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Photo by Luis Delfin, Quo, Mexico

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*Pablo Rudomin has carried out fundamental neurophysiological work on the functional organization of the spinal cord. His major contributions have centered on the mechanisms and pathways involved in the presynaptic control of the synaptic efficacy of sensory fibers. These studies have demonstrated that the intraspinal terminals of the sensory fibers are not hard-wired routes that send divergent excitation to spinal neurons but are instead dynamic pathways that can be centrally controlled to address information to selected neuronal targets.*

# Pablo Rudomin

## Introduction

When I was invited by Larry Squire to write my scientific autobiography, I hesitated because it was not just a matter of presenting a perspective of the research I have done throughout the years. Although science is universal, we scientists live in specific countries and are products of the circumstances that surround us. It is not the same to be a scientist in the United States or in Europe as to be a scientist in a country where science is not yet a tradition. For those who live in countries such as Mexico, the challenge has been, and still is, to create the material and social conditions required to have an active and productive system of science and technology. In Mexico, this process started not long ago and was headed by a small group of scientists and physicians who founded the institutions where many of my generation could work.

Although many of us benefited from their efforts, there is no such thing as a free lunch. We inherited the responsibility of doing the best science we could. This was not a matter of just having good working conditions. It was also the responsibility of training students, contributing to the formation of new investigators, and of developing the strategies to convince society and government that science and technology should be considered as a national priority. It was also the continuous and everlasting struggle against local indolence and bureaucracy.

Writing this text has been a journey to the past and an occasion to examine my scientific and personal endeavors under the perspective that one acquires with experience. What is clear to me is that all my contributions have been “me and my circumstances” as Ortega y Gasset used to say. It has been me and my origins, me and my family, me and my friends, me and my colleagues, and, of course, me and Mexico.

Seen in retrospective, for me to do science in Mexico has been a wonderful experience, despite all the drawbacks. It has been very rewarding to know that besides some scientific achievements, I could modestly contribute to the development of science. To quote Newton: “I was like a boy playing on the sea-shore, and diverting myself now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.” That is the way I feel. Science has been to me an enjoyable game that even now I like to play.

These are fascinating times to be in science—new findings and new discoveries every day. Yet, as time passes, I am more and more concerned

about our social inability to use the available knowledge to construct a free and peaceful world without racism and poverty.

## My Origins

I came from a Jewish family of immigrants. My father, Isaac, was born in 1896 in Smorgon, a small town, at that time part of Russia, and of Poland between World Wars I and II. He was from a rather poor family who migrated to the United States in the early 1920s, after the Soviet revolution. It was never clear to me how his parents, brothers, and sisters could enter the United States and why he, being the youngest in the family, went to Mexico where he stayed for a couple of years. He moved to New York around 1926–1927 where he remained until 1929, the height of the Great Depression. Back in Mexico, he worked as a peddler traveling around the country, selling the merchandise he could carry in a small suitcase. Later on, he settled in Mexico City and started a small business buying and selling metal junk.

The family of my mother, Sonia, arrived in Mexico in the mid-1920s. She was born in 1915 in Proskurov, Ukraine. Her mother, Rivka Barzaj came from a wealthy family that lost everything during the Soviet revolution. She was married to my grandfather Moses Zevnovaty, who soon after the wedding was drafted into the tsar's army and went to the front during World War I. He was caught and imprisoned somewhere in the Austrian-Hungarian camps where he remained until the end of the war. At that time, my mother was four years old.

Somehow, the family learned that Grandfather Moses was still alive, and my Grandmother Rivka traveled alone through devastated camps and cities until she found him. Apparently, it was necessary to pay for his release. He was a handsome man. Family stories relate that, while a prisoner, he was sent to take care of the gardens of a Hungarian duchess. She would not let him go when the war was over so, when my grandmother came, both escaped in the middle of the night, being chased by the servants. Back in Ukraine, they survived the pogroms and the revolution and somehow were able to leave for Mexico around the early 1920s.

To them, life in Mexico City was rather difficult. To complement the family's low budget, Grandmother Rivka walked through the streets selling live fish that she carried in buckets filled with fresh water. Later on, my grandfather got a job on one of the first tomato farms in Tamazula, Sinaloa. They stayed there some time until they moved to Guadalajara, where they opened a shoe store. By then, my mother was 17 years old. My grandparents had some friends in Mexico City, and they invited my mother to visit them. This is when she met my father. They soon married and settled in Mexico City. It must have been around 1933. I was born in June 1934.

## My First Years

I have vague memories of my first years at primary school. I have an image of myself as a shy boy, not very good at sports. When I turned 13 years old, I entered secondary school. One my teachers, Gilberto Hernández Corzo, introduced me to Oparin and his theories on the origin of life. The other, Luis O. Batres, was the first to talk of evolution and natural selection. He gave me some books to read. One was *Microbe Hunters* by Paul de Kruif, where he tells the stories of Leeuwenhoek, Spallanzani, Pasteur, Koch, Metchnikoff, and Ehrlich, among others. The other book was *Heroes of Civilization*. I believe it was written by José Rebolledo. This book described the life of Gutenberg, Columbus, Galileo, Franklin, and others that I do not remember now. What I do remember is that these readings had a great impact on me. I wanted to be a scientist even though I was not fully aware of what this meant in real life.

At that time, I discovered Verne and Dumas and was fascinated by their novels. I read most of them. It was also then that I learned about Galileo and Giordano Bruno and their problems with the Inquisition. What impressed me most was the reluctance (and even opposition) of the Church to accept the new concepts emerging from science. It was the search for knowledge that motivated me. I wanted to know. I wanted to learn. I had too many questions to ask and few answers. Because I came from a non-religious family, faith dogmas were unable to provide me the answers I was looking for.

In 1949, I left the secondary school and went to study at the Escuela Nacional Preparatoria of the National University. This was a new and exciting world. I made good friends and was exposed to a new and exciting environment. There was one, René Villanueva, whom I still remember with great affection. At home, my exposure to music was very limited—at most, Tchaikovsky and Chopin. René introduced me to Bach, Beethoven, Schubert, and Mozart. He later became the director of a well-known group of folk musicians. It was also a time of intense reading: Tolstoy, Dostoyevsky, Chekov, Gogol, Andreyev, Balzac, Victor Hugo, Dumas, Rolland, Istrati, Hess, and Gorki, and also the beginning of my awareness of social problems. I read Marx and Engels as well as Hegel and Kant.

## My First Steps in Science

When I entered the National Preparatory, I wanted to be a chemist. At home, my father allowed me to have a small laboratory, where I tried, together with Marcos Rosenbaum, a good friend of mine, to repeat some of the experiments that we learned about at school. It was mostly a game, but it was fun and quite motivating.

I had wonderful teachers such as Esteban Minor in mathematics, Antonio Ramírez-Laguna in biology, and Salvador Mosqueira in physics, all of whom I remember with gratitude and affection. It was at that time when

G. Hernández Corzo, with whom I kept in contact since I left secondary school, invited me to visit the research laboratories at the National School of Biological Sciences of the National Polytechnic Institute.

He was teaching there, and his brother Rodolfo was the director of the whole institute. I was captivated because I saw, for the first time, active laboratories and scientists who took their time to explain to me, a young inexperienced student, what they were doing. I learned that a fair number of the teachers were Spanish scientists who were able to escape from the civil war and settle in Mexico. It did not take me long to decide that this was a good place to study. And so it was.

I still remember some of my teachers with pleasure and gratitude. There were only a few students in the group, so we could really interact with all of them. I believe that this interaction, and knowing firsthand the research that some of them were doing, greatly contributed to my decision to become a scientist.

In 1952, I attended the physiology course given by Ramón Alvarez-Buylla. At the end of the course, he invited me to join his laboratory. He was around 33 years old at that time. He had come to Mexico from the Soviet Union where he had gone at the beginning of the Spanish civil war. He was a student of Pyotr Kuzmich Anokhin, himself a student of Ivan Petrovich Pavlov. During his stay with Anokhin, and later on in Mexico, he had made substantial contributions to understanding the information conveyed by single vagal chemo- and baroreceptor afferents.

When I joined his laboratory, he suggested that we should use the conditioned reflex as a tool to disclose which of the effects of a hormone were due to its direct action on the effectors and which resulted from activation of reflex pathways. We expected that effects mediated through a reflex action would be conditioned, while effects due to a direct action on effectors would not.

I started with adrenaline, Mauricio Russek with cyanide, and Juan Carrasco Zanini with insulin. The experiment I was to perform was relatively simple: to place a dog in a sound-isolated chamber and inject a small dose of intravenous adrenaline through a catheter while ringing a bell. After many of these trials, we would ring the bell without injecting adrenaline. As expected, we were unable to condition the increase in heart rate and blood pressure or the increase in blood sugar that was produced by the systemic injection of adrenaline. This was consistent with the well-known direct actions of this amine on the effectors. Quite surprisingly, we were also unable to condition the reflex bradycardia produced by the increased activation of the vagal baroreceptors that followed the rise in blood pressure, but we were able to condition the increase of glucose in the urine (glucosuria), even though there were no changes in glucose concentration in the blood. Later on, we found that conditioned glucosuria could not be produced in animals with chronically denervated kidneys and concluded that this effect

was mediated by reflex pathways that controlled tubular reabsorption of glucose. One pending issue was to disclose the afferent and efferent pathways involved in this reflex.

These studies led to my first paper, which was published in *Acta Physiologica Latinoamericana* (Rudomin, 1957). Since then, I have not followed the literature on nervous control of renal functions. The role of renal nerves on the regulation of glucose handling and other organic and inorganic solutes was questioned after observations that transplanted kidneys regulated glucose, sodium, and potassium adequately before renal reinnervation was achieved. However, direct assessment of the effect of splanchnicotomy on renal handling of glucose in dogs showed a decrement of tubular reabsorption with a consequent increased glucosuria (Szalay et al., 1977). Also, bilateral renal denervation in diabetic rats increased urinary glucose and reduced the content of the glucose transporter GLUT-1, indicating a role of renal nerves on the regulation of tubular glucose transport (D'Agord et al., 2003). It thus seems that, after all, the nervous control of the tubular reabsorption of glucose plays a role in the homeostasis of blood sugar level.

## My First Job

I earned my degree in biology by August 1956 and felt I should contribute to the house income. At home, they were not really eager for me to become a scientist. Jobs were scarce, and salaries were really low. Despite being a good student, I could not get a position as a research assistant in Alvarez-Buylla's laboratory or a teaching position at the school. The dream of my father was that I should study mechanical engineering and help him in his business. But I wanted to keep with science.

Finally we reached an agreement. Within the next year, I would look for a job in science. If I could not find it, I would then study mechanical engineering as my father wished and also help him in his business. A good friend of mine told me that Juan García Ramos, then working at the Institute of Neumology, was looking for somebody to help him with the experiments. García Ramos was a former disciple and collaborator of Arturo Rosenblueth. I went to see him, and I was hired as his assistant. The salary was more symbolic than real but was my first paid job.

With García Ramos, I studied the dynamics of pulmonary circulation. We used oxymetry to measure the effects of vagal stimulation and systemic adrenaline and acetylcholine on the oxygen concentration in the blood circulating through the carotid artery. In cats under constant ventilation, we found that the nervous system was able to regulate the number of alveolar capillaries involved in gaseous exchange. We also provided evidence for a direct vasodilator action of anoxia on the pulmonary capillaries, in opposition to the usual view of a vasoconstrictor action. The work I did

with García Ramos was published in 1957 and 1958 in *Acta Physiologica Latinoamericana* (García-Ramos and Rudomin, 1957, 1958).

## At the National Institute of Cardiology

After one year or so, García Ramos was leaving the Institute of Neumology to work at the department of physiology in the medical school of the National University. Because he had no way to find a position for me, he asked me if I would be interested in working in the department of physiology of the National Institute of Cardiology, headed by Arturo Rosenblueth.

I could not believe it. Rosenblueth was the most famous Mexican physiologist, and he had spent many years at Harvard working with Walter B Cannon and was a good friend of Norbert Wiener, with whom he had published a series of seminal papers. As a student of Alvarez-Buylla and as an assistant of García Ramos, I had attended Rosenblueth's lectures at El Colegio Nacional, the Mexican equivalent of the College of France. His lectures were really interesting, and I was impressed by his clarity of exposition.

So I went to see him. I still remember how nervous I was. I feared that he would soon discover the many things I did not know that I was supposed to know. And I told him about these concerns. He just smiled and assured me that I should not worry because I would not be alone but would work together with a more experienced investigator. We agreed that I would start to work on January 16, 1957.

We lived relatively close to the Institute of Cardiology, so on the morning of January 16, I walked to the institute. I was so happy! By noon, I went back home for lunch. Quite unusually, my father was there. He did not feel well, so I called the cardiologist. He came, took an electrocardiogram (EKG), and told me not to worry. He prescribed some medicines that I bought and gave him and went back to the laboratory. One hour later a neighbor called and told me I should come home immediately because something terrible happened. I hurried but it was too late. My father had passed away. He was alone with Malka, my 13-year-old sister. At that time, he was 62 years old.

While I am writing this, I still remember the sense of guilt I had for not having been there and perhaps having a chance to save him. My mother was in my father's shop and soon came. There was a sense of despair and impotency.

Soon after, the question was raised as to who should take care of my father's business. My mother, then 42 years old, used to help him, but this was not a place for a young woman. I learned that we lived day by day. My father had no life insurance and left no savings but also no debts. There was a family reunion, and they expected that I should help my mother at the shop. But to keep up with science was my dream, and I was not ready to give it up, precisely when I was just starting to work under Rosenblueth's guidance!

