Gastroparesis & Dysmotilities
Gpda Association
www.gpda.net

Jeanne Keith-Ferris RN, BScN, President / Founder

February 25, 2004

FDA, Dockets Management Branch
Room 1061, 5630 Fishers Lane
Rockville, MD
20852

RE: Citizens' Petition to FDA requesting transfer from HUD to PMA for Enterra Therapy

To Whom It May Concern:

Please find enclosed a Petition and White Paper.

The Petition cites the latest research which clearly supports efficacy for the Enterra Therapy device which is used to treat drug refractory Gastorparesis.

The Petitioners request a response in 180 days.

Questions may be directed to our non-profit association.

Thank you

Sincerely,

Jeanne Keith-Ferris, RN, BScN
President/Founder of GPDA

Cc: Mark B. McClellan, FDA Commissioner
Art Collins, CEO, Medtronic Inc, 710 Medtronic Parkway, Minneapolis, MN, 55432
Scott Ward, Senior VP and President of Neurology and Diabetes, Medtronic Inc.
Camille Farhat, VP and GM; GI and Neurology, Medtronic Inc.

Tel: 403-247 3215 Fax: 403-267-1986 E-mail: jkff@gpda.net

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Charitable Organization, Canada Customs and Revenue: 859541310RR0001

2004P-0091

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Mark B. McClellan
Commissioner of the Food and Drug Administration.
5630 Fishers Lane, Room 1961, HFA-305
Rockville, MD
20852

Re: Citizens' Petition to transfer Enterra Therapy from a HUD to a PMA status

Dear Commissioner,

Enterra Therapy is an implantable device used to treat intractable nausea and vomiting resulting from a chronic, life threatening, debilitating digestive disease. This digestive disease, called Gastroparesis, has precious few treatments.

Since the HUD designation for this device in 2000, many papers and abstracts have been published which unequivocally demonstrate the effectiveness of Gastric Electrical Stimulation. All now that stands in the way for PMA status is lack of awareness.

Our non-profit frequently hears the stories of the many Americans who have to fight so hard for insurance coverage in order to access this treatment, all the while these patients are suffering inhumanly from constant, non-stop nausea and vomiting. Canadian's too would like access to this treatment, but since it is not fully FDA approved, their government will not cover the cost to access this treatment option. Some patients do not win their insurance appeals and have no other options left to them. They are without hope.

In August, 2003, our non-profit association mailed a White Paper to your office, titled: "Gastroparesis and Related Digestive Motility Diseases, a Medical Crisis."

No exaggeration of the claims need be made–the evidence speaks for itself. Millions of Americans are suffering terribly due to Gastroparesis and they have very few effective treatments.

Please review the Petition and accompanying White Paper. We anticipate that the FDA will immediately contact Medtronic Inc and invite them to begin the process for transfer of Enterra Therapy to a PMA status. We wish a response to the Petition's requests in 180 days.

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CITIZENS' PETITION SEEKING IMMEDIATE ACTION BY THE FEDERAL FOOD & DRUG ADMINISTRATION (FDA) TO TRANSFER APPROVAL FROM THE "HUMANITARIAN DEVICE EXEMPTION" (HDE) TO PREMARKET APPROVAL (PMA) FOR: THE GASTRIC ELECTRICAL STIMULATION (GES), LEVEL III DEVICE, ENTERRA THERAPY™, MEDTRONIC INC. FOR THE TREATMENT OF SEVERE NAUSEA AND VOMITING FROM GASTROPARESIS

February, 24 2004

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1. Introduction

This citizen's petition is brought forth by the Gastroparesis and Dysmotilities Association (GPDA) on behalf of patients living with Gastroparesis who desire to have effective treatment options available in order to help improve their quality of life.

Medtronic Inc has an implantable device, called Enterra Therapy™ classified as a HUD (Humanitarian Use Device) since 2000, for treating patients with intractable nausea and vomiting of gastric dysmotility origin (Severe Gastroparesis) which is refractory to medical management.

In order for this device to have qualified for the HUD designation, it was subjected to the requirements establishing safety. A Humanitarian Device Exemption (HDE) application is similar in both form and content to a premarket approval (PMA) application, but exempt from the documentation of effectiveness required of a PMA.

A Humanitarian Device Exemption (HDE) is intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect, or are manifested in fewer than 4,000 individuals in the United States per year (see 21 CFR 814.102(a)).

Therefore, a Humanitarian Use Device is for a condition manifested in a small number of cases, and for which the device does not pose an unreasonable or significant risk of illness or injury; its effectiveness does not have to be demonstrated; and yet, it holds a probable benefit to the patient's health care management.

In the time that has passed since the Enterra Therapy™ received HUD designation in 2000, a number of research papers, published in peer review journals, have now clearly established the efficacy of this device.

Medtronic Inc is a responsible and reputable company presently taking all the correct steps in accordance with industry practices to bring the Enterra Therapy device to a PMA (premarket approval) status. Patients clearly want this.

However, this industry sponsored multi-center clinical trial is progressing very slowly, since the patient group that the treatment is targeted for are terribly ill and present a medically complex and challenging clinical picture.

When the obvious emerges, it is important for the obvious to be stated in order to speed along full FDA approval for this safe, reversible, and efficacious therapeutic device; thus unburdening patients from the arduous insurance appeal processes they currently have to navigate in order to access this treatment.

This petition will provide 1) an outline to the present barriers and burdens in accessing this HUD; 2) a patient profile; 3) an outline of the recent evidence of efficacy with Enterra Therapy; and 4) the petition will urge the FDA commissioner to undertake a review with the manufacture, of the current efficacy data and quickly bring this device to a PMA status in order to decrease patient suffering and save lives.

Definitions: unless otherwise stated, GES (Gastric Electrical Stimulation) and Enterra Therapy will be used interchangeably.

A. What barriers exist under the current HUD (Humanitarian Use Device) designation.

Most state Medicare providers recognize the HUD status for Gastric Electrical Stimulation (GES) and easily grant approval for Enterra Therapy. However, Gastroparesis like all the digestive motility diseases is poorly recognized and misunderstood. The '**average**' patient with Gastroparesis must go through 2 to 3 appeals that can take over 2 years for Social Security to approve their disability claim; then begins the wait for Medicare status. Therefore, some of these very ill patients may have to wait 3 to 4 years to finally get Medicare status. This statement can be verified by gastroenterologists who see a large number of Gastroparesis patients in their clinical practice. The prolonged wait for Medicare status compromises patient care.

Private insurance providers view the Enterra Therapy as "investigational" and clearly stipulate in their policies that Gastric Electrical Stimulation is not covered. Patients who are prescribed the Enterra Therapy by their doctors must prepare for an immediate denial from their insurance providers, and then begins the appeal process. Families need to be organized and show fortitude to present their case. On average, patients go through 2 to 3 appeals before they finally obtain insurance approval, if they get approval at all. Those who are overwhelmed with their illness and without good emotional support may find these barriers insurmountable.

One tragic example was brought to our attention; a young 32 year old, male, Type I diabetic; in one year, had been in the hospital more than at home due to uncontrolled episodes of vomiting from his Gastroparesis. His GI specialist recommended Enterra Therapy. Three insurance appeals later the young man's surgery was scheduled for Enterra Therapy. In the time that these lengthy appeals took place, his kidneys failed and he was placed on renal dialysis in the same week that his GES surgery was scheduled. The GI specialist cancelled the surgery due to dialysis and informed the family that if GES had been implanted before his kidneys failed the patient could have had the device. Now because of dialysis, the family has been informed he cannot obtain the device. Weeks later, this has been clarified and now the family awaits the IRB (Institutional Review Board) review for approving Enterra Therapy. This may take up to 3 months, all the while this young man's health continues to deteriorate as his family watches helplessly. A year has transpired in their pursuit to get this treatment for their son.

Severe Gastroparetic patients are very ill, with their lives tied to frequent hospitalizations; and feeding formulas. Enteral or parenteral nutrition takes many hours to infuse-- some must run 24 hours a day. These housebound / hospitalized patients are usually young women, in the prime of their lives with small children. They are suffering from an overwhelming, life threatening illness. Many are vomiting numerous times a day. Their sleep pattern is disrupted due to nocturnal symptoms. This coupled with constant nausea and sleep deprivation robs them of their ability to concentrate and makes them emotionally fragile. Somehow, they have to find the emotional reserves and physical energy to fight insurance appeals for a reversible, safe and efficacious treatment that holds hope of decreasing their crippling upper digestive symptoms.

2. Petitioners

This petition is submitted on behalf of the following petitioners.

Mr. and Mrs. LaCasper, [redacted] Their son, Type I Diabetic, is still waiting for his GES. It has been an agonizing year long wait due to red tape, insurance appeals and misunderstandings. The family feels helpless as they witness their young adult son's repeated hospitalizations due to uncontrolled vomiting and blood sugar levels. His Gastroparesis began to intensify over the last 4 years. The family feels strongly that their son's erratic blood sugar levels and constant vomiting helped to accelerate his kidney failure. He recently became a dialysis patient.

Dottie Plosgrove, [redacted] is an idiopathic Gastroparetic patient who was advised by her specialist to get the GES back in 1996. The device was still categorized by the FDA at this time as an experimental device so her insurance provider refused to cover the surgery. Several years later, they still refused to pay for it. Dottie fought for years with her insurance provider; then she fought for years to gain disability status and Medicare. Finally, through Medicare, she received her GES and is very happy with the results.

Debbie Ritter, [redacted]. Deb has been a Type I Diabetic for 37 years. As a young girl she suffered with nausea and vomiting due to erratic blood sugar levels. Over the past 10 years her nausea and vomiting intensified. By 1996 she was diagnosis with Gastroparesis. Nothing helped to manage her symptoms and many hospitalizations ensued. Her weight fell from 137lbs to 89lbs. GES was advised. Two insurance appeals failed. Deb was admitted into the hospital for end stage digestive failure from Gastroparesis and was told she was dying. A final call from her hospital bed to her insurance provider succeeded in convincing them. Rushed into surgery, she awoke free of nausea; the first time in over a decade. Deb now has a renewed life. She can eat and has gained weight. Her blood glucose levels are significantly more stable than they have ever been in 37 years.

Jennifer Sivils, [redacted] Jennifer is a young mother of 3 children. She suddenly fell ill with idiopathic Gastroparesis in 1998. Her weight fell from 157lbs to 98lbs. Her family witnessed her constant vomiting, hospitalizations and rapid decline. Jennifer's life was being sustained with parenteral nutrition since any food or liquids consumed would be vomited back-up. Medications did nothing to help her. Jennifer was enrolled in the WAVESS study group for GES. Jennifer and the other patients in this study group were a catalyst for bringing Enterra Therapy from an experimental designation to a Humanitarian Use Device designation by the FDA. Once Jennifer received her Enterra Therapy, she still needed to be maintained on parenteral nutrition. But once Enterra was implanted, slowly she began to gain weight, and for the first time, she was able to keep down broths and soups without vomiting them back-up. After 4 years, Jennifer is now off parenteral nutrition. She can now maintain her weight by eating and no longer must endure hospitalizations. She still gets tired and has infrequent bouts of nausea and vomiting, but she is thankful to be alive and to be able to eat again.

Beth Nelson, [redacted] Beth has idiopathic Gastroparesis which developed suddenly post-operatively from a surgery unrelated to her digestive system. She was 38 years old at the time and is a mother of 2 children. Beth never vomited from her Gastroparesis. Instead she developed extraordinarily intense nausea. The nausea was 24/7 and would wake her at night or prevent her from falling asleep. Beth could no-longer eat; and even the sight, smell or sound of food would intensify her nausea. Her weight fell from 140 to 107 and weakness ensured. Beth was placed on Propulsid (Cisapride) in June of 2000, which worked very well. She was able to gain 20 lbs. Propulsid was soon after pulled from the market and was no longer available. Her doctor's institution chose not to back the compassionate access program for re-accessing Propulsid. So when her supply ran out, she again started to lose weight due to unrelenting, intractable nausea. In June 2001, Beth had her GES placed. She awoke from surgery and was nausea free. Moths later, she had reoccurrence of nausea, but as time goes on she now has very little to no nausea and merely has to be cautions not to eat too much just before bedtime. She reports that GES has worked better for her than did the Propulsid for overall control of her symptoms. She has gained back her weight, is eating again and enjoys being a mother.

Barbara King, [redacted] In 1997, Barbara is a grandmother with 3 grown children. She started to have problems with slow transit constipation thought to result from autonomic nerve dysfunction. The constipation was refractory to all treatments. In 1999 her colon was removed. The year following, she began to develop small bowel and gastric dysmotilities. Taking IV medications through her central catheter line, nothing helped to halt the downward spiral wrought from constant nausea and vomiting. Barbara was no longer able to travel or visit her grandchildren. She was in and out of the hospital and in jeopardy of losing her job. Three insurance appeals had to be fought for the right to access Enterra Therapy. The insurance fights left her life in limbo. Her family had to financially come up with the money while still waiting for a decision by their insurance provider. Barbara recently received her implant and has had a significant reduction in her nausea and vomiting and now feels her life is no longer tied to a hospital.

3. Statement of facts

A. Patient profile

Gastroparesis is a neuro-muscular disorder of the stomach and shows a spectrum of severity from mild, through severe. On the mild end of this continuum, various medical labels exist to describe this group of 'dyspeptic patients.' This confusion is related to the paucity of scientific knowledge surrounding these disorders of the upper digestive tract. Mild Gastroparesis may be called: "non-ulcer dyspepsia," 'motility-like dyspepsia,' "Functional dyspepsia" or post enteric infection "dysmotility." Diagnosis therefore rests upon the findings of **symptoms**, since other standard 'tests,' are normal. Dyspeptic symptoms are: nausea, abdominal bloating, early satiety, a persistent feeling of fullness, mid epigastric discomfort or pain developing soon after a meal. **Signs** may consist of vomiting, abdominal distention and weight loss. No two experts will agree upon where the milder forms of digestive 'functional' disorders end and more severe forms of 'motility' diseases begin.

However, in its severe classical form, Gastroparesis is easily recognizable by most gastroenterologists. It includes the finding of delay in gastric emptying along with severe dyspeptic symptoms. In some cases, patients may experience weight loss and /or become malnourished, requiring supplemental support in the form of jejunostomy tube feedings or total parenteral nutrition in order to meet their nutritional needs. Often, diagnosis rests upon the experience of the clinician since there is not a great deal of research or consensus to guide the definition or diagnosis of this disease.

Eighty percent of Gastroparetic patients are females and the mean age of onset is 35 years.1 For Gastroparetic patients followed **over a 6 year period,** McCallum et al found 15% remained dependent upon Enteral/parenteral nutrition. For all the Gastroparetic patients that were followed during this 6 year period: 35% were Idiopathic, 29% Diabetic, 13% post surgical, 8% Parkinson's disease, 5% Collagen vascular disease, 4% CIP and the remainder misc.1

Patients with Gastroparesis are mostly young and middle aged women in the prime of life. They have frequent hospital admissions, loss of work time, and a dismal future.2

The most troubling signs and symptoms of severe Gastroparesis are unrelenting nausea and vomiting. This frequently occurs with abdominal pain due to the distended, poorly functioning stomach, and also pain from chronic acid reflux resulting from gastric stasis.

This constant nausea and vomiting leads to dehydration and electrolyte imbalances usually necessitating emergency room visits with concomitant spiraling malnourishment.

In severe Gastroparesis, nutritional compromise is the hallmark of these unrelenting symptoms for which there are no effective treatments. These patients show a slow, insidious progression of malnourishment and many will require jejunostomy tubes or total parentral nutrition to stabilize their weight. Even with the placement of 'tubes' to rehydrate and provide nutrition---this does not alleviate symptoms.3 Patients will still 'pool' secretions in their stomachs and vomit this up. Venting gastrectomy tubes allow for the drainage of stomach secretions and gastric decompression, but this further jeopardizes hydration and electrolyte balance—and again, this does not alleviate the confounding and enormously difficult to manage symptom of nausea.

Total Parenteral Nutrition carries its own risks of Small Bowel Bacterial Overgrowth, liver failure, and life threatening sepsis.

