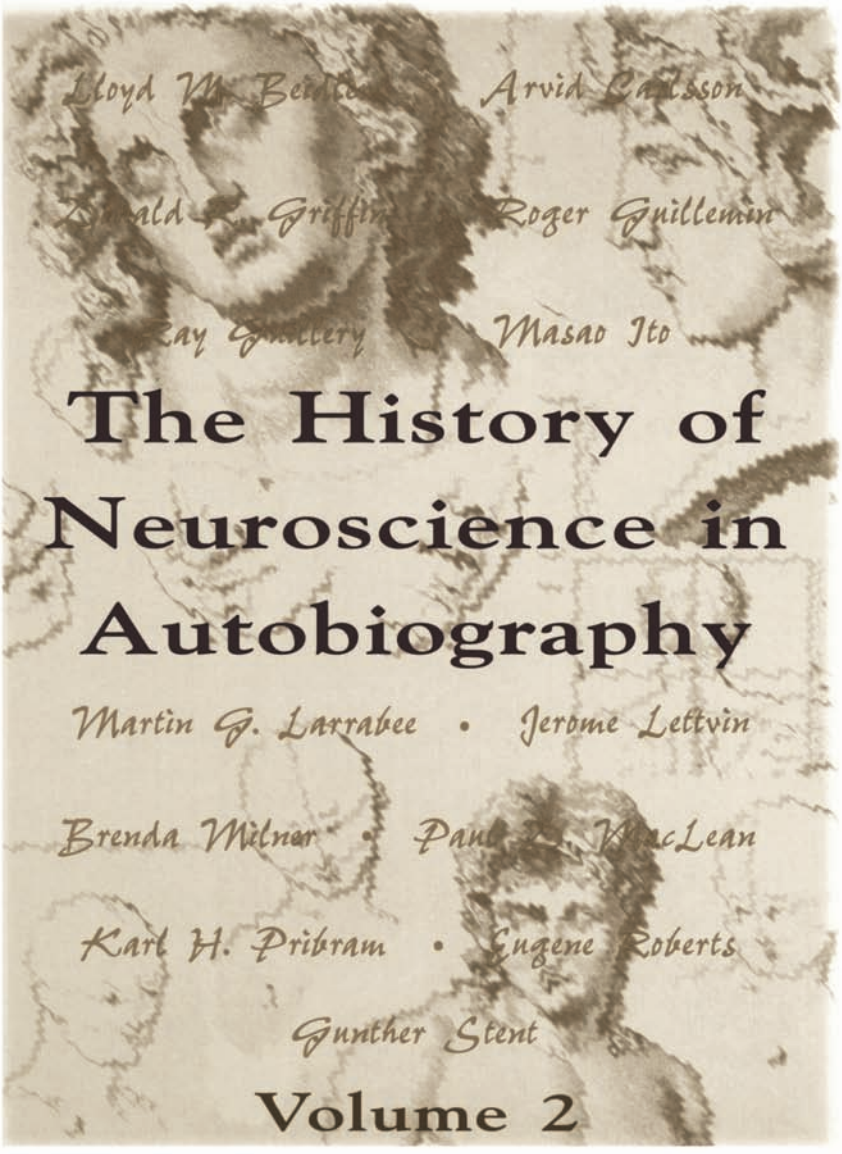

Edited by Larry R. Squire

The History of Neuroscience in Autobiography

VOLUME 2

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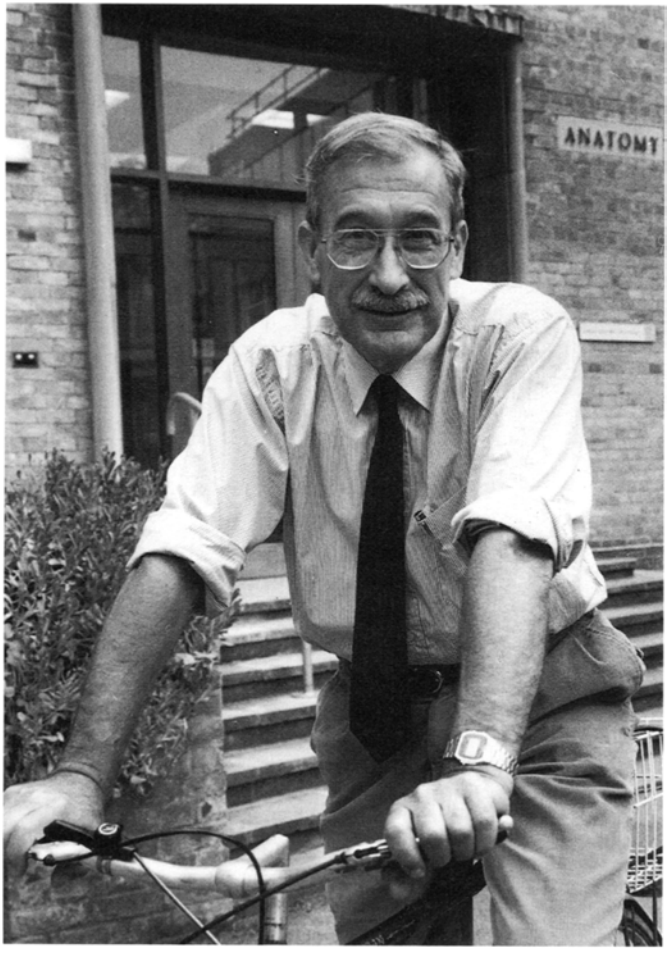
ANATOMY

Ray Guillery

BORN:

Greifswald, Germany
August 28, 1929

EDUCATION:

University College, London, B.Sc. (1951)
University College, London, Ph.D. (1954)

APPOINTMENTS:

University College, London (1953)
University of Wisconsin School of Medicine (1964)
University of Chicago (1977)
Oxford University (1984)
Visiting Professor, University of Wisconsin School of Medicine (1996)

HONORS AND AWARDS:

Fellow of the Royal Society (1984)
Fellow of University College, London (1987)

Ray Guillery is best known for his detailed characterization of the structural organization of the mammalian visual system. This work has focused on the lateral geniculate nucleus, and on mechanisms underlying the development of structural peculiarities in the visual system of albino animals.

The History of Neuroscience in Autobiography, Volume 2

Ray Guillery

Yet, when all has been said, you never talk about yourself without loss: condemn yourself and you are always believed: praise yourself and you never are.
—M. de Montaigne, *On the Art of Conversation,* translated by M. A. Screech.

I think success is if you can walk up to a mirror, look at yourself, and say: Hey, I like you. (Laughs.) I don't know, I don't know, I don't know. I really don't know whether I like myself. —Ben Green talking to Studs Terkel in *American Dreams.*

My Family

There is a strong line of biomedical research in my family. My father was a pathologist who had his first university appointment at Greifswald in Pommerania, where I was born in 1929, and where he had ambitions, never successfully fulfilled, to be a research scientist. He had trained as a pathologist at the Charité Hospital in Berlin, where, before their marriage, my mother had been a technician in the same department. In Greifswald during the 1920s he undertook some studies of cultured tissues. His father was an ophthalmologist who was trained as a physician in the German army and combined an active practice in Cologne with a serious research interest. He wrote on visual acuity; Gerald Westheimer and Heinz Wässle both knew of my grandfather's work and asked how I was related when we first met. Heinz, many years ago, gave me a bound copy of my grandfather's 1931 review on visual acuity. I like to imagine that it was written while we were visiting my grandparents in Cologne just before my parents' divorce in that year. I was photographed sitting on grandfather's lap; neither of us looks comfortable. The picture suggests that I was not yet house-trained. He was a formal man from a Rhineland Catholic family who may well have disapproved when his son married into a Russian Jewish family, and who must have been shocked by the divorce. My mother recalls him as distant, keeping the family at bay while he worked in his study.

Grandfather Guillery had married Maria Deiters, daughter of Hermann Deiters, music critic and biographer of Mozart, Beethoven, and Brahms. Hermann's brother, Otto Deiters, had taught at the University in Bonn and worked in Bonn as a physician. He had trained with Virchow in Berlin, and in Bonn, influenced by Max Schultze, he undertook a series of studies of the nervous system and inner ear. His studies of the nervous

system, published posthumously in a fine book in 1865, mark him out as an early, eminent neuroscientist, even though he was only 29 when he died. His greatest achievement was the first accurate description of nerve cells, complete with the axon and all of the dendrites (which were briefly called Deiters' processes) carefully microdissected and accurately drawn. He also included detailed illustrations of astrocytes in the book, as well as a complete atlas of the brain stem.

On my mother's side there was a medically qualified great aunt, my grandmother's sister, who worked as a general practitioner in Berlin and looked after our minor ailments. My maternal grandfather had been a successful apothecary in St. Petersburg before 1917, but by the time I knew him in Berlin, Nazi policies had put him out of work, and he used to take us for long walks in the Tiergarten. I remember him on a few occasions, when we were in the country, taking us to look for mushrooms. He taught me that until you know what you are looking for, you cannot see it; a basic principle of microscopy and mushrooming.

