Edward Jones

Born:

Upper Hutt, New Zealand
March 26, 1939

Education:

University of Otago Medical School, M.B., Ch.B. (1962)
Oxford University, D.Phil. (1968)
University of Otago Medical School, M.D. (with distinction) (1970)

Appointments:

House surgeon, Tauranga Hospital, New Zealand (1963)
General practitioner, Auckland, New Zealand (1964)
Demonstrator and Assistant Lecturer, Department of Anatomy, University of Otago Medical School (1964–1965)
Nuffield Dominions Demonstrator, Department of Human Anatomy and St. John's College, and Lecturer, Balliol College, Oxford University (1965–1968)
Lecturer and Associate Professor, Department of Anatomy, University of Otago Medical School (1969–1971)
Associate Professor and Professor, Department of Anatomy and Neurobiology, Washington University (1972–1984)
Professor and Chairman, Department of Anatomy and Neurobiology, University of California, Irvine (1984–1998)
Director, Neural Systems Laboratory, Frontier Research Program, RIKEN, Japan (1988–1996)
Distinguished Professor of Psychiatry and Social Sciences and Director, Center for Neuroscience, University of California, Davis (1998–2009)
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Honors and Awards (Selected):

Symington Prize, Anatomical Society of Great Britain and Ireland and the Queen's University, Belfast (1968)
Rolleston Prize, Oxford University (1970)
Cortical Discoverer Award, Cajal Club (1989)
M.D. (honoris causa), University of Salamanca (1997)
President, Society for Neuroscience (1998–1999)
Henry Gray Award, American Association of Anatomists (2001)
Karl Spencer Lashley Award, American Philosophical Society (2001)
Original member, Thomson Scientific/ISI Highly Cited Researchers Database (2001)
Member, National Academy of Sciences, U.S.A. (2004)

Edward Jones's work on the structure and function of the central nervous system is distinguished by enormous breadth and scope, both intellectually and technically. He has made seminal contributions to understanding the circuitry, cellular properties, and basic organizational plans of the cerebral cortex and thalamus, their development, functional interrelationships, plasticity, and pathology. His early work laid the foundations for the understanding of cortical connectivity, and he was the first to attempt to unravel the intrinsic circuitry of the cerebral cortex using electron microscopy. His was the first modern systematic classification of cortical interneurons, and in subsequent work his studies of their chemical characteristics form a basis for all subsequent studies. His book "The Thalamus" is one of the most cited publications in neuroscience. He is also a distinguished historian of neuroscience.

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When I was growing up I had no idea that one day I would find myself a successful scientist, a long-term citizen of another country, and writing my autobiography. It was a series of fortuitous circumstances, the advice of three key individuals, and some pieces of remarkably good luck that took me first into medicine and then into science.

New Zealand

I was born in New Zealand. The original family members had arrived there between 1850 and 1880 during the active phase of government-assisted immigration that followed British colonization. They had their origins in Northern and Southern Ireland, in Wales, England, and German Poland. The Joneses were the Northern Irish. They had been there from the time of the Ulster Plantation of 1610, the source of all the sectarian violence that has troubled Northern Ireland ever since. All of the family members were farm laborers or workers in the woolen mills of Gloucestershire. Initially, many of them did quite well in New Zealand, especially those who became dairy farmers, producing butter and cheese for a secure market in Britain. But families that were too large and periods of depression in the agricultural industry led to a decline in the fortunes of many of them so that by the time of my birth my branch of the family, while by no means destitute, was relatively poor. Neither my father nor my mother had more than an elementary school education, and throughout most of my time at home he worked as a bartender and she as a housemaid. A failed venture into shop keeping left us penniless, without a home and living with my maternal grandmother and her three unmarried daughters in a two-bedroom government-subsidized house. And I never saw again my other grandmother, my father's mother, who had lived with us and taught me to read and write at an early age. Between the ages of 10 and 13, until my parents got back on their feet, I was essentially a foster child, dependent for food and shelter on the kindness of a succession of uncles and aunts who had little enough themselves. My parents would eventually become managers of a series of small, brewery-owned country hotels, but that was after I had left home.

Children are resilient and I didn't think much about the precariousness of my childhood existence but, looking back, apart from being unable sufficiently to express my debt of gratitude to those kind uncles and aunts, I cannot help but wonder at how I managed to get onto a trajectory that would take me first to medical school and then to a career in science. The New

Zealand educational system, which was free, certainly helped and, despite the uncertainties of my youth, I was able to obtain an uninterrupted education throughout my high school years.

I spent my adolescent years in the provincial town of New Plymouth and during the early years of that period when I had no home to call my own, I was fortunate in having a small circle of friends with whom, after school and on weekends, I would roam the sparsely inhabited countryside surrounding the town, mostly by bicycle. We spent a good deal of time on beaches, along the banks of rivers, and rambling in the small stands of native "bush" that had escaped the deforestation of the 19th century when the province of Taranaki of which New Plymouth was the capital was transformed into the farms that today make up one of the most productive dairying areas of the world. Some of my friends were extremely knowledgeable about native plants and animals and from them I learned a lot. Perhaps it was at this time that the seeds of a later abiding interest in biology were sown. Perhaps contributing also was the time that I spent on an uncle's farm, where I learned to milk cows and manage the horses that were still being used at hay-making time.

I obtained my high school education at a good school, the New Plymouth Boys' High School, an all-male institution as the name indicates. Although dominated by rugby football, as all New Zealand boys' schools were, it had a solid academic reputation as well. I played my share of rugby (we were all made to) but I was drawn early to the academic side. Seemingly paradoxically, I excelled in English and Latin on the one hand and in geography and biology on the other. But in those days the latter two subjects were disciplines requiring a degree of skill at writing descriptions of maps and biological organisms or communities, and I discovered that I had a flair for descriptive writing that I hope I have retained to this day. As to the paradox, I could never really see the difference between putting into words what I was visualizing on a map or in a tide pool and writing a critique of a passage in *Paradise Lost* or *The Divine Comedy*. The term "descriptive" has negative overtones in today's science, but all science is descriptive. No one could argue that the Human Genome Project was anything but that. Where the word is used in a negative sense today, it is really being used as a synonym for "unfashionable."

I was never very good at math or physics and, although over the years I have taught myself statistics and have in fact done a lot of quantitative work, I remain mathematically weak. One of my early Ph.D. students, Steve Wise, on graduating presented me with a little book entitled *How to Teach Yourself Arithmetic*. (His other gift was a bull whip.) As a believer in the developmental plasticity of the brain, I am convinced that in brain development the early expression of verbal and written skills, such as I had exhibited under the tutelage of my grandmother, gives them dominance over that intuitive mathematical skill that the human brain normally develops and to

which teachers of mathematics direct their teaching. In a math examination, I always seemed to spend my time trying to decipher the written sense of a question rather than jumping intuitively, as my school fellows did, to the requisite formula for working it out.

The decision to go to University came late, toward the end of my last year in high school. It was a decision of some moment. No member of my family had ever attended University and my mother, as a child of the working class, was against it on the grounds that I would be taking myself out of that class. Expense was not an issue, for one of the remarkable things about New Zealand in those days and continuing even today is that University education was essentially free. Passing an entrance examination assured that the fees were paid and spending a fifth year in high school gave one a modest living allowance as well. A strong desire to continue learning, coupled with a certain competitive instinct, aroused by the realization that many of my classmates whose abilities were less than my own were going on to University, persuaded me that this was the right thing for me to do as well. The decision to try for entry into Medical School was in part also determined by that competitive instinct, for Medicine was reputedly then the hardest University course. Yet I was still drawn to English literature and the classics. It was around this time that I had discovered the "Penguin Classics," the paperback collection of translations of classical Greek and Latin as well as French, German, and other literature. In reading these works, I was strongly attracted to the idea of studying the humanities. It was a respected teacher of English at the high school who, knowing of my penchant for both literature and biology, persuaded me to go to Medical School, pointing out that a degree in English or the Classics limited one's opportunities to just these disciplines, whereas a degree in Medicine permitted one to pursue just about anything that one chose. For me, that turned out to be excellent advice and to that teacher I owe a great deal.

There was only one Medical School in New Zealand in those days: at the University of Otago in Dunedin, located in the southern part of the South Island. To gain entry, one had to spend 1 year studying Zoology, Physics, Chemistry, and Organic Chemistry at any one of the four New Zealand Universities and at the end of that year sit a competitive examination in which the top scorers qualified for one of the 100 places in the first-year medical class. There were in fact 120 places but 20 were reserved for the 20 students who invariably failed the first-year course and were given one chance to continue their studies. I was fortunate to gain one of the coveted places. One of the consequences of entry into Medical School after only 1 year in University was that most of us were quite young. I and two other members of the entering class had not yet turned 19.

The Otago Medical School was a very traditional one with the whole of the first year and two of the three terms of the second year devoted to Anatomy, Physiology, and Biochemistry with an examination—written,

practical, and oral—covering all of the material at the end. It was very demanding in the amount of learning required, and I doubt that any modern medical student would handle it without complaint. Most of us did handle it, but it was still possible to fail and be dismissed from the School. The Anatomists, led by Bill Adams, were exceptionally good teachers, although in 1958 they had not yet heard of the structure of DNA, revealed some 5 years previously. Biochemistry was still at the level of the Krebs cycle, to the elucidation of which the Professor, Norman Edson, had made significant contributions in his younger days. He opened his lecture on bile with the words: "Omnes Gallia in tres partes divisa est," at which fully 50% of the class laughed. Enough of us had previously had sufficient Latin to recognize the opening lines of Caesar's *Gallic War*. A modern medical class would undoubtedly ask if it were to be on the exam. There was some excellent neurophysiological research going on in the Department of Physiology under the leadership of Archie McIntyre. Archie had succeeded John Eccles in the chair which Eccles had held from 1944 to 1951 when he left to take up his position as founding Professor of Physiology at the new John Curtin School of Medical Research at Canberra in Australia. The first intracellular recordings from spinal neurons, the work for which Eccles in 1963 was awarded the Nobel Prize, were obtained in Dunedin. Eccles was remembered more for his irascibility than for his scientific achievements. Many years later, at a meeting in the Vatican, in introducing me to an audience, he described himself and me as being the only two neuroscientists who had been to Purgatory and back because we had both been on the faculty of the University of Otago. It was an unkind remark, but it reflected the difficulty that we both had had in setting up and maintaining a productive laboratory in one of the remotest medical schools in the world.

Early on I developed an affinity for Anatomy, not because of any abiding scientific interest but because of the discipline required in writing a clear and accurate description, using a standard terminology, of what I was seeing in the dissections in gross anatomy or under the microscope in histology. Putting visual observations into words, which has always been one of my strong points, was a skill honed in those early years. Coupled with it was a capacity for the visual representation of data, which stemmed from the drawings of cells and tissues observed under the microscope. Whenever I come across them today, I never fail to be amazed by the quality of those early drawings, made without the benefit of a camera lucida. Writing objectively and drawing accurately are not skills that are very much in vogue in science today, where the favored vehicles of scientific publication encourage superficiality, a gushing approach, and a liberal use of the Royal plural, and where the visual representation of data is usually confined to a couple of postage stamp-sized micrographs made mostly from laser confocal images that even if they could be seen are tokens, largely devoid of content.

