

## PD: More than a Movement Disorder

What exactly is Parkinson's disease?

How we answer this question is not just a game of definitions, nor is it getting easier. But finding the answer is important because how we define Parkinson's is likely to be the difference between success and failure as we look for clues to the cause(s) and for ways to combat it.

James Parkinson, the English physician who first defined the condition clinically almost two centuries ago, called it the "shaking palsy." More than a century and a half later, neurologists began to define it as one of several "movement disorders," characterized by the classic triad of rigidity and slowness of movement, as well as the "shaking," or tremor, that had long been associated with Parkinson's.

The focus on these motor symptoms and signs was dramatically sharpened in the 1960s by the discovery that they were due to a loss of dopamine-producing cells in the brain that make up an area known as the "nigrostriatal system" and that these motor symptoms could be improved by administration of the dopamine precursor L-dopa. Yet even at the time of this breakthrough, doctors were becoming increasingly aware that their Parkinson's patients were showing up in their offices with other symptoms — among them, such diverse complaints as fatigue, constipation, depression and even diminished ability to smell — that seemed to be as different from one another as they all were from the physical-movement symptoms that had served for so long as the defining characteristics of PD. Indeed, these motor symptoms have become so ingrained in the medical lexicon that we now call them "parkinsonism."

What does this mean for our understanding and management of Parkinson's?

I believe it means that we have been defining Parkinson's too narrowly, and by so doing, have been restricting our investigations too much upon one part of the brain — the dopamine-producing nigrostriatal system — at the expense of other crucial areas of investigation. Put bluntly, it is

increasingly clear that "parkinsonism" — the motor aspects of Parkinson's — is only one characteristic of what is increasingly becoming seen as a multifaceted and complex disorder. No person who lives with Parkinson's (PWP) needs to be told this. It is their reports as much as anything else that have been prodding Parkinson's specialists and researchers to look beyond their natural "turf" — the dopamine-producing nigrostriatal system — to examine other areas of the brain and body.

So how, in light of this broader and more complex clinical evidence, do we go about re-examining the scientific theory of Parkinson's? One good place to start is with the

German scientist F.H. Lewy, who identified a distinctive type of matter in the brains of people who die with Parkinson's called the Lewy body. The presence of Lewy bodies in the brain has long been considered the pathological hallmark of Parkinson's disease.

What is less widely recognized is that Lewy described these bodies not in the nigrostriatal dopamine system, but in other areas of the brain. Also, they have since been found in other parts of the body, including collections of nerve cells that lie just outside the spinal cord (known as sympathetic ganglia) and the wall of the gut. In fact, it seems increasingly likely that Parkinson's does not begin in the nigrostriatal system, but possibly in the lower brainstem and the olfactory bulb (the part that controls ability to smell) or even the nerves in the heart and intestinal tract ... and that only at a later stage of the disease does it begin to affect the nigrostriatal system.

It is also becoming apparent that many of these changes outside the nigrostriatal system cause non-motor clinical symptoms that often predate the motor symptoms of Parkinson's. These are therefore often considered "predictors," or "biomarkers," of Parkinson's. I would argue that calling them "predictors" misses the point. The evidence is increasing that they are not just advance warnings of Parkinson's but are actually part of the condition itself.

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Take, for example, rapid-eye-movement sleep behavioral disorder (RBD) which is characterized by agitation and physical activity during sleep. It turns out that nearly 40 percent of men diagnosed with RBD develop Parkinson's later in life — on average, 13 years later. In these cases, RBD is almost certainly Parkinson's disease in the lower brainstem, before it has affected the nigrostriatal system and caused parkinsonism. Among people who already have been diagnosed with PD, 50 to 60 percent exhibit physiological evidence of the disorder, indicating that RBD is a common (though not universal) clinical sign of people with diagnosed Parkinson's.

