

# Role of Chronic Infection and Inflammation in the Gastrointestinal Tract in the Etiology and Pathogenesis of Idiopathic Parkinsonism

## Part I: Eradication of *Helicobacter* in the Cachexia of Idiopathic Parkinsonism

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### ABSTRACT

**Background.** Neuronal damage in idiopathic parkinsonism may be in response to ubiquitous occult infection. Since peptic ulceration is prodromal, *Helicobacter* is a prime candidate.

**Aim.** To consider the candidature of *Helicobacter* in parkinsonism with cachexia.

**Methods.** We explore the relationship between being underweight and inflammatory products in 124 subjects with idiopathic parkinsonism and 195 controls, and present the first case-series evidence of efficacy of *Helicobacter* eradication, in parkinsonism advanced to the stage of cachexia.

**Results.** Association of a low body mass index with circulating interleukin-6 was specific to parkinsonism ( $p = .002$ ), unlike that with antibodies against *Helicobacter* vacuolating-toxin and cytotoxicity-associated gene product ( $p < .04$ ). Marked reversibility in both cachexia and disability of idiopathic parkinsonism

followed *Helicobacter heilmannii* eradication in one case, *Helicobacter pylori* eradication in another, follow-up being  $\geq 3.5$  years. The latter presented with postprandial bloating, and persistent nausea: following eradication, radioisotope gastric-emptying returned towards normal, and upper abdominal symptoms regressed. Reversibility of their cachexia/disability contrasts with the outcome of anti-*Helicobacter* therapy where eradication repeatedly failed (one case), and in non-*Helicobacter* gastritis (three cases). Antiparkinsonian medication remained constant. Intestinal absorption and barrier function were normal in all.

**Conclusion.** Categorization, according to presence or absence of *Helicobacter* infection, was a useful therapeutic tool in late idiopathic parkinsonism.

**Keywords.** *Helicobacter pylori*, *Helicobacter heilmannii*, eradication, idiopathic parkinsonism, cachexia, etiology and pathogenesis.

The pandemic of encephalitis lethargica in 1917 is an historic landmark for any "infection" hypothesis on the etiology of parkinsonism. Our interest [1–4] in the role of *Helicobacter* in idiopathic parkinsonism is founded on two observations in Australia. The first, by Strang in 1965, was of the increased prevalence of peptic ulcer prodromal to idiopathic parkinsonism [5], and the second was, of course, the association by

Warren & Marshall in 1983, of a Gram-negative bacterium, subsequently named *Helicobacter pylori*, with gastritis [6].

Cachexia in late idiopathic parkinsonism is usually intractable. This might not be so were chronic occult infection to blame. Surprisingly, weight loss is associated with increased energy intake, from 2 to 4 years prediagnosis [7]. High resting energy expenditure is reported, even after overnight deprivation of antiparkinsonian medication [8,9], but not consistently so [10]. We have previously described age trends and patterns, in circulating inflammatory markers [11,12] and *H. pylori* antibodies [2,3], which differentiate

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between subjects with idiopathic parkinsonism and controls. Further analysis examines whether being underweight can, in part, be explained in terms of elevated circulating markers or the presence of specific antibodies, in probands and controls. In a case series, we contrast the outcome of anti-*Helicobacter* therapy, with respect to body mass index (BMI), performance and dyskinesia, in two cases where treatment of proven infection succeeded, with experience 1, of eradication failure and 2, in gastritis, not attributable to *Helicobacter* after extensive search.

## Methods

Local ethics committees approved studies, written informed consent being obtained from participants.

### Statistical Modeling to Explain Cachexia in Idiopathic Parkinsonism

Further analysis building on existing data sets (2,3,11,12) explored associations of BMI with serum cortisol, interleukin-6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), and antibodies against *Helicobacter*. Independently living subjects with clinically definite idiopathic parkinsonism [13] were contrasted with healthy, parkinsonism-free controls. Ages spanned fifth to ninth decades (with additional controls from the fourth) and genders were balanced. Exclusions [2] were: 1, intercurrent or chronic physical illness; 2, clinical depression, dementia or other mental illness, or a score  $\leq 8/16$  on the Modified Tooting Bec questionnaire (and/or  $< 24/30$  on mini-mental Score); 3, other specific neurological disease; 4, cardiovascular/respiratory symptoms during normal activities; 5, arthropathy, musculoskeletal disorder or UK MRC muscle strength score  $< 4/5$ ; 6, inflammatory or neoplastic gastrointestinal disease; 7, history of eradication therapy for *Helicobacter*; 8, concurrent therapy with drugs which might be anti-dopaminergic, or with hypnotics or sedatives; and 9, recent change in life situation.

