

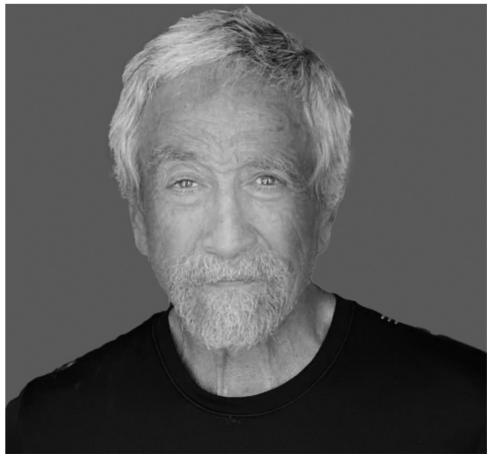
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Jack L. Feldman

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Jack L. Feldman

Born:

Brooklyn, New York
January 6, 1948

Education:

Polytechnic Institute of Brooklyn, BS, MS (Physics, 1968)
University of Chicago, PhD (Physics, 1973)

Appointments:

Postdoctoral Fellow, Université de Paris VI, France (1973–1974)
Postdoctoral Fellow to Assistant Professor, Albert Einstein College of Medicine (1975–1978)
Assistant Professor to Professor, Northwestern University (1978–1986)
Visiting Scientist, Karolinska Institute, Sweden (1982–1983)
Professor to Distinguished Professor, UCLA (1986–)
Chair, Department of Physiological Science, College of Letters and Science, UCLA (1991–1997)
Chair, Department of Neurobiology, David Geffen School of Medicine, UCLA (1996–2001)

Honors and Awards (Selected):

Research Career Development Award, NIH (1979–1984)
Swedish Medical Research Council Visiting Scientist Fellowship (1982–1983)
Guest Professor, Georg-August-Universität, Göttingen, FRG (1989)
Christian Anfinsen Lecturer, NIH (1989)
MERIT Award, NIH (1990–1997)
Julius H. Comroe Jr. Distinguished Lectureship, American Physiological Society (1995)
Society for Neuroscience Special Lecturer (2002, 2016)
Fellow, American Association for the Advancement of Science (2009)
Hodgkin Huxley Katz Prize, The Physiological Society (2016)
Faculty Research Lecture, UCLA (2018)
Outstanding Investigator Award, NHLBI, NIH (2017–2031)
David Geffen School of Medicine Chair in Neuroscience, UCLA (2022–)

Jack L. Feldman is a neuroscientist whose work redefined the neural basis of mammalian breathing. His research led to the discovery and naming of the preBötzinger Complex (preBötC), a small, anatomically defined region of the ventrolateral medulla that generates inspiratory rhythm. This discovery established that respiratory rhythm arises from a compact neural kernel rather than from a broadly distributed network, defining a unifying framework for the control of breathing in which a core circuit generates rhythm and recruits additional oscillatory and modulatory sites to shape breathing across behavioral and physiological states. Feldman and collaborators further showed that distinct microcircuits generate specific respiratory behaviors, including sighs, and that individual breaths likely arise from small amplitude burstlets emerging from transiently synchronized activity within the preBötC. Collectively, these findings established breathing as a mechanistically defined neuromotor process and articulated a general organizing principle by which small neural kernels generate, modulate, and sustain vital behaviors.

Jack L. Feldman

My path in life has been a mix of thoughtful planning, happenstance, and serendipity, including my fortunate timing of birth as a baby boomer.

Early Life

I was born in 1948 at Maimonides Hospital in Brooklyn, the first child of first-generation Americans. My grandparents on both sides had fled Eastern Europe in the early twentieth century, arriving at Ellis Island with little and settling in Brooklyn among other Jewish immigrants. Both grandfathers worked in the garment district, and both grandmothers ran households that anchored extended family life.

My father, Norman, the middle of three brothers, left college during the Depression and joined the New York City Fire Department, where he rose to the rank of captain. Though eligible for further promotion, he preferred the captain's work and later retired on a modest pension, continuing to work into his late sixties as a margin clerk on Wall Street. My mother, Frances, had a remarkable talent for sales and personal connections. She sold encyclopedias and cosmetics, and later worked as a personal shopper, bringing clothing directly to her customers' homes. From her, I learned how to communicate and negotiate, skills that proved unexpectedly valuable in science as well as in life. My parents eventually moved to South Florida.

To dig a bit deeper into my biological heritage, I sent a swab to 23andMe. Besides markers indicating 99.7 percent Ashkenazi Jewish heritage, my analysis revealed genetic markers shared by a large fraction of people of Asian descent, often attributed, somewhat whimsically, to Genghis Khan, a reminder that ancestry, like biology, is best interpreted cautiously.

I am the oldest of four brothers. We first lived on Brighton 5th Street, a block from the beach and a block from the elevated subway, in a small apartment surrounded by extended family. When I was in sixth grade, we moved to Fillmore Gardens, a modest neighborhood of attached apartments with ample open space and an abundance of boys my age. Most afternoons were spent outdoors in self-organized games: baseball, touch football, roller hockey, basketball, and a broad range of sports endemic to Brooklyn, New York: box ball, stickball, handball of various sorts, skelzie, stoop ball, and several others. There were no parents to be seen (except in Little League baseball); we were self-governing. While we might disagree on whether something was fair or foul, cheating usually resulted in being ostracized or facing the harsh consequences of tough play. Not quite the

Lord of the Flies, but we certainly learned to work and play together as peers. And no one ever got a trophy. This certainly catalyzed my innate competitiveness and my understanding of the value of teamwork.

Elementary and Junior High School

Elementary school was not memorable. At some point, my classmates and I were tracked. The "smartest" of us, as assessed by some testing voodoo, were placed in SP (Special Progress) at Marine Park Junior High School 278, which compressed grades seven to nine into two years, sending us on to James Madison High School as somewhat young sophomores. My SP class had around 30 kids. Surprisingly, although we might have been academic nerds, we developed a collective social life with parties most weekends. These parties were mostly prim and proper, with awkwardness exacerbated by the different timetables we each had for entering adolescence.

James Madison High School

I received a good education at Madison, where my classmates were mostly second-generation middle-class Jewish kids, many driven by their parents' desire for them to become professionals, which meant doctors or lawyers. My parents, particularly my mother, indeed felt that the only reasonable career paths were to become a doctor or a lawyer. Unfortunately for her, I was too curious about how the world worked, and I had no interest in the workaday life of a physician, nor in that of a lawyer. I did not realize I wanted to be a scientist; its appeal was invisible to me, except that it seemed to exist in a different space than doctors or lawyers. My brothers followed that path, though, with Bill and Marc becoming successful attorneys and Ted becoming a highly respected cardiologist. To my chagrin, whenever I was with my brothers in the presence of strangers, my mother would always refer to Ted as the "real" doctor in the family.

Madison High School had the secret sauce for amplifying the ability of some of its best students. Madison is among the top high schools worldwide in Nobel Laureates (second only to Bronx Science in the United States). Alumni also include three US Senators (Schumer, NY; Sanders, VT; Coleman, MN), the renowned Supreme Court Justice Ruth Bader Ginsburg, and, to be ecumenical, comedians Andrew Dice Clay and Chris Rock, and singer–songwriter Carole King. Alas, none of them coincided with my years at Madison.

The secret sauce escaped me. I did okay in high school but had no ambition to pursue high grades, mainly earning lazy As and B^+s. With my grades not being exceptional, SAT (formerly the Scholastic Aptitude and later Scholastic Assessment Test) scores that were not 99th percentile, and not being a standout catcher on the baseball team, I was not Ivy League material.

Polytechnic Institute of Brooklyn

I graduated from Madison at 16 (a convergence of my January birthdate and the SP program), driven by curiosity but with unformed ambition. I recognized that my talents and social skills beyond the street corner were limited; I did not write well, and I read very little. I was good at problem-solving, so I thought engineering was a good fit for me. I was particularly attracted to an experimental program at the Polytechnic Institute of Brooklyn (now the NYU Tandon School of Engineering), where a doctorate could be earned after only six years following high school. OK, I thought, I'll get a doctorate at 22 in something or other, and then still be young enough to figure out what I wanted to do. At Poly, like high school, I did well enough in my first two years to get high marks but was not particularly stimulated by any subject. My disinterest was evident in my attitude toward the organic chemistry course, which I found so dull that I skipped most lectures. The professor made it very clear that if I did not ace the final exam, I would fail. I crammed for the final and did indeed ace it, much to the professor's annoyance.

My friends and I realized that Poly, as a commuter school whose student body was mostly nerdy white males, was a heterosocial desert. So, we managed to form a branch of a national fraternity (Tau Epsilon Pi). About 20 friends joined, and we rented a townhouse, which led to a real social life. I was also active in student government, where I enjoyed interacting with my peers and debating with administrators on issues of concern to us. Long story short, I was elected president of the Student Council. I have little recollection of what I might have accomplished, but I realized that I had some talent for organization, but not much for genial sociability.

In my junior year, I took some advanced physics classes, and I suddenly became obsessed with trying to understand how the physical world worked. Classical mechanics was fun. I would often get lost (still do) in thinking about quantum mechanics and the origins of the universe. I tried to intuit such iconic ideas as the Pauli exclusion principle, black holes, hidden variables, and entanglement. I became deeply engrossed in thinking about special and general relativity, and I became hooked on trying to understand the nexus of space and time, as well as the connection between quantum mechanics and gravity. Suddenly, I wanted to become a cosmologist.

University of Chicago

As promised, I earned my bachelor of science in physics in three years, but I soon realized I needed to go elsewhere to study cosmology. I stayed at Poly for a fourth year, earning a master of science, and applied to a few schools renowned for their physics programs that were not on the East

Coast; I needed the distance. At the top of my list were the University of Chicago, where the celebrated astrophysicist S. Chandrasekhar held forth, and the University of California, Berkeley, stacked with Nobelists who revolutionized experimental nuclear physics. I will digress about how I ended up in Chicago.

