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JacSue Kehoe

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Northwestern University, B.A. (1957)
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Instructor, Brown University (1961)
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HONORS AND AWARDS:

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JacSue Kehoe was among the first scientists to take advantage of the mollusc Aplysia for electrophysiological analysis of synaptic transmission. She demonstrated that a single transmitter could produce multiple, independent conductance changes in a single postsynaptic cell and characterized the synaptic actions of many neurotransmitters.

JacSue Kehoe

When looking at the first volume of the series of *The History of Neuroscience in Autobiography,* the idea of a résumé of my life following those of Sir Alan Hodgkin and Sir Bernard Katz seemed ridiculous. As the years and the volumes go by, however, and my gods have been succeeded by mere mortals, the idea seems less intimidating, although still, given my trajectory, less than evident. Obviously, affirmative action is still alive and well and must play a role in this choice. In view of the tortuous path I took to the field of neurobiology, and the somewhat atypical approach I have taken in my scientific endeavors, my contribution will at least add variety to those previously published in the series.

From Childhood to College

My life was much too normal, enjoyable, and uneventful to make good reading. In short, I was born to very understanding, generous, intelligent parents who provided unfailing support for their three children and a loving home environment, of which many of my school friends were jealous. I was the third and last child—a status I thoroughly enjoyed, since I was not subject to the tighter parental reins and higher expectations that are typically reserved for the eldest.

Our father, with a mother and younger sister for whom he had to provide, was obliged to become full-time breadwinner of the family at age 16 when he graduated from high school. He had already been working as station master of the local train station by the age of 12. His lack of formal education was, nevertheless, undetectable thanks to his lively intelligence and avid curiosity. Our mother, on the other hand, was anticipating a much later generation. Although she was born at the end of the 19th century, the daughter of a shoe salesman, after graduating from university she began doctoral studies. Health problems did not permit her to complete the program, but even the idea of going for a Ph.D. was very atypical for women at that time. More typical, however, was her tendency to put her role as mother and homemaker in first place. Although she was a high-school English teacher until she retired at age 70, she insisted that we list her profession as "homemaker" whenever we were required to fill out forms. This curious request might also have reflected a deference to my father who, on the academic front, could not compete with her credentials. Although she clearly had crossed the professional frontier, she held very strongly to the woman's role as spectator rather than participant in anything bordering on what was at the time strictly a man's world (e.g., politics, finances, etc.).

My parents started their family shortly after the Wall Street stock market crash, but their jobs were not affected by the consequent Great Depression. Nor did either of the two world wars directly affect our family's well-being. My father was too young to be called up for World War I and was too old for World War II. The only other male family member of their generation, my mother's brother, was likewise out of sync with the draft. However, World War II did affect my father's job, since Chrysler Corporation, for which he worked at the time, joined the war effort and he was moved for the "duration" from a Detroit suburb to Evansville, IN. There my father could realize his dream of living in the country (a dream my mother clearly did not share) where we were put in the typical country school in which two grade levels functioned simultaneously in one classroom and where the school term ended in May so the children could participate in the farming activities. We were exempt from such activities, since, although we had a 14-acre "farm," the stables and cow barn were inhabited exclusively by rabbits, stray cats, dogs, rats, and a goat named Sammy. My father drove into the city each day for work, while the rest of us were bussed off to school (whether for teaching or being taught).

Between the ages of 6 and 10, my awareness of the war was limited to the hunt for milkweed pods used for making life jackets for the sailors (at least that is what we were told); collecting tinfoil from chewing-gum wrappers (I never knew for what purpose); and learning what we could about the ongoing, faraway battles from radio broadcasts and from newsreels when we went to the cinema. I remember celebrating VJ day by harnessing Sammy to a wagon and having her pull me in the rain down the local country roads. The most personal impact that the faraway war had on me occurred upon the return from hostilities of our school bus driver whose joyful expansiveness had been transformed into a tightly guarded sadness following his years in the midst of the conflict. Distinctly different and more dramatic pictures of these years have been drawn by many scientists of my generation, who were much closer to and much more affected by the war.

When the "war effort" was over, we moved to Ohio and to the city. School, which had been for me until that time more of a social activity than an academic pursuit, became a bit more of the latter with the return to an urban environment. My academic interests were still much more affected by the personality of the teacher than they were by the subject matter. That changed, however, in junior high school, where I encountered dramatic arts. From my early experiences helping direct school plays (as assistant to the dramatic arts' teacher), I started for the first time thinking along the lines of "when I grow up..." A major influence in affirming this orientation was the nearby presence of an excellent summer Shakespeare theater at Antioch

College in Yellow Springs, OH—close enough to Dayton, where we lived, so that I could regularly make the trip on my bicycle. I was indeed bitten, and it was because of the certainty in my choice that science subjects rapidly disappeared from my course load.

Consequently, in high school, I was clearly already headed away from, rather than toward, a scientific career. Meanwhile, my sister (the eldest of the lot) was following in the academic and educational footsteps of our mother, heading for a teaching career via Ohio State University (at $90 per quarter tuition, as I recall). My brother, the meat of the children's sandwich, was headed for the sciences with enthusiasm and excellence and was off to Deep Springs College ($0.0 per year), participating in a generally successful experiment in education begun by L.L. Nunn in 1917 which still nourishes the academic elite, in spite of one of its peculiarities—the obligation of manual labor as part of the curriculum.

On the other hand, when I was ready to fulfill my dreams of becoming a theater director, Northwestern University, the private institution which housed the most renowned spot for university theater training, was not so financially welcoming as the institutions chosen by my siblings. Consequently, I felt an obligation to work to earn my room and board. This I did, with a number of other theater students, by living and working in an "old ladies' home" as it was called at that time, but which has surely since found a substitute label. The so-called "home" offered room and board to Northwestern students in exchange for work as kitchen aides and waitresses. That meant rising at 6:00 AM to serve prunes and other less crucial breakfast items and, of course, to perform various chores at prescheduled hours during the day.

From Theater to Experimental Psychology

My first two years in speech school were unfortunately not very captivating (including courses in "lighting effects," "make up," etc.). These two years also revealed to me the ferocious competition in the field, making me realize that I was unlikely to become the director of the best Shakespearean theater on the continent. Given that realization, and the fact that I knew I did not want to direct community theater in Podunk, I slowly began readjusting my career orientation, while never losing my love of theater. Slowly, I say, since I had no clear alternative in mind. I tried a geology course, because I had always been drawn to the notion of reading history with rocks as my book, but I quickly realized that such "reading in the field" was not open to women at that time, and sitting in an office was not what I was looking for when leaning toward geology. I also dabbled a bit in life sciences by taking an introductory biology course and a course in what was obviously still Mendelian genetics at the time.

