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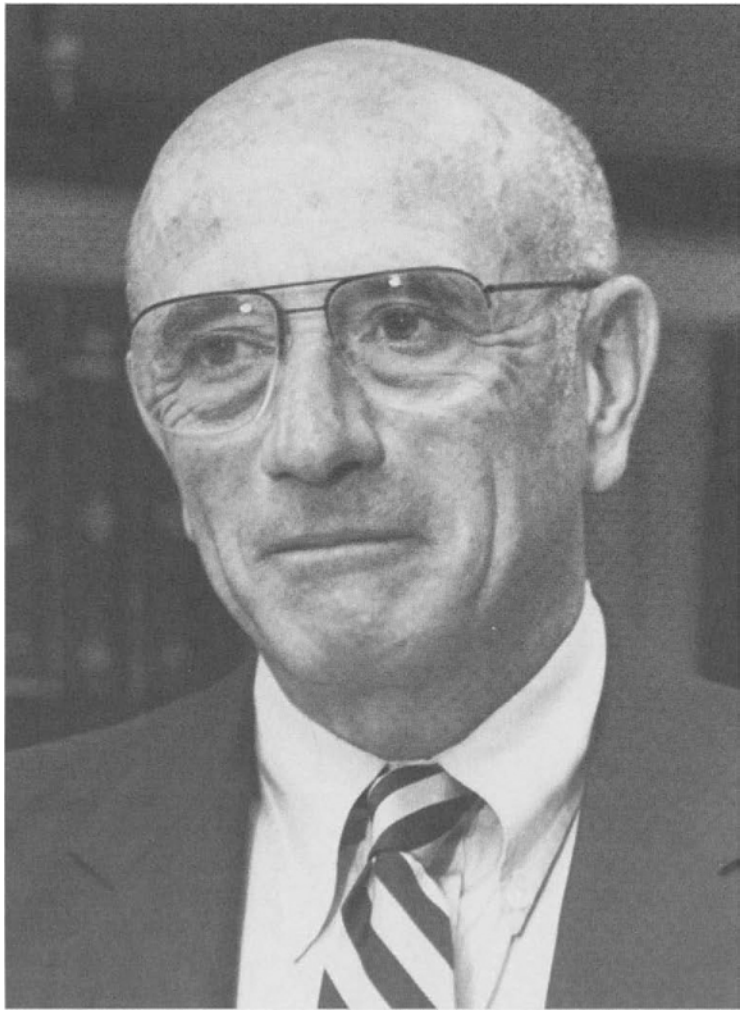

Edward R. Perl

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October 6, 1926

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University of Chicago (1943–1944)
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Edward Perl was a pioneer in the physiology of cutaneous afferent fibers. He made fundamental contributions to the physiology of pain and temperature senses, including the discovery of the several kinds of nociceptors, their specific central connections and their sensitization. He was instrumental in the formation of the Society for Neuroscience and served as acting president in its first year of existence (1969–1970).

Edward R. Perl

What led me to neuroscience? My selection of science as a career was far from happenstance. On the other hand, that I should spend my life working on the nervous system reflects a share of chance and not so chance encounters with people and circumstances. The following is mainly an accounting of those who shaped me, my ideas and research problems, and my many colleagues.

The story begins with my father, for if he had been a different man, I may have never made a career of science.

My paternal grandfather was the manager of a Swedish match factory in Kecskemet, Hungary. A family legend has it that the post had a hereditary link because an ancestor had invented a type of safety match and started a small factory that was later acquired by the Swedish firm. In any case, my grandfather and his children had experience with a sort of technology. My father, John Ignatius Perl, one of four surviving offspring, had the advantage of being the youngest child and was the only one who was sent to the university. As a schoolboy my father was an adequate student and an excellent athlete (track, gymnastics, and sculling crew). He started medical school at the University of Budapest (which after World War II became Semmelweis Medical University) prior to the beginning of World War I but was conscripted into the Hungarian Army to serve as a corpsman in an infantry battalion on the Russian front. His unit was captured and, after nearly starving to death, he escaped just prior to the Armistice of 1918 and finished medical school in Prague. He and my mother (Blanche Braun, the daughter of a miller and hotel owner in a Hungarian-speaking part of postwar Czechoslovakia) met while he was on a locum tenems. John Perl decided to leave the chaos of postwar central Europe for the promise of the United States. Mother agreed to wait while he established himself in the United States. He obtained a United States immigrant's visa in part upon a recommendation from a prominent Budapest professor who was impressed by his imaginative diagnosis of a butcher's epileptic seizures. Arriving in New York in 1923 with essentially no knowledge of English, he took a job moving heavy steel plate to learn the language. On passing medical licensure examinations, he started a residency in surgery at a Lutheran hospital in Chicago and saved enough

money to send for my mother, who arrived in New York on December 22, 1925. They were married the next day and I was born approximately 10 months later.

Father was a confident man physically and intellectually and was honest to a fault. He set an example of kindness to those in need or less able. At the same time, he was fiercely independent and proud. His strong sense of form and color led to a great interest in visual art. He was fascinated by science, the process of scientific discovery, and understanding of the physical world.

My parents had totally different personalities. My mother was quite feminine and meticulous in everything she did. She had a remarkable memory and learned extremely quickly but, as typical of women of her time, stayed in the background. She and my father had an affectionate relationship and only rarely disagreed. The latter occurred usually when mother was trying to soften the reaction to our misdeeds.

My sister, Eve Hildegarde, is approximately 15 months younger. She was born in Czechoslovakia; mother had to leave the United States while expecting until she obtained a permanent visa. Eve and I had a fairly typical sibling relationship. We were close enough in age to be both companions and competitors, although the latter was minimized by the even-handed parental handling. Eve was the kinder and more agreeable person, characteristics that I came to appreciate more as we grew older. The expectations for the two of us were quite different, being influenced by the mores of the 1930s. I was encouraged to do more typically masculine things and she the classically more feminine, but as it turned out we both ended up in science.

Growing Up

In those early years in Chicago, we lived in an apartment in a housing development in a region on the near north side populated by immigrants from Europe and which was close to the small Lutheran hospital where my father had trained and had staff privileges. Our parents wanted very much to integrate into American society. English was the only language spoken by and with the children, although they would sometimes speak in Hungarian to hide things from us.

Eve and I did not see much of our father during the week; he came home after we had dinner, and he left in the morning about the time we went to school. He worked Saturdays as well; however, he tried to spend Sundays with us. We had regular Sunday excursions, often to one of the Chicago museums. We visited the Museum of Natural History and the Museum of Science and Industry many times. Usually just the three of us made these visits, and our conversations during them actively stimulated interest in science and science discovery for both children.

Father was an avid fisherman. In the summer, the Sunday excursions were sometimes substituted by trips to nearby lakes or rivers. In the early 1930s, the Sunday and holiday fishing expeditions were limited to the slowly moving midwestern rivers. Nonetheless, it began a process of imprinting that led to a lasting hobby. As the family fortunes improved through the 1930s, the summer vacations took more of an exposure to less civilized areas. We went to northern Wisconsin and spent several weeks in fishing camps angling for pike, bass, and muskellunge.

I first encountered or became aware of electricity at about 7 years old and became acutely curious about it. This interest was heightened by a Christmas gift—a kit for electrical construction projects, including motors, electromagnets, and a simple crystal radio. The idea of electromagnetic wave transmission caught my imagination and sparked my exploration of electronics. As a grammar (lower) school student, I constructed a series of radios and progressively delved deeper into the mysteries of vacuum tubes, circuits, amplifiers, radio transmitters, and receivers. Eventually, at the age of 12, I became a radio amateur, having taught myself enough Morse code and elements of electronics to pass the licensing exam.

Lower school days are a blur in my memory. School lessons were trivial and most of my learning came from enthusiastic reading at home, sometimes into the wee hours of the morning while hidden under a blanket with a flashlight.

As mentioned previously, my father had a strong interest in visual arts, and his patients included many members of the art colony in Chicago during the 1930s. One of his artist acquaintances was Edgar Miller, who had come to the Midwest from Idaho. Edgar extolled the beauty of the intermountain west, particularly the wilderness of the Wind River Range in Wyoming. This led to several trips to Wyoming to spend the better part of a summer in the mountains. That in turn began a long-standing love affair with the mountains and fly-fishing for trout.

In the latter part of the 1930s, when we did not go to the West in summer, I was sent to a camp in southern Michigan. The camp experience taught me to live with a pack of frisky peers and to learn about riding a horse, paddling a canoe, shooting a rifle and a bow and arrow, and, most important, sailing a dinghy. My sister and I had learned to swim at quite early ages and we were comfortable in the water and strong swimmers by the age of 6. This affection for water and the things associated with fishing and boats had little demonstrable influence on my choice of a vocation. It did play an important role in the selection of where I chose to work.

The period from my ninth to my 13th birthdays was a busy time. I learned about electronic devices, read vociferously, and was encouraged by both parents to expand my intellectual horizons. On the other hand, school was a bore. My father encouraged me to become active in sports for both social and health reasons. I did not fit a common mold. I was a good

student, had an interest in electronic equipment, and a thirst for scientific knowledge, but I also was interested in sports and outdoor activities. Further, I was the son of a physician, which at that time was not common in a Chicago public school.

In 1939, my parents purchased a radio and phonograph that reproduced music with reasonable fidelity. This led to a systematic exposure to classical music. I was profoundly influenced and have gained great pleasure from that form of music ever since. The reproduction of music also shifted my interest in electronics from a preoccupation with radio communication to the reproduction of sound. I fell in love with classical opera and watched many performances of the Chicago Lyric Opera, acting as an usher in return for the privilege of sitting on the steps and listening during performances.

My world expanded sharply in 1940 when I entered a large public secondary school (high school) just before my 14th birthday. I was bound for college, which at that time meant that Latin was the foreign language of choice. In my case, my advisory teacher was the Latin teacher, Helen Reed, a remarkable person. Heavy set and middle aged, she not only taught Latin well but also was comfortable in helping students with mathematics and spoke numerous languages fluently. She once confided to me that it was her aim to learn a new language every year. School became exciting. I thoroughly enjoyed Latin with its logical rules; exposure to the history of the world of Roman times fed a teenager's imagination. Algebra and geometry also caught my attention. They too were logical with clear sets of procedures. Aside from Latin, my favorite course was spherical geometry, with its requirement of thinking in three dimensions. Unhappily, physics and chemistry were boringly taught. Moreover, I had learned many of the basic features of their material on my own. I had become interested in chemistry and had a simple inorganic chemistry laboratory in the basement of our home.

In our neighborhood there were open playing fields and as a primary school student I had played on some informal softball teams and sandlot football. However, I was more of an individualist than a team person, and athletics were organized in secondary (high) school. My strength as a swimmer first attracted me to that sport, but a foray into competitive swimming was unfortunate. I was disqualified in several races because of an occasional illegal leg stroke. I decided to try out as a runner and quickly became competitive at middle distances, becoming the school's best at these distances (600–880 yards).

These were serious times. World War II had begun in Europe the year before my entry to secondary school. The portent of the United States' eventual involvement was evident. This came home on Sunday, December 7, 1941. I was up early running my amateur radio station, trying to make long-distance contacts, and had a disappointing sudden break off of

contact from Hawaii. Several hours later, the announcement of the bombing of Pearl Harbor was made as a break-in news report on regular broadcast radio.

Declaration of war by the United States followed and the prospects for the future of a 16-year-old male changed dramatically. A lack of challenge represented by many classes in a public high school, aside from Latin and mathematics, and the developing psychology of a global war placed an urgency on education. I had become aware of an accelerated program for secondary students at the University of Chicago and, with the gentle encouragement of Helen Reed, I applied and was accepted in the program for early admission to college. Thus, in the early summer of 1943 I left Nicholas Senn High School in Chicago for the University of Chicago.

The University of Chicago represented a dramatic change. The atmosphere was intellectually exhilarating. The survey courses, representing the basic education program for students matriculating at the equivalent of the 11th or 12th grade, were mind expanding. Classes were often very good and even exciting, but one did not have to attend. Reading the material independently and then sitting for examinations allowed me to collect college credits rapidly. That first year at the University of Chicago proved momentous in other ways. With the country at war, it was clear that military service was on the horizon. I preferred it to be my choice and decided to volunteer for the Navy, largely because of my love of water. The U.S. Navy accepted me into the Officer Training Program (V–12), which eventually influenced my life greatly.

The concentration on theoretical and particle physics at the University of Chicago was less enticing than constructing electronic devices, and my earlier dream of a career in physics or electronics was blunted. My father had encouraged me to follow his footsteps and enter medicine. He was skeptical of engineering, pointing out that engineers rarely work independently. In his view, medicine and farming were examples of 'honest' lines of work serving other human beings and requiring serious effort. These ideas clearly influenced me. Thus, while the private practice of medicine did not appeal, medical knowledge and the place of research loomed attractive. Medicine was human biology and it had been impressed upon me that biology held many mysteries. Furthermore, living organisms had their own electrical phenomena. I began to think more positively about medicine and medical school.

