From: W.R. Everdell, The First Moderns (UCP: Chicago, 1997)

7 SANTIAGO RAMÓN Y CAJAL

THE ATOMS OF BRAIN

1889

But when classicism says "man," it means reason and feeling. And when Romanticism says "man," it means passion and the senses. And when modernism says "man" it means the nerves.

—Hermann Bahr, *The Overcoming of Naturalism: Sequel to "Critique of the Moderns"*

In October 1889, at the Congress of the German Anatomical Society at the University of Berlin, a short, powerfully built Spaniard with penetrating black eyes set up a small exhibit of drawings done on paper with colored inks. For the past two and a half years, alone in a spare room behind his house in Barcelona, he had been drawing them from nature through the eyepiece of a Zeiss, the most powerful optical microscope yet made. His subject was the brain of the embryo of a small bird, its cerebellum to be exact, and each thin slice of it had been cut, prepared and dyed using his own improved version of a painstaking two-step process recently discovered in Italy. Because Spain was not a place where new science was published at the turn of the century, he had had to edit and print his own journal in order to make his results known. Some of the German biologists at the Congress had made the effort to read those articles when they arrived in the mail in 1888, but the Spanish language had given them trouble. Cajal had tried giving his talk to the Congress in halting French (which was not much of an improvement), but it was the drawings and slides around which the professionals now crowded, amazed. Seeing made it plain. Each stained cell stood out perfectly against a background of staggering complexity, and no matter how many times the tiny fibers of one nerve cell met those of another, there was clearly no physical connection between them. The basic unit of the brain—the neuron—had been isolated.

The maker of these mind-changing pictures was not Picasso, who would not strut the streets of Barcelona for another seven years, or paint its Avinyo Street prostitutes until 1906. Eight years old in 1889, young Pablo Ruiz was already making accomplished drawings of birds, but they were of whole birds. No less diminutive, pugnacious, brilliant and ambitious than Picasso, this other Spanish artist, standing behind a laboratory

table in Berlin beside his pictures of birds' brains, was thirty years older. His art was the one we now call neuroscience, one which, a century later, has begun to look like the most promising of all the twentieth-century sciences. The artist's name was Santiago Ramón y Cajal.

Cajal could not be a neuroscientist in 1889, for the field had yet to be staked out. He had made his scientific debut as a medical researcher in the area called histology, or the study of tissue structure, a field first laid out by Bichat in the early years of the nineteenth century. The job of a histologist was to use that supreme biological tool of the nineteenth century, the optical microscope, to find and describe the cell structure of a heart muscle or a stomach lining. The hope was to discover how they worked and how they might go wrong, but the basic task was simply to classify—that is, to offer a taxonomy of the different tissues and the cells within those tissues. Of all sciences, taxonomy—Adam's task of distinguishing among things and naming them—is probably the least glamorous. Ernest Rutherford was later to say that all science was "either physics or stamp-collecting." Taxonomy was stamp-collecting. A good taxonomist had to be humble, as well as extraordinarily thorough and persistent, like Linnaeus, who founded biological taxonomy in the eighteenth century by naming and classifying some 4,000 species of animals and 6,000 species of plants.

This kind of tireless single-mindedness was very much in the character of Santiago Ramón y Cajal. He was the sort of person who would teach himself how to play championship chess, how to drop animals with a slingshot, or how to use a camera and make his own photographic plates. He was capable of spending months in a gym building up his body; of stealing books, eagles' nests, and even the bones in a graveyard for study. Tempted by the glamorous new subspecialty of bacteriology in 1885, and by medicine's sudden fascination with hypnotism in 1886, he always came back to general histology and its vision of life as a function of matter. Not many could have watched through a microscope for two hours straight, fascinated, as he was, by a white blood cell oozing its way through the wall of a capillary.

Tenacity showed up early in Cajal. When he was a boy of eleven, according to his own irresistible account, he built a cannon in his back yard. Once the gun was ready, he loaded it with stones and blew a good-sized hole in a neighbor's garden gate. The constable jailed Cajal for three days, much to the satisfaction of the boy's outraged father; but the sentence, which would surely have deterred almost any other child, made no impression on Cajal. As soon as he was released, he proceeded to build another cannon; and when that one blew up in his face and nearly blinded one eye, Cajal went on to steal the flintlock blunderbuss his father kept for show and shoot it off in secret with gunpowder he had made in a makeshift laboratory on the roof.[1]

Cajal described his motive in blowing things up as "a lively admiration for science and an insatiable curiosity regarding the forces of nature." Doubters may be reassured by the tale of how Cajal managed to hold on to his deepest vocation against the the kind of fundamental and long-term opposition that would have discouraged almost anyone else. That vocation, Cajal's first love, was not science, but painting. At "eight or nine years old I had an irresistible mania for scribbling on paper, drawing ornaments in books, daubing on walls, gates, doors, and recently painted façades." He could not do this at home "because my parents considered painting a sinful amusement."[2]

> My father . . . was almost completely lacking in artistic sense and he repudiated or despised all culture of a literary or of a purely ornamental or recreative nature. . . . This somewhat positivistic tendency I believe to have been not innate but acquired. . . .[3]

Deprived of paper and pencils by his family's poverty and his father's positivism, Cajal saved his centavos for them. Growing up in the classically rural town of Ayerbe in the shadow of the Pyrenees, he found color "by scraping the paint from walls or by soaking the bright red or dark blue bindings of the little books of cigarette paper, which at that time were painted with soluble colours."[4]

Such persistence finally wore down Cajal Senior, to the point where he was willing to take advice as to his son's vocation. He went straight to the town's leading painter-plasterer with Santiago in tow, showed him one of the boy's drawings and asked him whether it showed any talent. The contractor looked the picture up and down and pronounced it "a daub! . . . the child will never be an artist."

