



John Wilson Moore

BORN:

Winston-Salem, North Carolina
November 1, 1920

EDUCATION:

Davidson College, B.S. Physics (1941)
University of Virginia, Ph.D. Physics (1945)

APPOINTMENTS:

Radio Corporation of America Laboratories (1945–1946)
Assistant Professor of Physics, Medical College of Virginia (1946–1950)
Biophysicist, Naval Medical Research Institute (1950–1954)
Associate Chief, Laboratory of Biophysics, NINDB, NIH (1954–1961)
Professor of Physiology & Pharmacology, Duke University (1961–1988)
Professor of Neurobiology, Duke University (1988–1990)
Professor Emeritus of Neurobiology, Duke University (1990–present)

HONORS AND AWARDS (SELECTED):

Dupont Fellowship, University of Virginia (1941–1945)
Fellow: National Neurological Research Foundation for Scientists (1961)
Biophysical Society, Council and Executive Board (1966–1969; 1977–1979)
Biomedical Engineering Society, Board of Directors (1971–1975)
Trustee and Executive Committee, Marine Biological Laboratory (1971–1979; 1981–1985)
K. S. Cole Award, Biophysical Society (1981)
Fight for Sight Citation for Achievement in Basic Research (1982)

*John Wilson Moore initially became known for elucidating the action of tetrodotoxin and other neurotoxins using his innovative sucrose gap method for voltage clamping squid axon. He also was a pioneer in the nascent area of computational neuroscience, using computer simulations in parallel with experiments to predict experimental results and thus validate the concepts used in modeling. Intrigued by the possibility of applying his knowledge of physics to learn how neurons employ electricity to generate and transmit signals, he led the field in exploring how ion channels and neuronal morphology affect excitation and signal propagation. He developed electronic instrumentation of high precision for electrophysiology, the result of experience gained through an unconventional career path: early training in physics, assignments involving feedback in the Manhattan Project, and learning principles of operational amplifiers at the RCA Laboratories. His summers at the Marine Biological Laboratory in Woods Hole, MA, now exceeding 50, made much of his work possible and established the MBL as his intellectual home. In retirement, he developed the educational software *Neurons in Action*, coauthored with his wife Ann Stuart, that is now widely used as a learning tool in neurophysiology.*

John Wilson Moore

“I want to know about your life before me,” said Annie, my beloved wife and colleague of the past 35 years. We are obviously different in age, and she did not know about my life before the 1970s. And so I began telling her what I remember, usually on Saturday evenings. Sitting beside me with her MacBook, she typed as I talked. Her questions have drawn buried memories to the surface, causing neurons to fire that had for some time been quiescent. It has been great fun for us both. Thus, when Larry Squire so graciously invited me to write my autobiography, I had a considerable start. Here I attempt to encapsulate my career by recalling some of the events and people that influenced it and the collaborations that I have greatly enjoyed, both before and after Annie joined me.

1920–1937: Growing up

I was the oldest son of a feisty, overworked mother and a demanding, workaholic, educator father. We kids liked to say, “Dad might be the salt of the earth, but Mom was surely the pepper!” I adored my mother and came to deeply respect my father, a man of the highest integrity. Mother, a tiny, red-haired ball of fire, and interested in everyone but herself, was focused for most of her life on tending Dad, us four kids, and visiting missionaries and teachers. She longed for vacations at the coast but Dad would never consider such a frivolous waste of time! As high school principal, then superintendent, in Winston-Salem, North Carolina, he was too occupied with daily school crises during the academic year itself, while during the summers he felt that every day was precious for finding and hiring the best teachers and preparing for the fall. Only after Dad’s death, relieved of her duties, did Mom’s spirit soar, and well I remember her flirting with a med student even on her death bed. Mom finally saw the ocean when she was able to visit me in Woods Hole after Dad died.

After serving in the Cavalry during World War I, Dad became the math teacher at the Winston-Salem High School. He believed in the importance of sports as a complement to classroom learning, initiating both football and basketball in the high school and coaching both teams to play their best, but always fairly. Dad loved teaching, but he was advanced to principal because of his integrity and dedication to education. Then, fortunately for me personally, Dad was promoted from principal to superintendent just before I entered the high school. Several of his former students became members of

the school board and supported him strongly as he strove to improve the quality of all schools, black as well as white. His devotion to the school system was recognized by having a new school built and named after him. Dad, as Superintendent of Schools, partnered with his friend Terry Sanford, at that time the NC governor, in locating the now famous North Carolina School of the Arts in Winston-Salem.

Both Mom and Dad, improbably, were children of missionaries assigned to the same Presbyterian mission station in Kobe, Japan, although they did not grow up in Kobe together. Both were brought to the United States by their parents at the age of 7, my dad to be raised by his grandfather in North Carolina after his mother had died in Japan, and my mother to live with a foster family in South Carolina. Perhaps their shared unhappiness at having been abandoned by their parents helped draw them together as adults. Dad's grandfather, John Wilson Moore (for whom I was named), was truly a remarkable person, a self-educated farmer who brought up all of his children to become professionals: two physicians and two preachers. One of the preachers and Dad received honorary degrees from Davidson College at the same time.

In Winston-Salem we lived in a little house with a huge backyard graced by many tall, beautiful oaks. Upstairs there was a miniature apartment typically occupied either by missionary relatives on sabbatical or by teachers who were renting it for room and board. When we four kids were small, we were pushed into the unheated sleeping porch upstairs because the missionaries and the teachers got the bedrooms. I recall our little house often beset by missionary relatives, mostly Dad's, who were used to having servants in Japan, so when they visited us they just sat around being waited on by Mom. She was rightfully quite resentful of these annoying relatives who would stay for a week to a month.

I had been born with a short left leg and a club foot with only four toes. Despite this, Dad thought I should work hard and continuously on family duties. From an early age until I went to college, it was my job to shovel the coal into the furnace in the spooky basement and care for chickens. Behind the house was plenty of room for the eight chicken houses, where roughly 100 of Dad's premium breed, White Wyandotte chickens, lived. When I was about 5 years old, I began my assigned chicken chores: watering, feeding, and cleaning the droppings. The droppings provided fertilizer for the garden, which I was also assigned to tend. Once a year Dad showed and sold his prize-winning chickens at fairs. Prior to the showing, there was the ritual of chicken washing. Everyone from the family participated (often without Dad). Imagine dunking dozens of squawking, flapping chickens in a tub of water, soaping them to get the oil off, putting them in a bluing solution to make them more intensely white, rinsing and drying them, and placing them in shipping crates where they could not get dirty! Annie asks if I didn't resent the hard work. Of course I did! My social life was almost nonexistent. But my father was a man of such integrity and good will that I came to

realize he was trying to do what he thought was best for me. I am proud of the man he was and what he accomplished.

1937–1941: Davidson College

Since Dad was a teacher, and we were a family of four children, he did not have the money to send me to an elite college. Besides, there was no question as to choice; it had to be little Davidson College where Grandpa, Dad, and others in the family had been educated. As a teacher, Dad got a discount on my tuition; in addition, because of my club foot, enterprising Dad obtained a North Carolina state grant intended to help disabled kids to go to college. With these sources of help, Dad was able to pay for my room and tuition for all 4 years. I earned my board separately, however, by waiting tables in a boarding house.

These boarding houses were in a sense like fraternities. Although there actually were small frat houses on campus, neither I nor my friends were interested in this sort of life centered on parties and drinking. My hard-working friends all did quite well in their lives. Although two of my best friends died in World War II, our class turned out two college presidents, a seminary president, and the dean of Yale Divinity School. One friend, John McLucas, deserves particular mention. With training in physics and business, John eventually became the undersecretary of the Air Force who pushed for the drone surveillance aircraft; he was on the boards of a number of high-tech corporations and had a satellite named after him! When he and I met at a recent Davidson reunion and swapped stories about what we had been doing, his remark was, “Well I thought you were going to make more of yourself John—why don’t you do something important?”

Starting in my sophomore year, I also earned money as a T.A. and by running the gym, but only after I had proved myself. As an entering freshman I was small and wimpy despite my years of shoveling coal! I admired the muscle-bound senior running the gym and devoted myself to gymnastics, receiving the award for the most physical development at the end of my freshman year. As a sophomore I replaced my muscle-bound senior friend, managing the gym and being in charge of physical education for freshman for the other 3 years of college—and getting paid for it. I most enjoyed the horizontal and parallel bars. I loved the sensation of using the momentum of the body at precisely the right moment to be able to execute a handstand, or a backward or forward roll: it was exhilarating and gratifying. I even organized a half-time gymnastics demo at a basketball game. I also wrestled, enjoying the gracefulness of the sport. Even with a club foot I was able to enjoy athletics and develop the muscles that have kept me strong and active all my life; for example, I became a windsurfer at age 60, windsurfed the 10 miles from Woods Hole to Martha’s Vineyard and back, and only stopped this exhilarating sport at age 80!

Inspired by excellent Davidson professors, I became deeply interested in physics. Perhaps in the back of my mind I was considering becoming a professor, since it was clear that my math and physics teachers at Davidson enjoyed what they were doing. Professors Mebane and McGavock in particular had been my favorites. Both of them welcomed students to their homes and enjoyed the company of their students. In my freshman year, Mebane, the math teacher, standing in as a physics teacher for the regular professor on sabbatical, had to learn physics along with the students and in doing this provided one of the best learning experiences I had at Davidson. He was usually only one week or even one lecture ahead of the class, exciting for both professor and students. First, the professor could see the kind of problems the students would encounter since he was learning the material *de novo* as we were. Second, students and professor attempted to outwit each other, a game that Mebane relished. When I told Davidson President Bobby Vagt about this experience at my class's 60th reunion, Vagt was fascinated and suggested that he should shake up the teaching assignments of his faculty more often.

Bill McGavock taught differential equations. Because there were only three students (myself, Pat Hobson, and John McLucas) in this class, we met in his office. Most memorable for me from this class was that there was no sure path that you could follow and know that you would get a solution. McGavock told his students to assume a solution and see if you could find a fit. But this was very unsatisfactory to me: what if we didn't know what to assume? When analog computers became available later, they seemed to me a terrific advance for understanding math. After I had used an analog computer to solve differential equations, I could actually see the individual variables of acceleration, velocity, and position change with time and yet their sum was always the same. Would that I had had a graphics calculator as present-day students do.

In my senior year I did a small project for Professor Henry Fulcher on the viscosity of oils—his one research idea for which he had equipment. How different it is today to return to Davidson and see the well-equipped labs with professors who publish, along with their students, in premier journals.

It was 1941 when I graduated. Europe was torn by war. Many of my classmates had competed ROTC in college and would soon be off to war, but my foot deformity excluded me from ROTC and military service. Having fallen in love with the elegance of physics, I decided to go on to graduate school in this discipline. Little did I realize that as a physics graduate student I would be very much involved in the war effort.

1941–1945: Graduate School in Physics during World War II

In September 1941, I entered graduate school in physics at the University of Virginia. There I joined John Reisner, a Phi Beta Kappa scholar who had

been 2 years ahead of me at Davidson. His stellar performance at UVA must have been the reason that I was admitted there, sight unseen, even with a fellowship! John invited me to be his roommate and became my closest friend, constant companion, and mentor throughout my years at UVA. From UVA he went to RCA, joined the program to refine the electron optics for their electron microscope, and had an illustrious career there. Perhaps, then, it is not a coincidence that I also moved to RCA after completing my degree, and I remain happily indebted to him to this day.

New graduate students took a required course in machine shop as well as courses in physics; it was necessary to know from practical experience in the shop just what could and could not be made there. I had just gotten started when Pearl Harbor was bombed on Sunday, December 7. On Monday morning there was a barbed wire fence around the physics building and military guards at the door! At that point we new students learned that a small group in the Physics Department had been working on isotope separation for the war effort.

To get into the building, each student now had to be screened. There were secretaries at the entrance interviewing and filling out a detailed history for each student. My family has heard me often recount this amusing moment in my life:

Secretary: "Name of father and place of birth?"

John: "John Watson Moore; Kobe, Japan."

The startled secretary looks at me, shakes her head sadly, and says she doesn't think I will get in. I explain that my father is the son of a Presbyterian missionary to Japan. She relents a bit—well maybe. Next question:

Secretary: "Name of mother and place of birth?"

John: "Marjorie McAlpine; Kobe, Japan."

Secretary: "That does it."

She grabs the piece of paper and rips it out of the typewriter saying, "You'll never make it!" But after an explanation to higher authorities I was not only given clearance to enter the building but, in time, clearance to work on highly secret projects. Only gradually were we informed that our Physics Lab at the University of Virginia was one of several groups in the top secret Manhattan Project that were attempting to make a nuclear bomb before the Germans. The head of our group was Jesse Beams, who was trying to separate U-235, the radioactive isotope of uranium, from U-238 using centrifugation as the separation technique. Separating out the U-235 was absolutely critical for the building of the atomic bomb. We later learned that there were other locations where isotope separation by diffusion was being tested: the Naval Research Lab (Washington, D.C.) and a new Oak Ridge National

Lab (Oak Ridge, TN). After December 7, classes became secondary and work toward the war effort became the primary focus of the students.

The Giant Centrifuge

By the beginning of 1942, the whole department was fully engaged with designing and building a huge centrifuge with its required ancillary equipment. Uranium was to be centrifuged in the gaseous state, uranium hexafluoride. It was to be passed through a vertical inflow tube into a huge, revolving, vertical aluminum tube (this centrifuge was about 10 inches in diameter and 10 feet or more in length). In this way the gas would be exposed to a strong acceleration so the heavier U-238 particles would spin to the outside of the tube and the lighter U-235 particles would stay near the center. Concentric exit plumbing was required at the bottom of the cylinder to collect the separated U-235 and U-238.

Together the graduate students and professors faced a number of problems in this crucial effort. Since we were dealing with a small difference in weight (3 parts in 238), separation presented a real challenge. Clearly we had to spin the tube as fast as possible without breaking it in order to get separation of the isotopes. The extraordinary machinery needed to effect the separation was large and complex. Fortunately the physics building had a special, safe place for it, a tower for a Foucault Pendulum (a pendulum suspended from a high place that demonstrates the rotation of the earth by exhibiting a change in its plane of oscillation with respect to the floor). The tower was three stories high and, best of all, was built with thick stone walls in the solid manner of the 19th century. All of the students were pressed into the job of stripping the pendulum out of the tower and, with steel angle iron, acetylene torches, and arc welding, building a frame to hold the huge centrifuge tube, made in the physics shop. In the course of this labor I had to learn both kinds of welding. I attribute much of my fondness for “hanging out” with skilled laborers today to such projects in my early life that required me to learn, understand, and respect the truly professional skills involved in construction.

What supplied the power to turn this huge centrifuge tube? Our team decided that a steam turbine would be best because an electric motor would fall apart before it could spin the tube at high enough speeds. The plan was to build a turbine driven by high pressure steam supplied by the campus steam generator, a building 200–300 yards away from the physics building. As the construction of the centrifuge was proceeding in the tower, the university laid large, high-pressure steam pipes to the tower despite the long distance. The graduate students did the plumbing inside because the workmen doing the external piping did not have security clearance and were not allowed in the building. There must have been a booster in the building itself because it was necessary to have immediate, high steam pressure upon

opening the valve, both to get the centrifuge going and then to keep it accelerating through certain resonant frequencies. If the centrifuge's spinning had remained even for a moment at these resonant frequencies, the assembly would have wobbled and probably been destroyed.

