



Paths from Pesticides to Parkinson's

Freya Kamel

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the ice sheet, but that the interior is drained by a network of linked cavities.

With the help of a numerical model, the authors conclude that the growth of efficient subglacial channels is limited by the surface geometry of the ice sheet. The ice sheet margins usually exhibit steep surface slopes reminiscent of mountain glaciers, but the ice sheet interior is very flat, with a small hydraulic gradient driving water flow. In other words, little potential energy is available to enlarge water pathways by melting, while creep closure of channels by ice flow is faster than in the thinner marginal areas. Both effects preclude the development of an efficient channelized system, and water flux might be constrained to a system of linked cavities at high pressure.

These results suggest that current research of subglacial processes may be too narrowly focused on the efficient drainage system that evacuates surface water. Such channelized systems, by their very nature, occupy only a small fraction of the total area. Basal hydrology often differs considerably between neighboring boreholes, and many holes show little water pressure variation. Water pressure is often not even recorded in such boreholes, or the data are discarded because of their seemingly random variations, but they might hold important information on the conditions in large parts of the under-ice environment. Moreover, drill sites are usually restricted to areas lacking crevasses for practical and security reasons. Nothing is known about processes under the crevassed zones, which are subject to an extensional flow regime, in contrast to the compressional regime at topographic lows. The focus of past investigations on fast pressure variations in easily accessible areas might skew our perception of the system under investigation.

Basal motion is a distributed process that is controlled by water pressure and conditions everywhere on the ice sheet's bed and that is undoubtedly controlled by water drainage to the ice sheet base (8). But it is far from obvious how water pressure variations in a spatially confined area influence the behavior of the whole system. Lacking detailed information on bed geometry and sediment properties, one might reasonably consider the boundary zone between ice and bedrock as a self-organized critical system with interacting entities that exchange water depending on pressure gradients and evolving state variables (3–5), and tightly coupled with a spring-block model of stress transfer through the surrounding ice (9).

Considering the under-ice environment as a self-organized critical system explains why widely different conditions are simultane-

ously encountered in neighboring boreholes. To obtain a meaningful sample of variations in basal conditions requires a large number of holes spread over a representative area of the ice sheet, at distances of less than one ice thickness. Such an effort is larger than any of today's small research groups can handle. Drilling and instrumenting hundreds of holes simultaneously would require a concentrated and coordinated effort.

Even after decades of theoretical and experimental progress, we are just starting to understand the variety and interrelation of processes active in the inaccessible subglacial environment. In situ observations such as those presented by Meierbachtol *et al.* (1) and others (6, 7) are urgently needed to develop, test, and quantify predictive theories of subglacial processes. Only by understand-

ing the dynamics at the base of the ice sheets will it be possible to predict their future evolution under a changing climate.

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EPIDEMIOLOGY

Paths from Pesticides to Parkinson's

Freya Kamel

High-quality studies of specific chemical pesticides are needed to determine the relationship between exposure and risk of Parkinson's disease.

Interest in the relationship between exposure to pesticides and the risk of neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease (PD) is long-standing (1). PD, in particular, has been the subject of much debate in this context (2). Its symptoms typically occur later in life (at age 60 or older), with the destruction of neurons manifesting most obviously as loss of motor function. Decades of epidemiological studies have suggested that pesticide exposure is connected to the development of PD. Yet there is still much that is not clear about this relationship. The disorder likely has multiple contributing genetic and environmental factors, but how exposure to a particular chemical leads to neuronal loss and the symptoms of PD is not known. A recent meta-analysis indeed shows that epidemiologic data generally support an association between pesticides and the risk of PD (3). But what is needed is detailed information on the nature of exposure—which pesticides, at what dose, and for how long—to help design policies

and practices that prevent the relevant exposures. Also needed is information on the cellular and molecular mechanisms that, over time, lead from pesticide exposure to neurodegeneration and ultimately to PD. Although many questions still linger, some recent studies appear to be advancing the field.

It is well known that some pesticides are toxic to humans after acute exposure to a very high amount (poisoning). However, the effects of chronic, low-dose exposure to this diverse group of chemicals are not so clear. An analysis of over 100 epidemiologic studies establishes that pesticide exposure (in the absence of poisoning) is indeed linked to PD (3). PD risk increased with exposure to any pesticide (1.8-fold), to herbicides (1.3-fold), or to insecticides (1.5-fold). Risk associated with exposure to any pesticide (1.6-fold) and to herbicides (1.4-fold) was elevated in high-quality studies—those with adequate size, minimal potential for bias, and good information on PD diagnosis and pesticide exposure. Although its general conclusions are not surprising, the study highlights why such a wealth of data has limited impact. Heterogeneity of study quality and lack of detailed exposure information prevent results from being definitive.

