Pesticides and Parkinsonism: Is There a Link Between Environmental Toxins and Neurodegenerative Disorders?

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Multiple, converging lines of evidence from epidemiological, twin, and individual patient studies, as well as studies in animals, suggest that there may be a link between exposure to pesticides and the eventual development of Parkinson's disease (PD). Since PD is common and shares some features with other neurodegenerative disorders, there is a concern that long-term exposure to environmental factors, particularly pesticides, may play a role in the development of this class of disorders. Since these diseases usually develop late in life, and since the number of old people is increasing, the number of people affected by PD and the other neurodegenerative disorders is increasing and will continue to increase into the foreseeable future. As the case for an etiological link between pesticides and PD gets stronger, the need to invoke the "precautionary principle" will become more apparent. Physicians have a special responsibility to educate and provide guidance to colleagues, the public, and policy makers charged with regulating the chemicals in our environment. [M&GS 2000;6:86-90]

The publication of Rachel Carson's Silent Spring marked the beginning of an era [1]. This landmark book introduced many to the idea that there are unintended consequences associated with the use of pesticides. While most of us are familiar with the arguments calling for regulations to ban or limit lead, dioxins, DDT, and other compounds that have well-described consequences, there is a lingering concern that there may be other serious, unknown, consequences associated with the use of pesticides. These concerns are heightened by several recent studies that have strengthened the hypothesis that Parkinson's disease (PD) or, more properly, parkinsonism, may be caused by environmental toxins [2,3].

Parkinson's disease was described by James Parkinson in 1817. The disease that bears his name is characterized by tremor, bradykinesia (slowness), rigidity, and a loss of postural reflexes. PD is but one of a number of conditions that are all typified by akinesia and rigidity [4]. These conditions, which include progressive supranuclear palsy, diffuse Lewy body disease, corticostriatonigral degeneration, cortical-basal ganglionic degeneration, and many others, are referred to as forms of parkinsonism because

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of their resemblance to idiopathic PD [4]. Because of the similarities in the clinical manifestations of these disorders and an absence of clearly defined pathophysiological mechanisms that separate them into distinct nosological entities, many patients are diagnosed as having parkinsonism, or PD, until the emergence of distinguishing characteristics. This may take years. For some, a correct diagnosis may never be made or may be made only at autopsy.

Nature and Scope of Parksinson's

Parkinson's disease affects more than 500,000 Americans and costs the economy more than $20 billion per year [5]. It is second only to Alzheimer's disease among the neurodegenerative diseases. Parkinson's disease usually begins after age 50, and the incidence increases exponentially with increasing age. Between 1.5% and 2.5% of all Americans who reach the age of 70 have Parkinson's disease. As the population of the nation ages, the number of people with PD is certain to increase. Since some patients with PD have signs and symptoms that are seen in other neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, and others, there is some concern that they may share common pathogenetic mechanisms.

The cause of PD is unknown. After the 1916-27 influenza pandemic, large numbers of patients developed post-encephalitic parkinsonism. Typically, the signs and symptoms of this condition began less than 5 years after the acute illness, with 85% of all patients developing the syndrome within 10 years.

Speculations about environmental factors and the etiology of PD began almost two decades ago when several patients were identified who developed what appeared to be typical PD at an extraordinarily young age [6]. Epidemiological studies of these patients revealed that they were drug abusers who used so-called designer drugs--drugs usually manufactured in illicit laboratories designed to have structural characteristics similar to opiates. In the attempt to synthesize a meperidine-like drug, it was found that an unintended chemical reaction produced the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Further research showed that MPTP is a toxin that kills the dopaminergic neurons in the brain, producing a syndrome that is almost identical to typical PD [7,8]. It was not long before others noted that the structure of MPTP was similar to paraquat, a widely used herbicide registered by the US Environmental Protection Agency (EPA) used to treat crops, such as cotton, soybeans, sugarcane, and sunflowers.

Risk Factors

The structural similarity between MPTP and other pesticides triggered epidemiological studies designed to evaluate risk factors for the development of PD. These studies received additional impetus from the discovery that an extract from the plant cycas circinalis L. was linked to the development of a neurodegenerative disorder referred to as Parkinson-amyotrophic lateral sclerosis-dementia complex found in people from Guam [9]. The affected individuals appear to have eaten the seeds of the cycad, a traditional source of food and medicine among the Chamorro people. With westernization and changes in eating habits, this condition has died out.