"'But does the boy really show no aptitude for art?' 'None, my friend,' replied the wall scraper. . . ." But it would be years before Cajal himself could be convinced of this expert's wisdom. His father's dream was for Cajal to become a doctor, but Cajal remained an artist no matter what he did with him. Why, Cajal demanded, "exchange the magic palette of the painter for the nasty and prosaic bag of surgical instruments! The enchanted brush, the creator of life . . . be given up for the cruel scalpel, which wards off death. . . ." And so Cajal engaged his parents in what he called "a silent war of duty against desire" that went on for years. At his first school, Cajal neglected his classical subjects and caricatured the master with such persistence and skill that school administrators concluded the only way to stop him was to lock him up. The lockup was "the classic dark chamber—a room almost underground, overrun with mice," but even there Cajal found a way to make art. There was a tiny hole in the wall facing the town, and on the wall opposite the hole there appeared, to the boy's delight and astonishment, a moving picture of what was going on in the town square. It was upside down, but it was quite clear enough to draw. Thus Cajal, prohibited from going to the square, found that science could arrange for the square to come to him. He had discovered the camera obscura, "a tremendous discovery in physics, which, in my utter ignorance, I supposed entirely new."[5]

The discovery gave Cajal "a most exalted idea of physics," but his teachers continued to find him hopeless. Eventually he was sent away to the town of Jaca to learn his Latin from friars. Under the friars, who beat students and threw them at blackboards, Cajal quickly "conceived a loathing for Latin grammar" and a recurrence of his "madness over art." He didn't blame the friars much, for he knew his mind "wandered continually." Cajal judged his own understanding to be about as mediocre as his diligence, and his "verbal memory" to be less reliable than his "memory for ideas." When he reached age twelve his father tried him in another school in a larger town called Huesca—so large that Cajal later seriously opined that it had altered and enriched the neural connectivity of his brain. Within hours of arriving he had spent lunch money on paper and a box of paints. Within a week he was "drawing on the walls with chalk," and not long after, he remembered, he was able to draw a map of Europe for homework freehand and from memory. Proudly he included the many scores of noncontiguous states in the old German Confederation. After that the basket cells in a cerebellum would be child's play.[6]

In later years, Cajal professed to be happy he had not become an artist. His early drawings, he concluded, had shown an anatomical ignorance and a caricatural understanding of his subjects—"a tendency which many modernist and futurist painters to-day cultivate systematically with rapturous applause from superficial critics." He considered himself to have been an indifferent colorist who never understood the basic insight of his contemporaries, the impressionists, "that nature seldom presents an absolutely pure colour," or that gray is less a color than it is a scale of brightness. Here again he found the necessary self-deprecatory language in the Modern art that had since arisen in spite of him. "Who does not detect at first glance, by the loudness of its colouring, the unfortunate product of the unskilled painter or the dissident modernist, who from snobbery pays homage to the 'loud' school, slipping back unwittingly to the infantile phase of art?" Cajal finally extracted a year of artistic training from his father by spending a year as apprentice to a cobbler, but that year was the finish of his ambition. Once his slow and reluctant abandonment of art was complete, he remembered its lessons as lessons of failure. It had, he wrote, "led me to sharpen my observation of nature and to distrust memory;" or, in short, to become an observational scientist.[7] Cajal often called himself modern but never Modernist, and he used the word "modern" as a synonym for realistic, scientific, and materialistic. He seems never to have become aware of the literary and artistic movement turn-of-the-century Spanish critics were calling *Modernismo,* which was a Spanish version of French *Décadence* and symbolism. He became, in the end, more of a positivist than his father, intent on erasing every trace of the transcendent and mysterious in the study of nature, of mind, and of brain. If the true vocation of the artist is simply to see, Cajal's great discovery was that of an artist; but it was as a medical researcher, an analyst, a phenomenologist of the discrete that Cajal was to become a Modernist.

Taxonomy actually requires more than tenacity. It is more epistemologically challenging than any other science, more so even than fundamental physics.[8] It makes more innocent assumptions, and rarely examines them from the perspective of phenomenology—the mind's take on the putative outer world. What, in fact, are you seeing when you classify a thing and give it a name? Why are the edges that mark one thing off from another found in one place and not in another? Why are some categories appropriate for bringing things together and not others? If categories dictate or are dictated by a hypothesis, then why that hypothesis and no other? The mere act of distinguishing one thing from another raises the phenomenological problem. Worse, it raises the problem of infinites. Linnaeus, for example, had subscribed to the basic assumption we have come to call the great chain of being, including the so-called "plenitude" principle that there was no vacant place or "missing link" in the chain. If the principle were true, then nature would have to be a continuum, and if nature were a continuum, then the differences between species would have to be infinitesimal and the number of species infinite. This objection never seems to have occurred to Linnaeus, who died expecting the number of species in the world to top out at around 15,000. It did not take the nineteenth century long to show that there were more than twelve times that number of beetle species alone, and of course that is nothing compared to infinity.[9] As we shall see, it was only in 1900 that the concept of finite numbers of simple parts was brought in to solve the problem of species.

One might have expected it sooner. Mendel had in fact proposed it in 1865. As for the hypothesis that reduced all living things to a concatenation of similar parts—the celebrated "cell theory"—it was even older, dating from an article by Schleiden and Schwann back in 1839. Cells themselves had been found much earlier than that. In 1837, for example, Jan Purkinje had found the prominent cerebellum cells now named for him. Within the nervous system proper, histology had placed several kinds of cells before 1888, and some of the classic nineteenth-century textbooks of general histology, like Albrecht von Kölliker's in 1853 and Ranvier's in the 1870s, actually began with an exemplary nerve cell as the best way to introduce a student to the cell concept. Nevertheless, most of the central nervous system looked to nineteenth-century scientists as if it were mostly a partless, continuous mass.

Of course, the nerves were the object of intense attention in the old century, especially in Germany. There the universe that Hegel and the Hegelians had filled with spirit was being rapidly reduced to mere matter. Karl Marx was out of school. For young scientists, the goal that emergent positivism and fashionable materialism seemed most of all to demand was scientific proof that consciousness was only a byproduct of electricity and chemistry in the nervous system. It was in 1842 that four students of the great biologist Johannes Müller—Carl Ludwig, Hermann Helmholtz, Emil DuBois-Reymond, and Ernst Brücke—had sworn their oath never to admit that any "other forces than the common physical chemical ones" were needed for life.[10] That same year Helmholtz had submitted as his doctoral thesis measurements of the speed of an electrical impulse along the nerves of a frog. DuBois-Reymond would go on to publish the standard work on electrical transmission in the nerves, called *Studies on Animal Electricity.* Brücke would bring the neural materialist faith to Vienna, where he eventually passed it on to his lab assistants, including an aspiring young neuroscientist named Sigmund Freud.

