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William Maxwell Cowan

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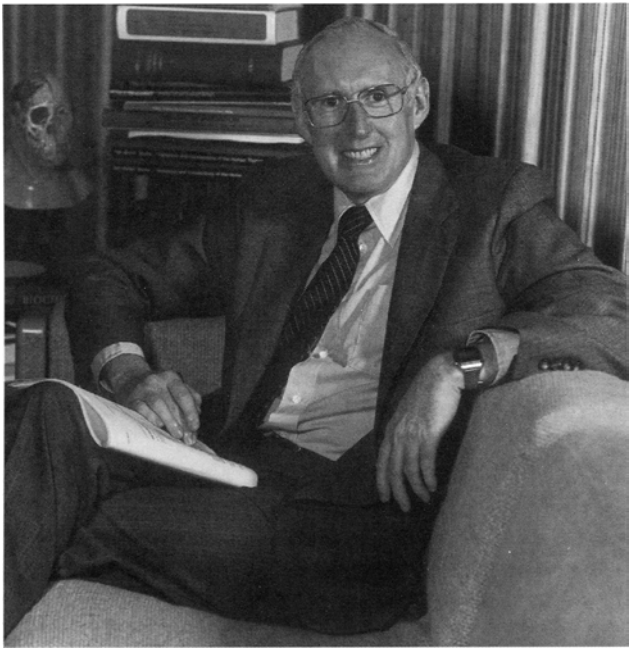

William Maxwell (Max) Cowan

BORN:

Johannesburg, South Africa
September 27, 1931

EDUCATION:

Witwatersrand University, B.Sc. (1951)
Oxford University, D. Phil. (1956)
Oxford University, B.M., B.Ch. (1958)

APPOINTMENTS:

Oxford University (1953)
Washington University School of Medicine (1965)
University of Wisconsin School of Medicine (1966)
Washington University School of Medicine (1968)
The Salk Institute for Biological Studies (1980)
Washington University (1986)
Howard Hughes Medical Institute (1988)

HONORS AND AWARDS (SELECTED):

Institute of Medicine (1977)
Society for Neuroscience, President (1977–1978)
American Academy of Arts and Sciences (1979)
Foreign Associate, National Academy of Sciences, USA (1981)
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Karl Spencer Lashley Award, American Philosophical Society (1984)
Foreign Member, Norwegian Academy of Sciences (1984)
Foreign Member, Royal Society of South Africa (1987)
American Philosophical Society (1987)
Honorary DSc., Emory University (1995)
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Max Cowan was a neuroanatomist who specialized in the developing nervous system and pioneered the application of modern neuroanatomical tracing techniques. A gifted scholar and administrator, he was the founding Editor of the Journal of Neuroscience, Editor of the Annual Review of Neuroscience for its first 25 volumes, and Chief Scientific Officer of the Howard Hughes Medical Institute for 13 years.

William Maxwell (Max) Cowan

I was born in Johannesburg, South Africa on September 27, 1931. My parents, Adam Cowan and Jessie Sloan Cowan (nee Maxwell), had emigrated from Scotland to South Africa in the early 1920s, together with my maternal grandparents and the rest of their family, just about the time that the full impact of the British government's decision to close many of the shipyards on the Clyde began to be felt. My father, grandfather, and the three eldest of my uncles had all been involved in one way or another in the shipbuilding industry, and by 1920 the prospects for shipbuilding seemed bleak. In a famous essay on *The Economic Consequences of the Peace*, Maynard Keynes had warned that moving too rapidly from a wartime to a peacetime economy could cause widespread unemployment and social upheaval. Unfortunately, his warning fell on deaf ears, and for much of the 1920s and 1930s the United Kingdom experienced an unprecedented depression. Anticipating that the situation was likely to deteriorate even further, my grandfather went to South Africa to explore the possibilities for engineering in the mines that were springing up along the "gold reef" of the Transvaal. Several months later he urged his family to sell everything they had and join him. My parents were engaged to be married at the time, and it took little persuasion for my father to decide to emigrate with my mother's family.

At first their best hopes seemed to be realized, but soon the mine workers went on strike for higher wages, and within weeks almost the entire industry ground to a halt. Refusing to meet the workers' demands, most mines were closed, and it would be almost 18 months before the workers were allowed to return—at a lower weekly wage than they had received before. In retrospect, it is difficult to know how the family survived this period. My younger uncles decided to abandon mining for other careers, but my father returned to working on structural engineering projects for different mining companies and in the mid-1930s for a private engineering firm where he rose from foreman to works manager. In 1940 he was asked by his company to take responsibility for repairs to ships damaged in the Indian Ocean, and for the next six years my family (consisting of my parents, my brother James, who was six years older than me, and I) moved to the post of East London on the East coast. At the end of World War II, we returned to Johannesburg.

The many moves my parents were forced to make meant that my brother and I had to change schools frequently. In one way I benefited from this. I had been taught by my mother to read, write, and do elementary arithmetic before beginning school when I turned six. Three months later I was transferred to a new school that had just opened. This school had too many second graders and resolved the problem by having an examination and passing on to the third grade the 20 or 30 of us who were judged to be able to cope with that grade. This meant that I had, in effect, completed the first three grades in little more than a year. It also meant that for the rest of my schooling I was two years younger than my classmates. The public schools I attended in Johannesburg were at best adequate, but I was fortunate in East London in being enrolled at Selborne College (named in 1907 for the Second Earl of Selborne, the High Commissioner for South Africa) which was one of the better schools in the country. When my family returned to the Johannesburg area, I stayed for about three months with friends to complete the academic year. While building a new house in a Johannesburg suburb, we lived for almost two years in Germiston, a small town outside the city. Here I completed the last two years of high school, "matriculating" with first class honors at the age of 15.

At the time I had given little thought to what I might do after graduating. One possibility was to join the law firm that my parents had used for some years, as an "articled clerk." This would enable me to work as an "apprentice lawyer" while attending the local law school part time. Since no one in my family had ever attended university, this seemed a reasonable route toward a professional career. Fortunately for me, when my parents and I met with the head of the law firm to sign the articles of agreement, he expressed surprise that I was just 15 and urged my parents to allow me to attend the University of the Witwatersrand ("Wits") full-time for at least one year. Having always taken his advice before, my parents agreed to this and I duly enrolled at the University to take a number of prelaw courses, including English, Afrikaans, Latin, History, and Economics.

That year proved to be decisive in my career. I enjoyed some of the work and did especially well in History and Economics, but soon began to have serious doubts about a career that would probably have involved mainly real estate law. And for the first time, I became seriously concerned about the enormous social disparity between white South Africans and the local African community, most of whom were either employed as domestic servants or in the lowliest (and often the most dangerous) positions in industry and in the mines. I was also much influenced by an elderly friend of my family who urged me to think of an alternative life of service to the community and suggested that I consider going to medical school. As the year progressed, this seemed more and more appealing. Although I knew that admission to medical school was extremely competitive, I thought I had probably done well enough in high school and in my courses at Wits to have a reasonable

chance. The one serious snag was that this was a six-year course for which my parents had not bargained. As it happened, the tuition was relatively low, and as I would be living at home and could probably earn some money doing various odd jobs at weekends and during the vacations, my parents finally agreed that I should apply.

The letter acknowledging that I had been accepted into the Medical School class for the following year indicated that although 120 students had been accepted, only 80 would be allowed to proceed to the second year because of space constraints. This meant that competition within the class was likely to be very keen. Like most medical schools that followed the British system of admitting students straight from high school, the first year courses consisted of Physics, Chemistry, and Biology. I had had a fairly good grounding in the physical sciences, but had never taken a biology course. Fortunately, the subject matter was inherently so interesting, and as it was given a decidedly "medical slant" by most of the faculty involved, I found myself more excited by biology than anything I had studied before. I also found that there was a ready market for the lecture notes I took, especially among the Afrikaans-speaking students in the class. Copying out and distributing my notes both aided my own studies and also provided a modest amount of pocket money. At the end of the year, I was ranked third in the class and was comfortably assured of a place in the second year.

In the two-month interval between the first and second years, I got a position as a trainee male nurse at a large, semi-private mental hospital on the outskirts of Johannesburg. This was my first exposure to psychiatry and to what seemed, at the time, to be the distressing treatment of patients with mental illness. Most of those suffering from depression were given electric shock therapy, without the benefits of muscle relaxants or tranquilizers. With three other male nurses, my role was to hold the patients down during their convulsions and, when they had regained consciousness, take them back to their wards, where they awaited their next treatment with growing trepidation. Patients suffering from schizophrenia were routinely given insulin shock therapy which, I was assured, was the best available treatment and, in some instances, seemed to benefit the patients. A number of patients who had failed to respond to all previous treatments were subjected to prefrontal lobotomies. This often enabled the families to cope with their previously intractable behavior, but a number I saw at the hospital seemed to be left in a zombie-like state requiring almost continuous care. My initial shock at what I witnessed during those two months gave way in time to a sense of the extraordinary mystery of how our brains must normally function and a feeling for the desperate plight of those whose brain function is impaired.

The second year curriculum consisted of Gross Anatomy, Histology, Physiology, and Biochemistry. Despite the enormous amount of sheer memorization involved and the general unpleasantness of dissection, I

quite enjoyed the courses taught by the Anatomy Department. The newly appointed Head of Physiology and Biochemistry, on the other hand, made these subjects almost incomprehensible to most of the students. Instead of traditional instruction, with lectures and laboratory exercises, he felt that the students should be exposed from the beginning to how scientists "think." To do this, the assembled class watched, listened, or tried to follow an ongoing series of discussions and debates in which all of the faculty participated. There was virtually no coherence in the subject matter from day to day. Studying textbooks was discouraged, and lab exercises were regarded as essentially a waste of time. The Professor himself tended to dominate every session, often going off on some wholly unrelated tangent that left the students bewildered and baffled. Sidney Brenner, who was in his final year, early on recognized that this was an absurd way to teach students who knew nothing about the subject and delighted in getting the Professor off the topic at hand and on to a wild intellectual goose chase. One of Sidney's favorite ploys was to interrupt with a question, "But what about the endocrines?" Rising to the bait the Professor would reply, "You're absolutely right, Sidney, one cannot forget the role of the endocrines," and off he would go, leaving the topic of the discussion, whether it was muscular contraction, temperature regulation, cardiac output, or whatever, as he held forth on "the endocrines." This was my first exposure to Sidney's puckish humor for which, as I later discovered, he was notorious and irrepressible.

Sidney Brenner

I had not realized until quite recently that Sidney Brenner and I had attended the same high school in Germiston, South Africa. He was six or seven years ahead of me, so I did not meet him until some years later when I was a second year medical student at the Witwatersrand University. Sidney was in his final year, having interrupted his medical studies to do a degree in genetics. He had had the most brilliant academic career and managed throughout his clinical years to do research and to teach in the Department of Physiology and Biochemistry. (This was to cost him an additional six months training in Internal Medicine, when the Professor of Medicine refused to give him a passing grade in his final examination, on the grounds that he had rarely, if ever, attended ward rounds.)

I mentioned that it was at Wits that I was first exposed to Sidney's sense of humor, but it was also here that I first discovered his innate and quite extraordinary kindness. Sidney recognized that the bizarre teaching approach adopted by the head of the Department of Physiology and Biochemistry was not teaching the students the fundamentals. About two-thirds of the way through the course, he realized that we could not possibly have learned any physiology and were in imminent danger of being failed by the external examiner at the end of the year. Quite on his own initiative, and

at considerable personal inconvenience, he organized a series of tutorials in which he tried to cover in a fairly systematic way the rudiments of biochemistry. Without this, I may never have passed the final examination. Almost everything I learned about biochemistry came from Sidney's seminars, and with my laborious reading of Best and Taylor's huge textbook I absorbed the basic physiology material as well.

I lost touch with Sidney about 2 years later, and it was not until after about another 18 months, in the fall of 1953, that I ran into him again. By this time I was at Oxford working on my doctorate and teaching as a junior faculty member in the Department of Human Anatomy. One late afternoon—it was probably in October or November—I was walking along South Parks Road, which marked the boundary between the science departments and the rest of the University. I was preoccupied and it was not until I had almost passed a duffle-coated figure when I suddenly realized it was Sidney Brenner. "Sidney," I said, "What are you doing here?" With characteristic absence of modesty he replied, "I'm teaching Hinshelwood mathematics." Sir Cyril Hinshelwood was Professor and Head of the Department of Physical Chemistry, a Nobel Laureate for his earlier work on the kinetics of chemical reactions, and a past President of the Royal Society and of the Classical Association. By general consent he was also the most brilliant linguist in Oxford, as fluent in Russian and Chinese as he was in French, German, Italian, Latin, and Greek. Also, if that were not enough, he was a painter of some distinction who had had several exhibitions at various galleries in London and elsewhere. Lately, he had become interested in bacterial growth which, to Sidney's chagrin, he insisted on treating as just another form of chemical kinetics. I gather Sidney had many arguments with his mentor, but apparently failed to convince him of the importance of genetics.

Shortly after Watson and Crick's paper on the structure of DNA appeared, Sidney went to Cambridge to view their model for himself and to talk to people who did believe in genetics. Crick was very impressed (as almost anyone would be) after talking to Sidney for an hour or more and tried to persuade him to join the group in molecular biology at the Cavendish. Unfortunately for Sidney, under the terms of his Beit Fellowship that had supported his stay at Oxford, he was obliged to return to South Africa for a year or two. This proved to be frustrating, but not a complete waste of time as he was able to work in a virology laboratory where he familiarized himself with the exciting work on phage genetics that had played such an important role in the creation of the emerging discipline of molecular biology.

As soon as the mandatory period had expired, Sidney returned to the United Kingdom and took up a staff position in what had now become the Medical Research Council Laboratory of Molecular Biology (LMB) at Cambridge. He was to remain at the LMB until he reached statutory retirement age, having served, after Max Perutz's retirement, as Director of the Laboratory. For many years, until Francis Crick left Cambridge for the Salk

Institute in the late 1970s, Sidney and Francis shared an office during what was one of the most productive collaborations in modern biology. As Francis once remarked to me as we talked of that period, "I always felt that any day that I did not spend at least an hour talking to Sidney was a wasted day."

I need hardly summarize the extraordinary series of seminal discoveries that emerged during that period. It is sufficient to simply mention some of the highlights: the elucidation of the general nature of the genetic code; the discovery of messenger RNA and the formulation of the "central dogma" of molecular biology—"DNA makes RNA and RNA makes protein"; and the introduction of the nematode worm *C. elegans* as a model system for the analysis of development. Sidney's role in all these discoveries was critical, and it is a continuing source of surprise to most biologists that his contributions during this period have not been recognized by the award of the Nobel Prize.[1] With the possible exception of Seymour Benzer, there is no one more deserving of such recognition.

When I emigrated to the United States, for a period of time I lost contact with Sidney. But in the mid 1970s, when I was trying to recruit a molecular geneticist to the Department of Anatomy and Neurobiology at Washington University, I wrote to him asking if he could recommend someone for the position. As it happened, Dr. Bob Waterston, an American postdoc working in Sidney's laboratory on a interesting aspect of genetic regulation in *C. elegans*, was planning to return to the United States. Bob had some reservations about joining a department that was so heavily committed to neurobiology, but at Sidney's urging he accepted the position. (Later, when I left Washington University, Bob transferred his appointment to the Department of Genetics. In due course he became Chairman of the Department and Head of Washington University's Genome Sequencing Center which, with the Sanger Center at Cambridge, has been responsible for sequencing the entire *C. elegans* genome and for contributing the major share of the data in the publicly supported human genome sequencing effort.)

