty members. It also revolutionized faculty recruitment by making it possible for basic scientists in clinical departments to become first-class citizens with access to all of the resources, including graduate students and postdoctoral support, that were available to their basic science colleagues so long as they were recruited through search committees dominated by PIBS. Helping to create PIBS and directing it for two years while Mike Bishop was away was a source of great satisfaction.

Closer to home, the campus supported our approach to the Keck Foundation to renovate a 10,000-square-foot floor of the laboratory building in which we were housed to create the Keck Center for Integrative Neuroscience. While it seemed too little space for a group our size, its crowding of the labs for eight terrific systems neuroscientists cheek by jowl gave rise to an unprecedented level of interaction that was almost entirely positive. Led by my friend Steve Lisberger, our center was the only medical school chosen by the Sloan Foundation to host one of its centers for theoretical neuroscience despite our lacking a mathematics, physics, or computer science department. Having worked with Chuck Stevens to get the Sloan Foundation engaged in supporting theoretical neuroscience by organizing summer workshops at the Santa Fe Institute, I was especially pleased that we were granted a Sloan Center.

I also was one of the leaders of the early planning for our new campus at Mission Bay, including visiting UC Regents in their homes and workplaces to help get our plan for its construction approved. The new campus was the key to converting a wasteland into what has now become a vital part of our city. I still have my hard hat and shovel from the groundbreaking for the first building.

Surprisingly, the years as department chair, an activity that consumed nearly half my energy, were among the most successful for my lab, with amazing students who did some of the best work the lab has ever done. While they mostly started in the lab before I became chair, their success is probably due to their being freed from detailed oversight by my being too

busy with administration. I also think that the lab's success was possible because Dr. Antonella Antonini, formerly a professor in Verona, Italy, joined as a research scientist. Having a brilliant, mature, scholarly scientist in the lab every day supplied a needed degree of knowledge and stability.

Ocular Dominance Columns

As new approaches became possible, I kept returning to the questions surrounding the roles of experience and neural activity in the development and plasticity of cortical columns in the cat, and we made numerous discoveries. Postdoctoral fellow Yoshio Hata showed anatomically that the plasticity of ocular dominance columns was reversed when the visual cortex was inhibited by infusion of muscimol during monocular visual deprivation during the critical period (Hata and Stryker, 1994), and student Takao Hensch showed that the spacing of developing ocular dominance columns could be regulated up or down by increasing or decreasing $GABA_A$-mediated inhibition during their development (Hensch and Stryker, 2004). Postdoctoral fellow Mike Crair showed that visual experience was necessary for the emergence of strong ipsilateral-eye responses at the onset of the critical period and that development was independent of visual experience before that time (Crair et al., 1998). Abruptly at the onset of the critical period, selective cortical responses fell apart in binocularly deprived animals but increased slightly with normal vision. In the course of these experiments, we improved the sensitivity of an anatomical tracing technique and discovered that an aspect of ocular dominance column development took place a week earlier than reported in one of my earlier papers. I definitely wanted to report it before anyone else, and I have never been so eager to get a new finding published quickly (Crair et al., 2001).

I was powerfully struck by the findings of experiments with postdoctoral fellow Josh Trachtenberg, who discovered that the time course of the effects of monocular deprivation during the critical period were much slower in the input layer (layer 4) than in the cortical layers above and below, where dramatic plasticity took only a day or two (Trachtenberg et al., 2000). Anatomical connections among neurons in layer 3 showed half-millimeter scale rearrangements in 24 to 28 hours, matching the rapid change in responses (Trachtenberg and Stryker, 2001). The slower plasticity in layer 4 appeared consistent with the time course of plasticity in its input from the LGN.

Despite this progress, I became discouraged that we would ever be able to figure out the mechanisms of plasticity with the approaches available in cats and ferrets. Our work had produced a lovely story about neural activity and visual experience in the development and plasticity of the visual cortex that had become part of the textbooks and had some clinical relevance, with lots of interesting phenomena and models that could make sense of them.

But in the end, these discoveries were at a level above that at which things actually happened in the brain. I feared that I would end my career with hand-waving. I needed another problem that would excite me.

The inferotemporal lobe representations of complex objects had intrigued me since the early reports of Charlie Gross. Studying this problem in monkeys and with human psychophysics was an exciting prospect. I followed the pioneering work from the Tanaka and Miyashita laboratories, wrote some *News and Views* pieces about it (Stryker, 1991, 1992), and prepared myself to abandon carnivores and development and turn to object perception in monkeys. This might have been a fruitful path to follow, as the work of Doris Tsao and other labs have shown. Indeed, I would have done so but for the next development.

Mutant Mice

Josh Gordon came to the UCSF medical doctor/doctoral program intending to study tumor viruses in Mike Bishop's lab. He took our introductory course in neuroscience, and because we had started PIBS, he was able to do a rotation and then join my laboratory. He joined it on the condition that we would begin to study genetically manipulated mice as an approach toward understanding the mechanisms of development and plasticity. I had been interested in doing this for some years, given that recombinant DNA made it possible to make mice in which interesting signaling systems were mutated. But mice were a big change, and I knew that my vision friends would tease me by singing "Three Blind Mice" if we were to switch. Josh's enthusiasm for this approach pushed me over the edge. Transgenic mice opened promising new approaches to understanding how the brain wires itself and adapts to experience.