The strongest common thread in all of my life's choices, though never expressed as such, was a constant underlying interest in animal and human behavior: observing it, understanding the variables that control it, and realizing how it could be modulated. This was clearly something that fascinated me in my short "career" directing plays: bringing out of people what they themselves did not know was in them. At least at that time, I was clearly more interested in the behavior of humans than in the behavior of the molecules of which they were constituted. This probably led me in my junior year of college to my first course in experimental psychology, and it was there that I was bitten a second time around.

My scientific debut revolved around a question that has become a very "hot" topic in neurobiology in the last few decades: memory and forgetting. My mentor, Benton J. Underwood, was one of the leading experimental psychologists interested in that field at that time. The experiments I performed for my honor's thesis involved using humans as subjects and nonsense syllables "à la Ebbinghaus" as the material to be learned and forgotten. My conversion to experimental psychology also added 20 more hours a week workload—20 hr waiting tables plus 20 hr analyzing data for professors in the Psychology Department. I do not recommend such a regime to others: though being motivated more by my courses in experimental psychology than by those in theatrical make up, I went through my last two years of college in a more or less comatose state, going to bed at 2:00 AM and rising to serve breakfast at 6:00 AM. But it was worth it. I was finally fully engaged in what I was doing and enjoying it.

From Experimental Psychology to Neurophysiology

The first real external manifestation of my latent interest in biology came when I had to choose a department of experimental psychology for graduate work. I homed in on either McGill University, where Hebb was the major attraction, or Brown University, where the program in so-called physiological psychology was very strong. I recognized that for understanding memory and other aspects of behavior it was clearly necessary to know the fundamentals concerning the functioning of the nervous system. Because the policy of both departments was to have a limited number of students, and since no graduate student was scheduled to leave the department at McGill that year, no one could enter. Consequently, I didn't have to make a decision myself, and I went off to graduate school at Brown, where Harold Schlosberg was then Chairman and an influential one at that. However, the physiological approach at Brown in the late 1950s was directed exclusively towards the study of sensory systems (either visual processes under Lorrin Riggs or the sensation of taste under Carl Pfaffmann), and I remained strongly attached to the study of memory, which at that time was being addressed exclusively by various methodologies used for the study of discrimination learning. At Brown, this methodology was primarily limited to the paradigm of positive reinforcement (in particular, Skinnerian) rather than that of so-called classical, aversive conditioning developed by Pavlov. For my Ph.D. thesis, I applied this methodology to the study, in pigeons, of paradigms used in the human studies of retention: proactive and retroactive inhibition.

Although for my final career destination I certainly would have profited enormously by a graduate school training concentrated on math, chemistry, and biology, I nevertheless continue to be thankful for the four years I spent at Brown in experimental psychology. It was a field that posed many questions of great interest to me, and I had the good fortune of spending my graduate school years with enthusiastic colleagues, both students and faculty, from whom I learned a great deal. Furthermore, I found the training I received to be very useful and "transferable" to other scientific disciplines, as well as to life itself. I remain particularly indebted to J.W. Kling (Jake) for the guidance he gave me in the acquisition of observational skills and in developing the notions of experimental control and methodological rigor. Whether such insistence is related specifically to experimental psychology or specifically to that department at that time, I don't know, but when I switched to biology, I found such considerations to be much less well developed. Other useful skills I brought with me were related to the necessity at that time to build all aspects of our experimental setups, using second-hand solenoid driven relays given to us by "Ma Bell" and stepping motors and the like purchased by weight on Canal Street in New York City. The shop work was obviously transferable, but by the time I fully entered neurobiology, transistors were replacing cathode tubes, and electronic circuits were replacing classical relay circuits.

A Few Rats and Squirrels Prior to Being Seduced by *Aplysia*

The year following my doctorate, I filled a temporary vacancy in Brown's Psychology Department, and then it was time to head for a job or a postdoctoral fellowship. I opted for the latter and will only mention briefly the kind of experience one could have, as a female candidate, at that time. Even though such might still exist now, it would be much more cleverly disguised, and I admit it was the first and last occasion upon which I felt directly confronted by a gender discrimination issue. In the interview I had for that postdoctoral position, I was bombarded with questions concerning an eventual marriage on my part, how I would anticipate handling a career once children came along, etc. Scientific questions seemed clearly secondary. Although I was obviously aware that such discrimination existed, up until that time my gender had never interfered with my career opportunities, so I was completely taken by surprise and left basically speechless. I was certainly not at all interested in pursuing a postdoctoral position with such a man, and

I believe the feeling was mutual. Instead I went off to a much more welcoming environment where the door to electrophysiology eventually opened fully for me.

I headed off to Washington, DC on a postdoctoral fellowship in Joseph Brady's lab at the Walter Reed Army Institute of Research headed by David Rioch. This lab was one of the first to put together a multidisciplinary group to study the biological bases of behavior. Again, however, I was still strictly a behaviorist and was continuing my studies of discrimination learning under the wing of William Hodos, who was studying the visual system of pigeons.

Although I was still fascinated by the questions that experimental psychology was posing at the time and spent part of the two years in Washington studying discrimination learning in rats and the parameters affecting hibernation in squirrels, I felt more and more pessimistic about being able to obtain answers that could go beyond the operational definitions which often fenced in our conclusions. This feeling, and the fortuitous presence of Felix Strumwasser in the lab next door to mine, resulted in a definitive change in my scientific orientation during the two years I spent in Washington, Felix was doing electrophysiological studies of circadian rhythms, using as one of his models a particular neuron in the central nervous system of *Aplysia californica* now known as R15, but labeled "parabolic burster" by Felix. Thanks to Felix's exclusive devotion to that very complicated neuron found in the abdominal ganglion, I was able to intercept the remaining ganglia of each *Aplysia* on their way to the trash can and use them for honing my skills as an electrophysiologist. With those ganglia, Felix's discarded cathode tube amplifier, and his very generous help, I began my studies of synaptic physiology.

