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The History of Neuroscience in Autobiography

Lynn T. Landmesser . Rodolfo R. Llinás

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Arnold B. Scheibel . Gerald Westheimer

Volume 5

Edited by Larry R. Squire



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The History of Neuroscience in Autobiography

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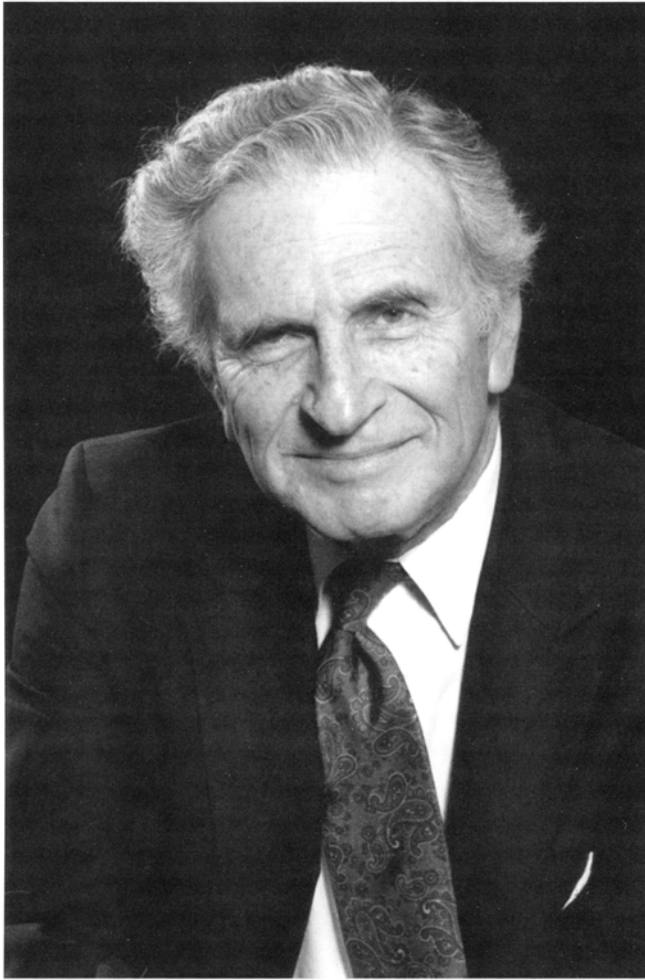
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Alvin B. Eckstein



Arnold Bernard Scheibel

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January 18, 1923

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Fellow, Royal Norwegian Academy of Sciences (1983)
Scientist of the Year, Alzheimer's Disease Research
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The Harriet and Charles Luckman Distinguished
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The California Biomedical Research Association
Distinguished Service Award (1998)
Distinguished Life Fellow, American Psychiatric
Association (2003)
Research Pioneer Award, Alzheimer's Disease
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Arnold Scheibel is known for his studies of the detailed architecture of the spinal cord, brain stem, and cerebral cortex and introduced the module concept into central nervous system research. His description of the recurrent axonal projection of the nucleus reticularis thalami led to the gatelet theory of selective attention. His Golgi studies of human brain tissue extended our knowledge about the nature of neuronal changes in senile brain disease and in schizophrenia. He demonstrated correlations between human cognitive activity and structural change, and emphasized the role of plasticity in the living reactive brain.

Arnold Bernard Scheibel

Patterns in Neuropil, or “passion in neuropil” as some friends interpreted it, was the title of my first and longest lasting research grant from the National Institutes of Health. The title spelled out the thrust and excitement that I have always felt for the fine structure in the nervous system. The fact that definable organizations of neurons, dendrites, and axons—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—might serve as vital substrates for cognition and behavior has, over the years, held me spellbound. With this in mind, I am grateful to the editor of *The History of Neuroscience in Autobiography* and the Society for Neuroscience for their invitation to look back over a period of more than half a century and share memories.

In the Beginning

Both sides of my family arrived in the United States in the decades after the Civil War. I should know when, but when one is young, one’s forebearers seem uninteresting, and when one is old enough to care, the sources are gone. My maternal grandmother’s family came from what was then part of southern Germany. My father’s family emigrated from the old Austro-Hungarian Empire. Dad’s family may have been vintners and there is apparently still a Scheibel aperatif or liqueur that is locally available in central Europe. Several of Dad’s uncles were architects who practiced in the Cleveland-Youngstown area and this flair with a pencil did not escape him. (I often wonder whether my own preference for neurohistology and neural circuitry, the fine architecture of the nervous system, was not another and somewhat more derivative expression of that same gene line.) Although Dad trained to be an architect, he quickly found that he was better able to support his family by working in the “front office”. And so he became an advertising and sales manager at a time when that was still a fairly exotic occupation. Among the experiences he shared with me was his being at the airfield on a foggy morning in 1927 when Lindbergh took off for Paris. Lindbergh was wearing a Bulova watch that Dad had just strapped

on his wrist, a model that was then sold widely and successfully as the "Lone Eagle."

Although Mother's education was cut short by financial reverses in her family (my maternal grandfather was saintly but not a business man), she remained until almost the end of her life an indefatigable reader and much of my interest in history and biography comes from her. During Mother and Dad's lives together, they had many differences but were in complete accord as to the importance of education for their young people.

I was born in the northwest part of New York City and spent the first 24 years of my life in Manhattan and the Bronx. Although one of the largest cities in the world, it was still thought of (in its pre-Big Apple days) as "little old New York" by its inhabitants and that is still the way I remember it. I was my parents' only child but when I was 5, my aunt died in childbirth and her newborn son was raised by my parents. The grief surrounding the death of my aunt pervaded the family for a number of years and, coming as it did in the latter part of 1928, it is somehow mixed in my mind with the gathering anxiety and suffering that followed the stock market crash and Great Depression, which followed shortly thereafter. As a "child" of the Depression, I still fancy I see its carryover in my unwillingness to spend money on myself. My cousin Milton, who became in every sense my brother was always gifted, always passionate, seldom predictable. Unlike me, he was excellent in chess, good in mathematics, and a bit of a rebel. He became an economist and spent part of his adult life in Washington as Executive Assistant Secretary for Defense under several administrations.

The most vivid memories of my childhood are those of the books that my dad arranged to come my way once I learned to read. *The Mysterious Universe* by Sir James Jeans leaves a special impress, with its discussions of recently discovered red giants like Betelgeuse and Antares, and the great matrix of dust that seemed to fill the galaxy. I also recall short biographies of the presidents, several lives of Lincoln, and *Compton's Pictured Encyclopedia*, which became my bible (and then Milton's) for several years. Interestingly, I remember no introductions to biology or much curiosity on my part in this direction (with the possible exception of Paul deKruif's *Microbe Hunters*). Outdoor sports were far down the list of encouraged activities. For my parents, life was a serious business and play was at best a slightly disreputable way of taking a necessary break from meaningful work. I am afraid that I was raised with the idea that professional athletes were little better than ne'er-do-wells or "bums." Under these conditions, it is not surprising that my graduation from Columbia College hung in the balance until I learned to swim (still a prerequisite for graduation at that time).

I remain perpetually grateful to my parents for their commitment to my education. The middle 1930s were marked by two educative experiences that still live vividly for me. One was the trip around the country that we

took by car in the spring of 1934. Dad was “between position” in those deep Depression days and they accordingly decided that it might be the time to kick over the traces for a few months. They assumed that I would learn more this way than I could possibly gain in my 6th grade school class. Considering that the vehicle of choice was a 1928 Nash without springs and an effective top speed of 38 mph, it was a valiant decision.

In the nation’s capital, it was a fortunate 11-year-old who could sit and listen while the United States Senate debated the proposed independence of the Philippine Islands or watch great jurists such as Brandeis, Cardozo, and Hughes (still meeting in the old Senate Chamber) consider the constitutionality of New Deal legislation. Further in our course toward the southwest lay the battlefields of the Civil War, Mississippi paddle wheelers, the gathering threat of the Dust Bowl, the memories of Tombstone, Arizona, and the citrus-loaded valleys of California. Luckiest of all was the fact that we made the trip just before the “homogenization of America” began. Aside from a few of the “new fangled” tourist cabins, the hotels or boarding houses we stayed in were often those that dated from frontier days. Another 10 years and they would all be gone, swallowed up by the omnipresent Hiltons, Sheratons, Best Westerns, and Holiday Inns.

The other lucky break was winning a scholarship at Horace Mann, a small, private middle school–high school at the northern edge of New York City. Rigorous discipline, sometimes great teaching (with the unfortunate exception of biology), small classes (five of us struggled through 4 years of Latin together), and a very active sports and extracurricular program helped me begin to spread my wings. I liked drama, writing, and illustration and actually took up track and tennis. The pattern continued at Columbia College, the (then) surprisingly small college arm of Columbia University, to which I also won a scholarship. Immature as I was through my college years, I still recognized the privilege of being exposed to instructors such as Lionel Trilling, Mark Van Doren, and Charles Frankel. It was a heady time, but I still was not sure where I was going.

As a liberal arts major, I took a short science sequence put together for those who would presumably have nothing further to do with these fields. The opening salvo here was a semester of physics taught by Professor John Dunning, then already deeply involved in the mysterious “Manhattan Project” going on behind plywood partitions just down the corridor in Pupin Hall. Things began to look up with geology and improved still more as fossils and life forms became the focus. I think I began to realize at that point that the study of living things was more interesting than I could have guessed. The strongly negative impression that had followed me from my unfortunate high school biology classes began to dissolve and I realized—almost reluctantly—that perhaps what I had been reading in my Great Books classes, about the appropriate study of mankind being man, might just be true.

Another conditioning factor was the approach of the war. With the attack on Pearl Harbor at the end of 1941, most of us became concerned with the relevance of what we were doing—or planning to do—in a nation now fully committed to a war effort for an indefinite period. Medicine now seemed to me to be the best way to combine my burgeoning interest in biology with a profession that would be useful and intellectually challenging. I was hardly equipped for medical school, having carefully avoided all premedical classes until that point. With a little advice from the pre-med advisor, a kindly organic chemist named Powell, I arranged to take the requisite 2 to 3 years of required courses in a hectic 15 months. These included biology, comparative zoology, embryology, organic chemistry, and qualitative analysis and they were taken whenever I could find a session scheduled. I attended extension evening classes, summer school, and a few graduate level classes. I remember taking the two-semester zoology course out of sequence, the second term before the first. It was certainly the hardest period of study I had yet known—and I found it exhilarating. With war pressures rising, Columbia offered a “professional options” program for those who planned to go on to graduate school. It was essentially a “4 years in 3” program, which allowed the first year of the following graduate experience to be counted as the final college year. I believe this was partly in response to the government’s need for young physicians and was followed by a similar “4 years in 3” compression in professional school. I was fortunate enough to be accepted at Columbia University Medical School (College of Physicians and Surgeons) and started with my class in April of 1943. With bitter fighting going on in the Mediterranean and the Pacific, and with the invasion of Europe certain to follow, we were a busy, anxious group in our first anatomy laboratory.