During my fourth year at Poly, now a first-year graduate student, the draft protocol was suddenly changed, as more soldiers were needed to support the war in Vietnam. I was on track to lose my graduate student deferment at the end of the academic year. I could only get an extension of my deferment if I convinced my draft board that my fourth year at Poly was actually my second year of graduate school. I made the case that, given the highly specialized six-year doctorate program at Poly, I was in the equivalent of my second year of graduate school and thus entitled to graduate student deferment. To be fair, I had taken several graduate courses in my junior year. By the time I met with my draft board, I had been accepted into the doctoral program in the Department of Physics at the University of Chicago. I argued that going there served the national interest, as I could not pursue my scientific goals at Poly. My draft board agreed. Just as the draft board formalized my deferment to attend the University of Chicago, I was accepted into the doctoral program in the Physics Department at UC Berkeley, then considered the premier department in the world. I did not have the chutzpah to go back to my draft board to make the case that going to Berkeley would be a better choice for me (particularly given my draft board's view of the antiwar politics at Berkeley). Fortunately, the radical left politics of the University of Chicago that fueled protests at the Democratic Convention in Chicago in the summer of 1968 had yet to occur. Otherwise, I probably would not have been granted a deferment to go to Chicago either.

Having never been to Chicago, I flew there in March 1968 to check it out, arriving on a glorious day, bright and sunny, though not much different than the mild weather during the preceding weeks in New York. Everyone on campus was aglow, smiling. I had a great visit and thought the University of Chicago would be a happy place for me. Only later, I found that I had arrived on the first day of spring weather, and everyone was transiently joyous as they were suddenly leaving behind a bitterly cold winter. Alas, the scene repeated annually. So much for an underpowered, poorly controlled experiment.

Except for the challenging winters, I loved the University of Chicago (still do). Unlike other institutions I subsequently worked at, where students and particularly faculty tend to stay within their academic and social silos, University of Chicago students and faculty were free-ranging intellectually, highly focused on their interests but literate in an unusually broad range of subjects, academic and otherwise. Its atmosphere was foundational for my free-range approach to neuroscience. The late 1960s

were an interesting time to be on a college campus, with its mix of antiwar politics (many of the Weathermen were fellow UC students), sex, drugs, and rock and roll. The University of Chicago had a robust marijuana and psychedelic subculture that catalyzed this mix.

For the summer after my first year (1969), I applied for a graduate student internship at the Lawrence Livermore National Laboratory (LLNL), run by the University of California. Although I knew that the LLNL was ground zero for the design of nuclear devices, I proposed working on phase transitions, a problem in classical physics. After applying, I was sitting on the quad at the University of Chicago with my girlfriend on a hot early spring day when I noticed, off in the distance, two guys in suits taking pictures of us. I mentioned this later to my departmental student counselor, who told me they were from the FBI and were asking about me, relevant to my getting security clearance to work at LLNL. I never considered that such a clearance was required. Much to my surprise, I was offered the internship. At orientation, I was given a badge boldly indicating that I had "top secret" clearance. I did not fit the LLNL mold, being the only one at the entire complex with a ponytail and scraggly beard, wearing jeans and shirts without pocket protectors. LLNL scientists and engineers would talk at lunch about megadeaths (decades before the metal band of similar name), sincerely, with straight faces. It was an enlightening summer. I was able to perform my physics calculations on the most advanced computers in the world (used otherwise to design nuclear bombs), have interesting conversations with bomb designers, and hang out in Berkeley.

I studied hard during my first year at the University of Chicago, knowing that I had to be at a high level to continue. The doctoral qualifying exam, quite famous, was a multiday test given to early second-year graduate students. The pass rate was less than 30 percent, and if one failed, there was only one additional attempt. If one were sufficiently brilliant, the test problems could be solved in a few lines, as exemplified by a book of solutions to such problems by Enrico Fermi, a renowned member of the Physics Department (1942–1954). One might think that Fermi's solutions involved mystical jumps, but that was not the case. Typically, he would begin with a statement I could reasonably make, followed by a logical progression of two to three lines, all within my ability to reason to the answer. Alas, my problem-solving ability was messy; each problem typically required an entire blue book. I passed on my first try and felt that I had dodged a bullet.

Learning to Write a Scientific Paper

Writing well was not a goal of mine in college. My writing seemed acceptable, but no more. I had no idea how bad it was. My epiphany about writing came in my cosmology class taught by Chandrasekhar. While the opportunity to study with him was a key factor in my decision to go to

graduate school at the University of Chicago, I knew little about him beyond his brilliance. In person, he was quite formal, particularly with his students, wearing the same outfit, an immaculate white shirt, a dark tie, and a dark suit to every lecture, and speaking with perfect Brahmin diction. His lectures were a marvel. In a nine-blackboard old-school lecture hall, he would write in a rectilinear, precise script, starting at the upper left of the top left board and, by the end of the lecture, making his way to the bottom right of the lowest right board. Many of his memorable scientific contributions to cosmology were transmitted in his books, which I read diligently. I found it remarkable that his text was exceptionally lean and sparkling, like a perfectly cut diamond. Not a word, equation, or even comma was out of place; every word was essential but no more. One day after class, I confessed to him that I was envious of his ability to write so well. To my surprise, he was offended, saying that whatever I might have admired about his writing was the result of sweat and grit (my terms, not his), not talent. "You think I just sit down and write the book as you read it? Far from that. I write a complete first draft of my book and then put it in my drawer, typically for six months. Then, starting at the beginning, I edit and rewrite the entire book. For every book, I have done this at least six times." Of course, such an unhurried pace is virtually impossible now. It worked for him, however, as he was awarded the Nobel Prize in Physics in 1983.

His comments disabused me of the notion that if your ideas are good enough, scientific writing does not matter, as long as your papers get published and your grants are funded. Given the time constraints of our contemporary scientific pursuits, with three- to five-year grant cycles, if colleagues and, more important, grant and paper reviewers did not understand your ideas, or you made them work too hard to do so, you would be out of business before too long. Certainly, one great discovery may buy you scientific immortality, but it may not buy you funding if it takes a decade for your colleagues to get it. Like many endeavors, great writing requires sweat.

Becoming a Neuroscientist

Immersed in the intellectual ferment of the University of Chicago, I experimented with psychedelics, as did many of my classmates. During one such experience, I had a simple but lasting realization. Although I had been trained to think of space and time as physical entities, my perception of them was constructed by my brain. That insight redirected my curiosity from cosmology to neuroscience. Once the experience passed, I began reading voraciously (e.g., Wiener and McCulloch on computation; Hodgkin, Huxley, and Katz on electrophysiology), and it became clear to me that understanding how the brain generates internal representations was both a profound and tractable scientific problem. From that point on, I was committed to studying the nervous system.

Why Work on Breathing?

If I wanted to work on the brain, where would I start? I saw no way to study space and time directly from the brain's perspective. I was enrolled in a physics department that had no faculty studying the nervous system. The most closely aligned with biology was my assigned adviser, Morrel Cohen. He was extending his landmark studies of cooperative phenomena in solid-state physics to slime molds, a problem of no interest to me. When I told him I wanted to work on the brain, he asked what I wanted to do. I said I wanted to understand, from first principles, how the brain interprets space and time. That goal was a nonstarter from Morrel's point of view, as he saw it as unsolvable: "Follow in the physicist's tradition and find a problem you could solve." I then suggested determining how I recognize my grandmother, but that was vetoed. Veto after veto, as problems posed were deemed unsolvable. Then I hit on breathing.

I knew a lot about oscillators, and breathing was an oscillatory behavior generated by the brain. All behaviors involve the nervous system processing interoceptive and exteroceptive signals to produce outputs, as in breathing. One can precisely measure the relevant inputs (carbon dioxide [CO_2], oxygen [O_2], lung mechanics) and outputs (muscle contraction, lung movement, airflow, blood gases) and relevant variables, as well as ultimately determine, in principle, the position and properties of each relay in the brain, from sensory inputs to motor outputs. This was a significant advantage in investigating breathing compared with many other complex behaviors, which cannot be evaluated directly and are studied mainly through surrogate measures (e.g., fear-related freezing). Moreover, data on breathing can be readily obtained in any mammal, including humans. I concluded that breathing was the only problem involving mammalian nervous system function and behavior that I could undertake as a physics graduate student who wanted to do theory but not do experiments. With the typical physicist's hubris, I thought I would solve this problem shortly, quickly moving on to much bigger (and sexier) problems. While I got that wrong, I did move the needle. My work established that mammalian breathing is generated by a small, anatomically defined neural kernel, the preBötzinger Complex (preBötC), whose intrinsic dynamics are necessary and sufficient to generate inspiratory rhythm and whose interactions with additional oscillatory and modulatory circuits give rise to the full flexibility of breathing across behavioral and physiological states.

When I first decided to work on the neural control of breathing, I had no prior knowledge of breathing beyond my personal experience as a breather. I had little interest in the physiology of breathing *per se.* Still, it was a solvable problem of brain function that could be foundational for understanding more complex behaviors, particularly those involving rhythms (e.g., walking, flying, chewing, and nystagmus). Indeed, my

argument in choosing such a "simple" problem was to ask: "If I wanted to learn English, would I start with the books of Dr. Seuss, which have many of the elements of English or those of James Joyce, who used the same elements for something so complex as to be impenetrable to many native speakers?" Memory, learning, language, and cognition were, in my humble opinion, way too complex to study (and in Cohen's view "unsolvable"). At the highest levels exhibited only in humans, doing critical experiments was technically and ethically out of bounds.

I had no ready contacts with neuroscientists at the University of Chicago, and I did not take the initiative to speak to them or seek a mentor. Given my goal of modeling the neural control of breathing, it was fortuitous that the University of Chicago had a Committee on Mathematical Biology, whose Chair was Jack Cowan, an accomplished mathematician who was having considerable success in modeling the visual system with Hugh Wilson. Jack was very welcoming to my proposal, though he readily admitted he knew nothing about the neurobiology or physiology of breathing. So, I took a self-directed path, reading the literature and textbooks on breathing (much of which treated the brain as a black box). To start my journey into neuroscience, I enrolled in the medical neuroanatomy course, which turned out to be a nightmare. My scientific cognitive processes were tuned to derive everything from the first principles, which were relatively few at my level in physics. I felt I could (ultimately) solve any problem in physics using Newton's laws, Maxwell's equations, the Schrodinger equation, and maybe a few others. This choice of fundamental physics may also have been a subconscious recognition that I lacked the extraordinary bandwidth needed to memorize the innumerable details foundational to many aspects of biology and medicine (although with the rapid emergence of artificial intelligence, that may no longer be the case). The neuroanatomy class seemed to have no first principles other than some generic homilies about development. What threw me was how readily the medical students memorized the names and locations of every nucleus and pathway, even when their proximity followed no functional scheme. I was impressed, however, by the intellectual challenge to identify the site of a lesion given a set of remarkably unrelated symptoms. At the time, solving such problems required a massive mental database. The challenge is now gone, as now you just need to get an MRI image without knowing anything about the underlying circuitry or behavior.

