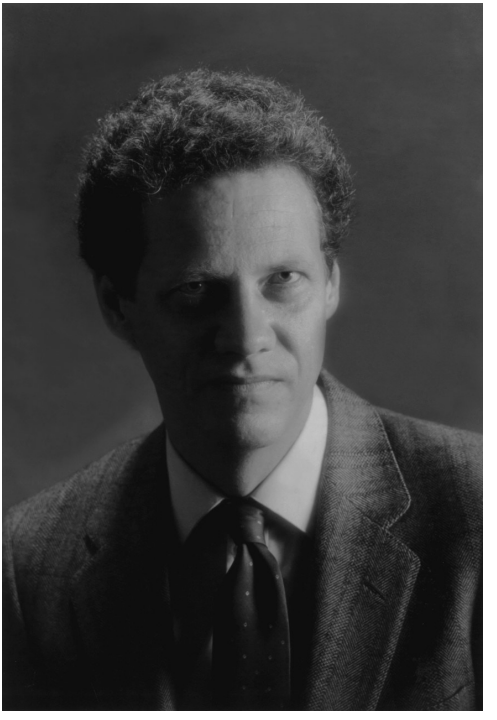
The History of Neuroscience in Autobiography
Volume 11

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

Larry W. Swanson

pp. 424–469

https://www.doi.org/10.1523/hon.011011



Larry W. Swanson

Born:

Camp Lejeune, North Carolina
December 13, 1945

Education:

Pomona College, BS in Biochemistry (1968)
Washington University School of Medicine, PhD in Neurobiology (1972)

Appointments:

Postdoctoral Fellow (Lab of W. Maxwell Cowan), Washington University (1972–1974)
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Research Assistant Professor, Department of Anatomy and Neurobiology, Washington University (1976–1979)
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Staff Scientist to Senior Member, Salk Institute for Biological Studies (1980–1990)
Assistant Adjunct Professor to Adjunct Professor, UC San Diego (1980–1990)
Investigator, Howard Hughes Medical Institute, at the Salk Institute (1985–1990)
Professor, Departments of Biological Sciences and Psychology, USC (1990–present)
Appleman Professor of Biological Sciences, USC (1995–present)
Founding Coordinator, Neuroscience Graduate Program (university-wide), USC (1996–2004)
Dean of Research, The College (M.O. Schapiro, Dean), USC (1998–2000)
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Visiting Scholar, Department of Neurobiology, UCLA (2007–2013)
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Visiting Scholar, Sainsbury Wellcome Centre for Neural Circuits and Behavior, UCL (2019)

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Javits Distinguished Neuroscience Investigator Awards, NINDS (1986–1993, 2006–2013)
100 most cited scientific researchers of the 1980s (one of two neuroscientists), ISI (1991)
100 most cited neuroscience researchers, 1980-2000; Institute for Scientific Info. (2001)
President, The Cajal Club (2004–2006)
Fellow, American Academy of Arts and Sciences (2005)
Member, National Academy of Sciences (2010)
Member, Grolier Club (2010)
President, Society for Neuroscience (2012–2013)
Secretary General, International Brain Research Organization (2015–2017)

Throughout his career, Larry W. Swanson has investigated the basic structure-function organization of mammalian neural systems controlling the three classes of motivated behavior that assure survival in all animals: ingestive (eating and drinking), reproductive (sexual and parental), and agonistic (fight-or-flight). Because the mechanistic explanation of behavior ultimately involves all parts of the nervous system, he has also applied network analysis tools to understand the basic wiring diagram of the nervous system.

Larry W. Swanson

> "To extend our understanding of neural function to the most complex human physiological and psychological activities, it is essential that we first generate a clear and accurate view of the structure of the relevant centers, and of the human brain itself, so that the basic plan—the overview—can be grasped in the blink of an eye."
>
> —Santiago Ramón y Cajal, 1909–1911 (chap. 2, p. 45)

Early Years

I was born at the end of the deadliest conflict in history and the beginning of an American golden age of economic prosperity. During most of World War II my father, Bernard, had served in the Pacific Theater as a major in the Marine Corps, and then toward the end became deputy chief for logistics at Camp Lejeune, North Carolina, a huge Marine Corps Base. He was born and raised on a farm in the American heartland near Hastings, Nebraska, and graduated from Hastings College before the United States entered the hostilities.

In contrast, my mother, Shirley, was born and raised in Las Vegas, Nevada, which at the time, still had many trappings of the Wild West. She graduated from the University of California, Los Angeles (UCLA) before joining the war effort as an administrative assistant to the Truman Commission investigating defense industry fraud and corruption in Washington, DC. It was there, on a blind date, that she met my father, and they were married in 1942 in San Diego, just before he shipped out to the Pacific islands. I made my entrance, almost exactly four months after V-J Day, on December 13, 1945, in the U.S. Naval Hospital at Camp Lejeune. My mother's roommate was Annie Glenn (Oncken, 1962), who was also having her first child—with her husband John, a highly decorated Marine Corps fighter pilot who, just 17 years later in 1962, would be the first American to orbit the Earth.

When I was about a month old, my parents moved to Las Vegas, and my father started and ran, with the help of my mother's father, a company that bottled and distributed soft drinks. This grandfather, William E. "Pop" Ferron, grew up in Utah. His own grandfather, General Friedrich Salomon, was surveyor general of Utah and had mapped out the territory with Brigham Young. Pop's father, Augustus Ferron, was a Central Pacific railroad engineer with a degree from City College of New York. He had been at Promontory Summit, Utah territory, when the first transcontinental railroad was completed there in 1869, and he loved to have his two boys tag

along on field trips through the state. When the time came, Pop headed east for a degree at the Philadelphia College of Pharmacy. After graduating, the adventuresome young man traveled south to Columbia for a gold mining venture with his brother, meant to raise a stake for starting his own business.

For his first business, Pop chose Las Vegas, which, roughly translated, means "the Meadows," because it had natural springs in the middle of the Mojave Desert. This made Las Vegas a convenient railroad stopping point for water and ice between Salt Lake City and Los Angeles, and, as he correctly surmised, an area of future growth. In 1917, he moved there with his bride, Ruth Cooper, whose family had roots in Stowe, Vermont.

Ruth was horrified. With a population of less than 2,000, Las Vegas still had dirt streets and wooden sidewalks, having incorporated only six years earlier. Undaunted, Pop used his gold mining stake to open the first independent pharmacy in Las Vegas, and respectability followed quickly. He was elected its third mayor in 1920 (UNLV Special Collections and Archives, 2019).

As a child, my maternal grandparents were relatively well off and highly respected in the community. At the same time, they had an adventurous spirit and loved to travel the world. They had the means to allow Ruth and their girls to travel to Southern California in the summers to escape the heat. They would travel by car (a two-day trek back then) followed by another car in case the first broke down. Being stranded in the desert was something to be feared especially as there were so few towns between Las Vegas and Los Angeles. This summer sojourn would continue into my youth, contributing greatly to my love of California.

In contrast, my paternal grandparents, Harry and May (née Joyce) Swanson, were from pioneer Swedish and Irish farming families that had emigrated to Nebraska in the 1870s. They were salt of the earth Midwesterners who moved to Las Vegas after the war to be close to their son and his family. The Ferron grandparents lived in a big house that we visited semiformally on special occasions; the Swanson grandparents lived in a working-class neighborhood and were a frequent, loving, and joyous presence in our lives.

I attended Catholic schools from first grade through high school. As a young child, I assembled a stamp collection, then a mineral collection, and eventually lost interest in them both; I'll get to my adult bibliomania later. Overall, it was a happy suburban upbringing, with a flavor of the Western U.S. adventuresome spirit, best displayed by the annual Helldorado Days festival celebrating the cowboy origins of Las Vegas. We'd all dress up in our boots and hats and watch the parade from the window of Pop's drugstore. And as often as possible, my friends, brothers Dave and Tim, and I explored the undeveloped desert a couple of blocks from our house looking for scorpions, snakes, weird cacti, and anything else unusual that caught our attention.

We were mostly isolated from the gambling-resort industry that grew exponentially in Las Vegas after the war. It was a different world. But it was fun every now and then to drive with the family down Fremont Street and along The Strip (where all of the hotel casinos were concentrated) and see the latest neon sign monstrosities. Our family rarely went to shows, although Gram and Pop would take us to one or another of the extravaganzas on our birthdays, always forgetting that they would include parades of semi-nude chorus girls strutting to the hit parade of the day. For the most part, I was unaware of how segregated our community was until something would escape the lips of Gram. I remember seeing Harry Belafonte with his young daughter on his shoulders at the Helldorado parade, a lovely family moment that was marred by my grandmother exclaiming, "What's *he* doing here?"

Growing up, I experienced two serious family events with long-term consequences. First, my youngest brother Tim had encephalitis when he was four years old (and I was nine). A private emergency flight from Las Vegas to the UCLA Medical Center saved his life, although recovery was slow, and subtle effects on motor and cognitive functions remain to this day. And second, after this tragedy, my father's long-term drinking problem grew much worse. He became more isolated from the family, and, finally, he died of alcoholism when he was only 48 years old. I cannot honestly say that he had any positive influence on my life or my future.

I did not show any real academic potential until high school, when I emerged as one of the better students in science and math classes. Keep in mind the bar was very low—the nun who taught us math in eighth grade couldn't do fractions. I also enjoyed English literature and art appreciation (those nuns had a better handle on these subjects). There was also plenty of time for friends and sports. I liked playing tennis, baseball, and basketball. In my junior year, our team won the Nevada State Division A Basketball Championship, defeating the Winnemucca Buckaroos, though I rode the bench for most of that game.

When the time came to think about college, there was no counseling program at Bishop Gorman High School, so I just applied to the University of California, Santa Barbara (UCSB) because I loved the ocean (those summer trips with my family, beginning when I was two, had a direct influence on this choice), and to Pomona College in Claremont, California, because the daughter of one of my mother's friends went there.

Pomona College and the Glimmerings of Neuroscience

I was accepted to UCSB and wait-listed at Pomona College—but eventually was offered a place at the small private institution on the fringes of the Los Angeles metropolitan region at the base of Mt. San Antonio, the tallest peak in the San Gabriel Mountains. I went there thinking I wanted to be

a physics major but struggled mightily with the introductory courses. My background at the tiny Catholic high school in Las Vegas had been woefully inadequate.

But two things happened in my freshman year: I did very well in my introductory psychology and human evolution courses, and most important, Francis Crick visited Pomona College for a week in the spring of 1965, to present the Robbins Lecture Series (Wellcome Library, 2020). He and James Watson had won the Nobel Prize three years earlier for their double-helix model of DNA and its implications for information transfer in living organisms.

Crick was now working on the "triplet code" involved in synthesizing protein from mRNA. In his first lecture, he wrote down on the blackboard a list of the known triplets, and in each of the next three lectures, he added ones that had been discovered since the previous lecture. It was a memorable experience, which was only heightened by his attendance at a "keg (beer-drinking) party" in the woodsy part of campus where a good time could be had by all—led by the charming, witty, and approachable Nobelist. Many years later when the University of Southern California (USC) faculty wanted to invite Crick for a lecture, his only stipulation was that the invitation had to come from the students.

