Portrait of Parkinson’s

From misfolded proteins to exercise and brain cell transplants, new ASU research is reshaping how Parkinson’s disease is detected and treated

By Richard Harth, ASU News
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The mountains encircling Phoenix were crisply outlined in the bone-dry air. Beyond them stretched the Sonoran Desert — vast and seemingly timeless.

Chris Clifton was slowing down, lagging behind her husband Patrick on their morning hike. This was unusual. Athletic and competitive by nature, Chris has always been the stronger of the two, hiking, biking, swimming and playing tennis from an early age. This morning was different.

She felt a heaviness in her stride.

“I started shuffling, and my dogs noticed and turned around, like, ‘What’s going on with your feet?’” Chris recalls.

Her pace slowed, and she noticed her little finger defiantly protruding at a strange angle.

“My legs felt like they were tree trunks. Or it’s like walking into the ocean with your feet buried deep in the sand, pushing against that weight.”

During a hill run in Phoenix’s Papago Park, Patrick overtook her, and she sensed something beyond any normal fatigue. Her body seemed to have adopted its own agenda. Days like this pass into weeks, then months — some better, some worse.

Persuaded at last to seek a medical evaluation, Chris Clifton arrived at Barrow Neurological Institute for an examination. Her neurologist asked her to perform a few simple tasks, watching the movements of her fingers, her hands, the way she walked. Within minutes, she had a diagnosis: Parkinson’s disease.

“I had the resting tremor, the shuffling, the changes in my gait, the bradykinesia,” she says, referring to the characteristic slowing of movement. “Looking back, it was all there.”

Clifton was officially diagnosed seven years ago, though she traces the first symptoms back several years earlier. Her experience illustrates one of Parkinson’s central challenges: By the time the disease becomes recognizable, it may already have been developing for years.

At Arizona State University, researchers with the ASU-Banner Neurodegenerative Disease Research Center are answering questions about how Parkinson’s develops and progresses, and creating new tools to diagnose and combat an affliction that has baffled medical science for centuries.

Recent developments offer hope that the disease can be diagnosed much earlier, before extensive damage occurs. New treatments, including transplantation of healthy neurons, are under intense investigation. And the latest findings are strengthening the case that strenuous exercise may be one of the best means of slowing the progression of Parkinson's symptoms — and perhaps the disease itself.

What is Parkinson's disease?

Parkinson's disease is now the fastest-growing neurodegenerative disease in the world. In the U.S. alone, over 1 million people are living with it. By 2040, it is believed that more than 17 million individuals will have Parkinson's disease.

The hallmark symptoms of the disease are motor symptoms, such as bradykinesia (slowness of movement), tremor at rest, muscle rigidity and problems with balance and coordination. These arise largely from the loss of dopamine-producing neurons in a region deep in the midbrain called the substantia nigra.

Dopamine is one of the brain's chemical messengers, carrying signals between nerve cells. In a healthy brain, dopamine-producing neurons in the substantia nigra help the nervous system initiate and smoothly control movement.

Parkinson's can also affect systems beyond movement. Patients may experience changes in sleep, mood, attention and memory, and some eventually develop significant cognitive impairment or dementia.

But what is driving this destruction? One major culprit appears to be alpha-synuclein, a protein normally found in nerve cells. In Parkinson's disease, some of this protein folds into the wrong shape and begins to clump together.

"In the brains of Parkinson's patients, normal proteins misfold. They change their shape and then they spread from one cell to another," says Jeffrey Kordower, founding director of the Neurodegenerative Disease Research Center.

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These abnormal forms can interfere with the cell's machinery. They may also act as seeds, inducing nearby alpha-synuclein molecules to misfold in turn and spreading the pathology through connected regions of the nervous system. Other misfolded proteins seen in Alzheimer's disease, such as tau and amyloid, are also routinely seen in Parkinson's patients.

Among the cells particularly vulnerable to this damage are the dopamine-producing neurons of the substantia nigra. As these cells die, dopamine levels fall, disrupting the brain circuits that control movement.

Spin cycle

More than 2,000 years after physicians first described and treated Parkinson's-like symptoms, medicine is still grappling with the harder problem: how to alter the course of the disease itself.

Increasingly, researchers are looking to something deceptively simple for part of the answer — exercise.

Ramon Velazquez, a researcher who studies neurodegenerative diseases including Alzheimer's and Parkinson's, has explored how factors ranging from nutrition to environmental exposures affect brain health. Exercise is another longstanding interest — one that brought him unexpectedly into Chris Clifton's life.

"As exercise intensity increases, your muscles release signaling molecules that can communicate with the brain and may support brain health," Velazquez says.

It was at a spin class at Lifetime Fitness in Phoenix that Velazquez first met Clifton.

"I didn't find out that Chris had Parkinson's disease until probably a few months after I first met her. And quite frankly, I was shocked, because she was literally on the bike next to me in a spin class and kicking my butt," Velazquez says. "As someone who's interacted with patients and understands the progression of these disorders, I was stunned to see that even after a decade, she really didn't show the typical symptomatology."

Clifton's relationship with exercise has not always been so straightforward. Soon after her diagnosis, as her legs grew heavier and episodes of freezing made it difficult to move, she became frustrated and stopped exercising. Medication eventually brought substantial relief, and she returned to increasingly strenuous activity.

Muscle to mind

Kordower, who has studied Parkinson's disease for decades, says strenuous exercise may do more than preserve strength and mobility in people with the disease. One clue is irisin, a hormone-like protein released by muscles during exercise that can reach the brain, where it may help counter some of the cellular damage associated with Parkinson's.