From the United States to France: October 1964

The decision leading to my next move was influenced more by nonscientific motivations than by scientific ones. I was footloose and fancy-free and, until then, had had little money or time to be able to travel. I thought I should take the opportunity to do so before I was tied down by either personal or job constraints. The scientific justifications were hence the second to be taken into consideration. The opportunities suggested to me were going either to Santiago, Chile, where I would be experimenting on cats (a very unpleasant prospect for a cat lover to overcome); to Warsaw where Jerzy Konorski used electrophysiological techniques to answer questions posed mainly at that time by psychologists; or to Paris where I could continue to work on *Aplysia* in the Institut Marey directed by Alfred Fessard.

Although Paris, which I had already visited, seemed a less exotic destination than either Santiago or Warsaw, I had already developed an appreciation for molluscan neurons, and so I decided to go to France, where the *Aplysia* model for electrophysiological studies had been born. Arvanitaki started using that preparation in the early 1940s. However, the benefits of the *Aplysia* preparation as a model for the study of synaptic transmission became apparent only after the successive collaborations of Hersch Gerschenfeld and Eric Kandel with Ladislav Tauc at the Laboratoire de Physiologie Cellulaire in Paris. Twenty years prior to the development of the patch clamp, large cells were the only ones that offered the possibility of recording from a cell whose membrane potential could also be controlled by penetrating the neuron with more than one relatively low-resistance microelectrode. These same traits also made possible the early voltage clamping in these neurons, which permitted a much more analytical study of membrane responses to neurotransmitters. The second opportunity that gastropods, in general, and *Aplysia* neurons, in particular, offer is the ability to work on the "same," homologous neuron from one *Aplysia* to the next. Because of the relative ease of cell identification, it quickly became possible to identify both the pre- and postsynaptic elements of a synapse, thus offering a very valuable tool for the study of synaptic transmission.

So, on October 3, 1964, with a NATO Fellowship in my pocket, I was off to Paris on "le France" (the recently constructed ocean liner that had made its first transatlantic voyage in 1962) to continue discovering the glories of *Aplysia* neurons. The trip over was a nice break from the frenetic pace of my departure preparations. The weather was gorgeous; the food was excellent; and many good books later I arrived at Cherbourg, and my life in the "old world" began.

Friends from the Northwestern Psychology Department had put me in contact with a French couple, Michel and Danièle Gervais, who had managed the very difficult task of finding housing for me in Paris, right in the middle of St. Germain des Près. Although, at that time, housing was very scarce, and telephones essentially nonexistent for anyone renting an apartment, they managed to find both for me. American tourists were still bringing toilet paper with them when going to France—something which was indeed not necessary—but I certainly did experience a feeling of going back in time when arriving from the United States. The window sill was my refrigerator, and in the extremely cold winter of that year, it became my freezer. Only considerably later did I realize how close, in fact, we were at that time to the end of World War II and all that that implied for slowing down the modernization of France.

When I first came to the Institut Marey, on the edge of the Bois de Boulogne, and joined the Laboratoire de Neurophysiologie Cellulaire headed by Ladislav Tauc, I was surrounded exclusively by those for whom French was not their native language. This did not have a positive effect on my acquisition of French, since English was the common language of the lab. Although I successfully passed a French language exam as a graduate student, it was not because of any knowledge of French, but rather because of the alacrity with which I could manipulate a dictionary—the use of which was tolerated in such exams at Brown. Consequently, I came to Paris knowing, but mispronouncing, "bonjour" and "au revoir." To my chagrin, upon meeting the Head of the Institute, Alfred Fessard, I accidentally pulled out the inappropriate one and said au revoir. He very graciously asked if I would prefer speaking in English or in French. I repeat graciously because M. Fessard had also been assuming that the "JacSue Kehoe" who was coming to his institute was male and more akin to a "Jaku Su Kiho" of Japanese origin, hence much better equipped than an American woman, as the "a priori's" dictated at the time, to be an excellent neurophysiologist.

The location of the laboratory led to an interesting introduction to one aspect of Parisian life. When walking through the Bois de Boulogne to reach the lab, I often noticed cars slowing down and frequently lowering their windows in order to, I assumed, ask directions. My French was not up to understanding their requests, much less to answering them. I later learned that this was a pick-up zone for prostitutes, and in spite of my atypical attire for such a job (usually jeans and a sweatshirt), some drivers seemed to consider me a candidate.

L'Institut Marey: Changes in a Behavioral Reflex Correlated with Changes in Associated Synaptic Potentials

My first studies in the Institut Marey were performed under the direction of Jan Bruner, a Polish scientist who came to neurophysiology with a psychological bent, as did I, and was interested in "plastic changes" defined by his mentor, Jerzy Konorski. Janek and Ladislav Tauc had already begun a series of observations in *Aplysia* correlating the diminution in amplitude of a behavioral reflex (the retraction of tentacles in response to water drops falling on the head) with the diminution in associated central, excitatory postsynaptic potentials. Eric Kandel at the same time was beginning a series of studies paralleling the changes in the gill withdrawal reflex and postsynaptic potentials (PSP) in identified neurons in the abdominal ganglion using a similar paradigm. As history has shown, Eric made the right choice in persevering in those studies. His unswerving path, coupled with the aid of a vast array of collaborators and an impressive battery of scientific tools, led him to Stockholm.

L'Institut Marey: Cholinergic Synaptic Transmission

I, being less persevering and much less well equipped for the job, became diverted by some observations I made while studying so-called habituation and dishabituation of PSPs in the pleural ganglia of *Aplysia*. In an attempt to identify the neurotransmitter eliciting the PSPs that were "habituating" upon repetitive stimulation of the *Aplysia's* head, I applied curare to the solution bathing the ganglion. This did not answer the question that I was asking, since the PSPs were unaffected by this well-known cholinergic antagonist. However, the spontaneous synaptic activity—rare in the cells I was using for this study—changed, and a very dramatic hyperpolarizing wave repeatedly appeared. It was this that caught my attention, and the synapses generating that response became the centerpiece of my investigations for the next three years.

A year had passed by this time, and it was once again the period of the fall migration of the *Aplysia* group to Arcachon—a migration not dissimilar in some respects to that of American neurobiologists who, in the late spring, migrate to the Marine Biological Laboratory at Woods Hole, MA. As is the case for the move to Woods Hole in the United States, at both ends of the Arcachon "season" it was necessary to tear down, transport, and rebuild the experimental setups. However, the trip to Arcachon consisted of only about 10 "Aplysialogues" who went off to the Atlantic coast where *Aplysia* came to the shore at that time of year for their last hurrah.