After he retired from the LMB, Sidney became a fairly regular visitor to the Salk Institute, where he continued to astonish us all by the breadth of his knowledge of virtually all aspects of biology and to delight us with his humor. I recall his saying on one occasion when he visited the Salk, having stopped off on the way first at Boston and then at Pasadena, that this has been an unusually interesting trip. In Boston, Ben Lewin, then Editor of *Cell*, the most successful new journal in biology, had complained about the large numbers of papers he was receiving each month. He asked Sidney if he thought they should consider publishing a second more or less parallel journal. "If you do," Sidney replied, "I suggest you call one of them

[1]Editorial note: Unfortunately, Max Cowan died before it was announced in the fall of 2002 that Brenner had won the Nobel Prize.

'Hard Cell' and the other, 'Soft Cell.'" (Some years later Lewin did put out a second journal, but under the more prosaic title of *Molecular Cell*.) At Pasadena, Sidney had spent some time with a well-known immunogeneticist who had bent his ear for some hours about the future of genetics and new methods and machinery for DNA sequencing. Sidney's report of this visit went something like this: "You know I've always been very skeptical about artificial intelligence, but having spent an afternoon with _____, I am now totally convinced that it exists."

Sidney currently directs a modest research institute near Berkeley. He is still full of new ideas about the future of genomics (and almost anything else one cares to mention), and every other month he has a piece in *Current Biology* that reminds us that his sense of humor is, if anything, even sharper than before. For example, only Sidney could propose that the Nobel Prize Committee in Stockholm revise its policies. As he tells it, on the prescribed day in October the awardee would receive an early morning phone call, "Professor ____, I am honored to tell you that you have been selected to receive this year's Nobel Prize for Physiology or Medicine." Once the excited recipient of the call had calmed down and stopped saying how shocked he was and how flattered and honored, etc., the heavily accented Swedish voice would say: "I must inform you, Professor _____, that the policy regarding the Nobel Prize has been changed. You now have to decide whether you want the honor or the money—you can no longer have both."

For more than 50 years, Sidney has been one of my scientific heroes. I am fortunate to have been his student and I am honored to be his friend.

An Introduction to Neuroscience

The only integrated course taught my second year was in the area we now refer to as neuroscience, although it was some 20 or more years before that name was introduced. The reason for this was that only one person in the brain sciences was competent to teach both neuroanatomy and neurophysiology. This was Dr. Michael Wright, at the time a senior lecturer in the Anatomy Department. Mike, as I soon came to know him, was essentially self-taught. Like Sidney Brenner, he too had interrupted his medical training to do a degree in anatomy, where he had concentrated on the nervous system. On completing his medical degree, he joined the faculty and soon established himself as *the* local authority on the nervous system. He had a slight stammer and was not a particularly fluent lecturer. But among all our teachers he stood out as not only extremely knowledgeable about his subject, but also determined to engage the interest of his students. I can still recall vividly the lecture he gave on synaptic transmission. This was based (as I later learned) on Eccles' recent review and restatement of his electrical hypothesis for both excitation and inhibition. For the first time my interest was piqued: how exciting it must be to understand something

about our brains and how they function. At the end of the lecture, when the other students had left the auditorium, I had the temerity to ask "what would one have to do to work in this field?" Mike's response was to say that if I did well enough in my second year courses, I could drop out of Medical School for a year and take a B.Sc. in Anatomy and focus my interest, as he had done, on the nervous system.

When the results of our first exams were posted, I went to see Mike again and was reassured that I would be accepted into the Department's B.Sc. program. My parents were concerned that this would add yet another year to my education, but were somewhat reassured that I would probably be given a teaching assistantship and, with it, tuition remission. Generally, only one or two students took this approach each year, but in my year six of us chose the B.Sc. program and were joined by a seventh student, Godfrey Getz, who had completed the third year before returning to do a degree in Biochemistry. Of the students in my own year, only two of us continued this diversion, taking a second year to take a B.Sc. Honors degree. My colleague, Bill Andrew, later spent several years as a medical missionary in Swaziland before becoming a consultant radiologist in Pretoria. Godfrey Getz went on to have a distinguished academic career in research, teaching, and academic administration at the University of Chicago.

I had not appreciated that the B.Sc. degree would entail majoring in two subjects, Gross Anatomy and Histology, or that Gross Anatomy included human paleontology. So the amount of time I could spend on neurophysiology, which had been my initial interest, was rather limited. In part because of this, and in part because I was awarded the degree with distinction in both majors, which had been achieved only once before—by Sidney Brenner, no less—I stayed on for a second year. During this year I spent a great deal of time with Mike Wright—much of it in building our own equipment—learning from him much more than neuroanatomy and neurophysiology. He encouraged me to read widely in philosophy, in the history of science, in politics, and in literature. In a special sense this year marked the beginning of my real education.

After completing the requirements for the B.Sc. Honors degree, I returned to the third year of Medical School, mainly Pathology and Pharmacology. But I had only spent about four rather boring months on these subjects when, out of the blue, I was summoned to see Professor Dart, the Head of the Anatomy Department. With characteristic shortness Dart began by saying, "How would you like to go to Oxford?" I was too surprised to answer intelligently, so he went on to explain that he had recently received a letter from his friend Professor LeGros Clark at Oxford, asking if there was anyone in his Department interested in the nervous system who might be suitable for a junior faculty position. After discussing this with Mike Wright, Dart had decided to put my name forward, although, as he was quick to point out, I should not let my expectations get out of hand because it was likely

that LeGros was interested in someone who already had a medical degree. The vacancy at Oxford had occurred because a former South African, Harold Daitz, who LeGros had recruited three or four years earlier, had died suddenly. But LeGros had been so impressed with him that he thought it just possible that another South African might be suitable. Dart promised to write to LeGros and, to my amazement, received a letter by return of post saying that Cowan sounds fine; he can do a D.Phil (Oxford's Ph.D) while working as a Department Demonstrator (a position roughly equivalent to a non-tenured Assistant Professor at a U.S. institution) at a salary of £500 per year. This time I was ready with my answer, and in little more than a month I set sail from Cape Town, arriving in Oxford on April 17, 1953.

Raymond Dart

It was not until I arrived in Oxford that I discovered that not all professors of Anatomy were like Raymond Dart, the Professor of Anatomy Wits. For generations, Dart had terrorized students by his irascibility and his intolerance of even the most minor error or infraction of the rules he had imposed. His infrequent visits to the dissection room were terrifying to even the bravest student. At any moment he could fasten on a hapless student and launch a verbal attack on his or her appearance, dress, or posture, with his voice rising in real or feigned anger that sent shivers of fear throughout the entire class. His brusque ferocity was legendary throughout the Medical School. One widely repeated story—probably apocryphal—was that on one occasion a rather mousy faculty member had haltingly announced that his wife was pregnant. "Good God, man," Dart was alleged to have responded, "Who do you suspect?" He was only slightly more accessible and a shade less intimidating to the students who dropped out of Medical School for a year or two to take a bachelor's or honors degree in Anatomy and Histology.

It was during the year I was working toward a B.Sc. in his department that I experienced first hand his wrath. The first occasion was when I gave a seminar on cutaneous sensation to the faculty and my fellow students. I had worked hard in preparing for the seminar and thought it had gone well. But no sooner had I ended than Dart, who had been sitting in the front row, jumped to his feet. "My God man," he railed, "If you have something to say, shout it out. Don't just stand there, holding on to the pointer as if for dear life." And with that he leapt onto the podium, his arms flung high as he repeated, "Shout it out. Let the world know what you think."

My second encounter with Dart was even more traumatic. I had not realized when I enrolled for the degree course that the degree in Anatomy included Anthropology. At the time I had little interest in comparative anatomy or physical anthropology and had paid little attention to either the lectures or the practical work. About a third of the way into the course,

I received a summons to meet "the Prof" in his office, together with Philip Tobias who served as course master for the anthropology program. At the appointed time Tobias and I met at Dart's door. Tobias knocked and Dart responded with a gruff "come in." But as we entered his office, he did not look up. Instead, he continued writing for what seemed to me to be half an hour, but was probably only a minute or two, but long enough to be intimidating. Finally, he looked up at Tobias and said "Well, what is it?" With that Tobias began listing how many lectures and labs I had missed and how far back I was falling in anthropology. When he finished, Dart said, "Is that all?" "Yes," I replied. Dart asked, "Then what the hell have you been doing?" I replied, "I've been working with Dr. Wright. You see I had only dropped out of Medical School for this year because I wanted to study the brain and especially neurophysiology. And for the past three months we have been building equipment."

When I stopped, my heart was beating fast and my palms were cold and clammy. Imagine my surprise when Dart suddenly turned on Tobias and asked, "Is that true?" "Yes," said Tobias—he had obviously talked with Mike Wright. "Then why are you bothering me?" Dart asked. He continued, "We get about 80 medical students a year through this Department, and hardly one of them has ever had an idea in his head. At last we find one interested enough to want to study something he's excited about, and you want to kill his interest by turning him into a measurer of bones like yourself." He had a few more choice words for Tobias, and just as I was beginning to feel sorry for him at this unexpected turn of events, Dart turned on me: "As for you young man, if you don't get the top mark in anthropology at the end of this year I will personally see that you are thrown out of this University. Now get the hell out of here!"

Fortunately, with some effort I was able to catch up with my colleagues, and, in time, I even began to find anthropology quite interesting. At the end of the year I was fortunate to get a "double first" (i.e., honors in both my major subjects) which did not escape Dart's attention. I recall walking down the hallway one day and being alarmed at seeing Dart and a visitor approaching. The most alarming thing was Dart's simian gait: head slightly lowered, brow furrowed, arms hanging loosely at his sides, a curious, almost slouching walk. To my surprise, as he reached me he stopped, turned toward the visitor, and said: "Oh, this is Cowan, one of our bright young boys." With that he turned and continued his Australopithecine-like progression.

In the mid-1970s, when I was Chairman of the Anatomy Department at Washington University School of Medicine, I heard that Dart (who was then in his 80s) was visiting Philadelphia. As he had spent almost two years in the 1920s working in the Anatomy Department at Washington University on a Rockefeller Fellowship, I thought it would be nice to invite him to give the Terry Lecture, named for Robert Terry, Washington University's first Professor of Anatomy and someone whom Dart had known and admired for

more than 50 years. Dart said he would be pleased to accept the invitation and duly came to St. Louis. While somewhat frail, in conversation he was as lively as ever, but, as I was pleased to see, a good deal more mellow.

In introducing him to the audience who attended the lecture, I commented briefly on his career. After completing his medical education in Sydney, Australia, he had gone to England to work under Sir Grafton Elliot Smith, at that time the doyen of British anatomy. When he returned from his stay in St. Louis, Elliot Smith had urged him to apply for the Chair of Anatomy at the newly formed Medical School at Wits in Johannesburg, South Africa. In due course he was appointed and took up the position in January 1923. The following year he made one of the most important discoveries in human evolution—the finding of the first Australopithecine fossil. The story of this discovery has been told frequently, so I shall not repeat it here. But what is less well known is that Dart's report of his finding in the journal *Nature* met with considerable skepticism by the leading British anatomists who, for the most part, were so enamored of the Piltdown skull that they found it hard to believe that the adoption of an upright posture preceded expansion of the brain. Moreover, many of them also remembered that before Dart left for South Africa, he had published a number of papers on the evolution and development of the vertebrate nervous system which not only challenged the conventional wisdom, but in at least one instance was demonstrably wrong. It would be more than 30 years before the correctness of Dart's interpretation of the Taungs baby came to be appreciated. But Dart's immediate response was typical; he refused to publish his next several papers in British journals. As I recall he sent his first post-Australopithecus Africanus paper to an obscure Japanese journal!

After saying all this and more, I ended the introduction by recounting my meeting with Dart and Tobias. In responding, Dart began his lecture by saying, "I can't recall the incident that Dr. Cowan has just recounted, but remembering how I used to be in those days, I must confess it sounds authentic!"

I cannot end my reminiscences about Raymond Dart without adding two further remarks. The first is that I am only one of many South Africans who got their start in science by taking advantage of the introduction to research provided by the degree courses for medical students that Dart had initiated. Although he did not personally participate to any significant degree in these courses (at least by the time I took my degree), he realized long before most other medical educators that the best way to excite students' interest in science is to give them an opportunity to be engaged in research as early as possible. The success of so many who took a B.Sc. or B.Sc. Honors degree during their medical training is a lasting tribute to Raymond Dart. The second thing I wish to add is an abiding memory I have of Dart that stands in striking contrast to his brusque and often frightening manner. It happened

during a lecture he gave on human evolution. At one point, he lifted onto the desk what looked like a shoe box. From this, with visibly trembling hands, he removed the original Taungs skull. For fully a minute he held it like a tiny infant in his hands, and from near the front of the lecture room I could see his eyes fill with tears. Was it, I wondered, because he continued to be overawed by the wonder of holding in his hands the first real link to our prehuman past? Or was it from the realization that after so many years he had finally been vindicated? Even his most vociferous critic, Sir Arthur Keith, had finally accepted the correctness of his views and had proposed that the Australopithecines should be called the "Dartians," although unlike the "Martians," they really were of this world. Whatever the reason, the moment was a touching one that revealed an aspect of Dart's persona that for the most part seemed to have been carefully concealed. Like so many men who present a remote and tough exterior, at heart he was as sentimental as anyone I have known in science.

I should also say that it is a source of special pleasure to me that it was largely through the efforts of my mentor at Oxford, Wilfrid LeGros Clark, that the Australopithecines came to be recognized as the earliest human ancestors. And for most of my years at Washington University, a plaster cast of the Taungs fossil stared down at me as I sat at my desk, a stern reminder not only of where I had come from (in more ways than one) but also of how I should (or perhaps better, should *not*) behave toward my colleagues and students.

LeGros Clark

It is impossible to express adequately my indebtedness to LeGros Clark. From my first meeting with him on the morning after my arrival in Oxford until his last brief letter to me some months before his death in 1971, he treated me almost like a son; he guided and nurtured my scientific career, advised me generously on every significant decision I made, and set the finest example of scientific excellence and sound judgment that I have known. In sum, I owe almost everything I have been able to achieve to his personal kindness, thoughtfulness, and encouragement. I had known of his many contributions to neuroanatomy before joining his department, but it was only later that I came to appreciate the importance of his contributions to comparative anatomy, to primatology, and especially to human evolution and in a larger sense through his books and lectures to all aspects of anatomy. To say that he was *the* outstanding anatomist of his generation hardly does justice to the range of his scholarship and the example he set for all who were privileged to know him. Two incidents will serve to illustrate how he influenced my own career, beyond the unique opportunity he provided by inviting me, an unknown student, to Oxford to be his colleague and for 20 years his friend.

Unknown to me he had applied, on my behalf, to the Nuffield Foundation for one of their greatly prized Commonwealth Fellowships. When, some time later, he told me that the Foundation had made an exception to their general policy of only awarding fellowships to individuals currently residing in one of the Commonwealth countries, I was both surprised and delighted; the stipend was significantly more than my Oxford salary, and the fellowship carried a number of other fringe benefits. But when he told me that one of the requirements was that fellows had to return to their own country for at least three years, he immediately sensed my disappointment. "How do you feel about returning to South Africa three years from now?" he asked. When I responded by saying that I had hoped that, if I did well enough, I would be able to continue working at Oxford, he said without a moment's hesitation, "That's what I hoped you would say; I'll let the Nuffield people know that you have declined their offer." Despite the trouble he had gone to, he gave not the slightest hint of annoyance; instead, I took his response as the best possible reassurance that he was pleased with my progress and that I could look forward to a continuing position in the department.

