Parkinson's Disease and the Environment: What Scientists Know and Want to Know

In June 2007, 40 leading scientists, physicians, and patient advocates were invited to Sunnyvale, California, to evaluate the latest research on possible environmental triggers of Parkinson's disease (PD). Their goal was challenging: to reach a consensus on what science knows about factors conferring vulnerability to this common but poorly understood illness. Among neurodegenerative diseases, its incidence in the United States is second only to Alzheimer's disease.

Over three days, experts in genetics, epidemiology, neuroscience, and biochemistry reviewed new insights into PD's neurological underpinnings. Participating colleagues in related fields critiqued the analyses and conclusions.

The participants then crafted a document outlining not only their points of agreement but also findings and interpretations of the data about which they were less certain. Together, these assessments offer a roadmap for both researchers and funding agencies; conclusions point to where investments in Parkinson's research would appear to hold the potential for the biggest and quickest payoffs in understanding why at least one person in every hundred over the age of 60 develops this disease.

Patients, their families, and others interested in why many people get Parkinson's disease—but most don't—may also glean some appreciation for how challenging it is for physicians to try to answer all of their questions. Although much is known, too many gaps in the data remain.

The good news: More details are emerging every month to help explain how this illness ravages its victims' bodies. Eventually, these should help point toward ways to prevent the disease, or at least limit the speed at which it progresses.

A list of the participants and their consensus document can be viewed at (http://www.healthandenvironmental.org). What follows is a synopsis of issues with which experts attending the Sunnyvale meeting grappled, as well as the broader scientific and societal landscape in which these questions and issues are being raised.

Please note: Although some terms you encounter may be unfamiliar, they are defined the first time they are used. If you forget what they mean as you encounter them again, simply go to the back of the document where you'll find a helpful glossary of terms.

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Why Parkinson's? Why Me?

Each year, more than 60,000 Americans receive the disquieting diagnosis that they've developed Parkinson's disease (PD). In the United States an estimated 1.5 million people live with the movement disorder, which is characterized by tremor, muscle rigidity, postural instability (balance problems) and a slowing of the ability of muscles to respond to such simple brain commands as to rise from a chair, to walk—even to pick up a spoon. In extreme cases, voluntary movements virtually cease.

The diagnosis is complicated because other health problems have similar symptoms. Also, not all of the primary symptoms may be present in the early stages of the disease. Indeed, about 25 percent of PD patients never have a tremor. Parkinson's disease affects each person a little differently.

However, recent studies have begun pointing to PD as far more than just a movement disorder. For instance, dementia, depression, and changes in cognitive abilities oftenemerge as prominant features in advanced stages of the disease. Moreover, a host of nervous-system symptoms indicate PD may eventually impact broad areas of the brain—areas that coordinate everything from mood to heart rate and gut activity.

Men are twice as likely to develop the disease, for reasons that elude science. And although a host of new treatments are emerging to help ameliorate or slow the progression of symptoms, no cure exists.

Against this backdrop, nearly everyone who develops PD eventually asks his or her doctor: Why me?

And in nearly every instance, physicians offer the same unsatisfying answer: We don't know.

Yet Parkinson's disease doesn't strike at random. It only appears to because scientists have uncovered so few concrete data about what sets in motion the biochemical changes that begin to damage brain cells and eventually disconnect muscle activity from neural commands.

Certainly, one's genetic inheritance can play an important role in susceptibility to disease—including Parkinson's. Yet determining how and when genes will typically exert their influence in PD remains poorly understood. Moreover, genes alone may explain only a small share of the incidence of this disease. For the vast majority of Parkinson's patients, other factors are triggers. These, for want of a better term, are called environmental influences.

Environmental triggers might include what we've been eating, pollutants to which we've been exposed, climatic features, even the body's responses to unrelated illnesses.

There has been significant progress in identifying potential environmental links to Parkinson's disease, but advances have been proceeding slowly. Reasons include the relatively modest funding for basic research into movement disorders generally. Another major obstacle: an absence of data in most geographic regions that record who has been diagnosed with PD.

Research on other illnesses has shown that such geographic disease registries are often a pivotal first step in identifying clusters of sickness that may help identify a common cause.

Further exacerbating the problem of linking environmental factors to Parkinson's disease is the fact that this illness primarily afflicts people over age 60. They may attribute some of the early signs of PD to the normal aging process. Some may have trouble remembering or articulating predisposing events that may have occurred many decades earlier. Moreover, as people age, they may develop unrelated chronic ailments that make an accurate diagnosis more difficult. Understanding which symptoms trace to any individual condition can prove challenging and confound the skills of general practitioners and PD experts alike.

This document reviews what's known or strongly suspected about environmental risk factors for Parkinson's disease. Keep in mind, however, that many additional triggers may emerge as scientists continue to study this disease.

What Is Parkinson's Disease?

PD is essentially a disorder caused by a progressive degeneration of nerve cells, or neurons. This illness bears the name of the British doctor, James Parkinson, who first characterized the "shaking palsy" in a research report nearly two centuries ago. It wouldn't actually be known as Parkinson's disease, however, for another 45 years. That's what the French neurologist Jean-Martin Charcot termed it when he and a colleague began reporting some additional symptoms of the disorder.

In those early days, Parkinson's disease was considered a mysterious syndrome targeting motor neurons, cells controlling our limb movements. Understanding of a primary underlying biochemical feature of these cells in PD—their diminished capacity to make dopamine—wouldn't emerge for almost another century.

That's when the Swedish neuroscientist Arvid Carlsson demonstrated that dopamine was a neurotransmitter, which means a chemical that facilitates communications between nerve cells. Until that time (the late 1950s) dopamine was not considered a neurotransmitter in its own right, but merely a feedstock for another nerve-signaling agent.

Carlsson showed dopamine was present and active in areas of the brain that controlled limb movement. For his pioneering studies on dopamine, Carlsson would later share the 2000 Nobel Prize for physiology and medicine with two other neuroscientists.

Because of where dopamine plays a critical role in the brain—the movement-coordination center, or striatum—Carlsson had suspected a diminished output of this neurotransmitter might be linked to Parkinson's disease. Others would confirm it was.

Indeed, shortfalls of dopamine seemed to explain PD's cardinal symptoms—impaired handwriting, reduced arm swing, and a limp or tremor that initially affects one side of the body. Drugs that boost falling dopamine production would become the first useful therapies for tremor and other movement impairments associated with PD.

However, too little dopamine couldn't explain all of the symptoms that can accompany Parkinson's disease. And that's because brain regions where dopamine is not a major communications messenger also suffer nerve damage. Indeed, these regions may become affected long before those associated with movement.

Is It All in Your Head?

Although too little or too much movement is what tends to characterize Parkinson's patients, in fact, the muscles are not where the disease chiefly manifests itself. The brain is.

Roughly a century ago, pathologists autopsied Parkinson's patients, and identified a deterioration of cells in a part of the midbrain known as the substantia nigra. This dark tissue—whose name means, literally, black substance—loses nerve cells that produce dopamine. Ordinarily, the brain makes copious amounts of dopamine, and nerves in the substantia nigra rely on this chemical to help them signal when nerves that control movement should become active. However, once normal dopamine production drops by more than 20 percent, nerves, known as the basal ganglia that coordinate movements in a specific region of the brain, can fire uncontrollably. This gives rise to the inappropriate movements—and sometimes diminished movements—that typify PD.