A number of epidemiological studies have sought to define risk factors for the development of PD. Oddly, cigarette smoking reduces the risk of developing Parkinson's disease [10]. Since PD was not described until the early part of the 19th century, many have suggested that PD is related in some way to the industrial age. This hypothesis is supported by several studies. In a 1989 case-control study in the People's Republic of China, Tanner et al. found that occupational exposure to industrial chemicals, printing plants, or quarries was associated with an increased risk of PD (relative risk range 2.39-4.5), whereas raising pigs, growing wheat, and village residence were associated with a reduced risk of PD (relative risk range .17- .57) [11]. Since chemical use was not characteristic of the Chinese agricultural system at that time, the authors linked industrial processes to the development of PD. A similar conclusion was drawn by Schoenberg et al. who found an age-adjusted prevalence ratio for PD of 341/100,000 among black residents of Copiah County, Mississippi, which was compared to an age-adjusted prevalence ratio of 67/100,00 in Igbo-Ora, Nigeria [12]. These studies attributed the difference to the degree of industrialization of the two sites.

Pesticides and PD

A number of studies have focused on pesticides and have linked exposure to an increased risk for the development of PD. In a case-controlled study involving 120 Taiwanese patients with PD and 240 hospitalized controls, the risk for developing PD was increased by 2.04 for living in a rural environment, by 1.81 for farming, by 3.22 for use of paraquat, and by 2.89 for other herbicide-pesticide use [13]. In an Israeli study, the incidence of PD was increased five-fold among the residents of three adjacent kibbutzim in the Negev desert who all drew on a common aquifer, and who were all exposed to similar agricultural chemicals [14].

Clustering of these cases suggested strongly that an environmental factor was responsible, such as drinking well water and/or exposure to agricultural chemicals. Additional support for the link between pesticides and PD came from the study of Semchuk et al., who performed a case-control study of 130 residents of Calgary, Alberta, Canada with neurologist-confirmed PD, and 260 age- and sex-matched controls [15]. Prior occupational herbicide use was the only consistent predictor for the development of PD. Hubble et al. formed similar conclusions, using different methods, in a study of rural and urban residents of Kansas [16]. They did a principle components analysis of data regarding residency, occupation, medical history, social history, and diet. In a further analysis, significant predictors for the development of PD, in order of strength, were pesticide use, family history of neurologic disease, and depression, with a 92% predicted probability for PD if all three were positive (odds ratio = 12.0).

Doubts have been raised in some minds due to differences in methodology, differences in the populations studied, and differences in the criteria used to make or confirm the diagnosis of PD. Nevertheless, the weight of the evidence gathered a decade ago suggests strongly that exposure to industrial chemicals, particularly pesticides, is a significant risk factor for the development of PD.

The role of the environment as a factor in the development of PD was given new focus by a recent twin study reported by Tanner and her associates [2], who evaluated almost 20,000 twin pairs and identified 193 twins with PD, employing the techniques of molecular biology to establish zygosity and comprehensive neurological evaluations by specialists in the diagnosis of PD. These data were used to calculate concordance rates for monozygous and dizygous pairs, stratified by age. Among twins with PD diagnosed after age 50 years, the pairwise concordance was 0.106 in the monozygous pairs and virtually identical at 0.104 among the dizygous pairs. Among twins diagnosed with PD before age 51 years, the concordance rates were 1.00 in monozygous pairs and 0.167 among the dizygous pairs. The relative risk for concordance for those diagnosed when younger than age 50 years was 6.0 and 1.02 for those diagnosed at age 50 or greater. Thus, among twins with one member affected by PD before the age 50, the second twin was 6 times more likely to develop PD if they were a monozygous pair rather than a dizygous pair. Zygosity had no effect on the risk of developing PD in the second twin if the disease developed after age 50. This near-identity for risk after age 50 showed clearly that PD that develops after the age of 50 is not likely to be due to genetic factors. These data suggest strongly that non-genetic, i.e., environmental factors, determine the risk of developing PD after age 50, the most common time for this condition to appear [3].

