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Parkinson's: the weirdest disease

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Commentary

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I have the weirdest disease. Oh, I know many people with chronic diseases make that claim, but I will challenge them, symptom for a symptom, side effect for side effect. For example, I would be less likely to have my disease if I had ignored my mother's pleas to drink my milk since milk-drinking is a risk factor. And much less likely to have my disease if I had been a heavy smoker. That's right, nicotine is a strong protective factor. One treatment for my disease makes it more likely that I will become a gambler. Another treatment can be rendered ineffective by lightning. The list of individuals with whom I share my disease includes Francisco Franco, Mao Zedong, and Adolf Hitler. And that is just the beginning.

Writing at my desk shortly after my 74th birthday, I noted my left-hand shaking. When I focused on it, it stopped shaking but then immediately began again when my attention was diverted. This was clearly the resting tremor of Parkinson's disease. At the time it did not seem like a big deal. Seven years earlier I had been diagnosed with prostate cancer with a Gleason score of seven out of ten. This score is not like Ms. Perry's fifth-grade weekly spelling test, where seven out of ten earned a silver star. On the Gleason test, seven out of ten may simply earn you an obituary. Once you have danced with the Big C, other partners seem bland. So, my Parkinson's disease was not likely to be a biggie, or so I thought. One year after the onset of my disease, an article was published reporting that people with Parkinson's disease are disproportionately likely to be diagnosed with prostate cancer, but a more recent study failed to replicate this. We are also known to be more susceptible to developing malignant melanoma. What is this all about? Genes, vitamin D, sunlight? Who knows. Welcome to the weirdest disease.

For the first several years I regarded my symptoms primarily as a nuisance. The tremor and slowed movements associated with the disease combined to make hand movements difficult. Getting things out of my pocket, fastening my seat belt, or doing buttons loomed increasingly large. I have been pleasantly surprised at how helpful strangers, especially women, have been as I struggle to fish out my credit card in the Safeway checkout line. As usual in such situations, personal vanity won out and the early symptoms that bothered me most were my Parkinson's-associated masked facial expression, making me look like Boris Karloff, and drooling. The latter is caused by a loss of the normal swallowing reflex, so that saliva pools in your mouth unless you intentionally swallow. Failure to do so results in drooling, which is socially noxious; on the road of life, it suggests that the next stop should be a nursing home.

Milk and Marlboros

Like most people who are diagnosed with a chronic disease, I wanted to know what had caused it. If I was going to have to live with a disease which effects almost 1 million Americans, I felt entitled to know where it had come from. We know that the definitive cause of Parkinson's disease is the death of dopamine-producing cells located in the midbrain. What we do not know in the vast majority of cases is what causes the cells to die.

The few cases for which we know the cause provide us with some clues regarding the others. For example, in the 1920s thousands of people developed the symptoms of Parkinson's disease following the epidemic of encephalitis lethargica, apparently caused by an infectious agent. Thus, we know that infectious agents can cause Parkinson's disease. It was the residual patients from this epidemic that were the subject of Oliver Sacks's book *Awakenings*, subsequently made into a movie starring Robin Williams as a doctor who gives the patients a new drug, producing a dramatic improvement in their symptoms. In a tragic coincidence, 24 years later Williams himself was diagnosed with Parkinson's disease, and 3 months later he hanged himself. Similarly, an outbreak of Parkinson's disease in the 1980s among individuals who had been exposed to a toxic chemical, methylphenyl-tetra-hydropyridine (MPTP), told us that chemicals may cause this disease. Head trauma can also cause Parkinson's disease, as was demonstrated by Mohammed Ali. And about 5% of cases, especially those beginning at a young age, are known to be caused by genes. Together these known causes account for no more than 20% of cases; the cause of the other 80% is still unknown.

