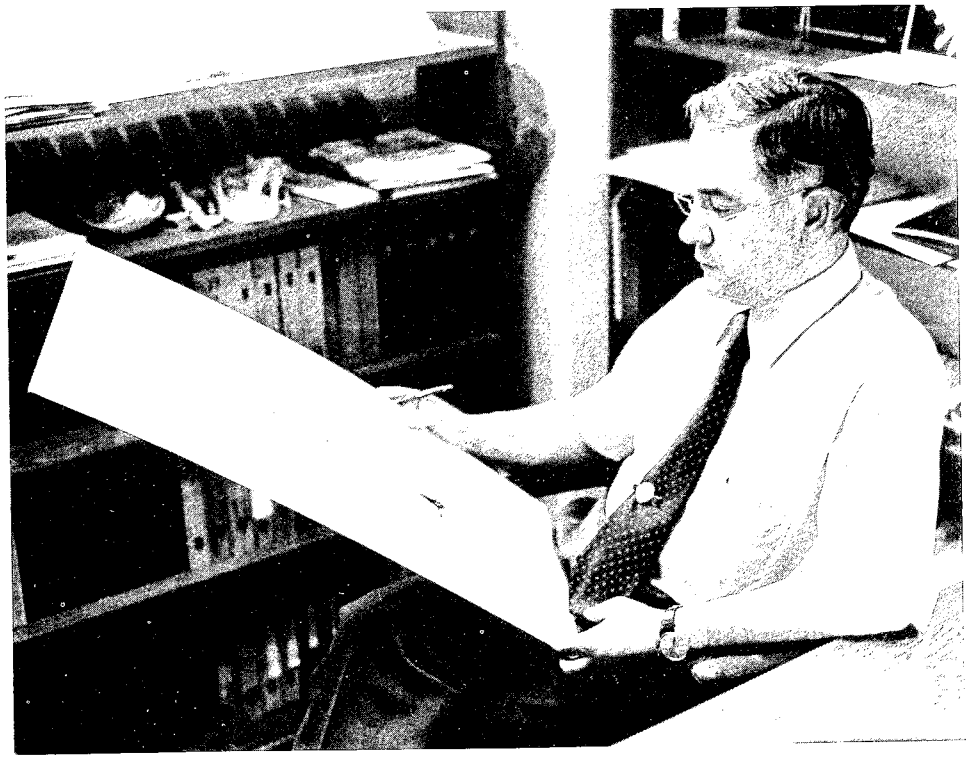
Exploring the Human Brain

BY MIGUEL MARIN-PADILLA, M.D.



Dr. Marin-Padilla is a professor of pathology at the Medical School, and specializes in pediatric pathology. A native of Jumilla, Murcia, Spain, he received his medical degree from the Granada University School of Medicine in 1955 and emigrated to America the following year. He served an internship at St. Francis Hospital in Jersey City, New Jersey, and then began his career in pathology as a resident at Robert Packer Hospital in Sayre, Pennsylvania. He spent two years as a resident at the Mallory Institute of Pathology in Boston, and joined the faculty at Dartmouth as an instructor in 1962.

An internationally recognized authority on the brain, Dr. Marin-Padilla has published extensively in his field and is an associate editor of the Journal für Hirnforschung, *an international publication devoted to the neurological sciences. His present research activities are supported by a five-year grant from the National Institutes of Health.*

In the letter that follows, Dr. Marin-Padilla tells of his search for a place to pursue his neurological research interests, and of the importance of that research to his life.

Dear Colleagues and Friends:

For the last ten years I have been studying the structural organization of the human brain, fulfilling at last a lifelong dream. It is a story which I would like to share with you.

It all began in an anatomy class during my first year as a medical student. We were more than two hundred students from every corner of Spain, and most of us had never met before, but we all shared similar dreams and aspirations, very much like those shared by all of you. My dream grew from a melding of that which I already knew and that which I was learning at medical school.

From my father, a lawyer and philosopher, I learned about the extraordinary capacity of the human brain to learn. The majority of human knowledge does not come from genetic coding, but is gained through teaching, tradition, culture and printed codes (books). Knowledge is something acquired, something which evolves and progressively develops, and consequently can be analyzed and studied.

From medical school, on the other hand, I was learning about the structural complexity of the human brain and, more importantly, about the methods available to study it.