After my parents' divorce I lived with my mother and sister in Berlin and had no contact with my father and his second family. As a result, I did not learn much about my father's side of the family until after I had started medical school in London. There I learned that the lateral vestibular nucleus was called Deiters' nucleus (it still was!). My grandmother's younger stepsister, Lisbeth Deiters, was a psychiatrist in Düsseldorf and one of the few of my German relatives who had still kept in touch with us after the war. So I asked her about Otto Deiters, and she wrote to me at length, sending me a copy of his book and a rare miniature photograph of him. Some years later (1965), shortly before she died, we wrote a brief note for *Experimental Neurology* about Otto Deiters.

I did not learn about my grandfather's research until I was an undergraduate anatomy degree student and saw his name in Polyak's book on the retina. I know I was intrigued to learn about these two relatives at the time, but no amount of introspection provides any hint that this knowledge seriously affected my career and served to turn me into a neuroanatomist with a strong interest in vision.

School Years

Before I started as a medical student at University College London in 1948 I had been to six different schools: one in Berlin, one in Switzerland, one in Holland, and three in England. Two of these schools gave me a solid basis for an independence of mind that was invaluable at the time, and that has served me well ever since. The first was in Berlin, where from 1935 to 1938, I attended the Rudolf Steiner school. This was about the only non-fascist school available to us, and it was being closed down by the Nazis. After my class was admitted there were no further admissions and ours

was permanently the youngest class. My sister recently reminded me that toward the end of our time there, we were required to conform to Nazi salutations and sing Nazi songs, much against the inclinations of our teachers. Not only did the school stand out as firmly as it could against the evils of the time, but it also had profound views on education which must have influenced me significantly during those three years in ways I was then too young to appreciate.

Later, from 1940 to 1946, I went to a Quaker school in Oxfordshire. Here, again, I was being educated by people who were swimming against the stream: pacifists in the midst of World War II. The Quaker belief in the "inner light," the individual's own source for moral judgements, played an important part in our education at that time. It is difficult to evaluate now how this influenced me, and (of course) I kept no notes, but I have a clear sense that I owe to these two highly moralistic schools a sense of independence and purpose that allowed me to grow up from 1938 onward with only sporadic and limited parental guidance. During the war we were Germans in England, officially labeled "enemy aliens" and required to register as such. We grew up during a period of intense enmity, yet when the war ended, I was an adolescent who was able to think of himself, proudly, as English; I experienced more anti-German sentiments from my Swiss school mates in 1938 than I did during the whole of the war in English schools. I suspect that this period of my life produced in me a curious mixture: of being very serious about anything that I could learn, but ignoring almost all of it. I have never been able to relate very productively to accepted dogma or fashionable and exciting advances until (often too late) I had been able to work them into my own slow and personal view of what is important. All too often, as many of my students and colleagues will confirm, the baby in what I saw as dull bathwater never stood a chance.

Given that my mother, who was one of a very small group of German Quakers, was classified as Jewish by the Nazis, we left Germany very late. In the fall of 1938 my mother was warned that the police were planning to take away our passports, and within 24 hours our family left Berlin, each with a passport. Mine had a big *J* stamped on it, which had been crossed out by an equally large *X* because my father had been able to prove that his forebears, who had moved from France through Belgium in the previous four or five generations, had all been "Aryan."

I know nothing about the preparations that my mother and grandmother must have made earlier. I can remember coming home from school one day to find everything had been packed. My sister had earlier been sent to a Quaker boarding school in Holland; my mother traveled to London, where she had a good friend (my godmother), who helped to get her a job as a housekeeper/nanny in North London, the only employment that was open to her; I was sent to Switzerland to be looked after by another friend of my mother's. My grandfather had died earlier; my grandmother, who in 1917

had fled from St. Petersburg, now traveled to Paris to join her oldest daughter. Both were later to flee from Paris, and after the war settle in New York. My grandmother's three sisters remained in Germany and all died there, two in a concentration camp in Poland.

I spent some months in Switzerland, amazed by the scenery after my urban upbringing in a Berlin block of flats. I lived in a large, square, vine-covered house next to Lake Zürich, went to school half-way up a steep hill behind the village, and at the weekends we would occasionally hike in the mountains. My first view of clouds from above still preserves its initial magic, even now that flight has made it almost banal. I rapidly, but temporarily, acquired the Swiss version of the German language. I had few friends in the school and was exposed to some bullying because the Swiss disliked the Germans. I was lonely, but not unhappy. The mountains, a beautifully hand-crafted model steam engine I was given for Christmas, and a chocolate factory in the next village along the shores of Lake Zürich, where a school friend's mother worked, represent the highlights that I can readily recall of this brief period of my ninth year.

Soon after Christmas, early in 1939, it was possible for me to join my sister in the school in Holland. Classes were in English and German, and we gleaned a small knowledge of Dutch. The school was in an impressive "castle," or manor, complete with moat. I was one of the youngest in the school; I had a sense that interesting things were happening around me, in the school and internationally, but never really found out what they were. I was confused and was not there long enough to form any clear impressions. At the end of the summer term we traveled to England to stay with my godmother in North London, meet my mother, and then briefly to join my mother, my grandmother, my aunt, and her young daughter in a vacation on the north coast of France in August. We returned to England a few days before the outbreak of World War II.

On September 3, 1939, the day the war started, my sister and I were scheduled to go back to Holland from England. Civilian shipping was canceled and we were left "stranded" in England. The family that employed my mother evacuated their children to Oxford where their uncle (Professor Carter) was professor of Botany. We stayed in their house briefly and I can recall large numbers of children playing complicated games in their seemingly large garden. When 45 years later we were looking for a house in Oxford, this same house was on the market, and the garden seemed a lot smaller. Certainly the house was too small for all of us in 1939 and my sister and I were sent to live with a family in North Oxford: an academic widow with two children slightly older than us. Here we learned about the English language and English ways of behaving. We did not then realize that we had entered a rare subculture: an Oxford academic family. The children's playroom was called the JCR (junior common room). When we had eaten enough we were taught to say: "Thank you, I have had an

elegant sufficiency," and we were only allowed second helpings at meal times if we had made a significant contribution to the conversation. For me this was a great stimulus to help me learn to speak the new language. In the evenings we listened to the radio or were read Dickens and other classics. My introduction to the English language was a curious mixture of Christopher Robin, Alice, Swallows and Amazons, Dickens, a radio comedy program called ITMA, and Lear nonsense verses. I enjoyed learning the new language, was young enough to learn it fast and old enough to enjoy the new sounds and meanings. Colin Roberts, my godmother's brother-in-law, a classicist and fellow of St John's College, took a gentle and kindly interest in my linguistic development, feeding me stories and rhymes when we met, including many limericks from among which "the young lady from Twickenham whose boots were too tight to walk quick in 'em" stood out for me. The waywardness of the rhymes and spellings had a great appeal after the formalities of the Germanic languages. My mother and sister never seemed to share my joy in these aspects of our new language.

We stayed with this family for a year. I went to a rather shabby preparatory school in North Oxford, where the pupils knew very little and where our teacher was convinced that Hitler would shortly win the war. He was very kind to me and another German-Jewish refugee, spoiling us in the belief (we thought) that if he was nice to the Germans, the Germans would later be nice to him. I spent a year in that school learning the language and little else. Then, thanks to the Oxford Quakers, I was able to go to a Quaker boarding school in Oxfordshire (Sibford School).

My sister stayed in Oxford for two years more and moved to a new home. This was the home of Professor W. E. and Mrs. Le Gros Clark, who had at the beginning of the war sent their two daughters to Canada for safety. He was the Dr. Lee's Professor of Anatomy, she worked as a volunteer for the Oxford Refugee Committee, and they had a large house in North Oxford. As a result, I spent much of my school holidays in the Le Gros Clark home, although I had my suppers and slept in a nearby boys' home that was entirely unappealing. However, I watched the rather silent and distant professor grumble his way through some parts of many days, and at the weekends there were occasions when I got to know him better.

He and I went off cycling in the country, and on one occasion we went farther afield by train to visit a model village, Beaconscott, halfway to London. The professor really enjoyed this. He took lots of photographs of the tiny houses and streets and let me watch later while he did the developing and printing in the department. He showed me his lab, including his animal house and some monkeys. These may just have been the monkeys he used to explore the possibility that each of the three pairs of layers in the primate lateral geniculate nucleus is concerned with passing messages about a different primary color on to the cerebral cortex (although I was probably just a little too late for them). The theory was wrong and was fiercely attacked

in 1951 by Gordon Walls who used the opportunity to write a clear and beautifully concise summary of geniculate organization. Le Gros Clark told me in the 1950s that he was deeply hurt by this attack, but when later in the 1960s I became interested in the lateral geniculate nucleus I found that Walls' book provided an extremely valuable and entertaining introduction to the problems of geniculate organization.

At the end of this period, during which I spent term time at school and the holidays between the Le Gros Clark's home and a boys' home, my mother, whose employment had so far been legally limited to domestic work, was able to find work again as a pathology technician. This was thanks to Ernst Chain who had known my godmother's family in Berlin. Chain had a younger colleague (Edward Duthie) who was given the job of organizing the pathology department at the Northampton General Hospital. Most of the eligible technicians were in the armed forces by then, and Chain knew that my mother's training in Berlin (under Lubarsch) must have been thorough. She went back to work as a technician in Northampton, and lived in a small flat where we could join her during the school holidays. Northampton is not very far from Oxford, and Edward Duthie not only ran the routines of the hospital lab, but also maintained an interest in some ongoing research projects. My mother was very impressed, and at second hand, so was I. I have no idea what the research involved, and I don't think my mother knew much more. I believe it was after the work on hyaluronidase, and before Duthie's involvement in the early days of penicillin research. I was able to visit the lab, see all the specimens in bottles, watch my mother sharpening microtome knives by hand, and see her cutting beautiful, even, long ribbons of paraffin sections. It was some years before I learned to appreciate how good she was at this.