Enlistment into the Navy took place shortly after my 17th birthday and I reported in July 1944 to the Naval V–12 Unit at the University of Illinois, Urbana/Champaign. The Navy may have been interested in me because of the background as a radio amateur and because I had some practical knowledge of electronics; however, when asked for a career choice on reporting for duty, I chose medicine.

Academic loads in officer training programs were heavier than usual. We were in classes year-round and our environment had a semblance of military conditions; however, the atmosphere was considerably softened by the university campus setting. Physical conditioning was, of course, part of the routine. With many men in the military services, there were few civilian male students. Those who participated in competitive athletics were excused from routine physical training, a provision that I found to my liking. While I was hardly a match for the local national champions in the middle distances, running in this fast company gave me pleasure. My course of study was typical premedical, with a heavy emphasis on the biology and chemistry missing from material taken at the University of Chicago. Chemistry was a strong point on the Urbana/Champaign campus and I remember organic chemistry to be a favorite. Despite our fairly heavy academic schedules and the demands of training for track, there was time for some extracurricular activity. I spent extra time on a research project in comparative anatomy and became good enough at the card game, bridge, to enter local tournaments.

At the end of 1 year on the University of Illinois campus, I had accumulated enough college-level credits to fulfill the prerequisites for medical school. Continuing beyond the minimum requirements was not possible for a military trainee in wartime. In the summer of 1945, I was transferred to the Great Lakes Naval Station in the outskirts of Chicago to await a decision on medical school. At the Naval Station the V–12 premedical trainees were assigned as corpsman to the hospital wards and given routine duties attending primarily to men injured in the course of the Pacific conflict, many very seriously. Word soon came that I had been accepted at the University of Illinois School of Medicine in Chicago to start in the autumn of 1945. Transfer from the Urbana/Champaign campus occurred shortly after the end of the war in Europe (V-E Day). The atomic bombs were dropped on Japan that summer, Japan surrendered, and World War II ended. Many people entering medical school class reported under military orders; however, by the end of 1945 the V–12 trainees were discharged into the reserves.

First Exposure to Neuroscience

Until the commitment to attend medical school, nothing had linked the nervous system to my ideas about a career, although I had thoughts about how one might combine an interest in electrical phenomena to human biology. They were given focus early in medical school when, as part of the course in anatomy, a special lecture was given by Warren S. McCulloch, a professor who headed a research unit at the Illinois Neuropsychiatric Institute (INI), part of the University of Illinois' medical complex in Chicago. He was an early proponent of the mathematical description of

neural functioning (cybernetics). It was an enthusiastic and spellbinding talk that laid out mysteries and promise of research on neural functioning. That lecture inspired me and was the beginning of my eventual affair with neuroscience.

My first intimate contact with biomedical research took place at the end of the first year of medical school. Despite deadly dull teaching, the material in physiology was stimulating. The summer between the first and second year was relatively free since the school had gone off the wartime, year-round class schedule. Two physiologists, Harold Wiggers and Ray Ingraham, needed technical assistants for a research project on the effects of depressant drugs, particularly barbiturates, on chances for survival after massive hemorrhage.

The University of Illinois Medical School was located in a downtrodden portion of Chicago's near southwest side. University housing for students was largely nonexistent; students lived in either fraternal houses or apartments in nearby tenements. I opted to live in my parent's apartment many miles away and commute. This facilitated my introduction to a Hungarian expatriate psychiatrist, Lazslo Meduna, at the INI. Meduna had been a pioneer in the use of insulin shock as an alternative to electrical shock for treatment of psychosis. Later, he proposed inhalation of carbon dioxide in high concentrations as a treatment for neurosis. Meduna introduced me to Warren McCulloch and to Fred and Erna Gibbs at the INI. The Gibbs were electroencephalographers who were early leaders in codifying the range of variation in the electrical activity of the brain that could be recorded through the scalp and the nature of changes associated with abnormal brain function. They invited me to learn the elements of electroencephalography and then trusted me enough to allow me to make sleep records on young children for the atlas that they were preparing. The Gibbs' laboratories were in the basement of the INI, which also housed Warren McCulloch and his young colleagues, Walter Pitts, Jerome Lettvin, and Patrick Wall. There was an electronics shop to keep the electrical recording equipment functional under the direction of Craig Goodwin, an electrical engineer. My interest in electronics and general enthusiasm for classical music, particularly opera, amused Goodwin and we became friends. The result was that along with anatomy, physiology, pharmacology, and other basic medical sciences, I learned something about recording systems for bioelectrical phenomena.

My first attempt to do an experiment involving neural mechanisms was supposed to be a test of the effects of CO_2 inhalation on neurons. It required operant conditioning of cats and then giving the animals a confusing choice. Training cats proved to be very difficult, and then they refused to become 'neurotic.'

The atmosphere in McCulloch's unit initially was intoxicating and I legitimized time spent in his laboratory by enrolling for academic credit as

a part-time graduate student. McCulloch and his coterie of associates, Pitts, Lettvin, and Wall, spent most of their time in the unit's library discussing and considering various theoretical approaches to the functional organization of the nervous system. That was heady stuff. I did not understand much of it. However, the gravity of their postulations and the complexity of the situations they were considering were impressive. To some extent the group deferred to Walter Pitts, whom the rest considered brilliant, and I remember how they applauded his attempts to define the function of the cerebellum. Elwood Henneman, another postdoctoral associate in McCulloch's group, had been an undergraduate at Harvard College and had attended medical school at McGill University in Montreal. Elwood interrupted a neurosurgical residency at the Montreal Neurological Institute to work in the Department of Physiology at Johns Hopkins School of Medicine that was headed by Phillip Bard. There, he was Vernon B. Mountcastle's contemporary, who had also left neurosurgical training to do research and then never returned to the clinic. Henneman and Mountcastle collaborated to produce classical electrophysiolological studies on the somatotopic projection to the ventral basal thalamus of cat and monkey.

When I came to the research laboratories at the INI, Elwood Henneman was the only one in McCulloch's group who regularly did animal experiments, studying supraspinal control of motoneurons and modulation of spinal reflexes. This was early enough in the days of electrophysiology for much of the equipment to be specially built. Special devices often required long waits. I tried to help Henneman with some of his needs and this led to our becoming friends. We shared a mystification about the relevance of the theories and speculations that McCulloch and his close associates were producing. Elwood was frankly skeptical of the lack of experimental testing and verification. While then I had only a medical student's knowledge about nervous functioning, his skepticism fueled my nagging uncertainty about the value of the theoretical approaches. This friendship with Henneman proved pivotal for my future and for the eventual direction of my scientific efforts.

Craig Goodwin may have been the only electronic engineer on the University of Illinois medical campus in Chicago. Consequently, he was frequently asked to offer advice about electrical equipment or electronic devices. One request came from a faculty member in the Department of Physiology, William V. Whitehorn, who was interested in the idea of using changes in the electrical properties of the chest to measure cardiac function on a beat-by-beat basis. This idea was generated by a publication from Germany a decade or more earlier, which argued that changes in chest capacitance mirrored changes in volume of the heart during the cardiac cycle. Goodwin suggested to Whitehorn that he talk to me about it. I was challenged by the idea of creating a design to measure chest capacitance

rapidly and accurately enough to capture changes associated with cardiac mechanical activity. My inspiration was that a device, based upon frequency modulation, could be suitable and relatively easy to implement. Within a few months we had developed a device that provided a signal that closely mimicked alterations in cardiac output for both animals and people. This project generated a short report at the American Physiological Society 1948 meeting in Detroit. The highlight of my first scientific meeting was not the presentation of our material but the opening reception. A kindly, older lady asked me about my interests. When I stated physiology of the nervous system, she said, 'you must come over and meet my husband.' He turned out to be Joseph Erlanger, who 4 years earlier had shared the Nobel prize with Herbert Gasser for their joint work unraveling the mystery of the compound action potential of peripheral nerve and its relationship to the cross-sectional diameter of the constituent nerve fibers.

The cardiac output project, with its electronics and experiments proving the concept, led to my switching graduate registration to the Department of Physiology and authorship of a first scientific paper (in *Science*). Eventually, the work was described in a master of science dissertation completed in 1951.

Even though I had moved to the Department of Physiology and was working on the project with Whitehorn, I still had considerable contact with Elwood Henneman. Elwood had suggested that I complete part of medical school as a visiting student at Harvard. Boston then was a medical mecca, and the summer of 1948 spent as a clerk on the Harvard Medical Service of the Boston City Hospital left an indelible impression. During my clerkship, the attending physician was Maxwell Finland, a pioneer in the use of antibiotics. I also made acquaintances who were to become long-time friends. One was Eugene S. Kilgore, another visiting student from the University of California at San Francisco. There were also two residents who became friends, Sidney Ingbar and Maurice Victor. Contact with Derek Denny-Brown, famous not only as a clinical neurologist and teacher but also as an investigator of nervous function, helped tilt my leaning toward neuroscience.

While I had not changed ideas of an eventual career in research, the notion of further clinical exposure of the type I had received in the medicine clerkship was attractive. I returned from Boston in the autumn of 1948 facing important decisions. Again, Elwood Henneman had a major influence. He urged that I obtain minimal clinical credentials. This required at least a year of experience as an intern after graduation from medical school. Given the leaning toward research on the nervous system, he also suggested that I consider a postdoctoral fellowship in Philip Bard's Department of Physiology at Johns Hopkins School of Medicine. Whitehorn supported these suggestions in his quiet way. The concept of

doing an internship, but arranging in advance a postdoctoral fellowship to follow, was appealing because I had no desire to commit to a full clinical training. The thought of experimentally exploring unknown biology had become a career goal. Also, at that point in life there seemed to be time. I would graduate from medical school in 1949 at age 22, an age at which a typical medical student would just be starting. Several clinical possibilities had crossed my mind, including neurology and neurosurgery, but for a 1-year general introduction internal medicine seemed appropriate. Henneman contacted his former colleague, Vernon Mountcastle, at Johns Hopkins, who in turn supported my application. Philip Bard agreed to accept me as a fellow in his department starting in September 1950, 2 months after I was to complete the internship year.

The internship year at the Boston City Hospital proved to be an unforgettable experience. The workload was heavy; however, despite the long hours, the scientific thinking in practical application to patient care was impressive. I had exposure to the ills of mankind and the available therapeutic approaches. I was not the best of 'house officers,' failing principally by a lack of efficiency in writing up the extensive reports made on each patient. I remember being behind on busy days in completing details of the patient notes; however, my patients seemed well cared for, even though the supervising residents were less than happy with incomplete narratives.

The Making of a Neuroscientist

I spent most of the summer of 1950 at my parent's retreat on Lake of the Woods in Ontario, Canada, dedicated to a revision of the master's dissertation with help from William Whitehorn. In the fall, my arrival in Baltimore was hardly auspicious. I drove from Chicago in a new automobile, reaching Baltimore at midnight when the temperature was 39°C. For a person acclimated to more temperate latitudes, the humidity was unbearably high. I survived the first night in an inexpensive hotel without air-conditioning and eventually adapted to the southeastern climate. The Johns Hopkins School of Medicine is located in a decaying part of Baltimore; but the then ethnic Italian area had a certain charm. Cooked food vendors working from the front of row houses were common. The Department of Physiology was housed in one of the older buildings, with high-ceiling rooms and dingy paint. The personnel were the important fixtures. Informally, I was more or less assigned to be directed by Vernon Mountcastle.

I came to Hopkins with little more than a student's understanding of the nervous system and no experience in using either the electrophysiological or the neuroanatomical tools that were the currency of Bard's department's work. There were few practical books on these laboratory techniques. One had to learn by example and experience. Therefore, I spent many hours

watching Mountcastle do surgical preparation of experimental animals and conducting electrophysiological experiments. In the course, I began to know something about the man, talking to him while sitting across the table watching him expose the cerebral cortex, the spinal cord, or peripheral nerves. Vernon Mountcastle was, as are most people, complex. He was Virginian by birth and basic attitude. He was compulsively careful, compulsively hardworking, and strongly opinionated. Those attributes, coupled with a substantial intelligence, made him a formidable model. He was a careful and precise surgeon and taught well the lesson of respect for tissue. The elements of electrophysiological techniques came more or less by osmosis. Nobody in that department was really trained in the theory or the construction of the electrical and electronic equipment needed to record vital electrical potentials. In fact, Bard and Mountcastle probably had accepted me as a fellow principally on the basis of the recommendation from Henneman that I knew something about electronics.

