Are Pesticides Causing Parkinson's Disease?

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Posted on June 19, 2009 http://www.alternet.org/story/140673/

This story originally appeared in OnEarth Magazine.

Jackie Christensen was 32 when her body began to betray her. She had just returned to work after the birth of her second son and when she tried to type, two fingers on her left hand refused to cooperate. "They wouldn't go where I would want them to on the keyboard," says Christensen, who at the time -- it was 1997 -- was co-director of the food and health program at the Institute for Agriculture and Trade Policy, a Minneapolis think tank. "I also had what they frequently call frozen shoulder, with a very low range of motion in my left arm."

The first neurologist Christensen went to responded flippantly to her suggestion that she might have multiple sclerosis, which she had self-diagnosed because of her relatively young age and the fact that she was female. "If you want me to write that down, I will," she remembers him saying, refusing to pursue the matter further. A second neurologist thought it was all in Christensen's mind and referred her to a psychiatrist. Over the next several months, her symptoms got progressively worse, and she finally consulted neurologist number three. His startling diagnosis: Parkinson's disease.

"I thought, 'I can't have Parkinson's because I'm not old,'" Christensen recalls. But a trial of the standard treatment, a drug called L-dopa, seemed to work. Based on that clinical observation, the diagnosis was confirmed. This was in 1998, when Christensen was not quite 35, and she has been on L-dopa, with varying degrees of success, ever since.

Why did a disease that usually affects people in their sixties and seventies, and that affects men more often than women, strike this vibrant young mother? Christensen, a lifelong environmental activist, suspected an environmental cause -- not only because she was politically inclined to, but because she knew that accumulating scientific information was pointing in that direction. In the past few years, Christensen has been part of a movement exploring a possible connection between exposure to environmental toxins -- in particular, the organophosphate pesticides -- and Parkinson's disease, through her work with the Collaborative on Health and the Environment, a national network of advocacy and scientific organizations. She is co-founder of CHE's working group on Parkinson's Disease and the Environment.

A cause-and-effect relationship between environmental neurotoxins and Parkinson's is difficult to prove. As with many other scientific efforts to establish disease causation through population studies, there will probably never be a smoking gun that settles things once and for all. Population studies can detect associations between certain suspected agents and diseases such as cancer, but it's hard to draw conclusions about what causes a disease from studies that can register only correlations. In the case of Parkinson's and the environment, however, there has been a steadily mounting consensus about such a connection, and the pace has quickened in the past year or so.

A January 2009 consensus statement from CHE, in collaboration with the Parkinson's Action Network, a patient advocacy group, found that there was "limited suggestive evidence of an association" between

pesticides and Parkinson's, and between farming or agricultural work and Parkinson's. This followed by just a few months the publication of*Environmental Threats to Healthy Aging*, a report co-authored by the Science and Environmental Health Network, a consortium of advocacy groups based in Ames, Iowa; it included a summary of 31 population studies that have looked at the possible connection between pesticide exposure and Parkinson's. Twenty-four of those studies, according to the report, found a positive association, and in 12 cases the association was statistically significant. In some studies, the group found, there was as much as a sevenfold greater risk of Parkinson's in people exposed to pesticides. In addition, in April 2009, scientists at the University of California, Los Angeles (UCLA), published a provocative study connecting the disease not only to occupational pesticide exposure but also to living in homes or going to schools that were close to a pesticide-treated field.

Taken together, 30-plus years of research add up to an increasingly persuasive conclusion: exposure to pesticides and other toxins increases the risk of Parkinson's disease, and we are only now beginning to wrestle with the true scope of the damage.

Parkinson's is the second most common neurodegenerative disease (after Alzheimer's) in the United States, affecting between 1 million and 1.5 million Americans. The majority of cases occur in people over 65, about 60 percent of them male. It leads to uncontrollable tremors, muscle rigidity, and the inability to direct your arms or legs to move when you want them to. People with Parkinson's often have a masklike, impassive expression. They may have difficulty speaking clearly and develop a characteristic shuffling gait. Cognitive skills usually are not affected, though some functions like memory and decision-making can be impaired, and, in the face of the gradual and inevitable encroachment of physical limitations, people with Parkinson's often become depressed.

In part because it can take many forms, Parkinson's disease is difficult to diagnose. Several movement disorders have been classified in the general category known as Parkinson's-like syndrome, or parkinsonism. Scientists are divided about whether Parkinson's disease and parkinsonism are even related in any meaningful way, beyond sharing some symptoms. The two conditions may not even involve the same brain defects. The strict definition of Parkinson's disease is a loss of cells in the substantia nigra, a small structure in the basal ganglia region of the midbrain (though other brain structures are now thought to be involved as well). The substantia nigra ordinarily secretes the neurotransmitter dopamine, which is involved in many of the brain's functions, including the control of motor activity.

