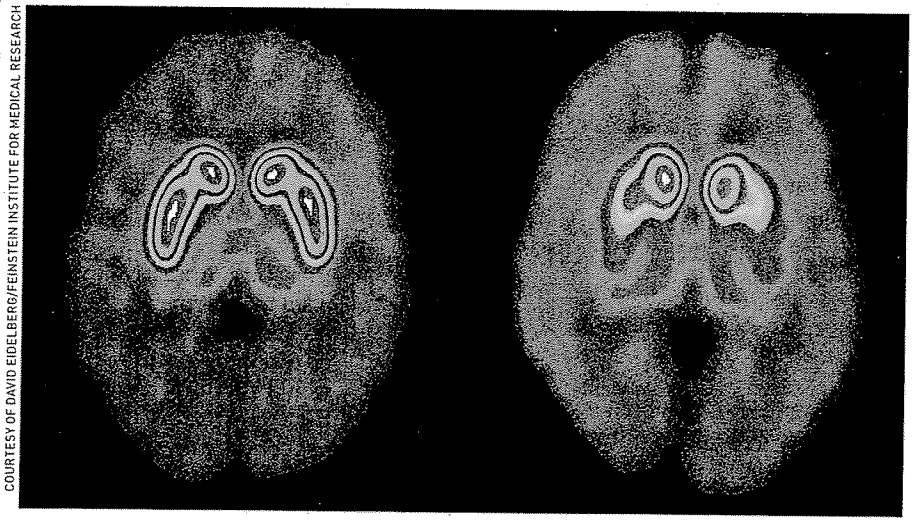

COURTESY OF DAVID EIDELBERG/FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH

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

SOPHIE L. ROVNER, C&EN WASHINGTON

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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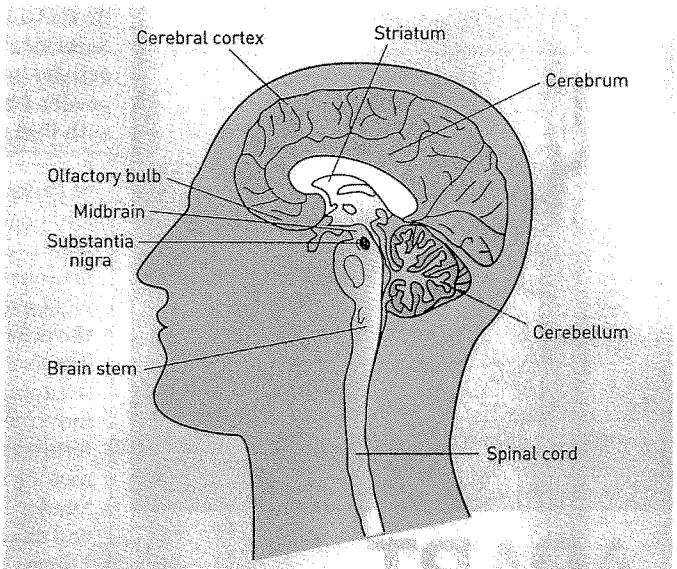
and serotonin. Declining levels of these two neurotransmitters cause some of the mood changes and other nonmotor symptoms of Parkinson's, Fahn said. Death of neurons that produce the neurotransmitter acetylcholine leads to attention problems and dementia.

In addition to the destruction of neurons, the other major pathological feature of Parkinson's is the formation of Lewy bodies inside neurons. These protein deposits appear first in the lower brain stem. As the disease worsens, Lewy bodies begin appearing higher in the brain stem, then in the substantia nigra, and eventually in the cerebral cortex.

"Years ago, we used to think that Lewy bodies were the cause of the disease," Fahn said. "Now we think it may be the other way around."

"The Lewy body may not be about cell death or destruction at all, but it may be about protecting the brain," added David J. Brooks, a neurologist at Imperial College, London.



MULTIFACETED Parkinson's disease affects several brain regions, including the substantia nigra and striatum.

Several pieces of evidence back this idea. First, the order in which neuronal functions deteriorate doesn't correlate with the order in which Lewy bodies appear in the affected brain regions, Brooks said. Furthermore, at least one type of Parkinson's doesn't generate Lewy bodies. And Lewy bodies are found only in neurons that are still alive, Fahn noted. So it's possible, he suggested, that Lewy bodies "may be a protective mechanism to fight the degenerative process. Maybe they're tying up toxic proteins that otherwise would kill the neurons." Once the level of toxic proteins reaches a critical mass, the Lewy bodies are overwhelmed and release their toxic cargo, which kills the neurons, he hypothesized.

Lewy bodies consist primarily of filaments of misfolded α-synuclein protein polymers known as fibrils. The function of normal α-synuclein isn't known for sure, though Virginia M.-Y. Lee, a neurobiologist who heads the Center for Neurodegenerative Disease Research at the University of Pennsylvania, believes that the protein may play a role as a molecular chaperone in the formation of synaptic proteins known as SNAREs.

A number of factors promote buildup and aggregation of abnormal α-synuclein. For instance, the accumulation of oxidative stresses over a lifetime might promote phosphorylation of α-synuclein, creating an aggregation-prone form of the protein. And abnormal α-synuclein clogs the neuronal machinery that metabolizes normal α-synuclein and other proteins.

JUST AS the fundamental cause of the disease remains cloudy, researchers are also uncertain why one person gets Parkinson's but another does not. They have identified some factors that contribute to the risk of getting the disease, however. "Age is the most important risk factor for Parkinson's," Fahn noted. Most cases are diagnosed in patients who are at least 60 years old, though early-onset disease can strike people as early as their 20s.

Being male is another risk factor. At any given age, a man is 1.5 times as likely to get the disease as a woman. "Some people speculate that estrogen protects against Parkinson's," Fahn explained. Serious head trauma is also associated with increased risk for the disease.

Genetic mutations can cause the disease. To date, 10 mutations correlated with the disease have been identified in six genes, including the genes for the α-synuclein, parkin, and LRRK2 proteins.