The second incident also occurred without my prior knowledge. In the fall of 1955, he attended a meeting in Johannesburg on the role of the Australopithecines in human evolution. While he was there he got hold of my parents' address and arranged to visit them at their home. On returning to Oxford, he came up to my office to say that he had been giving a good deal of thought to my career and felt that it would be important for me to complete my clinical training and take the B.M.B.Ch. degree. He had already consulted with the University authorities and had been assured that I could be admitted to the clinical school at the Radcliffe hospital in the spring and would not have to meet any of the preclinical requirements, except for Pathology and Pharmacology. In addition, I would continue my appointment as a Departmental Demonstrator (at a somewhat reduced salary) and would be promoted to a tenured University Lectureship when I had taken the degree. This was such a surprise that after thanking him for going to all this additional trouble I could not help asking why he was suggesting what seemed to me an entirely new direction. His answer was: "Two things. First, without a medical degree it will be very difficult for you to achieve the success your career deserves, at least in this country. And, second, when I told your parents how well you were doing and would soon have your D.Phil., your mother said to me, 'That's very nice, but we had always hoped he would become a real doctor.' So you owe it both to yourself and to your parents to do this." Needless to say, I took his advice and was able to complete my medical degree in about two and a half years after finishing the D.Phil in April 1956. But perhaps the kindest and most encouraging gift LeGros bestowed was the freedom to work on whatever topic I chose, while always making himself available for advice and guidance whenever I needed it.

Neuroanatomical Studies with Tom Powell

The first person in the Department of Human Anatomy Le Gros introduced me to was Tom Powell. Little did I realize that morning that Tom and I would work together over the next 13 years or that next to Le Gros himself, Tom would have the greatest impact on my work during my years at Oxford.

As we were walking upstairs from Le Gros's office he told me that he especially wanted me to meet a young clinical research fellow who had been in the department for about a year and a half. He told me: "His name is Tom Powell and although he originally came to Oxford to do neurosurgery with Hugh Cairns, I hope he will stay with us in the Department. He won the Hallet prize and we really need people who know Gross Anatomy as he does. He's been working with me on the thalamus and I'm sure you'll find him helpful." I had no idea what the Hallet Prize was or why this would indicate a good gross anatomist, but I was pleased to know that there was someone else working in the brain to whom I could look for help. When Le Gros introduced us, I was immediately impressed by Tom's friendly response. As we left his office he said, "If I can help you in any way, just let me know."

It was not long before I learned that the Hallet Prize was awarded each year to the top candidate in the primary examination for the FRCS (Fellowship of the Royal College of Surgeons) and that its receipt marked one as knowing essentially everything there is to know about gross anatomy. I also learned that in preparation for the "primary," Tom had spent a year as a Demonstrator in Anatomy at Cambridge, where he had not only mastered the minutiae of anatomy, but had seen Geoffrey Harris working out the direction of blood flow in the hypophysial portal circulation that, arguably, marked the real beginning of modern neuroendocrinology. Later, I learned that he had won scholarships to Edinburgh—at the time the leading medical school in the United Kingdom—and that on graduating he had determined to become a surgeon. After completing an internship he had gone to Cambridge, took the primary FRCS, and was then a surgical resident (to use the American title of this position) at the Royal Postgraduate Medical School with Hammersmith Hospitals. On completing the second part of the FRCS, he had essentially become "board certified" in surgery. But he had set his heart on a career in neurosurgery and had applied for an internship in Cairns' unit at Oxford. Cairns had established his service as the very best neurosurgical unit in the country and competition for places in his program was extremely keen. He only admitted people who had already completed the equivalent of a residency in general surgery. His standards, and those of his colleague, the American Joe Pennybacker, were known to be the most rigorous in the profession.

For some reason that I cannot recall (if I ever knew), Cairns was unable to have Tom begin his neurosurgical training right away and suggested that he spend a year or more doing research in the Department of Human

Anatomy under Le Gros Clark. Le Gros had been pleased to have Tom join him and assisted in Tom's obtaining a Medical Research Council Clinical Research Fellowship.

As it happened, Le Gros had received the brain of a patient who had died some 24 days after having almost the entire cerebral hemisphere surgically removed and felt that the analysis of the thalamus would be an excellent project for Tom's first experience in research. While several studies of near complete hemispherectomy in other mammals (including non-human primates) had been reported, this seemed like a unique case to observe the changes in the human thalamus. The analysis of this brain occupied much of Tom's first year in Oxford and resulted in his first publication, *Residual Neurons in the Human Thalamus following Hemidecortication*, that appeared in *Brain* in 1952. It was to be the first of over 160 papers he would publish over the next 42 years—efforts that constituted an extraordinary research contribution.

Tom's first experimental study was done in collaboration with Le Gros. It involved analyzing retrograde degenerative changes seen in the ventral posterior nucleus of the thalamus after more-or-less selective lesions of three of the cytoarchitectonic fields that comprise the somatosensory cortex in monkeys. The resulting paper appeared in 1953 shortly after I joined the Department. Le Gros had been responsible for most of the surgical procedures and Tom had carried out the detailed (and quantitative) analyses on which their primary conclusions were based. He had also written, as he showed me, four drafts of the paper before Le Gros was satisfied and sent it off to the *Proceedings of the Royal Society*.

About the time Tom began working in the Department, Le Gros recruited to the position of Departmental Demonstratorship a young South African who had for a short while been working in the Anatomy Department at Middlesex Hospital. This was H. M. Daitz, known to my colleagues in Johannesburg as Harold, but to everyone at Oxford as Max. Daitz soon made his presence known in the Department. He was thoughtful, smart, hard working, and unusually outgoing. At the Middlesex Hospital he had worked in an intellectual vacuum but surrounded by others doing research; he blossomed in Oxford. Like Le Gros Clark, who near the beginning of his career had carried out an important experimental study using the simplest of tools—a saucepan, scalpel, scissors, and surgical needle—to place lesions in the brains of rats, Daitz set out to study the hippocampus and its connections. Unfortunately, his life was cut short at the age of 29, and the field lost someone who would undoubtedly have become a major figure judging from the material he had collected and the notes he had made during his brief stay at Oxford.

At Le Gros' suggestion, Tom undertook to work up Daitz's unpublished work, and when I first met him he was in the process of putting the finishing touches on a paper that reported Daitz's first original discovery, namely,

that the fimbria are not solely a hippocampal efferent pathway as Cajal and others had stated, but contained afferents from the medial septal nucleus and the diagonal band of Broca which we now know to be the source of the cholinergic inputs to the hippocampal formation. The cellular changes in the septal region after fimbrial lesions had puzzled Tom for some time, and for the first few days I was in the Department we discussed them, looked at the slides, and discussed them further, until finally Tom felt satisfied that his initial conclusion was probably correct. This experience presaged the literally hundreds of hours that Tom and I were to spend over the next 13 years looking at slides, debating the significance of our observations (we always examined the experimental material independently), and trying to resolve difficulties in conference before writing up the results with each of us taking turns to "dictate" a section while the other wrote it down. When we had completed the draft, Tom would type it up, hunting and pecking on an old manual typewriter while I prepared the figures and the photomicrographs. We often had lunch and dinner together at the faculty club adjoining the science area. In the evenings we went back to the lab until 10:00 or 10:30 PM. We were both single at the time and work was the center of our lives. When we were not doing experiments or looking at the slides, we would spend hours on end talking, talking, and talking. For me it was wonderful to have such a colleague and friend, and as our work was going well, I could not have wished for a better start to my career (Fig. 1).

Fig. 1. Max Cowan (far left), Tom Powell (far right), and other lab members at Oxford in the early 1950s.

In many of the brains prepared by Daitz, the anterior thalamic nuclei had been incidentally damaged, and with LeGros' approval, Tom and I used some of these brains to analyze the selective projection of different parts of the medial mamillary nucleus. The large-celled lateral nucleus appeared to be unaffected.[2] Some of the other material Daitz had prepared began what was to be a long-term interest in the organization of the connections of the hippocampus, but apart from enabling us to clearly distinguish the fields that projected into the fimbria and the so-called dorsal fornix, the protargol-stained preparations were of only limited value.

While working up Daitz's material, Tom and I spent a good deal of time thinking about the projection of the midline and intralaminar nuclei. Unlike most of the rest of the thalamic nuclei, which undergo severe retrograde degeneration after lesions of specific cortical fields, the intralaminar nuclei (and especially the centromedian nucleus which is such a striking feature of the primate thalamus) show either no, or only minimal, changes even after virtually complete decortication. In addition, in the 1940s Morison and Dempsey had shown that low-frequency electrical stimulation of the intralaminar system elicited a "diffuse recruiting response" across the cortex. A number of alternative suggestions to account for these findings had been put forward, and most recently, Rose and Woolsey had reported that whereas the nuclei survived large cortical lesions, in rabbits in which the "rhinecephalic" structures were destroyed, the nuclei showed marked degeneration. They had not followed up on this observation, and so Tom and I planned a series of experiments, first in rats and later in rabbits, with lesions directed at the rhinecephalic structures in the basal forebrain, sparing as much as possible the neocortex. The results of these experiments were reported in 1954 and 1955 and seemed to us to establish fairly clearly that, whereas some of the smaller midline nuclei projected to the mediobasal forebrain, the intralaminar nuclei only showed degeneration when the lesions encroached on the striatum (caudate and putamen). There had been earlier findings compatible with the notion that the intralaminar nuclei were part of a thalamo-striate system, but to a large extent this view had been discounted. We were impressed—as was LeGros when we showed him our material—that the severity of the cellular degeneration was as marked as that seen in the principal nuclei after cortical lesions. In retrospect, however, we should have considered the possibility that the changes were

[2]I returned to this problem several years later when I was in St. Louis and was asked to examine several cat brains in which F.J. Fry at the University of Illinois, Urbana, had placed lesions at different levels in the mamillothalamic and mamillotegmental tracts either singly or in combination. Following his death, his family asked if I could prepare the work for publication. This was of interest to me because of my prior work on the mamillary connections, but especially because it provided a direct way to test the hypothesis that the existence of proximal collaterals protected neurons against axotomy.

not solely due to damage to the terminals of the axons of the intralaminar nuclei and perhaps given more attention to the much milder changes that from time to time had been reported in the nuclei after large cortical lesions.

At the time, we were excited by an entirely fortuitous observation in the brains of some of our experimental rabbits in which the cingulate cortex had been damaged, without involvement of the striatum or the thalamus itself. This was the finding that, in addition to the expected retrograde degeneration in the three anterior thalamic nuclei, there was marked cell loss in the medial mamillary nucleus. This prompted us to place additional lesions in different parts of the cingulate cortex in young rabbits, following on the lines of Rose and Woolsey's careful analysis of the projection of the anterior nucleus upon the limbic cortex. These experiments confirmed our earlier study that each major part of the medial mamillary nucleus projects upon a different component of the anterior thalamic complex and beyond these to the different cytoarchitectonic fields of the cingulate region. As neither LeGros nor Tom had been aware of such "retrograde transneuronal degeneration," for a few short days I felt I had actually made an original discovery. But, cautious as always, LeGros urged that we look closely at the early German literature in which so much had been reported but largely forgotten. To my chagrin I soon learned that between 1870 and 1884 Gudden had reported atrophy of the medial mamillary nucleus in his young rabbits with extensive cortical lesions. And further reading revealed that there were reports in the ophthalmology literature of primary optic atrophy (due to the death of retinal ganglion cells) in patients with long-standing lesions involving the visual cortex. (Some years later, when I was in Madison, WI, one of my graduate students, Jennifer Hart (later LaVail), and I found that cingulate lesions in neonatal and very young rats could result in degeneration beyond the anterior thalamus and mamillary nucleus, to the ventral tegmental nucleus which was known to project upon the medial mamillary nucleus).

Despite the cost of monkeys for experimental purposes, LeGros Clark felt it was important to obtain funds for Tom and I to place stereotaxic lesions in different parts of the caudate nucleus and putamen in a number of macaques to resolve in particular the long-standing issue of the projection of the centromedian nucleus. Although in some cases the incidental involvement of the internal capsule complicated the findings, it was clear from others that isolated lesions within the putamen resulted in clear-cut retrograde degeneration in the centromedian nucleus and equally convincing changes in the more rostral intralaminar nuclei including the nuclei centralis medialis and lateralis. The resulting paper in *Brain* seemed well received, and it was not until the introduction of new methods that we finally established that, in addition to their primary projection upon the striatum, the intralaminar nuclei have colleratal projections to the cerebral cortex.

During a short trip that Tom and I made to Brussels, at the invitation of Frederic Bremer, one of the outstanding neurphysiologists of his generation, we saw experiments being done on pigeons which seemed among the most tractable of all experimental animals. Since, in avian brains, the striatum comprises almost 90% of the telencephalon, it occurred to us that it might be of interest to examine the projections of the different thalamic nuclei upon the various striatal subdivisions. While the findings in this study proved to be of some interest to comparative neuroanatomists, it had a much longer impact on my own career, again through a wholly unexpected finding.

As we were compiling our study, we were joined for a year by a postdoctoral fellow who wished to learn some neuroanatomical methods. Because he was to be with us for such a short time, we suggested that he might examine the projection of the retina upon the diencephalon and midbrain of the pigeon, using the technique introduced in 1954 by Walle Nauta that clearly showed the course and termination of degenerating axons against a relatively clear background due to the active suppression of staining of normal axons. The findings confirmed what had been known for many years about the retinal projection, but the pattern of degeneration in one component of the visual system, the so-called isthmo-optic tract, seemed quite different in that it began within the isthmic region of the brain and proceeded centrifugally toward the retina. In Nissl preparations made some weeks after unilateral eye removal, the isthmo-optic nucleus (ION) of the opposite side was completely degenerated. What we had stumbled upon was a centrifugal projection within the visual system, that is, a pathway that arises in the brain and projects to the retina. Again, a search of the older literature revealed that this pathway had been described in the late 19th century by the Dutch neuroanatomist Wallenberg, but had been largely ignored. Some time later, one of Tom's students, James McGill, interrupted his medical studies to do a D.Phil. and chose to work on the detailed organization of the projection of the ION upon the retina and of the projection of the retina upon the ION, by way of the optic tectum. The ION and its connections were to play a large role in my subsequent career when in the mid-1960s and later I began working on the development of the nervous system.

But several things were to happen before this. I had begun my clinical training in the fall of 1956 and was able to supplement my demonstrator's salary by tutoring students at Pembroke College in Anatomy.

In the late summer of 1954, I learned that Mike Wright and his wife were coming to London—he to do electroencephalography at the National Hospital for Neurological Diseases in Queen's Square and she to continue her clinical training at the Hammersmith Hospital. Shortly afterwards, with LeGros' approval, Mike and I agreed to pick up on some of the work we had been doing at Wits on the use of "strychnine neuronography," although by this time it was clear that the complex pattern of "suppressor bands" that

Dusser de Barenne, McCulloch, and their colleagues at MIT had claimed to have found using this approach were almost entirely artifactual. We were still interested in the possible relationship of trains of strychnine spikes to the "spike and dome" recordings seen in petit mal epilepsy. And since, by this time, everything I had worked on had been done in collaboration with Tom Powell, it was natural that he should join us in this endeavor.

