RETHINKING THE BRAIN

How the songs of canaries upset a fundamental principle of science

BY MICHAEL SPECTER

Fernando Nottebohm has lived transfixed by the melodies of songbirds. He is sixty now, and it has been decades since he left the plains of Argentina—first to study agriculture in Nebraska, then zoology at Berkeley, before coming to rest, in 1967, at Rockefeller University, in New York. But his interest in birds has sustained him since his earliest childhood. "Finding out how birds sing and why they would bother and what it means has been the puzzle of my life," he told me when we met for the first time, this winter. Nottebohm is a courtly man, and though he has spent the bulk of his career at Rockefeller, his restrained demeanor seems out of place at the giant biotechnology mill on York Avenue. After all, this is the era of genomes and molecular biology; mice crafted from engineered genes and bred to live in Plexiglas boxes have come to dominate medical research. To Nottebohm's colleagues, his preoccupation with the song systems of zebra finches and canaries and with how black-capped chickadees remember where they hide their food has always seemed quaint, even touching—if perhaps beside the point. Yet, over the past three decades, in dozens of elegant experiments that produced results nobody had envisioned (and for years very few believed), Nottebohm's obsession with how birds learn to sing set off a chain of discoveries that have fundamentally altered the way scientists think about the brain. It has also opened a tantalizing, if tentative, new route toward treating degenerative conditions that are often considered beyond hope—from Parkinson's disease and multiple sclerosis to spinal-cord injuries, strokes, and Alzheimer's disease.

The bird brain has an undeservedly bad reputation. It's not easy to fly or to learn meaningful music. To do both is an anatomical triumph. Nottebohm was certainly not the first man to be beguiled by birdsong. Beethoven, Bach, and Vivaldi all transformed avian music into instrumental works; Mozart turned a starling's song into the closing variations of one of his best-known piano compositions, the Concerto in G. Nottebohm believed that if he could understand how birds acquire their songs it would make a wonderful model of the way the brain learns. Many birds produce just one tune and sing it until they die. Nottebohm was more interested in those birds, like canaries, which can learn new melodies each year. Canaries live, on average, for ten years, cover a wide octave range, and sing for several reasons: to announce themselves, to claim territory, and to scare away other males when they look for a mate. (Females rarely sing.) As Charles Darwin noted, a songbird's early, rudimentary attempts at vocalization—called subsong—have a lot in common with the babbling of a human infant. By the time canaries are eight months old, though, they sing like adults, and their habits never vary: they sing throughout the breeding season, in the spring, and then, during the summer molting season, they shed the songs as if they were feathers. The next spring, the same birds will turn up with an entirely new repertoire. Who was teaching the birds these new songs, Nottebohm wondered. And what was happening in their brains to let them learn?

"It's not that I was uninterested in human health, but I really cared most about birdsong as a model for the brain," Nottebohm told me when we met at his Rockefeller laboratory. He doesn't come to the lab often; most days, he can be found in the rolling fields of the university's ethological-research center, in upstate New York, among thousands of carefully tended canaries and zebra finches. "As it happens, there are some obvious connections between birds and humans. It was just a practical example of the ways in which scientific discovery is totally unpredictable. And the complexity of the brain—well, I have never stopped being amazed by it.

"I have always been intrigued by religious questions," he went on. "To what extent were people special? What is this thing called the mind, and how is it different from the brain?" Whether the brain was simply the sum of its molecules—"You're nothing but a pack of neurons" was how the Nobel laureate Francis Crick put it—or whether all that biology added up to something more has been debated for centuries. "We have some close relatives," Nottebohm said. "Chimps, even monkeys. But they can't speak. No primate can speak. It's only humans who do it. When you look around the animal kingdom, birds are one animal that attempts vocally to do anything like what we do."

By the early seventies, Nottebohm had begun to publish a series of remarkable observations that traced the genesis of birdsong to specific clusters of neurons—the cells into which memories are wired and through which complex actions are processed. First, almost by accident, he demolished the notion that handedness—the idea that one is born either right-handed or left-handed—was the exclusive province of humanity. The syrinx, the songbird's voice box, turns out to have two sources of sound, which originate on different sides of the trachea. In an attempt to establish their role in singing, Nottebohm cut the nerves leading to one side or the other. The results astonished him. Cutting the left nerve mostly silenced the birds; cutting the right had practically no effect. "Some property of their brain induced canaries to be left-handed singers," he told me. "With other birds the right side is dominant." If birds demonstrated such a

PHOTOGRAPHS BY MARTIN SCHOELLER

Fernando Nottebohm's experiments with birds have opened a new route toward treating diseases like Parkinson's.

uniquely human quality, Nottebohm reasoned, maybe the patterns of avian behavior would be relevant in other ways, too.

Next, he tried to figure out why male canaries sing and females almost never do. To his surprise, Nottebohm noticed that certain parts of the brains in the songbirds were as much as four times larger in males than in females. He also found that if you give testosterone to a female canary its song nuclei will double in size, and it will sing more like a male. "That was a real shock, because we had all been taught that an adult brain was supposed to stay the same size, with the same cells, forever," Nottebohm said. "It was one of the few uncontested facts about the brain. So how could it get bigger? That contradicted everything I had ever learned."

To study the environmental effects, Nottebohm compared the brains of birds kept in cages with those of birds that lived in the wild. Again, the differences were striking: a free-ranging chickadee, which has to avoid predators and forage for its food, produced larger numbers of new neurons in the hippocampus—the part of the brain that plays an essential role in the storage of memories—than a caged chickadee. In cold weather, a chickadee becomes desperate for calories; it must eat before it sleeps or it will die. So remembering the many places where it stashes seeds is of urgent importance.