The department had only two electrophysiological workstations and these were shared by several investigators. Therefore, the night or morning before an experiment, one had to arrange and test the equipment needed for one's particular protocol. This cold immersion type of teaching proved practical. There were so many steps to connecting the various devices that troubleshooting was a necessity. Only by having systematically learned about each device, its capabilities, and its behavior did one acquire the insight necessary to unravel problems.

Mountcastle was my principal mentor in not only surgery but also electrophysiological recording. I represented his de facto first postdoctoral trainee; however, other members of the department did influence me considerably, particularly Jerzy Rose, a classic neuroanatomist skilled in the analysis of central nervous system (CNS) structure by cytoarchitecture. Jerzy's office was directly across from the room to which I had been assigned and I saw him every day. He was considerably older than Vernon and extremely bright. While he was open and kind, he had an acerbic contempt for ignorance and lack of logic. Rose had a critical attitude, demanding evidence that set or complemented Mountcastle's high standards. He was also a well-balanced neurobiologist who had intellectually mastered the electrophysiological methods useful for study of cerebral functional architecture. Of the other people in the department, in addition to Mountcastle and Rose, only Philip Bard influenced me scientifically. Bard epitomized the gentleman scholar. He was courteous and considerate but often seemed aloof. He too was critical of poorly thought out experiments or inconclusive evidence, although he was more circumspect about it than either Vernon or Jerzy. His own work, done in part with Vernon, involved surgically produced lesions of the forebrain.

In the time spent in the Department of Physiology at Johns Hopkins, I did not work specifically with any of the established people. I observed

experiments that Vernon was doing on muscle afferent projection to the cerebral cortex. I watched Jerzy Rose struggle to make a good recording electrode for the thalamic single neuron recordings he was doing with Mountcastle. To a great extent, independence was my choice. It was important to me to do experiments that I had designed.

One issue then, as it remains, was the influence of anesthesia on observations on CNS function. The detailed maps of the bodily projection to the contralateral cerebral cortex obtained by Marshall, Woolsey, and Bard and then beautifully elaborated by Clinton Woolsey and colleagues were the product of experiments on animals deeply anesthetized with barbiturate. Other laboratories using different anesthetic agents had obtained results that differed, in part, from those reported by the Hopkins' group with respect to the presence of functional projections from the ipsilateral body. I was intrigued by the question of anesthetic effects and spent some time trying to use the 'encephalon isolé' developed by Frederick Bremer. My concept was to study evoked potentials produced by facial or auditory stimuli, which in this preparation retained connection to the brain. Unfortunately, there proved to be many problems with that preparation, and those experiments were abandoned.

After some months in Baltimore and exposure to evoked potentials recorded from the cerebral cortex, I became interested in the projection of the unmyelinated (C) primary afferent activity to the cerebral cortex. The published studies up until then had concentrated on responses evoked by stimulation of sense organs with rapidly conducting fibers. It had long been suspected that the C fibers carried information related to or associated with pain and temperature sense. The question arose, then, as to how to excite those fibers in isolation. C-afferent fibers had much higher electric thresholds than the myelinated fibers, and so any stimulus effective in exciting the former also initiated activity in the myelinated fibers, which conducted more rapidly. That would confound interpretation of any observed responses. Furthermore, the slow and wide range of conduction velocities of C fibers resulted in temporal dispersion, making detection of activity produced by populations of cells difficult. My idea to overcome the latter was to record the activity of single neurons from rostral centers using microelectrodes. The concept was sound, but it took a decade to make such experiments successful.

Overall, my experience in Baltimore was very positive. While no research was published, I learned much and had started to think and work on a problem that was to occupy me for the rest of my career. Mountcastle and Rose had planted the attitude and experimental approaches that would serve me in the future. Baltimore was a pleasant place to live, and I made a few friends outside of the department. Initially, I shared a tenement apartment with a graduate student, Jim Woods, who drove a gasoline truck at night to pay expenses; however, the apartment was

oppressive and eventually I moved to a room in a suburban home owned by an elderly Maryland dowager who wanted a young person in her house.

The different laboratories doing serious work on the functional attributes of the nervous system made the atmosphere at Johns Hopkins University in the early 1950s exceptional. In addition to Philip Bard's department, Steve Kuffler and colleagues had laboratories across the street in the Wilmer Eye Institute, and David Bodian in the Department of Anatomy was next door. There was also a group of biologists and biophysicists at the main (Homewood) campus several miles away. These included H. K. Hartline, Detlev Bronk (the president of the university), Martin Larrabee, and Philip Davies. Interaction between the laboratories in terms of day-to-day contact was not great, but there were informal exchanges. Mountcastle suggested that I go over and see what was going on at the Wilmer Eye Institute in Kuffler's laboratories. This led to my first contact with Steve Kuffler and his colleague, Cuy Hunt (C. C. Hunt). The latter was to have a major influence on me. This congregation of investigators interested in the nervous system led to an informal organization known locally as the 'Know Nothing Club.' The 'club' had no walls or roster but held episodic meetings that started with dinner at a large downtown Baltimore restaurant (Hauslers) during which considerable beer was downed. Then the group returned to the School of Medicine, where several talks were given describing current research. The presentations were serious. However, the audience was not always passive; sometimes caustic or humorous remarks were called out to interrupt the speaker. At one of these meetings, Hartline described his observations on lateral inhibition for which he was eventually to receive the Nobel prize. Hunt and Kuffler presented their analysis of the small nerve motor system in relationship to function of the muscle spindle. Biophysical studies were described by Bronk and others from the Homewood group. These informal meetings impressed upon me the value of contacts between scientists with shared interests, an impression that was a factor in the eventual creation of the Society for Neuroscience.

Walter Reed Army Medical Center

In mid–1951 I was notified that my medical degree made me subject to the physician draft for the armed services during the Korean Conflict. My previous military service was not sufficient to cover the time spent in training while on active duty in the Navy. I had a reserve commission in the U.S. Navy and could request active duty for what probably would have been an administrative job. Through the recommendation of Jerzy Rose, an alternative became available—joining a neurosciences research group directed by David McK. Rioch stationed at Walter Reed Army Medical Center in Washington, DC. I was called to active service in January 1952

as a medical officer in the U.S. Army and assigned directly to Rioch's unit. My immediate superior was Robert Galambos, a civilian auditory physiologist who had made important contributions on the frequency tuning characteristics of cochlear nerve neurons. Others in David Rioch's research unit included Michael Fuortes, a neurophysiologist, and Walle Nauta, a neuroanatomist. The latter had as a junior colleague another physician in uniform, David Whitlock, who became a good friend and collaborator.

Galambos' subunit focused on auditory problems. The army's air arm was faced with complaints of hearing loss, particularly by personnel flying or servicing jet airplanes. Most complaints were legitimate, reflecting cochlear damage by the loud jet noises and a lack of systematic protection against acoustic damage. On the other hand, some cases were thought to represent malingering to avoid dangerous duty or to seek disability status. Available tests of hearing depended on verbal reports from the subject. Galambos had the idea that an objective test could be derived from the use of the electroencephalogram and put me to work on that project. I had some experience in electroencephalography with the Gibbs in Chicago, but I was by no means an expert. It was decided that to improve my skills I would be sent to the Montreal Neurological Institute (MNI) to spend 2 months being trained in experimental electroencephalographic techniques by Herbert Jasper, a pioneering investigator.

Herbert Jasper was kind and friendly even though I had trained at two laboratories headed by researchers with whom he sometimes disagreed, the Gibbs in Chicago and the Johns Hopkins' neurophysiologists. Wilbur Penfield, the strong-minded neurosurgeon and director of MNI, embarrassed me several times during grand rounds by asking me to defend points of view on neurophysiological issues from the Johns Hopkins' group; however, otherwise the experience in Montreal was quite positive. Herbert Jasper sent me back to Washington with a refreshed knowledge of the basic needs and techniques for successful electroencephalography. On returning to Walter Reed, I set about organizing a laboratory for the electroencephalographic study. A crucial decision was the nature of the auditory stimulus. The normal audiometric technique was to use bursts or continuous pure tones of different frequencies. It seemed improbable that a continuous tone would evoke recognizable activity in the electroencephalograph. Much electrophysiological research on the auditory system then used a transient sound produced by a brief electrical pulse applied to earphone or loudspeaker. Responses to acoustic clicks of the type recordable from the exposed auditory cortex were not recognizable in the electroencephalographic tracings obtained from scalp electrodes. Infrequent clicks did evoke a 'startle response' that apparently was generated extensively across the cerebral cortex. It represented a response to a novel afferent input, whether auditory, tactile, or visual. I established that normal individuals regularly showed such a startle response to relatively faint,

infrequent click stimuli and that these could be used to establish the presence of functioning peripheral auditory transduction.

Before publishing these observations, I believed that additional data were needed. First, we lacked description of the range of sound frequencies that a click stimulus tested. The theoretically broad range of frequencies inherent to the brief electrical pulses used to generate clicks would be modified by the dynamic characteristics of the earphones producing the sounds. I convinced Galambos to obtain a high-grade microphone to record the output of the earphones. The resultant analog record of the click could be analyzed for its component frequencies by doing a Fourier transform, at that time a laborious manual technique. Luckily, the geological survey office in Washington, DC used Fourier transforms to study seismic waves and provided an analysis of our click frequencies. The publication on the startle response audiometry contained probably the first reported description of the sinusoidal frequency components of a click stimulus. A second limitation in our initial data was that all of the subjects had been male soldiers. Female graduate students from the University of Maryland, involved in clinical audiology at Walter Reed Army Hospital, agreed to participate in our study. One day, a particularly attractive blonde young woman showed up as a volunteer subject. Both my technician, Fred Thiede, and I were unattached and tossed a coin to decide which of us would ask her out. I won and, using a ruse, extracted a telephone number and address from Marjorie Patricia Herdt. Later, I telephoned and, although surprised, she agreed to join me for an evening. On returning home from that first date, she told her skeptical, older medical student brother that she could marry the man with whom she had been out. Fifteen months later and 47 years ago that happened.

The report describing the startle response audiometry was my first publication in neuroscience. I was then assigned clinical duties as a medical officer as an interpreter of electroencephalographic records, and I also examined patients with hearing-related problems. There still was time for experiments. An engineer, James Casby, had conceived of a technique for better localization of potentials recorded from surfaces such as cerebral cortex or the scalp based upon a laplacian transform utilizing a multicontact electrode. Casby and I agreed to give his method a practical test on the auditory cortex.

The experiments with the laplacian electrode focused my attention upon evoked cerebral potentials produced by primary afferent stimulation. At the time, it was understood that the pathway to the primary somatosensory cortex largely represented an output from the ventral basal thalamus, but it was unclear which cortical cells produced the activity recorded on the surface. David Whitlock shared my scientific interests in somatosensory systems, and we collaborated to establish that the surface positive evoked potential on the cerebral cortex inverted deep in the cortex to

negative field potentials indicating that the evoked surface potential was produced by activity of neurons in the deeper cortical layers.

In the last months of my army tour, I received offers of junior faculty positions from both the Department of Physiology at the University of Colorado and the Department of Physiology at the State University of New York (SUNY) Syracuse. The choice was not easy. The childhood trips to the western United States and the Rocky Mountains had left me longing to return to that magnificent mountain country. During a trip to Syracuse, the chairman of the Department of Physiology made a strongly positive impression. Gordon Moe was friendly, relaxed, and extremely clever in an unassuming way. Thus, despite a love for the western mountains, the decision was for Syracuse. Marjorie and I were married with Eugene Kilgore as best man on December 23, 1953, the anniversary date of my parent's and sister's marriages. The marriage took place in New York City at the same church where I had stood as best man for Eugene 3 years earlier. Remarkably, the priest who presided over our marriage vows had been Elwood Henneman's roommate at Harvard College. We arrived in Syracuse in early January 1954 with an automobile, a few suitcases of clothes, some wedding presents, and a bed as our possessions. We found an attractive apartment in short order, and I began the job of setting up the laboratory, preparing teaching materials, and adjusting to life as an independent academic.

Gordon Moe's leadership of the Department of Physiology matched his personality. He provided gentle, yet sometimes firm, guidance and encouraged independence. He provided adequate funds to set up a well-functioning electrophysiological laboratory for work on the nervous system within a few months of my arrival. For my initial project, I returned to the problem I had started thinking about in Baltimore—the central projection of peripheral C afferent fibers and how to block conduction in myelinated fibers and eliminate the effects of their activity. I used a relatively simple clamp to press the nerve between two surfaces adjusted by a fine screw as described by Gasser and colleagues (Clark *et al.*, 1935). The compound action potential of a stimulated nerve evoked by brief electrical pulses gave an indication of which population of fibers were activated but was relatively insensitive. I chose also to use the animal's reflex response recorded from the ventral roots of the input segment. The idea of controlling the nature of afferent input by reflex output proved fortuitous. As it developed, pressure on a peripheral nerve rarely if ever completely stopped conduction in rapidly conducting fibers without also seriously interfering with conduction of impulses by unmyelinated fibers and eventually completely blocking the nerve.

