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Pasko Rakic

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Petersen



Pasko Rakic

BORN:

Ruma, Former Yugoslavia
May 15, 1933

EDUCATION:

University of Belgrade, MD (1960)
University of Belgrade, PhD (1969)

APPOINTMENTS:

Resident in Neurosurgery, University of Belgrade Faculty of Medicine (1961–1962)
Clinical and Research Fellow in Neurosurgery, Harvard Medical School, Boston (1962–1966)
Assistant Professor, Developmental Biology and Genetics, Biological Institute, Belgrade (1967–1969)
Assistant to Associate Professor of Neuropathology, Harvard Medical School, Boston (1969–1978)
Professor and Chair of Neurobiology, Yale University School of Medicine (1978–2015)
Director, Kavli Institute for Neuroscience, Yale University (2004–2015)
Dorys McConnell Duberg Chair in Neuroscience, Yale University (1978–present)

HONORS AND AWARDS (SELECTED):

Member, National Academy of Sciences, United States (1985)
Member, Serbian Academy of Arts and Sciences (foreign member) (1985)
Karl Spencer Lashley Award, American Philosophical Society (1986)
Francois I Medal, College de France (1986)
Member, Croatian Academy of Arts and Sciences (foreign member) (1990)
Fyssen International Science Prize, Paris (1992)
Member, American Academy of Arts and Sciences, United States (1994)
President, Society for Neuroscience (1996–1997)
The National Academy of Medicine, United States (1999)
Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience (2002)
Kavli Neuroscience Prize (2008)
Member, Norwegian Academy of Science and Letters (foreign member) (2008)
Krieg Lifetime Achievement Award shared with Paul Allen (2010)
Child Mind Institute Award, New York City (2014)
Member, Royal Society London, United Kingdom (foreign member) (2016)
The Charles Branch Brain Health Award (2018)
Member, Royal Academy of Medicine, Spain (foreign member) (2018)
Connecticut Medal of Science (2019)
Sterling Fellow, Yale University (2020)

Pasko Rakic is recognized for his discoveries of the molecular and cellular principles of neuronal generation, migration, and differentiation that underlie the development and evolution of the brain, particularly the cerebral cortex. His pioneering studies of cortical neurogenesis in rodents, nonhuman primates, and humans led him to propose the radial unit and related protomap hypothesis of the development and evolution of the cerebral cortex, which explain how three-dimensional laminar, columnar, and areal organization of the cortex is built from a two-dimensional layer of neural stem cells in distant proliferative zones. Rakic then identified genes involved in specific developmental events and provided quantitative data for the overproduction and selective elimination of axons, synapses, and neurotransmitter receptors in the primate brain before they decline to adult levels during prolonged primate adolescence.

Pasko Rakic

I admit that it took me a long time to finally decide to write this autobiography. I had not responded to numerous kind invitations by Larry Squire, more recently joined by Thomas Albright. The idea behind the book series entitled *The History of Neuroscience in Autobiography* was not to write or document dry scientific facts that can be found in the original research papers, but rather to provide personal recollections and stories about your professional and private life and how it all happened, who inspired your choices and actions, and who were your role models. In addition, it should contain some interesting and unusual anecdotes. So, it is an arduous task, particularly if one has a long history, and I am probably one of the oldest neuroscientists who is writing this type of autobiography. Therefore, I was wondering who would be interested to read it when many of my colleagues that participated in some of these events are no longer with us? It is also rather difficult to make statements in personal terms, like “I made some significant discoveries,” without looking self-serving. I was also reluctant to spend the time necessary for writing an autobiography at the expense of my still very active enterprise. I finally did it now, because of my solitary disposition in my home as a result of COVID-19, which allowed me to indulge in reminiscence and to devote sufficient time to complete this difficult task.

Origin and Early Years

I was born in Ruma, a small town in Vojvodina, which was at that time a province in the Kingdom of Yugoslavia. Although this autonomous province is now part of the Republic of Serbia, members of my family were immigrants with multi-ethnic roots. My father, Toma Raki, the son of Anton Raki, was Croatian born in Istria, a peninsula at the Adriatic Sea, which at the time was part of Italy. My paternal grandmother, Maria Cukon, was also born in Istria and of mixed Croatian, Italian, and Albanian lineage. In 1924, to escape from rising fascism in Italy, my father emigrated to the newly formed South Slavic country named Yugoslavia. There, he met my mother, Juliana, who was born in Dubrovnik on the Dalmatian Coast of the Adriatic Sea. Her father, Miloš Todorić, was Serbian and her mother, Pepa Kuzma, was of Croatian and Slovakian ancestry. At the inauguration of the Kavli Prize in Oslo, when asked my origin, I explained that it is a rather complex issue. So, the narrator of the ceremony, Jon Storm-Mathisen said, “Maybe the best information would be to tell us where your ancestors were born?” I replied, “When my grandparents were born, the peninsula of Istria was part of the Austro-Hungarian Empire, in 1918 it became Italy, in 1946 it

became Yugoslavia, and in 1991 it became Croatia. Therefore, they lived in four countries without moving from the same house” (figure 1).

My father had innate intelligence and was particularly adept at working with numbers. In his new country, he attended a financial school in Novi Sad and subsequently earned a job as the district director of the Internal Revenue Service. At that time in Yugoslavia, in order to prevent the temptation of extending favors to local friends, district directors, and of course members of their families, were required to move from one town to another about every three years. It was emotionally difficult for me as a young boy to leave friends behind and then repeatedly try to make new friends in new places. Thus, later in my life, I related more to the people than to the places and never felt that I fully belonged anywhere. I was born in Yugoslavia, a country that no longer exists, and have lived the longest and made my professional career in the United States, which is a multi-ethnic society.

Apart from being devoted to raising two children, my mother was an avid reader and collected books that ranged from classical French, Russian, and American literature, like Honoré de Balzac, Fyodor Dostoevsky, and Sinclair Lewis, to the psychology classics, like Sigmund Freud and Alfred Adler. Reading books or even items in an encyclopedia during my childhood was the only escape from the cruel and senseless World War II that deeply affected our country. During German occupation, I saw people killed in the street or relatives disappearing overnight from my life without any trace. Some local people cooperated or participated in the quisling governments created by German occupiers, and three different national factions, Croatian fascists “Ustaše,” Serbian nationalists “Četnici,” and Marxist

Ancestors changed four
countries without moving
from the same house in
Istrian Pennisula at Adriatic



Figure 1. House of my ancestors in Istria Peninsula at the Adriatic Sea.

league of “Communists” killed my grandfather, one uncle, and a cousin during the war. Hence, I could say that I was a real Yugoslavian, as I was suffering equally at the hands of extremists from all sides.

For a while, I was seriously devoted to chess, memorizing entire movements made by the World Champions. At the age of 14, I was beating my classmate Vladimir Sokolov, who eventually became a world-class International Chess Federation master. Unlike Vladimir who persisted, however, I stopped playing chess at the age of 15, because I felt that it was too time-consuming and did not produce or explain anything. The exposure to chess at that critical developmental age, however, had a long-lasting positive effect on my thinking and selecting between various possibilities in the future. My mother had unrealistic expectations for me and insisted that I take strict classical piano music lessons. I did not have much enthusiasm or talent for the piano, and instead I mastered playing the accordion. I was sufficiently proficient to play in the school’s orchestra at weekly dance parties. However, I did not like this arrangement, as while I was playing, my friends were dancing with nice girls. Another, more enjoyable pastime was painting watercolors and drawing graphics, as well as creating wooden and metal models of trucks, tanks, and airplanes, which were not available as toys during the war. I was also quite athletic and was winning most of the 100-meter dash races and my class represented our school at the national competition.

Although I was raised as a Catholic, my parents were not religious and went to church only occasionally to attend Midnight Mass on the night of Christmas Eve. Perhaps motivated by resentment of the dominating atheistic communism in postwar Yugoslavia, I tried to find answers to some basic questions of life in religion. Also, Catholics were advocating forgiveness and were against killings. Thus, on my own, I decided to become an altar boy at the age of 8 and began to get up at 6:30 a.m. every morning and walk several miles to church to serve at the mass. There I would join the priest and listen to the long ceremony, which was at this time entirely in Latin language. I did not fully understand all the words but learned the entire mass by heart and even now remember some long passages. However, over time I found myself debating biblical explanations of the origin of the universe at meetings with my fellow altar boys, as well as with the priest. For example, I was upset to learn that Giordano Bruno was burned and Galileo Galilei was tried by the Roman Inquisition because of their views of the universe that were contrary to religious beliefs at the time. By the age of 14, I asked, “How could people who thought that the earth is flat teach us anything about the origin of the universe?” After I made this statement, our priest told me to leave and stop attending the group meetings. Thus, at that early age I realized that scientific facts and strict religious beliefs could be in conflict; and, intuitively, I have preferred to err on the side of science. Many years later my friend Michael Bennett, a member of the National Academy of Sciences

(NAS) and smart guy, told me, “Gentleman never talk about religion,” and I said, “If one aspect of being a gentleman is to be afraid to say what they think, then I do not have this particular aspect.” However, I do think that most religions have the basic intent to do some good and that the believers in the afterlife are lucky, and I still like to attend Midnight Mass for nostalgic music and sentimental reasons.

I obtained high school education in the town of Sremska Mitrovica, which even after the Communist takeover, continued education in the Austro-Hungarian-style gymnasium (equivalent to high school and junior college in the United States). The gymnasium had a strong emphasis on classics, history, philosophy, and literature, but also on algebra, geometry, calculus, and the natural sciences of biology and physics. I also had courses in Latin, French, and Russian languages, but unfortunately English was not recommended as a choice because it was used in the countries with a “rotten capitalist system.” My three-years-older sister Vera attended the same school and after completion entered university and received a diploma in higher mathematics, which at the time was rather unusual for a woman. I was a top student in the gymnasium class and was elected to be a leader of the debating Literary Club, which met monthly. I enjoyed vigorous discussions with both fellow students and professors. However, I was not a conformist and often took a position against the prevailing views, established dogmas, and authorities, a practice which I continued later in my life, sometimes to my detriment.

Higher Education

There was never any doubt in my mind that I should continue to seek the highest educational level possible, especially since education in socialistic Yugoslavia was free as long as one had good grades. Initially, I was interested in pursuing a career in art or architecture as they offered some level of freedom of expression, even in the socialistic society. However, my father thought that even art was controlled by communists and dominated by “socialistic realism” and convinced me to apply to medical school with the statement that, “If things do not work as well as you wish, it is better to be a mediocre doctor than a mediocre artist.” This advice was, perhaps, influenced by his experience of losing his life savings after the Socialists came to power in 1946 and expropriated all his holdings in the banks. He also told me at this time the popular proverb, “that knowledge is the only thing that cannot be taken from you.” Thus, I enrolled in Medical School at the University of Belgrade to hopefully learn some useful information.

Belgrade was, at that time, the capital of Yugoslavia, a country with a multi-ethnic population of about 20 million. It was a cosmopolitan city, with excellent classical music, opera house, and several repertory theaters that I regularly attended and enjoyed. I also kept in touch with art by writing

reviews for the major Belgrade newspapers about the avant-garde theater shows. I was also publishing reflective and satirical poetry. In addition, I earned some money by drawing cartoons and caricatures for the local satirical journals. Some of my friends suggested that I abandon medical school and become a professional writer and cartoonist, because “anybody can finish medical school, but only a few have talent for writing poetry and to create original cartoons.” However, my writing and drawing activity did not prevent me from getting top grade at the Medical School.

As the medical student with the best record in the class, I won a summer scholarship to Finland and spent two summer months in the Department of Gynecology at the Helsinki Medical School. I liked Finnish people and their customs, including hot nudist saunas at the coast of a cold lake, which I attended with my professor, his wife, and daughter. I was particularly impressed with Finnish women, whom I thought were nice looking, and I had several dates with Miss Helsinki, Karina Tapiovaara. This was my first trip abroad, and I also used this opportunity to visit several capitals of other Western European countries, including Vienna, Amsterdam, and Stockholm. I began to appreciate the value of freedom and expression of rights to have different views, which was being so strongly suppressed by the socialistic regimes.

