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COMMENTARY

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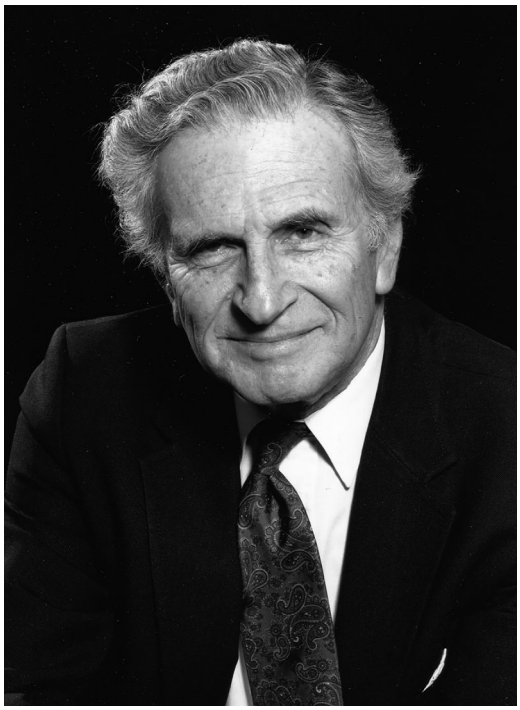
Arnold Bernard Scheibel, M.D. (1923–2017)



> . . .the formal minuet of cerebellar Purkinje cells, the stately files of neocortical pyramids with their cathedral-like dendritic arches, the overlapping swirls of inferior olive cells, or the town and country spotting of cell villages throughout the brainstem core. . . (A. B. Scheibel, 2006, p. 658)

On April 3, 2017, Arnold (Arne) Bernard Scheibel quietly greeted his mortality at the age of 94, leaving an impressive compilation of over 200 groundbreaking investigations on the fine structure of the nervous system. He was one of the original researchers in the field of neuroscience, having contributed to the foundational Boulder conferences in Colorado (Scheibel, 1979; Scheibel & Scheibel, 1967a,b). He also served as Acting Director (1987–1990) and Director (1990–1995) of the UCLA Brain Research Institute, ensuring its survival in the face of considerable economic turmoil. His legacy, however, extends well beyond his scientific contributions, with his generous and kind presence influencing generations of students and colleagues. The present retrospective provides but a brief glimpse into his rich life, one that is captured more fully in his characteristically modest autobiography (Scheibel, 2006).

Born in New York on January 18, 1923, Arne was an only child, although his cousin, Milton, was raised by Arne's parents, and came to be like a brother. Arne had a complex, evolving relationship with his father, a self-made, rather anxious man who worked tirelessly in industry, advertising, and a home-owned business to guide his family through the Great Depression. Arne was deeply influenced by his father's personal courage, and grew with age to appreciate his high standards and expectations. He credits his father for his artistic ability, which proved to be of tremendous value as Arne, like Ramón y Cajal before him, spent many hours drawing detailed recreations of neuropil (see Figure 1). We in the neuroscience community are fortunate that his childhood dream of becoming a great baseball pitcher was never realized. Arne's relationship with his mother was quite different, as he always felt very close to her. He viewed her as a strong, intelligent woman whose self-sacrificing nature provided the glue that held the family together during tumultuous times. Although she was not able to complete her formal education, she was an accomplished pianist and a voracious reader. Both parents emphasized the importance of education, which led Arne down a life-long academic path. This path came full circle in 2016 when, to honor his parents, he established two endowed chairs, one for his mother (the Ethel Scheibel Endowed Chair in Neuroscience in the Department of Neurobiology at the David Geffen School of Medicine) and one for his father (the William Scheibel Endowed Chair in Neuroscience at UCLA's Brain Research Institute). A third endowed chair was funded in 2017 by two former students, now husband and wife (neuroscientist Ronald P. Hammer and neuropsychiatrist Sandra Jacobson), to jointly honor Dr. Scheibel and his spouse, Dr. Marian Diamond (the Marian C. Diamond and Arnold B. Scheibel Chair in Neuroscience at UC Berkeley).