It was necessary, then, to know where the resonant frequencies occurred so that extra steam pressure could be supplied as the spinning tube approached them during its acceleration in order to overcome the potentially dangerous resonance. No electronic devices were yet available to measure frequency. However, it turned out that the physics department had an excellent frequency meter, piano-playing Professor Snoddy, who was blessed with perfect pitch! He was consequently given the duty of manning the steam valve, a wheel (imagine a small ship's wheel) that one turned in order to deliver more or less steam to the turbine. He would open the valve to let in steam to start the tube spinning, then, listening to the frequency of the sound made by the accelerating tube, begin to close the valve at a point just below the resonant frequency. By partially closing the valve he could let steam pressure build up. Then, by suddenly opening it again (imagine the wheel being furiously turned in one direction, then the other), he could supply a burst of steam to push the centrifuge through the resonant frequency. Since there were several harmonic frequencies as the tube spun faster and faster, this task had to be repeated during any one separation run; it required considerable skill and focused attention and was critical for the smooth operation of the device.

In 1942, as we were constructing the centrifuge and its plumbing, a young guy, Edward P. Ney, arrived with a mysterious new instrument called a mass spectrometer. This marvelous machine was to measure the ratio of the isotopes for each run of our centrifuge in order to evaluate the quality of the run; it turned out to be a special mass spectrometer just designed and built specifically for this purpose by Alfred O. Nier at the University of Minnesota. Nier was playing an important role in the Manhattan Project: as a pioneer in mass spectrometry, he had provided crucial samples of U-235 to the Uranium Committee, a tiny one that was used to show that this isotope, not U-238, was responsible for nuclear fission and then a larger sample requiring our newcomer Ney (along with another undergraduate student) to keep a mass spectrometer going 24 hours a day for 3 months! Nier's instruments became key in measuring the enrichment of uranium produced by the different separation methods under development at Oak Ridge, Columbia University, the Naval Research Laboratory, and our department at the University of Virginia.

I enjoyed interacting with Ed Ney, who had been assigned to bring us our designated mass spectrometer and make it work. Ed's remarkable intellect, and his level of understanding through his work with Nier, led me to think at first that he was already a Ph.D. although he only had a B.S. As well as being the mass spectrometer specialist for the Manhattan Project, he

joined our graduate program and upon his graduation was immediately offered an Assistant Professor position in our physics department. However, he returned to Minnesota and had a fabulous career in astrophysics recounted in his online obituary; for example, he flew the first space science experiment on NASA's manned flight Gemini 5.

Although our centrifuge was promising as a pilot model, the development of a production facility for it in New Jersey did not go well; the Manhattan Project's General Groves visited and closed our program in 1944. The diffusion method of separation at Oak Ridge was used to make the bomb. Nevertheless, centrifugation seems now to have become the standard tool for uranium isotope separation: think Iran.

The Naval Project: An Automated Target Tracker

In the Pacific, the Navy was having great difficulty in shooting down kamikaze aircraft with manually aimed gun directors linked to the anti-aircraft guns. The operator, on the deck of a rolling and pitching ship, had to attempt to keep the aircraft in his binoculars' field of view while trying to estimate where he thought the plane *would* be when the fired shell arrived there. The Navy shipped one of these massive and unwieldy gun directors to us so that we could experience their problems; the director was weighed down with the inertia of its synchronizing motors necessary to direct the gun and also was itself armored. Success in hitting the aircraft probably depended more on luck than skill, and certainly not on technology. Furthermore, the operator was in an extremely vulnerable position on deck. Thus, the mission for the UVA physics department was to build an automatic gun director using a new invention, a radar dish.

The department received one of the first of these highly secret radar dishes and the electronics to go with it. To develop and test the desired system, we physics students first needed to build a gimbaled 16 ft by 16 ft steel platform in the "backyard" of the physics building. We then had to employ oil-pressure-driven hydraulic motors, such as those used today in cranes, for moving the platform to mimic the rolling and pitching of the ship's deck. Similar hydraulic controls were used to move the super-secret radar dish now mounted on this virtual deck. (I commend whoever chose such an acronym, an easily remembered palindrome, for RAdio Detection And Ranging).

This new project required that we students learn about servo (feedback) systems as well as how to build the electronic circuits that would determine any deviation of the axis of the radar dish from pointing directly at the plane. Any error in pointing had to be sent to the hydraulic control system to move the dish so that the error was minimized. Indeed, we accomplished our goal, first with the gun on a steady deck with a fixed target, and then with a Piper Cub piloted by one of our students. Now we had to build a

circuit that would calculate the “lead angle”—the position where the moving plane would be after the time taken to fire the shell plus the time of the shell’s flight to meet the plane. After working out the problems in tracking a small plane in flight, we found that when the “deck” was in full motion, the tracking was almost as good.

We were rather surprised and gratified that we were able to build an automatic gun director even with the target being such a small plane having so little radar reflection signal. We proclaimed that our invention worked and so the system was passed on to the government for development. This was my first work with servo systems.

Finally My Dissertation: My First “Clamp”

I had started graduate school with a project to develop magnetic suspension for a centrifuge and finally, with the war over, I was able to finish it. My project was to suspend a small steel ball magnetically in a vacuum to minimize friction and then spin it to very high speeds. How fast could you spin the steel ball bearing until it broke apart? (I was behind a barricade for these experiments!) I used a light beam with a photocell to measure the vertical position of the ball in a glass tube and a feedback system to maintain the ball at a chosen level by adjusting the magnetic field—a “position clamp.” To measure the speed of rotation, a second photocell detected with each rotation a flick of dark from a small ink stripe on the side of the ball. I was able to spin balls at up to 10^8 G before they exploded—100 million times greater than earth’s gravitational force. Working like this with the concept of negative feedback, as in the gun director project, prepared me for my important year to come with Art Vance; indeed, the concept of stable control through negative feedback became central in my future life in research.

During graduate school I had met and married Natalie (Lee) Bayless, who later got her doctorate in biology, focusing on electron microscopy. With my thesis finished, we left for Princeton, New Jersey, where I had taken a job at RCA.

1945–1946: The Year at RCA That Changed My Thinking

Art Vance, Extraordinary Mentor and Master Engineer

At the RCA, where I did the equivalent of a postdoc, I was assigned to the group headed by Art Vance, the inventor of the operational amplifier and analog computer. I was put on relatively minor jobs of calculations for sending up a missile with a payload, but mainly I was learning as Art Vance took me under his wing. Vance was the second of two big, gentle guys who had gone

out of their way to help me. The first was a shop foreman in a woodworking mill where I was an apprentice during one of my high school summers. This kindly man with huge Popeye arms would not only show me what to do but would adjust the jobs to my strength so that I always felt competent and useful. He protected me from socializing with the older guys who were coarse and “spat chewin’ tabacca.”

Vance was brilliant and inventive, yet his common sense was dominating. Among his most important inventions was an extremely constant, roughly 100KV voltage supply which was absolutely required for the stable functioning of RCA’s new product, the electron microscope (EM). At this point RCA was the only company making EMs, in part because Vance was the only person in the world competent to make the requisitely stable power supply. RCA was quite proud of this product; it set RCA apart from other electronics companies. Vance also was a pioneer in loudspeakers and sound canceling. He described his imaginary “father’s Sunday morning quiet box” that he planned would come down around his chair, complete with light and newspaper inside, and have microphones to pick up the kids’ sounds and cancel them with external loudspeakers (think current noise-canceling headphones). It was these sorts of conversations with Vance and the engineers around him, in the big room with about 10 desks, that made RCA such a special place.

The Operational Amplifier

Of all of Vance’s inventions, the most far-reaching and important was negative feedback and the operational amplifier. With “op-amps” it was possible to carry out precise mathematical operations: addition, subtraction, integration, and differentiation.

To demonstrate the power of an appropriately connected array of op-amps, Vance’s lab constructed a 10 x 10 array to solve 10 simultaneous equations. RCA’s marketing arm, naturally wondering who would possibly find such a device useful, offered a prize to any RCA department for the most useful problem the array could solve. Who won?—the accounting department with the question “How much money should we assign to each of 10 different categories of income and expenditure to minimize the tax we pay?” To my knowledge the device was never marketed. Interestingly, the present-day artificial neural networks closely resemble this matrix equation solver—they are built on the same principles.

Vance combined the op-amp with another of his inventions, a high-speed electronic multiplier that used loudspeaker coils to oscillate light metal foils, allowing it to be orders of magnitude faster than the inertia-loaded electro-mechanical multiplier. In the early 1940s there was hope that these devices could be used in the war effort. Buzz bombs directed toward London

presented a special problem. They were so fast that the ram jet motor “buzzed” like a bee. It was impossible to track these bombs with conventional tracking devices designed to follow far slower aircraft. Vance used his new tools to make a tracker that was orders of magnitude faster than anything else available at the time. Although tests in London showed that it could actually track the bombs, the device was not actually used in the war because the equipment needed to intercept the bombs had not yet been developed.

Vance helped me rearrange my mindset so that I would think in terms of currents, which then allowed me to understand how op-amps could be used in biophysics and was crucial to my future work. I had learned about capacitors in physics in terms of the static ratio of voltage to charge (difficult to measure) but had not thought about capacitors from a dynamic point of view, where the capacitor determines the rate of change of the voltage. So now I thought of the current flowing into and out of a capacitor and completely ignored static charge considerations. It is interesting that this small difference in point of view was essential to my understanding of operational amplifiers: with op-amps the currents must sum to zero, so one always looks at the currents rather than the charge.

Later, at Duke, I developed a course with extensive notes on the use of op-amps to make precise analog instruments for a wide variety of needs. When digital logic devices came along, I extended the notes to show how op-amps could be connected to become digital logic elements, revealing the theoretical possibility of designing digital computers from analog devices! My students were enthralled and enthusiastically designed their own circuits. I printed two volumes of paperbound notes and wish I had published what I still consider exciting insights.

Applying the Op-Amp to Physiology

A few years later (1952), after I had entered the field of biophysics, this new understanding of capacitance was crucial in my immediately grasping the Hodgkin-Huxley (HH) equations, written in terms of currents. Since I had been schooled by Vance, it seemed natural to me to look at the equations this way and it was immediately obvious to me that the HH equations would be easily solvable on an analog computer.

Later, when I was using op-amps to make voltage clamp circuits for the squid giant axon, I realized that I could use them to improve on the conventional method of measuring membrane currents (previously used by Hodgkin and Huxley). I introduced the current-to-voltage converter, made of a single op-amp with a resistor in the feedback loop. This is by far the simplest, most precise, and most elegant way to measure current. Many innovations were happening in neurophysiology around that time, for example the capacity-compensation electrometer, and I was thrilled to contribute the current-to-voltage converter, along with the op-amp voltage clamp circuit.

1946–1950: The Medical College of Virginia

At RCA I was beginning to look for opportunities where I might use physics in a more unique way than by pursuing the engineering or mathematics on which RCA was focused. My wife Lee called my attention to an article about the Medical College of Virginia (MCV) and its forward-looking president, who wanted to begin to incorporate the physical sciences into the teaching and research in his medical school. I actually had been thinking of biology as a possibly interesting area in which to apply my knowledge of physics, so I wrote to the president suggesting myself! Certainly job hunting in science is different now! I visited and was offered a slot primarily teaching physics to pharmacy students.

Because space was at a premium at MCV, only a tiny room and a half was cleaned out for me, and these rooms were in the basement of the library. Here I prepared my lectures and built circuits for my research. I also developed close associations with several deeply interesting, forward-looking, and inspiring colleagues and began applying my physics training to biological problems. One colleague was Bob Ramsey, a smart, fun-loving, superb muscle physiologist whose graduate student and eventual wife, Sibyl Street, had dissected out single muscle fibers on which the two of them did length-tension measurements. It was said that Sibyl was the only person in the world who could do this dissection, so Bob had to marry her in order to keep his research going. Like me, Ramsey had a short leg and a limp, so of course I felt this as a bond between us.

Bob had summered at the MBL. He regaled me with stories of the biophysicist Kacy Cole, of sailing, of the fabulous delights of this amazing scientific Mecca. Since he knew that both Kacy and I were interested in electrical measurements of biological tissue, Bob thought that we should get together.

At the MCV I also interacted with George Zur Williams, a pathologist and oncologist. George was on the cutting edge of every one of his interests. As an oncologist, he was a pioneer in the use of radioactive isotopes to attempt to kill cancer cells. I actually helped out at several operations where I monitored the radiation that George was giving a patient. I also measured the flux of radioisotopes across muscle membrane with a jolly, highly respected German muscle physiologist named Ernst Fischer. Ernst had a small grant—almost unheard of at that time—and he was also able to give me some space in his lab. And I published with a dermatological surgeon, Hermann Nachman, who did skin grafts and wanted me to evaluate the quality of the skin by electrical measurements. My electrical impedance measurements of the properties of skin were presented at the meeting of the American Physical Society (APS), where a fateful encounter with Kacy Cole decided my next move and, indeed, the rest of my career. Bob Ramsey had set me up for this crucial meeting.

The Momentous Encounter with Kacy Cole

My APS talk on skin was scheduled as the last talk on the last day of the meeting, probably because the paper was in the “miscellaneous oddballs” session. There were five persons remaining in the room: the previous speaker, the chairman, the projectionist, one tall, lanky unidentified person roughly aged 50 or so with a cigarette hanging from his mouth, and myself. At the end of my talk the chairman uncomfortably asked whether there were any questions and the unidentified person actually asked a good question, revealing considerable knowledge of the topic. I responded: “Under these unusual circumstances would you identify yourself?” And this person responded in his slow drawl, almost as if it were a question: “Ken-neth Cole?”

I certainly knew about Kenneth “Kacy” Cole. From Ramsey I had heard about his adventures sailing Knockabouts in Woods Hole and, most marvelous, that he had crewed on a ship in the Great Lakes and had a sailor’s tattoo, of all things. I had read Kacy’s papers carefully because they presented a unique way of plotting the impedance measurements he had made of the eggs of various sea creatures—in fact I had plotted my data the same way. The notion of being a biophysicist by the sea was a romantic one for this young land-raised Winston-Salem native.

I responded, “Since I have read some of your papers, I can answer accordingly,” and then proceeded with my answer. Evidently the answer was satisfactory because Kacy waited for me to get my slides from the projectionist and we walked out together.

He said, “You know, I am in administrative work now (he was Scientific Director of the Naval Medical Research Institute, the NMRI) and I don’t get to do any lab work anymore.”

I said, “Yes, I had heard that from Bob Ramsey.”

To my surprise he said, “I would like to start my lab up again—would you run it for me?” He was that way—first impressions were terribly important with Kacy.

I replied, “Well, if I were to accept your offer, could we go back to Woods Hole in the summers as you used to do?”

“HMMMMM...(30-second pause)...OK,” said he.

“I accept,” said I.

From reading his papers I knew this was the sort of thing I was truly interested in, and he needed help. There were not many people available for him to choose from with my training and interests and at the right age! So the symbiotic deal was obvious to both of us and thus it happened very quickly. I had to pass a government service exam (GSA) to get my ranking as a civilian scientist but that was not too difficult. Clearly the Cole-Moore conversation occurred before the days of affirmative action.