Often a diagnosis of Parkinson's disease is made the way it was made for Christensen: by a trial run of L-dopa, which boosts dopamine in the brain. If it works, the problem must be Parkinson's. It's a circular kind of logic, but it's all that most doctors have. There still are no definitive blood tests or brain scans to make the diagnosis.

In trying to establish risk factors for Parkinson's, one of the first decisions investigators must make is which cases to include in their epidemiological studies. Some studies include all patients, those with parkinsonian syndrome as well as those with definitively diagnosed Parkinson's. Some researchers limit their study subjects to people with Parkinson's disease and a demonstrated reduction of dopamine.

One of the more restrictive studies is a small subset of the massive Agricultural Health Study (AHS), which began in 1993 and involves nearly 90,000 individuals licensed to apply pesticides to crops, as well as their families. The AHS, conducted by the National Cancer Institute and the National Institute for Environmental

Health Sciences with funding from the Environmental Protection Agency and the National Institute of Occupational Safety and Health, has tracked these workers to determine their risk of developing cancer and other serious diseases.

In 2002, scientists decided to look at a segment of this large database to assess the environmental risks for Parkinson's. This study-within-a-study, with the catchy acronym FAME (Farming and Movement Evaluation), compared the pesticide exposure of 114 AHS participants who have Parkinson's disease, as diagnosed by two specialists from the team, with exposure among 384 control cases matched for age, sex, and state of residence (either Iowa or North Carolina, where all the subjects are from). A group of scientists led by Caroline Tanner of the Parkinson's Institute of Sunnyvale, California, and Freya Kamel of the National Institute of Environmental Health Sciences looked at five possible risk factors in these 498 individuals: pesticide exposure; exposure to other neurotoxins; lifestyle factors such as diet, smoking, and caffeine use; the amount of melanin, or pigment, in the skin; and specific genetic variations, particularly those in genes involved in the production of dopamine or the metabolism of xenobiotics -- non-natural chemicals such as drugs and toxins that are transported and detoxified through pathways that scientists already understand.

The FAME study, the results of which are being prepared for publication next year, found that pesticide exposure was a significant risk factor for Parkinson's disease. The parent AHS study found that people who had been exposed to pesticides sporadically over a lifetime were 1.2 times more likely to develop Parkinson's than those who had not been. And when the exposure was heavy -- the kind of lifetime exposure seen in career pesticide applicators, or a single massive exposure as the result of a spill -- that increased risk jumped to 2.3 times. The riskiest pesticides were found to be some of those most commonly used in American agriculture, among them Paraquat and Trifluralin, both herbicides used to kill broadleaf weeds in food crops. (Paraquat is now restricted to commercially licensed users in the United States because of its toxicity, but it remains the second most widely used herbicide in the world, applied to more than 50 crops in 120 countries.)

These results were part of a cascade of findings pointing to a connection between environmental toxins, especially pesticides, and Parkinson's disease. As long ago as the 1970s, epidemiologists noticed that Parkinson's was more likely to occur in people who had grown up in rural areas, especially those who had lived on farms. But they were not sure which aspect of a rural background was relevant. Living near livestock? Drinking well water? Being exposed to pesticides? "It's been very difficult to pin down an explanation," Kamel says.

Pesticides seemed the most likely culprit. "Animal models have shown that specific pesticides can cause parkinsonian changes," Kamel says, "and we have mechanistic data also" -- that is, evidence of biological processes at the level of the interaction between brain cells and the chemicals in common pesticides -- that can explain how a cause-and-effect relationship might work. "To the degree we understand the neurological mechanisms that may be related to Parkinson's disease," Kamel says, "it seems that certain specific pesticides might play a role."

"Despite remaining uncertainties and data gaps," wrote the authors of the 2008 report by the Science and Environmental Health Network -- Jill Stein, Ted Schettler, Ben Rohrer, and Maria Valenti -- "the body of evidence linking pesticide exposure to Parkinson's disease fulfills generally accepted criteria for establishing causation." When combined with "extensive laboratory animal data" specifying the underlying biology of this relationship, they wrote, "collectively, this evidence supports the conclusion that pesticide exposures can cause Parkinson's disease in some people."

Like most other population studies, this one has no way of proving that, for any one individual, X definitely led to Y -- that Jackie Christensen's early-onset Parkinson's disease, for instance, was caused by her exposure to pesticides as a teenager. To Christensen, however, the causal connection is clear. Growing up in rural Minnesota, she spent summers working on local farms. In her early teens, this meant engaging in a practice known as "walking beans." A pickup truck would drop off a bunch of youngsters, including Christensen, at one end of a field, and they would walk the rows of soybeans, weeding as they went. Later, Christensen and her friends rode a "bean buggy," a rig attached to the front of a tractor from which they would spray the herbicide Roundup, sometimes dyed purple so they could see where it was landing, carefully aiming for the weeds and trying to avoid the beans. Often she was dressed in nothing more than a bathing suit and a baseball cap. "I had a great tan those summers," she wrote in the introduction to her book, *The First Year: Parkinson's Disease; An Essential Guide for the Newly Diagnosed*, "and I had no idea nor gave any thought whatsoever to what I might be exposing myself to, or what the effects might be. After the first day or two of spraying, I could no longer smell the odor of the herbicide. I do remember that when I would come home, my mother would immediately tell me to take a shower because I smelled like chemicals."