For a while the brain seemed to yield to this latest attempt to associate it with mind. It was in 1861 that French anthropologist Paul Broca discovered the area in the temporal lobe of the human brain that, when injured, seemed to prevent a patient from using grammar. Carl Wernicke found his own language "area," complementing Broca's, in 1874. For a while phrenology, the fashionable therapy of the 1840s that read mental function from the bumps on one's skull, looked like something more than junk science. In 1881 Freud's colleague Sigmund Exner wrote the standard text on the localization of functions in the brain, and in 1884 Exner's teacher, Theodor Meynert (who also taught Wernicke, Freud, and Auguste Forel), built his own general psychiatry text on his former student's localizations. Next to these philosophically adventurous experiments in physiology, collecting, observing, and describing nerve tissue—mere neurohistology—lost a lot of its glamor. It became an exercise for students and a subspecialty for cheerful toilers like Cajal.

The ancient discipline of psychology was powerfully affected by neural materialism. Professors of psychology, especially in Germany, began to worry that if the materialists were to achieve their goal of proving that the human psyche had no autonomy, no selfhood, then the psychology profession, the study of mind as a whole, might have to be abandoned. Both Wilhelm Wundt, a former Müller student who founded the first experimental psychology laboratory in Leipzig in 1879, and William James, the trained physiologist who founded the first U.S. Department of Psychology at Harvard in 1875, were driven by this anxiety.[11] Both found themselves in the 1880s writing their way toward philosophy and out of physiological psychology. By 1913, the American intellectual descendants of Wundt and James would find a paradigm for psychology that was both more materialistic and less, one that allowed the mind its wholeness by simply disallowing any questions as to how it worked. For vain efforts to understand mind and inconclusive investigations of brain function "behaviorism" substituted a bare input-output model, called the mind a "black box," and cut the whole subject of psychology loose from neuroscience for a century.

These sorts of attitudes meant that in the 1880s, as Cajal was beginning to publish his researches and before the microbe hunters had made their mark, neurohistologists were pretty solidly ensconced in a small corner of the learned world. Their territory was vast and various but no longer galvanizing for other scientists, since none of their new findings seemed to offer a major philosophical challenge. The decade's new terms—"cytoplasm," "nucleoplasm," and "mitosis" (complete with "prophase," "metaphase," and "anaphase")—and its new tool, the microtome tissue-slicer, invented by von Gudden, Mad King Ludwig's psychiatrist, presaged no new paradigm. The single great problem for the field was how to distinguish one structure from another in any nervous system larger than a snail's. Some worked with leeches, crayfish, and lampreys, dauntingly complicated but simpler than mammals or human beings. The central nervous system in *Homo sapiens,* which we now know contains something on the order of ten billion nerve cells with perhaps a trillion connections, appeared to histologists like Kölliker to be an inextricable tangle of fibers, interrupted only occasionally by cells with a recognizable structure. The fibers often thinned down beyond the resolving power of microscopes, and teasing them apart with dissecting tools seemed "an undertaking for a Benedictine."[12] Massed fibers seemed to form a good part of the cerebrum and spinal cord, which the professionals dubbed "gray matter;" and there was also a lot of "white matter," which some were beginning to understand took its color from the myelin sheathing around nerve fibers. Under the cerebrum there was even a patch of black matter, learnedly called, in Latin, *substantia nigra.* Differentiation of parts, or what the histologists called the "fine structure" of this great tangle, came with frustrating slowness. Between 1836 and 1838, a Müller student named Robert Rémak had suggested that most of these myriad fibers in the brain were processes attached to cells. In 1839 J. B. Rosenthal had described the *Achsencylinder* or axon, an extended fiber on some cells of the central nervous system, and in 1855 Rémak had proposed that each nerve cell had only one of them—though most of Rémak's students, including Kölliker, found the conclusion too bold. Otto Deiters, who died young after years of dissecting the neural tangle with threadlike needles and staring at it through his microscope, had left notes asserting that though axons were single and did not branch, other parts of the nerve cell did have tiny "protoplasmic processes" (we call them "dendrites") branching out from them.[13]

Optical microscopes had their limits, even with oil-immersion lenses; microdissection seemed beyond human skill; and dyes and stains were fuzzy, unpredictable, and unreliable. Locked away from the "fine structure" of the nervous system in the heroic age of chemistry, histologists fixed on the dyes and stains. They tested nearly every kind of chemical that came along in the nineteenth century, trying to find an elixir that would make nerves stand out against their impossibly undifferentiated background by coloring only one or two at a time. Their first historian, Gustav Mann, wrote in 1902 that "to be an histologist became practically synonymous with being a dyer," except that "the professional dyer knew what he was about, while the histologist with few exceptions did not know, nor does he to the present day."[14] The carmine dye pioneered by Joseph von Gerlach in the mid-1850s had one advantage: it was red. Aside from that it could not stain a single nerve with precision, and it could not stain all its processes, in particular the long axon, out to their ends. Indigo proved a little harder to work with and not much of an improvement. The new aniline dyes, tried out in 1859, were brilliant but they had much the same limitations, as did the methylene blue first applied by the soon-to-be famous bacteriologist Paul Ehrlich in the 1870s, or the "haematoxylin" he pioneered in 1886.

To the workers most involved, like Carl Weigert, who had invented several staining methods, it soon became clear that it was not just the dye that made a difference, but the preparation of the tissue both before and after the dye was applied. Tissue had to be "fixed" or it would alter or decay, but it shrank in some fixatives and lost features in others. Tissue's refractive index had to be chemically "cleared" or optical microscopes wouldn't work. Some procedures had to be done in the dark; some in acid-clean test tubes without metal touching the contents. Some dyes were oxidizing agents and had to be reduced in order to work; some were reducers that needed oxidizers; some worked better if they were allowed to deteriorate for a while. The relationships of reagents were so close and so hard to understand that the task of histologists became not to make a stain work, but to figure out how it had worked the first time—that is, to make it work more than once. Chromic acid, pioneered as a stain in 1843, eventually turned out to be more useful as a tissue bath, preparing cells to absorb more distinctive stains. In the 1860s Deiters and his teacher Max Schultze successfully used a salt of chromic acid, potassium bichromate, to give cells that had been fixed with the acid a purplish color, and tried the old carmine stain to make the result stand out further. Exner had found in the 1870s that "osmic acid" (osmium tetroxide in water) worked both as a preparation and as a stain, but that it only colored the sheathing of a fiber—the myelin—which meant that an axon's all-important terminations, which were unmyelinated, could not be seen. The extra time all these measures took is a good measure of the size of the dye obstacle. In the spirit of trying everything, someone was bound to try gold, and in 1872 Gerlach, the inventor of carmine, did so. He used the chloride, gold's only generally available salt, and found that it stained cells well enough to be worth its price. Gold quickly earned a place in the repertoire and inspired a long string of efforts to improve it. Freud's sixth published paper, in 1884, was a report on the improvements he had made in gold chloride staining.