1950–1954: The Naval Medical Research Institute

I moved to Washington, D.C., during the next summer (1950). Woods Hole was out of the question this first summer since the lab had to be set up from scratch. All that Kacy had brought with him to the NMRI from his previous institution, the University of Chicago, was his original Wheatstone bridge, made by Hewlett and Packard in their garage, (!) and an oscilloscope. So I designed chambers and bought a microscope; there was a small relay rack holding an oscillator, whose amplitude and frequency you could change, as well as the infamous Wheatstone bridge, a wide range of capacitors and resistors in both fixed and variable values, and the experimental preparation, frog muscle. These were all the tools necessary for impedance measurements.

Measuring the Impedance of Frog Muscle

A new Navy Lieutenant J.G., H. W. (Tony) Shirer, was assigned to work with me. Tony was smart, cheerful, and knowledgeable about electronics and simulations and we both enjoyed our time together at the NMRI. As one of our first endeavors together, Tony and I were able to continuously superfuse a sartorius muscle for more than a month! The muscle was mounted between two plates over which cellophane (from Kacy's cigarette box wrappers) had been stretched to protect the metal electrodes from degradation due to contact with biological molecules. Water and electrolytes could pass through the cellophane but not the molecules from the tissue. With this chamber we made electrical measurements of impedance, at first over short intervals and then daily for a month. At the end of the month we weren't sure if the fiber was actually still alive or if we were just measuring the system. So we took out the fiber, stimulated it, and it contracted! By including antibiotics we had made an excellent culture system, but the muscle fiber was really not a good project. The changes in impedance we observed in different solutions were very small and the interpretations were difficult, so we never wrote a paper.

During this time I sat on a biomedical engineering committee of the IEEE (Institute of Electrical and Electronics Engineers) with an inventive engineer named Wilson Greatbatch. In his shed, Wilson had developed the electronics and encapsulation of the first implantable pacemaker. (He licensed it to Medtronic and continued to improve its design and built-in battery; he went on to develop batteries with lifetimes approaching a decade for implanted devices.) He told us that the electrodes in contact with tissue deteriorated with age, a serious problem. Based on my experience with the frog muscle, I suggested cellophane or a similar material. I always wondered whether he took the suggestion and whether our efforts had in some small way aided pacemaker design. When I recently received my own pacemaker, I wrote a letter of thanks to Wilson—who wrote back and sent me a copy of

his book describing the extensive materials and tests to achieve long-term durability for implanted electrodes (Greatbatch, 2000).

Detection of Frostbite

At the NMRI was a young officer named Harold (Harry) Meryman, an M.D., who had joined the Navy to avoid going to the Korean War. He was a smart guy, a colorful character, quite sloppy, and therefore rather uncomfortable in the Navy uniform. His uniform tended to get filthy, particularly the white cap. There were inspections, times when all officers and corpsman had to be present and in good form for visiting, high-ranking officers. Meryman would forget about inspections until the last minute—so he would put chalk on his cap with a blackboard eraser. Meryman chose to live in an old abandoned canal-lock operator's cabin along the Potomac. This way he could live in natural surroundings, with wild animals around him, but close to the lab.

Harry was interested in the use of quick freezing in liquid nitrogen to preserve cells, and their subsequent recovery. I remember him showing me how he had preserved autumn leaves in full color by replacing the water in the leaves with glycerol. In particular he worked on the preservation of blood for transfusion by freezing. Inspired by Harry, I became intrigued with the possibility of freezing a bit of muscle in liquid nitrogen and restoring it to life. I made a tiny frame of Lucite, in the shape of a pipe wrench, so that the frog's sartorius muscle could be stretched over the top and frozen in glycerol. It worked; the muscle was alive when we warmed it up! One problem: upon warming, it contracted and broke the frame holding it.

An urgent message from the field came to Naval Medical about horrible frostbite in the Korean War: Is there any way you can determine whether soldiers and sailors have frostbite and its depth? By now radar was well developed and Harry and I wondered whether you could see a difference in the reflection of microwaves from normal versus frostbitten tissue. Since we were at a real naval station, we were able to scavenge a microwave generator, a detector, and the necessary waveguides. What would we use as frozen tissue? A piece of prime beef from the officer's mess was perfect. So we froze the surface in liquid nitrogen, hypothesizing that reflection of the microwaves would not occur until they got to live muscle where there were electrolytes (a conducting surface), and we would then observe a longer delay in the reflection. It worked! We reported the result (Meryman and Moore, 1953) and Harry was immediately shipped to Korea, although the fighting was over before he had a chance to use the method in the field.

Harry continued his experiments with freezing and reviving blood cells in the American Red Cross Lab he established at NMRI. He published a landmark paper for cryopreservation of red blood cells, a method still used around the world to save countless lives. This founder of the field of cryobiology moved on to study transplantation rejection and performed the first

experimental human tissue transplant on himself (typical Harry!). He was a truly marvelous guy and friend who died earlier this year before I had time to call and talk with him about my comments here.

Other Experiments and Colleagues at the NMRI

A biochemist named Nachmanson now entered the scene. Despite the beauty and universal acceptance of the HH equations, he was convinced, indeed obsessed, with the idea that acetylcholine was the basis of the propagation of the action potential. Nachmanson went to great lengths to argue with the many experiments that showed otherwise. One experiment was to apply acetylcholinesterase inhibitors to the sciatic nerve to see whether they blocked the action potential. Of course, they didn't. But Nachmanson then claimed that the inhibitors did not block the action potential because they did not get through the sheath. To many scientists, the Nachmanson idea seemed absolutely ridiculous, but he argued it quite publically and had to be reckoned with continually. I set out to try to squash the idea once and for all.

Here was my plan. Manuel Morales at the NMRI had brought an excellent chemist named Seymour Friess to the Cole lab. I persuaded him to join forces to stop Nachmanson. I had read that you could desheath the sciatic nerve of frogs by pulling off the sheath like a stocking. So Friess, my technician Whitcomb, and I dissected out the sciatic nerve of bullfrogs, measured the velocity of propagation of the action potential, stripped the sheath off, put acetylcholinesterase inhibitors on the nerve, repeated the measurement, then pulled the sheath back up and repeated the measurement once again. There was, of course, no change in the propagation with the inhibitor (Whitcomb et al., 1958). On the way to one of the first International Biophysical Meetings, held in Stockholm, I visited Bernard Katz and told him about my results with the desheathed sciatic nerve. We talked about his scathing review of Nachmanson's book which had recently come out. How could Nachmanson be so completely backward, arguing that acetylcholine was the basis of nerve propagation but did not work at the synapse (where, of course, it is the neurotransmitter)? Katz was very cordial, a person who did not seem to take himself terribly seriously, and we became good friends.

Next door to our basement lab was the lab of Morales and his student Joe Blum, an extremely energetic, delightful guy who had just come from the University of Chicago. Joe and I would renew our friendship when he later joined Dan Tosteson's department at Duke. From Joe I learned some interesting information about Kacy. In Chicago Joe had known George Marmont, who had made sophisticated electronic equipment for experiments in collaboration with Kacy when he was still in Chicago. It was Marmont who had first had the idea of putting the axial wire down the axon, causing quite a stir when he referred to it as a "rape" of the axon. He also had the idea for

the guard chambers. In particular, Marmont had made a current clamp for their MBL studies of the squid axon. When Kacy saw the current clamp equipment in use, he realized that voltage control offered a better method than Marmont's current clamp to understand the basis of excitation. But Marmont did not appreciate the extraordinary possibilities of the voltage clamp.

Joe told me that Marmont and Cole could not get along personally. Perhaps personal animosity kept Marmont from realizing the power of the voltage clamp, but he was so stuck on using current clamp to study the action potential that at the MBL the two collaborators had to split up the day. Marmont worked by day with the current clamp, recording many action potential shapes, but he was unable to understand the underlying processes. Kacy worked at night with the equipment switched to voltage clamp mode, recording only a precious few currents, but he was unable to interpret their roles in excitation. Hodgkin, then, visiting the MBL, recognized that Kacy's voltage clamp was the key to solving this fundamental problem. Kacy and Marmont published separately and later Marmont quit academia.

Other colleagues with whom I interacted at the NMRI were Terrill Hill, a very smart, mathematically oriented physical chemist; Dave Goldman, who as a graduate student under Kacy developed the membrane equations that bear his name; and Fred Julian, who worked in Goldman's lab and developed the sucrose gap technique with me.

Woods Hole and Hurricane Carol

Kacy kept his promise to go to the MBL, but each summer for the first few years was too short to make progress beyond finding the limitations of our squid chamber. It was in one of these first summers, in 1952, that Hurricane Carol sneaked up on us.

We were in the lab and I noticed that the water squirt bottle started to squirt on its own. I relieved the pressure and it started squirting again. A few minutes later I looked out the window and saw the ferry rushing into port and slamming against the dock—and there was the bottle squirting again! Clearly the barometric pressure was plummeting. It was at the time quite puzzling; the weather information in the early 1950s was poor. We had heard radio reports of a hurricane off Cape Hatteras, but it was said to be moving slowly. Everyone had come to the lab thinking that if it were to target the Cape it would take several days to travel that distance. The rising wind that morning had been out of the northeast, so people dismissed the blustery weather as a standard nor'easter.

But it was indeed Hurricane Carol, bringing disaster that lives vividly in the memories of everyone who was in Woods Hole at the time. She hit at full force at high tide. We were in the lab on the third floor of Lillie building where everyone had been doing experiments, oblivious to the danger.

Water started pouring over the seawall and into the basement of Lillie. This hurricane caused extensive damage and ended the scientific effort that summer.

Next summer, 1953, one of the first things Kacy and I did together was to use the new microelectrode technique to measure the voltage in the giant axon *in situ* in a squid that had been opened up and laid out flat. We wanted to know if the action potential *in vivo* was the same as that in the isolated axon. I got help at the MBL from Steve Kuffler and Carlos Eyzaguirre in penetrating the axon with microelectrodes that had to traverse the surrounding tough sheath. I had noticed in previous summers that dissected axons tended to run down with time; as they deteriorated, they depolarized and the undershoots of their action potentials became larger. We found that there was no undershoot *in vivo*, evidence that the undershoot in the isolated axon indeed represented a degradation to a lower resting potential from dissection time or damage.

The main consequence of these first few MBL summers was to remind Kacy that being at the MBL was what he loved—sitting at the setup in a Lillie lab, humming, dissecting, and doing experiments. Kacy's pleasure in dissecting and experimenting led within a few years to his quitting his administrative post at the NMRI and moving across Wisconsin Avenue to the new Building 10 of the National Institutes of Health. He took the position of Lab Chief with a decrease in responsibilities and salary; here he could return to experimenting. I went with him, pleased that I was the force that got him back into active science. At the NIH, Kacy was Chief of the Laboratory of Biophysics under Seymour Kety, the Director of the National Institute of Neurological Diseases and Blindness (NINDB). Kety, eyeing Cole's enthusiasm for his reduced responsibilities and his pleasure at working in a smaller setting, became intrigued with the notion and stepped down from the Director's position to head a laboratory himself!

1954–1961: The National Institutes of Health

Moving from the NMRI to the NIH

We didn't have much equipment to move from the NMRI to the NIH: just the old AC Wheatstone bridge, a microscope, an oscilloscope—practically nothing. Fancy electrophysiological setups with racks and isolation tables were not standard equipment in 1954. I have a vivid recollection of standing at the entrance of Building 10, an enormous new edifice, with a marbled foyer to inspire awe, and realizing that now everything was available to us: space and excellent facilities. So now I had to perform—no excuses! We had not only more space but very good mechanical and electronic shops and we could start to make a real electrophysiological laboratory. In this huge building at the time were Mike Fuortes, Kay Frank, and Charlie Edwards.

Eric Kandel was upstairs doing a postdoc with Wade Marshall (whose wife Louise helped found the Society for Neuroscience and actively recorded the history of the field).

This big building had come about because of the generosity of Congress. According to the NIH Web site, the NIH budget had expanded from \$4 million to \$100 million from 1947 to 1957, and the building was part of this expansion. In 1955 Jim Shannon became the Director of the NIH (1955–1968) and under his leadership it expanded even more, resulting in the “Golden Years” of the NIH. The story is frequently told that when Shannon would present the NIH budget to Congress, Lister Hill from Alabama and another forward-looking senator would say, “Jim—are you sure that’s enough?” Even if Shannon said his budget was enough, Congress would give him 25%–50% more, repeating this interesting phenomenon over several years. Why was this time so good to research? It was an expansive time—computers were just appearing and Sputnik had spurred extraordinary interest in science when it was launched in 1958.

The NIH shops were run by an efficient guy named Mike Davis, who assigned a young ex-Marine named Ed Harris to work with me. Ed devoted much of his time to making electrical and mechanical devices that I designed for Kacy’s and my research at the MBL. Because Ed’s work was excellent, when I moved to Duke in 1961 I proposed for him to be the department’s instrumentation person. In time at Duke I was able to employ him full time to work on voltage clamp projects until he died from cancer at a tragically young age.

Voltage Clamping Squid Axons at the MBL

With the move to the NIH we finally settled into a routine where we worked at the MBL in the summer months, typically from mid-May to mid-September, and at the NIH in the “off season” winter months. Kacy could go to the MBL for a longer time now that he no longer had administrative responsibilities. Experiments were done primarily in the summer. Back at the NIH in the winter, I read the scientific literature, analyzed the results of the previous summer’s experiments, planned the experiments for the upcoming summer, wrote manuscripts, updated equipment, and in general prepared for the intense experimental work at the MBL.

The first productive voltage clamping was at the MBL in 1955 or 1956. We employed Cole’s previous chamber where the axon was arranged lengthwise in a 1-mm slot that traversed three major saline pools (two guard pools and the central measuring pool), the axon draped over the ends. At one end Kacy would make a tiny snip, insert the axial wire, and thread it down the interior.

Enormous effort went into making the electrode. Even though extremely fine, it had to be stiff and straight, and carefully electroplated for low

surface resistivity. There were several different plating methods; we had to search for the best method to make the resistivity as low as possible. After a long, careful dissection . . . well, let's discuss "long." Kacy's idea of how to dissect an axon was to work slowly and carefully because when working with Hodgkin, he and Alan had once found that a very long dissection gave the finest result. On the other hand, Jose del Castillo, with whom I worked a few years later, dissected quickly with far greater manual dexterity and his axons typically gave excellent results.

Insertion of the internal wire was hazardous because when Kacy nipped the axon to put in the wire, any bathing seawater (containing calcium) contacting the internal axoplasm would quickly degrade the axon, turning the gelatinous axoplasm into soup. Also, simply making sure that the wire was properly aligned with the chamber took time and there was much cursing as the wire was inserted. But I think Kacy simply relished putting in this wire, humming and cursing, enjoying every minute of the hour or two he took to insert it. The yield of good axons, however, was quite low—perhaps one per day or two.

Kacy was a fine mathematician but not particularly knowledgeable in electronics, which was my strength. Now that I was at the NIH, I could design electronics and have instruments built to my specifications by Ed Harris. Because of my training with Art Vance at the RCA, I knew how to produce a high precision voltage clamp circuit with operational amplifiers. By the time I moved to Duke in 1961, op-amps became commercially available so I could use them rather than having Ed build my own op-amps.

I actually was able to improve on the quality of Hodgkin and Huxley's voltage measurements. First, I impaled the axon with a microelectrode, measuring the difference in membrane voltage between this microelectrode just under the membrane and a larger reference electrode outside. Hodgkin and Huxley's voltage sensor, the axial wire, was both physically and electrically remote from the inside of the axon's membrane. Membrane current flow through the intervening axoplasm produced a voltage drop across its resistance and thus introduced an error in their membrane voltage measurements. Second, I used an amplifier developed at MIT and shown to me by Jerry Lettvin, a brilliant and iconoclastic physician, engineer, neuroscientist, and poet, who visited Kacy from time to time. During these visits Jerry and I became very fond of one another. The MIT amplifier incorporated ultra-high input resistance as well as a circuit that compensated for the capacitance across the glass wall of the microelectrode. So with this more precise measurement of voltage I could now control the voltage across the membrane rather precisely.