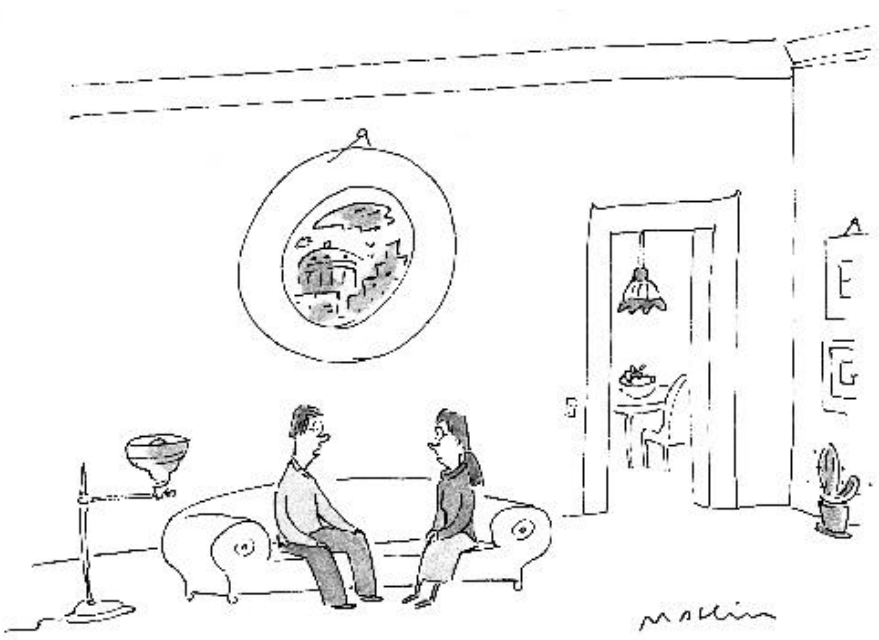
At first, Nottebohm had wondered if neurons grew in bulk to accommodate these challenges. In 1981, he wrote a paper, called "A Brain for All Seasons," in which he speculated that the cells swell and shrink at different times of year. But even as he wrote, he told me, he wasn't sure that he was right. "Damn it, I said, this is strange. It's not supposed to happen. We all know that brains in adult animals don't change. Cells die as you get older, and that's it. What was going on here?"

For many years, it had been held as one of neuroscience's basic principles that sophisticated animals—and certainly humans—are born with essentially every brain cell they will ever have. Throughout the twentieth century, attempts to suggest otherwise were dismissed, largely because neurons are not like other cells. After infancy, they don't divide and they don't grow. Although the process was not fully understood, brain researchers assumed that adding new memories and knowledge required us somehow to rewire the circuitry of cells that have been in place from the beginning of our lives. But one day in 1981, while Nottebohm was in the shower, he had the type of insight that happens in books far more often than in life. "I think I actually said the word 'eureka,' " he told me as we sat in the Rockefeller faculty cafeteria one snowy day last winter. "I dried myself off and went to my wife and said, 'Do you know what could explain all these changes we are seeing? What if every day new cells are born in the brain and others die? Wouldn't that explain why some birds learn new songs and forget old ones? The neurons filled with old memories could be exchanged for new ones.' I thought, Maybe the dogma of our lifetime was just completely wrong. My wife, Marta, was very excited and urged me to test this idea at once."

The more he thought about his idea, the more sense it made. If, in order to survive the winter, a black-capped chickadee had to remember hundreds of places where it had hidden food, or if a canary needed to keep the exact melody of a forty-note song in its brain in order to attract a mate, it might require more neurons than birds that didn't have such demands. "The idea that neurons in the adult brain come and go was considered the view of a lunatic," he said. "If you cut your arm, new cells will grow. If you cut your brain, it's going to stay cut. That's one reason strokes are so devastating and why brain injuries rarely heal. Neurons don't come back. But I decided to look again at that assumption. I have always been seen as one of those scientists with good intuition, but one who is maybe simple in his approach. Now people were saying my intuition had dried up. People in my own lab begged me to stop. I saw the pity in their eyes. They were saying, 'Fernando has lost it completely.' "

Nottebohm needed to prove that neurons were replaced in the adult brain. By the early sixties, technology had been developed to help. When a cell is about to divide, it starts making DNA. A radioactive hydrogen molecule attached to the thymidine needed for cell division could be injected into a brain cell and become a permanent part of the cell; if the cell divided, the resulting cells would all be marked as well. In that way, it would be possible to determine the time and place of any cell born after the injection. Nottebohm and one of his doctoral students, Steven Goldman, injected birds with the radioactive molecule every day for a week. Then they waited a month, killed the birds, and examined neurons from various parts of their brains. "What we found," Nottebohm told me, still shaking his head in surprise nearly twenty years later, "was a huge pool of labelled cells—and many of the cells were new neurons. Every bird, young or old, was producing thousands of them each day."

The discovery that new nerve cells are generated in an adult brain—the process is called neurogenesis—over-



"You want a child, I want a dog. Can't we compromise?"

turned a century of scientific theory. And it has the potential to do much more: if neurons are continually born in the brain of a human adult, as Nottebohm discovered they were with canaries, researchers might be able to influence how those neurons develop and to replace dying and failing cells with new ones. That would allow advances in the treatment of brain injuries and many types of degenerative disease. "That is the Holy Grail for us," said one of Nottebohm's former students, Arturo Alvarez-Buylla, who is now a professor of neurosurgery at the University of California, San Francisco. "What we are talking about is teaching the brain to repair itself with its own cells. It's not going to be a simple task. It's a type of magic, really, but eventually I think it's going to be possible. And for that we should thank Fernando and his birds."

"Do I detect a Middle Eastern accent?"

