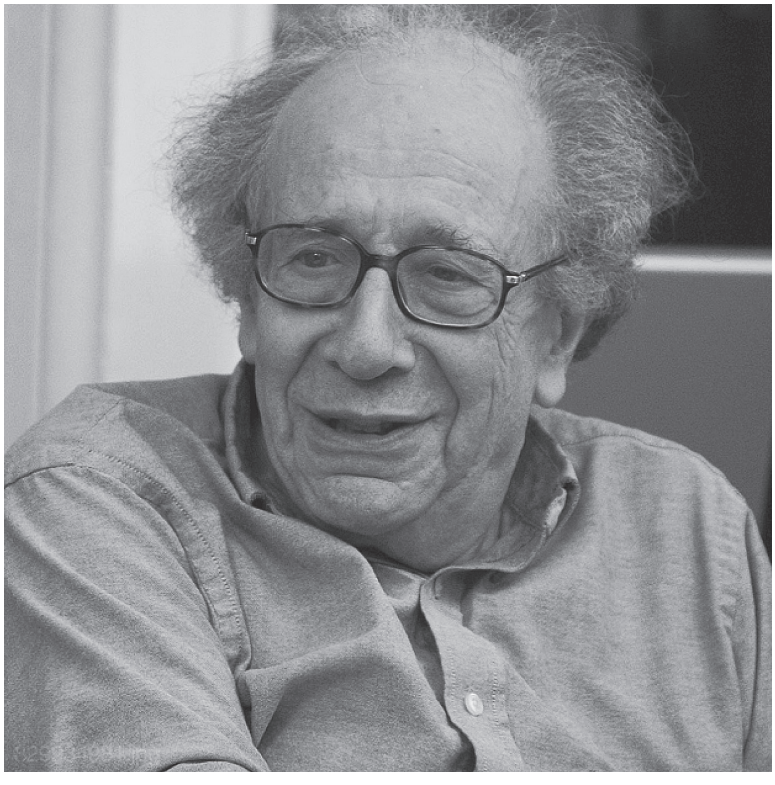

Philippe Ascher

Born:

Commercy, France
July 28, 1936

Education:

Ecole Normale Supérieure, Paris (1955–1959)
Faculté des Sciences, Université de Paris (1955–1959)
Doctorat d'Etat es Sciences Naturelles, Paris (1965)

Appointments:

Assistant, Faculté des Sciences, Paris (1959–1961)
Maître-Assistant, Faculté des Sciences, Paris (1961–1965)
Chargé de Recherches, Centre National de la Recherche Scientifique (1966–1968)
Maître de Conférences, Faculté des Sciences, Paris (1969–1972)
Professor, Université Pierre et Marie Curie, Paris (1972–2000)
Professor, Université Denis Diderot, Paris (2000–2004)
Professor, Université Denis Diderot (emeritus)

Honors And Awards:

Forbes Lecturer (1977)
Academia Europea (1989)
Académie des Sciences (Membre correspondant) (1990)
Luigi Galvani (Fidia Foundation) (1991)
Ipsen Foundation Prize (1992)
Richard Lounsbery Prize (1992)
Ulf von Euler Lecturer, Karolinska Institute (1993)
Warner-Lambert Lecturer, Society for Neuroscience (1993)
Dana Foundation Award (1994)
Physiological Society (Honorary Member) (2013)

Most of the work of Philippe Ascher has been devoted to the electrophysiological characterization of receptors to neurotransmitters. In his early studies of Aplysia *neurons, he characterized excitatory and inhibitory responses to dopamine as well as the mechanism of action of acetylcholine and of acetylcholine antagonists. After the introduction of patch-clamp methods, he moved to the study of glutamate receptors in vertebrate neurons. He is best known for the demonstration that extracellular Mg ions block the channels opened by activation of the N-methyl-D-aspartate (NMDA) receptors, and for the discovery that the activation of NMDA receptors by glutamate is allosterically modulated by glycine. He currently studies the motoneuron-Renshaw cell synapse that, in newborn mice, combines glutamatergic and cholinergic transmission.*

Philippe Ascher

I was born in 1936 in the eastern part of France. My father, who was the general practitioner of a small village, realized that war was coming and that the German border was too close. Thus, in 1937, he moved our family to another small village, in a remote part of the Massif Central. This did not prevent him from being taken prisoner by the Germans for five years, but it meant that the rest of us were saved from the worst. When my father returned in 1945, he decided that it was time to move to a more urban setting, so we went to Metz, the city where my mother had grown up. This is where I entered high school.

Until my last year of high school, I thought that I would go to medical school. However, my biology teacher at high school, who had been my mother's teacher as well and had taken an interest in my future, described the curriculum of the Ecole Normale Supérieure (ENS) in enthusiastic terms to me and to my parents. He suggested that I should try to enter this school. My parents liked this idea very much, mostly because they had enjoyed a series of novels by Jules Romains (*Les Hommes de Bonne Volonté*) in which the central characters are two students of the ENS. The series, which was a very ambitious and probably superficial attempt at describing French society, had had a vast readership in the 1930s. It painted the ENS as a wonderful place of freedom and intellectual exchange, the place to go if one wanted to pursue a career in academia, politics, or finance. For me, preparing for entry to ENS had the added advantage of necessitating a move to Paris, whereas going to medical school would have meant staying in a university near Metz. I therefore went to Paris, to the only *lycée* (school) at that time that gave the ENS entrance exam for studies in physics, chemistry, and natural sciences.

Neuroscience in Paris in the 1950s

After two years in an environment closer to that of a monastery than of a university, I entered the ENS in September 1955 with two other biology students: Jean Génermont, who would go on to become a geneticist, and Jean-Pierre Changeux, who at that time could probably have been described as a zoologist. While still in high school, he had discovered a new species—a parasitic marine copepod—and in the following years pursued his taxonomic studies in many French marine biological stations: Banyuls-sur-Mer, Roscoff, Arcachon, and Villefranche-sur-Mer. Although I did not share this particular passion, I accompanied him on many of these trips. I also participated in the geological and botanical excursions organized by the ENS,

which proved to be the main educational contribution of the school's natural sciences department. I have fond memories of these experiences, but they were peripheral to my main interest, which was the study of how the brain functions.

The word biology was nowhere to be found at the ENS. I had entered the section of natural sciences, which was divided into three laboratories: zoology, botany, and geology. Physiology was represented by a single person who had not done research for years. Biochemistry was absent. The laboratories organized the field trips that I mentioned earlier, but all of the courses were given at the Sorbonne, and these turned out to be deeply disappointing. The lectures on the nervous system were probably the worst. The head of the physiology laboratory at the Sorbonne, Alexandre Monnier, had been a respectable scientist, had worked with Graham Gasser, was a friend of Herbert Jasper, but he had espoused the theories of Louis Lapicque. Like many of his colleagues, Lapicque assumed electrical transmission from nerve to muscle but claimed that this required that the chronaxies of nerve and muscle be identical, and that curare altered the chronaxie of muscle. Both claims were wrong and, in the rest of the world, the articles of William Rushton and of Harry Grundfest in the 1930s had long led to the abandonment of this theory. Not in France, where it was the "official" explanation of synaptic transmission, the one that I had learned in high school and found presented again at the Sorbonne. The practicals in neurophysiology were all based on chronaxie measurements, using elaborate home made mechanical devices to measure delays. In his lectures about the action potential in 1956, Monnier was reading a text that had been printed for the first time in 1942. He never presented (neither at that time nor in the next 30 years) the work of Hodgkin and Huxley, although he knew them personally and was proud of having hosted them. Much later, when I asked him the reasons for this ostracism, he said: "At the beginning I did not believe it, and then it was passé." A course on the organization of the nervous system was given by Marcel Prenant, who had commanded a military underground unit during World War II, had been arrested by the Gestapo, and had been deported. He had been elected to parliament after the war and was a member of the central committee of the Communist Party but had obviously lost touch with science in the making. He placed on equal footing the concept of synapse and the reticular theory. This was in 1955–1956, and in Boston and in Buenos Aires, electron microscopists were about to produce the first images of synapses. A third professor was Henri Laugier. He had been the director of the Centre National de la Recherche Scientifique (CNRS) in 1939; during the war, he had organized the transfer to the United States of a number of the best French scientists, and after the war he had been active at the United Nations. But why did he insist on giving lectures on circulation when all of his research had been in biometrics and exercise physiology? I wanted to study the nervous system but could not turn to any of these people for advice.