For my dissertation, I constructed a computational model of the neural control of breathing. I proposed a central pattern generator (CPG) in the brainstem capable of producing breathing rhythms without requiring sensory input. My model, based on coupled nonlinear oscillators, anticipated several later experimental findings. I was delighted when I published my thesis in three papers in *Biological Cybernetics* (Feldman, 1975a, 1975b, 1976).

Note as we go forward in my journey, the common thread through my career was not breathing *per se*, but the conviction, imported from physics, that neurobiological functions must have discoverable organizing principles. The preBötC and retrotrapezoid nucleus (see "Naming the preBötC; Finding a Second Oscillator" section) emerged from that conviction.

Woods Hole (Summer 1973)

As I was completing my doctorate in winter 1973, I wrote to several labs seeking a postdoctoral position as a computational neuroscientist (though that was not the term of art at the time). I was turned down everywhere I applied because each lab felt it was competent in the required mathematics to analyze, interpret, and model its data and did not need anyone specializing in modeling. I was shocked, having celebrated the work of Hodgkin (see volume 1), Huxley (see volume 4), Katz (see volume 1), Rall (see volume 5), and many others, where the power of modeling was obvious. Alas, this was not the case, at least not to anyone I was interested in working with. This was a great disappointment, but I was resilient and formed a new plan. I resolved to learn how to do experiments and test my model of breathing rhythmogenesis. Serendipitously, I found a welcoming lab in Paris, which also fulfilled my need for some time away from the United States, as the politics of the war in Vietnam deeply scarred me. Before I went to Paris, I needed to learn how to do experiments investigating the nervous system. I was fortunate to be accepted into the Physiology Course at the Marine Biological Laboratory (MBL) in Woods Hole.

A terrific course at the MBL made for a great summer. The class was an eclectic mix of senior neuroscience graduate students and postdocs, and me, the odd man out, whose knowledge of (neuro)biology was quite limited. Our instructors were incredible, brilliant, and, most important, dedicated and patient teachers. John Dowling, Rodolfo Llinás, Mike Bennett, George Pappas, and Victor Whitaker were remarkable in explaining basic biological principles unknown to a physicist, and in answering my unfiltered questions to help me understand them.

I relished the work schedule. Lectures in the morning, perhaps an ocean swim at lunch, followed by an afternoon and evening spent in the lab conducting enlightening experiments on various marine creatures, occasionally interrupted by a walk to the Cap'n Kidd for a beer or two before returning, often working past midnight. It was like summer camp for a budding neuroscientist, far from the incipient challenges of looking for a job, writing grants, and publishing papers.

Using Oneself as a Test Subject

Most of the experiments in the course were designed for training, such as how to record from a particular cell in an *Aplysia* ganglion. One section

involved conducting experiments with synaptosomes from the squid optic lobe, which are fragments of presynaptic terminals reconstituted into tiny spheres that can be examined for various properties. We were given a cookbook of possible experiments, but we were also allowed to design our own. I jumped at the chance to test a hypothesis about the action of LSD (lysergic acid diethylamide). At the time, one idea about how LSD affected the brain was that it interacted with serotonin receptors. I proposed a two-stage experiment: (1) Determine if synaptosomes contain serotonin transporters, which would facilitate the recycling of released serotonin. (2) If there were a transporter, would LSD interfere with its function? Given approval and a modest budget, I bought radioactive-tagged serotonin and incubated it with fresh synaptosomes. Much to my delight, I observed significant radioactivity in the synaptosomes. Now I had a problem, because the second stage required high-purity LSD, and I had no idea where I could get any. While LSD could be had in the wilds of Woods Hole, I did not have the facility or the budget to determine its purity. One of my instructors suggested I speak to MBL Professor X. Serendipitously, Professor X had a bottle of pharmaceutical-grade LSD from Sandoz, a lineage of historical significance (Hofmann, 1980). He gave me the bottle, which contained enough LSD to intoxicate every sentient being within 10 miles, and cautioned me: "Weigh out what you need and make sure that there is no spillover. Never know if some idiot uses the balance after you, doesn't wear gloves, and then picks their nose." At this point, my experiment was a topic of discussion among our group. One of our distinguished faculty members inquired if there was any extra LSD. In a rare moment of misdirection, I stated I had only enough for my experiments.

Thus, provisioned with LSD, I repeated the initial experiment, first adding LSD to the bath, then radioactive serotonin. Much to my disappointment, LSD did not change serotonin uptake compared to the control. I went to Professor X, told him of my negative result, and asked how I could be sure that the bottle indeed contained unadulterated, unspoiled LSD. He said that the most expedient test was a biological assay, of which there were two. (1) The clam heart muscle was exceptionally sensitive to LSD and the preferred assay, but a bit tricky. (2) The human brain, which could detect ~40 μg of LSD. In the tradition of self-experimentation for scientific validation, I volunteered for the human brain assay, although I was concerned about placebo effects. So, I recruited my girlfriend, who was LSD naïve. Our validation test was conducted one evening in the waters off MBL at the most fortuitous time, as the *Noctiluca scintillans* was blooming. When disturbed, these dinoflagellates bioluminesce bright blue, but we saw a rainbow of colors as we swam through the water, confirming the LSD was bioactive. So, the conclusion from my experiment was that LSD does not affect serotonergic uptake in synaptosomes from the optic lobe of squid. Since this was the first biological experiment of my design, I wanted

it on the record, so I submitted an abstract to present orally at the end-of-course symposium. To prepare for the expected question, "What control did you use for the efficacy of LSD?," I asked a friend to pose another question as soon as I responded to this question, if asked. One of my professors did ask. I replied, "We did a biological control." Before he could ask a follow-up question, I called on my friend. Bullet dodged.

Paris (1973–1974)

With my newly acquired experimental armamentarium, I started my post-doctoral position at the Université de Paris VI, in a lab at Hôpital Saint-Antoine. This venture was a wise choice, as the journey was an intellectual, cultural, and personal awakening. My mentors, André Hugelin, Françoise Bertrand, and Jean-François Vibert, were physicians and physiologists who were relatively new to studying the nervous system. No other labs were working on similar projects nearby, so I was once again on my own. With my only lab experience being from the prior summer at the MBL, where I worked on squid, lobster, *Aplysia*, and octopus, I was unprepared to be thrown into a room, briefly shown how to perform experiments on cats, and then essentially left to do my proposed experiments.

Acute experiments were taxing, requiring several hours of experimental preparation to isolate and record activity from the phrenic nerve and stimulate the vagus nerve, and to expose the brainstem for recording single neurons, then recording for up to 24 hours. After some time, I found someone who knew something about how the brain might control breathing: Henry Gautier, a pulmonologist who had an excellent understanding of breathing pattern regulation. I managed to convince Henry to work with me, and we did a fascinating study of the interaction of the parabrachial nucleus and vagus nerve in modulating breathing pattern. I was elated that our experiment was successful and resulted in my first experimental publication in the *Journal of Neurophysiology* (Feldman and Gautier, 1976).

My decision to pursue a postdoctoral fellowship outside the United States was strongly driven by my desire to gain a broader perspective on the United States and the Vietnam War. I was highly motivated to absorb the Parisian culture, though I arrived with only a smattering of high school French. I took an immersive French language course during my first two months, which allowed me to order in restaurants and, when sufficiently courageous, to start a conversation with an attractive woman at a park, museum, bar, or café. To avoid falling into an American enclave, I found an apartment in a blue-collar neighborhood adjacent to the Bois de Vincennes, where no one spoke English, and no tourists were to be found. I had hoped to leave behind my long hair, beard, and jean-wearing University of Chicago days for a more civilized appearance. However, to

my dismay, beyond cutting my hair and shaving my beard, my plan was stymied as I quickly discovered that affordable French clothes did not fit me. So, off to the flea market for jeans and comfortable shirts.

The lab staff were critical of many aspects of the United States, particularly during Watergate. I found myself in a debate team position, defending US culture and even Richard Nixon, not one of my favorite presidents.

Becoming a Foodie

Until I lived in Paris, my diet evolved modestly from the kosher cuisine I grew up with. One evening, Georges Perec, a colleague with an encyclopedic mind and a mischievous sensibility, persuaded me to join him at the three-star Michelin restaurant Le Taillevent. When he ordered liver, I protested; liver was, in my experience, peasant food I had never liked. He smiled, a twinkle in his eye, and told me to wait. When I tasted it, my brain exploded, which, as a newbie neuroscientist, took on a profoundly different meaning. The flavors, textures, and aromas bore no resemblance to anything I had known. That meal taught me something unexpected: that even familiar things can be transformed when approached with craft, rigor, and imagination. It was a small lesson, but one that stayed with me and quietly paralleled what I was learning in science that depth often lies hidden in what initially seems ordinary.

My brother Ted, then an undergraduate at Harvard, visited me in Paris but showed little interest in French culture; his restaurant of choice was McDonald's. Determined to expose him to something different, and to satisfy my own appetite for a great meal, I secured a reservation at Paul Bocuse's restaurant in Lyon. We were seated side by side, backs to the wall, facing the dining room. Once the food began to arrive, the world narrowed to our plates; our conversation rarely extended beyond expressions of astonished pleasure. Midway through the meal, someone appeared at our table. I looked up to see Bocuse himself. I felt like a child meeting Jackie Robinson, greeting him in my halting French and shaking his hand. Ted, meanwhile, remained focused on his plate, announcing, perhaps a bit too loudly, that the food was "f$$kin' great." Bocuse seemed amused by this unfiltered enthusiasm. Finally, Ted looked up and, in a voice more suited to a Brooklyn street corner than a Michelin-starred dining room, said, "*Monsieur Bocuse, je viens de lire que vous aimez les milkshakes McDonald's.*" Bocuse smiled, winked, and replied, "*Très fort.*" Ted was delighted; he returned to Harvard with a story that, at last, made his fondness for McDonald's an asset rather than a liability.

