

## Commentary

---

# Parkinson's Disease and the Gut: 'The Wheel Is Come Full Circle'

Ronald F. Pfeiffer\*

*University of Tennessee Health Science Center, Memphis, TN, USA*

In summarizing his thoughts regarding the possible pathophysiology of the disease process he had just described in his 1817 treatise and which would ultimately bear his name, James Parkinson commented:

*"Although unable to trace the connection by which a disordered state of the stomach and bowels may induce a morbid action in a part of the medulla spinalis, yet taught by the instruction of Mr. Abernethy, little hesitation need be employed before we determine on the probability of such occurrence"* [1].

It is both ironic and remarkable that now, almost 200 years later, the question of interaction between the gut and the brain in Parkinson's disease (PD) has resurfaced to become the subject of a veritable tsunami of fascinating and tremendously important research that has potential ramifications not only for understanding the pathophysiology of PD but also for its treatment and even its diagnosis.

During the past 30 years, gastrointestinal (GI) dysfunction has gained recognition as one of the more frequent and troublesome nonmotor features of PD [2, 3] and pathology within the enteric nervous system (ENS), including Lewy body formation and alpha-synuclein deposition, has been identified as part of the disorder [4–6]. Loss of dopamine neurons within the ENS also has been reported [6]. Braak et al. have proposed that PD actually has its genesis within the ENS and spreads from there via the vagus nerve to the central nervous system (CNS), initially establishing a beach-

head in the medulla within the dorsal motor nucleus of the vagus (DMV) and progressing from there up the brainstem, eventually to reach the substantia nigra and beyond [7, 8]. It has further been proposed that the spread of pathology in PD may be from neuron to neuron in a prion-like process [9, 10]. The idea that PD might have its origin within the ENS has received epidemiologic support from findings that bowel dysfunction may become evident in individuals as much as 12–20 years before the classic motor features of PD make their appearance [11, 12]. Thus, the supposition has developed that the GI symptoms of PD and their development early in the course of PD are due to the involvement of the ENS during what is now labelled the premotor phase of PD.

However, things are not always as straightforward as they seem. The current report by Corbillé and colleagues [13], coupled with an earlier report by Annerino et al. [14], seem to clearly indicate that there is no actual loss of neurons in either the submucosal or myenteric plexus of the ENS in PD. Both groups of authors assert that the loss of dopamine neurons in the myenteric plexus reported by Singaram et al. (full disclosure: I was one of the et al.) almost 20 years ago was artifactual. They may be correct, but it may be worth noting that the patients studied by Singaram et al. were individuals with very severe constipation - so severe that 9 of the 11 had undergone colectomy because of intractable constipation (colon tissue from the other two was obtained at autopsy) - and thus they may not be comparable to the patients studied more recently in whom the presence and degree of constipation was not characterized but presumably was less severe. It also seems peculiar that an artifact would affect only the PD patients.

---

\*Correspondence to: Ronald F. Pfeiffer, University of Tennessee Health Science Center, Memphis, TN, USA. E-mail: rpfiffe@uthsc.edu.

Nevertheless, the recent reports seem quite convincing and thus call into question the origin of GI symptoms in PD. Do they arise from damage to the ENS or are they based on damage to the DMV and other structures within the CNS? The reports by Corbillé et al. and others suggest that the GI symptoms of PD may primarily be driven by changes within the CNS, although dysfunction within the ENS but without neuronal death also might play a role. Research using animal models of PD, such as the recent report of Zheng et al. in which 6-hydroxydopamine-induced lesions of the substantia nigra resulted in impaired gastric motility and impaired gastric emptying that could be prevented by vagotomy also support the conclusion that GI dysfunction in PD is the result of CNS damage [15]. But how then does one explain the emergence of GI dysfunction in PD-destined individuals as much as two decades before development of motor features and what is one to make of the deposition of alpha-synuclein within the ENS early in the course of PD?

Although the work by Corbillé and colleagues argues against neuronal demise in the ENS as an explanation for GI symptoms in PD, it certainly does not contradict the presence of pathology within the ENS in PD, nor does it negate the idea that the ENS is the birthplace of PD, even if it is not responsible for the GI symptoms that characterize the disorder. In fact, work from the same group of authors has charted new pathologic territory by reporting the presence of inflammation, with elevated levels of pro-inflammatory cytokines and evidence of glial dysregulation, within the ENS in colonic biopsies taken from PD patients [16, 17]. This, coupled with reports by others of increased colonic permeability in a mouse model of PD [18], provides additional fuel for the hypothesis proposed by Braak et al. that PD does indeed originate within the ENS and that the smoldering inflammatory fire triggered there by a still unidentified pathogen induces further changes that slowly but surely spread to ultimately involve the CNS and produce the classic features of PD. Thus, the wheel comes full circle back to Dr. Parkinson. However, if this is true, why neurons within the ENS do not die remains an intriguing mystery and there is most certainly more of the story yet to unfold.