Patients with Gastroparesis, even of **moderate** severity, are often disabled with nausea even with combined anti-emetic and prokinetic drugs. Though their weight may not be dangerously compromised, they are disabled due to upper digestive symptoms—**nausea presenting as the most common debilitating symptom for all Gastroparetic patients—be they: mild, moderate or severe. In moderate to severe Gastroparesis the nausea is so intense as to disrupt sleep patterns.**

Understandably **medical** management of symptomatic Gastroparesis does not provide robust symptom control for many, because no medical therapies are currently 'on the market' for these patients that have been developed for their disease. All current medications have been borrowed from other medical uses.

B. Current treatment options.

Current treatment options (medical and surgical) have really not changed for decades (excluding Enterra Therapy and Botox trials).

The diabetic Gastroparetic patients are a readily identifiable group of Gastroparetic patients that have been studied the most. Gastroparesis diabeticorum has been recognized as a serious complication of diabetes since the early 1940/s.4

A paper published in 1986 exploring the use of jejunostomy feedings in the management of Gastroparesis Diabeticorum outlined the limited treatment options for these patients. It discussed recent drug trials with metoclopramide and Domperidone and noted that clinical efficacy may diminish with time and patients become refractory to the drugs. 5

McCallum published a paper in 1985 titled "Review of the Current Status of Prokinetic Agents in Gastroenterology."6 In 2003, the drugs outlined in this paper are still the same; except for Propulsid (Cisapride), which is no longer available except through a compassionate use protocol.

Current medical management has less to offer now than it did back in the 1980's.

In the United States, only two drugs are FDA approved for treating Gastroparesis:

Metoclopramide (Reglan) initially approved in the 1960's in Europe for use as an antiemetic in pregnancy. Since then it has been used extensively as a prokinetic and antiemetic for treating Gastroparesis. This drug has a high rate of side-effects such as: restlessness, anxiety, drowsiness, depression, tremor, and muscle rigidity. Acute dystonic reactions are more common in younger patients, while tardive dyskinesia can occur in older patients. Overall, about 30% of patients have one or more adverse side effects and cannot continue using metoclopramide.1

Erythromycin was first developed in the 1950's but was not used in Gastroenterology untill some decades later. Numerous studies have proven that this antibiotic is highly effective in producing peristaltic contractions in the stomach antrum. This effect is gained at very low doses. In effect, it produces a 'dumping syndrome' in the stomach (emptying too rapidly). This might explain why individuals that need to use this drug for its 'antibiotic effect' have a good number of side effects, like nausea and abdominal cramping. Many patients using erythromycin for its prokinetic effect may also run into problems of increased nausea and abdominal cramping. As well, its prokinetic effects tend to wane after 6 months to one year.

Other common medical treatments:

Cisapride (Propulsid) was originally developed to treat severe nocturnal Gastro Esophageal Reflux Disease (GERD). When it was released in the 1980's, it was quickly recognized to have a broad range of pro-motility effects on various segments of the GI tract. It became widely studied for treatment of Gastroparesis, but was voluntarily pulled from the market in 2000 due to safety concerns. *Propulsid is still available under a restricted release, yet the restrictions are so great, most Gastroenterologists cannot take the time to fill out the enormous amount of paper work required to access this drug for their patients.* The FDA has never eased this access with a supplemental New Drug Application (sNDA) which would allow restricted marketing. The American Society of Consultant Pharmacists submitted a paper to the Food and Drug Administration (May 22, 2002, FDA Docket number: 02N-0115) recommending that Propulsid be brought back with appropriate safeguards. This has not occurred.

Domperidone (Motilium) is a dopamine receptor antagonist drug. It has been marketed world wide since 1978. It is in a broad pharmacological class of medications called the: 'Substitute Benzamides' which hail from the Phenothiazine psychotropic drug family. This broad category of drugs has been around for a long time. The Phenothiazine drugs were brought into use for psychiatry in the late 1940s and early 1950s. Metoclopramide and **Levosulpiride (Levobren, Levopraid)** all belong to this same pharmacological family. Levosulpiride is used widely in Europe as a prokinetic drug. Of this pharmacological class of drugs, Domperidone has the least central nervous system side effects; therefore it is well tolerated and now considered the first line drug choice for treating Gastroparetic patients. Domperidone is used worldwide. It has been extensively studied as a treatment for Gastroparetic patients and found to be safe and effective in controlling symptoms of nausea and vomiting. Despite this, it has never received FDA approval—though application has been brought to the FDA and was denied even against the panel's recommendation for approval.

Zelnorm (Tegaserod) has recently come onto the market. It is used to treat constipation predominate Irritable Bowel Syndrome—it is currently being investigated as a treatment for Gastroparesis, but still too early to say if it is showing effectiveness as a treatment option.

Note: patients with Gastroparesis must take promotility and antinauseat drugs for decades. There is a paucity of long term studies demonstrating safety and efficacy of these drugs and no longitudinal studies in pediatrics.

Sturm et al did a systematic analysis of available prokinetics for treating patients with Gastroparesis. His conclusion: response to medical treatment is suboptimal at best. 7

Lack of favorable medical response for those with more severe Gastroparesis has lead to investigation of surgical and other novel approaches. Surgical options too (other than Botox) have remained the same for more than 15 years.

Botox. injections into the pylorus have been studied in Diabetic Gastroparesis patients. It has about a 50% chance of producing a response of decreasing symptoms like vomiting and lasts for about 6 to 9 months. Long term use and complications have not been studied. Concerns regarding fibrosis developing in the pylorus due to long term Botox use have not been ruled out.

Surgical interventions for palliative treatments of severe diabetic and idiopathic Gastroparesis such as pyloroplasty, or elimination of the stomach through near total Gastrectomy (Billroth I, Antrectomy, Roux-En-Y) or addition of a venting gastrostomy; show little improvement in symptom management. A review of the literature by Reardon et al, of these surgical palliative procedures showed, that of 12 patients, only 3 had resolution of their symptoms, with the majority having no improvement or only temporary improvements, or a worsening of symptoms to include bilious vomiting.8

Experts agree that the entire stomach is affected in Gastroparesis; therefore, treatment by partial gastrectomy is unsatisfactory as a method to attempt to ameliorate symptoms. Treatment by total gastrectomy is used as a palliative measure; however, it is a major surgical procedure which carries risks of its own. This procedure has significant morbidity, and a mortality rate of 3.5%.9 Also, once the stomach is removed, the option no longer exists to take advantage of any new pharmacological therapies that may come along; and dependency on enteral / parenteral nutrition is permanent.

Of all the treatments outlined above, it must be pointed out that to date, Enterra Therapy is the only reversible treatment on the market that has been specifically developed and researched for Gastroparesis patients.

Sadly, one can list all the FDA approved treatment options for severe Gastroparesis in the above few paragraphs.

C. Morbidity and Mortality

Morbidity related to the symptoms of nausea and vomiting has been documented. Nausea and vomiting of any origin be it post operative, medication induced, enteric infection, motion sickness, or induced by pregnancy; are debilitating and very upsetting for family members to witness. A recent review by Hasler et al 10 examining the impact of nausea and vomiting cites these statistics:

- Gastroenteritis, food borne and non-food borne and other intestinal infections cost 3.4 billion dollars in the US.11
- In a 1980 study, acute enteric infections increased medical expenses by 1.25 billion and the lost productivity cost 21.8 billion.12
- In British studies looking at pregnancy-related nausea and vomiting, these researchers estimated the impact at a loss of 8.5 million working days per year. The severely affected women missed, on average, 62 hours of work during their pregnancy.13,14
- Employee productivity declined and resulted in increased health care costs for employees tracked during their course of chemo-therapy (the main symptoms interfering with productivity was nausea and vomiting).15
- A group of out patient surgical centers wanted to find out the impact of post-operative nausea and vomiting on recovery times. These symptoms created increased costs on average of $415 / patient. The increased time of recovery also was found to prevent the performance of 96 – 576 additional surgical procedures.16

Whatever the cause for nausea and vomiting, relief is basically sought from the same pharmacological armamentarium for symptom control; and results are mixed.

The episodes of nausea and vomiting cited above are transient yet this helps to provide an appreciation of the cost and degree of debilitation from these upper digestive symptoms.

Morbidity and Mortality of Gastroparesis

One published epidemiological study reflects **morbidity in Diabetic Gastroparesis patients by tracking rates of hospitalization.** Bell et al 17 investigated the number of hospitalizations and discharges in one year (1998) for patients with Diabetic Gastroparesis in the State of North Carolina. The results based on the North Carolina Hospital Discharge database showed there were 1,476 discharges with total charges of $11,378,466 over 7850 total hospital days.

This is only one state and one year. This data does not reflect the largest group of those suffering with Gastroparesis, namely the "idiopathic" group. This published scientific paper also does not take into account the number of patients who may be on enteral or parenteral nutritional support due to their Gastroparesis. These costs and morbidity can be extrapolated to the US population.

Patients tracked by Abell et al (Gastroenterology, 112(4): A2, 1997) showed the average yearly costs of hospitalization for Gastroparetic patients were $80,000 dollars per year. This is just the hospitalization costs alone.

There is a paucity of scientific literature to paint the full picture of the impact of Gastorparesis on people's lives. Few studies have looked at the symptom impact on patient's quality of life. This is evidenced by a "Pub Med" search using the search parameters: <quality of life survey,>. When IBS (Irritable Bowel Syndrome) is plugged into this parameter it yields 68 published papers; Crohn's diseases yields 103; colitis, 136; GERD (Gastro esophageal Reflux Disease), 130; Functional dyspepsia, 21; Functional abdominal pain, 20; Gastroparesis—6, even though Gastroparesis has the highest degree of morbidity and mortality within this list.

In Severe Gastroparesis, nausea and vomiting are intractable and can persist for years. It is these symptoms that make the patients miserable, keeps them housebound, sends them to hospital, causes

weight loss, devastates their quality of life / psychological status, causes them to be fatigued and unable to sleep.

For Gastroparetic patients, Nausea is debilitating. Vomiting can be life threatening. These two signs and symptoms along with other dyspeptic symptoms take away their desire and ability to eat thus intensifying the problem of malnourishment.

Mortality statistics exist for Gastroparesis. Overall mortality rates are 5% 18 and closer to 10% for specialists who see a preponderance of GP patients. Mortality rates for the diabetic Gastroparetic patients are much higher. Symptomatic Gastroparesis diabeticorum is associated with a grave prognosis. Approximately 30% die within 3 years; 56% may die within 5 years.19 A more recent, but small study by Abell et al shows similar comparisons. In a small group of 33 Gastroparetic patients using prokinetics and antiemetic therapy, (5 males and 28 females with a mean age of 42 years) followed for 10 years; mortality was 43% for the Diabetics and 13% for the Idiopathic patients. 20

D. The approach to symptom control in other disciplines

In the Cancer scientific literature, much is written about nausea and vomiting and its impact on cancer patients.

i. Some excerpts from the Cancer literature:

> Nausea and vomiting may be among the most discomforting, distressing side effects of cancer therapies. Despite advances in the pharmacologic and non pharmacologic management, nausea and vomiting remain two of the most dreaded side effects by cancer patients and their families.21-23

> Ballatori et al reports 24: "About 20 years ago vomiting and nausea ranked as the most distressing side effects of cancer chemotherapy from the patients' point of view. 25 Unfortunately, despite progress achieved with the $5HT_3$ receptor antagonists chemotherapy-induced nausea and vomiting remains a distressing adverse event. In fact, in two studies carried out after their introduction in clinical practice, nausea still ranks number 1 as the adverse event of chemotherapy of most "concern to patients, with vomiting ranking as the 3rd and the 5th most distressing symptom."26, 27

> "According to cancer experts, about 75 percent of people treated for cancer experience nausea and vomiting. These side effects of cancer treatment can drastically affect a person's quality of life."28

In cancer care, the signs and symptoms of nausea and vomiting warrant special registries and validated research tools:

> The Anti Nausea CHemOtherapy Registry (ANCHOR) study brought to light that Chemotherapy-Induced Nausea and Vomiting (CINV) remains a significant, under recognized problem for many patients undergoing chemotherapy for cancer, even with the use of standard anti-emetic treatments (agents used to manage CINV). The study also showed that healthcare providers underestimate the prevalence and burden of CINV on patients' daily lives. 29

> A quote from Steven Grunberg, M.D., professor of Medicine and Pharmacology, at the University of Vermont and lead study author of ANCHOR: "Preliminary results from the ANCHOR study brought to light what many cancer patients have long known - but have been reluctant to voice - that nausea and vomiting disrupt daily functioning." 29

The Cancer literature illustrates that standardized tools, many subjective, can be developed for looking at signs and symptoms of nausea and vomiting. This can guide the research into effective treatments. These tools also can be used in different institutions.

> Vomiting and retching are **objective** and definitive *signs*, obvious to the observer and patient and not dependent on the patient's impressions. 30
>
> *Symptoms*, such as nausea, arise from **subjective** components and dimensions unique to the individual—despite their subjective qualities— nausea affects a patients' self-care, coping abilities, and quality of life.31

Standardized tools, some validated and others not, have been used in CINV research. Tools such as: patient self assessment surveys; self-recorded daily emesis episodes; ranking of nausea severity on a visual analogue scale (similar to the pain "visual analogue scale). Also, instruments such as the "Functional Living Index—Emesis (FLIE)," this tool addresses the impact of CINV on physical activities, social and emotional function and ability to enjoy a meal.32

Finally, one of the best known tools is the "Nausea and Vomiting Symptom Distress Adaptation Scale" that was originally developed by Rhodes, Watson and Johnson. 33

Patients with Gastroparesis can suffer for decades with nausea and vomiting and often required two different classes of pharmacological anti-nauseant medication which are taken for years with mixed results. There are no registries or disease specific quality of life surveys to track the impact that nausea and vomiting have on patients with Gastroparesis.

ii. From Chronic Pain research

Chronic pain is analogous to chronic nausea. Both are subjective, both can be exceptionally difficult to control and both can be very debilitating.

Both too can result from a multiplicity of physiological phenomena originating either centrally (Central Nervous System) or peripherally to the CNS. Therefore the research approach into these two symptom entities can follow a similar path in the search for **effective therapeutic symptom management.**

Chronic pain research rests upon **subjective tools**, statistically valid and reliable, which are accepted by the research community to help measure the **efficacy** of new treatment measures. Though these tools may not be perfect, this approach has yielded a good many effective treatments which help relieve patient suffering. Not all tools have been validated. Nevertheless, they are used in research studies.

In pain research, **subjective** tools measuring primary outcomes such as the "Visual Analog Scale," "The McGill Pain Questionnaire," and the four-graded scale "4GS" are widely used in pain research; while secondary outcome measures such as: cost effectiveness, "health-related quality of life" (HRQOL) questionnaires, improvement in sleep, improvement in psychometric measures, and return to work, are frequently utilized.34

In Pain research, the evidence gathered from these research designs (primarily hinged on subjective tools) is acceptable to the FDA for demonstration of efficacy. Devices such as the Spinal Cord Stimulation have come to PMA's based primarily upon ***empirical evidence.***

Grabow et al undertook a comprehensive review of the scientific papers published, examining the evidence for efficacy of Spinal Cord Stimulation (SCS) devices. He looked at randomized controlled trials, cohort studies, case-control studies, case series, and case reports which described SCS as the primary treatment modality for patients with Complex Regional Pain Syndrome. Fifteen papers were included for analysis.

He concluded that **overwhelmingly the evidence for efficacy was empirical-- there were few randomized prospective studies on efficacy.** But, these devices ***suggested a significant therapeutic effect.***34

North et al also conducted a literature review regarding SCS focusing on recent studies investigating the efficacy of spinal cord stimulation for low back pain. In 2002, only two randomized prospective studies considering the efficacy of SCS as compared with other treatment methods had been published. North concluded: Most studies were limited by the same flaws, mainly retrospective. The ultimate efficacy of spinal cord stimulation remains to be determined. However, based upon current evidence, it may represent a valuable treatment option, particularly for patients with chronic pain of predominately neuropathic origin. 35

These SCS devices clearly represent a valuable treatment option for chronic pain, and patients are thankful to have access through a PMA status for these reversible devices that are safe, ***suggest efficacy***, and have an acceptable rate of complications.

