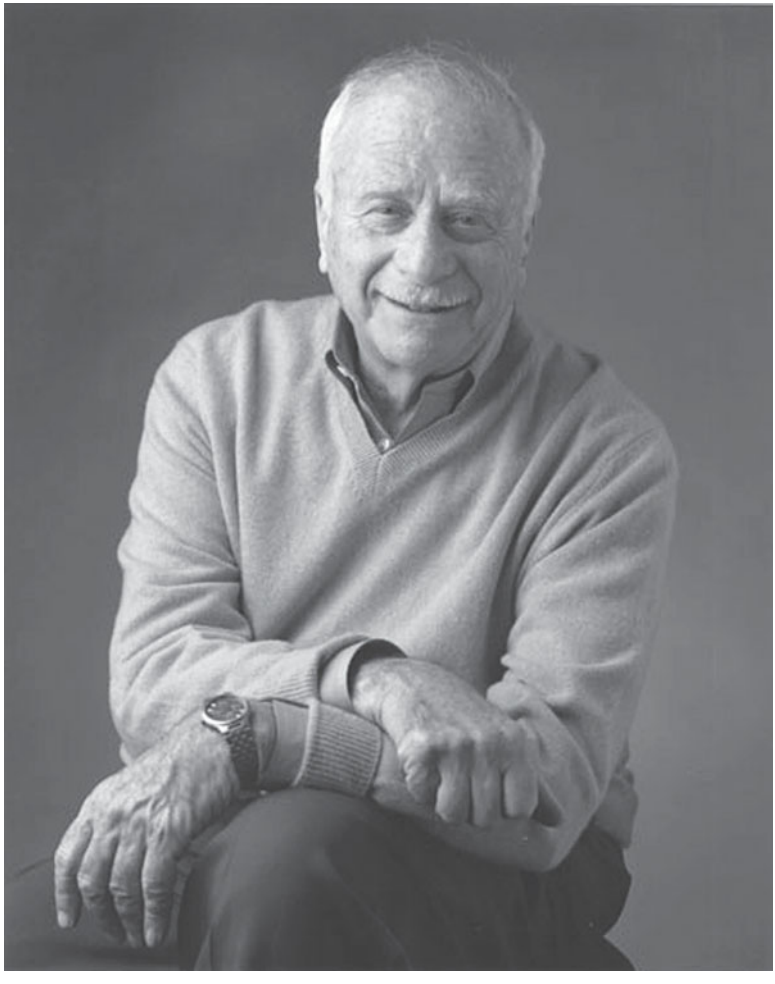

Lawrence Kruger

Born:

New Brunswick, New Jersey
August 15, 1929

Education:

Wagner College, B.S. (1949)
Yale University, Ph.D. (1954)

Appointments:

Research Associate, Institute of Living, Hartford, CT (1954)
Fellow, Johns Hopkins Medical School (1955)
Instructor, UCLA School of Medicine (1957)
National Research Council Fellow, Institut Marey, Collège de France, Paris (1958)
National Research Council Fellow, Oxford University (1958)
Senior Research Fellow, Department of Anatomy, UCLA (1959)
Department of Anatomy, UCLA (1960)
Department of Anatomy and Cell Biology, UCLA (1966)
Department of Anesthesiology, UCLA (1976–)
Distinguished Professor of Neurobiology, Emeritus, UCLA (1995–)

Honors and Awards (Selected):

Lederle Medical Faculty Award (1963–1966)
Editor-in-Chief *Somatosensory and Motor Research* (1983–1995)
Cajal Club–Nucleolus (1985–1986) and President (1986–1987)
Fogarty Senior International Scholar (1977, 1989)
Wellcome Visiting Professor, Albany Medical College (1981)
Javits Neuroscience Investigator Award (1984, 1991)
Horace W. Magoun Lecturer, UCLA (1997)
Getty Research Institute, Resident Getty Scholar (2001–2002)
Fellow AAAS (American Association for the Advancement of Science) (2006)
Endowment of Lawrence Kruger Neuroscience Scholarship at UCLA (2007)

Lawrence Kruger began his research with electrophysiological mapping and anatomical studies of visual and somatosensory systems. In somatosensory systems, he characterized the distinctive ultrastructure of peripheral nociceptor terminals, he described the C-fiber thalamic "pain" projections, and he compared the representation of the "lemniscal" and "anterolateral" systems at the brain stem level. He also carried out broad studies of sensory mapping and comparative neurobiology. This work led to some of the early studies characterizing the fine structure of normal and reactive astrocytes and oligodendrocytes. He described the migration of microglia, studied axonal degeneration in the periphery, and provided the earliest evidence of "continuous growth" of axons following laminar lesions of the cerebral cortex, a finding later supported by in situ hybridization. His later work on pain centered on characterizing the specialized peripheral distribution of lectin and peptide-labeled thin nociceptor fibers and on developing his concept of a sensory axon "noceffector" response to injury. He has also studied the early history of experimental neuroscience.

Lawrence Kruger

Controlling the narrative of one's life is a rich privilege that allows one to be more generous than is demanded of serious biographers, for autobiographies are easily imbued with callous self-promoting stigmata. The events in a scientist's life may engender the curiosity of those working in the same sub-specialties but will hardly be of sufficient interest to later generations of non-specialists to whom such memoirs might be addressed. Accordingly, this personal narrative includes events and scientific pursuits that seemed adventurous at the time and perhaps are still worthy of retrospection. It is directed toward revealing the context, driving force, and excitement in the scientific enterprise of academic research, including a brief description of the setting as well as the changes in the "establishment" that provide the fundamental materials of historiography. A personal retrospective of the limited and more intimate world of neuroscience as it blossomed in the last half of the twentieth century, before research teams became a dominant pattern, is presumably most valuable if it extends beyond individual scientific accomplishment and conveys some sense of success (and failure) in pursuit of scientific ideas and the seemingly extraneous factors that shape careers.

I grew up in the culturally and academically rich environment of Brooklyn, New York, the son of minimally educated Polish Jews who emigrated to New York before World War I. My father, possessing tailoring skills, opened a garment factory and manufactured ladies and children's coats until his retirement in his seventies, and my mother remained an energetic and witty "homemaker" for a full century. Summers were spent largely on a New Jersey country farm near New Brunswick, where I was born in 1929, the youngest of three children, during the great economic "depression" that enveloped the United States. Our family name, *Kpykr* in Cyrillic, is Polish for "crow," the bird, and was variously anglicized by Ellis Island officials—thus Kruger.

Music

While seemingly not germane to a scientist's memoir, it would be remiss to omit commenting on how music shaped my life significantly at many stages, but most profoundly when in junior high school. Probably the singular event in my early development was being taken by my younger sister to a concert by cellist Emanuel Feuermann, performing works for cello (with an orchestra I later played in), including a performance of the Dvorak concerto, providing

a moment akin to an epiphany and a strong desire to study the cello. The impact was immediate, and I knew I wanted a cello but was unable to persuade my parents to provide one for me until my Bar Mitzvah approached. By then, having progressed from agnosticism to an attitude more akin to antitheism, I was not above compromising and performed the ceremonials despite some distaste for the stultifying impact of religious practices. In return, I extorted the cello from my parents and agreed to perform the ritual ceremony, complete with speeches in Hebrew, Yiddish, and English in exchange for a decent instrument and lessons—an agreement that ultimately brought them almost as much pleasure as it did in altering my own life and developing a sense of dedicated self-discipline. This also ended the daily after-school Jewish education that had already developed the strong contrarian and occasionally iconoclastic tendencies of many youngsters who later pursued careers in science.

An abiding enthusiasm for classical music persisting into adulthood has been central to my personal development and daily activities throughout my entire career. Growing up in New York City where there were many amateur community orchestras and opportunities to play the major repertory and attend numerous low-cost concerts propelled what seemed a normal human propensity toward music into a passion that has been a central force in my life. I probably became a serious reader in my teens because I averaged hours each day on the subway with books in my cello bag. The details of my musical life somewhat reflect the narrative path of traditional autobiography that follows in relating scientific endeavors, but "musicophilia" is a common childhood occurrence that has enabled the development of an ability to organize and memorize intricate sequential patterns and huge quantities of seemingly meaningless retrievable information that persists throughout life. To the extent that my memory has served me well (despite recent signs of decline), I suspect this derives largely from the mnemonic power of music. Many of the happiest events of my life have been associated with music—especially the years of playing chamber music with friends, academic colleagues, and occasionally, outstanding professionals.

Early Education

My early education in the New York City public education system was generally excellent, especially the years at New Utrecht High School in Brooklyn. In addition to providing a quite decent orchestra program, most of my teachers sported Ph.D.s, a consequence of the desperate job situation that developed during the great economic depression. Its aftermath was evident in succeeding years in the general mind-set of seriousness that drove many youngsters to become dedicated book readers. The World War ended exactly on my 16th birthday, and in the next years colleges were inundated with returning GIs, making the choice of a college difficult. I was tempted by

music scholarship offers but opted for a small liberal arts college (Wagner) closer to home where I was able to reside on campus and complete preparation for a career in science in 3 years, quickly recognizing I was unreceptive to a career in medicine. Although initially drawn to psychology, I decided that study of the physiology of the nervous system was precisely what I wanted, easily choosing Yale because of its emphasis on, and reputation in, neurophysiology.

Yale Years

Arriving at Yale, a rather immature and insecure graduate student in physiology 2 weeks after my 20th birthday was initially intimidating, but the warmth and kindness of the faculty assembled by the chairman, John Fulton, created an atmosphere of breadth and intensity that was especially embraced by the steady flow of neurologists and neurosurgeons who fulfilled the year of research then required for completion of 5-year residency programs. Fulton's lab provided access to primates, good surgical facilities, and staff. Working with laboratory primates provided rich experiences and such personal memorable pleasures as my bottle-feeding a baby gorilla given to Dr. Fulton by celebrity hunter Frank Buck. In later years, primate experience and interest fostered my participation in the federal Regional Primate Centers program. Opposite my first "office"—best described as a closet for the department reprints and supplies that contained two student desks—was the Brain Tumor Registry originated by celebrated neurosurgeon Harvey Cushing and then supervised by Louise Eisenhardt, who trained the steady flow of clinicians in neuropathology in preparation for specialty board exams. She also served as editor of the *Journal of Neurosurgery*—funded personally by Dr. Fulton, who also created and funded the *Journal of Neurophysiology* and eventually relinquished ownership of both, among his philanthropies.

There were many sources of unusual kindness and generosity—especially from Fulton. An invitation to the spacious, elegant Fulton home was customary on an almost weekly basis following the weekly seminar whose speaker was the guest of honor, frequently a neurologist or neurosurgeon. The food and drink provided a lively party spirit as well as the joys of "shop-talk." Fulton enjoyed dictating letters to his secretary, seated with him in the back seat of his chauffeured limousine, composing his many letters as if they were to be read posthumously. No letter failed to receive a rather prompt reply. His lifestyle and extraordinary generosity plus his editorship of the first advanced, quality, multiauthored, influential book on the *Physiology of the Nervous System* had great impact abroad, as well as in the United States, and his hobby of book collecting was supplemented by an ardent interest in fostering neuroscience history. John and Lucia Fulton's Hamden home was built by the Swiss for the Chicago World's Fair and was transported for reassembly in Connecticut in the years after he was appointed to the

Yale Sterling Chair of Physiology at age 29. The extensive library of antiquarian books, largely in the history of science, was redolent of a book odor and atmosphere that has remained a source of comfort and excitement throughout my life. Dinners and parties at his home provided an extraordinary social milieu for the major figures in clinical neuroscience as well as basic scientists in mid-century, but the latter part of his career was marred by advancing poor health and such pressures as the red-baiting of the McCarthy era, which resulted in his being removed from the Physiology Chair and into the library with a newly created Chair in Medical History. The medical school Dean who removed him took over the Sterling Chair of Physiology himself, and the Department waned visibly with many staff and student departures in my latter years there.

The Yale graduate program in physiology was designed to produce teachers of the entire field of physiology rather than mere researchers. The five students who entered the program with me departed principally to enroll in a medical school curriculum elsewhere. Graduate students took courses with the medical students but were obliged to take the exams under customary controlled, competitive conditions whereas medical students took their exams home and submitted their papers anonymously. We also were obliged to take lecture and lab courses in each major specialty of physiology. We trained in other demanding disciplines as well, including physical chemistry and biophysics and had the pleasures of a history of medicine seminar (with Fulton) and seminars in the Biology Department where I met several extraordinary influential minds, including an aged, but exhilaratingly stimulating Ross Harrison, pioneer of neuronal tissue culture (then Emeritus and about my current age). Courses extended over 4 years and slowed the progress of thesis research, but there were many pleasant features of life at Yale. I dawdled and indulged in a rich musical life but finally completed my dissertation research after 5 years when pressed by the call to military service. Financial support at Yale came from a variety of sources, including my parents, but much came from research jobs, first from neurosurgeon Leonard Malis constructing various pieces of apparatus, and then from Lloyd H. Beck and Walter R. Miles in Psychology, which led to publication of my first psychophysical experiments in vision (Kruger and Boname, 1955) and the earliest attempts at establishing a scaling metric for subjective magnitude estimation in olfaction by scaling the intensity of aliphatic compounds of varying carbon chain length (Kruger et al., 1955a, 1955b); an idea derived from an introduction to S. S. Stevens at Harvard by Karl Pribram.

