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IN DECLINE PET scans show the deterioration in dopamine transporter activity in the brain of a person with severe Parkinson's (right) compared with that of a healthy person.

PICKING APART PARKINSON'S

Researchers are seeking earlier detection and method to slow progression of disabling disease

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INVESTIGATORS SPOKE WITH ENTHUSIASM about advances in Parkinson's research during a recent conference, but the origins of the neurodegenerative disease and the means to stop it remain maddeningly elusive.

"Doctors and patients alike are growing frustrated with the current slow pace of bringing new therapies to market," said actor Michael J. Fox during the opening ceremony of the first World Parkinson Congress. Although funding hikes have increased research activity, they haven't yet unearthed a cure for the disease, let alone an effective long-term treatment for symptoms. "I did a search on PubMed, and there were 15,000 citations about Parkinson's over the last seven years," noted Fox, who was diagnosed with young-onset Parkinson's disease in 1991. "But I'm not tying my tie any faster."

Fox is more than a spokesman for the disease. His foundation is the largest nonprofit funder of Parkinson's research. The conference itself was sponsored by the Movement Disorder Society, the National Institutes of Health, the U.S. Army Medical Research Acquisition Activity, and several other organizations. The meeting drew more than 3,100 researchers, physicians, advocates, and patients to Washington, D.C., on Feb. 22–26.

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's. Parkinson's afflicts 1 million people in the U.S. It spawns a galaxy of symptoms that initially affect quality of life and later become incapacitating.

Development of a tremor in one arm is typically the first warning sign for those stricken with the illness. As the disease progresses, voluntary movement throughout the body decreases and becomes slower. The patient develops rigidity or muscle stiffness and may become bent in posture. Balance can also become a problem. Some patients experience "freezing," a sudden but temporary loss of the ability to move. As brain damage spreads, many patients develop debilitating fatigue, severe constipation, and a decline in the sense of smell. Sleep disorders, depression, apathy, sexual dysfunction, cognitive impairment, and dementia often occur as well.

One of the main pathological hallmarks of Parkinson's disease is the deterioration and death of neurons that produce the neurotransmitter dopamine. Much of the neuronal damage occurs in the substantia nigra, a region in the midbrain that contains the cell bodies of the dopamine neurons. The axons of those neurons extend into the striatum, a section of the brain that controls movement. Loss of the dopamine nerve terminals in this region causes most of the motor symptoms of Parkinson's disease, said Stanley Fahn, chairman of the conference and director of the Center for Parkinson's Disease & Other Movement Disorders at Columbia University.

What causes the damage to dopamine neurons? The answer is multifaceted. "Rather than having one noxious factor, we are dealing with a plethora of factors," according to Serge Przedborski, a neuroscientist at Columbia. "I believe this cascade of multiple factors interacts to lead to the demise of dopamine neurons."

The details are sketchy, but the progression probably begins when a healthy dopamine neuron is exposed to an initiating factor such as abnormal α-synuclein protein, Przedborski said. He thinks the initial damage is exacerbated by secondary stressors such as protein aggregation, oxidative stress, mitochondrial dysfunction, hyperactivity in some parts of the brain due to the loss of dopamine, and activation of microglia. Microglia are central nervous system tissues made up of small cells that resemble macrophages.

THE BRAIN normally uses microglial cells to respond to an immune challenge, but microglia can also be activated by damage to neurons. In fact, microglia in Parkinson's patients become excessively active, giving rise to persistent inflammation in the brain. The cells secrete proteins such as interleukin-1β and inducible nitric oxide synthase. These cytotoxic molecules "flood the environment and stress neighboring compromised neurons, which are pushed to the edge and die, in turn activating more microglia," Przedborski said.

Dopamine neurons aren't the only ones to suffer damage. Parkinson's disease also kills neurons that produce norepinephrine

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