Subjective tools can drive the search for new treatments in symptom management like pain, all the while helping researchers better understand the underlying bio-therapeutic underpinnings. This approach can also be applied to nausea and vomiting.

iii. Gastroenterology research into nausea and vomiting of Gastroparesis

Gastric Emptying VS measures of symptom reduction: Which one should be the primary outcome measure for determining efficacy of therapeutic treatments?

Historically, it was thought that symptoms of Gastroparesis were due to delayed gastric emptying, and therefore much of the focus in therapeutic trials for Gastroparesis was based on the effect of an intervention on gastric emptying.

This conventional wisdom needs to be scrutinized. Studies cited below, Forster, Lin, Abell, show gastric emptying, as measured by scintigraphy, is only loosely associated with symptoms, if at all.

As well, the same theme runs throughout the literature looking at prokinetics. Again, research authors studying prokinetics which improve gastric emptying find that this may only modestly improve symptoms. They often conclude that gastric emptying and symptoms are unrelated to one another.36-38

Finally, a basic research study cited below by Chen et al also found no correlation between gastric emptying in canine models and the ability of GES to halt vomiting in vasopressin induce vomiting in these animal models.39

Gastric emptying as the primary outcome for determining effectiveness of pharmacological treatment has traditionally been used as the measure for effectiveness instead of looking at symptom measure outcomes. ***Dr E. Soffer,*** from the Cleveland Clinic Foundation, in Ohio alluded to this at the First International Task Force Meeting on Gastroparesis (Orlando, FL, 2003). He raised some basic issues with the designs of drug trails looking into effective treatments for nausea and vomiting of Gastroparesis. In general, he noted that pharmacological trials are well designed for testing postoperative nausea/vomiting or post chemo-therapy nausea/vomiting; however, he further pointed out that this is not the case with the study of drugs and reduction of symptoms in Gastroparesis.

Excerpt from Dr. Soffer's presentation at the Task Force meeting:

It is not infrequent with the design of pro-kinetic drug trials, that the end point for determining

drug trial success is the improvement of neurological functioning of the stomach (improved GE) rather than the outcome of improved symptom control in the patient.

Because of the recognized inconsistencies between gastric emptying and correlation to symptoms, Dr. Soffer is suggesting that perhaps GE is not a good measure for efficacy when searching for therapeutic interventions into symptoms like nausea and vomiting of Gastroparesis.

a. Gastric emptying studies by scintigraphy:

In 2000 international protocols were developed for a 4 hour gastric emptying (GE) study in order to **standardized** control values for interpreting results.40 This standardization for interpreting GE values was an important step forward. However, this approach is still considered a **screening tool** since it lacks sensitivity in tracking the early phases of GE. Also, most centers still employ the 2 hour GE study. This traditional approach to GE studies means each institution establishes its own protocols, thus lacking any uniformity across various institutions. Each center will vary in test meals, volumes, fat and caloric content; and varying protocols including duration of examination, timing of sampling of gamma counts after ingesting the meal, and the parameters used to analyze the data. 1

Facts about gastric emptying studies:

- **They are not universally standardized between institutions—therefore serve as a poor tool for comparing results between institutions.**
- **Really serves as a screening tool.**
- **Experts agree, evidence to date shows there is a poor correlation between GE and symptoms.**

The science around Motility is probably one of the least understood areas of gastroenterology. The physiological measure of gastric emptying and how it correlates to symptoms remains enormously controversial.

Further evidence of the shortcomings of GE studies and the correlation to symptoms: A clear phenomenon has been described by clinicians regarding some of their diabetic Gastroparetic patients who can present with profound delayed gastric emptying but who are free of dyspeptic symptoms. These patients are considered to have asymptomatic Gastroparesis. Evidence of the reverse can also be found by clinicians. Idiopathic Gastroparetic patients can initially be diagnosed with delayed gastric emptying only to have GE improve over time, yet they remain debilitated with nausea.

Gastric emptying may be valuable to know as sciences delves into the underlying mechanism of the disease process; and gastric emptying is important for over all gut function; but, as outlined here, it is not needed as a marker of efficacy for Enterra Therapy.

Gastric emptying is not an 'either/or;' or 'all or nothing,' direct measure of efficacy. All experts agree, there is not a consistent relationship between gastric emptying and symptoms. The understanding of the neuro/electrical activity of the stomach is still in its infancy. Many patients can have "disordered" emptying that is not necessarily delayed. Much is yet to be understood, but does not need to be fully comprehended in order to find therapeutic options to reduce symptoms in suffering patients.

b. Measure of symptom reduction

The measure of efficacy for the Enterra Therapy device is currently clouded by the concept regarding Gastric Emptying. **The Enterra device is a palliative treatment for intractable nausea and vomiting in patients with Gastroparesis; and is marketed as such.** This device does not need to show improvement in Gastric emptying before it passes muster on efficacy.

Palliative in the Oxford dictionary means: 'to alleviate suffering.'

The mandate for determining efficacy for anti-emetic, anti-nauseant interventions should follow the examples as described above which are applied by other medical disciplines.

As noted in the cancer and pain literature, **subjective tools** are developed for use to determine efficacy of new treatment approaches. This has been acceptable to the FDA and has resulted in finding new effective symptomatic treatments for patients.

Our current poor understanding surrounding motility diseases like severe Gastroparesis creates enormous difficulties in advancing effective symptom control measures for patients. It is the symptoms for which Gastroparetic patients seek relief. Even without full understanding of the dynamics of the disease, symptom relief can be a primary objective and will be a major benefit for Gastroparetic patients. This primary endeavor will drive the comprehension of underlying mechanisms.

Enterra Therapy has never purported to enhance GE, though the phenomenon has been observed; so even though this area remains controversial, is not necessary to consider it as a device for palliative treatment for symptoms of nausea and vomiting.

The arguments below will be set out to demonstrate that Enterra Therapy has the ability to significantly reduce nausea and vomiting in the target population and this effect reverses the disastrous impact of these symptoms on patients' lives through: reduced hospitalization, reduced health care costs, and improvement in quality of life scores. These primary and secondary measures are acceptable in other fields of medicine as measures of efficacy for symptom management.

4. Arguments:

A. Efficacy

Enterra Therapy must be judge by its ability to **reduce the symptoms of nausea and vomiting.**
As well, **control of nausea and vomiting caused by severe Gastroparesis has the added dimension for which to measure efficacy.**

The intense nausea and vomiting that the Gastroparetic patients suffer from, results in the loss of their desire to eat, or fear of eating, since food intake can trigger unrelenting symptoms. Therefore, the use of **secondary measures** of BMI (Body Mass Index), or the patient's ability to return to more normal eating patterns (from dependency on 'feeding tubes' to eating), and cost effectiveness by hospitalization reduction can all provide objective evidence of efficacy.

Some research papers examining the use of GES (Enterra Therapy) have utilized these primary and secondary measures to determine efficacy.56 -59

That said, many of the studies on GES do show modest improvement in gastric emptying around the 6 month mark. This has been correlated to improved glycemic control in the diabetic Gastroparetic patients. Glycemic measures then could also provide a secondary measure of effectiveness.

(Improved measures in gastric emptying seem to correlate with the amount of energy used with implantable devices. These devices (as mentioned below: known as "gastric pacing") are still experimental and not covered in this petition. Little is known about these experimental devices' and their ability to provide symptom control, though they demonstrate a powerful ability to empty the stomach).

We wish to establish that the Enterra Therapy passes the test for efficacy. This test is the last test needed in order to graduate from an HUD to a PMA category. A PMA category relieves patients of the burden of having to fight their case with insurance providers (which some lose) and permits much more rapid access to this safe, effective and reversible treatment option. This helps to save lives.

> In the regulations: *21 CFR 860.7(a)* the FDA specifically outlines the determination of safety and effectiveness of a device.

The Enterra medical device has already satisfied the sections of this regulation pertaining to safety. This is the requirement of an HUD status as mentioned in the Petition introduction.

Regarding establishment of **effectiveness** this petition will outline the published papers that fulfill the requirements of these regulations:

> 21 CFR 860.7 (a)(c)(2):
>
> Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and reasonably be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use....
>
> 21 CFR 860.7 (a)(e)(1):
>
> There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a **significant portion of the target population,** the use of the device for its intended uses and conditions of use, when accompanied by adequate direction for use and warning against unsafe use, will provide **clinically significant results.**

Some facts on Stimulation via implantable devices:

i. Equipment:

Enterra Therapy is: Gastric Electrical Stimulation using **high frequency and low energy stimulation** via two unipolar electrodes implanted in the circular muscle layer on the serosal side of the stomach either laproscopically or by laporotomy, with the transcutaneous leads and tissue pocket implanted neurostimulator which has a battery life of up to 5 to 10 years.

Other devices that also are called Gastric Electrical Stimulation (GES) require ***low frequency and high energy***. This approach **necessitates an external energy source** – also know as "Gastric pacing" (because it actually 'induces' gastric contractions at a rate similar to the normal native rhythm) are not discussed in this petition. These devices are still considered experimental.

With the exception of the leads, the Enterra implantable neurostimulator is a derivative of an implantable neurostimulator used to treat chronic neuropathic pain which was first marketed in the United States in 1984.

The pioneering device for Gastric Electrical Stimulation, then the genesis of an Enterra prototype and Enterra device, have been implanted in humans for the treatment of severe Gastroparesis for over 10 years now. The first implant patient was in January of 1992. These original patients have been followed and the data appears below. A very recent abstract on 10 years of experience with Gastric Electrical Stimulation is also cited. The majority of the target population has demonstrated persistent long term effectiveness of this potent anti-emetic, anti-nauseant device.

ii. What evidence presently exists in the published, peer reviewed journals which establishes efficacy of Enterra Therapy?

Papers are cited here, discussed and collated in tables to help compare the data. This does not represent the entirety of all the published and abstracted research on the Enterra Therapy, but represents the significant papers pertaining to Enterra Therapy.

Of interest, several of the papers in their opening comments don't even question the efficacy of the Enterra Device, since the data reviewed by these investigators state the device's effectiveness is unequivocal, and instead the investigators set out to try and discover by what means (the underlying bio-physiology) the device renders such a potent anti-emetic effect.

iii. Documentation of Expert Opinion

Two papers already provide a summary of key clinical studies done to date and a review of the literature. The expert analysis of this data will be quoted here. <u>This documents expert opinion.</u>

<u>Key summary of WAVESS study (International randomized double blinded cross over study of Enterra Therapy):</u>

> From McCallum RW, and Sabu GJ: "Gastric Dysmotility and Gastroparesis," **Current Treatment Options in Gastroenterology 2001**; 4: 179-191:
> Excerpts form the paper*: The device, manufactured by Medtronic...was recently shown by the multicenter WAVESS (World Wide Anti-Vomiting Electrical Stimulation Study) trial to significantly reduce vomiting and improve quality of life in patients with Gastroparesis.1 The WAVESS study group reported a more than a 50% decline in vomiting frequency in 93% of patients at 12 months and significant improvement in quality of life at 12 months. In a double-blind, crossover study, the WAVESS study group also demonstrated a clear patient preference of having the device turned on. In the majority of these patients, gastric emptying is improved significantly, but still has not returned to a normal state at 1 year.

*(Please refer to published paper for references refered to in the text).

<u>Review of GES (Enterra Therapy):</u>

> From: Lin Z, McCallum RW: "Treatment of Gastroparesis with electrical stimulation," **Endoscopia 2002**; 14(2)April/June: 45-58:
> Excerpts from the paper*: The efficacy of chronic GES with this implantable device (Enterra Therapy) in the treatment of symptomatic Gastroparesis was investigated in a multi-center World wide Anti-Vomiting Electrical Stimulation Study *WAVESS) trial, with promising results. Thirty-three patients with long-term Gastroparesis (17 diabetics, 9 men and 8 women, and 16 women Idiopathic Gastroparesis, mean age: 40 years) were studied for up to 12 months using the implantable device. During the abdominal surgery, one pair of unipolar electrodes, 10 mm apart, was placed into the muscularis propria of the stomach at about 10 cm proximal to the pylorus for electrical stimulation. The electrodes were secured to the serosa of the stomach using 5-0 silk sutures. The other ends of the electrodes were connected to the pulse generator which was

positioned in a subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus using standard techniques.

The initial design of the WAVESS study was a double-blinded crossover (one month of either ON or OFF) followed by 12-month open label. In the double –blinded section of the study, there was a clear preference (3 to 1) for having the device turned on. In general, the main symptom of vomiting and quality of life were significantly improved at 6 and 12 months of GES. In the majority of these patients, gastric emptying of solids was improved but still not returned to the normal by 1 year. Additional analysis of long-term GES indicated a 30% reduction in hospital use in the first year after implantation for these patients. Analysis of nutritional outcome has shown a significant increase in BMI. In addition, 75% of patients who were requiring jejunal feeding tubes had the tubes removed within 6 months and were eating .

Researchers' personal clinical experience with Enterra Therapy published in this same review article:

Since 1998, 55 Gastroparetic patients (39 diabetic, 9 post-surgical and 7 Idiopathic) with documented delayed GE have received high frequency GES by a permanently implanted gastric neurostimulator made by Medtronic (Minneapolis, MN) at the University of Kansas Medical Center. To date, 26 patients (21F, 5M, mean age: 40 years; 19 diabetic, 3 Idiopathic and 4 post surgical Gastroparesis) have completed evaluation of GES for 6 months and 18 for one year. Severity and frequency of nausea and vomiting, 4-hour GE of a solid meal, electrogastrogram (EGG) and status of nutritional status were evaluated at baseline (before implant), 6 and 12 months of GES. In comparison to baseline, nausea and vomiting were significantly reduced after 6 and 12 months of GES. (fig.9). The mean percent of gastric retention at 4 hours was 45$\pm$ 27% at baseline, 31$\pm$27% at 6 months and 44$\pm$34% at one year of GES. On average, the patients had gained 4 kg. after 6 months to one year of GES ($P<0.05$). Of 22 patients, 15 initially required jejunostomy tube feeding. 12 of these 15 patients had jejunostomy tubes removed within 6months of GES while only 2 patients were still requiring enteral nutrition by a jejunostomy tube at one year of GES. EGG was performed on each patient for 30 minutes in the fasting state and for 120 minutes after the meal simultaneously with gastric emptying monitoring as previously described. The postprandial EGG power (amplitude) was increased from -0.1$\pm$1.1dB at baseline to 2.6$\pm$1.2dB at 6 months($P<0.05$) to 1.6$\pm$1.9dB at one year of GES. The mean frequency of the gastric slow wave before GES was similar to those after 6 months of GES. The primary dysrhythmia was tachygastria at baseline and at 6 month of GES was not corrected. Three of the implanted devices have been removed due to infectious complications. In one patient with a history of non-compliance and a colostomy, a superficial skin infection was not cared with in time the device became irreversibly infected. In another patient, a percutaneous G-tube was unfortunately placed through the device pocket, causing the device was infected. In the third case, a superficial wound infection progressed to include the device. All these patients were diabetic. One patient with long-standing diabetes and renal failure died due to a cardio-pulmonary arrest unrelated to the device 10 months after implantation.

*(Please refer to the published paper for references referred to in the text)

2nd Review article from: Abell TL and Minocha A: "Gastroparesis and the Gastric Pacemaker: A revolutionary treatment for an old disease," Journal **MSMA, Dec. 2002**; 43(12): 369-374

"The current GES device (Medtronic, Enterra Therapy) is used for the treatment of the symptoms of Gastroparesis, especially nausea and vomiting. GES can be placed both temporarily, via endoscope and /or gastrostomy tube, to see if a given patient will respond to GES."