Crick's visit stimulated me to switch from physics to chemistry in my sophomore year. Two events the summer before also had an important influence on my future direction. Academically, I took a superb course in abnormal psychology at UCLA and became even more intrigued with psychology as a discipline. And socially, the Watts Riots took place in the middle of August 1965, just before I was to return to Claremont. The two Los Angeles communities are only about 40 miles apart geographically, but they are vastly separated culturally. This event was part of the much broader concerns of the 1960s: the civil rights and feminist movements along with anti–Vietnam War protests—to which I and the majority of my classmates at Pomona (and at colleges and universities around the country) were deeply committed.

The summer between my sophomore and junior years, I worked in Doug Henning's organic chemistry lab at Pomona, separating the terpenes in pine tar. I was miserable both with it and at it. So, I switched again—to a new specialty at Pomona, biochemistry. I also began taking more courses in comparative vertebrate anatomy and physiology, as well as in physiological psychology. I was introduced to the latter by Clifton Trafton, whose course on motivation and emotion, with a wonderful textbook by Paul Thomas Young, continues to inspire me. Two other illuminating textbooks were Richard Thompson's *Foundations of Physiological Psychology*, and Alfred Romer's *The Vertebrate Body.* For my term paper in comparative anatomy, I chose the organization of pathways between brain and spinal cord because they seemed like an obvious link between cognition, motivation, and behavior.

I was pretty much overwhelmed, but intrigued, by the complexity I began reading about. But, unlike my response to organic chemistry, I could easily see myself doing productive and interesting research on topics like these.

This formative undergraduate experience with molecular biology, psychology, and zoology at Pomona was directly aligned with physiological psychology, an already established branch of psychology. With the guidance of Clint Trafton, I began (in 1967) investigating graduate programs in the newly emerging interdisciplinary field of neurobiology. I found only two—at the University of Washington and at Washington University in St. Louis. I was rejected at the former and wait-listed at the latter, but eventually I was accepted just before graduation in 1968.

The previous 12 months had been socially invigorating. On one hand, the 1967 Summer of Love in San Francisco had spread quickly to college campuses in Los Angeles. But on the other, Vietnam War protests and Martin Luther King's assassination in Memphis on April 4 led many of us at graduation to wear black armbands over our academic robes. My mother was quite dismayed by this action. Shortly thereafter, on June 5, my friends and I witnessed the assassination of Robert Kennedy on live television. I was reminded of sitting at my desk as a high school senior and hearing the principal, a priest, announce over the intercom system that President John Kennedy had been shot and killed in Dallas.

Localizing Eating and Drinking Hot Spots at Washington University

In August 1968, I drove my Volkswagen beetle with its Gene McCarthy bumper sticker to St. Louis and a whole new world. This is where I got my doctorate, postdoctoral experience, and first academic job. More important, it's also where I met my wife Neely and we had our son, Reid.

Moving from Southern California to St. Louis in this era was culture shock, but I quickly recovered. I met Neely playing volleyball in October. We went to a Marx Brothers movie and a James Brown concert, and we have been best friends ever since. She was a French major from Chicago, and we got married at Bond Chapel (University of Chicago) on August 15, 1970. Her family could not have been more different than mine. Her father, Webb, grew up poor in rural Tennessee, went to graduate school at the University of Chicago after serving in the Army during the war, and became a labor relations executive for Sears, Roebuck and Company. In contrast, her mother Gaby's family were Romanian Jews who emigrated to Paris. She spent the war years in hiding with her mother while her father was imprisoned in a labor camp outside Paris. The young (she was 16 at the time) urban Holocaust refugee met her American soldier from the hills of Tennessee in Cannes on the French Riviera and were married a year later. Webb would be a great and loving influence on me for the short time I knew

him. He died of a Circle of Willis aneurysm at the age of 52, shortly after Neely and I married.

Before arriving in St. Louis, I had indicated a preference to work with Robert Wurtz, who was doing fascinating research on learning mechanisms in primates, but he had just moved to the National Institutes of Health (NIH). I was assigned instead to a young assistant professor, Vernon Perez, in the Psychiatry Department's Laboratory of Neuropsychology, who was proposing to test the hypothesis that "brain-specific" proteins influence the expression of motivated behaviors. The first two, S-110 and 14-3-2, had just been discovered in 1965 in that department by Blake Moore, and this was an exciting project to get started on.

Three young researchers formed the core of the Laboratory of Neuropsychology, Perez, Ted Cicero, and Larry Sharpe. They had all trained at Purdue with Robert D. Myers, who pioneered methods for injecting substances, and sampling fluids, in the brains of conscious, behaving rats, rabbits, and nonhuman primates using permanently implanted cannulae. I spent almost a year making hundreds of microinjections of S-100 and 14-3-2 into many different parts of the rat brain and recording food and water intake, as measures of hunger and thirst—with no statistically significant effects. In hindsight, this was not surprising; S-100 is expressed by astrocytes and 14-3-2 is a neuron-specific enolase involved in glycolysis. Despite the obvious failure of this approach, Perez wanted me to continue to push ahead in hopes of finding something, anything, to report for his grant.

The rationale for manipulating ingestive behaviors was sound. It was based on the groundbreaking work of Sebastian (Pete) Grossman, who, for his doctoral thesis work at the University of Chicago (Grossman, 1960), invented a method for delivering minute amounts of neurotransmitter-related molecules into discrete parts of the brain of freely moving rats and measuring the behavioral effects. He discovered that cholinergic drugs induced drinking behavior and adrenergic drugs induced eating behavior when delivered to the same site in the hypothalamus. Most important, he hypothesized that there may be neurotransmitter-coded systems in the brain for different classes of motivated behavior. This effect fascinated me, and the hypothesis has been the inspiration for my research program ever since.

I first saw this effect in Larry Sharpe's lab. When the experiments with Perez began looking unproductive, I asked Sharpe if I could work on ingestive behaviors with him and he agreed. After reading the literature, I thought the burning question in the field centered on localization of function (that is, exactly what parts of the brain are activated by microinjected neurotransmitter-related molecules?) and the clearest obstacle to progress was the relatively large volumes used to deliver the molecules in rat. Typically, the volume was around 1 μl (1 mm^3) with a diffusion gradient that could reach at least 2 mm in diameter—which invariably spread

to include multiple brain areas in the hypothalamus and other parts of the limbic system, hopelessly confounding interpretation. So, my first project was to develop a method for delivering much smaller volumes to the brain of freely moving animals. The results were a method for accurately and reliably delivering volumes as small as 0.04 μl (40 nl), my first research paper as lead author (Swanson et al., 1972), and as will become apparent later, a big advantage when I began my postdoctoral work in neuroanatomy.

Based on more than 1,000 forebrain and midbrain microinjections in the rat, the most sensitive and reliable hot spot for drinking induced by carbachol (a cholinergic agonist) and angiotensin II was localized to the periventricular hypothalamic zone, centered in the paraventricular nucleus (Swanson and Sharpe, 1973)—and this finding was confirmed in the monkey (Sharpe and Swanson, 1974). We were also fortunate to characterize the central angiotensin II receptors involved in the drinking response with Phil Needleman, who had synthesized a number of analogs, and also suggested pharmacological tests for cholinergic and adrenergic involvement (Swanson et al., 1973). By 1976, Needleman became chair of the pharmacology department before leaving for industry, eventually assuming the presidency of Searle in 1993.

The intellectual environment in the newly created Neurobiology Graduate Program was the best I have experienced in my career. Most of the chairs of the relevant departments showed up to seminars, leading by example, and it was a distinguished group: Max Cowan (anatomy), Carleton Hunt (physiology), Bill Landau (neurology), Oliver Lowry (pharmacology), and Roy Vagelos (biological chemistry). And there was the popular Saturday morning seminar series for students and faculty, with groups of presentations focused on particular topics and organized by Cowan.

My home department (psychiatry) was also special. It was led by Eli Robins and was one of the first departments of its kind in the United States to abandon psychoanalysis for clinically and experimentally based approaches to mental illness—hence, its Laboratory of Neuropsychology. And I learned more about critical thinking and basic experimental design from Larry Sharpe than anyone. He had a contrarian spirit that did not fit well in a clinical department, especially because he held a doctorate but was not a medical doctor, but he was my best friend in St. Louis at the time. On weekends, we often continued our lab discussions on the tennis court.

Neural Circuit Organization and the Neuroanatomy Revolution

As my thesis work wound down, I began thinking about postdoctoral positions and decided to pursue the behavioral hot spot I had identified. Following Grossman's original hypothesis, I wondered what neural connections might form the "thirst circuit" with its periventricular hypothalamic

"drinking center." This seemed like one of the more tractable problems in behavioral neurobiology because so much was known about the relatively straightforward physiology of body water regulation, making functional interpretations of circuit data more readily apparent. So, in 1971, off I went to the first annual meeting of the Society for Neuroscience at the Shoreham Hotel in Washington, DC, searching for a postdoc. I knew virtually none of the 1,200 attendees but did manage to interview four or five potential mentors working on one aspect of circuit mapping or another.

Because Oxford-trained Max Cowan was one of the leading neuroanatomists in the world, and because he was on my thesis advisory committee and had invited me to attend his lab meetings, I went to him for advice about which postdoctoral position to choose. In characteristic fashion, he critiqued each person I had in mind, and suggested instead that I stay and work with him. He said they had just developed an ideal method for the type of circuit analysis I wanted to learn and handed me a preprint of the soon-to-be-famous paper describing the autoradiographic method (ARGM) for tracing connections in the brain (Cowan et al., 1972). It had three fundamental advantages over the degeneration-based methods then in use: it was far more sensitive and thus had far fewer false negative results; it did not involve axons-of-passage that lead to false positive results; and it relied on the cell biology (anterograde intra-axonal transport of radiolabeled proteins) of intact neurons rather than on lesion-induced pathological changes. Cowan's offer was immediately accepted.

Earlier degeneration studies suggested that limbic parts of the cerebral hemispheres provide important inputs to the hypothalamus, so I started with a systematic reanalysis of septal region efferent connections (axonal projections) in rat. The ARGM required microinjecting a small volume of pathway tracer (^{3}H-amino acids) into a brain region of interest, and early studies in the Cowan group used relatively large volumes (0.5–1.0 μl) for preliminary studies. With the injection method developed earlier for behavioral experiments, I could now deliver tracer in a volume of about 20 nl, which allowed for much more precise localization of injection sites to the tiny subdivisions of the septum and other brain parts.

The analysis of septal projections soon expanded to include the interrelated hippocampal formation at the cortical level, and the hypothalamus subcortically. The result was a series of long papers between 1975 and 1979 in the *Journal of Comparative Neurology*, of which Cowan was editor at the time, that provided a wealth of new information on the highly interconnected "hippocampal-septal-hypothalamic" system. The hypothalamic part of the project was spearheaded in rat, cat, and monkey by a brilliant medical doctor–doctoral student, Clif Saper, who went on eventually to chair the Department of Neurology at Harvard's Beth Israel Deaconess Medical Center for almost 30 years and who made outstanding contributions to our understanding of neural mechanisms controlling the

sleep-wake cycle, thermoregulation, and many other components of autonomic regulation.

