THE EFFECTS OF STIMULATION OF NUCLEUS AMBIGUUS ON GASTRO-INTESTINAL MOTILITY AND SECRETION. F.D. Pagani, H.R. Orzechoski III, M.F. Norman, S. Marefat, D.K. Kasbekar, and R.A. Gillis. Depts. of Pharmacology, Anatomy, and Physiology, Georgetown Univ., Washington, D.C., and Smith, Kline, and French Labs., Philadelphia, PA.

The nucleus ambiguus (NA) has been demonstrated to be important for control of parasympathetic outflow to the heart. Recently, we have shown that activation of these neurons caused by microinjection of the GABA receptor antagonist drug bicuculline, causes an increase in gastric motility (Science 214:193, 1981). The purpose of the present study was to confirm this finding by electrical stimulation of this nucleus, and in addition, to determine whether stimulation of this site will influence gastric secretion and duodenal motility. The NA was stimulated (50Hz, 0.2msec., 200-250uamps for 10min) in chloralose anesthetized cats while monitoring antral and duodenal motility using extraluminal force transducers. Effects on gastric secretion (pepsin secretion and titratable acidity) were determined by inserting a cannula through a gastrotomy in the fundus to instill and collect 10ml aliquots of normal saline. The mucosa at the terminal antrum was sutured closed through a small gastrotomy along the greater curvature of the antrum to prevent gastric emptying. In five animals, electrical stimulation of the NA elicited pronounced antral contractions (Minute Motility Index increased by 7.7 ± 1.1) and sinus bradycardia (-98 ± 1.2 beats/min). No significant changes were observed in duodenal motility, pepsin secretion or titratable acidity of gastric secretions during a 10 min collection period. In a separate series of experiments, using the horseradish peroxidase retrograde tracing technique, we showed that parasympathetic innervation of the antrum originated only from the dorsal motor nucleus of the vagus (DMV) and not from the NA. Thus antral contractions elicited by NA stimulation presumably result from activation of cells in the NA that project to sites in the DMV which selectively influence the antrum. No changes in gastric secretion or duodenal motility were associated with NA stimulation.

INTERACTIONS BETWEEN CENTRAL REGULATORY MECHANISMS AND GASTRIC MOTILITY. Thomas F. Burks and William D. Barber. Departments of Pharmacology and Anatomy, University of Arizona Health Sciences Center, College of Medicine, Tucson, Arizona, 85724.

The central components of the regulatory mechanisms involved in gastrointestinal motility have not been adequately explored. We have recently identified single neurons in the brainstem that respond to phasic distention of the stomach by changes in their rates of discharge. Extracellular recordings of neural units in and near the tractus and nucleus solitarius were obtained in cats anesthetized with halothane and nitrous oxide. Phasic gastric distention was accomplished with an intragastric balloon attached to a respirator pump. Of the units that were phase-locked to the phasic gastric distention, most (42/46) displayed increased firing rates during the systolic phase of gastric distention and rarely fired during the diastolic phase. The mean discharge frequency per cycle of inflation was 4.7 ± 0.3 Hz with an average of 6.3 ± 0.6 spikes per burst. Most of the spikes (83%) in each burst occurred during the rising phase of the distention cycle. Occlusion of the outflow of the intragastric balloon during systolic resulted in rates of discharge of the brainstem units intermediate in frequency between those of the systolic and diastolic phases of phasic distention, suggesting either a dynamic component that occurs during the rising phase and/or rapid adaptation to sustained distention. When the rate of phasic distention was slowed, the duration of the spike bursts increased, but at a reduced frequency. The phase-locked discharges of the brainstem units disappeared after bilateral cervical vagotomy. Further, drug studies suggest that the neural discharge frequency per unit of gastric distention varies inversely with the distensibility of the gastric wall. The brainstem units we have identified may link central afferent projections from the stomach with the motor components of central reflex arcs. (Supported by USPHS Grant No. DA02163.)
SELECTIVE MOTOR AND SECRETORY PATHWAYS FROM THE HINDBRAIN TO THE STOMACH. H. S. Ormsbee III, W. P. Norman, A. R. Woodward Jr., D. K. Kashefi, F. R. Harley Jr., F. E. Pagani. Department of Surgery and Department of Pharmacology, Anatomy and Physiology, Georgetown University, Washington, D.C., 20007, Dept. of Surgery, University of Maryland School of Medicine, Baltimore, Maryland, 21201, and Dept. of Pharmacology, Smith Kline and French Laboratories, Philadelphia, Pa., 19101.

The aim of this study was to characterize the parasympathetic outflow from the cells within the dorsal motor nucleus of the vagus (DMV) to secretory and motor targets in the stomach. Sites in the DMV were electrically stimulated (300Hz, 0.2 msec, 100 to 200 uAmp) in chloralose-anesthetized cats. In a separate study, these sites were shown to be densely labelled with reaction product when horseradish peroxidase was injected in the gastric corpus or in the antrum. Antral motility was monitored with an extraluminal force transducer oriented to record circular muscle contractions. The mucosa of the terminal antrum was then closed to prevent gastric emptying and a tube was placed into the stomach to instill and aspirate 10 cc aliquots of normal saline every two minutes. Measurements were made of the frequency and amplitude of antral contractions, of the titratable acidity, of the pepsin activity, and heart rate before and during DMV stimulation. In five animals, electrical stimulation of the DMV elicited pronounced antral contractions (frequencies 3.7 ± 0.6/min., amplitude 34.0 ± 8.6 mm, pepsin activity 2.7 ± 0.8 uEq H+/min.), a significant increase in pepsin activity (4 ± 1.3 uEq 10 min.), and aimed brady-cardia (0.10 ± 0.08 beats per min.). No significant changes in titratable acidity were observed (-2.2 ± 1.4 mm HCl/10 min.). The motility, pepsin, and heart rate responses were blocked by cervical vagotomy. In a separate series of four cats, electrical stimulation of the cervical vagus significantly increased all measured indices of gastric function. These results suggest that antral motility and acid secretion receive separate and selective input from specific sites in the hindbrain. Cells within the DMV responsible for chief cell stimulation could not be separated from those stimulating the antrum.

EFFECTS OF STRESS ON GASTRIC FEEDING MOTILITY AND PLASMA B-ENDORPHIN LEVELS IN MAN. V. Stanghellini, B. C. Kao, V. L. E. Do, R. Zinsmeister, and J.-R. Mallalana. Gastroenterology Unit, Mayo Clinic, Rochester, MN. 55905.

In 12 healthy volunteers, we studied the effects of vertigo and cold pain (two stressful stimuli acting via the cervical nervous system) on the gastrointestinal motor response to an ordinary solid-liquid meal and on plasma levels of b-endorphin (b-EP). A multichannel low-compliance perfusion system connected to external pressure transducers was positioned fluoroscopically to record antral (4 sites, 1 cm apart) and duodenal (2 sites) pressure activity. Plasma concentrations of b-EP were measured by radioimmunossay. Blood pressure, pulse rate, skin conductance were also monitored. Vertigo (by otic stimulation with 10°C water; control, 37°C water) and cold pain (immersing hand in 4°C water; control, 37°C water) were simultaneously applied 10 min after the meal in each subject. The linear trend in this cumulative (log) motility index (MI) and the (log) difference between the maximum value of b-EP and the basal value were analyzed via 2-way factorial analysis of variance.

Mean Linear Trend MI

| Warm | Cold |
|------|------|
| Hand | 20.4 | 7.2 |
| Cold | 6.2 | (n=6) |

| Warm | Cold |
|------|------|
| Face | 7.1 |
| Cold | 18.8 | (n=6) |

The effects of labyrinthine stimulation and cold pain alone significantly reduced antral motility (P<0.05), while significantly increasing levels of b-EP (P<0.05) did not.

Propagations of duodenal contractions in patients after high-selective vagotomy (HSV). S. R. Reddy and W. E. Waterfall. Dept. of Surgery, McMaster University, Hamilton, Ont., Canada.

Characteristics of the propagation of duodenal spike activities before and after a test meal have been studied in 4 patients after HSV. Three sets of stainless steel bipolar electrodes were implanted at operation 5 cm apart, one on the stomach and two on the duodenum. Two or three recordings of gastroduodenal electrical activities were obtained from each subject before the electrodes were removed 5 days after surgery. After an overnight fast, control records were obtained for 30 min, following which a test meal was given and the recording continued for 60 min. The signals were electronically processed to eliminate electrical and mechanical noise. The SFAs were analyzed on a Nova mini-computer to detect peaks, to measure inter and intra contractile intervals, and to perform statistical analysis. The duodenal contractions occurred at the integral multiples of ECA frequency; a majority occurred at the ECA frequency. Meal abolished migrating myoelectrical complexes (MMC) and increased duodenal spike activity compared to phase I or II of the MMC. Furthermore, the distal duodenum became more active than the proximal duodenum. The percentages of contractions propagating in oral and aboral directions, or occurring locally were 31.3%, 30.8%, and 37.9% before meal and 42.0%, 11.6%, and 46.4% after meal respectively. The velocity of oral propagation was 6.21 ± 1.63 cm/sec which was not significantly different from that of aboral (7.38 ± 3.74 cm/sec). The ECAs were phase-locked during periods of contractions or no contractions and phase-unlocked during transitions from contractions to no contractions and vice-versa. In conclusion, the contractile activity in the human duodenum after HSV appears to be controlled by ECAs; it is increased after meal or oral propagation is present over aboral after eating; and, the velocity of propagation is similar in both directions as expected in this system of coupled relaxation oscillators.

ABSTRACTS OF PAPERS

ARE ALTERATIONS IN GASTRODUODENAL MOTILITY RESPONSIBLE FOR PREVIOUSLY UNEXPLAINED NAUSEA, VOMITING, AND ABDOMINAL PAIN? C. R. Cottrell, C. A. Sznisky, J. L. Martin, J. R. Mathias. Veterans Administration Medical Center and College of Medicine, University of Florida, Gainesville, Florida 32602.

We have investigated the motor function of stomach and proximal small intestine of five patients with unexplained abdominal pain, nausea, and vomiting. Despite a thorough medical and surgical evaluation of these patients, the exact diagnosis was undetermined. This study was performed with an improved recording probe with six microtransducers at 10-cm intervals enclosed in a flexible 8-F sheath. Five asymptomatic subjects served as controls. We studied: 1) gastric emptying by a radiolabeled solid-phase meal, 2) motor activity of gastroduodenal area (SD), and 3) effect of metoclopramide on relief of symptoms. Only the symptomatic patients had delayed gastric emptying and abnormal motility of the GD area. MMC characteristics for both groups follows:

| Controls | Patients |
|----------|----------|
| Migrating motor complex (MMC) | |
| propagation velocity (cm/min) | 6.9 ± 5.8 | 8.9 ± 4.4 |
| frequency (min) | 86.4 ± 13.7 | 62.9 ± 12.9 |
| retrograde propagation % | 2 | 100 |
| Antral dysrhythmia % | 0/5 | 3/5 |

All values expressed as mean ± SEM.

Antral dysrhythmia was defined as short bursts of 6-8 contractions/min or greater that occurred in either regular or irregular intervals. Metoclopramide did not significantly alter MMC characteristics or ameliorate antral dysfunction, but patients experienced mild symptomatic relief during a clinical trial. In summary, these studies indicate that 1) delayed gastric emptying may be associated with impaired gastric emptying by radiolabeled solid-phase meal. In conclusion, gastroduodenal dysmotility may be associated with delayed gastric emptying and important recording probe that provides objective criteria for evaluation and appropriate medical therapy.
ABSTRACTS OF PAPERS

EFFECT OF MORPHINE AND NALOXONE ON LOWER ESOPHAGEAL SPHINCTER PRESSURE AND GASTRIC EMPTYING IN MAN. E.B. Frank, F. Chang, M. Plankey, R.W. McCallum. Depts. of Medicine and Nuclear Medicine, Yale University, New Haven, Connecticut, 06510.