Hersch Gerschenfeld came to join the lab for the fall "retreat," and at this time Philippe Ascher began his tenure as a full member of the laboratory. Leaving his cat preparation behind at the Faculté des Sciences, where he obtained his doctoral degree studying the startle reflex, Philippe began his studies on dopamine receptors in *Aplysia* neurons. His arrival had many repercussions on my life in France. He was the first native French speaker in the lab, and my insistence that, in spite of his fluent English, all our conversations be in French greatly facilitated at least my vocabulary if not my accent, which was beyond repair given the 30 years I had already acquired before I said my first au revoir. Second, Philippe, with his thorough scientific background, provided me a much needed counselor in anything chemical. His help was particularly indispensable when I was struggling to make solutions using impermeant replacements for Cl ions, and I still tremble at the thought of losing or gaining a few zeros when determining drug concentrations. There was a joke circulating at one time whose "hero" received a lot of empathy from me. It concerns the captain of a ship who, just before addressing his crew, would run down to his cabin; open a locked box; and take out, read, and then return a small piece of paper before going back up to the deck to talk with his men. He was beloved, and so no one dared confront him with the question as to the significance of this seeming superstition. But when he died, they forced open the box, only to find written on the paper: starboard, right; portside, left! My locked-up paper is for reminding me how many zeros for pico, nano, micro, and milli. Once my calculations are made, it is still up to Philippe to reassure me that they are right. However, in a much broader way, Philippe's vast scientific knowledge and his characteristic generosity in sharing it have provided an indispensable reservoir into which I have been able to dip throughout my career as a neuroscientist.

Let us return after this aside to my fascination with the hyperpolarizing synaptic response I described earlier. To further understand its origin and its mechanism, I put together my own experimental setup to begin trying to locate the presynaptic cell responsible for this intriguing synaptic activity. The response was particularly intriguing since, upon further observation, it was found to consist of two components: one rapid and the other more slowly developing and longer lasting. The slower component hyperpolarized the cell well beyond the equilibrium potential for Cl ions, suggesting that it was the result of a synaptically induced increase in potassium conductance—something not yet dogma in neuronal synaptology, although already known as a potent mechanism underlying cholinergic inhibition in heart cells.

Once the presynaptic neuron was finally localized, it became relatively easy to demonstrate that the transmitter being liberated was acetylcholine, thanks to there being a battery of pharmacological tools active on vertebrate cholinergic receptors and already known to be similarly effective on invertebrate receptors. Serendipity, however, once more played a significant role in permitting me to find the most elusive antagonist—that for blocking the receptor mediating the potassium-dependent response. That receptor refused categorization in the classification system used for defining cholinergic receptors at the time. Neither curare nor atropine blocked it, and neither nicotine nor muscarine activated it. In desperation I started pulling bottles off the shelf, and lo and behold the contents of one hand-labeled bottle, bearing the letters "BTM," selectively blocked the K-dependent response. But finding out what that mysterious substance might be required contacting Hersch Gerschenfeld who had left a variety of compounds on the shelf after his collaboration in Paris with Ladislav Tauc. This compound turned out to be a Smith Kline and French product, better known as SK&F 6890, βTM-10, or methyl-xylocholine. By whatever name, it was certainly not developed for interacting with cholinergic receptors, but rather as an adrenergic neuron blocker. Had I known that, I would never have tried it on that synapse! It was, however, a critical tool for showing that the K-dependent response elicited synaptically and that the response elicited by exogeneous ACh were mediated by the same receptor.

One of my first presentations of these results took place at a meeting of the French Physiological Society in Toulouse. There I described the pharmacological characteristics of the two receptors mediating the synaptic inhibitory response, as well as the ionic mechanisms underlying the changes in membrane potential induced by activation of these receptors. In the audience was Angelique Arvanitaki, who was not in such an angelical mood that day. She opened fire by dismissing the notion of ion channels as an Anglo-Saxon obsession and followed that with a chauvinistic attack (always more vigorous from converted immigrants) concerning my choice of using *A. californica*, which she considered to be less intelligent than the local species of the beast. Since the subject of my studies was not intelligence, I had no particular opinion on that matter, but what became evident later in my studies of those receptors is that the receptor mediating the K-dependent response, i.e., the receptor that most interested me, was not expressed in the "local" species I later tested as an experimental preparation. I dare say that although I continue to be appreciative of the role Arvanitaki played in developing the *Aplysia* preparation as a model for electrophysiological studies, this "French" scientific experience did not encourage me to participate actively in the French Physiological Society thereafter.

In spite of Arvanitaki's lack of enthusiasm, I continued studying those elegant synaptic events which revealed (1) that more than one receptor for a neurotransmitter can co-exist on a given neuron; (2) that each of the receptors induced a different, independent conductance change (in this case, increases in Cl and K conductances, respectively); and (3) that the response to a given presynaptic neuron could be different for different postsynaptic cells. These findings, along with those concurrently coming out of Eric Kandel's lab, forced the recognition that a given transmitter could induce multiple, independent, membrane conductance changes in a single cell. The masking of the response mediated by one receptor by that of another receptor had led to many false interpretations about the mechanisms of neurotransmitter actions in many preparations.

Time for Important Decisions

The time had come when I was required to make active decisions about my future. I could no longer simply go with the flow. I had already overabused the generosity of the NSF and NIH, and I had a job in the United States waiting for a decision on my part. But I had a lingering sensation that I had not yet had my fill of France. This latter feeling led me to apply for a position in the Centre National de la Recherche Scientifique (C.N.R.S.), which, if successful, would permit me to work full time as a research scientist without mandatory teaching responsibilities. Given the limitations of my scientific background and the non-native character of my French, if I were to settle in France this definitely seemed like the best option for me (and for any student body). A successful entrance into this organization was soon followed by another important decision. I mentioned above the scientific savoir that Philippe kindly shared with all of us in the lab, but it was not only for that trait that I married Philippe in the fall of 1967. However, unlike Jim Watson who, in his recent autobiographical book, mixed in girls with genes and Gamow, I won't go into detail concerning the other criteria that helped me make an obviously complicated decision that entailed not only choosing a spouse, but simultaneously choosing a country.

In a delayed "honeymoon," we set off for the United States over the 1967 Christmas holidays so that Philippe could meet members of my family who were unable to attend our Paris wedding. En route to my parents' home, we visited the newly formed Neurobiology Laboratory at Harvard directed by Steve Kuffler. By that time part of my results were already published in *Nature*, and Steve had asked me to give a seminar. When I was in his office prior to giving my talk, he rather startled me with the comment, "So, you've realized your dream!" I certainly was not the "dreaming" kind; I functioned and still function much more on serendipity than on previously conceived dreams. But I later understood Steve's comment when seeing his somewhat similar attempts to analyze slow synaptic potentials in a much more recalcitrant mammalian ganglionic preparation that required considerably more effort.