Medical School and Beyond

Our class at P & S was one of the brightest, most articulate groups that had ever been selected. The sense of intellectual competition was also spurred by the rumor, probably incorrect, that the lowest 5% of the class each year would end up in the South Pacific! After the first 3 months of work, we were given the option of joining the Army or Navy and being sent back to school at the expense of the Armed Forces, with the agreement that we would spend 2 or more years in service as physicians once our training was complete. Because medical school costs, even then, were not inconsequential, most of us selected this option. I think the majority of us chose the Army although it was later agreed by all that the V 12 naval uniforms cut a far more rakish figure. After several weeks of tests and training at Camp Upton, a barren, barracked waste on Long Island where we were immensely unpopular with the Regular Army personnel (our unofficial title was

“those damned college f . . .”) we returned in uniform with our Army Specialized Training Program (ASTP) patches on our shoulders. Our orders to salute all officers, domestic and foreign, led to our saluting many a surprised doorman until we learned the difference. Another aspect of our new status, was the diet of frequent training films (primarily on the evils of gonorrhoea, syphilis, and unwashed mess kits) and the almost daily training parades held in the Armory, which just happened to be across the street from the medical school. Because we took turns drilling our student platoons, precise maneuvers were infrequent and marching catastrophes certainly not unknown. Our commanding officer, a gentle, Regular Army major who must have wondered what he had done to deserve this assignment, seemed resigned to the martial incompetence that surrounded him.

Like most other medical schools of the time, P & S had lost many of her clinicians to the war effort, and the compressed 4 years in 3 schedule put further demands on an overworked faculty. In retrospect, our teaching was spotty and a bit ataxic. I recall in particular our course in basic neurology—a fusion of neuroanatomy, a little neurophysiology, and a dash of clinical application. Six or eight neurology and neurosurgery faculty, some well within the category of “grand old men in the field,” shared the lecture load—and indeed, the lectures came across as if they were a load to them. It was an unfortunate introduction to the field. After the course, I made the first conscious decision about my future that I can remember making, namely whatever I did with my later life in the medical profession, it would have nothing to do with structures above the neck!

Instead of a summer vacation between the school years, there was a 2 week break. Between first and second years, a number of us were asked whether we would like to help out in anesthesia because the operative staffs were so thinned by the war. I think we were asked because we had just finished our course in general physiology and were thought to be knowledgeable about processes such as respiration. In any case, I found myself one morning administering ether (there were few other choices for a deep anesthesia in 1944) for a “partial gastrectomy” who also had some type of coronary insufficiency. The surgery was being performed by one of the distinguished gastrointestinal surgeons of the day, Dr. A. McGee Harvey, a physician who also deserves sainthood as we shall see in a moment. My understanding of basic physiology was shaky and my estimates of the depth of anesthesia of my patient at best approximate. While worrying about his cardiac status, I made what I thought was a useful discovery. Once under anesthesia, a patient could apparently be maintained exclusively on oxygen! His color *had* improved, and the operative procedure seemed to be going well. Dr. Harvey had gotten to the point where the stomach, suitably isolated and clamped, was folded back on the sterile field and ready for excision. At this critical point, the patient moved slightly, then threw his legs off the operating table and began to sit up. Instruments clattered

to the tile floor and there were audible gasps from the operating group. Dr. Harvey then proved the appropriateness of his candidacy for sainthood with the following comment, "Doctor, I think your patient is a bit light." I need hardly add that a good deal of ether was used for the rest of the procedure. In thinking back over episodes like this in those pressured but fortunately less litigious times, one cannot help but compare them with present concepts of medical ethics and professional oversight.

Another measure of medical training of the 1940s that comes to mind was our experience with "chest medicine," managed far downtown at the old Bellevue Hospital facility. Chest medicine was then virtually synonymous with tuberculosis, and the terrible open pulmonary lesions that characterized so many of the hospitalized patients were a real threat to students and staff in those preantibiotic days. Some of us felt protected by the unspoken assurance that doctors never picked up infections from their patients. Others of us, including myself, were not so sanguine. While I was working at Bellevue I followed my own version of a physical exam, which in these cases consisted primarily of percussion and auscultation of the chests of the unfortunate patients followed by demonstration or report to our attending physician. I would hyperventilate in the hall outside the room for a moment or two, then, while holding my breath, hurry in to percuss half the chest. After a brief return to the hall for more oxygen, I would return to the other half. Instructions to the patient were always managed in a low voice in order to lose as little oxygen as possible. Usually half a dozen trips in and out sufficed to finish the examination of one patient. In retrospect it seems absurd although the danger and anxiety were real enough. Several of our classmates became tuberculosis skin-positive after this experience and I believe one of us developed overt disease.

I wish I could report that the teaching of clinical medicine was inspiring. There is no doubt that the P & S faculty were usually of international caliber—with names such as Cournand and Richards for respiration and blood gases, Hanger and Patek for liver disease, Atchley for body fluids and electrolytes, and Loeb for early work with corticoids coming naturally to mind. But many of them also seemed remote and unapproachable and far from representing the human component in medicine that I expected. This memory has remained with me to serve as a constant reminder when I deal with patients or students.

Even with the uneven quality of the teaching experience, there was no doubt in my mind that I had made the right choice and that medicine was the greatest of the humanities. My interests flowed in the direction of internal medicine and with the fairly recent arrival of objective measuring devices such as the electrocardiograph, cardiology seemed increasingly attractive. My 15-month, mixed internship at the old Mount Sinai Hospital in New York (it was not yet a medical school) was a powerful experience during which I began to taste the rewards and anxieties of patient

responsibility. The major attending physician on our medical service was the Dutch physician, Dr. I. Snapper who taught us an important lesson in what he called the fundamental rule of life—the rule of “autas.” Loosely translated (I believe very loosely!) this means “do it yourself.” Accordingly, in addition to the physical workup, we did all of our own laboratory work during the first evening and night after hospital admission. It was not at all unusual for me to have the unfortunate new patient under the fluoroscope screen at one in the morning.

On some occasions, the etiology of the patients’ illnesses were sufficiently baffling to warrant the call for outside consultants. On the occasions when the consultant was a psychoanalytically trained psychiatrist, I was intrigued to see how easily a rich substrate of emotionally laden and possibly clinically relevant material could be obtained, often from the most unlikely looking patient. My few hours of psychiatric exposure at medical school clearly had not prepared me for the apparent breadth of emotional “disease” and psychopathology behind every clinical entity. It was an eye-opening experience and led me to consider psychiatry instead of cardiology as my future speciality. I think I would have preferred to finish residency training in internal medicine before going on to psychiatry, but these were unusual times. It was 1946–1947 and many young medical officers were returning from their stint in the recent war and it was appropriate that they get first shot at the house staff slots. Furthermore, I had the obligation of 2 years of Army medical service before me. I learned to my surprise that because the Army needed more psychiatrically trained physicians to help serve the returning veterans, they would prefer if I took an extra year of training. The prospect of doing something more exciting than routine physical examinations was enticing, and so I was determined to find a year of resident training in psychiatry before presenting myself to the Army. Again, the number of first-year residency slots in psychiatry were limited, but I found one open at the new Psychiatry Service at Barnes and McMillan Hospitals of Washington University in St. Louis. The young emigrant from New York City presented himself there at the end of June 1947, and the pattern of life changed forever.

Into the Realm of the Mind

Psychiatric training was both a challenge and a shock. The department was new, led by a genial lipid chemist named Ed Gildea, and the faculty were mainly local practitioners who were not primarily interested in teaching. The predominant psychiatric school they claimed to represent was Meyerian biological psychiatry although none of us could find out exactly what that meant. Schooled as I was in the medical model of disease, the more amorphous conceptual approach was difficult to comprehend.

In those pre-psychopharmacology days, our only therapeutic tools were chloral hydrate and amytal, insulin and electric shock, and psychotherapy. And the latter was the most baffling of all. As I recall, it took a "strike" by some of the house staff to convince the faculty to bring in a couple of local analysts to enlarge our experience in dynamic psychotherapy.

Nevertheless, the year served its purpose and by the time I departed for armed service, I knew the rudiments of my new profession. I might add that while at Washington University, I had occasional, fleeting contact with electrophysiologists George Bishop and James O'Leary. I did not have the time or the courage to explore what they were doing, but it was enough to alert me to the fact that there might be other approaches to the riddle of brain and mind.

My 2 years of active service with the Army Medical Corps, spent at Brooke General Hospital in San Antonio, served four important functions. It allowed me to broaden and reinforce my knowledge of the field of clinical psychiatry, including an unexpected foray into the new field of child psychiatry. It enabled me to meet and marry my first wife Madge, or Mila as most people knew her. I learned the rudiments of portrait painting. And it convinced me that the full-time practice of psychiatry, at least as I had so far experienced it, was not going to satisfy me.

The foray into child psychiatry was especially unexpected. Our commanding officer, a handsome white-haired gentleman, Colonel Rawley Chambers, was apparently advised by Army Headquarters that his unit would have the honor of developing the first child guidance clinic in an army general hospital setting, an obvious mechanism to provide better service to families who were part of the still large peacetime army. The colonel informed us of this decision from above and also of the fact that I would be the medical officer in charge. When I pointed out that I knew nothing of the field, the colonel suggested that I become informed immediately! I read the only book on the subject in the hospital library and so, by act of Congress, became a child psychiatrist. Working with a small staff of psychologists and social workers, things turned out far better than one would have expected, so much so in fact that I became the local authority on the subject and before leaving the service, was asked by the Hogg Foundation to open a child guidance clinic in Austin—presumably the first such facility in Texas. Fortunately, I had the good sense to decline this generous, if misguided, offer.

As already mentioned, I continued to have the uneasy feeling that what I was doing was not sufficiently entraining. Something was missing. I shared these concerns with our local consultant, Dr. Melvin Thorner, who suggested that I consider a year or two in a research laboratory. We discussed a few possibilities, the only one that I knew being the Bishop and O'Leary group in St. Louis. When Thorner mentioned Warren McCulloch in Chicago, I went to the literature and was impressed by the excitement

of his ideas. After a brief visit to McCulloch's basement laboratory at the Illinois Psychiatric Institute, I found the man as stimulating as his writing and so, at the end of June 1950, Mila, my brand new wife, and I set out for Chicago. The day after I was placed on inactive service and left San Antonio, the North Korean Army attacked South Korea and all armed forces appointments were frozen for the duration!