There are morphine (µ) and enkephalin (σ) opioid receptors in the brain and throughout the gut. The opiate antagonist, naloxone, binds more to σ receptors. In this study we investigated the effects of morphine and enkephalin on esophageal motor function and gastric emptying of solids and liquids. 8 normal subjects received bolus IV doses of morphine, 8 mg, and naloxone, 4 mg, on separate days in a randomized, double-blind fashion. Lower esophageal sphincter pressure (LESPP) was monitored continuously using a Dent sleeve motility catheter for a basal period and for 60 minutes after drug administration (±SEM mm Hg). (*p<0.05 vs basal LESPP).

|               | Basal | 5 MIN | 15 MIN | 30 MIN | 60 MIN |
|---------------|-------|-------|--------|--------|--------|
| Morphine      | 26.6+4.2 | 20.2+4.2 | 20.3+4.2 | 21.6+4.3 | 22.2+4.1 |
| Naloxone      | 22.12+2.9 | 25.85+3.1 | 27.63+4.4 | 26.05+4.4 | 26.55+2.5 |

There was no effect on esophageal contraction amplitude. The rates of gastric emptying of solids (S) and liquids (L) were determined simultaneously using a dual isotope technique. The solid phase marker ([14C]-sulfur-colloid-labeled chicken liver) and the liquid marker ([14C]-labeled water) measured antral and fundic motor function respectively. The test drugs were given immediately after the meal. The percent of each isotope retained in the stomach over 2 hours is summarized below (±SEM vs basal S).

|               | Basal | 5 MIN | 10 MIN | 30 MIN | 60 MIN |
|---------------|-------|-------|--------|--------|--------|
| Morphine      | 93.0 33.4 | 79.8 | 68.5 | 67.9 | 63.2 |
| Naloxone      | 93.5 51.6 | 77.5 | 71.4 | 69.9 | 66.7 |

We conclude that: 1) Morphine significantly reduces while naloxone stimulates LESPP. 2) Morphine significantly inhibits gastric emptying of both solids and liquids while naloxone results in a non-significant acceleration of solid food emptying; 3) Our data suggest that morphine relaxes LES and gastric smooth muscle, although its gastric emptying effects may also be explained by stimulation of duodenal smooth muscle; 4) Morphine's emetic properties are influenced by its actions on the stomach and esophagus.

IDENTIFICATION AND LOCALIZATION OF OPIOID RECEPTORS IN THE OPOSSUM LOWER ESOPHAGEAL SPHINCTER (LES): EVIDENCE FOR A DISTINCT MEMERIDIAN RECEPTOR. S. Batten and R.R. Copeland. Charles A. Dana Research Institute & Thorndike Laboratory, Harvard Medical School and Beth Israel Hospital, Boston, Massachusetts 02115.

Effects of different opioid receptor agonists, buprenorphine, ketocyclazocine, N-allylnormetazocine, (D-Ala², D-Leu⁵)-Enkephalin (DADL) and meperidine were investigated on the LES in vivo. The LES pressures (LESPP) were monitored with a continuously perfused assembly of catheters that was anchored in the sphincter. The opioid agonists were administered in the esophageal branch of the left gastric artery. Buprenorphine, ketocyclazocine, and meperidine caused dose-dependent reductions in the LESPP. Morphine significantly inhibited gastric emptying of both solids and liquids while naloxone results in a non-significant acceleration of solid food emptying; 3) Our data suggest that morphine relaxes LES and gastric smooth muscle, although its gastric emptying effects may also be explained by stimulation of duodenal smooth muscle; 4) Morphine's emetic properties are influenced by its actions on the stomach and esophagus.

PYLORIC SPHINCTER RESPONSE TO DUODENAL ACIDIFICATION: EVIDENCE FOR AN INTRINSIC MEDITATING REFLEX. J. Bayer, M. Meier, A. Ouyang, S. Cohen. Department of Medicine, University of Pennsylvania, Philadelphia, PA 19104.

While the pylorus has been shown to have qualities characteristic of a sphincter, it is unclear whether mechanisms mediating pyloric function are dependent on the antrum or duodenum. The aims of this study were to define the mechanism and specificity of feline pyloric contraction to duodenal acidification. Duodenal, pyloric and antral intraluminal pressures and serosal electrical activity were recorded using a six port assembly pinned precisely at the pyloric junction. Duodenal acidification resulted in a significant (p<0.01) increase compared to saline of pyloric slow waves with spike activity (77.8±3.5), mean amplitude of pyloric contraction (82.5±11.6 μmHg) and the duration of increased pyloric pressure (65.1±14.4 sec). The change in percent duodenal slow waves with spike activity following acid, 19.5±6.5% was also greater than after saline (p<0.01). Topical administration of hemicholinium, intra-arterial tetrodotoxin (2.5-5.0 μg/kg) or intravenous naloxone (1.0 μg/kg) totally blocked the pyloric response. Atropine abolished all duodenal and antral spike activity but had no effect on either the pyloric spike activity response (85.0±7.5) or the pyloric reflex suggests it occurs independent of the duodenal response.

NITROUS OXIDE EFFECTS OF SE-ENDORPHIN FRAGMENTS IN THE DOG INTESTINE. James J. Galligan, Hans Schoemaker, Thomas F. Burke and Thomas P. Bositis. Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ 85724.

Beta-endorphin and enkephalins are released into the systemic circulation by the pituitary and adrenal medulla respectively. While a number of stimuli are known to release these peptides no target tissue has been identified. The GI tract may be a target tissue for circulating endorphins. (Supporting this notion are recent studies demonstrating the presence of opiate receptors. In addition, several fragments of 8-endorphin are produced in brain tissues and possess opiate activity. The GI tract may also process circulating endorphins; 3) the atropine resistance of the pyloric reflex suggests it occurs independent of the duodenal response.

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MORPHINE INDUCES MIGRATING MYOELECTRIC COMPLEXES IN FED DOGS. G.I. Telford and J.H. Szurszewski. Mayo Clinic and Foundation, Rochester, MN 55905.

In fasting animals low dose morphine sulfate (50-300 μg/kg, i.v.), given 30-50 minutes after a migrating myoelectric complex (MMEC) appears in the duodenum, initiates another MMEC in the duodenum (within 5-10 minutes) which then migrates distally. Initiation of an MMEC by morphine works by a mechanism that is independent of normal fluctuations in plasma motilin. In view of this apparent motilin independent mechanism of the action of morphine in fasting animals, we repeated the experiments in fed animals. Animals were fed 1 can of Alpo dog food plus 1 tube of Nutrical dietary supplement. In the first 90 minutes after the meal, morphine (150-600 μg/kg, i.v.), in 1 of 8 trials in 4 dogs, initiated an MMEC in the duodenum that propagated distally while the stomach remained in a typical fed pattern of myoelectrical activity. Between 90 to 150 minutes after the meal when the stomach and small intestine were in a typical fed pattern of myoelectrical activity, morphine (150 to 300 μg/kg, i.v.) initiated MMECs in the duodenum that propagated distally (10 of 11 trials in 5 dogs). The stomach remained in the fed pattern of myoelectrical activity during this entire sequence of events. In all instances morphine induced MMECs were followed by periods of quiescence (phase 2) after which the myoelectrical activity returned to a fed pattern. We conclude: (1) in the first 90 minutes after feeding, the stomach and small intestine were refractory to stimulation by opiates. (2) After 90 minutes, even though the stomach and small intestine were still in a fed pattern of myoelectrical activity, the small intestine responded to opiates with an MMEC. (3) Morphine induced MMECs do not begin in the stomach in fed dogs. (Supported by NIH AM 17238 and AM 00741.)

FUNCTIONAL AND BIOCHEMICAL CHARACTERISTICS OF LOWER ESOPHAGEAL SPHINCTER (LES) SMOOTH MUSCLE. N.W. Wetsbrodt, D.A. Simmons, and R.A. Murphy. Dept. of Physiology, University of Texas Medical School, Houston, TX 77025 and Dept. of Physiology, University of Virginia, Charlottesville, VA 22908.

Smooth muscle from the LES of the cat was used to determine: 1) the stress developed by the circularly oriented muscle layer, 2) the contractile protein contents of the muscle layers, and 3) the level of phosphorylation of the 20,000 Dalton light chain (LC-20) of myosin. Strips of LES were placed in a muscle bath (force development) or superfused (biochemical determinations) and stretched to their optimum length for tension development. Spontaneous tone as well as the amplitude were 0.5x0.5x (SEM) x 10^7 N/m. Active stress increased to 1.0x0.19 x 10^7 N/m. In the presence of 10^{-4} M tetrodotoxin, both strips of LES, physiologically as well as being less than or equal to the LES, were homogenized and the contents of actin and myosin were determined by 200x-polyacrylamide gel electrophoresis. LES strips contained 36.35±3.5 mg of actin and 21.24±4.6 mg of myosin per g wet weight of tissue. Superfused strips were freeze-clamped, homogenized, and subjected to isoelectric focusing in 20% polyacrylamide gel followed by second-dimension electrophoresis in 0.3% SDS, 13% polyacrylamide gels. The myosin LC-20 existed in two forms which had the same isoelectric points as the phosphorylated and non-phosphorylated LC-20's of arterial smooth muscle. In LES muscle exhibiting resting tone, the phosphorylated LC-20 represented 27±12% of the total LC-20. We concluded that in terms of stress developed and contractile protein content, LES smooth muscle is similar to other non-arterial smooth muscles. Also, spontaneous tone may be associated with the identification of the myosin LC-20. (Supported by NIH Grant AM 19885.)

DEVELOPMENT OF INHIBITORY AND EXCITATORY MODULATION OF THE LOWER ESOPHAGEAL SPHINCTER IN THE CAT. D. Hillenmeyer and P. Biancani. Department of Pediatrics and Internal Medicine Rhode Island Hospital and Brown University, Providence, Rhode Island 02902.

We have previously shown that, although in vivo LES pressure is reduced in the kitten, the muscle is able to generate stresses that are greater or equal than the adult. In the present investigation, differences in response to electrical stimulation, nicotine and mastigrafic stimulation were compared in the 6 week old kitten and the adult cat in an in vitro LES preparation. Electrical stimulation ranged from 0.3 msec. to 1.0 msec. to 10.0 msec and three response curves with nicotine and bethanol from 10^{-7} M to 10^{-1} M. At low frequency and duration of electrical stimuli, relaxation of the LES in the kitten was significantly less than the adult, whereas at higher frequencies and durations both relaxed fully. Similarly, low concentrations of bethanol caused the kitten LES to contract significantly less than the adult, whereas at high concentrations both contracted fully. Paradoxically, the kitten LES responded with relaxation to lower concentrations of nicotine than the adult. At low doses of nicotine the adult LES showed contraction rather than relaxation. However, after incubation in nicotine, the adult LES showed a dose response curve to nicotine similar to that of the kitten. This indicates that nicotinic stimulation in the adult, besides inhibition, also causes contractile activity which is blocked by atropine, suggesting the presence of an excitatory cholinergic pathway not yet present in the kitten. We conclude that the kitten LES is less responsive to muscarinic stimulation and to electrical stimulation with parameters which evoke a neural inhibitory response. We suggest that kitten LES muscle is fully able to contract upon maximal stimulation, but that its ability to respond to sub-maximal stimuli is reduced.
ABSTRACTS OF PAPERS

THE EFFECT OF ISOSORBIDE AND HYDRAZINE IN PAINFUL PRIMARY ESOPHAGEAL MOTILITY DISORDERS. Mark H. Mellow, M.D., Washington, D.C. VAMC; Georgetown University School of Medicine, Washington, D. C.

Five patients with painful primary esophageal motility disorders underwent pharmacologic testing with isosorbide and hydralazine. While neither agent affected baseline amplitude or duration of distal esophageal contractions, pretreatment with hydralazine significantly blunted the response to bethaneehol (mean esophageal contraction duration 3.4 ± 4.8 secs after bethaneehol alone vs. 12.7 ± 1.8 secs after bethaneehol and hydralazine p<.005). Pre-medication with isosorbide was significantly less effective. In addition, while all five patients experienced chest pain in response to bethaneehol alone, only one of five experienced chest pain in response to bethaneehol after prior hydralazine administration; three patients had chest pain after prior administration of isosorbide. Patients placed on long-term oral hydralazine therapy experienced improvement in chest pain and dysphagia with concomitant decrease in amplitude and duration of esophageal contractions on repeat motility study (176.5 ± 21.8 mm Hg to 97.5 ± 27.0 mm Hg, p<.05, 1.3 + 0.8 secs to 3.2 + 0.3 secs, p<.005). Hydralazine appears to be of value in the treatment of diffuse esophageal spasm and other painful primary esophageal motility disorders.

The EFFECT OF THE ORAL CALCIUM ANTAGONIST, DILTAZEM, ON ESOPHAGEAL CONTRACTIONS IN VOLUNTEERS AND NUTCRACKER PATIENTS. J.C. Richter, T.J. Spurling, C.M. Gordove, D.O. Castell, Uniformed Services University, Bethesda, Maryland.