The preparation of the peripheral nerve in spinal cord for these experiments was time-consuming, and loss of the preparation due to total conduction block of the nerve was disastrous. I routinely began to dissect

nerves in both hindlegs. If one nerve was rendered nonfunctional, a nerve in the contralateral could be used to continue. Unexpectedly, once a single afferent volley of impulses in the sural nerve of one side evoked a ventral root reflex discharge contralaterally. This serendipitous observation led me to temporarily concentrate on crossed reflexes using both direct evocation of motoneuron discharges and evaluation of facilitory or inhibitory effects by changes in amplitude of monosynaptic reflexes from particular muscles. I sought an alternative to measuring hundreds of reflex amplitudes from photographic film records. A way of converting the voltage recorded over time to a value representing the integral was needed. The earlier experience with frequency modulation suggested that converting voltage to a frequency of events was a way to accomplish this. Brad Hisey, an electrical engineer and medical student, helped with the practical design for an analog to pulse frequency generator and for gating a digital counter to partially automate these measurements.

With experiments beginning to bear fruit, the situation in Syracuse was agreeable. The people in the department were pleasant and supportive. Marjorie had a job as an audiologist, and with our combined salaries we were relatively comfortable. There were many gray days in Syracuse, but the countryside nearby was attractive and the streams were cold enough to support trout. I again took up fly-fishing for trout. Hunting gamebirds was also a common sport in the area; walking in the woods in the autumn with a dog and a shotgun looking for roughed grouse to explode from underfoot was another diversion from long, lonely experiments. While Marjorie neither fished nor hunted, she often accompanied me. Teaching took time as well. I had taught small groups at Johns Hopkins but had never given a series of lectures to a large class. Despite some rough moments, the teaching went reasonably well. One quickly learned that to profess effectively it was important to develop a good rapport with the students. My first research grant from the National Institutes of Health helped fund the ongoing studies on the crossed reflexes. Marjorie became pregnant and our first child, Patricia Marie, was born in 1956.

The presence of a young neurophysiologist on the faculty aroused interest in the nervous systems in other departments. The Department of Anatomy wished to hire a neuroanatomist. Consulted, I recommended David Whitlock, who was finishing his tour of military duty. In due course, Dave joined the Department of Anatomy and once again we had the opportunity to collaborate.

Whitlock and I began experiments on a variation of the C-fiber projection studies I had left to analyze crossed reflexes. In the early part of the twentieth century, the spinothalamic tract in the ventrolateral white matter was established to be important for perception of painful contralateral stimulation. The nature of information conveyed by this tract and its

modification in higher centers were poorly understood. We used an experimental arrangement in which a transection of the dorsal columns of the spinal cord was done to eliminate another major ascending somatosensory pathway, the dorsal column–medial lemniscus system. This approach's advantage and weakness was the interruption of the input to higher centers by the rapidly conducting powerful lemniscal projections of the dorsal column pathway. We had preliminary results in cat before another major change occurred in our lives.

After I had spent several years at Syracuse, Cuy Hunt contacted me. He had accepted a professorship in New York City and wondered whether I would join him there. The opportunity of working in the company of a more senior and accomplished neurophysiologist and the scientific and cultural resources in New York City were appealing, but I was reluctant to live in a huge metropolitan area. I declined the offer, commenting that if he ever decided to move west to please again consider me. About 6 months later, Hunt approached me again, this time because he was contemplating a move to the University of Utah in Salt Lake City to chair of the Department of Physiology. He hoped to build a department of neurophysiologists and had also approached A. R. Martin and Carlos Eyzaguirre. Martin was a Canadian who had obtained his Ph.D. under Bernard Katz in London. Eyzaguirre, a Chilean, had left clinical medicine to do neurophysiological research and was at Johns Hopkins at the same time that we were there. Being in a group concentrating on neurophysiology with colleagues of this caliber was enticing, even though there was no change in rank (I had just been promoted to associate professor). In addition to the scientific prospects, Salt Lake City had other attractions. The physical surroundings of the valley nestled at the foot of the Wasatch Mountains looked attractive to a person coming from the snowbelt of upstate New York. Then there was the seductive beckoning of skiing, a sport that I had started to learn when in Boston. Gordon Moe understood the need of a young investigator to have others to talk to about common problems. That was important because he had been very kind to me and this made the decision that we should 'go west' easy.

Salt Lake City

The medical school at the University of Utah was poorly funded by the university and the state of Utah. Despite this, it had a considerable renown due to the entrepreneurial efforts of its faculty to obtain funds from the federal government. The Department of Medicine under Maxwell Wintrobe was one of the leading units in the United States and the Department of Pharmacology, chaired by Louis Goodman (the author of a leading textbook of pharmacology), was known internationally.

Salt Lake City was dramatically different from Syracuse. It was bright and dry, contrasting sharply with the often gray skies of upstate New York. The land and the people of the two communities also differed. The intellectual environment in the university settings was equally distinctive. SUNY-Syracuse was a health sciences subdivision of a statewide university system. The campus of Syracuse University was across the street, but there was relatively little interaction between the biologists of Syracuse University and the biomedical establishment at SUNY-Syracuse. The medical school at the University of Utah was an integral part of the campus, and, while physically separated, interaction between medical and other divisions was considerable. The most striking difference between the two situations was in the intellectual environment for me in physiology. Hunt was a clear-headed, logical, thoughtful scientist and teacher who was very active in the laboratory. Bob Martin was a clever, insightful, ingenious biophysicist comfortable with physical measurements. Carlos Eyzaguirre was quiet, perceptive, and hardworking. Hunt's postdoctoral associate from New York, Motoy Kuno, the son of a famous Japanese physiologist, was intellectually the equal of any of the young faculty and eventually became a close friend and collaborator. There were numerous others who passed through our department in the 14 years I spent in Salt Lake City; however, the principal influences on my work and our lives came from the original group who migrated with Cuy Hunt in 1957. It was exciting to be able to walk down the corridor and discuss experimental problems or approaches with knowledgeable colleagues.

One hesitancy in making the move to Utah, the loss of close contact and collaboration with David Whitlock and his anatomical background, was quickly circumvented. David and his wife Peggy were westerners; moreover, he was an enthusiastic fly-fisherman, and the western streams with their numbers of native trout beckoned. Accordingly, we arranged for Whitlock to come to Utah in the summer. Initially, we continued with the experiments on the spinothalamic projection, extending our observations on cat to the monkey using the severed dorsal column preparation. We established in the absence of the dorsal column–medial lemniscal system that there were at a minimum two functionally distinctive zones of somatosensory projection to the thalamus from the opposite side of the body. One was organized in a somatotopic fashion, whereas a more posterior region lacked a distinct topographic pattern. Our observations on what came to be called the PO region of the thalamus fit closely with morphological observations by Mehler and Nauta (1959) using silver impregnation of degenerating fibers. The thalamic studies put us into competition with Vernon Mountcastle, who had been analyzing the spinothalamic connection using a different approach. Both sets of studies defined the novel area in the posterior portion of the thalamus but ascribed quite different significance to them. Poggio and Mountcastle

(1960) argued that neurons of the PO region had a unique responsiveness to painful kinds of stimuli. Our preparations lacking the dorsal column–medial lemniscus input indicated that the PO thalamic region received information from ascending systems other than the dorsal columns but that it was not a selective nociceptive projection. Forty years later, I reflect upon those studies and believe that probably neither conclusion was truly on the mark in terms of the organization of the spinothalamic projections, but that our interpretation on place in function of the PO region may have been the closer to reality.

The Utah department's intellectual environment was also considerably influenced by short-term visitors. Cuy Hunt's extensive range of contacts brought visiting investigators, including Ian Boyd, A. S. Paintal, and A. K. McIntyre. The latter's sabbatical stay and subsequent visits were particularly important for me because the experiments he did with Hunt on the kinds of myelinated afferent fibers in cutaneous and subcutaneous nerves provided important background for our later work on the dorsal column nuclei.

Whitlock came to Utah for several summers. After completion of the studies on the 'spinothalamic' projections, we examined the functional arrangement of connections to the dorsal column nuclei with John Gentry. That work established the existence of distinctive, independent connections to neurons of these nuclei from different classes of primary afferent fibers and the presence of a form of lateral inhibition in certain of these connections.

As evident from the previous discussion, I had a strong interest in the signaling features of thin peripheral nerve fibers. Over the years, there had been numerous indications that thin peripheral fibers represented mediators of afferent messages associated with or important for pain and temperature sense. Nonetheless, some commentators did not accept this evidence to mean specificity in the selectivity of signaling by different afferent neurons. Past experience with the cardiovascular system led me to think about the sympathetic motor activity and its relationship to afferent input from somatic tissue. Classical studies had demonstrated a connection between sympathetically mediated reflexes of the cardiovascular system and the kind of stimuli that normally evoke pain. In the early 1960s, it seemed to me that the relationship between somatic afferent input and sympathetic reflex output was worthy of study and possibly represented an avenue to the problem of the functional signaling by unmyelinated afferent fibers.

A short diversion is needed to explain the next set of events. The University of Utah in Salt Lake City was relatively isolated from other major academic centers even at a time when air travel had become common. Invitations to scientists from other regions of the country or other countries was one way to blunt this isolation. Cuy Hunt attempted to call

attention to his new department and its neurophysiological focus by convening a meeting in 1959 dedicated to somatosensory mechanisms. He obtained funds from the National Institutes of Health to underwrite the conference. Two of these visitors became particularly important for my professional future. One was Yves Laporte, Professor of Physiology in Toulouse, France. Laporte had been trained in the United States, initially in St. Louis with George Bishop and subsequently at the Rockefeller Institute in New York where he and Cuy Hunt were contemporaries. The other was Janos Szentágothai, Professor of Anatomy in Pecs, Hungary. I had noted Szentágothai's name in the literature, particularly for an elegant study utilizing anatomical evidence to prove the monosynaptic nature of the masseter stretch reflex. Contact with these two visitors led to my visiting their departments in Europe and long-lasting collaborations.

Our second daughter, Anne Elizabeth, was born in Salt Lake City on March 9, 1958, and our son, John II, 2 years later on March 8, 1960. When we moved to Salt Lake City, we bought a seemingly attractive house on the side of Mt. Olympus overlooking the valley. Unfortunately, the house had many flaws, the result of inexpert construction. Maintenance of a house with problems on an academic salary demanded time that was better spent on experiments and family. Those considerations and an architect neighbor led to one of our four adventures in house building. We bought a lot higher up on the hillside that was fully covered with mountain scrub oak, and we went through the excitement and headaches of building a simple house.

These were heady times for our family. In addition to starting the house construction, I had contacted Yves Laporte in Toulouse about the possibility of spending a sabbatical there. He warmly invited me, an adventure that was made possible by a National Science Foundation Fellowship. Why France? Partly it was curiosity. I knew no French but liked the sound of the language and was attracted by the reputation of the French for art, food, and good wine. Adding to the mystique was the fact that we were very fond of our first foreign automobile, a Peugeot 403. Just prior to the beginning of the house construction, Motoy Kuno and I joined in a set of experiments on a classic feature of decerebrate rigidity, in which normally potent flexor muscle reflexes are sharply attenuated. We found that one could overcome potent inhibitory actions by summation of two independent excitatory actions and actually switch reflexes on and off. The new house was finished some months before we were scheduled to go to France. The Kuno family would live in our new house for the year in which we were away. The experience bonded our families.

Americans in France

The year in France (1962–1963) was a remarkable experience. The trip itself was an exciting start. The five of us—Marjorie and I and the three

children—crossed from New York to Le Harve on a somewhat older, medium-sized passenger ship that lacked roll stabilization. Even in a late summer crossing, the ship's movement caused moderate cases of seasickness in most of our party. Given our lack of French, the train ride to Paris, our first exposure to a simple Parisian hotel, and the drive to the Midi went smoothly. However, as we traveled south from Paris the ability to communicate in English became increasingly less. We arrived in the red-brick city of Toulouse, after detouring to the Mediterranean for a few days to pacify the children, to a gracious welcome by Yves and Beatrice Laporte. They had found us an almost ideal house in a new residential area just a few kilometers from the Faculté de Médecine.

There was much to learn in addition to the language. On the domestic side, we had to become accustomed to a different society—one in some ways structured more rigidly and in others more leniently—than ours. Our children appeared to adapt to the strict rules in French public schools. As Americans, we had eaten well and enjoyed a variety of foods, but the inventiveness, variety, and emphasis on quality in French cuisine was a surprise. The luxury of ready access to good bread, good soft cheese, flavorful vegetables, and fresh seafood from the ocean set new standards for us. France had few supermarkets in 1962, and shopping in the specialized small stores was a new game.

