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Modern Medicine and Its Love Affair with Levadopa: How Science Convinces Us That Hope is Never Gone

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Modern Medicine and Its Love Affair with Levadopa

How Science Convinces Us That Hope is Never Gone

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"Softly. Softly. With no sound Mr. Parkinson cracks his whip. Its lethal tip strikes me internally. Externally. I who climbed to the summit of St Mark's in Venice and lost my arms and hands against the color of the stones, I who stood on my window ledge sixteen stories high across from the Dakota to polish my casements to witness John Lennon's public memorial; I, who drove from Boston to New York in a hurricane on a Father's Day to leave flowers at my father's grave; I, who used to run on ice for winter exercise and walk everywhere in New York City, live now under the silent lash of Parkinson's disease. This slaver's whip instead of training speed and agility into my active body, once free, once indomitable, lays on my bones and muscles making them lag, no longer to be relied upon, no longer stable, buckling without a walking frame. And like a master on holiday at a luau, Parkinson slurps vital chemicals from my brain as if sucking milk through a straw from coconut. And when the coconut is drained dry what course is there but to toss it away? In any situation of domination there comes a time of adjustment when the constant presence of the limiter of existence is acknowledged as a force of life and when a grim partnerships takes hold — an association that breeds strength on both sides."

– My grandmother, Lois Swann, a novelist and the author of an upcoming book about her experience of Parkinson's Disease.

Parkinson's disease (PD) afflicts one million Americans today, exceeding the number of people diagnosed with multiple sclerosis, muscular dystrophy, and Lou Gehrig's disease combined. It afflicts my grandmother. It afflicts many grandmothers. And even worse, the best medical treatment for PD has side effects that are nearly as debilitating as Parkinson's disease itself.

Parkinson's disease is a neurodegenerative disease in adults caused by the atrophy of midbrain dopaminergic neurons. Dopamine is a neurotransmitter responsible for reward and pleasure, as well as movement and emotion. It is also a precursor for the neurotransmitter epinephrine, also known as adrenaline. Because of its role in movement, the loss of dopamine in individuals with PD triggers motor deficits like tremors, slowness of movement, trouble speaking, rigidity, and even loss of unconscious movements, like blinking. Genetics play a partial role, but recently epigenetic controls, like neuroinflammation and protein misfolding, have been implicated as major contributors.

The main brain structures affected by high dopaminergic density in PD include the basal ganglia, which have multiple networks throughout the brain. These include the striatum and substantia nigra, which may support motor control, associative learning and memory, and emotion. Knowledge of the underlying mechanisms is limited, but continues to develop all the time. The basal ganglia relay information between the thalamus, cortex, and primary sensory association areas of the brain, allowing integration of sensory and motor information. Once again, our little friend dopamine modulates the basal ganglia, although our understanding of the mechanisms are relatively new and increasingly complex.

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Levodopa, a synthetic dopamine precursor, is the current treatment of choice for Parkinson's disease. Levodopa works to increase dopamine synthesis, thereby restoring motor functions. It is often combined as Carbidopa-Levodopa, which my grandmother takes religiously from a cut-crystal dish, to decrease the likelihood of nausea. Unfortunately, Levodopa seems to over-stimulate dopamine production, and therefore induce the opposite symptoms of PD, which include excessive motor movement and cortical activity. A major side effect of Levodopa, dyskinesia, occurs in more than 50% of patients as a result of increased glutamatergic transmission. It seems that restoring dopamine neurotransmission overstimulates the limbic striatum, the region of the basal ganglia associated with reward, posture, and movement. Dyskinesia, or involuntary movement, manifests in Parkinson's patients who have taken Levodopa as symptoms called chorea or dystonia. The two symptom sets often coexist. Chorea, from the Greek word for "dancing," is also present in Huntington's patients and includes abrupt movements and tremors of the limbs, hands, and feet. Dystonia is another type of muscle spasm that can cause tremors, pain, and even twisting of the feet and hands. Parkinson's patients often experience painful leg cramps at night.

Physicians have classified Levodopa-induced dyskinesia using three characteristics: denervation of nigrostriatal dopaminergic neurons, intact postsynaptic basal ganglia, and, of course, Levodopa treatment. One study showed that primates with intact nigrostriatal dopaminergic circuitry did not develop dyskinesia unless an extremely high dose of Levodopa was administered. The same study showed dyskinesia to be worse on the more heavily lesioned side of the brain. This suggests that cells that produce dopamine need to be damaged for dyskinesia to manifest, but the basal ganglia need to remain healthy and connected.

In many diseases, an inflammatory response is quite common. When the brain undergoes an injury, microglia in the brain's white matter control the resulting inflammation, releasing lots of molecules, such as cytokines, to help fight the problem. The brain also rewires and adapts to its environment, which can affect cognition, or simply be a homeostatic mechanism. This is called plasticity. Neuron-microglia-astroglia circuitry controls the brain's neuroplastic response to Parkinson's disease. A 2016 University of Sao Paulo study looked at the role of neuroinflammation caused by Levodopa in PD. Neuromelanin released from dying dopaminergic neurons activates microglia, and unfortunately, the substantia nigra is particularly sensitive to stress caused by this inflammation. New research suggests Levodopa could aggravate the astroglial inflammatory response, which would exacerbate cell death in the substantia nigra, as seen in PD patients.

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The substantia nigra gets its name from the Latin word for "black substance". It is dark red in appearance from high concentrations of neuromelanin and iron, which seems to be involved in neuromelanin formation. Iron happens to be a reactive oxygen species and thus contributes to neurodegeneration. Angiotensin, released by dopaminergic neurons and glia, helps mediate iron concentrations and is also heavily involved in neuroinflammatory responses. By blocking angiotensin receptors, researchers at the University of San Paolo were able to decrease Levodopa-induced dyskinesia, suggesting a potential new treatment.

So, as dopamine dances between the brain's many structures, my grandmother has fluctuations in her motor control. This whiplash between the effects of PD and the effects of Levodopa might be regulated and managed by taking smaller and more frequent doses of the drug to prevent dyskinesia. But this solution is far from perfect, because instead of treating the cause (chronic death in the substantia nigra), Levodopa is treating the symptom. Chronic use of Levodopa is common and necessary. My grandmother takes Levodopa, yet still experiences constant pain. Our understanding of Levodopa-induced dyskinesia is still limited, so we must remain hopeful. We must take a leaf out of my grandmother's book: find hope in our ignorance, and beauty in our scientific curiosity.

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I'd like to dedicate this article to my grandmother, and thank her for writing the above piece for this article. I have spent my life learning from her how to live and love in the face of adversity. Her constant joie de vivre and continual grace has brought hope to her family, doctors, and readers.

I would also like to thank my family, professors, and friends for continuing to support my work in neuroscience, linguistics and chemistry.