After entering the clinical years of the medical course, of which there were three, I continued to teach anatomy to the first-year students, giving something like 50 tutorials a year to half the class. It seems a lot now but it did not seem unduly arduous at the time and it gave me experience in making oral presentations long before most of my colleagues. Again, the discipline of giving accurate verbal descriptions of the bones and other body parts was a challenge that I enjoyed meeting. For me, the clinical years were less interesting than the preclinical, I think, in large part because there were far too many students for the limited number of patients, Dunedin being quite a small city. There wasn't enough hands-on experience for my liking, and I found it irksome to have to thrust myself into a position in which I could examine someone with an interesting condition. Pharmacology and Pathology, which might have been expected to hold some interest for one with a strong predilection for basic science, never attracted me. The first was still in a very primitive state in which every neurotropic drug was held to exert its effect by operating on "the reticular formation," a nebulous part of the brain which I could never find described in morphological terms, and the second still in some kind of Victorian dark age.

During my years in medical school, my modest government bursary was insufficient to cover all my living expenses, so I was obliged to work in the vacations in order to supplement it. I was not alone in this. Many of my classmates were in the same position, and the majority of us worked at manual laboring jobs that offered temporary employment. Over the years, I worked collecting and stacking hay bales, on construction sites, and for three periods underground in a coal mine. I also served time as a bartender in the rough little village in which the mine was located. It was during these vacation jobs that I developed a lasting bond with working men and women that has always served me well in interactions with workers and trades people. I also acquired skills that have been useful in home remodeling projects.

I never regretted having to work so hard to pay my way through Medical School, although there were times when I would have loved to have spent a protracted period of time reading and writing or, even better, to have worked in a lab. Perhaps surprisingly, if I had worked in a lab it would not have been in Anatomy but in Physiology where, as I mentioned earlier, the Department in Dunedin had a strong tradition of neurophysiology and an active research program through which a significant number of medical students passed, some taking a bachelor's degree before returning to Medical School and some not returning at all but going on instead to a scientific Ph.D. Perhaps it was at that time that I began to become dimly aware that the forefront of medical science was no longer in Anatomy but in more experimental disciplines. As I write that, I realize that, unconsciously, I was already headed for an academic rather than a practicing medical career.

I was still reading widely, far outside the field of medicine, and especially in the classics. In one of my final examinations I can recall writing the answer to a question on syphilis from the perspective of Voltaire and his character, Dr. Pangloss, who in *Candide* lost his nose to the disease. I don't know what the examiner made of that, but I did not fail. Although penicillin had been introduced some 15 years earlier, syphilis was still with us then, mostly in its tertiary form. One of my patients in my final examination was a tabetic and, when confronted with a case of dementia, we were inclined to think first of general paresis of the insane, then of senile dementia and virtually never of Alzheimer's disease, which was considered to be exceedingly rare. It was through my continuing fascination with the 15th-century French writer François Rabelais that I met the second person who was to be influential in helping me shape my future career. I had first encountered Rabelais as a schoolboy in J. M. Cohen's Penguin Classics translation and had discovered in his irreverent and amusingly scatological writing not only the very essence of humanist ideals but also a mine of Renaissance medical information that probably formed the foundation of my later studies in medical and especially neuroscience history. It was through Rabelais that I met Erich Geiringer whose knowledge of the old French work was far greater than my own and who had a broad perspective on the history and culture of medicine that I and many of my classmates found fascinating. We had never met with such erudition or the cosmopolitan worldview that accompanied it. It was not to be found among our teachers in provincial Dunedin.

Geiringer had fled Vienna at the time of the *Anschluss* and completed his medical training at Edinburgh. He had come to Dunedin as a research fellow in the Department of Medicine. His experience of Nazi persecution in Austria had given him a determination to confront any form of authoritarianism, and this was always nascent in the provincial medical environment such as existed in Dunedin. The consequence was that he was always in trouble with the administration of the Medical School. When reprimanded by the Dean for visiting patients in the wards without wearing a white coat, his response—that Napoleon's physician, Jean-Nicolas Corvisart, had once been barred from *La Charité* for failing to wear a frock coat—was probably met with bewildered incomprehension. Not surprisingly, Geiringer soon left the Medical School to enter private practice and for the rest of his life he remained a prominent critic of New Zealand cultural attitudes and a thorn in the side of the New Zealand medical profession. Geiringer, like that high school English teacher before him, gave me the confidence to believe that a career in medicine was by no means incompatible with a satisfying intellectual life. We remained close friends until his death in 1995 and I cherish his memory.

We all spent the final vacation between the fourth and the final year in Medical School as clinical assistants at hospitals around New Zealand, and it was in these hospitals that most of us obtained our first in-depth clinical

experience, often with a considerable degree of responsibility. Then we moved into the final year, which was spent at one of the four teaching hospitals at Dunedin, Christchurch, Wellington, and Auckland. There, we gained a good deal more clinical experience in preparation for returning to Dunedin for the final examination and for the award of the degree of Bachelor of Medicine and Bachelor of Surgery (M.B., Ch.B.). Toward the end of my last year in Medical School, I had more or less made up my mind that I wanted to make a career in academic medicine and probably in basic science. With only one medical school in the whole country, there was obviously no clear route to this and so I felt it expedient to acquire the qualifications that would enable me to practice medicine in the event that my ambition was unrealizable. Knowing that, I determined to get as much clinical exposure as possible in the shortest time and took up a house surgeon's (intern's) position at a relatively small but extremely busy provincial hospital. There were only three of us on the house staff, and we had what was probably too much individual responsibility. Every third weekend from Friday evening until Monday morning, one of us was in charge of the entire hospital. There were senior staff that we could call on, of course, but we were expected to do as much as possible ourselves from the emergency room to the operating room and the inpatient wards. I didn't make too many mistakes, but those that I did make remain with me to this day. Most of the minor surgery devolved on us junior staff and in repairing wounds, and removing, probably unnecessarily, numerous appendices and tonsils, I gained skills that have served me well throughout my career. It was this that told me that if a slot was not available for me in basic academic medicine, I could probably make a satisfactory career for myself as a surgeon.

It was while at that provincial hospital that I had my first opportunity to write a research paper and to see it published. One day I had admitted a 17-year-old Maori man suffering from inoperable cancer of the stomach, and when I walked to the other end of the hospital I discovered in another ward his 21-year-old cousin who had been admitted with the same terminal condition. Initial enquiries revealed that one of their sisters in her 20s had in the recent past died of the same disease, and after further enquiries it became clear that the local Maori community and some of the older doctors in the region knew that many other members of the family had been afflicted with this terrible, early-onset disease for more than a century. The older members of the family, if they could be persuaded to discuss it, which they often weren't, thought that they were afflicted with a curse while the younger, better educated members were more inclined to blame a European, a Scot, who had married into the family in the 1830s. I was able to identify as many as a dozen cases of this early-onset cancer in the wider family and realized that this was a family at genetic risk for the disease. I wrote it up for publication in the *New Zealand Medical Journal* under the title of "Familial Gastric Cancer." There it lay, I thought forgotten, until many years later, in

1998, I was reminded of it when one of my postdoctoral fellows came into my office waving a copy of *Nature* and congratulating me on my status as a gastroenterologist. In that issue of *Nature*, Drs. Parry Guilford and Anthony Reeve of the University of Otago and their team of doctors and family members reported that they had identified the mutant gene that was the cause of this cancer. The authors very generously acknowledged my having brought it to light. By that time as many as 25 other members of the family, all at a young age, had been diagnosed with the disease and some had even had elective gastrectomies in an effort to avoid it. Despite my postdoc's irreverent remarks, I can take comfort in the fact that the mutated gene encodes for a cadherin and is thus a member of a gene family that is also expressed in the nervous system.

Apart from the cancer family, the other high point of my hospital year was my marriage to Sue, who has been with me ever since. She is a remarkably patient person who has always been willing to follow me along whatever new path I took and to make the best of whatever circumstances we found ourselves in at its end.

After leaving the hospital and spending a short time as *locum tenens* of a solo general practice, I was able to return to the University of Otago Medical School but, as there was no academic position in sight, I entered a program in which prospective surgeons spent a year as "demonstrators" in the Anatomy Department while preparing for the primary examination of the Royal Australasian College of Surgeons. For most of them, passing the examination and further clinical work gave them a Fellowship of the College and a stepping stone to a job in the United Kingdom, where they would sit the examinations for the Fellowship of the Royal Colleges of Surgeons at London or Edinburgh. Having one of these fellowships was a key requisite if one wanted to practice as a surgeon in New Zealand or Australia. It seemed to me that by starting out in the Anatomy Department I would be able to follow this same route if an academic position could not be realized.

I never did take that primary examination. As the year wore on, I found myself not only teaching the medical students their anatomy and histology but also more and more in helping the aspiring surgeons prepare for an examination which, for the amount of detail that it required, could be positively terrifying. In my second year, when I had been given a temporary assistant lectureship in Anatomy, I began to do some research. During my first year I had in fact written a short paper on a set of muscular anomalies found in one of the cadavers, interpreting them in developmental terms. It was a paper that might have graced any 19th-century anatomy journal, but it gave me an opportunity to exercise my talents for description and it did find a place in a respectable, if old fashioned, journal. More important, it led me to read about muscle and its innervation and to the muscle spindle, the low-threshold stretch receptor of striated muscle, whose pattern of sensory and motor innervation was then being revealed anatomically, not without a

modicum of controversy, in the laboratories of David Barker at Durham and Ian Boyd at Edinburgh. The physiology of the primary sensory endings had long been known from the work of Sherrington and that of the motor innervation by the work of Hunt and Kuffler at the Rockefeller University and later by that of Peter Matthews at Oxford, but the manner in which the two physiologically distinct classes of fusimotor fibers ended on the little nuclear bag and nuclear chain muscle fibers of the spindle was still a source of argument.

I commenced my muscle spindle work on the lumbrical muscles of the forepaw. Then and still now I could not believe that these tiny muscles, stretched from the tendons of the long flexors of the fingers to those of the extensors could have much to do with generating even fine movements of the fingers. They had to be a form of stretch receptor and that seemed confirmed by their having one of the densest concentrations of muscle spindles of all the muscles in the body. The species I used was the brush-tailed possum (*Trichosurus vulpecula*), chosen for its ready and free availability. It was a pest that had been introduced from Australia, and trappers from whom I obtained specimens were paid to help eradicate it. They never did. It is still a major pest that continues to eat its way through the forests. With little or no advice, I began staining the muscles with methylene blue and teasing out whole spindles with their innervating nerve fibers, using hedgehog quills mounted on sticks, the sharpest points that I could find. (The European hedgehog was another introduced species that had become a pest in New Zealand). In retrospect, I realize that I was doing something that few others were doing at that time, although the isolated muscle spindle was later to become a standard preparation in physiology. Using the methylene blue stain had its moments: in order for the stain to be effective in staining neural elements it must be applied in an oxygen-rich environment. Exposing the tissue to air while applying the stain was the traditional way of doing this, but I sought to do better by bubbling an oxygen/carbon dioxide mixture through the staining solution while perfusing it through the aorta. You can imagine what happened when the flask containing the perfusate and suspended above the laboratory bench burst under the applied pressure of the gas. If it got on your skin, you realized why it was called a "vital stain." It could not be removed until the keratinocytes that had been stained by it were turned over. And a white shirt was ruined.