Although my fare for our honeymoon was obviously not paid by the C.N.R.S., it was around this time when I was invited to a meeting in the United States and requested travel funds from the C.N.R.S. I was still in the lowest echelon on the C.N.R.S. ladder, so of course there would be no question of "first class travel." However, when I received what was supposed to be adequate financial assistance for making the trip, the restrictions they put upon my mode of travel support would have made it difficult for me to arrive on the other side of the Atlantic. Flying was not allowed; I was required to go by train!

May 1968

By this time, a few of us from the Institut Marey had moved to Gif sur Yvette, where much later the entire Institute was relocated in a new building. We, however, were in older buildings on the campus, and although rather isolated from the much denser activity in Paris, we could enjoy living for a year in the woods. This distance, however, did not keep us from a three-month's involvement with the others in our "home" lab during May 1968. In early 1967, the Laboratoire de Physiologie Cellulaire had already had a practice session for the student revolt of May 1968, so we were well prepared for the tumultuous events of the following year. Since the history of this general upheaval has been so widely documented, I will only give a brief description of the motivation leading young scientists to join this movement and mention how it dominated our lives for many months.

While the students in the United States were demanding that one "make love, not war!", in France, the students were pushing for an overhaul of the power structure of the French institutions. Within the framework of scientific laboratories, younger scientists such as we were making two major demands. The first demand was that the science should belong to those who, intellectually speaking, gave birth to the project and to those who actually did the science. In the hierarchical system in many European countries at that time, this was not always the case. Scientific results could basically be confiscated by those sitting at the top of the pyramid, without their having participated directly in the scientific project itself. Furthermore, since the system did not permit younger scientists to develop their own laboratories, they usually became older scientists stagnating in the same place in the pyramidal structure, bound to the scientific objectives of the chief. This was the background for the second demand: that younger scientists be given the right and the means of developing their own laboratories at a much earlier age, which would give them much more intellectual freedom in determining what science they actually could do and more recognition for having done it.

In practice, this period was occupied by unending "assemblées générales" at the Institut Marey where we were accused by the "higher ups" of being under the control of Moscow; with frequent street demonstrations first with students and later with workers as the "revolution" progressed; and with occasional visits to the Sorbonne where assemblies were taking place 24 hr a day. We also participated in study groups at the C.N.R.S. headquarters, where everyone participating, on both ends of the hierarchical pyramid we were trying to alter, was addressed in the informal "tu" form and the appellation "camarade" filled the discussion. We were, however, almost disappointed to find that the charter of the C.N.R.S. that we were intending to revise showed strong resemblance to what we had hoped to put in its place. It was clearly not the paper documents that needed to be revised, but rather the behavior adopted in applying the charter.

This period died down, as history books will tell you, and lives returned more or less to normal with a few scars in interpersonal relationships to remind us that the events had indeed occurred. Although much of the administration of French institutions rapidly returned to a "normal" pre-1968 functioning, repercussions of the 1968 student demands can be detected in the administrative structure of the post-1968 universities and, to some extent, in the nature of the interactions between colleagues of post-1968 generations.

Clearly, however, not all our hopes had been realized. As an example, it was in 1969 that, because of pressures instituted during the presidency of Charles de Gaulle, it was highly encouraged to have at least some publications in French. So I contributed a paper to the *Compte Rendu de l'Académie Française*. The paper was accepted, but only under the condition that I be listed in the index under the name of my husband: not only Ascher instead of Kehoe, but Mme. Philippe Ascher, instead of JacSue Ascher. I do hope that the few women who now are members of that hallowed institution have succeeded in changing that rule.

A Sabbatical Year at Downing Site, Cambridge, England: 1969

The fall of 1968 was occupied by the birth of our first son, David, and, two months afterwards, by our departure on our first "sabbatical." We were off to an old English farmhouse in a village of Cambridgeshire, where we lived with mice and dampness while doing research on Downing Site where Cambridge University's science departments were located. Taking our two-month old child and our *Aplysia* order forms with us, Philippe headed for the Pharmacology Department chaired by Arnold Burgen, and I was given hospitality by Gabriel Horn in the Anatomy Department. Both of us continued the work that we had, respectively, begun in Paris, surrounded by the lovely English countryside and aided by a wonderful woman, Sheila Coxall, who lived in our village and cared for David, our young son, while I was in the lab.

One repercussion of working in the lab of Gabriel Horn was that he arranged to include me as a visiting member of High Table at King's College in Cambridge. Today, that would seem evident and banal. However, in 1968 my admission to High Table, in fact, had some historical significance: it was the first time that a visiting female academic was given access, in her own right, to a Cambridge, all-male college. The advantages of this inclusion were mainly, for me, to be able to have use of the Combination Room, where I had the occasion to meet E.M. Forster and where a vast array of international newspapers were available daily. Most importantly, however, being a Visiting Fellow gave me access to the famous wine cellars of the College. My first attempts at ordering wine flustered the butler, who was not yet aware that a woman could possibly have such a right. What I was not given the right to have, however, was the snuff, a pleasure that the butler serving the cognac and port felt remained a man's prerogative. I didn't feel that it was a cause worth fighting for, so that frontier was left uncrossed.

One of my most marked memories of that year stems from the meeting of the Physiological Society at Cambridge, for which I had naively volunteered to do a demonstration. It was to take place on the top floor of the Physiology Department, but we didn't have the authorization to install our equipment there until the morning of the demonstrations. Philippe was back in France at that time, and I was still nursing my infant son. Luckily, I had an old graduate school friend, Joan Stevenson Hinde, who had also moved to the old world and lived close enough to us so that she could come to spend the night and be with David at 5:00 AM when I would be heading for Downing Site. Setting up the demonstration required moving all the equipment from the second floor of the Anatomy Department to the top floor of the Physiology Department—no small feat. No small feat also was the task I had set for myself, unexperienced in the ways of demonstrations. I stupidly decided to perform an experiment that had a probability of success under normal lab conditions of about one in five tries. The experiment involved simultaneous current clamp recordings from the cholinergic presynaptic neuron and from two postsynaptic neurons, while also injecting a potassium channel blocking agent in the presynaptic neuron and one of the follower cells. The K channel blocking agent was injected into the presynaptic neuron in order to induce a progressive increase in duration of the presynaptic action potential and, hence, a gradual increase in transmitter release. The increased release would then be reflected by an associated increase in the amplitude of both the Cl- and K-dependent elements of the postsynaptic response. The purpose of injecting the K channel blocking agent in the postsynaptic cell was to demonstrate the selective block of the K-dependent element of the response.