Three aspects of this work were particularly interesting and showed the power of the new methodology. First, contrary to a century of conventional wisdom, we found that the fornix, which ends in the mammillary body and anterior thalamus, does not originate in the hippocampus; instead, it arises in obscure retrohippocampal cortical fields including the subiculum and presubiculum. We first presented this novel finding in 1974 at a symposium where no one else mentioned finding similar results (Swanson and Cowan, 1974), prompting us to dash off a report to *Science* (Swanson and Cowan, 1975). Second, we discovered the efferent projections of the tiny suprachiasmatic nucleus (Swanson and Cowan, 1975), which had been shown recently to receive a direct input from the retina and to be the long-sought circadian rhythm generator. Third, the first detailed parcellation and connectional analysis was carried out for the preoptic region of the hypothalamus (Swanson, 1976).

Focus on the Paraventricular Nucleus as an Ingestive Behavior Hub

One day in 1974 Cowan got a phone call from a colleague in the Biology Department, Rita Levi-Montalcini, who, along with Stanley Cohen, would win the Nobel Prize 12 years later for their discovery and characterization of nerve growth factor (NGF). At the time of the call, she was moving back to spend most of her time at a lab in Rome but had just received word that an approved grant whose funding was on hold, unexpectedly had been activated. She asked if Cowan knew anyone who would be interested in coming to the other campus to work on the grant and spend the windfall. Luckily, Max asked me, and I readily agreed. My plan was to spend half my time doing the circuit analysis work with him, and the other half working on Rita's project, which was actually quite interesting. She had discovered that NGF microinjections into the locus ceruleus (a tiny brainstem nucleus with only noradrenergic neurons, almost reminiscent of a sympathetic ganglion) induced the sprouting of peripheral sympathetic axons into the brain, toward the injection site. The aims of the grant were to characterize this ectopic ingrowth of neurotransmitter-specific axons, presumably from the superior cervical ganglion.

My initial concern was to distinguish between ingrowth from the periphery, and possible ingrowth from the central noradrenergic system, which had been so elegantly discovered and described by Dahlstöm and Fuxe (1964) with the Falck-Hillarp histofluorescence method for biogenic amines. No one at Washington University was using the method, which required specialized equipment and skills, and painstaking controls to distinguish between dopamine, noradrenaline, and adrenaline. As an alternative,

I approached Boyd Hartman in the Psychiatry Department, who while working with Sidney Udenfriend at NIH had published the first paper to apply immunohistochemistry to central nervous system tissue (Hartman and Udenfriend, 1970). For this, they first purified bovine dopamine ß-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, and then used a specific antiserum to the protein as a marker for noradrenergic (and adrenergic) neurons. Boyd became not just one of my most valued collaborators but also one of my closest friends; he did not enjoy reading the literature, preferring instead to think originally and talk sensibly about any topic that came up.

Early immunohistochemical methodology was difficult also, but we managed to cut multiple series of cryostat sections through the length of the rat brain and to produce a complete account of the central adrenergic system—the first brainwide atlas of a neurotransmitter-specific system with immunohistochemistry (Swanson and Hartman, 1975). The technical experience and knowledge we gained soon proved invaluable in another context. However, experiments with Rita to retrogradely label the region where she had made her injections (locus ceruleus) with ^{125}I-NGF injected into the hippocampus proved fruitless, although, interestingly, we instead found retrograde labeling in the medial septal complex, which we knew from autoradiographic experiments projects to the hippocampus, and other evidence suggested was cholinergic. Unfortunately, or fortunately, as a last-minute control, I injected free ^{125}I into the hippocampus and also got retrograde labeling in the medial septum. The radiolabeled NGF I had obtained from Ralph Bradshaw in the Department of Biological Chemistry hadn't been cleaned up properly, and I never got a publication with Rita.

In 1975, we were generating material and beginning our analysis of hypothalamic projections, using as an initial guide the authoritative review by Nauta and Haymaker (1969), who had concluded, based on the older generation of degeneration methods, that the hypothalamus influences behavioral and visceral functions by a series of short descending connections through the reticular formation. But this view was shattered in a conceptually simple experiment by Kuypers and Maisky (1975) who used the new generation of axonally transported retrograde pathway tracers (horseradish peroxidase, HRP) to show that in cat the hypothalamus projects directly all the way to the spinal cord. It was not possible, however, in their brief report to determine which medial hypothalamic neuron groups were labeled.

I immediately began injecting HRP in the rat thoracic spinal cord and discovered that a major site of retrograde labeling was the paraventricular hypothalamic nucleus (PVH). On a visit to Cowan's office, I also found Saper and another colleague, Arthur Loewy, there, and they were discussing having done the same experiments in monkeys and cats, with similar results. Furthermore, we had found autoradiographically that injections spreading to include the PVH generated anterogradely-labeled descending

projections to the dorsal vagal complex (parasympathetic) and spinal intermediolateral column (sympathetic). We immediately teamed up to write a paper on our joint findings (Saper et al., 1976), which suggested a general connectional feature of mammals, and which played a seminal role in the future of each of our careers.

For me, this was an "aha moment" because three different findings came together. First, there was my thesis finding of a periventricular ingestive behavior hot spot centered near the PVH. Second, there was the observation from our DBH mapping study confirming that the PVH has perhaps the densest noradrenergic terminal field in the brain. Third, there was evidence from Dick Gold (1973) that the "hypothalamic feeding center" was not in the ventromedial nucleus, as conventionally assumed, but instead was associated with a part of the central (nor)adrenergic system dorsomedial to the ventromedial nucleus, presumably in the PVH. Interestingly, my inspiration, Pete Grossman, began following up Gold's work with a graduate student, Joe Kelly, and for his postdoctoral work, he came to Washington University to work with Boyd Hartman. As a side project with me, he found a variety of previously unreported oxytocinergic or vasopressinergic neuron populations that project to the posterior pituitary with the retrograde tracer HRP (Kelly and Swanson, 1980). Tragically, less than a year after the paper was published, Joe died of a metastasizing osteosarcoma of the leg, cutting short the very promising research career of one of the nicest people I have ever known.

Thus began an intense dissection of the PVH over 30 years that eventually resulted in the publication of approximately 40 papers. It was already well known that the PVH, along with the supraoptic nucleus, are the main sources of axons to the posterior pituitary that release oxytocin and vasopressin into the general circulation. Using immunohistochemistry, I initially showed that at least part of the PVH descending projection to the dorsal vagal complex used one or the other of these neuropeptides (Swanson, 1977), and that there was an ascending noradrenergic projection from the dorsal vagal complex to the PVH (Swanson and Hartman, 1980), providing a potential circuit substrate for autonomic-neuroendocrine coordination.

The next step was to determine whether PVH projections to the pituitary gland, dorsal vagal complex, and spinal cord arise from the same, or from different, neuron population(s). Hans Kuypers in Rotterdam had moved beyond HRP to develop a rapid method for determining axon collateralization patterns with multiple retrogradely transported fluorescent tracers. I wrote to him asking for tracer samples, which he kindly sent, and after testing them, I was unimpressed with results that involved huge injection sites and rather poor sensitivity. I wrote again asking for advice, and amazingly, he instead invited me to his lab to use the even better tracers they had developed in the meantime. This was even more amazing from a personal perspective because his mentor, Walle Nauta, and my mentor, Max Cowan,

were intense, world-class rivals. They both worked on the connections of essentially the same parts of the brain with the Nauta degeneration method, but now Cowan had developed the autoradiographic tracing method that rendered Nauta's degeneration method obsolete overnight.

I spent the summer of 1979 in Kuypers's lab, and it was the single most productive episode in my research career. I learned the methodology from Marina Bentivoglio, who was instrumental in developing it, along with Derek van der Kooy who had just left for Toronto. And Kuypers himself worked out a transpharyngeal surgical method for injecting tracer into the rat pituitary gland. The results laid the groundwork for all subsequent research on the PVH: in rat, three topographically (and functionally) distinct neuron populations project to the lower brainstem and spinal cord (autonomic, and as inferred later, behavioral control), to the posterior pituitary (magnocellular neuroendocrine system), and to the median eminence (parvicellular neuroendocrine system) (Swanson and Kuypers, 1980; Swanson et al., 1980). Neely and I remained friends with Hans until his untimely death several years later, after he had moved on to Cambridge as chair of the Department of Anatomy.

At summer's end, we returned to St. Louis, and in September, my first postdoc arrived—from Dick Gold's lab—Paul Sawchenko, whose thesis work focused on the role of the subdiaphragmatic vagus nerve in hypothalamic hyperphagia and obesity. An obvious question now concerned the organization of ascending noradrenergic pathways, with vagal sensory inputs in the medulla and PVH subdivisions at the other end, especially in light of convincing recent evidence from Sarah Leibowitz (1978) at the Rockefeller University that the PVH is the most effective site for norepinephrine-elicited eating (and drinking). To approach the problem, though, Paul spent the first six months developing and meticulously validating a method combining the most sensitive of Kuypers's retrograde tracers with immunohistochemistry for any desired neuronal antigen (Sawchenko and Swanson, 1981).

In the meantime, Cowan had accepted a position at the Salk Institute in La Jolla, and he invited several younger colleagues at Washington University to be independent members of his "mega-lab" there, including David Amaral, Dennis O'Leary, Brent Stanfield, and myself (after Tom Woolsey had turned down the offer). On one hand, it was an easy offer to accept: I had always wanted to get back to California, and the Salk was a superb and exciting place to do neuroscience research. But, on the other hand, Neely and I had a wonderful life in St. Louis and had made many friends. Our son, Reid (our pride and joy), was born there in 1977, I got my first NIH grant the next year, and the year after that, I got a tenure-track position in Cowan's Department of Anatomy and Neurobiology, with the proviso I teach gross anatomy to the medical students. It was a course I had never taken, and dreaded, but now in hindsight am grateful I suffered through—the insight

into how the body works has been invaluable. Smelling of formaldehyde for two years was a small price to pay, although Neely might have disagreed.

Salk Institute, CRH Neuron, and Molecular Switching Hypothesis

Not only was my earlier acquaintance from Pomona College, Francis Crick, at the Salk Institute in 1980 but also, and more tantalizing for our research, so were Roger Guillemin, who had won the Nobel Prize in 1977 for his characterization of hypothalamic peptide neurotransmitter-neurohormones controlling the anterior pituitary, and Wylie Vale, his former student and colleague who recently had split off to form his own lab. They were in a heated race to characterize the elusive hypothalamic "corticotropin releasing factor" that controls anterior pituitary ACTH release, and thus adrenal corticosteroids that regulate blood glucose levels, especially during stress. It was as intense as the earlier "Nobel Duel" between Guillemin and Andrew Schally for the first hypothalamic releasing factors (Wade, 1981).

After we arrived, Paul spent about a year finishing the analysis of ascending noradrenergic projections to the PVH, which was published in *Science* (Sawchenko and Swanson, 1981). We then spent another year characterizing, to the extent possible, the putative neurotransmitter content of all known inputs of the PVH as well of the different PVH neuron types with projections to the dorsal vagal complex and spinal cord.