I reasoned that the salary that I was about to earn would allow us to survive. We could pay the rent and buy food, and this would give us time to find an alternative solution. In the meantime, my grandfather, then 67 years old, agreed to help my mother. A few weeks later, Ilana, my oldest sister and her husband Zvi, came from Israel, where they were living. My brother-in-law agreed to work at the shop, so I could stay with science. Nevertheless, I felt guilty. I believe that this feeling contributed to my commitment to science throughout all these years, perhaps to convince myself that this was the right decision.

I worked in Rosenbluth's department for two and a half years. These were the days when open-heart surgery was beginning. Ernesto Deutsch and I were asked to examine the effects of successive periods of hypoxia on the excitability of the heart muscle and on the blood pressure-controlling mechanisms. We expected that this information could be of some use to the heart surgeons. In the normal animal, hypoxia increases blood pressure. We found that this response was reduced with successive episodes of hypoxia and eventually resulted in a blood pressure fall, even though the animal had recovered its control blood pressure. At the same time, the cardiac cycle was lengthened because of increased vagal activity. The auricular and auricular-ventricular conduction velocity was reduced, and the threshold of the cardiac muscle to direct activation was increased. Perhaps the most interesting feature of this work was the demonstration of cumulative changes in vasomotor control that gradually impaired the dynamic response to hypoxia. It was clear that the initial state of the system was a factor that determined the subsequent response of the system to situations that endangered its integrity (Rudomin and Deutsch, 1958).

With David Erlj and Peter Eberstadt, I examined the effects of hypoxia and of hypoventilation on the cardio inhibitory reflexes (Rudomin et al., 1959). We found that these procedures increased the reflex slowing of the heart (bradycardia) that was produced by electrical stimulation of the depressor nerve. We concluded that this effect was mostly due to the activation of circulatory chemoreceptors, which facilitated impulse transmission along the cardio-inhibitory reflex pathway. Soon after, Rafael Rubio and I showed that the increase in reflex bradycardia produced by hypoxia resulted from a preferential activation of lung vagal chemoreceptors (Rudomin and Rubio, 1959).

These findings led to a series of studies on the influence of asphyxia and of some drugs known to activate lung, aortic, and carotid chemoreceptors on the bradycardia produced by stimulation of the depressor nerve and of the bulbar reticular formation (Rudomin, 1959a,b). I found that reflex bradycardia was more facilitated after injecting small amounts of cyanide and veratridine into the right auricle than into the left auricle, a finding suggesting a possible contribution of lung chemoreceptors. In contrast, lobeline and phenyl-guanidine, assumed preferentially activate carotid and aortic chemoreceptors, were unable to facilitate the cardio-inhibitory reflex. These observations indicated that lung chemoreceptors and aortic and

carotid chemoreceptors played different roles in the homeostatic control of blood pressure and heart rate.

Seen in retrospective, I still believe that these were original and interesting findings that contributed to understanding the role played by circulatory chemo- and baroreceptors in vasomotor control. Unfortunately, all these findings were barely referred to by researchers in the field, most likely because they were published in Spanish in a Latin American journal of rather limited circulation. At that time, my English was rather poor (even now), and I was not encouraged by my mentors to publish in internationally reputed journals, mostly because they were convinced that we, as Mexicans, should publish our best contributions in Latin American journals.

## Starting a Family

In November 1957, I married Flora Goldberg, and we are still together after 56 years! This was the best decision in my life.

Flora's parents were born in Poland at the beginning of the last century. Because of their political activism, they were jailed and later forced to leave Poland. They went to Belgium and afterward to Paris, where Flora was born in 1935. When the Germans invaded France, being non-citizens of Jewish origin, had no other alternative but to leave Paris and escape to Nice, still part of "free" France. This was not an easy journey. The family was divided. Flora traveled with her mother (Ruth) and her small brother (Juan). Flora's father (David), who had joined the French resistance, traveled alone, while Flora's sister (Juliana) traveled to Nice with some family friends to meet her father. Flora and her brother and mother went through different towns, sometimes taking trains and other times walking through the woods, always hiding from the Germans and their dogs. They all arrived safely at Nice.

At the beginning of 1942, Flora's family was able to get a visa to Cuba. They traveled to Marseille and from there to Casablanca, where they took a cargo ship heading to Havana. The ship was also carrying many Spanish Republicans as well as some Jewish refugees from Austria who were granted a visa as political refugees by Gilberto Bosques Saldívar. He was a Mexican career diplomat. As a consul in Marseille, Vichy France, Bosques took the initiative to rescue tens of thousands of Jews and Spanish Republican exiles from being deported to Nazi Germany or Spain. So it happened that the boat went first to Jamaica and then to Veracruz. Flora's parents were tired and were sick of the trip and tried to stay in Mexico. It turned out that the minister of internal affairs, Miguel Alemán, later on president of Mexico, came to greet the refugees, and Flora's father could talk to him. He managed to get permission so that the whole family could remain in Mexico. This was very fortunate because they learned later on that many refugees heading to Cuba were forced to return to Europe, even though they had visas to enter the country. To return to Europe in those days meant to be sent to the concentration camps.

Once in Mexico, Flora's family settled in Tulancingo, a small textile town. After a couple of years, they moved to Mexico City, where I met Flora. She was studying chemistry at the National University, but one day Diego Rivera, who was a good friend of her parents, visited them at home and saw her drawings. He told her that she had talent for art. After some thought, she decided to leave chemistry and went to work in Diego Rivera's studio and later on to study art in La Esmeralda. She kept with art and has become a well-known, outstanding artist.

We have two sons. Isaac was born in 1959. He got his PhD in computer sciences at the University of Pennsylvania in Philadelphia, returned to Mexico where he spent almost 20 years, and he now lives in Barcelona, working at the Supercomputing Center. Adrian was born in 1963 and studied at the University of Southern California (USC) to become a movie director. He has made several films and now lives in Los Angeles. He has two sons and one daughter: Diego now 21, Sofia, 12, and Sebastian, 9.

While writing this section, I could not resist including some lines about the family of Flora's mother. She was born in Warsaw in 1909 and was brought up in a very religious Hassidic family, and had six sisters and two brothers. When the Germans invaded Poland, Stephanie, her oldest sister, was able to escape to Russia. She returned with the Russian army, leading them to Warsaw through the woods and small paths she knew well. Sometime after the end of the war, she was appointed as the Polish ambassador to Indonesia. I met her in the 1980s during one of my visits to Warsaw. She lived in a rather small apartment with her husband and had one daughter, Irena, who was married, had two children and lived close by. I was impressed by Stephanie's disenchantment with the political situation. She told me that that this was not what she had fought for, and that she had sympathies for the solidarity movement of Walesa. She died not long ago, and she was buried in Warsaw with military honors.

There was another sister, Anna. She was a young, gifted violinist who remained in Warsaw during the war. She assisted Janusz Korczak in the ghetto. Years later, when Flora's mother visited Warsaw, she learned that some friends had offered her a way to get out of the ghetto, but she had refused and said that she would never leave the children. She stayed and was arrested by the Schutzstaffel (SS) together with Janusz and the 200 orphans. They were all taken to Treblinka where they were murdered in August 1942.

Two other sisters, Leah and Itte, and their families were able to escape to Russia and ended up in Siberia. When the war was over, they all returned to Poland. Sometime later, Leah and her family went to Israel. Flora's parents helped them come to Mexico where they arrived in the early 1950s. Itte's family stayed in Poland until the mid-1950s, when one of their two sons, Ludwig Margules, got involved in the student uprising against Russian control and was to be arrested. Somehow, Flora's parents were also able

to bring them all to Mexico. Over the years, Ludwig became a well-known theater director and received the National Prize of Arts in 2003. He died in 2006.

## My Stay at the Rockefeller Institute: Studies on Cortical Neurons

During the fall of 1956, just before I started to work at the Cardiological Institute, I had the opportunity to travel to New York to visit my father's family. I thought this could be a good occasion to visit some research centers. I was advised by García Ramos to visit the Rockefeller Institute, where he had spent some time working with Rafael Lorente de Nó. At that time, I was already aware of the work of David Lloyd on spinal reflexes, and I went to see him. I also visited Vernon Brooks who had just returned from Canberra where he was working with J. C. Eccles. He was very open and spent a fair amount of time explaining the research he was doing.

While in Rosenblueth's department, I did all my work recording blood pressure and heart rate changes, first with a kymograph and later with a Grass polygraph. I felt it was important for me to learn how to record the activity of single neurons in the mammalian brain so I could use those techniques for the analysis of the functional organization of the cardio-inhibitory reflexes.

I told Rosenblueth that I wanted to learn these techniques and that the best way to do it would be to spend some time in a laboratory where they were already using them. He agreed, and I wrote Brooks who suggested I should apply to the John Simon Guggenheim Foundation for a fellowship. To my surprise, my application was approved, even though I was just starting and I had published only eight papers. It was clear to me that Rosenblueth's support was crucial.

We were about to leave for New York when we found out that the U.S. Embassy in Mexico would not grant a visa to Flora. This was rather unexpected because in 1956 she had spent several months in a farm close to New York, being trained to work in a kibbutz in Israel, where she intended to live. She had returned to Mexico because her 16-year-old brother was killed in a motorcycle accident.

We went to the U.S. Embassy to inquire about the reasons for such a decision. Somehow Flora appeared in their lists as member of a leftist group, and there was no way to convince them that they had the wrong information. It probably did not help that her parents were involved in political activism and that she was a student of Diego Rivera.

My first reaction was to write to the Guggenheim Foundation to inquire if I could transfer my fellowship to some place in Europe. They said that this was not possible! Giving up the fellowship after all the plans we had made was really very disheartening. It happened that I knew the husband of my

mother's cousin, Jack Kranis, who was a city councilman in New York and a good friend of the former mayor of New York City, William O'Dwyer. Quite naïvely, I believed that once I was there, he could help us get a visa for Flora.

So I went to New York and contacted him. Rather soon it became clear to me that there was nothing he could do (or wanted to do), particularly in those post-McCarthy days when people were still afraid of being involved in those matters. In addition, I was advised by my father's family in New York not to comment on the reasons why my wife and my six-month-old son, Isaac, were not joining me. They were afraid of losing their jobs. So I decided it would be unfair on my side to generate problems because of their association with us. Nevertheless, I contacted people at the Mexican Consulate to see if I could get some help from them. I gave myself a one-month period to see if something could be done. Otherwise I would return to Mexico.

In the meantime, I started to work with Vernon Brooks. I got involved in recording the activity of single pyramidal neurons in the motor cortex of the cat. These neurons were identified by their antidromic responses to stimulation of the pyramidal tract (Brooks et al., 1961a,b). Our studies indicated that the majority of the pyramidal neurons had a specific sensory modality. Their responses to tactile stimuli were fast adapting. In contrast, neurons responding to pressure and leg position had slow adapting responses. One of the most interesting observations was that the responses produced by tactile stimulation of the skin decreased with repetition and increased again after a brief interruption of the cutaneous stimulus or after a different type of afferent stimulation, just as happens during habituation and dis-habituation of behavioral responses.

Another interesting and related finding was that some cortical neurons had fixed, and others had labile, sensory fields. The neurons with labile fields had relatively small sensory fields that expanded with repetitive stimulation and shrunk after interrupting the sensory stimulus. The sensory fields of non-pyramidal neurons located in the posterior sigmoid gyrus were rather fixed, although those located in more rostral areas were clearly labile. These studies suggested the existence of two sensory-motor projections, probably with two different roles in movement control. The complexity of the involved pathways did not allow us a more detailed analysis of the mechanisms involved in this phenomenon but were, I believe, a starting point for studies in the cerebral cortex of behaving animals.

### Siena, Italy: Sensory Activation of Hypothalamic Neurons

Almost at the end of the month I got an invitation from the Mexican Consulate to attend a reception at the Waldorf Astoria in honor of the president of Mexico, Adolfo López Mateos, who was visiting the United States. I thought, naïvely again, that this was a good opportunity to ask him for some help to get my wife's visa. I wrote him a long letter explaining the entire situation. I also

mentioned that I was working in one of the most famous scientific institutions in the United States and that I was learning new methodologies to record neuronal activity that I intended to use upon my return to Mexico. So I went to the reception. When the president entered the room, there was a long line to greet him. I was shy, but some friends at the consulate, who knew the whole situation, pushed me to get in line and insisted I should give him the letter. I shook hands with him and shortly explained to him why I needed his support. He smiled and told me he would do what he could and handed the letter to a military aide that was at his side. By looking at his face, I could anticipate that nothing would happen and at that moment I decided to return to Mexico.

Next day, I met Vernon and explained to him why Flora had stayed in Mexico. It was not because of some problems with the leg of my son Isaac (he had a small congenital problem in one foot that required wearing special shoes) as I told him before, but rather because the U.S. Embassy denied her the visa, in view of her suspected "political activism." He was astounded and suggested we should talk with Detlev Bronk, then president of the Rockefeller University and, if I recall well, ex-officio member of the Science Advisory Council to President Eisenhower.

I knew who Detlev Bronk was because of his beautiful work on sensory receptors. So, Vernon and I went to see him. He was quite receptive, told me he would do his best, and asked me to write a letter explaining the whole situation. A couple of months later, Flora was contacted by the U.S. Embassy asking her if it was true that our son Isaac needed medical treatment that was available only in the United States. She told them that that we had good physicians in Mexico and that they should instead verify their information sources because they got it all wrong!

