SERGE BLOCH

PARKINSON'S DISEASE

4 BIG QUESTIONS

The characteristic brain pathology and motor symptoms of Parkinson's disease are well established. But the details of the disease's cause and course are much murkier.

BY SARAH DEWEERDT

	QUESTION	WHY IT MATTERS	WHAT WE KNOW	NEXT STEPS
1	***How does Parkinson's disease begin?***	Damage to neurons may begin up to two decades before symptoms appear. By the time the disease can be diagnosed clinically, it may be too late for disease-modifying therapies to work.	A variety of non-motor symptoms, including sleep problems, loss of smell and constipation, show up long before motor symptoms. But scientists don't know which individuals with these symptoms will develop Parkinson's.	Many scientists are searching for blood- or urine-based biomarkers, or imaging agents, that could objectively identify the risk of Parkinson's, but so far no leading contender has emerged.
2	***What is the role of the α-synuclein protein?***	If α-synuclein is one of the causes of Parkinson's, then therapies that stop it aggregating might be able to slow or even stop the disease's progression.	The brains of people with Parkinson's contain characteristic clumps of α-synuclein. But whether these clumps are the cause or merely a marker of the disease is not yet certain.	Several therapies that block α-synuclein are in early-phase clinical trials. And scientists are developing imaging techniques to detect α-synuclein in the brain. These might also aid early diagnosis.
3	***What is the role of the gut in Parkinson's disease?***	If the pathology leading to Parkinson's begins in the intestines, then it might be possible to stop the central nervous system from being affected by modifying gut microbiota or bolstering the health of the gut lining.	People with Parkinson's often develop gastrointestinal problems before motor problems emerge. Tell-tale aggregates of α-synuclein are found in neurons in the gut. But it is unclear whether gut pathology spreads to the brain, or brain problems spread to the gut.	Efforts to elucidate the earliest stages of Parkinson's will help to determine whether gut pathology is a cause. Broader efforts to understand the role of the gut–brain–microbiota axis in both health and disease could also pay dividends for those with Parkinson's.
4	***What is the best way to divide people with the disease into subtypes?***	Physicians need to be able to match the right drug to the right patient. Subtypes will help in the design of clinical trials of drugs and give patients and their families more information about the prognosis.	Patients with a tremor tend to have a better prognosis than do those with rigidity, slowness or mainly non-motor symptoms. Various mechanisms are thought to contribute to Parkinson's, but how the mix differs between individuals is unknown.	Genetic research has provided some clues. Studies in countries including the United Kingdom, Canada and Germany are tracking large patient cohorts. This should provide more information about the natural history of the disease.

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