However, emerging research indicates that these are far from the only brain cells that may be affected in Parkinson's disease. Some of the findings come from a team in Germany led by Heiko Braak at J.W. Goethe University. These scientists were curious about whether they could find any evidence that brain damage in PD patients progresses in some recognizable pattern.

And indeed it does. Writing in a 2003 paper in *Neurobiology of Aging*, they describe a fairly unvarying pattern of progressive damage—lesions—affecting brain neurons.

Braak's team showed that the substantia nigra "is not the first structure in the brain to develop PD-related lesions." Instead, the group found, the nerve damage begins far lower, in the brain stem, and then ascends with time into the substantia nigra and other areas.

Such findings "corroborate the assumption that the key lesions in PD begin developing—as in other neurodegenerative diseases—a considerable time prior to the appearance of [characteristic motor symptoms]," Braak's group concluded.

Indeed, animal studies indicate that some 50 percent of dopamine-making nerve cells may be dead or dying before an individual is diagnosed with PD, according to neuroscientist Silvia Mandel of the Technion-Rappaport Family Faculty of Medicine in Haifa, Israel.

Cause May Matter More than You Think

Understanding what triggered a case of Parkinson's disease is important for far more than settling the generally disquieting *why me?* question.

For instance, it would give researchers hints of where to look for underlying cell-altering mechanisms responsible for the disease. It's likely PD—as with cancer—can stem from any of many different causes. By understanding the initiating biochemical events, researchers may uncover ways to eventually halt the development or progression of this disease.

Knowing what triggered PD's emergence might also offer clues to the ultimate severity of an individual's symptoms, the pace at which they progress, even what treatment will prove most effective.

Moreover, data may eventually demonstrate that slowing or ameliorating the effects of PD will be more successful if begun during early stages of disease—before tremor and other characteristic symptoms emerge. In such cases, it becomes imperative to identify populations of people who face a greatly elevated risk of the disease and to screen them regularly for early markers of neurological change.

What kind of markers? Researchers might one day discover proteins in the blood, urine, or some other biological material that trace to characteristic changes in the brain. Such markers aren't yet known for this disease, but some have recently been found for Alzheimer's disease and other neurological disorders.

There is one imaging technology that can scout for abnormal protein-rich spheres—Lewy bodies—and other evidence of dying cells in regions of the brain ravaged by Parkinson's disease. Known as SPECT, for single-photon emission computed tomography—this nuclear-medicine technique uses emissions of gamma radiation from materials injected into the bloodstream to create digital images. A computer can reconstruct these images into three-dimensional pictures of interior structures. SPECT imaging can highlight damaged tissue or even the receptors for brain neurotransmitters, such as dopamine.

However, SPECT imaging is fairly expensive, not readily available in some smaller communities, and exposes the body to radiation. As such, this technology is not yet appropriate for broad screening of large segments of the population.

In fact, such screening is not even needed because, with few exceptions, clinicians cannot yet link an individual's development of Parkinson's disease with a particular environmental trigger. The encouraging news: growing cadres of researchers are aggressively probing to home in on just such links.

Puzzling Clues: Who's at Risk?

How's your sense of smell?

People with the classic tremor and motor difficulties typical of PD often have a poor sense of smell. Indeed, at least 70 percent of Parkinson's patients may suffer from such impaired olfaction, according to Caroline Tanner, who directs clinical research for the Parkinson's Institute. At the Sunnyvale meeting, she pointed to studies showing that nearly one-third of close

relatives of PD patients—their parents, children, or siblings—also can have an impaired sense of smell.

Does that mean these relatives face an elevated risk of developing PD?

Not necessarily. A host of brain problems may diminish olfaction. Head trauma is a common cause; it can damage nerves that conduct messages into the brain from smell receptors in the nose. For reasons that remain poorly understood, olfaction also diminishes naturally with age. Moreover, impaired olfaction can precede other neurological disorders. For instance, researchers at Rush Medical School in Chicago recently showed that losing one's sensitivity to smells can precede the development of Alzheimer's disease by up to a decade. So, a diminishing sense of smell is too nonspecific to signal incipient PD or even major vulnerability to this disorder.

However, waning smell sensitivity may serve as one of a constellation of symptoms that, when taken together, mark persons at elevated risk for developing Parkinson's disease. For instance, Tanner observes that PD patients commonly also exhibit such other nonspecific symptoms as chronic constipation, changes in the brain's pacing of heartbeats, and sleep problems.

In some cases, these symptoms may predate the tremors and more characteristic manifestations of PD. One Honolulu study, for instance, reported that daytime sleepiness was linked to increased risk of developing Parkinson's disease. The problem did not result from these people merely staying up too late.

REM sleep, named for the rapid eye movements that occur beneath closed eyelids, is ordinarily a deep and especially restful phase of any night's sleep. During this sleep phase, our muscles ordinarily undergo a near paralysis. So, your hand doesn't make a fist or your arm jab out in a punching motion if you dream of fighting off a mugger. However, some people suffer from REM sleep behavior disorder. Not only are these individuals prone to nightmares, but also to bursts of muscle movements—some of them violently active—as the body tries to act out events in dreams.

Daytime sleepiness in people who try to get a good night's rest might, therefore, signal undiagnosed REM sleep behavior disorder, commonly abbreviated as RBD. In fact, studies have begun pointing to RBD as a significant risk factor for PD.

In a landmark 1996 study, Carlos H. Schenck of the Minnesota Regional Sleep Disorders Center and his colleagues followed 29 men, all 50 and older, who had been diagnosed with the REM sleep disorder. Thirty-eight percent went on to develop Parkinson's disease, usually within a dozen years of developing RBD.

Ten years later, researchers in Spain, led by Alex Iranzo at the Hospital Clinic of Barcelona, investigated the neurological health of 39 men and five women in their late 70s who came into the clinic's sleep center and received a diagnosis of RBD. Twenty of the individuals—44 percent—went on to develop a neurologic disorder within five years. The most common diagnosis was PD, affecting nine people. Six more developed a dementia also characterized by a buildup of Lewy bodies in brain neurons.

In the British journal *The Lancet Neurology*, Iranzo's team concluded that RBD may point to people with early, symptomless neurologic disease. An accompanying commentary in that journal argued that "Patients with RBD may be the ideal candidates for clinical trials [to prevent or treat diseases such as PD]. And if such therapy ever becomes available, screening and identification of these patients will become an important public health measure . . . "

A related German study by Karin Stiasny-Kolster and her colleagues, published in *Brain* a year earlier, reported that among people with RBD and an impaired sense of smell, 18 percent went on to develop Parkinson's disease.

"Given the existence of advanced techniques for reliable measurement of olfactory performance," Braak's team says, an impaired sense of smell could prove useful "as one of the markers for early phases of PD." Similarly, his team notes, cues to this disease's development may be found in impairments of some of the brain's autonomic functions—such as heart rate, swallowing, sleep, and the pacing of food's transit through the gut. Each of these, in at least some PD studies, has been reported to precede the development of tremor and more classical Parkinson's symptoms.

Although these symptoms, especially when taken as a group, may help signal who faces an elevated risk of developing Parkinson's disease, these still don't point very selectively to a cause.

What about Genes?

Most people who develop Parkinson's disease do not exhibit symptoms until they are 50 or older. There are some, however, diagnosed at far younger ages—a few even in their teens.