Research was not a universal preoccupation at the Faculté de Médecine in Toulouse, although Laporte's group were active investigators. The research emphasis in the department was on the sensory characteristics of the muscle spindle and the influence of motor activity upon it. Before departing for France, I had started experiments on the relationship between afferent input and sympathetic reflex output at the spinal level. In Toulouse, I opted to work on a problem better suited to the available instrumentation. A young French postdoctoral investigator, Michel Leitner, and I began exploration of a question posed years previously by Gordon Moe. Moe had observed a cardiovascular reflex initiated by injection of norepinephrine into the descending aorta. In the search for possible afferent elements involved in this reflex, we were led to norepinephrine's enhancement of responsiveness of pacinian corpuscles of the cat mesentery. Recording from the thin mesenteric nerves and working in the peritoneal space proved a valuable background for future efforts on the sympathetic reflexes and adrenergic effects on sense organs.

The curiosity and affection for art fostered by my father's interests were broadened by exposure to the remarkable breadth of museums and architecture in France. We learned to admire the architecture of a church, the details of its capitals, and the mimicry of its gargoyles. There were castles and other grand houses to be seen and gardens of incredible precision and complexity. In addition to France,during the year Marjorie and I made our first trip to Italy, where there was a whole new set of art and architecture

experiences. There were feasts as well. Dining in France was considered a pleasure. Not only was the food good, varied, and, at that time, an exploration of 'nouvelle cuisine' but also a meal was a ritualistic experience. We began to eat at restaurants frequently. I developed a taste for fresh crusty bread that was never lost. Among other parts of this cultural expansion was a learned appreciation for the monotony of Gregorian chants. Our children shared in this broadening. We only recognized this many years later when they demonstrated the impact by their choices and memories.

There were several important consequences of the year in France for future work. Foremost was friendship with Paul Bessou, an ophthalmological surgeon who had given up clinical work to become Yves Laporte's research colleague. Bessou was traditional French to the core, precise and meticulous. He was an extraordinarily kind, enthusiastic, and generous man. A native of the Toulouse region, he taught us about the cuisine of Languedoc. Experimentally, he was superb at dissecting nerve bundles by the 'teased filament' approach to obtain single-unit (fiber) recordings from peripheral nerve. Eventually, we were to become collaborators during his several visits to the United States.

I was introduced to other French scientists by Laporte. In Paris, notably, it was Alfred Fessard and his wife Denise Albe-Fessard. Fessard was the dignified dean of French neurophysiologists, a professor in the College de France, who had devoted much of his career after World War II to helping young French neuroscientists (e.g., Yves Laporte) obtain training abroad. Fessard headed a research group housed in the Institut Marey, named after the famous French physiologist who made classic studies in motion of animals and men. The Institut Marey included many French neurophysiologists: Pierre Buser and his wife Arlette, Jean-Marie Besson and his wife, Marie-Jo, among others. Making these acquaintances during a trip to Paris from Toulouse led to several other visits to France.

Two months after our arrival in France, John Szentágothai invited me to make a visit to Hungary, then still very much behind the Iron Curtain of the post-World War II era. I could not resist an opportunity to see the country from which my parents had come. Marjorie was invited as well. In mid-October 1962, we traveled by train to Paris and planned to catch a flight to Budapest. The Cuban missile crisis and President John F. Kennedy's standoff with the USSR came to a head just as we left Toulouse. The officials at the United States Embassy advised that they expected no possibility of my being held hostage but that the trip could entail delays in return if hostile acts between the two powers took place. Given the three small children in Toulouse left in the care of a descendent of Toulouse-Lautrec, they suggested it might be best if Marjorie stayed in France. Accordingly, I traveled to Budapest alone and had a warm introduction to the country of my ancestors. I learned that it was not possible to talk about certain things in public or even to get information. Intensely curious about

what was going on in the confrontation over the missiles, I remember spending one night manipulating the radio receiver in my hotel room so that it could receive broadcasts from more than local stations and permit listening to British Broadcasting Corporation transmissions. Szentágothai's department in Pecs did much with little. He was a remarkable neuroanatomist with enthusiasm and flare. During that trip I met his young assistant, Miklós Réthelyi, who was to become his son-in-law, and set the stage for an enduring collaboration with Réthelyi.

Toward the end of the year in France, I made a trip to Edinburgh, Scotland, to visit Ainsley Iggo, Professor of Physiology at the Royal Dick School of Veterinary School of the University of Edinburgh. Iggo was a pioneer in the recording of activity from primary afferent C fibers. That visit proved most helpful since I learned his technique of easily making tiny razor blade knives, a tool that he had developed to aid in the teasing of peripheral nerves to record unitary discharges. That technique proved crucial for the success of my subsequent studies on sympathetic reflex output and then on primary afferent C fibers.

We returned to Salt Lake City from the foray to France and Europe a more worldly family with a better appreciation of European culture, an appetite for better cuisine, and some ability to communicate in French. The scientific rewards were less obvious. The many discussions with Yves Laporte and Paul Bessou made me think about primary afferent fibers, a process that had begun through the influence of Hunt, McIntyre, and Paintal. I came away with an abiding affection for France and an enthusiasm for restarting the experiments on spinal sympathetic reflexes.

Salt Lake City—Part II

W. Sherman Beacham was an unusual medical student at the University of Utah. He grew up in a small rural community in southern Utah and had worked as a farmer, truck driver, and fence layer until his late 20's when with a wife and three children, he started college. Physiology was taught in the first year of medical school. At the end of his first year he applied to do research over the summer. The study of spinal sympathetic reflexes was underway and I had evolved a good but difficult retroperitoneal approach to the sympathetic chain and the preganglionic rami. Beacham was a physically powerful man with large, work-scarred hands, yet in shor order he mastered delicate surgical dissection and the two of us worked together on the sympathetic preganglionic recordings. It proved to be a very satisfactory collaboration. At the end of that summer, we made an arrangement wherein he came in very early in the morning to start the preparation and when he went to class I took over. He returned in the late afternoon to see how the experiment was going and to help with the recordings. For some of the studies it was necessary to pare down short

preganglionic rami to obtain single unit recordings from individual preganglionic fibers. This gave me good practice in using the Iggo razor blade knives to separate fine filaments on short stretches of nerve. Beacham and I established in these experiments that the sympathetic system, as skeletal muscle, had reflex arcs mediated at the level of the spinal cord and that these reflexes were initiated by activity in the slowly-conducting primary afferent fibers of somatic nerves.

The friendship with Paul Bessou evolved into his coming to Salt Lake City to do experiments. Our first project was based on observations I had made in Toulouse when searching for the afferent neurons activated by norepinephrine. The thin nerves of the mesentery of cat contained a few fine myelinated fibers in addition to the occasional one from a Pacinian corpuscle. Bessou and I discovered that each mesenteric nerve supplying the small intestine had one or a few fibers from mechanoreceptors with thinly myelinated fibers that were preferentially excited by movement of the small intestine relative to its mesentery. Working with Bessou was a pleasure, and our uncovering of these mechanoreceptors received some attention. The experience further whetted my appetite for study of primary afferent neurons.

At this point, Antonio Fernandez de Molina came to my laboratory from Madrid, Spain. Together, we continued the studies on spinal sympathetic reflexes to establish that they were selectively vasomotor without notable involvement of direct action on the heart. This emphasized a degree of specificity of activity in sympathetic output that ran counter to common textbook dictum. Motoy Kuno, who was still at Utah, joined us in an analysis of preganglionic neuronal characteristics in microelectrode recordings from the spinal cord. Success in these experiments required some technical adjustments, particularly in the fabrication of high-impedance, extremely fine, micropipette recording electrodes.

The Documentation of Nociceptors: A Step Back in Time

Patrick Wall and I had been acquaintances from the days of the Illinois Neuropsychiatric Institute. In 1961 he sent me a review manuscript, written with Ronald Melzack, presenting their ideas about cutaneous sensation. In their review they argued against specificity of responsiveness of cutaneous sense organs using, in part, reasoning of the 'Oxford School' (Department of Anatomy, Oxford University—H. H. Woollard, G. Weddell, and D. C. Sinclair). In the 1950s this group had taken a dim view of ideas arguing for specific relationships between particular sense organs, their responsiveness to natural forms of stimulation, and the resultant sensation. Melzack and Wall suggested as an alternative to particular selective responsiveness of sense organs, a continuum of characteristics wherein the overall pattern of activity in a population of neurons signaled

the particular attributes of a stimulus, a concept similar to that proposed by the American psychologist, Nafe, approximately 30 years previously. It was an engaging, well-told, story; however, it did not fit my reading of the literature, particularly the behavior of afferent fibers and central neurons as observed in studies done in our department. I wrote to Wall saying that their manuscript contained interesting ideas, but that he should be prepared for criticism.

By 1965 I had decided that it was essential to establish a better understanding of afferent signaling by the unmyelinated (C) fibers regardless of the technical problems. It was clear from our studies as well as those of others that the reflexes evoked by small-diameter myelinated and unmyelinated fibers differed from those produced by activity in the larger diameter fibers; however, the information then available permitted only speculation about the characteristics of the thin sensory fibers giving rise to such different outputs. I had considerable experience by this time in teasing peripheral nerves and spinal roots to obtain recordings from single fibers and found that procedure to be a slow and tedious way to survey a mixed population. It seemed that an alternative method was needed. Why not use micropipette electrodes? Recording from nerve fibers with pipette electrodes had been established as possible but had not been employed as a way to sample a population in a peripheral neuron. I set about trying to record from the autonomic nerves using micropipettes. My hope was that microelectrode recordings would provide the needed large sample of afferent responsiveness of C fibers. At first, this technique seemed promising since there were a few very brief intracellular recordings of discharges from fibers conducting at C velocities but such recordings were too short lasting to permit testing of natural stimulation. I struggled with trying to improve the mechanical stability of the recording while awaiting the arrival of a postdoctoral fellow, Paul Richards (Dick) Burgess, who had applied as a consequence of the paper on the dorsal column nuclei that appeared in 1962 (Gentry, Whitlock, and Perl). Just before Burgess arrived, an article by Melzack and Wall appeared in the summer of 1965 in *Science* putting forth their 'gate theory' for pain. That proposal was an extension of the arguments presented in their earlier review of cutaneous sensory mechanisms. A premier postulate in the gate theory was the absence of specialized receptors for pain-causing stimuli. That publication fortified my resolve to learn what information was really transmitted by the C afferent fibers.

Dick Burgess was delayed in completing his dissertation at Rockefeller University. He arrived in late summer of 1965 just prior to my departure to France for 6 months as a visiting professor. We worked together long enough for me to show him my progress in the microelectrode recording technique. He was to attempt better mechanical stabilization to permit longer recordings from single C fibers.

The first trip to France had proven so successful that we eagerly looked forward to returning. It was an interesting sojourn but hard on the family. One major mistake was that we left our son at age 5 with a loving uncle and aunt, thinking that living in a big foreign city would be hard on him. A second error was in settling the family in a pleasant apartment in a suburb of Paris rather than in the city proper. This meant Marjorie did not have ready access to the advantages of the City of Light. I spent most of my time this visit teaching graduate science students with my limited and fractured French and accomplished little experimentally. Contacts with the French scientific community again were very cordial, but I learned from the outside how perverse scientific politics could be. Much energy could be spent in struggles for position. I gained practice in being a listener.

