Functional Dyspepsia and Chronic Idiopathic Gastric Stasis

Role of Endogenous Opiates

Francesco Narducci, MD†; Gabrio Bassotti, MD; Maria Teresa Granata, MD;
Manuela Gaburri, MD; Ferruccio Farroni, MD; Renato Palumbo, MD; Antonio Morelli, MD

• Chronic idiopathic gastric stasis can be responsible for unexplained dyspepsia. Because exogenous opiates inhibit gastric emptying and endogenouslike substances are present in the gastrointestinal tract, we tested the hypothesis that increased endogenous opiate activity may be responsible for chronic idiopathic gastric stasis. Eighteen patients with chronic idiopathic gastric stasis and ten healthy volunteers were studied by gastrointestinal manometry. Scintigraphic technique also was used, during which either intravenous saline or naloxone hydrochloride were infused. Manometry showed gastric hypomotility in ten patients and duodenal hyperdyskinesia in the remaining eight patients. Naloxone did not alter gastric emptying in healthy subjects or corrected gastric stasis in patients with gastric hypomotility, while it normalized gastric emptying in patients with duodenal dyskinesia. It seems that either gastroparesis or duodenal dyskinesia can promote gastric stasis and chronic dyspepsia, and endogenous opiates participate in the pathogenesis of gastric stasis in patients with duodenal dyskinesia.
(*Arch Intern Med* 1986;146:716-720)

Gastrointestinal motor dysfunction and gastric stasis can be responsible, in the absence of obstruction, for chronic nausea, epigastric discomfort, and vomiting.[1-11] In some patients, this condition either is secondary to other diseases (such as diabetic neuropathy[9,10] or prior gastric surgery[10,11]) or is a part of a more generalized neuromuscular disorder (chronic intestinal pseudo-obstruction[12]). In numerous cases, however, the chronic gastric stasis is observed in otherwise healthy subjects, a condition known as primary or idiopathic chronic gastric stasis.[2-8]

Morphine and related opioid substances are known to inhibit gastric emptying,[13-15] and this action is selectively reversed by opioid antagonists.[16] Recent studies have demonstrated the presence of endogenous opiatelike substances, the enkephalins, in the myenteric plexus of the gastrointestinal tract, with particularly high concentrations in the stomach and upper small bowel,[17-20] and of specific opioid receptors in the smooth-muscle cells of the stomach[21] and small bowel.[22] We speculated that hyperactivity of the endogenous opiates could be responsible for the chronic idiopathic gastric stasis. In this study we evaluated the effect of naloxone hydrochloride, a selective opioid antagonist,[13,23] on gastric emptying in patients with chronic idiopathic gastric stasis.

PATIENTS AND METHODS

Eighteen patients (30 to 59 years old, eight men and ten women) with chronic dyspepsia due to idiopathic gastric stasis and ten healthy volunteers (21 to 39 years old, six men and four women) participated in the study. The patients were admitted to the study according to the following criteria: (1) chronic (longer than one year) dyspeptic symptoms (nausea, vomiting, postprandial epigastric discomfort, early satiety); (2) normal findings from upper panendoscopy and hepatobiliary-pancreatic echography; absence of clinical and laboratory evidence for metabolic, endocrine, collagenous, neurologic, and other systemic disease; no history of long-term ingestion of drugs that could cause delayed gastric emptying; no prior gastric surgery; and (3) delayed gastric emptying as demonstrated by radionuclide transit studies. Informed consent was obtained from each subject.

In all subjects, gastrointestinal motor activity was studied by manometry. Furthermore, the effect of naloxone on gastric emptying was evaluated by two paired radionuclde transit studies, during which either saline or naloxone hydrochloride (40 μg/kg/hr, intravenously) were continuously infused in a randomized fashion.

Gastric Emptying Study

After at least eight hours of fasting, the subjects ate a meal consisting of three fried egg whites. The egg whites were labeled by stirring them with 0.2 mCi of technetium Tc 99m sulfur colloid while cooking. Previous studies showed that the radioactive label remains fairly well attached to the solid food after one hour of incubation at 37 °C in 0.1N hydrochloric acid or gastric juice under continuous agitation.[24] After ingestion of the meal, the subjects assumed the supine position and the abdominal radioactivity was measured by an external gamma camera each minute for one hour. All images were stored in a magnetic disk for data processing. After the delineation of the gastric area as the area of interest, the percentage of the radioactive label remaining in the stomach at 15, 30, 45, and 60 minutes was calculated.