After returning to Yugoslavia, during a regular histology course at the Medical School, which I also taught as a Student Aid, I was exposed to a book with Ramon y Cajal’s drawings. This book opened to me a universe of unbelievable complexity and beauty, formed by the black silhouettes of nerve cells, as well as Cajal’s imaginative thinking about how they may have evolved and function. This exposure to the “neuronal forest,” perhaps in addition to the compelling problems of neuropsychiatric diseases, drew my interest to the brain. Many years later, I was asked by Javier DeFelipe from the Cajal Institute in Madrid to write a foreword to his book entitled *Cajal, Neuronal Forest: Science and Art*, which I gladly did (DeFelipe, 2019; Rakic, 2019).

Residency in Neurosurgery and Fellowship to Harvard Medical School

Following graduation from medical school, I entered into an internship at the University Hospital and then enrolled in the residency program in neurosurgery. The training in neurosurgery was rigorous, but I was a bit disappointed as it did not meet my expectation as an intellectual endeavor. I also did not like that my daily activity did not depend on me, but rather on the strict schedule, which started very early in the morning and was prepared by the head nurse. There was no choice or creativity and most of the operated patients died almost at the same rate as the unoperated. Nevertheless, according to my professors, I was quite skillful with

my hands, and on my way to becoming a successful neurosurgeon with a secured university faculty position. However, during the second year of my residency, I met Hannibal Hamlin, a neurosurgeon from Boston (United States) who was visiting the Neurosurgery Department at the University of Belgrade. We went to dinner, and he liked very much our discussion about the brain and urged me to apply for an international fellowship to train at Harvard Medical School. He assured me that my rather poor English would not be an obstacle and that I would be able to learn. So, I applied and obtained a Clinical and Research Fellowship to be spent in the Department of Neurosurgery at Massachusetts General Hospital in Boston, which was chaired by William Sweet.

After arriving in Boston in the fall of 1962, I had my first Thanksgiving Dinner at Hamlin's home at 270 Benefit Street in Providence, Rhode Island. I had not realized that he was a descendent of the senator from Maine, Hannibal Hamlin, who was the 15th vice president during Abraham Lincoln's term. Some other guests at the dinner were descendants of the former U.S. president Van Buren and vice president Rockefeller. I went to the dinner in a tailor-made black suit with a white shirt and red tie that I brought from Yugoslavia to impress my new colleagues. To my surprise, the other guests at the dinner were dressed very casually in old, wrinkled shirts, cheap jerseys, and jeans. I learned my lesson; poor people in the United States at that time dressed up, and rich people tried to hide their wealth by wearing cheap clothing. These days both rich and poor try to dress as unattractively as possible. In the backyard of the house and before Thanksgiving turkey dinner, I played my first (American) football game with the other guests and spoiled my beautiful white shirt.

During my fellowship at Harvard Medical School, I had an additional assignment to perform some research on neuroanatomy of the human brain in the Warren Anatomical Museum, which was part of the Department of Neurology and Neuropathology. There, I was lucky to meet the world-famous neuropathologist, Paul Yakovlev. He was originally trained with the legendary Ivan Pavlov in his native St. Petersburg, and after the October Revolution, he escaped from the new Soviet Union and immigrated to France and worked in Paris with another famous neurologist, Joseph Babinski. Paul, a European-style intellectual, introduced me to the challenges and joys of studying the development of the human brain. He also instilled in me the idea that understanding of the human brain will not come from the study of single cells or identification of specific signaling molecules that we share with other creatures, but from unraveling the pattern of neuronal circuitry that is exclusively human and that underlies aspects of our unique mental capacity, such as language and abstract thinking. He also believed, like Albert Einstein, that the understanding of the meaning of a finding is as important as the finding itself. My original two-year fellowship transformed into a four-year stay in Boston, during which time I immersed myself in

analyzing the neuronal organization of the human brain in Yakovlev's collection. Paul was an erudite who loved history and introduced me to the classical literature on human brain development. He also showed me that research is fun, and when asked when he would stop working, Paul would reply, "I never did work!"

In addition to assisting neurosurgery operations and following patients' postoperative states, I was interested in neurology and regularly attended Tuesday's "Brain Cutting Sessions" at Massachusetts General Hospital, conducted by Raymond Adams, as well as Saturday's weekly conferences held by Norman Geschwind and Derek Danny-Brown at the Boston City Hospital. Nevertheless, because of my disillusion with neurosurgery, I devoted most of my time to learning about advances made in basic neuroscience research. I was particularly interested to probe fundamental questions, including exploration of the molecular and cellular mechanisms that enable initially uncommitted progenitor cells (now renamed stem cells) in the embryo to generate neurons that migrate to their proper areal and laminar destinations and form the mature human cerebrum, the most complex organ in the known universe.

Visit to the Moscow Brain Institute

Following my exposure to the human brain at Harvard, and my experience in research on the developing human brain for my doctoral dissertation after I returned to Belgrade, I was offered and accepted a two-month exchange program to visit the Moscow Brain Research Institute of the Soviet Academy of Sciences. There in 1967, I met several of the prominent Russian scientists, like Semen Sarkisov, Gregory Poliakov, and Tatiana Leontowich. They showed me at the microscope sections of Lenin's brain that were cut into serial tissue sections and stained by Cécile and Oskar Vogt. I was looking at the neurons in Lenin's auditory cortex and thought that these cells created speeches that influenced millions of people and changed the history of the entire world. During that time, I also went to St. Petersburg (then called Leningrad) to visit the Sechenov Institute of Evolutionary Physiology and Biochemistry.

I spent New Year's Eve 1968 at the home of Andrey Polenov, whose predecessors were on the ship *Aurora*, which fired guns at the onset of the October Revolution. It happened that during the time of my visit, the Soviet army invaded Czechoslovakia. My host toasted with a glass of slivovitz, which I had given him as a gift, with the words, "For the friendship without tanks." However, a KGB agent was also present at the dinner and reported that conversation. Nothing happened to Polenov, but the KGB suspected that I might be an American or one of Tito's secret agent. Josip Broz Tito indeed came in defense of Czech leader Alexander Dubcek, and all airplane flights to Yugoslavia were cancelled. Therefore, I could not leave

the Soviet Union and instead had become a candidate for deportation to a camp in Siberia. For days I was detained in Moscow's Hotel Ukraina (at Soviet expense) and was very scared. The person who was assigned to watch me was a nice young lady, who told me openly that I may be imprisoned in Siberia because I was suspected of being an American or Yugoslavian spy. She suggested that we walk out of the hotel to talk more freely, and I was happy to oblige. After hearing my recital of the Russian love poems by Fyodor Tyutchev, which I knew by heart, she was very impressed and began to like me. She did not believe that someone who is in love with subtle Russian romantic poetry, could hate Russia, and would be a spy. She also seemed to like me and was trying to help. Finally, one night at 2 o'clock after midnight, KGB agents picked me up and drove me to the Sheremetyevo Airport, which was at that hour closed for passenger traffic. They embarked me on a military cargo plane, which was loaded with arms destined for Uganda (Africa). The Soviets made a deal that if Yugoslavia allowed their plane to stop at Belgrade Airport to refuel, in return, they will dispose of me. Indeed, I was left after midnight at the Belgrade Airport, which was closed for the regular passengers. At that time, I was very frightened and decided never to visit Russia again, and so far, I have kept that promise, even though over the years I have been invited to several interesting meetings.

Changing from Medical to Basic Science and Enrolling in Graduate Program

After a productive experience in Boston (United States) and Moscow (Soviet Union), I returned to Belgrade (Yugoslavia) and decided not to rejoin the residency in the Harvard Neurosurgery Department. I thought that I could contribute more by doing basic research than by caring for individual patients, given that so much was unknown about causes and pathogenesis of congenital neuropsychiatric disorders. I also wanted to escape the routine duties in clinical medicine, especially because so little could be done for patients with neurological disorders or brain trauma without more knowledge about the brain. However, I recognized that to become a good basic scientist, I needed to learn more about genetics and molecular and cellular biology. Therefore, I decided to obtain a graduate degree in the Belgrade University program of Developmental Biology and Genetics. For my thesis dissertation, I decided that the question of how a complex organ like the human brain, which mediates thought and creativity, and develops from a single fertilized cell, is the most important question in medicine that probably could be answered by modern methods and creative thinking.

As part of my research on my doctoral thesis at Belgrade University, I used a recently available radioactive marker for DNA replication, (H^3 -thymidine- [3HdT]), to label the last cell divisions in viable tissue slice preparations of postmortem embryonic human cerebrum. I had smuggled a small

container with ^3HdT on my return from my previous visit to Boston. I can admit this unlawful act now because the statute of limitation has passed. However, I knew that ^3HdT has such weak radioactivity that it could not penetrate even a sheet of paper and could not endanger me or anyone else on the plane. This sample of radioactive chemical enabled me to perform experiments on human slice preparations to identify neural stem cells, which continue to divide “supravivally” (after death) in the tissue culture medium. I created the title “Supravital DNA Synthesis,” but because the initial observations and ideas in my dissertation were written in Serbo-Croatian language, Sidman helped me to make translation to proper English. Thus, his name was added to the authorship of the paper, which was published in *The Journal of Neuropathology and Experimental Neurology* (Rakic and Sidman, 1968). In the 18th century the classical anatomist, Wilhelm His, suggested that postmitotic neurons may migrate based on the examination of the histological preparations from embryonic human cerebrum. However, my work was the first direct experimental evidence that showed that in the several regions of the human brain that I examined, including the large and highly convoluted cerebral cortex, neurons are not generated locally. Rather, they actively migrate from the place of their origin in the proliferative centers near the cerebral ventricle to their final positions. In my doctoral thesis, I described that heavily radioactive nuclei, indicating cell division, are concentrated in the two distinct transient proliferative cellular layers situated near fluid filled cerebral ventricles. Based on these findings in my doctoral dissertation, I subsequently termed these transient cellular compartments ventricular (VZ) and subventricular (SVZ) zones. I also observed that heavily labeled cells but are rare or absent in the superjacent intermediate zone (IZ) and cortical plate (CP) below the pial surface.

Emigration to United States

On the basis of these fundamental discoveries and formulation of new concepts, I was offered a faculty position as an assistant professor in the Department of Neurology and Neuropathology at Harvard University in Boston, which was chaired by Raymond D. Adams. I did not have a problem obtaining a permit to leave Yugoslavia, because Marshall Tito was trying to create “communism with a human face” and was allowing emigration to the West, as he pointed out: “If people want voluntarily to be exploited by capitalists let them go.” Indeed, many including me wanted to leave. However, the U.S. Embassy in Belgrade presented some obstacles because at the time they had a strict quota for immigration from the Socialistic Republic of Yugoslavia, and I was told that I must wait at least two years before I could get a proper legal U.S. visa. Again, I was lucky that at that time (during Richard Nixon’s administration) the U.S. secretary of state was Elliot Richardson, the brother of the Massachusetts General Hospital

neuropathologist Edward Pierson Richardson, Jr., who enthusiastically supported my appointment. Elliot Richardson contacted the U.S. Embassy in Belgrade, which then called me on the very same day and asked me to come to their office to obtain my U.S. visa.

