Effect Of Secretin On Gastric Accommodation, Emptying, and Post-nutrient Challenge Symptoms in Functional Dyspepsia and Healthy Subjects

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Effect of secretin on gastric accommodation, emptying and post-nutrient challenge symptoms in functional dyspepsia and healthy subjects

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Hypothesis: Secretin enhances gastric accommodation and reduces post-nutrient challenge symptoms without altering gastric emptying in patients with functional dyspepsia with normal baseline gastric emptying.

Specific Aims:

1. To compare the effects of secretin vs. saline on satiation, fasting gastric volume, gastric accommodation and emptying, and symptoms in patients with functional dyspepsia with normal gastric emptying.
2. To compare the effects of secretin vs. saline on satiation, fasting gastric volume, gastric accommodation and emptying, and symptoms in healthy human volunteers.
3. To compare effects of secretin on satiation, fasting gastric volume, gastric accommodation and emptying, and symptoms in patients with functional dyspepsia with normal gastric emptying and in healthy human volunteers

Background

Functional dyspepsia (FD) is a very common cause of substantial morbidity, estimated to affect ten percent of the population, and manifest as abdominal pain after eating, present at least three days per week. It has been estimated that 40 percent of patients with this symptom complex consult their physician, with impact on their workplace attendance and productivity, and an economic impact in excess of 18 billion dollars in 2009 (1). Current medical treatment includes eradication of H pylori, acid suppression, prokinetic drugs, antidepressants, and psychological and alternative therapy, yet, despite this, many patients remain refractory to treatment, experiencing continued disabling symptoms (2).

Insights into the pathophysiology of this disorder provide clues suggesting possible dysfunction of the gastrointestinal hormone, secretin, and the possible therapeutic use of a secretin agonist or positive allosteric modulator (PAM) in the management of this syndrome. A prominent pathophysiologic feature of FD is defective gastric accommodation, with inadequate relaxation of the fundus of the stomach in response to eating responsible for the post-cibal pain. A key physiologic regulator of gastric accommodation is secretin. Additionally, the site of synthesis and secretion of this hormone is enteroendocrine S cells in the duodenum, a site recently described as being involved pathologically with inflammation and eosinophilia in FD (3). Secretin is believed to elicit gastric fundic relaxation through its effects on secretin receptors on vagal afferent neurons, which go on to release VIP and prostaglandins (4, 5). While these events have been well documented in animal models and healthy human subjects, there are no published data for the effectiveness of secretin in stimulating gastric accommodation in patients with FD.

Secretin and its potential role in functional dyspepsia

Insights into the pathophysiology of functional dyspepsia, with recent demonstration of inflammation with eosinophilia and mastocytosis in the duodenum (3, 6, 7), providing a possible lead toward reduced secretion of a potential mediator of post-prandial gastric accommodation, the gastrointestinal peptide hormone secretin. The dominant site of synthesis and secretion of this hormone are enteroendocrine S cells in the duodenum. Inflammation-induced damage to these cells could produce a deficiency. Since intraluminal acid is a prominent stimulant of S cell secretion, the attempts to treat functional dyspepsia with anti-secretory medications could actually exacerbate a secretin deficiency syndrome. This raises the possibility of the therapeutic use of a secretin agonist or a positive allosteric modulator of the secretin receptor for patients with functional dyspepsia.

A prominent pathophysiologic feature of functional dyspepsia is defective gastric accommodation, with inadequate relaxation of the fundus of the stomach in response to eating responsible for the postcibal pain. This was observed in 47% of 151 patients with functional dyspepsia in a Mayo Clinic study performed in the clinical practice of the PI (8). There are presently no generally effective medications to restore normal gastric accommodation, and there is only limited support, based on single-center studies, for the use of such diverse medications as clonidine, sumatriptan, and buspirone, many of which have central or vascular side effects, or acotiamide, a cholinesterase inhibitor approved for use in Japan, but not in the USA.

A key physiologic regulator of gastric accommodation is secretin. Secretin is believed to elicit gastric fundic relaxation through its effects on secretin receptors on vagal afferent neurons, which go on to release VIP and prostaglandins (4, 5). While these events have been well documented in animal models and healthy human subjects, there are no published data for the effectiveness of secretin in stimulating gastric accommodation in patients with functional dyspepsia.

We postulate that therapy that increases levels and/or effectiveness of secretin to relax the gastric fundus in FD patients will increase gastric accommodation and reduce post-cibal abdominal pain and other symptoms. This can theoretically be accomplished with a secretin agonist or a PAM increasing the biological response to physiologically-released secretin. Therefore, it is important to establish whether secretin can induce gastric accommodation in FD, supporting use of exogenous secretin, or, if the secretin response is blunted or absent, suggesting that an allosteric modulator might be important to develop for this application.

Currently, only natural secretin peptide is approved for clinical use, and is a safe and effective reagent that can only be administered parenterally for diagnostic purposes. No orally active secretin agonist or PAM has yet been reported.

Study Design

We will utilize single photon emission computed tomography (SPECT) methodology and gamma scintigraphy present in the GI laboratory of the outpatient Clinical Research Unit to study fasting gastric volumes and postprandial gastric accommodation responses and gastric emptying rates of a standardized meal in patients with functional dyspepsia and healthy subjects. Both groups will be studied twice, using crossover design, once with administration of secretin and once with placebo. This will provide each subject as his/her own control, as well as providing contrast in baseline and responsiveness to this hormone across the groups.

Rationale for Crossover design and selection of FD patients

The pathophysiology of functional dyspepsia includes:

a. Delayed gastric emptying

b. Accelerated gastric emptying (sometimes associated with impaired gastric accommodation)

c. Reduced postprandial gastric accommodation

d. Hypersensitivity to gastric mechanical distension

e. Hypersensitivity to duodenal nutrients

f. Duodenal inflammation

g. Combinations of different mechanisms

Given the interest in secretin, we shall select patients with **FD and prior documentation of normal or accelerated gastric emptying and/or reduced gastric accommodation.** Given the diversity of mechanisms, the most efficient way to appraise the effects of secretin or PAM is through a crossover design.

Eligibility Criteria

Functional dyspepsia patients (n=15) and healthy subjects (n=15) aged 18-65 years will be recruited, and enrolled after providing written informed consent. The goal is to obtain the completed crossover results from 10 healthy and 10 Functional dyspepsia patients. Once that criterion is satisfied, enrollment will stop. The FD group will be identified from Mayo Clinic patients living within a 50 mile radius (Olmsted and Goodhue counties) who have symptoms consistent with this diagnosis and who have been studied and found to have normal or accelerated gastric emptying. Subjects may be involved in study activity for up to six weeks from screening date to completion of all studies. The actual study will be conducted on two separate days, each involving 3-4 hours of study. These testing visits should be scheduled one week apart, but within 4 weeks.

Male and female subjects, aged 18 to 65 years at screening, who meet the following criteria, will be eligible for enrollment. A detailed history will be obtained with validated questionnaires [including Hospital Anxiety and Depression Inventory, Functional Dyspepsia Symptom Diary, abridged Bowel Disease questionnaire (for healthy subjects only) and the long Bowel Disease (for functional dyspepsia patients only) (Zigmond & Snaith 1983, Patient-Reported Outcome Consortium's Functional Dyspepsia Working Group 2018, Talley 1990, Talley 1990)].