A timed (10:30 AM–5:00 PM) venous blood sample had been taken, from an indwelling cannula, in the supine, rested subject. For a given assay (see *Biochemical and Immunological Methods*), sera were stratified between assay-runs for subject group, age and gender. Linear regression and (when BMI was dichotomized into  $<$  or  $= 20$  kg/m<sup>2</sup>) logistic regression models were used. Pre-determined, potential confounders of the rela-

tionships to weight of subject group and assay results were included.

### Case Series: Clinical and Laboratory Methods

Outcome in idiopathic parkinsonism was contrasted between case histories of successful *Helicobacter* eradication and one of failure. Failure of similar intervention to impact on progression of the parkinsonian syndrome in patients with gastritis, but without evidence of *Helicobacter* on biopsy, would further support the candidature of *Helicobacter*.

At endoscopy, individuals could opt for “light” sedation (intravenous midazolam: maximum dose 4 mg). Infection was proven by 1, gastritis with associated *Helicobacter*-like organisms on light microscopy (any of 6 biopsies: anterior and posterior antral, incisural, anterior and posterior corporal and cardiac); and/or 2, culture of *H. pylori* (either of two biopsies: antral and corporal, transported by courier to the *Helicobacter* Reference Laboratory, Health Protection Agency, London, UK); or, if culture negative 3, detection of *H. pylori* and “*Helicobacter heilmannii*”-like organisms by multiplex polymerase chain reaction (PCR) [14]. Standard operating procedures for culture and testing *H. pylori* in vitro susceptibility to metronidazole, clarithromycin, amoxicillin, and tetracycline were followed.

*Helicobacter* status was monitored non-invasively by [<sup>13</sup>C] urea breath test (UBT), and enzyme-linked immunosorbent assay (ELISA) value for serum anti-urease-IgG antibody (INFAI, Kestrel Healthcare Ltd, Basingstoke, UK and SIA417A, Delta Biologicals, Rome, Italy, respectively). (See *Biochemical and Immunological Methods*).

A pure culture of *H. pylori* isolated from patient 2, and control plates of *H. pylori* medium (Columbia horse blood agar, with Dent selective antibiotic supplement), were washed with distilled water or 50% v/v water/methanol. Washings eluted a second identical plate, the second eluate washed a third. The final extract was ultra-filtered (MW  $< 30,000$ ) twice, to remove bacteria and stored at  $-20$  °C. Ligand binding (MDS Pharma Services, Canterbury, UK) and bioassay (James Black Institute, King’s College, London) studies were performed.

A differential four-sugar test (urine assayed by simultaneous thin-layer chromatography) was used to measure intestinal absorption/permeability in the case series [15]. Fecal

calprotectin was used to screen for gut inflammation, serum antitissue transglutaminase antibody for celiac disease.