At that time, people leaving Communist Yugoslavia were allowed to take with them no more than \$20 in cash. On the first leg of the flight from Belgrade to Paris, I ordered a Coca Cola to taste it. I did not like it, but it did not cost me anything. So, on the flight from Paris to Boston, I ordered a martini, about which I knew from watching Humphrey Bogart drinking it with Ingrid Bergman in the movie *Casablanca*. However, it cost me \$3, so that I immigrated to the United States with a total possession of only \$17 and no relatives and no friends. Indeed, I left a unilateral, leftist Marxist, egalitarian society in which all are equally poor, to come to the American libertarian system, which at that time, emphasized individualistic competitive meritocracy and allowed opportunity to all. People usually say that I am highly competitive and that, therefore, America was great for me. It is interesting that today, many of the people who benefited from that American meritocracy now attack it as being inhumane and preach the Marxist ideology that I, and many others who escaped, left behind. However, I liked the capitalistic system of the United States, which at that time provided me with an opportunity to succeed according to my abilities.

Faculty Position at Harvard Medical School

I loved the opportunities at Harvard Medical School, which I considered to be unlimited. Because of my knowledge of human brain anatomy, I was asked to be the main lecturer in the neuroscience course, and in spite of my heavy accent, I was voted by medical students as the most popular teacher. In addition, before I received sufficient grant support for my research, I began translation of my doctoral thesis into English with the help of Richard Sidman, who was an excellent English writer. Part of this task was a description of my drawings of the developmental stages of the fetal human cerebral wall, based on the Golgi silver impregnation method. These findings led me to suggest new terminology for the basic cellular compartments in the developing cerebrum.

At that time Sidman was a member of the Boulder Committee for embryonic terminology, formed by the American Anatomical Association, and he presented my original drawings and my concepts and basic terminology at their meeting in Colorado. The members of the committee thought that this was very useful information and adopted my terms for the transient embryonic zones (VZ, SVZ, and IZ) as universal new terminology for the developing vertebrate nervous system. To make it clear that I created these terms, I was advised by my colleagues to sign my schematic drawing, which was reproduced in the Boulder Committee Report published in the

Anatomical Record (1970) as evidence of the original source of the concepts and terms (see review of this subject in Bystron et al., 2008). Only one additional significant transient cellular compartment, the subplate zone (SPZ), which was subsequently discovered by Ivica Kostovic in 1974, was added to the nomenclature (see details in Kostovic and Rakic, 1990). In addition, my postdoctoral fellow Donald Schmechel used the Golgi method to examine in more detail the macaque outer half of the SVZ, at the border to IZ. This zone generates some neurons destined for the superficial cortical layers, but produces mostly glial cells, which in primates outnumber neurons (Schmechel and Rakic, 1979a). Some of the radial glial cells even transiently stop dividing to serve as a stable cytoskeleton of the expanding CP (Schmechel and Rakic, 1979b). This subdivision of the SVZ was later confirmed by immunohistochemistry and named the outer subventricular zone (oSVZ) by Smart et al. (2002). The production of glial cells in this zone continues after birth and contributes substantially to the formation of secondary and tertiary gyri in primates, including humans (Rash et al., 2019; Arellano et al., 2021).

I was lucky that when I entered the field there was an influx of new methods in genetics, molecular and cell biology, electron microscopy, immunohistochemistry, and tracing techniques to detect the pattern of neuronal connectivity. I had an opportunity to meet MIT professor Francis O. Schmitt who created the Neuroscience Research Program (NRP) which was the first society in the world with this name. I was invited to the regular meetings to serve as “scribe,” which provided me an opportunity to meet and discuss issues with the best known intellectuals and researchers, including Nobel Prize laureates, such as Francis Crick, James Watson, John Eccles, Severo Ochoa, Jerry Edelman, Marshall Nirenberg, and even mathematician Ilya Prigogine. For example, Francis Crick was originally an expert in X-ray diffraction methods, but he recognized the value and importance of neuroanatomy (e.g., Crick and Jones, 1993). He made a serious effort to learn neuroanatomy from the world experts, like MIT professor Walle Nauta (also a member of the NRP). During dinner and continuing into late hours passing midnight, we would spend hours discussing the cellular and developmental mechanism of the visual system formation as well as radial unit hypothesis (RUH). Francis Crick thought that a physical diagram, similar to the Double Helix in genetics, also was needed for the developmental neurosciences and that my Radial Unit model was the most appropriate candidate for this. I was still young and honored that he found it worthwhile to spend so much time with me discussing various conceptual issues and valued and liked some of my ideas. I also benefited from the new advances and changing concepts made by my colleagues in developmental biology, too many to be listed here. Thus, I decided to build upon my initial discovery and to focus on the kinetics of progenitor cell proliferation, now called stem cells, and the mechanisms of neuronal migration. I also contributed to NRP publications

(e.g., Rakic, 1975b; 1980). The fact that the different neuronal classes must be produced at precise times and sequentially migrate to distant prespecified locations fascinated me to the extent that I was willing to devote, if necessary, the rest of my life to decipher how it works at the cellular and molecular level.

Initially, I used spontaneous mutation in inbred strains of mice as a model system to study how genes affect neuronal connectivity. Today the role of gene mutations on the synaptic pattern is being hotly pursued in *Drosophila* and *Nematode*. However, the first description of changes in synaptic organization due to single gene deficits was not obtained from a simple model organism but, rather, was based on electron microscopic examination of neurological mutant mice. In collaboration with Verne Caviness and Richard Sidman, the first evidence of abnormal synaptic contacts due to single gene mutation was obtained in mice named *weaver* and *reeler* (e.g., Rakic and Sidman, 1973; Caviness and Rakic, 1978). These initial studies that were carried out in mice with spontaneous mutations opened new fields for exploration (reviewed in Rakic and Caviness, 1995). I became interested in the cells that were considered non-neuronal or glial but serve as predecessors for all neurons. These cells, which can be well stained by Golgi silver impregnation method, were described by classical neuroanatomists and were referred to as “Epithelial cells,” “Radial cells,” “Fetal ependymal cells,” “Spongioblasts,” “Tanocytes,” and “Faserglia.” I proposed the term radial glia cell (RGC) that over time became universally adopted (Rakic, 1972).

The next logical question was how the neurons, after their last mitotic division, find the way to their proper positions in the increasingly distant and highly convoluted primate cerebrum. With the application of serial electron microscopic sections, combined with DNA labeling and immunohistochemistry, I discovered that migrating neurons find their way to the appropriate areal, laminar, and columnar positions within the cortex by following scaffolding formed by the elongated shafts of RGCs, a concept that became known as “glia guided neuronal migration” and the concept to which I devoted numerous studies (Rakic, 1971; 1972; 1973; 1978; 1981b). This was before the era of PowerPoint, so during my lectures, I was often trying to explain this extraordinary phenomenon by making drawings on a nearby blackboard (figure 2). With advances made in computer technology, I started to use computerized animations to illustrate this dynamic process based on my initial India ink drawings). On the basis of these discoveries, I proposed the RUH of cortical development and evolution, which provides insight into how the complex, three-dimensional (3D) organization of the brain is built from an initially two-dimensional layer of dividing neural stem cells (e.g., Rakic, 1988b; 1995). This model, despite some initial opposition to it, is now generally accepted and confirmed experimentally in my laboratory, as well as in many other laboratories (see review in Jones and Rakic,



Figure 2. Pasko lecturing by drawing the concepts or equations on the nearby board.

2010). Recently, it was supported by a multi-authored paper in *Science* (Grasby et al., 2020), which “identified 199 significant loci and found significant enrichment for loci influencing total surface area within regulatory elements that are active during prenatal cortical development, supporting the radial unit hypothesis.” As some of my colleagues say, “the 367 authors of this paper cannot be wrong!”

Migration of neurons occurs not only during the development of the cerebral cortex but also in many other regions of the large primate brain, and particularly dramatic migration occurs in the developing cerebellar cortex (Rakic, 1971). My first graduate student at Harvard, Richard Nowakowski, who joined this project, showed that neuronal migration along RGC glial fibers occurs also in the hippocampus (Nowakowski and Rakic, 1979; 1981). However, the transient population of RGCs is most remarkable in the large primate fetal cerebral wall where they span the full distance between ventricular and pial surfaces. It is obviously especially important for the development of the even larger human brain in which many neurological and neuropsychiatric disorders display neuronal dysplasia (e.g., Rakic, 1988a). At that time, minicomputers for three-dimensional reconstruction from electron microscopic images were not yet available. With the help of a friend and excellent neuroanatomist, Larry Stensaas from the University of Utah, we manually outlined images of migrating neurons and adjacent RGC fibers from the serial electron microscopic sections of the fetal monkey cerebral wall. I brought these images to the office of the NASA Space Division in Lowell, Massachusetts. They had an IBM 360/75 computer that was used to make the outer structure of the Apollo space vehicle that was sent to the Moon. It enabled us to rotate images to examine the relationship between

migrating neurons and RGC fibers. This computer had a much larger capacity than we needed. However, at that time, NASA was not busy and they agreed to help us free of any charge. We published the paper on computer-aided 3D reconstruction and quantitative analysis migrating neurons and RGC relationships based on serial electron-microscopic montages of fetal monkey brain in *Nature* (Rakic et al., 1974).

As a next step, I initiated a comprehensive autoradiographic study of the specific DNA replication marker ^3H -thymidine in nonhuman primates to determine the precise time of neuronal origin, routes of their migration, and settling pattern. I selected the Old World primate—rhesus macaque (*Macaca mulatta*)—because it possessed a similar cortical organization to that of humans. This project, which was supported by a large grant from the U.S. National Institutes of Health, provided the most comprehensive data and sequence of neuronal origin in any species at the time. I recognized that to obtain this amount of data from a large and slowly developing primate with state-of-the-art methods was extremely expensive. Indeed, the initial message from the NIH Study Section was that for this amount of money they could give five grants for research on small and fast developing species. My reply was: “You still will not know how this occurs in primates!” and they gave me the grant with a high priority score.

Among many instructive and biomedically relevant findings from this series of studies, we discovered that the genesis of neurons occurs at a strict areal and limited temporal schedule (Rakic, 1973). For example, in the cerebral cortex in the macaque monkey, both the beginning and ending of neurogenesis occur before birth and each cytoarchitectonic area has a different time window (Rakic, 1974; 1975b). This study induced the idea that determination of neuronal fate occurs at the time of the last cell division. See the section “Human-Specific Features” for more about this idea and why it is an evolutionary advantage, or even a necessity, for a species like humans, to keep accumulated knowledge for many decades in neurons that should not divide for the duration of their life.

These findings led to the proposed elaboration of the RUH with the protomap hypothesis, as a related model of how different regions of the cerebral cortex evolve during development and evolution to acquire most of their specialized molecular, anatomical, and functional properties through genetic programs intrinsic to the neuronal stem cells during their last division in the VZ and SVZ (Rakic, 1972; 1975b; 1988b; 1990). I was happy that, in spite of initial opposition to this concept by the researchers who overemphasize the role of the environment, the radial unit and protomap hypotheses became generally accepted as basic principles and have received support from numerous laboratories (e.g., Arcaro et al., 2020; Grasby et al., 2020). Furthermore, recent experimental studies, using genetically altered mice, viral gene transfer for tracing cell lineages, and the *in utero* electroporation method, confirmed the validity of my models (e.g., Miyashita-Lin

et al., 1999; Cholfin and Rubenstein, 2007). Contemplating the meaning of these findings, I admired the fact that Charles Darwin had a vision and the insight to propose the theory of evolution based on only crude observations available at the time. Our findings on molecular and cellular development of the mouse, monkey, and human brains clearly expose a progression that could have only occurred during evolution by random mutations of genes and their regulatory elements in our common ancestors.