Setting up the demonstration was interrupted by periodic returns to the farmhouse to nurse David. However, the biggest frustration was trying to find the cells in a room where the sun's rays were attacking my setup with a vengeance. I was getting desperate because the time was rapidly approaching when the demonstration was to begin, and I still had not been able even to find the relevant neurons because of the sun's glare. Finally, as the morning wore on, the earth's movements improved my chances. The aggressive rays of the sun finally gave way to a simply well-lighted room, and I managed to do what was necessary by the time the crowds collected. In that crowd was Alan Hodgkin, who came to me at the end of my demonstration to offer his congratulations not only on my science, but also on my English. I do believe that to be a unique event: an Englishman complimenting an American on his/her English. Obviously, he had been drawn into this ignominious position by seeing my Paris address.

Our year's end in Cambridge was a difficult one. Philippe was operated on in England for what turned out to be a benign tumor on his thyroid; Philippe's father had his first of many heart attacks; and Philippe, David, and I all experienced the Asian flu that struck so hard in the winter of 1969, which also provided us with the experience of David's first and only fever convulsions. We all recovered from these physical aggressions, and that aspect of the winter in Cambridge left no serious repercussions. However, we also learned at that time that my father's prostate cancer, which he had hidden from all of us, had metastasized to bone, announcing his premature death that occurred the following spring.

Opening the Door to a Lab of Our Own

When I began describing our year in England, I said that we were on a "sabbatical year." In fact, it did start out like that, since we both had research positions at C.N.R.S. and no teaching obligations, which permitted us, without constraints, to change our workplace to a foreign lab. However, we were eager to have our own laboratory, and the only possibility to obtain independent space was for Philippe, who had the appropriate diplomas, to submit his candidacy for a position at the Faculty of Sciences, the predecessor of what was to become the Universities Paris VI and Paris VII. Consequently, when a position opened shortly after our arrival in England, Philippe made an about face and returned to make the traditional visits to those who would be voting on his application. It was a happy event when Philippe was offered the position, but that meant that he had to return to Paris from Cambridge once a week (during university sessions) to give his lectures. Furthermore, this good fortune seemed less good when the building program that was to make space available for us was halted as a consequence of the student revolt of May 1968. So Philippe had gained the teaching responsibilities without the lab space promised to accompany them. For me, an additional problem was that upon this offer to Philippe it seemed almost depressingly clear that in many respects our future was becoming completely predictable. Having lived in eight different states of the United States in my first 30 years, the idea of "sitting still" seemed a strange and perhaps monotonous one to me. But on the other hand, once you're in the 5th arrondissement of Paris, why would you want to move elsewhere?

Ecole Normale Supérieure—The Lab of Our Dreams

Soon after our return from England, we were fortunately offered space at Ecole Normale Supérieure—the French "Grande Ecole" where Philippe had done his predoctoral studies—so the problem of job responsibilities without space no longer existed. We started out, the two of us alone, with little in the way of equipment, but with 500 m^2 and a superb view of Paris. Unlike my scientific discoveries, this laboratory was indeed "dreamed of" and was definitely not serendipitous. We had carefully considered what kind of laboratory we wanted to establish—that is, the type that May 1968 had not yet brought into being. We had considered the criteria we wanted to use when selecting colleagues to join us, and the relationships we would encourage among the scientists themselves and between the scientists and the supporting staff. Soon we convinced many other groups to join us, and in a short time the lab was bristling with activity. But the story of that development is Philippe's to tell, since it is he who had the "political" and administrative responsibilities that permitted us to realize our dream, as well as the scientific breadth to make it a continuing success. I would just like to profit from this occasion to thank all the members of that lab (secretarial, technical, and scientific) for helping us develop and maintain the kind of environment we were determined to create. Without a similar desire on their part, it would have been much more difficult to reach our goal.

Summering at Cold Spring Harbor

While still at Cambridge, we had received a letter from James Watson, who, though still physically at Harvard University, had been named Director of the Cold Spring Harbor Laboratory of Molecular Biology where he had spent many happy and productive moments in earlier years. The story goes that Jim was hoping to obtain money for cancer research from the Sloan-Kettering Foundation, but had learned that their interests were being redirected toward neurobiology. So he, in turn, reoriented his grant proposal and requested, and received, funding for a summer program in neurobiology at Cold Spring Harbor. We were invited to teach the laboratory course in electrophysiology that was to accompany the theoretical course organized by the Neurobiology Department at Harvard. This program demanded six weeks presence at Cold Spring Harbor in the summer, three weeks of which, for us, involved the intensive direction of ten very bright and very motivated students. The course was designed for scientists in other disciplines who wished to collaborate with or become neurobiologists themselves. The idea was interesting, and the students were certain to be excellent. However, the only way that it would be possible for me to accept such an offer was to be accompanied by my child and his extraordinarily devoted baby-sitter, Nicasia Ayesta. Jim seemed amenable to this demand, and the result was that with Nicasia, my $2\frac{1}{2}$-year-old son David, and a 6-month-old foetus weighing me down, I left for our first of 15 summers at Cold Spring Harbor. All were exhausting, but worth the exhaustion. Nicasia also found these summer sessions enjoyable, after she eventually realized that the booming sounds that broke the silence of our first night on campus (where we were living in unlocked houses) were not guns being fired (she had read a lot about New York, and confused the city with the state), but rather fireworks in celebration of the Fourth of July.

Philippe pulled out of the course after the third season, since he had a heavy teaching load during the academic year, and thoroughly enjoyed replacing the summer teaching by reading in the Carnegie Library on the campus. By the fourth year the experimental course was altered. As a complement to the *Aplysia* ganglion preparation that I taught, we added the neuromuscular junction taught by Enrico Stefani and Dante Chiarandini.