Previous clinical studies have shown calcium antagonists decrease lower esophageal sphincter pressure (LES). Recent animal studies suggest they are also potent inhibitors of peristaltic amplitude (Amp). In this study, we evaluated the effects of an oral calcium antagonist, diltiazem (DII) in 3 human volunteers (V) and 6 patients with chest pain and increased distal Amp - the nutcracker esophagus (NE). Esophageal contractions were measured using a pneumoelastic infusion system. LES was recorded in four lumens with slow pull-through technique. Peristalsis was measured 5,10,15,20 cm above LES in response to 10 wet swallows. DII (90,120,150mg) or placebo were given orally in double-blinded fashion on 4 separate days. LES and Amp were measured at 0,30,60,90 and 120 minutes, and supine blood pressure (SP), pulse and EKG were obtained simultaneously. Blood levels of DII were drawn at 90 minutes. Results are summarized below:

| DII (mg) | NE (mmHg) |
|---------|-----------|
| 0 min  | 120 min   |
| Placebo | Placebo  |
| 90 mg   | 120 mg    |
| 120 mg  | 120 mg    |
| 150 mg  | 120 mg    |

Gastric emptying during coronary angiography with ergonovine provocation. D.Lieberman and J.McAuliff, Oregon Health Sciences University, Portland, Oregon, 97201.

Many patients with chest pain of esophageal origin have normal routine esophageal manometry and do not have gastroesophageal reflux only upon provocation with Ergonovine Maleate. Ergonovine infusion may induce myocardial ischemia even in patients who failed to demonstrate coronary artery spasm during cardiac catheterization. We propose recording esophageal pressure simultaneously with Ergonovine infusion during angiography to enhance the diagnostic yield and reduce the risk of a second provocative test outside the cardiac lab. A manometric catheter is passed into the stomach prior to angiography. Pressure transducers are connected to a multichannel recording system. The tube is withdrawn to record esophageal pressure and velocity (r=.81, p<.05); the corresponding r values in the CP-only subgroup significantly increased their contractions amplitude and velocity (r=.81, p<.05); the corresponding r values in the CP-only subgroup significantly increased their contractions amplitude and velocity (r=.81, p<.05). These data suggest that significant reflux is very frequent among patients referred with CP or DYS, and that CP in reflux patients is associated with normal contraction amplitude and velocity to acid infusion, while DYS and HB denote significant deterioration in these functions.

REFLUX PATIENTS. D.L. Brand and D. Tom, Department of Medicine, VAMC, Northport and SUNY # Stony Brook, N.Y.

70 consecutive patients were studied with manometry during 10 dry swallows (D.S.) and 10 swallows during infusion of 0.3N HCl (A.I.) into the mid-esophagus at 2 ml/min, as well as acid-reflux and Bernstein tests and suction biopsies. 43 patients remained after exclusion of those with achalasia, neurologic, or other non-esophageal disorders causing their symptoms. Grouping patients by most severe symptom, significant reflux (defined as at least two abnormal "reflux" tracts) was found as follows: chest pain (CP) 21/22; dysphagia (DYS) 7/8; heartburn (HB) 13/13. Amplitude data (mean +/- S.D.) are given in mm Hg: Normal 6 96 +/- 26 114 +/- 34

| Type | Normal | CP/DYS | CP-only | HB |
|------|--------|--------|---------|-----|
| N    | 6 96 +/- 26 | 114 +/- 34 | 134 +/- 34 |
| CP/DYS | 25 | 60 +/- 37 | 79 +/- 53 |
| CP-only | 5 | 92 +/- 48 | 128 +/- 56 |
| HB   | 13 | 51 +/- 22 | 54 +/- 32 |

*P<.05 or **P<.01 compared to D.S. of Normals as significantly greater (p<.05) than D.S. in some group or significantly less (p<.05) than D.S. in CP-only CP-DYS, CP-HB and DYS-only subgroups, and HB patients all had significantly lower D.S. amplitudes than Normals, while CP-only patients did not. Normals, the CP-DYS group, and the CP-only subgroup significantly increased their contraction amplitude during both Ergonovine infusions, while CP-DYS and CP-only subgroups and the HB group did not. DYS-only has a significantly lower D.S. amplitude than Normals, while CP-only patients did not. Normals, the CP-DYS group, and the CP-only subgroup significantly increased their contraction amplitude during both Ergonovine infusions, while CP-DYS and CP-only subgroups and the HB group did not. DYS-only has a significantly lower D.S. amplitude than Normals, while CP-only patients did not. Normals, the CP-DYS group, and the CP-only subgroup significantly increased their contraction amplitude during both Ergonovine infusions, while CP-DYS and CP-only subgroups and the HB group did not. DYS-only has a significantly lower D.S. amplitude than Normals, while CP-only patients did not. Normals, the CP-DYS group, and the CP-only subgroup significantly increased their contraction amplitude during both Ergonovine infusions, while CP-DYS and CP-only subgroups and the HB group did not. DYS-only has a significantly lower D.S. amplitude than Normals, while CP-only patients did not. Normals, the CP-DYS group, and the CP-only subgroup significantly increased their contraction amplitude during both Ergonovine infusions, while CP-DYS and CP-only subgroups and the HB group did not. DYS-only has a significantly lower D.S. amplitude than Normals, while CP-only patients did not. Normals, the CP-DYS group, and the CP-only subgroup significantly increased their contraction amplitude during both Ergonovine infusions, while CP-DYS and CP-only subgroups and the HB group did not. DYS-only has a significantly lower D.S. amplitude than Normals, while CP-only patients did not.
It has been well documented that stimulation via the autonomic nervous system increases gastric motility and secretion. Close associations between post-ganglionic neurons and smooth muscle cells have been observed throughout the digestive tract; however, the presence of similar associations between nerve varicosities and epithelial cells of the gastric mucosa have not been clearly established. In search of nerve-epithelial cell close association, we examined, at the electron microscopic level, the entire basal membrane of serially sectioned gastric epithelial cells in the opossum. In addition, nerves in the area of the gastric glands were followed to determine their ultimate target structures. Evaluation of serial sections of three separate parietal cells showed that their basal membranes did not come in close contact (within 1000 Å) with any nerve axon or varicosity. Moreover, the axons passing near these cells ultimately were associated with smooth muscle cells in the adjacent connective tissue or to vascular elements. Additionally, the lateral membranes of these three parietal cells did not contact any endocrine cell in the epithelial sheet, although, other parietal cells in the area were adjacent to endocrine cells. We have also examined serial sections of an endocrine cell that was adjacent to a parietal cell, and no nerve axon that contained a significant accumulation of synaptic vesicles was observed within the basal membrane of this endocrine cell. Nest cells in the lamina propria were seen in close contact with axons and these cells often showed granule discharge. These findings have led us to postulate that mechanisms other than direct nerve stimulation of gastric epithelial cells may be responsible for the release of their secretions.

PROPAGATION OF SLOW WAVES IN GASTRIC ANTRAL MUSCLE IN 3 SPECIES. A.J. Bauer, B.C. Tam, K.L. Bowes, and Y.J. Kimura. Department of Physiology and Neurological Research Center, Eastern Virginia Medical School, Norfolk, VA 23501.

The mechanisms controlling the origin, frequency and direction of propagation of slow waves in the stomach are unknown. This is because most investigations have studied slow waves at the tissue level, and not at the cellular level where the regulatory mechanisms most likely occur. We have been able to make a preliminary observation that smooth muscle cells with glass microelektrodes. Using this technique, we have been able to study the direction and speed of propagation of slow waves within a well-defined population of cells. Thirteen male mongrel dogs were anesthetized and the entire stomach was removed through a midline abdominal incision. A patch of muscle 7-10 cm from the pyloric ring was dissected from the mucosa. Strips of muscle were cut (3 mm x 20 mm), parallel to either the longitudinal or circular fibers. These were pinned as an edge to the floor and side of a cylindrical physiological chamber and oriented such that the cells of the circular muscle layer could be impaled. Two cells were impaled simultaneously using independently suspended microelectrodes. Continuous recordings were made for periods exceeding an hour and the delay between spontaneous slow waves was quantified.

In most preparations oral dominance was observed, and the delay in recording slow waves between oral and aboral cells was constant. In a few preparations slow waves did not originate from a dominant site and activity appeared to originate uniformly throughout the sheet of cells. Conductive velocities were measured by impaling circular muscle cells. Circular cells were oriented side-by-side (strips cut parallel to the longitudinal fibers) and end-to-end (strips cut parallel to the circular fibers). These values were 1.2 cm/sec and 0.4 cm/sec, respectively.

A second preparation was used to evaluate the spread of excitation through the muscle. In these experiments, the muscle strips were turned on edge before the insertion of the glass microelectrodes. Occasional traces showed separate conduction pathways for the longitudinal and circular muscle. In one experiment, slow waves originating in longitudinal cells and then spread to the circular cells. The conductive velocity of these slow waves was calculated to be 44 cm/sec.

In conclusion, we have made precise measurements of conduction velocity in 3 dimensions in circular muscle. Using these data we have developed a model to describe the site of origin of slow waves. This model should prove extremely useful in determining the effect of localized stimuli on the origin, frequency and pattern of propagation of slow waves in gastric muscles.

PYLORIC RESISTANCE. K. Schulze-Delrieu and J.P. Wall. Gastroenterology Research Laboratories, University of Iowa, Iowa City, Iowa 52242.

The pyloric segment generates a high pressure zone on manometry; pressure is generated by structural forces and by tonic and phasic muscular activity. Now these forces are reflected in resistance to flow across the pylorus is not known. We, therefore, measured the pyloric resistance in dogs from cats and rabbits and tied cannulas into the antral and duodenal ends of the pylorus (as defined by the inter-and the distal structures, respectively). In the dog, the pylorus was cut open and the thickness of muscle was calculated to be 0.4 mm.

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ABSTRACTS OF PAPERS

NEUROEPITHELIAL CELL RELATIONSHIPS IN THE GASTRIC MUCOSA OF THE OPOSSUM. J. S. Dagle, B. C. Tam, and K. L. Bowes. Department of Biological Science, The University of Texas Health Science Center at Dallas, Texas 75235.

It has been well documented that stimulation via the autonomic nervous system increases gastric motility and secretion. Close associations between post-ganglionic neurons and smooth muscle cells have been observed throughout the digestive tract; however, the presence of similar associations between nerve varicosities and epithelial cells of the gastric mucosa have not been clearly established. In search of nerve-epithelial cell close association, we examined, at the electron microscopic level, the entire basal membrane of serially sectioned gastric epithelial cells in the opossum. In addition, nerves in the area of the gastric glands were followed to determine their ultimate target structures. Evaluation of serial sections of three separate parietal cells showed that their basal membranes did not come in close contact (within 1000 Å) with any nerve axon or varicosity. Moreover, the axons passing near these cells ultimately were associated with smooth muscle cells in the adjacent connective tissue or to vascular elements. Additionally, the lateral membranes of these three parietal cells did not contact any endocrine cell in the epithelial sheet, although, other parietal cells in the area were adjacent to endocrine cells. We have also examined serial sections of an endocrine cell that was adjacent to a parietal cell, and no nerve axon that contained a significant accumulation of synaptic vesicles was observed within the basal membrane of this endocrine cell. Nest cells in the lamina propria were seen in close contact with axons and these cells often showed granule discharge. These findings have led us to postulate that mechanisms other than direct nerve stimulation of gastric epithelial cells may be responsible for the release of their secretions.

PATTERNS OF GASTRIC LONGITUDINAL AND CIRCULAR MUSCLE CONTRACTIONS. B.C. Tam, K. L. Bowes, J. J. Kingsm. Surgery and Electrical Engineering, University of Alberta, Edmonton, Alberta, Canada, T6G 2G3.

Longitudinal and circular muscle contractions were assessed simultaneously by means of displacement gauges mounted on the inside of the canine fundus, corpus and antrum of the stomach. Threshold stimuli (<2 Hz) led to large reductions, high threshold stimuli (>8 Hz) led to large increases of pyloric pressure and produced large reductions of flow. In the pyloric segment, the pylorus generates a high pressure zone on manometry; pressure is generated by structural forces and by tonic and phasic muscular activity. Now these forces are reflected in resistance to flow across the pylorus is not known. We, therefore, measured the pyloric resistance in dogs from cats and rabbits and tied cannulas into the antral and duodenal ends of the pylorus (as defined by the inter- and the distal structures, respectively). In the dog, the pylorus was cut open and the thickness of muscle was calculated to be 0.4 mm.

