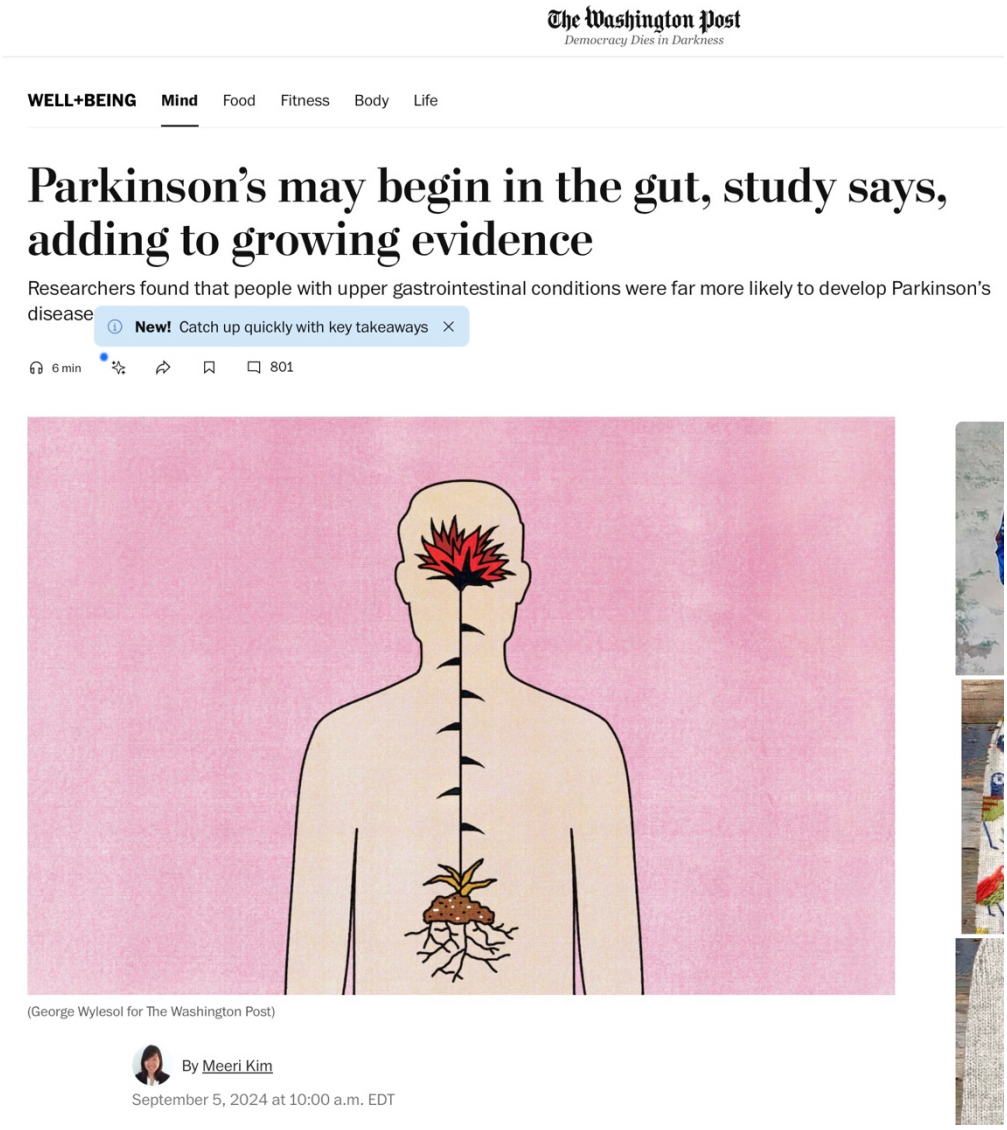

A new study adds to a growing body of evidence that Parkinson's disease, long believed to have its origins in the brain, may begin in the gut.

Gastrointestinal problems are common in patients with neurodegenerative disorders, to the point where a condition known as "institutional colon" was once thought to afflict those who lived in mental health institutions. In Parkinson's disease, the entire gastrointestinal tract is affected, causing complications such as constipation, drooling, trouble swallowing and delayed emptying of the stomach. These symptoms often appear up to two decades before motor symptoms such as rigidity or tremor.

"People have, for the longest time, described Parkinson's disease as a top-down disease — so, it starts in the brain and then percolates down to the gut, and

that's why patients have issues with their gastrointestinal tract," said study author Subhash Kulkarni, an assistant professor at Beth Israel Deaconess Medical Center. "Another hypothesis suggests that, in many patients, it may be a bottom-up approach, where it starts in the gut and goes all the way up to the brain."

Kulkarni and his colleagues found that people with upper gastrointestinal conditions — in particular, ulcers or other types of damage to the lining of the esophagus, stomach, or upper part of the small intestine — were far more likely to develop Parkinson's disease later in life. The study was published online Thursday in JAMA Network Open.

Trisha Pasricha, the senior author of the study, is the Ask a Doctor columnist for The Washington Post. She was not involved in the reporting of this article.

Mucosal damage is a risk factor for Parkinson's

The analysis involved 9,350 patients with no history of Parkinson's and who had had an upper endoscopy with biopsy between 2000 and 2005. Most were between the ages of 50 and 64 at the time of the procedure.

