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The History of Neuroscience in Autobiography

Ainsley Iggo • Jennifer S. Lund

Patrick L. & Edith Graef McGeer

Edward R. Perl • Donald B. Tower

Patrick D. Wall • Wally Welker

Volume 3

Edited by Larry R. Squire

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The History of Neuroscience in Autobiography

VOLUME 3

Edited by Larry R. Squire



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Bernice Grafstein

BORN:

Toronto, Ontario, Canada
September 17, 1929

EDUCATION:

University of Toronto, B.A. (1951)
McGill University, Ph.D. (1954)

APPOINTMENTS:

McGill University (1954, 1957)
Rockefeller Institute/Rockefeller University (1962)
Cornell University Medical College (Weill Medical
College) (1969)

HONORS:

Grass Foundation, Fellow (1961); Trustee (1965);
Vice-President (2000)
Outstanding Woman Scientist Award, American Women
in Science (1982)
Society for Neuroscience, President (1985–1986)
Dana Alliance for Brain Initiatives (1993)

Bernice Grafstein was trained as a physiologist, developed the potassium hypothesis of cortical spreading depression, characterized fast axonal transport, and first demonstrated transneuronal transport of radioactivity within the central nervous system. She also has carried out extensive studies of the regenerating goldfish visual system in the context of her broad interests in central nervous system regeneration.

Bernice Grafstein

People have been telling me lately that I am a role model. But for what role? I have not been a department chairman, or a dean, or even the leader of a large research team. Critical decisions in my life as a neuroscientist seem to me to have been determined by circumstances unique to my time and my temperament, and I have few if any helpful hints to impart to young people trying to chart their own future. I can only tell you where I have been and what I have done. Many of the events that made a difference can be attributed, as perhaps in everyone's life, more to chance rather than to careful consideration, and what will appear repeatedly in my story is how apparently random collisions have resonated with great consequence at a later time. So maybe this has to be my message: I often set out to do things that I was little prepared for but determined to pursue my own path, the path that felt right for me and not necessarily the path that the world around me would have accepted as appropriate.¹ It worked for me.

As a child growing up in Toronto in the mid-1930s, I did not think of my situation as unusual. That my parents and I lived in two rooms and we shared a single bathroom with six other people did not seem unusual; that I would enter kindergarten speaking almost no English did not seem unusual;² and that the only books in our home were a few of my old schoolbooks and a well-worn copy of Cinderella³ did not seem unusual. My father made his living as a sewing machine operator, stoically stitching side seams on men's pants, always with the specter of unemployment looming over him.⁴ It appeared to me, however, that everyone around us was experiencing the same financially stressed existence, although hoping for

¹ In that respect, perhaps not so different from many of the scientists whose autobiographies appear in this series.

² Yiddish was our household language, and even at the end of their lives my parents still could read English only with difficulty and write it not at all.

³ My first birthday present, given to me by school friends, to my great astonishment and delight, when I turned 6. Yes, I still have it.

⁴ I have a vivid memory of him sitting at the kitchen table anxiously counting his piecework tickets. Those precious scraps of paper that determined how much he would be paid seemed incongruously flimsy tokens of the effort that had gone into acquiring them.

better things to come. Many years later, I came across letters to my mother from the father and sisters that she had left behind in Poland, desperately begging her (who had so little) to help them (who had even less), and I was stunned to realize how grim and precarious life must have seemed to her. She was emotionally shattered, never to recover, when all her relatives were lost at the start of World War II. I was protected from all that, however, by notions of the inevitability of “social progress” and the dignity of honest work. I assumed that, unlike my mother, I would always be able to look after myself by getting a job.

It was therefore clear to me, when I was age 14, that to pay for the impossibly expensive orthodontic work I had been told I needed, I would have to get a job. In those World War II years even someone my age could be taken on as a hand in a book bindery, although I had to pretend that I was going to be working permanently, not just for the summer. I lasted 2 weeks. I was fired for reasons that were never made clear, but I was just as glad. I had already realized that I did not have the qualities—neither the muscle power nor the nimbleness of fingers nor the resistance to the boredom of repetitive tasks (nor a circadian rhythm that encouraged early rising)—that are necessary to become a successful member of the working class. I would have to hone my intellectual skills instead.

That did not seem unreasonable, since I was a conscientious student and my high school, Harbord Collegiate Institute, was then (and may still be now) one of Toronto’s most successful incubators of academic prowess. It was an environment that brought together students with a sense of mission, excellent teachers, and a tradition of accomplishment; an environment in which the most intellectually gifted individuals became nearly as celebrated as the football players and cheerleaders or the stars of the annual performances of Gilbert and Sullivan. The photographs of university scholarship winners lined the halls, and I was pleased to become one of them.⁵

Entering the University of Toronto in 1947, I enrolled in the Physiology and Biochemistry Honors Course⁶ since I had already decided that I was going to go into medical research. Discovering new things about the world seemed to me to be a worthwhile thing to do in life, and it was obvious that in research a job would never be difficult to find. I had briefly considered whether I should go to medical school, which one could enter directly from high school in those days. However, I could not resist the scholarships that

⁵ Imagine my pride when I recently visited the school and overheard a stranger point to my picture as that of “a world-famous biochemist.” Near enough!

⁶ I was following the example of some women I knew who had preceded me at Harbord Collegiate, such as Beatrice (Karger) Wittenberg and Edith Rosenberg, (both of whom went on to successful careers in physiology).

were being offered if I took a science degree because the scholarship money would buy my mother her first electric refrigerator. I had only the vaguest idea of what research meant. I had been captivated by the story of the discovery of penicillin and by the fact that this drug was being produced in a mysterious Gothic building that had aroused my curiosity for years. I had read *Microbe Hunters* (de Kruif, 1926) with great excitement (like many of my contemporaries who became scientists, I subsequently found out) and had felt a great sense of discovery in the biology class taught by Mr. Leslie Smith at Harbord (to his credit, this was not an uncommon result among his students). I had little hesitation, therefore, about making a commitment to a scientific career. Deciding one's future on such an inadequate basis at what may now seem an absurdly early age was not unusual, however, at that time in that place. "Vocational guidance" was still unknown, and students whose parents had experienced the Great Depression firsthand were strongly motivated to select a professional field and become qualified in it as rapidly as possible. There was also a sense of urgency remaining from the war years that had recently ended, especially since our classes were filled with veterans anxious to get on with their lives.

The curriculum in our course was rigidly prescribed, except for the choice in the final year between the physiology track and the biochemistry track. I do not think that with free options, however, I would have chosen as well. I would not have anticipated my pleased astonishment at the homologies of structure in different animals that I saw in the comparative anatomy course, my satisfaction as cellular patterns emerged in histology classes, the terrors of the organic chemistry lab,⁷ or for my complete incomprehension of the principles of physical chemistry.⁸

Luckily, I was a conscientious student, but I was fiercely determined not to be bound by the limitations of pure "scientism." Despite the tightly structured program of over 30 mandatory classroom hours per week, I spent more than the usual amount of effort on the few required humanities courses. I was a proud member of the University College Arts and Letters Club, the only one who was not an English major. I became the program director of the University of Toronto Film Society. The friends that I spent the most time with were graphic artists and filmmakers.

At some point I began to think that it would be interesting to study "how the brain works." But how to begin?

Even allowing for how little was known about neuronal function at that time,⁹ the nervous system was a minor ingredient in our educa-

⁷ One exercise required us to make TNT from nylon stockings.

⁸ Could a girl really have been expected to know how an engine works?

⁹ The only available synonym for "neurotransmitter" would have been "acetyl-choline", and asserting at a scientific meeting that it might act in the brain would have been an occasion for fisticuffs.

tion and indeed was not then a significant object of study anywhere at the University of Toronto. In that stronghold of carbohydrate metabolism, a monument to the supremacy of the liver and the pancreas, I left my instructors speechless when I informed them that a professor of psychiatry had signed on as supervisor of the major paper that I was required to write in my senior year. I had managed to convince him that a paper on the function of the brain in psychoanalysis was a good idea. My paper, I was informed, would be on the role of lipid metabolism in the production of fatty liver.

There was, however, one ray of light. In an obscure department in the School of Hygiene I had found someone who could be identified as a neurophysiologist, Vernon B. Brooks, who was finishing his thesis work on the neuromuscular junction for a degree from the University of Chicago. I spent a summer in that department at the end of my sophomore year, as a prelude to what I envisaged would be my career as a laboratory technician. It was a seminal experience for me—when I learned that the “doctors,” in their white coats donned specially for the occasion, were served lunch in the rooftop conservatory, whereas the technicians were expected to bring their bag lunches to the cafeteria adjoining the boiler room in the bowels of the building, I knew that I would be headed toward a Ph.D. degree.

When it came time to choose where I would do my Ph.D., it was the knowledge that Vernon had gone on to the physiology department at McGill University in Montreal that made me think that that was a place where the nervous system would be respected. Indeed, I seemed to be getting a special message when the keynote speaker at our graduation from the University of Toronto in 1951 spoke of the importance of the unity of Canada across the boundary of its two languages. I had been very good at French in high school. Surely, bilingual Montreal would welcome me.

