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(54) **METHOD AND APPARATUS FOR TREATMENT OF GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD)**

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(57) **ABSTRACT**

GERD is treated through a method and apparatus of stimulating the body organ to accelerate a discharge of contents from the duodenum of the patient to thereby encourage discharge of contents from the stomach of the patient across the pyloric valve and into the duodenum.

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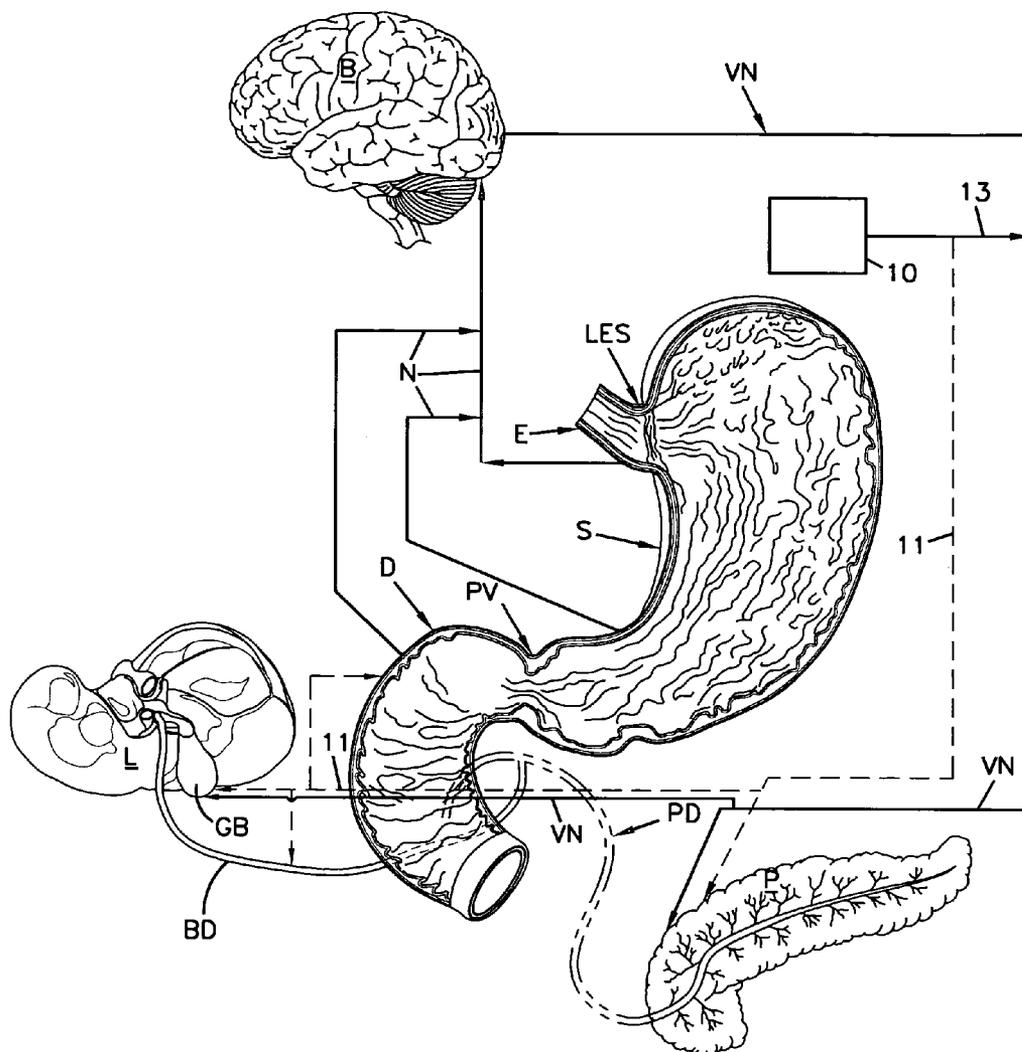