Gastrointestinal Manometry

Gastrointestinal fasting motor activity was measured after an overnight fast with a four-lumen intestinal tube (external diameter, 3.2 mm) for at least five hours. The recording sites were placed fluoroscopically in the terminal antrum, first duodenal portion, descending duodenum, and the ligament of Treitz. Each channel was perfused continuously at 0.1 mL/min with distilled water, using a low compliance perfusion system, and was connected to external physiologic pressure transducers, in their turn coupled with a rectilinear polygraph. The motor recordings were coded and read blindly. Various factors were analyzed. First, the cyclic variations of fasting motor activity were identified as previously described.[25] Briefly, phase 1 is characterized by motor quiescence, phase 2 by irregular but persistent contractions, and phase 3 by bursts of rhythmic contractions at the maximal frequency, ie, three to four per minute in the antrum and 11 to 12 per minute in the proximal small bowel. Afterward, the site of origin (antrum or duodenum), the propagation (migrating in oroaboral direction, simultaneous or retrograde), and the velocity of propagation from descending duodenum to the ligament of Treitz (centimeters per minute) of each phase 3 burst were assessed. Furthermore, the total duration of each interdigestive cycle (minutes between the termination of two consecutive phase 3 bursts) and the relative duration of phases 1, 2, and 3 at the descending duodenum (percentage of time of the total cycle duration) were calculated. Finally, a five-hour motility index (summation of the amplitude of contractions) was calculated in the antrum and descending duodenum. The statistical analysis was done with the analysis of variance and χ^2 analysis.

RESULTS

Fasting gastrointestinal motor activity from the healthy controls was characterized by cyclic succession of phases 1, 2, and 3. The mean cycle duration was 95.3 ± 25.3 minutes and the relative duration of phases 1, 2, and 3 was 57.9% ± 10.9%, 36.2% ± 9.4%, and 5.9% ± 1.4%, respec-

Accepted for publication Sept 4, 1985.
From the Gastrointestinal Unit, Departments of Medicine I (Drs Narducci, Bassotti, Gaburri, Farroni, and Morelli) and Nuclear Medicine (Drs Granata and Palumbo), University of Perugia (Italy).
†Deceased.
Reprint requests to Clinica Medica, Policlinico, Monteluce, 06100 Perugia, Italy (Dr Morelli).