Michael (Mike) Wright

Apart from a handful of close personal friends, two or three former colleagues, and perhaps a dozen of his students, Mike Wright is essentially unknown. Yet to those whose lives he touched, he will always be remembered as a fine scholar, outstanding teacher, and a wonderfully caring human being. I personally owe as much to Mike Wright as to any of my other mentors, and in an act of quite extraordinary generosity, he changed my entire life.

Mike, like so many of the junior faculty members I encountered in my first year or two at medical school, had interrupted his medical training to do a degree in science (he ended up doing an M.Sc.) and shortly after graduating was offered a faculty position. He had had an excellent academic record as a student, but what was most remarkable was that he had, entirely through his own efforts, become the most knowledgeable neurobiologist in South Africa (although the term neurobiology was not then in vogue). It is true that as a young scientist Raymond Darrt had published papers on the brains of some Australian reptiles and on this basis had arrived at a rather odd view of brain evolution, but there was no one else in Johannesburg at this time who had any first-hand experience of neurophysiology or neuroanatomy. To this degree Mike was a self-taught man.

I don't know what had prompted him to turn his attention to the study of the nervous system. Perhaps it was because as an infant he had suffered some form of neurological injury which left him with a marked foot drop, a somewhat unsteady gait, and a mild stammer. But by the time I met him, he had not only mastered the intricacies of neuroanatomy, including its esoteric and often capricious methods, but was aware of all the latest developments in neurophysiology and had learned enough about electronics to begin building his own equipment to record activity from the brain. It was probably because he was so engaged with the field that he became such an engaging teacher. Unlike most of his colleagues who were content in their lectures to rehash the contents of the prescribed textbooks, Mike made a point of introducing his students to the most recent new work in the field, while in no way trying to snow them with his erudition. Because of his slight speech impediment, he was not considered a good lecturer by those who judged lectures on the forcefulness of their presentation rather than their content; but to those of us who were disappointed by the generally low

level of medical school teaching, his lectures stood out as both intellectually exciting and challenging.

I have already recounted my first encounter with Mike (as he later insisted I call him) and how I soon came to work in his lab. Mike was very accommodating and made it possible for me to spend odd hours working with him, mainly constructing electrophysiological equipment. This was in the days before research grants, and most of Mike's work was funded out of his own pocket. I was able to help in a small way by selling the microscope my parents had given me for doing well in my first year of medical school. The proceeds of this sale enabled us to buy a cathode ray oscilloscope tube and some of the other components needed to build a recording set-up.

In a real sense my education began when I started working with Mike. As we sat on opposite sides of a lab bench, Mike would talk to me about science, philosophy, literature, and politics. Most days he would suggest that I read something, usually unrelated to my course work. It was through these "private tutorials" that I first became acquainted with the British empiricists, with Bertrand Russell, Wittengenstein, etc. What little I know about electronics I learned from him in those pretransister days, and I owe essentially all my grounding in neuroanatomy and neurophysiology to his patient yet demanding tutorials. It was because I had learned so much from Mike that year that I decided to spend a second year with him for a B.Sc. degree.

For my honors thesis Mike suggested that I describe the anatomy of the hypothalamus of the common South African baboon. In retrospect, this was a fairly boring exercise since the baboon hypothalamus proved to be no different from that of other primates that had been well described by others. But my real interest was in electrophysiology, and Mike taught me much both in South Africa and later when he was visiting England.

I have already described how I came to be recommended to Le Gros Clark by Raymond Dart, and Mike's role in this was an act of quite exceptional selflessness. As I left Dart's office, after I had learned that he would put my name forward, I began to wonder why Mike had not put his own name forward. He had a medical degree and also an M.Sc.; he had been on the faculty for a few years and had just completed an excellent textbook on the nervous system for medical students. In every respect he seemed ideally suited for the position and obviously much better qualified than I was. Yet the fact remained: he had recommended me. In retrospect, I should have gone directly to ask him why he had chosen not to seek the position. Regrettably, I did not do this and to this day do not know why he put my name forward.

When at Oxford I learned that Mike was coming to England, I contacted him on his arrival and arranged to visit him. This led to the suggestion of our once again working together. Tom Powell was eager to learn some electrophysiology, and this led to my working on a project with both my closest present colleague and my closest prior collaborator.

During their stay in London, Mike's wife Priscilla fell in love with a visiting Australian physician at the Hammersmith and shortly thereafter Mike fell in love with one of the EEG technicians with whom he had been working. Priscilla went to Australia and before long achieved some distinction as a clinical nephrologist. Mike returned to Johannesburg and was later joined by his friend and soon-to-be second wife.

I have always regretted that I did not keep in touch with Mike after his return to South Africa, and it came as a painful surprise, about two years later, to learn that he had died under rather tragic circumstances. I was later told that those last two years were very unhappy ones for Mike professionally. He had been approached by a group of neurologists to be responsible for their EEG service, as it was clear that he was the most experienced and knowledgeable person in Johannesburg. Mike agreed to do this, although he must have realized that it would leave him with little or no time for research. But, I understand that this was not the main source of his unhappiness. He had not been "reading" EEGs very long, when he realized that the neurologists were taking advantage of both their patients and him. There was no justification for ordering an EEG for the great majority of the patients he saw, and while he was being paid a rather modest fee for carrying out the procedure, analyzing the records, and providing a written report, the clinicians were billing the patients at what he considered an exorbitant rate. When he confronted the neurologists with this, they simply terminated the arrangement leaving him without his principal source of income. He became seriously depressed, and in 1961 he sadly passed away at the age of 37.

I have no doubt that had Mike lived in the United States or in the United Kingdom he would have had a substantial impact on the emerging field of neuroscience. He had a fine grasp of neuroanatomy and, although self-taught, was as knowledgeable about neurophysiology as anyone I knew. As it was, his scientific legacy was an excellent short textbook on the fiber systems of the brain and spinal cord, published by Wits and sadly long out of print, and the respect and affection of those few students whose lives he influenced so profoundly.

The Oxford Years

Each Tuesday and Thursday during the fall of 1954 Tom and I caught the first available train from Oxford to Paddington, and the "tube" to Queen's Square, where we spent the day in a partially darkened room observing photically driven strychnine spikes at different frequencies and for different periods of time. Two findings soon emerged. The first was that the maximum frequency the spikes could be driven was about 3.5/sec, and at this rate there was a progressive separation of the photic-evoked response and the strychnine response until after about 10 sec, when the separation was quite distinct, the train of strychnine spikes ceased to follow the evoked

responses. The second was that it was possible to record photically driven strychnine spikes well beyond the visual cortex, if reinforced by local strychnine applied at intervals of roughly every 7 min, spreading it seemed within the plane of the cortex, since it continued even when the non-visual cortex was undercut a la B. D. Burns. The first finding correlated well with the tendency of spike and dome seizures to last about 10 sec and then end abruptly. Also, judging from its rate of propagation, the spread of the strychnine activating mechanisms appeared similar to the so-called "deep response" Adrian had reported following direct electrical stimulation of the cortex.

By mid-December we felt we had enough data to work up our findings, and Mike agreed to come to Oxford over the Christmas holiday to work on the paper. This was my first experience of an English winter. It was not so much that the temperature was low, as the dampness of the cold and the absence of central heating that one felt most. The only heating in my rooms was from a small gas fire that one had to keep feeding shillings every hour or so. Unfortunately, we ran out of shillings in the middle of our first afternoon together and were reduced to wearing our overcoats and gloves while trying to analyze our recordings and preparing to write a draft of the paper. As soon as the pubs opened, we lost all interest in writing and made our way to the "local," not so much for liquid refreshment as for warmth and a renewed supply of shillings.

By the end of the holiday, we had completed the drafts of two papers which Mike said he would ask the head of the EEG lab, William Cobb, to look over and perhaps submit to the *Journal of Physiology*. His response was to say he would send them on to the *Journal of Physiology*. To our surprise, when we received the proofs, his name appeared as the first author (which followed the Journal's then policy of listing authors alphabetically), although he had not actually participated in the design or execution of the experiments or in their preparation for publication. In fairness I should add that Cobb suggested that we should present the work at the next meeting of the Physiological Society which was to be held at one of the London medical schools. But, when the time came, he was adamant that either Mike or I should present the paper before what he knew would be a formidable audience of neurophysiologists. Mike and I tossed a coin to determine who would face the music—I lost.

By contrast, LeGros had always insisted that his name *not* appear on any of the papers, even though his guidance had been critical and his careful, line-by-line reviewing of our papers before they were sent off to editors was exemplary. His scientific integrity revealed itself about this time in a very special way. During the years following the introduction of prefrontal leucotomy, there was considerable interest in the connections of the prefrontal cortex and especially those linking it to the hypothalamus. One day LeGros pointed out to Tom and me that some years before Mrs. Margaret Meyer who had worked as a research assistant in his lab had prepared and analyzed the

brains of several monkeys with lesions in different parts of the frontal cortex that had been stained by the Glees modification of the Bielschowsky technique. LeGros had alluded to some of the findings from this material in a brief review he had written for a special issue of the *British Medical Bulletin*, but the material, valuable as it was, had never been written up after Mrs. Meyer had moved with her husband to London. At his suggestion, we wrote to her and she enthusiastically endorsed the idea and made available to us all her lab notes and mappings of the changes seen in the hypothalamus and neighboring structures. As we usually did, Tom and I independently examined each brain, made our own sketches of the "degeneration" etc., and a week or two later got together to compare notes. Two things became immediately clear. First, we had confirmed all Mrs. Myers' findings, but, second, it did not seem to matter where the lesion was located, the "sheep's droppings" that were considered indicative of degenerating terminal axons in Glees' preparation were always found in the same locations (and in roughly the same amount). It occurred to us that degeneration of this type had been reported in a number of other papers that had been published over the past few years, after lesions of the fornix and areas as diverse as the temporal neocortex and entorhinal area. Even more puzzling was the fact that in all this material (which had been carefully stored in the Department) we could find no evidence that a normal control brain had been prepared (no doubt because it had been judged too costly to "waste a monkey").

It was with some trepidation that at the first opportunity we showed our findings to LeGros. But as soon as he examined the material and was convinced of the correctness of our findings, he insisted that we prepare a normal monkey brain and also obtain a suitable human brain from the Pathology Department. When these revealed exactly the same findings he insisted that we prepare a note for *Nature* pointing out that in the hypothalamus the Glees method gave rise to an artifact that had been mistakenly reported as evidence for degeneration after various cortical lesions. He had no hesitation about this. A serious mistake had been made, and the scientific community should be alerted to the fact. Our paper in *Nature* evoked a firestorm of criticism from one of those whose work done at Oxford had been called in question; Paul Glees and Mrs. Meyer were equally upset and let LeGros know their feelings in no uncertain terms. We only learned of some of this from LeGros who had adamantly defended us in private letters to those who had complained. Although the reason for this artifactual appearance has never been fully explained, over the years a number of other workers, including Walle Nauta and Janos Szentágothai, using quite different methods, confirmed our basic finding that many of the purported connections do not, in fact, exist. For me, this "vindication" was less important than the lesson I had learned from LeGros about genuine scientific integrity.

Unlike most medical schools I have known, Oxford proved to be extremely flexible. I was allowed to enroll in Howard Florey's remarkable

course in General Pathology and the much less inspiring course in Pharmacology while I was completing my D.Phil. thesis. Since the examinations did not have to be taken immediately after the course, I was able to postpone these until I was well into my clinical years. This is not something I would necessarily recommend, but it saved me more than six months and enabled me to complete the requirements for the B.M. B.Ch. degree in just over two years. While I was preoccupied with my clinical studies, in 1957 Tom spent a sabbatical year at Johns Hopkins, where he worked closely with Vernon Mountcastle and Gian Poggio and got to know Philip Bard, Jerzy Rose, Steve Kuffler, David Hubel, and Torsten Wiesel. This year had a profound effect on Tom's career. He published a number of important papers with Vernon on the functional properties of neurons in the postcentral gyrus of the monkey and participated in the earliest experiments on the poorly understood posterior complex of the thalamus with Vernon and Gian. His enthusiasm for the research climate in the United States was such that, on his return, I decided that at the first convenient opportunity I would try to visit it myself. Another consequence of his visit was that Larry Kruger, who had been in the Physiology Department with Jerzy Rose, came to Oxford for a six month postdoctoral fellowship, and when I returned to full-time teaching and research, we shared an office and the beginnings of a lifelong friendship. Visits to Oxford by Clinton Woolsey and Vernon Mountcastle—the latter to put the finishing touches on his papers with Tom—ensured that when I finally made it to the United States, I would find myself among friends.

In the mid-1950s we realized that the time had come to focus our further efforts on the tracing of efferent pathways using Nauta's important new method. We were aided in this by a succession of visitors to the Department, each of whom worked on the connections of different regions of the brain, including John Carman from New Zealand with whom we worked on cortico-striatal and cortico-claustral connections. Our own work focused on the efferents of the piriform lobe and on the relation between the olfactory system and the thalamus.

I was especially fortunate to have had as one of my best students at Pembroke College Geoffrey Raisman, who decided to do a D. Phil. under our supervision. Geoff brought enormous energy to his work, which included a complete reexamination of the afferent connections of the hippocampus which followed, but added extensively to, the work of Ted Blackstad and his colleagues at Aarhus, Denmark. Geoff's later EM work on the reorganization of synapses in the septum following its partial denervation did much to revive interest in the important subject of morphological plasticity in the central nervous system (CNS) and has continued over the years in his work on promoting CNS regeneration. It also provided what was to be one of the continuing foci of my own work when I moved to the United States in the mid-1960s.

The years I spent at Oxford were among the most enjoyable in my life. Shortly after completing my D. Phil., I was married to Margaret Sherlock, whom I had known for the better part of two years. She was teaching in a private orphanage in London and her dedication to the children under her care had convinced me beyond words of her sense of values and her commitment to the needs of others well beyond any self-ambition she may have had. Over the next few years our three children (Margaret Ruth, Stephen Maxwell, and David Maxwell) were born. We had a modest house in a 13th century village on the outskirts of Oxford. More or less concurrent with the completion of my medical degree, I was appointed to a tenured University lectureship (for which, as was the common pattern, I received an honorary MA, making me an official "Don"). I was given a lectureship to teach Anatomy to students at Balliol College, and although this meant that during each of the three eight-week Oxford terms I spent a good deal of time either demonstrating in the dissection room or in hour-long tutorials with one or two students in my rooms at Pembroke, I found that I enjoyed teaching and did not begrudge the time involved in preparing lectures or tutorials or in direct contact with students. This love of teaching has stayed with me, and it has been enormously gratifying to hear from time to time from former students that something I said in a lecture or a modest act of personal kindness had had a lasting influence on their lives.

Sabbatical to St. Louis

Apart from a planned sabbatical to the United States, I had not seriously thought of ever leaving Oxford. But when LeGros Clark reached mandatory retirement age, it soon became clear that life in the Department would no longer bask in the benign ways I had known since 1953. LeGros' successor, Geoffrey Harris, was a brilliant scientist whose work on the hypothalamic regulation of pituitary function is rightly regarded as the cornerstone of neuroendocrinology. But, while greatly admiring of his science, I soon realized that most of the resources of the Department were likely to be funneled into his research group. So when the time came for us to apply for visas for our sabbatical year, we took the precaution of applying for "green cards" that assured us that if we so chose we could return to the United States as resident aliens.