Animal studies have pointed to an intriguing role for irisin. The exercise-induced protein has been shown to enter the brain and reduce misfolded alpha-synuclein, protecting dopamine-producing neurons from damage. The findings raise the possibility that some of exercise's benefits in Parkinson's may arise from molecular changes set in motion by working muscles.

Irisin may also act more broadly against other abnormal proteins, including tau and amyloid, which play a role in Alzheimer's disease.

"We have data in small animals and in vitro that irisin will clear synuclein, tau and amyloid," Kordower says. "One drug, all three, and we think that can be very powerful."

Kordower was recently appointed vice president of the World Parkinson Coalition, the leading society for patients, caregivers, scientists and doctors.

Trigger points

Researchers increasingly understand how Parkinson's damages the brain. Why the disease begins is another matter. Only about 10% to 15% of Parkinson's cases are associated with known inherited forms. Clifton and one of her brothers both developed the disease, yet genetic testing found no known disease-causing mutation in either.

One suspected environmental risk factor is chronic pesticide exposure. Kordower points to studies linking the prevalence of Parkinson's to heavily treated golf courses. Other environmental triggers yet to be identified may also play a role.

Whatever combination of genes, aging and environmental exposures ultimately initiates the cascade of symptoms associated with Parkinson's, one fact remains: By the time its characteristic movement symptoms appear, the disease has often been developing silently for years. Kordower says patients may have already lost roughly 80% of normal dopamine function before the first obvious motor symptoms emerge.

Clifton's own diagnosis was almost entirely clinical: A neurologist watched her tap her fingers, move her hands and walk across the room. Within minutes, the pattern was recognizable as Parkinson's. Now, Kordower says, "The field is moving towards a more biologic definition."

Why this research matters

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One of the most promising new tools exploits the same peculiar behavior that allows misfolded alpha-synuclein to spread. A patient sample is mixed with normal alpha-synuclein in the laboratory. If abnormal seeds are present, they induce the normal proteins to misfold and aggregate, amplifying a tiny molecular signal until it becomes detectable.

The approach may allow researchers to distinguish Parkinson's from closely related disorders and, eventually, identify the disease before symptoms appear. The value of earlier diagnosis grows as new approaches to treatment come into view. One of the most ambitious is cell replacement.

Replace and repair

In 2022, ASU received three major grants from the Michael J. Fox Foundation to support Parkinson's research led by Kordower, including experimental approaches aimed at replacing lost dopamine-producing neurons and clearing abnormal alpha-synuclein.

The idea behind cell replacement is straightforward, even if accomplishing it is anything but. Create healthy dopamine-producing neurons from stem cells, then transplant them into the brain and give them a chance to survive, form connections and restore some of the dopamine signaling lost to Parkinson's.

There is reason to believe transplanted neurons can survive for decades. Kordower recently examined the brain of a Parkinson's patient who had received a fetal-cell transplant 27 years earlier. "The graft is still there," he says. "The graft looks healthy."

Earlier experiments relied on cells obtained from fetal tissue. Today, however, scientists can generate essentially unlimited numbers of replacement neurons in the laboratory without using fetal tissue.

Kordower is now involved in an early clinical trial in which 12 patients have undergone stem-cell transplantation. He cautions that this first study is designed primarily to establish safety and tolerability — not yet to prove that the treatment improves Parkinson's symptoms. Later controlled trials will have to answer that question.

The transplanted cells are intended primarily to restore dopamine signaling and improve Parkinson's motor symptoms. Cognitive decline, balance problems and other features of the disease arise from damage that extends beyond that circuitry. Further research is needed to address these symptoms.

Along the path

For Clifton, such treatments remain possibilities for the future. For now, living with Parkinson's means a continual awareness of the disease and the shifting demands it places on her body.

"With this disease, I think about it 24 hours a day," she says. "When I go to sleep, I think about it. When I wake up, I think about it."

Her medication demands constant attention as well.

"You're looking at timing for your meds, when they wear off, when they come back on," Clifton says.

Some days exercise leaves her exhausted while on others, she can go hours before realizing it is time for another dose. The unpredictability, she says, is part of the disease.

Yet most days she remains active, caring for her grandchildren, walking, hiking and returning to the spin classes that have become such an important part of her life. There have been losses: She no longer stands on the pedals during class because she worries about falling, and symptoms that had receded with treatment have begun to reappear.

Still, she says, "I feel better now than I felt 10 years ago."

Under a cloudless sky, the air barely astir, Clifton makes her way step by step through the desert. The stillness gives the landscape an illusion of permanence: jagged formations fixed against the horizon, ancient trails winding through the same dry washes. Clifton knows how quickly a body and a life can change. Ahead, the path threads between weathered outcrops and vanishes into the hills.

The Neurodegenerative Disease Research Center is a unit of ASU's Biodesign Institute. Parkinson's research at ASU is funded in part by the National Institutes of Health, the Michael J. Fox Foundation, and a generous gift from the Bob Bertrand family.

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Main image



New research is helping scientists piece together how Parkinson's disease begins and progresses in the brain. Graphic by Jason Drees/ASU

Text image(s)


LIFE TIME
LIFE TIME

Research in motion: Ramon Velazquez joins Chris Clifton for a spin class. Regular exercise is an important part of Parkinson’s care and can help improve mobility, motor symptoms and quality of life. Courtesy photo