The History of Neuroscience in Autobiography
Volume 11

Edited by Thomas D. Albright and Larry R. Squire
Published by Society for Neuroscience
ISBN: 978-0-916110-03-1

Mary B. Kennedy

pp. 104–137

https://www.doi.org/10.1523/hon.011004

Light Microscopy

Mary B. Kennedy

Born:

Pontiac, Michigan
July 4, 1947

Education:

St. Mary's College, Notre Dame, IN
Johns Hopkins University, Baltimore, MD

Appointments:

Assistant Professor of Biology, California Institute of Technology (1981–1984)
Associate Professor, California Institute of Technology (1984–1987)
Associate Professor with tenure, California Institute of Technology (1987–1992)
Professor of Biology, California Institute of Technology (1992–2002)
Allen and Lenabelle Davis Professor of Biology, California Institute of Technology (2002–2020)
Director of the Moore Center for Integrative Study of Cell Regulation, California Institute of Technology (2006–2012)

Honors and Awards (Selected):

McKnight Neuroscience Development Award (1984)
Faculty Award for Women Scientists and Engineers, National Science Foundation (1991)
Fellow of the American Association for the Advancement of Science (1991)
Javits Neuroscience Investigator Award, National Institutes of Health (1992)
Fellow of The American Academy of Arts and Sciences (2002)
Fondation Ipsen Prize in Neuronal Plasticity (2006)

Mary Kennedy is a pioneer in the elucidation of biochemical mechanisms underlying learning and memory. She was trained in traditional biochemistry, studying lipid metabolism in bacteria. After receiving her degree, she moved into the study of biochemical regulation in the nervous system and for the past 40 years, has studied control of synaptic plasticity in the postsynaptic spines of glutamatergic synapses. She first purified and studied calcium/calmodulin-dependent protein kinase II (CaMKII), showing that it is highly concentrated in the brain, particularly in the postsynaptic density, and becomes calcium-independent upon autophosphorylation, resulting in switch-like enzymatic behavior. She showed that CaMKII is a major target of calcium ion entering through N-methyl-D-aspartate (NMDA)-type glutamate receptors during induction of long-term potentiation. She expanded her study of the postsynaptic density by using microchemical tools and genetic engineering to discover new protein constituents, including PSD-95, the major scaffold protein of the postsynaptic density. She discovered PDZ domains within PSD-95 and, with Peter Seeburg, was the first to show the importance of PDZ domains for protein localization, including anchoring of NMDA receptors at the postsynaptic site. She has studied the roles of CaMKII and other synaptic proteins in the regulation of the number of AMPA-type glutamate receptors located at the synapse during activity-induced changes in synaptic strength.

Mary B. Kennedy

Like the *Tale of Two Cities*, my early life in science is two parallel stories. One is about the best that a scientific career has to offer. The other is a sad tale of the misogynistic barriers faced by women scientists of my generation. In my case, the latter tale is particularly grotesque; however, my story is not complete without it. I chose to use this autobiographical chapter to reveal how I got from Pontiac, Michigan, to Caltech, and to recount my experiences in the first six years there. Much of this material was difficult to write and may be difficult to read. But it is a story that should be told.

I have been blessed with many wonderful students and postdocs, most of whom don't appear in these pages. I hope they know that I appreciate their friendship, support, and hard work in the lab. I also fervently hope that I did more to help them along the way than some of my early mentors did for me. I also won't do justice to the many scientific friends and colleagues with whom I have shared meetings, dinners, and long satisfying talks. These are the people who kept me going. They include Eric Schwartz, Marge Livingstone, Kristen Harris, Eve Marder, Carol Barnes, Martha Constantine-Patton, Susan Goelz, Manfred Baetscher, Dana Aswad, Eric Nestler, Pietro DeCamilli, Tom Reese, Dan Johnston, Nelson Spruston, Ron McKay, Susan Catalano, Peter Seeburg, Hannah Monyer, Anne Young, Nancy Wexler, Barbara Wold, Judy Campbell, Pamela Bjorkman, Henry Lester, Kai Zinn, Marianne Bronner, and Leah Goentoro; most recently, they also include Regina Dugan, Marga Behrens, Bill Loomis, Tom Bartol, Terry Sejnowski, and Jost and Susanne Vielmetter. My four sisters and my brother—Beth, Janet, Nancy, Jean, and Tom—have been my secret weapon, providing me strength and sustenance when I most needed it.

Childhood

I was born in Pontiac, Michigan, in 1947 where my father, with a degree in educational administration, was a high school principal and my mother, although trained as an artist and teacher, was a homemaker. We lived outside Pontiac on Green Lake in a lovely house that my father built with a picture window looking out over the lake. When I was five years old, my parents' family had grown to three girls, and his principal's salary was no longer sufficient, so they moved to South Bend, Indiana, where my father opened a StrideRite shoe store.

My parents firmly believed that their primary parental role was to foster their children's independence. They allowed us to explore the woods and fields around Twyckenham Hills, our suburban housing development, at

will, and to find our own friends among our schoolmates and the many children who gathered at the community pool in the summer. I now realize that this early independence gave me a self-confidence and inner strength that served me well in my later career. Indeed, I would not have survived as a scientist without it.

In the 1950s, the Catholic grammar school that I attended taught "reading, writing, and arithmetic" well, but there was little education about science. Nonetheless, I became fascinated with the plants and creatures that I encountered in the woods and found library books to learn about them. At the age of about 10, I announced to my friends at the pool that I wanted to be a naturalist when I grew up. The older children politely told me that they didn't think that was a job. A naturalist was a person who walked naturally and talked naturally. Undaunted, I found an advertisement in a comic book that promised a microscope as a prize for selling a certain number of flower and garden seeds. I wrote away for the seeds and went door to door trying to sell them. I was not an outgoing child, and this task soon exhausted me. I had not specified flower seeds, and so I had a large number of vegetable seeds to sell in a neighborhood where home gardens were nonexistent. Tired of hearing me complain at the dinner table about not being able to sell the vegetable seeds, my father finally told me that he had found a "farmer friend" who would buy the seeds. I protested, but he assured me that this was true. The microscope was delivered, and I reveled in finding tiny creatures in ground water. This early curiosity, one could say passion, drove my interest in science. The passion was internal, and I can't point to any family history or single event that ignited it. I will add, though, that the seed-selling experience engendered a strong disinterest in business and selling, which persists to this day.

I attended St. Joseph's High School, a Catholic school across town near University of Notre Dame and run by the Holy Cross religious order. (Yes, this is the same high school attended by 2020 democratic presidential candidate Pete Buttigieg three decades later.) The classes were uneven in quality, but many were taught by student teachers from Notre Dame and were excellent. These included stellar courses in English literature and composition, an excellent introductory course in biology, and an "enrichment" course in mathematics during the summer at Notre Dame. During the years I was there, St. Joe was "co-institutional," meaning that girls' and boys' courses were taught separately in separate wings of the building. After-school activities and lunch period were "mixed." The only physics course was offered by a religious brother (the male equivalent of a nun) on the boys' side. In a sign of changing mores (this was 1968), several fathers of girl students (including mine) went to the men's and women's principals and informed them that it was not acceptable that girls were not offered a physics course. Unfortunately, the physics teacher informed them that he did not want to teach girls. This was my first introduction to the unique machismo

associated with the discipline of physics. So, instead, the school offered to arrange for girls to take their physics courses at local public schools in the last period of the day. Attending this course would have meant that I couldn't participate in any of the after-school activities. I was a cheerleader; so I declined the offer rather than give up cheerleading.

This segregated high school education had undeniable psychological effects on me and on the other girls. I believe that our teachers were committed to offering the best possible education to girls as well as boys. Fortunately for me, the classes at St. Joe, at that time, were "tracked" according to perceived academic ability. I was placed into college prep courses, populated, presumably, by those who tested well or had high grades. Whatever one might think of this practice now, it meant that I received a high-quality education (except in physics). However, by my senior year, I realized that many of my male friends, mostly also in "college-prep" courses, had internalized a notion of male dominance that made me uncomfortable. I was a pretty teenager and was often pressured for dates with maneuvers that I now understand were meant to demonstrate this dominance. I kept a distance from such behavior. However, in my senior year, I finally found a boyfriend whom I could talk to easily and who respected my intelligence. When his male peers discovered that we were an item, he was awarded a "lumber-jack shirt" for his "achievement" by a group that called themselves the "steady-fist club." (The idea was that their outstretched fists remained steady until they had kissed a girl.) This embarrassed him and even made him angry. We remained a young couple for two and a half years until his growing interest in religion, and my alienation from religion, led us to break up.

One last anecdote from this period of my life involves a conversation at a high school reunion that took place about three years after I graduated. A tall, pleasant young man whom I had known slightly struck up a conversation and asked me what I was planning to do after college. I said that I was going to attend graduate school in biochemistry. He smiled, looked down at me, and said, "Better be careful, no-one will want to marry you." I have never forgotten that. It was the first time I began to think that marriage might not be such a good idea for me.

College

I was faced with a difficult choice when I was admitted to the Unified Science program at the University of Michigan. My new boyfriend was going to attend Notre Dame, which at that time didn't admit women. I was also admitted to St. Mary's College, the girls' school across the road from Notre Dame. I had a starry-eyed impression of the University of Michigan because my mother had gone there; however, at the last minute, I decided that I didn't want to be that far away from my boyfriend, so I enrolled at

St. Mary's. My parents found a way to pay for me to live on campus beginning in my sophomore year.

Fortunately, St. Mary's has a well-deserved strong reputation as a liberal arts college. In retrospect, my preparation for later graduate work at Hopkins was strong. When I arrived at St. Mary's, it had just become possible for "St. Mary's girls" to major in physics by taking the advanced courses at Notre Dame. I decided to try a physics major because, I think, the denial of physics courses in high school made me anxious to try it when the opportunity arose. An incident in my sophomore year, when I took the first major's course in classical mechanics at Notre Dame, illustrates once more the atmosphere I faced as a young girl studying science in the mid-1960s. I enjoyed the mechanics course; the professor was a good teacher and supportive of the two girls who were enrolled in his class. I studied hard for the first test and worked together with some of the young men in the class to do homework problems and prepare for the test. The draconian practice at Notre Dame at that time was to post all the students' grades outside the door of the class after each test. When the grades were posted, I found I had scored the highest grade. Of course, this should have been a happy occasion. However, one of the young men with whom I had studied said to me, "Well, I'm not going to help *you* anymore." Again, that remark was seared into my memory. It is a perfect example of the negative feedback for a positive achievement that I would experience often in my career. I realized that I would be quite intellectually isolated if I majored in physics by taking the Notre Dame classes. This incident, together with a bewildering course in quantum mechanics, also at Notre Dame, soon sent me happily back to work on a chemistry major at St. Mary's.