It's possible that whatever environmental factor triggered an individual's PD occurred at an especially early age. However, recent studies have suggested another explanation for many of these early-onset cases: inherited gene mutations. These are permanent errors in the copying of a gene that will get passed along to future generations.

In June 1997, a team of scientists led by Mihael H. Polymeropoulos of the National Institute of Health's National Human Genome Research Institute reported finding the first Parkinson's disease gene mutation. Clues to its presence emerged from the study of a large Italian family, some of whose members emigrated to the United States in the early 1900s. In all, more than 60 members of the extended family—both in Europe and the United States—developed PD.

Ultimately, examination of the DNA from several of these individuals, along with that from a few Greek families with high rates of PD turned up a common mutation. It affects a gene that produces alpha-synuclein, a protein whose natural function remains unknown.

In Parkinson's patients, deposits of this protein can inappropriately build up in brain neurons responsible for controlling movement. The excess tends to deposit in tiny round features—the Lewy bodies mentioned earlier. These end up accumulating within nerve cells of the substantia nigra, where most of the brain's dopamine-making neurons reside. Although Lewy bodies had

been associated with Parkinson's disease since before World War I, it wasn't until 1999 that their primary ingredient would be recognized as alpha-synuclein.

So, did the mutant gene seen in some families at high risk for PD simply overproduce the protein? Or did it make a form the body couldn't easily eliminate? Those are current suspicions.

In 2000, Polymeropoulos's team would identify another mutation, this one associated with a few German families that also had an unusually high incidence of PD. Their defect, in a gene known as UCHL1, rendered cells where the gene was active unable to fully clean out their molecular excess. In this case, the excess would be alpha-synuclein and other proteins, though these proteins still perform some biological functions even when insoluable.

To date, scientists have linked Parkinson's disease with at least six other gene mutations Some of these inherited alterations in genes appear to increase the chance that someone carrying this variant will develop PD early—that is, below age 40—or very late. Among people born with at least one of the other gene mutations, disease typically occurs late, i.e., not until people reach their middle to late 80s.

Our genes come in pairs; we inherit a copy from each parent. Where a gene is dominant, it may exert its effect even if we inherit a copy from only one parent. For instance, the gene for brown eyes is dominant, so even if someone also inherits a gene for green or blue eyes, his or her eyes will end up brown.

The same holds true for disease-linked mutations. Some are dominant and can trigger illness even if we inherit a copy from only one parent. And that appears to be true for several of the genes that have been linked to PD.

However, gene mutations acting alone probably explain "less than five percent of all Parkinson's disease," according to epidemiologist William Scott of the University of Miami's Institute for Human Genomics.

That low number reflects a global average. In fact, inheritance of PD-linked gene mutations can be fairly common within certain ethnic groups, notes geneticist Andrew Singleton of the National Institute on Aging, a participant at the Sunnyvale meeting. For instance, he noted that some 10 percent of Portuguese individuals with Parkinson's disease possess such gene mutations, as do 20 percent of Ashkenazi (German) Jewish PD patients, and 40 percent of North African Arabs who have Parkinson's disease. "So," Singleton explains, in some populations, gene mutations appear to account for "a large proportion of Parkinson's disease."

Collectively, scientists at the Sunnyvale meeting concluded that such genetic mutations "account for fewer than 10 percent of PD in the US population."

However, even where PD-linked gene mutations don't act alone, they may still have some role in disease. For instance, some mutations may not foster disease except when some additional, normal gene is also present. And in families with high rates of Parkinson's disease, many

members may inherit both the mutation and some normally benign gene that can unleash the mutation's PD-fostering potential.

Or, some people with PD-linked mutations may need exposure to some triggering environmental influence. As epidemiologist Scott put it at the Sunnyvale meeting: "Genetics loads the gun," which may sometimes fire spontaneously, causing Parkinson's disease. But in cases where that metaphorical gun would not have gone off by itself, it would appear that "[environmental factors] can pull the trigger."

Although most PD researchers strongly suspect environmental factors can interact with gene mutations to cause PD, Singleton points out that no specific environmental factor has yet been *proven* to do so. But there are hints.

For instance, Scott's group found that within families—people who share many more genes in common with one another than with the general population—Parkinson's risk climbs with exposure to pesticides. Risk increased with both frequency of exposures and total cumulative exposures.

By comparing members of families who were exposed to pesticides with those who were not, Scott, *et al,* argue, it's possible to largely rule out that the association the researchers saw was due merely to genes. In fact, they conclude in the March 28, 2008, *BMC Neurology,* their findings suggest that families of PD patients "likely harbor genetic variants that are not sufficient on their own to cause disease but increase the susceptibility for disease development. An environmental insult, such as pesticide exposure, might exacerbate the effect of these genetic susceptibility factors and ultimately lead to sporadic PD."

In sum, genetic determinants of whether and when Parkinson's disease might develop are complicated and still being teased out.

This raises a natural dilemma. It's now possible to screen people for PD-linked gene mutations. Would there be much benefit, however, in knowing that one has inherited such a gene, especially if it may not cause disease unless turned on by some as-yet-unidentified environmental trigger?

It's a question most physicians—even neurologists—cannot easily answer.

About Risk Factors

Mention potential risk factors and most people envision dangerous behaviors such as smoking, lifestyle choices such as regularly dining on fatty foods, occupational hazards such as working with asbestos, or environmental exposures to disease-provoking agents such as ozone and cat dander. Scientists, however, often probe for positive *and* negative risk factors. The latter are features associated with a diminished chance of falling sick or dying prematurely.

A mix of such positive and negative risk factors have been associated with Parkinson's disease. However, it's important to recognize that because something is seen as a positive risk factor

doesn't mean it directly contributes to disease or that a negative risk factor protects against illness.

For instance, fair hair and blue eyes correlate with risk of sunburns and skin cancer. These physical traits identify people who have less skin protection than average from the sun's harmful ultraviolet rays. Obviously, it's the ultraviolet radiation that would cause skin cancer—not the mere presence of blond hair or blue eyes.

So, although some risk factors, such as inhalation of asbestos fibers, may directly cause harm, other risk factors may merely signal one's heightened or diminished vulnerability to some environmental trigger.

Take erectile dysfunction. Xiang Gao of the Harvard School of Public Health in Boston and his colleagues reported in the December 15, 2007, *American Journal of Epidemiology* on their analysis of 32,600 men participating in a long-running program called the Health Professionals Follow-Up Study. The researchers found that men who reported experiencing erectile dysfunction (ED) prior to 1986 were almost four times as likely to eventually develop Parkinson's disease as were men who had initially reported fine erectile function.

It's unlikely that a need for Viagra or some other ED medicine itself causes Parkinson's disease. Incipient vascular disease underlies most erectile dysfunction. It's therefore probable that some factor behind ED's vascular underpinnings either contributes directly to or signals some heightened susceptibility to what causes Parkinson's disease.

Moreover, many environmentally triggered diseases represent a multi-step process. Remove any one contributing step and disease may not occur or its severity may greatly diminish. That's likely to prove true with PD as well.

Are Pesticides a Problem?

A number of studies have found that agricultural workers sometimes face an elevated risk of developing Parkinson's disease. This has fueled an ongoing suspicion that agricultural chemicals—chiefly pesticides—are responsible.