Fortunately, I discovered a neuroscience laboratory outside of the university: the Institut Marey, directed by Alfred Fessard. Fessard was a professor at the Collège de France. The Collège had been created in the 16th century "to teach disciplines which were not yet recognized at university level," and that is the role it played after the war. Lapicque and Monnier had estranged French neurophysiology from the rest of the world, but Fessard had made contacts with scientists all over the world. Before the war, he had worked with Brian Matthews in Adrian's laboratory in Cambridge, and in 1939, he had joined Wilhelm Feldberg and David Nachmansohn in Arcachon for experiments on Torpedo (an electric fish) that lent strong support to the idea that acetylcholine (ACh) was involved in the transmission of excitation from the nerve to the electric organ. In 1955, he had organized a meeting in Gif-sur-Yvette (near Paris) that brought together Eccles, Fatt, Hodgkin, Matthews, and a great many other leading neurophysiologists. This meeting symbolized the reestablishment of links between French neurophysiology and the rest of the scientific world.

The Institut Marey was located near the then-small Roland-Garros tennis stadium, in a cottage where Etienne-Jules Marey had done his experiments on chronophotography. One room was still occupied by "Monsieur Bull" (Lucien Bull), Marey's assistant, who continued until his death in 1972 to build devices that allowed him to film very brief events, such as the explosion of hydrogen-oxygen mixtures. Alfred Fessard received me very kindly and offered me a choice between two advisors: Ladislav Tauc, who was studying *Aplysia* neurons, and Pierre Buser, who worked on the cortex of the cat. I was more interested in higher brain functions but still undecided. Then Alfred Fessard told me that the *Aplysia* preparation required quite a difficult dissection, and this statement (which was totally wrong, as I was to discover later) is what tilted the balance. I was not good at dissections, so I chose Pierre Buser. I have often thought of that conversation, which lasted only a few minutes. Alfred Fessard could have said more, and I could have asked for more. During the next 50 years, I had many talks of this type with students attempting to define their field of research and to choose their advisor, and I have tried to be a little more specific about the pros and cons of the laboratories that I described and to insist on their getting other opinions. But today the problem is often reversed—some students visit so many labs before choosing one that an excess of information seems to be the difficulty.

Pierre Buser

I worked in the laboratory of Pierre Buser from 1957 to 1965, with two major interruptions. In 1959–1960, I spent one year preparing for the *agrégation*, a competitive examination for teaching high school. I had no intention of teaching in a high school, but when I entered the ENS I signed a

contract with the French government in which I committed to preparing for this exam. I nearly failed, having done poorly in genetics and revealing my incompetence in botany. At one point, the president of the jury told me that I might have to accept a position in a high school in Saigon (the French were still in Indochina). I finally passed with a rank high enough to allow me to return to preparation for my PhD. The second interruption occurred toward the end of my thesis, when I had to do my military service. After some military training, I was sent to an air force laboratory in Paris that prepared a mouse for a zero gravity flight of a few seconds. We implanted electrodes on the vestibular nerve of mice. One of the mice was eventually selected and sent up in the Sahara desert; but on its return, the rocket did not land where expected, and when it was finally located, there was little left of the mouse.

At that time, the preparation of a thesis stretched over many years. Obtaining a thesis was a prerequisite for the position of associate professor, and thus was more akin to the "habilitation" of German universities than to a simple PhD. But there were no fellowships for graduate students, who usually had to take on a teaching position either in a high school or at a university. When I left the ENS in 1959, I immediately obtained such a position. I became an "assistant" at the Faculté des Sciences de Paris. What might seem unbelievable today is that after one year this became a permanent position. I was 24. If I had stopped any research but continued to assume my teaching obligations, I would not have been promoted, but I would not have been fired. Indeed, I recently learned of the death of an ENS student who had been recruited a year before me, never presented a thesis, published very little, but who went on to teach zoology for 40 years and was liked by students and colleagues.

My thesis was entitled "The Startle Reaction of the Cat Anesthetized with Chloralose." My first experiments with Pierre Buser were not on the startle reaction but on the pyramidal tract discharge elicited by various sensory stimulations in the cat anesthetized with chloralose (Buser and Ascher, 1960). We then realized that the multisensory inputs that reached the motor cortex were the same type as those that activated the "associative" cortical areas, and they likely originated in the reticular formation. But we also found that the striking startles observed under chloralose persisted in the absence of the motor cortex and thus probably involved some direct reticulospinal pathway. With a number of collaborators—in particular, Dora Jassik-Gerschenfeld and Gabriel Gachelin—we tried to sort out the circuits involved in the startle reaction. Toward the end of my thesis, I started becoming really excited about the fact that the startle reaction triggered by visual stimulation involved two pathways converging on the superior colliculus. Despite the fact that the anatomical lengths of the two pathways were very different, a compensation was introduced by the difference in the conduction speeds, bringing two synchronous signals to

the superior colliculus and from there to the reticular formation (Jassik-Gerschenfeld et al., 1966; Ascher and Gachelin, 1967).

Pierre Buser had worked on the reticular formation with Horace Magoun at University of California Los Angeles (UCLA) in 1953, and it is there that he had decided that the study of multisensory integration would be the primary focus of his research. When, in 1963, I announced to him that Hodgkin, Huxley, and Eccles had received the Nobel Prize, he shrugged and told me that he would have awarded the prize to Giuseppe Moruzzi and Horace Magoun for the identification of the subcortical centers regulating awakening and sleep. I later learned that, in 1957, the media had leaked that Magoun had been selected for the Nobel Prize before the Karolinska Institute Assembly overturned the choice. As for me, as much as I shared Buser's admiration for Moruzzi and Magoun, I had the feeling that (with the methods available to us at the time) we would not obtain a real understanding of the motor behavior that I had spent so many years studying. I was reinforced in this opinion by some nasty but pointed comments made by one referee of our papers. Thus, near the end of my PhD, I looked for another line of research. I considered analyzing sensory systems such as the visual system, which was the choice made later by my friend Michel Imbert, who had joined the laboratory of Pierre Buser shortly after me. I visited the laboratory of Yves Laporte, who analyzed the proprioceptive inputs from the muscle spindles. He invited me to Toulouse to observe an experiment. The experiment was programmed to last for two days. The dissection was started by Paul Bessou, a brilliant surgeon. Soon I knew I that I could not consider going in this direction because I noticed that Bessou had only taken five minutes for the laminectomy that I was doing in 25 minutes. I then considered another possibility, which was to try the second choice that Alfred Fessard had offered me, namely Ladislav Tauc and the *Aplysia* neurons. Hersch Gerschenfeld was a crucial influence on my making this decision.

Hersch Gerschenfeld

I first met Hersch and Dora Gerschenfeld in 1959 when they arrived at the Institut Marey from Buenos Aires for a stay of two years. Hersch has described in his (unfinished) autobiography his first encounter with Alfred Fessard, and the story (Gerschenfeld, 2009) actually ends on the statement by Fessard: "Le secteur, voilà l'ennemi, et la lutte contre lui ne finit jamais" (The fifty cycles [current interference], this is the enemy, and the fight against it never ends). Hersch worked with Ladislav Tauc, while Dora joined the group of Pierre Buser and worked with me. Hersch had an immediate influence on all the institute's graduate students and "postdocs" because of his ability to start conversations and discussions on scientific and non-scientific subjects. He readily perceived but deliberately ignored the existing divisions between the various groups (which were linked to conflicts

between the group directors) and, in a few months, convinced all the young investigators to lunch together and later to go to meetings together. At the scientific level, he brought us a view of the outside world and a historical perspective of the evolution of science. I was impressed by the fact that in his remote Argentina, where foreign visitors were rare, he had built a broad and critical picture of the world of neuroscience—its trends and its most active centers. I realized how limited and "Paris-centered" I had been until then.