So the whole process was again delayed. I kept waiting and working in the lab and visiting Mexico almost every two months. Staying in New York under those conditions was difficult for me, but I was fortunate enough to make good friends. One was Victor Wilson, who was next door. I used to visit him quite often and watch his experiments. We developed a close friendship that continues to this day. The others were Alexander Mauro, Keffer Hartline, and Harry Grundfest, who was a good friend of Rosenblueth and was at that time at Columbia University. They all expressed deep concern about what was going on and made my stay in New York bearable. I remember that I used to visit Keffer Hartline's lab to see his experiments with Floyd Ratliff on the *Limulus* eye. He told me once that I should know that many Americans opposed the witch-hunting started by McCarthy and encouraged me not to despair. A few years later, Alex Mauro visited us in Mexico and gave a magnificent series of lectures on membrane physiology. While at Rockefeller, I also became a good friend of Hiroshi Kuriyama, who was studying the excitation-contraction coupling in smooth muscle cells.

In the meantime, I learned that there were some fellowships to spend the summer at Woods Hole to work in the laboratory of Stephen Kuffler. This

was an attractive possibility, and I applied for support, which was granted. There I met Rodolfo Llinás, Richard Orkand, David Potter, and Ed Furshpan.

During one of his visits to New York, Raúl Hernández Peón, a well-known Mexican neuroscientist, told me that there were plans to create a neurological institute that would include a brain research unit that he would direct, and he invited me to join once I returned to Mexico. I still wanted to stay abroad and, in view of Flora's difficulties with the U.S. visa, I thought that it would be best to spend some time in Europe. He suggested Siena, Italy, where I could work with Zanchetti and learn the then "fashionable" stereotaxic techniques and single-unit recording that could be very useful for my future work. I liked the idea, particularly because I thought that Flora, being a plastic artist, would enjoy this visit.

On one of my visits to Mexico, I talked all this over with Rosenblueth. He was very supportive. Although he expected me to return to work at his department, he told me that there would be no problem if, at the end of my stay in Italy, I decided to work with Hernández Peón. Because I could not extend the Guggenheim Fellowship to Europe, he suggested that I apply to the Rockefeller Foundation.

In due course, the Rockefeller Foundation accepted my application for a fellowship and asked me to send them a formal assurance that, once back, I would have a position and facilities to work in at the neurological institute. I talked with Hernández Peón, and we both went to see his boss, Dr. Manuel Velasco Suárez, at that time vice-minister of health, who agreed to send the necessary assurances.

Just before leaving for Woods Hole at the end of the summer, I got a phone call from the U.S. State Department telling me that all was cleared up and that Flora would soon get her visa. However, by that time, we had already made all the arrangements to travel to Siena. Once there, I started the recording of unitary and population neuronal responses evoked in the diencephalon by sensory nerve stimulation with Alberto Zanchetti, Alberto Malliani, and Giancarlo Carli.

These were pioneering studies (Malliani et al., 1965; Rudomin et al., 1965a,b). Besides mapping the sensory projections in different diencephalic structures, including the hypothalamus, we addressed the issue of the possible local or remote origin of the recorded activity. We could show that in many instances monopolar recordings from the rostral part of the hypothalamus were not reversed when passing small currents through the recording electrodes, suggesting that they were produced by activity generated in remote regions. This was in contrast with other recordings that reversed their polarity from negative to positive, as expected if the sources become sinks and suggesting a local origin, in agreement with the recording of unitary activity in those regions. At the time when these studies were done, information concerning the sensory projections to the hypothalamus was rather scarce and fragmented. These studies are still cited and gave rise to more detailed investigations.

While in Siena, Malliani, who became a close friend, and I traveled every two weeks to Pisa to attend the seminars at Moruzzi's institute. There I met Moruzzi and Pompeiano and made two good friends: Emilio Bizzi, a former student of Zanchetti who had just moved to Pisa, and W. Alden Spencer, who was there for the summer. I developed a special relationship with him that continued until his unfortunate death in 1977. I still remember the long discussions we had afterward on the possible mechanisms involved in the plasticity of flexor spinal reflexes, an issue that captured my attention after I attended J. C. Eccles' talk on presynaptic inhibition, which was delivered at the symposium that Moruzzi organized in Pisa during the summer of 1961, just before I returned to Mexico.

My interest in the presynaptic control of transmitter release started one year earlier, during the summer at Woods Hole. This was the time when Stephen Kuffler and Joseph Dudel were writing their famous paper on presynaptic inhibition at the crayfish neuromuscular junction. In some species (I do not remember which), in addition to the excitatory axon, the muscles receive two inhibitory axons instead of one. So, the question rose whether both inhibitory axons were able to produce presynaptic inhibition. Although I was unable to complete these studies during the short time I was in Woods Hole, I remained interested in presynaptic inhibition.

My encounter with Eccles at the Pisa symposium was a rewarding experience. I had the opportunity to have a long talk with him. When he learned that I was in Rosenblueth's department in Mexico, he recalled the old disagreements they had pertaining to the electrical versus chemical origin of synaptic transmission in the central nervous system, even though they never had met personally. It was at this time that Ricardo Miledi returned to Mexico from Australia. He was back at Rosenblueth's place but had some disagreements pertaining to how much time he could devote to his own projects, and he was considering the possibility of moving to London to work with Bernard Katz. Eccles told me that if I ever had problems with Rosenblueth, I should consider the possibility of spending some time working with him in Canberra.

When I saw Anokhin at the Pisa symposium, I approached him and identified myself as a student of Alvarez-Buylla. He was quite receptive; he embraced me and started to tell everyone that I was his scientific grandchild! I learned through Alvarez-Buylla many of his views on functional systems that I believe have influenced my work. I still remember the faces of Eccles, Buser, and Bremer wondering what it was all about.

## The Center of Advanced Studies

While I was still in Italy, Rosenblueth was invited by the Mexican government to be the founding director of a new research institute. At the beginning, he was quite reluctant to accept this invitation and presented an ambitious plan with the hope that it would not be accepted. His idea was to

create a multidisciplinary research and graduate center. He asked for a fair number of full-time positions with good salaries, well-equipped laboratories, and academic and administrative independence.

To his surprise, all this was granted, and he had no choice but to accept. He was appointed as director in 1961 while I was in Italy. He started the whole project by inviting a small group of leading scientists in different areas as heads of departments, who were in turn asked to invite other scientists. He took care of the department of physiology and first invited García Ramos and Alvarez-Buylla. I was not invited at that time because I was already committed to join Hernández Peón's brain research unit upon my return from Siena.

In the early 1950s, Hagbarth and Kerr (1954) and Hernández-Peón and Hagbarth (1955) suggested that transmission of sensory information at the first synapse in the dorsal horn column nuclei was subjected to central control. Yet, the mechanisms involved in this control were unknown. I thought that if I was going to join the group headed by Hernández Peón, I could start searching for possible presynaptic control of the sensory information transmitted at the dorsal column nuclei as well as in other brain stem nuclei, and he was definitely interested.

But things do not always go as planned. Once in Mexico, it turned out that the whole project of Hernández Peón was breaking down, mostly because of discrepancies he had with Velasco Suárez. It was clear that this was not a place for me. So I went to see Rosenblueth for advice. He invited me to join the department of physiology at his new institution. Because one of the requirements was that only investigators with a PhD degree could be part of the staff, I had a four-year appointment during which I was committed to work toward my doctorate. This meant taking a series of courses (physics, mathematics, and statistics), doing experiments, and writing a thesis.

While they were constructing the new premises, we had provisional space, first at the medical school at the National Polytechnic Institute and later on at the school of physics and mathematics of the same institute. In the meantime, I took several courses in physics and mathematics. Soon after we moved to the new building, Leon MacPherson joined the group. He was a skilled British electronic engineer who had spent several years in Venezuela working with Gunnar Swaetichin on the visual system. He could not stand British weather and decided to stay in Latin America. Once I had the basic equipment (a Grass polygraph and a stimulator), I convinced him we should work together on the dynamics of the mechanisms involved in the maintenance of a steady blood pressure.

To this end, in anesthetized rabbits we lowered blood pressure by electrical stimulation of the depressor nerve. When the pressure dropped to a predetermined level, the pen-writer of the Grass polygraph activated a

microswitch that stopped the electrical stimulus to the depressor nerve and reapplied it when blood pressure recovered its original control values. This generated a series of blood pressure oscillations.

The relationship between the stimulation and non-stimulation periods allowed us to detect features of the system that we would not have been able to just by examining the system under stationary conditions. We found that when the blood pressure was driven away from its state of equilibrium, excitatory as well as inhibitory mechanisms were activated to restore the system to its original conditions. In intact preparations, the mechanisms that inhibited the vasoconstrictor activity induced by electrical stimulation of the depressor nerve were found to be coupled with those controlling recovery after the inhibition. They became decoupled by interrupting the information conveyed through the aortic and carotid vagal baroreceptors, as well as during deep anesthesia. That is, the effectiveness of the recovery after disturbing the system depended on the integrity of other baroreceptor afferents (see Rudomin and McPherson, 1963a,b).

I soon became aware that, to advance understanding of the central control of the cardio-inhibitory reflexes, instead of recording changes in heart rate and blood pressure as I did before, I should try to stimulate the depressor nerve and to record the reflex responses in the efferent vagal fibers that mediate heart slowing. In an initial series of experiments, I found that in the cat anesthetized with chloralose, stimulation of the depressor nerve as well as stimulation of trigeminal afferents and of the motor cortex or the pyramidal tract produced polysynaptic reflex discharges in both vagal nerves (Rudomin, 1965a,b).

I soon realized that these responses were not due to activation of the slow conducting vagal fibers inducing heart slowing but to activation of fast-conducting motor axons innervating the laryngeal muscles. Cortical stimulation produced early facilitation and a prolonged inhibition of the laryngeal reflex responses generated by vagal or trigeminal stimulation.

Having established that the reflex responses recorded in the vagus nerve were due to the activation of motor axons innervating the laryngeal muscles, I thought it would be important to examine the functional organization of these reflexes. As a first step, I selected the cricothyroid muscle for analysis, mainly because it was possible to record its activity without disturbing the larynx or its innervation, and also because this muscle received its sensory and motor innervation through separate nerve branches. This feature allowed me to examine changes in muscle activity during active shortening and passive stretch before and after proprioceptive denervation (Rudomin, 1966b,c).

At that time, the general view was that the cricothyroid muscle was activated during inspiration only. However, I found that in the lightly anesthetized cat, the cricothyroid muscle had its highest activity during the

expiratory phase of the respiratory cycle. By deepening the anesthesia, or by increasing the respiratory dead space, expiratory activity was reduced and motor units were recruited whose activation was instead maximal during inspiration. I assumed that the level of central excitability at that moment would determine whether the motor units were activated during inspiration or expiration.

Later on, I showed that stretching the cricothyroid muscle had little influence on its own activity, and when there was some effect, it was inhibitory. The passive shortening of this muscle produced by the contraction of the cricothyroid muscle on the opposite side also had little effect, in contrast with the intense activation produced by mechanical stimulation of the laryngeal mucosa or by trigeminal stimulation. These observations suggested that the changes in length and tension imposed on the cricothyroid muscle, in contrast with other skeletal muscles, do not initiate compensatory activity that opposes the induced changes in muscle tension and length.

Another interesting finding, related to the absence of proprioceptive control of the cricothyroid activity, was the lack of effects of deafferentation on the synchronized activity of the cricothyroid muscles on both sides. Afferent signals should play only a modulatory role, but the synchrony appeared to be centrally determined. This concept was developed later on by other investigators in the field, and it is now accepted as a basic principle of the organization of locomotion, which is assumed to result from highly correlated activity in the spinal neuronal sets responsible for the flexor-extensor alternation, still subjected to a central control.

It was never clear to me why, when I wrote these papers that were published in 1966, I did not relate the finding of the prolonged depression of laryngeal reflexes produced by stimulation of the trigeminal nerves or by cortical stimulation to presynaptic inhibition, even though at that time I was already aware of Eccles's work. Curiously enough, the journal reviewers also missed this point.

I remember that, in one of the department seminars, I suggested that such a prolonged inhibition could be of presynaptic origin. Rosenblueth, who attended the seminar, was very reluctant to accept that the synaptic efficacy of the sensory fibers could be subjected to a central control. In fact, he argued that all these findings could be properly explained using the model on spinal monosynaptic reflexes he developed with Norbert Wiener (Rosenblueth et al., 1949).

Nevertheless, it seemed to me that I should test more directly if the depression of the laryngeal reflexes produced by stimulation of the trigeminal nerve and of the motor cortex had a presynaptic component. To this end, I examined the effects of different experimental procedures on the excitability of laryngeal afferents ending within the solitary tract nucleus. I found that these afferents were depolarized by conditioning stimulation of other laryngeal afferents, as well as by stimulation of vagal and trigeminal

afferents, and that their synaptic actions were depressed with a similar time course. I also suggested that this inhibition had a presynaptic component (Rudomin, 1966a, 1967a,b). Quite interestingly, lung inflation, which produces respiratory inhibition via pulmonary stretch receptors, also depolarized the terminals of the laryngeal afferents.

An important and unexpected finding was that even though the vagal visceral afferents were able to depolarize the laryngeal fibers ending within the brain stem, they, as well as the aortic baroreceptors, showed no primary afferent depolarization by conditioning stimuli that very effectively depolarized the laryngeal afferent terminals (Rudomin, 1967b, 1968). This makes sense if we consider that the aortic baroreceptors are part of the homeostatic mechanisms that regulate blood pressure level, where it is essential to preserve information on the state of the variable to be controlled, in this case blood pressure via the information sent by the arterial baroreceptors. Presynaptic inhibitory mechanisms would clearly modify this information, and this could lead to a faulty regulation. In fact, I now believe that presynaptic inhibition should not be envisaged only as an inhibitory mechanism but rather as a means to change the information generated in the periphery in a “context depending” manner.