Most of the chemistry professors at St. Mary's were exceptional teachers. The advanced classes and labs were small, numbering perhaps 10 students. I loved learning the science and came away with a strong grounding in organic and physical chemistry, along with supporting courses in mathematics and genetics. Though I will never know for sure, the small size of the classes at St. Mary's might even have given me a better preparation than would the larger, more diverse classes at Michigan.

The curriculum at St. Mary's included a set of rigorous courses in English literature, philosophy, history, and languages. Critical reading and writing skills were emphasized in all of the classes. I have never regretted taking the time to acquire a liberal arts background. It gave me a broad perspective and has enriched every aspect of my life.

My nonacademic life at St. Mary's was more complicated. This was the late 1960s. The Civil Rights Movement had just culminated with the passage of the Civil Rights Act of 1964, the Vietnam War was heating up and young men of my age were being drafted. I had a strong interest in the public sphere and took my role as a citizen seriously. By my junior year, I had parted ways with my high school boyfriend and was spending time

with a relatively small group of students at Notre Dame and St. Mary's who actively opposed the war. While a few professors supported and encouraged us, we found ourselves in political conflict with many professors and other students. The fraught atmosphere of that time pervaded my college and graduate school years until the war ended. Because I was able to articulate political arguments clearly and easily, I often became an impromptu spokesperson. Many professors and administrators interpreted my words as intolerably brazen. On the one hand, these experiences deprived me of a significant portion of a socially comfortable young adulthood. On the other, they taught me how to fight for social change and honed a toughness that would stand me in good stead in my later career.

The Summer of 1969

In my junior year near the beginning of 1968, I began a relationship with a Notre Dame senior who was a student activist majoring in political science. Like many in that generation, he was wrestling with his own political views and what he wanted to do with his life. He moved to Georgetown to study for a degree in foreign affairs and soon joined the local chapter of Students for a Democratic Society (SDS), which was the foremost student organization opposing the war. We kept in touch and I visited him through my senior year and his first year of graduate school.

1968 was a turbulent year on most college campuses. I was passionately opposed to the war and traveled to Washington, D.C., to attend large "Mobilization" anti-war rallies. I also traveled to attend national meetings of SDS with my boyfriend, getting to know the other members of the "Washington D.C. collective." These were interesting, even somewhat bizarre experiences. The SDS leadership in Chicago had begun to explore far-left "revolutionary" ideologies. I watched, with what I now realize was scientific detachment, as individuals like Bernadine Dorne and Bill Ayres debated which ideological "line" was correct. I remember one meeting in a rural setting in which young people strutted across a stage, one after another, debating whether SDS should "take up the gun." In one vivid memory, I was riding on the passenger side of a car driven by my boyfriend with rain sliding off the windshield wipers. He asked me what I had thought about the discussion of "taking up the gun." I answered that it seemed to me the problem was that even if their wildest dreams came true and one million people took up the gun with them, there would be one hundred ninety-nine million people shooting back. He answered, "Well, see you're just a liberal."

By the end of my senior year, my boyfriend had "broken up" with me for another SDS member, but I had accepted a graduate school position in the Biology Department at Johns Hopkins and I wanted to maintain contact with the other individuals in the Washington collective. Most of them were not interested in fomenting violence, but rather wanted to live and

work in the poorer "working-class" communities and try to find a way to organize them to oppose the worst excesses of capitalism. I felt a commitment to remain in touch with their political movement, but I was also still committed to becoming a scientist. It seemed to me (naively) that I could be a connection between the scientific community and the left-wing student movement. These dual commitments led me to live for the summer before starting graduate school in a collective house with a group of SDSers from Washington who had decided to move to Baltimore to establish a movement there. Baltimore was still quite rigidly segregated; we moved into a row house in west Baltimore in the middle of a poor white neighborhood. The idea was to get to know our neighbors. I was much too introverted to do this well, and I recognized immediately that the neighbors thought we were quite odd. By the end of June, it was clear that I should get a summer job to help contribute rent and food for the group. I answered an ad and applied to work in a plastics factory in northwest Baltimore, using my real name. I did not mention my education beyond high school. On my first day, the foreman asked me solicitously why I wasn't going to college. (I realize now that he could tell right away that I was not from the same Appalachian background as most of the other workers.) I replied that my father wanted me to go to college, but I didn't like to read. He replied very kindly that I could major in something like chemistry. To this day, I don't know whether he knew my actual identity and my plans to attend Hopkins in the fall. This was well before the internet was invented, so a search of my name would have been difficult. He remained friendly and fair during my time working there.

My job was to work with others at various stations to assemble plastic trees for toy electric railroad train sets. We would be given a pile of cast tree trunks with wire branches, dip the wires into molten plastic and then roll them in brightly colored small foam shapes to mimic leaves. I didn't discuss politics at all, but rather approached this as a learning experience. One of my favorite co-workers was a middle-age Appalachian lady named Lily. She chatted happily with me as we worked. She learned that I was 21 years old and asked about my husband.

When I told her that I wasn't married, she looked genuinely surprised and said, "You's twenty-one and you ain't never been married?"

Before I could answer, the assistant forewoman, Hatty, who didn't want Lily to hurt my feelings, shushed her and said, "Now, Lily."

Lily answered, "Hell, Hatty, Ah didn't mean nothin'. If Ah 'uz twenty-one and knowed what Ah know now, Ah wouldn't be married neither!"

By the end of the summer, most of the workers seemed to accept me. When I confessed, just before I quit, that I was leaving to go to graduate school at Johns Hopkins, they seemed incredulous. Hatty just nodded knowingly, as if to say, "Sure. Sure."

My commitment to the student movement, and my time living in West Baltimore, set the stage for my nonacademic life at Hopkins. I maintained

my ties with the anti-war, left-wing student movement throughout my time in graduate school, although I quickly found the student movement at Hopkins and became less directly involved with SDS.

Graduate School

My years in graduate school, from the fall of 1969 through the summer of 1975, were truly "the best of times and the worst of times." I loved the academic work in the vibrant Biology Department on the Homewood campus of Hopkins and later in the Biochemistry Department at the Medical School. The coursework was exactly what I was looking for, preparing me to study the molecular mechanisms of individual cells, the basic units of life. As I entered graduate school, I had a strong interest in studying the cells of the nervous system, which enthralled me with their power and complexity. However, interdisciplinary study of "neuroscience" was still very new. I was advised to get a strong foundation in biochemistry to prepare me for later more specialized research. This seemed sensible to me. I still have the large blue cloth binders that I filled with detailed notes about "biochemistry and biological oxidation," "carbohydrate chemistry," and mechanisms of "gene expression," which were still mostly mysterious at that time. I took an optional course in advanced organic chemistry to better understand the chemical reactions of enzyme catalysis and metabolism, and a rigorous course in biophysical chemistry, which was actually an introduction to the young field of X-ray crystallography and the study of protein atomic structures.

In those years, the fields of biochemistry and cell biology were sufficiently cohesive that the Biology Department at Homewood held monthly evening symposia at which each of the faculty presented their latest work; their principal aim was to educate the graduate students. These were held in a large well-lighted hall with tiered seats facing a lab bench and blackboard. Saul Roseman was chair of the department and a leader in the study of membrane transport. Like most basic mechanisms, transport systems were first worked out in bacteria from which the constituent enzymes could be purified and studied in detail. Roseman's lab discovered and elucidated the enzyme system responsible for adenosine triphosphate (ATP)-driven sugar transport in *E. coli* (the "phosphotransferase system"). I clearly remember his evening presentation in my first year. He began by explaining that there are two kinds of scientists. One kind wants to posit simple models that might account for a given cellular process, and then design experiments to test whether the model might be correct. The other kind believes that "No biochemist is smarter than an *E. coli* cell." This statement had a strong influence on me. He was emphasizing that the best approach is often to let experiments guide your conceptual models of cellular mechanisms in a highly fluid manner. Saul Roseman was a brilliant teacher. He showed

us how to see the meaning and the limitations of data. I recall another time after a class in which we had examined the classic papers of Hodgkin and Huxley on the ionic basis of the action potential. One of the students insisted that those papers showed definitively the mechanism underlying the action potential. Roseman said, "No, what does that data actually show?" I realized that he wanted us to see that the data showed only the kinetics of the voltage-dependent fluxes of sodium and potassium ion across the membrane, but not the underlying protein mechanisms. When I said so, he answered, "That's right." It was many years later that biochemists, including Bill Catterall and Rod MacKinnon, demonstrated how the movements of transmembrane voltage-dependent ion channels generate action potentials. I gradually found that the questions that interested me most involved the intricate systems of protein mechanisms that underlie cellular function. These hours spent learning how to think about biochemical experiments were "the best of times" for me.

At the same time, the Vietnam War was spinning out of control and Walter Cronkite announced the infamous "body counts" every night during the evening news. These were "the worst of times." History was unfolding around us as the Berrigan brothers led a draft resistance; Daniel Ellsberg, in an act of conscience, released the Pentagon Papers to the *Washington Post*; Cronkite began reporting that the nightly "body counts" were generally considered to be unreliable; and we all knew that the war was a disaster and our government was lying to us about it. I somehow found time to affiliate myself with the student movement on campus, and with a loose confederation of left-wing groups in greater Baltimore that opposed the war.