Four general principles emerged from this work, which we summarized in the *Annual Review of Neuroscience* (Swanson and Sawchenko, 1983). First, neural inputs to the PVH are quite diverse; there are several dozen, and they are widely distributed in the brain. Second, every source of these neural inputs ended in more than one PVH subdivision, usually in a unique pattern. Third, every projection we examined that ended in the magnocellular PVH subdivision also ended in the supraoptic nucleus. And, fourth, PVH neurons with descending projections to the dorsal vagal complex and spinal cord may express multiple neuropeptides.

In the meantime, there was another breakthrough: Vale's group beat out Guillemin's group in fully characterizing "corticotropin releasing factor" (Vale et al., 1981), which could then be called corticotropin releasing hormone (CRH). Specific antisera allowed cellular localization of the 41-residue neuropeptide, and preliminary immunohistochemical mapping in rat by Floyd Bloom suggested that the neuroendocrine CRH neurons were localized to the "medial anterior parvocellular region" of the PVH (a feature that immediately caught our attention because of the established role of the PVH in eating behavior). In addition, they reported the existence of several intrahypothalamic axon tracts and one group of axons entering the midbrain medial longitudinal fascicle (Bloom et al., 1982).

To characterize the PVH distribution more carefully, we began a detailed mapping study that instead identified immunoreactive neurons and fiber tracts divided into three broad parts throughout the brain (Swanson et al., 1983). The first part consisted of CRH neurons distributed through all PVH subdivisions but concentrated in the dorsal medial parvicellular part, combined with a dense axon bundle from the PVH to the median eminence. This PVH-median eminence projection was the only one we detected in which immunoreactivity clearly increased after adrenalectomy, which removes glucocorticoid negative feedback on the brain. The second part consisted of neuron groups and interconnected fiber systems stretching from the amygdala to the medulla and associated most closely with the limbic system and autonomic control mechanisms. And the third part consisted of interneurons concentrated in layers two and three of the cerebral cortex. The results suggested that central CRH systems are involved in controlling both neuroendocrine, autonomic, and perhaps behavioral and cognitive responses to stress.

Further studies revealed that PVH parvicellular neuroendocrine CRH neurons also express vasopressin following adrenalectomy (Sawchenko et al., 1984), which was independently reported by four other groups (reviewed in Swanson, 1991). We then went on to show that each of the three different structure-function PVH neuron populations express a remarkable variety of neurotransmitter peptides—at least eight in CRH parvicellular neuroendocrine neurons; that at least three of the same neuropeptide genes (CRH, vasopressin, and angiotensin II) are expressed in each of the three distinct neuron types; and that glucocorticoid hormones differentially regulate the expression, and thus, ratios of these three common neuropeptides in the three neuron types (Swanson, 1991). The CRH parvicellular neuroendocrine neuron itself provided the prototype for a uniquely complex neuron type: one with neurotransmitter, paracrine, and endocrine functions mediated by different compartments of its axonal tree, and one in which the ratio of neuropeptides varied with endocrine status (Swanson et al., 1987).

In the end, this analysis of the PVH provided a clear circuit model for the hypothalamic integration of autonomic, neuroendocrine, and behavioral mechanisms in the control of motivated or goal-oriented behavior, using ingestive behavior as an example. The analysis also suggested that when neurons express more than one neurotransmitter and have axon collaterals to more than one site, then changes in the ratio of those neurotransmitters might lead to the molecular (chemical or biochemical) switching of information flow through an otherwise structurally unchanged circuit. This was a molecular switching of information flow hypothesis that also suggested a mechanism for transient "silent synapses" (Swanson and Simmons, 1989; Swanson, 1991, 1992a, 1996).

HHMI, Transgenic Mice, and the Promoter-Transcription Factor Craze

The phenomenon of neurotransmitter expression plasticity naturally led to the question of underlying molecular mechanisms (Swanson, 1983), and an opportunity to explore this emerging field soon emerged. In 1983, Vale's group had characterized rat hypothalamic growth hormone-releasing hormone (GRH), and using their antibodies, we had mapped the brain distribution of this neuropeptide, including its neuroendocrine neurons, which are in the hypothalamic arcuate nucleus rather than the PVH (Sawchenko et al., 1985). At about the same time, Ron Evans at the Salk and Geof Rosenfeld at UCSD were teaming up to examine regulation of growth hormone gene expression, which is restricted to anterior pituitary somatotropes in the normal adult rodent body.

Their most spectacular result was the creation of extremely large mice, by using a hybrid transgene containing the structural part of the growth hormone gene driven by a "super" promotor from the metallothionein-I gene, resulting in abnormally high levels of growth hormone during development. The adults could be almost twice the normal body weight (Palmiter et al., 1982). These "supermice" even captured public attention to the extent that somewhat tongue-in-cheek editorials appeared in the *New York Times* and *Washington Post*. Late-night television icon Johnny Carson devoted much of one of his nightly monologues to an hilarious analysis of possible repercussions (Myelnikov, 2020).

Collaboration with Ron and Geof was an obvious opportunity—combining their molecular interests and experience with our structure-function interests and experience. One of our first projects together established the principle that fusion genes with multiple promotor regions can display novel expression patterns that differ from the endogenous expression patterns of either part of the fusion gene alone (Swanson et al., 1985). Our example was the growth hormone-metallothionein fusion transgene: neither growth hormone nor metallothionein-I are expressed in the normal brain, but in transgenic mice, the fusion gene was expressed in specific sets of brain neurons, with the highest expression levels, remarkably, in the PVH and supraoptic nucleus.

Another early project involved characterizing the nervous system expression pattern of a novel neuropeptide, α-CGPR, which is expressed by tissue-specific alternative splicing of mRNA from the "calcitonin gene" into either calcitonin or α-CGRP (Rosenfeld et al., 1983). This was followed up with the discovery of a second gene that encodes ß-CGRP, a peptide differing from α-CGRP by a single amino acid residue, and the finding that the brain spatial distribution of the two peptides is remarkably similar qualitatively, but with strikingly different expression levels in each locus. This work was led by a remarkably talented graduate student, Susan Amara (Amara et al.,

1985), who went on to a distinguished career in research at Yale and the Vollum Institute, and in administration at the National Institute of Mental Health (NIMH).

These two projects had important side effects. Experimentally, they led us to develop *in situ* hybridization methods with Jeff Arriza, one of Evans's students, and Donna Simmons, my very experienced, hard-working, and innovative lab manager—who eventually published what became the standard protocol for *in situ* hybridization in the nervous system (Simmons et al., 1989). Conceptually, they led to one of the first reviews of transgenic animal use for the study of development and models of human disease (Evans et al., 1985). And practically, these projects led to Ron, Geof, and I being appointed Investigators of the Howard Hughes Medical Institute (HHMI) in 1985, about a year after Sol Snyder had tried to recruit me to an HHMI position at Johns Hopkins. Around this time, Ron and Geof agreed to concentrate on their individual research interests, and my lab collaborated with Geof on a number of projects involving GRH and prolactin transgene expression and its spatial localization—and on the brainwide distribution during development and in the adult of a large new family of homeodomain regulatory genes (He et al., 1989; Alvarez-Bolado et al., 1995). Several of these POU-domain transcription factors turned out to have dynamic expression patterns from the earliest stages of PVH and supraoptic nucleus development, but it remained for others to demonstrate their critical roles (reviewed in Swanson, 2009).

PHAL: A Powerful New Anterograde Pathway Tracer

As I began collaborating with Evans and Rosenfeld, Paul established his independent research program, focusing on CRH and its central mechanisms of action, and eventually was named the inaugural Wylie Vale Chair at the Salk, fitting recognition for his distinguished research career. But early on, he teamed up with Charles (Chip) Gerfen, who had come from completing his doctoral work in Ronald Clavier's lab at Northwestern University to work with Cowan on the chick visual system. Chip and Paul embarked on a gamble to find a better anterograde pathway tracing method than autoradiography, which avoided the axon-of-passage problem, but was difficult to interpret because projection patterns were inferred from silver grain patterns over histological sections. Chip had experience with the new wheat germ agglutinin-HRP bidirectional pathway tracer, but axonal labeling was "fuzzy"—not nearly as crisp as the immunohistochemical labeling Paul showed him for vasopressinergic or oxytocinergic axons—and it involved axons-of-passage. On a hunch, they screened other plant lectins and hit the jackpot: *Phaseolus vulgaris* leucoagglutinin (PHAL).

In a model of careful validation (Gerfen and Sawchenko, 1984), they established that, following their protocol, PHAL is transported only

anterogradely in axons; that it is virtually never taken up and transported by axons-of-passage; that axons and their collaterals are labeled with the clarity of Golgi preparations; and, as we now know, that it is about an order of magnitude more sensitive than the autoradiographic method in detecting axonal projections. In collaboration with Chip, we published the first experimental paper using PHAL to trace central pathways (Swanson et al., 1984). First, we established with PHAL (and the retrograde tracer True blue) the structural existence of a direct pathway from the substantia innominata (ventral pallidum) and lateral preoptic area to the "mesencephalic locomotor region," and then our wonderful Canadian colleague Gordon Mogenson (whose book, *The Neurobiology of Behavior: An Introduction*, 1977, was invaluable to my thinking) confirmed the monosynaptic nature of the connection electrophysiologically, showing a roughly equal proportion of excitatory and inhibitory responses. For anterograde pathway tracing in rats, the autoradiographic method was the method of choice for a dozen years; since 1984, the nongenetic method of choice has been PHAL.

From Ingestive to Reproductive, Agonistic, and Behavioral State-Motivated Behavior Circuits

During our decade at the Salk, I balanced Vale, Evans, and Rosenfeld collaborations with ongoing work on circuitry related to motivated behaviors. The first immigrant to our Salk lab was a doctoral student of Roger Gorski, the well-known UCLA behavioral neuroendocrinologist who had discovered the "sexually dimorphic nucleus of the preoptic area" in rat (Gorski et al., 1978). The student was Richard (Rich) Simerly, and after hearing a talk I gave at UCLA in 1981, he wanted to apply our methodology and thinking about the ingestive behavior circuit to Gorski's sexually dimorphic nucleus and to what (due in no small part to his own work) would become known as the sexually dimorphic circuit in rodents. He made the drive between Los Angeles and the Salk countless times for his thesis work, and later as a postdoctoral fellow in the lab. His determination and creativity paid off with 21 papers from our collaboration (see Simerly, 2002).

Some highlights of his work include a PHAL analysis of projections from the medial preoptic nucleus, which includes Gorski's nucleus (Simerly and Swanson, 1988), and identification and detailed structural characterization of the anteroventral periventricular nucleus, a tiny sexually dimorphic nucleus in the preoptic region that controls the estrous cycle (e.g., Simerly et al., 1985). He also demonstrated that naturally occurring changes in estrogen levels during the estrus cycle change the ratio of neuropeptide gene expression in specific neuron populations of the sexually dimorphic circuit (Simerly et al., 1989), supporting the molecular switching of information flow hypothesis mentioned earlier for the PVH and the ingestive behavior system.

As an interesting aside, while this work on the rat sexually dimorphic circuit was progressing, the lab next door was occupied by the visual system neuroscientist Simon LeVay, who had established his reputation working with Torsten Wiesel and David Hubel at Harvard. Unfortunately, there was no communication between the two labs, so we were stunned to see Simon's famous paper appear in *Science* (LeVay, 1991)—claiming that one of four sexually dimorphic preoptic nuclei differs between presumably heterosexual and homosexual men, and that the one preoptic nucleus that differs in homosexual men is roughly equivalent in size to the presumably heterosexual female preoptic nucleus.