The anatomy and physiology of the mouse central visual system had, of course, been studied 20 years earlier in pioneering work focused on the consequences of spontaneous neurological mutants maintained at Jackson Labs. The beautiful work by Ursula Dräger and David Hubel and by Alan Perlman's group on the visual cortex of the *reeler* mouse, in which cortical lamination is turned upside down, led to powerful conclusions, but hoping for additional spontaneous mutations was not a promising way to follow it up. These groups had solved, however, some of the problems of mouse anesthesia consistent with strong responses of neurons in the visual cortex.

Josh and I first worked on the mouse preparation to make visual cortex and LGN responses reliable. He then did the research that resulted in the foundational paper for our studies, and many other studies, of visual cortical plasticity in mice (Gordon and Stryker, 1996). He found that the mouse visual cortex indeed had rapid activity-dependent plasticity in response to monocular visual deprivation within a well-defined critical period peaking at four weeks of age. This finding set the stage for a huge number of

experiments, many by my lab, delineating the signaling systems responsible for this form of plasticity (e.g., Gordon et al., 1996). I didn't know whether Josh was excessively brave or merely foolhardy in his choice of a residency in psychiatry rather than in neurology or ophthalmology, where I was sure he would become a leader of his field. He told me he was not afraid to do something hard and that the experience in my lab was preparation for working on the most important problems of the brain.

Together with Michela Fagiolini, a new postdoctoral fellow whose doctoral degree was from the Maffei laboratory in Pisa, Antonella Antonini did foundational anatomical work on mouse visual cortex and on the changes in thalamocortical axons produced by monocular visual deprivation (Antonini et al., 1999), as she had done earlier with cats.

Takao Hensch came to do doctoral work in my lab after a postgraduate fellowship year with Masao Ito in Tokyo and Melitta Schachner and Wolf Singer in Germany. He was obviously brilliant, thoughtful, and careful. He always prepared thoroughly for experiments, and no one else in my lab has done as few unproductive ones. His joining my lab did wonders for my reputation in Asia and Europe. Takao started working on plasticity in cats, using cortical brain slice recordings to verify the actions of drugs we used to manipulate signaling and activity in the visual cortex (Hensch and Stryker, 1996). After collaborating with Josh on mutations of enzymes involved in excitatory transmission that altered critical period plasticity, he began work that has turned out to be tremendously interesting and important. A colleague in the Diabetes Center had mutated *Gad2*, one of the two enzymes responsible for synthesis of the inhibitory neurotransmitter, GABA. Its diabetes phenotype did not look very interesting, but the mice were fairly healthy. Hearing about this mutant, we realized that it might give us a means of studying the role of synaptic inhibition in cortical plasticity. Our colleagues were happy for us to have the mouse in the hope that we would find something interesting, with the proviso that they would publish the basic description of the mutant first.

Around the same time, another student in the lab, Jessica Hanover, had collaborated with Josh Huang in the Tonegawa lab on mice that constitutively overexpressed brain-derived neurotrophic factor (BDNF) and discovered that these mice have a precocious critical period by one week (Hanover et al., 1999). Josh Huang found that they also had a similarly precocious development of cortical inhibitory interneurons, so it was reasonable to speculate that the maturation of inhibition triggered or gated the critical period of plasticity, although this of course was only one interpretation among the many possible.

Takao found that the *Gad2*-deficient mice did not have a critical period (Hensch et al., 1998). Monocular visual deprivation simply did not cause the cortex to become less responsive to the deprived eye either at the normal time or earlier or later. While this by itself was somewhat interesting, the

entire mouse lacked *Gad2*, so it provided little evidence specifically about *cortical* inhibition. The important experiment was to determine whether we could rescue plasticity by a purely cortical manipulation. As it turns out, diazepam (valium) was an ideal reagent. It acts postsynaptically on GABA receptors to double their open time, essentially producing twice as much inhibition for each inhibitory action potential. We imagined that our having gotten rid of one of the two GABA-synthesizing enzymes would cut GABA release in half (an assumption later verified using in vivo micro-dialysis in Takao's independent lab), so diazepam ought to restore a normal amount of inhibition. Applying diazepam specifically to a small region of visual cortex in the *Gad2*-mutant mice during visual deprivation produced a normal critical period, providing powerful evidence that the level of intracortical inhibition is an essential trigger for critical-period plasticity.

This discovery was the basis of the early phase of Takao's independent career, first in his own lab at RIKEN in Japan (skipping a postdoc) and later at Harvard, during which he found out a great deal about the factors that regulate activity-dependent plasticity. Unfortunately for me but great for them, my terrific postdoc Michela Fagiolini and Takao fell in love so that she left to be with him in Japan before she could complete her main projects in my lab. Their three beautiful children are now in high school and college, and both she and Takao are doing great work in their labs at Harvard, so in their case, all is well that ends well. I will never forget my conversation with Michela that failed to persuade her to stay in my lab for another year and finish projects that would have enhanced her reputation: She tapped her fist on her chest and said, "But the heart, Michael; but the heart."