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REGULATION OF THE MUSCLES RESPONSIBLE FOR GASTRIC EMPTYING

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digestible solids. The preservation of nearly normal gastric

emptying after mucosal antrectomy suggests that this opera-

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digestible solids, but may regulate in part emptying of

indigestible solids, and contribute to the finding of lower fasting serum gastrin (59+5 vs 97+16

pg/ml, P<.05) after MA. Gastric emptying of liquids and --

much greater intraluminal (959+272 ng/g) than at

the corporal margin (2.0+1.1 ng/g) suggesting completeness

fusing technique on 5 occasions in each dog before and again

4 wk after MA. Fasting and postprandial serum gastrin were

also measured. RESULTS: Tissue gastrin concentration was

much greater in mid-antral mucosa (956+777 pg/ml) than at

the corporal margin (2.0+1.1 ng/g) suggesting completeness

of antral mucosal excision. This was further supported by the finding in fasting serum gastrin (956 vs 973

pg/ml, P<.05) and postprandial serum gastrin (976 vs 978

pg/ml, P<.05) after MA. Gastric emptying of liquids and

indigestible solids was unaltered by mucosal antrectomy,

while gastric emptying of solids was slowed somewhat

(Table). We concluded that the antral mucosa plays little role in gastric emptying and that the conse-

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digestible solids. The preservation of nearly normal gastric emptying after mucosal antrectomy suggests that this opera-

tion may be an option when antrectomy is indicated for pep-

tic ulcer disease. Support: USPHS NIH Grant AM18278.

Milk  % emptied from stomach + SEM

| Liquids at 30 min | Digestible | Indigestible |
|-------------------|------------|--------------|
| Control            | 73.6±11    | 45.9±22      |
| After MA 6075 NS   | 54.2±5     | 41.7±2 NS    |

ABSTRACTS OF PAPERS

REGULATION OF THE MUSCLES RESPONSIBLE FOR GASTRIC EMPTYING

BY ENDOGENOUS PROSTAGLANDINS. K.M. Sanders and C.D. Jones.

Our aim was to determine the role of antral mucosa in

controlling gastric emptying of solids and liquids. In 4

dogs, mucosal antrectomy (MA) was performed, excising the

antral mucosa via a circular corporal antrectomy, removing a circular border of sarcomeric muscles, anastom-
sing the corporal and pyloric mucosas endoantrally and reapposing the circular corporal and pyloric sarcomeres.

Excised antral mucosa was analyzed for gastrin by radio-

immunoassay. Gastric emptying of a digestible solid (50 g

of liver tagged with 250 cpm cyanoacetylene, an indigestible solid (40 radiopaque plastic spheres, 2 and 4 mm in

diameter), and a liquid (300 ml 11.6% dextrose i%) were

assessed simultaneously using a double-isotope duodenal perfusion technique on 5 occasions in each dog before and again

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THE ENTERIC MECHANISMS OF INITIATION OF MIGRATING MYOELEC-

TRIC COMPLEXES (MMC's). S. Sarna, R.E. Condon and V. Cowles.

Our aim was to determine the role of antral mucosa in

controlling gastric emptying of solids and liquids. In 4

dogs, mucosal antrectomy (MA) was performed, excising the

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EFFECT OF ANTIMOTILIN RABBIT SERUM ON MMCs AND PLASMA MOTILIN LEVEL IN DOG. K.Y. Lee, T.M. Chang, and W.Y. Chey. The Isaac Gordon Center for Digestive Diseases and Nutrition. The Genesee Hospital and University of Buffalo.

Previously we reported that iv infusion of antimotilin rabbit serum (anti-M) inhibited the MMCs from canine antrum and duodenum (Bug B ScT 25:735, 1980). As a contrast to investigate the role of endogenous motilin on MMCs, the study was carried out in 10 dogs with platinum electrodes in the antrum, duodenum, jejenum, and ileum. The effects of 3 occasions of MMCs from proximal duodenum, iv bolus injection of 1.0 ml anti-M was given at phase II in the proximal duodenum which was followed by slow infusion of 2.5 ml anti-M for 90 min in 8 dogs (siter; 1x125,000mm/1,000,000). iv anti-M resulted in inhibitions of 3-7 occasions of MMCs, revealing the time interval (time period between MMCs) from 103.0 ± 8.4, 102.5 ± 9.0, and 110.4 ± 15.4 after anti-M to 205.0 ± 39.0, 264.4 ± 35.4, and 130.2 ± 17.0 min after anti-M in duodenum, jejenum and ileum. The delayed MMCs in duodenum and jejenum were statistically significant (p<0.01). However, the initial delays in jejunal and ileal MMCs were followed by more frequent MMC-like activities which were independent of duodenal MMCs. Since it is possible that the local concentration of motilin at the receptor sites may be higher than that in the plasma, large doses of anti-M (1.0 ± 5.0) ml was given in 2 dogs. In both dogs, were prolonged inhibitions of MMCs were observed, lasting for 28.12,8 and 5 hrs in the antrum, duodenum, jejenum and ileum in dog which received 15.0 ml of anti-M. The total number of MMCs lasting 24 hr after anti-M was 0.5, 13, and 13 in antrum, duodenum, jejenum and ileum compared with that of 11 occasions during comparable period before anti-M in this dog. The plasma motilin level, 156.0 ± 363.7 pg/ml in phase I of 4 occasions of duodenum decreased to 20.5-59.8 pg/ml after anti-M also. When the MMCs returned in the duodenum, the plasma motilin level was elevated to 257.6 pg/ml.

The present study strongly suggests that the endogenous motilin plays an important role on generation of MMCs in the antrum and small intestines. However, possibly, there is another factor or factors which are responsible for the motilin-independend MMCs in the lower intestines.

SOMATOSTATIN (SRIF) AS A MODULATOR OF INTESTINAL MOTILITY: PROPOSED MECHANISMs OF ACTION. D.H. Teltebenbaum, I.S. Ginestrella, T.M. O'Dorisio, and W.E. Perkins. The Ohio State University and Adria Laboratories, Columbus, Ohio. 43210.

SRIF is a known inhibitor of gut contractility. SRIF, along with other peptides, has been located in neurons of the myenteric plexus (MP). Because of this close relation with neuronal structures and SRIF's ability to inhibit motilin, we investigated how SRIF modulates acetylcholine (Ach) release and contractility induced by caerulein (Cra; cholecystokinin-like peptide), neuropeptide (NP), and substances P (SP). An SP-induced release of vasovasostatic intestinal polypeptide (VIP) was also measured by RIA. The results of the Ach release studies are:

| Peptide | [peptide/mer] | Alone | SRIF | Tetrotoxin |
|---------|---------------|-------|------|-----------|
| C (1 x 10^-8) | 0.18 | 0.12 | 0.12 |
| NT (1 x 10^-6) | 0.44 | 0.12 | 0.12 |
| SP (1 x 10^-6) | 1.24 | 0.13 | 0.12 |
| K (0.025) | 0.74 | 0.17 | 0.17 |

SP-induced release of vasovasostatic intestinal polypeptide (VIP) was also measured by RIA. As post release values were:

- 55 ± 15 pg/min vs 10 ± 15 pg/min.
- 16 ± 8 pg/min vs 4 ± 8 pg/min.
- 4 ± 8 pg/min vs 1 ± 8 pg/min.

SRIF (5 x 10^-9M) significantly inhibited contractions in a manner suggesting competitive inhibition; however, SRIF failed to significantly inhibit SP. We conclude that: 1. CR modulates SP release activation of the nervous system in the guinea-pig MP. 2. The contractions, in part, are neurochemically mediated. 3. The site of SRIF inhibition may be at the interganglionic cell body. Further, SP may induce VIP release. Supported, in part, by GCRC-CRC, RR74.

MOTOR ALTERATIONS CAUSED BY CAMPYLOBACTER JEJUNI MAY BE RESPONSIBLE FOR ITS PATHOGENICITY AND CLINICAL PRESENTATION. C.A. Sminsky, J.J. Langer, and F.G. Nalbandian. The Ohio State University and the Department of Medicine, University of Florida, Gainesville, Florida 32602.

C. jejuni is one of the most common bacterial isolates in patients with diarrhea. Abdominal pain and bloody diarrhea are predominant clinical features of C. jejuni enteritis; however, the mechanisms involved in the pathogenesis are poorly understood. We previously reported two alterations in myoelectric activity—repetitive bursts of action potentials (RBAPs) and nonpropulsive migrating complex (MPC)—associated with invasive and noninvasive bacteria. We now investigated: 1) myoelectric effects of C. jejuni on rabbit small intestine, 2) whether a cell-free filtrate of C. jejuni alters motor activity, and 3) histologic alterations caused by the bacteria. The model consists of Ag-AgCl monopolar electrodes sewn to the serosa of an in vivo isolated loop of distal ileum in New Zealand rabbits. Myoelectric activity was studied after the following procedures were injected into the loop: 1) 1 ml of beef heart infusion broth (BHI), 2) 1 ml of 10^9 organisms/ml in BHI, 3) 0.91 ml/h infusion of 0.20 μm filterate of C. jejuni culture, and 4) heat-treated filtrate of C. jejuni (100°C for 3 min) for 3 values are expressed as the meanSEM. The results are:

| BHI | C. jejuni filtrate | Heat-treated filtrate |
|-----|------------------|---------------------|
| MAPS/0 h | 0.65 ± 0.61 | 0.35 ± 0.28 |
| RBAPs/0.750 h | 6.31 ± 2.0 | 5.00 ± 0.9 |

*p<0.001 compared with BHI controls.

Review of histologic sections reveals no significant alterations at 24 h, but after 48 h severe villous blunting with erosions and a cellular infiltrate were observed. This study indicates: 1) RBAPs are the predominant altered myoelectric activity induced by C. jejuni filtrate and NT- and NT-injected rats in a manner suggesting competitive inhibition; however, SRF failed to significantly inhibit SP. We conclude that: 1. C. jejuni releases a filtrate which alters motor activity, and 3) severe histologic alterations occurred only after prolonged exposure to C. jejuni. We propose that C. jejuni may produce nonpropulsive muscular contractions that may cause dissection of intervening small intestine and allow for intestinal stasis, bacterial proliferation, and epithelial damage.
**ABSTRACTS OF PAPERS**

**INFLUENCE OF CORONAVIRUS (TGE) INFECTION ON JEJUNAL MYOELECTRICAL ACTIVITY AND DURATION OF BACTERIAL OVERGROWTH IN THE EXPERIMENTAL BLIND LOOP SYNDROME.** P.C. Justus and L.E. McWerron. Veterans Administration Medical Center, Oregon Health Sciences University, Portland, Oregon.

The purpose of the present study was to examine the effect of coronavirus infection (transmissible gastroenteritis) on the myoelectric activity of the neonatal (10-18 day old) pig. The study was conducted on 6 healthy piglets obtained from a local herd at 3 days of age and fed a standard diet 4 times daily. At 7 days of age 4 bipolar Ag-AgCl electrodes were surgically implanted on the jejenum at 5 cm intervals beginning 20 cm below the ligament of Treitz. Four control recordings were made from each pig. These began at 9 am on the 4th post-operative day, 1 hour after the morning meal, continued through the noon feeding and gastric contractions finished at 4 pm. Animals were infected at 8 pm on the 8th post-operative day with a 1 ml oral dose (12 x 10^6) plaque forming units of a 0.1% gut suspension obtained from TGE infected piglets. Recorded sessions were continued in an identical manner for another 4 days beginning at 9 am the next morning. In pre-experiment recordings slow waves occurred at a frequency of 17.2 ± 0.3 c.p.m. (SEM). Spike activity predominated, occupying 91.0 ± 4.3 of the recording time in characteristic migrating enteric myoelectric complex (MEMC) and was unaffected by feeding. The activity front (phase II) of the MEMC occurred irregularly (X ≥ 5 ± 5 mins, range 6-156 mins) lasted 4.1 ± 0.9 mins and was propagated aborally at a speed of 0.03 mm/sec. Short (2-4 sec) bursts of spike activity were also observed, these occurred at a frequency of 69 ± 9/hr., mainly in phase II of the MEMC and were propagated aborally at a speed of 35 ± 15 mm/sec. All pigs developed diarrhea on the 2nd day post-infection. On the 3rd day post-infection the percent time occupied by spike activity was decreased to 75 ± 5 (p<0.05) and the short, rapidly propagated bursts of spike activity were decreased to 10 ± 5/hr (p<0.01). Infection had no effect on slow wave frequency or on the duration or frequency of the activity front. The results suggest that TGE infection may reduce the amount of propulsive activity in the jejunum of the neonatal piglet.

**ALTERED MYOELECTRICAL ACTIVITY AND DURATION OF BACTERIAL OVERGROWTH IN THE EXPERIMENTAL BLIND LOOP SYNDROME.** P.C. Justus and L.E. McWerron. Veterans Administration Medical Center, Oregon Health Sciences University, Portland, Oregon.