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Perhaps one of the most important unanswered questions is which pesticides are associated with PD. Of several specific pesticides or chemical classes of pesticides evaluated in the meta-analysis, only the herbicide paraquat was significantly associated with PD (2.2-fold increase in risk for ever having used the chemical). Paraquat, used to kill weeds and desiccate foliage before harvesting crops such as cotton, is one of the most widely used herbicides in the world. Thirty years ago, recreational drug users rapidly developed parkinsonism after acute exposure to a contaminant whose active agent, 1-methyl-4-phenylpyridinium (MPP+), has a chemical structure

similar to that of paraquat (2). Epidemiological data collected since then have been considered insufficient to establish a role for paraquat in PD. Recent studies, however, have provided stronger support. Notably, risk was increased not only for farmers and pesticide applicators (4, 5), but also for individuals working or living near sites where paraquat was used (6). Among farmers, those

who had used paraquat for less than 8 days had smaller increases in risk (2.4-fold) than those who had used it for more time (3.6-fold) (5). The compound rotenone is also of interest because like MPP+, it disrupts mitochondrial energy production. Rotenone, which is used as an insecticide and as a piscicide (toxic to fish), is less well studied than paraquat, but a recent study of farmers suggests that it too may be associated with PD (5).

The strong evidence from these epidemiological studies of paraquat and rotenone is particularly important because animal models have shown that chronic, low-dose exposure of adult animals to either pesticide results in many features of PD (7). Long-term exposure of adult mice to a low dose of rotenone was also found to replicate the gastrointestinal dysfunction found in PD, a nonmotor feature of the disease (8). Further, experimental studies using these pesticides and cultured cells are providing great insights into the cellular processes involved in PD, including mitochondrial dysfunction, oxidative stress, and inflammation (9, 10). These processes are affected by genetic variants found in familial PD and also play a role in sporadic PD (9). Paraquat increases oxidative stress whereas rotenone causes mitochondrial dysfunction, but the processes are interrelated and both

pesticides ultimately affect both mechanisms (1, 9).

Other specific pesticides with more recent and stronger evidence of association include organochlorine insecticides. A large study of French farmers found that these pesticides as a group are associated with PD (11). Although for most pesticides the amounts found in blood or urine reflect only current exposures, organochlorine insecticides are an exception, with half-lives of years. Two studies that measured the amounts of organochlorines in serum determined that dieldrin (12) and beta-hexachlorocyclohexane (13) were elevated in PD patients. This corroborates an earlier observation that the amounts of dieldrin and gamma-hexachlorocyclohexane (lindane) were increased in the brains of PD patients (14). Notably, dieldrin and lindane increase oxidative stress and inflammation, cellular processes involved in PD pathogenesis (1, 10).

While there is good progress in examining the effects of individual pesticides, they are frequently used in combination, and the effects of mixtures need to be evaluated. Exposure to multiple pesticides may increase the risk of PD more than exposure to any one alone. For example, paraquat increased risk only 1.3-fold, but paraquat with either of the fungicides maneb or ziram increased risk up to threefold (6). Head injury increases risk of PD, probably by increasing inflammation. By itself, head injury increased risk twofold, whereas head injury together with paraquat exposure increased risk threefold (15). Smoking, by contrast, is inversely associated with PD, and effects of dieldrin were evident only in nonsmokers (12). These studies are intriguing, but each combination of risk factors has been evaluated in only a few studies, and replication is crucial.

Genetic susceptibility may also modify effects of pesticides on the risk of PD. Studies of gene variants related to pesticide metabolism and transport, to mitochondrial dysfunction and oxidative stress, and to familial forms of PD suggest that associations of pesticides with PD are stronger in genetically susceptible individuals (7). Again, most studies have assessed effects of pesticides as a group; studies of genetic susceptibility will prove most fruitful when they focus on specific pesticides.

As for other neurodegenerative diseases, recent work is also expanding our understanding of the role of pesticides. Two high-quality prospective studies—one in France and one of an agricultural community in the United States—found that chronic, low-dose exposure to any type of pesticide increased the risk of cognitive impairment, Alzheimer's disease, and other forms of dementia that arise later in life (16, 17). In a meta-analysis of nine epidemiologic studies, exposure to any type of pesticide increased the risk of amyotrophic lateral sclerosis nearly twofold (18), and a prospective study of U.S. farmers found that organochlorine insecticides were associated with amyotrophic lateral sclerosis (18). These results must now be confirmed, and as with PD, more details are needed regarding the effects of specific compounds.

The recent epidemiological studies provide much needed advances in clarifying the pesticide-PD relationship. That cellular processes important to PD are affected by specific pesticides underscores the importance of the epidemiologic findings. The most pressing need is for high-quality studies with data that are sufficiently detailed to identify essential aspects of exposure. What is the important life stage and time frame for exposure? Is it duration or intensity of exposure that is important—or both? Does exposure affect the progression of PD as well as risk? Above all, information on specific pesticides is imperative, not only to create a basis for prevention but also to provide clues for experimental mechanistic studies that may suggest therapeutic strategies.

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Exposure. Epidemiological studies suggest that pesticide exposure may increase risk of Parkinson's disease.