In the end, however, it was not gold that did the trick, but silver—silver nitrate, in fact, which was one of the family of chemicals that had made photography possible at the beginning of the nineteenth century. The man who first used it correctly was a histologist named Camillo Golgi, from the Italian city of Pavia, who began publishing his observations "on the structure of the gray matter" in the *Italian Medical Gazette* in the summer of 1873.[15] He made it work by soaking the gray matter in potassium bichromate as before, but then he added a dilute solution of silver nitrate to the bath. The potassium bichromate already in the cells reduced the silver nitrate to metallic silver, which fell out as a precipitate. Silver stained the inside of the entire cell black, magnificently distinct against the yellow left by the chromates; but the real beauty of the new substance was that somehow it could stain cells in the middle of a three-dimensional cube of tissue, one cell at a time, all the way out to their ends, so that they stood out "like trees in a winter mist."[16] With it Golgi could make out a dendrite only 30 millionths of a meter long. Under proper conditions Golgi found he could even see the long axon of a nerve cell stained almost as far as the axon extended, and could at last distinguish between long- and short-axon nerve cells.

The idea was not altogether new, silver nitrate having been used by one histologist along with ammonia to stain nervous tissue,[17] and by another preceded by acetic acid to stain motor nerves, but the stain was very temperamental. So much depended on what you did to prepare the tissue before adding the silver that Golgi never stopped working on it. His papers began appearing in French and English journals in the 1880s, and his most comprehensive work, published in 1886, would eventually win him a Nobel Prize. By then the new staining method was being tried in histology labs all over Europe.

Spain, however, seemed not to be in Europe at all. In the nineteenth century Spanish medical researchers never considered the brain without leaving room for the soul, and it often took whole decades to naturalize a new technique. As an assistant in the Zaragoza Medical Faculty in 1880, Cajal had had to learn the art of lithographic engraving in order to get his papers illustrated accurately. He had been advanced enough to use gold chloride staining in his first published paper, and to suggest ammoniacal silver nitrate in his second, but no one else in Zaragoza had ever

tried silver. At the University of Valencia where Cajal had secured his first professorship in histology in 1883, researchers were still innocent of Golgi and his stain. When Cajal had interrupted his own researches to return to Zaragoza and pitch in as a bacteriologist on the cholera epidemic in 1885, he was still using the older stains himself. Cajal didn't get his first chance to see the silver-bichromate technique in use until 1887, when he paid a visit to Madrid as a judge for the national exam in descriptive anatomy and visited Luís Simarro, who had just come back from France. Simarro showed Cajal some examples of Golgi staining he had in his house, and later took him down to his lab in the unofficial biological institute in Gorguera Street to show him more. Cajal remembered being so impressed that he gave up all other methods, and began not only to apply the new staining technique but to tinker and improve on it. Soon he had added an extra step to the preparation sequence by making two separate soaks out of what had been a continuous procedure. His great discoveries were less than a year away.

Cajal had found his method just in time. The extraordinary hypothesis that the entire mass of the central nervous system was composed of the extensions of separate and distinct cells had already been advanced. In October 1886, Wilhelm His of Leipzig had asserted that there was no continuity between nerves, just as (recent research had shown) there was no continuity between nerves and the muscle cells they controlled. In January 1887 Auguste Forel, the Director of the Burghölzli Asylum in Zurich who would in the same year begin his work on hypnotherapy, published a paper on brain anatomy pointing out that "no one has yet seen" any such continuous connections between "outgrowths of the ganglion cells, the fibres [axons], or the protoplasmic processes [dendrites]" of one cell and those of another. Four months later in Oslo, Norway, Fridtjof Nansen, about to set off on the first expedition to cross Greenland, put a finishing touch on his neuroanatomy Ph.D. thesis and made the same observation. "A direct combination between the ganglion cells, by direct anastomosis of the protoplasmic processes does not exist."[18] Cajal had only just gotten his first look at the Golgi-stain lithographs in Luís Simarro's biology lab in Madrid and already there had been three separate attacks on the old theory of brain histology. Of course now, a century after the fact, it seems like an edifice was crumbling, but in 1887 the old hypothesis that all the nerve fibers of the gray matter were mutually connected in a single network was in no real trouble. This so-called reticular hypothesis (*reticulum* is the Latin word for network) was in fact vigorously promoted by Joseph von Gerlach, the man who had brought carmine and gold chloride to histology, and Theodor Meynert, the formidable Viennese. Its great champion was in fact none other than the discoverer of silver-chromate, Camillo Golgi himself. "Ruled by the theory," Cajal remembered, "we who were active in histology then saw networks everywhere." It was a beautiful theory and, he wrote, "As always, reason is silent before beauty."[19]

The way was therefore open to Cajal. He was the only one working on the problem who had both the technique and a mind that was ready to change. In November 1887, when he took up his new professorship in Barcelona, the first thing he did after moving his growing family into their new house in Riera Alta street was to set up his laboratory and start staining brain tissue. First came a two- to four-day soaking in 1 percent osmic acid and 3 percent potassium bichromate solution to harden the tissue and pervade it with chromate; then the 20 percent silver nitrate solution and thirty more hours of soaking to precipitate the silver. Next he would put the specimen in pure alcohol to harden it, mount and slice it with a microtome, then soak the slices in six to eight changes of pure alcohol to get rid of all the water. Finally he would clear their refractive index with oil of clove or bergamot, wash out the oil of clove with a solvent, varnish with a resin, and mount the specimen.[20]

Early the next year, after moving to a larger house in Bruch Street, Cajal began to work on the nervous system in earnest. 1888 was to be "my greatest year, my year of fortune."[21] Sensing the commitment it would require, he gave up chess, in which he had made himself an expert, for the next twenty-five years. In the back room he used as a laboratory Cajal had made one more change in the methods used by Golgi and the earlier researchers, one that had been missed by all his contemporaries, including His, Forel, and Nansen. He had decided to use embryos. "Since the full-grown forest turns out to be impenetrable and indefinable, why not revert to the young wood, in the nursery stage . . . ?"[22] was how he explained coming up with the rather off-putting idea of using unfledged, unhatched chicks to study the central nervous system. Its brilliance lay in the fact that the nervous system in almost all vertebrates is incomplete at birth. Though the nerves have grown dendrites and axons, not all of these are fully extended. Moreover, the "glial" cells have hardly begun their task of covering the nerve extensions with the ubiquitous white insulation called myelin.