<u>Inclusion criteria</u>:

- Able to provide written informed consent prior to any study procedures and be willing and able to comply with study procedures

- No medical problems or chronic diseases that could significantly affect GI function, other than functional dyspepsia, for that group

- Body mass index of 18-40 kg/m^2

- Female subjects must have negative urine pregnancy tests and must not be lactating prior to receiving study medication and radiation exposure. For females able to bear children, a hormonal (i.e., oral, implantable, or injectable) and single-barrier method, or a double-barrier method of birth control must be used throughout the study. Female subjects unable to bear children must have this documented in the medical record [i.e., tubal ligation, hysterectomy, or post-menopausal (defined as a minimum of one year since the last menstrual period)].

- Rapid or normal gastric emptying (GE) measured via scintigraphy in past 5 years for FD subjects

- Normal upper endoscopy (EGD) in past 5 years for FD subjects

Exclusion criteria:

- Significant change in symptoms since previous EGD and/or GE study for FD subjects

- Unable or unwilling to provide informed consent or to comply with study procedures

- Structural or metabolic diseases that affect the GI system

- Unable to stop acid reducers such as proton pump inhibitors, H2 blockers 3 days prior to study days

    - May permit antacids on as needed basis but must stop 8 hours before study days

- Unable to avoid the following over-the-counter medications 48 hours prior to the baseline period and throughout the study:

    - Medications that alter GI transit or motor function including laxatives, magnesium and aluminum containing antacids, prokinetics, erythromycin, buspirone, clonidine, tricyclic antidepressants, and secretin-norepinephrine reuptake inhibitors, buproprion, benzodiazepines (, ,), anticholinergics (tricyclic antidepressants, trazodone, cyclobenzaprine, antihistamines), anti-emetics (promethazine, prochloperazine, ondansetron)

    - Analgesic drugs including NSAIDs and COX-2 inhibitors

    - NOTE: Stable doses of thyroid replacement, estrogen replacement, low-dose aspirin for cardio-protection, low stable dose antidepressants of the SSRI class, and birth control (but with adequate backup contraception, as drug interactions with birth control have not been conducted) are permissible.

- History of recent surgery (within 60 days of screening)

- Acute or chronic illness or history of illness which in the opinion of the investigator could pose a threat or harm to the subject or obscure interpretation of laboratory test results or interpretation of study data, such as frequent angina, Class III or IV congestive heart failure, moderate impairment of renal or hepatic function, poorly controlled diabetes, etc.

- Any clinically significant abnormalities on physical examination or laboratory abnormalities identified in the medical record, as determined by the investigator
- Acute GI illness within 48 hours of initiation of the baseline period
- Females who are pregnant or breastfeeding
- History of excessive alcohol use or substance abuse
- Participation in an investigational study within the 30 days prior to dosing in the present study
- Any other reason, which in the opinion of the investigator, would confound proper interpretation of the study

Preliminary Data

We have conducted a search of Mayo Clinic database for patients with functional dyspepsia and identified 34 potential candidates for the study:

Pharmacokinetics and Dosing of Secretin

Synthetic natural human secretin

Pharmacokinetics and Dosing of Secretin: The standard dose of secretin used in exocrine pancreatic function testing is 0.2 mcg/kg IV over 1 min. This is also the dose used most commonly for radiographic procedures. This peptide has a half-life of approximately 2-4 min, yet has been observed to *elicit agonist responses at the exocrine pancreas for a much longer period of time (minutes to hours afterward*).

Dosing: We will administer the secretin at 0.2 mcg/kg IV over 1 min, immediately before initiating the Ensure administration. The placebo will be similar infusion of normal saline. Participants will receive the i.v. secretin dose on 1 occasion and the i.v. placebo on 1 occasion.

IND: Use of the medication will be as a proof of concept with pharmacodynamics measurements rather than with intention of developing secretin as a therapeutic. However, the medication is being provided by ChiRhoClin, Inc. who has requested a new IND from the FDA: the study will be conducted under the new IND number 141437.

Supply: Human Secretin for injection (16 mcg/10 ml vial) will be provided (60 vials) by ChiRhoClin, Inc, Burtonsville, MD and will be stored in and dispensed by Mayo Clinic Pharmacy. Secretin is available as a lyophilized sterile powder in 10-mL vials containing 16mcg of human secretin. The pharmacist will reconstitute with 8mL of saline for injection to yield a final concentration of 2mcg of human secretin/mL.

Randomization

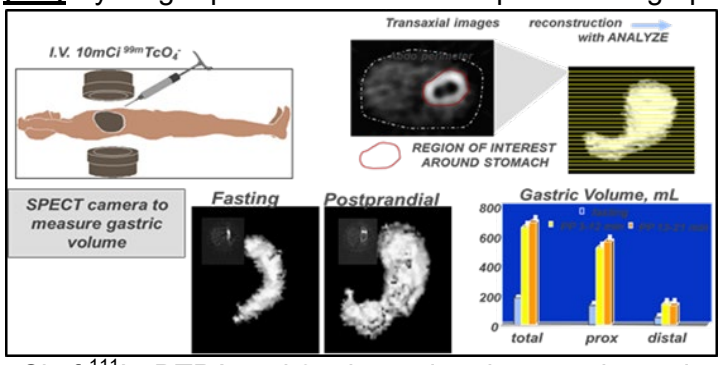
The randomization schedule will be generated before the start of the study in the Mayo Clinic Section of Biomedical Statistics and Informatics, and will be given to the research pharmacist. Medications will be *stored* in a monitored, climate-controlled environment according to manufacturer's directions. Monitoring records will be available for review to ensure quality control.

Experimental Procedures

Design: We propose to measure fasting gastric volumes, and postprandial gastric accommodation responses and gastric emptying rates of a standardized meal in functional

dyspepsia patients and healthy subjects during two testing periods. Participants in each group will be randomly assigned to receive secretin or placebo at the first sitting and the opposite for the second sitting. We will also measure acute food intake (meal size) in each participant, as the total volume ingested until they reach satiation, and postprandial symptoms. The plasma levels of several neuropeptides and hormones will be measured during fasting and postprandially to provide an initial understanding of the mechanism of action of secretin on gastric volume, accommodation and satiation indices.

Gastric Accommodation Measurements; Fasting and postprandial gastric volume (GV) by single photon emission computed tomography (SPECT [9]) developed and validated (including performance characteristics) in our lab. Using the ratio of postprandial volume over the fasting volume is a measure of the postprandial gastric accommodation. Radiation exposure listed in Appendix.