At this time I was given a small microscope for Christmas, and to go with it, my mother prepared serial sections through a guinea pig embryo, stained with hematoxylin and eosin. Although I spent a lot of time looking at these very attractive sections, I had no real clue about identifying the parts. My education had not prepared me to look for knowledge beyond what was in a set school course. I suspect that time spent looking at these essentially mysterious sections helped to prepare me for my later career.

Sibford was not a scholarly school. It was set in beautiful Cotswold country. We learned to enjoy the countryside, and I learned much from a local farmer's family where I stayed for one school holiday and where I visited during term time. They let me make butter, harness the horse (badly), and watch the pig-killing. The school did not expect its pupils to go to university and trained us accordingly. We all left at 16. Each subject was strictly limited. It was only in art, woodwork, and metalwork that one could strive for a perfection that was identifiable but beyond one's reach. As a result, I had a serious ambition to make and design furniture. However, my mother was keen to see me go to university, preferably medical school. I

made a poor effort to seek admission to an art school, but in the end, moved from Sibford to a grammar school, where I had two years to prepare for university.

I had been poorly prepared for the intensive two years of study in science I needed before taking the Higher School Certificate required for university entrance. This may have been a great benefit for me, because during those two years I had to learn to work hard and systematically, to catch up with the rest of the class in mathematics, physics, and chemistry. The biology was easier for me. It was taught by Malcolm Scott, who later taught in the Royal Veterinary College in Camden Town. He was informal, lively, and enthusiastic. Although he could be scathing when we did anything stupid, he tended to treat us as equals in a refreshing way. I was intrigued to meet him again quite recently when his wife, Patricia Scott, was given an award by the Research Defence Society during my spell as the honorary secretary of this organization.

University

In 1948 I borrowed £3 from my mother in order to pay the entrance fee for the London Intercollegiate Scholarship exam. As a result I won a scholarship to study medicine at University College London (UCL). My time as a medical student opened many new doors for me, but it took me a long time to realize just how lucky I had been to enter this particular academic environment. The first year, when I was commuting from Kew where my mother had a small flat, was intensive and hard work. At first I traveled by underground train and there had to read anatomy from an unillustrated text (Johnson's Synopsis); anatomical illustrations would have shocked other travelers. Later, I cycled to save money, and then moved closer to central London. It was a joy to learn that so much new knowledge was spread out for me. It was not only the shiny pages of new textbooks such as the beautifully illustrated Maximow and Bloom histology text, it was also having the free run of the shelves of the Thane library. I took to browsing and reading rather indiscriminately, fascinated by the way in which different authors, most since forgotten by me, dealt with difficult problems of physiology and anatomy.

I was still surprisingly naive. Although we had a fine course of lectures and some outstanding teachers, my inclination was to rely on books, rather than people. J. Z. Young's introductory lectures were a brilliant and original approach to the study of the human body, but I did not realize just how original until much later. Lovatt-Evans gave almost all of the lectures in the physiology course. He was lively and vastly entertaining. Bernard Katz gave the lectures on vision. He was erudite, very serious, and less easy to follow. He taught in some of the practical physiology classes and, on one occasion, admonished a student who was not doing the set experiment, but

had Maximow and Bloom open at the section on striated muscle. The student was told to put the book away, and as an aside was advised not to take the histologists too seriously when they described the complex arrangement of striations they thought they could see with their light microscopes.

Keith Richardson taught the histology classes during the first terms of the medical course. He was tightly organized throughout. Not only did he start and finish each lecture precisely on time, but every sentence was a complete and elegant structure. During this introductory course and for many years at UCL thereafter I learned from him a respect for order and precision. It was through the histology course that I was particularly stimulated to take an interest in anatomy. Looking back now this is perhaps surprising. The lectures were not as exciting as many others, nor as original, but they opened doors for a completely ignorant student who had not yet been taught the importance of recognizing originality, or creativity. I think Keith understood his audience.

The neuroanatomy was very badly taught and most of us had difficulty understanding the basics or discovering that the subject might be interesting. I spent a significant part of my first summer vacation, when I was not holidaying in France or making some extra money as a temporary ward orderly in a small West London hospital, working through Ranson and Clark. That *did* stimulate my interest.

Visiting scientists during my early years at UCL included Sperry, Broom, Marie Stopes, Bargmann, and many others. The medical students were expected to attend. This filled the lecture theatre and gave a good impression, but occasionally left some puzzlement. At one time, Lorente de Nó spoke about the vestibular nuclei, showing slide after slide of (to the students) uninterpretable Golgi preparations, each much like the other. One slide went up and Lorente said "uppa-side-down." The laughter that followed visibly annoyed the speaker. Heinrich Klüver spoke about temporal lobe lesions and showed movies of monkeys masturbating, something that the rather prim, though openly dirty-minded medical class was not ready for.

By the end of my first year I knew that I wanted a career as a research scientist. My brief spell as a ward orderly had convinced me that I did not want to practice medicine. The way forward was to do well in the exams (the "2nd MB") that covered the basic science subjects, and hope to gain another scholarship to support me for an extra, intercalated B.Sc. course in anatomy or physiology. I worked hard and did well and then had two interesting interviews, one with John Young and the other with Bernard Katz, suggesting that I work for a B.Sc. I chose to work for the anatomy degree (was Le Gros Clark's early influence involved?).

The anatomy degree was an almost new course. Two years earlier, P. K. Thomas had taken this degree as a solo enterprise; now I was one of four medical students taking time out (four terms) of the routine medical course to learn about anatomy as a science. I think we, and our teachers, made the

course up as we went along. It was difficult to see much planning but there was serious commitment and a developing sense of excitement about what we were learning.

The most important part of the course was a regular (once every week or 10 days) tutorial, with J. Z. Young. He would give each of us a couple of references and a subject (such as the pyramidal tract, the evolution of the hippocampal commissure, head segmentation, or Piltdown man), and then we would retreat to the library, read a great deal more, and produce an essay that could be read to the great man in about 15 minutes. And we did regard him as a great man and were suitably in awe of him. He would scrawl notes while we were reading, occasionally taking time out to answer an important telephone call, and then he would take the essay apart, often quite brutally. He would explain the biological and logical underpinnings of the subject and could do this even with subjects that were quite far from his own interests and background. I discovered later that compared to many anatomists, he did not know a great deal about the mammalian brain, but what he could do quite brilliantly was to show us how to think about it. It was this positive part of the tutorial, in which he convinced us that we had the capacity to generate some original thoughts and perhaps define some new problems, that almost always left a great feeling of achievement at the end of the tutorial, even though one knew well that one had written a pretty stupid essay.

We had "intercollegiate" lectures from professors in other London schools. Goldby on comparative neuroanatomy was serious, dull, and informative. Hamilton would lecture to a very small group of students on very early development, always after lunch. He would fix one with a fierce gaze, and the others would slowly drop off to sleep. Boyd was enthusiastic and highly specialized with a memorable collection of slides of early neural development. Cave was unscholarly with a well-honed collection of dirty stories, for which he had made a name for himself among London medical students. Amoroso taught us how to artificially inseminate a rabbit on one day and on the next collect the fertilized ova. He taught a small group of students of whom just one was a woman. He addressed almost all of his instruction to her, to her great delight. His charm compensated for Cave's crudities.

The best lectures and seminars were those held in UCL. Hans Gruneberg gave us a set of lectures on genetics and Michael Abercrombie organized a course of almost embarrassingly informal seminars on development. At first we were rather lost as to what was expected of us or what exactly the seminars were about, but as the series proceeded we realized that Abercrombie was thinking through the topics during the course of each seminar and we began to be able to share his thoughtful approach.

Keith Richardson taught a very sophisticated, practical histology class, where perfection was always expected and could never be attained. Donald

Sholl acted as a sort of avuncular figure who looked after us, supervised the practical aspects of our lab, taught us statistics, and even invited us to his home to meet his wife and three young children in a suburb in the far north of London. I remember being horrified at the feeding habits of a two-year-old.

The four terms passed quickly and served to convince me that I wanted a research career. I knew I had to work hard to win a scholarship that would support a postgraduate training. I enjoyed the course, hated the exams, which were surprisingly small-minded, but did well enough to win a scholarship and start on real research.

Starting a Research Career

At my first meeting with J. Z. Young at the start of my Ph.D. training, in 1951, he suggested that I do a study of bird cortex. I had already made up my mind to study the hypothalamus. It was attracting a fair amount of attention, it was clearly crucial in the control of the autonomic nervous system, W. R. Hess had won a Nobel Prize stimulating the hypothalamus and producing "affective" behavior, Stephen Ranson had investigated it physiologically and anatomically, and Le Gros Clark had written a book on it. Perhaps my bicycle rides with Le Gros did influence my career.