I will relate a few vignettes that illustrate the flavor of my activism during the first three years of graduate school (1969–1972). One of my lab rotations in the first year was with Dr. Doug Fambrough. I chose his lab because I was already interested in neurons and neuroscience. In the nearby affiliated Carnegie Institute, he was studying the cell biology of neuromuscular development and was affiliated with the Biology Department. I started out learning such basic procedures as how to measure protein concentration by the Lowry method. I was given a small desk in the lab and personalized the space by putting some pictures and newspaper clippings on the wall immediately in front of it. One of these was a clipping from the *Guardian* newspaper showing a five- by three-inch picture of Ho Chi Minh with a poem titled "Poem from Prison" below it. (Ho Chi Minh wrote dozens of poems in prison. I don't remember which of these it was; the poems usually expressed his love of the countryside of Vietnam and his desire to be free to help his people.) After a few days, Dr. Fambrough came to my desk and asked me, "Who's that ugly face?" I answered with a smile that it was Ho Chi Minh. He said that I should take it down because not everyone in the lab was against the war, and he didn't want politics in the lab. I took it down, but then thought about it overnight. I realized that if I allowed myself to be

censured at this stage of my career, the compromising of principles might never end. The desk space was, after all, assigned to me. I put the clipping back up. The next day, I found it taken down and put into my top drawer. I put it up again. The next day, Dr. Fambrough came to my desk and told me that it would be best if I found another lab to work in. I said that was a good idea. It was easy to move to another lab because I was still a first-year student and because several faculty members were more sympathetic to the anti-war movement than Dr. Fambrough. I recount this incident because it later became well known, in an exaggerated form, in the small neuroscience community surrounding the Harvard Neurobiology Department, which I later joined. I think it was spread by Paul Patterson whom I met later in my graduate career. Zach Hall once told me, with great amusement, that he had heard that I had put a poster of Mao Tse Tung on the lab refrigerator. That didn't happen.

At the beginning of my second year, the anti-war movement was at its peak and there had been a short but tumultuous student strike at the undergraduate Hopkins (Homewood) campus after the invasion of Cambodia in May 1970, demanding an end to military recruitment on campus. After a vote of the student body, military recruitment was ended, but only briefly. It was later reinstated after congress banned military spending at universities that didn't allow military recruiting. Later in June, in a display of hubris (as I judge looking back), the Hopkins SDS chapter decided to protest the sizable investment of the Hopkins endowment in South African Krugerrands. The Apartheid policy had not yet ended and there was a national movement for divestment in South Africa. It was mid-summer and many of the undergraduates had left campus, so the remaining students decided to stage a sit-in at the meeting of the governing executive committee of the university that was occurring on campus. A group of about 20 of us somehow opened the door of the meeting room, filed in, and sat down on the floor around the perimeter of the boardroom. Someone announced to the committee why we were there and what we wanted (divestment in South Africa). Needless to say, the committee was not pleased. Eventually, after stating our concerns, and after an angry dialogue, we left the room. The president of the university at that time was Lincoln Gordon, who had been an ambassador to Brazil under Presidents Kennedy and Johnson. He was fed up with student protests and ordered a faculty "trial" to decide how to punish those who had "invaded" the executive committee meeting. I have a few clear memories from this "trial." The faculty members picked as "judges" sat in front behind some tables and appeared intensely uncomfortable (head down, chairs pushed away from the table). The proceedings were recorded by a male court reporter on a small steno machine. Near the end, the student chaplain, Chester Wickwire, gave a short speech lauding the social consciences of the students and recommending no disciplinary action. Wickwire was eloquent; at the end of his speech, I recall clearly, the

court reporter took his hands off the steno machine and clapped. I found this moving. In the end, the faculty judges recommended no disciplinary action. However, Dr. Gordon was not satisfied with this recommendation and decided to suspend all of us for the summer academic period. For the undergraduates, this had little consequence. I was one of the few (perhaps only) graduate students who had participated. The consequence for me was that I lost my student housing for the summer, and I technically couldn't be paid a stipend or work in a lab for the summer. The faculty quickly figured out how to circumvent this problem for me. A history professor let me stay in a guest bedroom in his large home for the summer. I had met, and briefly dated, Paul Patterson who was a fifth-year graduate student working in the Medical School Biochemistry Department. His adviser, Dr. William Lennarz offered to have me rotate in his lab for the summer and eventually arranged to pay me after the summer ended. I remember Saul Roseman telling me in his chair's office that "he didn't know what I was doing for the summer." It was clear that he meant that he would not reveal that I was working at the medical school. I also remember Roseman quoting Thomas Jefferson to me, saying something about listening to the young people. Eventually, I decided to do my thesis work in the Lennarz lab and switched to the Medical School graduate program after my second year.

Another incident while I was still rotating at the Homewood campus, is worth retelling in the age of "Me, too." Because of my interest in neuroscience, I wanted to see how electrodes were used to record electrically from individual cells. A professor in the Carnegie Institute was routinely recording electrical signals from individual heart cells in culture. I asked if I could observe a recording session. He agreed and told me to come by late one afternoon. I detected something a little strange right away as he hovered over me while I was looking through the microscope. It was raining that day. After the recording session, he offered to drive me over to my dorm, which was a few blocks away. He put his hands on me as he helped me with my raincoat. When he parked his car at my dorm and got out of the car with me, I became quite uncomfortable. He asked if I wanted to get some coffee in the graduate student cafeteria on the ground floor. After we had coffee, he followed me up to my room. At this point, I knew what was happening. He followed me in the door. I sat in a single chair in the living room and he sat on the couch. He began talking about how we had a "chemistry." He was rather insistent about staying. Finally, I stood up and told him that he should "leave now," which he did. I was later told by a friendly faculty member that this same professor had stated in a faculty meeting about graduate students that I was spending too much time on "political stuff." The faculty member told me that this was inconsequential for the moment, but wanted me to know who had said it. The friendly faculty member didn't know about the incident in my dorm and I didn't tell him. In retrospect, I'm grateful for the strong sense of boundaries and relative fearlessness that my parents instilled in

me, and that I believe my Celtic heritage reinforces, because they allowed me to stand up to the offending professor.

The four years (1971 through 1975) during which I carried out my thesis work in the Lennarz lab were occupied with research on lipid metabolism in *Bacillus subtilis*. I learned fundamental procedures of biochemical research and experimental design. I also benefited enormously from the weekly journal clubs that were held in the department and for which attendance was mandatory. Learning to read, interpret, and present original research papers was at the center of my education in these years.

At the same time, I lived in a large community of leftist and feminist young people, living in the typical Baltimore row houses near the Homewood campus. During these years, the feminist movement was changing women's thinking throughout the country. In my community, I participated in "consciousness-raising groups" in which groups of women from different backgrounds shared experiences, worked through problems and read books together. I also participated in a small leftist reading group in which we read some of the fundamental "radical" literature, ranging from the Port Huron Statement (an idealistic statement of goals written by Tom Hayden at the forming of SDS) to the Communist Manifesto. When I had time, I went to demonstrations and teach-ins sponsored by various political groups. I was never a leader in these groups because my first priority was still my graduate work. However, these groups formed my social life and taught me how to be a political activist.

I recall one of the more exciting events, which illustrates the prevailing issues and tumult of these times. Someone at the Homewood campus, perhaps the chaplain, Dr. Wickwire, had gotten word that the Baltimore police planned to raid the home of some of the leaders of the Baltimore chapter of the Black Panther Party. A few years earlier, Fred Hampton, a leader of the Chicago Black Panther Party had been killed in his bed, along with several others, during a raid by the Chicago police and the Federal Bureau of Investigation (FBI). The students were determined that we would not allow this kind of night-time murderous raid to happen "on our watch." The Baltimore Black Panther house was located in the largely black residential area north of the Medical School campus. A large group of us decided to sit on the sidewalk outside the Panther house beginning in the early evening and staying through the night to prevent an attack on the Panthers. Someone cleverly decided to post a few students in parked cars on the routes that the police cars might use. They were to begin honking if they saw police cars approaching. I have a few clear isolated memories from that night. One involves hearing the sound of honking long after dark that warned us that police were approaching. I remember seeing two police cars pull up about a block and a half away from us across a vacant lot. Officers opened the trunk of one the cars and in the light from street lamps I saw them remove two large rifles from the trunk and hold them up high in front of them. I stood

up and moved to the edge of the group near the street where I could be seen. I was wearing my usual "uniform" consisting of a green surplus army shirt and jeans. At the time, I had long dark blonde hair and looked younger than my 23 years. A bit later, I recall seeing a police car move slowly down the street passing our gathering. The police chief, a familiar face to all of us, stared gloomily out the window of the back seat and looked right at me.

It is interesting to me that I felt no fear at that time. I felt pride that we were able to put our "white privilege" in the way of what could have been another tragic killing. I knew that the police were not going to shoot past a person that looked like me. The raid was apparently called off and all of the police cars left. Dr. Wickwire told us later that the police chief had chastised him for bringing all these young Hopkins kids into such a situation. I don't know whether any legitimate arrests were ever made. I do know that there was no shoot out. I believe the attention we brought to the situation may have caused the police to act with more caution. Several years later, in 1982, after a series of legal actions that went back and forth from district court to the 7th circuit court, to the Supreme Court, and back to district court, relatives of the murdered Chicago Black Panthers were awarded a total of 1.8 million dollars in damages. These law suits and others revealed illegal spying on Black Panthers and liberal student activists by J. Edgar Hoover's FBI in an elaborate and now infamous operation called COINTELPRO.

As I was finishing the last year of my thesis work, I arranged a postdoctoral fellowship with Dr. Edward Kravitz in the Harvard Medical School Neurobiology Department. I knew about this unique department because Paul Patterson had done his postdoctoral work there with Drs. Furshpan and Potter and subsequently had become a junior faculty member. After defending my thesis, I moved to Boston during the summer of 1975, driving a U-Haul to a group house in Woods Hole, on Cape Cod, rented by the Kravitz lab members. Ed and his lab were leading a portion of the summer course in neurobiology at the Woods Hole Laboratory.

Harvard Postdoc (mid-1975–1978)

The transition to the Neurobiology Department felt magical to me. I had long wanted to study the biochemistry of nerve cells and finally would have a chance to do so in the renowned Harvard Department. This interdisciplinary department was the first of its kind in the United States, perhaps in the world. It was founded by Dr. Stephen Kuffler, a pioneering cellular electrophysiologist, and its other senior members included Drs. Hubel and Weisel representing systems neurophysiologists; Drs. Furshpan and Potter, developmental cellular electrophysiologists; and Dr. Kravitz, an invertebrate neurochemist. Junior faculty members in each of these disciplines and in neuroanatomy were added gradually, including many future leaders of the newly integrated field of neuroscience; Zach Hall, Story Landis,

Paul Patterson, Ann Stuart, Ursula Drager, John Hildebrand, and Simon LeVay. Similarly, the list of students graduating from the department reads like a roster of leading figures in neuroscience. The magical feeling was accentuated by the ambience of Woods Hole, located on Vineyard Sound at the base of Cape Cod. The Marine Biological Library on the Woods Hole Oceanographic Institute campus is a repository of original work on marine species many of which have become model experimental systems for the study of nervous systems. It is also a quiet space where one can hide away and study in one of its many cubicles.