How could I have guessed what I would be getting into in Montreal? I knew nothing about neuroanatomy. I knew nothing about membrane potentials. I knew nothing about electronics. I knew nothing about espresso coffee, Hungarian pastry, or fine wine, staples of the good life in Montreal. I thought I knew about winter and snow—but not like what Montreal would provide! My French—how could I have known that it would turn out to be virtually useless in dealing with the French-Canadian dialect?¹⁰

However, the Department of Physiology at McGill did welcome me. The department had recently been reconstituted under the chairmanship of Frank C. MacIntosh, who had brought Benedict Delisle Burns and Arnold S. V. Burgin from England as his senior colleagues. Since I insisted that I was interested in the cerebral cortex, I was assigned to Burns as his first graduate student, my instructions being to follow him around and learn to

¹⁰ David Hubel's autobiography in this series (Hubel, 1996) would have given me a clue.

do what he did. That part was easy. The difficult part was to understand why he was doing what he did, and where he was going with it. He had developed a preparation to study the intrinsic electrical activity of the unanesthetized cerebral cortex by surgically undercutting a cortical area so that it was deprived of all neuronal connections with the rest of the brain while retaining its blood supply (Burns, 1950). My education in electrophysiology began when I joined him in trying to relate the abstractions of the electrical recordings from the cortex to the underlying cellular structure (Burns and Grafstein, 1952¹¹).

A critical consideration for me, of course, was to maintain my financial independence. In coming to McGill, I had had to insist on receiving the maximum stipend for a first-year graduate student, \$1500, but when it came to arranging for a second year, I felt that the proposed increase to \$1600 was not acceptable. I knew that another graduate student in the department had received \$1800 in his second year. I was told that the man deserved a higher stipend than I because of his higher living expenses: he had to pay the bill when he took girls out on dates, whereas I could expect to have many of my dinners paid for. I hastened to point out that being taken out on dates was no free ride—it required continual maintenance, such as having my hair done and making sure that I had a supply of undamaged nylon stockings to wear.¹² I do not know whether it was the force of my logic that was more effective or the embarrassment produced by my bringing up such unseemly personal matters, but I did get the higher amount. Whether that could be regarded as a blow for feminism, I am not certain. It made me sad to think that such an exchange should have been necessary.¹³

When it came time to select a topic for my Ph.D. thesis, I elected to use the isolated cortex preparation to study the phenomenon of spreading depression, which had first been described by Aristide A. Leão in 1944. Spreading depression proved to be more readily elicited in the isolated cortex than in the intact brain, probably because of the virtual absence of background activity in the isolated tissue. I was able to show that the neuronal depression, which spread slowly over the cortex and was accompanied by a powerful negative shift in the DC potential of the cortical surface, was in fact preceded by a period of neuronal excitation. This

¹¹ Looking at that paper recently, I realized that either we were pioneers in postulating the existence of dendrodendritic junctions, or neither of us knew the difference between a dendrite and an axon.

¹² What I really wanted to say was that “To each according to his needs” was not yet, as far as I knew, an established principle of the Canadian economy. However, I was not sure that this Marxian allusion would be appreciated for the jest that it was intended to be.

¹³ There will not be many instances of discrimination against me as a woman in this account. I believe that I had a great advantage in my visibility as one of the few women (often the only one) in most professional settings, which would have counterbalanced any discrimination if it did occur.

led us to suspect that something released during the excitatory phase might be the key to the depressive mechanism. The work of Hodgkin and Huxley (1947), showing “leakage” of K^+ from active nerves, was probably an important source for the idea that the accumulation of this ion in the extracellular space might play a role in spreading depression. Thus, intense local neuronal activity could result in an increase in extracellular K^+ sufficient to produce excessive depolarization and hence inactivation of the neuronal membranes, whereas diffusion of the ion away from the focus could produce activity in adjacent neurons, causing the same cycle to be repeated. I still appreciate Burns’s generosity in insisting that the papers resulting from my Ph.D. thesis work on this potassium hypothesis of spreading depression should appear under my name alone (Grafstein, 1956a, 1956b).¹⁴ I was very proud that my papers were taken sufficiently seriously that some young scientists in the laboratory of Wade Marshall at the National Institutes of Health (NIH) were rapidly put to work searching for evidence of the potassium change¹⁵ (Brinley *et al.*, 1960). I was amazed when Burns received a handwritten note from Alan Hodgkin analyzing the characteristics of potassium diffusion in the brain (cited in Grafstein, 1963). Also interested in spreading depression at that time was A. van Harreveld, who served as the external examiner for my Ph.D. thesis in 1954. A few years later, he suggested that glutamate (then becoming recognized for its excitatory function in the brain) might be an active agent in spreading depression, and he acknowledged that this idea derived from the K^+ -release model that my research had generated (van Harreveld and Fifkova, 1970). This work may have made a significant contribution toward current views about the role of glutamate in excitotoxicity.

While I was a graduate student I was only dimly aware of the prominence of some of the people then working on the nervous system at McGill, notably Donald Hebb in the psychology department and Wilder Penfield at the Montreal Neurological Institute. I did, however, become acquainted with Herbert Jasper, who was the EEG expert at the Neurological Institute and who occasionally visited Burns’s lab, bringing along some of his fellows and visitors, including David Hubel and Edward Perl (who, to my Canadian peacenik astonishment, appeared in a U.S. Army uniform). How could I have known that the world was full of paths that crossed again and again?

At McGill, for the first time in my life, I dared to not be a conscientious student. I had too many other interesting things and people to pay

¹⁴ It would be difficult for him to be so gracious in the present day, when every grant application would require him to prove his productivity and dominance, to say nothing of his being obliged to adhere to the rules of “responsible conduct” in determining authorship.

¹⁵ One of them was Eric Kandel, who may have had some mixed feelings about this assignment, which he was required to do before being permitted to get on with the work to which he was really dedicated.

attention to in Montreal, on both sides of the language divide. I came to know journalists, radio announcers, novelists, painters, TV producers, architects, film directors, and calypso singers; a ballet choreographer, an airplane test pilot, an Arctic explorer, and an ace hockey player. I tried my hand at radio, doing book reviews of science fiction novels and a lay explanation of Wilder Penfield's work. A memorable moment was winning first prize for my costume at the Mardi Gras ball of the McGill University West Indian Society.¹⁶

However, there was one event that eclipsed all these attractions—the International Physiological Congress held in Montreal in 1953. I thought everyone was making too much fuss about it before it began. When Ben Burns said he thought I should present a paper on my work, it did not seem to me that he was asking me to do anything at all remarkable. When he suggested that I should also give a live demonstration of recording spreading depression in the cat cortex, I casually agreed.¹⁷ I do remember, on my way to present my paper, closing my eyes briefly and dreaming for a moment of how thrilling it would be if this would lead to great international attention and acclaim. I was probably more excited, however, about the prospect of the champagne and caviar reception that was going to be given later that day by the Soviet physiologists,¹⁸ to whom I had been assigned as a guide during the meeting. Nevertheless, I think that that was when I really became committed to being a neuroscientist, suddenly aware of the broad sweep and significance of research on the nervous system and impressed by the dedication of the people participating in it.

It is a truth universally acknowledged, that a young person in possession of a new Ph.D., must be in want of a postdoctoral position. That had never occurred to me. I had just assumed that after I attained my doctoral degree my education would be at an end and I would finally be getting that long-awaited job, so I would be able to look after myself properly at last. Therefore, I was surprised but pleased when it was proposed to me that I should go abroad. Letters were written, old friends of the McGill physiology faculty were solicited, and arrangements were made for me to join the

¹⁶ I was Justice, jumping up blindfolded, carrying as her scales the lab's antique double-pan balance.

¹⁷ As might have been predicted by someone more experienced than I, the animal died in the middle of the demonstration, with many famous physiologists looking on.

¹⁸ The 1953 International Physiological Congress was the first scientific meeting in the West that they had been permitted to attend since the 1930s. It was the beginning of an era of international exchanges that included the founding of the International Brain Research Organization.

Department of Anatomy at University College London, headed by Professor J. Z. Young. I could not believe my luck—at last I was going to be able to find out the truth about so many perplexing British institutions that I had encountered in my Canadian childhood: Mrs. Tiggy-Winkle! *Swallows and Amazons!* Queen Victoria's birthday!

I was a little disappointed, I must admit, that it was the anatomy department at University College and not the physiology department that I was joining, since in my own mind I knew myself to be a physiologist. Also, I knew that the University College physiology department was populated by former colleagues and friends of Burns and MacIntosh. I believed that I belonged with them, and I hoped that at least by joining their regular morning tea sessions I could keep my physiological identity alive. Shortly after I arrived at University College, however, it was made clear to me that I could attend the physiology department tea club only as a specially invited guest. The first time I was invited I was introduced to a young man whom I immediately recognized to be a foreigner from his blindingly white shirt and crisp tweed jacket (as contrasted with the attire of our English colleagues, from whom wartime austerity had not yet entirely removed its mark)—it was Ed Furshpan, then beginning his postdoctoral years (during which his attire gradually subsided into proper British anonymity), who had come to work in the biophysics department headed by Bernard Katz.¹⁹ There were also many others, with names that were then familiar landmarks in neurophysiology and pharmacology, as well as younger people who would eventually make their mark.

The anatomy department also had its share of scientists with diverse interests relating to the nervous system. There was a major effort being given to analysis of nervous system structure with silver-staining methods, as exemplified by the work of D. H. L. Evans and Lawrence Hamlyn (1956). However, there was an increasing interest in electron microscopy, which had been recently set up in the department by Dave Robertson and was being used by him to study membrane structure in myelinated nerves (Robertson, 1957). This technique would soon be taken up by other members of the department, including George Gray, for his classic observations of synaptic structure (Gray, 1959), and Ray Guillery (described in Guillery, 1998).²⁰ Closer to my own interests, there were Brian Cragg, studying the electrophysiology of the hippocampus (Cragg and Hamlyn, 1957), and Donald Sholl, an early theorist of the structure of the cerebral cortex (Sholl, 1956).