The blind loop syndrome is characterized by bacterial overgrowth, malabsorption and diarrhea. We have reported increased, but antibiotic-suppressible, myoelectric activity in the blind loop rat model of bacterial overgrowth (Gastroenterology 78:1190, 1981). In this study we evaluated the relationship between the duration of bacterial overgrowth and altered motility in this model. Self-filling blind loop rats (SBLR), which do not develop bacterial overgrowth (BOLR), which do develop bacterial overgrowth (BOLR), were studied in separate groups. One, 2, 3, and 4 weeks after the blind loop surgery. Monopolar electrodes were placed on the blind loop, afferent and efferent jejunal segments. Myoelectric activity was monitored for 2 hours. The frequency of organized bursts of action potentials which involve all jejunal segments (OBAp) and the percent of total action potential activity spent in organized bursts (WAM-APF) were determined. The percent of slow waves occupied by action potential bursts greater than 1 second in duration (WSW-APF) were calculated for each jejunal segment. The results were:

| Segment          | 1 Week | 2 Weeks | 3 Weeks | 4 Weeks |
|------------------|--------|---------|---------|---------|
| SBLR              |       |         |         |         |
| OBAp (mean)      | 17.2   | 17.1    | 17.6    | 17.9    |
| WAM-APF (mean)   | 4.8    | 4.6     | 4.0     | 3.5     |
| WSW-APF (mean)   | 5.4    | 5.1     | 4.8     | 4.3     |
| BOLR (mean)      | 17.1   | 17.7    | 18.2    | 19.0    |
| OBAp (mean)      | 17.1   | 17.7    | 18.2    | 19.0    |
| WAM-APF (mean)   | 4.6    | 4.5     | 4.4     | 4.3     |
| WSW-APF (mean)   | 5.1    | 5.0     | 4.9     | 4.8     |

**12 HR. ESOPHAGEAL FUNCTION STUDIES IN RABBIT'S ESOPHAGUS.** J.E. Richter, S.B. Benjamin, D.O. Castell. National Naval Medical Center and the Uniformed Services University, Bethesda, MD.

With appropriate infusion systems, the amplitude (Amp) of esophageal peristalsis in normal subjects has been shown not to differ significantly from day to day. We have recently described a motility disorder in patients with chest pain/dysphagia characterized by high amplitude peristalsis in the distal esophagus (mean distal Amp > 120 mmHg), the nutcracker esophagus (NE). We have reported the degree of variability in distal Amp determined as the range between the highest and lowest mean Amp of serial (2-4 times) studies. Patients were normal (Normals), and (b) NE patients. We have also described the degree of variability in normal Amp as determined as the range between the highest and lowest mean Amp (NE Amp ± 95% CI). The results are:

**Average Amp of Distal Amp ± 95% CI**

| Group | Amp (mmHg) ± 95% CI |
|-------|--------------------|
| Normals | 19.8 ± 3.6         |
| NE     | 37.0 ± 6.1         |

p <0.02

We conclude that 1) inter-study variability of Amp in NE patients may require serial studies to confirm diagnosis; 2) excessive intra-study variability may be a clue to its presence; 3) this variability of Amp in NE must be considered when evaluating effects of therapy.
A MULTIPORT RELAXATION OSCILLATOR REPRESENTING A SLOW WAVE: INFLUENCE OF INPUT PORT ACTIVATION. B.L. Bardakjian, T.Y. El-Sharkawy and R.N. Diamant. Departments of Physiology and Medicine, University of Texas Medical School at Houston, Houston, TX 77030

The electrical and mechanical activities of the circular muscle layer of the proximal colon of the pig were studied in transverse strips using extracellular (action) electrodes and force transducers respectively. The strips were obtained from the inter-taenial region and consisted of the entire muscularis. They were studied in oxygenated Krebs solution at 37° C and at their optimal length (125% of their initial length). Under these conditions the circular muscle layer exhibited slow wave activity at a frequency ranging from 0.5 to 3 cpm (mean ± S.E.M.: 1.6 ± 0.1, n=54). Each wave had a superimposed spike burst and was associated with a phasic contraction. Cholinergic stimulation (carbachol or physostigmine) caused a dose dependent increase in the slow wave frequency and the number of spikes associated with each slow wave. Consequently the frequency and force of contractions was enhanced. Spontaneous activity was inhibited but not abolished by atropine (10^-6 - 5x10^-5 M): the slow wave frequency and the number of spikes associated with each wave were decreased. The nerve conduction blocker tetrodotoxin (TTX, 2x10^-7 M) had similar effects. Simultaneous addition of both drugs also inhibited but did not abolish spontaneous activity. To examine the possibility that the atropine and TTX insensitive slow wave activity was due to the tension under which these strips were studied, we examined the activity of 22 unstretched preparations. All these circular muscle strips showed spontaneous electrical and mechanical activity at a frequency of 1.2 ± 0.2 cpm. Atropine (10^-5 - 5x10^-5 M) on both atropine and TTX (2x10^-7 M) inhibited this activity but could not abolish it.

This study suggests that the circular muscle of the proximal colon of the pig exhibits a myogenic slow wave activity at a low frequency, that this activity controls the contraction pattern in this layer and that, unlike most other types of slow wave activity, its frequency can be modulated by cholinergic stimulation.

(Supported by MRC and Elsie Watt Foundation.)

ABSTRACTS OF PAPERS

PROLONGED OBSERVATIONS OF MYOELECTRIC ACTIVITY AND PRESSURE IN THE CANINE ILEOCecal SPHINCTER. E.M.M. Quigley, J. May Clinic, Rochester, Minnesota

To gain access to the canine ileocecal sphincter (ICS) we created loops consisting of 70 cm terminal ileum, ICS and 5-10 cm proximal colon. The segment of bowel, though luminal isolated, retained neuromuscular continuity with the intact ileum through a bridge of muscle. Myoelectric activity from ICS, ileum and colon was recorded from unipolar submucosal electrodes and intraluminal relaxation pressures were recorded from ileum and colon using 4 perfused side-hole catheters. To ensure accurate and continuous recordings of ICS pressure, a modification of the perfused side-hole catheter system originally described for study of the LES (Gastroenterology 71:263, 1976) was used. Six female mongrel dogs were studied. On each day ileal, ICS and colonic myoelectric and intraluminal pressure changes were recorded for 5-6 hr while fasted and for 4 hr following 50 g meat. Results: In vitro testing of the sleeve system revealed a low resistance to perfusion and satisfactory dynamic performance. Preservation of a normal slow wave gradient and propagation of 81% of all migrating myoelectric complexes (MDC) into the loop confirmed maintenance of neuromuscular continuity by the sleeve. The ICS electrode recorded ileal type slow waves with a mean frequency of 12.3 ± 0.35 cycles/min; 53% of all MDC's could be traced to ileum. The sleeve electrodes recorded a tonic pressure from the ICS (mean 30 cm H2O, range 12-40 cm Hg) upon which were super-imposed phasic waves. These waves were present 60% of total recording time; their maximum frequency (14/min) approximated that of ileal slow waves. Cyclic fluctuations in ICS tonic pressure occurred during fasting. Sustained elevations (to 55-90 cm H2O) lasting 14-46 min occurred on arrival of phase III of the MMC at the ICS. After food ICS baseline pressure was lowered (mean 26 cm H2O, range 7-38 cm H2O) and cyclic fluctuations were not seen. Conclusions: This preparation provided a useful model for long-term study of the ICS in vivo. Myoelectric activity and pressure at the ICS displayed cyclic variations during fasting, suggesting participation of the ICS in the cycle of interdigestive events.

ON THE NATURE OF THE SLOW WAVE ACTIVITY IN FIG COLONIC CIRCULAR MUSCLE. J.D. Hoitenga, N.R. Diamant and T.Y. El-Sharkawy. Departments of Physiology and Medicine, University of Toronto and Toronto Western Hospital, Toronto, Canada

The electrical and mechanical activities of the circular muscle layer of the proximal colon of the pig were studied in transverse strips using extracellular (action) electrodes and force transducers respectively. The strips were obtained from the inter-taenial region and consisted of the entire muscularis. They were studied in oxygenated Krebs solution at 37° C and at their optimal length (125% of their initial length). Under these conditions the circular muscle layer exhibited slow wave activity at a frequency ranging from 0.5 to 3 cpm (mean ± S.E.M.: 1.6 ± 0.1, n=54). Each wave had a superimposed spike burst and was associated with a phasic contraction. Cholinergic stimulation (carbachol or physostigmine) caused a dose dependent increase in the slow wave frequency and the number of spikes associated with each slow wave. Consequently the frequency and force of contractions was enhanced. Spontaneous activity was inhibited but not abolished by atropine (10^-6 - 5x10^-5 M): the slow wave frequency and the number of spikes associated with each wave were decreased. The nerve conduction blocker tetrodotoxin (TTX, 2x10^-7 M) had similar effects. Simultaneous addition of both drugs also inhibited but did not abolish spontaneous activity. To examine the possibility that the atropine and TTX insensitive slow wave activity was due to the tension under which these strips were studied, we examined the activity of 22 unstretched preparations. All these circular muscle strips showed spontaneous electrical and mechanical activity at a frequency of 1.2 ± 0.2 cpm. Atropine (10^-5 - 5x10^-5 M) on both atropine and TTX (2x10^-7 M) inhibited this activity but could not abolish it.

This study suggests that the circular muscle of the proximal colon of the pig exhibits a myogenic slow wave activity at a low frequency, that this activity controls the contraction pattern in this layer and that, unlike most other types of slow wave activity, its frequency can be modulated by cholinergic stimulation.

(Supported by MRC and Elsie Watt Foundation.)

INFRARED LIMITATION OF COLONIC PROPULSION: DOES IT REFLECT THE STRESS GENERATING CAPACITY OF CIRCULAR MUSCLE. William A. A. Muens and Rebecca L. Bowers. Department of Physiology, Univ. of Texas Medical School at Houston, Houston, TX 77030

Previous studies demonstrated that when the intrinsic propulsive behavior of cat colonic segments is evaluated under conditions requiring hydrostatic work, the net amount of fluid ejected during each propulsive complex decreases as the capacitance of the attached evaluation system decreases. The aboral pressure at which electrical stops occurred when this capacitance was limited to 36 cm of H2O. Since the cessation of fluid propulsion occurs at a constant aboral pressure, it has been concluded that the net amount of aborally ejected fluid per propulsive complex is limited by intraluminal pressures. Two general mechanisms may account for the pressure limitations imposed on intestinal propulsion. Intraluminal muscle may be incapable of generating the contractile forces required to induce further propulsion once a luminal pressure of 36 cm of water is reached; or, intraluminal control systems may inhibit further propulsion when a limiting pressure is attained within the lumen. An investigation of the myogenic mechanism was begun by determining if propulsion is limited by the ability of circular muscle to produce active stress. Mathematical relationships were developed to predict the circumferential stress that occur in colonic segments when they are attached to a propulsion evaluation system. Data from previous studies conducted in our laboratory on the mechanics of cat circular muscle were used to calculate the circumferential stress during spontaneous and intraluminal stress occurring during a propulsive complex when the intraluminal pressure is at 36 cm of H2O is never greater than 240,060 dynes cm^-2 and is probably around 120,030 dynes cm^-2. The maximum active component of circumferential stress that can be generated by circular muscle under these test conditions averages 2,759,836 dynes cm^-2. Since circular muscle can actively produce 11 to 21 times more stress than is needed to begin reduction of the luminal diameter at a given radius, it is concluded that colonic propulsion is not limited by the active mechanical properties of circular muscle when circumferential stresses are at a maximum.
RADIAL SPHINCTER FUNCTION IN DIABETES MELLITUS: COMPARISON OF CONTINENT AND INCONTINENT DIABETICS WITH NON-DIABETIC CONTROLS. L.S. Schiller, L.A. Santa Ana, and J.S. Fordtran. Baylor Univ Med Ctr, Univ Texas HSC and VA Med Ctr, Dallas, TX. Chronic diarrhea (D) and fecal incontinence (F) are well recognized complications of long-standing diabetes mellitus. However, anal sphincter function has not been systematically explored in these patients. To do this, 30 diabetics were evaluated with a questionnaire, physical examination, stool collection and tests of anal sphincter function. These tests included anal sphincter manometry with a perfused catheter system, and tests of continence for a 1.8 cm. solid and for a 1.5 cm. liquid-leak test. 