Gastric Emptying

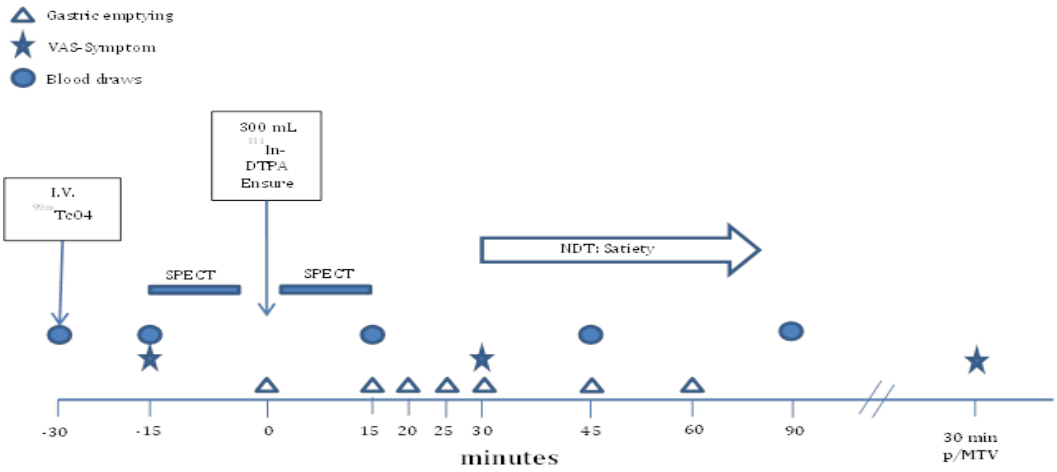
To assess gastric emptying during the satiation test (10), the first 300 mL of Ensure® will be radiolabeled with 50 µCi of ^{111}In-DTPA and 2-minute duration anterior and posterior scans of the abdomen will be obtained right after the Ensure is ingested and then 15 minutes (which will be after the end of SPECT imaging) at 5 minute intervals and then through 30 minutes from first 300mL of Ensure®. Radiation exposure listed in Appendix.

Plasma Measurements Blood draws (18 cc each) will be taken during fasting (in two occasions) and postprandially (at 15, 45 and 90 minutes after starting ingestion of Ensure) during the gastric function measurements. We will measure plasma levels of GIP, pancreatic polypeptide, and glucagon-like peptide-1 (GLP-1). A blood sample for possible future DNA testing will be collected also.

GLP-1 will be measured as the biologically active GLP-1 (active and total) using a 2-site, non-competitive immunoassay based on enzyme-labeled quantification of GLP-1 detected by a fluorogenic substrate. Total **GIP** will be measured using a two-site sandwich immunoassay using a total GIP ELISA kit (Millipore Corp, Billerica, MA, USA); the antibody used specifically recognizes human GIP (1-42) and GIP (3-42), but not other forms of oxyntomodulin, GLP-1, or GLP-2. Pancreatic polypeptide will be measured (at Mayo ICL) on the same plasma samples using radioimmunoassay technique.

Satiation (11) by Ensure® nutrient drink test with ingestion (1kcal/mL, 11% fat, 73% carbohydrate, and 16% protein) at a constant rate of 30ml/min to measure volume to fullness (VTF), and MTV. This will start 30 minutes after the initial 300 mL of Ensure was ingested. Briefly, participants record their time from their first intake to when they reach 5 levels of fullness. These levels of fullness are from 1) first sensation; 2) mild satiety; 3) moderate satiety; 4) severe satiety and 5) maximum satiety. Nutrient intake is stopped when subjects reach the maximum satiety. Time and total volume consumed to maximum satiety is calculated and the time and total volume is also calculated to moderate satiety Postprandial symptoms of fullness, nausea, bloating, and pain are measured 30 minutes after the meal using 100mm horizontal visual analog scales, with the words “none” and “worst ever” anchored at each end. Before starting any gastric testing, we will assess the volunteer’s current symptoms using the Functional Dyspepsia Symptom Diary and then again along with the postprandial symptoms questionnaire 30 minutes after the meal. Questionnaires used are in Appendix.

Study Schedule



Measurement/Outcomes

Participants will undergo the following tests on two separate occasions, each lasting 3-4 hours:

- Single photon emission computed tomography (SPECT) to calculate fasting gastric volume and postprandial gastric accommodation
- Gastric emptying (by scintigraphy) of Ensure after 30 minutes
- Measurement of volume to fullness (mL), maximum tolerated volume (MTV), postprandial symptoms on satiation (nutrient drink) test

Pharmacodynamic Endpoints

Comparison of the effects of secretin vs. placebo (saline) on the following gastrointestinal functions in FD patients and healthy subjects:

- Difference in fasting gastric volume
- Difference in gastric volume after the 300 mL Ensure meal for secretin vs. placebo
- Difference in gastric emptying of radiolabeled Ensure after 30 minutes
- Volume to fullness (sensation of usual postprandial fullness) and maximum tolerated volume (MTV).
- Difference in postprandial symptoms 30 minutes after ingesting maximum tolerated volume of Ensure

Sample Size Determination

Sample size assessment for primary aim to examine the *within* dyspepsia patient response when receiving Secretin versus Placebo. Sample size is based on the results of primary endpoints in the Mayo Clinic lab [data show mean ± SD). Within 10 dyspepsia patients, assuming a two-sided paired T test (80% power, α=0.05) in this crossover trial demonstrable differences for secretin compared to placebo is **21% in fasting gastric volume**, **13.0% in**

postprandial gastric volume and **16.6% in amount of gastric retention of Ensure at 30 minutes** based on the coefficients of variation observed from the Mayo Clinic laboratory of Dr. M. Camilleri in prior studies as shown in the table below.

Response	Mean	SD	Effect size detectable (absolute [% of mean], n=10 Based on cross-over design
Fasting gastric volume, mL Post prandial gastric volume, mL	273 848	57 111	56.8mL (20.8%) 110.6mL (13.0%)
Gastric emptying expressed as retention of Ensure at 30 mins, (%)	72	12	11.95 (16.6%)
Volume to fullness, mL	755	330	328.5mL (43.5%)
Maximum tolerated volume, mL	1283	400	398.5mL (31.1%)
Peak postprandial GLP-1, pmol/L	18.8	14	13.94pmol/L (74.1%)

Therefore the study is powered to detect clinically relevant effects of the study medication.

A similar analysis will be conducted in the healthy human volunteers based on the cross-over design, and the anticipated effect sizes that would be demonstrable in this second group is similar to that summarized above for patients with functional dyspepsia.

A subsidiary (secondary) analysis will compare the response using secretin in FD and healthy volunteers. This will be a 2 sample, unpaired analysis of the observations on secretin treatment, with ten patients in each cohort.

The table below shows the effects sizes demonstrable for the comparison between FD and health, using a 2-group analysis (unpaired analysis), again a two-sided test at $\alpha=0.05$, with 80% power.

Response	Mean	SD	Effect size detectable (absolute [% of mean], n=10 Based on 2-group comparison
Fasting gastric volume, mL Post prandial gastric volume, mL	273 848	57 111	75.5mL (27.7%) 147.0mL (17.3%)
Gastric emptying expressed as retention of Ensure at 30 mins, (%)	72	12	15.9 (22.1%)
Volume to fullness, mL	755	330	437mL (57.9%)
Maximum tolerated volume, mL	1283	400	530mL (41.3%)

Peak postprandial GLP-1, pmol/L	18.8	14	18.55pmol/L (98.8%)

Statistical Methods

It is anticipated that all primary and secondary endpoints will be normally distributed. We will use parametric tests to assess study parameters. If the data are not normally distributed we will use non-parametric tests.

For the primary aim, comparison of responses in the 10 completed dyspepsia patients for secretin versus placebo, as well as the subsidiary, analogous study conducted in healthy volunteers, the analysis will be a paired test, either a paired t test or signed rank test.

For the secondary aim, comparison of 10-15 dyspepsia patients with 10-15 healthy controls for responses after receiving secretin, the analysis will be either a two-sample t test or a rank sum test.