### Biochemical and Immunological Methods

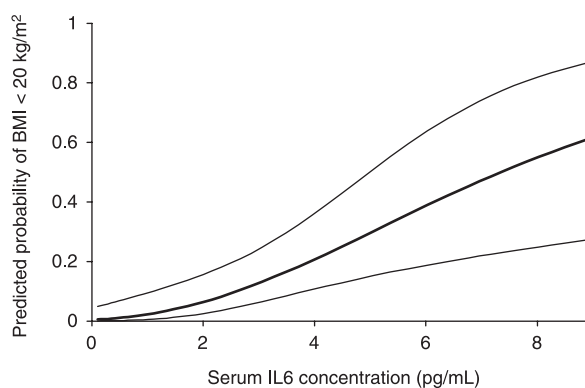
Serum was stored at  $-20^{\circ}\text{C}$ . Between-assay coefficients of variation, for the samples assayed in duplicate, were 5.9, 4.8, and 2.9% at 77, 339, and 1086 mmol/l, respectively, for cortisol radioimmunoassay (Cort-A-Count, Diagnostic Products Corp., LA); 13.0 and 9.0% at 5.4 and 7.8 pg/ml for IL-6 ELISA (Biosource International, Camarillo); 11.7 and 13.6% at 17 and 143 pg/ml for TNF- $\alpha$  ELISA (Medgenix Diagnostics SA, B-6220 Fleurus, Belgium); and 13.0, 8.0, and 6.0% at an ELISA value of 0.8, 2.4, and 5.9 for anti-urease-IgG antibody. Presence/absence of antibodies to VacA and CagA on Western Blotting was noted: each assay contained a negative and a positive quality control (RIDA *Helicobacter* Blot IgG, Quadratch Diagnostics Ltd, Epsom, UK). Blots and the developed control (k) strip, supplied with each kit, were scanned and magnified, to maximize precision of band detection.

## Results

### Explaining Cachexia in Idiopathic Parkinsonism

One hundred and twenty-four subjects with idiopathic parkinsonism were 4.1 kg (95% confidence interval [CI] 1.2, 7.0) lighter ( $p = .006$ ) than the 194 controls (2.8 kg after height, gender and age adjustment,  $p = .03$ ). Their (adjusted) weight tended to be lower, the greater the functional incapacity ( $-2.7$  kg [ $-7.2, 1.8$ ] per Hoehn & Yahr [11], Stage [II–V]). Height correction may underestimate effects: shorter standing height in parkinsonism ( $-1.7$  [ $-4.0, 0.0$ ] cm,  $p = .1$ ) encompasses an artefact from flexed posture. Even so, more probands (9.7%) than controls (4.1%) fell below the desirable (20–25 kg/m<sup>2</sup>) BMI range ( $\chi^2$  test,  $p < .05$ ).

Low BMI was associated with increased serum IL-6 in 91 subjects with parkinsonism (Fig. 1), but not in 132 controls. This differentiation is seen in the interaction between the effects of subject group and IL-6 concentration on BMI status ( $p = .006$ , after gender and age adjustment). In idiopathic parkinsonism, the odds for having a low BMI increased fivefold per log<sub>e</sub> unit higher the IL-6. A similar differential



**Figure 1** Relationship (mean, 95% CI) of being underweight to circulating IL-6, in 91 subjects with idiopathic parkinsonism. The odds ratio for having a low BMI increased by 5.4 (95% CI 1.8, 16.3) per log<sub>e</sub> unit higher the IL-6 ( $p = .002$ ). IL-6 concentrations  $> 5$  pg/ml are generally considered high.

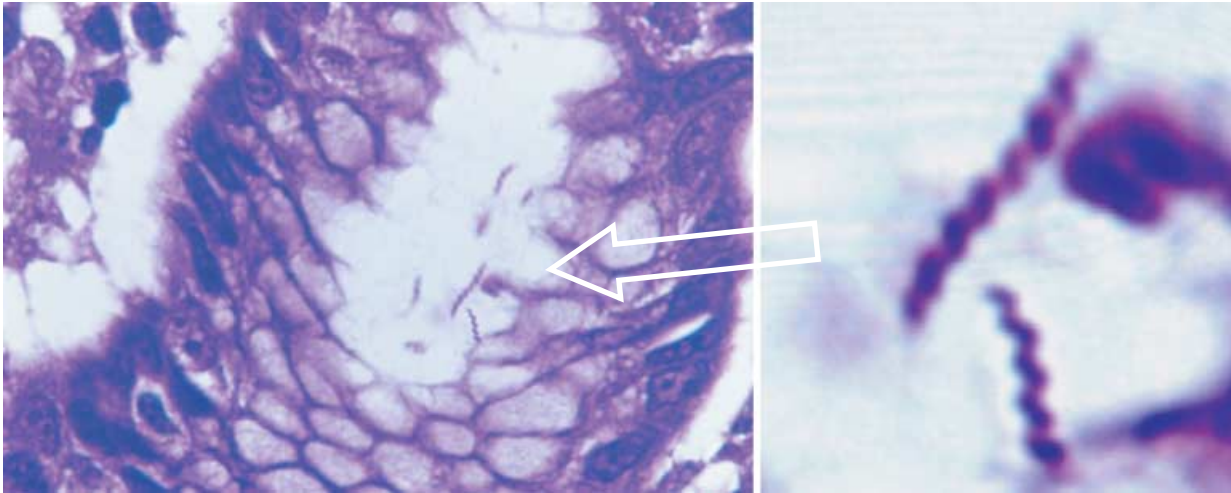
pattern for cortisol did not reach statistical significance. However, the odds for being underweight in 115 subjects with idiopathic parkinsonism tended to increase markedly the higher the cortisol concentration (odds ratio [OR] 4.3 [0.7, 25.3] per log<sub>e</sub> unit,  $p = .1$  after adjustment for sample timing), with no such trend in 184 controls.