A technique that greatly advanced our work on visual cortical plasticity was the work of one of the trainees in our Sloan Center for Theoretical Neuroscience, the goal of which was to bring scientists trained in a hard, theoretically grounded science such as mathematics and physics into neuroscience, either to become neurobiologists or else theoreticians who, unlike most, actually would understand the neurobiology about which they were theorizing. Valery Kalatsky, a physicist trained in Russia and Texas, joined my lab. We had used images of an intrinsic optical signal associated with brain metabolism to view the patterns of activity elicited by different visual stimuli in cats and ferrets for many years. It had been taught to me by its inventor, Amiram Grivald, over a visit to his laboratory at the Rockefeller (in Torsten Wiesel's group there) where I got to know their postdoc Tobias Bonhoeffer. The intrinsic signal was tiny, a fractional change in reflectance of at most a few parts in 10,000. While it was also present in mice, we found it too small and too variable to be of use for quantitative study of such a small brain. Val Kalatsky and I thought of a way to measure it much more precisely by imaging it over repeated stimulus cycles and analyzing the component of the signal at the frequency of stimulation, similar to the way that Tony Norcia was able to measure visual evoked potentials in

babies who attended to the stimulus screen only briefly (Norcia and Tyler, 1985). This approach was successful, allowing reproducible measurement of response strength as well as the construction of high-resolution topographic maps (Kalatsky and Stryker, 2003). It had the advantage that it is almost completely noninvasive—light is the only thing that enters the brain—and could be measured accurately through an intact skull.

Megumi Kaneko, who trained as an anesthesiologist in Japan but abandoned clinical work to do doctoral work in neurobiology, took great advantage of intrinsic signal imaging for our studies of ocular dominance plasticity after she joined the laboratory as a postdoctoral fellow. She first did a series of more than 40 wild-type mice to evaluate the stability of the magnitudes of the intrinsic signal responses in visual cortex to the two eyes. She found them to be remarkably stable, neither eye's response fluctuating more than 10% from day to day. The relative cortical responses to stimulation of the two eyes in the binocular segment of the visual field was exactly what would be expected from microelectrode recordings of a population of single neurons in the binocular zone of the visual cortex.

Megumi tracked the changes in response over the course of monocular deprivation during the critical period and found an initial dramatic decrease in response to the deprived eye for the first two to three days while the response to the open eye remained stable. As deprivation continued for an additional two to three days, the response to the open eye became much stronger in a second phase of plasticity, and surprisingly, the response to the deprived eye also increased to some extent. Finally, when the deprived eye was reopened during the critical period, responses in both eyes returned to their original levels (Kaneko et al., 2008a; Kaneko et al., 2008b). We knew that N-methyl-D-aspartate (NMDA) receptors were implicated in at least the first phase because of its blockade by even low doses of the NMDA-receptor blocker CPP. But what accounted for the later phases? The Malenka lab had found a phenomenon of homeostatic synaptic scaling in hippocampal slices and cultures that was dependent on tumor necrosis factor alpha (TNFα) signaling and was prevented by null mutations of TNFα or pharmacological depletion of TNFα (Stellwagen and Malenka, 2006). It seemed possible that cortical activity was sufficiently depressed after the first phase of plasticity produced by monocular deprivation for homeostatic synaptic scaling to be the cause of the second phase. Indeed, the open-eye responses never increased in TNFα mutants or when TNFα signaling was blocked pharmacologically (Kaneko et al., 2008b). These experiments established homeostatic synaptic scaling as the basis for the second phase of ocular dominance plasticity.

Earlier work on cats from the labs of Wolf Singer and Carla Shatz and my own lab had suggested that ocular dominance plasticity might result from a competition for limiting quantities of brain-derived neurotrophic factor (BDNF), although my lab's later findings indicated that our

interpretations of these pharmacological experiments were misleading (Gillespie et al., 2000). BDNF was known, however, to be released in response to neural activity in some circumstances. Our UCSF colleagues Kevan Shokat and Pam England had come up with a perfectly selective and effective chemogenetic means of blocking signaling of the BDNF receptor, TrkB, in mice. Megumi used this approach to do experiments that showed, surprisingly, that blocking TrkB had no effect on either the initial or second phase of ocular dominance plasticity, conclusively refuting the earlier hypothesis about competition for BDNF. However, blocking TrkB completely prevented the third phase, the recovery of responses after reopening the deprived eye, as well as the reduction in open-eye responses that normally accompanies it (Kaneko et al., 2008a). This finding was consistent with the recovery of deprived-eye responses being mediated by the formation of new synaptic connections (or the expansion of existing ones) because of the known requirement for BDNF-TrkB signaling for the formation of new synapses in neuronal cultures.

These two experiments gave us an anatomical hypothesis for the substrate of ocular dominance plasticity: the loss of deprived-eye synapses in phase 1, the preservation of synapses in phase 2 with a homeostatic increase in their strength, and the regrowth of deprived-eye synapses in phase 3 after reopening the eye. Only recently have we been able to provide anatomical evidence for this hypothesis by tracking the dendritic spines and axonal boutons of layer 2/3 cells using 2-photon microscopy (Sun et al., 2019).

Map Formation and Organizing Connections Between Visual Areas

After our experiments on ocular dominance columns convinced me that spontaneous neural activity could guide the wiring of neural connections in development, I wondered whether neural activity guided the formation of precise topographic maps, a process that is innate in the sense that it develops early and does not depend on experience. A large part of the reason for turning to ferrets was the hope that I could use them to study map formation in the visual system. But try as I did for years, I had made no progress on this problem in ferrets. In the meantime, compelling experiments on gradients of ephrins and eph-receptors seemed to indicate that the problem of map formation was solved and that it was all due to chemospecificity—not lock and key, as Sperry had proposed, but gradient matching. But most of this work had been done on the superior colliculus (a.k.a. optic tectum) or, to a limited extent, in the LGN, both of which receive direct retinal input, and it was not known whether a similar mechanism operated in the cortex.