FIG. 1

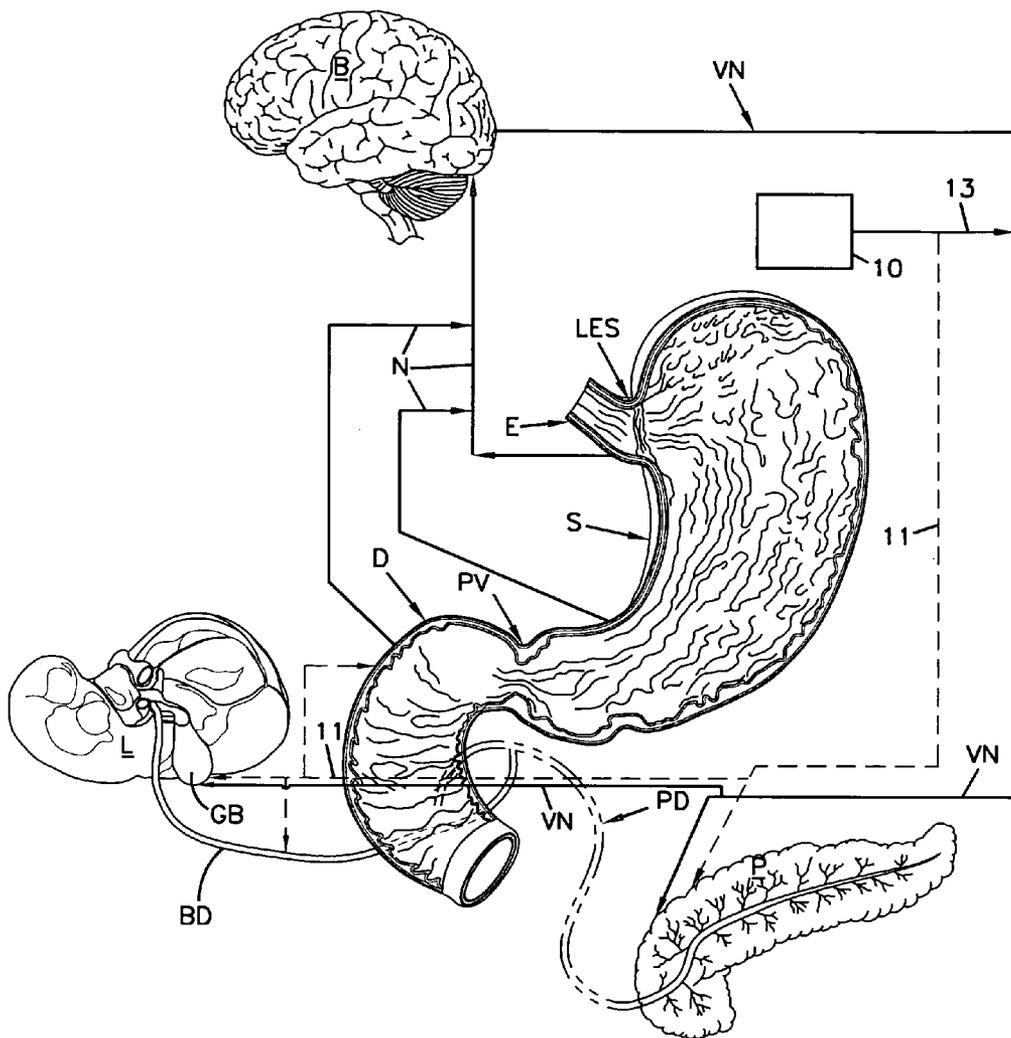
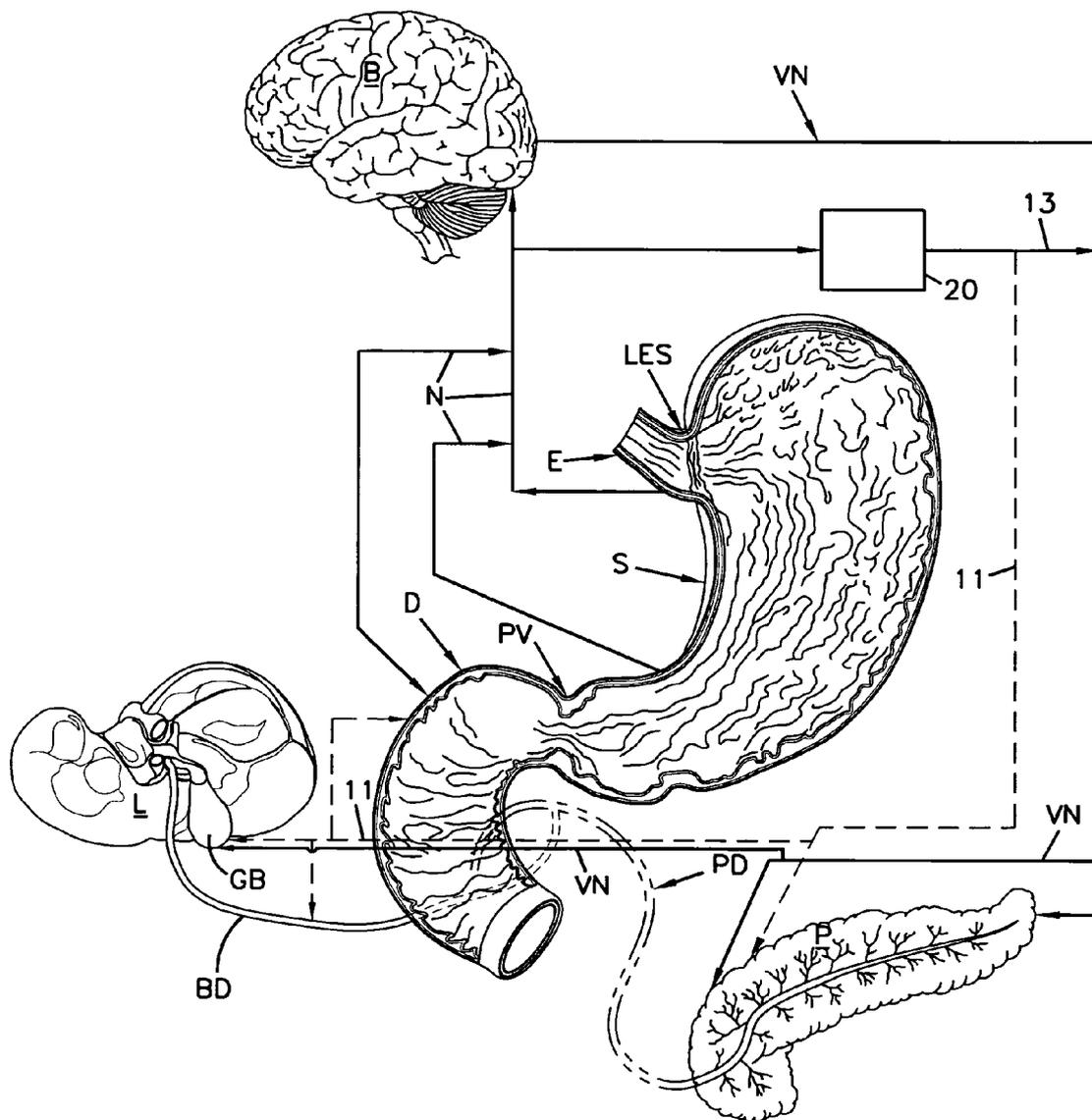