LeVay had been deeply affected by the AIDS epidemic and decided to abandon the visual system for the human hypothalamus, with a neuroanatomical study suggesting that human sexual orientation has a biological substrate. With that, he left academic science and transitioned into an author of scientifically balanced, popular books on gender identity and related topics. It was at that point, after the dust had settled, that we became friends, reconnecting in Los Angeles at a small cocktail party arranged by Neely for Luc Montagnier, who would go on to share a Nobel Prize for his discovery of the human immunodeficiency virus.

Next came Wally Lind (1982) from Kim Johnson's lab at the University of Iowa, Christer Köhler and Lena Haglund (1983) from Sweden, and Dennis Brittain (1984), my only graduate student in San Diego. Wally's thesis work had been on the role of the subfornical organ in drinking induced by circulating angiotensin-II, and he went on with us to characterize central projections of the subfornical organ with PHAL (Swanson and Lind, 1986) and to describe with immunohistochemistry the whole central angiotensin-II system (Lind et al., 1985), including an angiotensinergic subfornical organ to PVH connection (possibly explaining the angiotensin-induced drinking I had explored in my own thesis), and the dynamic expression of angiotensin-II in PVH neurons under the influence of glucocorticoids (Swanson et al., 1987). Unfortunately, Wally became discouraged with the slow pace of a research career and left to try his hand at creative writing.

Christer and Lena worked on the hypothalamus and hippocampus, most notably with the PHAL method. Lena described in detail the projection from the supramammillary nucleus to the hippocampal formation (Haglund et al., 1984); and Christer and I made the startling discovery that the lateral entorhinal area projects to the entire cerebral cortical mantle (Swanson and Köhler, 1986). Christer went on to a distinguished career in big pharma and Lena, a medical doctor, headed a medical branch in Strängnäs, about 60 miles from Stockholm.

Dennis did a superb PHAL analysis of complex brainwide projections from the infralimbic area of prefrontal cortex, using a Nikon Magiscan image analysis and mapping system. His valuable thesis (Brittain, 1988)

was never published as a journal article, however, and he left science for an engineering startup.

In 1984, we also saw the arrival of Alan Watts and his bride, Graciela Sanchez-Watts. At my request, Neely found the two of them a tiny studio apartment near the beach. Imagine her horror when she went to pick them up. After waiting for quite a while for them to appear, she located a pay phone (there were no cell phones at the time) and called to say that no couple with lots of luggage had gotten off any of the trains. It was then that I told her that maybe they were waiting at the trolley stop because they were coming in from Mexico. Oh, and by the way, they had a baby with them. Finally finding them, Neely was furious (at me, not at them). The "baby," Kathya, was 12 years old (from Graciela's previous marriage), and Neely was taking them to a tiny studio apartment barely large enough for two, let alone three. Despite my gaff, we remain colleagues and friends to this day, and still laugh about the first meeting. Alan is a now a professor of Biological Sciences at USC (in the lab next to mine), and Graciela is a research associate; she is a superb histologist specializing in immunohistochemistry and *in situ* hybridization and is the Watts lab manager.

Alan had trained in neuroendocrinology with George Fink at Oxford, where Graciela was a radioimmunoassay technician. For his thesis, Alan examined the effects of lighting schedules and gonadal steroid hormones on luteinizing hormone release from the anterior pituitary and was now interested in hypothalamic circuitry controlling cyclical luteinizing hormone release. For this he, Graciela, and I began with a careful reexamination of projections from the suprachiasmatic nucleus, because of its obvious role in the behavioral state system as the endogenous circadian rhythm generator and entrainer. A combination of PHAL and retrograde tracer-immunohistochemical methods was used (Watts et al., 1987; Watts and Swanson, 1987), and one finding stood out in particular. By far the densest terminal field was in what we named the subparaventricular zone, which stretched dorsally near the third ventricle and then arched below the PVH, and which, it turned out, generates basically the same output pattern as the suprachiasmatic nucleus itself only stronger—perhaps acting as a second-stage differentiating amplifier. He also demonstrated a natural diurnal rhythm of preproCRH mRNA in PVH neurons that correlates with daily fluctuations of corticosterone, providing another example of neurotransmitter expression plasticity influenced by steroid hormones (Watts and Swanson, 1989a). Finally, he developed and validated a combined *in situ* hybridization-immunohistochemistry-double retrograde tracing method that was applied to PVH projections to spinal cord and median eminence in the same animal (Watts and Swanson, 1989b).

The next big arrival, in 1987, was special indeed: Ju Gong from Xi'an, who four years later in 1991 would be the first neuroscientist elected to the Chinese Academy of Sciences. I had met Ju in 1984, when I spent a month

at the Peking Union Medical College under the sponsorship of the World Bank, which was evaluating Chinese institutions of higher education for major investment. My assignment was quite vague, and upon arrival, I was surprised to learn that I would be teaching a neuroanatomy course to about 50 professors from 23 universities around China. My second surprise was discovering that after my lecture, in English of course, it was repeated in Chinese by one of the professors—Ju Gong, whose delivery of the material was much better than mine! After the course was over, Ju invited us to his university and accompanied Neely and me to Xi'an on the 24-hour train, an unforgettable adventure. It turned out that he had grown up in Shanghai, the son of influential international publisher parents, and his English, and knowledge of American culture, were astonishing. Choosing to continue his medical training in China rather than fleeing to Taiwan with his parents, his career path seemed assured until the arrival of the Cultural Revolution in 1966. Forced to train uneducated peasants in the countryside to become physicians cut short the promise of an international research career. It wasn't until the end of this period that he was able to resume his research, losing more than 15 precious years in the process.

Ju had done the first study in China with the Nauta degeneration method in 1965, but to retool after the Cultural Revolution he did two sabbaticals, first with Tomas Hökfelt (1985–1986) at the Karolinska Institutet, and then with us at the Salk, where his project involved a then obscure part of the septal region called the bed nuclei of the stria terminalis (BST), which was known to receive a massive input from the amygdalar region. Ju used an insightful combination of cytoarchitectonic and chemoarchitectonic analyses to parcel the BST into about a dozen distinguishable nuclei and areas (Ju and Swanson, 1989; Ju et al., 1989), which laid the groundwork for a rational attack on their projections. I asked Ju to send me a student to carry out this project, which he promised to do when the right one came along.

The last postdoc coming to the lab in La Jolla (1988) was Newton Canteras, a medical doctor–doctoral graduate who had studied in São Paulo with Juarez Ricardo, a student of Nauta's who discovered in rat the ascending projections of the nucleus of the solitary tract to the hypothalamus (including the PVH) and endbrain. Newton's first project was to characterize with PHAL the brainwide projections of the posterior amygdalar nucleus (Canteras et al., 1992) and adjacent ventral subiculum (Canteras and Swanson, 1992), which end massively in restricted hypothalamic nuclei. Their significance for motivated behavior control circuits—and specifically those related to defensive–agonistic behaviors—became clear later.

Although our research was advancing quickly, all was not well. In the last half of the 1980s my impression was that the research leadership at HHMI, and a few of the younger, influential professors at the Salk, projected an air of disdain for anything other than molecular neuroscience. Cowan, in

his new role as chief scientific officer at the HHMI, even suggested directly that I "become a molecular biologist," as he had done in an administrative way, while dismissing his earlier career as a neuroanatomist. Cowan had gained the political power he had long aspired to and wielded a heavy stick against those who did not follow his lead—I was caught in the crosshairs. I enjoyed synergistic collaboration with the molecular biologists, and used their tools, but my core research interests were too deeply rooted in systems neuroscience. So, around 1988, I began exploring possible moves to UCLA and USC.

Then I got a phone call from Richard F. (Dick) Thompson, whose groundbreaking textbook I had used in college, and who was working out the neural circuit for Pavlovian learning in mammals (Thompson, 2013). He had been recruited from Stanford, where he served as chair of the Human Biology Program, to USC, and had just been appointed director of its unique Program in Neural, Informational, and Behavioral Sciences (NIBS), complete with a new research building. With this innovative, university-wide blend of neurobiology, computer science, and psychology, USC had a stated goal of being number one in U.S. neuroscience by the mid-1990s (Barinaga, 1988). Thompson wanted me to join the mix of new recruits. After protracted negotiations I accepted USC's generous offer, and with mutual disaffection, parted ways with the HHMI, crystallized by a personal talk at one of the HHMI research meetings with Paul Greengard (an HHMI investigator and senior advisor) in Bethesda. He knew I was uncomfortable and asked if I wanted to continue with the HHMI; I said no, and the final decision was then made for me.

Although our son Reid had a wonderful time growing up in the San Diego area, Neely and I loved Los Angeles and were excited to move to Manhattan Beach in the summer of 1990. During the next decade, the NIBS Program had great success (though never reaching number one), but by 2007, new administrations had lost interest and the provost (Max Nikias) and dean of the college (Howard Gilman) dissolved what was left of the NIBS Program to the dismay of most neuroscientists around the university.

Move to USC and a Long-Term Plan

The transition from San Diego to Los Angeles was relatively easy because a key group decided to move with me to the brand-new USC lab: Donna Simmons, Newton Canteras, and Dave Warren, my superb administrative assistant. Graciela Sanchez-Watts and Alan Watts came a year later, with Alan holding an independent tenure-track position and Graciela working as a research associate in his lab. Since then, Alan's lab has focused on neural mechanisms underlying eating behavior and the control of blood glucose levels.

I took the opportunity during the moving process to reevaluate my research priorities and to develop a long-term plan that was buffered by

a generous annual research fund as part of my recruitment package. The plan was simple and based on what I was most interested in and on what I was best at. The strategy was to finish a systematic examination of rat amygdalar-septal-hypothalamic circuit organization with the PHAL method (or a better one if it came along)—with the expectation of revealing basic organizing principles in the circuitry controlling different classes of motivated behavior. In essence, we would use the model developed for the PVH and ingestive behavior to uncover circuits underlying expression of the two other classes of motivated behavior common to all animals: reproductive (sexual and parental) and defensive/agonistic (fight or flight).

My first project was to finish and publish the rat brain atlas I had begun working on in 1974 at Cowan's suggestion. It had taken years of trial and error to find a suitable histological methodology, but finally, celloidin embedding was chosen, and at the Salk, I cut, Nissl-stained, and mounted serial transverse sections of the brain to be used for the atlas. Evans and Rosenfeld saw what I was doing and quipped that I was generating a library of brain sections, analogous to the genomic libraries they were generating. Then I photographed a selection of 73 levels on 4" x 5" negatives that were used for making prints on 16" x 20" sheets of photographic paper. In hindsight, it was fortunate the project had dragged on so long: Adobe Illustrator was first released in 1988, and I used it to create the atlas-level map that accompanied each atlas-level photomicrograph.

