

Chapter 2

Epidemiology of Gastroparesis

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Introduction

Despite the enormous public health impact of gastroparesis (GP), several gaps in our knowledge still exist. This chapter focuses on the epidemiology of GP with particular attention to those studies which have attempted to shed light on the conflicting definitions of the disorder, its most common etiologies, the incidence, prevalence, and the changing secular trends. The socioeconomic burden of GP in terms of costs, morbidity, and impact on patients' quality of life (QOL) are also explored.

Definitions

Patients with GP can exhibit a broad spectrum of clinical manifestations, but symptom severity correlates poorly with the degree of delay in gastric emptying [1]. The clinical manifestations of GP include nausea, vomiting, postprandial pain and early satiation in the absence of mechanical obstruction. The American Gastroenterological Association (AGA) consensus has stated that pain is not a common concern in

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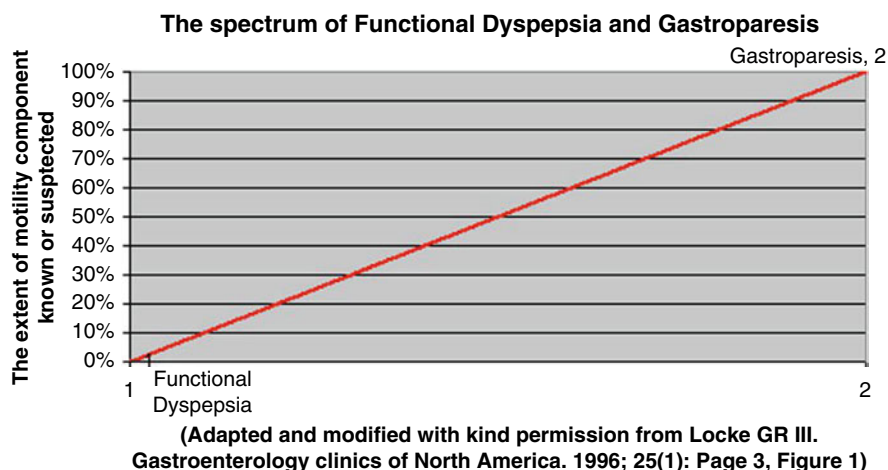


Fig. 2.1 The continuum of dyspepsia and gastroparesis

patients with GP, but two studies have observed that the prevalence of pain in GP can be as high as 89% [2]. However, the severity of abdominal pain does not seem to correlate with the degree of delay in gastric emptying [2].

GP is thus defined as upper GI symptoms in the setting of delayed gastric emptying; obstruction must be excluded before making a firm diagnosis. However, this broad simple definition is problematic for a number of reasons.

Mildly delayed emptying overlaps with functional dyspepsia (FD). Some experts in the field have proposed that delayed gastric emptying and GP are two different entities, and that the diagnosis of GP should be restricted only to those with grossly delayed gastric emptying [3]. Others have proposed the confusing term “gastroparesis-like” syndrome to describe patients with dyspepsia but normal emptying, which for all intents and purposes is FD [4]. Although there is a significant overlap of symptoms, still others have argued that it is the extent of disordered motility that differentiates FD from true GP [5] (Fig. 2.1).

GP may be acute, or chronic if symptoms persist for more than three months [6]. The two most common causes of GP are idiopathic and diabetes mellitus. Even in the absence of symptoms of GP, in those with insulin-treated diabetes, delayed gastric emptying may predispose to poor control of glucose concentrations, particularly hypoglycemia in the early postprandial period [7]. In contrast, in patients with type 2 diabetes (T2DM) who are not managed with insulin, delayed gastric emptying may represent an advantage providing better glucose homeostasis. Whether the definition of GP should be broadened to include these patients with disordered glycemic control attributable to GP is unresolved.

Variation in defining what constitutes GP is also limited by the absence of standardization in interpreting scintigraphy, i.e., the cut off applied, variations across centers in the volume and composition of test meals, the posture of patients during GES, duration of testing, and calculations of emptying as $t_{1/2}$ or % retention [8]. Despite recent efforts to standardize GES, many institutions still use 2 h scanning which may have lower sensitivity and specificity than 4 h scanning; this may potentially underestimate patients with GP and thus the true prevalence of the disorder [8]. A 4-h gastric emptying scan showing a delay in gastric emptying three standard deviations above normal using a standard test meal, regardless of symptoms, seems to represent a practical definition of GP that is at least specific.