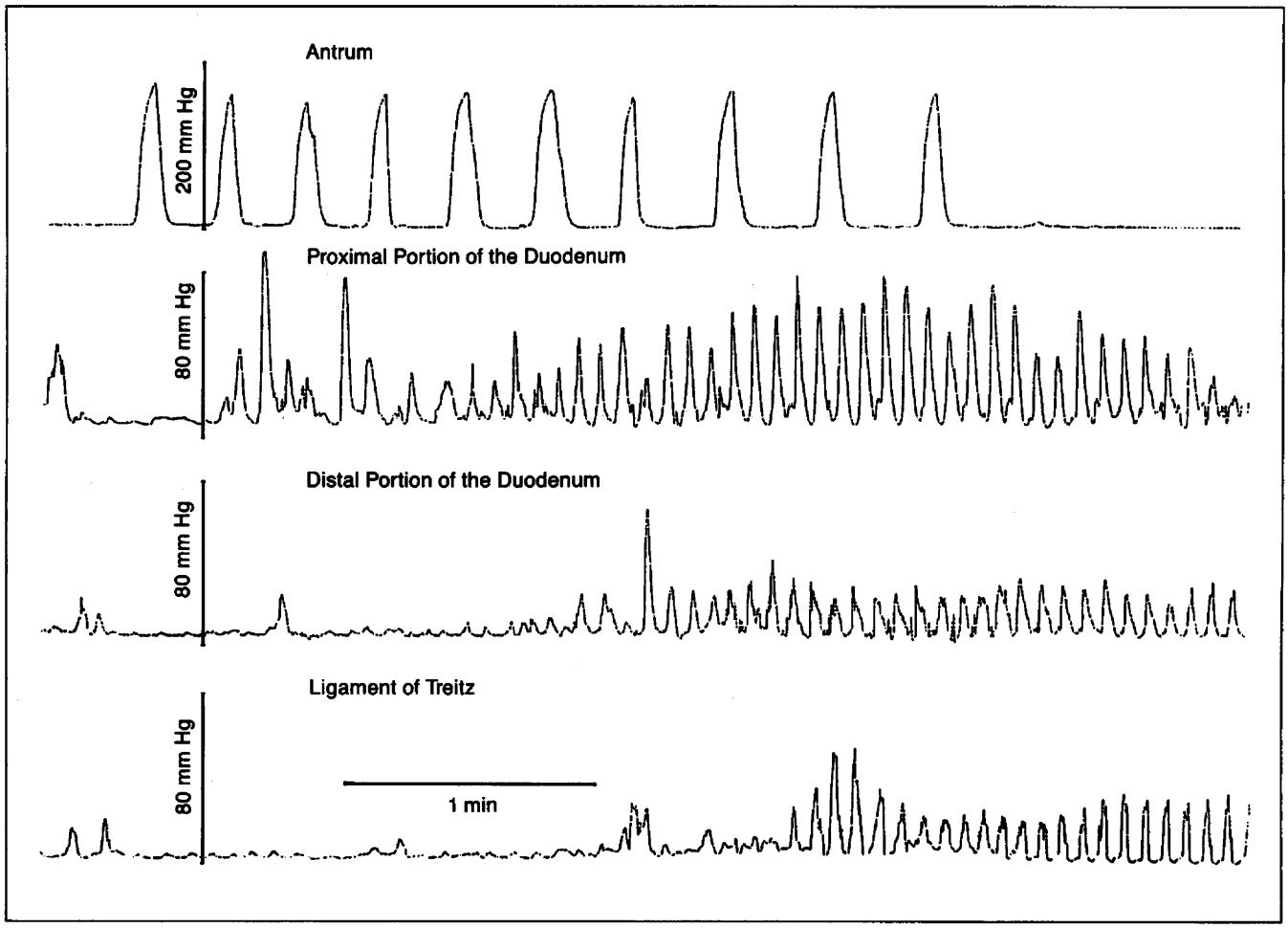


Fig 1.—Phase 3 interdigestive motor activity originating in antrum and migrating aborally.

tively. Sixty-three percent of the phase 3 bursts commenced in the antrum and all propagated distally at a mean propagation velocity of 7.6±2.3 cm/min (Fig 1). In all normal subjects at least one phase 3 burst originated in the antrum.

Gastrointestinal motility was abnormal in patients with chronic idiopathic gastric stasis. All patients had a cyclic succession of phase 1, 2, and 3 with a mean cycle duration (117.5±31.2 minutes; $P>.05$) not different from that of controls. Only 25% of phase 3 bursts, however, originated in the antrum ($P<.001$ vs controls) and 27% of the activity fronts showed an abnormal propagation along the duodenum (simultaneous or retrograde) ($P<.001$). Ten patients had complete absence of gastric phase 3 activity (Fig 2), while the other eight patients had one or more phase 3 bursts starting in the antrum. The other manometric factors were significantly different in these two patient subgroups (Table), suggesting a distinct pathophysiologic condition. In the patients without gastric phase 3 bursts, the antral motility index was significantly lower than in controls and remaining patients, while their duodenal motor activity was near normal (gastroparesis group). The patients with gastric phase 3 bursts had a normal antral motility index but their duodenums were hyperdyskinetic (Fig 3 and Table) (duodenal dyskinesia group). The gastroparesis and duodenal dyskinesia groups did not differ in age, sex, severity, and duration of symptoms, or in severity of gastric retention.

Naloxone had no effect on gastric emptying in the healthy

Manometric Features in Patients and Controls

	Controls (n=10)	Patients: Gastroparesis (n=10)	Patients: Duodenal Dyskinesia (n=8)
No. of phase 3 bursts starting in antrum	26/41	0/35*	14/20†
5-hr antral motility index ($\times 10^{-3}$)	29.1±12.7	16.5±5.1*	30.4±12.8†
No. of abnormal duodenal phase 3 bursts	0/41	5/35*	10/20*†
5-hr duodenal motility index ($\times 10^{-3}$)	107.4±31.7	101.9±41.3	159.1±50.2*†
Mean cycle duration, min	95.3±25.3	115.5±32.1	121.2±30.1
Time of duodenal phase 1, %	57.9±10.9	46.8±29.6	12.2±5.2*†
Time of duodenal phase 2, %	36.2±9.4	47±37.5	81.9±6.9*†
Time of duodenal phase 3, %	5.9±1.4	6.2±2.1	5.9±1.8

*Significant difference vs controls.
†Significant difference vs gastroparesis.