I generated some very pretty preparations of muscle spindles and was able to prepare two papers from the work that were published in the *Journal of Anatomy* and in *The Anatomical Record*. In one of them I was convinced that the bag and chain intrafusal fibers could indeed be innervated by the same fusimotor fiber, in agreement with Barker but at variance with Boyd. What I realized later was that in order to put this study on a more solid footing, I should have been directly demonstrating the sensory or motor character of the numerous nerve fibers innervating the spindle by

selectively cutting the dorsal or ventral roots of the spinal nerves from which they arose. There was rarely any doubt about identifying the annulo-spiral endings of the Group IA primary afferent fiber, but the distinction between the terminals of the thinner Group II fibers and those of the fusimotor fibers was not always clear in normal preparations. Eventually, I suspect, I would have come around to doing rhizotomies and the surgery involved would not have presented any difficulties for me. But in the absence of advice, it did not happen and something intervened to cut short my muscle spindle days.

Oxford

Halfway through that second year, a piece of exceptional good luck came my way, a piece of good fortune that I still marvel at. I was offered the opportunity to take up a fellowship at Oxford University. The fellowship was called a Nuffield Dominions Demonstratorship and had been endowed by William Morris, Lord Nuffield, one of the founders of the British automobile industry. It was offered to young medical graduates from the old colonies of Australia, New Zealand, and South Africa—not to those from Canada because Canadians didn't buy British cars. It gave appointees the opportunity to spend up to 3 years working in an Oxford clinical or basic science department and came with a generous stipend and travel allowance. Initially, I was somewhat overawed by my good fortune and wondered if I would be capable of performing up to the standards of one of the greatest Universities in the world, but I was encouraged by others who had been previous holders of the award, and it was from those who had spent their years in the Department of Human Anatomy at Oxford that I was directed to that department and to working with the third person who played a profound role in helping me shape my future career: Dr Thomas P. S. Powell.

Tom Powell, informed of my wish to work with him, wrote accepting me into his laboratory and telling me that he would have me work on the connections of the somatosensory cortex. I wrote back thanking him but admitting that I knew little about the somatosensory cortex or its connections and asking for advice as to what I should read in advance. Back came the reply, 2 weeks later and on one of those flimsy blue "aerograms" that were the chief means of international correspondence, there being no Internet in those days and international telephone calls prohibitively expensive, at least from New Zealand. It said: "Read nothing until we see the results of the first experiment." It was appropriate advice because virtually nothing had been written up to that time on the connectivity of any part of the cerebral cortex. The little work that had found its way into the literature had been carried out with the old Marchi technique that had long been out of favor mainly for its inability to stain finely myelinated and unmyelinated fibers, or with strychnine neuronography in which every part of the cortex seemed connected to every other part.

The lack of connectivity data did not mean that the cerebral cortex was otherwise neglected. By this time the primary motor and sensory areas of many mammals, including those of the human, had been mapped by the stimulation or evoked potential techniques in animals, primarily by Clinton Woolsey and his students. Vernon Mountcastle, in using the single-unit technique, had discovered the cortical column in the cat's somatosensory cortex and he and Tom Powell (the two had worked together during Powell's sabbatical in 1958) had extended this work to the somatosensory cortex of the macaque monkey, relating the selective responses of neurons to deep or cutaneous stimuli to their locations in different cytoarchitectonic areas of the postcentral gyrus. David Hubel and Torsten Wiesel had commenced their ground-breaking work on the cat's visual cortex, some of the subcortical connections of which were beginning to be mapped anatomically by the Nauta technique. But there was clearly a need for systematic, in-depth studies of the connectivity of individual, functionally defined areas of the cortex.

I didn't entirely follow Tom Powell's advice. I attempted to read the papers that were then emerging from his laboratory on the connections of the hippocampus, but I have to confess that I found them virtually incomprehensible. I had simply not studied central nervous system (CNS) anatomy at that level of resolution before. But I made a note of the writing style and saw how I could emulate it. If Tom recognized that the draft of our first paper was written in imitation of his style, he did not admit it.

Arriving with Sue in England in late December of 1965, both she and I were struck, as probably many visitors from the old colonies were, that what we had absorbed in our British-oriented education but never experienced now acquired relevance. There were the long rows of terrace houses that we had never seen, the babies taking the air on even the coldest afternoons by being placed in their prams in "the area," the shilling in the gas meter that was the sole means of keeping warm, the first squirrel scampering across the snow-covered ground as we enjoyed our first English breakfast. (Unlike virtually all other northern hemisphere vermin, the squirrel had never been successfully introduced into New Zealand). The buildings of Oxford were just being cleaned of their centuries of accumulated grime, and the beautifully warm Cotswold stone of the Colleges was emerging to be seen at its best.

The day after our arrival in Oxford, I visited the Department of Human Anatomy and met Tom Powell and his colleague of more than a dozen years, Max Cowan. Both were to have a significant influence over my future career. Tom had trained as a neurosurgeon before joining Sir Wilfrid Le Gros Clark, the head of the Department of Human Anatomy in 1951. Max had come from South Africa in the middle of his medical student years to complete his degree at Oxford and to work also in Le Gros Clark's department. Le Gros had retired by the time I arrived in Oxford, being replaced by another

distinguished British scientist, Geoffrey Harris, so I can only claim indirect descent from one of the most famous of all neuroanatomists. Working together from 1953, Tom and Max had initially used the retrograde degeneration technique and normal silver staining to work out the connections of the hippocampus and striatum—to the extent that these could be unraveled with what, in comparison to later techniques, were low-resolution techniques. In the years prior to my arrival in Oxford, the two had turned to the recently introduced Nauta technique, a method for visualizing neural connectivity by the selective silver staining of axons and their terminal ramifications undergoing Wallerian degeneration as the result of surgical destruction of their cells of origin. The great advantages of this technique were not only that it stained degenerating axoplasm and thus both myelinated and unmyelinated fibers but also that it did so against a clear background from which the staining of all other, normal axons was suppressed. It was from use of this technique that those papers on the hippocampus that I had found incomprehensible came. Max had recently returned from a sabbatical year in the Department of Anatomy at Washington University, where he had learned electron microscopy, and during the same period Tom had introduced the method at Oxford, after conferring with George Gray and others at University College London.

It was a good time to be commencing a career in what was to become neuroscience. Thanks to improvements in the Nauta technique, it was now possible to use it in what may be regarded as a high throughput manner to investigate circuitry in the CNS. And the introduction by Karnovsky in 1965 of the mixed formaldehyde/glutaraldehyde fixative for electron microscopy now made it possible to perfuse an animal and obtain well-fixed tissue from any part of the brain or spinal cord. Prior to that, adequate preservation of ultrastructure could only be obtained by dicing the tissue into tiny pieces and immersing them in osmium tetroxide or, for the cerebral and cerebellar cortices, dripping osmium tetroxide onto their surfaces. Perfusion with the mixed aldehydes temporarily stabilized cell membranes and intracellular organelles so that a desired brain region could be accurately removed and later be postfixed by osmium tetroxide, thus preserving lipids and other macromolecules permanently. Although there were attempts to perfuse with osmium, these rarely worked and it was decidedly hazardous as well.

At my first meeting with Tom and Max, Tom told me: "You can join any College that you like—mine is St. John's." It was clear what my choice should be, so I went to meet the Senior Tutor at St. John's, walked with him to the Sheldonian Theatre where he exchanged a few Latin phrases with the Vice Chancellor and I became an advanced student and a candidate for the D.Phil. As an advanced student, I was entitled to wear a gown somewhat longer than that worn by the undergraduates and when, after Max's return permanently to the United States, I inherited his Lectureship at Balliol College, I was entitled to wear an even longer one and to enjoy dining rights.

Even though all of us, Tom especially, taught extensively, the Powell lab was a hive of experimental activity. Beginning with me were Joel Price, a Rhodes Scholar who had just completed his undergraduate degree; Janet Kemp, who had just returned from a period in Walle Nauta's laboratory at MIT; and Geoffrey Raisman, who had just returned to the lab after completing his medical degree. It was the custom in Oxford to take time off to do the D.Phil degree in the 2 years between the basic and clinical years of the medical curriculum and Geoff had had a very productive time during that period when he did all that work on the hippocampus that had so perplexed me. Over the years, many other students passed through Tom Powell's lab in this way, all of them producing high-quality work. Some went on to become successful neuroanatomists in British and foreign Universities, but the majority of the graduates of his lab became leaders of British medicine in fields as diverse as pathology, ophthalmology, infectious disease, and military medicine.

Joel Price began working on the connectivity of the olfactory bulb in the rat, Janet Kemp on the corticostriatal projection, and I on the connections of the somatosensory cortex, first in the cat and later in the monkey, all of us using a combination of the Nauta technique and electron microscopy. Geoff Raisman commenced working on the electron microscopy of fornical and other inputs to the septum and after he had succeeded to Max's University Lectureship and Fellowship of Pembroke College, and left to form his own independent lab, this turned into one of the first studies of synaptic plasticity in the brain.

The Nauta work and the electron microscopy proceeded in parallel. The first involved the placement of lesions in the cerebral cortex or thalamus to cause the degeneration of the efferent and afferent axons of the cortex that could then be selectively stained. The second was a combination of both normal morphology and degeneration-based identification of the terminals of the pathways revealed with the Nauta technique. I was soon making most of the surgical lesions and for the Nauta studies I also usually cut the sections, stained and mounted them. For the electron microscopic studies, Tom's long-standing technician, Ron Brooke, cranked out long runs of thin sections on a regular basis for all of us. This was an exciting time for the electron microscopy of the CNS. As mentioned earlier, the introduction of fixation by perfusion with mixed aldehydes greatly facilitated access to well-fixed tissue from any part of the brain, and new features of neural ultrastructure were emerging on a regular basis. The synapse had, of course, been recognized at the electron microscope level much earlier and, in fragments of cortex fixed directly in osmium tetroxide, George Gray had been able to demonstrate the ultrastructure of the dendritic spine in the cerebral cortex and the presence of two kinds of synapse in which the pre- and postsynaptic membranes were thickened asymmetrically or symmetrically. He called them Type I and Type II, respectively. The duality was not something

that all electron microscopists of the nervous system were then prepared to accept, thinking the two forms of synapse to be no more than the two ends of a continuum. However, it has stood the test of time and represents one of the most fundamental features of CNS organization. Every session on the electron microscope seemed to yield a new set of images that required identification, and I can recall always bringing to those morning coffees and afternoon teas, which were a regular feature of the Powell lab, a file of unusual electron micrographs for discussion and argument. There were often surprises such as the appearance of a cilium on a cortical neuron, but others were much more relevant and formed part of the mounting knowledge base of CNS fine structure: confirmation of Gray's two synaptic types; pedunculated and sessile dendritic spines, invariably with one asymmetrical synapse and occasionally a symmetrical one on each; the identification of pyramidal and nonpyramidal cell somata by their different complements of synapses, those on the former being all symmetrical and those on the latter a mixture of both types; the peculiar membrane undercoat that allowed the initial segment of the axon to be identified; the recognition of the presence of synapses on the initial segment, which at first was hard to believe; in the thalamus, structures that looked like dendrites but which contained synaptic vesicles and made synaptic contacts. Perhaps most dramatic of all was the growing recognition, stemming from Uchizono's work on the cerebellar cortex, that in aldehyde-fixed material, the synaptic vesicles of boutons making asymmetrical synaptic contacts remained spherical while those contained in terminals making symmetrical synapses flattened and became ovoid. Because Uchizono had made his observations in a structure in which he could identify that the asymmetrical/round vesicle synapses were made by excitatory neurons and that the symmetrical/flattened vesicle synapses were made by inhibitory neurons, the implication was that in the cerebral cortex, too, excitatory and inhibitory synapses might be identifiable by the same morphological features. Acceptance of this as another fundamental principle of neural ultrastructure also came slowly and it was not until Marc Colonnier, in a paper containing a fold-out plate with 100 synapses illustrated side by side, demonstrated the clear bimodality of structure, that it became recognized.

