Roughly one million Americans have Parkinson's disease. Treatments control some symptoms, but nothing can stop the degeneration of neurons in the brain. Why are these neurons dying? Finding the answer could lead to a cure.

BY SALLY POBOJEWSKI

When Neurons Die

CLINT BLOWERS

Parkinson's disease doesn't strike suddenly like a heart attack or stroke. It sneaks up on you gradually. The first sign is often a tremor or shaking in one finger. Sometimes, it begins with a loss of balance or difficulty moving. It can start with sleep disturbances or a diminished sense of smell. But even though the initial symptoms vary, the cause is always the same: Neurons in the brain are dying.

At first, the effects of Parkinson's disease are barely noticeable. But as more brain cells die, the symptoms get worse. A small tremor in one finger leads to a pronounced tremor in the entire arm. Loss of balance and unsteadiness may lead to frequent falls and life in a wheelchair. And in addition to the physical disability, about 75 percent of all Parkinson's patients eventually develop dementia.

About one million Americans have been diagnosed with Parkinson's. The average age of onset is around 60, so people often live for many years with the frustrating symptoms of this progressive neurodegenerative disease.

Researchers don't know what causes neurons in the brain to die, but they know that neurons which produce dopamine — an important chemical messenger in the brain — are particularly vulnerable. Loss of dopamine is a defining feature of Parkinson's disease. Without a steady supply of dopamine, the brain can't control the coordinated firing of neurons required to stop and start muscle movement. A lack of dopamine also makes it difficult for the brain to regulate neurons that control blood pressure, digestion and heart rate.

Roger Albin

"The loss of dopamine explains many symptoms of Parkinson's disease, but it's only part of the picture," says Nicolaas Bohnen, M.D., Ph.D. (Fellowship 1998), a professor of radiology and of neurology in the Medical School, who is also a physician at the VA Ann Arbor Healthcare System.

Bohnen and other U-M researchers have found that other types of neurons in the brain are affected by Parkinson's disease, too. This includes cholinergic neurons that produce a different chemical signal called acetylcholine and are known to be involved in Alzheimer's disease.

"There's actually broad neurodegeneration across many types of neurons in the Parkinsonian brain," says William Dauer, M.D., the Elinor Levine Professor of Dementia Research who is also an associate professor of neurology and of cell and developmental biology in the Medical School. "We don't really know which neurons take the first hit. Once a cell starts to dysfunction, a lot of things go wrong. It's as if you arrived at the scene of a four-car pile-up, but you didn't see it happen. It's hard to know what caused it."

U-M researchers believe that different patterns of neural cell deterioration could explain why the type and severity of Parkinson's symptoms vary so widely from patient to patient.

"It's very clear from clinical experience that Parkinson's patients are not a uniform population," says Roger Albin, M.D. (Residency 1988), the Anne B. Young Collegiate Professor of Neurology who is also the chief of neuroscience research for the Geriatrics Research, Education and Clinical Center at the VA Ann Arbor Healthcare System. "We think there may be subtypes of Parkinson's disease and different subtypes may require different treatments."

"If you have the more benign subtype — tremor-predominant disease — the symptoms may be more visible, but actually these people are not that impaired or disabled," adds Bohnen. "They are still walking well, they aren't falling and they don't have dementia. On the other hand, patients with balance-predominant disease who fall often may not have much visible tremor, but they actually have much greater disability."

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Biomarkers and Early Diagnosis

The nuclei of dopamine-producing neural cells are packed together in a small structure located deep within the brain. Projecting arms called axons extend from cell nuclei into the striatum — the part of the brain that uses dopamine to control motor nerves in the body. In Parkinson's disease, something causes these axons to degenerate, cutting off the vital supply of dopamine and killing the neural cell.

A dead neuron is gone forever, so the best time to begin treating Parkinson's disease would be before symptoms appear and too many brain cells have been lost. But there are two problems: First, doctors have no way to stop the neurons from dying. Current treatments help control motor symptoms, but do nothing to prevent or slow down progression of the disease. Second, even if preventive treatments were available, there's no simple screening test to identify those who are at risk for developing Parkinson's disease.

That's why scientists at the U-M and other research institutions are searching for Parkinson's disease biomarkers — signs of early neural degeneration that can be detected long before clinical symptoms develop.

"We believe this prodromal period can last for 7 to 10 years," says Bohnen. "When we see someone in clinic with a tremor, the tremor may be just two months old, but biologically speaking, this person may already be halfway through the disease course."

Parkinson's disease can be diagnosed in its early stages using a PET scanning technique to detect the level of dopamine in the brain. However, these scans cost thousands of dollars and require specialized equipment and expertise not available outside major academic medical centers like the U-M Health System. For use in the general population, a screening test must be inexpensive and easy to administer in a doctor's office.