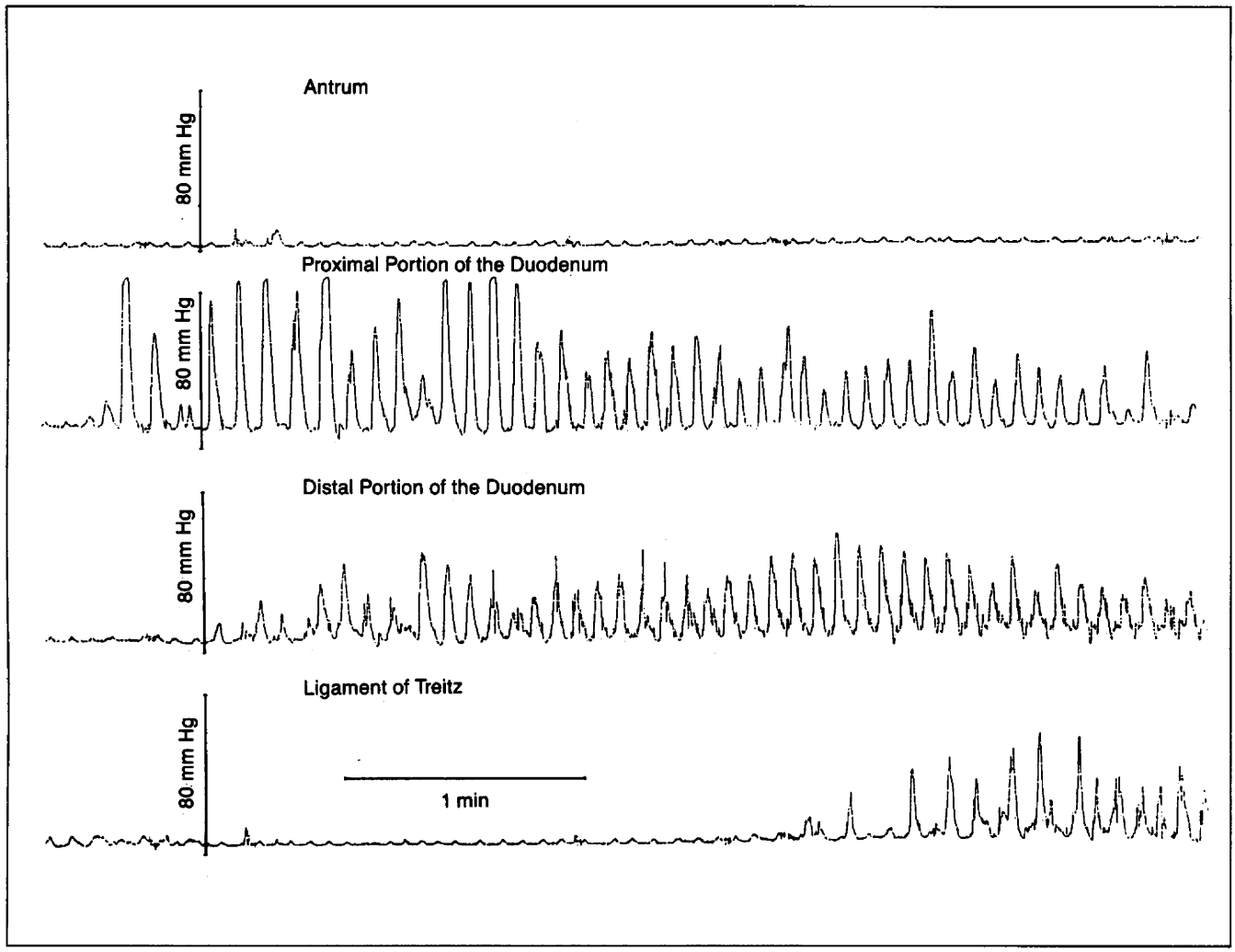


Fig 2.—Duodenal phase 3 activity migrating aborally along duodenum, but not preceded by gastric phase 3.

volunteers (data not shown) or in patients with gastroparesis (Fig 4). The opioid antagonist, however, produced a significant acceleration of gastric emptying in patients with duodenal dyskinesia (Fig 4).

COMMENT

The relationship between idiopathic gastrointestinal motor dysfunction, gastric stasis, and chronic "functional" dyspepsia has been previously reported.[1-6] The present study suggests that two different abnormalities of gastrointestinal motility can be responsible for gastric stasis. Absence of gastric phase 3 bursts and antral hypomotility have been previously observed in diabetic gastroparesis[10] and in idiopathic antral motor dysfunction[1]; as is easily understandable, gastric hypomotility can cause, in the fed state, poor grinding and propulsion of food. The other patients with normal gastric function had features of duodenal hyperdyskinesia; in the postprandial state a dyskinetic, hyperactive duodenum could cause a functional obstruction to gastric emptying. This concept is in accordance with the demonstration that duodenal resistance plays an important role in the modulation of gastric emptying, in physiologic conditions[26-30] as well as in experimentally induced small-bowel dyskinesia.[31] The different effects of naloxone on gastric emptying observed in these two subgroups of patients (Fig 4) further support our claim that gastroparesis and duodenal dyskinesia are distinct pathophysiologic conditions.