On returning to Salt Lake City, I was disappointed to find that Dick Burgess had made only limited progress. One advance was the discovery that a small nerve innervating the back of the cat leg, the posterior femoral cutaneous, had a relatively soft connective tissue sheath that allowed smooth microelectrode penetration. Stable recordings from C afferent fibers had not been possible. We both believed that the question was one of mechanical stability, although it was unclear as to whether the instability resulted from tiny movements of the preparation or from 'creep' of the electrode within the tissue. Regardless, we continued the trials, partially encouraged by regular stable recordings from myelinated fibers. To temper our boredom during long experiments, we routinely tested each unitary response from myelinated fiber independent of the electrical 'search' pulse, by mechanical stimulation of the region supplied by the nerve. Responses were evocable from almost every 'unit' by gentle mechanical stimuli: the effective stimuli and responses regularly confirmed the descriptions for the cat hairy skin receptors reported in previous studies. One night, about a month after I had returned from France, we encountered a response to the search electrical stimulus of a relatively slowly conducting myelinated fiber. Our routine of testing by gentle mechanical stimulation yielded no activity. After some minutes of fruitless trial, one of us, and we cannot remember whom, picked up a tissue forceps and pinched the skin in the middle of the nerve's receptive field. This evoked a burst of impulses. We looked at each other across the experimental table, both recognizing what we may have seen, and then systematically explored the unit's responsiveness. This fiber had an elevated threshold for mechanical stimulation compared to the other sensory fibers that we had previously encountered. We decided to temporarily abandon the search for recordings from unmyelinated fibers to concentrate on examining the occurrence of similar high-threshold mechanoreceptive fibers. I insisted that we focus attention on fibers conducting under 40 m/sec to eliminate distraction by the many forms of low-threshold mechanoreceptors comprising the

population supplied by the faster fibers. In addition, we made our search as unbiased as we could, selecting units to be studied by their response to the electrical stimulus and only thereafter using strong 'natural' stimulation. Our survey encountered many such high-threshold mechanoreceptors. The minimal effective stimuli varied, although all required more intense mechanical stimuli than did previously described cutaneous mechanoreceptors. In addition to the elevated thresholds, these sensory units had unique receptive fields in the skin, which supported the idea that they represented a separate class. C. S. Sherrington in his classic book, *The Integrative Action of the Nervous System*, argued that pain ordinarily was evoked by damage of tissue and proposed calling stimuli strong enough to damage tissue 'noxious.' From this he suggested that one might name sense organs responsible for pain, noci-receptors (nociceptors). We adopted his terminology for our new class of afferent units, labeling those that required overtly damaging stimuli for excitation as nociceptors. Our initial survey in cat showed that of approximately 500 afferent myelinated fibers conducting slower than 50 m/s, 15% fit the classification as nociceptors.

The notion of specific sense organs acting as nociceptors was controversial, particularly because of publicity associated with the gate theory proposal. At this juncture it seemed to me essential to determine whether similar afferent fibers existed in other species, particularly primate. Utilizing the same microelectrode recording technique and experimental approach, mechanical nociceptors were found to be a significant fraction of the slowly conducting myelinated fibers of the primate (squirrel monkey). The two studies published in 1967 and 1968 on high-threshold myelinated fibers documented evidence of a set of sense organs for the mammalian skin which are specifically responsive to very strong mechanical stimuli of the type normally associated with pain.

Paul Bessou returned to Salt Lake City for another working visit shortly after the work on the primate myelinated fiber nociceptors was completed. We decided to tackle the question of C fibers by dissection, encouraged by our experience with the mesenteric nerves. We had the arrogance to think that if Iggo and Paintal had been successful in recording from single unmyelinated fibers in filaments teased from peripheral nerve, we should be able to do so. Bessou and I were careful to do an unbiased search, dissecting with razor blade knives, sharpened needles, and the fine watchmaker's forceps, to isolate responses from individual fibers responding to the electrical search stimulus. Isolation of discharges from a single unmyelinated fiber proved less difficult than we had imagined. While the yield was not great, working in shifts we had success in every experiment, averaging about two useful recordings per experiment. We found the unmyelinated fibers in cat peripheral nerve to be much more varied than expected, identifying at least four distinctive sets of primary sensory units. Importantly, there proved to be more than one kind of C fiber nociceptor,

and these differed from each other and from the myelinated type in many ways. One C nociceptor gave a reliable response to noxious heat, which often became more vigorous on repeated tests. This enhancement of response (sensitization) subsequently became a much studied phenomenon by us and other investigators.

The attempts to use microelectrodes to record from unmyelinated sensory fibers continued to frustrate Burgess, but he persisted. The turn in that work came when one day Sherman Beacham looked at Burgess and said, 'Why don't you try to record from the dorsal root ganglion neuron cell bodies rather than from the peripheral fibers?' Burgess took this suggestion seriously and soon had the procedure working by carefully selecting ganglia from particular segments with relatively soft connective tissue. Bessou and I joined forces with Burgess and obtained valuable data on sensory neurons with unmyelinated fibers that were vigorously excited by innocuous stimuli. Many years later, I used the technique of recording from dorsal root ganglia neurons to study the relationship of immunocytochemical evidence for particular peptide to the signaling features of a neuron.

In the period from 1964 to 1969, I had responsibilities on the national scene as a scientific reviewer on National Institutes of Health panels and as a member of the National Board of Medical Examiners. The former provided a broad view of biomedical science since the panels to which I was assigned dealt with research requests covering the full spectrum of physiology and associated fields. Trying to judge and thereby predict how to forge new directions in an area of science was a revealing experience. The work with the National Board of Medical Examiners was intellectually less rewarding. It consisted largely of editing questions of the multiple choice type, although that work did tune one's ability to write for unambiguous meaning. Carl Gottschalk, from the University of North Carolina at Chapel Hill, was also a member of the physiology test section of the National Board of Medical Examiners, a contact that had consequences a few years later.

As I think back upon the time between 1964 and 1969, those years seemed highly charged. In 1964, Cuy Hunt left the University of Utah to chair the Department of Physiology at Yale University. Carlos Eyzaguirre from within our department at the University of Utah was chosen to succeed him, but Carlos was on sabbatical leave in Chile. I acted in his place for several months and found that the administration of a small academic unit was not too demanding.

The Western Nerve Net and the Society for Neuroscience

While the University of Utah was a relatively large institution, the number of people in a given subdiscipline such as neuroscience was

limited. Despite relatively frequent visitors, we still felt somewhat isolated. The issue of isolation gained importance as graduate students and postdoctoral fellows began to join our laboratories. Remembering the meetings of the Know Nothing Club at Johns Hopkins, I thought that similar convocations would prove stimulating and educational for us and for our young colleagues. Years before at meetings of the American Physiological Society, I had met Theodore Ruch and his colleague, Harry Patton. Ruch and Patton had moved to the University of Washington at Seattle where initially Ruch and then Patton directed the Department of Physiology. Their departments, as ours in Utah, had a concentration of people doing research on the nervous system. Seattle in the 1960s suffered from a degree of the isolation we felt in Salt Lake City. Patton agreed to join in informal, episodic meetings on nervous system research done in our departments. The idea was for the meeting site to switch between universities. Initially, most of the attendees were from the University of Washington and the University of Utah, but later friends and colleagues at other institutions were included (e.g., Donald Kennedy from Stanford University and David Whitlock, who had moved from Syracuse to the University of Colorado). The general plan for these meetings was to have the younger people present their work. In part, the focus on the young scientists was a rebellion against the domination of many established scientific meetings by more senior individuals. To legitimately utilize research funds for travel expenses, I named the alliance the Western Nerve Net. Planning of the meetings and selection of those invited was highly informal. I had a list of names and telephone numbers in a drawer in the lower right-hand corner of my office desk. About once a year Harry Patton and I would set a date and negotiate a place for the next meeting. Approximately 50–75 people attended. The word of the meeting's success spread and soon we had inquiries from institutions not originally in the consortium.

Scientific interest in the nervous system and its mechanisms was burgeoning in the 1960s. Part of that growth was related to the development or appearance of new tools that permitted exploration of cellular events. Our small and informal organization in the western United States mirrored similar groups in larger urban centers and at the international level by the International Brain Research Organization (IBRO). The latter was organized under the auspices of the United Nations as an umbrella organization for national societies. A requirement for a country's affiliation with IBRO was sponsorship by the academy of sciences or equivalent organization. To meet that requirement the National Academy of Sciences of the United States formed a Brain Research Committee, one of whose tasks was to encourage development of organizations or an organization to sponsor scientific work on the nervous system.

Ralph W. Gerard, a member of the Brain Sciences Committee who advocated the formation of a national society dedicated to research on nervous systems, was empowered to explore this possibility. In late summer 1968, in conjunction with the International Union of Physiological Sciences meeting in Washington, DC, Gerard invited me along with other representatives of local groups who had held research meetings on the nervous system to attend a discussion on the question of a new organization. About 20 of us showed up at an anteroom in a large Washington hotel on a steamy day. Gerard's idea was to form an umbrella organization similar to IBRO for the local groups that would become chapters. During the meeting I argued that science on the nervous system would be best served if the scientists determined the nature of the organization they needed or wanted. Possibly because of the logic of this argument, or my outspoken advocacy, Gerard chose me as chair of a group of 10 of the attendees to do what I had suggested—determine whether a society was wanted and, if so, what its nature should be. Some financial resources were provided from the National Academy of Sciences and National Research Council (NRC), including the part-time assistance of Louise Marshall, an NRC staff member who acted as secretary of the Brain Research Committee.

Linda Ruiz was my part-time secretary in Utah. By telephone and letters, Linda and I arranged a survey by the organizing group and other people in key regions of the country. We found overwhelming support for the formation of a scientific society directed at fostering research on the nervous system. Surprisingly, the main wish was not for an umbrella organization for local chapters. Rather, an organization that would arrange a national, interdisciplinary meeting on nervous system research was desired. This was reported to the Brain Sciences Committee chair, Neal E. Miller, a physiological psychologist from Rockefeller University, and to Ralph Gerard. I was encouraged to take necessary steps to form such an organization. The first step was to define the society's purposes and its structure. It seemed to me most efficient to produce a draft constitution and bylaws and then to circulate them to the organizing committee and members of the parent Brain Sciences Committee. One snowy, winter weekend I sequestered myself in our study at home and drafted what, with small changes, eventually became the initial bylaws of the proposed organization. The society's main purposes were defined at this time: dissemination of information about scientific advances on work in the nervous system, education of its membership and the public at-large about advances and knowledge of nervous systems, and encouragement of interdisciplinary contacts by scientists interested in nervous mechanisms. The draft constitution and bylaws received general approval with but few modifications.

A provision to limit tenure of the officers and governing council was an important part of the initial bylaws. Many of my contemporaries were

dismayed by the tendency of scientific societies to be governed by what appeared to be a dynasty of older individuals who were no longer active in the laboratory and promoted one another for leadership positions. There may be no way to avoid politics in human societies, but I thought the new society would have a healthier start if its leadership turned over regularly in a democratic fashion. The bylaws were presented to a meeting of the Brain Sciences Committee in June 1969 which gave unanimous approval to their use for incorporation of the organization. There were approximately 20 people at that meeting, including representatives of the federal government agencies that supported research on nervous systems. We were the initial founders of the organization that came to be called the Society for Neuroscience. The group elected me president of the new society, but I chose to take the title of acting president. In my view, a democratic organization needed a leader elected by a representative membership. The Society for Neuroscience was incorporated shortly thereafter, and we began to actively invite membership. By late autumn that year there were more than 700 members, which led me to start plans for the first annual meeting. Planning for the 1971 meeting and for the formal election of a full slate of officers began in January. Vernon Mountcastle took over as elected president in spring 1970, when the society had more than 1000 members. From the beginning, the society was a phenomenal success. The annual meeting became very large but retained popularity, in part, because it attracted young investigators by innovation in the science represented and by the judicious use of a variety of formats. Currently, the society is in its 31st year, with a membership in the vicinity of 30,000. I expended considerable effort over nearly 2 years on the plans and organization of the Society for Neuroscience. In retrospect, it was time well spent.

Salt Lake City II—Continued

Despite the work on the formation of the Society for Neuroscience, we made good progress in the laboratory. Dick Burgess' cousin, Burgess Christensen, a graduate student in biomedical engineering, initially came to the laboratory to learn how to record from peripheral afferent fibers. After completing his dissertation he returned as a postdoctoral fellow in 1967. Following cementing of the existence of the cutaneous myelinated fiber nociceptors, it appeared essential to establish their central connections. Preliminary experiments in recording from the spinal dorsal horn suggested that the combination of stimulation of an intact peripheral nerve electrically in a graduated fashion along with activation of afferent fibers in that nerve by physiological stimuli had promise. I proposed such experiments to Christensen, with the addition of the use of a marker dye in the recording electrode to identify its recording location. The thalamic work with Whitlock had indicated the importance of establishing anatomic

loci as precisely as possible. We found a focus of activity in the most superficial part of the dorsal horn to be evoked by slowly conducting myelinated fibers. Extracellular recordings from single neurons established that certain superficial dorsal horn neurons were selectively excited only by intense mechanical stimulation of the skin. The recording loci from which such selectively activated neuronal activity occurred congregated around the most superficial layer of the gray matter of the dorsal horn, the marginal zone (Rexed's lamina I). Until then, there had been few reports of selective activation of any CNS neurons by noxious stimuli, and none implicated the outermost part of the spinal gray matter. We found other neurons in the same narrow zone to be responsive to innocuous skin cooling. These observations took on a special significance since earlier anatomical and neurological literature suggested that this part in the spinal cord contributed fibers to the crossed spinothalamic tract, a pathway implicated in conveying information essential for normal pain and temperature sense. These studies on the spinal marginal zone represented our second line of evidence showing pain and temperature sense to have functionally selective neuronal substrates, quite contrary to tenets of the Melzak and Wall gate theory.