FIG.2



METHOD AND APPARATUS FOR TREATMENT OF GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD)

[0001] This application is a divisional of application Ser. No. 10/358,093, filed Feb. 3, 2003, which application is incorporated herein by reference.

I. BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention pertains to the field of treatment of gastro-esophageal reflux disease (GERD).

[0004] 2. Description of the Prior Art

Gastro-esophageal reflux is a physical condition in which stomach acids reflux, or flow back from the stomach into the esophagus. Frequent reflux episodes may result in a more severe problem known as gastro-esophageal reflux disease (GERD). GERD is the most common form of dyspepsia, being present in approximately 40% of adults in the United States on an intermittent basis and some 10% on a daily basis as described in U.S. Pat. No. 6,098,629 Johnson et al., dated Aug. 8, 2000.

[0005] As indicated in Johnson et al., dyspepsia, or heartburn is defined as a burning sensation or discomfort behind the breastbone or sternum and is the most common symptom of GERD. Other symptoms of GERD include dysphasia, odynophagia, hemorrhage, water brash and pulmonary manifestations such as asthma, coughing, or intermittent wheezing due to acid aspiration.

[0006] GERD is generally considered to be the result of a motility disorder which permits the abnormal and prolonged exposure of the esophageal lumen to acidic gastric contents. Hunt, "The Relationship between the Control of pH and Healing and Symptom Relief in Gastro-Oesophageal Reflux Disease", *Ailment Pharmacol Ther.*, 9 (Suppl. 1) pp. 3-7 (1995). Many factors are believed to contribute to the onset of GERD. These include transient lower esophageal sphincter (LES) relaxations, decreased LES resting tone, delayed stomach emptying and an ineffective esophageal clearance.

