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American Academy of Arts and Sciences (1982)
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Fernando Nottebohm is a pioneer in the study of the neurobiology of vocal learning in birds and was the first to describe their forebrain's song system and some of its salient features: sexual dimorphism, seasonal changes in size, hormonal sensitivity, and the relation between its volume and song-learning potential. The work of Nottebohm and his colleagues also provided the first incontrovertible evidence that new neurons continued to be added to the adult brain of a warm-blooded vertebrate, where they were born by division of radial cells. Most surprising, perhaps, was the evidence that many of these neurons were ephemeral, being added at times of peak memory load, lasting for a few weeks or months, and then disappearing. He saw this turnover of neurons as a process of self-rejuvenation that enabled new learning to occur. His findings challenged some well-established dogmas.

Fernando Nottebohm

Growing Up in the Pampas

I was born in Buenos Aires in 1940, a second-generation Argentine. My father was Guillermo Oscar Nottebohm, my mother Amelia Grant Menzies. My father's family came from Germany, Belgium, and Holland, my mother's from Scotland.

No one was very religious at home, except for my sister Florencia, who went to a convent school and every Sunday herded her three younger brothers to church. My mother did not come with us, and when I asked her why, she said that she communicated with God directly. So did my dad. I gave up religion at age 16.

Animals fascinated me, and I was able to observe them and to enjoy them at my family's ranch, Estancia La Maya, in southeastern Cordoba province. I spent much time there when not at school. La Maya was northwest of Buenos Aires, an eight-hour trip by train. In pampas country, with an average rainfall of some 900 mm, its park and meadows seemed always replete with birds, which I spied with my binoculars. I grew familiar with their habits, sounds, and nests; I knew where to find them and was immensely happy in their company. Of course, there were other attractions to ranch life. My older brother, Guillermo, and I rode every day with the gauchos and enjoyed working with cattle, but I always kept an eye open for birds and what they did. My favorite author was William Henry Hudson, born in the pampas south of Buenos Aires in 1841, the son of American settlers at a time when Indian incursions were still much feared. As a boy and a young man, Hudson was an observer of nature. He left for England at age 33 never to return. Many years later, he wrote a wonderful book, *Far Away and Long Ago* (1918), in which he told about his youthful adventures among birds. When I was in my early teens, that book represented all I wanted to be—an able observer of nature and a writer. Unfortunately, by the 1950s, the pampas had changed a lot; they no longer were the enchanted world that Hudson knew. Now agriculture was prevalent. Fortunately, my father was much fonder of cattle than of crops, and so at La Maya as much land was devoted to pastures as to crops, and this rotation protected the rich soil as well as the wildlife. Now, 60 years later, pesticides and herbicides squeeze greater profits from the land, but many of the birds are gone, even some that were very common before, such as tinamous and the burrowing owls.

Determinism or Free Will?

I had my first “scientific” insight at age 17, influenced, I suppose, by things I read, but I experienced it as if I had worked it out on my own. I took it as a given that the mind was inside the head and part of the normal function of the brain and therefore had all the attributes of matter. How did matter behave? I reasoned that if substance “A” was defined by its properties, then, under any set of conditions, the outcome of its interactions with other substances would always be the same. Apply that to all kinds of matter and all the combinations in which it occurs, brain included, and the result was determinism. Things happened, and the outcome was either predictable or, due to chance events, unpredictable. Either way, there was little room for freedom of choice, and therefore little room for sin. This insight did not change my ways but made me wonder at the paradox of “free will” and the reliability of our mind as a witness to ourselves. What to make of consciousness and the feeling it gave us of being in charge? I have been fond of paradoxes ever since.

School

My formal schooling took place in Buenos Aires; I attended the Escuela Argentina Modelo for grade school and the Colegio Nacional de Buenos Aires for high school. Both were all-boys schools, the Colegio the best one in Argentina. Teachers there were also professors at the University of Buenos Aires and very knowledgeable, but they worked through a set curriculum that was meant to inform, rather than encourage discussion or original thinking. This curriculum included six years of Latin, three years of French, and three years of German or English. I chose German because I had learned English at home. Periodically, I grew tired of school and on lovely days, hopped on a train to Tigre, at the edge of the Parana Delta, just an hour away. There I would settle into a canoe and, with a picnic and binoculars, paddle into the rivers and marshes of the delta. Sometimes I took a book, so that I could read as the canoe rested among the reeds or on a quiet bank. Such sweet truancy! I would be back home for supper. My parents knew of these little excursions. Because I did well at school, they did not interfere with the way I managed my time.

In my last year in high school, I had to decide what to be when I grew up. I had several interests. One of them was politics. Argentina’s dictator, Peron, had been ousted by the army in 1955, after 12 years of what I remember as a mix of fascism, populism, cronyism, intimidation, and plain thievery, though many of the poor regarded Peron as an idol. It now seemed as if democratic institutions might flourish and that the country might experience a renaissance. A couple of years after Peron’s departure, I went with

a friend to observe the meeting of a constitutional assembly. This assembly would be the doorway to Argentina's democratic future. Ever the naturalist, I brought with me a pair of binoculars so that from the balcony I could observe the politicians close up. After witnessing endless maneuvers, posturing, and delays during which nothing at all was accomplished, I tired and returned home much disappointed. I lacked the patience and stomach for politics.

The Magnet of the Big Unknowns

My curiosity was drawn more strongly to the big unknowns—the origin of the world, of life, of humans, of consciousness and mind, and I was, of course, much drawn by my love of nature and, in particular, birds. I admired the work of Charles Darwin and had become acquainted with that of Karl von Frisch, who described the dance language of bees. I also had read a great book on the history of philosophy by Will Durant and a book on cosmology. Nothing, I decided, would please me more than to spend the rest of my life delving into these matters and studying nature. I asked my father to send me to Oxford or Cambridge, but he thought this was a weak plan. Scientists in Argentina, he explained, were very poorly paid, philosophers even a rarer breed, and neither occupation would land me a job with which I could support a family. Moreover, at that time, university positions were often assigned on the basis of politics, not merit, which made a career in science doubly risky. I remember my father repeatedly asking, "Do you want to be a bohemian?" I was not sure what a bohemian was but from the face he put on when he asked, I decided I probably did not want to be one.

Become a Rancher?

My father offered a compromise. He suggested I go to the United States to learn the latest about farming and ranching and then return to Argentina and work with him and help him manage the family lands. This would secure my income, and on weekends I still could lose myself among the birds I loved. I agreed to this plan. It coupled the adventure of going abroad and sampling new intellectual horizons with the reward of a safe return. I was very close to my mother, father, and siblings, and so my studies abroad would entail only a temporary separation.

In January 1959, two months after my 18th birthday, I flew to Miami. It was my first time on an airplane. I fell desperately in love with one of the stewardesses, a girl from Chile, but she left the plane in Lima. In Miami, I boarded a Greyhound bus that would take me to Lincoln and the school of agriculture of the University of Nebraska. When I arrived there, Lincoln was deep in snow. My friend Fernando Lagos, a fellow Argentine and agronomy student was waiting for me, and I settled in. Lagos and I became close friends.

The school of agriculture organized a rodeo each spring for university students, and I signed up to ride a bull and a bronco. The bull was a shaggy Scottish highlander with broad horns. The bronco was a huge, white, and very ill-tempered horse named Tombstone. I had to ride both animals bare-back and did well with the bull, even earned a prize, but the bronco ride was brief. After the ride, the bull circled back, rammed its head on my buttocks, and tossed me into the air. That was my most interesting day at the School of Agriculture.

I stayed in Nebraska a full year. During that summer, I worked as a hired hand at a ranch near Valentine, in sandhill country. I milked cows, put up hay, painted barns, built fences, and rounded up cattle. On Sundays, I spied on nature, and in the evenings, I read. I realized that summer that I was not cut for either farming or ranching. I loved the outdoors but was not interested in cattle, corn, or hogs. My mind was on other things and so, when I returned to Lincoln in the fall, I went directly to the library and looked at the catalogues of some of the best universities, searching for the blend of courses that would help me get to where I wanted to go. I was accepted at the University of California at Berkeley and allowed to transfer into the zoology department as a sophomore. Despite this change in course, I was glad that I had entered the United States through the Midwest because there I encountered many of the values that made the country great; I found the people hard working, sensible, polite, generous, and warm. I realized, as had my father, that my choice would have lasting consequences, for it was then that, like W. H. Hudson, I veered away from Argentina. Toward the end of his life, Hudson wrote to his brother, who stayed in Argentina, that he had often wondered how things might have gone if he had never left the enchanted land of his youth. In England, Hudson became a naturalist of renown, but he treasured most the years he spent among the birds of the pampas. When, later, I was asked by young Argentines for advice on studying abroad, I recommended that they do so but only if their interests were so deep that to forgo them would feel like torture; otherwise, they should not desert family, friends, language, and land. Once trained abroad and imprinted with standards of excellence, fair play, and opportunity, it is difficult to return to the setting where one started. Moreover, he who leaves early has no godfathers that will pave his return. I never received a job offer from Argentina—not once.