An amazingly talented postdoctoral fellow, Jianhua Cang (JC), joined the lab and began to work on this project, on which we sought out and found the perfect collaborator: David Feldheim at the University of California, Santa Cruz, 90 minutes south of UCSF. Dave was an expert in eph/ephrin

signaling and not only had mutant mice but also had histochemical reagents that revealed eph/ephrin protein distributions. Dave's lab found that there were gradients in the primary visual cortex of ephrin-A2, A3, and A5, so JC studied the null mutants of each one by using intrinsic signal imaging to reveal the topographic maps in visual cortex and by tracing the precision of anatomical projections from the LGN to V1. The results were disappointing at first because no phenotype was evident in any of the mutants. Dave pointed out that eph/ephrin binding is fairly promiscuous, so we then tried all the double mutants, without finding any effect. At long last, after Dave was able to make mice with the triple knockout of all three ephrin-As, JC found the cortical map of azimuth to shrink and to become rotated, displaced, and far less precise. Of course, the entire mouse carried the mutation, so these findings did not prove that the ephrin signaling defect was in the cortex. Using in utero electroporation to misexpress ephrin-A5 in the cortex at a time before map formation, Megumi Kaneko shifted the map when the extra ephrin was to one side of V1 and disorganized it when in the middle. These experiments demonstrated that specific eph-A/ephrin-A signaling guides map formation in the visual cortex (Cang et al., 2008).

We next turned to the role of neural activity. Markus Meister and Rachel Wong in the laboratories of Dennis Baylor and Carla Shatz at Stanford had extended the earlier findings of Galli and Maffei by showing that apparently random waves of spontaneous activity propagated across the retina and drove the ganglion cells during the period that map formation was taking place, long before the retinal ganglion cells responded to stimulation of the photoreceptors (Meister et al., 1991). This was the ideal pattern of activity for driving map formation in models. The retinal waves during the first postnatal week were driven by nicotinic cholinergic signaling, and a cholinergic receptor mutation disrupted the organization of the waves but did not block activity (McLaughlin et al., 2003). JC studied these mutant mice and found that maps of azimuth in visual cortex and the anatomical projection from the LGN to visual cortex were indeed very much less precise than normal (Cang et al., 2005). Again, we had to confront the issue that always makes interpretation of mutant animals difficult. In this case, there is cholinergic signaling in the visual cortex, so the effect of the mutation might not be the product of its disruption of retinal activity but instead a direct action on cortex. Collaborating with my colleague David Copenhagen's laboratory, we showed that a drug delivered only to the retina of wild-type mice during the first week of development copied the effect of mutation on neural activity; JC found that the drug also reproduced the mutation's effects on the cortical map.

At this point, we had proved that both patterned retinal activity and ephrin-A signaling were important for cortical map formation, but were they the whole explanation? With the Feldheim lab again, we disrupted both retinal activity and ephrin-A signaling and completely prevented the forma-

tion of the map of azimuth (Cang et al., 2008b). Surprisingly, the map of elevation was almost intact, a topic for future study. In the superior colliculus as well, the same factors as in visual cortex were responsible for map formation (Cang et al., 2008a), but it appeared that the timing was slightly different, with the effects of ephrin signaling operating somewhat earlier than those of retinal activity.

Layer 5 cells in the visual cortex project to the superior colliculus, and the map of the cortical projection is perfectly aligned with that of the direct retinal input to the colliculus. We took advantage of a mouse that the Lemke laboratory had created by ectopically expressing an Eph receptor in half the retinal ganglion cells, producing a duplicated map of azimuth in the superior colliculus but (for reasons now understood but too long to explain here) only a normal single map in visual cortex. The superior colliculus also has a normal single gradient of ephrin signaling. When activity is disrupted, we found that the cortical projection to the colliculus looks normal, forming a single map. When retinal activity is present, the corticocolliclular projection, which develops later than the direct retinal projection to the superior colliculus, aligns itself with the retinal input, forming a duplicated map. This indicates that correlated activity can override the chemical gradients in the development of precise connections between these two areas (Triplett et al., 2009).

Our last paper on map formation is one the papers that I am most proud of. My doctoral student Melinda Owens joined Dave Feldheim and his former postdoc Jason Triplett, by then in his independent lab, to study the interaction between neural activity and the chemical gradient in more detail. Using the Lemke mouse that makes a duplicated map in the superior colliculus, we asked what happens if the strength of the ephrin gradient for map formation is made weaker so that it is comparable to the effect of the structured neural activity. We found that when the mice had half the level of ectopic Eph expression in one population of ganglion cells, map formation was clearly stochastic: sometimes duplicated, sometime single, and sometimes different between the two hemispheres or between the lateral and medial portions of one superior colliculus (Owens et al., 2015). A computer model of map formation as a stochastic process influenced by both neural activity and chemical gradient exactly reproduced these findings, showing the same variability when the two factors were equal in strength. These results were a culmination of our work on the formation of retinotopic maps, a process that I believed we had fully explained, and I felt ready to retire the problem. No other episode in my life as a scientist has been more satisfying or has had more wonderful co-workers.

