

## **Autobiography**

I was born in Ruma, a small town in Vojvodina, a province in the former Kingdom of Yugoslavia. Although this province is now part of Serbia, my family had multi-ethnic roots. My father, Toma Rakic, the son of Anton, a Croatian, was born in Istria, which, at the time, was part of Italy. My grandmother, Maria Cukon, was also born in Istria, the daughter of parents of Croatian, Italian and Albanian lineage. In 1924, after the rise of Fascism, my father immigrated to the newly formed South Slavic country. There, he met my mother, Juliana, who was born in Dubrovnik on the Dalmatian Coast. Her father, Milos Todoric, was Serbian and her mother, Pepa Kuzma, was of Croatian and Slovakian ancestry. My father was Director of the Districts of Internal Revenue Service, which required the family, including my older sister, Vera, to move from one town to another about every 3 years. As a young boy, this was very difficult for me, as I had to leave friends behind and then try to make new friends repeatedly. Thus, I always related more to people than to 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 a professional career in the United States.

Apart from being devoted to raising her two children, my mother was an avid reader and collected books that ranged from French and Russian literature to Sigmund Freud and Alfred Adler. Reading was the only escape from the cruel and senseless World War II that deeply affected our country. I saw people killed in the street or disappearing overnight from my life without a trace. I lost a grandfather, uncle and a cousin who were killed by different factions in the War. My favorite pastime was to grab a book that might have been above my age level, and I even enjoyed even reading items in the Encyclopedia. For a while, I was seriously devoted to chess, memorizing entire movements used by the World Champions. At the age of 14, I was beating my classmate Vladimir Sokolov, who persisted and eventually became a world-class master. Unlike Vladimir, I stopped playing chess at the age of 15, because I felt that it was time-consuming and did not produce or explain anything. I enjoyed painting watercolors and doing graphics, as well as creating wooden and metal models of trucks, tanks and airplanes, which were not available as toys during the War.

Although I was brought up as a Catholic, my parents were not religious. I became an altar boy at the age of 8, and during the next several years, I found myself often debating

about divine origin and explanations of life and the universe with my fellow altar boys, as well as with the priest. During that time, I was deeply upset to learn that Giordano Bruno was burned and Galileo Galilei tried because their views of the universe were contrary to religious beliefs at the time. By the age of 14, I realized that scientific facts and religious beliefs could be in conflict; and, I have preferred to err on the side of science.

I attended high school in the town of Sremska Mitrovica, which, even after the Communist takeover, continued in the Austro-Hungarian gymnasium style of education, with an emphasis on classics, history and literature, but also philosophy and natural sciences. I was a top student in the class and was elected to be a leader of the debating literary club. I enjoyed vigorous discussions with both fellow students and professors. I often took a position against the prevailing views, established dogmas and authorities, a practice which I continued later in my life, sometimes to my own detriment.

There was never any doubt in my mind that I should continue to seek the highest educational level possible, especially as education was free at the time. Initially, I was interested in pursuing a career in art or architecture as they offered freedom of expression, but my father convinced me to enroll in medical school with the statement that “if things do not work 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 possessions and life savings after the Socialists expropriated the banks in 1946, and his recognition that knowledge is the only thing that cannot be taken from you. Thus, I enrolled in Medical School at Belgrade University to learn some useful information.

Belgrade was, at the time, the capital of Yugoslavia, a country with a multi-ethnic population of about 20 million. It was a very cosmopolitan city, with excellent classical music, opera and several repertory theaters that I regularly enjoyed. I kept in touch with art by writing reflective and satirical poetry as well as critiques of avant-garde theater. I also earned some money by drawing cartoons and caricatures for the local newspapers. These activities did not prevent me from getting top grades, for which I won a scholarship to Finland. This was my first trip abroad and I used this opportunity to visit several other Western European countries. I began to appreciate the value of freedom and expression of views. During a histology course at the medical school, I was exposed to Ramon y Cajal’s drawings, which to me, opened a universe of unbelievable complexity and beauty, formed by the black

silhouettes of nerve cells as well as his imaginative thinking about how they may have evolved and functioned. This exposure, perhaps more than the compelling problems of neuropsychiatric diseases, drew my interest to the central nervous system.