At the end of the summer, we moved back to the Harvard Medical School labs on Longwood Ave. Ed's lab worked on the lobster nervous system, focusing on discovering the identity and roles of neurotransmitters in the large identifiable neurons in lobster ganglia. Ed's early work had established the inhibitory role of gamma-aminobutyric acid (GABA) in the lobster nervous system. When I arrived, he was focused on understanding the biochemistry and actions of the biogenic amines octopamine, dopamine, and serotonin, which are secreted into the lobster hemolymph by specific neurons and appeared to play a modulatory role in the nervous system. Ed patiently taught me to use a dissecting microscope to remove lobster ganglia and leg nerves and prepare them for experiments. Because of my background in organic biochemistry, I was assigned to determine how the biogenic amines were inactivated and metabolized after they were released. For the first several months, applying my expertise in this way seemed a reasonable trade-off for the feast of new learning that I enjoyed as a member of the department.

The postdoctoral fellows from all the labs met weekly for "shadow" reading sessions in which we studied the course material and original papers that made up the department's graduate courses. This curriculum was brilliantly organized and included critical reading of a series of original papers by Hodgkin and Huxley, Bernard Katz, Ricardo Miledi, and others, covering the electrophysiology of axons and synapses. I also read early papers describing the cellular and subcellular anatomy of the brain, which I found particularly fascinating, and I developed a strong curiosity about the molecular composition of the various structures that could be seen within synapses in the electron microscope. We studied papers of Hubel and Wiesel in which they used extracellular single-cell recording in the visual cortex to map out the receptive field properties of neurons in the cortical layers, including ocular dominance columns, work for which Hubel and Wiesel would eventually be awarded the Nobel Prize. During the time that I was in residence, Hubel, Wiesel, and Simon LeVay were working out the physiology and anatomy of "orientation columns" in the visual cortex. Because the understanding of neuronal biochemistry was still quite rudimentary at this time, reading in this area included mostly papers about the properties of basic neurotransmitters (glutamate, GABA, acetylcholine, peptides, and

biogenic amines) and Dale's principle, which held that each neuron synthesized and used only one transmitter. We now know that Dale's principle is an oversimplification and that many neurons release both a "major transmitter," such as glutamate, GABA, and acetylcholine, and a modulatory "co-transmitter" peptide or biogenic amine. The nature of the acetylcholine receptor at the neuromuscular junction was still unknown; indeed, some still speculated that it was not a protein at all but rather a configuration of lipids that was perturbed by release of acetylcholine.

The two and a half years that I spent in the Kravitz lab and the Harvard Neurobiology Department offered the richest and most dense learning experience of my life. I moved into a shared house with Marge Livingston, Josh Sanes, David Furster, and Charlie Gilbert, all of whom became major figures in the neuroscience community. We shared many meals and stimulating conversations. Socially, I dated Eric Schwartz, a retinal physiologist, from whom I also learned a great deal. In my research, I succeeded in showing that octopamine, dopamine, and serotonin were inactivated by two processes in the lobster bloodstream, βalanine substitution at the amine group, and sulfation of the ring hydroxyl groups. I believe that I also contributed to the biochemical sophistication of the members of the department through various group presentations. I particularly remember being proud of a presentation that I made on Peter Mitchell's "chemiosmotic hypothesis" for ATP synthesis in mitochondria, for which he was soon awarded the Nobel Prize in 1978. This mechanism is now, of course, standard textbook fare. In 1977, however, it was just becoming accepted.

Unfortunately, despite all that I was learning, I became increasingly anxious about my future because I knew that I wanted to be prepared to investigate more fundamental biochemical processes, such as synaptic regulation, and I increasingly felt that I wanted to work in a mammalian system. I had been trying to arrange a project in Dr. Wiesel's lab with Charlie Gilbert to identify neurotransmitters in the retina. Charlie seemed to agree to this project, but then began it with no communication with me. When I objected that I would like to be included in the planning for the project, he became angry and it was clear that the collaboration would not be possible. I wasn't able to find a way to satisfy my research desires within the neurobiology department and eventually left on a somewhat sour note. Around the same time, I had become interested in the work of Paul Greengard, who was beginning to study regulatory protein kinases in the brain. This field was in its absolute infancy but seemed promising because of the important role that protein phosphorylation had been shown to play in glucose metabolism in the liver and heart. In early 1978, Josh Sanes, who had been an undergraduate student in Dr. Greengard's lab at Yale, invited him to give one of the lunch-time seminars that were an important part of the intellectual life in the Neurobiology Department. I spoke with Dr. Greengard after his talk, and he immediately responded to my interest in his work. A few months

later, he returned to Boston and invited me to dinner. In my very unsettled state, Dr. Greengard's interest became a possible salvation. Thus, began an association that both defined my future career and later badly damaged it.

Yale Postdoc (1978–1980)

In 1978, I was a relatively naive and rather unhappy 30 year old, looking for a way to work in a mammalian system on neuronal biochemical mechanisms, a field that I loved. Therefore, the attention that I received from Paul Greengard was like warm sunshine after a cold rain. It soon became apparent that his interest was both scientific and romantic; at least that is how I saw it. He was a charming man, when he chose to be, and I was completely hooked. We spent a great deal of time talking about his research and about neuroscience, in person and on the phone, but also began spending an equal amount of social time together in the last few months of my time in Boston. I knew that he was married, but rationalized that his wife, whom I later came to like very much, appeared to me to be preparing herself to leave the relationship. When I was unable to find a satisfactory position in the Harvard Neurobiology Department, Greengard agreed that it seemed logical for me to move to his lab to do a second postdoctoral fellowship. I had little experience to prepare me for the problems that can arise when one is involved in a personal relationship with one's mentor.

I was very good at hiding the personal side of my relationship with Dr. Greengard from those in his lab. I found a nice apartment and maintained a normal social life with my peers, making time for trysts with Greengard when he traveled or when his wife was away. I often visited museums with him and very much enjoyed learning from his cultural experience as well as scientific conversations. Looking back, I realize that this affair offered me a widened view of both the scientific and cultural world that would not have been available to me otherwise. Intense intellectual relationships between men and women easily lead to sexual attraction, and are too easily disrupted by it, especially when the attraction is not mutual. As a result, in a male-dominated profession, women are often denied access to the kind of ongoing, informal intellectual exchange that occurs naturally among male mentors and students, and even among male peers. To this day, I don't believe that anyone in the Greengard lab knew of our personal relationship. Indeed, I told no one about it, and it remained hidden. A few in the lab seemed to notice that I appeared to be a "favorite" and, I think, resented it. For the most part, I got along well with others in the lab and acquired several lifelong colleagues and friends.

In the 1970s, the National Institutes of Health (NIH) were well funded and laboratories like Greengard's at Yale were large and amply supported. Ten to twelve postdocs, three or four students, and several technicians were crowded into a suite of five laboratory rooms and offices

surrounding a walk-in cold room, instrument rooms, and larger offices for Dr. Greengard and his secretary. I arrived in the lab after postdoc Howard Schulman had published two papers establishing the presence in rat brain homogenates of a calcium-dependent protein kinase activity that depended on the recently discovered calcium-dependent regulatory protein (CDR, later named calmodulin). Many brain "substrate proteins" for this kinase activity could be seen as bands in the phosphate-labeled gels published in Howard's papers. Calmodulin-dependent protein kinases had only recently been discovered in other tissues. Thus, Howard's papers received a lot of attention. Howard had accepted a job as assistant professor at Stanford and Greengard wanted me to continue with the task of characterizing the brain calcium-dependent protein kinases. I readily agreed because this was exactly the kind of mechanistic research that most interested me, and I wanted to learn more about techniques of protein biochemistry and enzymology. At this juncture, I learned that Greengard had "forbidden" Howard to work on calcium-dependent protein kinases in the brain at Stanford, apparently believing that he somehow owned the field of calcium-dependent phosphorylation in the brain. This was my first indication of Greengard's extreme territoriality about his scientific work and it seemed odd to me because there was so much to be done. At Stanford, Howard decided to investigate the role of calcium-dependent phosphorylation in regulating biogenic amine metabolism, and eventually, appropriately, resumed work on brain calmodulin-dependent kinases. I proceeded to develop an assay to measure phosphorylation of "protein I" (now known as synapsin I) by calcium/calmodulin-dependent protein kinase. I used the assay to fractionate distinct brain calcium/calmodulin-dependent protein kinases by chromatography, distinguished by their specificity for phosphorylation of different parts of the synapsin protein. The goal was to understand how many such protein kinases we could detect, and, eventually, how and where they carry out their regulatory roles.

I shared a small office with Dana Aswad, now at the University of California–Irvine, and Annette Dolphin, now at University College London. In a nearby room, Wieland Huttner and Pietro DeCamilli were working out ways to purify synaptic vesicles. They soon showed with cell biological and electron microscopic techniques that synapsin I is a peripheral synaptic vesicle protein. Susan Goelz, who became a close friend and later led the development at Biogen of the first biologic treatment for multiple sclerosis, worked in another of the Greengard rooms next to Eric Nestler, who was finishing up his thesis work. At that time, the Greengard lab was a seedbed for future leaders in research on neuronal biochemical mechanisms.

As I had done at Harvard, I worked six- and seven-day weeks in the lab, reading, planning procedures, and carrying out experiments to understand more about the molecular characteristics and specificity of brain calcium/calmodulin-dependent protein kinases. This pace of work was my own choice;

I found it exhilarating to be able to focus completely on solving puzzles that I had been curious about for so long. Immersing oneself in scientific benchwork is, I suspect, rather like working in an art studio. I became oblivious to potential distractions because the creative process was intensely rewarding. After a year of work, I had identified two distinct protein kinases, which later were called CaMKI and CaMKII. CaMKII seemed to be the most abundant, so I focused on the trial-and-error process of purifying it by then-standard protein chemistry techniques. As I examined increasingly purified fractions, I noticed that two of the prominent brain substrate proteins, a doublet of 50 and 60 kDal proteins present in approximately a 2:1 ratio, co-purified with the protein kinase activity. I recognized this as a clue that these might be autophosphorylated subunits of the kinase itself, and I shared this possibility with the lab.

