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## Hot on Parkinson's Trail

**Scientists have amassed evidence that long-term exposure to toxic compounds, especially pesticides, can trigger the neurological disease.**

By Marla Cone  
Times Staff Writer  
November 27, 2005

MERCED, Calif. — A thousand acres stretched before him as Gary Rieke walked briskly behind a harvester, the parched, yellow stalks of rice sweeping against his knees. Stopping to adjust a bolt on the machine, Rieke struggled to maneuver a wrench with his trembling fingers.

It was 1988, and Rieke was in his mid-40s, too young and too fit to feel his body betraying him. For two decades, he had farmed in the heart of the San Joaquin Valley, and he knew what he wanted his hand to do. But for some frustrating reason, it refused to obey.

Unbeknownst to Rieke, by the time he noticed the slightest tremor, some 400,000 of his brain cells had been wiped out. Like an estimated other 1 million Americans, most over 55, he had Parkinson's disease, and his thoughts could no longer control his movements. In time, he would struggle to walk and talk.

Rieke, who was exposed to weedkillers and other toxic compounds all his life, has long suspected that they were somehow responsible for his disease.

Now many experts are increasingly confident that Rieke's hunch is correct. Scientists have amassed a growing body of evidence that long-term exposure to toxic compounds, particularly pesticides, can destroy neurons and trigger Parkinson's in some people.

So far, they have implicated several pesticides that cause Parkinson's symptoms in animals. But hundreds of agricultural and industrial chemicals probably play a role, they believe.

Researchers don't use the word "cause" when linking environmental exposures to a

disease. Instead, epidemiologists look for clusters and patterns in people, and neurobiologists test theories in animals. If their findings are repeatedly consistent, that is as close to proving cause and effect as they get.

Now, with Parkinson's, this medical detective work has edged closer to proving the case than with almost any other human ailment. In most patients, scientists say, Parkinson's is a disease with environmental origins.



**BODY BETRAYED:** Gary Rieke stands in one of the rice fields he used to farm before Parkinson's disease forced him to retire. He has long suspected that pesticide exposure played a role in his illness.  
(Robert Durell / LAT)

Scientists are "definitely there, beyond a doubt, in showing that environmental toxicants have to be involved" in some cases of Parkinson's disease, said Freya Kamel, an epidemiologist with the National Institute of Environmental Health Sciences who has documented a high rate of neurological problems in farmers who use pesticides.

"It's not one nasty thing that is causing this disease. I think it's exposure to a combination of many environmental chemicals over a lifetime. We just don't know what those chemicals are yet, but we certainly have our suspicions."

For almost two centuries, since English physician James Parkinson described a "shaking palsy" in 1817, doctors have been baffled by the condition.

In most people, a blackened, bean-size sliver at the base of the brain — called the substantia nigra — is crammed with more than half a million neurons that produce dopamine, a messenger that controls the body's movements.

But in Parkinson's patients, more than two-thirds of those neurons have died.

After decades of work, researchers are still struggling with many unanswered questions, such as which chemicals may kill dopamine neurons, who is vulnerable and how much exposure is risky.

Expressed in legal terms, pesticides are not guilty beyond a reasonable doubt — but there is a substantial, and rapidly growing, body of evidence, many scientists say.

Clues and breakthroughs are emerging from an odd menagerie of laboratory flies, mice, rats and monkeys, from bits of human brain, and from farmers like Rieke.

And it all started with a junkie named George.

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It was July 1982, and a 42-year-old patient named George Carrillo had lingered in Santa Clara emergency rooms and psychiatric units for more than two weeks. He seemed catatonic, unable to move or speak. Dr. Bill Langston, who ran a neurology department, was brought in to try to figure out what was wrong.

Langston gently lifted the man's elbow. His arm was stiff, moving like a gearshift. Langston had seen this odd, rigid movement many times before, in patients with Parkinson's disease.

But this was no ordinary Parkinson's patient. His symptoms had developed virtually overnight.

The doctors soon tracked the source: a botched batch of synthetic heroin that contained MPTP, a compound that acted like an assassin, targeting the same neurons missing in Parkinson's patients.

Langston had stumbled across a powerful chemical that unleashed an immediate, severe form of Parkinson's.

Still, it was obvious that synthetic heroin wasn't the culprit for most Parkinson's patients. People are exposed to some 70,000 chemicals in their environment. Which others could cause the disease?

A few days later, a chemist contacted Langston. The formula for the heroin compound, the chemist said, "looks just like paraquat." Paraquat has been one of the world's most popular weedkillers for decades. It was a good place to start.

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Since that discovery, scientists have conducted hundreds of animal experiments, at least 40 studies of human patients, and three of human brain tissue. They have found "a relatively consistent relationship between pesticide exposure and Parkinson's," British researchers reported online in September in the journal *Environmental Health Perspectives*.