The Department of Physiology at the University of Utah had a small doctoral graduate program, although most of its trainees were postdoctoral. Sherman Beacham had left Utah to do a residency in internal medicine at Stanford University. He returned to collaborate with one of the graduate students, Diana Kunze. I encouraged them to examine visceral afferent fibers, and they concentrated on those innervating the kidney and made valuable observations on renal pelvic afferent innervation. As Diana Kunze's dissertation adviser, I urged her to do a totally independent study. She chose to analyze neuronal activity in the efferent innervation of the heart and emerged from this trial of independence as a competent investigator. Her subsequent success has been a pleasure.

Takao Kumazawa from Nagoya, Japan, joined the laboratory in the late 1960s. We immediately started a survey of unmyelinated primary afferent fibers in the monkey and began a long series of experiments on the projection of thin primary afferent fiber to the dorsal horn of monkey. The aim of these studies in primate was to determine whether the observations on cat reflected an organization that held for species closer to human beings. After the experiments with Kumazawa were well under way, I had another invitation to France as a visiting professor, this time from the Faculté de Science, Université d'Aix-Marseille. The invitation was arranged by Maurice Hugon, who had been a candidate for the Doctorat d'Etat in Paris when I was there in 1965. Hugon spent a year in Salt Lake City doing animal experiments that completed his dissertation work. In addition to the social and cultural attractions of another visit to France, the invitation provided an opportunity for an experiment on primate and humans that

I had wanted to try since the time of observations with Burgess on the myelinated fiber nociceptors.

The idea was to record from single myelinated fibers using a micropipette, determine their responsiveness to various forms of natural stimulation in the periphery, and then stimulate the recorded fiber by passing current through the microelectrode. Using baboons that were to be euthanized, I tested this approach on peripheral nerves and determined that passing current through a micropipette electrode recording from a given fiber excited only that fiber. With the help of highly cooperative French neurosurgeons and their patients undergoing exploratory biopsies for neuromuscular disease, the plan was to have a human subject report the sensory experience perceived as a consequence of activity in a single peripheral sensory neuron. In the human trials, the microelectrode recording from the human nerves failed because of the density of the connective tissue in adult human beings. Failure of these experiments was a great disappointment; however, a decade later, with the help of Herbert Hensel and his colleague F. Konietski from Marburg, Germany, we succeeded in making such correlative observations.

The visit to France did not prove explicitly successful scientifically, but it represented a memorable experience for our family. The children survived French public school for the third time, and we delighted in living in the small town of Cassis, a fishing village near Marseille. I was committed to return to the United States in late spring of 1970 to give the Bishop Lecture at Washington University in St. Louis. We were away from Marseille during the Easter break, and on return the concierge of the Faculté des Sciences told me I had a telephone call from someone who did not sound like an American. John Graham, an associate dean at the University of North Carolina at Chapel Hill, had called because they were searching for a chair of the department of physiology. At his urging, I agreed to stop in Chapel Hill on my return to France from St. Louis.

There were several reasons why I was willing to consider a move. Research had gone well for the past decade at the University of Utah, and I enjoyed living near the mountains with the opportunities to fly-fish in the summer and ski in the winter. On the other hand, it was frustrating to lack local colleagues with expertise in neuroanatomical and neurochemical methodology. I had never seriously considered living in the south; however, Chapel Hill was a special place for Marjorie. She remembered it fondly from childhood when she had visited an uncle who had attended the University's school of law and later worked there.

I had the pleasure of meeting George Bishop during the visit to Washington University in St. Louis in June 1970. Bishop's experiments with Gasser and Erlanger in the 1920s and then the later work by Bishop and colleagues in the 1930s had helped usher in the era of electrophysiology. Washington University had an impressive presence in the

neurosciences. Cuy Hunt had moved there from Yale and once again had built a strong department. We discussed my coming to work there, but the large city gave me pause even though working there could have been stimulating.

Chapel Hill was notably different from the large midwestern city of St. Louis. The town was small, in a semirural setting, and dominated by the university. The medical school was part of the main campus, and the atmosphere was of erudite gentleness. People had a politeness inherent to the culture of the southern United States. One could easily walk from the medical school to the downtown area. Frankly, I was charmed, and I returned to Cassis enthusiastic about the prospects. Other features made the situation at the University of North Carolina attractive. The medical school was expanding. There was an interest in and a commitment to building the neurological sciences. Moreover, the institution was prepared to provide substantial resources for strengthening of physiology. On our return to Salt Lake City, I began serious negotiations with the University of North Carolina. Carl Gottschalk, chair of the search committee, was important in the recruitment efforts. After several trips to Chapel Hill, including one with Marjorie, I was ready to move provided at least one of my Salt Lake City colleagues could be enticed to join me. I was particularly interested in Motoy Kuno, and when he agreed I accepted the invitation to move to Chapel Hill as professor of physiology and chair of the department.

Chapel Hill and the University of North Carolina

Marjorie was enthusiastic about the move. It would bring her back to the east coast and to a town that she had admired as a child. Convincing our children that a move was desirable proved more difficult. They had friends in Salt Lake City, but perhaps the most important negative was the move away from the mountains and the opportunities for skiing that were close by. All three children had become excellent snow skiers to the point that they stood out. We promised that they would be taken back to Utah in the wintertime so that they could ski. Thus, in the summer of 1971 we began the long trek across the country in an automobile filled with three children, a dog, and several cases of wine to two small adjacent apartments in a new complex near the university. The house we were having built was completed the better part of a year later. The family survived those first months in the two apartments in relatively good humor considering that the autumn in 1971 was the wettest we would encounter in Chapel Hill over the next 29 years.

The position in Chapel Hill brought new and much increased responsibilities. At Utah my teaching was limited to a team-taught course for medical students. Including the laboratory sessions, this represented only

a few weeks a year. The rest of the time was available for research. At Carolina, the department of physiology, while small, taught courses not only for medical students but also for several groups of health science professional students. Furthermore, there were graduate courses to be given for physiology and biomedical science students. Additional people were needed to increase the research activity in the department and for assistance with teaching. Thus, a first and a continuing task for the new chairman was to recruit faculty, the first recruit being Motoy Kuno. Over the next decade, the department grew from a cadre of 8 to well over 20.

Arranging and implementing the teaching proved a major challenge. The school of medicine in Chapel Hill had just completed a curriculum reorganization that had abolished the course in medical physiology. Physiology did not have responsibility for any part of the medical curriculum. Our faculty was to contribute in courses organized around various systems of the body (e.g., heart, kidney, and pulmonary) and directed by others. I was invited to help organize an offering on the nervous system that combined neuroanatomy, neurophysiology, and neuropathology. A course in physiology eventually was reintroduced in the medical curriculum at the request of the students after I had given a series of informal, unscheduled noon lectures on cardiovascular physiology. In due time, medical physiology regained an appropriate place in the preclinical medical curriculum at North Carolina and was regularly acclaimed by the student body. The course in neuroscience was easier. It had been assigned a place in the medical curriculum and only needed a reasonable plan and good teaching. I organized the material so that neuroanatomy was taught in small groups in the laboratory from illustrations, models, and brain slices, and the neurophysiology part was taught mostly by lecture with some corollary small group sessions. Neuropathology was also a combination of lecture and laboratory, although years later the neuropathology material moved to the general pathology course. While arranging the department's teaching took substantial time in the early years, it seemed both appropriate and essential that a department in an academic institution serve well its primary responsibility. This conviction came not from my personal abilities as a teacher. I am not relaxed and amusing enough to excite students in a large classroom; however, it was easy to recognize that students respond positively to thoughtful, good-intentioned offerings.

Chairing a department in a large American university spawns opportunities and obligations other than those associated with faculty recruitment and teaching. There were numerous committees that seemed an inescapable part of university life. Being a chair also results in one receiving increased attention on the national scene. It is difficult to refuse responsibilities for doing some of the essential tasks to operate the machinery for one's field of professing and science. Then there is the issue of financing science for a group larger than oneself and a limited

number of research colleagues. That also took time from experiments and scholarship.

Takao Kumazawa, fortunately, had made the migration from Salt Lake City to Chapel Hill and was crucial in keeping the experimental work going. The first years at the University of North Carolina were spent completing the studies on primate unmyelinated primary afferent fibers and the analysis of neuronal activity in the superficial dorsal horn of monkey. Jorgen Boivie from Sweden and Bruce Lynn from London also joined us in Chapel Hill in the early 1970s. Boivie brought a valuable asset, a solid appreciation of CNS anatomy, and helped set up our facilities for neurohistology.

While it had not been my intention to focus my research on 'pain' per se, our work had led to that concentration. One issue that had gained prominence in the 1970s was acupuncture and its use in China for analgesia and treatment. Bruce Lynn and I undertook testing the traditional Chinese tenets of acupuncture concerning the relationship between point or region of acupuncture and the structure effected. We could not confirm the classical Chinese description of the correlation of body region treated and body region affected, even though we found that a profound analgesic-like effect could be demonstrated in a small proportion of normal human subjects.

The work with Kumazawa on the most superficial layers of the spinal dorsal horn of primate showed that region to be functionally complex; neurons with differing afferent input tended to have distinctive locations. It became clear that the existing morphological information was not adequate to help explain these results. Alan Light approached me in 1976 about a postdoctoral fellowship. He and several other groups had independently developed the technique of labeling the processes of individual central neurons using the neuronal retrograde tracer agent, horseradish peroxidase (HRP). Light was an energetic enthusiast and we quickly settled arrangements for him to come to Chapel Hill. At the time, Miklos Réthelyi was visiting from Hungary. He and Szentágothai had studied the substantia gelatinosa (spinal gray lamina II) using histological approaches based on the Golgi silver impregnation technique, and he brought a morphologist's insight. Réthelyi, Dan Trevino (another visitor), and I had already started a project to define the central projections of primary afferent fibers in the dorsal horn utilizing autoradiographic labeling of whole peripheral nerve. Light brought a potentially more powerful technique, use of iontophoretic marking of single fibers from a recording electrode, which could provide details about morphology of individual functionally defined primary afferent fibers.

Making the intracellular marking procedure work for small neurons and the thin primary afferent fibers innervating them in the superficial parts of the dorsal horn proved to be a challenge. Light and others had used the technique on the larger neuronal elements but failed with small fibers and

cells. The secret for labeling functionally identified, thin myelinated fibers or the small cells of the superficial dorsal horn with HRP proved to be the use of very fine micropipette electrodes. When such electrodes contained HRP or other large protein markers, they developed very high resistances, which made it difficult to make electrophysiological recordings and to extrude marker substance. With an amplifier locally designed, Light and I were able to label individual, functionally identified, thin myelinated fibers to determine their central terminations. The same equipment provided detailed morphology of laminae I and II neurons, whose afferent input had been established by electrophysiological recording. We found that the peripheral functional selectivity of the thin primary afferent fibers determined in earlier work was correlated with particular and unique termination patterns in the spinal cord. These observations lent further support to the idea of specificity in the neuronal function and connectivity related to pain and temperature sense.

There were many notable personal events during that first decade in Chapel Hill. Our children made the transition to adulthood with remarkably few unfortunate events, completing their school years and their first stages of university work. Not only did the family survive their adolescence and maturing but also we stayed friends. I look back upon that period with a sense of guilt. I spent too little time with the children and too much at work even though I am unsure that their outcomes could have been better. As the children began to attend college and lead independent lives, Marjorie and I found ourselves in a large house by ourselves. She prompted purchase of a piece of land situated in the middle of Chapel Hill within easy walking distance of the university. We built another house and moved in during the late summer of 1979. A few weeks later we had our first experience with a hurricane in the new dwelling. Marjorie prompted a substitute activity for relaxation by suggesting that we explore sailing. With the help of my old sailing friend, William Greene, and several short-term charters, sailing became a part of our life. We soon had a small, cruising sailboat harbored on the North Carolina coast in the tiny hamlet of Oriental that we often visited on weekends. Sailing proved to be a good substitute for the fly-fishing and skiing excursions of the West.