Just before I arrived in the Greengard lab, Dr. Phil Siekevitz's lab at Rockefeller had published two important papers reporting the isolation and characterization of a subcellular fraction that he termed the postsynaptic density (PSD) fraction. It was prepared by centrifugation from synaptosomes after lysis and removal of lipids with mild detergent. Siekevitz et al. presented evidence that the fraction was derived from the dense structure seen at postsynaptic membranes in electron micrographs of the brain. The work was anchored in the tradition of George Palade with whom Phil Siekevitz had studied; and I found the papers to be elegant and convincing. Of course, many skeptics complained that the isolated structures observed by electron microscopy were simply nonspecific aggregates produced by the treatment of synaptosomes with mild detergents. However, I thought the structures were too regular to be completely nonspecific and I was excited because the method opened up the possibility of studying in detail the protein composition of this mysterious organelle. In 1980, Siekevitz followed up with a study of PSD fractions in different brain regions. His group had seen the Schulman papers, and they included an autoradiogram showing that the PSD fraction contained a calcium/calmodulin-dependent protein kinase. The two most prominent substrate proteins for the calcium/calmodulin kinase had the same pattern in gels as the two phosphorylated proteins that were co-purifying with CaMKII. Interpreting scientific data often involves pattern recognition. I began to suspect that a portion of CaMKII might be immobilized in the PSD fraction and mentioned this to the M.D./Ph.D student who had begun working with me. A few years later, she and Greengard would race to try to publish this finding ahead of my lab at Caltech.

In mid-1979, as I was finishing up the first project that I would publish from the Greengard lab, I was contacted by Jim Hudspeth, a professor at Caltech, who asked if I would be interested in applying for an assistant professorship at Caltech. I hadn't yet applied for any faculty jobs because my research output was still small. However, I had presented my recent work

at various meetings, and Jim had heard about me from former colleagues at Harvard where he had been a graduate student. At that time, the number of young people who had interdisciplinary training in biochemistry and neuroscience was still small and the Harvard Neurobiology Department was a popular source of new faculty in neuroscience. Caltech wanted to build its faculty in neuroscience having hired Hudspeth and David Van Essen, both of whom were graduates of the Harvard department. I felt this was an offer I couldn't ignore, although I had never lived on the west coast and felt some trepidation about moving so far from family and friends. Greengard was cautiously supportive of my applying for the job. After a visit and a seminar, I was offered the job and eventually accepted the offer in early 1980, agreeing to start the appointment in January of 1981. I was convinced by the quality of the Caltech faculty, the beautiful campus, and the generous start-up package that would allow me to build my own well-equipped and well-funded lab.

In the months after I accepted the Caltech appointment, both the personal and the professional relationship with Greengard deteriorated. We were seeing much less of each other and I had begun casually dating postdocs from other labs. To my surprise, this seemed to enrage him, and he began criticizing my work in the lab and trying to insert new lab members into the work that I was finishing up. The most egregious problems occurred when I tried to discuss with him the work that I would begin at Caltech. I explained a few ideas that I had about related areas of investigation, but Greengard finally insisted that the entire field of protein phosphorylation in the brain was his field. I recognized this as an attempt to fatally wound my ability to begin a new lab on strong footing. I had come to his lab, bringing my expertise in neuroscience, to establish myself in the field of regulatory biochemistry in the brain. During one final discussion in the Yale lunchroom, I told him that since he didn't seem to want to agree to any of the proposals that I had made, I would continue with the project I had been working on in the lab. I was passionate about the work, and I had come to the lab to enter that field. He stood up from the table in a rage and stalked off. The next months were unpleasant, but I finished enough work for a second paper, and wrote a grant that eventually was funded, enabling me to arrive at Caltech in January of 1981 with an NIH grant.

First Six Years at Caltech (1981–1986)

The six years of my assistant professorship at Caltech best epitomize "the best of times and the worst of times" that I alluded to earlier.

I arrived at Caltech in early January 1981, leaving New Haven after a snowfall. Mid-winter in Los Angeles means mild temperatures from 50 to 70 degrees and occasional rainfall. I remember seeing a lighted sign on the freeway reminding drivers to "Drive safely in winter weather." Being a

seasoned snow driver, I wondered what winter weather they were referring to, until I realized with amazement that it was the rain! Another immediate impression upon moving from the east coast was how clean the cities were compared with Boston, New York, or New Haven. In Pasadena, I found flowering trees along with tall palms and desert succulents. I rented an apartment near Caltech and started on my new job with no close friends or colleagues nearby for support. Thus, the first year was both exhilarating and lonely. I had designed the layout of my new lab myself, and it was finished by the time I arrived; the major equipment was already in place, installed by Bill Lease, the divisional equipment manager. My second-floor office, which I still occupy, has a large window overlooking a lily pond, jacaranda trees, and the administration building. I quickly began staffing the lab with a technician and students. During the first years, I also worked every day at my own bench. My first student, Mark Bennett, finished the purification of CaMKII and used biophysical measurements of its Stokes radius and sedimentation coefficient along with other biochemical measurements to show that the kinase is a dodecamer composed of alpha (50 kD) and beta (60 kD) subunits in a 3:1 ratio. This quantitative analysis has stood the test of time. We were lucky that Jeremy Brockes, who occupied a lab near mine, was an expert in methods to generate monoclonal antibodies with selected specificity, a technique that had been invented only recently. My second student, Ngozi Erondu, generated a high-affinity specific monoclonal antibody against the alpha subunit and used it to document the extremely high concentration of CaMKII in the hippocampus (2%) and cortex (1%), and lower concentrations in other brain regions. The three of us worked together to show that a 50 kD protein in Siekevitz's PSD fraction, which he had termed the "major PSD protein," was the alpha subunit of CaMKII. In 1984, I was invited to give a major talk at a well-attended symposium on calcium regulation in the brain at the annual meeting of the Society for Neuroscience. These first five years were happy ones in which I was able to build on the work I had started in New Haven and to teach bright young people, in the lab and in the classroom, about both protein biochemistry and neuroscience.

However, the wolves were gathering. I didn't know, and didn't think about, what was being pursued in the Greengard lab, 2,000 miles away. Our work on the presence of CaMKII in the PSD fraction was published in the *Proceedings of the National Academy of Science USA* in December 1983. Two months later, in February 1984, a very similar paper by Kelly, McGuinness, and Greengard appeared in the same journal. I knew that the fortuitous appearance of our paper in the last month of 1983, followed by his paper in 1984 would infuriate Greengard, who hated to be "scooped" even more than most of us. In the next few years, I would confront the perils of working in an interdisciplinary, male-dominated, and emotionally overheated field.

A third graduate student, Stephen Miller, began examining the possible effects of autophosphorylation on the enzymatic activity of CaMKII and soon

noticed that after the two subunits became fully phosphorylated, the rate of protein kinase activity was somewhat reduced, but it was also independent of the addition of calcium or calmodulin. We first submitted the work to the *Journal of Biological Chemistry*, but we were told, correctly, that we needed to show that the effect of autophosphorylation was reversible by dephosphorylation by a protein phosphatase. Steve set out to do these experiments. In the interval, John Lisman visited Caltech from Brandeis to give a neuroscience seminar. He saw Steve's work and pointed out, with excitement, that this property of the kinase might match a situation he had written about in a theoretical paper in which he postulated that such a kinase activity could "outlast protein turnover." He thought that this situation might allow protein phosphorylation to encode long-term memories and was thrilled to hear about an autophosphorylating kinase located in the PSD. Steve eventually showed that protein dephosphorylation did, in fact, reverse the calcium-independent activity. We then proceeded to show that the autophosphorylation occurred essentially entirely within a single dodecameric holoenzyme and not between holoenzymes. This result disappointed John. Nonetheless, we had shown that several sites were phosphorylated, and we postulated that the resulting slow pace of dephosphorylation might allow the kinase to act as a kind of switch, maintaining its activity for a brief period of time after a transient rise in postsynaptic calcium had triggered the initial activity. Two minor dramas followed from this work.

The first involved a long delay in the review of our revised manuscript by the *Journal of Biological Chemistry*. While we were waiting to hear about the manuscript, I was invited to present the work at MIT. During the dinner after the talk, I mentioned that the revised work had been stuck in re-review at *Journal of Biological Chemistry* for longer than normal. I recall Professor Frank Solomon looking alarmed; he told me to pull the paper immediately and send it to *Cell*. It had not occurred to me that reviewers might be holding up the manuscript to allow someone else to submit the finding. At the time, *Cell* was a growing niche journal that I, correctly, thought of as a kind of club. However, I did as Solomon suggested and our paper appeared in *Cell* four months later in March 1986. To my amazement, a short paper from another lab reporting the same reversible calcium-independent activity after autophosphorylation, appeared in the *Journal of Biological Chemistry* three months after ours appeared in *Cell*, having been submitted in February 1986. The senior author of that paper was indeed a reviewer at the *Journal of Biological Chemistry*. Frank Solomon was wiser than I about what can happen with reviews in a competitive field.

This unsettling incident echoed another that had occurred during review of an earlier paper of ours in the *Journal of Biological Chemistry*, also authored by Stephen Miller, reporting purification of a cerebellar form of CaMKII and documenting a difference in its subunit composition. The paper was rejected for reasons that had little to do with its accuracy. Then

a few month later, a very similar paper was published from the Greengard lab in the same journal. Steve was furious and completely disillusioned. I called the editor of the *Journal of Biological Chemistry* and asked how this could have happened. He checked into it and discovered that Ed Krebs had handled the review of both papers. Our paper was submitted three months later than the Greengard paper, which hadn't yet appeared in print, so Krebs had rejected ours. The editor explained to him that this was not the correct procedure and told us that the journal would publish our paper as quickly as possible. A few days later, I received a call from Dr. Krebs, who apologized for the mistake. I will never know whether or not either of these two incidents involved deliberate reviewer misconduct.

The second minor drama was the reaction in the neuroscience community to the notion that CaMKII might act as a "switch," as we suggested in the *Cell* paper. Before about 1970, the term neurobiology had referred to anatomical and electrophysiological studies of the vertebrate brain, nerve ganglia of invertebrates, or individual neurons. In 1966, Steven Kuffler established the interdisciplinary Harvard Department of Neurobiology that included physiology, biochemistry, histology, neuroanatomy, and electron microscopy in a single department. Kuffler was a visionary and he recognized that the field of biochemistry, which had its roots in microbiology, was on the verge of great progress in understanding molecular mechanisms in specialized cells of multicellular organisms. However, as is often the case in interdisciplinary fields, electrophysiologists usually had superficial training in molecular disciplines. Similarly, those trained in biochemistry and cell biology had often been taught to avoid studying the most complicated cells, and knew little about the most salient mechanistic questions in neurobiology. With my years of training in both areas, but principally in classical biochemistry, I was still a rare bird.