Elsevier, under the editorial guidance of Nello Spiteri, did a wonderful job of publishing *Brain Maps: Structure of the Rat Brain* (Swanson, 1992b), hardbound in oversized format, on thick paper. It had several unique and useful features. First, there was a complete, internally consistent terminology hierarchy, with annotations to the primary literature covering all structures in the hierarchy. Second, there was a foldout flat map of the central nervous system, analogous to Mercator's wall map of the globe. It was, in essence a fate map of the two-dimensional neural plate, and allowed for the display of any and all connections (crossed or uncrossed) on a single template. Third, all maps were provided in vector graphics format (Swanson, 1993) so any type of spatial data from our lab, or any other lab, could be plotted and displayed on standard reference templates, making comparisons between datasets easy, and simultaneously eliminating the need to make new pen and ink drawings for each experimental brain to be published.

These features proved invaluable when neuroinformatics began taking shape a few years later. And they were complemented and expanded when Gonzalo-Alvarez Bolado and I created a companion atlas, *Developmental Brain Maps: Structure of the Embryonic Rat Brain* (Alvarez-Bolado and Swanson, 1996), which grew out of our experience mapping developmental expression patterns of the POU-III homeobox gene family (Alvarez-Bolado et al., 1995) mentioned earlier.

Comprehensive Analysis of Connections and Circuits

Newton Canteras provided continuity between the Salk and USC in this domain. He went on to publish detailed accounts of projections from the medial amygdalar nucleus, ventromedial hypothalamic nucleus, and dorsal and ventral premammillary nuclei (see Swanson, 2000a), being the first to plot and publish his PHAL results on the new digital atlas (Canteras et al., 1992). On returning to the University of São Paulo, where he is now a professor in the Institute of Biomedical Sciences, he carried out a series of experiments involving exposure of a rat to a natural predator (cat), eliciting an innate defensive behavioral response, and examining the brain for increased Fos levels. Luckily, many of the Fos-labeled hypothalamic nuclei were interrelated by connections he had been studying with PHAL, and one region in particular stood out as the most heavily labeled: the obscure dorsal premammillary nucleus. When it was lesioned with ibotenic acid, the defensive behavioral response was eliminated (Canteras et al., 1997). These early findings by perhaps my most creative student-collaborator stimulated a large body of ingenious and pioneering research on the brain circuitry mediating defensive and other agonistic behaviors (see de Lima et al., 2019).

The first new additions to the USC lab were three outstanding doctoral students, Richard H. (Rick) Thompson in 1990, and Gorica Petrovich and Eleni Markakis in 1991. With respect to circuit analysis, Rick accomplished three main things as a graduate student and later as a postdoctoral fellow. First, he characterized in great detail the neural outputs and inputs of the dorsomedial hypothalamic nucleus (see Thompson and Swanson, 1998). Then he recognized and analyzed with PHAL the interconnections of a visceromotor pattern generator network in the periventricular hypothalamus, with the dorsomedial nucleus being its predominant node (Thompson and Swanson, 2003). Finally, he developed and validated a sophisticated double coinjection method for identifying chains of interconnected regions. Each injection was a mixture of an anterograde and retrograde tracer, and he used the method to define the neural system in which a tiny dorsomedial nucleus accumbens "hedonic hot spot" for eating behavior is embedded (Thompson and Swanson, 2010).

Gorica tackled the exceptionally difficult problem of subsystem organizational principles in the myriad of connections between the amygdalar region, hippocampal formation, and hypothalamus (Petrovich et al., 2001). As a postdoc with Dick Thompson and me, she followed up on the molecular switching of information flow hypothesis. Using *in situ* hybridization, Gorica demonstrated a conditioned increase in enkephalin (but not other neuropeptide) mRNA levels within neurons of the central amygdalar nucleus after rats were placed in an environment they associated with an unpleasant experience. She went on to study forebrain mechanisms of hunger control and is now a professor of psychology at Boston College.

Eleni came from Margaret (Peggy) Hollyday's developmental neuroscience lab at Bryn Mawr where she was involved in studies of chick spinal cord motoneuron pools. With us, Eleni carried out a detailed, global analysis of neuroendocrine motoneuron developmental birthdates with a combined BrdU-immunohistochemical-retrograde tracing methodology she developed (Markakis and Swanson, 1997).

Pierre-Yves Risold came to the lab in 1991 as a postdoctoral fellow after working on the localization of hypothalamic peptides with Claude Bugnon and Dominique Fellmann at the Université de Franche-Comté in Besançon. He and Canteras began by performing a detailed PHAL analysis of projections from the various parts of the anterior hypothalamic nucleus (Risold et al., 1994), long implicated in agonistic behavior, but then switched to a conceptually important reexamination of subsystem interactions between the hippocampal formation, septal region, and hypothalamus. The results, which were first summarized in *Science* (Risold and Swanson, 1996), showed how different domains in hippocampal fields CA3 and CA1 project upon a new parceling scheme for the lateral septal nucleus, which then shares bidirectional connections with various subsets of hypothalamic nuclei with identified functional attributes. The details of this new way of looking at functionally specialized hippocampo-septal-hypothalamic subsystems were published in two monograph-style articles (Risold and Swanson, 1997a, 1997b) and led Pierre to then perform more experiments and summarize the literature on the overall relationship between the hypothalamus and cerebral cortex (Risold et al., 1997). Pierre is now an associate professor at the Université de Franche-Comté in his hometown of Besançon.

Hong-Wei Dong, a young medical doctor (and doctoral candidate) arrived in 1997 from Xi'an, where he was trained by Ju Gong. Recall that 10 years earlier I had asked Ju to send me a student to work on BST connections, and Ju had finally found the right match. Hong-Wei was worth the wait. He spent about six years on a meticulous PHAL analysis of BST projections to the rest of the brain that resulted in eight long papers, which stand as the most systematic and thorough examination of axonal projections related to any single major part of the brain in mammals (see Dong et al., 2001; Dong and Swanson, 2006). Hong-Wei went on from USC to the Allen Institute for Brain Science, where he created their mouse brain reference atlas (Dong, 2007) modeled on our rat *Brain Maps* (Swanson, 2004), after which he was recruited by Arthur Toga to UCLA and then USC, to develop and head up a mouse connectome project. He is now a professor in the Department of Neurobiology at UCLA.

My last doctoral student, Lee Cenquizca, started the same year Hong-Wei arrived. We decided the time was ripe to reexamine the projections of hippocampal field CA1 with the PHAL method, and he covered all dorsoventral (septotemporal) levels with injections. The results showed that field CA1 has much more extensive projections to the rest of the cerebral

cortex than previously thought and that different dorsoventral levels generate projections to different sets of cortical areas (Cenquizca and Swanson, 2007). The results also showed that only the ventral pole of field CA1 projects to the hypothalamus, innervating nuclei involved in controlling motivated behavior, and to midline thalamic nuclei (Cenquizca and Swanson, 2006). Although admitted to medical school, and having his choice of postdocs, Lee decided the most worthwhile thing he could do next was give back to the community where he grew up and is now a professor in the life sciences at Los Angeles City College.

We began a systematic attack on the last remaining enigma of the hypothalamus, the lateral zone, which lasted from around 1992 until funding ran out in 2015. The greatest impetus during this period was the recognition in the lateral hypothalamic area of two distinctive neuron groups with very different projections—the parasubthalamic nucleus (Goto and Swanson, 2004) and subfornical region (Goto et al., 2005)—and this led us to a new parceling scheme with about two dozen parts (Swanson et al., 2005) and a new guide for connectivity analyses. The person who took up this new strategy was Joel Hahn, who had just finished his doctoral work on hypothalamic circuitry related to ovulation with Clive Coen at King's College London.

Joel meticulously analyzed and superbly illustrated the inputs and outputs of five parts of the lateral hypothalamic area middle group and he found, with coinjections of PHAL/cholera toxin B, that they have the most complex set of connections of any known part of the nervous system (Hahn and Swanson, 2010, 2012, 2015). Although we did not quite finish analyzing all parts of the lateral hypothalamic zone (grant reviewers said that despite excellent productivity and important technical innovations, we were "just completing a dataset" without functional analysis, a point I return to in the Epilogue), clearly it is a highly differentiated part of the brain, with roughly the same number of parts as the thalamus, although not as clearly distinguishable. The lateral hypothalamic zone is a rich continent waiting to be explored thoroughly, as the thalamus was a century earlier.

The Birth of Neuroinformatics

Since my thesis work on ingestive behavior hot spots, the research just outlined had been guided by Grossman's hypothesis about the existence of "motivation-specific circuits" (Grossman, 1960), which I am sure was heavily influenced by Eliot Stellar's brilliant review, *The Physiology of Motivation* (Stellar, 1954). So, as the connectional data accumulated, new insights into subsystem organization began to emerge, first with my friend Gordon Mogenson in a paper called "Neural Mechanisms for the Functional Coupling of Autonomic, Endocrine and Somatomotor Responses in Adaptive Behavior" (Swanson and Mogenson, 1981); then in "The Neural Basis of

Motivated Behavior" (Swanson, 1989) and "Cerebral Hemisphere Regulation of Motivated Behavior" (Swanson, 2000a); and finally, in *Brain Architecture: Understanding the Basic Plan* (Swanson, 2003). But the amount of relevant neuroscience data was accumulating at an unmanageable rate.

The Institute of Medicine (National Academy of Medicine since 2015) recognized the information explosion obstacle and charged a Committee on a National Neural Circuitry Database, which met during 1989–1990 and was chaired by Joseph C. Martin (then dean of the UCSF Medical School), to recommend solutions. I was fortunate to serve on the committee, whose final vision could be rephrased in today's jargon as "create Google Earth for the brain" and whose work was summarized in a prescient book, *Mapping the Brain and Its Functions: Integrating Enabling Technologies into Neuroscience Research* (Pechura and Martin, 1991). Its publication could be said to mark the birth of neuroinformatics, which was nurtured by an ambitious, decade-long Human Brain Project: Neuroinformatics (HBP) that began in 1995, was sponsored by 16 federal organizations, and was coordinated by the NIMH (Huerta et al., 1993, 2006).

USC was awarded a first- (and second-) round HBP program project grant under the leadership of Michael Arbib, whose doctoral advisor in mathematics at MIT was Norbert Wiener, the brilliant founder of cybernetics. In hindsight, the best outcome of this funding was the working collaborations it promoted between faculty and students in computer science and neuroscience. I began to learn about database technology and my computer science colleagues began to learn about experimental methodology in the life sciences—and we all struggled to figure out how to merge the two in useful ways for both communities (Dashti et al., 1997; Swanson, 2001), a struggle that continues at an excruciatingly slow pace. The bioinformatics that earlier grew out of molecular biology had two great advantages: a powerful and simple conceptual framework, the double-helix model of DNA (Watson and Crick, 1953), and sequences of linear information (encoded as nucleic acids or amino acids) for databases. In contrast, neuroinformatics had the most complex three-dimensional object known to science, the brain, and no overarching conceptual framework at the systems level.

Gully Burns was the first postdoctoral fellow to join our HBP efforts, in 1997. He was just finishing his doctorate of philosophy at Oxford, and for it had collaborated with Malcolm Young at the University of Newcastle upon Tyne on a project to analyze, with multidimensional scaling and cluster analysis methodologies, rat brain connectivity data they had collated from the literature. On the basis of this experience, one important reason he was drawn to our group was the complete, internally consistent, and hierarchically organized nomenclature I had developed for the digital rat brain atlas described earlier (Swanson, 1992). Basically, his goal was to develop a hybrid textual-visual database system, using the nomenclature table for labeling data tables and the digital atlas for displaying spatially indexed information

in a stack of spatially registered vector graphics layers (Shahabi et al., 1999; Dashti et al., 2001; Burns et al., 2006).