Other clues to the causes of Parkinson's disease have been sought in prospective, longitudinal studies. In such studies data on dietary habits, smoking, and other aspects of lifestyle are collected from large groups of people who are then followed over many years to see what

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diseases they develop. For example, the Nurses' Health Study collected data from 121 700 nurses in 1976, then followed them for 30 years, during which time 508 nurses developed Parkinson's disease. Such prospective studies have identified both risk and protective factors for this disease, two of which are especially surprising. The first of these is milk drinking. Five prospective studies identified milk, but not cheese, yogurt, or butter, as a risk factor for Parkinson's disease, especially in men. The more milk people drank, the greater the risk of developing the disease. In one prospective study carried out in Hawaii, the men who drank the most milk more than doubled their chances of developing Parkinson's disease later in life (Jiang, Ju, Jiang, & Zhang, 2014).

What is going on here? Everyone knows that milk is one of the most healthful foods; it says so on the ubiquitous milk cartons in school lunch programs. Why do you think your mother always told you to finish your milk? Celebrities smiled at us with their milk mustache as part of the 'got milk?' advertising program. Is this some kind of bovine betrayal, a revenge of the cows? The risk does not appear to be related to the calcium or vitamin D in milk but may be associated with the fact that milk decreases serum urates, which are thought to be a protective factor for Parkinson's disease.

Even more surprising than milk as a risk factor for Parkinson's disease is nicotine being one of the strongest protective factors. This is true not only for smoking cigarettes but also for smoking cigars or pipes and for chewing tobacco. And it is equally true for men and women. It was first reported in the late 1950s but was assumed to be a statistical artifact until the 1990s when several prospective longitudinal studies also reported it to be true. Present smokers have the lowest rate of Parkinson's disease, followed by past smokers and then by people who have never smoked. The risk is inversely related to how long and how heavily the person smoked (Ascherio & Schwarzschild, 2016). Epidemiological studies have reported correlations between the rate of smoking and rate of Parkinson's disease in several countries; for example, in the USA as women began to smoke more in the 20th century fewer developed Parkinson's disease. Similarly, as smoking has decreased among men there are suggestions that the prevalence of Parkinson's disease is increasing. The magnitude of protection conferred by smoking reduces the risk of acquiring Parkinson's disease by more than half (Morozova, O'Reilly, & Ascherio, 2008).

This finding has troubled public health experts because it is so counterintuitive. Everyone now knows that smoking is bad, that the Marlboro man died from lung cancer and that smoking causes several other cancers as well as chronic obstructive pulmonary disease (COPD), heart disease, and stroke. Extensive efforts have been made to explain away the nicotine findings, but all have failed. Nicotine remains one of the strongest protective factors against Parkinson's disease, perhaps because of its neuroprotective effects.

Freezing and drowning

Parkinson's disease is a progressive disease. Although I have always considered myself to be a progressive person, this is definitely not what I had in mind. After experiencing tremor and stiffness for about 7 years, my symptoms moved on to the next phase of the disease, politely called postural instability. This implies that I have bad posture, which is true but is the least of my problems. My sense of balance has slowly decreased so that, rather than walking around the house, I more often lurch unstably through an increasing labyrinth of grab bars and handrails. The experience is like being drunk all day, with all the mechanical disadvantages of being drunk but none of the cognitive advantages. (Aside, sotto voce: No, Lucas and Olivia, of course, Grandpa has never *really* been drunk.) A cane has become my best friend and a walker looks increasingly attractive. All efforts are designed to avoid the bête noire of Parkinson's disease – the fall. Early on I was disabused of the idea that it cannot happen to me when, at the top of the stairs, I realized I was carrying too much, tried to turn around, and fell backwards. My back made a perfectly symmetrical hole in the wallboard.

Associated with postural instability is one of the strangest symptoms of Parkinson's disease – freezing. This consists of a transient inability to move, usually lasting for only a few seconds and occurring most often when the person is starting to walk or turning around. It is also more likely to occur when the person is in a narrow space such as a doorway or closet. Thus, I am able to walk for 2 miles without freezing but, while making my breakfast and having to turn in our narrow kitchen, I freeze often. Freezing is dramatically illustrated in a YouTube video, accessible as Parkinson's bicycle, in which a man experiences marked freezing until put on a bicycle, which he rides with ease. Such an odd disease!