We were not alone in making the observations on normal tissue. There were several other laboratories, notably those of Alan Peters and Sanford Palay, simultaneously publishing similar findings. What we spearheaded was the application of degeneration techniques positively to identify the origins of the synapses that we were observing in the cortex and thalamus. Marc Colonnier while working at University College London had shown that, if the cortex was undercut and the animal left to survive for a few days, synaptic terminals in the overlying cortex whose axons had been cut underwent a distinct reaction characterized by increased electron density, shrinkage, and astrocytic engulfment. Colonnier and Guillery in London

and Szentágothai and his students in Budapest had also shown that the terminals of the optic tract in the lateral geniculate nucleus, degenerating as the result of tractotomy could also be identified by electron microscopy, although here the appearance was one of remarkable neurofilamentous hyperplasia. The two forms of terminal degeneration initially caused some confusion until it gradually became clear that it was mainly the large terminals of thick axons in subcortical structures that underwent the initial neurofilamentous reaction before passing to the electron-dense phase that terminals of thinner axons such as those in the cortex directly underwent.

For Tom Powell and me, the ability to recognize degenerating synapses at the electron microscopic level gave us the opportunity to make lesions in the sources of the axonal pathways that we were identifying light microscopically with the Nauta technique, and to determine the nature of their terminations in the cortex or thalamus of the cat. After my departure from Oxford, Tom and his students were to extend this work to the cortex of the monkey with highly productive results. From our electron microscopic studies on the somatosensory cortex, there emerged a lengthy series of papers that took up a whole issue of the *Philosophical Transactions of the Royal Society*. The terminations of ipsilateral corticocortical and commissural fibers and of thalamocortical fibers were identified, and I think it came as a surprise to many that most of these terminations, especially those of the thalamocortical fibers, were on dendritic spines of pyramidal cells. At the time the view of cortical connectivity was a remarkably simplistic one, namely that afferent fibers ended on some nebulous form of "stellate" or "granule" cell that transferred the input to the pyramidal cells, the output cells of the cortex. Anyone reading Cajal would have recognized that the afferent inputs were to a large extent focused on pyramidal cells and that the collaterals of pyramidal cell axons formed a set of intracortical connections that was far denser than those formed by the ascending axons of layer IV stellate cells. Unfortunately, nobody was reading Cajal at that time. It was inevitable that we should extend our studies to the terminations of corticothalamic fibers in the thalamus, and out of them emerged the first evidence for the extremely large number of synapses formed by these thin fibers and the concentration of their terminals on the second- and third-order dendrites of the thalamocortical relay cells. In comparing the fine structure of the ventral posterior nucleus of the thalamus with that of the medial and lateral geniculate nuclei, we found that they were organized along similar lines, in the cat dominated by the peculiar, glial-ensheathed glomeruli in which the large terminal of a subcortical afferent fiber, making contact with the proximal dendrite of a relay cell, lies surrounded by terminals that would later prove to be the presynaptic dendrites of inhibitory interneurons.

The electron microscopic studies were obviously informed by the studies going on in parallel at the light microscopic level with the Nauta technique.

When we commenced these studies, the corticocortical and commissural connections of the cerebral cortex were virtually virgin territory. Some work had been done on the subcortical projections of the motor and visual cortex, including in the case of the latter, by Laurence Garey who had recently left Tom Powell's lab to complete his clinical work and who would eventually return, but there was virtually nothing on other areas and no work with the Nauta technique had been done at all on the thalamocortical projection. As our work advanced, it became clear that we were not alone in recognizing the deficiency of knowledge about the corticocortical and commissural connections of the cortex. Adrian Morrison and Hans Kuypers with Deepak Pandya were soon found to be doing similar work, the first on the cat and the second two on the monkey.

Out of my 3 years of work with the Nauta technique on the somatosensory cortex of the cat and monkey, there emerged a number of principles that have stood the test of time and work with higher resolution techniques. They are now so well established that they may seem commonplace, but at the time they were new. Homotopic and heterotopic connections across the corpus callosum was one of the first when it was recognized that the primary somatosensory cortex of one side not only projected to its homolog on the contralateral side but also to the contralateral second somatosensory area. Specificity of ipsilateral corticocortical connections was another: the primary somatosensory area did not project widely but very specifically to the second somatosensory area, to the primary motor cortex and to anterior parietal cortex (area 5). There was also topographic specificity in the sense that different parts of the body representation in the primary somatosensory area only projected to corresponding parts of the motor or second somatosensory representations, and a similar topography observed in area 5 implied that it too would have a representation of the body surface that matched that in the primary area. When we turned to making tiny, needlepoint lesions in the postcentral gyrus of monkeys, we were also able to show that a small part of the body representation did not project locally much beyond its own representation, and we were able to show differences in the connections of areas 3, 1, and 2 that made up the primary somatosensory area as defined by evoked potential and single-unit mapping. We observed a similar topographic specificity in the corticothalamic projection, not only in that it projected back only to the thalamic nucleus from which the cortical area received input, in the case of the somatosensory area, the ventral posterior nucleus, but also that the body topography seen in the intracortical connections was also preserved in this connection as well.

As the last step in the sequence of studies on the connectivity of the somatosensory cortex, we made stereotaxically localized lesions in the ventral posterior nucleus of cats and monkeys and traced the degenerating thalamocortical fibers to their target. Here, the same kind of organization based on body topography was also revealed. But it was also evident that the

projection to areas 1 and 2 in the monkey was substantially less dense and made up of finer fibers than that to area 3. On the basis of past work with the retrograde degeneration technique, this might have been interpreted as implying that the projection to areas 1 and 2 would be made up of branches of fibers projecting to area 3. In the language of Rose and Woolsey, derived from their observations of the differences in the severity of retrograde degeneration ensuing from cortical lesions, the projection to area 3 would be an essential projection and that to areas 1 and 2 a sustaining projection. I was never comfortable with this interpretation since it seemed to fly in the face of Mountcastle and Powell's evidence for the modality specificity of inputs to areas 3, 1, and 2. It was only many years later that I was able to confirm that separate thalamic cells projected to the cytoarchitectonic areas of the postcentral gyrus, including to the subdivisions of area 3, areas 3a and 3b, which had in the meantime been revealed as the recipients of low-threshold muscle spindle and cutaneous inputs, respectively.

At this time, the generality of corticothalamic projections was only just becoming apparent. Long before, some had even doubted their existence or thought them confined to certain thalamic nuclei only, but with our work and that of others in the field it soon became evident that all areas of the cortex projected back to the thalamus. What remained unclear was whether a given cortical area projected back only to the thalamic nucleus from which it received its afferent input. As the work on the somatosensory cortex progressed, we were able to analyze in parallel the brains with lesions of the visual and auditory cortical areas of the cat, the first prepared by Laurence Garey and the second by Irving Diamond who had spent a brief sabbatical in the Powell laboratory in the months preceding my arrival in Oxford. The results of this analysis served to confirm many of the principles that were emerging from the work on the somatosensory area and out of it came a paper on "Interrelations of Striate and Extrastriate Cortex with the Primary Relay Sites of the Visual Pathways," which became a so-called citation classic, and in the papers from the auditory cortex there came a "principle of reciprocity" of corticothalamic and thalamocortical connectivity. This principle stressed that the projection from a small patch of cortex terminated only in the part of the thalamic relay nucleus that contained the cells projecting to that patch. The principle stood for many years and served as a means of deducing thalamocortical connectivity when direct observation of thalamocortical fibers was not feasible. Only with the emergence in the 1990s of higher resolution techniques for tracing individual corticothalamic fibers to their terminations in the thalamus did it become evident that the extent of the corticothalamic projection from a column of cortex could exceed that of the set of thalamic cells providing input to that column.

In using the degeneration-based Nauta technique, we and others were always aware of what was called the "fiber of passage problem," that is, the fear that some or all of the axonal degeneration stained and taken to

indicate the projection of cells in a nucleus or cortical area could have ensued from interruption of fibers arising from cells in another region and passing through the region of cells lesioned, thus giving rise to a false-positive result. This was less of a problem in the cortex where, by simply stripping off a square of pia mater, one could devascularize the underlying cortex without causing significant damage to the deeper white matter. Making lesions of the thalamus was another matter. Stereotaxis was, of course, well known and had been used for years in neurophysiological experiments, and there were reliable stereotaxic atlases of the cat thalamus by Jasper and Ajmone-Marsan and of the monkey thalamus by Olszewski. But obviously, in relying on axonal degeneration to chart the cortical projections of a thalamic nucleus, there was the fear that the passage of an electrode through overlying cortex, white matter, and other nuclei would cause sufficient damage to lead to a spurious result. As a consequence, the study of thalamocortical connections lagged behind that of structures that lay on the surfaces of the cerebral hemisphere, cerebellum, spinal cord, or brainstem. We thus sought approaches to the thalamus that would permit an electrode to enter the ventral posterior nucleus without traversing other thalamic nuclei and minimizing damage to structures overlying the thalamus. It was here that our surgical skills became useful. In the cat, we found that we could introduce an obliquely angled, horizontal electrode that entered the ventral posterior nucleus from behind and laterally, avoiding the cortex and all other nuclei—providing, that is, that we first removed the tentorium cerebelli, which in the cat is bony. That required some skill because there was always a danger of tearing the lateral venous sinus and that would mean the end of the experiment. For the monkey, with a large temporal lobe, this approach was not feasible, so we introduced the electrode horizontally through the visual cortex and superior colliculus, first ascertaining by control passages of an electrode that we could identify the degeneration ensuing from any damage to these structures.

Determining the actual terminations of a set of degenerating axons was another source of contention, because the Nauta method that most neuroanatomists were using at that time undoubtedly did not stain degenerating terminal boutons. As a consequence, we quickly learned that if certain individuals were likely to review our papers, we had to speak of "preterminal" not "terminal" degeneration in describing the pattern of termination of a set of degenerating axons. This has always seemed an unnecessarily pedantic circumlocution to me, for the staining of ramifying degenerating axons, which was readily distinguishable from that of the degenerating parent axons, surely betokened termination in the region in which they lay. Even later, when new variants of the Nauta technique, notably that of Fink and Heimer, were confirmed by correlative electron microscopy to be staining degenerating terminals, there were still holdouts against the use of "terminal degeneration." It all seems curiously irrelevant now.

Analyzing degenerating terminals at the electron microscope level also had its vicissitudes. I have mentioned the confusion briefly engendered by the appearance of the electron-dense and the neurofilamentous reactions in the terminals of cut axons, but here there could be other problems as well. Initially, few if any of us realized just how quickly terminals could degenerate, be phagocytosed, and disappear. You had to find the optimal survival time and this varied for different fiber systems. It could be remarkably short in fine-fibered systems. Failure to recognize this and, finding no degeneration of terminals in the dorsal horn 4 or more days after sectioning the dorsal roots of the spinal cord, led some to announce that these fibers did not terminate in the dorsal horn. Where would modern studies of pain mechanisms be if that had held up? It was only when other investigators used survival times as short as 24 hours that the terminations of the fine dorsal horn afferents were revealed. The terminals of thicker fibers degenerated over a longer time course but not too long. Finding no degeneration of terminals in the lateral geniculate nucleus after removal of an eye 2 weeks previously, and still finding none after increasingly longer survival periods, led others to announce that the use of terminal degeneration at the electron microscopic level was an unreliable method for studying connections.