Neural Transplantation to Induce Juvenile Plasticity in Adult Mice

One conclusion that had emerged from our studies of development and plasticity during the critical period in early life was the crucial role of cortical

inhibition in triggering plasticity. Two UCSF friends and colleagues, Arturo Alvarez-Buylla and John Rubenstein, had studied the development of inhibitory interneurons and their long tangential migration from the site at which they were generated in the ganglionic eminences into the developing neocortex. My postdoc Sunil Gandhi and Arturo's medical doctor/doctoral student Derek Southwell came up with a wild speculation: Would embryonic inhibitory neurons trigger plasticity if they were transplanted into mature cortex? Arturo and I went along with their idea because we were confident that both of them would have other experiments that could be counted on to be productive if this one failed. We knew that the normal critical period peaks at 35 days after the inhibitory neurons are generated, around postnatal day 28 (P28). When these cells were harvested from a donor mouse shortly after they were generated at embryonic day 13 (E13) and transplanted into the visual cortex of a P10 host, they migrated and differentiated into the same types of neurons in the same cortical layers that they would have become had they been left in the donor. Strikingly, they induced a second critical period of plasticity 35 days after transplantation, long after the end of the normal critical period of the host (Southwell et al., 2010). No other manipulation that we knew of, and certainly no other manipulation of inhibition, could do the same thing to give the brain of an older animal the plasticity it has in early life.

We have gone on in a series of papers with the members of our laboratories to study this phenomenon in the hope that understanding its mechanism would lead to a therapy for recovery from brain injury or maldevelopment, and a company (which I have no part in) was founded to explore the therapeutic use of neural transplantation. We found out that only two of the many types of interneurons had the capacity to rekindle juvenile plasticity after transplantation (Tang et al., 2014), and that the transplanted neurons had to be able to release their inhibitory neurotransmitter GABA in order to do so (Priya et al., 2019). We also found that the transplanted neurons trigger changes in host circuitry to create the second critical period rather than establishing a parallel circuit of their own (Hoseini et al., 2019). But we still do not know how they do it, and our work on this problem continues.

Alert Mice and Adult Plasticity

After completing a spectacular doctorate on zebrafish at Stanford, Cristopher Niell joined the laboratory to work on a mammal in which visual responses would have much greater specificity. Cris did the first really thorough and quantitative study of visual cortical receptive fields in the mouse (Niell and Stryker, 2008), a task that we had previously punted on, doing only enough to measure ocular dominance. Cris's experiment was foundational. It was greatly facilitated by the use of 16-site silicon microelectrodes, which increased the rate at which we could measure responses by an order of

magnitude over the tungsten electrodes (designed by David Hubel 45 years earlier) with their single recording site that we had previously used. Up to this point, we had always studied responses and plasticity in anesthetized animals, and my, and other, experiments had made it clear that plasticity is not induced under anesthesia. We wondered whether the properties of neurons were similar when the mice were alert, under conditions in which plasticity could be induced.

After trying several unfruitful approaches, we adopted the apparatus just designed in David Tank's lab, in which a mouse with its head fixed stands or runs on a 20 cm polystyrene foam ball floating on air. Mice needed only a few minutes of experience to adapt to this apparatus, and they seemed alert and happy, ready to grab a sunflower seed or nibble at angel-hair pasta as readily as when they were in their home cage. We studied the receptive fields of neurons in the visual cortex in the alert animals exactly as we had done in anesthetized mice, and, to our relief, found that their properties were essentially identical (Niell and Stryker, 2010). However, the visual responses were much stronger when the mice were walking or running than when they were standing alert and still. We thought that this difference might be trivial, perhaps due to a little vibration of the eyes during locomotion, but when we made simultaneous recordings from the LGN, the responses did not change when the animals started to run. We concluded that we had discovered a new cortical state induced by locomotion that does not change spontaneous activity or the stimulus selectivity of each neuron but merely increases the gain of visual responses.

Cortical state had previously been studied only in sleep and during anesthesia, so we hoped to delineate the circuit that put the cortex into the high-gain state. Moses Lee, a medical doctor/doctoral student, joined Cris in stimulating the excitatory neurons of the midbrain locomotor center optogenetically, which made the mice run and put the cortex into the high-gain state. But the interesting finding was that turning the stimulus frequency or intensity down to the point that it no longer induced running still caused the change in cortical state. This implied that it was not making the legs move but some ascending projection that regulated cortical state (Lee et al., 2014). Tracking down which projection seemed difficult. A new postdoc from Josh Huang's lab, Yu Fu, had studied and helped to create mouse lines that could be used to manipulate specific classes of inhibitory neurons. Yu Fu went directly to the visual cortex and labeled various types of neurons one at a time, looking for the cells that carried the signal of locomotion to the cortex. We knew that most visual cortical cells are not driven by anything at all in the dark, so we used 2-photon calcium imaging to look for cells that responded to locomotion in the dark. A minor class of interneurons expressing vasoactive intestinal peptide (VIP) fired reliably whenever the mice walked or ran, and none of the other cell types did so (Fu et al., 2014). These VIP cells received powerful cholinergic input from a specific nucleus

of the basal forebrain, which receives input from the midbrain locomotor center. Optogenetically activating VIP cells in stationary mice mimicked the effect of locomotion on cortical state in sedentary mice, and photolytically damaging the VIP cells (blowing them away) prevented locomotion from putting the cortex into the high gain state.