A prominent group of cellular electrophysiologists were studying the phenomenon of long-term potentiation (LTP), which they believed to be a substrate of memory formation. In the mid-1980s, the hypothesis that LTP was triggered by a transient influx of calcium ion into individual synapses through N-methyl-D-aspartate (NMDA)-type glutamate receptors was gaining favor. In our paper in *Cell*, we had discussed the mechanistic possibilities and limits of the switch-like behavior of CaMKII in the synapse in relation to synaptic potentiation. John Lisman began to talk about CaMKII as *the* memory molecule, and to my amazement, many neurobiologists lauded this idea. John even suggested to me that we should collaborate: he would be the theorist and I would be the experimentalist. That was a gross misperception of my intellectual stance. I still believed Saul Roseman's maxim that "no biochemist is smarter than an *E. coli* cell." Certainly, no scientist is smarter than a neuron! I knew that the mechanism we had uncovered, together with the abundance of CaMKII in the cortex and PSD, meant that CaMKII was likely an important player in mechanisms of synaptic plasticity. However, my

previous training had taught me that biochemical mechanisms in cells are comprised of highly interconnected networks of reactions that provide flexibility in response to the environment as well as robust homeostatic adjustments. Surely, a function as critical to evolution as memory does not reside in the properties of a single enzyme. I believed it was much more important to probe the synapse, and the PSD structure, for the other proteins that are regulated by CaMKII, and thus to begin to unravel the biochemical network regulating memory formation. Most electrophysiologists were not primed to listen to this argument. It probably didn't help that I was female, and that Paul Greengard had spread the notion that I had somehow stolen all my ideas from him. Unfortunately, the brief frenzy about CaMKII as the memory molecule led to some ugly scenes. For example, when Stephen Miller presented his work at a large meeting of the Society for Neuroscience in 1985, Professor Jimmy Schwartz stood up and berated him saying that he had already discovered this mechanism in Aplysia. He was referring to a recent paper from his lab that had been influenced by a discussion I had had with him at an earlier Cold Spring Harbor meeting. Schwartz had shown me an autoradiogram of proteins that were phosphorylated in a calcium-dependent manner within an Aplysia homogenate. It showed a prominent pattern resembling the alpha and beta subunits that we had identified in mammalian brain. I pointed to these bands and told him that they might well be the Aplysia CaMKII. No good deed goes unpunished. Schwartz apparently took this suggestion as fact; his student carried out some studies in the Aplysia homogenate and suggested that autophosphorylation might make the Aplysia calcium-dependent kinase "autonomous." We cited his suggestion in our *Cell* paper, but only as a suggestion. No biochemist would consider studies on an enzyme in a protein mixture adequate to define such a mechanism. After all, we had appropriately been required to show that the calcium-independent activity of our purified kinase was reversible by a purified protein phosphatase! This incident was an example of the ill feelings that too often arise when two fields that converge in interdisciplinary work hold different standards of proof. I was offended by the notion that Schwartz would consider his experiments in Aplysia homogenates equivalent to our work with purified proteins. Schwartz's work had appeared before our *Cell* paper was published, but after Miller had already shown in the lab the effect of autophosphorylation on pure CaMKII. Schwartz's paper had had little influence on our thinking. Nonetheless, Schwartz and others at Columbia, including Eric Kandel, apparently continued to believe that I had somehow stolen Schwartz's finding. Some months later, Schwartz wrote me a handwritten letter apologizing for his behavior toward my student Stephen Miller. Schwartz said that he had been "attracted to me as a woman" and had thought of me as a "guardian angel of his work," so he was upset by our overlapping work. I am grateful for his self-insight; but it illustrates how fraught this overheated field was for any scientist, much

less a young woman with an expertise that was not well understood by most neurobiologists.

Meanwhile, my student Mark Bennett had learned the basics of molecular cloning from Norman Davidson's lab and sequenced the first full cDNA clone of a CaMKII subunit, the beta subunit, which we published in 1987. As the time approached for my tenure review, I believed that my lab had accomplished a great deal. And with the publication of the work on autophosphorylation and the cloning of the beta subunit, we had clearly differentiated ourselves from the Greengard lab. Unfortunately, my confidence in the importance of our good work and in the influence at Caltech of my reputation in the neuroscience community was overly optimistic.

Tenure Year

The saga of my tenure review at Caltech began with the formation of a tenure review committee in early 1986. The committee was formed six months earlier than normal. I assumed this reflected the fact that I had already accomplished enough to be awarded tenure. Instead, I later learned, Lee Hood, the divisional chair, wanted the decision to be made while he was on a sabbatical due to end in December 1986. The divisional chair was supposed to be neutral, and Hood, I was later told, wanted to be able to speak against me at the faculty meeting. Hood wanted the acting divisional chair, James Strauss, to preside at the voting meeting.

The chair of the tenure review committee was Mark Konishi, a revered neuroethologist who studied bird song. The assignment was difficult for him because he knew that my work had been important, but he had little depth in biochemistry himself. On the other hand, the two biochemists appointed to the committee had little knowledge of neuroscience. The entire process was mired in the chasm between the "molecular biologists" and the "neurobiologists" in the division. In the years leading up to 1986, the field of molecular biology had been burgeoning because of the introduction of genetic engineering in 1975. Similarly, neuroscience was becoming an interdisciplinary field and was also making great scientific strides. In several research institutions, there were struggles between the two fields for recognition and resources. At Caltech, this battle had grown nasty; the simmering war between them broke into the open during my tenure review.

The full story of the two-year process of my tenure review, in which an initial negative decision driven by a group of molecular biologists was reversed by the provost and trustees, would require a book. Here I will provide a few highlights and anecdotes that illustrate the flavor of this time for me. Because the issue very nearly entered the formal legal arena before it was resolved, I learned a great deal about the relevant, supposedly confidential, events that underlay my tenure review—much more than a young faculty member would normally come to know.

The report of the tenure review committee was submitted to the Biology Division in May 1986. It recommended my promotion to tenure, with one dissent by one of the biochemists. As the report was being prepared, I had been invited to apply for a tenured job at MIT and the faculty of their Biology Department had voted in favor of the appointment. We were awaiting approval of the dean. I was told that most of the 10 outside letters of recommendation obtained by Caltech were quite positive. A few were lukewarm, but none were negative. When my three year contract had come up for renewal in 1983, Paul Greengard had not been willing to provide a letter. Mark Konishi believed this was inappropriate on Greengard's part, and he did not ask him for a letter regarding the tenure decision. The tenure committee was also aware of Dr. Schwartz's complaints and so he was not asked for a letter. However, Eric Kandel from Columbia was asked for a letter and I'm told that he wrote that I had shown that CaMKII has two subunits. "Perhaps in the future she will be more creative."

The meeting of the tenured Biology faculty to vote on my tenure occurred on September 20, 1986. In the meeting, Mark Konishi and his committee were surprised by an angry attack by Lee Hood, Eric Davidson, and other molecular biologists, and were not prepared for it. Lee Hood stated that he did not like me and resented that I had questioned him openly about certain fund-raising initiatives discussed earlier in the division. One of the molecular biologists stated that it was "no big deal" that I purified CaMKII from the brain because it is a "very abundant enzyme"—one of his students had purified a protein that represented only a few tenths of a percent of the protein in the tissue of origin. I recognize now that this demonization of my voice and the discounting of the importance of my lab's work reflected a subtly misogynistic inability to recognize a female as an independent authority. These remarks offended the neurobiologists, all of whom supported my promotion to tenure and felt ambushed by the hostility. The meeting ended with a split vote and deep anger between the two factions of the division. There were enough negative votes a few weeks later that the Institute Academic Council, which consisted of the chairs of all the divisions, the provost, and the president, accepted the acting Biology Division chair's recommendation that I not receive tenure.

Word of the controversy had reached MIT and the dean there refused to approve the appointment that had been voted on by the MIT Biology faculty. This news finally caused me to slip into what I now recognize was a reactive depression. I became unable to eat anything other than milk for a few weeks, and lost 20 pounds over the next few months. I knew the decision was unfair, and others from inside and outside the division told me as much. Mark Konishi and David Van Essen had submitted a memo of concern to the provost, mentioning, among other things, the personal animus brought into the discussion by Lee Hood. One department chair from another university told me that he thought the decision might be "actionable." I didn't know

what that meant. He told me that it might be illegal under the provisions of the Civil Rights Act, which forbade employment discrimination on the basis of sex.

Here is where Caltech's recent history came into focus. In 1977, the Humanities and Social Sciences Division had denied tenure to literature professor Jenijoy LaBelle. She filed a complaint with the Equal Employment Opportunity Commission, which investigated and found Caltech to have a "pattern and practice" of discrimination on the basis of sex and race. The Commission sued Caltech on her behalf, a particularly strong action. One of the most salient pieces of evidence was a comparison of her tenure case to the most recent male who had received tenure in the Humanities and Social Sciences Division. LaBelle's case on paper was much stronger. Caltech settled the case, and LaBelle eventually received tenure. In the wake of this case, the trustees had admonished all of the divisions to make a better effort to hire women faculty. Indeed, my hiring in 1981 had been influenced by this mandate. Nevertheless, in 1986, Caltech had a total of only nine female professors (eight without me), 3% of the total faculty. I had been the first female hired in the Biology Division, a second had previously been hired in Chemistry and, after receiving tenure, was given a joint appointment in Biology. Thus, I was also the first female to undergo a tenure review in the Biology Division. These numbers meant that Caltech had among the lowest proportions of female faculty of all universities in the United States.

A friend of mine from the Jet Propulsion Laboratory, Robert Nelson, referred me to John McTernan, a Los Angeles civil rights and labor lawyer who had represented his father, a famous labor organizer, in a 1955 Pennsylvania Sedition Act case. In the midst of my depression, McTernan gave me invaluable help in organizing documents and information to construct a case. I clearly recall one early conversation in which he repeatedly asked me, "Why are you doing this?" I became annoyed because I thought the answer was obvious. Finally, I blurted out, "Because I think what they did was wrong and I don't want to let them get away with it." He smiled, and never asked me the question again. I later realized that it is important for a lawyer to clearly understand his client's goals and also to be sure the client herself understands her goals. In some labor cases, the client actually wants a monetary settlement. In fact, the issue of a monetary settlement came up later at Caltech.