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Fernando Nottebohm holds a chair at one of the nation's most prestigious universities, and his research is considered beyond reproach. "Intellectually, Fernando is a free spirit, which is what I admire most about him," Eric Kandel, of Columbia University, said when I called to ask about Nottebohm's work. Last year, Kandel won the Nobel Prize for research into how synapses in the brain affect learning and memory. "He turned out to be absolutely right about neurogenesis, and it has led to one of the great paradigm shifts of modern biology."

Nevertheless, Nottebohm's discovery that adult birds give birth to a steady stream of new brain cells was hardly greeted with jubilation; Kandel himself was highly skeptical. In 1984, Nottebohm presented his most important findings to a conference in New York sponsored by the Institute for Child Development Research. He demonstrated not only how canaries produce new neurons but also how those neurons function at times when memory was particularly essential. He also mentioned, in an offhand way, that if new neurons could integrate themselves so successfully into the brains of adult canaries, perhaps that would be the case with humans. Many in the audience were hostile to the idea; others laughed. Skepticism is the prime currency of science, and challenging a basic belief about how the brain works brought much of that attitude to the surface. Researchers wanted to know how Nottebohm could be sure these new cells were neurons. The brain is composed mostly of glial cells—often seen as the glue that binds neurons together. But there are many types of neurons, and it is not always easy for a professional to distinguish between them and glia, even under a microscope or after using sophisticated labelling techniques. Nottebohm's colleagues also wanted to know how he could be certain that the cells were new, and how they had managed to migrate from one part of the brain to function in another.

There was another, largely unspoken, response to Nottebohm's research. "People basically said, 'Even if this is true, big deal. It's just birds. All they do is fly around,' " Charles G. Gross told me. Gross, a professor at Princeton for thirty years, knows about the skepticism of colleagues. He withstood a wall of disbelief in the late sixties after discovering the neurons that the brain uses to recognize faces. "First, people said Fernando must be wrong," Gross told me. "He suggested from the start this could have important implications for learning and memory in humans. But when they saw how convincing his work was . . . people smiled and said, 'Old Fernando found a cute thing about birds.' "

One important reason for the doubts about Nottebohm's work was that questions had been raised by Pasko Rakic, who is perhaps the foremost student of the primate brain in America. Rakic, who for many years has been the chairman of the neurobiology department at the Yale University School of Medicine, has spent much of his life looking at the brains of rhesus monkeys, which are closely related to humans; and although few believed that primates could generate new neurons, the proposition had never been tested when Nottebohm released his findings on canaries. It didn't take long for Rakic to recognize the significance of the studies, though. The implications for humans "of even a minute turnover" of neurons would be "enormous," he wrote in a widely read paper called "Limits of Neurogenesis in Primates," which he published in 1985. New brain cells would mean new ap-

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Elizabeth Gould, with two of her children. At Princeton, she pushed the field of neurogenesis further than anyone else had.

proaches to even the most terrible neurological problems and diseases.

Rakic's paper described his study of the brains of twelve rhesus monkeys ranging in age from six months to eleven years. He injected each of the monkeys with specially labelled thymidine and then killed them after intervals that varied from three days to more than six years. The labelled thymidine allowed Rakic to trace the development of neurons in the brain of every monkey he studied; by following the labels, he was able to examine more than a hundred thousand individual cells in each of them. The results were not ambiguous. "Not a single" cell with the physical characteristics of a neuron born after infancy "was observed in the brain of any adult animal," Rakic wrote. Although he acknowledged that no biological finding is ever final, he concluded that the dogma should stand: by the time a monkey—and, by inference, a human baby—is a few months old, it has all the neurons it is going to get.

Not long ago, I went to New Haven to visit Rakic. He is sixty-seven years old, a nearly bald, dapper man with a wry sense of humor. Rakic has been in America for years and his English is flawless, although he has retained the accent of his native Yugoslavia. Rakic showed me his slides; cells from monkey brains were stored in boxes scattered around his office. There were thousands, all neatly labelled. "You know, I am often considered as the bad guy in this discussion of neurogenesis," Rakic said. "People want the new cells because they think it offers new hope. And they think I am the guy who always says, 'Read my lips—no new neurons.' But that was never really my position. I did not object to Fernando's birds. I only objected when he said that what he saw in canaries could be applied to human beings."

Rakic says that it makes no biological or evolutionary sense for human adults to replace the building blocks that provide their memories. "We learn our memories and store them in synaptic circuits and in neurons," he said. "If you replaced them, you would not have those memories anymore. I speak with this accent because I use the neurons that were wired into my brain when I learned how to talk. Then, unfortunately, when I learned English as an adult, those neurons were still in control of my vocal cords. If I were somehow able to replace them, as canaries do, I would speak perfect English. But if I then went back to Europe I wouldn't recognize my own mother, because the new neurons in my brain would never have seen her."

Rakic argues that gradually, over millions of years, humans traded the ability to make new neurons for the ability to keep them. For an adult human to shed thousands of neurons and slip a few thousand new ones into the same space would be a bit like trying to rip out two floors of the Empire State Building and replace them brick by brick without affecting the rest of the building. "Even if you could do it, it would be a Faustian bargain," Rakic said. "Perhaps you would get rid of the neurons that gave you problems and get new ones that worked right. And the price for that could be that you—as a unique person with a unique group of memories—would no longer exist.

"You could take a canary from Northern California, put it in Southern California, and the next year it might even sing with a Southern California accent. That's a hell of a trick, particularly since after all these years I still speak with a Croatian accent. But, when Fernando stood up and said that even while we are talking you are making a bunch of new neurons in your brain, I simply said no, you don't. We have never seen that. It just doesn't make sense."