We discussed the options briefly, came to no clear decision, and I went off and started work on the hypothalamus. About six to eight weeks later I met J. Z. in the corridor and he suggested that it was time we discussed my progress. I went to speak with him and he suggested, as though he had just thought of it, that it might be a good idea if I were to work on the hypothalamus. We agreed, discussed strategy briefly, and then I was left largely to myself until I had the first draft of a thesis. At that stage he gave us enormous independence, for which I was grateful. He was willing to argue and discuss when we had something interesting, but the process of finding a suitable area of research was an important part of our research training.

The view, widely held today, that good research should be addressing a "soluble" problem owes much to K. Popper and more to P. B. Medawar. The more realistic view, that some of the most important research one can do is to look in a challenging area, such as the brain, and there work to define a soluble problem, is a less fashionable view I learned from J. Z. Young. Solving the soluble problems is often far easier than finding them.

I had just two years for my Ph.D. I worked in a part of D. A. Sholl's lab for most of the time, but on my own projects. He treated me paternalistically in a rather narrow way, but he encouraged me to attend seminars that A. J. Ayer held regularly. They were open to all, and outsiders like me could listen without having to expose their ignorance. The fast interchanges of incisive arguments were fascinating and in marked contrast to another exercise in logic I undertook at that time. I met regularly with Professor Woodger, Professor of Theoretical Biology at the Middlesex Hospital. Woodger would

explain to me on a one-to-one basis his system of logic as applied to biology. I recall that he proved to me, conclusively, that if several species evolved from a common ancestor, then there must be intermediate forms. This did not seem a very enlightening conclusion to me, but I did not doubt then, nor do I now, that his careful, pedantic approach did help me to think clearly about biological problems.

During my first year I studied the structure of the nerve cells in the hypothalamus, using a variety of reduced silver and Golgi stains. I thought I had an interesting thesis topic when I found that histograms plotting the lengths of dendritic segments between branch points always showed marked, regularly spaced peaks, suggesting that there was a "unit length" for hypothalamic dendritic segments. Sholl, a trained statistician, made me plot more and more segments until the peaks disappeared. I have occasionally thought about returning to this project! Adding more animals, non-uniform in size, must inevitably have made the peaks disappear.

I was also starting to take an interest, then fashionable, in the extent to which one could establish quantitative relations between the number of cells in a relay, their input fibers, and their output fibers. This made more sense when the nerve cell was still considered as the unit of neural function than it does today. Now it would be difficult to define the units whose quantitative relationships might throw some light upon functional relationships.

The mamillary bodies, a part of the hypothalamus, were ideal for my quantitative study; the cell group is well defined, the inputs come in the fornix, and the output goes largely in the mamillothalamic tract, both well-delineated fiber tracts. So I started to count nerve cells and nerve fibers. This could have ended as a very dull piece of numerology, but I was lucky. I soon found that some of my sections of the fornix gave counts of 100,000 fibers, whereas others gave 200,000. Both came from the postcommissural fornix; the difference was disconcerting and could not be ignored. I worried at it for a while and then noticed that the lower numbers were nearer the termination of the bundle in the mamillary bodies, as though the fornix were losing half of its fibers on the way. This loss was present in rabbit, cat, and rat (later I found it in the monkey, too), and so, together with a very detailed review of much of the older German literature, I was able to put together a thesis before my two years had passed. I was offered an assistant lectureship in 1953 as my scholarship ended.

I was lucky to get that far. In 1952, when I was just starting on the counts of the fornix, I almost stopped that line of research. My sister persuaded me, now that I was a student of anatomy, that I should once more contact the Le Gros Clarks. I was hesitant, but wrote and was invited for tea. When I arrived, the professor, who had just returned from a trip to Australia, was still out in the Parks with two of his young research fellows, learning how to throw a boomerang. When they came in, I was introduced to Drs. Daitz and Powell, and we settled down to tea and talk about neuro-

anatomy. Daitz was studying the fornix and, among other things, was counting the fibers. This did not increase my self-confidence. Having chosen to work on the hypothalamus I should have expected some competition from Le Gros Clark's team, but this was closer than I could reasonably have expected. I went away feeling low and doubtful about my thesis research. But I was committed, did not have much time left, and had to proceed with the planned research.

Not long after this, Daitz rather suddenly and, very sadly, died. I learned that he had been counting the subcommissural fornix, so my counts of the postcommissural fornix were complementary to his. Tom Powell took over this research and, very generously, suggested that we do the research jointly. This started a long and stimulating interaction with Tom Powell and before long with Max Cowan, who came to Oxford at about that time to do his thesis research. They would come to London or I would go to Oxford several times each year and our discussions of research projects proved extremely stimulating for me. At UCL at that time there was no one who had a truly expert knowledge of the mammalian brain. I could speak with Tom and Max, and very occasionally with Le Gros Clark, about almost any problem of method, or neuroanatomy, and learn something new. Often, at the end of our meetings I would feel very insecure. I was working alone, and slowly feeling my way into the subject. They had a head start, and Le Gros Clark's broad knowledge and experience. Their production of papers in the mid- and late 1950s was impressive and, for me, intimidating. Many years later, Tom once told me that he found our meetings stressful, too. He was concerned because I had learned from John Young to ask interesting questions about the brain; that was something he envied and felt he had not gained from his association with Le Gros Clark.

At the end of my Ph.D. training I no longer had the exemption from military service provided by my student status. My upbringing as a Quaker had taught me pacifism and I had registered as a conscientious objector, and so at the end of my training, I had to attend a tribunal. To my surprise, John Young came to support me in this. He also played an important role in helping me to make the decision not to finish my medical training. I received a great deal of advice to stay in medical school from almost all of my colleagues (and even from my father, a distant figure who wrote me stilted, formal German letters, and had earlier advised me that I could not get into medical school because I had no Latin). I was told that I could not expect to have a successful career without a medical qualification. John Young's support of my career at that point was crucial. He pointed out that if I wanted to study the brain, the three to four years needed to become medically qualified would probably help me very little. He said (I was 24 at the time) that the next three or four years were likely to be my most productive and I should be careful not to waste them. I took his advice, have never regretted it, and am still grateful for it. I don't think I gave any consideration to the

very short professional life of great-granduncle Deiters, but perhaps I should have.

Assistant Lecturer and Lecturer at UCL, 1953–1960

Once I had an appointment on the staff of the Anatomy Department I felt a sense of freedom I had never known before. Although I still had to work for tenure, I thought I stood a reasonable chance and was not overly worried about finding some other employment if I should fail. I had essentially complete freedom in my choice of research, funding was no problem because all I needed in the way of glassware, chemicals, animals, and other material was provided without question, by the department. I was given a small lab where I could do more or less as I liked. Also, for the first time in my life I was no longer constrained in my personal finances. I was making an income of £450 per annum. I moved into a small flat in Old Compton Street in Soho.

Previously, I had lived in a single room in a large house in Gloucester Terrace overlooking the goods yard of Paddington Station. There was noise and soot from the steam trains, but the rent was only £1 a week and there were four other medical students in the house who provided agreeable company. Three were from St. Mary's Hospital, which was close by. After I moved I kept up with my friends from St. Mary's and through them, met another St. Mary's medical student, Margot Pepper. She agreed to become my wife in December 1954, and joined me in the Soho flat for the first stage of 30 years of a very happy marriage. She was completing her medical degree while I was getting a start on my research.

My first project grew out of my thesis. I had to find out about the fibers that left the fornix on the way to the mamillary bodies. The fornix fibers are extremely thin and the techniques available then did not allow me to trace any of them. Fortunately, at that time Walle Nauta had developed a stain that would reveal very fine degenerating, unmyelinated fibers. The method was published in 1954, but earlier than that, Bill Hayhow, who was visiting from Australia and studying the lateral geniculate nucleus, had got hold of a cyclostyled copy (photocopying was not yet available) of the method. With this new method I was able to trace the fibers from the fornix to the anterior thalamic nuclei. I started to write the paper, and as I was close to finishing, Walle Nauta himself visited the department. I showed him my results and he very quietly and very charmingly told me that he had found the same thing and had already submitted the paper to the *Journal of Comparative Neurology.* That was not good news, but good science bears repeating. I finished writing and then submitted my paper to the *Journal of Anatomy,* where we published then. The *Journal of Comparative Neurology* had a publication delay of nearly two years and the *Journal of Anatomy* took about a year; so both our papers appeared in 1956, and Nauta never claimed priority.

Nauta had developed the method primarily because he had been interested in studying the fiber pathways of the hypothalamus. It was important to define how the hypothalamus is connected to the rest of the brain, and the new method provided a fine opportunity for exploring this. It never occurred to me that my next project, a study of the fiber pathways of the hypothalamus, would be likely once again to coincide with Nauta's research plans and that he was likely to be way ahead of me; or perhaps it did occur to me, but I was too brash to worry.

I started to make small lesions in the hypothalamus in rats and cats, often using a difficult ventral approach in order not to damage other parts of the brain, and traced the degenerating fibers that connect this small part of the brain to the rest of the central nervous system. I had to teach myself the surgical approach from books and practice dissections. There was no help to be got from colleagues in the department. Once, when I was working on the approach through the soft palate in a cat, Lodvick Evans, a more senior colleague, stopped by and watched me struggling for a while. He asked what I was doing. I told him; there was a long silence, and then he said, in his strongest Welsh accent, "If I were you I'd go through the rectum," and left.