Books on Parkinson's disease usually describe freezing as feeling like your feet are glued to the floor. At least in my case, that is not quite the way it feels. Rather I would liken it more to T.S. Eliot's lines in The *Hollow Men*: 'Between the idea/And the reality/Between the motion/And the act/Falls the Shadow'. I decide to move and my brain sends a message to my feet but the message does not get through, apparently becoming sidetracked on the route. There are several strategies for breaking the freeze, including shifting your weight, taking baby steps, stepping over an imaginary line on the floor, counting, marching, or touching something. However, if you try and move before your feet are ready to go you will quickly confirm the law of gravity. Freezing in public can be quite embarrassing; a useful strategy is to pretend that you are deep in thought about some very important issue.

Parkinson's disease is full of surprises. I discovered this after having the disease for 7 years when we went to Maine for a week at a lake. I dove into the water from the dock, as I had done many times in the past, but suddenly discovered that I had lost my ability to swim. I had great difficulty keeping my head above water and, when I made swimming motions, I went nowhere. I briefly panicked and considered calling for help but with great effort, I affected an inelegant dog paddle that got me to the children's play area, where I could stand. At the time swimming problems were not listed in any of the books on Parkinson's disease, so it was a real surprise. It also reminded me of the drowning death of a good friend with Parkinson's disease 10 years earlier, and in retrospect, I realized what had probably happened. I later discovered that 1 year prior to my swimming episode an article had been published in a scientific journal describing three individuals with Parkinson's who had drowned after having undergone deep brain stimulation (DBS); the article implied that the neurosurgical procedure was to blame (Bangash et al., 2016). Two years after my experience another article described swimming problems in many Parkinson's patients, with or without DBS. Using underwater videos the authors showed that the problem was a lack of coordination between the upper limbs and lower limbs and an inability to keep the

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body parallel to the water (Neves et al., 2020). The experience led me to have a much greater appreciation of the complexity of normal body movements that we take for granted. I am reminded of this daily as I struggle to get out of bed or out of a car.

One final example of Parkinsonian symptoms adds an odd postscript to the discussion. Although the disease is best known for taking away people's motor skills, several studies have claimed that in a subgroup of individuals Parkinson's disease increases their creativity. One study claimed that this paradoxical augmentation of artistic talent occurs in as many as 20% of affected individuals (Inzelberg, 2013). The increased creativity may occur in individuals who have already exhibited artistic talent or may occur in individuals who have previously shown no special talent. Under the first category, Salvador Dali is often discussed since he developed Parkinson's disease in his later years. One study cited another artist who claimed that her Parkinson's disease enhanced her paintings and made them more vibrant.

Even stranger are the claims of individuals who, prior to the onset of their Parkinson's disease, had exhibited no special artistic talent. One individual, who had previously never written poetry, composed poems that won an international poetry prize. Another individual, who had previously shown no special literary skills, wrote a historical book that won a literary prize. It should be added that all of the individuals described in the studies were being treated for their Parkinson's disease with medication which enhances dopamine; this could explain at least some of their increased creativity. Indeed, there should be some bonus for having this unpleasant disease.

Gambling and lightning

There are two major treatments for Parkinson's disease – medications and DBS. Various medications have been available for 60 years in an effort to increase dopamine in the brain. The most widely used is levodopa, which is remarkably effective, especially in the early stages of the disease. However, levodopa also has side effects, and these tend to become more common and more severe as the medication is used for longer periods and at higher doses. The most common side effects are nausea, dizziness caused by a drop in blood pressure, and sleepiness, which may come on suddenly. Depression may also be a medication side effect, but it can also be a symptom of the disease, a logical reaction to having the disease, or all three. Decreased mental acuity is also listed as a side effect of the medication; however, since cognitive decline may also be a disease symptom it is difficult to differentiate the two.

The most serious side effects, usually beginning after several years of use, are involuntary movements, called dyskinesias, and hallucinations, which are usually visual.