Although he spent most of his adult life in California, he noted that, emotionally, he remained a New Yorker. In 1944, he graduated from Columbia College with a liberal-arts major. This broad intellectual background resulted in a life-long Renaissance-like interest in and impressive knowledge about variety of topics beyond neuroscience, including art, literature, aviation, language, music, and history. Under the practical pressures of World War II, he decided to pursue an M.D. at Columbia University College of Physicians and Surgeons. Although initially not impressed with the state of neurology and neurosurgery at the time, interactions with psychoanalytically trained psychiatrists opened the door for his life-long interest in the neural substrates. It was during his 2 years of psychiatric training at Brooke General Hospital in San Antonio that he met his first wife, Mila (Madge), which was the beginning of a very rich, decades-long research partnership.

In 1950, Arne and Mila moved to Chicago to work with several researchers, including Warren McCulloch, Ray Snider, and Ben Lichtenstein. It was during this time that he obtained a strong foundation in neuroanatomy, and first became familiar with Ramón y Cajal's (1911) *Histologie du Système Nerveux*, most of which he translated into English on his own. This was a transitional moment as he now had a window

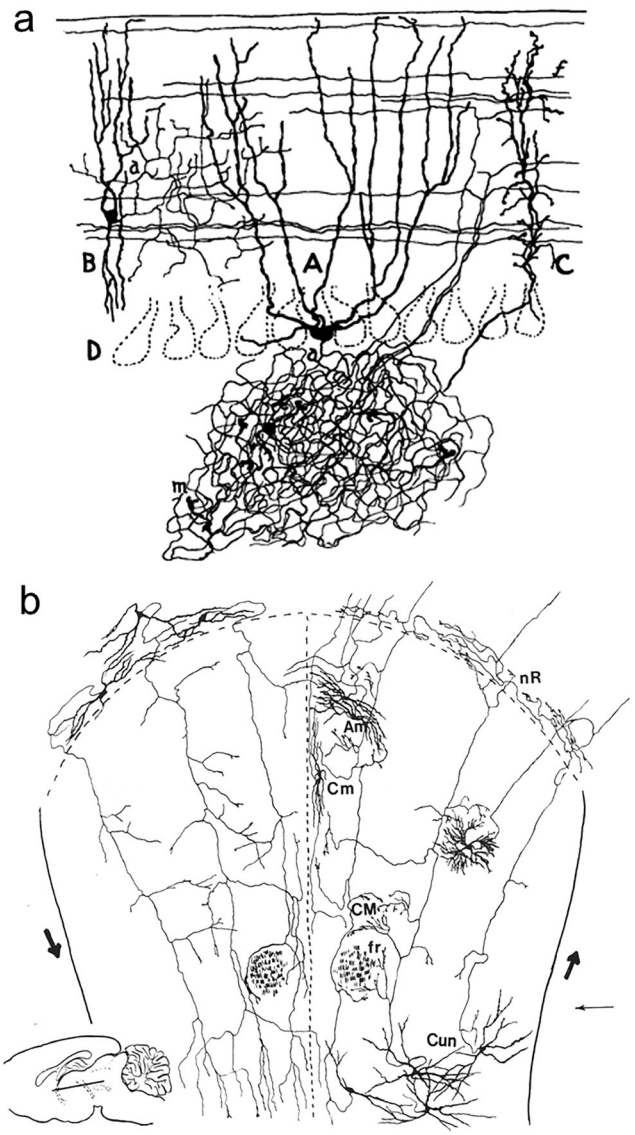


FIGURE 1 Two of Arne's drawings of neuronal architecture: the top one from an early paper and the bottom one from a publication 30 years later. The top image (a) represents a cross-section of cerebellar cortex in an adult cat, illustrating several structures: A and B, stellate cells, with their axons, *a*; C, a climbing fiber from the inferior olive that appears to contact parallel fibers of granule cells *f*; D, outlines of Purkinje cells bodies; and *m*, mossy fiber terminations. The relatively orderly circuitry of the cerebellum always intrigued Arne, and he appreciated that more extensive comparative Golgi work had been done in recent years on this structure (Jacobs et al., 2014). The bottom image (b) is a cross-section (see inset) through the mes- and di-encephalon, illustrating reciprocal connections between tegmental cells in the nucleus cuneiformis (Cun) and the reticular nucleus of the thalamus (nR) in an infant rat. Other labelled structures are: CM = centre median; Cm = central medial; Am = anterior medial nuclei. Arne believed that the reticular formation and the more rostral nR constituted the core circuitry for diffuse modes of consciousness, a topic of interest he maintained for several decades. The top image is adapted from Figure 9 of Scheibel and Scheibel (1954); the bottom image is adapted from Figure 27 of Scheibel (1984/2011)