Hersch introduced me to the study of neurons and synapses, and he communicated his enthusiasm to me. The description of ACh receptors in *Aplysia* neurons (Tauc and Gerschenfeld, 1962) impressed me— not only by its content but also by its aesthetics. I thought that the figures looked nicer than those of the papers I was reading or writing, and I decided that it was due to the fact that they were describing "basic" processes. Hersch made me discover pharmacology, a subject I had never heard of until I saw the dose-response curves that he was constructing with Enrico Stefani on snail neurons after his return to Argentina. Hersch also introduced me to the comforting notion summarized in the title of the book, *From Neuron to Brain* (Nicholls and Kuffler, 1976): Working at the cellular level not only provides meaningful data on neuron physiology but can also significantly advance the understanding of higher functions of the brain.

My discussions with Hersch Gerschenfeld decisively impacted my shift to the cellular level, which was the line I was to hold for the next 40 years. As soon as I had defended my thesis, I applied for a position at the CNRS (which allowed me to pursue research full-time); I was accepted and entered the Tauc laboratory.

Dopamine and the Na-K pump

In 1965, there was no commercial supply of *Aplysia* in France; to obtain *Aplysia*, the Tauc laboratory transferred all its set-ups for two months to the marine biological station of Arcachon, where the animals entered the bay in September to lay their millions of eggs before dying. I joined the lab in September 1965. I once again met Hersch Gerschenfeld, who was visiting for the summer, and Jan Bruner whom I knew from my previous time at the Institut Marey. I also met Jacsue Kehoe, an American postdoc who had joined the Tauc group the year before. Shortly after that encounter, we decided to share our lives and for this reason, from this point on, my story partially covers the same ground as the chapter that she wrote in this same series (Kehoe, 2004).

In Arcachon, I collaborated with Tauc and Gerschenfeld on the study of a neuron that received two different synaptic excitatory inputs, only one of which was blocked by tubocurarine. We concluded that the neuron was excited by two different transmitters (Gerschenfeld et al., 1967) and

were probably wrong. I suspect that the second synaptic potential was due to an electrical synapse. When we returned to Paris, Tauc suggested that I study the effects of dopamine on *Aplysia* neurons. That year, we began having *Aplysia* shipped to Paris from various places in France and soon from California; thus we could perform experiments all year long. I applied dopamine electrophoretically on various neurons and found that, depending on the neuron, dopamine could be excitatory, inhibitory, or both (Ascher, 1972). This extended to dopamine an observation that had been made for ACh and turned out later to be true in molluscan neurons for most neurotransmitters. I then became intrigued by the effects of dopamine on the giant cell called R15. Dopamine produced in this cell a hyperpolarization that, contrary to what was expected from an increased ionic conductance, could not be inverted by hyperpolarizing the cell. In the spring of 1968, I realized that one possible explanation was that dopamine activated the Na-K pump, which Roger Thomas had recently confirmed to be electrogenic in a series of spectacular experiments on snail neurons (Thomas, 1969). Indeed the dopamine effect was blocked by ouabain, a blocker of the Na-K pump. I sent a communication for the June 1968 meeting of the Physiological Society in Oxford. When the meeting opened, May 1968 disruptions had brought the lab to a near standstill, and I could not present much more than my initial observations. I returned to experiments in the autumn when Jacsue and I arrived in Cambridge for a sabbatical year. By that time, I had doubts about my interpretation because I had found that, in smaller neurons hyperpolarized by dopamine, the response could be inverted near the potassium (K^+) equilibrium potential. Then, in early 1969, Pinsker and Kandel proposed (Pinsker and Kandel, 1969) that, in another giant *Aplysia* neuron (R2), the hyperpolarization produced by ACh was due to activation of the electrogenic /Na-K pump. Under other circumstances, I would have been very depressed. But the interpretation of Pinsker and Kandel (like mine) was open to doubt; Jacsue had described a response to ACh in smaller neurons, which inverted exactly at the K^+ equilibrium potential. It took her little time to show that, in these smaller cells, ouabain produced a depolarizing shift of the K^+ equilibrium potential, which reduced or abolished the hyperpolarization seen near resting potential. We attributed the shift of the K^+ equilibrium potential produced by ouabain to a loss of internal K^+ until Alan Hodgkin convinced us that it was better explained by an accumulation of extracellular K^+. We concluded that the absence of inversion in the giant cells was readily explained by the large electrical distance between the soma and the (axonal) ACh receptors (Kehoe and Ascher, 1970).

1968

The year 1968 rocked France. At the Institut Marey, work stopped for nearly three months, innumerable assemblies were held, and very violent

exchanges occurred. Two authors of the *History of Neuroscience* series—Denise Albe-Fessard and Jacsue Kehoe—have described in contrasting ways how they perceived the same set of local events (Albe-Fessard, 1996; Kehoe, 2004), and one will not be surprised if I say that my perception was closer to Jacsue's. Looking back at what happened, I think that inside the academic world, as elsewhere, the major cause of agitation was the desire of the younger generations to have some say in what was at that time exclusively decided by our elders. They were not dictators nor were they incompetent, but they considered that their experience and maturity gave them the right to make most of the important decisions alone. We felt that we were living in a patriarchal society. The revolt was spontaneous, and in many ways, healthy. But the spontaneity meant that that there was no plan for what was to replace the old system. Before 1968, many people had attempted to diagnose the problems of the French universities and research organizations and had proposed remedies. These discussions continued during the "events." But when the agitation ended, we discovered that we had not changed the structures but only accelerated the transfer of power between two generations. The members of the new generation differed from those of the previous one in style, but they held just as firmly to their newly acquired powers. These powers were less extensive because they were shared by more people. This situation had a good side and a bad side because it complicated many collective enterprises. I have never regretted the old days, but in the following years, I noticed that some of the most successful French laboratories and institutions were those that preserved centralization and limited "democracy." One of the reasons why the Ecole normale supérieure has fared better than most universities in organizing its research is probably that its director is chosen by the government, whereas French university presidents are elected by those that they administer and to whom they therefore must make promises.

In 1970, on the assumption that the explosion of 1968 had been due to an excessive number of students in the giant University of Paris, the government decided to split it into a series of smaller universities. Why not? But, fearful of starting new disagreements, it was decided that the split would not be organized by any committee and would simply follow the political lines of the time. I belonged to the faculté des sciences (science faculty), which occupied a massive complex along the Seine. We were told that the buildings would be divided between two universities that had expressed interest in science departments. They were initially named Paris 6 and Paris 7 (now "Pierre and Marie Curie" and "Denis Diderot"). The faculty members were free to choose which of the two universities they wanted to join. Paris 6 was to be controlled by an association of conservatives and communists, united by their belief in the need for order and hierarchy. Paris 7 would regroup the leftists, where *tu* (you) was the rule and where it was promised that every teacher, whether assistant professor or full professor, would have the same

duties and the same rights. I was tempted by Paris 7, but I realized that most of the physiologists were planning to stay in Paris 6, which meant that choosing Paris 7 could result in an enormous teaching load. I decided to stay with the majority of the physiologists. For symmetrical reasons, the biochemists decided to move as a block to Paris 7. Thus, when the split was completed, Paris 6 had only one biochemist, and Paris 7 had only two physiologists. Paris 6 had also lost all social sciences and humanities; and Paris 5, to which I was to move later, had only medicine and law. Forty years later, we all agree that the process selected for the partition was absurd. The government has recently tried to encourage regroupings aimed at reconstituting "multidisciplinary" universities; but money is scarce, fiefdoms have been constructed, and the process will take many years—even if the political distinctions that had informed the splits in 1970 have long been forgotten.

On a personal level, 1968 taught me crowd control. For many years after 1968, teaching in a university lecture hall meant that one might be interrupted for reasons either futile or important but rarely linked to the subject of the lecture. Among the higher-ups, university presidents could expect to find themselves "sequestered" for a few days by committees of students, who might protest a decree requiring foreign students to have knowledge of French, a reduction in the length of the holidays, or a decision to discontinue a course on the history of cinema. In the innumerable meetings of 1968, I found that I had learned a number of tricks that allowed me to exercise a reasonable control over the students in my classes.