¹⁹ Apparently biophysicists, unlike anatomists, were allowed to take tea with physiologists.

²⁰ I remember Ray explaining to me how he was using colored food pellets to study visual behavior in tortoises.

And, of course, there was J. Z. himself. Usually preceded by a telephone call from his secretary, asking to speak to “Professor,”²¹ the door of my lab would burst open, he would throw a sheaf of papers on my desk, ask “What do you think of that?,” and fly out before I could collect myself to answer. His greatest contribution to my education came from the display of his vast energy, his wide range of interests, and his unfettered imagination rather than from any specific attention to what I was trying to do. Presumably, he was encouraging me, like the others in his department, to follow my own direction.

The task that I had set for myself as I had embarked for England in the fall of 1955 was to examine the electrophysiological activity elicited in cerebral cortex by a single input, the corpus callosum. Using a modification of Burns’s isolated cortex preparation that preserved the callosal connections, I found that these connections were not only organized to join corresponding points on the two hemispheres but that there were different sets of connections joining corresponding cortical laminae at the two points (Grafstein, 1959), suggesting that maintenance of the laminar pattern of activity was important in callosal function. This study, the first that I carried out entirely on my own in a laboratory that I had set up by myself, has been one of my favorite pieces of work, although it hardly set the world agog. When I presented it at a meeting of the Physiological Society near the end of my stay in London, the only comment it received was from a colleague who remarked that he had not understood a word of it, but for elocution and deportment I got full marks! Still, it managed to find its way into reference lists for nearly 30 years.

I will not indulge myself in recalling the many well-known neuroscientists that I met during those years (in most cases, these would have been occasions more memorable for me than for them), but there are a few whose names still evoke the flavor of that time in a special way—David Potter, Jack Diamond, and Tom Sears, who, together with Ed Furshpan, invited me to join their informal journal/drinking club; Steve Kuffler, who visited Ed and David to discuss their now-classic experiments on electrical transmission at synapses²² (Furshpan and Potter, 1959); and Paul Greengard, who was working at the Medical Research Council in Mill Hill.

After 2 years in London, I was asked to return to the McGill physiology department as a junior faculty member, which was to my great relief since I did not know what I would have done otherwise. I resumed working with Ben Burns on electrophysiological studies of the visual system (Burns *et al.*, 1957), prepared to reassume my role as his disciple, and I was quite

²¹ I thought at the time that she was remarkably inefficient in keeping track of his movements. It was only decades later that I came to realize that she was probably just warning me, in an English way, that he was on his way to see me and I had better start looking busy.

²² Just when I thought it was safe to forget about it.

startled when one of the senior members of the department asked me when I was going to start my own research. Taking the hint, I returned to the corpus callosum to redefine the pattern of differential connectivity by following the changes that it underwent during development (Grafstein, 1963). I soon found myself wondering about the structural determinants of axon size and conduction velocity, and the conditions required for axon outgrowth, for myelination, and for the formation of synapses. Apparently the anatomical mind-set had rubbed off on me, after all (or was this a prescient insight into the multidisciplinary future of research on the nervous system?). More important, however, was the realization that the study of development had a special dimension for me: for perhaps the first time here were things that I really wanted to know about.

I had become serious about my job.²³

It is difficult to believe how unusual my interest in nervous system development was at that time.²⁴ Mammalian embryology seemed to be a subject mostly directed to medical students, with the development of the central nervous system (CNS) usually touched on only briefly, apparently a feature too essential to ignore but too embarrassingly complicated to describe in detail. Trying to identify the gurus in the field with whom I might study, I soon fixed on the name of Paul Weiss, the author of a celebrated textbook, *Principles of Development* (Weiss, 1939), who was at the Rockefeller Institute in New York. However, my informant there (Vernon Brooks again!) reported that Weiss was no longer actively working on the nervous system. Another name I was given was that of Viktor Hamburger, to whom I wrote in 1960 to ask whether I might spend the summer in his laboratory at Washington University to learn experimental embryology techniques. I explained to him that I was not interested in embryology as such, but I believed that “some of the problems facing neurophysiologists might be more amenable to approach through a study of the developing organism.” He welcomed me graciously, although he made it clear that he did not think much of the project I had proposed to do in his lab—interchanging wing and leg buds in the chick embryo to determine which would become dark meat and which would become white.

No one who knows Viktor could doubt that being at his side would be a memorable experience. He was patient, though critical, in teaching me the

²³ Maybe other people also recognized my new dedication since I was soon invited to join the International Brain Research Organization, then in its formative stages. I never knew who had nominated me, although I suspected that it had been Herbert Jasper, who served as its first executive secretary.

²⁴ One outspoken Young Turk of neurophysiology dismissed it as what you turn to when you run out of ideas. He is now a famous neuroscientist, and he may have changed his mind since his curriculum vitae contains several papers on early development.

techniques that he had developed over the years, beginning in Hans Spemann's laboratory in Germany in the 1920s (Hamburger, 1996). He led me to important works in the neuroembryology literature, including Bradley M. Patten's *Early Embryology of the Chick* (1951), in which the first 4 days of the chick embryo's life are described with such thrilling clarity that it may still serve as a bible for anyone beginning to study development.²⁵ Although modest about the research that he was doing at that time, Viktor was unrestrained in his praise of the work of his colleagues. The most notable of these was Rita Levi-Montalcini, who also spent time with me showing me the techniques she was using in her experiments on nerve growth factor and the new antibody that she had for it. She was awe-inspiring in both her technical skill in manipulating embryos and her passionate dedication to her work. Unfortunately, first Rita and later Viktor had to leave St. Louis after a few weeks, but what they had given me in that short time remained a valuable resource that I would continue to draw on for many years thereafter.

St. Louis in the summer was not a place where I was eager to linger once Rita and Viktor were gone. On an impulse I decided to go west, counting on being welcomed by neurophysiologist colleagues in Los Angeles and Pasadena. It was a dazzling experience, especially my visit to Roger Sperry's laboratory at Caltech.²⁶ Sperry was of course interested in my work on the corpus callosum because he was deeply immersed in the split brain experiments, requiring transection of the callosal fibers, which were eventually to earn him the Nobel prize. Also proceeding in his laboratory were experiments on regeneration of the optic nerve in goldfish. I was impressed to see how readily optic pathway lesions could be performed in the fish, but I found it difficult, with my inexperienced eyes, to evaluate the histological evidence (eventually published by Attardi and Sperry in 1963) that the regenerating axons reconnected to their original sites on the optic tectum.

As I contemplated the trip back home from California that I had been planning for the Labor Day weekend, I found myself picturing the deserted streets that I would face in Montreal and the friends still away on vacation, and decided to make a stop in Chicago, where the American Psychological Association was going to meet. I expected that I would find some people I knew at the meeting, but I certainly did not expect that I would find a physiologist like Patrick Wall, whom I had first come to know in England. Unlike myself, who had little excuse for being there, he had been invited to present his work with Ronald Melzak (whom I knew,

²⁵ Viktor also told me that it was possible to hypnotize a chicken by touching its beak to the floor and drawing a chalk line outward from the beak's tip. I think I actually succeeded in doing it one time, but I still cannot quite believe it.

²⁶ I had met Sperry years before in Montreal, possibly at the International Physiological Congress, and again when he visited J. Z. Young in London.

of course, from McGill) on the gate—theory of pain. Pat was surprised to hear that I was interested in nervous system development—he had been having discussions with Paul Weiss about getting a neurophysiologist to work in collaboration with both of them in revisiting some of Weiss's early experiments on nerve regeneration. That sounded just dandy to me.

Working in Weiss's lab became a dream so attractive that I could hardly bear to contemplate it. However, there were more obstacles than I had realized, since I was reluctant to give up the security and independence of a faculty position to become a postdoctoral fellow again. I tried to console myself by searching for alternative paths into the world of development.²⁷ One of these was to enroll in the embryology course at the Marine Biological Laboratory in Woods Hole in the summer of 1961, so I applied for a fellowship from the Grass Foundation.

Actually, the Grass Foundation was not an obvious choice. True, they provided fellowships for young neurophysiologists at the MBL, and I was still a reasonably young neurophysiologist and on my way to the MBL. However, Grass Fellows went to Woods Hole to do research, in those days mostly in Steve Kuffler's lab. When I was awarded a Grass fellowship to take a course, I was proud of my skill in convincing the Grass trustees that what I wanted to do was important, and that I was a good person to do it, even though it was not what they would usually support. It did not enter my mind that, as I learned years later, I was already known to some of the trustees. Never could I have imagined that the presentation I had made at the International Physiological Congress in Montreal had been attended by Albert Grass, the president of the foundation.²⁸ I was also not aware that one of the trustees was Robert Morison, who had worked on spreading depression, and whom I had buttonholed years before at an American Physiological Society meeting in Atlantic City to tell him about my work. I now suspect that awarding me a fellowship must have been what they considered their "annual frolic," a gamble on an interesting but dubious investment. I daresay they thought that the other Grass Fellows that year,

²⁷ I looked for collateral sprouting in the cerebral cortex after eliminating various sensory inputs, including cutting the nerves to the whiskers in infant rats (a decade too early). I also became interested in the maturation of urinary bladder innervation and was consulted by a young urologist who was trying to stimulate the denervated bladder. I was horrified to find that he had been using as stimulator an old electroshock machine that could only put out 60-cycle alternating current directly from the power supply transformer. I expertly brought out a proper electrically isolated square-wave stimulator with variable stimulus duration and frequency and, knowing all about chronaxie and rheobase and utilization time and electrode polarization and tissue impedance, I expertly calculated the parameters for optimal stimulation with minimum power dissipation. My expert conclusion was that a 60-cycle sine wave would be best.