Causes of Gastroparesis

GP is important but is uncommon; while some estimates suggest that up to 4% of the American population may be affected, this is likely an overestimate (see below) [9]. The etiology of GP is multifactorial with over 90 causes identified in the literature [10] (Table 2.1). The mean age of onset of GP is 34 years (range: 15–72) [11]. Soykan et al. studied a cohort of 146 patients finding 36% were idiopathic, 29% diabetic, 13% postgastric surgery, 7.5% Parkinson's disease, 4.8% collagen vascular disorders, 4.1% due to intestinal pseudoobstruction, and 6% from other miscellaneous causes [9]. Although chronic causes of GP are usually irreversible, the acute cases often resolve after correction of the underlying etiology. Idiopathic gastroparesis (IGP) comprises the largest group of patients and when further subdivided, 23% may have a suspected viral etiology [9].

Table 2.1 Secondary causes of gastroparesis in the population

Probable cause of gastroparesis, <i>n</i> (%)	Definite gastroparesis (<i>n</i> = 83)	Definite plus probable gastroparesis (<i>n</i> = 127)	Definite plus probable plus possible gastroparesis (<i>n</i> = 222)
Idiopathic	41 (49.1)	55 (43.3)	70 (31.5)
Diabetes mellitus	21 (25.3)	39 (30.7)	103 (46.4)
Connective tissue disease	9 (10.8)	12 (9.4)	15 (6.8)
Hypothyroidism	1 (1.2)	2 (1.6)	5 (2.3)
Malignancy	2 (2.4)	4 (3.1)	11 (5.0)
Gastrectomy/ fundoplication	6 (7.2)	10 (7.9)	12 (5.4)
Drugs	19 (22.9)	29 (22.8)	54 (24.3)
End-stage renal disease	4 (4.8)	7 (5.5)	19 (8.6)

Note: Three diagnostic definitions were used: definite gastroparesis – delayed gastric emptying and typical symptoms; probable gastroparesis – typical symptoms and food retention on endoscopy or upper GI study; possible gastroparesis – typical symptoms alone or delayed gastric emptying without GI symptoms. Causes of gastroparesis are not mutually exclusive

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Prevalence of Gastroparesis

Data on the prevalence of a disease often sheds light on the burden of disease to society, but for GP, this is difficult to ascertain. Population-based data assessing the extent of GP are scarce. As symptoms do not identify GP, questionnaires alone do not provide robust estimates [1]. Furthermore, population-based studies applying GES are not available.

The most robust data relating to the prevalence of GP are based on a large historical cohort, the Rochester Epidemiology Project (REP), a medical record linkage system in Olmsted County, Minnesota. The REP was used to identify community residents with GP based on strict definitions of definite GP (delayed gastric emptying by standard scintigraphy and symptoms of GP), probable (symptoms of GP and food retention on endoscopy or upper GI study) and possible GP (typical symptoms alone or delayed gastric emptying by scintigraphy). Among the 222 eligible cases of GP studied between 1996 and 2006, only 83 patients met the strict criteria for definite GP with 82% being female (with 44 probable and 95 possible cases) [10]. The most common cause of definite GP was idiopathic (49.4%), followed by diabetes (25.3%) [10]. The overall age-adjusted prevalence of definite GP per 100,000 persons in January 1, 2007 was 37.8 (95% CI, 23.3–52.4) for women and 9.6 (95% CI, 1.8–17.4) for men. Overall, this study indicated that although GP is an uncommon condition in the community, it still represents a major disease burden given the poor prognosis, lower survival and requirement for continuous chronic medical care (see below).

Effect of Ethnicity on Prevalence

No data exist on the prevalence of GP in Hispanics or blacks and therefore whether ethnic differences may influence the epidemiology of GP is unknown. The prevalence of dyspepsia in studies from Europe and North America is reported to be 3–40%, but the rates of GP cannot be determined [12–14]. Generally, studies indicate that the prevalence of chronic GI symptoms, including dyspepsia, is lower in Asian countries as compared to the West [15]. However, Chang et al. reported delayed gastric emptying in 59% of male Chinese subjects with T2DM presenting with upper GI symptoms [15].