I was also able to improve the measurement of the membrane current. Hodgkin and Huxley had measured the current by the voltage drop across the resistance of the bathing solution, but I realized I could measure current directly with a current-to-voltage converter. Art Vance never knew that,

through his influence on me, he made a major contribution to the design of this wonderful new technique in neurobiology, membrane current measurement using the voltage clamp.

Back at the NIH in the winter of 1956, I was joined by Jose del Castillo, a Spaniard, who was one of my favorite collaborators of all time. He was swarthy, athletic, handsome, and delightful to work with. Jose was also extremely dexterous, with a sharp intellect to match his facile hands. We were somehow perfectly compatible. Jose had trained with Katz in England and then had worked for a few months with Jerry Lettvin at MIT. Jose and Jerry had tried to study the frog node following a method similar to that of Frankenhauser and Dodge. I thought that Jose and Jerry's system had problems since their records looked curious, so I proposed that Jose and I join together and use electronic feedback in order to measure the nodal currents more accurately.

We set up a "Vaseline gap" clamp to record currents from a single node of a single axon dissected from frog sciatic nerve using Vaseline as a seal on either side of the node. A major problem was that the resistance of the seal could never be high enough for us to measure the voltage across it accurately because there was always fluid between the Vaseline and the myelin sheath. So I designed an electronic feedback circuit to increase the effective resistance enormously by electronically forcing the voltage drop across one of the gaps to be minimized to a few microvolts. Jose and I published this circuit under the title "An Electronic Electrode" (Moore and del Castillo, 1959).

Then, at the MBL the next summer, Jose and I did a simple experiment that led to more ramifications than we expected. We inserted an axial wire into a squid axon and measured the velocity of propagation of the action potential from one end of the wire to the other. As expected, the time for the action potential to travel from one end of the wire to the other was essentially zero because the wire had short-circuited the axon's internal resistance and the region in which the wire was located was now isopotential. But, unexpectedly, the waveform of the spike became more and more unusual as it approached the region with the wire, reflecting its difficulty of propagating into this region. I later followed up these experiments with Monte Westerfield at Duke to establish the importance of geometry in the generation and propagation of action potentials.

At the MBL, Jose and I would experiment in the morning, plan our next experiments at Nobska Beach after a swim, draw the plans in the sand, and then return to the lab mid-afternoon to carry out the experiments we had just discussed. This relaxed routine was marvelously productive and in part it worked because Jose was so very quick with his dissections. We also started a tradition: when we had a good axon, we would throw it to the ceiling like a piece of cooked pasta, and there it would stick, the threads we had used to tie off each end hanging down like tiny stalactites. For years these axon threads hung from the ceilings of the labs we rented each summer!

Committing to the MBL

In the 1950s, the MBL decided to offer parcels of its substantial land holdings in Woods Hole to scientists in the hopes of seeding a community that would return to the Laboratory summer after summer. In 1955 I jumped at the chance to buy a lot on F.R.Lillie Road (for \$800!) when it became available. Dozens of other investigators bought parcels on Lillie and Wilson Roads—a mass migration of scientists to a summer settlement. I hired a carpenter to put up a shell of a house, as some of us did, and then my task was to complete the interior. Nobody had much money, so many of us had to build the interiors of our own houses. By this time Lee and I had adopted three children (Reid, Marjorie, and Steve) and you can't imagine what it was like to try to do experiments, build a house interior, and deal with a family. But now all of us scientists were in the same wonderful situation, with our own house in Woods Hole and the expectation of many future summers in this inspiring environment. We had an immense gratitude for the chance to work at the MBL and tried to give back to the Lab over the ensuing years by working on committees and as Trustees, and eventually donating money.

Wintering Back at the NIH

Back at the NIH, Dick Fitzhugh and I were joined in the Cole lab by a mathematician named Knox Chandler. Knox was engaging, generous, and fun—just a delight to be around. He was lucky to be able to go to Cambridge off and on to work with Hodgkin. In particular he, Hodgkin, and Richard Adrian published a very important paper (Adrian et al., 1970) in which they used three electrodes to create a space in a muscle fiber where there was uniform voltage and then measured the current in that part. It was an ingenious application of the voltage clamp to a preparation that had appeared impossible to clamp because of its contractility.

The paper of Knox's that had most impact on me was one with Hodgkin to solve the problem of the erroneous amplitude of the action potential, where it surpassed the equilibrium potential for sodium ion (ENa). This error by Kacy (Curtis and Cole, 1942) set back progress on understanding the action potential for several years; later, in a series of papers, Ichichi Tasaki again reported huge amplitudes that called into question the voltage clamp work of Hodgkin and Huxley.

The conventional way of measuring the action potential at the time was with the axon's glass cannula, drawn out into a long, small-diameter capillary. The cannula was about the diameter of the axon, but at the point of insertion it narrowed into the capillary, which was threaded along the axon's axis. The capillary was filled with conducting solution; a wire back in the cannula measured the internal voltage picked up by the capillary. Hodgkin had realized that there would be a time delay in measuring the action

potential via this long capillary because its high internal resistance would slow the voltage signal. So he, with Huxley (1945), and then with Katz (1949), inserted a wire to short-circuit this resistance. Hodgkin must also have been aware that there would be a capacitive current flowing through the glass wall of the cannula into the electrometer when the action potential reached the end of the axon tied to the cannula. Thus, as the action potential traveled up the capillary into the cannula, the capillary's high resistance and cannula's capacitive current combined to produce an erroneously large action potential.

Spurred by Tasaki's continued publication of oversized action potentials, Chandler and Hodgkin (1965) published unequivocal evidence of capacitive current artifacts; they showed records similar to Tasaki's that overshoot ENa using his method, then action potential records that never exceeded ENa when the wire was present in the capillary. In our correspondence, Huxley has asked whether I have insight into how Kacy could have made his error of the strangely high action potential. Although Kacy proposed that his was an error from overcompensation for capacity, it seems to me that his error was the same as Tasaki's: the lack of the short-circuiting wire in the capillary.

Colleagues at the NIH

There were many splendid colleagues at the NIH. I particularly enjoyed interactions with Kay Frank and Mike Fuortes—I liked to look at their data, talk circuits, and exchange manuscripts with them. They had started to voltage clamp spinal motoneurons of the cat, working together off and on, so their experiments were closely related to mine. Their experiments derived from those pioneered by Jack Eccles (later Sir Jack). Jack's recordings made him think that the impulse initiated in the initial segment, the portion of axon between the hillock and the myelin, because of a lower threshold there (Coombs et al., 1957). Kay and Mike came to the same conclusion and actually drew a published diagram assigning a lower threshold to that region. In their simulations, Fred Dodge and James Cooley altered the parameters of the HH equations so that the threshold for the action potential was lowered in the motoneuron's initial segment in their simulations.

Later, I became quite intrigued with this problem and took it up with Monte Westerfield; he and I showed in both experiments and simulations that morphology alone could cause the impulse to be initiated at the region where the large-diameter soma became a small-diameter axon (analogous to the initial segment). But when Monte and I tried to publish the hypothesis that geometry alone could explain impulse initiation at this juncture, my good friend Fred was the referee and rejected our paper! We argued our case; he argued in response that if readers were presented with two groups (him and us) doing simulations of the same process, yet disagreeing, then

they would be prejudiced against simulations! Monte was quite careful with the wording, I asked to have a new reviewer, and the paper was accepted.

At about this time Ladislav Tauc visited Mike and Kay from France. He was putting electrodes into the huge cell bodies of *Aplysia* neurons and finding that the action potentials recorded there were quite small. His explanation for these diminutive action potentials was that there must not be many channels in the soma, making it difficult, if not impossible, for the spike to invade from the axon. But the records looked just like my records, taken with Jose, in which we had put a wire down the axon to mimic a soma. We found that as the impulse struggled to invade this “soma” section of axon, its amplitude was smaller and had a curious shape. So I felt that the change in geometry might explain Tauc’s observations rather than a decreased number of channels. Tauc’s observations added to those of Eccles, and of Frank and Fuortes on the motoneuron, in ratcheting up my interest in how a neuron’s impulse might propagate or fail to propagate into its component parts. What happened to its waveform at branch points? At transitions between myelinated and nonmyelinated sections? Monte Westerfield and I would revisit this question later.

Jack Coombs, a splendid electronics engineer, visited us from Jack Eccles lab in Australia for a few months. Coombs’ skills made us realize the utility of having an electronics engineer, so when he went back to Australia we hired John Gebhart to work on these very high impedance preamplifiers (also called potentiometric circuits) to measure potential. The sharp microelectrodes we were using to read the voltage just under the membrane required a special circuit because the preamplifier tubes had a capacitance to ground. We were using a capacitance compensation circuit previously shown to me by Jerry Lettvin; it was described in the Report of War Research from his Research Lab of Electronics at MIT (in the Plywood Palace, Building 20, sadly now demolished). John Gebhart and I worked out an analog simulator of this negative capacitance circuit—the first simulation of a circuit and perhaps the first time I worked back and forth between a simulated circuit and the real thing. John and I published a paper on the simulation of the circuit (and of course we made the circuit itself) to demonstrate the principles for capacity compensation. We also simulated (and made) a “chopper circuit” that drastically reduced the DC drift; the chopper converted DC drift into a square wave whose amplitude could be minimized by negative feedback.

Jerry Lettvin and the Frog’s Eye Paper

The Institute of Radio Engineers (IRE), that later became the IEEE, wanted to have an issue of its journal devoted to biomedical engineering. At the suggestion of Britton Chance, I was asked to be a guest editor. I invited Jerry to write an article on his high impedance preamplifier for measuring voltages

with microelectrodes. In the spring of 1959, as I left the Federation Meetings to board a plane, I met Jerry getting off the plane to come to the same meeting. He yelled “John—I’ve got a very special and important paper and I want to publish it as soon as possible. Can you please include it in your special issue?” I agreed to consider it as soon as he completed his assigned article. He accepted the challenge and brought the manuscript to Woods Hole that summer to show me. I read it and realized it was indeed ground breaking, but the title was quite boring, unworthy of such a remarkable paper, and would not attract readers. I thought that perhaps the title had been written by one of his coauthors, Walter Pitts or Warren McCulloch.

John: I ACCEPT the paper but REJECT the TITLE, which is certainly not yours.

Jerry: That’s true.

John: Then give me a better title in your own words.

Within milliseconds, Jerry came up with his now famous title: “What the Frog’s Eye tells the Frog’s Brain.” I wrote this title on the manuscript and, as guest editor, accepted it: no further review, no delay, only one revision—the title. This is a more complete telling of the story of how this memorable title came about than appears in Jerry’s Autobiography (Volume 2 of this series, p. 235). There he wrote a paragraph entitled “The Frog’s Eye” in which he refers to the title with the parenthetical statement (for which I am much indebted to John Moore).

Although this classic paper was published in 1959 in an obscure journal for neuroscientists, it is now widely known and referenced.

I Leave Kacy’s Lab

Kacy was running out of scientific ideas and being more and more difficult to work with. I was becoming increasingly restless in the lab and indeed was spending much of my time now back at the NMRI, working with Fred Julian in Dave Goldman’s lab to develop the sucrose gap. Kacy didn’t bother to interview or even inquire about people—he just used his first impressions. He was fixated on mathematicians, offering a job to Robert Taylor (who had been a postdoc with Huxley) sight unseen. On the other hand, he did not take Abe Shanes, a pharmacologist and enthusiastic guy working at the NIH who would have contributed a badly needed, broader perspective to the lab.

The situation between Kacy and me deteriorated. The final straw was when Kacy made Robert Taylor the author on work not done by him but by del Castillo and me. Robert had suggested to Jose and myself, as we were headed to the MBL, that it might be interesting to try procaine on the squid axon. We did this experiment, made figures (I still have the originals), wrote up the results, gave the manuscript to Kacy to read, and the next thing we

knew was that Kacy had made Robert the sole author on the paper! I was furious. Jose and I had done the work—what right did Taylor have to author this paper when he hadn't done the work? When he hadn't written the paper? I could no longer work under these circumstances and had to leave.

1961–1968: TTX and the Sucrose Gap at Duke

As I started looking for other jobs in the Bethesda area so as not to move the family, an opportunity became available to do postwar research at the Johns Hopkins Applied Physics Lab in Silver Spring, MD. The job did not really interest me, but I had said a tentative yes anyway—I was absolutely intent upon leaving Kacy. But a few days later I received a call from Dan Tosteson, who had been in another lab at the NIH. He and I attended biophysics seminars together and, by the questions he asked, I knew he was a most remarkable person. In his call he said he was accepting the chairmanship of the Departments of Physiology and Pharmacology at Duke and wanted Paul Horowitz and me to join him there and in fact his taking the chair was contingent on the two of us joining him. The Duke opportunity—doing the biophysics I enjoyed, being in a university setting, being close to my parents, and with Dan as Chair—was irresistible.

From the beginning of his Chairmanship of the two departments at Duke, Dan's focus on research, his own and that of the faculty, was either matched or exceeded by his intention to improve medical education. Dan played a key role in changing the medical curriculum, both at Duke and also as dean of Harvard Medical School where he completely reoriented its curriculum to a model now being followed by other medical schools as well.

Beginning at Duke

The dean of Duke's medical school, Barnes Woodhall, was the host of a "recruiting dinner" for me, held at the Hope Valley Country Club where he was a member—the most elegant setting in town at the time. At this dinner were: Dan, the future dean of Harvard Medical School; Phil Handler, Chair of Biochemistry and future president of the National Academy of Sciences; and Jim Wyngaarden, future director of the National Institutes of Health!

Phil later (1963) asked me whether I would take his son Mark to Woods Hole to work with me at the MBL for the summer. Of course I took Mark—with unexpected and far-reaching consequences having to do with his parents, Phil and Lucy. They came to visit Mark in Woods Hole, were smitten with the place, and began to take their vacations there, renting houses. Shortly thereafter Phil was named president of the National Academy. When the Academy was looking for a place to hold conferences and an estate became available on Quissett Harbor (next to Woods Hole), a gorgeous

setting on a promontory overlooking the harbor and Buzzards Bay, Phil grabbed it for the Academy.

And that was not the end of my influence through providing opportunities for scientists' sons. DeWitt (Hans) Stetten, Jr., who would eventually become Deputy Director for Science at the NIH, heard from Phil that I had taken Mark and thought the opportunity would be great for his son George. So of course I took George, who went on to become a professor of Bioengineering and Robotics in Pittsburgh. Hans had been bringing his family to Woods Hole every summer since the late 1950s. The magic of Woods Hole is irresistible, it seems.

Working in Duke's Bell Building

I started at Duke in the fall of 1961 and Ed Harris came with me. Ed, a former Marine was proud of being tough but was extremely gentle and kind, not the Marine stereotype. Like other Marines, he had tattoos on his arms; later, when he drove a 24-foot U-Haul to Woods Hole filled with racks of expensive electronics and huge wooden boxes packed with scientific equipment, he deeply enjoyed the responsibility, driving the 15 or so hours straight through in his Texas boots, and arriving triumphant at the MBL loading dock at precisely the predicted moment. One year he even thwarted a possible hijacking! In time, Ed and I constructed tool cabinets and equipment boxes that rolled on heavy duty castors for rapid loading and unloading of the truck in my lab's annual migration to the MBL. We would even transport to the MBL some shop equipment such as a drill press and a Minimax (a combination of a lathe and a milling machine) because we frequently modified equipment as we did experiments. Ed took special pride in building my voltage clamps. I would try out his clamp at Woods Hole, redesign it after a summer's work, and then he would modify the design in the winter.