²⁸ Is it possible that he had indeed thought it worthy of "great attention and acclaim," as my wistful dream then had been? Surely he could not have been present at my "live" demonstration at the congress.

who were following a more conventional path of training in neurophysiology, would be more certain to make a mark in the field—their names were Zach Hall and Robert Wurtz.

The summer at Woods Hole was for me, as it is to this day for many young scientists, a mind-altering experience. The embryology course was not in the best of shape since it was just beginning to evolve from a classical descriptive program, systematically charting the development of various classes of marine organisms. The mantra “DNA makes RNA makes protein” still needed frequent repetition. I was self-conscious at first about being back in the classroom among students, some of them undergraduates; however, they were as intent on learning as I was, the animals we were studying were fascinating, and the feeling of going back to the roots of science by doing experiments with the simplest of equipment (Grafstein, 1961) was inspiring. Of course, the whole Woods Hole environment worked its magic on me: a physical setting that promotes the contemplation of the sea and the sky and the living things in them, the congregation of many scientists displaying their intellectual wares, and the removal from the exigent patterns of everyday life all added to a sense of the presence of new dimensions and the promise of new possibilities.

It was not easy to translate my sense of exaltation into the realities of experimental science. A senior colleague at McGill, Arnold Burgen, encouraged me to examine regeneration in lower animals, as a model easier to manipulate than development in mammals, and in 1961 we began a study of retinal regeneration in newts, taking advantage of the fact that after removal of the retina the pigment cell layer can give rise to a new retina (Stone, 1950).²⁹ We were trying to test Roger Sperry’s hypothesis that during regeneration of the optic nerve “specific chemoaffinities” operate to produce selective synaptic connections between the axons of ganglion cells at any point in the retina and neurons in a matching locus in the optic tectum (Sperry, 1951).³⁰ In the end, our results did not rule out

²⁹ In preparation, I visited Leon Stone, who was an expert in this field but had not been very active in it for years. He told me that the following year he would be retiring and would “finally be able to get something done,” a view of retirement that I still find endearing.

³⁰ Noting that Sperry’s experiments generally involved the regeneration of axons from a coherent array of retinal ganglion cells, we asked whether the postulated chemoaffinity would be manifested even if the retinal ganglion cells were scrambled. Although the retinal ganglion cells would be unlikely to survive transplantation, we decided to produce a disorganized retina by rotating an outer ring of the pigment layer before allowing retinal regeneration to proceed. Our results showed that the new retinal ganglion cells usually formed a coherent projection to the tectum, even if the pigment layer from which the retina had been directly derived had been disarranged, so that the ganglion cells did not necessarily reestablish connections to the same parts of the tectum as their forebears (Burgen and Grafstein, 1962; Grafstein and Burgen, 1964). These findings were precisely confirmed years later (Cronly-Dillon and Levine, 1974).

the operation of specificity but indicated only that, whatever the origin of the specificity, it "must be assumed to be reintroduced into the retinal neurons during retinal regeneration" (Grafstein, 1964). Although our findings might have been construed as being inconsistent with Sperry's views, Sperry forgivingly agreed that they gave new information about the specification process.

Meanwhile, my dream of working in Paul Weiss's laboratory had begun to come true. With the path having been smoothed by Pat Wall, I found that by mid-1962 I had overcome all the problems of job negotiation, the complexities of the immigration process, and the agony of dealing with household movers.³¹ I was thrilled to be an assistant professor at the Rockefeller Institute (shortly thereafter to become Rockefeller University), with its glamorous new facilities, in a city of incomparable excitement and sophistication.³² I was looking forward to interacting with Weiss in reexamining with "modern" electrophysiological techniques some of the phenomena of motor system regeneration that he had first investigated using smoked-drum recording nearly 40 years earlier (Weiss, 1924)—a neglected field indeed. The very first day, I was startled when Weiss, leading me from his spacious office into what I might have presumed to be a broom closet, proudly announced "It's all yours!" My first diplomatic mission was to persuade him that the DC electrometer amplifier that took up a large part of the counter space would not be adequate for anything modern that I might have expected to do. I then had to find out what experiments Weiss had in mind for me. He was more involved with his other interests, particularly the cinematic illustration of motility of axons in culture (Weiss *et al.*, 1962).

I read Weiss's old papers over and over again, looking for clues. There was no question that the motor phenomena were as he had described them. In adult axolotls in which a supernumerary limb had been transplanted close to the normal limb when the animals were still immature, the transplanted limb moved in synchrony with the

³¹ As a blessing in disguise, my apartment in Montreal had been broken into shortly before I was due to leave for New York, and almost everything of value, as well as most of my clothes, had been stolen. Talk about a new start!

³² But frightening — it would be months before I was comfortable venturing off the Rockefeller campus. My fear was probably intensified by my awakening to the reality of the Cuban missile crisis. Watching John Kennedy's landmark speech on the television set in the Rockefeller Faculty Club, I realized that my Canadian indifference to the situation was no longer appropriate. I kept remembering a friend's remark when he heard that I was coming to New York: "Welcome to Ground Zero!" Some joke. For weeks I would flinch every time I heard an airplane passing overhead.

normal limb, apparently irrespective of the particular nerves that had innervated them. Weiss was convinced by his own scrupulous observations and an analysis of historical data that regenerating axons would only innervate the muscles of the transplanted limb in a random way. He had therefore attributed the simultaneous activation of corresponding muscles in the two limbs to mechanisms that he designated "myotypic specificity" and "modulation" (Weiss, 1936). By this, he meant that each muscle possessed an invariant and embryonically established specific identity, which acted to impress a new "modulus" on whatever motor neuron had happened to innervate it, thus restricting the activity in that neuron to messages appropriate to its muscle. He proposed that the routing of activity was determined by the motor centers in the spinal cord, which were presumably "endowed with a capacity to produce a corresponding variety . . . of modes of motor impulses, each one exclusively appropriate to a single muscle" (Weiss, 1936, p. 528). Thus, the establishment of a correct activity pattern was ostensibly the result of purely functional properties of the system rather than structural adjustments. On the other hand, Roger Sperry, who had been Weiss's graduate student at the University of Chicago, had interpreted the phenomena in a more structural context. In a continuing and eventually bitter divergence from his previous mentor's influence, Sperry came to the conclusion that when correct motor function was restored in the course of nerve regeneration, it was the consequence of selective reinnervation of the appropriate muscles (Sperry and Arora, 1965), consistent with the chemoaffinity principle that he had originally elaborated for the visual system.

Sorting out these various currents was not an easy task for me. I believed that it was difficult to invoke the chemoaffinity hypothesis to explain recovery of function in a limb innervated by apparently inappropriate nerves. On the other hand, it was difficult to invoke functional mechanisms in motor centers of species in which the fundamental rules of spinal cord organization and neuromuscular connectivity had not been worked out. Ultimately, I found that branching of axons in the normal axolotl spinal cord and limb was much more extensive than previously imagined, and that even nerves of apparently antagonistic function could receive axons from a single motor neuron. This raised the possibility that, as a result of axon branching, the transplanted and normal limbs might be receiving a nerve supply of similar origin, even if the two had initially been provided with different nerves. Thus, it would be difficult to determine whether the establishment of appropriate movements was due to functional or structural modifications. I hoped that I might obtain less ambiguous results from an investigation of the "homologous response" of transplanted toad muscle (Weiss, 1936). In this

experiment, a single muscle from the contralateral leg was transplanted to the back of the toad and a "foreign" nerve inserted into it; Weiss claimed that even when the transplanted muscle received an incontestably inappropriate innervation, it contracted in synchrony with its normal twin. Unfortunately, I could not elicit this synchrony with any degree of reliability in adult toads,³³ and I did no better when I used immature toads less than 2 cm in length.³⁴ Eventually, I was faced with the question of what to do with the results of several years' work done under Weiss's direction that apparently undermined, if it did not actually contradict, his ideas. I asked the advice of a colleague, an accomplished spinal cord physiologist. He advised me not to try to publish them at all: "No one is interested in that stuff any more."

I was concerned, of course, about Weiss's reaction. It would have been difficult not to be intimidated by him. His autocratic manner and critical impatience with nearly every new idea presented to him prevented any real scientific dialog. Even a mild objection to his views was peremptorily dismissed, and diverting him from his own agenda was virtually impossible. I learned that even when his impulses were not unfriendly ones, they might be expressed in disconcerting ways. When I had come to him, after about a year in his laboratory, to tell him my secret, that I was about to get married,³⁵ he was touched that I had confided in him and looked around for a present he could give me to mark the occasion. He settled on a reprint of a paper by Karl Lashley, after carefully ascertaining that he still had a second copy.³⁶

Weiss could not have been mistaken for anyone's kindly uncle, but he was a figure to be reckoned with in the developmental science of his time, and the whole story of the important role he played still

³³ I was grateful to have available to me the advice and support of Norman Robbins, who was a graduate student in Weiss's lab. In search of toads, we made an excursion one dark night to the New York Botanical Garden, creeping through a hole in the fence with flashlight and bucket in hand. I felt uneasy in the deserted park (but not as uneasy as I should have, in retrospect) and was glad to be leaving after several hours without success, when we came across a single enormous toad in the middle of the path. I did not have the heart to bring it out.

³⁴ Uncertain about what to feed them that would be small enough, I hit on the idea of using ants, which I could find in abundance in the sandy Rockefeller grounds. This turned out to be a mistake—the ants terrorized the toads by biting them on the toes.