Today, the notion that connectivity in the developing central nervous system is initially more widespread than in adults is commonplace. However, it was not a popular notion at the time when I discovered that in the primate embryo, the central projections from the two eyes are intermixed in their first brain target, the lateral geniculate nucleus, before segregating into six eye-specific layers, and this occurs before birth. I was inspired by the research by David Hubel and Torsten Wiesel and their students Marge Livingstone and Simon LeVay, who shared with me their exciting findings about the organization of ocular dominance in cats and macaques (LeVay et al., 1975; Hubel et al., 1975). By manipulating visual connections in the embryo, I obtained the first direct evidence that in the nonhuman primate visual system competitive interactions between axons starts before birth. Thus, segregation of ocular dominance columns begins before animals are exposed to vision. In addition, we found that prenatal eye nucleation prevents this process (Rakic, 1976b). This paper was published before the famous Nobel winning report on ocular dominance segregation in primates (Hubel et al., 1977) and the findings were subsequently confirmed by additional studies (e.g., Rakic, 1977; 1981a; Meissirel et al., 1997; Kuljis and Rakic, 1990). Specific neuronal classes of areas 17 and 18 are generated independently at different times (Rakic, 1976a) and as subsequently shown are divided into independent subareas before and without visual input (Rakic, 1991b; Bourgeois and Rakic, 1996; Arcaro et al., 2020). Our use of a strict, time-consuming, and tedious quantitative analyses of developing human and primate brain sections processed with Golgi and electron microscopic methods paid off. We discovered that neurons began to form connections even before they arrive at their final positions. For example, callosal neurons send their axons to the opposite hemisphere while still migrating across fetal cerebral wall to the CP (Schwartz et al., 1991) and thalamocortical axons make transient connections with the SPZ neurons (Kostovic and Rakic, 1990; Rakic, 1991a).

At about that time Nada Zecevic, who received her MD degree in Belgrade, attended my course on developmental neurobiology when I was there and decided to change her career from clinical neurology to basic neuroscience research on the developing human brain. She obtained a U.S visa and joined my laboratory in Boston, and we collaborated on many papers, even after she obtained a faculty position at the University of Connecticut (e.g., Zecevic et al., 1989; Zecevic and Rakic, 1991; 2001; Radonjic et al., 2014). Toward the

end of my stay in Boston, Carla Shatz, who received PhD training with David Hubel and Thorsten Wiesel, decided to join my lab as a postdoctoral fellow. Initially, she continued to work on the development of the efferent connections in the primate visual system (Shatz and Rakic, 1981). However, she was very fascinated by research on the transient embryonic SPZ conducted by Ivica Kostovic, who was working in my lab at the same time (e.g., see review in Kostovic and Rakic, 1990). When I decided to leave Harvard and move to Yale, Carla did not want to transfer with me from Boston to New Haven and, therefore, did not use the full term of the fellowship. In addition, she received an attractive offer to take a faculty position and open her own lab at Stanford University. However, she decided to continue work on the SPZ in developing cats, rather than monkeys, “because they are less expensive.” She did that in spite of my advice to continue work on macaques. I was pleased that 40 years later, during dinner at a restaurant in Amsterdam following a meeting at the Brain Institute, Carla admitted that my advice was probably correct and that few scientists these days work on developing cats, which anyway have a quite different organization of the visual system compared with primates. However, she became one of the most successful neuroscientists in the world, eventually best known for her excellent work on neuronal plasticity and neuroimmunology.

Horrific Incident at Boston Fenway

I enjoyed living in Boston, a cosmopolitan city with several top-level universities, excellent symphony orchestra, and international restaurants. When I was discussing with my friends my negotiations to possibly move to Yale, they told me, “Why should you leave a big and nice city like Boston and go to crime-ridden New Haven?” Then, I explained what happened to me in the nice downtown city of Boston in 1975. After picking up Ivica Kostovic from Logan Airport, who had come from Yugoslavia to join my lab, I was driving him to Harvard in my Volvo sedan. I stopped at the red light at Fenway, near the Boston Museum of Fine Arts, and suddenly a man opened the door, entered the car, and placed a gun on the back of my head shouting, “Drive, or I will kill you!” I was so stunned that I stalled the car and felt the gun directly touching the back of my head while the intruder continued to verbally threaten to kill me. I shouted back, “Wait a minute, I am on your side, but this is a standard shift car, and I am trying to start running it again.” Indeed, I did, but as I was driving, I suddenly saw several police cars with many policemen around, who started shooting at my car. My car’s windows, including the front windshield, disintegrated into small glass pieces, like cubes of sugar. The next several seconds were the worst and scariest in my life. My heart stopped beating and I was wondering why the police shot at my car, maybe Ivica was some kind of criminal drug dealer” I did not know that it was possible, but in a few seconds, I reviewed all my life

and was wondering why I ever came to this country. Then I saw some blood on the floor of the car and decided to open the door and jump out, letting Ivica and the gunman to continue moving with flat tires and without the driver until it hit the cars parked on the street side. One policeman grabbed Kostovic from the car and used the knee to neck maneuver to hold him to the ground. Then one other policeman shouted, “These are not the guys.”

What happened was a remarkable coincidence. Police were parked there because the Irish prime minister was giving a talk in the Museum of Fine Arts, and there was some suspicion that the Irish National Liberation Army was planning to assassinate him. While stationed there, the police received a telephone message that “Three dangerous armed men committed a robbery on Newbury Street are driving in a foreign car toward Fenway.” It turned out that on the way they stopped and dispersed, and one of the robbers commandeered my car. Thus, police thought that we were the three armed men who wanted to kill the Irish prime minister and started shooting at us. This was big news, and this is the only time when Ivica and I were featured on the front page of the *Boston Globe* newspaper (figure 3).

However, this incident in Boston had another interesting consequence. After the former Yugoslavia divided into several smaller but independent states, for a short time Ivica Kostovic was vice president of Croatia. I was joking with my other postdocs, who were unsuccessfully looking for positions: “If you cannot make it in science, you can always become vice presidents of a country.” In 1997, in this capacity as vice president, Kostovic met the transitional administrator of the United Nations agency UNTAES, Jacques Klein, who did not as yet want to remove sanctions against this new country because, “some cities, like Vukovar in Slavonia Province of Croatia, were still not safe.” Then Ivica told him his story about being kidnapped in



Fenway Drive Boston, Mass, USA, 1975

Boston Globe

Gun battle wounds 2, 3 charged in robbery

Two men were wounded yesterday — one a robbery suspect and the other an innocent bystander — during a wild, running gun battle between police and a holdup suspect in the Fenway.

...pump and leveled his gun at the officers but surrendered without firing a shot. Burgett fled on foot. Ptl. James Bickerton spotted Burgett a short time later at the corner of...

Two men were wounded yesterday — one a robbery suspect and the other an innocent bystander — during a wild, running gun battle between police and a holdup suspect in the Fenway.

Figure 3. Incidence at Fenway Park in Boston.

Boston by an armed robber, and Klein recognized that there are places in the United States that are as dangerous as in Croatia, and he removed the sanctions and opened the process of peaceful reintegration of this region into Croatia.

Move to Yale University

In 1978, I was recruited to Yale School of Medicine by famed cell biologist and Nobel Laureate, George E. Palade, to become the Dorys McConnell Duberg Professor of Neuroscience and the founding chair of the Section of Neuroanatomy. I had a New Year's Eve dinner at Palade's home with his wife Marilyn Farquhar, and they convinced me that my dedication to basic science will be appreciated at Yale Medical School. At that time, Yale was ranked among the top universities in the world, and I decided to accept this position. However, my decision was influenced by the possibility to be joined by my wife-to-be, Patricia Goldman. Unlike some other universities that did not like recruitment of couples to the same department, Palade told me that Yale would not mind this and said, "We can get two for the prize of one."

When we met, Patricia was already a highly successful neuroscientist at the National Institute of Mental Health and was recruited to Yale at my suggestion, where we would get married. She also decided to retain her already recognized last name and add a hyphen to take mine and become Goldman-Rakic. We were working in different subfields of neuroscience, so we did not publish many papers together, but we were each other's constructive critics, regularly commenting on each other's manuscripts before submission. We were also organizing multidisciplinary meetings and applied for Center and Program Project grants. Our common denominator in science was our interest in the biological basis of the highest brain cognitive functions that make us human. Thus, together we founded a new journal *Cerebral Cortex*, now a well-established and high-impact journal, which became a force in this research area. We were devoted to fostering the new multidisciplinary approach through various functions at the Society for Neuroscience for which we both served as presidents (figure 4). Over the years, Pat helped me build and transform the Section of Neuroanatomy into a thriving, modern Department of Neurobiology. She was focused on the organization, physiology, and pathology of the prefrontal association cortex in nonhuman primates and was so successful that many people think that probably only her premature death prevented her from receiving the Nobel Prize (e.g., see Arnsten and Rakic, 2022). Together, Pat and I attracted the Kavli Institute for Neuroscience to Yale, which was awarded only after her premature death. Fred Kavli, who visited us at Yale and enjoyed red vintage wine at dinner in our house, stated that "the Kavli Institute at Yale should focus on the research of the cerebral cortex, the only organ which can make connection between the smallest particles (nanoscience) and the



Figure 4. Pat and Pasko at the meeting together.

largest—universe (astrophysics).” The dean’s adviser at that time suggested that Fred also meet the director of Interdepartmental Neuroscience Program and chairs of Neurology and Psychiatry, but he refused: “Students are supported by tuition, and disease by NIH, I want to understand biological bases of human cognitive capacities via cerebral cortex.” Fred Kavli told me that he visited Yale University only because Pat and I worked on the cerebral cortex. He would probably turn in his grave if he learned that his wishes were totally ignored after I stepped down as director. I learned my lesson, and when I gave over \$6 millions to Yale, I requested that my gift be spent while I was still alive because if given as an endowment, Yale administrators possibly would not respect the donor’s wishes.

The move to Yale was also an opportunity to select some new direction for my research. With the support of the Ford Foundation, Yale was able to establish a timed breeding colony of nonhuman primate, macaque monkeys, providing an opportunity to study the development of some primate-specific features. I resisted the temptation to use some of the new and popular experimental methods that can be performed only in simple

animal models to focus on what is possible to do in primates, including human. I became convinced that understanding the human cerebral cortex is the most important subject in science at the basic, medical, as well as philosophical level. I defended this position when I was invited to participate in the 2014 Science Forum in NYC. For this occasion, the famous actor and panelist Alan Alda assembled a distinguished panel of scientists that included several Nobel and Kavli Laureates in various disciplines ranging from cancer research and neuroscience to nanotechnology and astrophysics. To start the Forum, Alan gave us a probing question, "What is the single most important question in science? Please do not list several, I want only a single subject." I dared to argue that the single most important subject is "An understanding of the human cerebral cortex." I met with some resistance from the Forum participants, "What do you mean? How about origin of the universe?" argued one astrophysicist, citing a new Nobel Prize winning theory of cosmic inflation. To that I replied, "Which organ was used to make this theory?" By the reaction of the audience and from the panel's subsequent responses, it seemed that I won that argument because without cortex there is no astrophysics. However, I must admit that it is possible that, as mice are incapable of understanding the equation $E = mc^2$, the human brain may not be capable of solving the problem of the origin of the universe.

To focus on the understanding of the development and evolution of the human brain seems obviously a worthwhile and positive endeavor, but surprisingly I learned that it also had some negative consequences. When I presented lectures stating that one probably cannot adequately model human language disorders in rodents, many in the audience were not only unhappy but some were even negative. This response was quite disappointing to me because, although I worked mostly on human and nonhuman primates, I greatly valued research on inbred strains of mice and used them as a model system to understand some basic principles of neuronal interactions in the brain (e.g., Rakic and Sidman, 1973; Caviness and Rakic, 1978). In the book entitled *Mouse Brain Development* (Goffinet and Rakic, 2000), I declared that "mouse is perhaps the best model system to study genetic brain disorders." However, I also recognized that despite the superficial similarity, cerebral cortex in mice and primates, including humans, are significantly different. Thus, I organized some meetings with participants who use different model systems that range from nematode and fruit fly to carnivores and primates (e.g., Easter et al., 1985). Finally, I decided to study the development of the brain simultaneously in three mammalian species—mouse, macaque monkey, and human, to learn from the similarities as well as from the differences that occurred during the process of mammalian brain evolution. This was not commonly done in the same laboratory, but I was hoping to obtain specific anatomical and molecular comparative data relevant to the evolutionary and developmental basis of uniquely human

mental capacities. Therefore, in collaboration with scientists in other fields, I applied transgenic technology to delete or manipulate mammalian homologs of several Nematode, *Drosophila*, and rodent genes (e.g., BMPs, Caspase-9, Cx43, CPP32, FGFs, JIP1, Jnk1-3, MeCP2, MEKK4, METTL7B, Numb, Notch, WNTs, and too many others to be listed) involved in programmed cell death, migration, and differentiation as well as creation and maintenance of neuronal connections in mammals. The results showed that cortical development and evolution do not depend on a single gene or regulatory element, but rather on a combination of many (e.g., Kwan et al., 2012; Franjic et al., 2022). We uncovered similarities between species but also some human-specific genetic pathways that also were supported by the work of Christopher Walsh (Huang et al, 2020).