Berkeley and Peter Marler

In January 1960, I drove from Lincoln to Berkeley, with a stop at the Grand Canyon, and immediately fell in love with my new destination—the Spanish accents of the buildings, the broad sunny lawns, the palms and eucalyptus trees, and the many flowering plants. I loved the blend of people and cultures and the palpable ferment and diversity of ideas, though I missed

the beauty and charm of the Argentine girls and felt clumsy with a language that was not my own. I would spend two and a half years as an undergraduate in Berkeley and another two and a half for my PhD; those were among my happiest days.

I enrolled in the zoology department and that first semester I met Peter Marler, who taught Zoology IB. Marler was an Englishman with one PhD in botany and one in zoology. He had arrived from Cambridge a few years earlier, and he was a master lecturer. He paced in front of the class as he told us about the evolution of vertebrates, his voice lowered, his eyes fixed on an imaginary horizon, his brows working up and down. At times, his posture and movement would evoke the animals that roamed the land millions of years ago. I remember his conspiratorial tone as he introduced the first mammal, a small, furtive thing that was no match for the lumbering dinosaurs of the day; yet it was smarter, the improbable hero in a struggle for dominance that would unfold over millions of years. That was the kind of grand drama I wanted to learn about. It was difficult not to be inspired and want to learn more. I was glued to every word of Marler's and realized that I had finally found what I wanted to be.

Marler had trained as an ethologist under Professor William H. Thorpe of Cambridge University, who was the first to use the sound spectrograph to describe vocal learning in a songbird, the chaffinch (*Fringilla coelebs*) (Thorpe, 1958). The sound spectrograph turned sounds into a visual display that showed how loudness and frequency changed over time. Thorpe (1958) used this instrument to do a detailed analysis of how song was learned. Marler had, as part of his thesis, described the geographic distribution of chaffinch song dialects in Scotland. He had also noted how chaffinch song differed in various Atlantic islands and how these differences were related to the relative richness or paucity of the local avifauna. Marler suggested that when many different species communicated vocally, the channel for each would be narrower, promoting the use of signals that were more distinct and less variable. In California, Marler was testing Thorpe's insights and those from his own chaffinch work, using a common California songbird, the white-crowned sparrow, *Zonotrichia leucophrys*, which also had song dialects (Marler and Tamura, 1964). I learned from Marler to go for the broadest, simplest questions, and to articulate the findings so they never sounded like dogma. His insights were "suggestions" of how things might be, and they were worded so that further data could modify them without loss of face. Marler built on the insights from his chaffinch and white-crowned work using still other songbirds. Taken together, his field and laboratory observations on song learning led him to propose the existence of an innate "instinct to learn" that determined the what, when, and how of learning. This view departed radically from that of B. F. Skinner, a Harvard psychologist who taught that, with proper reinforcement, animals could be made to perform even very unnatural behaviors. Of course, these two outlooks

were not mutually exclusive, for although one emphasized the limitations or guidance built into a natural learning program, the other one focused on the power of conditioning to modify behavior. These ideas interested me a lot. Just as earlier I had wondered about the reliability of our mind as a witness to ourselves, now I wondered how often we were held back by limitations built into our ability to know. Was our world restricted by unsuspected programs in our minds?

Until Marler's appearance on the scene, the field of animal communication had been full of anecdotes but light on basic science. Marler suggested broad rules that were based on the physics of sound transmission, the properties of binaural sound perception, the relation between sender and receiver, and the nature of the behavioral and environmental context. For example, his approach suggested that sounds used in communication would differ physically depending on whether they must conceal or reveal the position of the emitter. Moreover, from the context of a signal and the response of the receiver, he inferred what kind of information was conveyed. His approach was fresh, didactic, and compelling. It stressed field observations, comparative studies, and laboratory experimentation, and its principles could be applied to all sensory modalities and all groups of animals, whether invertebrates, amphibians, fish, primates, or birds. Marler was also enthusiastic regarding field experiments.

In later years, Marler spent equal amounts of time studying vocal communication in birds and primates, including a stay with Jane Goodall in Kenya studying vocal behavior in free-ranging chimpanzees. Marler's students studied the vocal behavior of diverse primates throughout the world, reflecting Marler's intense desire to come to grips with the conditions that might have led to vocal learning and the emergence of language in humans. It will be clear from my description of the man I encountered teaching Zoology IB that this was an extraordinarily lucky break—I had found someone that walked on water.

During my undergraduate years at Berkeley, I tried to put together a curriculum that acquainted me with many levels of biological thinking, such as ethology (Peter Marler), ecology (Frank Pitelka), anthropology (Sherwood Washburn), comparative psychology (Mark Rosenzweig), behavioral endocrinology (Frank Beach), marine biology (Donald Abbott), comparative anatomy (Wilbur Quay), embryology (Richard Eakin), comparative physiology (Paola Timiras and Walter Freeman), neurophysiology (Donald Wilson), biochemistry (Melvin Calvin), cell biology (Max Alfert), genetics (Kurt Stern), and human neuroanatomy (Marian Diamond). This was a rich fare, later supplemented in graduate school by courses in philosophy of science (Paul Feyerabend) and history of science. During those years, I also enjoyed taking courses in German and in German literature that allowed me to explore aspects of the mind that went beyond the factual description and objectivity of science. I remember, in particular, my thrill at reading

Kafka. However, and to my lasting chagrin, I did not take courses in the then-young field of molecular biology, something that I would now put high on my agenda. With this notable exception, I felt I had brought together many of the lines of expertise that I would need to think about matters that interested me.

During the last year of their undergraduate studies, students in the zoology department at Berkeley could take an “honors course” consisting of research in a chosen laboratory. I chose Marler’s lab for this, and my project was to work on the biology of sound production by the syrinx. There was already literature on this topic. Marler was very supportive, and I put together a transparent pressure chamber that mimicked the pressurized inter-clavicular airsac that surrounds the syrinx in birds. The syrinx and trachea of a rooster were placed inside this chamber and connected in such a way that air could flow from the bronchi past the sound generating membranes of the syrinx and out the trachea. I was able to manipulate the flow of moist air, the configuration of the syrinx, and the pressure in the air space surrounding the syrinx. The crowing touch, suggested by Marler, was to use a stroboscopic light while sound was produced to see at what frequency the membranes of the syrinx would seem to stand still. That was the fundamental frequency of the sound produced.

I received my bachelor of science degree in June 1962, three and a half years after my arrival in Lincoln, Nebraska. At Marler’s invitation, I joined his laboratory as a doctoral student. The invitation was conveyed by Mark Konishi, who was then close to finishing his doctoral work with Marler and with whom I had developed a close friendship (both of us enjoyed skiing). I answered that same day. I could not think of a better opportunity to further advance my interests, and I had no alternative plans. I was still keen on all the big questions about origins that I have mentioned earlier. I hoped that, by focusing on vocal learning, I would eventually be able to find my way back to these issues, though I did not know how this might come about, if at all.

I Find the Girl I Love

In the summer of 1963, I met a lovely Argentine girl, Marta Seeber, who was finishing high school in San Francisco. Not only was she beautiful but loved animals and nature and had a great sense of humor. Half a year later we were married in Buenos Aires, and I entered the happiest period of my life. Marta was from then on an invaluable partner in many of my scientific adventures. Her thinking was clear and incisive, and she was superb at editing what I tried to put down on paper. I later learned of studies that showed that most immigrants to the United States marry others born not more than 10 miles away from their own birth site. In a figurative sense, it is like salmon going back to their home stream, but in this case, while staying abroad. *Porteños*, as the people from Buenos Aires are called, have

a strong “dialect” and perhaps this common dialect influenced our choice. It is a phenomenon that others have studied in birds.

We rented an apartment at 2727 Hearst Avenue, on the road up to the Lawrence Radiation Laboratory. We saw President Kennedy from our doorstep when, during a visit to the university, he was driven up the hill to visit the cyclotron. It was a marvelous time in the United States—a time full of hope and promise, and the young people (and in particular university students) felt very much a part of it, inspired by a president that, I believe, most of us loved. Less than a year later, President Kennedy was dead.