into the intricate, three-dimensional neural substrate that gives rise to an individual's cognitive and emotional world. The classic Golgi technique had now been passed to a new researcher, one eager to continue exploring the dense forest of the brain (see Figure 1,2). The next few years were a productive time for refinement of the Golgi impregnation (including a variant developed by Lorente de Nó, Ramón y Cajal's last student), collegial interaction, and travel. When Mila contracted poliomyelitis, it became important to move to a warmer climate, which led to his 1952 appointment at the University of Tennessee Medical Center in Memphis. Here, the initial "Scheibel and Scheibel" investigations were completed on the cerebellar climbing fibers (Scheibel & Scheibel, 1954) and the inferior olive (Scheibel & Scheibel, 1955). These were "the Scheibels" first publications in the *Journal of Comparative Neurology*, and it should be noted that, ever the gentlemen, the second "Scheibel" in such publications was always Arne. A Guggenheim Fellowship (1953–1954) subsequently allowed them to travel to Europe, where they expanded their neuroscience connections. At Moruzzi's Neurophysiology Institute at Pisa, they first met Alf and Inger Brodal, who became life-long friends (Scheibel, 1988b); it is also rumored that Dr. Scheibel became known as "Arne" in a subsequent visit with the Brodals at the Neuroanatomy Institute in Oslo. Moreover, the Guggenheim year afforded Arne the opportunity to visit the Cajal Institute in Madrid, where he experienced firsthand the master's drawings and Golgi preparations.

Toward the end of these travels in 1955, they accepted an invitation from Horace Magoun to UCLA, where Arne received a joint appointment in the Departments of Anatomy and Psychiatry, a position he held for 55 years. The next 21 years would be a period of extensive exploration of neural-function relationships, guided by electrophysiology and Golgi neurohistology. These early years were particularly fulfilling as the Scheibels worked together. Preliminary inquiries on the reticular formation, which suggested an idiosyncratic convergent pattern of input on reticular neurons (Scheibel, Scheibel, Mollica, & Moruzzi, 1955; see Figure 1a), were expanded into an extensive series of studies that contributed to the concept of neural modules (Scheibel & Scheibel, 1958) and pacemaker control systems (Scheibel & Scheibel, 1965a,b). From here, the research expanded both caudally into the spinal cord, where they discovered dendritic bundles in motoneurons (Scheibel & Scheibel, 1970b), and rostrally to the thalamus, specifically the reticular nucleus of the thalamus (nR in Figure 1b). Careful analyses of the neuronal architecture suggested that the nR served as a "gateway" for modulating communication between the thalamus and the cerebral cortex (Scheibel & Scheibel, 1966, 1967b), thus playing a crucial role in selective attention. From here, the research examined the termination of thalamocortical and callosal axons on pyramidal neurons (Globus & Scheibel, 1967a,b), setting the stage for subsequent cortical research. Finally, now firmly situated in the cortex, they provided one of the first modern morphological descriptions of the idiosyncratic giant pyramidal cells of Betz (Scheibel & Scheibel, 1967b). These all were thorough and carefully researched investigations; indeed, Arne believed that the only way to be truly original in research was to ignore the literature.

Much of this work was completed at Arne's home in Encino because, during the last 14 years of her life, Mila was too ill to travel.