History has a long reach. People like McTernan have been devoting their lives to the legal preservation of civil liberties for a century or more. My activist history had prepared me to fight for my own rights in this situation.

The first crucial step was an appeal of the Academic Council's negative tenure decision to the Academic Freedom and Tenure Committee (AFTC) within Caltech. As I emerged from the worst of my depression, I submitted an appeal in February 1987 outlining the sequence of events and the

problems with the tenure process. Two of the members of this committee knew me from service on other institute committees. One of them later told me that he had kept careful notes for me to use later, if I needed them in a legal action. Both of them made sure that the incidents and procedural flaws that they believed were improper were all included in the report. The hearing of my appeal by the six member committee took several months. I, and the provost, finally received their report in early June 1987. It documented many irregularities in the tenure procedure, including instances in which the faculty handbook was not followed. It concluded that the committee could not say whether or not a perfect process would have yielded a different outcome, so they did not recommend reversing the decision. At this point, events moved into high gear.

Eleanor Searle, a senior history professor at Caltech, who had previously served as vice-chair of the faculty, had told me to bring her the report as soon as it was released. I remember putting a copy in a manila envelope and dropping it through the mail slot at her home because she wasn't there when I arrived. I also gave her a copy of my most recent NIH grant review. Somehow, I had managed to submit the grant renewal several months earlier, and it had received a "priority score" at the 1.9 percentile, meaning that it was among the two or three highest scoring proposals of the 100 or so reviewed by the panel in that cycle. Eleanor had moved to Caltech from UCLA where she had served on the Staffing Committee. Thus, she had quite a bit of experience with tenure cases. She called the next day to say that the committee at UCLA would have been "falling about laughing" at the report I had given her. She believed that it was laughable that the AFTC had documented personal hostility and many flaws in the process and yet had not recommended reversing the case. She planned to talk to the provost about it as soon as she could, and she had given the material to a law professor from the University of Southern California (USC) who was visiting the Caltech Humanities and Social Sciences Division for the summer term. The law professor's wife was a neurobiologist who told him that most researchers would kill for a priority score as high as I had received. The USC professor told Eleanor that he knew who should see this material. He brought it to Judith Resnik, a professor at USC law school who had recently argued a case before the Supreme Court in which the Rotary Club of Duarte, California, had been expelled from the National Rotary Club for admitting women. Resnik convinced the Supreme Court that because the National Rotary Club is a business organization, the expulsion violated the Civil Rights Act and must be reversed. Within a week, I was given her number to call. She later told me that she rarely agreed to help in such cases, but the law professor who had shown her the material was normally so conservative that she believed the denial of tenure must be egregious. Resnik is a font of energy and her energy revived me. We talked extensively on the phone. When she learned the low percentage of women on the Caltech faculty, she was shocked and

became more committed to helping. She was not in a position to act as my "lawyer of record," so she ultimately found a former student who worked in a Westwood law firm to act as my formal legal representative to Caltech, but Resnik continued to advise me.

Barclay Kamb had been newly appointed Caltech provost at the beginning of 1987. This was fortunate for me because he had been one of the few division chairs who had initially argued in favor of promoting Jenijoy LaBelle to tenure. Through the summer, Eleanor Searle became a messenger between Kamb and me. I soon learned that he was not pleased with the report of the AFTC for the same reasons that Eleanor had found it laughable. Eleanor told him that she wanted to be loyal to Caltech, but she needed to inform him that I had the help of a very talented lawyer at USC (Resnik) who had argued before the Supreme Court. I learned that institute administrators regarded it as disloyal to consider legal action against the institute. Many administrators felt that it was appropriate to tell faculty or employees that they should not consult outside lawyers. I believe that if we are a country of laws, the institute should accept that sometimes employees will need their own lawyers and may need to bring litigation in a dispute. However, Eleanor wanted to be able to act as a messenger between the provost and me, without being seen as an adversary. I greatly admired her diplomatic skill in helping Provost Kamb work through the difficult situation he found himself in.

Kamb told Eleanor that I should have the lawyer contact him. So I went to see the "lawyer of record" from the Westwood law firm that Resnik had obtained for me. This lawyer then wrote a polite letter to the provost introducing herself, saying that her firm was representing me, and listing all the federal and state laws that they believed Caltech had violated. Kamb interviewed a few possible defense attorneys who told him not to let the case get to court. Throughout this time, he also met with me more than once, and he asked that I not take action without letting him know first. I agreed to that, and explained to him that I was in constant contact with Resnik, as well as the lawyer from the Westwood firm.

During this period, Kamb began receiving unsolicited additional letters from neurobiologists supporting my promotion to tenure. Zach Hall, who was then chair of the Physiology Department at the University of California–San Francisco, had suggested this action and volunteered to organize it.

At one point in this interval, Eleanor called me to say that someone had suggested to Kamb that Caltech offer me $25,000 to drop the issue. I was stunned by this news because such a thing had never occurred to me. I blurted out, "I don't want their goddamn money." Eleanor replied, "Oh, I'm so glad you said that." I never heard another word about it.

As he planned his strategy, Kamb enlisted the help of Trustee Shirley Hufstedler, a distinguished jurist who had sat on the Ninth Circuit Court

of Appeals. I knew that I had won when Kamb called me at 9:00 p.m. one night to tell me that he had spent the day talking with Hufstedler and she saw the case my way. As in the LaBelle case, my tenure case on paper was much stronger than that of the previous male who had been awarded tenure in the division. There was one hitch. Resnik had let me know that the statute of limitations for filing a "charge of discrimination" with the Equal Employment Opportunity Commission (EEOC) was the next day. I had let Kamb know this, which was why he called me late at night. I was preparing to drive down to the EEOC office in Los Angeles the next day to file a complaint. But Kamb told me that Hufstedler had asked me to please not file because it would be easier for her to convince the trustees if I was not in "an adversarial position" with Caltech. I told Kamb that I would have to talk to Resnik and called her immediately. I clearly remember her saying, "Oh, that Shirley! You have to file. You can't pass the statute of limitations without losing your legal options." We finally came to the decision that if Kamb would write a letter to me "stipulating" that the "act of discrimination" had not occurred on the day that the faculty voted, but rather six weeks later when the Academic Council voted, we would not need to file the complaint right away. Kamb immediately agreed and early the next day, he walked over to my office and gave me the required letter.

With Hufstedler's help, Kamb convinced the rest of the administration and the trustees that I should be promoted to tenure. Apparently, he asked Hufstedler to explain this to Lee Hood. Finally, on July 30, I watched Kamb walk over to my office from the administration building carrying a brown paper bag and a letter. The letter notified me of my promotion to tenure and the bag contained a bottle of champagne that he presented to me.

In a small way, this episode illustrates once again how important it is who holds power in our institutions. For the rule of law to survive, it isn't enough to have laws on the books. They must be enforced. The only means of enforcement is through the individuals in positions of power throughout our institutions.

The neuroscientists and many friends who had given me help and support celebrated with me. Without my friend Susan Goelz who had moved with her husband to Caltech to do postdoctoral work, Eleanor Searle, Jenijoy LaBelle, many women of the Organization for Women at Caltech, Robert Nelson, Peggy Renner, John McTernan, Zach Hall, Barclay Kamb, Shirley Hufstedler, and my sisters and brother in the Seattle area, I wouldn't have survived this period. The difficult year also took a toll on my students who were bewildered by the turmoil they witnessed. They couldn't help but feel that it had something to do with their work; I tried to assure them that it didn't. All of them accepted excellent postdoctoral fellowships; Mark Bennett, Ngozi Erondu, and Stephen Miller went on to hold senior positions at pharmaceutical companies.

Epilogue

Having finally secured full independence, and a new NIH grant, I was able to steer my lab toward a project I had always wanted to take on; the molecular identification of the proteins that make up the postsynaptic density. Ironically, we began to use techniques that Hood and his collaborators had advocated, gas phase sequencing of proteins in gel bands, followed by cDNA cloning, to fully identify the more abundant proteins in Siekevitz's PSD fraction. This approach led to the identification of PSD-95, for which my lab is best known, as well as synGAP, densin, and subunits of the NMDA receptor. Other labs began adding to the list, and we now know the identities of essentially all of the major PSD protein scaffolds and enzymes. With Peter Seeburg's lab, we discovered that PDZ domains in PSD-95 mediate interaction with specific ligands at the carboxyl tail of NMDA receptors. PDZ domains also underlie many other protein interactions in the PSD and control immobilization of NMDA- and AMPA-type glutamate receptors at the postsynapse. The task now is to understand how the protein lattice is assembled and how the PSD is reshaped during increases and decreases in synaptic strength (i.e., LTP and long-term depression [LTD]). As I had always known, changes in synaptic function, driven by structural processes, including modulation of PSD structure, spine shape and size, and the number of glutamate receptors at each synapse, are determined by interconnected regulatory networks, much like those of metabolism itself. New concepts such as liquid-liquid phase separation of protein mixtures are providing new ways of approaching these questions. NIH has recently shifted neuroscience funding away from biochemistry and cell biology toward circuit tracing. If NIH should choose again to adequately fund the biochemical study of neurons and synapses, U.S. universities can still lead in this critically important area.

The environment for women at Caltech has now changed dramatically for the better. After 1987, I and my female, and some male, colleagues worked hard to push back on sexist attitudes and make changes to improve the work and study environment for women. Caltech began to work even harder at hiring female faculty and gradually most of the divisions have reached at least a critical mass of women, and about half of the undergraduate student body is female. It is still difficult for assertive women to gain influence in the administration. Many male scientists still have difficulty recognizing a woman as an independent authority. The more congenial women are usually chosen for administrative positions. However, I have observed that this has also meant that overly aggressive men have less influence than they used to, and obvious sexist attitudes are not rewarded. One of the most insidious social influences that has held women back is reflexive negative feedback (both subtle and blatant) for positive achievements when they do not conform to a female stereotype. I believe that my resistance

to the negative feedback for my positive achievements by Lee Hood and his colleagues, and the courageous help that I received from many others on the Caltech faculty helped to shock the Caltech culture into recognizing that hiring more women and treating them appropriately is necessary for a modern scientific institution to survive.