³⁵ To Howard S. Shanet, then a faculty member of the music department at Columbia University and conductor of the Columbia University Orchestra, as well as author of *Learn to Read Music* (and more recently of *Philharmonic: A History of New York's Orchestra*). I cannot imagine now why I considered it necessary to have kept it a secret.

³⁶ I was therefore not completely surprised that when my son was born a few years later, Weiss again celebrated the occasion by sending me a reprint. Mrs. Weiss saw things rather differently—she sent a luxurious blanket for the baby carriage.

remains to be told. His ideas were original, firmly derived from specific experimental observations, and strongly expressed. His book, *Principles of Development*, was an inspiration to many young scientists for a long time after it first appeared in 1939. He was never one to be bound by the accepted scientific paradigms. He would freely cross the boundaries of the conventional disciplinary categories in order to find the appropriate biological preparations and techniques for investigating the problems that he thought were important; he would interpret his experiments in terms of their most essential observation-based elements and simultaneously embed them in the most general picture of biological principles; and he would support his arguments with examples drawn from a world of biological objects that appealed to his strong visual sensitivity, ranging in one case from the ultrastructure of a ciliated protozoan to the surface texture of a leopard's tongue (Weiss, 1969). One of his most impressive qualities was his ability to delineate a specific phenomenon and invent an apposite name for it. Terms such as "contact guidance," "homologous response," "selective fasciculation," and "myotypic specificity," once they were attached to specific experimental paradigms, would stick in the mind. If his personality invited dispute, his terminology provided his opponents with a firm framework for argument and stimulated them to further investigation.³⁷ The reactions he provoked probably transformed every field that he involved himself in. What is unfortunate, nevertheless, is that so many of his formulations eventually turned out to have been faulty, even though not incorrect. What may have undone him was his sense that the principles he laid down were impregnable because they were founded on the most meticulous observations and punctiliously logical inferences, surpassing those of his critics. What he often failed to recognize was that in his search for overarching principles, he might be trying to formulate a unitary explanation for a phenomenon that actually involved many separate mechanisms. Characteristically, he was able to point out to his opponents the detailed steps that they were omitting in their arguments, but was unable to see that very weakness in his own.³⁸

I was greatly relieved, therefore, that my failure to progress with the problem of motor system regeneration, when I eventually summarized my

³⁷ One scientist confessed to me, ruefully, that he had devoted years of his life to trying to prove Weiss wrong.

³⁸ The homologous response in the transplanted axolotl limb, for example, was eventually shown to be due to the selective reestablishment of appropriate neuromuscular connections as a result of many separate mechanisms, including selection by the regenerating axons of the correct pathway, especially in the nerve plexuses (*pace* Sperry); superior functional efficacy of neuromuscular connections formed by the anatomically correct nerves; and regression of incorrect connections (Grafstein, 2000).

results for Weiss toward the end of 1964, did not seem to trouble him particularly. He seemed not at all perturbed that my findings might be less consistent with his ideas than with ideas of specific reconnection that were identified with Roger Sperry. In fact, in his summary report of a workshop session at the Neurosciences Research Program³⁹ at about that time, Weiss claimed to embrace the idea of specificity in regeneration, with reservations only about the necessity of uncovering the detailed mechanisms involved [although he still insisted that these might include functionally coded activity patterns that could serve as “messages for selective reception” (Weiss, 1965)].

Sperry, on the other hand, was adamant about disengaging his views from any associated with Weiss. In a statement that he insisted on appending to the same report, Sperry reasserted his own primacy in the development of the idea of “selective, chemotatic (sic) growth of specific fiber pathways and connections governed by an orderly pattern of specific cytochemical affinities that arise out of . . . embryonic differentiation” (Sperry, 1965). He believed that throughout their long association Weiss had assimilated his (Sperry’s) contributions without adequate acknowledgment, and that there had been “a buildup in the literature of a complex web of ambiguity, forced terminology, and confusion of issues that [was] almost impossible to untangle for anyone not intimately acquainted with the underlying history.” He was not content that Weiss should just confirm that specificity was operating in the growth and termination of regenerating axons; he believed that he had been deprived of the opportunity that Weiss had promised him to publicly “get things out in the open, face the issues and clarify points of controversy.” His frustration would have been familiar to the many scientists who tried over the years to get some satisfaction from challenging Weiss.⁴⁰

I was a reluctant spectator to this clash of titans. I had not found any evidence to support Weiss’s views, but accepting the chemoaffinity hypothesis meant assuming the presence of forces and interactions that I believed still remained to be unambiguously demonstrated, or at least experimentally defined. I believed that I could do that best by going back to the goldfish visual system, which was the model that appeared to present the most clear-cut evidence of specificity of regeneration.

³⁹ The Neurosciences Research Program, which was founded by Francis O. Schmitt in the early 1960s, sponsored a series of such conferences on emergent issues in neuroscience and disseminated the proceedings as reports in the *Neurosciences Research Program Bulletin*.

⁴⁰ For the relatively positive tenor of my own interactions with Weiss I have to give credit to my husband. Being a man of great tolerance for others’ idiosyncrasies (evidently including mine), and with a historical perspective that enables him to appreciate that good may come even from the rule of tyrants, he helped me overcome the frustrations and disappointments that dealing with Weiss inevitably engendered.

Weiss was not averse to my changing direction.⁴¹ By that time, however, he was preoccupied with the new position that he was going to take as dean of the Graduate School of Biomedical Sciences at the University of Texas at Houston. Although he would not be resigning completely from Rockefeller University, I was uncertain about what would happen to my position since it was accepted that when a laboratory head left, the laboratory closed and the lower ranks were expected to depart quietly.⁴² I was grateful when two senior members of the Rockefeller faculty, Keffer Hartline⁴³ and Frank Brink, both of whom had previously worked with Detlev Bronk, the president of Rockefeller, offered to speak to Bronk on my behalf. He granted me more than just a reprieve. Astonishingly, he assigned some of Weiss's lab space to me.⁴⁴ Although still only an assistant professor, I became the head of the Laboratory of Developmental Neurophysiology, reporting directly to the president of the university, equally entitled to his attention (at least in principle) as other lab heads, even Nobel prize winners.

It was an intoxicating experience for a young scientist. One of the most stimulating aspects was the presence of the Rockefeller graduate students, who were invited to taste as many as possible of the delights that the place had to offer, fluttering from laboratory to laboratory, pollinating ideas and collaborations.⁴⁵ They were encouraged not only to broaden themselves scientifically but also to bring into the university a range of musical, artistic, and intellectual experiences that the faculty would have been too preoccupied to organize. Another unique feature, still remembered with affection by many of us from those days, was the dining

⁴¹ But it was difficult for me to discard entirely my preoccupation with the amphibian motor system. Eventually, it led to an analysis of the organization of the frog spinal cord that was carried out by my graduate student at Rockefeller, William Cruce (1974). I believe that this ignited his lasting interest in comparative neuroanatomy and development, which I like to think justifies the support that I received over those years that were without publishable results.

⁴² An idiosyncrasy of the Rockefeller system was that salaries were paid in advance at the beginning of each month. Sometimes it was only when the July paycheck was deposited into your bank account that you knew that your appointment had been renewed for the coming year.

⁴³ I admired Hartline tremendously. One of his early works had been the first scientific paper I had ever read, and I was in awe of his unwavering record of scientific contributions, all confined to studies of the limulus eye and remaining at the forefront of conceptual and technological innovation for about 40 years. The impairment of vision that he suffered from in his late life was an irony that moved me profoundly.

⁴⁴ Arbitrary decisions were not unusual at Rockefeller in those days. A widespread rumor was that one laboratory head, who was blind, upon returning from vacation and tapping his way with his cane along the corridor, could not find the door to his laboratory. In his absence it had been blocked up when the space was assigned to someone else.

⁴⁵ There was also a sweetener: students who joined a laboratory were assigned their own additional space.

room in which lunch was served. Its main feature was a long, narrow table, and the custom was to sit at any available place.⁴⁶ Therefore, one might find oneself sitting beside a newly arrived research associate or beside a long-established Nobel laureate, beside a famous scientific recluse or beside someone one shared lunch with quite often but could not remember his or her name and were embarrassed to ask after such long acquaintance.⁴⁷ With service by waitresses of the old family retainer variety, it was a remarkable opportunity to exchange a wide range of information and ideas, and it facilitated the formation of friendships that would otherwise be difficult to establish in the vast impersonal tumult of New York.

In my study of regeneration of retinotectal connections in the goldfish, my plan was to search for evidence that the growing optic axons found their correct synaptic partners by the exercise of "chemoaffinity" along their route. This was to be done by determining the relationship of the axons to one another as they progressed toward their destination.⁴⁸ In addition to electrophysiological and histological techniques, I proposed to use the new approach of radioactive labeling of the regenerating axons⁴⁹ by means of a method that had recently been worked out in Weiss's laboratory to demonstrate material moving from the retina into the optic nerve (Taylor and Weiss, 1965). This method was based on the phenomenon that Weiss had characterized about 20 years earlier (Weiss and Hiscoe, 1948) and that had come to be designated "axoplasmic flow." Observations of the configuration of nerves that had been mechanically compressed had led Weiss to the conclusion that the integrity of the axon was maintained by a stream of material originating in the cell body and propelled by peristaltic-like waves along the axon,⁵⁰ the stream advanced at a rate of a few millimeters per day, i.e., equivalent to the rate of emergence of the new axon during regeneration. These ideas had been largely ignored by a community of scientists who were more inter-

⁴⁶ Weiss, however, spoke with some nostalgia of the "old days" when each laboratory group marched in together to seat themselves in order of their rank.