Mid-August in Chicago was not the best time to show up for work in a laboratory. Most of the staff were on vacation or at meetings. McCulloch had arranged that I relearn my neuroanatomy with a neuropathologist, Dr. Ben Liechtenstein who kindly gave me time and interest—gifts that I will always cherish. Mainly, I had come into possession of something I had never owned before—free, unstructured time. Rather uncertainly at first, I began to spend half days and then full days in the University of Illinois library, reading about this new field of brain research that I had dared wander into. I do not remember the process or progression, but pretty much by chance I sat down with the two-volume work, *Histologie du System Nerveux* by Ramon y Cajal (1911). I leafed through it noting that my French was just adequate to the task.

The next few days came as close to being a transforming experience as I ever hope to know. I had just looked into my own version of Chapman's Homer! Here were images of neural structure and circuitry that must form the substrate for all of the behavior and all of the cognitive and emotional capabilities that I had ever considered. I was entranced by the beauty and intricacy of the drawings, and by the Golgi technique that made them possible. As soon as McCulloch returned to the laboratory, I told him about my enthusiasm for neural architecture. He liked the idea and suggested I immediately go down to see Heinrich Kluver at the nearby University of Chicago. Apparently the word was out that Kluver had just devised a stain that revealed fine structure in an exciting fashion. It turned out to be the new Kluver-Berrara stain, resembling a combination of Nissl and Weil preparations in the same section. It was clearly going to be a powerful control method, but nothing like the precious Golgi that I had just discovered. Again at McCulloch's suggestion, I went crosstown to the Northwestern Medical School to see Ray Snider, a neurophysiologist whose wife had worked with Lorente De No, one of the last great practitioners of the Golgi method, and a student of Cajal. With the Cajal-Lorente version of the Golgi method in my hand, I suddenly felt tied into the long and prestigious tradition of classic neurohistology. Dr. Snider was both interested and hospitable and allowed me to come to his lab twice a week from that time on. This provided me with my first halting essay into animal neurophysiology. Unfortunately we tackled a problem—the direct current (DC) shifts in cerebellum—that was rather intractable for the time, given the primitive state of our recording equipment and our own insensitivity to

the need for non-polarizing electrodes. Nonetheless I am grateful to Ray for his patience and the opportunity to share ideas.

The McCulloch laboratory was dominated by Warren whose broad interests and almost poetic approach to the brain set a tone, if not exactly a work program, for us all. He was famous for his rejoinder to those who could not follow his ideas—"Don't bite my finger, look where I'm pointing." A group of equally interesting younger workers surrounded him and tried to match experiments to his ideas—men such as Jerry Lettvin, Paul Dell, Pat Wall, Turner MacLardy, and the mathematician Walter Pitts—all of whom were productive on their own. I can still see Warren's tall, somewhat stooped, tweed-clad figure striding the halls of the basement lab, talking animatedly to anyone who would listen. He provided me with a unique introduction to the world of brain research. (Note that the term neuroscience was not to come into existence for another 10–15 years.)

In selecting an area for my own first neurohistological research project, my discussions with Ray Snider and Warren led to the brainstem reticular formation. Horace W. (Tid) Magoun had just departed from Chicago (to everyone's astonishment) for the west coast to become the Chair of Anatomy at the new UCLA School of Medicine and had left as his legacy exciting new ideas on the role of the reticular core of the brainstem. With Ruth Rhines (Rhines and Magoun, 1946) he had demonstrated the downstream modulatory control exerted by the core on spinal mechanisms. Working with Giuseppi Moruzzi (Moruzzi and Magoun, 1949), he had shown the role of the core in controlling cortical excitability and, by inference, levels of consciousness. Little was known of its internal structure and connections save what Cajal (Ramon y Cajal, 1911) had shown about the former and Papez (Papez, 1926) using the venerable Marchi method, about the latter. It seemed like the ideal subject matter for a psychiatrist seeking substrate!

Space was made for me "upstairs" in the neuropathological laboratory of Dr. Ben Lichtenstein, where I experienced the initial emotional highs and lows that the notoriously fickle Golgi method could trigger. But, when it worked, it was beautiful and it took me into a new world—the world of neuropil. Then, and for some years thereafter, I did all of my own cutting and processing and, in retrospect, these were the most enjoyable of my research years. One literally *knew* each section as it came off the microtome and carried it individually through the processing fluids. There was nothing quite like the excitement of "that first look" while the mounting medium was still wet, to see what surprises might lurk therein. Because each Golgi impregnation showed, at best, a small vignette of the neuropil fields that lay before one, reconstruction of the architecture of the entire field was truly a cognitive enterprise—a great spatial reconstruction based on the synthesis of image fragments and intuition. I have worked subsequently with

other techniques such as evoked potentials, extra- and intracellular microelectrophysiology and immunohistochemistry, but I know of no excitement and satisfaction such as that offered by the Golgi method. It represented a kind of melding of science and art that seems to have less place in today's research.

During our first 5–6 months in Chicago my wife Mila, a talented and sensitive psychotherapist, worked as a psychiatric social worker at the Great Lakes Naval Training Station, north of Chicago. Poliomyelitis struck her in December. She survived with moderate sequelae but a long delayed postpolio syndrome (not recognized in those pre-Salk and Sabin days) took its eventual toll. During her long recovery, she became increasingly interested in the neurohistological work that I brought home to be close to her. With an old, late 19th century sliding microtome that I had bought from a German refugee scientist, we set up a tissue processing “line” on the dining room table. Mila learned fast and thus began a collaboration that was to continue for some years while her health permitted. Because she did not read French, I began to translate relevant portions of the Cajal *Histologie* for her until, over the years, we had a considerable portion of the two-volume classic in accessible (if at times somewhat stilted) English. More recently, the job has been accomplished with elegance by the Swansons. By early spring, we felt that we might have enough data to present and, because Mila now seemed well enough to travel, we sent our abstract to the American Anatomical Society, which met in Detroit in 1951 (the Society for Neuroscience did not yet exist). It was a fairly primitive description of dendrite fields in the medullary reticular formation but it did give us the chance to see and hear many of the prominent people in our new field. It was a particular thrill to meet Dr. Magoun, who expressed interest in following our work.

As the work on internal architecture of the reticular core proceeded (along with many sideward glances at the seductive cerebellar cortex), it became clear that we could not tell where the downstream effects carried by the reticulospinal tracts, as earlier defined by Papez (Papez, 1926), were implemented. The Marchi tracking method used by Papez became silent when the terminal, nonmyelinated parts of each axon were reached, and the Nauta methods for impregnating degenerating presynaptic terminals were still several years in the future. While searching, I found in some obscure source that now eludes me reference to a staining method devised by Rasdolsky that was supposed to polychromatically stain degenerating terminals. If this could be made to work, we could throw light on how the descending Magoun and Rhines effects were implemented.

With this as our goal, I arranged with the technician in Warren's lab to have a sterile setup in the operating room ready for us at the end of the working day. Mila and I would come down after 5 PM when the coast was clear and make lesions in appropriate sites of the brainstem of a series

of cats. Finishing by 10 PM or so, I would then take my wife out for a Chinese dinner, our cat still sleeping off its anesthetic, well swaddled on the back seat of the car. Thus each recovering animal got several days of home attention and personal nursing, while our apartment built up a backlog of fleas. The Marchi technique provided few difficulties but the Rasdolsky counterstain refused to work, so nothing new was found.

Among the distinguished faculty then working at Illinois Neuropsychiatric Institute were the neuroanatomist and then editor of the *Journal of Comparative Neurology*, Gerhard Von Bonin, and the neurocytologist-neurosurgeon, Percival Bailey. Both of these men had the patience to sit through my one and only presentation in Warren's lab and both were supportive. Dr. Von Bonin told me he would like me to read a manuscript that had just been submitted for publication(!), and Dr. Bailey complemented me on having "sitzfleisch." I am very grateful to both of these men, for their encouragement and support over the years.

Although I now had a National Institutes of Health (NIH) fellowship and planned to work for a full 2 years in McCulloch's laboratory, it became clear to me that we must not spend another winter in Chicago. The painful muscle spasms that had characterized the early phase of Mila's polio, unaccountably continued and were exacerbated by cold weather. At Dr. Magoun's invitation, I made a quick trip to California but felt that there was, as yet, no lab space where Mila and I could work together. The medical center was still a large excavation in the hill overlooking Westwood, and Magoun's group traveled all the way to Long Beach several times a week to do their experimental work. The only other direction to seek a warm climate was south and after a bit of looking, I decided on the University of Tennessee Medical Center at Memphis. Here I was fortunate enough to be given joint appointments in the Departments of Psychiatry and Anatomy, and Mila and I were given our own small laboratory. Drs. Theron Hill, Chair of Psychiatry, and Roland Alden, Chair of Anatomy, saw to it that we had what we needed to start work until our first grant came through.

In Memphis, I worked on my psychiatric ward all morning, then joined Mila during the afternoons and evenings in the laboratory. This was a time of intensive work and continuous excitement. In addition to drawing the relevant Golgi material, I did all of our own photography including development and printing, both in black and white and in color. As we pushed ahead slowly with the reticular core, trying to understand the patterns of axonal neuropil and the distribution and length of axon trajectories, it became clear that the reticular formation was not rich in short-axoned cells as generally believed. In fact we found none. Local collateralization seemed to account for "neighborhood circuitry." At the same time, adjacent structures often stained brilliantly and as a result, our first two full-length papers were on the cerebellar climbing fiber (Scheibel and Scheibel, 1954) and the inferior olive (Scheibel and Scheibel, 1955) The latter became the

basis for a Master of Science degree in Anatomy that the University of Illinois awarded me early in 1953. The former described one of Mila's earliest findings, a climbing fiber collateral to the large Golgi type II cell of the cerebellum. John Szentagothai saw our paper (they were both published by Von Bonin in the *Journal of Comparative Neurology*) and generously coined the name "Scheibel collateral." Collaterals were also found extending to basket and stellate cells, thereby appreciably expanding the influence of climbing fiber input to the inhibitory systems of the cerebellar cortex. The reticular core material slowly matured and at the next American Anatomical Society meeting, Mila and I gave our only "back to back" presentations. She talked about patterns of axonal output and I about input. I think that the concept of "the Scheibels" first took form here and became a cherished part of our life together as long as she lived. Although we did not think of Memphis as our final home, it provided us with experience on how to manage a simple laboratory operation and gave us the time to think and work together. But, unknown to us, other things were brewing.