I thought then, with youthful optimism, that if I had an appropriate method, I could study and elucidate any structure regardless of its complexity. I also thought that if I could understand the structural organization of the human brain, I should be able to understand the human mind and how it learns. In essence, that was my dream.

With these ideas in my head, I felt as Archimedes, the Greek philosopher, must have felt when he claimed that he could move the world if given a place to stand and a fulcrum. I had the same idea and knew where to find the appropriate method, but I did not have a place to stand. It took me eighteen years to find an appropriate place to stand. During those years I learned and did many things, but never lost sight of my dream.

The works of two great men have influenced my thoughts since my student days. From reading the works of Cajal, a Nobel laureate Spanish neuroscientist, on the structural organization of the nervous system, I have found inspiration and gained an appreciation and understanding of basic nervous structure. Cajal's ideas and concepts are the foundation of modern neuroscience. From him, I also learned how to study the structural organization of the human brain and of the need for patience and self-discipline in doing so.

On the other hand, from the works of Piaget, a Swiss psychologist, I have learned about the cognitive development of the child. Piaget's views that the intellectual faculties of a child develop progressively following a sequence of several well-established stages are in agreement with my own. A correlation between the intellectual developmental stages of Piaget and the structural develop-

ment of the brain of a child remains to be made. To be able to correlate the ideas of these two great men has been an ambition of mine for a long time. Perhaps, someday I may be able to accomplish this.

After graduation, I went to work as a pediatrician in a small city in southern Spain. Within a year, I began to feel "intranquil." I was not moving toward my dream; I still had no place to stand. Some of my friends urged me to go to America and pursue my dream. I was easily convinced and I quickly set about making preparations.

Six months later, I arrived in New York City, full of enthusiasm, unable to speak a word of English, and unaware of what was ahead of me. The next six years of my life were confusing, vague, sometimes unreal and generally indescribable; I was always 'on the run.' I had no time to think or to read or to talk, only time to work and time to rest. Internship — residency — specialty, one after another with first fifteen, then twenty and later thirty days of vacation yearly. After two years of this, I called for help and married Teresa, my girl friend since medical school, and everything improved considerably with her at my side.

I came out of this six-year long tunnel alive and contented. I found myself a fully qualified pathologist with excellent training in pediatric and developmental pathology, with satisfactory command of the English language, and with a considerable understanding of the American way of life. I was ready to slow down my pace and to accelerate my thoughts.

I decided to pursue an academic career and, encouraged by Professors Mallory and Robbins of the Mallory Institute of Pathology in Boston, I accepted a pathology instructorship at Dartmouth Medical School in 1962 and moved to Hanover with my wife and two small children. I remember vividly that I was called a "brave missionary pathologist" by my Boston colleagues at the going-away party at the Institute. They did not realize that I was already eagerly searching at this time for tranquility and time to put my thoughts in order and to continue the pursuit of my dream.

During the next five years, I participated actively in teaching, in service (pediatric pathology) and in various research projects. I investigated in detail the embryogenesis of clinical and experimentally induced dystrophic disorders, the embryogenesis of malignant testicular tumors and various types of skeletal developmental abnormalities. Then, having acquired a sound background in the understanding of the structural organization and embryonic development of normal as well as pathological tissues, and having a secure academic position, I decided that the time had come for me to begin the study of the human brain. At last, I had found a place to stand.

I completed all my research projects, asked permission to leave for one year to study the classical silver methods at the Cajal Institute in Madrid, Spain, and sent an application to the National Institutes of Health asking for economic support for my family and me. Permission granted and a NIH grant awarded, we sailed one morning in June 1967 from Boston to Spain.

At the Cajal Institute I learned the classical silver methods and found only one, the rapid Golgi technique, suitable for my purpose. This method, named after Camilo Golgi, Professor of Pavia, is the only one capable of staining the whole nerve cell (neuron) by covering it with an ultra-thin layer of silver nitrate. The nerve cell stained with this method became visible as a tree-like structure (Fig. 1) against a transparent reddish background. Only this method permits us to see the whole neuron as it is found within the brain. It also permits the analysis of the overall structural organization of the neuron, the number and orientation of the dendritic branches through which the neuron receives information, and the number and distribution of the axons through which the neuron sends information to other neurons or structures.

My first study, for which I used slides of brains prepared by Cajal more than eighty years before, was to find out the number and the normal distribution of the dendritic receptors (postsynaptic structures) of the neurons in the motor cortex of the newborn and young children — something which had never been done before. This study documented the normal patterns of synaptic distribution of the motor cortex, and the findings were later used for comparison with the abnormal synaptic distributions found in mentally retarded children.