My decision to perform research on nonhuman primates was not without some other consequences and was not easy to defend, even to some of my close relatives and in-laws. My justification was that our animals are treated humanely and are not exposed to any pain or procedures that doctors do not perform on their patients. I was once confronted in the front of Sterling Hall at the Yale Medical School by a protestor from the People for the Ethical Treatment of Animals (PETA), holding an offensive poster that asked, "Why do research on animals"? I replied, "If your son or mother are sick with a disease that can be cured only by the antibodies made in an animal, would you allow it, or let them die?" He gave the usual answer that it is a hypothetical situation, but in such a case, he would allow use of the animal. So, I said, "You care about your family more than the families of others!" Protestors did not return with the offensive posters.

One of the major goals was to perform electron microscopic quantitative analysis of synaptogenesis in nonhuman primates to explore in greater detail Peter Huttenlocker's finding on human postmortem tissue that cortical synapses are initially overproduced before declining to the adult level. On my invitation, Jean-Pierre Bourgeois decided to leave a job at the Pasteur Institute in Paris to spend several years working on this project in my lab. He performed detailed quantitative analysis first in the macaque visual cortex and found enormous overproduction of synapses (Rakic et al., 1986, 1994; Bourgeois et al., 1989). In addition, time-consuming 3D quantitative analyses showed that during the period of maturation before puberty, monkeys lose about 2,500 synapses every second in the visual cortex alone and a total of about 30,000 in all cortical areas every second during the day and night in these three years. This looked unbelievably large, so even my wife Patricia said that it might be nonsense. So, for the first time in my career, I asked the editor in chief of the *Journal of Neuroscience* (at that time Dale Purves) to assign my paper to the hardest reviewers possible because I did not want to be a fool. He apparently did, but I only know that one of them was Francis Crick, who acknowledged his identity and who accepted the paper (Bourgeois and Rakic, 1993).

At about the same time, my first graduate student at Yale, Anthony LaMantia, found that axons of the corpus callosum in macaque monkey are 60 percent overproduced, before decreasing to the adult level (LaMantia and Rakic, 1990). We then found that similar decline occurs in anterior commissure (LaMantia and Rakic, 1994) as well as in other large axonal tracts (e.g., Rakic and Riley, 1983a, 1983b). We also discovered that a population of GABAergic neurons in the SPZ, form transient synapses, is also eliminated (Meinecke et al., 1992). These discoveries led me to propose the selective elimination hypothesis as a mechanism for tuning synaptic connections by interaction with the environment during the period of most intense learning. My colleague and friend Jean-Pierre Changeux found that similar overproduction and elimination occurs during development of neuromuscular junction, but he called it “selective stabilization.” We were joking during dinner in a nice Paris restaurant that it is actually the same phenomenon that we termed differently. When we looked at the glass of wine on the table, I said that it is half empty and he said that it is half full, and we are both right. These days selective elimination or stabilization is commonly called “pruning” (e.g., Keshavan et al., 1994). We also discovered that major neurotransmitter receptors are similarly overproduced (Lidow et al., 1989, 1991). Only recently we found that although childhood and adolescence does represent a period of the highest decline in dendritic spine number, surpassing the adult values for two- to three-fold, overproduction and developmental remodeling of cortical circuitries continues throughout the third decade of life, before stabilizing to the adult level (Petanjek et al., 2011).

In collaboration with Pat Levitt, who came to my laboratory after working with Bob Moore at the University of California, San Diego, we documented using immunocytochemistry at the light and electron microscopy levels, the early separation of neuronal and glial cell lineages (Levitt and Rakic, 1980; Levitt et al., 1981). This work has modified traditional ideas about phenotypic neuronal specification, suggesting that the basic phenotype of cortical cells is specified close to the time of a cell’s last division. Many other members of my lab, including Tarik Haydar, Matt Sarkisian, and Joshua Breunig, applied the most advanced molecular methods to study lineage transition from RGCs to Intermediate Neuronal Stem Cells during development and maintenance of the embryonic cerebrum (e.g., Haydar et al., 1999, 2000, 2003; Breunig et al., 2007b; Liu et al., 2008)—a subject that now also is studied in many other laboratories. With another postdoctoral fellow Robert Williams, we created and patented a 3D counting method for numbering cells in serially sectioned brain tissue (Williams and Rakic, 1988). He was also engaged in creating experimentally novel cytoarchitectonic areas within the visual cortex in developing macaque cerebrum (Rakic et al., 1991). This was an important finding, because reduction of the area V1 did not cause expansion of V2, but rather acquired a totally different (novel) features, which support the protomap hypothesis. Comparing monkey data

on timing of the emergence of selected developmental landmarks indicated that the same early development occurs in humans. By necessity, we were working on the development of new methods and modification of existing methods (e.g., Rakic and Goldman-Rakic, 1985; Williams and Rakic, 1988; Cameron and Rakic, 1994; Kornack et al., 1995; Ang et al., 2003; Miska et al., 2004; Micali et al., 2020; Morozov et al., 2020).

I was lucky to work with a highly talented PhD student, Chia-Yi (Alex) Kuan, who emigrated with an MD degree from his native Taiwan and was admitted to the Yale neuroscience graduate program. He was crucial for forming my collaboration with Richard Flavell, chair of the Department of Immunobiology at Yale, who was the world leader in creating single-gene mutation in mice. In this collaboration, Kuan obtained evidence of the enormous importance for the role of programmed cell death/apoptosis in normal brain development as well as in pathogenesis of many brain malformations (Kuida et al., 1996; Young et al., 1997; Kuan et al., 1999, 2000). Alex was imaginative and productive, and we published about a dozen papers on this subject that became highly cited in several fields of biology. Alex obtained a faculty position and has established a successful laboratory, and our collaborations has continued.

At about the same time, Nenad Sestan, who also had already received an MD degree from the University of Zagreb in Croatia, came to my lab to obtain a PhD at Yale. He was both an original thinker and technical maverick. As part of the research on his doctoral dissertation, he rotated through the lab of a *Drosophila* specialist Spyros Artavanis-Tsakonas and established a collaboration between his and my labs. Through this effort, Nenad discovered the role of Notch gene signaling in neuronal differentiation and neurite outgrowth, which were published in two *Science* papers within the same year (Sestan et al., 1999; Qi et al., 1999). Although he has received many opportunities and offers to take attractive and lucrative jobs elsewhere, he remains at Yale, where he established his own large laboratory. He advanced quickly and at a relatively young age became the Cushing Endowed Professor in the Department of Neuroscience, with joint appointments in Genetics, Psychiatry, and Comparative Medicine. Nenad is presently considered to be of the most successful developmental neuroscientists, has been elected to the National Academy of Medicine (NAM), and has received many prestigious prizes. His recent study in *Nature* on reviving the brain of a dead pig gained international recognition from 355 different news outlets making it one of the most recognized scientific breakthroughs of the year and placed Nenad on the list of “ten people who mattered in science.”

It is interesting that three people of Croatian origin (P. Rakic, I. Kostovic, and N. Sestan) end up exploring evolution, development, and congenital disorders of the human cerebral cortex. Ivica Kostovic became the founder and director of the Croatian Brain Institute, which is devoted to research of the human brain, so our laboratories have continued to

collaborate (e.g., Duque et al., 2016). Among the few neuroscientists who share the enthusiasm and recognize the necessity to explore human differences are Christopher Walsh at Harvard (e.g., Huang et al., 2020) and Javier DeFelipe at the Cajal Institute (e.g., Eyal et al., 2016), although John Rubenstein (e.g., Raju et al., 2018) and Arturo Alvarez-Buylla (e.g., Sorrells et al., 2018) have also made important contributions. Without such research, we would still be ignorant about basic molecular and cellular events that underly cortical expansion and elaboration in humans that enables creation of our civilization.

One feature that is most prominent in the human brain is elaborate and deep secondary and tertiary cerebral convolutions. With Brian Rash, who joined my lab as a postdoctoral fellow, we provided new insight into the cellular mechanisms of gyrification. At that time, the mechanisms underlying gyral development became controversial, with some disputing the classical Van Essen model of the role of white matter connections and suggesting instead that cortical gyri occur because of an increase in neurogenesis of the superficial layers neurons in the underlying hotspots of the oSVZ. However, many studies have shown that cortical neurogenesis and settling of neurons into the cortical plate in primates, including humans, is finished before gyral development and that the oSVZ produces mainly oligodendrocytes and astrocytes during the period of gyrification (Rash et al., 2019; Arellano et al., 2021). More specifically, we showed that in the developing macaque cerebrum, secondary and tertiary gyri form after the completion of neurogenesis, driven primarily by the rapid growth of intracortical neuropil and subjacent axonal fascicles in the white matter influenced by intracortical neurotrophin signaling through brain-derived neurotrophic factor (BDNF) (Rash et al., 2019).

I recognized that a multidimensional and dynamic process of brain development cannot be fully explained by the study of a single gene or single molecule and that we need to understand underlying cell-to-cell interactions. Over the years, my laboratory has identified several membrane polypeptides as well as voltage- and ligand-activated ion channels on the surface of migrating neurons and radial glial cells. These factors contribute jointly to cell orientation and recognition of migratory pathways through differentially distributed cell adhesion molecules that lie between the surfaces of migrating neurons and adjacent RGC fibers. These same factors also regulate the rate of nuclear movement in migrating neurons by controlling the dynamics of cytoskeletal proteins (Rakic 1972, 1978; Komuro and Rakic, 1992, 1993, 1996; Breunig et al., 2007b; Torii et al., 2009; Rash et al., 2016). About that time, Eva Anton, who graduated from Duke University, joined my lab because of his belief that the molecular mechanisms of neuronal migration in the central nervous system have a good chance to be solved by modern neurobiological methods. Indeed, Eva used the most advanced methods for studying cell movement in the cerebral cortex *in vitro*. He explored the

functional significance of two novel molecules that recently had been identified on the radial glial cell surface membrane. He also generated an antibody to a new type of molecule that may serve as a signal for cessation of cell migration at the interface between the cortical plate and marginal zone of the embryonic cerebrum (Anton et al., 1996, 1997, 1999). I recognized that this work needed diverse knowledge, and together with another talented graduate student of mine, Joshua Breunig, we explored diverse molecules and cell phenotypes involved in this complex process. So far, we have identified that at least 20 diverse molecules, some of which were initially discovered in invertebrates, control specific phases and components of neuronal stem cell proliferation and migration in the cerebrum. These include the mode of neuronal proliferation, phenotype determination, establishment of polarity, detachment from the local substrate, and rate of nuclear and somal translocation to the proper areas, layers, and columns of the cerebral cortex (e.g., Breunig et al., 2007b, 2008, 2010).