Best of all, the silver-chromate stain works better in embryos. When Cajal looked at the first chick cerebellum, what he saw was a lot of extraordinarily long axons, completely uncovered and stained brownish-black to their very tips, exposed to his objectifying gaze. It was obvious to him that every fiber belonged to a particular cell. They did not go through the wall of any other cell; they came up close enough to touch it, but they never actually did. He could see where they ended. Obvious as always were the Purkinje cells with their many thick branches and prominent cell bodies, but now it became clear that the fuzzy structures enclosing those bodies were the branching ends of the axons of entirely different nerve cells whose own cell bodies were tiny. They enclosed the Purkinje cell like a basket around a melon, but they never penetrated it. Cajal stared through the microscope and drew exactly what he saw. Then he drew his conclusion: the famous central network, "that sort of unfathomable physiological sea, into which, on the one hand, were supposed to pour the streams arising from the sense organs, and from which, on the other hand, the motor or centrifugal conductors were supposed to spring like rivers originating in mountain lakes" did not exist at all. "By dint of pretending to explain everything [it] explain[ed] absolutely nothing." The truth was that the entire central nervous system was like a telephone exchange in which each nerve cell communicated only with such other nerve cells as were touched by the ends of its axon. The alternative was "protoplasmic pantheism . . . pleasing to those who disdain observation. . . ."[23]

Today Nansen is remembered as an Arctic explorer and statesman; Forel as Jung's predecessor at Burghölzli, Kokoschka's portrait subject, and one of Freud's sources on hypnotism. As for His, he is best remembered as the doctor who stood by when they exhumed the body of Johann Sebastian Bach, and made careful measurements of the great man's skull. The reason is that they had only guessed at Cajal's conclusion. They had not proved it. Proof required that patient, endless work with chemicals, needles, microtomes, microscopes, and lithographic plates, the sort of work Freud had learned how to do long before he became a doctor, when Brücke had set him to study the nervous system of the lamprey in 1876. In 1882 Freud gave a lecture on "The Structure of the Elements of the Nervous System" based on what he had learned from the lamprey and later the eel and the crayfish. At the point in this lecture, published in 1884, where he had taken up the implications of the network theory, three of Freud's biographers pronounced that he had proposed the neuron and anticipated Cajal.[24] They were wrong. Freud had not seen through the network and, as we shall see, had a very different professional destiny.[25] Soon he would abandon the psychological microcosm for what he hoped was the Big Picture. In 1889, two months before Cajal traveled to Berlin to convince the Congress of Anatomists of his new idea, Freud went to Paris to learn from the Experimental and Therapeutic Hypnotists, whose Congress coincided with the World's Fair. (The Congress of Physiological Psychology also met in Paris during the Fair, and there, just to compound the irony, was William James.) Thus Cajal brought his new idea, together with the indispensable hard-won proof, to a rather small gathering of men who practiced a well-established but not very fashionable discipline. Perhaps because of that, they treated him extremely well. The Belgian van Gehuchten, who had been Cajal's faithful correspondent, withdrew his opposition to the new hypothesis on the spot, as did, soon after, the Basel professor, Lenhossék. The Swede, Retzius, was skeptical but kind. Even Wilhelm His marveled and applauded, and the formidable Berlin expert, H. Wilhelm G. von Waldeyer-Hartz, was unexpectedly welcoming. As for the patriarch of the Society, Albrecht von Kölliker, he swept Cajal into his carriage, took him to his hotel, and gave him a dinner. Promising to have everything Cajal wrote published in Germany, Kölliker said, "I have discovered you and I wish to make my discovery known in Germany."[26]

In November, Cajal returned to Spain and got back to work; but the rest of the histological world continued to reverberate. Between October and December 1891, the great Waldeyer published a series of six long articles in the *German Medical Weekly* on the whole state of the question of the fine structure in neuroanatomy. There he attributed the new gray-matter-discontinuity hypothesis to Cajal and gave it the name "neurone doctrine." These articles gave rather more credit to Waldeyer than Cajal thought he deserved, but there is no doubt they secured Cajal's scientific reputation for the rest of his life.[27] News of his discovery passed beyond the small world of histology and became an example of "science," ever progressing in the nineteenth-century manner. Soon people who knew no science to speak of would have some inkling of what Cajal had found. Never again would he be anonymous and unsupported, though he never stopped behaving as if he were. In 1894 the British Royal Society offered him its most prestigious award in biology, the Croonian Lectureship.[28] England's leading neuroanatomist, Charles Sherrington, invited Cajal to stay with him in his home in London when he gave the lecture. There Sherrington was amazed to discover that Cajal would clean his own bedroom, hang out his sheets, and lock his bedroom door in order to prevent the traveling laboratory he had set up there from being disturbed.[29]

In the 1890s Cajal advanced and provided evidence for four additional hypotheses about the nervous system. The first of these, which has acquired the name of the "Law of Dynamic Polarization," asserts that the axons of nerve cells are always outputs for nerve impulses and that dendrites are always inputs. Signals did not, therefore, spin around in an endless circuit, but instead went only one way until they stopped and were received.[30] The second of Cajal's later hypotheses is the idea that neurons grow from the ends of the axons at a point analogous to the root hair of a plant. Cajal found this in chick embryos in 1890 and called it the "cone of growth."[31] The third of these ideas Cajal advanced in 1892 and eventually called the "Chemotactic Hypothesis." Wondering why the growth cones of axons followed one trajectory instead of another and how growing axons could go such long distances to make the "right" connections, Cajal suggested they found their way by following trails of chemicals already laid down among the other nerves.[32] These three hypotheses are now conventional wisdom so taken for granted that Cajal's name has become completely detached from them, and they are taught as if anatomists had always known them. Fair enough, since Cajal never found a proof for them and indeed there was never anything in his experimental repertory that could have provided one. The fate of the fourth hypothesis, as we shall see, is not yet known.