Later experiments led by Yu Fu and Megumi Kaneko revealed a dramatic form of plasticity that takes place only when the cortex is in the high-gain state. When mice that were monocularly deprived for many months, mimicking human *amblyopia ex anopsia*, were shown a particular stimulus repeatedly during locomotion for an hour per day for five days as adults, the response of the visual cortex to that specific stimulus recovered as it would never have done otherwise (Kaneko et al., 2014). In intact adult mice, exposure to a specific stimulus during locomotion increased the response by 50%, and this increase persisted for weeks, while the same procedure had no effect when synaptic release from the VIP neurons was blocked (Fu et al., 2015). Megumi Kaneko tracked the responses of individual selective neurons using 2-photon microscopy and found that the persistent response enhancement, which we dubbed "stimulus-specific enhancement" (SSE), was not only stimulus-specific but also was specific to individual cortical neurons (Kaneko et al., 2017). Neurons selective for 45-degree lines were enhanced by exposure to 45-degree lines during locomotion, but exposure to 135-degree lines had no effect on them. Another postdoctoral fellow, Maria Dadarlat, took advantage of newer silicon probes with 64–128 recording sites that allowed simultaneous recordings from up to 100 single neurons. Her work showed that the representation of information about the visual world in the responses of cortical neurons was greatly increased during locomotion (Dadarlat and Stryker, 2017). To have the same degree of confidence in the identity of a stimulus being shown to a running mouse for 100 msec would take three to five times as long if the mouse were alert but just standing there.

We are actively pursuing the idea that this high-gain state, which in the mouse we can turn on by locomotion, is the one that in humans is turned on by selective attention. We are currently testing whether this is the circuit responsible for perceptual learning, which also requires selective attention.

Modeling Visual Cortical Circuits using a more Naturalistic Stimulus, Optic Flow.

Responses to the normal stimuli used in visual physiology experiments lend themselves to simple linear-nonlinear models but do not explain the reliable but highly selective responses of mouse visual cortical cells to what they see in the real world. Natural images, though, are hard to understand and mathematically nearly intractable. Optic flow is a ubiquitous feature of the natural visual world as an animal runs through it, but unlike natural

images, it is well understood and mathematically tractable. My old friend Steven Zucker, a mathematician and computer scientist who had been an external faculty member of our Sloan Center for Theoretical Neuroscience in the 1990s, had done interesting work in his own lab on the properties of optic flow and its implications for perception. Steve and I decided to study optic flow in mice as a "baby step" toward understanding vision in the natural world and as a new stimulus to enrich a novel approach to modeling the neural circuits that give rise to visual cortical responses. Postdoctoral fellow Mahmood Hoseini, a doctor of physics who had rapidly become a spectacular experimental neuroscientist, used 128-site microelectrodes and found that many neurons in the mouse visual cortex respond strongly and selectively to optic flows that have no energy in the models of cortical responses derived from conventional grating stimuli (Dyballa et al., 2018). This collaboration is carried out by hour-and-a-half-long Zoom videoconferences every week between Steve and his student Luciano Dyballa at Yale and Mahmood and me at UCSF, and it works surprisingly well, perhaps because we all know one another from visits and are friends. We have reason to be optimistic that the new analytic approaches and data will give us insight into the operation of visual cortical circuits, and we are pursuing this work actively.

Antivivisectionists

At times, I have been the target of antivivisectionists who would like to put a halt to the animal research that is the only hope for ameliorating human injury and disease. Dealing with this has sometimes been challenging for me and my family, but I am sustained by the knowledge that the public is with us and that it is only a few extremists among the activists who might actually be dangerous.

In 1981, when I was a beginning assistant professor, antivivisectionists broke into the UCSF animal care facility, did some damage, and took videos of animals, including my cats, some of which had an eyelid sutured for studies of critical-period plasticity. Other cats in those cages were actually completely blind as a result of tetrodotoxin infused into their eyes, but of course they looked normal. Months later, the producers of *60 Minutes*, then as now one of the most widely viewed programs on television, told the university that they were going to do a segment on the antivivisectionists using pictures of my cats, and they invited us to send someone to appear on the segment and respond. Wisely the university declined to send anyone. Fortunately, at that time the district attorney in San Francisco believed in law enforcement, and I was told that he threatened to charge CBS as an accessory-after-the-fact to the break-in if they used the videos. Eventually, it was agreed that CBS could use the videos so long as they did not identify the institution or investigator involved. The wonderful correspondent Ed Bradley hosted the *60 Minutes* segment, in which unbelievably creepy

people argued against animal research and narrated the videos from the break-in, trying to elicit sympathy for the poor cats with one eyelid sutured shut, comparing them to the "happy" ones jumping about the cage with both eyes open (which, unbeknownst to the antivivisectionists, were actually totally blind). Near the end of the segment, Ed Bradley asked the chief representative of the antivivisectionists whether, if his child had a disease that could be cured by the research being done on those cats, would he still want the research to be stopped. He replied with something like, "Well, I might be weak, but no, I would not want the research to be done." Bradley's last words before going to the commercial at the end of the segment were "You've got to be kidding!" That *60 Minutes* segment, in which the true personalities and nature of the antivivisectionists were revealed to a wide public, was a disaster for their movement, and they left us alone for several more years. Surprisingly, CBS recycled its expensive videotapes in those days, and no copy of the segment still exists to provide the antivivisectionist's exact quotation.