These first years at Duke were in the Bell building, an old dilapidated structure I detested because the cancer researcher who obtained the money for it was a racist who insisted on "his" building having black and white restrooms. In the spring of 1961, in preparation for my fall arrival at Duke, I had discussed the renovation of my space with the building planners and expected that it would be completed when Ed and I arrived in the fall. But instead we found that absolutely nothing had been done. Inquiring why, I found that "they were just waiting to be sure that it was exactly what I wanted." Furious, Ed and I did it ourselves. In those days we had a great deal of freedom with the building code. Certainly that sort of unprofessional construction in a lab would not be allowed now.

The Sucrose Gap Chamber

Following our own lab renovations at Duke, Ed reproduced the precision electronic circuits and equipment that had been carefully worked out at

NIH. He also built two sucrose gap chambers, one for lobster axons and one for squid giant axons, both chambers improving on that first one designed and used at NMRI for lobster axons. The squid axon chamber allowed exploitation of the squid axon's increase in diameter and length over that of the lobster in three major ways:

1. While the exposed length of the “artificial node” (between the streams of flowing sucrose) was about the same as for lobster axon, it was a much smaller fraction of the overall length of the squid axon. Thus, the voltage uniformity in the squid axon “node” was far superior to that for the lobster.
2. The surface-to-volume ratio for a length of squid axon was far smaller than that for the lobster. This allowed us the luxury of much longer experiments before axoplasmic ions leached into the flowing sucrose, degrading the quality of the voltage control of the “nodal” membrane.
3. We were able to add a sliding holder for the axon, allowing the axon to be translated longitudinally through the flowing streams.

These factors together provided great flexibility and dramatically increased our experimental success rate as well as the ratio of experimental to dissection time.

For example, one could avoid spots along the axon that had been damaged during dissection and choose very active areas for the node. Furthermore, a fresh area of axon node could be chosen for the next experiment. This made possible repetitions of a single protocol on a single axon—analogueous to an assembly line. In contrast, the axial wire voltage clamp had required that the dissection of the whole length of the axon be damage-free, greatly reducing the probability of a successful experimental day.

Discovering the Action of TTX

I had heard Toshio Narahashi talk a few times at meetings and was intrigued that in Japan he had used the infamous puffer fish poison tetrodotoxin (TTX) on muscles and found that they were no longer excitable. TTX is the poison well known in Japan to be concentrated in the ovaries of this tasty fish. Chefs must be trained in the careful removal of the ovaries and preparation of the fish; should they make a mistake and cause a death, they in turn are expected to commit *hare kare*. Minute quantities of TTX can kill a person: the first sensation is a numbing of the lips, followed in a short time, depending on how much one had consumed, by paralysis of the nerves and muscles of breathing. So TTX was thought to act on nerves in some fashion.

Toshio thought that TTX might act by blocking the sodium conductance in nerve and muscle. Since I was studying sodium currents in axons, he and I had a mutual interest in applying TTX to axons in voltage clamp to test this hypothesis. He joined me at Duke and we, along with a medical student, Bill Scott, worked on axons from lobsters purchased at a local fish market. In spite of the disadvantage of ion depletion from the lobster axons in the sucrose flow, necessitating brief experiments, we showed a definitive block of the sodium current and nearly full recovery on wash out. Fortunately, TTX's action is clean, precise, and unequivocal, so we did not need to do a large number of controls for a definitive answer and my first TTX paper (Narahashi et al., 1964).

Toshio then came with me to the MBL the next summer and we continued the TTX work but on the squid axon, generating the first in what would be a series of five papers. In the squid axon, TTX reproduced the data we found on the lobster axon; again the results were clean and unequivocal. Ironically, the downside of this almost perfect poison was that there was no controversy in the literature about its action and very quickly it was subsumed into the neurophysiologist's tool kit much like an amplifier or oscilloscope. Soon it was not necessary to reference our papers and Toshio and I were forgotten, it seemed! Well, perhaps not entirely: Some 20 years later there was a meeting devoted to TTX and saxitoxin (STX) where Toshio and I were guests of honor. We were appreciative, having felt somewhat slighted at the beginning of the "TTX era."

Actually, there was one small, incipient controversy, but one with a delightful outcome. At a meeting, Mordy Blaustein (who had replaced Fred Julian in David Goldman's lab at the NMRI) reported that TTX blocked only at voltages below E_{Na} but not above it (in contrast to our published work). Because Mordy was working with lobster axons, using the original chamber that Fred Julian and I had designed for these nerves, he may not have understood that ions could be leached from this small-diameter axon and confound his observations. It was very important to resolve this difference. So I invited Mordy to come to Woods Hole and do experiments with Toshio and myself on the squid axon. I made it clear that I wanted us to be able to agree on the data but that he would be free to publish separately if he did not agree with our interpretation. Working together, we three confirmed that Toshio and I had been correct: TTX blocked the currents whether the Na current was flowing out or in through the channels. I strongly recommend this sort of approach as a good way to avoid unnecessary controversy for we quickly solved the problem, had fun, were coauthors on two papers, and have stayed best of friends ever since.

Toshio had to leave me after our first year together because his visa had run out. Two years later he returned as an assistant professor and eventually occupied space adjoining mine when we moved to the Nanaline Duke building in 1968. At this point he began to run his own lab and we did fewer

projects together. Later Toshio became chair of the Pharmacology Department when it finally split off from Physiology. I have continued to be amazed by, and envious of, Toshio's efficiency in everything he does. Toshio frequently would have collaborators come for only a single day with assurance of success in an experiment. I could never be so confident.

During Toshio's absence, another Japanese scientist, Mitsuru Takata, joined me and a Chinese neuroscientist, C. Y. (Eric) Kao, visited from Stanford. Eric brought yet another toxin, tarichatoxin, extracted from the eggs of a California salamander by two Stanford biochemists, Harry Mosher and Frederick Fuhrman. Kao and Fuhrman had shown that it blocked the action potential in frog nerve and wanted to know whether its action was similar to that of TTX. Mitsuru Takata and I tried the toxin on voltage-clamped lobster axons and found that it blocked sodium currents in precisely the same way as TTX. But was tarichatoxin TTX itself, or was it another compound that affected the sodium current in the same way as TTX? I took a sample of TTX to Stanford where Mosher found that its infrared spectra matched that of tarichatoxin. But did this mean that the two toxins had *exactly* the same structure—that the eggs of an American salamander and the ovaries of a Japanese puffer fish were making exactly the same poisonous compound? In due course it was decided that the two toxins were indeed exactly the same, and it was gratifying that our voltage clamp results for the two toxins were identical.

At a small meeting in Miami, Toshio Narahashi and I talked about the effect of TTX on the squid axon. Bernard Katz (later Sir Bernard), listening in full attention mode, immediately wanted to know where to get this magic bullet. As soon as he received some TTX he exploited its blockage of sodium channels to study presynaptic calcium currents in isolation (Katz and Miledi, 1967, 1969). Also at this meeting of about 25 people was Trevor Shaw, who had been planning to come to Duke to work with Schmidt-Neilson but decided, as we rode together to the airport, to work with Toshio and myself to use TTX to count the number of sodium channels in an axon. The experiment used the walking legs of lobsters because they were innervated by bundles of very small nerves, giving us a lot of surface area. We estimated this area from cross sections of the nerve bundle seen in electron micrographs, made by Brenda Eisenberg, although this estimate was tempered as usual due to fixation. Although we guessed that there were about a dozen per square micron, we put a question mark in the title (Moore et al., 1967). At my retirement party, Jim Hudspeth teased me publicly by suggesting that we should have been more confident, or at least more adventuresome, in the title—perhaps “There are damn few sodium channels . . .”

During this exciting TTX time I gave a major talk at a Federation Meeting. In the published paper from this talk I cite a reference from *Playboy Magazine*! Why? Well, the author, Ian Fleming, published two of the James Bond 007 adventures there. At the end of *From Russia with Love*, the female

spy jabs her high-heeled spike into the leg of 007, the hero, and 007 flops to the floor. It turns out that she had TTX in the spike of the heel. But at the beginning of the sequel, *Dr. No*, we are told that 007's colleagues, recognizing that he must have been poisoned by TTX, gave him artificial respiration and saved his life. To my dismay, Ian Fleming's knowledge of TTX had not come from reading my papers. Instead he had spent time in Japan, where he had heard the TTX lore and had presumably been warned about eating *fugu*.

Teaching a New Field: Excitable Membranes

In my first years at Duke I began teaching graduate students with a fine new colleague about 10 years my junior, Paul Horowicz. Paul, a modest and dignified scientist, was scholarly and thoughtful, well read, and rather formal, especially in his dress; he was an extremely nice person with a great sense of humor and was a joy to have as a close colleague. Paul was recruited by Dan Tosteson, who had known him at Washington University in St Louis where Paul had been a brilliant student. Paul had then been a postdoc with Hodgkin, distinguishing himself by doing the single muscle fiber dissections of the tour-de-force Hodgkin and Horowicz papers. (Remember that this very difficult dissection had been done by only one other person, Sybil Street, Bob Ramsey's graduate student.) Paul and I often met with Dan at his house, especially in the early days of expanding the department, where Dan would seek our advice before he took action. (Dan was a great chairman, especially in seeking advice of the faculty on tricky issues; when he decided to make a political decision unpopular with the faculty, he would always take the heat.)

Paul and I designed and taught a new course called "Excitable Membranes" concentrating on the axon, my specialty, and muscle, which was his. Inventing this particular course was especially exciting because both of us were immersed in the field and also because Paul was probably the best muscle physiologist in the country at that time. We taught the course as a seminar and at least one student blew it away, as I now describe.

It happened in the section of the course where we discussed the Hodgkin-Huxley equations. One student in the class, Frank Starmer, although only an undergraduate, was in the bioengineering department and had access to *the* Duke IBM Computer. At that time universities rarely could afford more than one single mainframe computer. This sacred machine was overseen by a faculty committee from the math and physics departments, a Holy of Holies committee. Faculty who wanted computation done were required to write a program of instructions on a typewriter and then hand the program to clerics who would punch cards to put into the computer. So the scientists, "the commoners," would come to the outer vestibule of the temple and bring their offering of punch cards to a junior priest, who in turn

would take the punch cards to the high priest, who in turn would run the machine; the answer would then come back from the Holies in the opposite direction. A corollary of this arrangement was that the computer committee had a lot of power and did not want anyone else buying a computer at Duke. So all purchase orders for computers were routed through the committee for approval. This committee had a choke collar on anyone trying to do computation on campus.

One Monday morning Frank showed up with a pile of computer printout paper. Along the length of the paper, the abscissa, the time axis was displayed and across the paper, the ordinate, was voltage—like paper in a chart recorder. He had actually programmed the digital computer to calculate not only one but two action potentials in succession! I was awed! After his Ph.D. from UNC, Frank returned to Duke and joined Eugene Stead's Department of Medicine as an Associate in Biomathematics; in 1971 he was a founding member of Duke's Computer Science Department. After retiring from Duke, he continued working elsewhere in information technology and learning tools and is now helping to shape the curriculum at the new Duke-National University of Singapore.

Before Frank left Duke he brought to my lab a smart and amiable fellow named Gus Grant, an M.D. cardiologist working on ion channels. Two decades later I felt quite comfortable calling Gus right before leaving for Woods Hole and asking whether he could see me on the spot for symptoms that made me suspect I needed a pacemaker. He not only saw me—he put me straight into the hospital. I now have a fine pacemaker: its existence in my body is the result of a diagnosis by Gus, who was introduced to me by the best student in my first excitable membranes course, and of a design originally by Wilson Greatbatch, with whom I had served on the Biomedical Engineering Group of the IEEE!

My First Computer

In the 1960s there were two types of computer, analog and digital. The Duke IBM Computer was digital and had the advantage of accuracy, but the processes of loading, running, and plotting were slow. Analog computers were much faster but less accurate and uncommon in universities. But because I had been influenced by Art Vance toward analog computers, and having used one to solve the HH equations at the NIH with Dick Fitzhugh, I requested an analog computer built by Electronic Associates, a TR48, in my first grant application to the NIH.

I actually got a call from Ralph Stacy who was on the NIH Study Section considering my application. He was the primary reviewer of my application. Of course nowadays such an unethical call would be prohibited.

"John, this is Ralph. On that analog computer you are asking for—are you absolutely sure you have asked for enough components to solve the HH

equations? This is your last chance to change before we approve.” Those days will never return!

The computer was approved and the money was committed for my work. Incredulously, the Duke computer committee blocked the purchase of this computer! How ridiculous it was that I had to waste my time writing a strong letter to higher authorities at Duke to be able to purchase the machine I needed for my research. Some things indeed have changed for the better.

The TR48 was about 6 feet long, 4 feet high, and had a front panel with plug boards wired to the amplifiers and components behind. I programmed it by simply leading wires from one banana plug jack to another. Individual units carried out particular operations. While the accuracy of the analog computer was limited to 1 part in a thousand, it was quite fast and speed was what was important to me. I wanted to solve the HH equations for the membrane (stationary) action potential on a fast analog computer so that I could see how varying parameters would affect it. Furthermore, this computer allowed me to simulate my experimental results and also was useful in revealing the fatal flaw in an approach called the “ramp clamp,” which some neuroscientists (including Kacy Cole) were enthusiastically embracing as a technique to speed up voltage clamp data acquisition (Fishman, 1970).

After a while, however, I needed the accuracy of the digital computer. I found that the Digital Equipment Corporation (DEC) made a machine called a PDP8, a Precision Data Processor—and guess what? That machine was *not* flagged in the Duke purchasing department because the word “computer” was not in the title! I asked the DEC representative if the name purposefully hid the identity of the machine from university purchasing departments and he said “you betcha.” Similarly, a machine made by Honeywell was called a Digital Data Processor to avoid the word computer. Obviously the computer purchasing problem extended beyond Duke.

An Explosion of Collaborations

I continued to attract a host of visiting colleagues, perhaps because we had developed a fast, reliable voltage clamp and recording system along with an axon chamber where multiple experiments could be performed on a single axon. Werner Ulbricht was a visiting German scientist who joined Toshio and me to internally perfuse squid axon using the roller for axoplasm extrusion that was loaned to us by Alan Hodgkin. Jerry Lettvin and his postdoc Bill Picard brought cesium to the MBL from MIT and we all, including Takata, Ted Bernstein, and John Pooler, my first graduate student, put cesium on the squid axon. Jerry had proposed that cesium would not go through the membrane and indeed our experiments showed no cesium current. Jerry came to Duke later with another idea: reasoning that because calcium ions in sea water partially blocked sodium and potassium currents, the trivalent lanthanum would be far more effective at doing this job.

Again Jerry's intuition was validated, using lobster axons. Toward the end of our time in the Bell building a young guy from the NIH named Bert Shapiro brought us yet another toxin—condylactis toxin from the sea anemone—to test on the axons. (I found out later that Bert had been Annie's T.A. at Swarthmore when she was a freshman in 1961.) People simply showed up with substances—it was a productive and lovely time. I also took on my first postdoc, Nels Anderson, who applied the voltage clamp to smooth muscle and, after his postdoc years, continued this work independently in the department.