Covariate analysis may be conducted using a regression model, including gender and BMI as covariates, since these may significantly affect gastric functions such as satiation maximum tolerated volume, and smoking and gender since this may significantly affect drug levels of secretin. It is unclear if these covariate analyses will be required given the small sample sizes (n=10 in each group)

Safety Considerations

Informed consent

A complete description of the study will be presented to each potential study participant and signed and dated informed consent will be obtained before any study specific procedures are performed.

Demographics and medical history

A medical history and review of body systems along with demographic data will be obtained for all patients during the screening period (Days -30 to -1). Data that will be recorded in the source document/CRF include gender, race, date of birth, cigarette smoking history, alcohol use, drug abuse history and concomitant medication use.

Physical examination

A physical examination will be performed during the screening period to confirm eligibility.

Concomitant medication review

A review of concomitant medications will be conducted during the screening period and at every study visit. Any medications taken by study patients or changes in dose regimens will be recorded on a Concomitant Medication CRF.

Vital signs and weight

Vital signs will be obtained in the sitting position. Body temperature (°C), respiration rate (breaths/minute) and weight will be recorded at each time point when vital signs are measured. Height (cm) will be measured at the screening visit.

Pregnancy testing

Urine pregnancy testing will be done for women of childbearing potential at screening. Urine pregnancy testing will be done on day 1 prior to randomization to study drug and placebo and at the final study visit or earlier if the patient is discontinued.

A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >12 consecutive months; or women with documented plasma follicle-stimulating hormone level >35IU/mL]. Women who are using oral, implanted or injectable contraceptive hormones, an intrauterine device, barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy) will be considered to be of childbearing potential.

Adverse Events:

Adverse Event Grading will be in accordance with the severity grading scheme of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

Study Stopping Rules:

Individual:

1. Acute hypersensitivity reactions (CTCAE Grade 3, 4, or 5)
2. Severe abdominal pain, hypotension, diarrhea or vomiting requiring hospitalization (CTCAE Grade 3, 4, or 5)

General:

1. Development in 3 or more participants of severe abdominal pain requiring hospitalization (CTCAE Grade 3, 4, or 5)
2. Development in 3 or more participants of hypotension requiring i.v. hydration or hospitalization (CTCAE Grade 3, 4, or 5)
3. Development in 3 or more participants of diarrhea requiring i.v. hydration or hospitalization (CTCAE Grade 3, 4, or 5)

4. Development in 3 or more participants of vomiting requiring i.v. hydration or hospitalization (CTCAE Grade 3, 4, or 5)

Safety Monitoring Duration

As the half-life of i.v. secretin is approximately 2-4 minutes, the drug should be eliminated from the bloodstream within 16-20 minutes. Thus planned study duration of 3 to 4 hours past secretin infusion is an adequate timeframe for adverse event monitoring prior to discharge home. They will remain monitored in the Clinical Research Trials Unit (CRTU) for the entirety of their two individual study visit days.

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Appendix

Satiation test: Levels of Fullness Questionnaire

Nutrient Drink Test

Protocol: IRB# _____

Name:_____ Clinic #_____ Date_____

Start Time: _____

Satiety (Level of Fullness)

First Sensation (1): _____

Mild Satiety (2): _____

Please notify staff when you have reached this level

Moderate Satiety (3): _____ _____

Severe Satiety (4): _____

Maximum Satiety (5): _____Stop Time.

Please return form to GI Lab.

Staff Use Only.

Total # of cans _____

Total Volume Consumed: _____

Time _____

Satiation test: VAS Symptom Scales

Nutrient Drink Test

Protocol: IRB# _____

Name:_____ **Clinic #**_____ **Date**_____

Please return form to GI Lab

Please indicate below your level of nausea:

None **Worst Ever**

Please indicate below your level of fullness:

None **Worst Ever**

Please indicate below your level of bloating:

None **Worst Ever**

Please indicate below your level of abdominal pain:

None **Worst Ever**

Gastric Accommodation and Gastric Emptying tests: Radiation Exposure

SPECT (upper table) and Gastric Emptying (lower table)

Investigator: Dr. Michael Camilleri RSC Number: _____

Model: Adult

				Organ/Wt (organ doses are in mGy)													
RAM	Activity per administration (mCi)	Activity per administration (MBq)	Number of administrations	Testes 0.1	Ovaries 0.1	Breast 0.05	RBM 0.12	Lung 0.12	Thyroid 0.05	Bone 0.01	Colon 0.12	Stomach 0.12	Bladder 0.05	Liver 0.05	Esoph 0.05	Other: S 0.025	Remainder 0.025
Tc-99m Non-Absorbable Markers (liquid, injection)	10	370	2	0.96	19.24	0.39	3.70	0.74	0.02	3.40	74.00	43.66	5.18	3.18	0.25	45.14	2.69
In-111 Non-Absorbable Markers (liquid, oral)	0.1	3.7	2	0.22	3.11	0.03	0.72	0.04	0.00	0.23	11.32	0.89	0.89	0.25		3.70	0.29
Total				1.18	22.35	0.42	4.42	0.78	0.03	3.63	85.32	44.55	6.07	3.43	0.25	48.84	2.98
Effective Dose				0.12	2.23	0.02	0.53	0.09	0.00	0.04	10.24	5.35	0.30	0.17	0.01	1.22	0.07

E (mSv): 20.40

	Remainder organ	adrenal	brain	kidney	muscle	pancreas	SI	spleen	thymus	uterus	Weighted Average	
	Mass (g)	14	1420	310	28000	100	640	180	20	80		
Tc-99m Non-Absorbable Markers (liquid, injection)	Organ dose	2.66	0.00	4.88	2.74	8.14		5.40	0.25	11.84	2.69	
In-111 Non-Absorbable Markers (liquid, oral)	Organ dose	0.15		0.31	0.31	0.33		0.24		1.26	0.29	0

Subject Initials: _____

Screen Number: _____

Questionnaire: Hospital anxiety and depression questionnaire (Zigmond & Snaith 1983)

Please read each item and **circle** the reply which best describes how you have been feeling during the past week. Don't devote too much time to your responses; your immediate reaction will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up' :

   Most of the time
   A lot of the time
   Occasionally
   Not at all

2. I still enjoy the things I used to enjoy :

   Definitely as much
   Not quite so much
   Only a little
   Hardly at all

3. I get a frightened feeling, as if something awful is about to happen :

   Very definitely and quite badly
   Yes, but not too badly
   A little, but it doesn't worry me
   Not at all

4. I can laugh and see the funny side of things :

   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all

5. Worrying thoughts go through my mind :

   A great deal of the time
   A lot of the time
   From time to time
   Only occasionally

6. I feel cheerful :

   Not at all
   Not often
   Sometimes
   Most of the time

7. I can sit at ease and feel relaxed :

   Definitely
   Usually
   Not often
   Not at all

8. I feel as if I am slowed down :

   Nearly all the time
   Very often

Sometimes
Not at all

9. I get a frightened feeling, like ‘butterflies in the stomach’ :

   Not at all
   Occasionally
   Quite often
   Very often

10. I have lost interest in my appearance :

    Definitely
    I don’t take as much care as I should
    I may not take quite as much care
    I take just as much care as ever

11. I feel restless as if I have to be on the move :

    Very much indeed
    Quite a lot
    Not very much
    Not at all

12. I look forward with enjoyment to things :

    As much as I ever did
    Rather less than I used to
    Definitely less than I used to
    Hardly at all

13. I get sudden feelings of panic :

    Very often indeed
    Quite often
    Not very often
    Not at all

14. I can enjoy a good book or TV program :

    Often
    Sometimes
    Not often
    Very seldom

Sign_____ Date _____

Questionnaire: Functional Dyspepsia Symptom Diary (Patient-Reported Outcome Consortium’s Functional Dyspepsia Working Group 2018)

Subject Initials: _____

Screen Number: _____

Functional Dyspepsia Symptom Diary *(*Am J Gastroenterol. 2018; 113: 39–48)

***FDSD* Item**	**0=No; 10=Worst imaginable**										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Stomach pain.											
2. Burning in the stomach.											
3. Nausea											
4. Bloating											
5. Stomach fullness											
6. Early satiety											
7. Burping/belching rating											
8. Burping/belching bother											

Questionnaire: Abridged bowel disease questionnaire (Talley, 1990) (healthy subjects only):

Subjects Initials _____

Screen Number _____

In the past 12 months, have you experienced the following?