## My First Studies in the Spinal Cord

I met Guillermo Pilar in 1958, when he arrived from Argentina to work at the Cardiological Institute with Arturo Rosenblueth and Jesús Alanís. From Mexico, he went to Salt Lake City to work with Robert Martin on synaptic transmission in the ciliary ganglion of the chicken. Around 1983, I visited him, and I had the opportunity to meet several really outstanding investigators who were working in the department headed by C. C. Hunt. I met Carlos Eyzaguirre, with whom I developed a long-lasting friendship, as well as Edward Perl and Motoy Kuno. If I remember correctly, Dick Burgess was there. I met him while a student at the Rockefeller Institute, and we remained good friends for many years. What really impressed me was the analysis that Motoy Kuno made of the quantal nature of synaptic transmission of muscle spindle afferents on spinal motoneurons, and I invited him to visit us in Mexico. To my surprise, a few months later, I got a letter from him saying that because he entered the United States with an exchange visitor visa, he was required to leave for some time before being able to re-enter the country. He was not very eager to return to Japan and felt attracted to the idea of spending a year or so in Mexico. I went to see Rosenblueth, and he agreed to appoint Motoy as visiting investigator. He arrived in Mexico with his family in the summer of 1965 and stayed for one whole year.

It was known at that time that antidromic stimulation of the ventral roots or the motor nerves could inhibit spinal monosynaptic reflexes via the Renshaw cells that were activated by the motoneuron axon collaterals.

Although pharmacological studies already supported a possible cholinergic activation of the Renshaw neurons, we felt that it would be important to show that acetylcholine was indeed released in the spinal cord by stimulation of the motoneuron axon collaterals, and that this release was correlated with the activation of the Renshaw cells.

So, inspired by the demonstration of acetylcholine release by stimulation of the vagus nerve in the perfused frog's heart by Otto Loewi many years before, we devised a method to perfuse the deafferented spinal cord *in situ* to stimulate muscle nerves and measure the acetylcholine collected in the perfusate. The acetylcholine content would be examined using some of the biological assays available at that time (blood pressure fall in the eviscerated cat or inhibition of muscle tone in leeches).

After several disappointing attempts, we were finally able to show that stimulation of the motor nerves increased the acetylcholine release by 1.9–9 times (Kuno and Rudomin, 1966). The amounts of acetylcholine released by stimulating the motor nerves with different frequencies showed a high correlation with the changes in the activity of the Renshaw neurons in response to these same stimulation frequencies. The injection of dihydro-beta-erythroidine, which blocks Renshaw cell activation, had no effect on acetylcholine release. It thus seemed fair to conclude that the intraspinal collaterals of the motoneurons release acetylcholine (Ach), as in their peripheral branches, and that this Ach activates Renshaw cells in the spinal cord.

While writing this text, I thought how nice it would have been if we would have had the analytical methods that are now available. But at least I learned how to handle the leeches with chopsticks and also to use chopsticks to eat Chinese and Japanese food!

Motoy wanted to stay in Mexico for a longer time, but he returned to the United States because he felt indebted to C. C. Hunt, at that time at Yale. The collaboration with Motoy Kuno shifted my research on presynaptic inhibition from the brain stem to the spinal cord. I learned from Motoy that if one has a dream he should pursue it until it becomes real. I have had several dreams through my professional life and in moments of doubt, or when I was ready to give up, Motoy's example was always inspiring.

## Variability of Monosynaptic Reflexes: A Fresh Look at an Old Problem

In 1965, Harold Dutton joined the department of electric engineering in the institute where I was working. He was born in Yucatan, the son of Thomas Dutton who settled in Mérida in 1906 and was the British consul for many years. If I recall correctly, Harold had one PhD from MIT in systems control and another in mathematics from Columbia University.

I met Harold at the institute's cafeteria. He was interested in feedback control of muscle reflex activity and used to ask questions for which I had no answer. While attempting to explain to him the differences between pre- and

postsynaptic inhibition, he asked me: “Regardless of the involved mechanisms, how does the system ‘know’ that the inhibition produced by afferent conditioning volleys is pre- or postsynaptic?” In other words, were there any differences in the features of the responses of the motoneuron population to a given Ia input when they were inhibited to the same extent pre- or postsynaptically?

While discussing this with Harold, I recalled the paper of Barron and Matthews (1935), where they described the intermittent conduction of impulses in sensory fibers and regarded this as a mechanism of inhibition. Their findings suggested to us that, in addition to the mean of the monosynaptic reflexes, we should also measure their fluctuations. Online measurements were essential for doing the experiments. At that time, we had no digital computers to measure the reflexes and to calculate their fluctuations. Based on his experience with analog computation, Harold used operational amplifiers, condensers, and resistances to construct a device that allowed real-time continuous estimates of the mean and variance and correlation of the monosynaptic reflexes (Dutton and Rudomin, 1968).

With this system in operation, we found that monosynaptic reflexes inhibited by conditioning stimuli that produced a strong primary afferent depolarization (PAD) had a smaller variability than reflexes inhibited by stimuli assumed to produce only postsynaptic inhibition (Rudomin and Dutton, 1967, 1969a). We explained these effects by assuming that the spontaneous activity of some neuronal networks produced a background-correlated depolarization of a substantial number of muscle spindle intraspinal terminals, and that conditioning volleys to cutaneous nerves would temporarily reduce such a correlated PAD as well as the fluctuations of the monosynaptic reflexes (Rudomin and Dutton, 1968, 1969b). This interpretation was further supported when we showed that the correlation between the monosynaptic reflexes generated simultaneously in two different populations of motoneurons was reduced by conditioning stimuli that produced PAD (Rudomin et al., 1969).

In short, these studies indicated that the variability of monosynaptic reflexes was not just “noise” in the system but was the result of the activity of specific sets of neurons involved in the control of the information transmitted by the afferent fibers.

In 1967, Dutton and I sent a note to *Brain Research* describing the effects of conditioning stimuli producing pre- and postsynaptic inhibition on the mean area and variance of monosynaptic reflexes. A few weeks later, we got back the manuscript with a rejection note from the editor, K. Akert. This letter included no comments about why the note was rejected. I was surprised and wrote back to Akert asking him for the reviewer’s remarks. I think I mentioned to him that I believed that, besides publishing research articles, one of the roles of scientific journals should be to provide proper scientific feedback, particularly to young investigators in “developing” countries.

Soon after, Akert sent me a copy of the reviewer's remarks. If I remember well, the reviewer said: "This is very interesting but neither me, Lundberg, nor Lloyd found something like this." He also pointed out that because I was not showing the original records, but just the area of the reflexes, it was not clear if the electronic gate we used to measure the area comprised only the monosynaptic component or if it also included oligosynaptic components. This was a reasonable concern. I then wrote back a detailed response to Akert asking him to forward it to the reviewer. I suspected that the reviewer was J. C. Eccles, but I said nothing.

In the meantime, Dutton and I revised the note and included all the remarks made by the reviewer. We also added one figure with original records of the monosynaptic reflexes and their areas and submitted the note to *Nature*. A couple of weeks later, I met Rodolfo Llinás at a meeting in Mexico City. At that time, he was already working with Eccles in Chicago. I told him the whole story about the paper we sent to *Brain Research* and that I was sure Eccles reviewed it. He said that he was present when Eccles was reading the paper and that he commented he would not recommend its publication.

I was disappointed because I thought that Eccles's concerns were quite mild and did not justify the rejection. So I told Rodolfo that I would travel to Chicago to present him my data. He became somewhat anxious and asked me not to mention our conversation. I told him not to worry.

I wrote Eccles that I was visiting Chicago and that I would like to discuss recent findings with him. He agreed. Yet, I felt it would be good to have the opinion of somebody else before seeing Eccles. I thought of William Willis who was in Dallas and was co-author with Eccles and Robert Schmidt of many papers on presynaptic inhibition. Even though we had never met before, I wrote him, and he invited me to give a seminar on my way to Chicago.

Meeting Bill was really nice, and it was the beginning of a friendship that has lasted many years. Years later, he came to work with us in Mexico, and I worked with him when he moved to Galveston. So I visited his lab in Dallas and gave a seminar. He found our findings sound and interesting. At the end of the talk, he invited me to have dinner in a fancy restaurant. When we arrived, I stepped out of the car and took my old briefcase with me. Halfway to the restaurant, Willis said: "You don't need to carry your briefcase to the restaurant. Why don't you leave it in the car?" I replied, "If I were in Mexico, I wouldn't do it." Well, he said, "You are not in Mexico!" Because I had just met him I did not want to start an argument, so I went back to the car and left the briefcase. But halfway to the restaurant I told him, "Let me be a little distrustful and pick up my passport, airplane ticket, and money." He just looked at me and smiled.

After the dinner, we returned to the car and found that somebody had broken in and taken away my briefcase! Bill was really sorry, and he apologized. I was really relieved because I had taken the money and

documents with me. Suddenly, I realized that the briefcase had all the material I intended to show to Eccles. But, fortunately, in my hurry to leave for the restaurant, I had forgotten to pick up my slides from the lecture room.

I left the next morning for Chicago. Rodolfo Llinás came to pick me up at the airport. I was really worried about not having all the material with me that I was to show to Eccles. Rodolfo suggested that early in the morning we should go to the lab's darkroom and use the slides as negatives to make paper copies. We did that. The copies were still wet when I showed them to Eccles. Suddenly he said: "Now I understand." I asked him, "Now?" He hesitated and said, "Well, you were not very clear at the beginning." After a thorough and fruitful discussion of our data, I left without telling him that I knew he had reviewed my paper.

A few days later, I returned to Mexico and found three letters on my desk. One was from Eccles, which I still have, saying that he had reviewed my paper and that he was apologizing for not having understood the relevance of our observations. He added that he wrote to the editor of *Brain Research* that he should accept the note for publication. The second letter was from Akert saying that Eccles wrote him about our meeting, and that he would be very happy to publish the note. The third letter was from *Nature* saying that our paper was accepted for publication (Rudomin and Dutton, 1967). So I sent a copy of this letter to Akert with a paragraph that said that next time he should be more receptive to papers sent by young scientists working in developing countries such as Mexico.

A couple of weeks later, I got a letter from the Dallas police. They had found a briefcase with some letters addressed to me and assumed it was mine. I wrote them back explaining all that had happened, and I asked them to send the briefcase to Willis so that he could send me just the contents. One day I came to the lab, and I saw a big box. I opened it, and there was my old briefcase, all destroyed. I was glad to recover all the material, particularly my old pipe. Bill must have paid a fortune to ship it by air.

Several years later, during the International Congress of Physiology in Paris, I was invited to have dinner at Denise Albe Fessard's house. Akert was sitting close to me. I was wearing a badge with my name, and he just looked at me and said, "I am really sorry about what happened with your paper several years ago, but what else could I do if the Nobel Prize told me not to accept it?" I just said: "You should have listened to me and sent him back my reply and asked for a second opinion."

## My Sabbatical at the National Institutes of Health

If I recall well, it was December 1962 when Rodolfo Llinás, with whom I developed a close friendship while I was in Woods Hole, visited Mexico on his

way from Canberra to Colombia. He was waiting for his fiancée, Gill, to join him in a couple of days. They had decided to be married in Mexico before going to Colombia, and he asked me to be his wedding witness.

She came one day before Christmas. I think it was the morning of the 24th. All the government offices were to close by noon. I used my best skills to convince the judge to marry them and so he did. A couple of days later, both of them left for Bogota to meet Rodolfo's family.

I agreed to send them the marriage certificate as soon as possible so that Gill could enter the United States. When I went to pick up the certificate, I found that the marriage was not valid. Both required permission from their embassies because they were not Mexican citizens. It was a rather complicated business to have it all straightened out, and I asked for help from our institute's legal adviser. Even so, it took him several weeks to arrange things with the embassies and with the judge.

In the meantime, Rodolfo flew to Minnesota and left Gill in Bogota. Rodolfo's father was calling me every day to see if we were finally able to get those documents. After a couple of weeks, everything was arranged, and Gill could join Rodolfo.

I had long talks with Rodolfo about his experience in Canberra, and it seemed to me that it would be a rewarding experience to spend some time working with Eccles. Soon after, I wrote him a letter reminding him of our conversation in Pisa. I had no response until a few months later after he received the Nobel Prize. He told me that he had a long list of visitors and that my visit was not feasible at that time. A couple of years later, I got an invitation from him telling me that if I still wanted to come he had one open position for a visiting scientist to start, if I recall well, around the fall of 1967.

We had already made all the necessary arrangements for the Australian sojourn when I got a phone call from Eccles telling me that he was moving to Chicago because he was going to be 65 years old and could not continue with his appointment in Canberra, so there was no point for me to go if he was not going to be there! This was very frustrating. David Curtis told me years later that I could have gone anyway and worked with him or with somebody else because I was already appointed as visiting scientist.

It was around that time when I came across the superb series of papers published in 1967 by Frank, Rall, Burke, Nelson, and Smith. I still recall the emotion I felt when I read those papers, and I decided that this was the place to go. I wrote Michael Fuortes, whom I had met while in Woods Hole in 1960, and he arranged a six-month visit starting in the fall of 1968. Six months was a very short time for a sabbatical. I thought it would be nice if I could also spend some time working with Vernon Mountcastle so, in the future, I could examine the role of presynaptic inhibition in behaving monkeys during the execution of specific motor tasks. To this end, I applied—again with Rosenblueth's support—to the Guggenheim Foundation for a second fellowship.

The summer of 1968 was a difficult year in Mexico. It was just before the Olympics, and there was a growing demand, mostly by young students, to have a more open society. This feeling was also shared by many faculty members. The government's disastrous response was repression. I left Mexico in September 1968 and stayed in Phil Nelson's house while I searched for a place where Flora and our two children could stay comfortably. I found a small apartment in Bethesda, just walking distance from the laboratory.