But the most bizarre side effect of the dopamine-enhancing medications used to treat Parkinson's disease is an urge to gamble. This is said to occur in approximately 5% of patients, usually involving slot machines but also including lottery tickets, bingo, and casino gambling. One man was said to play slot machines all night long. A woman was described who played slot machines for 12 h a day, stealing money from her family and selling her jewelry to pay for her losses. Many of the patients who are affected with this gambling addiction lose large amounts of money and, in some cases, have to declare bankruptcy. In most cases, gambling addiction can be controlled by decreasing or discontinuing their dopamine-enhancing medication.

The second standard treatment for Parkinson's disease is the use of DBS which has been available for approximately 25 years. It consists of a battery-powered pulse generator that is neurosurgically implanted in the brain to control the tremors. The pulse generator is connected by a cable to a battery implanted in the chest wall and is activated or deactivated by an external electromagnetic source.

DBS has been a major advance in the treatment of Parkinson's disease, especially for patients who no longer respond to dopamine-enhancing medications. However, because electromagnetic fields have become so widely used in everyday life, the pulse generator may be inadvertently deactivated, causing an abrupt recurrence of the person's symptoms. In a few cases, this has led to emergency rehospitalizations. Among the devices known to have turned off the deep brain stimulators are mobile phones, store theft detection devices, airport security devices, dental tools, and electrical welding equipment. One man had his deep brain stimulator turned off while he was repairing his car radio. Another man had a violent recurrence of his symptoms when dancing past a large loudspeaker in a discotheque. A patient in Beirut, Lebanon with severe Parkinson's disease and a deep brain stimulator required emergency hospitalization when his device was suddenly switched off while he was sitting quietly at home. It turned out that the Lebanese prime minister had passed his house in a vehicle specially equipped with electromagnetic radio-jamming equipment used to de-activate remote explosive devices (Blomstedt, Jabre, Bejjani, & Koskinen, 2006). But perhaps the oddest one of all was the 66-year-old woman with DBS whose house was struck by lightning. Electronic devices in her home that were on at the time were destroyed. Her deep brain stimulator was turned off by the lightning but not otherwise harmed (Prezelj, Trošt, Georgiev, & Flisar, 2018).

Coda

My inquiry into the odd details of Parkinson's disease yielded an unexpected gift – a new friend. In 1817 James Parkinson, a 62-year-old London physician, published a 66-page monograph describing for the first time the symptoms of the disease to which his name would later become attached. He had previously published useful descriptions of gout and typhoid fever as well as the first description of the death of a child from a ruptured appendix. His interests extended to public health and he published medical information for laypersons, including an illustrated children's book on safety.

However, Parkinson's real interest was in geology and paleontology. He spent much of his free time collecting fossils, several of which bear his name and published three volumes on *Organic Remains of a Former World*, regarded as the first standard authority on the subject in England. In 1807 Parkinson and 12 others formed the Geological Society of London, the oldest geological society in the world. As if that was not enough, in his earlier years Parkinson had been a prominent political and social reformer. Writing under the pseudonym 'Old Hubert', he published pamphlets on the effects of poverty, the need for universal suffrage, the right of workers to organize and the importance of civil disobedience. For example, Parkinson wrote: 'It is repellent for free people to crouch like a camel to be loaded with every injustice a corrupt government can pile onto their backs.' Clearly, Parkinson was one of the most interesting and accomplished men of his generation.

But what of the future for those of us with Parkinson's disease? The obligatory adjective 'progressive' is never far from our vision despite the cheerful tone of most Parkinsonian blogs. Pneumonia

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and the consequences of falls are the most common disease-related causes of death. The most feared, however, is dementia which some studies report as occurring in as many as 80% of patients in the third stage of the disease. I deal with this on a daily basis by weighing whether and how much medication to take, and on a yearly basis by having a full neuropsychological battery. But my ultimate outcome, as the Greeks taught, has been determined by the Three Fates who assign individual destinations to each mortal at the time of birth. Beginning in Shakespeare's time these women were often referred to as the Weird Sisters, an appropriate designation for those determining the outcome of this weird disease.

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