I learned quite a lot about the pathways that go through the hypothalamus, especially the medial forebrain bundle, which links the hypothalamus to the mid-brain and the septum, but also about the fornix and the mamillary bodies. I was able to publish the results in the *Journal of Anatomy* again, and one paper, which appeared in 1957, later became a citation classic. I had been lucky to have been able to exploit an entirely new method on a part of the brain that was of interest to a great many people. I had spent a lot of time earlier trying to stain the fine fibers of the hypothalamus with various old silver methods. They all produced interesting results but none revealed fibers so that one could trace them reliably through the very dense fiber meshwork of the hypothalamus. The Nauta method was a very significant advance and for the next 10 to 15 years it provided a new way of studying the pathways in all parts of the brain. At national meetings in the United Kingdom and the United States papers based on the method tended to dominate, until the electron microscope took over, and I can remember colleagues complaining in private about the "Nauta bandwagon." The method became available to me just when I needed it and when it was still very new. Because I had tried so many other methods, I was ready to exploit it as soon as I heard about it.

My entry into electron microscopy was more delayed. University College London had one of the earliest and finest electron microscopy labs in the country. This was thanks to John Young's foresight. He brought Dave Robertson over from the United States and set him up in what seemed to us at the time a very extravagant lab. It was to last a long time and served to train many successful electron microscopists. One of the first of these was

George Gray, whose classification of cortical synapses and description of the dendritic spines as postsynaptic specializations will long stand as major achievements.

I knew George well at this time (in the late 1950s). We lived near each other north of London, and his oldest son was much the same age as ours, so at weekends we would take the children for country walks and George and I would talk shop. He tried hard to persuade me to take up electron microscopy, telling me of all the great things there were to be discovered. My reaction was rather negative because I had a program of study which, at that stage, simply was not asking any fine structural questions. I did not want to make up new questions just so that I could use an exciting technique that was rapidly becoming fashionable. However, it wasn't long before a question presented itself.

Brian Boycott and I were studying lizards and found that our neurofibrillar silver stains showed up some curious structures in the brains that were present when the animals were kept in the cold but not when they were kept warm. The electron microscope was the ideal tool for looking more closely at these structures. Some of the structures we were seeing were like the classical ring-like, neurofibrillar terminal boutons that Santiago Ramón y Cajal and others had described as characteristic of some, but by no means all, synaptic junctions. Oddly, such ring-like structures are not seen in cerebral cortex and other regions that are densely populated with synapses. We found that the neurofibrillar structure was formed within the synaptic terminals by bundles of neurofilaments. The classical neurofibrillar methods showed this cytoskeletal element of the synapses; they did not show the whole of the terminal. These conclusions raised some historically imporant points about early views of synaptic structure and also proved critical for the interpretation of fiber degeneration at synaptic terminals. However, they were very difficult for many colleagues to understand and accept, and did not lead to general acceptance. The issues became unimportant as better methods for tracing fibers and studying synaptic relationships became available. For me, these observations served as a useful introduction to electron microscopy of synaptic structures and of degenerating fibers.

A Sabbatical Break, 1960–1961

By 1959 I had spent six years on the staff of University College. I had been heavily involved in the teaching of the B.Sc. students and in all parts of the medical anatomy course; my research on the fiber pathways in the hypothalamus and thalamus and my new interest in electron microscopy all seemed to be going well. I started to think about taking a sabbatical break, preferably in the United States. Tom Powell had just come back from a very successful period at Johns Hopkins University, where he had worked

closely and productively with Vernon Mountcastle. He had been particularly impressed by Jerzy Rose, and strongly advised me to go and work with Jerzy, who had just moved to the University of Wisconsin at Madison, to join Clinton Woolsey. We now had two young sons and a third on the way. Finding funds that would suffice to support the whole family was not easy.

I applied for a Rockefeller Travelling Fellowship, and was interviewed at the Medical Research Council by a panel that included Dale and Hodgkin. They were unreasonably kind to me. Hodgkin congratulated me on my publications even though the list must have looked extremely thin to him, and they awarded me the Fellowship. When Jerzy found out how much money the fellowship paid he immediately arranged to add a significant sum to it. Jerzy was very considerate of such things. Unfortunately, the Rockefeller people would not allow that, threatened me with horrible tax problems, and I had to give the money back.

The plan in my Rockefeller application was to look at a thalamocortical relationship that Rose and Woolsey had just described and labelled as "sustaining projections." Whereas the classical description of the thalamus, based on the studies of Le Gros Clark, Earl Walker, and Rose and Woolsey had each major thalamic nucleus going to one area of the cerebral cortex, Rose and Woolsey now proposed that a single thalamic nucleus might project to more than one cortical area. This was (and still is) an extremely important change of view, and it seemed to me that the Nauta method might be suitable for demonstrating some of the these postulated dual projections. So I went to Madison to undertake a Nauta study; but it was not to be.

Jerzy Rose was moving away from anatomical problems to physiological problems concerned with hearing; Woolsey had a very old nine-channel oscilloscope that had never been properly exploited that he wanted to use, so I was encouraged to join them in a project that would look at thalamocortical pathways by stimulating thalamic cells and recording evoked potentials in the cortex with nine surface electrodes at once. I did argue in favor of the (to me) much more promising Nauta method and Woolsey agreed to let me try the method. However, he was at that time in the middle of a project (he was usually in the middle of several projects) on pathways linking separate lobules of the cerebellum, and we agreed to give the method an initial trial on the cerebellum. Anyone who has tried mounting frozen sections of the cerebellum will know that I had a difficult problem. Each separate lobule gets twisted in processing and has to be teased out as the section is mounted on a glass slide.

My chief problem, however, was that almost every available surface in the histology lab was devoted to cutting and staining the Nissl sections that the lab depended on at that time. There was no space for my silver staining. Woolsey found a surface where I could work but it was a long way from running water and a sink; these have to do heavy duty for the Nauta stain.

I had to carry my staining dishes back and forth across the corridor. I got the sections stained, mounted them, and was rather pleased with the result. However, when I came in the next morning, I found Clinton Woolsey on his hands and knees trying to clean some small(ish) silver nitrate stains I had made on the floor between the labs. The stains didn't come out; silver nitrate stains don't. We said no more about the cerebellum or the Nauta method, and I rather wasted the rest of my year stimulating the thalamus and recording the evoked potentials nine times faster than anyone before; at least during the relatively brief periods when all nine channels of the oscilloscope were working.

Although the experimental work I did during that year was almost worthless, in the long run the year was not wasted. I learned how other people thought about the nervous system, not only in Madison but in several labs which I was able to visit briefly, including Palay's, Bullock's, Mountcastle's and Poggio's, Nauta's, Pinckney Harman's, and F. O. Schmitt's. In Madison, Jerzy Rose was always willing to argue, sometimes perversely just to have an argument, but often instructively, and during the year I learned much from him. He was unusually stubborn. The first time I met him he took me into his office and showed me some really very poor silver stains. He was new to silver staining at that time. I looked at them, listened to his arguments, and then commented that I thought the staining was too incomplete for his conclusions. This was tactless and stupid, even though I had by then spent nine years with silver stains of various sorts. Rose's reaction was controlled incandescence, and it was more than two hours before I got out of his office. Jay Goldberg, who was waiting to see Jerzy about another matter, was surprised that my first visit should have taken so long. He laughed when later I told him what had happened. In spite of this start, Jerzy always treated me with great generosity and patience.

Jerzy taught us to be extremely critical and circumspect. He had thought deeply about neuroanatomy and was able to pass his wisdom readily to others. He wrote discussions that carefully circumnavigated every possible objection or problem. It was hard to catch him out, but he had extraordinary blind spots. He refused to believe that the corticospinal tract of rodents travels in the posterior columns, and needed a lot of persuading that red blood cells of birds have nuclei; he insisted that all the cells he was seeing in sections of a pigeon's brain were white cells indicative of infection. He was completely unconvinced when we once tried to persuade him that *dandelion* did not rhyme with *perihelion.*

Back to London (1961–1964)

When we returned to London I was keen to get back to electron microscopy. George Gray and I continued our studies of neurofibrils by looking at nerve

cells of the leech which were known to have unusually coarse fibrils, and by looking at degenerating nerve fibers in several species in situations where the neurofibrils were known to increase. Peter Ralston came to University College with previous experience of peripheral nerve stains. He and I studied the Nauta stain with the electron microscope to show that the method did stain synaptic terminals, a point denied by many at the time, possibly due to the poor quality of their preparations, but perhaps just a misinterpretation of the sections. Marc Colonnier was then studying the visual cortex with the electron microscope and he and I initiated a study that was to change my career and give it a sense of direction it had previously lacked. In the cortex, many of the incoming fibers form synapses on slender dendritic spines. When Marc cut the incoming fibers and studied their degeneration he found that some of the spines were shed, but that the postsynaptic nerve cell itself seemed unaffected. This was in marked contrast to what was then thought about the monkey's lateral geniculate nucleus, where Glees and Le Gros Clark had earlier described incoming retinal axons making rather large, one-to-one synapses directly on the cell bodies of lateral geniculate cells. When the retinal axons are cut, the geniculate cells show quite marked degenerative "transneuronal" changes and, in addition, the retinal axons show a dramatic neurofibrillar increase, which the cortical axons never show. We thought we would use the electron microscope to compare the two situations and learn more about the details of the degenerative changes, hoping especially to understand the basis of the transneuronal changes at the simple geniculate synapse and possibly relate it to the neurofibrillar changes.