QUESTION	YES	NO
1. 2 or less than 2 bowel movements/week		
2. Excessive straining or sensation of incomplete evacuation of stool on more than 25% of occasions		
3. Lumpy stools on more than 25% of occasions		
At least 3 months of continuous or recurrent symptoms of:		
4. Abdominal pain or discomfort relieved by defecation		
5. Abdominal pain or discomfort associated with a change in stool frequency		
6. Abdominal pain or discomfort associated with a change in stool consistency		
7. More than 3 bowel movements per day		
8. Loose watery stools		
9. Bloating		
10. Swallowing difficulties		
11. Upper abdominal pain after meals more than once a month		
12. Abdominal bloating after meals		
13. Nausea regularly more than once a month		
14. Vomiting regularly more than once a month		
15. Heartburn regularly more than once a week		
16. Acid reflux regularly more than once a week		

Sign_____ Date _____

Questionnaire: Long bowel disease questionnaire (Talley 1990) (functional dyspepsia patients only)

Subject Initials: _____

Screen Number: _____

A QUESTIONNAIRE OF GASTROINTESTINAL SYMPTOMS

Please answer ALL questions. If you are uncertain, please write down your best guess. It is easy to miss questions, so *please check that you haven't left any out as you go.* If you wish to comment on any questions or qualify your answers, use the space in the margins; these comments will be read and taken into account.

All information provided will be kept confidential.

Thank you for your help.

First we would like to ask you some questions about TROUBLE SWALLOWING (a feeling that food sticks in your throat or chest) in the last year.

1. Have you had difficulty swallowing in the last year? (Check one)

1 ☐ No → **Please go to question 9 on PAGE 2.**

2 ☐ Yes → **Please answer the following questions.**

↓

2. When in your life did this trouble swallowing FIRST begin, as close as you can recall? (Check one)

1 ☐ In the last 6 months
2 ☐ 7 months to 1 year ago
3 ☐ More than 1 year to 2 years ago
4 ☐ More than 2 years to 5 years ago
5 ☐ More than 5 years to 10 years ago
6 ☐ More than 10 years to 20 years ago
7 ☐ More than 20 years ago

3. How many times have you had this trouble swallowing in the last year? (Check one)

1 ☐ Less than once a month
2 ☐ About once a month
3 ☐ About once a week
4 ☐ Several times a week
5 ☐ Daily

4. How bad is your trouble swallowing usually? (Check one)

1 ☐ MILD - can be ignored if I don't think about it
2 ☐ MODERATE - cannot be ignored, but does not affect my life-style
3 ☐ SEVERE - affects my life-style
4 ☐ VERY SEVERE - markedly affects my life-style

5. Does it hurt (is it painful) when you swallow? (Check one)

1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

6. What do you have trouble swallowing? (Check one)

1 ☐ Both solid foods and liquids
2 ☐ Solid foods only
3 ☐ Liquids only

7. Has your trouble swallowing gotten progressively worse in the last year? (Check one)

1 ☐ Yes, rapidly worse
2 ☐ Yes, slowly worse
3 ☐ No, has <u>not</u> gotten worse

8. Does your trouble swallowing come and go so that there are times when you have <u>no trouble</u> no matter what you eat? (Check one)

1 ☐ No
2 ☐ Yes

Next, we would like to ask you some questions about heartburn in the <u>last year</u>.

9. Have you had a <u>burning</u> pain or discomfort behind the breast bone in your chest in the last year? (Please do NOT count pain in your stomach or pain from heart trouble.) (Check one)

1 ☐ No → **Please go to question 16 on PAGE 3.**

2 ☐ Yes → **Please answer the following questions.**

↓

In this survey the term "heartburn" will be used to mean a <u>burning</u> pain or discomfort behind the breast bone in your chest. When answering these questions, please do <u>not</u> count any other sensations as "heartburn".

10. When in your life did this heartburn FIRST begin, as close as you can recall? (Check one)

1 ☐ In the last 6 months
2 ☐ 7 months to 1 year ago
3 ☐ More than 1 year to 2 years ago
4 ☐ More than 2 years to 5 years ago
5 ☐ More than 5 years to 10 years ago
6 ☐ More than 10 years to 20 years ago
7 ☐ More than 20 years ago

Please check that all questions that apply to you have been answered.

11. How many times have you had heartburn in the last year? (Check one)

1 ☐ Less than once a month
2 ☐ About once a month
3 ☐ About once a week
4 ☐ Several times a week
5 ☐ Daily

12. How bad is your heartburn usually? (Check one)

1 ☐ MILD - can be ignored if I don't think about it
2 ☐ MODERATE - cannot be ignored, but does not affect my life-style
3 ☐ SEVERE - affects my life-style
4 ☐ VERY SEVERE - markedly affects my life-style

13. Has your heartburn awakened you at night in the last year? (Check one)

1 ☐ No
2 ☐ Yes

NOTE: When we say "often" we mean more than 25% of the time in the last year.

14. Does your heartburn often travel up toward your neck? (Check one)

1 ☐ No
2 ☐ Yes

15. Is your heartburn often made better (eased) by taking antacids (like Amphojel, AlternaGEL, Gaviscon, Maalox, Mylanta, Riopan, Rolaids or Tums)? (Check one)

1 ☐ No
2 ☐ Yes
3 ☐ I have not taken antacids for heartburn

We would now like to ask you about other complaints you have had in the last year.

16. How many times have you had a feeling of WANTING TO THROW UP (nausea) in the last year? (Check one)

1 ☐ None
2 ☐ Less than once a month
3 ☐ About once a month
4 ☐ About once a week
5 ☐ Several times a week
6 ☐ Daily

Please check that all questions that apply to you have been answered.

17. **How many times have you ACTUALLY THROWN UP (vomited) in the last year?** (Check one)
    1 ☐ None
    2 ☐ Less than once a month
    3 ☐ About once a month
    4 ☐ About once a week
    5 ☐ Several times a week
    6 ☐ Daily

18. **Have you thrown up (vomited) bright red blood in the last year?** (Check one)
    1 ☐ No
    2 ☐ Yes

19. **Has your <u>food</u> come back up into your mouth or throat in the last year?** (Please do not include vomiting) (Check one)
    1 ☐ No
    2 ☐ Yes

NOTE: When we say "often" we mean more than 25% of the time in the last year.