As a young adult, Christensen had a single massive chemical exposure, during a political demonstration that involved wading into the Mississippi River in St. Louis. Wastewater treatment runoff made the water as neon green as Mountain Dew. She says it's "anybody's guess" what was in the water, but since many of the industries in St. Louis at the time discharged their wastes into the river, she says the brew probably included organophosphate pesticides, dry cleaning solvents, and other compounds. "After that action, within an hour I had a headache," she says, "and I was nauseated and felt fatigued and lousy for a week. I know now that those are common symptoms of acute pesticide poisoning. At the time I didn't think about what was causing it. I was 25 and thought I was bulletproof."

Since the British physician James Parkinson first described the "shaking palsy" in 1817, Parkinson's disease has been linked to a variety of possible environmental causes, both natural and artificial. It has been linked, too, to genetic factors, dating back to the beginning of the twentieth century, when early-onset Parkinson's was first found to run in a few scattered, unlucky families. Those who study the connection between Parkinson's and the environment suggest that it's probably the combined result of having a genetic predisposition to the disease and a dangerous exposure to some sort of neurotoxin. A favorite expression of people in this field is that "genetics loads the gun and environment pulls the trigger."

In the 1950s, scientists noticed that a large proportion of the Chamorro people, who live on the Pacific island of Guam, were gripped by a syndrome that rendered them stiff and immobile by middle age. It looked a lot like Parkinson's disease. What made the situation so fascinating (and so perplexing) was that in some patients the symptoms were closer to two other neurodegenerative diseases -- Alzheimer's and amyotrophic lateral sclerosis (Lou Gehrig's disease). After decades of research, scientists discovered that the culprit was a local dietary staple: a rodent known as a fruit bat. The bat drank nectar from the cycad tree, from which it received a concentrated dose of a brain toxin, the amino acid beta-methylamino-L-alanine (BMAA). When people ate the meat of the fruit bat, they ingested huge amounts of BMAA. The story was told in 2002, when the journal*Neurology* published an article about the fruit bats and their "biomagnification" of BMAA. The findings are still the subject of some debate, but they were consistent with the accumulating picture: that at least some environmental agents might account for at least some forms of parkinsonism.

In 1982, six young people showed up in emergency rooms in northern California unable to move, speak, or eat on their own. This time the detective work was accomplished much more rapidly. It took only a few weeks for William Langston, then a neurologist at the Santa Clara Valley Medical Center in San Jose, to put the story together. The patients were all heroin users, and they had all used a batch of garage-concocted heroin that was contaminated with the chemical compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, or MPTP. "At the molecular level, very little separated a toxic chemical from a harmless one," Langston and John Palfreman wrote in their book, *The Case of the Frozen Addicts.* But that small chemical change was enough to turn the designer heroin into one of the most potent known neurotoxins, virtually wiping out all the cells of the substantia nigra, which produces dopamine. MPTP has a molecular structure very much like the herbicide Paraquat. So the "frozen addicts" were taken as further evidence that both pesticide exposure and MPTP could be related to the same kind of dramatic brain damage.

The tragedy of the addicts (who recovered some function with L-dopa treatments) had a silver lining. MPTP turned out to be an excellent way to create parkinsonian symptoms in experimental animals -- a necessary first step in the search for a cure.

Scientists also observed these symptoms in groups of people exposed to unrelated compounds, such as heavy metals. One in particular, manganese, was implicated in a 2006 study of residents of the steelmaking town of Hamilton, Ontario, who had a higher-than-expected rate of Parkinson's disease. Investigators attributed this to the manganese content of particulate air pollution from factory emissions. It turns out that manganese is an ingredient in the widely used fungicide Maneb.

But pesticides remain the clearest culprit. One study found that in the brains of people who had died of Parkinson's disease, the substantia nigra had higher levels of Dieldrin (an organochlorine pesticide no longer approved for use in the United States) and of lindane (an insecticide occasionally still used to treat scabies and lice) than did the brains of people who had died of other causes. Laboratory studies have also provided important clues to the connection between pesticides and brain damage. When human brain cells are grown in culture and exposed to a variety of chemicals, several widely used pesticides -- in particular, Paraquat and Rotenone, a natural pesticide approved for use in organic foods -- have been shown to cause increased levels of alpha-synuclein, a protein in the substantia nigra, similar to the levels that are seen in people with Parkinson's disease.

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