[0007] Treatments for GERD include lifestyle changes such as weight loss, avoidance of certain foods (e.g., coffee, caffeine, alcohol, chocolate) that exacerbate the symptoms of GERD and avoidance of excessive bending. Elevation of the head of a patient's bed helps prevent nocturnal reflux. While these avoidance strategies may be helpful there is relatively little data pointing to the efficacy of lifestyle modification for the treatment of GERD.

[0008] Certain medications used for treatment of GERD have been administered for years with varying success. Conventional antacids such as Tums® and Roloids® may, in some patients, produce short-term relief but often have side effects including diarrhea and constipation.

[0009] Other drugs have been more effective at controlling GERD but fail to treat underlying causes of the disease and have been proven to be extremely expensive and not readily available to all patients due to such expense. Examples of such drugs are H₂-receptor antagonists (which control gastric acid secretion in the basal state) and proton pump inhibitors (which control meal-stimulated acid secretion).

Hunt, id. Both classes of drugs can raise intragastric pH to or about 4 for varying durations. Hunt, supra.

[0010] Surgery treatments are also known for the treatment of GERD and include techniques for bulking the lower esophageal sphincter such as techniques described in U.S. Pat. No. 6,098,629 Johnson et al, Aug. 8, 2000. Other surgical techniques include placement of pacemakers for stimulating muscle contractions in the esophageal sphincter, the stomach muscles or in the pyloric valve. U.S. Pat. No. 6,104,955 to Bourgeois, U.S. Pat. No. 5,861,014 to Familoni.

[0011] A summary of GERD treatments can be found in DeVault, et al., "Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease", *Amer. J. of Gastroenterology*, Vol. 94, No. 6, pp. 1434-1442 (1999).

[0012] Notwithstanding multiple attempts at various types of treatment, GERD continues to be a serious disease proving to be difficult to treat by any of the foregoing prior art techniques. In view of the foregoing and notwithstanding various efforts exemplified in the prior art, there remains a need for an effective treatment for GERD. It is an object of the present invention to provide a novel treatment and novel apparatus for the treatment of GERD.

II. SUMMARY OF THE INVENTION

[0013] One inventive aspect of the present disclosure relates to methods and devices for treating GERD by stimulating the duodenum of a patient to accelerate gastric emptying.

[0014] According to a preferred embodiment of the present invention, a method and apparatus are disclosed for treating gastro-esophageal reflux disease of a patient. The method includes stimulating a body organ to accelerate a discharge of contents from a duodenum of a patient to thereby encourage discharge of contents from a stomach of the patient across a pyloric valve of the patient and into the duodenum. The apparatus of the invention includes a signal generator for generating a stimulation signal. A conductor electrically connects the signal generator to the body organ to accelerate a discharge of contents from the duodenum of the patient to encourage gastric emptying.

III. BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIG. 1** is a schematic representation of a gastric-emptying feedback loop with a patient-controlled stimulator for stimulating an organ of the loop; and

[0016] **FIG. 2** is a view similar to **FIG. 1** with an automatic controller replacing the patient-controller of **FIG. 1** and with feedback circuits to the automatic controller schematically represented.

IV. DESCRIPTION OF THE PREFERRED EMBODIMENT

[0017] With reference now to the various drawing figures in which identical elements are numbered identically throughout, a description of the preferred embodiment of the present invention will now be described.

[0018] With initial reference to **FIG. 1**, a gastric emptying feedback loop is shown schematically for ease of illustration. The feedback loop illustrates a patient's stomach S

which is provided with food from the esophagus E. A lower esophageal sphincter LES is shown positioned between the esophagus E and the stomach S. The lower esophageal sphincter normally provides control of reflux of stomach contents into the esophagus E.

[0019] On a proximal or lower end of the stomach S the stomach discharges into the superior duodenum D which is an upper portion of the intestines. The superior duodenum D and the stomach S are separated by a pyloric valve PV which opens to permit gastric emptying from the stomach into the duodenum D.