20. **Have you <u>often</u> been troubled by <u>burping (belching) up gas</u> through the mouth in the last year?** (Check one)
    1 ☐ No
    2 ☐ Yes

21. **Have you <u>often</u> been troubled by hiccups in the last year?** (Check one)
    1 ☐ No
    2 ☐ Yes

22. **Have you lost weight in the last year without deliberately dieting?** (Check one)
    1 ☐ No
    2 ☐ Less than 7 lbs.
    3 ☐ 7 lbs. or more

23. **Is your appetite in the last year compared with before:** (Check one)
    1 ☐ Decreased?
    2 ☐ About the same?
    3 ☐ Increased?

Please check that all questions that apply to you have been answered.

24. Have you <u>often</u> lost your appetite and felt full soon after starting to eat so that you could not finish a normal meal in the last year? (Check one)

1 ☐ No
2 ☐ Yes

Next, we would like to ask you some questions about stomach, belly or tummy pain in the <u>last year.</u>

25. Have you had an ache or pain in your stomach or belly (gut) in the last year? (Please do NOT count cramps or pain with menstrual periods, heartburn, or chest pain.) (Check one)

1 ☐ No → **Please go to question 45 on PAGE 8.**

2 ☐ Yes → **Please answer the following questions.**

↓

Stomach or belly pain can be difficult to describe and sometimes more than one type of pain can occur. Please think about the usual or primary type of pain you have. We would like to ask you some questions <u>only</u> about the USUAL or PRIMARY pain in your stomach or belly.

26. Have you had this same ache or pain more than SIX times in the last year? (Check one)

1 ☐ No
2 ☐ Yes

27. How bad is the ache or pain u*sually*? (Check one)

1 ☐ MILD - <u>can</u> be ignored if I don't think about it
2 ☐ MODERATE - <u>cannot</u> be ignored, but does <u>not</u> affect my life-style
3 ☐ SEVERE - affects my life-style
4 ☐ VERY SEVERE - <u>markedly</u> affects my life-style

28. Does the usual ache or pain EVER WAKE YOU FROM SLEEP AT NIGHT? (Check one)

1 ☐ No
2 ☐ Yes

29. Does this pain come and go periodically? (Periodically here means periods of at least a month with no pain, with periods in between of weeks to months when there is pain.) (Check one)

1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

30. How many times did you get this pain in the last year? (Check one)

1 ☐ Less than once a month
2 ☐ About once a month
3 ☐ About once a week
4 ☐ Several times a week
5 ☐ Daily

31. When this pain occurs, how long does it usually last? (Check one)

1 ☐ Less than 30 minutes
2 ☐ 30 minutes to 2 hours
3 ☐ More than 2 hours to 6 hours
4 ☐ More than 6 hours

32. When in your life did this ache or pain FIRST begin as close as you can recall? (Check one)

1 ☐ In the last 6 months
2 ☐ 7 months to 1 year ago
3 ☐ More than 1 year to 2 years ago
4 ☐ More than 2 years to 5 years ago
5 ☐ More than 5 years to 10 years ago
6 ☐ More than 10 years to 20 years ago
7 ☐ More than 20 years ago

33. Does this ache or pain often occur BEFORE meals or when hungry? (Check one)

1 ☐ No
2 ☐ Yes

NOTE: When we say "often" we mean more than 25% of the time in the last year.

34. Does this ache or pain often occur IMMEDIATELY AFTER (less than 30 minutes) meals? (Check one)

1 ☐ No
2 ☐ Yes

35. Does this ache or pain often occur 30 minutes to 2 hours AFTER meals? (Check one)

1 ☐ No
2 ☐ Yes

36. Is this pain often made BETTER (relieved) by burping (bringing up air through the mouth)? (Check one)

1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

37.Is this pain <u>often</u> made BETTER by having a bowel movement? (Check one)

1 ☐ No
2 ☐ Yes

38. Is this pain <u>often</u> made BETTER by eating? (Check one)

1 ☐ No
2 ☐ Yes

39. Is this pain <u>often</u> made BETTER by taking antacids (like Tums, Riopan, Mylanta, Maalox, Gaviscon or Rolaids)? (Check one)

1 ☐ No
2 ☐ Yes
3 ☐ I don't take antacids

40. Is this pain <u>often</u> made WORSE by food or milk? (Check one)

1 ☐ No
2 ☐ Yes

41. Do you <u>often</u> have MORE bowel movements when this pain begins? (Check one)

1 ☐ No
2 ☐ Yes

42. Do you <u>often</u> have LOOSER bowel movements (stools) when this pain begins? (Check one)

1 ☐ No
2 ☐ Yes

43. Do you <u>often</u> feel bloated and actually see your belly swell up? (Check one)

1 ☐ No
2 ☐ Yes

44. Have you seen MUCUS in your stools in the last year (that is, white or green slimy material)? (Check one)

1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

An important purpose of this study is to learn about bowel habits in the community in the last year.

45. In the last year, how regular were your bowel movements? (Check one)

1 ☐ Often had constipation (more than 25% of the time)
2 ☐ Sometimes had constipation (less than 25% of the time)
3 ☐ Alternating diarrhea and constipation
4 ☐ Sometimes diarrhea (less than 25% of the time)
5 ☐ Often had diarrhea (more than 25% of the time)
6 ☐ Usually normal

46. What is the longest number of days you have ever gone without having a bowel movement in the last year? (Check one)

1 ☐ 2 days or less
2 ☐ More than 2 to 4 days
3 ☐ More than 4 days to 1 week
4 ☐ More than 1 to 2 weeks
5 ☐ More than 2 weeks

47. How many bowel movements do you usually have in a WEEK? (Check one)

1 ☐ 1 or less
2 ☐ 2
3 ☐ 3-4
4 ☐ 5-8
5 ☐ 9-12
6 ☐ 13-16
7 ☐ 17-21
8 ☐ 22-26
9 ☐ More than 26

48. In the last year, did you need to take anything to help you have a bowel movement (such as laxative, enema, or suppository, but not including fiber products)? (Check one)

1 ☐ No
2 ☐ Yes, sometimes (less than 25% of the time)
3 ☐ Yes, often (more than 25% of the time)
4 ☐ Yes, usually (more than 75% of the time)

If yes, what did you take? _____

Please check that all questions that apply to you have been answered.

49. In the last year, have you needed to strain a lot (for more than 1 to 2 minutes) to have a bowel movement? (Check one)

1 ☐ No
2 ☐ Yes, sometimes (less than 25% of the time)
3 ☐ Yes, often (more than 25% of the time)
4 ☐ Yes, usually (more than 75% of the time)

50. How severe was your straining with bowel movements in the last year? (Check one)

1 ☐ I never strain with bowel movements
2 ☐ Very mild
3 ☐ Mild
4 ☐ Moderate
5 ☐ Severe
6 ☐ Very severe

51. In the last year, have your stools been loose or watery? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

52. In the last year, have your stools been hard? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

53. In the last year, after finishing a bowel movement, have you felt there was still stool that needs to be passed? (Check one)

1 ☐ No
2 ☐ Yes

54. In the last year, have you experienced an urgent need to open your bowels that made you rush to the toilet? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

55. Have you noticed ANY BLOOD in your stools or in the toilet bowl in the last year? (Check one)

1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

56. In the last year, did you ever press your finger in or around the anus (back passage) to help a bowel movement come out? (Check one)

1 ☐ No
2 ☐ Yes

57. How much time did you usually need to spend each time on the toilet to move your bowels during the last year? (Check one)

1 ☐ Less than 5 minutes
2 ☐ 5 to 10 minutes
3 ☐ More than 10 minutes up to 30 minutes
4 ☐ More than 30 minutes up to 1 hour
5 ☐ More than 1 hour

58. In the last year, did you have to position yourself other than in the sitting position to help a bowel movement come out? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

If yes, which position usually? _____

59. In the last year, did you <u>feel</u> there was a <u>blockage in your rectum or anus</u> (back passage) which made it difficult for you to pass the stool? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

Please check that all questions that apply to you have been answered.