Twenty-three full-length papers emerged from my productive 3 years in Tom Powell's laboratory. If a reader thinks, however, that my whole life during that time was spent at the lab bench, he or she would be wrong. At least once a month Sue and I would make our way to London or to Stratford-upon-Avon and attend a performance of the National Theatre or Royal Shakespeare Company. In those days it was possible to see Olivier, Gielgud, Guinness, and most of the younger actors and actresses who later came to dominate the British and international stage for less than 5 shillings (a quarter of a pound). And every Sunday was spent exploring the English countryside with its often charming villages, old churches, and pubs. It is something that many years later Sue and I continue to enjoy on our visits to England and Wales. It was during our time in Oxford that our daughter, Philippa, was born, delivered at the Radcliffe Infirmary by no less a person than the Regius Professor of Obstetrics and Gynaecology, John Chassar Moir himself.

I was also haunting the Bodleian Library, where one could obtain from the stacks any book ever published in Britain and most of those published elsewhere, and where in the Radcliffe Science Library one could still see on open shelves all the volumes of the *Philosophical Transactions of the Royal Society*. I also spent time in the bowels of the library of the Royal Society of Medicine in London seeking out old medical works. My focus was on the development of ideas about sensation and perception and out of this came my first major historical paper on the rise of ideas about the sense of position and movement, highlighting the contributions of Henry Charlton Bastian, the coiner of the term *kinesthesis*.

Sue and I also managed to take one lengthy European trip each year. British restrictions on the export of currency at that time permitted us to take only £50 each. We traveled in a small car and slept in campgrounds in an even smaller tent that the German campers used to bring their children to laugh at. In the course of these trips, in addition to visiting the major centers in France, Germany, Austria, Scandinavia, the Netherlands, and Italy and some more remote ones such as the Dalmatian coast and the Norwegian fjords, I had my first experience at giving seminars when I paid visits to the Departments of Anatomy at Oslo and Rotterdam, the Max Planck Institut für Hirnforschung at Frankfurt, and the Brain Research Institute at Zürich. In those places, I enjoyed the hospitality of Alf Brodal, Hans Kuypers, Rolf Hassler, and Konrad Akert. Prior to my talk in Frankfurt, Hassler took me aside and, knowing I was a New Zealander, asked me if I could speak in Colonial rather than Oxford English since he felt that the audience would understand it better.

New Zealand Again

It was with considerable sadness that Sue and I and our young daughter said goodbye to Oxford and England. Under the terms of the Nuffield Demonstratorship, holders were expected to return to their own countries for 5 years (in my case reduced to 3 years). It was essentially a gentlemen's agreement and many individuals in fact broke it and remained in Britain. I could have done so as well but felt that I had a responsibility to the Department of Anatomy in Dunedin which in my absence had promoted me to a permanent position and whose Faculty had been so supportive of me in obtaining the Nuffield award. In any case, Sue and I thought that we would eventually find our way back to Oxford. That was not to be.

We ended our days at Oxford, as I had begun mine, in the Sheldonian Theatre, where, sitting on those excruciatingly uncomfortable hard benches in its upper tier, we heard a concert by Sviatoslav Richter, the concluding work of which, the "Pictures at an Exhibition," was played in the manner that only he could. We departed soon after. On our way back to New Zealand we were generously entertained in St. Louis by Max and Margaret Cowan. Max, after 2 years at the University of Wisconsin, Madison, had recently assumed the Chair of Anatomy at Washington University. Little was I to know that one day I, too, would find myself a member of its faculty. Sue and Philippa went on separately to New Zealand, and I embarked on a 3-week tour of U. S. universities, giving seminars at several of them. The hospitality that was extended to me by such people as Irving Diamond at Duke, David Bodian and Vernon Mountcastle at Johns Hopkins, James Sprague at the University of Pennsylvania, Ray Guillery at Madison, Torsten Wiesel at Harvard, and Larry Kruger at UCLA was exceedingly generous, and my talks with Irving Diamond and Torsten Wiesel in particular were later to

help persuade me that my family and I could adapt satisfactorily to life in a culture which at that time was essentially foreign to us. In the course of this peripatetic tour, I was flattered to be offered faculty positions at two of the prestigious institutions mentioned, but I declined them, feeling that I had a commitment to New Zealand and still convinced that eventually I would find my way back to the United Kingdom. How things might have been different had I accepted, I do not know.

The 3 years that I spent back in New Zealand were productive ones despite a heavy teaching load and the relative isolation from the rest of the scientific world. It is hard to imagine now a scientific environment where journals arrived by surface mail 3 months after their publication and where many routine laboratory supplies, mostly obtained from Britain, took a similarly protracted time course before delivery. Commonly, chemicals obtained in this way arrived in poor condition. Glutaraldehyde, for example, arrived with a pH of close to 3, much of it having been oxidized to glutaric acid and requiring lengthy passage through activated charcoal for purification.

I was eventually able to obtain most of the equipment that I needed for light and electron microscopy, including a new Philips electron microscope, one of only two in New Zealand at that time. But in the early days I had to make do with a number of items that were really quite out of date. I may have been the last person routinely to have cut thin sections with a prototype model Cambridge-Huxley ultramicrotome in which a lever was elevated and then allowed to drop in order to cut the sections. After a year, thanks to a small grant from the New Zealand Medical Research Council, I was able to buy a modern Porter-Bum model. The necessity in the early days for making do with ancient equipment had its amusing side. Needing a sliding microtome for cutting frozen sections, I applied to the chief technical officer in the Anatomy Department—he was called the Steward. He took me to a room that seemed filled with Victorian junk and extracted from it a classic AO sliding-block microtome, a beautiful old instrument but clearly past its prime. Thereupon the following exchange took place: Jones: "It's a bit old, isn't it?" Steward (drawing himself up to his full height): "This was bought for Dr. Denny Brown in 1923." Derek Denny Brown, like myself, had started out in that Anatomy Department before moving to Oxford to work with Charles Sherrington and then on to the United States, where he became Professor of Neurology at Harvard Medical School. There seemed little to be gained in pointing out that this was the year in which Denny Brown had retired from Harvard. It was only later, after a visit to the medical history museum at Melbourne University in Australia where the same instrument had pride of place in its own case and beneath spotlights, that I learned that mine had in fact been built in 1909 and that it had been bought secondhand for Denny Brown! Apprised of that, the Dean of the Medical School bought me a new sliding microtome.

The last paper from the Oxford years was written after my return to New Zealand. Prior to leaving Oxford I had analyzed the brains in which I had made the cortical lesions in monkeys that permitted Janet Kemp to define the topography of the corticostriatal projection. These lesions were scattered across the greater part of the surface of the hemisphere and involved both primary and secondary sensory and motor areas and many association areas as well. From these brains it was possible to define the chains of cortico-cortical connections (now called hierarchical) leading away from the primary areas and across the association areas, with eventual convergence of pathways emanating from somatosensory, auditory, and visual cortex in areas of the frontal and temporal lobes. It was one of the first studies of its type, for investigations of the association cortex lagged even further behind those of the primary areas. I wrote it up as "An Anatomical Study of Converging Sensory Pathways in the Cerebral Cortex" and sent it off to Tom Powell. Now Tom had an unusually Calvanistic approach to publication and felt that if, as in this case, he had not sweated over the analysis of the results, as he invariably did with all his students, then he did not qualify to be an author. He, therefore, suggested that we submit it over my name only. I, naturally, demurred so he submitted it to Brain but accompanied it by a personal letter to the Editor, Denis Williams, apologizing for submitting yet another lengthy study and saying that it would be the last for some time. In a couple of weeks, back came the following note from Williams: "Dear Tom, Your importunity softens me, but the prospect of years of silence for the price of acceptance seems to me a bargain. The paper will appear as it stands . . . . . ." I wish one could negotiate publication that easily today. The paper was duly published; it became one of our most widely quoted papers and one still sees it referenced in studies of higher order processing in the cerebral cortex.

In New Zealand I continued the same themes that I had followed in Oxford, using the axonal degeneration-based techniques to pursue thalamic and cortical connectivity of the areas intercalated between the visual, auditory, and somatosensory areas of the cat, work which led to a lengthy monograph on the organization of the suprasylvian gyrus of the cat in which, among other things, areas 20 and 21 were identified for the first time. There were also studies of cortical and thalamic connections in my old animal friend the brush-tailed possum, a member of the class of diprotodont marsupials in which the absent corpus callosum is replaced by the remarkable *fasciculus aberrans* joining the two internal capsules across the top of the anterior commissure. In the thalamus of this animal we were able to dispel the myth that in animals low on the supposed evolutionary scale, the three great sensory pathways converged to a considerable extent in the thalamus. They definitely did not and in fact the possum ventral posterior nucleus, in containing barreloids that project to barrels in the somatosensory cortex, is comparable to that of the mouse. In this work I was joined by Chris Heath,

a recent medical graduate who would later, like me, go as a Nuffield Dominions demonstrator to Oxford where he worked in the University Laboratory of Physiology with Charles Philips defining the Group I afferent input to area 3a of the monkey.

At the electron microscopic level, the chief focus was on the structure and connectivity of the medial geniculate nucleus and the source of its input, the inferior colliculus. It was from this work that the commonality of afferent terminal organization in the thalamic sensory relay nuclei that we had recognized at Oxford was further confirmed. In this work I was joined by Tony Rockel, like Chris Heath another recent medical graduate and one who would go on to Oxford to work with Tom Powell. In the course of this work they described what for a long time became a recognized principle of cerebral cortical organization, namely the uniformity of cell numbers in columns extending through the thickness of the cortex, regardless of species. Although it has never been entirely ruled out, the weight of evidence now seems to be that this may not always be correct.

It was during the work on the inferior colliculus that I put into practice an approach that I had become convinced in Tom Powell's lab was essential if we were further to unravel the internal circuitry of any brain region. Electron microscopy, although at the synaptic level of organization, had too narrow a field of view and could not readily reveal the cell-to-cell connections, especially those that formed the chain of connections leading from input to output. It is an issue that still exercises the minds of neuroscientists, especially those who work in the cerebral cortex, and for which there is no easy solution short of the sheer brute force reconstruction of millions of thin sections or the painstaking intracellular injection of dyes into cells and the reconstruction of the synapses made by their axons in serial electron micrographs. In attempting to deal with this issue in those early days it became clear to me, and to a number of other neuroanatomists of the time, that it was necessary to reexamine the cells of the CNS and, armed with the new knowledge derived from electron microscopy, to try to understand where each type fitted into the circuitry of the regions in which they were located. To do this, we turned to the old Golgi technique, which was still the only method available for visualizing CNS neurons in their entirety. Tony Rockel had a real flair for the Golgi technique and, as I watched him building up the picture of cellular organization, including the peculiar stacks of lamellae that form the basis for the tonotopic organization of the central nucleus, I realized that it was this technique that had to be applied if we were ever to construct a circuit diagram of the cerebral cortex. I had already determined that in the next phase of my research, which I knew would have to be conducted outside New Zealand, I would return to the fine structure of the cerebral cortex and use the Golgi technique to inform what I would be seeing at the synaptic level.