[0020] Also schematically illustrated in FIG. 1 are nerve paths N providing signal flow paths from both the superior duodenum D and the stomach S to the brain B. An efferent Vagal nerve VN connects the brain B to the pancreas P of the patient. A conduit (pancreatic duct PD) extends from the pancreas P and discharges into the superior duodenum D.

[0021] The presence of food contents within the duodenum D (such contents being referred to as "chyme") may prevent passage of gastric content of the stomach S past the pyloric valve PV into the duodenum D. As long as such gastric contents cannot be passed into the duodenum D, such contents can be forced retrograde past the lower esophageal sphincter LES and into the esophagus E creating the symptoms and discomfort of GERD. The contents discharging from the stomach S into the duodenum D are acidic (and high osmolality) and reside in the duodenum D until pH is elevated (close to a neutral pH of 6-7) and osmolality is normalized.

[0022] The elevation of pH and reduction of osmolality of chyme in the duodenum D results from exocrine secretion being administered from the pancreas P and from bile from the liver into the duodenum D. This raises the pH and lowers the osmolality of the duodenum D content permitting discharge from the duodenum D and thereby permitting gastric emptying across the pyloric valve PV.

[0023] According to the present invention, gastro-esophageal reflux disease (GERD) results from a derangement of the feedback loops involved in upper GI digestion and motility control. This problem encompasses receptors and reflexes that regulate the propulsive contractions of the stomach, upper duodenum and biliary tree and the secretions of the exocrine pancreas. The interaction of these receptors and reflexes control gastric emptying (by coordinating gastric propulsive contractions and sphincter [primarily pyloric] tone) and regulate the pH and osmolality of the chyme in the duodenum. This chemo-regulation is mediated through control of bile delivery and stimulation of secretion by the exocrine pancreas of fluid delivered to the superior duodenum. Chey et al., "Neural Hormonal Regulation of Exocrine Pancreatic Secretion", *Pancreatology*, pp. 320-335 (2001).

[0024] Normally, ingestate delivered to the stomach is mixed by low intensity gastric mixing contractions with the enzymatic, ionic, including hydrogen ion (H^+), and water secretions of the glands of the stomach. When the material is adequately reduced in size and is a smooth consistency, the fluid, now called chyme, is delivered to the ampulla of the small intestine by the much stronger propulsive, or emptying, contractions of the stomach coupled with transitory relaxation of the pyloric sphincter. This material is at a very low pH (about 2) and high osmolality, which activates

receptors, including those for H^+ and osmotic pressure, which are abundant in the wall of the ampulla. This receptor activation initiates the series of reflexes that cause pancreatic exocrine secretion to be delivered into the superior duodenum and ampulla. This fluid contains digestive enzymes, water and buffering compounds to raise the pH, and reduce the osmolality, of the chyme.

[0025] Once a neutral pH and physiological osmolality are achieved, then propulsive contractions in the superior duodenum move the chyme out of the superior portion into the length of the duodenum; At which point the stretch and baro-receptors in the ampulla allow the pyloric sphincter to relax and another bolus of gastric contents is delivered into the ampulla by the peristaltic gastric emptying contractions. This material, at a very low pH (less than 2), activates hydrogen ion (H^+) on receptors of the ampulla (upper most portion of the duodenum) causing the pancreatic fluids to be delivered to the material in the ampulla restarting the cycle as described above. Chapter 3, "The Stomach", *Gastrointestinal System*, 2nd Ed., M. S. Long editor, Mosby Publisher, London (2002).

[0026] If the control system is down regulated by, for example, by increased pH of gastric contents entering the ampulla, feedback may thereby be reduced from the H^+ receptors in the duodenum that stimulate pancreatic exocrine secretion and bile delivery to the duodenum, then movement of chyme from the superior duodenum is delayed, causing delay of gastric emptying. Mabayo, et al., "Inhibition of Food Passage by Omeprazole in the Chicken", *European J. of Pharmacology*, pp. 161-165 (1995).

[0027] In GERD, this reflex is inhibited in such a way that the stomach empties more slowly so that the gastric emptying contractions force gastric contents to flow retrograde into the esophagus. This is a result of the situation in which the gastric emptying contractions are vigorous but must operate against a contracted pyloric sphincter. These vigorous peristaltic contractions eventually begin to force gastric contents to flow retrograde into the esophagus because of the inherent imbalance between a very strong pyloric sphincter and a much weaker gastro-esophageal sphincter. The delay in gastric emptying is directly related to a slow down in the transport of chyme out of the ampulla and superior duodenum. The drugs used to treat this disease raise pH further dampening the hydrogen-receptor-pancreatic secretion loop, further delaying gastric emptying. Benini, "Gastric Emptying and Dyspeptic Symptoms in Patients with Gastroesophageal Reflux", *Amer. J. of Gastroenterology*, pp. 1351-1354 (1996).