The work has revolutionized the thinking about Parkinson's, shifting the decades-long debate about whether its roots are genetic or environmental. Among the research leaders are UCLA, the Parkinson's Institute in Sunnyvale, Calif., which Langston founded and now directs, and Atlanta's Emory University, each named national centers for Parkinson's research in 2001 and given a total of \$20 million in federal grants.

Head trauma contributes to some cases of Parkinson's, and it probably explains why boxer Muhammad Ali was stricken. But why does it afflict others with seemingly nothing in common, such as the late Pope John Paul II and actor Michael J. Fox?



**‘IT NEVER GETS BETTER’:** Retired farmer Gary Rieke at home with his wife, Linda. “Every year, there are things that we all take for granted that my dad can no longer do,” said his son, Greg. (Robert Durel / LAT)

A couple of genes seem to play a role in early onset of Parkinson's in the small percentage of people who are afflicted at a young age. But for 90% of people who get the disease, a broad array of environmental factors are believed responsible. In fact, when Parkinson's patients have identical twins who carry the exact same genes, most of the twins do not contract the disease.

"All told, the forms of Parkinson's with a known or presumed genetic cause account for a small fraction of the disease, likely 5% or less," epidemiologists Dr. Caroline Tanner of the Parkinson's Institute and Lorene

Nelson of Stanford University reported in 2003.

To pinpoint which environmental exposures are most important, scientists are trying to unravel how genes and toxic chemicals interact to destroy brain cells. One leading theory is that pesticides cause over-expression of a gene that floods the brain with a neuron-killing protein.

Exposure to chemicals early in life, followed by toxic exposures in adulthood, may be especially important, triggering a slow death of neurons that debilitates people decades later.

Compounds with little in common, such as a fungicide and an insecticide, apparently can team up to administer a one-two punch, decimating brain cells.

"Pesticides and related industrial chemicals, those classes of compounds, clearly are associated with some cases of Parkinson's," said Gary Miller, a toxicologist and associate professor at Emory University's Rollins School of Public Health. "The question is, how many? 5%, 10%, 50%? In a chemical-free society, people would still get Parkinson's disease. It would just occur later in life and at a lower incidence."

Even 5% would involve 50,000 Americans alive today.

More than 1 billion pounds of herbicides, insecticides and other pest-killing chemicals are used on U.S. farms and gardens and in households. Nearly all adults and children tested have traces of multiple pesticides in their bodies.

So far, animal tests have implicated the pesticides paraquat, rotenone, dieldrin and maneb — alone or in combination — as well as industrial compounds called PCBs, or polychlorinated biphenyls.

Pesticide industry representatives stress that there are many risk factors and insufficient evidence implicating any specific pesticide. Scientists agree that they cannot specify an individual culprit.

"We know for sure that if you expose animals to certain pesticides, it will kill the same neurons as Parkinson's disease. That's a fact. In humans, there is high suspicion, but there is no definite proof," said Dr. Marie-Francoise Chesselet, director of the UCLA Center for Gene-Environment Studies in Parkinson's Disease.

A connection to rural living or farming has turned up worldwide. Scientists first observed a high rate of Parkinson's in rural areas in the early 1980s in Saskatchewan, Canada. Since then a dozen published studies have reported an increase of 60% to 600% among people exposed to pesticides, according to the British scientists' review.

Still, the science of epidemiology has inherent weaknesses. Most of the human studies, for example, relied on patients' memories — most of which cannot be validated — to report their pesticide exposures.

"You need to be cautious in drawing conclusions when you know there are flaws in these studies," said Pamela Mink, an epidemiologist who evaluated the human studies in a peer-reviewed report partly funded by the pesticide industry.

Most patients probably were exposed decades before their diagnosis. Because there is no national registry for Parkinson's, as there is for cancer, no one knows whether rates are high in places such as the San Joaquin Valley.

Among those trying to obtain more definitive answers, UCLA environmental epidemiologist Dr. Beate Ritz has contacted nearly 300 Parkinson's patients and 250 healthy people in Tulare, Fresno and Kern counties. She is pinpointing their pesticide exposures down to the day, the pound and the street corner by overlaying their addresses with California's extensive agricultural database, which details pesticide use on farms since the 1970s.

Also, 52,000 farmers and other pesticide applicators have been tracked by federal researchers since the mid-1990s and one goal is to document their exposure and see how many wind up with Parkinson's.

Animal studies provide more evidence but also have weaknesses. Mink and toxicologist Abby Li, who co-wrote the report financed partly by industry, concluded that the human and animal data "do not provide sufficient evidence" to prove pesticides cause Parkinson's.