Finlay D. Dick of the University of Aberdeen (Scotland) Medical School reviewed the recent literature addressing PD and pesticides, and in the June 2006 *British Medical Bulletin* reported that although many studies "found an association between pesticides and PD, . . . no one [causative] agent has been consistently identified."

At the Sunnyvale meeting, epidemiologist Freya Kamel of the National Institute of Environmental Health Sciences identified some of the pesticides under suspicion. Her list included organochlorine insecticides, such as dieldrin; herbicides such as paraquat, diquat, and glyphosate; fungicides such as maneb and dithiocarbamates; and organophosphates, such as the insect- and mite-killing parathion.

However, she noted that limitations on the data urge some caution in rushing to judgment on the role of pesticides in triggering PD.

Some studies, for instance, didn't focus on many people. That can weaken the studies' statistical significance, limiting the ability of its investigators to rule out that any apparent association with Parkinson's disease isn't simply due to chance. Sometimes, information on the magnitude or duration of exposures was weak. In still other instances, workers were exposed to many agricultural chemicals making firm PD links to any one of them impossible.

Such statistical weaknesses can plague even projects that were well designed and meticulously carried out.

For instance, a 2005 study by University of Washington researchers noted evidence of an apparent pesticides link to Parkinson's disease. Researchers had surveyed 250 men and women who had PD and another 388 who did not. Occupational exposure to agricultural chemicals—especially by people charged with directly applying pesticides—seemed to elevate one's chance of developing Parkinson's disease. However, the statistics were not strong enough to rule out that the observed associations were simply due to chance.

Still, Kamel could point to a few fairly strong studies.

In one, researchers led by Alberto Ascherio of the Harvard School of Public Health investigated pesticide exposures among 143,000 participants of the long-running Cancer Prevention Study II Nutrition Cohort. More than 7,800 of its participants reported having chronic exposures to pesticides, including 1,956 farmers, ranchers, and fishers.

Overall, "individuals exposed to pesticides had a 70 percent higher incidence of PD than those not exposed," the researchers reported in a 2006 paper in *Annals of Neurology*. That rate is in the same ballpark as rates reported four years earlier in a study involving nearly 8,000 male Hawaiian plantation workers growing pineapple or cane sugar.

Pesticides are used liberally on these crops. Men employed at least 11 years faced a 70 percent higher risk of developing Parkinson's disease than newer plantation workers. PD incidence among those employed at least two decades was higher still—nearly double the background rate.

Taken together with laboratory animal studies on pesticide links to PD, the plantation-worker data "implicate occupational pesticide exposure as a likely factor responsible for increased incidence of PD," concluded Helen Petrovich, of the Pacific Health Research Institute in Honolulu, and her coauthors.

Pesticides vary dramatically in their chemistry, function, and toxicity. Even well-designed and carefully conducted studies often have been unable to identify which ones might pose the biggest PD risks.

Consider a 2007 study reported in *Occupational and Environmental Medicine* by Dick and his colleagues. They probed for links between pesticide exposure and Parkinson's disease in workers

from five European countries: the United Kingdom, Italy, Sweden, Romania, and Malta. This study collected pesticide-exposure histories for 767 individuals with Parkinson's disease and almost 200 more with other types of Parkinson-like movement disorders. These were compared against chemical exposures by nearly 2,000 men and women free of these diseases. Persons who had sustained substantial occupational exposure to agricultural chemicals were 40 percent more likely to have developed Parkinson's disease than were those with little or no exposure.

Which pesticides? Unfortunately, the researchers found, the agricultural workers generally didn't know or couldn't remember.

That's one feature that distinguishes another 2007 paper, this one led by Kamel and her colleagues at three federal agencies and the Parkinson's Institute in Sunnyvale, California. It reviewed pesticide-exposure data for almost 80,000 US men and women. Among these participants, 161 persons ultimately developed Parkinson's disease. In the *American Journal of Epidemiology*, the scientists report finding that PD risk rose with the number of days a worker had been exposed to pesticides, and especially with having a job that required frequently applying pesticides.

Not surprisingly, the study found a PD link with exposure to some—but not all—pesticides. Among those linked with increased risk: the herbicides dicamba, pendimethalin, trifuralin, paraquat, 2,4,5-T, butylate, cyanazine; the insecticides dieldrin, maneb/mancozeb, and phorate; the fungicides chlorothalonil and benomyl; and the soil fumigants carbon disulfide/carbon tetrachloride; ethylene dibromide, and methyl bromide.

At the Sunnyvale meeting Kamel noted that a host of animal and test-tube studies "support the human data" by pointing to the mechanisms by which many current and formerly used pesticides might promote Parkinson's disease.

For instance, she noted, paraquat, maneb, and several other pesticides cause PD symptoms and other neurochemical changes in lab animals. Paraquat, dieldrin, and a few other pesticides poisoned dopamine-making cells that were growing in the test tube. In at least one study, paraquat and dieldrin were among pesticides that caused neural cells to begin accumulating alpha-synuclein. And several studies that administered rotenone—a broad-spectrum insecticide—have created a disease in rodents that mimics Parkinson's disease in nearly every respect.

A review of the pesticide-PD link by researchers in the United Kingdom concluded that, "at present, the weight of the evidence is sufficient to conclude that a generic association between pesticide exposure and PD exists." However, big caveats persist, its authors noted in the February 2006 *Environmental Health Perspectives*. For instance, they argued that the data were "insufficient for concluding that this is a causal relationship or that such a relationship exists for any particular pesticide compound"—alone or in concert with other environmental factors.

Although data remain fairly fuzzy the fact that so many studies have observed some trend of increasing PD risk with pesticide exposure "is a fairly strong piece of evidence," Kamel argued at the June 2007 Sunnyvale meeting.

Diabetes and Meddling Metals

Certain other environmental factors also have been linked with an increased likelihood of developing Parkinson's disease, albeit less strongly. Among these is development of diabetes and exposure to certain metals.

Some of these links remain curious. For instance, several studies have shown an elevated incidence of PD among patients with type 2 diabetes. The disease develops after the body begins ignoring the presence of much of its insulin. Once known as adult-onset diabetes, this metabolic disease increasingly has been showing up even in children.

But why would such a disease constitute an *environmental* risk factor? Many lifestyle factors have been strongly linked to heightened risk of diabetes—particularly obesity, sedentary lifestyle, and diets rich in fats and rapidly digested carbohydrates (such as sweet snacks, rice, potatoes, and breads). Moreover, some pollutants and toxic chemicals have recently been reported to heighten one's chance of developing diabetes. Among these are dioxin, arsenic, DDT, and some now-banned insecticides such as chlordane.

Why a metabolic disorder might be tied to Parkinson's disease remains murky. The apparent strength of the link, however, is tantalizing.

In one recent study, Finnish physicians followed PD incidence in more than 51,000 adults for roughly 18 years. Over that time, 324 men and 309 women were diagnosed with the disease. PD patients proved roughly 85 percent more likely than the persons without Parkinson's disease to also have developed diabetes—even after accounting for obesity, age, and other factors that appear to predispose people to the type 2 form of the disease. The findings appeared in the April 2007 *Diabetes Care*.

Three years earlier, researchers at Rush University Medical Center in Chicago observed a similar link in elderly Catholic clergy. They followed 822 of these individuals—both men and women—for up to eight years with detailed annual physical exams. Those who had type 2 diabetes proved more likely than the other volunteers to develop muscle rigidity and problems with gait—the ability to walk. "Diabetes may be a previously unrecognized risk factor for progression of parkinsonian-like signs in older persons," the researchers concluded.