Mucosal damage — an erosion, break, or sore in the mucous lining of the gastrointestinal tract — was associated with a 76 percent greater risk of developing Parkinson's disease during the follow-up period, an average of 14.9 years for the whole cohort. Specifically, mucosal damage was defined as the presence of erosions, esophagitis, ulcer, or peptic injury on upper endoscopy or pathology reports.

Perhaps most notably, patients in the study suffered from their gastrointestinal issues long before discovering they had Parkinson's, most probably because they began experiencing motor symptoms. The average lead-time between the first detection of mucosal damage and an eventual diagnosis of Parkinson's was 14.2 years.

"We absolutely need to keep an eye on these patients who have a history of mucosal damage on their endoscopy," said Delaram Safarpour, an associate professor of neurology at Oregon Health & Science University, who was not involved in the research. Early detection of Parkinson's disease would allow doctors to treat these patients before they havemotor symptoms, when neuroprotective treatments become available in the future, Safarpour said.

Study supports 'gut-first' hypothesis

The results appear to support the "gut-first" hypothesis, proposed in 2003 by German anatomist Heiko Braak after several autopsy studies. As opposed to the "brain-first" hypothesis, it states that Parkinson's begins as misfolded proteins in the nerves of the gastrointestinal tract.

When the gut-first hypothesis "first came out, there was a lot of skepticism in the field," said Ted M. Dawson, Leonard and Madlyn Abramson professor in neurodegenerative diseases at Johns Hopkins University School of Medicine, who was not involved in the study. "But the evidence has been accumulating, and this study is another step in the stairway to acceptance that the gut is a major pathway by which Parkinson's can occur."

Normally, proteins fold into an ordered three-dimensional structure to become biologically functional. Misfolded proteins fail to achieve this form and can cause neighboring proteins to misfold, leading to large, toxic aggregates that disrupt the function of cells, tissues and organs in the body. For example, Alzheimer's disease is characterized by aggregates of amyloid-beta protein in the brain that form harmful plaques.

A neuronal protein called alpha-synuclein is the culprit in Parkinson's disease, and a diagnosis is typically confirmed by the discovery of alpha-synuclein pathology in the post-mortem brain. Several studies suggest that misfolded alpha-synuclein can spread from the gastrointestinal tract to the brain via the vagus nerve, a neural superhighway that connects the two.

For example, people with their vagus nerve cut — a last-resort treatment for peptic ulcer disease — have a lower likelihood of developing Parkinson's disease. Autopsy studies, including Braak's own experiments, have found aggregations of alpha-synuclein in the stomachand lower esophagus of Parkinson's patients, but not in controls. And studies in mice show that misfolded alpha-synuclein injected into the gut does travel to the brain, leading to Parkinson's-like motor symptoms and cognitive decline. Severing the vagus nerve completely protects the mice against such effects.

Rise in number of Parkinson's cases

Globally, the number of people with Parkinson's disease has doubled in the past 25 years, with some experts referring to this exponential surge as a "Parkinson pandemic." Parkinson's is the fastest growingneurological disorder worldwide, even surpassing Alzheimer's disease, according to

the Global Burden of Disease study, which pooled health outcomes data from 195 countries.

Much of the increase is because of an aging population, but the rise in incidence persists after adjusting for age-related factors. Only about 10 percent of cases can be traced to genetics, with the vast majority labeled as "sporadic" — without a known cause. Solving the mystery of why some people develop Parkinson's and others don't could lead to options for early detection, treatment and hopefully, one day, prevention.

The current findings suggest that damage to the lining of the gut could possibly be an inciting event that triggers the initial misfolding.

"It can be hypothesized that a destruction or rupture of the mucosal membranes leads to an aberrant deposition of alpha-synuclein in the mucosal tissue," Kulkarni said. "The damage to the mucosa is not allowing normal housekeeping functions to occur, and accumulation of alpha-synuclein always causes it to misfold."

In future work, Kulkarni and his colleagues plan to investigate the cellular and molecular changes that occur with mucosal damage and its effects on alpha-synuclein in the gut. Until then, experts recommend heightening monitoring of patients with mucosal damage and the timely treatment of conditions that may lead to mucosal damage, such as peptic ulcer disease, esophagitis and *H. pylori* infection.

"If we treat these patients appropriately, and the follow-up shows that the mucosal damage has been improved, is that enough to prevent future risk of Parkinson's disease or not?" Safarpour said. "I think that's an important point that needs to be studied."

"There is reason for caution, but there is no reason for panic. We are not saying that every person who has mucosal damage is going to develop Parkinson's," Kulkarni said. "There is an association and increased risk, and we have to figure out what are the mechanisms by which we can decrease the risk in these patient populations."

https://www.washingtonpost.com/wellness/2024/09/05/parkinsons-disease-gut-study/

We have gotten such things backwards for so long. If something isn't seen as primarily in our precious "mind" or brain, we refuse to credit it. Perhaps it is a aversion to mortality—"You mean I am not forever my consciousness?"—or a religious/spiritual refusal to give the body primacy in existential matters, but we need to rework all such concepts to fit it all together better in an under-standing that will not only be more true, but also better, not to be feared. TJB