Left Hypoglossal Dominance

Marler spent the 1964–1965 academic year studying primates in Africa, and I spent the year as a guest in the laboratory of W. H. Thorpe in Cambridge. During that year, I set out to test a suggestion advanced by Konishi (1965). He had noticed that if a white-crowned sparrow was deafened after it had mastered its learned song, this song would be retained with great accuracy; he wondered how this was achieved. Might proprioceptive feedback play a role? I tested this idea by denervating the syrinx. Denervation would debase the sound produced, but would the altered pattern remain stable? If yes, this would suggest that the learned motor program was no longer dependent on feedback. If the answer was no, this would suggest that, as motor output and associated auditory and proprioceptive feedback were altered, stability broke down. These experiments would be conducted with hearing and deaf individuals. In retrospect, it was a complicated experiment, and results could be difficult to interpret. Yet, I did it, and the outcome was totally unexpected—a classical example of looking for A and finding B.

During my year in Thorpe’s sub-department of animal behavior, I had just one room to myself. It held my desk, my surgery, and all of my birds. The morning after I did my first bilateral syringeal denervation, I unlocked the room, flipped the lights on, and walked in. The operated chaffinch was on a perch and looking well but upon my arrival got agitated and started to hop from perch to perch and breathe ever more laboriously, producing a sharp wheezing sound; then it fell to the floor of the cage and died. The same fate awaited my second bilateral denervation and then, bearing in mind what I had seen in my earlier pressure chamber experiments, I understood. The walls of the syrinx are soft, and as air flows by, they are drawn into the lumen of the bronchi, like lips, creating a narrow aperture through which air must flow; air streaming past a narrow aperture creates turbulence and, in birds, the periodicity (or not) of this turbulence accounts for the quality of the sounds we hear. These sounds are modulated by the syringeal muscles that set the size and shape of the aperture past which air flows, and by abdominal muscles, acting on the abdominal air sacs, that set the pressure head of the outflowing air. I inferred that during inspiration the role of the syringeal

muscles must be to maintain the syringeal lumen fully open so that inspired air flows unhindered. Otherwise, the walls collapse (Bernoulli effect), with accompanying wheezing, a phenomenon that to some extent must also occur during expiration. In this light, the syringeal muscles have a dual role: (1) enablers of air flow and (2) voice production. When I entered the room, the birds were alarmed, then became agitated—breathing harder—and this led to asphyxia.

I wondered how to avoid this unwanted outcome. Perhaps unilateral denervation would still yield a useful result, and that is where I got lucky. For no particular reason, I denervated the *left* syringeal half in a number of chaffinches and, in all, song was severely modified. Then, one day, I denervated the right syringeal half: the song was unaltered. Fearing I had made a mistake, I repeated the operation a second time in the same bird and still no effect, and then a third time, now sectioning the three roots of the hypoglossal nerve that provide the innervation to the right side of the trachea and syrinx, and still no effect. Suddenly, I understood: I had discovered song handedness—left hypoglossal dominance for the production of learned song. I repeated the same operation in many more chaffinches (Nottebohm, 1971, 1972) and, later, in canaries (Nottebohm and Nottebohm, 1976), always with the same result. If anything, left hypoglossal dominance was, in my birds, more robust than handedness in humans because I never found a right-handed chaffinch or canary. I noticed, too, that when nerve section was not followed by regrowth, it was just the muscles of the denervated side that atrophied, becoming very thin and colorless. I carefully inspected the syrinx and could find no reason why one side would be dominant for the production of learned song. The two syringeal halves were mirror images of each other. The only difference was that the muscles on the left side were somewhat heavier than their right counterparts, but this I attributed to differential use. Intriguingly, in a majority of chaffinches and, later, canaries, the right syringeal half was not totally silent but contributed a few high frequency sounds, so that one could imagine a division of labor with one side producing low frequencies, the other high frequencies. Yet, when the dominant left syringeal half was denervated in juvenile chaffinches before the onset of singing, then the right intact side developed accurate imitations of external models so that—a bit like the hands of humans—both sides were, at the onset, equipotential and each could on its own do the entire song. The exception was that unilaterally denervated birds could not copy harmonically unrelated simultaneous sounds. In canaries, I found that this potential for dominance reversal persisted into adulthood, perhaps because canaries are able to learn a new song every year. The discovery of singing handedness and its reversal (Nottebohm, 1971, 1972a, 1977; Nottebohm and Nottebohm, 1976; Nottebohm et al., 1979) had not been predicted and came as a surprise. I have known, since, that all true discoveries come as surprises.

Field Work

Even as I explored the topic of song handedness, there was a part of me that also wanted to study the biology of vocal learning in the field—dialects in the rufous-collared sparrow, *Zonotrichia capensis*, and vocal imitation in wild parrots, *Amazona amazonica*. I pursued that work from 1966 through 1974, including two years spent in and out of the jungles of Trinidad, together with my wife. During those years, I learned a lot about field biology but did not come across an issue that, in my view, was basic and ripe for cracking. Eventually, I realized that I would not be effective in both lab and field and gave up field work after publishing some of my observations (Nottebohm, 1969b, 1972b, 1975, 1976; Nottebohm and Selander, 1972; Handford and Nottebohm, 1976).

The Song System

In birds, I had found a learned vocal skill produced by a single, specialized organ that showed handedness similar to that in humans. What next? Would these birds also show hemispheric dominance for the production of learned song? To address this question, I had to smoke out the brain pathways responsible for the acquisition and production of learned song. Harvey Karten suggested, correctly, that I first make an atlas of the canary brain. For this, I teamed up with Christiana Leonard, whom I knew from Berkeley. She was now a wonderful neuroanatomist in the laboratory of Carl Pfaffmann at Rockefeller, and she had a great technician, Tegner Stokes, with whom I did much of the actual work. Once the atlas was done (Stokes et al., 1974), we identified the medullary motor neurons that innervated the muscles of syrinx and trachea. We then placed lesions around the known forebrain auditory projection of birds, Field L, hoping to find a site that, when lesioned, affected song—perhaps an avian equivalent of Broca's area in humans. We found such a site (Nottebohm et al., 1976) and called it the hyperstriatum ventrale, pars caudale (HVC); but this was an error because HVC was really part of what then was called the neostriatum and now is known as the nidopallium. Because the abbreviation HVC was already established in the literature, I decided to stick with it and have it stand for “high vocal center.” Some find this use of English and the assigning of a function unorthodox and so, when referring to HVC, they add “abbreviation used as a noun” in brackets. I find this silly and confusing. There are precedents for using English and functional terms in brain anatomy (e.g., “optic tectum” and “olfactory bulb”), so why not “high vocal center”? The high vocal role of HVC is supported by connectivity, physiology, and behavior. Much research from several laboratories has shown that this anatomically discrete nucleus is, indeed, the headwaters of the “song system” (See Figs. 1 and 2).

The 1976 report showed that HVC projects to two other discrete anatomical nuclei, the “robust” nucleus of the archopallium (RA), which in turn projects to the hypoglossal motorneurons that innervate the muscles of the trachea and syrinx (nXIIIts), and Area X, that we now know is part of the basal ganglia. Interestingly, much as HVC-RA-nXIIIts provides the backbone of the descending pathway for the production of learned song (1976), HVC also receives input from the auditory forebrain, as first described by Kelley and Nottebohm (1979) and subsequently in greater detail by Vates et al. (1996) and Mello et al. (1998). Katz and Gurney (1981) provided the first neurophysiological evidence that HVC receives auditory input. HVC’s pre-motor and auditory profile is reminiscent of Broca’s area in humans.

The existence of discrete forebrain nuclei that controlled a specific learned skill seemed contrary to the findings of Karl Lashley (1950), whose lesion work in rats had suggested that the impairment of maze performance was proportional to the amount of cortex destroyed and not dependent on lesion of any one particular site. Perhaps these very different outcomes had to do with the fact that song is a learned motor skill produced by a special purpose organ, the syrinx. By contrast, running a maze—though a motor activity—is not much of a motor “skill,” and it does not depend on a specialized organ for maze running.