Cambridge (1968–1970)

I did not choose Cambridge in the logical way I recommend to students who look for a postdoc. In the middle of the 1968 events, Arnold Burgen—who was at that time the head of the department of pharmacology in Cambridge—gave a lecture at the Institut Marey. I liked it and asked if I could go to his lab. He agreed. He left me free to continue my current project on dopamine receptors in *Aplysia* neurons, gave me access to an electrophysiology setup, and offered to pay for the *Aplysia*, which were flown in every other week from California. I shared them with Jacsue (who was at the Cambridge anatomy department); she took the pleural ganglia, and I took the abdominal one. Because she worked on ACh receptors, the *Aplysia* were bought with a grant from the Tobacco Research Council. I did not realize at that time how compromising that could be.

We had just arrived in Cambridge when I learned that an associate professorship had just been opened at the University of Paris. I decided to apply. In comparison with the teaching-free CNRS position, rejoining the university meant an instructional load of three lectures a week (it would become much worse later). This was a handicap; but during the May 1968 events, our relationship with Ladislav Tauc had deteriorated and a position

at the university was a way to attain complete independence. I was elected by a margin of one voice and felt a bit guilty about the result; my rival was the biology teacher who had prepared me for entry at the ENS and for whom I had great admiration. As a Jew, his career had been interrupted during the war (he had been expelled from his job), and he had completed his thesis by experimenting on frogs at home.

I then returned to Cambridge, but I still had to prepare and deliver my three weekly lectures (on subjects that I had never taught before: cardiac and renal physiology). I traveled to Paris each Friday evening, gave my three lectures on Saturday morning, and returned home in the evening. Despite this hard schedule, I have wonderful memories of that year. Probably my major surprise was how accessible senior scientists were. Alan Hodgkin, in particular, would meet with us as often as we wanted. You had to be prepared, though, because he kept his slide rule at hand and from time to time would ask for numbers rather than qualitative statements. Bernard Katz, whom we visited in London, was similarly welcoming. Until then (during my thesis years in France), I had had very few scientific discussions outside of the lab or of the Marey Institute. It was in Cambridge that I caught the "anglophilia," which I shared with Alfred Fessard and Yves Laporte in France. Later, this exposed me to many attacks from French colleagues, some of whom were excellent scientists but also inveterate nationalists.

Starting the Laboratoire de Neurobiologie at the Ecole Normale Supérieure

When we returned to Paris in 1970, Jacsue and I were not well received. The tensions of 1968 had not completely abated, and we found ourselves "exiled" in a temporary building in Gif-sur-Yvette, where the Institut Marey was to be transferred in the following years. Teaching meant long commutes between Gif and Paris and many days without running experiments. I started filling my time doing theoretical work on the Na-K pump. I realized that the electrogenicity of the pump could be incorporated into the Goldman-Hodgkin-Katz equation describing the membrane potential. I showed my work to Alan Hodgkin and Roger Thomas, but when I tried to publish the modified equation, one referee found it uninteresting and suggested that I return to experimental work; the other kindly pointed out that the equation had been already proposed by Mullins and Noda in the discussion of a 1963 paper (Mullins and Noda, 1963). Following the advice of the first referee was then my only choice. This was greatly facilitated by the fact that, in the meantime, I had discovered empty lab space at my alma mater, the ENS.

I was informed of the existence of vacant space by a friend who told me that the ENS physics department was worried that zoology intended to occupy most of the nine floors of the new biology building that had just been completed. I contacted the ENS scientific director, Michel Hervé, who

showed interest. There was no publicity about an opening. No other candidate was considered. I was not interviewed by any committee. I only met the head of the physics department, Yves Rocard. The only question that he asked was related to the ongoing split of the Paris University into 13 universities. Which university would I join? I said: Paris 6. It seems that he would not have accepted me if I had said Paris 7, which hosted a dissident group of physicists. He then handed me a bank check for a thousand francs, which I used the next week to purchase a water distiller. The machine never worked (the water pressure on the ninth floor was too low), but I kept it for many years as a souvenir of our arrival.

The ninth floor was large enough to allow us to invite colleagues to join us, and within a year we were accompanied by Jean Massoulié, Claude Bergman, and then Hersch Gerschenfeld. Hersch had fled the 1966 Argentinian coup, found hospitality in Stephen Kuffler's lab in Harvard, and was now back in France—this time without any hope or intention of returning to Argentina. It was Hersch who proposed that our group call itself Laboratoire de Neurobiologie, a homage to Kuffler who had invented the word neurobiology. We received help from the CNRS and from the Délégation Générale à la Recherche Scientifique (DGRST), two national funding institutions. The DGRST, which disappeared in 1981, helped with the development of new research fields. It gave us a starting grant in the frame of a "concerted action" to develop the study of biological membranes. The CNRS then picked up where the DGRST had left off and provided us with regular support every four years. For the last 40 years, the CNRS has been attacked as insufficiently productive, and it has been repeatedly proposed that most of its powers should be transferred to universities. In my experience, the CNRS has done a better job of evaluating and supporting science than have our universities, and I hope that it resists further attacks.

Intracellular Chloride Ion Concentrations

The first postdoc who arrived at ENS was Diana Kunze (in 1971), followed by Tim Neild (in 1973). Diana knew how to make electrodes filled with liquid ion exchange resins, and we decided to measure the internal chloride ion (Cl^-) concentration (Cli) in *Aplysia* neurons. There were reports that in some neurons there was a difference between the values of the Cl^- equilibrium potential, E_{Cl}, and the value of the resting potential, E_m, suggesting the existence of active Cl^- transporters, which had not yet been identified. With Diana Kunze and Tim Neild, we measured Cli in *Aplysia* neurons and concluded that E_{Cl} was more negative than E_m (this implied an active extrusion of Cl^-) and that the resting Cl^- conductance was low (Ascher et al., 1976). This last claim contradicted the high values of the Cl^- conductance reported by Arthur (Buzz) Brown and John Russell (Russell and Brown, 1972). However, these authors had worked in high external K^+,

and we attributed their high values to the activation of synaptic Cl^- conductances by transmitters released under these conditions. This did complicate the relation of Diana Kunze with Buzz Brown a bit but did not prevent her from marrying him. With Tim Neild, we also used the Cl^- electrodes to measure Cli in the squid axon. Mauro (1954) and Keynes (1963) had reported a high Cli using Ag-AgCl microelectrodes, but Neild and Thomas (1974) had raised some doubts about these values. Tim and I went to Roscoff, the French biological station where squids could be obtained in good condition. We confirmed the values of Mauro and Keynes; E_{Cl} is indeed less negative than E_m in squid axon.

Relaxation and Channel Block

In 1975, Alain Marty became my first graduate student. A former student of the Ecole Polytechnique, he had taken courses in neuroscience in Paris, had gone for a year to work with Alan Finkelstein at Albert Einstein, and had come back to start his PhD. We decided to characterize the kinetics of an excitatory current induced by ACh in a small group of *Aplysia* neurons, and to this end, we implemented the new approaches that had been developed for the study of the end-plate ACh receptors: noise analysis and voltage jumps (Ascher et al., 1978 a,b). The most surprising observation was made when we applied voltage jumps in the presence of ACh antagonists. We had applied voltage jumps in control conditions and observed what Adams (1975) and Neher and Sakmann (1975) reported at the endplate—during a hyperpolarizing voltage step, the current shows an instantaneous increase (due to the increase of the driving force) then a slow increase indicative of a voltage sensitivity of the closed-open reactions. However, in the presence of the ACh antagonist, tubocurarine (curare), the inward relaxation seen at negative potentials was followed by an outward relaxation, which indicated that the effect of curare was voltage dependent. This was surprising because curare was widely assumed to be a competitive antagonist, and we had expected that it would just scale down all the currents. Alain Marty was the first to understand what was happening, namely that curare was acting as a slow channel blocker and was entering the channels at a rate slower than that of the increased openings induced by the voltage step. In preceding years, the concept of channel block in the case of the voltage dependent ion channels had been strongly developed by Clay Armstrong, and it was already extended (Adams, 1976) to the ACh-activated channels of the endplate. What was surprising was the fact that the process occurred for curare, a prototypic competitive antagonist.