It was a swinging biophysical gang at Duke. In particular I enjoyed knowing Richard Adrian who worked with Paul Horowitz for a year or two. He was a superb scientist, a warm and gentle person, and went on to become a Lord like his Nobel Laureate father, Edgar. I thought if all the Lords of England were like Richard, the country would be extremely well governed. Dan and Paul were rather well known in Europe, so there was a huge European influx of visiting scientists; between us all we had a steady stream of people coming through. Dan would question the visitors relentlessly at their seminars and then have dinner at his home for the visitors afterward—with perhaps a dozen of us—and continue to question them intensely. He had bought an old mansion in the main part of Durham, previously the home of a tobacco executive, so the house was near Duke and was large enough to accommodate many people. He created an unusually intellectual atmosphere that knew no time or location limits.

Visiting Takata in Japan

Here I digress to discuss some highlights of a trip to an International Physiology Meeting in Japan in 1965. Mitsuru Takata, who had just gone back to Japan and was living in Osaka, was also at the meeting and had invited me to be his guest after the meeting. Mitsuru and his wife had hired a taxi to take us to visit a famous palace in Kyoto. We knew that Japanese were not allowed into this palace—only foreign visitors of importance were allowed to enter. Consequently Mitsuru expected to return to the taxi. But when we arrived at the gate, the gatekeeper said, "Tour already left—take him to join group." Mitsuru was flabbergasted and overjoyed to be able to see the palace and of course rushed in with me to catch up with the tour.

The second day the Takatas became comfortable with me and hesitatingly asked whether I would stay with them in their little home in Osaka. Osaka was not far from Kobe, where my parents had been born. I was delighted and overwhelmed with their hospitality. What a tiny place they occupied, sleeping on futons that were pulled out from hiding every night. That night we both bemoaned the war. Neither of us had been directly involved, me because of my club foot and he because of a deformed left hand. The next morning his wife played on a shakuhachi, finishing a lovely, quiet,

gentle, friendly interlude in their home overnight. The contrast between the home and the very noisy Japanese bustle outside was a shock.

I met Toshio for the trip back to the United States. We had to refuel at Honolulu, arriving very early on a Sunday morning. Here was a Japanese and an American, sitting side by side, discussing the Sunday morning of December 7, 1941.

Moving to the Nanaline Duke Building

The Physiology Department was in dispersed locations for the first 7 years of Dan's chairmanship, so it was a pleasure for the department finally to be all together when, in 1968, we moved to the Nanaline Duke building, the result of Dan's and Phil Handler's efforts. At this time an absolutely charming Australian named Peter Gage came to work with Paul but suggested also working with me on the squid giant synapse at the MBL. Perhaps he was lured by the idea of Woods Hole as much as by the experiments! Peter and I attempted to find the reversal potential of the postsynaptic response at the squid synapse, even though it was quite difficult to voltage clamp, as a clue to the identity of the neurotransmitter. We found that the reversal potential extrapolated to the sodium equilibrium potential—that is, the transmitter caused a change only in the sodium conductance rather than a change in both the sodium and potassium conductances known to be caused by acetylcholine at the frog neuromuscular junction. This made acetylcholine unlikely to be the transmitter. Returning with me from the MBL after the summer of 1968, Peter completed the year with Paul, then could not resist returning to the MBL in the 1970s for more experimental fun with me.

Within 2 years of moving to the Nanaline Duke building my dear colleague Paul Horowicz was called to be chair at Rochester, to my sorrow, and worse, he took with him Clay and Clara Armstrong. Several other members of the department left to become chairs elsewhere. Within the next 5 years the "Camelot years" of the department would be over as the department split into separate Physiology and Pharmacology Departments, Toshio became chair of Pharmacology, and then Dan left to become dean at Harvard Medical School.

1968–1975: Modeling Action Potential Propagation

In the early 1960s, our sucrose gap voltage clamp experiments on axons were manually controlled: we would set the parameters (amplitude, duration) of a voltage step, push a button to trigger it, observe the resulting current on the oscilloscope screen, and photograph the traces with a Grass Instrument camera (a movie camera allowing each frame to capture one set of traces).

The tedium of recording data and then developing the film, plus the delay in the analysis of the filmed traces, drove me to devise faster methods for storing and retrieving such data. Analog tape recorders were available but were completely impractical for capturing a current trace lasting only a few milliseconds followed by the interminable seconds between pulses. It dawned on me that a small digital storage buffer could hold a single trace, quickly stored, which could then be read out to an FM analog tape recorder during the interval between pulses. However, we needed an Analog-to-Digital (A/D) converter that would follow the extremely fast sodium current transients, a device much faster than any commercially available A/D converter at that time. Fortunately I was able to improve on contemporary logic design and employ the electronic skills of Ed Harris to build an augmented count-up count-down converter. With a four-bit shift register to keep track of recent up/down changes, it was able to take accurate data points at 4 microsecond intervals; with each tick of the clock, the shift register was queried in order to determine the size of the next up or down step (Moore and Harris, 1972).

We purchased a “small” storage buffer with a magnetic core memory of 4096 words of 10 bits each; small is in quotes because while the actual number of bits was small, the box holding it had to be rack-mounted and was at least a foot high! (In contrast, today’s flash cards can store gigabytes of 32-bit words.) The readout of the current record was at a very slow rate so that an FM analog tape recorder could save the traces for later plotting out with a pen on an X-Y plotter. This system—several relay racks filled with electronic boxes custom-made by Ed Harris—worked reliably for many years.

Lab Computers Become Commercially Available

Hoping to further speed up the storage and retrieval of traces and also record the time, temperature, and holding and pulse potentials of the experiment, I purchased a LINC8 computer. The LINC8 was built by DEC, merging its own PDP8 with the LINC (Laboratory INSTRument Computer) developed at the Lincoln Laboratory at MIT. It had a built-in A/D input and D/A output; it used DEC’s logic boards of transistors, resistors, and capacitors to do digital logic. This computer, a double-bay relay rack on wheels, could be programmed to take data and store it on digital magnetic tapes available from DEC. However, because the LINC8’s A/D converter was slow and had poor resolution, we needed to continue to use our own, much faster A/D converter and buffer memory.

I had been incredibly fortunate at this time to attract as a graduate student Ronald Joyner, a whiz at math and programming. Ron quickly accepted the challenge to design programs to interface the LINC8 computer with our equipment, programming it to control the voltage, read the current, and

store this information on digital tape for later analysis. He wrote programs using FOCAL, a proprietary language for DEC machines, adding his own new functions. The LINC8's clock triggered the voltage clamp (whose parameters were programmed), it stored the voltage and current data in our external buffer memory, and then it read these values onto the DEC tape between pulses (Joyner and Moore, 1973). Now we could quickly record a whole family of currents in response to, say, 12 voltage steps, put on a toxin, see the effect on the family, wash it off, and wow—we were suddenly in a full production mode! This computer became our workhorse for voltage clamp experiments on the squid giant axons.

In addition to his Ph.D., Ron received his M.D. at Duke and then he stayed on with me as a postdoc. He is now a professor in the Department of Pediatrics at the Emory School of Medicine. Ron has continued to make unique contributions in both his cardiac studies and computer modeling, amply demonstrated by his novel “coupling clamp” technique where he couples a real cell to a real-time simulation of a model cell.

A Sabbatical at the Rand Corporation

I now became interested in the possibility of simulating a simple neuronal network, so in 1969 I took a sabbatical with a splendid mathematician, Don Perkel, at the Rand Corporation in Santa Monica, California, where such simulations were being attempted. Don had written software programs to simulate nerve cells on a time-sharing machine, built at Rand, that was called the Johnniac for Johnny Von Neumann, the legendary computer scientist. He had also written software for an IBM 360-50 to model a network of nerve cells. I wanted to use this program to learn how much detail was required to describe the simplest of networks (two interacting identical cells) in order to achieve a realistic output reproducing experimental observations. Several years previously, Leon Harmon of Bell Labs had attempted to simulate the performance of two such interacting neurons in a locust, but his very basic model failed to match biology. Ted Lewis at Berkeley added axonal and synaptic delay to Harmon's, but the simulations were still not realistic. Although I had access to Perkel's network program on an IBM 360-50 computer at Cal Tech, it had not been debugged, and I failed to answer my question. Nevertheless, I developed a much deeper appreciation of the challenges of network simulation through this attempt and through long discussions with both Don Perkel and Ron MacGregor at Rand.

We Finally Simulate Propagation

Returning to Duke, I set about evaluating integration methods with Fidel Ramon, a playful Mexican M.D. postdoc (now a member of the Faculty of Medicine of the National Autonomous University of Mexico), in order to find

the optimal method for achieving speed and accuracy in simulating the action potential and, ultimately, propagation. We tested four different integration methods, modifying one to achieve the accuracy and speed that would make optimum use of the slow digital computers of that era. But Fred Dodge, the newly appointed Editor-in-Chief of the *Biophysical Journal*, rejected our paper (again!). We were perplexed by this rejection because his participation and help was acknowledged in the paper! It turned out that he thought that a simulation-only paper was inappropriate for a biophysics journal. So we published the paper in the *Journal of Theoretical Biology* (Moore and Ramon, 1974); later a chagrined Fred apologized, saying that he had to refer many requests for information about the accuracy of integration methods to our paper in a competing journal!

Meanwhile, Ron Joyner was working out a method to simulate propagation by solving the cable equation for the axon. He also developed a powerful computer simulation for our electronic voltage clamp. Using these two simulation tools, Ron, Fidel, and I then looked at the quality of the data that could be obtained with the sucrose gap. We wrote a series of papers in which we detailed the simulation methods, simulated a single axon and then a bundle of fibers in a sucrose gap, described how the equipment and axon interacted, and all along compared our simulations with experimental results. I was particularly fond of the papers from this work, which took an approach that had not been done before and thus broke new ground in the field. In 1975 this series of four papers was readily accepted by Fred Dodge, who had changed his mind about simulation papers, and they took up much of one issue in the *Biophysical Journal* (vol. 15, no. 1).

By the way, in the summer of 1974 I attended a party in Woods Hole and spent some time talking with a young neurophysiologist named Ann Stuart, an Assistant Professor in Steve Kuffler's Neurobiology Department at Harvard Medical School, who was studying the synapses of the huge photoreceptors of giant barnacles. We had earlier been introduced to one another (in 1968) in John Nicholl's lab where Ann was a graduate student; now we probably engaged in a typical conversation of the "What sort of research do you do?" type that happens in Woods Hole. Possibly we even discussed the fact that both of us enjoyed sailing. At the time I was married, so there was no reason for either of us to have attached any special significance to this meeting. I did note that as a woman scientist, particularly an electrophysiologist, Ann was a rare species at the MBL. When we met again the following summer, my personal situation was completely different and sailing became a more important topic of conversation and activities.

1975–1979: Duke, MIT, and Harvard

In parallel with the effort to make progress in simulations with Ron and Fidel, I continued to work during this time on toxins. In the spring of 1973

I had received a letter from a Princeton undergraduate, Monte Westerfield, asking for a position as a technician. When I discovered he had been voltage clamping a molluscan neuron as an undergraduate, I convinced him to be my graduate student instead. Monte was a creative, imaginative, hardworking, fearless, and productive student. He is now in the Biology Department at the University of Oregon, where he has led the department to eminence in the field of zebrafish neurodevelopment. There Monte established and directs the Zebrafish International Resource Center.

Monte and I worked on various toxins as well as on simulations of morphology (described later). One particularly important toxin was that of the Florida red tide organism, *Gymnodinium breve*. George Padilla, a colleague in my department, purified the toxin and then Monte, Y. S. Kim (a postdoc of Narahashi's) and I tested it on squid axons in Woods Hole. In contrast to the New England red tide toxin, saxitoxin, which blocks sodium channels like TTX, the Florida toxin drove the nerve into spontaneous activity by shifting the kinetics of the sodium channel so that it tended to be in the open state. Thus, both red tide toxins acted on sodium channels but differently, albeit both with lethal outcomes for the victim. We also teamed up with Peter Gage who, looking for an excuse to get back to Woods Hole, showed up with the extremely deadly maculotoxin from the little blue-ringed octopus that lives on the Australian coast. We found that maculotoxin had two actions: it blocked the sodium channel (and later analysis proved that one component was TTX), but it also shifted the kinetics. In another summer, Peter brought funnel web spider venom, which turned out also to shift the sodium channel kinetics so that the channel was always open.

We Simulate Propagation Through Morphological Changes

Meanwhile, Ron's simulation of axonal propagation was truly a major step forward, leading to a long-desired direction for the lab—to be able to explore how channel currents interact with changes in morphology. My dream was to simulate the voltage waveform throughout the whole neuron: in the dendrites, through the cell body, into the axon, and into the axon's branches.

Over the next few summers at the MBL, Monte joined Ron, Fidel, and me in simulating morphological changes in a neuron in parallel with experiments on the squid axon. These experiments, derived from those with Jose del Castillo, involved threading a wire down a squid axon to short-circuit a region of the axon, effectively making this region one of larger diameter with the resulting larger capacitance. Using a microelectrode, we probed the voltage transients as the impulse propagated from the normal region of the axon into the "large diameter" region and vice versa, observing the temporal and spatial pattern of the voltage. When an impulse in the normal axon attempted to invade the large diameter "soma," we found an extremely steep temperature dependence that determined whether it succeeded

or failed. Our simulations and experimental results agreed almost precisely, giving us confidence in our understanding. Ron, Monte, and I also found a steep temperature sensitivity for antidromic propagation from a branch into the giant axon. Exploring further, we measured and simulated the changes in membrane current in the vicinity of a step change in morphology.

These experiments with antidromic invasion led us naturally to reopen the question of the initiation of the action potential: When a neuron suddenly shrinks from a soma of large diameter into an axon of much smaller diameter, where does the action potential begin? We could stimulate the “soma” through the internal wire and then, with a microelectrode, record the voltage at different positions along the rest of the axon. From these experiments it was clear that the spike always initiated in the portion of the axon adjacent to the larger-diameter portion that mimicked the “soma.” Simulations agreed with the experiments. Further, Monte showed that the membrane could be charged faster in the region of axon adjacent to the “soma” than in either the soma or further out the axon. We concluded that the threshold was lower in the axon segment neighboring a soma by virtue of its faster rate of charging (shorter time constant). We suggested that this consequence of geometry was sufficient for impulse initiation at this site.

Working at the MBL

During these summers we occupied the corner lab on the third floor of Lillie Building that looked over Eel Pond and the old “Supply Department” that housed the tanks of squid, toadfish, dogfish sharks, skates, horseshoe crabs, and other experimental animals. John Valois and his staff in the Supply Department communicated with their boats via a radio transmitter on the Lillie building roof directly above us. The signals from this transmitter occasionally caused surges on our current traces that led us to a quick scramble to turn off the voltage clamp so that the axon would not be “fried.” Luckily these signals were not too frequent. Ah, the peculiarities of working at the MBL in those days! Salt water sometimes leaked from the sea water tables in the labs above, dripping through the floor onto the equipment in the labs below. Huge temperature swings in the animal holding tanks occurred when one investigator increased the flow of sea water to his or her tank, thereby reducing the flow to (and raising the temperature of) another investigator’s tank. Midnight stir-fries of squid mantles, cooked in woks in lab hallways, brought out investigators from their darkened rooms and long experiments. Odoriferous buckets of invertebrate carcasses waited for morning pickup in the hallways. But all of this was simply quaint to those of us who led the charmed life of working at the MBL. In our lab, the spent axons hung down from the ceiling in increasing numbers, a testimony to the incessant and productive work of the summer.