But before talking about any other types of investigations, let me try to describe briefly the structure of the human brain by using an imaginary model. Think of the human brain as an oblong asteroid covered by an immense forest (cerebral cortex), composed of more than 10 billion individual trees (neurons) with hundreds of billions of connections (roots and branches) among them. In this immense cerebral forest, no two tree-neurons are alike and all are invisible. In order to study the tree-neurons, we must penetrate the forest using a vehicle (microscope) and a method to paint individual tree-neurons to make them visible. Once in the forest, the area one is able to explore becomes infinitesimally small. The surface of the cerebral forest is about 160 million square micrometers; the entire motor region (precentral gyrus) represents only 75,000 square micrometers. The area of the motor region which I have explored, that which controls the voluntary movements of the hand, represents only 5,000 square micrometers.

I have been exploring this small area of the cerebral forest for about 10 years and have studied in detail only a few hundred of its tree-neurons. I am far from knowing the complete structural organization of this small region, or all of its neuronal types, or even all the fundamental functional interrelationships among its tree-neurons. Let me add that there are many areas of this cerebral forest which have never been explored, and that we do not yet have a complete and clear understanding of the structural-functional relationships of any particular region within it.

Let me try to put all of this in a different perspective. Imagine that the human brain is a planet inhabited by 10 billion people as diverse and as different as we are. Suppose that we approach one region of this planet, like New England, and land in a small area of it, say Hanover. It is possible that after a few years we might have learned many things about the Hanoverians, such as their customs, appearances and language. We would need much more time if we wished to understand the reasons for their behavior, their origin and development, or the meaning of their cultural environment. This knowledge, although very limited, is obviously important and necessary if we are ever going to understand the people of that planet. However, it would be of no great use if we were to land in another area of that planet inhabited by people with a different language, a different architectural model, and a different cultural background. To know these new people, we would have to land where they are and spend years living amongst them. To thoroughly understand the people of the whole planet would take many lifetimes, an army of explorers, and innumerable journeys, but it could be done.

But this analogy is still complex and incomplete. Let us try to reduce the entire cerebral forest with its billions of tree-neurons to only one and analyze it. I have selected for this exercise the giant pyramidal cell of the motor region (Fig. 1), the most majestic tree-neuron, indeed the

giant sequoia of the human cerebral forest. This tree-neuron, often called the Betz cell after its discoverer, a Russian "explorer", is more than 2,000 micrometers tall. It is characterized by a large vertical dentritic trunk with lateral and terminal branches and by basal dendrites arising from its nuclear region. This tree-neuron receives information through three different areas: a) through the many thousands of spines (Fig. 2) covering its entire dendritic surface (axo-spinodendritic synapses); b) through the spineless areas of the dendrites (axo-dendritic synapses); c) through the spine-free surface of its nuclear region (axo-somatic synapses). All together a tree-neuron of this size has more than 20,000 surface receptors through which it receives information. These large tree-neurons are probably capable of handling more than 20,000 bits of information at any time and deciding which one should reach its emitting or sending apparatus (the axon). Therefore, the popular idea that the human brain is like a computer should be replaced by a more appropriate one, namely that each one of its billions of neurons might represent a computer in itself.

The sending-information apparatus (the axon) of this tree-neuron probably makes contacts, through axonic collaterals, with thousands of distant tree-neurons of the cerebral forest. It sends excitatory or inhibitory impulses which result in different functional or behavioral patterns depending on the types of the tree-neurons, the region of the forest, or the functional status of the tree-neurons contacted by its axon. The understanding of the different behavioral patterns running through the same pathways is also of crucial importance. It is like using the same telephone line to speak in several different languages. It will only work if the receiver is able to understand the different messages.