After receiving my MD degree, I entered internship and then residency in neurosurgery; and, during the second year, obtained a Clinical and Research Fellowship in the Neurosurgery Department at Harvard Medical School in Boston, chaired by William Sweet. I was assigned to do research on the neuroanatomy of the human forebrain in the Department of Neuropathology. There, I met pioneer neuropathologist, Paul Yakovlev, who originally trained with Ivan Pavlov in his native Saint Petersburg, and then with Joseph Babinski in Paris, where he emigrated after the October Revolution. 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 discovery of a single signaling molecule that we share with other creatures, but from unraveling the neuronal circuitry that underlies our mental capacity. He also believed, like Einstein, that the meaning of a finding is as important as the finding itself. My original two-year fellowship transformed into a four year stay, during which I immersed myself in analyzing neuronal organization of the human brain in Yakovlev's collection and the literature on human brain development.

After returning to Belgrade, I decided to abandon my career in neurosurgery and to obtain a graduate degree in Developmental Biology and Genetics. I thought that I could contribute more through research than by patient care, since so much was unknown. I also wanted to escape the routine duties in clinical medicine, especially since so little could be done for patients with neurological disorders or brain trauma without more knowledge of the brain. Finally, and most importantly, I thought that the question of how the complex organ that mediates our thought and creativity, develops from a single fertilized cell, is not only the most important question in medicine, but also in the humanities, and that it could probably be answered by modern methods and creative thinking.

As a part of my doctoral thesis, I used a recently available marker for DNA replication, ( $H^3$ -thymidine) to label the last cell divisions in viable slice preparations of fresh, postmortem embryonic human cerebrum. This was, to my knowledge, the first use of the slice preparation to identify neural stem cells, that continue to divide "supravivally" (after death) in the culture

medium. This work helped me to obtain direct evidence that none of the neurons in the large and highly convoluted human cerebral cortex are generated locally. Rather, they migrate from the proliferative centers to their distant positions, a phenomenon suspected since the 19<sup>th</sup> century, but not experimentally proven in humans. More specifically, I discovered in my experiments that the cell nuclei became heavily radioactive, in the two distinct transient proliferative layers near fluid filled cerebral ventricles, which I termed the ventricular and subventricular zones. The Boulder Committee in the U.S. adopted these terms in 1970, which are now generally used in developmental neurobiology. Based on these discoveries, I was offered an assistant professorship of neuropathology at Harvard Medical School, and I immigrated to the United States in 1969.

From the start, I loved the opportunities and competitive spirit in the United States. Harvard provided unlimited possibilities, and I was lucky to enter the field when there was a sudden influx of new methods in genetics, molecular and cell biology, electron microscopy, immunohistochemistry and tracing of neuronal connectivity. I also benefited from the 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 first on the kinetics of neuronal proliferation and the cellular mechanisms of neuronal migration. The fact that the different neuronal classes have to be produced at precise times and sequentially migrate to distant pre-specified 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.

I decided to study development of the brain simultaneously in three species - mouse, macaque monkey and human, to learn from the similarities as well as from the differences. This was not commonly done in the same laboratory, but I was hoping to obtain specific anatomical and molecular data relevant to the biological basis of human mental capacities. As a first step, I initiated a comprehensive <sup>3</sup>H-thymidine autoradiographic study of neurons in non-human primates to determine the precise time of origin and routes of their migration. I selected the macaque monkey, 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 yet on the time and sequence of neuronal origin in any species. Among many instructive and biomedically relevant findings from this

series of studies, I discovered that the genesis of the cerebral cortex in the macaque monkey both begins and ends before birth. Comparing timing of emergence of selected developmental landmarks indicated that the same is true in humans.

The next logical question was how the neurons, after their last 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 radial glial cells. This transient population spans the full thickness of the fetal cerebral wall and is especially important for a large, developing human brain in which many neurological and neuropsychiatric disorders display abnormal neuronal migration. The computerized animation of this dynamic process, based on my India ink drawings, is provided at (<http://rakiclab.med.yale.edu/MigratingCorticalNeuron.html>). Based on this discovery, I proposed a **radial unit hypothesis** of cortical development and evolution, which provides insight into how the complex, three-dimensional organization of the brain is built from an initially two-dimensional layer of dividing neural stem cells (e.g.: <http://rakiclab.med.yale.edu/RadialMigration.html>).

This finding led to the related proposal of the **protomap hypothesis**, as a model of how different regions of the cerebral cortex evolve and 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 ventricular and subventricular zones. I was happy that, in spite of initial opposition, these two hypotheses became accepted as principles and have received support from numerous laboratories, as well as from our more recent studies, using genetically altered mice, viral gene transfer for tracing cell lineages and the *in utero* electroporation method. 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 occurred during evolution by a random mutation of genes.

