

Down link

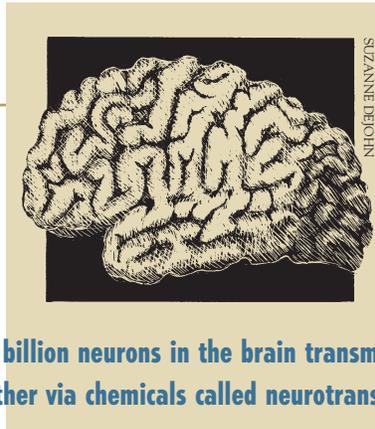
By Meredith Curtis

In 1866, British physician John Down, M.D., was the first to describe a form of mental retardation that was later named for him—Down syndrome. In 1959, French physician Jerome Lejeune, M.D., Ph.D., was the first to discover a chromosomal abnormality in humans—Down syndrome's underlying genetic defect, a malformation called trisomy 21, in which three, rather than two, copies of chromosome 21 are present. And in the early 1970s, DMS pathologist Miguel Marin-Padilla, M.D., was the first to link mental retardation to structural abnormalities in the brain. He found that the cerebral cortexes of patients with Down syndrome contained underdeveloped neurons with fewer dendrites (the branchlike projections from neuron cell bodies) and deformed dendritic spines (spiny projections from the dendrites).

Some 100 billion neurons in the brain transmit signals to each other via chemicals called neurotransmitters. Impulses travel along the cable-like axon of a neuron and release into the synapse (the gap between neurons) neurotransmitters that bind to dendritic spine receptors on a nearby neuron. But malformed dendrites don't receive signals properly, disrupting this intricate network.

Stain: Research on dendritic spine receptors stretches back to the late 19th century, when Spanish histologist Santiago Ramon y Cajal, M.D., first discovered and mapped the structures using a staining method developed by rival scientist Camillo Golgi, M.D. (Both men won the Nobel Prize in Medicine in 1906 in recognition of their work on the structure of the nervous system.) The Golgi stain, introduced in 1873, is a silver chromate solution that selectively darkens individual neurons, making their structure visible. One hundred years later, Marin-Padilla was the first to use the Golgi stain method to analyze brain tissue from children with Down syndrome.

In his first investigation, Marin-Padilla compared tissue from the cerebral cortexes of two recently deceased infants—an 18-month-old child with trisomy 21 (Down syndrome) and a newborn with another form of mental retardation related to trisomy of chromosomes 13 to 15 (Patau syndrome)—to similar tissue from six deceased infants who were neurologically normal. The samples from both mentally retarded infants showed structural abnormalities in their dendritic spines. The brain from the newborn with Patau syndrome had fewer, but longer and more twisted, dendritic spines than did the normal newborn brains. In the child with trisomy 21, the dendritic spines were even more unusual—long, thin stalks attached to prominent, rounded terminal heads. Marin-Padilla published these findings in an



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article for the journal *Brain Research* in June 1972.

In 1974, Dominick Purpura, M.D., of Albert Einstein College of Medicine published similar findings about neurons in infants with severe seizures and cognitive impairment of unknown origin. He noted that the dendrite abnormalities were related to the infants' age and to the severity of their retardation but was unable to pin

down any functional consequences associated with these changes.

In 1976, Marin-Padilla published a structural analysis of the brain of a 19-month-old Down syndrome child who had died at DHMC from acute gastroenteritis. Her family gave permission to have her brain prepared for study within two hours of her death, ensuring a high level of tissue preservation. There was some cerebral edema, or swelling of the brain, likely because the child had been on a respirator. It was possible the edema was responsible for the many damaged neurons in the cerebral cortex.

Selective: But Marin-Padilla noticed that many abnormal neurons were next to normal ones. He realized that such selective damage was probably due not to edema, but to a genetic defect. He had observed the same kind of dendritic spine abnormalities in his 1972 study. Once again, some neurons had dendrites covered in very long, thin, twisted spines with skinny stalks and enlarged terminal heads; some had dendritic spines that were much shorter than usual; and some large motor neurons had a surprising scarcity of dendrites.

He speculated that these variations in spine length represented various stages of degeneration: the long-spine stage came first, its abnormal structure resulting from altered gene expression; progressive degeneration occurred because the neuron could not maintain such a large membranous surface area (the longer and more numerous the dendritic spines, the greater the surface area of a dendrite). These aberrations and resulting impaired function would explain the decreased coordination in children with Down syndrome. And perhaps the sporadic loss of neurons in Down syndrome could explain the Alzheimer-like symptoms of some patients.

Call: Marin-Padilla also found that the long-spined dendrites were surprisingly similar to dendrites in developing prenatal neurons in normal brains. This potential link between mental retardation and normal early development was exciting. Other studies had demonstrated that sensory deprivation in early development could alter the structure of cortical dendrites. He closed his 1976 paper with a call for further research into structural changes in the developing brain.

Others have answered that call. We now understand, for instance, that an impoverished environment during early childhood can adversely affect the brain's structure and function. Marin-Padilla is investigating other areas of neuroscience now but will probably be best remembered for his landmark histological studies 30 years ago. ■

"Bench to Bedside" explores the research underlying advances in clinical medicine. Meredith Curtis is a junior at Dartmouth College, majoring in biogenetics. This essay is adapted from an article in the Spring 2004 Dartmouth Undergraduate Journal of Science.