We had published our initial observation in *Nature* (Marty et al., 1976) but soon discovered that it did not have a strong impact. I understood why when I went to London in 1977 to discuss the possibility of a sabbatical year at St George's Hospital with Humphrey Rang and David Colquhoun.

I found that they attributed the bizarre behavior of curare to the fact that we were looking at *Aplysia* neurons rather than vertebrate neurons. The fact that Manalis (1977) showed a voltage-dependent block by tubocurarine in striated frog muscle barely changed their view. David Colquhoun half-jokingly said that they were only interested in "hairy animals." Thus I decided that, during my stay in London, I would show them that what was valid for *Aplysia* was valid for vertebrates. And indeed, with Humphrey Rang and William Large, we showed that ACh antagonists in the submandibular ganglion of rats behaved very much as in *Aplysia* (Ascher et al., 1979). After Humphrey became convinced of the phenomenon, he became a powerful ally in propagating the gospel of channel block to interpret the effects of "ganglioplegics" and their sensitivity to the frequency of stimulation, enjoying the "upset (of) a number of apple carts" (Rang, 1997). He also analyzed why compounds that had a similar voltage dependent block had different functional effects and found that this could be explained by considering trapping, a notion that had also been proposed by Clay Armstrong but that we had not exploited in *Aplysia*.

Magnesium Ions Block the Channel of N-Methyl-D-Aspartate Receptors

When I returned from England, I started using patch-clamp, which Alain Trautmann and Steve Siegelbaum had already introduced in the lab (Alain Marty was still in Göttingen for his postdoc). With Sol Erulkar (who was on a sabbatical leave), we started dissociating snail neurons and looked for ACh-activated channels, but the success rate of our experiments was extremely low. After Sol departed, I realized that, with the arrival of tight-seal whole-cell recording, giant invertebrate neurons had lost one of their major technical advantages, even though their handicap as models for receptor pharmacology remained severe. It was time to shift to vertebrate neurons. With Linda Nowak, the new postdoc who had arrived from Ann Arbor, we decided to try primary cultures of mice cortical neurons. We had no hood, no incubators, and, for a whole year, we obtained the cultures from laboratories within walking distance—those of Jeanine Koenig or Alain Prochiantz. We wanted to see single channels opened by neurotransmitters, and I think that we selected glutamate because it was the cheapest drug to start with. For many weeks we did not see any response, until I remembered an article in which Jeff Watkins and his colleagues had described a "non-competitive" effect of magnesium ions (Mg^{2+}) on the glutamate receptors selectively activated by N-methyl-D-aspartate (NMDA receptors). We prepared a Mg^{2+}-free ringer and readily observed that glutamate induced a large noisy current in the whole-cell mode and the expected single-channel currents in outside-out patches. Adding Mg^{2+} reduced the whole-cell current and introduced a negative resistance around resting potential. At the single-channel level, Mg^{2+} transformed long openings into bursts of briefer

openings. Piotr Bregestovski then joined us and participated in the analysis of these effects. Alain Trautmann had written the programs required for the analysis of the records, and the model used by Neher and Steinbach (1978) in their study of the effect of local anesthetics on ACh nicotinic channels turned out to apply readily to our system (Nowak et al., 1984; Ascher et al., 1988).

The basic experiment was so simple that we were worried it might be published by somebody else before we had finished our analysis, and we were right to be afraid. We only overtook Mark Mayer and his colleagues by a few weeks (Mayer et al., 1984). They had not analyzed single channels, but they had a significant advantage over us: Mark Mayer had been Watkins' student and knew the pharmacology of glutamate receptors. We had suspected that the voltage-dependent channels that we were looking at were those of NMDA receptors. But we did not try to confirm it by using specific agonists or antagonists, and we had not tried to understand why we did not see a "non-NMDA" component when we applied glutamate. (We understood later that our perfusion was so slow that the "non-NMDA" receptors were completely desensitized.) I viewed our observation from the point of view of a biophysicist rather than of a pharmacologist, and what I considered most exciting was that we had discovered a voltage-dependent system that was based on channel block by an endogenous ion and thus radically different from the voltage sensors involved in Na and K channels. Meanwhile, Mark Mayer and his colleagues characterized the NMDA receptors with the adequate pharmacological agents and developed Watkins's suggestion that variations of the extracellular Mg^{2+} concentration could modulate the NMDA responses. Neither of our two groups could predict that what we had uncovered would be promoted to a key functional role in plasticity, coincidence detection and memory.

The success of the Mg^{2+} block as a mechanism involved in plasticity sent the studies of the detailed mechanisms of the block to the backseat. We, and many others, later used site-directed mutagenesis to try to understand this block, and we identified some crucial amino acids. For a time, the localization of the blocking site in the transmembrane electric field was slowed by the "crossing of the deltas," namely the fact that the blocking site for external Mg^{2+} seemed paradoxically deeper in the membrane than the blocking site for internal Mg^{2+} (Johnson and Ascher, 1990). The problem was solved by Antonov and Johnson (1999), who found that the voltage dependence was strongly regulated by external and internal permeant ions. But a complete physical description of the block is still not available.

The Effect of Glycine on N-Methyl-D-Aspartate Receptors

Jon Johnson arrived in Paris in 1985. By that time, we had installed a culture room and had even recruited a technician (my sister, Dani Lévy) to take care of the cultures. Although the cultures looked alright, I was preoccupied by the fact that the responses that we induced with glutamate were

ten to a hundred times smaller than those reported by Mayer et al. (1984), and I wondered whether we were missing some crucial technical procedure.

Jon's initial project was to construct concentration-response relationships. While trying to evaluate the stability of the response to a given concentration of glutamate, he was confronted with bizarre effects. The amplitude of the response seemed to depend on the speed of application; it was larger when the perfusion was slower, and when we maximized the speed of application by using the "U-tube" method, which had been introduced by Krishtal and Pidoplichko (1980), the response seemed to desensitize very rapidly. Furthermore, an off response was observed at the end of the application.

Jon tested a myriad of biophysical theories until he understood that the odd behavior of the response had little to do with biophysics and kinetics. His decisive observation consisted of analyzing the response of an outside-out patch in a culture dish in which the perfusion had been stopped after the addition of NMDA. When an outside-out patch was made by pulling the pipette away from the cell, it immediately showed the characteristic single-channel activity associated with activation of NMDA receptors. However, if the patch was then lifted toward the surface of the dish, the frequency of the single-channel currents decreased, and then increased if the patch was lowered back toward the bottom of the dish. This was a very strong suggestion that the cells at the bottom of the dish released a factor facilitating the response to NMDA, and that this factor was progressively diluted as one moved away from the bottom. This interpretation was soon confirmed when Jon devised a new system of NMDA application using two parallel tubes and showed that applying NMDA dissolved in fresh culture medium elicited only a very small response. However, if one replaced the fresh culture medium with "conditioned medium" taken after a few hours in contact with the neurons, one observed a large response that did not desensitize and showed no off component.

The fast decay of the response to NMDA applied in slow perfusion or with a U-tube was thus not due to desensitization but to the washing away of the ambient "factor." The return of this factor, when the application was stopped, explained the off response. And the large responses of Mayer et al. (1984) were likely due to the fact that they used electrophoretic applications of NMDA or glutamate, which did not modify the concentration of the ambient factor. My doubts regarding the technical competence of my sister turned out to be unfounded.

The experiment using the conditioned medium also offered a method for identifying the potentiating factor produced by the neurons. For this identification, we oscillated between a systematic approach of fractionation of the conditioned medium and "fishing expeditions." The latter approach is not favored by textbooks and grant referees, but it was a way of trying to relieve the frustrations of the fractionation. And it was in one of these unreasonable attempts that Jon decided to test simple amino acids. He prepared two tubes,

each containing nine amino acids. At the last minute, and despite the fact that we "knew" that glycine was an inhibitory transmitter, he added a third tube containing glycine. For a reason now forgotten, he applied this compound first and found that it completely mimicked the effects of the conditioned medium (Johnson and Ascher, 1987). Jean-Philippe Pin soon confirmed with high pressure liquid chromatography that glycine was present in the conditioned medium.