60. Have you had problems with leakage of stool (accidents or soiling because of the inability to control the passage of stool until you reached a toilet)? (Check one)

☐ No → Please go to question 70 on PAGE 13.

☐ Yes → Please answer the following questions.

↓

61. In the last year, did you have to take medication (like antidiarrheals, Lomotil, Imodium AD, etc.) to prevent leakage of stool? (Check one)

1 ☐ No
2 ☐ Yes, sometimes (less than 25% of the time)
3 ☐ Yes, often (more than 25% of the time)
4 ☐ Yes, usually (more than 75% of the time)

If yes, what did you take?_____

62. When in your life did this problem with leakage of stool <u>first</u> begin, as close as you can recall? (Check one)

1 ☐ In the last 6 months
2 ☐ 7 months to 1 year ago
3 ☐ More than 1 year to 2 years ago
4 ☐ More than 2 years to 5 years ago
5 ☐ More than 5 years to 10 years ago
6 ☐ More than 10 years to 20 years ago
7 ☐ More than 20 years ago

63. In the last year, did you <u>ever</u> wear a pad to protect your underclothes from soilage or leakage of stool? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

64. In the last year, when was the leakage of stool <u>most</u> frequent? (Check one)

1 ☐ While awake
2 ☐ While asleep
3 ☐ There was no difference in leakage while asleep or awake

Please check that all questions that apply to you have been answered.

65. When leakage of stool has occurred in the last year, did you have problems with leakage of liquid or runny stool? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time that leakage occurred)
3 ☐ Often (more than 25% of the time that leakage occurred)
4 ☐ Usually (more than 75% of the time that leakage occurred)

66. When leakage of stool has occurred in the last year, did you have problems with leakage of solid, or formed stool? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time that leakage occurred)
3 ☐ Often (more than 25% of the time that leakage occurred)
4 ☐ Usually (more than 75% of the time that leakage occurred)

67. When these "accidents" with leakage of stool occurred in the last year, how much stool typically leaked out? (Check one)

1 ☐ A small amount, with a stain about the size of a quarter
2 ☐ Moderate amounts (often requiring a change of pad or underwear)
3 ☐ Large bowel movements of liquid stool (often requiring a complete change of clothes)
4 ☐ Solid or formed stool

68. In the last year, have you been able to tell when this leakage of stool was about to occur? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

69. In the last year, have you had difficulty telling the difference between the need to pass gas and the need to pass stool? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

Please check that all questions that apply to you have been answered.

Questions 70 - 74 are for women, if you are a man, please go to Question 75 on page 14.

70. In the last year, did you ever press your finger in or around the vagina (front passage) to help a bowel movement come out? (Check one)

1 ☐ No
2 ☐ Yes

71. Have you ever given birth to a child? (Check one)

1 ☐ No
2 ☐ Yes
If YES, how many children? _____
number by vaginal delivery? _____
number by Cesarean section? _____
number for which forceps were used? _____

72. Have you had any injuries to your anus (back passage) during childbirth which required surgical repair? (Check one)

1 ☐ No
2 ☐ Yes
3 ☐ I have never given birth
If YES, what repair was done? _____

73. Have you ever had a protrusion of the rectum through the opening of the vagina (called a rectocele)? (Check one)

1 ☐ No
2 ☐ Yes
If YES, when? _____

74. Have you ever had a protrusion of the rectum through the anus (called a rectal prolapse)? (Check one)

1 ☐ No
2 ☐ Yes
If YES, when? _____

Please check that all questions that apply to you have been answered.

75. In the last year, have you had slow leakage, or dribbling, or urine throughout the day? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

76. In the last year, have you worn a pad to protect your underclothes from leakage of urine? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

77. In the last year, have you had leakage of urine when you coughed or sneezed? (Check one)

1 ☐ Never
2 ☐ Sometimes (less than 25% of the time)
3 ☐ Often (more than 25% of the time)
4 ☐ Usually (more than 75% of the time)

78. In the last year, when leakage of urine has occurred, were you aware of the need to urinate before the leakage occurred? (Check one)

1 ☐ I have no leakage of urine throughout the day
2 ☐ Never
3 ☐ Sometimes (less than 25% of the time)
4 ☐ Often (more than 25% of the time)
5 ☐ Usually (more than 75% of the time)

Please answer the following questions regarding other urinary symptoms.

79. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating? (Check one)

1 ☐ Not at all
2 ☐ Less than 1 time in 5
3 ☐ Less than half the time
4 ☐ About half the time
5 ☐ More than half the time
6 ☐ Almost always

Please check that all questions that apply to you have been answered.

80. During the last month or so, how often have you had to push or strain to begin urination? (Check one)

1 ☐ Not at all
2 ☐ Less than 1 time in 5
3 ☐ Less than half the time
4 ☐ About half the time
5 ☐ More than half the time
6 ☐ Almost always

81. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? (Check one)

1 ☐ Not at all
2 ☐ Less than 1 time in 5
3 ☐ Less than half the time
4 ☐ About half the time
5 ☐ More than half the time
6 ☐ Almost always

To help interpret the results of this survey, we would like to ask some questions about your activities, habits and work. Please be assured that all information will be kept strictly confidential.

82. Please indicate the IMPORTANCE of each of these ACTIVITIES to you by writing down a number from 1 to 5.

1) Not at all important
2) Minimally important
3) Moderately important
4) Very important
5) Extremely important

Sports/Recreation _____
Work around the house _____
Social/Entertainment _____
Family relationships _____
Travel _____
Sexual life _____
Work (occupational) _____
Are you retired? ____ Yes ____ No

Please check that all questions that apply to you have been answered.

83. Next, please indicate whether ANY problems with your BOWEL FUNCTION have affected each of these same activities in the LAST YEAR. (Do NOT include problems related to TEMPORARY illnesses, flu, etc.) (Write down a number from 1 to 5 on each line.)

1) I have had no problem with bowel function
2) I have bowel problems, but am not affected
3) Mildly affected
4) Moderately affected
5) Severely affected

Sports/Recreation _____
Work around the house _____
Social/Entertainment _____
Family relationships _____
Travel _____
Sexual life _____
Work (occupational) _____

84. Next, please indicate whether problems with LEAKAGE OF STOOL have affected each of these same activities in the LAST YEAR. (Write down a number from 1 to 5 on each line.)

1) I have had no problem with leakage of stool
2) Not affected
3) Mildly affected
4) Moderately affected
5) Severely affected

Sports/Recreation _____
Work around the house _____
Social/Entertainment _____
Family relationships _____
Travel _____
Sexual life _____
Work (occupational) _____

Please check that all questions that apply to you have been answered.