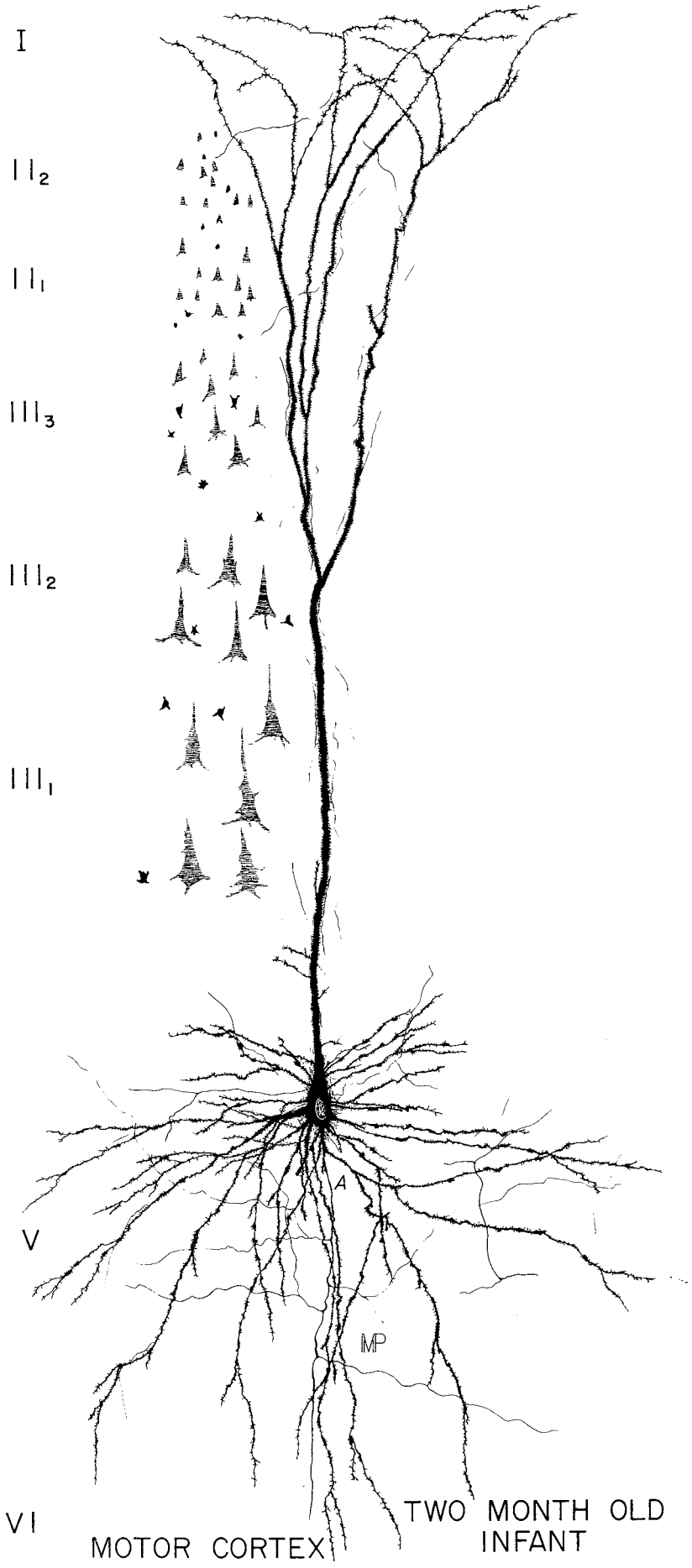


Figure 1. Camera lucida drawing (from rapid Golgi preparations) of a giant pyramidal neuron of the motor region of the cerebral cortex of a two-and-one-half-month-old child illustrating the tree-like structure of some brain cells. This particular type of neuron is an important link in the complex inter-neuronal chain which controls the voluntary movement of the hand. It is more than 2,000 micrometers tall and has more than 20,000 surface receptors which receive information. Its sending-information system, the axon (A), makes contacts with thousands of other neurons throughout the brain. The complete understanding of the function of a single neuron like this one will indeed represent a giant step in the understanding of the human brain.

This giant pyramidal tree-neuron is an important component of the mechanism which controls voluntary movements of the hand. These movements are among the most complex patterns of behavior (manual construction, writing, painting, sculpturing, 'seeing' and 'reading' for the blind, 'speaking' for the mute) known to man. Understanding how a single tree-neuron receives, integrates, analyzes and transports information, makes decisions, and then discharges information will be a giant step in the understanding of the entire cerebral forest (human brain). I hope that these analogies have helped in bringing into clear focus for you the magnitude and complexity of the problem. As a morphologist, I feel we need to continue the exploration of this forest in order to establish the structural organization of its tree-neurons, because only after this structural organization is established will the neurobiologist, neurophysiologist, neuropharmacologist or neuropsychologist be able to move knowledgeably about in it.