At that time we were still fixing tissues in osmium tetroxide, and it was not until we started to use aldehyde fixation that we began to get acceptable preparations of the geniculate. We were amazed by the synaptic complexity of the nucleus. The simple one-to-one synapse was not to be found. We published an account of our results, showing the complex relationships of retinal axons with other synaptic structures. Our paper appeared shortly after J. Szentágothai had published a detailed account of geniculate structure. He wrote me and commented on the fine quality of our pictures but pointed out that we had made a mistake about the polarity of some of the synapses formed by the retinal fibers. These fibers had to be postsynaptic to other axons in the nucleus so that experimentally observed depolarization of retinal fibers could be explained. This had been observed by several groups after repetitive firing of optic nerve fibers, and interpreted as "presynaptic inhibition" in accordance with J. C. Eccles' observations in other parts of the brain. Our preparations showed the retinal fibers as presynaptic, and so they have subsequently proved to be. It is always a mistake to make the anatomy fit the physiology. If it does fit, that is encouraging. If not, then there is a problem to be solved, and it was my interest in this problem that later led me into a detailed study of the lateral geniculate nucleus. The

problem is not really resolved yet. Probably the depolarization of the retinal axons is due to the accumulation of extracellular potassium. The retinal axons end in unusual synaptic complexes called *glomeruli,* within which astrocytic processes are rare. In most parts of the brain astrocytes are next to synapses and serve to mop up extracellular potassium. The structure of the glomeruli (not the synaptic polarity) may well be responsible for the depolarization seen in the optic nerve fibers, but the possible functional significance of these relationships remains unexplored.

I enjoyed my time back in London. In 1961 Le Gros Clark had offered me a position in Oxford but because this would have meant a salary drop I stayed at University College. In 1963 I was promoted to a *Readership,* which made my career look secure. However, it also made me look critically at the future. There were no significant challenges ahead, except for possibly heading an anatomy department somewhere, which I was then not inclined to do. I was receiving job offers from the United States and started to look at those seriously. D. Bodian invited me to Johns Hopkins, and Al Berman, who had moved from Woolsey's group to the Anatomy Department at the University of Wisconsin, was urging me to join that department. Margot was working part-time as a general practitioner and our daughter, Jane, was born in 1963. Career opportunities for both of us looked more promising in the United States and after long consideration, preparing lists of pros and cons, and finding the pro list much the longer, we decided to move back to Madison. I tried to finish my major research projects, wrote a long review with George Gray on synaptic structure, closed the chapter on the leech, taught the last group of B.Sc. Anatomy students, 12 of them, and stayed just long enough to see the exam list, headed by Semir Zeki.

Madison, 1964–1977

The time I spent in Madison was perhaps the most productive part of my career. We lived a short walk from the lab and the schools, and the children grew up to think of Madison as home. Margot worked part-time in the nearby University Health Clinic and when the children were older she started a residency in dermatology. Over the years I was joined by a series of stimulating neuroanatomical colleagues. Max Cowan joined the department in 1966 and when he left Semir Zeki came for a year, followed by Peter Ralston. I had superb technical staff, Grayson Scott taking charge of the electron microscopy and Elaine Langer of all of the light microscopy and photography. I participated in the teaching of neuroanatomy to medical students and developed a course for graduate students, early on working on this with Max, and later with Semir, and then Peter. I enjoyed this teaching, and spent the whole of my 20 years in the United States without teaching any of the other subjects that I had been trained to teach at University College: no gross anatomy, no histology, no embryology. To some extent I

missed this, but there were too many other things to do at the time for me to have serious regret.

When I came to Madison I wanted to look at the problem that Szentágothai had raised about presynaptic inhibition. This had been demonstrated in the spinal cord, in the posterior column nuclei, and in the lateral geniculate nucleus. I wrote a grant application proposing to look in the geniculate and posterior columns, to compare the two situations. The grant was funded but the geniculate part of the work proved so complex and rewarding that I never properly explored the posterior columns.

It was clear to me that the knowledge we had of the lateral geniculate nucleus was surprisingly incomplete and, in places, either muddled or wrong. I tried hard to arrive at a more "complete" view of the nucleus, including its laminar structure, the structure and origin of its afferents, and the fine structural details of synaptic arrangements in the nucleus. Peter Ralston was looking at the ventrobasal thalamic nucleus at the same time and the similarities between his results and mine gave strong support for the view that there is a "general pattern" of organization that characterizes the thalamus, a view that also came out of the work being done concurrently at Oxford by Tom Powell and Ted Jones.

At this time I was primarily a descriptive anatomist, a term that is often, especially in grant reviews, linked with "merely," as though the work were easy or unnecessary. The important roots of neuroscience in accurate descriptive accounts are often overlooked, and the joy of arriving at a reasonably accurate and lasting description of a structural relationship is not as widely appreciated as perhaps it should be. It was a chance observation made in 1968 that was before long to take my research in a new, and quite unexpected, more interpretative and experimental direction.

I was looking at the laminar structure of the cat's lateral geniculate nucleus, puzzled by the reports that the cat has three geniculate layers, two innervated from one eye and only one from the other. I was pleased to find a small extra layer of fine fiber degeneration, making the score two-all. It became clear that earlier accounts of three layers of fiber degeneration, called *A, A1,* and *B,* had been based on inadequate Nauta stains and a confusion about what exactly was to be called layer *B.* In order to cut through the muddle I described the layers as *A, A1, C,* and *C1* (*A* and *C* receiving from the contralateral eye, *A1* and *C1* from the ipsilateral eye), dropping *B* into limbo. This upset many people, and still leaves newcomers wondering about what happened to *B.* It pleased me to have two layers connected to each eye, even though they weren't matched in size or in structure. But the pleasure was not to last. It wasn't long before Terry Hickey, with the more sensitive autoradiographic method found yet another layer, *C2,* making the score 3-2. We still don't have a clear idea about exactly what the lateral geniculate nucleus is doing for one eye that it doesn't do for the other.

During the course of these studies, one cat showed an unusual laminar structure. I was puzzled by this until I saw in my notes that it had been a Siamese cat and recalled that Siamese cats are commonly cross-eyed. A second Siamese cat showed the same abnormality. It did not take long to find that all Siamese cats are abnormal: many of the fibers that would normally take an uncrossed course from the eye to the lateral geniculate nucleus, instead take a crossed course. The complex implications of this relatively simple abnormality are intriguing. We can ask about the developmental mechanisms producing such an abnormality at the optic chiasm (the site of the partial crossing). The answer is not yet clear. We can also ask about the visual capacities of an animal that receives part of its visual input as a mirror reversal of the normal; and we can make some instructive comparisons between normal and Siamese cats in their reactions to visual deprivation. Jon Kaas and I looked at many of the electrophysiological problems, and Vivien Casagrande and I studied some of the visual behavior of normal and visually deprived Siamese cats. The implications of these studies are not easily summarized. They showed that nerve fibers, even when they take a wrong route, can still make the topographically correct connections on the other side of the brain. More surprisingly, they showed that in some cats, the abnormal messages from the lateral geniculate nucleus are suppressed in the cerebral cortex, whereas in other cats, the pathway going from the lateral geniculate nucleus corrects the aberrant mirror reversal. This took some working out because David Hubel and Torsten Wiesel had reported the second sort of cat (correcting), and all our cats were of the first sort (suppressing). Because each result implied different anatomical connections, we undertook the anatomical studies and were lucky that after studying 10 cats that all matched the suppression, we found one that matched the correction. We named them "Boston" and "Midwestern" pathways, respectively, and the terms were so apt that they stuck.

These observations opened many new doors. Siamese cats represent a form of albinism and it became evident quite early that all mammalian albinos have the same sort of chiasmatic abnormality. The results started my interest in the visual pathways of albinos, in the development of the optic chiasm, and also in the development of the thalamocortical pathways which had demonstrated their remarkable capacity to adapt to the abnormal inputs by correcting the pattern of the pathway that goes to the cerebral cortex.

One interesting outcome arose from my (private) speculation that the Siamese cat might provide a useful model for studying binocular competition. In a normal mammal each hemisphere receives inputs from two eyes, and these inputs are arranged so that they match retinotopically, allowing single cortical cells to receive from a single point in visual space through the left and the right eye. Wiesel and Hubel had been studying the effects

of early visual deprivation in one eye, which produces blindness in the deprived eye and corresponding cell shrinkage in the parts of the lateral geniculate nucleus innervated by that eye. They had good but indirect evidence that the deprivation acts by upsetting a competitive balance that characterizes normal development and normally allows both eyes to develop equal access to the appropriate part of the cortex, each eye connecting to cortex through one of two competing geniculocortical pathways. Because most of the representation of vision in one cerebral hemisphere of a Siamese cat comes from one eye only, it seemed to me that one could test the competition hypothesis, since there should be no competition in the large monocular part of the Siamese visual pathway.