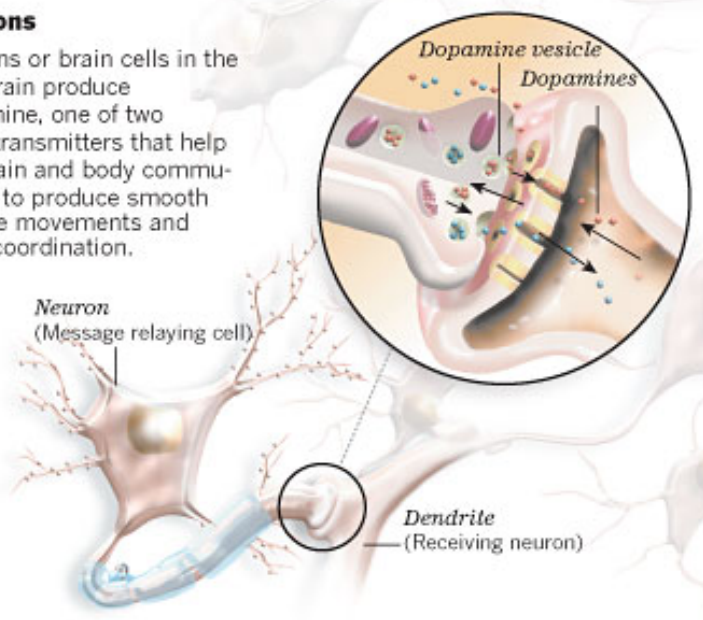
Scientists first tested paraquat in rodents, but the findings were inconclusive. Neurologist Tim Greenamyre showed that rotenone, a pesticide, could kill rats' dopamine neurons and cause Parkinson's symptoms. But since rotenone is a natural plant compound that is not used much on farms, it was not a likely source of the human disease.

# Parkinson's and pesticides

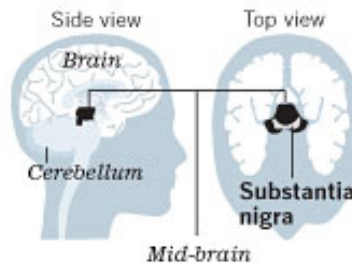
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## Neurons

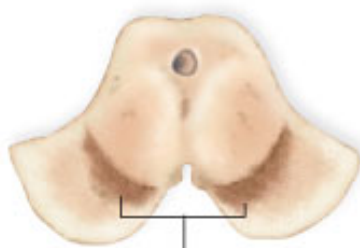
Neurons or brain cells in the mid-brain produce dopamine, one of two neurotransmitters that help the brain and body communicate to produce smooth muscle movements and body coordination.



People with Parkinson's disease lose 60% to 80% of their dopamine-producing neurons in a part of the mid-brain called the substantia nigra, hindering communication between the mind and body. Scientists think some pesticides may kill neurons in the substantia nigra.



## When dopamine is present



In a normal mid-brain, the substantia nigra has cells that are pigmented, or colored black, a byproduct of dopamine production.

## Absence of dopamine



Parkinson's patients have a lack of this pigmentation because they lost so many neurons.

Source: Medline Plus

LORENA ISIGUEZ Los Angeles Times

Neurotoxicologist Deborah Cory-Slechta has presented the most compelling evidence yet on how everyday environmental factors can play a role in Parkinson's disease. Her theory was that testing one chemical at a time for its impact on the brain was misguided.

"It's not how humans are exposed," she said. "You don't get a single dose of a pesticide. You get chronic, low-level exposure."

She injected mice with paraquat and the fungicide maneb. Use of the two sometimes overlaps on farms. Alone, paraquat and maneb did not harm mice in her laboratory. But "when we put them together, we were astounded," Cory-Slechta said.

The most dramatic damage was in mice exposed to maneb as fetuses and then to paraquat as adults. Their motor activity declined 90% and their dopamine levels plummeted 80%.

The amounts used in those tests "are not high levels of exposure. These are very, very low doses," said Cory-Slechta, who now directs Rutgers University's Environmental and Occupational Health Sciences Institute.

Paraquat and maneb are

unlikely to be the only combination with such a devastating effect. Yet the U.S. Environmental Protection Agency considers only single exposures when approving pesticides, an approach that "doesn't mimic environmental reality," Cory-Slechta said.

"There may be hundreds, if not thousands, of other compounds that are silent killers of dopamine neurons," said Dr. Donato Di Monte, director of basic research at the Parkinson's Institute.

"Each of these risk factors, they kill 10, 20 or 30% of your neurons. It's like eroding a house on a cliff, and the house finally falls over.

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With so much emerging human and animal data, Chesselet predicts that "in two years, we will have a preponderance of evidence" against some classes of chemicals. Kamel thinks specific pesticides will be pinned down within five years.

For Rieke, it is impossible to determine which chemicals may have played a role in his disease. He owned two dry-cleaners — handling industrial solvents for seven years — and for 25 years he mixed and applied at least a dozen herbicides and insecticides on his Merced farm.

At 59, Rieke had to sell the farm and retire. Now 64, he seems 10 years older despite taking seven medications daily.

"Every year, there are things that we all take for granted that my dad can no longer do," said his son, Greg. "There's no cure, and it never gets better. There's not a lot of hope, if you will."

Though it's too late for Rieke, scientists are confident they'll soon be able to predict who is vulnerable to environmental assaults on their brains.

"That would be the Holy Grail for us," Miller said. "To actually pinpoint people at risk of this disease and protect them."

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### **Parkinson's and pesticides**

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