St. Louis

As time passed in New Zealand, it became increasingly clear that a return to an underpaid junior post at Oxford would not be realistic and I turned my attention to the United States and to Max Cowan, who was happy to offer me a faculty position in his new department at Washington University. In preparation for the move, I wrote my first National Institutes of Health (NIH) grant application from New Zealand. It was funded after my arrival in the United States and was continuously renewed for the next 37 years. If I should have expected some recognition from the National Institute of Neurological Disorders and Stroke (NINDS), the NIH Institute that had funded the grant, of this long-standing support when I chose not to renew the grant, I would have been mistaken.

The family, now made up of Sue, myself, Philippa, and our son, Christopher, who had been born in Dunedin, set out for St. Louis in January 1972 and arrived there soon after. The first year there was not a happy one. Within days of our arrival, Max announced that he was leaving for another university, which was disconcerting to say the least. He never did leave but his flirtation with this and other universities went on throughout my first year; it was most unsettling to his entire faculty and not conducive to the development of good relations among them.

I commenced working, as I had planned, on the classification of neurons in the somatosensory and motor cortex of the squirrel monkey, using the Golgi technique. Making these studies in a monkey was a fortunate choice because, as the different cell types began to become evident, it was much easier to match them to the types that Cajal had originally described in the cortex of another primate, the human, and cell types that had not been seen since Cajal's day began to emerge. In the intervening years, most Golgi studies of the cortex had been carried out on rodents and cats in which the cortical neurons are less stereotyped than in primates and in which certain forms may even be absent. I can take credit, I am told, for rediscovering the double bouquet cell that Cajal had thought was unique to the human. I shall never forget my amazement in watching the long bundle of axon collaterals appear as I drew the first of these cells with the camera lucida. The bundle gradually filled up a series of panels of tracing paper that extended from the microscope continuously over the floor of my office and out into the laboratory. Comparing these cells with the large basket cells, the neurogliaform cells, and the chandelier cells which Cajal had never seen (probably because he invariably used material from infants in which their distinctive morphology is not yet developed) convinced me that it was possible to make a classification of cell types that could serve as a basis for developing a circuit diagram of the cortex. I was not alone in this. Others, such as Jennifer Lund, Alan Peters, and Janos Szentágothai and his students, working on the visual cortex of monkeys, rats, and cats, respectively, had all recognized this as well.

In my first classification of cortical neurons in the monkey, I stressed that they fell into two classes: those with substantial numbers of dendritic spines and those without. Among the first group were the pyramidal neurons, all of whose axons left the cortex, and the small spiny neurons of layer IV with their strongly recurrent axon branches extending upward into supervening layers as far as layer I. I could never persuade myself to call these spiny stellate neurons, as people were doing in the visual cortex, for in the areas that I was looking at they were drawn into an elongated form with a lengthy ascending dendrite. Lorenté de Nó in the mouse called them star pyramids. It was these cells that led me to insist that cortical neurons should be divided into pyramidal and nonpyramidal forms and not into pyramidal and stellate forms; this quickly caught on.

Apart from the small spiny neurons of layer IV, all the other nonpyramidal neurons of the cerebral cortex were essentially aspiny and this has subsequently been shown to be a hallmark of cortical GABAergic interneurons. They all differ in size, in configuration of the dendritic tree, and especially in their axonal ramifications. Among them, six stereotyped forms could be recognized in the monkey. These I called Types I through VI, the large basket cells being Type I, the double bouquet cells Type II, and so on. The small spiny cells of layer IV, being interneurons as well, were referred to as Type VII. Much later, like the pyramidal neurons, they were shown to be glutamatergic and excitatory. My use of a Type classification rather than the colorful terms applied to the cortical neurons by Cajal and others got me into trouble for, when at a meeting in Germany in describing my types and referring to the use of the older terms by Szentágothai as reflecting the usage of a classical middle European romantic, he retorted by saying that in referring to the neurons as mere types, I was attempting to reduce the brain to a piece of classic British understatement. He won, and we continue to use the older, morphologically descriptive names.

I hadn't planned on doing any further connectional work of the type that I had carried out in Oxford and Dunedin. Indeed, in completing the monograph on the suprasylvian gyrus of the cat I can remember remarking to Chris Heath: "Well, that's the last of the great connection tracing studies." How wrong I was. Before my arrival in St. Louis, an autoradiographic technique, based on the axoplasmic transport of radioactive amino acids which, after injection around the cell bodies of neurons were converted into macromolecules and transported to the terminals of the axons, had been devised. A number of different laboratories had been involved in perfecting the technique, among them those of Anita Hendrickson, Steven Edwards, and Max Cowan. It offered many advantages over the Nauta techniques for the tracing of connections, not the least of which was its freedom from the "fiber of passage problem" since axons, even if they took up the radiolabeled amino acids, did not possess the metabolic machinery that would allow them to convert the amino acids into the macromolecules that

were the form in which the radioactivity was retained after aldehyde fixation. Then, shortly after my arrival in St. Louis, Jennifer Lavail in San Francisco and Krister Kristensson and Lars Olson in Stockholm recognized that the phenomenon of retrograde axoplasmic transport could be harnessed as a technique for studying connectivity. Here, protein molecules, notably horseradish peroxidase (HRP), which could be visualized by a simple enzymatic reaction and had previously been used as a marker for extracellular space at the electron microscopic level, after being injected into the terminal field of a set of axons, would be taken up by those terminals, transported in their parent axons backward to their cell bodies of origin, and thus serve as a marker for connections. The opportunity to apply these two new techniques was too good to miss, even though it distracted me somewhat from my principal objective of unraveling the circuitry of the cerebral cortex. I commenced work with the autoradiographic technique on thalamocortical connections in monkeys, work in which I collaborated very successfully with Harold Burton and in which we charted the outputs of nuclei around the caudal pole of the ventral posterior nucleus that were thought to form components of the central pain pathways, with observations on the projections of the nuclei of the pulvinar and of the medial geniculate complex as well. Out of this work came a very comprehensive parcellation of the cortical areas on and around the insula and the observation that it was only in the granular, primary sensory areas of the cortex that thalamic afferents ended in layer IV. In nonprimary and association areas they ended only in the deeper part of layer III and even in the granular areas the terminations in layer IV extended well up into layer III. Surprisingly, this observation has never entered into the consciousness of the majority of neuroscientists and we still hear of layer IV as being the terminal layer for all thalamocortical projections.

The autoradiographic technique also permitted me to restudy the cortical connections of areas 3, 1, and 2 in the postcentral gyrus, confirming many of my earlier observations made with the Nauta technique and to make new ones. Among the latter was the surprising finding that areas 3a and 3b did not project forward to the motor cortex but back into areas 1 and 2 from which the somatosensory projections to the motor cortex emanated.

In applying the HRP technique I made the unexpected discovery that the intralaminar nuclei of the thalamus projected not only to the striatum, as Tom Powell and Max Cowan had shown with retrograde degeneration techniques, but also to the cerebral cortex. Tom and Max had discounted this, seeing the modest cellular degeneration that occurred in the intralaminar nuclei after cortical lesions as a form of anterograde transneuronal atrophy consequent upon the loss of corticothalamic fibers. Others, notably Marion Murray, had disagreed, seeing the cellular reaction as truly retrograde in character and thus indicative of a cortical projection. When I showed Max Cowan the retrogradely labeled cells in the intralaminar nuclei after

the first injection of HRP in the cortex, his response was a single word and it was uncharacteristically profane. Others, notably Herbert Jasper, who had felt that a widespread cortical projection from the intralaminar nuclei to the cerebral cortex formed part of a cortical arousal system, were delighted.

Working in the main with my first American student, Steve Wise, we mapped the laminar distribution of the cells of origin of the corticocortical, commissural, and subcortical projections of the somatosensory and motor cortex in the monkey, and Steve used both autoradiography and HRP to map out the connections of the somatosensory cortex in the rat much as I had earlier done using the Nauta technique in the monkey. Steve also carried out our first studies on the development of thalamocortical and commissural connections in the rat, studies that were to continue at the hands of Mary Kay Floeter, Karen Valentino, David Schreyer, and Isobel Scarisbrick. I myself focused on the reticular nucleus of the thalamus, plotting out its two-way innervation by the collaterals of thalamocortical and corticothalamic fibers passing through it and its output to the nucleus of origin in which these fibers begin or end, a pattern that forms one of the bases of thalamocortical function. This is one of my earlier papers that continues to be widely referenced.

While all this was going on, I became more and more convinced of two things. First, that it was imperative to localize the origin and terminations of axons as demonstrated anatomically in relation to the physiologically recorded properties of their nuclei or areas of origin and termination. Second, that it was necessary to present the visual evidence for origins and terminations in specific nuclei or areas in wide-field, low-magnification photomicrographs that unequivocally identify the nucleus or area as regions with defined anatomical identities. I was firmly convinced of the latter when, during my first year in St. Louis, I joined Alvin Berman of the University of Wisconsin, Madison, in preparing an atlas of the cat forebrain that was published in what publishers call an elephant folio. The huge 16-inch by 18-inch photomacrographs were made as contact prints from large glass plates that had been exposed on an old horizontal optical bench of the type used by neuroanatomists of bygone years for illustrating brain cytoarchitecture. Ever since, I have made a specialty of photomacrography, first optical and later digital, and some of my current work, as we shall see, continues to involve this.

The value of photomacrography of this kind can be seen in the comprehensive study that Chisato Asanuma and I, working in collaboration with Thomas Thach and using the autoradiographic technique, made on the terminations of the major afferent pathways from the spinal cord, dorsal column nuclei, deep cerebellar nuclei, globus pallidus, and substantia nigra in the ventral nuclear complex of the monkey. This work enabled us to say, by contrast with the prevailing view, that the terminations did not overlap

and where they ended in the same nuclei, as with the spinal and deep cerebellar inputs, they interdigitated rather than converged. This was not a view that pleased all; and our redrawing of some of the borders between nuclei drew ire as well. I have never ceased to be amazed at how so many of my colleagues, mostly electrophysiologists, seem to conceive of the monkey thalamus as a series of pages from Olszewski's atlas. Had they read his text, they would have seen that where we were drawing new borders they were in regions where he regarded his divisions as "provisional." Gradually, I am pleased to say, our divisions have become generally accepted. When later, Giorgio Macchi and I and then Tatsuo Hirai and I in our atlas of the human thalamus, attempted to extend our nomenclature to the human thalamus, thus rationalizing the different nomenclatures that had been applied to experimental primates and humans, we experienced similar resistance mainly from European sources from whence the human nomenclature had sprung. I am pleased to say that, here also, our rationalization of the nomenclature has begun to catch on in neurosurgical circles.

As to neurophysiological techniques, I have always used them in the service of neuroanatomy, not the reverse in which a trivial piece of anatomy is appended to a neurophysiological study in order to satisfy an editor or a review panel. I gradually taught myself neurophysiology and reinforced it during a brief sabbatical at Monash University, Australia, working with David Tracey in the laboratory of Robert Porter with whom I had overlapped in Oxford. Using single- and multiunit recording techniques, David Friedman and I were able to produce a high granularity map of the body surface in the monkey ventral posterior nucleus and to show from tiny injections of radioactive amino acids that its central cutaneous core projected to areas 3b and 1 while the anterior part of its shell region, which received inputs from low-threshold muscle afferents, projected to area 3b, and the posterodorsal part, in which neurons were activated by less clearly definable deep stimuli, projected to area 2. Other work, carried out on the thalamus of the cat with intracellular recording and injection techniques, enabled Chen-Tung Yen and me to recover for anatomical analysis thalamocortical neurons defined in terms of their sensory inputs, one of the few studies of its type ever carried out.