Prevalence by Etiology of Gastroparesis

Given the causes of GP are multifactorial, the prevalence of GP in the general population is best assessed by considering the potential risk factors and underlying pathophysiology of the disorder.

Prevalence of Diabetic GP

The prevalence of GP in tertiary referral centers is reported to be 30–50% of type I diabetes (T1DM) and 15–30% of T2DM based on cross-sectional studies [16–18]. For example, in one referral center delayed GES was present in 50–65% of patients with diabetes [16]. However, the selection bias inherent in this approach may seriously overestimate the true prevalence in the community. A large population-based study done by Bytzer et al. evaluated 423 subjects randomly selected from the community with diabetes; they observed that “gastroparesis-like” symptoms were more common in diabetic (11–18%) than nondiabetic people [19]. Moreover, those diabetic subjects reporting poor glycemic control had higher rates of upper GI symptoms (OR 2.45; 95% CI, 1.50–3.98). Hence, conflicting evidence exists as to whether GI symptoms are more common in T2DM which comprises 90–95% of cases of diabetes [20].

Still other studies have failed to establish an association between GI symptoms and DM [21]. For example, one study using records through the REP in subjects with T1DM and T2DM suggested that the prevalence of GI tract symptoms (other than constipation) in patients with DM in the community was similar to persons without DM and, in particular, symptoms of GP are not more common in diabetics than in the general population [21]. However, this database (REP) has some shortcomings, including its predominantly Caucasian and homogeneous population. Another population-based study of 15,000 Australian adults found that those with T1DM treated with oral hypoglycemic medications with or without insulin therapy and those with poor glycemic control were more likely to suffer from nausea/vomiting and upper GI or dysmotility symptoms [22].

The natural history of GP is explored in a subsequent chapter, however, in a longitudinal study done by Jones et al. of 20 patients with DM followed over 12 years, only a minimal change in gastric emptying and GP symptoms was seen over time, despite evidence for progression of autonomic neuropathy [23]. Acute hyperglycemia delays emptying and may worsen symptoms such as nausea and vomiting by this mechanism, while insulin-induced hypoglycemia accelerates gastric emptying substantially, even when the latter is abnormally delayed [24]. Studies on the prevalence of GP during euglycemia are lacking.

Prevalence of Idiopathic Gastroparesis

The proportion of patients with gastroparesis with IGP in a study at a referral center by Soykan et al. was 35.6%, comprising the largest group of GP patients in the cohort; 23% reporting acute viral gastroenteritis preceding their symptoms [9]. Strikingly, a history of physical and sexual abuse was reported in 62% of females with IGP but the relevance of this association remains unclear.

Incidence of Gastroparesis

The true *incidence* of GP in population-based settings is uncertain. However, a recent study done in Olmsted County, Minnesota evaluated incident cases of GP diagnosed either at Mayo Medical Center or Olmsted Medical Center between January 1, 1996 and December 31, 2006 [10]. Through the Mayo Clinic's common medical record system, data on 80% of the entire population in this county are made available with 96% of the population seen at least once during any given 4-year period thus providing the capability for population-based studies. Investigators in the study defined incident case of GP as any new case diagnosed over the 10-year period. When GP is defined by symptoms and delayed gastric emptying (definite GP), the age adjusted (to 2000 US whites) incidence of definite GP per 100,000 person-years for 1996–2006 in Olmsted County, Minnesota, was 9.8 (95% CI, 7.5–12.1) for women and 2.4 (95% CI, 1.2–3.8) for men [10]. The incidence of definite GP was significantly greater in women than in men and, as expected, the prevalence rates were higher among women than men, age-adjusted being 4:1 [10]. Patients with advanced age over 60 years or older had a peak incidence of 10.5 per 100,000 person-years, suggesting that the incidence of gastroparesis may increase with advancing age [10] (Fig. 2.2). These numbers remained similar irrespective of the different diagnostic criteria used [10].