These summers resulted in our children experiencing the thrill of walking on grass (an activity forbidden at the time in all Paris parks) and living their lives out of doors as opposed to within the walls of a Paris apartment. For us it provided friendships and scientific encounters with the current and future American neurobiology community. Finally, although our scientific interests did not yet overlap, we developed close and enduring friendships with many of the Cold Spring Harbor community, including Jim and Liz Watson, whose children were of similar ages to ours; Bill Udry, who as Managing Director had the task of finding housing for us each summer; and Helen Parker, whose work as Administrative Secretary was growing exponentially with the expansion taking place at Cold Spring Harbor under Jim's direction. Last, but far from least, I have been grateful for the opportunity to know Barbara McClintock, whose complete dedication to science was unique. She was in her cornfields throughout her career. Thanks to the appreciation that the Carnegie Institution of Washington had for her unstinting efforts over the period during which she was unable to convince many members of the scientific community of the importance of her findings, she was able to persevere unhindered, and without distraction, in the research that, many years later, was recognized by the Nobel Prize.

Erice, Sicily: 1973

During the years that followed the full publication of my studies on cholinergic synapes, I had on the docket a number of rather special international conferences where I was to describe those studies. Sir Bernard Katz had asked me to lecture at the International School of Biophysics, a two-week event in Erice, Sicily, scheduled for the spring of 1973. Although I had the greatest confidence in my data, which revealed a very clear picture of transmitter activation of two pharmacologically distinct membrane receptors, each of which controlled a distinct ion permeability in the membrane, I found it a bit frightening to be addressing students of biophysics who must surely have had a more acceptable view of how ions move across membranes or across anything as far as that goes. With no chemistry, physics, or biophysics in my background, I was certain that my imagination led to a rather personal view of the process, but I picked up the challenge in spite of it, deciding that as good as the students might be at understanding ion movements, they were likely unable to penetrate my imagination.

However, once again, I was certainly not ready to leave my sons (aged 1 and 4) for two to three weeks, so I was forced to add conditions to my acceptance, as had been done for Cold Spring Harbor, i.e., in this case, that Philippe be accepted as a student in the course and that we could also include Nicasia in our housing arrangements. The laboratory of Professor Borsellino in Camoglie, Italy, handled the administration of the International School of Biophysics, and they very generously made our participation as a family possible. It was an exciting course, a wonderful place in the clouds, and a precious opportunity to become acquainted with Professor Katz, one of the neuroscientists Philippe and I most admire.

Two Full-Time Jobs: Motherhood and Science

Participation in congresses where I presented the data on the cholinergic synapses continued, with trips to Israel and Leningrad leaving marked memories, not only because of the place and people involved, but also because in *both* instances I was obliged to leave my younger son in the process of coming down with scarlet fever and not at all happy to see his mother leave the country. In addition, during the trip to Israel, David, our older son, silently choked on a piece of meat and was only saved because Philippe's father, a doctor, noticed his blue face which had silently fallen onto his plate. Although I have always been thankful not to have been present, I have never been able to get rid of slight guilt feelings over not having been there to assume my maternal duties. David once did his best to encourage these guilt feelings. One morning when I was to leave for the lab, David developed a high fever which was quickly attributed to the onslaught of measles (against which vaccinations were not yet given in France). Once the diagnosis was made, I left him with the baby-sitter and went off to the lab. That evening upon my return David, in tears, said, "Maman, never *ever* leave me again when I'm ill!"

In the spring of 1975, when about to go off to a symposium in Leningrad, I tried to console my younger, 3-year-old son, Ivan, by telling him that when I returned I would be bringing him a Russian doll. It was only over a year later that I realized how much my departure had affected him when I heard him telling a story, as was his wont, to other children about a very sad child whose mother was leaving, but had promised that she would return with the gift of a Russian doll. Although a sad event for Ivan, the trip for me left fond memories since I was able to develop very close friendships with Ella Zeimal and Michel Michealson—the latter Head of the Pharmacological Laboratory of the Institute of Evolutionary Physiology and Biochemistry in Leningrad. The friendships were characterized by the intensity of relationships developed with Soviet scientists at that time who were hungry for contact with the outside world and who had to make the most of such occasions. The friendship with Michealson was abruptly shortened, however, since, even at the time of the symposium, he was already seriously ill with tuberculosis and was able to resist its aggression for only another few years.

Following a number of other symposia, I began to feel increasingly bothered by my frequent absences from the children. With the birth of the children, I found myself with two full-time jobs, since I was as fascinated by child rearing as I was by neurobiology. Although I, of course, could not be with them continually, I profited from the liberties offered by a pure research position in C.N.R.S., which permitted me to organize my own schedule to maximize the amount of time spent with my children. Until they reached school age, I put them to bed around midnight, so I was able to spend the evening with them, and I would go off to the lab when the baby-sitter arrived at 8:30 AM as they continued to sleep until noon. This permitted me to spend almost all of their waking hours with them, while permitting me to maintain a full research schedule. Since my C.N.R.S. position did not involve teaching responsibilities, and since I worked almost always alone, I was able to organize my time independently of others.

My involvement in child rearing was the major factor that made me limit my participation in conferences that required long distance travel. In addition, however, I had become bothered by the repeated presentations of data concerning a subject that had already become second place in my interests. Furthermore, given that I had no one replacing me at the experimental post when I was away, I could no longer spare the time that was needed to advance my studies on other synapses. Those synapses were more difficult to analyze since the transmitters mediating the synaptic activity remained an enigma. I was soon to realize the luck I had had by starting my synaptic studies with a synapse whose transmitter was possible to identify pharmacologically, and a transmitter for which the molluscan receptors resembled sufficiently those of their vertebrate friends so that pharmacological tools were available for dissecting the multiple elements of the synaptic events.

A Glimpse from Afar of the Political Situation in the United States: Mid-1970s

An interesting influx of mail arrived for me in the mid-1970s. I was clearly being courted to offer my candidacy to about 10 different biology and pharmacology departments, from New York University to Berkeley and throughout the United States. I am not certain exactly what new legislation had been enacted at that time, but it clearly had put in jeopardy the federal funding of many laboratories if they could be accused of discrimination on the basis of gender. I have also not followed the statistics that resulted from that affirmative action movement, but I do believe opportunities for women in American university science programs have improved since then. Although I greatly appreciated having been considered for such professional opportunities, I had no desire to leave my C.N.R.S. position in France or to force my family to change continents.

Noncholinergic Synapses and Other Transmitter Receptors

To the outside observer, little seems to unite the work I performed over the next 15 to 20 years in *Aplysia* neurons. However, all the questions I attempted to answer were stimulated by experiments designed to determine the transmitters being liberated at a number of synapses for which I had identified the pre- and postsynaptic neurons. This search led me to evaluate receptors for various amino acids, amines, and occasionally peptides, but unfortunately never did lead to the identification of the transmitters used at those synapses. For most of my synaptic studies following those on the cholinergic synapse I was therefore obliged to accept my failure to identify the transmitter involved and to live with the consequent limitations on the information I could obtain about certain aspects of the underlying mechanisms at those synapses.