Such findings also hint at an explanation for PD's link with heart disease. A May 2006 study by a team at Columbia University scouted for signs of mild parkinsonism in elderly men and women without dementia. Some 16 percent of the 2,286 people that they evaluated had mild parkinsonism—such as muscle rigidity and tremor. Elan D. Louis and Jose A. Luchsinger reported that this segment of the study population also proved more likely than people without signs of mild PD to have diabetes, heart disease, stroke, or peripheral vascular disease (usually a narrowing of vessels that carry blood to the legs, arms, stomach or kidneys due to a buildup of fatty deposits).

However, as so often happens in science, some findings directly contradict others.

An example of this shows up in a study of PD patients in the Seattle area. Researchers at the University of Washington found that in their analysis of 352 newly diagnosed Parkinson's patients and 484 people about the same age who were free of the movement disorder, having diabetes appeared to have *lowered* an individual's risk of developing PD.

These apparently contradictory data don't necessarily mean that any of the studies' findings are wrong or that the studies were performed poorly. Rather, it may mean that one or more of the investigations may not have recruited enough people, have run long enough, included a sufficiently representative sample of the population to be able to identify or characterize risks accurately, or accounted sufficiently for other possibly confounding factors (such as health, occupation, or diet).

Indeed, that's why research groups often try to *replicate* the findings of others by essentially repeating an investigation in people, animals—even cells—that may identify limitations to the findings. Then, scientists often look at the combination of studies collectively and evaluate the "weight of the evidence." If most of the data point to one conclusion, and a few point toward another, researchers will tentatively assume the majority findings valid. And keep accumulating additional data.

Parkinson's disease risks from exposure to metals offer another example of contradictory data. Several studies suggested that inhalation of "welding fumes"—air pollution rich in iron and manganese—might be linked with an elevated risk of PD. Yet studies that set out explicitly to test this hypothesis have largely come up empty.

In other words, the data don't clearly indict these metals—or firmly exonerate them.

Of course, that's not the nuanced message you'll receive perusing websites sponsored by attorneys for plaintiffs who claim they've been harmed. One, for instance, states flatly that "manganese can cause Parkinson's disease" and then asks individuals who think they might have been harmed from workplace exposures to submit details of their manganese claim "for a free, no obligation case review." Another website for a North Carolina lawyer noted that a lawsuit over exposure to welding fumes was settled, compensating a shipyard worker "more than $1 million" for his neurological symptoms. That site claimed there are many thousands more cases being prepared against welding companies.

However, science and the law are very different. Science hasn't proven the link, even if some companies find it prudent to settle rather than defend themselves in the face of uncertain science.

What is that science?

A 2005 Mayo Clinic study used magnetic resonance imaging (MRI) to study the brains of eight career welders who had developed significant neurological problems after years of working in a poorly ventilated environment. Five exhibited tremor, one a shuffling gait, and all exhibited a number of neurological problems. MRI scans showed an abnormal signal in the same part of each patient's brain—the basal ganglia, which coordinates movement. Over time, as some of the

men left welding or underwent therapy to remove manganese from their bodies, the signal weakened or disappeared.

A second study that year, this one by researchers at Karolinska University Hospital in Stockholm, also found basal ganglia problems—including Parkinson's disease—in Swedish welders. This study compared the reported incidence of PD and other movement disorders among nearly 50,000 welders during a roughly 40-year period beginning around 1960. The scientists compared this rate to the rate of those same problems in other workers. In this massive nationwide study, the researchers reported finding "no support for relation between welding and Parkinson's disease or any other specific basal ganglia and movements disorders."

Yet a third study published that year by researchers from three medical schools and the Parkinson's Institute also looked at the welders' issue. In a study examining the medical records of 2,249 patients with PD or Parkinson's symptoms, a number of professions were significantly overrepresented among people with these movements disorders. Welders, notably, were not among them.

So, does that mean previous links to manganese are spurious?

Not necessarily. In 2000, researchers at the University of California, Santa Cruz, exposed rats to a chemical that induced PD-like reductions in the brain's production of dopamine. However, the animals exhibited normal behavior and their ability to walk and run appeared unharmed—unless they had also received injected manganese.

Animals exposed to both, despite having the same dopamine condition, exhibited a number of adverse neurological changes, such as less activity in frightening situations, gait abnormalities, and impaired balance. Donald R. Smith and his colleagues concluded that manganese might exacerbate the neurological impacts of dopamine loss—even if it was not responsible for that dopamine loss.

Three years later, Karen M. Powers and her colleagues at the University of Washington linked diets high in iron to a 70 percent increased risk of developing Parkinson's disease. People who consumed diets especially rich in both iron and manganese faced almost double the risk of developing PD as did persons who typically ate foods low in these metals.

At the June 2007 meeting in Sunnyvale, Jane Hoppin of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, reviewed evidence linking PD to metals. As for manganese, it can be toxic, she acknowledged. Affected individuals even exhibit problems with controlling movements. However, although some of these movement issues appear commonly in PD, the manganese poisoning actually seems to create "a different type of movement disorder," she said.

It creates "some parkinsonism—but not PD," she concluded. Scientists at the Sunnyvale workshop agreed there were insufficient data to link welding or manganese with PD. The group did not rule out that some heavy metals might play a role in Parkinson's disease. However, it concluded that current data, although somewhat suggestive, remain inconclusive.

For instance, Hoppin noted that "iron levels are higher in patients with Parkinson's disease and that some dysfunction in cell regulations contributes to that." Although an inappropriate iron buildup may foster PD, she said, most of that buildup stems from "an incorrect processing of iron in people with PD."

Bottom line: this would suggest that any iron problem might not be environmental so much as some undiagnosed biological trait in a small share of the population.

Lead is another story.

Hoppin pointed to a December 2006 paper that measured lead concentrations in the blood and bone of 121 people with Parkinson's disease and another 414 people without the neurological disorder. Steven Coon of the Henry Ford Health System in Detroit and his colleagues divided all of the subjects into four groups—or quartiles—based on how much lead was measured in their bodies. For those in the highest quartile, Parkinson's disease risk was double that of people in the lowest lead quartile.

"I think this is the strongest evidence to date for an association with lead," Hoppin told the Sunnyvale workshop. Then again, she added, "it's really the only evidence to date."

Head Trauma and Drugs

Muhammad Ali is one of the better-known champions of Parkinson's research. Its value is something the three-time world heavyweight champion learned the hard way. Being knocked around the boxing ring for many years may have contributed to his Parkinson's disease. Although not appreciated when Ali first started boxing, head trauma now appears to pose a significant risk of neurodegeneration. The link remains tentative, but data supporting this continue to grow.

For instance, in one study, researchers at the Mayo Clinic in Rochester, Minnesota, compared risk of Parkinson's disease among nearly 200 individuals who suffered a serious head injury over a two-decade period and a similar number of people who never experienced such head trauma. People who sustained major head injuries were more than four times as likely to develop PD as were other people their age and gender.

The risk appeared limited to cases where a patient had experienced loss of consciousness or severe injury. Among these individuals, the likelihood of developing Parkinson's disease was 11 times that in the trauma-free individuals.

At the Sunnyvale workshop, Samuel M. Goldman of the Parkinson's Institute noted that risk of PD also seems to increase with the number of head injuries, with loss of consciousness associated with injuries, and with the duration of unconsciousness.