The family was scheduled to arrive in Washington by October third. But just one day before, the news covered with detail the events in Mexico City. Many persons, mostly students, were killed while they were gathered in a demonstration. I was alarmed and worried and I called home. Fortunately, everything was all right with the family, and they were ready to travel.

The next day, I went to the airport to greet them, but they did not show up. I was worried because I thought that perhaps the borders were closed in view of the events of the previous day. It took me several hours to contact them. They were fine but had missed the flight because they were not aware of the change in the winter time schedule. They arrived the next day after a long detour. They came to Washington via Chicago, where they were delayed for several hours by immigration even though by then Flora had a valid visa.

I started to work in the neural control section. The lab chief was Karl Frank, who was also responsible for one of the NIH extramural programs. Robert Burke was a member of the section and had recently returned from Lundberg's department in Goteborg. Ladislav Vyklicky came from Prague and was to stay for six months, and Felix Zajak had just joined as a postdoctoral fellow.

I still remember that just several weeks before I started to work at NIH, there was an international meeting in Washington where Manfred Zimmermann presented observations that were not supporting the gate theory of pain proposed by Melzack and Wall. According to this theory, activation of C fibers was expected to inhibit the background PAD in large cutaneous afferents and lead to a concurrent presynaptic facilitation of their synaptic effectiveness and activate nociceptive pathways. Yet, Zimmermann's observations showed that C fiber stimulation during selective electrical block of the A fibers in a cutaneous nerve produced instead negative dorsal root potentials that were taken as a sign of primary afferent depolarization and presynaptic inhibition of the cutaneous afferents (see Janig and Zimmermann, 1971).

One problem with Zimmermann's experiments was that the C fibers were activated synchronously, and it was not clear if these fibers transmitted nociceptive information, as required to test Melzack and Wall's proposal. Ladislav suggested we should instead use radiant heat, which was known to activate C fiber nociceptive afferents in a more selective manner.

Our studies showed that pulses of intense radiant heat applied to the plantar pad in unanaesthetized spinal cats evoked post-synaptic excitation of flexor and post synaptic inhibition of extensor motoneurons as well as negative dorsal root potentials (DRPs) and hyperexcitability of cutaneous intraspinal terminals due to primary afferent depolarization (PAD; see Vyklicky et al., 1969; Burke et al., 1971).

To the extent that PAD causes presynaptic inhibition, these observations indicated that pulses of intense heat applied to the skin, instead of producing presynaptic facilitation as proposed by Melzack and Wall, presynaptically inhibited transmission from the affected primary afferent fibers to second order neurons, thus confirming and expanding the observations of Zimmermann.

At the end of the six months at NIH, I was supposed to move to Mountcastle's laboratory in Baltimore. The adaptation of the children to life in Bethesda was rather difficult because of the change in language and environment. Yet, six months later, they were already adjusted to school and had made new friends. Moreover, living within walking distance from the laboratory allowed me to spend more time with my wife and children, even during those long-lasting experiments when we used to take turns during the evening so I could walk home and have dinner with the family. It was not at all surprising that I was somewhat reluctant to move to Baltimore and start all over.

I drove to Baltimore to meet Mountcastle. I arrived early and Gian Poggio, whom I knew from Italy, was there. We had a long chat, and he warned me about the disadvantages of living close to the lab. It was a dangerous neighborhood, particularly at night, and it was clear that I would need to live far away and commute every day. This further discouraged me from leaving Bethesda. While waiting for Mountcastle to arrive, with Gian's approval, I lit up a cigar. The first thing Mountcastle said when he entered the room was: "Pablo, if you are going to work with me, better give up your cigar!" I thought at that moment that this was not a polite way to ask me to give up smoking, which I would certainly do if he would have been more courteous. It seemed to me that he was an authoritarian person, and I wondered whether I could really enjoy working with him. So I told him: "My dear Vernon . . . if you force me to choose between you and my cigar, the decision is made: I keep my cigar."

I then returned to Bethesda, talked with K. Frank, and he invited me to stay for six more months. Seen in retrospective, my response to Mountcastle was clearly arrogant and foolish, but, curiously enough, over the years we became good friends. In fact, when he was president of the Society for Neuroscience, he invited me to become part of the board of publication trustees of the journal that was launched in 1981.

I spent part of the remaining months in Bethesda finishing the analysis of the data on PAD and radiant heat. In addition, because Robert Burke was

primarily interested in the mechanical properties of single motor units, we started a new series of experiments where we examined the changes in muscle tension produced by intracellular stimulation of single motoneurons with different stimulation paradigms (Burke et al., 1970, 1976).

We found that the tension output of slow-twitch motor units was quite sensitive to the patterns of stimulus intervals in the train. The presence of only one stimulus interval that was much shorter than the others in the train could cause a marked, long-lasting tension enhancement. We suggested that this “catch” property could extend the range of output tensions that can be produced by a given motor unit without a large change in mean firing frequency of the motoneuron. This effect could be of functional significance because double discharges at short intervals are not uncommon, particularly during stepping (when motor units fire in short bursts). This was long before the discovery of the plateau potentials in motoneurons (Hounsgaard et al., 1984, 1988).

While at NIH, I developed a special friendship with Robert Burke that has lasted throughout all these years and also with Ladislav Vyklicky until the end of his life. My relationship with Karl Frank was also very special. He encouraged me to write my first NIH grant application and advised me on how to do it. This grant was funded in 1971 and was renewed throughout the following 38 years. It allowed me to stay and work in Mexico.

## Back in Mexico

While in Bethesda, I considered the possibility of not returning to Mexico because of the government’s authoritarian repression of October 2, 1968. I commented on this to Vernon Brooks who had already moved to Canada, and soon after, I got a letter from Szerb, the chairman of the physiology department in the medical school in Halifax. He invited me to visit the department and to consider the possibility of working there. I still remember that I flew from Washington to Boston and from there to Halifax. When I arrived, the immigration officer told me that I could not enter Canada because I had no visa! Fortunately, it was a small airport and Szerb, who came to pick me up, arranged my admission.

The visit to Halifax was really nice. I stayed a couple of days, visited several laboratories, and gave a lecture. I left with the idea of moving there once I finished my commitment with NIH. It was Saturday afternoon when I flew back to Boston. To my surprise, I could not re-enter the United States because I had an exchange visitor visa that was valid for one entrance only. It did not matter that I told the immigration officer that I just went out to give a lecture in Halifax, that I was working at NIH, and that my family was in Bethesda. He was ready to send me back to Halifax, which meant I would need to stay there for the weekend and then go the next Monday to the U.S. consulate for a visa!

I really did not know what to do, so I asked the officer to call his chief, with the hope that he would understand the whole situation and allow me to enter the United States. He came, but all was hopeless. As a last resort, I told him that I was expected at NIH that evening to perform a series of important experiments that required my presence and could not be postponed. I asked him to call some of my colleagues at NIH to confirm my story and took out my pen to write the phone number where he should call. He looked at the pen—it was one of those black ballpoint pens that everybody used at the lab, labeled as “Property of the U.S. Government.” To my surprise, he said: “Now I believe you. You can enter the U.S.!”

A couple of months later, when I was about to decide between returning to Mexico or accepting Szerb’s invitation and moving to Halifax, I got a letter from García Ramos, who recently became the chairman of the physiology department at CINVESTAV. He invited me to return to the department at the end of my sabbatical leave.

García Ramos studied medicine at the Escuela Médico Militar and became a close collaborator of Rosenblueth at the cardiological institute beginning in 1945. When Rosenblueth became director of the new institute in 1961, Ramos joined the department of physiology as full professor. I had worked with him in 1956 and, at that time, we got along pretty well. However, as acting chairman, he was quite authoritarian and our relationship became somewhat crisp, particularly during the 1968 events, when many of us were demanding more participation in the government decisions that affected our lives and professional activities. Nevertheless, his invitation was conciliatory; he assured me that things would be different and that I would have more participation in the definition of department policies.

It was about time to make a decision, when Bob Burke and I went to visit Ladislav. He had spent six months at NIH and then moved to Philadelphia to spend another six months at the school of dentistry. It was just a couple of weeks before he and his family were returning to Prague. Yet, it was not clear to both of us why Ladia wanted to go back, particularly at that time when the Prague Spring was over, the Soviet tanks were in the streets, and many persons that were against the invasion were put in jail.

According to Bob, because Ladislav was already in the United States with his wife and kids, it should not be a problem to arrange things so they could stay for a longer period of time. Ladia said that, if everybody left Prague, who would stay there to keep things moving? He felt very committed to the institute and to his colleagues and decided that the best he could do was to return, even with the risk of being imprisoned.

I was impressed with his decision, and I am sure that his example, together with Flora’s and my strong commitment and gratitude to Mexico for having so generously accepted our families, contributed to our decision to return to Mexico.

The work that I did together with Harold Dutton between 1967 and 1968 (Rudomin and Dutton, 1969a,b; Rudomin et al., 1969) showed that correlated fluctuations of the monosynaptic reflexes were reduced by conditioning stimuli that produced PAD and presynaptic inhibition. At that time we suggested that this effect resulted from the reduction and/or desynchronization of the activity of the PAD mediating interneurons.

Once back in Mexico, José Madrid and I decided to examine the effects of sensory stimuli on the correlation between the monosynaptic responses of pairs of individual motoneurons (Rudomin and Madrid, 1972). As expected, conditioning stimulation of cutaneous nerves was found to reduce the correlation between the monosynaptic responses of the pairs of motoneurons. We also found that the changes in the joint firing probabilities of the motoneuron pair allowed a fair prediction of the changes in population variance. Using the Shannon-Wiener definition of information, we also found that the reduced joint firing increased the information transmitted by the two-neuron ensemble. Yet, it was not clear if this effect was of presynaptic origin.

To this end, together with Robert Burke, we examined the effects of conditioning volleys to muscle and cutaneous nerves on the monosynaptic potentials elicited in pairs of motoneurons by stimulation of muscle spindle (Ia) afferents (Rudomin et al., 1975a). As expected, this correlation was positive and was reduced by conditioning volleys to cutaneous nerves. Quite often, these changes occurred without affecting the mean EPSP amplitude and time course, suggesting a presynaptic origin.

Further evidence supporting a presynaptic origin of the fluctuations was obtained later when we showed that the mean and variance of the Ia-motoneuron monosynaptic EPSPs could be reduced by conditioning volleys to sensory nerves without affecting the monosynaptic EPSPs elicited in the same motoneurons by stimulation of the ipsilateral vestibulo-spinal tract (Rudomin et al., 1975b).

In the late 1980s, Lorne Mendell visited our laboratory. One of the questions pending from our previous study on the fluctuations of Ia-EPSPs was the extent to which the reduced correlation between pairs of Ia monosynaptic EPSPs induced by conditioning stimulation of cutaneous nerves could be ascribed to changes in the background synaptic activity generated by neurons acting on the Ia afferents and/or motoneurons. To this end, we recorded the monosynaptic EPSPs produced in single motoneurons by stimulation of a single muscle spindle afferent (Solodkin et al., 1991).

We found that the differences in mean EPSP amplitude for a given connection under conditions of low background synaptic noise (no muscle stretch) and high background synaptic noise (induced by stretching the homonymous muscle) were minimal. Yet, in some cases, the increased variance observed during the EPSPs evoked under low noise conditions was reduced during high noise conditions.

Using de-convolution techniques, we also found that the variance of the “noise free” EPSPs was smaller than the directly measured EPSP variance. These differences were explained by assuming a negative correlation between the Ia-EPSPs and the baseline synaptic noise. Simulation studies revealed that the variance increase during the EPSP was highly dependent on the correlation between signal and noise, suggesting that non-linear interactions between background activity and evoked EPSPs could also affect the interactions among neurons within the network. In other words, the reduction of the correlated fluctuations of the monosynaptic reflexes induced by conditioning stimulation of sensory nerves could be due, at least in part, to reduced activity of the interneurons acting on the Ia-motoneuron pathway.

## Comparative Studies on Presynaptic Inhibition

### *Frogs*

In 1972, when David Carpenter, whom I had met while I stayed at NIH, came to our laboratory for a three-month visit, we thought it would be interesting to study the functional organization of PAD in other vertebrates besides mammals, and we focused on the frog. To this end, we developed an *in vitro* preparation of the neuroaxis together with the left hind limb nerves that were dissected and left in continuity up to their entrance to the muscles (Carpenter and Rudomin, 1973).

In this preparation, we could show that stimulation of the motor axons produced dorsal root potentials (DRPs) that were larger than the DRPs produced by stimulation of sensory nerves. The DRPs produced by stimulation of nerves innervating the extensor muscles were larger than those produced by stimulation of nerves to flexor muscles. We thought that this made some sense because when the frog jumps there is a descending activation of extensor muscles, and in this case, the motor-nerve-induced PAD could prevent interfering influences of sensory inputs during the jump. This being the case, we assumed that the effectiveness of the descending fibers would not be subjected to presynaptic control.

With Silvio Glusman (Glusman and Rudomin, 1974), we recorded the field potentials produced by antidromic stimulation of motor axons and of the lateral column, in the intact as well as in the chronically deafferented spinal cord of the frog. We found, as in the cat, that the synaptic effectiveness of the fibers descending through the lateral column (probably vestibulo-spinal) was not subjected to a presynaptic (GABAergic) modulation. In addition, we could show that in the chronically deafferented spinal cord the antidromic stimulation of motor nerves no longer produced the intraspinal current flows associated with PAD. Ultrastructural studies made in frogs with chronic dorsal root lesions or with chronic spinal

hemisections further indicated that the degenerated terminals of the damaged descending fibers, unlike the afferent fibers, showed no close appositions from neighboring interneurons suggesting axo-axonic synapses (Glusman et al., 1976).