Although I have not found answers for any of the "big questions" during these ten years, I have discovered small things which are worthy of mention. In one of my explorations, I came across a small neuron which had never been previously recognized. This small neuron sends information to the giant pyramidal neurons, forming a pericellular nest of axonic terminals around their bodies. I have named them "the basket cells" of the human motor cortex because they are similar to the basket cells of the cerebellum discovered long ago by Cajal. With the aid of Professor Stibitz of the department of physiology, I have been able to determine the three-dimensional structure of this small neuron. We have made a three-dimensional computer reconstruction of it which can be rotated, thus permitting us to visualize it from above, below, or in profile. These "basket cells" are flat neurons which occupy a specific and narrow rectangular space within the motor cortex. They belong to the group of "short-circuit" neurons which are so abundant in the human brain. Their function remains poorly understood.

In studying the motor cortex of mentally retarded children with chromosomal abnormalities, I found that some of the neurons were abnormal. They were underdeveloped, with a reduced number of dendritic branches, and all showed bizarre structural abnormalities in their dendritic-spine receptors (Fig. 2). These abnormalities imply a structural basis (synaptic dysfunction) for the incoordination and mental retardation exhibited by these children.

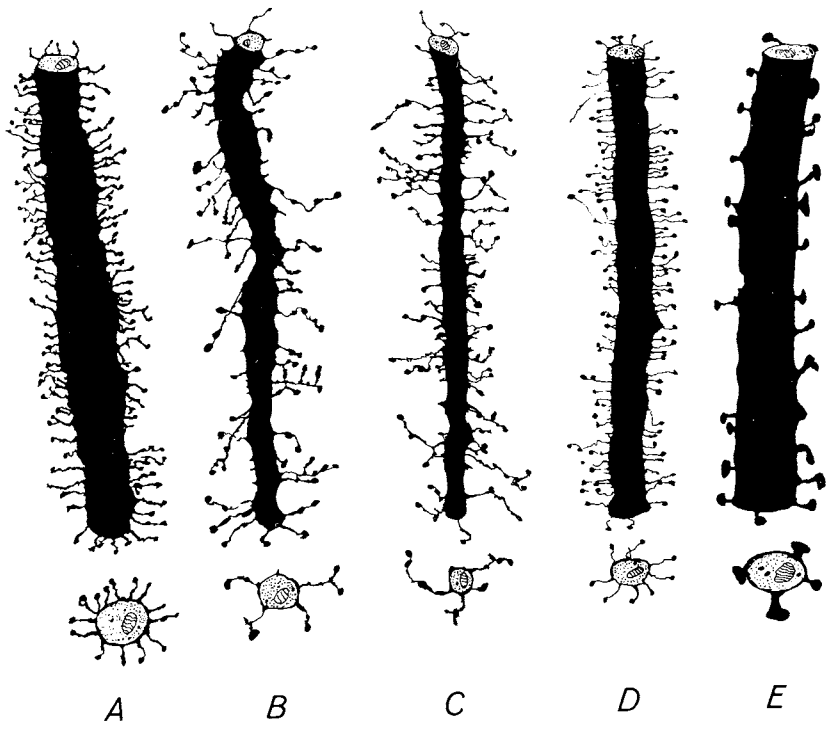


Figure 2. Detail of the mid-region of the vertical dendritic trunks of several giant pyramidal neurons from the cerebral cortices (motor region) of a normal newborn (A), a newborn with 13-15 trisomy-Patau Syndrome (B), and a 19-month old girl with 21 trisomy-Down Syndrome (C, D, E). They illustrate the reduction and the bizarre structural abnormalities of the dentritic-spine receptors (post-synatic structures) of the motor neurons encountered in the cerebral cortex of these children. Such structural abnormalities imply some degree of synaptic dysfunction in the motor neurons which could explain the degree of mental retardation and motor incoordination which characterize these abnormal children.

Thus, for the first time a link between mental retardation and structural abnormalities of the fibrillar-neuronal organization of the cerebral cortex appears to have been established. This provocative concept provides a completely new approach to the study of the problem of mental retardation.

Exploring the human cerebral cortex-forest has been rewarding and even exciting, although at times I have found myself totally lost and disoriented. To explore this immense forest, one also needs two important ingredients which are very scarce these days, namely, time and patience. If sometimes you do not know what to do, I recommend that you get yourself a microscope and a can of paint (Golgi Brand) and become an explorer of this immense and intriguing forest. Possibly, you will find that you are the first man or woman who has penetrated that particular region of the forest in which you have chosen to land.