Another recent publication described five patients who had developed reversible parkinsonism after exposure to organophosphates [17]. These patients did not have the classical form of the disease, in that they did not improve after the administration of anti-parkinsonian drugs (typically, PD improves after pharmacological treatment, whereas other indistinguishable akinetic-rigid syndromes, such as striatonigral degeneration may not respond). Three of these patients came from the same family, suggesting a genetically determined susceptibility to these compounds. At a recent symposium on Parkinson's disease, researchers from Atlanta reported on the development of an animal model of Parkinson's disease using rotenone [18]. Systemic administration of this pesticide caused degeneration of the neural pathways implicated in the development of PD.

Common Toxic Factor

These data demonstrate that there is increasing, credible evidence that exposure to environmental toxins, particularly pesticides, may lead to the development of PD. Because of similarities among neurodegenerative diseases as a group, and particularly because of the data implicating a common toxic factor causing the PD-demential-amyotrophic sclerosis complex in Guam, the relationship between pesticides and the etiology of PD may be an indication of a more widespread problem.

We are awash in a sea of chemicals. According to the EPA, 4.5 billion pounds of pesticides are used in the US each year. We use 77 million pounds of organophosphates: 60 million pounds are used in agriculture and 17 million pounds are used in homes, on lawns and golf courses, and for other non-agricultural purposes. According to the Foundation for Advancements in Science and Education, the US exported more than 338 million pounds of pesticides during 1995 and 1996. This total included at least 21 million pounds of pesticides whose use is forbidden in the US. Most of these shipments were directed to the developing world. In the 1980s more than 200,000 deaths were attributed to organophosphate poisonings in developing countries, largely among agricultural workers [19]. Whether exposed workers will develop additional health problems, including PD, remains to be seen.

In the landmark publication Pesticides in the Diets of Infants and Children, experts from the National Academy of Sciences showed clearly that organophosphate residues are present in easily detectible amounts in our water supply [20]. Because children consume more water per unit body weight than adults, they are particularly vulnerable. The report found that children were frequently exposed to pesticide residues in excess of a reference dose and that, for some, these exposures were high enough to cause symptoms of acute organophosphate poisoning.

Implications for Policy

At the time of that report, pesticide tolerances were defined largely by the industry that manufactures them. These tolerances were based on agricultural practices and were not related to worker or consumer health. This is changing. As a part of the Federal Insecticide Fungicide and Rodenticide Act (FIFRA), the EPA is reviewing pesticide use to make more appropriate decisions concerning the use of these compounds. The 1996 Food Quality Protection Act further requires that uses must be "safe," in that EPA must conclude "with reasonable certainty that no harm will come from aggregate exposure" to these compounds. By aggregate exposure, the act intends that all exposures, including those in food, water, and residential sources must be considered. Cumulative effects from multiple pesticides must be considered. Exposures must account for the special sensitivity of children and infants. In another important departure from prior regulatory standards, multiple endpoints must be considered, including possible endocrine effects. It will no longer be sufficient to conclude that a pesticide is safe as long as it does not cause cancer.

As a consequence of these findings, the National Institutes of Health has issued a special request for applications (RFA ES-00-002, The role of the environment in Parkinson's disease), directed at the neuroscience community, for research studies that focus on the role of the environment and Parkinson's disease. This call will be answered, but proving that there is an unequivocal link between the use of pesticides and the development of Parkinson's disease is likely to be difficult, if not impossible. It is more likely that the weight of the evidence will increase slowly. Since pesticide exposure begins early in life, a lifelong avoidance of these ubiquitous compounds may be required.

What is the responsibility of physicians? Since society as a whole derives benefits from pesticides, the debates concerning their use are likely to intensify. The best answers will not come easily. There is, as yet, no smoking gun linking pesticides and neurodegenerative disorders. Yet the evidence forging that link is getting stronger. At the present time, there are no known cures for any of the neurodegenerative disorders. The effective therapies, directed at the symptoms of PD, all have side effects and limitations. The ability to prevent PD would be welcome.

On entering into the practice of medicine, physicians subscribe to the Hippocratic Oath and its fundamental tenet "first do no harm." This principle is gaining acceptance in environmental law and practice in the form of the "precautionary principle." Briefly stated, the precautionary principle asserts that scientific proof of a causal link between human activity and its effects is not required before preventive actions should be taken. Physicians have a commitment to their patients and are obligated to collect and evaluate data that can help define the etiology of PD and other diseases linked to environmental exposures. Converting these data into educational programs and policies that inform and benefit all is a daunting, but essential, task. Opposition to the precautionary principle from those with a vested economic interest in the chemicals it would limit should not stop us from combining good science and responsible actions.

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