Overseas

To my great surprise, I received a letter from Percival Bailey, suggesting that we consider a Guggenheim Fellowship year overseas, and the intimation that he would support our application. This remarkably generous offer was too good to miss, even though I had some concerns as to whether Mila could handle the day to day stress of a foreign lifestyle. Feeling that our greatest need was some electrophysiological experience to enable us to begin to correlate our anatomical data with function, we applied to work with Ragner Granit at the Royal Caroline Institute in Stockholm. Granit suggested rather that we should work with his young anatomist colleague, Bror Rexed, who had recently described the laminar organization of the spinal grey matter. This would not have supplied the research need we were trying to fill, and at the same time, I began to realize that living in Stockholm would not be unlike living in Chicago, from whose rigors we had recently escaped. Looking southward again, an obvious solution presented itself. Moruzzi, in Pisa, who had worked with Magoun on the ascending effects of the reticular core, was now pursuing extracellular microelectrode techniques—exactly what we needed to have. Moruzzi cordially accepted us for the next academic year.

On our way to Pisa, we stopped at Madrid and made our sentimental journey to the Cajal Institute. We carried with us a bag of our own Golgi photographs and drawings. The Institute was empty, except for the diener, a cordial young man named Pedro Manzano who, it turned out, had grown up literally at the master's knee and was a pretty fair neurohistologist on his own. When we showed him what we had brought, he warmed even more, addressed us as "maestro" and immediately brought out sheathes of

original drawings by Cajal. To cap the climax, we were allowed to study some of Cajal's Golgi stained material, using one of the master's microscopes. Most surprising to us was the beauty and vibrancy of the slide sections, some of them certainly 40 or 50 years old. It was an experience never to be forgotten. I might add that some 35 years later when Marian and I were in Madrid, and made another sentimental journey to what was left of the Cajal Institute, we were greeted by a dignified old man—Pedro Manzano—still shepherding the remainder of Cajal's magnificent legacy.

We arrived in Pisa in late August and found lodgings in the Hotel Victoria where we had the option of rooming in the "old wing" or the "new wing." Because the former had been built in the 14th century and the latter in the early 16th, we opted for the latter. Our picture postal card view, of the "lung-Arno"—the sweeping curve of the Arno river—was certainly the crowning attraction of our little room. Pisa, a university town of some 80,000 people, was still recovering from the recent war. Feelings ran high against both Germany and the United States and most of the bridges across the Arno were graffiti-decorated with great signs demanding "a basso, bomba atomica" (down with the atomic bomb). Moruzzi's Institute was located about a half mile from the hotel, somewhat beyond the Scuole Normale where Galileo had worked more than 300 years earlier. The Institute was situated in a four-story palazzo with marble floors, great staircases, and an amphitheater. Our coworker and staff member, Amilcare Mollica, seemed to feel we were preferable to the previous Institute visitor, a young German investigator named von Baumgarten who, as a former Luftwaffe pilot, Mollica was convinced, had carried out strafing runs over Pisa during the war. Our mutual project was to work out patterns of convergent input upon brainstem reticular cells using extracellular microelectrode recording techniques. Starting as we did at the beginning of September and operating on three or four cats each week, it took until December before we managed to obtain useful data. In retrospect, it is hard to account for our problems because, by today's standards, the experimental approach was very simple.

It was a great day in September when Moruzzi, *Il Professore*, returned to the Institute. He was a large man and we all watched with interest from the upstairs window as he slowly unfolded himself from his tiny Fiat, an unusually small car known locally as a "topellino" or "little mouse." Actually we had rather restricted contact with him during the year, except in the late spring when we worked together on the preparation of our manuscript. One exception to this was when he descended from his upstairs living and working quarters to perform, with almost ritual gravity, the decerebration procedure that he had learned from Bremer some years earlier and that allowed recording experiments to proceed without further anesthesia. A long series of expired cats soon taught us to perform the decerebration quietly without professor's participation. The microelectrodes were flexible

insulated wire of 12 or 37 micra, inserted by hand with ivory-tipped forceps. This laborious method was used instead of rigid microelectrodes because of our concern with respiratory and cardiovascular movements transmitted to the brainstem.

By spring time, it had become clear that each reticular neuron was the center of a widespread convergent pattern of inputs from ascending sensory systems, from brainstem and cerebellar neurons and in many cases from cerebral cortex, and that the "mix" of afferents on each cell was, so far as we could tell, idiosyncratic. The manuscript went through four or five drafts before we all reached agreement on its contents and it could be sent off to the *Journal of Neurophysiology* (Scheibel et al., 1955). Moruzzi's rigorous approach to data analysis proved a powerful learning experience. While at the Institute, we developed a rapid 2- to 3-hour histological method for establishing the position of the recording microelectrode tip. Because the usual procedure took several days and the new method gave consistently useful results, Moruzzi encouraged us to publish the method (Scheibel and Scheibel, 1956).

During the short winter break, we traveled north through Europe to visit several research centers. Most memorable was our several days spent with Oscar and Cecile Vogt at their institute in the Black Forest. Here, for the first time we saw what appeared to be neurohistological correlates of certain cognitive abilities. This became the germ for an entire program that I mounted in our own laboratory many years later. Before we left this picture-book setting, the Vogts paid us the ultimate compliment of asking us to stay, learn their methods, and assume direction of their institute when they retired. Although we felt we could not do this for many reasons, the warmth and generosity of their offer will always remain in my mind.

Our most powerful personal experience by far during our time in Pisa was meeting Alf and Inger Brodal from Oslo, who visited the Moruzzi Institute for a couple of weeks in the early spring. Alf, Inger, Mila, and I struck up an immediate friendship, a kind of elective affinity, which developed over many a lunch or dinner together, cooked in their little downstairs Institute apartment over a one-burner gas stove, and flowered during a short but memorable Roman holiday weekend. As a result, we joined Brodal the following August at the Neuroanatomy Institute in Oslo (after short visits to Denise Albe-Fessard in Paris and Turner MacLardy in London). Working in the office of Fred Walberg, Alf's young colleague, we tried to synthesize the Oslo school's data on inferior olive derived from Gudden and Gleys methods with our own Golgi material (Scheibel et al., 1956). The results were not particularly significant, but the relationship was, and our personal and scientific friendship became lifelong.

By the time we returned to Memphis, Magoun had formally invited us to join him in California. As a result, we pushed along our research program, and I taught almost continually to make up for the time we had

spent in Europe. During this short time, we tried to formulate our thinking on the role of oligodendroglia after demonstrating small numbers of axon terminals on the surfaces of many of these glial cells. These data were presented at what I believe was the first symposium devoted to neuroglia. It was chaired by William Windle at the NIH in the spring of 1955 (Scheibel and Scheibel, 1957). Transmission to oligodendroglia of samples of information inputs to neighboring neurons still makes good sense to me but I know of no further development of these data¹.

California

California really was the new world. We were surrounded by a group of enthusiastic, young neurophysiologists and neuroendocrinologists, all assembled in the new Department of Anatomy, all attracted by the combined magic of a dynamic new medical center and “Tid” Magoun. I was particularly happy to have a joint appointment in the Departments of Anatomy and Psychiatry, which allowed me to maintain at least some contact with my clinical specialty. Norman Brill, the new Chair of Psychiatry, and Magoun showed us our “digs,” the west wing of a World War II vintage bachelor officers quarters (boq) on the nearby Brentwood Veterans Administration Hospital grounds. The east wing was already occupied by the neurophysiologist Jim Olds who had recently described the positive and negative reward centers of the brain. The north wing was the domain of Sam Eiduson and his biochemistry group, involved with the relatively new amine, serotonin. With a large animal room in the center, our little converted barracks, Bldg. T 45, formed what was probably the first research institute at the center. Of course we were hot in summer and cold in winter, but we had space, and the opportunity for collegial interaction when we needed it. Crude and rickety as it was, I still look back to the almost 7 years of our occupancy of T 45 as a very special time.

It took time for us to assemble the material for a functioning electrophysiology laboratory, but Golgi neurohistology is less demanding of equipment and we were soon in operation. In this first couple of years, while trying to get used to the idiom and lifestyle of southern California, we began to establish the major features of reticular formation neurons. We were surprised at the axonal extent of large reticular cells. Some had bifurcating axons projected caudally into the spinal cord and rostrally into the diencephalon and even beyond, an enormously diverse topography on

¹Recent communications by Bergles and colleagues (*Nature* 2004;405:187–191; *Nature Neurosci.*:24–32) have described GABAergic and glutamergic synapses on oligodendrocyte precursor cells in hippocampus that are reminiscent of our own observations of synaptic terminals on oligodendrocytes in newborn animals.

which to exert their effects. We were also surprised at the extreme degree of rostro-caudal compression shown by the dendrite systems of many reticular neurons. Their fancied resemblance to horizontally oriented stacks of poker chips led us to the idea of modularity. This may have been the origin of the module concept of organization of the nervous system, which is now quite familiar. These observations formed much of the basis for our presentation at the Henry Ford Symposium on Reticular Formation of the Brain that was held in Detroit in 1957 (Scheibel and Scheibel, 1958). Our talk followed an elegant presentation by Walle Nauta and Hans Kuypers (Nauta and Kuypers, 1958), which demonstrated the correlative power of their axon tracing techniques with ours, revealed neuropil patterning. We were very flattered, although not tempted, when right after the presentation, Ralph Gerard asked us to consider moving to the new institute he was developing at Michigan.

One of our first attempts at physiological analysis involved following the development of cortical and subcortical electrical rhythms in very young cats. We surgically implanted arrays of surface and depth electrodes in postnatal kittens and followed them through the next few weeks of their lives, combining multichannel electroencephalographic recording and behavioral observation. Tentative correlations were established between cortical activation patterns and discriminative responses to sensory stimuli with neurohistological patterns as revealed by Golgi impregnations. We were particularly intrigued by the very large amplitude delta waves from deep medial temporal sites that accompanied the first moment or two of suckling by the hungry animal. As satiety approached, the waves disappeared. Because we chose the poetic but otherwise inopportune name of "pleasure domes" for these waves, it was probably just as well that we published only in the bound proceedings of several meetings rather than in a peer-reviewed journal (Scheibel, 1962).

In exploring the activity of individual reticular neurons to repetitive stimulation in immobilized, locally anesthetised adult cats, we discovered how quickly such elements habituated to a familiar signal. It was clearly not a fatigue phenomenon because a slight change in the input completely restored the original intensity of response. Clearly, our cells loved the original and unexpected and were progressively "turned off" by the familiar and humdrum (Scheibel and Scheibel, 1965a). In doing this study, we found that we were recording from individual neurons for increasingly long periods of time (up to 9 hours) and, because of this, a new and unexpected property of reticular neurons was noted. Cells appeared to cycle through alternating periods of sensitivity and insensitivity to various sensory inputs. The most usual pattern we found in the relatively small number of cells that we could follow for very long periods was alternation between responsiveness to an exteroceptive stimulus from the body surface followed by responsiveness to an interoceptive stimulus such as respiratory movements or other slow

endogenous rhythms. We followed a few of these cells through as many as three cycles of responsiveness, and it seemed fairly clear that the succeeding patterns were mutually exclusive. It was almost as if some (hierarchically higher?) pacemaker control system was manipulating the responsiveness of groups of reticular cells alternately to the outer and inner worlds. We wondered whether this might be a mechanism to prevent individual neurons from being drawn increasingly into the input-output transactions of single neural domains (Scheibel and Scheibel, 1965b). There were several fascinating theoretical aspects to this possibility that we wished to explore. Unfortunately, rapidly increasing health problems made further work impossible for Mila. This was the last study that we shared in the laboratory.