In patients with idiopathic gastrointestinal motor dysfunction and chronic gastric stasis of foods, the disease may concern the integrity of the gastrointestinal smooth-muscle cells themselves or the control mechanisms of their function. Gastrointestinal motility is controlled by neural, humoral, and myoelectric mechanisms.[32] Since exogenous opiates have a profound effect on gastrointestinal motility[33-35] and since the gastrointestinal tract is rich in endogenous opiatelike substances,[17-20] it is possible that the endogenous opiate system participates in the control of gastrointestinal motility. Morphine has long been known to inhibit gastric emptying,[13,33] and more recently it has also been shown that the exogenous administration of synthetic enkephalins produces a delay in gastric emptying in humans.[14,15] The mechanism(s) of gastric stasis produced by exogenous opiates has been a matter of controversy. Early studies attributed this delay to pylorospasms[36]; exogenous opiates have also been shown to produce a decrease in the number of antral contractions whose strength, however, seems to be increased.[37,38] Finally, duodenal spasm is now generally accepted as the major mechanism of the inhibition of gastric emptying induced by opiates.[33,34] Indeed, mor-

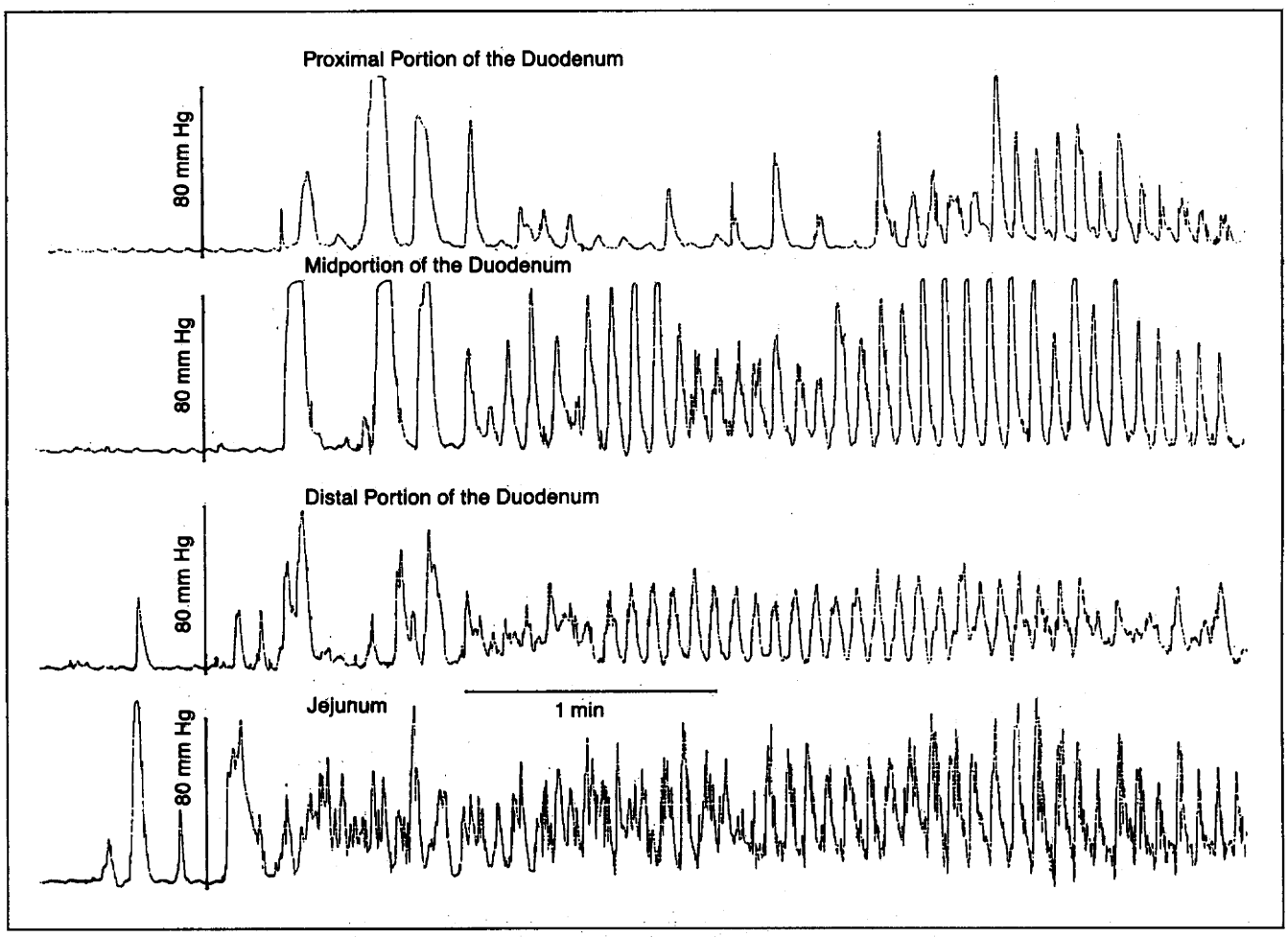
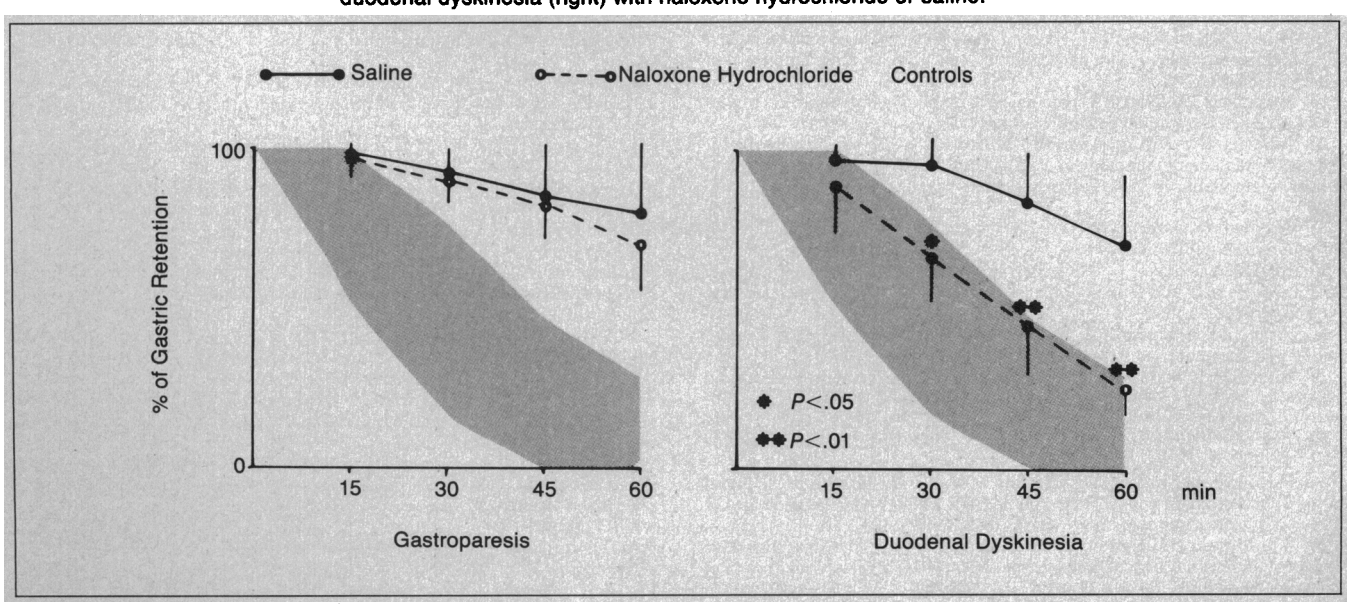


Fig 3.—Retrograde phase 3 activity in duodenum; also note high-amplitude, long-duration contractions at beginning of phase 3.

Fig 4.—Gastric emptying in patients with gastroparesis (left) and duodenal dyskinesia (right) with naloxone hydrochloride or saline.



phine increases small-bowel motility[39] and induces the premature appearance of migrating myoelectric complexes[40] that differ in several respects when compared with the spontaneous or motilin-induced migrating myoelectric complexes[41]; also, exogenously administered analogues of endogenous opiates increase small-bowel motility.[39,42] This increased motor activity fails to accelerate the transit and actually delays it along the entire small bowel.[33,43-45]

In physiologic conditions, the role of endogenous opiates in the modulation of gastrointestinal motility is still unclear. In accord with previous studies,[46] we observed that naloxone had no effect on gastric emptying in healthy humans. In experimental conditions, however, slowing of gastric emptying and stimulation of endogenous opiates may be related to each other.[47,48] Naloxone is a specific opioid antagonist,[23] and this drug has been shown selectively to normalize gastrointestinal motor abnormalities and gastric stasis[34,35,40,49] induced by exogenous opiates but not similar abnormalities otherwise produced.[49] Therefore, the response to naloxone observed in patients with duodenal dyskinesia suggests that a disorder of endogenous opiate function was largely responsible for causing gastric stasis in these patients.