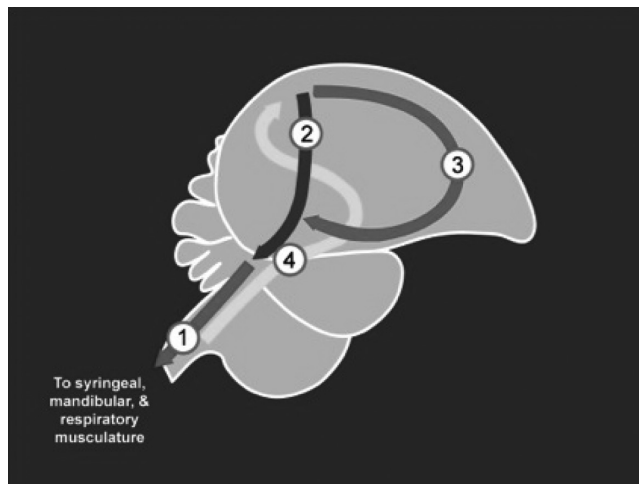


Fig. 1. The song system can be imagined as consisting of four modules. Module #1 is in the brain stem and shared by vocal learners as well as by non-vocal learners. Module #2 is a telencephalic module that tells module #1 what to do. Module #3 starts from module #2 and then returns to it; it is necessary for vocal learning but not for production of learned song. Modules #2 and #3 are very well developed in vocal learners, less so or absent in non-learners. Module #4 is the ascending auditory pathway that conveys information about the sounds to be imitated and auditory feedback about the sounds produced. From Nottebohm, 1993.

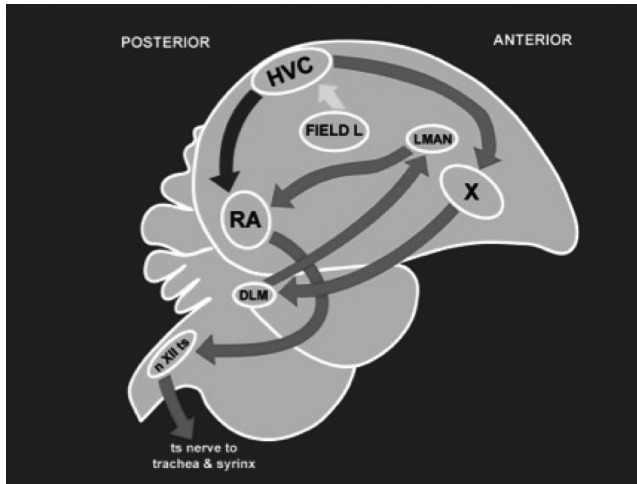


Fig. 2. Schematic diagram of the nuclei and connections of modules #2 and #3 and their relation to modules #1 and #4. All the connections shown are ipsilateral, and each right and left brain half duplicates the anatomy of the other side. Abbreviations: HVC, high vocal center; RA, robust nucleus of archipallium; X, area X of basal ganglia; LMAN, lateral part of the magnocellular nucleus of the anterior nidopallium; DLM, medial portion of dorsolateral thalamic nucleus; nXII, tracheosyringeal part of the hypoglossal nucleus; Field L, auditory nidopallium. The color code for the four modules of the song system is the same for both figures. From Nottebohm, 1993.

Hemispheric Dominance and Its Reversal

My interest in vocal learning had led to the accidental discovery of syrinxal “handedness.” I was a “lefty” as a child but was schooled to become right-handed. I still draw with the left and can write with either hand. Handedness interested me and so I took to the readings of not just Paul Broca but also Hans-Lukas Teuber and Norman Geschwind and many others concerned with such matters. It was now time to look for handedness in the central song system. In the absence of a corpus callosum, most of the song system’s forebrain circuitry is ipsilateral as are its descending pathways. The left HVC, for example, controls the performance of the left RA and of the left syrinxal half. In adult canaries, lesions to the left HVC have a much more devastating effect than those of the right one, and the quality of song following such a left lesion is reminiscent of the highly variable subsong of juveniles. Yet, seven months later, this same canary has learned to produce a new, normal song, this time under right side control; the new song is silenced if the right tracheosyrinxal nerve is cut, evidence that dominance had flipped from one side to the other (Nottebohm, 1977). By then, I felt that the 1976 publication on “Central Control of Song in the

Canary” had planted the germinal seed of a new field, the neurobiology of vocal learning, which nicely complemented the ethological work of Thorpe and Marler.

Two Pathways—One to Learn, One to Know

In 1976, I did not understand the significance of the projection from HVC to Area X, nor did I realize that, though embedded in what then was called “Lobus parolfactorius,” it was really part of the avian basal ganglia. Lesions to Area X in adult canaries did not alter song (Nottebohm et al., 1976). In 1984, a key study by Sarah Bottjer and Arthur P. Arnold showed that though an intact Area X was not necessary for the production of learned song, it was necessary for song learning. The importance of this observation became apparent when the circuit connections of Area X became fully understood. We knew that HVC projected to Area X (1976) and that the lateral nucleus magnocellularis of the anterior neostriatum (LMAN) projected to RA (Nottebohm et al., 1982). Then, in 1987, Okuhata and Saito (1987), working in Japan, reported that Area X projected to nucleus DLM of the thalamus and that DLM projected to LMAN. This connectivity, also shown in Figure 1, was confirmed by Bottjer et al. in 1989. By then, we realized that the *song system* included two forebrain circuits, an “anterior” one (HVC→Area X→DLM→LMAN→RA) necessary for vocal learning and a “posterior” one (HVC→RA) necessary for the production of learned song. Once a song has been learned, it is HVC that “knows” and executes the pattern. All the nuclei of these two pathways are anatomically discrete. HVC is at the headwaters of both these circuits, and RA provides the common exit point from forebrain to brainstem (Figure 1). The arrangement described here seems to be general among songbirds.

Vocal Variability Is Necessary for Vocal Learning

In 1991, Constance Scharff and I looked more closely at how the “anterior” pathway contributed to vocal learning and suggested it had two roles: (1) as an information channel necessary for learning and (2) as a modulator of plasticity necessary for learning. These two roles seemed to be differently represented in Area X and LMAN. Although early lesions of Area X yielded results reminiscent of early deafening, with the bird producing in adulthood variable, abnormal song, early LMAN lesions resulted the day after in a drastic reduction in note diversity and variability, with no further changes. The idea that LMAN played a crucial role in fostering circuit plasticity necessary for learning was not farfetched because the same RA neurons that received input from HVC also received input from LMAN (Canady et al., 1988); moreover, these cells projected to the motor neurons that innervated the syrinx. However, the neurophysiological nature of the relation between

LMAN and RA was not understood until the laboratories of Michael Fee at MIT (Ölveczky et al., 2005; Aronov et al., 2008; Andalman and Fee, 2009) and Brainard and Doupe at University of California, San Francisco (UCSF) (Brainard and Doupe, 2000; Kao et al., 2005) showed how this worked. In a nutshell, Fee calls LMAN a “noise generator” whose input to RA promotes the vocal variability that is necessary for learning. This “noisy” input is not totally random because, given access to auditory feedback, it helps shape motor signals crafted by the HVC-RA axis. Intriguingly, the same LMAN neurons that project to RA also send a collateral back to Area X (Vates and Nottebohm, 1995), but the consequences and system’s logic of this feedback are not yet understood.

Ontogeny and Origins of Vocal Learning

My work has always been driven by immediate questions as well as by deeper and more speculative ones, and the origins of vocal learning falls into the latter category. It is easy to imagine how some traits evolved, but in other cases, the sequence is not obvious. How did modification of a non-learning vocal system—as inferred to exist in chickens (Konishi, 1963) and doves (Nottebohm and Nottebohm, 1971)—lead to the emergence of auditorily guided vocal learning? This, to me, remains a fascinating question. It was a standard approach among students of human evolution to state that “language” (which was not separated from “vocal learning”) arose in humans as societies became more complex and there was a need to convey more information. I thought we might be able to do better with birds. Take the case of the chaffinch. The earlier a male chaffinch is deafened, the more rudimentary the song it produces in adulthood, suggesting that the interaction between hearing and motor output starts well before the imitation of a specific model (Nottebohm, 1968). Next, a careful analysis of vocal ontogeny suggests that the food-begging calls of juvenile chaffinches give rise to two distinct sounds that occur in subsong, the “chirp” and the “rattle” (subsong being the babbling stage of birds before external models are incorporated). Modification of these two subsong components then seems to give rise to all the sounds of adult song. I suggested that in this manner each stage in vocal ontogeny provides auditory and motor cues and guidance for the next one, culminating in the imitation of an external model (Nottebohm, 1972a). Such self-assembly need not be very different from the way organs put themselves together, but the key difference is, of course, the role of auditory feedback.