While involved with these single unit studies, I remained all-too-aware of the statistical insignificance of the individual neuron and thought a great deal about problems involved in sampling simultaneously from a larger cell population. With this in mind, I designed several microelectrode yokes for holding small clusters of microprobes, the individual elements within 400 to 500 micra of each other. The earlier designs moved the cluster as a unit. The final model allowed individual control of each electrode. Although it was possible to capture and record units with one or two of the electrodes, the tissue distortion produced by penetration of an adjacent probe sometimes caused loss of an already captured unit. Early results were moderately encouraging but our personal situation made further work in this direction impossible. Multiple simultaneous unit recording is only now becoming a reality to the neurophysiologist.

In a very different vein, I can remember having a number of discussions with a faculty colleague from neurology, Charles Markham, on the role of the reticular formation in controlling the vestibulo-ocular reflex arc. Charlie was interested in this system and went on subsequently to do outstanding work on the role of motion-induced eye movements in the selection of astronaut and cosmonaut candidates. Out of our discussions developed a research study, which included another colleague from psychiatry, Ronald Koegeler revealing the unusually powerful suppressive effects of basal ganglia stimulation on saccadic movements (Scheibel et al., 1961). At about the same time, another colleague from psychiatry, Fred Worden, was visiting the laboratory to learn neurohistology. Fred would come to the laboratory and park his new Bentley next to Charlie's vintage Rolls Royce and Ron's vintage Jaguar. I distinctly remember parking my Ford behind another laboratory building lest I destroy the effect!

Tid Magoun had struggled for 10 years to make his dream of a Brain Research Institute a reality. When it finally came to fruition in 1962, all of the outlying UCLA neuroresearch programs including ours were called in to take their places in the new laboratory space. By then, I did not want to move, having been spoiled by a couple of thousand square feet of

research space and the relaxed camaraderie of our little *troika* with Jim and Sam. Nonetheless, the Veterans' Administration facilitated our departure by announcing plans for immediate destruction of the boq buildings. They were as good as their word and today the site of our old lab remains a parking lot.

With Mila's continued illness, a new life pattern developed that was to last until the end of her life 14 years later. Because I wished to spend as much of my time with her as possible, it became necessary to find a full-time neurohistology technician who could provide us with the Golgi-stained material needed for further work. We were unusually fortunate in finding Miss Lore Liepmann who came out of semiretirement to work with us for some years until she left for permanent retirement in Sweden. Although I very much missed the thrill of shepherding each section through as I always had, Lore's contribution to our work was of incalculable value and I remain deeply in her debt. I learned to do virtually all of my research at home, going "downtown" only to give my lectures, check out the students, and receive more material for Lore. During the next decade and a half, we were also fortunate in having a group of gifted younger colleagues do their doctoral work in the laboratory. To mention only two, Larry Stensaas and Eugene Millhouse were both talented and a continual delight and they have remained my friends over the years. Larry did a seminal study on the development of the hippocampus (Stensaas, 1968), which is frequently quoted today, and Gene's Golgi analysis of the internal structure of hypothalamus (Millhouse, 1979) has also maintained a prominent place in the literature.

The following years, although physically and emotionally demanding, were productive of a number of insights. It had seemed wise to widen our neurohistological horizons so that other neuropil patterns in different parts of the nervous system might give us yardsticks against which we could compare the patterns characteristic of the reticular core. The spinal cord, although sometimes considered the "simplest" part of the Central Nervous System (CNS) immediately became a challenge and a delight. I will mention only two of the many observations that intrigued us.

Renshaw cells were a term given by John Eccles to a supposed group of short-axoned elements near the motoneuron pool. They were considered to be the necessary intercalated substrate for inhibition and by extension became the term applied to any short-axoned cell in the CNS whose role was believed to be inhibitory. Careful study of our Golgi material failed to reveal any short-axoned cells in the spinal grey matter (Scheibel and Scheibel, 1971a). We found many spinal interneurons, of course, from whose axons emerged collateral systems that played back over motoneurons. We were forced to conclude that these collateral extensions of typical long-axoned projecting interneurons were the only possible candidates for the Renshaw role (Scheibel and Scheibel, 1971a). Our interpretation was later born out by both anatomical and physiological studies in other laboratories.

However, our finding so troubled Eccles that he refused to write or speak to us again, a really painful loss because I had had the chance to meet and speak to him only a few years earlier, on his return from Stockholm and his Nobel Award and we had corresponded since then.

While studying motoneuron dendrite systems in transverse and sagittal planes of section, it became clear that in the latter, dendrite systems tended to be organized in tight clusters we called bundles (Scheibel and Scheibel, 1970). It was well known that motoneuron somata arranged themselves in exclusive groupings, muscle by muscle. But once the dendrite stalks started streaming rostrally and caudally, it seemed almost as if they sought contact with dendrites from nuclei other than their own. Dendrite bundles were subsequently found in other sites including the cerebral cortex and brainstem. We literally stumbled across the apparent plasticity of these dendrite bundle complexes when we had the chance to compare samples of adult rat reticular core with those from neonatal animals. Since the time of Cajal, it had been well known that the rapid Golgi method is most effective in very young animal tissue and rapidly loses its sensitivity with the development of myelin. Accordingly, most of our work had been done with the brains of animals in the first 10 days to 2 weeks of life. While trying to perform the Golgi stain on coronal (cross) sections from young adults, we were pleased to find a small number of effective impregnations of the lower brainstem. We were surprised with the result. In the postnatal animal, reticular cell dendrites radiate out freely into the surrounding neuropil and are generally spine covered. In the mature animal, we found that the dendrites had lost their spines and were grouped into bundles similar to those we had seen in spinal cord. The dramatic loss of spines suggested a fundamental change in the wiring pattern of these dendrite, while the unexpected reorganization into bundle complexes suggested equally dramatic alterations in the mode of dendritic operation (Scheibel et al., 1973).

The functional role of these enigmatic structural complexes continues to elude us. Among several other possible interpretations that were made over the next few years, we suggested that they might conceivably provide a site—an intrafascicular micromilieu—for the laying down of central programs coding output patterns peculiar to the neural structure; in other words, a possible site for memory storage (Scheibel and Scheibel, 1975). Although supportive data for this supposition has not developed, there is a small but growing literature on dendrite bundles that keeps the issue alive—a structural paradigm in search of a function.

Our studies of the thalamus, which extended over a period of more than 5 years, presented some of the most enjoyable and the most challenging problems we were to face in examining the fine structure of the CNS. The range of neuropil patterns found in the many nuclei that make up the thalamic complex is remarkable as is the diversity of their input and output connections, the nature of their interactions with each other, and

the details of their relations with cerebral cortex. The neuroanatomical building blocks in the field at that time were the structural descriptions of Cajal (Ramon y Cajal, 1911) and the connective studies of A. Earl Walker (Walker, 1938) with additional contributions from O'Leary on the lateral geniculate (O'Leary, 1940) and Herrick on the diencephalon of the tiger salamander (Herrick, 1948). The sheer beauty and diversity of the systems we saw resulted in a number of contributions of which two come particularly to mind.

The importance of the thalamic intralaminar (nonspecific) systems had been recognized for more than 20 years as central to thalamocortical substrates of consciousness and patterns of sleep-wakefulness. Our reconstructions based on thousands of Golgi-stained preparations were able to picture the actual course and relations of such fiber systems, both thalamocortical and corticothalamic. The latter, in particular, with their idiosyncratic and convergent terminal patterns suggested circuit architecture reminiscent of that in contemporary computer systems (Scheibel and Scheibel 1967a, 1971b). The role of the nucleus reticularis thalami (Cajal's "noyau grillage") had remained enigmatic for many years. Literally wrapped around the outer surfaces of the thalamus, separating it from the immediately adjacent internal capsule, it had been considered by many investigators (although not all) as the last link on the pathway from upper brainstem to cerebral cortex. Our Golgi studies showed that virtually all reticularis cell axons projected caudally onto thalamic and mesencephalic neurons and that all thalamocortical and corticothalamic axons traversing the nucleus reticularis made collateral connections with these cells (Scheibel and Scheibel, 1966, 1967a). A plausible interpretation for these connections involved a feedback control system, probably inhibitory, interposed between thalamus and cortex, thereby controlling the nature of thalamo-cortico-thalamic intercourse. Subsequent physiologic investigations documented the inhibitory effect of reticularis cell bursts (Schlag and Waszak, 1970), while immunohistochemical studies demonstrated the GABAergic nature of reticularis cells (Houser et al., 1980). It was subsequently shown that prefrontal cortex also had access to these gating cells (Yingling and Skinner, 1975) and so the potential for voluntary control was added, at least by inference, to the mechanisms of cortical input gating. This cluster of findings with their implied relation to selective attention, hypnosis, and placebo phenomena have given me a good deal of satisfaction over the years.

During this time, a young physician named Al Globus joined the laboratory. He had been in medical practice for several years but decided the time had come to take a *wanderjahr*. Although he had had no research experience, I liked his sense of adventure and his obvious interest in neural substrate. Al stayed with us for a couple of years and our mutual interest in axodendritic topography resulted in several reports identifying the sites

of termination of a specific thalamocortical sensory influx (in this case the visual system) (Globus and Scheibel, 1967a) and also of corpus callosal fibers (Globus and Scheibel, 1967b). Synaptic coupling sites proved to be quite specific. Most surprising to us was the fact that, in the rabbit at least, primary sensory fibers entering cortex terminated principally on the apical shafts of fifth layer pyramids as they ascended through layer 4. Although we could not rule out some contacts on the layer 4 stellate cell population, they seemed not to be the primary postsynaptic receptive element as perceived wisdom dictated. Callosal fiber terminations, on the other hand seemed sharply limited to the oblique branches of pyramidal cell apical shafts. The studies were based on the placement of small lesions in the presynaptic path, followed by study of dendrite spine distortion or loss in the target synaptic zones. More elegant and revealing techniques are available today and should be used to reevaluate these findings that are of considerable importance in understanding dendritic computational mechanisms.