Compared to women, men showed a) longer sphincters (4.6 ± 0.2 vs 3.7 ± 0.2 cm, p = 0.006); b) greater resting and squeeze pressures at the orad station (p < 0.001), except in the anterior position. Conclusions: The human anal canal has marked radial and longitudinal variations of pressure which will influence interpretation of comparative studies. Results from the orad station suggest a major contribution from the levator ani which can be distinguished by the present methodology. The role of separate muscle groups in the maintenance of normal anal function or in the disorders of continence may be elucidated by these approaches.

ANAL SPHINCTER FUNCTION IN DIABETES MELLITUS: COMPARISON OF CONTINENT AND INCONTINENT DIABETICS WITH NON-DIABETIC CONTROLS. L.S. Schiller, L.A. Santa Ana, and J.S. Fordtran. Baylor Univ Med Ctr, Univ Texas HSC and VA Med Ctr, Dallas, TX. Chronic diarrhea (D) and fecal incontinence (F) are well recognized complications of long-standing diabetes mellitus. However, anal sphincter function has not been systematically explored in these patients. To do this, 30 diabetics were evaluated with a questionnaire, physical examination, stool collection and tests of anal sphincter function. These tests included anal sphincter manometry with a perfused catheter system, and tests of continence for a 1.8 cm. solid and for a 1.5 cm. liquid-leak test.

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ABSTRACTS OF PAPERS

EFFECTS OF PROSTAGLANDINS ON ELECTROMYOGRAPHY OF CAT COLON. J.L. Conklin, and S. Anuras. Department of Internal Medicine, University of Iowa, Iowa City, Iowa 52242.

Prostaglandins (PGs) are found throughout the gut, can cause diarrhea, and their production by the gut increases in diarrheal states. Since certain diarrheal states produce distinctive changes in the electromyogram recorded from the colon we chose to study the effects of PGF\textsubscript{2\alpha} and PGE\textsubscript{2} on the electromyogram of cat colon in vitro. Colon strips (20 cm x 1 cm) were mounted in a bath perfused with Krebs' solution gassed with 95% O\textsubscript{2}, 5% CO\textsubscript{2}. The electromyogram was recorded from circular muscle using 6 silver-silver chloride glass-pore electrodes spaced 3 mm apart. Strips were exposed to PGF\textsubscript{2\alpha} and PGE\textsubscript{2} at concentrations of 0.001-1.0 μg/ml. PGF\textsubscript{2\alpha} decreased slow wave (SW) frequency in the proximal colon and increased SW frequency in the distal colon. The effect of PGE\textsubscript{2} on SW frequency in the proximal colon was maximal at 0.1 μg/ml. At this concentration PGF\textsubscript{2\alpha} decreased the SW frequency by 50% (p < 0.05). The effect of PGE\textsubscript{2} on SW frequency in the distal colon was maximal at a concentration of 1.0 μg/ml. At this concentration PGF\textsubscript{2\alpha} increased the SW frequency by 15% (p < 0.05). PGE\textsubscript{2} also uncoupled SW activity. PGF\textsubscript{2\alpha} had no effect on SW frequency or coupling. Migrating spike burst (MSB) frequency was increased significantly by both PGF\textsubscript{2\alpha} and PGE\textsubscript{2}. PGE\textsubscript{2} at 0.1 μg/ml decreased MSB frequency (p < 0.05), and PGF\textsubscript{2\alpha} increased MSB by 50% (p < 0.05). Conclusion: PGF\textsubscript{2\alpha} effects the electromyogram of cat colon in a way similar to diarrhea agents. PGs, especially PGE\textsubscript{2}, may be important modulators of colonic motility.

MECHANICAL AND INTRACELLULAR ELECTRICAL ACTIVITY OF THE OPOSSUM SPHINCTER OF ODDI. J.M. Becker, J.A. Brzozowski, and J.H. Szurszewski. Department of Physiology, Mayo Clinic and Foundation, Rochester, MN 55905.

Extracellular myoelectric recordings of the opossum sphincter of Oddi (SO) have demonstrated propagating phasic bursts of spike activity superimposed on regularly occurring low voltage spontaneous oscillations. Phasic contractions of the SO are associated with these electrical changes. The aim of this study was to define intracellular electrical activity and simultaneous mechanical activity of the opossum SO. Two millimeter segments of distal bile duct and surrounding SO circular muscle were excised, opened, and pinned to the floor of an organ bath with the circular layer upward. Intracellular microelectrode techniques were used to record electrical activity while simultaneously monitoring mechanical activity with a force transducer. The mean (± SE) value of the intracellular resting membrane potential was -55 (± 1.5) mV. Spontaneous electrical activity consisted of slow waves with superimposed bursts of spike potentials. Mean (± SE) duration of the electrical complex at 50% maximum amplitude was 1.0 (± 0.4) sec. The frequency of spikes within a burst ranged from 6 to 15 Hz. The mean maximum rate of rise of the spike potential was 0.7 (± 0.1) V/sec. The peak amplitude of the spike often overshot zero potential. Each spontaneous electrical complex was accompanied by a large (3-5 g) phasic contraction. Co-energetic stimulation with carbachol depolarized the membrane, increased the frequency of spike bursts, and increased both phasic and tonic mechanical activity. This preliminary study suggests that the sphincter of Oddi muscle can be evaluated quantitatively with intracellular electrophysiologic techniques. These intracellular recordings provide a cellular basis for spontaneous spike bursts detected with extracellular recording techniques. (Supported by NIH AM 17238 and AM 07198.)
MOTILITY OF THE CANINE CYSTIC DUCT. A.S. Clanachan, D.P. Courtney, and G.W. Scott, Departments of Pharmacology and Surgery, University of Alberta, Canada.

(i) Under pentobarbital anaesthesia the two ends of the CD were cannulated and the duct was perfused with saline solution (37°C) at constant pressure. The flow rate through the duct was recorded (electromagnetic flow-meter) and after bolus injections of the test solutions into the hepatic artery. Mean flow rates (10 dogs per agonist) were plotted against each dose of agonist.

(ii) Cystic ducts were excised from anaesthetized dogs, opened longitudinally and divided transversely into four equal strips (i.e. circular orientation). Standard organ-bath techniques were used to record contractile responses of the strips of tissue to (i) force displacement transducers. After 30 minutes stabilization at 0.5 g tension non-contractile responses were recorded in each strip (n=10 per agonist).

Results - All responses were dose/concentration-related.

Equal responses were obtained from the four strips in any one duct (in vitro). The Table arrows indicate flow increases (t) or decreases (&) in vivo, and contraction (†) or relaxation (‡) in vitro:

| Flow (in vivo) | Tension (in vitro) |
|---------------|--------------------|
| Ach NA Ad-Ad AH H H2 CCK CCK-OP |
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| † † † † † † † |

Conclusions - Appropriate stimuli can produce relaxation and contractile responses and, in the intact CD, can affect resistance to flow through the duct. The duct appears to be capable of sphincter-like activity, and responds to a variety of neurotransmitter and hormonal agents. The contractile response to CCK appears to be paradoxical because it would resist outflow from the contracting gallbladder; it is not known whether it occurs under physiologic conditions.

ABSTRACTS OF PAPERS

MOTILITY OF THE CANINE CYSTIC DUCT. A.S. Clanachan, D.P. Courtney, and G.W. Scott, Departments of Pharmacology and Surgery, University of Alberta, Canada.

The contractility of the cystic duct (CD) was studied in vivo and in vitro. The effects of graded concentrations (range 10^-4 to 10^-4 M) of acetylcholine (Ach), norepinephrine (NA), adrenalin (Ad), histamine (H), and acetylcholcylosin (CCK, range 0.01 to 30 Ivy units) and CCK-octapeptide (CCK-OP) were recorded, before and after appropriate blocking agents.

Under pentobarbital anaesthesia the two ends of the CD were cannulated and the duct was perfused with saline solution (37°C) at constant pressure. The flow rate through the duct was recorded (electromagnetic flow-meter) and after bolus injections of the test solutions into the hepatic artery. Mean flow rates (10 dogs per agonist) were plotted against each dose of agonist.

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CONTROL MECHANISM OF THE SPONTANEOUS IN VITRO CONTRACTIONS OF THE OPOSSUM SPHINCTER OF ODDI (SO). J.P. Helm, J. Christensen, W.J. Dodds, S. Sarna. Medical College of Wisconsin, Milwaukee, WI and the Univ. of Iowa, Iowa City, IA.

The opossum SO segment, 3 cm in length, has spontaneous peristaltic contractions in vivo that propagate toward the duodenum. To study SO contractile activity in vitro, SO segments from 20 opossums were suspended in a bath while 4 force displacement transducers. After 30 minutes stabilization at 0.5 g tension non-contractile concentration-contraction responses were recorded in each strip (n=10 per agonist).

Results - All responses were dose/concentration-related.

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NEURAL CONTROL OF SPHINCTER OF ODDI MOTOR ACTIVITY IN THE CAT. L. Behar and P. Biancalani. Department of Medicine, Rhode Island Hospital and Brown University, Providence, R.I. 02902.

We have previously shown the existence of an intrinsic excitatory pathway to the cat sphincter of Oddi (SO). It consists of opiate neurons that activate serotonergic neurons which in turn stimulate excitatory receptors on post-ganglionic cholinergic neurons and on smooth muscle cells. The contribution of these excitatory neurons to SO motor function was assessed by using specific antagonists which cause block at several sites along this pathway and by 5-HT depletion: 1) A combination of atropine and methysergide in doses sufficient to block the excitatory effect of exogenous serotonin and enkephalin markedly reduced the amplitude and frequency of phasic contractions and decreased tonic pressures (P<0.05); 2) 5-HT depletion by reserpine and fluoxetine had similar effects. Pretreatment with reserpine abolished the SO motor response to enkephalins and caused significant decreases in the frequency and amplitude of phasic contractions and in tonic pressures compared to controls (P<0.05). Treatment with fluoxetine, which specifically depletes 5-HT, also blocked the effect of enkephalins and markedly decreased the amplitude and frequency of phasic contractions with a reduction in tonic pressures (P<0.05); 3) The specific opiate antagonist, naloxone, blocked the effect of enkephalins but not of 5-HT, decreased the amplitude and frequency of phasic contractions, and decreased tonic pressures. We conclude that endogenous opiates, through this intrinsic excitatory pathway, may regulate SO phasic contractions and tonic pressures and may contribute to the maintenance of SO motor activity either directly or by balancing the influence of non-cholinergic, non-adrenergic inhibitory neurons.

EFFECTS OF INDOMETHACIN AND DIETARY CHOLESTEROL ON GALLBLADDER SIZE AND MOTILITY. K.A. Protaschi, W.J. McRorie, and L.E.T. Williams, Jr. Division of Surgery, Boston University Medical Center, Boston, MA 02118.

Bile lipid composition and gallbladder (GB) steatosis contribute to cholelithogenesis. Lipids in bile may influence not only cholelith precipitation but GB emptying as well, and prostaglandins are possible mediators in this process.

We used a hysteresis technique to study the effect of cholesterol and indomethacin on the fasting volume (Vf) and stiffness of the guinea pig gallbladder. Animals received 6 or 12 weeks of control diet (M1), 0.5X cholesterol diet (M2), subcut. indomethacin (M2), or cholesterol diet plus indomethacin (M3). The fasting GB volume was measured at laparotomy, and biliary mechanics were studied by inserting a catheter in the GB after ligation of the sphincter of Oddi. GB pressure was recorded continuously during repeated infusion and withdrawal of the Vf, in both the resting and CCK-stimulated state. This gave highly reproducible hysteresis curves from which gallbladder stiffness could be calculated.

We found that Vf was not affected by indomethacin (1.7cc vs. 1.9cc control), but cholesterol diet significantly increased Vf to 2.4cc (P<0.05). Preliminary data from animals receiving cholesterol and indomethacin suggests that indomethacin blocks this effect. Cholesterol did not significantly alter GB stiffness; however indomethacin decreased stiffness from 11.76 cm Hg to 6.52 cm Hg (P<0.001). In all animals, CCK significantly increased GB stiffness.

These results indicate that dietary cholesterol alters fasting GB volume and this could reflect increased biliary stasis. Indomethacin decreases biliary pressures, and may counteract the effect of cholesterol on fasting volume.

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ABSTRACTS OF PAPERS

DOES CAERULEIN STIMULATE THE ENTERIC CHOLINERGIC NEURONS THROUGH A RELEASE OF SUBSTANCE P? William M. Yau and Michael L. Yau. School of Medicine, Southern Illinois University, Carbondale, IL 62901.