Our decision to spend the year in St. Louis was quite fortuitous. Ed Dempsey, who was Head of the Anatomy Department at Washington University, had just completed a difficult five-year term as Dean of the School of Medicine and had come to Oxford for a "mini-sabbatical" with a long-term friend, Graham Weddell, a Reader in our Department. As it happened, Ed and I had offices across the hall from each other, and in the course of our frequent chats, he persuaded me that with three children it would be virtually impossible to live in the United States on the $7000/year stipend offered

to Rockefeller Traveling Fellows. Instead, he offered me a one-year-long appointment in his Department at roughly twice the salary. He also pointed out that his Department was well equipped with electron microscopes—whose use I was anxious to learn—and that he would himself be returning to full-time research for much of the year. I knew a good deal about Washington University Medical School (WUMS) with its long tradition in neuroscience: Erlanger and Gasser had won the Nobel Prize for their work done there on the compound action potential; Lorente de Nó, Cajal's last and greatest student, had spent time in the adjoining Central Institute for the Deaf; and of special interest to me was the fact that Viktor Hamburger and his colleagues Rita Levi-Montalcini and Stanley Cohen in the Biology Department had just discovered the first neuronal growth factor, NGF, and had clarified for the first time the existence of widespread neuronal death during the normal development of the sensory ganglia and certain regions of the spinal cord itself.

I shall leave for another occasion an account of the bizarre process of obtaining the immigrant's visa from the U.S. Embassy in London. Suffice it to say that all was soon set for our departure and on or about September 1, 1964, we arrived in St. Louis. It had been cold and wet when we left Oxford for Heathrow Airport, but when we arrived in St. Louis on a TWA flight at about 4:00 PM the temperature was 98° and the humidity must have been close to 95%! Stepping off the plane, in coats and sweaters, we felt as if we had been immersed in a hot bath. Our situation was not helped by discovering, several minutes later, that our luggage had been unloaded in Cincinnati where we had an hour or two layover.

By the time we arrived and checked into our hotel, the children were exhausted, having been on the go for more than 18 hr. Unfortunately for Margaret and me, their internal clocks caused them to wake up at about 2:00 AM, hungry, asking for breakfast, and generally disoriented by their new environment. Luckily, we had ordered sandwiches before going to bed and these sufficed until the coffee shop opened.

Two memories stand out from that first week in the United States. First, when we went to breakfast and ordered eggs and bacon, the waitress asked: "How do you want your eggs?" I said, innocently, "just fried." "Sunny-side up," she responded. I looked out the window. The sun was already up, the sky was clear, and the day promised to be as hot as it had been the day before. "Yes," I said, "it does look like a sunny day." I also remember on our third day, while I was at the medical school, there was a flood in the bathroom which excited the children, but momentarily alarmed Margaret.

Before we left Oxford, Ed Dempsey had written to say that we should not make arrangements for accommodation or the purchase of a car. I learned why during my first day in the Department. Apparently, Ed had been invited by the Secretary of the Department of Health, Education & Welfare to go to Washington to work on President Johnson's Health Care program and

expected to be there for at least a year. So he planned to offer us the use of his house in University City, at a reasonable rent, and to sell us his car, a 1957 Buick sedan for its book value of $100! These arrangements suited us just fine, but I did wonder why he had not told us earlier that his plan to return to research and to work had perforce been set aside.

The Dempsey's house proved to be more than adequate for our needs. It seemed to have every electronic device RCA made for domestic use: a large color TV, several electrical tooth brushes, radios, washing machine, dryer, trash compactor, etc., and a small but good library. (I later learned that Dempsey had a specially close relationship with RCA and had purchased a number of RCA electron microscopes, and I couldn't help wonder if this was somehow related to the number of RCA items in his home.) The 1957 Buick, on the other hand, left much to be desired. Its fuel consumption was excessive, and during the course of the year we had to spend $300–$400 for various repairs, to say nothing of the frustration of frequent breakdowns, usually at the most inconvenient times.

Second only to the surprise of learning that Dempsey was not going to be present was the shock of learning that I was expected to teach Gross Anatomy throughout the first semester of my stay. The Head of the Gross Anatomy program, a wonderful, charming—but very tough—woman named Mildred Trotter (or "Trot" to her colleagues and generations of medical students) upon hearing that I was joining the Department had insisted that I teach in her course, seemingly on the grounds that English anatomists are all expected to teach most aspects of anatomy, including Gross Anatomy. Since, at that time, Gross Anatomy consumed about 400 "contact hours"—most of them in the dissecting room—this meant that I would spend a good deal of the first five months of my sabbatical teaching and would only be able to do research for about 2 or 3 hr per day.

This experience, however, turned out to be one of the more enjoyable during my year in St. Louis. The first-year medical students were, on average, not much smarter than those I had taught at Oxford, but as they had all completed four years of college before entering medical school (as opposed to entering directly from high school) they were generally more mature and more committed to their studies. Spending long hours in the dissecting room, I took the opportunity to get to know many of them and continue to hear from some of them even over 30 years later.

For many of the students the chance to talk to a Professor about their work, their pasts, and their career expectations was unusual. One told me that in the four years he had been at college (one of the larger Midwestern land-grant institutions with a student body in excess of 35,000) he had never actually spoken to a Professor. They lectured, of course, but left more direct contacts to Teaching Assistants. At Oxford, by contrast, each student met with his tutor, usually singly but sometimes with a fellow student, for at least an hour each week.

Gross Anatomy is not a difficult subject, but it requires an unusual amount of rote learning. It has been estimated that a medical student learns about 15,000 new terms in his/her first year. Most of these are anatomical, but in addition to assimilating (and remembering) the names of the hundreds of bones, muscles, joints, tendons, nerves, arteries, veins, and the component tissues of all of the organs of the body (including the brain), they have to know the relationships of each of these to the others—the attachments of muscles to particular parts of bones; the course of arteries, nerves, and veins, from their origin to their terminations; etc. To "enliven" all those dry facts, I tried to relate the material to the clinical experiences the students would encounter in their later years and when they entered clinical practice. We also tried to enliven the otherwise fairly boring process of dissection-based learning in other ways.

I recall one occasion when the students were about to dissect the heart. Two young women in my section, both intelligent and serious students, had become good friends, but were from completely different backgrounds. One was from New York and politically well to the left of center. The other was from Wyoming and characteristically conservative. I'm not sure if they ever discussed politics, but in an election year, politics was very much in most people's minds. Recall that this was 1964: Goldwater, the darling of the extreme right was challenging Johnson (LBJ) for the presidency. Not only were the differences between the two parties more clear-cut than in most elections (Johnson spoke of "not sending American boys to fight a war that Vietnamese boys should fight on their own": Goldwater's reply was that "extremism in defense of liberty is no vice" and his supporters rallied around the slogan: "In your heart you know he's right"), but the issues of war in Southeast Asia versus a war on poverty in America seemed to sum up the alternative courses open to the electorate.

The night before the students were to open the heart, I surreptitiously inserted a small strip of paper in a gelatin capsule of the type we used for preparing material for electron microscopy and placed this into the left ventricle of the cadaver the two women were dissecting. The next morning I took the New Yorker aside to urge her (without telling her why) to stay back and let her Wyoming colleague open up the heart. About 30 min later, the ventricle was opened up and I was called over by the two students who wondered why this strange-looking capsule was lodged inside. I suggested to our western student that she remove it and look inside. By this time several other students and two instructors had gathered around the dissection table. Cautiously, the capsule was opened and the strip of paper removed. "What does it say?" asked the New Yorker, in all innocence. "Well, it says," responded her colleague, "In your heart you know he's *WRONG*." This was greeted with laughter and cheers all around from the largely pro-Johnson students.

A second memory from my hours in the dissecting room stems from meeting one of the more brash students who informed me that he was an

authority on the pineal gland. Since so little was known about the pineal at the time, I was prompted to ask what he felt made him an authority on the gland. "Oh, I've published four papers on it," was his smug response. "In that case," I said, "you might well be," since no one I had met had published more than two papers on the subject. As he seemed anxious to convince me of his standing in this field, he promised to let me have reprints of the papers at our next meeting. When he gave these to me I took them home and read them over that weekend. When I saw him the following Monday, I said, "I must be missing something, so correct me if I'm wrong; but, as I read these papers in the order in which they were published, I got the impression that the first paper described the development of an enzyme assay; the second describes the levels of the enzyme in the pineal; the third reports that the assay was not as specific as you first thought; and, finally, the fourth paper concludes that since the assay was not specific, the data in the second paper were inconclusive." "I wouldn't put it quite that way," he responded, "but I guess you could get that impression." "Tell me," I asked, "how long did you work in the lab to be able to publish these four papers?" "Oh, I spent the whole 10 weeks of that summer working on that project," was his reply. Four papers from a ten-week stint as an undergraduate told me all I needed to know about the quality of his "research experience" and what it promised for his future career if he planned to do research.

My other experiences teaching Gross Anatomy were more rewarding, and by the end of the semester I felt I had learned a lot about U.S. medical students, about the folly of having them spend so much time learning the minutiae of the subject (which most would forget within weeks of the final exam), and especially how pleasant this particular group of students were. A few years later, when I returned to Washington University as Head of the Anatomy Department, the class arranged a welcoming party for me, and a number of the students have kept in touch with me over the years and many have gone on to have very successful careers as clinical investigators. In addition, I got to know several of the faculty since we spent so much time together.

The senior person, Mildred Trotter, became an especially good friend and was helpful in instructing both Margaret and me on how to behave like Americans. "Women should not go out to luncheon without white gloves" was the sort of advice she freely dispensed. Her social sense, we learned, came from having been a student of Robert Terry, the first Head of the Department who—as she told us—would not only tell her whether or not she should wear a hat, but exactly which one was appropriate for each occasion. During the later 1940s Trot had spent a good deal of time in Hawaii on behalf of the U.S. Army, trying to identify soldiers killed in action in the Pacific from examination of their skeletal remains. Over the years she had measured, weighed, and determined the ash content of the hundreds of skeletons that Terry had accumulated and on this basis she felt confident

that she could identify whether a particular bone (especially the longer limb bones) was from a white or black individual, male, or female. Together with other material, such as clothes, dog tags, etc., this enabled many remains to be returned to their families. About the time I arrived in St. Louis, Trot received an invitation to give a lecture on her anthropological work at University College London. It was some time since she had done much in the way of research, and she was reluctant to accept the invitation. She finally agreed to do this if I would assist her in organizing the material.

This was not easy. Most of her work had been done on the skeletons of the cadavers dissected over the past 40 years by successive generations of medical students. Until about 1950 most of the cadavers came from the local charity hospitals; a majority were black males; there were fewer whites and comparatively few females. Most were poorly nourished, had many untreated illnesses, and, in a word, were hardly representative of the population as a whole. While the race of each cadaver was noted, it was unclear how homogeneous the groups were or if the recorded ages were correct. Despite these limitations, the mass of data she had collected was unique and when presented in an orderly and unpretentious way formed the basis for her lecture, which was well received.

The one faculty member whom I got to know best was Robert (Bob) Laatsch. Bob was a WUMS graduate, who after an internship had been persuaded to join the Department as an Instructor. Before I met him he had done a fair amount of electron microscopy and was technically very good at cutting ultrathin tissue sections. As we both taught in the Gross Anatomy class, I spent a fair amount of time with him and discovered that, while he was interested in research, he was studying no specific project and had no publications from the two years he had been in the Department. So I asked if he would like to join me in looking at the ultrastructual organization of the hippocampus and some of its connections. (At Oxford I had been working on this topic at the light microscopic level for some time with my student, Geoffrey Raisman.) Bob seemed pleased at this suggestion, but soon realized that to do this properly he would need to perfect completely a different approach to tissue fixation than he had used before.

Fortunately, others had described ways to fix brain tissue by perfusion that enabled one to see excellent tissue preservation and to select carefully oriented blocks of tissue for thin sectioning. Once we had gained a good sense of the normal fine structure of the tissue, I did a number of experiments in which the commissural connections (from the opposite side) were interrupted at varying postlesion intervals. In these we were able to clearly identify degenerating axon terminals in the appropriate regions. This work resulted in two papers in the *Journal of Comparative Neurology* that appeared in 1966 and 1967. Although in retrospect I think they were fairly modest contributions, at the time they attracted a fair amount of attention because they were among the earliest studies in which degeneration

in identified axon terminals was used to study connections in the CNS.

An incidental observation we made during this work was of an unusual membrane specialization at nodes of Ranvier which we thought might be significant for the flow of current at nodes during impulse conduction. We sent a short note about this finding to *Nature*, which, for some unknown reason, delayed its publication for several months, by which time others reported the same findings.

Once my teaching obligations were over, I was able to visit several other universities around the United States, and at many of these I gave seminars about the work my colleagues at Oxford and I had done over the previous two or three years. Following a visit to Johns Hopkins to give a seminar, John Dowling and I were able to combine our different expertises to identify experimentally, at the EM level, the mode of termination of the centrifugal fibers to the pigeon retina upon a distinct group of amacrine cells. But the most useful experience followed a seminar in the Biology Department at Washington University, during which I pointed out that the isthmo-optic system and other parts of the avian visual system would be wonderful subjects to analyze using the methods that Hamburger and Levi-Montalcini had perfected. I still recall vividly Viktor jumping up and saying in his wonderfully animated way: "You must do those experiments while you are here, and I'll ask one of my research assistants, Eleanor Wenger, to drop what she has been doing, to work with you." Thus began my direct involvement in developmental neurobiology, and for much of the rest of my year in St. Louis, Eleanor and I worked together making partial and complete excisions of the chick optic vesicle and optic cup, preparing the material by the special staining procedures Rita had perfected and the more conventional neuroanatomical methods I was familiar with. It would be a year or more before I could get around to analyzing the material, and in the meantime we had to return to Oxford so I could complete my teaching obligations, prepare to sell our home, and plan for a new life in the United States. We had so greatly enjoyed ourselves during the year, I had come to realize that it would be a great deal easier to support my research through NIH grants (rather than depend on the generosity of the Department Head), and in the relatively short while we had been in the country, we had made so many good friends that our qualms about leaving the United Kingdom (and especially Margaret's extended family) were largely overcome.

The University of Wisconsin

During our stay in St. Louis, I had the opportunity to visit several of the leading medical schools on the two coasts and the universities of Chicago and Wisconsin (Madison) in the Midwest. To my surprise, I was approached about the possibility of faculty positions at several of these institutions and,

in retrospect, may have done well in accepting any of them. Washington University pressed me to stay on; the University of Chicago's offer was financially extremely attractive; and because of my contacts at Hopkins, it too was very appealing. In the end I decided to take the offer from Madison, not only because of my past associations with Ray Guillery (with whom Tom Powell and I had published two papers prior to his joining the "brain drain") and with Clinton Woolsey, but also because I was so impressed following my interview with James Crow, who, as I later learned, was acting Dean of the school.

My appointment was to be in the Anatomy Department, and it came as something of a surprise when in the summer of 1966 I quickly learned that with the notable exception of Ray, the Department left much to be desired, and the students were in a very different class from those I had grown used to at Oxford. Nevertheless, our family enjoyed Madison (even its long, cold winters), and I especially enjoyed my interactions with the fine group of scientists that Woolsey and Rose had assembled in the Department of Neurophysiology.