⁴⁷ Fortunately, one could look them up in the photographic directory that Rockefeller provided to everyone. It was in loose-leaf form so that it could be kept constantly up to date, with pictures of those who left being discarded without a trace.

⁴⁸ I was greatly embarrassed when I noticed, too late, that in one of my reports to Dr. Bronk a helpful secretary had uniformly changed the spelling of the destination of the optic axons from the "tectum" to the "rectum."

⁴⁹ This was not based entirely on scientific considerations. I was pregnant at that time and did not feel that I could meet the physical demands of electrophysiological experiments that I would personally have to carry out, whereas I could call on other people to assist with the labeling experiments. This enabled me to keep active in the lab until one Friday evening when I felt *really* tired. The next morning my son, Laurence Paul Shanet, was born.

⁵⁰ Many of Weiss's hypotheses stressed physical-mechanical mechanisms. He prided himself on having been trained originally as an engineer rather than a biologist.

ested in mechanisms of neuronal conduction and synaptic transmission that could be measured on a timescale of milliseconds rather than in "housekeeping" functions that were calibrated in terms of days. This began to change when Droz and Leblond (1962) showed that after radioactive amino acid became incorporated into protein in nerve cell bodies, a wave of radioactive protein could be detected in the axons, moving at a rate consistent with values that Weiss had previously ascribed to axoplasmic flow. When I applied this method to the goldfish visual system, however, it became clear that the radioactivity was arriving in the optic tectum many times faster than expected, and that the early arriving material was preferentially directed to the axon terminals, as opposed to the more slowly moving wave in the axon trunks (Grafstein, 1967). There had to be a special mechanism for fast transport of protein distinct from the slow transport that could be identified with axoplasmic flow.⁵¹

Shortly after submitting this work for publication, I prepared to present it at an informal research-in-progress seminar at Rockefeller. Almost immediately after the seminar announcement went out, I received a telephone call from Bruce McEwen, whom I had never met but whose name I recognized as a recent addition to the Rockefeller faculty. "I think we ought to talk," he said, which was a very good idea since he had been at work in a laboratory at the other end of the Rockefeller campus, likewise doing experiments on radioactive labeling of the goldfish visual system. Fortunately, instead of the uncomfortable prospect of competing with each other at such close quarters, we developed a profoundly satisfying collaboration (McEwen and Grafstein, 1968), later also including other members of our laboratories such as David S. Forman and Nicholas A. Ingolia, that produced some noteworthy contributions toward the characterization of the fast and slow components of axonal transport (Grafstein and Forman, 1980).⁵²

⁵¹ The term "axoplasmic flow" has persisted in the literature to this day, even though the picture that it evokes, that of a sluggish river within the axon, is clearly outdated. Weiss, who originally referred to it as "axoplasmic convection," subsequently tried some variants, including "axonal flow" and "neuroplasmic flow" (Weiss and Mayr, 1971), but these were less successful. All are now replaced in most search indexes by the term "axonal transport."

⁵² Axonal transport is now widely appreciated as an essential mechanism in axonal maintenance and regeneration (Grafstein, 1995). Studies of fast axonal transport eventually led to the discovery of a previously unknown family of motor proteins, the kinesins, which are responsible for active translocation of organelles in many kinds of cells. In neurons, kinesin is the basis of fast transport from the cell body to the axon terminals. Fast transport in the reverse direction is attributable to the action of another motor protein, dynein. The mechanism of slow transport is still unclear, but it is usually thought to involve the polymerization dynamics of microtubules and neurofilaments.

I never did reach my original objective—to use radioactive labeling to study specificity in the regeneration of goldfish optic axons. Instead of asking why the regenerating axons went where they did, I turned to the question of why they should regenerate at all, in contrast to their mammalian counterparts which were notoriously unable to do so.⁵³ I found that the amount of radioactive protein transported in the regenerating goldfish axons was greatly increased above normal, and that the retinal ganglion cell bodies were dramatically enlarged. Fortunately, Victor Wilson, a good friend and fellow neurophysiologist at Rockefeller, passed on to me a job inquiry he had received from a neuroanatomist, Marion Murray, who had been working at McGill University on radioactive labeling of protein and cell proliferation in the rat brain. What an ideal combination for my interests! Our ensuing work together, on changes in morphology and axonal transport of regenerating retinal ganglion cells (Murray and Grafstein, 1969; Grafstein and Murray, 1969), presaged for both of us an enduring involvement in nervous system regeneration.⁵⁴

One of the obligations that I undertook when I was assigned my own laboratory at Rockefeller was to create a course on the development of the nervous system. Teaching at Rockefeller was an optional activity. There were few formal courses,⁵⁵ and the teaching for the most part consisted of tutorials by individual members of the faculty. However, there seemed to be no limit to the resources made available to anyone who did want to teach. The course that I put together in 1966–67 (it had 12 students, which was considered a large class at Rockefeller) took advantage of everything that I had ever learned about the developing nervous system. In addition to lectures that I gave on key topics, there were seminars by individuals deliberately selected because their work was no longer likely to be familiar to students. These individuals included Weiss, of course; Rafael Lorente de Nó, who had once been known for his classic Golgi studies of the developing brain;⁵⁶ Carl Speidel, noted for his early microscopic observations of living nerves in tadpole tails, whom I had met when I had been

⁵³ Not their fault, it turns out. They can do fine when they have better neighbors (Villegas-Perez *et al.*, 1988).

⁵⁴ She still professes to be indignant that her first assignment was the unreasonable requirement to make radioactive injections into goldfish eyes in total darkness. But how else were we supposed to find out how axonal transport was affected by variations in neuronal activity?

⁵⁵ One was the biennial neurophysiology course, a lecture and laboratory course established by Vernon Brooks and Victor Wilson that I participated in as an expert on the physiology of the cerebral cortex.

⁵⁶ But used the occasion instead to educate us on why he still disagreed with Hodgkin and Huxley.

in Woods Hole; and William F. Windle, who had done extensive studies on primate brain development as well as CNS regeneration and had recently become head of the Rusk Institute of Rehabilitation Medicine in New York.⁵⁷ There was also a series of laboratory sessions in which the students inspected living chick embryos under the guidance of Patten's *Early Embryology of the Chick* and made transplants of limb buds and eye vesicles,⁵⁸ they examined silver-stained sections of the embryonic nervous system,⁵⁹ they rotated eyes in newts and made lesions of the retina and optic nerve in goldfish,⁶⁰ and they set up embryo chick dorsal root ganglia for nerve growth factor assays.⁶¹ I had the opportunity to give the course in that elaborate form only once. However, it subsequently evolved into a tutorial course that was so well appreciated by the Rockefeller students that I was invited to present it in alternate years for 20 years thereafter.⁶² I am proud of the number of outstanding young neuroscientists, some now well-known in their field, that came to developmental neuroscience under my instruction.

Whatever the attractions of being at Rockefeller University, I did not feel secure there. I was uncomfortable not having a senior person who might value my accomplishments and to whom I might turn for advice or assistance.⁶³ I longed for a place where I felt needed rather than tolerated. It was Victor Wilson who came to the rescue again: He told me that the physiology department at Cornell University Medical College was looking for a neurophysiologist. The search, which had in fact been going on for years, but somehow without success, was being renewed. It seemed like just what I was looking for. A physiology department in a prestigious medical school (just across the street from Rockefeller, so I would not have

⁵⁷ I was glad for the opportunity to establish my bona fides with Windle because I suspected that I had left him somewhat bewildered on a previous encounter. A few months after I arrived in New York, I had been seized by the absolute necessity of getting away to someplace completely dark at night and completely quiet. I had taken the next plane to Puerto Rico and presented myself, without preamble, at the NIH Center for Perinatal Studies in San Juan, which Windle then directed, asking for help in finding a place to stay. Windle was puzzled, but graciously hospitable, even after it became clear that I was not part of the high-level NIH committee that was at that very moment arriving for a site visit to evaluate his performance.

⁵⁸ Thank you, Viktor Hamburger.

⁵⁹ Thank you, Rita Levi-Montalcini.

⁶⁰ Thank you, Leon Stone and Roger Sperry.

⁶¹ Thank you again, Rita.

⁶² Even after leaving Rockefeller, I remained a member of the adjunct faculty.

⁶³ Whom I might have asked, for example, whether I had really deserved no increase in salary for 4 years.

to change where I lived) and badly in need of someone who would teach in my area of expertise but who was flexible enough to teach in other areas, including laboratory instruction⁶⁴— it sounded exactly like the system I had cut my teeth on.⁶⁵

When I met with President Bronk to discuss the situation, I was surprised to learn that he had been chairman of the same department many years earlier. However, the circumstances had apparently not been happy ones since he was only there about a year before, as he put it, “Luckily the war came along” and he had a reason to depart. He assured me that it was not necessary for me to leave Rockefeller,⁶⁶ and that I should not accept the job at Cornell until he could ensure that I would not be treated badly (an irony, in view of the poor record of advancement of women at Rockefeller then and for years afterward).

Whether with his intervention or not,⁶⁷ it did not appear to me as though I was going to be treated badly at Cornell. I could look forward to setting up a new lab, the promise of a faculty position for a junior associate, and a promotion in rank.⁶⁸ I also had, I knew, strong support from Thomas

⁶⁴ I did draw the line, though, at working on Saturdays, which had been the rule until then.

