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BRAIN DAMAGE

only the smallest molecules can pass through their walls. The vessels thus act as a protective filter against most chemicals or other substances that might be damaging to the brain. Most dangerous molecules can't get through this filter, which is known as the blood-brain barrier.

With these kinds of defenses, how had MPTP—if indeed it was MPTP—managed to slip into George's brain and wreck his life?

Pondering this question, Langston reread for the tenth time the *Journal of Psychiatry Research* article. In the footnotes the authors had cited a number of old articles which had inspired Barry Kidston. As the Valley Medical Center library didn't have these articles, Langston drove to Stanford to use the library system there. He consulted chemical abstracts and looked up all literature relating to the synthesis of MPPP and made a list. Then he walked downstairs to the electronically controlled stacks to begin his search.

Langston located the stack which contained the *Journal of Organic Chemistry* for 1947. He found the right volume and began searching for the article "Piperidine derivatives: Part III" on page 894. He flipped through, looking for the right page: 892, 893, 899, 910 . . . Langston thought he had made a mistake. He checked again. There was no page 894 or page 895. There were no pages 896, 897, or 898. All the pages relating to the article were missing. They had been razor-bladed out. Annoyed, Langston looked for the next reference, in the *Journal of Pharmacology and Experimental Therapeutics*. He found volume 91 and began searching for the first page of the article, "Piperidine derivatives with morphine-like activity." Again, the article was gone. His next reference was an article from the same journal, published in 1948, "Pharmacologic studies on analgesic piperidine derivatives." Yet again, the article had been torn out of the volume. Langston's imagination began to go wild. This must have been the very library where the California designer-drug chemist had done his research. Perhaps he had stumbled onto the trail of the person whose acts had

The brain is an organ of awesome complexity, but it has one big flaw. Once nerve cells in the brain die, they are gone forever. Brain cells cannot replicate after injury to replace nonfunctioning or dead nerve cells. Unlike skin after a wound, they can never grow back. We are, therefore, all born with a full complement of neurons; after birth our brains will never produce another nerve cell.

Because of this vulnerability, the brain has evolved several lines of defense against losing nerve cells in the first place. One of these is physical. To cushion it from outside blows, the brain floats in a special liquid—cerebrospinal fluid—which also surrounds the spinal cord. The brain and spinal cord are also sheathed in three layers of membranes and encased in bone.

The second line of defense is against chemical damage. The blood vessels in the brain are not like the blood vessels in the rest of the body. They are constructed so tightly that

crippled Connie. If so, why hadn't the chemist used the photocopying machines? Perhaps he wanted to limit competition from other designer-drug makers?

Returning to VMC, Langston looked in on George. L-dopa had completely transformed him. He could move and talk virtually as well as before the tragedy. He seemed to enjoy the attention he was getting and liked talking to the media. Over the short time they had known him, Langston and Ballard had discovered George to be an extraordinary character. Small, thin, wiry, and very tough, George had been involved in many criminal enterprises, from petty theft to narcotics and prostitution. He had served time at some of California's most famous jails. He had a wife and children, but they had turned him out years before.

For all this, he had an artistic streak within him which might have flowered if his upbringing had been different. He liked to paint and write poetry. George, who had grown up in Silicon Valley, had never stuck with anything. He had wanted to be a singer but had ended up dealing drugs. He had tried marriage and a family and ended up as a petty criminal. He had never held a steady job.

In a few days George would be returned to jail to serve out his sentence, but Langston would make sure he came to VMC for regular follow-ups.

Juanita had responded so well to L-dopa therapy that Langston had discharged her to outpatient care. Langston had found her to be a sweet, caring person, and like George's, her story had drawn him in. Born on January 2, 1952, in Fontana, near Los Angeles, Juanita was one of eight children. Her family had moved to Gilroy in the agricultural heartland of California and she attended school in Watsonville until the eighth grade. As a child growing up, her favorite activity was going to church and her ambition was to become a nun. But things didn't turn out that way. She began taking drugs when she was twelve years old and gave birth to an illegitimate son in her teens. Thanks to a warm, supportive family, Juanita had somehow stumbled through life before taking the bad heroin. Langston in-

tended to keep seeing her on a regular basis to monitor how the L-dopa was working.