Irrespective of subject group (124 with parkinsonism, 194 without), the odds for being underweight nearly tripled in the presence of both anti-VacA and -CagA antibodies, or of anti-VacA alone. The presence of both antibodies increased the odds for being underweight by 2.8 (1.1, 7.5), that of anti-VacA alone by 2.8 (1.1, 7.2), after adjustment for age and gender ( $p < .04$  in both cases). Also irrespective of subject group (89 with parkinsonism, 142 without), the odds for being underweight tended to double per log<sub>e</sub> unit higher the TNF- $\alpha$  (OR 2.0 [0.9, 4.6],  $p = .09$ ).

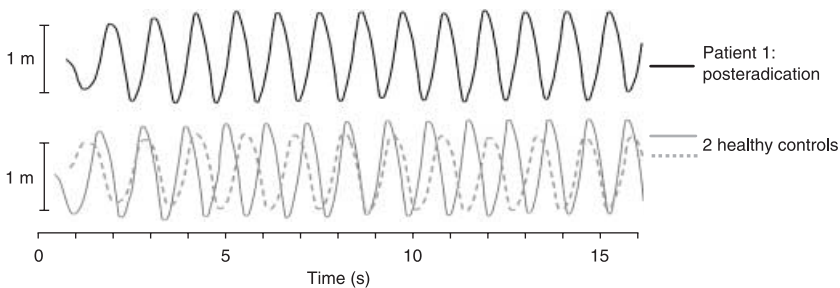
Anti-urease antibody status was not predictive of low BMI (123 with parkinsonism, 193 without).

### Case Series: Successful Helicobacter Eradication

Patient 1, a 76-year-old man, 13 years from diagnosis of clinically definite idiopathic parkinsonism [13], was wheelchair-bound, without assistance, for over a year (functional incapacity, Stage V). He was on a fixed regimen (which remained constant subsequently) of long  $t_{1/2}$  dopamine agonists, buccal monoaminoxidase-B inhibitor, and six daily doses of levodopa



**Figure 2** *Helicobacter heilmannii*-like organisms in gastric antrum of patient 1. Large spiral organisms were present in all biopsies, most frequent in antrum (cresyl-fast violet stain). No *H. pylori*-like organisms were identified. Chronic inflammation was mild to moderate in antrum, mild in corpus. Occasional neutrophils infiltrated crypts. There was no atrophy or intestinal metaplasia. Eradication of the organisms left a minor presence of chronic inflammatory cells, and occasional dilated pits, in antrum alone.



**Figure 3** Documentation of normal gait 1 year post-eradication of *H. heilmannii* in patient 1. The patient had come from transfers-only to having gait indices, at free-walking speed, comparable to the two gender-, age- and height-matched controls. Vertical displacement represents stride-length, static peaks and troughs double-support times. Gait indices describe the brady/hypokinesia of parkinsonism, and document a key daily living activity [11].