The editor of *Nature* insisted that we add a "physiological hypothesis" to the manuscript, and we suggested that glycine could spillover from glycinergic terminals toward neighboring glutamatergic synapses. In making this suggestion, I had been influenced by the electron micrographs of Yasuko Nakajima showing glycinergic and glutamatergic boutons close to one another on the dendrites of the Mauthner cell. Later I became attached to this idea and spent a lot of time trying to prove it, first in the cerebellum, where glycinergic terminals from some Golgi cells have been described next to the glutamatergic mossy fibers on the granule cell dendrites; then in motoneurons, where the anatomy suggests a situation similar to that of the Mauthner cell. Both sets of experiments were unsuccessful, but the hypothesis is probably true and was clearly validated in at least one example by Ahmadi et al. (2003) in the dorsal horn of the spinal cord. Meanwhile, the discovery of the "glycine site" and the fact that it is also activated by D-serine had attracted a lot of interest in pharmaceutical laboratories, and the site was promoted as crucial in diseases as varied as stroke and schizophrenia. To date, no breakthrough seems to have occurred but this has been the case with all the studies on drugs acting on the NMDA receptors, and it may indicate that these receptors are actually too important and too widespread to constitute a good pharmaceutical target.

Postdocs or Graduate Students?

The Laboratoire de Neurobiologie had been created in a limited space, the ninth floor of the building, and all members of the lab had agreed that, if they felt that they needed to expand, they had to find another institution. For me, it meant that I would not have more than one setup and thus would not take more than one postdoc or one graduate student every year. Choosing postdocs or graduate students was therefore a difficult decision. I took my first graduate student—Alain Marty—soon after my arrival at ENS. My second graduate student was Dominique Chesnoy-Marchais, who was introduced to electrophysiology by Alain Marty during my year in London and with whom I later studied a series of slow inhibitions induced by various transmitters in *Aplysia* neurons (Ascher and Chesnoy-Marchais, 1982; Chesnoy-Marchais and Ascher, 1982). We were intrigued by the fact that the responses were not independent and seemed to involve a common element. We failed to identify this element, however, which was later shown to be a G-protein (Sasaki and Sato, 1987).

In the following years, I felt that I could not give graduate students all the attention that they needed, and I relied mostly on postdocs or on colleagues from abroad who were on sabbatical. I have already mentioned the first postdocs, Diana Kunze, Tim Neild, Jon Johnson, and Linda Nowak. They were followed by William Sather, who arrived in 1988 and stayed for two years. It was Bill who discovered that if one keeps the suction on while pulling an outside-out patch, the nucleus of the cell often remains at the tip of the pipette, leading to the formation of what we called a "nuclear patch." This configuration has the basic advantages of an outside-out patch but a much larger surface, allowing for much larger currents. Bill and I used it to analyze the kinetics of NMDA receptors; we were joined by John MacDonald and Graeme Henderson, both on sabbatical leave, and Stéphane Dieudonné, a graduate student (Sather et al., 1990, 1992; Henderson et al., 1990). Another memorable postdoc was Ralf Schneggenburger, who made the very curious observation that the multiple states of NMDA receptor channel openings did not have the same reversal potential. With help from Stéphane Dieudonné, we managed to explain this by a model in which gating is coupled with permeation (Schneggenburger and Ascher, 1997), an idea that Alain Marty and Dominique Chesnoy-Marchais had developed earlier (Marchais and Marty, 1979) but that now gained much greater strength.

In 1992, having been criticized by various committees for not taking enough graduate students, I decided to comply with their recommendations by enrolling not one but two graduate students the same year: Pierre Paoletti and Stéphane Dieudonné. I was violating my own rules, but both turned out to be excellent choices.

I proposed to Pierre Paoletti that we continue the study of internal Cl^- regulation, but this objective was soon forgotten when, during manipulations aimed at changing the internal Cl^-, we concluded that the effects we observed were due to changes in volume. From there, we went to experiments that showed that NMDA receptors are sensitive to mechanical deformations (Paoletti and Ascher, 1994). We then began a collaboration with Jacques Neyton, a former Gerschenfeld student who had done a postdoc with Chris Miller at Brandeis University and, while there, had acquired a deep understanding of the structures and models of ionic channels. Jacques Neyton had decided that it was time for us to take advantage of site-directed mutagenesis to analyze the NMDA receptors. He rapidly trained himself in molecular biology, brought Xenopus to the lab, and very soon he made us enter the modern era of channel research. Pierre and I, and later Jürgen Kupper, joined him in the experiments that led us to characterize the binding site of internal Mg^{2+}, various modulatory sites of external Mg^{2+}, and finally the binding site of Zn^{2+} (Paoletti et al., 1995; Kupper et al., 1996; Paoletti et al., 1997). Since that time, Pierre has vigorously developed this line.

When Stéphane Dieudonné entered the lab, he joined us in our attempts at modeling the kinetics of NMDA receptors and was of great help. I would have been happy if he had continued in this direction, but he soon told me that he was more interested in synapses and networks than in channels, and he made a strong case for developing this line of research. I could not resist his arguments, which were those of a true physiologist. He very rapidly learned from Alain Marty and Isabel Llano how to prepare cerebellar slices and went on with this preparation. He has built his group along this line, has recently developed a very original fast scanning two-photon microscope that allows him to combine electrophysiology, imaging, and optogenetics, and he is also applying his mathematical virtuosity to the modeling of networks.

My last postdoc was Mariano Casado. He had become familiar with NMDA receptors during his first postdoc with Juan Lerma in Madrid. He joined me in 1995, and our first series of experiments was a follow-up of the work that I had done with Pierre Paoletti on the mechano-sensitivity of NMDA receptors. We tested the effects on NMDA receptors of molecules (arachidonic acid, lysophospholipids) that are assumed to induce a change in the curvature of the lipid bilayer and to produce a mechanical deformation of the embedded proteins. We did indeed observe effects that were compatible with this hypothesis (Casado and Ascher, 1998). We could have continued the biophysical study of mechano-sensitivity, which is still not understood at the molecular level. But such a search would have been more exciting if we had evidence for this sensitivity's physiological role . I had tried to show that it was involved in the chemotropic turning of growth cones induced by glutamate (Zheng et al., 1996). This was not successful but opened my views on the possible role of presynaptic NMDA receptors and made me more receptive to Mariano's suggestion to study presynaptic NMDA receptors. Mariano had been intrigued by the fact that, in the cerebellar granule cells, NMDA receptors containing a particular subunit (NR2C) are very abundant but do not seem to contribute much to the post synaptic currents. He wondered whether they could be presynaptic. The hypothesis is wrong, but it was believable, and Stéphane Dieudonné and I joined Mariano to test it. Soon we were very excited by the observation that, in rats aged 15–20 days, NMDA induced a depression of the synaptic current elicited in Purkinje neurons by stimulating the parallel fibers, and because the Purkinje cells have no NMDA receptors at this age, the effects were best explained by presynaptic NMDA receptors (Casado et al., 2000). It was difficult to convince editors and referees of this interpretation, but we carried on; in the next step, Mariano made me violate my vows about never working on the process known as long-term potentiation (LTP) and long-term depression (LTD). In fact, the last paper that I signed before leaving the ENS was one attributing cerebellar LTD to presynaptic NMDA receptors on the parallel fibers (Casado et al., 2002). After my departure, Mariano continued along this line, and I think that he is close to breaking the last resistance to our initial claim.

Pierre Paoletti, Jacques Neyton, Stéphane Dieudonné, and Mariano Casado remained at the ENS when I left. Although the Laboratoire de Neurobiologie later dissolved into a larger Institut de Biologie, they have helped make this institute particularly noteworthy in the field of neuroscience, in France and abroad.