While in Paris, I became a serious bicyclist. On many weekends, I rode solo to destinations such as Chartres and Fontainebleau. In September, I took the train to Lyon and cycled south to Marseille, then east along the Mediterranean with occasional inland detours, continuing to Pisa and Florence. After a brief rest, I took the train north to Lausanne and then

rode back to Paris. I averaged roughly 80 miles a day, without a fixed itinerary, starting early each morning and stopping wherever I felt the day ended. Two moments from that trip stand out. (1) Arriving in Monaco one morning, soaked in sweat after hours on the road, I asked a gendarme for directions to the casino. He replied that the best route for me was directly east out of Monaco and, at his insistence, he escorted me to the border. (2) After departing Florence, I arrived in Lausanne late at night without access to my bicycle. When I could not find an affordable hotel, I slept on a park bench by the lake and was gently awakened at dawn by a gendarme, who kindly advised me to move along. After a café crème and a croissant, I retrieved my bike and resumed the journey to Paris.

I returned from Paris having advanced my scientific goals and broadened my cultural horizons, with a more enlightened perspective on America. I was happy to return home. My lesson learned was that both science and adventure reward curiosity and resilience.

Albert Einstein College of Medicine (1975–1978)

After 18 months in Paris (including several months having fun in Henri Korn's lab, poking neurons), Morton Cohen, a prominent figure in the neural control of breathing, offered me a postdoctoral position in the Physiology Department at the Albert Einstein College of Medicine, an ideal segue to home. Returning to the United States was quite positive, both professionally and personally.

Meeting My Wife, Courtney

My good friend and coauthor from Paris, Henry Gautier, visited me in New York shortly after I returned to the United States. He was urbane, a sophisticated Parisian, and I racked my brain trying to figure out something we could do in New York that he could not do in Paris. I eventually proposed the Laser Light Show at the Hayden Planetarium. We got there a bit early before the evening show and sat on the entrance stairs, chatting. Near us was an attractive woman dressed in the elegant casual style popular on the Upper West Side. She was by herself. I said hello, and we began to chat. We married before long, and we are still together, having raised three sons and enjoying our six grandkids (see figure 1), all of whom live close by. Serendipity!

Failure Leads to Discovery

Mort and I conducted a series of experiments to probe the role of the parabrachial nucleus and its interactions with pulmonary afferents, building



Fig. 1. I am grateful and proud to be Courtney's husband; Ion, Ilya, and Dylan's father; and Felix, Jacob, Hugo, Ethan, Max, and GiGi's grandfather. Their love, support, tolerance, and patience have been and are central to me. I cannot imagine being here otherwise. Going forward, I am working hard to be the best I can be for my family, friends, and colleagues, a goal and challenge I undertake with gratitude and humility.

on his longstanding research and my postdoctoral work on the effects of parabrachial nucleus lesions on breathing. What was novel about the experimental design was the use of a pump I developed in Paris. Under normal experimental conditions in anesthetized, paralyzed cats, inspiratory air flow controlled by the pump was cycled on and off by inspiratory phrenic nerve activity to maintain a regular pattern of rhythmic inspiratory lung inflation, even though the diaphragm was inert. We could then compare cycles with lung inflation (airflow on) to cycles without lung inflation (airflow off).

Unfortunately, with the pump on, we were unable to detect any respiratory-modulated neural activity in the pons. This was quite unexpected, given Mort's previous publications. We were bewildered. Then, suddenly, in one experiment while recording this nonrhythmic activity, our pump failed. While we were frantically fixing it, there was no lung inflation, and we heard over the loudspeaker the sudden onset of a sustained, rhythmic chant from a large population of pontine inspiratory neurons. Upon repairing the pump, we observed complete suppression of pontine respiratory-modulated activity during lung inflation. The activity immediately reverted to rhythmic activity when the lungs were not inflated. This result was totally unexpected and highly reproducible, a serendipitous finding, one of the great joys of science. We followed up on this study in a series of experiments, e.g., (Feldman, Cohen, and Wolotsky, 1976). Sadly, we still do not understand how this happens or why.

Within a few months, I was promoted to assistant professor. My intention was to explore whether there was a more straightforward,

incisive method for studying breathing than *in vivo* in cats. Given the extraordinary success of studies using *in vitro* slices and chunks of brain and spinal cord from rodents, I thought that was the way to go. I visited a lab at Harvard where I learned to record activity in slices of the rat hippocampus, but that was not enough because I did not yet understand how to exploit *in vitro* techniques to study breathing. I kept these ideas on the back burner, and ultimately, they came to full fruition at Northwestern.

Out of the Blue, an Unsolicited Job Offer (1978)

My first public talk in the United States was an abstract of my postdoctoral work presented at the American Association for the Advancement of Science meeting in Washington, DC. This talk changed my career trajectory because, afterward, James (Jim) Houk approached me with an offer of a faculty position. Jim was about to move from Vernon Mountcastle's (see volume 6) Physiology Department at Johns Hopkins to become the chair of physiology at Northwestern University Medical School. His vision was to build a physiology department staffed by faculty who investigated the neural control of various organ systems, and pulmonary physiology was among them. Before exchanging any paperwork, he invited me to visit Chicago. I was reluctant to return to Chicago as I had some bad memories: I was victim of a traumatic robbery in my Hyde Park apartment by four armed, strung-out junkies, as well as still mourning the murder of my karate instructor near his Hyde Park apartment. Nevertheless, I did visit. I liked what I saw. I resonated with Jim's vision for his department, and I accepted what in retrospect was a modest offer, but one that was enough to start my lab. Soon, I was on my way back to Chicago.

Northwestern (1978–1986)

Married now, with a young son, Ion, my wife and I moved back to Chicago in the fall of 1978. We settled in Evanston, which offered a straightforward L commute to the medical school, a route I biked when the weather permitted. The winter weather was immediately challenging, as the first year we had more than 90 inches of snow, which given the constantly freezing temperature, never melted.

My Next Act: Building a Lab

I started writing grants and, much to my surprise, it went smoothly (thanks in no small part to following a modified Chandrasekhar protocol). I concurrently submitted applications for a traditional R01 and a Research Career Development Award, both of which were funded after flying through the

study section on the first try. I successfully recruited two postdoctoral fellows, Dexter Speck from the University of Kentucky and Donald McCrimmon from the University of Wisconsin. We worked hard, often doing two 24+ hour experiments per week. Courtney was wonderfully tolerant of this schedule, though Ion for a while thought I had another family, particularly because I had a bed (really a convertible couch) in my office. Work-life balance was ever challenging, and somehow, with love and sweat, we managed.

Stockholm (1982–1983)

My obsession with finding a better way to study breathing, especially the potential for *in vitro* studies in chunks of brain containing intact circuits, kept getting stronger. I visited Rodolfo Llinás (see volume 5) at New York University to examine his perfused heart preparation but decided that, given the intact blood-brain barrier, his preparation would not provide the platform I sought; the control of the brain's extracellular environment was problematic, and there were challenges with the osmolarity of the perfusate. Searching the literature, I concluded that the lamprey spinal cord preparation was optimal as a foundation for investigating rhythmic movements in mammalian slices. Sten Grillner (see volume 9), the leading expert in vertebrate motor control, was making remarkable progress with this preparation, unlocking the circuit for lamprey locomotion. Clearly, the Karolinska Institute was the place to be. Sten generously extended an invitation to take a sabbatical; he helped secure a fellowship from the Swedish Medical Research Council, which made it affordable. Courtney was up for the adventure, and Ion, now age four, was game. Like my adventure in Paris, Stockholm provided fresh snow to carve my own path.

The lamprey preparation was amazing, especially in the hands of Peter Wallén (Wallén et al., 1985), Sten's senior associate, with whom I did experiments. It was astonishing that one could remove the spinal cord from an adult lamprey yet still find the coordinated rhythmic motor nerve output underlying swimming. Recording from individual neurons was like shooting fish in a barrel; filling them with fluorescent dye in real time and seeing the result in a fictively swimming lamprey was breathtaking (Note: English is filled with words and expressions inspired by breathing.) I was privileged that Tomas Hökfelt often came by to discuss experiments, particularly as related to his interests in neural chemotype.

Stockholm was wonderful. We lived in the Wenner-Gren Center, an international residence for families of foreign scientists; it was like living at the United Nations. Moreover, our Swedish hosts were most welcoming, and our interactions with them were incredibly warm and friendly. We took some time to adjust to the diet, which involved lots more fish than we were accustomed to, but it was all fresh and delicious. Buying wine took

some discipline: One did not just pick up a bottle at any hour, and the ultimate sin was not stocking up in time for a weekend meal with guests. We were taken aback at Thanksgiving when a turkey we bought tasted quite unusual. We found out that it had been raised on fish meal! Moreover, experiencing the winter and summer solstices, along with the weeks before and after, was a permanent lesson that geography matters. Our second son, Ilya, was born at Danderyd Hospital, healthy but with one hitch: We had to modify his intended middle name (Björn to Bjorn) because the US passport application would not accept a name with an umlaut.

Communicating with Dexter and Don, who were working hard at Northwestern, proved challenging. This was before the Internet, and international phone calls were prohibitively expensive. We exchanged minitapes weekly by airmail, accompanied by whatever data could be packaged. Because it was a feedback loop with a long delay, we had to gather our thoughts for each package. We had to be disciplined in ways that are hard to imagine for anyone raised on current technology. With two trips to the United States, including one for SfN, it somehow worked.