Loss of dopamine is the classic sign of Parkinson's disease. Without a steady supply of dopamine, the brain can't control the coordinated firing of neurons required to stop and start muscle movement.

Nicolaas Bohnen

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An impaired sense of smell, caused by degeneration of olfactory neurons in the brain, is an early biomarker present in 95 percent of Parkinson's patients during the prodromal period. It also is common in people who later develop Alzheimer's disease. Loss of smell develops so gradually, many people aren't even aware of it.

"A smell test is probably the closest thing to an inexpensive screening biomarker for use in large populations of patients," says Bohnen. "Just like you have a screening colonoscopy at age 50, I would envision that once you reach 50, you'd need a smell test every year."

Martijn Müller, Ph.D., assistant professor of radiology, is planning a future U-M research study with 200 older adults who will be asked to identify different odors in simple scratch-and-sniff tests. The study's main goal is to determine if older adults who have lost their sense of smell, but have no symptoms of either Parkinson's or Alzheimer's disease, show brain changes indicative of either disease on PET scans.

Loss of smell isn't always a sign of disease, however; it's also part of the normal aging process. Determining the cut-off for a normal age-related loss of smell will be another important goal of the study.

Because there are no treatments to slow the progression of Parkinson's disease, early diagnosis won't change how the disease is treated, according to Albin. But identifying people in the prodromal stage of disease is important, so they can take part in clinical trials of experimental drugs to help prevent or postpone neural degeneration.

Mutant Genes and Bad Proteins

When Bill Dauer was a neurology resident during the early 1990s, medical students were taught that Parkinson's disease was caused by toxins in the environment. "People were looking for associations to things like living in a rural environment, drinking well water and exposure to insecticides," recalls Dauer. "Now we think that up to 50 percent of your risk may be genetic. We have yet to identify a bona fide environmental toxin with a clear link to Parkinson's."

"Most people would say there are complex inter-relationships between genetic risk factors and environmental risk factors," adds Albin. "There's only one very clear environmental factor that's been identified and it is a protective factor. It appears that if you smoke cigarettes, you are less likely to develop Parkinson's disease."

Dauer says that scientists have identified mutations in five genes that are clearly linked to human disease. But together they account for only about 5 percent of all cases of Parkinson's. These rare, inherited forms of the disease are most common in younger adults. But in 95 percent of cases, there is no genetic mutation and symptoms don't appear until late in life.

Bill Dauer

Even though genetic mutations have been linked to just a few inherited types of Parkinson's, Dauer believes these genes contain important clues to the common sporadic form of the disease. He's especially interested in two genes called LRRK2 and synuclein. Working with research colleagues at the U-M and at Columbia University, Dauer is trying to understand the normal function of these genes in the brain and what happens when something goes wrong.

Dauer believes there's some unknown link between the activity of synuclein and LRRK2 proteins in the brain that can lead neurons down the path toward degeneration and cell death. "Our goal is to understand the normal role of these core proteins, which clearly are involved in Parkinson's, and how their function is disrupted by disease-causing mutations," he says. "Understanding a protein's role is a tall order, but it is the most important way forward."

Looking Inside the Brain

Positron emission tomography (PET) scanning is a computer-assisted imaging technology that produces detailed 3-D images of the brain. David E. Kuhl, M.D., a U-M professor emeritus of radiology, was a pioneer in the development of PET technology during the 1960s and 1970s. Since then, a team of U-M physician-scientists with expertise in neurology and radiology has developed new ways to use PET imaging to diagnose patients and advance the study of neurodegenerative diseases.

PET scans make it possible to see what's happening inside the brains of people with Parkinson's and other neurodegenerative diseases. U-M scientists have developed an important PET scanning method that detects a loss of dopamine. The technique uses a radioactive tracer that binds to neural axons that produce dopamine.

PET scanning also can be used to detect acetylcholine activity in the brain. U-M researchers have used the technique to study neurochemical changes in different regions of the brain that occur as patients develop dementia. They have discovered that decreased levels of acetylcholine correlates with the development of dementia in people with Parkinson's disease.

Using a different imaging technology — magnetic resonance imaging, or MRI — Bohnen and his colleagues are studying inflammatory changes in blood vessels deep within the brain. They have discovered an intriguing connection between the degeneration of dopamine-producing neurons in Parkinson's disease and blood vessel changes

AUSTIN THOMASON, U-M PHOTO SERVICES

caused by cardiovascular disease. Understanding the link to inflammation could open new avenues for future treatments for neurodegenerative disease, he says.