I was immediately attracted to several neurosurgeons arriving at Yale, choosing Karl Pribram as my advisor and then as thesis advisor. His support nurtured much of my professional and personal growth and provided a sense of being part of his family—a friendship of great importance in my early development. I also began working with two young neurosurgeons—Leonard (Len) Malis and A. J. (Joe) Berman, starting experimental work in my first

year despite the heavy load of the medical curriculum and other courses. My earliest research experience exposed me to the rigors of surgical technique in primates, which seemed more glamorous than neurological exams, and the behavioral testing of monkeys with various motor cortex lesions (Berman et al., 1954). Our findings ultimately convinced the open-minded Fulton that rostral frontal lesions involved the proximal musculature rather than a specific extra-pyramidal spasticity; a view that Fulton had previously espoused. The distinction between localization of sites underlying production of flaccid and spastic paralysis was a "hot" subject at that time for clinicians. But recording electrically evoked potentials from the motor cortex proved most promising and led to the major theme of my Ph.D. dissertation and first neurophysiological paper (Malis et al., 1953) using a primitive lab setup left behind by Warren McCulloch that Len Malis helped me modernize. In turn, I helped Len in construction of a number of devices of his design (notably a cassette changer for cerebral angiography and the electronics for a bipolar split-forceps tissue coagulator for surgery). We later worked together pursuing an electrophysiological analysis of the complex triple wave response

Fig. 1 Team assembled in research laboratory at Marineland, Florida in 1956 to map the sensory cortex of the dolphin (in tank). From left to right: Joe Hind (Wisconsin), Jerzy Rose and Larry Kruger (Johns Hopkins), Len Malis (Mt. Sinai Hospital, New York), John Lilly (NIH), and Karl Pribram (Institute of Living, Hartford). Vernon Mountcastle (Johns Hopkins) snapped the photo and Clinton Woolsey (Wisconsin) is beyond the camera view.

evoked in cat visual cortex (Malis and Kruger, 1956). This provided valuable experience in the use of the machine and electronics shops while adding to financial support and developed a strong friendship through continuing collaboration with a brilliant, supportive mentor (Malis became Chief of Neurosurgery at Mt. Sinai Hospital in New York and later was a dominant figure in microneurosurgery).

Malis and Berman urged me to switch to medical school and offered personal financial assistance, but observing their travails in medical practice during my summer "vacation" easily convinced me that dealing with human illness on a daily basis was not my ambition. I also was engaged in behavioral studies (Pribram et al., 1956) and received an invitation to write a review article with Pribram on the rhinencephalon that would be presented at a symposium on olfaction at the NY Academy of Science in which we systematized primary, secondary, and tertiary connections of the olfactory bulb as a set of "limbic" systems, a construct instigated by Paul MacLean. Surveying the literature and writing with Pribram was a joyous experience and was supplemented by a valuable, instructive critique delivered personally in a most kind all day visit by Hans-Lukas (Luke) Teuber (who then invited me to give my first invited seminar at New York University [NYU]). This was spoiled when my draft board decided that I should consider giving up graduate school to serve my country in the Korean War! The day I presented this paper preceded my plea that evening at my draft board to continue student deferment. The presentation went fine, but I was reclassified 1A and realized I must focus on completing my degree requirements quickly. The paper (Pribram and Kruger, 1954) was enormously successful, was reprinted in a book of readings, and elicited far more reprint requests (common in that era) than any dozen subsequent original research efforts. My dissertation research revealed the nature of cutaneous and muscle afferent projections to the monkey "motor" cortex, including their independence from the thalamic and postcentral tactile projection, and also presented a variety of experiments on the nature of the electrical response and the spinal pathway (Kruger, 1956).

Before reporting for military induction, I had arranged with Bob Galambos to work in his lab at the Army's Walter Reed Hospital after basic training but, fortunately, military induction was interrupted by a perceptive orthopedist who noticed my scoliotic back and asked whether it was painful. Answering truthfully that it was not problematic, I was doubted and soon sent home with a 4F designation. The impending induction into the army had provided strong impetus for completing my dissertation and its defense, but the prospect of fighting in the Korean War left me with an uncertain future and many loose ends in my research and personal life. Fortunately, I was able to continue work in Pribram's lab, which had recently moved to a hospital setting—the Institute of Living in Hartford, Connecticut. There I found an intellectually compatible, interactive group with two others

(Mort Mishkin and Larry Weiskrantz) completing their Ph.D. theses with Karl. I also was able to complete the behavioral study for my thesis on the effects of total ablation of somatosensory areas I and II in monkeys. This was the first such study to reveal virtually complete degeneration of the putative thalamic tactile neurons while preserving some somatosensory performance ability despite a profound tactile defect (Kruger and Porter, 1958). This required building an infrared scanning device for observing the animal's performance in the dark by employing the Nipkow disk "flying spot" principle. Developing new techniques seemed of paramount performance, and I soon embarked on making and implanting multiple-lead electrode pads across the pre- and postcentral gyri of monkeys (methods learned from Jose Delgado at Yale). This offered an opportunity to learn some basic electroencephalography with Charles Henry, head of the electroencephalographic (EEG) lab and a wry, stimulating teacher. The resulting report (Kruger and Henry, 1957) was received with unexpected enthusiasm, but it also helped me realize how limited such methodologies were then for clinical practice, resulting in a premature bias that the EEG was a poor indicator of neuronal activity and would yield little, further reinforcing my commitment to basic science. This transition period enabled arranging a postdoctoral fellowship with Jerzy Rose in the Physiology Department at Johns Hopkins to learn some neuroanatomy, having become painfully aware of my deficiencies in preparing the rhinencephalon review (Pribram and Kruger, 1954). A trip to Baltimore led to the decision to obtain dolphin brains to study the cerebrum of a mammal lacking a peripheral olfactory system.

I learned of the possibility of obtaining dolphins from a fellow student I knew while living at the Yale Hall of Graduate Studies, F. G. Wood, Jr. ("Woody"), who later became Curator in Marineland Florida. He offered two specimens, and Pribram prevailed on Kao-Liang Chow and Karl Lashley to remove the brains and ship them to Baltimore for me. Shortly after, with Lashley's impending mandatory retirement at age 65, an attempt was made to recruit Pribram as his successor as Director of the Yerkes Laboratory of Primate Biology. This served as an excuse to drive to Florida with Pribram and spend a few days with Lashley, as well as to visit Marineland where we were able to perfuse and optimally preserve the brains from another two dolphins, which were brought to Baltimore en route home. The time spent with Lashley was fun, but rather strange. He was ardent about music, collecting chamber music parts that he crudely bound by hand and later gave to the Jacksonville music conservatory. He played the cello in an unorthodox position with the left thumb pointing upward. He had also built window boxes with light bulbs to contain the instruments and fight the moisture, although that proved rather ineffective. I enjoyed arguing with him about his ideas of "equipotentiality" and "mass-action" in cerebral cortex function, maintaining that this was as wrong-headed as his notions about cortical cytoarchitecture. Remarkably, that had a salutary outcome, and I heard

stories of his days as a graduate student in parasitology at Johns Hopkins, living with psychophysicist Carney Landis and John B. Watson. Watson who later was the Chairman of Psychology at Johns Hopkins and proceeded to revolutionize the Madison Avenue world of advertising. Such intimate encounters and brashness have largely disappeared in the contemporary world of "big science."

Johns Hopkins

I approached Jerzy Rose at Hopkins specifically to gain a foundation in neuroanatomy but also because the rhinencephalon review with Pribram had proved unexpectedly "popular." Jerzy suggested that I engage in something original, and we had agreed that a description of the "olfactory brain" of dolphins, lacking an olfactory organ, might be an instructive anatomical exercise. However, publication of such an account in a smaller porpoise by Breathnach proved a propitious excuse for me to turn instead to the thalamus—for which Rose was an internationally recognized authority. The dolphin brain was challenging, and I decided to pursue an arduous analysis of thalamic nucleus volumes in a series of mammals, including a dense series of the sheep brain that I cut, stained, and mounted myself. This was the only time I ever indulged in routine histological preparation of significant scale in my entire career, and it taught me the value of a capable technician. Preparing the illustrations of the very large dolphin thalamus was a time-consuming ordeal and outlining the various nuclei in serial photomicrographs for each species to make measurements involved many instructive discussions with Jerzy and extensive planimetry. This was my trial by fire in trying to become an anatomist. The sheer size of the sections presented a difficult problem for producing illustrations,and employed the tedious task of inking individual neurons on montaged direct positive 8×10" prints and then bleaching the photo. Nevertheless, a hefty 66-page paper ultimately was accepted by Elizabeth Crosby (serving briefly as editor for the *Journal of Comparative Neurology*) with congratulations for the rare feat of requiring no corrections or changes—a tribute to the typist never again repeated. The findings indicated that the "association" or "intrinsic" thalamic nuclei were enormously expanded in the cetacean brain, paralleling primate evolution, and also exhibited some specialized features (Kruger, 1959). Jerzy had an enormous impact upon my personal, as well as scientific development. He imparted his brilliance with brio or a feigned humility that quite failed to conceal a remarkable wit and warm heart that delighted those few who had the good fortune of knowing him well.

A subsequent trip to Marineland with a distinguished team to study the dolphin sensory cortex electrophysiologically proved a difficult adventure, largely because of difficulty with anesthesia. Mountcastle courageously intubated the trachea with a human size cannula while we wedged blocks to

keep the jaw open. But barbiturates and the mechanical respiratory pump designed by John Lilly at National Institutes of Health (NIH) proved inadequate for long-term mapping. The cortex was successfully exposed by craniotomies performed by Malis, Pribram, and Clinton Woolsey, and we obtained some surface electrocorticograms. The perfused brains provided suitable material for morphological study of the whole brain (Kruger, 1966), in addition to the thalamus (Kruger, 1959).

Life as a postdoc in the Hopkins Physiology Department was vastly more stimulating than I had expected, with most of the department usually attending lunch together and engaging in vigorous, often argumentative discussions that displayed impressive critical capacities and competitive spirit. Having been reared as a "compleat" physiologist, trained to teach all subjects, I was tapped by the Chairman, Philip Bard, to teach in the cardiac and renal lab exercises for medical students. But I had no contact with the neurophysiological aspects except for demonstrating the cardiac and respiratory effects of sympathetic and vagal stimulation in large dogs and in turtles. I widened my horizons across the street in the hospital where I frequently enjoyed my first coffee with Earl Walker (Chief of Neurosurgery), who usually had completed his first procedure and "rounds" by the time I was beginning my workday. I also found David Bodian enormously stimulating and

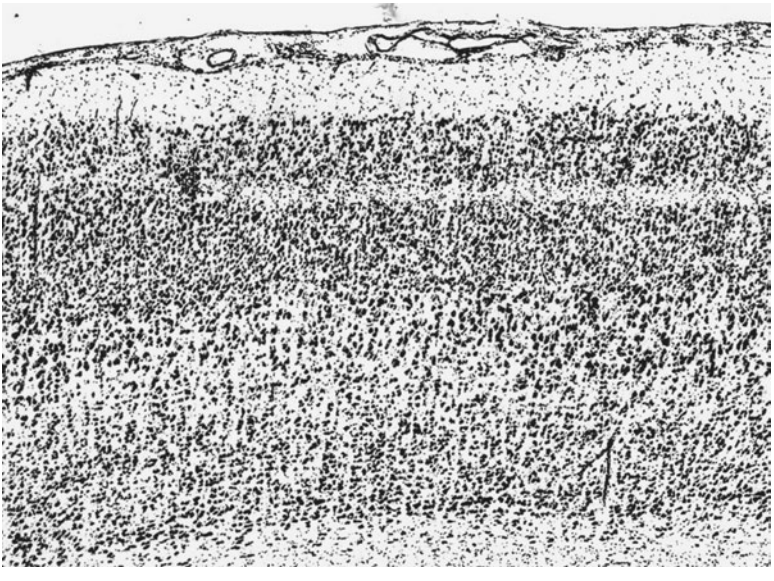

Fig. 2 Nissl-stained section of a laminar lesion in rabbit occipital cortex 42 days after irradiation with a monoenergetic beam of 20 million electron volt deuterons. The thin lamina lacking neurons was shown by other methods to reveal prolific growth of axons within weeks after the lesion.

kind, but it was in Steve Kuffler's lab in Ophthalmology where I found my closest friends—Charles Edwards, Torsten Wiesel, Bob Bosler, and others, who incorporated me into their personal lives and also helped me ripen into a scientific world that was blossoming rapidly. Monthly meetings with drinks and dinner at the then new NIH or Bethesda Naval Hospital brought regular contact between the Baltimore/Washington neuroscience communities, resulting in a high level of camaraderie and sophisticated "shop talk."

In addition to the scientific world, my musical life in Baltimore was glorious. The new principal cellist of the Baltimore Symphony, Richard Kay, was a colleague in various amateur orchestras during our teen years in New York and lived near my apartment (and also helped me get Damien Kuffler started studying the cello). He provided cello tutelage and introduced me to professionals in the orchestra. Within a year I was invited to impose my musical tastes for an hour each week upon the listeners of WBJC-FM, broadcasting from Baltimore Junior College. For the next 3 years I studied and played the string quartet repertory weekly with a great quartet violinist, William Kroll, at the Peabody Music Conservatory, and I practiced regularly at the home of our fine first violinist, Janet Lehninger, wife of the Chairman of Biochemistry. I also formed a close friendship with the concertmaster of the Baltimore Symphony, Lotze Steinhardt, who could sight-read almost anything and with whom I gleefully explored twentieth-century chamber music. On various occasions he helped me entice key Symphony players to record unusual combinations at the WBJC studio for my weekly radio broadcasts.

In the lab, working strictly on morphology every day was a difficult discipline, and observing the quality of single-neuron recording obtainable with the new, low-impedance, platinized indium microelectrode developed by Jerzy had me champing at the bit to do experimental work again. I started by recording from the olfactory bulb of the turtles left over from those purchased for teaching the medical cardiac physiology labs but found that recording and isolating single neurons was far easier than controlling the delivery of odorant stimuli. I soon gave up and used the remaining turtles to make forebrain lesions to study thalamic projections in reptiles using the retrograde neuronal atrophy technique under the tutelage of Rose, the master of this method. This also soon was abandoned (although I later pursued the problem elsewhere in lizard and alligator). Instead, we attempted to employ this method to analyze the cortical terminations of thalamic projection neurons by making lesions of different laminar depth in the cerebral cortex.