Direct evidence that hearing was important for the early, pre-imitation stages came many years later from work that Wan-Chun Liu did with chipping sparrows. Chipping sparrow males learn their song by imitation, but females do not sing. In these birds, the food begging calls of juveniles are much more variable in males than in females and, as I had surmised in the chaffinch, in this case too, they transition into subsong. Importantly,

whereas early deafening affects the food-begging calls of male chipping sparrows, it does not affect those of females. In males, but not in females, food begging seems to be part of a vocal learning program that depends on intact hearing and is guided by hearing (Liu et al., 2009).

The observations on chipping sparrows were of interest in another way. We used immediate early gene (IEG) expression to identify which of the song nuclei were active during food begging (Jarvis and Nottebohm, 1997), and there was only one, RA, in which a rise in IEG expression was driven by food begging. Intriguingly, lesions of RA did not stop food begging in males but just made them as stereotyped as in females (Liu et al., 2009). These observations suggest that hearing-dependent vocal variability is an early and necessary event in the ontogeny of vocal learning, and therefore, perhaps, also in its evolution. Might juveniles that disguise their vocal identity through increased vocal variability be fed more frequently by their parents? If so, the origins of vocal learning may be rooted not in the need to communicate more information, but in the need to obfuscate and misinform. Does this sound like a human ploy?

It is perhaps no accident that the most recent publication from my laboratory focuses on the song pathways of a passeriform (same order as the song learning oscines), the Eastern Phoebe, *Sayornis phoebe*. Phoebe song develops normally in deaf individuals yet goes through a protracted ontogeny suggestive of a role for practice. These birds have a rudimentary RA-like region in their forebrain but, apparently, no HVC, LMAN, or Area X, or at least none that can be easily recognized. These observations remind us of how difficult it is to imagine how the song system or language evolved, with each stage offering a selective advantage (Liu et al., 2013).

Brain Sexual Dimorphism

Neuroscientists had never before had anything as anatomically discrete as the *song system* responsible for the acquisition and production of a narrowly defined, learned, communicatory behavior; nor had we had before the neural substrate for a learned behavior that was particularly well developed in males and less so or not at all in females. Perhaps because of this lack of precedent, none of us had predicted or expected that the song system would be sexually dimorphic. Indeed, when Stokes, Leonard, and I produced our atlas of the canary brain we used males and females interchangeably, on the assumption that gender would not matter.

Eventually, our eyes told our brain otherwise. Arthur P. Arnold and I noticed independently, he in zebra finches and I in canaries, that the song system showed marked sexual dimorphism, and this was the first example of gross sexual dimorphism in the vertebrate brain. This discovery was unexpected because until then the brains of male and female vertebrates had

been thought to be much the same, with hormones and experience accounting for differences in performance.

Male canaries sing much more than females, and their song is much more complex; female zebra finches, *Taeniopygia guttata*, do not sing at all. Arnold (who was my first PhD student) and I found that HVC and some other song nuclei were several-fold larger in males than in females. The extreme case was in the zebra finch, in which some of the song nuclei are vestigial in females (Nottebohm and Arnold, 1976). Earlier observations had shown that many song nuclei have receptors for androgen (Arnold et al., 1976) and estrogen, which then raised the issue of whether the dimorphisms we observed could be altered by hormonal treatment. Mark Gurney, in Konishi's laboratory, showed that female zebra finches treated with estradiol during their first month after hatching developed a male song system. In adult female canaries, testosterone treatment doubled the size of some song nuclei and induced male-like song. As this happened, the dendrites of one class of RA neurons doubled in length and formed many new synapses (DeVoogd and Nottebohm, 1981a; Canady et al., 1988). This hormone-dependent plasticity in the adult brain was as novel as the dimorphism itself.

Seasonality

Once I realized the potent effect that gonadal hormones could have on the morphology of the adult brain, I wondered how the male canary brain fared under seasonally changing hormone levels. I compared the size of song nuclei in males soon after they finished their breeding season with that of others in full breeding condition. The result was astounding. HVC was twice as large in the spring as in late summer, after breeding ended (Nottebohm, 1981b). The effect was also present but less strong in nucleus RA.

Brain Space for Learning

The year 1981 was a good one for me. It was then, too, that I made another simple and satisfying observation. The size of nucleus HVC was related to the complexity of the song repertoire. Taking advantage of the very clear anatomical boundaries of this nucleus, it was possible to estimate its volume rather closely. There was no systematic difference between right and left HVC—in itself a puzzle—but HVC volume was a good predictor of learning potential. Canaries with a relatively simple song, defined by number of different song syllables, might have a large or small HVC, but birds with the more complex songs always had large HVCs (Nottebohm et al., 1979). This correlation has held when comparing populations of a same songbird species (Canady et al., 1984), and others have shown it holds across species comparisons. Apparently brain space for learned song is at a premium.

Two Dogmas

In the early 1980s, the neurosciences harbored two prevailing beliefs. The first one was that the number of neurons in the brain of adult, warm-blooded vertebrates was reached soon after birth, an idea that went back to the classical work of Santiago Ramon y Cajal. Neuron numbers could decrease in adulthood, as in neural degenerative disorders, but no new ones could be added. The other, much more recent but equally widespread belief was that learning occurred at the level of synapses and could be explained by changes in synapse efficacy and numbers. Because synapses could change in number and in efficiency even in adulthood, many thought these changes could account for all changes in behavior. In computer terms, the hardware was provided by an existing population of neurons and their projections—the circuits of the brain—and the software was provided by malleable synapses.

Science is supposed to be the province of hard facts, yet I have been often surprised by how few hard facts there are. What we see in brain slices is determined by how the tissue is harvested and fixed, by the protocols used for different stains, by what the animal had been doing before it was killed, and so on. What we see might be an artifact that bears little relevance to what is in the living brain of an animal leading a natural life. What we do not see might not be there or might be there but be invisible. In short, science is replete with “observations” that, upon closer scrutiny, turn out to be interpretations and inferences, which leaves enormous room for error.

One day I pondered about anatomical seasonality in HVC and RA. Was it really a case of growth and retraction of dendrites and synapses, much like leaves that grew in the spring and were shed in the fall? Was this a good metaphor? Why was it that the seasonal changes were more marked in HVC than in RA? And why assume that these changes occurred in a constant set of neurons? Was it possible that neurons came and went and that the players in HVC were not always the same? I could not resist sharing these thoughts with Marta. Can you imagine, I mused, how this would set everything on its head? She liked this line of thinking a lot, for she favored bold science. We talked about it and laughed; it all seemed so improbable.

I also shared these thoughts with one of the young members of my laboratory, Steve Goldman, a very bright MD–PhD student; we talked about how to test for the possibility that new neurons were added and subtracted from HVC. He volunteered to do the work with help from my technician, Sue Kasparian, and begged me not to talk to others about this project. He was afraid that people would think we were ignorant, or worse, stupid. They used a method for birth-dating cells that was well established among embryologists. It relied on tritiated thymidine that was injected systemically and found its way into cells where it became incorporated into newly synthesized DNA. The tritium was an unstable isotope of hydrogen with an extra electron. As tritium reverted to a more stable form, it gave off a pulse of

energy that oxidized a silver grain in an overlying photographic emulsion. This technique is called autoradiography. The principle behind autoradiography had been used by clinicians treating cancer; if enough radioactively labeled thymidine was concentrated by the nuclei of dividing cells, the energy it gave off would fragment existing DNA and kill the cells. However, this required high doses that also killed other, non-cancerous dividing cells and did not kill cancerous cells that at the time were not dividing, so this approach had been given up as a cancer treatment.

Adult Neurogenesis

We thought our chance of finding new neurons in the adult brain would be maximal in adult female canaries treated with testosterone, in which, as explained earlier, HVC volume doubled over a period of a few weeks. Some of our birds were treated with testosterone and some were not, and they were killed at various intervals after receiving the tritiated thymidine injections. The results were most rewarding. Birds allowed to survive 14 or more days showed, in cresyl violet-stained material, many labeled cells with relatively large and clear nuclei, which looked like neurons. “Label” was the appearance of a least five exposed silver grains over the nucleus; many cells had many more, making the nucleus of these cells look like a sliver of cucumber with pepper grains on top. Birds killed two days after tritiated thymidine treatment had no labeled neurons, yet showed many labeled cells on the ventricular wall immediately above HVC. We suggested that this was where the new neurons were born and that they then migrated from there into HVC. Our observations seemed to exclude the possibility that existing neurons gave rise to new ones by dividing *in situ*.