Although we were quick to adopt the newest and the most advanced methods, we also continued to use the older techniques, such as electron microscopy, in combination with immunocytochemistry and autoradiography. I collaborated with Pat's group (e.g., Schwartz et al., 1991) but was also lucky to have in my lab two excellent electron microscopists, one who emigrated from Japan, Hitoshi Komuro, and one who emigrated from Russia, Yury Morozov. They were research scientists in my lab and were engaged in many projects, including national and international collaborations on the various topics that required ultrastructural, subcellular localizations of specific molecules (e.g., Komuro and Rakic, 1992, 1993; Berghuis et al., 2007; Breunig et al., 2008; Dominquez et al., 2013; Datta et al., 2020; Galvin et al., 2020; Morozov et al., 2020).

We were also very active in research on the effect of genetic and environmental factors on brain development. By manipulating the speed and pattern of neuronal migration using various genetic (e.g., *reelin*, *Notch*, *Lis1*, *Neuropeptide-Y*, *TCF4*, *Connexin 43*, *Numb*), environmental (e.g., x-rays, ultrasound), and chemical factors (e.g. alcohol, antidepressants, cannabis, and opioids), we discovered the hidden abnormalities of neuronal positioning and small changes in synaptic pattern (e.g., Levitt et al., 1984; Kuljis and Rakic 1989; Lidow et al., 1989; Schull et al., 1986; Qi et al., 1999; Sestan et al., 1999; Ouimet et al., 1992; Kuida et al., 1996; Algan and Rakic, 1997; Anton et al., 1999; Li et al., 2003, 2019; Ang et al., 2006; Breunig et al., 2007a; Selemon et al., 2005, 2009, 2013; Rash et al., 2018; Morozov and Rakic 2009; Liu et al., 2012) that cannot be discerned by routine examination of the postmortem human brain (e.g., in the so-called idiopathic cortical digenesis). These findings opened a new window into understanding pathogenesis of congenital brain malformations, which I termed "neurodislocation syndrome." This concept provided insight into how individuals with seemingly "normal" brains display major neurological and neuropsychiatric

conditions. Specific molecules and cellular mechanisms that place neurons into proper position proved to be universal and have spawned studies of surface mediated interactions in other brain structures that are now carried out by developmental neurobiologists all over the world.

I was also lucky that Kazue Hashimoto-Torii and her husband Masaaki Torii, who received their graduate degrees in Japan, joined my lab. They discovered the relationship between Reelin and Notch signaling pathways and how this cooperation regulates neuronal cell migration from the proliferative centers to the embryonic cerebral cortex (e.g., Hashimoto-Torii, 2008). They also discovered the role of ATP and gap junctions in interkinetic and multipolar phase of neuronal migration (Liu et al., 2008, 2010). They left my laboratory at Yale after obtaining faculty positions at George Washington University, but our collaborations have continued, resulting in several manuscripts, including one on the development of a novel fluorescence reporter system in mice (Hashimoto-Torii, 2014). These heat shock proteins and factors may be potentially very useful as the means to detect prospective disorders before the appearance of visible symptoms and before the pathological effect becomes irreversible.

Role of Genes vs. Environment

As evident from my bibliography, I was initially fascinated by the effect of the environment on brain development, which was popularly known as “plasticity.” However, the more I learned about brain development, through my own work as well as from the large literature, including papers being evaluated in the journal *Cerebral Cortex*, the more I became aware of evidence indicating that the basic human characteristics, including temperament; talent for singing, arts, or sports; and basic intelligence, are inherited and thus, depend on the combinations of genes. It was Seymour Benzer, during our dinner at Caltech where they tried to recruit me, who finally convinced me that genes are primary. He repeated to me several times during our dinner in Pasadena (California): “Genes are very, very stubborn.” Indeed, I learned that there are no two human beings that are created equal because of genetic variance. Even identical twins are different. This eternal debate about the roles of genes and the environment led to the one that was held at Oxford University Library in the United Kingdom between Colin Blakemore and me, with the presence of some other notable developmental neuroscientists like Zoltan Molnar (figure 5).

Colin asked, “OK. You, Pasko, believe in the crucial role of genes, but what is your estimation, 75 percent genes–25 percent environment?”

I replied, “100 percent genes.”

He was upset: “Do you mean that environment does not play a role?”

I answered, “Yes, environment is also 100 percent.”

Colin, “So, you want it both ways, do you want to be president of USA?”



Figure 5. Debate at the Oxford Library in the United Kingdom.

To which I answered, “No, I will disappoint you. I cannot be president. I was not born in USA and have the birth certificate to prove it.” I also cited Niles Bohr that, “Opposites are not contradictory but complementary.”

Furthermore, the initial question was not correct, it should have been, “What is primary and what is secondary?”

I said, “The answer is of course genes because without the brain created by genes, the environment would have nothing to influence.”

I was dedicated to exploring the development and evolution of the entire cerebral cortex, including all areas since, for example, even primary visual cortex in rodents and primates is dramatically different. Therefore, we explored species-specific differences in cortical organization. However, perhaps in part due to Pat’s interest, I was perusing peculiarities of the association areas of the prefrontal cortex. She had evidence that rodents do not have the types of connections like the primate prefrontal cortex with its input from the structures like part of the pulvinar, which does not even exist in rodents. After one of her talks at University of California, Los Angeles, she was asked by the founding father of neuroethology, Ted Bullock, “These are nice neurophysiological studies, but they are expensive to perform in monkeys, so why don’t you do it in mice?”

Pat replied, “Would you use mouse as a model system to study the development of wings?”

Ted said, “No, I would not. Mice do not have wings.”

Pat won the argument with her reply, “Mice do not have prefrontal cortex.” So even now, many years later, I am collaborating with Pat’s former postdoctoral fellow Amy Arnsten, now the Kent Professor of Neuroscience and Psychology at Yale, on the cellular and molecular organization of the

prefrontal cortex in macaque monkey (e.g., Datta et al., 2020, 2021; Galvin et al., 2020). My justification for this extraordinary effort is that it is not possible to model the structure in an organism that does not have it.

Among various chemical and physical environmental factors influencing prenatal brain development, we also examined the effect of exposure to ultrasound waves (USW) on the developing brain in pregnant mice. We found that it has an effect in developing mice (Ang et al., 2006) and therefore advised that, as is done for the X-ray, which is harmful, USW also should be used only when medically indicated. However, because this test was done in quickly developing small mice, there was a question of how much effect USW have on the large, slowly developing brain in humans, which also have much thicker abdominal and uterine walls. Proper testing in nonhuman primates, such as the macaque monkey, is very time-consuming and extremely expensive, and I was informed that NIH would not consider this as an additional research grant for me since I already had two. I was discussing this issue with Nobel Laureate Salvador Luria from MIT, who was very interested in this issue and he said, "You should not worry, I am on the board of the Rockefeller Foundation and you should submit it there." To my and his surprise, Sheldon Segal, a distinguished reproductive biologist, who served as the director for Population Sciences at the Rockefeller, rejected my grant application on September 4, 1983, with the statement: "It is difficult to understand what significance we could learn from a few monkeys that has not already been revealed by literally thousands of human fetuses . . . overall, negative about the need for study." Both Salvador Luria and I were stunned by this reply since this was like saying, "What can we learn from studying the effect of smoking in animals that we cannot learn from millions of healthy and smiling over 70-year-old individuals." However, I was persistent and eventually received funds from the NIH for the USW project, but indeed it took a lot of time to obtain the proper number of USW exposed and controls in slowly developing monkeys and to wait for their postnatal maturation to examine and perform statically significant analysis of effects on developmental cellular events. At the time of this writing, we are completing this prolonged double-blind study, which revealed the same small, but statistically significant effect of USW on migration of cortical neurons in the primate telencephalon (Duque and Rakic, work in progress).

Human-Specific Features

By studying simultaneously development and organization in three mammalian species, we recognized that there are human-specific features. One of the most unusual is the existence of a stream of migrating cells from the ganglionic eminence of the human fetal telencephalon to the thalamic nucleus pulvinar in the diencephalon (Rakic and Sidman, 1969). I initially described this structure in my doctoral thesis and named it corpus

gangliothalamicus. It is a relatively large cellular stream clearly visible using basic histologic stains, but we added new methods to determine that they are indeed postmitotic migrating prospective GABAergic neurons (Letinic et al., 2001). This structure so far could not be found in the developing brain of any other species, including rodents, carnivores, and nonhuman primates. Another feature that seems to be present only in primates, including human, is that a subclass of GABAergic neurons originate in the proliferative zones of the dorsal telencephalon (Letinic et al., 2002; Radonjic et al., 2014). Some aspects of the RGC proliferation are also different (e.g., Kornack and Rakic 1998) and some of the genes and regulatory elements are human specific (see review by Molnar et al., 2019; also see the newest data by Franjic et al., 2022). Another type of species-specific features are large quantitative differences. For example, primates have much more interstitial neurons in the subcortical white matter than in the lateral geniculate nucleus (LGN) (Kostovic and Rakic, 1980). Yet, there are hundreds of physiological studies on the LGN and none on the interstitial neurons. I was compelled to quote Georg Hegel: “quantity changes lead to quality changes.” This issue of species-specific differences deserves our attention because there is no question that some features of the cortical neuronal organization in primates are different than in any other mammalian species (e.g., Reilly et al., 2015; Duque et al., 2016; see also reviews in Rakic 2003, 2009; Clowry et al., 2010; Kwan et al., 2012; Cotney et al., 2013; Reilly et al., 2015; Molnar et al., 2019; Silver et al., 2019; Geschwind and Rakic, 2013; Arnsten and Rakic, 2022).

Our initial analysis of time of cell origin using DNA replication markers revealed that the neurons serving the most precious mental functions, such as the cerebral cortex in primates, including humans, have neurogenesis limited to the developmental period, and postmitotic neurons last the entire life span and are irreplaceable (Rakic, 1974; Rakic and Nowakowski, 1981). These findings led me to suggest that the stability and longevity of the neuronal populations in the adult primate, including the adult human brain in general and cerebral neocortex in particular, may be an evolutionary adaptation for the retention of learned and stored information over the prolonged life span of the individual (Rakic, 1985). In contrast, fish and amphibians continue neurogenesis during their entire life, and the salamander can regenerate an entire spinal cord, but mammals are drastically reduced in this capacity. I was wondering why this seemingly useful capacity would be systematically reduced during evolution. This steady decrease in adult neurogenesis during evolution seems to have occurred at the expense of the capacity for regeneration and natural turnover of neurons that exists and is prominent in many lower vertebrates. This subject was not within my main research interests, but I noticed that some scientists, as well as the popular press, initially strongly contested my conclusions. This subject came in focus when Elizabeth Gould published in *Science* paper claiming that thousands of new neurons are added daily to the prefrontal cortex of the adult macaque

monkey (Gould et al., 1999). This was a stunning claim, and Eric Kandel commented in the *New York Times* (October 15, 1999), that “this idea was perfectly possible, given how little was known about the brain system for ultimate long-term memory storage.” I said to Eric at one of our many dinners: “If this is true, you should return your Nobel Prize since you established that memory is preserved in the pattern of synapses, and newly generated neurons in human would need more than 8 months to form a first synaptic contact.” In the subsequent article in *The New Yorker* (July 1, 2001), I was portrayed as a dogmatic, male chauvinist who attacked a talented young woman, Elizabeth Gould from Princeton, who made a huge discovery and destroyed the old dogma. Pat cried when she read this article, but I decided not to reply to this uninformed and offensive article. Instead, I offered to visit Princeton to examine the original slides, and if such cells indeed existed, I would accept it. They refused! However, I am happy that many other labs, including the Gould lab, could not replicate her findings. My original statement of the limit of the primate cortex also has been confirmed by different methods, including carbon-14 birth dating of neurons in the adult human cerebral cortex (Bhardwaj et al., 2006). Most important, Alvarez-Buylla has shown that it is nonexistent or negligible in adult human hippocampus (Sorrells et al., 2018). I was gratified that this finding and its message against unrealistic hopes has helped to redirect neural stem cell research, from how to replace degenerating or injured neurons, to how to preserve them. A postdoc in my lab, David Kornack, became interested in this subject of adult neurogenesis and confirmed my original findings (e.g., Eckenhoff and Rakic, 1988; Rakic and Kornack, 1993; Kornack and Rakic, 2001; Rakic 2002b). After getting a faculty position at the University of Rochester, he tried to continue doing research in support of the concept that the lack of adult neurogenesis may be an evolutionary advantage. However, at many study sections for scientific peer review, he encountered difficulties obtaining grants on this subject because of the opposition of the true believers in human adult neurogenesis.