Laminar Lesions

The ordeal of descriptive and quantitative neuroanatomy had frustrated my desire to do experimental work on thalamic degeneration. We finally hit upon developing a method for making cerebral cortex lesions of varying depth to

elicit retrograde thalamic neuronal atrophy, which then was still a major tool for studying connectivity. An earlier attempt by Dusser de Barenne at Yale employing thermocoagulation brought minimal success, and our attempts to construct a device controlling the depth of a high-speed rotor proved impractical. Destroying the surface vasculature was critical and this was uncontrollable, but the frustration of failure led me to discuss the problem with Len Malis, who continued to nurture much of my development. He semi-seriously suggested employing a mono-energetic particle beam of ionizing radiation that theoretically would penetrate the cortex down to a fixed depth with accuracy. Crude estimates suggested that this would require a high-energy particle generator, and after consulting physicist colleagues it became evident that we would need a linear accelerator or cyclotron of substantial size. A phone call to the Brookhaven National Laboratories, near Cold Spring Harbor, elicited interest. When we examined the range-energy ("Bragg") curves for positive-charge particles, it became evident (assuming the brain approximated water in density) that the Brookhaven cyclotron would be suitable, and that it might be possible to destroy a layer in depth due to the "Bragg effect"—essentially an increase in energy release as particles slowed and increased their collision rate. This idea intrigued physicist Charles Baker, who supervised the Brookhaven cyclotron facility. Len and I soon irradiated the striate cortex in two cats in which we crudely guessed at dosage and irradiated the cortex through two bone trephinations. A few weeks later, I perfused the brains and gave them to Jerzy's technician, Cecilia Bisson (who had prepared the dolphin brain sections). This enabled us to examine the cytoarchitecture, with taunts from Jerzy that this was a "shot in the dark" (indeed, it was). But it seemed interesting to observe the effects of controlled, focal ionizing radiation of the brain in the puzzling "atomic era" following the Hiroshima bomb.

When the first sections emerged the result was startling. There was a layer devoid of neurons in the striate cortex but a seemingly normal neuronal population above and below. The irradiated site revealed a thin layer with neurons destroyed (basically absent) and apparent minimal gliosis, with a sharp border ($\sim$10 μm or one neuron wide) at the end of particle range. We knew of the sharp "Bragg curve" peak of energy release at the end of range of positive-charge particles, but a precise laminar lesion in the middle of the cortex seemed a wild dream, especially after we were able to vary lesion depth and width. Jerzy, recognizing a potential powerful new tool, mobilized us into launching a large study of the smooth rabbit striate cortex, and we were soon immersed in a project that dominated much of my effort for the next decade. Later the work continued with the better controlled measurable radiation beam obtainable from a larger cyclotron at University of California at Berkeley (UC Berkeley).

By the time we published our first report on the two cats in *Science* (Malis et al., 1957), we already were deeply immersed in extensive material

from dozens of rabbits irradiated at Brookhaven. When we finally were able to measure dose accurately, our guess estimate proved wrong by about 17-fold, indicating we had stumbled on the correct dosage range fortuitously. Malis designed an ionization chamber that enabled suitable measurement, and we soon geared up to extend our findings in a larger series of cortical lesions. We assembled a team and obtained approval, lab appointments, and support from the Atomic Energy Commission to design and perform experiments at the Brookhaven cyclotron. We spent 2 days (the maximum cyclotron time they would allot to our study) briefly irradiating the cortex of each batch of rabbits. Jerzy and I then drove them back to Hopkins where over the next 2 years I anesthetized, perfused, and removed the brains of ~300 rabbits at a fixed schedule of postirradiation intervals. As the youngest team member, I was obliged to wear a film badge although it is doubtful that I ever was exposed to harmful dosages. (The badge proved irrelevant for the particle energies employed, and I was not even required to wear it regularly.) I mounted the anesthetized rabbit with open scalp and a lead shield with an opening at the end of the beam pipe over the lesion area we sought. I then emerged for the several minutes of irradiation, retrieving the animal for wound closure and recovery, repeating this routine for each animal. Only years later, looking back on this as a contribution to dosimetry—the first and most extensive study of neuronal, glial, and vascular sensitivity to ionizing radiation measured in suitable physical (rather than radiological) units—did we realize the importance of our efforts to the pioneering radiation-hazard studies begun by Tobias and Gofman at UC Berkeley.

The neuroanatomical findings proved far more interesting than expected. We soon examined features other than neuron injury and death over a wide range of parameters and discovered to our surprise that the laminar zone of neuronal loss revealed apparent destruction of axons in the early stages but that later the axonal pattern exhibited what we interpreted as "luxuriant growth." The dictum that axonal regrowth after injury was feeble at best in the mammalian central nervous system (CNS) was firmly inculcated since the work of Cajal on degeneration and regeneration, which led him to conclude that neuronal connectivity was "fixed and immutable." Profuse growth was quite unexpected and with lesions that resulted in a glial scar, the axonal regrowth failed to penetrate the glial "scar." As a result, the lamina resembled the axon-rich non-neuronal zonal lamina (layer I) of cerebral cortex, thus forcing us to consider that axonal growth might be a basic property of all neurons but was aborted here by the glial obstruction. The axonal pattern of the laminar lesion basically resembled the proliferation seen at the edges in plant pruning. While static morphology could not directly establish the principle of functional "plasticity", it nevertheless opened the door to considering possibilities of dynamic network growth as a basic feature of neurons. The reception of the initial documentation in the *Journal of Comparative Neurology* (Malis et al., 1960, Rose et al., 1960) elicited great interest and

invitations (Kruger, 1965) and in the long run profoundly altered the direction of my career.

California Summer

An interlude in the hectic pace arose in the spring of 1957 from my attendance at a seminar on the history of neurology conducted by Oswei Temkin, an extraordinary medical historian with remarkable language skills and broad training in medicine and history. We were joined each week by a visitor on sabbatical leave at NIH, Horace W. ("Tid") Magoun, who had a passionate interest in neuroscience history. He drove from Bethesda weekly with his wife Jean, and after several dinners together he invited me to University of California at Los Angeles (UCLA) for the summer. This was my first academic position, "Acting Instructor" in the History of Medicine division of the Department of Anatomy, where I would prepare a poster presentation on illustrations of the brain before 1800 for the 75th-year celebration of the American Anatomical Association. Baltimore summers were miserably hot and uncomfortable (the air-conditioning was lacking in the lab and my apartment). Work was less than optimally productive the previous year, and most people escaped for long vacations. I had never been far from the East Coast and finally arranged driving cross-country to Los Angeles in early June, a great adventure that changed my future in ways that I could hardly imagine. Before leaving I easily found most of the rare works in the excellent Hopkins Medical Library with Temkin's help and guidance. Others came from the National Library of Medicine and Yale, all professionally photographed at Hopkins and billed to the UCLA Biomedical Library through Magoun. Mountcastle encouraged me to read H. L. Menken (the "sage of Baltimore") on the subject of southern California, who raged that the "place stinks of orange blossoms," was filled with "morons," and that everything is "bigger and better" and rather vulgar, but once I reached the Rockies the West looked enchanting.

Finding a cello was my first concern after landing a simpatico place to live, and the assistant conductor of the Baltimore Symphony arranged contact with his brother in Los Angeles (LA), Ennio Bolognini; a flamboyant, fabulous cellist who opened doors into the music world of LA, including an introduction to a luthier near UCLA who offered a practice room in his shop, loaned me a "factory" instrument and introduced me to people to play chamber music. Within 2 weeks, my musical life had blossomed, and I was allowed the use of an instrument on consignment in the shop, the Stradivarius cello that once belonged to composer Felix Mendelssohn. The first concert I attended at UCLA's Royce Hall was a celebration of Igor Stravinsky's 75th birthday, with the composer conducting a world premiere of his ballet "Agon" and attended by many world-famous local musicians, all of whom I naturally imagined lived in New York!

The music world, the invariably comfortable warm days and cool evenings, the exotic beautiful greenery and the warmth and spirit of the people I met was enchanting. In addition, I started doing experiments with an enthusiastic young scientist, Ellis Berkowitz (later a distinguished otolaryngologist). Together we electrophysiologically mapped the olfactory, somatic, visual, and auditory projections to the cerebral cortex of alligators and prepared a series of ablations for later thalamic degeneration studies (Kruger and Berkowitz, 1960).

In addition to all of these happy developments, I drove to UC Berkeley one week, accompanied by another visiting scientist, Herbert J. A. ("Bert") Dartnall from the Institute of Ophthalmology in London. Together we removed a California grey whale brain from an estimated 35 ton specimen brought in by a commercial whaling company operating in San Francisco Bay. I quickly fixed and blocked it for shipment back to Baltimore for histological study. In addition, with darkroom facilities at UC Berkeley provided by Gordon Walls, I was able to dissect the whale eyes and the retina for Dartnall (a trained chemist reluctant to dissect the eye), who later made rhodopsin extracts from the retina, revealing that cetacean visual pigments were essentially similar to those of other mammals. I originally had arranged this trip to visit Cornelius Tobias (at the cyclotron facility of the UC Berkeley Physics Department), who had published the suggestion that the Bragg peak theoretically could achieve hypophysectomy in humans without surgery. I presented a seminar to a small group showing the initial results of our experiments, which had employed this principle with the Brookhaven cyclotron, and was received with considerable excitement. The Director, John Lawrence (brother of Nobelist Ernest Lawrence, who devised the first cyclotron), expressed enthusiastic interest, and I was encouraged to consider returning to California to continue the radiation lesion experiments using the vastly superior accelerator facilities in UC Berkeley. There was another inducement to return to California. I was enamored of my productive summer experience at UCLA, and the Anatomy Department there was courting me to join the faculty after a postdoctoral stint I planned in Europe. The UCLA position was enabled by the NIH Senior Scholar program, which provided faculty salary plus research grant support with a nonbinding commitment of the institution to pick up the tenure-track salary within 5 years. Ultimately, the courtship from UC Berkeley could not compete with the prospect of Magoun's planned new Brain Research Institute at UCLA or with the attractions of the cultural life in LA, especially its music world. But UC Berkeley's interest later enabled me to continue with a very large series of cortical laminar lesions in rats, begun in UC Berkeley in the summer of 1960 where I also taught in a summer biophysics course with Tobias. Clearly, it would not be an exaggeration to acknowledge that the California summer sojourn in 1957 abruptly transformed my future.

Transition to Europe

I returned to Hopkins with a sense of exhilaration and excitement and the unexpected trophy of a decently preserved large mysticete whale brain to compare with the dolphin material, plus the brain of an Indian elephant that I had perfused at the Baltimore zoo the previous spring. It seemed I might have been destined to become an authority on large brains per se, but the lure of experimental work prevailed, and I prepared the dolphin brain studies for publication. My last year in Baltimore was quite full, with trips to the Brookhaven National Labs, where I was appointed a Research Associate. Between the trips to and fro with the rabbit cages in my car, the regime of timed removal of irradiated brains and a significant contribution to teaching in the physiology labs for medical students, I doubt that I could have sustained my good spirits in that era if not for the richness of my personal musical life. I worked hard in the lab, including weekends, but managed to play regularly with two string quartets and continued to study at the Peabody Conservatory and to play in its orchestra under Elliot Galkin, with whom I periodically played string quartets.

I applied for and received a National Research Council (NRC) Fellowship and by the summer of 1958 I was ready to start a new postdoctoral position at the invitation of Sir Wilfred Le Gros Clark at Oxford, with plans for experiments with Tom Powell on the reptilian thalamus, but the new lab building where I was to work was not yet completed and I was asked to postpone coming, although I had already accepted the NRC Fellowship. The happiest solution seemed accepting Denise Fessard's invitation to come to Paris and work with her until late fall, and this was rapidly arranged. This was a richly rewarding experience of life and work in a style I could never have fantasized.

Paris

Meeting Denise Albe-Fessard at the 1956 International Physiological Congress in Brussels, my first European visit, had resulted in a stimulating exchange about a somatic projection to the thalamus that she had reported. This was distinct from the established tactile map, which is confined to the ventrobasal complex as detailed by my Hopkins mentors and friends—Rose, Mountcastle, and Henneman. Albe-Fessard had described a non-somatotopic projection to the region of the thalamic *centre médian* while employing chloralose anesthesia. This was evidently distinct from the controversial crude "map" that approximated the posterior group, with unit activity driven by putatively noxious stimuli as reported from Hopkins by Poggio and Mountcastle. Their technique employed a cumbersome fully-awake cat preparation requiring surgical denervation of the head. Inviting a young investigator from the Hopkins Physiology Department struck her as a potentially

beneficial means of entering the fray, so she invited me to her Paris lab as a presumptive neutral observer, (although admittedly I was not unbiased), and she loved the challenge.

The Institut Marey was a marvelous place to work, located next to the tennis stadium (*Stade Roland Garros*) and demolished before the end of the century when the French Open tennis tournament became commercially important and expanded into the space of the two huge College de France installations. A huge lab had been built there for Professor Etienne-Jules Marey, largely devoted to recording physiological activity. It became a center for the emergence of cinematography in the late nineteenth century. Marey in Paris, and Muybridge at Penn collaborated with the Stanford "farm," and both independently obtained multiple frame images of animals and people in motion. Alfred Fessard, Institute Director and distinguished *Collège de France* Professor, who had obtained postdoctoral training in physiology at Cambridge, was writing extensively from his broadly informed and imaginative outlook, and was no longer a bench scientist like his physicist wife turned neuroscientist, Denise. In addition to the Fessards, Pierre Buser was another group leader with broad interests, and all three shared a focus on cellular neurophysiology, having exploited the technology of using glass micropipettes to obtain intracellular recordings from electric organs and neurons of a variety of electric fishes. Alfred Fessard was also a key figure in fostering invertebrate cellular neurophysiology in postwar France and in developing the marine station in Arcachon.