This story became Steven Goldman’s thesis work. By the time we got our results, we also became aware that we were not the first to use radioactively labeled thymidine to look for neurogenesis in the adult brain. Joseph Altman had used this very same approach and published observations in which he reported that neurons born in adulthood were added to the granule layer of the dentate gyrus of the hippocampus, to the olfactory bulb, and to cortex. Altman had published his observations between 1962 and 1970, but they had not gained wide acceptance—Ramon y Cajal’s dogma persisted. There were good reasons for this. First of all he had, like us, used stains that were not selective for neurons; second, he did not try to discriminate between a label that may have been incorporated during DNA repair and a label incorporated during the S-phase preceding mitosis; third, he did not systematically pursue the possible origin of the new neurons. These uncertainties proved sufficient for the rest of the field to adopt a wait and see attitude.

Steve Goldman and I were a bit crestfallen that we had not been first to plant our flag in this new field. At the same time, it was true for Altman as for us that the evidence for adult neurogenesis remained open to challenge.

I asked Pasko Rakic, an experienced developmental neuroanatomist from Yale, to be the outside member of Goldman's thesis committee. I knew that Rakic was very opposed to Altman's claims of adult neurogenesis and so expected that he would be a stern evaluator of our work. Pasko looked at our slides, went over our protocols, and pronounced the data real, if yet not conclusive, for the very same reasons that he and others had found Altman's data not conclusive. It was our good luck that Viktor Hamburger, from Washington University, heard about our work; he invited me to St Louis to lecture, and I brought some of our slides. He, like Pasko, felt the data were real and of interest and suggested we submit them for publication in the *Proceedings of the National Academy of Sciences* (Goldman and Nottebohm, 1983), which was a tremendous help.

Testing Beyond Reasonable Doubt

Steve Goldman then went on to finish the medical part of his training at neighboring Cornell Medical School; I decided to focus on all the pieces of data that were still missing and that would test, beyond reasonable doubt, whether adult neurogenesis was or was not a real phenomenon in the brain of adult, warm-blooded vertebrates. I use the latter wording because work by others had already shown that in fish—the body, brain, and eye of which continue to grow after sexual maturity—new neurons are added to the brain and spinal cord as the whole animal becomes larger.

After Steve left, Sue Kasparian and I did an inventory of where in the brains of adult male canaries new neurons (i.e., tritiated thymidine-labeled cells that looked like neurons in cresyl violet stain) occurred. We found them in great numbers through most of the forebrain but not in the cerebellum, thalamus, diencephalon, or medulla. This was not without interest because the forebrain is usually credited with the processing of perceptual information and with the planning, acquisition, and execution of complex behaviors and learning.

A Heroic Experiment

We needed irrefutable evidence that the cells we called “new neurons” were neurons and were new. I knew that if I gave adult male canaries injections of tritiated thymidine at eight-hour intervals for two weeks and killed them one month later, 10 percent of HVC “neurons” (i.e., cells that looked neuron-like with the cresyl violet stain) were labeled. I satisfied myself that this label was likely proof of birth by comparing the amount of label per cell with that seen in other cell types known to continue to proliferate in adulthood, such as endothelial cells and glia.

I then teamed up with John Paton, an excellent and painstakingly careful neurophysiologist who had trained with Bob Capranica at Cornell. We

argued that if one were to record randomly from neurons in HVC, one in 10 would have been born during the previous four to six weeks. What we needed was to use a hollow glass electrode with a very slender tip, so that it could penetrate a neuron without killing it. This hollow electrode was filled with horseradish peroxidase that could be extruded into the neuron after recording from it so that later, as the tissue was harvested, that individual neuron could be recovered.

We applied this approach to adult male canaries that had received tritiated thymidine for two weeks one month earlier. We knew, from the work of Katz and Gurney, Konishi, and Margoliash that many neurons in HVC responded to sound, so we gathered data as follows. As the electrode advanced through HVC, its entry into a neuron was revealed by a change in resting potential; this neuron might show further changes in electric current in response to sound playbacks. The cell was filled with horseradish peroxidase and harvested later in 100- μ m thick sections that allowed a fairly good characterization of the cell's anatomy—soma, dendrites, dendritic spines, and axon. Then, this thick section was thin sliced, yielding sections that were only 6-micra thick, which were then incubated for autoradiography. These various steps proved extraordinarily laborious and at each step many things could go wrong. After 12 months of full dedication to this project, Paton had full sets of information from 77 neurons. Seven of these—the uncanny 10 percent we had hoped for—had a fine array of exposed silver grains over their nucleus, and of these, three had responded to sound. This experiment provided, for the first time, firm evidence that cells born in an adult warm-blooded brain became neurons and that at least some connected to existing circuits so that, in fact, they were working neurons. It was this publication, which came out in *Science* in 1984 that, I believe, changed the thinking of many—so that now, adult neurogenesis loomed like a real possibility. As Eric Kandel commented to me years later, it was a sea change in thinking.

Hope for a New Neurology

That same year, at the behest of Jane and Peter Pattison's Institute for Child Development Research, I organized a conference on "Hope for a New Neurology" at the Waldorf Astoria hotel in New York. The title for the conference undoubtedly struck some as hyperbole, but I felt it was justified. Clearly, neurons were born in the brain of adult, warm-blooded vertebrates and, in our material at least, they could find their way and establish connections. Our findings, I felt, added credence to Altman's claims. All around, this seemed like a most hopeful moment for a field such as neurology. My friend Fred Plum, head of neurology at Cornell Medical School, had confided to me that often times the best advice for patients with brain damage was, "Get a good nurse and, if you are religious, pray." We now might have the

beginning of something better. Shirley Bayer lectured at that meeting about her evidence for neuronal addition to the adult hippocampus of rodents, while Joseph Altman, her husband, by then retired, sat in the audience. Pasko Rakic spoke about his search for adult neurogenesis in the brain of juvenile and adult macaques. That search produced no positive evidence, and Rakic was still of the opinion that the phenomenon did not apply to primates and was not relevant to humans; he was not even convinced that it occurred in mice. In my opinion, what mattered was the conceptual breakthrough. We now knew for sure that the adult brain had not lost the potential to give birth to new neurons and to recruit them into existing circuits. The 100-year-old dogma had sprung a leak.

Soon after that conference, I went to see Jerome Posner, head of neurology at Sloan Kettering Memorial Hospital in New York. That hospital specialized in treating cancer patients, of which quite a few had a very limited life expectancy. I asked him if it might be possible, with patient consent, to give some a low dose of tritiated thymidine and then to look for labeled neurons in their brains after they died. I reasoned that, if this could be done with patients of a diversity of ages and other backgrounds, we might see if the human brain ever recruited new neurons as my canaries did. Posner was interested but a few weeks later told me that his ethics board had vetoed the project on the grounds that someone might accuse the hospital of conflict of interest. Subsequently, a study using terminal patients was done in Sweden, and it revealed the addition of new neurons to the adult human hippocampus. More of this work needs to be done.

New Neuron Origin and Migration

Next on my agenda was to identify the cell type that, in my canaries, gave rise to new neurons and how they migrated from birth site to work site. The initial work with Steve Goldman suggested that they were born in the ventricular zone (VZ) facing the forebrain's lateral ventricle, but this was tentative and details were missing. I was lucky, again, that the right person to build on this initial observation was in my laboratory, Arturo Alvarez-Buylla, a doctoral student from Mexico. A little bit earlier, a postdoctoral fellow in my lab, Daniel Buskirk, made a remarkable observation. Dan had been searching for monoclonal antibodies that might help us recognize cells or stages of cells that would help us visualize the choreography of adult neurogenesis. One day he came with a slide that showed what he feared might be an artifact and wanted to know my opinion. The slide showed a cresyl violet-stained section through the adult canary forebrain with many antibody-positive gold-brown fibers streaming through it. The fibers emanated from small cells on the surface of the lateral ventricle. I almost jumped out of my skin. "Dan," I said, "we are looking at radial glia in [the] adult brain!" Embryologists had, of course, long been aware of the importance of radial

glia during brain development, when they were thought to guide the migration of neurons. In mammals, these radial glia disappeared before the end of embryogeny. Now, we had radial glia in the forebrain of adult canaries. Follow-up work by Alvarez-Buylla showed that the antibody that displayed these cells was selective to vimentin (Alvarez-Buylla et al., 1987).