The issue disappeared after Rakic published his paper, in 1985. He is a persuasive man, and those who believed that adult neurogenesis mattered decided that it mattered only in lower animals, where the complexities of human memory did not exist. By chance, however, in 1989, in another laboratory at Rockefeller University, a young postdoctoral researcher in behavioral neuroscience named Elizabeth Gould, who was investigating the action of specific hormones in the brains of rats, stumbled onto something in her research that didn't add up. Gould had arrived at Rockefeller that year to work with Bruce McEwen, one of the world's leading experts on how stress affects the brain. "We noticed that if we took the adrenal glands out of a rat many cells in the hippocampus rapidly began to die," she told me not long ago. People with Addison's disease, which is caused by a severe deficiency of the hormones normally created in the adrenal glands, suffer similar cell destruction. "The effect is massive," Gould said. "You don't even need statistics to see it." Yet, when she counted the cells that remained, she could detect no decrease in the number of neurons. She was stunned. Gould asked herself, "Were our accounting methods completely screwed up? How could thousands of cells disappear and there still be the same number as there were before?"

Gould, who was then twenty-six, went to the Rockefeller library in search of some precedent for the bizarre effect she had noticed. (This was before the Internet provided the most efficient way for a scientist to review what had previously been published in her field.) "I have strong memories of sitting in this ancient room, looking through the Index Medicus, and going back a long, long time until I finally found evidence of adult neurogenesis," she said. She found what she was looking for in a series of reports published beginning in 1962—the year Gould was born—by a researcher at M.I.T. named Joseph Altman. At the time, the new technique of labelling a cell with thymidine to determine the birth date of neurons was used in newborns, since adult animals were not thought to create new neurons. But Altman decided to try the technique with adults. He published several papers in the most reputable scientific journals, claiming that new neurons are formed in the brains of adult rats, cats, and guinea pigs—a discovery that Nottebohm later made with canaries. Because the techniques Altman used were primitive, however, they were open to reasonable doubt. It was a classic example of a discovery made ahead of its time. At first, Altman was ignored, then he was ridiculed, and finally, after failing to receive tenure at M.I.T., he moved to Purdue. With no recognition, he was quickly forgotten. The field almost dried up. A decade later, Michael Kaplan, a researcher at Boston University and later at the University of New Mexico, used an electron microscope to supply more compelling evidence that several parts of the adult brain, including the cortex, also produced neurons. He, too, met resistance from researchers who did not find his work convincing. ("Those may look

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like neurons in New Mexico," Kaplan remembers Rakic saying at the time. "But they don't in New Haven.") Kaplan had published his findings in important journals and even suggested a novel way to test the phenomenon in humans, but he, too, was ignored, and he left the field.

Gould barely knew Nottebohm in 1989, although their labs were only a few hundred yards from each other. But she also came across his work in the library, and suddenly it all clicked. "I realized what had to be going on," she told me. "The brain was making new neurons to compensate for the ones that died. That is why the numbers didn't change. It was so simple, but it was one of these things you were trained not to think about." With McEwen's support, Gould shifted the focus of her research from hormones to neurogenesis. "For a long time, although nobody was interested in what we were doing and we couldn't get our papers into fancy journals, there was a sustaining excitement to it," she said. "I felt that if I don't study this no one else will. It was interesting and it was potentially very important. But I have to tell you I also enjoyed it because the field was so small."

For eight years, Gould carried out her work on neurogenesis in McEwen's lab. In 1997, she moved to Princeton. She was thirty-four, with many publications to her name; but neurogenesis had only sporadic scientific support and she was as far out on a limb as a researcher can go. In little more than three years, however, she had been given tenure and a full professorship—a previously unimaginable leap in her department at Princeton—having demonstrated with new and more convincing techniques that cells are born in the brains of adult rats. She pushed the field further than anyone else had. The year Gould arrived in Princeton, she reported that neurons were produced in the hippocampus of adult tree shrews (which are similar to early primates). In humans, the hippocampus is the principal area where Alzheimer's disease develops.

The next year, she published a paper demonstrating that a New World monkey, the marmoset, also makes neurons as an adult. (Primates that live in Africa and Asia—places that Europeans had explored before Columbus—are known as Old World monkeys; New World monkeys live in Central and South America.) Then she repeated the work using macaques, Old World primates that are more closely related to humans. Finally, in 1999, she and her colleagues discovered that not only are cells produced in the adult primate brain but they even appear in the neocortex—the most sophisticated region of the brain, which is responsible for language and complex thought. It was her most controversial work and it has yet to be repeated, but Gould reported that these new cells had migrated to the cortex from another part of the brain, had quickly developed into mature neurons, and had integrated themselves into the circuitry there.

Gould, whose background was in behavioral psychology, also undertook a series of experiments that suggested a strong relationship between the number of neurons an animal generates and the challenges it faces. Certain types of events seem to require the adult brain to make more neurons, and others appear to prevent that from happening. She found, for instance, that a brain needs to "use it or lose it"—if new cells are not put to work, they will die more rapidly than if they have a purpose. Also, through several studies in which she examined the effects of stress on the brain, Gould demonstrated the adverse effects that social subordination or fear can have: expose a rodent to the scent of a predator (in this case a fox) and it will become so anxious that its production of new neurons will quickly fall away. The studies, when combined with results from others, echoed Nottebohm's earlier research with birds and showed not only that new neurons were generated by adults but that active animals appeared to generate more of them.

There was one problem with Gould's work, though. The results seemed to contradict the theories of Pasko Rakic, and he has not been reticent about suggesting that Gould's methods were flawed. Disagreement and debate require scientists to repeat their studies; it's a fundamental precept that if you can't repeat something it cannot be taken seriously. Yet this was debate of a different order. Rakic, a former president of the Society for Neuroscience, is one of the seminal researchers in his field. In order to avoid a clash with someone so eminent, Gould would have had to permit herself to become marginalized, like Altman, or follow her predecessor Kaplan out of the business. She had no intention of doing that.