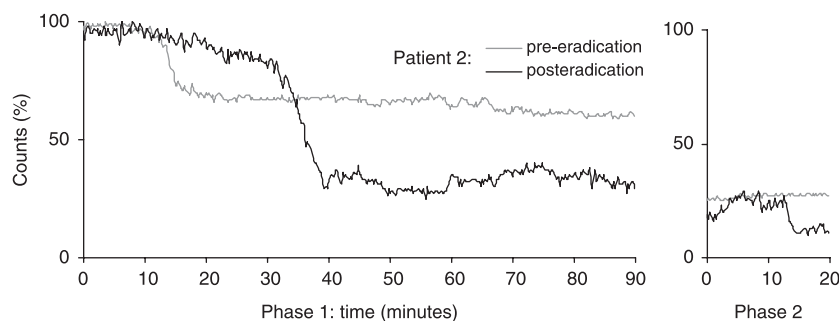
(50 mg)/decarboxylase inhibitor taken with a catecholamine-O-methyltransferase inhibitor. Dyskinesia was gross. He had no spontaneous gastrointestinal complaints, the only clue to gastritis being that he avoided chilled drinks. BMI was stable at 19.3 kg/m<sup>2</sup>. Haemoglobin and white cell count were normal, but lymphocytes were low ( $1.0 \times 10^9/l$ ). The UBT for *Helicobacter* was positive.

Appearances at esophago-gastro-duodenoscopy were "normal". CLOtest (Ballard Medical Products, Draper, UT) was positive, but color-change unusually slow. Histological examination (Fig. 2) showed antral-predominant chronic gastritis with *H. heilmannii*-like organisms [16]. *H. heilmannii* may represent more than one taxon [14]. Transmission from cats/dogs is reported and similar organisms infect pigs [17]. Patient 1 has never lived/worked on a farm or kept pets. As expected, culture was negative [14]. Biopsies were PCR-positive for *H. heilmannii*

16S rRNA, but not for its ureB. PCR for *H. pylori* vacA was negative.

Six weeks after "triple therapy" (a week's twice-daily omeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1 g), UBT was negative. The patient became independent of wheelchair with occasional mild dyskinesia. BMI increased to 21.1 kg/m<sup>2</sup>. Severe dyskinesia, at 14 weeks, signaled recrudescence/reinfection: UBT was positive. He took two weeks' ranitidine bismuth citrate (400 mg twice daily), metronidazole (500 mg thrice), and oxytetracycline (500 mg four times), followed by 1 month's omeprazole. Repeat biopsy, 11 months later showed almost complete resolution of gastritis, with no organisms. No villous atrophy was seen in distal duodenum. PCR targeting *H. heilmannii* and *pylori* was negative. Four years after eradication, serum anti-urease IgG-antibody titre continued to decline, and UBT to be negative. (His spouse was negative on both tests throughout.)

**Figure 4** Return of gastric emptying towards normal in patient 2. Radionuclide gastric emptying studies are shown. At 0 minute, the patient had finished the standard 99 m-technetium Dowex-resin test-meal. She walked for 30 minutes between phases 1 and 2. Prior to eradication of *H. pylori*, it took > 90 minutes for activity to fall to < 50%, only 36 minutes 10 weeks after.



Following eradication, dyskinesia rapidly became minimal. Lassitude and incapacity regressed over the following year, when he was able to walk 2–3 miles and gait analysis was normal (Fig. 3). At 4 years, he remained independently mobile, mastering, as an emeritus academic, previously neglected computing skills. In parkinsonism, “bradyphrenia” inhibits the flow of thought and makes such multitasking difficult [18]. BMI was 22.6 kg/m<sup>2</sup>, blood lymphocytes  $1.2 \times 10^9/l$ .

Patient 2, a 64-year-old woman, 8 years from diagnosis of clinically definite idiopathic parkinsonism, lived alone, independently, despite falls (Stage III). Parkinsonism was stable, on similar, fixed antiparkinsonian medication to Patient 1, but with four (50 mg) levodopa doses daily. This, and long-established thyroid-replacement therapy, remained constant throughout. She had persistent nausea, worst in the morning, with 10 years postprandial “bloating”. She could eat little at a time. BMI had fallen from 20.7 to 17.0 kg/m<sup>2</sup> over 19 months. Her bowel habit of “missing the occasional day” had recently changed to once weekly. Total white cell count was normal, but lymphocytes low ( $0.77 \times 10^9/l$ ). UBT was positive.