Selected Publications

Kennedy, M.B. and Greengard, P. Two calcium/calmodulin-dependent protein kinases, which are highly concentrated in brain, phosphorylate protein I at distinct sites. *Proc. Natl. Acad. Sci. USA* 78: 1293–1297, 1981.

Kennedy, M.B., McGuinness, T., and Greengard, P. Partial purification, characterization and comparison of soluble and particulate calmodulin-dependent synapsin I kinase activities. *J. Neurosci.* 3: 818–831, 1983.

Kennedy, M.B. Experimental approaches to understanding the role of protein phosphorylation in the regulation of neuronal function. *Ann. Rev. Neurosci.* 6: 493–525, 1983.

Bennett, M.K., Erondu, N.E., and Kennedy, M.B. Purification and characterization of a calmodulin-dependent protein kinase that is highly concentrated in brain. *J. Biol. Chem.* 258: 12735–12744, 1983.

Kennedy, M.B., Bennett, M.K., and Erondu, N.E. Biochemical and immunochemical evidence that the "major postsynaptic density protein" is a subunit of a calmodulin-dependent protein kinase. *Proc. Natl. Acad. Sci. USA* 80: 7357–7361, 1983.

Miller, S.G. and Kennedy, M.B. Distinct forebrain and cerebellar isozymes of Type II Ca^{2+}/calmodulin-dependent protein kinase associate differently with the postsynaptic density fraction. *J. Biol. Chem.* 260: 9039–9046, 1985.

Erondu, N.E. and Kennedy, M.B. Regional distribution of Type II Ca^{2+}/calmodulin-dependent protein kinase in rat brain. *J. Neurosci.* 5: 3270–3277, 1985.

Miller, S.G. and Kennedy, M.B. Regulation of brain type II Ca^{2+}/calmodulin-dependent protein kinase by autophosphorylation. A Ca^{2+}-triggered molecular switch. *Cell* 44: 861–870, 1986.

Bennett, M.K. and Kennedy, M.B. Primary structure of the ß-subunit of brain type II Ca^{2+}/calmodulin-dependent protein kinase deduced by molecular cloning. *Proc. Natl. Acad. Sci. USA* 84: 1794–1798, 1987.

Miller, S.G., Patton, B.L., and Kennedy, M.B. Sequences of autophosphorylation sites in neuronal type II CaM kinase that control Ca^{2+}-independent activity. *Neuron* 1, 593–604, 1988.

Kennedy, M.B. Regulation of synaptic transmission in the central nervous system: long term potentiation. *Cell*, 59, 777–787, 1989.

Patton, B.L., Miller, S.G., and Kennedy, M.B. Activation of type II CaM kinase by Ca^{2+}/calmodulin is inhibited by autophosphorylation of threonine within the calmodulin binding domain. *J. Biol. Chem.* 265, 11204–11212, 1990.

Kennedy, M.B., Bennett, M.K., Bulleit, R.F., Erondu, N.E., Jennings, V.R., Miller, S.G., Molloy, S.S., Patton, B.L, and Schenker, L.J. Structure and regulation of type II Ca^{2+}/calmodulin-dependent protein kinase in central nervous system neurons. *C.S.H. Symp. Quant. Biol.* 55, 101–110, 1990.

Cho, K.-O., Hunt, C.A., and Kennedy, M.B. The rat brain postsynaptic density fraction contains a homologue of the Drosophila discs-large tumor suppressor protein. *Neuron* 9, 929–942, 1992.

Patton, B.L., Molloy, S.M., and Kennedy, M.B. Autophosphorylation of type II CaM kinase in hippocampal neurons: Localization of phospho- and dephospho-kinase with complementary phosphorylation site-specific antibodies. *Molec. Biol. Cell* 4, 159–172, 1993.

Kennedy, M.B. The biochemistry of synaptic regulation in the central nervous system. *Annu. Rev. Biochem.* 63, 571–600, 1994.

Moon, I.-S., Apperson, M.L., and Kennedy, M.B. The major tyrosine-phosphorylated protein in the postsynaptic density fraction is N-methyl-D-aspartate receptor subunit 2B. *Proc. Natl. Acad. Sci. USA* 91, 3954–3958, 1994.

Kornau, H.-C., Schenker, L.T., Kennedy, M.B., and Seeburg, P.H. Domain interaction between NMDA receptor subunits and the postsynaptic density protein PSD-95. *Science* 269, 1737–1740, 1995.

Omkumar, R.V., Kiely, M.J., Rosenstein, A.J., Min, K.-T., and Kennedy, M.B. Identification of a phosphorylation site for calcium/calmodulin-dependent protein kinase II in the NR2B subunit of the N-methyl-D-aspartate receptor. *J. Biol. Chem.* 271, 31670–31678, 1996.

Apperson, M.L., Moon, I.-S., and Kennedy, M.B. Characterization of Densin-180, a new brain-specific synaptic protein of the O-sialoglycoprotein family. *J. Neurosci.* 16, 6839–6852, 1996.

Kennedy, M.B. The postsynaptic density at glutamatergic synapses. *Trends Neurosci.* 20, 264–268, 1997.

Chen, H.-J., Rojas-Soto, M., Oguni, A., and Kennedy, M.B. A synaptic Ras GTPase-activating protein (p135 SynGAP) inhibited by CaM kinase II. *Neuron* 20, 895–904, 1998.

Ouyang, Y., Rosenstein, A., Kreiman, G., Schuman, E. M., and Kennedy, M.B. Tetanic stimulation leads to increased accumulation of Ca^{2+}/ calmodulin-dependent protein kinase II via dendritic protein synthesis in hippocampal neurons. *J. Neurosci.* 19, 7823–7833, 1999.

Walikonis, R.S., Jensen, O.N., Mann, M., Provance, D.W. Jr., Mercer, J.A., and Kennedy, M.B. Identification of proteins in the postsynaptic density fraction by mass spectrometry. *J. Neurosci.* 20, 4069–4080, 2000.

Kennedy, M.B. Signal processing machines at the postsynaptic density. *Science* 290, 750–754, 2000.

Walikonis, R. S., Oguni, A., Khorosheva, E. M., Jeng, C.-J., Asuncion, F. J., and Kennedy, M.B. Densin-180 forms a ternary complex with the a-subunit of CaMKII and a-actinin. *J. Neurosci.* 21, 423–433, 2001.

Oh, J. S., Manzerra, P., and Kennedy, M.B. Regulation of the neuron-specific Ras GTPase activating protein, synGAP, by Ca^{2+}/ calmodulin-dependent protein kinase II. *J. Biol. Chem.* 279, 17980–17988, 2004.

Vazquez, L.E., Chen, H.-J., Sokolova, I., Knuesel, I., and Kennedy, M.B. SynGAP regulates spine formation. *J. Neurosci.* 24, 8796–8805, 2004.

Carlisle, H.J. and Kennedy, M.B. Spine architecture and synaptic plasticity. *Trends Neurosci.* 28, 182–187, 2005.

Kennedy, M.B., Beale, H.C., Carlisle, H.J., and Washburn, L.R. Integration of biochemical signalling in spines. *Nat. Rev. Neurosci.* 6, 423–434, 2005.

Shifman, J. M., Choi, M.H., Mihalas, S., Mayo, S.L., and Kennedy, M.B. Ca^{2+}/calmodulin-dependent protein kinase II is activated by calmodulin with two bound calciums. *Proc. Natl. Acad. Sci. USA* 103, 13968–13973, 2006.

Lûcic, V., Greif, G.J., and Kennedy, M.B. Detailed state model of CaMKII activation and autophosphorylation. *Eur. Biophys. J.* 38, 83–98, 2008.

Carlisle, H.J., Manzerra, P., Marcora, E., and Kennedy, M.B. SynGAP regulates steady-state and activity-dependent phosphorylation of cofilin. *J. Neurosci.* 28, 13649–13683, 2008.

Pepke, S., Kinzer-Ursem, T., Mihalas, S., and Kennedy, M.B. A dynamic model of interactions of Ca^{2+}, calmodulin, and catalytic subunits of Ca^{2+}/calmodulin-dependent protein kinase II. *PLoS Comput. Biol.* e1000675, 2010.

Marcora, E. and Kennedy, M.B. The Huntington's disease mutation impairs Huntingtin's role in the transport of NF-kB from the synapse to the nucleus. *Human Mol. Gen.* 19, 4373–4384, 2010.

Carlisle, H.J., Luong, T.N., Medina-Marino, A., Schenker, L.T., Khorosheva, E.M., Indersmitten, T., Gunapala, K.M., Steele, A.D., O'Dell T. J., Patterson, P.H., and Kennedy, M.B. Deletion of densin-180 results in abnormal behaviors associated with mental illness and reduces mGluR5 and DISC1 in the postsynaptic density fraction. *J Neurosci.* 31, 16194–16207, 2011.

Kennedy, M.B. Synaptic signaling in learning and memory. *CSH Perspect. Biol.*, a016824, 2013.

Stefan, M.I., Bartol, T.M., Sejnowski, T.J., and Kennedy, M.B. Multi-state modeling of biomolecules. *PLoS Comput. Biol.* 10, e1003844, 2014.

Walkup, W.G.t., Washburn, L., Sweredoski, M.J., Carlisle, H.J., Graham, R.L., Hess, S., and Kennedy, M.B. Phosphorylation of synaptic GTPase-activating protein (synGAP) by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and cyclin-dependent kinase 5 (CDK5) alters the ratio of its GAP activity toward Ras and Rap GTPases. *J. Biol. Chem.* 290, 4908–4927, 2015.

Bartol, T. M., Keller, D.X., Kinney, J.P., Bajaj, C., Harris, K.M., Sejnowski, T.J., and Kennedy, M.B. Computational reconstitution of spine calcium transients from individual proteins. *Front. Synapt. Neurosci.* 7:17. doi: 10.3389/fnsyn.2015.00017, 2015.

Walkup, W.G.t., Mastro, T.L., Schenker, L.T., Vielmetter, J., Hu, R., Iancu, A., Reghunathan, M., Bannon, B.D., and Kennedy, M.B. A model for regulation by synGAP-β1 of binding of synaptic proteins to PDZ-domain 'slots' in the postsynaptic density. *eLife* 5, e16813, 2016.

Mastro, T.L., Preza, A., Basu, S., Chattarji, S., Till, S.M., Kind, P., and Kennedy, M.B. A sex difference in the response of the rodent postsynaptic density to synGAP haploinsufficiency. *eLife* 9, e52656, 2020.