In the middle of the HBP era, a Romanian student, Mihail Bota, finished his doctorate with Arbib and joined our group as a postdoctoral fellow to develop a comprehensive Brain Architecture Knowledge Management System (BAMS). The first outcome was a *Perspective* article for *Nature Neuroscience* in which Mihai, Hong-Wei, and I accomplished two things. First, we laid out the basic problems associated with establishing the fundamental structural architecture of brain circuitry as a prerequisite for explaining behavior mechanistically. And, second, we introduced version 1.0 of BAMS (Bota et al., 2003), which went through a series of enhancements (see Bota et al., 2014). One of the basic problems with building federated database tables appropriate for inference engines was a total lack of nomenclature standardization, something foreign to more advanced fields like chemistry and electrical engineering.

During HBP meetings in San Diego, Arthur Toga (UCLA), Douglas Bowden (University of Washington), Steve Koslow (NIMH), and I informally discussed the problem of nomenclature chaos at length, and we agreed its solution was fundamental to progress in neuroinformatics. Bowden decided to evaluate and systematize terms in current use, and eventually implemented *NeuroNames* (Bowden and Dubach, 2003). Building on the nomenclature tables in *Brain Maps* (Swanson, 1992), I decided to take a comprehensive historical approach instead. During the course of this work, we proposed a solution to the neuron classification problem (Bota and Swanson, 2007a) and organized the first (and unfortunately only) International Neuroinformatics Coordinating Facility (INCF) Workshop on Neuroanatomical Nomenclature and Taxonomy, in Stockholm (Bota and Swanson, 2008). Finally, nearly 20 years later, the project culminated in the publication of a massive, 1,054-page book, *Neuroanatomical Terminology: A Lexicon of Classical Origins and Historical Foundations* (Swanson, 2015), and a supplement on the cerebral cortex (Swanson and Hof, 2019), that together laid out a defined and internally consistent vocabulary for all parts of the nervous system in humans and other mammals.

Connectomes

Shortly after Francis Crick died on July 28, 2004, the Salk Institute held a memorial service with Jim Watson as a featured speaker. At the reception afterward, I was surprised when Watson approached me with the anecdote that when Crick came to the Salk and switched his interests to neuroscience, the first thing he told Watson was that a physical wiring diagram was needed, analogous to the double-helix model. Then I was even more surprised when he said he hoped I would work with him and others at Cold Spring Harbor Laboratory to accomplish such a goal. This led to a

joint proposal that Partha Mitra (whom I'd met at a McKnight Foundation Meeting), John Doyle (Caltech), Hans Breiter (Harvard), and I made to the Keck Foundation in Los Angeles for a pilot Brain Architecture project, which was approved in 2006 for three years and centered at Cold Spring Harbor. At the end of those three years, a position paper advocating a coordinated effort to determine brainwide connectivity in model organisms was written by Partha with input from 36 other committed researchers, including myself, John Doyle, Hans Breiter, and Jim Watson (Bohland et al., 2009).

Coinciding with these developments, Olaf Sporns, Giulio Tononi, and Rolf Kötter made a conceptual breakthrough when they gave the name "human connectome" to a comprehensive structural description (database) of the network of elements and connections forming the human brain, analogous in principle but not in practice to the human genome, which had been inspired by Watson and Crick's double-helix model (Sporns et al., 2005). This stimulated us to put the rat connectional data entered in BAMS into a connection matrix, with about 10% of all possible connections accounted for—mostly from data generated in our own lab (Bota and Swanson, 2007b)—and to begin thinking about a more systematic approach to connectomic approaches in rat and mouse (Bota et al., 2012).

The stimulus for a mouse brain connectome came from Hong-Wei Dong after coming from UCLA to one of our lab meetings in August 2008. With youthful enthusiasm and optimism, he told me he thought he could do a complete mouse connectome in two years quite cheaply—using the double-coinjection method Rick Thompson was developing, and eventually published (Thompson and Swanson, 2010)—if only he had the right microscope. Three months later, I was in St. Louis at a meeting organized by Marc Raichle. At dinner with Marc and Olaf Sporns, I mentioned the possibility of a mouse connectome project. Marc was particularly enthusiastic and helpful, especially with Tom Insel, director of the NIMH, who was promoting large-scale projects for neuroscience (Insel et al., 2004). So, in the end, Hong-Wei got his microscope through a supplement to one of Toga's large grants in 2009, and then got his own NIMH funding in 2012. The two-year prediction is long forgotten, although excellent progress has been made (by the Allen Institute for Brain Sciences as well), but nevertheless, a great deal remains to be done to achieve a complete and systematic mouse brain connectome using the latest technology.

My last graduate student arrived in 2011. Ramsay Brown had taken my *Brain Architecture* course as an undergraduate, and he was inspired by the idea of creating a "Google map for the brain." He was an enthusiastic, outgoing, fast-thinking computer nerd. Building on a foundational model of nervous system structural connectivity that Bota and I had published the year before (Swanson and Bota, 2010), Ramsay began by creating a formal modeling language, in reality, an internally consistent notation scheme for the systematic description, unambiguous communication, and automated

digital curation (with bar codes) of neural connectivity (Brown and Swanson, 2013). He then created a prototype interactive online brain mapping application (Brown and Swanson, 2015). Impatient, he took a master's degree, and successfully entered the world of web-based startups, echoing Dennis Brittain's departure from the Salk lab in the late 1980s.

The Ongoing Neurome Project

In 2013, we began an in-depth discussion about how to adopt a more systematic approach to probing the rat connectome, starting at the rostral end with the cerebral cortex and then, if feasible, working our way caudally through the classic major subdivisions (Swanson, 2000b). Unbeknownst to me, Bota began collating the experimental pathway tracing literature on rat cerebral cortical association connections and about a year (and nearly 4,000 hours of work) later he had assembled data on the existence of 1,923 macroconnections between the 73 cortical regions in the analysis. There are 5,256 possible connections between 73 regions, and he found data for more than 80% of all possible connections. The resulting directed and weighted connection matrix for rat cortical association connections was foundational. First, it suggested that this approach was feasible and that perhaps the greater part of the rat connectome was already in the literature, based on research published since the neuroanatomy revolution of the 1970s (Swanson, 1999). And, second, it prompted us to invite Olaf Sporns to join the project as the network analysis expert. Mihai had earlier gotten Olaf involved in a neuroinformatics project to analyze the relationship between molecular expression patterns and neuron populations (Bota et al., 2012). Olaf readily agreed to the new proposal.

Our first paper, on the organization of the cerebral cortical association network, appeared in 2015 (Bota et al., 2015). In it, we suggested that to explain behavior in mechanistic terms it would be necessary not just to understand the basic wiring diagram of the brain but also to understand the basic organizing principles of the nervous system as a whole—how the brain communicates with and directs the rest of the body—thus extending the concept of a connectome to that of a neurome. Unfortunately, this paper coincided with the end of our NIH grant support for neuroinformatics (as mentioned earlier, our NIH support for experimental research also ran out that year), and Mihai, who had been an exceptionally hardworking and valuable colleague, left for positions with Maryann Martone's neuroinformatics group at UCSD, and then with Pavel Osten and Partha Mitra at Cold Spring Harbor.

At that point, Joel Hahn joined the effort and together with Olaf, we decided to go for the rat neurome at the macrolevel of analysis, using the basic strategy we had developed for the cortical association network, which

Jeff Lichtman and I summarized in the *Annual Review of Neuroscience* (Swanson and Lichtman, 2016). At the time, we thought a rat neurome project might take about 10 years for the three of us to complete, without external funding, which we have not yet received (except for three years of partial support for Joel's salary from the Kavli Foundation, thanks to Miyoung Chun). Joel's first major contribution was the creation of an elaborate, conditionally formatted Excel worksheet (Axiome) to record connection report metadata and port it to MATLAB for network analysis by Olaf (Swanson et al., 2016). This tool speeded up by an order of magnitude the expert collation procedure and, at the same time, increased its accuracy—making the estimate of a 10-year project realistic.

With Mihai gone, I decided to collate again the cortical association network and extend the analysis to cortical commissural connections. Our cortical association paper was the most complete to date, but it had not broken significant new ground—similar analyses had already been done on monkey, cat, and mouse by others. But cortical commissural connections had not been analyzed systematically, nor had any major subcortical nervous system subdivision. This collation identified connectional data for 94% of the 23,562 possible connections between 144 cortical regions on both sides of the brain, strengthening our hypothesis that most of the rat neurome might already be in the literature (Swanson et al., 2017). The network analysis revealed small sets of intracortical hubs, rich club members, and subsystems as well as a set of 14 unexpected "rules" associated with the distribution of commissural connections. This included the observation that there is an order of magnitude more heterotopic connections (from a particular region on one side, to a noncorresponding region on the other side) than homotopic connections (from a particular region on one side, to the corresponding region on the other side).

To date, we have published eight papers on the rat neurome, covering the intrinsic network connectivity of the bilateral cerebral cortex, cerebral nuclei, endbrain (cerebral cortex and nuclei together), thalamus, hypothalamus, interbrain (thalamus and hypothalamus together), and forebrain (endbrain and interbrain together). As a member of the National Academy of Sciences, I was fortunate to have quick access to quality publication of our findings in their *Proceedings*.

References to the earlier work are found in the forebrain paper (Swanson et al., 2020), which is based on 375,020 separate reports expertly collated from the experimental pathway-tracing literature about an axonal connection from one forebrain gray matter region to another gray matter region. Because there are 216,690 possible macroconnections between the 466 forebrain gray matter regions on both sides of the brain (466^2-466), on average there are almost two (actually 1.7) different reports in the literature for each possible connection. This figure is complemented by the fact that evidence

was found for the presence or absence of 95% of the possible 216,690 connections, thus leaving only 5% of the possible connections completely unexplored. The analysis of this rich dataset, which represents a halfway point in our neurome project, is notable for several reasons.

First, the forebrain connectome is sexually dimorphic, so separate analyses and network features are associated with the adult male and female rat. Second, in addition to being weighted and directed, all forebrain connections have a provisional sign: they are associated with excitatory/glutamatergic or inhibitory/GABA synaptic transmission, with all of the usual disclaimers, as first done for the hypothalamic connectome (Hahn et al., 2019). Third, the extremely enlightening multiresolution consensus clustering method introduced by Lucas Jeub, Olaf Sporns, and Santo Fortunato (Jeub et al., 2018), and first applied to the endbrain connectome analysis (Swanson et al., 2018), was used to create a hierarchy of forebrain structure-function subsystems based on sets of highly interconnected regions. There are 166 structure-function subsystems or modules, arranged such that there are just two at the top level and 92 at the bottom level of the hierarchy, which now acts as a powerful hypothesis-generating engine for experimental manipulation of the intra-forebrain wiring diagram.

Our experience thus far clearly shows that analysis of subconnectomes (whether in cerebral cortex, hypothalamus, or forebrain) yields fundamental insight into the intrinsic network organization associated with particular subconnectomes, and also shows that network features change when anatomical coverage of a network changes. Thus, basic design features of an entire nervous system wiring diagram cannot emerge until a neurome project is completed.