In 1899, when Clark College in Worcester, Massachusetts celebrated its tenth anniversary, its president, William James's first Ph.D. student, G. Stanley Hall, invited the stars of European science to give lectures to celebrate. Ludwig Boltzmann arrived to discuss the paradoxes of physical and mathematical continuity. The mathematician M. E. Picard talked of Peano's foundations of arithmetic. The three other speakers were all brain scientists: Ramón y Cajal, Forel, and Angelo Mosso, who had all sailed over together on a French Line ship from Le Havre. Cajal spoke first, trying to sum up in three lectures what was then known about the structure of the cerebrum. Using large colored placards, he described all the new neurons and neural fibers he had isolated, the consequences of their separate existence, the direction of impulses in the fibers, and the curiously precise way in which the fibers extended themselves into the numbingly complex space made up of the cells and fibers that were already there. Forel followed with a flamboyant talk on the possibilities of brain science in which he claimed that he and Wilhelm His had been first with the neuron doctrine. Of this claim Cajal says nothing in his autobiography beyond profuse references to Forel's intelligence and charm.

What struck Cajal more than Forel's belated claim was the astonishing attitudes the Americans demonstrated on the subject of his homeland. When the invitation came in the mail, Cajal had asked his government whether he ought to accept it. It was, after all, only a few months after San Juan Hill and the devastating defeat of Spain by the United States in the Spanish-American War—a war the United States claimed had been fought to free Cuba from Spanish cruelty. Cajal knew exactly what Spain had done in Cuba, because he had seen it for himself. In 1874, doing his military service in the Spanish army's medical corps during an earlier colonial war, he had watched as the Spanish Governor-General tried to cut Cuba into three pieces with two barbed-wire fences running north and south, the better to control the insurgent population. In Cajal's view, the scheme, which inspired a later Governor-General named Valeriano Weyler to develop the concentration camp, had been not only cruel but impractical. As skeptical of Spanish intentions as he had been of Spanish strategy, Cajal hadn't liked having his patriotism called on to endorse the incompetence, peculation, and stupidity of Spanish imperialism in Cuba. Indeed, soon after this trip, in order to reconcile his deep and continuing loyalty to Spain with honest criticism, Cajal would begin writing his memoirs. But the Americans he met during his east coast tour struck him as obtusely simple and bewilderingly oblivious of the effect they had had on so many of the world's peoples. In the unexpected heat of a New York City hotel in July as he waited to go on to Worcester, Cajal found triumphant modernity in the sixteen-year-old Brooklyn Bridge, but a touch of irony in the newer Statue of Liberty. To insistent questions from the American press about how he would improve the United States, Cajal tactfully offered little beyond uniform praise of democracy, except a Victorian putdown of feminism and a suggestion to build laboratories for bacteriology and histology. He reserved for a footnote in his memoirs the point he had wanted to make about American imperialism. "One cruelty never justifies another [and] those who argue thus seem to forget that only powerful nations can commit certain excesses with impunity."[33] He arrived in Worcester with a raging headache on the eve of the Fourth of July, and was treated next day to twenty-four hours of songs, cheers, rocket explosions, and citizens firing rifles into the air.

As Cajal dealt with his increasing fame, the "neuron doctrine" was becoming orthodoxy with histologists, neuroanatomists and psychologists, and Cajal's extraordinary pictures began to enter the ken of nonscientists. In 1900 northern Europe's greatest early Modern artist, the Norwegian Edvard Munch, painted a picture of his sister Laura, wrapped in a shawl and seated forlornly in a chair. She was chronically insane and Munch would paint her many times; but in the foreground of this painting, now called *Melancholy (Laura),*[34] there is a table with a strange design in dark blue, red, white, and gray. As the viewer comes in for a closer look she realizes that the strange design has come out of the sketch book of Santiago Ramón y Cajal. It is a sagittal section of cerebral nerve tissue viewed in tight perspective and painted in the colors of histological stain.

In 1906, the sixth Nobel Peace Prize was awarded to Rough Rider Theodore Roosevelt, a decision which, as Cajal wrote drily, "produced great surprise, especially in Spain."[35] Cajal was himself in Stockholm to see Roosevelt accept the prize, because the Swedish Academy had awarded Cajal the 1906 Nobel for medicine. Half of it, anyway. The other half had gone to Camillo Golgi, "very justly adjudicated to . . . the originator of the method with which I accomplished my most striking discoveries,"[36] wrote the ever tactful Cajal. They met for the first time when they were introduced at the ceremony. The next day Golgi gave his Nobel acceptance lecture, and the day after that Cajal gave his, both in French. Cajal's lecture, "The Structures and Connections of Nerve Cells," was a sustained defense of the independence of the neuron. Golgi's, "The Neuron Doctrine, Theory and Fact," was a sustained attack on the same idea.[37] To the end of his life, Golgi, the inventor of the reduced silver nitrate stain, would maintain his faith in undifferentiated neural networks. Cajal, who had made the stain his instrument for discovering the neuron, was unable to convince Golgi of the truth of his discovery even as they shared a Nobel Prize for it.

It was in the year 1906 that Cajal's disciple Sherrington coined the word "synapse" to describe the junction between one nerve cell and another.[38] Cajal was increasingly lionized as evidence continued to mount for his central doctrine of neural atomism, and for the Dynamic Polarization, Growth Cone, and Chemotactic hypotheses. Cajal's fourth hypothesis, however, never proved out in his lifetime and remains in dispute at this moment. This is the view that the phenomenon we call memory is a product of particular states of the entire brain or neural network. Memory, thought Cajal, was not the effect of some chemical or of changes in one or a few nerve cells; it was, he thought, a global property of the entire brain. Such a view is very much in the center of debate in the last decade of the twentieth century—the Decade of the Brain—and, if it turns out to be true, could make Cajal the most important progenitor of twentieth-century neuroscience, and turn Freud (who was the star attraction at Clark University's twentieth anniversary ten years after Cajal) into an artifact.[39] The brain may not govern, as the nineteenth century thought. It may simply "emerge," an undetermined consequence of the simple interactions of more than ten billion cells making a trillion connections. The mind may not govern either, as Freud would insist ten years after Cajal had found the neuron. It may emerge instead, conscious and unconscious, in the same way, a way that never occurred to the nineteenth-century mind of Sigmund Freud, but did occur to the nineteenth-century mind of Santiago Ramón y Cajal once he had made a twentieth-century hypothesis about the atoms of brain.