The Silvey brothers had also responded very well to L-dopa, and were being treated in Watsonville by their physician, Dr. Murphy, and the consulting neurologist, Jim Tetrad. David and Bill Silvey had grown up in Watsonville and had been abusing drugs since their early teens. Apart from occasional work as laborers and truck drivers, the brothers had not found steady work and were in constant trouble with the law. They were well known to the Watsonville police and had long criminal records. Thanks to Drs. Tetrad and Langston (and, of course, the L-dopa) they could both move again. So far, they had kept out of trouble and had not gone back to abusing drugs, but Langston suspected it would just be a matter of time before they did.

As far as Langston knew, Toby Govea was the first person to have taken the bad heroin and developed symptoms. He reported first taking the heroin in late April, yet because his condition was not correctly diagnosed, it was August before he was put on L-dopa. Toby responded very well to a mixture of L-dopa and bromocriptine (a drug which prevents the L-dopa wearing off too suddenly) taken every three hours. His symptoms virtually disappeared, although they returned immediately if the medication was lowered or stopped.

The patient that Langston was most worried about was Connie Sainz. Initially she had been put on three 10/100 Sinemet (carbidopa combined with L-dopa tablets), but getting little effect, Langston had doubled the dose. Connie had regained some facial expression and was able to talk a little, but it seemed the dose was still inadequate.

Eventually, Langston had increased Connie's dose to six 25/250-milligram tablets, combined with bromocriptine to make the L-dopa last longer. This time it worked. Connie's parkinsonism was reversed and she was able to move and talk.

Connie and the others were walking and talking, thanks to L-dopa, a remarkable drug that had transformed the lives

of Parkinson's disease sufferers. Before L-dopa, the average life span of patients with Parkinson's disease was seven to ten years. As a medical student Langston had read the astonishing story of brilliant medical research which led to L-dopa's discovery. In the 1950s, before Parkinson's had even been linked to dopamine, the Swedish scientist Arvid Carlsson had carried out a series of ingenious experiments in which he gave rabbits reserpine—a drug which for a few hours causes them to become very slow, apathetic, and nearly paralyzed; even their ears wilt. Carlsson theorized that their "motor problems" resulted from a chemical imbalance in a region of the brain called the striatum and wondered if the rabbits' condition could be correlated with a depletion of the common neurotransmitter dopamine.

To test his theory, Carlsson had set out to reverse the animals' parkinsonism. He injected a substance called dopa, which passed into the rabbits' brain, where it could be converted into dopamine. The results were dramatic: dopa restored dopamine levels to normal in the rabbit striatum, and completely reversed the symptoms of immobility. Carlsson was aware that reserpine was capable of causing a Parkinson's-like condition in humans. Putting all of this together in a now famous lecture at the National Institutes of Health in 1958 as part of the First International Symposium on Catecholamine Metabolism (later published in 1959), Carlsson suggested that a dopamine deficiency might be the neurochemical basis of Parkinson's disease. It was one of those flashes of insight that characterize great discoveries in modern science. Yet Carlsson's proposal that dopamine was important for motor behavior was at first greeted with great skepticism, even downright rejection, from several leading authorities.

However, Carlsson's work did not go without notice. It attracted the attention of a young Austrian scientist, Oleh Hornykiewicz. Following Carlsson's suggestion that a shortage of dopamine might be the critical factor in Parkinson's disease, Hornykiewicz obtained human autopsied brains for analysis. Hornykiewicz and a coworker, Herbert

Ehringer, discovered that the brains of deceased patients with advanced Parkinson's disease had virtually no dopamine in the striatum. Then, together with the Austrian neuroscientist and physician Walther Birkmayer, Hornykiewicz continued this work, reporting that not only was the striatum depleted of dopamine, but also the substantia nigra. Hornykiewicz and Birkmayer then made the obvious suggestion of trying to increase the supply of dopamine to a patient with advanced Parkinson's disease. The question was, would dopa do for people what it had done for rabbits?