In the early 1970s, the DRPs produced by antidromic stimulation of the ventral roots and/or motor nerves were assumed to be generated by the activation of cholinergic axon collaterals that would in turn activate the GABAergic interneurons that produce PAD. Yet, very little was known about the intraspinal mechanisms involved in the generation of these potentials. In 1978, José Galindo and I examined the effects of gallamine on the intraspinal field potentials and DRPs produced by antidromic stimulation of motor fibers (Galindo and Rudomin, 1978).

We found that gallamine increased the duration of the negative field potentials produced by antidromic activation of motoneurons, often without changing their amplitude. This resulted in an increased passive spread of the antidromic action potential toward the dorsal dendritic regions, where afferent fibers terminate. In addition, antidromic stimulation of motor axons produced a late negative dorsal root potential (VR-DRP) that was depressed after gallamine administration. Quite unexpectedly, we found that abolition of the VR-DRP was frequently associated with the appearance of short latency, conducted responses in the dorsal roots that we interpreted as being generated by electrical interaction between motoneurons and afferent fibers. These findings suggested that the motoneuron-afferent fiber interaction initially described by Decima (1969) and Decima and Goldberg (1969) in the cat could be a consequence of such coupling. Seen in retrospect, it is possible that our inability to confirm Decima's findings (Gutnick et al., 1975) was due to a limited passive spread of the antidromic action potential toward the distal dendrites in the motoneuron.

With Ana Cardona (Cardona and Rudomin, 1983), we focused our attention on the possible effects of the activation of serotonergic pathways on the homosynaptic depression of the monosynaptic responses produced in the frog spinal motoneurons by repetitive stimulation of the lateral columns. We knew from previous work that their synaptic effectiveness was not subjected to a GABAergic control of the type seen in afferent fibers.

We developed a preparation that included the isolated spinal cord and brain stem nuclei. Serotonin added to the bath, or stimulation of the brain stem midline raphe nuclei, but not of the lateral reticular formation, reduced the magnitude of the low frequency depression of the motoneuron responses produced by stimulation of the lateral column. These actions were abolished by methysergide, a specific antagonist of serotonin. It thus seemed that the magnitude of the homosynaptic depression of monosynaptic responses of motoneurons could be controlled by descending serotonergic mechanisms, and we suggested that these effects could be an important component of the arousal behavior mediated by the brain stem raphe nuclei.

Studies on the action of descending fibers on PAD elicited by stimulation of afferent fibers and/or stimulation of the motor axons were continued in the 1990s with Hortensia González and Ismael Jiménez (González et al., 1992, 1993). These studies showed that, as in the cat, stimulation of the bulbar reticular formation produced PAD in cutaneous afferents and inhibited the PAD elicited in muscle spindle afferents.

### *Stingrays*

In the mid-1970s, I spent several summers at the Marine Biological Institute in Galveston working with William Willis and Robert Leonard on the functional organization of the spinal cord of the stingray (Leonard et al., 1978; Rudomin et al., 1978). Quite unexpectedly, we found that the dorsal (afferent) and ventral (motor) roots do not merge in the peripheral nerves but run in different fascicles that can be separated by dissection. We found that the sensory branches of the peripheral nerves have mostly A $\alpha$  and A $\delta$  fibers and relatively few C fibers. Electrical stimulation of one nerve increased the intraspinal excitability of A $\alpha$  and A $\delta$  fibers in nearby nerves. However, in contrast with what is observed in the frog spinal cord, antidromic stimulation of motor axons produced no PAD. It was not clear, however, if the axon collaterals of the motor fibers activated some inhibitory interneurons like the Renshaw cells in the cat.

We also analyzed the locomotion patterns in the stingray (Leonard et al., 1979). These animals swim with an active elevation-depression sequence of the pectoral fin resembling an extension-flexion sequence. During forward locomotion, this sequence passes caudally along the pectoral fin. Immediately following high decerebration, stingrays are capable of locomotion, and the pattern of muscle activity closely resembles that of intact animals. Spontaneous and midbrain evoked rhythmic motoneuron discharges could be recorded in paralyzed, decerebrated animals. In contrast to dogfish sharks, stingrays with high spinal transections do not locomote.

Unfortunately, it was not possible for me to continue with this work because other commitments prevented me from visiting Galveston during the summer, but Robert Leonard took over and spent a fair amount of time on the characterization of some of the descending fiber systems involved in the control of motor behavior.

### The Search for the Primary Afferent Depolarization-Mediating Interneurons

In the mid-1970s, I spent my sabbatical in Goteborg working with Elzbieta Jankowska. Our goal at that time was to identify the last order interneurons that mediate the PAD of muscle and cutaneous afferents. The question was where to look in the spinal cord. Available evidence was not clear about this, although there were a couple of papers by Eccles and collaborators where

they assumed that these interneurons were somewhere in the dorsal horn and intermediate zone.

The idea was rather simple but technically difficult. It required impalement of a single afferent within the dorsal horn or intermediate zone to record the PAD produced by stimulation of muscle and/or cutaneous afferents as well as by intraspinal stimuli applied at different depths in the spinal cord. We found that the shortest latencies of the sensory evoked PADs were compatible with activation of a pathway involving two interneurons (Jankowska et al., 1981). The lowest threshold PADs produced by intraspinal stimulation appearing with the shortest latencies (about 0.8 ms) were attributed to direct activation of the last-order interneurons in contact with the afferent fiber and were found when stimulating fairly restricted areas within laminae V–VI for group I muscle afferents and within laminae III–IV for cutaneous afferents. Both areas corresponded to the regions where the largest monosynaptic field potentials were evoked by fibers receiving presynaptic depolarization. It thus seemed that the first and last order interneurons mediating the PAD were located within these areas.

To work with Elzbieta was one of the most rewarding scientific and personal experiences in my life. It was also the beginning of an enduring friendship. Once back in Mexico, we aimed to record the spontaneous activity from interneurons in laminae V–VI and use the interneuronal spikes to trigger the averaging of the DRPs from the central end of a small dorsal rootlet. In addition, we used the sucrose gap technique to disclose, by means of spike triggered averaging, the motoneuron synaptic potentials (VRPs) associated with interneuronal activity (Rudomin et al., 1987).

With this approach, we were able to identify one group of interneurons located in the intermediate zone that appeared associated with short lasting inhibitory VRPs but not with DRPs (Class I interneurons) and a second group that was time locked to slower inhibitory VRPs and also to short latency DRPs (Class II interneurons). Subsequent studies with Jiménez, Quevedo, and Solodkin (Rudomin et al., 1990), showed that the postsynaptic inhibition produced in motoneurons by Class I interneurons was glycinergic and that the inhibition associated with Class II interneurons was most likely GABAergic.

The finding that the activity of Class II last-order interneurons was associated with postsynaptic inhibition in motoneurons as well as with a monosynaptic DRP in afferent fibers, suggested that pre- and postsynaptic inhibition could coexist. This was an unexpected finding considering that the general view was that pre- and postsynaptic inhibition were mediated by separate spinal pathways. However, later on, Maxwell and collaborators provided ultra-structural evidence showing that the same synaptic bouton could make synapses with the motoneurons and also with the afferent fibers contacting these motoneurons (Maxwell et al., 1990).

The functional implications of the coexistence of pre- and postsynaptic inhibition have been discussed in several publications (for review,

see Rudomin and Schmidt, 1999). Activation of Class II interneurons by supraspinal inputs, for example, during the execution of a voluntary movement, would transiently inhibit the motoneuron and at the same time depolarize the Ia afferents synapsing with that motoneuron, thus ensuring that the activity conveyed by these afferents does not interfere with the programmed descending inhibition.

### Primary Afferent Depolarization and the Potassium Accumulation Hypothesis

In the earlier 1970s, Somjen and Lothman (1974) and Kriz et al. (1974) used ion exchange resins to measure the concentration of potassium ions in the spinal cord. They found that stimulation of the dorsal roots and/or of the tibial nerve with strong, high-frequency trains increased extracellular concentration of potassium ions from three to about ten micromoles in the dorsal horn and intermediate zone. This led to a proposal by Vyklicky and collaborators (Kriz et al, 1974) that the increase in the extracellular potassium was the main cause of PAD. This contributed to the view that the PAD elicited under these conditions was rather unspecific because potassium accumulation would depolarize neighboring neurons and afferent fibers (for review, see Rudomin and Schmidt, 1999).

These findings were somewhat puzzling because there already were several observations that could not be easily explained with the potassium accumulation hypothesis. For example, Eide et al. (1968) and Rudomin et al. (1975b) showed that conditioning stimulation of sensory nerves inhibited the Ia monosynaptic EPSPs recorded in spinal motoneurons without changing their time course and also without inhibiting the monosynaptic EPSPs produced in the same motoneuron by stimulation of descending fibers. Yet, it seemed possible that the descending fibers reached the motor pool without giving collaterals to the dorsal horn and to the intermediate zone where potassium accumulated following stimulation of sensory nerves.

But it was not until the late 1970s, when Elzbieta Jankowska and Ingemar Engberg visited Mexico, that we tried to approach this question more directly by measuring the effects produced by conditioning stimulation of sensory nerves on the intraspinal threshold of single Ia and descending fibers, both ending closely to each other in the intermediate zone (Rudomin et al., 1980). Group I afferent terminal arborizations, both in the intermediate and motor nuclei, appeared to be the target of specific presynaptic depolarizing (presumably GABAergic) pathways. Rubrospinal, but not vestibulo-spinal, fiber terminals were weakly depolarized by stimulation of sensory nerves but such a presynaptic depolarization did not appear to result from the activation of GABAergic pathways.

Extracellular accumulation of potassium due to massive activation of neuronal elements seemed to account for the depolarization of the rubrospinal terminals. However, judging from the relatively small changes

in the firing threshold of the rubrospinal terminals, the depolarization produced by non-GABAergic pathways appeared to be rather small and possibly of no consequence for synaptic transmission, in contrast with the transmitter-mediated depolarization that depressed synaptic transmission.

Yet, the challenge was to measure the local changes in potassium concentration at the site where conditioning stimuli increased the excitability of single group I muscle and cutaneous afferents. For several years, I invited Ladislav Vyklicky to visit Mexico to do these experiments together, but I was never successful because his government would not allow him to leave Prague. I learned later that my mistake was to invite Ladia by name instead of asking for collaboration with somebody "expert in presynaptic inhibition that had developed electrodes to measure changes of potassium in the spinal cord"!

In 1983, I was invited by the director of the Mexican Council of Science and Technology (CONACyT), Edmundo Flores, to join him on an official visit to Poland, Hungary, and Czechoslovakia. While in Prague, I told him about all those failed attempts to have Ladislav visit our laboratory in Mexico. At the meeting, Edmundo Flores stated that he saw no point in pursuing a collaboration program with Czechoslovakia, because Mexican scientists were not allowed to invite persons with whom they wanted to collaborate. He gave as an example my failed attempts to invite Ladislav. They first suggested I should instead come to Prague, but Edmundo Flores insisted that I was the vice president of our Academy of Sciences and that my duties prevented me from leaving the country for an extended period of time, as required to perform the research we had in mind, and that they should instead allow Ladislav to work with us in Mexico. The Czechoslovakian authorities left the room and a couple of minutes later they returned and told us that they would allow Ladislav to spend three months in Mexico.

Ladislav brought the ion exchange resin he was using in Prague, so we could soon start experiments. The idea was to measure changes in the extracellular concentration of potassium at the same site where we tested changes in the intraspinal threshold of single muscle afferents.

To my delight, we found quite soon that stimulation of afferents from flexor muscles could strongly reduce the intraspinal threshold of single Ia and Ib afferents (from muscle spindles and tendon organs, respectively) ending within the intermediate zone without significantly changing the concentration of potassium measured at that same intraspinal site. In contrast, stimulation of cutaneous afferents, particularly with high-frequency trains, produced a smaller PAD of the tested afferents despite the notorious increase in extracellular potassium (Jiménez et al., 1983, 1984).

It was clear that there was no correlation between the magnitude of the PAD of muscle afferents and the changes in the local concentration of potassium ions. At the beginning, Ladia was somewhat skeptical about these findings, but since they were consistent and were obtained using the same resin that he used in Prague, and since he could not blame the air pollution that

often interfered with the filling of the micropipettes, nor the Mexican cats, he ended up accepting the evidence.

This settled a discussion of many years. By excluding extracellular accumulation of potassium ions as the main cause of PAD, the GABAergic hypothesis for the origin of PAD became more feasible. The selectivity of PAD would then depend on the location of the GABAergic axo-axonic synapses in the intraspinal arborizations of the afferent fibers.

## Functional Organization of the Pathways Mediating Primary Afferent Depolarization

Until the late 1970s, changes in PAD were mostly inferred from changes in the DRPs, which are electrotonic recordings of the depolarization generated remotely in the intraspinal terminals of the afferent fibers. This prevented proper identification of the afferent fibers subjected to PAD. Later on, PAD was inferred by measuring the changes in the amplitude or area of the antidromic compound action potentials recorded in sensory nerves after intraspinal stimulation (Rudomin and Dutton, 1968).

In 1979, after I returned from Goteborg, we developed a computer-controlled procedure that allowed a continuous estimate of the intraspinal threshold of single afferent fibers (Madrid et al., 1979). In contrast with intrafiber recordings of PAD that lasted only a few minutes, this method allowed us to measure for hours the changes in the intraspinal threshold of single afferents produced under different experimental procedures and infer the changes in PAD. A similar system was developed by Curtis almost at the same time (Curtis, 1979).