At endoscopy, mucosae appeared normal but, despite overnight fast, the stomach contained considerable food-residue consistent with delayed emptying (Fig. 4). CLOtest was almost immediately positive. Histology showed mild pangastritis with *H. pylori*-like organisms, focal atrophy in antrum and corpus, and intestinal metaplasia in cardia. *H. pylori* was cultured from antrum and corpus, and a week of omeprazole/clarithromycin/amoxicillin prescribed in accordance with in vitro sensitivities. Patient 2 was never anemic, with MCV being normal. However, serum vitamin B<sub>12</sub> and ferritin concentrations were low: parenteral B<sub>12</sub> and oral iron were prescribed.

UBT was negative 6 weeks after triple-therapy. Nausea regressed rapidly, and defaecation

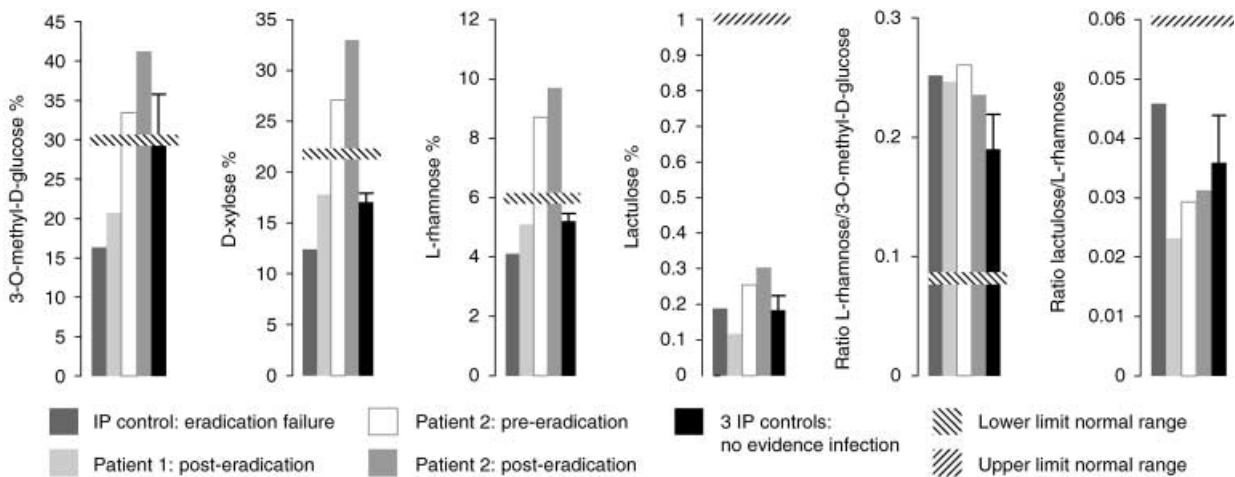
became daily. Neither *Clostridium difficile* toxin nor routine pathogens were reported in stool.

There was marked increase in energy, and balance was improved. She threw herself back into work as café chef and manager. BMI increased to 19.1 kg/m<sup>2</sup> by 10 weeks, gastric emptying improved markedly (Fig. 4). Rapid change towards normal, in gastric and emptying bowel habit, following *H. pylori* eradication suggest reversible damage by its products. They could also be pharmacological effects involving or mimicking a neurotransmitter or neuropeptide. Aqueous and lipid solvent culture plate washings were investigated. (See *Ligand-binding Assay and Bioassays on H. pylori Ultrafiltrate*.)

UBT remained negative 3.5 years later, with continuing fall in anti-urease antibody titre. She was robust, without nausea but with borderline constipation. BMI was 22.7 kg/m<sup>2</sup>. Lymphocyte count had increased to  $0.96 \times 10^9/l$ . Repeat endoscopy, confirmed *H. pylori* eradication (CLOtest, histopathology, culture and molecular methods). Focal atrophy and metaplasia persisted. Changes suggesting early autoimmune gastritis, like that of pernicious anaemia, were seen in corpus.