⁶⁵ The standard teaching assignment in the physiology department at McGill each year had been about 30 lectures and 20 half-days in the teaching laboratory, and I had had to become, whether I liked it or not, the designated expert on kidney physiology and digestion. It did not seem excessive because everyone shared the load equally, from the chairman on down. Of course, those were times when publishing a single major paper a year was considered to be a commendable level of research activity.

⁶⁶ He also assured me that although government funding for research had become noticeably tighter in the previous few years, that situation could not continue long before things improved again. Who knows, perhaps in his earlier years, to judge from his record of achievement, he might have even been able to bring that about.

⁶⁷ At the time, I may have underestimated his interest in my future. About 5 years later, I was surprised to receive a warm note from him commenting on the announcement of a special lecture that I had been invited to give at the Eastern EEG Association. Apparently, he had been keeping an eye on me.

⁶⁸ In addition to their professional implications, my transactions with Cornell at that time had a profound impact on my personal life. During one of my initial interviews, I mentioned the quandary that my husband and I were in because he had recently been told that he had early bladder cancer, and he was being given contradictory advice about whether chemotherapy or radiation should be undertaken. Then, just a few days before he was scheduled for his first radiation treatment (to which he had finally steered himself, despite the unpredictable disabilities it might engender), we received a telephone call from Roger Greif, a senior member of the Cornell physiology department with whom I had been negotiating, who told us that he had made an appointment for my husband to consult with a Cornell surgeon. I will remain forever grateful for Roger’s intervention. The resulting decision, to wait and see how the condition might be progressing before undertaking any treatment, saved us from a lifetime shadowed by concern and uncertainty since no cancer ever developed.

Meikle, an influential member of the Cornell Anatomy Department.⁶⁹ Ironically, just as I took up my position at Cornell, which was presumably predicated on my being willing to be a physiology teacher for all seasons, there was a major revision of the curriculum and most of my teaching duties became confined to a new interdisciplinary neuroscience course that combined teaching in neurophysiology, neuroanatomy, and neurology. Robert F. Pitts,⁷⁰ the chairman of the physiology department, had some reservations about this change, since he believed that it devalued the role of physiology in the medical curriculum. Looked upon as the harbinger of the new order, I did not find it easy at first to integrate myself into the life of the department, but after a few years my sense of belonging was improved considerably when the current chairman, Erich E. Windhager, took over. My satisfaction was also greatly enhanced by the arrival in the physiology department in 1973 of another neurophysiologist, Dan Gardner, who not only has taken off my shoulders the burden of learning more about biophysics than I care to, but also has been an infallible source of knowledge about virtually everything I have ever had occasion to consult him about in the field of neuroscience and beyond.^{70a} Moreover, from the beginning, Fred Plum, Chairman of Neurology, went out of his way to make me feel welcome among his faculty and staff, giving me an opportunity for a view into the world of clinical neurology that few basic scientists could then have had and the incentive to educate myself about the interface between basic and clinical neuroscience.

Shortly after I had moved to Cornell in 1969, accompanied by Roberta Alpert as technician (she was to be my helper and ally for nearly 20 years) and with Nicholas Ingoglia as postdoctoral fellow, we were joined by Irvine G. McQuarrie, who was already well into his residency in neurosurgery at Cornell but was eager to take a Ph.D. degree. It was very brave of him to be willing to undergo, at about 6-month intervals for a number of years years, the painful alternation between being an autocrat of the operating

⁶⁹ I had come to know him through the New York Brain Function Group, a salmagundi of neuroscientists at diverse institutions around the city, including outposts at Queens College, Hunter College, Mount Sinai Hospital (not yet a medical school), and the Museum of Natural History. The informal monthly meetings of the group may have been more notable for their dinner arrangements than their scientific content, but they did provide an opportunity for us to get to talk to one another and to visit one another's laboratories. Hard to believe, but it was lonely being a neuroscientist in those days, with so few of us at any one institution. A key member of the group was Robert Thompson, at Hunter College, who was the custodian of the mailing list and who was subsequently a member of the committee that laid the groundwork in 1968 for the establishment of the Society for Neuroscience.

⁷⁰ He was renowned as a kidney physiologist, although he had made notable contributions in neurophysiology, particularly in the control of respiration and cardiovascular function, but he had left the field many years before for reasons that were not entirely clear.

^{70a} Including quotations from Jane Austen.

room and a graduate student on the lowest rung of the laboratory totem pole. He brought a special clinical perspective to our research, and the work that he initiated, on the effect of a prior lesion in improving regeneration (McQuarrie and Grafstein, 1973), became an important theme in our collaborative enterprise (Grafstein and McQuarrie, 1978).

Most of the work in my laboratory throughout the years has involved the regenerating goldfish visual system, with a continuing focus on axonal transport and the role it might play in defining the process of regeneration (Grafstein, 1991). One of the exceptions was an investigation comparing transport in the optic nerves of normal mice and retinal-degeneration mutants in order to ascertain whether the presumptive difference in physiological activity had any effect on the transport process (Grafstein *et al.*, 1972). When a colleague asked whether there were any differences in transport to the cerebral cortex, I was at first embarrassed that this accomplished behavioral scientist might have forgotten that the optic axons did not connect directly to the cortex. However, I decided that it would not be too much trouble to look into this: it would only require taking samples from the brains of the animals from the original experiment, which were still available, preserved in fixative.⁷¹ Against all expectation I found that indeed some of the radioactivity transported in the optic axons was transferred to neurons of the lateral geniculate body and conveyed in their axons to the visual cortex (Grafstein, 1971). I knew that this was an important result, providing the first direct evidence of transfer of materials from one neuron to another, possibly including materials that might serve as trophic factors. It was soon taken note of by David Hubel and Torsten Wiesel, who used this method of transneuronal labeling for their classic demonstration of ocular dominance columns in the striate cortex (Wiesel *et al.*, 1974). I am grateful to them for the care that they have taken to acknowledge my role in initiating this technique (Hubel, 1996).

Heading into the 1970s, I found myself on the wavefront of two scientific revolutions. One was the use of axonal transport methods to define neuronal connections, taking advantage of anterograde transport from the

⁷¹ Since we often had occasion to think of new experiments that we could have done with the original material, it became the custom in the lab to store the preserved heads of the animals that had received intraocular injections of radioactivity. Eventually, the 3,000 sample vials became a problem—the radioactivity disposal people would not take them because the tissues had been fixed with picric acid (explosive!) and the hazardous-materials disposal squad would not accept them because they were radioactive. I think that I finally managed to make the point that the trace amounts of either that were present, especially after 20 years, were unlikely to pose a hazard to anyone.

cell body to the axon terminals,⁷² as well as retrograde transport of materials taken up by the axon terminals and conveyed to the cell body (Cowan and Cuénod, 1975). The other, evolving more slowly, was a renewed interest in regeneration in the CNS, for which I think much credit must be given to William Windle.

In 1970, Windle organized a conference in Palm Beach that brought together a group of scientists working on diverse aspects of regeneration to determine whether the “newly enriched technology of the biological scientist” might offer any hope for answering the question of why the mammalian CNS showed such poor regeneration (Guth and Windle, 1970). Windle had organized a similar conference about 15 years earlier (Windle, 1955) that had been attended by some of the scientists whom we now recognize to have made classic contributions to the fields of nervous system regeneration and development (Grafstein, 2000). There had been little obvious outcome from that earlier meeting, but Windle was induced to organize the 1970 conference on the instigation of Alan Reich, a paraplegic, who was president of the National Paraplegia Foundation, an organization of spinal cord injury victims and their families. As editor of the journal *Experimental Neurology*, Windle was in an advantageous position to perceive new developments in the field of regeneration research; therefore, the scientists invited to the conference were a mix of old regeneration hands and bright new faces. I felt quite at home in that company since the work that Marion Murray and I had done on regenerating goldfish retinal ganglion cells had just been published, although I found it difficult, then and even years later, to explain to spinal cord injury victims why they should care about goldfish. However, I was regularly invited to the conferences, which took place in Florida approximately every 2 years over more than a decade, and I eventually became one of the principal organizers for several of them after Windle retired (e.g., Veraa and Grafstein, 1981).

For many of the invited scientists, the Florida conferences provided the first occasion to have contact with people with spinal cord injuries. This produced an acute awareness of the dimensions of the clinical problem⁷³ and a special sense of urgency about the progress of the research on nervous system regeneration. Interest in the conferences also spread

⁷² The delineation of axon terminal fields by transported radioactivity was an obvious feature of even some of the earliest autoradiographic studies (Grafstein, 1967; Weiss and Holland, 1967). However, it was at a meeting of the American Association of Anatomists in 1971 that for the first time the labeling could be seen even from the back of the lecture room as a result of the localized application of a highly concentrated solution of radioactive precursor (Cowan *et al.*, 1972). An audible gasp went up from the audience, and I knew that the race was on.

⁷³ Since then I have seen to it that a long-term spinal cord injury patient should be presented to the medical students in the neuroscience course at Cornell each year.

through the community of patients and laypeople involved with the problem of spinal cord injury, leading to many similar conferences elsewhere⁷⁴; and it led to the proliferation of voluntary groups anxious to attract scientists to the problem and willing to raise funds to support their research. I served on the scientific advisory boards of several of these organizations and was also a member of the committee to select the recipient of the Wakeman Award for Research in the Neurosciences, a prize honoring regeneration research, which was originally established in connection with the Florida conferences⁷⁵ and is now awarded under the auspices of Duke University. An important activity of the lay interest groups has been to lobby, with impressive success, at the level of both federal and state government for increased funding for regeneration research (Grafstein, 2000).