I needed to raise some Siamese kittens with a monocular lid suture in order to make this test. I got three young Siamese cats, two female and one male, and waited for them to mature and breed. They took forever. At the end of about a year or more I suddenly realized that I had been stupid. And it was sudden, and rather exciting. A normal cat has a part of the visual pathway that is monocular. We all do. If you shut one eye, the part of the visual field that you lose is monocular, and this monocular part of the visual field has its own representation in a well-defined part of the lateral geniculate nucleus and cortex. There could be no competition in this part of the system. The situation had been well summarized by Gordon Walls in the book he had written about the lateral geniculate nucleus and Le Gros Clark's color experiments. So now I realized that if a monocular suture acted by upsetting the competitive balance in the geniculocortical pathway, in a normal cat the monocular segment of the pathway should be spared. Why hadn't Wiesel and Hubel seen this in the lateral geniculate cells of their cats? And why hadn't I thought about it earlier? When I looked at the Wiesel and Hubel paper the result was obvious in their illustrations: the monocular segment was spared!

Deciding on the next step was not easy. A theoretical paper based on the published photographs would probably be ignored even though the logic was compelling. One needed some measurements to make a convincing case. Dennis Stelzner and I raised three kittens with monocular lid suture, then prepared the sections and measured the cells. It was months before we had the results, and naturally I was sure that an idea as obvious as this one could not be ours alone. But it was. We published the result and convinced many people. I was able to exclude other explanations later by further experiments, and with Murray Sherman, was able to show that in any monocular part of the visual field (naturally occurring or experimentally created) there is sparing, not only of the geniculate cells but also of visual capacity, which is lost after monocular deprivation for the main, binocular part of the visual field. Writing the first paper on the competition was surprisingly difficult. New thoughts, even when they are clear in one's head,

are difficult. I wrote most of the paper while on vacation with the family in Door County, Wisconsin. During the day we enjoyed the scenery and Lake Michigan. In the quiet evenings I worked to get my thoughts organized.

The Move to Chicago, 1977–1984

The work that I did in the early and middle 1970s led to several interesting job offers and made me think seriously about our future in Madison. The children were growing up, Margot had started her residency but was not sure that there was a slot for her in the Madison dermatology program to complete her third year, and I saw my future in neuroscience at Wisconsin as limited. When I spoke to the dean of the medical school, who at that time was a surgeon, about the importance of graduate training in neuroscience, which was receiving no financial support, he asked whether I wasn't just wanting to have fun. The answer—of course—was yes. I regarded teaching and introducing others to neuroscience as fun; no one could possibly have wanted to do it for the money. I was invited to look at the Anatomy Department at the University of Chicago, where on my first visit it was made clear to me that an outsider would not be welcome. The university was also planning to build a neuroscience program and had an interesting and lively group of neuroscientists. When the dean, Dan Tosteson, rang me after my visit to ask whether I would be interested in a position in Anatomy I said that I was not; I wanted to have my cake and eat it too. I wanted the environment of the expanding neuroscience program that the university was planning but I did not want the administrative responsibilities that would go with the Anatomy appointment. Dan Tosteson said he would arrange for me to have my cake and eat it too, and he did. I was given an appointment as chairman of a new Committee on Neurobiology and as a member of the Department of Pharmacological and Physiological Science, and Margot was able to complete the third year of her residency at the University of Chicago, later moving into a staff position in Dermatology.

Al Heller was the head of my new department, and our shared views about the academic goals of the new neurobiology program made my seven years in Chicago run smoothly. Al did the heavy duty administration, involving me occasionally, and I was able to focus on the developing graduate program and on the research in my lab. Later, after I had moved to Oxford, I realized that I had also had some necessary lessons in administration. Al never actually provided tutorials, but I learned a lot by just watching and listening.

My research shifted gradually during my time in Chicago. I had moved the core of my Siamese cat colony in 1977, but was to lose it to disease within a few years. I continued to work out the basic structure of the lateral geniculate nucleus in cat and rabbit, and started to look more closely at the developmental problems raised by the albino abnormality. We started to

define the stages in the development of the visual pathways in normally pigmented and albino ferrets. Ferrets were attractive for this because they have a visual system very similar to the cat's, but they have larger litters and the young are born at a very much earlier developmental stage, so that one can undertake experiments in postnatal ferrets that would have to be prenatal in cats.

In the late 1970s I was surprised to receive an invitation to a conference at Leeds Castle in England on the optic chiasm. I was to give the introductory talk. Although the optic chiasm, which is the region where some of the fibers going from the eye to the brain cross, and where an abnormal contingent crosses in albinos, had been of obvious interest to me in relation to the albino abnormality, I knew very little about it. Leeds Castle is a beautiful and luxurious building in a fine setting, the conference sounded interesting, I still had a mother to visit in England, and I accepted. Then I had to start reading about the chiasm. The literature was confusing, I gave a rather bad introduction, enjoyed the lavish hospitality of Leeds Castle, and sat through fierce arguments, illustrated by gruesome movies, about the best approach to a tumor near the chiasm: through the nose, the frontal lobes, or the temporal lobes. I came away guilty about my inadequate knowledge and determined to find out more about the optic chiasm. Working out exactly how the fibers that go from the retina to the brain relate to each other took up much of my time in Chicago, and later in Oxford. The pathway is intricate and complex, and early attempts to understand the development of the chiasm were necessarily flawed in the absence of clear information about the structure that was actually developing. The pathway consists of functionally distinct fiber groups, which Chris Walsh was able to show develop at different times, and which have distinct crossing patterns in the chiasm. That is, there is not one simple rule for all of the fibers.

In Chicago I also started to do some difficult intrauterine experiments in order to look at the developmental mechanisms that could produce the Boston pattern of geniculocortical connections in some animals and the Midwestern pattern in others. We were able to show that in the development of the geniculocortical pathway there is a mechanism that is independent of retinal inputs and another that depends on these inputs. In a normal cat both would tend to produce the same result, but in a Siamese cat, where the retinal input to the lateral geniculate nucleus is reversed relative to normal, they would produce opposite results, and so exactly which type of circuit is developed depends upon which mechanism happens to be dominant. These experiments also produced some unexpected and very puzzling results about the development of the optic chiasm. Removal of one eye, very early in development, before any of the fibers had reached the chiasm, produced an abnormality in the pathway formed later from the other eye, an observation that had previously been reported for mice by Pierre Godement. The surviving pathway behaved rather like one coming

from an albino eye, in growing few, if any, uncrossed fibers. Hector Chan showed later, in Oxford, that this pathway was not like the albino pathway in its detailed anatomy. Rather, it seems that in normal development the uncrossed fibers need the crossed fibers from the other eye to accompany them on their journey beyond the chiasm. Carol Mason and Pierre Godement were able to show that when the crossed fibers from one eye are lost, the uncrossed fibers from the other eye stall at the chiasm.

I enjoyed my time in Chicago. I had stimulating colleagues with high scholarly standards. We had keen students and the neuroscientists formed a productively interactive group. I had no idea of leaving until Tom Powell, who was still in the Oxford Anatomy Department, suggested that I consider moving to Oxford to head that department when Charles Phillips retired in 1983. Tom had been passed over as the head of that department some years earlier. He knew now that he would never be made head, and encouraged me to think of myself as a candidate for the post. Margot and I had both spent some of our childhood in Oxford, we had a notion that eventually we might want to retire in England, and a move well before retirement seemed sensible. Our children's education was almost completed and we felt that we could afford the major drop in salary that the move would entail. When Colin Blakemore, who was an elector for the anatomy post came through Chicago and asked if I was interested, I was ready to say yes. The job was offered to Gordon Shepherd first who, fortunately, decided against the move. Then we went through a long and complicated negotiation that included a promise of a job for Margot from the dermatologists and, for me, a complex correspondence containing many subordinate clauses and attempts to explain an administrative structure that I later learned was not understood by anyone.

The Department of Human Anatomy at Oxford, 1984–1996

In Oxford I had to take greater administrative responsibilities than I had had in Chicago. The department had a history of poor industrial relations with its technicians. The administrator wanted to be in charge of the department, did not trust the staff and was, in turn, not trusted by them. There were existing antagonisms that made some of our meetings difficult and tense. The first few years were not easy, but there was enthusiasm about research and teaching in the department that made the job enjoyable for me in spite of the difficulties. After three years the department was able to hire a new administrator, David Dongworth, who, unlike his predecessor, had had postdoctoral research experience, and had also worked for the Medical Research Council before moving to Oxford. He understood what was needed for the creation of a good research environment. Gradually he took over more and more of the running of the department and ran it smoothly and well. There were no more industrial hearings for me to attend and I

knew that our financial affairs were in capable hands. I could concentrate on other things. He was everything that a good administrator should be and helped to build a strong, friendly, and enthusiastic department, which I was very sorry to leave when I reached retirement age in 1996.