Gould, an animated woman with long dark hair, is the youngest tenured member of the Princeton psychology department, and among the most prominent. She is sought after by other universities, teaches what she wants, and this year was able to persuade Princeton to buy a four-hundred-thousand-dollar confocal microscope for the exclusive use of her lab. She is tenacious; her third

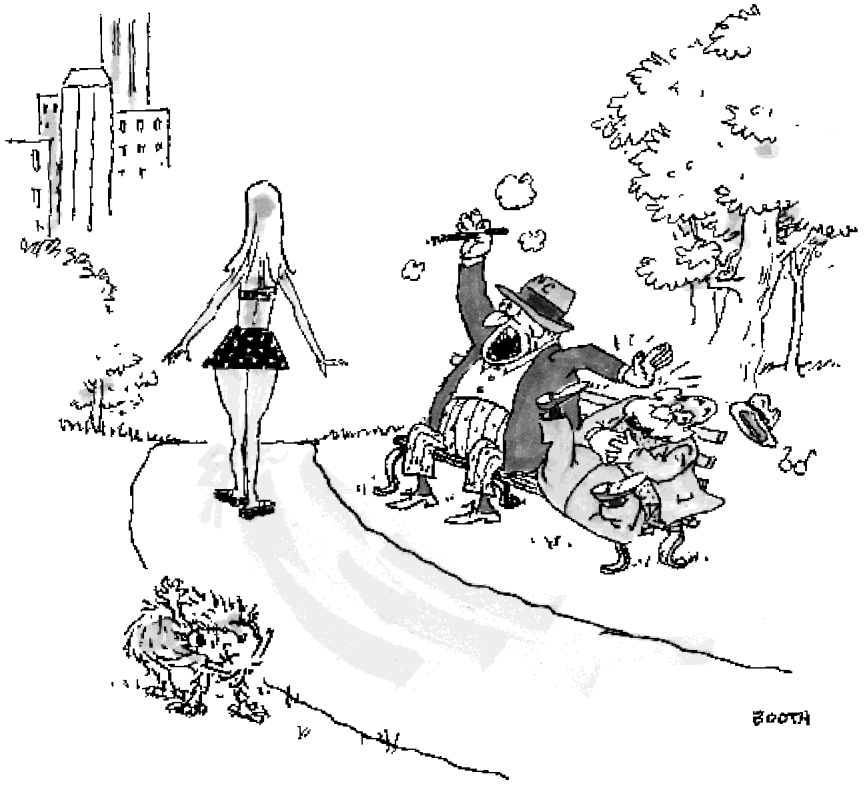
child was born last November, and four days later she was standing in Peyton Hall, lecturing to a roomful of students. Gould grew up on Long Island, went to college at St. John's and graduate school at U.C.L.A., and then married her high-school sweetheart. (He is a vascular radiologist at a Philadelphia hospital.) When I asked her how she came to select U.C.L.A. for graduate school, she replied, not completely in jest, "Good weather." Not until she received a Ph.D., in 1988, did she think seriously about an academic career. "I was not one of these people who knew when they were a little kid that they wanted to be a scientist," she told me. "I was not a person who had some quest or problem in my destiny to solve. Basically, I wanted to have a good time. I hung around the beach, and I thought psychology was reasonably interesting. It wasn't until I came back to New York and I was doing my postdoc at Rockefeller that I became so consumed by it."

In most ways, Gould is a typical bench scientist: driven, perfectionist, aggressively interested in teasing out the most inexplicable elements of a complex story. Yet her rise has not been without complications. Gould told me that when her first child, a girl, was born, just as her career was taking off, in 1991, she didn't see how she could continue to teach. "I had decided to put her in day care and go right back to work," she said. "Then she was born and I fell in love with her and I thought she couldn't possibly survive without me. I was at this weird point of moving from a postdoc to the junior faculty, and I had to write big grants to keep moving up, and for a while there I was just falling apart. My husband was really great. He said, 'You know, you worked so hard to get to this point, if you give up you are going to be miserable. You will feel like a failure.' If he had said something else—if he had said, 'Oh, it's terrible, I can see how you feel, why don't you just take a year off'—well, that would have been bad in the end. Bad for me, for my children, and for my work. I would have never been happy in my life if I had taken that turn. So I bit the bullet. It was hard, but I went back to work."

Gould's controversial successes do not always thrill her. "You can find yourself thinking about what you should do next to satisfy your critics, instead of what is the most interesting thing you could do as a scientist," she told me. "That is the route right to death. When you make decisions about your life based on what the scientific community is saying, you should quit. I think about that a lot these days. I mean, if you are doing your research for some other scientist, why even bother?"

Gould has a compelling air of distracted urgency. She manages to be both completely focussed and endearingly forgetful at the same time. ("I left my slide carrousel once in a cab in Boston, once at a conference in Greece, once in Maryland, and once in D.C. I got it back from the cab in Boston. But losing a carrousel with all your work in it four times is not a good record. I took it as a sign.") With the demands of a family, a full teaching schedule, and many experiments constantly in progress, Gould turns away speaking engagements by the dozen. She often finds conferences a useless distraction, and acknowledges that the politics of such events make her queasy—mostly because she is not one of the boys. It is an attitude that worries her mentor, Bruce McEwen. "There is a danger," he told me. "There is the green eye of jealousy, and Liz has to face that. If she were a pretender on her way up, she would be dead. But she is a full professor and already widely recognized in our field. So I think she can ride out the opposition. . . . But I have intended to have a talk with her, at least when her youngest kid is a little bit older. Because, frankly, I think she could be hurting herself. You don't have to love it or focus on it, but you have to play the game you are in. It just gets misinterpreted if you withdraw, and I don't want that to happen to her."