#### Case Series: Comparators

Eradicating *Helicobacter* seems central to any effect of antimicrobials plus acid suppressant on parkinsonism. Forty-six months after two failed eradication attempts, biopsy, in a man aged 74 year (15 years from diagnosis of idiopathic parkinsonism), showed pangastritis with *H. pylori*-like organisms. They were resistant to clarithromycin and metronidazole, sensitive to amoxicillin (to which he reported allergy) and tetracycline. One week of omeprazole, tetracycline and rifabutin (bismuth avoided due to renal impairment) failed to revert UBT [19]. He had gone from



**Figure 5** Intestinal absorption and barrier function in six patients with idiopathic parkinsonism (IP). Absorption of 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose, expressed as percentage of oral dose recovered in urine over 5 hours is shown one year post-eradication in patient 1, and pre-eradication and 6 months post in patient 2 [15]. (Any effect of impaired gastric emptying on 5 hours sugar absorption in patient 2 appears small.) These are contrasted with values from one IP patient in whom eradication failed and means (+ SE) for 3 in whom gastritis was not attributable to *Helicobacter*. Absorptive (rhamnose/glucose) and permeation (lactulose/rhamnose) ratios, used to minimize effect of nonmucosal factors, are normal in all.

independently mobile to confined to chair without assistance (Stage V). BMI declined steadily, from 24.1 to 18.8 kg/m<sup>2</sup> at 68 months, lymphocyte count from 1.3 to 1.19 × 10<sup>9</sup>/l. Increasing dopamine agonist dosage failed to ameliorate deterioration. Levodopa was constrained to 50 mg twice daily by gross peak-dyskinesia.

Additional support is given to the candidature of gastric *Helicobacter*, as one type of driving infection, by failure of antimicrobials/acid suppressant to impact on parkinsonism with *Helicobacter*-negative gastritis. A man of 76 years and women aged 73 and 64 (with progressive idiopathic parkinsonism and taking background antiparkinsonian medication similar to that in patients 1 and 2) had dyspepsia with antral-predominant gastritis. Although biopsy-negative for *Helicobacter* (CLOtest, histology, culture and molecular methods), each opted to take a week's first-line *Helicobacter*-eradication therapy. Neither patients nor physicians saw any alteration in progression of parkinsonism. Three years later, the first two were cachectic and chair-bound with intrusive dyskinesia. The third's gait had deteriorated to a shuffle by 2 years; she died suddenly of myocardial infarction.

Absorptive and permeability ratios were normal in the case series (Fig. 5). Postintervention calprotectin and transglutaminase antibody were negative.

#### Ligand-binding Assay and Bioassays on *H. pylori* Ultrafiltrate

No specific binding was found to dopaminergic, adrenergic, muscarinic or histaminic receptor classes/subtypes, or to dopamine, adrenergic/noradrenaline or serotonin neuronal-uptake transporters. No muscarinic, histaminic or cholecystokinin-like activity was detected in mouse stomach, or guinea pig gallbladder or ileum, bioassays.

#### Discussion

While interim results of an efficacy study suggest that eliminating *Helicobacter* infection can alter the course of untreated idiopathic parkinsonism [4], the present case series suggests that this still holds true at the stage of cachexia. If the mechanism were simply improved absorption of antiparkinsonian medication, one would hardly expect the gross dyskinesia of patient 1 to become minimal after successful eradication. Earlier and higher peak concentrations achieved by accelerated gastric emptying could increase the efficacy of short  $t_{1/2}$  medication (here, levodopa), but at the expense of "peak" dyskinesia. Moreover, the effect of *Helicobacter* eradication on the area under the 4 hours levodopa concentration/time curve is small [20], and not commensurate, in our experience, with the striking U-turn in

performance of these patients. However, loss of antagonism of medicinal effects (e.g. by inflammatory products) might combine increased efficacy and a raised dyskinetic ceiling.