In 1980, I returned to France as a visiting professor at the Faculté des Sciences in Paris. This time the invitation came from Denise Albe-Fessard. My responsibilities were largely to work with young people in her laboratory. With one of these, Jean Azerad, I set out to do experiments that were inspired by the histochemical reports that markers for substance P and somatostatin appeared in partially nonoverlapping populations of dorsal root ganglion neurons. The idea was to record from dorsal root ganglion cell bodies and determine the kind of natural peripheral stimulation that would effectively excite them and to label the cell with a dye. Afterwards, immunocytochemistry was to be used to determine the nature of the

constituent peptide substance. Conceptually easy, this proved to be difficult practically. Immunocyochemistry was favorable in the rat, which led us to try the experiments first on that species, but we immediately ran into problems. The dorsal root ganglion peptide-containing cells were small in diameter, and in rat the high-impedance micropipette electrodes that had worked well in peripheral nerve and spinal cord did not consistently yield stable recordings from them. Azerad suggested trying guinea pigs. Guinea pigs are born with more completely developed nervous systems than rats and are free ranging from the time of parturition. Moreover, the immunocytochemical staining of dorsal root ganglion neurons for neuropeptides worked well in the guinea pig, and electrophysiological recordings from small dorsal root ganglion neurons were more successful than those in rat. While we were doing these experiments in Paris, an English physiologist, Sally Lawson, visited the laboratory; she was also interested in the differing peptide content of dorsal root ganglia neurons. On returning to Chapel Hill, I did many of these experiments with inconsistent results due largely to difficulties with the histochemical procedures for immunocytochemical identification in combination with the dye labeling of the neurons. Sally Lawson subsequently perfected the technique of using combined markers for dorsal root ganglion neurons, and we later successfully collaborated in providing a long-sought correlation between functional signaling attributes of primary sensory neurons and their content of certain neurally active peptides.

The guinea pig preparation provided an answer to another question. Alan Light and I had shown the distinctive central termination patterns of thin myelinated afferent fibers using the transport of horseradish peroxidase from elements identified and labeled at the junction between the dorsal roots and the spinal cord. That type of information was needed for the unmyelinated fibers; however, the technique of recording from the latter with micropipettes worked too rarely to be useful. Why not label the cell body in the dorsal root ganglia? With Yasuo Sugiura, a neuroanatomist from Japan, we set a target of defining the central termination pattern of functionally identified DRG neurons with unmyelinated C fibers. After numerous trials of various putative labeling molecules, we found the lectin, *Phaseolus vulgaris* leukoagglutinin (PHAL), to be a suitable for defining the central ramifications of unmyelinated primary afferent fibers after application to neurons of the dorsal root ganglia. Unfortunately, PHAL was transported quite slowly, so even for distances as short as 2–4 mm, 2–4 days were required for transport into the spinal gray matter. This meant doing experiments in a semisterile fashion and maintaining an anesthetized animal for up to 6 days by constant nursing care. Three of us, Yasuo Sugiura, Chong Lam Lee, and I, watched over the guinea pigs. The yield of fully successful trials was low, but with persistence we managed to establish basic attributes of the central termination of

identified cutaneous unmyelinated afferent fibers. Sugiura, on his return to Japan, would establish that not only do cutaneous afferent fibers with different functional characteristics terminate differently but also they differ as a group from termination of unmyelinated fibers from visceral structures. Thus, the 1980 visit to France eventually paid important scientific dividends.

I met Herbert Hensel of Marburg, Germany, a pioneer in studying peripheral thermoreceptors, in the early 1970s. One of his studies was on thermoreceptive afferent fibers innervating human skin. We discussed my unsuccessful attempt to stimulate functionally identified primary afferent fibers in a conscious human subject. He proposed a modification of the technique to use fine metal electrodes of the type developed for percutaneous microneurography. A set of trial experiments in Hensel's laboratory failed because of difficulties with the metal microelectrodes. However, shortly thereafter Hensel's colleague, F. Konietzny, came to Chapel Hill. With members of our laboratory personnel as the experimental subjects, we concentrated on thin afferent fibers. In a few weeks we were able to document an unequivocal correlation between the functional attributes of primary afferent fibers and the nature of the sensation that a human subject reported. Our observations on percutaneous stimulation of peripheral sensory fibers paralleled similar observations by Torebork and Ochoa.

Despite progressively heavier administrative responsibilities, the 1980s were scientifically satisfying and productive due to the quality of my associates. In addition to Alan Light, who was to become independent during this period, Yasao Sugiura, Virginia Shea (graduate student), Christopher Honda (graduate student), Steve Schneider, Elizabeth Bullitt, Charles Vierck, and Sigfried Mense made experiments possible and successful. Virginia Shea recorded activity from single unmyelinated afferent fibers using the microdissection (teased filament) technique. She found the rabbit ear to have an unmyelinated population similar to that in the cat hairy skin. Following division of the nerve supplying much of the afferent innervation of the ear, the unmyelinated population regenerated to regain characteristics remarkably close to those found in control animals. Honda's dissertation experiments explored deeper parts of the spinal cord for responses to visceral afferent input. With Christopher Honda and Sigfried Mense, I returned to recording from the thalamus to demonstrate that, in cat, afferent input from the myelinated cutaneous nociceptors projected to ventrobasal thalamic regions, closely adjacent to the main tactile nucleus of the ventral basocomplex. This work provided another example of selective handling of nociceptive information by the CNS.

The studies showing the selectivity of signaling by the thin primary afferent fibers, and their central termination in particular parts of the spinal cord raised the issue of synaptic mediators. In part, the questions led to the effort to correlate peptide content in primary afferent neurons

with their functional characteristics. It had become evident that the action of most neuroactive peptides did not have characteristics that could account for fast synaptic transmission. Important issues included not only the nature of the chemical mediators but also whether all primary afferent fibers utilized the same chemical agents. An effective experimental approach required better access to the synaptic regions and control of environmental variables than was possible *in vivo*. Furthermore, such basic issues appeared equally well approached in smaller, more readily available, and less expensive mammals than cat and monkey. I convinced Steve Schneider that we should try an *in vitro* preparation of sagittal section of the hamster spinal cord with attached dorsal roots. In our hands, the hamster sagittal slice, in an organ bath perfused with oxygenated artificial spinal fluid, proved robustly viable and permitted stable intracellular recordings. Our initial observations strongly implicated glutamate in fast transmission between primary afferent fibers and neurons of laminae I–III of the spinal cord. In some neurons, though, there were clues that other excitatory agents may play a part in primary afferent input. The most Herculean of these experiments was our attempt to utilize a preparation that consisted of skin, a cutaneous peripheral nerve, dorsal root ganglion, and a spinal cord slice. Many of these preparations failed due to block of afferent conduction along the thin peripheral nerve. Schneider's dogged persistence prevailed, and we accumulated reasonable evidence showing that glutamate was the important agent for fast synaptic transmission from the myelinated fiber nociceptors.

The Afferent Fiber Sympathetic Linkage

In the late 1980s, Kumazawa sent his former student, Jun Sato, from Nagoya. Sato had experience in teased fiber preparations, and we decided to tackle a problem prompted by long-standing clinical evidence that implicated sympathetic activity in pain and other symptoms of the classic syndrome of causalgia. We knew from Virginia Shea's experiments that sympathetic stimulation did not have notable excitatory action on C fiber nociceptors in normal animals. The question was whether after nerve injury the effects of sympathetic stimulation were different. Sato and I quickly determined that the prior, partial injury of the major nerve to the rabbit ear resulted in sympathetic stimulation or small, close arterial injections of norepinephrine to have excitatory action on a proportion of intact C fiber polymodal nociceptors. Pharmacologically, the excitation was mediated by a subset of α adrenergic receptors. Trying to establish whether the effect of the nerve injury is the result of a change in number or character of adrenergic receptors proved frustrating. Antibodies to the receptors were not available when we started. Genes for α adrenergic receptors had been cloned, so our first efforts were with

in situ hybridization histochemistry, attempting to identify the changes in mRNA of dorsal root ganglion neurons after nerve injury. The results were inconsistent, which in retrospect possibly reflects low levels of the message. Antibodies for certain α adrenergic receptors usable in histological preparations eventually became available, and using them Lori Birder and I were able to provide evidence for an upregulation of an α_2 adrenergic receptor in dorsal root ganglia following nerve lesions. Other explorations of the change in responsiveness of cutaneous nociceptors to sympathetic amines showed that such effects were also produced by sympathectomy alone. This and the time course of the development of responsiveness to the adrenergic agents suggest a phenomenon possibly related to the old observations of denervation supersensitivity that are manifest after loss of sympathetic innervation to an effector organ. These observations on phenotypic changes in sense organ sensitivity appeared early in the explosion of evidence during the 1990s on the capacity of adult neurons to change phenotype as a consequence of environmental factors, past history, or injury.

Electrophysiology in the 1990s

At the time the initial observations with Sato were made on the adrenergic effects upon cutaneous nociceptors, I was acutely frustrated with the ever-mounting administrative work demanded from a departmental chair. I asked my mentor and friend, Vernon Mountcastle, over a beer at a meeting in Stockholm on a sunny Swedish day what he thought about resigning the position as chair. He looked at me without a smile and said, 'It would be the happiest day of your life.' This coming from a man who spent well over a quarter century as chair of a department enboldened me to devote more time to experimental work. At the end of 1989, I resigned, recognizing that in stepping down from the chairmanship I would be giving up more than just administrative responsibilities. The ability to modulate the direction of the department would be lost as well, and the ability to influence the university would lessen by far. Nonetheless, I look back upon that decision with only the regret that I did not make it earlier.

The experiments with the effects of nerve injury upon the response of sensory receptors to sympathetic activity led to other studies. Susan Tucker, a urologist who knew of our studies, noted that symptoms of interstitial cystitis, a disorder affecting mostly women and usually beginning during the childbearing years, had hallmarks of nerve injury and the production of alterations in sensory activity. Virginia Shea returned to the laboratory to work on this question. It took a massive effort by her and Rong-Sheng Cai to establish the characteristics of sensory receptors innervating the bladder so that they could properly evaluate effects of injury to the sympathetic innervation. They eventually established that partial

injury of the sympathetic supply to the bladder to enhance responsiveness of the mechanoreceptors of the bladder to bladder filling. That work is still ongoing and may influence ideas about mechanisms behind the appearance of interstitial cystitis.

Jing Li joined my laboratory as a graduate student in 1988. I suggested to Jing that we approach the question of purine transmission in the spinal superficial dorsal horn. In part, this project was an extension of several observations. Robert Fyffe and I had produced evidence in the early 1980s that ATP had selective excitatory action on neurons of the superficial dorsal horn. Also, work with Steve Schneider and Jacques Nasstrom had implicated glutamate as a principal fast excitatory transmitter in this region but left clues that at particular synapses some other agent may be involved. Jing Li started with the sagittal spinal cord preparation that we had used but quickly developed a transverse slice from the hamster to permit better placement of recording electrodes. Furthermore, the transverse slice facilitated use of tight-seal, whole cell (patch-type) recordings, which proved more stable than those obtained with fine micropipette electrodes. Tight-seal recording also provided the advantage of much lower noise, thereby permitting observation of miniature spontaneous synaptic activity. Those experiments showed that ATP had selective excitatory effects upon neurons of the superficial dorsal horn and that its breakdown product, adenosine, was a potent inhibitory agent as well. The effect of ATP was direct, putatively mediated by a specific receptor, and its actions on given cells was to produce inward current and secondarily to facilitate responsiveness to glutamate. We also showed a breakdown product of ATP, adenosine, to produce inhibitory effects on neurons of laminae I and II. It acted postsynaptically to open potassium channels and presynaptically to decrease external calcium influx, thereby suppressing spontaneous release of synaptic mediator.

The studies on adenosine uncovered differences between the effects of agents interfering with Ca^{2+} channels on responses in neurons evoked by dorsal root input and on spontaneous excitatory events occurring in the same neurons. At the time, Juping Bao had joined the laboratory in somewhat unusual circumstances. She was medically trained in China as an obstetrician but could not practice in the United States and volunteered to help with histology. Within a few weeks we hired her as a technician. She proved so able that I then asked her to become an investigator. She quickly taught herself the transverse slice preparation and learned electrophysiology in the process. Together, we tackled the problem of the relationship of calcium channels to spontaneous transmitter release using pharmacological tools. We were able to show that spontaneous excitatory postsynaptic currents were modulated by entrance of calcium from extracellular sources through different calcium channels than those responsible for the evoked release of transmitter produced by action potentials in presynaptic fibers.

Tim Grudt, an able and willing collaborator, joined me in 1996. He was well trained in *in vitro* electrophysiology and had worked on the substantia gelatinosa of the trigeminal region. He chose to come to our laboratory because he wanted to establish a better understanding of the functional organization of the superficial dorsal horn. I proposed to him that we make a systematic effort to determine the functional interconnections within this region. We are still struggling with this problem. I am particularly pleased to have had a superior colleague at this stage of my career.

In Conclusion

Currently, I am in my 74th year. I consider myself most fortunate in having both the health and the energy to continue to be enthusiastic about learning more about the functional connections of thin afferent fibers and the organization of the CNS that deals with their messages. I am grateful to the University of North Carolina for the extended opportunity to be a scientist and to the long-standing support from the National Institutes of Health that has made biomedical science possible in the United States.

One does not know what tomorrow will bring, but today I still look forward to the pleasure that comes from a successful experiment or that of an evening's sail, the excitement of seeing a trout or salmon rise to a fly, or of the smile of a grandchild. I close this on the way to ask Marjorie for a dinner rendezvous.

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