"**Evidence for efficacy of GES (Enterra Therapy):**

The use of GES results in not only improvement of symptoms but also **enhances quality of life**. In addition, its use results in overall reduction of health care costs over the long run.

i. **Improvement of symptoms*:**
The most impressive, and often dramatic effect of GES is a marked reduction in the symptoms particularly nausea and vomiting. Studies have consistently shown that over eighty percent of patients have at least a 50% reduction in nausea and vomiting.41-45 About fifty percent have at least an 80% reduction in these two symptoms, with some patients having an almost total elimination of vomiting. This has been demonstrated in short-term, as well as long-term studies which included a double-blind randomized phase of GES in patients with gastorparesis.44

ii. **Improvement in Gastric Emptying:**
A majority of studies have shown a consistent improvement in solid gastric emptying at one year as measured by radionucleotides using a standardized low fat meal. 40,44

iii. **Improved pancreatic function:**
Chronic pancreatitis has been associated with Gastroparesis. GES has been demonstrated to be associated with a significant improvement in pancreatic output, as measured by stool elastase. This improvement appears to be mediated, in part by pancreatic polypeptide. This may indicate a role for GES in the treatment of chronic pancreatitis but has not yet been studied.46

iv. **Improvement in autonomic function:**
Abnormalities of the autonomic nervous system are frequently associated with Gastroparesis and other GI motility disorders and may account for many of the associated symptoms. GES has been associated with an improvement in autonomic function over one year. The primary changes have been an increase in cholinergic function and a decrease in adrenergic function. These changes have been apparent in both traditional autonomic function testing such as EKG R to R interval testing and capillary photo-phlethysmorgraphy as well as by newer methods such as heart rate variability on the Holter Monitor using power spectrum analysis.48

v. ***Improvement in measures of enteric nervous system:***
GES has been associated with improvements in the gastric electrical rhythm. EGG is a measure of the enteric nervous system. Studies show an overall normalization of the EGG.47,48

vi. **Improvement in nutritional status*:**
Use of GES results in clinical and statistically significant improvement of nutritional status of Gastroparesis patients as measured by body weight and serum albumin at one year. Much of that improvement is in the first 3 months of therapy. In one study, serum albumin went from 3.4 to 3.7 whereas mean weight increased from 149.9 pounds to 162 pounds at three months.49 A recent report demonstrated a significant reduction in HgA1c in patients with Diabetes Mellitus after GES.50

vii. **Reduced hospitalization*:**
Several studies, including data from a randomized study, have shown a reduction in hospital days in patients post GES implantation. In one recent study, the mean number of hospital days/year went from 48.8 to 27.8 days/year over one year.43

viii **Reduced use of health resources*:**
Another recent study has demonstrated a reduction in utilization of health care resources in patients with GES. Health care costs decreased from $6,972/month to $1,878/month over a three year period.51 An investigator Derived Independent Outcome Measurement Scale (or IDIOMS) which measures severity of illness, intensity of medical services as well as underlying chronic illnesses, correlated well with improvements in symptoms, costs and other health related quality of life measures.

ix. **Improvement in quality of life*:**
GES results in significant improvements in quality of life as measured by the SF-36, when studied for one year.46 Six of the eight SF-36 sub scores named (Physical

functioning, Psychological, Bodily Pain, General Health, Vitality, and Social Functioning) were significantly improved at 6 and 12 months compared to baseline levels. At 12 months, the Physical Composite Summary (PCS) score and the Mental Composite Summary (MCS) score increased to 32.4 and 45.1 from baseline levels of 25.8 and 36.1 respectively. In fact, the 12 month PCS score was within one standard deviation of the normal range (50±10)."

*These measures have been recognized by other medical disciplines as demonstration of efficacy for symptomatic control.

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iv. **Enterra Therapy and impact on Mortality**

Another small study has recently presented as a poster: "Effects of Gastric Electrical Stimulation on Outcome and Mortality of Diabetic Gastroparesis." Abel et al presented this as a poster at the American Diabetes Association's 63 Scientific Sessions on June 15th 2003 in New Orleans, LA.

Summary: a quote from Kevin Blanchard, MD, one of the lead investigators: "Patients we see with Gastroparesis have symptoms that are often quite severe. GES actually improves all the parameters that we could measure. Patients tend to feel better. We also note decreased mortality among these patients."52

In this study, 41 patients were grouped as follows: 5 men and 4 women with Diabetes (DM) and gastroparesis with a mean age of 48.4 years, and 6 men and 26 women with idiopathic gastroparesis with a mean age of 37.9 years. These patients had received up to 8 years of GES with follow-up ranging from 2 to 8 years.

Researchers then compared the patients' baseline weekly vomiting frequency score (WVFS, 0-4), Gastrointestinal Total Symptom score (TSS: 0-50) and solid gastric emptying to the latest follow-up data. They compared patient mortality data with a group of medical controls consisting of 5 men and 28 women with gastorparesis, representing a mean age of 42 years, who were treated with antiemetic and prokinetic drugs and followed for up to 10 years (range 7 to 10 years).

In the GES group, WVFS and TTS improved for all by a mean of 53.3% ($P<0.01$). The DM subgroup improved significantly by a mean of 73.9% ($P<0.01$). Solid gastric emptying also improved for the entire GES group by a mean of 56.3% ($P<0.01$), but was less in the DM sub group (mean 49.8%).

Mortality in the GES group was 22% for the DM and 6% for the idiopathic group. In the medical controls, mortality was 43% for the DM group and 13% for the idiopathic medical controls.20

v. Enterra Therapy: Impact on reduction in health care costs through reduction in hospitalization and reduced need for enteral/parenteral nutrition.

An abstract by: Luo J, Abell TL, Nash K, Cutts T: "Gastric Electrical Stimulation is Associated with Reduced Health Care Costs, Compared with Baseline Costs and Medical Controls" (also presented as a poster at: the American Diabetes Association's 63 Scientific Sessions on June 15th 2003 in New Orleans, LA).

This abstract followed five patients (a subset of the GEMS study group) were tracked and compared medical controls. These medical controls have had their data published (GE 112(4): A2, 1997). The 'medical controls' represented a group of Gastroparesis patients who had been enrolled in an out-patient program designed to help reduce their hospital admissions by use of various techniques and combined anti-nauseant therapies; but not GES.

Baseline health care costs were considerable for both groups. Post GES, health care costs decreased significantly for GES patients. GES was associated with significant and sustained reduction in health care costs, compared to their baseline values as well as against the 'medical controls.' Please see Table I and II below:

Table I

The Medical Cost ($/mo) of the GES Group Versus the MED Group at Baseline and Different Follow-up Times

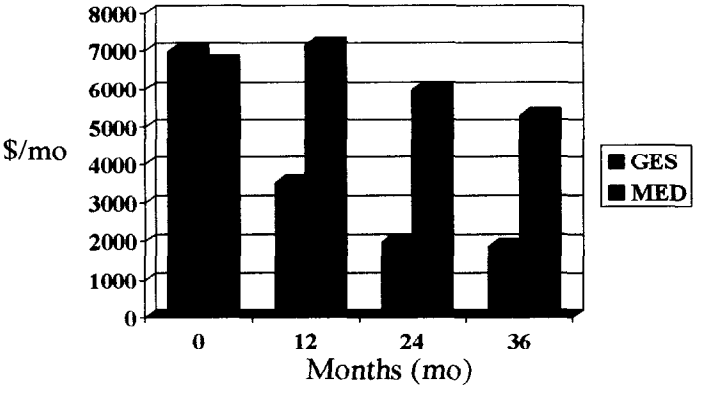
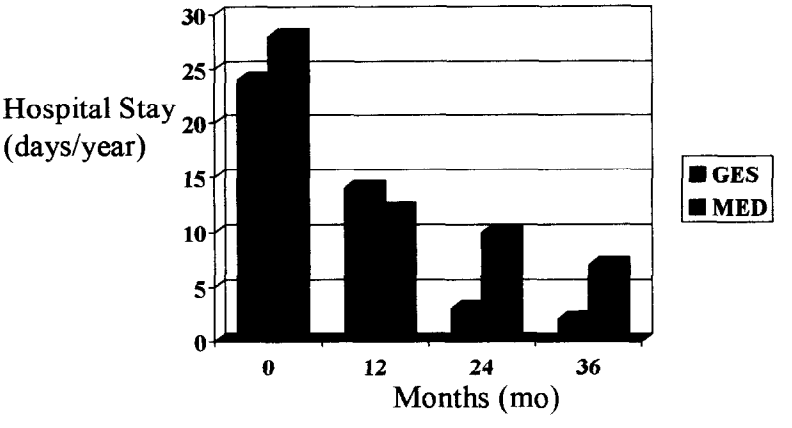


Table II

Length of Hospital Stay for the GES Group Versus the MED Group at Baseline and different Follow-up Times



In the: **Lin Z, McCallum RW: "Treatment of Gastroparesis with electrical stimulation," Endoscopia 2002; 14(2)April/June: 45-58**, publication, these authors reviewed literature on GES, they too concluded that:

GES indicated a 30% reduction in hospital use in the first year after implantation for these patients. Further, the WAVESS study showed a 75% reduction in the need for parenteral/enteral nutrition.

All the published papers that have been cited below, all show reductions in hospitalization and reduction in need for enteral/parenteral nutrition; **this clearly demonstrates significant cost savings.**

vi. Published Papers

Below is the collated information from 7 published research papers, and one abstract (Curuchi). Two of these papers were multicenter trials one of which was a double blinded cross over study. The abstract paper shows 10 years of experience, from three centers, on 133 patients with GES.
These research data are primarily derived from the most clinically challenging patients.

TABLE III. Methodology

Study Citation Year published	Study design	Number of Pts.	Description of severity documented	Primary Outcome(s)	Secondary Outcome(s)
Familoni 41 1997	Case study	One	Yes	Sx measures, VF: vomiting frequency and GE	
Foster 53 2001	Large single center study	25	Yes	Sx measures, VF and GE	
Lin 54 2002	Prospective study	15	Yes	Myoelectrical activity GE correlation to symptom measures	
Abell 55 2002	Prospective multicentered unblinded study	38	Yes	Sx measures, VF and GE	BMI Changes to nutrition patterns and Prokinetics and/or anti-emetics use
Abell 56 2003	Study group a subset of GEMS* Longitudinal study ST, Intermediate and long term follow-up of 5yrs.	12	Yes	VF TSS Total Symptoms Scores	Quality of Life Measures BMI and wt stabilization Blood Albumin Route of nutrition
Abell 57 2003	Multicentered, Randomized Double Blinded Cross over study	33	Yes	VF· vomiting frequency, TSS GE	Quality of Life measures
Forster 58 2003	Large single centered study	55	Yes	TSS VF GE	Quality of Life measures. SF-36 BMI and Wt Reduction in Hospitalizations Diabetic Hemoglobin A1C
Curuchi 59	Ten year experience from 3 centers	133	Not available **	Mortality TSS VF GE	Quality of Life measures not reported in Abstract

(Patient – Pt., Vomiting Frequency – VF, Gastric emptying – GE, Treatment –Tx, Symptoms – Sx, History – Hx, Gastroparesis – GP, Jejunostomy tube – J-tube, WAVESS: World Wide Anti-Vomiting Electrical Stimulation Study, Body Mass Index -- BMI).

* GEMS Study Group. Electrical stimulation for the treatment of Gastroparesis: preliminary report of a multicenter international trial (abstr). Gastroenterology 1996;110:A668

** Abstract just accepted (February 22, 2004) for publication in Gastroenterology and will be presented as a poster at Digestive Disease Week, New Orleans, LA, May 16 – 19, 2004.

Four other recent abstracted papers are not included in the above table but have been mentioned in the review summary by Abell et al.

TABLE IV. Patient Characteristics.

Study Citation	Age Mean(range)	Sex F/M	Duration of symptoms Mean(range)	Idiopathic	Post-surgical	Diabetic	Documentation of Severity
Familoni 41	29, single Pt.	F				X	Refractory to all medications as evidenced by continued hospitalizations and no change in GE
Forster 53	41(21-66)	19/6		3	3	19	14 with J-tubes All, repeat hospitalizations in previous yr. All documented wt loss
Lin 54	41(27-66)	11/4		4		11	Refractory to standard medical therapies
Abell 55	37 5(18-49)	29/9	All Pts highly symptomatic >1 yr prior to study	24	5	9	Refractory as evidenced by significant wt. loss even with standard prokinetic/antiemetic drugs.
Abell 56	35. 7(19-48)	8/4	Mean 7 3 yrs	9		3	All with a Hx of hospitalizations, Refractory to 2 classes of Prokinetics and 2 classes of anti-emetic medications
Abell 57	38. 9(19-65)	24/9	Mean· 6. 3yrs Range: 1 – 28 yrs	16		17	Study criteria of severity defined as VF >7/week GE: >60% @ 2hrs >10% @ 4hrs. GP Sx > 1 yr Refractory to 2 of 3 classes of Prokinetic And 2 of 3 classes of antiemetics.
Forster 58	40.5 (21-66)	41/14	Mean: 9.9 yrs.	7	9	39	All Patients were part of previous study groups WAVES, or CUESS, or HUD protocol 25 Pts. On J-tube feedings at baseline
Curuchi 59				109***		24	

(Patient – Pt., Vomiting Frequency – VF, Gastric emptying – GE, Treatment –Tx, Symptoms – Sx, History – Hx, Gastroparesis – GP, Jejunostomy tube – J-tube, WAVESS: World Wide Anti-Vomiting Electrical Stimulation Study, CUESS: Compassionate Use of Electrical Stimulation Study, Body Mass Index -- BMI). ***This number represents idiopathic and post-surgical patients.

**Outcomes of cited papers,
Summaries are provided below.**

Familoni et al is an earlier case study looking into the emerging evidence of efficacy with use of higher frequencies of gastric electrical stimulation in controlling symptoms, nausea and vomiting and improving gastric emptying (GE). This patient with long standing diabetes mellitus (DM) could only tolerate liquids and was refractory to all available prokinetics. As well, she had been participating in a drug trial of Cisapride for 24 months without relief of symptoms. The only change in her treatment plan was the application of GES. Upon application of GES, she showed reduction in vomiting from an average of 3 times/day to 3 times/week. Nausea and abdominal pain were also reported as greatly decreased. Incremental improvements of liquid GE were also demonstrated to be well above baseline on weeks 1, 4, 15, and 52.

Excerpts from research paper: of note, on week 40 the patient made an unexpected visit to the emergency department due to greatly increased symptoms of nausea, vomiting and pain occurring for about 2 weeks. This unexpected visit provided a control for the efficacy of GES in alleviating symptoms. In the ER it was discovered that the stimulating electrode was no longer working. Upon stimulation at the second electrode site her symptoms resolved. It was not known for how long her electrode had malfunctioned, but return of stimulation resolved her complaints. Also, at 56 weeks, she again complained of increased symptoms. It was established that the electrodes were no longer viable. Symptoms increased around events of disrupted stimulation.

Forster et al, this large single centered prospective study wanted to explore GES impact on symptoms of nausea and vomiting and GE. Included in the study were patient representatives of the 3 largest groups which make up Gastroparetic sufferers; namely, the diabetic; idiopathic; and post-surgical sub groups. A patient profile of severe Gastroparesis is also provided in the paper's introduction. Of the 25 patients studied, 14 were dependent upon j-tube feedings; the entire study group had an average of 6 hospitalizations and 25 lb weight loss prior to enrolling in the GES study.

Methods: During follow-up appointments, symptom severity was assessed at baseline, 3 months, 6 months and 12 months utilizing a self-administered questionnaire. Patients were able to rate a variety of subjective symptoms and frequency of vomiting. Development of this questionnaire and the statistical tools used to analyze this data are documented in the paper.

Results: Symptom severity and frequency—on average—showed a remarkable and statistically significant decrease in both nausea and vomiting by 3 months and this was sustained throughout the study period of 12 months. Three patients did not appear to benefit from the GES. These 3 patients were diabetics, and two of them had had diabetes for the second and third longest of any of the diabetics enrolled in this study (26 and 30 years).

Improvement in GE showed a numerical improvement of statistical significance only at the 3 month interval. As expected, there was individual variation in GE.

The authors pointed out that improvement in symptoms of nausea and vomiting did not parallel improvement in gastric emptying times.

The authors noted two other secondary measures observed to illustrate the effective anti-emetic action of GES: by 3 months, 7 patients were able to have their jejunostomy tubes removed and by 6 months, 4 more j-tubes were removed. These patients were sufficiently comfortable with eating again that they no longer required enteral nutrition.

As well, the patients experienced a significant gain in body weight. The average weight of 60.1 $\pm$ 2.2 kg at baseline rose to 62.6 $\pm$ 2.7 kg (P= 0.003 by paired t tests) at 6 months.