Or take the issue of olfactory function (sense of smell). There is now literature suggesting loss of smell as an early sign of Parkinson's, with some studies showing olfactory abnormalities in up to 100 percent of people with Parkinson's. The German neuroanatomist H. Braak has observed that the olfactory sense is one of the first areas of the central nervous system to be affected by Parkinson's and should therefore be a part of a multifaceted diagnostic battery to detect "pre-parkinsonian" PD.

Another area of scientific interest is autonomic dysfunction — that is, problems with bodily functions over which we have no conscious control, such as the beating of the heart, sweating or bowel function. Several studies have shown that most, if not all, people with Parkinson's experience a loss of one component of the autonomic innervation of the heart (this phenomenon is known as sympathetic cardiac denervation). One could speculate indeed that fatigue, one of the most common complaints among people with Parkinson's, might be traced to diminished heart function.

Then there is the matter of constipation, another very frequent complaint among people with Parkinson's. First noticed by the eagle-eyed Dr. Parkinson, this problem was traditionally attributed to lack of activity, or inadequate hydration, or both. Then, in the late 1980s, scientists noticed the presence of Lewy bodies in the autonomic nervous system of the lower bowel, as well as in the esophagus. This suggests that swallowing, lower bowel and even bladder dysfunction are direct manifestations of the pathological process that underlies Parkinson's, and in fact may be one of the earliest features.

Lending support to this hypothesis is a surprising finding from the famous Honolulu Heart Program, a long-term study of 8,000 Japanese-American men born in the early years of the last century, and who have been followed medically since the 1960s. Unexpectedly, the study showed that men who reported less than one bowel movement per day in midlife were more than four times as likely to develop Parkinson's than men who reported two or more movements per day.

How do we connect the dots among these wide-ranging

observations? Increasingly, scientists are looking to do just this. One group has recently explored the link between the RBD syndrome and loss of the sense of smell. Their finding: an astonishing 97 percent of the RBD patients had also experienced loss of olfactory function.

How precisely we proceed from here — what new studies are needed, what symptoms we should be studying, how we can connect the dots among them, whether in fact we need to rename Parkinson's to redirect attention beyond its exclusively motor symptoms — is far from clear, and will require the attention of scientists from a variety of specialties and viewpoints. What is clear is that our concept of Parkinson's must change, perhaps radically.

We need, among other things, to broaden the clinical definition of Parkinson's to include all of the syndromes described in this article along with depression, anxiety and other problems that are commonly reported among people with the condition. This will serve as a constant reminder that we need to look at our patients as more than just victims of a failing nigrostriatal system, and look at a variety of other symptoms and signs — many of which do not traditionally fall within the purview of the neurologist. (This last point, incidentally, suggests that we either need to develop multi-disciplinary teams to treat these patients, or find some way to ensure that the neurologists who care for them seek much more diverse training.)

We also need to recognize that the observations reported in this article have profound implications for the investigation of the causes of PD, suggesting the need for studying mechanisms of neurodegeneration that underlie the entirety of the condition, not just the part that leads to problems with movement. Knowing how the disease evolves from its inception could be hugely important in suggesting clues to its cause. The process will also have implications for efforts to modify and slow disease progression before motor symptoms have emerged. Waiting until motor symptoms are clinically manifest, as we do today, forces us to confine our therapeutic efforts to the advanced stages of PD, when its burden may be too heavy and the options too limited.

I close by noting that none of the new dimensions of PD I have discussed here will be news to Parkinson's scientists. What may be new is that they are coming together in compelling ways and this process in turn is generating a growing interest in addressing them as a group. This will be important for the wellbeing of patients, for the understanding of doctors and for the potential of science to solve the Parkinson's mystery.

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If you have or believe you have Parkinson's disease, then promptly consult a physician and follow your physician's advice.

This publication is not a substitute for a physician's diagnosis of Parkinson's disease or for a physician's prescription of drugs, treatment or operations for Parkinson's disease.