Life in Paris was like entering into a series of fortuitous dreams. On arrival I was invited for Sunday dinner by a family in Boulogne close to my friend Roger Hahn (a UC Berkeley science historian). By the end of the day I was invited to live in their house close to the lab as a guest "boarder." It was a large wooden chalet built by the Swiss for a nineteenth-century Paris Exposition, wedged into an idyllic lot between the Bois and the *orangerie* of the adjacent Rothschild estate. Other guests at my first Sunday dinner included the brother-in-law of host Mme. Nelly Cahen, who arrived with his "musical friend," composer Francis Poulenc. Nelly had studied cello with the great cellist Pierre Fournier, and when I moved in the next day, she invited me to choose one of her two instruments and brought me boxes of music. The cello again proved key to a copious life of music and exhilarating work. Inexpensive housing, though lavish for my needs, rendered my stipend sufficient for purchase of my first new auto, a Renault Dauphine. Whenever time permitted I explored the wonders of France and also managed to visit Switzerland and Germany, including a trip to visit Oskar and Cecile Vogt, in whose lab Jerzy had trained glorious first experiences.

The lab experiments were demanding, often extending into early morning of the next day, but the results proved fruitful from the very beginning. The thalamic map, obtained by employing limb nerve volleys in chloralose-anesthetized cats seemed quite different in distribution and properties from

the tactile or "posterior group" projections reported from Hopkins. Most surprisingly, there were very late responses (> 0.5 seconds), suggestive of peripheral C-fiber latencies. While awaiting tissue processing so that I could reconstruct the electrode tracks in transverse and sagittal planes, we moved ahead trying to record intracellularly using glass micropipettes with a sealed chamber system and microdrive that Denise had built. The results were exhilarating, yielding not only what were apparently the earliest intracellular thalamic recordings but also the discovery of responses with long but remarkably fixed latency. These were suggestive of a creditable, slow specific thalamic "pain" projection generated from C-fiber input. I completed the anatomical reconstructions later in Oxford and, with several trips back that winter and spring, produced seemingly important papers detailing a new thalamic pain projection before returning to the United States (Albe-Fessard and Kruger, 1959, 1962; Kruger and Albe-Fessard, 1960). My last trip was during the Oxford spring vacation in time to finish a decent draft with Denise amid grimaces portentive of the onset of childbirth. When we agreed the paper was finished, she calmly and radiantly announced that the contractions were now strong and more frequent, prompting me to hurry to my car as *le patron*, Alfred Fessard, mobilized to prepare and bring her downstairs, and I drove them to the *clinique* in Boulogne where Jean Francois Fessard was born several hours later. Denise beamed with pride but was distressed that she would miss the first lecture at the College de France the next day by Vernon Mountcastle.

In addition to the experiments, I became language-proficient in French and made several new friends at the Institut Marey through the Fessards. These included an elderly Englishman, Lucien Bull, (Marey's assistant in the late nineteenth century who was still experimenting with high-speed photography and cinematographic methods), Yves Galifret, Pierre Buser, Arlette Rougeul, Jean Massion, Jan Bruner, and two eastern Europeans, Tauc and Szabo (both of whom I helped to come to UCLA). The diversity of ideas and techniques used by this group was amazing in their originality, excitement, and technical achievements. They also exposed me to the irresistible culture of French lifestyle.

Oxford

By fall the new labs at Oxford were ready and I pursued my original plan. The move to Oxford by car via the Dover ferry on Guy Fawkes Day in 1958 (wondering why effigies were being burned to greet my arrival) seemed a harsh diversion into cold and wet weather. After a week living at Halifax House, I found "digs" on Holywell Street, the oldest part of the city, with a chilling ceiling and three walls to the outside. This "rooming house" near the lab housed a collection of delightful people—including several undergrads (one, Verne Caviness, later became a neuroscientist) who had elected not to live in college, as well as those who could not (postdocs and others).

The "Prof," Sir Wilfred Le Gros Clark, who often introduced me as a "former colonial," initially installed me in an office with a Russian neuroanatomist, Tatiana Leontovitch, from the Moscow Brain Research Institute, expecting to see feathers fly between the American and Russian "cold warriors." But we got along famously, sharing jokes about English academics and having much enlightening political discussion. Her stay was short, and the remainder of my time was in an office/lab shared with Max Cowan, who had just returned from completing his clinical training and was ready to start new experiments and a significant teaching load. He and his wife Margaret became lifelong friends, although Max periodically "blamed" me for luring him to the United States, where he developed a remarkable and influential career.

I devoted more of my time at Oxford working on the electrophysiological studies from Paris than on the studies of experimental degeneration in the lizard thalamus and telencephalon with Tom Powell (Powell and Kruger, 1960), but life was full. I had obtained a fine eighteenth-century William Foster cello and found a rich musical life in Oxford and London. I also had opportunities to present my work in various places, including the Anatomical Society where I showed the results of the cortical laminar lesion experiments performed at Brookhaven and analyzed at Hopkins. This was received with unusual kindness and enthusiasm by the chair, Frank Goldby, Professor of anatomy at St. Mary's and elicited an invitation from J. Z. Young at University College, London. I also presented to the Physiological Society the electrophysiological sensory mapping study of the alligator olfactory, somatic, visual and acoustic cortex (from the previous summer at UCLA). There was much interest and encouragement, including comments from Lord Adrian (who amusingly confessed that he had demonstrated the "cochlear microphonic" at the Physiological Society in alligator decades earlier but discovered that the heart had stopped—although the cochlear potential endured). Andrew Huxley questioned why the thin reptilian cortex should display larger evoked potentials than the thicker cat and monkey cortex. Visits to Cambridge as a guest of William Rushton and Sir Brian Matthews who at that time was interested in modeling the dolphin acoustic system led to other invitations, including presenting a seminar in Edinburgh followed by warming up in the cold winter by playing cello sonatas with my host David Whitteridge at the piano. Whitteridge and Adrian later provided moral support at a Ciba Foundation symposium organized by Yngve Zottermann on Pain and Itch in the spring, where I first presented the putative pain projection findings from Paris and met several European pain researchers.

UCLA

While in Europe I was courted for an academic position in biophysics at the Berkeley Lawrence Lab at UC where I would have access to excellent accelerator facilities for continuing the laminar lesion work and was also sought by Magoun and Sawyer (Chairman of Anatomy) at UCLA where a new Brain

Research Institute was under construction. The UCLA offer and the musical life of LA were clearly more tempting. The NIH Senior Fellowship I had applied for was awarded, so I returned to Hopkins for the summer of 1959 to work on the laminar lesion papers with Jerzy Rose and in September arrived at UCLA/NIH funding a decently equipped lab being vacated by Carlo Terzuolo, who left for Minneapolis a few months later. His pharmacologist postdoc, Bob Siminoff, was still there trying to finish some experiments but was most willing to work with me on single neuron recording in the medulla. My initial plan was to map the tactile "lemniscal" projection in the dorsal column nuclei, producing the first figurine maps of the cat medulla, and contrast the "lemniscal" properties of the dorsal column nuclei with trigeminal neurons of the "spinothalamic" anterolateral system believed to contain putative "pain" neurons (Kruger et al., 1961). We were joined in this study by Paul Witkovsky, a graduate student in zoology after Siminoff left, a similar study in a few alligators (Kruger and Witkovsky, 1961) with Paul brought similar results and also a refutation of George Bishop's argument that the dorsal column-lemniscal system was a recent acquisition of mammalian evolution. Later I was joined by my first postdoc, Francois Michel from Lyon, and we proceeded to map the trigeminal system in detail, searching for "pain" neurons but finding only tactile-driven discharges (Kruger and Michel, 1962a, 1962b, 1962c). I naively concluded that Pat Wall was correct in denying the existence of "nociceptors" but continued to pursue trigeminal studies for over a decade, eventually realizing that my initial well-received ideas about pain were as erroneous as my negative assumption, an important lesson learned slowly.

While applying for grant funds to gear up for continuing the cortical laminar lesion work, I was fortunate in being offered access to the superior cyclotron facilities at UC Berkeley. There was a smaller cyclotron at UCLA (the first, built by Ernest Lawrence) and run by David Saxon (later University of California President) who was most encouraging helpful in gaining access to the high-energy UC Berkeley accelerator provided sufficient range to make lesions deep into squirrel monkey striate cortex and the opportunity to perform many hundreds of laminar lesions in rat cortex. This proved logistically complicated as it involved shipping animals, assembling a large team and obtaining funds from the Atomic Energy Commission, although obtaining a contract and ample funding proved rather easy.

No longer a postdoc trainee and arriving at UCLA a ripe bachelor, there were predictions that my status was susceptible indeed, within a matter of weeks I met Virginia (Ginny) Findlay, my future wonderful partner in life. It was love at first sight, and a year later we married and soon started a family with the birth of our daughters, Erika and Paula—mothers of our treasured grandchildren. My musical life was largely devoted to playing string quartets but also in the UCLA and community orchestras and the Chancellor's Committee on Fine Arts Productions, the last five as Chair. I also became

deeply involved in fund-raising for the arts and presided over a newly formed organization, The Friends of the Performing Arts at UCLA.

Raising a family in LA on a modest academic salary wasn't always easy, and job offers all involved administrative responsibilities something I knew I didn't want and for which I felt unsuited. But most important, we loved life in LA and wanted to stay there. We were rescued from temptation by a surprise initiated by the Chairman of physiology, Wilfried Mommaerts, who, unknown to me, had instigated my nomination for the Lederle Medical Faculty Award, ten of which were awarded nationally; each year each medical school allowed one nominee. Receiving the salary supplement that came with this award enabled our family and work to thrive at a critical time in my career and the subsequent generosity of the UC Academic Senate review process propelled me forward to professor rank at age 36.

My first UCLA lab was in the Religious Conference Bldg. In 1959, I planned, together with my new lab neighbor Susumu Hagiwara (whom I met in Steve Kuffler's lab), to move into adjacent labs of the new Brain Research Institute (BRI) where I would launch into diverse areas of research. Grant funds were readily available, and all of my applications were funded! I also applied to the new Eye Institute at NIH for funds to explore the alligator nervous system. My first graduate student was Tom Heric, who had a special interest in reptiles and sought me out when he learned I had worked with alligators. We worked together on the properties of the electrical response of the optic tectum and obtained the first retinotopic reptilian map in the alligator (Heric and Kruger, 1965, 1966). Tom then left to obtain a medical degree, not an uncommon event with our graduate students in that era. Horst Schwassmann, a zoologist postdoc from Clinton Woolsey's lab, soon followed, and we mapped the visual projection in a variety of teleosts (Schwassmann and Kruger, 1965a, 1968). He soon persuaded me to import foveate fish, including the species with the most specialized vertebrate eye, *Anableps*, the "four-eyed" fish. Fortunately, he developed independent research projects on circadian rhythms in electric fishes and the early development of the brain and visual system in fishes because we were unsuccessful in keeping imported *Anableps* alive. Nevertheless, the Office of Naval Research offered me a grant and military air transport of our equipment into Brazil, leading to our arranging teams to work at the Museu Goeldi in Belem, where Horst and I set up to successfully map the *Anableps* tectal projection. We also described the operation of the remarkable "double" pupil and the dioptric mechanism, and we quantified the retinal sense cell population (Schwassmann and Kruger, 1965a)—a most successful project we enjoyed immensely. We were joined by teams from the Hagiwara and Bullock labs working on electric fishes of the Amazon basin, and while they were using the setup, I plunged into netting the exotic regional butterflies for Hagiwara's collection.

The appeal of comparative neurology was much influenced by Ted Bullock and Hagiwara, both of whom were superb mentors and wonderful friends with brilliantly original minds. They chose exotic animal models to address fundamental problems. Although I did not collaborate and publish with them, I doubt that I would have remained at UCLA without the support of their friendship, scientific impetus, and inspiration. Both recognized those key scientific questions that are amenable to analysis and then chose the optimum preparation for solving the problem. Susumu's impact was enormous on a daily basis, and I was in awe of his prodigious insights that led to developing the giant squid synapse for simultaneous intracellular pre- and postsynaptic recording, illuminating sensory coding mechanisms in low- and high-frequency electroreceptors, and discovering calcium currents in the barnacle eye. These were among several high points in the career of one of the truly great neuroscientists of the twentieth century.

The first of my comparative sensory physiology papers was derived from the experiments in the summer of 1957 in which we mapped the olfactory projection to the lateral pyriform cortex of the alligator by electrically stimulating the olfactory bulb or tract and the dorsal pallial overlapping projections from visual, acoustic, and somatic inputs. I added the thalamic degeneration that followed cortical lesions to the report on sensory mapping (Kruger and Berkowitz, 1960) and for several years proceeded with mapping sensory projections in various animals. During this period, I was diverted by Magoun (to whom I was much indebted for nurturing my career at UCLA) because of my past experience with dolphins. On his sabbatical leave in 1957, Magoun had worked with John Lilly at NIH and had become interested in Lilly's work on dolphin behavior. He also learned that Per Scholander at the Scripps Oceanographic Institute at University of California at San Diego (UCSD) was interested in building a lab in La Jolla for dolphin research and asked me to contact him about possible collaboration with the UCLA-BRI. Scholander wanted to build a lab and a research vessel and already had preliminary architectural plans for both by the time of our first visit to La Jolla. I thought it unlikely that the University of California and federal funding agencies were likely to support this fanciful and expensive project, and I confessed my reticence about getting further involved with this to Ted Bullock, who in stern fatherly fashion admonished my negativity and advised me to cooperate. If the proposal lacked sufficient merit, it presumably wouldn't be funded. Our proposal to NSF seemed anomalous but was apparently strengthened by the component from the UCLA-BRI requesting lab space and financial support for work and construction at UCSD! To my amazement, this huge installation was enthusiastically approved and we were delighted, but Scholander was disconcerted that they wanted the research vessel the *Alpha Helix* built in the United States rather than the shipyard in Norway that he had his heart set on for its construction. All of this stretched over several years and by the time it was completed, Bullock and Hagiwara had agreed to

move to Scripps at UCSD and to join the country's first Neuroscience Department in the new medical school. The same temptation was also dangled to me by my former Yale colleague, Stanley Mills, who was deeply involved in forming the new medical faculty. I planned my first sabbatical at NIH and after a few months moved to UCSD in 1968 where I worked in the lab assigned to me for the UCLA-BRI. I later happily turned this over to Horst Schwassmann, who was obviously qualified and suited for the Scripps environment. Ginny and I, with our two young children, broadened our outlook in this stimulating milieu and continued to visit over the years for social and scientific reasons, but we were attached much too closely to the big city of LA, with its vibrant music, art, and theater scene, and I had become deeply immersed in the performing arts program at UCLA.