This has begged the question: does head injury lead to PD directly or does it merely accelerate the development of disease in people destined to get it?

It's an issue Goldman's group has been exploring in a unique population: twins. And while the jury is still out, he says "there's some suggestion that this may be true." In families where both twins would eventually develop Parkinson's disease, his team found that symptoms emerged earlier in the twin who had experienced serious head injury at some point in his or her past.

Why does some blow to the noggin matter? At this point, no one's sure. However, Goldman observes, head trauma can trigger changes in blood flow to various parts of the brain that may persist for years, even after "run-of-the-mill, moderate head injuries." Something known as oxidative stress can accompany such injuries. That oxidation sets in motion chemical chain reactions that can be quite biologically damaging.

In the United States alone, an estimated 3.4 million head injuries occur each year. Although the number may seem large, Goldman notes that Parkinson's disease typically won't show up for years to decades. The good news: this means there is a "window of opportunity for intervention," he says. Unfortunately, what that intervention should be remains an enigma.

An even bigger population exposed to potential Parkinson's risks are people who take medicines. Many drugs affect the processes that seem to drive PD's progression or that have been identified as risks for PD. For instance, some turn on enzymes that may switch oxidation on or off in the brain. Some turn on or off the inflammation that can lead to cell injury or repair. Some aggravate diabetes. Some ratchet up dopamine production or diminish its activity.

It's not hard to imagine that one or more of these drugs—acting alone or together with some genes—might perturb activities in the brain in ways that could initiate or promote Parkinson's disease, according to Stephen Van Den Eeden of Kaiser Permanente in Oakland, Calif.

In fact, the situation that focused on the potential for drugs—or indeed, any environmental agent—to trigger PD symptoms was a spate of poisonings in the 1980s. The victims were a few people looking to get high on a synthetic, heroin-like narcotic known as MPPP. Soon after taking it, many of them began developing Parkinson's symptoms. Not only were they very young, but the progression of their disease was more rapid than had ever been witnessed previously.

This new parkinsonism was traced to an impurity known as MPTP. It developed in some batches of sloppily produced synthetic heroin. Although the MPTP was not directly toxic, a metabolite known as MPP^+ turned out to target dopamine-producing cells. Although the movement disorder it causes resembles PD, researchers have, over the years, identified some distinctive differences. For example, it does not produce Lewy bodies, which are considered to be a hallmark of PD. Still, this drug and the brain damage it causes have pointed the way toward investigating other environmental triggers for Parkinson's symptoms.

Evidence for Some Ironic Benefits

Some research has suggested that a history of vigorous exercise early in life may help protect against PD development. Israeli researchers have also linked substantial consumption of green

tea—or certain antioxidant compounds derived from the tea—to a reduced risk of Parkinson's disease, at least in animals and test-tube studies.

However, there is a certain irony to many of the lifestyle factors that have been linked with reduced risk of Parkinson's disease. That is they're not what most physicians would advocate as healthful. Among factors that have been linked with a diminished risk of PD: heavy caffeine consumption, smoking, high concentrations of cholesterol in blood—especially in women – diets rich in unsaturated fats, and high blood concentrations of the gout-fostering chemical urate.

The best known of these potentially protective environmental factors is cigarette smoking. Its correlation with a diminished incidence of PD has been witnessed in many studies, including an analysis of 12,000 men and women reported in the July 2007 *Archives of Neurology*. Beate Ritz of the University of California, Los Angeles, and her colleagues noted that people who smoke may develop Parkinson's disease, but at only about half of the rate seen in individuals who had never smoked.

The findings came from a synthesis of data from 11 previously published studies dating back to 1960. "For two decades, researchers have speculated that tobacco prevents Parkinson's," a report in *Science News* noted. But it quoted Maryka Quik of the Parkinson's Institute as concluding that the new Ritz analysis "is extremely convincing."

Experts at the Sunnyvale meeting also deemed the science "sufficient to conclude with confidence that cigarette smokers have a lower risk of PD than non-smokers."

People with diabetes may actually reap the biggest smoking benefit. Parkinson's disease risk among men who smoked is lower than in the general population, according to a 2006 study by Karen M. Powers and her colleagues at the University of Washington. However, people who experience the biggest reduction in PD risk are smokers with diabetes, they reported.

It's important to emphasize that authors of none of these papers would advocate anyone smoking to reduce PD risk. That's especially true because it's not clear how or why smoking might be beneficial. Indeed, it's possible that any benefit will depend on an individual's genetics. Moreover, smoking's ability to harm is legendary. Cigarette smoking's ability to elevate an individual's risk of cancer, heart disease, and lung disease far outweigh its apparent potential to diminish an individual's chance of developing Parkinson's disease.

However, there's a chance that nicotine—independent of tobacco products—might be used therapeutically. Indeed, Quik's team at the Parkinson's Institute announced preliminary success in monkeys treated with MPTP to induce Parkinson's symptoms. In December 2007, the researchers reported that when given nicotine, the monkeys needed far less medicine to control their Parkinson's symptoms.

And then there's caffeine, a drug naturally found in two of the most popular beverages consumed throughout the world—coffee and tea. A variety of studies have correlated diets high in caffeinated coffee with a reduced risk of Parkinson's disease.

The scientific support for coffee's benefit "isn't quite as good as it is with smoking," noted G. Webster Ross at the Sunnyvale meeting. Still, in some studies its benefits appeared "very strong" and coffee "has consistently shown a [PD] risk reduction of around 30 percent."

The brew's apparent benefit is also dose dependent: As consumption climbs, the risk of developing Parkinson's disease steadily falls. "This seems to be independent of other potential confounders," says Ross, who works for the Pacific Health Research Institute.

The protective effect is stronger in men—and less complicated. For instance, Ross noted that data from the huge and long-running Nurses Health Study, administered by the Harvard School of Public Health, indicate that although moderate coffee drinking appears to reduce a woman's risk of developing Parkinson's disease, abstaining from the brew or drinking lots actually elevated PD risk. In addition, the Harvard team has shown that any PD protection afforded postmenopausal women by coffee drinking seems to disappear if they also receive hormone-replacement therapy.

Although most studies have only questioned individuals on coffee drinking habits, the presumption, Ross says, is that the brew's caffeine is responsible for any benefit. Indeed, he notes, people who preferentially drink decaf coffee have the same risk of developing Parkinson's disease as abstainers. Reinforcing suspicions about caffeine's role: tea drinkers and people who drink caffeinated soft drinks also have a somewhat diminished risk of PD.

Urate offers another provocative link.

Rich diets and certain medicines can cause high concentrations of uric acid to build up in blood. When the body cannot metabolize—break down—this chemical or when other conditions overwhelm the body's ability to metabolize uric acid, salts of it develop. They're known as urate.

When crystals of urate build up in joints, gout—a type of arthritis—can develop. Excess concentrations of uric acid and urate have also been linked with kidney stones and cardiovascular disease. With this kind of bad reputation, it may come as quite a surprise that several studies have correlated high concentrations of urate with a reduced risk of Parkinson's disease.

At the Sunnyvale meeting, Michael Schwarzschild of Massachusetts General Hospital in Boston described the results of several of those studies. And when the findings of these are taken together, he said, urate begins "emerging as one of the most robust inverse associations with the risk of Parkinson's disease." In other words, as concentrations of urate in the body climb, the risk of PD falls.