Creation of the Department of Biology at the Ecole Normale Supérieure

When I arrived at the ENS in 1970, I had fond memories of my student years there, even if I had not enjoyed the dominance of biology by zoologists, botanists, and geologists. By 1970, some biochemistry had been introduced by a small group working on insect pheromones, but molecular biology, cell biology, and physiology were still absent. Much as in the 1950s, the students (the number of which had been substantially increased) were still invited to train in "natural sciences," and to concentrate on the subjects required to teach biology and geology in high school.

For the first ten years, I had no legal existence. My laboratory was at the ENS, but I taught at the Université Paris 6, which paid my salary. I was not given a key for entering the ENS building at night, the lab had no mailbox, and we had to get our mail through the secretary of the zoology laboratory. Everything changed in 1981, when the ENS got a new director, the mathematician Georges Poitou, who decided that the time had come for renovating the biology department. He set up a committee to analyze the state of affairs. The president of this committee, François Jacob, soon produced a scathing report on the occupation of the various floors and recommended calling for new groups. Then a search committee, presided over by Jean-Pierre Changeux, started recruiting these groups. The biology department was formally created in 1987. Its first director was Pierre Joliot, a professor at the Collège de France whose laboratory was at the nearby Institut de Biologie Physico-chimique. Pierre Joliot was not a former student of the ENS and had always been a severe critic of the "self-satisfaction" and pretense of ENS students and former students. Georges Poitou convinced him that becoming the director of the department was a unique opportunity to correct the defects that he had denounced. In a few years, the building filled itself with a series of small and dynamic groups, most of which were not directed by former ENS students—a novelty! Among these groups there were a significant number of neurobiologists like Patrick Charnay, Alain Prochiantz, and Antoine Triller.

When, in 1991, I was asked to succeed Pierre Joliot, I did not hesitate long. I knew that accepting would not increase my scientific productivity, but I felt that I owed Georges Poitou a debt of gratitude for all that he had done—not only his renovation of the biology department but also his other accomplishments. In 1985, he had succeeded in fusing the old all-male ENS

with the "ENS de jeunes filles." He also introduced the cognitive sciences at the ENS, which were later to become a full department. By the time he died, in 1989, the department of biology had been strikingly transformed. A solid international scientific council had kindly but firmly insisted on reallocating space among the groups and was starting a new wave of recruitments. We had introduced major changes in the curriculum by organizing undergraduate teaching at the local level, allowing the most motivated students from the university to join the students of ENS in programs that involved lab internships, and by "outsourcing" the students' preparation for the high school teaching certificate (the *agrégation*).

The physicist Etienne Guyon, who succeeded Georges Poitou as head of the ENS, followed the path that Poitou had charted. He had to deal with the complex attitude of Claude Allègre, who became minister of education and research in 1997. Claude Allègre was ambivalent about the ENS; he recognized that it was an elite institution, but in the socialist lexicon, "elitist" was a derogatory term. He also thought that the ENS was too Parisian, and "decentralization" was the new fashion. I had difficult negotiations with him on the graduate fellowships for the students of ENS. He wanted the students to disperse all over France so as to "irrigate" all French universities. The students, meanwhile, wanted to go to the best labs, many of which were in Paris. Claude Allègre was quite the bully, but in the end, he gave me most of what I had asked for.

Les Saints Pères

By 2003, Jacsue and I were reaching official retirement age. We decided to leave the ENS to join Alain Marty at the Centre Universitaire des Saints Pères of the Université Paris Descartes. Alain Marty had left the ENS in 1994 to join Erwin Neher at the Max Planck Institute in Göttingen. In 2000, he decided to return to France. He knew that his funding would be less comfortable in France than in Germany—although he had not realized that "less" meant one order of magnitude less. He also knew that the Centre des Saints Pères, in which he was offered space, had a checkered history.

The huge building was built in 1953 and has 36,000 m^2 of labs and lecture halls plus an equivalent surface of extraordinarily wide corridors designed to allow for the rapid evacuation of a few thousand students in a minimum amount of time. The building was destined to host the students applying to the medical school (which number in thousands), as well as research laboratories. In 1958, a new statute, initiated by Robert Debré, introduced the notion that professors teaching in medical schools could become full-time employees with a triple duty (clinical practice, teaching, and research). In 1960, a decree indicated that those satisfying the three requirements would receive a dual salary: one for clinical work, the other for teaching and research. This was a clever way to evade the French law under

which the salary is independent of the field of research inside a university; philosophers are paid at the same level as computer scientists, and we have no football coaches. The special statute of medical school professors created jealousy among members of other disciplines but probably limited the flow out of academia of many clinicians.

The new statute encouraged medical school professors to do research, but it implied that the university had to provide them with laboratory space. In Paris, the Centre des Saints Pères was seen as providing this space. However, the center had no place for patients, and the most active researchers soon found that it was more practical for them to do research in the hospitals where they were seeing their patients. After a few years, the center became a strange place where most of the laboratory space was silent but not completely empty (because professors without much research activity jealously held onto the space that they had been allocated). The situation remained stagnant until the mid-1990s, when a group of chemists who had arrived in 1972 decided to transform the building into a proper center for scientific research. They encountered relatively little resistance, and in a few years, the building began taking on a new life. One advantage it had over the ENS was its much larger surface (nearly 10 times more), which meant that Alain Marty was given a reasonably large space. He offered a large room to Jacsue and me.

The main theme of Alain Marty's lab is the study of cerebellar organization. Initially, I decided to participate in this topic and tried to support the hypothesis that the glycine released by glycinergic neurons could potentiate the NMDA response of a neighboring glutamatergic synapse. The cerebellum offered such a possibility at the convergence between Golgi cells and mossy fibers on the granule cells. I had not succeeded in convincing Stéphane Dieudonné to conduct this experiment, and I was not successful in showing the expected result (although I still think that the hypothesis may be correct). I then met Boris Lamotte d'Incamps, whom I had known as a student at the ENS in the 1970s and who, directed by Daniel Zytnicki, was working on the spinal cord in the neighboring laboratory. I thought that the glycine-NMDA interaction also could be studied in the spinal cord and asked him to introduce me to this difficult preparation. After unsuccessful attempts on the intact spinal cord of newborn rats and mice, we started making slices. Then two papers appeared describing the co-release of ACh and glutamate by the motoneurons at the motoneuron-Renshaw cell synapse (Mentis et al., 2005; Nishimaru et al., 2005). I convinced Boris to join me in the study of this synapse, and we have not left it since then because we are convinced that it is, and will remain for some time, one of the few central nicotinic synapses that can be studied with the same level of refinement as that used for glutamatergic or GABAergic central synapses (Lamotte d'Incamps and Ascher, 2008; Lamotte d'Incamps et al., 2012). We hope to understand the significance of the presence on Renshaw cells of a

bewildering variety of nicotinic receptors, as well as the functional role of the co-release of ACh and glutamate by the motoneurons.

Starting a French MD-PhD program

When I arrived at the Saints Pères, the director of the center, Jean-Claude Chottard, was ending his mandate. I had first met Jean-Claude in 1968. He was an exceptional teacher of chemistry, which he taught to medical students at the Saints Pères, but I had also invited him to teach it to the biology students of the ENS. In the early 1970s, he had made an early attempt at improving the training of medical students by adding science courses to their curriculum. (In France, students enter medical school after receiving only one year of basic science courses.) At about the same time, the ENS started recruiting two or three students each year in an embryonic MD-PhD program. Despite the fact that this recruitment was open to students from all French universities, the students prepared at the Saints Pères formed a large fraction of the successful recruits. I had been in charge of the MD-PhD students at the ENS from 1975 to 2003, and it had been an exciting experience because they were extremely bright and motivated. The experience had also been extremely frustrating because many deans of the Parisian medical schools showed indifference, if not hostility, to the students' efforts to obtain a dual training.