As Birkmayer and Hornykiewicz reported in a paper in 1961, after injecting dopa the results were dramatic. "The effect . . . was, in short, a complete abolition or substantial reduction of akinesia. Bedridden patients who were unable to sit up, patients who could not stand up from a sitting position, and patients who, when standing, could not start walking, performed all these activities with ease . . . they walked around with normal associated movements and they could even run and jump . . . This dopa effect reached its peak within two to three hours and lasted, in diminishing intensity, for 24 hours."

Birkmayer and Hornykiewicz's findings were independently replicated by Andre Barbeau in Canada, who for the first time gave the drug orally. But there were problems. Barbeau ran out of money (dopa was at the time very expensive) and couldn't continue his experiments. Birkmayer and Hornykiewicz became pessimistic about dopa as a treatment for Parkinson's disease because of the difficulties in administering large amounts of dopa without producing nausea, vomiting, and hypotension in the patients. It was not until 1968, when George Cotzias, a scientist and physician at the Medical Research Center, Brookhaven National Laboratory, in New York, reported dramatic effects with oral dopa in *The New England Journal of Medicine*, that the drug finally became a therapeutic reality. Cotzias had succeeded partly by using a pure "levo-" ("L-") dopa form of dopa. (Just as our hands are identical but not superimposable, molecules of identical structure can be left- or right-

sided too; this is denoted by and "L" (levo) for left, and "D" (dextro) for right). All earlier studies had been done with a mixture of the two forms. Also, Cotzias used a graduated-dose regime: starting with very low doses of L-dopa, he slowly increased the amount given until patients could tolerate large doses without adverse effects—an average dose of around 5800 milligrams of L-dopa. Prior to that, most groups had been working with 50 to 100 milligram doses.

By the early 1970s L-dopa was in widespread use, hailed as a miracle drug—the answer to Parkinson's disease. Patients who were severely crippled with Parkinson's could, after L-dopa, move and talk almost normally. It was as if their disease vanished for as long as the dopamine remained in their brains—typically about three or four hours. So dramatic was the effect of L-dopa that the clinical trials into its efficacy were stopped. It clearly worked. Basic research into Parkinson's disease waned. Surely, most physicians agreed, L-dopa was the answer.

The first glimmerings that all was not well came when some physicians (Andre Barbeau was the first) began to notice that after several years of using L-dopa successfully, many patients experienced strange side effects. While initially these reports were dismissed, by the mid 1970s physicians agreed that L-dopa therapy had its problems. First, with time many patients started developing excessive movements known as dyskinesias, which could become so severe that physicians were forced to decrease the dose of L-dopa, even though it was needed more than ever because of advancing disease. Second, after a patient used L-dopa for a few years, the medication was effective for less and less time. To sustain the miracle, L-dopa had to be taken more and more frequently—in some cases as often as every forty-five minutes. Moreover, with time patients developed a tolerance to the medication, needing more and more L-dopa per dose to achieve any satisfactory therapeutic effect.

The most devastating problem, however, concerned rapid fluctuations—so-called on-off effects—in which the medicine's power to combat Parkinson's disease seemed to van-

ish suddenly, leaving a patient frozen or stuck midway through a movement or conversation. Minutes or sometimes hours later the medication could just as inexplicably switch back on. These rapid fluctuations seemed to occur randomly, making it literally impossible for some patients to undertake any planned activities.

Some patients also experienced confusion, agitation, paranoia, and hallucinations with long-term L-dopa therapy, which were even more disruptive and at times more disabling than the illness itself.

Many strategies were attempted to avoid these side effects. Some physicians favored putting the most severely affected on periodic "drug holidays," where for several weeks patients would be taken off all L-dopa, in an attempt to restore some of the medication's original effectiveness and decrease the sensitivity to side effects. Other doctors juggled cocktails of drugs, combining L-dopa with medications which modified its action.

By 1980, it was clear that the initial optimism over L-dopa had been misplaced. It was not a cure after all, nor was it the final answer to Parkinson's disease. Patients certainly lived longer in 1980 than in 1960, but their long-term prospects remained bleak. More than a decade of experience of using the drug showed that L-dopa did not stop the progression of the disease. Even as patients took L-dopa, their dopamine-making neurons continued to die.