Another interesting laboratory colleague was Robert Lindsay, an early trainee in the new field of neurocomputation. The orientation of our work had always been in the classic qualitative and descriptive mode but I felt that time and new technology suggested the necessity of becoming more analytic and quantitative. To prepare for Bob's arrival, we bought a state-of-the-art Digital PDP 8 computer, a floor standing monolith with rows of flashing lights and a large tape deck mounted on its front surface. Bob rapidly "tamed" the new artifact and the eventual result was a couple of reports describing in semiquantitative terms some relationships between dendrite length and branching number (Lindsay and Scheibel, 1974). From my own naive point of view, it appeared that the mountain had labored and produced a mouse. In retrospect, I feel that if I could have provided conceptually sophisticated leadership, more might have come from this approach. With today's highly automated instrumentology, such studies are routine.

I must speak also of David Brunswick, never a member of our laboratory and yet very much a part of our lives at that time. David had taken his degree in physiology with Cannon in the early 1930s, then gone to Vienna for personal analysis with Freud. Returning to Los Angeles just before World War II, he rapidly became an accepted and practicing member in the local psychoanalytic community. Unlike most of his colleagues, he remained interested in possible neurophysiological substrates of the psychodynamic concepts he dealt with each day, and so he found his way to our laboratory on the Veterans' Administration grounds. David was a short-statured, almost child-like man with penetrating insights and a straightforward manner. I think he lived for the day when Mila's health would improve to the point that I could return full time to the laboratory and start some experiments with him on the role of hypothalamus in the id instinctual impulses. That time, unfortunately, never came. By the time I was able to return

full time, David had passed away, but the memory of his gentle, enquiring nature and unfailing patience will live with me.

During the long period of Mila's illness, we were on occasion invited to participate in meetings. With perhaps two exceptions, we were unable to attend, but I was unwilling for our work to be omitted. Several alternatives were practiced. Most frequently, I sent our manuscript to the editor or meeting chair who was usually gracious enough to publish our contribution along with those that had been presented. On one occasion, I remember a manuscript written for a New York Academy of Sciences Meeting, which we entitled "The Anatomy of Constancy" (Scheibel and Scheibel, 1977). For various reasons a great deal of personal feeling became invested in this work, so much so in fact that we started the manuscript with a biblical quotation from the Book of Ruth:

"Whither thou goest, I will go;
and where thou lodgest, I will lodge."

Perhaps there were some presentiments of the end of our life together. I was, therefore, more than grateful when one of the editors, a colleague of ours, Bernice Wenzel, kindly volunteered to read the paper for us. On another occasion, I literally telephoned the full text of our paper in to one of the symposium editors in New York, reading the text and describing each slide in detail as it was to appear in the presentation. All of this was tape recorded at the other end of the line and copies of the slides were sent on. I understand that the tape and slide show were presented (despite some grumbling from one of the senior investigators at Columbia that it would never work) without a hitch and was applauded and discussed in its turn like any other "live-presented" contribution.

The final 2 years of Mila's life were particularly difficult ones with two episodes of surgery and periods of prolonged physical pain and increasing depression. Just 4 months before her own death, our long time friend and colleague, Jim Olds, died of a massive heart attack. His wife, Nicki, begged us to be with her at the ceremony at Cal Tech to help celebrate Jim's distinguished life and career. It was difficult to refuse her request and so, bundling Mila up, we joined Nicki on a rather dark and blowing November afternoon. I gave one of the tributes for our friend. Mila developed what appeared to be a viral pneumonia, shortly thereafter, with a pattern of hyperesthesia and pain almost like a thalamic pain, syndrome. She died shortly before midnight, on New Year's Eve, 1976.

Adjustment

It was undoubtedly fortunate for me that this was a busy time. In the laboratory, a graduate student, Tom Davies, was finishing a conjoint neuroanatomical and neurophysiological study on the ontogenetic development

of somatosensory thalamus (Davies et al., 1976). A dynamic young physician from Mexico, Jesus Machado-Salas, was completing his thesis study on age-related changes in the brain of the mouse (Machado-Salas et al., 1977). And I was continuing our exploration of the aging and senile human cerebral cortex. In addition, my period of intensive teaching of functional neuroanatomy was about to begin. Daniel Pease, Chair of our Department of Anatomy, kindly suggested that he would find a teaching replacement for me and that I take the quarter off. However, I chose to carry on as best I could and in retrospect, it was the right thing. After profound loss, both body and mind suffer, but an unforgiving schedule may be the most forgiving in the long run.

In the early 1970s, the nature of brain aging, both normal and abnormal, had become a subject of growing interest. With the increase in life expectancy that became obvious in the second half of the 20th century and the swelling number of "senior citizens," a whole range of behavioral and tissue changes were recognized and a new speciality, geriatric medicine, was in process of being born. When I was in medical school in the early 1940s, we were taught that Alzheimer's disease was a rare degenerative brain disease of "old women" and that we would be lucky to see two or three during our entire practice. Suddenly, Alzheimer's disease and other related degenerative syndromes were of major concern. Our old cerebral *bete noir*, senile arteriosclerosis, was losing importance and was being replaced by amyloid plaques and neurofibrillary tangles.

The chair of a planned symposium on the aging brain asked me to present a paper on human age-related cerebral cortical changes. When I told him that I had not done any work in this area, he suggested that with the techniques available in our laboratory, that deficit could quickly be remedied. Taking him at his word, I obtained tissue from the cerebral hemispheres of a group of old patients and studied them with several Golgi modifications (Scheibel et al., 1975). Some of the changes in neuronal and vascular morphology were striking, and this started a program which continued for several years. Some cortical material showed only modest loss of dendritic spines and occasional nodulation of dendrite shafts, while in others, there was obvious loss of dendrite branches, tortuosity of many of the remaining shafts, and progressive swelling and loss of the smooth triangular silhouette of pyramidal cells. In even more advanced disease, the cell bodies that remained were shrunken and distorted and often surrounded by glial cells. The capillary loops of cortical vasculature also looked distorted and nodulated. With the help of scanning electron microscopy, it later became clear that these vessels had lost their normal investment of fine axon fibers and terminals (the pericapillary plexus) and were infiltrated with masses of amyloid. In some places, these had apparently been disgorged, leaving gaping holes in the vessel wall (Scheibel et al., 1987). Inadequacies of the histories that accompanied some of the older

tissue specimens and the largely nonquantitative nature of my approach resulted in an initial impression that pathological changes of this sort were an invariable concomitant of the aging process. It took several years and some quantitative studies such as those of Conner and Diamond in aging rat cortex (Conner et al., 1982) and those of Paul Coleman in human material (Buell and Coleman, 1979) to separate out phenomena of "normal" from "abnormal" aging.

One interesting variant of this pattern was picked up in the relatively small number of familial presenile Alzheimer's disease specimens that we examined. Although the dendrite systems of neocortex and archicortex (and in some cases, even cerebellum) were ravaged, there were numerous localized areas of explosive new growth, small clusters of newly developing, spine-covered dendrite tissue appearing almost like the "last gasp" of a dying dendritic system (Scheibel and Tomiyasu, 1978). I have never seen this phenomenon in any other type of tissue and can only imagine that it represents attempts at restitution by degenerating neurons.

Several of the graduate and postdoctoral students in the laboratory were involved in various stages of this work and I mention them with affection: Taihung (Peter) Duong, Ron Hammer, and Roland Jacobs as well as a group of talented undergraduates. However, none of our work on human tissue would have been possible without a reliable tissue source, and here I express my gratitude to a friend and colleague who, I believe, never stepped into our laboratory. Uwami Tomiyasu was pathologist at the Wadsworth and Brentwood Veterans' Administration hospital and had, over the years, built up and nurtured a brain bank, often over the protests of her administrators. Uwami was always there when we needed human specimens, whether it be epilepsy, aged brain, schizophrenic specimens, or normal controls. She is no longer with us, but maintains her place of honor in our memories and as a coauthor on many of our papers.

The venerable Golgi techniques proved their usefulness again in the study of several other clinical syndromes. The Department of Neurology and the Division of Neurological Surgery at UCLA were among the pioneers in developing surgical programs for the treatment of seizure disorders, particularly complex partial seizures (temporal lobe epilepsy). Following the program model initiated by Wilder Penfield at Montreal some years before, this provided an opportunity for both treatment and research. Our neurosurgeon at that time, Paul Crandall, was often able to make block resections of medial temporal lobe tissue, which provided precious opportunity to look for neurohistological substrates of the ictal process. In the limited number of specimens that we received, it was possible to identify a group of degenerative changes in neurons of prosubiculum and hippocampus (particularly CA 1), including loss of dendrite spines, nodulation and distortion of dendrite shafts, total loss of dendrite system, and disappearance of cells. Areas of gliosis were found and on occasion we noted fields of hippocampal

dendrites “bent” toward gliotic areas, presumably because of torsion and shrinkage produced by the glial scars. An unexpected finding was the frequent presence of small aneurysmal outpouchings on the capillary plexus, a Golgi-based observation that we later confirmed with scanning electron microscopy (Scheibel, 1980). The amount of pathological change appeared related to the length of disease history, thereby suggesting a progressive course. The etiology and pathogenesis of mesiotemporal sclerosis remain enigmatic but disturbed neuroembryogenesis must still be considered along with a number of genetic, perinatal, and postnatal insults.

For a number of years I had served as a psychiatric consultant at Camarillo State Hospital, giving lectures to the resident physicians and seeing patients whom the staff were especially anxious to present. As in the case of most state institutions at that time, the patient population included a broad spread of psychiatric illness but schizophrenia, in its many manifestations, represented the largest fraction of the patient population. For much of the first half of the 20th century, schizophrenia was believed to be a “functional psychosis” based in the supposed emotional turmoil of early family life. With the introduction of chlorpromazine and the first generation of psychopharmacological agents in the mid 1950s, interest began to develop in a candidate’s underlying organic mechanisms. Of these, the “dopamine hypothesis” was the model most frequently invoked. I had become intrigued by certain clinical similarities in the symptomatology of patients with temporal lobe epilepsy and those with schizophrenia. For this reason, I was more than interested when, in 1975, the retiring director of Camarillo, Philip May, tipped me off to the fact that the hospital was about to discard the collection of material from its brain bank. Some of the material was still in good condition and I was able to bring back to the laboratory perhaps a dozen “schizophrenic brains” and an equal number of specimens from patients with other syndromes, which would serve as our “non-schizophrenic controls.”