The laminar lesion project was my principal focus during my first decade at UCLA, largely driven by the necessity for obtaining more persuasive evidence for axonal amputation followed by prolific re-growth than could be obtained within the limitations of silver "staining" methods. The fortuity of contacts and cooperation that developed from the many directions that I pursued while studying anatomical growth and degeneration in the cortex and thalamus can hardly be overstated. The electron microscopy derived much of its impetus from numerous technical advances made in Dan Pease's lab in the Anatomy Department; particularly with respect to the rapid perfusion of neural tissue with aldehydes, and details such as tissue oxygenation, embedment, staining, and so on. Dan was preparing a monograph on electron microscopy (EM) methodology and his promising student, David Maxwell, who was immediately given an assistant professor position, expressed an interest in examining the fine structure of laminar lesions. A fast fast-growing friendship between our wives and kids, as well as our personal camaraderie and mutual scientific interests, led to a warm, intense collaboration. This involved preparing many hundreds of laminar lesions at various cortical depths, doses, and survival times to gain insight into the fine structure and sequence of events using the modern electron microscopic techniques recently mastered by David.

Light microscopy proved unexpectedly successful in visualizing a profound vascular response in the laminar lesion zone by employing vascular injection (Rose et al., 1960), but the seeming proliferation of vessels required electron microscopic analysis. The first glimpse proved dramatic, largely because we employed very rapid intra-cardiac aldehyde perfusion of the brain. At the lowest magnification there appeared a horizontal black stripe. At higher magnification the stripe encompassed a zone that apparently lacked neuron somata but that was replete with profiles permeated with small dense granules that we soon identified as glycogen. It immediately became evident that small vessel walls, especially those of capillaries, displayed profiles surrounded by glycogen-filled (and thereby "labeled") processes that we reasoned must be astrocytes. Indeed, glycogen and microfilaments

proved the distinctive "markers" of astrocyte processes, and we soon learned the necessity of maintaining the oxygen supply during perfusion so as to avoid the very rapid depletion of gycogen (Maxwell and Kruger, 1965a). The ease of identifying astrocyte processes, especially in damaged tissue, also enabled us to characterize normal and reactive oligodendrocytes (Kruger and Maxwell, 1966a, Maxwell & Kruger, 1966). Most gratifyingly, the production of a circumscribed lesion without vascular disruption provided an unanticipated insight into the origin of microglia from vessel wall elements. We also attempted to understand the source and "reactive" process that involved the elusive "microglial" cell and soon realized that vascular "pericytes" of small vessels became devoid of the distinctive amorphous, extracellular "basal lamina" that normally demarcated the boundary between mesodermal and ectodermal cells and tissues. Our account of the fine structure of the reactive "microgliocyte" (Maxwell and Kruger, 1965b) was well received but not without controversy, and our views on the classification of all normal and reactive glia elicited some excitement as well as greatly appreciated friendly encounters with two invited seminar speakers, David Bodian and Alan Peters, who were then the leaders in this field. I pursued this again years later, with postdoc Murray Matthews from Bill Willis's lab. Murray was interested in pursuing the electron microscopy of reactive glia, and I prepared a series of rabbit sensory cortex ablations to examine the "gliosis" in the thalamic projection nuclei accompanying retrograde neuronal atrophy. The findings largely mirrored what we had seen in irradiated cortical laminar injury sites. But without direct injury the perivascular changes were more readily amenable to analysis, and we obtained some excellent micrographs demonstrating the passage of hematogenous elements across the vascular basal lamina and into the neuropil (Matthews and Kruger, 1973a, 1973b). I gained considerable technical knowledge from Murray, who continued with this project in his first academic post.

The other striking finding made earlier (Rose et al., 1960) was that it was possible to destroy neurons and their processes with minimal gliosis in a sharply demarcated layer, the edges of which revealed apparently intact neurons 10 to 15 microns above and below the laminar lesion zone. But the big surprise was that within a few weeks the zone of neuron soma destruction was filled with "silver-stainable" axons thus indicating rapid and prolific axon growth in the mammalian cerebral cortex. This defied the established dictum that little more than "abortive" growth could be seen in the adult CNS. With higher radiation doses, gliosis became quite apparent, and a scar blocked the radial growth of axons and gave the laminar lesion zone the appearance of the normal zonal lamina (layer I). But regardless of dose, the growth of axons appeared to be "luxuriant." Although initially based on quantitatively unreliable silver impregnation methods, the later electron microscopic observations confirmed the rich bed of axons while revealing that silver methods did not reliably "stain" all axons. These observations thus

supported the hypothesis of "continuous growth" of axons in adult CNS (Kruger, 1965). The findings also indicated that on a quantitative basis the characterization of axonal growth was more complicated than we initially had envisioned, although the general principle was apparently correct. Although EM of laminar lesions importantly provided the means for characterizing the specialized features of irradiated neuropil, and yielded insight into the process of continuous axon growth that had previously eluded neuroanatomists, the phenomenon was not yet susceptible to rigorous quantitative analysis.

We inferred from Nissl-stained preparations that dendrites also grew back into the aneuronal lamina, a finding later supported by an EM study when I was joined at UCLA by a talented and energetic visiting scientist from Hungary, Joseph (Joscka) Hamori. This collaboration and friendship brought much pleasure to my family and worklife, and resulted in the first fine-structural account of the process of degeneration in dendrites (Kruger and Hamori, 1970), something that could not have been achieved by any other known method. Dendritic growth proved even more exotic than the expansive axonal growth pattern that resembled the "pruning" effects seen in gardening (although I was admonished for considering this analogy openly and later avoided it). Our hypothesis of continuous axon growth was largely ignored, perhaps in part because others could not follow up the observations without first mastering the costly and cumbersome methods from particle physics. Its implications for connectional "plasticity" became apparent decades later while studying neuronal growth with GAP-43 mRNA autoradiography (Kruger et al., 1993).

The large UC Berkeley cyclotron provided a larger range of particles, including particles with high enough energies to penetrate to the deep layers of the cortex. This made it possible to produce a critical lesion in the smooth striate cortex of squirrel monkeys and demonstrated that such a lesion, which destroys all projections to the bottom of the granular layer (IV), elicits profound neuronal retrograde atrophy of the thalamic dorsal lateral geniculate nucleus and that the geniculate cells are not sustained by their projections to layers V and VI. These findings were consistent with and were published together with a large study of the afferent and efferent connections of the rabbit striate cortex (Kruger and Malis, 1964).

The UCLA team, which was organized with David Maxwell to work at UC Berkeley, also amassed a collection of several hundred animals where we had accurate measurement of radiation parameters as well as control of size, depth, and site of lesion placement. However, human factors sometimes intervene to alter what seem like the best of circumstances. I naively failed to recognize obvious signs of my close friend's faltering health. David's first hospitalization and bout of seizures signaled serious disease problems and interrupted the closest and happiest daily work collaboration I could have hoped for. It took some time before I was able to recognize and come to

grips with its horrific impact. The gradual decline and ultimate demise of someone I deeply admired and cared about took an enormous toll on our personal lives and especially the lives of his family. The ties of our wives and children helped for awhile, but the work situation could not endure the complexity of a dysfunctional disease state and forced us to recognize that we had run "out of steam" in pursuing a very demanding project. Having written all of the applications for funding, I felt obliged to inform the funding agencies of our decision to wind down the laminar lesion project. I was fortunate in having continued my electrophysiological interests and activities, which gradually enabled me to obtain funds to change direction. Twenty-first century readers may be astonished to learn how research funding has changed in just a few decades. Individual researchers, rather than lab teams, were the general rule, and the granting agencies, principally the NIH and the NSF (but also the Atomic Energy Commission), fostered productive young scientists with extraordinarily generous attention and assistance. Throughout my career they funded every grant application I submitted and with special helpfulness at each of my several transitions in research direction.

Comparative neurology studies continued during this period and included publication of an extensive series of EM papers with Maxwell. These revealed many new observations that helped characterize the fine structure of glia and the axonal degeneration patterns in nonmammalian vertebrates (Kruger, 1969; Kruger & Maxwell, 1966a, 1967, 1969) and in the transition zone of the trigeminal root (Maxwell et al., 1969). But my attention gradually migrated to further mapping studies, including the retinotopic projections to the pretectal thalamic nuclei (Siminoff et al., 1967), and the still unexplored rat superior colliculus (Siminoff et al., 1966). A pair of talented undergraduate brothers, Steve and Paul Feldon (both later distinguished medical academics), produced the first topographic map of the visual projection to the cat superior colliculus (Feldon et al., 1970) and discovered its unexpectedly specialized ipsilateral projection. I published invited reviews of some of this work (Kruger, 1969, 1970) and also completed the first map of the primate (macaque) sensory trigeminal nuclear complex with Mayo Clinic neurosurgeon F. W. L. ("Fred") Kerr, who came over a 4-year period to learn electrophysiological methods and to escape some Minnesota winter months (Kerr et al., 1968; Kruger, 1971). In dissociated chick sensory ganglion cell cultures that I had brought back from Silvio Varon's lab at UCSD, Penny Coates unexpectedly discovered EM evidence of distinct synaptic contacts between the ganglion cells, despite their absence in mature mammalian ganglia (Miller et al., 1970). This project fizzled, largely for technical reasons.

An important diversion arose when Ed Perl invited me to Salt Lake City to observe experiments that he and Dick Burgess had been pursuing in their study of "nociceptor" fibers. Although I had read Perl's findings with Bessou on C-fiber specific nociceptors and was also aware of Ainsley Iggo's findings in visceral C-fibers, I had maintained that there were no observable specific

"pain" neurons in the "anterolateral system." Perl felt that I should observe an experiment in his lab, serving as critic. Flattered by the friendly invitation from someone I had long admired, and confident in my biased view, I was delighted to participate in this challenge. However, I was quickly persuaded that they were indeed on solid ground and that my negative observations could be easily discounted. This manner of resolution of scientific differences fostered further collaboration with Perl's lab after he moved to the University of North Carolina. It also developed into a lifelong friendship and led to later collaborative publications (Kruger et al., 1981; Perl and Kruger, 1996) as well as his help in constructing a more accurate, controlled tactile stimulator. But all of this was not without bringing turmoil into my scientific life. I was joined by a recent UCLA physics Ph.D., Bernard Kenton in pursuing quantitative studies of slowly-adapting mechanoreceptors and by UCLA neurosurgery residents, James Mosso and Douglas Kirkpatrick, in analyzing the brain stem trigeminal nuclear complex. These latter studies were motivated by the claim of Ian Darian-Smith's trigeminal study, which had suggested that the difference between "lemniscal" and "spinothalamic" properties were simply quantitative in nature, an idea that incited my periodic contrarian tendencies.

The thrust for studying quantitative differences between "lemniscal" and "anterolateral" properties collapsed rather quickly for lack of evidence. Yet it was not a totally wasted effort because the first experiment with Jim Mosso in which we recorded from the spinal trigeminal nucleus caudalis yielded an unexpected surprise—certainly for me. After demonstrating the pattern of sensitive mechanoreceptor representation in the first microelectrode penetration, the first isolated unit in the next puncture yielded a large spike that I couldn't seem to activate. Mosso insisted that this surely might mean it could be a pain or temperature-driven cell. To my amazement we found it was excited by cold, hardly surprising to a neurosurgeon, and he immediately became confident that we also would find cells driven by noxious stimuli capable of eliciting pain in an awake animal. Indeed, he was correct, and we proceeded to re-map the trigeminal sensory complex in anesthetized cats. We found superficial neurons with properties of the nociceptor afferents that Perl and Burgess had demonstrated to me in Utah, and we excitedly published our findings (Mosso and Kruger, 1972, 1973). By then, Ed Perl had completed a superb analysis of the spinal cord marginal layer dorsal horn units, and our findings basically confirmed his results for the "anterolateral system" component of the trigeminal representation, something not found in the "lemniscal" principal trigeminal sensory nucleus (Kirkpatrick and Kruger, 1975).

Extensive quantitative data with Bob Siminoff on reptilian cutaneous receptors (Siminoff and Kruger, 1968) followed by more extensive data with Bernie Kenton (Kenton and Kruger, 1971; Kenton et al., 1971), soon revealed that the application of S. S. Stevens' "power law" and the application of

"information theory" advocated by Gerhard Werner and Vernon Mountcastle was problematic. Every mechanoreceptor neuron, by its very nature, displays a somewhat variable threshold followed by a sigmoid function that ends in a plateau. While plotting the results on log-log coordinates can yield a power function, Kenton, using the resources of UCLA's new computer center soon discovered that the "best fit" curve was rarely, if ever, best described by a power function. We ended up writing an extensive review using our new data, as well as previously published findings of others, arguing that it seemed unreasonable to ascribe the same power function value to neurons from the periphery to the somatic cortex as well as to behavioral estimates derived from subjective magnitude scaling (thus implying that the nervous system was simply a net linear operator). We sent a copy to Baltimore and to Dominick Purpura for consideration for publication in *Brain Research*. He advised me as a friend that, despite the failure of referees to counter our arguments, we were treading on dangerous ground and perhaps should reconsider what promised to become controversial. Werner and Mountcastle understood our arguments but disagreed with our conclusions. After an awkward but friendly phone conversation with Gerhard Werner and Kenton's urging that it was "healthy" to subject such issues to the judgment of the scientific community, we decided to proceed with publication (Kruger and Kenton, 1973). In retrospect, there are no victories in such controversies and, although our arguments were never effectively attacked and refuted, I later came to regret succumbing to iconoclastic urges—especially risking my relationship with Mountcastle, who continued to treat me with the same level of kindness as in the past, during my Hopkins years.