Both substance P (SP) and caerulein (CAE) are peptides known to nodulate release of neurotransmitter from the enteric cholinergic neurons. In an attempt to examine the mechanism of action of these peptides on the enteric cholinergic neurons, a specific SP antagonist (SPA, D-Pro2, D-Phe7, D-Trp7-SP) was employed. Isolated myenteric plexus-longitudinal muscle strips from the guinea pig small intestine were used. Isometric mechanical contractile activity was evaluated by intracellular injection of depolarizing electrical current pulses, increased numbers of action potentials in the presence of the Substance P antagonist suggested that neuronal excitability was augmented by the putative antagonist. The results were the same when the Substance P antagonist was microinjected onto the neurons. We conclude that the (D-Pro2, D-Phe7, D-Trp7-SP) analog of Substance P is not a Substance P antagonist of enteric ganglion cells.

(Supported by NIH Grants NS17363 and AM26742.)

JEJUNAL MANOMETRIC STUDIES IN ASYMPTOMATIC RELATIVES OF AUTOSOMAL RECESSIVE TYPE OF FAMILIAL VISCERAL MYOPATHY. S. Anuras, F. A. Mitros, S. S. Shirazi, and J. B. Green. Departments of Medicine, Pathology and Surgery, University of Iowa, Iowa City, Iowa 52242.

Familial visceral myopathy is characterized by degeneration and fibrosis of smooth muscle of the gastrointestinal tract and sometimes of the urinary tract. In most reported families, the disease is transmitted by an autosomal dominant gene. A visceral myopathy family with an autosomal recessive transmission was identified. This family has about 1500 members in 7 generations. Three patients, the proband (a 24-y-o female) and her brother and cousin, were found to have the disease. All 3 were the products of internmarriages. All patients had gastric atony, moderate dilatation of the entire small bowel and multiple diverticula. Microscopic examination of the entire small bowel revealed fibrosis, mainly of the longitudinal muscle layer, which was indistinguishable from the dominant transmission type of visceral myopathy. Jejunal manometry was performed on six asymptomatic relatives (the proband's mother and five siblings). All these relatives had normal gastrointestinal contrast x-rays and normal esophagogastroduodenoscopy. Jejunal manometric studies were performed by using a low compliance system. The relatives were fasted overnight, and record was made for 4 hours during fasting, and 2 hours following a 650 calorie balanced meal. The results were compared to 10 normal controls. During the fasting period, four (the mother and three siblings) out of six relatives had no phase 1 in some of the migrating motor complex cycles. Durations of phases 2 and 3 were normal, except the duration of phase 3 in the mother was 3 times longer than in normal controls. All 4 relatives who lacked phase 1 had higher motility indices (summation of amplitude of contractions per minute) in phase 2 than normal controls (p<0.05). We conclude that abnormal small bowel motility could be heterozygotes of the disease in this family.
MUSCLE LAYER OF THE CANINE GALLBLADDER AND CYSTIC DUCT.
G. W. Scott, and J. Chansoria. Department of Surgery, University of Alberta, Canada.

The single "chromosomal layer" of the gallbladder (GB) and cystic duct (CD) more closely resembles the muscularis mucosae than the other muscle layers of the intestine. Its morphology was studied in GBs and CDs removed from 13 dogs under pentobarbital anesthesia. The specimens were opened, fixed in Bouin's solution for 24 hours and blocks were embedded in paraffin with key orientation. Serial sections 6 microns thick were cut in the 3 planes and stained with Masson's and trichrome. The thickness of the muscle layer was measured in transverse sections using a micrometer eyepiece in the microscope. Measurements were at identical sites in the GB fundus, neck, junction of GB and CD, mid CD and junction of CD and common bile duct. The three-dimensional arrangement of muscle bundles was traced through serial tangential sections (i.e., cut parallel to the mucosal surface).

Results. There was a continuous muscle layer extending through the submucosal region of the GB and CD. A sphincter-like arrangement of muscle ("sphincter of pickle") was not found at the GB-CD junction. On transverse and longitudinal sections the layer appeared to be made up of transverse (i.e., circular), longitudinal and oblique muscle bundles separated by prominent amounts of connective tissue. However, serial tangential sections it was found that the muscle bundles joined to form a lattice-work arrangement. The interspaces were filled with connective tissue and contained networks of vessels and nerves. The muscle bundles were thickest and formed the tightest mesh in the gallbladder. The thickness of the muscle layer also changed from GB to CD: GB fundus 94.1 ± 8.3, junction GB-CD 29.9 ± 6.3, junction GB-CD 29.9 ± 6.3, mid CD 22.6 ± 2.2, junction CDBC 17.6 ± 1.3 μm (P < 0.001).

Conclusion. Although the muscle layer is continuous it has a tight (GB) and loose (CD) lattice or mesh-work arrangement. It therefore differs markedly from the internal circular and longitudinal muscle layers and only superficially resembles muscularis mucosae. It is capable of exerting tension in multiple axes.

EVIDENCE THAT SUBSTANCE P IS NOT RELEASED FROM HYPOTHALAMIC HEMISECTIONS IN THE ISOLATED RAT COLON. D. L. Kreulen, Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ 85724.

There is evidence that in the guinea pig substance P is released from intrinsic intestinal nerves and is responsible for the hyoscine-resistant contraction in that tissue (Franco et al., Naunyn-Schmeid. Arch. Pharmac. 296, 1978). This hypothesis was tested in the isolated smooth muscle of the rat colon. Contractions of circularly-oriented strips (10-15 cm long x 2.5 mm wide) of the distal colon of rats were used at optimal length. All preparations contracted in response to Substance P (Edso(nM) EDb0(pM) ED50(pM) 'chronic' 26.4±3 (n=7) 32.0±7.5 (n=11) 3.6±0.73 (n=9) 'acute' 9.7±4.2 (n=10) 4.6±0.8 (10) 2.4±0.25 (5) (P<0.01). Maximal responses to all agents were less in the 'acute' GBs, but this difference was significant (P<0.05) for only bradykinin (contraction 0.73±0.13 g vs 'acute' 0.25±0.05 g). In the 'chronic' GBs histamine and bradykinin induced contractions were reduced after indomethacin treatment, whereas in the acute GBs the contractions were potentiated.

Conclusion: Contractile responses are different in chronic and acute gallbladder disease. Part of this difference may be due to effects of prostaglandin-like substances.
THE BENEFICIAL EFFECT OF METHYL PGF2A TO DIMINISH CAUSTIC ESOPHAGEAL INJURY. D R Siner, I R Fletcher, D O Castell, and C L Eastwood. East Carolina University School of Medicine, Greenville, North Carolina. Uniformed Services University, Bethesda, Maryland, and University of Massachusetts Medical School, Worcester, Mass.

We utilized a baboon model for hyperacute esophagitis (HE) to test the protective effect of methyl PGF2. Twenty animals were divided into four treatment groups; intravesophageal acid (A), A pretreated with IV Indomethacin (I) (1.5 mg/kg) (A+I), A pretreated with IN plus SQ methyl PGF2 (1.25 ug/kg) (A+IN+I), and control (C). Peristaltic activity (AMP), velocity (V), duration (D), and LES pressure were recorded before and after the 120 min infusion, at 24 hrs and at 7 days. Endoscopic photographs were graded for the degree of injury by a blinded observer. Amp in distal esophagus in all groups was significantly lower than C after 120 min (p<0.02). Amp progressively decreased by 24 hr and was significantly lower than C with A and A+IN. After 24 hr, however, the A+I group had significantly higher Amp than A (-16 ± 6 mmHg vs -75 ± 21 mmHg; p<0.05) and was not significantly different from C. Amp returned to normal by 7 days after injury without treatment. Proximal AMP, V or D were not changed by any treatment. LES pressure was decreased by A at 24 hr (p<0.05); significantly less by A+IN at 24 hrs (+15.5 mmHg). Endoscopic-graded injury was greatest after A and A+IN; less after A+IN+I at 24 hrs. Pathologic changes were similarly worst after A; less after A+I+IN. We conclude: (1) HE produces a decreased LES pressure; (2) Methyl PGF2 pretreatment with IN to decrease endogenous prostaglandin synthase does not prevent decreased AMP or endoscopic injury; (3) replacement of methyl PGF2 after IN pretreatment significantly improves functional and endoscopic injury.

DEFINITION OF THE PREVALENCE OF BARRETT'S ESOPHAGUS IN PATIENTS WITH CHRONIC PEPTIC ESOPHAGEAL STRICTURES. H. Sperling, J.E. Richter, P.L. Nielsen, D.O. Castell. Departments of Gastroenterology and Nuclear Medicine, National Naval Medical Center, and the Uniformed Services University, Bethesda, Maryland.

The "nutcracker esophagus" (NE) is a primary motor disorder of the esophagus characterized by chest pain and/or dysphagia in patients with increased amplitude peristaltic contractions in the distal esophagus. In our initial studies, we have demonstrated prolonged radionuclide transit (RT) in patients with NE. We have further evaluated this technique in an attempt to correlate manometric parameters and RT in this group of patients. Fourteen patients with the NE and 10 manometrically normal controls underwent 2 swallows of Tc-99m sulfur colloid in 10 cc of water. RT was defined as the time from entry of radionuclide into the esophagus to a return to 10% of peak radioactivity in the distal esophagus. All RT studies were blindly interpreted. RT in normals was 6.8 ± 0.2 sec (X ± 1 SE); 2) RT in the NE was abnormal in 13/14 patients. 26.5 ± 4.7 sec (X ± 1 SE). This value is significantly increased when compared to normal subjects (p<0.03); 3) Chaotic bolus activity defined as uncoordinated bolus transit was seen in 9/14 patients; 4) There was no correlation between RT and basal amplitude in the distal esophagus or lower esophageal sphincter (LES) pressure. Conclusions: 1) The NE is a functional abnormality of the esophagus manifested by prolonged RT; 2) There is no correlation between values of peristaltic amplitude or LES pressure and RT; 3) The etiology of this ineffective high amplitude peristalsis and its relation to the transit abnormality is unclear; 4) The NE represents a primary esophageal motor disorder.
ESOPHAGEAL MANOMETRICS IN CRICOPHARYNGEAL DIVER- 
CULAE. L. Choiniere and A. Lyes
Esophageal Motility Laboratory, Dept. of Surgery,
Toronto General Hospital, Toronto, Canada, M5G 1L7

There is still controversy regarding the manometric abnormalities, if any, coexisting with crico-
ephyngeal (Zenker’s) diverticulae. Eleven pa-
tients with radiographically proven Zenker’s di-
verticulae were studied using the Honeywell MP-3
and Visicorder 1508-B recording system. Six pa-
tients had a normal resting tone cricopharyngeus
(UES). In all of these, relaxation was complete, and
in 5 co-ordination of pharynx and cricopharyn-
geus was good. In one patient with a low-normal,
and 3 with a hypertensive UESs, relaxation was in-
complete. One hypertensive UES relaxed completely.

Pharyngeal motor waves are normal in 5 of 6
with a normal UES but reduced in amplitude in all
patients with reduced UES tone. Patients with a
normal UES have lower esophageal sphincter pres-
sures (LES) ranging from hypotensive to normal,
and more motor abnormality in the body of the eso-
phagus. This suggests that patients with crico-
ephyngeal diverticulae may fall into two general
groups, those with a generalized motor dysfunc-
tion from pharynx to LES and those with fairly
normal motor function.

ABSTRACTS OF PAPERS

PREDICTIVE VALUE OF DUODENAL ACID LOAD DETERMINATION IN
DUODENAL ULCER DISEASE. L.S. Fischer and A. Dubois.
USUHS and NNM, Bethesda, Maryland.

The clinical course of duodenal ulcer (DU) disease is
variable and unpredictable. This retrospective study
designed to determine if a subset of patients with more
aggressive disease could be identified on the basis of ab-
normalities in basal and stimulated gastric acid output and
acid emptying rate. Two groups of DU patients were studied: 1) 10 patients with intractability, i.e., occurrence within
2-27 months of relapses and complications; 2) 4 patients
without clinical relapse. Normal values were obtained in
11 healthy subjects without digestive diseases. We used a
eye dilution technique to determine concurrently basal and
stimulated gastric acid output, fractional emptying rate,
and the duodenal acid load. Stimulation was produced se-
quently by a 250 ml water load and by pentagastrin i.v.
(6 ug/kg/hr). Basal and load stimulated acid outputs
were significantly greater (p < 0.01) in patients with intract-
ability (9.1 + 1.8 and 19.5 + 2.7 mEq/hr, mean ± SE), than
in other DU patients (3.1 + 1.5 and 7.2 ± 4.3 mEq/hr),
and in healthy controls (3.2 ± 0.5 and 7.4 + 1.2 mEq/hr), but
fractional emptying rates were not significantly different.