Conversely, our experience also suggests that a rather complete neurome for at least one mammal, the rat, is already in the literature at the macroscale of analysis. This is the result of almost 50 years of research with experimental pathway tracing methods by around 275 laboratories. Because generating this type of circuitry data has been the focus of our lab throughout that 50-year period, it may not be surprising that, as outlined earlier, we have generated about 26.3% of the connection reports for the forebrain analysis. Other major contributors include groups headed by Clif Saper (4.6%), Robert Vertes (3.4%), Joel Price (2.9%), and Sara Shammah-Lagnado (2.6%). It is no coincidence that three of the five groups originated in Max Cowan's Anatomy and Neurobiology Department at Washington University in the 1970s, or that about 55% of the connection reports were published in the *Journal of Comparative Neurology* (1 of 53 sources), which was edited by Cowan from 1968–1980, and by Saper from 1994–2011. Finally, it is encouraging to see that the results of this truly basic research may begin to find translational research applications, exemplified by a recent network hypothesis about possible mechanisms underlying the pattern of tauopathy spread in Alzheimer's disease (Small and Swanson, 2019).

History, Cajal, Books, and Teaching

Cowan's Department of Anatomy and Neurobiology in the 1970s arguably had the best concentration of structural neuroscience-neuroanatomy expertise ever assembled, with major contributors including, among others, Max himself, Ted Jones, Richard and Mary Bunge, Joel Price, Tom Woolsey, David Gottlieb, Arthur Loewy, and Clif Saper. Part of the excellence was a pervasive respect for precedence and the history of science that was probably a by-product of Max, Ted, and Joel's training at Oxford. Fortunately, the entrance to the superb Medical School Library, directed by Estelle Brodman, was just one flight of stairs down from my lab, making it easy to carry out the scholarship expected in traditional anatomical and physiological publications. But another part of the excellence was a pervasive admiration for the work of Santiago Ramón y Cajal, whose late-nineteenth-century neuron doctrine and law of functional polarity were the cornerstones of modern neuroscience at the cellular and systems levels of analysis.

In 1978, I spent the summer at the University of Bergen through the invitation of Wilhelm Harkmark and Bolek Srebro, doing a Golgi study of neurons in layer two of the hippocampal formation's presubiculum—and I wondered whether Cajal had already described the neurons I was drawing. We were staying in the house of psychology professor Holger Ursin, who was on sabbatical at UCSD and who had a copy of Cajal's two-volume masterpiece, the *Histologie* (1909–1911), on his shelves. I asked Neely if she would translate the appropriate chapter (she was a French major in college), and she did an excellent job; Cajal had briefly mentioned three different types of neuron in layer two, but none were illustrated.

Coincidentally, three years later Cowan was approached by the *Consejo Superior de Investigaciones Científicas* (Madrid) about overseeing an English translation of the *Histologie*, and I soon gave him a copy of Neely's translation, which I had edited for scientific content and style. In 1984, Max finally received a first payment from the *Consejo* and gave the job of doing an initial translation to Neely. That money allowed her to buy an IBM PC, introduced only a year earlier. Four years later, Neely finished her job, but Max had moved on to the HHMI and was too busy for the project. I felt Neely and I could finish the job, but as proof of principle suggested we first translate Cajal's short but key precursor, *Nouvelles Idées sur la Structure du Système Nerveux chez l'Homme et chez les Vertebrés* (1894). We discussed the plan over margaritas at dinner one night with a new Salk arrival from Yale, Charles (Chuck) Stevens, and through a contact of his at MIT Press, Fiona Stevens (no relation), we secured a contract for the translation (Swanson and Swanson, 1990). Then, in 1991, Neely and I signed a contract with Oxford University Press, arranged by Jeffrey House (who was married to Fiona Stevens), for the *Histologie* translation, which was published in 1995 (Swanson and Swanson, 1995). To round things out, Neely and I translated

a third book of Cajal's, his entertaining and still quite instructive *Reglas y Consejos sobre Investigación Cientifica: Los tónicos de la voluntad* (*Advice to a Young Investigator*; Swanson and Swanson, 1998). It was an honor and profound learning experience to deal so intimately with Cajal's written work. It is also remarkable to see how his reputation as the greatest scientist in Spain's long history, and as an artist, continues to grow (Saltz, 2018).

Considering my love of neuroscience history, it is no surprise that one of my favorite pastimes (aside from family, friends, and travel) is collecting books related in one way or another to the structure and function of the nervous system. This bibliomania really started in 1979. On our way back from the summer in Kuypers's Rotterdam laboratory, we stopped in London, and at an eye-opening visit to Dawson's of Pall Mall bookstore, Neely and I bought a copy of Bernhard Siegfried Albinus's magnificent *Tabulae Sceleti et Musculorum Corporis Humani* of 1747. It remains a cornerstone of my collection, along with the acquisition over 40 years later of a copy of Dryander's 1537 *Anatomiae*, the first book devoted to brain anatomy. Over the years, it has been a pleasure to get to know and work with many book dealers and collectors, including Jeremy Norman, Barbara Rootenberg, Malcolm Kottler, the late Michael Thompson and William Conrad Cooper, James Tait Goodrich, Bruce Fye, Ove Hagelin, Arthur Lyons, Eugene Flamm, Fritz-Dieter Söhn, and Christian Westergard, along with Daniel Lewis and Joel Klein at the Huntington Library.

I also have found teaching a rewarding way to pass along ways of thinking and knowledge to the next generation. My introduction was as an assistant in neural science courses that Max Cowan and Ted Jones gave at Washington University. But the real work began during the Salk years, when I volunteered from 1982 to 1989 to teach the neuroanatomy course required of all first-year neuroscience graduate students at UCSD. It had previously been taught by the eminent neuroscientist Robert Y. Moore, but he had moved on to Stony Brook University. I gave all of the lectures and labs, which was an invaluable learning experience. After I left for USC, my close friend Harvey Karten, another eminent neuroscientist who came to UCSD in 1986, took over. Then, when we moved to USC, I offered a similar course for the Neurobiology Graduate Program, and this UCSD-USC coursework led to the book *Brain Architecture: Understanding the Basic Plan* (Swanson, 2003). It was not a traditional neuroanatomy textbook detailing all of the major components of the nervous system and the connections between them. Instead, it focused on overall design principles and a novel set of four basic structure-function subsystems.

Administration

I was determined to spend an absolute minimum amount of time on administration, and a maximum on research, until I got a call in 1998 from the

dean of the college at USC asking if he could come over to my office to talk. He asked if I would take over the job of dean of research for two years from molecular biologist Maria Pellegrini, who was leaving for the Keck Foundation. I said no, but within 10 minutes, he convinced me to do it half-time, focusing on the larger issues and continuing my research at the same time. The dean was Morton O. (Morty) Schapiro, who went on to great success as president of Williams College, and then Northwestern University. He was the best administrator with whom I ever worked, but at the end of the two years, I felt I was doing two full-time jobs and decided to focus on one—my real love, research.

To me, one aspect of research has been giving back to the community through professional organizations, first and foremost the Society for Neuroscience. Since that first meeting in 1971 when I was looking for a postdoc, I have attended every single meeting. One accomplishment as president (2012–2013), and later as co-chair with Magda Giordano of the 50th Anniversary Planning Group, was to help ensure that the first 50 years of the society's history was thoroughly and objectively preserved and documented. A second enriching experience has been membership in the Cajal Club, the oldest neuroscience organization in North America, having been founded one midnight in 1947 by a group of socializing brain researchers at the annual meeting of the American Association of Anatomists (Whitlock, 2007). In typical club fashion, I was recruited late one night at a New Orleans bar in 2003 (during a Society for Neuroscience meeting) by Charles (Chuck) Ribak, Efrian Azmitia, and John Morrison, and served as president from 2004 to 2006. Highlights from that appointment included transitioning from the American Association of Anatomists meeting to the Society for Neuroscience meeting, and two successful international conferences, one at the Karolinska Institutet in 2006 to celebrate the 100th anniversary of the Nobel Prize to Cajal and Golgi (Swanson et al., 2007), and the other at the National Autonomous University of Mexico's Institute of Neurobiology in Querétaro (Mexico), on degeneration and regeneration in the nervous system (Ribak et al., 2009). And later, as historian and archivist, I orchestrated transfer of the Club archives to the Louise M. Darling Biomedical Library at UCLA (which also holds the Society for Neuroscience archives) with the help of Chuck and Russell Johnson, Curator of the History and Special Collections for the Sciences. Finally, I had the honor of serving as secretary general (2015–2017) of the International Brain Research Organization (IBRO), where I helped launch Young IBRO, an initiative to incorporate a diverse group of younger researchers into the deliberations and decision making of the organization.

Epilogue

Looking back, I have been exceptionally lucky. I had inspirational mentors at Pomona College and Washington University, a truly outstanding

succession of students and collaborators, and invaluable administrative support from David Warren and Cathleen Crayton. But most important, I have a loving and supportive family in Neely, Reid, and Reid's partner Lee. I could not have been prouder in 2010 when I accompanied Reid—both of us in USC's academic gowns—as he received his doctorate in computer science. And I was exposed to a whole different creativity subculture through Neely's Los Angeles career in television production and as a lecturer in USC's School of Cinematic Arts. What fun and enlightenment to interact with directors like my very good friend Arvin Brown, producers like another friend, Alice West, writers like David E. Kelley, and actors like Mariette Hartley, Peter MacNicol, Kate Burton, Rita Moreno, Loretta Divine, and Michael York. Imagine my surprise to learn that Sharon Stone, who was introduced to me by Neely while she was working on set, had read *Brain Architecture* as part of her desire to learn as much about the brain as she could following her cerebral aneurysm surgery. How fulfilling to learn they are as interested in learning about the brain as I am in the whole creative process of television.

And, of course, timing is always a critical factor. I was in on the beginning of the 1970s experimental neuroanatomy revolution and rode the crest of that wave thanks to NIH support until 2015, when another wave began forming—one that focused on systems neuroscience, theoretical network analysis, and the relationship between neural circuits and behavior. But with waves there are troughs, and structural biology (including neuroanatomy) has always had its ups and downs. This, despite the basic principle that structure and function are equally important, two sides of the same coin, which has been driven home to me from teaching the systems component of introductory biology for almost 20 years at USC.

For me, the turn of the twenty-first century was a trough when elite journals would publish structural analyses only if they were a component of, and supported, functional analyses. The same generally held true for the funding of NIH grant applications. Of the approximately 5,000 RO1 grants related to neuroscience, only a handful were focused on in-depth analyses of structural problems, a major shift from 20 years earlier. History proves that this is a short-sighted, counterproductive, and unbalanced approach to the life sciences, especially because a new generation of powerful structural neuroscience tools has been developed recently. Accurate and reliable structural analyses of lasting value are time consuming, whereas small, focused studies add precious little when appended as afterthoughts to functional analyses. The best long-term outcome for neuroscience, and for the life sciences generally, depends on two basic ingredients. One is a healthy balance between structural and functional analyses, and the other is a healthy balance between experimental and theoretical approaches, like that found in more established fields, such as physics.

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