Complications such as device pocket infection were found to be at an acceptable level.

In this paper, a panel discussion is documented with panelists providing critique. Of note, one of the investigators describes the phenomenon observed but unable to capture in the data. To quote Dr. Forster: "The data do not show how miserable a lot of these patients are, and when they come back , (for follow-up post GES implantation) a lot of them have gone out to eat, which they haven't been able to do for a while. A lot of them have been in the hospital for extensive periods of time prior to this procedure and once it has been put in and they get used to it, after a couple of weeks, they're not only out of the hospital, but they're able to get out and eat in restaurants."

Lin et al study sets out to investigate **by what means** the Enterra device renders such dramatic improvements (as published by other researchers) in reducing the degree of nausea and vomiting in drug refractory Gastroparetic patients.

They utilized two-channel serosal recording leads to directly measure gastric myo-electrical activity before and during GES in 15 patients for 3 months. Even though this paper's primary aim was to observe myo-electrical activity and analyze changes in wave patterns during fasting and meals—**these investigators also acknowledged that their patients had significant reduction in nausea and vomiting but little improvement in gastric emptying.**

Results of symptom scores Before GES, and at 3 month follow-up:
Nausea score (0-4) 3.3 ± 0.3 @ 3 months: 1.3 ± 0.6 (<0.01 P value (t test))
Vomiting Frequency (0-4) 2.3 ± 0.5 @ 3 months: 1.1 ± 0.5 (<0.01 P value (t test)).

Abell et al this was a non-placebo controlled, multi centered, international, feasibility study looking at 38 highly symptomatic Gastroparetic patients. This study is very detailed and thorough looking at a variety of measurable variables and observations. Even though this study was non-placebo, mid way through the study period, 10 patients inadvertently had had their GES turned off. This resulted in a dramatic increase in their symptoms.

Documentation of severity is outlined in the study. All patients had intractable symptoms of at least one year duration. All had had trials of prokinetics and antiemetics and despite these interventions 14 patients required enteral nutrition and a further 5 were on parenteral nutritional support and all patients had experienced significant weight loss prior to entering the study. Each patient had been carefully screened to exclude eating disorders such as anorexia nervosa. The vast majority of these patients were diagnosed as idiopathic Gastroparesis patients and the remaining patients were diabetic and post-surgical.

This Study also provided for an unblinded period at 6 months where patients voluntarily had their devices turned off for one week in order to compare symptoms in the previous week.

Baseline screening included assessments of gastrointestinal symptoms, GE, body weight, and use of anti-emetics, prokinetics and nutritional support status. Assessments were done at each follow-up visit of: 3, 6, and 12 months and during the unblinded one week off period at 6 months.

This study also included a phase I and phase II step, utilizing temporary GES in the phase I portion of the study. This temporary GES phase was used as a screening period to help identify patients who are 'responders' to GES and therefore will derive benefit from therapy. Parameters for 'responder' are clearly defined in the paper.

The breakdown of measured parameters for each assessment period is detailed in the paper. The results as summarized by the authors: "(GES) overall showed 35/38 patients (97%) experienced > 80% reduction in vomiting and nausea. This effect persisted throughout the observation period (2.9 – 15.6 months, 341 patient-months). GE did not initially change, but improved in most patients at 12 months. At 1 year, the average weight gain was 5.5% and 9/14 patients initially receiving enteral or parenteral nutrition were able to discontinue."

This improvement was seen in these previously intractable symptomatic patients who had tried all available prokinetics. Most experienced a rapid and sustained symptomatic improvement. GE, if it did improve, was not seen until late into the observational period.

Complications: no cardiac arrhythmias were observed during the study. The infection rate observed was within the range of recent reports on cardiac pacemaker implants.

Two patients did not show improvement with GES. Their cases resulted in total gastrectomy as an attempt for palliation of their symptoms.

"A subset of 27 patients who were available and willing to be re-examined more than 12 months after implantation were subsequently reevaluated after the end of the study. Three had died (1 from lung cancer, 1 from heart failure, and 1 related to organ transplantation). Three patients had the device removed due to infections or erosions, and 2 of these patients (both diabetic) remained symptom free after removal of the pulse generator. In the remaining 18 patients, with a mean follow-up time of 30 months, the pulse generator was functioning well. In these patients, median vomiting frequency was 0 episodes per week versus 28 weekly episodes at baseline."

Writer's note: for these 18 patients, their sustained response to GES is dramatic.

Writer's note, these international participating study centers were in: USA, Canada, France, Belgium, Sweden, Germany and the Netherlands providing a nice cultural mix. Since nausea -- like pain, is a subjective symptom which can be modulated by cultural and social background—the fact that all of these patients experienced a parallel reduction in symptoms speaks to the potent, yet to be understood effectiveness of GES.

Abell et al This was a double blind, placebo controlled, international investigation with the primary aim to examine the efficacy of Enterra Therapy; also known as the 'WAVESS' (World Wide Anti-Vomiting Electrical Stimulation Study) study has recently been published in Gastroenterology, 2003.

Documentation of severity showed that patients had a mean duration of symptoms for 6.2 years and the majority were idiopathic. Fourteen of these patients required either enteral or parenteral nutrition; all were documented as refractory to two of three classes of prokinetic and two of three classes of anti-emetic medications; and all demonstrated delayed GE on scintigraphy at 2 and 4 hours.

Many parameters were measured at baseline and through the 4 follow-up visits at 1, 2, 6 and 12 months. The measured parameters included:

- WVF (Weekly Vomiting Frequency) and symptom severity
- Nausea, early satiety, Bloating, Postprandial fullness, Epigastric Pain, Total Symptom Scores
- SF-36 (a well recognized, universally utilized and validated general quality of life questionnaire)
- Two sub measures derived from the SF-36: Physical Composite Score and the Mental Composite Score.
- Adverse events
- Hospitalizations
- Route of supplemental nutrition
- Glycosalated hemoglobin in the diabetic patients and,
- GE times at 2 and 4 hours.

Summary of results: At the end of the blinded phase, vomiting frequency decreased by 50% in the total patient group for those whose device was turned 'on' compared to those with the device in the 'off' setting ($p=0.05$). Also, a 3 to 1 patient preference for the 'on' setting was expressed before unblinding. During

Phase I (blinded double cross over), Total Symptom Scores (TSS), started to show improvement, in the 'on' vs. 'off' setting, but did not reach statistical significance till phase II.

In Phase II (unblinded) all the patients were switched to the 'on' position and followed up at 6 and 12 months. Results showed a significant drop in WVF. Compared to baseline the vomiting frequency dropped by 72% for the combined group of patients; 83% for the Idiopathic sub-group and 63% for the diabetic sub-group. As well, Physical and mental quality of life scores improved significantly compared to baseline (p=less than 0.05); TSS improved significantly from baseline (p=less than 0.05). Finally, GE showed statistically significant improvement for the combined groups at the 12 month follow-up; but (the authors noted) improvement varied widely and there was no association between changes in symptoms and gastric emptying. This is consistent with findings in other studies in Gastroparesis. These authors went on to state that the effect of GES is due to factors beyond gastric motility and dysrhythmias.

Of the 14 patients on enteral or parenteral nutrition, half no longer needed this route of nutrition at 12 months and were able to keep their food down—thus eating more normally. This had been something unachievable with medication.

All measurable parameters, for the patients who completed the 12 month study, showed improvements; many statistically significant as with: weekly vomiting frequency, total abdominal symptom score, GE tests and quality of life measures and as mentioned—some returned to eating once again.

Abell et al, this cited paper provides for a long term follow-up of a sub-set of patients from the original GEMS study group. 12 patients continued on with long-range follow-up after the initial 12 month study with the GEMS group. These 12 patients had additional follow-up sessions between 1 to 2 years and at 5 years. All patients at baseline (before GES) had symptoms of long duration—mean 7.3 years. Their Gastroparesis was associated with Diabetes in 3 patients and Idiopathic in 9 patients; consisting of 4 men and 8 women and a mean age of 35.7 years.

Measured parameters; from baseline and at 3, 6, and 12 months, then again between 1 – 2 years and at 5 years with GES; consisted of: TSS, laboratory blood work including albumin (a protein marker of nutritional status), weight, BMI (Body Mass Index), method of nutrition, (either oral, enteral or parenteral nutrition), WVF, and overall health-related quality of life measures.

Summary of findings: In the short-term follow-up period (0 – 12 months), gastrointestinal symptoms improved in all patients with a significant improvement in nutritional status. Patients' average weight increased as well as BMI from baseline. Blood work also showed improvement in mean serum cholesterol levels (180.6 $\pm$ 13.2 at baseline to 216.8 $\pm$ 19.7 at 3 months. This trend peaked at 6 months); and serum albumin levels changed from 3.5 $\pm$ 0.2 at baseline and peaked at 3 months; increased lymphocyte count from 30 $\pm$ 3.1% at baseline to 32.6 $\pm$ 5.9% at 12 months ($p>0.30$ by ANOVA). One patient had a low baseline lymphocyte count of 7.4 % at baseline that improved to 18.5% by the third month after GES.

Finally, patient route of nutrition changed from baseline. 8 patients had been on oral only nutrition with 2 on enteral and 2 on parenteral nutrition. At the one year follow-up one enteral patient was able to convert to oral only nutrition and one parenteral dependent patient was also able to convert to oral only nutrition. At the 5 year follow-up period, only one patient was requiring enteral and oral nutrition. An over all change of 30% compared to baseline.

All measured parameters showed improvement from 3 months and persisting through to 5 years showing enduring, statistically significant changes to: TSS, WVF, weight, and BMI measures. As well, 2 health-related quality of life measures showed improvement from baseline.

Forster et al, in this cited paper, Forster et al studied 55 patients from April 1998 till November 2001: 9 were from the original WAVESS study group, 32 from the CUESS study group (this was a prospective trial for determining compassionate use of the device (pre-HUD designation)) and 14 patients post HUD

designation. This collection of patients represented a very ill population—many steadily losing weight and on enteral or parenteral nutrition at baseline. Average duration of symptoms was 9.9 years.

Measured parameters were taken at baseline then 6 and 12 months. These parameters consisted of: gastric emptying; total symptoms score; severity and frequency of nausea/vomiting; quality of life measures utilizing the SF-36 questionnaire; body weight and body mass index; and finally—Hemoglobin A1C in the diabetic patients.

Outcomes post GES:

- Six patients died, all diabetic and none related to the GES.
- GES had to be removed from 4 patients, all diabetic; three due to infections and one due to a small bowel volvulus. All patients recovered.
- In 3 other patients, the device needed to be moved or replaced. One was relocated due to migration of the device (patient was feeling so much better he had returned to golfing—this activity is felt to have caused the device migration) because the leads had lost contact with the stomach. The above mentioned patient with volvulus had GES replaced 9 months after surgical correction of the volvulus. The final patient was in a car accident, fracturing her sternum. Seven days after the accident her Gastroparetic symptoms dramatically increased—examination revealed that one of the leads had become detached from the force of the accident. The lead was replaced and her symptoms improved very soon after the surgery to correct the displaced lead.

Summary of results: of the compliment of patients followed for 12 months, gastric emptying was significantly improved at 6 months, but the numerical difference was small. This improvement was not sustained at 12 months. However, a third of these patients did achieve normal gastric emptying (<10% remaining at 4 hours on scintigraphy). Of this third, 58% were diabetic patients, 25% idiopathic, and 17% post surgical.

Gastrointestinal total symptom scores for both severity and frequency were significantly improved at 6 months ($P<0.05$). Total symptom scores remained significantly reduced at 12 months, this despite the lack of overall continued improvement in gastric emptying.

Quality of life parameters improved dramatically with mental composite scores approaching normal, rising from 37 to 48. Most of this improvement occurred in the first 6 months.

Patients demonstrated a marked decrease in the need for hospitalization. In the year prior to GES placement, the average days spent in the hospital was: 57 ± 9 (range: 0 to 252). The year following GES, this fell to 17 ± 3 days (range 0 to 69; $P<0.05$). This dramatic reduction in hospitalization could explain the improved quality of life scores.

Nutritional parameters also showed improvement, with the average patient showing a body weight increase by almost one kilogram and the body mass index increasing by 0.4 units. This improved body weight translated to the majority of patients having their jejunal feeding tubes removed and no one remained on parenteral nutrition. At baseline, 25 patients were on J-tube feedings (1 had a gastrojejunostomy); after GES, only 8 remained on j-tube feedings by 12 months.

The authors went on to conclude that GES is a potent anti-emetic despite not consistently showing improvements to gastric emptying times at 12 months. Yet, one third of the patients did achieve normal emptying at 4 hours after 12 months of therapy and they did not come exclusively from one etiologic sub group.

Improvements in weight, eating, quality of life measures, and reduction in nausea and vomiting clearly makes life more tolerable for the majority of these patients. These improvements need to be viewed from the perspective that these patients are young (average age 40.5 years) women (76%) and men in the prime years of their life and they can be returned to families and employment activities resulting from GES therapy. It must be kept in mind that these patients were terribly ill at time of GES implant and losing

ground with continued weight loss or persistence with nutritional support, all previously unresponsive to standard medical interventions.

For the diabetics, improvements in symptoms also allowed for better eating habits and improvement in glucose control. GES is able to markedly decrease or halt nausea and vomiting. This then translates to a number of advantages for diabetic patients:

- GES demonstrated reduced HbA1C and sustained improved glucose control. This could help reduce the occurrence of future diabetic complications because of improved blood glucose control.
- Also, reduction in vomiting makes the patients better candidates for pancreas transplantation, since immunosuppressant can be taken orally and predictably absorbed without vomiting.

Curuchi et al is a very recent abstract which has been accepted for publication and will appear in Gastroenterology this spring as well as being presented as a poster at the Digestive Disease Week (DDW) in New Orleans, LA, May, 2004. This abstract report provides data on 10 years of experience with GES from three centers. The published paper will also feature health related quality of life measures. This data is not available at this time for inclusion in this petition.

Evaluation of both safety and efficacy was the primary focus of this research project. Mortality rates were also tracked and compared to medical controls who had received traditional care and management for their Gastroparesis. The medical controls had also been followed for ten years. The controls have had their data published and represented 33 patients, 26 non diabetics and 7 Diabetic patients. (see *Diabetes* 52: A191, 2003).

Methods: All patients had consented for GES. Their presenting diagnosis, type of implant, survival, most recent gastric emptying (compared to baseline symptoms) was documented.

Ten years of experience at 3 centers tracked the results of patients coming in to receive their GES. One hundred and thirty three patients participated. Of these, 122 were permanent implants, and 11 temporary. Eight patients had their devices removed, most commonly due to infections. Eleven patients underwent replacement of their devices for battery change or other technical problems.

The results from 3,622 patient months (equating to 301.8 patient years of experience with GES) showed that of the 109 non diabetic Gastroparetic patients (post surgical and Idiopathic), 9 of the 109 had died (most from their primary disease) compared to 2 of the 26 non-diabetic controls. This represents a mortality rate of 12% VS 13% for controls.

More dramatic was the mortality rate for the diabetic patients who had GES VS controls. The Diabetic patients with GES (n=24) showed a mortality rate of 6% compared to the Diabetic controls who had a mortality rate of 43% (3 deaths out of 7).*

Data on the total GES patient group showed a persistent and enduring ability to decrease total symptom scores and vomiting frequency compared to baseline in these patients; as well as showing improvement in gastric emptying at 2 hours and 4 hours.

Baseline values for total group of GES patients VS follow-up:

Total Symptom Scores (0 to 50) =.....38.4 VS 18.2 at follow-up
Vomiting Frequency (0 to 4) =.....3.57 VS 1.44 at follow-up
Gastric Emptying time @ 2 hours =.....59.6 retention VS 39.3 at follow-up
Gastric Emptying time @ 4 hours =.....29.16 retention VS 14.9 at follow-up

No deaths were attributed to the devices.

The authors conclude that: GES has proven to be safe and effective for the last decade. Efforts need to continue to help identify which patients will benefit most from GES and under what conditions.

The fact that GES has been repeatedly replicated-- showing over all: significant reduction in nausea and vomiting and improvement in secondary measures, by different investigators in different institutions, and for years post implantation, resoundingly shows efficacy.