I spent considerable time in Stockholm revising a major review about the control of breathing. At the time, the *Handbook of Physiology* was the most prominent and widely read compendium of reviews in physiology and neuroscience. At prior SfN meetings, I made the acquaintance of Floyd Bloom (see volume 7) and convinced him that I was on to something with my studies of breathing. Subsequently, Floyd, as editor of the *Handbook* volume "Intrinsic Regulatory Systems of the Brain," invited me to contribute a chapter on the neural control of breathing. This was an invitation I could not refuse, for if done right, it could provide significant recognition for what I was doing. I was very compulsive about writing this review. I read hundreds of papers, going back to early studies. Much to my shock, I discovered that many recent papers had miscited, misstated, or misrepresented prior work, and these errors had propagated over time, much like the elementary school game (Telephone) where an initial statement gets twisted as it is passed around the room until it has little resemblance to the original. I did my best to set the record straight. After working on my first draft for about eight months at Northwestern, I sent it to Floyd for his advice and editing, clearly indicating that I was prepared to make any necessary changes. Several months later, I was shocked when Floyd wrote to me to say that my manuscript had been *rejected* and would not be published. I was beyond depressed, as I had sacrificed so much to get this done. I thought of all the experiments I did not do while writing the chapter. It turned out that Floyd had sent my draft to Vernon Mountcastle for review, apparently indicating that it was my submission for publication. Mountcastle, an outstanding senior neuroscientist and an experienced editor, ripped my draft to shreds. His obvious irritation that the draft was filled with typos and redundancies, and certainly lacked his customary

formal writing elegance, exacerbated his negative review. I wrote back to Floyd, pleading for a chance to revise the manuscript. Floyd agreed to accept a revision, though he made it clear that unless it met the highest standards and satisfied the reviewer, it would be rejected. I weighed the career prospects of devoting time to what might be a futile effort, but I chose to give it a shot while in Stockholm. After months of revising, I submitted my revision. My brain let out a profound sigh of relief (see the "Sighs" section) when it was accepted and published in the *Handbook of Physiology* (Feldman, 1986). As I had hoped, the published review had a significant positive impact on both the relevant science and my career. In rereading the review recently, I was quite pleased with how on point I was in summarizing the field as it stood in 1986, well before the paradigm shift that came with our subsequent discovery of the preBötC.

Northwestern Redux

Returning to Northwestern, I resumed my work with renewed clarity and focus. I was privileged to be joined in 1984 by a third postdoc, Jeffrey C. Smith, who was the first "outsider" from the neural control of breathing silo that I was fortunate to recruit. Jeff had made his mark in respiratory mechanics and concluded that the most interesting problems in pulmonary physiology were in understanding how the brain controlled breathing. Jeff was a deep thinker and rapidly absorbed the relevant neurobiology, and we had great intellectual chemistry. I enlisted Jeff in my search for the site and mechanisms that generate breathing rhythm. We realized that the next essential step was evident in a paper by T. Suzue (J. Physiol., 1984), who showed that the *en bloc* brainstem and spinal cord from a neonatal rat, *in vitro,* could generate a breathing rhythm. Jeff spent considerable effort in reproducing and delineating the properties of the *en bloc* preparation, at which point we decamped to UCLA. This story continues in the "UCLA (1986–Present)" section.

Consulting

Because breathing is essential to life, my knowledge of the neural control of breathing has occasionally been called on outside the laboratory. While at Northwestern, I was asked to consult on several problems that underscored how principles of respiratory neurobiology could bear on real-world questions far removed from basic science. Two consults were memorable.

First, in 1984, I was asked to review autopsy findings in the death of a naval officer initially ruled a suicide, where significant blood was found in the lung alveoli, raising questions about the sequence of events leading to death. After reviewing the autopsy report, I advised that additional forensic analysis was warranted before drawing firm conclusions that it was a

suicide. The case was subsequently examined at a higher level, though I was not informed of any ultimate resolution.

Second, I was recruited by the US Department of Defense (DoD) in 1984 to advise on mechanisms underlying respiratory failure following exposure to nerve agents, which primarily cause death through central respiratory arrest. The DoD was struggling to develop countermeasures to the use of nerve gases that were, at the time, in tanks in Eastern Europe and ready to be deployed in any conflict. Although a research contract was approved to investigate this problem, logistical and administrative complications delayed contract award until I moved to UCLA. The fate of this contract is discussed in the "DoD Redux (1986–1987)" section.

These episodes were interesting, occasionally unsettling, and reinforced for me that understanding how the brain controls breathing has implications that extend well beyond the laboratory (as we are now exploring the effects of breathwork on emotion, discussed in the "Breathing and Emotion" section).

UCLA (1986–Present)

About the time I was awarded the DoD contract at Northwestern, I got an inquiry about a faculty position from the Kinesiology Department at UCLA. Such a department might seem a strange landing spot for a neuroscientist. Yet there was a cohort of departmental faculty interested in movement control that I could interact with, including Reggie Edgerton. However, most faculty were focused on issues that held little interest for me (e.g., the psychology of figure skaters). I was curious enough to take a look despite, as a New Yorker, my holding many negative views of LA (Beach Boys, sunshine, yeah, but not a place where people worked nights and weekends doing science). I visited UCLA in late March 1985. Chicago was still in winter mode, streets still covered with snow and ice, and the only outdoor smell was dog urine. I arrived at LAX on an early spring evening. I was immediately intoxicated by the scent of the star jasmine just starting to bloom, awakening my hypothalamus from its prolonged winter dormancy. The next day was all sunshine and shirtsleeves, and my eyeballs strained from noticing all the students wearing T-shirts, shorts, and sandals and, by Chicago standards, dressed as if they were at the beach. That evening, returning to my hotel around 10 p.m., I turned on the news. I came across a segment where a reporter was questioning pedestrians on Ventura Boulevard about how they were coping with the "cold weather." It was still 50+°F, a temperature not reached in Chicago for the past several months, and here locals thought it was freezing. I was sold; all I needed to do was work out the details.

We moved to LA in July 1986 and never looked back. We were fortunate to have immediate solutions to two big problems we faced: expensive

housing and schools for our sons. UCLA, aware of the challenges of attracting faculty to a city with outrageous housing prices, built a community of 58 homes within a few miles of campus that were sold at below-market prices. We bought in, fantasizing that living in a community of faculty would be a modern-day Bloomsbury. That was not the case, as many of our faculty neighbors rarely ventured outside their academic silo, and after several years, we moved out. The challenge of schools was initially solved by Ion's admission to the University Elementary School, a UCLA school run by its Department of Education, which occasionally admitted children of UCLA faculty. We quickly adapted to the rhythms of LA, which were very different from those in New York and Chicago. Our third son, Dylan, was born about a year after we arrived.

DoD Redux (1986–1987)

In negotiating my move to UCLA, the DoD agreed to move the contract for studies on nerve gases. Unfortunately, the DoD work did not end well. The DoD would not release the first tranche of research funds until a special hood capable of handling minute amounts of nerve gas was in place. Fred Eiserling, dean of Life Sciences, agreed to pay for the hood upfront, with reimbursement from the DoD upon completion. Not surprisingly, there was a lot of red tape and significant construction costs for such a hood, and it took some time to get it done. So long, in fact, that by the time the hood was certified, there were budget issues at the DoD, and they unilaterally canceled my contract. This was a disaster for me, as I was paying a postdoc to work on this project with my NIH funds, overspending these accounts on the assumption I could recoup the costs when the DoD money arrived. It took me almost two years to pay off this debt, at great cost to my ongoing research. Moreover, the DoD initially refused to reimburse UCLA for the hood's cost, infuriating Fred. Eventually, we managed to get the DoD to pay for the hood, but I would never again seek DoD funds.

My First Graduate Student

While in the process of leaving Northwestern, I was contacted by Guosong Liu, a recently arrived Chinese graduate student at the University of Illinois, Chicago. He was looking for a project on the nervous system that would challenge him and put his considerable experimental and computational skills to use. I was most impressed, and I convinced him to enroll as a graduate student at UCLA. Guosong's ambition was also considerable. He was interested in basic synaptic function and set his bar at research comparable to Hodgkin-Huxley. His ultimate paper with me demonstrated that synaptic transmission onto motoneurons was indeed quantal (Liu and Feldman, 1992), but his real interest was in plasticity, learning, and

memory. When on the faculty at MIT, he showed that elevating brain Mg improved synaptic function of neurons in mouse hippocampal culture, and subsequently, at Tsinghua University, he showed it improved cognitive function in behaving mice. He then synthesized an Mg salt (in collaboration with Fei Mao, a brilliant chemist) that readily crossed the blood-brain barrier (MgThreonate; MgT). He received a notice from the Food and Drug Administration that led to sale of MgT as generally recognized as safe (GRAS), and he formed a company, Neurocentria. The relevance to my story is that I became a scientific consultant for Neurocentria, which exposed me to a world outside my academic silo: how discoveries made in the lab can transition to the real world, and what factors come into play when attempting to monetize one's discoveries.

Light Bulb Moment: Finding the noeud vital

In my 1986 *Handbook of Physiology* chapter, I reviewed efforts starting with Galen (~200), leaping ahead to 1761, to find the site in the brain generating breathing rhythm, referred to as the *noeud vital*. Attempts to isolate the *noeud vital* by Legallois (1813) involved using blunt spatulas to transect the brainstem of otherwise intact rabbits, crudely isolating the rhythmogenic site in the brainstem. More than 170 years later, when we had the *en bloc in vitro* preparation going, we realized we could redo the transection experiment with much better precision. Jeff would place the *en bloc* brainstem and spinal cord of a neonatal rat vertically in a vibratome, rostral side up, while recording rhythmic inspiratory activity from the C4 ventral root, which innervates the diaphragm. As he took thin (~75 μm) slices off the top, the C4 rhythm was unaffected until he got to about the middle of the medulla, when, within one or two cuts, all rhythmic activity disappeared. This was highly repeatable across brainstems. He then did the experiment with the caudal side up, recording rhythmic inspiratory activity from the hypoglossal nerve (XIIn). As he took sections initially in the spinal cord, and then in the caudal medulla, there was no change in XIIn rhythm. But when he got near the obex, an additional cut or two eliminated the XIIn rhythm. Taking these experiments together, we hypothesized that these boundary cuts bracketed a key element for breathing rhythm generation. Much to our amazement and satisfaction, neonatal rodent slices cut with these boundaries generated rhythmic bursts from the XIIn that we verified were inspiratory-modulated. We thus demarked the critical medullary section that was the source of the rhythm. Moreover, the rhythm appeared to originate in the ventrolateral quadrant of the slice, a region not demarked in any atlas; ultimately, as described in the "Naming the preBötC" section, we named it the preBötC.