40. Whitman, "Europe, the 72d and 73d Years of These States" (1850), "France: The 18th Year of these States," and "O Star of France," in *Poetry and Prose,* 406, 377, 519.
41. "I have never had the common Puritan ideas about France," said Whitman to Traubel in 1888. Horace Traubel, *With Walt Whitman in Camden* (Boston, 1906), 1:461.
42. "Mme Blanc" [Thérèse Bentzon], "Les poètes américains," *Revue des deux mondes,* 1 June 1872.
43. Emile Blémont, "La Poésie en Angleterre et aux Etats-Unis," parts 1–3, *Renaissance artistique et littéraire* 7 (8 June 1872); 11 (1872); 12 (1872).
44. Rimbaud to Ernest Delahaye, June 1872, in *Oeuvres complètes,* 266.
45. Rimbaud, "Promontoire," in *Oeuvres complètes,* 149.
46. Whitman, *Poetry and Prose,* 203; Rimbaud, *Illuminations,* in *Oeuvres complètes,* 75.
47. Rimbaud to Paul Demeny, 17 April 1871, in *Oeuvres complètes,* 246–47; Whitman, *Poetry and Prose,* 49, 203, 210.
48. The free verse achieved by the Cuban poet José Martí in *Versos libres,* written in 1878–1882, was especially early; but it was not published until after Martí's death in 1895.
49. Laforgue, "Une femme m'attend," *La Vogue* 2, no. 3 (2 August 1886).
50. Whitman, *Poetry and Prose,* 258–59.
51. Laforgue, "L'Hiver qui vient," *La Vogue* 2, no. 5 (16 August 1886); reprinted in *Poésies complètes II* (Paris: Gallimard Poésie, 1979), 181–84; trans. William Jay Smith in *Selected Writings of Jules Laforgue* (New York: Grove Press, 1956), 90–91.
52. Arkell, *Looking for Laforgue,* 196–97.
53. *Walt Whitman Review,* 1957; Stuart Merrill, "Walt Whitman (à Léon Bazalgette)," *Le Masque* (Brussels), 2d ser., nos. 9 and 10 (1912); trans. in Henry S. Saunders, *An Introduction to Walt Whitman: with Two Scarce Whitman Portraits* (Toronto: Henry S. Saunders, 1934). Since it is very hard to find, I offer Merrill's anecdote in its original French:

> *Nous* [Stuart Merrill, Sturges, and MacIlvaine] *allions en un mot entendre le verbe qui plie à son rythme l'histoire de l'avenir, le Chant lyrique de la sainte démocratie. . . . Je venais de recevoir de Paris quelques numéros de La Vogue dont l'un contenant une traduction des Enfans d'Adam par Jules Laforgue. . . .*
> *—Ah! comme je suis heureux qu'on me traduise en français! s'écria-t-il.*
> *—Et quels poèmes de moi a-t-il traduits? demanda-t-il*
> *—Les Enfans d'Adam, répondis-je.*
> *—J'étais certain qu'un Français tomberait sur ce passage.*

Merrill, *Prose et vers* (Paris: A. Messin, 1925), 234–38.
54. Ezra Pound, "A Pact" ("Contemporanea"), *Poetry* (April 1913).
55. T. S. Eliot to Sholom Kahn, *Walt Whitman Review* 5, no. 3 (1959).

SEVEN

1. Santiago Ramón y Cajal, *Recollections of My Life* (Cambridge: MIT Press, 1989), 69–75.
2. Ibid., 36.
3. Ibid., 37.
4. Ibid., 36.
5. Ibid., 40–42, 44–46.
6. Ibid., 45, 53, 55, 58, 78, 82–83.
7. Ibid., 40–41, 92–93.
8. "Naming is an extremely important act in science." Steven Rose, *The Making of Memory: From Molecules to Mind* (New York: Anchor Books/Doubleday, 1992), 41.
9. "[T]axonomy . . . is a murky endeavor, for nothing in science raises so much controversy as attempts to classify and order the universe of observables. From the days of Linnaeus. . . . This disputatiousness is partly because the universe is a continuum, and our endeavors to identify discontinuities owe as much to our own human ingenuity and determination as they do to the material reality of what is being classified." Rose, *The Making of Memory,* 118.
10. Quoted in Siegfried Bernfeld, "Freud's Earliest Theories and the School of Helmholtz," *Psychoanalytic Quarterly* 13, no. 3 (1944), 348. The date is given as 1847 rather than 1842 in Gordon M. Shepherd, *Foundations of the Neuron Doctrine* (New York: Oxford University Press, 1991), 31.
11. Cajal had no anxiety on this score, but he understood the question. "And our much talked of psychological unity? What has become of thought and consciousness in this audacious transformation of man into a colony of polyps?" (Cajal, *Recollections,* 296). Modern neuroscience glories in addressing just this question.
12. Cajal, *Recollections,* 305.
13. Otto Deiters, *Untersuchungen über Gehirn und Rückenmark des Menschen und der Säugethiere* (Brunswick: Vieweg, 1865); in Shepherd, *Foundations,* 42–44, 47.
14. Gustav Mann, *Physiological Histology* (London: Oxford University Press, 1902); in Arthur Smith and John Bruton, *Color Atlas of Histological Staining Techniques* (Chicago: Year Book Medical, 1977), 9.
15. Camillo Golgi, "Sulla struttura della grigia del cervello," *Italian Medical Gazette,* 2 August 1873; trans. in Shepherd, *Foundations,* 84–88.
16. Rose, *The Making of Memory,* 259.
17. The ammoniacal silver nitrate occasionally exploded if left standing around in the lab.
18. In Shepherd, *Foundations,* 122. Cf. Cajal, *Histology,* trans. M. Fernán-Núñez (Baltimore: Williams and Wilkins, 1933), 413.
19. Cajal, *Recollections,* 303.
20. Ibid., 306; Cajal, *Histology,* 681; Dorothy F. Cannon, *Explorer of the Human Brain* (New York: Henry Schuman, 1949).
21. Cajal, *Recollections,* 321.
22. Ibid., 324.
23. Ibid., 336–38.