A Major Change in My Personal Life

During the summer of 1975, I met Ann Stuart again. At this point I was essentially a free man and actually dating a little, since Lee had left me and we were in divorce proceedings. Annie, with her student Duane Edgington, was sharing a set of small lab rooms in the Whitman building (now Rowe) with Joel Brown, his postdoc and her dog, and Larry Pinto. It was rather a tight arrangement, especially as colleagues like Phil Dunham and myself were in the habit of increasing the density when stopping by to discuss MBL politics with Joel. It turns out that Annie and I were noticing each other on these visits and inquiring discretely of our colleagues about each other's "significant other" status. When Annie showed up in my Lillie building lab to inquire about how to voltage clamp her photoreceptor's presynaptic terminal (later discovered to have been an excuse to get my attention), I was rather pleased. So when I saw her looking for dropped keys one evening on the lawn I became Sir Galahad: I galloped off to a nearby police officer, found that he had indeed picked up the keys as I had hoped, and presented them to Annie with a knightly flourish. We began a little game of trying to bump into each other on the MBL campus that no doubt will be recognized by the many persons who are happy victims of romances started there. When does he/she retrieve mail? Which seminars does he/she attend and how can I position myself to sit near where he/she sits? And so on. By the end of the summer all of this Woods Hole-style courting had paid off and we could often be found sailing together in my Javelin, or swimming together at Stony Beach in the *Noctiluca* after dark. That summer was somewhat less scientifically productive for both of us!

Sabbatical at MIT

That fall Annie returned to Boston and her lab in the Harvard Neurobiology Department, I returned to Duke, and both of us were miserable. So I asked my long-time friend Jerry Lettvin if I could have some space and an office in his lab at MIT where I could do simulations and write papers (and be close to Annie) on a half-year sabbatical. There, in Jerry's space, I encountered a sharp young neurologist, one of the first M.D./Ph.D.s, named Steve Waxman. In looking at the nerves from autopsies of patients who had been stricken with multiple sclerosis and then been in remission, Steve had found results of great interest to me: that the internode proximal to the demyelinated region was much shorter than usual. He and I, and his mathematician postdoc (Mike Brill), began to talk about simulating propagation in myelinated fibers, so I asked Ron Joyner to write a program for us to do this. Ultimately Steve and I, with Brill and Ron as coauthors, wrote two papers on propagation in myelinated fibers and its dependence on internodal length. Although Steve and I were together for a relatively short time, we developed

a lifelong friendship, and I am delighted when he and his wife Merle occasionally show up at our door on Lillie Road. Steve went on to an illustrious research career as chair of Neurology at Yale and Director of the Research Center at the Veterans Affairs (VA) Hospital. Recently, after receiving the highest scientific honor of the VA, the Middleton Award, Steve gave up the chair at Yale to fully focus on his research at the VA.

Michael Hines Joins the Lab

Around this time, back at Duke in the winter, Joe Blum and I realized that we both needed a professional mathematician programmer. Joe, my former colleague at the NMRI, was now a professor in our physiology department working on the hydrodynamics of ciliary motion and fluid flux, and he wanted to model these processes. We hired a young Ph.D. from the University of Chicago named Michael Hines. Mike pretty much answered Joe's questions in 2 years, then turned his attention to my problem of simulating a propagating action potential.

The complexity of solving the action potential in *space* as well as in time—that is, as it traveled along a simple axon of uniform diameter—required hours, even on the fastest digital machine available. I decided to put into action what I had learned from Art Vance and couple the memory of a digital machine with the speed of an analog machine. So in 1975 the LINC8 in the lab was superseded by an analog-digital hybrid system. It ran along one wall for well over 30 feet: a DEC PDP15 (occupying four relay racks); an analog machine (EAI 690) made by Electronic Associates, a manufacturer of sophisticated analog computers mostly used in the aeronautical industry; a fast, accurate Hybrid Interface (A/D and D/A converters) (EAI 693); and an X-Y plotter.

With it, Mike was able to simulate the action potential traveling down an axon so rapidly that the action potential was just a wave streaking across the oscilloscope screen! Fred Dodge now popped back into the picture again, this time as a site visitor evaluating our grant for renewal. Fred saw the impulse propagating and asked whether we could slow it down so that he could follow it! But when given the problem of solving propagation in a neuron with complex morphology, the hybrid's speed was limited by the necessity of multiple iterations of the modified Euler method. Soon, however, extraordinary increases in the speed of digital machines, where iterations could be eliminated by implicit numerical integration, caused Mike to move his simulations to a new, small, fast PDP11 DEC computer.

I soon took Mike with me to the MBL. I thought it was important for him to participate in squid experiments for several reasons. First, I wanted him to get a feel for biological variability, not common amongst mathematicians. I thought Mike really needed this sense if he was going to attempt to simulate nerve cells. Second, I wanted to intrigue him with our experiments

by having him participate in them. My plan worked well: it helped to give Mike a unique view of how his professional mathematical skills could be applied to neurobiology.

Sabbatical with Ed Kravitz at Harvard

In the spring of 1978, after too many semesters apart, Annie and I at last married and she joined Ed Perl's Department of Physiology at the University of North Carolina in Chapel Hill. During her transition year, Torsten Wiesel, then the chair of Neurobiology at Harvard, found space for me for an office, and I arranged to work with Ed Kravitz and Silvio Glusman to attempt to understand the basis of facilitation in the presynaptic terminal of the lobster motoneuron. Our plan was to voltage clamp a presynaptic terminal and directly measure the calcium currents to ascertain whether more calcium current entered during the second impulse. While this project ultimately did not succeed, Ed, Silvio and I had a wonderful time together and I started to ponder what happens to calcium in the presynaptic terminal. Our many fruitful discussions stimulated my desire to model the facilitation problem.

At that time it was becoming clear that calcium buffering, as well as calcium extrusion by an ATP-driven pump, must be taken into account in understanding what happened to this important ion after it entered the terminal and caused transmitter release. So I interested my student Norman Stockbridge, a good programmer, in the dissertation project of modeling the complex spatial and temporal distribution of the calcium concentration in a presynaptic terminal. The model was a simplified system including calcium channels, calcium pumps, and intracellular buffering. Mike Hines also became intrigued by calcium, and the two of us eventually wrote a paper together on simulations of calcium entry, binding to a buffer, and being pumped out (Moore and Hines, 1986). We showed that calcium entering the cell accumulates in the buffer not far from the membrane so that a subsequent entry of calcium causes the submembrane calcium concentration to be transiently higher with each additional pulse. The transient concentration change is huge next to the membrane but insignificant at the center of even a $1\mu\text{m}$ cylinder due to buffering; the transients are damped out with radial distance from the membrane. Indeed, there is residual calcium, but it is away from the region just under the membrane, where the pump pulls the concentration from its high value to a very low value to terminate release.

1979–1985: Photoreceptor Synapse, Lizard Neuromuscular Junction, and NEURON

The Barnacle Photoreceptor Synapse

In the fall of 1979, Annie and I at last found ourselves living in the same state, and even in the same house! We were extremely lucky to purchase a

dream house on a lake in Chapel Hill, with great blue heron and a variety of other waterfowl (and, eventually, beavers) right there in our back yard. We continued to migrate to the MBL in the summers and indeed decided in the summer of 1981 to work together there along with Annie's student Jon Hayashi, measuring the input/out relation at the synaptic terminals of barnacle photoreceptors (Hayashi et al., 1985). This collaboration formed part of Hayashi's dissertation in which he reported a process of adaptation at this synapse that enabled it to function over a huge dynamic range.

In February 1983 we had a son, Jonathan. Both Annie and I had been invited to give presentations in the coming summer at the International Society of Physiologists meeting in Sydney, Australia, and at a satellite meeting on the Great Barrier Reef. At the tender age of 6 months, Jonathan accompanied us to San Francisco, Hawaii (where we stopped for a week to time-shift and indulge in a mutual passion, windsurfing, assisted by Annie's mother, Pedie, our babysitter), Sydney, Hayman Island on the Barrier Reef, Fiji, Los Angeles, and back home. It worked so smoothly that we had no hesitation in accepting invitations to speak the next summer in Jerusalem, and Pedie was of course happy to accompany us again as babysitter. But this second trip was not as charmed: while taking time after the meeting to see the Mount of Olives, Annie and Jonathan fell off of a camel when the saddle strap broke. Jonathan was not hurt as he fell on top of Annie; she, on the other hand, ended up having an adventure, first in an Arab hospital and then in Hadassah Hospital, with a broken collar bone and a concussion.

The Lizard Neuromuscular Junction

Annie and I stayed in Woods Hole in the winter of 1985–1986 on sabbaticals and Alberto Mallart joined me there to try to measure currents at the neuromuscular junction (NMJ). At the meeting in Jerusalem, Alberto and I had discovered a mutual interest: he wanted to do simulations and I was intrigued with his preparation, the lizard NMJ, and with his “loose patch” method of measuring currents and release simultaneously. During this collaboration, my postdoc Clark Lindgren came to Woods Hole to learn the lizard preparation. Back home at Duke, Clark and I were able to model and also to measure the pre- and postsynaptic currents at different release sites within the boutons of the NMJ in the same record (Lindgren and Moore, 1989). I later added this work as a tutorial to the *Neurons in Action* educational software that I published with Annie in order to show students how simulations could assist the interpretation of experimental results. Since finishing his postdoc, Clark has held a faculty position at Grinnell College.

Developing NEURON

At this time, back at Duke, Mike Hines was pushing the limits of simulation software. He had originally been writing programs for the digital computer

in FOCAL (for me to use); this had quickly escalated to the CABLE program (in HOC, Higher Order Calculator) that solved the propagation of the action potential along the axon. Now he was expanding and enhancing CABLE, developing it into the NEURON simulation environment (Carnevale and Hines, 2006), a more sophisticated tool that could handle complex morphologies, including tapering diameters and channel densities. Mike had come up with an ingenious way to speed NEURON's calculations for complex morphologies (Hines, 1984) that now made it possible to simulate a full stylized motoneuron with dendrites, soma, hillock, and myelinated axon. This was a significant advance because NEURON could now handle individual dendrites, not just the collapsed dendritic tree of the Rall model used by Dodge and Cooley. We assigned channel densities to each component of the cell as well as we could from values in the literature, but we had the option of varying the densities to see how the change affected the performance of the neuron. The synaptic inputs on the dendrites could be assigned locations, conductances, and times of onset. When values were assigned on the basis of published current records from voltage clamp steps in motoneuron somata, we could now see that the spike was actually initiated in the axon, not the hillock.

Soon after it was built, I demonstrated this model for Bert Sakmann at the MBL and showed him that simulations indicated that the impulse was actually generated out in the myelinated axon and back-propagated through the soma into the dendritic tree. I was delighted when he and others later observed both generation in the axon and back-propagation in central nervous system (CNS) neurons, verifying the prediction from the simulations. Later Annie and I incorporated this model into our *Neurons in Action* software.

1990–2007: Conceiving, and Finally Publishing, *Neurons in Action*

In November of 1990 I was forced by federal law to retire. A delightful fest of the occasion brought a number of good friends and former colleagues to Duke for the day. I was especially surprised and pleased that my NIH grant manager and friend, Gene Streicher, came from Washington for the occasion. Dan Tosteson was the Master of Ceremonies, flying down from Boston, where he was then dean of Harvard Medical School. The talks by Knox Chandler, Toshio Narahashi, Monte Westerfield, and Jim Hudspeth represented different facets of my professional life: Knox from my days in the Cole lab; Toshio, my early collaborator on the TTX experiments; Monte, my former student; and Jim, reflecting the new colleagues I had gained through my marriage to Annie.

Dale Purves (also a long-time friend of Annie's), who had become chair of the new Department of Neurobiology at Duke (in the new Bryan building

opened in 1990), let me retain a lab, an office, and an office for Mike Hines, whose work on NEURON was now supported by the NIH. Mike and I still worked together modeling complete neurons with soma, hillock, and dendrites, but we were focusing on intracellular calcium and neurotransmitter release as well.

Because the movie that Monte, Norm, and I had made in the 1970s was so helpful in visualizing an impulse propagating along an axon, both into and out of a soma, I had earlier urged Mike to program NEURON to display voltages moving in space. Mike did a fabulous job building this movie function into NEURON, and as a result I could now make glorious moving displays on my desktop computer as the simulation progressed. But how could I show these simulations to an audience? These were the days before laptops connected to projectors. In particular, in 1992 I had been invited to give a talk in Genoa, Italy, and wanted some way to show these movies. I made a videotape of the movie displayed on the computer screen and also converted it into European format, enabling me to show my movies in Italy in one format and at seminars in the United States in the other format. Movies became a central feature of the learning tool *Neurons in Action*, my next big endeavor.

The idea for *Neurons in Action (NIA)* occurred to me in 1992 when the first Web browser, Mosaic, appeared on the scene. When Mike showed me that NEURON could be launched by clicking a link on a Web page, I had an epiphany regarding teaching. At that time I had been teaching neurophysiology to graduate and medical students using NEURON to show the properties of action potentials. My “lectures” were a series of questions: “What would happen to the amplitude of the action potential if I decreased the external sodium concentration by 50%,” and so on. I changed a NEURON parameter, had the students predict the outcome and vote on the answer, and then ran the simulation to see who was correct. I saw that the students were engaged with the simulations and that misconceptions were cleared up on the spot. My epiphany was to realize that I could write these lectures as tutorials in HTML that a browser could then display and link to NEURON simulations. It would be a new learning tool, with which students could learn as they asked and answered their own questions as well as mine, specifying NEURON’s parameters. It would free the action potential and other neuronal signals from the textbook, where they were stuck in figures.

It took several years to persuade Annie to help me make my dream a reality. She became convinced while assisting me in a lab for Duke medical students and seeing for herself how this new way of learning engaged the students. The early tutorials were very much in my rather playful, but perhaps disorganized, style, with fonts that were different colors or larger or smaller, depending on what I thought needed emphasis. Annie argued that publication would require the style to be more consistent and professional,

with more explanation and easier navigation, and she appointed herself the one to impose order on the chaos! As we developed a consistent set of tutorials and added hyperlinked information, she tested our efforts on her own students in both graduate and undergraduate classes and in both lecture and lab settings. By 1998 we were able to submit a prototype to Andy Sinauer that convinced him to publish this unusual book/CD, and at a price affordable by students. We signed a contract with a deadline.

The next 2 years, then, saw a constant, herculean effort to complete this project. The text had to be not only correct but also targeted to explaining the results of the simulations, sometimes counterintuitive. The simulations had to work properly no matter what parameter the user chose. The interface had to be friendly even to an inexperienced undergraduate. During this time our teenage son Jonathan had inserted himself into the project, ultimately becoming so crucial to the effort that we dedicated *NIA* to him. “Dad,” he said at the start, “your Web pages are terrible—let me do them.” His programming skills made the program work on both the Mac and PC platforms and with both browsers of the time, Netscape and Internet Explorer. Furthermore, he created its graphics and an explanatory movie (available at the Sinauer Associates and *NIA* Web sites), he designed and still maintains the Web site (<http://neuronsinaction.com/>), and he became Annie’s HTML tutor. It was a time of very intense, devoted work in the whole family.