Gould told me that she isn't even certain that she wants to continue with neurogenesis, and although she would not say it directly, Pasko Rakic is clearly part of the reason. When I went to see Rakic at Yale, he spent a long time disputing some of her latest findings; he could find no evidence of neurons in the cortex, and he is convinced that Gould (together with her Princeton colleague Charles Gross) made a mistake in labelling the cells. (They, on the other hand, wonder whether Rakic is fully comfortable with the complicated new molecular-labelling techniques needed to do this research.) A week after we met, Rakic telephoned me. "I wanted to tell you about something, but I didn't know if it was appropriate," he said. He went on to say that after consulting with a Yale University ethicist he had decided he could



"Rouse yourself, Weintraub! The miniskirt is back!"

go ahead. "We examined the slides from that Gould study and photographed them and we did not find new neurons. I asked for permission to use the slides in a paper I am writing," Rakic told me. "And they refused." It was an extraordinary accusation, so I asked Gould about it. She said that Rakic had asked to visit her lab, but that she was about to deliver her third child, had preeclampsia, and thought she might have to be induced into labor at any moment. So she sent Rakic the slides,and, as is not uncommon in scientific disputes, he interpreted the data differently. (Gould and Gross intend to use the slides in an article they are writing and don't want Rakic to publish them first.)

That was only the latest skirmish between Gould and Rakic. In the fall of 1998, they came close to a very public showdown at a scientific forum in Los Angeles. Earlier that year, Gould had found neurogenesis in adult macaques; Rakic had not. Before a scheduled press conference, at the annual meeting of the Society for Neuroscience, Rakic suddenly announced that he, too, had discovered neurogenesis in Old World monkeys. Rakic told me that evidence was hard to find because the brain produced so few of the new cells. Gould disagrees, noting that she has found the phenomenon in rats, mice, tree shrews, marmosets, and two species of macaques and has never noticed a significant difference in the quantity of new cells.

At Princeton, Gould shook off several direct questions about Rakic. After I visited Yale, however, I asked again whether she thought his continued skepticism about her research was fair. In replying, she finally permitted herself to look back on this steady opposition to her work. "When I was studying adult neurogenesis in the hippocampus of the rat," she said, "the rat was unimportant [to Rakic]. When we found adult neurogenesis in the hippocampus of the marmoset, a New World monkey, the New World monkey was unimportant. Then, when we studied adult neurogenesis in the hippocampus of the macaque, an Old World monkey that Rakic has studied throughout his career, our methods were faulty. Then he used these same methods to demonstrate the identical finding. Now that we have found adult neurogenesis in the neocortex of the macaque, it is our methods again."

FIRST YEAR

It was our first home—
our damp, upstairs,
one-year aerie—
above a tree-lined area
nearer the city.

My talkative, unsure,
unsettled self
was everywhere;
but you
were the clear spirit of somewhere.

At night
when we settled down
in the big bed by the window,
over the street light,
and the first crackle of spring

eased the iron at
the base of the railings,
unpacking crocuses,
it was
the awkward corners of your snowy town

Fernando Nottebohm, who admires Rakic and considers him one of the most insightful people in neuroscience, was more direct. "Pasko has taken on the role of hard-nosed defender of standards," he said. "And that's fine—it's even warranted. But we have to keep in mind that he missed this discovery altogether. It's something he should have seen, and he just blew it. And, frankly, as much as I hate to say this, I think Pasko Rakic single-handedly held the field of neurogenesis back by at least a decade."

At first glance, San Diego seems a strange place to claim as the capital of American brain research. It is filled with seals sunning themselves on the beaches and tourists in search of aquatic adventures. People seem constantly to be hovering in the air, hang gliding from promontories above the Pacific Ocean. When I was there, during the Buick Invitational golf tournament, the conversation almost everywhere, as absurd as it now seems, centered on whether Tiger Woods would get his groove back. Yet, if you ride around La Jolla for long, you will almost certainly drive past the Scripps Research Institute or the Salk Institute for Biological Studies. Neither is far from Nobel Drive or, for that matter, from the Burnham Institute or the University of California, San Diego, which has one of the world's foremost centers of brain research. In fact, San Diego has far more than its demographic share of members of the National Academy of Sciences, not to mention Nobel laureates. Francis Crick, the eighty-five-year-old president emeritus of Salk, still shows up at his office. There are also dozens of private companies spread along the sun-drenched coast with names like Advanced Tissue Sciences and Neurome.

Scores of laboratories at universities and in private industry are now in on the search for the origins, mechanism, and meaning of neurogenesis. But if Elizabeth Gould has one genuine competitor—and a complete antithesis—it is Fred Gage, who is co-director of the Laboratory of Genetics at the Salk Institute. Where Gould guards her privacy and declines invitations to most meetings, Gage is one of America's most public scientists. Gage, who is fifty, holds one of three endowed chairs at Salk. He is the chairman of the scientific advisory council of the Christopher

which filled
the rooms we made
and stayed there all year with
the burnt-orange lampshade,
the wasps in the attic.

Where is the soul of a marriage?

Because I am writing this
not to recall our lives
but to imagine them,
I will say it is
in the first gifts of place:

the steep inclines
and country silences
of your boyhood,
the orange-faced narcissi
and the whole length of the Blackwater

strengthening our embrace.