The idea of obtaining new neurons at old age is apparently very attractive and popular among nonspecialists and lay people. For example, I attended the Yale fundraising dinner, and Ted Turner, founder of CNN, and his wife Jane Fonda, were sitting next to me.

After learning that I am a neuroscientist, her first question was: “Is it possible that I can get some new neurons?”

She did not like my reply that “it is unlikely and would actually be counterproductive.”

I was also a participant of the famous debate at the satellite meeting on the topic of adult neurogenesis where two presidents of the Society for Neuroscience, Fred (Rusty) Gage and I, tried to be presidential and paraphrase statements made by former U.S. presidents.

Rusty paraphrased President George Bush and claimed that I said, “Read my lips: No new neurons.”

I replied by paraphrasing President John Kennedy, “Ask not what new neurons can do for you; ask what you can do for your old neurons.”

Rusty is a good friend and an excellent neuroscientist with whom I have several papers (e.g., Brennand et al., 2015), but in the research area of adult neurogenesis, he like many others, believe that although small, it may have huge importance and that stimulating its increase may help many neuropsychiatric disorders. Indeed, an enormous amount of money has been spent on research on how supposedly new adult neurons can prevent and heal aging disorders. Many, notably Arvid Carlsson, a Nobel laureate from Göteborg, strongly complained that this field was highly supported at the expense of funding research on how to prevent the decline of neurons or heal existing neurons. I was surprised and disappointed that so many scientists are still using inadequate methods in this field even though there is clear evidence of the significant technical and conceptual problems (e.g., Arellano et al., 1999; Kuan et al., 2004; Breunig et al., 2007a; Duque and Spector, 2019; Duque et al., 2021; Franjic et al., 2022).

Another contentious argument that I was involved in is my criticism of the implicit assumption by numerous publications that neural structure for human language is evolutionarily related to bird singing abilities and that human cerebral cortex is an expansion of the mouse cortex with the addition of a few association areas. I argued that a bird’s song does not have genetic, anatomic, or functional substrates in common with the human language, which involves abstract thinking as advocated by Fernando Nottebohm. Human language is basically a cortical function, the structure that birds do not have. In addition, in my opinion, the *Foxp2* was inappropriately called the “language gene” because it is also expressed in the rodent spinal cord. Furthermore, there is no presently living species that should be classified as lower or higher because, for example, birds are as advanced in their phylogenetic tree as humans are in theirs.

When I was at a meeting on evolution at the Royal Society in England, Fernando asked me, “How do you know, without doing more research, that birds do not have language?”

I replied, “I know; if they had language, they would tell me!”

I argued that the work on bird singing is an excellent contribution to understanding the path of their evolution, but they are not our ancestors. It was not a new and original idea because it is well established that presently living animals evolved from extinct common ancestors, as so clearly and eloquently formulated by Charles Darwin. Unfortunately, it is often a forgotten truth that many young neuroscientists, and even members of the NAS, seem not to know or choose to ignore. This is the reason why in my lectures I emphasize the old truth that all presently living species are equally evolved from a long extinct ancestor, which we cannot examine. I also make the point that rodents, like mice, are closer to humans than carnivores, like ferrets and dogs, who were separated from the primate phylogenetic tree

7 million years before mice. At a large meeting on the development of the cerebral cortex in Greece, attended by more than 250 researchers, I asked the audience to raise their hand if they knew that rodents are evolutionarily much closer to human than carnivores. Only a few hands went up, including one by evolutionary biologist Leah Krubitzer who supported my statement. I was stunned by the lack of knowledge of this basic information by the researchers who work on the cerebral cortex in mice. However, I do not blame them. It is the fault of their mentors who ask them to learn complex techniques and perform time-consuming experiments and do not teach them some basic facts and the history of the subject. I had many useful and animated discussions at some meetings, but my main reward was the positive messages that I received from participating students, who thanked me for pointing out this simple truth. They were indoctrinated in their courses that humans have evolved from the simpler animals that are used as the model systems, rather than, as suggested by Darwin, we derived from a common ancestor, which we will never be able to examine.

Because studies on brain development in the valuable and endangered primate species probably will never be repeated, my concern was how to preserve this material to be useful for the present as well as future generations. Over many decades, the late Patricia Goldman-Rakic and I accumulated large collections of stained and unstained slides, electron microscopy blocks, and frozen tissue that can be utilized with the application of new staining and molecular methods. I urged younger members of the Yale faculty, Alvaro Duque and Lynn Selemon, to create the Macaque Brain Resource, designed to utilize the available material for new studies on the brain of nonhuman primates without sacrificing additional animals (e.g., Duque et al., 2019). I believe so much in this project that I have personally donated more than \$6 million for its creation and maintenance. In addition, Duque and Selemon applied and were awarded an NIH grant to support the Macaque Brain Resource. It recently became an Independent Center at Yale University School of Medicine. The unstained sections and EM block of the tissue from developing monkey brain are available to scientists from around the world who visit the Macaque Brain Resource Center at Yale. Scientists may process material with new antibodies and molecular and cellular markers. Access to this resource is available by arranged visits or through remote access of digitized images of slides via website access (<https://medicine.yale.edu/neuroscience/macbrain/>).

Administrative Duties

I served for 37 years as department chair, the longest length of time of any chair in the history of Yale University. My chairmanship spanned seven Medical School deans, starting with Bob Berliner, and five presidents of the university starting with Bartlett Giamatti. As one of my friends said, "If

you survived seven deans, you must be doing something wrong.” Some of the deans did not like my nonconformist, straightforward, and direct style. However, they may have kept me as a chair for so long because our department was never in the red, and our members had very large grants, including several big Center and Program Projects. We never received adequate space and the department was relatively small. Nevertheless, in 1996, it was ranked number one in the world with only 10 faculty members (five females and five males). The equal ratio was not planned that way, and I did not perform an “affirmative action” search. I just selected the best, and it turned out to be about 50–50. For example, I recruited and promoted Susan Hockfield to her tenure and eventual provost position before she left Yale to become the first woman president of MIT. This was a friendly departure since I provided a positive recommendation and subsequently was a frequent guest at her dinners and stayed at her MIT residence on the Charles River in Cambridge, Massachusetts. Other notable members, who unfortunately left Yale, were Mriganka Sur, Pat Levitt, Anna Wang Roe, David McCormick, and Patricia-Godman-Rakic, who left under worse circumstances. I also recruited Michael Schwartz and Michael Crair, who become dean’s advisers for education and research. Despite the internationally recognized success of the Neurobiology Department at Yale, our space was kept at a minimum because some of the deans did not appreciate the value of basic brain research and instead favored genetics. However, I took advantage of this fact and remembered the advice from the famous neurophysiologist Otto Creutzfeldt who said, “Chairman should never allow a department to become big.” Indeed, I did not mind that the department was small as this gave me a chance to devote more time to my research. Our department was also a good example of diversity and my group at Yale is like the United Nations. Remarkably, 12 out of 12 recent members were born in 12 different counties! That also was not planned—again, I tried to select the best.

After stepping down as chair, I retain a full-time faculty position. This allows me to spend even more time on research so that the past few years have become even more productive. Our research remains unique as recognized by many study sections. For example, I recently received a large 10-year MERIT award from the NIH to support an active lab of about eight members with different scientific backgrounds. We are presently as productive as ever.

Traveling and Lecturing to Transfer Knowledge to the Next Generation

During all these years I have hoped that my research will be useful to other scientists at both a conceptual and a clinical level. To this end, I have given lectures at numerous meetings and visited institutions in more than 35 countries on five continents. I enjoyed traveling and frequently

have visited some of the world's most magnificent cities (Paris 21 times, Stockholm 17 times, Madrid 15 times, London 14 times). I have close relationships with many French scientists, including Jean-Pierre Changeux, Jacques Glowinski, and Michael Imber, and was invited several times to spend weeks in the residence at Rue de l'Universite and to give biweekly lectures at the local institutions. I am also on the board of Oxford University in the United Kingdom.

As a recipient of a Selby Fellowship in the Australian Academy of Science, I was required to visit seven cities on this continent, spending at least two days at each city to give two lectures, one for the general public and one for the scientists. When asked how I did that tedious task, I said, "To the general public, I gave the most detailed and complex lecture," and so the attendees said, "He is very smart, I did not understand anything." And for the specialists, I gave a very simple general lecture, so that even scientists could understand. I also have had many visits to Israel because Pat was on the Advisory Council of the Weizmann Institute in Rehovot. During some of those visits, we had the privilege and honor to be driven by Yadin Dudai in his car to see some of the most precious places in this part of the world, with his personal explanations about their historical significance. I also had great experiences visiting China several times, including the last one as a member of the U.S.-China Scientific Exchange Committee chaired by Torsten Wiesel. After the main meeting in Beijing and as a guest of the Chinese Government, my present wife, Sandra, and I visited some of the most treasured historical monuments in the history of the world, including the Great Wall of China and Terracotta Warriors in Xi'an City.

I considered that the most effective way to propagate your ideas is to participate in multidisciplinary international meetings. I attended far too many meetings to list each one, and so I will select one that was most unusual and memorable. I was a participant at several meetings of the Pontifical Academy in the Vatican that were held in the very same building in which Galileo was tried. The other notable participants include Rita Levi-Montalcini, John Eccles, Patricia Goldman-Rakic, János Szentágothai, and Vernon Mountcastle. At one of these meetings, Sir John Eccles, who later in his life became a dualist and started to believe in independent Worlds of Religion and Science, presented his idea that the World of God commutates with the World of Brain through the Radial Units of Pasko Rakic. He discussed the RUH and related issues in several of his many books (e.g., Eccles, 1989). To Sir John's dismay, Vernon Mountcastle said plainly, "This is nonsense." This was an additional nail in the coffin of the relationship between these two great neuroscientists. I was embarrassed by the whole situation and tried to play innocent and said that I did not understand these issues and arguments. Sir John accepted my excuse, "Pasko is honest, he admits that he does not understand it." The local permanent members of the Pontifical Academy and the Pope himself actually accepted the concept

of evolution with the idea that seven days in the Bible is only symbolic and that each “day” may last millions of years.

It seems rather unlikely that someone born in Ruma (not Roma), a small provincial town in Yugoslavia, would later in life entertain for dinner in my private dining room about 15 Nobel Prize winners. These were not group gatherings but rather individual dinners with a lot of discussions over a nice glass (or two) of wine. In fact, I often served Grgich Hills’ chardonnay from Napa Valley, the same wine that was served in the White House during the dinner meeting of Ronald Regan and Mikhail Gorbachev when they were talking about “breaking down” the wall. It is interesting that Miljenko Grgich was born on the Adriatic coast and after graduating from the University of Zagreb, he emigrated to the United States to become a winemaker in Napa Valley, which eventually obtained a Prize in Judgment of Paris as the best white wine and placed American wine at the top of the world. Discussions with Nobel Laureates were always animated. They seemed to like the wine, and I was happy that they really listened and appreciated my opinion.

My discoveries, concepts, and graphic illustrations of the developmental events underlying brain structure and function have been well received and highly cited. I have published more than 350 scientific papers that according Google Scholar are reaching the mark of 90,000 citations with h-factor of 147. Some scientists do not appreciate morphometric data, but many foundations and institutions are interested in the hard data when selecting prize winners. I had a lunch long ago in Boston with the founder of the Institute for Scientific Information, Eugene Garfield, and told him that many scientists and administrators think that the number of citations does not necessarily correlate with the quality of the contribution. For example, Elizabeth Gould has thousands of citations of papers that have been proven wrong. So, Eugene replied: “Citation index does have one high correlation: those who have less citations like it less.” It is difficult to find a contemporary review article or textbook in neuroscience that does not refer to my contributions, although I complain that sometimes they forget to mention my name. However, Francis Crick once told me, “When they describe your discoveries as common knowledge and do not cite your name, that means that you really made it.”