Consequently, Arne would stay home to take care of her, only commuting to UCLA to give lectures and to procure more neural material for research. Arne lived in this house for 53 years and, for those who knew him, it very much reflected his true character: stately, comfortable, warm, and welcoming. The entrance, off of a local side street, consisted of a 200-foot-long driveway, covered with a tree branch and ivy canopy that formed a tunnel. At the end of the tunnel was a relatively large tract of land for Encino. Once on the premises, the rest of the city disappeared, engulfing one in an almost palatial retreat. The main dwelling was a Spanish-style ranch house built in 1935 by the actress Ann Dvorak. It was bordered on one side by an old stable, and on the other by a small guesthouse and a greenhouse; the back opened up to a small orchard and a swimming pool. The entire property was a circumfusion of botanical richness, dominated by an ever-sprawling *Rosa banksiae* rosebush (although, with a trunk 10 inches in diameter, it was more like a tree) that endeavored to overtake the entire property with its wandering, reticulum-like dendritic extensions. In later years, the guesthouse served as the location for Arne's monthly evening seminars, where a multi-disciplinary gathering of researchers (e.g., Joseph Bogen, John Schumann, Eran Zaidel, Joaquin Fuster, Lorente de Nó), postdoctoral scholars, and graduate students would discuss a variety of neurocognitive topics. The discussions were always insightful and stimulating; at the end of the evening, the focus would inevitably return to Arne, who would eloquently explain the relevant neuroanatomy and thoughtfully summarize the main take-home messages for the evening. These meetings eventually led to a series of on-campus affinity groups, and formed the impetus for the UCLA Integrative Centers of Neuroscience Excellence, which facilitate cross-disciplinary, collaborative interactions among researchers. This was not only home for Arne, but also the nourishing wellspring of immeasurable intellectual stimulation.

After Mila died in 1976, the research focus gradually shifted to more clinical applications. One series of studies focused on the degenerative sequelae of Alzheimer's disease (Scheibel, Duong, Tomiyasu, 1987; Scheibel, Lindsay, Tomiyasu, & Scheibel, 1975; Scheibel & Tomiyasu, 1978; Scheibel, Wechsler & Brazier, 1986), and another on disorientation of pyramidal cells in the hippocampus of individuals diagnosed with schizophrenia (Conrad, Abebe, Austin, Forsythe, & Scheibel, 1991; Kovelman & Scheibel, 1986; Scheibel & Kovelman, 1981). Overlapping with the clinical research were major personal changes as, in 1979, Arne received an invitation from Dr. Marian Diamond at UC Berkeley to talk about the reticular core and its relation to consciousness. Marian was a well-established neuroscience force in her own right, as one of the pioneering investigators exploring the effects of environmental enrichment on the brain (Bennett, Diamond, Krech, & Rosenzweig, 1964; Diamond, 1967, 1988). It was a fortuitous invitation and an instant attraction, resulting in their marriage in 1982, creating a personal and professional bond that lasted for the rest of their lives. Their wedding was a private affair with the ceremony poolside at Arne's house in Encino. The next morning, Arne put Marian on a plane to Berkeley because she had to teach. He then went to work, where his graduate student, Taihung (Peter) Duong, asked him what he had done over the weekend. Arne matter-of-factly stated: "Oh, I worked on a manuscript, got married, and reviewed a paper." And that was that. Although they maintained a commuter relationship, with Arne at UCLA and Marian at UC Berkeley, they were never really apart—they consistently enriched each other in the truest sense of the concept.