The most threatening episode for me came in 2001, when I was one of a number of keynote speakers at the International Union of Physiological Sciences meeting in Christchurch, New Zealand. Unknown to me, New Zealand, like the United Kingdom, had an active antivivisectionist movement, and I was surprised to be met at the airport by a secret service contingent that told me I should be under their guard for my entire time in the country. This was at a time when there was wide popular interest in animal research into critical periods because of its implications for child development, and I was scheduled to do several local television and radio shows, one of which was the New Zealand equivalent to PBS *Science Friday*. The first night, sleepless because of the time change, I snuck out of my hotel room to take a walk while the secret service slept in the two rooms to either side, and ended up being recognized and running from a group of antivivisectionists into a hotel that locked its door after me. The antivivisectionists were arrested by the police for trying to break down the door. Thereafter, I did what I was told by my guards.

Apparently, yellow journalism was then at least as prominent in New Zealand as in the United Kingdom. The day before I was to speak at the meeting, an open letter from the antivivisectionists was reproduced at the top of the front page of a major national newspaper:

> The "good" California "doctor" is a target. Such evil should not be allowed to exist. Our efforts in the next few days will show the world that we will not tolerate the presence or existence of such a monster. While the "conference" has heavy protection, there are still many opportunities for us: Long-distance firearms, explosive devices, "accidents," gas/chemical attack, additives to food and drink. These are just some of the resources we have access to, but there are some not listed. Before this person leaves New Zealand,

> he may be dead! Our only regret would be that his suffering would not be as long and hard as that of his innocent victims.

Another newspaper had a large picture of my face, above the fold on the front page, on a poster held up by one of the protesters.

I then declined to do any television, hoping not to be recognized as widely. However, I did do radio interviews about the science, but not about the politics. One interview had been scheduled for the mayor's office but was moved, without informing the radio audience, to a more secure place. A group of antivivisectionists broke into the mayor's anteroom and slammed the receptionist against the wall when she would not open the door to the office, which they then broke into. Fortunately, this assault was captured on video and the perpetrators were arrested.

At the same time, my family and I received a threatening letter at UCSF, which my secretary read to me over the phone. It seemed that this might not be an ordinary nut case but instead someone related to the New Zealand terrorists. I phoned the UCSF chancellor, and he and the UCSF police chief arranged with the Marin County sheriff to keep my house and family under 24-hour observation from a hillside nearby. Other than my wife and the school head and our next-door neighbor, no one else was informed, but our children were escorted by hand between the school and our car each day. As it turned out, the person making the threat was soon jailed for assaulting someone else, and the surveillance was ended.

What struck me most was the advice and encouragement I received from two courageous European scientists at the meeting who, unlike me, for whom the threats were transient and mostly far away, had endured continuing threats over years where they lived and worked, at the cost of great stress to them and their families. If they did not surrender and renounce animal research, then neither would I.

Outside Community Engagement

I have always believed in contributing to the wider community, and while I have served on the boards of various nonprofits and participated in MIT visiting committees and Howard Hughes Medical Institute investigator reviews, I have rarely had much free time. I have, however, devoted considerable time and energy to two institutions that are particularly close to my heart. I believe that Deep Springs college had a tremendous influence on me and that I owe it a lasting debt. I expect that I would have turned into an effete snob, a very different person, had I not gone there. So I was happy to join the board of trustees of the college and chair it for five years. I was proud that I could promptly and positively mobilize support to take care of major difficulties there, for some of which I shared the blame. UCSF is a health science campus without undergraduates, so it was exciting for me to

be immersed in contemplating and helping to make the liberal arts education at Deep Springs more nearly ideal, as well as to review the operation of the ranch and of campus life. The limit of two four-year terms on the board left a hole in my existence when this thing that I had attended to and often worried about multiple times a week was no longer part of my life. Since then, I have been thrilled to see Deep Springs flourish under new leadership, becoming coeducational when at the time of the 100th anniversary of its founding, the California Supreme Court finally dismissed lawsuits that had prevented it from doing so.

Three years after the founding of the Allen Institute for Brain Science, I was asked to join its scientific advisory board (SAB). The Institute was creating a definitive and comprehensive atlas of gene expression in the mouse brain. Microsoft co-founder Paul Allen usually came to the SAB meetings and asked questions that stimulated further research. It was his vision to create a new kind of institution for brain research, where open, team science could flourish to do something that simply would never be done in academics or industry—to pursue large, well-defined scientific goals, with high-quality control and clear performance milestones. Inspired by the policy of the human genome project for prompt release of data to the wider community, the Institute adopted the motto "Fueling Discovery." I bought into the vision completely and found my interactions with Paul, the other members of the SAB, the Institute president Allan Jones, and its leading scientists very exciting. Over the years since, my belief and involvement in the Allen Institute, which now includes Institutes for Cell Science and Immunology, has increased, and I am proud to have helped lead it on the course it has taken. With the untimely passing of Paul, my work on the board of directors, as well as on scientific advisory groups, has become a much larger responsibility, but one that I cherish. I do believe that some questions in biology will benefit enormously from the large-project, open, team science approach of the Allen Institute as a supplement to the conventional small-lab approach taken in academics.

Family

I had the great good fortune to fall in love with Barbara Poetter during the later portion of graduate school. She was then a freelance writer and later a book editor at Little, Brown, and we lived together, poor but happy, in Cambridge, Massachusetts. As the daughter of a management consultant who became a United Nations diplomat working on small-business development and who took his family to live in various developing countries, including Kenya, she had an understanding of the larger world that was rare among people I knew. She was amazingly self-sufficient, having traveled alone by bus through the Middle East at age 16, joining archeological digs and social service projects. Her self-sufficiency made it possible for me to do frequent all-night and weekend experiments and take our fun together

when our work permitted. We married a few months before driving to San Francisco where I started at UCSF. She then worked as a copy editor on scientific books and papers, and we enjoyed the west-coast culture and natural world, eating dinner at 9:30 p.m. and splitting a bottle of inexpensive wine most nights until our children were born.