The latter years at Washington University were the early years of what was to become called chemical neuroanatomy. This was the era when immunocytochemistry was being perfected and when the growing availability of antibodies to neuroactive substances made it possible to study the chemical properties of neurons and neuronal pathways in terms of their neurotransmitters and other neuron-specific molecules. It was the availability of an antiserum to glutamic acid decarboxylase (GAD), the enzyme involved in GABA synthesis, that led us back to the cerebral cortex. Working in collaboration with Caroline Houser and James Vaughn, we showed that all the nonspiny neurons of the monkey cortex and their synapses were GABAergic. Soon after that, Stewart Hendry and I were able to show that a small

population of GABA cells in superficial layers of the cortex and in the white matter underlying it was also immunoreactive for various neuropeptides, notably cholecystokinin, substance P, or neuropeptide Y.

University of California, Irvine

I left Washington University to take up the position as chair of the Department of Anatomy at the University of California, Irvine. It was soon to become the Department of Anatomy and Neurobiology but, it being in the University of California, this name change was not accomplished without vehement argument. It was a small department that could be easily administered and this gave me plenty of time to continue to pursue experimental studies. Although it required some academic building at first, the department was soon generating more research grant income than any other department in the medical school; it was eleventh among anatomy departments nationwide and in the UC system second only to UC San Francisco, whose anatomy department had more than three times the faculty. I was obviously very proud of this, but it was a terrible indictment of the clinical departments at UC Irvine.

At UC Irvine the work on the chemical characterization of neurons in the monkey cortex continued. We were fortunate, thanks to the generosity of Piers Emson, to be among the first laboratories to have access to antibodies to the calcium-binding proteins, parvalbumin and calbindin, and in using these we could for the first time divide the GABAergic, nonspiny neurons of the cerebral cortex into subtypes. Those such as the large basket cells and the chandelier cells expressed parvalbumin while those such as the double bouquet cells expressed calbindin. A key member of my laboratory in carrying out this work was Javier DeFelipe from the Cajal Institute in Madrid, who identified the remarkable, candle-like terminals of the chandelier cells as ending on the axon initial segments of pyramidal cells and the regular minicolumnar arrangement of the bundles of double bouquet cell axons as they descended through the cortex, ending in the inhibitory synapses that I had seen so long ago on some of the dendritic spines on the side branches of apical and basal dendrites throughout the thickness of the cortex. At the same time, Stewart Hendry in the lab was demonstrating the activity-dependent down-regulation of GAD immunoreactivity and up-regulation of the alpha subunit of Type II calcium/calmodulin-dependent protein kinase (CAMII kinase) immunoreactivity in ocular dominance columns of the monkey visual cortex deprived of input by removal of or injection of tetrodotoxin into an eye. Later, when molecular techniques were introduced into the lab, Deanna Benson was to show, using in situ hybridization histochemistry, that these changes were the result of down- or up-regulation of gene expression. The monocularly deprived monkey visual cortex became one of the best models for the demonstration of activity-dependent changes in gene

expression and Stewart Hendry, Molly Huntsman, and Brahim Tighilet were to use it extensively in demonstrating the effect of lack of afferent activity on expression of glutamate, neuropeptides, the subunits of the GABA-A receptor, the subunits of ionotropic glutamate receptors, and other subunits of Type II calcium/calmodulin-dependent protein kinase. Fengyi Liang extended this work by using an epilepsy model. We were also able to show that the alpha subunit of CAMII kinase was only expressed in glutamatergic neurons of the forebrain. Xiao-Bo Liu confirmed this electron microscopically by showing its presence at glutamatergic synapses and its absence at GABAergic synapses in the cerebral cortex, hippocampus, and thalamus.

Physiological work was going on in parallel with all this anatomical work. George Huntley mapped the monkey motor cortex by microstimulation and showed, using injections of tracer at defined sites in the representation of a structure such as a finger that such a site has horizontal intracortical connections, formed by the collateral axons of pyramidal cells in layers II and V, which spread throughout the hand representation and thus form a substrate for the recruitment of motoneurons projecting to the many different muscles engaged in any movement. We also continued our intracellular staining of neurons and axonal terminations in the cat thalamus. This work, carried out by Chris Honda, Harry Schwark, Tatsuo Hirai, and Chen-Tung Yen, resulted in the only preparations of injected medial lemniscal axons that have ever been acquired, and the injected cells, in being taken to the electron microscopic level by Xiao-Bo Liu, furnished some of the few preparations in which the synaptic geography of thalamic neurons has been delineated in a quantitative manner. Liu and Richard Warren complemented this work on the thalamic relay cells by a study in which the labeled axons of cells in the reticular nucleus were traced to their terminations in the ventral posterior nucleus and showed that their synapses formed a far greater proportion of the inhibitory synapses on relay cells than did those of the intrinsic interneurons. We followed this up by demonstrating that the synapses of corticothalamic collaterals dominated the inputs to the reticular nucleus and that in the ventral posterior nucleus they ended predominantly on relay neurons rather than on interneurons.

At around the same time, Aric Agmon joined the lab and introduced us to the oblique thalamocortical slice from the mouse that he and Barry Connors had developed and to patch clamp recording in vitro. This preparation enabled Aric and Richard Warren to demonstrate, along with other labs, how the interconnected thalamo-cortico-thalamic network could generate low-frequency oscillations, dependent upon the low-threshold calcium conductance in relay cells and the interaction between the inhibitory reticular nucleus input to these cells and the reentrant excitation of reticular cells by the collaterals of the cortically projecting axons of the relay cells. Later, in the same in vitro preparation, Peyman Golshani, my last M.D., Ph.D.

student, would show that the corticothalamic input to the reticular nucleus is up to three times more powerful, as measured by the recording of unitary excitatory postsynaptic currents, than that to the relay cells, even though the inputs are formed by branches of the same axons, an effect that we showed depends upon the expression of up to three times as many GluR4 subunits of the ionotropic glutamate receptor at the synapses in the reticular nucleus. Aric Agmon was also brilliantly to exploit the thalamocortical slice preparation in studying the ingrowth of thalamocortical fibers into the somatosensory cortex during development in the mouse, showing that this occurred as directed growth and elaboration of terminations rather than as an early diffuse ingrowth with later withdrawal of so-called exuberant branching.

By this time, autoradiography had been phased out as a neuroanatomical tracer and newer tracers had come on the scene, notably the fluorescent dyes for retrograde tracing, wheat germ agglutinin conjugated HRP for anterograde and retrograde tracing, and *Phaseolus vulgari*s leukoagglutinin (PhAL) for anterograde tracing. These we exploited in studies of spinal and medial lemniscal inputs to the monkey thalamus and in revisiting thalamic projections to the postcentral gyrus, mostly in work carried out with Estrella Rausell. One of the discoveries from the application of immunocytochemical staining of the monkey thalamus for the calcium-binding proteins was that relay cells in that thalamus were either parvalbumin or calbindin immunoreactive and that nuclei differed in the proportions and distributions of each cell type. In tracing lemniscal and spinal pathways to the thalamus, we found that they ended in complementary fashion, the lemniscal fibers around parvalbumin cells and the spinal and spinal trigeminal fibers around calbindin cells. Moreover, when we looked at the cortical projections of the two classes of cells, we found that the parvalbumin cells projected in topographic order to layer IV and deep layer III of the somatosensory cortex, while the calbindin cells projected diffusely over adjacent areas and ended only in more superficial layers. It was a pattern that we were to find repeated in other thalamic nuclei and their cortical projections and it was from this that my theory of a specifically innervated and projecting thalamic core and a diffusely innervated and projecting thalamic matrix was developed.

The concept of activity-dependent cortical plasticity was beginning to make itself felt in the laboratory and, unlike most specialists in the field, I found it hard to believe that the representational plasticity that one sees in the somatosensory cortex after section of peripheral nerves or amputation of a digit or part of a limb could be due entirely to intracortical mechanisms. Remembering from my work with Tom Powell that deafferentation of CNS neurons commonly led to transneuronal effects, even to degeneration, I was convinced that if these were occurring at lower relay centers such as the dorsal column nuclei and thalamus then they would be projected upward to

the cortex and reinforce or even induce the representational changes that were occurring there. It also seemed to me that we were too focused on the point-to-point topography in the cortical projections of individual thalamic cells and that, if we looked at the projection of the population of thalamic cells that received input from, say, a finger, this would outline a much larger cortical domain so that, if an adjacent part of the representation were deactivated, then inputs in these widespread projections that had previously been suppressed would be revealed and serve as a basis for expansions of the map of an intact finger into that previously occupied by an amputated one. It was not a view that many would accept. To give it support we had to prove that there was widespread overlap in the thalamocortical projection and that withdrawal of part of this projection would not lead to a silent area in the cortical map. So with Estrella Rausell we showed using anterograde transport of differently colored fluorescent dyes injected into defined parts of the thalamic representation of the body surface that the projection emanating from 0.1 mm^3 of the thalamus could subtend as much as 20 mm^2 of the cortex, with extensive overlap of inputs from different parts of the thalamic representation. Then with Paul Manger, who had mapped the representation of the face and intraoral structures for the first time at high density in the somatosensory cortex, we began to make a series of lesions of increasing size in the thalamus, after which we examined the cortical map with multiunit recording arguing that, because of the overlap in the thalamocortical projection, smaller lesions would have little effect upon the map but that as they increased in size parts of the map would drop out, perhaps being replaced by expanded representations of adjacent parts.

We found in support of our hypothesis, but with considerable surprise at its extent, that we could destroy as much as 25% of the hand representation in the ventral posterior nucleus before the cortical representation of the hand began to shrink. Our view that deprivation of sensory inputs would have effects upon lower centers would be magnified by the divergence of projections from these centers to the next higher center and thus onto the cortex received vindication when, thanks to Tim Pons, we were given the brains of a number of the so-called Silver Spring monkeys that had survived for up to 20 years after sustaining dorsal rhizotomies of all the nerves innervating the upper limb. In these animals, in which multiunit mapping had revealed an expansion of the intact face representation into the silenced upper limb representation in the somatosensory cortex and thalamus, Tim Woods and I showed that there was a progressive transneuronal atrophy of the cuneate and external cuneate nuclei and of the upper limb region of the ventral posterior nucleus, with some but by no means huge loss of neurons in both sites; in the thalamus the atrophy led to collapse of the face representation into that formerly occupied by the upper limb representation. From this we argued that, as deafferented neurons were undergoing transneuronal atrophy, they would likely be withdrawing their axons from

higher centers and that this would promote expression of hitherto silent inputs from adjacent, unaffected regions, with expansion of the cortical map of those regions. This was, of course, conjecture but later, in experiments carried out on monkeys surviving for 2 or more years after section of the cuneate fasciculus at the first cervical level, Alessandro Graziano and I were able to show directly by anterograde labeling of the axons of atrophying cells that they did indeed undergo loss of terminal branches and reductions in the number and size of their terminal boutons in both the thalamus and cortex. I anticipate that after 20 years, as in the Silver Spring monkeys, this effect would have been even greater.