One of the strongest of these studies was led by Marc Weisskopf of the Harvard School of Public Health, in Boston. His research team, which included Schwarzschild, analyzed data collected from some 18,000 men participating in a long-running Health Professionals Follow-up Study. The participants were divided into four equal groups, based on urate levels in the body. The risk of Parkinson's disease for those in the highest quartile was 55 percent lower than for those in the bottom quartile of urate. The researchers shared their findings in the September 1, 2007, *American Journal of Epidemiology*.

This apparently protective association held even after accounting for other potentially confounding factors, such as a participant's age.

Several months later, Schwarzschild and some of the authors on the earlier study examined the effect of urate-promoting diets on PD risk among the same participants. And they found that men eating diets that were expected to foster urate developed Parkinson's disease at about half of the rate seen in men eating foods least likely to promote urate.

They conclude that "data support urate as a potentially protective factor in PD and suggest that dietary changes expected to increase plasma urate level may contribute to lower risk." They published their findings in the April 1, 2008 *American Journal of Epidemiology*.

Schwarzschild's team has also begun exploring the potential for urate to slow the progression of established Parkinson's disease. Finding something that slows the rate at which symptoms worsen "is the holy grail of therapeutics," he notes.

At the Sunnyvale workshop he reported that although the findings are preliminary, he and his colleagues have detected "a dose-dependent decrease in the rate of [PD] progression." In other words, symptoms in patients with the highest urate concentrations tended to worsen at a slower pace than in Parkinson's patients with relatively low blood concentrations of urate.

This compound's potential protective effect appeared stronger in men. Then again, men typically have higher urate concentrations than do women.

Because uric acid is a breakdown product of chemicals known as purines, foods expected to foster urate would be rich in purines. These include organ meats (such as kidneys and liver), sardines, anchovies, seafood, mushrooms, beer, and certain vegetables like peas and cauliflower. However, researchers caution that before physicians advocate urate-enriching diets or patients attempt to self-medicate on such foods, any potential benefits "should be weighed against expected adverse effects"—including painful gout and other chronic diseases.

Tracking These and Other Provocative Leads

Studies have identified a number of additional features as possible triggers for Parkinson's disease. In some communities, people whose drinking water comes from private wells appear to face a higher risk of the disease than do those getting municipally supplied water. A suspicion that some pollutant may elevate risk is tantalizing but unproven.

A few studies have also suggested that diets rich in dairy foods might elevate PD. Or that people with sedentary lifestyles are at higher risk. And PD incidence appears to be well above the norm for farmers and farm workers.

Unfortunately, data for all of these associations are weak. Some studies lacked the number of participants to rule out an association due to chance. Or there might be alternative explanations

for the apparent risk. In some instances, a study might not be tightly enough controlled to do more than offer leads worth testing another way.

That's one reason why a number of researchers would like to see a national registry to track who develops Parkinson's disease, where they live, and various aspects of their family and work history.

If a cluster of disease turns up in the farm belt, it might point to certain agricultural chemicals in use there. If it only occurs in a few regions, the registry might point to some geologic explanation, such as some mineral in the soil or contaminant in the water supply. If the disease turned up in certain professions or ethnic groups, it might point to other risk factors, such as foods, cosmetics, or interactions between genes and something in the environment.

Currently, only Nebraska maintains such a registry. Begun in 1996, it has periodically shut down and restarted, based on the availability of funding. The data it's accumulated—shared only with researchers—come from physicians when they diagnose a new case or from pharmacists as they fill a prescription for medicines used to treat PD.

Although California has also signed a Parkinson's registry into law, the state provides no money for the acquisition or management of data. For that, the Parkinson's Institute has been soliciting private donations, both to run the project and to analyze the initial data the registry takes in.

The Muhammad Ali Parkinson's Research Center, in Arizona, has begun a volunteer national registry. It's limited, however, by the fact that people must actively seek out the organization and submit data. Moreover, there is no way to know how well these individuals represent Parkinson's patients around the nation.

A few issues are clear, however. One is that regardless of lack of definitive proof that any one environmental factor causes PD, many of the people living with Parkinson's disease firmly believe that environmental factors played a role in their illness' onset. Another is that people affected by PD are extremely anxious for information about potential causes and cures for the disease. And finally, there are many PD patients who would like to use the emerging data about environmental factors to encourage precautionary actions that just might prevent future cases of Parkinson's disease.

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GLOSSARY

Alpha-synuclein (α-synuclein) The name of a gene (also called *PARK1*) and of the protein that's made when this gene is turned on. This protein, whose natural function is largely unknown, is a primary constituent of the Lewy bodies found in certain dopamine-producing brain cells of Parkinson's patients. Recent studies have shown that PD can develop in people born with a mutant form of the alpha-synuclein gene or whose brain cells, for whatever reason, simply produce too much alpha-synuclein.

Autonomic A part of the nervous system controlled by the brain, independent of conscious action. For instance, heart rate, body temperature, and blood pressure are controlled by the body's autonomic nervous system.

Basal ganglia A cluster of nerve cells in the brain that coordinate movement. This cluster spans several segments of the brain, including its substantia nigra, striatum, and globus pallidus.

Bradykinesia Slowed movement, one of the four main symptoms of PD

Consensus statement A document drawn up by a group of people, often a panel of experts, that describes facts or conclusions upon which all agree.

Dopamine The major neurotransmitter, a chemical that ferries messages between nerve cells, in the brain's basal ganglia. Parkinson's disease is characterized by reduced production of this neurotransmitter.

Gait Manner or pace of walking. The muscle rigidity associated with PD often leads to a slow, shuffling walk and susceptibility to stumbling.

Gene Portions of DNA within the chromosomes that possess the code for making a particular protein. When activated, a gene triggers the production of a protein that turns on or modulates some specific biological activity.

Idiopathic Some disease or symptom of unknown cause.

Lesion A site of damage or detrimental physical change to biological materials. It can refer to anything from chemical changes in DNA or cells to wounds or abnormal growths in tissues.

Lewy bodies Round elements in dopamine-producing nerve cells of the substantia nigra that emerge following tissue damage or as these cells are dying. First described in 1912 by Friederich Lewy, it would be another 87 years before the primary constituent—alpha-synuclein—of these structures would be identified. Although a hallmark of PD, Lewy bodies are also a major feature of two other brain diseases causing dementia.

Motor difficulties Inability to coordinate the movements of voluntary muscles. Such difficulties, a hallmark of Parkinson's disease, can result in a halting or shuffling gait, occasional inability to

move—almost as if one's feet are glued to the floor, and a slowed walk. Stumbling may occur because of an accompanying impaired sense of balance.

MPPP (for (1-methyl-4-phenyl-4-propionoxypiperidine) An illegal opiate, a synthetic drug capable of inducing heroin-like euphoria. An occasional byproduct of this drug's preparation in the 1970s and '80s was an impurity known as MPTP.

MPTP (for 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) An impurity that showed up in some batches of the illicit opiate MPPP, due to poor production techniques. In the brain, MPTP becomes transformed into a chemical that kills dopamine-producing cells. This triggers an especially rapid development of Parkinson's symptoms—sometimes within just days.

Mutation Permanent alteration in a gene, one that can be passed along to future generations. Some pollutants, such as radiation or toxic chemicals, induce mutations. Others appear to just occur spontaneously—for no apparent reason.