At this point (1990), Jeff won a Humboldt Fellowship to work in Diethelm Richter's lab at the Georg-August-Universität, Göttingen.

Richter's work on the intact anesthetized cat brainstem had led him to a compelling model in which inhibition was essential for the rhythm of breathing. Fortunately, Klaus Ballanyi, a postdoctoral fellow in Richter's lab, highly experienced in recording neurons in *in vitro* studies, worked with Jeff. Among the neuron types they found were intrinsic bursters, also referred to as pacemaker neurons. Jeff returned to UCLA nine months later, and we continued these experiments.

Naming the preBötC

In the 1980s, the consensus was that the kernel for generation of the breathing rhythm was the ventrolateral nucleus of the solitary tract (vlNST), as proposed by Ramón y Cajal. The principal contemporary evidence was the report by Eugene Merrill that this region had respiratory rhythmic activity but did not receive any afferents from within the brainstem. Hence, he argued unequivocally that the vlNST must be the rhythm source, and his view prevailed. I found the logic weak, however, as it confounded the absence of evidence with evidence of absence. I designed a simple experiment made possible by advances in tract tracing. Together with Madhu Kalia, a neuroanatomist with considerable experience in such experiments, we injected horseradish peroxidase into the vlNST and found an afferent projection from the rostral ventral respiratory column, just caudal to the nucleus ambiguus (Kalia, Feldman, and Cohen, 1979). Wanting to share this finding, I wrangled an invitation to present this work at a meeting on the neural control of breathing in Stockholm in 1978. After my presentation, Merrill stood up and, to be polite, strongly disagreed, effectively convincing everyone I was wrong.

At the next international meeting in 1980 on control of breathing in Hirschhorn, Germany, Merrill announced his "discovery" of a brainstem projection to vlNST, precisely the projection we described a year earlier, but much to my dismay, with no acknowledgment on his part of this fact. I stood up after his talk and reminded everyone that we had identified this projection at the previous meeting, apologizing for having only recently published the result. Everyone was excited about this projection, because it gave a new target for the source of rhythm. At the meeting banquet, there was a buzz that this region, which did not appear to be labeled in any atlas, needed a name. I was pretty freaked out that the choice of name might include "Merrill," and so, after consuming a considerable amount of wine, I stood up and proposed a toast to this newly identified region. I was too hasty, though, as I did not have a name in mind (other than "not Merrill"). On the table was a bottle of Bötzinger wine, which I impulsively grabbed and suggested that we name the region after this wine, emblematic of this meeting, and because we did not know its mysteries, I suggested we call it the Bötzinger Complex. My colleagues, also well lubricated, toasted my suggestion, and it stuck.

In retrospect, as painful as it was, my disagreement with Merrill mattered because it challenged me over the next few years to conduct the experiments that finally resolved the question, ultimately establishing the preBötC as the kernel of the generation of the breathing rhythm. Episodes like this are uncomfortable, but they are often the price of challenging entrenched assumptions and narrowing the path to decisive experiments. The disagreement with Merrill concerned the location of the rhythm generator; a subsequent conflict with Diethelm Richter (see the section "From Discovery to the Paradigm: The preBötC Is Both Necessary and Sufficient to Generate the Mammalian Inspiratory Rhythm") concerned what kind of mechanism could generate a rhythm at all.

Over the next few years, no experiments followed that supported the thesis that the Bötzinger Complex was the rhythmogenic site, so we continued our search for it elsewhere. In 1988, when Howard Ellenberger, Jeff Smith, and I identified a region that we were pretty sure was the rhythmogenic kernel, we struggled to find a name. Given its proximity to the Bötzinger Complex, we thought we could anchor the name there. The problem was that the region we identified was caudal to the Bötzinger Complex and, according to neuroanatomical convention, we should have named it the "postBötzinger" Complex. I thought that was a bad choice, because it sounded odd to label as "post" the site that was the origin of breathing rhythm. Accordingly, we declared the site the "preBötzinger Complex" (preBötC). We used the name for the first time in an abstract for the European Neuroscience Meeting in 1990.

Our story about the newly christened preBötC as the site generating breathing rhythm was so compelling that I thought we could submit to *Science* (I did not consider sending it to *Nature* because a previous paper I had submitted there years earlier was rejected with the editor's comment: "Breathing is not of sufficient general interest"). This work was ultimately published in *Science* in 1991 (Smith et al., 1991), firmly establishing a new anatomical term, as stated in the title: "Pre-Bötzinger Complex: A brainstem region that may generate respiratory rhythm in mammals." I should note that the inclusion of the word "may" in the title was deliberate. At the time, our evidence supported a strong hypothesis but not a settled paradigm. In retrospect, such provisional language is now uncommon in titles, even though it more accurately reflects how scientific understanding evolves.

From Discovery to the Paradigm: The preBötC Is Both Necessary and Sufficient to Generate the Mammalian Inspiratory Rhythm

The now paradigmatic paper in *Science* has a fascinating citation history. Initially, it was hardly cited because colleagues did not embrace our ideas. Citations then increased slowly for about a decade, until we published our

paper establishing the presence of preBötC *in vivo* (Gray et al., 2001), after which they rose sharply for perhaps another decade. Citations then gradually faded as hundreds of papers as well as its inclusion in textbooks and atlases established the preBötC as part of the breathing–brain zeitgeist, so that citation of the original work was no longer a scholarly necessity. This cycle of rejection to acceptance is well known, worth quoting, and with which I have had some experience:

> All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.
>
> —Arthur Schopenhauer, philosopher (1788–1860)

> Four stages of truth: This is worthless nonsense; This is an interesting, but perverse, point of view; This is true, but quite unimportant; I always said so.
>
> —J. B. S. Haldane, physiologist (1892–1964)

An important way science advances is in resolving disagreements. Here, Diethelm Richter, who felt that postsynaptic inhibition was critical for rhythmogenesis, strongly disagreed with our conclusion that inhibition was not essential. Also, he and many colleagues felt that our physiological data were problematic because they were obtained from *in vitro* slices of neonatal rat brain, not intact rats. He reluctantly agreed to be a coauthor of the paper submitted to *Science*. Two decades later, Bert Sakmann told me that when he congratulated Diethelm on the publication of this paper, Diethelm said it was all wrong. Bert did not know how to respond at that time, but when he ultimately told me, we agreed that the issue had been well resolved in our favor. Nonetheless, as Diethelm's negative opinion was widely circulated in the field, it delayed the eventual acceptance of the preBötC as the paradigmatic kernel for generating breathing rhythm and serves as a classic example of the aforementioned aphorisms about truth.

Our initial evidence for the role of the preBötC in generating breathing rhythm necessarily relied on neonatal *in vitro* preparations for isolating circuit-level mechanisms that could not be resolved *in vivo* at the time. Criticism of these experiments, while understandable, did not undermine the core prediction that a compact medullary kernel generates inspiratory rhythm. The dispute was not whether the rhythm existed in slices, but whether the mechanism inferred *in vitro* would be foundational for the rhythm *in vivo*, a testable prediction. After several years of struggling to design an *in vivo* test, I was fortunate to have Paul Gray, a graduate student, join the lab. Paul, in addition to being very clever, had a specific

goal as my doctoral student: "Jack, my goal is to prove you wrong." I enthusiastically endorsed this effort; if I was wrong, I wanted to be the one to discover it first. Paul conducted a series of foundational experiments. He found that he could increase the XIIn inspiratory frequency *in vitro* by application of Substance P (SP). He suggested we do immunohistochemistry to look for the SP receptor. I thought the experiment would not be informative, because I expected the receptor to be widespread. He proved me wrong, as a few weeks later, Paul sat me down at our microscope to show me the immunostains for the neurokinin 1 receptor (NK1R; i.e., the receptor for SP). My brain exploded as I saw extraordinarily dense labeling in the preBötC and very little in its surround. Fortuitously, Jens Rekling, an exceptionally talented and thoughtful electrophysiologist, joined the lab. He had previously classified preBötC inspiratory neurons into two classes, suggesting that one class was rhythmogenic, a significant advance that remains underappreciated. Building on this finding, he followed up on Paul's observation, showing that SP directly depolarized some preBötC neurons.

Light Bulb Moment: preBötC Passes a Critical Test

We were fortunate that these experiments were published in *Science* (Gray et al., 1999) in an issue that featured a fantastic paper by Doug Lappi and colleagues, who devised a clever way to ablate neurons expressing NK1Rs with an engineered saporin toxin. We immediately realized that we could now test our prediction that the preBötC was essential for generating breathing patterns *in vivo*. We predicted that ablating preBötC neurons using Doug's toxin would irreversibly perturb breathing. I confess I was anxious about conducting this experiment because, if our prediction were wrong, most of our ideas about the fundamental nature of the preBötC would have to be significantly revised or even discarded. But we followed our lab mantra that "one cannot do anything interesting if one is afraid of failure" and proceeded with the experiment. I was thrilled and relieved when our prediction was confirmed. Ablating NK1R preBötC neurons in awake behaving mice irreversibly perturbed and ultimately abolished all breathing rhythms. Publication of this paper in *Nature Neuroscience* (Gray et al., 2001) convinced all but our most extreme critics that the preBötC was for real. At this point, we were at stage 3 of Schopenhauer and stage 4 of Haldane in the acceptance of the preBötC.

A Model System for Studying Locomotion

While working on the *en bloc* preparation, Jeff noticed that if he kept the hindlimbs facing up while still attached to the isolated neonatal rat spinal cord and then pinched the tail, the legs would generate a bicycle-like movement (Smith and Feldman, 1987; Smith, Feldman, and Schmidt, 1988).

We developed this into a *bona fide* preparation for studying locomotion, and published a brief note, but we did not have the bandwidth to exploit it to unravel circuits for locomotion (Smith and Feldman, 1987). Several years later, a number of investigators adopted this preparation, and it proved exceptionally useful for delineating circuitry in the spinal cord for mammalian locomotion.

What Underlies Rhythm Generation?