RELATIVE POTENCIES OF AMPHIBIAN, PORCINE AND CANINE
BOMBESIN-LIKE PEPTIDES ON SMOOTH MUSCLE OF CANINE STOMACH.
E. Mayer and J. Walsh, VA Waddsworth Hospital Center,
Los Angeles, CA 90073.

Exogenous bombesin infusion produces powerful stimula-
tion on gastric motility in vivo. To determine the mecha-
nism of action and to compare bombesin-like peptides (BLP)
from different species an in vitro assay for canine antral
muscle was used. Circular (CAM) and longitudinal (LAM)
muscle strips were mounted in an organ bath and mechanical
activity was measured by isometric recordings. BLP increased frequency and amplitude of spontaneously occurring
contractions in CAM and LAM. The effect on frequency of
LAM and CAM was unaffected by tetrodotoxin (10^-5M) and
atropine (10^-6M) whereas the effect on amplitude of LAM was
blocked by both agents. In CAM threshold concentrations
for stimulation of frequency were between 10^-13-10^-11M.
maximal response was 8-6 contractions per minute
and half-maximal response was at peptide concentra-
tions of 10^-10M. Frequency responses of CAM to acetyl-
choline (ACh) and the following BLP were compared (number
of amino acid in parentheses):

Synthetic amphibian bombesin (14), synthetic porcine
gastrin-releasing peptide GRP (27), natural amphibian lite-
rin (9) and two recently isolated natural canine BLP (27,10)
with identical C-terminal decapptide. At threshold con-
centrations amphibian bombesin was approximately 10,000
times more potent than ACh. Dose-response curves of all BLP
were similar and not significantly different.

These data suggest that BLP have a powerful chrono-
tropic effect on canine antral muscle in vitro, that this
effect is myogenic and that amphibian, porcine and canine
BLP in this system are equipotent.

GASTRIC TONE. K. Schulze-Delrieu and J. P. Wall.
Gastroenterology Research Laboratory, University of Iowa,
Iowa City, Iowa 52242.

Changes in the resting length or tone of the gastric
musculature keep the pressures within the gastric lumen in
narrow limits despite marked fluctuations of intragastric
volume. Experiments on gastric tone have been done mostly
in intact animals; in order to learn more about any intrin-
sic controls of gastric tone, we measured the tone of iso-
lated cat stomachs in physiologic solution by isotonic and
isotonic means. For isotonic recordings, the clamped
stomach was filled or emptied to predetermined volumes and
the resulting luminal pressures were recorded. Filling was
followed by pressure peaks which by subsequent accommoda-
tion were brought down by as much as 100%. Conversely on empty-
ing the stomach, adaptive contraction followed an initial
pressure nadir and approximated the final pressure plateau
to that on filling the stomach. The amplitudes of accom-
modation and adaptive contraction increased with total gas-
tric volume and the rate of volume changes. Both responses
were abolished by exposure of the isolated stomach to NAcH,
but persisted when TTX, hexamethonium or atropine (at
10^-7M) were added to the physiologic solution. For iso-
tonic recordings, the stomach was preloaded with 100 ml
of physiologic solution and its luminal volumes monitored
while the pressure head on an outflow cannula was system-
atically altered. Stomachs emptied the volume with pres-
sures below 7 cm Hg and increased it with higher pres-
sures. Our experiments show that adaption of tone occur
in isolated stomachs and probably reflect an intrinsic
property of the gastric musculature.

(A-17)
COMPARATIVE EFFECT OF GASTRIN ON H+ SECRETION, ANTRODUODENAL MOTILITY AND THE INTERDIGESTIVE MOTILITY COMPLEX (IDMC) IN MAN. G. Dooley, H. Miranda, J.K. Valenzuela. University of Southern California, GI Section, Los Angeles, California.

In dogs gastric stimulants secretion, antral contractions and converts the IDMC pattern to that of the fed state. The physiological significance of the gastric effect on motility in man is not demonstrated although stimulation of H secretion is well known. We decided to compare the effect of gastrin infusion on H secretion, and antral motility. The serum gastrin levels achieved were compared to postprandial levels. Five healthy male subjects, mean age 21 yrs. had 2 studies on different days.

The two tests were given five hours apart. The first test was done in the morning after a 12 hour fast. Gastrin was infused intravenously at a rate of 10 micrograms/min. Baseline, frequency, amplitude, and duration of contractions were measured. The second test was done after a 12 hour fast. Gastrin was infused intravenously at a rate of 10 micrograms/min. Baseline, frequency, amplitude, and duration of contractions were measured.

Species differences in the effects of prostaglandin E2, and indomethacin in the two layers of jejunal smooth muscle. M. Prithoda and R.W. Sumners. Department of Internal Medicine, Veterans Administration and University of Iowa Hospitals and Clinics, Iowa City, IA 52246.

The effects of graded doses of PGE2, and of indomethacin on the two muscle layers of the jejunal wall were compared in the opossum and the dog. Longitudinal (LM) and circular (CM) muscle strips were studied in an organ bath in oxygenated Krebs solution at the length of optimum tension. Spontaneous contractions were recorded using a polygraph and were analyzed in an investigator. Baseline, frequency and duration of contractions were calculated and compared using paired t-tests. A motility index was used to show the effects of test drugs on the regulation of fasting motor activity in postprandial and antral motility.

Mean Phase II CR (0-1 min): B 2.16 +/- 0.74 2.30 +/- 0.75 A 2.84 +/- 1.63 2.10 +/- 3.00 t = 1.50 < .025 (t-test for unpaired values)

The phase II contraction rate was greater in the AC group as compared to normals, with and without CCK-OPT. The contraction rate decreased in normals and in alcoholics with CCK-OPT, and the decrease was greater in the AC group. The correlation of the phase II contraction rate was negatively correlated with the phase II contraction rate in normals (r=-.73, p<.022) but not in AC group.

Chronic alcohol ingestion may induce an abnormal phase II motility pattern characterized by: 1) high contraction rate, 2) exaggerated suppression by CCK-OPT, 3) lack of correlation between contraction rate and basal trypsin output.

SEARCH FOR A LOW FREQUENCY COLORFUL PACESetter POTENTIAL IN THE DOG. Kleinbach, J.B., A. Schlueter, J.B. Amens, and C.E. Dodge, VA Medical Center and University of California, San Diego, Ca. 92161.

Low frequency canine electrical activity was measured on a pen-writing recorder specially modified with high pass filters with 3 second time constants. Four dogs were prepared with electrodes sewn to the serosal surface of the distal ileum, and the ascending colon. The physiological significance of the autonomic nervous system in the regulation of fasting motor activity in postprandial and antral motility.

With electrical stimulation of 5 ms, 50 msec pulses, the pacemaker could be paced at periods of 50, 60 and 30 seconds. The propagation time to an electrode 12 cm away was 14.18 and 25 seconds. This propagation-frequency relationship is similar to the pacemaker potential of the stomach and small bowel.

Fluoroscopic observations, made with barium sulfate in the colon, showed large contractions moving in an aboral direction with a frequency of 1.5 cps and a wavelength of 20 cm. Superimposed on these low frequency contractions were low amplitude contractions with a frequency of 4 cps and a wavelength of 1 cm moving in the opposite direction. The two types of contractions indicate at least two pacemakers present in the colon simultaneously.
ABSTRACTS OF PAPERS

EFFECT OF SECOVERINE HYDROCHLORIDE ON CANINE COLONIC MOTILITY. S.K. Barna, P. Northcott and L.W. Belbeck, Medical College of Wisconsin, Milwaukee, WI 53226 and McMaster University, Hamilton, Ontario, Canada.

The effect of Secoverine hydrochloride, a selective GI smooth muscle muscarinic blocker, on colonic motility was studied in 4 conscious dogs, each implanted with 4 equidistant strain gauges on the colon. The dogs were fasted for 24 hrs before each experiment. Each experiment consisted of 2 hrs of control recording and 2 hrs of post-meal (291 gm, 527 Cal) or 1 hr of post-neostigmine (15 ug/kg, i.v.) recording. Two experiments were done in each dog with meal alone, 2 with neostigmine alone, 2 with neostigmine + 2 mg Secoverine, and 2 with neostigmine + 4 mg Secoverine. Secoverine was administered 10 to 15 min prior to meal or neostigmine. Three types of contractions were observed - rhythmic contractions at a frequency between 3-16 c/min, tonic contractions superimposed with rhythmic contractions. Motility indices were determined for 10 min intervals by summing the product of duration and maximum amplitude of all three types of individual contractions. There was no significant difference between the colonic motility indices before and after a meal or before and after meal + Secoverine (P>0.05). Ratios of mean motility post-injection to mean motility pre-injection were calculated for the three drug conditions: neostigmine, neostigmine + 2 mg Secoverine, and neostigmine + 4 mg Secoverine. Both Secoverine conditions (2 mg and 4 mg) produced motility ratios significantly less than the neostigmine alone by a ratio (P<0.05) of 4 mg. Secoverine significantly lowered the total motility index ratios during the first 30 min period following neostigmine but had no significant effect during the next 30 min period. The ratio of maximum motility index peak post-neostigmine was significantly lower for 4 mg Secoverine but not for 2 mg Secoverine. In conclusion, there was no increase in colonic motility following neostigmine for the first 30 min period.

Supported by Kali-Duphar Laboratories, Inc., Columbus, Ohio.

MANOMETRIC ABNORMALITIES DURING SPONTANEOUS CHEST PAIN IN PATIENTS WITH PRESUMED ESOPHAGEAL SPASM. R. Cloose, O. Landau, A. Staiano, J. Schlachter. Division of Gastroenterology, Washington Univ. School of Medicine, St. Louis, MO 63110.

Eleven patients with negative cardiac evaluations and frequent chest pain presumably from esophageal dysmotility were studied to determine the manometric abnormalities which occurred during spontaneous chest pain. Seven of the 11 also complained of dysphagia, and mild to severe abnormalities were observed on standard esophageal manometric In over half of the cases. For this study peristaltic waves were recorded from the distal esophagus using a probe with 2 intraluminal pressure transducers spaced 5 cm apart. The devised system isolated the patients to ambulate ad lib while peristalsis, swallows, and respiration were recorded on a chart recorder out of view. Patients were allowed to drink liquids and eat soft foods, each meal included via a signal box the onset and duration of typical chest pain. Mean length of study was 220 minutes (range 132-310). Nine patients developed typical chest pain while being monitored. Tracings were coded, blindly evaluated for wave amplitude, wave duration, and presence of abnormal peristalsis during and immediately prior to each pain episode, and then compared to control periods at the beginning and end of each study. Changes in baseline pressure were also examined during pain episodes compared to the non-pain period.

Results: (n=7)

| Condition | Mean Change from control |
|-----------|-------------------------|
| Pre-pain  | 15.1 ± 7.2              |
| Pain      | 10.0 ± 5.2              |
| Pre-pain  | 14.1 ± 6.6              |
| Pain      | 11.0 ± 5.7              |

None of the changes were significant at the 0.05 confidence level. Conclusions: 1) No significant manometric changes were observed in the distal esophagus prior to or during episodes of typical chest pain in patients with presumed dysmotility-induced pain. 2) Analysis of esophageal peristalsis utilizing usual parameters may be illogical in the investigation of patients with chest pain.

PROCESSING OF GASTROINTESTINAL (GI) SPIKE ACTIVITY FOR CONTRACTILE SIGNALS. S.N. Reddy, R. Daniel, J.L. Yu, W.R. Waterfall, L. Belbeck, Departments of Surgery, Neurosciences and Electrical Engineering, McMaster University, Hamilton, Ontario, Canada L8N 3Z5.

We have developed a methodology for obtaining GI contractile signals, without recourse to strain gauges (SGs), from electrical activity recorded by bipolar electrodes. The method is based on the assumption that the spatial and temporal summation in a spike burst is reflected in the ensuing contraction. The method consists of (a) filtering the electrical activity to remove slow waves and their harmonics, (b) full-wave rectification of the resulting spike activity, and (c) filtering the rectified signal for envelopes or spike differentiated contractions (SCs) on contractions recorded by SGs. The method and its application have been tested on dog by implanting electrodes and SGs opposite electrodes while SGs reflects global activity and are conditioned by the physical characteristics of the gauges. However, the SCs and SGs did exhibit a linear relationship in that a) the number of contractions per unit time was almost identical in each case, and b) the motility index was computed in both cases, as areas under the curves, were linearly proportional (r=0.9) and c) visual inspection exhibited one-to-one correspondence between SG and SC contractions. In conclusion, this method can be used to test whether spikes are the sole determinant of contractions. In the human small intestine, it allows the investigation of the propagating characteristics of contractions and motility indices. This research was supported by the Medical Research Council of Canada.