

Summary of International Scientific Task Force On Gastroparesis May 17, 2003 Orlando, Florida

GPDA is proud to have organized this first Task Force meeting on Gastroparesis.

The Task Force really was a "think tank" to address the dearth of scientific knowledge surrounding Gastroparesis. The over-bridging task for this think tank will be for the [development of an International Registry and Database for Gastroparesis](#).

Several months of phone conferences and planning led up to the gathering of 32 internationally recognized scientists and motility physicians, to thrash out the questions on what information could be used to construct such a database. The enormity of what is *not known* about Gastroparesis made this appear as a daunting task.

Jay Pasricha, MD, of the University of Texas Medical Branch was the visionary behind this process and chairman of the planning committee. His opening remarks helped to frame our vague understanding about Gastroparesis that still characterizes this disease.

Here is a sample of Dr. Pasricha's opening remarks: "There are in fact some very simple and fundamental questions about this disease or syndrome, or whatever we want to call it, 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 diagnosis 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 worse quality of life among all the patients we see (in our GI clinics)."

The overall Goal for this first Task Force will be to start a Database. This will allow for the building of an infrastructure to further our understanding of gastroparesis. Examples of this infrastructure are: the building of a Database and later a Tissue bank. These steps will facilitate funding, and attract the attention of federal and private institutions.

The acronym suggested for this Registry and Database is: GRAND, Gastroparesis Registry and National Data Base. This idea has since been expanded to an International scope.

For developing this Database, the Task Force was divided into 4 working groups:

- Team I: Epidemiology, Natural History and Testing
- Team II: Pathophysiology, Pathobiology
- Team III: Treatment
- Team IV: Database Development.

Each group was charged with reviewing existing information, then working through the day, to develop a consensus as to what information to put into the Database. The key role of the Database is to support future research projects and have these projects fundable.

Finally, a series of future Task Force meetings, perhaps meeting annually, will need to address:

- Development of consensus guidelines and definitions for gastroparesis,
- Development of diagnostic and therapeutic guidelines, especially for the general Gastroenterologist, and
- Systematic literature updates for patients and scientists.

Dr. Pasricha thanked the other members of the planning committee of: Dr. Jiande Chen, Dr. Henry Parkman, Dr. Robert Summers and Jeanne Keith-Ferris, BScN (GPDA).

Next, **Fernando Azpiroz, MD**, President of the European Society of Neurogastroenterology and Motility gave a brief report.

Richard Gilbert, MD, spoke next and provided insights into the ground work that has coincidentally been done in the past 24 months. Dr. Gilbert had previously been approached by the American Motility Society for construction of a computer "mark-up" language (software) for handling 'motility' data. This computer language has since been developed by Dr. Gilbert and his team. Called the "Gastrointestinal Markup Language" (GIML) it is now available. Some refinement of the language will be necessary, but this program can provide the basis for the International Registry and Database for Gastroparesis.

Dr. Gilbert also provided a critique of CORI (Clinical Outcomes Research Initiative-this is a database for Endoscopy). The lessons learned from the CORI project can provide guidance for the undertaking of GRAND.

Frank Hamilton, MD, of the NIH (the National Institutes of Health); representing the NIDDK (National Institutes of Diabetes and Digestive and Kidney Diseases) division next addressed the audience. Dr. Hamilton reviewed the main mission of the NIH, which is to improve the health of the American population through support of basic and clinical research. The NIH's definition of Gastroparesis is: "delayed gastric emptying in the absence of mechanical obstruction." Dr. Hamilton went on to outline how this definition of Gastroparesis can fall under different institutes within the NIH. Research support for

Gastroparesis does not necessarily fall exclusively under the auspices of the NIDDK division. For instance, the NIH institutions dealing with Rheumatology, or Neurology would be involved in supporting

research where Gastroparesis is a secondary problem in disorders like Scleroderma, Duchenne Muscular Dystrophy, or Familial Dysautonomia. If there are specific viral causes to Gastroparesis, then the Allergy Institute of the NIH would be the primary source for research funding. The Idiopathic, gastric dysrhythms, and of course the Diabetic Gastroparetics, all fall under the umbrella of the NIDDK.