The long-standing focus on pacemaker neurons and recurrent inhibition in modern rhythmogenesis research arose from compelling biological parallels. For example, given that the continuous breathing rhythm is as vital as the continuous heartbeat and that coupled autonomous pacemaker cells drive cardiac rhythm, the idea naturally emerged that the breathing rhythm might similarly depend on neurons with intrinsic bursting properties. This view was supported by extensive data in invertebrates, showing that neurons with pacemaker properties play a key role in several rhythmic behaviors. Our work supported this view by demonstrating pacemaker properties in preBötC neurons in *in vitro* conditions (though, alas, they have yet to be found *in vivo*). With Christopher Del Negro, an exceptionally talented and thoughtful postdoc, we were able to test this hypothesis explicitly by simply looking at the effect of antagonizing the two currents that contribute to intrinsic bursting in single preBötC neurons: the persistent Na current and the nonspecific cationic (CAN) current. Yet after blocking these currents to abolish pacemaker properties in preBötC neurons, the preBötC still generated a similar rhythm (Del Negro, Morgado-Valle, and Feldman, 2002). We concluded that pacemaker neurons were not essential for rhythmogenesis but could play a role in modulating or stabilizing its pattern. The pacemaker neuron hypothesis was supplemented by the complementary proposal that recurrent inhibition served as a rhythmic "off-switch," that is, terminated each inspiratory burst, ending one breathing cycle and initiating the next. Wiktor Janczewski, a talented research associate with deep knowledge of breathing and extraordinary skills in *in vivo* experiments, tested the obligatory role of inhibition in adult rats. By blocking inhibitory currents in preBötC with conventional pharmacology, we showed that the breathing rhythm persisted and remained robust (Janczewski et al., 2013). We concluded that inhibition was not essential for generating breathing rhythm but could play a role in modulating or stabilizing its pattern.

Light Bulb Moment: New Idea for Rhythm Generation

With both the pacemaker and inhibitory "off-switch" models failing key tests of their essential importance for driving breathing rhythm, we were at an impasse. Fortuitously, Kaiwen Kam and Jason Worrell, talented, creative, and highly perceptive postdocs, noticed something in *in vitro* preBötC population activity that we had all missed. Each burst of

preBötC inspiratory population activity was preceded by a brief period of low-level activity referred to as "preinspiratory." What they noticed was that the regular interval between bursts was occasionally interspersed with one twice the normal duration. When that happened, there was a low-level "burstlet" in the preBötC about the expected time of the missing burst. As excitability was lowered, more bursts were skipped, and in their temporal place were burstlets. We hypothesized that these burstlets were the rhythmogenic kernel, not the bursts. We then formalized and published this idea (Kam, Worrell, and Feldman, 2013), which rapidly passed through Schopenhauer's three stages of truth and is now apparently accepted as a working paradigm for rhythm generation. We refer to it as Burstlet Theory.

We spitballed a lot of ideas about how burstlets were generated. Their low levels of activity at the single neuron level would exclude mechanisms requiring significant depolarization. At this point, Sufyan Ashhad, a postdoc of penetrating intelligence and considerable imagination, a talented electrophysiologist, and a computational modeler, joined the lab. We asked ourselves how a network could increase its activity without individual neurons each increasing theirs. We speculated that synchrony would do it. That is, asynchronous excitatory inputs to a neuron may not summate to cause it to fire but simply synchronizing the inputs could do it. Sufy then conducted a series of experiments to test this hypothesis, found short latency synchrony between and among preBötC neurons (Ashhad and Feldman, 2020), and then modeled optimal conditions for rhythm generation (Ashhad et al., 2023), and everything fell into place. In brief, the key rhythmogenic process, at least *in vitro* and predicted *in vivo*, is that burstlets trigger bursts, and that short latency *synchronization* of a subpopulation of preBötC neurons is the primary mechanism for generating burstlets.

As our initial work on the burstlet and synchrony hypotheses was all conducted *in vitro*, the question remained whether these observations were relevant to the intact animal. Here, Evgeny Bondarenko, a postdoc with a deep understanding of breathing and considerable skill as an *in vivo* experimentalist, collaborated with Sufy to investigate whether burstlets are present in *vivo*. Confirming our prediction, they found burstlets, which we also speculated provide a mechanism for rapid switching between breathing patterns during sniffing, vocalizations, and other behaviors. Our working hypothesis was that burstlets and synchrony are essential elements in rhythmogenesis for breathing, and by extension may be a more general mechanism by which neural microcircuits switch states, as during pattern recognition or decision making.

Light Bulb Moment: Finding a Second Oscillator

Since our discovery and investigation of the preBötC, we thought that both phases of the breathing rhythm (i.e., inspiration and expiration) came from

the same oscillator. We likened it to the tick-tock of a pendulum or the day/night of the rotating earth, in which a single oscillator produces two phases. In about 2000, while reviewing a paper on neural activity near the facial nucleus (parafacial region), I noticed something I had not seen before that the authors had not commented on. The manuscript supported the authors' hypothesis that this region, which they called the parafacial respiratory group (pFRG), was the principal source of breathing rhythm, not the preBötC. This was not an undiscovered region, as in 1989 (Smith et al., 1989), we had identified a distinct projection from ventral to the facial (VII) nucleus to the ventral respiratory column. As this region was not denoted in any atlas and because of its proximity to the trapezoid body, we christened it the retrotrapezoid nucleus (RTN), hypothesizing that it was potentially rhythmogenic and a site for central chemoreception of CO_2. The manuscript I was reviewing provided further evidence of a second oscillator in the RTN/pFRG. In an *en bloc* preparation from neonatal rat, in a recording from the RTN and inspiratory motor output (XIIn and C4 ventral roots), we observed rhythmic inspiratory nerve bursts, with occasional much longer intervals between bursts. Yet in the RTN, there were rhythmic bursts of activity following inspiratory bursts, coincident with the expiratory motor output that was also present when there were longer periods between inspiratory bursts. It looked as if the RTN was keeping a regular rhythm, coincident with the period between inspirations (i.e., expiration), but the inspiratory motor bursts were skipping beats. Working with Nick Mellen, an exceptional postdoctoral fellow who, among his many talents, spoke about eight languages, we realized that these inspiratory nerve intervals were quantized. Looking through our prior unpublished data, we found similar results. What was going on? Here, we had an ethical dilemma. There were data in the manuscript that the authors had not commented on, which suggested to us an important insight into the breathing CPG. Though we were committed to the confidentiality of the manuscript, were we obligated to act as if we had never seen the data? We decided to follow up on our extant data, but to keep everything we found inside the lab until this manuscript was published. We set up some new experiments that profoundly changed our perspective. Indeed, there were skipped inspiratory bursts, with intervals between bursts in quantal multiples of the base period. We realized that there must be a second oscillator coupled to the preBötC that generated expiratory activity, consistent with our hypothesis that the RTN had rhythmogenic potential. We kept our observations confidential for several months until the paper I reviewed was published. Then we submitted our paper, presenting our dual oscillator hypothesis (Mellen et al., 2003) and fully acknowledging the results from the other paper. In numerous key follow-up studies done by Silvia Pagliardini and Robert Huckstepp, both insightful, hardworking, and dedicated postdocs, we provided substantial support for the hypothesis that the

preBötC was the essential generator of inspiratory rhythm and was coupled to a distinct parafacial oscillator, the RTN (our current preferred name is the lateral parafacial nucleus), which generated active expiration (Pagliardini et al., 2011; Huckstepp et al., 2015; Huckstepp et al., 2016). Here again, this idea went through the multiple stages of truth over about five years.

In retrospect, we should have identified the second oscillator a decade or more earlier, but I was ignorant of a key point (likely because I lacked formal training in pulmonary physiology). In normal breathing at rest (eupnea), expiratory airflow is passive, resulting from elastic recoil of the lung and chest wall. It becomes active by recruitment of expiratory muscles only when metabolic demand requires significantly increased total airflow or when behaviors require active expiration, such as speech and cough. So, in our *in vivo* anesthetized preparations, there was no "active" expiration, and thus no ongoing activity to detect. We ultimately showed that at rest, this expiratory oscillator in RTN is actively inhibited, and a combination of disinhibition and excitation likely underlies the initiation and maintenance of active expiration (Pagliardini et al., 2011; Huckstepp et al., 2015; Huckstepp et al., 2016).

Breathing and Emotion

Another important aspect of breathing that I was long oblivious to is its profound impact on emotion and cognition. A convergence of four factors sparked my interest in this topic.

Rostral Connections from/to preBötC

To understand the mechanisms underlying preBötC functions requires a map of its afferent and efferent projections. Cindy Yang, a thoughtful and meticulous postdoc, discovered extensive rostral overlapping efferent projections of both excitatory and inhibitory preBötC neurons, as well as significant monosynaptic afferents onto preBötC neurons from rostral regions, extending up to the thalamus (Yang and Feldman, 2018; Yang et al., 2020). These findings established the presence of both direct and indirect ascending projections of preBötC neurons that could influence nonrespiratory functions, especially emotion and cognition, and descending (i.e., suprapontine) projections that could transmit signals related to emotion, cognition, and volition to affect breathing pattern.

Sighs

A new chapter began with a phone call out of the blue from Kevin Yackle, a Stanford medical doctor–doctoral student deeply invested in understanding the breathing CPG. I found this curious, as he was in the lab of Mark

Krasnow, a renowned biochemist, whose studies of the *Drosophila* tracheal system were far from those investigating the neural control of the mammalian breathing CPG. Kevin said that as an undergraduate at UCLA, he took a course in systems neurobiology in which I gave a guest lecture on breathing, and he was hooked. Krasnow granted him leave to develop his project, initially aimed at identifying key molecules in the breathing CPG. From our initial conversation, I realized Kevin was special and that his exceptional intellect and enthusiasm would be a great addition to our field. I became a shadow mentor. Within a year, I got him invited to a triennial breathing conference in the Netherlands. We chatted regularly. About a year later, one of my former undergraduate mentees, Neil Schwartz, who was now a neurologist at Stanford, invited me to give Grand Rounds. At the end of my visit, I stopped by Krasnow's office, where Kevin and Peng Li, a talented postdoc, joined us. As we were wrapping up the meeting (I had a plane to catch), Mark mentioned that they had identified a unique molecule in the brainstem breathing CPG. Excited and curious, I naturally asked what the molecule was. Mark said he was not ready to reveal the identity of this molecule as Kevin, Peng, and he wanted to pursue it first. I was disappointed, having been trained as a mammalian electrophysiologist, where unpublished data would be readily shared, while it aged gently for years before publication. As I was walking out the door, I realized there was one unusual (for us) molecule we had worked on but not yet published. So, I said we had done "some work on bombesin." "Was that the molecule?" I asked as I rushed to catch my flight. When I got to the airport, my cell rang, and it was Mark. He said that the molecule they identified was a bombesin-related peptide. Then he asked what bombesin did, and my response was (tongue in cheek): "I'm not telling."