Windle played an important role in stimulating the growth of this field, not only by enhancing its prominence in the scientific and lay communities but also by stimulating the efforts of many young scientists who became interested in regeneration research (Clemente, 1985). I feel greatly indebted to him for promoting my work even though I was not a product of his laboratory. He gave me the opportunity to relate my contributions in regeneration research to the problem of spinal cord injury, highlighting their value as investigations into a model of successful regeneration, even if it was outside the usual mammalian paradigms (Grafstein, 1986).

My increasing visibility in the field led to invitations to present lectures, to write review articles, to sit on grant-awarding boards, and to attend conferences.⁷⁶ A singular honor was to be invited to be a member of the National Advisory Council of the (then) National Institute of Neurological and Communicative Disorders and Stroke, the body that gives final approval to extramural grants awarded by the institute. Perhaps my favorite invitation was to participate in a meeting convened by NASA in 1982, the Joint Neurosciences Working Group for the Space

⁷⁴ One of the most prominent of these has been a continuing series of conferences at Asilomar, organized by Frederick Seil under the auspices of the Office of Regeneration Research Programs of the U.S. Department of Veterans Affairs.

⁷⁵ Windle and Sperry shared the prize in 1972 and Hamburger and Weiss in 1978. The nomination of Weiss on the first of these occasions had been scuttled by the comment "Paul Weiss has been wrong too often," made by an eminent neurophysiologist who was notorious for his about-face on some critical scientific issues.

⁷⁶ An important rule I made for myself, however, while my son was young, was to turn down most of the invitations that would have required me to be away from home overnight. This may have caused me to miss some career-advancing opportunities, but it was a necessity for me in striking a balance between my personal and professional goals.

Platform/Station.⁷⁷ Our charge was to design experiments that would take advantage of the gravity-free environment in space,⁷⁸ to be carried out in a facility that was not going to be ready for at least 20 years. It was amusing to be brainstorming experiments without knowing what new discoveries and techniques might arise in the years that would pass before they could be carried out; a more difficult task was deciding how many animals would be needed and how large the cages should be. A follow-up letter from the McDonnell Douglas Astronautics Company a couple of years later, asking to know what measurements I wanted to have taken on the space station so the design process could be started, seemed equally unreal.⁷⁹

In addition to the usual perquisites of a reasonably successful research career, there have been some aspects of my scientific life from which I have derived continuing satisfaction. One has been my association with the Society for Neuroscience. I was not always a neuroscientist. First I was a neurophysiologist. That means that before there was such a word as “neuroscience,” I was one of a group of members of the American Physiological Society who met in an Atlantic City hotel room before the start of the spring meeting each year to hear the breaking news in neurophysiology.⁸⁰ We came to know one another’s names and faces, and it was not surprising to find them turning up again as members of the Society for Neuroscience when it was founded. I was one of the cohort on the first membership list and an author on several of the 270 papers that were presented at the first annual meeting in 1971.⁸¹ What really made that meeting special for me, however, was that I was asked at the last minute to fill in for a senior member of the society to participate in a symposium that was supposed to be geared to the general public and students. The paper that I presented, “The Inner Life of the Nerve Cell,”⁸² was enthusiastically received, including gratifying attention in an article about the meeting that appeared in the *New York Times*.⁸³

⁷⁷ At the time, there were some very important Cold War-related implications in whether it would eventually turn out to be a “Platform” or a “Station”—one or the other was supposed to have more threatening militaristic connotations.

⁷⁸ Fish in space! Yes! (They have since been flown on the space shuttle. I am not sure whether it made any difference to them.)

⁷⁹ However, now that I have become acquainted with the astronaut Dan Barry, who has walked in space, it seems to me to be perfectly reasonable that some of the tasks he had to carry out might have been planned by someone 20 years earlier, which is not so long ago, after all.

⁸⁰ It was usually a group small enough to fit into a single restaurant for dinner afterward, and some of us have some indelible memories of those events, don’t we?

⁸¹ It was assumed that these would be oral presentations. There was a single session that experimented with what “may prove to be a valuable alternative,” i.e., posters.

⁸² I made a point of differentiating between the neuron’s “nutritive life” (featuring axonal transport, of course), its “intellectual life” (physiological activity), and its “sex life” (none, alas).

⁸³ My mother’s only comment: “Why didn’t they put in your picture?”

I was an early member of the council of the society and then graduated to treasurer. However, being president was the most fun. The executive director of the society, Nancy Beang, managed to make me feel, as she presumably does for each incoming president, that although only serving for a year I was really running the society during that time. Suddenly, it seemed possible to do something about the various annoyances and apparently unreasonable restrictions that every member must feel. What I soon came to appreciate, however, is what an enormous undertaking is involved in carrying out the many functions of the society and also the important role the society plays in advancing the communal interests of its members. As the first woman to become president of the society, I felt a special obligation to highlight and promote the role of women, making certain, for example, that the speakers in the presidential symposium I organized were all women.⁸⁴ Another duty I had was to decide whether to invite Vice President George Bush to speak at the opening of the society's annual meeting that was to take place in Washington while I was president of the society. As a Canadian, I did not feel qualified to make this decision on my own. However, the many members and officers of the society whom I asked for an opinion were divided in about equal numbers between the view that the office of the vice president would lend such dignity to the occasion that there was no question that he should be invited, and the view that this particular vice president had behaved so shabbily that his presence would be offensive. What was surprising to me was that I could not have predicted which individuals would have been on which side of this issue. What was even more surprising was that after having unambiguously expressed their opinions, many of the people I had polled came back to tell me that they had changed their minds—with about equal numbers in each direction! My decision eventually rested on wise advice from a past president of the society: any action that would cause such divisiveness among the society members was best not taken.

There were other administrative affairs of the society that needed some tuning up, but the issue that engaged me most was to try to bring some sanity to the exuberant carnival that passes for the annual meeting. I thought that the most useful aid would be for each person to have an individual schedule of where to go and when to go there. Accordingly, I took the first steps toward the development of the society's computerized itinerary planner, which has since passed through several stages (some admittedly more satisfactory than others) and is still being improved. The annual meeting program is also being brought up to respectable electronic communication standards with the institution of online submission of abstracts and a searchable abstracts database. I am sure that there will be

⁸⁴ The symposium, which was on sexual differentiation of the brain, threatened at some moments to become the first X-rated event at a Society for Neuroscience meeting.

further technological changes that may affect how the meeting is experienced, but these are unlikely to diminish its spectacular impact on our lives in neuroscience.

Another continuing source of professional growth and personal gratification for me has been my relationship with the Grass Foundation. The foundation was established in 1955 by Albert and Ellen Grass, the founders of the Grass Instrument Company. The company began with the design of the first EEG machine in 1935 and grew to become internationally known as a major developer and purveyor of instruments for research in neurophysiology as well as clinical EEG equipment. Through the foundation the Grasses hoped to foster the careers of young people who were entering research on the nervous system, thereby acknowledging the link that the Grasses had to the scientific community and enabling them to maintain their involvement in that community. Like many former Grass fellows, I felt a great affection for the foundation as an institution that had enabled me to participate in the MBL experience, but I was especially pleased when, in 1965, I was invited to become a member of the board of trustees of the foundation in order to bring the perspective of Grass fellows to the affairs of the board. I eventually became a life trustee,⁸⁵ giving me the opportunity over so many years to keep in touch with new faces and breaking developments in neuroscience. Equally important, however, has been the special experience of coming to know the Grass family, their selflessness and sense of dedication, their insight into people, and their innovative ideas for contributing to an important and enduring cause. Ellen Grass in particular, as a woman of impressive strength of character, generosity, and virtuous ideals, has been a great inspiration.⁸⁶

What need I say more, except that I have now been at Cornell University Medical College (which changed its name on its 100th anniversary to the Joan and Sanford I. Weill Medical College of Cornell University) for over 30 years? I am Professor of Physiology and Biophysics and the Vincent and Brooke Astor Distinguished Professor in Neuroscience.⁸⁷ Clearly, I have not been treated badly. A few years ago, when I decided to take my first sabbatical leave and finally go back to studying the development of the nervous system, one of the former students in my course on developmental neuroscience at Rockefeller, Steven A. Goldman, invited me to join his laboratory in the neurology department at Cornell. Some of the work that

⁸⁵ And now vice-president.

⁸⁶ Learning to drive a car in my late 50s was only one of the things I was stimulated to undertake by her example.

⁸⁷ I believe that the endowment of the Astor chair was strongly aided by the efforts of Tom Meikle, who was by then Dean of the Medical College.

I did there is contained in a paper on transmission of calcium waves in pia-arachnoid cells (Grafstein *et al.*, 2000).⁸⁸ Although I had started working on the pia-arachnoid with the intention of trying a new path in a little-explored field,⁸⁹ as I had done with some success more than once before, I was surprised to find that it had led me back to thinking about spreading depression and even to looking things up in my Ph.D. thesis. Recently, I have been devoting much thought and effort to teaching, which has included the choreographing of a new interdisciplinary neuroscience course, Brain and Mind, with subject matter ranging from neuronal ultrastructure to psychopathology. I am a member of the General Faculty Council of the medical college and serve on the admissions committee, among other assignments. I am developing a proposal to make research grants available to senior scientists who want to try a new path in a little-explored field.

It has turned out to be a really good job.

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⁸⁸ I am very grateful to Steve and to Maiken Nedergaard for having given me this opportunity to refurbish my professional qualifications.

⁸⁹ Various granting agencies have short-sightedly failed to agree that this ought to qualify me for a career development award.

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