Dr. Hamilton went on to discuss the Diabetic Gastroparesis problem. The Diabetic Gastroparetic group is a better defined group and the relative prevalence is known. For instance, approximately 50% of Type I Diabetics have Gastroparesis. If one looks at the total number of Diabetics in the US population, and then extrapolates that a third to half of these diabetics are affected by Gastroparesis, this represents a tremendous number of people affected (millions); however, Dr. Hamilton went on to say, there is very little research being done on Diabetic Gastroparesis (based upon grant applications received by the NIH).

Some NIH successes:

In the NIH fiscal year 2000, two million dollars was set aside to stimulate research into motility disorders. The NIH received 76 applications and was able to fund 12 of those grants, 2 of them involving Diabetic Gastroparesis. Some of these NIH grants supported basic research projects into the "Interstitial Cells of Cajal." This has advanced the basic understanding of the physiology of "motility" science.

Some NIH disappointments:

Several years ago, Congress allocated 100 million dollars to the NIH for Diabetes related research. Once the money is committed, the NIDDK has the option of pulling money aside and putting it to a particular focus. What is amazing, in the two years that the money was committed, no applications for Diabetes related Gastroparesis research grant applications were received by the NIH. NIDDK was disappointed that the scientific community did not heed the call to take advantage of the golden opportunity that was out there.

Dr. Hamilton's message to the scientific community is very simple: "you have to apply for grants in order to get funded." And persistence is the key word, if your grant application is turned down, don't give up re-apply!

The NIH receives 27 billion dollars each year for supporting clinical and basic research.

Dr. Hamilton went on to thank the organizers of this Task Force meeting and emphasized that this meeting is a very effective mechanism to help provide a "Road Map" to stimulating the search for answers into Gastroparesis. *He then invited the group leaders and organizers to come to Washington and make a presentation to the NIH director outlining a strategic plan to address Gastroparesis.*

Glenn Eisen, MD, gave a presentation on the CORI (Clinical Outcomes Research Initiative) Database. The CORI Database is a national data repository of endoscopic examinations with nearly 685,000 records. Founded in 1996 by the American Society for Gastrointestinal Endoscopy (ASGE), CORI is a not-for-profit research organization and is funded by grants and industry partners.

The uses of the CORI data are for observation of chronic GI diseases, insight into GI practice patterns, the evaluation of endoscopic therapy effectiveness, and recruitment of physicians/patients for prospective research studies.

Presentations by Teams:

Team I report (Epidemiology, Testing and Natural History): given by Nick Talley, MD

Dr. Talley's opening remarks centered on the controversy in the scientific community about the link between symptoms of dyspepsia and gastric emptying. Many studies show a poor correlation between the two. He succinctly put it: "we know a lot about the symptoms, but we know very little about Gastroparesis."

If a database is to be used to measure different aspects of the symptoms, then understanding these controversies is critical. He cited literature to explore this theme. In therapeutic trials where gastric emptying improvement was the target, this achieved outcome did not necessarily result in reduced symptoms. Dr. Talley next reviewed the currently available tools, and what would be the best questionnaires/surveys for measuring:

- Symptoms
- Quality of Life
- Psychiatric, and
- Health Economic cost analysis

The point was also made regarding the importance of using validated measures.

There are many 'generic' quality of life measures; the SF-36 is an example. No Quality of Life measures have been developed specifically for Gastroparesis. Having a 'disease specific' Quality of Life measure has the advantage of being 'sensitive.' (In other words, the data collected more accurately reflects the disease's specific symptoms and their impact on quality of life). Some disease specific Quality of Life measures have been developed for Irritable Bowel and Functional Dyspepsia.

Dr. Talley also mentioned that Gastric Emptying Studies are not standardized, so it will be difficult to include this information into a Database.