Two experiments followed soon thereafter. The first one combined the use of tritiated thymidine and the anti-vimentin antibody; its purpose was to visualize the relation between newly born cells and radial fibers. This experiment was conducted in the forebrain of canaries anterior to HVC. One day after treatment with tritiated thymidine, there were lots of labeled cells in the lateral wall (ventricular zone) of the lateral ventricle. Starting three days later, small, elongated cells with radioactively labeled nuclei could be seen immediately next to the ventricular zone (VZ), and then at longer survivals, further and further away from the VZ; the cells were, in their great majority, closely apposed to vimentin-positive fibers. By the end of the second week, the small, fusiform cells had reached most corners of the forebrain; their numbers peaked by day 20; after that, they declined, although those of labeled neurons increased. At its peak, on day 40, the cohort of labeled neurons was just one-third the peak number of labeled fusiform cells. We drew four inferences: (1) the small cells moving away from the VZ were young migrating neurons; (2) their migration was guided by the fibers of radial cells; (3) as the small, elongated cells reached their destination, they differentiated into adult neurons; and (4) only a fraction of the young neurons produced was still present 40 days later (i.e., there was, such as during embryogeny, an overproduction of new neurons in the adult brain) (Alvarez-Buylla and Nottebohm, 1988).

Neuronal Stem Cells

Follow-up work showed that, one hour after tritiated thymidine, 80 percent of VZ cells labeled with thymidine were positive for vimentin, and many of these cells gave rise to vimentin positive fibers. The number of silver grains over these vimentin positive cells fell by half when the material was collected one day after thymidine treatment. This study suggested that the principal dividing cell type in the VZ was the radial glia, which, we suggested, played two roles in adult neurogenesis: (1) they acted as neuronal stem cells; and (2) they guided neuronal migration. Because of this dual role, we decided to call them "radial cells" rather than lump them together with other glial cell types (Alvarez-Buylla and Nottebohm, 1988).

Taken together, my laboratory had established beyond reasonable doubt that neurons continued to be produced in the adult forebrain, had shown where they were produced, had revealed the identity of the neuronal stem cells, had shown how the new neurons migrated, and had provided evidence that at least some of them joined existing circuits.

In the years that followed, I focused on understanding why adult neurogenesis occurred in the first place. What was its context and significance? Initially, the temptation was to assume that it had to do just with seasonal changes in song, but clearly the phenomenon was broader than this because new neurons were added to many parts of the adult canary forebrain. Yet nucleus HVC stood out as an excellent place to unravel the significance of the phenomenon because we knew so much about its anatomy, circuitry, and function.

Do the Same New Neurons Encode and Decode Learned Song?

Many new neurons are added to canary HVC between the ages of one and eight months, when sexual maturity is achieved. We knew that the majority of song syllables that male canaries use during their first breeding season appeared between post-hatching days 60 and 120, when young canaries make the transition from the highly variable “subsong” to the more structured, but still variable, “plastic song” (Nottebohm et al., 1986). Perhaps new neurons in juveniles provided malleable circuitry for vocal learning. However, new neurons were still added at eight months when males were ready to breed and their song was stereotyped. What to make of this? Though I have emphasized that HVC plays a key role in the production of learned song, HVC neurons also respond to sound (Katz and Gurney, 1981). This response then propagates down the descending motor pathway, so that even the hypoglossal motor neurons innervating the syrinx respond to song playbacks, with different parts of the hypoglossal nucleus responding selectively to playbacks of different syllables (Williams and Nottebohm, 1985). Alvin Liberman and colleagues (1967), working on sound perception in humans, had suggested in their “motor theory of speech perception” that phonetic decoding required an understanding of how speech sounds were produced. Heather Williams and I interpreted our findings as supportive of a “motor theory for song perception in birds.” Perhaps HVC’s RA-projecting neurons play a role not just in song production but also in song perception, a view endorsed as well by Margoliash and Konishi (1985) and Margoliash (1986); and this role may differ between the two hemispheres (Cynx et al., 1992).

The motor theory of song perception—and its implication for the role of the HVC→RA neurons fitted well with the work that George Ojemann had done in humans. Ojemann was a neurosurgeon working on epilepsy. It was important for him to map speech cortical areas before surgery so that he could avoid unnecessary disturbance of areas important for speech perception or production. He showed that cortical stimulation of infero-frontal sites in the hemisphere dominant for speech that interfered with sequential orofacial movements also interfered with phonetic decoding; under such conditions, patients were not able to discriminate between “aba” and “apa” (Ojemann and Mateer, 1979). The evidence for this seeming convergence of

perception and production suggested that I had, by a very indirect route, returned to one of the big issues that so intrigued me as a youngster—the issue of “consciousness”—that the words we spoke, thought, and heard were all, perhaps, part of the same, elusive, conscious “self” and perhaps even vested in the same cells and circuits.

Windows for Recruitment and Survival

During the next 20 years, many studies from my lab focused on the relation between vocal learning and the recruitment of new HVC neurons. To my surprise, new HVC neurons were added to the HVC of adult male canaries during every month of the year, but seasonal differences in numbers could be as high as sixfold. Peak neuronal recruitment occurred in late summer and early fall and again in late winter, right before the onset of the breeding season (Kirn et al., 1994). These were times when the birds added, modified, and replaced many song syllables (Nottebohm et al., 1986). Intriguingly, the peaks in new neuron recruitment were preceded by peaks of cell death. The dying cells were identified as shriveled or fragmented dark staining nuclei (“pycnotic”) that looked very different from the round, pale nuclei normally seen in tissue stained with cresyl violet. Of course, we did not know whether the pycnotic nuclei were those of neurons; but we suspected they were part of a process of neuronal replacement in adult male canaries. Eventually, we obtained direct evidence about the survivorship curves of neurons added to the adult canary HVC at various times of year (Kirn et al., 1991, 1999; Kirn and Nottebohm, 1993; Nottebohm et al., 1994; Alvarez-Borda et al., 2004)

Neurophysiology Characterizes the Modus Operandi of HVC→RA Neurons

A majority of the new neurons added to the HVC of adult male canaries could be backfilled from RA. Years later, in a study that used zebra finches, Michale Fee from MIT showed that, as these birds sang, individual HVC→RA neurons fired during a 6-msec window with each neuron firing always at the same time during delivery of the song motif; different HVC→RA neurons fired at different times (Hahnloser et al., 2000). Fee has argued that the firing of these neurons, like a metronomic device, determines successive instants of song. Or, to put it differently, the learned pattern is encoded by the order of firing of the HVC→RA neurons and by the connections they form in RA, where David Vicario had shown that the muscles of the songbird vocal tract are represented. Such a modus operandi solves the age-old problem of “who” tells the brain what to do. In our canaries, the “conductor” function apparently shifts from one set of HVC→RA neurons to the next every 6 msec. As this happens, the instructions delivered to the “musicians”

in the RA “orchestra pit” are updated every 6 msec and in this manner, plus any feedback loops that may occur, the song plays itself. Interestingly, these HVC→RA neurons are the neurons replaced when canaries discard old songs and acquire new ones; the neurons acquired in the spring disappear much sooner than neurons born in late summer, most of which are still around eight months later when the new breeding season starts (Kirn et al., 1991; Kirn and Nottebohm, 1993; Nottebohm et al., 1994). That is what one would predict if the new neurons that learn the new song in late summer—early fall are the ones that sing it the following spring.

Use Them or Lose Them

People sometimes forget that when you count new neurons of a particular birth date you do not count the number produced, but the number that is still around. That is why I prefer neuronal “recruitment” to neuronal “production.” We seldom know how many new neurons were produced. Testosterone treatment of adult female canaries does not alter the number of new HVC neurons produced but markedly affects their survival (Rasika et al., 1994). Similarly, the number of new neurons counted in the HVC of adult male canaries killed 38 days after birth-marker (bromodeoxyuridine) treatment differs markedly depending on whether the birds were or were not allowed to sing from day 30 to day 38. Singing interdiction occurred by waving a hand every time a bird started to sing. The birds allowed to sing from day 31 to day 38 had 40 percent more bromodeoxyuridine-labeled neurons in HVC (Li et al. 2000). The same study showed that singing upregulated the expression of brain derived neurotrophic factor (BDNF) in HVC—the more the singing, the greater the level of expression—and that most of this upregulation occurred in HVC→RA neurons. Earlier work had shown that the testosterone-dependent survival of new HVC neurons in female canaries was mediated by a heightened expression of BDNF in HVC; direct infusion of BDNF at a site adjacent to the HVC of adult female canaries promoted the survival of new HVC neurons (Rasika et al., 1999). Thus, not only is there a temporal relation between new neuron addition and the learning of new song (Kirn et al., 1994) but the act of singing itself and the attendant hormonal changes promote the survival of these new neurons—the ones we count.