Neurodegeneration Deterioration of nervous-system tissue, such as in the brain, that leads to a progressive loss of function.

Neurology This is the field of medicine and research that focuses on the nervous system. A neurologist is a medical specialist trained to diagnose and treat nervous-system disorders caused by disease and injury. Parkinson's disease is a neurologic disorder.

Neurons Nerve cells that send and receive electrical signals. PD develops as a result of damage to particular families of neurons, especially those (motor neurons) that trigger the activity of muscles.

Neurotransmitter A chemical that relays a signal across the small gap separating the end of one nerve cell from the beginning of another. The brain's diminished ability to make dopamine, one of the neurotransmitters active in transmitting signals in its motor-control areas, is a hallmark of Parkinson's disease.

Olfaction Sense of smell. For reasons that remain unknown, most people with Parkinson's disease suffer a diminished threshold to smells.

Oxidation Chemical reaction in which an ion—a molecule with an unpaired electron—robs a neighboring molecule to obtain the missing electron. This process can be quite damaging to cells. Indeed, the body relies on this process to destroy aged cells, foreign intruders such as germs, or molecular trash. However, if the process isn't kept in tight control, healthy cells may be injured or damaged, contributing to disease. To shut down oxidation, the body employs any of several compounds known as antioxidants.

PARK A family of genes—nine are known so far—that have been associated with significantly increasing the chance an individual will develop Parkinson's disease. They code for a range of proteins that play a role in the disease. For instance, *PARK1* codes for alpha-synuclein and *PARK5* for UCLH1.

Parkin one of the genes implicated in causing a rare, early-onset form of PD.

Parkinsonism Several disorders characterized by motor impairments include bradykinesia, muscle rigidity, tremor, and problems with gait and balance. The primary form, known as Parkinson's disease, tends to be idiopathic—meaning it has no known cause. In fact, "most forms of parkinsonism are idiopathic," according to the National Institute of Neurological Disorders and Stroke.

Parkinson's disease (PD) A progressive, degenerative disease affecting the central nervous system, named for James Parkinson, who first described it in 1817 as "the shaking palsy."

Postural instability Impaired balance, one of the four main symptoms of PD.

Quartile Twenty-five percent of the members in a group of participants in a research trial. All participants are stratified by some characteristic, such as weight, exposure to some substance such as a pollutant, consumption of some food, or amount of some substance in the body. This allows comparisons of the lowest and successively higher groups.

REM sleep behavior disorder (RBD) REM, which stands for rapid eye movement, is a phase of deep sleep, where the muscle activity normally becomes disengaged from thoughts—dreams. However, in some people, the muscles tend to inappropriately act out what's happening in a dream. Many such people actually experience frequent nightmares and violent kicking and arm movements. People who experience this sleep disorder are at greatly elevated risk of developing neurological disorders, especially Parkinson's disease.

Striatum A region of the brain where dopamine-producing neurons release this neurotransmitter.

Substantia nigra An area of the brain that controls movement. PD symptoms develop and worsen as the dopamine-producing nerve cells in this region die off.

Nigrostriatal Relates to or joins the corpus striatum and the substantia nigra in the brain. In this context, the *nigrostriatal* dopamine pathway degenerates in Parkinson's disease.

Rigidity One of the four main symptoms of PD, this stiffness can affect the limbs and trunk. Affected parts of the body resist movement, even when pushed by another individual.

Risk factors Habits (such as smoking), biochemical features (such as high cholesterol or high blood pressure), environmental exposures (such as lead in drinking water), events (such as pregnancy late in life), and behaviors (such as a sedentary lifestyle) that have been correlated with a significantly elevated—or reduced—chance that some health endpoint (sickness, chronic disease, even death) may occur.

SPECT A type of three-dimensional X-ray imaging of the brain. SPECT stands for: single-photon emission computed tomography.

Tremor One of the four main symptoms of PD, this trembling can affect the hands, arms, legs, jaw, or head.

UCHL1 A gene that codes for the body's production of a particular protein (ubiquitin carboxy-terminal hydrolase L1). This protein usually helps a cell dispose of what it doesn't need—trash. A mutation—or defect in this gene (sometimes known as *PARK5*)—can result in cells that accumulate toxic concentrations of certain wastes (see http://www.in-cites.com/papers/MihaelPolymeropoulos.html).

ADDITIONAL SOURCES OF INFORMATION ON PARKINSON'S DISEASE

GOVERNMENT ORGANIZATIONS

Medline Plus (A service of the National Library of Medicine)
Parkinson's Disease
http://www.nlm.nih.gov/medlineplus/parkinsonsdisease.html

National Institute of Neurological Disorders and Stroke
NIH Neurological Institute
PO Box 5801
Bethesda, MD 20824
Ph: 800-352-9424

And its Parkinson's disease home page
http://www.ninds.nih.gov/disorders/parkinsons_disease/detail_parkinsons_disease.htm

and condensed version:
http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm?css=print

Nebraska Parkinson's Disease Registry
Nebraska Dept. of Health and Human Services
Data Management Section
PO Box 95026
Lincoln, NE 68509-5026
Email: parkinsons@dhhs.ne.gov
http://www.hhs.state.ne.us/ced/parkinsons/index.htm

PRIVATE ORGANIZATIONS

American Parkinson Disease Association
135 Parkinson Avenue
Staten Island, NY 10305
Ph: 800-223-2732 or 718-981-8001
Email: apda@apdaparkinson.org
http://www.apdaparkinson.org/user/index.asp

The Collaborative on Health and the Environment

PO Box 316
Bolinas, CA 94924
Ph: 415-868-0970
Email: info@HealthandEnvironment.org
http://www.healthandenvironment.org

The Michael J. Fox Foundation for Parkinson's Research
Church Street Station
PO Box 780
New York, NY 10008-0780
Ph: 800-708-7644
http://www.michaeljfox.org/

National Parkinson Foundation
1501 N.W. 9th Avenue / Bob Hope Road
Miami, Florida 33136-1494
Ph: 800-327-4545 or 305-243-6666
Email: contact@parkinson.org
http://www.parkinson.org

The Muhammad Ali Parkinson Center, a National Parkinson Foundation Center of Excellence
500 W. Thomas Rd., Suite 720
Phoenix, Arizona 85013
Email: info@maprc.com
http://www.maprc.com/

The Parkinson Alliance
PO Box 308
Kingston, New Jersey 08528-0308
Ph: 800-579-8440 or 609-688-0870
http://www.parkinsonalliance.org/

The Parkinson's Action Network
1025 Vermont Ave, NW Suite 1120
Washington, DC 20005
Ph: 800-850-4726 or 202-638-4101
Email: info@parkinsonsaction.org
http://www.parkinsonsaction.org/

The Parkinson's Disease Foundation
1359 Broadway, Suite 1509
New York, NY 10018
Ph: 800-457-6676 or 212-923-4700
Email: info@pdf.org
http://www.pdf.org/

The Parkinson's Institute
675 Almanor Avenue
Sunnyvale, California 94085-2934
Ph: 800-655-2273
http://www.thepi.org/site/parkinson/

Parkinson's Disease Trials
Ph: 800-801-9484
http://www.pdtrials.org/front/

We Move
204 West 84th Street
New York, NY 10024
Email: wemove@wemove.org
http://www.wemove.org/
Parkinson's disease home page
http://www.wemove.org/par/