Golgi analysis of the schizophrenic material revealed unexpected findings in the hippocampus. The usually precise arch of the cornu ammonis with its regular files of hippocampal pyramidal cells was disturbed. Ordinarily, the pyramids and their apical shafts are aligned in soldier-like arrays. In these specimens, the cells and their shafts appeared spatially disorganized, pointing in all directions. This anomaly of organization was present in all 8 of the brain specimens that could be processed but absent in the 10 non-schizophrenic control brains. I was familiar with the fact that the literature already contained some reference to schizophrenia-related pathology including decreased brain size, enlarged ventricles, and gliosis and cell shrinkage in the basal forebrain. However, these hippocampal findings appeared to be the most specific yet described and I realized that the pathology might also provide clues to pathogenesis of the syndrome. Nonetheless, Mila’s increasingly severe illness and the imminence

of two surgical procedures took precedence and the work was put aside. The findings were finally organized for presentation a few years later and first aired in 1981 at the Society for Biological Psychiatry Meeting in Chicago (Scheibel and Kovelman, 1981). The amount of cellular disarray was immediately obvious but the results were admittedly descriptive and qualitative. I was joined in this endeavor by Joyce Kovelman, a graduate student who had recently entered the laboratory and chose to make this finding the subject of her doctoral thesis work. Joyce, a hard-working and talented student, agreed that we should develop another series of hippocampal specimens from schizophrenic brains and subject them to quantitative analysis, thereby providing a more rigorous statement of the amount of disarray affecting the hippocampal cell ensembles. This group of brain specimens was obtained from the Veterans' Administration Hospital brain bank. The histories of these patients suggested more fluctuating disease courses, unlike the profoundly ill, lifelong hospitalizations that had characterized the first group of patient material that I had received from Camarillo. Perhaps as a result, the extent of hippocampal pyramidal cell disarray seemed less severe, suggesting a spectrum of pathology reflecting the severity of the underlying disease. Nevertheless, the Nissl-stain based measurement paradigm developed by Joyce revealed significance differences between schizophrenic patients and non-schizophrenic controls particularly in the anterior third of the hippocampus or "pes" (Kovelman and Scheibel, 1984). Because of the size of the study and the difficulties involved in measurement and recording during those precomputer days, only left hippocampi were considered. Several years later tissue specimens from the right hippocampus were studied by another graduate student in the laboratory, Andrew Conrad, and similar results were obtained, making it unlikely that the schizophrenic "process" was unilateral (Conrad et al., 1991). We felt some concern that these findings might conceivably be related to the psychotropic drugs to which virtually all schizophrenic patients had been exposed since the mid 1950s. The Yakovlev collection housed at the Walter Reed Army Medical Center in Washington, D.C. provided an invaluable source of stained and mounted tissue from psychotic patients obtained before the drug era. Examination of this material also revealed cell disarray in some schizophrenic patients thereby mitigating this area of concern.

In terms of pathogenesis, several converging lines of reasoning pointed to a fault in neuroblast migration during the early- and mid-second trimester of pregnancy as causal to the hippocampal cell disarray. The process of migration appeared significantly dependent on the integrity of a group of neuronal cell adhesion molecules (NCAMs) whose importance had been initially explored by Gerald Edelman (Edelman and Chuong, 1982). The genetic mouse mutants, "reeler" and "staggerer," served us as putative physical models for the disturbed migrational process, although

not necessarily the etiology. At about this time, discussions with Sarnoff Mednick (personal communication and Mednick et al., 1987) and later reports from Finnish and English research groups underlined the import of maternal influenza virus infection during the early second trimester of pregnancy in subsequent development of schizophrenia in the offspring. In fact, Mednick's data indicated that mothers who had had influenza during their second trimester had a 300% greater chance of producing a schizophrenic child. We were especially struck by the fact that influenza is one of a very small number of orthomyxoviruses possessing the enzyme, capsular neuraminidase, which affects the binding properties of NCAMs. Thus putative links existed between influenza infection and disturbed neuroblast migration, and between the migrational difficulty and schizophrenia. Although there is no reason to believe that maternal influenza infection is the only significant etiologic factor in the development of schizophrenia, it highlights the importance of the period of fetal development in the pathogenesis of this psychotic disease.

Although never a major direction of laboratory effort, work with the scanning electron microscope holds a special place in my heart. Its remarkable ability to demonstrate three-dimensional structure at high magnifications, well beyond those available to the light microscope, made it in some ways another Golgi method, writ large! Several of the graduate students working with us at that time, notably Itzhak Fried and Linda Paul, joined in our studies of hippocampus and cerebellar cortex. However, I think I was most pleased with a short report we published on the apparent nonadhesive nature of axospinous dendritic synapses (Scheibel and Paul, 1985). We were able to demonstrate that after tearing and separating small blocks of brain tissue along natural cleavage planes, presynaptic axosomatic terminals always carried with them a fragment of postsynaptic membrane from the neuronal somal surface, leaving a small pit. However, those terminals pulled away from dendrite spines invariably separated "cleanly" without any evidence of membrane adhesion. We assumed that these observations argued for axo-somatic "hard wiring" and a more temporary and reversible type of synaptic articulation on dendrite spines. This result appeared then—and still appears—to be intuitively attractive in light of other studies that identify the spinous synapse as a "site of learning change."

Early in 1979 I received an invitation from Professor Marian Diamond at the University of California, Berkeley, to give a seminar on consciousness and the reticular core to her neuroscience graduate students. Pleased by this invitation from a colleague I had never met, I made the first visit of my adult life to the fabled Bay Area. Many things combined to make it an unforgettable experience, not the least of which was Marian's dynamic personality and sensitivity. We immediately found a great deal to share, and over the next couple of years our relationship deepened, culminating

in our marriage in 1982. I have been forever grateful for this wonderful gift of emotional and intellectual companionship that came to us both in our middle years. We have continued to work at our respective institutions, maintaining a "commuter marriage," which, I understand, is becoming increasingly common among professional couples. As an extra plus, I have gained a family of four superb grown children, their own mates and a cadre of grandchildren. Clearly, Marian has been a most significant discovery in my life.

Neuropil and Cognition

Possible substrate relationships between neural structure and special cognitive "gift" had first been shown to me by Oscar and Cecile Vogt in their Black Forest laboratory many years before. The idea had remained with me, although the prospect of acquiring brain specimens from the especially gifted remained a daunting enterprise. However, as our laboratory became more adept with quantitative applications of the Golgi methods, an alternative idea presented itself. Why not use the behavioral and cognitive attributes of each individual in such a way that each brain became its own control. Several studies resulted from this strategy, based in the collaborative work of my graduate students, Itzhak Fried, Linda, Paul, Rod Simonds, and Bob Jacobs, undergraduates Jim Slotnick and Linda Kao, and our long-suffering statistical consultants, Alan Forsythe and Sondra Perdue.

Casual scanning of the Vogts' material, 30 years earlier, had suggested to me the presence of a more complex neuropil (the cells seemed farther apart), in sensory receptive layer 4 in the primary visual cortex of an artist with the lifelong gift of eidetic imagery (photographic visual memory). Marian's quantitative studies of the response of rat cortex to sensory enrichment had convincingly shown that enhanced processing loads led to dendritic growth (Diamond, 1988). Accordingly, using Golgi-stained human cerebral cortex, we compared two areas along the primary sensory strip (areas 3, 1, 2), the one receptive to hand and finger input, the other to input from the surface of the trunk. Basilar dendrite systems in the latter area were, as we hypothesized, significantly less complex than those in the former, presumably reflecting the more limited range of sensory input and processing associated with the trunk. Coincident examination of typical prefrontal and parietal association areas (areas 9, 40) revealed complex and idiosyncratic patterns whose significance we could only speculate upon (Scheibel et al., 1990).

In a related study, we compared the dendrite organization of supra-granular pyramidal cells in the left and right opercular zones (Broca's area) in the inferior frontal gyrus with the orofacial area of the motor strip just behind (Scheibel et al., 1985). As we conceived it, the former provided the substrate for language formation; the latter controlled the motor

substrate. We found that dendritic complexity of opercular tissue significantly exceeded that of the motor strip, a finding that seemed appropriate in terms of the presumably more subtle processing problems involved in word selection and organization. "Branchiness" of the dendrite patterns in tissue from the left Broca area exceeded that from the right as we expected with one exception, and this turned out to have been a left-handed individual. However, to our surprise, total dendritic length of the basilar skirts from cells in both left and right hemispheres was comparable. This stumped us until Itzhak had the good idea of counting the numbers of dendritic branches of each order (counting from proximal to distal). We then found that most of the dendrite length in the language dominant hemisphere was made up of higher order (more distal) dendrite branches. Lower order branches constituted the greater part of dendritic arbors on the nondominant side. We soon came to think of the adult dendrite arbor as a temporo-spatial record of dendritic development with these left-right differences in branch length representing differential growth sequences peculiar to the two hemispheres and to the areas involved. We deduced that greater length of lower order branches suggested that areas of right hemispheric cortex might "lead" the left during the first year of life and that as language processing began to develop during the second and third years and beyond, higher order branches might develop more extensively on the language-dominant left side.

Testing this challenging idea became the basis for Rod Simond's doctoral thesis as he studied these language-related areas in an age-graded group of human infant cortices from 3 months to 72 months of age (Simonds and Scheibel, 1989). The results clearly indicated an initial overall right hemisphere advantage in dendrite length until the end of the first year, followed by a more rapid growth, especially of higher order dendrite segments on the left side, presumably as language patterns developed. Careful evaluation of the data revealed another interesting dendritic characteristic. During the process of development, there might be retraction or absorption of some of the earlier dendritic growth (the more proximal segments) as later-appearing branch orders developed. The literature also suggested that in the absence of language development during the critical first 6–10 years of life, adequate language capability and left cerebral dominance might never appear. The interaction of cultural and social factors with the structure of neuropil and the reactive plasticity of the dendritic tree seemed indeed boundless.

Another body of data was provided by the comprehensive study of Wernicke's area by Bob Jacobs who considered a number of factors impinging on dendritic neuropil, including maturation and aging, gender, hemispheric difference, and environment (Jacobs and Scheibel, 1993; Jacobs et al., 1993). Bob did an elegant job. Most exciting here was the apparent relationship between education level and the extent of the dendritic tree.

Subjects with a college and/or graduate level education had significantly more dendritic tissue than those with a high school education, who in turn exceeded those with less than high school education. We assumed that these results were not directly coupled to the level of education itself, but rather to the richness and variety of subsequent life experiences that extended periods of education allowed. It was also realized that an alternative explanation could be entertained, namely that the higher education levels attained by some might be the *result* of their inherently more complex dendritic systems rather than the *cause*. Experiments are more likely to throw light on correlation than on causality. However, several decades of animal-based research have stressed the significance of challenge and enrichment in shaping the cortical microenvironment, thereby lending credence to our assumption.