Prevalence studies are also very much needed but are beyond the scope of this Registry and Database; yet this is vital information. Questions like: what happens to

people out there? Do they all come and see physicians, and how many just put-up with the symptoms? There is lot a lot of "dyspepsia" out there-how much is this linked to Gastroparesis? All of this is essentially unknown.

Dr. Jan Tack brought up some points of discussion after the Team I presentation: The Gastroparesis Cardinal Symptom Index-is currently in use in the EU (European Union). This survey tool has been developed to evaluate the impact of pharmacological therapies on symptom control in Gastroparesis (Currently being used in a Cisapride vs. placebo controlled study). Publication of the validation of this symptom measure will be out soon.

Dr. Tack also discussed the very poor correlation between symptoms of Gastroparesis and gastric emptying (GE) studies. *(author's note: this controversy creates a lot of practical problems for patients seen by the general Gastroenterologist and can lead to an encounter between patient and physician, where the patient is left feeling that their symptom's are being minimized by the doctor. This highlights the need for more published research in order to improve patient care and sensitivity by the general GI physician).* Dr. Tack went on to say: the basic value of symptoms is very, very important; the predictive value of symptoms is not really useful. GE is a one moment in time measure, while symptom assessments are usually recorded over the past week or month. These two measures need to be more closely tied together. Symptoms should be measured (with a validated symptom index questionnaire) in the window after the test meal is given for the GE study, and the GE study meal should be standardized. This would generate a better correlation between symptoms and GE. This could be incorporated into the database, by using a standardized questionnaire administered in the window of time during the GE meal. This would take a multicenter approach, but could be done. Published data from this type of symptom correlation could help clear up this controversy.

Team II report (Pathophysiology, Pathobiology): Given by Jan Tack, MD, PhD

Dr. Tack began his report by providing a broad definition of Gastroparesis: "A chronic mechanical failure of the stomach from any cause." Some causes are:

- Denervation (Diabetes)
- Autonomic Neuropathy (diabetes)
- Myopathy (scleroderma, muscular dystrophy)
- Metabolic (thyroid disease, Diabetes)
- Post operative (Billroth II with vagotomy)
- Gastritis (Inflammation)
- Infiltration (eosinophilic disease)
- Drugs (Narcotics, Beta Blockers)
- Obstruction (pyloric outlet obstruction/spasm)
- Enteric ischemia

One study (Kendall 1993) showed the percentages of what sub-sets make up all Gastroparesis cases. The top 3 causes were: Idiopathic: 33%, Diabetic: 24%, and

Post gastric surgery: 19%.

Dr. Tack elaborated on the definition of 'mechanical failure' to include:

- Abnormalities in the tone of the stomach muscle (as in the problem of poor 'accommodation' in the fundus of the stomach). This also encompasses problems of "dumping" of liquids that can be a component of Gastroparesis.
- The "classical" understanding of Gastroparesis-that is, 'antral' hypo- activity-either muscular contractions within the antrum of the stomach that are too weak or too infrequent to grind and propel food.
- Sensory abnormalities-the sensations of 'fullness' and pain that accompanies Gastroparesis. (Perhaps nausea is also an abnormal sensory component).

A system for grading the severity of Gastroparesis (Grades I - III) was also put forth by team member Dr. Konrad Schulze. It is based upon "clinical parameters" and could be useful for interventional trials of medications or therapeutic devices.

Dr. Tack also discussed the minimum 'work-up' for diagnosis of Gastroparesis. The minimum would consist of a history and physical exam, upper gastrointestinal (GI) Endoscopy and a GE test.

Other suggested tests for centers with the capability would be:

- Gastric Accommodation test
- Satiety test
- Gastro-duodenal manometry (Motility testing)
- EGG

The published scientific literature examining the underlying 'pathophysiology' of Gastroparesis is scarce. Dr. Tack did review some of this information, looking at Diabetic and Idiopathic Gastroparesis. Here is a sampling:

Diabetic pathophysiology and Gastroparesis:

- Loss of intrinsic nerves (nerves inside the gut) probably plays a major role in Diabetic Gastroparesis.
- One can conjecture that the gastrointestinal and cardiovascular problem of diabetes probably follows a similar picture of pathophysiology.
- Also the problems of micro-vascular disease affecting Diabetics would also affect the extrinsic (external) nerves of the gut, leading to problems of constipation and/or diarrhea often seen as complications in Diabetes.
- As well, changes to metabolic pathways caused by diabetes have shown a loss of Nitric oxide pathways. This alters the function of numerous smooth muscle systems.
- Finally, "Interstitial Cells of Cajal" are also found depleted in Diabetic Gastroparesis.