"When you look at MRI scans of older people, it's very common to see tiny spots of signal in the brain's white matter," explains Bohnen. "We've learned that these white matter changes are much more common in people who have cardiovascular risk factors like obesity, high cholesterol, high blood pressure and inflammation. Parkinson's disease patients with more white matter changes were more likely to have balance problems and dementia."

Deep Brain Stimulation

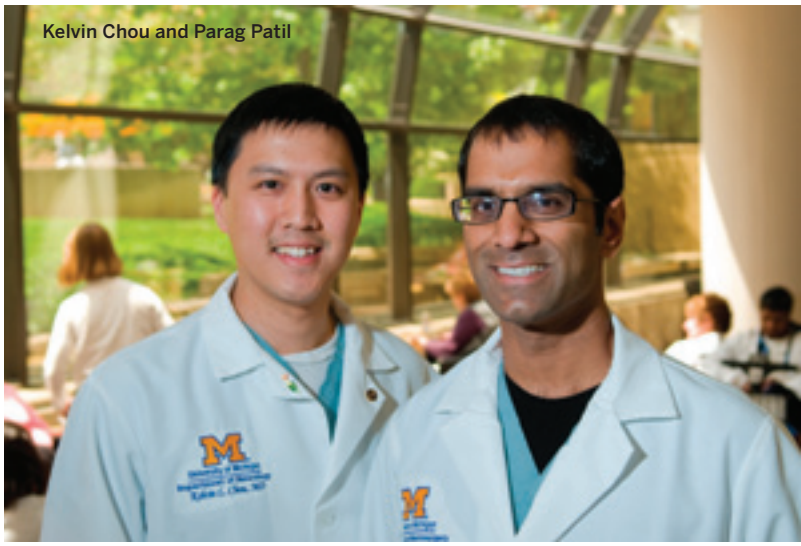
Treatment of Parkinson's disease was revolutionized in the 1960s by the introduction of L-DOPA, a drug that supplements the brain's dwindling supply of dopamine. Fifty years later, L-DOPA and related drugs are still the main treatment for the classic motor symptoms of Parkinson's disease. Unfortunately, the beneficial effects of these medications diminish over time. So what can patients do when the drugs stop working?

Before the 1990s, there were few options. Now many patients can be helped by a surgical procedure called deep brain stimulation or DBS. In this procedure, electrodes are inserted through the outer areas of the brain until they reach an area about the size of a pea called the subthalamic nucleus. Once the electrodes are in place, electrical pulses are delivered to control the motor symptoms of the disease. The frequency and voltage of the pulses are controlled with a pacemaker-like device implanted in the chest.

Although no one knows exactly how or why it works, clinical studies have shown that DBS is a safe and effective procedure for many patients with Parkinson's disease, says Parag Patil, M.D., Ph.D., an assistant professor of neurosurgery and of biomedical engineering and co-director of the U-M Surgical Therapies Improving Movement (STIM) Program.

"By giving electrical stimulation at a specific frequency, DBS overrides the abnormal electrical signals in the brain caused by Parkinson's disease," Patil says. "The brain doesn't get as confused and so symptoms improve."

"Research studies have shown that DBS is more efficacious than medication alone for more advanced cases," says Kelvin Chou (M.D. 1998), an associate professor of neurology and of neurosurgery, who co-directs the STIM program. "On average, people are able to reduce their medications by about half after surgery."


Kelvin Chou and Parag Patil

Approximately 30 DBS procedures take place at UMHS each year. The number of procedures has grown about 30 percent each year since the STIM program was established in 2006. Patil is the neurosurgeon who performs the DBS procedure, and he emphasizes that success requires much more than the skills of a good surgeon.

"The best way to think about the U-M program is as an integrated team," says Patil. "It's one of the things that sets us apart from other programs. In addition to a close working partnership between neurology and neurosurgery, we also have a speech pathologist, an electrophysiologist, a neuropsychologist, a social worker and others on the team. And we have an active translational research program looking at how to improve the procedure and patient outcomes."

The entire team evaluates each patient and decides whether the patient is likely to benefit from DBS. Education programs are provided to help patients have a clear and realistic understanding of what to expect after the procedure. Like all surgical procedures, there are risks and side effects associated with DBS.

"Overall, the benefits of DBS far outweigh the risks in the correct and appropriate patient," says Chou. "We have data now showing that motor symptom control can be fairly well-maintained for at least 10 years. Our multidisciplinary expertise and experience can make a big difference in patient outcome."

U-M's clinical scientists agree there are still many unanswered questions about Parkinson's disease, but Bohnen says it's important to remember how much progress has been made.

"If you look over the last century, we've come a long way," says Bohnen. "Fifty years ago, many people with Parkinson's disease ended up in nursing homes. Today, many patients can live at home and have a normal life span. New medicines and treatments like deep brain stimulation have made a difference in quality of life." [M]

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