Langston was not sure if Connie, George, and the other addicts would succumb to the same kind of side effects as Parkinson's disease sufferers and if so when? In regular Parkinson's disease patients, the more troublesome side effects usually don't show up for five or more years. For the time being at least, L-dopa was working its miracle with the frozen addicts.

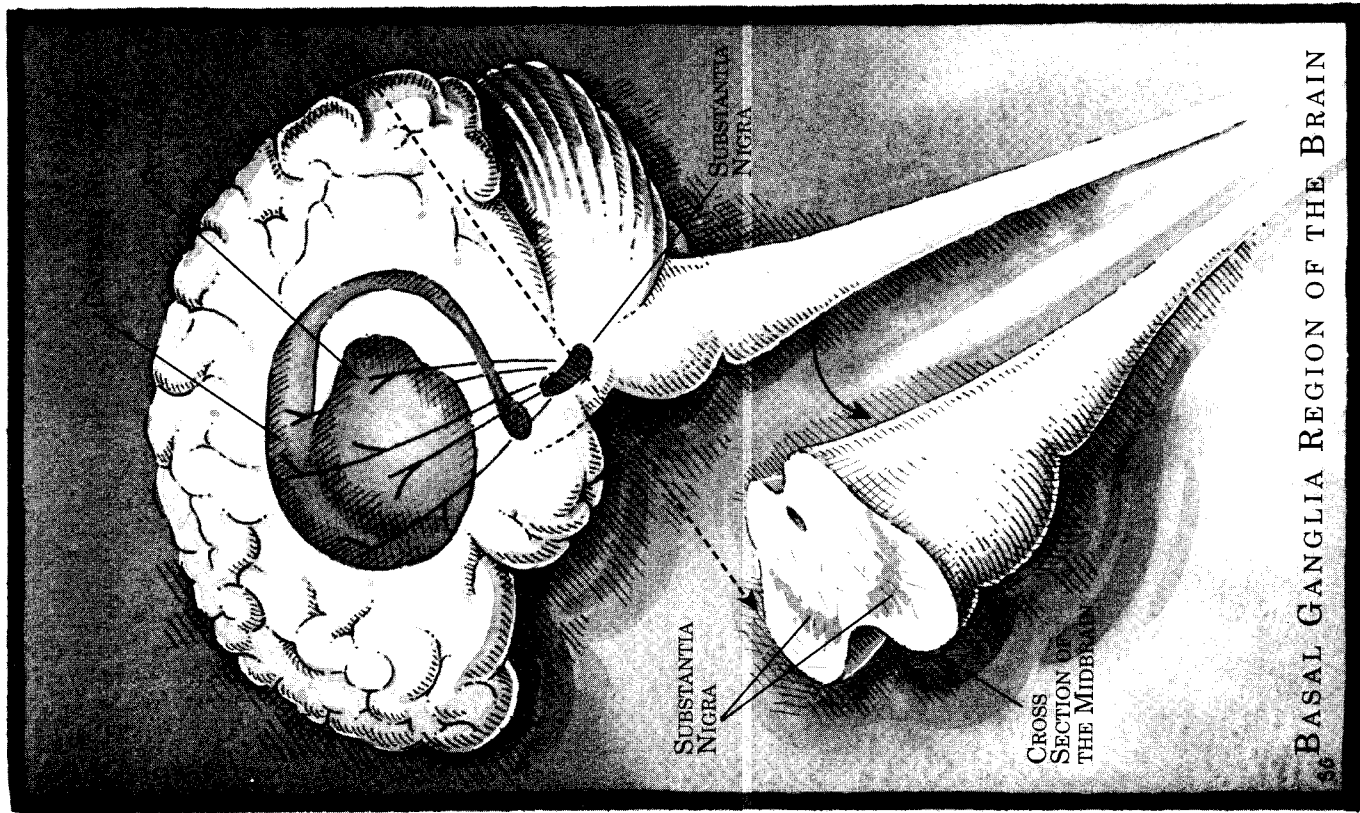
In George, Langston had found the quintessential case for his neurobehavior unit. George's paralysis, his facial masking, his drooling, his stare, all resulted from a lesion—probably a very tiny lesion—in his brain. Something in the drug, probably MPTP, had killed some of George's brain

cells, thus destroying his capacity for voluntary movement. L-dopa had restored that capacity, at least for the time being.