I had only been there a little more than a year when, out of the blue, I was visited by Ollie Lowry from WUMS. Ollie was chairing the search committee that had been appointed to recruit a new Head of Anatomy. In the meantime, Ed Dempsey had returned from Washington and resigned to become Chairman of Anatomy at Columbia. I was impressed by Ollie's candor when he told me that the WUMS' first choice had been Walle Nauta, but they had been unable to lure him away from MIT. I had not given any thought before this of the possibility of taking on the administrative responsibilities of a department chair, but agreed to visit the WUMS and meet with the search committee. It was an open secret that WUMS had just passed through a very difficult period, mainly focused on the one side by the determination of Mr. Queeny, Chairman and President of Monsanto, who was President of the Hospital Board and thought that the hospital should close its "charity wards" and be run like an efficient business corporation and on the other side by the faculty who stood firmly behind the school's traditional academic policies. But things had changed quite rapidly. Mr. James McDonnell (of the McDonnell Douglas Aircraft Company) had replaced Queeny on the Hospital Board; a new administrative structure had been put in place in the Medical School; and, perhaps most importantly, the school had succeeded in recruiting a number of outstanding new department heads, including Roy Vagelos (later CEO of Merck) in Biochemistry, Cuy Hunt in Physiology, and Phil R. Dodge in Pediatrics.

After a good deal of heart searching and equivocation (I was especially concerned that I had been at Wisconsin for such a short time and was not at all sure of my competence to rebuild a department that was reduced to just two associate professors, two instructors, and three graduate students), I finally decided to take the risk, having become convinced from my meetings

with the Dean, the Vice-Chancellor (Bill Danforth), and several of the department heads that they were determined to be helpful. It was going to take about eight or nine months before new laboratory space could be constructed for me, so in the end I spent almost two years at Madison before moving to St. Louis in the summer of 1968. Much of the intervening time was spent in the Department of Neurophysiology, where I profited greatly from almost daily discussions and arguments with Jerzy Rose. I was also joined at this time by two graduate students, Jennifer Hart (who as mentioned earlier would become Jennifer LaVail) and Jim Kelly, and later by one of Jim's colleagues in the Zoology Department, David Gottlieb. The three of them formed the nucleus of my new lab at WUMS, with each of them working on a different problem in neural development.

Return to St. Louis

Almost from my arrival in St. Louis, Cuy Hunt and I found that we shared many of the same interests in teaching and neuroscience and agreed to develop our work more or less in parallel. Cuy had begun his research career at Rockefeller; had written two classical papers on the γ-efferent control of muscle; and had already built two excellent departments, first at the University of Utah and later at Yale. He had all the qualities of a fine administrator: soundness of judgment, excellence of taste in the selection of faculty, and an architect's eye for transforming rundown space into first-class research laboratories. I have always remembered fondly his advice and encouragement and the generous way in which he effectively removed all the usual barriers that so commonly divide academic departments.

It took me much longer to rebuild the Anatomy Department (Fig. 2), but with the clear determination that although we would certainly teach the required courses in Gross Anatomy, Histology, and Neuroanatomy as rigorously as before, the research focus of all the initial appointments would be in what was now generally referred to as neurobiology or neuroscience.

Among the first faculty appointments I was able to make were Harold Burton, who had been a postdoctoral fellow at the University of Wisconsin, working on the physiology of the somatosensory system, and Joel Price, who had been a graduate student at Oxford with Powell and for his thesis had completed one of the best fine structural studies of the olfactory bulb with its unusual pattern of reciprocal dendro-dendritic synapses. A major coup was the joint recruitment from Columbia University College of Physicians and Surgeons of Richard and Mary Bunge to independent faculty positions. Richard's work on the structure of central and peripheral myelin had quickly found its way into the standard textbooks. Mary's later work on the structure of growth cones set the standard for years to come. Together, Richard and Mary added immeasurably to the entire life of the Department: their teaching was exemplary; their laboratory a model of creativity and friendliness;

Fig. 2. The faculty of the Department of Anatomy and Neurobiology at WUMS in the late 1970s. Standing (left to right): David Menton, Estelle Brodmann (Departmental Librarian), Richard Bunge, Arthur Lowey, Dave Gottlieb, Tom Thach, Dick Bischoff, Roy Peterson, Tom Woolsey, Joel Price, and Mark Willard. Seated (left to right): Harold Burton, Bob Waterston, Mary Bunge, Larry Swanson, Max Cowan, Ted Jones, Mildred Trotter, Ted Cicero, Adolf Cohen, Len Tolmach, and Charlene Gottlieb.

and their advice and judgment, given freely and generously, was appreciated by all who were fortunate to come in contact with them.

Later we were joined by Edward (Ted) Jones who had been a New Zealand fellow at Oxford with Tom Powell and in his three years there set a research pace as astonishing for its quantity as its quality. After an obligatory period back in Otago, Ted and his family emigrated to the United States, where he has spent the rest of his distinguished career, mastering almost every useful technique and applying them with imagination and astonishing energy to a wide range of scientific problems from the somatosensory and motor systems to the pathology of schizophrenia and other developmental brain disorders. After several years at WUMS, he served as Chair of Anatomy at the University of California, Irvine and more recently as Director of Neuroscience at UC Davis. In 1999 he served with distinction as President of the Society for Neuroscience.

A measure of the breadth of the Department's research activities is its inclusion of Tom Thach, well-known for his contribution to motor learning in the cerebellum; John Chirgwin who, while in Rutter's laboratory at UCSF,

had cloned the insulin gene; and Bob Waterston who joined us from Sidney Brenner's lab at the MRC Laboratory for Molecular Biology. With John Sulston, Bob led the U.S./U.K. effort to sequence the genome of the nematode *C. elegans* and later played a major part in generating human and mouse expressed sequence tags (ESTs) and in the human genome effort, which reported its final draft of the genome in the summer of 2000.

My own group grew slowly. In addition to the students who came with me from Wisconsin, about a year later I was joined by Larry Swanson, who for his Ph.D in the Department of Psychiatry had done one of the first immunohistochemical studies of the nonadrenergic system of the brain and soon became a first-rate neuroanatomist familiar with almost all areas of the CNS. On completing an internship in surgery, Tom Woolsey who, while he was a medical student at Johns Hopkins, with Hendrik van der Loos discovered the exquisite "barrels" in layer IV of the mouse cerebral cortex and had been able to show that each barrel was uniquely associated with one of the mystacial vibrissae arranged in rows and columns across the whisker pad of the animal's snout also joined me. No more elegant demonstration of functional localization in the cortex exists, and over the years Tom, with a succession of students and other colleagues, explored the problems it posed with indomitable persistence and style. As the group expanded, our regular lab meetings began to attract others, including several faculty members, and by the mid-1970s these "Saturday morning seminars" came to be regarded as a central focus for the exchange of ideas where, in the most informal setting (lubricated by free coffee and doughnuts), students, postdocs, and faculty met each week to learn from each other. To see Viktor Hamburger, already well into his 70s, assiduously taking notes from a seminar by a recent postdoctoral fellow is an image deeply burned in the memories of most of us.

Editorial and Other Neuroscience-Related Activities

Shortly after moving from Madison to St. Louis, I was approached by Jerzy Rose, on behalf of the Editorial Committee of the *Journal of Comparative Neurology (JCN)* and the management of the Wistar Press Publications, about the possibility of being Editor-in-Chief of the journal. The *JCN* was the oldest scientific publication devoted to the nervous system, having been founded in 1891 by C. Judson Herrick. Its title reflected Herrick's own interest and to a large extent the principal research interest in the field at that time. Unfortunately, over the years it had not only lost its primary focus, but with only minimal resources was having great difficulty in keeping abreast with the newer journals in the field and even with its own publication schedule. By the mid 1960s it had an extensive backup of papers and was more than a year behind the listed publication date. This led the Wistar Press to seriously consider dropping *JCN* from its list, and it was only at the suggestion

of two of the Editorial Board Members that it considered extending the life of the *JCN* for a further two years, provided a new Editor was appointed, the backlog of papers was dealt with, and a new focus was given to the Journal.

I had never seriously considered taking on such a responsibility, but after meeting with the Board and being reassured of their determination to radically change the journal, I agreed to serve for an initial period of two years. Given a free hand to make whatever changes were considered necessary and sufficient resources to carry them out, I made every effort to transform *JCN* into a modern neuroscience publication covering most aspects of the field, with only one concession—the title of the journal was to remained unchanged.

In the end it took about four years to put the changes into effect, and I think it is fair to say that by the mid-1970s *JCN* was successfully competing for many of the most interesting articles in the field. Indeed, the rate of publication more than doubled, and it was soon recognized as the most successful of the Wistar publications. Its success, however, came with a price, in this case an enticing bid from a commercial publication house that Wistar Press felt it could not forgo, even though it was clear that the new publication expected the journal to abandon its not-for-profit status. I was opposed to this change and indicated that if the sale went forward, I would resign as Editor after one year, during which a new Editor could be appointed. By this time I had served for 11 years, and it seemed an appropriate time to step aside and for someone else to take over. In addition, I had been asked to help launch the *Journal of Neuroscience*, which I did, serving for several years as the Editor-in-Chief, and I felt that obligation would preclude me from continuing to give the *JCN* my full attention.

By the early 1970s, the unprecedented growth of the Society for Neuroscience had attracted several publishers as a fruitful field into which to expand their portfolios. One of these was the Annual Reviews Inc. (ARI), a not-for-profit organization that had been started by J. Murray Luck, a Stanford biochemist, to publish authoritative and archival reviews in several areas of science. The Editor-in-Chief and CEO of ARI was encouraged by his Board to look into the possibility of beginning a new series in neuroscience, and at the next annual meeting the Society organized open meetings that were attended by about 250 individuals to discuss this possibility. Despite some reservations that such a series might adversely impact those in psychology and physiology, there seemed to be considerable support for the idea, and, with the Board's approval, the *Annual Review of Neuroscience* was launched in 1978, with an Editorial Committee consisting of Eric Kandel, Zach Hall, Richard Thompson, and myself. I had agreed to serve as Editor for 5 years, but by the simple expedient of ignoring my letter of resignation at the end of the 5th year, Bill Kaufman extended my appointment at 5 yearly intervals, for now well over 25 years!

Developmental Neuroanatomy

Beginning in the interval before I left Oxford and through my years at Wisconsin, my work began to follow two closely related lines. Much of the material prepared by Eleanor Wenger showed that early removal of the developing vesicle and optic cup resulted in death of a significant proportion of the cells in the trochlear nucleus, which in its time course paralleled that seen in normal animals which had been termed "naturally occurring cell death." This parallelism suggested that the causative mechanism, whether spontaneous or induced by the excision of the trochlear mesoderm, was likely to be the same. Also, unexpectedly, we found that the induced ganglion cell degeneration we observed in the ciliary ganglion was followed after the shortest of intervals by secondary degeneration in the accessory oculomotor nucleus which, in birds, provides the preganglionic parasympathetic outflow to the ciliary ganglion. This implied that not only did immature neurons die when they were surgically separated from their natural peripheral targets, but also that the degenerative process could extend even further back, in a manner not unlike the retrograde transneuronal degeneration in the anterior thalamic/mamillary nuclear system we had reported earlier in rabbits and rats.

But my greatest interest lay in the ION. Here we found that very early, partial lesions of the optic vesicle could lead to a small, rounded eye and a correspondingly small, but otherwise normal-looking ION. When the lesions were placed somewhat later (the difference was only a few hours), that part of the nucleus which corresponded to the partial optic cup lesion showed marked cell death in the relevant sector of the ION, but the rest of the nucleus looked normal. By contrast, when the entire optic vesicle or cup was completely ablated, there were no signs of the ION. This type of center/periphery interaction had been pioneered in the motor and sensory systems by the great Ross Harrison and his many students (especially Sam Detwiler) and had served as the basis for Viktor's classic study of the effects of early limb ablation in chicks and for his classic study with Rita on the sensory ganglia. Fortunately, by this time (the mid-1970s) several new methods were becoming available. With Bill Crossland and then Peter Clark, a postdoctoral fellow from the United Kingdom, we were able to extend the story of the ION a good deal further, and in Peter's hands it continued to be a rich source for other work for a decade or more.

Our attempts to study in greater detail many of the events in early neural development were increasingly frustrated by the limitations of the experimental methods available. This was true also of the methods used to trace pathways in the mature nervous system, which depended for the most part on the induction of degenerative changes following the placement of destructive lesions. This caused my colleagues and me to think of alternatives that would take advantage of such physiological properties of neurons as their

ability to synthesize proteins in the cell body and then actively transport them along the lengths of their processes. Cajal had recognized that the cell body served as the "trophic center" of the neuron, but it was not until years later that Weiss and Hiscoe showed by constricting nerves at different levels that the contents of axons are in continuous flow, mainly centrifugally from the cell body toward the axon terminals, but also retrogradely back toward the cell body. When isotopes became available for biological studies, Taylor and Weiss showed that proteins formed by introducing a labeled amino acid into the eye could be traced back to the visual centers of the brain. This soon led to a great outpouring of work on axonal transport, much of it led by Bernice Grafstein and her students. Ray Lasek at Denver demonstrated very elegantly that after labeling dorsal root ganglia one could trace the central course of the sensory pathways in the spinal cord, but stopped short of introducing the label directly into the brain itself to analyze intracerebral pathways.

At about this time, I met Anita Hendrickson who was in the Department of Ophthalmology at the University of Washington in Seattle. Anita had injected labeled tracer into the eyes of a group of monkeys and had followed it to the lateral geniculate body. But, most importantly, she had shown that a considerable proportion of the labeled proteins had reached the terminals of the optic nerve fibers and could be clearly seen overlying the retino-geniculate synapses. Joining forces with Anita, Tom Woolsey, David Gottlieb, Joel Price, and I set out to develop an experimental protocol for using this "autoradiographic method" for tracing pathways from the site of the uptake of the label by cell bodies (but, importantly, not by fibers of passage) to their terminal projection fields and for demonstrating its usefulness in a variety of different neuronal systems.

The paper describing the method and discussing frankly both its advantages and its limitations appeared in *Brain Research* in 1972 (Cowan et al., 1972). At the time it attracted considerable interest, and Walle Nauta whose suppressive axonal degeneration method had given such an impetus to neuroanatomy was kind enough to refer to it as the most significant advance in the field in nearly two decades.

Equally important, however, was a report in *Science* by my former student Jennifer LaVail and her husband Matt, who were then postdoctoral scientists in Richard Sidman's lab. Following on an observation by Olson that peripheral axon terminals could take up exogenous proteins and transport them retrogradely to the cell body, the LaVails showed that the enzyme horseradish peroxidase (HRP; for which there was a simple histochemical staining procedure) could be used to determine the sites of origin of central neural pathways. Although it was later found that HRP could be transported bidirectionally, this meant that for the first time axonal pathways could be analyzed without destroying either their origins or terminations. Also, from the point of view of our own interest, it was now possible to study

the development of neural systems in ways that only a few years before seemed quite impossible.

It is hardly necessary to list the many topics we now began to study—from the precise time of arrival of optic nerve fibers at their terminations within the tectum, to the identification that early in development some neurons migrated to ectopic sites yet sent their axons to the correct targets, while others that attained their correct locations projected to inappropriate regions. Quantitative analyses of silver grain distributions enabled us to show that axons that project to the same region compete for synaptic space, and at least in one region (the dentate gyrus) the outcome of this competition was determined on a "first come first served" basis.