Early during my time in Oxford I was approached by a committee representing the European Neuroscience Association (ENA) to ask whether I would take on the editorship of a journal they were planning to start. Michel Cuénod, Per Andersen, Anders Bjørklund and Wolf Singer represented the ENA and were visiting several English publishing houses to explore possibilities. When they were asked who would edit the new journal they decided that they had best come to an early decision on this. The evening before their meeting with Oxford University Press they were dining in Oxford. I had moved to Oxford recently, so they rang and asked me to join them for their dessert to discuss my possible candidacy. We had moved house that day, it had been one of our coldest January days, and I was dirty, cold, and tired; but I realized that this editorship might give me an opportunity to get to know European neuroscientists in a way that is not generally easy for someone who has recently moved from one continent to another. So we met, and I later agreed to become the first editor of the new journal. It was hard work to set up new procedures and policies, but it was rewarding. I did get to know many of the active neuroscientists in Europe, and found that working with them was a delight. We got the journal started, and later on some of the same colleagues helped to set up a much needed European body (The European Biomedical Research Association) to address issues related to animal experimentation. More and more new legislation was coming from the European Union in Brussels, and there was a need for a body that could address these issues from a European, rather than a national, perspective. Thanks to Mark Matfield, the very energetic executive director of the new body, it got off to an excellent start.

The research of my lab in Oxford focused on two separate issues. One was to learn more about the optic chiasm and its development. I was able to summarize much of our current knowledge on this in a review written with Jeremy Taylor and Carol Mason shortly before my retirement. The other was a study of the thalamic reticular nucleus and a group of transient cells, closely related to the reticular nucleus.

Work on the reticular nucleus had started for me in a single study done in Madison with Vicente Montero and Clinton Woolsey. We had been able to show that small injections of two different radioactive tracers into visual cortex produced two clearly distinct loci of anterogradely transported label not only in the lateral geniculate nucleus (this was expected), but also in the thalamic reticular nucleus. Because the reticular nucleus at that time was considered to be a diffusely connected cell group, this result was a surprise and stood out as rather an exception to knowledge of the reticular nucleus.

I did not follow this clue any further until after I had moved to Oxford more than seven years later. Then I encouraged John Crabtree to look more closely at this issue. Herb Killackey, who was visiting Oxford at the time, expressed one of the problems succinctly when he asked how single points in the visual field are represented in the thalamic reticular nucleus. We knew that in the lateral geniculate nucleus they are represented by the "lines of projection" that Gordon Walls had described clearly in his book and P. O. Bishop has discussed in his autobiographical chapter (*The History of Neuroscience in Autobiography*, Vol. 1). John and Herb published a very beautiful paper in the first issues of the *European Journal for Neuroscience,* defining a then rather surprising mapping of visual cortex and retina onto the reticular nucleus. We now know that for each major sensory pathway (vision, hearing, touch), which relates to its own sector of the reticular nucleus, the relevant sensory surfaces are accurately mapped via connections coming from cortex and from thalamus. Many of the details of the mapping established by different pathways coming from thalamus or cortex still remain to be defined. These are likely to prove important in the proposed role of the reticular nucleus in attentional mechanisms, and I hope that in the next few years it will be possible for colleagues in Madison, where I am now working in a "post-retirement" capacity, to define the major features of these pathways.

When I was first looking at the radioactively labeled fibers that pass from visual cortex to thalamus I was struck by a change in the appearance of the pathway that occurs some distance before it reaches the thalamic reticular nucleus. It looked as though the fibers might be establishing contacts or a change in direction in this region. Careful inspection showed very few scattered cells in this region, which Annemarie Clemence and John Mitrofanis then demonstrated clearly and labeled the *perireticular* nucleus. John went on to show that these cells were the surviving remnants of a transient cell group, rather like the cortical subplate. The cells are there early in development just as the corticothalamic and thalamocortical fibers are growing past, and once these fibers have entered their appropriate course, the cells disappear as though they play a role in the development of the fiber pathway. The further study of this still quite mysterious cell group took up much of the other research efforts in the Oxford lab with Gary Baker, Eion Ramcharan, and Niels Adams during the next few years.

My time in Oxford was rewarding and enjoyable from the point of view of my research and my administrative duties, but not for my teaching or my personal life. The instruction of undergraduate students at Oxford is dominated by the tutorial system, which can provide excellent opportunities to students and teachers, but by tradition excludes professors from instruction other than the giving of formal lectures. Graduate students receive virtually no formal instruction, so that my contacts with students were limited for much of my time. Students automatically tended to turn to

their tutors or their research supervisors. The curious tradition of relieving staff from most teaching duties when they were elevated to professorial rank tended to exclude many of Oxford's most senior staff from the mainstream of the university's educational enterprise, which in Oxford is focused on the colleges.

On the personal side, we found when we got to Oxford that the promise of a job for Margot was not going to be kept. Moving two careers is never easy and perhaps we were unwise to trust the reassurances we were both given. Margot was left in limbo for a considerable time, with no honest recognition of the promises that had been made, and she never found a really suitable professional opportunity in England. It was a bad experience. We separated toward the end of our time in Oxford and she is now once again practicing as a dermatologist in Madison.

Retirement 1996–

In 1996 I reached the mandatory retirement age at Oxford, and as this time approached I began to wonder about what I would do with my time. When an opportunity arose for me to return to Madison, to undertake some studies of thalamic anatomy with John Harting and other colleagues, I welcomed it enthusiastically. John had originally come to Madison in the 1970s to spend time as postdoctoral fellow in my lab. He is now head of the Anatomy Department and, working with Sherry Feig and Dave Van Lieshout, had been doing some beautiful light and electron microscopical studies of thalamic and tectal fiber pathways. They had all of the techniques I needed to attack some of the problems that still intrigued me about the thalamus. I had been corresponding for some years with Murray Sherman about the thalamus. He had earlier spent a sabbatical year in Oxford as the Newton-Abraham Visiting Professor and we had formed a habit of fruitful argument, which in recent years we continued by e-mail. This led to the development of a number of ideas about thalamic structure, many of which were included in a review we wrote just before I retired. Now I have an opportunity to look into some of these ideas in my semiretirement. John Harting has given me generous lab space and I am once more starting to do experimental work. The main thrust of our current research derives from an observation that was published in 1972 from the Madison Anatomy Department by Larry Mathers, a student of Peter Ralston's. This had long puzzled me but never seemed to fit into a general scheme. Larry found that nerve fibers that innervate the pulvinar nucleus of the thalamus from the cerebral cortex have large terminals that look just like fibers from ascending sensory pathways (visual, auditory) in other thalamic nuclei. This is in contrast to the cortical fibers that innervate primary relay nuclei for vission, audition, and other senses, which are much smaller and clearly distinguishable. Evidence currently available suggests that the small endings

modulate transmission through the thalamic relay, whereas the large endings provide the primary source of the information that is transferred. More recently, similar large cortical afferents have been found in other thalamic nuclei that receive few or no ascending afferents, so-called "association" nuclei, such as the mediodorsal nucleus or the posterior group. It now looks as though there are two distinct sorts of corticothalamic fiber, one with large and the other with small endings, and that these take origin from different groups of cortical cells. Nuclei that receive the large endings from cortex can be regarded as having their primary function in the relay of messages from one cortical area to another, in contrast to the classical relay nuclei, such as the lateral geniculate nucleus, which relays ascending visual information from the retina to the cortex and is subject to modulatory influences from the cortex via the smaller endings. Working out the details of this dual corticothalamic connectivity, and perhaps looking more closely at the thalamic reticular nucleus, promises to provide me with an interesting retirement.

Overview

It is not easy to summarize my life. Certainly the invitation to write about it has served as a stimulus for thinking about it and for that I am grateful. I had not fully realized before writing how lucky I have been in the forces that have shaped my career. Inheritance and environment seem to have combined smoothly to turn me into a neuroscientist; it almost looks as though I had no choice at all. I have always enjoyed the teaching but have felt more comfortable with a small group than in a formal lecture. The administrative duties were the most difficult and took me longest to learn. I should have built up the Oxford department more and left it in a stronger position, but I was never able to put my heart into the necessary "empire building." I ended my career thinking of the department, in an admittedly parochial way, as the best small anatomy department in the world. It was the research that I enjoyed most and have focused on in this account. I have had many excellent students and coworkers and in the space available here have only mentioned a few of them in relation to particular high points of the research. They have provided essential stimulation in daily interactions, in arguments about details of particular research problems, and in our regular weekly lab meetings. For the descriptive work and for the experimental, interpretative studies, the day to day focus on each problem as it developed and took shape has been the most demanding and the most rewarding part of my career. It is very difficult to understand or to describe what it was that I was doing. How does one shape facts and ideas into coherent (publishable) advances in knowledge?

> When you have carried some stuff round with you a very long time and mulled over it, and scraped together everything about

> it that might be useful—then it works, then something may come of it. You get an idea, it sticks in your head, or in your feelings; it is like a lump of clay in your hands, you try to work everything into it that you see, you think and dream of nothing but this one thing. That is the way you get it done.

This quotation, from H. T. Lowe-Porter's 1939 translation of Thomas Mann's *Lotte in Weimar* (published by Secker and Warburg), is about the creation of great poetry. Although I have been concerned with a very different product, the process of creating something new seems remarkably similar, no matter what the level. Perhaps the quote appeals to me because I share Goethe's birthday. The amount of work and mulling over that is required for the production of a new description or a new idea, even a quite simple one, is always surprising. The reward comes rarely, but just often enough to keep you at it.

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