In addition, work done in zebra finches suggests that the act of imitating a song model also regulates new neuron recruitment. Zebra finch males exposed to adult song master their imitation of the model between post-hatching days 45 and 90; by 90 days, their song is stable. Their recruitment of new HVC neurons drops sharply after day 65. However, juveniles prevented from hearing or seeing an adult male have no model to imitate, and their song remains very variable. In these birds, a greater number of new HVC neurons continue to be recruited until 150 days of age. Apparently,

having imitated a song diminishes the recruitment of new HVC neurons in juveniles (Wilbrecht et al., 2006). Neuronal learning may peak at a particular neuronal age; learning programs may take this into account so that neurons of the right age are available.

Ephemeral Neurons

Studies with other songbirds confirmed what 20 years of work had revealed in the canary song system—that neuronal recruitment peaks at times of peak memory load. My favorite one was done with free-ranging chickadees, *Parus atricapillus*, a common forest bird in the northeastern United States, and conducted by a very hard working and talented Israeli scientist, Anat Barnea. Chickadees hide many food items in late summer and early fall, one item per hiding place, to be retrieved later during the cold winter months. Adult chickadees also recruit many new neurons into their hippocampus, and this recruitment also peaks in late summer to early fall. Most of the new neurons live for a period of six to ten weeks, and then gradually disappear. Intriguingly, this recruitment of new neurons is twice as high in rostral as in caudal hippocampus, suggesting different rates of memory turnover. It also is twice as high in free-ranging chickadees as it is in chickadees of the same age and population kept in a large outdoor aviary (Barnea and Nottebohm, 1994). To me, this was a reminder of the very different workloads placed on the brain of free and captive individuals. Those just studying the brains of laboratory-housed animals may be missing something.

Another study, using adult zebra finches, showed that the rate of neuronal recruitment in caudal nidopallium (NC), a part of the forebrain that processes auditory and visual information, doubles when males or females are placed in a novel and more complex social setting. In that case, it was the caudal reaches of NC that showed greater recruitment and turnover; in this case, too, the majority of the new cells were ephemeral (Lipkind et al., 2002; Barnea et al., 2006; Barkan et al., 2007; Adar et al., 2008). In all cases reviewed up to this point, peaks in neuronal recruitment coincided with peaks in information load—new song learning, food caching peaks, peaks in complexity/novelty of social stimulation, or peaks in expected learning needs (delayed song imitation in juveniles kept as isolates).

Why Replace Neurons?

An earlier heading referred to two dogmas. The first one stated that neurons were not born in the CNS of adult, warm-blooded vertebrates. Joseph Altman valiantly challenged that dogma, but his evidence was not compelling. The songbird studies challenged it too and proved beyond reasonable doubt that new neurons continued to be added, many of them to be replaced again and again, a new concept in brain function.

The second dogma states that learning is explainable by changes in the number and efficacy of synapses—synapses are the learning software. Plenty of evidence supports this idea. But if all learning takes place at synapses, and they retain full plasticity, why replace neurons in the adult, healthy brain? Neuronal production and replacement in the adult brain suggests there is a limitation in the synapse hypothesis. I estimate that in my songbirds, using the song system as the norm, some 5 percent of the brain's neuronal classes continue to be produced, and some have been shown to fall into the “replaceable” category. These neurons presumably occur at junctions in existing circuits where synaptic plasticity does not suffice to provide the full flexibility needed. The evidence available suggests that this phenomenon is much more common in birds than in the laboratory mammals studied so far. Why? My suspicion is that this has to do with two avian conditions: light weight and long life. Perhaps birds, despite their relatively large brains, must economize on brain costs. It might be energetically cheaper to replace brain cells, and the memories they hold, than to carry around all the memory space that will ever be needed and a lifelong store of experience. Still, why replace cells at all? My suggestion is that the very plasticity of synapses challenges the permanence of memories. For true memory stability, at least at the temperature and metabolic rate of birds, the secure solution may be to lock information in place by irreversible changes in gene expression. This “lock” would take the form of “freezing” all synapses in a neuron (input and output) at the settings when learning occurred. These changes may provide memory stability but at the price of blocking future learning—hence the neuron replacement solution and my suggestion that in some circuits the neuron, not the synapse, may be the unit of learning. I have not tested this idea. Undoubtedly, someone else will settle this point.

Doubt Everything

Some years after I finished my canary work, a splendid doctoral student from England, Clare Walton, joined my laboratory and made an observation in zebra finches that reminded me of the difference between facts and inferences and how careful one must be about generalizations. As mentioned earlier, zebra finches learn their song only once, before they reach sexual maturity at approximately 90 days of age. The song mastered by then is the one that male zebra finches sing for the rest of their life, which in captivity can extend for up to 10 years. However, there is a kind of song learning that continues after day 90 because, if young adult males are deafened soon after mastery of their song, it deteriorates over a period of two to three weeks as if the motor pattern were completely forgotten. Yet, if deafening occurs when the bird is older than two years, then deterioration is so slow as to take more than a year (Lombardino and Nottebohm, 2000). We do not know how this

“engrainment” of the learned pattern comes about, but Walton’s observations may be relevant.

Zebra finches are not seasonal, and the size of their HVC does not change after sexual maturity. I had assumed from this fact that their population of HVC neurons was stable. I was wrong. Clare Walton discovered that the population of HVC neurons in zebra finches doubles during the first year after sexual maturity, and this happens without gross changes in HVC volume or, for that matter, song. During that year, the HVC→RA neurons become smaller and more closely packed. Neuronal addition continues to occur in future years, though at a decreasing pace. At no time after sexual maturity did Clare find any evidence of culling of existing HVC→RA neurons, regardless of their date of birth. Thus, in these birds, adult neurogenesis leads to a net gain in neuron numbers. It is possible that the new neurons are connected like their older peers, strengthening the stereotypy of the learned song, which could explain why as time goes by song becomes more resistant to deafening. But the significance of this doubling in neuron numbers must remain speculative. Do female zebra finches place so much stock on male song stereotypy that this extra addition of neurons is worth the investment? Or could it be that the new neurons in the HVC of the intensely sociable adult zebra finches play no role in song production but instead serve to better perceive, recognize, and memorize the sounds of others? Perhaps the new neurons serve both purposes. We do not know; but Clare’s observations (Walton et al., 2012) are a reminder of the benefits of having a broad, comparative database before drawing general conclusions. To this day, we have no direct evidence of the role served by neurons born in the adult songbird brain.

The Story Ends

I have told my story. It started in the pampas with a love for birds, nature, and the big questions, then it focused on one—the biology of vocal learning. How had this wonderful trait come to be, and how did the brain manage it? It was a big question, and I have not answered it, but I have learned that simple questions sometimes behave like fireworks—they fragment, and the constellation of new questions is even more beautiful than the previous single one, each glowing in the nightly sky of our ignorance. It is the way of science.

Looking back, I wonder if my style of doing science was the best one. I tried to move fast, leapfrogging ahead. I hoped that others would follow and fill in the gaps. That did not always happen. Yet, it was a style I enjoyed. Discoveries seemed to be waiting around each corner.

In my early twenties, the airplane that flew me from the United States to Argentina and back would spend many hours high above the Matto Grosso and its meandering rivers—so much to see, so little known. I had

read as a child that somewhere in all that greenery, near the Rio das Mortes, Colonel Fawcett, the British explorer, had disappeared. It was the land of headhunters. Much of the Matto Grosso is gone now, but a wilderness is still out there, beyond where our mind can reach. How enormously thrilling! We need so much to have them both—the known and the unknown.

Acknowledgments

Those that read my story will realize I am a very lucky man. I had loving parents that encouraged me and supported me. I ran into a wonderful man, Peter Marler, and learned from him and his student and friend, Mark Konishi. I got a splendid job at Rockefeller University, where all my time was my own and was well supported. I was in the United States in the golden era of American science. During 32 years, I had a generous partner in the National Institutes of Mental Health. I received further and timely help from two private individuals, Howard Phipps and Herbert Singer. Through it all, I had the wonderful encouragement, stimulation, and hands-on help of my wife, Marta, and of her elegant, inquisitive and playful mind. Ever the triple-tasker, she also gave us two magnificent children, Lawrence and Olivia, and a lovely home. At Rockefeller, I enjoyed a fabulous group of young people that as doctoral students and post-doctoral fellows brought to my laboratory their talents, enthusiasm, and trust. But the greatest acknowledgment goes to the beautiful birds I studied. They charmed me as a child and gave me their secrets. I have been a very lucky man.

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