Shortly thereafter, Bernice Grafstein made the seminal observation that some of the transported label was released or escaped from the axon terminals where it became available for uptake by the second order neurons. LeVay, Hubel, and Wiesel took advantage of this to use the autoradiographic technique to map the distribution of the so-called "eye-dominance columns" in the visual cortex, and later Rakic showed that the initial overlap in the distribution of the inputs from the lateral geniculate nucleus was progressively refined later in development. It was an exciting time for neuroanatomists and several long-standing problems (such as the projection of the intralaminar thalamic nuclei and of the cells of the reticular nucleus itself) were finally laid to rest. Others that had been bedeviled by the "fiber of passage" problem (such as the precise origin of the "hippocampal" projection to the mamillary complex) were at last settled. It was gratifying that several of these studies were done at Washington University, but even more gratifying to see these new methods used by both neuroanatomists and neurophysiologists throughout the United States, Europe, Japan, and elsewhere.

The essentially digital nature of the silver grains seen in autoradiographs had prompted us to use grain counts to define more precisely the borders of projections. But manually counting grains was tedious, and so with the help of colleagues in the Department of Electrical Engineering, especially Donald Wann and one of his students, Mike Dierker, we began to explore the possibility of developing a variety of computer systems for quantifying morphological data. A contract I negotiated with the National Eye Institute provided the funds required to design and build the necessary hardware (this was some years before computer-controlled Z-axis focusing became standard on light microscopes) and to write the operational programs. My colleague in the Anatomy Department, Tom Woolsey, was especially helpful in all this and deserves much of the credit for the ultimate success of the systems that were developed and for a period used by colleagues at Washington University and elsewhere, until a few years later when commercially available instruments were produced. Among the systems we developed were: (1) a fully automated program for the counting of silver grains in autoradiographs; (2) an interactive program for determining the three-dimensional structure

of Golgi-impregnated neurons or physiologically identified cells with an appropriate label such as HRP or biocytin, that gave precise measurements of individual dendrites, dendritic branching patterns (primary, secondary, third order, etc.), and, if needed, the location and densities of spines and of axons and collaterals (the reconstructed tree-like images could, of course, be rotated and viewed from any spatial angle); (3) a program for determining the diameters of myelinated axons taken directly from electron micrographs; and (4) a digitized tablet for measuring areas of any displayed image. These various programs were duly published and made readily accessible to other investigators, a number of whom came to Washington University to use our facility.

Two other technical developments engaged our attention during this period. The first, and in terms of its ultimate usefulness, most important was developed by Gary Banker, who in the mid-1970s came to my lab as a postdoctoral fellow from the group at the University of California, Irvine. This was the development of a culture system for growing dissociated hippocampal neurons (from E16-E18 day rat fetuses). Our aim was to produce cells that could survive for long periods in a chemically defined medium to follow the development of their processes; and, if they formed synapses *in vitro*, to study their physiological properties. At the time this seemed a fairly long shot, but Gary's persistence finally paid off, and in due course cultured hippocampal neurons were to become one of the most widely used preparations in cellular neurophysiology and for the study of short- and long-term changes in neurons under different physiological conditions.

The second technical development arose when, in the late 1970s, Jerry Pine, a high energy physicist from Cal Tech, spent a sabbatical year in our lab developing a "chip" on which neurons could be grown and form connections with each other. The chips contained up to 100 sites in which the cells could be electrically stimulated and from which their activity could be recorded. Jerry's original idea was to see if these artificial systems could be "taught" to conduct information in specific patterns. By the end of the year, several such chips had been made, and their ability to stimulate cells grown on them were tested (by concurrent intracellular recordings) and found to be surprisingly successful. Unfortunately, because of other demands on his time when he returned to Pasadena, Jerry did not pursue the problem. But some years later, the basic idea was adapted for studying the activity of fairly large populations of retinal ganglion cells, and out of this emerged the important work done in Carla Shatz's lab at UC Berkeley on the key role of propagated waves of spontaneous activity in the early refinement of retino-geniculate connectivity.

In 1972 I was asked by Jim Watson to participate in the first neuroscience course to be taught at Cold Spring Harbor (CSH). Most of the other participants were from the Harvard Neurobiology Department, and I was mainly involved in lectures and demonstrations on neuroanatomy and

neural development. This was my first exposure to such high intensity teaching and to the outstanding students who are attracted to CSH. Among those in the first course were George Zweig, co-discoverer of quarks, Seymour Benzer, and three young molecular biologists who were to form the core of the molecular neuroscience group at the Salk Institute. This proved to be a wonderful three weeks, and I was pleased to return again and again over the next decade. In addition to attracting Mark Willard, who joined my lab later that year as a postdoctoral fellow (having been trained at UC Berkeley as a phage geneticist), my short stay at CSH was to have an unexpectedly long-lasting effect on my life.

One of the hitherto unaddressed problems in the study of axonal transport was that very few of transported proteins were known. Mark seemed to be in a good position, given his past experience, to do something about this, although at the time my lab was ill-equipped for such work. Fortunately, in a conversation with Roy Vagelos, I had mentioned this, and Roy responded by saying that one of his postdoctoral fellows was leaving unexpectedly and he would be glad to let Mark have the use of the vacated lab space. The fact that Roy was always looking for tennis partners and Mark happened to be an unusually good player sealed the arrangement. Within about two years Mark had identified more than 60 different proteins in the optic nerves of rabbits that were transported in at least four different phases as judged by their rate of movement along the length of the axons. Later, with one of his graduate students, he identified a protein, GAP 43, whose expression was significantly increased in regenerating amphibian optic nerves and regenerating peripheral nerve fibers and was one of the first to be associated with axonal growth.

My First and Only Experience with Parapsychology

Washington University has been singularly fortunate in the support it has received from the leaders of St. Louis business and society, and during the 1960s and 1970s no one was more supportive than James McDonnell, founder of the McDonnell aircraft company and later Chairman of McDonnell Douglas, one of the nation's leading aerospace companies. In the early 1960s, "Mr. Mac," as he was generally referred to in St. Louis, had played a critical role in maintaining the traditional relationship between the School of Medicine and Barnes Hospital; he had generously endowed the University's planetary science program and had provided funds for the creation of the new Medical Sciences building and endowed its Department of Genetics. Not surprisingly, the University was always quick to respond to any new proposal he suggested. It was in response to one such suggestion in 1978 that I first got to know Mr. Mac personally. This is how it came about.

Out of the blue, one afternoon I received a phone call from the Chancellor of the University, Dr. William (Bill) Danforth. "Max," he began, "what do you think about parapsychology?" The truth is I didn't think much about it and was brash enough to say so. But I was intrigued to know why he would call to ask me. The reason, as soon became clear, is that he had been approached by Mr. Mac about the possibility of creating a research program in parapsychology which he was willing to support very generously. The disturbing thing is that Mr. Mac was insistent that the program be located in the School of Medicine and further that it should be associated with the Department of Anatomy & Neurobiology. Even more disturbing was that he had indicated that he wanted me to head it up. I was about to protest that there was no way that I could possibly participate in something that I regarded as completely phony when Bill said: "You know, Max, the University never says 'No' to Mr. Mac, and while I respect and share to some degree your skepticism, I wonder if you would be willing to read a book that has apparently caught Mr. Mac's imagination. It's by two physicists from SRI (formerly the Stanford Research Institute) and is about a phenomenon they call 'remote viewing.'

If it was difficult for the University to say no to Mr. Mac, it was impossible for me not to agree to a request like this from Bill Danforth. In due course, a copy of the book arrived on my desk and over the following weekend I read it. As I expected, the book was wholly unconvincing, and the claims it made were dubious to say the least. In essence the authors claimed that everyone has the capacity to receive images of a scene perceived by another individual at some remote location. In support of this claim, they had taken people to various locations in and around Palo Alto, CA, and asked them to concentrate on the scene before them. Concurrently, a second group of individuals at some remote site were asked to concentrate on visual images that came to mind and to record what they had "seen." These reports were then judged by a third party (probably the authors) and given a score based on how closely the report matched the original scene. On this basis they concluded that the reports were astonishingly accurate and calculated that the probability of their reports being due to "mere chance" were on the order of one in more than a billion. I was unimpressed. The reports given were extremely vague; most read something like this: "I see some grass in the foreground; there are clouds in the sky, and I think there is some water and a building to one side." My sense was that they could apply to almost any outdoor scene, and the judgment of the scorers seemed entirely arbitrary and in every case gave the remote viewer the benefit of the doubt. But the fact that the authors claimed that anyone could "remote view" immediately suggested a fairly simple set of experiments to test the validity of their idea.

I soon got back to the Chancellor and told him how the claims for remote vision could be tested, but suggested that if Mr. Mac wanted us to pursue it,

we should insist that the "experiment" be done secretly, that someone else be involved (we settled on Sam Guze, who was Chairman of the Department of Psychiatry and Vice Chancellor for Medical Affairs), and, most importantly, that we not ask Mr. Mac to fund it. Bill said he would discuss this with Mr. Mac and Sam Guze, and in due course I was given the go-ahead.

We began by taking as a given that no special subjects were needed; we decided to use a number of truly "naïve" individuals who would only learn about the nature of the experiment just before participating. We felt it important also to eliminate most of the weaknesses in the SRI study by selecting in advance about a dozen views and photographing each scene from the position that the viewers would scan it. In an attempt to quantify the results, we placed in the viewer's field of view three objects: large cards cut into square, triangular, or circular shapes and colored red, green, or yellow. For each viewer, the site to be used and the mix of card was determined just before the start of each experiment using a set of random numbers. Either Sam or I then drove the viewing subject to the chosen site, told the subject where to stand and what to look at (including the three selected cards) for about 5 min at exactly the same time as the remote viewer was instructed to concentrate on any image that came to mind. The remote viewer sat in a quiet room adjacent to Sam's office. At the end of the session (usually after about 10 min) the remote viewer was asked what he/she had seen and then specifically questioned about anything unusual (i.e., the cards) that they may have seen. Finally, they were presented with photographs of all 12 scenes and asked to indicate if any of them corresponded to the image they had seen.

It came as no surprise to Sam and me that not one of the remote viewers came up with anything approaching the correct scene. A number "guessed" that it was the famous Gateway Arch (which we had deliberately excluded from the selected scenes), and none mentioned the cards or anything remotely like them. We repeated the experiment about ten times and finally abandoned it when, quite by chance, one of the subjects, an attractive young woman, while standing on a corner viewing the St. Louis Cathedral was propositioned by two passing motorists (we had not known that this particular location was commonly used by some of the city's streetwalkers!).

Sam and I decided that I should let Mr. Mac know the result of the experiment, and so on the following Saturday afternoon I went to his home for "tea." Mr. Mac was a generous host and a careful listener. I recounted what we had done, why we had tried to make the experiment more rigorous than that done by the group at SRI, and our conclusion that we had found no evidence at all for "remote viewing." When I finished, he thanked me, said he was impressed at the way the experiment had been done, but then added that he wasn't really surprised at the outcome because he had never accepted the idea that everyone has the capacity for remote viewing. He believed

it was a unique ability and was sure that there were individuals who had the ability. Would we, he asked, be willing to try the experiment again, only this time with a subject who was known to have the "ability?" He had heard that the CIA employed such individuals and that there was some concern that the United States, by failing to explore this area fully, was falling behind the Soviets. When I said that we would, although I remained skeptical, he picked up the phone at his desk and placed a call to Stansfield Turner, the Director of the CIA.

A few minutes later, Mr. Turner returned the call. After hearing what Mr. Mac was interested in, Mr. Turner said he would have two or three of the Agency's experts fly out to St. Louis to brief Mr. Mac about their experience in this area and to give him the name of one of their most useful subjects. I was impressed that Mr. Mac had such clout, but declined his invitation to be present at this briefing. Several days later, Mr. Mac called me to say that he had been given the name and telephone number of one of the CIA's most respected subjects and to ask if I would contact him.

With Bill Danforth and Sam Guze's approval, I called the man in question. After identifying myself and saying that we would like him to visit St. Louis (at our expense and with the promise of a fairly generous honorarium), he said he would be delighted to participate in such an experiment and was especially pleased that a respected university was prepared to take the subject of remote viewing seriously. I responded by saying that while in general the experiment we hoped to conduct followed the lines of the SRI study (with which he was familiar), we would be introducing a few additional elements that would enable us to determine whether the reported "viewing" was statistically significant and not merely random. Before I had a chance to elaborate on this or to describe exactly what changes were planned, he erupted quite violently. "There is no way I would participate in such a sham; it's obvious you have 'negative psi' and I can tell from your voice that your 'negative psi' would block any chance that the signals from the viewer would reach me." With that he slammed down the receiver—end of conversation, end of experiment.

The following Saturday afternoon I met again with Mr. Mac to tell him what had happened. He seemed disappointed that we had not been able to carry out the test and reiterated that he still believed that such extrasensory phenomena existed. Apparently, while he was an undergraduate at Princeton he had taken a trip across the country. One evening, he found himself in a small, Midwestern town, and, having nothing better to do, he explored the local library. A book on parapsychology caught his eye, and before the library closed, he had read enough to convince himself that this was the most exciting field he had encountered. On returning to Princeton, he told his faculty advisor that he wanted to drop Engineering and major in Psychology with a view to study extrasensory perception (ESP) and other paranormal phenomena. Fortunately perhaps for aeronautical engineering,

his advisor rejected this idea out-of-hand (advisors could do that in those days). But ever since then he had remained interested in the field and, as I later learned, had from time to time contributed to various parapsychological studies at other institutions.

Concealing my skepticism, I said, "Would you agree, Mr. Mac, that such phenomena as ESP and 'remote viewing' must ultimately be mediated by the human brain?"

"I agree with that," he answered, and immediately I saw an opening. "Perhaps the problem lies in the fact that we don't know enough about how our brains work. We may be trying to understand the paranormal when we still know very little about the normal functioning of the brain. It's like trying to put a man into space or on the moon, before Kitty Hawk has left the ground."

"Now you're talking my language," he said, sitting up and slapping his thighs as he often did when he was excited. He continued, "You might be right. I need to think about this."

I don't know if my comments had really struck home. I do know that a few weeks later, Mr. Mac invited a group of neuroscientists to make a presentation about research opportunities in the brain sciences; and some months later, by which time I had left Washington University for the Salk Institute, Mr. Mac gave $10 million to endow a program on Higher Brain Function under the Directorship of my good friend, Sid Goldring, Chairman of the Department of Neurosurgery.

That concluded my "foray" into parapsychology, but a year or two after I had moved to San Diego, our son, Stephen, who had remained in St. Louis, sent me a cutting out of the local newspaper that provides an interesting afterword. Apparently, a faculty member in the Physics Department at Washington University had thought of a "fool-proof" psychokinesis experiment that had impressed Mr. Mac sufficiently for him to underwrite its testing (to the tune of $500,000). When an advertisement was placed seeking volunteers to participate in the experiment, "James Rande, the Magician," who has made a career of debunking such things, had two of his student magicians apply. Some time later, the faculty member announced that he had discovered two subjects who displayed extraordinary psychokinetic power in his experiment. Hearing of this, Rande contacted him and urged that he not publish his finding because this was just the sort of thing that lent itself to a magician's sleight of hand. Unfortunately for the faculty member, for the University, and for Mr. Mac, this rather pointed warning was ignored. You can imagine how embarrassed they all must have felt when Rande's two students came forward to explain how they had fooled the fool-proof test. For myself, I was glad that we had conducted our experiment without fanfare and that I had asked for no financial support. It was more than 10 years before I told a few close friends about this episode, and this is the first time it has seen the light of day.