As I look back on these efforts of ours, and of similar efforts in other laboratories, to identify brain correlates of behavior, cognition, and special gift, it is obvious that we were addressing some of the central problems of neuroscience. These, along with consciousness, sleep and wakefulness, and learning and memory constitute a kind of roll call of honor for the faithful of the profession, the holy grails of ultimate attainment in the brain sciences. Considering that serious research goes back scarcely 150 years, our quest has not been without reward.

Other Aspects of Academia

The triad of research, teaching, and administration has long been the essential underpinning of the academic life. Of the three, I have been most delinquent in the category of administration. I think this reflects, in part, a retiring nature and a reticence on my part to “take charge,” along with a strong sense of devotion to the laboratory and my students. I cannot deny the warm feelings (and surprise) I experienced when in the early 1980s, our beloved medical school dean, Sherman Mellinkoff, asked me to serve with him as Associate Dean, following the sudden death of the former Associate Dean, the much admired Ted Rasmussen. Although I felt totally unprepared for a position like this and told Sherman so, I was also loathe (or too selfish) to leave our then-developing research program on the aging brain. Sherman was a gentle and empathic man and took my refusal graciously, but I have always felt some remorse that I refused him, even though I am still convinced it was the right decision. It was even more unexpected when shortly thereafter, I was asked to have my name put forward for Director of the National Institutes of Aging following the departure of Robert Butler. I appreciated the honor involved in the invitation but was not tempted. The prestige presumably connected with initiating programs at a national level, developing budgets, and testifying before congressional committees

had far less appeal to me than the lure of the next series of brain sections and the secrets they might hold.

The one exception to this pattern developed when, in 1987, the new medical school dean, Kenneth Shine asked me to serve as Acting Director of the Brain Research Institute (BRI) at UCLA. As an early member and advocate of our Institute, I felt a strong sense of responsibility for the organization, as its former director, my long-time colleague, Carmine Clemente, stepped down. While my motivation might have been good, my timing was not, as the state promptly moved into a time of recession and shrinking budgets. After 3 years in the “acting” category, I suggested to Dean Shine that, while I did not particularly care what I was called, I felt that our Institute deserved a “real” director. He took the hint and instituted a search whereupon, again to my surprise, I was asked to continue in office as director. With minimal funding support we instituted a group of programs that might enrich the scope of institute activities while providing us with a higher profile. These included an active outreach teaching program by our students in the community schools (K through 12), the development of a series of interdisciplinary “affinity groups” to encourage transdiscipline interaction amongst our large membership, honorary lectureships (Magoun, French, Eiduson) to bring exciting speakers to UCLA, and monthly laboratory presentations (“Labs on View”) to acquaint all of us with work going on within the institute. During this period, we completely reorganized the curriculum of the BRI’s crown jewel, the Interdisciplinary Graduate Teaching Program (IDP) and the results were encouraging in terms of faculty enthusiasm and student morale. I was fortunate in receiving the wholehearted support of the institute membership as well as that of our small but devoted BRI staff, and could step down in 1995, after completing my full 5-year term, with real satisfaction. The chronic rumblings for “disestablishment” of the BRI were heard no more and the director who followed me, Alan Tobin, with increased financial support from Dean Levey, has added measurably to the impact of the Institute on all of our professional lives.

As a faculty member, teaching has always been a part of my life, starting with the University of Tennessee where the admission of a new medical school class each semester, guaranteed a neuroanatomy class to teach each half year. At UCLA, with a sparkling young group of neuroscientists to draw on, Magoun put together a basic neurology course taught by a cadre of experts, each a master in his or her own field. The content was up-to-the-minute and probably excellent; the result was disastrous. I was not surprised because I had experienced a similar type of instruction while a student at the College of Physicians and Surgeons, with the same unfortunate results. This teaching by “cameo appearance” as I thought of it, offered a series of vignettes without continuity, unless, of course, all of the instructors sat through all of each others lectures—an expenditure of time

that few were willing to make. I finally achieved the luxury of chairing and teaching an entire course in the 1980s, first with the newly developed graduate level course in functional neuroanatomy and somewhat later with the undergraduate course in our new and growing neuroscience major. We taught on the quarter system and 10 intensive weeks of contact with motivated students, graduate or undergraduate, proved to be an unmitigated joy. Colleagues often wondered about the work involved in my giving all of the lectures and laboratories, aided only by one or two teaching assistants who had usually taken the course the previous year. I could assure them that it was far easier than trying to chair a course with a half a dozen or more other instructors, none quite clear what you wanted from them, or what the students had already heard.

In these circumstances, I found a deep source of enjoyment in my teaching. I think the main pleasure grew out of the challenge of trying to build with them a total image of their own nervous system in action. Snatches of neuroscience history, personal stories, "thought experiments," case material and, of course, the laboratory were all used to make the subject matter alive and personal. The pleasure of watching many of them grow with the course was powerful and sustaining, helped along, I am sure, by the narcissistic gratification involved in leading and challenging them. It was not an idle choice, therefore when, toward the end of the 1990s, after almost 50 years of research, I decided to close my laboratory and devote myself to full-time teaching. Now, almost 5 years later, I still miss research at times and I have been known to show withdrawal symptoms when visiting some colleague's active laboratory. Nonetheless I feel I made the right choice and look forward, with the usual anticipation—and trepidation—to beginning the next class.

Although I must admit that the real challenge and thrill of teaching came to me somewhat later in life, I have always felt the excitement of discussion and argument among individuals from varying backgrounds tackling a problem of common interest. The old Spanish style home that we bought in 1959 had a separate three-car garage and guest room, all somewhat the worse for wear. We converted this into a rather casual meeting room that could hold 20 or more people. Starting shortly thereafter we began to have small faculty-student meetings here, discussing a paper or subject of interest. Things seemed to flow more easily in this off-campus (usually evening) setting. Visitors or foreign guests have been with us at times and the meetings have become something of a tradition. They also served in some sense as a model for the affinity groups that were started during my term as director of the institute.

Another bonus of academic life is the travel that becomes a natural part of it. Many are the attractions of national and international travel, the meetings and interaction with colleagues, and the exposure to new ideas being only some of the more obvious benefits. As already mentioned,

after the first few years together, Mila and I were virtually unable to travel, or even to leave our home. The situation later with Marian was very different and some of our most rewarding memories are of trips we have taken together. Two that were particularly memorable were our 6 weeks in China in 1985 and, a few years later, our 4 weeks in Kenya. In China, we lectured rather widely in Shanghai and Beijing. Although we had been assigned a full-time interpreter and guide, the capable, young Anne Yeh, most of our classes or seminars refused her services. It seems that by that time (and this was virtually 20 years ago), the young university people were already well trained and fluent in conversational and scientific English and preferred to listen on their own. We were impressed by their invariable attentiveness and concern—reflecting, if not genuine interest in the subject, at least Chinese politeness and appreciation for scholarship. We were the first foreigners to address the students of the Chinese Naval Research Institute. I remember the picture book setting in an enormous amphitheater with row upon row of motionless cadets, all in their dress whites, almost as far as the eye could see. I cannot remember the subject of my lecture there, but I know I felt as if I were acting in a Busby Berkeley film extravaganza of the 1930s. We met with invariable hospitality and sensitivity to our needs. However, I do remember a more mixed reception, one morning at about 6:30 as we joined the citizens of Xian to do Tai Chi'ih in the street. Marian was an old hand at this and fit right in but I was clearly a novice and my version of Tai Chi'ih could more appropriately be called 'My Chi'ih'—and an obvious surprise to them.

Most of our time in Kenya was spent in Nairobi where we had the opportunity to lecture to medical students and young faculty people, as well as learn how giraffes keep their brains oxygenated. Our host, Professor Kimani, had done research on this subject and had been able to identify the importance of the highly muscular, contractile walls of the carotid arteries in forcing blood all the way up to the cranial cavity. The obligatory overland safari was an unmatched experience as was Marian's quick ascent of Kilimanjaro. However, no matter where you are, there are certain areas of invariant interest. In both Shanghai and Nairobi, when we had roundtable meetings with the students so that everyone could talk, the two most predictable questions were (1) how did we meet each other and (2) in the States, do young people engage in premarital sex.

I have already mentioned that I learned the rudiments of portrait painting while I was on active duty at Brooke General Hospital in San Antonio. Over the years, this has been a favorite diversion. I found that soft pastel was my medium of choice because one can work "fast" without sacrificing the infinite subtlety of facial structure and expression I particularly liked to suggest rather than delineate, leaving as much as possible for the viewer to reconstruct internally. I did notice, however, that during intense research periods of drawing neuropil patterns directly from microscope to

paper, I completely lost the spontaneity of my pastel work and literally had to put it aside for months at a time. Clearly precision and impressionism were unable to exist simultaneously in my brain.

Another lifelong pleasure is the reading of history and cosmology. I see no particular dichotomy here because both are involved in trying to understand where we came from and how we got here, albeit with different time lines! However I do not believe I would take kindly to the craft of the professional historian. The archive-immersed life of a Gibbon or Ranke does not sound attractive. To make history and then write about it like Churchill is more appealing, although few of us have the opportunity to do that. But perhaps, in the long run, those of us who have had the privilege of doing scientific research are, in some ways, following that course after all. The history we attempt to create is the product of our own wonderment, and the history we write is the manuscript that becomes a part of the substance of our field.

As I look back over our field during this last half century, exciting and turbulent as it has been, the name of Francis O. Schmitt looms large. A first-rate investigator himself, Frank became, an outstanding entrepreneur and evangelist for the totality of the brain research disciplines. With his Neurosciences Research Program (NRP) starting in the early 1960s and the four great conferences on the neurosciences held in Boulder, Colorado in 1966, 1969, 1972, and 1977, Frank virtually created the concept and the reality of neuroscience as one overarching discipline. The magisterial volumes that resulted from these conferences remain the most comprehensive and satisfying statements of the state of the neural research arts in the third quarter of the 20th century. It was a privilege to be included in several of these volumes (Scheibel and Scheibel, 1967, 1970; Scheibel, 1979).

I suppose no exercise in retrospection is complete without some reflection on what might have been done differently. From this vantage point, one sees the missteps and can trace the sequelae, but even with that luxury, I do not think I would have made major changes. I feel fortunate that I found my way into academic life, fortunate that I was able to combine structural research with some clinical work, and fortunate to have lived my life with the two very special women, Mila and Marian, both of whom could share, albeit in very different ways, my professional life with me.

The joys involved in deciphering patterns in neuropil have been accompanied by those of watching bright young minds unfold. Students grace one's youth and enrich one's later years. Here too I have been lucky, and many of my students have remained warm friends over the years, wherever they may be. Above all, to be a teacher is to play a very special life role, whose challenges and rewards are beyond price. I am proud to be a teacher. But looking forward is more profitable than looking back.

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