Multisensory Projections

Electrophysiological mapping studies were becoming less appealing when I was fortunate in recruiting a truly outstanding, talented postdoc in Barry Stein. He immediately displayed leadership and independence and developed imaginatively designed experiments with other postdocs. He became a treasured lifelong confidant, and I look back bemused about his complaint that I would not put my name on his papers from my lab unless I had participated in them. This was a policy copied from Jerzy Rose that has largely disappeared in this era of large research teams. I greatly enjoyed working with Barry Stein and Elemer Labos from Budapest on visual development in the kitten midbrain but recognize with clear hindsight that my criticisms may have hindered the progress of the studies that emerged (Stein et al., 1973a, 1973b, 1973c). When Labos returned to Hungary and Braulio Magalhaes-Castro arrived from Brazil, Barry was intent on demonstrating the overlapping of sensory patterns in the cat superior colliculus. Again, my role as critic probably slowed completion of a quick report to *Science* followed by detailed accounts (Stein et al., 1975, 1976). Barry continued to pursue the

theme of interaction between sensory systems and built a vigorous program at Bowman Gray, where he developed and chaired an excellent Neuroscience Department. When he left UCLA, I decided to relinquish further work on the visual system except for completing a study characterizing the properties of the tactile neurons of the cat superior colliculus with a postdoc from Japan (Nagata and Kruger, 1979). I informed the Eye Institute (NEI) at NIH that I was not planning to apply for grant renewal. This resulted in a phone call and letters from NEI staff offering assistance to enable me to continue, something that now would seem most unlikely. But I was becoming aware that I was spread too thin and that my interests were moving in other directions, particularly toward the possibility of exploiting the development of what promised to become truly powerful anatomical tracing methods.

Axonal Transport Labeling

Acquiring new techniques from scratch with inexperienced young people was among the great delights of "teaching" or, more accurately, reciprocal mentoring. Learning together equalized personal relationships and provided a stimulus for continuous questioning and testing of new ideas. In this, I was most fortunate in welcoming the arrival of a psychologist postdoc from University of Southern California (USC), Sam Saporta, who felt some need of learning neuroanatomy, and also a youngster clearly headed for college and medical school, Sanford (Sandy) Feldman, who was energetic, original, imaginative, and open to anything new and challenging.

Sam and I started by using the newly introduced method of retrograde transport tracers for exploring the thalamic projection to the somatic cortex in the rat (Saporta and Kruger, 1977) and cat (Saporta and Kruger, 1979). We observed a distinctive pattern that was different between species, suggesting that the cat possessed a distinctive interneuron population lacking in rats. We also pursued anterograde axonal tracing in the primate visual system with tritiated adenosine, which proved elegant but represented a last gasp of our visual grant (Kruger and Saporta, 1977). That summer we indulged in the luxury of a last stab at adventurous "field work" by planning experiments at the newly established International Brain Research Laboratory in Kotor on the Yugoslavian Adriatic coast, with which UCLA just had formed a collaboration. We had hoped to study the highly specialized visual system of the large species of the strange teleost *Hippocampus*, which was resident in the Adriatic Sea, but our hosts were unsuccessful in obtaining specimens. We then turned to demonstrating the new tract-tracing methods to the Yugoslavs, while exploring some of the Dalmatian coast and the mountains, meeting many interesting people and especially those with artesanal skills. A stop en route in England elicited an invitation from Aidan Breathnach to spend a sabbatical at St. Mary's, London. The idea was to learn

their advanced methods in freeze-fracture replication, with the aim of rapidly preserving unfixed tissue and with the longer-term goal of achieving antibody labeling at the EM level as well as learning from the leading expert on cutaneous fine structure. Although no publishable scientific results emerged from our summer adventure, we returned from a memorable, invigorating experience eager to move forward.

Our interests attracted Larry Furstman, a retired orthodontist from the UCLA Dental School faculty, whom I had met while lecturing to dental students on the specializations of trigeminal innervation that were relevant to the dentistry curriculum. Furstman was interested in learning new techniques, and I asked Sam Saporta to help him with horseradish peroxidase retrograde axonal tracing from the dental pulp to the trigeminal ganglion. This resulted in the first demonstration of this strategy in the peripheral sensory nervous system (Furstman et al., 1975) and launched our serious interest in applying new technologies to the study of the peripheral sense organs. During this period Sandy Feldman, then a college student working in successive summers, completed a remarkable and comprehensive study of the retrograde and anterograde labeled lemniscal pathway in the rat, which included early studies of the complex trigeminal pathways (Feldman and Kruger, 1980; Kruger, 1979) and was followed by further studies with a longtime neurosurgeon friend Ronald Young (Kruger and Young, 1981; Young and Kruger, 1981). In addition, Sandy and Sam helped my histology technician, Sharon Sampogna, in preparing a rat brain stereotaxic atlas, which was to be illustrated in the three major axes in matching, closely spaced fiber and cell-stained sections. The initial photographs were completed largely by Sandy, but this project was placed "on hold" until many years later.

Freeze-Fracture

A 7-month sabbatical leave fostered an exhilarating family vacation in Europe, enabling our now adolescent daughters to freely explore the world in ways that were impossible while living in the Los Angeles hills. It was a profound change of pace and in the fall, when Ginny returned home for the girls to continue in their home school, I immersed myself in the hands of Breathnach's staff in the Anatomy Department at St. Mary's, London, trying to master the skills of freeze-fracture replication in unfixed peripheral nerve. It was a tough task in an arduous discipline. The findings revealed original, interesting specializations of the membranes and cytoplasmic channels of the Schwann cell sheath (Kruger et al., 1979) and elicited invitations in Europe and the United States to present my findings. However, the aim of antibody labeling of axonal membranes, which we also pursued in some abortive attempts upon returning to UCLA, was not achieved until others exploited the technology successfully almost two decades later. Although

the sojourn was only a rather limited success, it expanded my understanding of the ultrastructure of cutaneous innervation from Breathnach's extensive material that he had accumulated for his EM atlas of human skin.

Return to Somatosensory Research

With this background I felt emboldened to pursue the electron microscopy of nociceptor endings in the skin, a project Ed Perl and I had discussed over several years after we felt convinced that there truly were discrete punctate "spots" constituting the receptive field of high-threshold mechanoreceptors. This involved fruitful and enjoyable trips to Perl's lab, where "spots" were identified and marked with fine insect pins. Thus began the long, slow process of thick and ultrathin sectioning which resulted in the first electron micrographs and characterization of loci containing physiologically identified nociceptor endings penetrating into the stratum spinosum of the epidermis (Kruger et al., 1981). I also found great pleasure in studying polysaccharide changes and the fine structure of chromatolysis in spinal motoneurons (Magalhaes-Castro and Kruger, 1981) with visiting Brazilian postdoc, Heloisa Magalhaes-Castro. But by the late 1970s, neuroscience was expanding too fast for me to continue dabbling in whatever caught my fancy or to indulge in the serendipity of pursuing the interests of visitors, unless they were directly related to the somatosensory system that was now the basis for my entire funding. Nevertheless, opportunistic play still hovered irresistibly when I received a joint appointment in anesthesiology from Ronald Katz, the new Chairman recruited to UCLA, whose principal clinical interest was in pain research. This appointment not only widened my horizons and interactions but also brought me into contact with an ingenious engineer, Arnold Lee, who designed a fine air-jet tactile stimulator that moved across the skin surface in a controlled manner that my expanding lab group used to study more complex features of CNS sensory discharge properties (Castiglioni and Kruger, 1985; Golovchinsky et al., 1981; Ray et al., 1985). This stimulator, in addition to a controlled displacement device designed by Ed Perl, attracted the interest of Tom Woolsey, with whom I became closely associated in the creation of a new specialty journal, *Somatosensory Research*. Tom reasoned that if we could control the mechanical parameters of single vibrissa movement, and especially if we could achieve better spatial resolution, it should be possible to study metabolic labeling with tritiated 2-deoxy-D-glucose, a recent tool for functional labeling. I had become interested in exploring "bifunctional reagents" (binding sugars by oxidation with periodate to form aldehydes to be cross-linked with lysine), thereby limiting migration of sugar moieties. Tom happily agreed to visit UCLA to conduct some experiments and perhaps enjoy our summer weather. Working together was a joyous undertaking, and Tom took the brain tissues back to St. Louis, Missouri, where his graduate student, Dianne Durham, had been using a variant of

this method of "metabolic labeling" for her thesis on whisker representation. Astonishingly, in addition to labeling known sites of vibrissal representation, we radioautographically visualized individual labeled neurons for the first time (Durham et al., 1981). Such diversions glow among the happiest adventures in a scientific career, although this particular adventure had little impact on the direction of my lab. Its greater impact secured a friendship that fostered our incursion into scientific publishing and the creating of a new journal.

The Publishing World

The original impetus for a specialty journal in the somatosensory field came from Seymour Weingarten of Guilford Press, an entrepreneurial enterprise in a world suddenly exploding with new journals. Seymour discussed the feasibility, need, and leadership issues with numerous leaders in the field, myself included, and I confess feeling flattered when he concluded from his various discussions that he wanted me to assume the role of founding Editor. I was reticent about the large responsibility and the danger of still another distraction, recognizing that I was easily vulnerable to such "sidebars" in my career. I already served on several journal editorial boards, including the *Journal of Comparative Neurology*, which I eventually served energetically for three decades, but the challenge of forming a new enterprise, selecting an editorial board, and forming the policies and style proved an irresistible temptation. I agreed to assume this responsibility for a term not to exceed 10 years, with the proviso that Tom Woolsey would serve as Associate Editor and later follow as editor at the end of my tenure. It actually took 12 years before Tom could arrange to take over the continuously evolving structure of *Somatosensory and Motor Research*. In the next decade it became one of the many smaller journals swallowed up by larger publishing conglomerates, and it has thrived under Woolsey's able guidance. In retrospect, insistence on a limited term as editor proved a sound decision.

The opportunity to set up our own rules for the journal was actually fun, and I enjoyed wrestling with policy together with Tom and Seymour. My role model was *Journal of Comparative Neurology* editor Sandy Palay, who personally copy-edited many articles and often insisted on evaluating referee reports in his comments to the authors. This is a rare practice but proved most gratifying when my remarks to the authors included critical appraisal of the review. I tried hard to serve the cause of authors and to protect their egos from unfair battering, and I often doctored their fumbling with English usage especially for the Anglophone-deficient. Guilford Press supplied a salary for a part-time secretary—a speed typist who knew the cello literature and who also possessed the organizational skills requisite for managing a journal. Our mutual interest in music and her nurturing of a new flock of students and postdocs brought a fresh spirit to the lab, but later

her unexpected cancer and death reinforced my decision to relinquish journal editing as originally planned.

Broader exposure to the publishing world brought new projects, including the organization and publication of a symposium on pain mechanisms with John Liebeskind, my distinguished colleague and pal in Psychology (Kruger and Liebeskind, 1984). I also returned to our rat brain atlas material after working with Sidney Landau on the neuroscience component of a Wiley dictionary in 1986. When Landau moved to Cambridge University Press (CUP), he convinced me to publish the material accumulated for our stereotaxic atlas. After some discussions with Larry Swanson at the Salk Institute (whom I met when he was a postdoc in Max Cowan's lab), I phoned Sam Saporta in Tampa, with whom I had initiated this project when he was a postdoc in my lab. We agreed to move forward with what we nicknamed "The Ratlas"—a title unfortunately nixed by the CUP "syndicate" just before going to press. The final product (Kruger, Saporta & Swanson, 1995) contained a compact series of closely spaced, labeled photomicrographs of fiber and cell-stained matching sections in the three major axes with a text explaining the principles employed for nomenclatural assignments. Unfortunately, CUP failed to get the atlas reviewed in *Science* or *Nature*, and it was not marketed energetically, although reviews in smaller journals were consistently positive. A larger format atlas by Paxinos and Watson containing far fewer photomicrographs but numerous drawings of outlined structures remained far more popular. Also, Swanson soon followed with an excellent, huge new outline atlas of his own using an advanced and freshly reasoned large format that proved successful. Although still accessible, sales of our atlas have dwindled as it became apparent that labeled photos without outline drawings was not the wave of the future and certainly not a commercial success. Nevertheless, this did not deter later successful book projects (Kruger, 1996b, 2001; Kumazawa et al., 1996).

Deafferentation

By the mid-1980s, the activities of my lab had shifted primarily to the peripheral nervous system and to electrophysiological studies of the spatial organization of cutaneous sensitive mechanoreceptors (Castiglioni and Kruger, 1985; Kruger, 1983; Ray and Kruger, 1983, 1985). I soon learned that the directional effects of hair stimulation were largely determined simply by the pattern of hair innervation, such that the nerve spike sequence was reversed when moving in the opposite direction. Recruiting new people, the morphological studies soon dominated my interests, and postdoc Barbara Rodin wanted to pursue her behavioral observations on deafferentation with anatomical studies of the putative sprouting that might account for the apparent self-mutilation of denervated limbs. We learned that axonal transport labeling did not support earlier reports of putative sprouting (Micevych

et al., 1986; Rodin and Kruger, 1984a; Rodin et al., 1983) and soon became immersed in controversy concerning whether deafferentation leads to pain, thus explaining the self-mutilation of denervated limbs in rats. Rodin discovered that simply housing males and females together eliminated the strange self-mutilatory behavior. We submitted a paper to the journal *Pain* that editor Patrick Wall rejected, strenuously defending his belief that denervation elicits pain and unpersuaded by the private facetious suggestion that "love conquers all." We responded by assembling discordant findings and submitted an extensive review elsewhere (Rodin and Kruger, 1984a). The debate eventually ended in heated controversy with Wall at a conference in Alsace (Kruger, 1991). I knew Wall from Yale, where he was an instructor whom I had admired enormously in the neurophysiology course, and I had fond memories of his quirkiness as well as his inspirational arguments. He was already embroiled in controversy, initially in his futile denial of the existence of specific nociceptors (a view that I too had once erroneously supported), and then more recently in defense of his "gate control" theory, the details of which were in serious conflict with several findings concerning dorsal horn organization from Ed Perl's lab. Wall's ideas were widely admired among pain clinicians at that time, and the combative exchanges were less than pleasant, enduring for another decade when Perl and I joined in writing an historical account (Perl and Kruger, 1996). But one learns from such experiences that insights derived from original observations, rather than competing ideas, constitute the principal propelling force of scientific progress. Final judgment of such controversies must await the hindsight of future students.