My years at UC Irvine were characterized by other activities, some of them nonscientific. My arrival there coincided with the publication of the first edition of my book *The Thalamus*, which to my surprise became one of the most referenced works in neuroscience. I have to confess that I wrote it in order, as I said at the time, to get the thalamus out of the way so that I could concentrate on the cortex. Indeed, at that time and over ensuing years Alan Peters and I were editing a series of books entitled *Cerebral Cortex* that attempted to bring knowledge of the cortex in review form to the neuroscience community. But as a reader of the foregoing will have observed, I was drawn more and more into the thalamus, and this attraction was enhanced by my growing association with two of the most talented thalamic neurophysiologists of modern times, Mircea Steriade and Rodolfo Llinás. With them I developed close friendships and enjoyed recurrent battles over interpretations of data. The battles go on with Rodolfo but those with Mircea sadly ended when he died. With them I wrote one book and with Mircea and a third talented neurophysiologist, David McCormick, we wrote and edited a two-volume work entitled *Thalamus* that was only superseded when the second edition of my own *The Thalamus* was published in 2007.

The middle of my UC Irvine period was highlighted by publication of a translation that Javier DeFelipe and I made of all Cajal's works on the cerebral cortex. Javier translated the Spanish into what I can only describe as an intermediate language, which I converted into a form of English that I hoped would capture some of the character of Cajal's orotund style while maintaining readability; and I struggled my way through translations of various French and German publications in which some of Cajal's work had appeared. Every word was fought over. I never became fluent in Spanish but I learned sufficiently to be able, when having an honorary M.D. conferred upon me by the University of Salamanca, to give the first and last parts of my acceptance speech in Spanish, at the conclusion of which the rector complimented me—on my English! Javier and I also edited and reworked Raoul May's earlier translation of Cajal's *Degeneration and Regeneration of the Nervous System*. This was done mainly during 1989 when I spent a brief sabbatical as visiting fellow at my old Oxford College, St. John's, in a year in which I helped my old mentor and friend, Tom Powell, into retirement. Since then, Javier and

I together or individually have published a number of works on Cajal, whom I have come to see not only as a great observer but as one who unerringly was able to extract fundamental biological principles from his observations, while also recognizing his huge capacity for self-promotion, uncommon in his era but which would do credit to any modern would-be Nobel prize winner. I have never been particularly comfortable with that sort of thing, perhaps on account of my upbringing in a determinedly egalitarian corner of empire.

During 8 years of my UC Irvine days, I was also the part-time director of a laboratory in Japan. With Masao Ito and Keiji Tanaka, mine was one of the three labs of the Frontier Research Program at the RIKEN Institute that quickly expanded and eventually grew into the RIKEN Brain Research Institute. I would travel to Japan three or four times a year, invariably spending at least one long period of a month there when I would bring a team of former students and postdocs, invariably including Marco Molinari, who had worked with me at UC Irvine, and some of his Italian colleagues, notably Elizabetta dell'Anna and Mariella Leggio, and we would work hard at neuroanatomical studies of the monkey auditory cortex. In the course of these, the duality of the parvalbumin and calbindin thalamocortical projection systems was again substantiated and a comprehensive chemoarchitectonic map, with correlative single-unit mapping, was produced. Tsutomo Hashikawa, my deputy, was the mainstay of this work, while Yasuo Kawaguchi carried out his important work on cortical interneurons distinguished not only by the expression of one or other of the calcium-binding proteins but also on the basis of their tonic or burst-firing properties, the first study of its kind. A third member of the team was Hisayuki Ojima who, in his intracellular studies of neurons in the cat auditory cortex, demonstrated the widespread distribution of intracortical and subcortical branches of layer V corticothalamic cells and the highly focused nature of the collaterals and thalamic terminations of the layer VI corticothalamic cells.

At the end of my days at UC Irvine, I was elected President of the Society for Neuroscience and took up that position after I moved to be Director of the Center for Neuroscience at UC Davis. The year of my Presidency coincided with the end of the Congress-mandated Decade of the Brain, during the course of which the NIH budget had been more than doubled. A feature of my Presidency was the meeting that the Society organized at the National Academy of Sciences building in Washington, DC, that, apart from allowing us to highlight the contributions that had been made to the understanding of the brain by showcasing some of the Society's best speakers, was attended by prominent individuals who had helped shape the Congress's policy toward science and medicine and included the late Senator Edward Kennedy, a number of Congressmen and women, and the actor Christopher Reeve. The latter part of my Presidency was less satisfying. It was becoming clear that all was not well in the central office and that radical

changes would have to be made. But doing this precipitately would have placed the success of the annual meeting, upon which the Society's financial survival depended, in jeopardy. I, therefore, elected to proceed slowly and it took two subsequent presidents before the problems were solved, and a new administration put in place, with the effect that the Society is flourishing and is a far more professional organization that it had been in the past.

University of California, Davis

I was recruited to UC Davis and its Center for Neuroscience by the persuasive powers of my long-standing friend and occasional collaborator, Leo Chalupa. There, I experienced a highly supportive administration that was determined to move the university ahead in the field of neuroscience and to do it in a manner that integrated neuroscientists across the College of Biological Sciences, the School of Medicine, the College of Letters and Science, and other smaller entities. I was given the opportunity to add 10 more faculty to the Center, which had been founded mainly as a cognitive and systems-oriented center by another old friend, Michael Gazzaniga, and to add the dimensions of cellular, molecular, and developmental neuroscience. Given sufficient resources of laboratory space and startup funds, I was able to compete effectively with other, perhaps better known institutions and to recruit some of the finest younger neuroscientists, all of whom are now rising to their peak years and are bringing recognition to UC Davis in the way that those who had the confidence to appoint me would have wished.

Much of the research that has been carried out in my lab at UC Davis has been a continuation of that commenced at UC Irvine and I have already mentioned some of it. Increasingly, chemical neuroanatomy has become molecular neuroanatomy as we have looked at patterns of expression of genes involved in the major neurotransmitter systems of the brain and in its development, with recent forays into the discovery of genes, often of unknown or unexpected function, that determine the phenotype of neurons and of nuclei in the thalamus and of areas of the cerebral cortex. This is work that has been conducted primarily by Karl Murray and Prabhakara Choudary, working at times in collaboration with Leo Chalupa. There has been one last foray into the field of connectional neuroanatomy when Alessandro Graziano and I carried out a series of experiments in monkeys that debunked the view that all the fibers arising from pain and temperature-specific neurons in the dorsal horn of the spinal cord terminate in a tiny, calbindin-immunoreactive nucleus at the caudal end of the thalamus, a nucleus that no one else, including me, has ever seen.

As I have grown older, my research program has become less expansive than in the past and is now focused in two areas. One of these involves a remarkably successful consortium made up of scientists and clinicians

at UC Irvine, UC Davis, the University of Michigan, Stanford University, Cornell-Weill Medical College, and the HudsonAlpha Research Institute. Generously funded by the Pritzker family and by the NIH, it focuses upon discovering genes that confer susceptibility to schizophrenia, major depression, and bipolar illness and on their expression patterns in normal and diseased brains. Thanks to the efforts of Dr. William (Biff) Bunney and his staff at UC Irvine, the consortium has built up one of the most thoroughly characterized human brain banks in the world, and we have spent a good deal of time in developing methods for ensuring that the tissue from brain slices frozen at autopsy can be recovered at a level of histological quality that rivals that obtainable in experimental animals. The consortium has also, through years of often frustrating effort, developed guidelines that determine to what extent the process of death (the agonal state) will interfere with the validity of gene expression profiling. The brain bank had its origins at UC Irvine, where Biff Bunney and I had collaborated on a number of projects, the most important of which, carried out by Schahram Akbarian in my lab, revealed the consistent down-regulation of expression of GAD in superficial layer neurons of the dorsolateral prefrontal cortex in the brains of schizophrenics, an observation that, unlike many in the field of schizophrenia research, has been replicated many times. Since then, with Huda Akil, Jack Barchas, Richard Myers, Alan Schatzberg, and Stanley Watson and their teams, Dr. Bunney and I have pursued many avenues of molecular-genetic research into the bases of these complex but important diseases. Results for us, as for all others in the field, have been frustrating and it seems clear that what were once thought to be powerful techniques that would help us unravel causes and effects have proven to be inadequate. Nevertheless, newer generation of techniques of increasing analytical power are being introduced all the time and one can expect some breakthroughs in fundamental knowledge to emerge from them soon.

The rest of my research time is now being spent in developing Web-based atlases of brain structure and connectivity at high resolution for the neuroscience community, visible at http://www.brainmaps.org. In these, which cover many species, mammalian and nonmammalian, but with a special focus on monkeys, serially sectioned brains are presented at a resolution matching that obtainable with the best microscopes and zoomable in real time from low magnification to one in which individual neurons can be visualized at a resolution of 0.4 microns per pixel. We are continuing to add to this extensive database, notably in collaboration with Harvey Karten, one of the most broadly knowledgeable neuroanatomists that I know, and are slowing bringing to it the serially sectioned brains of monkeys in which anatomical tracers have been injected into functional areas of the cerebral cortex. In these, scientists can determine for themselves patterns of connections and reinterpret older descriptions made with less satisfactory

techniques. Because so few connectional studies are being made now, even though it is a time when those on the cerebral cortex can be extremely valuable for interpreting the results of functional imaging studies, it seems important to make this kind of material widely available. Unfortunately, only a relatively small number of experimental brains can be provided. It is a pity that the slide collections of the older generation of connectional neuroanatomists have never been archived in accessible form. Sadly, when most old neuroanatomists retire, their slide collections are consigned to the nearest dumpster. I once offered to retrieve some of the best collections, digitize the sections, and make them available on our Web site. It would have required some resources of course but when I made overtures to NIH about it providing those resources, my approach met with studied indifference.

Looking Back

Over the years, as a reader will have seen, I have had the privilege of being able to pursue many different avenues of personal scientific interest. I have never felt constrained by any particular experimental model, brain area or technique. One of the most flattering remarks made about me in one of those tedious reviews that we in the University of California must routinely subject ourselves to was: "He's the last person left who can work on any part of the brain." I am not sure that that is entirely true anymore but it once was, probably because of all that teaching that I had had to do early on in all areas of anatomy. I have even managed to produce papers on the hippocampus, that structure that so puzzled me when I was starting out and trying to read Tom Powell's papers. In casting such a wide net as I have, I hope that I have made some small contributions to fundamental knowledge and that I have given value to those agencies, public and private, that have had the confidence to provide me with the funding necessary to pursue my multifaceted research career. I could not have done any of this without the help of a succession of students and postdoctoral colleagues, many of whom I have attempted to name in the foregoing, nor without the dedicated and expert assistance of a number of skilled technicians, particularly Bertha McClure in St. Louis and Phong Nguyen in California. Most of all, I could not have done it in the absence of the understanding support of a devoted wife and family, which now includes three growing grandchildren.

Do I regret the path not taken, the one that might have led me to a career in literature or the classics? Not a bit. That English teacher of so many years ago was right: I have had unparalleled opportunities to pursue many areas of personal interest both inside and outside the field of science. But the second edition of *The Thalamus* does commence with Ovid and end with Euripides. And it is the *Times Literary Supplement* that, in the face of Sue's complaints, I read at the breakfast table, not *Science* or *Nature*.

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