[0028] The present invention is directed towards reestablishing the link between gastric emptying and pancreatic secretion delivery, thereby addressing the main pathology of this disease by shortening chyme residence time in the superior duodenum so that intestinal contents move into the distal digestive tract in a more normal manner. According to a first embodiment, this is done by stimulating the H^+ ion receptors or by stimulation of the pancreas directly or via its para-sympathetic innervation (pre-ganglionic Vagal nerves). Stimulation of pancreatic exocrine secretion has been shown by direct stimulation of the thoracic vagus nerves in dogs. Kaminski et al., "The Effect of Electrical Vagal Stimulation on Canine Pancreatic Exocrine Function", *Surgery*, pp. 545-552 (1975). This results in a more rapid (normal)

neutralization of chyme in the ampulla, allowing it move down the duodenum more quickly so that gastric emptying is returned to a more normal pace.

[0029] Acidity (pH) can be assessed by measuring bicarbonate. It will be understood that references to -H includes such indirect measurements. Also, effects of the therapy described herein can be assessed and/or controlled by measuring an indication of pancreatic exocrine secretion or bile (e.g., HCO_3^-).

[0030] An alternative embodiment uses gastroscopic delivery of a paralyzing agent (e.g. botulism toxin) to the pyloric valve along with use of H_2 antagonists or PPI's to manage the acidity of the chyme reaching the duodenum.

[0031] As an additional alternative to pancreatic stimulation, the gall bladder can be stimulated to encourage bile movement into the duodenum. Shown schematically in the figures, the gall bladder GB resides below the liver L. The gall bladder is connected to the small intestine (specifically the duodenum D) via a bile duct BD. The bile duct BD can discharge directly into the duodenum D or via the pancreatic duct PD as shown. The bile can normalize the chyme to accelerate duodenal emptying. Bile consists of bile acids (detergents that emulsify lipids), cholesterol, phospholipids, electrolytes such as (Na^+ , K^+ , Ca^{+2} , Cl^- , HCO_3^-) and H_2O . Chapter 4, "The Liver and Biliary Tract", *Gastrointestinal System*, 2nd Ed., M. S. Long editor, Mosby Publisher, London (2002). The gall bladder GB or bile duct can be stimulated indirectly via stimulation of the vagal nerve VN or directly stimulated by an electrode or other stimulator.

[0032] As illustrated in the figures, an electrical stimulator 10, 20 which may be implanted is provided which alternatively may be directly connected to the Vagal nerve VN (e.g., via stimulation pathway 13) or the pancreas P (e.g., via stimulation pathway 11 shown in dashed line) to stimulate the pancreas directly or indirectly to excrete exocrine into the duodenum D (or more distally into the small intestine—e.g., into the jejunum) and increase the pH of chyme in the duodenum D as described. Alternatively, the same can be done to promote bile release by stimulating the bile duct BD or the gall bladder GB either directly (e.g., via stimulation pathway 11) or indirectly (e.g., by stimulating Vagal nerve VN via stimulation pathway 13). In other embodiments, the duodenum D can be stimulated directly (e.g., via one or more electrodes or other stimulators as indicated by pathway 11) to cause propulsive contractions that accelerate duodenal emptying. The frequency may be varied to maximize the response and selectively stimulate exocrine instead of endocrine secretions. Rösch et al., "Frequency-Dependent Secretion of Pancreatic Amylase, Lipase, Trypsin, and Chymotrypsin During Vagal Stimulation in Rats", *Pancreas*, pp. 499-506 (1990). See, also, Berthoud et al., "Characteristics of Gastric and Pancreatic Responses to Vagal Stimulation with Varied Frequencies: Evidence for Different Fiber Calibers?", *J. Auto. Nervous Sys.*, pp. 77-84 (1987) (showed frequency-response relationship with insulin, i.e., significantly less insulin was released at lower frequencies—2 Hz v. 8 Hz—also, frequency-response curves evidenced distinctly different profiles for gastric, pancreatic and cardiovascular responses.) Slight insulin release can maximize pancreatic exocrine secretion. Chey et al., "Neural Hormonal Regulation of Exocrine Pancreatic Secretion", *Pancreatology*, pp. 320-335 (2001).