Sinauer was just figuring out how to edit a multidimensional project like this one, where many of the pages were not sequential, as in a book, but hyperlinked from a number of different loci. Furthermore, marketing a CD project was novel for Sinauer, so Annie spent literally the entire 1999 meeting of the Society for Neuroscience in the Sinauer booth, explaining our new learning tool to interested faculty and students who stopped by. We finally published *NIA* in 2000.

In 2004 we obtained a Course, Curriculum, and Laboratory Improvement grant from the NSF that enabled us to completely redesign *NIA* and its file structure, bringing it in line with changing technology and adding many more tutorials, and Version 2 (*NIA2*) was published in 2007. This generous grant supported technical help for solving some rather tricky problems as well as a professional evaluation team (whose findings are detailed on the *NIA* Web site). Jonathan’s increasingly sophisticated programming skills, and his gentle insistence on taking control of Annie and me at certain stages, were crucial in this effort. We are thrilled that our learning tool is being used to teach neurophysiology in undergraduate as well as graduate courses and, indeed, all over the world. I can’t describe my joy in discovering, for example, that the Dali Lama’s monks and nuns, exiled in India, recently used *NIA2* in order to understand neuronal signaling, or that it is being used in various courses in African countries.

The Present

I am simply unable to stop working because I enjoy it so much! For example, writing this autobiography made me reflect on the exciting beginnings of computational neuroscience in this country, and how the field has continued to accelerate in parallel with the spectacular advances in computer power, so I was pleased when recently invited to publish an online article on this subject (Moore, 2010). Responding to requests, Annie and I have been designing new tutorials for *NIA2* and discussing how to append them to the current version. Additionally, we are working on simulations for a *Calcium in Action* set of tutorials that explore how channels, pumps, buffers, and diffusion determine the concentration of calcium just under the membrane. Every day I am grateful for Wilson Greatbatch's pacemaker that keeps me alive and for the luck of having a spouse who shares, and helps me develop, my professional interests and enthusiasms.

How magical can a career be? It has been as if its path was guided by a benevolent hand through college, graduate school, RCA, the NMRI, and the NIH to Duke. In Woods Hole, the underside of the drawbridge used to display infamous graffiti: "Charmed men walk the streets of Woods Hole." I have always felt that I was one of them. I have had the opportunity to explore electrical and ion channel properties of neurons by doing experiments in parallel with computer simulations. The NMRI, the NIH, Duke, and the MBL gave me the chance to collaborate with many outstanding colleagues from around the globe and to learn from superb students and postdocs, collaborations resulting in lasting friendships. Such memories and friendships remain a source of delight and inspiration.

Acknowledgments

I have attempted, by describing their work and our interactions throughout this biography, to thank my colleagues, students, and postdoctoral fellows for bringing such joy to my work while we experimented and discovered together. I regret that space limitations do not allow me to include everyone by name and note their many contributions to the fullness of my life. I cannot overstate my gratitude for NIH's support of our efforts for three decades, guided by Gene Streicher. Finally, I am indebted to my soul mate, Annie, who initially suggested that I record the memorable portions of my life and then patiently helped me prepare this autobiography, taking time from her own interests of mentoring students and playing chamber music. We have had as close to a perfect marriage as is possible.

Selected Bibliography

Adrian RH, Chandler WK, Hodgkin AL. Voltage clamp experiments in striated muscle fibers. *J Physiol* 1970;208:607-644.

- Beams JW, Young JLIII, Moore JW. The production of high centrifugal fields. *J Applied Physics* 1946;17:886–89
- Brill MH, Waxman SG, Moore JW, Joyner RW. Conduction velocity and spike configuration in myelinated fibers: Computed dependence on internode distance. *J Neurol Neurosurg Psychiatr* 1977;40:769–774.
- Buchwald HD, Durham L, Fischer HG, Harada R, Mosher HS, Kao CY, Furchman FA. Identity of tarichatoxin and tetrodotoxin. *Science* 1964;143:474–475.
- Carnevale NT, Hines ML. *The NEURON Book*. Cambridge, UK: Cambridge University Press, 2006.
- Chandler WK, Hodgkin AL. The effect of internal sodium on the action potential in the presence of different internal anions. *J Physiol* 1965;181:594–611.
- Cole KS. *Membranes, Ions, and Impulses*. Berkeley & Los Angeles, CA: University of California Press, 1968
- Cole KS, Moore JW. Liquid junction and membrane potentials of the squid giant axon. *J Gen Physiol* 1960;43:971–980.
- Cole KS, Moore JW. Ionic current measurements in the squid giant axon membrane. *J Gen Physiol* 1960;44:123–167.
- Cole KS, Moore JW. Potassium ion current in the squid giant axon: Dynamic characteristic. *Biophys J* 1960;1:1–14.
- Cooley JW, Dodge FA Jr. Digital computer solutions for excitation and propagation of the nerve impulse. *Biophys J* 1966;6:583–599.
- Coombs JS, Curtis DR, Eccles JC. The generation of impulses in motoneurons. *J Physiol* 1957;139:232–249.
- Curtis HJ, Cole KS. Membrane resting and action potentials from the squid giant axon. *J Cell Comp Physiol* 1942;19:135
- del Castillo J, Moore JW. On increasing the velocity of a nerve impulse. *J Physiol* 1959;148:665–670.
- Dodge FA Jr, Cooley JW. Action potential of the motoneuron. *IBM J Res Dev* 1973;17:219–229.
- Fishman HM. Direct and rapid description of the individual ionic currents of squid axon membrane by ramp potential control. *Biophys J* 1970;10:799–817.
- Gage PW, Moore JW. Synaptic current at the squid giant synapse. *Science* 1969;166:510–512.
- Gage PW, Moore JW, Westerfield M. An octopus toxin, maculotoxin, selectively blocks sodium current in squid giant axons. *J Physiol* 1976;259:427–443.
- Greatbatch W. *The Making of the Pacemaker*. Amherst, NY: Prometheus Books, 2000.
- Hayashi JH, Moore JW, Stuart AE. Adaptation in the input/output relation of the synapse made by the barnacle's photoreceptor. *J Physiol* 1985;368:179–195.
- Hines ML Efficient computation of branched nerve equations. *Int J Biomed Comput* 1984;15:69–76.
- Hodgkin AL, Huxley AF. Resting and action potentials in single nerve fibres. *J Physiol* 1945;104:176–195.
- Hodgkin AL, Katz B. The effect of sodium ions on the electrical activity of giant axon of the squid. *J Physiol* 1949;108:37–77.
- Joyner RW, Moore JW. Computer controlled voltage clamp experiments. *Ann Biomed Eng* 1973;1:368–380.

- Joyner RW, Moore JW, Ramon F. Axon voltage-clamp simulations. III. Postsynaptic region. *Biophys J* 1975;15:37–54.
- Joyner RW, Ramon F, Moore JW. Simulation of action potential propagation in an inhomogeneous sheet of coupled excitable cells. *Circ Res* 1975;36:654–661.
- Joyner RW, Westerfield M, Moore JW. Effects of cellular geometry on current flow during a propagated action potential. *Biophys J* 1980;31:183–194.
- Joyner RW, Westerfield M, Moore JW, Stockbridge N. A numerical method to model excitable cells. *Biophys J* 1978;22:155–170.
- Julian FJ, Moore JW, Goldman DE. Membrane potentials of the lobster giant axon obtained by use of the sucrose-gap technique. *J Gen Physiol* 1962a;45:1195–1216.
- Julian FJ, Moore JW, Goldman DE. Current-voltage relations in the lobster giant axon membrane under voltage clamp conditions. *J Gen Physiol* 1962b;45:1217–1238.
- Kao CY, Fuhrman FA. Pharmacological studies on tarichatoxin, a potent neurotoxin. *J Pharmacol Exp Ther* 1963;140:31–40.
- Katz B, Miledi R. A study of synaptic transmission in the absence of nerve impulses. *J Physiol* 1967;192:407–436.
- Katz B, Miledi R. Tetrodotoxin-resistant electric activity in presynaptic terminals. *J Physiol* 1969;203:459–487.
- Lindgren CA, Moore JW. Identification of ionic currents at presynaptic nerve endings of the lizard. *J Physiol* 1989;414:210–222.
- Meryman HT, Moore JW. The detection and measurement of freezing in tissue. *J Applied Physiol* 1953;6:12–21.
- Moore JW. A personal view of the early development of computational neuroscience in the USA. *Front Comput Neurosci* 2010;4:20. doi: 10.3389/fncom.2010.00020. http://www.frontiersin.org/computational_neuroscience/10.3389/fncom.2010.00020/abstract
- Moore JW. Electronic control of some active bioelectric membranes. *Proc IRE* 1959;47:1869–1880.
- Moore JW. Operational amplifiers. In: Nastuk WL, ed. *Physical techniques in biological research*. Academic Press, NY: 1963;6:77–97.
- Moore JW Voltage clamp studies on internally perfused axons. *J Gen Physiol* 1965;48:11–17.
- Moore JW, Blaustein M, Anderson NC, Narahashi T. Basis of tetrodotoxin's selectivity in blockage of squid axons. *J Gen Physiol* 1967;40:1401–1411.
- Moore JW, Cole KS. Membrane potentials of the squid giant axon *in vivo*. *Fed Proc* 1955;14:267–276.
- Moore JW, Cole KS. Resting and action potentials of the squid giant axon *in vivo*. *J Gen Physiol* 1960;43:961–970.
- Moore JW, Cole KS. Voltage clamp techniques. In: Nastuk WL, ed. *Physical techniques in biological research*. New York, Academic Press: 1963;6:263–321.
- Moore JW, Cox EB. A kinetic model for the sodium conductance system in squid axon. *Biophys J* 1976;16:171–192.
- Moore JW, del Castillo J. An electronic electrode. *Inst Radio Engrs Natl Conv Rec* 1959;7,Part 9:47–50.

- Moore JW, Gebhart JH. Stabilized wide-band potentiometric preamplifiers. *Proc IRE* 1962;50:1928–1941.
- Moore JW, Harris EM. Voltage clamp data processing. In Agin D, ed. *Perspectives in membrane biophysics*. New York: Gordon and Breach Science Publishers, Ltd. 1972;169–185.
- Moore JW, Hines ML. Some consequences of intracellular calcium binding on the phasic synaptic transmitter release. In Rahamimoff R, Katz B eds., *Calcium, neuronal function and transmitter release*. Boston: Martin Nijoff 1986:115–140.
- Moore JW, Joyner RW, Brill MH, Waxman SG. Simulations of conduction in uniform myelinated fibers: Relative sensitivity to changes in nodal and internodal parameters. *Biophys J* 1978;21:147–160.
- Moore JW, Narahashi T. Tetrodotoxin's highly selective blockage of an ionic channel. *Fed Proc* 1967;26:1655–1663.
- Moore JW, Narahashi T, Shaw TI. An upper limit to the number of sodium channels in nerve membrane? *J Physiol* 1967;188:99–107.
- Moore JW, Narahashi T, Ulbricht W. Sodium conductance shift in an axon internally perfused with a sucrose and low-potassium solution. *J Physiol* 1964;172:163–173.
- Moore JW, Ramon F. On numerical integration of the Hodgkin and Huxley equations for a membrane action potential. *J Theor Biol* 1974;45: 249–273.
- Moore JW, Ramon F, Joyner RW. Axon voltage-clamp simulations. I. Methods and tests. *Biophys J* 1975a;15:11–24.
- Moore JW, Ramon F, Joyner RW. Axon voltage-clamp simulations. II. Double sucrose-gap. *Biophys J* 1975b;15:25–36.
- Moore JW, Stockbridge N, Westerfield M. On the site of impulse initiation in a neurone. *J Physiol* 1983;336:301–311.
- Moore JW, Stuart AE. *Neurons in Action: Computer Simulations with NeuroLab*. Sunderland, MA: Sinauer Associates, 2000.
- Moore JW, Stuart AE. *Neurons in Action Version 2: Tutorials and Simulations Using Neuron*. Sunderland, MA: Sinauer Associates, 2007.
- Moore JW, Ulbricht W., Takata M. Effect of ethanol on the sodium and potassium conductances of the squid axon membrane. *J Gen Physiol* 1964;48:279–295.
- Moore JW, Westerfield M. Action potential propagation and threshold parameters in inhomogeneous regions of squid axons. *J Physiol* 1983;336:285–300.
- Narahashi T, Anderson NC, Moore JW. Tetrodotoxin does not block excitation from inside the nerve membrane. *Science* 1966;153:765–767.
- Narahashi T, Anderson NC, Moore JW. Comparison of tetrodotoxin and procaine in internally perfused squid giant axons. *J Gen Physiol* 1967;50:1413–1428.
- Narahashi T, Moore JW, Scott WR. Tetrodotoxin blockage of sodium conductance increase in lobster giant axons. *J Gen Physiol* 1964;47:965–974.
- Narahashi T, Moore JW, Shapiro BI. Condylactis toxin: Interaction with nerve membrane ionic conductances. *Science* 1969;163:680–681.
- Narahashi T, Moore JW, Poston RN. Tetrodotoxin derivatives: Chemical structure and blockage of nerve membrane conductance. *Science* 1967;156:976–979.
- Pickard WF, Lettvin JY, Moore JW, Takata M, Pooler J, Bernstein T. Cesium ions do not pass the membrane of the giant axon. *Proc Natl Acad Sci USA* 1964; 52:1177–1183.

- Ramon F, Anderson N, Joyner RW, Moore JW. Axon Voltage-clamp simulations. IV. A multicellular preparation. *Biophys J* 1975;15:55–69.
- Ramon F, Joyner RW, Moore JW. Propagation of action potentials in inhomogeneous axon regions. *Fed Proc* 1975;34:1357–1363.
- Ramon F, Moore JW. Ephaptic transmission in squid giant axons. *Am J Physiol* 1978;234:C162–C169.
- Ramon F, Moore JW. Propagation of action potentials in squid giant axons. The effect of membrane inhomogeneities. *J Gen Physiol* 1979;73:595–603.
- Stockbridge N, Moore JW. Dynamics of intracellular calcium and its possible relationship to phasic transmitter release facilitation at the frog neuromuscular junction. *J Neurosci* 1984;4:803–811.
- Stuart AE, Hayashi JH, Moore JW, Davis RE. Currents in the synaptic terminals of barnacle photoreceptors. In Rahamimoff R, Katz B, eds., *Calcium, neuronal function and transmitter release*. Boston: Martin Nijoff 1986:443–455.
- Takata M, Moore JW, Kao CY, Fuhrman FA. Blockage of sodium conductance increase in lobster giant axon by tarichatoxin (tetrodotoxin). *J Gen Physiol* 1966;49:977–988.
- Takata M, Pickard WF, Lettvin JY, Moore JW. Ionic conductance changes in lobster axon membrane when lanthanum is substituted for calcium. *J Gen Physiol* 1966;50:461–471.
- Tasaki I, Luxoro M. Intracellular perfusion of Chilean giant squid axons. *Science* 1964;145:1313–1315.
- Westerfield M, Moore JW, Kim YS, Padilla. How *Gymnodinium breve* red tide toxin produces repetitive firing in squid axons. *Am J Physiol* 1977;232:C23–C29.
- Westerfield M, Joyner RW, Moore JW. Temperature sensitive conduction failure at axon branch points. *J Neurophysiol* 1978;41:1–8.
- Whitcomb ER, Friess SL, Moore JW. Action of certain anticholinesterases on the spike potential of the desheathed sciatic nerve of the bullfrog. *J Cell Comp Physiol* 1958;52:275–300.