It is clear that the initial question about neuromorphological correlates of cognitive abilities was planted when Arne visited Oscar and Cecile Vogt in Germany during his Guggenheim Fellowship years. However, it was perhaps the influence of Marian that led him to explore the neurobiology of higher cognitive functions formally (Scheibel, 1988a; Scheibel & Wechsler, 1990). This was to be his last major area of inquiry, but in his recollection, perhaps the most fulfilling as it also returned him to the passions he felt as a psychiatric resident. The initial exploration focused on pyramidal neurons in Broca's area and the primary motor cortex, noting that basilar dendritic complexity was greater in the former region than in the latter (Scheibel et al., 1985). Similarly, in an exploration of primary somatosensory cortex, basilar dendritic systems were more complex in the hand/finger region than in the trunk region (Scheibel, Conrad, Perdue, Tomiyasu, & Wechsler, 1990). These were groundbreaking studies in humans, both suggesting a positive association between dendritic complexity and the computational demands placed on pyramidal neurons in a specific cortical region. A final study documented a positive relationship between education (and its associated lifetime experiences) and basilar dendritic extent in Wernicke's area (Jacobs, Schall, & Scheibel, 1993; Jacobs & Scheibel, 1993), findings that echoed in humans the non-human enrichment studies of Marian, and paved the way for more extensive quantitative neuromorphological investigations in humans (Jacobs et al., 2001) and other large mammals (e.g., African elephant: Jacobs et al., 2011; humpback whale: Butti et al., 2015). Although Arne closed his research laboratory at the end of the 1990s, he always followed this subsequent Golgi research with great interest (Jacobs & Scheibel, 2002; see Figure 2). For those familiar with the technique, the anticipatory excitement of putting a fresh Golgi preparation under the microscope never fades with age. Indeed, Arne once noted that the Golgi stain was "the only histological technique with personality" (Scheibel & Scheibel, 1978b, p. 90), and it is clear that the technique is, over 140 years after its discovery by Golgi (1873), still opening neuromorphological vistas.

Although Arne's active research had come to an end, his commitment to teaching flourished. Indeed, he was a master teacher, receiving the UCLA Distinguished Teaching Award in 1997. His lectures were captivating, guided tours through the nervous system: a stream of effortless narratives with fluid, blackboard illustrations serving as familiar landmarks. He could draw any brain structure, any cross section, at any angle with ease. A 2-hr lecture would be over before one realized it, and the students would have 20 pages of detailed notes in front of them. Lectures were linked together with the intricacy and fluidity of pastels blended on a canvas as Arne would reintroduce previous structures by referring to them as "our old friends." He also half-threatened, upon occasion, to lecture in iambic pentameter.

If research engaged his brain, then teaching emanated from his heart (so to speak). He claimed that his love of teaching increased from year to year. In 2010 at the age of 87, however, he decided to retire because he realized that advancing age would interfere with teaching.