Many times since the tragedy, Langston had tried to imagine what had been going on under George's skull. When George had lain frozen in the hospital bed, his nerves still carried information to his brain from the outside world: the image of the doctors, the sound of their voices discussing him, the searing odor of the smelling salts they put under his nose. His brain interpreted this information in the context of past experiences and then sent out commands which passed down nerves to different parts of his body. He tried to call out. He tried to flinch. He tried to hit one of them. But his body didn't respond.

While only weighing three pounds, George's brain, like all adult brains, had some 100 billion cells, called neurons, each neuron being able to connect with thousands of other neurons. The upper portion of a brain—the cerebral hemispheres—can be thought of as the cap of a mushroom and the rest of the brain, as its stem. This so-called brain stem connects the brain to the spinal cord. This region of the brain also regulates all of the normal body functions: heart rate, blood pressure, breathing. Cranial nerves exit from the brain stem that control muscles in the face, tongue, eyes, ears, and throat, and return sensations from these parts back to the brain. In the very top of the brain stem is the substantia nigra, the tiny region of cells which normally makes dopamine, but which in George's case (like Barry Kidston's) had in all probability been destroyed by the bad heroin.

Under the microscope, neurons look quite different from other cells in the body: they have extensions. Sprouting out from the cell body are masses of short, tiny branches, called dendrites, which connect with other cells. These dendrites receive incoming messages. Most nerve cells in the brain also have one long fiber which can extend considerable distances—up to several meters in the case of certain nerve fibers that run from the brain to the spinal cord. This fiber,



BASAL GANGLIA REGION OF THE BRAIN

Axons from the substantia nigra, a major source of dopamine, extend to the striatum, a critical nerve junction that incorporates the caudate nucleus and the putamen. This dopamine pathway is essential for normal movement; it enables the thought of moving to be converted into the act of moving. When the cells of the substantia nigra begin to die, as in Parkinson's disease, dopamine production drops and movement becomes increasingly difficult to initiate and carry out.

the axon, can branch many times, and carries outgoing electrical impulses to other cells, connecting with the dendrites of those cells.

In healthy people, axons from the substantia nigra extend about two centimeters to the striatum, a critical nerve junction affecting movement, positioned deep in the base of the mushroom cap. The end of a single axon has many thousands of tiny nerve endings that can form connections with the dendrites of other neurons in the striatum. Axon and dendrite don't actually touch, but pass chemical messages at microscopic junctions called synapses. Axons pass these messages to dendrites by releasing chemicals—neurotransmitters (in the substantia nigra, the neurotransmitter dopamine)—which cross the synaptic space and bind to the other neurons' membranes. If MPTP had indeed destroyed the neurons in George's substantia nigra, this would explain why no dopamine was getting through to his striatum and why he froze up. It would also explain why L-dopa, which has the effect of replacing the missing dopamine, worked.

Based on the pathology of the Kidston case and his observations of the California cases, Langston was convinced that MPTP had slipped through the blood-brain barrier and killed the cells of the substantia nigra. It had also occurred to him that figuring out just how this happened might turn the entire field of Parkinson's disease upside down.

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RESEARCH WARS

August 1982

After Langston's call, Dr. Irwin J. Kopin, chief of the Laboratory of Clinical Science for the National Institute of Mental Health, and a coauthor of the *Journal of Psychiatry Research* paper, and Sandy Markey began an intensive review of NIH's investigation into Barry Kidston.

Kopin was a rising star at NIH. It was strongly rumored that within a few months he would become scientific director of the National Institute of Neurological Diseases—one of the most powerful jobs in neuroscience. In this position he would be a key figure in brain research, overseeing dozens of research projects.

The NIH is a highly political institution. To succeed there, a person must be not only a good scientist but also an accomplished student of power. Kopin understood power and sensed the importance of what had happened in California. Some unknown clinicians at a county hospital in San Jose had apparently stumbled on an epidemic of drug-