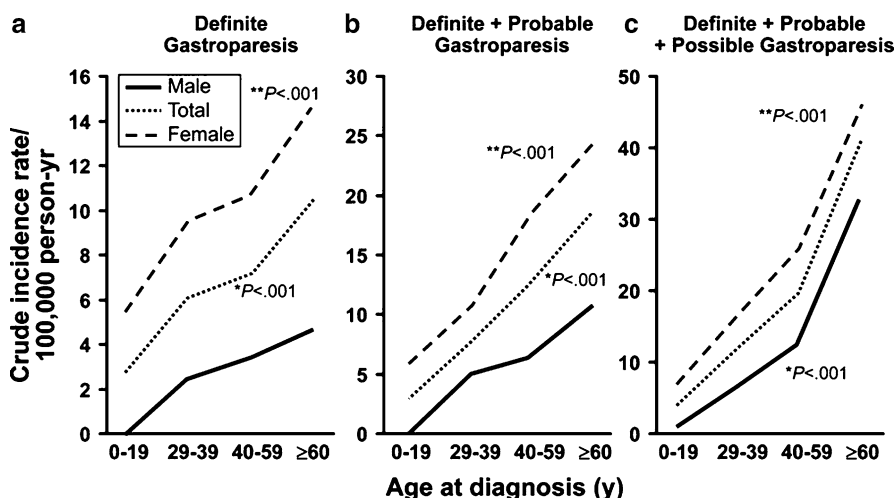


Fig. 2.2 Age-specific incidence of gastroparesis in Olmsted County, Minnesota, 1996–2006 (From ref 10, with permission)

Risk Factors and Predictors of Disease Progression in GP

One aim of epidemiology is to identify homogeneous subgroups in the population who are either at a particularly high or low risk for developing GP. A problem inherent in cross-sectional studies is that the etiologic risk factors cannot be differentiated from associations with no causal relevance.

Influence of Gender and GP

Based on studies done in referral centers, a female predominance of GP exists with a female to male ratio of 4:1 [10]. Some studies have shown that gastric emptying is slower in females compared to males and may also be related to the phase of the menstrual cycle with slower gastric emptying seen during the luteal phase of the menstrual cycle (when progesterone levels are high) versus the follicular phase or menopause (when progesterone levels are low) [25]. However, other studies have failed to show correlations between prolonged gastric emptying and phases in the menstrual cycle, instead demonstrating only postlag gastric emptying rates were slower in women than in men [26]. Furthermore, Monas et al. argue that the greater prevalence of GP in females may reflect the difference in health care seeking behavior, with females seeking health care more frequently than men in general [26].

Hyperglycemia in Diabetics and Gastric Emptying

In diabetes, delay in gastric emptying may be due to elevations in the plasma glucose concentrations [7]. Blood glucose concentration of >8 mmol/l versus 4 mmol/l in healthy subjects and diabetics are associated with delay of both solid and liquid emptying [7]. A profound effect on motor function throughout the GI tract can be seen with any acute change in the blood glucose concentration, which is independent of any intrinsic neuropathy [24].

Hospitalizations

The number of hospitalizations for GP has been increasing in the past decade [27]. In the USA, hospitalizations for a primary diagnosis of GP have been increased, especially among the elderly from 1995 to 2004 [27] (Table 2.2). The data are based on all-payer inpatient care database, the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) in the USA covering 20% of hospitals. Strikingly, hospitalizations for GP as the primary diagnosis increased from 3,977 in 1995 to 10,252 in 2004 (+158%) and using GP as the secondary diagnosis there was an increase of 136%. These statistics represent an overall increase of 138% in the

Table 2.2 National estimates of length of stay, total charges, and number of in-hospital deaths due to gastroparesis as the primary diagnosis, gastroparesis as the secondary diagnosis or a common upper GI condition as the primary diagnosis in the USA, 1995 and 2004

Outcome	1995			2004		
	Length of stay	Total charges	In-hospital death	Length of stay	Total charges	In-hospital death
Gastroparesis related hospitalizations						
Primary diagnosis	29,187	47,726,558	60	62,296	208,263,570	57
Secondary diagnosis ^a	455,234	863,291,147	1,454	849,667	3,291,756,583	1,709
Other upper GI conditions as primary diagnosis ^a						
GERD	268,302	569,048,424	122	258,741	1,266,554,967	53
Gastric ulcer	604,436	1,295,370,569	3,096	478,210	2,233,560,923	2,120
Gastritis	592,254	1,008,033,754	1,269	507,760	2,078,923,132	839
Nausea/vomiting	132,182	200,905,164	326	208,139	685,351,009	304