Idiopathic Gastroparesis:

- The pathophysiology is completely unknown, but probably heterogeneous (many different underlying causes).
- Human tissue studies are almost non-existent.

- Recent viral infection is often implicated in some types of Idiopathic Gastroparesis. The database could be used to input information on blood samples to look for correlation of antibodies suggesting a recent viral infection followed by the onset of Gastroparesis.

Next, Dr. Tack reviewed what animal models have been developed for use in the study of pathophysiology and Gastroparesis.

Dr. Tack finished up by stressing that in order to advance our knowledge about Gastroparesis, it will be vital to have human tissue samples for studying. This brings up the need for a tissue bank, ideally centralized with standardization for handling tissues. These samples would need to be collected and integrated with descriptive information such as: demographics, medications, GE results, etc. Full thickness tissue samples could be collected at time of G/J tube placements or placement of electrodes for Gastric Electrical Stimulation (GES). The new "HIPAA" (Health Insurance Portability and Accountability) regulations would need to be followed for consent.

The last topic, re-visited again, was the need to standardize the GE test to enable comparing results between centers and utilizing this information in a Database.

Team III report (Treatment): given by Edy Soffer, MD

Dr. Soffer began by raising some basic issues with the designs of drug trails. In general, pharmacological trials are well designed for testing postoperative nausea/vomiting or post chemo-therapy nausea/vomiting; however, this is not the case with the study of drugs and Gastroparesis. These trials tend to not be well designed.

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.

Dr. Soffer echoed what the other teams have been saying, for development of a Database, it will be very important to have standardized:

- Questionnaires
- Physiological tests/studies (GE).

Standardizing these elements would be the greatest advantage of a Database.

Next, current treatment approaches were discussed starting with the least invasive approaches to the more invasive options. Incorporation of these into a Database was examined:

- Diet therapies are often recommended, but no uniform approach has been used to either standardize these or test which recommendations are the most effective in helping to control symptoms or improve outcome measures (example of

an outcome measure: BMI: Body Mass Index).

- Pharmacological agents: could use the Database to test some novel treatment approaches (like Sildenafil) and to revisit some older prokinetics agents for drug trials. The advantage of a Database is the ability to pool resources for testing.

- Drug study trials assessing the control of nausea using a combination of agents could be another area of investigation.

- Other novel treatment approaches such a Botox injection into the pylorus. A well designed trial, carried out at multiple centers, could provide insights into the effectiveness of this treatment option.

- Alternative medicine, like acupuncture and acupressure, could be tested using a Database.

- A Database could help to quantify and qualify some of the issues arising from the Enterra Device (GES). Many technical issues still need to be worked out regarding: pulse parameters in treatment approaches, which patients are the best candidates, and issues like electrode placement.

Finally, the discussion came up regarding, what 'are' we treating. Gastroparesis is a heterogeneous problem with undoubtedly many different underlying pathophysiologies. The search for what mechanisms are responsible for the symptoms needs to continue. Patient selection for research is important, and how to define what we are dealing with-this needs to be examined.

Lee Kaplan, MD, presented information on a method for categorizing heterogeneous patient populations into sensible groups in order to conduct research. This is called "phenotyping." Phenotyping is taking observations then stratifying similar characteristics into meaningful, more homogeneous groups. What is important to understand is the observations are 'research quality' observations with well defined parameters.

Dr. Kaplan's work is in the area of obesity. He has helped to develop a database in order to conduct research in this field. His work draws many parallels to this initiative for a Gastroparesis Database.