With this method, we examined the effects of a variety of segmental and descending stimuli on the intraspinal threshold of single Ia and Ib afferents (Rudomin et al., 1983). We found that Ia fibers were depolarized by conditioning stimulation of group I afferents from flexor muscles but not by stimulation of cutaneous afferents, nor by stimulation of the reticulo-spinal, rubro-spinal, and cortico-spinal fibers (Type A PAD pattern). In contrast, Ib afferents were depolarized by all of these conditioning stimuli (Type B PAD pattern). This led to the proposal that the PAD of Ia and Ib afferents was mediated by separate sets of last-order PAD mediating interneurons. This assumption differed from the suggestion initially made by Eccles et al., (1952) that the same last order interneurons mediated the PAD of both Ia and of the Ib fibers.

In a more detailed study made in 1986 (Rudomin et al., 1986) we found, in addition to the two PAD patterns described earlier, that many Ib fibers were also depolarized by reticulo-spinal and rubro-spinal stimuli but not by cutaneous stimuli that instead inhibited the PAD elicited by stimulation of gr I flexors (type C PAD pattern).

These observations were still compatible with the proposal that the synaptic efficacy of Ia and Ib fibers is presynaptically controlled by at least two different sets of interneurons. This possibility was particularly attractive

in view of their extensive convergence onto the same spinal cord interneurons because this could, at least in principle, allow independent adjustment of length feedback and force feedback to the needs of specific motor tasks.

In these studies, group I fibers were classified as Ia and Ib on the basis of their peripheral thresholds and conduction velocities. It thus seemed necessary to have a more reliable identification of the afferent fibers whose PAD patterns were being investigated. This was achieved by intrafiber recordings of the PAD from afferents whose peripheral axons were left in continuity, so we could also record the orthodromic action potentials produced by muscle stretch and contraction and use them to classify the afferents as either from muscle spindles or from tendon organs.

These studies confirmed the general conclusions derived from studies where Ia or Ib fibers were classified on the basis of their peripheral thresholds, conduction velocity, and projection to the motor pool (Jiménez et al., 1988). As in the previous study (Rudomin et al., 1986), we showed that most tendon organs had a type C rather than a type B PAD pattern.

One question that remained open was whether there was any correlation between the PAD produced by conditioning volleys to muscle nerves and the functional characteristics of the target muscle spindle afferents, for example, their responses to muscle stretch. We investigated this with Manuel Enríquez (Enríquez et al., 1996a). By using a variety of tests for receptor identification, we found that the largest proportion of muscle spindle afferents had a type A PAD pattern. However, there also was a significant number of spindle afferents with a type B and with a type C PAD pattern. In confirmation of previous studies, most tendon organs had a type C PAD pattern, a fair number of them a type B PAD pattern, and some a type A PAD pattern.

Quite interestingly, we found that the profile of PAD patterns of the population of functionally identified group Ia and Ib fibers changed after chronic nerve crush (Enríquez et al., 1996b). Two to three weeks after the nerve crush, there was a significant increase in the number of Ia afferents with a type C PAD pattern, while most tendon organs showed a type B and few a type C PAD pattern. These changes were partly reverted by six months after the nerve crush and probably reflect changes in central connectivity and/or synaptic effectiveness of the pathways that mediate the PAD of these two sets of afferent fibers. We suggested that the changes in the PAD patterns of the reconnected Ia afferents were due to an increased ability of supraspinal structures to produce PAD that could be part of a compensatory mechanism that allows central control of inadequate information arising from the damaged fibers.

### Selectivity of Primary Afferent Depolarization

In 1987, Hans Hultborn and collaborators (Hultborn et al., 1987) devised a clever non-invasive method to examine in humans changes in the synaptic

effectiveness of muscle spindle afferents synapsing with motoneurons. They found that just prior to a voluntary muscle contraction there was a differential modulation of the tonic presynaptic inhibition of Ia muscle spindle afferents; it was reduced in Ia afferents innervating the muscles that were to be contracted and increased in Ia afferents innervating the non-contracting muscles. Encouraged by these findings, we started a series of studies aimed to examine with more detail the effects of conditioning stimulation of sensory nerves, motor cortex, and bulbar reticular formation on the intraspinal threshold of pairs of collaterals of the *same* or different single afferent fibers that ended in close vicinity or in different spinal segments (Eguibar et al., 1994, 1997; Quevedo et al., 1997; Lomelí et al., 1998).

We found that stimulation of some regions in the motor cortex could have differential effects on the PAD of pairs of collaterals of the same fiber. That is, cortical stimuli could reduce the intraspinal threshold of one collateral without affecting the threshold of another collateral of the same fiber or else inhibit the PAD in one but not in the other collateral. We also found that the PAD produced by group I flexors in pairs of collaterals of the same muscle spindle afferent could be differentially inhibited by conditioning stimulation of cutaneous and articular afferents, and that such a differential inhibition was under supraspinal control.

I really don't remember when I met Robert Schmidt, but it was surely during one of the Society of Neuroscience meetings. With time we developed a friendly relationship that changed to an active scientific collaboration. During one of his visits to Mexico in the early nineties, we examined the changes in the PAD of muscle afferents elicited by stimulation of joint afferents (Quevedo et al., 1993) that led to a series of studies on the selectivity of the pathways mediating PAD in joint afferents and on the changes in their synaptic effectiveness during the inflammation produced by the intradermic injection of capsaicin (Rudomin and Lomelí, 2007; Rudomin et al., 2007; Rudomin and Hernández, 2008).

Altogether, these observations indicated very clearly that the intraspinal collaterals of the afferent fibers are not fixed routes for information transmission, as was assumed for many years, but rather dynamic substrates in which the information flow can be centrally directed to particular neuronal targets as needed for the execution of specific motor tasks. These studies provide a clear demonstration of local character and selectivity of PAD in muscle and in articular afferents.

## Where Are We Now?

Our interest in the neuronal circuits and synaptic mechanisms that regulate the relationship between individual and population monosynaptic responses started in the early 1970s (Rudomin and Madrid, 1972), but it was not until 1987 that we tried to identify the spinal interneurons that mediate PAD of group I afferents (Rudomin et al., 1987).

As discussed earlier, we found neurons that had the features expected for last-order interneurons mediating PAD and presynaptic inhibition of group I afferents. It was then when we became aware that the spontaneous action potentials of these neurons were not only time locked to DRPs and VRPs but were also preceded by a slow negative cord dorsum potential lasting 50–150 ms that started 10–20 ms before the interneuronal spikes. This fortuitous observation raised the possibility that the neurons that we assumed mediated PAD were driven by neurons located in more dorsal regions of the spinal cord.

But it was not until the end of the 1990s that we started a series of systematic observations with Manjarrez aimed to disclose the origin of the spontaneous cord dorsum potentials (CDPs) that preceded the spontaneous activation of the PAD-mediating interneurons (Manjarrez et al., 2000). As expected, we found spontaneous CDPs similar to those disclosed using interneuronal spike-triggered averaging. A detailed analysis of the intraspinal field potentials associated with these CDPs indicated that they were generated by the activity of neurons located in the dorsal horn, which responded to electrical stimulation of low-threshold cutaneous nerves, often with monosynaptic latencies.

Recording the spontaneous CDPs simultaneously from different sites in the lumbosacral spinal cord further indicated that a fair number of them appeared synchronously along several spinal segments (Manjarrez et al., 2003). Later on, we found that the coupling between the CDPs recorded from nearby segments on the left side (L5 and L6) was partly reduced after an interposed lesion of the ipsilateral dorsolateral fasciculus (DLF) and completely abolished after a contralateral DLF lesion at the same level (García et al., 2004). These findings were consistent with our previous suggestion that the CDPs were generated by a longitudinally distributed set of interconnected neurons on both sides of the spinal cord.

Already, in 1987, we had noted that most of the CDPs associated with the activity of Class I interneurons were negative (nCDPs), while those associated with Class II interneurons were negative–positive (npCDPs). This led to the proposal that separate sets of dorsal horn neurons generated the nCDPs and the npCDPs (Rudomin et al., 1987). However, more recent experiments (Chávez et al., 2012) have provided evidence suggesting instead that both the nCDPs and npCDPs are generated by the same ensemble of interconnected neurons that are distributed along several segments, in agreement with our previous proposal (Manjarrez et al., 2000).

The generation of nCDPs or npCDPs appeared to depend on the synchronization between the spontaneous firing of the neurons in the network. Under conditions of weak synchronization, nCDPs were preferentially generated. Increased synchronization, as seen after the acute section of a cutaneous nerve, would increase the temporal summation of the synaptic actions in some sets of interneurons and recruit the segmental pathways mediating PAD (Chávez et al., 2012).

Fractal analysis of the spontaneous CDPs simultaneously recorded from several segments has further indicated that the fluctuations of the CDPs are not random but have an underlying structure, even after the acute section of a cutaneous nerve or after partial spinal lesions (Rodríguez et al., 2011). This raised the question of the meaning of “fractal structure” in terms of functional neuronal interconnectivity.

To approach this question, we assumed, as a working hypothesis, that the magnitude of the correlation between the spontaneous CDPs recorded from a given pair of segments represents the strength of the synaptic connectivity among the neuronal ensembles generating these CDPs. It then follows that the correlation between pairs of CDPs recorded from different segments in the lumbosacral cord represents the spatio-temporal configuration of the connections among the different segmental sets of neurons involved in the generation of the CDPs. That is, the “state” of neuronal functional interconnectivity.

We have found quite recently that intradermic injection of capsaicin produces a long-lasting increase in the spontaneous and evoked activity of dorsal horn neurons responding to noxious and non-noxious stimuli. But the most impressive finding is the change that capsaicin produces in the patterns of correlation among the spontaneous activities recorded from different spinal segments. They acquire a *different, albeit structured*, configuration that may persist for a couple of hours. Quite interestingly, the systemic injection of very small amounts of lidocaine transiently resets the patterns of intersegmental correlation to the configuration observed before capsaicin. The resetting produced by systemic lidocaine could underlie its analgesic action observed in humans during inflammatory and neuropathic pain.

We are now facing the question of how to explain these changes in terms of neuronal connectivity. One possibility could be that the network has a limited repertoire of small groups of highly coherent neuronal aggregates (modules?) with relatively stable interconnections and that capsaicin and lidocaine switch from one configuration to another, selected from the available repertoire.

An alternative possibility would be that all these changes are the expression of a self-organizing system that has compensatory mechanisms that prevent its disintegration when subjected to perturbations that exceed a certain limit. Once this limit is exceeded, the system is destabilized and leads to a rupture of internal structure. If the perturbation persists, the different neuronal ensembles are reorganized and lead to a new structure capable of dealing with the perturbation.

Although we still lack many of the concepts and tools necessary to deal with these kinds of questions, the evidence so far collected provides a better understanding of the dynamics of neuronal networks and how they may adjust themselves to the ever-changing needs of the organism. These adjustments are not random but appear to be highly structured and can be viewed as part of homeostatic processes that tend to preserve the integrity of the organism.

Seen in retrospective, it would appear that our studies on presynaptic inhibition were variations of the same theme. What is interesting, however, is that as time went by, our way of perceiving these questions shifted from a static and relative reductionist view to a more dynamic, multidimensional approach. As Anders Lundberg once told me when I was somewhat discouraged by going back to the same old questions: “More than moving in closed circles, it seems that you have been moving in ascending spirals. That is, you have been viewing the same problems, but with a different perspective.”

To study the way in which the different neuronal networks interact is now one of the most important challenges faced by the neurosciences. This knowledge is required to understand, a little more, the generation of voluntary movements and of some basic cognitive processes including those mechanisms that contribute to pain perception—also how we learn, how we forget, and how these functions are changed during aging and different pathologies.

## My Incursions in Science Policy

I wondered for a while whether or not to include this section in my “scientific autobiography.” I am still not very sure because to some of the readers the names and situations may have no meaning. But I decided to do it because, as I stated in the introduction, the conduct of science depends on the particular conditions in each country. It may be perhaps a little anecdotal, but these were my circumstances and no others.

### *The Academy Prize in Science and the National Program of Basic Sciences*

Since 1961, the Mexican Academy of Sciences delivers the yearly Prize in Science in recognition of the scientific contributions of young investigators (less than 40 years old). In 1971, the academy awarded two prizes, one to Manuel Peimbert, a well-known astrophysicist, and another to me.

Before 1971, the academy’s awards were presented at the National University, but that year the awards were delivered by the president of Mexico, Luis Echeverría, at the National Palace. This ceremony had a special meaning because the relations between the scientific community and the government were at their lowest since the 1968 events.

During the February 1972 ceremony, President Echeverría, who took office in 1970, invited Peimbert and me to join him in a visit that he was about to make to Japan in a couple of weeks. It was precisely then when R. Burke and I were starting to have successful simultaneous intracellular recordings from pairs of motoneurons, and the idea of going to Japan was not really appealing to me.

So I thanked the president for his invitation and told him that I had a distinguished scientist visiting my lab for a few weeks and that we were doing rather difficult but important experiments that were just coming out and that it would be a pity to interrupt them at that moment. He replied

very politely that I should not worry, that this was a standing invitation, and that I should visit Japan whenever I could do it.

The ceremony continued and Eugenio Méndez Docurro, who was the first director of the recently founded Council of Science and Technology (CONACyT), stood up and announced that the president extended his invitation to the wives of the awardees to travel with him to Japan. I could just see the smiling face of Flora and knew in that moment I was to go to Japan!

As I expected, at the end of the ceremony, Flora asked me if I was going to Japan, and I said: “Well I am not sure because I have a lot of work to do at the lab,” and she replied, “You may not go, but I am going since the president invited me.”