—Eavan Boland

Reeve Paralysis Foundation, a member of the scientific steering committee of the Michael J. Fox Foundation for Parkinson's Research, and president-elect of the Society for Neuroscience, among many similar positions. He is on the editorial board of scientific publications ranging from the *Journal of Comparative Neurology* to *Research and Perspectives in Alzheimer's Disease*. Gage's curriculum vitae lists two hundred and ninety-seven scientific articles, and it isn't even up to date. In comparison with Gould's lab, where just five or six scientists work closely together, Gage's laboratory at Salk is a vast scientific field house, with revolving teams of researchers pursuing dozens of projects.

Gage is accomplished, but he is also well known for being well known. When I was in La Jolla one day and was introduced as a reporter to a Salk researcher, she said, "Oh, then you must be here to see Fred Gage." A rangy man with thinning sandy hair and a mustache on the verge of drooping, he has the manner of a mellow Californian. Gage grew up in Rome, and he is a descendant of Phineas Gage, who, in 1848, was a foreman on a railway-construction crew in Cavendish, Vermont. One day, an explosion shot a thirteen-pound tamping spike into his skull and out again, ending up twenty-five yards away after running through his brain. Gage didn't die or even become permanently incapacitated, but his personality changed completely (and not for the better). The accident turned him into the most famous brain patient in American history.

In the nineteen-eighties, Fred Gage lived for several years in Lund, Sweden, where he worked with the scientist Anders Björklund on some of the earliest fetal-cell-transplant approaches to treating Parkinson's. Fetal cells are flexible because they have not yet fully developed, and it was widely hoped that, once implanted in the brain, they would be able to "train themselves" to become the type of neurons that fail in Parkinson's patients. By the beginning of the eighties, experiments at Lund and at the Karolinska Institute, in Stockholm, had demonstrated that fetal-tissue grafts could replace cells that were destroyed by Parkinson's and other diseases, like juvenile diabetes, and that in many cases the grafts could restore the lost functions, at least temporarily. Yet there have always been doubts that placing the cells into such highly organized and established circuitry would work. One recent study has been particularly discouraging, suggesting that transplanted cells, while capable of surviving, and even adapting to their new surroundings, may actually be able to hijack the brain, becoming uncontrolled and malevolent.

Fetal-tissue research had obvious implications, though, and the work set Gage, and scores of other scientists, on a quest: How could you program cells in the brain so that they develop normally when other cells start to fail? Stem cells, which are created at the earliest stages of embryonic development, seem to provide an answer. (Stem-cell science often employs frozen embryos left over from in-vitro fertilization, and the field has become the most recent battlefield in the war over abortion. Within the next few weeks, the Bush Administration is expected to decide whether to allow scientists to continue using public funds for such research.) A week doesn't pass without encouraging reports of the potential for stem cells to treat any number of diseases. Stem cells can mature into almost every type of cell a human needs, and the most promising results have come with cells taken from the brain. If neuroscientists can make cells, particularly new neurons, grow in adult brains, they should, in theory, be able to find ways of getting them to emerge at the right time in the right places. That has already proved possible in animals. One Italian researcher, Angelo Vescovi, after extracting just a few stem cells from the brain of a healthy mouse, can now routinely grow the equivalent of several brains' worth of tissue in laboratory dishes.

Gage performed experiments that demonstrated that age affects the production of new neurons in rats, and he also showed that if a mouse has regular exercise—something as simple as running on a device that looks like a miniature Ferris wheel—the number of new neurons will increase. Rodents are not humans, though, and Rakic's theory that

adult neurogenesis is likely to play a diminished role in advanced animals was not encouraging. It was hard to know how to test humans, since researchers cannot sacrifice them or take slices from their brains to study under a microscope. In 1998, though, Gage and his colleagues at Salk, along with a team from Sahlgrenska University Hospital, in Sweden, managed to use an approach that had initially been suggested by Michael Kaplan in 1982. It was the last piece of the neurogenesis puzzle, and in many ways the most vital.

Gage's team knew that many cancer patients receive injections of a chemical marker, bromodeoxyuridine, or BrdU, which allows cancer specialists to assess how many new cells are being born. Since BrdU attaches itself to every new dividing cell, and not just to those with cancer, Gage's team realized that it could also reveal whether new neurons are being formed. Gage and his group studied five people between the ages of fifty-seven and seventy-two who had cancer of the throat or the larynx. After the patients died, the researchers looked for BrdU in several sections of their brains, and found that primitive neural stem cells had divided and created from five hundred to a thousand new cells each day. "All of the patients showed evidence of recent cell division," Gage said at the time. "It's interesting to note this was not a particularly young or healthy group of people, so new cell growth may usually be even more prominent than we observed."

Gage's study had just five patients, a number that could not support definitive conclusions. But the Gage paper, when added to the earlier primate work of Gould (and also to that of Rakic, who in 1998 reported seeing new neurons in rhesus monkeys), unleashed a flood of research, political maneuvering, and idle speculation. The implications were too promising to ignore. Neither Gage nor Gould is a clinician; their job is to figure out the fundamental principles of science. Still, each receives scores of messages a month from people who wonder whether there is a magical elixir that can reverse a stroke or save somebody they love from a deadly neurological condition. At least one medical group has promoted its ability to grow human stem cells in laboratory dishes and transplant them into the brain of a sick person.

"It's absolutely heartbreaking," Gage told me. "I get these E-mails asking whether people should spend fifty thousand dollars on this stuff. And it's just theft. We are a long way from that kind of treatment, and I can't give anybody any reason to hope for what may never happen. On the other hand, I am not frightened to admit that I believe this information is going to be useful to sick human beings. How soon, or for what specific conditions, I cannot say. But I really do believe that this will eventually work."