For instance, obesity:

- Is a complex disorder (not clear if it is a disease or phenomenon),
- Has multiple sub-types,
- Its pathophysiology is poorly understood, and
- Current therapies are inadequate.

The use of Phenotyping patients can provide for the development of a lot of therapies without necessarily understanding the underlying pathophysiology of a disease/syndrome.

This Obesity Database places an emphasis on extremes of phenotypes and looks closely at these individuals to help understand the underlying pathophysiology. However, also Phenotyping into subsets of the larger population of patients helps to uncover trends.

Next, Dr. Kaplan outlined some general principles to help use 'Phenotyping' as a research method:

- Fully define the problem and set parameters,
- Collect data as objectively as possible, and
- Use standardized approaches for the data collection.

Some examples of phenotypic parameters are:

- Symptoms,
- Clinical history,
- Environmental exposures, and
- Genetic characteristics.

Finally, Dr. Kaplan concluded that stratifying the disorder along phenotypes can accelerate the development and testing of therapies. One can then begin to identify patho-genetic mechanisms. This can lead to identifying clinical predictors for outcomes that will help to perpetuate the whole research process.

The final lecture before lunch was provided by ***Kenton Sanders PhD***. For the past 15 years, Dr. Sanders has done extensive basic research into the pathophysiology of Diabetic Gastroparesis. He acknowledged the support NIH grants have provided through the years in sustaining this research.

Details on this lecture will follow later.

Afternoon reports by teams, recommending what information should be included in a Database on Gastroparesis.

Team I report given by Nick Talley, MD

Concluding remarks by Team I:

Team I felt it important to focus on epidemiology for their component of the Database development. This role would primarily be involved in the generation of descriptive statistics. It would be up to the other Teams to provide the hypothesis 'drive' for supporting the funding of this Database.

Team I did discuss the topic of how to define Gastroparesis. The realization was evident that this task would require a consensus meeting dedicated to this end and was presently beyond the scope of this first Task Force.

In short, for the Gastroparesis Database to succeed it needs to:

- Start out small,
- Requires dedicated investigators, and
- Will need to be located in specialize motility centers.

The Gastroparesis Database should begin with the Diabetic Gastroparesis patients

since this is fundable and some argue that it is a more homogeneous group that is readily identifiable compared to the Idiopathic group.

The Database design could follow a similar model as outlined by Dr. Lee Kaplan with regard to the "Obesity Database" model. That is, focusing on the severe 'phenotypes' to include in the Database. This has the advantage of getting at the pathophysiologic mechanisms. This information could be extrapolated back to the larger Gastroparesis patient population. Full thickness biopsy could be obtained on these extreme phenotypes and this would be helpful in obtaining genetic markers for this disease.

Idiopathic Gastroparesis was discussed; however, the information known about this group of patients is even less compared to the Diabetic group.

For Database development, Team I chose a number of questionnaires that could be utilized. Here are their recommendations:

- For Quality of Life measures: the "**Pain and Dyspepsia Index**" (it has been validated in Dyspepsia, but not Gastroparesis so this is a limitation). Also, a generic Quality of Life measure, the **SF-36** would be useful; and ideally, a disease specific Quality of Life measure should be developed.

- Sorting out upper and lower GI syndromes would be helpful, so the "**Bowel Disease**" questionnaire, along with "**GI Current Symptoms**" questionnaire could be included.

- For Psychological measures: the "**BSI-18**", "**Brief Symptom Index**" would be recommended. This is a very short personality measure.

For diagnostic test collection, besides recoding the test results, it will be important to include relevant demographic information, relevant antecedent factors and current therapy.

- Some of the challenges for a Database:

- Data entry is a challenge for a busy GI specialist; however, questionnaires could be entered by the patients at a computer terminal.

Gathering of just descriptive statistics is not readily fundable, therefore this component of the Database must be linked with other research projects (hypothesis driven research projects).

Finally, population based studies are required to determine the incidence and prevalence of Gastroparesis, but this is beyond the scope of the Gastroparesis Database and would be a future step that needs to be addressed.