Several hours later, I returned to the lab and had a phone call from the director of our institute, Guillermo Massieu. “Pablo,” he told me, “How could you say no to the president? Your refusal could be interpreted as a rejection because of the 1968 events when he was minister of interior. Think about how important it could be for science and for our institute to have a renewal of relations between the scientific community and the government.” A few minutes later, I got a phone call from the president of the academy, Raúl Ondarza, who expressed similar concerns and asked me to accept the president’s invitation.

A couple of days later, I was still considering whether or not to join the president on his trip to Japan when I got an invitation to attend the presentation by Méndez Docurro of the first-year activities of the Council of Science and Technology. The meeting was to be held at the official residence of the president in “Los Pinos” in front of distinguished members of the scientific community and the directors of academic and research institutions—not more than 30 persons. It was clear that I could not ignore this invitation. So there I was.

When President Echeverría entered the room, everybody went to greet him. I was shy and stayed in the back of the room. The president looked at me and said: “Now Rudomin, tell me, are you coming with me to Japan?” So I had no option but to say, “Yes, Mr. President. It will be an honor for me to join you on that trip.”

The trip to Japan was very interesting. In addition to meeting some of the most distinguished Japanese scientists (if I recall correctly, I met Yasuji Katsuki, Masao Ito, Kazunori Furukawa, and Toshinori Hongo), I also visited some of the science-based industries. But above all, it meant the possibility of having contact with persons involved in the design and conduct of the Mexican government’s scientific policy. Soon after returning from the trip to Japan, I got an invitation from the new director of CONACyT, Gerardo Bueno, to become part of an advisory group. I soon found that few of the activities of the council contemplated support of basic research. After long and sometimes tough discussions, I was able to convince G. Bueno to start a program specifically addressed to support research in basic sciences.

He asked me to chair this program, but I was concerned that this would distract me from my research. I remember I discussed this with a good friend, Jerzy Plebansky, who was at that time chairman of the department of physics at CINVESTAV. He was born in 1928, in Warsaw, where he stayed during the war, and he was a specialist in the field of general relativity and mathematical physics. He told me: "Pablo, it does not matter what you decide, you will always be sorry. The question is if you are sorry for having done it, or for not having done it." Good advice for somebody expert in general relativity! I ended up accepting Bueno's invitation because I thought it would be unwise on my part not to do it, particularly after my comments at the academy's award ceremony that the government was not supporting science as it should.

I chaired the National Program for Basic Sciences for eight years, three with Gerardo Bueno and five with Edmundo Flores as directors of CONACyT. Support to basic sciences has continued since and is now part of the regular activities of the council. Yet, the struggle to substantially increase the support to those activities and to science in general is still going on.

#### *The Mexican Academy of Science and the National System of Investigators*

In 1979, I was awarded the National Prize of Sciences, the highest distinction given by the government. Soon after, I was invited by the president of the Mexican Academy of Sciences to run as a candidate in the election of the next president of the academy.

As elected vice president of the academy, it soon became clear to me that the academy activities were mostly centered on local issues, and that very little was done to expand our relationship and collaboration with other academies. I was particularly interested in developing a good and standing relationship with the National Academy of Sciences in the United States, at that time presided over by Philip Handler. He was quite receptive when I wrote him, and we organized a meeting between the directive boards of the two academies to discuss possible collaboration that was scheduled for May 1981. As a result of this interaction, we were able to start several collaborative projects, some of which still are in operation.

I took over as president of the academy in November 1981. My first commitment was, of course, to convince the government of the need to increase the support for science. This became an urgent matter when, on September 1, 1982, President López Portillo nationalized the banks and limited the acquisition of foreign currency. Even research institutions could not get the currency to acquire and import the necessary substances that scientists needed to keep up with their research. CONACyT was also unable to get all the necessary funds, and scientists turned to the academy.

Unfortunately, there was little we could do because this happened a few weeks before the end of President López Portillo's term in office.

The federal administration changed on December 1, 1982, and Miguel de La Madrid became president of Mexico. It was also the end of my appointment as chairman of the National Program of Basic Sciences in CONACyT, but I still had one year left as president of the academy. A couple of days later, I received a phone call from the office of the new minister of education, Jesús Reyes Heróles, that he needed to contact me urgently. I called and arranged a meeting for the next day.

I knew Reyes Heróles from a trip we took together to Argentina, on which we had been invited by President Echeverría. I asked myself: "Why such urgency, just two days after his appointment?" I thought that the hurry was because he would invite me to join his team, and I could not sleep all night. Next morning, I said to myself: "If I couldn't sleep all night for this, it means that to be involved full time in public administration is not for me."

So I went to see Reyes Heróles. When I entered his office, he was smoking a cigar and offered one to me. After recalling our trip to Argentina he told me: "Pablo, I liked very much the speech you gave a couple of weeks ago during the ceremony of the academy awards, and I want you to help me to improve science in this country." I answered: "It will be an honor." He then asked me "What would be the first thing you would do?" I answered: "To set up a program where good scientists could get the support and salary they need to do their research, without looking for extra jobs or becoming administrators or politicians!" He then asked me: "Does this apply to all? What about you?" I answered "Beginning with me." "OK," he added, "Let's start with this."

And it was then when I presented to him the proposal of creating a program based on the recommendations made in a panel organized by the academy several weeks before, which took as a starting point the proposal originally presented by Carlos Gual when he was the academy's president. This program considered salary compensation for the scientists as well as the funds they required to perform their research.

Reyes Heróles asked for names of people whom he could invite to work with him. I gave him a list of several scientists whom I knew well and believed would be interested. Among them was Jorge Flores, a renowned physicist and former president of the Mexican Academy of Sciences (1976–77). He was soon contacted by Reyes Heróles and appointed as vice minister of education.

As vice minister, Jorge Flores started to work on this project, which was to be announced by the president of Mexico during the award ceremony that I chaired as president of the academy. José Sarukhan, who succeeded me as president (1984–85) and Jorge Flores, together with Salvador Malo, worked on the elaboration of the bylaws for a program named "National System of Investigators" that was formally initiated July 26, 1984.

This is not the place to discuss in detail the achievements and the limitations of this program that started around 30 years ago and is still functioning. The number of investigators incorporated into the program has increased with the years. It started with 1,396 investigators. By 2011, 27 years later, there were 17,637 members.

Besides the increased number of scientists incorporated into the system, I feel that this program changed the way that society perceives scientific activity. Although it was initially conceived as a selective mechanism to provide salary compensation to the investigators in times of crisis, with time, it became a symbol of “status” in the sense that being a scientist was socially relevant.

*El Colegio Nacional and the Science Advisory Council  
for the President*

Throughout all these years, I have received several public recognitions for my contributions to science, among them the award given by the Mexican Academy of Sciences in 1972, the National Prize of Sciences in 1979, and Spain’s “Principe de Asturias” prize for scientific investigation in 1987. I must say that the Principe de Asturias was particularly gratifying because it signaled an international recognition for the work I performed in Mexico during so many years and gave me the opportunity to have a stronger interaction with Spanish scientists and to develop a collaboration that is still vigorous.

In 1993, I was appointed a member of El Colegio Nacional. El Colegio Nacional was founded on April 8, 1943, for the purpose of promoting Mexican culture and scholarship in a number of different fields. It is a life-long appointment and is meant to include the most distinguished personalities in science and in the humanities. As an elected member of El Colegio Nacional, I have delivered a series of public lectures, usually 10 per year, in different academic and scientific institutions throughout the country. These lectures have been mostly addressed to students in different areas such as medicine, biology, chemistry, and engineering. The attendance has been really impressive, usually between 150 and 200 per lecture. After the lecture, I spend some time with a small group of students answering their questions and discussing relevant issues in education and science with them. Some of these students have appeared to be really motivated by science, and a couple of them ended up working for some time in my laboratory.

In addition, as member of El Colegio Nacional, I have had the opportunity to interact with several of the most distinguished personalities in Mexico (outside of science) whom I would not otherwise have met in my daily routine. The discussions with them, at our monthly meetings, have enriched my vision of different aspects of life in Mexico and led to the organization of a series of symposia and publications where many of us have presented

our views and studies on different issues of general interest, such as “The Frontiers of Complexity: The Mysteries of the Brain,” “An Integrative Vision: Universe, Life, Man, and Society,” “The Concept of Reality: Truth and Myths in Science, Philosophy, Art, and History,” and “Free Will versus Determinism.”

In 1988, some of the members of El Colegio Nacional talked with President Salinas about the possibility that the executive branch of the Mexican government should create a science advisory group of whom the president could ask opinions on specific issues of national relevance. In 1989, in response to these suggestions, President Salinas created the Consejo Consultivo de Ciencias (Science Advisory Council). This council was formed, in an honorary and voluntary manner, by those scientists who had been awarded the National Prize of Sciences. It was to be coordinated by one of them, elected from among the council members.

The first general coordinator was Dr. Guillermo Soberón, member of El Colegio Nacional, former rector of the National University, and former minister of health. The council could not have been in better hands. During his appointment as general coordinator, he promoted a series of studies on issues of national relevance that were then sent to the president. He also organized several meetings with President Salinas where the members of the advisory council could present him with studies and opinions on significant issues in science and technology.

He promoted the creation of the Prize “Mexico” that was awarded to scientists from Ibero-America (with the exception of Mexico because they already had access to the National Prize of Science) for their contributions to science and technology. This award is now given annually and is handled by the Science Advisory Council and CONACyT.

In addition, Dr. Soberón was instrumental, together with California congressman George Brown, in the creation of the United States–Mexico Foundation for Science. As general coordinator of the advisory council, Dr. Soberón was a member of the governing board of the foundation.

In May 1995, I was elected as Dr. Soberón’s successor, but it was not until 1996 that I could have a formal meeting with President Ernesto Zedillo. My first task was to learn his plans pertaining to the destiny and activities of the Science Advisory Council. When we met, he expressed his interest in its continuation. Among the plans he had for the council was a study of the structural changes required for a better and steadier support of research in science and technology in order to make them more responsive to national needs.

Together with specialized lawyers, we analyzed the third article of the Mexican constitution that explicitly indicated the commitment of the Mexican State to support scientific and technological research. This was the basis for the revision of the bylaws necessary to comply with the constitutional mandate.

Revision of the bylaws required a close collaboration between the Scientific Advisory Council, the Mexican Academy of Sciences, CONACyT, and the ministry of education. In the process, I learned how difficult it is to make a law and how careful one should be with each word, to avoid erroneous interpretations and, at the same time, not to transform the law into a straightjacket.

After we had the first draft, we met with the commissions of science and technology of the Congress. It took some time to have a text that was satisfactory to all. Once available, it was submitted to the presidential legal advisers. This meant additional discussions and changes until finally, President Zedillo sent the proposal to the Congress on December 15, 1998. It was approved unanimously by April 30, 1999, and published by the executive branch on May 21, 1999.

Proper application of the law required decisions at the highest level in the government. In August 1999, I presented a study to President Zedillo suggesting the creation of a cabinet of science and technology headed by the president himself and integrated with the ministers of education, health, environment, agriculture, economy, and treasury, and with the director of CONACyT and the general coordinator of the Scientific Advisory Council as invited guests. The idea was that they should meet several times per year to advise the president and make decisions on important issues pertaining to science and technology, including the application of the law.

President Zedillo approved the proposal. The bill creating the cabinet was published on December 2, 1999. The cabinet met only once, on May 9, 2000, but even so, it was able to decide about several important issues, among them the creation of special funds for research in priority areas that would be supported by CONACyT and by other government agencies (health, education, etc.). These programs are still active. The Cabinet on Science and Technology has been recently revived, after 12 years of hibernation during the past two administrations.

My first term as general coordinator of the advisory council was for three years, and I was re-elected for another term. The last year was under the presidency of Vicente Fox. He appointed José Sarukhan as commissioner. He had, among other things, the responsibility of dealing with science and technology. We had a good interaction and started to analyze possible strategies aimed to further strengthen and increase the funding of scientific research. Unfortunately, he resigned two years later, and the proposed changes were not implemented.

## Epilogue

Seen in retrospective, to be involved in scientific policy was very time-consuming. I worked hard not to be away from the laboratory, and I could do it to some extent because I had the enthusiastic collaboration of my

colleagues and students, who were not afraid of remaining for long hours with experiments, as well as family's understanding and support. I am now back full time in the laboratory and with my commitments to El Colegio Nacional. This, together with the time I now spend with my family, fills up all my days. Unfortunately, traffic in Mexico City is so hectic and unpredictable that it often prevents me from meeting with friends I have made through the years. This is the price we pay for living in an overcrowded but still attractive place such as Mexico City.

We have still a long way to go. We need to teach our students and our young investigators to be more self-confident and more competitive and to seek quality instead of quantity in their scientific contributions. We also need to convince our authorities to reduce administrative and bureaucratic obstacles that, instead of helping, prevent and delay scientific research.

Yet, being in a country like Mexico has its advantages. I am now almost 80, and I can be active thanks to the institutional support that provides me space, technical and secretarial help, and a small amount for current expenses. I compare my privileged condition with that of some of my peers in the United States or in Europe. Some retired because they became tired of dealing with grant applications and merciless competition. Others were forced to retire to make space for the new generations. I wondered whether I could have done my research if I had moved to one of these countries. I doubt it because here in Mexico I had time to think, and I was not enslaved by the inevitable need to justify my existence. Unfortunately, this is not the case for most of our young investigators who, unable to find the proper research positions in our academic institutions or in the industry, must leave the country. I just hope that working conditions soon will be sufficiently attractive so that these young people stay in Mexico.

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