The Salk Institute

In the early 1970s, Roy Vagelos and I were being recruited by other institutions—Roy to develop Biochemistry at Princeton and I to create a joint Department of Anatomy and Physiology at Stanford. Neither of us felt disaffected at WUMS, but we were concerned about the quality of the School's graduate programs and the perceived contrast in the quality of the basic science departments at the Medical School and the Biology Department on the main campus of the University. Bill Danforth responded to this concern forthrightly with imagination and remarkable generosity. As a result of his efforts the University created a Division of Biology and Biomedical Science that brought together, under one administrative structure, the Biology Department and the five basic science departments at the Medical School. Several new faculty positions were approved, and five new, interdepartmental graduate programs were created that more closely paralleled the structure of modern biology than the traditional departmental academic programs. Roy was appointed Director of the new Division, and with the considerable enthusiasm of most of the faculty there was an almost immediate improvement in the quality of the graduate students who began applying for admission. When, some three years later, Roy left Washington University to become Vice President for Research at Merck, I was asked to succeed him and continued in this role until 1980 when I moved to the Salk Institute.

Quite by chance, my later move to the Salk Institute also derived from the summer spent at CSH. The following spring, in 1973, at the urging of the Salk faculty members who had taken the neuroscience course, the President of the Salk, Fred de Hoffman, invited me to spend five or six weeks of the coming summer in La Jolla. Here, I gave an extended series of seminars on different aspects of neuroscience (including lectures/demonstrations on the human brain) that were well received and attracted a number of faculty and postdoctoral scientists from both the Salk and the University of California, San Diego (UCSD). The following year I was surprised to be invited to become a non-resident fellow of the Institute (a group corresponding roughly to an external scientific advisory board). Among the other non-resident fellows at the time was Steve Kuffler, and each year Steve and I spent an enjoyable 10 days meeting the group of neuroscience faculty, attending the Institute's annual meeting at which all new appointments and promotions were approved, and walking along the lovely beaches of La Jolla.

When I joined WUMS in 1968, I had indicated to the Dean and the Selection Committee that I felt one should not view a Chairmanship as a life sentence and that a term of about 10 years was long enough. At the end of the 10 years I reminded the Dean of this and said that I would like to consider stepping down from the Department Chair and the Directorship of the Division. It was certainly not because I was frustrated or disaffected. The Department was going well, I had terrific colleagues, and we enjoyed

living in St. Louis and had made many lasting friendships. But I felt it was time to do something different and, in particular, to return to near full-time research. WUMS seemed willing to accommodate me in whatever way it could, but I soon realized that only by making a "clean break" could I truly escape being involved in the University's affairs.

As it happened, just about this time Mr. Sol Price (founder of the famous "Price Clubs," now Costco) approached the Salk Institute about the possibility of the Weingart Foundation, on which he served as Chairman and CEO, making a substantial gift for the creation of a new neurobiology laboratory at the Institute. Although neuroscience activities at the Salk had grown significantly within the previous few years, especially with Francis Crick's decision to move from Cambridge to La Jolla and the recruitment of Floyd Bloom's large group in pharmacology, basic endocrinology, and neurophysiology, the offer from the Weingart Foundation was too good to pass up. Within a matter of some weeks, Fred de Hoffman, Francis Crick, and Steve Kuffler persuaded me to move my group from St. Louis to the Salk as soon as the new laboratories could be constructed.

I was singularly fortunate at the time to have several very able young colleagues in the Department who had been with me for two or three years and, in Dennis O'Leary, a quite remarkable graduate student, all of whom were keen to move to California. Collectively, their work embraced most of the various strands we had been working on over the years, and, at the same time, the new space that was provided allowed us to consider adding a new dimension in cortical physiology. We were also greatly helped by being invited to become an active participant in the Clayton Foundation for Biomedical Research, a Texas-based medical research organization that was required to spend a significant proportion of assets in medical research in the state of California. The generous and stable support provided by the Clayton Foundation assured us that we could expand our activities in new directions, and it is a privilege here to acknowledge the generosity of the Trustees of the Foundation and the confidence they placed not only in my group, but in the Salk Institute as a whole, which they continue to support.

Among those who moved with me from St. Louis was Larry Swanson, who on completing his postdoctoral fellowship had stayed on as a Research Assistant Professor and had been joined recently by a postdoctoral fellow of his own, Paul Sawchenko. Larry and Paul continued their detailed analyses of the connections of several regions of the basal forebrain and hypothalamus. Because of their considerable neuroanatomical expertise at the Salk, they were soon in much demand from the peptide biologists for help and from some of the molecular biologists like Geoff Rosenfeld and Ron Evans who were working on the early development of the anterior pituitary. Larry subsequently moved to the University of Southern California, but Paul moved steadily up the academic ranks to a full Professorship with his own productive laboratory, where over the years he has had several significant

contributions, many in collaboration with Wylie Vale and his colleagues. Among his other contributions of note was the development, with one of my postdoctoral fellows, Chip Gerfen, of the use of the kidney bean lectin, Phaseolus vulgaris-leucoagglutinin (PHA-L), which combines all the best features of the other axonal tracing with a level of detail of axonal and dendritic organization seen in the very best Golgi preparations. Since its publication, this approach has proved to be a most useful neuroanatomical method, as indicated by the frequency with which it is cited.

Another member of our group who moved with us from St. Louis to La Jolla was David Amaral. Before joining the lab in St. Louis, David had done a careful analysis using the Golgi technique of the structures of the neurons in the rat hilus. This region had never been carefully examined since the classic Golgi work on the hippocampus by Cajal and his student, Lorente de Nó. David's reexamination provided a number of new insights, and his work on the structure of the neurons in the rat hilus became a classic in its own right.

In our lab David extended our project on the connections of the primate hippocampus and parahippocampal region, bringing to this work a level of thoroughness and attention to detail that has characterized his studies ever since. At the Salk David continued his primate work and initiated an important collaboration with Larry Squire and Stuart Zola-Morgan, which included some interesting studies on the human brain. David left the Salk after several years for a position at Stony Brook and then settled at UC Davis, where he now directs a major program on autism.

Two others moving with us from St. Louis rounded out our group. These were Brent Stanfield, who as an undergraduate had worked with Gary Lynch and Carl Cotman at UC Irvine and had for personal reasons been with me successively as a graduate student and postdoctoral fellow, and Dennis O'Leary, my last graduate student, who had started his studies in St. Louis, but moved with us to complete his experiments at the Salk, returning to Washington University only to defend his dissertation. Until moving into science administration at the NIH in the late 1990s, Brent had carried out several studies on plasticity in the hippocampus following the selective removal of various efferent pathways. He was also the first person to show beyond doubt that some proportion of the cells generated in the adult dentate gyrus are indeed neurons and that their axons could be integrated into the existing mossy fiber system that links the dentate gyrus to the *regio inferior* of the hippocampus. Dennis did his thesis work on the development of the visual system in both chicks and rats. In addition, Dennis and Brent established a very productive collaboration involving studies of various aspects of neural plasticity and development, which continued for a number of years. When I left the Salk, Dennis came with me back to Washington University, where he established his own lab and independent reputation and where he stayed for a few years before the Salk attracted him back to La Jolla where he remains today.

Joining the group from St. Louis at the Salk was Richard Andersen from Vernon Mountcastle's group, where he had begun working on the functional properties of neurons in the parietal cortex of awake, behaving monkeys. Richard's initial work at the Salk was concerned with how the properties of visually responsive neurons in the parietal cortex were influenced by the angle of gaze. The success of this initial work soon led to his recruitment, first to MIT and later to Cal Tech, where he continues to direct a large and vigorous research group.

Shortly after our arrival in La Jolla, we heard from Han Kuypers at Rotterdam that he and his colleagues were using a number of fluorescent dyes, with different emission spectra, which were readily taken up by axon terminals and retrogradely transported to the cell bodies where they bound to different cellular components. They provided us with samples of two such dyes, nuclear yellow, which labeled nuclei brightly yellow, and true blue, which in the fluorescent microscope labeled the cytoplasm a brilliant blue. Together they made it possible for the first time to experimentally identify distant axon collateral pathways. Injections of each dye into putative collateral projection sites could, after a survival period of a few days, enable one to detect "doubly-labeled neurons" if axon collaterals were present. Larry Swanson, Paul Sawchenko, and I immediately set about testing the usefulness of this approach to resolve a long-standing problem in the hippocampus. Previous work from our lab and others had established the basic organization of the projections of each of the two major regions of the Ammon's horn (or hippocampus proper), originally termed the *regio superior* and *regio inferior* by Cajal. In the case of the *regio inferior*, David Gottlieb and I had also shown that there is a striking feature in the efferent projections: the region projects to identical sites on the two sides. Furthermore, the ipsilateral association and crossed (or commissural) projections follow identical courses and terminate in the same subregions. This, of course, raised the questions whether the *regio superior* consisted of a single population of neurons, each of which sent collaterals to all the field's known projection sites, or if neighboring cells projected independently to each site. In Larry and Paul's hands, the new double-labeling method resolved the issue straightforwardly and unequivocally. All the many projections of the *regio inferior* arise as collaterals of a single and uniform population of pyramidal neurons.

For our developmental studies we soon found that the new dyes offered yet another advantage: they were essentially non-biodegradable. This meant that one could follow the fates of cells (and their connections) over long periods of time. Brent Stanfield, Dennis O'Leary, and I first used this approach to resolve another long-standing issue in cortical development, namely, whether changes in connections that occur in the course of development are due to the deaths of some cells within a population of interest or if they could be due to the selective elimination of certain early formed collateral projections while the parent cells (and their other axon collaterals) persisted.

Naturally occurring cell death and selective synapse elimination had both been described in many regions of the nervous system, but in a number of others it was not clear which phenomenon accounted for the observed changes over the course of development. For example, as Innocenti and his colleagues had shown, early in postnatal life all regions of the cerebral cortex appear to extend callosal projections to the opposite cerebral hemisphere. Later, however, many regions clearly lack such callosal projections, and the question that arises is: Is the early "exuberant projection" (to use Innocenti's apt phrase) refined by the death of a proportion of the cells in specific regions or to the selective loss of their callosal branches with the persistence of the neurons themselves? By labeling the entire early cohort of neurons with early callosal projections with one dye shortly after birth, and by allowing the animals to survive beyond the refinement period (at about 3–4 weeks postnatally in rats) and then labeling extensively with a second dye, Brent and Dennis were able to show that, as far as can be judged, many if not all the original cells survive and maintain their other projections, although their early callosal projections can no longer be demonstrated. This somewhat unexpected but very satisfying finding provided a decisive observation that connectional refinements in the CNS can involve the selective elimination of specific, long-range axon collaterals and not just terminal branches as had been thought for sometime. Brent and Dennis quickly extended this initial set of findings to a number of other cortical projections, and this phenomenon of collateral elimination has proven to be a fundamental principle in the development of the cerebral cortex.

The Howard Hughes Medical Institute

The six years I spent at the Salk Institute were among the most enjoyable of my career. It was a privilege to be associated with so many outstanding colleagues, to get to know and spend many hours discussing neuroscience with Francis Crick, and to be able to assist some other colleagues such as Ron Evans, Steve Heinemann, and Jim Patrick as they established themselves among the early group of molecular neuroscientists. However, in the summer of 1986, I was lured back to Washington University as Provost and Executive Vice-Chancellor. This, I had thought, was to be my last academic position. But within two years I became convinced that academic administration on such a broad front made it virtually impossible to keep abreast with biomedical research. Fortunately, as I became convinced of this, I was approached by Purnell Choppin (who had just been appointed President of the Howard Hughes Medical Institute [HHMI]) about the possibility of my joining the HHMI in the position he himself had occupied as Vice-President and Chief Scientific Officer.

I had been associated with HHMI since the fall of 1983, when it considered starting a fourth research program in neuroscience to complement

the longer established programs in Metabolic Regulation, Genetics, and Immunology. Before launching the new program, the Medical Advisory Board (MAB) invited a group of neuroscientists to meet with them at the Institute's New Headquarters in Coconut Grove, FL. This meeting confirmed the decision to go forward and set up neuroscience research groups at the MGH, Columbia University College of Physicians and Surgeons, UCSF, Hopkins, and Yale.

Shortly after the meeting in Coconut Grove, I had a telephone call from Dr. George Thorn, Chairman of the MAB, asking if I would join the MAB for a few months while the program was being established. I readily agreed, since it seemed that this new infusion of support for the field could have a major impact, given the magnitude of the Institute's endowment. (This had been established for the first time by the decision of the Trustees to sell the Institute's sole asset, the Hughes Aircraft Company, to General Motors for just over $5 billion.)

Several months later, Don Fredrickson, who had been appointed President of the HHMI, visited each of the MAB members about the possibility of establishing yet another research program; this resulted in the appointment of a number of outstanding X-ray crystallographers at several sites where HHMI had established relationships. It was during my meeting with Don Frederickson that the possibility of beginning a joint UCSD/Salk Institute HHMI unit was first raised, and in due course Ron Evans and Larry Swanson at Salk and Geoff Rosenfeld (and later Charles Zucker) at UCSD were appointed as investigators.

The evident success of HHMI's research programs from the time they were reorganized in the mid-1980s has been the subject of much discussion by others. Here, it will perhaps suffice to say that it obviously involved a number of related factors. Included among these are the size of its endowment and the resources this made possible; the careful selection of those appointed as investigators and the fact that they were all subject to rigorous scientific review by knowledgeable panels of experts; and the considerable assistance provided to the HHMI by the many universities, medical schools, and research institutions with which it was associated. An especially important factor was the decision to broaden the pool from which the HHMI could draw investigators from an initial relatively small number of medical schools to "competitions" open to essentially all research universities and research institutions. Equally important was the strong commitment of the Trustees to ensure that the primary focus of the HHMI be the support of biomedical research, both basic and clinical of the highest caliber.

One word about the HHMI's neuroscience program may be of particular relevance in the present context. This was the decision to concentrate the HHMI's efforts initially in the areas of cellular, molecular, and developmental neuroscience. Given that these areas showed the greatest prospect for rapid (and substantial) progress in the 1980s, in retrospect, this decision

was clearly a wise one. However, it was also recognized that in time the program should be broadened to include systems neuroscience and beyond this cognitive neuroscience more generally. This expansion began in the early 1990s with the appointment of several investigators working on different aspects of sensory perception, learning, memory, and computational neuroscience. Since no constraints were placed on what investigators would pursue, the program provided a degree of flexibility that enabled individuals to move into new areas to avail themselves of new techniques and even to completely change direction. Their success in this speaks for itself, but it would be misleading if I were not to say that it has been especially gratifying to observe how the program has developed and to have had the opportunity to play some part in its evolution.

As biomedical research continues to provide us with greater understanding and with powerful new tools, the scientific community has, I think, a dual responsibility. One is to push forward the frontiers to make medical advances possible, to understand what cancer is, to develop new ways of treating cancer, to prevent heart disease, and to develop ways of preventing, ultimately, disorders such as Alzheimer's disease and depression. But science also has a second responsibility to society, which is to point out what we need to be concerned about as a society and to bring to bear humane, balanced, and thoughtful ways of dealing with the advances that come from biomedical research. Scientists need to speak to these issues.

Basic science is concerned with trying to understand the underlying basis of disorders, and it does that by trying to understand the underlying basis of normal biological processes. But out of that understanding come ways to prevent and ultimately, I think, to overcome the devastating disorders that affect humanity, recognizing of course that mortality is a reality of life and that we have to learn as a society to face death with equanimity, humanity, and dignity.

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