A Glutamate Receptor Forces Me to Learn a New Trade

A very likely transmitter candidate for one set of the synapses I have been studying over the last 10 years is glutamate. However, since the pharmacological characteristics of the glutamate receptors on *Aplysia* neurons differ so markedly from those of mammalian glutamate receptors, it has been very difficult to find effective antagonists for the molluscan receptors. Nevertheless, the study of these receptors has not been without rewards.

Although in mammals, glutamate has been known as "an excitatory amino acid," it has long been known that glutamate can elicit, in invertebrate neurons, an inhibitory response by increasing Cl conductance via a receptor that appears to be related to the mammalian inhibitory glycine receptor. Furthermore, glutamate can also induce in some cells an increase in K conductance, as do essentially all other "classical" neurotransmitters tested on molluscan neurons. However, I found that the glutamate-induced K conductance, unlike the increase in K conductance activated by other transmitters in both mammals and molluscs (whether amines, amino acids, or peptides), does not require the intervention of a G-protein.

My conviction concerning the ionotropic nature of the glutamate-induced K conductance was reinforced by the discovery in 1999 of a glutamate-gated K channel in cyanobacteria (Chen et al.). This has encouraged me to reinforce the interpretation of my electrophysiological data by trying to pull out the proposed glutamate-gated K channel from *Aplysia* cDNA. Even if that receptor does indeed exist, my task will not be an easy one, since it is expressed in only a few *Aplysia* neurons. Nevertheless, the opportunity of learning some of the tricks of molecular biology has been fun and, hence, worth the effort. While honing my cloning skills by pulling out a more frequently expressed and better understood ionotropic receptor, I have managed to have some encouraging success. This success is surely due to the good training I received from Cristina Alberini during her month's visit to our lab in January 2001 and to the follow-up support generously offered by Jonathan Bradley, who was working in our laboratory until the summer of the same year. Both were very patient instructors indeed!

From the 5th Arrondissement to the 6th Arrondissement—2002

When Philippe's mandate as Director of the laboratory we had formed 31 years earlier expired, we wanted to make space for the incoming director and let the younger generations in the lab spread their wings. Fortunately for us, Alain Marty and Isabel Llano, previously members of our lab at Ecole Normale Supérieure, had just returned from Göttingen where they had spent six years in Erwin Neher's laboratory. They were in the process of setting up a new laboratory at the Université Paris V on the Rue des Saints Pères and were eager to have us join them. Although we have lost our view of the Val de Grâce, and the daily contact with our colleagues of "l'Ecole," we have gained the view of a gorgeous 18th century "hotel" that houses the Ecole des Ponts et Chaussées (renovated just in time for our arrival one year ago) and the company of a number of delightful young scientists working with Isabel and Alain.

For Better or For Worse: My Approach to Science and a Big Thanks to C.N.R.S. for Making It Possible

My real love in science has always been the experimental phase. As one sees and evaluates the data coming out of an experiment, there is not only the pleasure of finding answers to the questions being asked, but there are also new problems being exposed—exciting new avenues presenting themselves for further research. This love of the hands-on element in the scientific endeavor was the major reason for which I chose to work alone. Also, given my limited background in the general field of biology, I was hesitant to take on students who deserved wider scientific support than I could hope to offer them. Finally, having no constraints offered by the schedules of collaborators has permitted me the much desired flexibility to be able to organize my time as a function of my children's needs. Given my approach to science, my limited scientific background, and the demands made by active motherhood, I was very fortunate to have a pure research position such as only an organization like the C.N.R.S. can offer.

Except for a few brief visits from foreign colleagues, I only bent my "work alone, no-student" rule upon one occasion. When Eve Marder asked to come as a postdoctoral fellow, I felt from her application that all she would need was a month of training on the techniques I could teach her that would transfer well to her current experimental preparation, and since we had sufficient equipment and space at the time (1973), I could help her develop her own setup and let her fly on her own. This was done, and having Eve in the lab was a delight for everyone.

My personal career goal has been accomplished, since I was only looking for the kind of enjoyment and personal satisfaction I have consistently obtained over the years through solving each of the experimental problems as it was posed. However, my way of "doing" science is clearly often not the most effective means of having a serious impact on science or on other scientists. Being unable to follow up certain electrophysiological observations with supplementary biochemical analyses meant that some of these findings were more or less left in limbo. For anyone starting out in the field today, a multidisciplinary approach is clearly a must. However, if one judges by the way many laboratories function today, the change brought about by the multidisciplinary approach has not only affected the science, but has also altered the structural and social characteristics of laboratories themselves. To a certain extent, it is time for another May 1968.

Times have clearly changed since the period of my gods, who spent their career at the bench and whose enthusiasm and prestige were nourished strictly by the science they produced and not by empire building. It is clear that much of the transformation in neuroscience over the last 20 years was necessary as the discipline became much more expensive, with electrophysiology having become one of many approaches to the study of the brain. Modern genetics, molecular biology, neurochemistry, and modern imaging techniques have, in conjunction with electrophysiology, led to many extraordinary discoveries that would not have been possible without the marriage of the various disciplines. However, this marriage has also led to an exponential growth in budgets and often to an almost industrial approach to neursocience. For many scientists, the search for funds has often dominated the search for answers to scientific questions. The two or three colleagues at the bench have often become assembly lines of postdoctoral candidates reporting to higher ups, with the higher up resembling much more a chief executive officer than a scientific investigator or a thesis advisor. Furthermore, many recent scientific publications pass through Madison Avenue before arriving at Main Street. What used to be "Effects of This on That," which were then judged to be exciting or not by colleagues reading the findings in peer reviewed journals, are now often subject to the interests and "hype" of private publishers looking for more immediate satisfaction.

Finally, power has become a significant factor in our science, and as in many other situations, power can, and often does, corrupt. I find myself becoming an environmentalist who would like to breathe less polluted air, returning to the time when being among "well known" scientists was an exhilarating, positive experience. I do not think this is simply naive nostalgia. I truly believe that the times have changed: that the motivations and the mores of many in the community have changed and usually not for the better. Do we not have an obligation to try to reign in the negative "social" aspects occurring with the transformation of our field, while benefiting from the positive scientific progress it has permitted? Young scientists joining the field should be given the possibility of enjoying the excitement and enthusiasm of true scientific endeavor untainted by Madison Avenue and Wall Street.

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