Why bombesin? Wiktor Janczewski ran across a paper reporting a relationship among stress, sigh rate, and the release of bombesin-related peptides from the hypothalamus. We conjectured that the preBötC could be involved, and we devised a quick, cheap experiment: inject bombesin directly into the preBötC to see whether it affected sigh rate. In one of those memorable moments in the lab, the first time we did this, the sigh rate in an adult rat went from about 25 per hour to 500 per hour, with little change in baseline normal breathing frequency. The obvious next step was to antagonize preBötC bombesin receptors, and to our amazement, when we did this, sighing stopped. Then, using a targeted neurotoxin developed for us by Doug Lappi, saporin tagged to bombesin, Silvia Pagliardini ablated the preBötC subpopulations that expressed the bombesin receptors. Over several days, as the toxin ablated these neurons, the sigh rate dropped to essentially zero. In retrospect, these data were revelatory and engaging, but we let the data sit on the shelf until Kevin's observation made us realize we might have a compelling story. We immediately agreed to collaborate.

Combining our divergent technical expertise with deep knowledge across molecular and cell biology, electrophysiology, and networks, we identified a four-neuron circuit in which neurons in the parafacial region that contain bombesin-related peptides project to preBötC neurons that express their cognate receptors. In adult rodents, when these preBötC neurons are exposed to bombesin peptides, rhythmic sighing results (Cui et al., 2024). We took these findings to mean that sighs had a dual purpose: (1) maintain lung health (all mammals sigh to reinflate alveoli that are constantly spontaneously collapsing; adult humans sigh about 12 per hour to maintain lung patency), and (2) modulate emotional state (sighs are calming). We put together a compelling story of a well characterized microcircuit driving a critical behavior and published it in *Nature* (Li et al., 2016). The paper went viral, with stories in major newspapers and other conventional and unconventional media outlets worldwide, including *The Onion*.

Cdh9

Our collaboration continued as Kevin Yackle, who had identified many potential molecular markers for preBötC neurons, investigated the properties of preBötC neurons expressing the cell adhesion molecule Cdh9. Working with several outstanding investigators at Stanford (including Liqun Luo and John Huguenard), we concluded that the locus coeruleus, a structure not directly involved in generating breathing movements, which receives inputs from preBötC Cdh9 neurons, conveys signals that can affect emotional state. We were quite excited to have identified a neural circuit linking breathing to emotion modulation (Yackle et al., 2017). This paper in *Science* went viral, too, and even *Cosmopolitan* wrote about it.

Learning to Meditate

Our studies on sighs and Cdh9 awakened me to the fact that breathing is a behavior that does more than just regulate blood gases and control airflow for reflexes and phonation. I became curious how breathing could affect emotion in humans. Here again, I decided to do my own underpowered (n = 1) experiment, spurred by an article in the *New York Times* about mindfulness. Believe it or not, I had been living in Los Angeles for more than 25 years and had never heard of it. My interest aroused, I googled mindfulness and discovered that UCLA had a Mindful Awareness Research Center that offered courses. I immediately enrolled, with two intentions: (1) to see whether the breathing component in the practice of mindfulness is essential to its effects on emotion and pain, (2) to see if I could levitate (I was a teenage fan of Kung Fu movies, so why not). After several weeks of mindfulness practice, I concluded that the breathing exercises were potent modulators of emotion (though I have yet to achieve success in levitating).

My curiosity further piqued, I tried to figure out how I could demonstrate that the effect of breathing on emotion was indeed the case and to determine its underlying mechanisms. In a lengthy discussion with Raquel Abreu, a thoughtful and meticulous postdoc, we agreed that we would try to develop a model of "meditation" in mice.

Teaching Mice Breathwork

After about two years of failing to train mice to breathe slowly, Raquel hit on a highly reproducible way to slow the breathing frequency in awake mice. Using this protocol, she slowed the breathing of awake mice for 30 minutes a day for four weeks and transferred them to Michael Fanselow's lab, which has world-class expertise in assessing fear. In another one of those exhilarating discoveries that makes being a scientist unique, we found that these mice, subsequent to slow breath training, were considerably less fearful than control mice (de Sousa Abreu et al., 2024).

I wrote an exploratory R21 grant to the National Center for Complementary and Integrative Health (NCCIH) to test various mechanisms that I and others postulated could underlie the effect of breathing on emotion. My application was not warmly received. Shortly thereafter, I delivered a Special Lecture at the 2016 SfN Annual Meeting, which included a brief discussion of our ideas on the relationship between breathing and emotion. After my lecture, Wen Chen, a branch chief at NCCIH, approached me, expressing considerable interest in my ideas, and encouraged me to resubmit for funding. With her guidance and support, we received R01 funding.

Interest in breathwork, both inside and outside the neuroscience silo, began to grow. We wrote a review in *Nature Reviews Neuroscience* (Del Negro, Funk, and Feldman, 2018) that was accompanied by a cover drawing of a "meditating" mouse, and later a review in *Annual Review of Neuroscience* (Ashhad et al., 2022) with "breathing" and "emotion" in the title. Andrew Huberman, in the early stages of developing his online presence, invited me to sit for a podcast. We had a wonderful discussion. The published comments were interesting and quite unlike those that I would receive after a lecture or seminar. One of my favorites was "I hope a science biopic gets made someday, where DeNiro gets to play Dr Feldman. NYC is my homeland, and Dr F has the most perfect old-school accent to top off his engaging wealth of knowledge." Consequent to this and other podcasts, I'm occasionally recognized in public. On one occasion, I was sitting at home with a roofer, and while writing his estimate, he noticed my full name at the top of the form and asked, "Did you do a podcast on breathing?" "Yes," I replied. He practically jumped out of his chair and said, "That was one of the f$$king greatest things I ever heard!" Recently, I stepped way outside my silo in a podcast with Tyrone Lindqvist of the band Rüfüs Du Sol to discuss the band's discovery of breathwork. Tyrone summed up the impact succinctly, saying that

the band went from "whisky shots to ginger shots." Tyrone invited me to the band's Rose Bowl concert, along with my sons and their partners; it was epic. I now fully realize there is real hunger among nonacademics for sensible, understandable descriptions of how the world works, breathing included.

Influential Experiences

Reviews

An important research activity for me has been writing major reviews and textbook chapters, starting in 1986 with my *Handbook* chapter and followed by another every few years. I have been privileged to coauthor these reviews with talented postdocs and colleagues, including Sufyan Ashhad, Mort Cohen, Howard Ellenberger, Greg Funk, Sten Grillner, Kaiwen Kam, Don McCrimmon, Gordon Mitchell, Gene Nattie, Jens Rekling, Jeff Smith, and, especially, my brilliant and hardworking intellectual partner Christopher Del Negro. For me, each review provided an opportunity for reeducation, a chance to catch up, and time to rethink and reinterpret the state of the discipline.

Becoming a Chair

My first substantive experience in academic leadership arose within the Kinesiology Department in the UCLA College's Division of Life Sciences. At the time, neuroscientists in the college were scattered across multiple departments, with no unified voice in recruitment, curriculum, or long-term planning. Some senior faculty even questioned whether neuroscience constituted a legitimate discipline, an attitude that seems remarkable in retrospect but was genuine at the time. In response, Reggie Edgerton, Art Arnold, and I, together with many colleagues across the Life Sciences, organized an *ad hoc* undergraduate major in neuroscience. As international interest in neuroscience grew, this effort evolved into formal recognition as the Interdepartmental Undergraduate Program in Neuroscience, for which I served as the inaugural chair.

During this period, Kinesiology was losing traction as an undergraduate major. Working with colleagues, we reshaped the program into what became Physiological Science. When the sitting chair's term concluded, I was asked to assume the role. Although reluctant, as my priorities were research and family, I agreed to serve. One of my first initiatives as chair was to help revise the Life Sciences core curriculum, which at the time emphasized molecular and cellular biology and behavior, with little attention to integrative physiology. Students could recite the molecular components of cardiac excitability yet had little understanding of how the heart functions as an organ. I advocated for and helped implement curricular

changes that introduced organ-level physiology into the core, including a new course focused on integrative physiological function.

After several years as chair of Physiological Science, I was approached during a search for a new chair of the Department of Neurobiology in the School of Medicine. The department, newly renamed from Cell Biology and Anatomy, needed renewal. Although the search initially focused on external candidates, none ultimately accepted. When asked for my assessment of the department's challenges and prospects, I spoke candidly, emphasizing the need for a clear scientific identity and sustained investment in faculty. I had not sought the position, but following further discussion, I agreed to take it on. The appointment came with the resources necessary to rebuild the department, including multiple new faculty lines. Recruiting and integrating these faculty over the subsequent years was demanding but deeply rewarding. I stepped down after six years as chair, proud of the department's revitalization and its continued trajectory.

Conclusion

Looking back, what surprises me most is not that breathing proved to be a fruitful scientific problem, but how long it took me to recognize the complexity underlying its apparent simplicity. The preBötC and RTN did not answer all questions about breathing, nor were they meant to. Instead, they reframed the problem, opening doors not only to mechanisms but also to translation, pathology, and, more recently, to understanding how breath links brain, body, and emotion. These discoveries emerged in part from my responses to resistance to ideas I proposed that challenged entrenched assumptions about where rhythm could arise and which mechanisms were deemed plausible. The consequent disagreements, sometimes uncomfortable and personal, were, in retrospect, productive because they clarified which questions mattered most and which experiments would ultimately be decisive. The challenge now is not whether kernels exist, where they are located, or what their fundamental properties are, but instead how their collective dynamics give rise to the flexibility, robustness, and variability of this fundamental behavior. Breathing turned out to be a lifelong problem. That was not my plan. But in retrospect, it was precisely the right one.

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