After two years, we had our first child, Matthew, and bought a house a five-minute drive from the lab. After another two years, we had a second, James, and then a third, Emily, three years later. Barbara worked 80% time after the first, 60% time after the second, and 40% time after the third, making it possible for me to work ridiculous hours in my lab. I went home for dinner, but lacking an office in our tiny house, it made sense for me to go back to the lab after the children went to sleep every night. My presence in the lab meant that I was there to participate in all of the late-night microelectrode recordings, and I believe it made our research much better. But it was possible for me to have both this and a wonderful family that did not suffer from my overwork only because Barbara was always there. The children were a delight, each one a completely different person, but all enjoyed our weekly excursions to Ocean Beach, 10 minutes away from our house, to the UCSF campus for swimming lessons, and to Golden Gate Park for bike riding and museum visits. I now regret that we did not take more trips to the mountains in the winter for cross-country skiing, which the children did from age 3 or 4, or more summer vacations in Europe, which happened only when I had accumulated enough frequent flyer miles to make the trips affordable, or in Hawaii, for which the airfare was cheaper. During our sabbatical year in Oxford when Matthew was 7, we lived on Boars Hill, and he and his brother went to the local school opposite the 14th-century church, whose vicar came weekly to the school to give moral instruction. It was a wonderful family time together, with lots of vacation in the United Kingdom and in France outside Oxford's three eight-week terms per year.

Seven years later, I became department chair, and we moved across the Golden Gate Bridge to a bigger house in an idyllic community surrounded by redwoods where the public schools were great, the children could go everywhere on their bicycles, and I could no longer go to the lab after supper. We soon had our fourth child, Jenny Marie, and I had the gift of lots of time with her as the older children wanted to spend less and less time with parents. All of the children have found fulfilling careers, and all but Jenny Marie live in San Francisco. The three older ones have found wonderful spouses and have given us our first grandchild, with two more now on the way. All of us in the Bay area get together every few weeks for dim sum in the city, and we often see them at our house on weekends. They are the source of my greatest happiness.

Perspective

It is good for one's self-esteem to realize that even scientists whose work changed the field mostly disappear. The stories of their lives and how their discoveries were made are forgotten, but the field continues in its altered direction. I was recently shocked to find that none of the 20 graduate students in our first-year course knew the name of Steve Kuffler—one of the figures in neuroscience I had admired most at their age. Yet they all knew about the center-surround receptive fields that Kuffler had discovered.

I was tremendously fortunate to be part of three institutions that each believed, with some justification, that it was creating the future. I feel lucky to have known the founders whose animating visions had created those institutions. Hans-Lukas Teuber founded a new Department of Psychology and Brain Science at MIT to study the mind as Helmholtz would have intended were he alive in the 1960s, from human patients through psychophysics, neuroanatomy, and neurophysiology to cognitive science. Steve Kuffler founded the Neurobiology Department at Harvard that came to define the term *neurobiology*, from biochemistry through neurophysiology. We at the UCSF Neuroscience Program and PIBS tried to be like Harvard's department but more open, more humble, and freer to engage with our colleagues in the rest of modern biology than Harvard was when I was there. To be present in the early years in which these institutions were flourishing was truly thrilling.

I feel lucky to have had a life in science at the dawn of the true golden age of my field. Seemingly chance occurrences got me to this place: admission to Deep Springs, the high-paying job cleaning rat cages, the arbitrary choice to go to East Africa instead of graduate or medical school, the good fortune of rejection by Penn sending me to MIT to work with Peter Schiller, the chance that I gave a lunch seminar at Harvard neurobiology, and the flyers I took on ferrets and then on mice. The constant feature has been the good will and integrity of nearly everyone I have known in my career. My science friends, many of whom I did not have space to mention, have been a great joy. Most of all, it has an extraordinary privilege to work with the young people who have joined my lab, letting me profit from their energy, brilliance, and in many cases friendship, and I hope that I have given them some fraction of what my mentors gave me. Their names, in approximate chronological order, follow.

PhD Students:
Kathleen R. Zahs
Kenneth D. Miller
Holger Reiter
Barbara Chapman
Edward S. Ruthazer

Joshua Gordon
Takao Hensch
Deda C. Gillespie
Michael A. Silver
Sharif Taha
Jessica L. Hanover
Laila Dadvand
Matthew Caywood
Melinda Owens

Postdoctoral Fellows:
Axel Schoppmann
Margaret I. Law
Robert Levy
David Waitzman
Jonathan Horton
Gary Baker
Yoshio Hata
Michael Crair
Michela Fagiolini
Tony Pham
Joshua Trachtenberg
Christopher Trepel
Naomi Ruff
Naoum Issa
Virginia Desa
Marcos Frank
Valery Kalatsky
Jianhua Cang
Megumi Kaneko
Tatyana Sharpee
Masaaki Sato
Marianne Fyhn
Torkel Hafting Fyhn
Sunil Gandhi
Cristopher Niell
Dan Darcy
J. Sebastian Espinosa
Yu Fu
Maria Dadarlat
Nikhil Bhatla
Yujiao (Jennifer) Sun
Mahmood Hoseini
Benjamin Rakela

Research Faculty:
Antonella Antonini
Siegrid Löwel

Research Support:
Sheri Strickland Harris

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