24. In *Freud, The Biologist of Mind* (New York: Harper, 1983), 16, Frank J. Sulloway cites without examination the assertions of R. Brun ("Sigmund Freuds Leistungen auf dem Gebiete der organische Neurologie," *Schweizerische Archiv für Neurologie und Psychiatrie* 37 [1936], 200–207), Smith Ely Jelliffe ("Sigmund Freud as a Neurologist," *Journal of Mental and Nervous Diseases* 85 [1937], 696–711), and Ernest Jones (*The Life and Work of Sigmund Freud,* vol. 1 [New York: Basic Books, 1953], chapter 14).

25. "If we assume," said Freud at the point in his lecture where the neuron idea would have been most likely to come up, "that the fibrils of the nerve have the significance of isolated paths of conduction, then we should have to say that the pathways which in the nerve are separate are confluent in the nerve cell: then the nerve cell becomes the 'beginning' of all those nerve fibers anatomically connected with it. . . ." Freud, "Die Struktur der Elemente des Nervensystems," *Jahrbücher für Psychiatrie* 5 (1884); in Shepherd, *Foundations,* 72–73. Freud is clearly talking about a network whose connections lie within cells rather than of independent neurons.

26. Cajal, *Recollections,* 357.

27. "Waldeyer, the illustrious biologist of Berlin . . . giving a resumé of Cajal's ideas and discoveries in a German weekly only baptized them with a new word, 'neurone'. . . ." Cajal, *Histology,* 287.

28. Cajal, "La fine structure des centres nerveux," Croonian Lecture at Royal Society, Burlington House, London, *Proceedings of the Royal Society, London,* Series B, 55 (1894), 444–67.

29. John C. Eccles, *The Physiology of Nerve Cells* (Baltimore: Johns Hopkins University Press, 1957), 10.

30. Cajal, "Leyes de la morfologia de las celulas nerviosas," *Revista trimestriel del micrografia* 1 (Madrid, 1897). Referenced in Cajal, *Histology,* 454. Arthur van Gehuchten helped Cajal pursue this hypothesis.

31. Cajal, "A Quelle époque apparaissent les expansions des cellules nerveuses de la moëlle épinière du poulet?" *Gaceta médical Catalana* 13 (1890), 737–39. Cf. Cajal, *Histology,* 461.

32. An article by Cajal in *Anales de la Sociedad Española de Historía Natural* (1892) describes neural pathways from the olfactory area (smell) to the hippocampus (memory), chemical "neurotropism" of growth cones, and a proposal for a "neurotropic" theory of nerve growth. Cf. Cajal, *Histology,* 482; also Cannon, *Explorer of the Human Brain,* 157.

33. Cajal, *Recollections,* 488.

34. Now in the Munch-Museet, Oslo.

35. Cajal, *Recollections,* 550.

36. Ibid., 546.

37. *Les Prix Nobel 1904–1906* (Stockholm: Norstedt, 1906).

38. Charles Scott Sherrington, *The Integrative Action of the Nervous System* (New Haven, Conn.: Yale University Press, 1977).

39. "Of broader interest is the potential significance of the neuron doctrine as one of the great ideas of modern thought. One thinks here for comparison of such great achievements of the human intellect as quantum theory." Shepherd, *Foundations,* 9.

EIGHT

1. "Hard" and "soft inheritance" are the terms used by Ernst Mayr in his comprehensive history, *The Growth of Biological Thought* (Cambridge: Harvard University Press, 1982), 677–79.

2. Emilio Roig de Leuchsenring, *Weyler en Cuba: Un precursor de la barbarie fascista* (Havana: Paginas, 1947), 93.

3. Byron Farwell, *The Great Anglo-Boer War* (New York: Norton, 1976), 393.

4. Richard E. Welch, *Response to Imperialism: The United States and the Philippine-American War, 1899–1902* (Chapel Hill: University of North Carolina Press, 1979, 1987), 36.

5. Daniel B. Schirmer, *Republic or Empire: American Resistance to the Philippine War* (Cambridge, Mass.: Schenkman, 1972), 225–26.

6. Thomas Pakenham, *The Boer War* (New York: Random House, 1979), 547; and map in A. Ruth Fry, ed., *Emily Hobhouse* (London: J. Cape, 1929).

7. Pakenham, *Boer War,* 523.

8. Philip Magnus, *Kitchener: Portrait of an Imperialist* (New York: Dutton, 1968), 186.

9. Pakenham, *Boer War,* 548.

10. Ibid., 538.

11. Ibid., 535.

12. Ibid., 539.

13. Schirmer, *Republic or Empire,* 227.

14. *Times* (Manila), 4 November 1901.

15. Farwell, *The Great Anglo-Boer War,* 397.

16. Nelson Miles, *Serving the Republic* (1911; Freeport, N.Y.: Books for Libraries Press, 1971).

17. John Adams, *Defence of the Constitutions of the United States,* in *Works,* ed. Charles F. Adams (Boston: Little, Brown, 1856), 4:401.

18. Jon M. Bridgman, *The Revolt of the Hereros* (Berkeley: University of California Press, 1981), 85–86, 184–91.

19. "The Putumayo Revelations," *The Illustrated London News,* 20 July 1912.

20. The authenticity of this telegram is in dispute. See Robert F. Melson, *Revolution and Genocide: On the Origins of the Armenian Genocide and the Holocaust* (Chicago: University of Chicago Press, 1992).

21. John S. Kirakossian, *The Armenian Genocide: The Young Turks before the Judgement of History,* trans. Shushan Altunian (Madison, Conn.: Sphinx Press, 1992).

22. Nicolas Werth, "Félix Dzerjinski et les origines du KGB," *L'Histoire* 158 (September 1992), 38.

23. Ibid., 38–40.

24. Ibid., 40–41.

25. Hitler seems to have asked, "Who talks nowadays of the extermination of the Armenians?" in August 1939. It was first printed by the *Times* (London) on 24 November 1945. Yves Ternon thinks Hitler was speaking of all the Poles, in-