Table reproduced with permission from Wang et al. Gastroparesis-Related Hospitalizations Am J Gastroenterol. 2008 Feb;103(2): Page 321, with permission *GERD* gastro esophageal reflux disease

^a Some hospitalizations had GERD, gastric ulcer, or nausea/vomiting as the primary diagnosis and gastroparesis as the second diagnosis. These hospitalizations were included in both groups

USA during 1995–2004. Moreover, when GP was compared to other GI diseases, such as gastroesophageal reflux disease (GERD), gastritis, and peptic ulcers, GP patients had the longest length of hospital stay and the second highest total charges in 1995 and 2004 [27]. GP patients, as compared to patients with predominantly nausea and vomiting, experienced more inpatient procedures, a longer length of stay and higher total charges. Similarly, the likelihood of in-hospital death was lower for patients with GERD as the primary diagnosis than for those with GP. The dramatic increase in hospitalizations for GP seen after 2000 is unexplained, but may be reflective of an increasing incidence of GP and DM, changes in the GP diagnostic criteria and modes of diagnosis, the lack of treatment options subsequent to the removal of cisapride from the US market 2000, and approval of the gastric electrical stimulator by the Food and Drug Administration.

Economic Impact of GP

While GI diseases in the USA cost over 40 billion dollars in health care expenditures, the inpatient cost of GP as primary diagnosis increased dramatically from \$48 million in 1995 to \$208 million in 1998 [28]. Moreover, this upward trend in costs may continue, as GP increases with the increased incidence of DM [27].

Based on the North Carolina Hospital Discharge Database from 1998, Bell et al. found that patients with diagnoses of both DM and GP were hospitalized for an average hospital stay of 5.3 days per admission and accumulated an average cost of \$7,709 per hospital visit with medicare as the primary payer (52.1%) [29]. Most of these patients were admitted directly from the emergency department (56.2%) [29]. As a result, patients with both DM and GP incurred about US \$11 million in charges in that year with 7,800 hospital days for 1,500 discharges.

Impact on Health-Related Quality of Life

Health-related quality of life (HRQOL) is an important outcome for patients with chronic illnesses, in general, and has recently gained much interest in the epidemiological literature. Although studies in GP patients are limited, HRQOL is reduced in patients with gastroparesis [30, 31]. Systematic reviews in patients with FD suggest that impairment of HRQOL exists in patients with moderate to severe FD treated in a referral setting, and El-Serag et al. suggest that the same would be true for GP [32]. Talley et al. studied whether delayed gastric emptying in “meal-related” dyspepsia impairs QOL, finding that although QOL is impaired in patients with FD as demonstrated by the SF 36 (generic HRQOL instrument) and Nepean Dyspepsia Index (NDI), only female sex, epigastric pain, and nausea, but not delayed gastric emptying, were associated with an impaired total QOL score [30]. We speculate that an effective therapeutic response in patients with GP will lead to a corresponding improvement in HRQOL, although large randomized controlled trials would be necessary for a definitive determination.

Mortality

Long-term studies in patients with GP indicate that GP is probably not a benign disease, and has considerable morbidity with a poor prognosis given the limited current therapeutic options [33]. Mortality from GP is highest in the decompensated GP patients more at risk of developing complications [9]. For example, Soykan et al. found over a 6-year follow-up period that 7% of those with GP had died with 22% of patients with GP needing either long-term enteral or parenteral feeding. Twenty-six percent of these patients did not respond to medical therapy and 6% underwent gastric electrical stimulation. Mortality in the 10 patients that died was attributable to metabolic derangements, cardiac complications, renal failure, suicide, and/or bowel ischemia due to adhesions.