In summary, either gastroparesis or duodenal dyskinesia can promote gastric stasis and chronic dyspeptic symptoms. Endogenous opiates seem to be involved in the pathogenesis of gastric stasis in patients with duodenal dyskinesia.

References

1. Rees WDW, Miller LJ, Malagelada JR: Dyspepsia, antral motor dysfunction and gastric stasis of solids. *Gastroenterology* 1980;78:360-365.
2. You CH, Lee KY, Chey MY, et al: Electrogastrographic study of patients with unexplained nausea, bloating, and vomiting. *Gastroenterology* 1980;79:311-314.
3. Perkel MS, Hersh T, Moore C, et al: Metoclopramide therapy in 55 patients with delayed gastric emptying. *Am J Gastroenterol* 1980;74: 231-236.
4. Telander RL, Morgan KG, Kreulen DL, et al: Human gastric atony with tachygastria and gastric retention. *Gastroenterology* 1978;75:497-501.
5. Cottrell CR, Sninsky CA, Martin JL, et al: Are alterations in gastroduodenal motility responsible for previously unexplained nausea, vomiting, and abdominal pain? *Dig Dis Sci* 1982;27:650-654.
6. Malagelada JR, Stanghellini V: Gastrointestinal manometry in 104 patients with unexplained nausea and vomiting, abstracted. *Gastroenterology* 1983;84:1237.
7. Malagelada JR: Physiologic basis and clinical significance of gastric emptying disorders. *Dig Dis Sci* 1979;24:657-661.
8. Malagelada JR: Gastric emptying disorders: Clinical significance and treatment. *Drugs* 1982;24:353-359.
9. Snape WJ, Battle WM, Schwartz SS, et al: Metoclopramide to treat gastroparesis due to diabetes mellitus. *Ann Intern Med* 1982;96:444-446.
10. Malagelada JR, Rees WDW, Mazzotta LJ, et al: Gastric motor abnormalities in diabetic and postvagotomy gastroparesis: Effect of metoclopramide and bethanechol. *Gastroenterology* 1980;78:286-293.
11. Stanghellini V, Malagelada JR: Gastric manometric abnormalities in patients with dyspeptic symptoms after fundoplication. *Gut* 1983;24: 790-797.
12. Schuffler MD, Rohrmann CA, Chaffee RG, et al: Chronic intestinal pseudo-obstruction. *Medicine* 1981;60:173-196.
13. Jaffe JH, Martin WR: Narcotic analgesics and antagonists, in Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics.* New York, Macmillan Publishing Co, 1980, pp 494-534.
14. Lamki L, Sullivan S: A study of gastrointestinal opiate receptors: The role of the mu receptor on gastric emptying: Concise communication. *J Nucl Med* 1983;24:689-692.
15. Sullivan SN, Lamki L, Corcoran P: Inhibition of gastric emptying by enkephalin analogue. *Lancet* 1981;2:86-87.
16. Nimmo WS, Heading RC, Wilson J, et al: Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *Br Med J* 1979;2:1189-1191.
17. Polak JM, Sullivan SN, Bloom SR, et al: Enkephalin-like immunoreactivity in the human gastrointestinal tract. *Lancet* 1977;1:972-974.
18. Linnoila RI, DiAugustine RP, Miller RJ, et al: An immunohistochemical and radioimmunological study of the distribution of [MET^5]- and [LEU^5]-enkephalin in the gastrointestinal tract. *Neuroscience* 1978;3: 1187-1196.
19. Gershon D, Erde SM: The nervous system of the gut. *Gastroenterology* 1981;80:1571-1594.
20. Go VLW, Johnson G, Angel F, et al: Quantitative distribution of substance P and MET-enkephalin in canine gut, abstracted. *Gastroenterology* 1982;82:1069.
21. Bitar KN, Makhlouf GM: Specific opiate receptors on isolated mammalian gastric smooth muscle cells. *Nature* 1982;297:72-74.
22. Bitar KN, Makhlouf GM: Opiate receptors are present on circular and selectively absent from longitudinal muscle cells of the intestine, abstracted. *Gastroenterology* 1983;84:1107.
23. Paterson SJ, Robson LE, Kosterlitz HW: Classification of opioid receptors. *Br Med Bull* 1983;39:31-36.
24. Narducci F, Granata MT, Morelli A, et al: Evaluation of Tc-99-m-sulfur colloid–tagged cooked egg whites as a marker of solid food in the human stomach. *J Nucl Med Allied Sci* 1983;27:162-163.