Labeled Pathways and Pain

Axonal labeling and the effects of selective denervation became the promising morphological tools for exploring peripheral nociceptors. With the help of a talented electron microscopy technician from China, Yung Yeh, and new colleagues using the new tools of immunohistochemistry, we propitiously timed applying these powerful methodological advances to the study of the somatosensory system. We began with the inner surface of the tympanic membrane of the rat, which (although sparsely innervated) is supplied solely by C-fibers. We first did an EM study of the readily characterized "nociceptive" endings of this structure and also examined the effect of sympathectomy (which was negative for the epithelial innervation) and the effect of neonatal capsaicin treatment (which selectively destroys thin sensory fibers). These important findings were most gratifying (Yeh and Kruger, 1984), providing new insights and incentive to pursue such methods and combine them with peptide antibody labeling in cutaneous fibers (Kruger et al., 1985).

My research direction was now moving toward newly emerging molecular tools. During this period Nick Brecha was recruited to the VA Hospital

and the Department of Medicine at UCLA to establish a lab to study peptidergic innervation of the gastrointestinal (GI) tract and to continue his studies of peptides expressed in the retina. I soon started working with him and the young people in his lab, enabling us to visualize the substance P- immunoreactive epidermal innervation and also to eliminate these fibers by neonatal capsaicin treatment (Kruger et al., 1985). When Catia Sternini in Brecha's lab developed a robust antibody to calcitonin gene-related peptide (CGRP) by conjugation to limpet hemocyanin, we decided to explore distribution patterns of this peptide as a possible nociceptive fiber marker throughout the body as well as in the central nervous system. We already had clues about the importance of CGRP (the earliest example of alternative gene expression) from Larry Swanson at the Salk Institute, who was working on its expression in the brain with Geoffrey Rosenfeld at UCSD. The effectiveness of Catia's antibody in withstanding some limitations of routine immunohistochemistry in aldehyde-fixed tissues, a seemingly small technical advance, profoundly accelerated her career as a leader in gastroenterology research and enabled us to progress rapidly. I also formed a close friendship with Patrick (Pat) Mantyh, who introduced receptor-binding techniques to Nick's lab. I became intrigued with how these techniques might identify the functional (but non-synaptic) tissue targets of the peptides we were visualizing. Pat was surveying sections of entire animals and asked me to see if together we could make sense of the odd array of putative tissue targets for atrial natriuretic factor (ANF), a peptide expressed by right atrium cardiomyocytes. Aside from expected localization sites in the kidney, there were several puzzles, e.g., sites in brown fat pads and endocrine organs. I enjoyed the challenge of returning to my early physiology training and examined tissues of the entire body in several species including humans (Mantyh et al., 1986) and also in the brain (Mantyh et al., 1987). Pat was enormously inventive as well as energetic, and he managed to obtain surgical specimens from human cases of ulcerative colitis and Crohn's disease, which provided the first evidence of quantitative changes in substance P binding levels in small blood vessels and lymph nodes in the pathological tissues (but not changes in other relevant peptides). I found great pleasure in working with Pat and his brother Chris (Gates et al., 1988). The insight gained from this diversion was far more important for the future direction of where I was headed than I could have realized at the time (Kruger and Mantyh, 1985), and it led Pat to examine alterations in peptide receptor-binding sites in disease (Mantyh et al., 1988a, 1988b, 1994). After leaving UCLA, he made important strides with an animal model of bone cancer pain.

Our first papers reported the CNS distribution of the CGRP components in the somatic pathways traceable to the rat thalamus and provided further evidence that the "pain" pathway was somewhat distinct from the "classical" somatic afferent system (Kruger et al., 1988a). Comparison of CGRP immunoreactivity with its receptor-binding sites (Kruger et al., 1988b)

revealed unexplained "mismatches" that we explained in "quasi-hormonal" terms.

By this time, having reached the decision to focus on the versatile and idiosyncratic molecular biology of nociceptors, I had the good fortune of joining Gerald Edelman's newly formed Neuroscience Institute at Rockefeller University, a "think tank," where on sabbatical leave for several months I was able to confer with various experts. This proved a valuable respite from the mind-set of bench work, and it enabled me to prepare a new NIH proposal devoted to what seemed some critical questions in the anatomy related to pain This resulted in my receipt of an NIH Jacob Javits Award, which provided generous support for my next decade of research. Among the several other dividends of being in New York was learning from Jane Dodd and Tom Jessell at Columbia University, about their survey of monoclonal antibodies relevant to sensory ganglion cells, which included new insight into glycoconjugate expression. Returning to UCLA, I was joined by a truly brilliant and talented Johns Hopkins medical student, Jim Silverman, a precocious pianist who shared my passion for music and possessed a fierce, expansive, and open intelligence. He was interested in everything emanating from my lab. The decalcification of whole rat heads enabled examination of the peptidergic innervation of the interior of teeth, bones, and other tissues of special interest, including cornea and tympanic membrane. These tissues (and later the testicular wrapping) proved to be excellent transparent specimens for thin whole-mount preparations and allowed detailed topographic analysis. Jim decided to explore galactose epitopes, and we started reading about lectins together as he started testing relevant candidates. This later led to finding lectin substitutes for FRAP-like staining in nonrodent mammals, solving the mystery of its seeming absence in these animals (Silverman and Kruger, 1988a, 1988b). Eventually, we realized that lectin-positive sensory ganglion cells and their axons constituted a distinctive phenotype of the thin fiber population associated with nociceptors, as discussed below.

The study of CGRP innervation in the peripheral nervous system, employing the strategy of examining the entire body of small rodents, altered my outlook on the meaning of peptide targets. We were soon discovering specialized regions in decalcified heads that revealed unexpected patterns lacking in conventional accounts. If there was a moment resembling an epiphany, it was when we examined the amazingly rich CGRP innervation of teeth, especially the molars. The molars contained fibers seemingly entering all the dentinal tubules. The quantity of dentinal tubule fibers in molars exceeded the number in "biting" teeth, skin, tongue, and even the cornea (Silverman and Kruger, 1987). Although the corneal surface plays a critically necessary role in detecting, and protecting from, potentially damaging stimuli, the interior of the enamel of most molar teeth would rarely, if ever in a lifetime, be exposed to noxious stimuli. This seemed to make little sense

from a functional point of view because the tooth pulp and the dentinal tubules of the grinding teeth presented the densest innervation anywhere in the body. Yet these were among the least likely loci to be exposed to sensory stimuli of any imaginable kind! I soon learned from dentist colleagues that denervation of teeth often leads to their fracture and deterioration, but it was not obvious why the interior of the most densely mineralized tissue of the body would require more than a few nociceptive axons for signaling noxious stimuli, axons that would never be excited from the interior of most teeth. We proceeded with an extensive account of the variety of peripheral patterns of CGRP innervation where the functional role might not be limited to pain per se. In describing cutaneous and deep limb structures, we acknowledged that periosteal sensory fibers could be excited by a strong mechanical blow to the limb, but we questioned why the interior of long bones required such sensory nerve supply (Kruger et al., 1989). I opined that this meant that the thin "sensory" fibers in the interior of bones, as in teeth, must surely be specialized for an effector "trophic" function, although Mantyh consistently maintained they were important for nociception (Kruger and Mantyh, 1985; Mantyh et al., 1994). Indeed, he later proved his point in a series of contributions from his lab in Minnesota. Our collaboration was one of my richest learning experiences, as well as the basis for a highly gratifying friendship.

We were aware that CGRP immunoreactive fibers were rich in the vicinity of blood vessels, but we had never seen anything even vaguely suggestive of a synaptic contact with a vessel wall despite the presence of dense peptide receptor-binding sites. What if the several peptides then called "sensory peptides" were not sensory at all but served their known vasoactive function? It suddenly appeared possible to question whether "pain" fibers were principally serving a sensory role or an efferent effector role via the nonsynaptic terminal release of peptides that would reach distant specific peptide receptor-binding sites. This idea would also explain the multiplicity of neuropeptides and their various receptor-binding sites. The rich supply of peptide-containing "sensory" fibers terminating near blood vessels might be perpetually functionally active by controlling blood flow via regulation of smooth muscle wall elements and controlling permeability of capillary endothelium. Different peptides would have various functional requirements. This idea also seemed consistent with the specificity of receptor-binding site labeling patterns for different peptides. Most importantly, a continuous effector role might account for the vast number of thin "sensory" fibers that would never be activated, except in the rare event of a potentially noxious stimulus that might elicit pain. The idea that sensory ganglion cells, which we had called "nociceptors," were normally and principally serving an effector role, and only rarely serving as detectors of noxious stimuli that might lead to the complex response known as pain, was first presented at an international meeting of pain researchers at Lake Louise, Canada (Kruger, 1987, 1988). There I suggested

we recognize the role of the vast thin fiber system as "no*ceffector*," in recognition of their principal role. The neologism received an understandably cool reception from pain researchers unwilling to give up the sensory status of axons derived from sensory ganglion cells, but the concept was readily accepted.

We soon became immersed in further analysis of the distribution of CGRP in peripheral tissues because we predominantly labeled the small sensory ganglion cells and their thin-fiber axons associated with nociceptors. We then compared these tissues with others in a search for molecules specific to the "pain" pathways. This initiated Jim's energetic efforts to identify those epitopes underlying FRAP-like staining in the dorsal horn of rodents that ultimately led to characterization of this phenotype in several mammals, including humans (Silverman and Kruger, 1988a). This also led to further analysis of the selectivity of thin fibers to various structures employing specific lectin "markers," and to the realization that the IB4 lectin-positive sensory ganglion cells constitute another distinctive nociceptor population that is unrelated to the peptidergic-innervated blood vessels. Armed with Catia's "super" CGRP antibody, and exploiting whole-mount preparations (e.g., cornea and tympanic membrane), we embarked on exploration of other botanical lectins specific to sensory neurons, which was a key important step in identifying nociceptor subclass markers (Silverman and Kruger, 1990a, 1990b). This work resulted from the rash of original findings and from some new ideas about nocicieptor functional classification and anatomical distribution alluded to above. It culminated in a particularly arduous, but rather complete account, of the distribution of peripheral "sensory" fiber distribution, especially the rich variety of CGRP fibers in the head. This provided even more numerous examples of structures that were not likely to be sources of "pain," including autonomic ganglia, the broad variety of chemosensory epithelia that we had reviewed for a handbook (Kruger and Mantyh, 1989), and even the acoustic and vestibular apparatus (Silverman and Kruger, 1989, 1990a).

The enormously interesting details of this work serve as testimony to the scholarly energy of Jim Silverman, who returned to Johns Hopkins to complete his medical degree and ultimately entered a neurology residency in St. Louis. My close personal involvement with him and the psychiatrists dealing with his anorexia and other psychiatric problems left me profoundly depressed for some time when I learned of his suicide, the sadness of having failed a talented, brilliant mind. Without the stimulus of a capable, younger mind unintimidated by the emerging wonders of molecular biology, my momentum inevitably wavered and waned, but I was fortunate to hook up with Jen Yu Wei, who came to UCLA from Dick Burgess's lab. He was exceptionally adept at C-fiber recording and readily persuaded to the "noceffector" concept, which enabled productive collaborative efforts, including early attempts to ascertain peptidergic control of mast cells (Kruger and Wei, 1991;

Wei et al., 1992, 1994). He later exploited his expertise in supervising my final Ph.D. student, David Adelson, whose fine thesis work in splanchnic C-fibers revealed their sensitivity to reactive oxygen species and their polymodal character (Adelson et al., 1996, 1997).

Nociceptor Morphology

An earlier serendipitous meeting with Takao Kumazawa, through Ed Perl, suggested that perhaps the ideal preparation for studying nociceptor fine structure might be the specialized layer of specific "polymodal" nociceptors on the surface of the testis tunica vasculosa of dogs. Kumazawa's lab had begun characterizing these, recording from single fibers in an in vitro preparation. An invitation to work in Kumazawa's lab in Nagoya led to tantalizing initial electron microscopic findings (Kruger et al., 1988a) and repeated visits to Japan. Two visits included my wife and provided opportunities for unforgettable tourism in that beautiful and extraordinarily hospitable country. When Kumazawa was forced into mandatory "retirement" on the day of his 65th birthday, the project continued in what became the laboratory of his student and successor to his chair, Kazue Mizumura, the first woman neurophysiologist in Japan to reach this status. This seemed destined to become a long, ambitious project, but a fruitful one.