As well, GES demonstrates persistent, enduring and potent reduction of symptoms, primarily of nausea and or vomiting, as well as secondary gains in stabilization of weight and for some, more normalization of eating patterns. This results in improved quality of life and mental health, based upon standardized, recognized, validated measures.

The phenomena experienced by patients and observed by experts cannot be ignored. The bulk of evidence presented, including one double blind cross over study, makes a powerful case for efficacy—as powerful as for those devices already on the market with PMA status.

Medicine is not an exact science. The tenants of medicine are to provide compassionate care and alleviate suffering. Patients need to fully access a revolutionary treatment that can bring hope, and for many, relief from their chronic, debilitating illness.

5. Conclusions:

The literature demonstrates that GES effectiveness has an overall rate for palliative control of nausea and vomiting as high as 70 to 80% with enduring results. This potent anti-emetic, anti-nauseant effect, allows patients to feel better, eat better, gain weight and stay out of the hospital. One small study has demonstrated a decrease in mortality rates for GES patients.

Gastroenterologists who are beginning to use GES are finding these results extrapolated to their own client base.

It must be recognized that for these severely ill patients, GES is not a magic wand. Patients cannot expect a complete return to health and well-being post GES. Compared to where they were -- the depth of their suffering and despair -- they are thankful to gain some, or a large measure of relief. Even more profound is the ten years of experience with GES showing a decrease in mortality rates for diabetic patients with GES vs. those without. Some patients are also able to return to a more active lifestyle post GES. These all suggest a very potent anti-emetic effect with the ability to diminish the continuing eroding effects of intractable nausea and vomiting.

Not all will respond, but **all must have a right to access,** without hindrances, something that is safe, reversible and has now been proven effective; especially when taking into consideration how precious few treatment options for symptom relief are available for this patient group.

Of interest, some of the literature demonstrates the technique of temporarily placing electrodes via the endoscope, as a means of patient selection for which the device has a greater probability of long term success. This is a very responsible and logical approach. As well, investigators are scrutinizing the stimulus parameters in an attempt to continually improve the clinical management of symptoms. This work undoubtedly would speed up once PMA status is granted.

6. Environmental impact / Certification

Medtronic Inc, in following "Good Manufacturing Practices" has already satisfied the requirement of environmental documentation under 21 CFR 25.33(g). This would have been required for the HUD status.

The undersigned certifies, that, to the best of knowledge and belief of the undersigned, this petition includes all information and views upon which the petition relies, and includes representative data and information known to the petitioners' which are unfavorable to the petition. To the petitioners' knowledge, no other similar issue, act or transaction to this petition is under consideration.

7. Agency action requested:

The FDA immediately:

- **Refers this petition to their Gastroenterology and Urology Devices Advisory Panel for review and comments.**
- **The Commissionaire reviews this pertinent literature with Medtronic Inc and immediately invites Medtronic Inc to begin the process to transfer the Enterra Therapy Device from a HUD status to PMA status.**

Petitioners' are requesting a response to this Petition within 180 days.

Dated this 24 Day of February, 2004.

On behalf of all petitioners,
Jeanne Keith-Ferris, RN, BScN

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White Paper:

"Gastroparesis and Related Digestive Motility Diseases, a Medical Crisis."

Prepared by:
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August 19, 2003

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White Paper

"Gastroparesis and Related Digestive Motility Diseases, a Medical Crisis."

Prepared by:
Gastroparesis and Dysmotilities Association (GPDA)

August 19, 2003

Synopsis

The aim of this White Paper is to call attention to a very serious group of digestive disease neuromuscular disorders that for too long have received little research funding. This White Paper is intended for wide dissemination among the House and Senate, the Director of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) Commissioner.

This paper serves to outline the scope of the crisis. The 4 main categories of severe paralytic digestive Motility diseases; specifically: Gastroparesis, Chronic Intestinal Pseudo-obstruction, Colonic Inertia and Achalasia cost U.S. taxpayers billions of dollars annually. Significant morbidity and mortality statistics exist for this group of digestive diseases.

This Paper will help to inform government officials of the cost of human suffering and impediments, due to lack of FDA approval, to accessing the few treatment options that currently exist. These impediments push up the cost of health care and increase mortality.

On May 17th, 2003 in Orlando, Florida, the First International Scientific Task Force on Gastroparesis was convened (see appendix I). This Scientific think tank attempted to address the enormity of the problem surrounding the most common of the digestive neuromuscular diseases: Gastroparesis. The task is daunting, since so little is known about Gastroparesis and limited recourses exist-- to even outline its prevalence; let alone search for effective treatments. Gastroparesis and the other related digestive Motility* diseases share this paucity of scientific data and treatment options. Very little scientific headway has been made over the past 20 years. Collectively, these are not rare diseases.

These diseases are in need of "catch-up" work to help redress this current situation. These diseases afflict men, women and children. Very limited resources exist in the private sector to correct the crisis. Patients and families need hope that their government will provide the leadership to help advance the search for effective treatment options.

This White Paper is very important and timely since government action can help advance the initiatives that have come out of the Task Force meeting.

Quick Facts about the Digestive Motility Diseases Medical Crisis:

Digestive Motility diseases:

- Have mortality statistics;
- Are disabling;
- Cost taxpayers billions of dollars annually;
- Currently **do not have any** pharmacological therapies specifically tailored to these diseases;
- The one effective **treatment device** is extraordinarily difficult to obtain as it is presently approved only under humanitarian release by the FDA. This lack of full approval increases health care costs and mortality rates;
- Pharmacological therapies that have been used in treating Motility diseases, and are effective, are not available because they lack FDA approval;
- Social Security claims for disability are very difficult to obtain; this in part may be due to the lack of understanding by government officials regarding the seriousness of these Motility diseases;
- No consensus guidelines exist for the adult Motility diseases, hence misdiagnosis and mismanagement of these diseases frequently occurs;
- No standardization of diagnostic methods currently exists;
- No statistics exist to outline the extent of the problem;
- Few resources exist in the private sector to correct the crisis; and
- Very little resources have been spent by the NIH investigating the pathobiology, especially for the adult and pediatric Idiopathic group of digestive Motility diseases.

- Finally: The US government-- through NASA-- has spent close to 20 million dollars researching the effects, and methods to ameliorate, Motion Sickness for space and military personnel. Motility patients live with "motion sickness like symptoms" on a daily basis for years. This sum of money represents a greater amount than has been spent by the government on research into all of these lethal Motility diseases. In 2000 the National Institutes of Health (NIH) spent 2 million dollars on Motility research (1). Most of this was on basic research. Very little, if any research dollars have been spent by the NIH on the search for effective treatment options for these Digestive Motility diseases.

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1. Report by Dr. Frank Hamilton (Branch Chief; Gastrointestinal Motility Program Director; Gastrointestinal Mucosa and Immunology Program Director; AIDS Program Director, NIDDK) to the First International Scientific Task Force on Gastroparesis, May, 2003, Orlando, Florida.

* The terms 'paralytic,' 'Motility' and 'neuromuscular' may be used interchangeably when describing this group of diseases.

Pediatric Digestion and Motility Disorders Society, Inc.

"Progressing Pediatric Gastroenterology through Research and Education"

August 29, 2003

Dear Senator/Member of Congress:

On behalf of the Board of Directors of The Pediatric Digestion and Motility Disorders Society (PEDS), we are writing to express our full support of the efforts of the Gastroparesis and Dysmotilities Association. The Association has prepared the enclosed White Paper entitled "Gastroparesis and Related Digestive Motility Diseases, a Medical Crisis" for your review. The White Paper details the scientific aspect of this debilitating disease in both the adult and pediatric population.

PEDS is a registered Not- For-Profit 501(c) (3) organization incorporated in New York State, and has been funding research since 1989, both locally and on the national level. PEDS assisted in the language of an Appropriation Bill in 1998. **The language was appropriately contained in House Report 105-205, House Appropriation Committee Report H.R. 2264.**

The mission of PEDS is to raise funds for the education and research of Pediatric Gastrointestinal Motility Diseases and its related disorders. We are asking for your support to assist in improving the quality of life in both the adult and pediatric patients afflicted with gastrointestinal motility diseases. Research funds will allow earlier detection, improve treatment protocol, therefore decreasing overall healthcare costs.

We are willing to meet at any time to further answer and discuss any questions you may have. Thank you for your attention and consideration of this issue.

Respectfully,

Marcella A. LoFaso
Founder

Michael J Quinn
Chairman

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August 20, 2003

To Whom It May Concern:

The Association of Gastrointestinal Motility Disorders, Inc. (AGMD) is in full support of the Gastroparesis and Dysmotilities Association in the call for funding for research in the specialized field of digestive motility diseases.

There are an increasing number of people who are affected by these debilitating disorders, however, unfortunately, there are few options available for the treatment of these problems. For many of these diseases, there remains to be no cure and research is at a minimum.

Digestive motility diseases may affect people of all ages including infants and children. The quality of life in people with these diseases can be gravely compromised by their inability to eat and digest food normally.

Our non-profit international organization has been in existence since 1991 and has served as a strong advocate in the promotion of research and its mission to educate both members of the medical community and the general public about these life-altering diseases.

AGMD is privileged to have this opportunity to share its voice with others in the immediate unified call for funding and research for digestive motility diseases. We appreciate the efforts of the Gastroparesis and Dysmotilities Association and all those working towards helping those with these diseases. Funding for research is critical in order to find treatments and cures that will make a difference in the lives of so many patients and their families.

With respect and gratitude

Mary-Angela DeGrazia-DiTucci
President/Patient/Founder

Contents

Introduction

Digestive disease Motility disorders are also known as paralytic disorders of the digestive tract. These *gastrointestinal (GI) neuromuscular diseases* are characterized by weak, spastic and / or flaccid muscular tone within a regional segment; or extending through the entire length of the digestive tract.

Gastrointestinal *Motility* refers to the digestive tract's ability to contract, mechanically digest and propel food along its hollow passageway. This muscular activity is orchestrated through a host of neurochemical events working in exquisite balance of excitatory and inhibitory regulation. Science's understanding of the underlying biophysiology is still evolving.

Disorders of Motility are impairments of mechanical *functions* of the esophagus, stomach and intestines that interfere with digestion, absorption and nutrition. The hallmark of these diseases is the lack of any tangible abnormalities such as tumors, ulcers or inflammation to explain the symptoms. This impaired *function*, resulting in weak, uncoordinated or absent muscular activity, can be so pronounced as to mimic an intestinal blockage. Food and secretions just pool or sit and do not move downward, but instead may be vomited back-up. These diseases are characterized by cellular abnormalities within the digestive nervous system, often detectable with full thickness biopsies. However, the neuromuscular deficiency is one yet to be elucidated.

Motility impairments can occur as regional or general problems within the digestive tract and each region has its own diagnostic term. Some individuals can suffer with a blending of Motility problems which extend from the esophagus down through the colon. It is not uncommon for these Motility diseases to be associated with Autonomic Nerve Dysfunction resulting in urinary retention, labile blood pressure coupled with significant heart rate variations and sweating abnormalities.

Diagnosing Motility diseases is fraught with difficulties. Extensive investigations using standard diagnostic tests such as blood work, abdominal ultrasound, computerized tomography, endoscopy, barium swallow, barium enemas and colonoscopy may all culminate in normal results. Ordering the proper tests is incumbent upon the skill and expertise of the treating Gastroenterologist. "Manometry," or "Motility testing," considered by Gastroenterologists who specialize in Motility diseases as a very valuable tool in confirming the diagnosis of Motility problems, is provided by very few treatment centers. No doubt some restriction to obtaining these tests is due to inadequate reimbursement for the time consuming job of reading these complex 'Motility' tracings. So, only the very dedicated, specialized centers provide this form of testing. As well, electrogastrography (EGG) is a helpful adjunct diagnostic tool that provides valuable indirect evidence of digestive neuro-electrical rhythms. Yet reimbursement for this assessment procedure also is very poor and creates barriers to its widespread use.

Gastroparesis:

Gastroparesis is the most commonly disabling Motility disease. The term Gastro refers to the stomach and paresis means weakness or paralysis. This disease is also called "delayed gastric emptying" to describe the observed phenomenon found with Gastric Emptying studies. The abnormal tone within the stomach interferes with its ability to effectively digest a meal (accommodation of a meal; grinding; mixing nutrients with secretions; and finally moving the mixture out). The resulting undigested material sits for hours within a distended stomach. Gastroparesis is further characterized by the vomiting of undigested food many hours after a meal and the formation of Bezoars—congealed balls of retained food elements that cannot exit the stomach. Gastroparesis is often found in association with abnormal Motility within the duodenum, and esophagus. Thus, Gastroparesis can at times, be part of a larger diffuse Motility disease. Esophageal spasms can result and cause profound pain that mimics a myocardial infarction, and often leads to emergency room visits with attendant additional costs to rule out heart abnormalities. The delayed gastric emptying that occurs in Gastropareis may lead to a back up into the esophagus and cause secondary Gastro-esophageal Reflux Disease (GERD).

The symptom complex of Gastroparesis, collectively called 'dyspepsia' is expressed as: nausea, abdominal pain (frequently occurring after a meal), early satiety, abdominal bloating and heartburn. This dyspepsia can be episodic or constant. The nausea will frequently build to a crescendo of vomiting necessitating emergency room visits for intravenous re-hydration. These episodes also cause spiraling malnourishment.

For the most severe forms of Gastroparesis, bouts of nausea and vomiting are a daily occurrence and can persist for years. These unrelenting symptoms lead to chronic malnutrition and slow deterioration.

McCallum et al (1) cited statistics that followed Gastroparesis patients for a 5 year period. Over this time, 15% of all patients were still dependent on enteral or parenteral nutrition. In other words, this group required nutritional support via tubes surgically

1. McCallum RW, George SJ: Gastroparesis. *Clinical Perspectives in Gastroenterology* 2001 May/June; 147-154.

implanted into either the small intestine to by-pass the non-working stomach or intravenously called: Total Parenteral Nutrition (TPN). In both forms of nutritional support, a liquid formula is infused through a catheter via an infusion pump. For enteral support, a catheter is run through the abdomen into the small intestine (jejunostomy). For TPN, a catheter is threaded through the chest wall into a large vein (central venous catheter) or a PICC line (Peripherally inserted central catheter).

Infusion rates can be very slow in enteral feeding due to intestinal spasms or slow with TPN due to vascular spasms. A 'meal' can take many hours to infuse. This intervention usually does not halt nausea and vomiting. To try and control the frequency of vomiting, patients may also need a 'venting' ostomy placed in the stomach to help access and suction out retained gastric secretions.

Gastroparesis, as with all the Motility diseases, presents with varying degrees of severity. For less severe forms, dietary changes can help to moderate the symptom complex. Yet subsisting on oral liquid nutrition or restricted diets is challenging. Even in less serious cases patients may still suffer with sub-optimal nutrition resulting in weakness and fatigue. Then there is the hidden, unrelenting symptom of nausea. It is the most commonly reported symptom of Gastroparesis. This confounding symptom is exceptionally difficult to control and is very debilitating.

Gastroparesis carries a 5 % mortality rate (2) while some specialists who see a preponderance of Gastroparetic patients in their clinical practice, report mortality rates of up to 10% and rates even higher for Type I Diabetic Gastroparesis patients.

Chronic Intestinal Pseudo-obstruction (CIP)

Chronic Intestinal Pseudo-obstruction is the diagnostic name applied to the regional paralytic disease affecting the small intestine. It often leads to a general failure of the entire digestive tract. Also called CIP, this Motility disease has the greatest degree of morbidity and mortality. CIP usually has an insidious onset and may take 3 to 10 years for an accurate diagnosis to be obtained. The diagnosis of CIP is usually preceded by several years with nonspecific abdominal symptoms. During this time, many patients may undergo multiple surgical interventions in the attempt to find a mechanical bowel obstruction. Delayed gastric emptying (Gastroparesis) is also frequently found with CIP as well as puzzling autonomic nerve (ANS) dysfunction symptoms, interfering with bladder, heart and other systems under the control of the ANS.

