

White Paper:
**“Gastroparesis and Related Digestive Motility
Diseases, a Medical Crisis.”**

Prepared by:
Gastroparesis and Dysmotilities Association (GPDA)

www.gpda.net
Author: Jeanne Keith-Ferris, RN, BScN

August 19, 2003

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 inadequate 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 four 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.

Furthermore, the Paper will help to inform government officials of the cost generated by human suffering, as well as of the impediments that exist, due to lack of FDA approval, to accessing the few treatment options currently available. These impediments raise 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 since limited resources exist to even outline its prevalence, let alone to 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 in spite of the fact that collectively, these are not rare diseases.

These diseases, afflicting men, women, and children, are in need of “catch-up” work to help redress the current situation. 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 them;
- 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 found to be effective, are not available because they lack FDA approval;
- Social Security claims for disability are very difficult to obtain; this may be due in part to the lack of understanding by government officials regarding the seriousness of motility diseases;
- No consensus guidelines exist for 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 limited 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 researching the effects of, and methods to ameliorate, motion sickness for space and military personnel. Motility patients live for years experiencing symptoms similar to motion sickness on a daily basis. 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 on motility research (1), most of which was spent on basic research. Very few, if any, research dollars have been spent by the NIH on the search for effective treatment options for these digestive motility diseases.

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.

Introduction.....1
 What are digestive motility diseases?
 -Gastroparesis.....2
 -Chronic Intestinal Pseudo-obstruction.....3
 -Colonic Inertia.....4
 -Achalasia.....4
 How are these diseases acquired.....4
 Prevalence.....5
 Cost to Society.....8
 Human Cost.....9
 Quality of Life.....9
 Treatments.....10
 Social Security and Digestive Motility diseases.....13
 Recommendations.....13
 Gastroparesis Task Force Faculty: Appendix I
 Diary in the Life of a Gastroparesis Sufferer: Appendix II

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, which 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 blend of motility problems that 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 gastroenterologists. 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. Thus, only the very dedicated, specialized centers provide this form of testing. Electrogastrography (EGG) is another helpful, adjunct, diagnostic tool that provides valuable, indirect evidence of digestive neuro-electrical rhythms. Yet reimbursement for this assessment procedure is also very poor, thus creating barriers to its widespread use.

Gastroparesis:

Gastroparesis is the most common 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 digest a meal effectively — that is, the accommodation of a meal, the grinding of food, the mixing of nutrients with secretions, and finally the excretion of the mixture. 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, which are 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 gastroparesis may lead to a back-up into the esophagus causing 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. Dyspepsia can be episodic or constant. The nausea will frequently build to a crescendo of vomiting necessitating emergency room visits for intravenous rehydration. These episodes also cause spiraling malnourishment.

In 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 five-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 in the small intestine to bypass the non-working stomach or inserted intravenously, known in this case as total parenteral nutrition or 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 with enteral feeding due to intestinal spasms or, in the case of TPN, due to vascular spasms. A meal can take many hours to infuse. This intervention usually does not halt nausea and vomiting. To attempt to 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. In 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 from three to ten years for an accurate diagnosis to be obtained. The diagnosis of CIP is usually preceded by several years' experience of 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 and can further be found to have an associated puzzling autonomic nerve (ANS) dysfunction. The ANS problems add to the symptom complex with other puzzling, non-digestive related difficulties of: urinary retention, heart rate variability, postural changes in blood pressure and sweating abnormalities.

The symptoms of dyspepsia described above also occur with CIP, but the small bowel functional impairment in these patients causes a far greater degree of intense abdominal pain which often requires the use of narcotics. 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.

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, the only treatment option left for these patients is an intestinal transplant. Before the advent of total parenteral nutrition in the 1970s, 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”. Achalasia is characterized by dysphasia (difficulty in swallowing) of solids 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 that acts 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, a term that denotes an *unknown, primary* cause of the motility disease.

Other acquired forms of motility diseases are those that occur as a secondary result of 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 transplants, 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 and 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 among the highest health-care utilization, medication use, and time lost from work of 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 is the diabetics at 24%, followed by post-gastric surgery patients and those suffering from 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).

3. Frank L, Kleinman L, et al: Upper Gastrointestinal 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 from more severe forms of gastroparesis and these numbers are growing.**

For comparison, the prevalence of 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 from gastroparesis would be 3 million** (1.6 million diabetics and 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 show 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 is also responsible for damaging nerves in the digestive tract, which then 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.

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

Achalasia: is a rare disease, generally 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 convened in Orlando, Florida on May 17, 2003 helped to outline the difficulty in articulating the full picture — specifically of gastroparesis but generally of all the motility diseases. To quote Dr. Jay Pasricha's (7) opening remarks from the May 17, 2003 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 it is;*
- *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 from severe digestive motility diseases exceeds the prevalence of many other severe digestive diseases like inflammatory bowel diseases.**

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 and \$1,000 per day, or \$90,000 to \$360,000 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 to \$405 per day. Medicare is also limited as it only pays 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 (due to the lack of pharmacological treatments for motility diseases), coupled 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 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, dressings, 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 7,850 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 affect diabetic glycemic control in an adverse way, thus accelerating complications from diabetes and increasing hospital utilization costs.

The total burden to society resulting from digestive motility diseases runs into the billions of dollars from hospital costs, time lost from work, medication costs, and cost of specialized formulas.