At UCLA we had applied lectin and peptide labeling to peripheral nociceptors in whole-mount preparations of the tunica vasculosa of the rat testis and found a striking dichotomy between the specific distribution of peptidergic and lectin-positive termination sites as well as selective ganglion-cell labeling (Silverman and Kruger, 1988b). The perivascular distribution of CGRP peptide-labeled fibers in the testicular whole-mounts was distinct from the distribution in lectin-labeled fibers. I had already obtained successful electron micrographs of the electrophysiologically characterized and marked receptive fields from the dog testis experiments in Kumazawa's lab (Kruger et al., 1988a). Having markers for two distinct populations of nociceptors seemed an exciting prospect, but it was apparent that the peptide labels would prove complicated, as studies of the densities of neuropeptide receptor-binding sites in the spinal cord of arthritic rats were reduced for several peptides but surprisingly not for CGRP (Mantyh et al., 1988a). Pursuit of this project became a prolonged arduous task, and the EM reconstruction became my final laboratory venture, as described below (Kruger et al., 2003a).

Italy

My final sabbatical (1989–1990) was spent in Marina Bentivoglio's lab in Verona learning new EM labeling methods with Giancarlo Balercia and reviewing joint interests with Marina (Balercia et al., 1992; Bentivoglio et al.,

1991). Ginny and I found immersion in Italian life, especially the camaraderie, food, and music, one of our happiest and most productive experiences, not least of which were the enduring friendships and a habit of subsequent Italian summer vacations. I also loved the bemused tolerance of the Italians when I attempted lectures brutalizing their language. Interspersed time was spent in Milan where a musical friend, Alfredo Leonardi, Associate Director of the Mario Negri Institute, was consistently able to arrange concert and opera tickets at the Teatro alla Scala. He introduced me to *Caterina Bendotti* in his Institute, who serendipitously was in need of my anatomical expertise. Working with her in Milan and learning methodologies for in situ hybridization by studying the neuronal growth marker GAP-43 mRNA in the adult brain provided a propitious introduction to the wonders of gene expression. Initially, I couldn't make sense of the pattern nor devise a sensible hypothesis relating to the earlier immunoreactivity findings. On returning to UCLA I obtained two additional probes from Rachel Neve, reconfirmed the findings and prepared extensive autoradiographic illustrations (Kruger et al., 1992, 1993). Then it suddenly dawned on me that the simplest, most parsimonious explanation of select labeled granule cell populations must lie in the concept of continuous growth in adult axons. The idea derived from the enormity of the cerebellar granule cell's fiber expanse as well as the pattern in the hippocampal CA3 field. The submitted lengthy paper was accepted with most gratifying reviews and editorial praise, and I seemed to have come "full circle" with the "continuous growth" hypothesis. But I did nothing to "advertise" the idea and, to my great disappointment, later articles citing the paper seemed to have missed the point. The discouragement added to the frank depression I suffered following Jim's death. My final anatomy student, Daphne Bolden, continued with these probes in sensory and autonomic ganglia for her thesis (Bolden et al., 1996), but it was becoming increasingly evident that my training was inadequate for the oncoming explosion of molecular biology techniques. Within a decade, in vivo neurite fluorescence enabled direct visualization of the dynamics of axon growth with elegant 2-photon videomicroscopy.

Neuropathic Pain

Extending into my sixties, I decided to venture into devising a new model of painful neuropathy, stimulated by the confluence of several ideas, people, and circumstances. An animal model for producing a painful mono-neuropathy had been developed at NIH by Gary Bennett who simply tied several loose sutures around the rat sciatic nerve. This resulted in nerve swelling accompanied by limb withdrawal when the affected foot was exposed to innocuous tactile and thermal stimuli. I had long puzzled about the role of the perineurial epithelial sheath, in part due to conversations with Rafael Lorente de Nó, whom I lunched with regularly during his declining years at UCLA.

Rafael had published pioneering work on the ionic mechanisms of nerve conduction in desheathed nerves some 50 years earlier and was still obsessed by this subject. He called my attention to how, upon slitting the perineurial nerve sheath, fluid emerged under pressure as the fibers splayed through the opening. I had seen this again recently at the lab bench with Wei and Adelson, and I had wondered about the source of the intraneurial pressure. I also became aware of clinical observations of painful nerve entrapment and serendipitously (once again) was approached by Jack McDonald, then Chair of Anesthesiology at Ohio State, who arranged his sabbatical year with me. Jack had established an impressive clinical reputation employing peripheral nerve block for painful compression neuropathies, and he agreed to join us in devising a satisfactory method for measuring intraneurial pressure. We recruited for this task the ingenuity of engineer Arnold Lee in anesthesiology. The project was hardly trivial, and together we exerted considerable effort foundering with measurements but ultimately abandoned the project. Nevertheless, I did entice my postdoc, Tony Mosconi, to divert some of his effort to EM examination of nerve entrapment "compression." Rather than tying a series of loose ligatures, as in Bennett's model, we applied longitudinally split polyethylene tube "cuffs" of various internal diameter to control the magnitude of sciatic nerve compression and to observe related behavioral effects. To our surprise, compression was not the critical factor. Cuffs ranging from loose bracelets to tight constrictions consistently produced pain-like behavior, and Tony proceeded with an attempt to correlate nerve fiber morphological changes with pain behavior. A crude correlation of altered nerve fiber spectrum with "pain behavior" proved unpersuasive (Mosconi and Kruger, 1996), but we had devised a controllable new experimental animal model of peripheral neuropathy-induced pain that remains in use in the lab of my close colleague Igor Spigelman (Neubert et al., 2000). Failure to obtain suitable intraneurial pressure measurements, McDonald's departure, and Lee's sudden death made abandoning this failing project inevitable, and I felt obliged to evaluate seriously my future plans.

My NIH pain grant renewal application was voted a second Javits Award by the Study Section, enabling continued support, but I was aware of running low on steam and self-esteem as a result of the unpromising future of the neuropathic pain project, especially after Mosconi and my EM technician found tenure-track teaching positions in southern California. Reaching the age of 65 suddenly underscored the need to ponder the future just as a propitiously timed University "Very early retirement incentive program" provided several incentives for replacing costly full-time positions by younger faculty with growth potential. My department (now Neurobiology) was in serious turmoil downward and in need of fresh talent. Our other retirement-age faculty were already long beyond their period of NIH grant support, and their contributions to teaching was also in obvious decline. My interest

in teaching had declined as well, and the offered incentive of a "Recalled-Emeritus" position with gradually diminishing teaching obligations over a 5-year period and a full pension proved quite tempting. A generous recall stipend, supported incrementally from my extramural grant funds as my teaching dwindled, rendered the decision rather irresistible. Discussing the matter with Ginny, we agreed that it was indeed apposite to plan the "retirement" that neither of us had contemplated seriously, recognizing that the putative "golden years" would prove meaningless without a productive lifestyle. Ginny had returned to work earlier as we approached the costly college years of our girls, and she had grown into a gratifying niche in the office of an LA County Supervisor. Her work focused largely on mountain open-space protection, and she then became deeply immersed in the County museums as well as art and music issues, a job for which she proved ideally suited and that also enriched both our lives.

The decision proved easier than I imagined, enabling gradual wind-down of lab operations, the making of arrangements for my associates, and the possibility of dedicating myself primarily to serial reconstruction of characterized nociceptor terminals while preparing for future research and writing activities. I pragmatically arranged with Alan Light and his expert EM technician Anahid Kavookjian to continue with the serial thick and thin sectioning of nociceptor receptive field "spots" that had been delimited and marked while in Japan. The trips and long-distance Chapel Hill interactions fared better than working in relative isolation. Much of the task required gaining skill in using software for serial reconstruction that, with impatient perseverance, finally enabled me to characterize and illustrate the illusive "pain" sense organ, whose fine structure was inadequately understood. It was probably the most time-consuming project of my entire career (Kruger et al., 2003a).

The long-accepted designation of nociceptors as "free" nerve endings was misleading and inaccurate. Each axon remained ensheathed in thin Schwann cell processes that extended to its ending. There is little in life that is truly "free." Most interesting and unexpected was the generally ignored elaborate membranous and ultimate vesicular network within the most distal part of the terminal. The network was continuous with narrow strands of the smooth endoplasmic reticulum within axons that had been recognized decades earlier by Droz as the "axonal reticulum." But the axons were not easily identified as ending in a granular arrangement without serial sections. The atypical axolemmal accumulations of uniform, clear, spherical "synaptic" vesicles could only be established by serial reconstruction. These are clearly non-synaptic vesicles, and they are distinct from the granular variety we had already shown to contain peptides by EM labeling and that have distant targets identifiable by their receptor-binding sites (Kruger, 1996a; Kruger and Halata, 1996). The functional significance of the nociceptor axonal reticulum and granules and their relation to clear vesicles remains

ambiguous. But these findings led to writing a modern account of sensory terminals and their variety of vesicular arrangements with colleagues active in the field, Felix Schweizer and Alan Light (Kruger et al., 2003a). This was for a "festschrift" dedicated to the original discoverer of synaptic structure, my Yale neuroanatomy teacher, Sanford (Sandy) Palay. "Winding down" from my original scientific trajectories, I was drawn into joining other lab programs where my anatomical expertise was needed, and I soon became involved with the morphological analysis of Brian Koos's interesting exploration of the role of the thalamus in control of respiratory function in newborn sheep and specifically the contribution of adenosine receptors (Koos et al., 1997, 1998, 2000). I also more energetically turned my attention to several promising original neuroscience history projects that I had held in abeyance, should they remain unexplored. These concerned the seventeenth-century development of comparative neurology and its subsequent impact on early animal experimentation (Kruger, 2003, 2004, 2005; Kruger and Swanson, 2007). I also became more deeply involved through service on the History Committee of the Society for Neuroscience (SfN), including a period as Chair, which brought (thanks to the efforts of Gordon Sheperd) the opportunity to join with 17 national scientific organizations in setting up "recent" history Web sites for our respective disciplines. This was organized and funded by the Sloan Foundation, inspired by their belief that the Internet would be required as a storage medium in the digital age and that we might otherwise witness the disappearance of our historiographic documentation. They encouraged each society to devise and implement its own approach, later gathering us together for evaluation and future planning. I enjoyed this exercise immensely for the 2 years that were devoted to building the initial Society for Neuroscience's Web site for Recent Neuroscience (WReN). Having served for 4 years on the initial Council of the SfN, and having served a term on most of the committees over the years, this seemed a logical finale.

The return to history pursuits in my "waning" years encouraged me to follow up on other neglected aspirations from the past. It maintained the discipline of going to "work" on a daily basis, but with freedom to indulge diverse interests, especially my passion for music and art. The latter was fostered by finding a copy in the UCLA Library of the history of cinematography written in French in the 1920s by Lucien Bull (assistant to Marey, the *Collège de France* Professor of Physiology in the late nineteenth century). It was Lucien who had befriended me when I arrived at the Institut Marey in 1958. He had remained active into his eighties, in addition to writing a history of cinematography. I was soon immersed in examining the history of multiple frame imaging from Marey's perspective, as a physiological recording device, but also in the context of modern knowledge of how we observe the world in frames between saccades. Learning that the Getty Research Institute in Los Angeles was planning a year-long theme, "Frames of Viewing,"

a colleague recommended my inclusion as a resident scholar. To my amazement and delight I was invited to be the solitary neuroscientist Getty Scholar among 12 art "historians" in 2001–2002. This shifted my interests to reading recent literature on the neural mechanisms underlying human vision, and it fostered an intense interest in the recent evolution of the art world and its scholarly activities, though I did wander at times into arenas related to neuroscience (Kruger, 2005). My current scholarly activity is devoted largely to more recent perspectives that an aging neuroscientist might bring to the profound change in modern understanding of synaptic and non-synaptic neuraI interaction (Kruger and Otis, 2007) as well as to more recent perspectives that I might bring to understanding artistic expression. Having formed fulfilling collegial friendships at the Getty Research Institute, my latter years have been immeasurably gratifying enriched by interaction with their programs and facilities.

Looking back on over 50 years of active neuroscience research, I realize that much of the most joyous and precious aspects of the quest for discovery were the shared moments, whether as student, coinvestigator, or teacher. Our academic positions (and salaries) have largely been justified by lecturing increasingly larger classes of professional students of medicine and dentistry in steadily diminishing hours—despite the enormous expansion of knowledge. The joy of "teaching" is found in the intimate moments of interactive intellectual experience and discourse that derive from training and collaboration. The richest gratification has been the individual contacts with faculty colleagues, postdoctoral, and graduate students and the mentoring of undergraduates undertaking a project in my lab. Several of these proudly published papers as sole or lead author. A few recently have touched me in expressing their appreciation by honoring me with the endowment of a student neuroscience scholarship in my name at UCLA, one of the most gratifying of the pleasures of our profession. Of course, nothing quite beats the exhilaration of vigorous "journal club" discussions of recent critical papers or, best of all, the bench discovery of something wondrously beautiful and unexpected, the best motivation for a career in neuroscience

Writing a memoir, in the opinion of novelist Ian McEwen, is to "become an employee of your former self." This is someone horribly difficult to accommodate, especially when somewhat older and wiser. Having indulged in the athleticism of self-recognition, this exercise emerges as somewhat dismaying because of its dearth of shared anecdotes that would probably be of greater interest to modern readers than my research contributions. Looking back has enabled me to recognize that everyone has his own ghosts, and mine were notably the illness and demise of productive minds that participated prominently at critical times in my career, thereby shaping shifts in direction. My career immersion in attempting broad "hands-on" versatility perhaps would not be countenanced favorably in the modern era, nor would funding be accessible without tight boundaries of research interest. Yet I

was permitted the adventure of dabbling in several distinct fields, which provided a constant stimulus for learning new techniques and challenging the hypotheses of the ever "new" neurobiology. The adventure and thrill of each discovery becomes ephemeral retrospectively because its impact seems progressively less important. Even the most profound advance in twentieth-century biology, the "discovery" of the structure of DNA, surely would soon have been uncovered without Watson and Crick. By the same token, technological progress usually provided the landmarks of new discovery and research direction in neuroscience. What Henry James, a century ago, called "the poor, palpable, ponderable, probeable laboratory brain" remains the most challenging subject of scientific inquiry. Perhaps each account of earlier careers may illuminate some of the larger changes in the ongoing development of neuroscience research.

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