Initially, I worked mostly alone and performed most of the experiments with help from technicians, and it may be considered unusual that on three of the five most cited papers, I am the sole author! However, over the years, as neuroscience research became a multidisciplinary activity, I have enjoyed the benefits of highly productive collaborations with my talented and dedicated students, postdoctoral fellows, and colleagues. Modern neuroscience research requires experts with different backgrounds, and without these interactions, at both technical and intellectual levels, this work simply could not be possible. The debates with my students and postdocs at regular lab

meetings or individually were essential for my creative thinking and balance of my views. I was not a strict adviser, but rather I tried to learn from them. I liked controversies, and when my student won an argument, this would make two people happy: my student and myself. I have lived during the time of globalization of science; and over the years, I have had more than 50 graduate and postgraduate students from more than 20 countries, most of which became highly successful neuroscientists and, presently, seven are chairing a department or an institute. I consider my students as my children.

During my lectures, I often return to my roots and try to entertain the audience with my drawings and anecdotes (figure 1). I was illustrating my findings and conceptual models by personal drawings using pen and India ink. My four-dimensional (three dimensions of space plus time) drawing of the development of cerebral cortex is reproduced in medical textbooks around the world. Carl Hugo Lagercrantz, professor of Pediatrics at the Karolinska Institute in Stockholm, in his book *Infant Brain Development* (Springer, 1996), translated to several languages, cites my paper on RUH, including the illustration of the four-dimensional (space and time) model of neuronal migration to the cerebral cortex. Interestingly, on page 10, he also reproduced one of my cartoons on the problem of how relying on a single method, like gene expression, can be misinterpreted. Apart from my talks, which were full of factual details as well as broad conceptual generalizations, I became known as an authentic and original reviewer, as indicated by some of the titles in the reputable journals: “A Small Step for the Cell—A Giant Leap for Mankind: A hypothesis of Neocortical Expansion during Evolution” (*Trends in Neurosciences*, 1995), “Young Neurons for Old Brains?” (*Nature Neuroscience*, 1998), “The Importance of Being Well Placed and Having the Right Connections” (*Annals of the New York Academy of Sciences*, 1999), “Discriminating Migrations” (*Nature*, 1999), “Illegal Immigrations” (*Neuron*, 2000), “Neurocreationalism: Making New Cortical Maps” (*Science*, 2001), “Neuroscience: Immigration Denied” (*Nature*, 2004), and “No More Neurons for You” (*Science*, 2006). However, I was also engaged in editing several comprehensive reference books that have a large and diverse audience (e.g., Rakic and Singer, 1988; Gazzaniga et al., 2009; Singer et al., 2019; Rubenstein and Rakic, 2020).

Over the years, I was rewarded for my scientific achievements by election to memberships of academies and foundations, including the U.S. triad (the National Academy of Sciences, NAS; the American Academy of Arts and Sciences; AAAS, the National Academy of Medicine, NAM) as well as the Royal Society (London) and the Spanish and Norwegian Royal Academies. For many years, I was also on advisory boards of institutions like RIKEN (Tokyo, Japan), Dahlem Conferences (Berlin, Germany), the National Alliance for Research on Schizophrenia and Depression (NARSAD; now called Brain and Behavior Research Foundation) (New York City), the DANA Foundation (New York City), and the Max-Planck Institute for

Developmental Biology (Tubingen, Germany). At these remarkable organizations and institutions, I had opportunities to interact with intellectuals like Masao Ito, Otto Creutzfeldt, Karl-Friedrich Bonhoeffer, and Christiane Nüsslein-Volhard, and I learned a lot from them. I was also offered the opportunity to become president of IBRO, which included use of an apartment in the center of Paris, but I did not accept it, because I was afraid that it would take time away from my research activity. I also did not accept the invitation to the White House to celebrate Obama's Brain Initiative because I did not like that it was created at the expense of other fields and without increasing the overall NIH budget. When some of my colleagues said, "How can you refuse the honor to be one of those who were invited to the White House?" I replied, "Yes, it is indeed an honor to be invited, but it is an even bigger honor to be the one who has the courage to decline it."

However, I did support and contribute to the negotiation and lobbying about another White House initiative by George H. W. Bush's administration called "Decade of the Brain" (1990–1999), which was also implemented with only a modest overall NIH budget. I had an opportunity to visit Congress several times and have had lunch with influential politicians like senator Mark Hatfield, chair of the Appropriations Committee of the U.S. Congress (figure 6). I tried to persuade him to make a more substantial increase during a very nice conversation about the prospect of the Decade of the Brain. Unfortunately, the amount of money dedicated to this endeavor was less than we expected. As pointed out by Dominick Purpura, former chair of Neuroscience and dean of the Albert Einstein Medical School in New York, none of the 10 proposed goals were actually achieved. One of the goals was a promise to find a cure for Christopher Reeve's quadriplegia. However, I recognized that if Chris, whom I met, had fallen from a horse in Belgrade in 1962, when I was a resident in neurosurgery, he would give them the definition of this term that was popular in Yugoslavia, "A pessimist is an optimist with information!"

I suppose because of my activity on behalf of neuroscience, I was elected and accepted the position to serve as the 26th president of the Society of Neuroscience (1995–1996). This job was indeed very time-consuming, but I take pride that during my presidency, we had successful negotiations to obtain support for the Decade of the Brain. In addition, during my presidency and with Publication Committee members Solomon Snyder and Peter Strick, we succeeded to make the *Journal of Neuroscience* available online in spite of the strong opposition of some Council members who were worried irrationally that the cost would eventually result in an increase in annual dues for students. I am also one of only two members of the SfN who attended all 49 annual meetings. Larry Swanson being the only other one with a similar record. The 50th in-person meeting was canceled because of COVID-19. In addition, I also served on many of the Society's committees. Looking back, I spent almost a full year in hotels attending SfN meetings.



Figure 6. Lunch at U.S. Capital, with Director of the Appropriation Committee Mark Hartfield.

Over the past 50 years, I cannot help but notice a dramatic change in the evaluation of science and neuroscientists. Of course, enormous progress has been made in the use of the most sophisticated technology and accumulation of a huge number of new facts. However, one of the problems is that students are not taught about the history and philosophy of science so that some of them think that all this started after the introduction of the internet. In addition, in the past, the significance of the contributions was the main or only question that mattered. As I pointed out in my *History of Neuroscience Lecture*, these days, major questions about scientists are their geographic location, gender, ethnic origin, and skin color. Unfortunately, presently these are the dominant issues at many universities, foundations, and learned societies. In this respect, I must admit that the communists were more open-minded and rational, and when they declared that religion is not important, they never asked the applicant's religion. If it is not important, why ask? The communists were also better educated and understood the philosophy of equality and were aware that there could be different opinions. Another difference is that they had a sense of humor, and even Marshall Tito laughed at the jokes about himself.

Private Life

My private life has been closely related to my professional life, and it has been eventful but in general very happy. Before I emigrated to United States, I married a Serbian woman, Ljiljana Lekić, who was a student at the University of Belgrade. After our wedding, we emigrated to the United States, and she initially became a technician in our new department at

Harvard Medical School. After about two years, she entered a PhD program, and her mentor and thesis adviser and was my friend and collaborator Richard Sidman. I was stunned to learn that during that time they started a sexual affair because he was much older than she was, but also he seemed to have a very nice family with two children. However, after learning of this relationship, we divorced, and they married. In those days, there was not the institutional disapproval of faculty–student relationships that there is today. In retrospect, I was actually very lucky that my first marriage ended in divorce relatively quickly, which gave me an opportunity to marry again and spend the next 25 wonderful years with Patricia Goldman-Rakic. She was my beloved wife, devoted friend, and great supporter. She was also a very trustworthy and honest person, and I appreciated these qualities. We had a wonderful marriage. Then, while I was visiting Japan in 2003, she died after being struck by a car while crossing a street near our home in New Haven.

Pat's death was devastating to me to the extent that I needed psychotherapy sessions because I felt survivor guilt, with an irrational feeling that if I had not gone to Japan to give the talk, this tragedy would not have happened. I also thought that I would never again have a romantic relationship with any woman or marry again. However, contrary to my expectations, I was very lucky again to meet another truly wonderful woman in New Haven, Sandra Biller. She also lost her husband under tragic circumstances, and we understood each other. In addition, this is a different relationship because she is a psychotherapist and not a basic scientist, and we do not work in the same place. However, we discovered that we have much in common and we wed, not just to console each other, but also to support each other psychologically (figure 7). She is an extraordinary person with whom I share many interests, such as the love of art. After seeing some of my research papers and my drawings on gene structure, she was inspired to make a sculpture “DNA of Love” that is displayed in my home (figure 8). We also enjoy discussions about the meaning of life and have learned how to age together. She retained her nice house in the woods at the edge of the Quinnipiac National Park, and I kept one in downtown New Haven. We have a large library of over more than 3,000 books, mostly on brain subjects, including some classics, such as Wilhelm His (1889), Ludwig Edinger (1895), Korbinian Brodmann (1925), and Santiago Ramon y Cajal (1895), that are considered as relatively rare antiques.

Outside of science and art, I am also interested in national and international world politics (as entertainment). Sandra and I were actually invited to the White House after I received the Kavli Award since U.S. presidents invite to a reception only Nobel, Kavli, and Pulitzer prize winners. In the Oval Office, G. W. Bush looked at Sandra and said, “Do you know that I am the only president of the United States who was born in Connecticut—and, did you know, they did not vote for me! At any rate, you have a wonderful



Figure 7. Sandra and Pasko at the 2008 reception for the Kavli Prize in Oslo (Norway).



Figure 8. DNA of love.

smile!” She replied, “Pity I did not know that you are so charming; otherwise, I would have voted for you!”

I am an avid competitive tennis player who runs after every ball like it is the Wimbledon Final. I played regularly with many famous neuroscientists like Jack Cooper and Alan Wagner until they passed away. However, even these days, I continue to play regularly and enjoy beating younger players, including my students. This, besides the genes and two glasses of wine a day, is the reason that I enjoy excellent health and thus far have not spent a single night in the hospital.

Concluding Remarks

Looking back on my long scientific career, I recognize how fortunate I have been and how small the chances were that someone born in Ruma (not Roma!) could achieve this much in this highly competitive field. I also recognize that one must have luck. Here is one remarkable example. One evening in the summer of 1962 at about 6:30 p.m., after finishing with the assistance of the removal of a neuroglial tumor in the neurosurgery operating room, I received a call from my professor that a neurosurgeon from Harvard, Hannibal Hamlin, was visiting Belgrade Medical School. Because his host was not free that evening, I was asked whether I would join him for dinner this evening in one of Belgrade’s best restaurants. I said I would be happy to, but only if I can cancel a 7:00 p.m. date with my girlfriend at downtown square Terazije. So, I called her, and after five long rings she replied, out of breath, and said that she was already at the stairs when she heard the telephone ringing and ran back to her apartment to answer the call. She agreed to cancel our date and let me go to dinner at such a fine restaurant. If she was one step more down the stairs and had not answered the telephone, I would not have gone to the dinner and would not have met Hamlin, who suggested and helped me apply for a Fulbright Scholarship in the United States. This is how life depends on luck and unrelated occasions, but as one multiple Open Golf Champion said when it was reported that he won with a lucky shot, “Yes, I was lucky the last seven times.”

At the end, if I have to select a single sentence of advice that had a crucial influence on me, it would be the words of my high school teacher who said, “Always ask how and why.”

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