The dyspeptic symptoms described above also occur with CIP, but this group of patients also suffers to a far greater degree from intense abdominal pain. This intense pain often requires narcotic use. The narcotics then have the effect of further slowing down the weak digestive tract. Intractable constipation is also a predominate symptom with CIP. Secondary problems such as 'Small Intestinal Bacterial Overgrowth,' commonly occur and greatly impair the already compromised digestion. As well, co-morbidity of chronic pancreatitis, gall bladder failure, and or liver impairment is not uncommon.

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2. Ibid

Intractable nausea, vomiting and the vomiting of bile are seen with CIP. Nutritional support for this group of patients is more dependent upon total 'parenteral' nutrition (TPN). This method is required since little nutrient absorption can occur from the non-functioning intestines. People on parenteral nutrition, on average, suffer approximately two life threatening 'blood' infections each year as a complication of this form of 'feeding.' TPN also carries a risk of liver failure. If liver failure ensues from TPN then the only treatment option left for these patients is an intestinal transplant. Before the advent of Total Parenteral Nutrition in the 1970's many more patients died of CIP.

Colonic Inertia:

Colonic Inertia is the regional Motility disease that primarily affects the colon. It too is characterized by weak to flaccid tone with uncoordinated contractile activity within the colon. Its onset is insidious. This Motility disease causes severe abdominal distention, pain and great risk of severe fecal impaction leading to complete blockage with intestinal rupture. A rupture results in spillage of fecal matter into the abdominal cavity causing a life threatening infection known as 'peritonitis.' Surgical remedies are not always a quick fix since the motility disturbances can progress farther-up the digestive tract causing unremitting symptoms of abdominal pain and dyspepsia.

Achalasia:

The Motility disease affecting the esophagus is known as "Achalasia," meaning "failure to relax." Characterized by dysphasia (difficulty in swallowing) of solid and liquids; substances entering the esophagus become trapped due to the persistent contraction of the lower esophageal sphincter (LES), a ring-like muscle surrounding the esophagus and acting like a valve at the Gastroesophageal junction. Achalasia is further characterized by weak to absent peristaltic waves within the esophagus. If unable to pass naturally into the stomach, these trapped contents must be expelled through voluntary regurgitation. Patients present with a number of symptoms, depending upon the stage at which the disease is diagnosed. In addition to the aforementioned difficulty in swallowing and regurgitation, these symptoms can include severe chest pain due to esophageal muscle spasms (a sub-condition known as 'vigorous Achalasia'); heartburn/GERD; coughing; wheezing; and pneumonia. Progressive intolerance for food substances and consistencies, along with unanticipated obstructive instances, adversely affects a patient's general quality of life. Indeed, the unpredictable nature of the aperistalsis and LES malfunction makes Achalasia an oppressive condition, with frequent choking, dramatic weight loss and malnutrition commonly experienced.

How are these diseases acquired?

Hereditary forms of Motility diseases do exist, but are not dealt with in the context of this White Paper. Of the non-hereditary Motility diseases, the largest groups are the 'Idiopathic." This term denotes that the *primary* cause of the Motility disease is *unknown.*

Other acquired forms of Motility diseases are those that occur as a secondary result to a primary, systemic disease. Autonomic neuropathy from Diabetes is a common pathway to Digestive Motility diseases. As well, collagen diseases like Scleroderma can lead to

devastating Motility problems. Chronic renal failure, advanced Liver disease or Liver failure, Heart and Lung transplant patients, AIDs, Parkinson's disease, Familial Dysautonomia, Muscular Dystrophy, Hypothyroid disease, some types of gastric surgery and paraneoplastic diseases, can all develop paralytic Motility diseases to a devastating degree. This is by no means an exhaustive list.

Prevalence

Dyspepsia as a symptom complex is not a rare finding in the *general population* and its expression results in significant impairment in quality of life and time lost from work. In the DIGEST study (3), surveys were conducted in the general community. Individuals were randomly selected. A total number of 2,056 people across North America were interviewed. Those who reported significant dyspepsia with 'Motility like' symptoms (nausea, vomiting, bloating, fullness after a meal, etc.) had amongst the highest health care utilization, medication use and time lost from work for all the dyspeptics interviewed. This paper went on to speculate that these survey results corresponded to a rate of dyspepsia in the general population of 35% and further, in the North American population, 18% of these dyspeptics, experience substantial upper gastrointestinal symptoms of dyspepsia with marked impairment in quality of life. The Canadian data available further breaks down its study population to reveal the incidence of chronic nausea with substantial vomiting at a 2% rate within the whole study group.

- The upper Digestive Motility diseases discussed in this White Paper represent the **severe spectrum of dyspepsia** symptoms coupled with the *signs* of vomiting and weight loss.

For all forms of Gastroparesis, (Idiopathic and Secondary causes) Kendall et al (4) provides a break down of causes: **33 % of all those with Gastroparesis are Idiopathic.** The next largest group to acquire Gastroparesis are the diabetics at 24%, followed by post gastric surgeries and Parkinson's disease. These categories make up the preponderance of all Gastroparesis causes. These statistics are also supported by a more recent publication by McCallum et al (5).

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3. Frank L, Kleinman L, et al: Upper Gastrointestinl Symptoms in North America. Prevalence and Relationship to Healthcare Utilization and Quality of Life. *Digestive Diseases and Sciences* 2000 April; 45 (4): 809-818.

4. Kendall BJ, McCallum RW: Gastroparesis and the Current Use of Prokinetic Drugs. *The Gastroenterologist* 1993; 1: 107-114.

5. McCallum RW, Daaboul B: Abnormal Gastric Emptying. *Best Practice Medicine.* URL: merck.praxis.md/bpm/ga/gastricemptying, 1999; Dec.

Approx 10% of all diabetics suffer with more severe forms of Gastroparesis (6). In the United States, Diabetics make up 5.8% of the total population or approximately 15.7 million Diabetics (Source: American Diabetes Association). The trends show that Diabetes is on the rise in the United States. This then equates to approximately **1.6 million Diabetics suffering with more severe forms of Gastroparesis and these numbers are growing.**

For comparison, the prevalence for Inflammatory Bowel disease (Crohn's and colitis) is 149 people per 100,000 (Source: Crohn's and Colitis Foundation). For the entire US population this represents approximately 450,000 people. A rare disease as defined by the US government is any disease afflicting 200,000 people or less. (Source: NORD).

- A conservative estimate for numbers **of Americans suffering with Gastroparesis would be 3 million** (1.6 million diabetics an equal number of Idiopathic Gastroparetic patients).

- Idiopathic Gastroparesis shows a strong female predilection with onset occurring in the prime of life—18 to 50 years of age.

CIP: Little information is available on the Prevalence of CIP, but about 5% of all Gastroparetic patients are found to have an associated CIP. Also, CIP affects men, women and children equally, and reported rates are: 50,000 individuals throughout the United States.

Colonic inertia-- again getting at the prevalence rates is difficult; however, Chagas disease numbers are available and provide some insight as to the prevalence of Colonic Inertia.

Chagas disease is caused by a parasite endemic to Central and South America. The infection can produce lethal heart complications, and also is responsible for damaging nerves in the digestive track which leads to Motility diseases, most commonly within the colon (mega colon). Recent estimates indicate that 350,000 people in the United States have Chagas disease.

- The largest group to have Colonic Inertia is the Idiopathic group.

- Mega colon (a complication of Colonic Inertia) carries about a 3% mortality rate.

- Idiopathic Colonic Inertia shows a female predilection.

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6. Johns Hopkins Medical Institutions, Gastroenterology and Hepatology Resource Center. Website: http://www.hopkinsgi.org. Search topic: *Gastroparesis.*

Achalasia: is a rare disease, Achalasia generally is believed to affect approximately 1 in 200,000 people with all age groups represented and with no gender preference.

The availability of statistics to tell the real story is appallingly lacking especially considering the seriousness of these disorders, all of which carry mortality statistics.

The Task force on Gastroparesis that recently convened in Orlando Florida on May 17 helped to outline the difficulty in articulating the full picture-- specifically Gastroparesis; but generally about all the Motility diseases. To quote Dr. Jay Pasricha's (7) opening remarks from the May 17, Orlando Task Force on Gastroparesis:

There are in fact some very simple and fundamental questions about this disease, (Gastroparesis) that despite the last 20 years of progress really haven't come a long way in answering. For instance, we still don't know:

- *how prevalent is it;*
- *what is the best way to define it;*
- *what is the best way to diagnose it;*
- *what causes it;*
- *what is the underlying pathophysiology;*
- *what is the natural history (the course of the illness);*
- *and then, just some practical things like the nausea, why is it so much more difficult to control.*

And of course, the bottom line is how we can find effective treatments for this group of patients who probably have the worst quality of life among all the patients we see (in our GI clinics)."

These comments made by Dr. Pasricha really help describe the present situation for all of the serious forms of paralytic Motility diseases presented in this White Paper.

- **The sum of all who suffer with severe Digestive Motility diseases exceeds the prevalence of many other severe digestive diseases like Inflammatory Bowel diseases.**

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7. Pankaj Jay Pasricha, MD: Chief, Division of Gastroenterology and Hepatology, Department of Internal Medicine. University of Texas Medical Branch at Galveston. Opening remarks to the First International Scientific Task Force on Gastroparesis, May 17, 2003, Orlando, Florida.

Cost to society:

The cost for one patient on home TPN will vary depending upon the formula, other treatments, lipid content and supplies. The range is between: $250-$1000 per day; or $90,000 to $360,000 dollars a year. This range would represent the most conservative to the most expensive cost. Medicare reimburses based on grams of protein and lipid content. The range for Medicare coverage would be $225-$405 per day. Medicare is also limited as they only pay for the TPN and not any other drugs or therapies. The cost for TPN goes up substantially if this treatment is received within a hospital setting. Patients with Gastroparesis and or CIP may be maintained on home TPN for years. Complications from poor symptom control (few pharmacological treatments for treating these Motility diseases) couple with complications from this form of feeding often necessitate frequent trips to the emergency department and/or hospitalization.

On average, one Gastroparesis patient costs $85,000 dollars a year for hospital based costs alone. This cost does not reflect enteral / parenteral feedings, home health care, time lost from work, medications, special formulas and supplements, dressing and infusion pumps (if enteral / parenteral dependent), etc. (8).

Data from Diabetic Gastroparesis patients is more easily extracted since this is a readily identifiable group.

Bell et al (9) investigated the number of hospitalizations and discharges in one year (1998) for patients with Diabetic Gastroparesis in the State of North Carolina. The results based on the North Carolina Hospital Discharge database showed there were 1,476 discharges with total charges of $11,378,466 over 7850 total hospital days.

This is only one state and one year. This data does not reflect the largest group of those suffering with Gastroparesis, namely the "idiopathic" group. This published scientific paper also does not take into account the number of patients who may be on enteral or parenteral nutritional support due to their Gastroparesis. These costs can be extrapolated to the US population.

- Gastroparesis can significantly adversely affect Diabetic glycemic control thus accelerating complications from Diabetes and increasing hospital utilization costs.

The total burden to society for Digestive Motility diseases runs into the billions of dollars; from hospital costs, time lost from work, medication costs, and cost of specialized formulas.

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8. Abell TL, MD; Assistant Professor, University of Mississippi Medical Center; division of Digestive Diseases, Jackson, Mississippi: abstract submitted for publication. Information provided by personal communication.

9. Bell RA, Jones-Vessey K, et al: Hospitalizations and Outcomes for Diabetic Gastroparesis in North Carolina. *South Med. J.* 2002 Nov: 95(11): 1297-9.

Quality of life

The impact on quality of life is devastating. One must also recognize that the idiopathic group is often initially misdiagnosed and provided inappropriate treatments. For the severe intractable vomiting Gastroparestic patients, some ill informed specialists may initially recommend a total gastrectomy (which often does not resolve symptoms and only further devastates quality of life).

Patients frequently run the gauntlet of an implied psychiatric overlay to explain the symptoms of their severe neuromuscular digestive diseases. For children who suffer with Idiopathic or acquired Motility disease, even less scientific knowledge is known. Munchausen by proxy is often a differential diagnosis that families must struggle against in their desperate attempt to halt their child's suffering of nausea, vomiting, abdominal pain and weight loss.

Very small children can suffer with bouts of vomiting, frequent retching and tears of discomfort. This suffering brings a weight of despair to parents unable to comfort their child. There is nothing more difficult than watching your child fail to thrive and toil against these horrible symptoms.

Adolescents, who need enteral, parenteral, or nasal duodenal / +jejunum nutrition to stabilize dramatic weight loss, must also deal with the acute psychological impact of body image changes (this age group is particularly sensitive to this issue); these interventions being necessary to stop the downward spiral of malnourishment and dramatic weight loss. Further, school age children and adolescents who are learning skills of socialization miss out on this aspect of their growth and development. Isolation caused from unremitting symptoms, and malnourishment, impacts their mental health. This age group is especially venerable as they struggle for acceptance with their peers; even lacking the energy to try and 'keep-up' to their peers. Older adolescents have continued failures with dating, since developing relationships are constantly interrupted by unpredictable symptom flair-ups or hospitalizations.

Chronic illness and the daily battle against symptoms is emotionally exhausting. Emotional reserves are also spent due to sleep pattern disruption caused by unrelenting symptoms of heartburn, esophageal spasms, nausea, vomiting, abdominal pain, and abdominal distention.

These patients are also faced with the hopelessness that comes from being confronted by their specialist and told that nothing more can be done for them. With so few treatment options, the specialists too are frustrated and feel powerless.

Nausea requires special mention. It leads to invisible suffering with devastating and debilitating results. It is one of the most frequent symptoms for upper Digestive Motility diseases. Nausea is a profound symptom—and a protective mechanism in all mammals. Animals and humans who have been exposed to toxic or noxious substances that produce acute nausea and vomiting will passionately avoid the offending substance for years later. A testament to the debilitating effects of nausea and vomiting, NASA has spent approximately 20 million dollars researching the effects of motion sickness and

investigation into treatment options for astronauts and military personnel. Some Motility patients face years of devastating endless cycles of nausea and vomiting.

Families call out for help. It is not uncommon for professional health care providers to get phone calls from desperate families members. One can hear the near panic in their voices as they plead: "can't something be done to stop the suffering!" The impact on family members witnessing the wasting away of a loved one is devastating.

Abdominal pain—drugs used to treat the severe abdominal pain commonly found in CIP further slow down the digestive tract. This results in the need for frequent enemas and / or bowel irrigations.

The family unit is stretched to the limit emotionally, financially and socially as they attempt to cope with Paralytic digestive diseases. These diseases shatter many families which results in increased rates of divorce or separation.

Suicidal ideation in the patient is not an uncommon report. Faced with overwhelming symptoms, bodily changes, chronic to severe malnourishment, house bound with feeding tubes, and told that they have tried all the available medications to no avail, these severe neuromuscular digestive diseases rob a person of their will to live.

Simple social gatherings for meals, no longer hold any joy, but instead bring anxiety. Planned outings or vacations are not to be planned on since symptom flair-ups will leave the patient / families canceling activities at the last moment.

Treatments:

McCallum published a paper in 1985 titled "Review of the Current Status of Prokinetic Agents in Gastroenterology."(10) Prokinetic drugs are the medications that help to speed up the digestive tract. In 2003, the drugs outlined in the above paper are still the same; except one important drug in the armamentarium is no longer available—Propulsid (Cisapride).

Propulsid was a highly effective drug, so much so that parents of children with CIP fought for limited access in order to keep their children alive. The American Society of Consultant Pharmacists submitted a paper to the Food and Drug Administration (May 22, 2002, FDA Docket number: 02N-0115). This paper bemoans the loss of Propulsid from the market (11). Titled: "Statement on Risk Management of Prescription Drugs," outlines the loss of Propulsid due to the weakness of the current system for evaluating safe use of medications and recommended Propulsid be brought back with appropriate safeguards.

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10. McCallum RW: Review of the Current Status of Prokinetic Agents in Gastroenterology. The American J. of Gastroenterology 1985: 80 (12); 1008-16.

11. "Statement on Risk Management of Prescription Drugs." From the American Society of Consultant Pharmacists, May 22, 2002. Submitted to FDA, Docket #02N-0115. Thomas R. Clark RPh, MHS, Director of Professional Affairs, ASCP.