In 2003, Christian Bréchot, the director of Institut National de la Santé et de la Recherche Médicale (INSERM, which is to the CNRS what National Institutes of Health is to National Science Foundation), decided to start a nationwide program reinforcing the scientific background of medical students interested in research. Christian Bréchot had noticed that among the candidates recruited at INSERM for full-time research positions, the proportion of those with a medical degree had fallen from 30 percent in the 1980s to less than 6 percent in 2001. His analysis of this trend suggested that one factor was a lack of science training in the medical curriculum. He asked Jean-Claude Chottard and me to participate in his project, which resembled what we had tried to accomplish with moderate success until then. In the following months, we saw with admiration how he developed his project, negotiated with the deans, and then convinced the Schueller-Bettencourt Foundation to lend financial support. The program, called Ecole de l'Inserm Liliane Bettencourt, has recruited about 20 students a year for the last 11 years, and some of the students who completed the curriculum are now starting their own research. As it happens, many of the students in the program have chosen neuroscience as their major, and I have been accused of letting my own preferences influence the students' choice of orientation. I usually reply that, if students prefer neuroscience over the other disciplines, it is simply because in addition to having all the interesting aspects of other sciences, it also deals with problems that are of interest to non-scientists. And so it makes for better conversation starters and makes it easier to flirt.

Teaching in France and Abroad

When I left the CNRS for a university position in 1969, my teaching load was three lectures a week. I taught physiology and later biophysics and pharmacology; but with age, I was given the privilege of specializing in neuroscience. I taught large classes and small ones and enjoyed both. I did not mind adding a few other teaching experiences. The most exhilarating ones were the courses at Cold Spring Harbor on techniques in electrophysiology in which I participated for a few years with Jacsue Kehoe and a number of friends. The students were impressive in their motivation, the depth of their questions, and in the speed at which they mastered the techniques we were presenting them. This extraordinarily stimulating environment—plus the beauty of the surroundings—made us feel that we were living in another world. Our children spent the summers with us and enjoyed them immensely. I often think that these summers played a major role in their decision to pursue their studies in the United States.

After I retired, I accepted the invitation of John Nicholls and Jack McMahan to participate in a few of the neurobiology courses that they organize each year in various countries with support from the International Brain Organization (IBRO). I accompanied them to Uganda, Jordan, China, and Cameroon. This was a very interesting experience and was probably the ultimate contrast with the Cold Spring Harbor courses in terms of the working conditions, which were often quite primitive, but similar in terms of the students' intense engagement.

My memories of teaching, however, are colored more darkly by the period following the arrival of the socialist government in 1981. In 1982, the new government decided to increase the teaching load of all university staff, nearly doubling it. This was based on reports showing that many professors did very little research beyond their three lectures a week. The new rule allowed universities to avoid recruiting new faculty despite the increase in student enrollment. But for those who were doing research, teaching became exhausting and running experiments became difficult. This increased the advantages of those who were full-time investigators in the CNRS or the INSERM. Entering these organisms became the Holy Grail for all the top PhDs, and the universities were unable to recruit the most active researchers.

In addition to this, the government drafted a law that would entrench and amplify what I had long considered a major weakness of our university system, namely the fact that there is no entrance selection for the university. Any student who has obtained a baccalaureate can enroll. This had not been too bad when the baccalaureate was only granted to a small fraction of the high school students but became dramatic when the number of students with a baccalaureate increased enormously. Universities were inundated with students and found themselves unable to react. The best students started abandoning the universities to enter "selective" institutions such as medical schools and engineering school. In the undergraduate courses that

I taught, I soon had difficulties introducing the Nernst equation because students did not know or remember what a logarithm was.

For many years, vigorous criticism about the absence of entrance selection at French universities had been made by Laurent Schwartz, who was to become one of my most influential mentors. He was a mathematician who had earned a Fields medal in 1950, and he was famous among the students not only as an extraordinary teacher but also as a political activist. During the Algerian war of independence, his support of a negotiated settlement had made him a target of the Organisation de l'Armée Secrète (OAS), a French terrorist organization; as a student, I had spent a few nights standing guard at his home to prevent a possible bombing. Laurent had been successful in defending Russian mathematicians against persecution and also in reorganizing the science curriculum at the famed Ecole Polytechnique. In other words, this was someone who had succeeded in most of his enterprises. In 1981, he thought that his leftist credentials would give him some political clout. But when he saw that his recommendations were ignored, he started an organization called Qualité de la Science Française, which I joined as one of his lieutenants, and we tried to stop the passage of the new law.

We lost. This was the only battle that Laurent Schwartz ever lost. In the years that followed (until his death in 2002), he would say that he had seen the end of Nazism, the end of apartheid in South Africa, the end of the Berlin Wall, but I would not see the introduction of entrance selection into French universities."

If I mention this fight here it is because I think that the weakness of our university system darkens the future of neuroscience in France by reducing the number of adequately trained students. The students of the MD–PhD programs are extraordinary, full of questions and curiosity, but very few will actually go into research. The engineering school students are very bright and wonderfully prepared to conduct experiments, but they are discouraged by the difference between the salaries they can expect in academia and those that are offered elsewhere. The students of the Ecoles Normales Supérieures (there are three in France) are well prepared and less afraid of low salaries, but there are too few of them to match the country's research needs. And in the universities, the students with high potential do not receive the training that they deserve because they are buried in the (average student) majority. Yet we know that the future of neuroscience depends on students who not only have broad experience in biology but who are not afraid of computational modeling, optics, and structural biology—to note only a few techniques requiring significant knowledge of the "hard" sciences.

The Uncertain Future of French Neuroscience

I entered the field of neuroscience in a country still reeling from the war, with very few figures who inspired respect or who could give us advice. Yet once we had defined our own field, we met few obstacles. There was

an enthusiasm for the development of science in the country and in the government. New positions opened every year. We felt confident that all those who were deserving and who were imaginative would make it. In addition, a number of the previous system's defects were progressively corrected. The excessive power of the "mandarins," the professors at the top of the old system, was severely reduced, if not abolished, after 1968. To start an independent team was difficult, but the development of research centers outside Paris ("decentralization") offered new opportunities to those in search of independence. There was no system of post-doctoral fellowships, but this forced students to go abroad, learn English, and to discover other ways of organizing research. At the Institut Marey, where I began my research, English was the common language of exchange and of publication, but this was an exception in France. In the early 1960s, attendance at an international meeting was only reimbursed by the CNRS if you promised to deliver your communication in French. Angélique Arvanitaki refused to use the word "ionic channel" because it was an "Anglo-Saxon" expression. Michel Jouvet insisted on publishing his main observations in French. This chauvinism slowly disappeared. This year, a law allowing lectures in English in graduate courses encountered vigorous obstruction in parliament but was finally passed, and this may help France attract more foreign students.

Thus, for many years, I felt that French science was catching up and progressively eliminating the handicaps inherited from the war and from obsolete structures. But more recently, I have begun to feel that the changes we managed to implement were not commensurate with the simultaneous changes in the way that science, and in particular biology, is pursued. I already mentioned the problem of the training of science and medical students. Another problem is that budgets have not kept up with the increase in the cost of research and its tools. In the 1990s, when I joined the scientific boards of a few Max Planck Institutes and read not only the scientific reports but also the financial documents, I was appalled by the difference with our support at ENS, which was considered a privileged institution in France. And finally, there are problems in the way that funding is organized. When I considered bringing some former ENS students back from the United States (such as Catherine Dulac, Emmanuel Mignot, Daphné Bavelier and Alexandre Pouget), I found that French institutions lacked the tools required for such repatriations. We could not offer starting grants, positions for collaborators and postdocs, or decent salaries. Very recently, France introduced competitive individual grants and post-doctoral fellowships, a move that we would have welcomed in prior years. But in a context of restrictions, this has only meant a further and dramatic reduction of the basic recurrent support.

It is probably too early to conclude that France is sliding back. Year after year, we still produce people who are bright and well-trained, and some of them will have the courage to pursue a career in research. Both the CNRS and the INSERM have been stripped of much of their capacity to define their own policies and their long-term strategies, but they have successfully

resisted elimination attempts and could well recover their strength. The recent emergence of the European Research Council has raised new hopes. Thus I fluctuate in my predictions. Some mornings, as I roam through the first floor of the Saints Pères looking in vain for a functional elevator, among thousands of students (most of whom have no hope of entering the medical curriculum given their high school record and should have been told so), I decide that we are definitely going downhill; but in the afternoon, a discussion with a bright and enthusiastic student can still trigger optimism. Let us hope this optimism will prove justified.

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