Today, the notion that the central nervous system is plastic is commonplace; but, 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 initially intermixed in their first brain target, the lateral geniculate nucleus, before segregating into six eye-specific layers. By manipulating connections in the embryo, I also provided the first direct evidence for the competitive interactions among axons subserving visual connections before birth; and, discovered that the optic and cortico-cortical connections, as well as cortical synapses and neurotransmitter receptors, in nonhuman primates are initially overproduced before declining to the adult level after puberty. These discoveries led to the proposal of the ***selective elimination hypothesis***, as a mechanism for tuning synaptic connections by interaction with the environment during the period of most intense learning, which today is commonly called “pruning”.

In 1979 I was recruited to the 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 chairman of the Section of Neuroanatomy. I was joined by my wife-to-be, Patricia Goldman-Rakic, who was recruited from the National Institute of Mental Health, and who herself was already a well-established and highly successful neuroscientist. She was my beloved wife, devoted friend and great supporter, but we were also each other’s constructive critics in science. We were working in different subfields of neuroscience and had only a few papers together, but we regularly commented on each other’s manuscripts before submission. Our common denominator in science was our interest in the biological basis of the highest brain function. Thus, we founded together a new, now well established, high impact journal, *Cerebral Cortex*, that 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. Over the years, Pat helped me to build and transform the Section of Neuroanatomy into a thriving, modern Department of Neurobiology and together attract the Kavli Institute for Neuroscience to Yale.

My laboratory at Yale continues to be devoted to the molecular mechanisms that control neuronal proliferation and migration. I concluded that this multidimensional process cannot be explained by the discovery of a single gene or molecule, but by a full understanding of the complex cellular and molecular interactions that govern it. 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 that contribute jointly to cell orientation, recognition of migratory pathways through differential cell adhesion and also regulate the rate of their nuclear movement by controlling the dynamics of cytoskeletal proteins. We found that at least 20 diverse molecules, some of which were initially identified in invertebrates, control specific phases and components of neuronal stem cell proliferation and migration, such as 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. Importantly, by manipulating the speed and pattern of neuronal migration using genetic tools and environmental factors, we discovered hidden abnormalities of neuronal positioning that cannot be discerned by routine postmortem examination of the human brain. These observations have opened a new insight into the pathogenesis of major neurological and neuropsychiatric disorders, such as childhood epilepsy, autism, developmental dyslexia and mental retardation. These cellular mechanisms 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.

Our 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, last the entire life-span and are irreplaceable. This finding led me to suggest that the stability and longevity of the neuronal populations in 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. I hypothesized that this limit of adult neurogenesis may have occurred at the expense of the capacity for regeneration and natural turnover of neurons that exists and is very prominent in many lower vertebrates. This area was not within my main research interests, but my conclusions were initially contested by other scientists as well as the popular press. However, my original findings in the primate cortex have been confirmed in several mammalian species in other laboratories by different methods, including Carbon 14 birth dating of the human cerebral cortex. 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.

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 institutions in over 30 countries on five continents; and, I was pleased that according to the Institute of Scientific Information, my papers have been, at this writing, cited more than 35,000 times. Initially, I worked mostly alone, and performed most of the experiments with help by the technicians; and, I am a sole author of three of the five most cited papers. However, over the years, as neuroscience research became multidisciplinary, I have enjoyed the benefits from 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 at regular lab meetings or individually, were essential for my creative thinking and balance of my views. I liked controversies, and when my student won an argument, this would make two people happy: my student and myself. I have lived at the time of globalization of science; and over the years, I have had over 50 graduate and postgraduate students from more than 20 countries, most of whom became highly successful neuroscientists and, presently, seven are chairing a department or an institute.

My private life has been eventful and happy. After a brief first marriage, I spent over 25 wonderful years with Patricia Goldman-Rakic before her untimely death in 2003 after being struck by a car while crossing the street near our home. In 2010, I married Sandra Biller with whom I share love and an interest in art. Although I now have two stepsons, I also consider my graduate students and postdoctoral fellows, with whom I keep in close touch, as my offspring. Outside of science, I am interested in world politics, and I am an avid tennis player.

Before the Inaugural Kavli Prize for Neuroscience, I received recognition by the Gerard Prize from SFN, Lashley Award from the American Philosophical Society, Bristol-Myers Squibb, Pasarow, Marta Philipson, Henry Gray, Weinstein-Goldenson, Kreig and Fyssen Foundation Awards. I served as President of the Society for Neuroscience and was elected a member of the National Academy of Sciences (USA), American Academy of Arts and Sciences, Institute of Medicine (USA), Croatian Academy of Science and Art, Serbian Academy of Sciences and Arts and the Norwegian Academy of Science and Letters.