[0033] With a patient control stimulation as shown in FIG. 1, the patient may activate the stimulator 10 by remote transmitter to stimulate an electrical charge either after eating (e.g., about 60 to 90 minutes after eating) or on onset of GERD symptoms. It will be appreciated that there are a wide variety of nerve stimulators and organ stimulators available for implantation and are commercially available and which include connectors for connecting directly to nerves.

[0034] FIG. 2 illustrates an additional embodiment where the patient activated loop is replaced with an automatic loop having a programmable stimulator 20 which receives as an input signals from sensors in the duodenum to measure pH, osmolality or strain (e.g., from baro-sensors) on the duodenum indicating filling or may measure acidity in the esophagus or strain on the lower esophageal sphincter LES or stomach S all of which may be provided to the implantable controller 20 which can be provided with desirable software to process the incoming signals and generate a stimulating signal to either the Vagal nerve, the pancreas P, the gall bladder GB, the bile duct BD or the duodenum D (or jejunum) directly in response to such received signals. It will be appreciated that stimulators and controllers are well within the skill of the art. U.S. Pat. No. 5,540,730, which is hereby incorporated by reference in its entirety, teaches a neurostimulator to stimulate a vagus nerve to treat a motility disorder. U.S. Pat. No. 5,292,344, which is hereby incorporated by reference in its entirety, teaches gastrointestinal sensors including pH sensors.

[0035] With the foregoing detailed description of the present invention, it has been shown how the objects of the invention have been attained in a preferred manner. Modifications and equivalents of disclosed concepts such as those which might readily occur to one skilled in the art, are intended to be included in the scope of the claims which are appended hereto.

What is claimed is:

1. A method for treating gastro-esophageal reflux disease (GERD) of a patient comprising:

- treating a body organ to accelerate a discharge of contents through at least a portion of a small intestine of the patient to thereby encourage discharge of contents from a stomach of the patient across a pyloric valve of the patient and into said small intestine.
2. A method according to claim 1 wherein said portion is a duodenum of said patient.
3. A method according to claim 1 wherein said treating is a stimulation selected to increase a pH of said contents of said portion of said small intestine.
4. A method according to claim 1 wherein said treating is a stimulation selected to decrease an osmolality of said contents of said portion of said small intestine.
5. A method according to claim 1 wherein said organ is a pancreas of said patient and said treating is a stimulation of said organ selected to stimulate delivery of an exocrine secretion from said pancreas to said portion of said small intestine.
6. A method according to claim 5 wherein said pancreas is stimulated directly.
7. A method according to claim 5 wherein said pancreas is indirectly stimulated by stimulating at least a nerve of said pancreas.

8. A method according to claim 5 wherein said stimulation is initiated by said patient.

9. A method according to claim 5 wherein said stimulation is initiated by a controller operatively connected to stimulating electrodes and having an input operatively connected to a sensor.

10. A method according to claim 9 wherein said sensor senses a pH level of said portion of said small intestine.

11. A method according to claim 9 wherein said sensor senses a degree of filling of said portion of said small intestine.

12. A method according to claim 9 wherein said sensor senses a degree of osmolality within said portion of said small intestine.

13. A method according to claim 9 wherein said sensor senses a degree of motility within said portion of said small intestine.

14. A method according to claim 1 wherein said treatment includes delivery of a paralyzing agent to said pyloric valve.

15. A method according to claim 14 wherein said delivery is done in conjunction with agents to manage acidity of a content of said portion of said small intestine.

16. A method according to claim 15 wherein said agents are selected from a group including H₂ antagonists and PPI's.

17. A method according to claim 5 wherein said stimulation is an electrical stimulation.

18. A method according to claim 17 wherein said stimulation is at a frequency selected to encourage exocrine secretion without excess endocrine secretion.

19. A method according to claim 1 wherein said treating is a stimulation selected to encourage bile delivery to the portion of said small intestine.

20. A method according to claim 1, wherein the body organ is a duodenum of said patient.

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