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 severely intractable vomiting experienced by gastroparetic patients, some ill-informed specialists might 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 from 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 toil against these horrible symptoms and fail to thrive.

Adolescents, who need enteral, parenteral, or nasal duodenal/jejunal nutrition in order to stop the downward spiral of malnourishment and to stabilize dramatic weight loss, must also deal with the acute psychological impact of changes in body image, a particularly sensitive issue for this age group. Further, school-age children and adolescents, who would normally be learning socialization skills, 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 vulnerable as they struggle for acceptance by, and even lack the energy to keep up with, their peers. Older adolescents experience continual failures with dating, since developing relationships are constantly interrupted by unpredictable symptom flare-ups or hospitalizations.

Chronic illness and the daily battle against symptoms are 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 of 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. As a testament to the debilitating effects of nausea and vomiting, NASA has spent approximately \$20 million researching the effects of space motion sickness and investigating treatment options for astronauts and military personnel. Some motility patients face years of devastatingly 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 family 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.

As for abdominal pain, drugs used to treat the more severe forms commonly found in CIP further slow down the digestive tract, resulting 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. Increased rates of separation and divorce are the results of families shattered by these diseases.

Suicidal ideation in the patient is not an uncommon report. Faced with overwhelming symptoms, bodily changes, and chronic-to-severe malnourishment — being house-bound with feeding tubes, and being told that all available medications have been exhausted to no avail; patients are robbed 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 flare-ups will leave the patient/families canceling activities at the last moment.

Treatments:

McCallum published a paper in 1985 entitled “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 that one important drug, namely in the armamentarium, namely Propulsid (cisapride), is no longer available.

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). Entitled “Statement on Risk Management of Prescription Drugs”, the paper outlines the loss of Propulsid due to the weakness of the current system in evaluating safe use of medications, and further recommends that Propulsid be brought back with appropriate safeguards.

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 approved by the FDA for treating gastroparesis and they are:

- Reglan (metoclopramide), originally formulated in the early 1960s to treat vomiting in pregnant women, has limitations due to significant central nervous system side effects.
- Erythromycin, an antibiotic first developed in the 1950s, later found to be useful in treating digestive motility diseases.

For treating CIP, the above drugs are available as is the following:

- Sandostatin (octreotide) 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 late 1980s, 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 from severe motility diseases. Propulsid was on the market until it was 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 that 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. Released in February 2000, this new medication was barely on the market when it was 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 no 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 overturned 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.

Not one drug currently available on the market for the treatment of these lethal digestive motility diseases was specifically formulated for such purpose.

Implantable devices:

Medtronic Inc. markets a gastric electrical stimulation device for the treatment of 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 mortality rates were cut in half for the implanted diabetic gastroparetic patients vs. those who had not been implanted with 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. Those who qualify for the Enterra device (Medtronic gastric electrical stimulation) are very ill; they are physically weak from malnutrition, psychologically devastated, and on long-term disability. When doctors approve the Enterra device, patients must then prepare for themselves for an immediate denial from their insurance company since the device is not **fully approved by the FDA**. 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 one's case. Not all patients have the skills to persevere — these are the patients who will probably not be successful in obtaining the device. In other words, many devastatingly ill patients who could benefit from this implantable device don't receive it because they lack the strength to fight the enormous challenge of insurance appeals.

Medtronic is currently conducting a trial of the gastric electrical stimulation device to gain full FDA approval. However, since most patients are far too ill to travel to the study centers, enrollment is poor. Therefore *full* FDA approval continues to move at a snail's pace.

Implantation of this device has been in effect now for close to nine years. A group of implanted patients have been followed for this duration, and the long-term outcomes reflect the same evidence cited above, that is, a marked improvement in patients' quality of life and nutritional status, as well as a decrease in mortality. **This evidence alone provides a strong statement as to the safety and efficacy of this device.**

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

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 of 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 two to three appeals that can take over two 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, makes 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 such as functional digestive disorders. Currently the reverse situation exists: more money has been spent on research at the other end of the spectrum on 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 disease 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 group), and to 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 through funding. These centers could act as information clearing houses to provide educational materials to patients and as 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 the findings 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 of the fact that pediatric motility diseases grow into adult motility diseases.
- **NASA has developed expertise through their research into motion sickness. 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 grant full approval quickly 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 with Lotronex (alosetron).**
- **The FDA needs to approve domperidone, a very effective prokinetic drug currently available worldwide, but not yet available in the United States.** Domperidone has become a first-line medication choice by many gastroenterologists for treating motility diseases.

Acknowledgements:

Medical Review of Document:

Thomas Abell, MD; Assistant Professor, University of Mississippi Medical Center.
Division of Digestive Diseases, B-136, Jackson, MS, 39216.

Richard Gilbert, MD; Department of Mechanical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 5-026, Cambridge, MA, 02139

Thomas Nowak, MD; 1907, West Sycamore, Kokomo, IN, 46901

Henry Parkman, MD; Assistant Professor of Medicine, Gastroenterology Section,
Department of Medicine, Parkinson Pavilion - 8th Floor, Temple University Hospital,
Philadelphia, PA, 19140

Konrad S Schulze, MD; Department of Internal Medicine, Division of Gastroenterology.
University of Iowa Hospitals/Clinics, 4551 JCP, Iowa City, IA, 52242.

Editing revision, 2005

Elizabeth Gooden, Calgary, AB, Canada