## REFERENCES

- [1] Parkinson J (1817) An essay on the shaking palsy. London: Whittingham and Rowland.
- [2] Pfeiffer RF (2003) Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol*, **2**, 107-116.
- [3] Pfeiffer RF (2011) Gastrointestinal dysfunction in Parkinson's disease. *Parkinsonism Relat Disord*, **17**, 10-15.
- [4] Kupsy WK, Grimes MM, Sweeting J, Bertsch R & Cote LJ (1987) Parkinson's disease and megacolon: Concentric hyaline inclusions (Lewy bodies) in enteric ganglion cells. *Neurology*, **37**, 1253-1255.
- [5] Wakabayashi K, Takahashi H, Ohama E & Ikuta F (1990) Parkinson's disease: An immunohistochemical study of Lewy body-containing neurons in the enteric nervous system. *Acta Neuropathol*, **79**, 581-583.
- [6] Singaram C, Ashraf W, Gaumnitz EA, Torbey C, Sengupta A, Pfeiffer R & Quigley EM (1995) Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. *Lancet*, **346**, 861-864.
- [7] Braak H, Rüb U, Gai WP & Del Tredici K (2003) Idiopathic Parkinson's disease: Possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm*, **110**, 517-536.
- [8] Braak H, de Vos RA, Bohl J & Del Tredici K (2006) Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett*, **396**, 67-72.
- [9] Olanow CW & Prusiner SB (2009) Is Parkinson's disease a prion disorder? *Proc Natl Acad Sci USA*, **106**, 12571-12572.
- [10] Olanow CW & Brundin P (2013) Parkinson's disease and alpha synuclein: Is Parkinson's disease a prion-like disorder? *Mov Disord*, **28**, 31-40.
- [11] Abbott RD, Petrovitch H, White LR, Masaki KH, Tanner CM, Curb JD, Grandinetti A, Blanchette PL, Popper JS & Ross GW (2001) Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology*, **57**, 456-462.
- [12] Savica R, Carlin JM, Grossardt BR, Bower JH, Ahlskog JE, Maraganore DM, Bharucha AE & Rocca WA (2009) Medical records documentation of constipation preceding Parkinson disease: A case-control study. *Neurology*, **73**, 1752-1758.
- [13] Corbillé A-G, Coron E, Neunlist M, Derkinderen P & Leboviev T (2014) Appraisal of the dopaminergic and noradrenergic innervation of the submucosal plexus in PD. *J Parkinsons Dis*, **4**, 571-576.
- [14] Annerino DM, Arshad S, Taylor GM, Adler CH, Beach TG & Greene JG (2012) Parkinson's disease is not associated with gastrointestinal myenteric ganglion neuron loss. *Acta Neuropathol*, **124**, 665-680.
- [15] Zheng LF, Song J, Fan RF, Chen CL, Ren QZ, Zhang XL, Feng XY, Zhang Y, Li LS & Zhu JX (2014) The role of the vagal pathway and gastric dopamine in the gastroparesis of rats after a 6-hydroxydopamine microinjection in the substantia nigra. *Acta Physiol (Oxf)*, **211**, 434-446.
- [16] Devos D, Leboviev T, Lardeux B, Biraud M, Rouaud T, Pouclet H, Coron E, des Varannes SB, Naveilhan P, Nguyen J-M, Neunlist M & Derkinderen P (2013) Colonic inflammation in Parkinson's disease. *Neurobiol Dis*, **50**, 42-48.
- [17] Clairembault T, Kamphuis W, Leclair-Visonneau L, Rolli-Derkinderen M, Coron E, Neunlist M, Hol EM & Derkinderen P (2014) Enteric GFAP expression and phosphorylation in Parkinson's disease. *J Neurochem*, **130**, 805-815.
- [18] Kelly LP, Carvey PM, Keshavarzian A, Shannon KM, Shaikh M, Bakay RAE & Kordower JH (2014) Progression of intestinal permeability changes and alpha-synuclein expression in a mouse model of Parkinson's disease. *Mov Disord*, **29**, 999-1009.