Team II report given by Jan Tack, PhD, MD

Concluding remarks for Team II:

Dr. Tack reported that Team II held divergent opinions as to what types of patients would be valuable to include in the Database. The consensus was it would be best to stay with a closely defined patient group for the initial development of the Database.

Therefore, the characteristics for selecting patients for inclusion into the Database would be:

- Patients with well documented delayed gastric emptying, and
- The test used for documenting the delayed gastric emptying would be from a center with recognized standards of gastric emptying studies (Standards set forth by the American Motility Society).

It will also be important for each center to register what gastric emptying test was used, what range of normals their center has established, and what was the value for this particular patient.

Other tests values that could be entered into a Database are:

- EEG, and
- Barostat tests.

Antroduodenal and small bowel Manometry were also considered very important to include, however, these tests are the least standardized of all the tests. The Database should also capture information on patients who suffered an acute onset of Gastroparesis, especially if precipitated by a viral illness. Blood work could be taken and a list of candidate viruses could be registered. Team II also felt strongly that tissue resections were vital to help detect lesion in the neuro-musculature. The American Motility Society has developed standardized guidelines for handling tissue biopsy, and this now could be applied. Tissues samples should be taken on every patient who has an invasive procedure:

- At time of GES, electrode placement,
- Surgical placement of 'feeding' tubes, or
- Gastrectomies or partial gastrectomies.

Information for the handling of resected tissue could be kept on the Database website. Centralization of tissue processing would be ideal, but unrealistic at this time. A "prominent center" could be developed through a grant application.

The Database should also have incorporated a follow-up system in order to track and follow patients.

Discussion followed Team II's presentation. Much of the discussion focused on the need for standardization of test like the GE test and the antroduodenal manometry. Dr. Summers championed this issue. Dr. Gilbert also stressed that it will be almost

impossible to make sense of data unless it is standardized. Suggestions were made that a very limited number of centers, who now have standard test, would enter data into the Database.

Dr. Mintchev also argued against the inclusion of the EGG test since in his opinion this test grossly over diagnosis gastric dysrhythmia. His feeling was that it will be important to stick to the mainstream tests like the Gastric Emptying study.

Dr. Tack felt that the Database could move forward even without standardization.

Team III report given by Edy Soffer, MD

Concluding remarks for Team III:

Dr. Soffer discussed patient selection for treatment trials and concurred with Team II's rationale that patient selection should follow the criteria of delayed gastric emptying.

Next the discussion focused on what pharmacological agents to start with that could be tested utilizing the Database. It was decided that Sildenafil would be a good choice and fundable.

[Dietary recommendations could also be developed and standardized utilizing the Database. A registered dietitian would need to be consulted and a few, recently published articles on Gastroparetic diets, could serve as guidelines.](#)

It was felt that the specific Gastroparesis subsets that could be included for treatment studies would be the Diabetics, Idiopathic and post surgical (vagotomy) patient groups.

Finally, Dr. Mintchev raised the point that for 'electrical device' development, more manpower is needed in order to investigate the technical issues. For trails of different devices, it will be important to have more centers exploring the various parameters to find the optimum approaches (examples: optimal electrode placement, number of electrodes, electrical pulse parameter settings, etc).

Warren Starkebaum, PhD, Medtronic/Industry representative, had a comment for the group, he reiterated what many have said throughout the day-it is an advantage to us (industry) who are developing therapies, to have better standardization of the clinical measures (tests).

Team IV, report given by Richard Gilbert, MD

Synthesis for Database development:

First, Dr. Gilbert gave an overview and made some general comments:

- It is easy to underestimate the complexity of data gathering.

- Stumbling blocks will continue to be definitions-for instance how do we define certain symptoms, and what do we mean by abnormal gastric emptying and test standardization.

- For the Database to succeed, it needs to start out small and simple, this may be less laudable, but it is do-able.

He then instructed each group to come up with a one page summary report that will need to be fortified by phone conferences and then presented to the AMS.

Chung Owyang, M.D., President of the American Motility Society said that they would welcome the proposal and the AMS would back the initiation of the Gastroparesis Database.