25. Vantrappen G, Janssens J, Hellemans J, et al: The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. *J Clin Invest* 1977;59:1158-1166.
26. Miller J, Kauffman G, Elashoff J, et al: Search for resistances controlling canine gastric emptying of liquid meals. *Am J Physiol* 1981;241: G403-G415.
27. Bortolotti M, Pandolfo N, Nebiacolombo C, et al: Modifications in gastroduodenal motility induced by the extramucosal section of circular duodenal musculature in dogs. *Gastroenterology* 1981;81:910-914.
28. Bass P, Russel J: Gastric emptying of liquids: Role of the small intestine, in Chey WY (ed): *Functional Disorders of the Digestive Tract.* New York, Raven Press, 1983, pp 157-165.
29. Keinke O, Ehrlein HJ: Effects of oleic acid on gastric emptying and gastroduodenal motility, in Labò G, Bortolotti M (eds): *Gastrointestinal Motility.* Verona, Italy, Cortina International, 1983, pp 143-145.
30. Williams NS, Miller H, Meyer JH: The site of chemoselective resistance to gastric emptying, in Labò G, Bortolotti M (eds): *Gastrointestinal Motility.* Verona, Italy, Cortina International, 1983, pp 147-150.
31. Cranley B, Kelly KA: Small intestinal regulation of gastric emptying. *Gastroenterol Clin Biol* 1983;7:703-704.
32. Johnson LR (ed): *Physiology of the Gastrointestinal Tract.* New York, Raven Press, 1981.
33. Ambinder RF, Schuster MM: Endorphins: New gut peptides with a familiar face. *Gastroenterology* 1979;77:1132-1140.
34. Konturek SJ: Opiates and the gastrointestinal tract. *Am J Gastroenterol* 1980;74:285-291.
35. Rozè C, Dubrasquet M: Endorphines, enkèphalines et tube digestif. *Gastroenterol Clin Biol* 1983;7:177-188.
36. Kreuger H: The action of morphine on the digestive tract. *Physiol Rev* 1937;17:619-645.
37. Silbiger ML, Donner MW: Morphine in the evaluation of gastrointestinal disease. *Radiology* 1968;90:1086-1090.
38. Thor P, Walus KM, Krol R, et al: Effects of met-enkephalin and morphine on the motor and myoelectric activity of the stomach. *Pol Przegl Chir* 1979;51:659-665.
39. Burks TF, Hirning LD, Galligan JJ, et al: Motility effects of opioid peptides in dog intestine. *Life Sci* 1982;31:2237-2240.
40. Sarna S, Northcott P, Belbeck L: Mechanism of cycling of migrating myoelectric complexes: Effect of morphine. *Am J Physiol* 1982;242:G588-G595.
41. Sarna S, Condon RE, Cowles V: Morphine versus motilin in the initiation of migrating myoelectric complexes. *Am J Physiol* 1983;245:G217-G220.
42. Davis TP, Culling AJ, Schoemaker H, et al: β-Endorphin and its metabolites stimulate motility of the dog small intestine. *J Pharmacol Exp Ther* 1983;227:499-507.
43. Farrar JT: The effect of drugs on intestinal motility. *Clin Gastroenterol* 1982;11:673-682.
44. Quigley AMM, Phillips SF, Wienbeck M, et al: The effect of morphine on motility, flow and transit in the human ileocolonic junctional region. *Gastroenterol Clin Biol* 1983;7:727-728.
45. Prokop EK, Caride VJ, Wienchenbach K, et al: Validation of a scintigraphic method for determination of small intestinal transit time: Effect of metoclopramide and morphine, abstracted. *Gastroenterology* 1983;84:1277.
46. Frank EB, Lange R, Plankey M, et al: Effect of morphine and naloxone on lower esophageal sphincter pressure and gastric emptying in man, abstracted. *Gastroenterology* 1982;82:1060.
47. Danquechin-Dorval E, Muller GP, Eng R, et al: Role of endogenous opiates in radiation-induced suppression of gastric function, abstracted. *Gastroenterology* 1984;86:1064.
48. Stanghellini V, Zinsmeister AR, Go VLW, et al: Opiate and adrenergic blockers modify the gut response to stress, abstracted. *Gastroenterology* 1983;84:1320.
49. Lefebvre RA, Willems JL, Bogaert MG: Gastric relaxation and vomiting by apomorphine, morphine and fentanyl in the conscious dog. *Eur J Pharmacol* 1981;69:139-145.