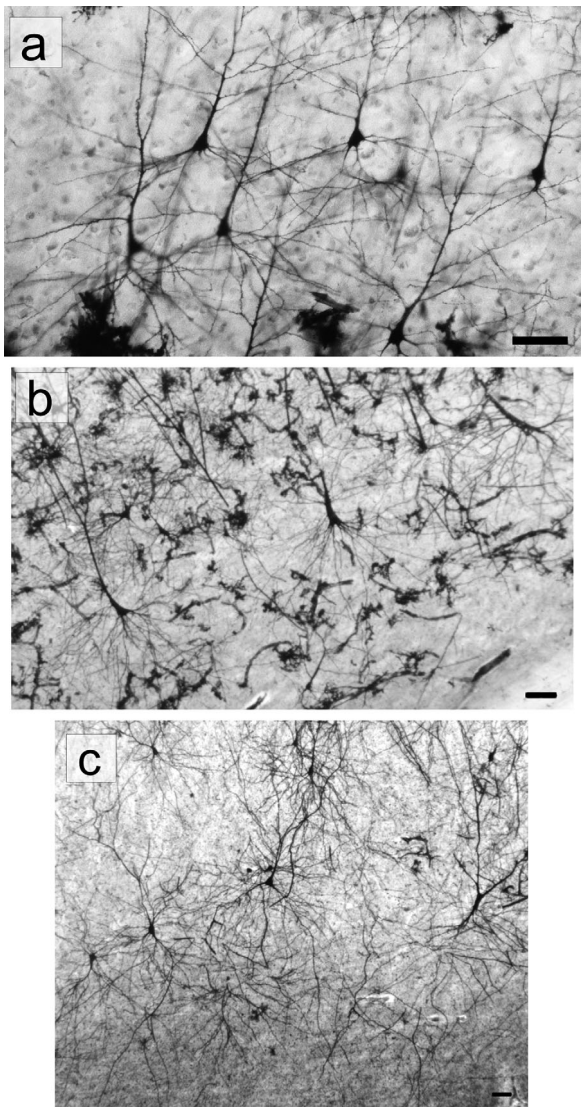


FIGURE 2 Photomicrographs of neocortical forests in three different species: (a) human; (b) humpback whale; and (c) African elephant frontal cortex. These images illustrate why Golgi impregnations remain the gold standard for investigations of the three-dimensional architecture of cortical circuitry. These specific photomicrographs reveal considerable variation in neuronal morphology across the three species. In the human (a), one sees typical pyramidal neurons in prefrontal cortex with singular apical dendrites ascending in parallel to the pial surface. In the humpback whale (b, adapted from Figure 6a of Butti et al., 2015), prominent magnopyramidal neurons in the visual cortex similar to the solitary cells of Meynert (1867) are present, with basilar skirts that tend to descend toward the underlying white matter. Finally, in the elephant (c, adapted from Figure 4 of Jacobs et al., 2011), neuronal architecture in the frontal cortex varies dramatically from other mammals, with a large variety of (atypical) pyramidal neuron morphology. When looking at such images, Ramón y Cajal (1989/1937, p. 364) once queried: "Is there in our parks any tree more elegant and luxuriant than the Purkinje cell of the cerebellum or the *psychic cell*, that is the famous cerebral pyramid?" These kinds of Golgi-impregnated neural landscapes are responsible for sustaining Arne's (and other's) life-long fascination with neuronal morphology—every new slide was an adventure that, again in the words of the master, infused the researcher's brain with "noble and lofty inquietudes" (Ramón y Cajal, 1989/1937, p. 592). Scale bars = 100 μm

Arne felt that the most important task for academicians was to train the next generation, although he also felt they were constantly teaching him in return. Too modest to be concerned about his legacy, he did, however, note that he would like to be remembered as someone who was delighted and honored to teach younger people. He shared this passion for teaching with Marian—a reason they wrote *The Human Brain Coloring Book* (Diamond, Scheibel, & Elson, 1985), which is still the gold standard for teaching human neuroanatomy. The teaching went beyond the university classroom as he developed an outreach program (Project Brainstorm), whereby UCLA students taught neuroscience basics to local K-12 schools. Similar programs have emerged across the U.S. In their later years, Arne and Marian also travelled internationally to China and Africa to share their joint neuroscience wisdom. Finally, even into their 80s, they never stopped teaching as they wrote ~30 neuroscience columns for their retirement community on a variety of topics (e.g., Your Brain and William Shakespeare; Emotion, Heart, and Brain; Your Brain and the Mona Lisa). The culmination for both of them may have been their active involvement in a 2016 documentary by Gary Weimberg and Catherine Ryan: "My love affair with the brain: The life and science of Dr. Marian Diamond" (http://lunaproductions.com/brain/).

It is impossible to gauge the impact of a person's life. A retrospective examination of Arne's teaching at UCLA estimated that he had taught over 700 graduate students, 1,200 undergraduates, 800 medical students, 200 psychiatric residents, and guided many research students (Bones, Robinson, & Jacobs, 2007). Many of these students have become professors themselves. Arne's professional influence thus clearly extends across generations in ways that younger students will never even know. As for Arne, the person, his psychoanalytic training meant that he always knew what to say, when to say it, and exactly the best way to phrase it. When he talked with someone, he conveyed sincere compassion and interest, as if that individual were the only person in the world. He made everyone feel special. Arne was a man filled with dignity who walked gently on this earth. Like a pebble dropped in the middle of a calm lake, he generated ripples that touched everyone on the shore with grace.

Bob Jacobs*

*Although I bear all responsibility for any mistakes or omissions in the above, this retrospective has been very much a collaborative effort on behalf of many individuals personally touched by Arne. I am grateful for their insight, kindness, compassion, and generosity: Catherine Ryan, Gary Weimberg, Rick Diamond, Penny and Glen Alpert, Taihung Duong, Ron Hammer, and Patrick Hof. I would also like to thank Madeleine Garcia for assistance with the figures. Finally, I am honored and humbled by the emotional support I have received from former students who, in some small way through my lectures, indirectly experienced Arne's humanity and deep appreciation of neuronal architecture.

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