The loss of Propulsid means increased reliance upon an older drug – Reglan, for treating Digestive Motility diseases. The paper goes on to outline the risks, sometimes serious, with use of Reglan, yet these risks are largely ignored.

There are only two drugs FDA approved for treating Gastroparesis, they are:

- Reglan, (Metoclopramide) was originally formulated in the early 1960's to treat pregnant women's vomiting. This drug has limitations due to significant central nervous system side effects.

- Erythromycin an antibiotic first develop in the 1950's, later found to be useful in treating Digestive Motility diseases.

For treating CIP, the above drugs are available as well as:

- Sandostatin (Octreotide) this drug was developed for treating certain types of cancers and acromegaly but has been found to have beneficial effects in the clinical management of CIP.

[*Again, the drug that was the first line choice for treating CIP and Gastroparesis was Propulsid. When it was released in the late1980's, it was quickly recognized to have a broad range of pro-motility effects on various segments of the GI tract. This was welcome news for people suffering with severe Motility diseases. Propulsid was on the market till voluntarily pulled in June, 1998. It had been used by millions of Americans and millions of dosages taken.*

Propulsid is still available under a restricted release, yet the restrictions are so great, most Gastroenterologists cannot take the time to fill out the enormous amount of paper work required to access this drug for their patients.

To contrast the above situation: Lotronex (Alosetron), a drug used for irritable bowel sufferers (diarrhea predominant) was voluntarily pulled from the market by its manufacturer. This new medication had just been released in February 2000 then pulled in November 2000 due to adverse effects. It was linked to some deaths. However, the drug had greatly improved quality of life for many individuals. The FDA announced June 7, 2002 the approval of a supplemental New Drug Application (sNDA) that allows restricted marketing of Lotronex. ***There is not a similar ease of accessing Propulsid for Motility patients.***

Domperidone (Motilium); is a drug used worldwide and now considered a first line drug choice for treating Gastroparesis and CIP. This drug is not available in the United States because it is not yet FDA approved. The lack of FDA approval is not related to safety concerns since this drug has a long track record. It is a very effective medication that improves symptoms and quality of life for many of these patients. In the past, an application for FDA approval was brought forward. A nearly unanimous recommendation for approval was over turned and the drug was denied].

- Limited surgical options exist for treatment of CIP. Permanent TPN or Full intestinal transplantation is all that is available for the most severe types of CIP.

Currently, on the market, not one drug is available for treating Digestive Motility diseases that has been specifically formulated for these lethal diseases.

Implantable devices:
Medtronic Inc has a Gastric Electrical Stimulation device for treating drug refractory Gastroparesis. **Enough evidence now exists** for general agreement among Gastroenterologists, that the device is effective in controlling symptoms. It has shown efficacy in reducing vomiting, and some patients are able to come off their enteral / parenteral feedings. Studies have shown the device significantly reduces hospitalizations and improves overall well being and quality of life for patients. Further, the device has shown to decrease mortality rates especially in the Diabetic Gastroparetic patients. One research paper showed that Diabetic Gastroparesis mortality rates were cut in half for the implanted Diabetic patients vs. the Diabetics with out the device (12). This device is available on a restricted *humanitarian* release category by the FDA. It has yet to receive **full** FDA approval.

This limited *humanitarian* category creates huge barriers for the patient:

Patients who qualify for the Enterra device (Medtronic, Gastric Electrical Stimulation device) are very ill; they are physically weak from malnutrition, psychologically devastated, and are on long term disability. When their doctors approve the Enterra device—then the patient must prepare for an immediate denial from their insurance company—because this 'device' is not **fully** FDA approved. The insurance appeal process is not for the faint of heart. It takes a high level of skill, family support, perseverance and organization to 'present your case.' Not all patients have the skills to persevere—these patients probably don't get the device.

Many patients who could benefit from this implantable device don't receive it due to the enormous challenge of insurance appeals. These individuals are very ill. They don't have the strength to fight.

Medtronic is currently conducting a device trial to gain full FDA approval. Enrollment is poor since patients are far too ill to travel to the study centers. Therefore *full* FDA approval is moving at a snails pace.

This device has now been implanted in patients for close to 9 years. A group of these patients have been followed for this duration. The long term outcomes reflect the same evidence cited above: improvement in patient's: quality of life, nutritional status, and has shown a decrease in mortality. **This evidence alone provides a strong statement to the safety and efficacy of this device.**

How many patients die due to their inability to access this effective treatment device is unknown

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12. Abell TL, MD; ADA Poster, presented at the American Diabetes Association meeting, New Orleans. June, 2003.

Social Security

The lack of understanding and recognition regarding the severity of Digestive Motility diseases on the part of government officials creates huge problems for patients who need to navigate the Social Security / Medicare process. The average patient must go through 2 to 3 appeals that can take over 2 years for Social Security to approve their disability claim; then begins the wait for Medicare status. In the meantime, patients receive restricted / rationed medical care that can erode their symptom management and nutritional status. Even legislative language pertaining to 'Disabilities' and what disorders constitute disabilities, make no mention of the severe digestive Motility diseases outlined in this White Paper.

Recommendations: Congress can enable the NIH with funding to implement these concrete aims.

- **Limited research dollars should be spent on the more severe forms of Motility diseases especially in light of the fact that collectively, these are not rare diseases.** This action will have a 'spill down' effect for the less severe forms of motility problems: like Functional digestive disorders. Currently it is the other way around. More money has been spent on research at the other end of the spectrum for the less severe, non-lethal, "Motility like" functional diseases.

- **At a minimum, research budgets** should match the current level of government spending on Inflammatory Bowel diseases research.

- **Funding for a Database and Registry should be a top priority** in order to gather accurate prevalence statistics, provide profiling of these diseases (especially the Idiopathic groups), and act as a research tool. This also will help to stimulate private industry to search for effective pharmacological treatments.

- **Regional Centers of Excellence need to be established** and supported though funding. These Centers could also act as information clearing houses to provide educational materials to patients and a resource to the Professional community. Centers of excellence could also be funded for improved diagnostic equipment.

- **Centralized tissue banks need to be established** to help accelerate the identification of the underlying pathobiology of these diseases. Currently, full thickness tissue biopsies for Idiopathic Gastroparesis patients are rarely taken. So the search for the underlying pathobiology has not yet begun.

- **Research into enteric nervous and muscle tissue regeneration needs to be supported.**

- **Consensus meetings** need to take place, and be published, in order to disseminate accurate information to the medical community. This will greatly improve patient care and help to save lives.

- **Consensus meetings on "acquired" and Idiopathic forms of Digestive Motility diseases need to occur for the pediatric and adolescent community,** especially in light that these pediatric Motility diseases, grow into adult Motility diseases.

- **NASA has developed expertise from Motion Sickness research. NASA could provide assistance in helping to research effective treatment options for symptom control in patients with Motility diseases.**

The FDA can help reduce health care costs and save lives:

- **The FDA needs to quickly apply full approval for the one device that provides effective treatment for many patients with severe 'drug refractory' Gastroparesis** so that patients have ready access to this effective treatment option. This will save taxpayers considerable money by reducing hospitalization costs and will help to save lives.

- **Barriers for accessing Propulsid need to be removed following the example of a similar re-release as with Lotronex (Alosetron)**

- **The FDA needs to approve a very effective prokinetic drug that is currently available world wide, but not yet available in the United States.** The drug, called **Domperidone,** has become a first line medication choice by many Gastroenterologists for treating Motility diseases.

Acknowledgements:

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Appendix I

The American Motility Society: First International Scientific Task Force Meeting on Gastroparesis.
Faculty:

- Thomas Abell, M.D.; The University of Mississippi Medical Center, Jackson, MS.
- Fernando Azpiroz, M.D., Ph.D.; Hospital General, Vall d'Hebron, Barcelona, Spain.
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- Jiande Chen, Ph.D.; University of Texas Medical Branch, Galveston, TX.
- James Christensen, M.D.; University of Iowa Hospital and Clinics, Iowa City, IA.
- Michael Crowell, Ph.D.; Novartis Pharmaceuticals Corporation, East Hanover, NJ.
- Glenn Miles Eisen, M.D., M.P.; Vanderbilt University Medical Center, Nashville, TN.
- Hashem B. El-Serag, M.D., MPH; Houston VA Medical Center, Houston, TX.
- George T. Fantry, M.D.; University of Maryland, Baltimore, Baltimore, MD.
- Gianrico Farrugia, M.D.; Mayo Clinic, Rochester, MN.
- Robert S. Fisher, M.D.; Temple University Hospital, Philadelphia, PA.
- Richard Gilbert, MD.; MIT, Cambridge, MA.
- William L. Hasler, M.D.; University of Michigan, Ann Arbor, MI.
- Lee Kaplan, M.D.; Massachusetts General Hospital, Boston, MA.
- Raj Kapur, M.D.; Children's Hospital and Regional Medical Center, Seattle, WA.
- Kenneth Koch, M.D.; Wake Forest University, Winston-Salem, NC.
- Brian E. Lacy, M.D., Ph.D.; Johns Hopkins Bayview Med. Center, Baltimore, MD.
- Anthony J. Lembo, M.D.; Beth Israel Deaconess Medical Center, Boston, MA.
- Richard G. Locke III, M.D.; Mayo Clinic, Rochester, MN.
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- Thomas V. Nowak, M.D.; Kokomo, IN.
- Kevin Olden, M.D.; Mayo Clinic Scottsdale, Scottsdale, AZ.
- Ann Ouyang, M.D.; Milton S. Hershey Medical Center, Hershey, PA.
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- Henry Parkman, M.D.; Temple University, Philadelphia, PA.
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- Jan Tack, M.D., Ph.D; University Hospitals Leuven, Leuven, Belgium.
- Nicholas Talley, M.D., Ph.D.; Mayo Clinic, Rochester, MN.
- Gervais Tougas, M.D.; McMaster University Medical Center, Hamilton, ON, Canada
- Sean M. Ward, Ph.D.; University of Nevada, Reno, NV.

Appendix II

A Day in the Life of Gastroparesis

I wake each morning with urgency to make it to the bathroom in time to drain my stomach via my tube in my stomach (g-tube) in order not to vomit the bile/acid/gastric secretions that collected through the night. If I do not make it in time, I spend the first 20 minutes vomiting the garbage that gathered in my stomach overnight. I usually do not make it to the bathroom in time. I'm nauseated, my stomach hurts and my throat burns regardless what happens upon awaking.

The next order of business is taking the course of medication that makes my life bearable. Let's crush this, measure that, decide if it's time for this, then all of the medicine is pushed through the small tube in my small intestine. Now it's time to set up the tube feeding for the day. I gather supplies to get the tube feeding infusing through the same little tube (j-tube) in my small intestine

I always want to go back to sleep, because I have not had a good night's sleep in more than three years. I wake up every few hours with nausea and pain. I try to lie there and ignore what's going on, but it usually leads to getting up to take some medication through my little tube in my small intestine to see if I can indeed go back to sleep. I pray it's time for something for the nausea, if not I lie in bed waiting for enough time to pass to take something else to help.

Once the medication absorbs, I have an hour or two that is bearable. The nausea is somewhat under control; the sore throat lessens as the hours go by and the pain is still there but can be ignored for a bit.

I try to decide what to do for the day. My doctors have refused to let me return to work years ago since I am on tube feedings, suffer from low blood sugar, and I have developed a seizure disorder.

I take a seat at my desk and I try to catch up on the postings on the online support group that I started for patients with gastroparesis.

I no longer work due to this hideous disease, so I decide what can be accomplished today. Do I have enough strength to mop the floor? Is there enough energy to straighten the house a bit? Usually the answers are no, so I sit at the computer desk. Some days even sitting at the desk is too much.

January 26, 2004

Dear Dr. Meyers,

You have been my doctor for many years and I know I have been a challenging patient. My diabetes has caused a number of problems and yet, with all the surgeries, neuropathy, pain and blindness, I have survived. My quality of life was never really very good. Heart problems and panic really interfered with a happy and healthy life.

I think that I have always been depressed to some extent. Sometimes more seriously than others, but with help I am doing rather well. My physical health was what had caused so many psychological problems for me. I knew there was something wrong with me when I started having so much nausea and vomiting. You and Dr. Burmaster had taken care of me off and on for more than 20 years, but the interruptions in care were because of HMO's. I had been seen by well over 30 MD's . Cardiologists, Gastroenterologists, Endochronologists and Internal medicine men. I had blood work, urine and stool tests, upper and lower GI's, X-rays, CT scans, MRI's, Colonoscopy's and I can't count the Endoscopies I went through.

In 1996 I was told I had gastropareses but there was nothing they could do. I would have to live with it. Before that diagnoses I was told that I was just a nervous and anxious person and a lot of it was in my head. I went from a normal weight of 137 lbs, to 89 lbs just before I had a gastro pacer placed. (Thanks to YOU) You were educated and aware of neurostimulators, and you referred me to Dr. John Allen. He thought I would make an ideal candidate for this type of surgery. I became a part of the Entera Project he and Dr. Eric Johnson were involved in at Northwestern. My insurance company denied us and even after appeals, we were denied. I finally called Medica myself, from my hospital bed in October 2002. They approved the surgery probably 48 hours before I was expected to expire, I had the surgery, and when I woke, I ate my first meal and it stayed down. WOW!

You were the only doctor who performed the gastric emptying test. You tried me on medication for neuropathy. I was always aware of my stomach trouble. I remember when it first started. 1983! I had nausea and vomiting all the time but I thought it was because my blood sugars were so out of control. I have always had issues with constipation. But the nausea and vomiting began interfering with my life style and by 1996 I was really ill. You put me on motility medication with not a lot of success and you even suggested a peg be placed. I had been so ill for so long, a peg was not an option. As far as I was concerned, if it was my time to go, then that was the way it was going to be.

Because this pacer has saved my life, you must realize that I am an advocate for the FDA to approve its use nationally and not just as a Humanitarian Use Device. I have become involved with a grass roots organization out of Canada, GPDA (gastropareses, dismotilities association.) This is a non-profit organization. Its goal is to push the FDA to approve the device. It depends on donations and grants to go forward. Doctors and Insurance Companies AND PATIENTS need to be educated and made aware of the possibilities a pacer could do for them. I wish I had this information when I was sick. Some of the people from

Canada are involved with attending legislative and congressional meetings to lobby them to kick some sense into the FDA. There is one major problem facing this association. It was developed and is run by people with gastropareses. Their strength and courage is overwhelming to me. We need petitions for patient's signatures to send to those who make the decisions about this sort of thing. There are so many who suffer with this condition. I am not looking through rose-colored glasses. I understand the pacer is not a cure for many of these people. Particularly those with idiopathic gastropareses. But for the hundreds of thousands of diabetics, the gastro pacer may be the only thing that will save their lives.

I have sent you 3 different pamphlets that talk about motility diseases. I would ask you to take a look at them and share them with your colleges. If you think the information in them would be appropriate for your patients to read, please make them available in your waiting room. If more people were informed, I think they would be more able to talk to their doctors, with some real knowledge about their conditions. Many of the people who could be of significant help to this organization are just too sick to get involved. I, on the other hand was given another chance and I will what ever I can do to assist in this effort.

There are no GPDA chapters in the United States. There is contact information on the backs of these pamphlets. I am able to get as many as I need. I do not have enough at this time to send them out to every physician, but I am starting by sending only a few to 20 offices.

I don't think I ever personally thanked you for all you have done and are still doing for me. My quality of life has changed so much. Tom and I go out to dinner now and our social life has picked up. Not to mention the stress is gone now and we are both very relaxed and know what to expect with the little problem of pain (smile).

I will be seeing you toward the end of February for a pre-op physical. I am having eye surgery on the 4th of March. I am really pretty excited about it. I have ptosis and I am having a lot of extra skin removed from my lids. At the same time, we are privately paying to have the fat bags removed from under the bottom lids. I will have so much more light and I will probably look 20 years younger. I won't look so tired or angry all the time. But to have more light is the goal I am after.

I want to thank you for reading this letter, Dr. Meyers. You are a very important person in my life and I know you are as concerned as I am regarding motility diseases. They are real and not enough medical professionals know enough yet.

I will see you soon. Thank you in advance for distributing this information.

Warmest Regards

Debbi Ritter

Debbi Ritter

[redacted]

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