Other data suggest that in diabetics, GP is associated with higher risk of morbidity, but not mortality. Australian patients with type 1 and 2 diabetes were assessed by scintigraphy, GI questionnaires and autonomic nerve function testing at the Royal Adelaide Hospital [17]. The subjects were followed up 9 years later and of 86 patients, 21 had died (24%) with causes of death related to renal and cardiovascular disease. Those patients who had died had longer duration of diabetes, higher scores based on autonomic testing, retinopathy, and slower esophageal transit than those who were alive, but no differences in solid or gastric emptying were evident. A large study by Hyett et al. of a cohort of patients in a tertiary care referral center, conducted from 2000 to 2008, evaluated whether delayed gastric emptying in diabetics predicted morbidity and mortality [33] (Fig. 2.3). The study compared diabetics with symptoms of GP and delayed emptying based on gastric emptying scintigraphy to those with only symptoms of GP, and found that delayed GES was a predictor

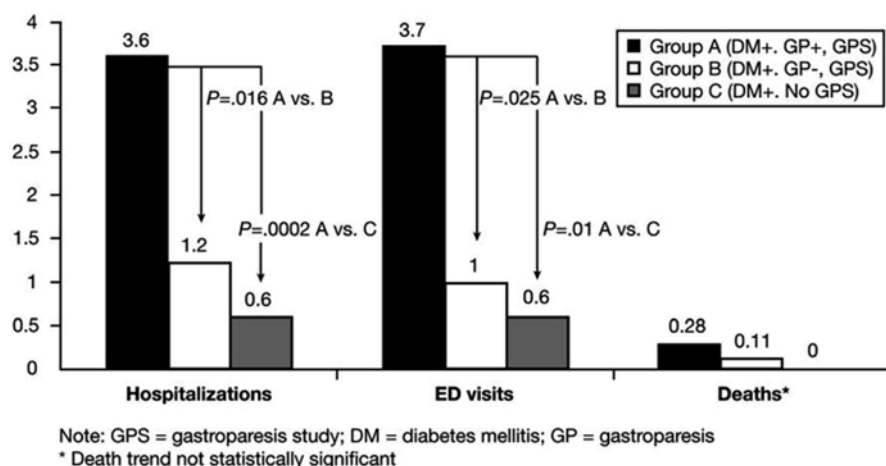


Fig. 2.3 Outcomes between groups per 1000 patient days (Reproduced with permission from [33])

of worse prognosis with more hospital days per 1,000 patient days (25.5 vs. 5.1), emergency room visits, more office visit procedures, such as upper endoscopy performed and increased prevalence of other comorbid conditions, such as coronary artery disease, and hypertension. However, delayed gastric emptying alone in diabetics was not associated with higher mortality. More work is needed to define whether diabetic gastroparesis impacts on mortality.

The 5-year estimated survival of Olmsted County residents with definite GP (symptoms and diagnostic testing consistent with GP) was 67% (95% CI, 60–75%), significantly less than that expected in that population of 81% [10]. Among the causes of death in this cohort were cardiovascular diseases (24.6%), respiratory failure (23.2%), and chronic renal failure (15.9%). Older age at diagnosis was associated with decreased survival. Nondiabetic GP in this cohort was also associated with a better survival than diabetic GP. Other data suggest that postviral GP has a better prognosis and a shorter duration of disease than IGP [34].

Future Studies

Several gaps exist in our current knowledge on the epidemiology of GP. Some of these deficiencies are attributable to the suboptimal definition of GP and a lack of differentiation from FD. We lack a clear understanding of ethnic differences in patient populations with GP. Furthermore, an understanding of the natural history of GP as it relates to the pediatric population is unknown. The NIDDK created a GP registry in 2006 to undertake an observational study to clarify the epidemiology, natural history, clinical course, and outcomes of GP, and this should answer some of these questions. Future technologies, such as swallowed wireless motility capsule using telemetry (SmartPill, SmartPill, Inc., Buffalo, NY), offer a nonradioactive method for assessing gastric transit time in the ambulatory setting [35]. Once such tests become affordable and widely available for use in the general population, the current estimates of incidence and prevalence of GP in the general population may change significantly.

Conclusions

GP represents a major disease burden associated with increased emergency room visits, hospitalizations, complications and poorer survival, especially in the elderly. Because the natural history of GP has been investigated only over the past decade, the long-term outcome is not clearly defined. More aggressive strategies to screen diabetics for GP, and better defined management strategies for all affected are necessary to reduce the morbidity and mortality associated with this usually chronic and debilitating condition.

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Gastroparesis

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