85. Did you <u>ever</u> smoke cigarettes regularly (at least 1 cigarette per day for at least 30 days)? (Check one)

1 ☐ No
2 ☐ Yes
↓

At what age did you start? _____years
When smoking the heaviest, how many packs did you Smoke per day? _____
How many packs per day do you currently smoke? _____
If you stopped smoking, at what age did you stop? _____

Next, there is a question about drinks that contain alcohol (that is, beer, wine, or other liquors like whiskey, vodka, gin, or brandy). One drink is equal to a can of beer, a glass of wine, or shot of spirits.

86. How many drinks a WEEK have you had on average in the last year? (Check one)

1 ☐ None
2 ☐ 1 to 2 drinks a week
3 ☐ 3 to 6 drinks a week
4 ☐ 7 to 10 drinks a week
5 ☐ More than 10 drinks a week

87. Do you drink coffee? (Check one)

1 ☐ No
2 ☐ Yes
↓

Decaffeinated or regular usually? _____
How many cups per day usually? _____
Does drinking coffee bring on or worsen your heartburn?
1 ☐ No 2 ☐ Yes

Please check that all questions that apply to you have been answered.

88. Current marital status: (Check one)

1 ☐ Married
2 ☐ Single
3 ☐ Widowed
4 ☐ Divorced
5 ☐ Separated
6 ☐ Other

89. Are you presently: (Check one)

1 ☐ Employed
2 ☐ Unemployed
3 ☐ Retired
4 ☐ Full-time homemaker
5 ☐ Full-time student
6 ☐ Disabled

90. Please indicate your educational training. (Check one)

1 ☐ Professional training beyond college
2 ☐ College graduate (4 years)
3 ☐ Some college
4 ☐ High school graduate
5 ☐ 10-11 years of school, include some high school
6 ☐ 7-9 years of school, grade school graduate
7 ☐ Under 7 years of grade school

91. Indicate your racial background (optional):

1 ☐ Caucasian
2 ☐ Hispanic
3 ☐ African American
4 ☐ Native American
5 ☐ Asian/Pacific Islander
6 ☐ Other _____
7 ☐ Unknown

Please check that all questions that apply to you have been answered.

Next, we would like to ask you questions about your general health.

92. **Do the muscles in your arms or legs feel as though their strength has decreased?** (Check one)
1 ☐ No
2 ☐ Yes

93. **Do you get muscle craps or "Charley horse" in your arms or legs, particularly during exercise?** (Check one)
1 ☐ No
2 ☐ Yes

94. **Do you have any numbness, heat sensation, or prickly feeling in any part of your body?** (Check one)
1 ☐ No
2 ☐ Yes

95. **Do you faint on changing your position?** (Check one)
1 ☐ No
2 ☐ Yes

96. **Do you have blurring of vision with prolonged reading?** (Check one)
1 ☐ No
2 ☐ Yes

97. **Do you have episodes of overheating because you sweat insufficiently?** (Check one)
1 ☐ No
2 ☐ Yes

98. **Do you sweat on your face after eating cheese or red wine?** (Check one)
1 ☐ No
2 ☐ Yes

99. **Do you feel your heart racing or pounding with force?** (Check one)
1 ☐ No
2 ☐ Yes

100. **Do you have chest pain that is brought on during exercise?** (Check one)
1 ☐ No
2 ☐ Yes

101. **Do your legs swell and does your finger leave an imprint if you press on your ankle or foot?** (Check one)
1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

102. Do you have cloudy or blood-stained urine? (Check one)

1 ☐ No
2 ☐ Yes

103. Have you needed laser treatment of your eyes? (Check one)

1 ☐ No
2 ☐ Yes

104. Have you needed treatment for cataract? (Check one)

1 ☐ No
2 ☐ Yes

It is important for us to know about the medications that you are taking.

105. Are you taking any of the following medications? (Please check those you are taking)

1 ☐ Aspirin, Ibuprofen, Advil, Motrin, Voltaren, Naprosyn
2 ☐ Antacids
3 ☐ Zantac, Axid, Pepcid, Tagamet
4 ☐ Prilosec, Prevacid
5 ☐ Propulsid
6 ☐ Laxatives
7 ☐ Imodium
8 ☐ Lomotil
9 ☐ Cardizem, Isoptin, Verapamil, Adalat, Procardia
10 ☐ Clonidine, Catapres
11 ☐ Insulin

106. Please list below any <u>other</u> medication that you are taking:

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

Please check that all questions that apply to you have been answered.

Another important purpose of this study is to learn about your previous health and visits to the doctor.

107. How many times have you visited a doctor or a physician for <u>any</u> reason in the last year? (Check one)

1 ☐ None
2 ☐ 1 to 2 times in the last year
3 ☐ 3 to 5 times in the last year
4 ☐ 6 to 10 times in the last year
5 ☐ More than 10 times in the last year

If you have visited a doctor, why did you go?_____

108. How many times have you been hospitalized for <u>any</u> reason in the last year? (Check one)

1 ☐ None
2 ☐ 1 to 2 times in the last year
3 ☐ 3 to 5 times in the last year
4 ☐ 6 to 10 times in the last year
5 ☐ More than 10 times in the last year

If you were hospitalized, what were the reasons?_____

109. How many times in the last year have you visited your doctor or physician for problems with your bowels? (Check one)

1 ☐ None
2 ☐ 1 to 2 times
3 ☐ 3 to 5 times
4 ☐ 6 to 10 times
5 ☐ More than 10 times

110. How many times in the last year have you visited your doctor or physician for problems with leakage of stool? (Check one)

1 ☐ None
2 ☐ 1 to 2 times
3 ☐ 3 to 5 times
4 ☐ 6 to 10 times
5 ☐ More than 10 times

Please check that all questions that apply to you have been answered.

Is there anything else you would like to tell us about your health problems? If so, please use this space for that purpose.

Also, any comments that may help us understand these problems better will be appreciated, either here or in a separate letter.

Finally, please complete the following symptoms checklist.

IMPORTANT: **For each of the complaints or problems below, please indicate how often it occurred and how bothersome it was <u>in the last year</u>.**

Write down a number from 0 to 4 for all 16 questions below in <u>both</u> columns.

<u>HOW OFTEN</u>?	**<u>HOW BOTHERSOME</u>?**
0 Not a problem	0 Not a problem
1 Occurs about once a month	1 Slightly bothersome when occurs
2 Occurs about once a week	2 Moderately bothersome when occurs
3 Occurs several times a week	3 Severely bothersome when occurs
4 Occurs daily	4 Extremely bothersome when occurs

		HOW OFTEN? (0-4):	HOW BOTHERSOME? (0-4):
1.	Headaches	_____	_____
2.	Backaches	_____	_____
3.	Asthma (wheezing)	_____	_____
4.	Trouble breathing	_____	_____
5.	Insomnia (difficult sleeping)	_____	_____
6.	Fatigue (tiredness)	_____	_____
7.	Depression (feeling sad or blue)	_____	_____
8.	General stiffness	_____	_____
9.	Heart palpitations (pounding or racing)	_____	_____
10.	Joint pains	_____	_____
11.	Eye pain associated with reading	_____	_____
12.	Dizziness	_____	_____
13.	Weakness	_____	_____
14.	Nervousness or shakiness	_____	_____
15.	Hot or cold spells	_____	_____
16.	High blood pressure	_____	_____

Please check that you have answered <u>all</u> 16 questions--every question should have a number from 0 to 4 in the "How Often?" <u>and</u> in the "How Bothersome?" columns.