Eradication could, of course, affect the pathogenesis directly. An inflammatory or immune process could be driving both cachexia and parkinsonism. Here, we link being underweight in idiopathic parkinsonism to circulating IL-6 concentration, just as it is in aging, cancer, chronic heart failure, rheumatoid disease and AIDS [21]. It seems, indeed, not to be simply the result of eating less [7–9] due to parkinsonian disability or gastric pathology. There appears to be a similar link between low BMI and serum cortisol in parkinsonism. Interleukin-6 and cortisol may be markers, rather than mediators, in this context. In healthy adults, serum IL-6 concentration increases with age, with an upward shift in parkinsonism equivalent to more than 10 years of ageing [12]. Cortisol appears to do (continuing) harm in parkinsonism with respect to gait, or mirror something harmful [11]. Significant, but “physiological,” elevation of circulating cortisol is found in idiopathic parkinsonism. Two *H. pylori*-specific antibodies were related to being underweight irrespective of the presence of parkinsonism, as serum TNF- $\alpha$  appears to be. Circulating TNF- $\alpha$  is associated with abnormal postural and psychomotor responses in parkinsonism [12]. It increases with age, but is not elevated overall in parkinsonism. However, there is evidence for suppression early in the course, elevation late.

Examination of a *Helicobacter* extract gave no evidence of pharmacological activity, but more lipid-soluble, and less water-soluble, molecules may have been missed. Shake-flask cultures might provide more bioactive material than culture-plate washings.

Reversibility of disordered gastrointestinal motility in patient 2 could reflect the gut being in the front line of an active process. Early satiety and bloating, suggestive of delayed gastric emptying, are common, but may be attributable, at least in part, to antiparkinsonian medication. Dopamine inhibits gastric motility; reduces gastric tone, intragastric pressure, lower esophageal sphincter tone and antro-duodenal coordination; and inhibits vagal acetylcholine release [22]. Inconsistency in the clinical effect of antiparkinsonian medication on gastric emptying may reflect underlying disease activity [23,24]. The nausea in patient 2 disappeared with the improvement in

gastric emptying, and so is unlikely to have been due to stimulation of dopamine D<sub>2</sub>-receptors in area postrema and vomiting centre.

A change in bowel flora cannot be excluded as the cause of the persistent reversibility of the severe constipation in patient 2. However, dopamine stimulates colonic motility in healthy subjects [22], and, characteristically in parkinsonism, intestinal transit-time is slow. The deviation in frequency of defaecation from that of healthy age/gender-matched controls [25,26], precedes diagnosis by, on average, three decades. Indeed, depletion of jejunal dopamine, with levodopa-responsive hypomotility, is a forerunner of parkinsonism in the MPTP (1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine) animal-model [27]. Degeneration of vagal motor-nuclei is well-described in idiopathic parkinsonism, but the colon also shows degenerative changes. These are dopamine depletion, loss and damage to myenteric dopaminergic neurons [28], and Lewy bodies in enteric plexus and sympathetic ganglion neurons [29].

We conclude that current classifications of “neurodegenerative” disease may be too partisan, and hence prejudicial for prophylaxis or halting progression. Diagnosed chronic brain disease within life is the tip of an iceberg, clinical presentation an ill-defined point in phenotype evolution. Environmental etiological and/or pathogenic insult(s) may not, universally, persist beyond diagnosis. Should they do so, detection and eradication may allow some reversibility even in late disease.

A therapeutic note is that a single course of anti-*Helicobacter* therapy was not sufficient in two of the three infected cases. Treatment failure is known to be more frequent in nonulcer than ulcer-dyspepsia [19]. Should a high failure rate be found in a larger sample of probands with idiopathic parkinsonism, rapid metabolism of proton pump inhibitors resulting from polymorphism in cytochrome P450 2C19 should be considered. Polymorphism of P450 2D6 is already described in idiopathic parkinsonism [30,31]. Lymphopenia may be another adverse host-factor. One course of therapy was not sufficient in our *H. heilmannii*-infected patient. Current guidelines for *H. pylori* treatment have not been adequately tested against *heilmannii* [17], but “common” anti-*Helicobacter* therapy had a failure rate of 5/12, which may include reinfection [32]. We have found only 1/41 patients, with idiopathic parkinsonism and biopsy +ve for

*Helicobacter*, to have *H. heilmannii* (unpublished observation). This is in line with the highest reported prevalence of *H. heilmannii* infection, that is 2% of gastric biopsies [14,32].

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