We had been sitting in Gage's study, above his lab at Salk. His phone there only dials out; it's the one place where he can escape the frenzied research he directs. Outside the window, across the hills, the sky above the Pacific was filled with the Mylar sails of hang gliders. "It's astounding, and as we learn more about basic biology we are going to be able to take these stem cells and reproduce the steps inside them and make them behave in a specific way," he told me. "It's very complicated, but you have to remember one thing: the embryo does it. It develops the whole system. So if we can learn how the embryo does it we can make something fairly similar to what is lost in certain illnesses. And when we do that we are in business."

One morning last winter, I drove up to Rockefeller University's Center for Field Research to see Fernando Nottebohm and his birds. The center—a cluster of austere farm buildings not far from Poughkeepsie—is an estate that was bequeathed to the university in 1971. For many years, Nottebohm shared it with two senior colleagues. These days, behavioral science is not in vogue, and nobody uses the place except him and his lab mates. A foot of snow had fallen the night before I arrived, and the place was silent. As I left my car, however, I heard a muted whirring in the distance; it sounded like an electrical appliance. By the time I reached the main house, the whirring had turned into the rising crescendo of birdsong.

This is where Nottebohm and Ofer

Tchernichovski, who is an assistant professor at Rockefeller, and their colleague Thierry Lints are trying to create the first detailed molecular map of how a bird's brain changes as it learns to sing. Nottebohm and his team are now studying how the brain changes physically—including an analysis of which genes are affected and in what way—every time a young bird opens its mouth.

The lab is filled with sensitive recording equipment, thousands of gigabytes of computing power, stacks of compact disks onto which tens of thousands of birdsongs have been recorded, and a few dozen Igloo beer coolers, which Tchernichovski has transformed into soundproof booths for baby birds. There are also a thousand bright-yellow canaries, and fourteen hundred zebra finches each no bigger than a child's fist. Many of the birds live in room-size cages filled with trees and a long cuttlebone, on which they can sharpen their beaks.

There is no other research facility in America like the field center. "People are not using birds in scientific research now," Nottebohm said, as we stomped through snowdrifts between his office and one of the main houses. "Behaviorists love rats. They can watch them run the mazes; it gives them lots of numbers. That's the American approach, because Americans believe, above all, in statistics. There is also this feeling that mice and rats are like little people.

"But I look at it in a different way," he continued. "What kinds of things do animals do in their natural circumstances, what kind of problems do they have, and how do they solve them? For a brain scientist like me, that is a much nicer approach, because brains are not all-purpose machines. They have evolved to deal with specific existential problems: How do you make it through a year with all kinds of different seasons? How do you claim and defend a territory? How do you find a mate? How do you look after your offspring? How do you remember where you hid your seeds?"

That, of course, is the leitmotiv of Nottebohm's career: you can understand how animals behave, and how their brains function, only if you watch them live normally. It has been Nottebohm's singular perception that behavioral analysis alone would never explain how birds learn to sing, and that just examining

the molecular basis of the cells won't do it, either. "Unless you understand the needs, the habits, the problems of an animal in nature, you will not understand it at all," he said. "Put rats and mice into little plastic boxes and you will never fully comprehend why they do what they do. Take nature away and all your insight is in a biological vacuum."

With help from Bell Laboratories, Tchernichovski, a transplanted Israeli with a first-rate ear and a deep knowledge of computers, designed a program that takes control of what a bird can learn and traces it by the second. First, he built a sophisticated sound system into a five-dollar plastic model of a bird, "the type you put on a Christmas tree," he told me. When the baby birds are thirty days old, the researchers place them in a cooler with the plastic father, which is perched in the center of what is essentially a tiny recording studio. The chicks respond immediately to its songs. They quickly get used to the plastic bird. Two big red keys are at the back of the cooler, and it doesn't take long for a young bird to realize that it can make the plastic model sing by pecking on the keys. The computer registers every move the bird makes, recording how many notes it sings, how often it pecks the keys, the exact composition of each song, and the vocal register the bird uses. The system then analyzes every note.

Tchernichovski whistled a bit of Gershwin. The computer immediately recorded his version of "Rhapsody in Blue," analyzed the vocal patterns, the notes, the syllables, and the timing. Suddenly, the plastic bird in the middle of the cage is singing Gershwin. "If we wanted to, we could then have the young bird learn that song," he told me with a big smile, since Gershwin is a bit too complex for a songbird to master. Birds learn to sing by the time they are two months old, but it has never been possible to understand the process very well. What is learned and what is programmed from birth? The computer system has finally permitted the team to try to provide an answer.

"Now, if we want to say a certain note was learned at a certain instant, we can take the bird and sacrifice it the second we see him learn that note," Nottebohm said. "Then we can look at what genes are expressed and what cells are there in the brain. We will literally be able to pull those cells out of the brain and say, 'How have you changed the way your genes work?' That is something we will need to know if we are ever going to program the brain to make up for its problems."

Nottebohm is delighted—up to a point—to see that Gage and Gould, as well as experts at the National Institutes of Health and in every major center of science, are now fully engaged in the field that for so long was his alone. He told me more than once—never sourly—that he was surprised by how little publicity Rockefeller sought for his research. Neurogenesis is hardly ever mentioned in the university's brochures, and that also surprises him. "I have always had a passion for clinical relevance," Nottebohm told me as we strolled from one room filled with canaries to the next. "I wanted to discover lovely basic things and I wanted to listen to the music of the birds. But there is so much suffering out there, and it would be so nice to have a solution. Yet I have to admit it's not quite as exciting for me as it was. For so long, this field was my backwater, my sandbox. And I enjoyed it. I saw Eric Kandel"—his friend who had just won the Nobel Prize—"not long ago, and he said, 'You must be so happy that all the things you said turned out to be true,' and of course I am. But, honestly, it used to be much more fun when nobody believed it. In science, by the time everybody tells you it's true you have to scratch your head and look for another business." ♦

"Why do I need to go to Europe when Europe is her

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